TARGETS IN HETEROCYCLIC SYSTEMS

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Dear Reader,

Volume 7 (2003) keeps the international standard of THS series and contains eleven chapters, covering the synthesis, reactivity, and mass spectrometry of different heterorings. Reviews from Italy, Russia, and Spain are present in this book.

Comprehensive Reviews reporting the overall state of the art on wide fields as well as personal Accounts highlighting significative advances by research groups dealing with their specific themes have been solicited from leading Authors. The submission of articles having the above-mentioned aims and concerning highly specialistic topics is strongly urged. The publication of Chapters in THS is free of charge. Firstly a brief layout of the contribution proposed, and then the subsequent manuscript, may be forwarded either to a Member of the Editorial Board or to one of the Editors.

The Authors, who contributed most competently to the realization of this Volume, and the Referees, who cooperated unselfishly (often with great patience) spending valuable attention and time in the review of the manuscripts, are gratefully acknowledged.

Orazio A. Attanasi and Domenico Spinelli
Editors

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REGIO- AND STEREOSELECTIVE ADDITION REACTIONS OF CARBON NUCLEOPHILES TO EPOXIDES

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Abstract*. The enantioselective addition of dialkylzinc reagents and the addition of lithium enolates of ketones to 1,2-epoxides, as tools for the construction of new C-C bonds, are described. In the addition of dialkylzinc compounds, high levels of enantiselectivity are obtained by means of chiral copper-catalysts derived from chiral non-racemic phosphoramidites. The addition reaction of lithium enolates of ketones has been carried out both in the inter- and in the intramolecular version to give γ–hydroxy ketones (C-alkylation products), accompanied in some cases by the corresponding hydroxy enol ethers (O-alkylation products).*

Contents

1. Introduction

Epoxides are oxygen heterocycles widely utilized as versatile synthetic intermediates. Their reactions are dominated by the electrophilic nature of the epoxide and generally involve cleavage of the strained three-membered ring, and include a wide range of nucleophilic ring openings.[1] The nucleophilic ring opening of epoxides by carbon nucleophiles is a frequently used method for the generation of new carbon-carbon σ bonds and this approach has been particularly valuable in the field of the synthesis of natural products.[2]

Among the carbon organometallic nucleophiles that successfully alkylate epoxides are organolithium compounds,[3] organomagnesium reagents,[4] organocopper,[5] organozinc,[6] organoaluminum[7] and organolanthanide reagents.[8] In many cases the utility of the reaction is curtailed owing to competing reactions arising from the Lewis acidity or basicity of the organometallic reagent. Among the organometallic reagents used, the organocopper compounds are known to be as one of the most efficient to accomplish the nucleophilic substitution of an epoxide in a highly chemo- and stereoselective manner.[5] In particular, copper-catalyzed alkylation of allylic epoxides has been frequently used as an efficient entry to allylic alcohols.[9] Allylic epoxides can be considered as a particular and special class of allylic substrates because they combine the reactivity of epoxides and that of allylic substrates, allowing a wide range of synthetic transformations.[10] However, to the best of our knowledge, there have not been any reports about the catalytic enantioselective addition of organometallic reagents to these carbon allylic electrophiles, even if this approach could be an intriguing challenge in organic synthesis.

As regards functionalized organometallic reagents, simple ketone or ester enolates work poorly and more nucleophilic metallated enamines,[11] hydrazones[12] and stabilized organolithium reagents, for example metallated dithiane[13] give generally clean reactions and high yields. However, due the low reactivity with metal enolates, it is frequently advantageous to activate epoxides by addition of a Lewis acid. The reaction of ketone metal enolates with epoxides has received less consideration, in spite of the fact that it may offer a reasonably simple, direct route to γ-hydroxy ketones (γ-HKs), an interesting class of difunctionalized compounds.[14,15] The synthetic value of the regio- and stereoselective alkylation of allylic epoxides with stabilized *C*-functional nucleophiles such as malonates, β-diketones, β-ketoacids and β-ketosulfones in the presence of palladium(0) catalysts is relatively well documented.[16] However, only a few examples describes the addition of non-stabilized nucleophiles to π-allylpalladium complexes.[17] Recently, Malacria described a regio- and stereoselective palladium(0)-catalyzed alkylation of vinyloxiranes with non-stabilized lithium ester enolate nucleophiles, giving access to highly functionalized allylic alcohols (S_N2' addition).[18] Very recently, a non-catalyzed addition of lithiated dithianes to allylic epoxides has been reported by Smith III.[19] The latter reaction is remarkable in that the regiochemistry can be determined by the steric nature of the dithiane. Unecumbered dithiane anions afford S_N2 adduct, whereas sterically encumbered anions lead primarily to S_N2' addition. Also the catalytic enantioselective addition of *C*-functional nucleophiles, such as stabilized or not-stabilized nucleophiles, to these carbon allylic electrophiles has not been reported to date even if this approach could give a straightforward access to polifunctionalized molecules in enantioenriched form.

The present account describes the recent efforts of our research group in these fields.

2. Enantioselective addition of dialkylzinc reagents to allylic epoxides.

Nucleophilic attack to an allylic epoxide can in principle take place on three of the four consecutive functionalized carbon atoms (pathways *a*,*b*,*c*, Figure 1) and the allylic alkylation is accompanied by a ring-opening process in which the leaving group is maintained in the final product. Nucleophilic addition to the least hindered oxirane carbon (carbon 1) affords the 1,2-addition product (path *c*). Nucleophilic attack to the oxirane carbon adjacent to the carbon-carbon double bond (carbon C-(2), allylic position) affords the regioisomeric S_N2 addition product, usually obtained in ring-opening reactions (path *b*). Finally, the conjugate addition of the nucleophile to vinyl carbon C-(4) gives the corresponding S_N2' addition product

(path *a*). Much work has been centered on developing conditions to obtain each of these three products selectively. While path *c* is not commonly observed, paths *a* and *b* have been widely used in the synthesis of natural products.[9] The factors which favor nucleophilic attack by route *b* (direct addition or S_N2) and/or route *a* (conjugate addition or S_N2') usually rely heavily on the type of reagent.

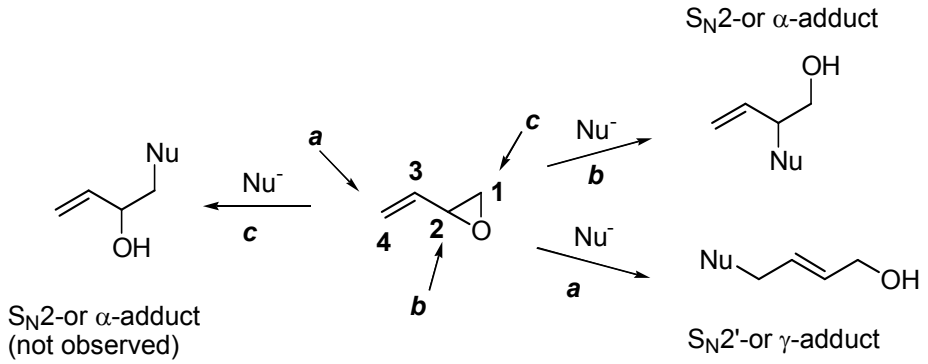


Figure 1. Possible reaction pathways for the nucleophilic ring-opening of an allylic epoxide.

2.1. Copper-catalyzed kinetic resolution of allylic epoxides with dialkylzinc reagents.

Copper-catalyzed alkylation of allylic epoxides has been frequently used as an efficient entry to allylic alcohols.[9] As dialkylzincs are hard alkyl nucleophiles, but usually too weak to react with allylic epoxides, it is tempting to consider the possibility of generating a cuprate in situ by a transmetallation reaction leading to more reactive and selective species. The use of organozinc reagents in copper-catalyzed allylic alkylation has been described only quite recently.

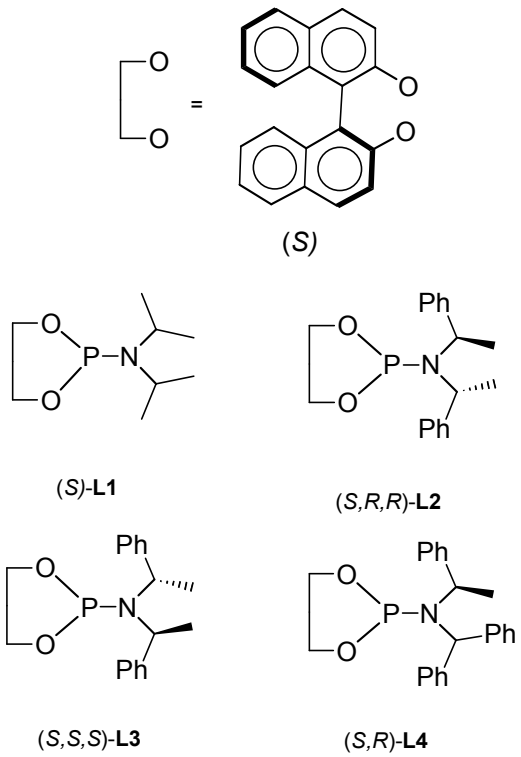
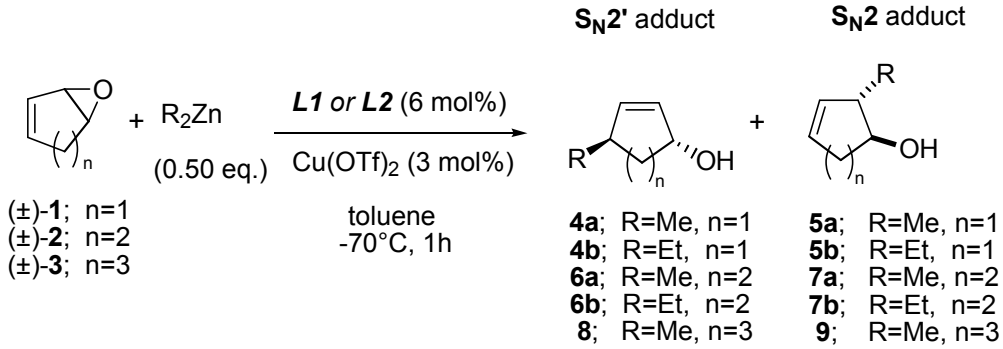


Figure 2. Ligands used for the copper-catalyzed enantioselective allylic alkylation ring-opening reactions of small ring heterocycles with dialkylzincs.

Organozinc reagents have the advantages of being broadly tolerant to various functional groups, of transmetallating easily to other transition metals and to possess an inherent low reactivity. The first novel procedure for the selective S_N2' addition of organozinc reagents to vinyloxiranes was reported by Lipshutz, who described an effective alkylation of allylic epoxides with functionalized organozinc reagents under mild conditions.[20] The remarkable results obtained by Feringa et al.[21] in the addition of organozinc reagents to enones prompted us to verify the effectiveness of the chiral copper complexes of Binol-based phosphoramidites (such as ligands **L1-L4**, Figure 2) in the *anti*-stereoselective conjugate addition of organozinc reagents to allylic 1,2- and 1,4-epoxides.

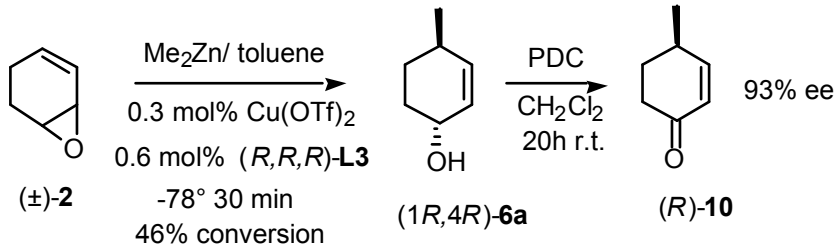
Our preliminary results showed that the reaction of 1,3-cyclohexadiene monoepoxide **2** with Me_2Zn (1.5 eq.) in the presence of $Cu(OTf)_2$ (3 mol%) afforded a complex reaction mixture containing a small amount (8% combined yield) of a ca. 1:1 mixture of allylic alcohols **6a** (*anti*-S_N2' pathway) and **7a** (*anti*-S_N2 pathway), respectively (Scheme 1).



Scheme 1

This result can be drastically changed when a phosphoramidite is used as the chiral ligand.[22] For example, the preventive addition to the reaction mixture of a catalytic amount (6 mol%) of chiral phosphoramidite (*S*)-**L1** gave a dramatic increase in the conjugate addition pathway. Thus allylic alcohol **6a** was obtained with a good regio- (S_N2'/S_N2 =13) and enantioselectivity (62% *ee*). This is a typical example of a *ligand-accelerated catalysis effect (LAC)*:[23] without the ligand, the reaction is much slower and proceeds without regioselectivity. The best results (>90% *ee*) were obtained by the use of (*S,R,R*)-**L2**, deriving from (*S*)-2,2'-binaphthol and sterically demanding bis-(*R*)-1-phenylethylamine[21b] especially when six- and seven-membered monoepoxides **2** and **3** were used.[22] The highest enantioselectivity was observed in the addition of Me_2Zn to **3** (96% *ee*). In this case, the regioselectivity (S_N2'/S_N2 ratio) was even better than that obtained in the stoichiometric addition of MeCu(CN)Li to vinyloxirane **3**.[9a]

The synthetic utility of this new procedure was also demonstrated through the first catalytic asymmetric synthesis of both (*R*)-(+)- and (*S*)-(-)-2-cyclohexen-1one (**10**).[24] Chiral non-racemic 2-cyclohexenones are attractive building blocks for the synthesis of a variety of natural products and are usually obtained from the "chiral pool", from (*R*)-(+)-pulegone or (*S*)-(+)-carvone or by means of conventional racemate resolution methods. These procedures are often long and tedious, and the overall yields obtained are generally quite low. The key step of our straightforward approach is the S_N2' addition of Me_2Zn to racemic **2** to give enantiomerically enriched allylic alcohol **6a** (93% *ee*, 89% yield based on the reacted epoxide) which can easily be oxidised to the target compound (Scheme 2).

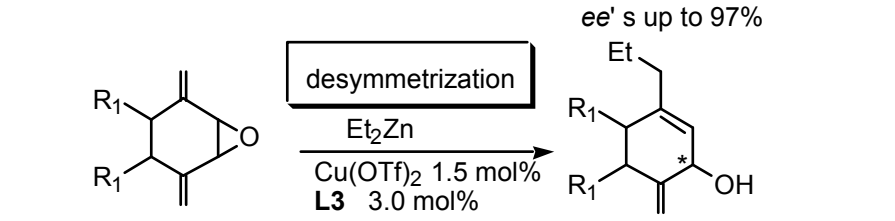


Scheme 2

This step was optimised as far as enantio- and regioselectivities and work-up procedures are concerned. The striking ligand-accelerated catalysis by the chiral copper complexes with phosphoramidite **L3** permitted a very low catalyst loading (0.6 mol%). Very similar results can be obtained by the use of chiral ligand **L2**. Compared with other multistep syntheses, our two step procedure is simple and starts from commercially cheap and readily available reagents.[24] Moreover, our simple work-up procedure, based on filtration and distillation, qualifies for a further scale-up. As a large number of dialkylzinc reagents are available by standard methods,[25] it is reasonable to assume that other optically active 4-alkyl-2-cyclohexenones (and 4-alkyl-2-cyclohexenols) can be synthesized by this procedure, allowing a novel, easy, flexible and practical multigram-scale synthesis of this interesting class of compounds by the use of minimal amounts of Binol-derived phosphoramidites.

2.2. Copper-catalyzed enantioselective desymmetrization of symmetrical allylic epoxides.

Desymmetrization of a symmetrical molecule to yield an enantiomerically enriched product is a widely used and rational synthetic strategy. An area where examples of desymmetrization reactions are scarce is the catalytic enantioselective construction of C-C bonds.[26] Encouraged by the results obtained with racemic allylic epoxides[22] we were intrigued by the possibility of the addition of dialkylzincs to the enantiotopic faces of prochiral symmetrical allylic 1,2-epoxides, thus avoiding the intrinsic limitations of a kinetic resolution process. With this aim, the not previously described *meso*-methylidene cycloalkane epoxides **11a-c**, bearing enantiotopic methylidene moieties in an allylic position with respect to the endocyclic oxirane ring, were synthezised and studied.[27] The symmetrical epoxide **11a**, which can easily be obtained from naphthoquinone in two steps, was our model substrate. Ligand **L3**, deriving from (*S)*-Binol and (*S*)-bis-phenylethylamine resulted in a matched combination affording the corresponding bis-allylic alcohols **12a-c** with a good yield and a high regio- and enantioselectivity (Scheme 3).[28]



11a, R_1: =CH-CH=CH-CH=
11b, R_1: -CH_2-CH=CH-CH_2-
11c, R_1: -H

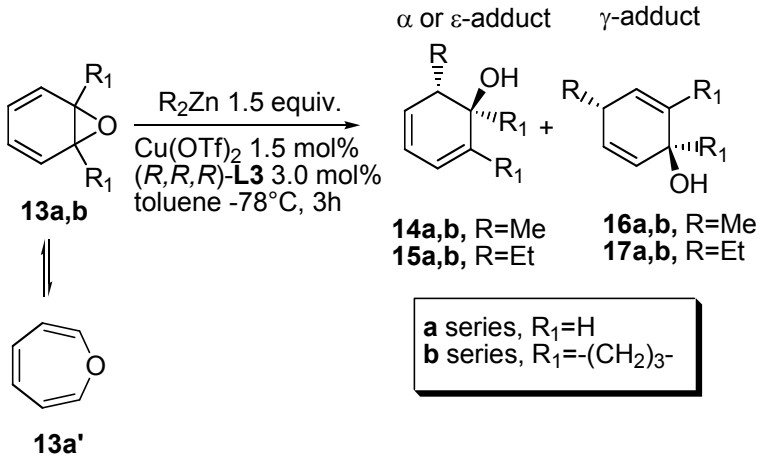
12a, R_1: =CH-CH=CH-CH=
12b, R_1: -CH_2-CH=CH-CH_2-
12c, R_1: -H

Scheme 3

The highest selectivity was obtained when the conformationally less constrained vinyloxirane **11c** was used. In this case, the addition product, the bis-allylic alcohol **12c,** was obtained (90% yield) with a 97% *ee*

and a regioisomeric ratio of 98/2. Evidently, in this case, the chiral catalyst's ability to discriminate between the enantiotopic reaction sites is maximized.

The effective chiral recognition of two enantiotopic faces of prochiral symmetrical allylic epoxides prompted us to search for even more appealing desymmetrization reactions. For example, arene oxides are very reactive compounds which have been subjected to several studies since the demonstration that these compounds are formed from aromatic hydrocarbons by the microsomial enzyme fraction of mammalian liver.[29] There are only few dated reports dealing with ring-opening reactions of arene oxide carried out with organometallic reagents.[30] Moreover, none of these procedures employing organometallic reagents are catalytic or enantioselective. We have recently described an unprecedented catalytic and enantioselective trapping of highly reactive symmetrical arene oxides offering a new route to enantioenriched dihydroaromatic alcohols, not easily accessible by means of other synthetic methods.[31] Benzene oxide (**13a**) and indan-8,9-oxide (**13b**) were examined as symmetrical arene-oxide substrates (Scheme 4).

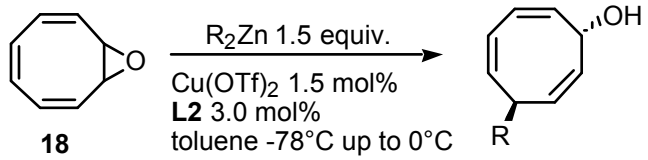


Scheme 4

Benzene oxide is known to exist in equilibrium with its tautomeric valence structure, the oxepin **13a'**. This compound exists mainly as oxepin at room temperature, even if the oxide component **13a** determines the reactions of the system with most agents. Epoxide **13a** was allowed to react at -78 °C (1h, 95% conversion) with Me_2Zn (1.5 equiv) in the presence of a catalytic amount of $Cu(OTf)_2$ (0.015 equiv) and the chiral ligand (*R,R,R*)-**L3** (0.030 equiv) to give a crude reaction mixture consisting of the not previously reported regioisomeric dienols **14a** (α-adduct) and **16a** (γ-adduct). The reaction with Et_2Zn gave a slightly different result, with a predominance of the achiral γ-adduct **17a**. In this case the substituted enantioenriched dihydroaromatic α-adducts **14a** (93% *ee*) and **15a** (64% *ee*) were obtained with a complete *anti* stereoselectivity. Indan-8,9-oxide (**13b**), containing a tetrasubstituted epoxide, is known to exist only in the oxide form. The copper-phosphoramidite catalyzed addition of R_2Zn at -78 °C to **13b** (3h, 95% conversion) gave a ca. 80:20 mixture of the corresponding α- and γ-adducts **14b** and **16b** (R=Me) and **15b** and **17b** (R=Et). It is remarkable that the α-adducts **14b** (≥95% *ee*) and **15b** exclusively derive from an *anti*-stereoselective 1,6-addition pathway and therefore have been more appropriately called ε-adducts (Scheme 4).

The monoepoxide of 1,3,5,7-cyclooctatetraene (COT) (**18**) is also a symmetrical molecule and it has several distinctive features with respect to the other symmetrical vinyl oxirane substrates examined.[32] In fact,

COT-monoepoxide has a special structure imposed by three consecutive double bonds where the double bonds and the epoxide ring are not in the same plane. There have been several papers indicating the easy isomerization of COT-monoepoxide in reactions with cationic[33] or anionic reagents.[34] On the other hand, there are very few reports dealing with the ring-opening reactions of epoxide **18** with nucleophiles. The ring contraction isomerization to the seven-membered trienyl carboxaldehyde that in turn adds the organometallic reagents delivering substituted cyclohepta-trienyl alcohols, was the most common reaction observed when organometallic reagents were employed with this substrate.[35] Moreover, Matsuda reported that the reaction of **18** with Et_2CuLi in Et_2O under various reaction conditions resulted in the formation of polymeric material.[36] The only reported addition of an alkyl group to COT-monoepoxide without ring contraction make use of RLi in Et_2O and afforded 4-alkyl-2,6-cyclooctadien-1-ones through a 1,5-sigmatropic rearrangement.[37]



19a, R=Me (65% yield, >90% *ee*)

19b, R=Et (90% yield, 86% *ee*)

19e, R=Bu (78% yield, 82% *ee*)

19f, R=Cy (72% yield, *ee* n.a.)

Scheme 5

We have recently found that the combination of Grignard reagents together with a catalytic amount of CuCN gave cleanly the corresponding trienyl alcohol addition product with a high yield and complete conjugate regioselectivity.[38] Even better results were obtained by the use of stoichiometric amounts of copper salts in combination with Grignard reagents. Moreover, a highly enantioselective desymmetrization of COT-monoepoxide (**18**) with dialkylzinc reagents and chiral copper complexes of phosphoramidite ligand **L2** has been reported as well (Scheme 5).[39] The less reactive Me_2Zn delivered the corresponding S_N2'-adduct **19a** (65% yield) with the best enantioselectivity (>90% *ee*).

The dihedral angle between the double bond and the medium plane containing the two oxirane carbons in epoxide **18** is ca. 60 °. It is noticeable that in spite of this remarkable geometric constraint, an S_N2'-cuprate addition is achieved by the appropriate *in situ* generation of an organocopper reagent. This is the highest deviation from coplanarity ever observed in an allylic-type alkyation reaction.[40]

2.3. Copper-catalyzed enantioselective desymmetrization of symmetrical allylic 1,4-epoxides.

Also the ring opening of allylic 1,4-epoxides or oxabicyclic alkenes with organometallic reagents, has provided different approaches to the synthesis of both monocyclic and acyclic compounds with control of the relative and absolute stereochemistry.[41] These approaches usually utilize a nucleophilic attack to the double bond with concomitant expulsion of the bridging oxygen in a regio- and stereocontrolled manner to give the corresponding *syn* and *anti* adducts **B** and **C**, respectively (Figure 3).

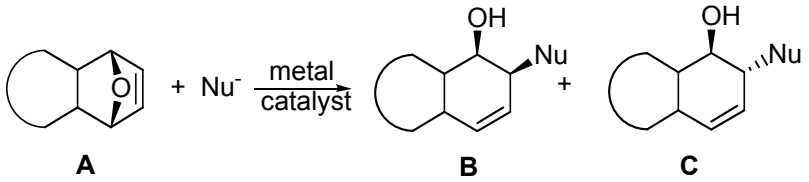
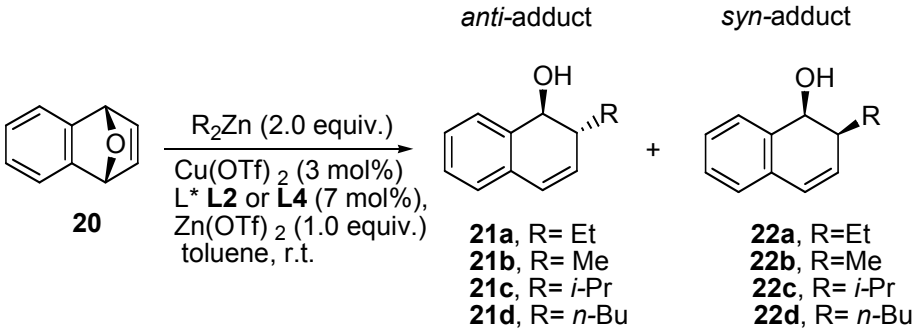


Figure 3. Nucleophilic ring opening of [2.2.1]-oxabicyclic alkene **A**.

However, the enantioselective symmetry-breaking of symmetrical oxabicyclic compounds with carbon nucleophiles has not been described until recently.[42] In this area, Lautens reported an highly enantioselective palladium-catalyzed ring opening of oxabicyclic alkenes with dialkylzincs.[43] More recently the same author has described a high enantioselective rhodium-catalyzed ring opening of meso oxabicyclic alkenes with aryl-alkenyl boron compounds.[44] Waymouth described an asymmetric zirconium-catalyzed addition of Et_3Al to oxabicyclic alkenes.[45] It should be noted that these asymmetric transformations afford the *syn*-addition products. Lautens reported also several rhodium-catalyzed asymmetric ring opening reactions of oxabicyclic alkenes with different nucleophiles proceeding with *anti*-stereoselectivity.[46] In particular, as regards carbon-carbon bond forming reactions, malonate nucleophiles were employed.

As organocuprates are effective in the ring opening of oxabicycles and copper-phosphoramidite catalysts show high regio- and enantioselectivities in the ring opening of allylic 1,2-epoxides with dialkylzinc reagents, we envisioned that the copper-catalyzed asymmetric ring opening of oxabicyclic alkenes might be feasible. Oxabenzonorbornadiene **20**, derived simply by a Diels-Alder reaction between furane and antranilic acid, was considered as our model substrate.[29] It should be noted that the copper-phosphoramidite catalyst is essential to obtain the *anti* stereoselective pathway and in the absence of the copper-phosphoramidite catalyst, no significant reaction takes place. In fact, the addition of Et_2Zn alone (140 h, r.t.) gave only the starting material and only a trace amount of *syn*-adduct **22a**. On the other hand, the addition of Et_2Zn to **20** catalyzed by $Cu(OTf)_2$ (3.0 mol%) gave only the *syn*-adduct **22a** (full conversion, 55% isolated yield after 18 h at r.t.).

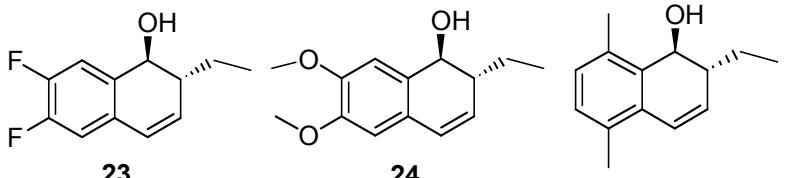


Scheme 6

All the minor amounts of *syn* adducts obtained throughout this work are racemic and probably derive from an uncatalyzed reaction pathway. Facing the low reactivity of Et_2Zn in the copper-catalyzed alkylative ring-opening of **20**, we examined variations of reaction parameters (solvents, Lewis acids, copper salts and ligands) and found that anhydrous $Zn(OTf)_2$ was highly beneficial to the obtainment of the *anti* adducts **21a-d** with a high yield and stereoselectivity (Scheme 6).[47] The role of this additive in the ring opening reactions of oxabicyclic compounds seems to be that of a Lewis acid favoring the ionization of the bridgehead carbon-

oxygen bond. The enantioselectivity of the reaction can also be improved by the use of the new phosphoramidite **L4**. With this ligand compound **21a** can be obtained with 92% yield and 94% *ee* in 13 h.

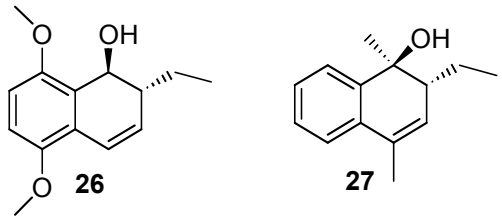
Next, the ring opening with Et_2Zn of other oxabenzonorbornadienes bearing substituents in various positions with respect to the endocyclic oxygen was undertaken. Chiral phosphoramidites **L2** (7 mol%) and $Cu(OTf)_2$ (3 mol%) gave the best results with these substrates in terms of the stereoselectivities obtained. Scheme 7 indicates all the enantioenriched dihydronaphthols that can be obtained with uniformly high *anti* stereo- and enantioselectivities. In particular, it was possible to obtain adduct **25** as a single diastereoisomer with >99% *ee*. Furthermore, it should be noted that it was possible to obtain adduct **27**, containing a tertiary benzylic carbon atom, with a high level of diastereo- and enantioselectivity. It is remarkable that our protocol is the only current example of an enantioselective *anti* ring opening of oxabicyclic alkenes with a carbon nucleophile. The addition is complementary to the palladium-catalyzed *syn*-selective ring opening with dialkylzincs reported by Lautens,[43] allowing a new entry to *trans*-dihydronaphthols with a high enantioselectivity.



23 58% isolated yield; *anti/syn*=83:17; *ee (anti)*= 80%

24 65% isolated yield; *anti/syn*=90:10; *ee (anti)*= 88%

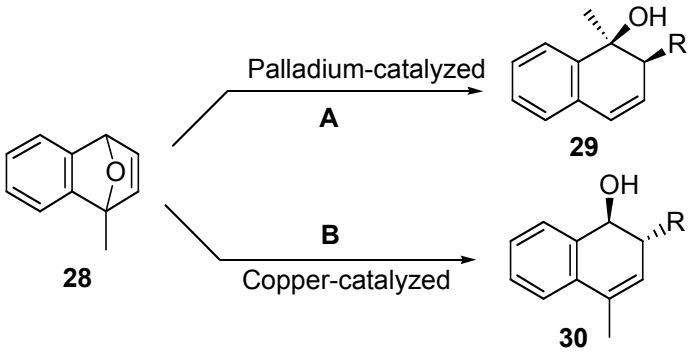
25 90% isolated yield; *anti/syn*=99:1; *ee (anti)*= >99%



26 82% isolated yield; *anti/syn*=90:10; *ee (anti)*=97%

27 85% isolated yield; *anti/syn*=92:8; *ee (anti)*= 92%

Scheme 7

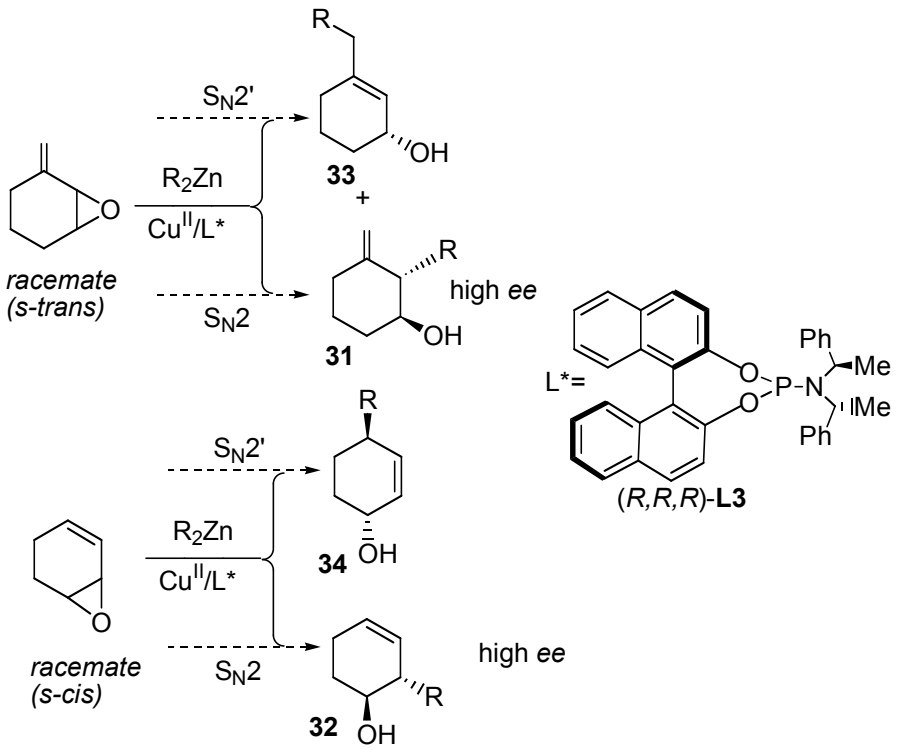


Scheme 8

Also the regioselectivity is complementary to the palladium-catalyzed protocol. For example, the application of the palladium-catalyzed to the unsymmetrical substrate **28** afforded *cis*-dihydronaphthol **29** with overall retention of configuration was selectively obtained (pathway A), thus excluding an ionization mechanism (Scheme 8). On the contrary, our copper phosphoramidite-catalyzed kinetic resolution of **28** exclusively afforded dihydronaphthol **30**, which is stereo- and regioisomeric to the tertiary alcohol **29** obtained by the Pd-catalyzed protocol (pathway B).

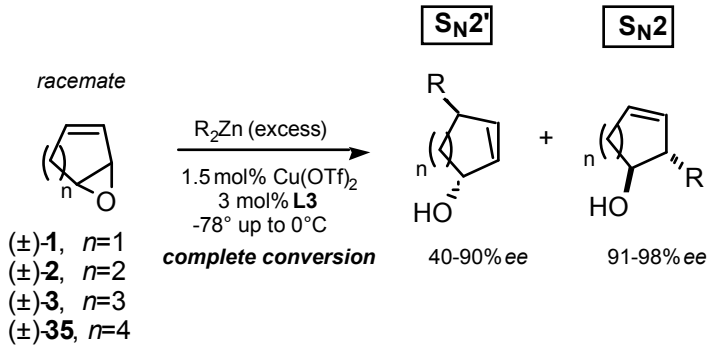
2.4. Regiodivergent kinetic resolution of allylic epoxides.

Kinetic resolution of a racemic mixture is a well-established methodology for the preparation of optically active compounds.[48] However, the major drawback with this approach is that a maximum of only one half of the racemic starting material is converted into non-racemic products. Parallel kinetic resolution (*PKR*) is an interesting strategy recently introduced, in which both enantiomers of a racemate can be converted into different products.[49] This conceptual variation usually requires the use of two different stoichiometric chiral reagents in parallel. *PKR* concerning catalytic processes that forms carbon-carbon bonds are however very rare.[50] During our study on the copper-catalyzed enantioselective kinetic resolution of cyclic 1,2-allylic epoxides, we observed that the amount of the homoallylic alcohol S_N2 adducts **31** and **32** increased with the increase of conversion of the allylic epoxide and furthermore the *ee* of this homoallylic alcohol was always greater than 90%! Moreover the regioselectivity of the reaction could be drastically changed in favor of the S_N2' addition products **33** and **34** when a racemic chiral ligand was used, indicating that it is the chirality of the chiral ligand that determine the regioselectivity outcome. This unexpected behavior led to the discovery of a new, highly stereocontrolled transformation of a racemic mixture by an organometallic reagent and chiral catalyst to give separable regioisomeric products (Scheme 9).[51]



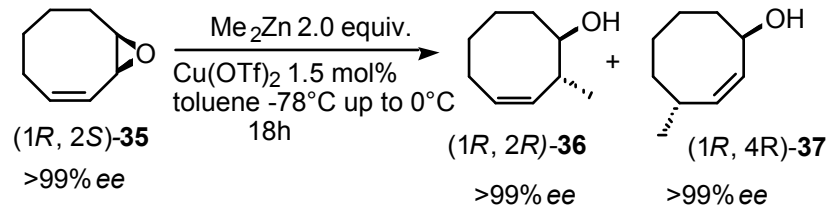
Scheme 9

After this initial finding we have recently shown that enantioselective regiodivergent kinetic resolution (*RKR*) is also effective for a variety of cyclic 1,3-diene monoepoxide having a blocked s-*cis* conformation (*n*=1,2,3,4, R=Me, Et, Bu) (Scheme 10).[52] Phosphoramidite **L3**, derived from (*R*)-BINOL and (*R*)-bis-phenylethylamine,[21b] was the chosen ligand because it proved to be slightly superior to its diastereoisomer (*S,R,R*)[21c] with respect to the extent of regiodivergency, and the enantioselectivity of the alcohol reaction products. The *RKR* process was particularly efficient when 1,3-cycloheptadiene monoepoxide (*n*=2) was employed. With this substrate the regiodivergency is practically ideal and regioisomeric alcohols of type S_N2' and S_N2, having opposite configuration at the hydroxyl group-bearing carbon, were obtained in almost equal amounts and with a high enantiomeric excess (>90% *ee*) with all the dialkylzincs used. Evidently with this substrate, the asymmetric matching of the chiral ligand with the enantiomers of the substrate is noteworthy.



Scheme 10

In order to obtain more definite evidences that there is *a complementary enantiomer-dependent regioselectivity,* enantiomerically pure epoxide **35** was treated with a copper catalyst deriving from both (*S,S,S*)-**L3** or (*R,R,R*)-**L3** (Scheme 11). In the presence of (*R,R,R*)-**L3**, (1*R*, 2*S*)-**35** reacted with Me_2Zn to give with complete regioselectivity the corresponding enantiopure allylic alcohol (1*R*,4*R*)-**37a**, whereas when (*S,S,S*)-**L3** was used, the corresponding homoallylic alcohol (1*R*,2*R*)-**36** was obtained with a good selectivity.[51] In this way, it was clearly demonstrated that it is possible to control the regioselectivity of the copper-catalyzed addition reaction of dialkylzincs to an enantiomerically pure cyclic allylic epoxide simply by choosing the appropriate enantiomer of phosphoramidite **L3**.

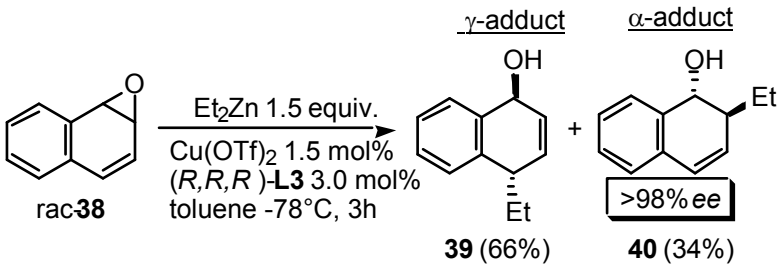


chiral ligand (*S,S,S*)-**L3**	81	:	19
chiral ligand (*R,R,R*)-**L3**	<2	:	>98

Scheme 11

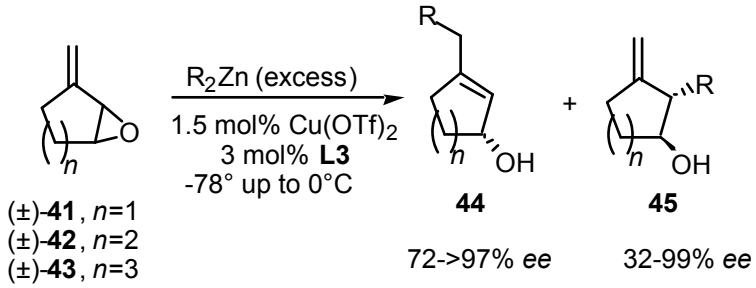
As regards allylic epoxides having blocked s-*cis* conformation we examined also naphthalene 1,2-oxide (**38**). Despite its extreme chemical reactivity, due to the tendency to spontaneous epoxide ring-opening

and aromatization, the addition of Et_2Zn (1.5 equiv) to racemic **38** in the presence of $Cu(OTf)_2$ (0.015 equiv) and chiral ligand (*R,R,R*)-**L3** (0.030 equiv) proceeded very cleanly to afford a 66:34 mixture of regioisomeric dihydronaphthols **39** (γ-adduct) and **40** (α-adduct), the latter with a remarkable enantioselectivity (Scheme 12).[31]



Scheme 12

The enantioselective regiodivergency is operative also when racemic exo-methylene epoxides **41-43**, which possess a blocked s-*trans*-conformation, are used (Scheme 13). Particularly worhty of note is the regiodivergent behavior in favor of the formation of the homoallylic alcohol of type **45** (S_N2-adduct) exhibited by Me_2Zn in the reaction with epoxide **43**. In this case, the minor regioisomeric allylic alcohol **44** (*n*=2, R=Me) was obtained with a very high enantioselectivity (>97% *ee*) and when the reaction was carried out in accordance with a kinetic resolution protocol (Me_2Zn 0.50 equiv.), **45** (*n*=2, R=Me) was the main reaction product.



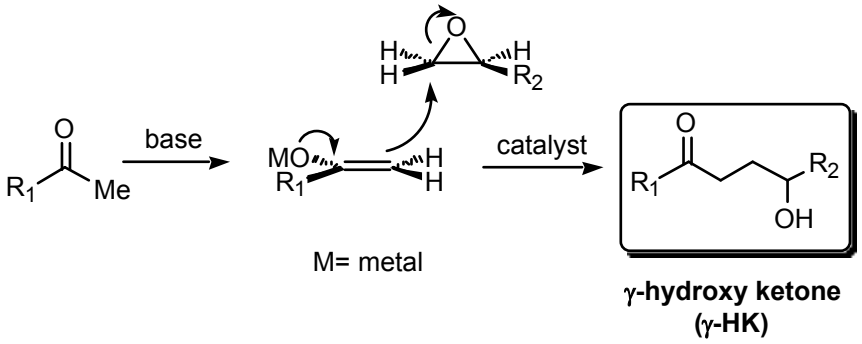
Scheme 13

Considering that in an enantioselective *RKR* process, the product obtained with the higher *ee* is commonly associated with the slower reaction, the above observations about epoxide **43** would indicate that under our reaction protocol, the S_N2' addition can be, in some cases, the slower pathway inside the addition process. In summary, we have shown that the outcome of the enantioselective regiodivergent kinetic resolution of racemic allylic epoxides with dialkylzinc reagents is effective for a variety of cyclic substrates. The most fascinating and unusual aspect is certainly that the regioselectivity of the reaction depends directly on the absolute configuration of the chiral catalyst. This new process allows the obtainment of several new allylic and homoallylic alcohols with good up to excellent enantioselectivities. In most cases, the allylic and homoallylic alcohol reaction products can easily be separated by chromatography on silica gel.

3. Addition reaction of lithium enolates of simple ketones to 1,2-epoxides. A new reaction

The stereoselective aldol reaction between metal enolates of ketones and aldehydes has been extensively studied, and has become one of the most powerful methods for the stereocontrolled construction

of the C-C bond.[53] On the contrary, the related reaction which makes use of 1,2-epoxides as the electrophile to give γ-hydroxy ketones (γ-HKs) in a very simple way, has been the object of much less consideration. (Scheme 14).[14] γ-HKs may be utilized as building blocks for the construction of more complex molecules, or profitably cyclized to polysubstituted tetrahydrofuranes and related bicyclic compounds, or to other important carbocyclic or heterocyclic compounds.[15]



Scheme 14

The lithium enolate of cyclononanone was shown by Schreiber to react with propene oxide in the presence of $AlMe_3$, but this was only an isolated report and the protocol did not become a general one for this type of addition reaction.[54] Dilithiooxime,[55] anionized Shiff bases and *N*,*N*-dimethylhydrazones of ketones[56] react with 1,2-epoxides to yield corresponding protected γ-HKs. However in this case hydrolysis of the corresponding intermediate oxime, imine or hydrazone is necessary in order to get free compound.[55,56]

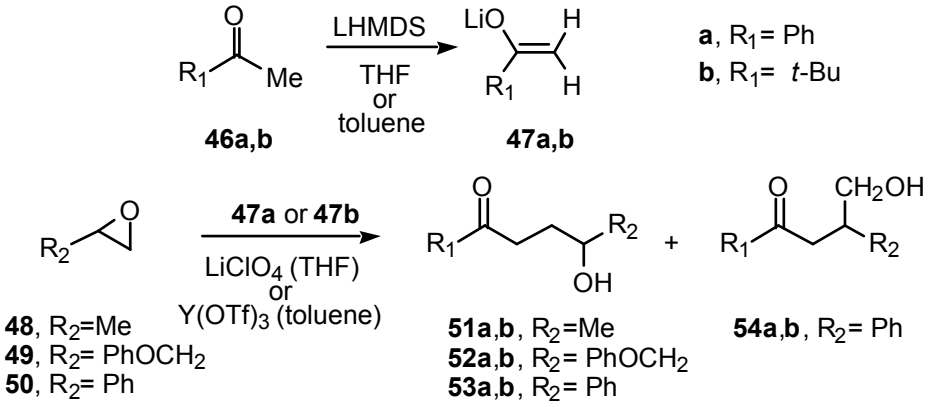
3.1. Li^+- and Y^{+3}-promoted addition of lithium enolates of ketones to epoxides. Synthesis of γ–hydroxyketones

The discovery of the metal salt catalyzed method for the ring opening of 1,2-epoxides with amines, azide and cyanide ion to give under mild conditions and in fair yields the corresponding opening products (β-amino alcohols, β-azido alcohols and β-hydroxy nitriles, respectively)[57] prompted us to verify if this new methodology could be successfully applied also to the direct nucleophilic displacement of 1,2-epoxides by lithium enolates of simple ketones.

It was initially found that the reaction of some representative epoxides **48**-**50** with lithium enolates **47a** and **47b** derived from acetophenone (**46a**) and pinacolone (**46b**), respectively, in the presence of $LiClO_4$ or $Y(OTf)_3$ afforded in good to excellent yield, the corresponding γ-HKs (**51**-**53a,b**).[58,59] In this first approach to this practically new nucleophilic addition reaction to oxiranes, ketones **46a** and **46b**, which generate enolate species possessing homotopic faces, were chosen in order to have no diastereoisomeric implications (Scheme 15). Lithium enolates **47a** and **47b** were generated in anhydrous THF ($LiClO_4$-promoted protocol) or toluene [$Y(OTf)_3$-promoted protocol] by means of lithium bis(trimethylsilyl)amide (LHMDS) which was preferred to lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) because of the lack of implications due to competitive aminolysis by the free amine (hexamethyldisilazane) on 1,2-epoxides under metal salt catalysis,[57a] as sometimes observed with diisopropylamine and 2,2,6,6-tetramethylpiperidine derived from LDA and LTMP, respectively.[60] The $Y(OTf)_3$-catalyzed reactions occur under particularly mild conditions compared with the corresponding $LiClO_4$-promoted ones: lower

temperature (0 °C or rt, in the case of the less reactive epoxides) and shorter reaction times. Furthermore, only 10% mol amount of the catalyst [$Y(OTf)_3$] is required in order for the addition reaction to occur. The reactions are completely regioselective, with the attack of the nucleophile (lithium enolate) on the less substituted oxirane carbon to give the *contra*-Markovnikov type product (γ-HKs **51-53a**,**b**).[61] The only exception is given by styrene oxide (**50**). In this case, if the $LiClO_4$-promoted reaction affords only some amount (9-12%) of the Markovnikov-type addition product (**54a,b**), the $Y(OTf)_3$-promoted protocol yields substantial amount of the same product (40% of γ-HK **54a** and 85% of γ-HK **54b** from enolate **47a** and **47b**, respectively). As a consequence, with epoxide **50** the alternate use of the $LiClO_4$- and the $Y(OTf)_3$-catalyzed procedures for the lithium enolate nucleophilic addition makes it possible to obtain a nice regioalternating process (Scheme 15).[58,59]

The catalytic effect of $LiClO_4$ and $Y(OTf)_3$[62] in this reaction appears to be ascribable to the strong ability of Li^+ and Y^{+3} to coordinate tightly to the oxirane oxygen, thus favoring the nucleophilic ring opening process. In the case of epoxide **50**, the oxophilicity of Y^{+3} is decidedly able to allow the attack of the enolate on the benzylic oxirane carbon, reasonably through a slightly carbocationic transition state.[63]

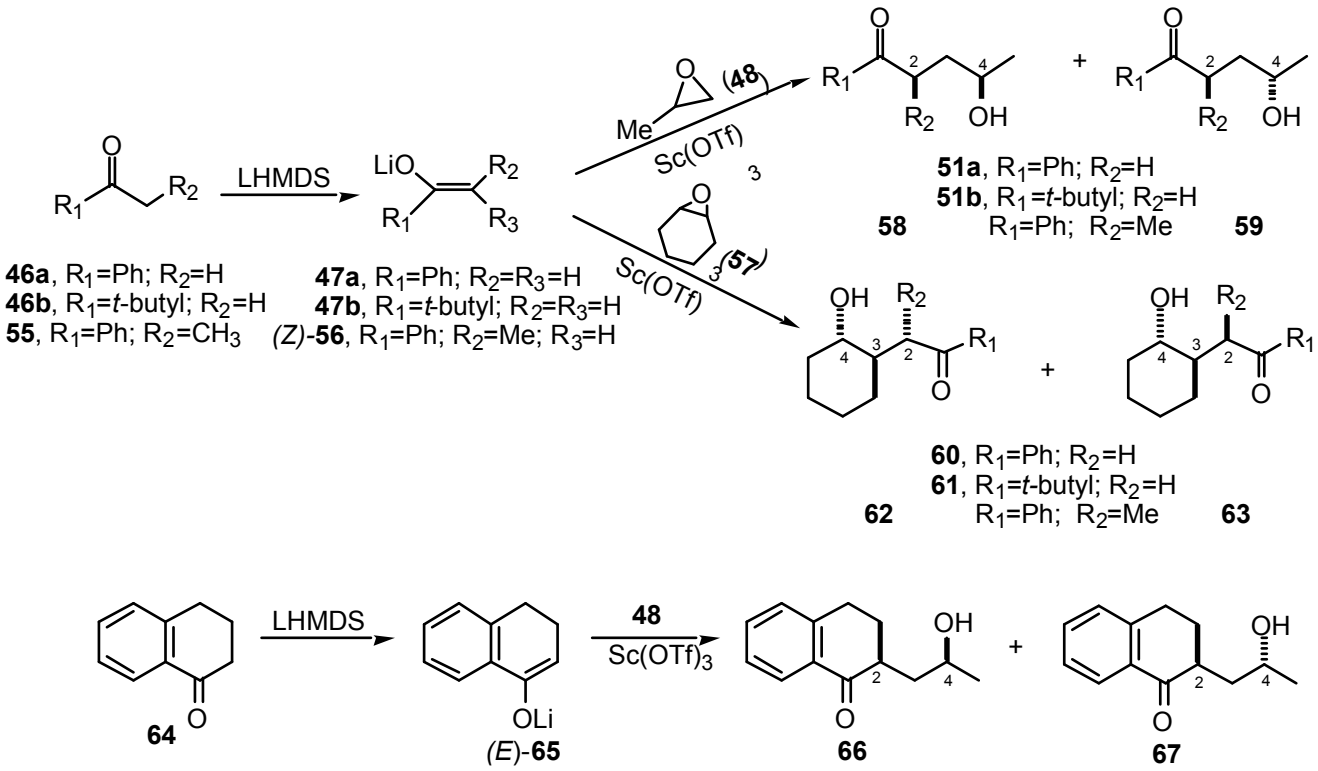


Scheme 15

3.2. Sc^{+3}-promoted addition of lithium enolates of ketones to epoxides. Diastereoselectivity of the reaction

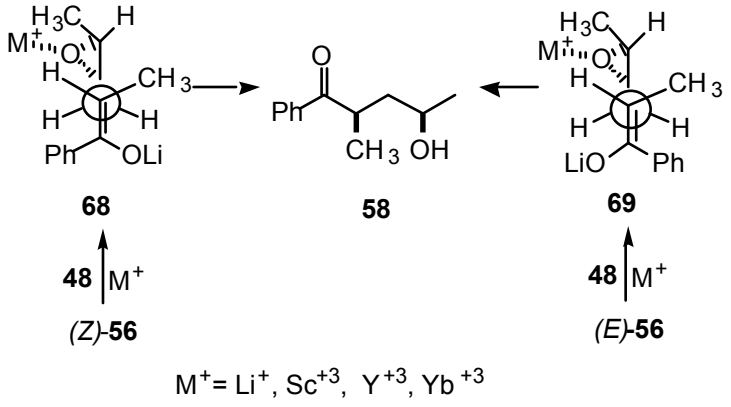
Other metal salts, different from the originally used $LiClO_4$ and $Y(OTf)_3$, were examined as possibly more efficient catalysts. The results obtained in the addition reaction of enolates **47a** and **47b** to propene oxide (**48**) and cyclohexene oxide (**57**) clearly indicated that scandium triflate [$Sc(OTf)_3$] (10%mol) is a particularly effective catalyst in this reaction, superior than the previously described ones, affording a satisfactory yield of the corresponding addition products (Scheme 16).

The contemporary use of this more efficient protocol and ketones lithium enolates possessing enantiotopic faces, made the examination of the diastereoselectivity of the addition reaction to epoxides possible. The $Sc(OTf)_3$-catalyzed addition reaction of lithium enolates (*Z*)-**56**[64] [derived from propiophenone (**55**)] and *(E)*-**65** [derived from α-tetralone (**64**)] to epoxides **48** and **57** turned out not to be selective, affording mixtures of the corresponding *syn* and *anti* adducts with only a slight preference for the *syn* adduct (*syn*/*anti* ratio= 55:45). In the case of **48**, the reactions were completely regioselective with exclusive attack of the enolate on the less substituted oxirane carbon, and in the case of **57** completely anti-stereoselective, no trace of the corresponding *syn* addition product being found (Scheme 16).[65]



Scheme 16

Following these observations, the correct Newman projection of the reasonably more stable open (non-chelated) transition state **68** hypothesized for the metal salt-catalyzed addition reaction of enolate (*Z*)-**56** to epoxide **48**, would indicate the *syn* diastereoisomer as the major one.[66] This predominance should also be independent of the geometry of the starting enolate [see transition state **69** hypothesized for the reaction of the diastereoisomeric enolate (*E*)-**56**] (Scheme 17).



Scheme 17

As a consequence, the lack of selectivity observed in the addition reaction of enolate (*Z*)-**56** and (*E*)-**65** to epoxides **48** and **57** appears to be somewhat surprising. Control experiments carried out by taking in the reaction solvent (toluene) the pure addition products, γ-HKs *syn* (compounds **58** and **62**) and *anti* (compounds **59** and **63**)[67] in contact with LHMDS (3 eq) showed that both the *syn* and the *anti* adducts speedily give an equilibrating mixture of *syn* and *anti* adducts in a ratio (45:55) very similar to the one observed in the corresponding addition reaction. This clearly indicates that the composition of the crude

addition reaction mixture is under thermodynamic control.[68] Accordingly, when the reactions between enolate (*Z*)-**56** and epoxides **48** and **57** are quenched after a reasonably short reaction time (1 h), a significantly increased amount of the corresponding *syn* diastereoisomers is obtained.[65] The use of enolates (*Z*)-**56** and (*E*)-**65** in the reaction with epoxides **48** and **57** constitutes a general procedure for the synthesis of α-alkyl-γ-HKs (Scheme 16).

The structures of γ-HKs were determined by X-ray diffraction of a suitable crystal of the corresponding *p*-nitrobenzoate (*syn* γ-HK **58**) and through reductive cyclization to tetrahydrofurane derivatives by the BF_3-Et_3SiH protocol (γ-HKs *syn* **62** and *anti* **63**). In the case of γ-HKs **66** and **67,** their relative configuration were derived from their relative amount in the crude reaction product.[65]

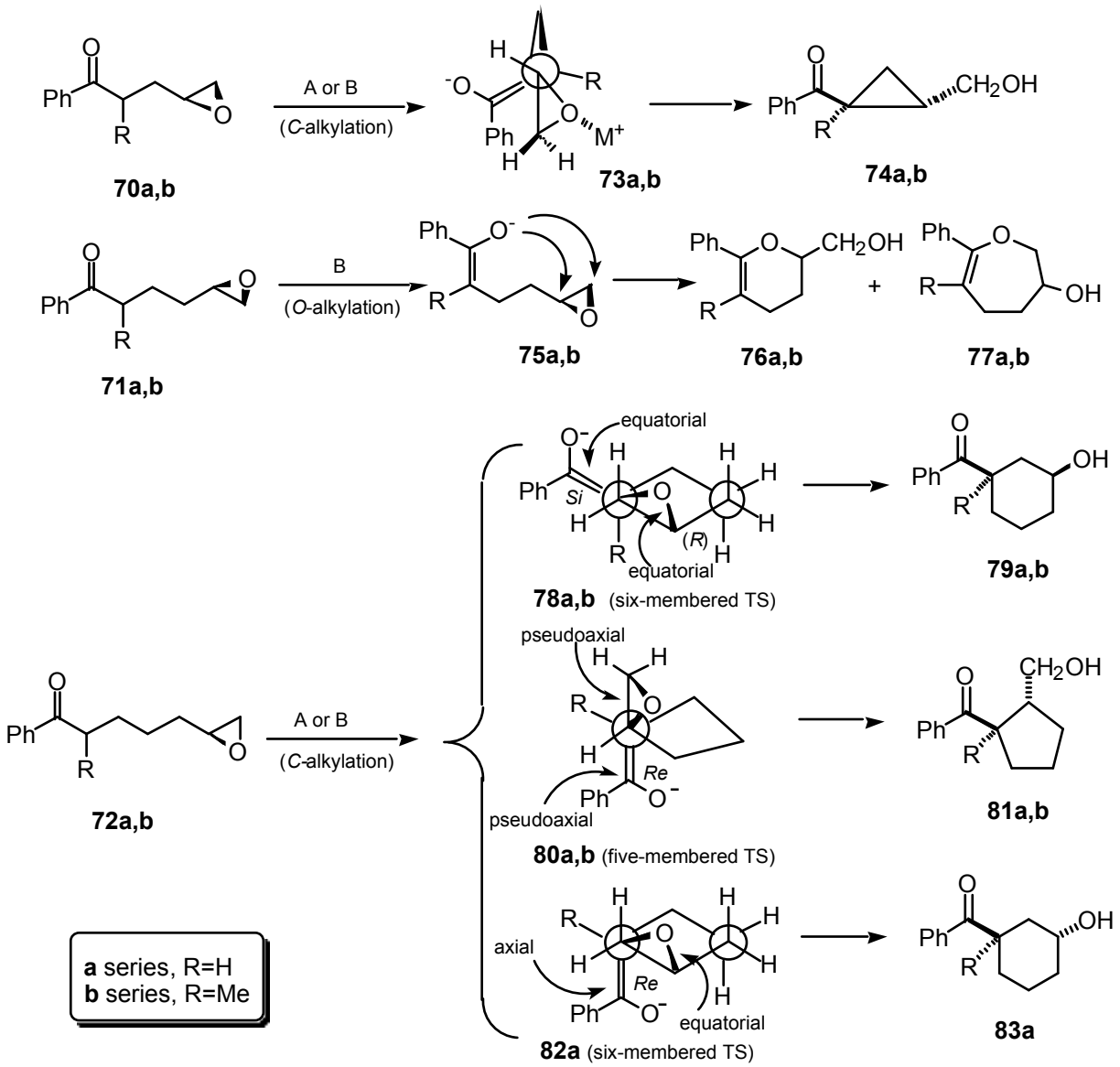
3.3. Intramolecular version of the addition reaction. Cyclization of epoxy ketones

A variety of stabilized carbanions have been widely used for the intramolecular ring-opening of 1,2-epoxides. Most commonly these carbanions are stabilized by adjacent electron-withdrawing groups (EWGs) such as cyano, sulfonyl, carbonyl or sulfur-containing groups.[1] When the EWG is a carbonyl, some ambiguity may result from the presence of two nucleophilic sites (C and O) which may intramolecularly displace the oxirane ring leading to the corresponding *C*- or *O*-alkylation products, respectively.

In order to examine the intramolecular version of the addition reaction of lithium enolate of ketones to epoxides, our LHMDS/$Sc(OTf)_3$ protocol (procedure A) and, for comparison, the *t*-BuOK/*t*-BuOH protocol (procedure B), a previously described procedure for cyclization of epoxy ketones,[69] were applied to some representative epoxy ketones, such as 4,5- (**70a**), 5,6- (**71a**) and 6,7-epoxy-1-phenyl-1-alkanone (**72a**) and the corresponding α-methyl derivatives (epoxides **70-72b**), in view of the possible straightforward obtainment of cyclic γ-HKs (Scheme 18).[70]

The cyclization of epoxy ketones **70a,b** by means of procedures A and B afforded only the cyclopropane *trans* derivative **74a,b** (a *C*-alkylation product, Scheme 18),[71] no trace of *cis* diastereoisomer or of any regioisomeric products (attack on the less substituted oxirane carbon of **70a,b**) or opening products derived from an *O*-alkylation process being found in the crude reaction mixture. The exclusive formation of γ-HK **74a,b** in this reaction can easily be justified on the basis of a highly favored Markovnikov-type 3-*exo* cyclization mode,[72] in which both alkyl groups are trans to the newly forming C-C bond, as shown in structure **73a,b** (Scheme 18).

A completely different result was obtained when the homolog 5,6-epoxy ketones **71a,b** were subjected to the same cyclization protocols. In this case, while the LHMDS/$Sc(OTf)_3$ procedure turned out to be unexpectedly inefficient leading only to complex reaction mixtures, the *t*-BuOK/*t*-BuOH protocol on epoxy ketones **71a,b** afforded only *O*-alkylated products, the hydroxy enol ethers (HEEs) **76a,b** and **77a,b** (Scheme 18). The complete absence, under these conditions, of corresponding *C*-alkylation products can be attributed to the reasonably low stability and/or consistent strain associated with the four- and five membered transition state (TS), necessary for their formation from **71a** and **71b**.[73] The appreciable selectivity observed towards the HEE **76** (77-83%) (a favored 3-exo cyclization mode)[72] can be justified by the larger stability of a six- than a seven-membered TS. The cyclization reactions of the 6,7-epoxy ketones **72a,b** (procedures A and B) afforded mixtures of both the *contra*-Markovnikov- (the cyclohexane *cis* derivatives **79a,b**) and Markovnikov-type regioisomers (the cyclopentane *trans* derivatives **81a,b**), with some amounts, in the case of **72a**, of the Markovnikov-type *trans* diastereoisomer **83a** (Scheme 18).



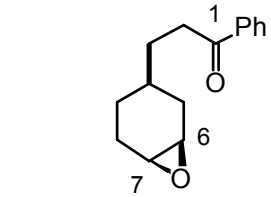
Scheme 18

On the whole, the LHMDS/$Sc(OTf)_3$ protocol (procedure A) appears to be superior to procedure B, showing in general a better overall yield, a more stereoselective result (*cis* **79a** : *trans* **83a** = 85:4), and a satisfactory regiochemical result (only 12% of regioisomer **81a** was present). At the same time, with the *t*-BuOK/*t*-BuOH protocol (procedure B), a complete regioselectivity was observed (compound **81a** was not formed), but the stereoselectivity was poor (*cis* **79a** : *trans* **83a** = 73:27). On the reasonable assumption that the most favorable TS for these cyclization reactions are those in which the double bond of the enolate and the oxirane C-C bond of the molecule can adopt a staggered *anti* conformation,[65] the two regioisomeric γ-HKs **79a,b** and **81a,b** arise from a reactivity of the enolate by its *Si* or *Re* face, respectively, as shown in structures **78a,b** and **80a,b** of Scheme 18 [enolate (*Z*) of the (*R*)-stereoisomer shown]. In this framework, the larger amount of γ-HK **79a,b** obtained in all the experiments may reasonably be attributed to the greater stability of the six-membered **78a,b** over the five-membered TS **80a,b**, which, moreover, makes it possible for the nucleophilic attack to occur at the less hindered primary carbon of the oxirane ring. As for the small amount of the *trans* isomer **83a** present in the crude reaction product from epoxy ketone **72a**, this seems to arise from a reactivity of the *Re* face of the corresponding enolate through the less stable *gauche* TS shown in

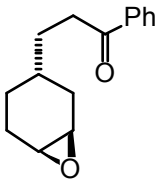
structure **82a** (Scheme 18). γ-HKs **79a** and **81a** turned out to be stable under the basic experimental conditions (LHMDS, toluene), indicating that the cyclization reaction is, in this case, under kinetic control.[65,70]

In epoxy ketones **70-72a,b** the oxirane moiety is inserted at the end of a carbonyl-containing aliphatic chain and the possible reaction with the corresponding enolate portion is substantially subjected to few conformational constrains, with the only requirement of an anti-stereoselective addition fashion.[1]

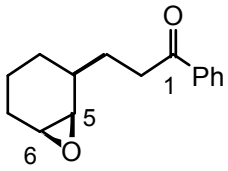
In order to evaluate the potential of the same reaction in epoxy ketones systems in which the conformational requirements of the addition process could play a more decisive role, the intramolecular version of this reaction was extended to some epoxy ketones in which the carbonyl-containing aliphatic chain (a phenone of different length) is differently disposed with respect to the oxirane functionality inserted into a cyclohexane ring. Some 3,4-, 4,5-, 5,6- and 6,7-epoxy ketones derived from cyclohexene oxide were thus prepared: the 6,7-epoxy ketones **84** and **86**, the 5,6-epoxy ketones **85** and **87**, the 4,5-epoxy ketone **88** and the 3,4-epoxy ketone **89**. Epoxides **84**, **85** and **88** are regioisomers in which the distance between the carbonyl and the oxirane functionality is progressively reduced. In the pairs **84** and **86**, and **85** and **87**, the distance between the two functionalities is formally the same, but there is a difference in the position and length of the carbonyl-containing aliphatic chain. In **89** the two reactive functional groups are at the lowest possible distance allowing the presence of an active methylene group between them. Epoxy ketones **84** and **85** were used as a mixture of the corresponding diastereoisomers *cis* (**c-84** and **c-85**) and *trans* (**t-84** and **t-85**).[74]



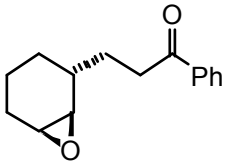
c-84



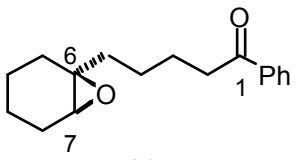
t-84



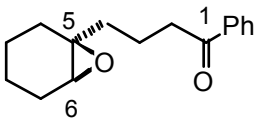
c-85



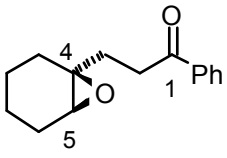
t-85



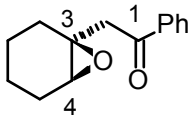
86



87

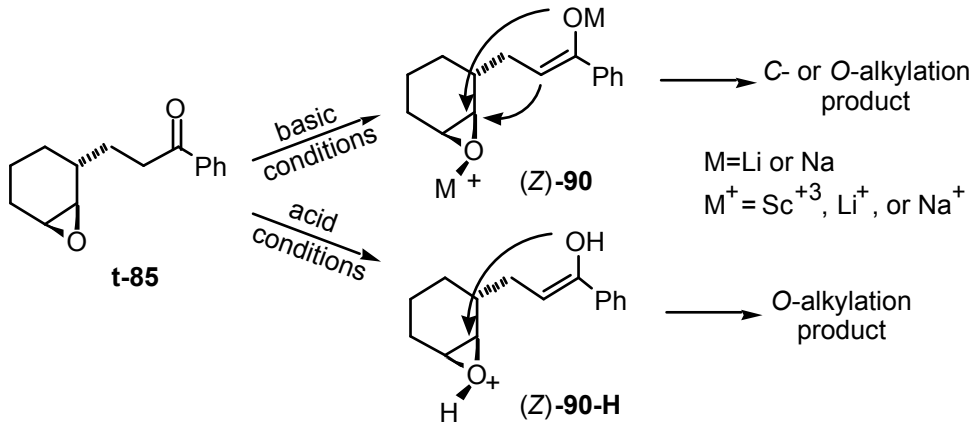


88



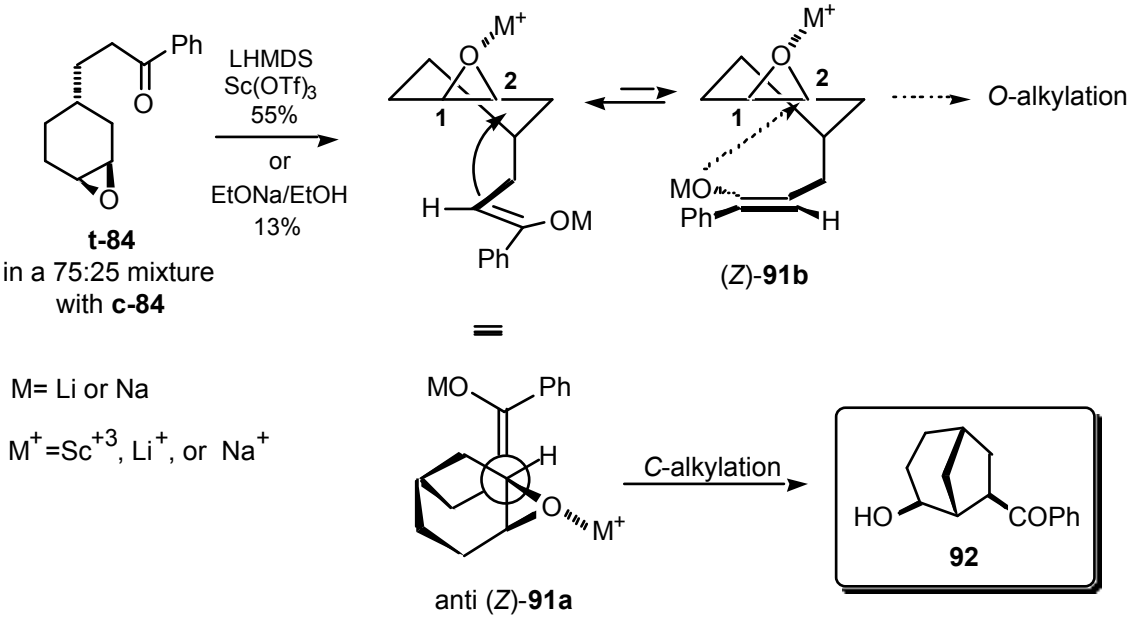
89

Epoxy ketones **84-89** were subjected to several cyclization procedures both under basic and acid reaction conditions: *i*) the LHMDS/$Sc(OTf)_3$/toluene protocol and the more common EtONa/EtOH protocol as examples of cyclization reactions under basic conditions, and *ii*) treatment with acid resin (Amberlyst 15) in an aprotic polar solvent (CH_2Cl_2), as an example of cyclization reaction under acid conditions. As shown in Scheme 19 only for epoxy ketone **t-85**, taken as an example, the incursion of the corresponding (*Z*)-metal enolate (**90**)[75] or enol form (**90-H**) under basic and acid conditions, respectively, with subsequent nucleophilic attack on the *O*-metal-coordinated (basic conditions) or *O*-protonated oxirane ring (acid conditions), is reasonably admitted. It is to be stressed that while, on the one hand, *O*-alkylation products are reasonably possible both under alkaline (LHMDS or EtONa) and acid conditions (Amberlyst 15/ CH_2Cl_2), on the other hand *C*-alkylation products are possible only under alkaline conditions.



Scheme 19

The trans-diaxial requirement (Fürst-Plattner rule)[76] for the intramolecular addition reaction of the metal enolate or enol form of epoxy ketones **84**-**89** to the corresponding semi-rigid cyclohexane-derived oxirane ring could be decisive in these systems not only in determining, in accordance with or opposite to Baldwin's rule,[72] the oxirane carbon to be nucleophilically attacked, but also in affecting the nature of the addition product (*C*- or *O*-alkylation product).

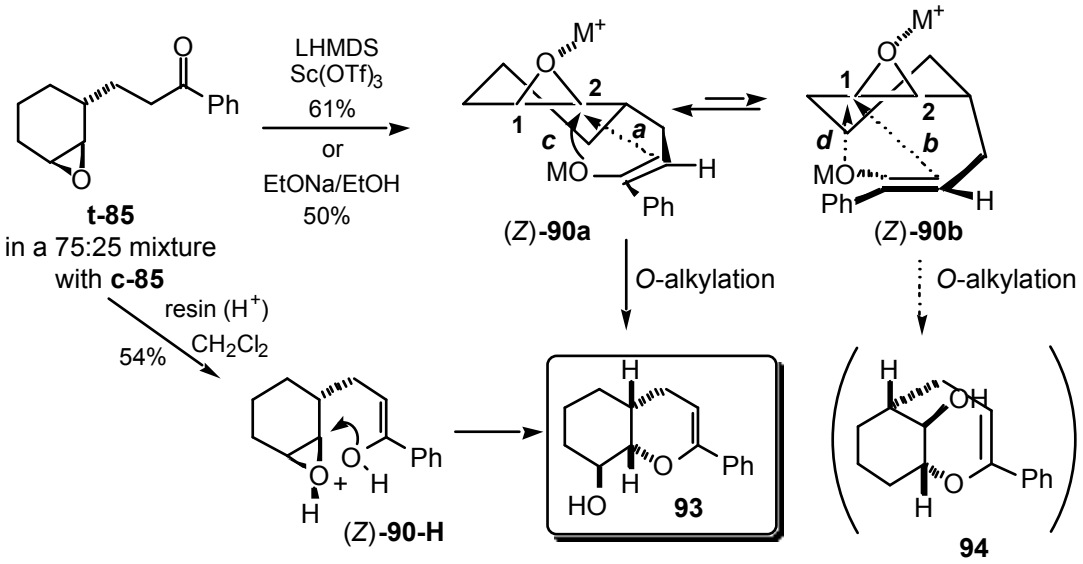


Scheme 20

Treatment of epoxide **t-84** (in the 75:25 mixture with diastereoisomer **c-84**)[77] with LHMDS in the presence of $Sc(OTf)_3$ afforded the γ-HK **92** (a *C*-alkylation product), as the only reaction product (Scheme 20). The exclusive formation of **92** is reasonably justified by means of a 5-membered transition state (TS) (a favored 5-*exo* cyclization process)[72] in which a favorable *anti* arrangement between the unsaturated system of the corresponding (*Z*)-enolate portion and the C-C oxirane bond is nicely achieved, as shown in *anti* (*Z*)-**91a**. The same result (lower yield) is obtained also by application of the alternative EtONa/EtOH alkaline protocol. Because of the necessary incursion, at least, of a 7-membered TS [dotted arrows in (*Z*)-**91b**, Scheme 20], *O*-alkylation products are never observed with epoxy ketone **t-84**, either under alkaline or acid

reaction conditions. Accordingly, application of the acid protocol to the 75:25 mixture of **t-84** and **c-84**, leads only to recovery of unreacted starting epoxides.

Consistently different is the behavior of the regioisomeric *trans* epoxide **t-85** (in the 75:25 mixture with diastereoisomer **c-85**). In this case, the *C*-alkylation pathway is not possible in either of the two reactive conformations (*Z*)-**90a** and (*Z*)-**90b** of the corresponding metal (*Z*)-enolate (Scheme 21), because of the implication of a 4-membered TS [(*Z*)-**90a**, pathway ***a***] or the unsurmontable distance between the two reactive centers [(*Z*)-**90b**, pathway ***b***]. All this makes an *O*-alkylation pathway highly competitive to the point that HEE **93** is the only reaction product with attack of the nucleophile [enolate (*Z*)-**90**] on the C(2) oxirane carbon through a six-membered TS (a favored 6-*exo* cyclization process),[72] as shown in (*Z*)-**90a** (pathway ***c***).[78] HEE **93** is also obtained by the alternative basic protocol (EtONa/EtOH) and under acid conditions [incursion of the protonated enol (*Z*)-**90-H**], thus giving an example of a regioconvergent process (Scheme 21).

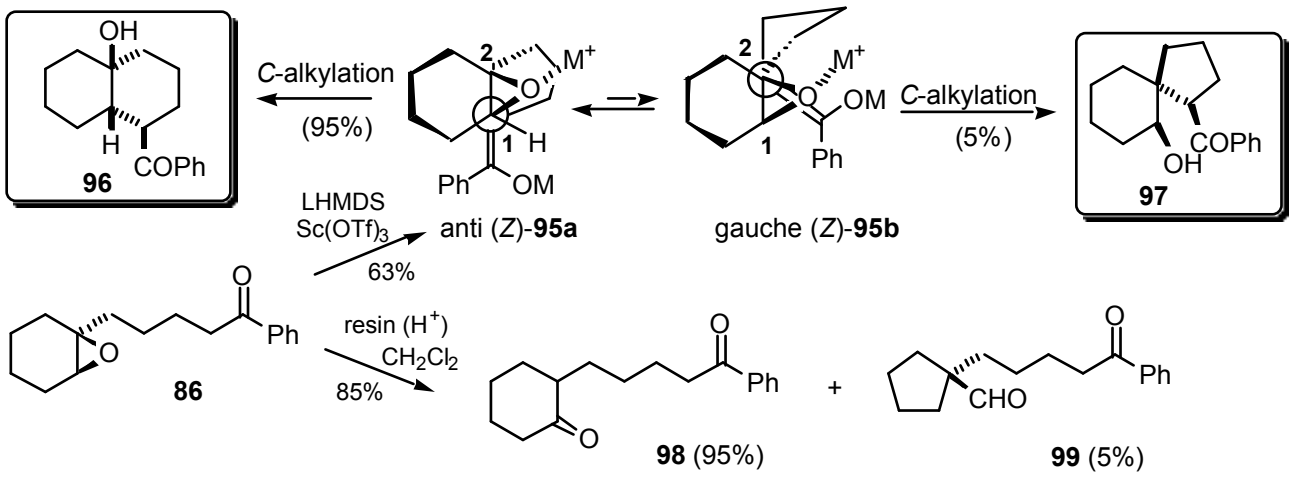


Scheme 21

In the case of the epoxy ketone **86**, the long carbonyl-containing side chain allows an easy reactivity, under the alkaline protocols, of the corresponding enolate (*Z*)-**95a,b** to give only *C*-alkylation products, the bicyclic γ-HK **96** (through a disfavored 6-*endo* cyclization process) (95 %) and the spiro γ-HK **97** (through a favored 5-*exo* cyclization process)[72] (5 %), by nucleophilic attack on C(1) and C(2) oxirane carbon, respectively. The decidedly larger amount of the bicyclic compound **96** in this reaction is consistent with the preferential TS *anti*-(*Z*)-**95a** if compared with the alternative TS *gauche*-(*Z*)-**95b**, reasonably less stable, leading to the spiro compounds **97**. The EtONa/EtOH protocol is uneffective and leads only to the recovery of the unreacted starting epoxide. No *O*-alkylation products are observed either under acid or alkaline conditions, probably due to the extremely large cyclic TS (7- or 8-membered ring) which would necessarily be involved in their formation. As a consequence, the acid protocol leads only to isomerization products, the diketone **98** and the oxoaldehyde **99** in a 95:5 ratio (Scheme 22).

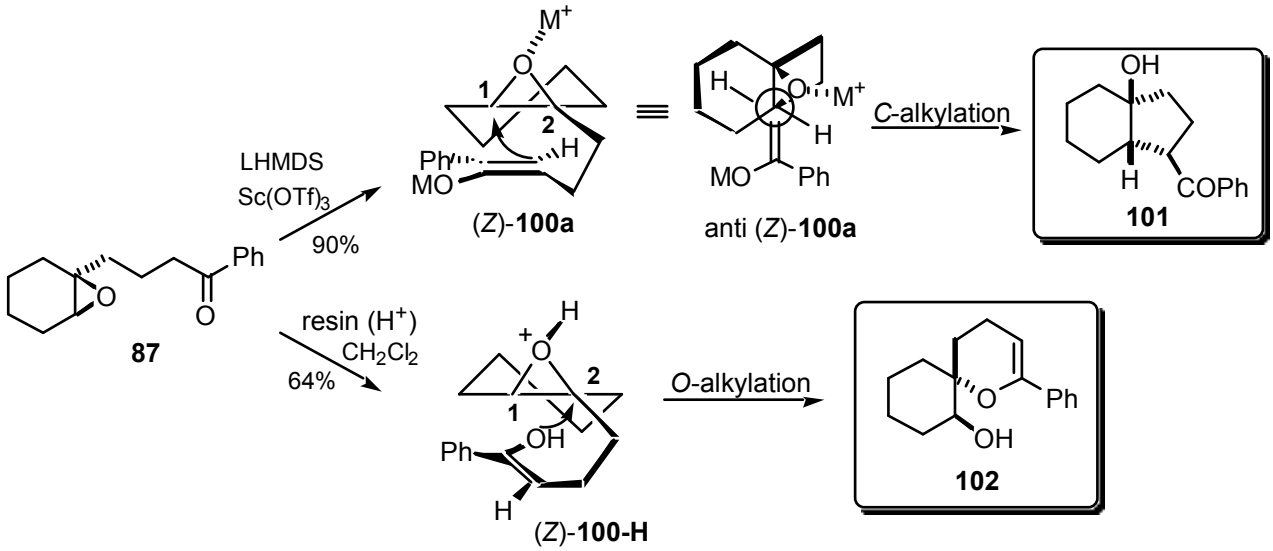
Due to the appropriate length of the side chain, epoxides **87** and **88** are the only epoxy ketones so far studied that show a chemoselective behavior depending on the reaction conditions. In fact, while *C*-alkylation products, the γ-HK **101** from **87** and the γ-HKs **104** and **105** from **88**, are obtained under alkaline

conditions, *O*-alkylation products, the HEEs **102** from **87** and **106** from **88**, are respectively observed under acid conditions (Schemes 23 and 24). The γ-HK **101** comes from a classically favored TS such as *anti* (*Z*)-**100a**, through a 5-*endo* cyclization process, which, even if disfavored by Baldwin's rule,[72] is the only possible one in these conditions, considering that the formation of 4-membered cyclic products has never been observed under our experimental conditions (Scheme 23).[73]



Scheme 22

The EtONa/EtOH protocol is ineffective and the starting epoxide is recovered completely unreacted. As shown in (*Z*)-**100-H**, when the reactivity is transferred to the corresponding enol form (acid conditions), a six-membered TS may easily be obtained and the HEE **102** is obtained as the only reaction product. In this case, the acid-induced ring opening process of the oxirane ring toward the tertiary C(2) oxirane carbon may play an important role in directing the attack of the nucleophile (Scheme 23).

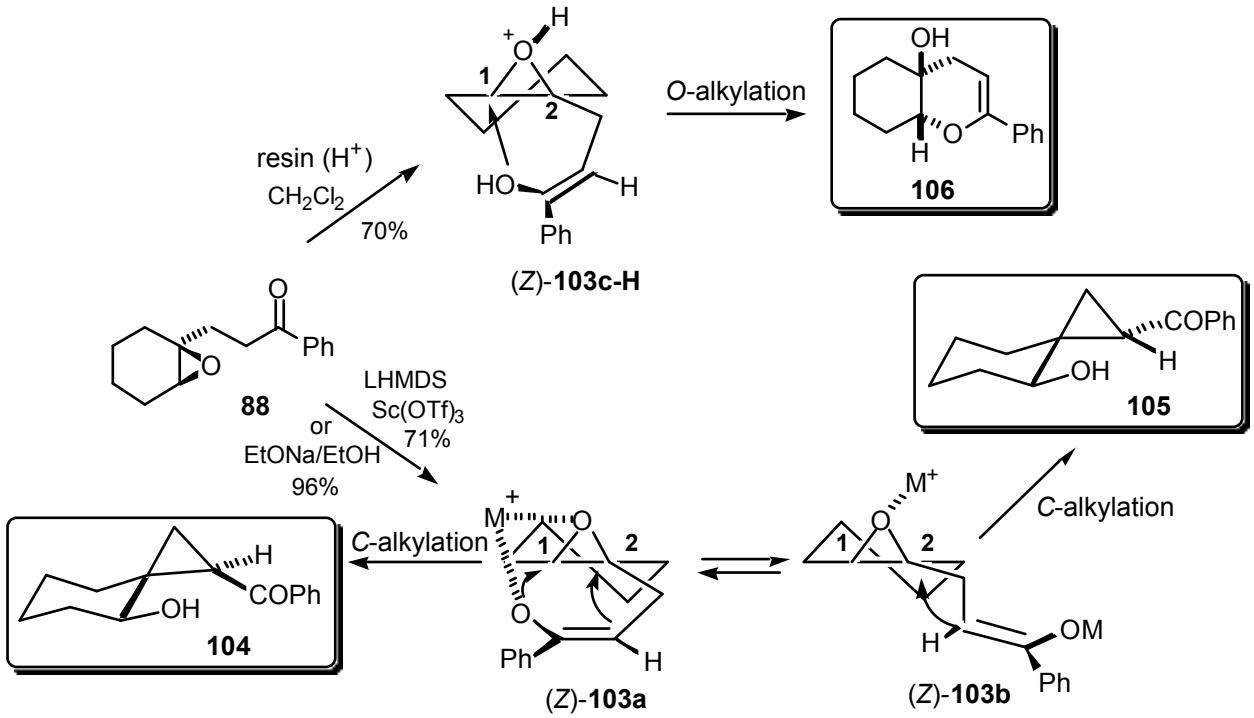


Scheme 23

Diastereoisomeric spiro γ-HKs **104** and **105** arise from a reactivity of the epoxide **88**-derived metal enolate (*Z*)-**103** (from LHMDS) in the two possible conformations **a** and **b**, through a highly favored 3-membered TS (a 3-*exo* cyclization process) (Scheme 24).[72] The higher amount of **104** so far obtained under the LHMDS/$Sc(OTf)_3$ protocol (**104**:**105** ratio = 76:24) may be reasonably justified on the basis of a

chelation process, through a metal species (Li^+ and/or Sc^{+3}) present in the aprotic reaction solvent (toluene), between the enolate and oxirane oxygens, only possible in (*Z*)-**103a**. Accordingly, when the same reaction is carried out using the alternative alkaline protocol (EtONa/EtOH), an inverted stereoselectivity was obtained and the "non-chelation" product, the γ-HK **105**, turned out to be the main reaction product (**104**:**105** ratio = 14:86), as a result of a strongly diminuished chelation capability of the enolate counterion (Na^+) in the protic solvent (EtOH).

Under acid conditions, epoxide **88** affords the bicyclic HEE **106**, reasonably through the six-membered TS (*Z*)-**103c-H**, which, even if disfavored by Baldwin's rule (a 6-*endo* cyclization process), is, for structural reasons and application of the Fürst-Plattner rule, the only one reasonably possible in this system (Scheme 24).[72,76]

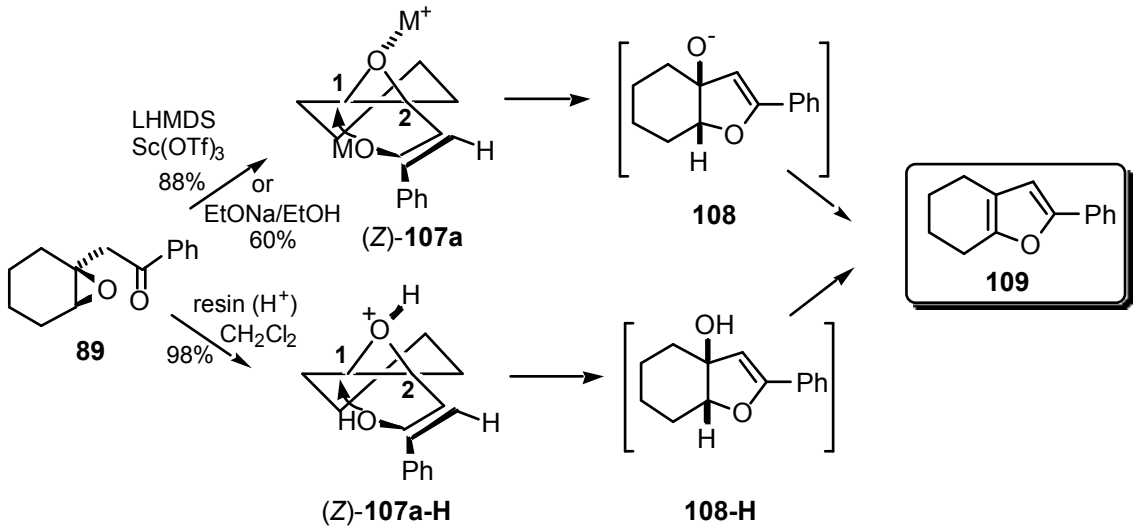


Scheme 24

Epoxy ketone **89**, both under alkaline and acid conditions, affords the tetrahydrobenzofurane derivative **109**, as a consequence of a cyclization process in which the primary reaction product, the HEE **108** (or **108-H**), undergoes an easy elimination process to give the corresponding aromatic system (Scheme 25). The HEE **108** (or **108-H**), an *O*-alkylation product, is the only product allowed, for structural reasons, by a cyclization process in this system through enolate (*Z*)-**107a**, under alkaline conditions, and enol (*Z*)-**107a-H**, under acid conditions, respectively. The chemical behavior so far observed with epoxide **89**, even if interesting, had already been previously observed in other related systems.[79]

The cyclization reactions of cyclohexene oxide-derived epoxy ketones **84-89** have indicated that the Fürst-Plattner rule mostly drives the nature of the cyclization product in these epoxy ketone systems to the point that, if a *C*-alkylation process is not possible for strictly structural reasons or for reasons linked to the incursion of a 4-membered or strained 5-membered cyclic TS, the alternative constantly less-strained *O*-alkylation pathway takes place. Under alkaline conditions, where the LHMDS/$Sc(OTf)_3$/toluene protocol appears superior and more generally applicable than the alternative EtONa/EtOH one, when a clear *C*-alkylation process is allowed, the alternative *O*-alkylation process is not observed. In these conditions, the

combination of the Fürst-Plattner rule and the favored *anti* TS determines the nature (bicyclic or spiro) of the γ-HK obtained in each case.



Scheme 25

Under acid conditions, *O*-alkylation products are classically obtained, with the only exception of epoxides **t-84** and **86**, and in some cases, depending on the corresponding behavior under alkaline conditions, a nice regioconvergent or chemoselective procedure may be achieved by using alkaline or acid cyclization reaction conditions. On its own, the acid cyclization process appears to be sensitive to stereoelectronic effects and the attack of the nucleophilic enol oxygen on the more substituted oxirane carbon, when allowed by strain effects and the Fürst-Plattner rule, is highly favored. Even if allowed by the previous considerations, 4- and 7-membered cyclic products are never observed under any conditions.

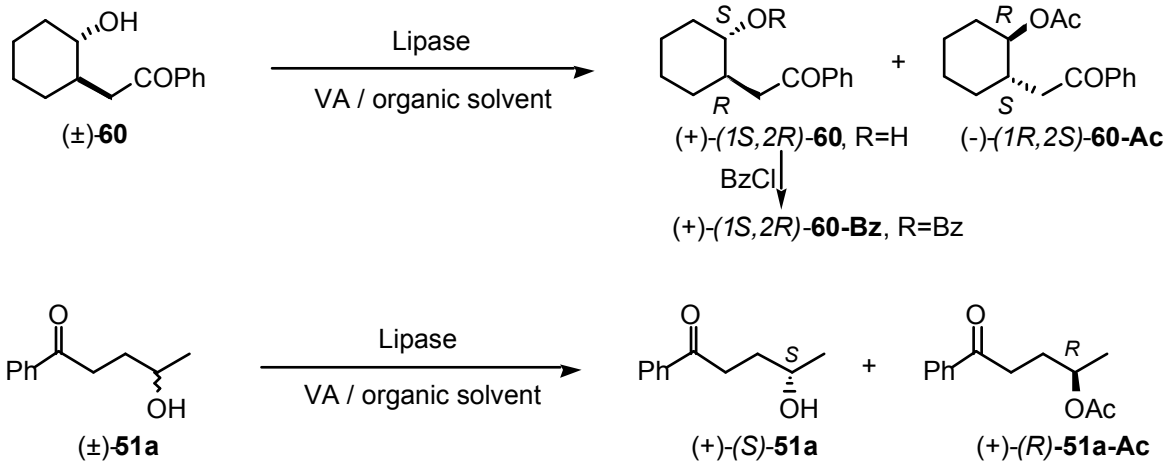
3.4. Synthesis of enantiomerically pure γ-HKs

In view of the growing general interest in enantiopure compounds and the possibility of the introduction of enantiopure γ-HKs, or some simple derivatives of these, into the chiral pool, as useful enantiopure building blocks, we examined the possibility of obtaining enantiomerically pure γ-HKs by kinetic resolution of two representative racemic γ-HKs, the (±)-*trans*-2-(benzoylmethyl)-1-cyclohexanol (**60**) and the aliphatic (±)-4-hydroxy-1-phenyl-1-pentanone (**51a**), by means of a lipase-catalyzed transesterification procedure.

The racemic γ-HKs (±)-**60** and (±)-**51a** were submitted to kinetic resolution by means of lipase-catalyzed enantioselective acylation in an organic solvent using vinyl acetate as the acetylating agent.[80]

The best results were obtained with the cyclohexane system (±)-**60**, by means of a lipase PS supported on Hyflo Super Cell. In this system the lipase PS was extremely selective towards the (-)-*(1R,2S)*-**60** enantiomer, and after 50% of conversion, both the acetate (-)-*(1R,2S)*-**60-Ac** and the recovered unreacted γ-HK (+)-*(1S,2R)*-**60**, which were easily separated by flash chromatography, turned out to be enantiomerically pure (*ee* >99%).[81] Subsequent saponification of acetate (-)-**60-Ac** with K_2CO_3 in MeOH at r.t. afforded enantiopure (-)-*(1R,2S)*-**60** (*ee* >99%), thus completing the resolution process of racemic (±)-**60**. The high enantioselectivity observed for both the acetate (-)-**60-Ac** obtained and the γ–HK (+)-**60** recovered in the transesterification reaction of (±)-**60** with lipase PS points to a large difference between the kinetic reaction

constants of the two competing acetylation processes of the enantiomers of γ-HK **60**, so much so that the acetylation reaction essentially stops as soon as the (-)-*(1R,2S)*-**60** enantiomer has reacted. This was demonstrated by the fact that reaction times (6 h) decidedly longer than the time (3 h) required for an almost perfect 50% conversion did not result in any significant modification of the conversion ratio between the unreacted γ-HK (+)-*(1S,2R)*-**60** and the acetate (-)-*(1R,2S)*-**60-Ac** (Scheme 26).



Scheme 26

With the aliphatic γ-HK system (±)-**51a**, the corresponding enzymatic resolutions were not so successful as with the conformationally semirigid substrate (±)-**60**. In spite of many modifications introduced by changing both the enzyme and the reaction conditions, the *ee* values of the acetylated product **51a-Ac** were not superior to 42%, the best result being obtained, also in this case, with lipase PS supported on Hyflo Super Cell. It is worth noting the interesting behaviour of lipase AK, which mainly gave the acetate (-)-*(S)*-**51a-Ac**, while all the other lipases used gave the acetate (+)-*(R)*-**51a-Ac** as the major enantiomer.

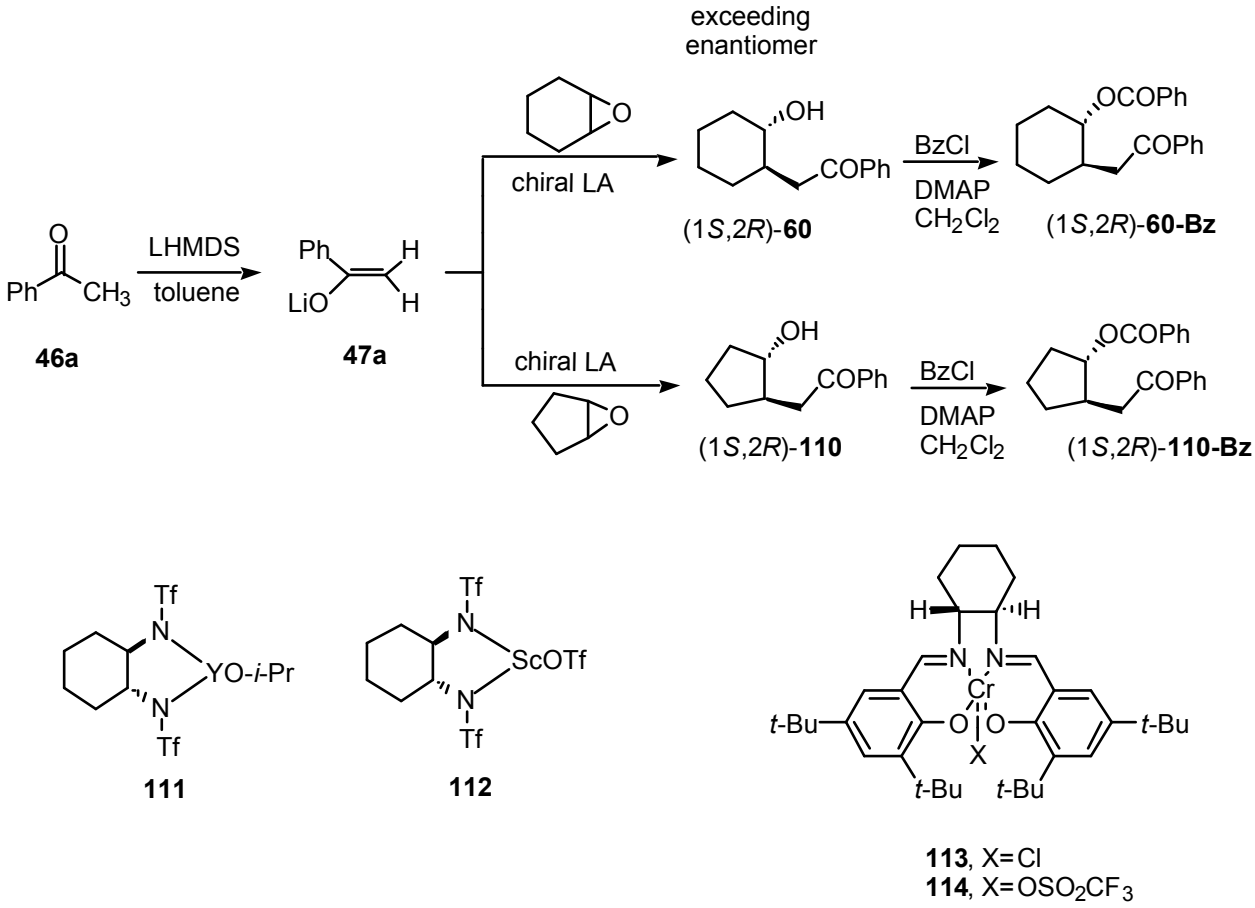
This unexpectedly large difference in the chemical behaviour towards the lipase-catalyzed acetylation process could reasonably be attributed to the consistently different conformational situation in the two systems, the semirigid (±)-**60** and the decidedly more mobile (±)-**51a**, which shows up the discriminatory ability (enantioselectivity) of the enzyme.[80]

3.5. Enantioselective addition of lithium enolate of acetophenone to cycloalkene oxides

The enantioselective nucleophilic ring opening of symmetrical 1,2-epoxides (meso epoxides) by the use of a chiral catalyst has become an attractive method in modern organic synthesis for the preparation of optically active compounds.[82] This procedure offers the advantage of constructing two adjacent stereogenic centers in a single operation and of not suffering from any regiochemical complications. The enantioselective ring opening of symmetrical 1,2-epoxides by heteronucleophiles has been widely investigated. The most interesting results are obtained with thiols,[83] halide ions,[84] and very efficiently with N_3^-.[85] On the contrary, the enantioselective catalyzed addition of *C*-nucleophiles to meso 1,2-epoxides is an almost unexplored area,[86] in spite of the fact that this reaction may constitute a powerful tool to obtain enantiopure polyfunctionalized compounds.

The nucleophilic addition of enolate **47a** to cyclohexene oxide was taken as an adequate model reaction, using scandium and yttrium chiral complexes, such as **111** and **112**, as chiral Lewis acids (LA) to

achieve an enantioselective ring opening process. Unfortunately, the use of these complexes led to very poor yields and *ee* of the reaction product, γ-HK **60** (Scheme 27). Slightly better (16% *ee*), but still unsatisfactory results were obtained when Yb(camph)$_3$ was used as the promoter.[59,87]



Scheme 27

Considering the amazing efficiency of chiral (*R,R*)-(salen)CrCl **113** in catalyzing the enantioselective azidolysis of meso 1,2-epoxides with $TMSN_3$,[85a] this chiral LA was used in the reaction of enolate **47a** with cyclohexene oxide. γ-HK **60** was obtained in a low yield (23%), but with an encouraging *ee* (45%). The best *ee* (84% *ee*) was obtained when a 1:1 enolate:epoxide ratio was used. However under these conditions a considerable negative influence on the isolated yield was observed. The use of hexane instead of THF, as the solvent, gave slightly better yields of the addition product **60**, but depressed the *ee*.[87]

Since some amounts of the corresponding *trans* chlorohydrin were observed upon exposure of cyclohexene oxide to **113**, a modification of Jacobsen's catalyst appeared to be necessary in this case. Thus, (*R*,*R*)-(salen)Cr(III)(OTf) **114**, the triflate analogue of **113**, was prepared. The use of **114** as the chiral LA in the addition of enolate **47a** to cyclohexene oxide leads to fair isolated yields and a satisfactory *ee* (64-65%). The obtained enantioselectivity appeared to be in this case less sensitive to the enolate:epoxide ratio. As before, the use of hexane as the only solvent lowers the *ee*.

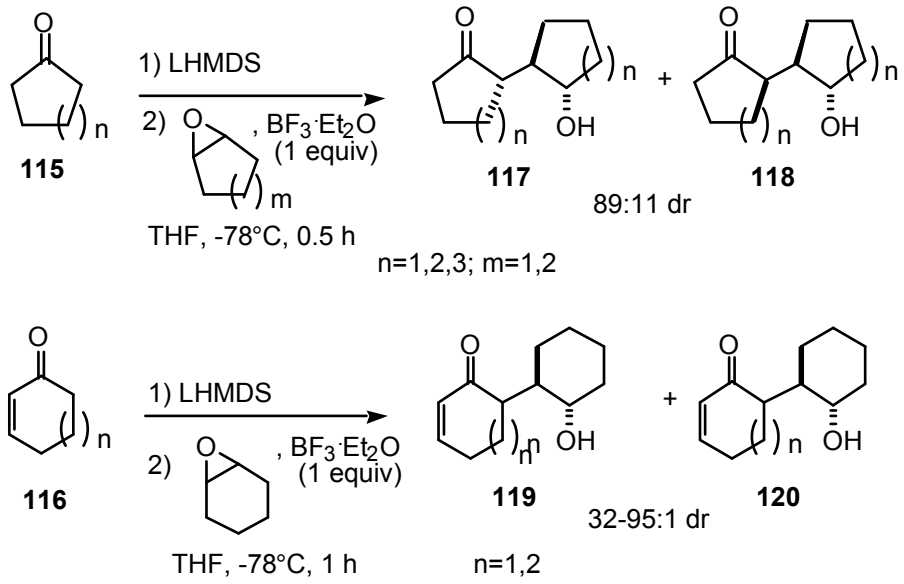
The addition reaction of enolate **47a** promoted by the chiral LA **113** or **114** was then extended to cyclopentene oxide to give the corresponding γ-HK **110** (18-21% isolated yields) which was obtained with *ee*'s (62-63%) lower than those of the corresponding reaction of cyclohexene oxide (Scheme 27).

Complessively, the results would indicate that if on one hand the enantioselectivity is encouraging, on the other hand the yields are decidedly unsatisfactory. Moreover, the yields seem to be linked to the amount

of chiral catalyst used as to indicate that the reaction needs a a stoichiometric and not a catalytic amount of the promoting agent.[87]

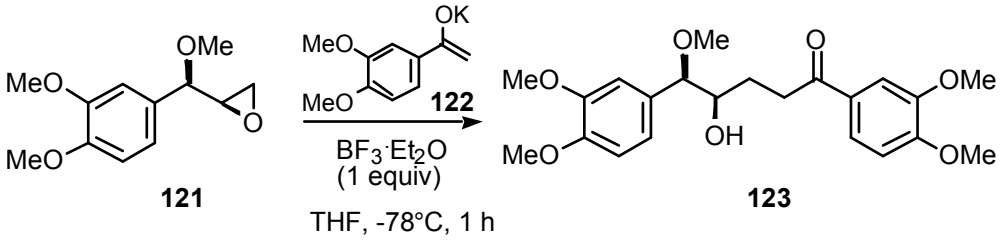
3.6. A recent new protocol for the addition of lithium enolate of ketones to 1,2-epoxides

Recently, Posner reported a simple, mild (-78 °C) and rapid (<1 h) way to activate epoxides toward nucleophilic opening by ketone lithium enolate anions by means of $BF_3{\cdot}Et_2O$ (1 equiv). Lithium enolates derived from five- to seven membered cycloalkanones (**115**) and cycloalkenones (**116**) nucleophilically open cyclopentene and cyclohexene oxides in fair yields to give corresponding γ-HKs *syn* **117** and **119** and *anti* **118** and **120**, respectively, with high 4-8:1 (in the case of cycloalkanones) and 32-95:1 (in the case of cycloalkenones) diastereoselectivity (Scheme 28).[88]



Scheme 28

Application of this procedure to the potassium enolate **122** of an aryl methyl ketone derived from acetophenone in an opening reaction with the monosubstituted epoxide **121**, constitute the key step in a short synthesis of the γ-HK aglycon (**123**) of the natural product curculigine (Scheme 29).[88b]



Scheme 29

4. Conclusions

It is worth mentioning that while there are several successful examples of asymmetric ring-opening reaction of epoxides with heteronucleophiles there are few reports dealing with the enantioselective ring opening of epoxides with carbon nucleophiles. In particular, the use of organometallic reagents in enantioselective ring opening reactions has been described only sparingly. We have demonstrated that

flanking a double bond to an oxirane ring can give rise to more possibilities of asymmetric nucleophilic ring opening of the heterocyclic ring by an organometallic reagent. We have succeeded in developing one of the few successful combinations of an organometallic reagent and an external chiral ligand for the enantioselective addition of dialkylzinc reagents to allylic 1,2- and 1,4-epoxides. Chiral copper complexes of phosphoramidite ligands, having an electron deficient phosphorus atom, proved to be highly effective catalysts for effecting these transformations. Also the desymmetrization of symmetrical 1,2- and 1,4-epoxide to yield enantiomerically enriched ring-opened products has been addressed. The ease of the reaction procedure commonly employed gives a good level of practicability to our method and the possibility to access several allylic and homoallylic alcohols in an enantioenriched form.

The challenge remains of an effective development of new, stereocontrolled protocols making use of Grignard reagents, which are the most readily available carbon nucleophiles.

The addition reaction of lithium enolates of ketones to 1,2-epoxides has been studied and profiteably introduced in synthesis, both in the inter- and intramolecular version. The cyclization reaction of appropriate epoxy ketones can lead to interesting bicyclo, oxabicyclo, spiro and oxaspiro compounds depending if a *C*- or an *O*-alkylation process occurs. In some cases the use of basic or acid cyclization reaction conditions can afford a nice regioconvergent or chemoselective process, depending on the structure of the starting epoxy ketone.

Our current studies are focused on expanding the scope of our procedure to other small ring heterocycles and to other primary organometallic reagents and metal enolates. Moreover, also the catalytic enantioselective ring opening of allylic epoxides with metal enolates remains to be addressed.[89]

Acknowledgements

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67. Actually, γ-HK **62** is an *anti,anti* and **63** is a *syn,anti* diastereoisomer. However, for the sake of uniformty with γ-HKs *syn* **58** and *anti* **59**, only the relative configuration of the C(2) and C(4) carbons

of the zig-zag chain is considered (Scheme 16) in giving the simplified nomenclature *syn* and *anti* to **62** and **63**, respectively.
68. (a) Contrary to a previously reported result (ref.65), also *anti* γ-HKs **59** and **63** epimerize under basic conditions, as stated in the text. (b) Examination of the molecular models of *syn* **58** and *anti* **59** diastereoisomers in their corresponding reasonably preferred intramolecularly hydrogen-bonded seven-membered ring conformation gives evidence of the greater stability, in aprotic solvent, of **59** compared with **58**: in **59** both methyl groups are in a pseudoequatorial position, whereas in **58** they are in a less favorable pseudoequatorial-pseudoaxial relationship. Analogous considerations can be used in the case of diastereoisomers *syn* **62** and *anti* **63**.
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78. Nucleophilic attack on the C(1) oxirane carbon and the alternative formation of the regioisomeric HEE **94**, through (*Z*)-**90b** (pathway ***d***) and a reasonably less stable 7-membered cyclic TS (a 7-*endo* cyclization process),[72] has been ruled out by structural evidences.
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89. Part of this account is reprinted with permission from Elsevier (ref. 58, 59, 70, 74 and 80) and American Chemical Society (ref. 65) which are gratefully acknowleged.

RECENT DEVELOPMENTS IN THE CHEMISTRY OF ISOXAZOL-5-ONES

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This paper is dedicated to Alessandro Marchesini (1938 - 2002) to remember a dear friend and colleague and to acknowledge his important contribution to the chemistry of isoxazol-5-ones.

Abstract. *Recent advances on the chemistry of isoxazol-5-ones have been surveyed, considering both synthetic approaches and reactivity.*

Contents

1. Introduction

In this review there are considered isoxazol-5-one and its substituted derivatives. The fully reduced compounds, *i.e.* isoxazolidin-5-ones have not been included. Similarly, benzocondensed isoxazolones are not reviewed.

The literature has been surveyed for the last years, from 1992 to the first months of 2003. Review articles have been published during this period. A paper dedicated to 3,4-disubstituted isoxazol-5-ones was

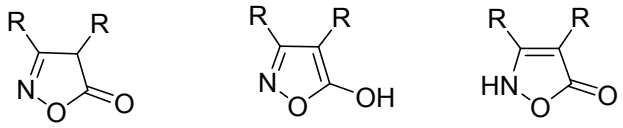
published in 1994[1] and a review on reactions with bases and nucleophiles in 1999.[2] Much information until 1995 can be found in Katritzky[3] where, however, a specific section dedicated to isoxazolones is not present.

Patents dealing with isoxazol-5-one derivatives are numerous, as a consequence of the importance of this ring in compounds of interest in the photographic and pharmacological fields. However, patent literature has been considered only exceptionally because it adds little to the chemical knowledge of this heterocycle.

For the sake of clarity and better identification of items of interest, the matter has been divided into sections, which cover properties of isoxazol-5-ones (section 2.), synthetic approaches (section 3.), reactions of isoxazol-5-ones (section 4.), isoxazol-5-ones as starting reagents for heterocycles (section 5.), pharmaceutical studies (section 6.).

2. Properties of isoxazol-5-ones

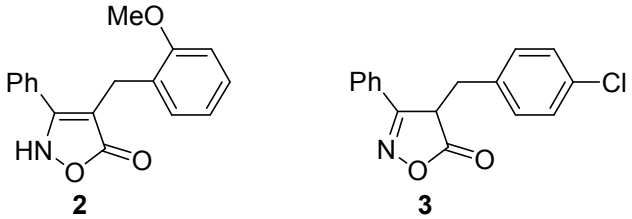
Since long the three tautomeric forms of isoxazol-5-ones have been recognised and designated as CH- **1a**, OH- **1b**, and NH-form **1c**, respectively (Scheme 1).



1a: CH-form **1b:** OH-form **1c:** NH-form

Scheme 1

In the literature they are considered, but generally not identified in specific cases, *i.e.* the classical lactone form being represented in most schemes. In chloroform solution the CH-form is generally predominant, whereas in dimethylsulfoxide the CH-form can not be detected. OH- and NH-forms are predominant in the solid state, probably because of better hydrogen-bonded associations.[4] However, X-ray studies on crystalline 4-(2-methoxybenzyl)-3-phenylisoxazolone **2** and 4-(4-chlorobenzyl)-3-phenylisoxazolone **3** (Scheme 2) showed that the former exists in the NH tautomeric form and the second in the usual lactone form, thus showing different supramolecular assemblies. Convincing explications of this different behaviour exist.[5]

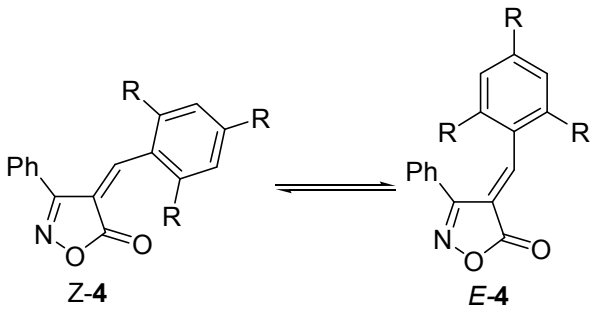


2 **3**

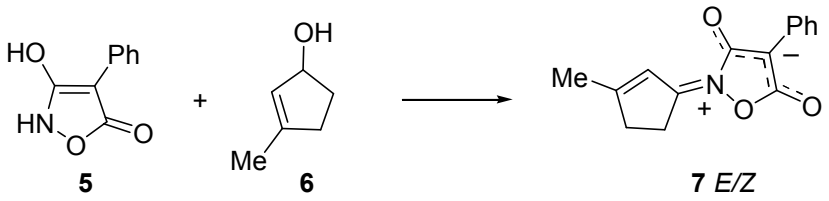
Scheme 2

The tautomerism of 4-acylisoxazol-5-ones was studied. The enol form typical of β-ketolactones predominates.[6] Highly substituted arylmethyleneisoxazol-5-ones **4** show an equilibrium in which the *E/Z* isomers are present (Scheme 3). This was demonstrated by NMR techniques and is proton-catalysed.[7]

Finally, the reaction of 4-phenyl-3,5-dihydroxyisoxazole **5** with α,β-unsaturated cyclic ketones, for example **6**, gave pairs of isomeric isoxazolium enolates *E/Z*-**7** (Scheme 4).[8,9]



Scheme 3

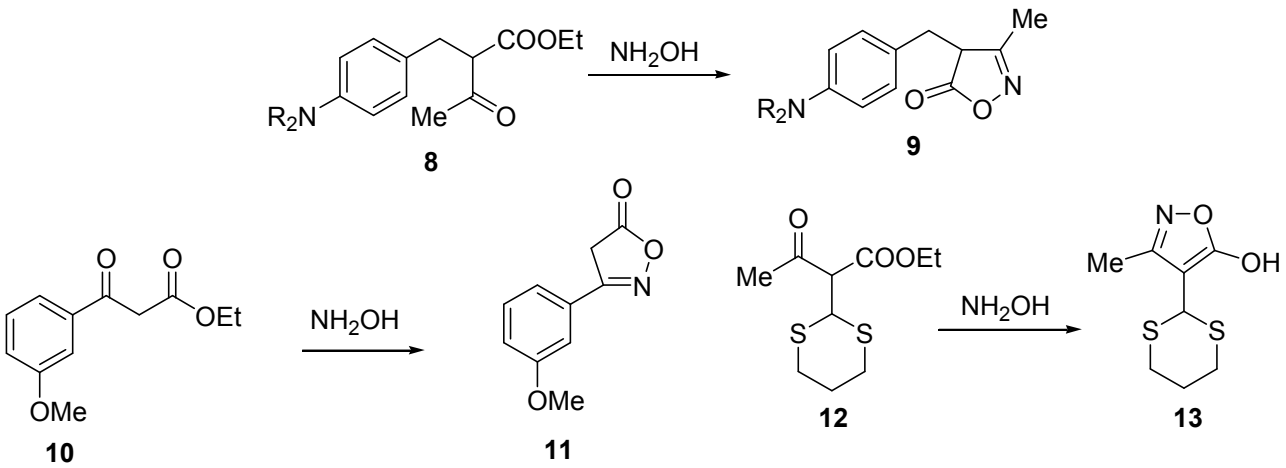


Scheme 4

3. Preparation of isoxazol-5-ones

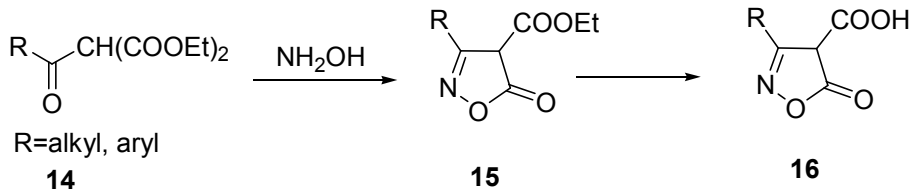
3. 1. Synthetic approaches to substituted isoxazol-5-ones

No really new methods or completely original procedures for the synthesis of substituted isoxazol-5-ones have been developed and reported in the period considered. Obviously, many new compounds were prepared, but synthetic methods were previously described or only slightly modified procedures were employed. Not surprisingly, the most used method involves the long known condensation reaction of β-keto esters with hydroxylamine. Some examples of this synthesis are reported in Scheme 5.[10-12] Other cases are to be found in the literature.[13-17]



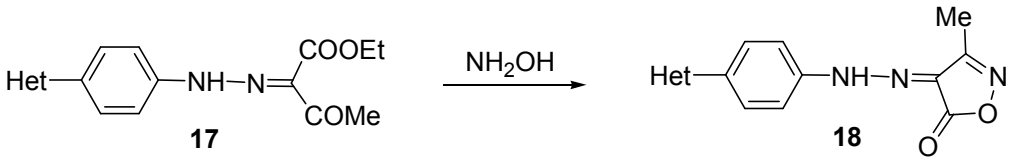
Scheme 5

Several substituted isoxazol-5-one derivatives were obtained according to this general scheme starting from β-dicarbonyl compounds. For example, the reaction of acyl malonates **14** with hydroxylamine has been reported to produce the corresponding 4-ethoxycarbonyl derivatives **15** and, on prolonged reaction, the free acids **16** (Scheme 6).[18]



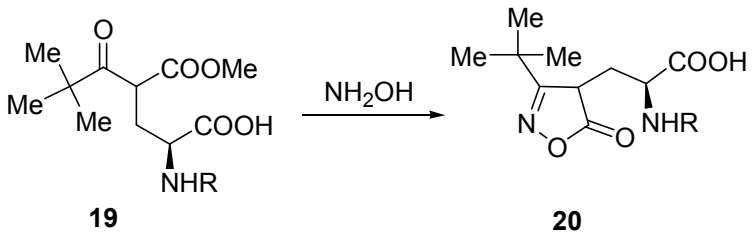
Scheme 6

Similarly, hydrazones **17** produced the expected hydrazonoisoxazol-5-ones **18** (Scheme 7) (for another approach to hydrazonoisoxazol-5-ones see Section 4.3.).[19]



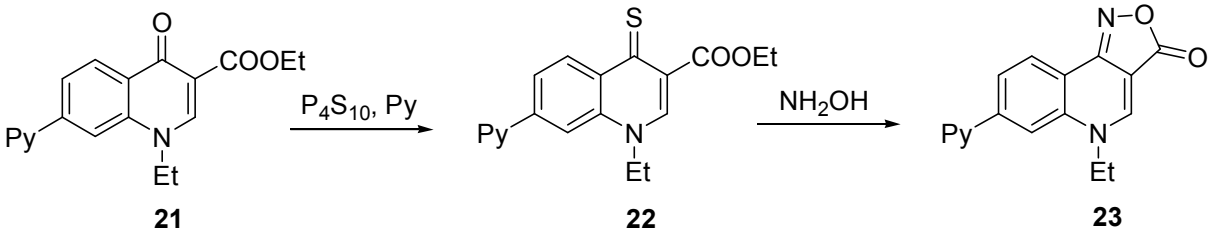
Scheme 7

A synthesis of amino acids **20** containing the isoxazol-5-one substituent has been reported using the protected **19** as starting material and performing the synthesis of the ring by the usual method (Scheme 8).[20]



Scheme 8

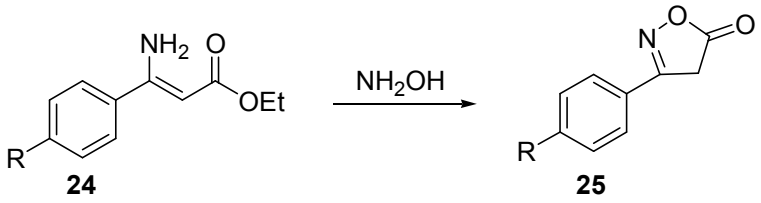
In one case (Scheme 9) a more favourable course of the condensation with hydroxylamine to give **23** was obtained starting from β-thionoester **22** which is easily prepared from the corresponding keto compound **21**.[21]



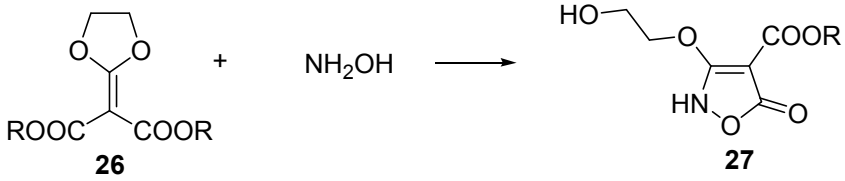
Scheme 9

Another useful modification of this synthetic approach (Scheme 10) employed β-enaminoesters **24**, instead of the corresponding keto compounds, obtaining **25**.[22]

Protection of functional groups can be usefully exploited to produce substituted compounds, as in the case of the reaction of the available acetals **26** (Scheme 11). With NH_2OH they gave the corresponding isoxazol-5-ones **27**.[23]

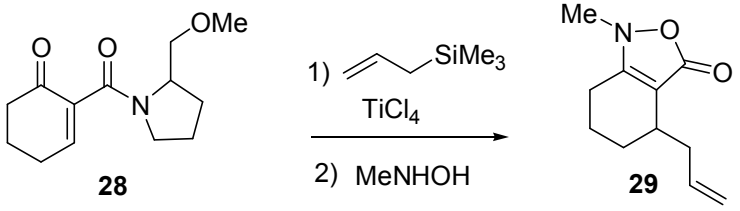


Scheme 10



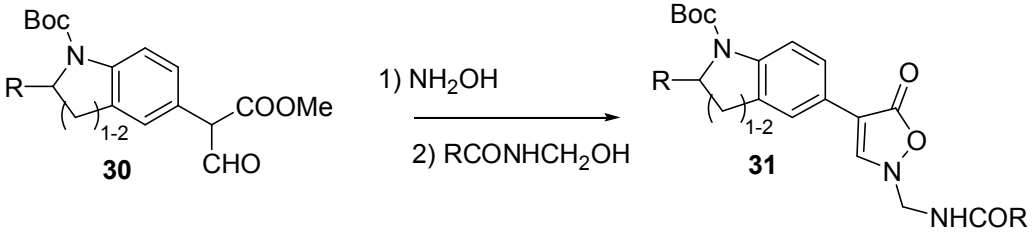
Scheme 11

An interesting approach to chiral condensed isoxazol-5-ones has been reported (Scheme 12). Conjugate addition of allyl silanes and enol silyl ethers to chiral 2-amidocyclohexenone **28** occurred in excellent yield with high diastereoselectivity depending on molar ratio of $TiCl_4$. Subsequent reaction with MeNHOH gave the corresponding isoxazolone **29**.[24]

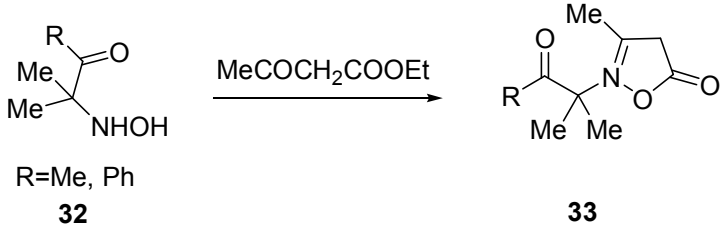


Scheme 12

N-Alkylated compounds **31** were obtained by alkylation (see section 4.1.) after ring closure. An advantageous technical modification of this procedure is that it could be easily performed as an one-pot reaction starting from **30** without the need to isolate the unsubstituted isoxazol-5-ones (Scheme 13).[25]



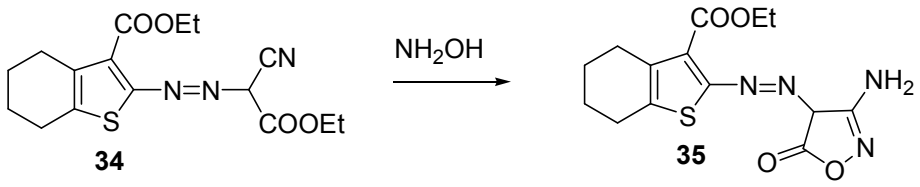
Scheme 13



Scheme 14

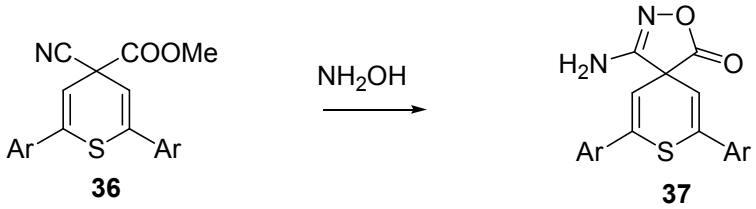
Clearly, *N*-alkylated compounds can also be obtained by the use of substituted hydroxylamines. A particular case is the use of α-hydroxyaminoketones **32** which reacted with ethyl acetoacetate in presence of sodium methoxide, affording the corresponding *N*-substituted isoxazolones **33** (Scheme 14).[26]

3-Aminoisoxazol-5-one **35** was prepared from substituted alkyl cyanoacetate **34** (Scheme 15).[27]



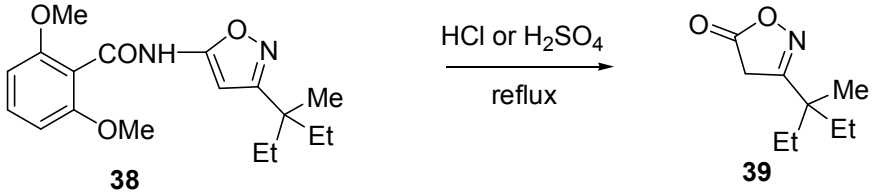
Scheme 15

Also, some spiranic amino derivatives **37** were prepared by this route (Scheme 16).[28]



Scheme 16

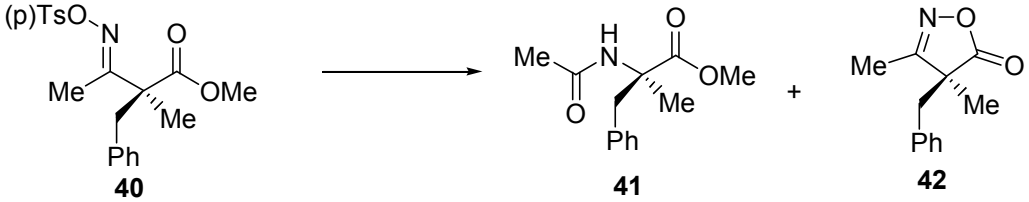
An unexpected entry to isoxazol-5-ones was by hydrolysis of 5-acylaminoisoxazoles: 3-(1-ethyl-1-methyl-propyl)-isoxazol-5-one **39** was formed from the herbicide isoxaben **38** on hydrolysis with aqueous acid at reflux (Scheme 17). This reaction was explained as a direct substitution.[29]



Scheme 17

3.2. Isoxazol-5-ones by intramolecular cyclization

Intramolecular cyclization processes are less frequent than intermolecular ones. However, they are attractive and used.

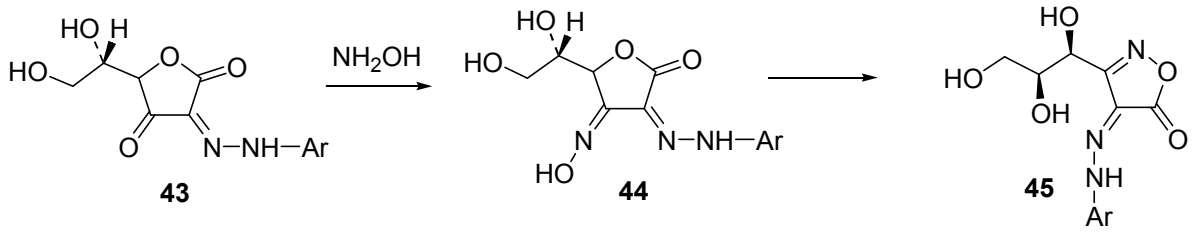


Scheme 18

The simplest case is the formation of the isoxazol-5-one ring from oximes of β-ketoesters. It is long known, but the use of tosylated oximes is recent. Compound **40** and the corresponding mesylates gave, under

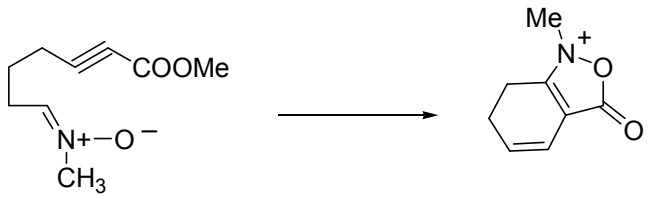
controlled acidic conditions, a moderate yield of the corresponding isoxazol-5-one **42** together with a Beckmann-rearrangement product **41** (Scheme 18).[30]

An interesting case of intramolecular cyclization reaction has been reported. 2-Arylhydrazones of dehydro-L-ascorbic acid **43** are good precursors of heterocycles, among them isoxazol-5-ones **45**, which were obtained by careful treatment with base of the oxime intermediate **44** (Scheme 19).[31]



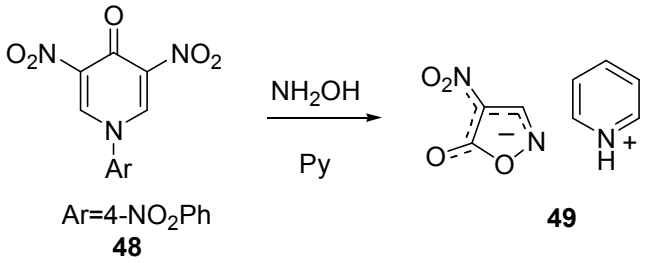
Scheme 19

A bicyclic isoxazol-5-one **47** was obtained by thermal rearrangement of a nitrone derivative containing a conjugate triple bond **46** (Scheme 20). One plausible mechanism of this unusual rearrangement has been provided.[32]



Scheme 20

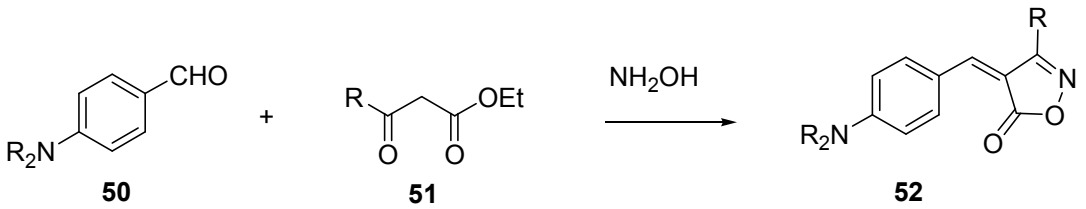
3,5-Dinitro-1-(4-nitrophenyl)-4-pyridone and its omologues **48** were reacted with hydroxylamine giving 4-nitroisoxazol-5-one **49** (Scheme 21). The result was rationalised by double ring transformation in sequence. Owing to the α-effect of the substituent the 4-position of the pyridone becomes an electrophilic site. The N and O atoms of NH_2OH attacked at the 2- and 4-positions of the pyridone ring, respectively. The formation of 4-nitroaniline and 2-nitroacetaldehyde, derived from pyridine opening, gave the desired product.[33]



Scheme 21

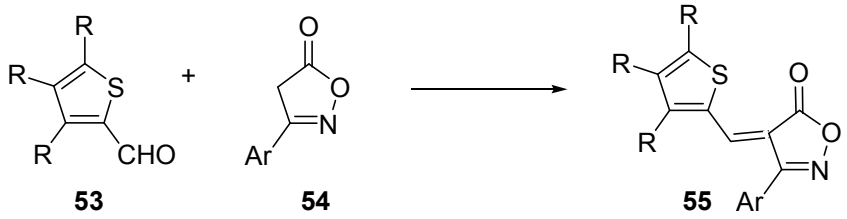
3.3. Synthetic approaches to 4-alkylideneisoxazol-5-ones

Also in the case of alkylideneisoxazol-5-ones no really new methods for their synthesis have been developed and classical procedures are still preferred. For example, the reaction of aldehydes **50** with β-dicarbonyl compounds **51** and hydroxylamine afforded products **52** (Scheme 22).[10]



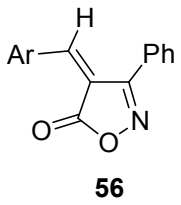
Scheme 22

To this one-pot procedure is sometimes to prefer another possibility, well known since long, which is the condensation of aldehydes, preferably aromatic, as **53** (Scheme 23), with isoxazol-5-ones **54** without substituting groups at C-4.[11]



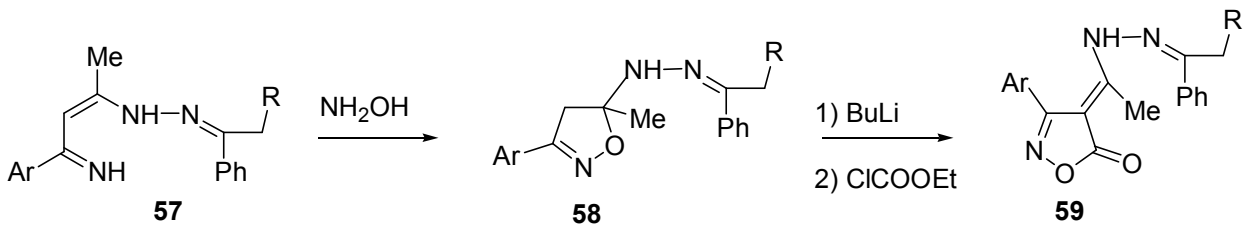
Scheme 23

Experimental enhancements have been found. 3-Phenylisoxazol-5-one and aromatic aldehydes were condensed to 3-phenyl-(4-arylmethylene)isoxazol-5-ones **56** (E isomers) in presence of Al_2O_3-KF without solvent under microwave irradiation (Scheme 24).[34]



Scheme 24

The reaction of hydrazones 57 with NH_2OH gave 5-hydrazono-4,5-dihydroisoxazoles **58** (Scheme 25). These compounds were transformed into isoxazol-5-ones **59** by treatment with BuLi and ethyl chloroformate, respectively.[35]

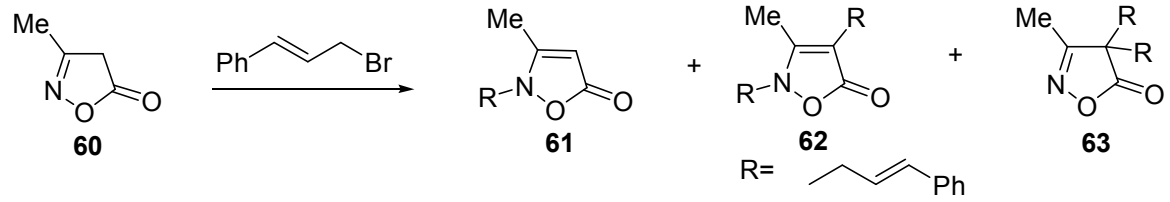


Scheme 25

4. Reactions of isoxazol-5-ones

4.1. *N*-, *O*- and *C*-alkylation and acylation of isoxazol-5-ones

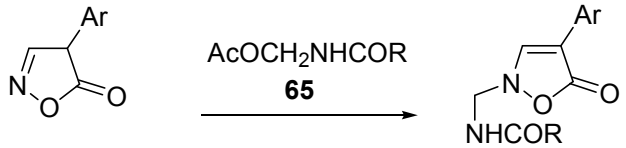
Alkylation and acylation of isoxazolones have been reported in several cases. As expected, three sites of attack are possible and more than one product may be formed. Surely, further studies are still necessary to clarify the rules governing the selectivity of this complicate reaction. In general, N-alkylation seems to be preferred. As an example, the allylation reaction of 3-methylisoxazol-5-one **60** using a Pd(0) catalyst gave very poor selectivity forming three products **61-63** (Scheme 26).[36]



60 **61** **62** **63**

Scheme 26

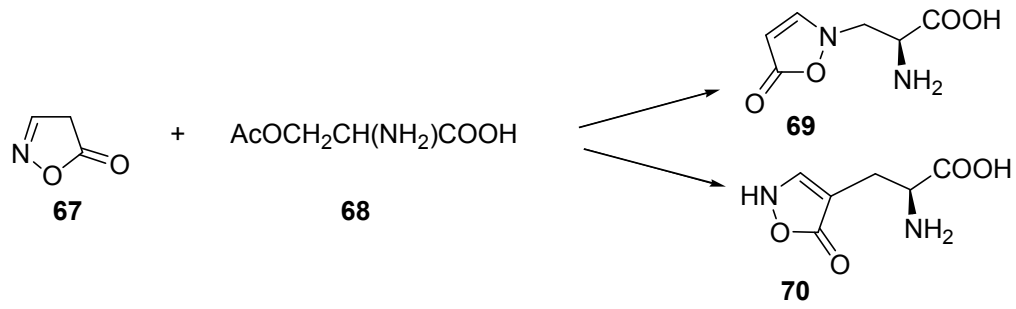
N-alkylation has been used for the preparation of isoxazol-5-ones bearing complex substituents at the nitrogen atom. Accordingly, compounds **66** were prepared from isoxazol-5-ones **64**, obtained by the method of Marchesini,[37] using *N*-alkylation with **65** (Scheme 27).[38]



64 **66**

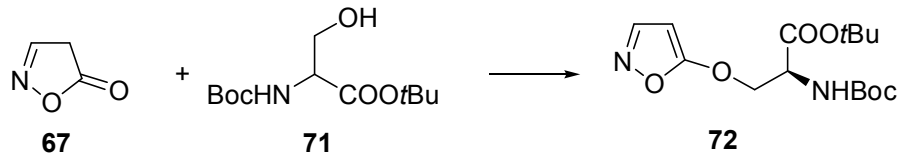
Scheme 27

An interesting and promising method to prepare both *N*- and *C*-alkylated compounds is by enzymatic route. *O*-Acetyl-L-serine **68** and isoxazolone **67** were made to react in presence of cysteine synthases purified from plants of the genus *Lathyrus* and afforded a mixture of the *N*- and *C*-alkylated isoxazol-5-ones **69**,**70** (Scheme 28).[39]



67 **68** **69** **70**

Scheme 28

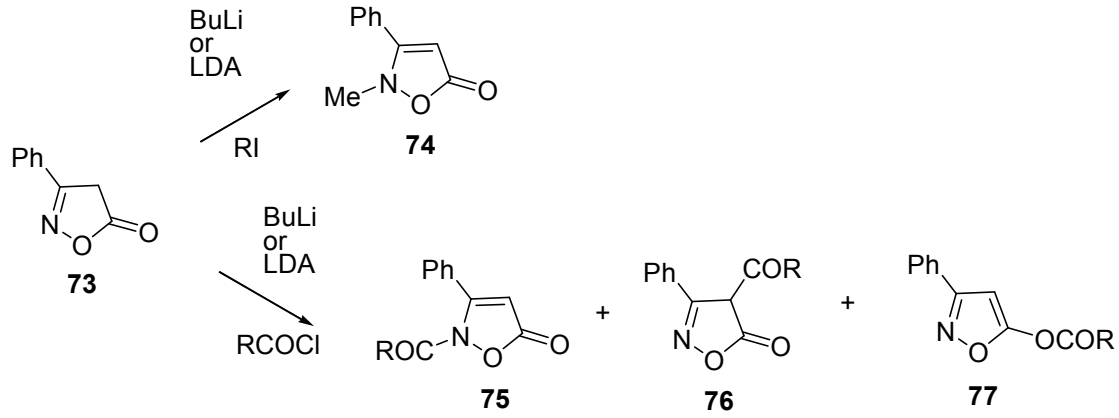


67 **71** **72**

Scheme 29

Isoxazol-5-one **67** reacted with *N*-Boc-L-serine *t*-butylester **71** according to the Mitsunobu reaction and gave the *O*-alkyl derivative **72** that was then transformed into the free acid (Scheme 29).[40]

3-Phenylisoxazol-5-one **73** afforded the corresponding lithium salt on reaction with BuLi or LDA. The salt gave with methyl iodide 2-methyl-3-phenylisoxazolone **74** (Scheme 30). Instead, acylation of the same lithium salts afforded a mixture of *N*-, *C*-4 and *O*-substituted derivatives **75**-**77** the former being estimated as the most aboundant.[41]

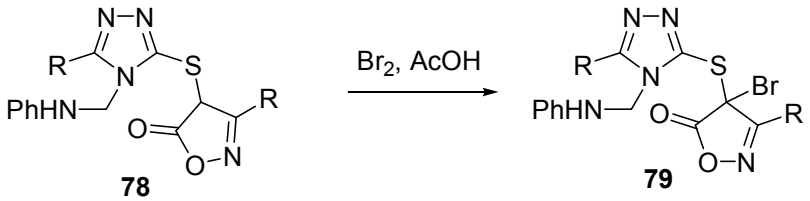


Scheme 30

Isoxazolones without substituting groups in position 4, such as **73**, can be acylated by acid chlorides, anhydrides or carboxylic acids in presence of carbodiimides to give both the *O*- and *N*-acylated products. Aliphatic acid anhydrides and chlorides generally reacted at nitrogen, but aroyl halides gave preferentially *O*-acylated products. The groups present at C-3 have great effect. Different conditions and presence of groups at C-3 may strongly influence the reaction.[42]

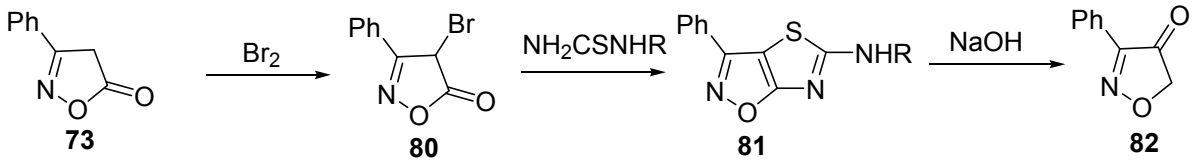
4.2. Halogenation reactions of isoxazol-5-ones

Isoxazol-5-ones without groups at C-4 were chlorinated with sulfuryl chloride or better with trimethylsilyl chloride in dimethylsulfoxide and gave the corresponding 4-chloro derivatives, useful starting materials for further conversion.[43] Ethyl 3-phenyl-isoxazol-5-one-4-carboxylate was readily brominated with bromine in apolar solvent to afford the corresponding 4-bromo derivative.[18] The substituted isoxazol-5-ones **78** were readily brominated by bromine in acetic acid (Scheme 31).[44]



Scheme 31

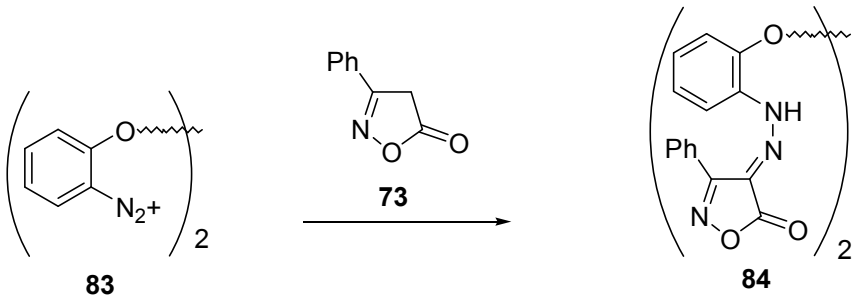
3-Phenyl-isoxazol-5-one **73** was brominated to afford 3-phenyl-4-bromoisoxazol-5-one **80** and made to react with thiocarbamide derivatives. Bicyclic heterocycles **81** were formed and on hydrolysis with sodium hydroxide the 4-isoxazolone **82** was obtained (Scheme 32). It is suggested that this cycle may be used to convert isoxazol-5-ones into isoxazol-4-ones.[45]



Scheme 32

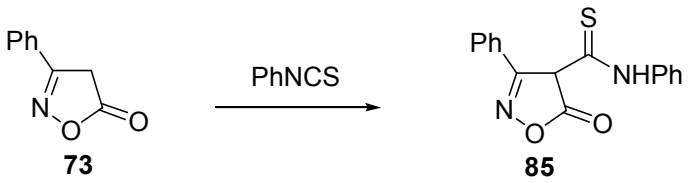
4.3. Reaction of isoxazol-5-ones with electrophilic reagents

The active methylene group of isoxazol-5-ones is one preferred reaction site for many electrophiles. For example, diazonium salts are reactive and an application is the synthesis of compounds **84** through condensation of **83** with 3-phenylisoxazol-5-one **73** (Scheme 33).[12]

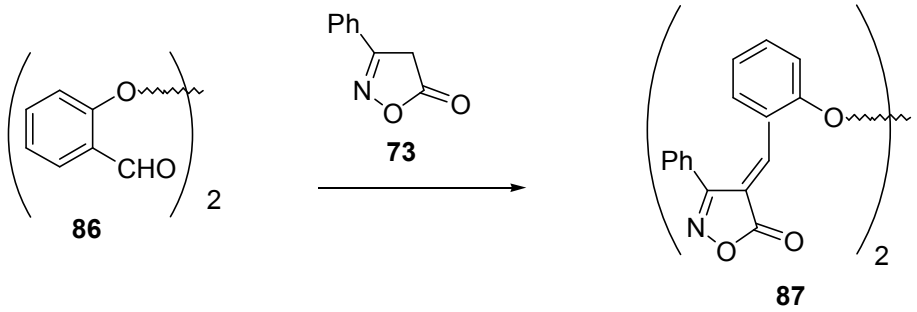


Scheme 33

The reaction of 3-phenyl-5-isoxazolone **73** with phenyl isothiocyanate in DMF/NaH afforded the corresponding thiocarbamoyl derivative **85** (Scheme 34).[46]



Scheme 34

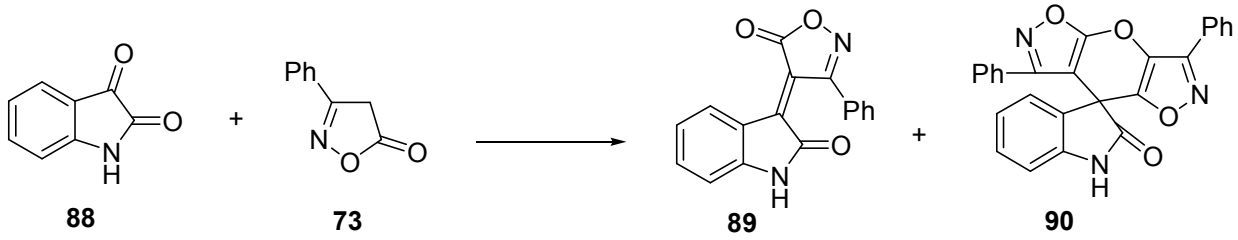


Scheme 35

As said previously (section 3.3.), the aldol condensation reaction of aldehydes and ketones is one of the most frequently encountered in the field of isoxazol-5-one chemistry. The very important alkylidenisoxazol-5-ones are formed, sometimes as intermediates in a more complex reaction pathway. A typical example (Scheme 35) of condensation is the synthesis of bis-difunctional compound of formula **87** containing two

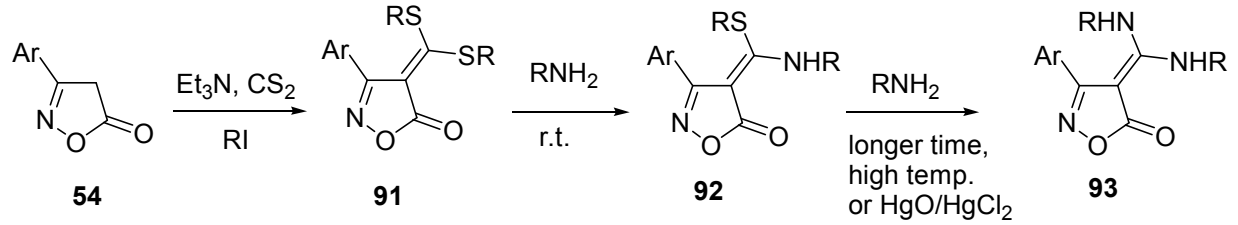
isoxazol-5-one moieties which were prepared by condensation of bis-aldehydes **86** with 3-phenyl-isoxazol-5-one **73**.[13]

New condensation techniques were found as in the case of 3-phenylisoxazol-5-one **73** which was condensed with aromatic aldehydes to obtain products of formula **56** in presence of Al_2O_3-KF without solvent and under microwave irradiation (the *E* isomer was formed) (Scheme 24).[34] Though less reactive, also ketones may be used as shown by the condensation reaction of **73** with isatin **88** in refluxing ethanol. Two reaction products were formed, the simple condensation product **89** being the major one. Besides, a lower amount of the spiranic compound **90** was detected (Scheme 36). A reasonable mechanism for its formation was proposed.[47]



Scheme 36

The base promoted reaction of isoxazol-5-ones with carbon disulfide in presence of alkylating agents is of interest because this route provides a relatively easy entry to compounds which bear in position 4 a methylene group having two hetero substituents. 3-Arylisoxazolones **54** were readily condensed with CS_2 in presence of base and alkylating agents affording the isoxazolones **91** (Scheme 37). Several cases were reported. The products containing two alkylthio groups were the starting materials for the preparation of compounds containing a *N*- and a *S*-substituent **92** or two *N*-substituents **93** which can be the same or different.[48,49]



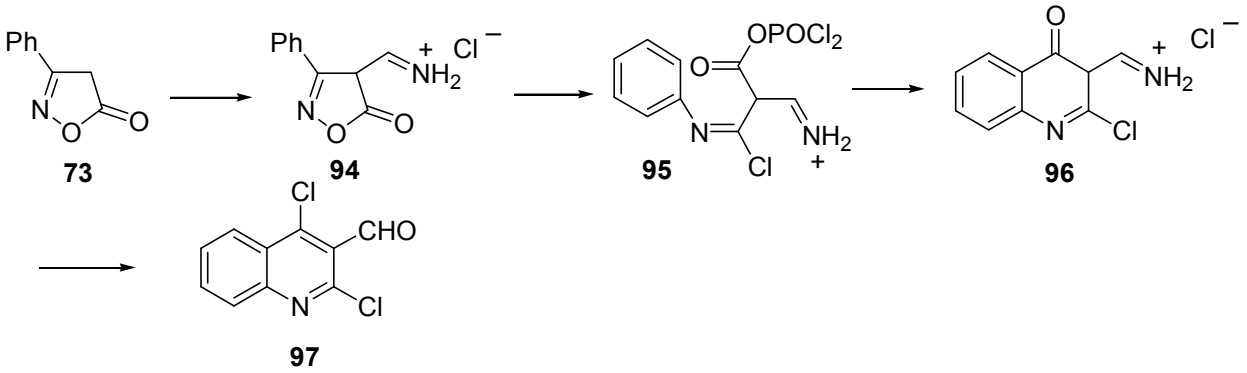
Scheme 37

4.4. Vilsmeier-Haack reaction of isoxazol-5-ones

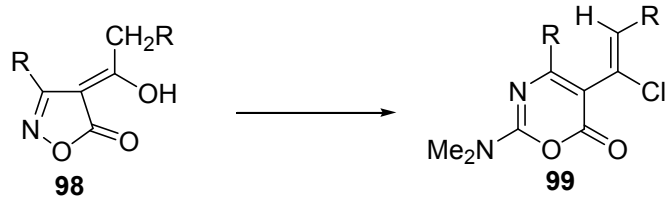
The Vilsmeier-Haack reaction on 3-phenyl-isoxazol-5-one **73** resulted in 2,4-dichloroquinoline-3-carbaldehyde **97** through a novel rearrangement. This reaction (Scheme 38) involved the transformation of the primary Vilsmeier-Haack product **94** which underwent heterolytic ring fission of the N-O bond of the isoxazolone and simultaneous migration of the phenyl group to the electron deficient nitrogen (Beckmann-type mechanism) followed by the attack of chloride ion to form **95**. Then, intramolecular attack of the phenyl group of **95** on the carbonyl group produced **96** and hydrolysis affords **97**.[50]

The Vilsmeier-Haack reaction was also applied to 4-(α-hydroxyalkylidene)isoxazol-5-ones **98**. When 2.5 mol. eq. of the Vilsmeier reagent were used, only one product was obtained, *i.e.* the corresponding 2-

dimethylamino-5(α-chloroalkenyl)-1,3-oxazin-6-ones **99** (Scheme 39). The *Z*-isomers were the exclusive or prevalent products.[51]



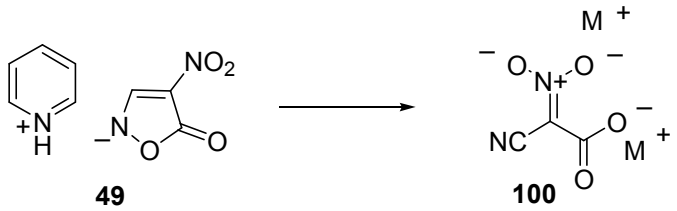
Scheme 38



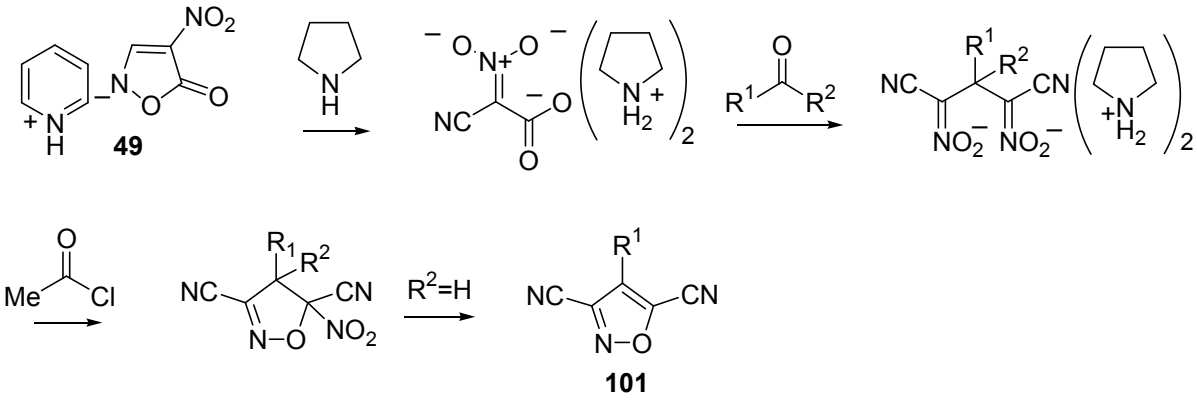
Scheme 39

4.5. 4-Nitroisoxazol-5-ones

A section is devoted to this interesting and accurately investigated class of isoxazol-5-one derivatives which are precursors or synthetic equivalents of useful reagents.



Scheme 40



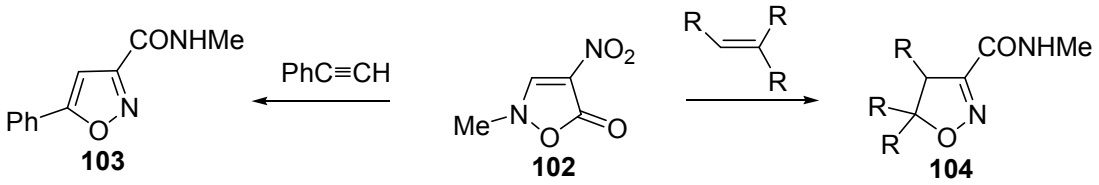
Scheme 41

The ring cleavage of the pyridinium salt of 4-nitroisoxazol-5-one **49** under mild basic conditions, for example tertiary amines, affords the aci-form of cyano-nitroacetate **100** (Scheme 40). The ring opened

product **100** has three different functional groups at the same carbon atom. Accordingly, it is an useful building block for the synthesis of poly-functionalised compounds.[52,53]

An application of this very useful reactant is in its participation to multistep reactions (Scheme 41). Thus, on reaction with acetone and acetyl chloride, isoxazole **101** was formed in fair yield.[53]

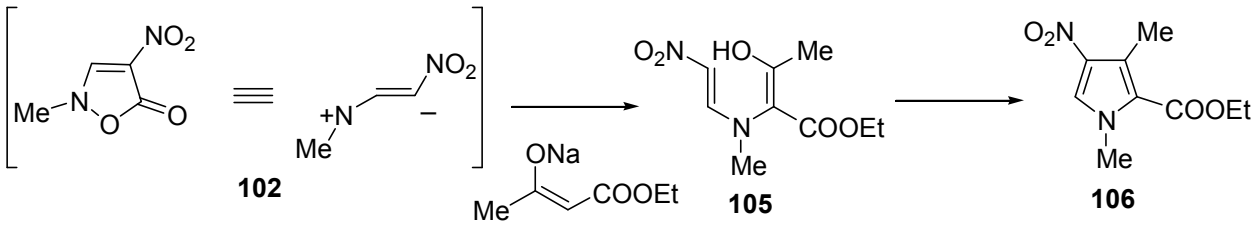
2-Methyl-4-nitro-3-isoxazol-5-one **102** is the precursor of a carbamoyl nitrile oxide. On reaction of **102** with phenylacetylene, the isoxazole **103** was obtained under controlled conditions (Scheme 42). Similarly, reaction of **102** with various alkenes produced substituted isoxazolines **104**.[54,55]



Scheme 42

Nitroisoxazolones are synthetic equivalents of dipolar nitroenamines (Scheme 43). The reaction of **102** with the enolate of ethyl acetoacetate at 70 °C produced nitropyrrole **106** in moderate yield. At lower temperature nitroenamine **105** was obtained as the main product. This is an useful and uncommon procedure to obtain nitroenamines which can be easily cyclised to pyrroles. The procedure was optimised.[56]

This synthetic scheme is applicable also to β-diketones.[57]



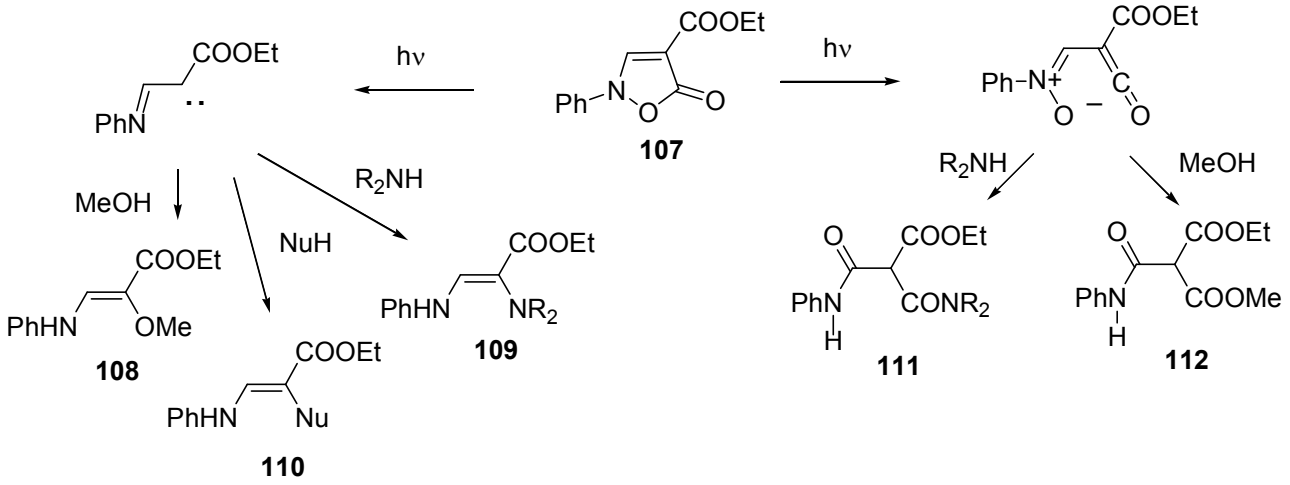
Scheme 43

4.6. Thermolysis and photolysis of isoxazol-5-ones

The photochemical fragility of the ring and the relatively easy elimination of carbon dioxide makes these heterocycles keen to decomposition under photochemical and thermal conditions. Thermal treatments were generally made by the technique of flash vacuum pyrolysis (FVP).

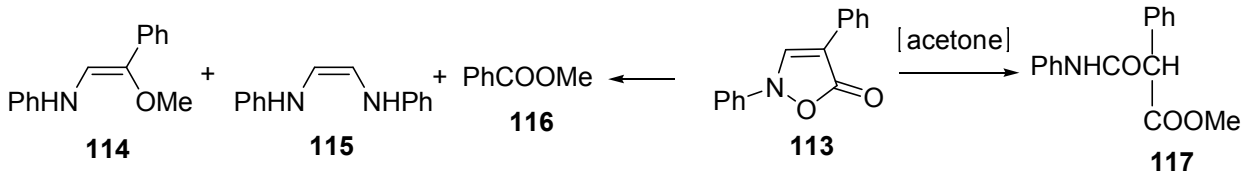
Photolysis of ethyl 2-phenylisoxazol-5-one-4-carboxylate **107** in alcohols and other nucleophilic reagents was studied. In Scheme 44 is reported the general mechanism of this reaction and the products obtained from isoxazolone **107**. The formation of an intermediate iminocarbene formed from loss of CO_2 was proposed together with the formation of an isomeric ketene. Carbene was trapped by methanol to give the final product *i.e.* acrylate **108**, whereas the ketene afforded the derivative of methanetricarboxylic acid **112**. When the photolysis of **107** was effected in presence of amines two different pathways were observed, both confirming the above mechanism. One pathway produced the isomeric ketene which was trapped as methanetricarboxylic acid amides **111**, the second afforded the carbene which was trapped as 2,3-diaminoacrylates **109**. A further development was through photolysis of **107** in middly acetic media. The

carbene was efficiently trapped by bromide, chloride, acetate, cyanate anions to give addition products **110**.[58-60]

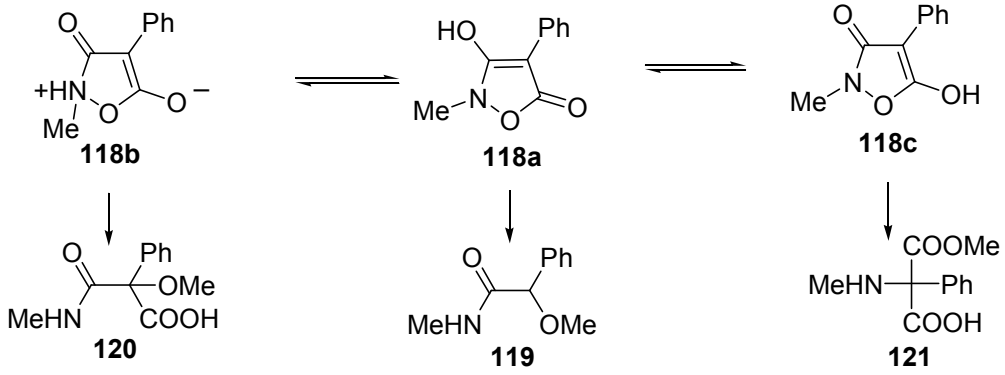


Scheme 44

An analogous outcome was obtained in the photolysis of 2,4-diphenylisoxazol-5-one **113** (Scheme 45). Three products were formed, *i.e.* compound **114** formed by capture of methanol by the carbene and compounds **115** and **116** arising from the ketene. The presence of acetone or other triplet sensitizers induced a third competitive pathway. This mechanism involves the triplet states and a new product **117** was formed in addition to those obtained previously.[61]



Scheme 45

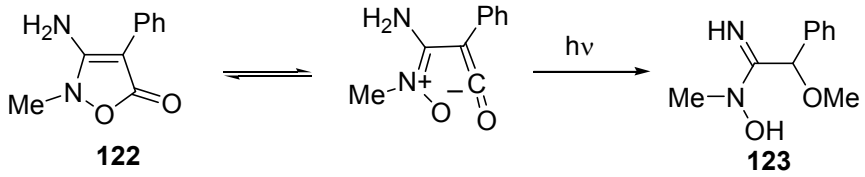


Scheme 46

Attention was paid to the photolysis of 3-hydroxyisoxazol-5-one **118a** (Scheme 46) which was found to follow a different pathway. The hydroxy group was involved in the photolytic process and a mixture of three products was obtained. The amide **119** was the product derived from the expected iminocarbene.

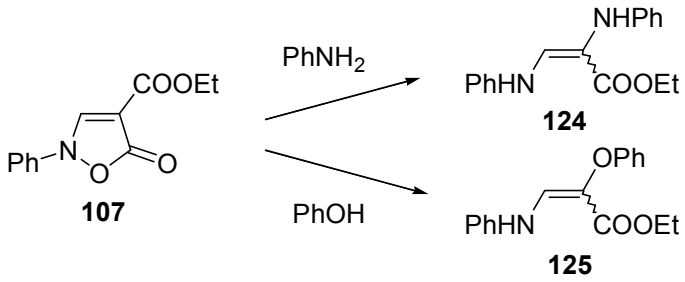
Instead, amino acids **120** and **121** were suggested to arise from the tautomers **118b** and **118c** from the well known valence bond isomerization of isoxazolones to aziridines, following thermolysis or photolysis and very likely by a concerted process.[62]

3-Aminoisoxazol-5-one **122** underwent photolysis to the nitronoketene isomer, giving amidine **123** after loss of CO (Scheme 47). The same material, on FVP, gave *N*-methylbenzamide.[63]



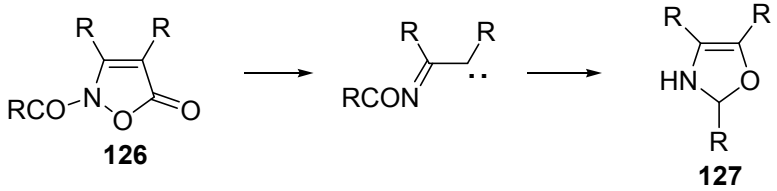
Scheme 47

Photolysis of **107** in presence of phenols, enols, anilines, enamines, aryl thiols and thioenols afforded enamines, for example **124**,**125**.[64]

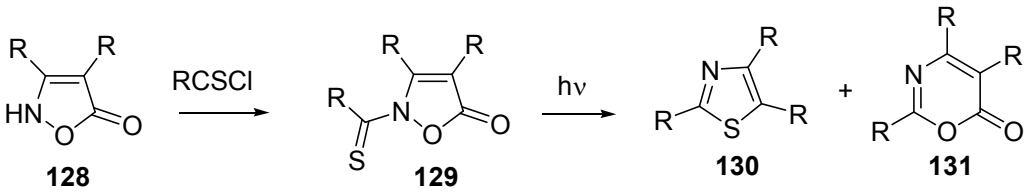


Scheme 48

The FVP or the photolysis of *N*-acylated isoxazol-5-ones **126** gave oxazolines **127** through CO_2 loss and formation of an iminocarbene intermediate which underwent an intramolecular cyclisation involving the oxygen of the acyl group (Scheme 49). Under photochemical conditions, acylisoxazolones with EWG at C-4 gave high yields of oxazolines, while those with electron donating groups at C-4 gave poor yields. A reverse behaviour was observed under thermal conditions.[65,66]



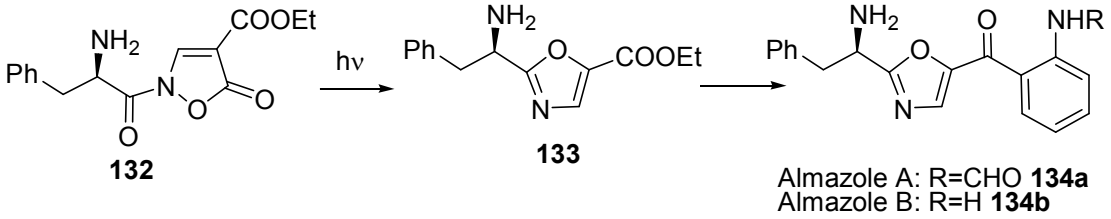
Scheme 49



Scheme 50

A related reaction is that of isoxazol-5-ones **128** with thiocarbonyl chlorides (Scheme 50) to afford *N*-thioacylisoxazol-5-ones **129**. Under photochemical conditions loss of CO_2 occurred. Intramolecular cyclisation of the iminocarbene afforded thiazoles **130**. When **128** had EWG, loss of CO_2 and sulfur resulted in the formation of 1,3-oxazin-6-ones **131**. This happened also if compounds **129** were reduced by Ph_3P. The mechanism was clarified.[67,68]

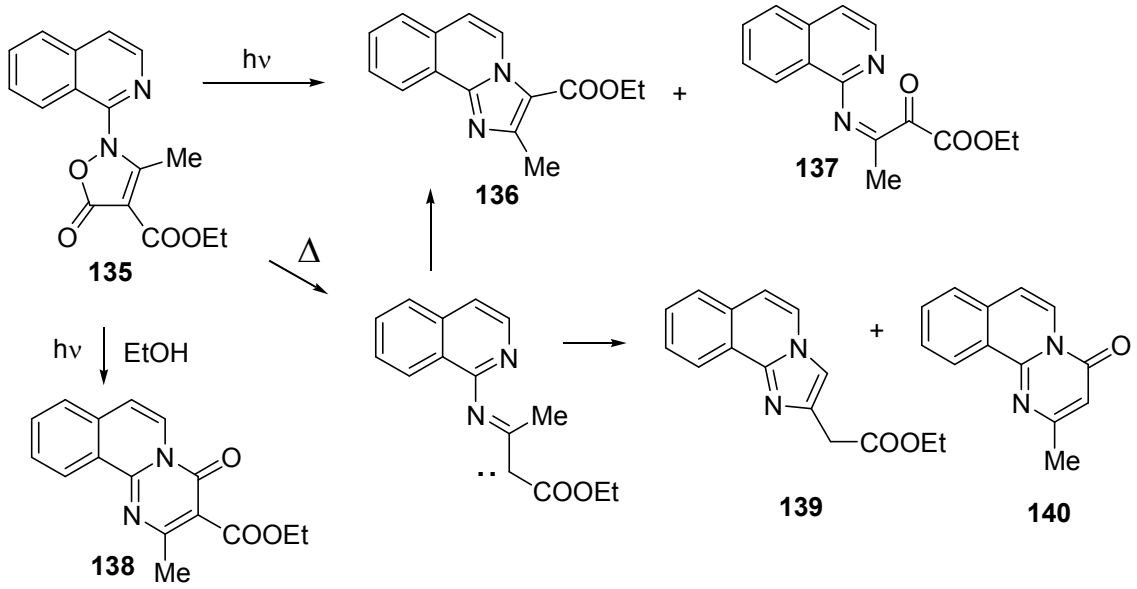
An application of the good reactivity of *N*-acylated isoxazol-5-ones was their use in the synthesis of almazole A and B **134a**,**b** *via* photochemical conversion of **132** into the corresponding oxazole **133** and further transformation.[69,70]



132 **133**

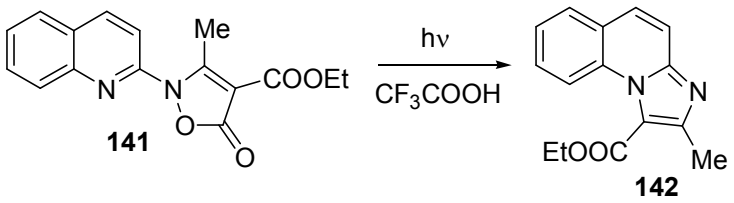
Scheme 51

An accurate study was made concerning the photolysis of the isoquinolinyl-isoxazolone **135** (Scheme 52) which gave the imidazo[2,1-*a*]isoquinoline derivative **136** and α-keto ester **137**. The ratio of products **136** and **137** was wavelength- and solvent-dependant. The photolysis of **135** in ethanol gave also pirimidine **138**. Pyrolysis of compound **135** gave as a major product **136** together with **139** and **140** *via* the carbene which reacted intramolecularly with the nucleophilic group or underwent insertion into CH bond.[71]



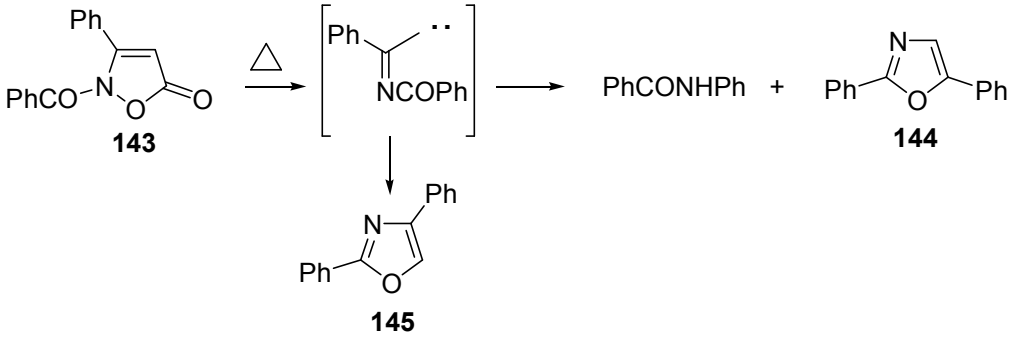
Scheme 52

If the photolysis was done in presence of trifluoroacetic acid the pathway involving the ketene was totally blocked and compound **141** gave the imidazole derivative **142** as the only product (Scheme 53). Possibly, the role of acid may be to speed up the reversion of the ketene to the isoxazolone, allowing the slower carbene formation to dominate. Another explanation is that the excited state of the isoxazolone ester is readily protonated leading to decomposition to the carbene and not to the ketene.[72]



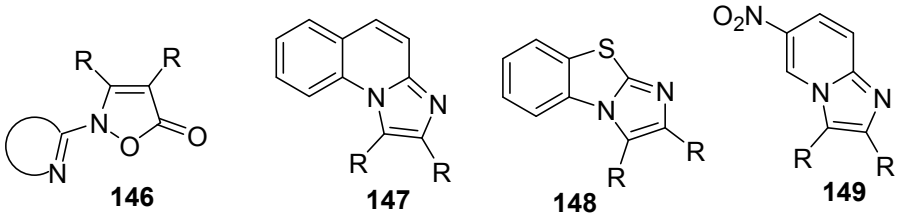
Scheme 53

When 2-benzoyl-3-phenylisoxazol-5-one **143** was heated at 600 °C both benzanilide and 2,5-diphenyl oxazole **144** were isolated in addition to the expected 2,4-diphenyloxazole **145**. Compound **144** could arise from a rearrangement of the intermediate carbene.[73]



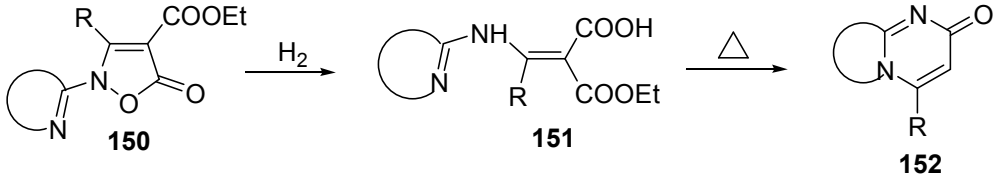
Scheme 54

FVP was applied to a number of 5-oxo-2,5-dihydroisoxazol-5-ones **146** (Scheme 55) substituted at N-2 with *N*-heterocycles including isoquinolines, quinolines, benzothiazoles, quinazolines, phenantridines, pirimidines and pyridines. Annulated imidazoles, *e.g.* **147**-**149**, were produced in excellent yields.[74]



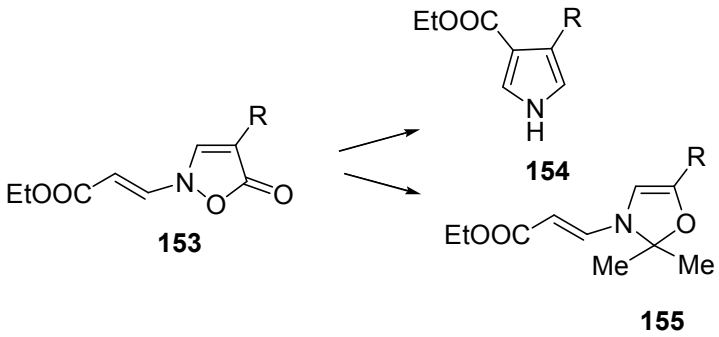
Scheme 55

Related isoxazolones **150** were first hydrogenated to give 3-aminoacrylates bearing a *N*-heterocyclic substituent **151** and then submitted to FVP. This method afforded the pyrimidine-annulated heterocycles **152** (Scheme 56).[75]



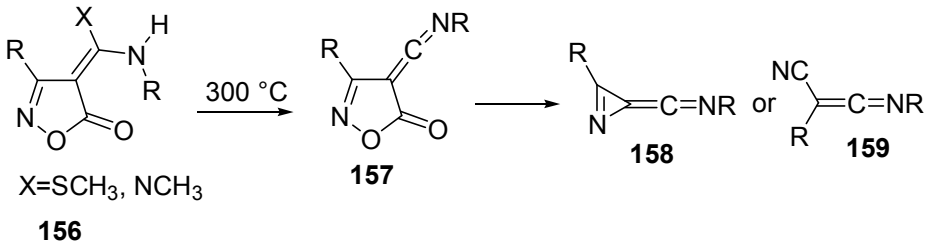
Scheme 56

Some *N*-alkenylisoxazol-5-ones **153** have been pyrolysed to form pyrroles **154**, through a carbene intermediate (Scheme 57). Also, photolysis in acetone gave the same carbene captured by the solvent to give **155** or the pyrrole products.[76]



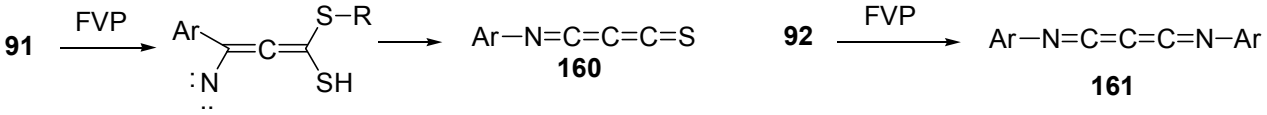
Scheme 57

FVP of isoxazol-5-ones **156** (Scheme 58) led to the formation of ketenimine intermediates **157** (isolable if bearing highly crowded groups) from which extrusion of CO_2 at higher temperatures formed keteneiminoazirines **158** or cyanoketeneimines **159** *via* a diradical or a nitrene.[77]



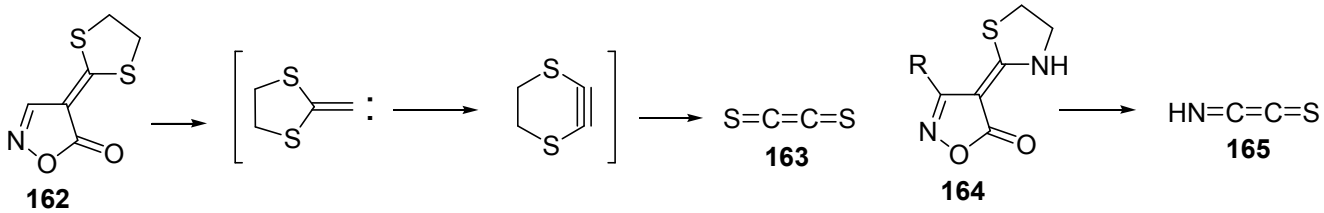
Scheme 58

The use of isoxazol-5-one as precursors of cumulenes or heterocumulenes is still an active field. Compounds of formula **91** were useful as precursors of labile iminopropadienetiones **160** (Scheme 59). When subjected to FVP they afforded an unstable nitrene intermediate which, according to a series of rearrangements, produced the expected **160**. Similarly, starting from the nitrogen-containing analogues **92**, bis-iminopropadienes **161** could be obtained.[48,49]



Scheme 59

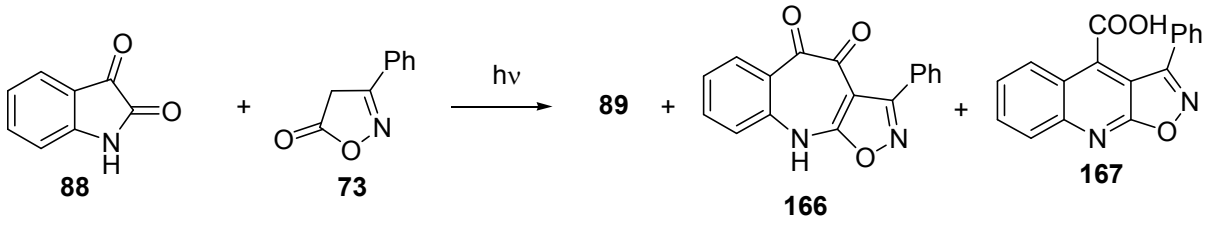
FVP of compound **162** (Scheme 60) gave cumulene **163** with the mechanism indicated. Similarly, the analogous nitrogen derivative **165** was obtained by FVP from isoxazolone **164**.[78]



Scheme 60

The reaction between isatin **88** and isoxazolone **73** was carried out under photochemical irradiation (Scheme 61) and products **166** and **167** were formed besides **89**. Product **166** was explained by condensation

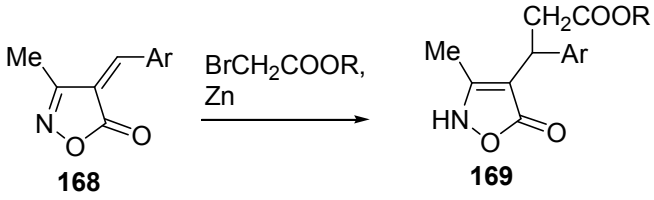
of isatic acid deriving from the photochemical decomposition of isatin with the enol of the isoxazolone while **167** derived from isatic acid on reaction with the methylene group of **73**.[47]



Scheme 61

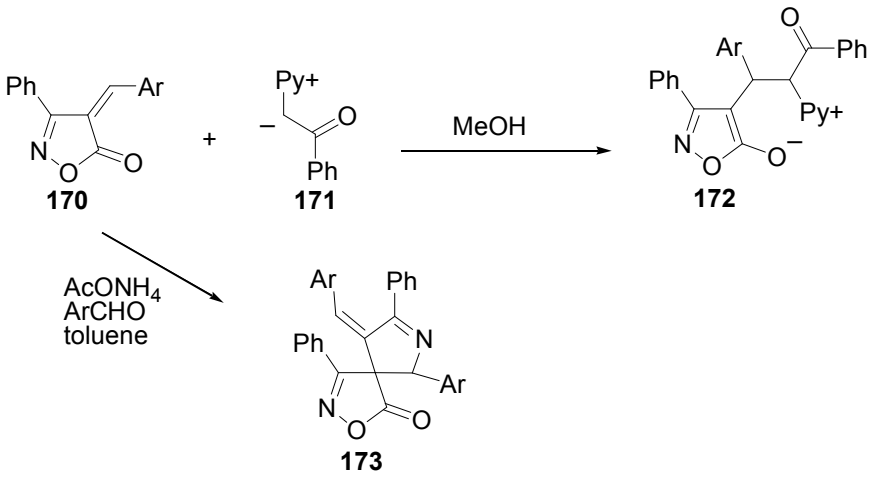
4.7. Michael additions of ylides to arylmethyleneisoxazol-5-ones

Reaction of 4-arylmethylene-3-methylisoxazol-5-ones **168** with ethyl bromoacetate in presence of zinc (Scheme 62) afforded 1,4-addition products **169**. In no case the carbonyl group of the lactone participated in the reaction.[79]



Scheme 62

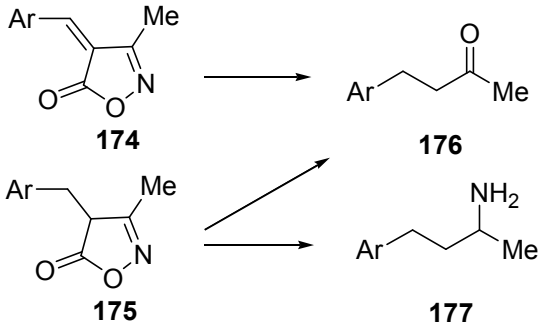
Isoxazolones **170** were made to react with pyridinium ylide **171** generated *in situ* (Scheme 63) in methanol. The reaction produced the olates **172** in good yields. Two mechanisms were considered, *i.e.* Michael addition of ylide to substrate or cycloaddition followed by ring cleavage. When the reaction was done in benzene or toluene at reflux with ammonium acetate and aryl aldehyde, spirans **173** were formed.[80,81]



Scheme 63

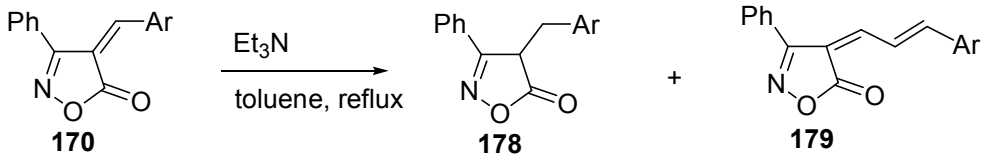
4.8. Reduction of arylmethyleneisoxazol-5-ones

Different results were obtained in the hydrogenation of isoxazol-5-one derivatives, for example compounds **174** and **175** gave butanones **176** with H_2, Pd/C in AcOH, whereas from **175** butanamines **177** were formed by H_2, Raney Ni in MeOH.[82]



Scheme 64

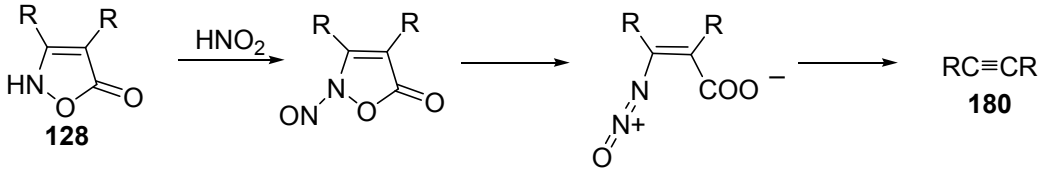
4-Arylmethyleneisoxazol-5-ones **170** were reduced by a new and mild method using tertiary amines able to act as hydrogen donors as triethylamine or other tertiary amines (Scheme 65). In refluxing toluene 4-arylmethyl-isoxazol-5-ones **178** were formed in satisfactory yields. Besides the reduced compounds the reaction afforded also chain lengthened products, *i.e.* the cynnamylidene compounds **179**.[5]



Scheme 65

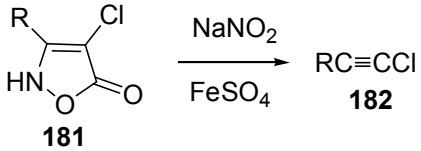
4.9. Alkynes from isoxazol-5-ones

Acetylenes have been obtained occasionally from isoxazol-5-ones, as in the case of the pyrolytic cleavage of 3-phenyl-4-(2-methoxybenzylidene)-isoxazol-5-one which afforded a mixture of products, among them 2-methoxyphenylacetylene.[83] However, far more interesting is the intended use to produce alkynes from isoxazol-5-ones which are powerful starting materials. The existing methods have been enhanced and applied to important cases. The reaction of isoxazol-5-ones **128** with $NaNO_2$ and $FeSO_4$ in AcOHaq. afforded acetylenes **180** in moderate to good yield (Scheme 66). Nitrosation at the N atom produced the *N*-nitroso compound which underwent ring scission and loss of CO_2 and N_2O to give the acetylene.[84-86] This is especially suited for the synthesis of large-ring acetylenes.[85]



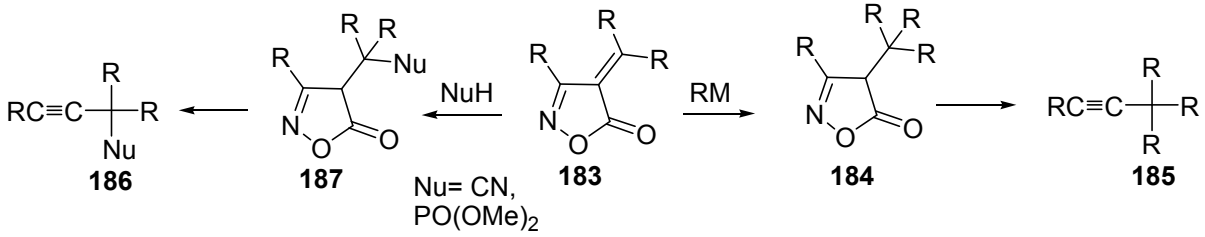
Scheme 66

The 4-chloro derivatives **181** are useful starting materials for conversion into 1-chloroalkynes **182** upon treatment with $NaNO_2$ and $FeSO_4$ in AcOHaq (Scheme 67).[43]



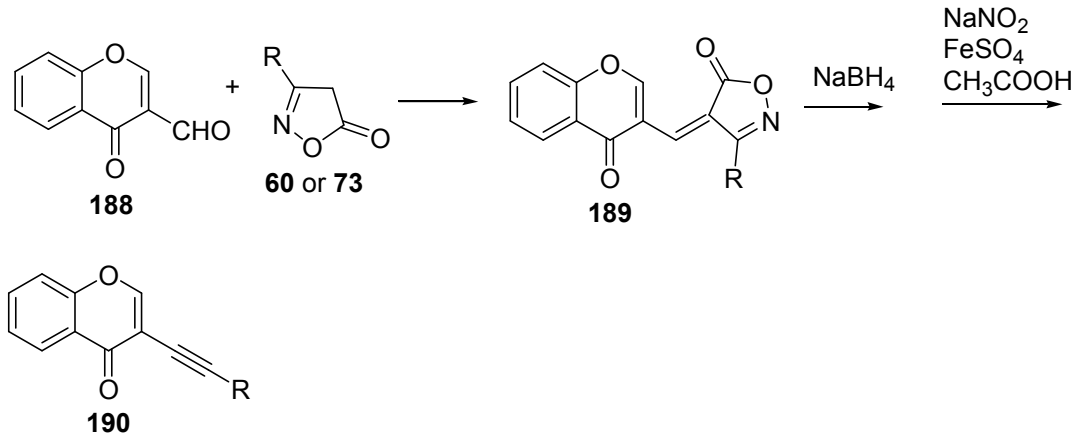
Scheme 67

α-Branched alkynes **185**, **186** can be easily assembled (Scheme 68) by a Knoevenagel-type condensation of 4-unsubstituted isoxazol-5-ones with aldehydes or ketones, giving **183,** followed by conjugate addition of an organometallic reagent, giving **184**, or another nucleophile, giving **187**, followed by nitrosative cleavage of the heterocyclic ring.[87,84]



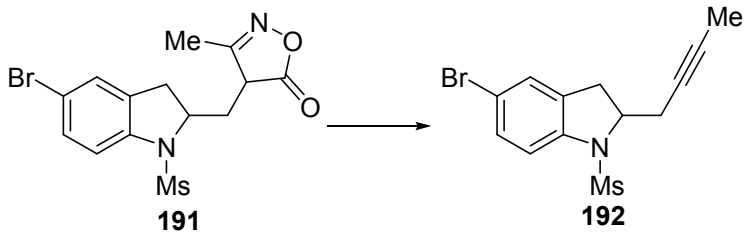
Scheme 68

The problem of the difficult preparation of alkynyl heterocycles has been satisfactorily solved by this method. 3-Alkynylchromones **190** were obtained (Scheme 69) by condensing aldehyde **188** with 3-methyl or 3-phenylisoxazol-5-one **60** or **73** to produce the corresponding alkylidene derivatives **189**, reducing with $NaBH_4$ according to the method of Marchesini[86] and reacting with $NaNO_2$ and $FeSO_4$.[88]



Scheme 69

Similarly, alkynyldihydroindole **192** was obtained from the corresponding isoxazolone **191**.[89]

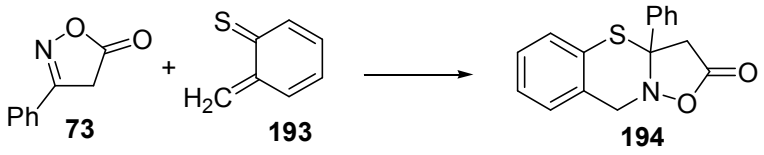


Scheme 70

4.10. Cycloaddition reactions

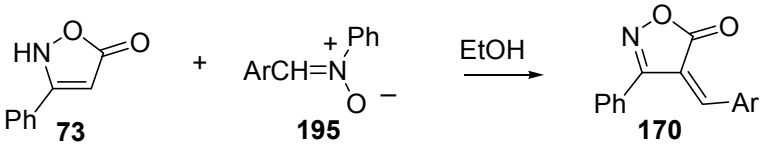
A variety of cycloaddition reactions have been reported in which isoxazol-5-ones or their methylene derivatives are involved. Isoxazol-5-one **73** (among with other heterocycles with a C=N bond) was studied

in the reaction with benzothiete 193 (Scheme 71). A [8π + 2π] cycloaddition yielded 1,3-benzothiazine derivative **194**.[90]



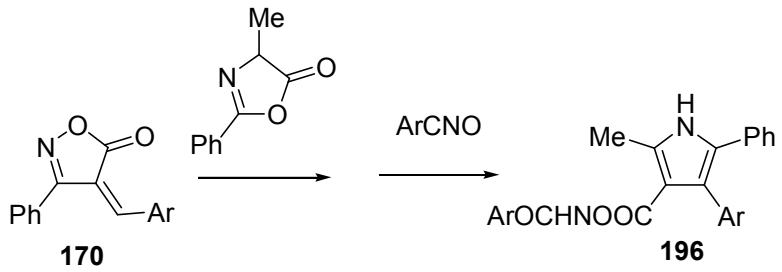
Scheme 71

The reaction of **73** (Scheme 72) with nitrones **195** afforded 4-(arylmethylene)-3-phenylisoxazol-5-ones **170** and PhNHOH. The formation of **170** was assumed to proceed *via* an initial 1,3-dipolar cycloaddition of the nitrone to the double bond of **73** to give an intermediate which underwent transformation into **170** by elimination of PhNHOH.[91]



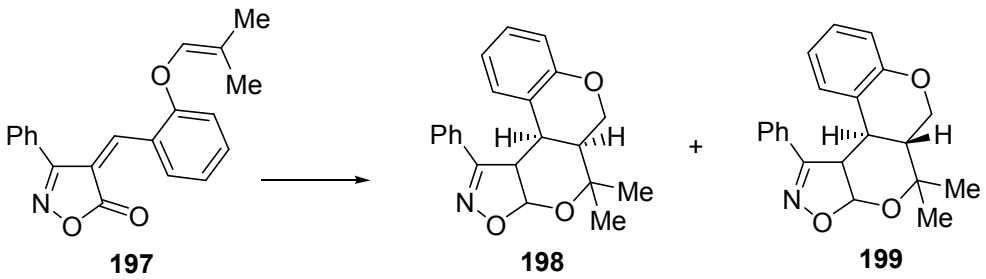
Scheme 72

From 4-arylmethyleneisoxazol-5-ones **170** and using sequential 5-oxazolone and nitrile oxide cycloaddition (Scheme 73), the regioselective synthesis of 3-pyrrolyl hydroxamates **196** may be achieved.[92]



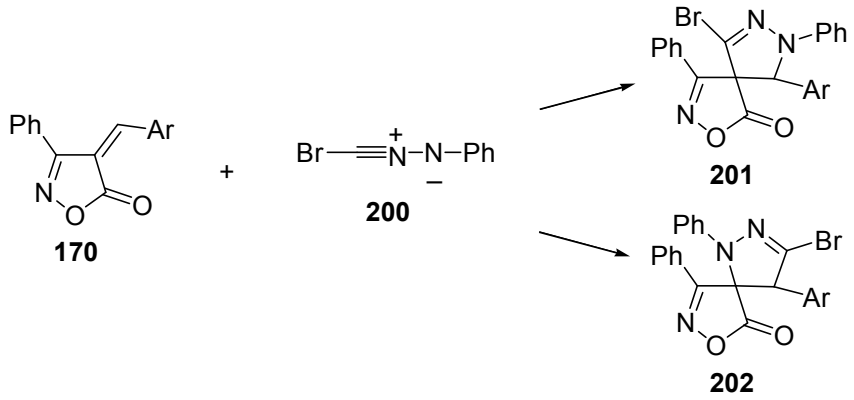
Scheme 73

The intramolecular hetero-Diels-Alder reaction of isoxazol-5-one **197** was studied at high pressure up to 5 kbar and gave adducts **198** and **199** (Scheme 74). A clear pressure-induced increase in diastereoselectivity was observed. High pressure favors endo transition states and the formation of the *cis* product **198**.[93]



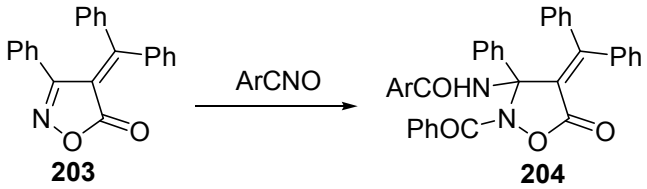
Scheme 74

C-Bromo-*N*-phenylnitrilimine **200** reacted with **170** affording the corresponding cycloaddition products **201** and **202** (Scheme 75). Stereochemical control was good and the regiochemistry was in agreement with the expected one on the basis of theoretical considerations.[94]



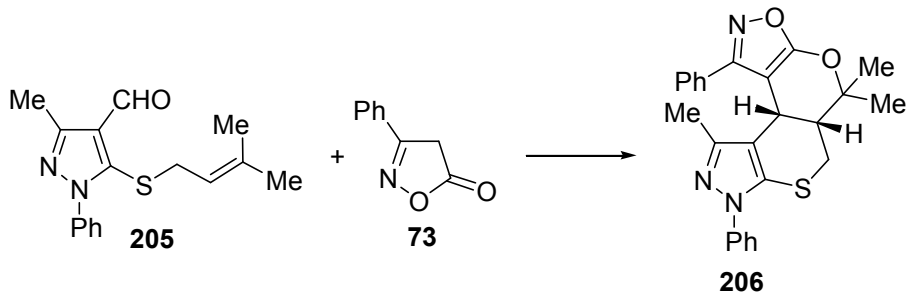
Scheme 75

It is known since long that disubstituted methyleneisoxazolones which can give prototropic tautomerism undergo a cycloaddition reaction with nitrile oxides through the NH-tautomer. 4-Diphenylmethylene-3-phenylisoxazol-5-one **203**, incapable of prototropic tautomerism, afforded with nitrile oxides a new reaction path (Scheme 76) yielding, although with poor yield and besides other products, compounds **204**.[95]



Scheme 76

The Tietze process of domino Knoevenagel condensation/intramolecular *hetero*-Diels-Alder cycloaddition was successfully applied (Scheme 77) to the synthesis of the tetracyclic heterocycle **206** starting from aldehyde **205** which was condensed with isoxazolone **73**.[96]



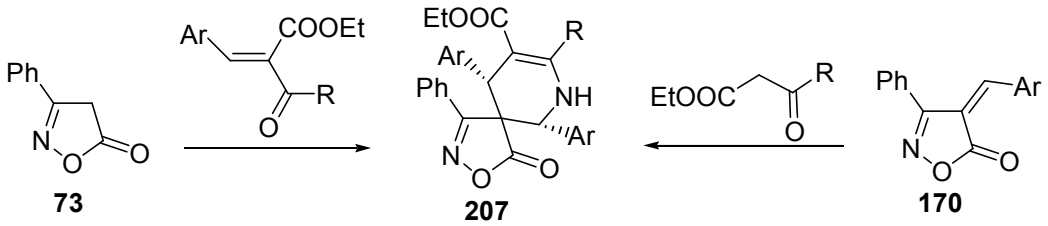
Scheme 77

5. Heterocycles from isoxazol-5-ones

In the field of heterocyclic rings transformations, many syntheses of different heterocyclic systems starting from isoxazol-5-ones were reported. Recent results confirm that this heterocyclic system is a

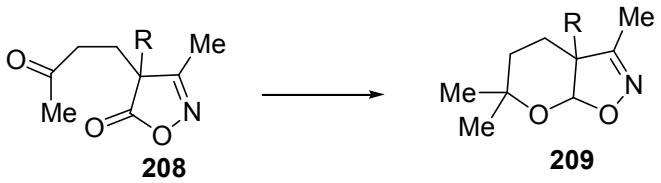
powerful tool in heterocyclic synthesis. Owing to the great variety of products it is not easy to classify the reactions leading to heterocycles. Very generally, two classes exist, *i.e.* formation of compounds in which the isoxazolone ring is mantained and, more interesting, the formation of different heterocycles by rearrangement.

3-Phenylisoxazolone **73** was reacted with α,β-unsaturated carbonyl compounds in presence of aryl aldehydes and ammonium acetate (Scheme 78) affording spirotetrahydropyridine-3-carboxylates **207**. The products were also obtained from arylideneisoxazol-5-ones **170** and β-ketoesters. This was a tandem process firstly involving Michael addition of isoxazolone to olefin to give an open-chain intermediate followed by ring-closure. The reaction showed high diastereoselection.[97]



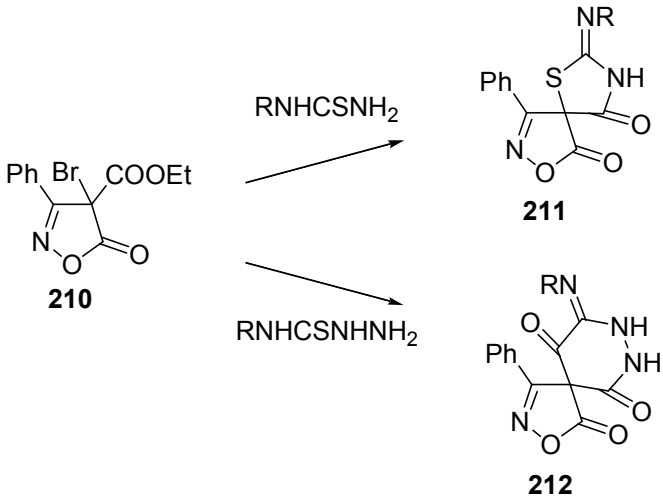
Scheme 78

Similar results were obtained starting from chalcones.[98] Derivatives of pyrano[3,2-*d*]isoxazolines (**209**) were obtained by intramolecular cyclisation. Compounds **208** were reacted sequentially (Scheme 79) with MeMgBr, $NaBH_4$ and BF_3 yielding **209**.[99]



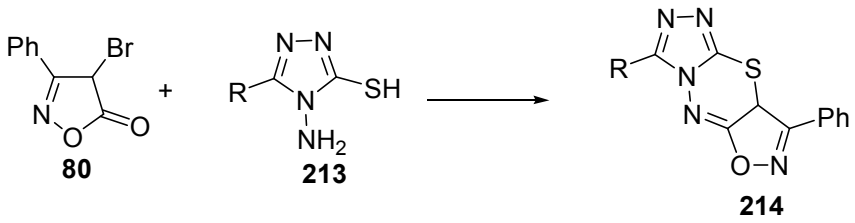
Scheme 79

4-Bromoisoxazol-5-one **210** reacted with substituted thioureas or thiosemicarbazides giving **211** and **212**, respectively (Scheme 80).[18]



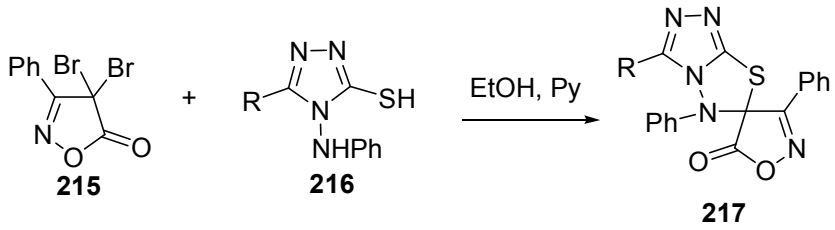
Scheme 80

Another application (Scheme 81) of brominated isoxazolones was the condensation between **80** and 1,3,4-triazoles **213** which easily afforded compounds **214**.[44]



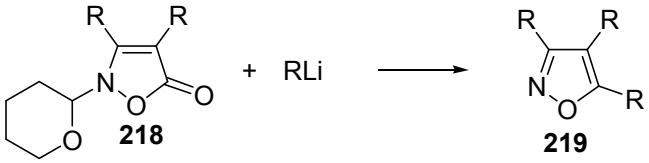
Scheme 81

The dibromo compound **215** was condensed with 1,3,4-triazoles **216** and produced in one step the condensation products **217** (Scheme 82).[44]



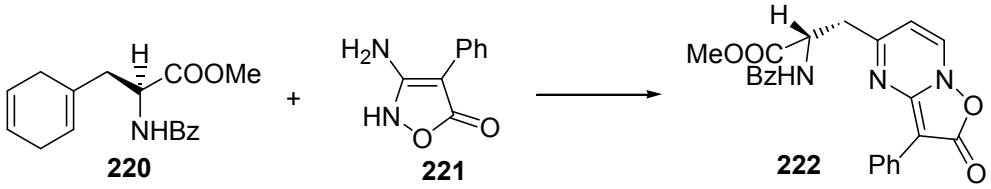
Scheme 82

The reaction of N-protected 3,4-disubstituted isoxazol-5-ones **218** with alkyl- and aryllithium compounds gave through the ring opening, after acidic work-up, the corresponding tri-substituted isoxazoles **219** in very good yields (Scheme 83).[100]



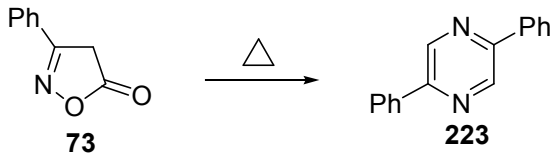
Scheme 83

The reaction of the ozonolysis compounds derived from **220** with 3-amino-4-phenylisoxazol-5-one **221** gave the condensed heterocycle **222** (Scheme 84), from which useful amino acid derivatives could be obtained.[101]



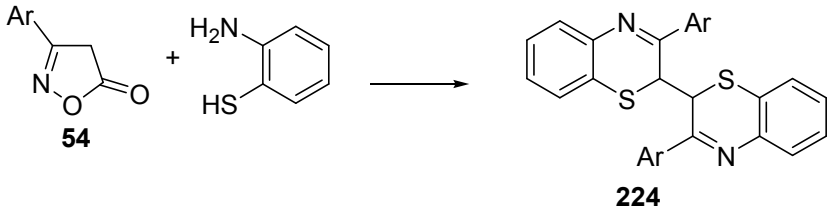
Scheme 84

The following examples belong to the second class, in which the isoxazolone ring is cleaved and rearranged to give different heterocyclic systems. The simplest result (Scheme 85) was the obtaining of 2,5-diphenylpyrazine **223** on pyrolysis of 3-phenylisoxazol-5-one **73**.[102]



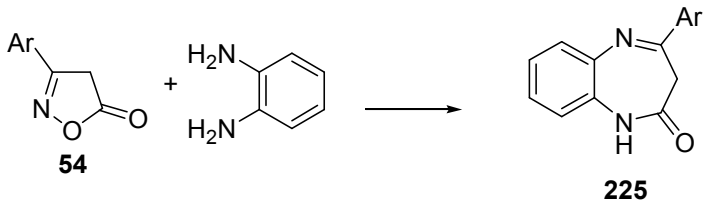
Scheme 85

1,4-Benzothiazines **224** were obtained starting from 3-arylisoxazol-5-ones **54** and 2-aminothiophenol (Scheme 86). The nucleophilic attack of the amino group at C-3 was the starting step.[103]



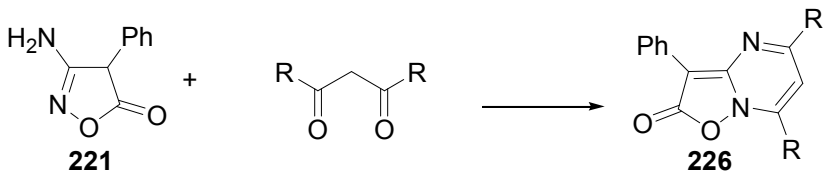
Scheme 86

Differently, the same substrates **54** reacted with 1,2-benzenediamine under acidic conditions through a nucleophilic attack of the amino group at C-5 (Scheme 87). 4-Arylbenzodiazepin-2-ones **225** were obtained and substituted 2-methylbenzimidazoles as minor products. An oxime intermediate was formed which then underwent ring closure.[4,104]



Scheme 87

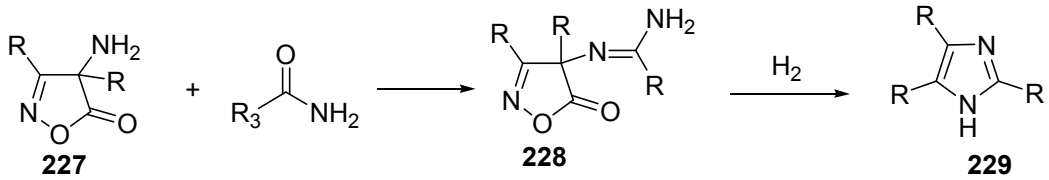
The reaction of 3-aminoisoxazol-5-one **221** with 1,3-dicarbonyl compounds under acid catalysis (Scheme 88) gave isoxazolo[2,3-*a*]pyrimidine derivatives **226**.[105]



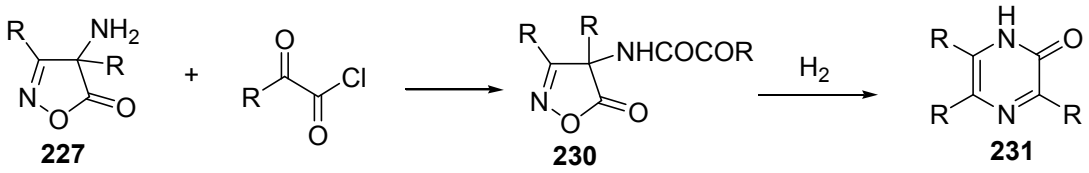
Scheme 88

4-Aminoisoxazol-5-ones **227**, easily obtained from the corresponding isoxazolones, can be used to prepare imidazoles, pyrrolo[2,3-*d*]isoxazoles and pyrazin-2-ones (Scheme 89 and 90). For example, the reaction of **227** with dimethylformamide or acetamide gave the corresponding amidines **228** which, on catalytic hydrogenation, afforded imidazoles **229**, *via* hydrogenolysis of the N-O bond, decarboxylation, intramolecular cyclisation and elimination of dimethylamine. In the case of acetamidines heating under reflux in dioxane solution produced cyclisation to pyrrolo[2,3-*d*]isoxazole derivatives.[106]

Reaction of **227** with 2-oxoacid chlorides afforded the corresponding α-oxoacid amides **230** (Scheme 90). On catalytic hydrogenation in presence of Lindlar catalyst in ethanol tri-substituted pyrazin-2-ones **231** were formed.[107]

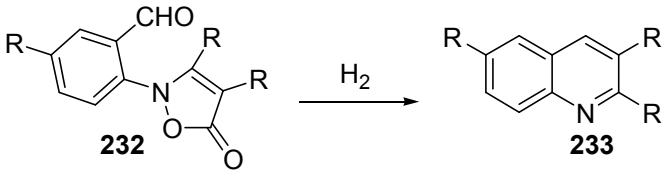


Scheme 89



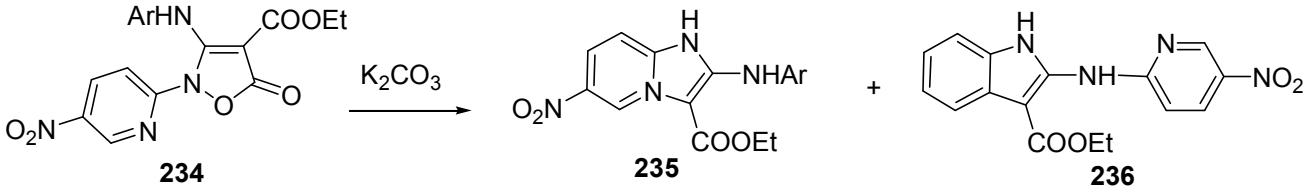
Scheme 90

Nucleophilic addition of 5-substituted-2-fluorobenzaldehydes to 3,4-disubstituted isoxazol-5-ones afforded the corresponding N-arylated products **232** (Scheme 91). On catalytic hydrogenation of these with Pd/C in ethanol 2,3,6-trisubstituted quinolines **233** were formed *via* N-O hydrogenolysis, decarboxylation and intramolecular ring closure of an enamine intermediate.[108]



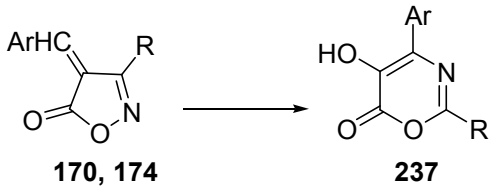
Scheme 91

2-Aryl-3-arylaminoisoxazol-5-ones **234** underwent solvolysis to form 1,3-dipoles that gave intramolecular cyclisation (Scheme 92). Besides indoles **236**, imidazo[1,2-*a*]pyridine derivatives **235** were isolated as second products. The ratio of products is controlled by the electronegativity of the aryl substituents. FVP and photochemical rearrangement showed a similar behaviour.[109,110]



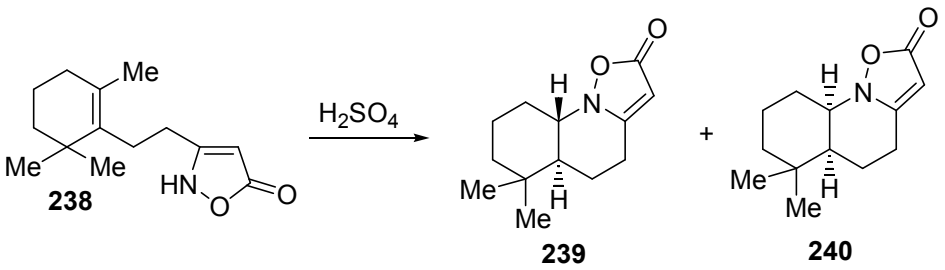
Scheme 92

The synthesis (Scheme 93) of 5-hydroxy-1,3-oxazin-6-ones **237** starting from 4-arylideneisoxazol-5-ones **170**,**174** *via* epoxidation with *t*-butylhydroperoxide and thermal rearrangement of the epoxydation products was reported.[111]



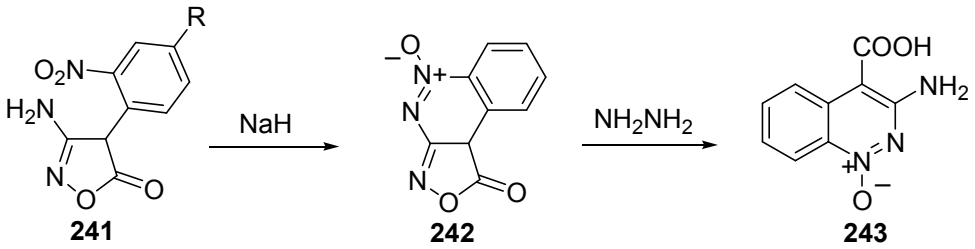
Scheme 93

Reaction of 3-(2-cyclohexenyl)ethylisoxazol-5-one **238** with H_2SO_4 (2 mol.eq.) afforded the two diastereomeric tri-cyclic products **239** and **240** (Scheme 94). This unexpected preference for ring closure *via* formation of a C-N bond is of synthetic interest giving an access to nitrogen heterocycles by acid-mediated cyclisation which is generally precluded by the preferential protonation of the amino group.[112]



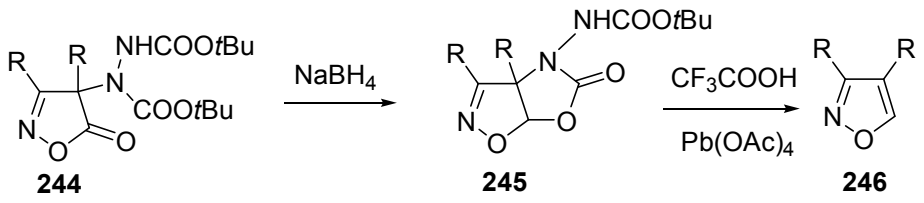
Scheme 94

The treatment of 3-amino-4-(2-nitroaryl)isoxazol-5-ones **241** with NaH (Scheme 95) gave ring closure through aldol-like condensation between the amino and nitro substituents to afford isoxazolo[3,4-*c*]cinnolin-1-one 5-oxide **242**. Chemoselective reductive cleavage with NH_2NH_2 of the isoxazolone ring in this heterocycle allowed an efficient synthesis of 3-aminocinnoline-4-carboxylic acid 1-oxide **243**.[113]

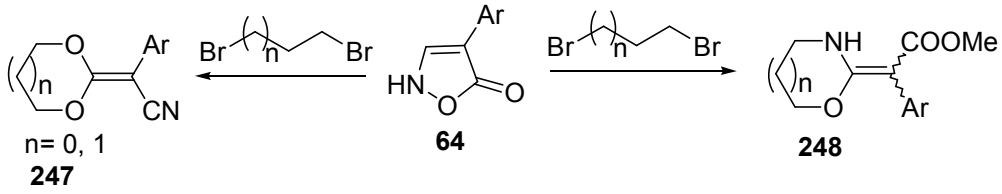


Scheme 95

The reaction of 3,4-disubstituted isoxazol-5-ones **128** with di-t-butyl azodicarboxylate under catalysis by triethylamine gave the corresponding 4,4-disubstituted isoxazol-5-ones **244** (Scheme 96). $NaBH_4$ afforded reduction of the carbonyl group. The intermediate 5-hydroxyisoxazolines were not isolable and cyclised to the oxazolo[4,5-*d*]isoxazole ring systems **245**. These compounds can be transformed into the corresponding isoxazole derivatives **246**.[114]



Scheme 96

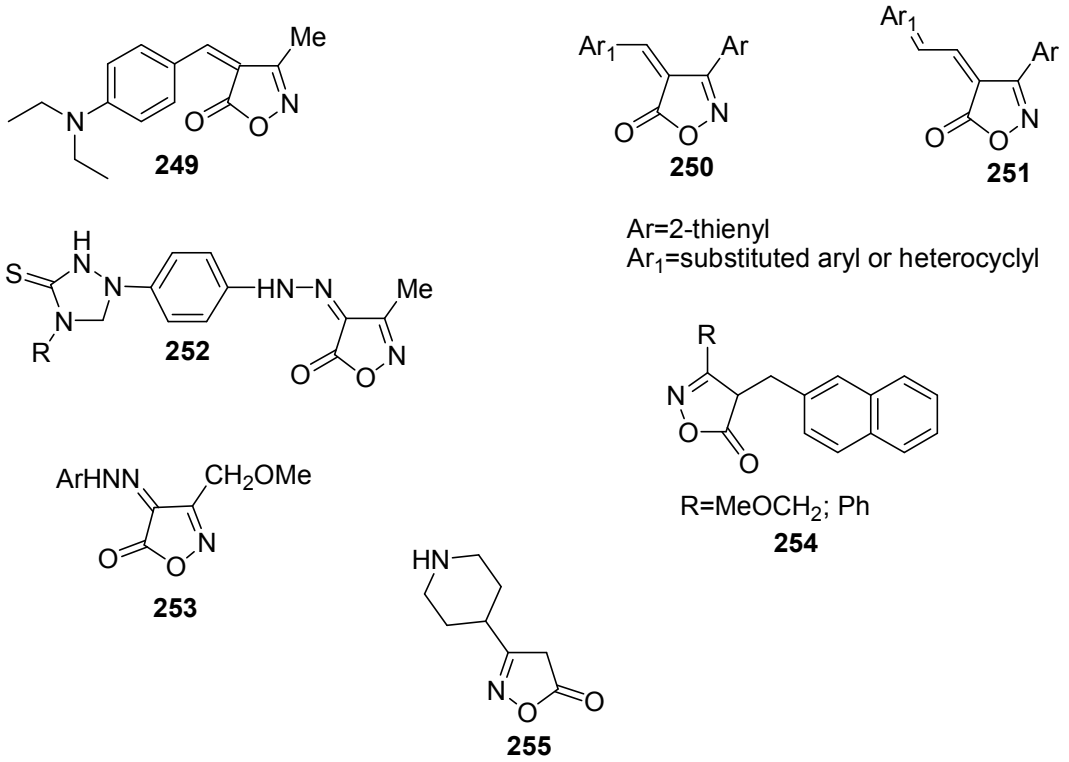


Scheme 97

The N-alkylation and O-alkylation products of 4-arylisoxazol-5-ones **64** (Scheme 97) were used to synthesize ketene O,O-acetals **247** and N,O-acetals **248**. The mechanism of this reaction was clarified.[115]

6. Pharmaceutical studies on isoxazol–5-ones

The isoxazol-5-one ring is contained in several compounds claimed, mostly in the patent literature (not covered by this review), to be active as potential drugs (Scheme 98). A computer study showed that structure **249** is a good model for searching candidate compounds with androgenic and anti-androgenic activity. A series of modifications was tested and useful compounds were identified.[10] A series of arylidene compounds **250** and **251** were found to be active as inhibitors of PKC and in *in vitro* and *in vivo* models of graft-versus-host-disease.[116] Compounds **252** showed *in vitro* fungicidal activity and low bactericidal activity.[19] Arylhydrazones **253** have been suggested as antibacterial and anticonvulsant agents.[117] A family of acidic azoles, among which compounds **254**, showed significant plasma glucose-lowering activity and are useful as potential antidiabetic agents.[118] Compound **255** was prepared and showed affinity for GABA-A receptor.[119]



Scheme 98

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APPLICATION OF MICROWAVE IRRADIATION, SOLID SUPPORTS AND CATALYSTS IN ENVIRONMENTALLY BENIGN HETEROCYCLIC CHEMISTRY

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Abstract. *We describe our contribution to the application of supported reagents and microwave irradiation in green protocols for heterocyclic chemistry. We have included the synthesis of coumarin derivatives, aromatic compounds from furan derivatives, α- and β-substituted alanine derivatives, 1,3,5-triazines and quinoxaline-2,3-diones. In all cases shorter reaction times were required than in the corresponding reactions using classical thermal heating and the contaminating inorganic acids commonly used as catalysts in these reactions were avoided.*

Contents

1. Introduction

Over the past few years there has been a growing movement toward pursuing chemistry that takes into account the knowledge that the consequences of chemistry do not stop with the properties or efficacy of a given molecule. Chemists also have a responsibility to avoid pollution and to protect the environment.

This new approach has mobilized chemists from all over the world to use their creativity to develop new synthetic methods and techniques that minimize or completely eliminate the use or generation of substances hazardous to human health and the environment. This is how Green Chemistry has arisen – not as

a new branch of chemistry but from the conviction that we, as chemists, must be aware of the effects of the science in which we are engaged.

The principles of green chemistry cover such concepts as:[1]

- Atom economy: the design of processes to maximize the incorporation into the final product of all materials used in the process.
- Making the use of solvents and auxiliaries unnecessary wherever possible and innocuous when used.
- The design of energy efficient processes.
- The use of catalytic reagents (as selective as possible) are superior to stoichiometric ones.
- The use of renewable feedstocks.

Among these principles, the use of heterogeneous catalysis is one of the keystones of this new concept.[2] Heterogeneous catalysts can be filtered off and reused, thus providing significant environmental benefits in terms of waste reduction.

Following the same concept, reactions involving supported reagents on silica, alumina and clays have received attention in recent years. These reactions were initially run in the presence of an organic solvent.[3] However, an even more green alternative is the use of a supported reagent in the absence of any solvent, in so-called "dry media" conditions.

These solvent-free conditions have advantages over the reaction in the conventional phase: faster reactions, different selectivities and easier work-up procedures. The recyclability of some of these solid supports makes these processes truly green.

In the design of energy efficient processes, microwave radiation is an unconventional energy source whose usefulness in synthetic organic chemistry has been increasingly recognised in recent years.[4] Microwave heating uses the ability of some compounds to transform electromagnetic energy into heat. A simple model representing the interaction between microwaves and matter considers that, in the presence of an electric field, polar molecules stretch to align their dipolar moment parallel to the electric field. If the molecules are bound by intermolecular forces such as hydrogen bonds or van der Waals interactions, these cohesive forces prevent the positional adjustment and the energy is dissipated as heat. Thus, microwave radiation heats only the reactants and solvents, not the reaction vessel itself, and the temperature increase is uniform throughout the sample.

Spectacular accelerations have been observed in numerous organic reactions but, even more importantly, the reactions are often more selective and produce greater quantities of a desired molecule and smaller amounts of contaminating by-products. Reactions that do not occur under thermal conditions, or result in very low yields, can be successfully carried out or improved using microwaves.[5]

Solvent-free conditions are especially suitable for microwave activation and several advantages are evident for this approach.[6] In the absence of solvent the radiation is absorbed directly by the reagents, so the effect of microwaves is more marked. In particular, when reactions are carried out with a solid catalyst without solvent it is difficult to achieve thermal activation using conventional heating. Mineral oxides are often poor conductors of heat and conventional methods lead to non-homogeneous heating and to overheating. Under microwave irradiation, however, organic compounds absorbed on the surface of inorganic oxides absorb microwaves and the heating is homogeneous.

The practical feasibility of these microwave-assisted solvent-free protocols has been demonstrated in useful transformations involving oxidation, reduction, protection/deprotection, rearrangement reactions and in the synthesis of heterocyclic systems on inorganic solid supports.[7]

In this review we describe our contribution to this environmentally benign microwave approach in heterocyclic chemistry. The general procedure for the reactions described involved absorption of the reactants onto the mineral supports and exposure of the reaction mixture to irradiation in a focused microwave reactor. In each case the power and temperature were controlled and measured. In some cases, the use of a domestic microwave oven was also considered.

2. Microwave activation in environmentally friendly heterocyclic chemistry

2.1. Synthesis of coumarin derivatives

Coumarin and its derivatives find their main application as fragrances, pharmaceuticals and agrochemicals.[8] Numerous synthetic routes to the coumarins have been described, including the Pechmann,[9] Perkin,[10] Knoevenagel,[11] Reformatsky[12] and Wittig[13] reactions. Of these approaches, the Pechmann reaction has been the most widely applied method for the preparation of coumarins since it employs very simple starting materials and gives good yields of 4-substituted coumarins.[14] Various procedures have been developed and in all of them mixtures of the reagents were allowed to stand overnight or for a number of days, depending on their reactivity, or were heated above 150 ºC. The reactions usually occur by electrophilic aromatic substitution and generally employ non-regenerable catalysts such as metal chlorides and mineral acids. However, these conventional catalysts have to be used in excess and this leads to increased levels of environmental pollution.

A modification of the Pechmann reaction involves the use of an α,β-unsaturated carboxylic acid and this permits the synthesis of coumarins substituted in either the pyrone, the benzene ring or both.[15] However, it is one of the few ways to prepare coumarins that do not bear a 4-alkyl substituent – compounds that are impossible to obtain by a normal Pechmann reaction. This reaction was shown to proceed by esterification followed by ring closure, both processes that are proton-catalysed.[16]

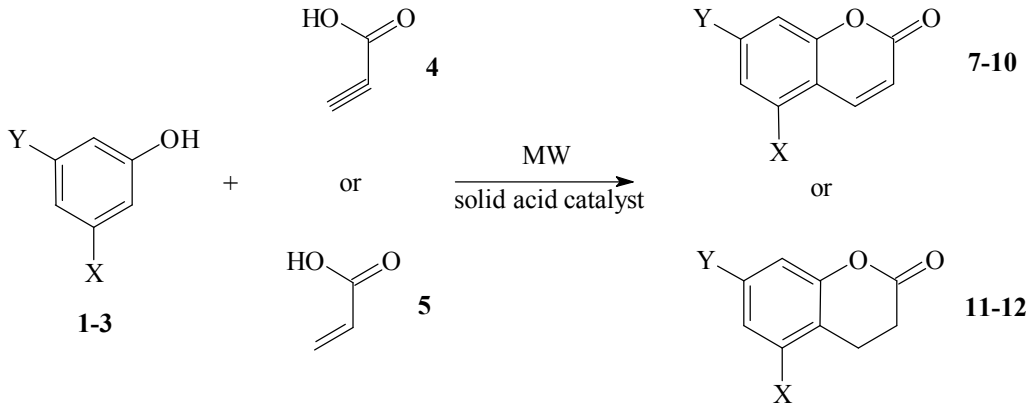
Consequently, a need existed for efficient and heterogeneous catalytic methods for this reaction that used inexpensive, easily handled and non-polluting catalysts. Replacement of mineral acids by solid acid catalysts[17] such as zeolites,[18] clays[19] and sulfonic acid resins[20] would result in simplified product recovery and a reduction in undesirable waste streams. However, such conditions require high temperatures, longer reactions times and, in some cases, gave lower yields. These are typical reaction conditions that can be appreciably improved by the use of microwaves.

Our aim in this respect was to use solid acid catalysts and microwave irradiation to provide a quick, simple and environmentally friendly route to coumarin or substituted coumarins. The reactions were performed in the absence of solvent and at atmospheric pressure.

2.1.1. Synthesis of dihydrocoumarin and coumarin derivatives. Modification of the Pechmann reaction.

Following the modification of the Pechmann reaction, we examined the condensation of phenol (**1**), 1,3-dihydroxybenzene (**2**) and 1,3,5-trihydroxybenzene (**3**) with propynoic (**4**), and propenoic (**5**) acids using

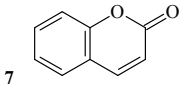
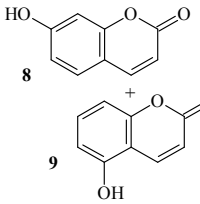
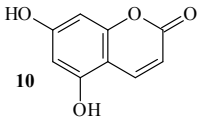
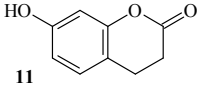
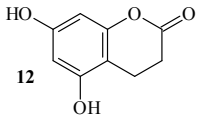
different solid acid catalysts and microwave irradiation (Scheme 1).[21] The condensations were performed in the absence of solvents and the reaction conditions were optimised to obtain the best yield.



1: X=Y= H; **2**: X= H, Y= OH; **3**: X=Y= OH , for compounds **7-12** see Table 1.

Scheme 1

Table 1: Synthesis of coumarin derivatives that are unsubstituted at position 4. Reactions catalysed by solid acid catalysts using microwave irradiation or classical methods.[21]

Entry		Catalyst	Reaction conditions Microwave irradiation[b]	Conventional Heating	Product	Yield %
1	**1** + **4**	Dowex[a]	15 min. 180W 120 ºC		 **7**	41
2		Dowex[a]		15 min. 120 ºC		0
3	**2** + **4**	Dowex[a]	10 min. 30W 120 ºC		 **8** **9**	**8**:69+**9**:31
4		Dowex[a]	4 min. 30W 84 ºC			**8**: 56
5		Dowex[a]		10 min. 120 ºC		**8**: <1
6		Amberlyst[20]		20 h *p*-$ClC_6H_4CH_3$ 150 ºC		**8**: 40
7	**3** + **4**	Dowex[a]	11 min. 30W 80 ºC		 **10**	98
8		Dowex[a]		11 min. 80 ºC		47
9	**2** + **5**	Mont. KSF	10 min. 30W 95 ºC		 **11**	72
10		Mont. KSF		10 min. 95 ºC		0
11		Amberlyst[20]		4 h toluene reflux		73[c]
12	**3** + **5**	Mont. KSF	10 min. 180W 110 ºC		 **12**	84
13		Mont. KSF		10 min. 110 ºC		22

[a] Dowex 50x2-200.
[b] Temperature determined at the end of the reaction.
[c] In addition to this product trace amounts of 3,4,6,7-tetrahydrobenzo[1,2-b:5,4-b']dipyran-2,8-dione were detected.

The results of a comparative study on the synthesis of coumarins involving classical heating in conjunction with solid acid catalysts, both with or without solvent, and microwave irradiation are shown in Table 1. From these results it is clear that the reaction time is reduced from several hours to only a few minutes on using microwave irradiation, indicating that microwaves play an important role in rate enhancement in these reactions. The products are also obtained in excellent yields with the exception of the reaction involving phenol (entry 1) – a consequence of the lower activation of the benzene ring. A similar reaction between phenol and acrylic acid catalysed by Zeolite H-Beta in toluene at 111 ºC after 24 hours led to the corresponding coumarin in only 6% yield.[16]

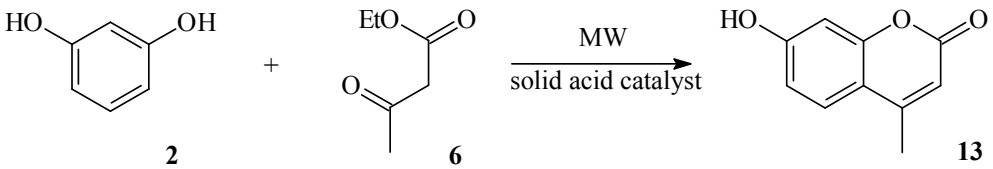
Open-chain products were not detected in any of the above cases.

On the other hand, the use of microwave irradiation in the reaction between 1,3-dihydroxybenzene and propynoic acid (entries 3–6), selectively gave coumarins **8** and **9** with an improvement in the yield for the synthesis of 7-hydroxycoumarin (**8**).

Moreover, under microwave conditions (entry 9) we were able to avoid the formation of 3,4,6,7-tetrahydrobenzo[1,2-b:5,4-b']dipyran-2,8-dione, a compound that is formed by two consecutive reactions when a solvent is used (entry 11).[15]

2.1.2. Pechmann reaction

In order to assess the efficiency of our procedure, ethyl acetoacetate was reacted with 1,3-dihydroxybenzene as an approach to 4-substituted 7-hydroxycoumarins. In this case three steps are involved; transesterification, hydroxyalkylation and dehydration. It is well known that both transesterification and hydroxyalkylation reactions can be proton-catalysed.[22] 7-Hydroxy-4-methylcoumarin, which is a useful starting material in the synthesis of an insecticide (Hymecromone), is obtained in this reaction in *quasi* quantitative yield (97%) by employing Amberlyst-15 under microwave irradiation.



2 **6** **13**

Scheme 2

Table 2: Synthesis of 7-hydroxy-4-methylcoumarin catalysed by solid acid catalysts using microwave irradiation or classical methods.

Entry	Catalyst	Reaction conditions		Yield %
		Microwave irradiation	Conventional Heating	
1	Amberlyst	5 min. 60W 90 ºC		97
2	Sulfuric acid[23]	2 min. Unknown temp.		72
3	Amberlyst[15]		4 h toluene reflux	81
4	Mont. K10[19]		4 h 150 ºC	96

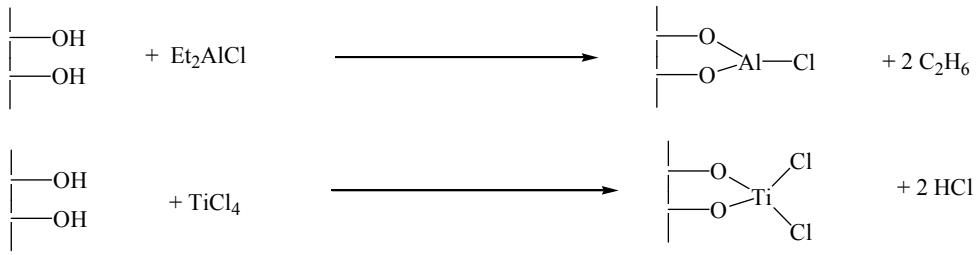
As can be seen from the results in Table 2, the reaction time required using microwaves was lower in comparison to classical conditions (entries 1 *vs* 3 and 4), while yields were improved in relation to previously reported microwave conditions using mineral acids (entries 1 *vs* 2). These facts demonstrate the advantages of using solid acids. Moreover, under our reaction conditions the hydrolysis of the β-keto ester is avoided, whereas this reaction occurs to a significant extent (entry 3) when cation exchange resins are used.[14b]

2.2. Tandem Diels–Alder aromatization reaction of furans

Diels–Alder reactions of furan and its derivatives have received a great deal of attention for two main reasons. Firstly, furan and some of its derivatives are inexpensive compounds obtained from agricultural by-products.[24] Secondly, the cycloadducts are versatile intermediates in the preparation of carbohydrates and other biologically active compounds[25] and have been further elaborated to substituted arenes.[26]

The use of furans as dienes has encountered problems related to their sensitivity to the most common Lewis acid catalysts, the easy reversibility of their reactions, and the formation of by-products. In view of these drawbacks, a range of special reaction conditions has been developed.[27]

Heterogeneous catalysts such as $ZnCl_2$, $TiCl_4$ and Et_2AlCl supported on silica gel have shown great utility as Lewis acid catalysts. The structures of these systems are not known in great detail but it is believed that silica-supported $ZnCl_2$ consists mainly of a dispersion of small particles of $ZnCl_2$ on the surface of silica gel. On the other hand, treatment of silica gel with $TiCl_4$ or Et_2AlCl results in the displacement of two chloride or ethyl groups, respectively, by the silanol groups of the silica gel (Scheme 3).[28] These catalysts can be stored and recovered after the reaction without loss of catalytic activity.



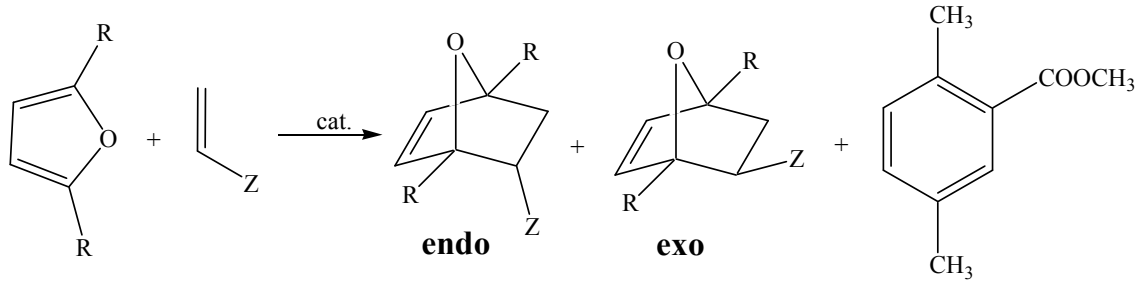
Scheme 3

Microwave irradiation has been applied successfully to cycloaddition reactions.[29] Particularly when sensitive compounds are involved, the rapid heating induced by microwave radiation leads to the formation of the products under mild reaction conditions and with short reaction times. This process avoids decomposition or side-reactions and, in certain cases, leads to increased yields.

The reasons outlined above encouraged us to explore the joint use of silica-supported Lewis acids and microwave activation in Diels–Alder reactions between furan derivatives and different dienophiles. The results of these reactions were compared with those obtained under conventional conditions.

2.2.1. Diels–Alder reaction of furans

Firstly, we compared the behavior of furan (**14**) and 2,5-dimethylfuran (**15**) in reactions with methyl acrylate (**16**) and acrylonitrile (**17**) catalyzed by silica and by three silica-supported Lewis acids at room temperature (Scheme 4 and Table 3).[30]



14: R = H
15: R = CH_3

16: Z = $COOCH_3$
17: Z = CN

18: R = H; Z = $COOCH_3$
19: R = CH_3; Z = $COOCH_3$
20: R = H; Z = CN
21: R = CH_3; Z = CN

22

Scheme 4

The results obtained were found to depend on the nature of both the diene and the dienophile. As reported previously,[31] Zn(Si) is a better catalyst than Al(Si) or Ti(Si) for Diels–Alder reactions involving α,β-unsaturated nitriles such as acrylonitrile, and good yields of the corresponding cycloadducts were obtained with this catalyst. The use of this dienophile in conjunction with furan as the diene produced the *endo* cycloadduct (**20n**) as the major product, with the situation being reversed on using 2,5-dimethylfuran, which gave the *exo* cycloadduct (**21x**) as the major product. Any catalysis due to the support can be ruled out because the reaction was not promoted by silica gel (Table 3).

Table 3. (**n** = *endo*, **x** = *exo*)

Diene	Dienophile	Catalyst	t(h)	Yield % (18–22)	n/x	Yield of 22 %
14	**16**	SiO_2	24	75	86:14	-
		Zn(Si)	24	75	81:19	-
		Ti(Si)	24	71	73:27	-
14	**17**	Zn(Si)	3	78	67:33	-
		Ti(Si)	24	-	-	-
15	**16**	SiO_2	24	24	66:34	-
		Zn(Si)	24	25	65:37	-
		Al(Si)	24	32	75:25	6
		Ti(Si)	2	8	62:38	-
		-	24	-	-	14
15	**17**	SiO_2	3	-	-	-
		Zn(Si)	3	79	37:63	-
		Al(Si)	3	-	-	-
		Ti(Si)	3	15	38:62	-

In the reactions carried out with methyl acrylate as the dienophile, the use of silica-supported Lewis acids resulted in good yields of the corresponding cycloadducts **18n** and **18x** when furan was used as the diene.[32] However, the yields obtained with this dienophile and 2,5-dimethylfuran were much lower. These results do not indicate that 2,5-dimethylfuran is necessarily less reactive than furan, rather that the difficulty in obtaining good yields is due to competition from other reactions.

The first of these competing reactions is the retro Diels–Alder reaction. The equilibrium position changes from one diene/dienophile to another. The second competing reaction, which is not observed in the case of acrylonitrile, is ring-opening of the cycloadducts followed by aromatization to yield methyl 2,5-dimethylbenzoate (**22**).

In an attempt to improve the results we decided to assess the effect of temperature on the reactions. However, we found that the use of conventional heating gave irreproducible results. It is known that mineral oxides are poor heat conductors and that conventional methods result in inhomogeneous heating and, in certain cases, to overheating. In order to avoid this problem we investigated the use of microwave activation in the reaction of 2,5-dimethylfuran with methyl acrylate and acrylonitrile, using a focused microwave reactor under pressure in an argon atmosphere.

In agreement with previous studies, silica gel was found to be fairly inefficient in promoting these reactions. The use of methyl acrylate led to an increase in the amount of aromatic product, probably accompanied by an increase in the retro Diels–Alder reaction. In fact, only a small amount of cycloadduct was obtained when a Zn(Si) catalyst was used. In the reactions involving acrylonitrile, the corresponding aromatic product was not obtained.[30]

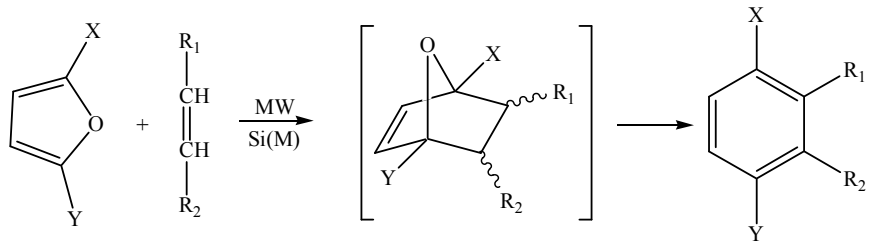
The observed differences between carbonyl and nitrile compounds was not easy to explain and it was necessary to carry out theoretical studies of the different reaction pathways.[30]

2.2.2. Synthesis of benzene derivatives by ring-opening of Diels–Alder cycloadducts

As mentioned previously, one application of the Diels–Alder cycloaddition of furans stems from the fact that the resultant oxabicycloheptene derivatives are valuable intermediates for the synthesis of arenes. These oxabicycles are easily prepared through cycloaddition reactions and, furthermore, the oxygen bridge can be opened by a variety of methods.[33] However, only in a few cases is it possible to obtain benzene derivatives in a single step[34] and a mixture of compounds is usually obtained.[35,33d] It should be pointed out, however, that these kinds of reactions have usually been performed in two steps using homogeneous catalysis and, under these conditions, long reactions times are required.

In a previous study we had observed the formation of the aromatic compound methyl 2,5-dimethylbenzoate in the reaction between 2,5-dimethylfuran and methyl acrylate. When the reaction was carried out in a focused microwave reactor the amount of this product was much greater, showing that its formation could be favored by microwave activation. Our aim was to design an environmentally benign procedure that avoided the use of the polluting homogeneous catalysts commonly employed and, in order to achieve this, reduced reaction times were required.

The process described here is procedurally simple and employs readily available chemicals, thus making it a promising and useful route to a wide variety of polysubstituted benzenes whose synthesis is difficult by other methods. The reactions were performed in hermetically sealed Teflon tubes in a domestic microwave oven in which high pressures are probably reached.



15, **23**, **24** **16**, **17**, **25**, **26** **22**, **27-33**

15: X = Y = CH_3; **23**: X = OCH_3, Y = H; **24**: X = CH_3CH_2, Y = H
16: R_1= $COOCH_3$, R_2 = H; **17**: R_1 = CN, R_2 = H
25: R_1 = R_2 = -$CONCH_3CO$- ; **26**: R_1 = R_2 = CN

Scheme 5 (For compounds **27**–**33** see Table 4)

As shown in Scheme 5, furan derivatives undergo Diels–Alder reactions with dienophiles (**16**, **17**, **25** and **26**) to give 7-oxabicyclo[2.2.1]hept-2-enes as intermediates. The desorption of these intermediates would give the oxabicyclic compounds. However, under solvent free conditions this step is not easy and the co-ordination of the silica-supported catalyst with the oxygen bridge favors ring opening, leading to aromatic products in only one step.

The results of the study into the synthesis of arenes by microwave irradiation using silica-supported catalysts are shown in Table 4.

We found that furan derivatives (**15**, **23** and **24**) react with different dienophiles under microwave irradiation conditions within 25–45 min, affording in one pot the aromatic products indicated in the Table 4. The results obtained depend greatly on the reaction conditions, the nature of the Lewis acid used as a catalyst, and the level of activation of the furan ring.

The nature of the catalyst has, in some cases, a spectacular effect on the yields. The use of Si(Ti) gives the best results and the arene derivatives were obtained in good to excellent yields. It is remarkable that the use of SiO_2 (entry 5) does not promote any reaction at all. This result shows the importance of the catalytic activity of the metal. Moreover, microwave irradiation plays an important role in the reaction (see Table, entry 12 *versus* entry 13). The use of classical heating in an oil bath under comparable reaction conditions (temperature and reaction time) leads to a dramatic decrease in the yield of the aromatic product.

The incorporation of an electron-donating group in position 2 of the furan has often been employed to enhance the reactivity of the heteroaromatic ring system.[34] In our case, reactions involving 2-methoxyfuran (**23**) exhibited a very high regioselectivity, with formation of the more crowded compounds when asymmetric dienophiles were used (entries 16 and 20). Moreover, reaction with fumaronitrile afforded 3-methoxyphthalonitrile in excellent yield (entry 28). This fact could be related to the stabilization of the intermediate carbocation by the methoxy group. It should be remarked that the previously reported synthesis of phthalonitriles from furan derivatives required a two-step procedure and ring opening of the cycloadduct is usually performed in basic rather than acidic conditions.[36] On the other hand, the reaction of 2-ethylfuran (**24**) with *N*-methylmaleimide demonstrated that this reaction can be successful when less reactive furan derivatives are used, albeit in moderate yields (entry 32).

Moreover, it should be noted that treatment of the three furan derivatives with *N*-methylmaleimide (**25**) gave rise to new *N*-methylphthalimide derivatives, one of which was obtained in quantitative yield (entry 12).

Table 4: One-pot synthesis of arenes catalysed by silica-supported Lewis acids using microwave irradiation or classical methods.

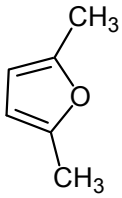
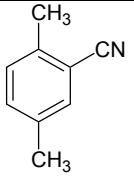
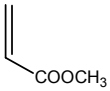
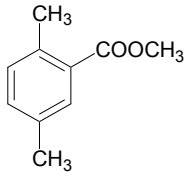
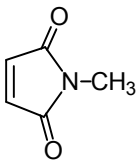
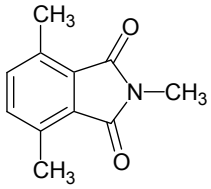
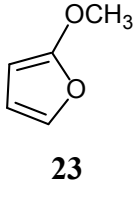
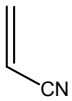
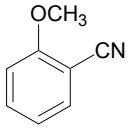
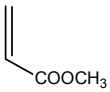
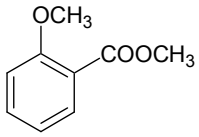
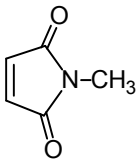
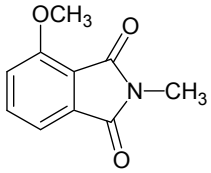
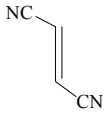
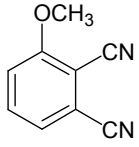
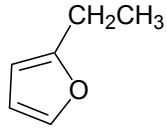
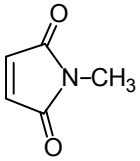
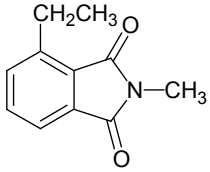
Entry	Diene	Dienophile	Catalyst	Reaction conditions: Microwave Irradiation[a]	Reaction conditions: Conventional Heating[b]	Product	Yield (%)
1	 **15**	 **17**	Si(Zn)	45 min.		 **27**	23
2			Si(Al)	45 min.			50
3			Si(Ti)	45 min.			50
4			Si(Ti)		45 min. 120 ºC		7
5		 **16**	SiO_2	45 min.		 **22**	0
6			Si(Zn)	45 min.			25
7			Si(Al)	45 min.			65
8			Si(Ti)	45 min.			92
9			Si(Ti)		45 min. 120 ºC		10
10		 **25**	Si(Zn)	45 min.		 **28**	50
11			Si(Al)	45 min.			83
12			Si(Ti)	45 min.			100
13			Si(Ti)		45 min. 120 ºC		14
14	 **23**	 **17**	Si(Zn)	25 min.		 **29**	13
15			Si(Al)	25 min.			54
16			Si(Ti)	25 min.			60
17			Si(Ti)		25 min. 120 ºC		29
18		 **16**	Si(Zn)	25 min.		 **30**	<3
19			Si(Al)	25 min.			30[c]
20			Si(Ti)	25 min.			62[d]
21			Si(Ti)		25 min. 120 ºC		13[c]
22		 **25**	Si(Zn)	25 min.		 **31**	34
23			Si(Al)	25 min.			55
24			Si(Ti)	25 min.			88
25			Si(Ti)		25 min. 120 ºC		31
26		 **26**	Si(Zn)	25 min.		 **32**	<3
27			Si(Al)	25 min.			9
28			Si(Ti)	25 min.			88
29			Si(Ti)		25 min. 120 ºC		<3

Table 4 (continued)

Entry	Diene	Dienophile	Catalyst	Reaction conditions: Microwave Irradiation[a]	Reaction conditions: Conventional Heating[b]	Product	Yield (%)
30			Si(Zn)	45 min.			28
31			Si(Al)	45 min.			29
32			Si(Ti)	45 min.			45
33	**24**	**25**	Si(Ti)		45 min. 120 ºC	**33**	19

[a] All microwave reactions were carried out at 780W.
[b] The reaction temperature was determined at the end of a blank reaction using microwave irradiation.
[c] In addition to this product, 10% of methyl 3-methoxybenzoate was obtained.
[d] In addition to this product, trace amounts of methyl 3-methoxybenzoate were detected

2.3. Preparation of α- and β-substituted alanine derivatives

The development and application of new and practical methods for the preparation of structurally diverse amino acid derivatives is of fundamental importance due to the widespread use of these compounds in practically all areas of the physical and life sciences.

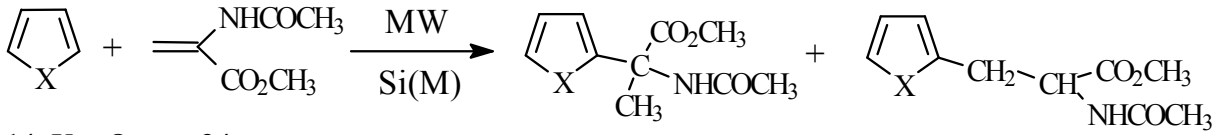
N-Acyl-α,β-didehydroamino acids have proven to be useful intermediates in the asymmetric and non-asymmetric synthesis of α-amino acids.[37] The potential value of the *N*-acyl-α,β-dehydroamino acid esters in synthetic chemistry is derived mainly from their ready availability and the intrinsic reactivity of their double bonds due to the presence both of acylamino and ester groups, which facilitate the nucleophilic attack at the α and β positions. In particular, alanine derivatives are known to behave as dienophiles,[38] dipolarophiles[39] and electrophiles[40] in Michael-type reactions. On the other hand, enamides such as methyl α-acetamidoacrylate can act as α-amidoalkylation reagents, most often after protonation at the terminal carbon atom.[41] These reactions are usually performed using homogeneous catalysis, although in these cases long reaction times are required. For this reason we found it of interest to study the reaction of methyl α-acetamidoacrylate with different heterocycles and carbocycles using heterogeneous catalysis assisted by microwave irradiation under solvent-free conditions. In all cases the catalysts were obtained by treatment of silica with $ZnCl_2$ [Si(Zn)],[42] Et_2AlCl [Si(Al)][43] or $TiCl_4$ [Si(Ti)].[28] The most important objectives of this work were:

1. To decrease the reaction times.
2. To avoid the use of the polluting homogeneous catalysts commonly used in this field.
3. To study the chemo- and regioselectivity of the reaction, *i.e.* competition between α-amidoalkylation, Michael addition and Diels–Alder cycloaddition was observed.
4. To determine the reactivity of these alanine derivatives with aromatic systems.

The process described here, because of its procedural simplicity and the use of readily available chemicals, represents a promising and useful route to a wide variety of aromatic α-amino acids with potential therapeutic action.[44]

Methyl α-acetamidoacrylate (**34**) reacted with heterocycles or carbocycles under microwave irradiation within 10–30 minutes to afford the α- and/or β-substituted alanine derivatives. This method provides access to aryl-substituted amino acid derivatives as well as to amino acids containing a β-tertiary carbon. The reactions were usually performed at atmospheric pressure in a focused microwave reactor – the exceptions

being the reactions involving furan. In the case of furan, owing to its low boiling point, a modified Fisher–Porter reaction vessel was used. Our study began with furan and pyrrole (Scheme 6) and the best results for each compound are shown in Table 5.



14: X = O **34**
35: X = NH

Scheme 6

In reactions involving furan, although almost complete conversions were observed, yields were low because both reagents can decompose; furan by ring opening and the alanine derivative by polymerization. With pyrrole both α-amidoalkylation and Michael addition took place. Catalysts such as Si(Ti) or Si(Al) favored the α-amidoalkylation product (entries 5 and 6) while the use of Si(Zn) exclusively gave the Michael addition product in 70% yield (entry 4). The use of classical heating, *i.e.* an oil bath under similar reaction conditions (time and temperature), gave product **42** in only 14% yield. However, with *N*-benzylpyrrole the only reaction observed was α-amidoalkylation. The best catalyst was Si(Ti) (entry 10).

This reaction was extended to other benzocondensed heterocycles, including indole (**37**) and azoles such as pyrazole (**38**), with the aim of obtaining tryptophan derivatives and β- and α-(1-pyrazolyl)alanine derivatives as synthetic precursors of anticonvulsant agents.[45]

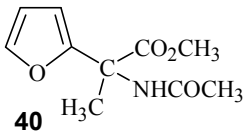
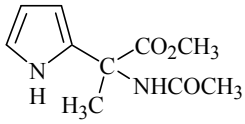
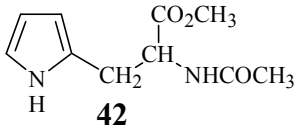
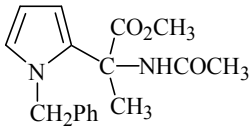
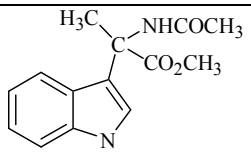
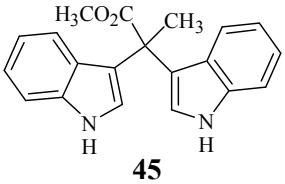
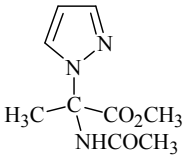
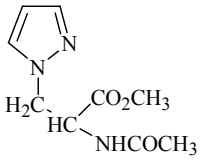
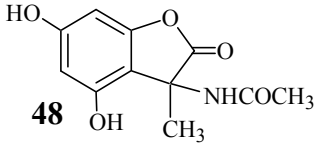
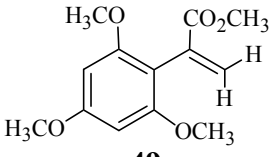
Reactions with indole (Table 5, entries 11–15) afforded the bisindolyl derivative (**45**) as the main product. This product was obtained by elimination of acetamide and reaction with a second equivalent of indole. The assistance of the indole system in the elimination of acetamide controls the formation of the symmetric dimer. This elimination process occurred to a lesser extent when the reaction was performed at 50 ºC and it was also found that an increase in the amount of *N*-acetyl-α,β-didehydroalanine methyl ester used, under the same conditions, gave a 50% yield of the α-amidoalkylation product (**44**), which was the main product (entry 14). When we used similar conditions under conventional heating the yield of this product was only 12%, a fact that clearly demonstrates the activation effect of microwave irradiation.

We performed the reaction with pyrazole under similar conditions (Table 5, entries 16–19) and, in these cases, addition at N-1 was observed. The selectivity depended on the reaction conditions and the Lewis acid used as a catalyst, although a mixture of α-amidoalkylation and Michael addition products was always obtained.

The competition between α-amidoalkylation and Michael addition reactions can be thought of in terms of an enamine-imine equilibrium, which is activated by the presence of the Lewis acid (Scheme 7). According to this scheme, the reaction of a good nucleophile with the electrophile, which is not activated by co-ordination to an acid center, takes place in the β-position.

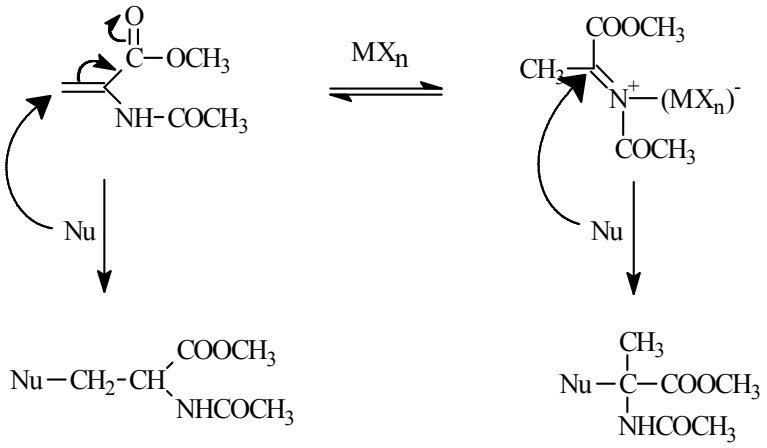
This behavior is observed for heterocycles bearing sufficiently acidic NH groups that are able to react with aluminum and titanium Lewis acids to form a good nucleophile in an irreversible way (Scheme 8). For this reason the Michael-type reaction is not observed with the Zn catalyst.

Table 5[46]

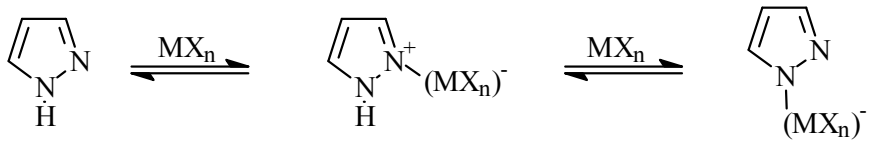
Entry	Heterocycle	Catalyst	Reaction Conditions	Products	Yield (%)
1	Furan (**14**)	Si(Zn)	15 min 150 W 50 ºC	 **40**	**40**: <3
2		Si(Al)	15 min 150 W 50 ºC		**40**: 16
3		Si(Ti)	15 min 150 W 50 ºC		**40**: 18
4	Pyrrole (**35**)	Si(Zn)	15 min 270 W 100 ºC	 **41**  **42**	**42**: 70
5		Si(Al)	25 min 150 W 70 ºC		**41**: 51+**42**: 12
6		Si(Ti)	30 min 120 W 80 ºC		**41**: 32+**42**: 27
7[a]		Si(Zn)	15 min 100 ºC		**42**: 14
8	N-Benzyl-pyrrole (**36**)	Si(Zn)	15 min 285 W 100 ºC	 **43**	**43**: <3
9		Si(Al)	10 min 240 W 70 ºC		**43**: 26
10		Si(Ti)	15 min 240 W 60 ºC		**43**: 44
11	Indole (**37**)	Si(Zn)	15 min 270 W 100 ºC	 **44**  **45**	**45**: 37
12		Si(Al)	15 min 150 W 70 ºC		**44**: 39+**45**: 54
13		Si(Ti)	15 min 150 W 70 ºC		**44**: 18+**45**: 22
14		Si(Al)[b]	15 min 90 W 50 ºC		**44**: 50+**45**: 23
15[a]		Si(Al)[b]	15 min 50 ºC		**44**: 12
16	Pyrazole (**38**)	Si(Zn)	10 min 240 W 80 ºC	 **46**  **47**	**46**+**47**:<3
17		Si(Al)	10 min 240 W 80 ºC		**46**: 17+**47**: 24
18		Si(Ti)	10 min 240 W 80 ºC		**46**: 7+**47**: 6
19		Si(Al)[c]	10 min 210 W 80 ºC		**46**: 7+**47**: 41
20	1,3,5-Trihydroxy-benzene (**3**)	Si(Zn)	15 min 285W 100 ºC	 **48**	**48**: 41
21		Si(Al)	10 min 240W 60 ºC		**48**: 37
22		Si(Ti)	10 min 240W 60 ºC		**48**: 46
23	1,3,5-Trimethoxy-benzene (**39**)	Si(Zn)	20 min 240W 110 ºC	 **49**	**49**: 91
24		Si(Al)	15 min 270W 110 ºC		**49**: 23
25		Si(Ti)	15 min 270W 110 ºC		**49**: 32
26[a]		Si(Zn)	20 min 110 ºC		**49**: <3

[a] Conventional heating. [b] In this reaction a molar ratio indole:methyl α-acetamidoacrylate of 1:2 was used.
[c] In this reaction a molar ratio pyrazole:methyl α-acetamidoacrylate of 2:1 was used.

Such an equilibrium is not possible in furan or *N*-substituted pyrrole derivatives due to the absence of an NH group and, consequently, only α-amidoalkylation is observed.



Scheme 7



Scheme 8

Given that aromatic amino acids of the phenylglycine type have found applications in the synthesis of semisynthetic penicillins and cephalosporins,[48] we attempted to perform the reaction with carbocycles.

The reaction involving 1,3,5-trihydroxybenzene gave the product from an α-amidoalkylation followed by a transesterification reaction – although the reaction order could also be reversed. The best catalyst was Si(Ti), although the aromatic amino acid derivative was obtained in only moderate yields. Finally, the reactions between the trimethoxybenzene derivative and **34** using silica-supported Lewis acids as catalysts gave the product arising from the α-amidoalkylation reaction and elimination of acetamide. Effective co-ordination between the Lewis acid and the alanine derivative (as is shown in Scheme 7) can be deduced in these cases.

The reactions reported here show that Si(M) systems are not sufficiently strong to produce the reaction to any great extent unless a very activated carbocyclic or heterocyclic compound is used. In order to increase the yields we carried out several reactions employing other, stronger acid catalysts such as a Brönsted acid (*p*-toluensulfonic acid) or an ion exchange resin (Dowex).

In this sense, the reaction involving *N*-benzylpyrrole (**36**) shows an increase in yield up to 68% when *p*-TsOH was used in catalytic amounts. The best result was obtained under microwave irradiation using a temperature of 80 ºC and a reaction time of 15 minutes. Under conventional heating conditions the yield was only 30%.

The reaction of 1,3,5-trihydroxybenzene produced a benzofuran derivative. This synthesis is reminiscent of the preparation of coumarin derivatives described previously by us.[21] As a consequence, we tested the use of a Dowex resin as the catalyst in this type of reaction. The use of this resin gave the

benzofuran derivative in 64% yield after 10 minutes of microwave treatment. Once again conventional heating did not give any reaction.

Finally, bases such as $NaHCO_3$ and Na_2CO_3 were used in the reaction with pyrazole in order to improve the synthesis of the β-substituted alanine derivative **47**. The best results were obtained with Na_2CO_3. The pyrazole did not decompose under these conditions and we therefore increased the ratio of methyl α-acetamidoacrylate (**34**), a change that favored the reaction and afforded a yield of 80% after only 15 minutes of microwave irradiation. It is important to bear in mind that the use of comparable conditions involving classical heating does not give any reaction at all.[46] Moreover, it is interesting to note that the synthesis of this product was reported by Pleixats *et al*.[40c] to require 144 hours and gave only 54% yield. The reaction time is reduced considerably with the method described here and also avoids the use of contaminating catalysts.

In conclusion, the formation of the α- or β-substituted alanine derivative depends on the co-ordination of the Lewis acid with methyl α-acetamidoacrylate and the presence in the aromatic system of acidic NH groups. When the aromatic compound is sufficiently reactive, the best catalyst is Si(Zn) because this does not lead to decomposition of the reagents. With compounds of lower reactivity, however, a stronger catalyst like Si(Ti) or Si(Al) is required. When competition between α-amidoalkylation and Michael addition occurs, Si(Ti) and Si(Al) favor the first reaction whereas Si(Zn) favors the latter. The use of heterocycles like furan and *N*-benzylpyrrole or carbocyclic systems gives only α-amidoalkylation. Less reactive heterocycles did not react and three activating groups are required for carbocycles.

2.4. Synthesis of 1,3,5-triazines

1,3,5-Triazines have been used as templates in the synthesis of supramolecular porphyrin systems,[48] as complexation agents in analytical chemistry,[49] as multi-step redox systems,[50] as stationary phases in HPLC resolution of racemic compounds,[51] as enantio-differentiating coupling reagents[52] and as high-loading scavenger resins for combinatorial chemistry.[53]

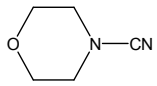
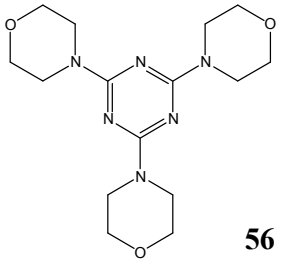
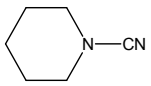
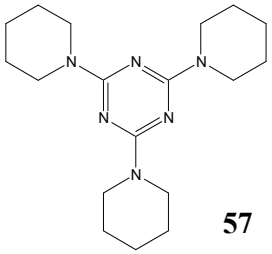
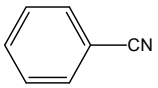
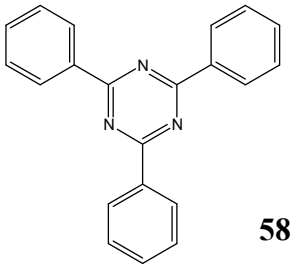
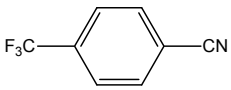
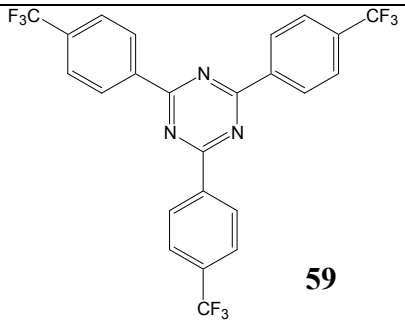
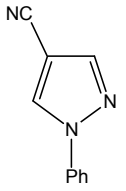
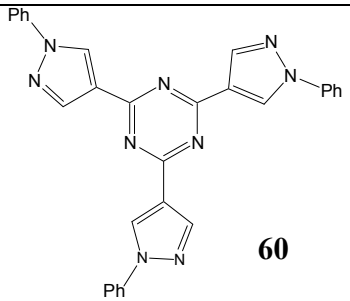
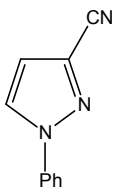
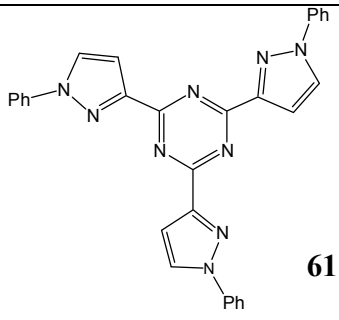
The synthesis of 1,3,5-triazines has been performed by cyclotrimerization of nitriles catalysed by acids, bases[54] or activated magnesium.[55] These reactions require strong reaction conditions, *i.e.* high temperatures, pressures and long reaction times and, in most cases, give only moderate yields. Alternatively, the use of very strong and highly polluting acids[54f] or metals[55] can be considered.

We discuss here the cyclotrimerization of nitriles to afford 1,3,5-triazines in solvent-free conditions using Si(Ti), Si(Zn) and Si(Al) as catalysts. These systems represent a green alternative to the use of lanthanide ions. For the sake of comparison, we also studied the commonly used lanthanide catalyst yttrium trifluorosulfonate $Y(OTf)_3$. Piperidine and morpholine were used as nucleophiles to induce the cyclotrimerization. We used conventional heating and microwave irradiation as the energy sources and the reactions were performed under pressure in closed vessels. The best results from these reactions are collected in Table 6.

Reactions under microwave irradiation conditions gave the best results in conjunction with short reaction times.

However, when the reaction time was increased to 24 hours under conventional heating the yields were greatly improved in most cases. Such extended reaction times cannot be employed with microwaves.

Table 6[56]

Starting material	Catalyst	Reaction conditions	Product	Yield(%)
 **50**	$Y(OTf)_3$	160 °C, 210 W, 1 h,	 **56**	37
	Si(Zn)	200 °C, 24 h		60
	Si(Zn)	200 °C, 120 W, 30 min[a]		50
	Si(Al)	200 °C, 24 h		22
	Si(Al)	200 °C, 120 W, 30 min[a]		37
	Si(Ti)	200 °C,120 W, 30 min[a]		37
 **51**	$Y(OTf)_3$	200 °C, 24 h	 **57**	31
	$Y(OTf)_3$	200 °C, 120 W, 30 min[a]		40
	Si(Zn)	200 °C, 24 h		75
	Si(Zn)	200 °C, 120 W, 30 min[a]		35
	Si(Al)	200 °C, 24 h		72
	Si(Ti)	200 °C, 24 h		63
 **52**	$Y(OTf)_3$	200 °C, 24 h	 **58**	55
	Si(Zn)	200 °C, 24 h		13
 **53**	$Y(OTf)_3$	200 °C, 24 h	 **59**	42
	Si(Zn)	200 °C, 24 h		35
	Si(Al)	200 °C, 24 h		6
	Si(Ti)	200 °C, 24 h		5
 **54**	$Y(OTf)_3$	200 °C, 24 h	 **60**	30
	Si(Zn)	200 °C, 24 h		30
	Si(Al)	200 °C, 24 h		0
	Si(Ti)	200 °C, 24 h		8
 **55**	$Y(OTf)_3$	200 °C, 24 h	 **61**	66
	Si(Zn)	200 °C, 24 h		15
	Si(Al)	200 °C, 24 h		39
	Si(Ti)	200 °C, 24 h		50

[a] 210W during the first 2 minutes.

The results obtained were slightly better when $Y(OTf)_3$ was used instead of the silica-supported Lewis acids, although the simple manipulation, possible re-utilization and known environmental advantages make the silica systems excellent catalysts for the cyclotrimerization of nitriles. As described previously, these catalysts can be recovered and stored for up to one month, a property that gives rise to high conversions without loss of catalytic activity.[28]

It can be seen from the results that, of the modified silica gels, Si(Zn) gave the best results. This fact has been explained in terms of the Hard and Soft Acids and Bases Principle (HSAB): Zn, which is softer than Al and Ti, coordinates more effectively with the soft N atom of the nitrile. The only exceptions to this rule is derivative **55**, where the presence of a second coordinative nitrogen in the pyrazole makes Si(Ti) the best catalyst.

2.5. Synthesis of quinoxaline-2,3-dione: a synthetic model for radiolabeled compounds

A large number of molecules of biological interest have been labeled with short-lived positron-emitting radionuclides for *in vivo* evaluation by positron emission tomography (PET). The production of these radiopharmaceuticals requires optimization of procedures so that all reactions occur as efficiently and as quickly as possible. In optimizing radiochemical yields a variety of reaction parameters may be manipulated, such as solvent polarity, temperature, pressure, reaction time, specific catalysts, molar ratios of reagents or modification of the substrate or the radiolabeling precursor for optimal reactivity.

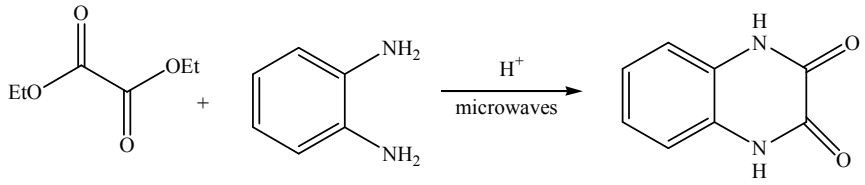
The first successful use of microwave techniques to speed up the synthesis of radiopharmaceuticals for PET was reported in 1987.[57] A number of radiolabeling procedures using different organic reactions have subsequently been reported.[58] The use of microwave technology instead of conventional heating offers the potential for simplifying the technical apparatus used in some multi-step syntheses. For example, the cavity does not retain heat after treatment of the sample. The same apparatus can therefore be used for different reaction vessels or, alternatively, the same vessel requiring several different temperatures for successive chemical transformations. The increased rates reported using microwaves provide a means of decreasing reaction times, thus increasing the final radiochemical yield of radiopharmaceuticals. This has the practical implication that less starting radioactivity is required to produce a given amount of radiotracer or that radiolabeling routes that were previously inaccessible may now be possible.

In radiolabeling, incorporation of a label in ring positions is particularly attractive since they should be metabolically stable *in vivo*. The advantages and potential problems of using microwaves in this area were demonstrated in the synthesis of the heterocycle 2,3-dihydroxyquinoxaline, a basic structural unit in antagonists of the excitatory amino acid receptor system.[59]

Abnormal excitation by neurotransmitters can eventually cause the death of neurons. Such a mechanism may be involved in the neuronal loss observed in neurodegenerative diseases such as ischemia, epilepsy, traumatic brain injury, Parkinson's and Alzheimer's disease. Drugs that act specifically to antagonize excitatory neurotransmission may therefore provide a means of treating degenerative disorders. PET scanning techniques provide a means of investigating *in vivo* the biodistribution and interaction of such drugs when properly labeled with the excitatory amino acid (EAA) receptor systems.

Stone-Elander and co-workers developed a method for labeling quinoxaline-2,3-diones for a PET study of its biodistribution. Their group also attempted to use monomodal microwave heating to accelerate the cyclocondensation of diethyl oxalate (**62**) with 1,2-phenylenediamine (**63**) and analogs[60,61] to generate

quinoxaline-2,3-diones (**64**) (Scheme 9). Typically the cyclization proceeds slowly in refluxing solvents and/or mineral acids.[62] Acidic media couple very efficiently with oscillating microwave fields, a process that allows for very rapid heating of such samples. However, when the high microwave input powers required for this cyclization were used, the closed vessels exploded and only very low yields were obtained.



62 **63** **64**

Scheme 9

In collaboration with Stone-Elander, our group developed the successful use of solid supports and solvent-free media with focused microwave fields to achieve this heterocyclization.[63]

The influence of the solid support and/or acidic media, temperature and time of treatment were screened in a large number of experiments. When the reactions were carried out using the supports together with solvents that couple well with microwaves (H_2O, CH_3CN, DMSO and propylene carbonate), only trace amounts of **64** were obtained. The trends observed for solvent-free conditions are demonstrated by the results given in Table 7.

Table 7

Entry	Solid Support	Acidic Reagents	T_{med} (ºC)	Time (min)	Yield (%)
1	SiO_2	-	160	3	21
2	KH_2PO_4	-	160	3	31
3	KH_2PO_4	-	150	6	46
4	Dowex 50x8	-	150	3	33[a]
5	KSF	-	130	2	29[a]
6	-	9N H_2SO_4	150	4	19[b]
7	-	2M HCl	85	3.5	15[b]
8	-	*p*-TsOH[c]	130	3	54

[a]Complex product mixture. [b]Extensive hydrolysis of **62** to oxalic acid. [c]Catalytic amount.

In the absence of solvents, comparable yields were obtained using Dowex 50x8 and KSF. However, other unidentified products were obtained and the Dowex resin began to degrade at T_{med} > 100 ºC. Cleaner mixtures, but with lower yields, were obtained with silica (of the supports tested) and the highest yields in this respect were obtained with anhydrous KH_2PO_4. In comparison, the use of both H_2SO_4 and HCl predominantly led to decomposition of the ethyl oxalate to the less reactive oxalic acid, even though some product could be obtained when the vessels were not closed and the temperatures were carefully monitored.

It has been previously reported that[64] esterifications performed on acidic solid supports are not associated with complete displacement of the equilibrium since the chemisorption and competing hydrolysis

occur before the water evaporates. Trace amounts of *p*-toluensulfonic acid (*p*-TsOH) were found to greatly improve the esterification yields. Indeed, the use of *p*-TsOH nearly doubled the yields compared to those obtained with the solid supports.

In many types of chemical process, one or more of the starting materials may be particularly precious. The conversions in such processes are often maximized by manipulating the polar ratios of the substrates. In the method described by Stone-Elander and co-workers for radiolabeling of these molecules, the carbon-11 was first introduced in diethyl oxalate and 1,2-pheylenediamine and its analogs were therefore present in large excess.[52] In these cyclocondensations the use of a 10-fold excess of **63** gave better conversions of **62** with SiO_2 and KSF supports. Of the solid supports tested, SiO_2 gave the best yields and the cleanest mixtures. The use of *p*-TsOH gave 94% yield of the desired product in just 2.5 minutes (Table 8).

Table 8

Entry	Solid Support	Acidic Reagents	Ratio[a] 62:63	T_{med} (°C)	Time (min)	Yield (%)
1	SiO_2	-	0.1:1	140	1	56
2	SiO_2	-	0.1:1	140	3	89
3	KH_2PO_4	-	0.1:1	140	3	31
4	Dowex 50x8	-	0.1:1	150	3	[34]
5	KSF	-	0.1:1	170	3	63[c]
6	KSF		0.5:1	170	3	36[c]
7	-	9N H_2SO_4	0.1:1	150	3	8[d]
8	-	*p*-TsOH[e]	0.1:1	140	2.5	94

[a]The amount of **63** was constant and **62** was varied. [b]Based on the limiting reagent. [c]Complex product mixture. [d]Extensive hydrolysis of **1** to oxalic acid. [e]Catalytic amount

4. Conclusions

The combination of supported reagents and microwave irradiation has been used to carry out different reactions in short times and with high conversions without the need for solvents. The recyclability of some of these solids supports makes these processes eco-friendly green protocols.

The synthesis of a range of coumarin derivatives has been achieved using heterogeneous catalysts under microwave irradiation. Two types of reaction, the reaction of phenols with α,β-unsaturated carboxylic acids and the Pechmann reactions, are readily catalysed by cation-exchange resins such as Dowex or Amberlyst and Montmorillonite.

A variety of benzene derivatives can be synthesised in a single step by cycloaddition of furans followed by ring opening of the oxabicyclo intermediate by the action of silica-supported Lewis acids under microwave irradiation. This method represents a simple, general and useful alternative for the preparation of some polysubstituted benzenes whose synthesis is difficult by other methods. The same silica-supported Lewis acids are effective catalysts for the cyclotrimerization of aliphatic and aromatic nitriles to 1,3,5-triazines and for the synthesis of a range of alanine derivatives by reaction of α-acetamidoacrylate with

heterocycles such as furan, pyrrole, indole, pyrazole and benzene derivatives. For *N*-benzylpyrrole or trihydroxybenzene the use of stronger acid catalysts, such as *p*-TsOH and Dowex resin, improves the yields.

Finally, the use of solid supports and solvent-free conditions was critical for obtaining good yields in the acid-catalysed diamidation with concurrent heterocyclization to give quinoxaline-2,3-dione. The reaction was rapidly achieved using microwave dielectric heating and this approach avoided the conventional methods in which substrates were heated with corrosive mineral acids for prolonged periods.

In all cases the advantage of using microwave irradiation is not exclusively in the acceleration of the reaction. Indeed, most compounds gave very low yields or did not react when the reactions were performed using classical heating methods in an oil bath under comparable reaction conditions (time and temperature).

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INTRAMOLECULAR PALLADIUM-CATALYSED ANNULATIONS: ADVANCES IN AZAPOLYCYCLIC INDOLE SYNTHESIS

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Abstract. *Intramolecular palladium-catalysed annulation reactions giving rise to indole rings a- or b-annulated with five or six membered azacycles are reviewed.*

Contents

1. Introduction

Palladium-catalysed route to heterocyclic compounds is a well exploited synthetic approach as demonstrated by the massive growing-up of the literature devoted to this research field.[1] In particular, palladium-catalysed annulations involving formation of either carbon-carbon or carbon-nitrogen bonds, have proven to be very useful in the synthesis of indole and polycyclicindole derivatives.[1,2] In this review we present an exhaustive past-decade coverage of the intramolecular palladium-catalysed annulation processes devoted to the synthesis of indole rings a- or b-annulated with five or six membered azacycles (Figure 1). Thus far, intramolecular palladium-catalysed annulation reactions have been employed only for the synthesis of the ring systems reported in bold in Figure 1; moreover the structures depicted in series I and II, have been synthesized only by palladium-catalysed C-N bond formation.

In particular, the main focus of this review is to highlight the most relevant approaches to these heteropolycycles, involving intramolecular annulation reactions catalysed by palladium salts or complexes. Synthetic processes involving a catalytic step in the earlier stages of the synthesis and devoted to the preparation of starting materials are not included, whereas domino reactions involving a palladium-catalysed step in the construction of the polycyclic structures are reviewed.

The results reported in the literature clearly demonstrate that such catalysed annulation reactions represent an important strategy in the field of heterocyclic synthesis as well as in medicinal and natural product chemistry, and posses practical advantages with respect to classical synthesis in terms of yields, versatility and environmental impact. We hope that this work will encourage the research of new applications devoted to the synthesis of other classes of azaannulated indoles.

2. a-Azaannulated polycyclic indoles by intramolecular palladium-catalysed C-N bond formation

Katayama and co-workers are involved since several years[3] in the chemistry of pyrazolo[1,5-a]indoles which represent a class of strong antiproliferative agents.[4]

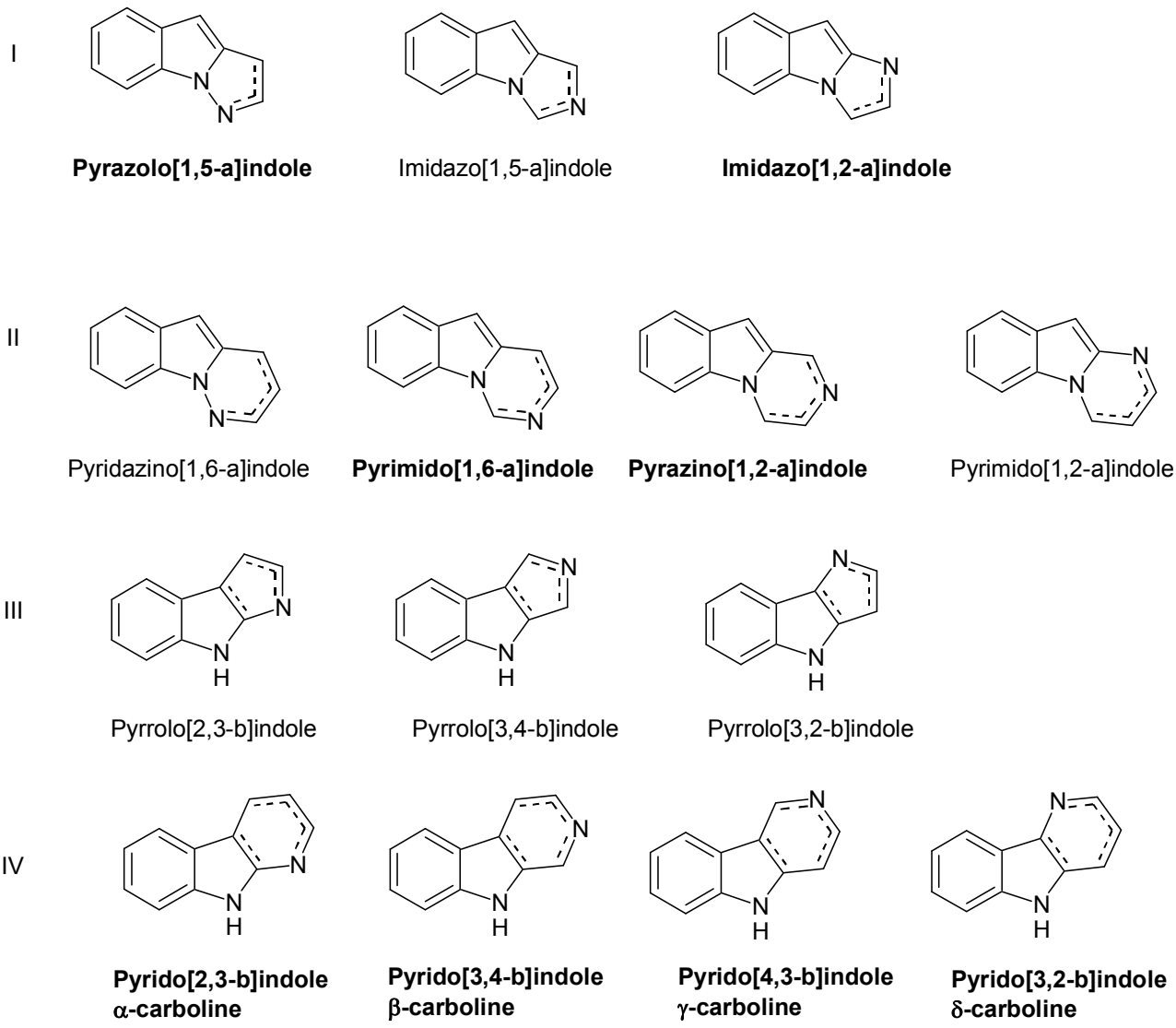
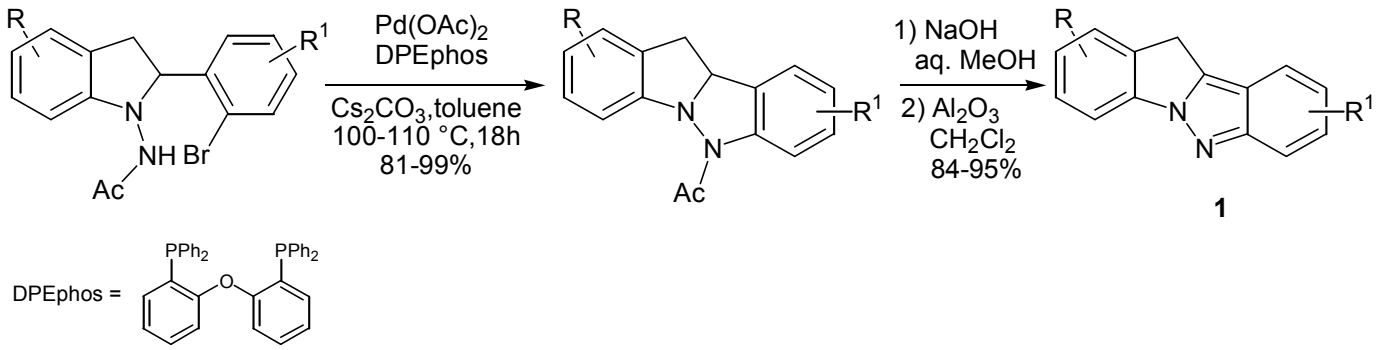


Figure 1

During the course of their studies they planned to synthesize indolo[1,2-b]indazoles **1** by palladium-catalysed intramolecular *N*-arylation reaction starting from *N*-acetamino-2-(2-bromo)arylindolines, which in turn, are easily available by standard methodologies (Scheme 1).[5]



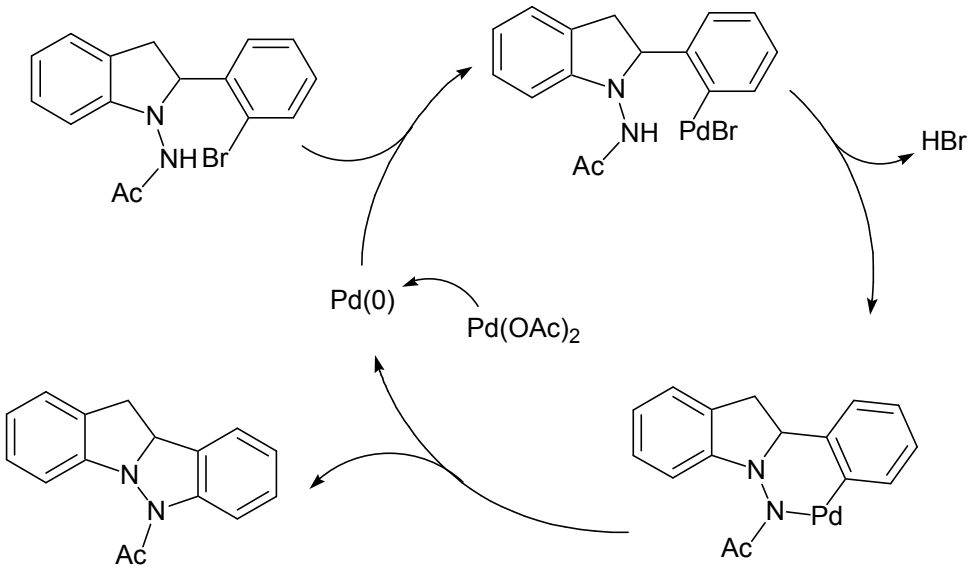
Scheme 1

The intramolecular C-N bond formation, catalysed by palladium acetate, represents the key step in the process, giving rise to the desired and potentially active compounds **1** after hydrolisis followed by air

oxidation.

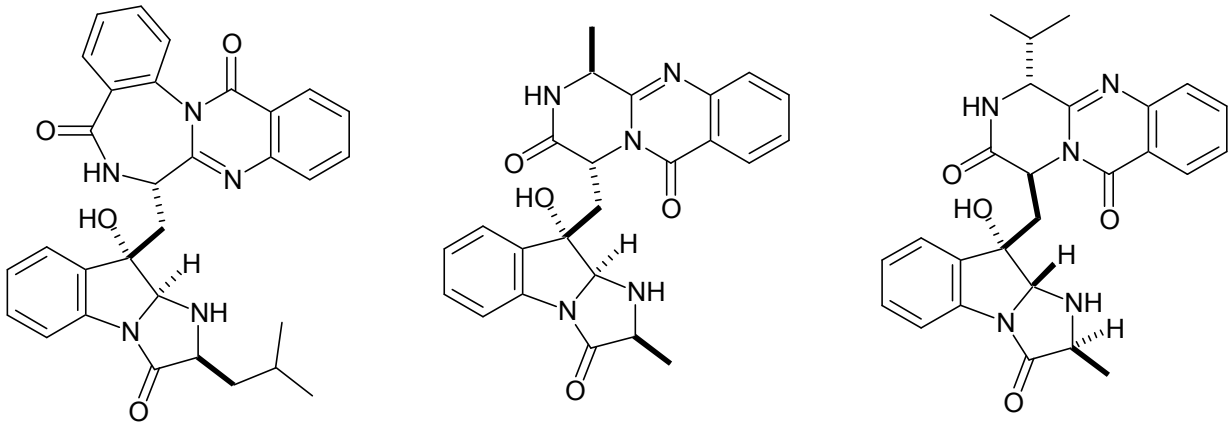
The cyclisation protocols for the intramolecular palladium-catalysed *N*-arylation reactions of secondary amides and carbamates were previously developed by Buchwald and co-workers.[6]

As reported by Buchwald, Pd(0) is the active catalyst and the catalytic cycle involves oxidative addition of Pd(0) to the C_{sp2}-bromine bond, coordination and deprotonation of the NH group to form a palladacycle intermediate which gives the *N*-arylated product by reductive elimination of Pd(0) (Scheme 2). The use of bidentate phosphine ligand such DPEphos instead of a triarylphosphine improves the yields and decreases the quantity of catalyst needed to accomplish the transformation.[6c]



Scheme 2

A Buchwald-type intramolecular amidation reaction[6] represents also the key step in the synthesis of naturally occurring asperlicin, fumiquinazoline and fiscalin alkaloids, which contain an imidazoindolone moiety (Figure 2).

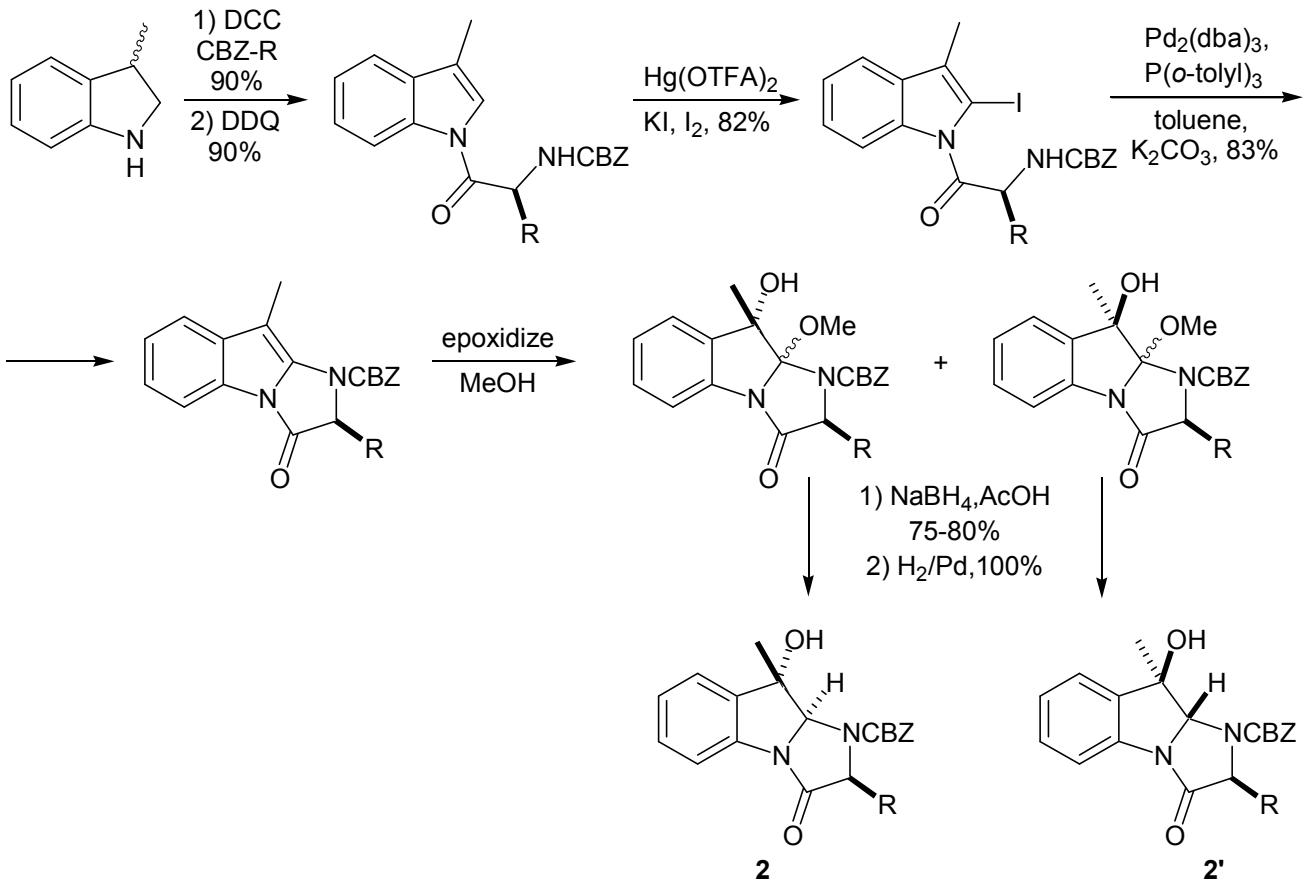


Asperlicin Fumiquinazoline A Fiscalin A

Figure 2

Asperlicin is a potent cholecystokinin antagonist isolated from a strain *Aspergillus alliaceus*.[7] Recently, the fumiquinazolines A, B, C, E, F, G, possessing moderate cytotoxic activity, were isolated from a strain of *Aspergillus japonicus*,[8] whereas the antifungal fumiquinazolines H and I were isolated from a fungus of the genus *Acremonium*.[9] Alkaloids of the fiscalin series A, B and C were isolated from the broth extracts of the fungus *Neosartorya fischeri*, and tested as inhibitors of the substance P binding.[10]

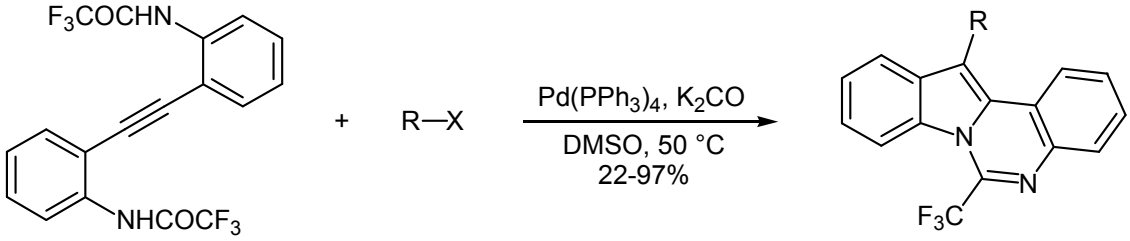
The most recent approach to the imidazoindolone fragment of these alkaloids was realized by Snider group which tested a new synthetic pathway involving a palladium-catalysed step.[11] The new procedure was initially applied to the preparation of model compounds **2** and **2'** (Scheme 3) and then extended to the synthesis of the more complex target compounds. Thus, condensation of 3-methylindoline with *N*-CBZ-L-alanine and oxidation with DDQ affords the corresponding acylated indole which was subjected to mercuration with Hg(OTFA), exchange with KI and then iodination giving rise to the appropriate building block for the palladium-catalysed intramolecular *N*-arylation reaction. The annulation conditions are those reported in the former works of Buchwald[6b] and provided the crucial imidazolindolone in 83% yield. Completion of the model study required epoxidation-reduction sequences to finally afford **2** and **2'**.



Scheme 3

Cacchi and co-authors developed a different approach to the intramolecular palladium-catalysed C-N bond formation. They widely used domino aminopalladation-reductive elimination reactions for the construction of functionalised indole rings from terminal or internal alkynes[2b,12] and recently reported the extension of this methodology to the synthesis of indole[1,2-*c*]quinazolines.[13] In particular, indole[1,2-*c*]quinazolines **3** with R=aryl or vinyl were synthesized starting from bis(*o*-trifluoroacetamidophenyl)-acetylene which reacts with aryl or vinyl halides and triflates in the presence of a palladium catalyst (Scheme

4). On the basis of their previously reported results the authors successfully employed $Pd(PPh_3)_4$ and K_2CO_3 as precatalyst species and the base, respectively. The reaction proved to be strongly influenced by the nature of the solvent and the highest yields and reaction rates were obtained in DMSO at 50 °C.

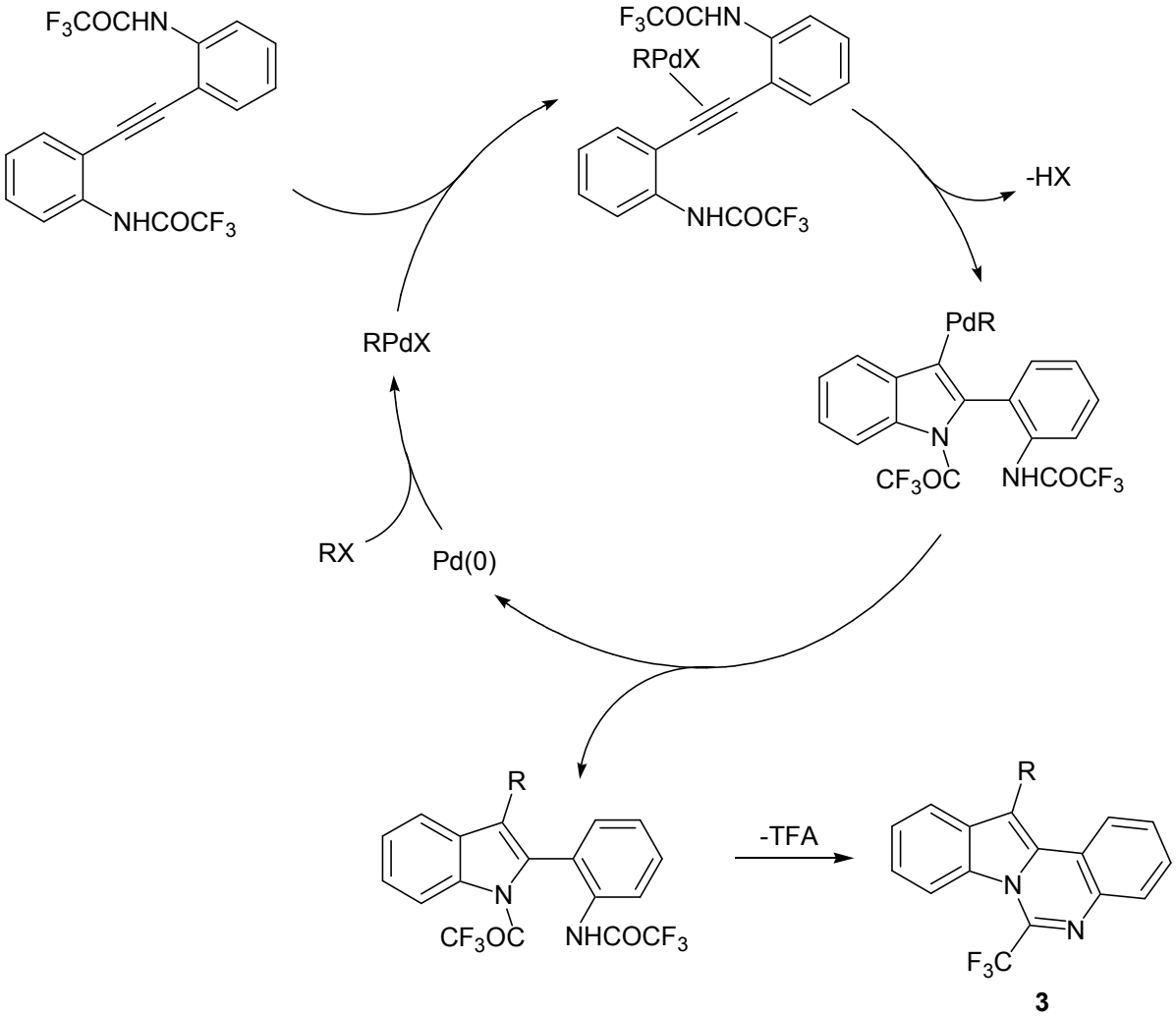


3

RX = aryl iodides, aryl bromides, vinyl iodides, vinyl bromides or vinyl triflates.

Scheme 4

The formation of the indoloquinazoline nucleus involves the intermediacy of an indole derivative generated from the corresponding η^2-alkyne-organopalladium complex by intramolecular aminopalladation-reductive elimination pathway. The domino process became then enriched by a new step in which the tetracyclic derivative was generated by intramolecular nucleophilic attack and elimination of trifluoroacetic acid (Scheme 5).



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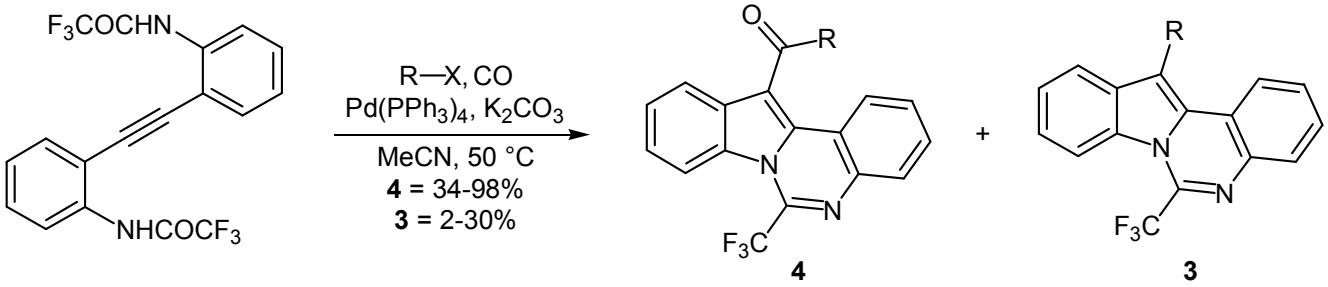
Scheme 5

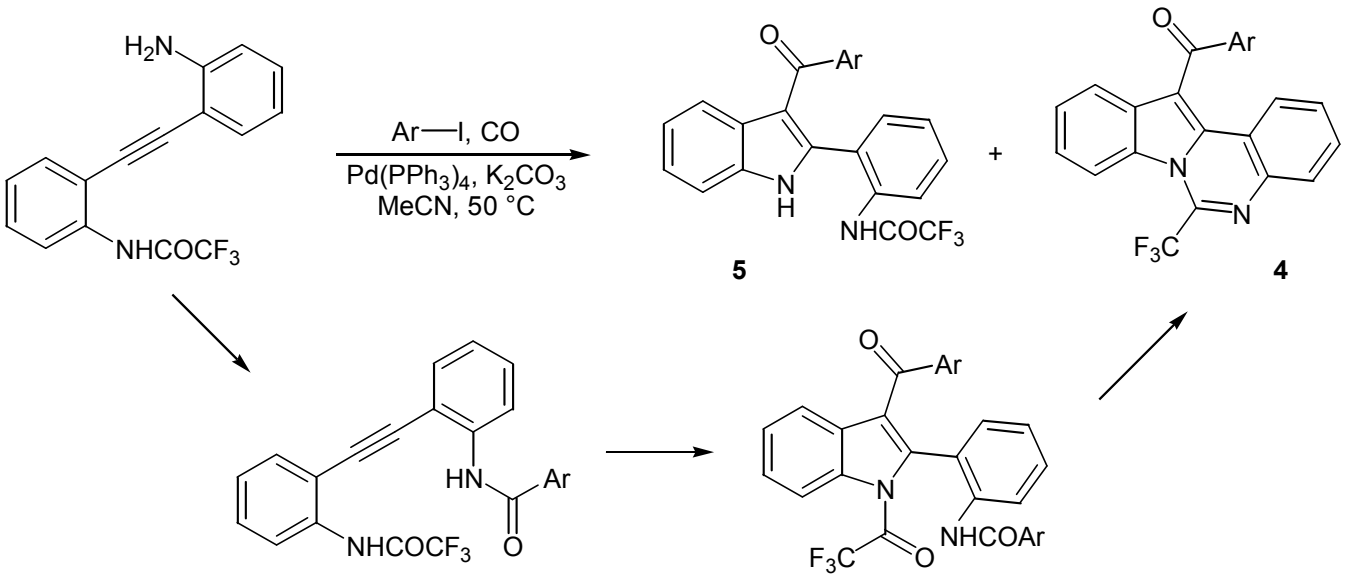
Likewise, the same research group obtained the 12-acylindolo[1,2-*c*]quinazolines **4**, beside variable amounts of non-cabonylated derivatives **3**, from bis(*o*-trifluoroacetamidophenyl)acetylene and aryl or vinyl halides and triflates in the presence of carbon monoxide (Scheme 6). The best standard reaction conditions employ $Pd(PPh_3)_4$ and K_2CO_3 in anhydrous acetonitrile at 50 °C under 5 bar of carbon monoxide.[14]



RX = aryliodides, vinylbromides or vinyltriflates.

Scheme 6

The reaction is effective only with bis(*o*-trifluoroacetamidophenyl)acetylene as starting compounds. When *o*-(*o*-aminophenylethynyl)trifluoroacetanilide was reacted with aryliodides under standard conditions the 3-acylindole derivatives **5** were isolated beside the indolequinazolines **4** (Scheme 7). Moreover, detailed studies showed that **4** are not generated from **5** by intramolecular nucleophilic attack of the indole nitrogen to the carbon of the ortho trifluoroacetamido group. Instead, the formation of the indolequinazoline derivatives involves the following key steps: 1) conversion of the free amino group into the corresponding amido derivative via acylation with an acylpalladium complex formed in situ, 2) aminopalladation-reductive elimination-intramolecular cyclisation domino reaction to afford the final product **4** (Scheme 7).[14]



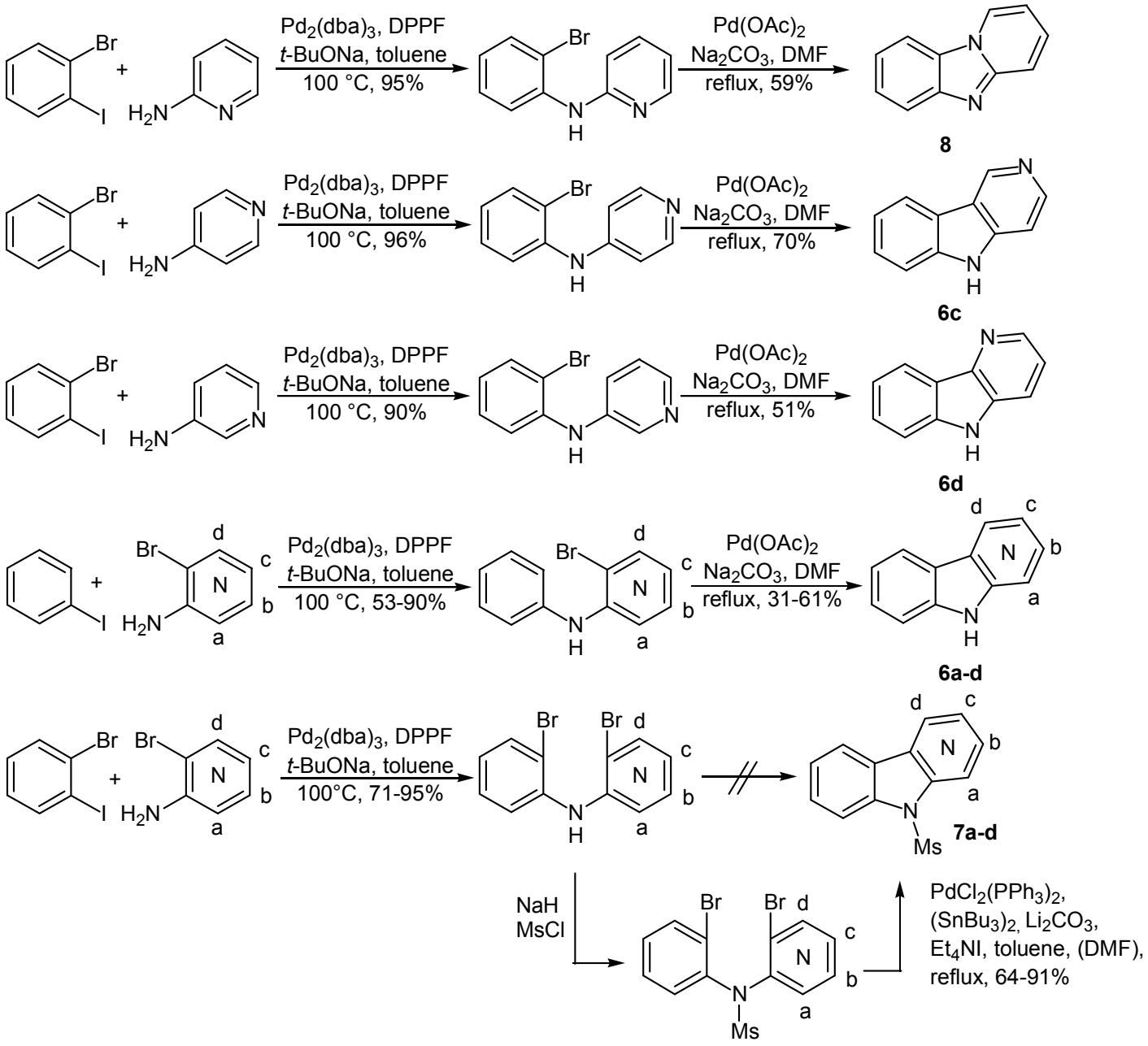
Scheme 7

It is worth to note that the synthesis of indoloquinazolines **3** and **4** was realised by domino palladium-catalysed reactions with formation, in a single step, of three and four new bonds, respectively.

3. b-Azaannulated polycyclic indoles by intramolecular palladium-catalysed C-C bond formation

There are no reports concerning the synthesis, by intramolecular palladium-catalysed reactions, of indole derivatives corresponding to the structures depicted in series III (Figure 1), whereas palladium-catalysed synthesis of the carbolines depicted in series IV have been extensively studied by several research groups. Carboline nucleus play a central role in many therapeutic agents and is found in numerous natural alkaloids. Many synthetic routes to these heterocycles have been developed and also the intramolecular palladium-catalysed approach has been widely used for the synthesis of the simplest terms of this class, such carbolines and carbolinones, as well as in multistep preparation of naturally occurring compounds.

For example, Sakamoto and co-workers in a recent paper[15] described the preparation of all four parent carbolines. Their strategy consists of the combination of two palladium-catalysed reactions, namely the amination reaction of iodobenzenes with aminopyridines and the intramolecular arylation reaction of *ortho*-bromo- or *ortho,ortho'*-dibromoanilinopyridines (Scheme 8).



Scheme 8

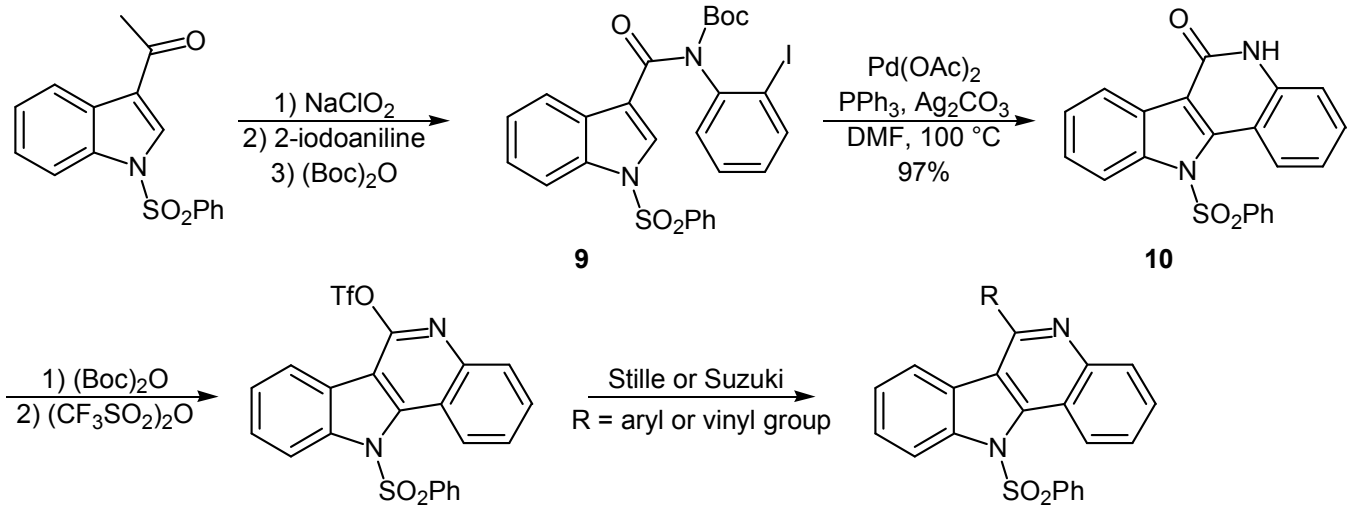
In the first step three different series of anilinopyridines, namely the 2- 4- and 3-(2-bromoanilino)pyridines, the four isomeric *o*-anilinobromopyridine and the four isomeric *o*, *o'*-dibromo-anilinopyridine where prepared in moderate to high yields starting from the appropriate iodoaryls and aminopyridines following the procedure optimised by Buchwald[16] and Hartwig.[17]

The second step regards the formation of a new intramolecular C-C bond and was achieved, for the bromoanilinopyridine derivatives, by an intramolecular heteroaryl Heck reaction[18] in the presence of palladium acetate as catalyst and sodium carbonate as base. Although the cyclisation by intramolecular arylation reaction of 4- and 3-(2-bromoanilino)pyridines gave γ- and δ-carbolines **6c** and **6d** in 70 and 51% yield, respectively, the cyclisation reaction of 2-(2-bromoanilino)pyridine failed to give the corresponding α-carboline and the pyrido[1,2-*a*]benzimidazole **8**, which resulted from the cyclisation reaction at the pyridine ring nitrogen, was isolated in 59% yield.

Whereas this route presents some drawbacks related to the unavailability of all four carboline isomers, the reactions performed with *o*-anilinobromopyridines under the same experimental conditions gave the corresponding four carbolines **6a-d** 31-61% yields.

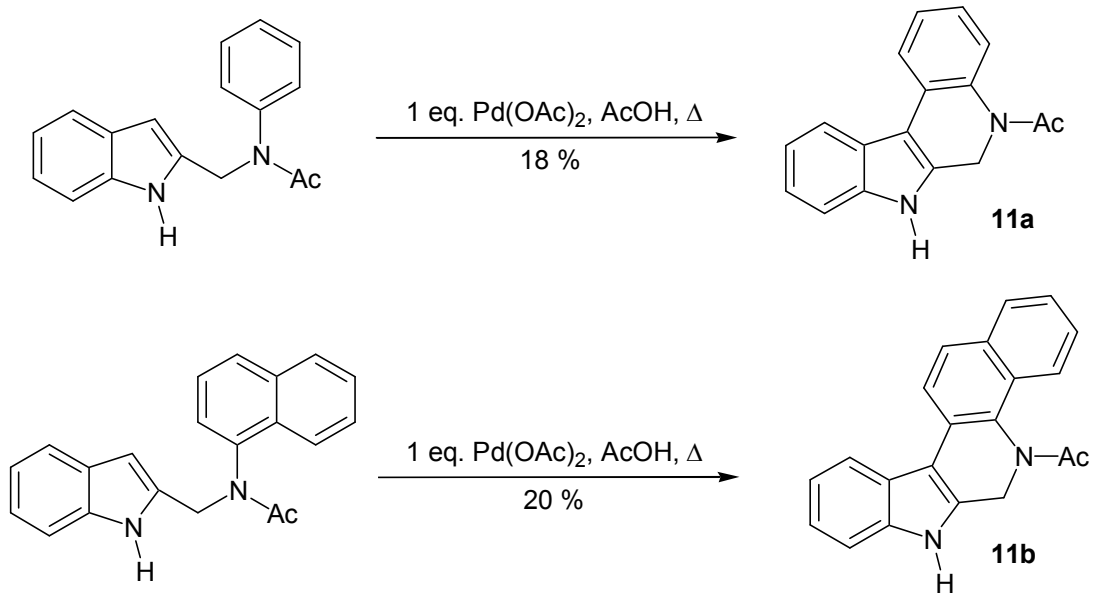
Finally, in order to improve the yields of the cyclisation step the authors examined a third method involving as key intermediates the *o*,*o'*-dibromoanilinopyridines, which were converted to the corresponding *N*-methylsulphonylderivatives and then subjected to the cyclisation step by Stille-Kelly coupling reaction[19] with hexabutyldistannane in the presence of dichlorobis(triphenylphosphine)palladium, lithium carbonate, and tetrahethylammonium iodide in toluene or toluene/DMF under reflux. Under these conditions *N*-methylsulphonylcarbolines **7a-d** were obtained in 64-91% yields.

As a part of a program devoted to the search of new anticancer agents, Mérour et al. became interested in the synthesis of 6-substituted indolo[3,2-c]quinoline.[20] They planned to generate the six-membered ring of the quinoline system by an intramolecular Heck[18a] reaction of the *N*-Boc-*N*-2-iodophenyl-3-indolecarboxamide **9** prepared in three steps from easily available compounds (Scheme 9). The amide was protected with the Boc group in order to prevent deiodination on the phenyl ring during the Heck reaction. Optimal cyclisation conditions were found to be palladium acetate (20%), triphenylphosphine (40%) and silver carbonate in DMF at 100 °C. The obtained (97%) compound **10** was then converted to the corresponding triflate, which represent the building block for the preparation of 6-substituted derivatives, by Stille or Suzuki coupling (Scheme 9).



Scheme 9

An oxidative cyclisation process giving rise to benzo- and naphtho-β-carbolines **11a,b** (Scheme 10), was reported by Srinivasan.[21] The reactions were performed by refluxing an equimolar amount of *N*-(1*H*-indol-2-ylmethyl)-*N*-phenyl-acetamide or *N*-(1*H*-indol-2-ylmethyl)-*N*-naphtalen-2-yl-acetamide and palladium acetate in acetic acid for 1 h. Oxidative cyclisation[22] occurs by direct palladation of the indolylmethylacetamide affording a σ-arylpalladium(II) complex which by subsequent insertion reaction on the aryl ring and β-hydride elimination results in β-carbolines **11a,b**. This approach, however, retains some limitations: the reaction is stoichiometric with respect to Pd(II) specie which was reduced to Pd(0) during the oxidative cyclisation step, moreover the yields are poor and the method has not a general application. For example when the *N*-acetamide was substituted with a *p*-methoxyphenyl or a *p*-tolyl moiety the cyclisation failed.

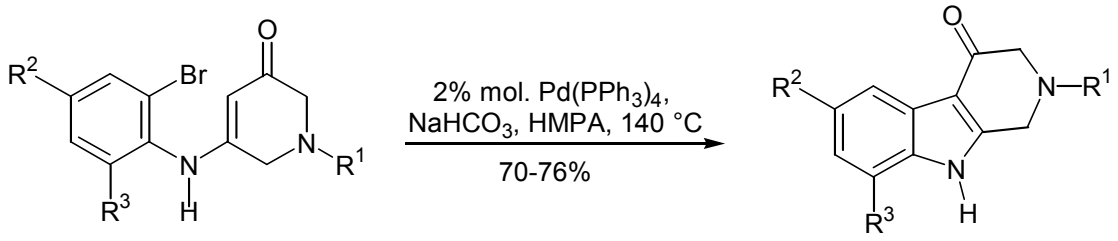


Scheme 10

The synthesis of β- and γ- carbolinones has attracted some attention in the past decade and the development of new synthetic methods is still an active research area. The β-carbolin-2-one nucleus occurs in some natural alkaloids[23] and in various molecules with different pharmacological activities, *i.e.* antitumoural agents[24] and HLE inhibitors.[25] The less common γ-carbolin-4-one framework occurs in a 5-HT_3 receptor antagonist,[26] and in some potential antitumoural agents.[20]

In 1995 Chen and co-workers published a palladium-catalysed synthesis of tetrahydrocarbolin-4-ones **12** starting from bromoenaminones.[27] The reaction is an extension of the intramolecular Heck protocol[18] and emploies for the first time, beside the usual arylbromide, an enaminone system as olephinic moiety. The reactions were performed heating at 140 °C for 2 h a solution of the appropriate bromoenaminone in hexamethylphosphoric triamide in the presence of only 2% mol. of palladium tetrakis and 2 equiv. of sodium hydrogen carbonate (Scheme 11).

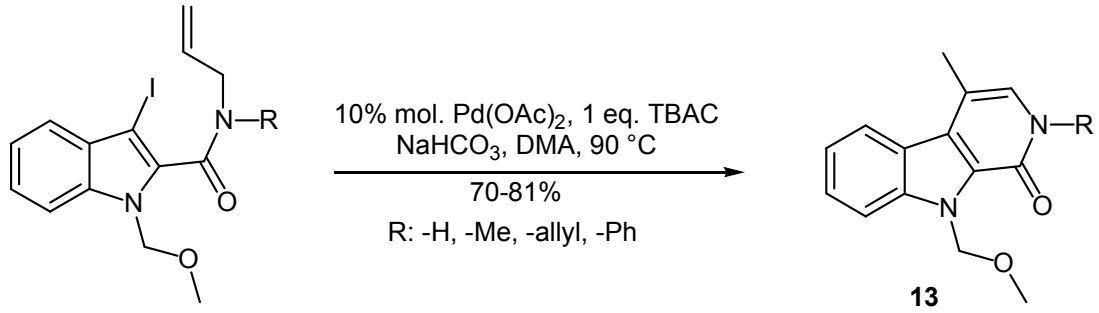
A catalytic Heck-type approach to the synthesis of both β and γ-carbolinones was recently developed by Beccalli and co-authors.[28] The authors employed as starting material a series of 3-iodo-indole-2-carboxylic acid allyl-amides and 2-iodo-indole-3-carboxylic acid allyl-amides obtained by reaction of the corresponding acyl chloride with the suitable allylamine.



R^1: -Bn, -COOEt
R^2: -H, -Me
R^3: -H, -Me

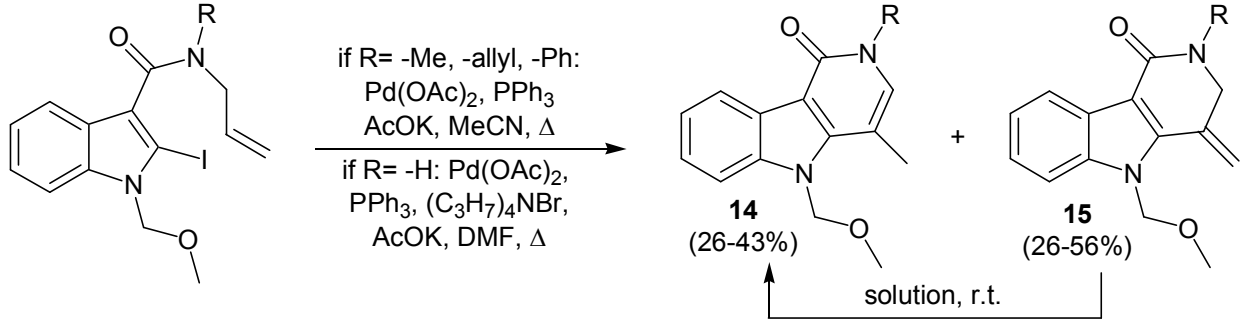
Scheme 11

The cyclisation step to give β-carbolinones **13** in moderate to good yield was performed in dimethylacetamide at 90 °C, using a catalytic system composed by 10% mol. palladium acetate, 1 equiv. of tetrabutylammonium chloride and 2.5 equiv. of sodium hydrogen carbonate (Scheme 12).



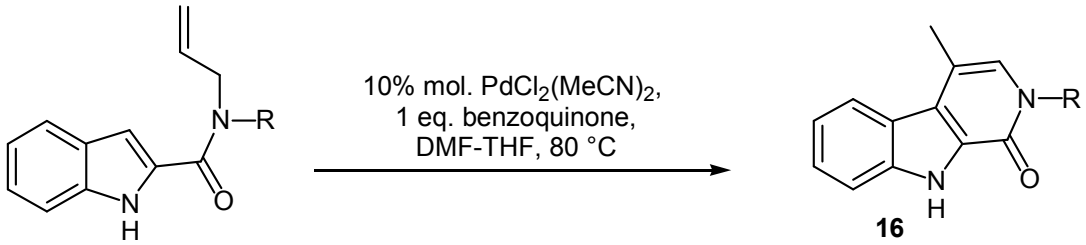
Scheme 12

On the other hand the annulation reaction to give γ-carbolinones resulted in a mixture of two isomeric compounds **14** and **15**. The cyclisation of tertiary allyl amides gave best results using a catalytic system composed of 10% mol. palladium acetate / 20% mol. triphenylphosphine / 3 equiv. of potassium acetate and refluxing the reaction in acetonitrile. Otherwise, secondary allyl amides needed different conditions to obtain the annulated compounds: 5% mol. palladium acetate, 15% mol. triphenylphosphine, 1 equiv. of tetrapropylammonium bromide, 4 equiv. of potassium acetate in DMF at 80 °C. It was also been observed that the isomeric γ-carbolinones **15** with exocyclic double bond isomerise in solution in a short time to the more stable isomers **14** (Scheme 13).



Scheme 13

As extension of this work, Beccalli and co-workers reported a very useful example of intramolecular palladium-catalysed oxidative annulation reaction of some indolic substrates without halogen substituent on C-3.[29] The cyclisation reaction of the indole tertiary 2-*N*-carboxamides with 10% mol. $PdCl_2(MeCN)_2$ as catalyst and benzoquinone as reoxidant agent, in a mixture of DMF-THF at 80 °C for 45 min. resulted in β-carbolinones **16** in good yields (Scheme 14).

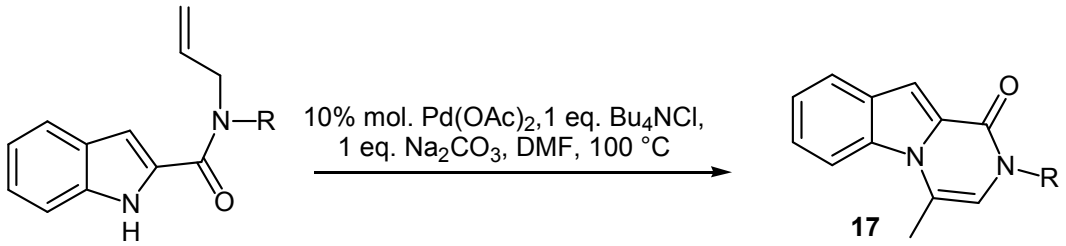


R= -H (0%); R= -Me (97%); R= -allyl (91%); R= -Ph (80%); R= -cycloexyl (94%).

Scheme 14

The mechanism proposed by the authors involves the direct palladation of the aromatic C-H bond giving a σ-aryl palladium complex, followed by an Heck-type double bond addition and β-hydride elimination.

It is interesting to note that changing the catalytic system and the reaction conditions it was possible to switch the reactivity of 1*H*-indole-2-carboxylic acid allylamides toward the construction of pyrazino[1,2a]indole system **17** via an intramolecular palladium-catalysed amination reaction of a double bond.[29(b)] The authors tested different catalytic systems and the best results were obtained using 5% mol. palladium acetate, 1 equiv. sodium carbonate and 1 equiv. tetrabuthylammonium chloride in DMF at 100 °C (Scheme 15).

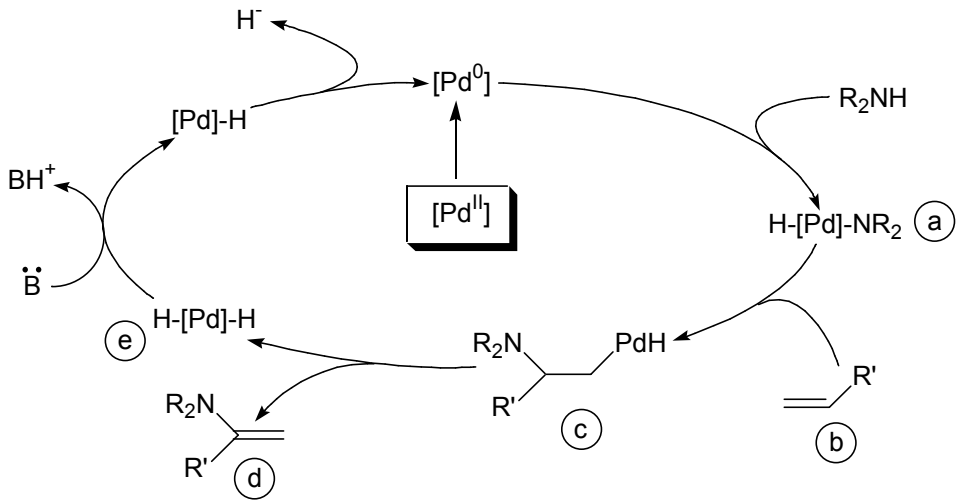


R= -Me (74%); R= -allyl (77%); R= -Ph (65%); R= -cycloexyl (79%).

Scheme 15

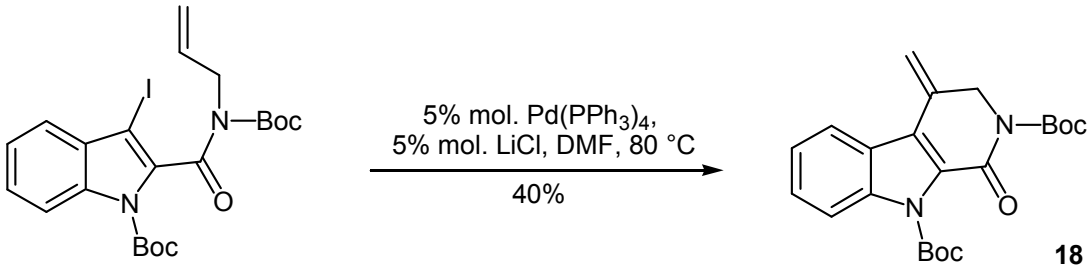
It has been argued that the presence of base and tetraalkylammonium salt was crucial to obtain the pyrazino[1-2a]indole derivative in satisfactory yields. The mechanism proposed involves the preliminary activation of the N-H bond, by way of oxidative addition of the indole moiety R_2NH to the coordinatively unsaturated metal center in a low oxidation state to give a hydrido-amido complex (**a**). Then, the reaction occurs at the Pd-N bond with the insertion of the olefin (**b**), generating a 2-aminoalkyl complex (**c**). The most common decomposition of the latter is by β-hydride elimination, leading to an unsaturated amine (**d**) as the oxidative amination product. The authors hypothesize that dehydrogenation reaction takes place to convert the resulting dihydride metal species (**e**) into the active catalyst species. Afterwards, the base and the

tetrabutylammonium chloride salt are essential to assist in the regeneration of zerovalent palladium catalyst (Scheme 16).



Scheme 16

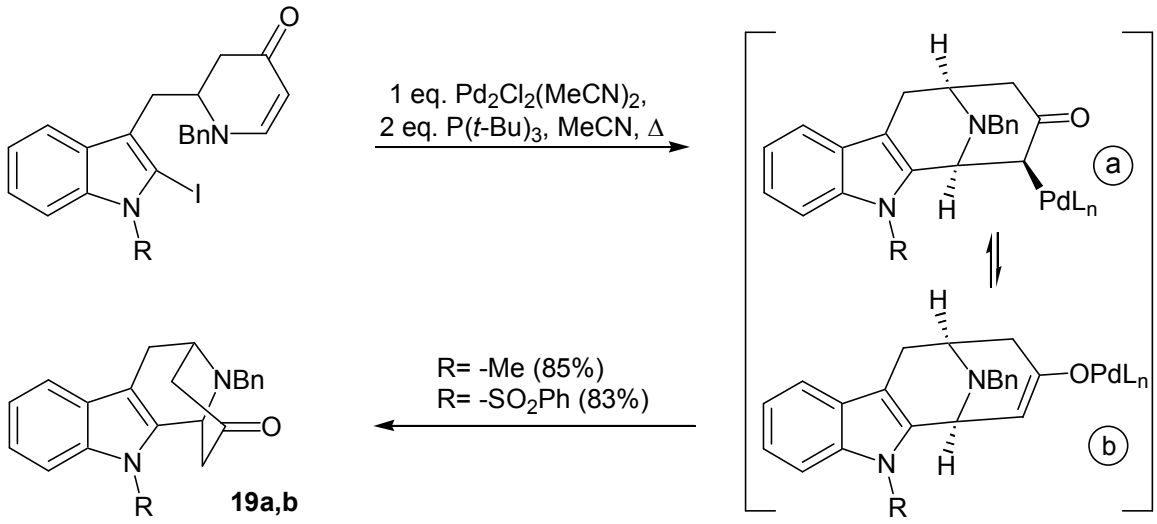
Mérour and coll., in the course of a research focused on the preparation of large fused lactams as innovating scaffold in medicinal chemistry (*i.e.* CDK inhibitors)[30], obtained, as a by product, the 4-methylene-tetrahydro-β-carbolin-1-one **18** in 40% yield, starting from the *N,N*-Boc protected 3-iodoindole-2-carboxylic acid allylamide (Scheme 17).[31] The catalytic system used (5% mol. palladium tetrakis and 5% mol. lithium chloride) can probably represent a suitable alternative to those used by Beccalli and co-workers for the preparation of analogous structures.



Scheme 17

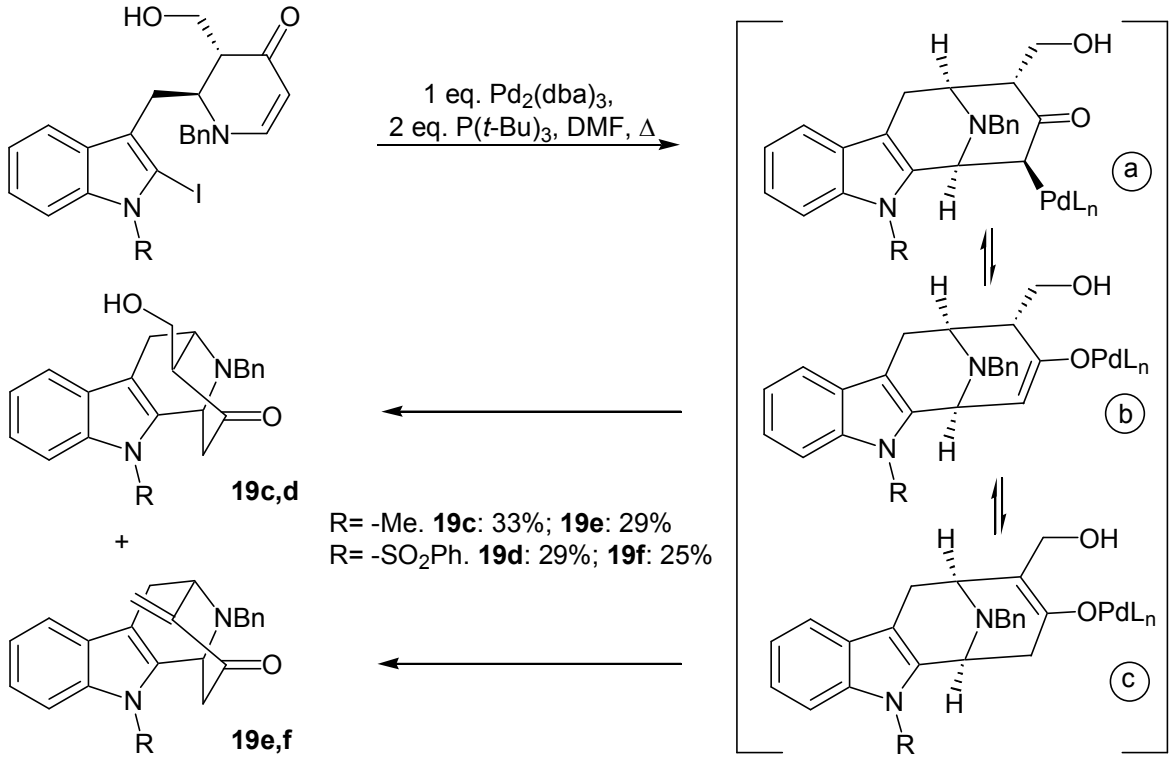
The palladium catalysed intramolecular approach to β-carboline alkaloids has been developed in the Merck laboratories. Kuethe and co-workers explored a new synthetic route to the tetrahydro-β-carboline framework of the ajamaline/sarpagine alkaloids.[32] These alkaloids, isolated from various species of Alstonia and Rauwolfia, show a plethora of biological and pharmacological proprieties.[33] The key step of the synthesis was the intramolecular cyclisation of the 2-(2-iodoindolylmethyl)-4-pyridones derivatives. After some failing attempts under standard radical initiation conditions (Bu_3SnH, AIBN, toluene, reflux) and anionic cyclisation conditions (*t*-BuLi, -78 °C, THF), the authors chose to investigate a transition-metal approach. The lack of β-hydrogen available in intermediates (**a**) or (**b**) for completion of the Heck-type catalytic cycle determined the choice to explore some reductive Heck conditions. However, all attempts furnish only the reduced 2-indolylmethyl-4-pyridones derivatives. Nevertheless they found that when the 2-(2-iodoindolylmethyl)-4-

pyridones derivatives were subjected to Heck conditions employing a stoichiometric amount of palladium(II) (1 equiv. $PdCl_2(MeCN)_2$, 2 equiv. P(*t*-Bu)$_3$, MeCN, reflux) the desired products **19a-b** were obtained in 85% and 83% isolated yield respectively (Scheme 18).



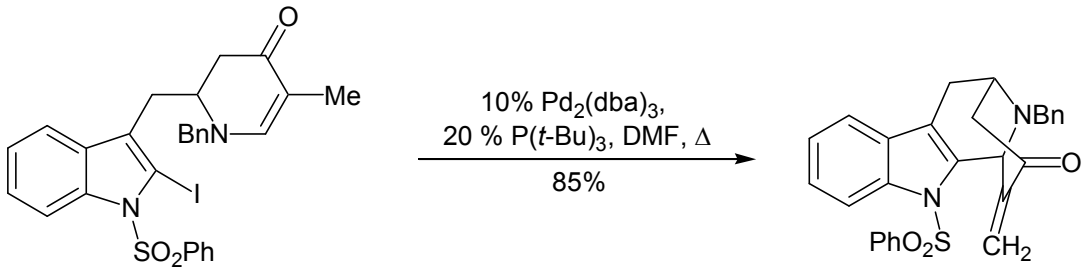
Scheme 18

On the other hand, it is interesting to note that the reaction of the 2-(2-iodoindolylmethyl)-4-pyridone derivatives bearing a hydroxymethyl moiety on C3, under similar conditions ($Pd_2(dba)_3$, P(*t*-Bu)$_3$, DMF, 100 °C) gave a mixture of the desired products **19c-d** and exocyclic methylene compounds **19e-f** arising from intermediate (**c**) (Scheme 19).



Scheme 19

Even though the use of stoichiometric palladium has limitations, this method provides an easy access to these complex alkaloid skeletons in a stereocontrolled manner. Finally Kuethe and coll. also prepared a ajamaline/sarpagine-type framework *via* catalytic intramolecular Heck cyclisation followed by β-hydride elimination.[32] To do this, the 2-(2-iodoindolylmethyl)-4-pyridone derivative bearing a methyl group on C5 was reacted with 10% mol. $Pd_2(dba)_3$, 20% mol. P(*t*-Bu)$_3$, in DMF at 100 °C to furnish the desired product **19g** in 85% yield based on recovered starting material (Scheme 20).

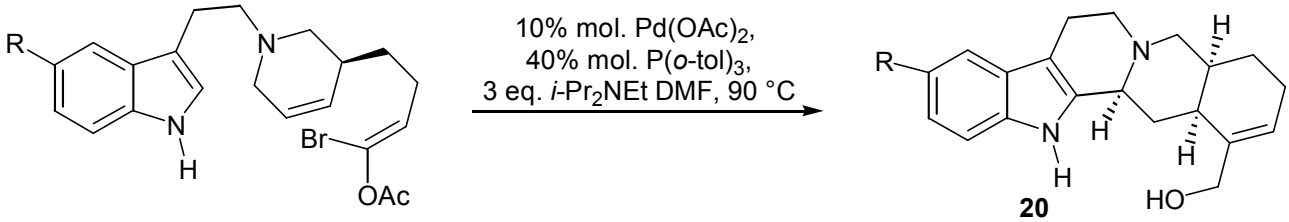


19g

Scheme 20

The research group of Ogasawara was interested in a stereocontrolled construction of the yohimbine alkaloids[34] by employing the intramolecular Heck annulation of an appropriate chiral starting material.[35] They achieve their purpose by means of treatment of some allyl acetates derivatives with palladium acetate (10% mol.) tri(*o*-tolyl)phosphine (40 % mol.) and Hünig base (3 equiv.) in DMF at 90 °C to afford the acetate of (-)-nitraina and his 10-metoxy-derivative **20** (Scheme 21).

The authors argue that, although the yields were far less then satisfactory, the single step generation of compounds **20** from bromides under the Heck conditions was extremely important on account of the chance to obtain the cyclisation products in a stereospecific way and devoid of to use acidic catalysis as previously reported.[36]



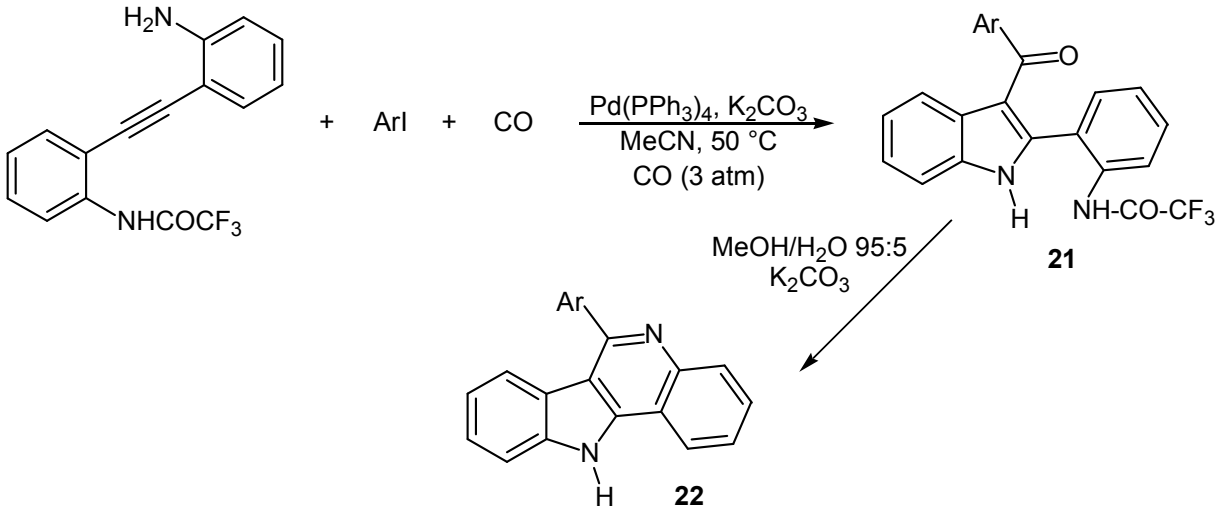
20

R= -H (8%); R= -OMe (21%).

Scheme 21

4. b-Azaannulated indoles by palladium-catalysed C-N bond formation

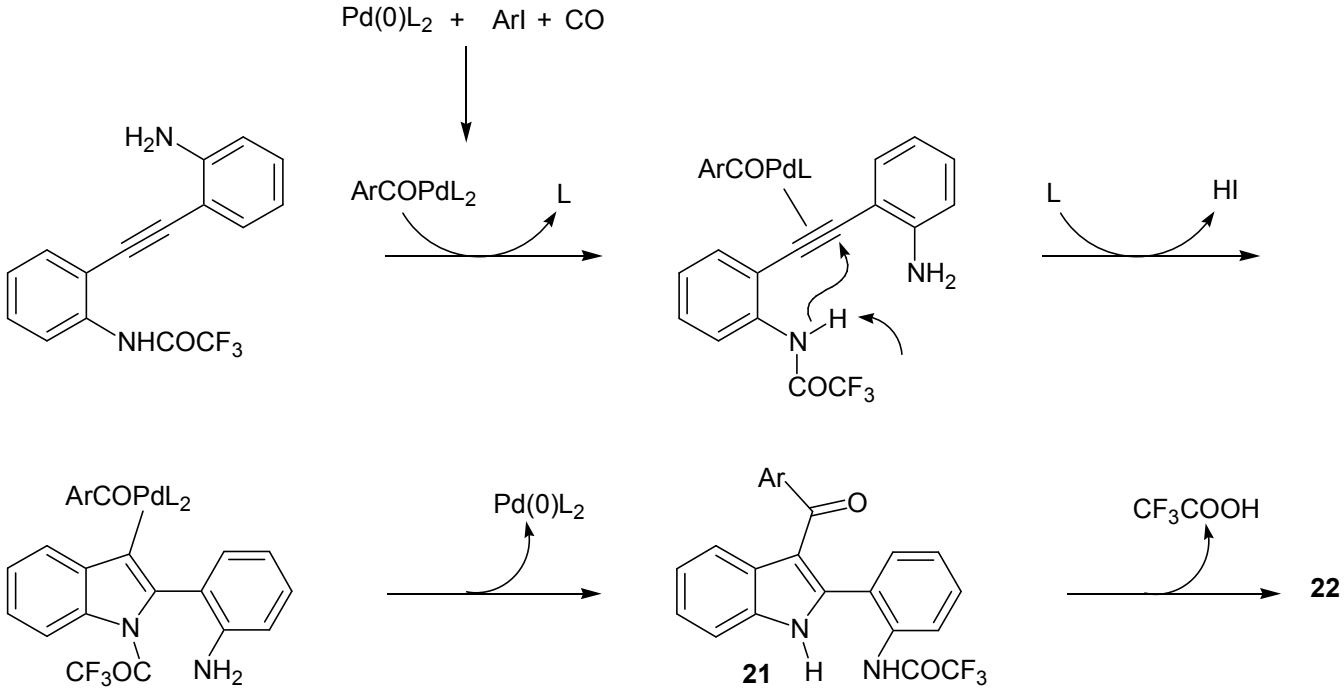
Both Cacchi and Larock groups applied and extended their studies on intramolecular annulation of alkynes based respectively on amminopalladation/reductive elimination domino reactions and on palladium catalysed iminoannulation reactions, to the synthesis of polycyclic γ-carboline derivatives. Cacchi and co-workers made an extensive study on the synthesis of the indole[3,2-*c*]quinolines **22** through a one-pot palladium-catalysed carbonylative cyclisation of 2-(2'-aminophenylethynyl)trifluoroaceanilide with aryl iodides followed by the cyclisation of the resultant 3-acylindole derivatives **21** (Scheme 22).[37]



Scheme 22

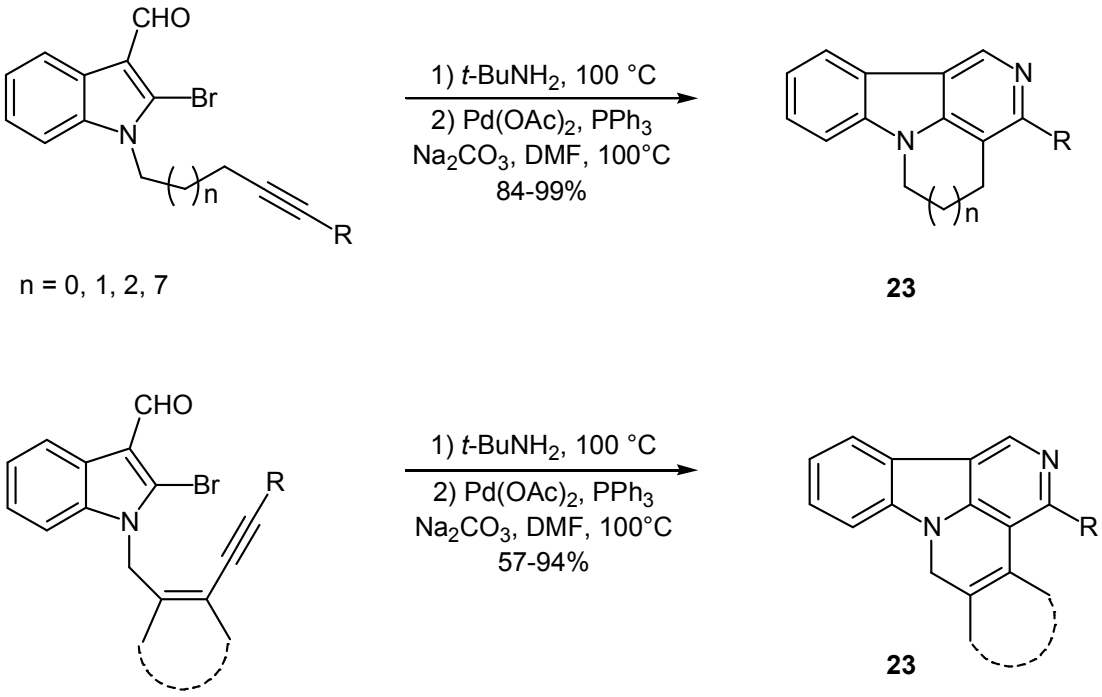
The reactions were carried out in a stainless steel vessel in acetonitrile at 50 °C using $Pd(PPh_3)_4$ as precatalyst, potassium carbonate as base and under 3 atm of carbon monoxide. Hydrolysis of the trifluoroacetamido group and subsequent cyclisation were performed in a mixture of methanol and water in the presence of potassium carbonate.

The proposed reaction mechanism is similar to that described by the same group for the synthesis of indole[1,2-*c*]quinazolines, scheme 5, and involves the formation of an acylindole as intermediate (Scheme 23). Nucleophilic attack of the nitrogen atom of the trifluoroacetamido group across the carbon-carbon triple bond, activated by coordination to an acylpalladium complex, generate a σ-acylpalladium intermediate which subsequently undergoes reductive elimination of palladium(0) specie to give **21** and finally a transamidation reaction to yield **22**. The acidity of the nitrogen-hydrogen bond plays an important role in the cyclisation step and when bis(2-aminophenyl)acetylene was employed in the cyclisation reaction none of the indole derivative was formed.



Scheme 23

Recently, Larock and co-worker reported the full details of the palladium-catalysed intramolecular imminoannulation of 2-bromo-1H-indole-3-carboxaldehydes containing an alkyne tether at the indolic nitrogen atom, affording γ-carboline derivatives **23**, with an additional ring fused across the 4- and 5-positions (Scheme 24).[38]



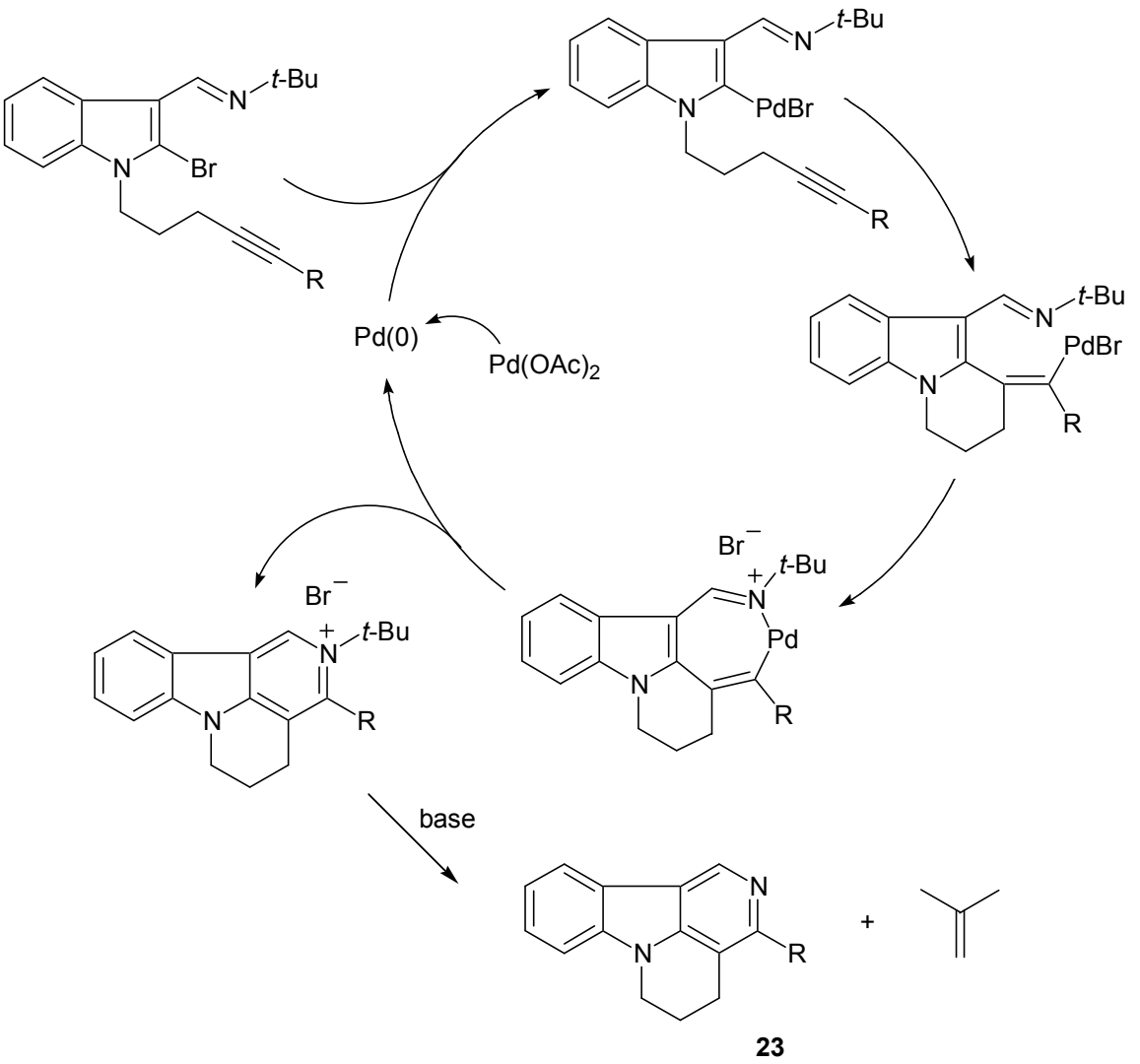
Scheme 24

This intramolecular iminoannulation methodology is limited to those tethered indoles with a CH_2-N bond linkage but tolerates different R groups. Tethered indoles containing aryl, alkyl, alkenyl, hydroxy, ester and pyrimidyl functionalities afforded the desired annulation products in excellent yields. Only when R is a hydrogen or a trimethylsilyl group a different behaviour was observed and the reaction give rise to a mixture of γ-carbolinium salts with a *tert*-butyl group on the nitrogen along with the desired compounds.

The reaction mechanism parallels with that already reported by the same group for the intermolecular imminoannulation reactions (Scheme 25).[39]

Oxidative addition of indolyl bromide to Pd(0) produces an organopalladium intermediate which adds across the tethered triple bond through an *exo-dig* addition, producing a vinylic palladium intermediate, which then reacts with the neighbouring immine group to form a seven-membered palladacyclic immonium salt. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt and regenerates Pd(0). As previously suggested by Heck[40] the *tert*-butyl group apparently fragments to relieve the strain resulting from the interaction with the substituent present on the vicinal carbon atom.

From several years Yang and co-workers are interested in palladium-catalysed cyclisation of various conjugated (**24**) and non-conjugated (**25**) α-(*o*-bromoanilino)alkenenitriles.[41] The feature of these compounds is the presence of an olefin and cyano groups oriented in similar proximity to the bromine atom. As a consequence, palladium-catalysed cyclisation may theoretically occur by two competitive pathways, namely by attach of the organopalladium intermediate on the olefinic function or on the cyano group.

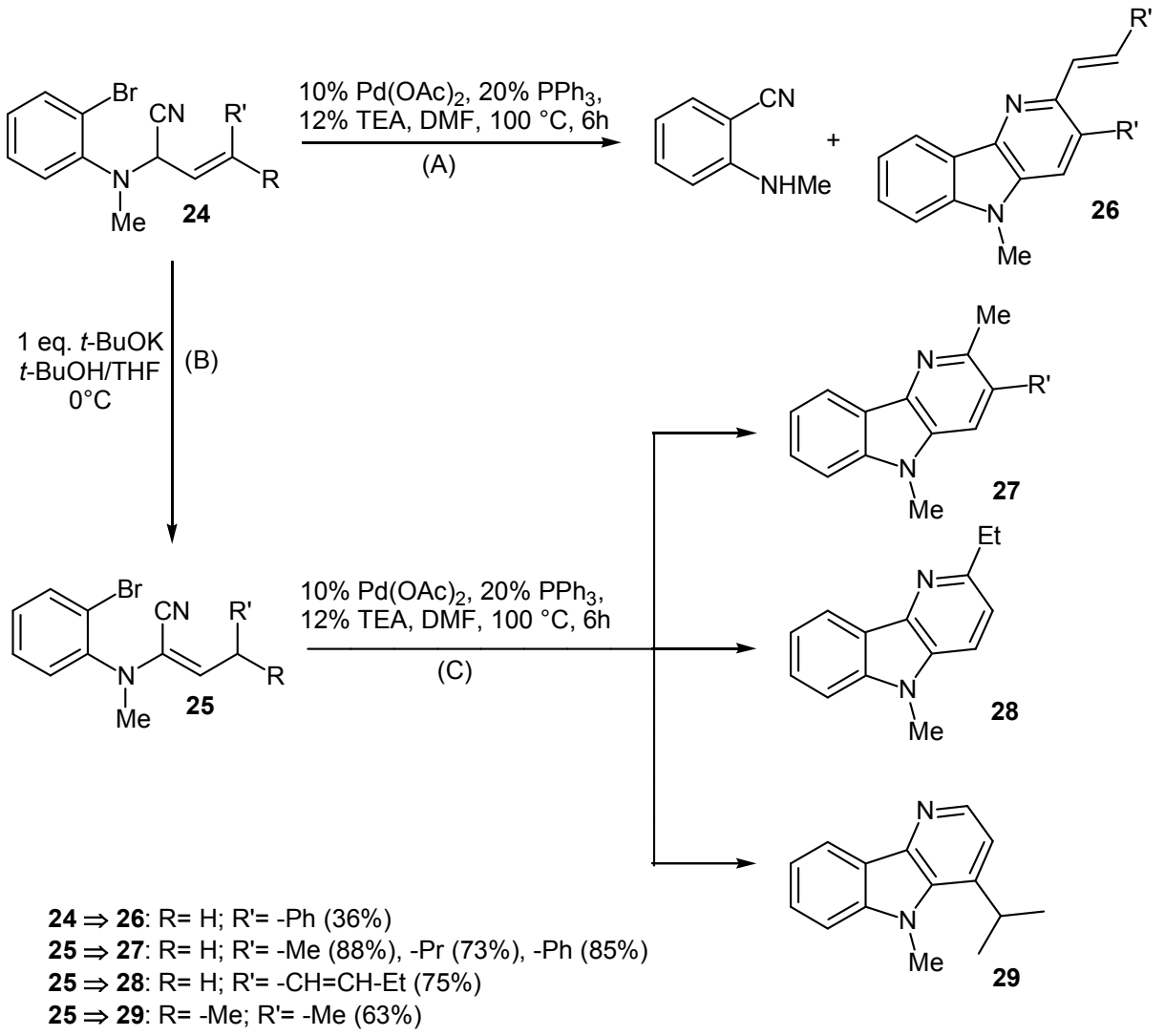


Scheme 25

The studies reported by the authors explained that the second path was absolutely the most covered and affords differently substituted δ-carbolines (Scheme 26). In a typical procedure α-(2-bromoanilino)alkenenitriles **24** in DMF were treated with 10 % mol. palladium acetate**,** 20 % mol. triphenylphosphine and 1.2 equiv. of triethylamine for 6 h at 100 °C under an argon atmosphere to give 2-methylamino benzonitrile and δ-carboline **26** in 38 and 36% yields, respectively. Unfortunately this reactions gave the desired δ-carboline only when R' is a phenyl group (Scheme 26, A).

The authors suggest a possible mechanism for the palladium-catalysed annulation reaction. The oxidative insertion of Pd(0) into the bromophenyl groups results in an organopalladium compound that undergoes cyclisation by attack on the cyano group, giving an iminoindoline intermediate. This might yield an iminium ion which is subsequently hydrolyzed to give 2-(methylamino)benzonitrile and an aldehydes. Only when R' is a phenyl group, the palladium amide reacted further with cinnamaldehyde to give **26**. Thus, this process might involve electrocyclisation, H-shift and elimination of palladium and HBr.

Under the same reaction conditions, the palladium-catalysed reactions of the conjugated bromoanilinoalkenenitriles **25** (obtained as *E*/*Z*-mixtures from **24** through treatment with strong base, Scheme 26, B) afforded δ-carbolines **27**-**29** in 63–88 % yields (Scheme 26, C). In the opinion of the authors the different behaviour observed in formation of **27**, **28** and **29** is reliant on the nature of R' group on **24**.

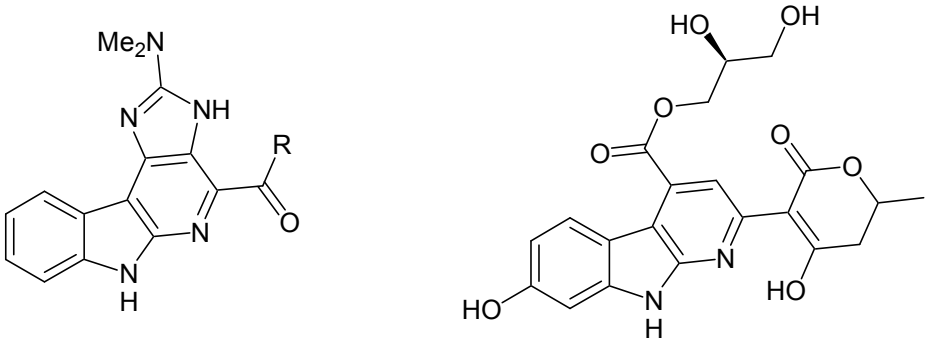


Scheme 26

When R' is a butenyl group, the organopalladium intermediate had the potential to undergo 6π electrocyclisation and subsequent elimination of palladium and HBr to generate the δ-carboline **28**. In the other cases the organopalladium intermediate could not undergo electrocyclisation thus the reaction occur toward the capture of an ethyl group from triethylammonium cation and subsequent elimination of palladium and HBr, followed by electrocyclisation and oxidative aromatization to furnish the δ-carbolines **27**. Finally, when both R and R' are methyl groups the organopalladium(II) intermediate underwent electrocyclisation and oxidative aromatisation in a different way to yield the 4-isopropyl-δ-carboline **29**.

Recently, some alkaloids having a pyrido[2,3-b]indole nucleus (α-carboline) have been isolated and characterized. These include the cytotoxic grossularines isolated from the marine tunicate *Dendroda grossularia*[42] and the neuroprotector mescengricin, isolated from *Streptomyces griseoflavus* (Figure 3).[43]

With the aim to propose an alternative approach to α-carboline nucleus, substituted with easily modifiable functional groups and suitable as building blocks for the construction of the reported natural products, Dodd and Abouabdellah planned and realized the synthesis of the fused butyrrolactone **30** (Scheme 27).[44] Thus, 2-bromoindole-3-carboxaldehyde was *N*-methylated and then subjected to condensation with the enolate of the 4-*N*-Boc-aminobutyro-γ-lactone to yield the corresponding aldol product.

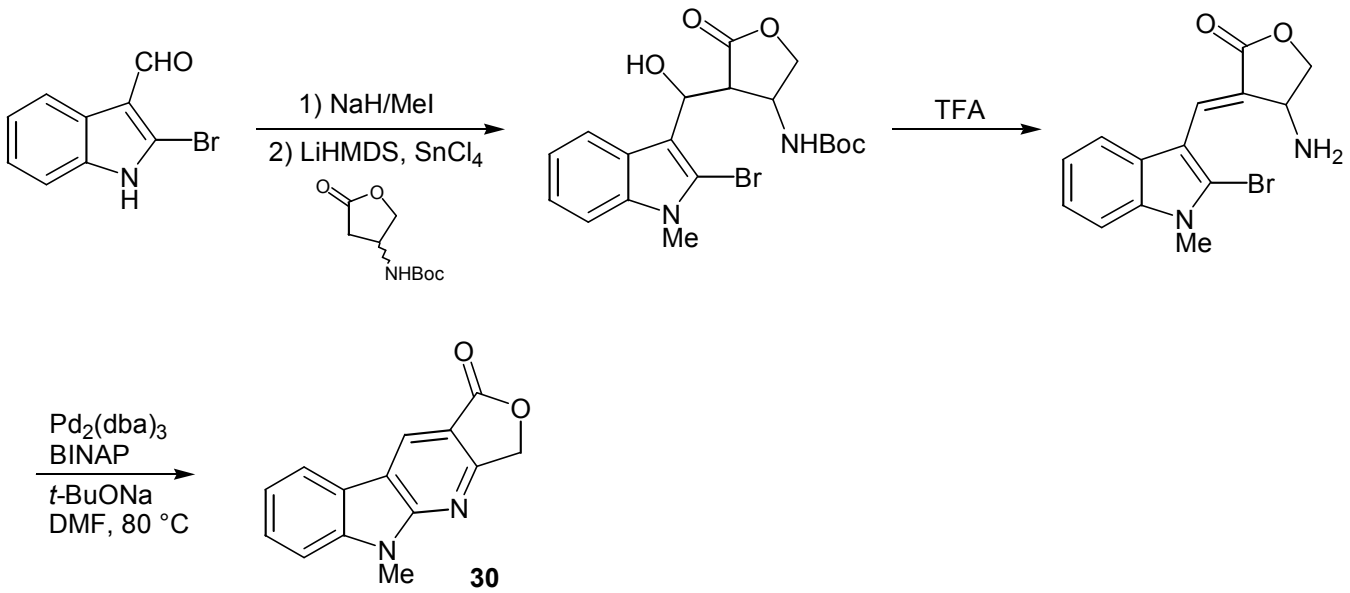


Grossularines
R = 3-indolyl
R = *p*-hydroxyphenyl

Mescengricin

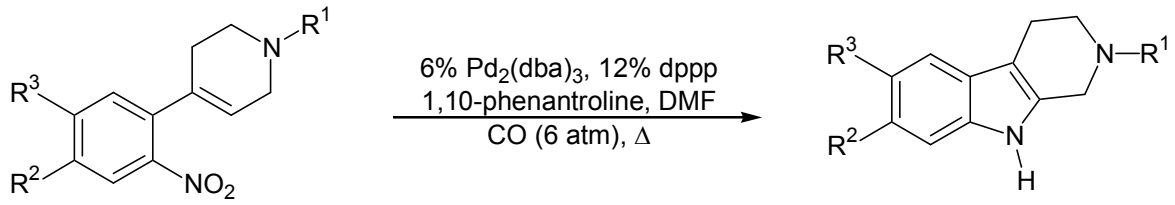
Figure 3

Treatment of this latter compound with trifluoroacetic acid produces simultaneous *N*-deprotection and dehydration to the. corresponding insaturated amine which was finally subjected to intramolecular palladium-catalysed *N*-arylation following the conditions reported by Buchwald[16] and Hartwig.[17]



Scheme 27

Söderberg and co-workers had developed a relatively mild palladium-phosphine catalysed reductive *N*-heteroannulation of 2-nitrostyrenes forming indoles[45] and carbazolones.[46] Recently they applied this methodology to a short synthesis of two naturally occurring β–carbolines.[47] The key step was the palladium-catalysed *N*-heteroannulation of differently substituted 4-(2-nitro-phenyl)-tetrahydro-pyridines. The latter are easy obtained *via* Stille cross-coupling reaction of suitable aryl stannane with vinyl triflate. For cyclisation step a few catalytic systems were tested but best results were obtained with 6% mol. bis(dibenzylideneacetone)-palladium, 12% mol. 1,3-bis(diphenilphosphino)propane, 12% mol. 1,10-phenanthroline, and 6 atm of carbon monoxide in dimethylformamide at 80 °C. By this way β–carbolines **31** were obtained in 50-81% yields (Scheme 28).

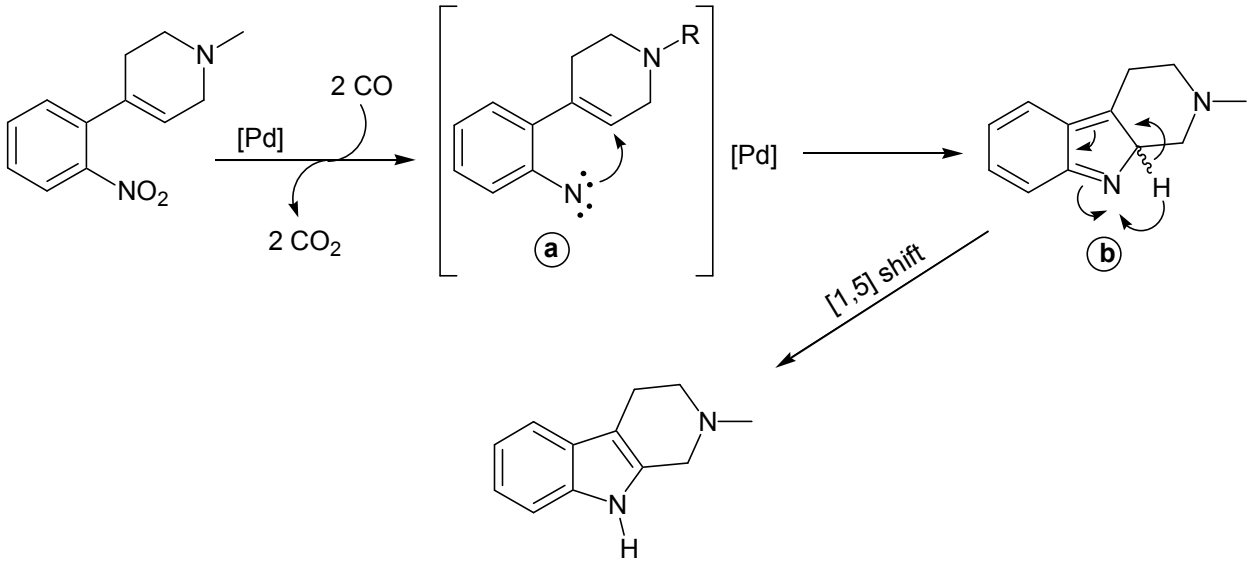


31

R^1= -Me; R^2= -H; R^3= -OMe: (80%).
R^1= -Boc; R^2= -Cl; R^3= H: (81%).
R^1= -Bn; R^2= -Cl; R^3= -H: (61%).
R^1= -Ts; R^2= -Cl; R^3= -H: (50%).

Scheme 28

The most plausible route for the reductive *N*-heterocyclisation of 4-(2-nitro-phenyl)-tetrahydro-pyridines **22** is depicted in Scheme 29. Firstly, deoxygenation of the nitro group by carbon monoxide would occur to give the corresponding nitrene intermediate (**a**), along with the generation of CO_2. This electrophilic nitrene could attack the olefinic carbon to form a nitrogen-carbon bond (**b**), followed by a hydrogen transfer via a [1,5]-sigmatropic rearrangement to give the corresponding β-carbolines.[48]



31

Scheme 29

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HETERO DIELS-ALDER APPROACH TO OXATHIINS

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Abstract. *The hetero Diels-Alder reaction of α,α'-dioxothiones and ortho-thioquinones with electron-rich dienophiles represents a simple and convenient method for the preparation of 1,4-oxathiins and benzoxathiins. The scope of this cycloaddition reaction as well as the potentials of the cycloadducts obtained will be described in this chapter. In particular the use of glycals as dienophiles and the applications of glyco-condensed oxathiins will be evaluated*.

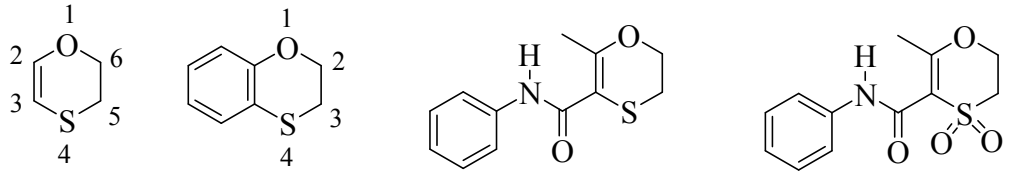
Contents

1. Introduction

The 5,6-dihydro-1,4-oxathiins and the analogue benzofused derivatives are quite uncommon heterocyclic systems. The parent compounds **1** and **2** are reported in Figure 1 and will be indicated as oxathiins and benzoxathiins thereafter. Since almost four decades ago a keen interest has been devoted to these compounds due to the wide range of biological activities associated with their structure. Indeed in 1966 appeared a report[1] describing the systemic fungicidal activity of oxathiins **3** and **4** marketed with the name Vitavax® and Plantavax® respectively.[2]

Furthermore, the use of oxathiin systems as inhibitors of HIV-1 reverse trascriptase[3,4] or the activity of benzoxathiins as adrenoreceptor antagonists[5,6] and oestrogen receptor modulators[7] can easily explain the

interest arisen around these compounds which, in the last 30 years, appeared more frequently in patents than in publications. Recently a review[8] on the synthesis, applications and properties of 1,4-hetero-substituted 2-cyclohexenes, including oxathiins and benzoxathiins, has been published.



1 **2** **3** **4**

Figure 1. Structures of parent 5,6-dihydro-1,4-oxathiin **1** and benzoxathiin **2**, and fungicides Vitavax® (**3**) and Plantavax® (**4**)

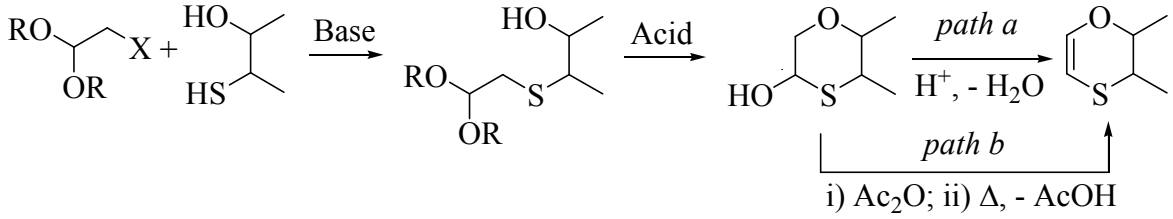
In this chapter, that covers the literature till the end of 2002, we will focus our attention on the opportunities disclosed by a new Diels-Alder approach to these heterocyclic systems. Moreover, the known classical procedures for the preparation of oxathiins and benzoxathiins and their more relevant chemical transformations will be reported as well.

2. Synthesis of oxathiins by "classical" methods

The available methods for the construction of the 1,4-oxathiin ring can be suitably divided into two groups. Those procedures concerning the ring closure of the six-member ring obtained from acyclic precursors or, alternatively, the preparation of the oxathiin skeleton by ring enlargement of 1,3-oxathiolanes.

2.1. Oxathiins from acyclic precursors

Condensation of 1,2-hydroxythiols with β-haloacetals represented a valuable method for the construction of the six member ring of oxathiins.[9-11] The formation of the double bond was obtained from the intermediate cyclic emiacetal by acid catalysed elimination of H_2O (*path a*) or, more conveniently, *via* acetylation of the hydroxy group followed by the thermal elimination of AcOH (*path b*) (Scheme 1).



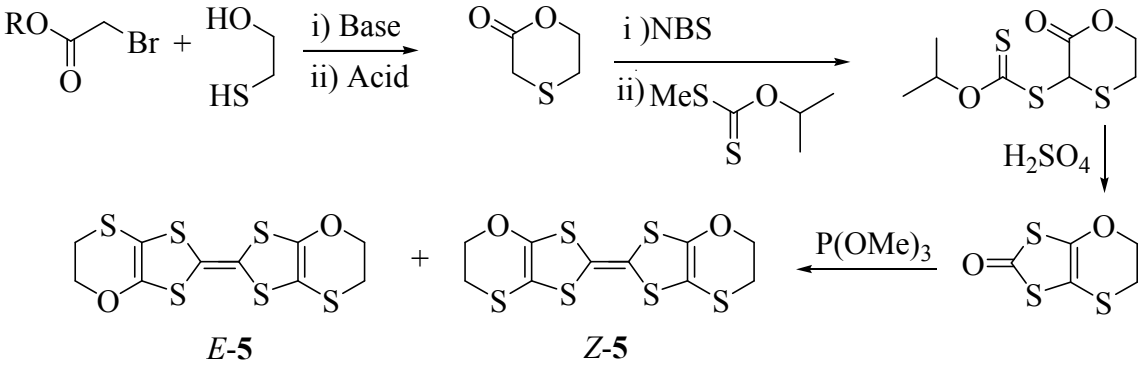
Scheme 1

Following a slightly modified procedure, the reaction of 1,2-hydroxythiols and β-bromoesters gave the *E* and *Z* tetrathiofulvalene condensed oxathiins **5**. The potential applications of such compounds as new materials were reported as well[12] (Scheme 2).

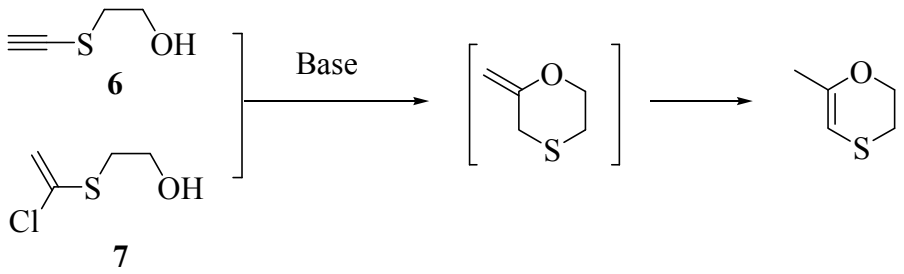
α,β-Unsaturated-β'-hydroxy sulfides **6** or **7** were used for the base-mediated preparation of oxathiin rings.[13,14] In any case the thermodynamic *endo*-olefin was obtained as single reaction product (Scheme 3).

The reaction of oxiranes with β-mercapto ketones[15] represented a further general approach to the synthesis of poly-substituted oxathiin derivatives. This procedure allowed the formation of the internal

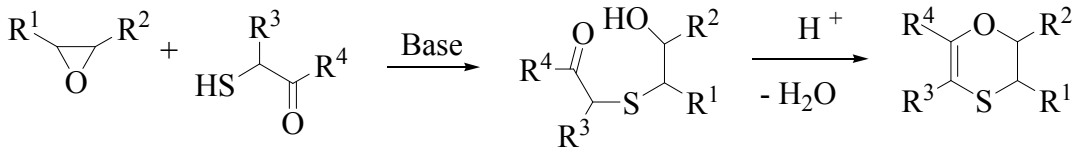
double bond by a facile base-catalysed dehydratation. No control was reported for the regio- and/or the stereochemistry of the reaction (Scheme 4).



Scheme 2



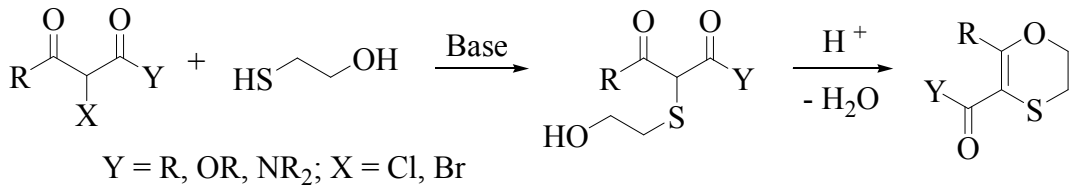
Scheme 3



Scheme 4

Recently, β-mercapto ketones were reported as suitable starting materials for the synthesis of oxathiins also when reacted with terminal alkenes in the presence of $Mn(Acac)_3$. Low yields are usually obtained.[16]

The most common and well studied method for the preparation of oxathiin heterocycles was the condensation of 1,2-mercapto ethanol with a 2-halogenated-1,3-dicarbonyl compound, followed by an acid-promoted ring closure[17,18] (Scheme 5).



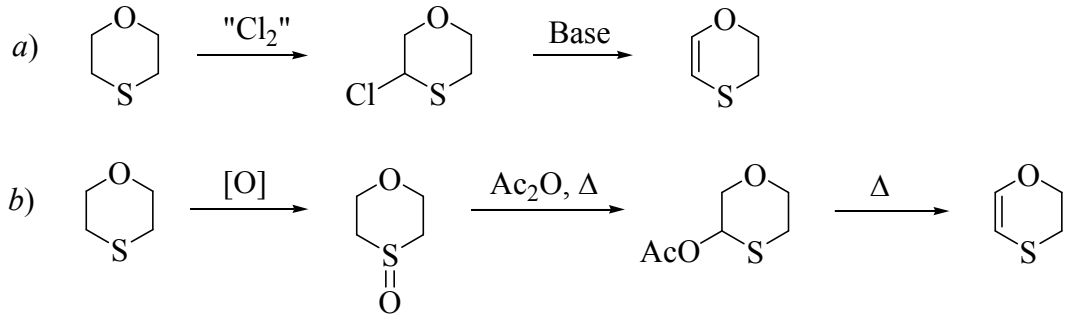
Scheme 5

This procedure, originally patented for the preparation of Vitavax® **3** and Plantavax® **4**, was recently extended to the solid supported synthesis of biologically active perfluoro oxathiins.[19]

2.2. Oxathiins from cyclic precursors

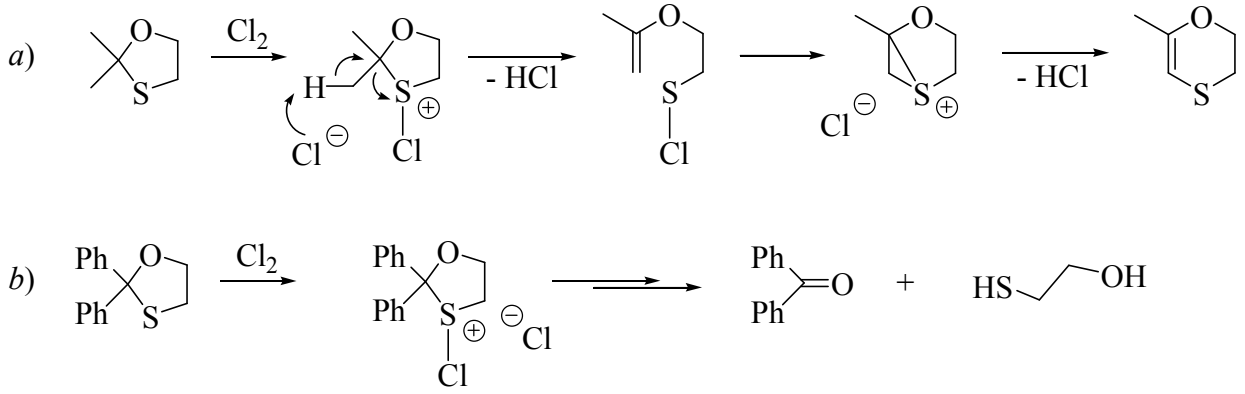
The transformation of a saturated 1,4-oxathiane ring into an oxathiin system did not find any practical

application. Indeed, two of the possible sequences: α-chlorination and dehydrohalogenation[20] (Scheme 6, eq *a*), or oxidation at sulfur, Pummerer reaction and acetic acid elimination[21] (Scheme 6, eq *b*) always gave poor results.

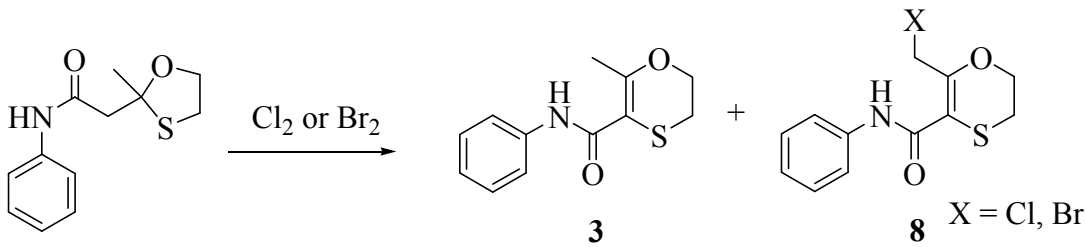


Scheme 6

The possibility to obtain an 1,4-oxathiin heterocycle from an 1,3-oxathiolan ring was firstly reported by Wilson in 1965 who demonstrated that the reaction of 2,2-dimethyl-1,3-oxathiolane with chlorine afforded 2-methyl-1,4-oxathiin in 54% yield (Scheme 7).[22] The mechanism proposed foresees the initial formation of a chlorosulfonium salt that evolves in a transient sulfenyl chloride which, in turn, gives rise to the six member ring via a bicyclic episolfonium salt (Scheme 7, eq *a*). The mechanism was confirmed by the same author who proved that without hydrogens at C-2 of oxathiolane ring (i.e. 2,2-diphenyl-1,3-oxathiolane), chlorination afforded the starting ketone and 1,2-mercapto ethanol without formation of the oxathiin ring[23] (Scheme 7, eq *b*).



Scheme 7

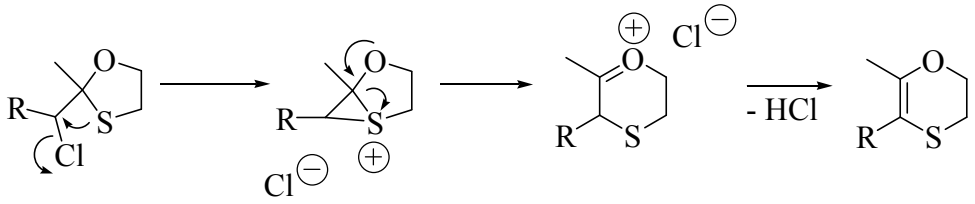


3 **8**

Scheme 8

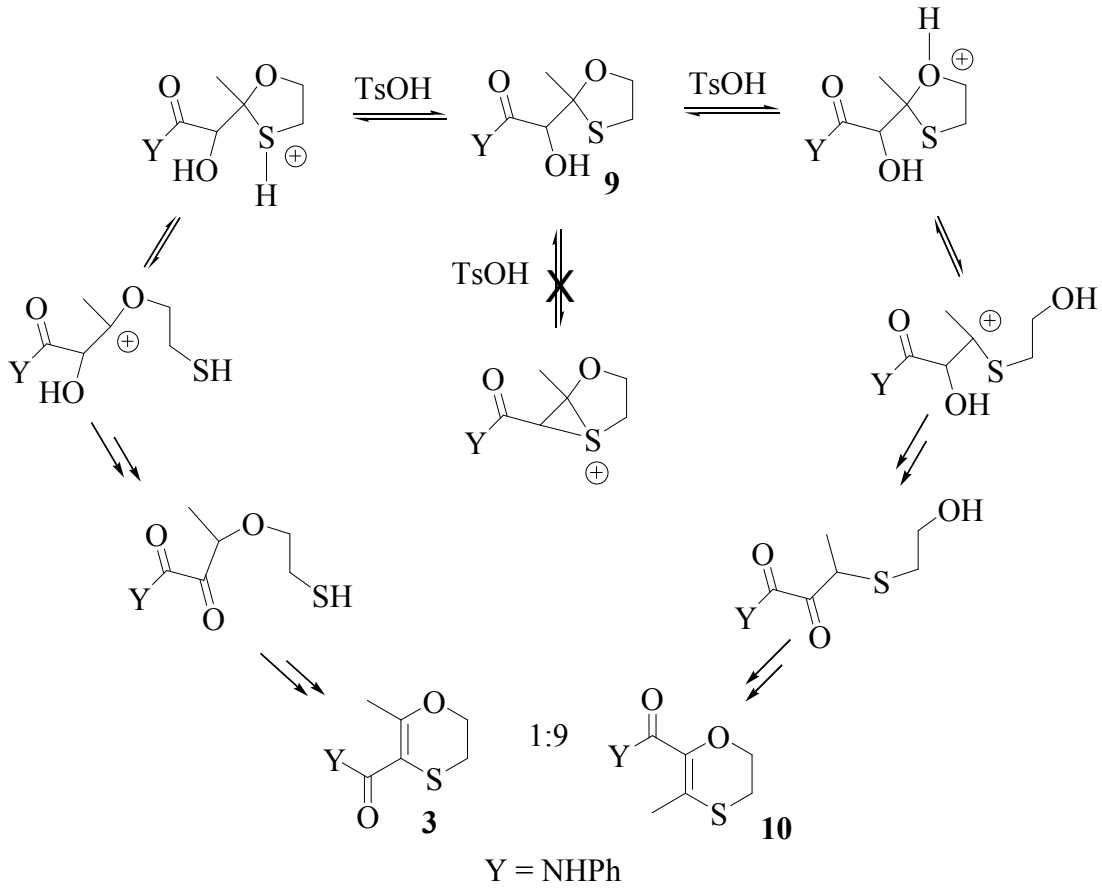
This reaction has been studied and applied by several other authors[24-26] and it was also optimised[27] for the synthesis of Vitavax® **3** (Scheme 8). In the latter case chlorination (or bromination) of the required oxathiolane gave the desired ring enlargement together with the formation of 2-methylhalogenated derivative **8** as a constant side product of the reaction (see Section 4.2.) (Scheme 8).

In a closely related method, 1,4-oxathiins were obtained by reacting β-halo-1,3-oxathiolanes with bases.[28,29] Also in this case an episolfonium salt, able to evolve to a six member heterocycle, was proposed as the key intermediate of the process (Scheme 9).



Scheme 9

A similar sequence was expected by the acid catalysed reaction of β-hydroxy-1,3-oxathiolane **9**. On the contrary, a 1:9 regioisomeric mixture of Vitavax® (**3**) and derivative **10** was obtained.[30] Probably in this case two ring-open carbocations are preferentially formed as intermediates in the place of the expected bicyclic episolfonium salt, with lack of regioselectivity (Scheme 10).



Scheme 10

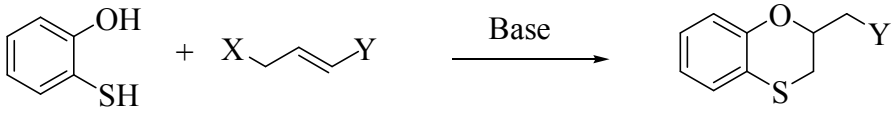
Eventually, also 1,3-oxathiolane-*S*-oxides can be transformed into 1,4-oxathiin rings[31] even though such process resulted less convenient than those previously described.

2.3. Synthesis of 1,4-benzoxathiins

The synthesis of benzoxathiins, of general structure **2**, can be generally achieved following the same procedures reported for the aliphatic analogues. Thus the reaction of *ortho*-hydroxy thiophenols with β-

haloacetals[32] or β-haloketones[33] led to the formation of the expected benzo-fused oxathiins.

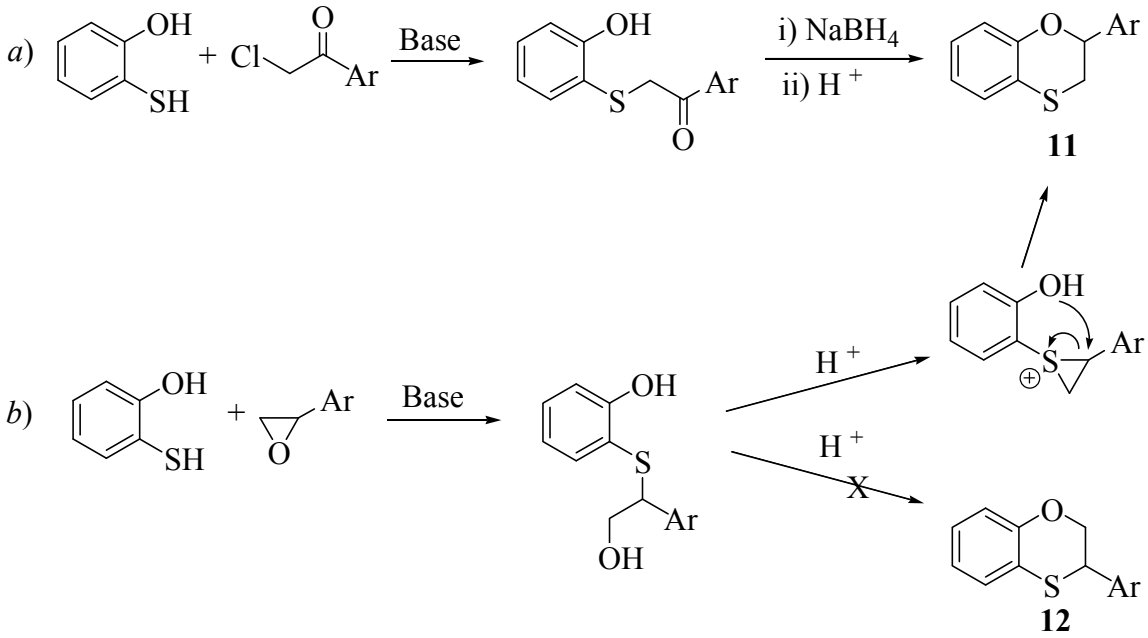
The formation of the six member ring was similarly achieved reacting *ortho*-mercapto phenol with a β-halo Michael acceptors[34,35] as reported in Scheme 11.



X = Cl, Br; Y = COOR, CN

Scheme 11

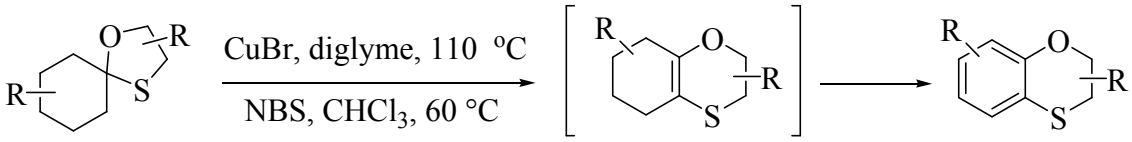
However, in several cases these classical methods failed in the regiocontrolled preparation of 2 and/or 3-substituted benzoxathiins. For example, during a study directed to the preparation of a new family of non-glycosyl sweetener,[36] the classical procedure using *ortho*-hydroxy thiophenols as starting material was effective only for the preparation of the 2-arylsubstituted benzoxathiin **11** (Scheme 12, eq *a*) but failed for the synthesis of the corresponding 3-arylsubstituted derivative **12**. In fact when *ortho*-hydroxy thiophenols was reacted with an aryl substituted epoxide, the formation of an intermediate episolfonuim salt led again to the isolation of derivative **11** instead of to the expected regioisomer **12** (Scheme 12, eq *b*).



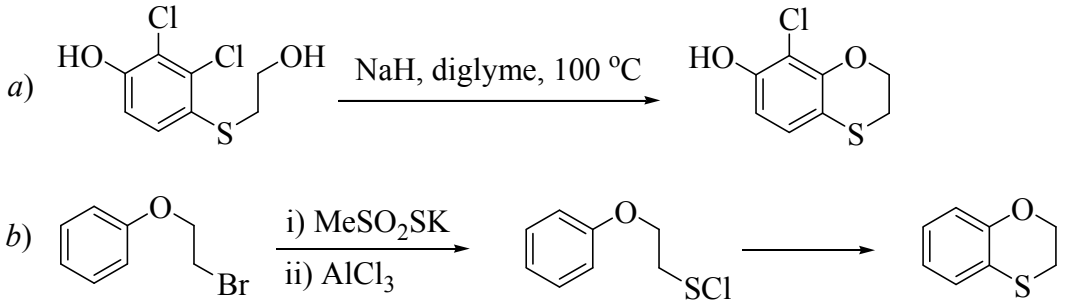
Scheme 12

Thus, other methods have been developed for the preparation of benzoxathiins including the rearrangement of cyclohexanone derived 1,3-oxathiolanes followed by an "in situ" aromatisation of the cyclohexene condensed oxathiin. Interestingly the reagents used for the rearrangement, CuBr or NBS, were also able to promote the ring aromatisation[37,38] (Scheme 13).

The formation of the benzo-condensed ring can be alternatively obtained using a S_NAr or a S_EAr as final step. In particular a nucleophilic substitution from a β-hydroxy-*ortho*-chlorosulfide[39] or the S_EAr of a transient sulfenyl chloride,[40] Scheme 14 eq *a* and *b* respectively, have been reported as efficient procedures for the formation of the benzoxatiin heterocyclic system.



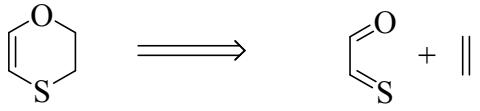
Scheme 13



Scheme 14

3. Diels-Alder approach to oxathiins

A six member heterocycle can in any case be disconnected considering a Diels-Alder reaction. In the case of 5,6-dihydro-1,4-oxathiins of type **1** such disconnection foresees the possibility to have an α-acyl thione as diene (Scheme 15).

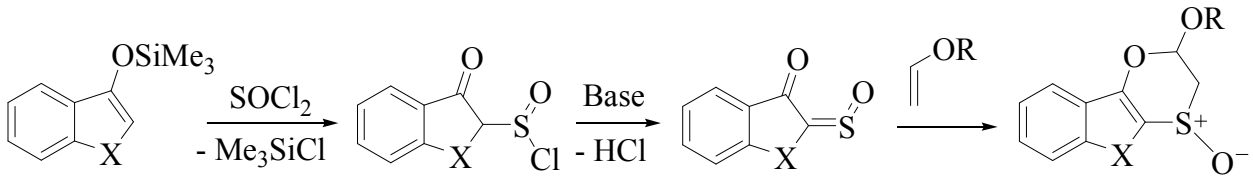


Scheme 15

Although elegant and simple, this approach suffers of the lack of a practical method for the synthesis of oxothiones as suitable dienes. The first reports on this reaction appeared roughly 20 years ago as here briefly discussed.

3.1. Early results

Zwanenburg[41] and Still[42-44] demonstrated the possibility to generate transient α-oxosulfines (thione-*S*-oxides) and trap them as dienes to give the corresponding oxathiin-S-oxides (Scheme 16).



X = CH_2, S

Scheme 16

However this approach revealed to be rather than general, usually it required large excess of dienophile and, in same case, gave controversial results. Thus, no practical application appeared after the initial promising reports.

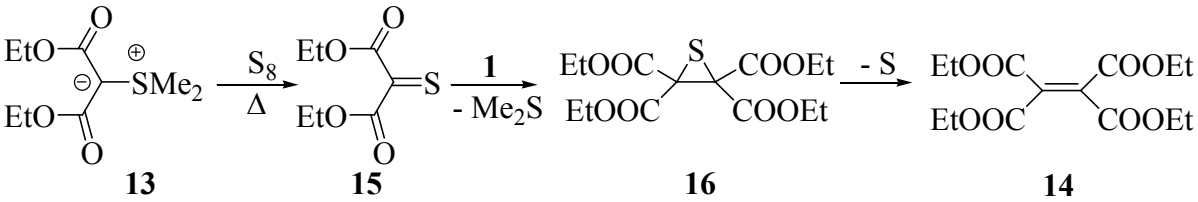
Roughly 10 years ago we developed a new and simple strategy for the generation of α,α'-dioxothiones

and *ortho*-thioquinones which revealed to be very efficient electron-poor bis-heterodienes. This allowed us to "rediscover", develop and successfully apply the Diels-Alder approach to oxathiins as hereafter described.

3.2. α,α'-Dioxothiones as electron-poor heterodienes

α,α'-Dioxothiones are transient conjugated thiocarbonyl derivatives generally trapped as dienophiles in [4+2] Diels-Alder reactions.[45]

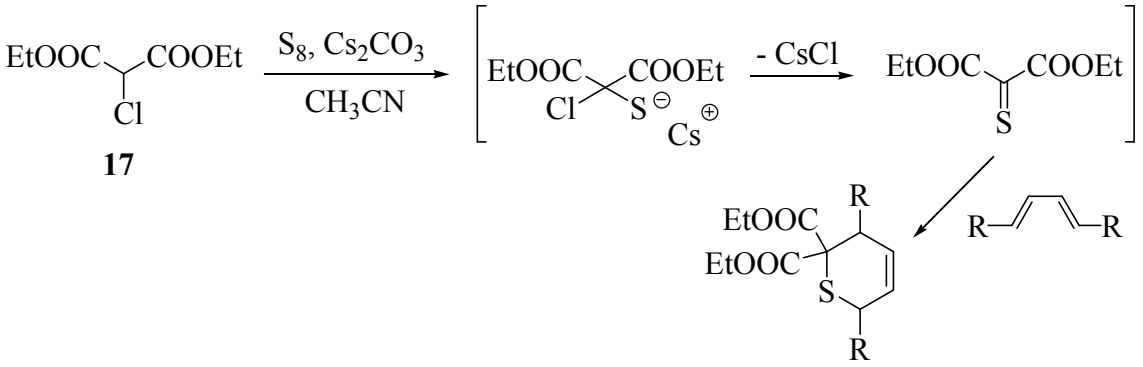
Up to now, very few examples concerning the synthesis of α,α'-dioxothiones have been reported. In a first example,[46] the ylide **13** was heated with a slight excess of elemental sulfur in *ortho*-chlorotoluene to give the olefin **14**, quantitatively. The authors proposed the initial formation of the thio-dicarbonyl **15** which, reacting with the starting ylide **13**, gave the episulfide **16**. Episulfide **16** was unstable under reaction conditions and eliminated sulfur to afford **14** (Scheme 17).



13 **15** **16** **14**

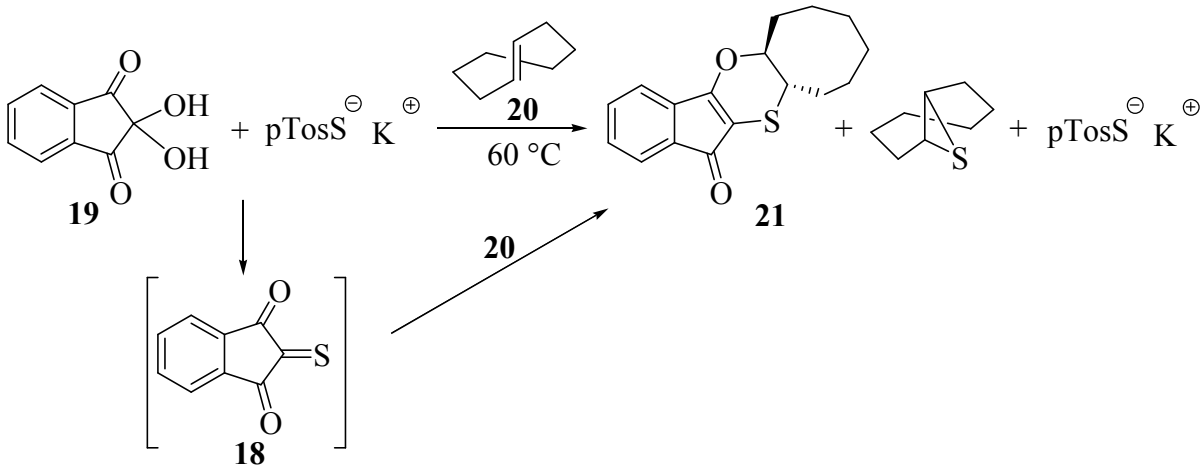
Scheme 17

A second example reported the treatment of the chloro ester **17** with a suspension of sulfur and cesium carbonate in acetonitrile. An intermediate chalcogen carbonyl was formed which underwent a [4+2] cycloaddition with a variety of conjugated dienes[47,48] (Scheme 18).



17

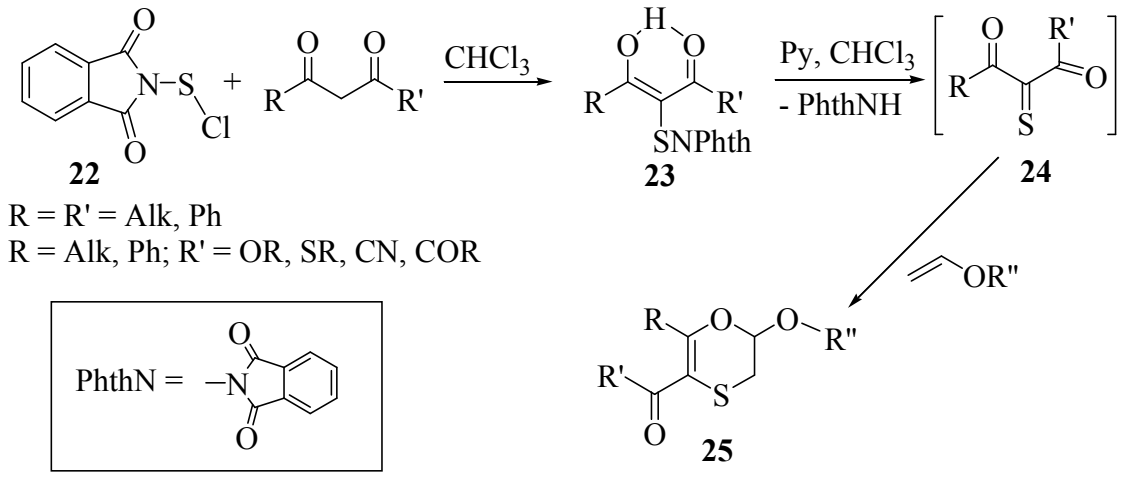
Scheme 18



Scheme 19

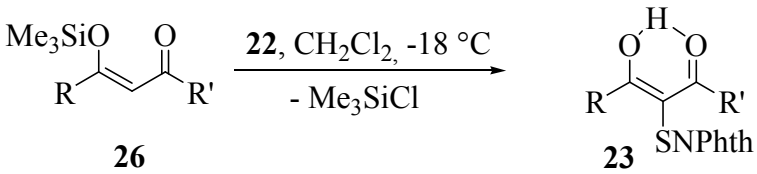
More recently, the α,α'-dioxothione **18** was synthesized from ninidrine (**19**) and potassium thiotosylate. Thione **18** was trapped through a [4+2] cycloaddition with trans-octene (**20**) to give the corresponding 1,4-oxathiin **21** and trans-octene episulfide[49] (Scheme 19).

In 1993 we reported[50] a novel synthesis of α,α'-dioxothiones which relies on the easy cleavage of sulfenyl phthalimides in the presence of mild bases. As a matter of fact, phthalimidesulfenyl chloride **22**, PhthNSCl (Phth = Phthaloyl), reacts with β-diketones, β-ketoesters, β-ketothiolester etc. (Scheme 20) to afford α-acyl-*N*-thiophthalimide derivatives **23** which can easily generate the reactive thione derivatives **24**. These transient species can act as heterodienes in reactions with electron-rich alkenes (e.g. enol ethers) thus giving rise to 5,6-dihydro-1,4-oxathiin derivatives[50,51] **25** (Scheme 20).



Scheme 20

Alternatively, sulfenamides **23** can be prepared by reaction of silyl derivatives **26** with **22** in dichloromethane at -18 °C (Scheme 21).



Scheme 21

In this strategy the key reagents are the phthalimide derivatives **23** which are simply prepared by reacting phthalimidesulfenyl chloride **22** with β-diketones or β-ketoesters under very mild reaction conditions. The phthalimide derivatives so obtained are generally highly stable compounds which can be purified by crystallization and stored for years without any appreciable decomposition. β-Dicarbonyl derivatives **23**, in $CDCl_3$ solution at room temperature, are generally present only in their enolic form, as it can be deduced by ^1H NMR spectra.[51] Capitalizing on the easy preparation of dicarbonyl sulfenamides like **23** and on their efficient transformation into thiones like **24**, a wide number of 1,3-dicarbonyl derivatives as well as of electron-rich dienophiles have been employed to give the corresponding 1,4-oxathiins[51] as depicted in Table 1 for hetero substituted alkenes and in Table 2 for carbon-substituted alkenes.

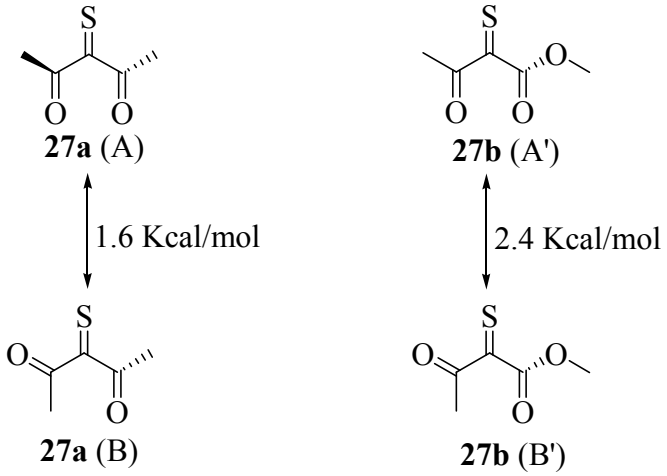


Figure 2. *Ab initio* calculated absolute minimum (A, A') and reactive (B, B') conformers of **27a**,**b**

As perfectly supported by ^{1}H and ^{13}C-NMR, 1,4-oxathiins are always formed as single chemo- and regioisomers, thus proving the chemo- and regiospecificity of the cycloaddition. As a matter of fact, the only regioisomer formed is always the regioisomer with the ketone oxygen of the acylthiones linked to the heterosubstituted carbon of the dienophile, moreover in all the reactions involving β-ketoesters (R= Alk, R'= OR, SR, etc. see Scheme 20) the chemospecificity of the cycloaddition is maintained with the exclusive participation of the ketone carbonyl. In parallel with experiments, quantum mechanic calculations were carried out.[51] In particular, α,α'-dioxothiones **27a**,**b** and ethyl vinyl ether (**28**) were minimized with a geometry optimization *ab initio* calculation using a 3-21G* basis set implemented via a Spartan program for PC. Interesting features revealed by the calculations include the conformational energy minima for thiones **27a**,**b**. In the case of **27a** the low energetic conformer shows the two carbonyl groups oriented with dihedral angles of about 100 °C with the thiocarbonyl group (unfavorable conformation for a reactive Diels-Alder diene see Figure 2, A). Perturbing the molecule so that with one of the O-C-C-S dihedral angles becames 0 °C creates another minimum only about 1.6 kcal mol^{-1} less stable than A (Figure 2, B). Therefore, a reactive geometry for cycloaddition is easily accessible at room temperature.

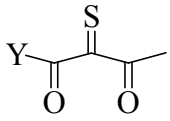
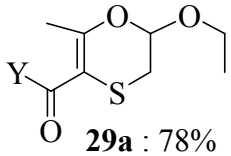
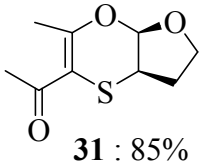
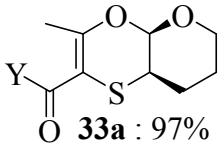
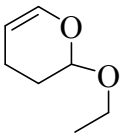
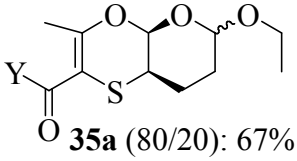
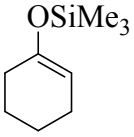
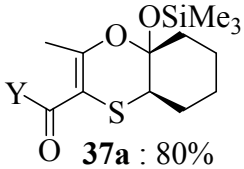
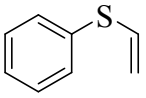
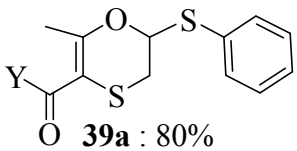
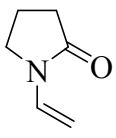
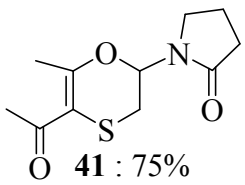
In the case of thione **27b** the more stable conformer shows the ketone carbonyl and thiocarbonyl having a dihedral angle of 160 °C (an almost "transoid" conformation, see Figure 2, A') while the ester carbonyl and the C=S have a dihedral angle of 55.3°. Forcing the ketone carbonyl and the thione groups into a "cisoid" conformation, another minimum conformer is produced (Figure 2, B') that is about 2.4 kcal mol^{-1} less stable than A' (Figure 2).

Looking at the energies of the molecular orbitals, it is clear that, as expected for inverse electron-demand Diels-Alder reactions, the orbitals involved in the cycloadditions are the HOMO of the dienophile and the LUMO of the diene (Figure 3). The shape of the MO, supplied by the program used, showed that the symmetry of the HOMO of **28** and of the LUMO of **27a**,**b** is optimal for superimposition and that the favored interactions (i.e. the orbitals with the largest coefficients) are found on the sulfur atom of the thiones **27a** or **27b** and on the vinyl methylene of **28**.

When different stereoisomers can be formed in the cycloaddition, an interesting stereoselectivity is always observed (see for example entry 4, Table 1). In any case, indeed, retention of the dienophile geometry was observed for both cyclic (Table 1) or linear alkenes (see entries 2,4 Table 2).α,α'-Dioxothiones are also efficient enophiles; when generated in the presence of poor electron rich-dienophiles possessing an allylic

hydrogen like 2,3-dimethyl-2-butene or 1-methylstyrene, the latter behavior predominates with formation of the thiophilic "ene" adduct regioselectively (see for example Table 2, entry 5, derivatives **51** vs. **52**).

Table 1. Oxathiins obtained by cycloaddition of thiones **27a,b** with hetero substituted dienophiles.

Entry	Diene[a]	Dienophile	Cycloadduct[a] : isolated yield[51]
1	 **27a,b**	 **28**	 **29a** : 78% **29b** : 67%
2	**27a**	 **30**	 **31** : 85%
3	**27a,b**	 **32**	 **33a** : 97% **33b** : 88%
4	**27a,b**	 **34**	 **35a** (80/20): 67% **35b** (80/20): 61%
5	**27a,b**	 **36**	 **37a** : 80% **37b** : 54%
6	**27a,b**	 **38**	 **39a** : 80% **39b** : 54%
7	**27a**	 **40**	 **41** : 75%

[a] **a**: Y = Me; **b**: Y = OMe

Due to the easy access to dioxothiones, we also prepared chiral non-racemic α,α'-dioxothiones deriving from β-chetosters bearing a chiral auxiliary in the ester or/and in the ketone residue. These dienes showed an attracting ability to discriminate between the enantiotopic faces of several dienophiles[52] (Table 3). The analysis of the diasteroisomeric excess clearly indicated that the distance between the chiral auxiliary

and the reactive diene is crucial for good facial selectivity in the cycloaddition. Thus the best results were obtained when the auxiliary is directly linked to the ketone carbonyl which participates in the reaction (see Table 3, entry 4,6,7) or when a phenyl group likely "covers" one of the two faces of the diene (see Table 3, entry 1).

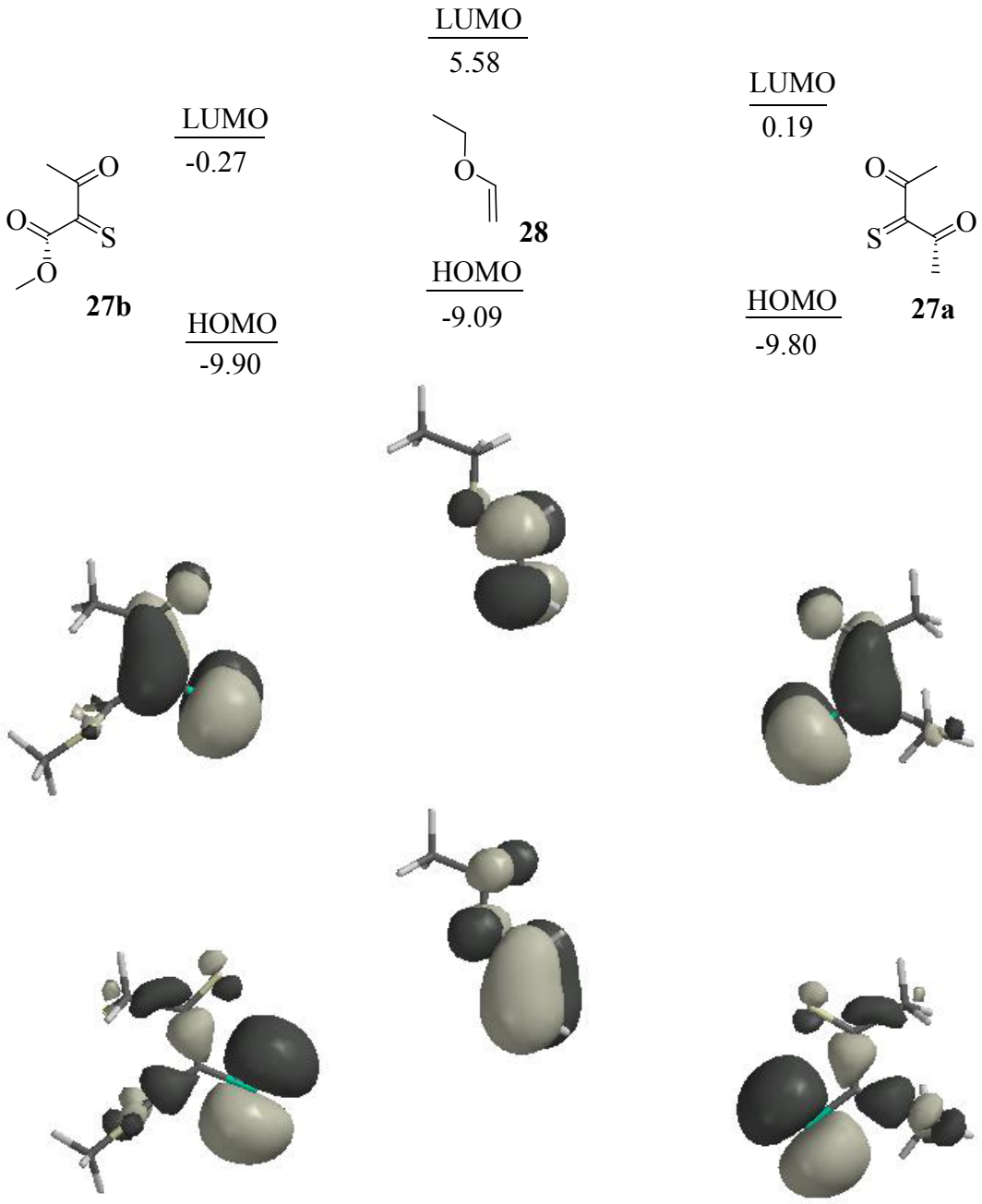
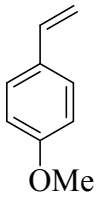
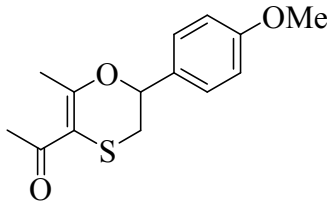
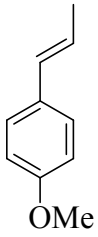
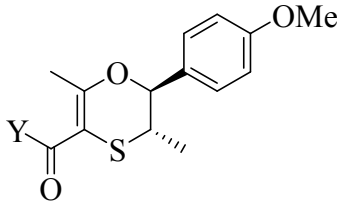
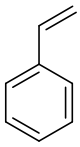
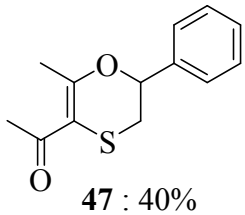
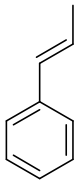
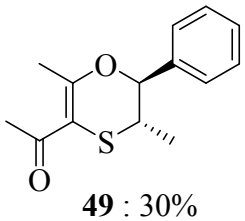
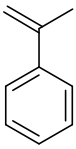
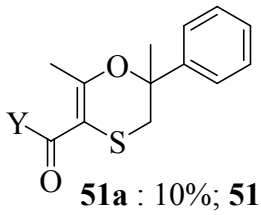
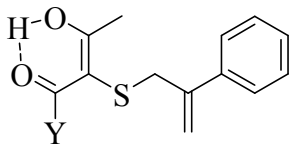


Figure 3. *Ab initio* calculated energies (eV) and shapes of HOMO and LUMO MO's of thiones **27a**,**b** and vinyl ether **28**

3.3. Ortho-thioquinones

Mono *ortho*-thioquinones can be considered the aromatic analogues of α-oxothiones. First reported by Chapman in 1971,[53] *ortho*-thioquinones **65** (see Scheme 22) are generally prepared under harsh reaction conditions.[54,55] Likely for this reason, although the appealing structure, they did not find practical applications for many years.

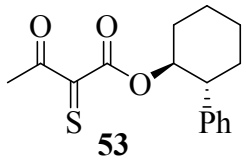
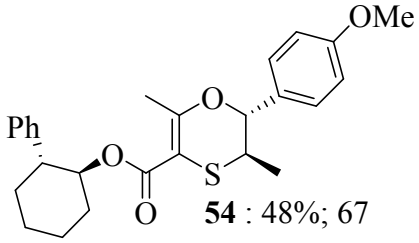
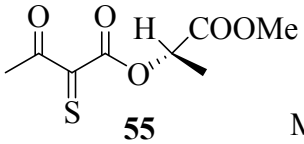
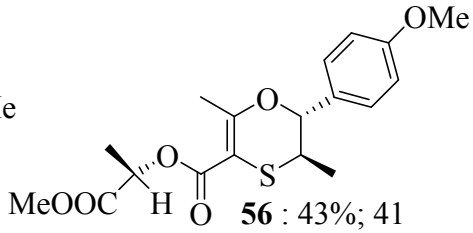
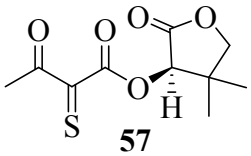
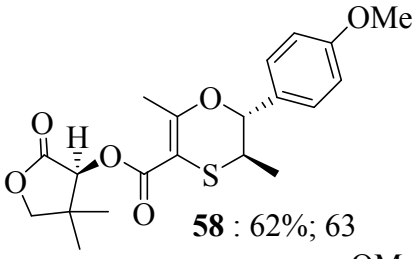
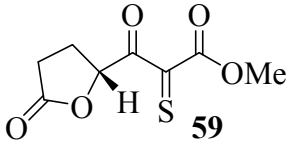
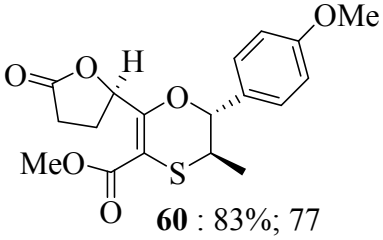
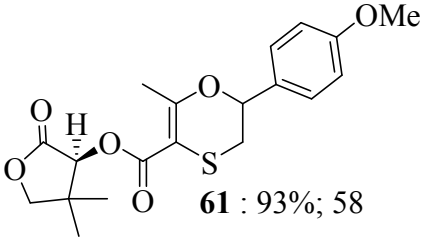
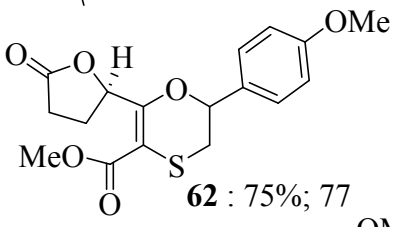
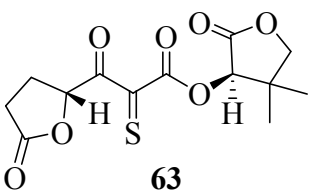
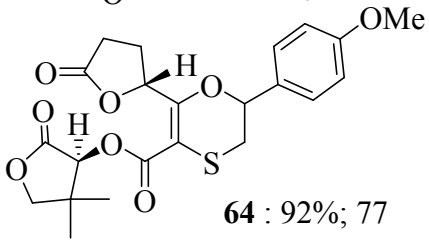
Table 2. Oxathiins obtained by cycloaddition of thiones **27a,b** with carbon-substituted dienophiles.

Entry	Diene[a]	Dienophile	Cycloadduct[a] : isolated yield[51]
1	**27a**	 **42**	 **43** : 50%
2	**27a,b**	 **44**	 **45a** : 83%; **45b** : 58%
3	**27a**	 **46**	 **47** : 40%
4	**27a**	 **48**	 **49** : 30%
5	**27a,b**	 **50**	 **51a** : 10%; **51b** : 21%  **52a** : 58%; **52b** : 63%

[a] **a**: Y = Me; **b**: Y = OMe

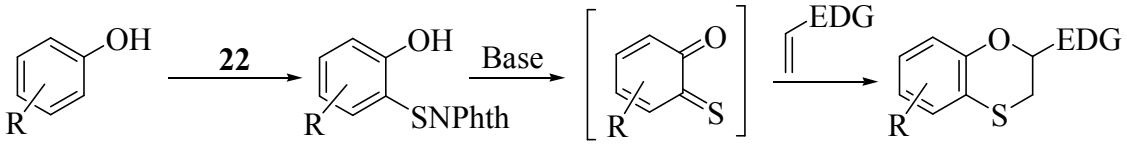
In 1994 we reported a simple method for the formation of **65** by reacting the corresponding *ortho*-hydroxyphthalimides **66** with weak bases, under mild conditions. Hydroxyphthalimides **66** are, in turn, obtained through an *ortho*-regiospecific S_EAr between phenols **67** and phthalimidesulfenyl chloride **22**.[56] In other words this procedure represents the direct extension of the previously described generation of dioxothiones (Scheme 22).

Table 3. Asymmetric hetero Diels-Alder reaction of chiral non racemic α,α'-dioxothiones.

Entry	Dienophile	Diene	Cycloadduct : isolated yield; % de[52]
1	**44**	 **53**	 **54** : 48%; 67
2	**44**	 **55**	 **56** : 43%; 41
3	**44**	 **57**	 **58** : 62%; 63
4	**44**	 **59**	 **60** : 83%; 77
5	**42**	**57**	 **61** : 93%; 58
6	**42**	**59**	 **62** : 75%; 77
7	**42**	 **63**	 **64** : 92%; 77

Examples of direct reactions of sulfenyl halides and activated arenes exist, but frequently in these cases polysubstitution is especially observed with phenols.[57] Phthalimidesulfenyl chloride **22**, in fact, reacts with

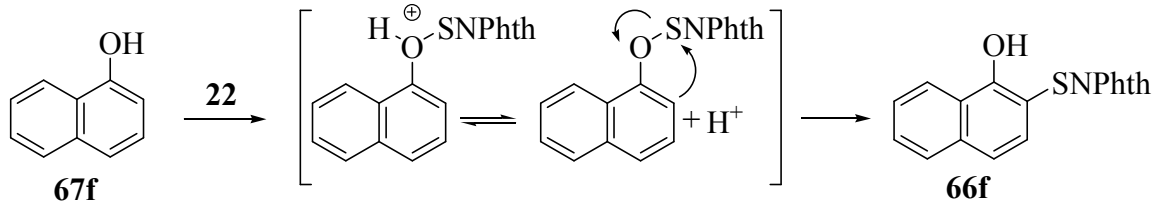
activated arenes, including phenols, at room temperature and without catalyst, giving only monosubstitution products. No trace of disubstituted derivatives was ever detected, even when highly activated phenols were reacted with an excess of **22** for long reaction times. In Table 4 are presented some of the phenols **67** used and the corresponding sulfenamides **66** isolated (Table 4).



Scheme 22

All the substrates reported in Table 4 are activated phenols which undergo regiospecific sulfenylation affording the corresponding sulfenamides **66a-h**. For substrates **66a-d**, the regioselectivity observed is predictable on the basis of substituent and steric effects; by contrast it appears less evident for **66f** and **66h**. In the case of the latter, although the formation of two different regioisomers would be expected, the phthalimidesulfenyl group enters exclusively *ortho* to the hydroxyl substituent.

A rationalization of these experimental results could be ascribed to the formation of a sulfenic ester as intermediate followed by a nuclephilic attack of the *ortho* carbon to the sulfenic sulfur, thus forming the observed phalimidesulfenyl derivatives, as indicated in Scheme 23 for α-naphthol **67f**.[58,59]



Scheme 23

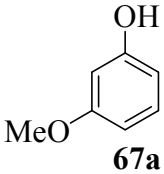
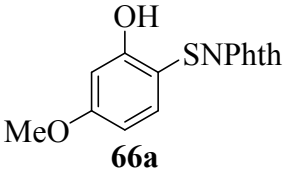
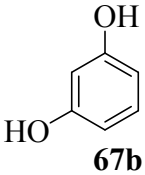
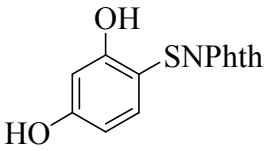
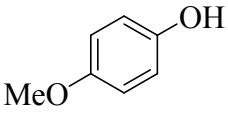
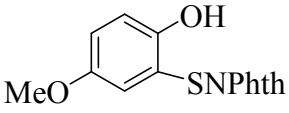
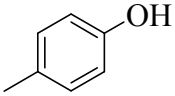
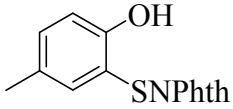
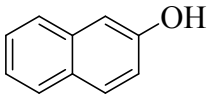
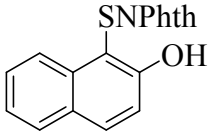
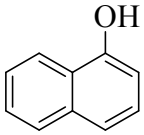
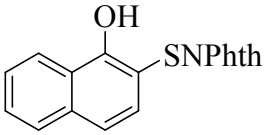
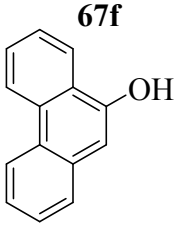
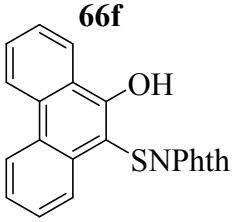
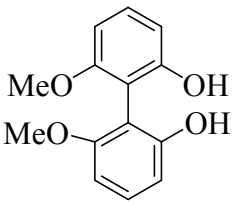
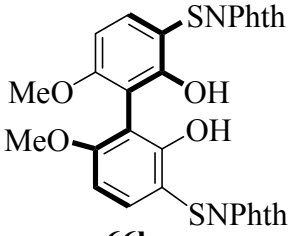
The general and simple preparation of *ortho*-thioquinones **65** allowed us to study their reactivity in detail and demonstrate their efficiency as electron-poor heterodienes towards a variety of electron-rich alkenes as dienophiles.

Our first studies concerned the reaction of phthalimides **66a-g** (see Table 4) with ethyl vinyl ether and pyridine in chloroform at 60 °C to obtain the 1,4-benzoxathiin cycloadducts **68a-g** (Scheme 24).

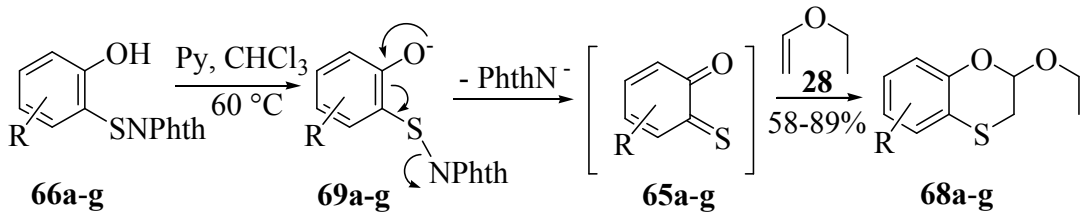
The mechanism of the reaction likely involves pyridine deprotonation of the hydroxyl group to give phenates **69a-g** which undergo phthlimide anion elimination to form the transient *ortho*-thioquinones **54a-g**, trapped as electron-poor dienes by ethyl ether **28**[59] (Scheme 24).

In all the examples reported in Scheme 24 the adduct where the oxygen of the *ortho*-thioquinone is linked to the hetero-substituted carbon of ethyl vinyl ether was formed as single regioisomer. Quantum mechanic calculations carried out on *ortho*-thioquinone **65e**, also in this case indicated that HOMO-LUMO MO's energies are in agreement with an inverse electron-demand Diels-Alder reaction and the orbital coefficients calculated confirmed that the favourite interaction involves the oxygen of **65e** and the hetero substituted carbon of ethyl vinyl ether **28**.[59]

Table 4. Selection of *ortho*-hydroxy-*N*-thiophthalimides **66** prepared reacting **22** with phenols **67**.

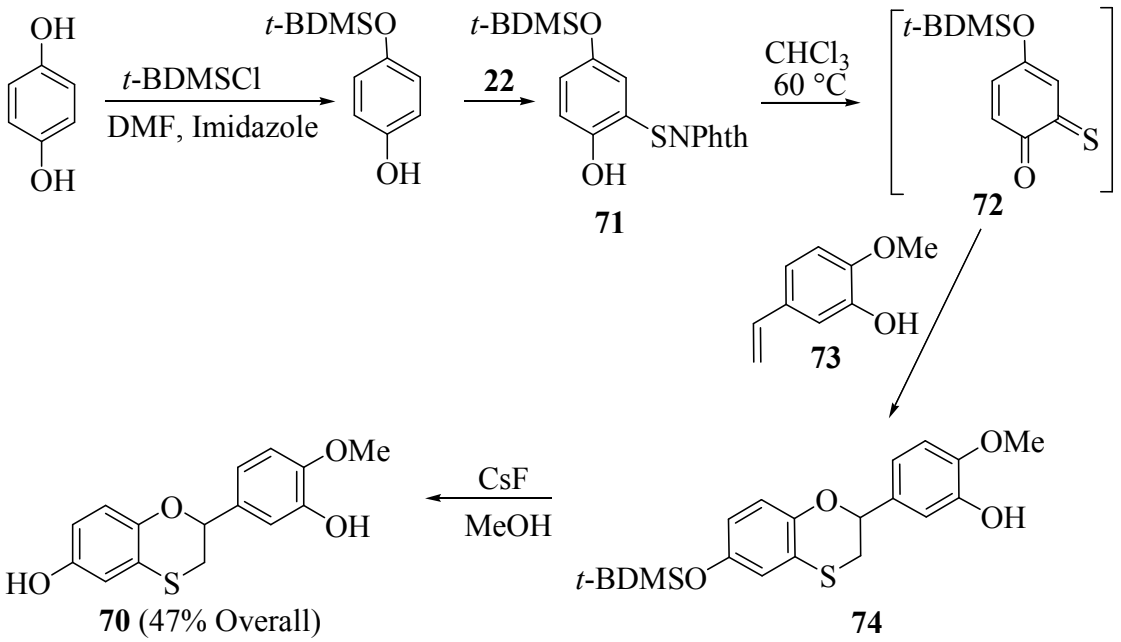
Entry	Phenol	Product	Yield, % [58,59]
1	 **67a**	 **66a**	64
2	 **67b**	 **66b**	92
3	 **67c**	 **66c**	66
4	 **67d**	 **66d**	46
5	 **67e**	 **66e**	98
6	 **67f**	 **66f**	35
7	 **67g**	 **66g**	80
8	 **67h**	 **66h**	94[61]

The versatility of *ortho*-thioquinones as efficient electron-poor dienes was widely verified reacting the latter with a large number of electron-rich dienophiles already reported in Table 1 and 2. All the cycloadducts were obtained in good yield with a total control of the regiochemistry and with retention of the geometry of the alkene. Worthy of mentioning is the total synthesis of the isovanillin-containing derivative **70** which is known to be 500 times as sweet as sucrose.[38]

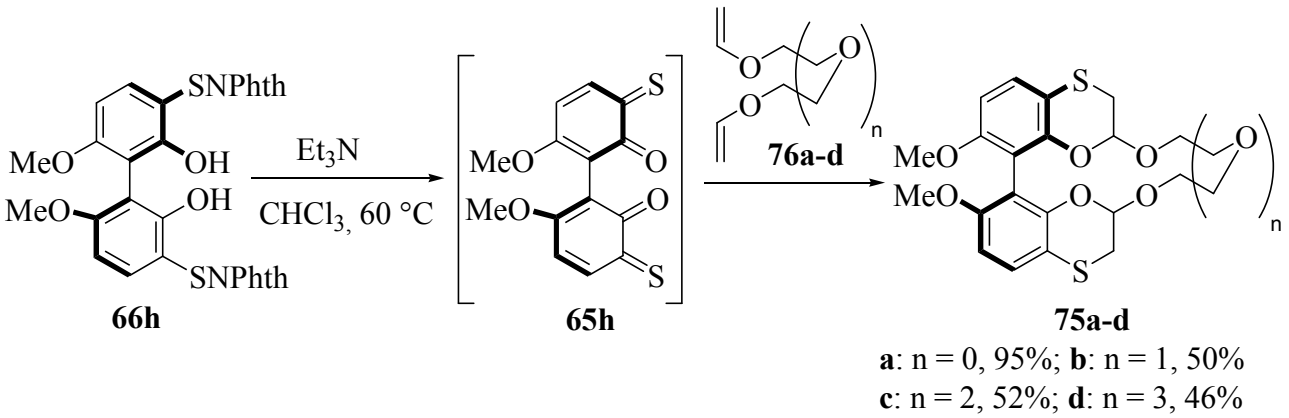


Scheme 24

As depicted in Scheme 25, the synthesis of **70** started from *para*-hydroquinone which was monosilylated with *tert*-butyldimethylsilyl chloride and regioselectively sulfenylated with **22** to afford **71**. Under the standard conditions, sulfenamide **71** generated the corresponding thioquinone **72** which was cycloadded to the styrene **73** thus affording the silyl derivative **74**. Desilylation of **74** gave the expected non-glycoside sweetener **70**[59] in a 47% overall yield (Scheme 25).



Scheme 25

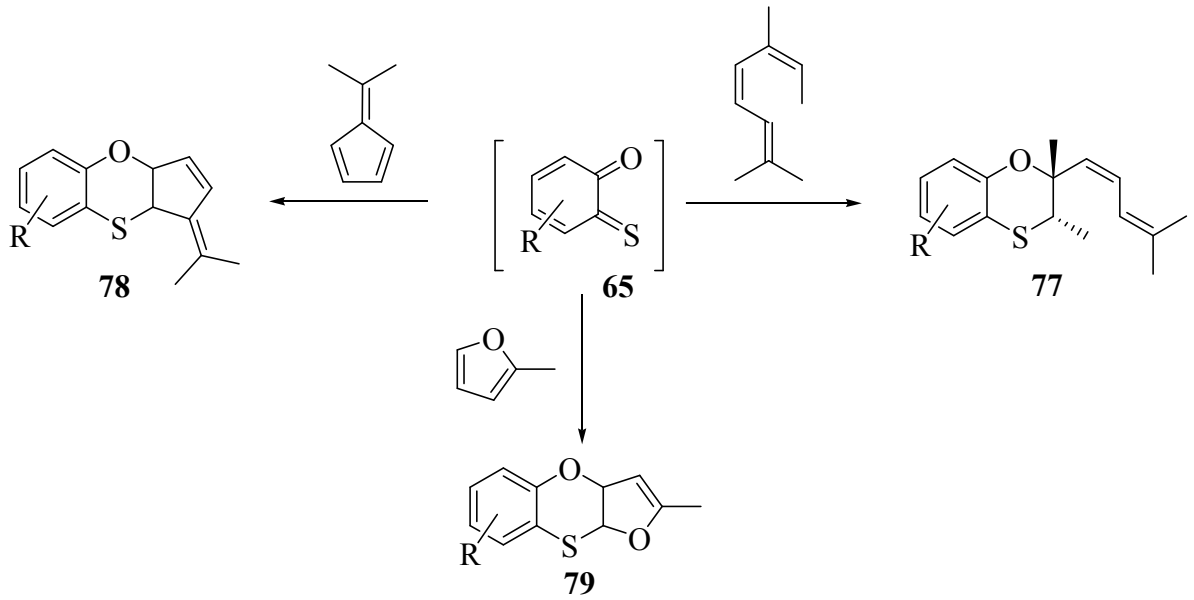


Scheme 26

The treatment of atropisomeric C_2 symmetric biphenol **67h** (see Table 4) with phthalimidesulfenyl chloride (**22**) allowed the regioselective formation of the 3,3'-thiophthalimide biphenol **66h**, successfully used as precursor of bis-electron-poor diene **65h** for the preparation of macrocyclic C_2 symmetric ligands

75a-d, as showed in Scheme 26.[60,61] Different bis-enol ethers **76a-d** were employed, thus giving crown ethers **75a-d** with different ring size. The crown ethers where isolated as a mixture of only two diasteromers (the major with one C_2 axis, the minor without).[61]

Recently, Nair and co-workers applying our methodology for the generation of *ortho*-thioquinones, showed that 1,3-dienes,[62] including cyclic dienes[63,64] and heterodienes,[65-66] participate as dienophilic counterpart in the cycloaddition reaction with **65** to give the benzoxathiin derivatives **77-79** usually with good yields (60-90%) and with a complete control of the regiochemistry as expected, also in this case, considering the coefficients of the orbitals involved in this inverse electron demand cycloaddition (Scheme 27).



Scheme 27

3.4. Glycals as dienophiles

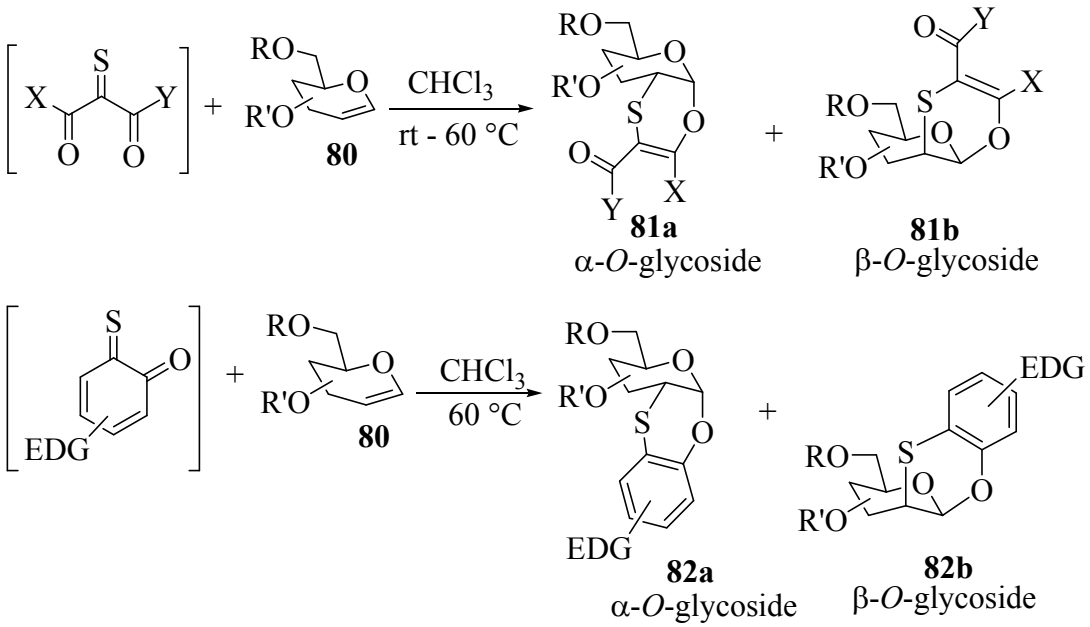
The smooth and efficient synthesis of α,α'-dioxothiones and *ortho*-thioquinones, as well as their successful employment as electron-poor dienes in inverse electron-demand Diels-Alder reactions, allowed us to develop a new and efficient method to prepare *O*-glycosides stereoselectively.

As a matter of fact, α,α'-dioxothiones and *ortho*-thioquinones can be trapped with 1-glycals **80** as electron-rich dienophiles, to give the corresponding 2-deoxy-2-thio-*O*-glycosides **81a,b** and aryl 2-deoxy-2-thio-*O*-glycosides **82a,b**[67,68] (Scheme 28).

Both α,α'-dioxothiones and *ortho*-thioquinones react with differently substituted 1-glycals **80** with total chemo- and regioselectivity and with high or total stereoselectivity. Thiones are generated in situ, in the presence of glycals, from the parent phthalimide derivatives, with pyridine or ludine, in chloroform as solvent. Cycloadditions are generally performed at room temperature or 60 °C.

In Table 5 are reported some representative *O*-glycosyl cycloadducts.[69,70]

The cycloadditions are inverse electron-demand Diels-Alder reactions since the smallest differences in energy are between the HOMO of the glycals dienophiles and the LUMO of the oxothiones. Glycals employed in these reactions may be differently protected or unprotected, however acetates lower the HOMO of the glycal so that it adds to only very reactive heterodienes; in fact when the energy gap exceeded 8 eV, no reaction occurs.[69]



Scheme 28

Unlike the usual regiochemistry, the stereochemical outcome of these cycloadditions cannot be rationalized by a single variable.

The results in Table 5 suggest that a sure influence on the face selectivity of the cycloaddition is the steric effect of axial substituents on the glycals. In the three equatorial glucal series (entry 1,5,6), the general rule of a preferred below-plane selectivity is satisfied.[71,72,73]

In the ribal example (entry 4), the substituent at C-3 is not truly axial so that a modest selectivity is observed. In this case the selectivity can be improved by using a more hindered protecting group at the oxygen.[69] In the case of arabinal (S_4, axial group at C-4) (entry 7) the total up-face selectivity was observed.[70]

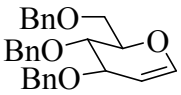
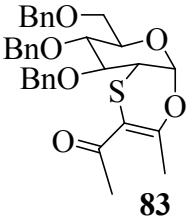
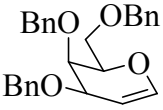
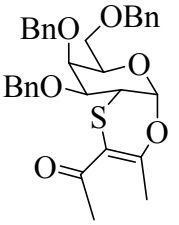
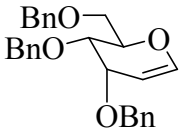
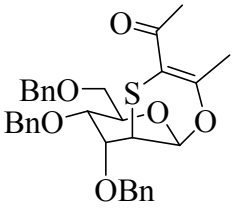
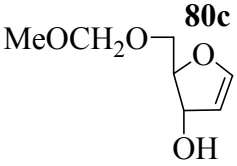
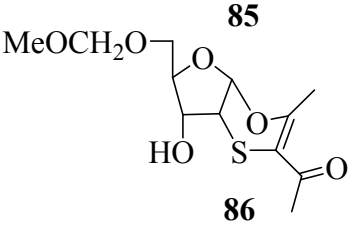
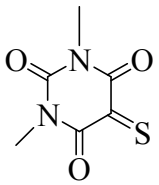
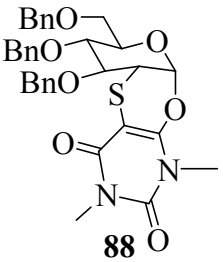
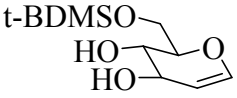
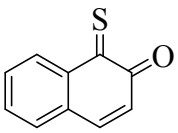
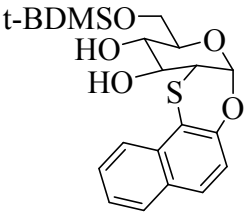
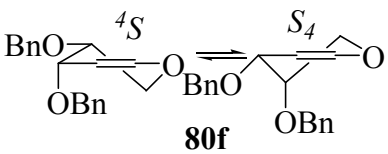
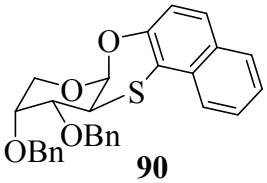
To evaluate the role of solvent on the rate and the selectivity of the cycloaddition, a series of unsubstituted and differently substituted glycals were cycloadded to the electron-poor *ortho*-thioquinone **65f** in chloroform, dimethylformamide and dimethyl sulfoxide,[70] and to the oxothione **27a** in methanol and *tert*-butanol.[69]

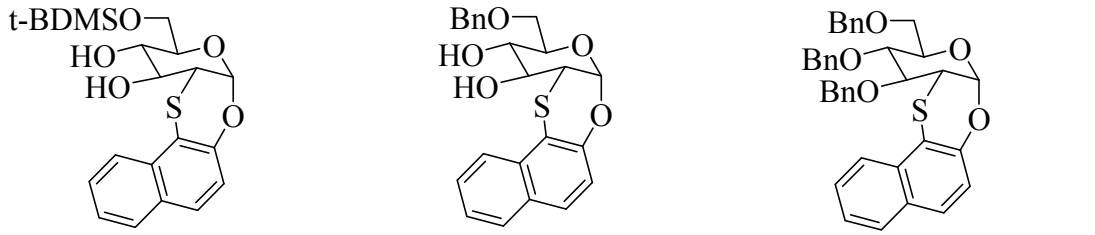
The use of polar solvents dimethyl sulfoxide and dimethylformamide generally reduces the face selectivity of the cycloadditions, however selectivity is still observed if hydrogen bonding between the solvent and the hydroxyl groups of the glycal is possible (Figure 4, **89** and **91**). In fact selectivity is diminished when this hydrogen bonding is not possible (Figure 4, **92**).

The effect of solvent on cycloaddition rate is a complex phenomenon. With H-bond donor solvents, methanol and *tert*-butanol, it is small, with the largest effect observed about a factor two. The situation is more complicated in the case of **65f** in dimethyl sulfoxide or dimethylformamide as solvents, since the reduction of the cycloaddition rate in these cases is likely due to side reactions observed for **65f** which effectively reduce the concentration of the diene in the reaction media.

Noteworthy, cycloadding glycal **80a** with **27a** or **65f** in methanol, along with the bottom- and top-face cycloadducts **83**, **92** (Scheme 28) and **93** (Figure 5), methyl glycoside **94-96** were isolated as well, suggesting that, under these conditions, the mechanism of the reaction might not be a *true* cycloaddition but might pass through a charged intermediate of type **97-99** (Figure 5).[69,70,74]

Table 5. A selection of glycofused oxathiins prepared by cycloaddition of dioxothiones and *ortho*-thioquinones with glycals.

Entry	Dienophile	Diene	Cycloadduct	α/β Ratio	Yield, % [69,70]
1	 **80a**	**27a**	 **83**	19 / 1	80
2	 **80b**	**27a**	 **84**	α	73
3	 **80c**	**27a**	 **85**	β	68
4	 **80d**	**27a**	 **86**	4/1	74
5	**80a**	 **87**	 **88**	9/1	64[73]
6	 **80e**	 **65f**	 **89**	20/1	76
7	 **80f**	**65f**	 **90**	β	77



89 (DMSO, α/β = 2.7/1) **91** (DMSO, α/β = 3/1) **92** (DMSO, α/β = 1.2/1)

Figure 4. Structures and α/β ratios for cycloadducts **89**, **91** and **92**

This efficient protocol for the stereoselective preparation of *O*-glycosides was successfully employed to synthetized pharmaceutically or biologically attracting compounds such as a 2-deoxy analogue (**100**) of the antitumor antibiotic BE-12406B, the tyrosine α-glucoside **101** and a family of nonpeptide ligands (**102a-d**) for the human tackykinin NK-2 receptor as reported in Figure 6.[70,75]

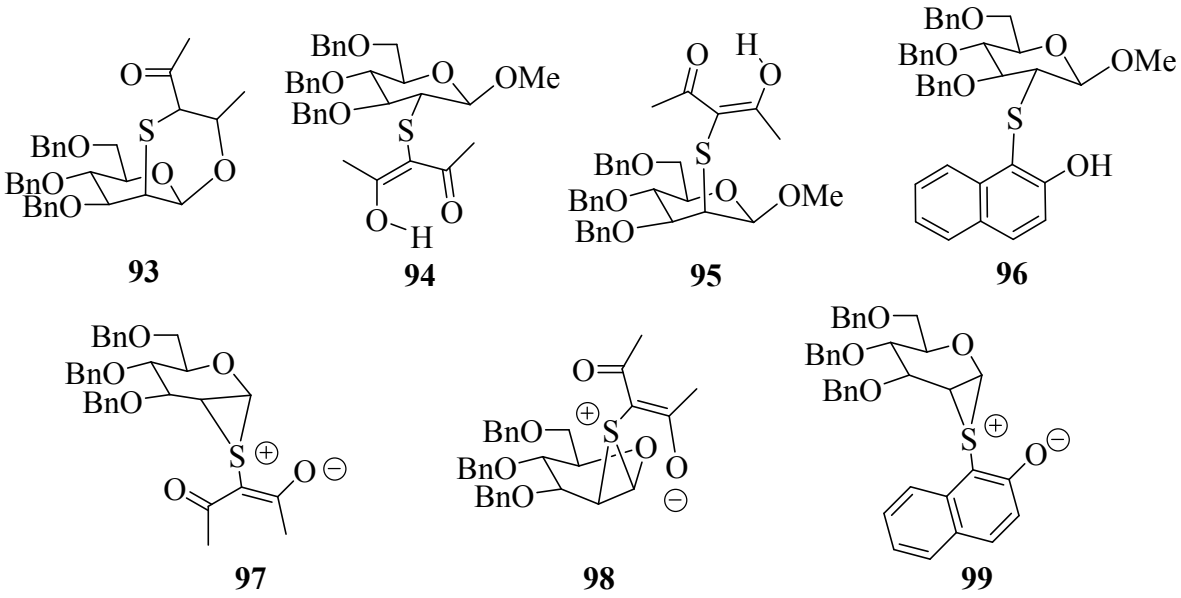


Figure 5. Products and possible intermediates in the reaction of **27a** and **65f** with **80a** in methanol

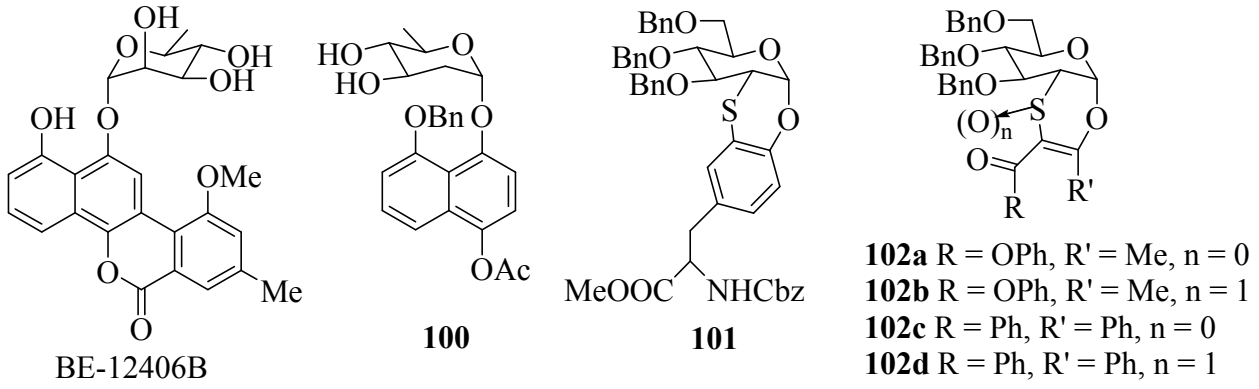
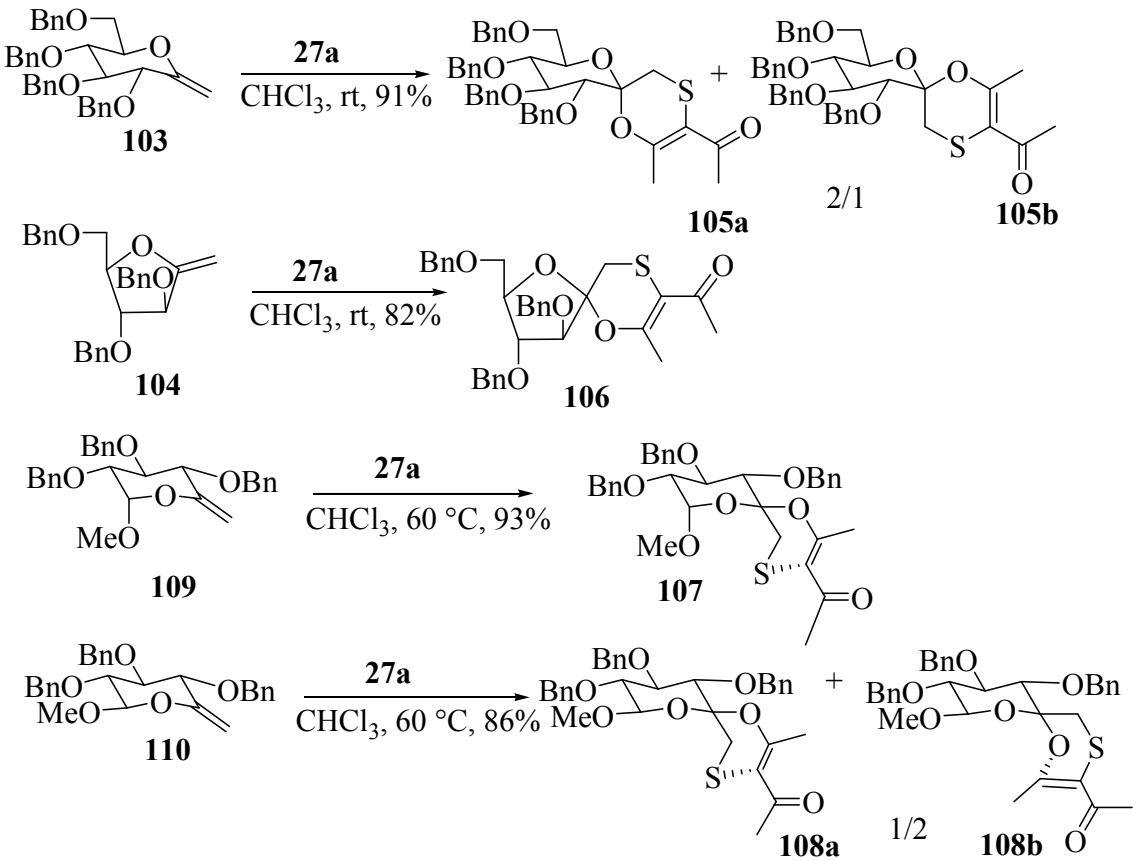


Figure 6. Biologically valuable glyco-fused oxathiins **100-102**

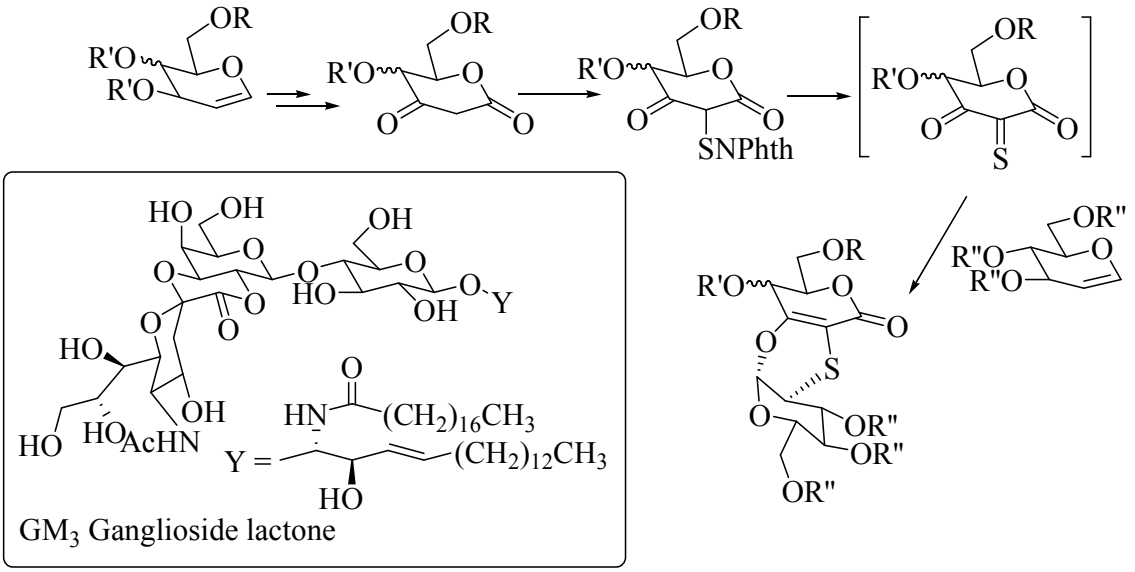
Easily achievable glycoexoenitols were also successfully cycloadded with α,α'dioxothiones and *ortho*-thioquinones to prepare enantiomerically pure thiospiroacetals.[76] Tetra-*O*-benzylglucohexenitol **103** and tri-*O*-benzylarabinohexenitol **104** were employed as electron-rich dienophiles and reacted with heterodiene **27a** to give the spiro derivatives **105** and **106** respectively (Scheme 29).

The cycloadditions were completely regio- and stereoselective. As a matter of fact, spiroacetals **105a,b** were isolated as a 2/1 mixture of stereoisomers while spiroacetal **106** was obtained as unique stereoisomer (Scheme 29).



Scheme 29

The assignment of the regio- and stereochemistry depicted in Scheme 29 for **105** and **106**, achieved by ^{1}H, ^{13}C and 2D NMR spectra of the crude mixtures, indicated for major (**105a**) or single (**106**) stereoisomers the geometry with two anomeric effects (i.e. the thermodynamically more stable).[76,77]



Scheme 30

A new class of spiroacetals, with the spirocentre located at C-5, of type **107** and **108a**,**b** were prepared starting from glycoexoenitols **109** and **110** and heterodiene **27a** (Scheme 29). In the case of exoenitol **109** (OMe group at C-1, axial) the cycloaddition was regiospecific and totally stereoselective, thus suggesting a disfavoured approach of the diene toward one of the two faces of the double bond of the dienophile.

A further successful extension of this procedure regarded the synthesis of enantiomerically pure α,α'-dioxothiones from carbohydrates and their cycloaddition with 1-glycals to afford enantiomerically pure 2-deoxy-2-thiodisaccharides (Scheme 30).

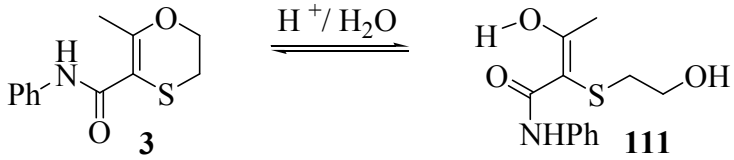
This promising new protocol for oligosaccharides synthesis is actually under investigation to be applied for the preparation of an analogue of the GM_3 ganglioside lactone.[78]

4. Reactivity of 1,4-oxathiins

The 1,4-oxathiin structure is probably more interesting for the biological activities related than for the chemical features pointed out. Nevertheless, the spectroscopic properties of these compounds have been investigated[8,14,79,80] and some interesting applications arose from the study of their chemical behaviour, as summarised in the next Sections.

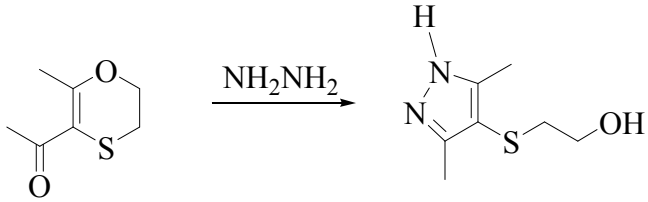
4.1. Ring opening

The first paper dealing with the reactivity of 1,4-oxathiins regarded their acid catalysed ring opening.[81] The same reaction was reported on fungicide **3** to give 2-thiosubstituted β-ketoester **111** which, in solution, is 100% in enolic form[82] (Scheme 31).



Scheme 31

Ring opening of 1,4-oxathiins can be also achieved by means of bases,[82-84] in this case, choosing a suitable reagent, the ring opening can be followed by a new ring closure as in the reaction with hydrazine reported in Scheme 32.

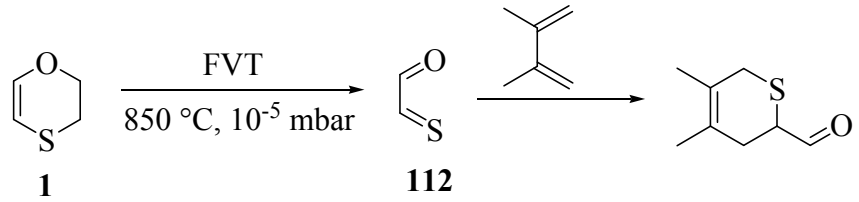


Scheme 32

Following a completely different approach, the ring opening of 1,4-oxathiins was achieved by Flash Vacuum Thermolysis (FVT) that caused a retro Diels-Alder process and the formation of an oxothione.[85,86] Indeed, the parent thioxoethanal **112** was generated from **1** at 850 °C and 10^{-5} mbar and trapped as dienophile across the carbon-sulfur double bond (Scheme 33).

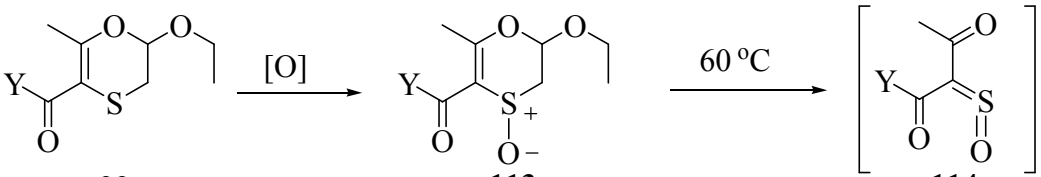
A retro Diels-Alder (RDA) process from 1,4-oxathiins can represent indeed an alternative method to obtain α-oxothiones. However, it suffers from the harsh conditions required to promote the RDA reaction.

During our studies on the reactivity of oxathiins we noticed that the oxidation at sulfur of derivatives **29** to give sulfoxides **113** promoted the retro cycloaddition reaction allowing the generation, under very mild conditions (i.e. $CHCl_3$, 60 °C), of the α,α'dioxosulfines **114**[87,88] as reported in Scheme 34.



1 **112**

Scheme 33

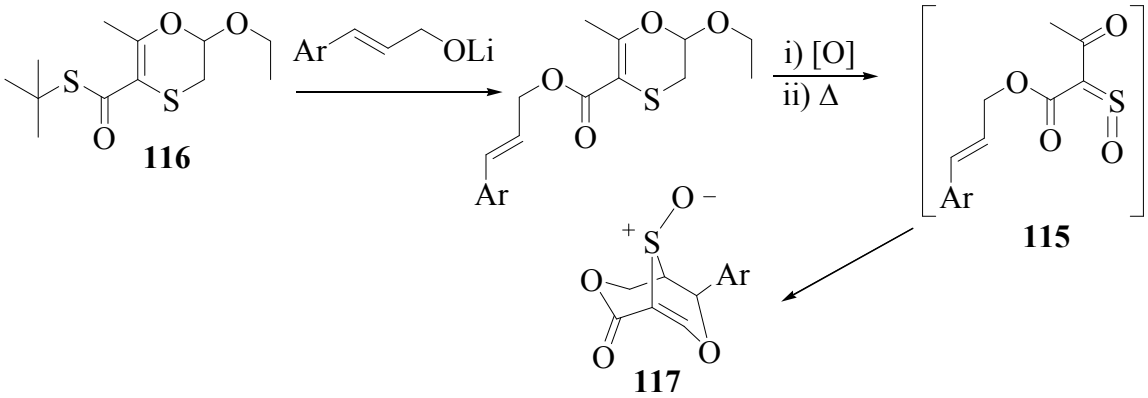


29 **113** **114**

Y = Alkyl, OAlkyl

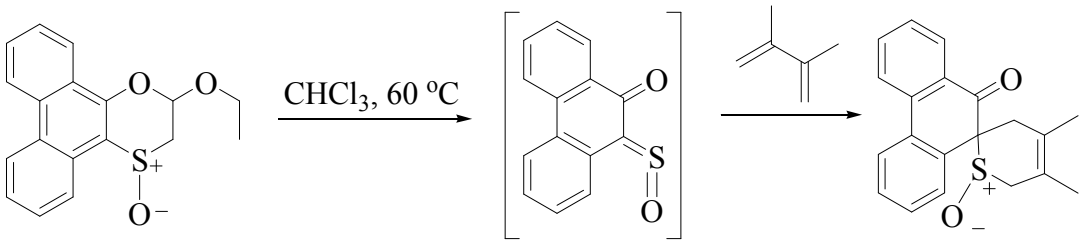
Scheme 34

This procedure, which represents a valuable alternative to those previously described,[41-44] allowed the easy access to a new family of very reactive electron-poor dienes (and/or dienophiles) since the oxygen on sulfur decreases the energy of the LUMO of these dienes with respect to the orbitals of the corresponding oxothiones. Thus thione-*S*-oxides **114** gave the oxathiin cycloadducts even with simple alkenes, like for example 2,3-dimethyl-2-butene, which were unreactive as dienophiles towards the corresponding α,α'dioxothiones.[88] Moreover, exploiting this strategy, it was possible to carry out an intramolecular cycloaddition reaction by generating the oxosulfine **115** bearing an internal dienophile.[89] Thus, starting from oxathiin **116**, the sequence reported in Scheme 35 allowed the isolation of bicyclic compounds **117**.



116 **115** **117**

Scheme 35

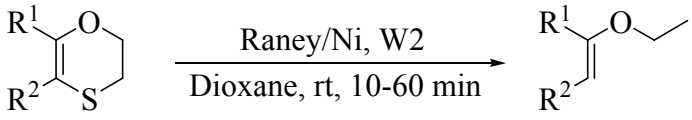


Scheme 36

The feasibility of such RDA reaction was further demonstrated by the generation, under the same reaction conditions, of *ortho*-thioquinones-*S*-oxides from the corresponding benzoxathiins and their trapping as dienes or dienophiles[90] (Scheme 36).

4.2. Reduction and oxidation

Among the possible reductions of the oxathiin ring, the reductive desulfurization has been studied in more detail and it allowed interesting applications. Raney-nickel has been quite often the reagent of choice and its use has been optimised for the efficient preparation of *E*-alkyl vinyl ethers from oxathiins without affecting the carbon-carbon double bond[91] (Scheme 37).

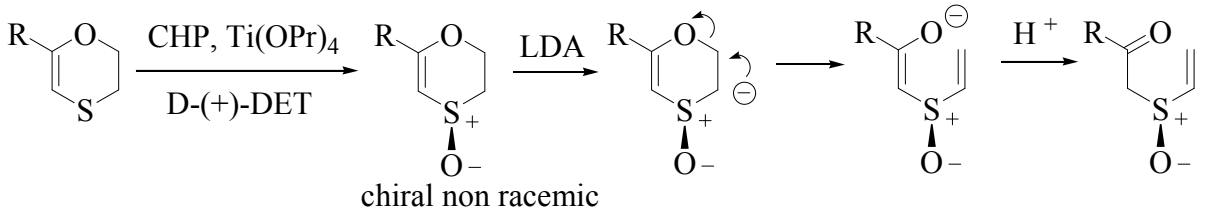


Scheme 37

We observed similar results in the desulfurization of glyco-condensed oxathiins as reported in the next section.

Oxidation of sulfur in 1,4-oxathiins is a very simple reaction, it can be run with several oxidising agents, including MCPBA, H_2O_2, ROOH, Oxone etc., with the formation of the corresponding sulfoxide or sulfone as function of the stoichiometry and conditions of the reaction.[87-90,92] The formation of the sulfoxide occurred with a very good or complete diastereoselectivity with the preferential forming of the compound with the sulfoxide oxygen laying in a pseudo-axial position. Sulfoxides were also obtained with high enantioselectivity using the Modena modification of Sharpless oxidation with cumene hydroperoxide (CHP) as oxidising agent. Chiral oxathiin sulfoxides, prepared following this procedure, can then be transformed into non racemic β-ketosulfoxides by reaction with lithium diisopropyl amide (LDA)[92] (Scheme 38).

Another interesting aspect of the oxathiin-S-oxide chemistry was its behaviour under Pummerer reaction conditions. Although all the procedures requiring high temperature should be avoided due to the possible retro Diels-Alder reaction, the use of very reactive Pummerer promoting, like $(CF_3CO)_2O$, gave preferentially, even at low temperature, an additive process with the formation of adducts **118** instead of the classical α-functionalization. Compounds **118** were found to be rather unstable and by hydrolysis or heating were transformed into oxathiolanes **119** or derivatives **120** respectively[93-95] (Scheme 39).

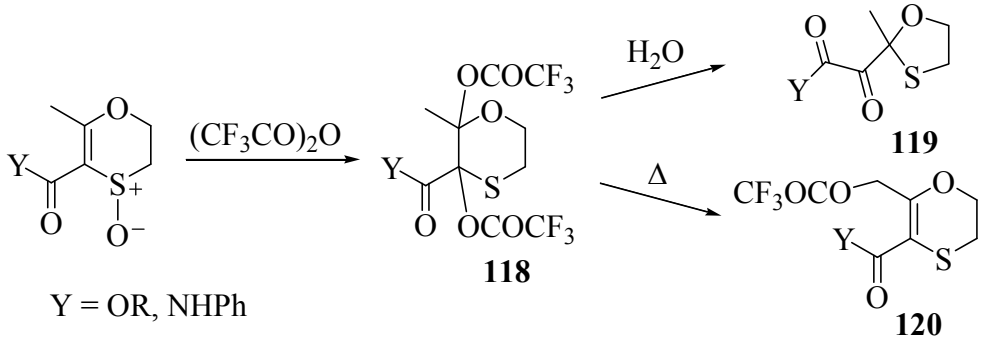


chiral non racemic

Scheme 38

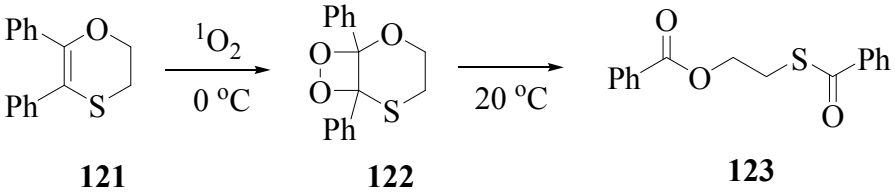
Compounds like **120**, which can be seen as the products of a vinilogous Pummerer reaction, have been already described in the synthesis of oxathiins by halogenation of 1,3-oxathiolanes[25,27] (see Scheme 8) and were indeed obtained by direct chlorination of oxathiins.[96]

Several efforts were devoted to the selective oxidation of the endocyclic double bond of oxathiins. A first report[97] indicated singlet oxygen ($^1O_2$) as the reagent of choice for this transformation at least for diphenyl substituted oxathiin **121** (Scheme 40).



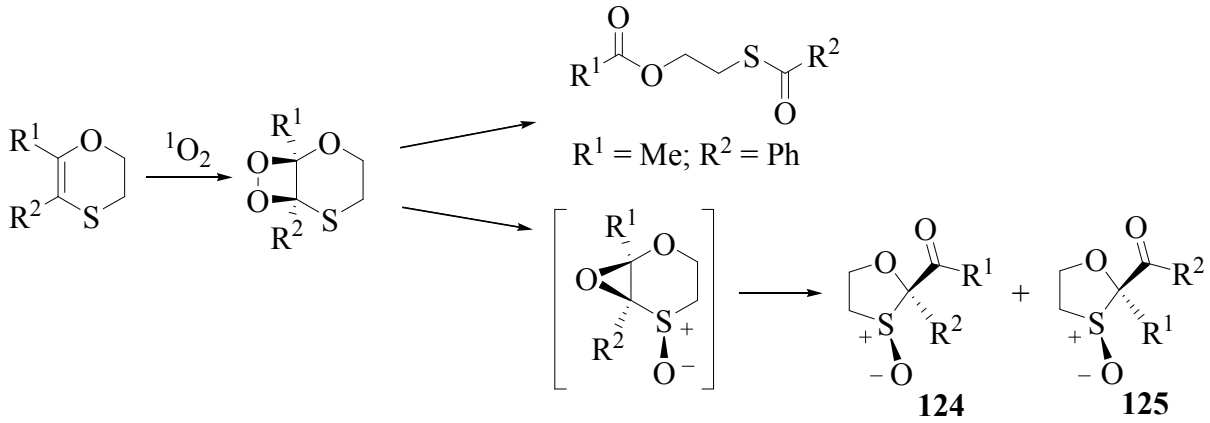
Scheme 39

As a matter of fact, the initially formed dioxoethane **122** was converted into the dicarbonyl derivative **123** simply by increasing the temperature of the reaction mixture from 0 to 20 °C (Scheme 40).



Scheme 40

More recent and detailed studies[98,99] showed that this reaction is very sensitive to the nature of substituents on the oxathiin ring and to the photo-oxygenation conditions. Indeed, an open chain bis-ester derivative was obtained for alkyl or aryl substituted oxathiins, but in the presence of carbonyl of carboxyl groups the intermediate dioxetane evolved to give 1,3-oxathiolane-*S*-oxides of type **124** and **125** (Scheme 41).

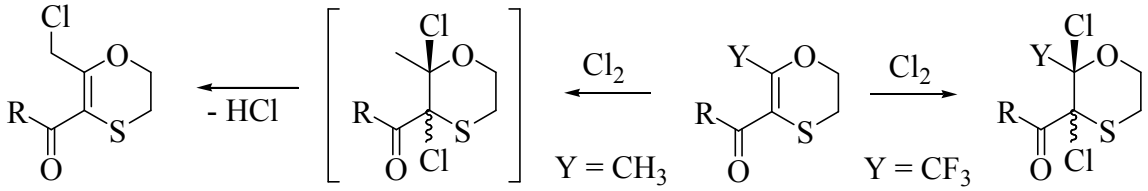


R^1= Alkyl, Aryl, COOMe
R^2 = COY: Y = Alkyl, OAlkyl, NHAlkyl

Scheme 41

Eventually a clean chlorination of the internal double bond of oxathiins was reported in the case of 2-

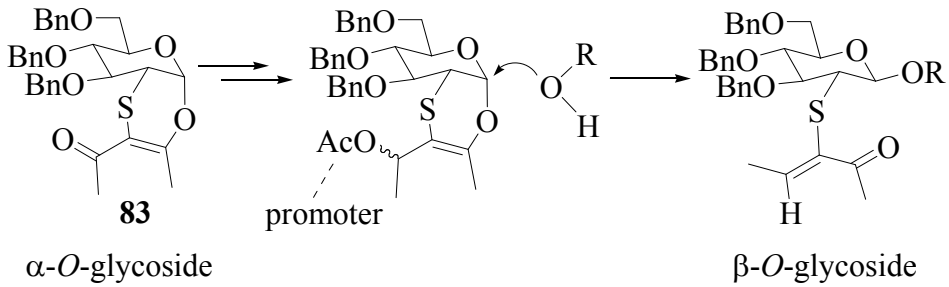
trifluoromethyl-substituted derivatives which obviously does not suffer from the halogenation at this position[96] (Scheme 42).



Scheme 42

4.3. Glycocondensed oxathiins

Glyco-fused 1,4-oxathiins like **81a** can be easily transformed into unusual glycosyl donors which, after "remote activation",[100] react efficiently with glycosyl acceptors to give enantiomerically pure 2-thio-β-*O*-glycosides. As a matter of fact, conversion of the α,β-unsaturated ketone of **83** into an allylic acetate produced a system suitable to undergo remotely triggered substitution at the anomeric carbon atom, *anti* with respect to the oxathiin ring to afford the corresponding β-*O*-glycoside (Scheme 43).



Scheme 43

The glycosylation is performed at room temperature, in dichloromethane as solvent and in the presence of catalytic amounts of methyltriflate as promoter.[101,102] The timing of quenching is crucial for the success of β-glycosidation: the colour change practically indicates the beginning of isomerization from β to α.

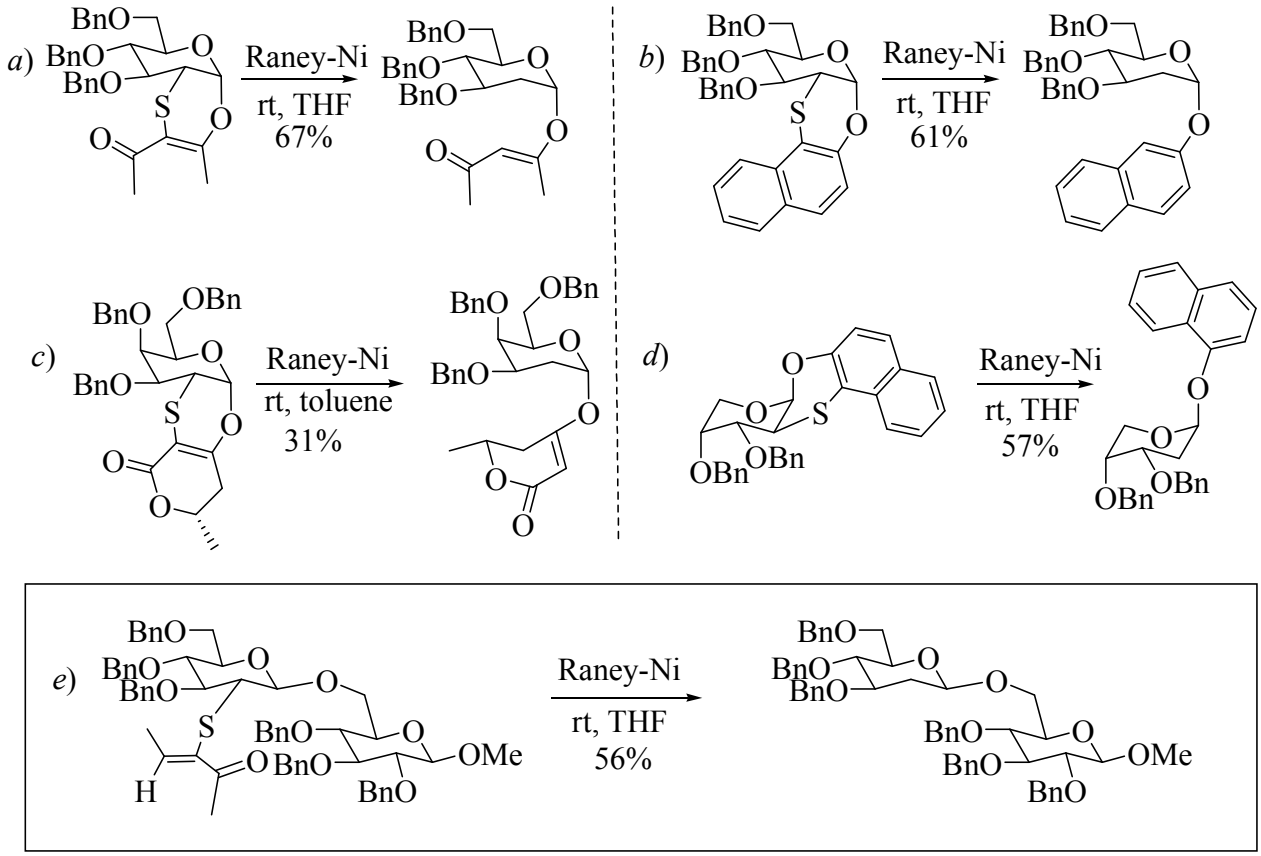
Several glycosyl acceptors were employed to prepare the corresponding β-*O*-glycosides with a total stereocontrol.[103] 2-Deoxy-2-thio-α- or β-*O*-glycosides can be directly transformed into the corresponding 2-deoxy derivatives by reductive desulfurization with Raney-nickel.[67,70] 2-Deoxy-*O*-glycosides are formed under very mild conditions (rt or 0 °C) without undergoing epimerization of the anomeric centre (Scheme 44, eq *a*-*e*).

Unfortunately, yields are variable since they strongly depend upon the age and the quality, from batch to batch, of the nickel catalyst. In addition, a problem of elimination competing with reduction can sometimes occurs[104] (Scheme 45).

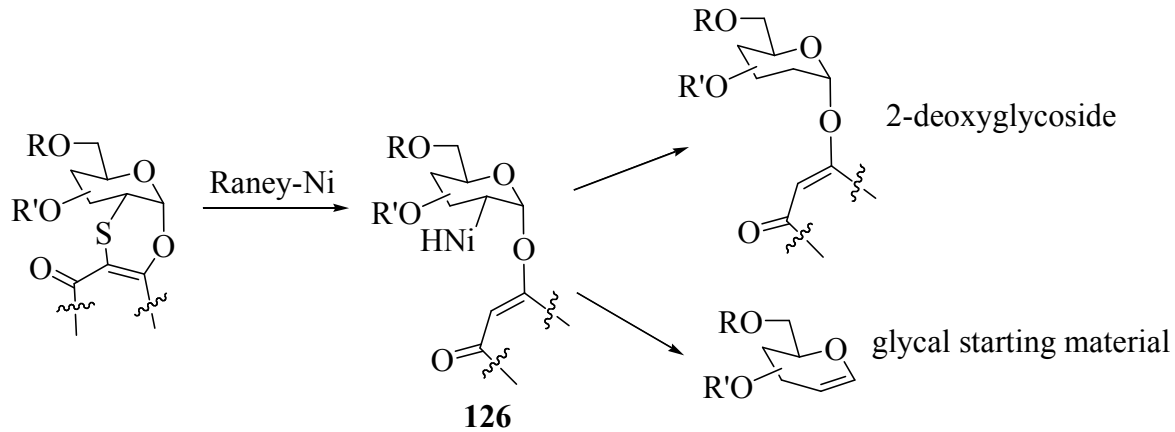
Although not completely clarified, the formation of a "Ni-H" intermediate **126**, (see Scheme 45), was hypothesized to rationalize the formation of elimination products. Indeed, the latter can afford the desired 2-deoxy derivative by reductive elimination of nickel, or undergo the elimination of nickel alkoxide thus producing glycal starting material.

As above reported for 1,4-oxathiins rings, the oxidation at sulfur of glyco-condensed oxathiins is a very simple reaction which allows the formation of the corresponding sulfoxide or sulfone, depending on the

stoichiometry and conditions of the reaction. Sulfoxides are always obtained with a total diasteroselectivity.[75,76]



Scheme 44

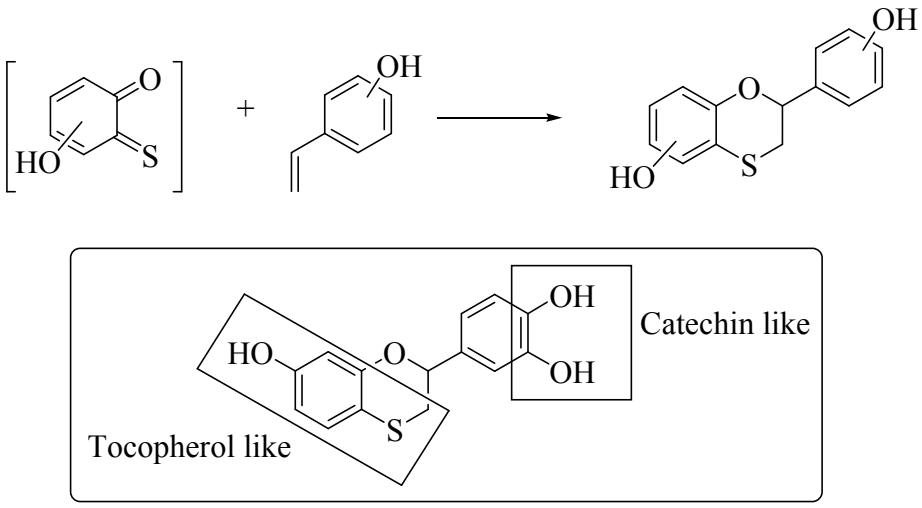


Scheme 45

5. Applications of 1,4-oxathiins

Throughout this chapter we mentioned the relevance of the 1,4-oxathiin structure for the biological activities related.[8] From the initial discovery[1,2] of the systemic fungicidal activity of Vitavax® (**3**) and Plantavax® (**4**), several other reports proved the different activities of 1,4-oxathiin ring-containing molecules. Indeed it seems that these hetero-substituted six member rings can interact with different biological targets since it has been reported their activity as inhibitors of HIV-1 reverse trascriptase,[3,4] adrenoreceptor antagonists,[5,6] oestrogen receptor modulators,[7] nonpeptide ligands for the human tackykinin

NK-2 receptor,[70,75] as well as non-glycosyl sweeteners.[36] Recently we demonstrated[105] that polyhydroxy substituted benzoxathiins obtained from the reaction of *ortho*-thioquinones with styrenes (Scheme 46) are also efficient antioxidant derivatives. Interestingly, as function of the position of the hydroxyl groups on the two aromatic rings, these compounds are able to parallel the ability as radical scavengers of flavonoids (like catechin) or/and tocopherols, the two most important families of natural polyphenolic antioxidants.[105] Due to the huge number of pathologies related to a high concentration of free radicals in living tissues the possibility to control their amount by means of efficient radical scavengers represents a valid way to control several of the most common and dangerous modern diseases, including cardiovascular diseases, stroke and cancer.



Scheme 46

6. Conclusions

1,4-Oxathiin heterocycles are challenging targets, known since many years for their differentiated biological activities. Despite several methods are available for their preparation, the regio- and/or stereocontrol in the formation of the six member ring, as well as the synthesis of polysubstituted oxathiins, often remain unresolved problems.

The hetero Diels-Alder approach to 1,4-oxathiin derivatives, using α,α'-dioxothiones or *ortho*-thioquinones as electron-poor dienes and several electron-rich alkenes as dienophiles, has disclosed the way to the easy stereocontrolled synthesis of these appealing compounds, allowing the efficient preparation of 1,4-oxathiins bearing a variety of substituents on each position of the carbon skeleton.

In particular, glyco-condensed 1,4-oxathiins can be selectively prepared, following the above mentioned procedure, when the dienophiles employed are differently substituted glycals.

These recent acquisitions clearly suggest that the study of the chemical behaviour and the biological properties of 1,4-oxathiins is a still growing and fruitful field in modern heterocyclic chemistry.

Acknowledgements

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NUCLEOPHILIC ADDITIONS TO NITRONES: AN ALTERNATIVE GATEWAY TO ISOXAZOLIDINES, PYRROLIDINES AND RELATED COMPOUNDS

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Abstract. *Nucleophilic additions to nitrones are emerging as useful tools for the construction of a great variety of nitrogenated products. Among these compounds, saturated nitrogen-containing heterocycles, particularly, isoxazolidines and pyrrolidines are of high interest. The present review surveys the recent synthetic efforts that are focused on the preparation of isoxazolidines, pyrrolidines and related compounds using nucleophilic addition reactions to nitrones as key steps of the syntheses.*

Contents

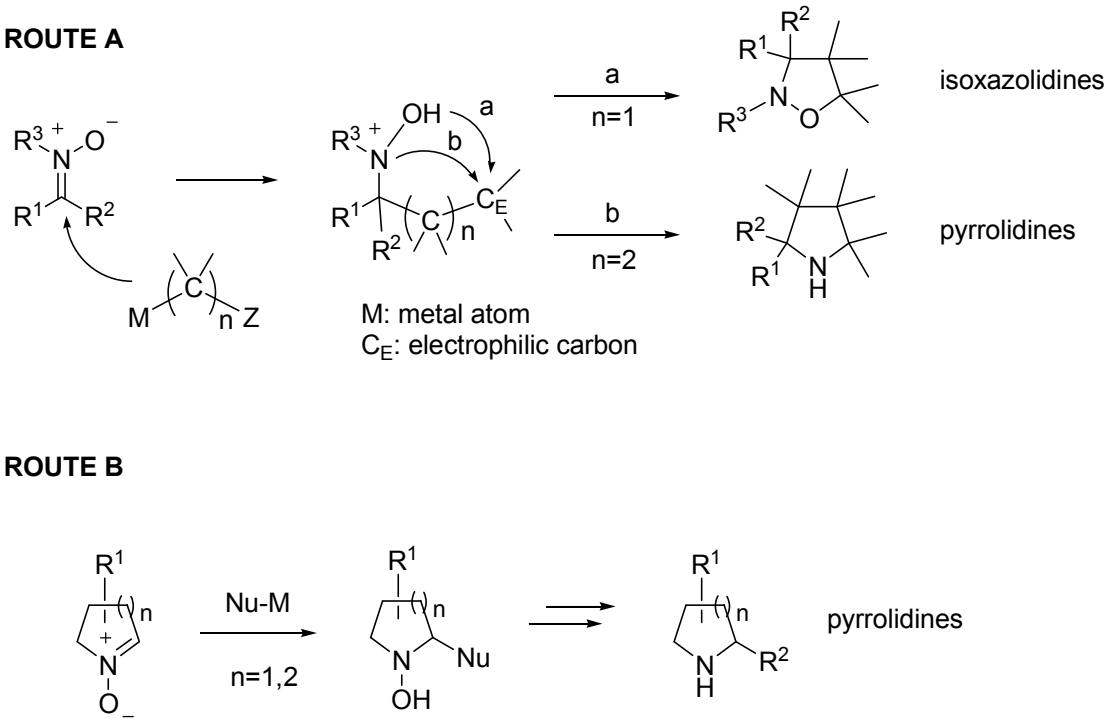
1. Introduction

Isoxazolidines and pyrrolidines form important families of heterocyclic compounds, as simple heterocycles or forming part of more complex structures.[1] In addition, substituted isoxazolidines play an important role in organic synthesis as precursors of 1,3-aminoalcohols and chiral auxiliaries.[2] There are a vast number of methods for preparing pyrrolidines and they have been reviewed elsewhere.[3] Typically, isoxazolidines are prepared through the cycloaddition reaction between a nitrone and an alkene. This reaction has also been extensively studied and several treatises and reviews can be found in the literature.[4] In fact, nitrones can also be used as building blocks for the construction of heterocyclic systems different from isoxazolidines via 1,3-dipolar cycloaddition reactions. The elegant approach recently described by Hanessian and co-workers[5] for the synthesis of pyrrolidines is an example of that utilization.

There is an alternative for the use of nitrones in the synthesis of nitrogenated heterocycles: nitrones can also be used as electrophiles reacting with a variety of nucleophiles.[6] Two different strategies are possible: i) a two-step process in which the initial nucleophilic addition to the nitrone is followed by a spontaneous (or induced) cyclization (route A) and ii) a direct nucleophilic addition of organometallic reagents to cyclic nitrones (route B). This approach leads to N-hydroxy pyrrolidines that can be immediately converted into functionalized pyrrolidines.

In this review, syntheses of isoxazolidines and pyrrolidines from nitrones are described, which are not cycloaddition reactions as concerted processes. Instead, it is the aim of this report to review nucleophilic additions to nitrones leading to the above mentioned heterocycles through stepwise processes. In some instances, particularly those leading to isoxazolidines, the whole reaction scheme could be considered as a

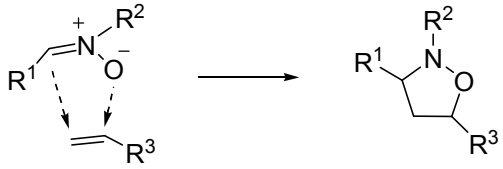
formal [3+2] cycloaddition but in order to avoid any confusion, only reactions following stepwise mechanisms have been considered in this review.



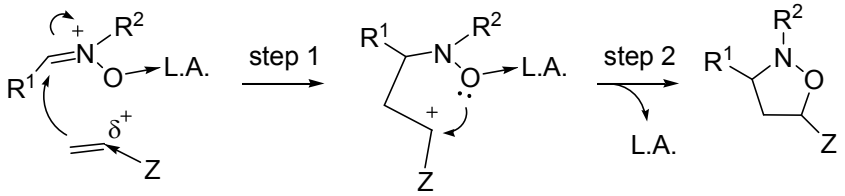
Scheme 1

2. Synthesis of isoxazolidines and related compounds

The cycloaddition between a nitrone and an alkene is a concerted but asynchronous process.[7]



1,3-dipolar cycloaddition
(concerted process)



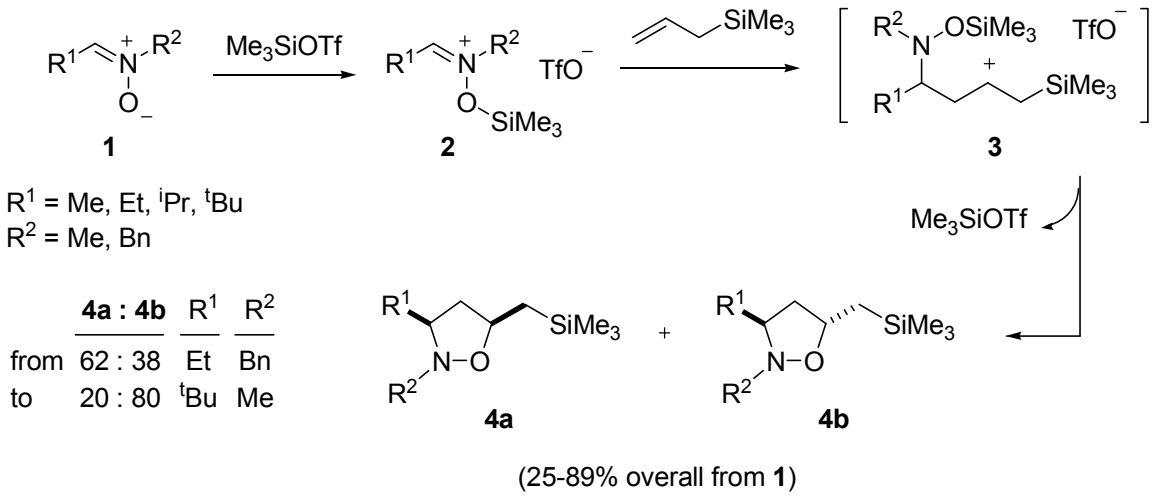
nucleophilic addition
(stepwise process)

Scheme 2

Depending on the electronic characteristics of the alkene the reaction is considered as a "normal electronic demand" (for electron-poor alkenes) or "inverse electronic demand" (for electron-rich alkenes) cycloaddition. However, if we consider the electronic character of a nitrone, the reaction with strong nucleophilic alkenes may turn into a "so asynchronous" process that actually can be considered as a two-step

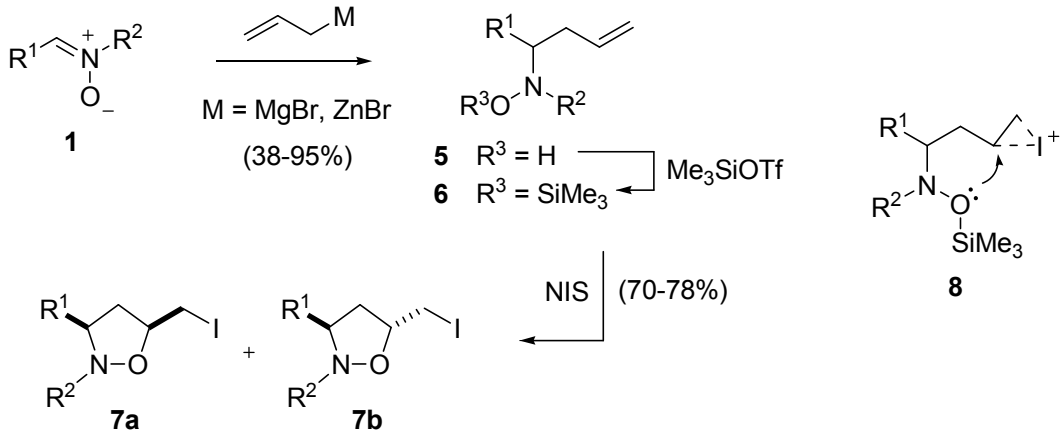
reaction (Scheme 2), particularly if the nitrone is activated with a Lewis acid in order to generate *in situ* an iminium salt.

The reaction of nitrones with allyltrimethylsilane represents an example of this situation. Whereas the thermal reaction[8] needs temperatures higher than 100 ºC the reaction catalyzed by trimethylsilyl triflate takes place at ambient temperature.[9] The initial step of the reaction, i.e.: silylation of the nitrone oxygen is a fast process that could be even observed by NMR spectroscopy. The iminium salt formed reacts immediately with allyltrimethylsilane to give the intermediate carbocation, which evolves to the cyclic isoxazolidine regenerating the catalyst. The reaction shows low *cis/trans* selectivity (Scheme 3) although a slight preference for *trans* compounds is observed with branched substituents at the nitrone carbon.



Scheme 3

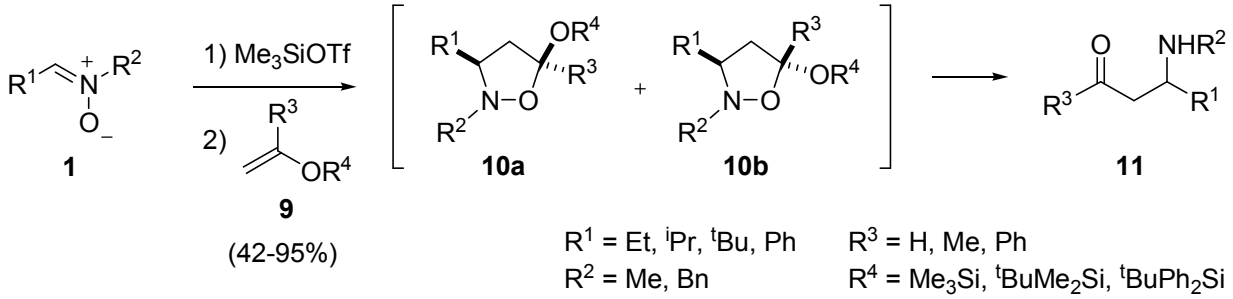
The addition of allylic organometallic reagents to nitrones affords homoallylic hydroxylamines **5**.[10] Then, the addition of an iodinating agent, such as N-iodosuccinimide or iodine chloride, to the previously silylated hydroxylamine **6** induces spontaneous ring closure to isoxazolidines **7**.



Scheme 4

The methodology showed in Scheme 4 clearly illustrates the capability of hydroxylamines for acting as nucleophiles via a stereoelectronically favored attack to an activated alkene through intermediate **8**.

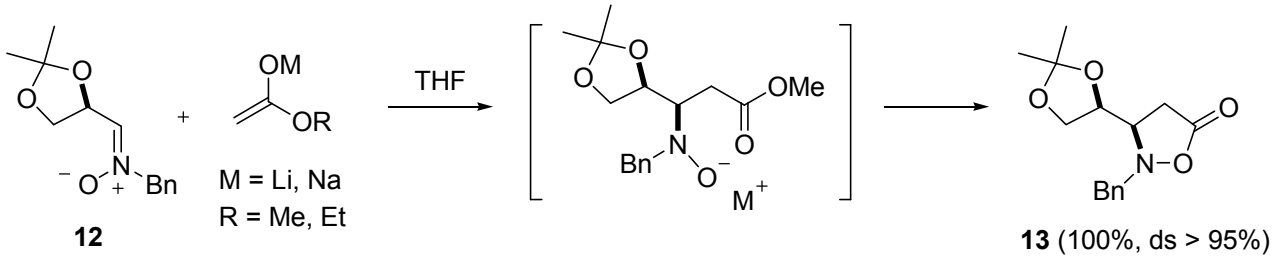
A method quite efficiently exploiting the presence of both nucleophilic and electrophilic centres at the proper distance has been reported by Trombini and co-workers.[11] The trimethylsilyl triflate-promoted addition of silylenol ethers **9** to nitrones gives 5-siloxy isoxazolidines **10** (Scheme 5). The reaction is carried out in the presence of 1.0 equiv of the promoter because the use of catalytic amounts of trimethylsilyl triflate requires higher reaction times or temperatures to achieve acceptable conversions.[11a]



Scheme 5

As the authors invoked in the original paper, the reaction quite probably proceeds via a carbocation generated from the nucleophilic attack of the silyl enolate to the iminium salt resulted from the silylation of the nitrone, in a similar way to that illustrated in Scheme 3. The *cis/trans* selectivity of the reaction is low, but quite rewardingly, the mixture of isoxazolidines could be easily converted into β-aminoketones **11** by treatment with the Zn-Cu couple. The whole process starting from the nitrone constitutes an alternative to the Mannich reaction.

A similar approach consisting of the direct addition of lithium and sodium ester enolates has been reported by Merino and co-workers.[12] The reaction takes place smoothly at low temperature without any additive. The only product of the reaction is the corresponding 5-isoxazolidinone, thus indicating the *in situ* cyclization of the initial adduct. With the chiral non-racemic nitrone **12** derived from D-glyceraldehyde the reaction is completely stereoselective and only one diastereomer is obtained (Scheme 6). The synthetic utility of this transformation resides on the further conversion of **13** into isoxazolidinyl nucleosides, a new type of heterocyclic nucleoside analogues with promising biological activities.[13]

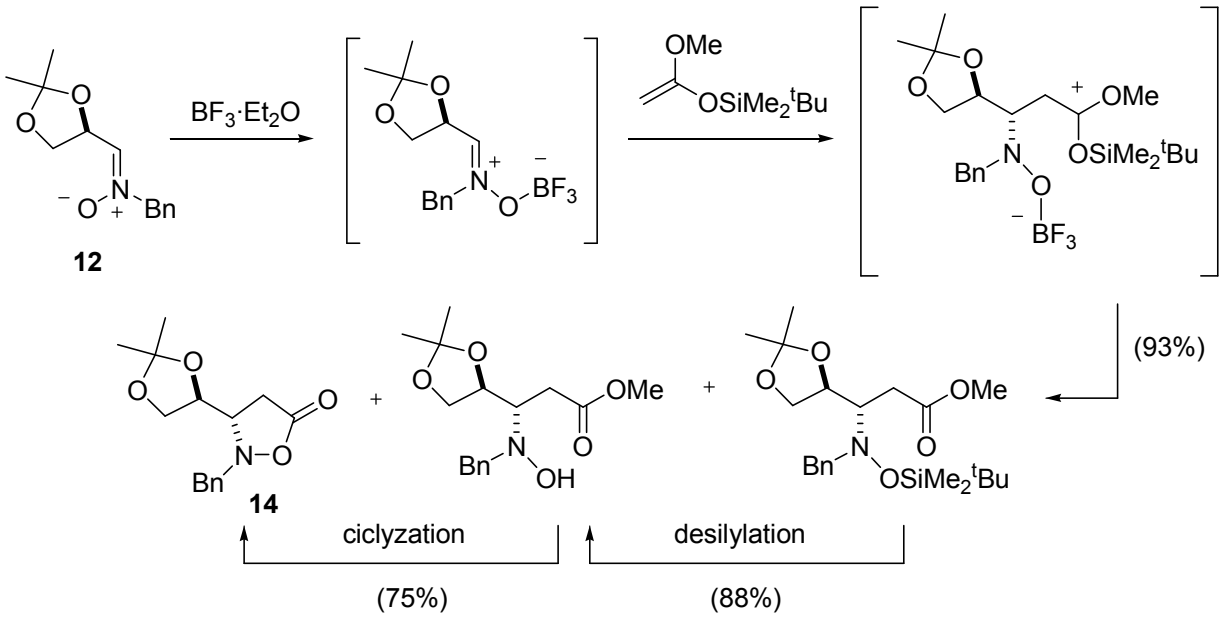


Scheme 6

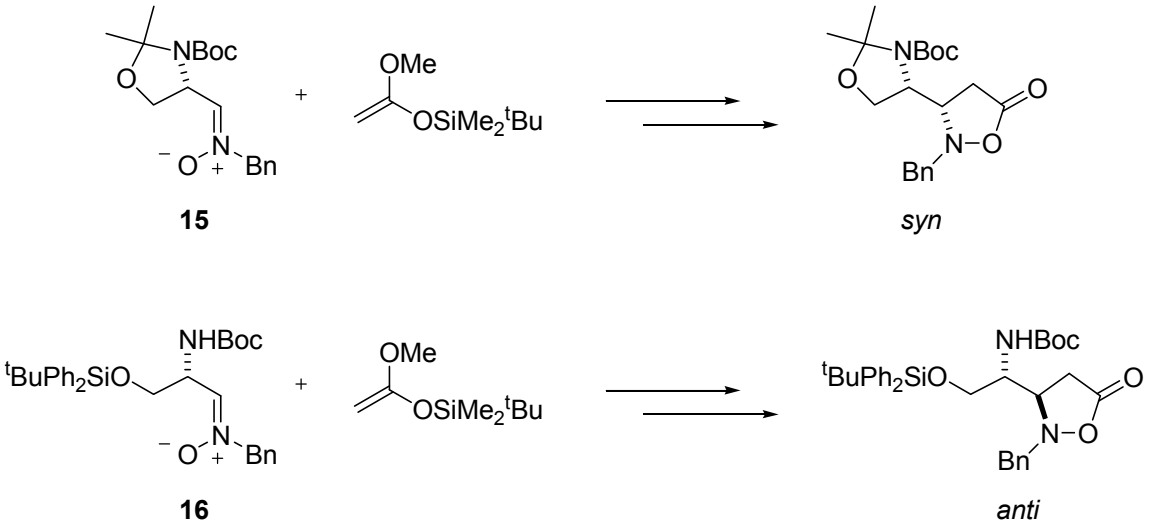
The reaction can also be carried out in the presence of Lewis acids such as diethyl aluminium chloride, in order to control the stereochemical course of the reaction. Unfortunately, under those conditions low chemical yields are obtained because of the formation of a less reactive aluminium enolate.

The addition of silyl enol ethers derived from esters (i.e. silyl ketene acetals) is also possible. In that case, however, the cyclization is not spontaneous even though the reactions need activation by a Lewis acid.

In general, the product of the reaction is the corresponding O-silylated hydroxylamine.[14] With nitrone **12**, however, a complex mixture of silylated and free hydroxylamines, and the expected 5-isoxaozlidinone **14** is obtained (Scheme 7).[15] By adjusting the amount of Lewis acid, it is possible to obtain the cyclic compound in good yield. In addition, the crude reaction mixture could be transformed into **14** in a one-flask procedure via a reaction sequence involving desilylation and cyclization. Interestingly, by using boron trifluoride etherate as a promoter of the reaction only the *anti* adduct **14** is obtained. It is worth noting that compound **14** is the epimer of compound **13** in Scheme 6, so the whole methodology allows the stereocontrolled construction of the isoxazolidine ring as pursued with the use of diethylaluminium chloride mentioned above. The addition of silyl ketene acetals can also be carried out with α-amino nitrones derived from α-aminoacids to prepare analogues of nucleoside antibiotics.[16]



Scheme 7

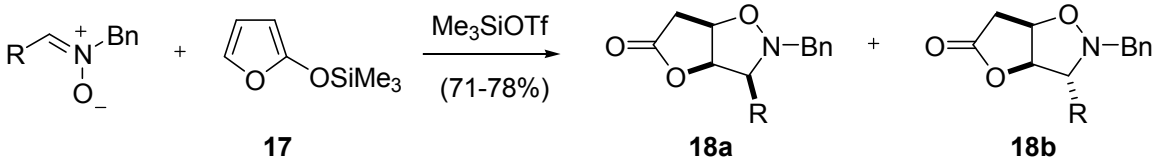


Scheme 8

Within this context, with nitrones derived from L-serine tunable diastereofacial selectivity depending on the protecting groups of the α-amino moiety is observed.[17] Whereas α,α-diprotected nitrone **15** gives rise

to the *syn* adduct, the α-monoprotected nitrone **16** affords preferentially the *anti* adduct. This behaviour has been observed previously with other nucleophiles.[6c] Because of the complexity of the reaction mixtures obtained after the addition step, the transformations illustrated in Scheme 8 need desilylation and cyclization additional steps to obtain pure isoxazolidin-5-ones.[16,17]

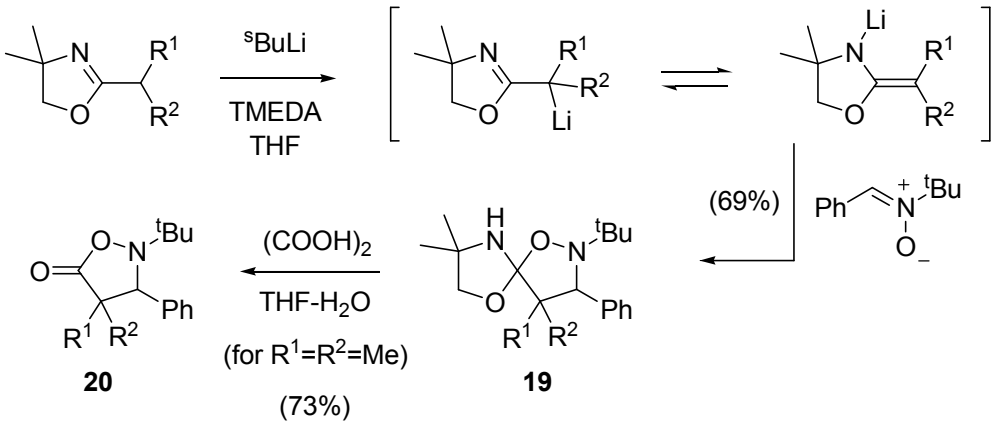
The reaction between nitrones and 2-(trimethylsiloxy)furan **17** constitutes a new entry to fused isoxazolidines (Scheme 9). Compound **17** behaves like a silyl ketene acetal, the reaction being catalyzed by trimethylsilyl triflate.[18] In general, mixtures of compounds are obtained and with chiral substrates, the observed diastereofacial selectivity is only moderate.[19]



17 **18a** **18b**

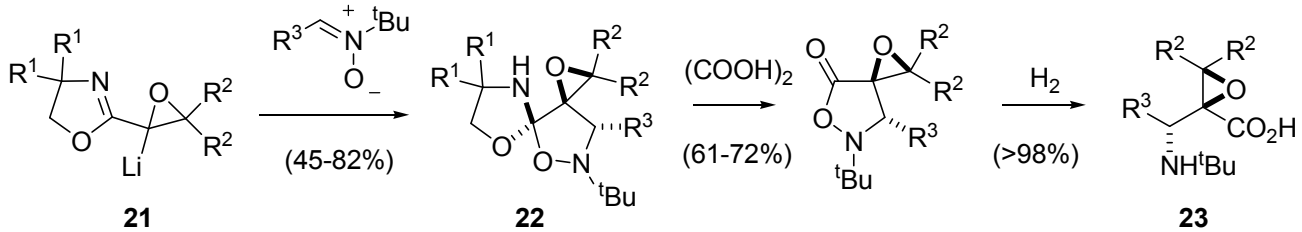
Scheme 9

Florio and co-workers have reported the addition of lithiomethyl oxazolines to nitrones.[20] The reaction affords spirocompounds **19**. The reaction is strongly dependent on the reagents; thus, whereas the adducts derived from methyl oxazolines (R^1=R^2=H) eliminate under acidic conditions to give alkenyl oxazolines,[21] those derived from isopropyl oxazoline (R^1=R^2=Me) are stable and they can be transformed into isoxazolidin-5-ones **20** by treatment with formic acid (Scheme 10).



20 **19**

Scheme 10



21 **22** **23**

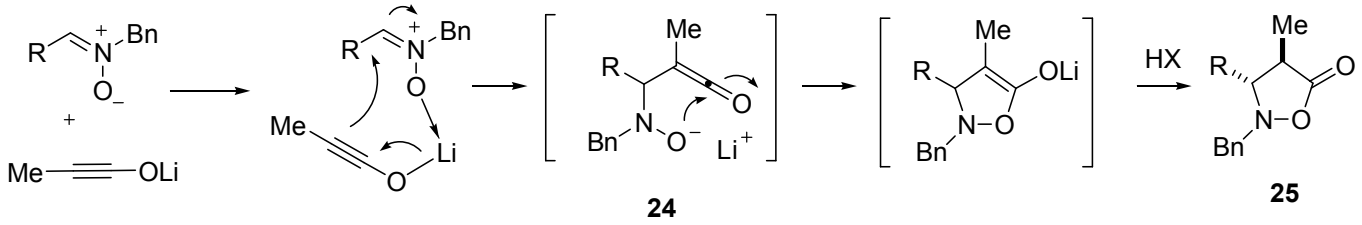
Scheme 11

α-Chloromethyl oxazolines (R^1=H, R^2=Cl) also afford alkenyl oxazolines, but branched α-chloromethyl oxazolines (R^1=Me, R^2=Cl) lead to spirocompounds that evolve to oxazetidinones.

Oxazolinyloxyranyllithiums **21** also provide spiro compounds suitable of being converted into isoxazolidin-5-ones en route to α-epoxy-β-aminoacids **23** (Scheme 11).[22]

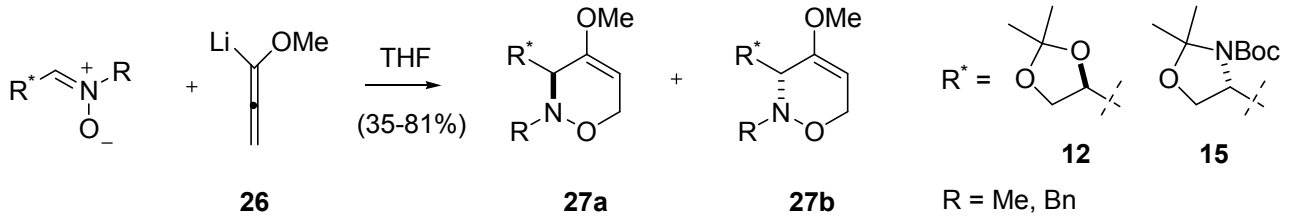
The intermediate trioxadiazaspiro[2.0.4.3]undecanes **22** can be isolated and fully characterized before their conversion to isoxazolidin-5-ones by acidic hydrolysis.

Another closely related reaction to the addition of enolates to nitrones is the condensation with ynolates (Scheme 12). Although the authors described the reaction as a 1,3-dipolar cycloaddition in their original paper,[23] the electronic characteristics of the reagents clearly denote a stepwise mechanism for the whole process. The obtention of a *syn* adduct in the asymmetric version of the reaction with nitrone **12** supports the two-step mechanism.[24] Whereas all nucleophilic additions to **12**, in the absence of any additive, lead to *syn* adducts,[6c] cycloaddition reactions with the same nitrone afford preferentially *anti* adducts.[25] Thus, according to a reactivity similar to that observed for ester enolates illustrated in Scheme 6 it is possible to postulate the formation of the intermediate ketene as indicated in Scheme 12. A further intramolecular attack of the nucleophilic nitrone oxygen to the ketene function results into compound **25** after the corresponding proton donation.



Scheme 12

The addition of lithiated methoxyallene **26** to nitrones giving rise to 3,6-dihydro-2H-1,2-oxazines **27** is another example of nucleophilic addition followed by an *in situ* cyclization.[26] The reaction can be completely stereocontrolled, in the case of α-alkoxy nitrones, following the reaction conditions previously developed by Merino and co-workers.[6a-c] The obtained cyclic compounds are used as useful building blocks for the construction of several nitrogenated products including pyrrolidines.[27]

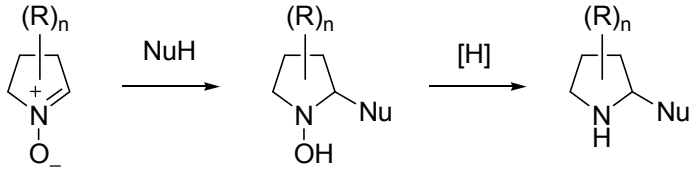


Scheme 13

3. Synthesis of pyrrolidines and related compounds

The main tool for the synthesis of pyrrolidines through nucleophilic additions to nitrones is the use of cyclic nitrones (Scheme 14). This obvious strategy requires versatile synthetic methods for the preparation of those compounds. In this regard, Brandi and Goti have explored extensively the preparation of compounds **28**, particularly those in which the substituents are hydroxyl groups (R=OH).[28] Such compounds can be prepared from easily available carbohydrates by cyclization to the corresponding N-hydroxypyrrolidine and

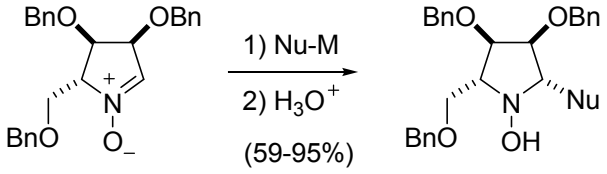
further oxidation. This approach has now become the most practical way to generate polyhydroxy cyclic nitrones with a desired configuration. In addition, a number of synthetic approaches to **28** from other sources are also available from different laboratories.[29]



28

Scheme 14

Cyclic nitrones are usually more reactive than acyclic ones. Good chemical yields and stereoselectivities are obtained from the addition of organometallic reagents including organolithium[30] and Grignard[31] derivatives to the cyclic nitrone **29** (Scheme 15). These reactions have been applied by Petrini and co-workers for the synthesis of alkaloids such as (-)-anisomycin[32] and (+)-lentiginosine[33] starting from nitrone **30** as a common substrate (Scheme 16).

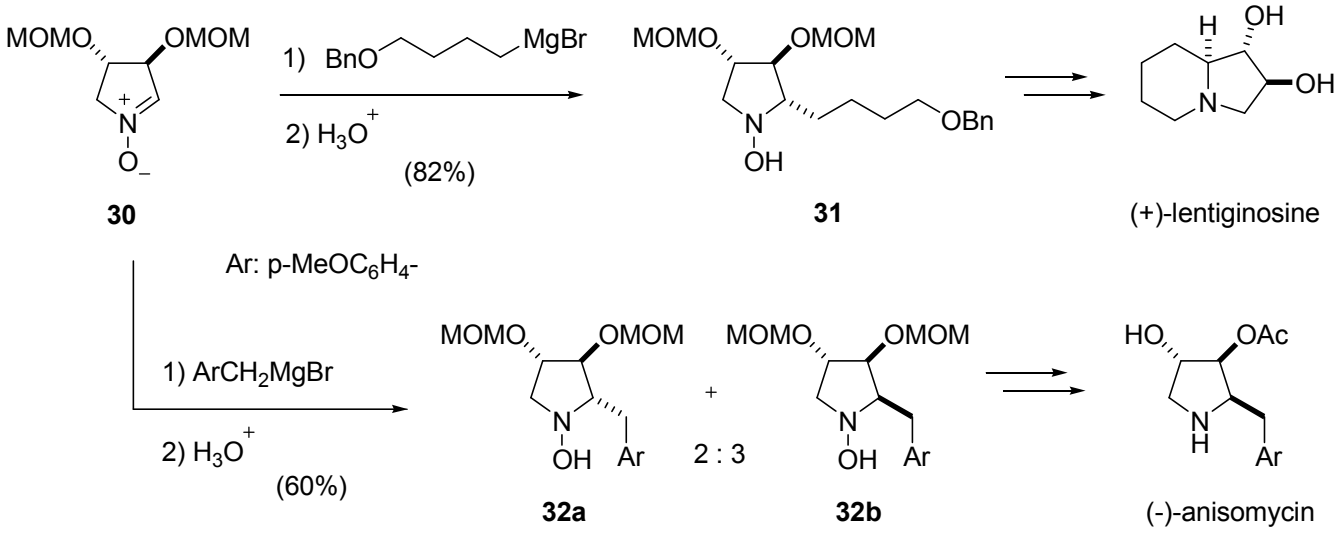


29

Nu: methyl, phenyl, 2-thiazolyl, 2-furyl

M: Li, MgBr

Scheme 15

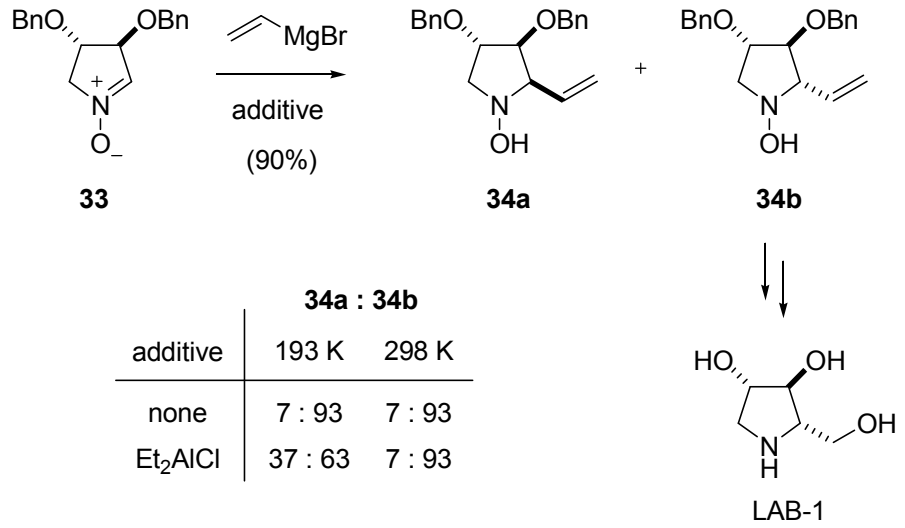


Scheme 16

The reaction outlined in Scheme 16 shows to be quite dependent on the nucleophile. Whereas the addition of a linear alkylmagnesium bromide leads to **31**, the precursor of (+)-lentiginosine, with a complete

anti selectivity, the addition of a benzylic Grignard derivative provides a 2:3 mixture of isomers. Indeed, in the last case, the *syn* adduct is preferentially formed.

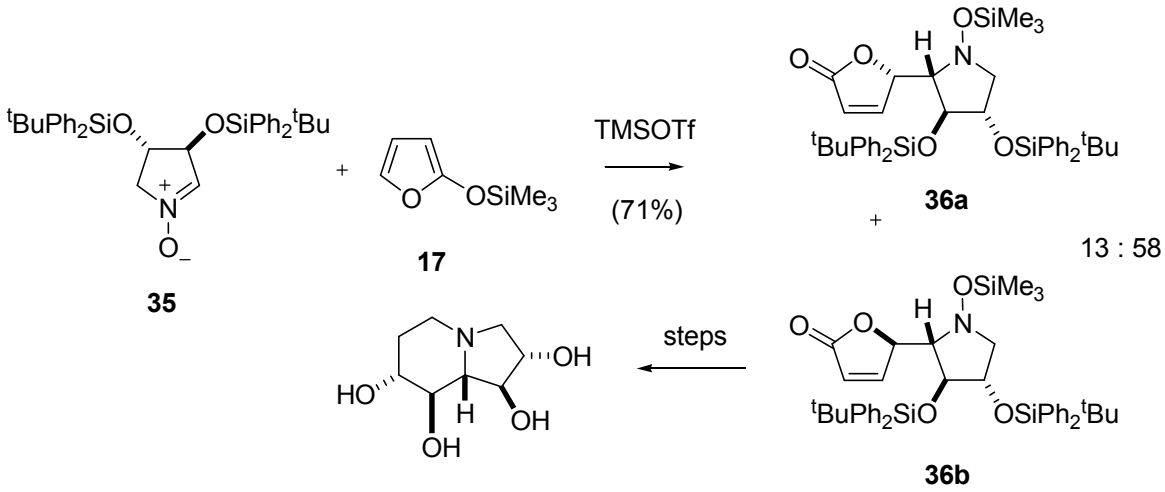
On the other hand, the stereoselectivity of the reaction can also be strongly dependent on the substitution of the pyrrolidine ring. In contrast to acyclic nitrones, Lewis acids are not effective in controlling the stereochemical outcome of the reaction. Moreover, in some particular case, such as that of nitrone **33**, loss of selectivity is observed at low temperature, only when the reaction is conducted in the presence of diethylaluminium chloride. This behaviour is explained based on an exceptional entropic control.[34]



	34a : 34b	
additive	193 K	298 K
none	7 : 93	7 : 93
Et_2AlCl	37 : 63	7 : 93

Scheme 17

In fact, the use of different protecting groups in nitrone **33** does not lead to any loss of selectivity. The exceptionality of nitrone **33** is confirmed when other cyclic nitrones exhibit a high selectivity whatever the additive or temperature is selected.[35]

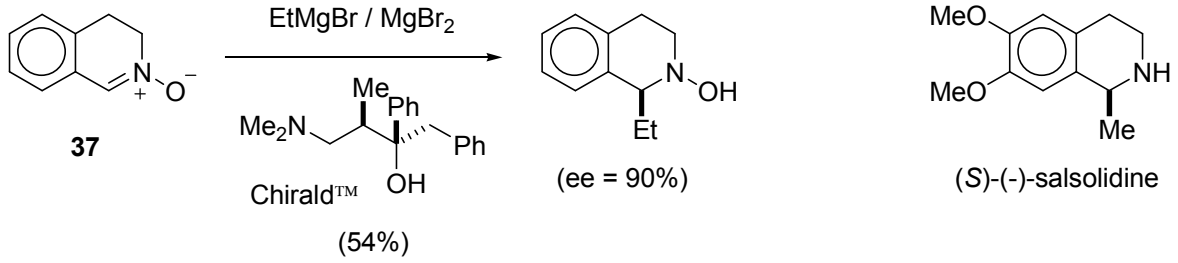


Scheme 18

As indicated before in Scheme 9, 2-(trimethylsiloxy)furan **17** adds to nitrone smoothly in the presence of trimethylsilyl triflate. Thus, the addition to the cyclic nitrone **35** affords the corresponding substituted N-hydroxy pyrrolidines **36** as a 13:58 mixture of isomers (both presenting a *trans* configuration with respect to

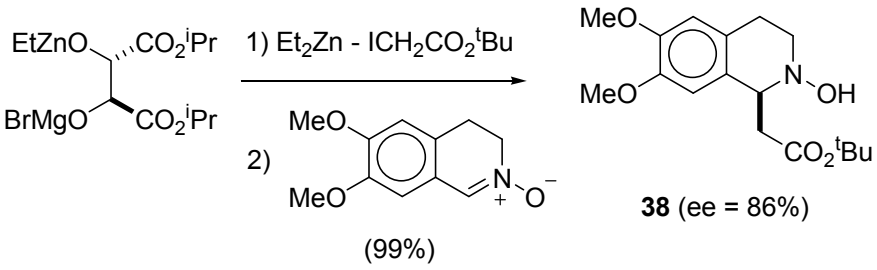
the α-alkoxy substituent. Compound **36b** is further converted into polyhydroxylated indolizidine as indicated in Scheme 18.[36]

The nucleophilic addition of Grignard reagents to related 3,4-dihydroisoquinoline N-oxide **37** can be carried out in an asymmetric way[37] using several chiral catalysts the best results being achieved by Chirald™ (Scheme 19). The same authors have reported the asymmetric addition of dialkylzinc reagents,[38] a reaction that has been used for synthesizing the alkaloid (S)-(-)-salsolidine.[39]



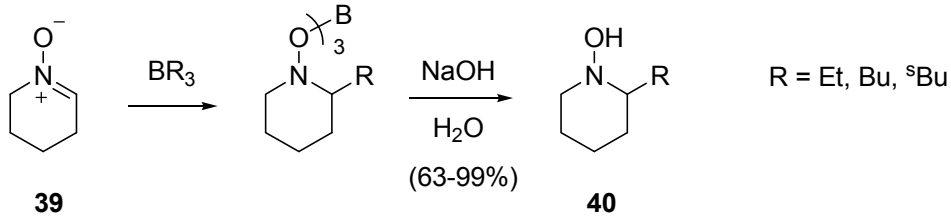
Scheme 19

Similarly, it is also possible to carry out the asymmetric addition of a Reformatsky-type reagent generated *in situ* from diethylzinc and iodoacetic acid ester;[40] the best enantiomeric excess observed for this reaction is 86% in the case of compound **38** (Scheme 20). Recently, Watanabe and Kitahara have used a Reformatsky addition to a five-membered cyclic nitrone as a key step in the total synthesis of the glutamate receptor antagonist kaitocephalin.[41]



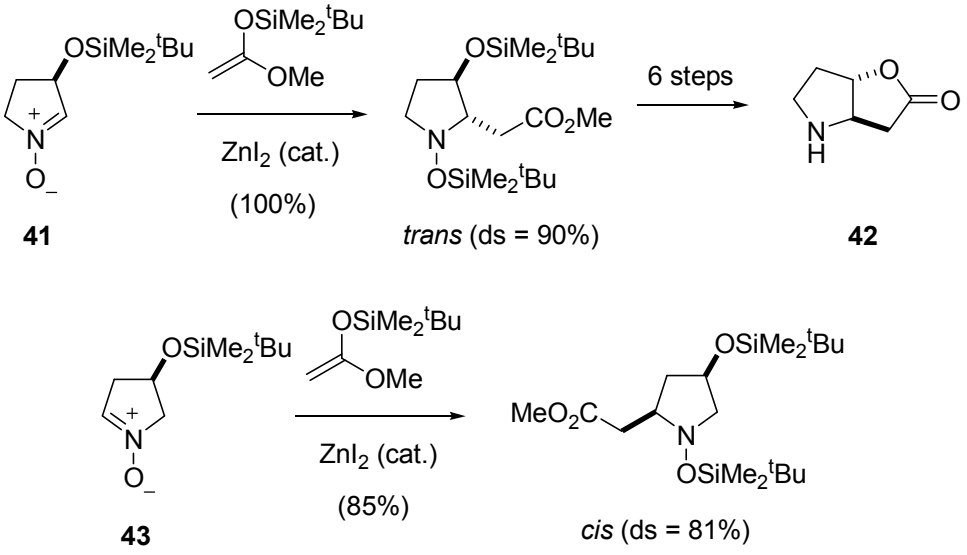
Scheme 20

Six-membered cyclic nitrones also react with trialkylboranes to give the corresponding alkylated hydroxylamines **40** (Scheme 21).[42] The ideal stoichiometry for the reaction should be a 3:1 nitrone:borane mixture, although, in practice, a 2:1 ratio is preferred for nitrone **39**.



Scheme 21

Murahashi and co-workers described the addition of a silyl ketene acetal to the cyclic nitrone **41** in the presence of catalytic zinc iodide.[43] The reaction, which showed a high trans selectivity, is a key step in the synthesis of the Geissman-Waiss lactone **42** (Scheme 22).

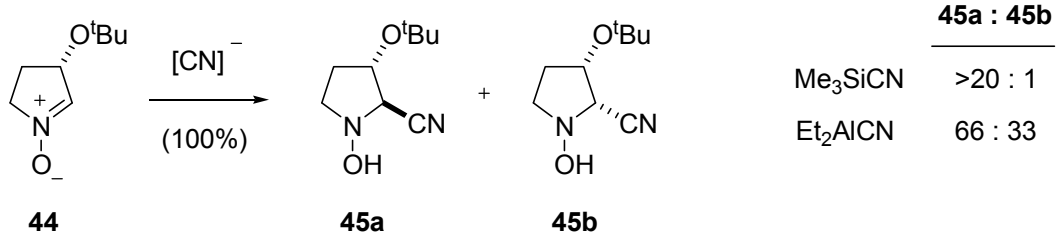


Scheme 22

On the other hand, the isomeric nitrone **43** reacts with the same reagent to afford preferentially the *cis* isomer.[44] This difference of behaviour is explained by assuming steric repulsions between the incoming nucleophile and the zinc iodide moiety coordinated to the nitrone oxygen.

The same group, using a similar methodology, but just changing the silyl ketene acetal by a chiral enolate also reported the asymmetric synthesis of substituted indolizidines of synthetic utility.[45]

The nucleophilic addition of cyanide to cyclic nitrones is greatly influenced by the cyanide reagent. A complete selectivity is achieved with trimethylsilyl cyanide, the product being obtained in quantitative yield.[46] On the other hand, cyanation with diethylaluminium cyanide gives, in good yield, considerable lower *cis/trans* selectivity. This behaviour, illustrated in Scheme 23 for nitrone **44** can also be found for other cyclic nitrones. In the study carried out[46] it is demonstrated that both entropic control and reversibility could be discarded, thus assuming the observed difference of selectivity to be strictly due to the cyanating reagent (Scheme 23).

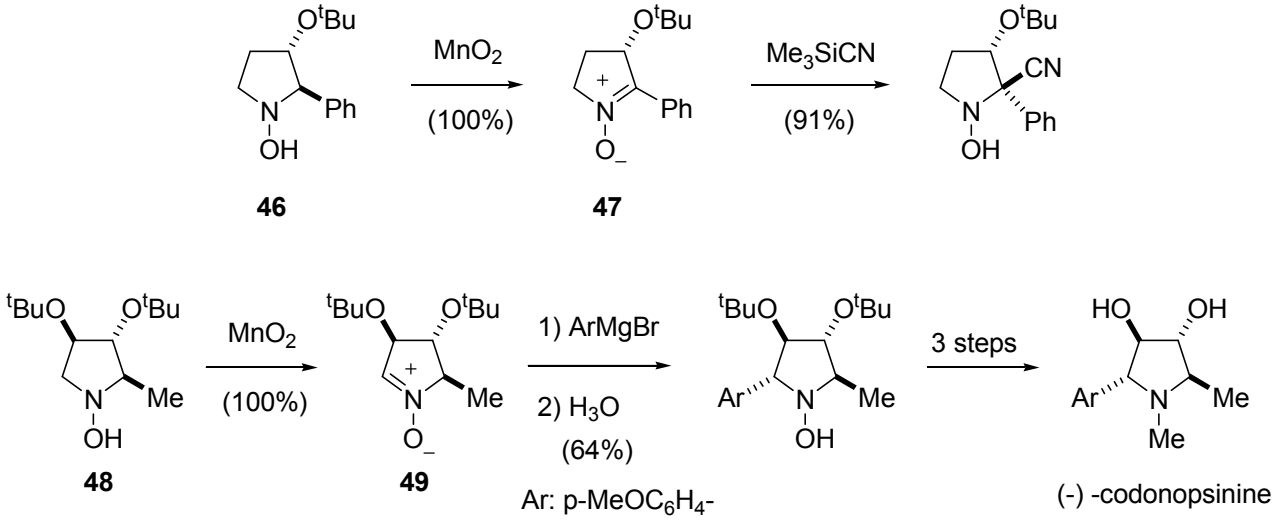


Scheme 23

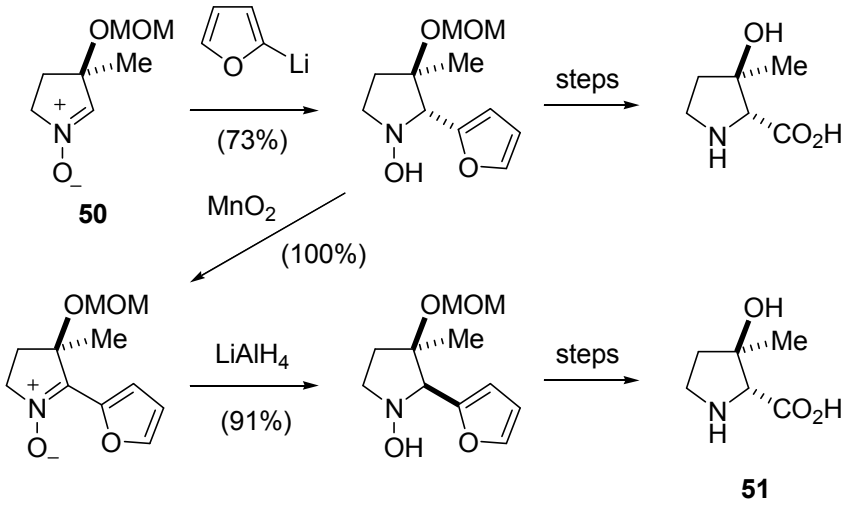
The hydroxylamine obtained from the nucleophilic additions to cyclic nitrones can be re-oxidized thus opening a door to a second addition. In this iterative methodology, the regioselectivity of the oxidation step is crucial.

Whereas hydroxylamine **46** gives preferentially nitrone **47**, hydroxylamine **48** affords **49** under the same conditions. Both nitrones undergo further addition to yield highly substituted pyrrolidines. In the case of compound **49**, the methodology is exploited for preparing the alkaloid (-)-codonopsinine.[47]

Analogously, the addition-oxidation methodology can be applied to nitrone **50** to prepare (2R,3S)-3-hydroxy-3-methylproline **51** a key component of the apoptosis inductors polyoxypeptins (Scheme 25).[48] The synthesis makes also use of the well-known furan-to-carboxyl equivalence.[49]



Scheme 24



Scheme 25

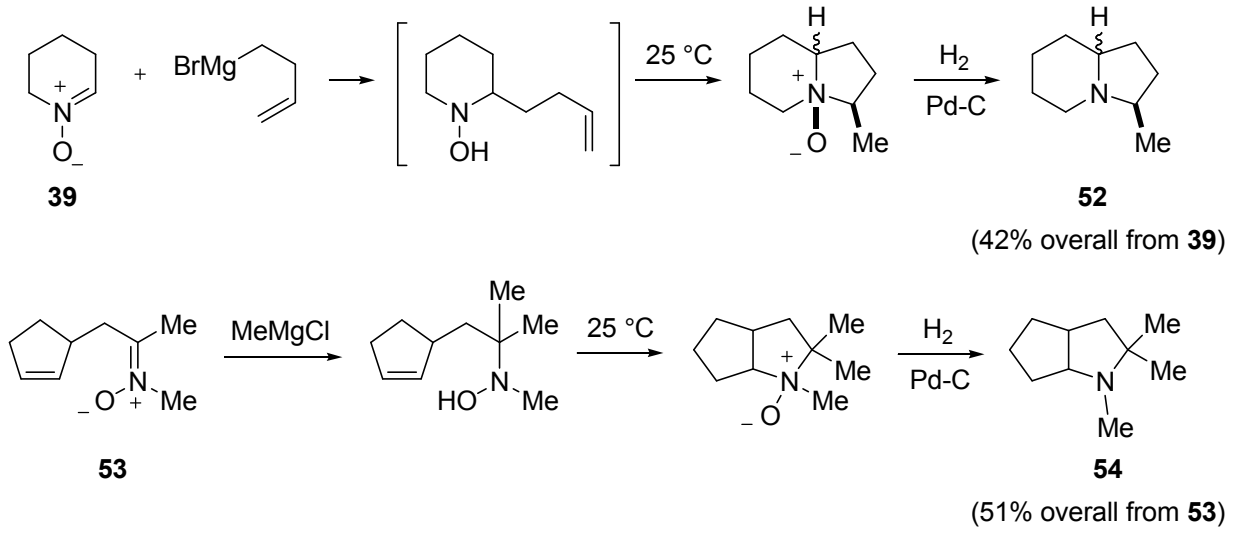
The reduction of cyclic ketonitrones as shown in Scheme 25 has also been described in an enantioselective way by using diphenylsilane in the presence of chiral ruthenium (II) phosphine complexes.[50]

Ciganek developed a method for the synthesis of pyrrolidines based on the intramolecular cyclization of alkenyl N,N-disubstituted hydroxylamines prepared *in situ* by a nucleophilic addition to a nitrone.[51]

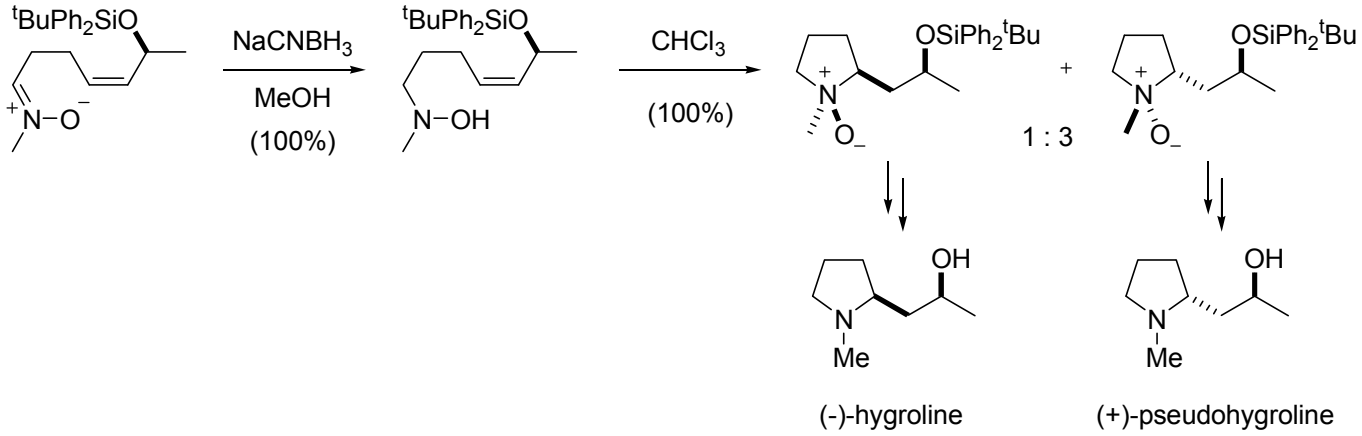
The reaction (a reverse Cope elimination) affords pyrrolidine N-oxides that can be easily reduced to the corresponding pyrrolidine (Scheme 26). Both acyclic and cyclic nitrones can be employed as starting materials. By this methodology, fused systems such as indolizidines **52** and pyrrolizidines **54** are prepared.

The reverse-Cope chemistry showed in Scheme 26 has been further exploited by Knight and co-workers not only with organolithium compounds[52] but also with Grignard derivatives.[53] In the case of using chiral non-racemic α-alkoxy nitrones, complete diastereofacial selectivity is observed.[54] By using this

approach the same group has prepared the alkaloid (-)-hygroline and its epimer (+)-pseudohygroline (Scheme 27).[55]



Scheme 26

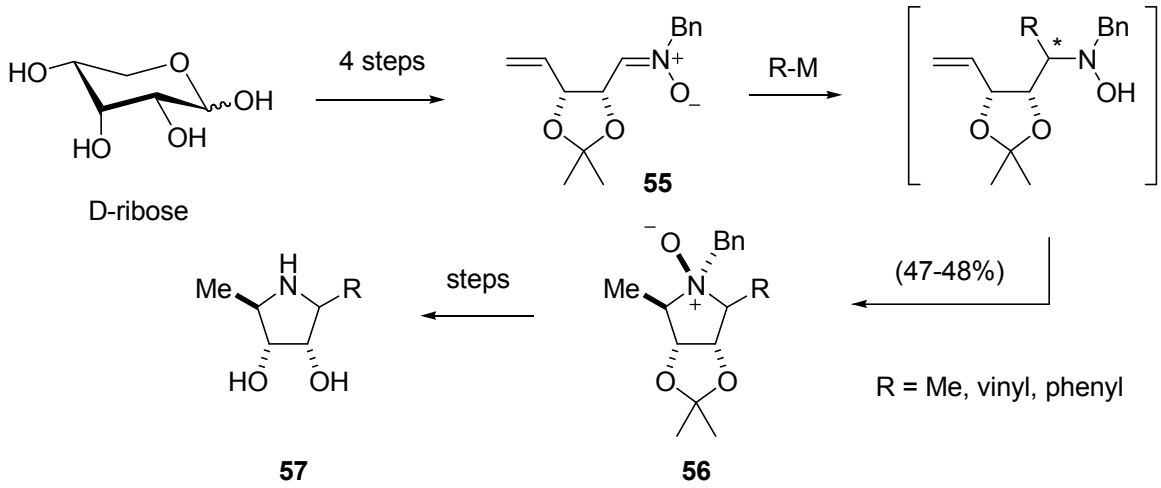


Scheme 27

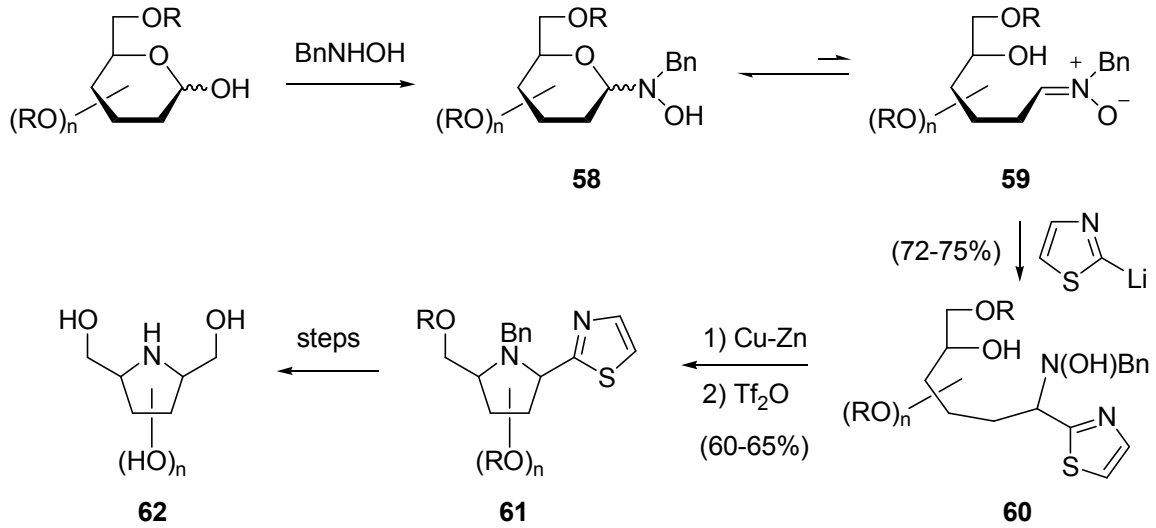
Several potential inhibitors of glycosidases have been prepared by Jäger and co-workers using the reverse-Cope approach.[56] Optically pure iminopolyols are synthesized from the D-ribose derived nitrone **55** upon nucleophilic addition of the corresponding organometallic reagent and Cope-House cyclization as key steps. Further elaboration of the obtained N-oxide **56** provide the target pyrrolidines (Scheme 28).[57]

The diastereofacial selectivity of the nucleophilic addition varies from moderate to excellent depending on the nucleophile. The best results are obtained with allylmagnesium bromide and benzyl magnesium bromide, which afford only one detectable diastereomer.[57a]

Dondoni and co-workers have reported the addition of lithiothiazole to N-glycosylhydroxylamines **58** in equilibrium with the open-chain nitrones **59**.[58] The synthesis of compounds **58** had been previously reported by Merino and co-workers[59] from the corresponding aldoses and further improved by Goti and co-workers.[60] The obtained adducts **60** are transformed into thiazolyl pyrrolidines **61** by conventional chemistry (Scheme 29). These compounds are further converted into iminopolyols **62** by applying the thiazole-to-formyl conversion protocol, reduction and deprotection.

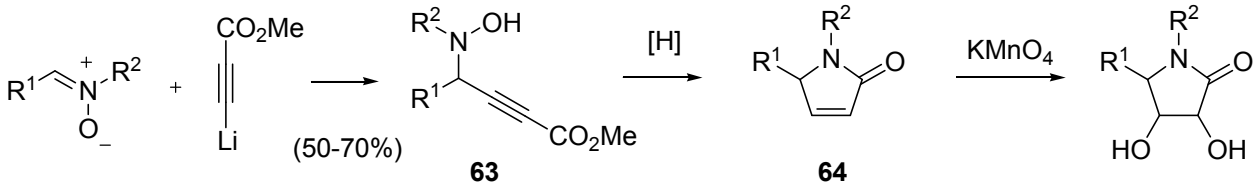


Scheme 28



Scheme 29

In closing this section, another scarcely exploited approach has to be mentioned. The addition of methyl propiolate to nitrones affords propargyl hydroxylamines **63**, which can be cyclized to pyrrolin-2-ones **64** (Scheme 30).[61]



Scheme 30

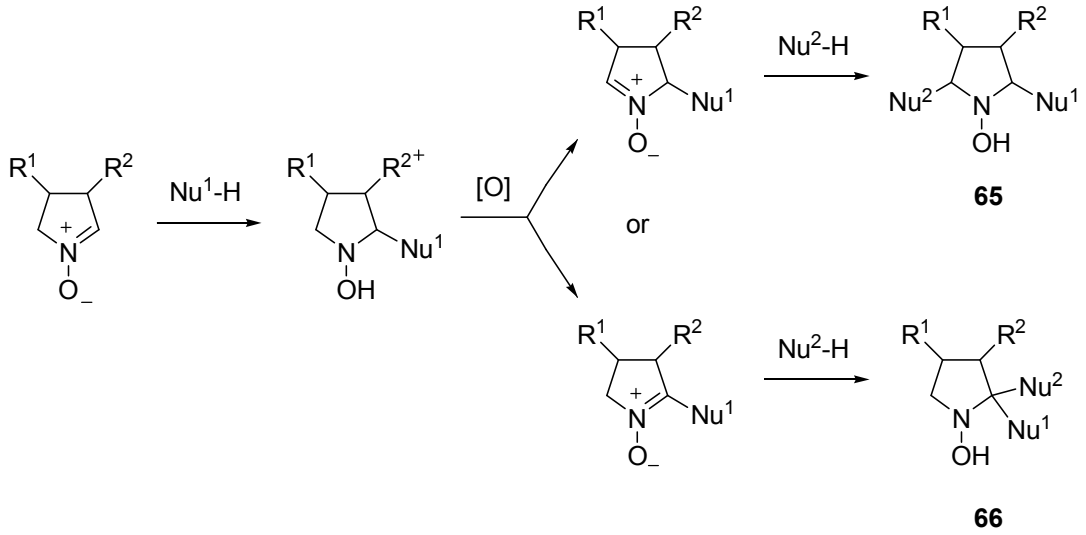
By using the appropriate conditions[62] it is possible to reduce the triple bond to give predominantly the *cis* isomer which spontaneously cyclized to the pyrrolin-2-one. The presence of the double bond gives the possibility of further functionalization of the pyrrolidine ring as illustrated in Scheme 30.

4. Conclusions

Nucleophilic additions to nitrones provide a ready route to key intermediates that can be used in the synthesis of nitrogen heterocycles such as isoxazolidines and pyrrolidines. For the synthesis of

isoxazolidines, nucleophilic addition processes are an alternative pathway to the well-known cycloaddition route. Moreover, in the case of chiral non-racemic α-alkoxy nitrones the nucleophilic addition reaction is complementary to the cycloaddition one because of the opposite diastereofacial induction observed. By choosing the appropriate substrate, and carrying out the adequate chemical transformations, this complementarity can be used in preparing enantiomers from a single source (enantiodivergent approach).[63]

In the case of pyrrolidines, the nucleophilic addition reaction to cyclic nitrones is a quite versatile methodology for introducing a variety of nucleophiles into the pyrrolidine ring. The possibility of oxidizing the resulting hydroxylamine to carry out a second nucleophilic addition increases the benefit of the methodology. By controlling the regioselectivity of the process, it will be possible to prepare both fully substituted pyrrolidines **65** and quaternary substituted compounds **66** (Scheme 31).



Scheme 31

In summary, as it has been attempted to demonstrate in this review, nitrones are excellent versatile starting materials for isoxazolidines and pyrrolidines. In view of the potential future developments, the use of nitrones as electrophiles for constructing nitrogen heterocycles will continue to grow during the next years, as increasingly effective methods are developed for securing regio- and stereocontrol of the nucleophilic addition reactions.

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63. For an example of that enantiodivergency carried out in our laboratories see refs. 15 and 17, and references cited therein.

PATERNÓ-BÜCHI REACTION ON FURAN: REGIO- AND STEREOCHEMISTRY

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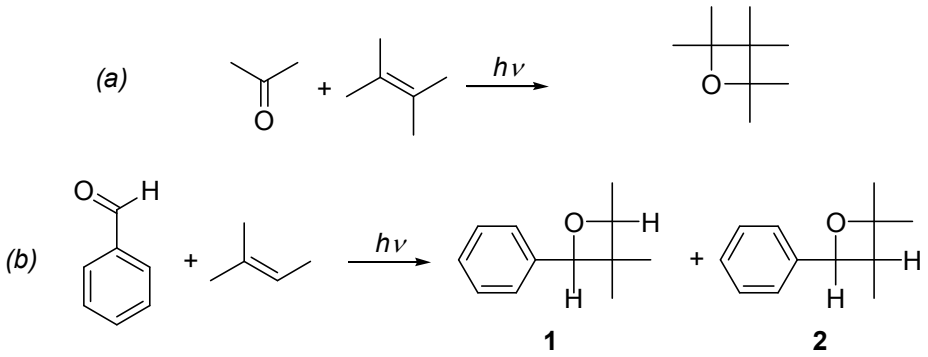
***Abstract**. Different approaches in order to explain regio- and stereoselecivity of the Paternò-Büchi reaction on furan derivatives are discussed. A new approach based on the relative stability of both the products and the biradical intermediates is presented.*

Contents

1. Introduction

The Paternò-Büchi reaction is a [2+2]-cycloaddition reaction between a carbonyl compound and an alkene [Scheme 1(a)].



Scheme 1

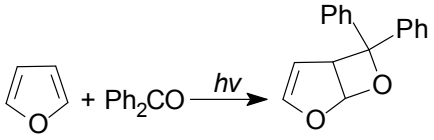
The regiochemistry of this reaction appeared a difficult problem to solve from the first work. Paternò performed a reaction between 2-methyl-2-butene and benzaldehyde and he could not assign the exact structure of the product: he was not able to distinguish between **1** and **2** [Scheme 1(b)].[1] Büchi solved the problem showing that **1** was the actual product.[2] Furthermore, in the first reaction described the stereochemical behaviour of the reaction was not examined, but several stereoisomers could be obtained.

Regio- and stereochemical behaviour of the Paternò-Büchi reaction was not always understood. For several years the comprehension level of these two factors resembled the description of some problems connected with the evolution of photochemistry made by Ciamician in 1912: "In ordinary organic chemistry the reactions often takes place in some definite way; but the photochemical reactions often furnishes surprises and proceed along quite different lines".[3]

The Paternò-Büchi reaction is a photocycloaddition of an n,π* carbonyl compound to an alkene in the ground state from either the S_1 or the T_1 state. In a theoretical study the Authors showed that there are two conical intersection points located near the C-C and C-O bonded biradical regions of the ground state. Furthermore, for C-O attack, the triplet surface must cross the singlet to reach a diradicaloid minimum. For C-C attack, the triplet biradical minimum is located at the same geometry as the conical intersection between the two singlet states, and the efficiency of the intersystem crossing will be determined by the nature of the spin-orbit coupling. Thus, for the triplet, the reaction path can be predicted by the most stable biradical rule.[4] The biradical intermediate in the reaction between benzophenone and electron-rich alkene has been determined by using laser flash photolysis.[5,6]

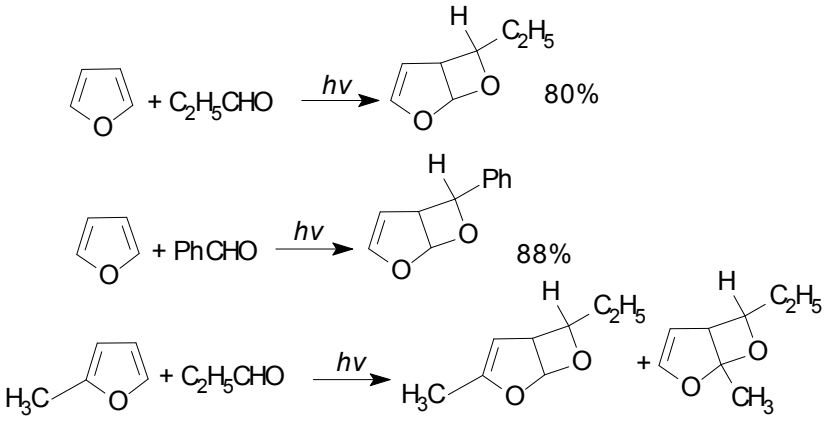
2. The Paternò-Büchi reaction on furan derivatives

The first report on the photochemical reactivity of furan towards carbonyl compounds appeared in 1966. Schenck reported that the irradiation of benzophenone in furan gave the corresponding adduct in 94% yield (Scheme 2).[7] The structure assignment was confirmed by Gagnaire et al. on the basis of the NMR analysis of both the products of the same reaction and of the reaction between 2,5-dimethylfuran and benzophenone.[8]



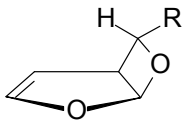
Scheme 2

Two years later furan and 2-methylfuran were found to react with propanal and benzaldehyde. NMR spectral data supported the formation of the same type of products (Scheme 3).[9]

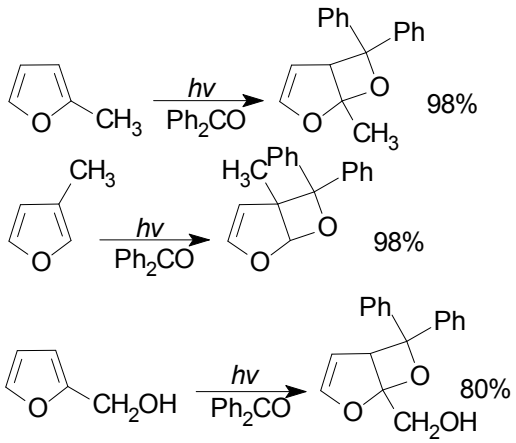


Scheme 3

The structure of the products was confirmed also by NOE analysis.[10] The yields were very high. In this case, the authors did not specify the *exo* or *endo* stereochemistry at C-6 on the dioxabicyclo[3.2.0]heptene skeleton. This problem was solved some years later assigning the *exo* configuration to this carbon.[11]

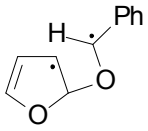


When 2-methylfuran was used, a mixture of regioisomeric products was obtained, but the authors did not report the regioisomeric ratio. In contrast with this result, other authors reported a complete regioselectivity in the reaction between substituted furans and benzophenone: in these reactions the coupling occurred on the most hindered side of the molecule (Scheme 4).[12,13]



Scheme 4

The Japanese group supposed that the reaction involved the formation of the biradical **3**, due to the attack of the n,π* triplet oxygen on the site of higher free valence or higher electron density of the furan ring.

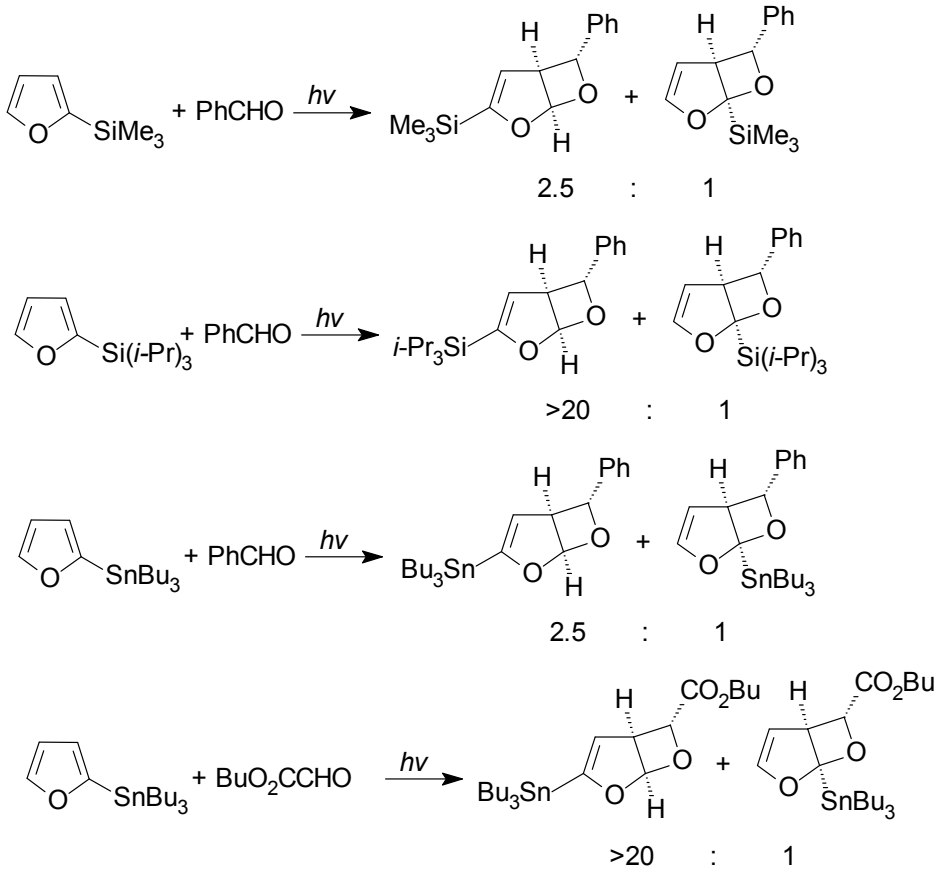


3

Afterwards, the same group tested the reaction on a large group of aliphatic and aromatic aldehydes and ketones.[12] They found that ketones reacted giving lower yields than the corresponding aldehydes: in particular acetone, butanone, and acetophenone gave yields in the range of 0.9-1.7%; furthermore, the oxetane yields increased with the number of carbon atoms: with acetaldehyde they obtained 15% yield, while cyclohexylcarbaldehyde gave 27% yield and benzaldehyde 35%.

The kinetics of the reaction is in agreement with a mechanism involving the formation of the biradical **3**.[14] More complex carbonyl compounds were used to give the corresponding adducts. *n*-Butyl glyoxylate gave the adduct with furan in 77.3% yield, while diethyl ketomalonate gave the corresponding product in 30% yield.[15]

Good regioselectivity was observed using silyl and stannyl furan derivatives: the reaction in this case occurred on the less hindered side of the molecule (Scheme 5).[16]



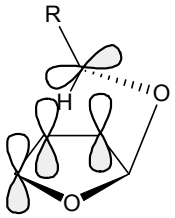
Scheme 5

On the contrary, 2-furylmethanol gave low regioselectivity.[17] 2-Silyloxyfuran gave no regioselectivity when the reaction was performed in the presence of aldehydes, while a good regio- (on the most hindered side of the furan) and stereoselectivity (*exo*) was observed in the presence of ketones.[18]

3. Approaches to the explanation of regio- and stereoselectivity

3.1. Griesbeck rule

The high *exo* stereoselectivity of the reaction has been extensively studied: the formation of the product occurs on a triplet 1,4-biradical which must be converted into the singlet biradical to give the product. Three mechanisms operate for the interaction between singlet and triplet states of 1,n-biradicals: electron-nuclear hyperfine coupling (HFC), spin-lattice relaxation (SLR), and spin-orbit coupling (SOC). HFC is an important control factor for biradicals with long carbon chains between the radical centers. SOC plays a dominant role in biradicals with shorter distances between the radical centers, whereas SLR seems to contribute only marginally. SOC is strongly dependent on the geometry of the triplet biradicals: in particular, SOC decreases with increasing distance between the two spin-bearing atoms. The best geometry to have SOC requires that the axes of the *p* orbitals at the radical centers are perpendicular to each other. In order to explain the pronounced *exo* stereoselectivity, a secondary orbital effect can be postulated: an interaction between the rather flexible α-oxy radical center and the allyloxy ring localized radical in **4**, likely plays a major role (Scheme 6).[19,20]



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Scheme 6

This approach has been used also to explain the observed regio- and stereoselecetivity on silyloxyfuran derivatives.[18] In this case steric effects between the substituents due to the perpendicular position of the orbitals involved in the SOC process could explain the observed regiochemistry.

3.2. Scharf's rule

In order to explain both regiochemistry and stereochemistry of the Paternò-Büchi reaction on furan derivatives the pattern represented in the Scheme 7 on the basis of the work of Scharf can be used.[21]
The formation of all the possible biradicals are reversible reactions; the consequence of this hypothesis is, in agreement with the theoretical study, that the formation of more stable intermediate is preferred, while all the other isomers undergo retrocleavage. The following ring closure is an irreversible step, determined by spin-orbit coupling,[20] that allowed the formation of the more stable compound (Figure 1).

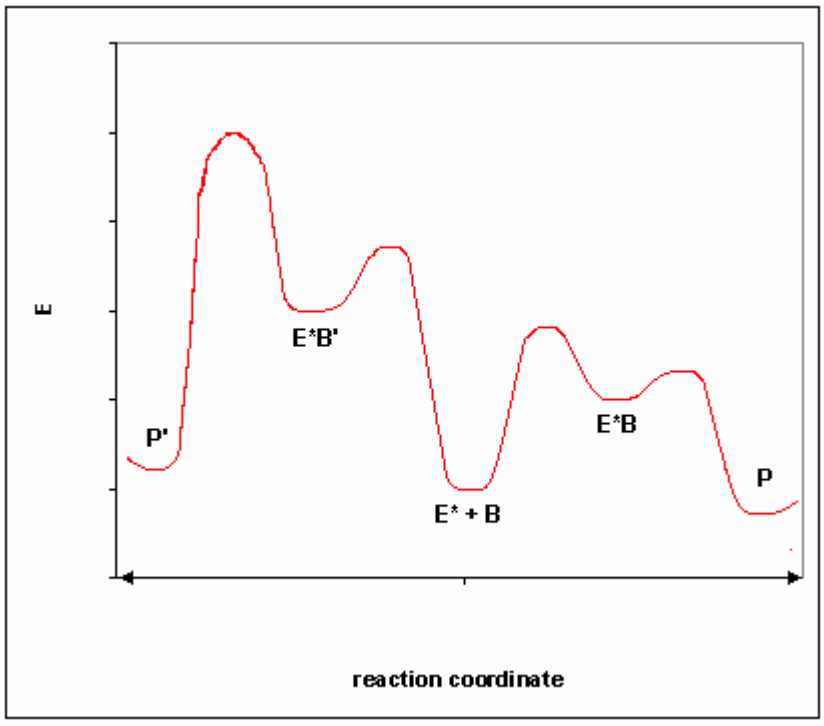
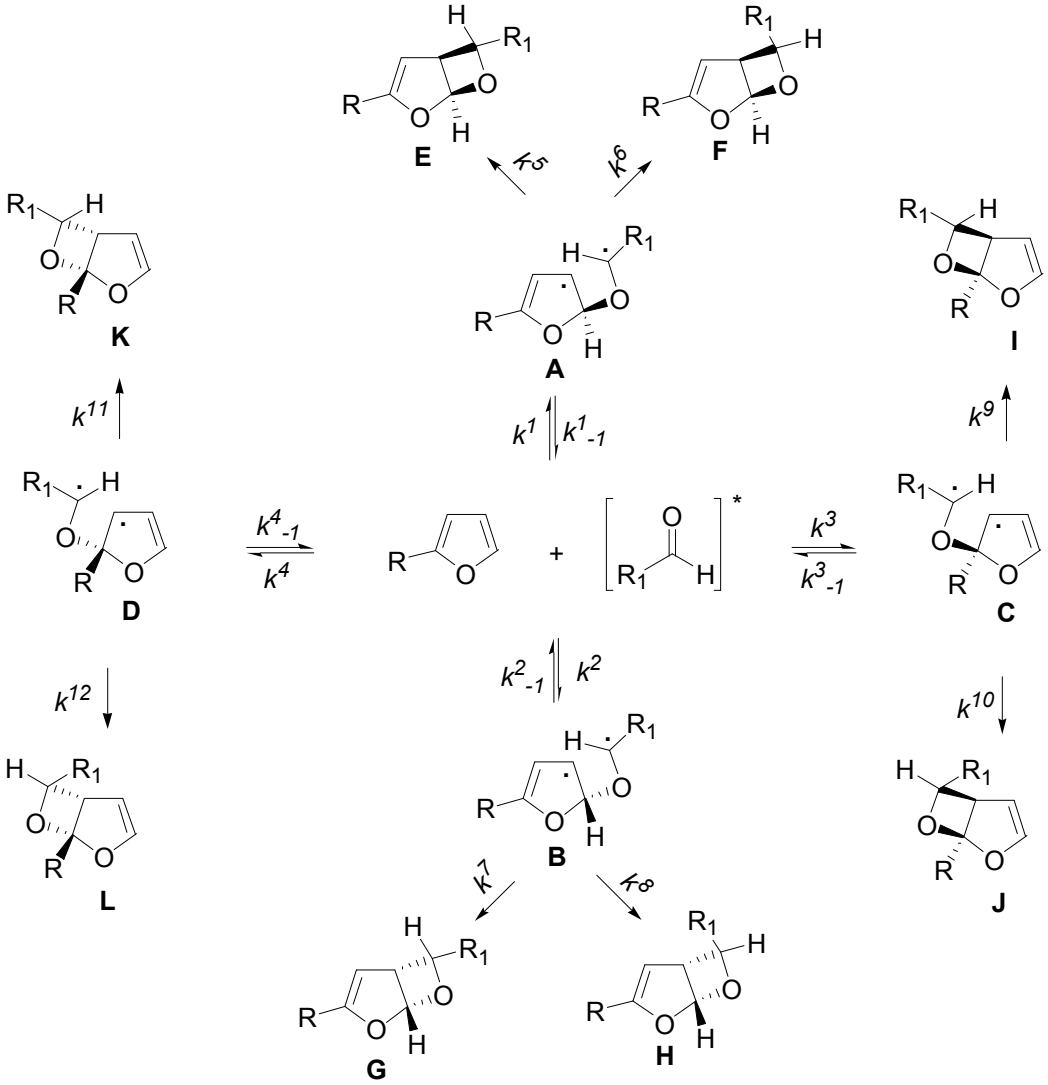


Figure 1. Possible kinetic behaviours in the Paternò-Büchi reaction. E* is the excited carbonyl compound, B the olefin. E*B e E*B' are the possible biradical intermediates. P and P' are the possible products.

A first question is related to the position of attack of the oxygen atom on furan. The oxygen atom can attack the α or β carbon on the furan ring. Schenck reported that the irradiation of benzophenone in furan

gave the corresponding adduct in 94% yield (Scheme 7): this adduct derives from the attack of the oxygen atom on the α carbon on the furan ring.[7]



Scheme 7

This problem can be solved assuming a frontier orbitals control in the attack of the carbonyl compound to furan.[22] The HOMO of furan has energy of –0.32 eV and the atomic coefficients of this orbital (Figure 2) are in agreement with an attack of the carbonyl oxygen on the α carbon.

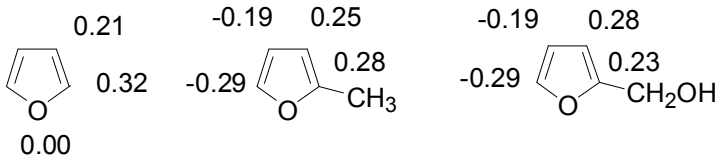


Figure 2. Atomic coefficients in the HOMOs of some furan derivatives.

In the case of furan, the only stereochemical question is related to the formation of the *exo* isomer. The structures of the possible adducts deriving from the attack of benzaldehyde in the α position of furan are depicted in Figure 3. The *exo* isomer is more stable than the other isomer, in agreement with the experimental results.

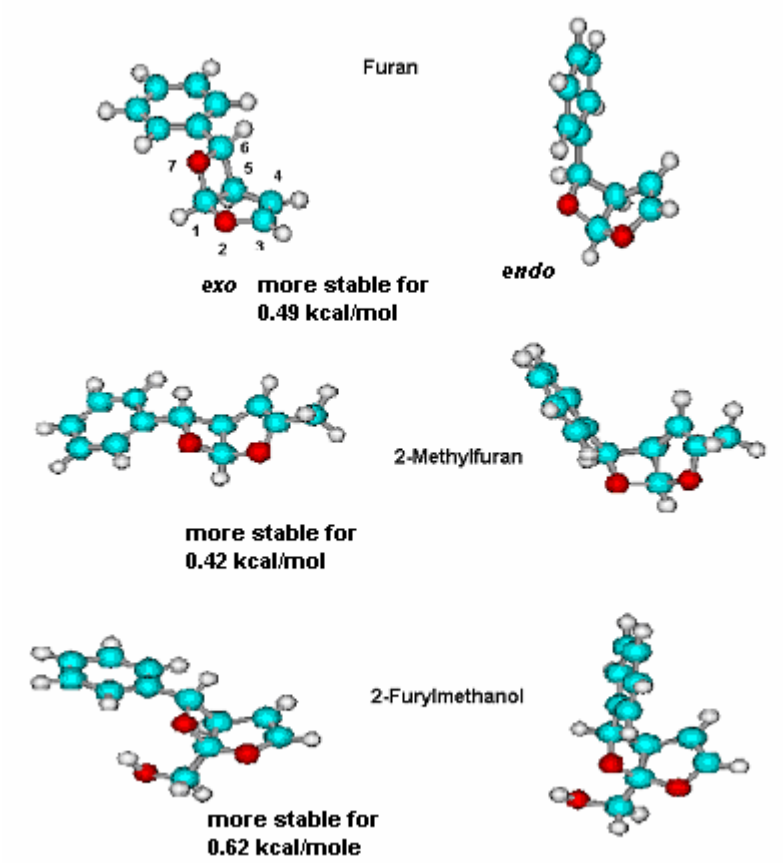
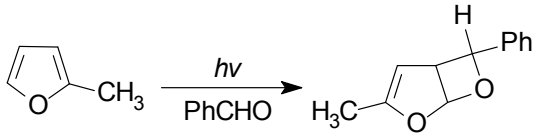


Figure 3. Structure and energy of the possible adducts in the case of furan, 2-methylfuran, and 2-furylmethanol.

2-Methylfuran and 2-furylmethanol could gave the adducts on different double bonds. In the case of 2-methylfuran the reaction with benzaldehyde occurs on the less hindered side of the molecule (Scheme 8),[22] while 2-furylmethanol and the corresponding silyl ether showed low regioselectivity.[23] The HOMO of 2-methylfuran and 2-furylmethanol showed the atomic coefficients reported in Figure 2. These data are in agreement with an attack of the carbonyl oxygen on the α carbon.



Scheme 8

In order to explain the regioselectivity the energy of the possible biradical intermediates **6** and **7** in the case of 2-methylfuran and **8** and **9** for 2-furylmethanol can be considered (Figure 4). The biradical intermediate **7** is favoured on **6** for 1.18 kcal mol^{-1}, in agreement with the observed regioselectivity. The calculations of the biradicals from 2-furylmethanol showed that **8** is more stable than **9** for 0.8 kcal mol^{-1}. This difference could account for the preferential formation of the product deriving from the attack on the most hindered side of the molecule. Furthermore, it can account for the formation of two regioisomers. Also in this case the *exo* stereochemistry can be explained considering the relative stability of the possible adducts (Figure 3).

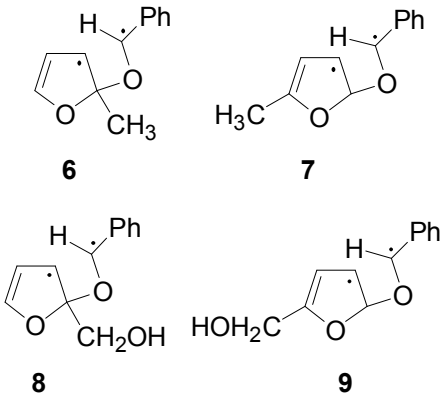
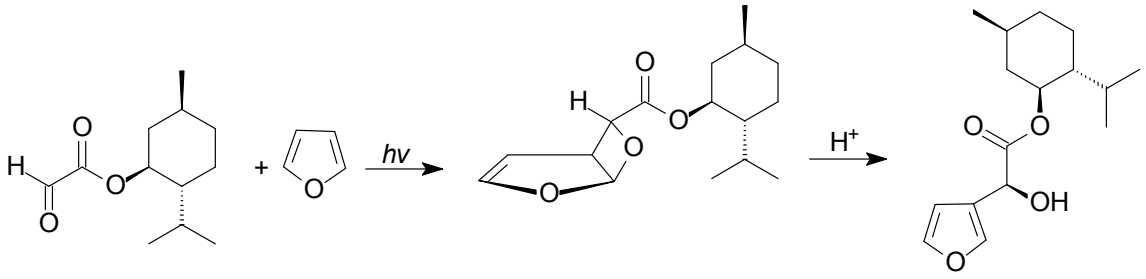


Figure 4. Possible biradical intermediates in the reaction of 2-methylfuran and 2-furylmethanol.

4. Asymmetric reactions

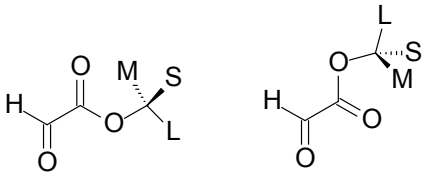
The reaction of glyoxylates with furan can be performed also using chiral glyoxylate. In particular, the use of *R*-(-)-menthol, chiral 2-octanol, and chiral 2,2-dimethyl-3-butanol as chiral auxiliaries gave the corresponding oxetanes in high yields. These compounds can be converted into the corresponding 3-substituted furans. These furans showed low enantiomeric excess (Scheme 9).[24]

On the basis of the experimental data the configuration of the oxetane was 1*R*, 5*S*, 6*S*.



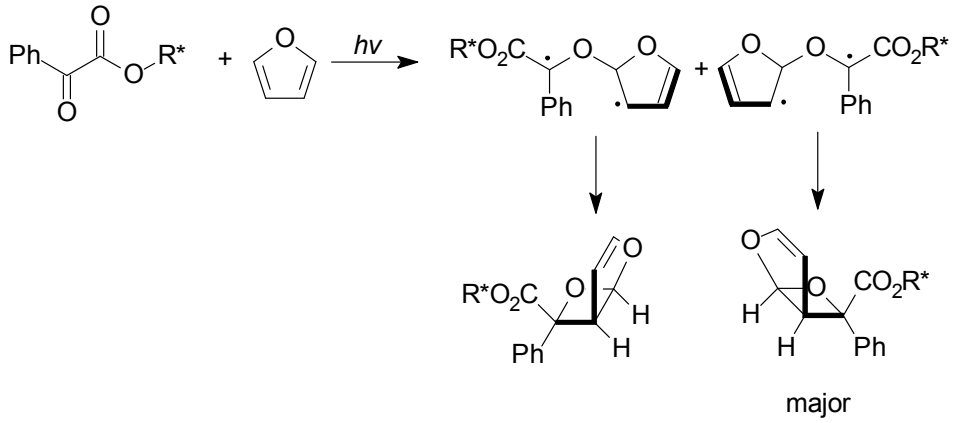
Scheme 9

The low optical purity was explained considering that two conformers of the glyoxylate can approach furan.



The use of chiral phenylglyoxylate gave better results. The use of chiral alcohols gave diastereoisomeric excess in the range of 4-80% (Scheme 10).[25-27]

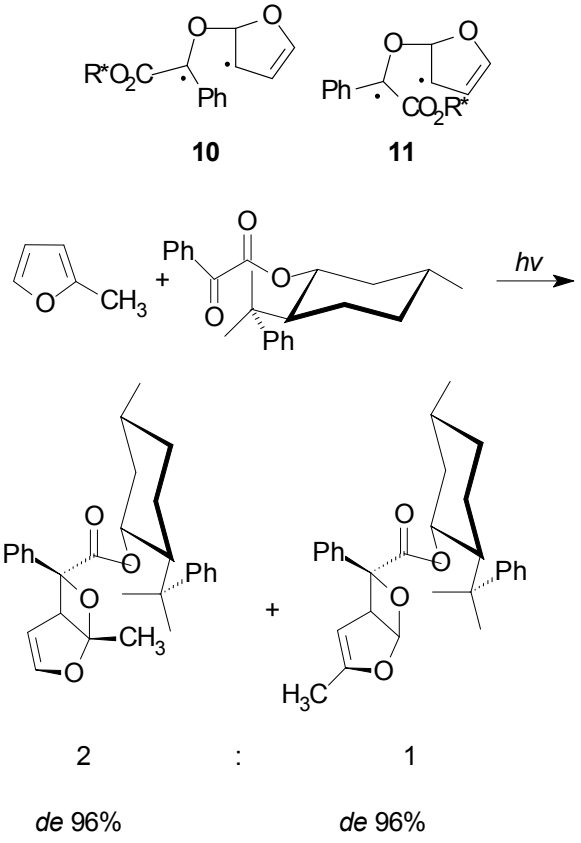
The authors observed also an important variability of the diastereoisomeric excess in function of the temperature, with the presence of an inversion temperature. These results were explained assuming that the diastereoselection is produced on two levels: 1) the preferred formation of the diastereoisomeric 1,4-biradical intermediate **10** and 2) the preferred retrocleavage of the energetically unflavoured diastereoisomeric intermediate **11** to the starting materials.[28]



Scheme 10

The diastereoisomeric excess in the high-temperature region ($T>T_{inv}$) is dominantly controlled by steric effects of the chiral auxiliaries, whereas in the low-temperature region ($T<T_{inv}$), the nature of the olefin has a dominating influence.

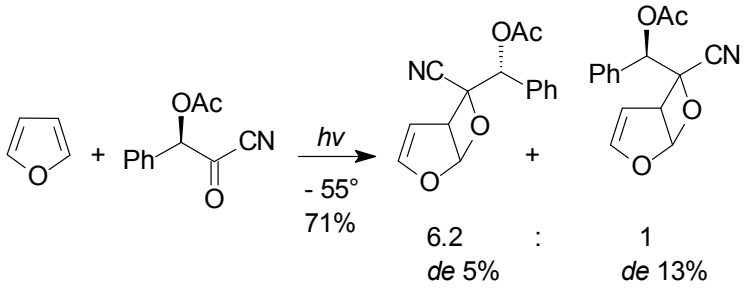
When the reaction is carried out on 2-methylfuran, a 2:1 regioisomeric mixture was obtained with a very high diastereoisomeric excess (Scheme 11).[21]



Scheme 11

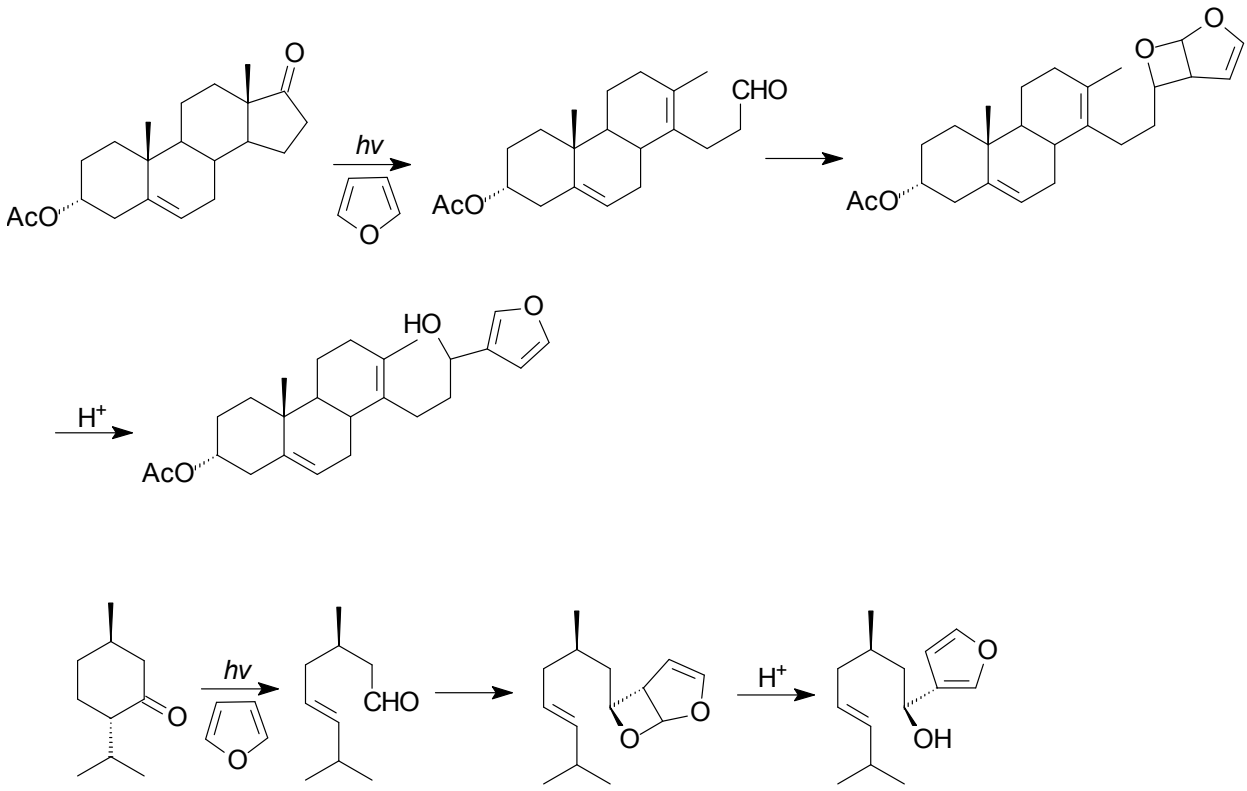
Isatine derivatives gave the corresponding cycloadducts with high stereoselectivity when irradiated in the presence of furan and benzofuran.[29]

The reaction of furan with acyl cyanides yields the corresponding oxetanes but both diastereoisomeric *endo*- and *exo*-oxetanes are formed (Scheme 12). When chiral acyl cyanides are used low asymmetric induction is observed.[30]



Scheme 12

Furan reacts also with chiral ketones. In this case, an α-cleavage reaction before the 2+2 cycloaddition modifies the expected products (Scheme 13). When (-)-menthone was used as a substrate a chiral product was obtained as 2:1 diastereoisomeric mixture where the most abundant product has 1*R*, 3*R* configuration.[31]



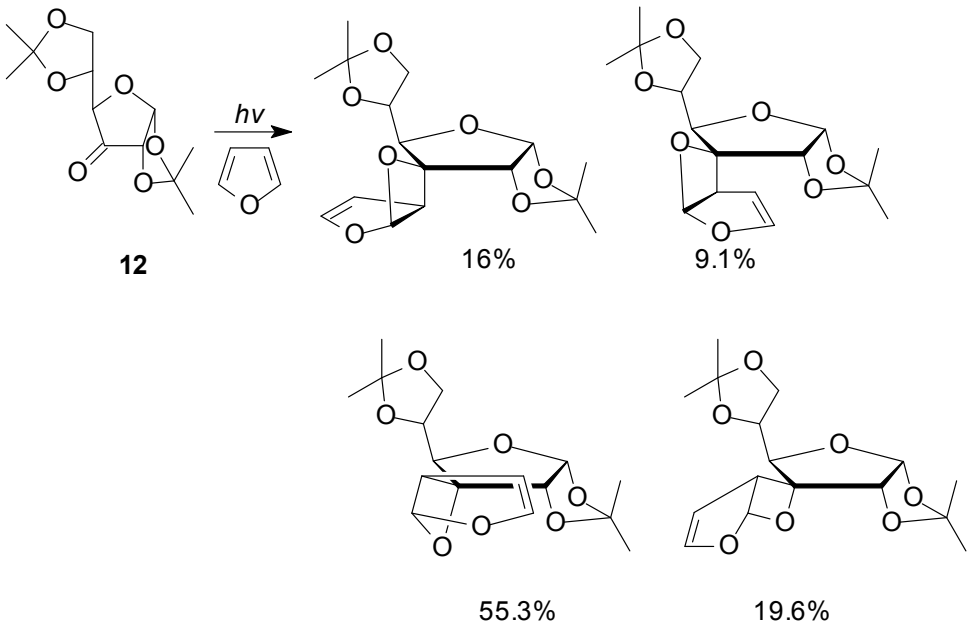
Scheme 13

When the reaction was performed on carbohydrate **12**, a complex reaction mixture was obtained (Scheme 14).[31,32]

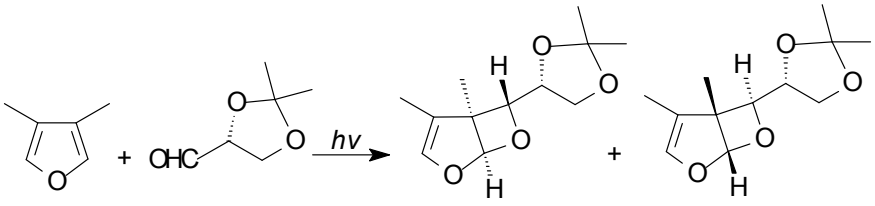
Attempts to obtain stereoselective Paternò-Büchi reactions were performed carrying out the reaction between 3,4-dimethylfuran and *R*-isopropylidene glyceraldehyde. The coupling products were obtained with an overall yield of 35% as a 1.2:1 mixture of diastereoisomers. Furthermore, the compound **13** was obtained with 54% ee (Scheme 15).[33,34]

This behaviour suggests the operation of a mechanism that is insensitive to the substitution pattern of chiral aldehydes. Reaction between an excited aldehyde (singlet or triplet state) and furan proceeds with initial carbon-oxygen bond formation to produce either of the two biradical species. The stereocenter adjacent to the carbonyl is now in a 1,4-relationship to the newly formed stereocenter at the acetal carbon and

is expected to exert little influence as a stereocontrol device.[33] The extensive racemization observed probably reflects the photolability of the aldehydes towards racemization under the conditions of the reaction.[34]

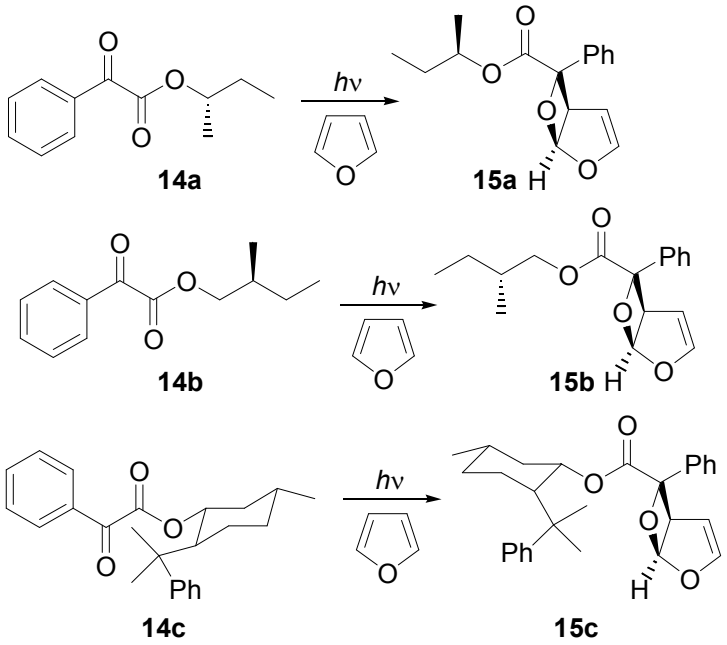


Scheme 14



Scheme 15

Nevertheless, compound **13** can be used in a chiral synthesis of the bicyclic part of asteltoxin confirming the assigned absolute configuration.[34]



Scheme 16

5. An explanation of diastereoselectivity

The diastereoselectivity of the Paternò-Büchi reaction was studied using as substrates some chiral phenylglyoxylates.[35]

Considering the stereochemical behaviour of the reaction, while the reaction with 8-phenylmenthol glyoxylate (**14c**) gave a high diastereoisomeric excess (95%), the reaction with the glyoxylate ester **14a** gave only 15% *de* and the reaction with the glyoxylate ester **14b** resulted in no diastereoselectivity (Scheme 16).

To explain the observed diastereoselectivity the energy of the triplet biradical intermediates in the reaction with furan was considered (Figure 5).

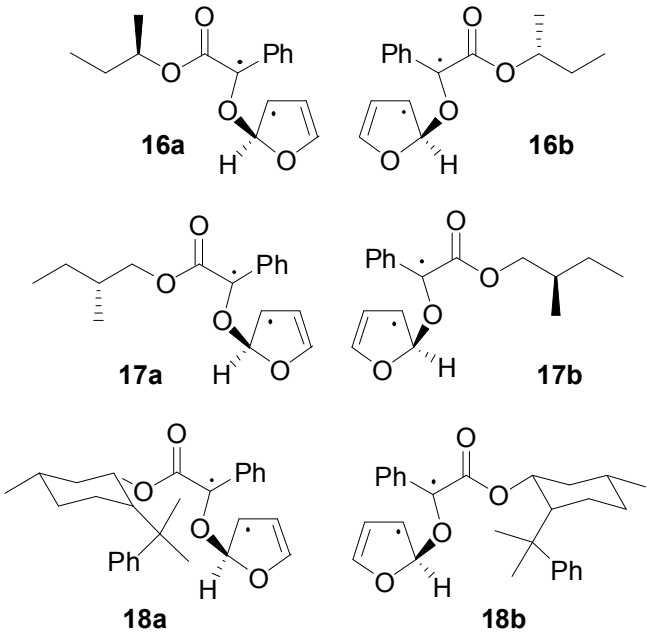


Figure 5. Possible biradical intermediates in the reaction of furan with chiral phenylglyoxylates.

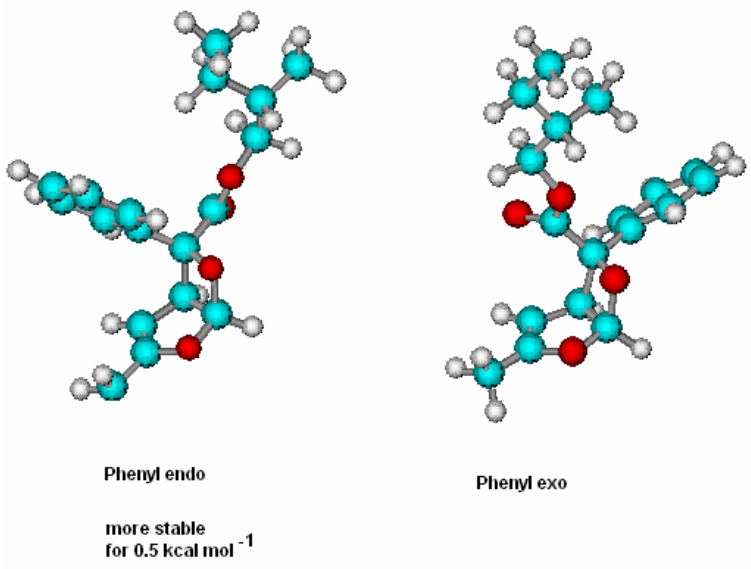


Figure 6. Structure and energy of possible adducts in the case of chiral phenylglyoxylates.

Calculations on these biradical intermediates showed that **16a** (the precursor of **15a**) was more stable than **16b** by 0.73 kcal mol^{-1}. Furthermore, **17a** and **17b** differed by only 0.02 kcal mol^{-1}, in agreement with the observed no stereoselectivity of the reaction. Finally, the biradical intermediate **18a** showed to be more

stable than **18b** by 21.9 kcal mol^{-1}: also this result is in agreement with the observed high diastereoisomeric excess. Furthermore, the selective *endo* configuration of the phenyl group can be explained considering the relative stability of the reaction products (Figure 6).

6. Reactions in zeolites

To improve diastereoselectivity, reactions in an organized medium were carried out. Selective absorption on the surface of the solid could improve diastereoselectivity. Recently, the transposition of tropolonic ethers has been reported in literature.[36] This transposition can be obtained with high stereoselectivity carrying out the reaction on zeolite in the presence of a chiral inductor [(-)-ephedrine] and in the presence of a chiral alkyl substituent on the ether.

The reaction of **14a-c** in the presence of NaY zeolite gave the adducts **15a-c**. It is noteworthy that this type of procedure allowed us to improve diastereoselectivity: while, in the reaction in solution, **15a** was obtained with *de* = 15%, the reaction in an organized medium gave *de* = 37%. While **15b** was obtained as a mixture of diastereoisomers, the use of the zeolite allowed reaching 18% diastereoisomeric excess. Also in the case of **15c**, obtained in solution with *de* = 95%, the use of the zeolite increases the diastereoisomeric excess reaching the value of 98%.

The above described results can be understood assuming the hypothesis that the absorption on a solid support is able to amplify the difference between the energy of the biradical intermediates.

7. Diastereoselectivity in the reaction with furylmethanol derivatives (Adam rule)

The diastereoselectivity of the Paternò-Büchi reaction can be determined by the presence of some substituents, *i. e.* the presence of chiral substituents on the alkene. Adam showed that allylic alcohols reacted with benzophenone to give the corresponding adducts with high regio- and diastereoselectivity (Scheme 17)[37-39]

The diastereoselectivity dropped drastically in presence of protic methanol and totally disappeared for the corresponding silyl ethers. These data are in agreement with the presence of a hydroxy directing effect in the Paternò-Büchi reaction. *Threo* stereoisomer can be favoured through the formation of an hydrogen bond between triplet excited benzophenone and the substrate in the exciplex, while the formation of the *erythro* stereoisomer would be less favoured due to allylic strain (Scheme 18).

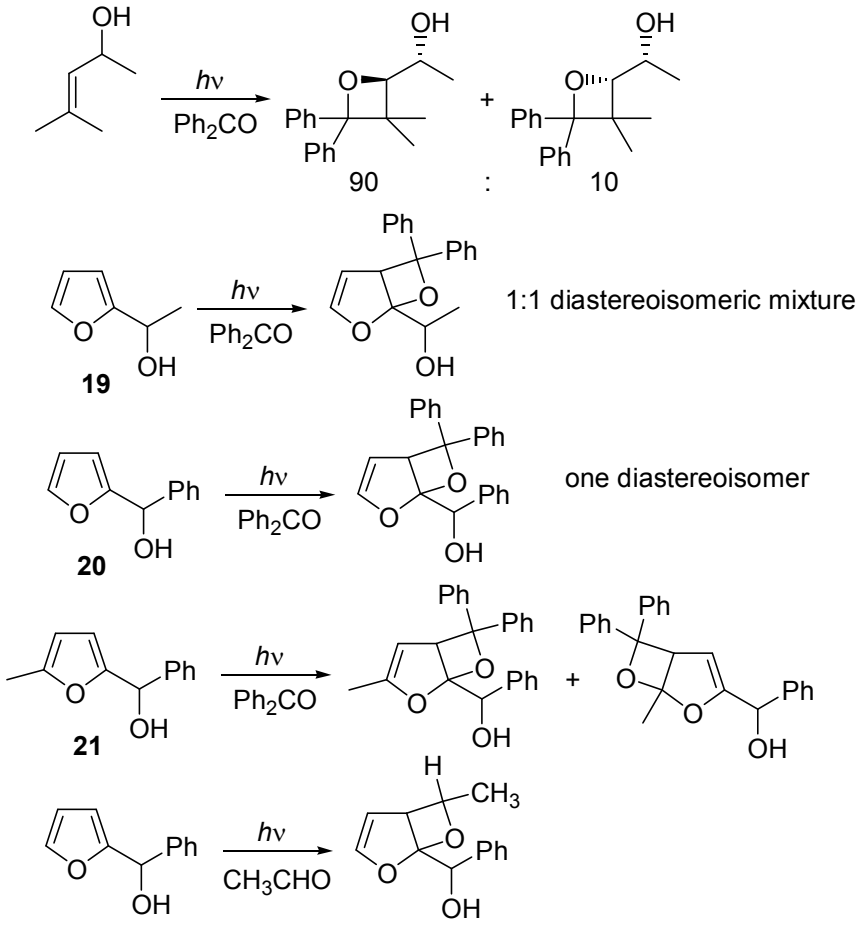
The formation of hydrogen bond to direct the Paternò-Büchi reaction has been considered by other researchers. Diastereoselective cycloaddition has been obtained using chiral enamide,[40,41] or in the reaction of allylic alcohols with naphthalene rings.[42]

When unsymmetrical carbonyl partners such as acetophenone or benzaldehyde were used high diastereoselectivity was observed to give the corresponding *cis* isomer. The regioselectivity was high with acetophenone but lower with benzaldehyde.[38]

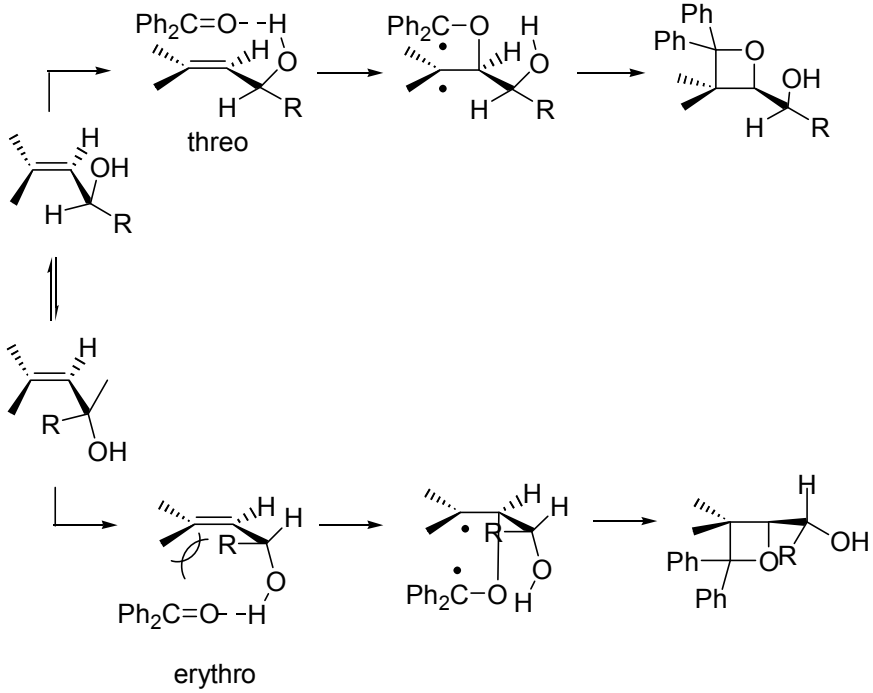
Cis diastereoselectivity can be explained by using the Griesbeck rule on the possible triplet biradicals formed in the reaction. Steric interactions are minimized when the biradical assumes the optimal conformation and this conformation accounts for the formation of the observed stereoisomer.[43]

When chiral allylic alcohols were used as substrates in the reaction *cis* diastereoisomers were formed. Furthermore, also in this case, a pronounced *threo* diastereoselectivity was observed, in agreement with a

less pronounced hydroxy directing effect when acetophenone and benzaldehyde were used.[38,43] Chiral allyl ether gave the corresponding adduct with high diastereoselectivity.[44]



Scheme 17



Scheme 18

The reaction of allylic alcohols with carbonyl compounds was tested also on a particular type of allylic alcohol such as 2-furylmethanol derivatives. While the reaction of 2-furylmethanol with benzophenone showed low regioselectivity, the presence of larger substituents on the carbon bearing the alcoholic function allows a high regioselectivity (Scheme 17).[23] Furthermore, when 2-furylethanol (**19**) was used as substrate a 1:1 mixture of stereoisomers was obtained, while, when 1-(2-furyl)-benzylic alcohol (**20**) was the substrate, only one diastereoisomer was obtained (Scheme 17).[23] NOE experiments are in agreement with a 1*RS*, 1'*RS*, 5*RS* configuration. The high diastereoselectivity observed was confirmed using optically active **20**.

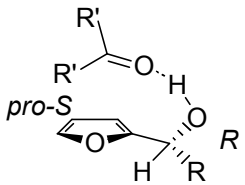
The regioselectivity of the reaction was explained on the basis of the relative stability of the diradical intermediates: DFT study showed that the biradical obtained on the most hindered side of the molecule was more stable than the other.[45] The nature of the intermediate is in agreement with the observed ρ value in a Hammett free energy correlation.[23]

When 5-methyl-2-furyl derivatives were used as substrates a different regioselectivity was observed. Compound **21** gave a 1:1 mixture of regioisomers, when irradiated in the presence of benzophenone, and a single regioisomer in the presence of benzaldehyde (Scheme 17).[46] In agreement with the results obtained with 2-furyl derivatives, the products deriving from the attack on the side bearing the alcoholic function were obtained as a single diastereoisomer, while those deriving from the attack on the side bearing the methyl group were obtained as a mixture of diastereoisomers. Then, a hydroxy group near the reaction center is needed to have diastereoselectivity.

The reaction of 2-furylmethanol derivatives with aliphatic aldehydes and ketones gave the corresponding adducts with high regioselectivity but no diastereoselectivity (Scheme 17).[45]

The observed diastereoselectivity in the reaction with aromatic carbonyl compounds clearly shows that it increases in relation to the nature of the substituents on the carbon bearing the alcoholic function as described by Adam. However, while Adam considers the allylic strain with a methyl group as the driving force for the diastereoselectivity, in this case, the methyl group is not present: therefore, allylic strain can not be used to explain diastereoselectivity.

2-Furylmethanols showed a preferential conformation able to induce, through the formation of a hydrogen bond between the alcoholic function and the carbonyl compound, the high diastereoselectivity observed (Scheme 19).[23]



Scheme 19

The lack of diastereoselectivity in the case of aliphatic carbonyl compounds represents a problem. By using aliphatic ketones we can exclude that this effect is due to a short-lived singlet excited state. Our results can not be explained on the basis of 1,3 allylic strain as reported by Adam. In fact, the same "allylic" substrates were used giving high stereoselectivity with aromatic aldehydes and ketones and no stereoselectivity when using aliphatic aldehydes and ketones.

Recently, Griesbeck reported that stereoselectivity in 2+2 cycloaddition reactions between carbonyl compounds and allylic alcohol derivatives can increase with the possibility of hydrogen-bonding interactions with singlet as well as triplet excited carbonyl states prior to bond formation.[43] However, aliphatic and aromatic ketones could give the same hydrogen bond interaction with the hydroxy group in the furan derivatives, while the stereoselectivity is different. This is an open question; recently, a dependence of diastereoselectivity on the relative stability of the biradical intermediates involved has been supposed on the basis of theoretical calculations.[35] It could be an interesting and unified approach to the problem.

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MASS SPECTROMETRY OF SIMPLE INDOLES PART 1: ELECTRON IONISATION, PHOTO-IONISATION AND ELECTRON CAPTURE IONISATION

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In memory of Professor Vincenzo Sprio

Abstract. *The review is devoted to the gas-phase ion chemistry studies of simple indoles by using several mass spectrometric methods. A screening of the papers concerning mass spectrometry studies of indoles to select those related to their behaviour under different ionising conditions (electron ionisation, photo-ionisation and electron capture ionisation) has been done and the results have been reported and critically discussed.*

Contents

1. Introduction

Indole is the commonly name used for identifying the benzopyrrole in which the benzene ring is fused to the 2- and 3- positions of the pyrrole. Indole (and its isomer isoindole), has ten π-electrons free to circulate throughout the molecule, and two of these electron originate from the nitrogen atom.

The behaviour in chemical reactions, the appreciable resonance energy (197 kJ mol^{-1}) and NMR spectra evidence that this molecule is aromatic. It belongs to the group of heterocycles designated as π-excessive heteroaromatics,[1] which means that the π-electron density on its carbon atoms is greater than that on the

carbon atoms of benzene, and it implies that this molecule is highly reactive towards electrophilic reagents. Indoles could be protonated by strong acids and in some cases this results in dimerisation or polymerisation.[2] However indoles appear to have appreciable stability in concentrated acids where they are completely protonated.[3]

Indole gives many of the same electrophylic substitution reaction as does pyrrole, but in indole $C_{(3)}$ is the preferred reaction site. The NH group is relatively acidic (pK_a=17) and forms the anion in the presence of strong bases.[4] Although the electron pair of this anion is orthogonal to the π-system, it nevertheless increases reactivity at $C_{(3)}$ toward electrophiles. As a consequence the indolyl anion has ambident properties in alkylation and acylation reactions.[2] Indoles can also undergo several organic reactions, i.e reactions with carbenes to give ring expansion and Diels Alder addiction.[2]

The development of indole chemistry began in the mid-nineteenth century with the intensive research of the dye indigo.[5-7] In 1866 indole was prepared by Baeyer,[8] who later proposed the present formula of indole.[9]

Indoles are widespread as natural alkaloids, conjugated in various degrees with terpenoidic residues to form complex structures. In this fashion over one thousand different natural alkaloids are characterised by the presence of simple precursors as the aminoacid tryptophan and the related amine tryptamine. A large number of these alkaloids presents biological activity, being the indole nucleus also present in curare alkaloids, used as neuromuscular blocking agents, in the *Vinca* alkaloids (vinblastine, vincristine, vindesine) used as anti tumoral agents and also in various poisons as strychnine and related compounds.

The interest to indole compounds is more recently grown in relation with the discover of the potent antioxidant activity of the human hormone melatonin. This latter substance has proved five times more effective than glutathione in capturing hydroxyl radicals,[10] and five hundreds times more effective than dimethyl sulfoxide in safeguarding chromosomes from radiation induced damages.[11] Besides, it inactivates lipoperoxyl radicals[12]and nitrogen monoxide.[13,14] The potent free radical scavenge activity of melatonin could be related to the electron rich indole nucleus. The protection effect on cellular membrane[15] and the evidenced presence of this hormone in the cell nucleus as well as the potential activity as anti tumoral agent[16,17] are very attractive for pharmaceutical industry.

The occurrence of the indole moiety in several natural compounds of biological and pharmacological interest, prompted extensive studies of the indole chemistry in solution phase, as well as a large number of mass spectrometric investigations. In fact, more than one thousand papers are reported in literature, most of them strictly concerning analytical applications.

The aim of this review is to discuss and summarise with a critical approach the fundamental aspects of the gas-phase ion chemistry of indoles under different ionisation techniques, without the claim to be comprehensive (i.e. indolenine and indoline derivatives, fused indoles and indole alkaloids have not been considered). The ionisation techniques are commonly distinguished in hard and soft on the ground of the internal energy which is related to the extension of the fragmentation reactions. However, in order to describe the gas-phase ion chemistry, we prefer to distinguish between ionisation techniques not involving mass variation (electron ejection or electron capture processes) and those involving chemical reactions with matter transfer (protonation, cationisation or proton loss) and consequently affording ionic species with mass variation. This first part of the review concerns electron ejection or electron capture ionisation techniques

and in particular the electron ionisation (EI), photo-ionisation (PI) and electron capture ionisation (ECI) studies on simple indoles.

2. Electron ionisation

The behaviour of indole and indole derivatives under electron ionisation conditions has been widely studied and the first paper was reported by Beynon and Williams in 1959.[18] This technique is still largely applied and exploited especially in the field of analytical investigation on simple and non highly polar indole derivatives taking advantage of high resolution (HR) measurements and of a series of auxiliary techniques, i.e. mass analysed ion kinetic energy (MIKE) and linked scan experiments, energy resolved mass spectrometry (ERMS), collision induced decomposition (CID) and tandem masss spectrometry (MS/MS).

2.1. Indole

The 70 eV EI mass spectrum of indole **1** (Fig. 1), as expected for an unsubstituted aromatic heterocycle, shows the molecular ions (117 Th = m/z) as the base peak and few other peaks. The molecular ions lose HCN and H_2CN to give relatively strong peaks at 90 Th and 89 Th respectively, together with a smaller peak at 116 Th due to the $[M - H]^+$ ions (Scheme 1).

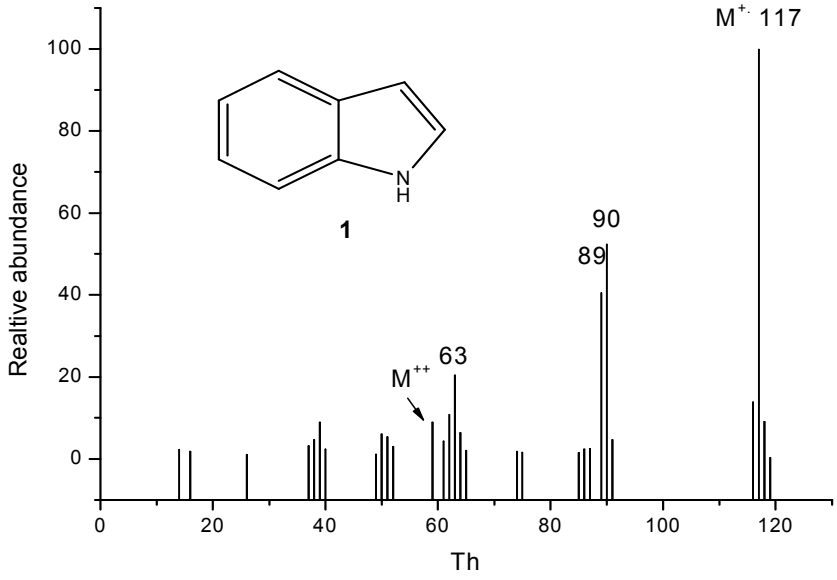
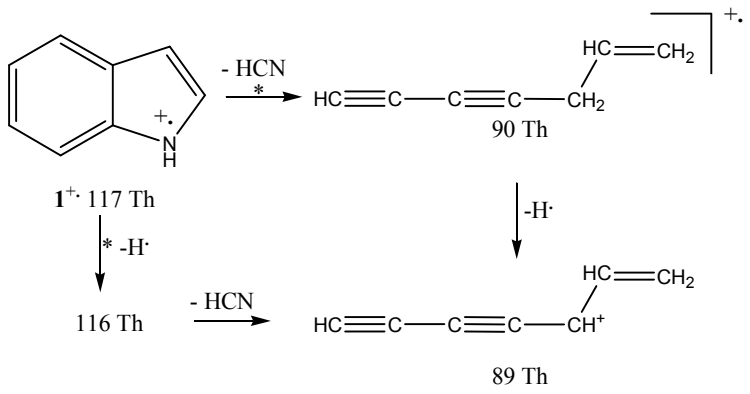


Figure 1: EI/MS (70 eV) of Indole **1** adapted from NIST library[19]

The EI/MS of 1-deuterioindole and 3-deuterioindole evidenced as only the hydrogen atoms at 1- (21 %) and 2- (79 %) positions are involved in the HCN elimination. The peak at 89 Th is not shifted in the EI/MS of 1-deuteroindole, so indicating that the NH hydrogen is lost with the H_2CN fragment.[20] Noncyclic structures have been indicated for both ions at 90 Th and 89 Th.[21] A peak at 58.5 Th, corresponding to the double charged molecular ion $\mathbf{1}^{++}$, is observed.

Cardoso and Ferrer Correia[22] more recently studied the unimolecular[23] and collision induced decompositions (CID)[24] of the molecular ion of indole ($\mathbf{1}^{+\cdot}$). The unimolecular decomposition of the metastable singly-charged molecular ions $\mathbf{1}^{+\cdot}$ indicates the losses of HCN and $H^{\cdot}$. In fact, the mass analysed

ion kinetic energy (MIKE) spectrum of $\mathbf{1}^{+\cdot}$ is dominated by the $[M - HCN]^{+\cdot}$ (90 Th, 84 %) and $[M - H]^{+}$ (116 Th, 15 %) ions. The $[M - H_2CN]^{+}$ ions at 89 Th are instead observed only in the CID MIKE spectrum of $\mathbf{1}^{+\cdot}$ (using He as collision gas), which shows the peaks at 116 Th (22 %), 90 Th (29 %) and 89 Th (22 %).[22] This should mean, in our opinion, that the $[M - H_2CN]^{+}$ formation involves a two steps and a high energy requiring process.



Scheme 1

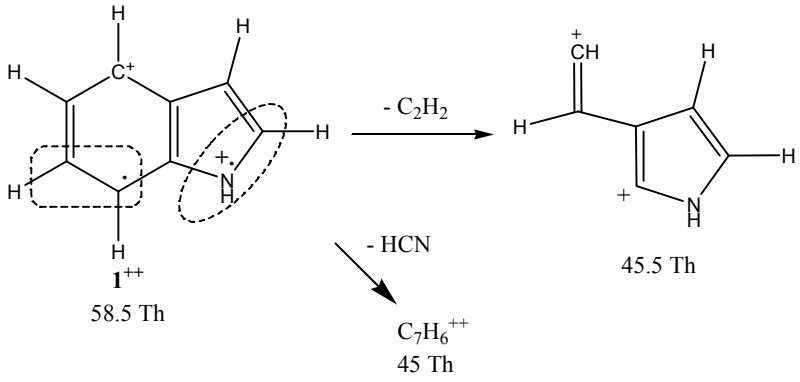
The dissociations of doubly-charged molecular ions $\mathbf{1}^{++}$ were studied by Perreault *et al.*[25] and more recently by Cardoso and Ferrer Correia.[22] The doubly-charged ions dissociate by elimination of neutral species, affording doubly-charged ions, or by charge separation reactions affording two singly-charged ions. In particular, the MIKE spectrum of $\mathbf{1}^{++}$ evidences three charge separation reactions plus three neutral-expulsion reactions (Table 1).

The CID spectrum (collision energy 100 eV, Ar collision gas) shows the same peaks with different relative intensities. The main peak is due to the 39^{+} ($C_3H_3^{+}$) ions, followed by those at 45.5 Th due to the 91^{++} ($C_6H_5N^{++}$) ions, together with new peaks of small abundance corresponding to the 51^{+}($C_4H_3^{+}$) and 63^{+} ($C_5H_3^{+}$) ions.[25]

The diradical structure $\mathbf{1}^{++}$ (Scheme 2) has been suggested. This, in fact, could account for the preferential C_2H_2 loss with respect to the HCN one (4 : 1), as the radical site localised in the bonding orbital in the hydrocarbon region would be expected to preferentially lose C_2H_2.[25]

Table 1: Unimolecular decompositions of the dication indole $\mathbf{1}^{++}$ ($C_8H_7N^{++}$, 58.5 Th)

Neutral expulsion reactions	Intensity	Ref.
117^{++} ($C_8H_7N^{++}$) → 115^{++} ($C_8H_5N^{++}$) + H_2	Very strong	25
117^{++} ($C_8H_7N^{++}$) → 91^{++} ($C_6H_5N^{++}$) + C_2H_2	strong	25
117^{++} ($C_8H_7N^{++}$) → 90^{++} ($C_7H_6^{++}$) + HCN	weak	25
Charge separation reactions		
117^{++} ($C_8H_7N^{++}$) → 90^{+} ($C_6H_4N^{+}$) + 27^{+} ($C_2H_3^{+}$)	weak	25
117^{++} ($C_8H_7N^{++}$) → 89^{+} ($C_7H_5^{+}$) + 28^{+} (H_2CN^{+})	strong	22, 25
117^{++} ($C_8H_7N^{++}$) → 78^{+} ($C_5H_4N^{+}$) + 39^{+} ($C_3H_3^{+}$)	strong	22, 25



Scheme 2

On the other hand, Cardoso and Ferrer Correia measured the kinetic energy released (KER) from the peak width at the half height of MIKE spectra[23,26] that upon charge separation reaction could be used to calculate the inter-charge distance.[27,28] In particular, they calculated the intercharge distance for the main charge separation reactions (Table 2).[22]

Table 2: Intercharge distance for the charge separation reactions of the dication indole $\mathbf{1}^{++}$ ($C_8H_7N^{++}$, 58.5 Th)

Reaction	KER (eV)	r (Å)	Ref.
117^{++} ($C_8H_7N^{++}$) → 89^+ ($C_7H_5^+$) + 28^+ (H_2CN^+)	2.6	5.4	22
117^{++} ($C_8H_7N^{++}$) → 78^+ ($C_5H_4N^+$) + 39^+ ($C_3H_3^+$)	2.9	4.9	22

The above reactions involve opening of the six- and five-membered rings. Interestingly, the measured distances resulted, within the experimental error, quite close to those estimated using molecular models and considering point charges.

2.2. Alkylindoles

The EI/MS of mono-methyl indoles **2-4** have been studied and their main fragmentation routes are summarised in Scheme 3.[18,21,29]

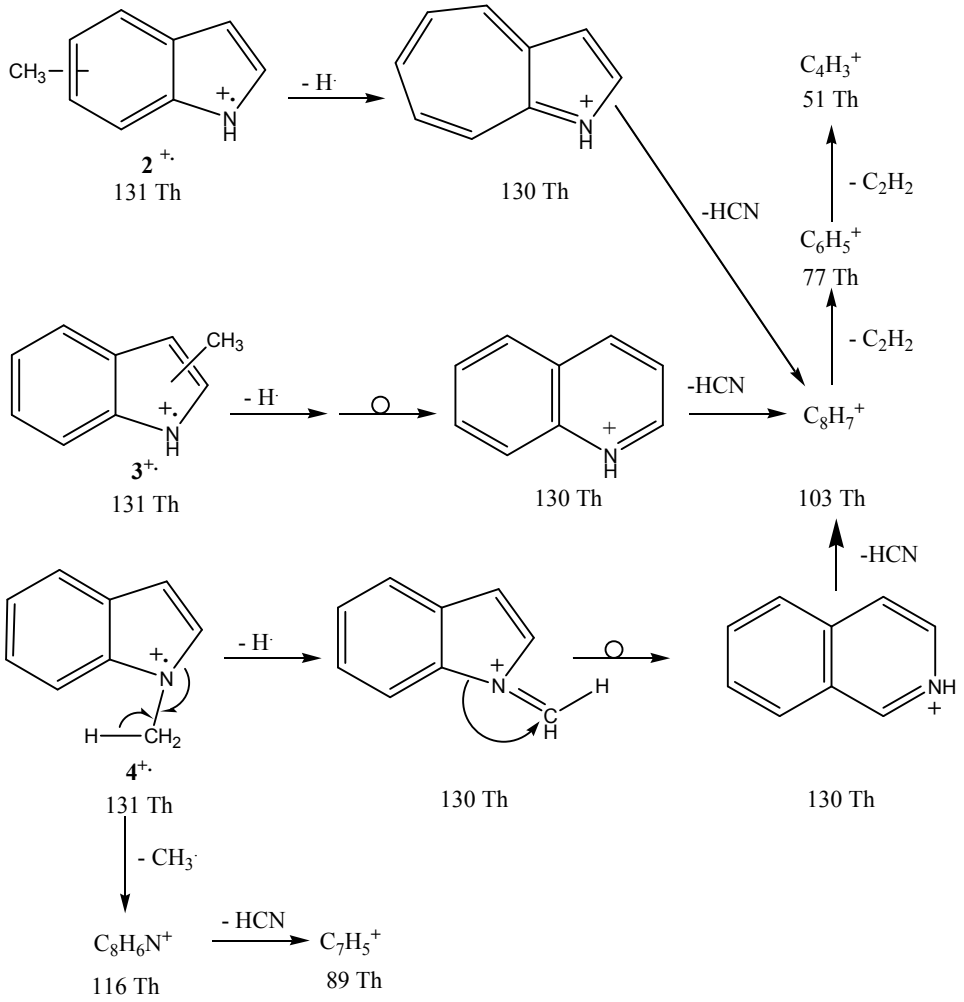
All these compounds are characterised by an abundant hydrogen atom ejection from the molecular ions (base peak for **2** and **3**, and 84% for **4**), followed by sequential losses of HCN and C_2H_2. In particular the EI/MS of 4-, 5-, 6- and 7-methylindoles (general formula **2**) are very similar, so indicating the formation of common intermediate ions (130 Th).[21]

Owing to labelling of 2-methylindole **3a** with ^{13}C at C-2 , it has been observed that 86 % of such a carbon atom is lost as HCN, so indicating that the methyl carbon atom is inserted between C-2 and C-3 in the ring expansion process.[29]

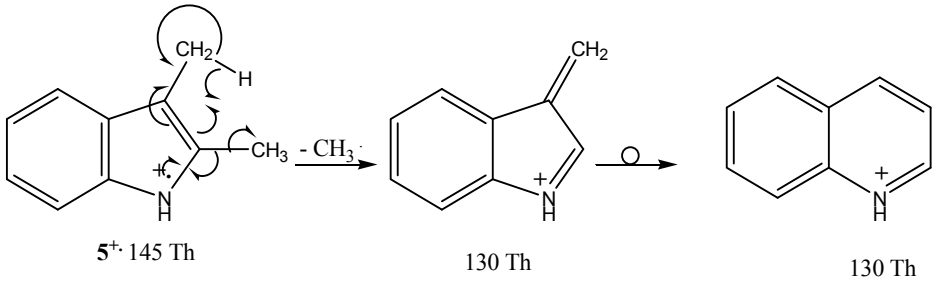
Concerning the 1-methyindole **4**, the EI/MS of the isotopomer labelled with ^{13}C at the methyl group shows that 52 % of the label is retained in the ion formed by consecutive HCN loss. This indicates the isoquinolinium structure for the $[M - H]^+$ ions.[29]

The molecular ions of **4** also undergo a competitive fragmentation pathway involving the sequential losses of methyl radical and HCN.[29]

Several dimethyl indoles have been examined by Beynon and Williams.[18] Their mass spectra are characterised by intense peaks for the $[M - H]^+$ ions, that can rearrange to methylquinolinium ions. It has also been observed the loss of methyl radical from the molecular ions, and this becomes particularly abundant for 2,3-dimethyl indole **5**. This is probably due to the assistance of the hydrogen migration shown in Scheme 4.

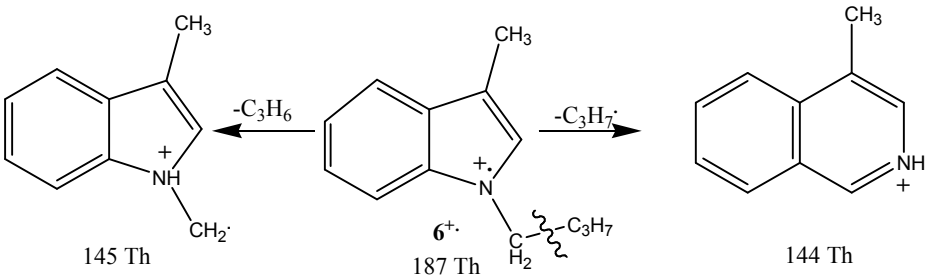


Scheme 3



Scheme 4

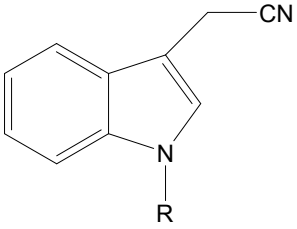
Long chain alkyl indoles behave like to the corresponding arenes. So the main fragmentations arise by α–cleavage accompanied by alkene elimination, probably through a McLafferty rearrangement as shown for 1-n-butyl-3-methylindole **6** in Scheme 5.[18] These simple fragmentation pathways have been widely used for characterisation of alkylindole derivatives, even with functionalised alkyl chain, e.g. γ-indolemicenic acid,[30] tryptophan and tryptophan derivatives,[31,32] melatonin and melatonin metabolites[33-36] and of several other 3-alkylindoles.



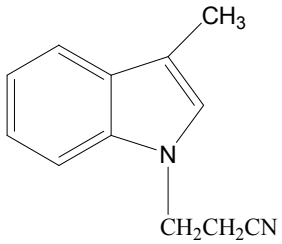
Scheme 5

The EI/MS of the cyanoalkylindoles **7-11** (Table 3) have been more recently reported together with those of other indole derivatives, and their fragmentation patterns have been proposed on the basis of metastable ion studies and accurate mass measurements.[37]

Table 3: Th values and relative abundances (%) of the main peaks in the EI/MS of cyanoindoles **7-11**



7: R = H
8: R = CH_3
9: R = CH_2CH_2CN
10: R = $COCH_3$



11

7		**8**		**9**		**10**		**11**	
Th	%	Th	%	Th	%	Th	%	Th	%
156,$M^{+\cdot}$	100	170, M^+	99	209,$M^{+\cdot}$	22	198,$M^{+\cdot}$	37	184, $M^{+\cdot}$	34
155	100	169	100	169	100	155	100	183	9
130	61	155	9	155	5	130	60	144	100
105	61	144	60	144	1	128	32	130	6
91	2	130	5	130	3	115	11	115	13
52	98	128	15	128	12	103	18	103	6
40	72	115	13	115	20	102	19	102	6
		103	5	102	9	89	11	91	6
		102	12	89	5	77	30	77	13
		101	14	77	7	63	12	51	6
		77	7	63	8	51	14		
		51	9	51	13	43	83		
		40	11	40	13				

The Authors asserted, without experiments with labelled compounds, that the $[M - H]^+$ ions responsible of the base peak (155 Th) for compound **7** are formed by loss of the hydrogen atom from the indole nitrogen.

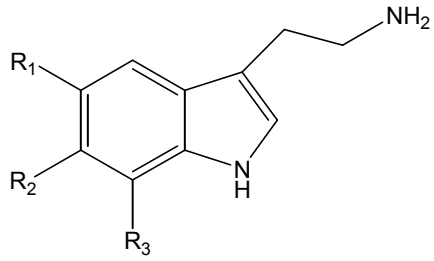
In our opinion this statement could be not correct as the loss of one of the α-methylene hydrogen should be in line with the reported ring expansion affording, in this case, cyanoquinolinium ions.

Furthermore, it has been proposed[37] that the loss of the CH_2CN radical, which affords the base peak at 169 Th, for compound **9**, arises from the 3-position. Instead, the $CH_2CN^{\cdot}$ loss from the CH_2CH_2CN group linked at the heterocyclic nitrogen is surely to be preferred. As matter of fact, the EI/MS of compounds **7** and **8**, bearing a CH_2CN at 3-position alone, show the lack or a small peak (5%) corresponding to the loss of a 40 Da fragment. The other reported fragmentations do not require further comments.

2.3. Indoleamines and tryptamines

EI/MS (Table 4), MIKE and CID-MIKE spectra, high resolution (HR) and linked scan experiments B^2/E = constant were used by Traldi and co-workers[38] to study the fragmentation processes of the biogenic indoleamines tryptamine **12** and serotonine **13**, together with those of 5,6- and 5,7-dihydroxytryptamine (**14** and **15**, respectively), which are powerful serotoninergic neurotoxins formed when a defect on the metabolism of **13** occurs.[39,40]

Table 4: EI mass spectra of compounds **12-15**

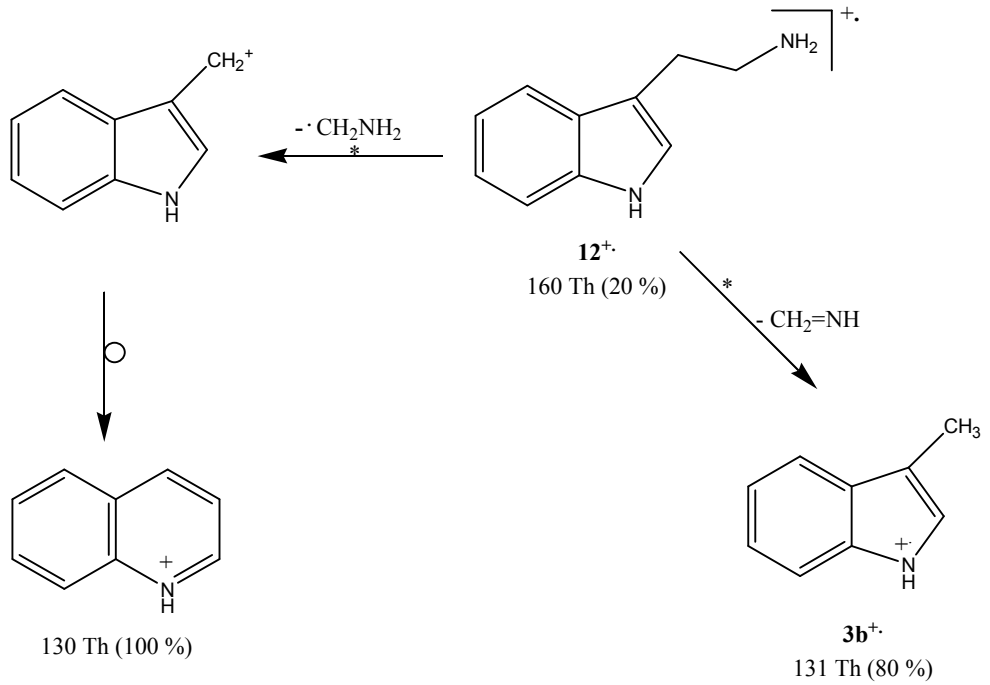


12: $R_1 = R_2 = R_3 = H$
13: $R_1 = OH$; $R_2 = R_3 = H$
14: $R_1 = R_2 = OH$; $R_3 = H$
15: $R_1 = R_3 = OH$; $R_2 = H$

Compounds	Th (%)
12	161(3), 160(20), 132(7), 131(80), 130(100), 129(6), 128(4), 117(2), 116(3), 103(13), 102(9), 101(2), 89(2), 77(3), 76(22), 75(4), 63(4), 52(2), 51(6)
13	177(3), 176(28), 174(3), 160(2), 158(3), 148(10), 147(78), 146(100), 145(7), 133(2), 131(12), 129(3), 119(5), 117(9), 116(3), 105(5), 91(11), 90(4), 89(7), 81(6), 80(6), 77(8), 65(9), 63(7), 52(5), 51(7), 50(4)
14	192(25), 191(3), 186(7), 178(6), 177(5), 176(5), 171(4), 170(4), 164(5), 163(66), 162(100), 161(7), 150(9), 149(70), 148(11), 146(7), 133(7), 132(8), 131(5), 130(26), 129(4), 120(9), 119(4), 118(7), 116(12), 114(90), 113(60), 111(95), 105(17), 103(34), 99(7), 97(32), 96(7), 93(16), 92(6), 91(9), 89(12), 86(16), 84(66), 83(92), 81(10), 78(15), 76(87), 75(31)
15	131(2), 130(7), 114(100), 112(56), 105(6), 104(5), 98(6), 94(13), 91(5), 85(12), 83(54), 81(6), 78(6), 77(20), 76(100), 73(7), 71(10), 70(17), 69(35), 68(11), 67(9), 66(96), 64(33), 63(98), 62(50), 60(91), 59(24), 57(16), 56(30), 55(20), 54(38), 53(15), 52(26), 51(11)

The molecular ions of tryptamine **12** (160 Th) are quite abundant (20 %) and the most abundant peaks in the EI mass spectrum at 131 Th (80%) and 130 Th (base peak) originate from CH_2-CH_2 bond cleavage with and without H rearrangement, respectively (Scheme 6).

The ions at 131 Th are the more abundant fragment ions also in the CID-MIKE spectrum of **12**. The CID-MIKE spectrum of these ions is identical to that obtained for the molecular ions of 3-methylindole **3b**, evidencing that 131 Th ions from **12** and the molecular ions of **3b** have the same structure. The loss of HCN from the molecular ions (affording the ions at 133 Th) through indole ring cleavage, already described for other indole derivatives,[41] was observed only in MIKE and CID-MIKE experiments.



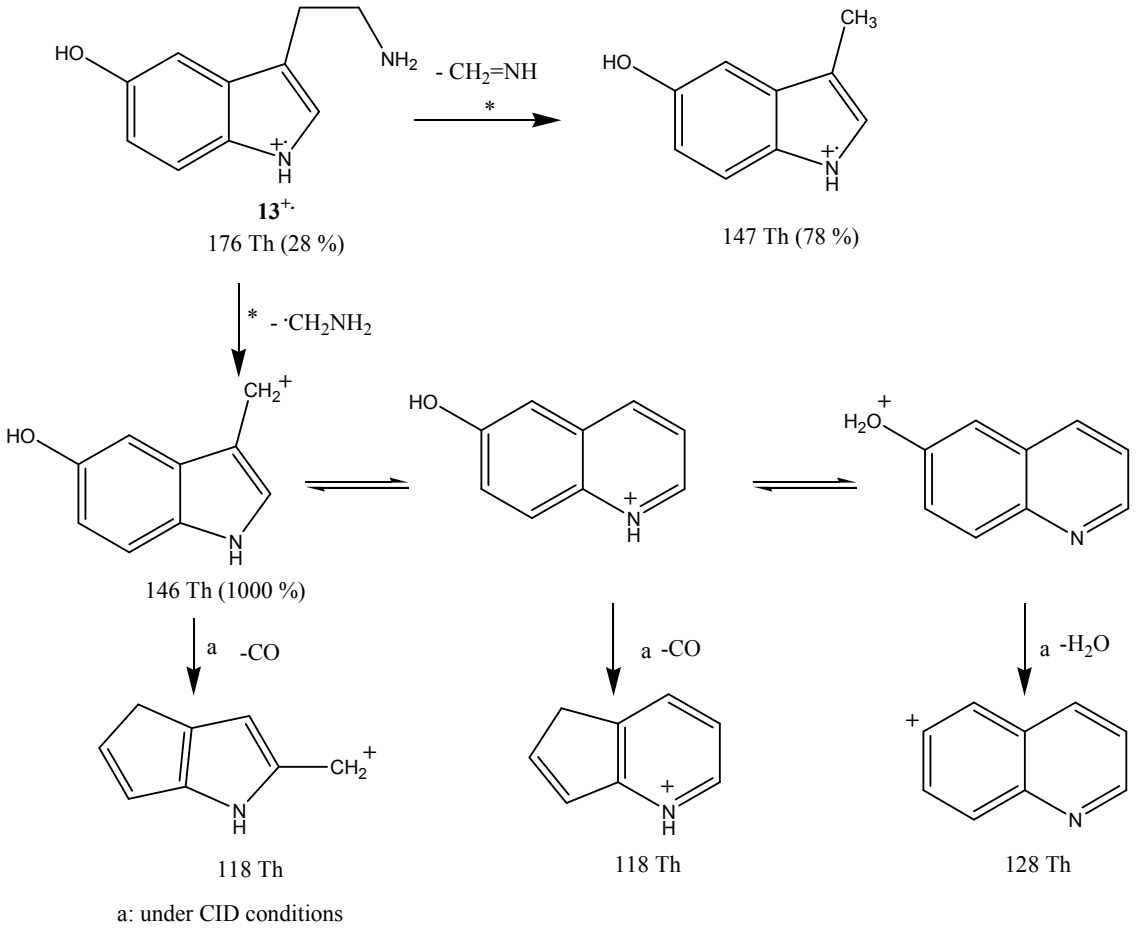
Scheme 6

The behaviour of serotonine **13** is very similar. In fact the most abundant peaks of the EI/MS are due to the molecular ions (176 Th, 28%), the $[M - CH_2{=}NH]^+$ ions (147 Th, 78%) and the $[M - CH_2NH_2]^{+\cdot}$ ions (146 Th, base peak). However, the CID-MIKE spectrum of the ion at 146 Th shows, beside the expected elimination of CO (which is a typical behaviour of phenols) as main process, the competitive elimination of H_2O, that cannot be explained by a species maintaining the 5-hydroxyindole structure. Hence, a rearranged structure which may account for the observed H_2O elimination was proposed (Scheme 7).

Concerning the 5,6-dihydroxytryptamine **14** and the 5,7-dihydroxytryptamine **15** , only the former was vaporised in the magnetic instrument used, giving an EI/MS which was substantially similar, with the appropriate mass shift, to those of **12** and **13**. To overcome the problem of the vaporisation of **15**, both **14** and **15** were analysed by using always EI, but a different mass spectrometer, i.e. an ion trap mass spectrometer (IT/MS). In this case the sample underwent fast heating by infrared irradiation close to the ion trap, which was proved to be highly effective for sample vaporisation.[42] As matter of fact, reliable mass spectra for both **14** and **15** were obtained, even if the molecular ions at 192 Th are of low abundance and the spectra are very similar each to other and then not useful in order to characterise the two isomers.

However, a distinction between the isomers **14** and **15** was achieved by energy resolved mass spectrometry experiments (ERMS). ERMS essentially consists in obtaining MS/MS data by varying kinetic

energy of the precursor ion. By IT/MS instrument CID can be performed applying a supplementary AC voltage (called tickle voltage) between the two end-cap electrodes, and the most effective approach to achieve ERMS data is based on the variation of "tickle voltage". In the case of **15**, the formation of the ion at 122 Th (a low intensity ion in the EI/MS) by CID of $M^{+\cdot}$ resulted energetically more favoured than for **14** (i.e. at a tickle voltage of 600 mV, this ion has a relative intensity of 25 % for **15** and only of 8 % for **14**), that allows a good distinction between the two isomers.



Scheme 7

The electron ionisation induced fragmentation of tryptamine **12** and serotonine **13** together with those of gramine **16** have been also studied by Cardoso and Ferrer Correia with the aid of MIKE, CID-MIKE and two-dimensional mass spectra (or metastable mapping).[22] The two-dimensional mass spectrometry is achieved by collecting data on the BE plane, and gives complete information on the decompositions occurring in the different part of a multi-sectors mass spectrometer.[43] In their hands, the only unimolecular decomposition of the molecular ions in the metastable energy window (MIKE spectra) involves imine elimination, with hydrogen migration at the 2-position of the indole. This should be apparently in contrast with the finding that the resulting ions have the same structure of the molecular ions of 3-methylindole **3b**,[38] but consecutive rearrangements could agree with both the suggestions. The CH_2-CH_2 bond cleavage requires higher energy, as it occurs by CID. Of course, molecular ions associated with a larger internal energy which decompose into the ion source mainly decompose by this pathway.

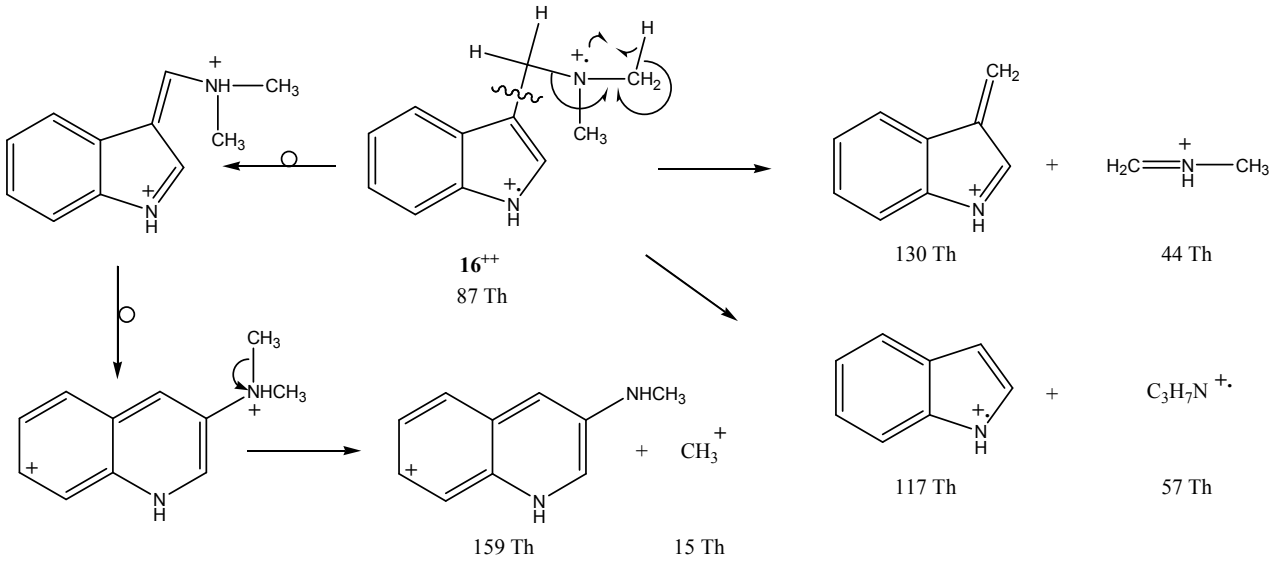
In the same work the MIKE spectra of the doubly charged molecular ions of **12, 13** and **16**, were also studied and the intercharge distance by kinetic energy release (KER) for the charge separation reactions was determined (Table 5).[22]

Table 5: Intercharge distance for the charge separation reactions of the dication, **12**$^{++}$ ($C_{10}H_{12}N_2^{++}$, 80 Th), **13**$^{++}$ ($C_{10}H_{12}N_2O^{++}$, 88 Th), **16**$^{++}$ ($C_{11}H_{14}N_2^{++}$, 87 Th)

Comp.	Reaction	KER (eV)	r (Å)	Ref.
12	160^{++} ($C_{10}H_{12}N_2^{++}$) → 131^+ ($C_9H_9N^+$) + 29^+ ($CH_2{=}NH^+$)	*	*	22
13	176^{++} ($C_{10}H_{12}N_2O^+$) → 147^+ ($C_9H_9NO^+$) + 29^+ ($CH_2{=}NH^+$)	*	*	22
	176^{++} ($C_{10}H_{12}N_2O^+$) → 158^+ ($C_{10}H_{10}N_2^+$) + 18^+ (H_2O^+)	2.8	5.1	
16	174^{++} ($C_{11}H_{14}N_2^{++}$) → 117^+ ($C_8H_7N^+$) + 57^+ ($C_3H_7N^+$)	2.7	5.3	22
	174^{++} ($C_{11}H_{14}N_2^{++}$) → 130^+ ($C_9H_8N^+$) + 44^+ ($C_2H_6N^+$)	3.3	4.4	
	174^{++} ($C_{11}H_{14}N_2^{++}$) → 145^+ + 29^+	*	*	
	174^{++} ($C_{11}H_{14}N_2^{++}$) → 159^+ ($C_{10}H_{11}N_2^+$) + 15^+ (CH_3^+)	1.9	7.4	

*Composed peaks, not measurable

These findings lead to describe the charge separation reactions of the gramine **16** as reported in Scheme 8.



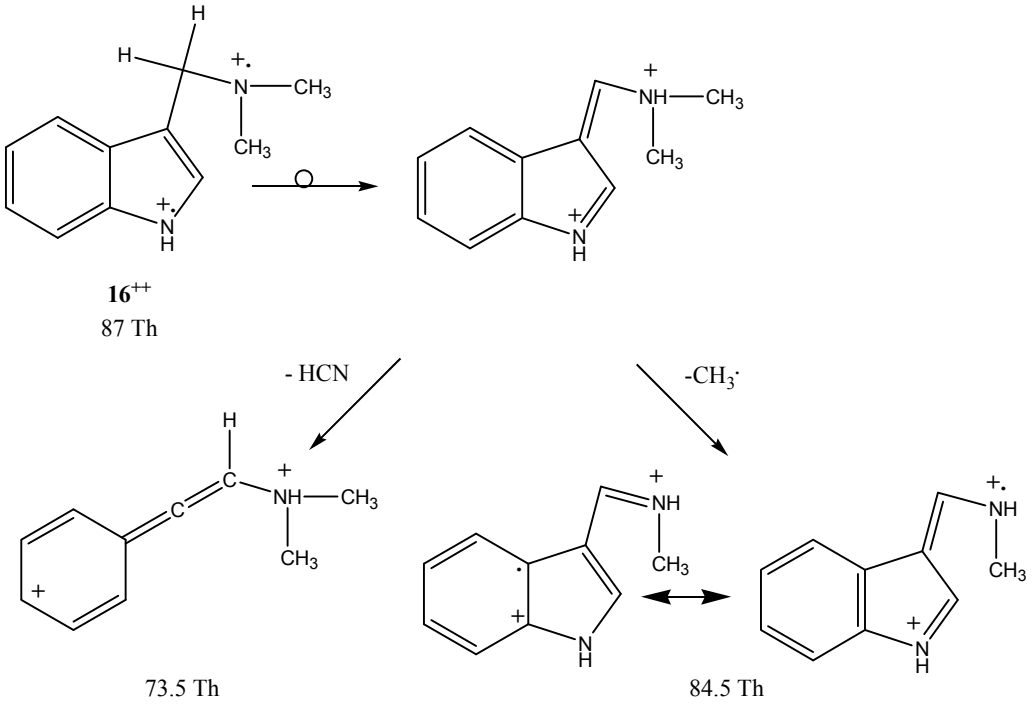
Scheme 8

For gramine **16**$^{++}$, beside the large peaks due to the charge separation reactions of table 5, sharp peaks due to elimination of HCN and methyl radical were also observed (Scheme 9).

The behaviour under EI conditions of melatonin (N-acetyl-5-methoxytryptamine) **17**, and of its isomers **18-25** (Table 6) has been studied with the aid of metastable ion experiments by Diamantini et al.,[44] with the aim to achieve useful MS methods in order to distinguish them.[44]

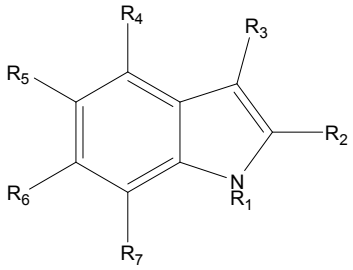
Melatonin **17** is the main hormone secreted by the pineal gland which regulates circadian rhythms in mammal and, more recently, has been established of clinical relevance for the prevention and cure of several diseases.[45]

The 70 eV EI/MS of **17-25** are quite similar. They are characterised by abundant ions at 232 Th ($M^{+\cdot}$), at 173 Th (due to cleavage of the CH_2-N bond with H rearrangement), which is responsible of the base peak excepted for **24**, and at 160 Th (CH_2-CH_2 bond cleavage).



Scheme 9

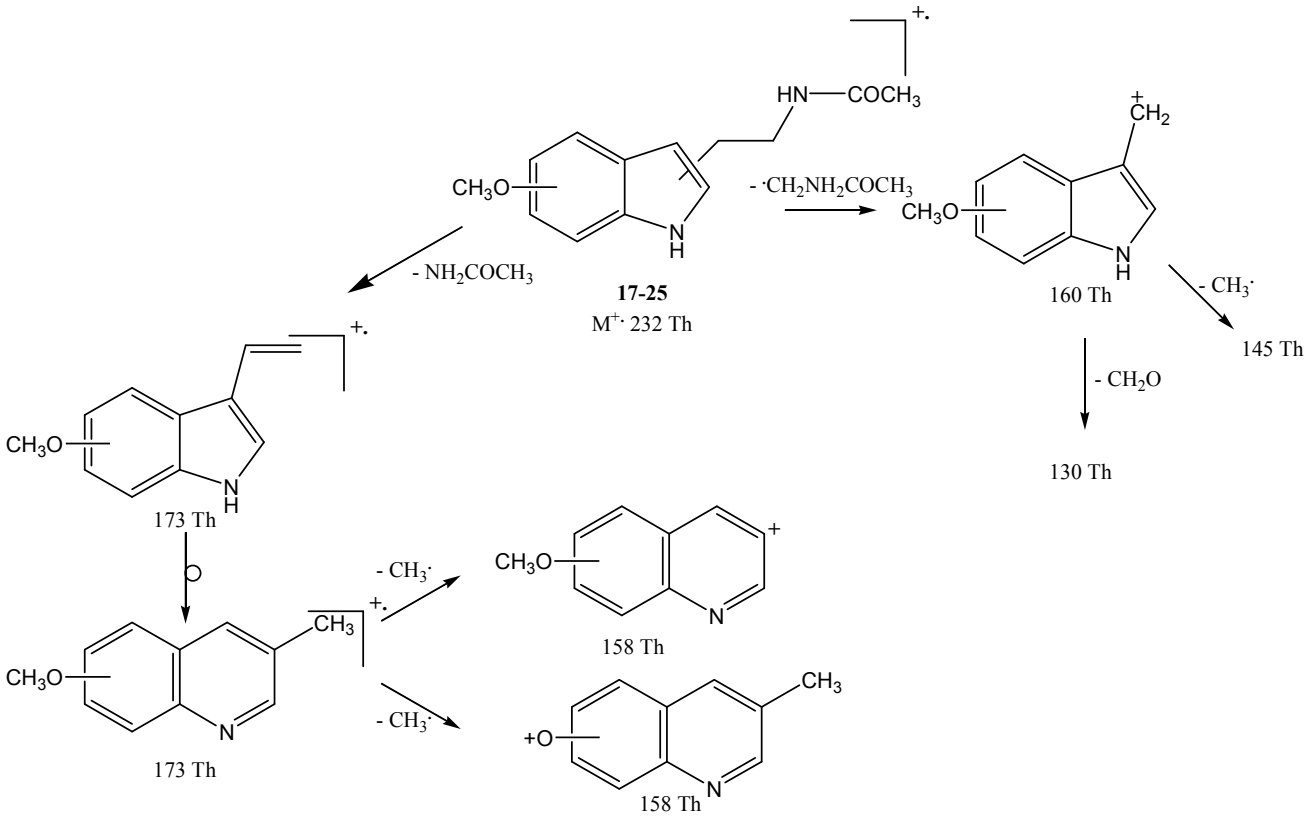
Table 6: Relative intensities (%) of the main peaks in the 70 eV EI/MS of compounds **17-25**



17:	$R_1 = R_2 = R_4 = R_6 = R_7 = H$	$R_3 = (CH_2)_2NHCOCH_3$	$R_5 = OCH_3$						
18:	$R_1 = R_2 = R_5 = R_6 = R_7 = H$	$R_3 = (CH_2)_2NHCOCH_3$	$R_4 = OCH_3$						
19:	$R_1 = R_2 = R_4 = R_5 = R_7 = H$	$R_3 = (CH_2)_2NHCOCH_3$	$R_6 = OCH_3$						
20:	$R_1 = R_3 = R_5 = R_6 = R_7 = H$	$R_2 = (CH_2)_2NHCOCH_3$	$R_4 = OCH_3$						
21:	$R_1 = R_3 = R_4 = R_6 = R_7 = H$	$R_2 = (CH_2)_2NHCOCH_3$	$R_5 = OCH_3$						
22:	$R_1 = R_3 = R_4 = R_5 = R_7 = H$	$R_2 = (CH_2)_2NHCOCH_3$	$R_6 = OCH_3$						
23:	$R_1 = R_3 = R_4 = R_5 = R_6 = H$	$R_2 = (CH_2)_2NHCOCH_3$	$R_7 = OCH_3$						
24:	$R_2 = R_3 = R_4 = R_5 = R_7 = H$	$R_1 = (CH_2)_2NHCOCH_3$	$R_6 = OCH_3$						
25:	$R_1 = R_2 = R_3 = R_6 = R_7 = H$	$R_4 = (CH_2)_2NHCOCH_3$	$R_5 = OCH_3$						

Compound	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
232 Th, $M^{+\cdot}$	52	64	48	45	35	61	37	77	40
173 Th	100	100	100	100	100	100	100	53	100
160 Th	90	75	95	60	56	96	46	100	59
158 Th	1	9	2	24	13	22	9	1	18
145 Th	3	-	-	17	-	9	13	-	10
130 Th	3	4	2	2	2	2	2	3	5

The ions at 173 Th can rearrange, through a ring enlargement, to the aromatic quinoline structure, which in turn loses methyl radical affording the ions at 158 Th (Scheme 10).



Scheme 10

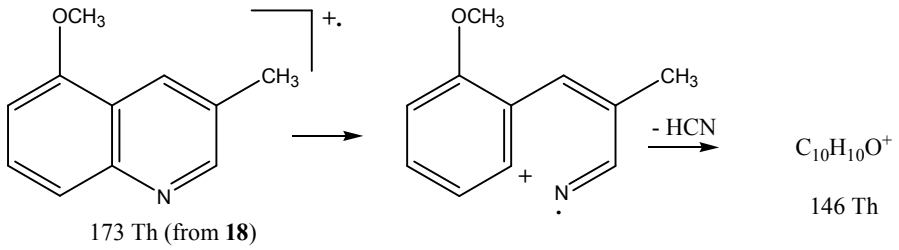
Table 7: Relative intensities (%) of the main peaks in the MIKE spectra of the EI-generated $M^{+\cdot}$ ions (232 Th) of compounds **17-25**

Compound	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**
189 Th	3	2	4	2	3	2	2	4	2
173 Th	100	100	100	100	100	100	100	100	100
160 Th	20	7	15	9	12	14	6	22	9
147 Th	-	-	-	-	-	-	-	25	-
145 Th	3	1	5	4	3	3	3	2	3
141 Th	2	-	2	3	3	2	2	-	2
130 Th	3	4	2	2	2	2	2	3	5
115 Th	2	1	1	1	1	1	1	2	2

Except for the peak at 189 Th due to the loss of $CH_3CO^{\cdot}$, the MIKE spectra of compounds **17-25** (Table 7) show the same peaks observed in the 70 eV EI/MS and are quite similar each to other. Only the N-substituted compound **24** behaves in lightly different way, as it shows the loss of the whole side chain with H rearrangement, affording a quite intense peak at 147 Th with the same structure of the molecular ion of 6-methoxyindole.

The MIKE spectra of the 173 Th ions of **17-25** evidence that the most favoured unimolecolar decomposition process of these ions involves the ejection of methyl radical. The compound **18** alone shows

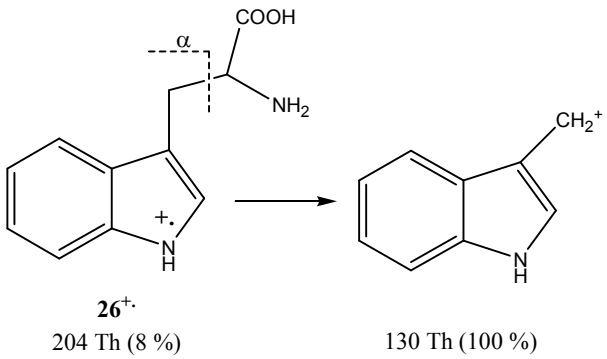
also a very intense peak at 146 Th, due to a favoured elimination of HCN, that could be rationalised by the effect of the 4-methoxy group in activating the cleavage of the C-N bond of the 173 Th ion (Scheme 11).



Scheme 11

2.4. Tryptophans

The EI/MS of tryptophan **26** shows the molecular ions at 204 Th and is dominated by the base peak at 130 Th (Scheme 12), the other peaks having relative intensities less that 10%. A similar behaviour is observed for its esters.[31,32]



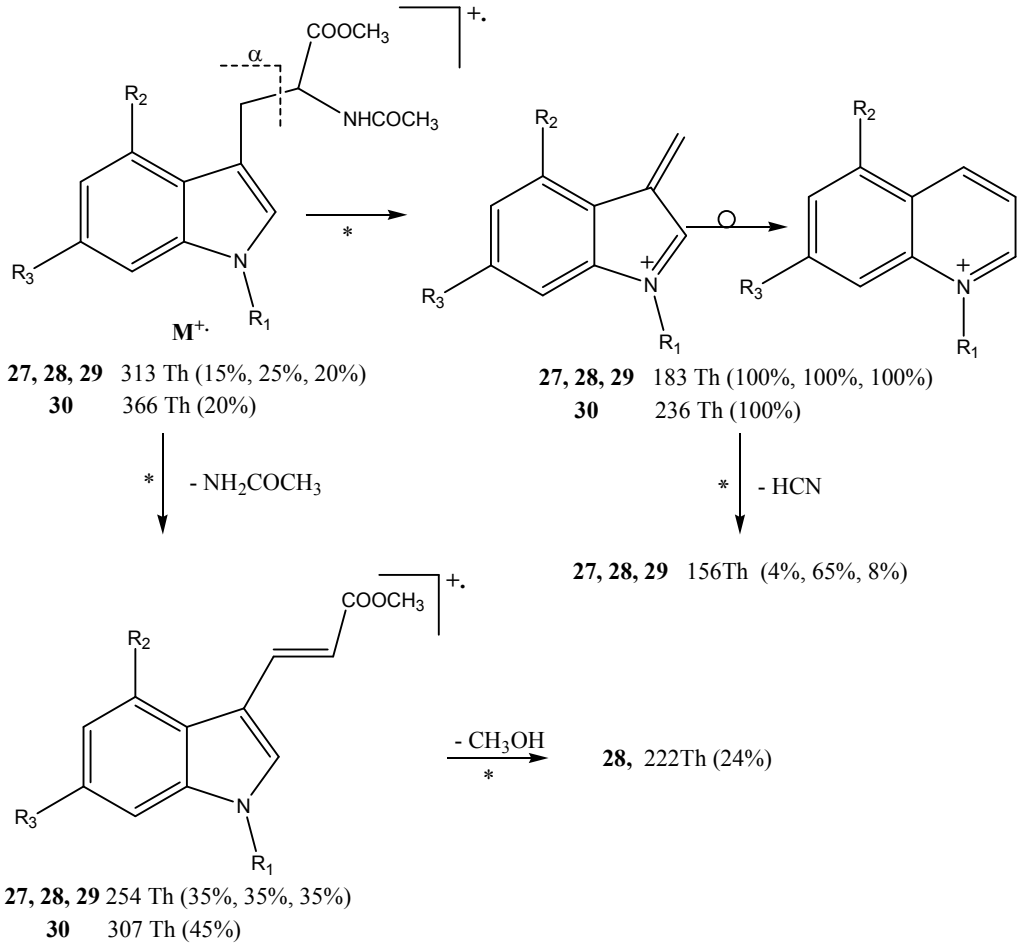
Scheme 12

Different MS techniques (EI/MS, HR-EI/MS, MS/MS) have been recently applied by Giorgi *et al.*[46] to study the modified tryptophan isomers **27-29**, together with the related compound **30**. Unlike to the quite frequent similarity of the EI/MS from positional isomers in substituted hetero-aromatic compounds,[47] the EI induced fragmentations are the same for **27-29**, but their great difference in the relative abundances results in being distinctive and depending on the position of the α-cyanoethyl substituent at the indolic ring (Scheme 13). The molecular ions (313 Th) are observed even if they are not very abundant, and the base peak at 183 Th is due to the loss of $CH(COOCH_3)NHCOCH_3$ radical from $M^{+\cdot}$, followed by HCN elimination affording the ion at 156 Th. Another common process followed by isomers **27-29**, likely to melatonin **17** and its isomers **18-25**,[44] yields the fragment ions at 254 Th produced by NH_2COCH_3 elimination (confirmed by accurate mass measurements in HR-MS experiments). The methanol elimination from the ions at 254 Th was observed only for **28**, where a proximity effect between the 3-substituent and the α-cyanoethyl group could occur.

The behaviour of compound **30** is qualitatively very similar, and its EI/MS shows the same ions with the appropriate mass shift.

The CID-product ion mass spectra obtained by selecting the molecular ions of isomers **27-29** evidence a behaviour similar to that shown by high internal energy ion inside the source, the most abundant ions being

at 254 Th and 183 Th. Some less abundant ions, could be related to regiochemical reactions whose occurrence depends on the position of the α-cyanoethyl group at the indolic ring. For instance, the ions at 222 Th (formed by loss of methanol from the ions at 254 Th) are specific for isomer **28**, while the ions at 227 Th (formed by HCN loss from the ions at 254 Th) are characteristic of isomer **27**.



27 $R_1 = CH(CN)CH_3$ $R_2 = R_3 = H$
28 $R_1 = R_3 = H$ $R_2 = CH(CN)CH_3$
29 $R_1 = R_2 = H$ $R_3 = CH(CN)CH_3$
30 $R_1 = R_3 = CH(CN)CH_3$ $R_2 = H$

Scheme 13

The analysis of the CID-product ion mass spectra obtained by selecting the species $[M - NH_2COCH_3]^+$ (254 Th) of **27-29**, shows two main decomposition pathways, one involves the fragmentation of the substituent at 3-position, the other involving the fragmentation of the α-cyanoethyl group.

Under CID condition a very strong regiochemical effect regarding the most abundant product ions was observed (Table 8). In particular, while for isomers **27** and **29** the most abundant fragment ions are at 223 Th (loss of methoxy radical), for compound **28** they are at 222 Th (loss of methanol).

The Authors suggested the formation of a new fused five membered ring to explain the high abundance of the ion at 223 Th. The loss of methanol from the $[M - NH_2COCH_3]^+$ of **28** could be due to proximity effect with the α-cyanoethyl at the position 4.

Finally, the presence of an intense peak at 239 Th (loss of methyl radical) for **29**, leads to an unequivocal isomer distinction. It seemed reasonable that the loss of methyl group originates from the α-

cyanoethyl at the position 6. In fact, abundant loss of both methoxy and methyl radical are observed in the CID-product ion mass spectra obtained by selecting the species $[M - NH_2COCH_3]^+$ (307 Th) of compound **30**.

Table 8: Relative intensities of main peaks of the CID product ion spectra by selecting the $[M - NH_2COCH_3]^+$ ions (254 Th) of compounds **27-29**

Compound	239 Th	223 Th	222 Th	212 Th	196 Th	179 Th	169 Th
27	20 %	100 %	-	21 %	31 %	-	7 %
28	4 %	-	100 %	10 %	-	7 %	-
29	92 %	100 %	-	24 %	24 %	18 %	11 %

The CID-product ion mass spectra obtained by selecting the species $[M - CH(COOCH_3)NHCOCH_3]^+$ (183 Th), which should be reasonably rearranged to quinolinium cations (Scheme 13) is dramatically different for each of the isomers **27-29**. In particular, the most intense product ions are at 129 Th (100 %), due to the loss of the α-cyanoethyl radical) and at 130 Th (73 %, due to the loss of C_3H_3N) for compound **27**, while the same peaks are present only at trace level for **28** and **29**. The spectrum of the isomer **27** is dominated by the peak at 156 Th (due to HCN elimination) that is present only in small amount for the other two isomers, while the most intense peak in the spectrum of **29** is at 168 Th (due to methyl loss).

So, this study evidenced the possibility of isomer distinction by EI/MS and that the selectivity of distinctive fragmentation can be greatly increased by CID of either the molecular ion or the most intense fragment ions produced in the ion source. Moreover, it has been demonstrated that each compound **27-30** maintains its own distinctive structure not only after the ionisation process, but also after several decompositions.

2.5. Arylindoles

The behaviour of 1-phenylindole **31**, 2-phenylindole **32**, 3-phenylindole **33**, 3-(2-pyridyl)-indole **34** and 2,3-diphenylindole **35** under EI conditions has been investigated by Powers[20] and Jennings[48] (Table 9).

The loss of $CH_2N^{\cdot}$ from the molecular ion, affording the ions at 165 Th $[C_{13}H_9]^+$, formulated as the florenyl cations, is the predominant fragmentation for compounds **31**, **32** and **33** and constitutes the main fragmentation in the first field free region.

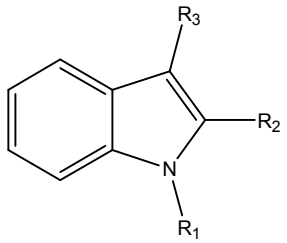
This suggests that the molecular ions undergo a considerable skeletal rearrangement before the loss of $CH_2N^{\cdot}$. The same loss also occurs for **34** and **35**. Furthermore, other competitive fragmentation reactions occur without scrambling, as evidenced by the fact that the loss of C_6H_5CHN and C_6H_5CN are mainly observed for **31** and **32**, respectively. Quite abundant $[M - H]^+$ ions are observed for the compounds **31-35**.

2.6. Methoxyindoles and hydroxyindoles

Several indoles of biological interest contain hydroxyl or methoxyl groups on the benzenoid ring. The EI/MS of 5-methoxyindole **36**, 6-methoxyindole **37** and 7-methoxyindole **38** have been reported (Table 10).[20] The molecular ions (147 Th) are very abundant and the main fragmentation route involves the

consecutive losses (metastable supported) of $CH_3^{\cdot}$ (132 Th), CO (104 Th), HCN (77 Th) and C_2H_2 (51 Th). A less important pathway involves the loss of $CH_3O^{\cdot}$ (116 Th) followed by the consecutive eliminations of HCN (89 Th) and C_2H_2 (63 Th). The 6-methoxyindole **37** can be distinguished by the base peak at 132 Th, due to methyl loss so evidencing an higher stability of these ions with respect to the $[M - CH_3]^+$ ions arising from the molecular ions of both **36** and **38**.

Table 9: relative intensities of 70 eV EI/MS main peaks of compounds **31-35**



31: R_1 = Phenyl $R_2 = R_3 = H$
32: $R_1 = R_3 = H$ R_2 = Phenyl
33: $R_1 = R_2 = H$ R_3 = Phenyl
34: $R_1 = R_2 = H$ R_2 = 2-Pyridyl
35: R_1 = H $R_2 = R_3$ = Phenyl

Compound	**31**		**32**		**33**		**34**		**35**	
Ions	Th	%	Th	%	Th	%	Th	%	Th	%
$M^{+\cdot}$	193	100	193	100	193	100	194	100	269	100
$[M - H]^+$	192	12	192	7	192	12	193	50	268	28
$[M - HCN]^{+\cdot}$	166	4	166	4	166	59	167	7	-	-
$[M - CH_2N]^+$	165	17	165	20	165	22	166	16	241	6
$[M - CH_2N - C_2H_2]^+$	159	2	159	3	159	2	160	4	-	-
$[M - CH_2N - HCN]^+$	-	-	-	-	-	-	159	6	-	-
$[M - C_6H_5]^+$	116	29	116	1	-	-	-	-	-	-
$[M - C_7H_5N]^+$	95	12	95	15	95	2	-	-	-	-
$[M - C_7H_6N]^+$	94	11	94	15	-	-	-	-	171	21
$C_6H_5^+$	77	5	77	4	-	-	-	-	-	-
$C_5H_4N^+$	-	-	-	-	-	-	78	5	-	-

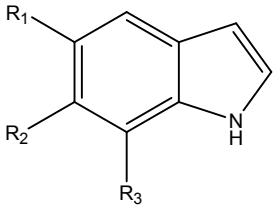
The isomers 5,6-dimethoxyindole **39**, 6,7-dimethoxyindole **40** and 4,7-dimethoxyindole **41** were studied by EI/MS and EI/MS/MS using either high or low energy CID and IT/MS experiments.[49,50] The EI mass spectra of **39** and **40** are very similar and the main difference is due to the relative abundances of the ions at 116 Th and 119 Th, while the isomer **41** is distinguishable from the other two isomers owing the low abundances of the ions at 106 Th and 116 Th (Scheme 14).

The different behaviour of the three isomers was rationalised on the base of CID experiments performed selecting the main ions. The CID spectra of the molecular ions (177 Th) evidence the same processes, i.e. the consecutive losses of methyl radical and CO affording the ions at 162 Th and 134 Th.

While the CID spectra of the fragment ions at 162 Th do not show sufficient differences for isomer characterisation, those of the ions at 134 Th are very different. In fact these ions competitively lose $CH_3^{\cdot}$ (119 Th), H_2O (116 Th), HCN (107 Th) and CO (106 Th) for both compounds **39** and **40**, but with different

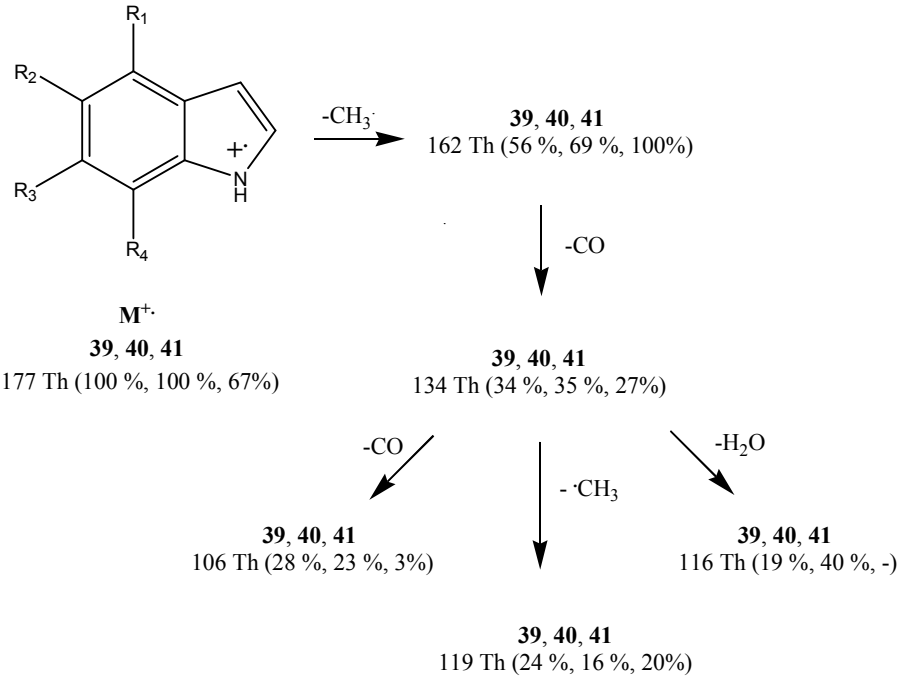
yields. The ions at 134 Th generated from the isomer **41** fragment mainly by losing $CH_3^{\cdot}$, CO elimination is drastically reduced and H_2O elimination completely absent.

Table 10: relative intensities of 70 eV EI/MS main peaks of methoxyindoles **36-38**



36: $R_1 = OCH_3$ $R_2 = R_3 = H$
37: $R_1 = R_3 = H$ $R_2 = OCH_3$
38: $R_1 = R_2 = H$ $R_3 = OCH_3$

Compound	**36**		**37**		**38**	
Ions	Th	%	Th	%	Th	%
$M^{+\cdot}$	147	100	147	100	147	100
$[M - H]^+$	146	6	146	7	-	
$[M - CH_3]^+$	132	65	132	100	132	71
$[M - OCH_3]^+$	116	5	116	5	116	12
$[M - CH_3 - CO]^+$	104	38	104	66	104	83
$[M - OCH_3 - HCN]^+$	89	5	89	9	89	13
$[M - CH_3 - CO - HCN]^+$	77	6	77	21	77	19
$[M - OCH_3 - HCN - C_2H_2]^+$	63	3	63	7	63	5
$[M - CH_3 - CO - HCN - C_2H_2]^+$	51	6	51	14	51	11



39: $R_1 = R_4 = H$; $R_2 = R_3 = CH_3O$
40: $R_1 = R_2 = H$; $R_3 = R_4 = CH_3O$
41: $R_2 = R_3 = H$; $R_1 = R_4 = CH_3O$

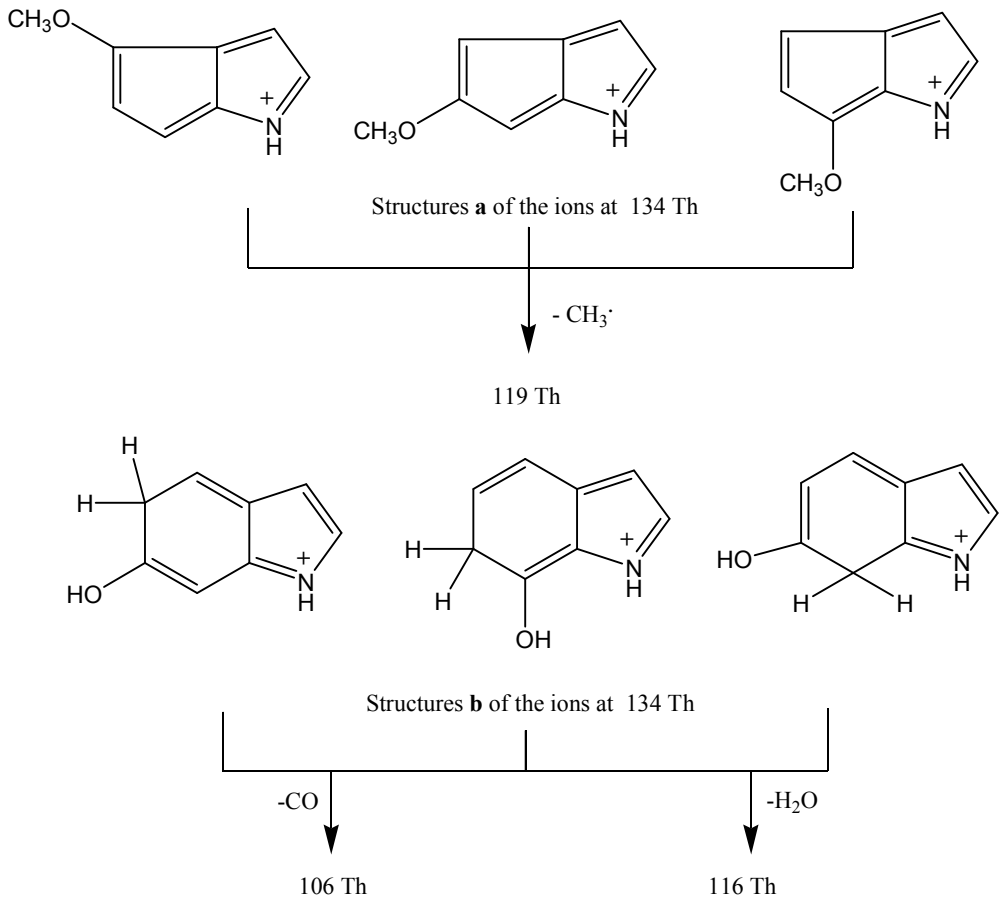
Scheme 14

These findings have been rationalised by the possible occurrence of two different mechanisms affording two types of different structures (**a** and **b** of Scheme 15) for the ions at 134 Th. Structures of type **a** could be considered responsible of the $CH_3^{\cdot}$ loss (affording the ions at 119 Th), whereas structures **b** lose H_2O and CO giving the ions at 116 Th and 106 Th, respectively.

The existence of two structurally different ions at 134 Th was also proved by IT/MS^n experiments. Likely multisector instruments the IT/MS allows several consecutive MS/MS experiments. So the Authors followed two different ways to generate the fragment ions at 134 Th: directly by electron ionisation and alternatively through the following consecutive CID decompositions:

$$177\ Th\ (M^{+\cdot}) \rightarrow 162\ Th \rightarrow 134\ Th$$

The ions at 134 Th in turn were subjected to collision with helium under identical conditions. Considering that the two competitive mechanisms for the formation of ions **a** and **b** should require different activation energies, the different amount of internal energy in the precursor ions at 162 Th, due to the activation method used, could influence the relative yields of the species. As matter of fact, the CID mass spectra of the ions at 134 Th of both **39** and **40** produce the ions at 119 Th, 116 Th and 106 Th when generated by EI (ions **a**), whereas the ions at 119 Th are completely absent when generated by CID (ions **b**). So the formation of ions **a** involves an activation energy higher than that for the formation of ions **b**.

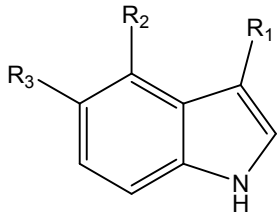


Scheme 15

It has been reported that hydroxyindoles bearing the hydroxy group linked to the benzenoid ring give, as competitive fragmentations, the consecutive losses of CO and HCN and *viceversa.*[20] However more recent studies indicate that, for the 3-hydroxyindole **42**, 4-hydroxyindole **43** and 5-hydroxyindole **44** (Table 11), the primary decomposition pathways consist of competitive losses of CO and $CHO^{\cdot}$ leading to the ions at 105 Th

and 104 Th, respectively.[49] These ions further decompose through $CN^{\cdot}$ and HCN losses giving ions at 78 Th and 77 Th.

Table 11: Relative abundances of the main ions of the 70 eV EI/MS of the hydroxyindoles **42-44**



42 $R_1 = OH$; $R_2 = R_3 = H$
43 $R_2 = OH$; $R_1 = R_3 = H$
44 $R_3 = OH$; $R_1 = R_2 = H$

42		**43**		**44**	
Th	%	Th	%	Th	%
134	9	134	8	134	9
133	100	133	100	133	100
132	15	132	11	132	12
105	14	105	19	105	18
104	32	104	40	104	39
-	-	79	5	79	7
78	2	78	11	78	19
77	15	77	10	77	14
-	-	52	15	52	8
51	6	51	7	51	8

Table 12: Relative abundances for product-ion spectra of precursor ions at 105 Th and 104 Th of hydroxyindoles **42-44**

Compound:	**42**		**43**		**44**	
Precursor ion	Th	%	Th	%	Th	%
105	104	72	104	100	104	100
105	78	8	78	-	78	-
105	77	19	77	-	77	-
104	78	-	78	48	78	47
104	77	100	77	52	77	53

The EI/MS of **42-44** do not lead to distinguish between the three isomers, that could be of interest as they are present in small amounts in the human urine with a concentration considerably higher in patient with malignant melanoma.[51] While the CID MS/MS spectra of the selected daughter ions at 105 Th and 104 Th (Table 12) lead to an unequivocal characterisation of **42**, do not allow to distinguish between the isomers **43** and **44**. An analysis by energy resolved mass spectrometry (ERMS) was carried out by Evans *et al.*[49,52] utilising an ion trap mass spectrometer (IT/MS) by varying the AC voltage (tickle voltage) and a triple stage quadrupole mass spectrometer (QQQ). The breakdown curves (i.e. the plots of the relative abundances of the

molecular ions at 133 Th, the ions at 105 Th and 104 Th *viz* the kinetic energy of the molecular ions) are quite different for the three isomers. In particular, the high dependence of their daughter-ion ratio on the kinetic energy of the molecular ions could characterise the three isomers **42-44**. The abundance of the ions at 104 Th is not dramatically changed, while a sensible increase of the ions at 105 Th is observed for **42**. A comparable increase of both ions is observed for **43**, while the ions at 104 Th undergo a dramatic increase overcoming the intensity of the molecular ion peak for **44**. Even if with different trends, comparable results were obtained by both QQQ and IT/MS.[52]

Indoles oxygenated at 2 and 3 positions are commonly named oxindoles and indoxyles, respectively. These compounds exist in the carbonyl form rather than in the tautomeric hydroxyindole forms. They give many reaction of the carbonyl compounds, although under certain conditions they react as tautomers.[2]

The EI/MS of the 3-hydroxyindole **42** (Table 11) and of the 2-hydroxyindole **45** (Fig. 2) show the loss of CO (metastable supported) as the main fragmentation route of the molecular ions.[20,49] However, as the CO loss is also the main fragmentation reaction of phenols, there are no evidences that the oxindole structure **45'** is preferred in the gas phase too.

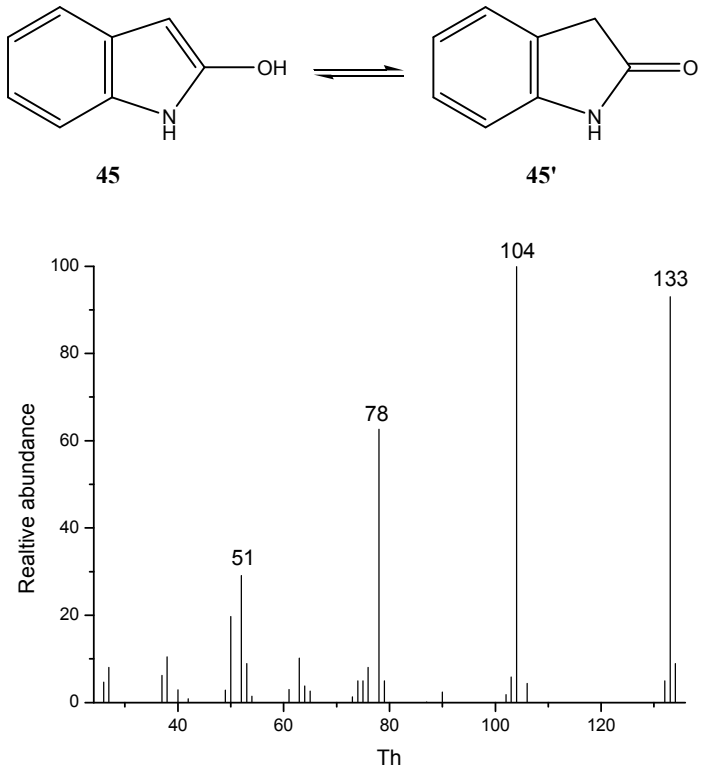


Figure 2: EI/MS (70 eV) of compound **45** adapted from NIST library[19]

On the other hand, the EI/MS of the N-[2-(5-methoxy-2-oxo-2,3-dihydro-1H-indole-3-yl)-ethyl]-acetamide **46'**(Fig. 3a), the oxindole structure of which in solution has been well established by ^{1}H-, ^{13}C-, HETCOR- and 2D-COSY- NMR experiments, is very close to that of its isomer 6-hydroxymelatonin **47** (Fig. 3b).[53]

In particular both these compounds behave similarly to melatonin **17** showing abundant molecular ions at 248 Th, the formal loss of acetamide (189 Th) and CH_2-CH_2 bond cleavage (176 Th). The remarkably

abundant $[M - CH_3]^+$ ions at 161 Th for **47**, produced by loss of the methyl linked to the methoxy group, are due to the formation of a favoured ortho-quinoide structure.

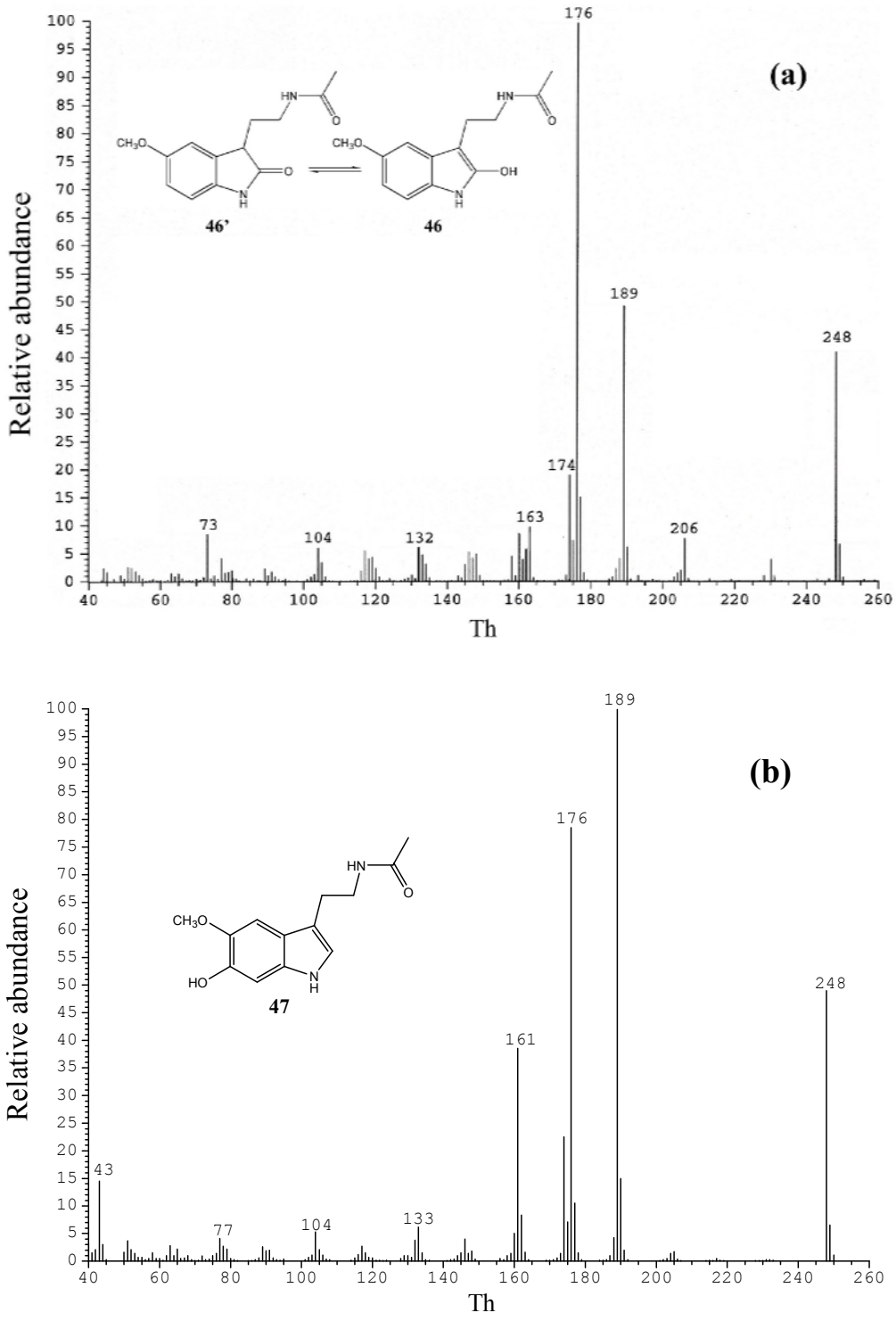
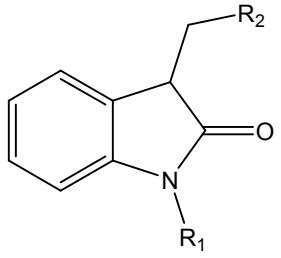


Figure 3: EI/MS (70 eV) of compound **46**[54] (**a**) and of compound **47**[19] (**b**)

The similar behaviour of **46** and **47** suggests the occurrence of hydroxymelatonin structures for both compounds in the gas-phase. Semi-empirical molecular orbital calculations on optimised geometries of radical ions indicate that the structure $\mathbf{46}^{+\cdot}$ is thermodynamically more stable than that of $\mathbf{46'}^{+\cdot}$ (22 kJ mol^{-1}

ca.), while an opposite result is found for the neutral molecules. Even with the approximation and limitation due to semiempirical method calculations, such a result could justify the mass spectrum pattern, since an isomerisation **46'**$^{+\cdot}$ → **46**$^{+\cdot}$ could occur before the fragmentation.[36] The EI/MS of six simple oxindoles **48-53** (Table 13), together with those of several pseudoindoxyle and indolenine derivatives, have been studied by Rodrìguez et al.[54]

Table 13: Principal ions in the 70 eV EI/MS of 3-substituted oxindoles **48-53**



48:	$R_1 = H$	$R_2 = H$
49:	$R_1 = H$	$R_2 = C_6H_5$
50:	$R_1 = H$	$R_2 = CO_2CH_3$
51:	$R_1 = H$	$R_2 = CON(CH_3)_2$
52:	$R_1 = CH_3$	$R_2 = CON(CH_3)_2$
53:	$R_1 = (CH_2)_2CN$	$R_2 = CON(CH_3)_2$

48		**49**		**50**		**51**		**52**		**53**	
Th	%	Th	%	Th	%	Th	%	Th	%	Th	%
147	60, $M^{+\cdot}$	223	29, $M^{+\cdot}$	205	18, $M^{+\cdot}$	218	29, $M^{+\cdot}$	232	27, $M^{+\cdot}$	271	53, $M^{+\cdot}$
132	19	205	2	173	14	173	8	160	96	225	15
118	100	146	5	162	2	146	74	146	22	199	21
104	28	132	21	145	100	145	100	128	100	158	100
		117	2	132	13	128	41	117	64	146	17
		104	4	117	18	117	70	103	22	128	26
		91	100	104	4	104	11	91	50	117	11
				90	8	90	28	72	76	103	7
						72	57	42	88	72	26
						46	96				

Relatively abundant molecular ions are present, and two main fragmentation routes have been evidenced. The first one involves the loss of the 3-substituent CH_2R_2 as radical (affording the ions at 132 Th for **48-50** and at 146 Th for **52**), followed by CO elimination. The second one involves the loss of $R_2^{\cdot}$ (not reported for **50**), yielding ions which undergo competitive losses of $H^{\cdot}$ and H_2CO.

The benzylic cleavage, affording $CH_2R_2^{\cdot}$ loss, should be related to the oxindole structure, whereas the R_2 loss could be related to the 2-hydroxyindole structure, so indicating that in some extent a tautomerism of the molecular ions could occur.

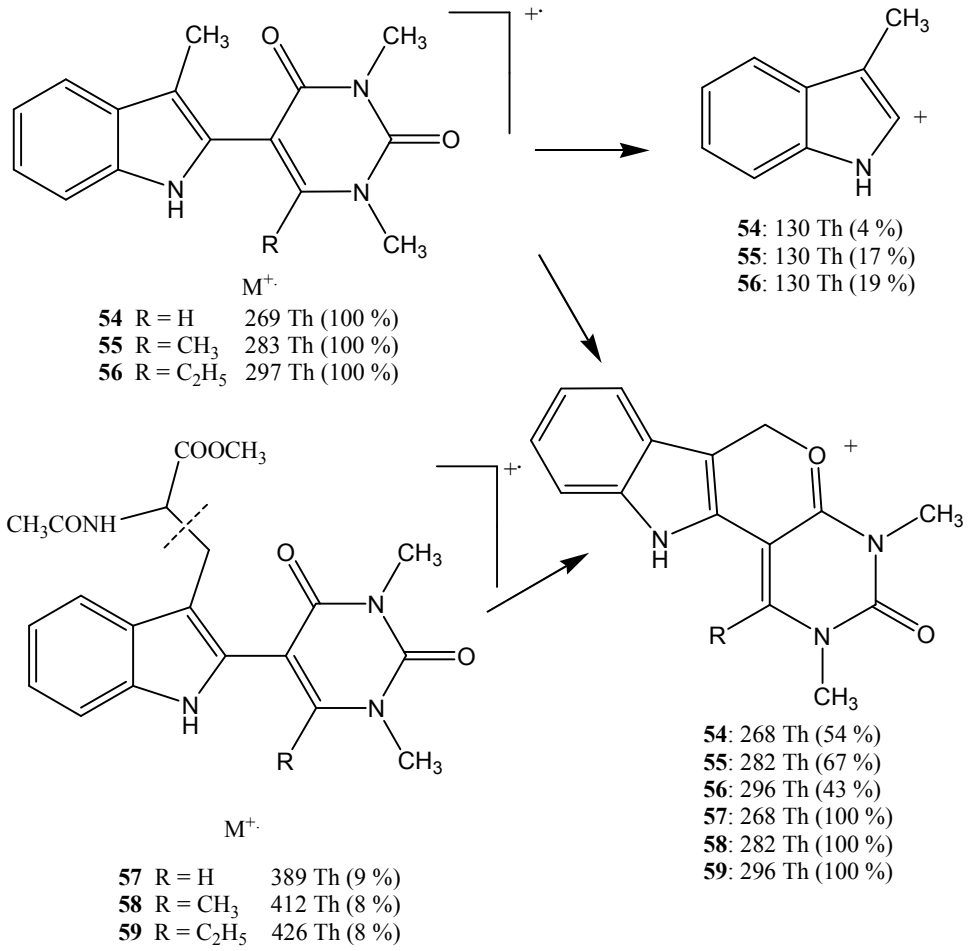
Each oxindole also gives characteristic fragmentations of its R_2 substituent. The molecular ions of **50** undergo consecutive methanol and CO eliminations and a similar behaviour is observed for **51**, which shows dimethylamine elimination followed by CO loss from the molecular ions, affording the ions at 173 Th and 145 Th, respectively. In the EI/MS of **51** an intense peak due to dimethylamonium ions at 46 Th is also observed. The base peak, in the EI/MS of **49**, is due to the tropylium ions at 91 Th and that of **53** (at 158 Th)

to the loss of CH_3CN from the $[M - R_2]^+$ ions (199 Th). Oxindoles **51-53** give also abundant ions at 72 Th, due to the $[O=C=N(CH_3)_2]^+$ ions.

Finally, the loss of CH_2 from the ion at 117 Th $[M-CH_2R_2 - CO]^+$ to give the ion at 103 Th, reported for compound **52** and **53**,[54] is not convincing, as methylene elimination is generally not occurring in EI/MS.

2.7. Variously substituted indoles

The EI/MS of functionalised indoles, i.e. aldehydes, ketones, carboxylic acids, amides, esters and nitriles, offer very few surprises, as they are dominated by the characteristic fragmentation of the functional group. The breakdown of the indole ring also occurs as consecutive reactions. Proximity effects involving the NH hydrogen migration in elimination reactions frequently take place for 2- or 6-substituted carboxyl derivatives.[20] Even if the EI induced fragmentations of variously substituted indoles do not show relevant aspects, the easy identification of the substituents, makes the EI/MS an useful tool for structural characterisation of relatively complex derivatives.

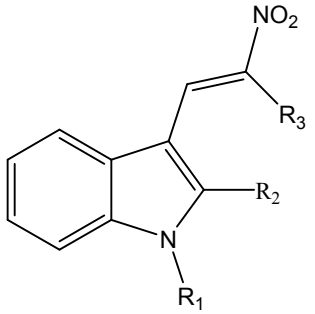


Scheme 16

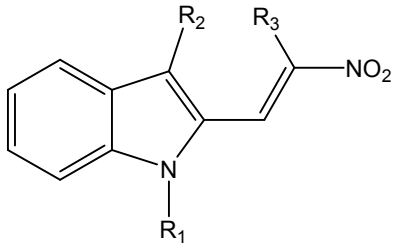
The EI/MS of 1,3-dimethyl-5-(3-alkyl-1H-indol-2-yl)-uracils **54-59** have been studied by Plaziak and Celewicz.[55] The molecular ions of **54-56** are responsible of the base peaks, while they show a relatively small abundance for **57-59**. The main fragmentation involves the loss of $H^{\cdot}$ for **54-56** and of the $CH(NHCOCH_3)COOCH_3$ radical for **57-59**, for these latter compounds the resulting ions are responsible of the base peaks. However, the cyclic structure (Scheme 16) attributed to the product ions, was not supported by experimental data, so it results only speculative. These ions lose the substituent linked at 6-position of

uracil as radical, while compounds **54** and **57** give raise to fragmentation reactions of the uracil ring. Finally, the cleavage of C-5 uracil-C-2 indole bond, affording the ions at 130 Th is observed for **54-56.**

Table 14: Relative abundances of the main peaks in the 70 eV EI/MS of 3-(2'-nitrovinyl)-indoles **60-71** and of 2-(2'-nitrovinyl)-indoles **72-79**



60-71



72-79

Compound	R_1	R_2	R_3	$M^{+\cdot}$		$[M\text{-}NO_2H]^+$		$[M-OH]^+$		$[M\text{-}NO_2H\text{-}R_3]^+$	
				Th	%	Th	%	Th	%	Th	%
60	H	H	H	188	100	141	80	171	9	140	32
61	CH_3	H	H	202	100	155	80	185	20	154	36
62	H	CH_3	H	202	68	155	74	-	-	154	60
63	CH_3	CH_3	H	216	100	169	81	-	-	168	69
64	H	C_6H_5	H	264	26	217	100	-	-	216	42
65	CH_3	C_6H_5	H	278	53	231	82	261	1	230	36
66	H	H	CH_3	202	100	155	61	185	9	140	9
67	CH_3	H	CH_3	216	100	169	75	199	3	154	31
68	H	CH_3	CH_3	216	95	169	92	199	8	154	72
69	CH_3	CH_3	CH_3	230	88	183	100	213	9	168	94
70	H	C_6H_5	CH_3	278	47	231	100	-	-	216	26
71	CH_3	C_6H_5	CH_3	292	50	245	100	275	1	230	41
72	H	CH_3	H	202	98	155	75	185	16	154	100
73	CH_3	CH_3	H	216	100	169	91	199	35	168	99
74	H	C_6H_5	H	264	39	217	100	247	2	216	36
75	CH_3	C_6H_5	H	278	100	231	98	261	2	230	58
76	H	CH_3	CH_3	216	100	169	39	199	7	154	49
77	CH_3	CH_3	CH_3	230	100	183	42	213	15	168	3
78	H	C_6H_5	CH_3	278	80	231	94	261	2	216	20
79	CH_3	C_6H_5	CH_3	292	100	245	91	275	2	230	82

The EI/MS of 3-(2'-nitrovinyl)-indoles **60-71** and of 2-(2'-nitrovinyl)-indoles **72-79** have been reported by Rodrìguez *et al.* (Table 14).[37] The molecular ions of **60-79** are very abundant, being responsible of the base peak for several derivatives. The other common fragmentation routes involve the loss of HNO_2 followed by the loss of R_3 as radical. Most of these compounds lose OH radical. The abstraction of the

olefinic hydrogen has been claimed to be involved in $OH^{\cdot}$ and HNO_2 losses. The base peak at 44 Th for compound **62** has been explained by loss of acetylene from the $[M - HNO_2 - R_3]^+$ species, affording the ion at 128 Th which, by fragmentation of the indole ring, gives the $C_2H_6N^+$ ion. The base peaks of compounds **68**, **72** and **78** at 168 Th, 154 Th and 230 Th (not reported in Table 14), respectively, are due to the consecutive losses of HNO_2 and $H^{\cdot}$ from the molecular ions.

The base peak of compound **65** at 217 Th (not reported in Table 14) has been attributed to the consecutive losses of HNO_2 and CH_2 from the molecular ions. The Authors attributed the CH_2 loss deriving from R_1 and asserted that all the described fragmentation routes were supported by metastable ion data. However, in our opinion, the not common CH_2 loss is doubtful.

3. Photo-ionisation

It is possible to produce ionisation by means of a beam of ultraviolet light of sufficiently short wavelength. The use of photons has the advantage that the energy of the bombarding particle is accurately known. The first combination of photo-ionisation (PI) and mass spectrometry was reported by Lossing and Tanaka.[56]

3.1. Indoles and methylindoles

The only paper concerning PI/MS of simple indoles is reported by Hager and Wallace.[57] They studied indole **1**, 5-methylindole **2a**, 7-methylindole **2b**, 2-methylindole **3a**, 3-methylindole **3b** and 1-methylindole **4** by two-laser photo-ionisation supersonic jet mass spectrometry. The cooling of the molecular internal degree of freedom, by use of supersonic expansion,[58] concentrate population in the lowest vibrational and rotational levels of the ground electronic state. This implies a substantial peak sharpening that dramatically simplify the electronic spectra. Furthermore, the use of moderate light intensities makes this ionisation technique very soft, leading to the exclusive production of molecular ions in the mass spectra.[59,60] The mass spectral photoionisation results for **1**, **2a**, **2b**, **3a**, **3b** and **4** are summarised in Table 15.

Table 15: Adiabatic ionisation energies (IE) for compounds **1**, **2a**, **2b**, **3a**, **3b** and **4**

Compound	**1**	**2a**	**2b**	**3a**	**3b**	**4**
IE, eV	7.7602	7.3799	7.7136	7.6708	7.5143	7.4008

The presence of methyl group, on depending of its position, induces valuable differences in the adiabatic ionisation energy. The major perturbation effects are observed for **2a** and **4** compounds. These significant differences of the adiabatic ionisation energies make the technique a powerful and versatile tool for analytical purposes. In fact it is possible to distinguish and quantify even a mixture of these isomers also at trace levels.

4. Electron capture ionisation

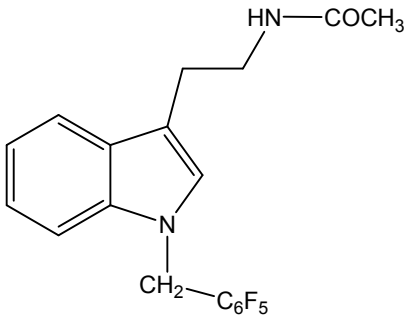
The low sensitivity for the production of negative ions relative to positive ions under EI conditions led to the use of a gas to obtain thermal electrons in order to improve resonance electron capture yield. In fact, chemical ionisation plasmas contain electrons of low energy produced either trough collision deactivation of those directly arising from the filament, or mostly from primary ionisation reactions of the gas that generate

two low-energy electrons. Even if the gas into the ion source has the above described function, this technique is often indicated with the misleading term "Electron Capture Negative Chemical Ionisation (ECNCI)". However, elements with high electron-affinity must be present in the molecule to give high ionisation efficiency.[61-63] Hence, indoles should be derivatised by introduction of fluorinated groups.

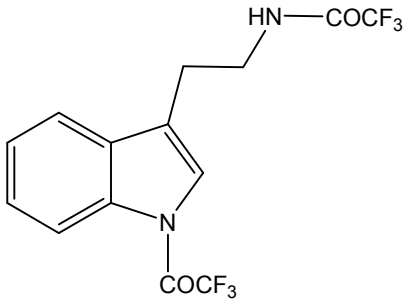
4.1. Tryptamine derivatives

Bosin and Faull[64] developed procedures for the isolation of pharmacologically active indoles from biological samples and for introduction of electron-capturing groups (pentafluorobenzyl or trifluoroacetyl). In this context, Table 16 reports the electron capture ionisation (methane) mass spectra of indole ethylamine derivatives **80** and **81**. In the same paper several fused indoles, not treated in the present review, are also reported. The negative molecular ions $M^{-\cdot}$ are abundant in the spectra of both **80** and **81**, accompanied by ions corresponding to HF elimination, while the base peak for **80** (at 201 Th) is due to the loss of the stable pentafluorobenzyl radical.

Table 16: Relative abundances of the negative ion mass spectra of compounds **80** and **81**



80



81

Compounds	**80**		**81**	
Ions	Th	%	Th	%
$M^{-\cdot}$	382	45	352	100
$[M - HF]^{-\cdot}$	362	20	332	50
$[M - C_6F_5CH_2]^-$	201	100	-	-

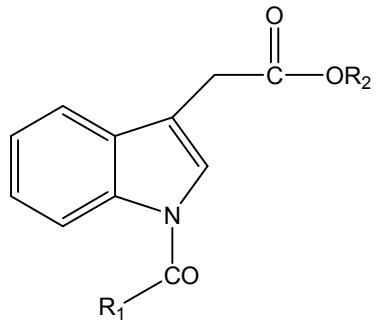
4.2. 5-Methoxyindole-3-acetic acid derivatives

The ECI/MS (methane) of the N-trifluoroacetyl/pentafluoropropionyl-O-trifluoro/pentafluoropropyl/ heptafluorobutyl ester derivatives **82-89** (Table 17) of 5-methoxyindole-3-acetic acid (an endogen methoxyindole found in the pineal gland of mammals,[65] including humans[66]) as well as those of the corresponding 5-[$^2H_3$]-methoxyindole-3-acetic acid and 5-methoxyindole-3-[$^2H_2$]-acetic acid deuterium labelled derivatives, have been reported by Li et al. [67]

The fragmentation depends in large extent by trifluoroacetylation versus pentafluoracylation at the indole nitrogen. For the N-trifluoroacylated derivatives **82-84** relatively abundant molecular ions $M^{-\cdot}$ were

observed, and the base peaks are due to the $[M - HF]^{-\cdot}$. The other significant fragment ions were the $[M - CF_3CO]^-$ and $[M - CH_2CO_2R_2]^-$ which arise by simple carbon-nitrogen bond cleavage at the indole nitrogen or by simple carbon-carbon bond cleavage at the 3-position side chain, respectively. Interestingly, the negative charge is mainly retained in the indole nucleus rather than in the trifluoroacetyl CF_3CO or perfluoroalkyl R_2 groups. In this case, the stabilization through charge delocalisation plays a role more important than the presence of the electronegative fluorine for the charge repartition.

Table 17: Relative ion abundances in negative ion mass spectra of compounds **82-89**



82:	$R_1 = CF_3$	$R_2 = CF_3CH_2$
83:	$R_1 = CF_3$	$R_2 = C_2F_5CH_2$
84:	$R_1 = CF_3$	$R_2 = C_3H_7CH_2$
85:	$R_1 = C_2F_5$	$R_2 = CF_3CH_2$
86:	$R_1 = C_2F_5$	$R_2 = C_2F_5CH_2$
87:	$R_1 = C_2F_5$	$R_2 = C_3H_7CH_2$
88:	$R_1 = CF_3$	$R_2 = C_6F_5CH_2$
89:	$R_1 = C_2F_5$	$R_2 = C_6F_5CH_2$

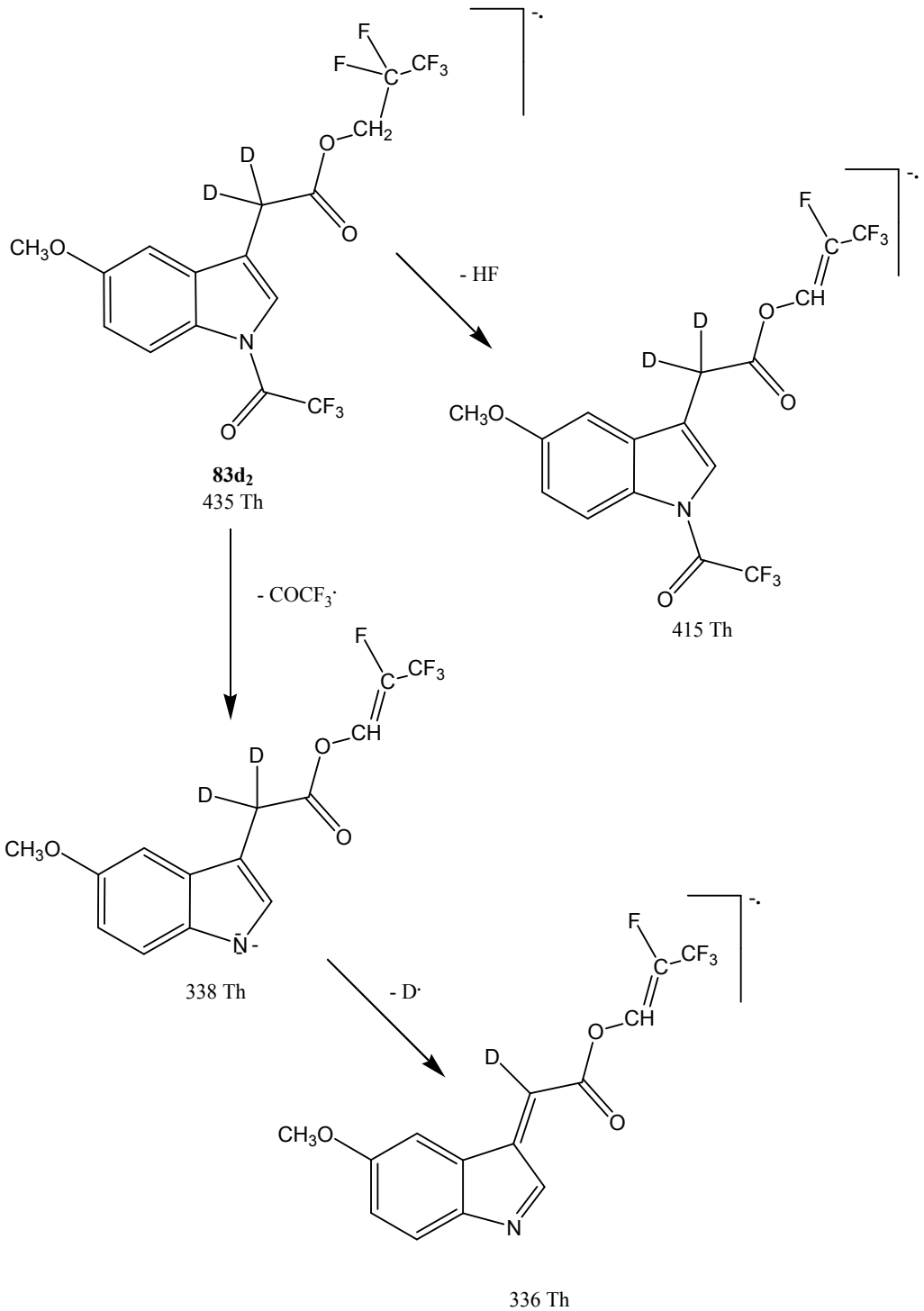
Comp	$M^{-\cdot}$ [a]	$[M - HF]^{-\cdot}$ [b]	$[M - HF - CF_2CO]^{-\cdot}$ [b]	$[M - CF_3CO]^-$ [a]	$[M - CH_2CO_2R_2]^-$ [a]	Others
	Th (%)	Th (%)	Th (%)	Th (%)	Th (%)	Th (%)
82	383 (48)	363 (100)	285 (33)	286 (56)	242 (18)	-
83	433 (46)	413 (100)	335 (44)	336 (49)	242 (21)	-
84	483 (51)	463 (100)	385 (60)	386 (55)	242 (36)	300 (20)
		$[M - HF]^{-\cdot}$ [b]	$[M - HF - C_2F_4CO]^{-\cdot}$ [b]	$[C_2F_5CO]^-$	$[C_2F_4CO]^{-\cdot}$	
85	433 (-)	413 (9)	286 (40)	147 (100)	128 (5)	-
86	483 (-)	463 (9)	335 (419	147 (100)	128 (5)	-
87	533 (-)	513 (12)	386 (44)	147 (100)	128 (8)	-
		$[M - R_2]^-$ [b]	$[M - CO_2R_2]^-$ [a]	$[C_2F_5CO]^-$	$[C_2F_4CO]^{-\cdot}$	
88	481 (-)	300 (100)	256 (57)	147 (-)	-	204 (15)
89	531 (-)	350 (89)	306 (100)	147 (80)	128 (54)	204 (63)

[a] Shifted up 3 and 2 mass unities for the corresponding derivatives 5-[$^2H_2$]methoxyindole-3-acetic acid and 5-[$^2H_2$]methoxyindole-3-[$^2H_2$]acetic acid, respectively.

[b] Shifted up 3 and 1 mass unities for the corresponding derivatives 5-[$^2H_2$]methoxyindole-3-acetic acid and 5-[$^2H_2$]methoxyindole-3-[$^2H_2$]acetic acid, respectively.

Further, relatively abundant $[M - HF - CF_2CO]^{-\cdot}$ fragment ions were observed for N-trifluoroacetyl derivatives **82-84**. Similarly, the spectra of the N-pentafluoropropyl derivatives **85-87** show relatively intense peaks for the $[M - HF]^{-\cdot}$ and $[M - HF - C_2F_4CO]^{-\cdot}$ ions. Some contrasting questions arise about these

fragmentations. In fact the Authors asserted that "*When the methylene hydrogens in the 3-position side-chain were replaced by deuterium, the [M - HF]$^{-\cdot}$/[M - HF - CF_2CO]$^{-\cdot}$ ions became the [M - DF]$^{-\cdot}$/[M - DF - CF_2CO]$^{-\cdot}$ ions, as exemplified in the ECNCI mass spectrum of the n-pentafluoropropyl ester derivative of 5-methoxyndole-3-[$^2H_2$]acetic acid shown in Fig.2. Thus HF elimination from the molecular ion involved specifically the H/D in the methylene unit at the 3-position side chain, and most probably the fluorine of the trifluoroacetyl group at the indole ring*".[67]



Scheme 17

However, the mass spectrum reported in the original paper[67] shows that the molecular ions of the α,α-dideuterio isotopomer of **83** (**83d$_2$**) at 435 Th lose only HF, giving the ions at 415 Th, not DF as asserted and

reported in the Table 17 (Table 1 of the original paper). Instead the peak for $[M - HF - CF_2CO]^{-\cdot}$ at 335 Th for the unlabelled derivative **83**, really becomes 336 Th for **83d$_2$** , evidencing the presence of the $[M - DF - CF_2CO]^{-\cdot}$.

A similar behaviour is also observed for the α,α-dideuterio isotopomer of **85** (**85d$_2$**). In fact the mass spectrum of this latter compound shows the $[M - HF]^{-\cdot}$ ions at 415 Th and those at 286 Th due to $[M - DF - C_2F_4CO]^-$. If this is true, two simple competitive reaction channels could explain these findings:

- HF elimination (for both labelled and unlabelled derivatives) from the molecular ions, involving probably an ester methylene hydrogen (trough β-elimination reaction);
- loss of $CF_3CO^{\cdot}$ or $C_2F_5CO^{\cdot}$ followed by the H loss (D for α,α-dideuterio labelled compounds) arising from the α-methylene group of the side chain linked at 3-position.

This could easily account for the $[M - HF - CF_2CO]^{-\cdot}$ for **83** and $[M - HF - C_2F_4CO]^{-\cdot}$ for **85**, that should be better represented as $[M - CF_3CO - H]^-$ and $[M - C_2F_4CO - H]^{-\cdot}$ ions, respectively. This behaviour is summarised for dideuterio derivative **83d$_2$** in Scheme17. Incidentally, a large delocalisation involving also the carboxyl oxygen is achieved for the ions at 336 Th.

Further, no molecular ions were found in the spectra of N-pentafluoropropionyl derivatives **85-87**, that present the base peak at 147 Th due to the $C_2F_5CO^-$ ions. The O-pentafluorobenzyl derivatives **88** and **89** show abundant $[M - C_6F_5CH_2]^-$ and $[M - C_6F_5CH_2CO_2]^-$ ions.

5. Conclusions

The high stability of the indole moieties also as radical cations obtained by EI is evidenced by the scarcity of indole ring fragmentation reactions from the molecular ions that are essentially observed for the simple indole **1** itself and for arylindoles. Generally, breakdown of the nucleus occurs following the more favoured fragmentations involving the substituents that allows an easy identification of the nature of the substituents. In particular, alkyl substituents undergo α-cleavage (with respect to the indole ring), it follows ring expansion with final ring opening and ring cleavage. These processes have been studied also with the use of labelled compounds.

Concerning oxindoles, for which the tautomeric hydroxyl form has also to be considered, it has been individuated that some fragmentation reactions can be used as distinctive for each form.

The structural information on doubly charged molecular ions and their fragmentation reactions, either naturally occurring or collision induced, have been discussed.

PI/MS studies have evidenced that the adiabatic ionisation energy is strictly related to the position of the methyl group in methylindoles.

The radical anions formed by ECI do not produce ring cleavage reactions. It is worth of note that, in spite of the presence of perfluoroalkyl and/or perfluoroacyl groups, the negative charge is mainly retained in the indole moiety. This should reflect the high stability of indolyl anions in the gas phase, that parallels the relatively high acidity of indoles in condensed phase.

Finally, HR/MS, MIKE, linked scan, ER/MS and MS/MS methods resulted powerful and suitable for identification and characterisation of indoles, including isomers. This is of particular interest, as several natural and synthetic indoles and their metabolites explicate important biological and/or pharmacological

activities. In fact, their characterisation with other techniques is not easily achieved when they are in present (as often occurs) at trace levels in living organisms.

Acknowledgements

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SYNTHETIC USE OF 2*H*-AZIRINES IN PREPARATIVE ORGANIC CHEMISTRY

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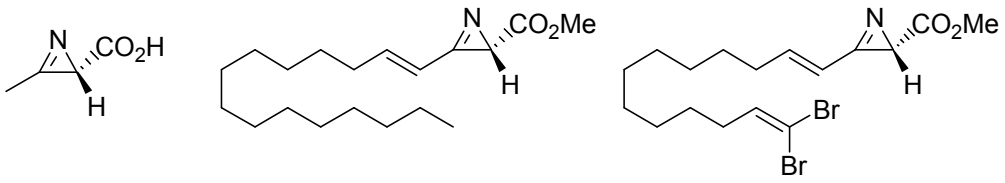
Abstract. *The high synthetic potential of 2H-azirines as valuable reagents for the construction of acyclic compounds and heterocycles is discussed.*

Contents

1. Introduction

The azirine ring has been found in several natural products. The first 2*H*-azirine-containing natural product isolated was Azirinomycin[1] **1** (Figure 1). Azirinomycin, isolated from *Streptomyces aureus*, and its methyl ester were found to exhibit broad-spectrum antibiotic activity *in vitro* against both gram-positive and gram-negative bacteria.[2] More recently, the azirine-containing natural products (*R*)-(–)- and (*S*)-(+)-dysidazirine **2** and (*S*)-(+)-antazirine **3** were isolated from the marine sponge *Dysidea fragilis* (Figure 1).[3,4] Two isomeric azirines have been designated by *Chemical Abstract* and *The Ring Index*,[5] as 1*H*-azirine **4** and 2*H*-azirine **5** (Figure 2). The structure, biological applications, and the synthetic chemistry of these

heterocycles have been extensively explored since the mid–1960s.[6] This review will concentrate on the chemistry of monocyclic 2*H*-azirines as key intermediates for the preparation of acyclic and cyclic nitrogen containing derivatives.



Azirinomycin **1** (*S*)-(+)-Dysidazirine **2** (*S*)-(+)-Antazirine **3**

Figure 1. Some natural products containing the azirine ring.

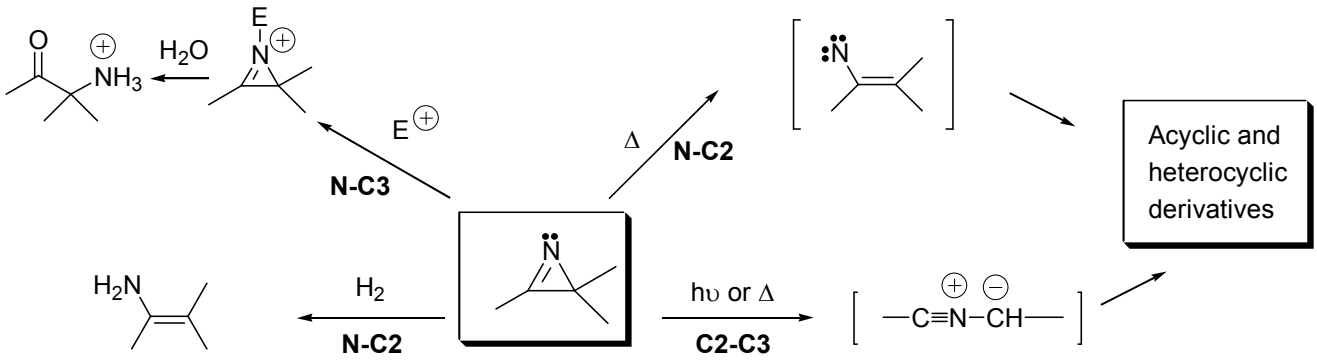
4 **5**

Figure 2. 1*H*- and 2*H*-azirines.

2. Synthetic application of 2*H*-azirines to the preparation of nitrogen-containing derivatives

2.1. Synthesis of acyclic compounds

The chemistry of 2*H*-azirines has been explored extensively due to the high reactivity of this ring system. These substrates are ambident reagents and are capable of acting in organic reactions as nucleophiles involving the nitrogen lone pair and electrophiles through the imine carbon-nitrogen bond (N-C3) (Scheme 1). The high ring strain, the reactive π-bond and the lone pair on the nitrogen atom favour the regioselective ring cleavage of the cyclic system. Ring opening of azirines by thermal and photochemical reactions could involve carbon-nitrogen single bond cleavage (N-C2), to give unstable nitrenes or enamines.[6o,7] On the other hand, cleavage of the carbon-carbon single bond (C2-C3) of 2*H*-azirines is less common than the former and the intermediates formed, such as imino diradicals or nitrile ylides, can react further with a wide range of reagents leading to acyclic and cyclic derivatives (Scheme 1).[8] In the following sections we will focus on the use of azirine derivatives for the synthesis of acyclic compounds such as amines, imines, enamines, azadienes, amino acids, peptides and related structures.

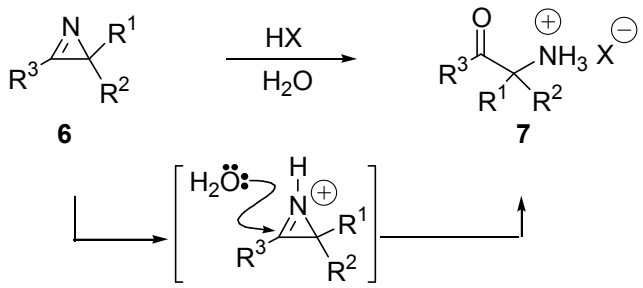


Scheme 1

2.1.1. Amines

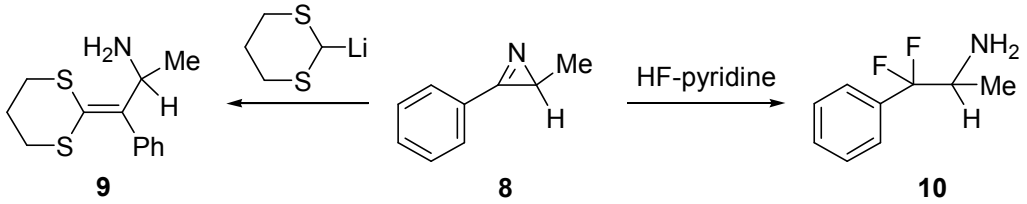
The most common reaction of azirines involves the addition of nucleophiles to the ring. Due to the strain of the three-membered ring, the electrophilic character of the C-N double bond is higher than in a normal imine. Therefore, azirines react with nucleophiles at the N-C3 double bond, to produce substituted

aziridines,[6l,6m] which may undergo further reaction by ring-opening. Acid catalysed hydrolysis of azirines **6** to α-aminoketones[6l,9] or their corresponding salts **7** represents the simplest reaction of these compounds (Scheme 2).



Scheme 2

Allyl amines result either from the addition of diazomethane to 2-aryl-3-methyl-2*H*-azirine[10] or by the reaction of lithium derivatives of 1,3-dithianes on 3-phenyl-2*H*-azirines **8**. In this case, the reaction affords *C*-functionalised aziridines that open to give primary allyl amines **9** (Scheme 3).[11] However, treatment of azirines **8** with hydrogen fluoride/pyridine (Olah's reagent) promotes the ring-opening leading to the formation of primary amines **10**, with the introduction of fluorine atoms in the β-position to the nitrogen, such as the methamphetamine derivative shown in Scheme 3.[12] The synthesis of fluorine-containing compounds, especially α-fluoroalkylamines,[13] is an area of increasing interest in organic chemistry because the incorporation of fluorine into a molecule dramatically alters its physical, chemical and biological properties.[14]



Scheme 3

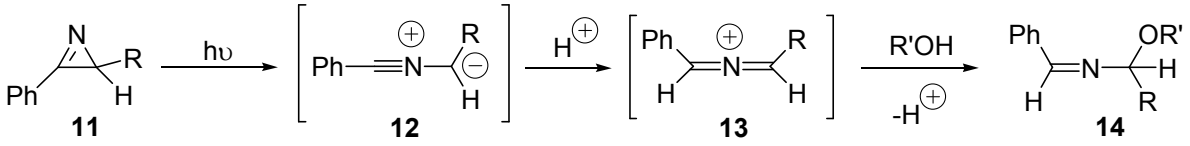
2.1.2. Imine and enamine derivatives

In this section we will focus on the use of azirines in the preparation of more complex nitrogen-containing open-chain derivatives such as imines, enamines and azadienes.

2.1.2.1. Imines

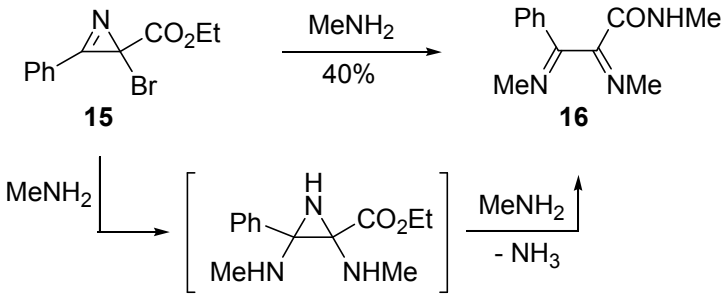
Acid-catalysed nucleophilic addition of aniline to 2,2-dimethyl-3-phenyl-2*H*-azirine in the presence of perchloric acid has been observed to give α-ammonioisobutyrophenone anil perchlorate.[15] However, on photolysis of 2*H*-phenylazirines **11** in acetonitrile or alcoholic solutions with 248 nm laser light, benzonitrile ylides **12** are formed (Scheme 4). With alcohols as solvents, the nitrile ylides are protonated[16] to yield azallenium cations **13**, which can be trapped by the alcohol leading to the formation of alkoxyimines **14**. These compounds were obtained in the course of a mechanistic study on reactivity of 2*H*-azirines, and, therefore, the reactions were carried out at micromoles scale instead of preparative scale. Nevertheless,

benzonitrile ylides derived from phosphine oxide **12** (R = $POPh_2$) have been trapped by reaction with water generating the corresponding amides.[17]



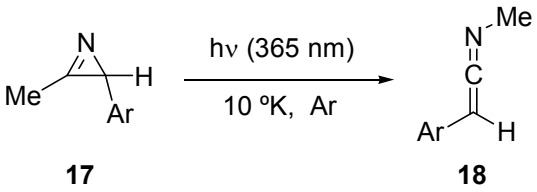
Scheme 4

Diazadienes or α-diimines such as **16** are obtained from 2-halo-2*H*-azirines **15** containing electron-withdrawing groups and a large excess of methylamine (Scheme 5).[18] The reaction consists of a halide displacement and addition to the iminic double bond, followed by opening of the aziridine ring, elimination of ammonia, and amminolysis of the ester group.



Scheme 5

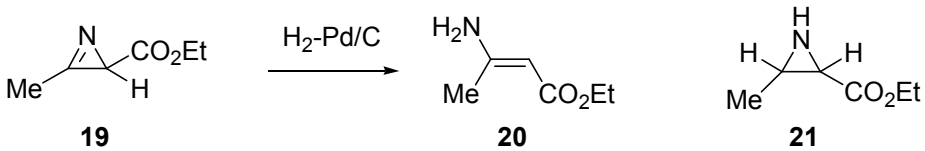
Keteneimines **18** resulting from the photochemical rearrangement of 2*H*-azirines **17** at low temperature matrices were detected by IR spectroscopy, but not isolated.[19] Therefore, so far the reaction has little preparative interest (Scheme 6).



Scheme 6

2.1.2.2. Enamines

Catalytic hydrogenation (palladium or Raney nickel catalyst) surprisingly results in the ring opening of azirines through the N-C2 bond cleavage.[20] The resulting imines or primary enamines are not usually isolated and, in most instances, their existence has only been inferred.

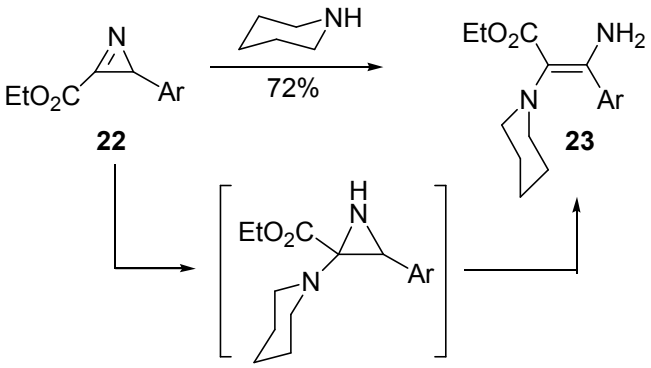


Scheme 7

It seems clear that in order to stabilize the primary enamine group, the presence of an electron-withdrawing group on the β-carbon of the enamine is required.[21] For instance, the reduction of azirine **19**,

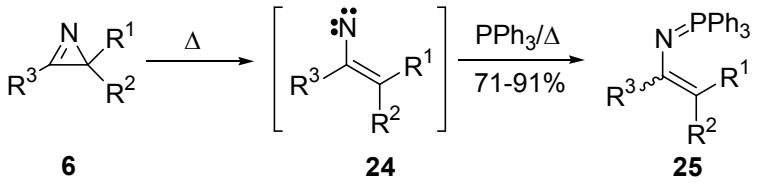
containing the carboxylate group, gives the stabilized enamino ester **20** (Scheme 7), although the reaction may not first proceed through the aziridine **21**, since the latter is difficult to reduce with hydrogen and palladium on carbon.[20a,22]

Recently a new synthesis of primary enamines **23** that seems to involve an N-C3 bond cleavage on 2*H*-azirine-3-carboxylates **22** when they are treated with primary and secondary aliphatic amines, has been reported (Scheme 8).[23]



Scheme 8

N-Protected primary enamines can also be prepared from azirines given that the vinyl nitrenes **24** resulting from the thermal opening of the formyl- or cyano-susbstituted azirines **6** can be trapped by triphenylphosphine to afford conjugated phosphazenes **25** (Scheme 9).[24] These compounds can be considered, from a synthetic point of view, as *N*-functionalised enamines and are similar to the *N*-vinylic phosphazenes obtained by the Staudinger reaction of vinyl azides and phosphines.[25] Nevertheless, the formation of phosphazenes may not necessarily involve the intermediacy of vinyl nitrenes and could also be rationalized *via* direct nucleophilic attack of the phosphines on the nitrogen atoms of the azirines.



6 **24** **25**

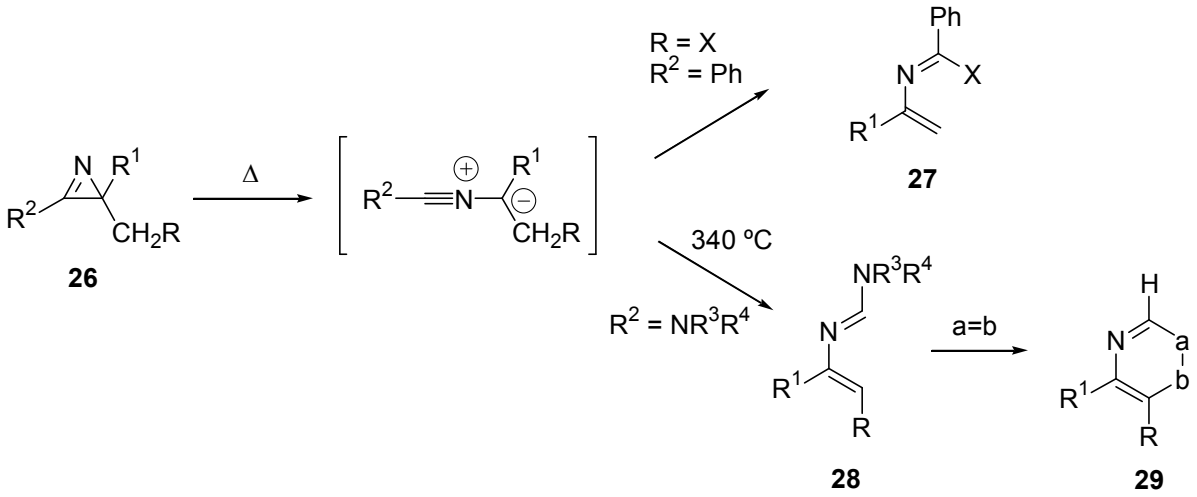
Scheme 9

Likewise, when thermolysis of 2-vinylazirines (R^2 = CH=C(Me)CO_2Me) was carried out in the presence of tris(dimethylamino)phosphine, the nitrene was trapped as the corresponding phosphazene derived from conjugated enamine although other two compounds, resulting from cyclization of the intermediate nitrene were also obtained.[26]

2.1.2.3. Azadienes

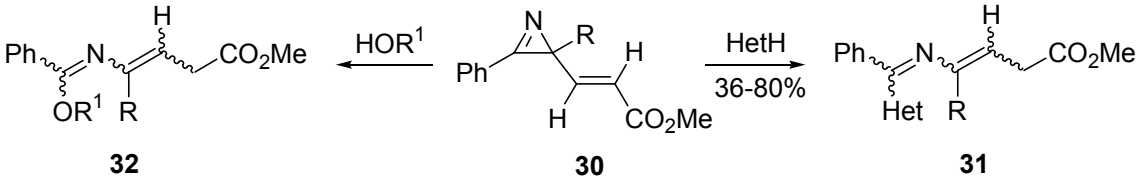
Azirines can also be used for the preparation of heterodienes, versatile synthons in the building of many classes of heterocycles. The isomerization of azirine containing a good leaving group (R = X) to 2-azadiene **27** which happens through a 1,3-dipole intermediate, has been reported.[8f] Moreover, the C2-C3 bond of 3-amino-2*H*-azirines **26** can be cleaved by pyrolysis at 340-400 ºC[27] and the so-obtained 2-azabuta-1,3-dienes of type **28** have proven to be useful heterodienes for the synthesis of heterocycles **29** *via* Diels-

Alder reaction (Scheme 10). In the last decade, 2-azadienes **28** have proved to be excellent synthons for the preparation of nitrogen heterocycles in inter- and intramolecular reactions[28] and less drastic conditions for their preparation have been developed.[29]



Scheme 10

An alternative route to get azadienes such as **31** and **32**, implies the reaction of methyl 3-(2-methyl-3-phenyl-2*H*-azirin-2-yl)prop-2-enoate (or azirineacrylates) **30** with some heterocyclic nucleophiles or simple alcohols such methanol or ethanol (Scheme 11).[30] Hegedus *et al*. reported an elegant method of synthesis of electron rich 1-alcoxy-2-azadienes when Fischer carbenes were exposed to sunlight in the presence of 2*H*-azirines.[31] Likewise, the reaction of azirines with wolfram or molybdenum complexes provides ring-opened compounds *via* initial complexation of the azirine nitrogen with the metal.[32] 3-Amino-2*H*-azirines undergo a ring-opening reaction with cleavage of the N-C2 bond where the major products isolated are acrylylamidines.[33]



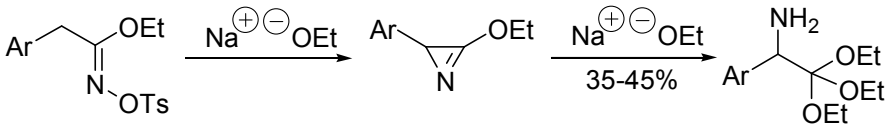
R = H, Me

HetH = imidazole, pyrazole, 2-ethylimidazole, 3,5-dimethylpyrazole

Scheme 11

2.1.3. Amino acids and related amino phosphorus derivatives

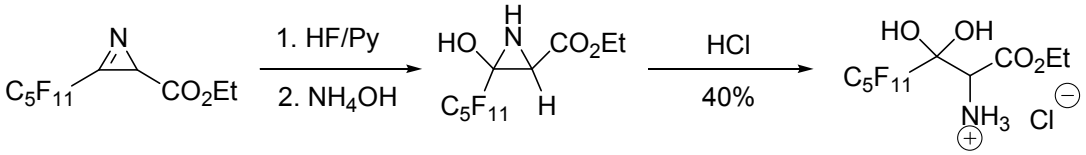
The preparation of α-amino acids derivatives is one of the most important uses of azirines. As mentioned in section 2.1.1, the acid catalysed hydrolysis of azirines produces, through the formation of the corresponding aziridines and subsequent ring-opening, α-aminoketones[11,9a,9b,9c] or their corresponding salts. A light modification of the starting azirine can open new ways for the preparation of α-amino acids. α-Aminoorthoesters **35** are formed in moderate yield by treatment of 3-ethoxyazirines **34** precursors (*O*-tosylhydroxymates **33**) with a excess of sodium ethoxide (Scheme 12).[34] These α-aminoorthoesters, synthetic equivalents of α-amino esters, are converted into the corresponding imines in good yield by reaction with aldehydes.



33 **34** **35**

Scheme 12

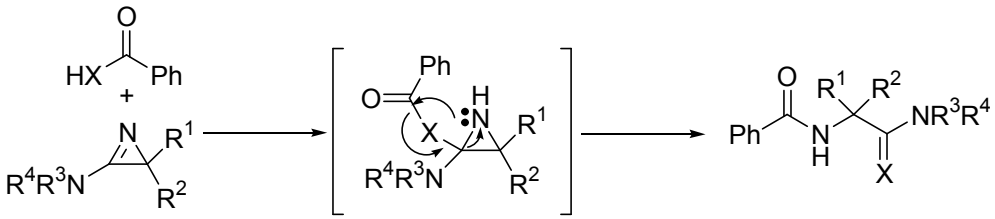
Functionalised amino ester **38**, containing a perfluoro substituent at the β-carbon, has been obtained by addition of HF/pyridine (Olah's reagent) to the highly electrophilic 3-(perfluoroalkyl)-2*H*-azirine[35] **36**. In this case, the intermediate 2-hydroxyaziridine **37** can also be isolated as a stable compound presumably due to the electron-withdrawing perfluoroalkyl group (Scheme 13).



36 **37** **38**

Scheme 13

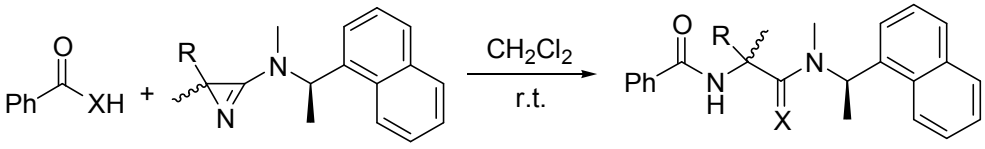
Carboxylic and thiocarboxylic acids can open 2,2-disubstituted-3-amino-2*H*-azirines **39** under mild conditions to furnish diamides[36] **40** (X = O), which are also α,α-disubstituted α-amino acid derivatives, or thiodiamides[36,37] **40** (X = S), respectively, in good yields (Scheme 14).



39 **40**

Scheme 14

This reaction has been extended to 2-monosubstituted-3-amino-2*H*-azirines[38] and to azirines with a chiral substituted amino group. Although better yields were obtained when enantiomerically pure 3-amino-2*H*-azirines **41** were opened with thiocarboxylic acids, the use of carboxylic acids led to optically pure 2,2-disubstituted glycines **43** (Scheme 15).[39]



41

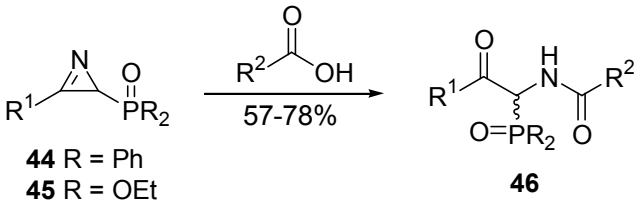
42 X=S 64-99%
43 X=O 39-92%

Scheme 15

These chiral azirines have also been used in peptide synthesis as building blocks to incorporate α,α-disubstituted α-amino acids into model tripeptides, and the thiodiamides (X = S) are useful substrates for the

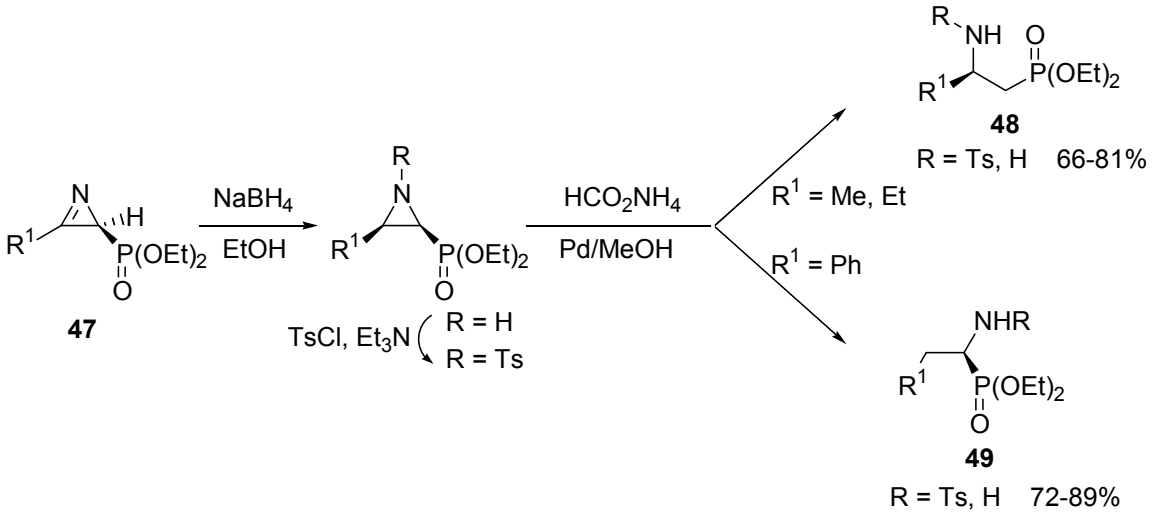
synthesis of enantiomerically pure 1,3-thiazole-5(4*H*)-thiones (*vide infra*). Similarly, addition reactions and cleavage of the C-N double bond of 3-amino-2*H*-azirines occurs upon hydrolysis with potassium hydrogen phosphate in water, with activated phenols or thiophenols,[40] with cyclic enolizable 1,3-diketones,[41] or with sulfinic acids.[33b]

Recently, carboxylic acid promoted ring-opening has been applied for the first time to azirines containing phosphorus substituents, such as 2*H*-azirine-2-phosphine oxides **44** and phosphonates **45** leading to the formation of α-ketamides **46** containing a phosphine oxide or phosphonate group in the α-position (Scheme 16).[42] This reaction can be used as a model of an acid-catalysed ring-opening reaction of these substrates and the generated functionalised ketamides have been used for the preparation of phosphorylated oxazoles (see section 2.2.3.).



Scheme 16

Other phosphorylated analogues of amino acids such as β-**48** and α-aminophosphonates **49** can be obtained in enantiomerically enriched form, by borohydride reduction of 2*H*-azirine-2-phosphonates **47** followed by ring-opening (Scheme 17).[43] Compounds related to those above, such as α-amidophosphine oxides, have been obtained as a result of photochemical cleavage of the C-C bond of 2*H*-azirines, and subsequent trapping of the intermediate nitrile ylide with water.[17]

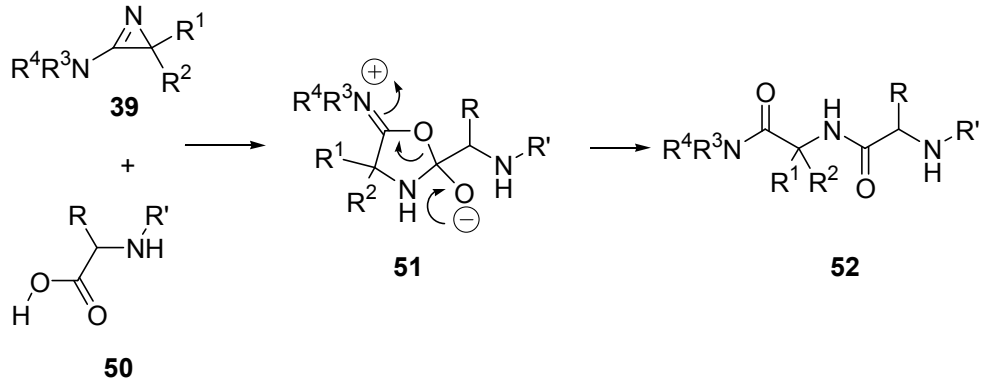


Scheme 17

2.1.4. Peptides and related compounds

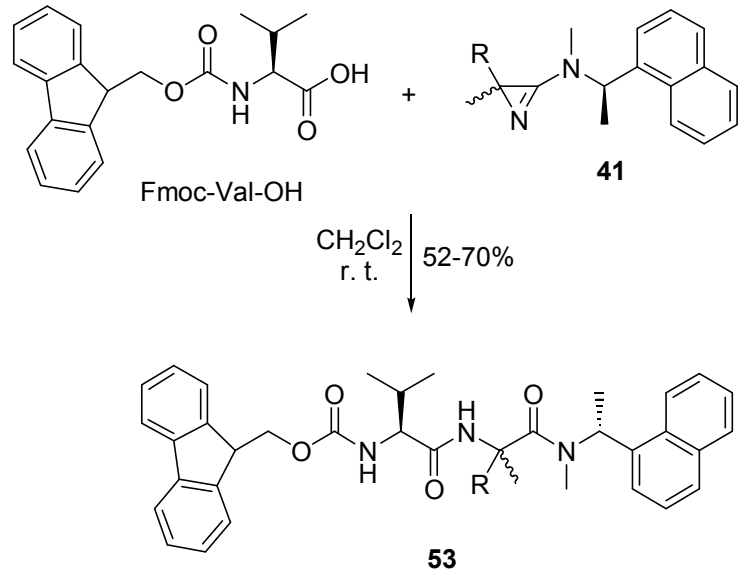
Ring opening of azirines in the presence of acid derivatives can be extended to functionalised carboxylic acids. The use of amino acids instead of carboxylic and thiocarboxylic acids (see section 2.1.3.) for the ring opening of 2,2-disubstituted-3-amino-2*H*-azirines, leads to the synthesis of peptides containing an additional α,α-disubstituted amino acid, as shown in Scheme 18. Thus, 3-amino-2*H*-azirines **39** react

readily with the carboxylic group of an *N*-protected aminoacid **50** followed by ring expansion to form a zwitterionic oxazolone **51** which undergoes ring opening to form a diamide **52**.[6j] It should be pointed out that no additional reagents are required under the very mild conditions needed for the coupling with **39**, and no by-products are observed.



Scheme 18

This so-called "azirine/oxazolone methodology" constitutes an attractive method for insertion of α,α-disubstituted α-amino acids into dipeptides, and has been extended to the use of chiral azirines,[39a] for the preparation of enantiomerically pure dipeptides. In the example shown in Scheme 19, the reaction between unsymmetrically 2,2-disubstituted-2*H*-azirin-3-amines **41** with chiral auxiliary amino groups and the amino acid Fmoc-Val-OH yielded the corresponding dipeptides **53**.

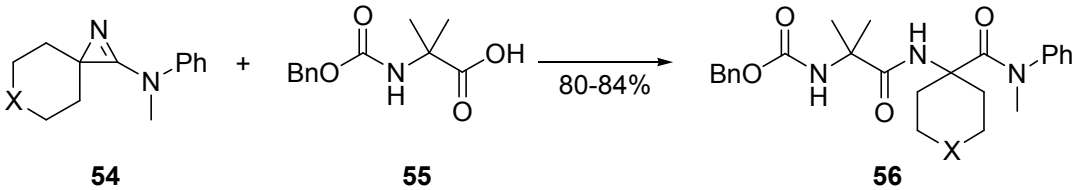


Scheme 19

This methodology has been widely applied to the formation of peptide with backbone modifications. For instance, peptides that contain α,α-disubstituted α-amino acids are of particularly interest because of their conformational constrain, stabilizing or inducing secondary structures such as β-turns, and α- or 3_{10} helices.[44] In this context, heterospirocyclic 3-amino-2*H*-azirines **54** react with aminoacid **55** to produce di- and tripeptides containing heterocyclic α-amino acids **56** (Scheme 20).[45]

Other peptides that can be prepared by using this methodology are those containing α-aminoisobutyric acid (Aib) and isovaline (Iva) amino acids, characteristic members of the peptaibols. In this context, several

3-amino-2*H*-azirines, like those shown in Figure 3, have been prepared and used as synthons of dipeptides containing Aib and Iva in the synthesis of some model peptides.[46] Other azirines derived from proline have also been used as Aib-Hyp ((2*S*,4*R*)-4-hydroxyproline) dipeptide synthons which form tri- or tetrapeptides by treating them with several *N*-protected amino acids or peptides, respectively.[47]



54 **55** **56**

Scheme 20

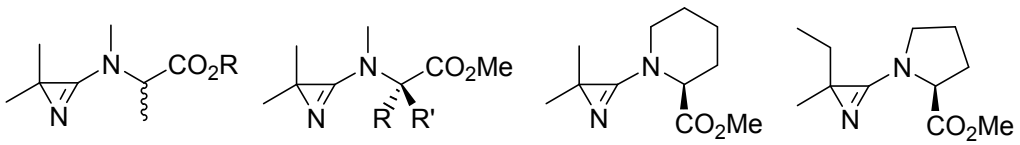
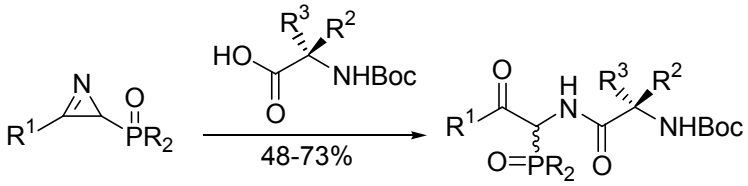


Figure 3

Ring-opening of azirines containing phosphorus substituents **44** and **45** with *N*-protected amino acids provides a useful method to prepare optically active phosphorylated α-ketamides **57**.[48] This formation of pseudo phosphapeptides can be regarded as a peptide chain elongation which introduces a α-ketamide containing a phosponate or a phosphine oxide group into the *C*-terminal end of the aminoacid (Scheme 21).



44 R = Ph
45 R = OEt

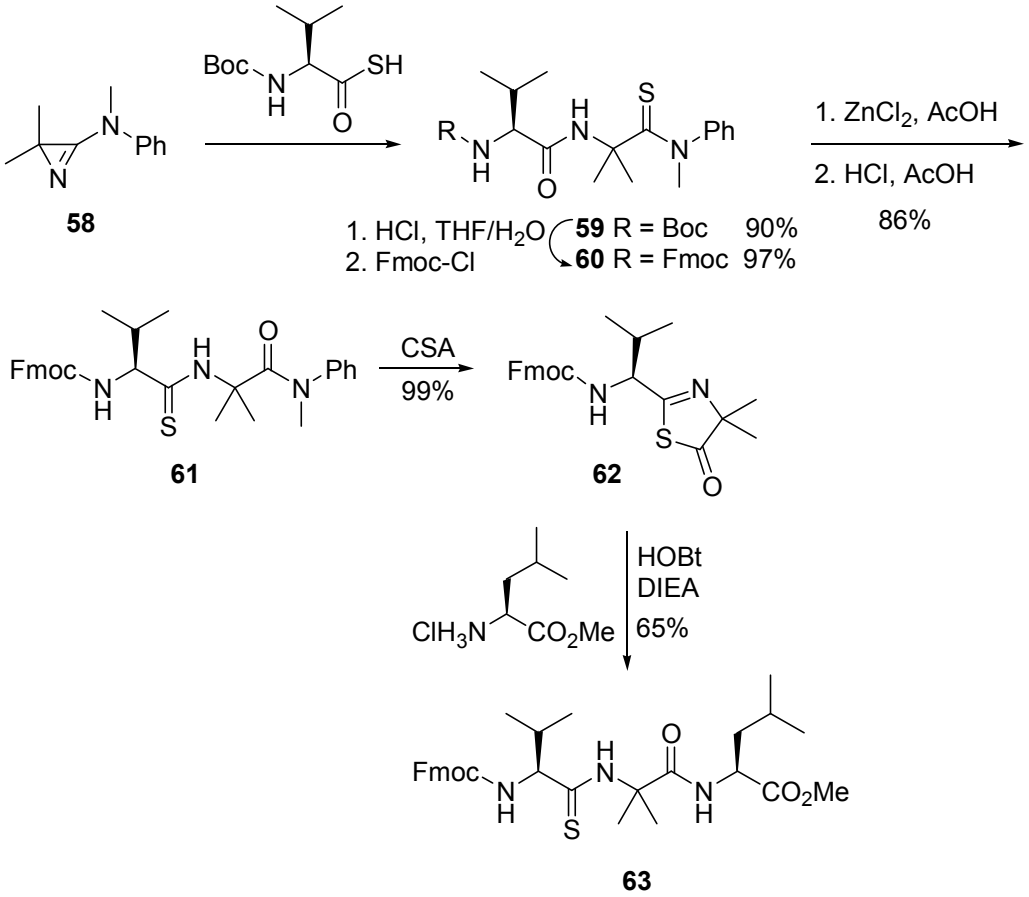
57

Scheme 21

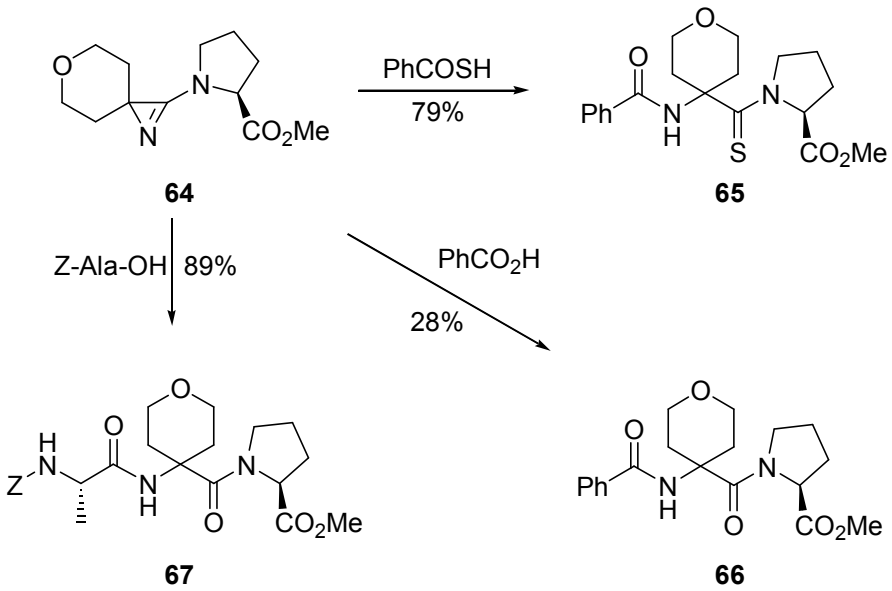
When an *N*-protected α-amino thioacid is employed as the acidic partner of the reaction, endothiopeptides **59**, peptides containing one or more thioamide groups instead of amide bonds,[49] are obtained. In order to avoid the epimerisation of the product, a variation of the "azirine/oxazolone" method that includes a novel thioamide isomerization, has been developed and applied to the synthesis of **63**, the segment of a decaendothiopeptide, as shown in Scheme 22.[49d] Further modifications of this procedure have been carried out to prevent the formation of 1,3-thiazol-5(4*H*)-imines and 1,3-oxazol-5(4*H*)-imines during the activation of the peptide with coupling reagents, and to prepare endothiopeptides that contain more than one amide group replaced by a thioamide function.[50]

The combined use of heterospirocyclic 3-amino-2*H*-azirines **64** derived from proline and simple carboxylic or thiocarboxylic acids gives good yields of dipeptides **66** or endothiodipeptides **65**, respectively. The reaction also works with *N*-protected amino acids such as Alanine and Leucine to form tripeptides **67**, which after hydrolysis, can react again with an azirine to produce tetrapeptides (Scheme 23). This method

has been employed for the synthesis of a nonapeptide which is an analogue of the *C*-terminal nonapeptide of the antibiotic peptaibol *Trichovirin* I 1B.[51]



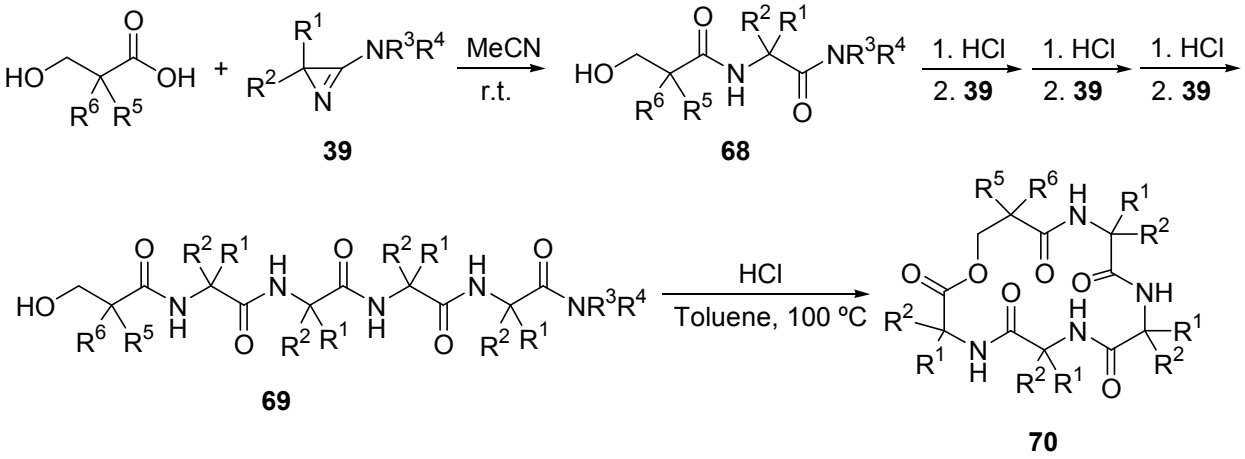
Scheme 22



Scheme 23

Besides endothiopeptides, the "azirine/oxazolone" methodology has been also applied to the synthesis of some more complex oligopeptides, particularly those containing α-aminoisobutyric acid residues such as the sequence (12–20)-nonapeptide of the ionophore alamethicin,[52] the segment (1–10)-endothiodecapeptide

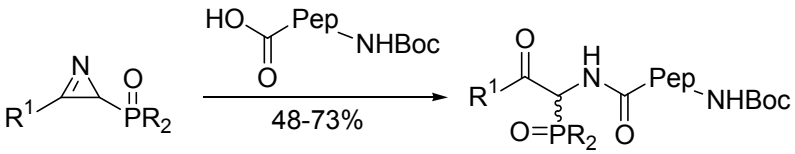
of the apolar zervamicin IIA,[53] and the *C*-terminal segment (6–14) of the peptaibole *Trichovirin* I 1B.[54] 2,2-Disubstituted 2*H*-azirin-3-amines **39** have also been used as building blocks of α,α-disubstituted α-amino acids for the preparation of 16- and 19-membered cyclic depsipeptides. The linear precursor **69** can be made by this strategy and then the 16-membered cyclic depsipeptides **70** are formed by acid-catalysed direct amide cyclization (Scheme 24).[55]



39 **68** **69** **70**

Scheme 24

This fruitful methodology has been further extended to the preparation of phosphapeptide analogues. Thus, ring-opening of 2*H*-azirine-2-phosphine oxides **44** and phosphonates **45** with *N*-protected di- or tripeptides instead of amino acids, provides a useful method to synthesize optically active phosphorylated α-ketamides containing peptide residues **71** (Scheme 25).[48]



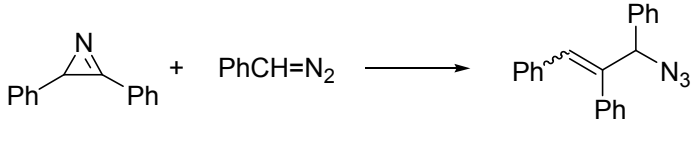
44 R = Ph
45 R = OEt

71

Scheme 25

2.1.5. Other acyclic compounds

Diphenylacetonitrile has been obtained by base treatment (K_2CO_3) of 2,2-diphenyl-2*H*-azirine in a 85% yield,[56] while the allylazide **73** shown in Scheme 26 is isolated in good yield from the reaction of 2,3-diphenyl-2*H*-azirine **72** and phenyl diazomethane.[57]

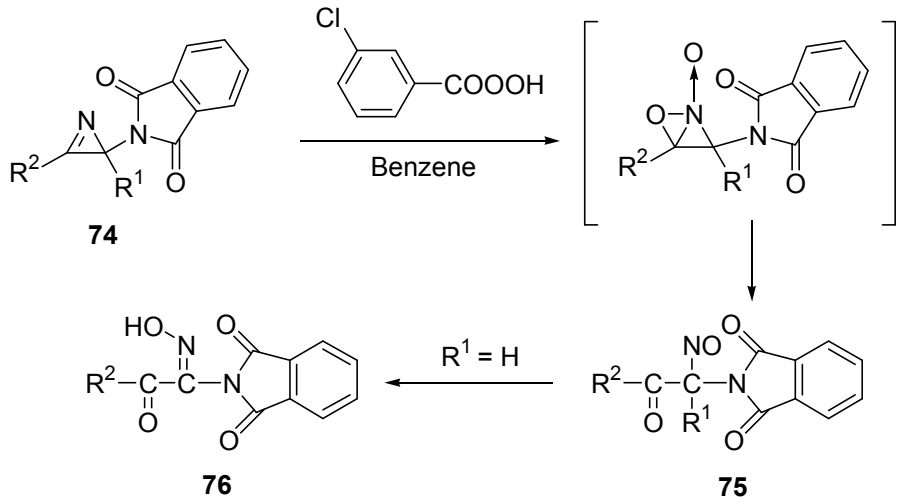


72 **73**

Scheme 26

The oxidation of 2*H*-azirines gives acyclic or cyclic derivatives as in the case of 2-phtalimidoazirine **74** when 3-chloroperbenzoic acid is used as oxidizing agent. The mechanism of the reaction seems to involve

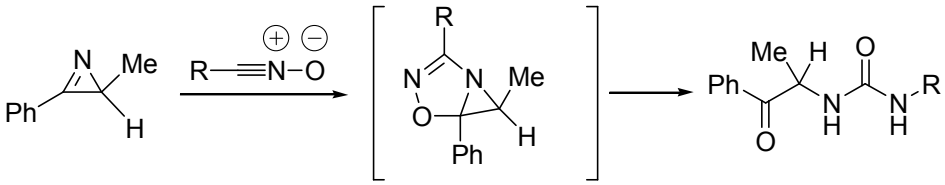
initial epoxidation of the C-N bond to produce α-nitrosoketones **75** and α-oximinoketones **76** (Scheme 27).[58] A similar mechanism may be involved in the oxidation of 2,3-diphenyl-2*H*-azirine to isoquinoline-*N*-oxide.[59]



74 **76** **75**

Scheme 27

Functionalised *N,N'*-substituted urea derivatives **78** can be obtained in high yield when aromatic nitrile oxides react as 1,3-dipoles with 2-methyl-3-phenyl-2*H*-azirines **8**. The formation of the ureas assumes the initial generation of a cycloadduct **77** from a 1,3-dipolar addition between the nitrile oxide and the azirine (Scheme 28).[60]



8 **77** **78**

Scheme 28

2.2. Synthesis of heterocyclic compounds

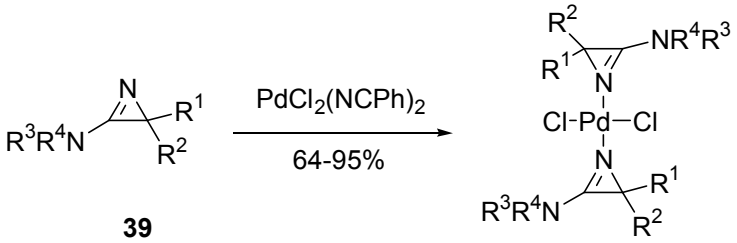
Strained cycloolefins are excellent dipolarophiles[61] and dienophiles[62] in [4+2] cycloaddition processes. In a similar way, the strained C-N double bond of 2*H*-azirines is more reactive than that of normal imines. Therefore, the C-N double bond of 2*H*-azirines can participate not only in carbon-carbon and carbon-heteroatom bond formation but also as a dienophile or a dipolarophile in thermal symmetry-allowed [4+2] cycloadditions with a variety of dienes and 1,3-dipoles.[6d,63]

2.2.1. Three-membered rings

2.2.1.1. Azirines

The synthesis of metal-coordinated 2*H*-azirines and the metal-induced reactions of azirines **39** ($R^1 = R^2 = R^3 = R^4 = Me$) have opened a new area in the chemistry of this small ring heterocycle. Transition metal complexes of the type $(azirine)_2MX_2$ (M = Pd, Zn) such as **79** were obtained by the reaction of azirine with

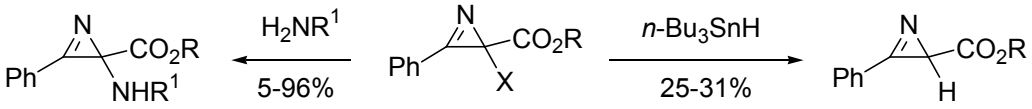
palladium reagents[64] or with transition metal halides[65] (Scheme 29). However, the reaction of azirines with tungsten or molybdenum complexes provides ring-opened compounds *via* initial complexation of the azirine nitrogen with the metal.[66] Likewise, insertion reactions, dimerizations,[67] intramolecular cyclizations, and intermolecular addition reactions of azirines are known to be promoted by transition metals.[68]



39 **79**

Scheme 29

The dehalogenation of 2-halo-3-phenyl-2*H*-azirine-2-carboxylate **80** using sodium borohydride or tributyltin hydride can be performed and 3-phenyl-2*H*-azirine-2-carboxylates **81** are obtained in moderate yields (Scheme 30). The yields obtained for these reactions are certainly a consequence of the competitive side reactions namely the reduction of the iminic bond or azirine isomerization when sodium borohydride is used or radical coupling reactions when tributyltin hydride is the reducing agent.[69] 2-Halo-2*H*-azirines **80** have also been used in nucleophilic substitution using potassium phthalimide and aniline as nucleophiles, and this allows the preparation of new 2-amino substituted 2*H*-azirines **82** through halide displacement.[18b]

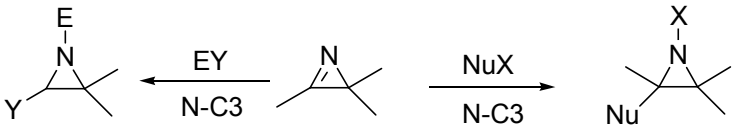


82 **80** **81**

Scheme 30

2.2.1.2. Aziridines

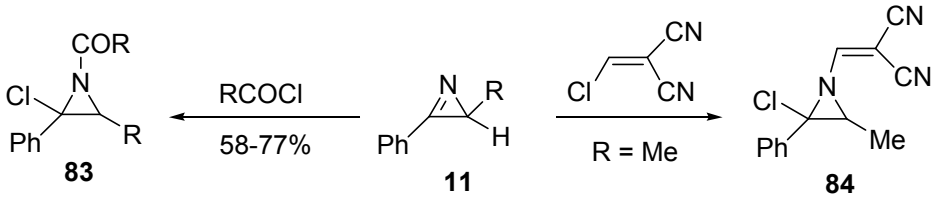
Addition reactions on azirines at the C= N bond have proven to be a useful method for the preparation of substituted aziridines. These processes are not limited to nucleophilic attack (NuX): hydrides, organometallic compounds, amines, thiols, alkoxides etc…, given that electrophilic reagents (EY) can also be used in order to obtain single or functionalised aziridines involving addition reactions to the N-C3 bond of the heterocycle (Scheme 31).



Scheme 31

C-N bond formation has been observed when 2*H*-azirines **11** react with acylating agents such as acid chlorides in benzene to give the *N*-benzoyl-2-chloroaziridines **83** in good yield by formal addition of RCOCl to the double bond[9b,70,71] (Scheme 32). These *N*-acyl aziridines are converted in polar solvents or by heating into oxazole and dichloroamide.[72] In a similar way, the *N*-functionalisation of azirines can also be achieved

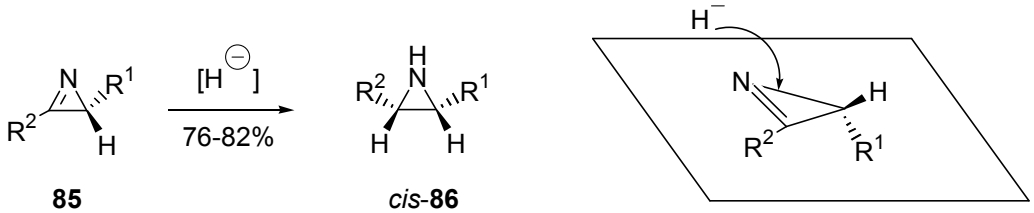
when vinyl halides are used as electrophilic reagents. Thus, 2-chloro-*N*-vinylaziridines **84**[73] can be obtained by *N*-vinylation of azirines **11**, as shown in Scheme 32.



83 **11** **84**

Scheme 32

Aziridines can also be obtained when azirines were treated with nucleophilic reagents. Several 2*H*-azirines have been reduced to *cis*-aziridines with lithium aluminium hydride or sodium borohydride in a highly stereospecific manner.[74] This reaction has been used as a method to proof the *cis*-configuration for simple aziridines,[75] for fluoro-substituted aziridines,[35] and for aziridine carboxylates **86** ($R^1 = CO_2R$).[76] Similarly, azirines derived from phosphine oxides **85**[77] ($R^1 = P(O)Ph_2$) and phosphonates **85**[78] ($R^1 = P(O)(OEt)_2$) have been reduced to aziridines using sodium borohydride, to give the *cis*-aziridines **86** exclusively (Scheme 33). Diastereoselectivity of the reduction can be explained by the high exocyclic dihedral angle at the saturated carbon atom that could hinder the nucleophilic attack of the hydride ion on the iminic bond with the bulky substituent on the same side. Therefore, the approach of the hydride is more favourable from the side opposite to the group at the 2-position and *cis*-aziridines **86** are formed exclusively. [(2*H*-Azirin-2-yl)methyl]phosphonates **85** ($R^1 = CH_2P(O)(OEt)_2$) have been subject to reduction with $NaBH_4$ resulting also in the predominant formation of disubstituted *cis*-aziridines **86**.[79] In a similar way, 2,3-bis(trifluoromethyl)azirines have been reduced with $LiAlH_4$ to the corresponding aziridines.[80]



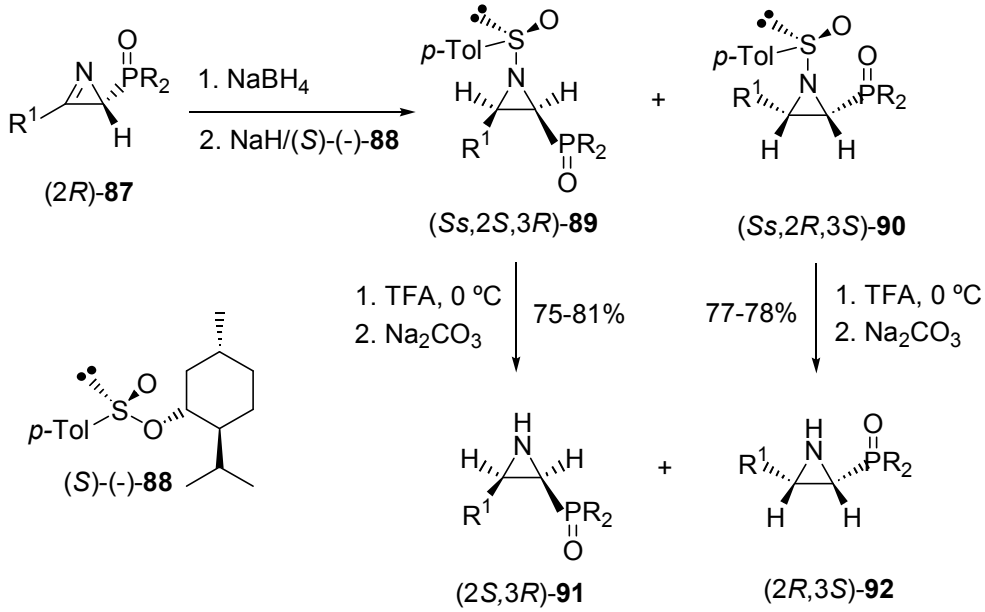
85 *cis*-**86**

Scheme 33

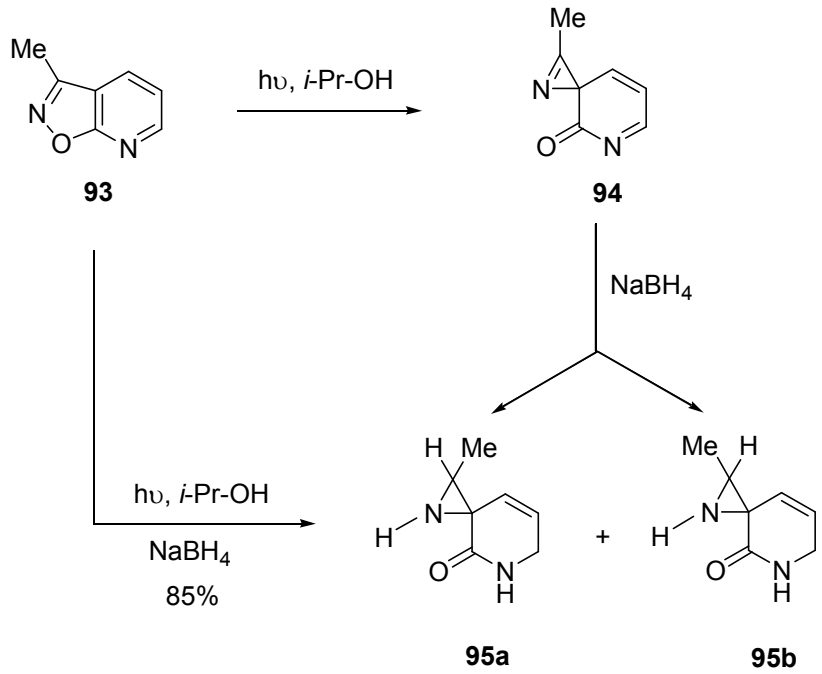
Likewise, enantiopure (+)-(*Ss*,2*S*,3*R*) and (+)-(*Ss*,2*R*,3*S*)-*cis*-*N*-sulfinyl aziridines **89** and **90**, respectively, have been prepared from azirine phosphine oxides or phosphonates **87** when chiral (-)-(*S*)-menthyl *p*-toluenesulfinate **88** is used.[77] The diasteroisomeric substituted aziridines **89** and **90** are isolated and they can be treated separately with trifluoroacetic acid at 0 ºC to afford enantiopure (+)- and (-)-aziridines **91** and **92**, respectively (Scheme 34).

Sodium borohydride is thermally inert towards bicycle **93**, however it is able to trap the spiroazirine intermediate **94** generated by photochemical irradiation in the presence of the hydride giving diasteroisomeric spiroaziridines **95a**,**b** (Scheme 35). Such compounds are the main products when the photorearrangement is stopped at about 40% advancement.[81]

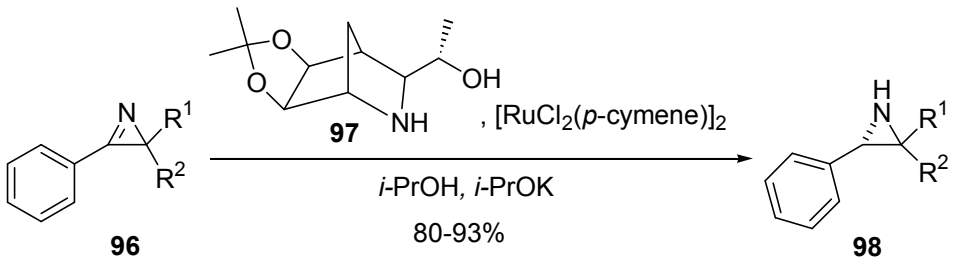
The enantioselective reduction of aromatic 2*H*-azirines **96** can be performed when chiral catalysts are employed (Scheme 36). Using the chiral aminoalcohol-$[RuCl_2(p\text{-cymene})]_2$ **97** catalysed asymmetric transfer hydrogenation reaction yields aziridines **98** in up to 70% ee.[82]



Scheme 34



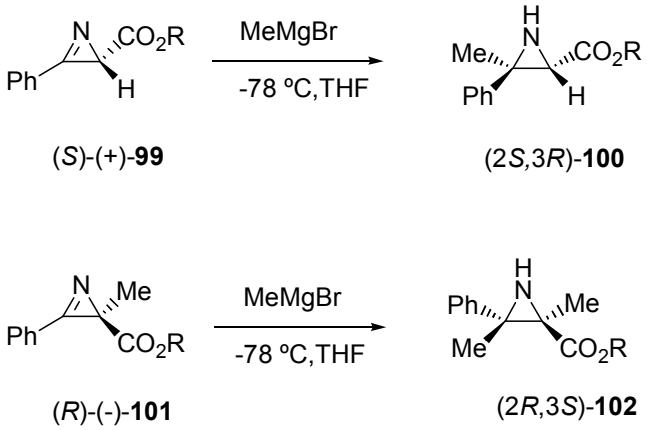
Scheme 35



Scheme 36

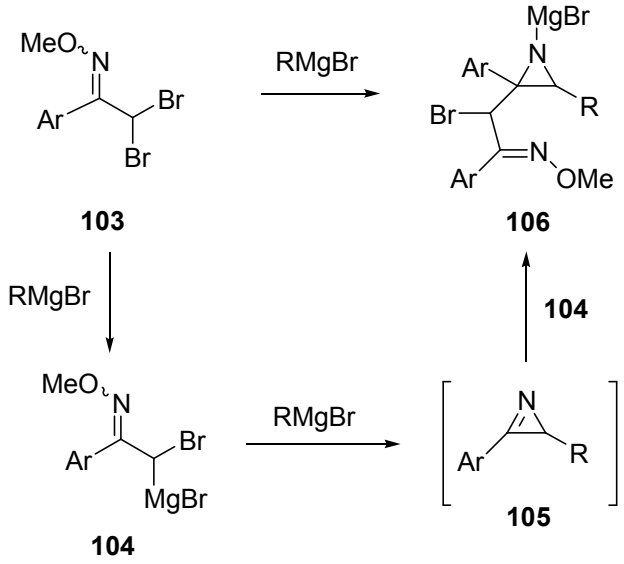
Carbon-carbon bond formation can be achieved with organometallic reagents to provide substituted aziridines. Likewise, Grignard reagents have been shown to react with 2*H*-azirines to give aziridines. The few reports of the addition of Grignard reagents to 2*H*-azirines reveal that the aziridine product is formed by

attack at the least hindered face.[83] However, recent results which involve the addition of methyl magnesium bromide from the more hindered face of 2*H*-azirine-2-carboxylate esters **99** and **101** have resulted in a new methodology for the asymmetric synthesis of 3,3-disubstituted aziridine-2-carboxylate esters **100** and **102** respectively.[84] These results seem to be a consequence of chelation of the Grignard reagent with the ester group (Scheme 37).



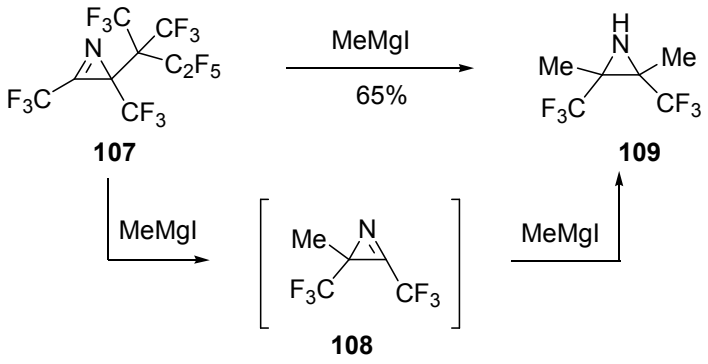
Scheme 37

Functionalised aziridines can also be prepared from halogenated oximes in the presence of Grignard reagent. Reaction of oxime **103** with *n*-BuMgBr provides aziridine **106**. The authors propose a plausible mechanism involving an azirine intermediate **105** as depicted in Scheme 38. Bromide-magnesium exchange affords carbenoid **104**,[85] and nucleophilic addition of this intermediate **104** to the highly reactive azirine affords **106**.[86]



Scheme 38

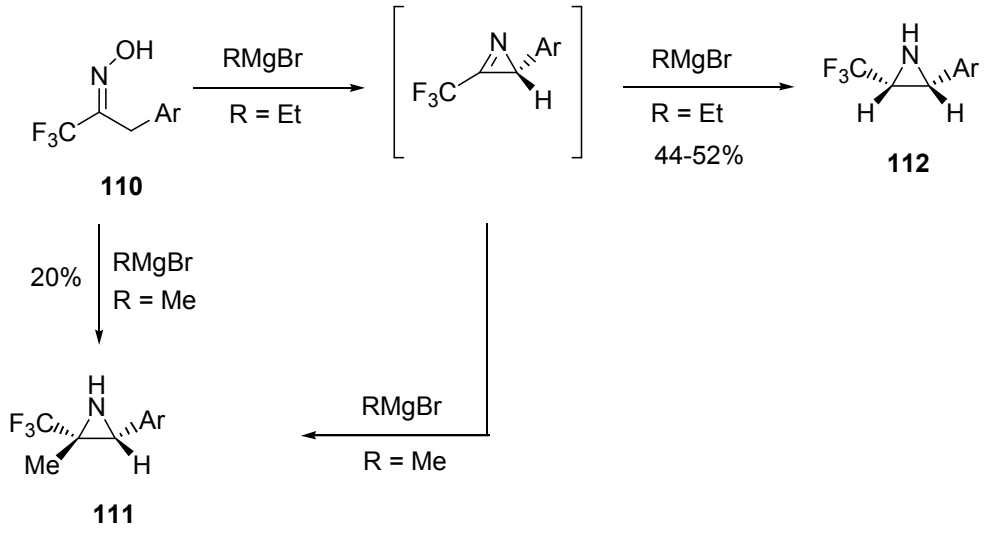
Special behaviour has been observed in azirines containing trifluoroalkyl substituent. Reaction of perfluoro[2,3-dimethyl-2-(3-methylpentan-3-yl)]-2*H*-azirine **107** with methyl magnesium iodide affords 2,3-dimethyl-2,3-bis(trifluoromethyl)aziridine **109** (Scheme 39). The perfluoroalkyl group in this process seems to act as an excellent leaving group in its own ring to give unstable 2-methyl-2,3-bis(trifluoromethyl) azirine **108**. Subsequent nucleophilic attack of methyl magnesium iodide explains the formation of aziridine **109**.[80]



107 **108** **109**

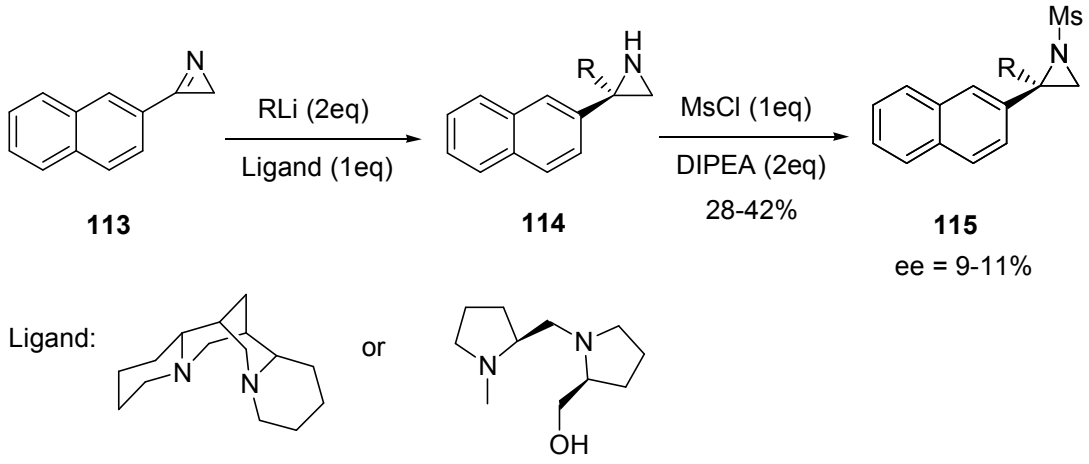
Scheme 39

Secondary aziridines **111**, substituted with a trifluoromethyl group can be prepared by reacting Grignard reagents with oximes **110** bearing a trifluoromethyl substituent in very low yield (Scheme 40). However, contrary to the results obtained with non-fluorinated substrates, ethyl magnesium bromide act exclusively as a reducing agent affording aziridine **112**.[87]



110 **112** **111**

Scheme 40



113 **114** **115**

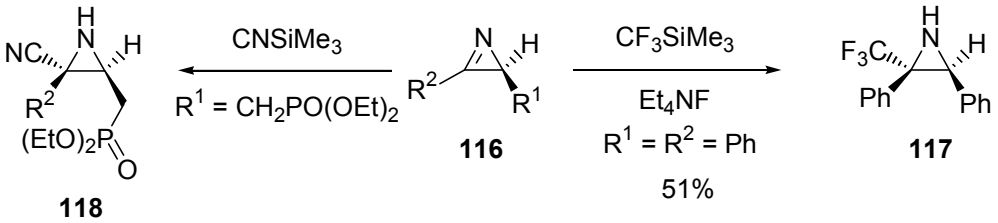
ee = 9-11%

Scheme 41

Another useful route for the preparation of aziridines is the asymmetric addition of organolithium reagents to C-N double bond of 2*H*-azirines. 3-Phenyl-2*H*-azirines react with lithium derivatives of 1,3-

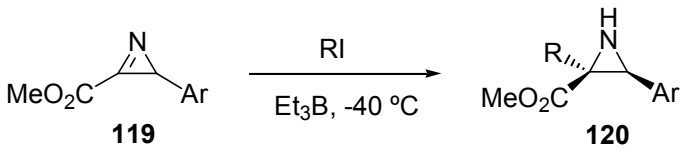
dithianes to afford *C*-functionalised aziridines.[11] The 3-(2-naphthyl)-2*H*-azirine **113** was used as a model substrate in the first enantioselective addition of organolithium reagents to azirine **113** in the presence of chiral ligands, furnishing aziridine **114** and, on mesylation, *N*-substituted aziridine **115** (Scheme 41).[88]

Fluoroalkyl and cyan nucleophilic reagents can also be used in order to prepare functionalised aziridines. *N*-Unsubstituted trifluoromethylaziridines **117** may be prepared by the reaction of (trifluoromethyl)trimethylsilane[89] with azirine **116** ($R^1 = R^2 = Ph$) as shown in Scheme 42,[90] while, addition of trimethylsilyl cyanide to [(2*H*-azirin-2-yl)methyl]phosphonates **116** ($R^1 = CH_2PO(OEt)_2$) yields, stereoselectively, the highly functionalised corresponding *trans*-aziridines **118**.[79] In a similar way, the addition of cyanide to other substituted 2*H*-azirines[91] has also been reported.



Scheme 42

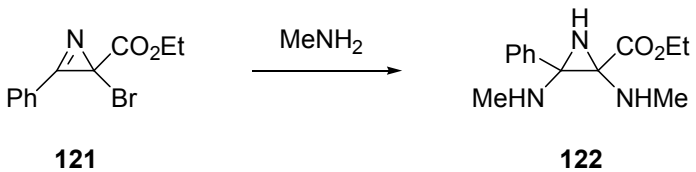
Radical processes can also produce carbon-carbon bond formation in azirines. So, the 2*H*-azirine (Ar = 2,6-Cl_2-C_6H_3) **119** acts as an effective radical acceptor for secondary and tertiary alkyl iodides mediated by triethylborane (Scheme 43). These reactions proceed with a high degree of stereoselectivity. Only one single diastereoisomer **120** can be detected as a consequence of the addition, which is controlled by the position of the aryl group and occurs from the less hindered face of the azirine ring.[92]



Ar = 2,6-Cl_2-C_6H_3

Scheme 43

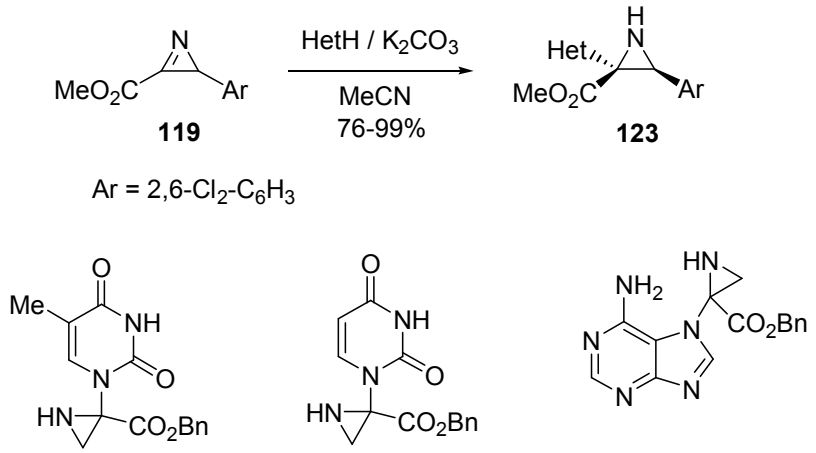
In addition to hydride and organometallic compounds, other nucleophilic reagents containing heteroatoms have been shown to react with 2*H*-azirines to give functionalised aziridines. 2-Halo-2*H*-azirines have been used in nucleophilic substitution using potassium phthalimide and aniline as nucleophiles, and this allows the preparation of new substituted 2*H*-azirines through halide displacement.[18b] However, reaction of azirines **121** with methylamine undergoes not only halide displacement but also addition to the imine double bond to give substituted aziridine **122** (Scheme 44).



Scheme 44

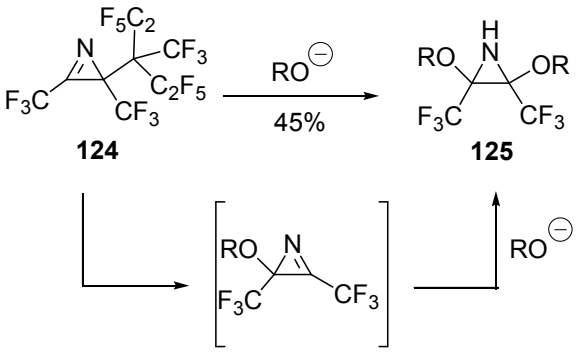
The nucleophilic addition of a variety of five-membered aromatic nitrogen heterocycles to the C=N bond of methyl 2-(2,6-dichlorophenyl)-2*H*-azirine-3-carboxylate **119** gives functionalised aziridines **123**.

The reaction is, in most cases, highly stereoselective.[93] This type of reaction has been extended to heteroaromatic nitrogen compounds such as benzimidazole, thymine, uracil, adenine and other nucleobases add to the C-N double bond of the azirine to give 2- substituted benzyl aziridine-2-carboxylates in moderate yield (Scheme 45).[94]



Scheme 45

Perfluoroalkylazirine **124** reacts slowly with alkoxides to give a series of substituted 2,3-dialkoxy-2,3-bis-(trifluoromethyl)aziridines **125**. These compounds are much more stable than the starting perfluoroalkylazirines **124**. Initially, loss of perfluoro 3-(3-methylpentyl) group, as an excellent leaving group, takes place. Substitution with alkoxide group and addition of the nucleophile to the C-N double bond of azirine gives 2,3-dialkoxy-2,3-bis-(trifluoromethyl) aziridines **125** (Scheme 46).[80]



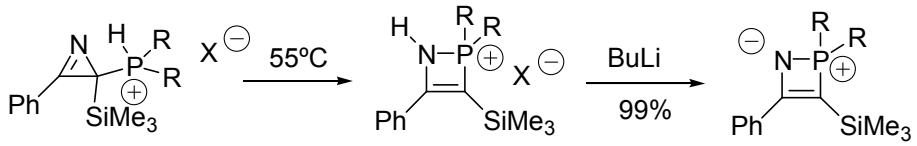
Scheme 46

Sulphur nucleophiles have also been used in reactions with 2*H*-azirines-3-carboxylic esters for the formation of carbon-sulphur bonds to obtain substituted thiophenylaziridines.[23,95] Reaction of (1*R*)-10-(*N*,*N*-dialkylsulfamoyl)isobornyl-2*H*-azirine-3-carboxylates with thiophenol gives functionalised aziridine compounds in 58% yield and in an optically pure form. X-Ray crystallography has established that the newly formed stereogenic centre has the *S*-configuration.[94b] On the other hand, aziridine phosphonates can be obtained by nucleophilic addition of phosphites to azirines.[96] Likewise, base-catalysed addition of dimethyl phosphite to (2*H*-azirin-2-yl)methylphosphonate proceeds with high selectivity to yield *trans*-bisphosphonate substituted aziridines with excellent yields.[79]

2.2.2. Four-membered rings

Ring expansion of 2*H*-azirines to four-membered heterocycles takes place when a chloroform solution of phosphonium salt **126** derived from phosphineazirine is heated at 55 °C affording the *N*-protonated

azaphosphete **127**, in very high yield. Addition of one equivalent of base (BuLi) to aminophosphonium salts **127** generates the four-membered ring **128** in nearly quantitative yield (Scheme 47).[97]

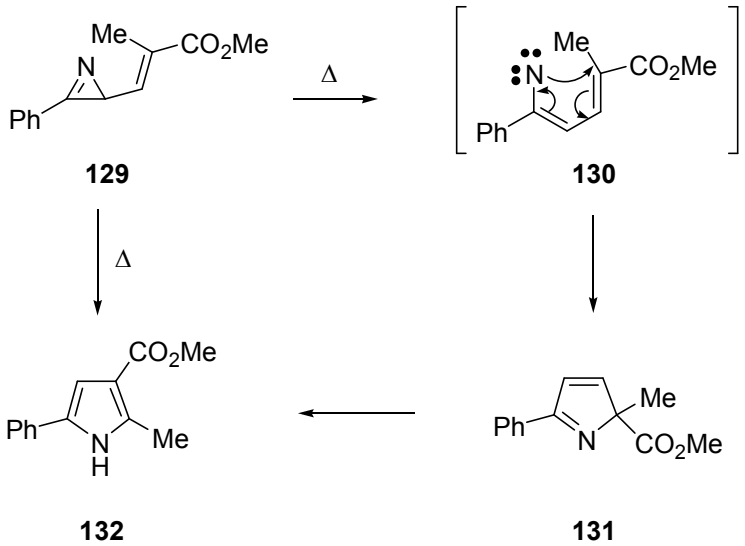


126 **127** **128**

Scheme 47

2.2.3. Five-membered rings

Azirines have also been widely used for the preparation of five-membered heterocycles by ring-expansion of these strained heterocycles. Pyrrole derivatives can be obtained by thermal treatment of vinylazirines and ring-expansion of the strained three-membered heterocycles.[98,99] For example, upon thermolysis of vinylazirine **129**, Padwa *et al*.[26] obtain substituted pyrrole **132**, *via* formation of vinyl nitrene **130** and subsequent ring expansion (Scheme 48). The rearrangement was envisaged as occurring by an electrocyclic reaction followed by a 1,5-sigmatropic methoxycarbonyl shift and subsequent tautomerization.

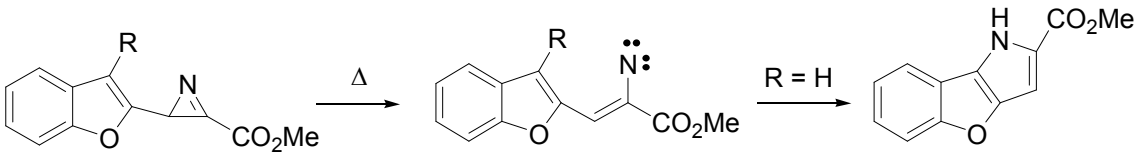


129 **130**

132 **131**

Scheme 48

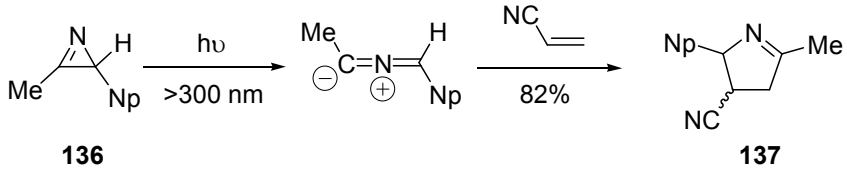
An interesting example studied by Taniguchi *et al*.[100] has been used for the synthesis of fused heterocycles. Intermediate vinyl nitrene **134**, generated by ring opening of azirine **133**, undergoes mainly electrocyclic ring closure to the five-membered ring **135** when R = H (Scheme 49). However, insertion reactions take place to form either the six-membered ring in the case of methyl substituted derivatives (R = Me) or the azepine when aryl substituted compounds are used (R = Ph).



133 **134** **135**

Scheme 49

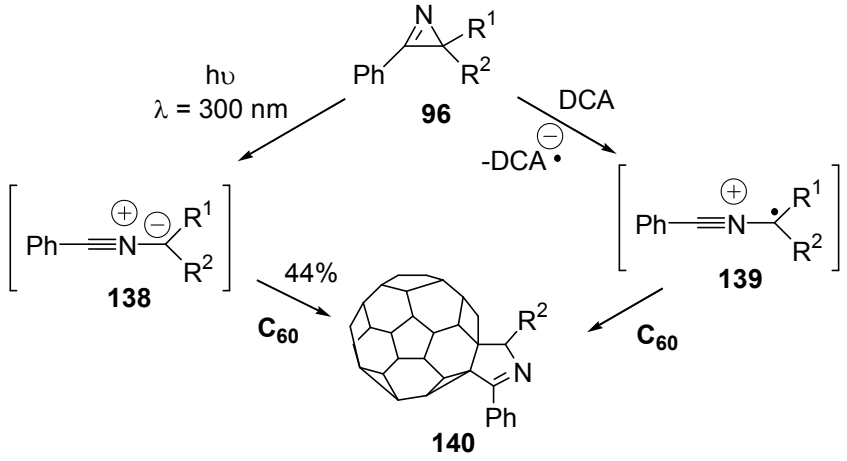
Photochemical irradiation of 3-methyl-2-(1-naphthyl)-2*H*-azirine **136** with the short-wavelength (>300 nm) in the presence of a dipolarophile such as acrylonitrile gives pyrrol derivatives **137**. The heterocycle is formed by the cleavage of the C-C bond of the 2*H*-azirine ring[19b,101] and subsequent 1,3-cycloaddition (Scheme 50). Even more recently, fluorine substituted fused aziridinopyrrole derivatives[102] have been obtained by 1,3-dipolar cycloaddition of dimethyl acetylenedicarboxylate with unstable azirinium difluoromethanides generated from 3-aryl-2*H*-azirines with difluorocarbene.



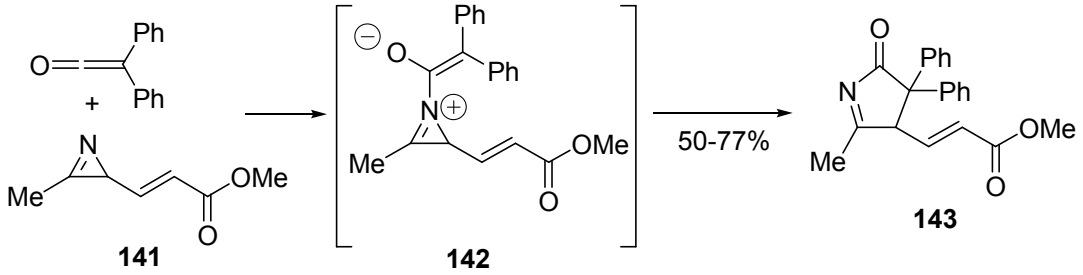
136 **137**

Scheme 50

An exohedrally functionalised fullerene such as 1,9-(3,4-dihydro-2,5-diphenyl-2*H*-pyrrolo)-[60]fullerene can also be prepared by the [3+2] photocycloaddition of nitrile ylide to C_{60} fullerene (Scheme 51). The nitrile ylide **138**, which was generated by direct irradiation of 2,3-diphenyl-2*H*-azirine **96** (R^1 = H, R^2 = Ph), adds to C_{60} acting as 1,3-dipolarophile with formation of a C_1 symmetrical [60]fullerene **140**. Mechanistic studies revealed a second reaction pathway, for example, the addition of azirine under photoinduced electron transfer (PET) conditions using 9,10-dicyanoanthracene (DCA) as a PET sensitiser and light above 400 nm wavelength. In this case the addition obviously occurs *via* a 2-azaallenyl radical cation **139**.[103] Aliphatic 2*H*-azirines are not suitable because they have a shorter excitation wavelength than the phenyl substituted 2*H*-azirines with forbidden π-π* transitions of the phenyl group (Scheme 51).



Scheme 51

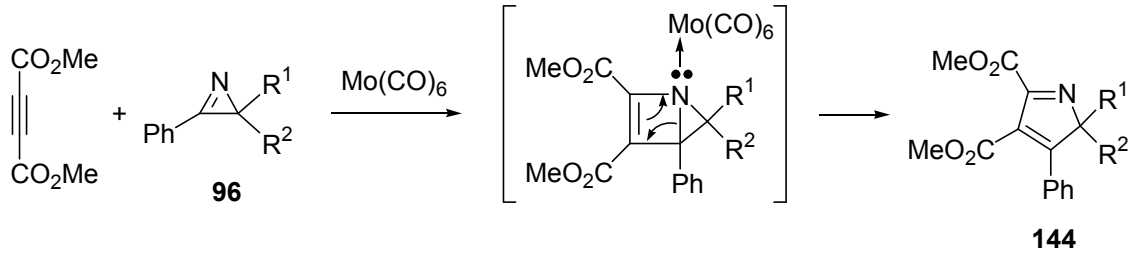


Scheme 52

Electrophilic addition of heterocumulenes and subsequent ring expansion of the *N*-vinylazirine ring **142** to five-membered heterocycles **143** has been observed when 2*H*-azirine-2-methylacrylate **141** react with

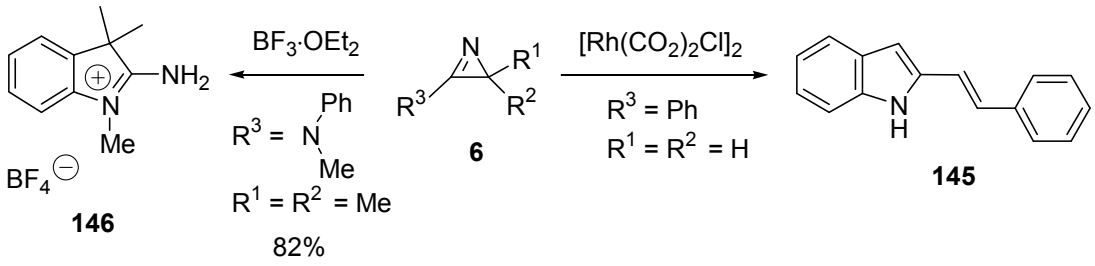
diphenylketene (Scheme 52). An insertion reaction of two carbon atoms of diphenylketene into the N-C2 bond of azirine has been reported to give 5-pyrrolin-2-ones **143**.[104]

The bimolecular cycloaddition of dimethyl acetylenedicarboxylate with 3-phenyl-2*H*-azirines **96** (R^1 = R^2 = Me) in the presence of molybdenum hexacarbonyl complexes[105] has also been studied (Scheme 53). The resulting pyrrole derivatives **144** appear to arise from an initial [2+2] cycloaddition followed by a ring opening reaction.[106]



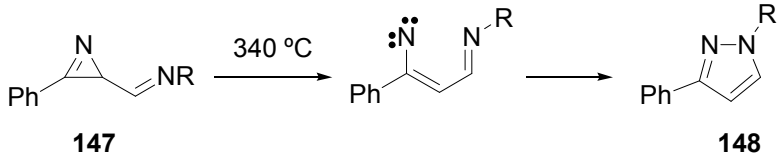
Scheme 53

Not only pyrroles but also indoles can be obtained by ring expansion of azirines. 3-Aryl azirines **6** (R^1 = R^2 = H, R^3 = Ar) are converted to 2-styrylindoles **145** in the presence of rhodium carbonyl compounds as catalyst.[107] Addition of an equimolar amount of boron trifluoride to a stirred solution of 2-dimethyl-3-[*N*-methyl-*N*-phenylamino]azirine **6** (R^1 = R^2 = Me, R^3 = PhMeN) in THF gives 2-amino-1,3,3-trimethyl-3*H*-indolium tetrafluoroborate **146** in good yield (Scheme 54).[108]



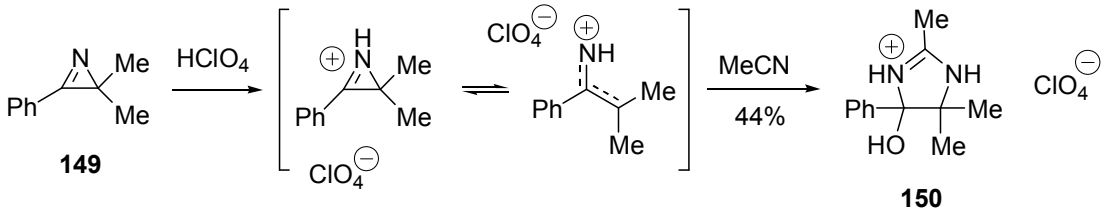
Scheme 54

The azirine ring is also a useful synthon for the preparation of five-membered heterocyclic compounds with two nitrogen atoms. In a similar way to that reported for 2-vinylazirines, the corresponding ring expansion of iminoazirines **147** could afford the five-membered heterocycles containing two nitrogen atoms. Formation of pyrazoles **148** is observed during thermolysis at 340 °C, and seems to occur *via* C-N ring bond cleavage followed by electrocyclization (Scheme 55).[109]



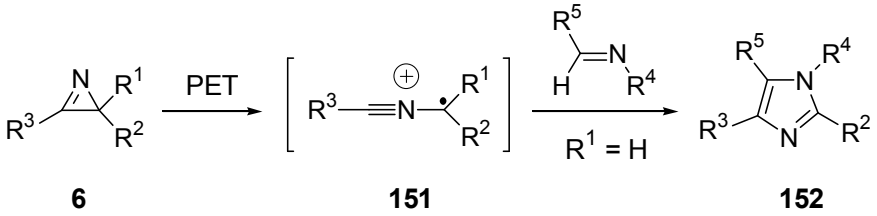
Scheme 55

2*H*-Azirines undergo ring-opening reactions with very strong protic acids, such as $HClO_4$, HCl and RSO_3H, under non-nucleophilic conditions. The protonated azirine system has been used for the synthesis of acyclic and heterocyclic compounds.[9a] For example, treatment of 2,2-dimethyl-3-phenyl-2*H*-azirine **149** with anhydrous perchloric acid and acetonitrile gives imidazolinium perchlorate **150** (Scheme 56).



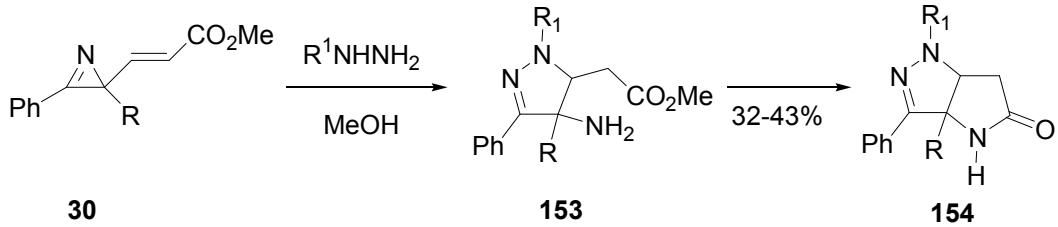
Scheme 56

Recently, the first example of dimerisation of 3-phenylazirine to 2,4-diaryl-2-methyl-2*H*-imidazoles has been reported using iron dichloride as promoter of the reaction.[110] An alternative approach to the generation of reactive intermediates from an 2*H*-azirine **6** has been explored during the last decade. Certain cyanoarenes can be photoexcited at a relatively low wavelength (350 nm) and this excited sensitiser will then extract an electron from a 2*H*-azirine species to form a reactive intermediate, the azaallenyl radical cation **151** (Scheme 57). Photoinduced electron transfer (PET) intermediate **151** is more reactive than the nitrile ylide and it will add to simple imines to give a substituted imidazole such as **152**.[111] In a similar way, the formation of 3-phenylimidazol[1,5-*a*]pyridine by photolysis of 3-phenyl-2-(2-pyridyl)-2*H*-azirine has been described.[112] This result is in agreement with some reports on the cycloaddition of nitrile ylides to pyridine, quinoline and isoquinoline affording heterocondensed imidazolines.[113]



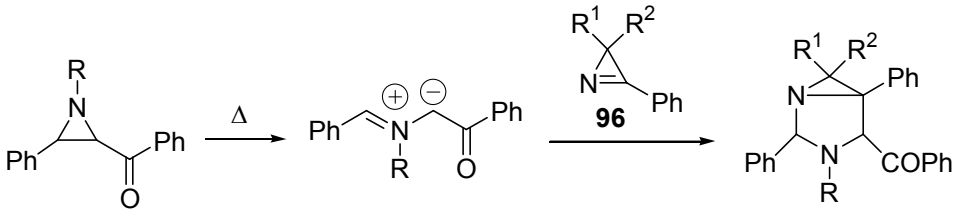
Scheme 57

Bicyclic pyrazole systems can be prepared by the nucleophilic addition of amine derivatives. The reaction of the functionalised vinyl-2*H*-azirine **30** with hydrazines as nucleophiles in methanol produces hexahydropyrrolo[3,2-*c*]pyrazol-5-ones **154**.[114] The process is assumed to involve intramolecular interception of an unstable 4-aminopyrazoline intermediate **153** resulting from C-N double bond cleavage (Scheme 58).



Scheme 58

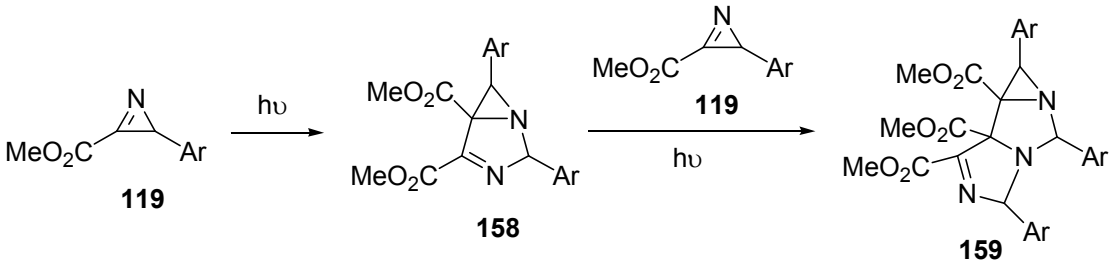
Likewise, bicyclic imidazole derivatives can be prepared by 1,3-cycloaddition processes involving azirines as dipolarophiles. Aziridines **155** undergo thermal ring opening in a conrotatory manner to generate azomethine ylides **156**. These azomethine ylides **156** are 1,3-dipoles and can participate in cycloadditions with 2*H*-azirines **96** ($R^1 = R^2 = H$) acting as the 2π-component to give bicyclic heterocycles **157** (Scheme 59).[115]



155 **156** **157**

Scheme 59

In the absence of a dipolarophile, the intermediate nitrile ylide generated by photolysis of an azirine adds to the precursor azirine, and several examples of bicyclic dimers are known. This aspect of the photolytic reaction is well illustrated by the trimerisation reaction of 2*H*-azirine carboxylates **119** in which a polycyclic heterocycle **159** is formed, presumably by cycloaddition of the initially formed dimer **158** to the nitrile ylide, generated by electrocyclic ring opening of a third molecule of azirine (Scheme 60).[116]

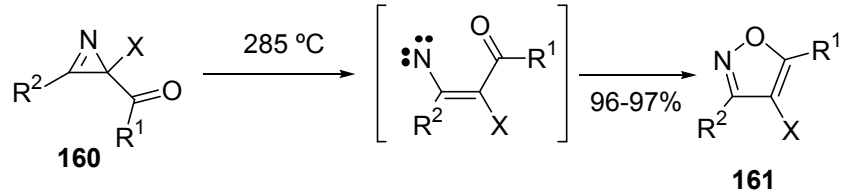


119 **158** **159**

Scheme 60

Similarly, other five-membered heterocyclic compounds containing two heteroatoms, such as nitrogen and oxygen atoms, can be prepared using azirines. The remarkable wavelength-dependent photoreactions of 3-methyl-2-(1-naphthyl)-2*H*-azirine can be observed in matrices at 10 ºK and in solution at room temperature. Irradiation of this azirine with long-wavelength light (366 nm) exclusively gives the products formed by the cleavage of the C-N bond of the 2*H*-azirine ring. The products derived from the C-C bond cleavage are predominantly obtained in the irradiation with the short-wavelength (>300 nm), leading to the synthesis of oxazoline derivatives.[19b,101]

Intramolecular ring expansion of azirines to five-membered heterocycles by photochemical isomerization[117] of amido or carbonyl azirine to 1,3-oxazoles *via* C-C bond cleavage has been observed. Thermolysis of 2-halo-2*H*-azirines affords 4-haloisoxazoles in high yield. For example, 2-benzoyl-2-halo-2*H*-azirines **160** can be easily converted into the corresponding isoxazoles **161** (Scheme 61). However, more drastic thermolysis conditions are required in the case of 2*H*-azirine-2-carboxylate derivatives.[118]

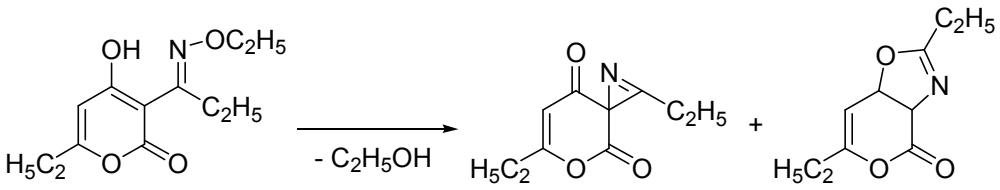


160 **161**

R^1 = Ph, OMe, OEt
R^2 = CO_2Me, Ph
X = Br, Cl

Scheme 61

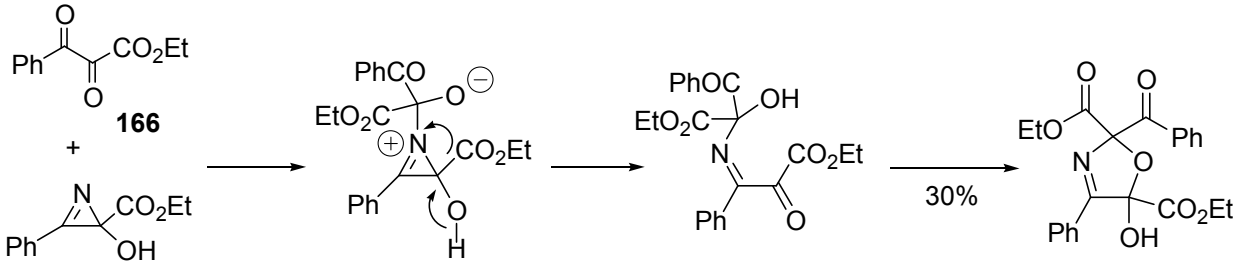
However, other five-membered heterocycles such as bicyclic oxazoles, can be obtained by flash vacuum pyrolysis of 6-ethyl-3-(1-ethoxyiminopropyl)-4-hydroxy-2*H*-pyrane-2-one **162**, when these compounds are heated between 300-400 ºC (Scheme 62). Isolated reaction products at 350 ºC are 6-ethyl-3-spiro-3-(2-ethyl)azirin-2*H*-pyran-2,4-dione **163** and isomeric 4,7-diethyl-2*H*-oxazol-(3,4-*d*)pyran-2-one **164**. As long as the reaction temperature is raised, the amount of **162** diminishes, **163** disappear and the only product is **164**.[119] Formation of oxazole **164** seems to occur by C-C ring opening of azirine.



162 **163** **164**

Scheme 62

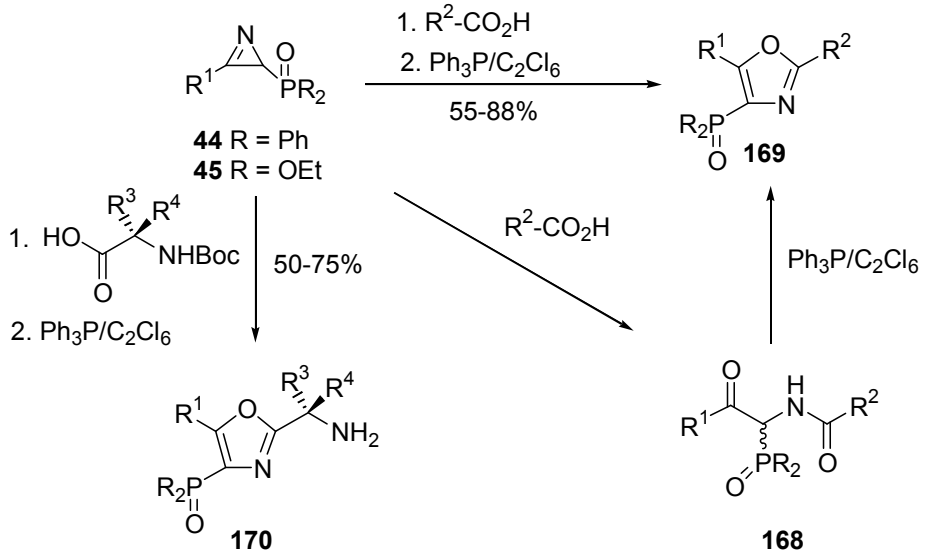
Ring expansion of the strained three membered heterocycle of 2*H*-azirines has been described for the synthesis of oxazolium salts by reaction of azirines with very strong protic acids, such as $HClO_4$, HCl and RSO_3H, under non-nucleophilic condition.[9a] Substituted azirines react also with some carbonyl compounds by electrophilic addition and ring expansion leading to the synthesis of functionalised oxazoline derivatives. Reaction of 2-hydroxy-2*H*-azirine **165** with the diketoester **166** leads to ring opening to give 3-oxazoline **167** (Scheme 63). The reaction probably entails the nucleophilic attack of the azirine on the carbonyl group followed by ring opening and intramolecular nucleophilic addition with formation of the five-membered heterocycle.[18b] Likewise, the mild base-promoted reaction of methyl 3-phenyl-2*H*-azirine-2-acetate with aldehydes and acetone also provides a simple route to the 3-oxazolines.[120]



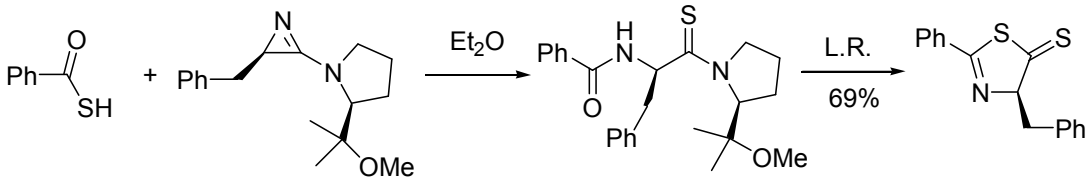
Scheme 63

The ring opening of 2*H*-azirines derived from phosphine oxides **44** or phosphonates **45** with carboxylic acids gives phosphorylated ketamides **168** (Scheme 64). Ring closure of ketamides **168** with triphenylphosphine and hexachloroethane in the presence the triethylamine leads to the formation of phosphorylated oxazoles **169**.[42] This process can be extended to the reaction of 2*H*-azirines derived from phosphine oxides **44** and phosphonates **45** with *N*-protected aminoacids to give the synthesis of optically active oxazoles containing amino alkyl residues **170**. Similar results are obtained when azirines reacted with *N*-protected peptides.[48] This process can also be extended to thioacids for the preparation of five-membered heterocycles with nitrogen and sulphur atoms. The reaction of diastereoisomers (*R*,*S*)-**171** and (*S*,*S*)-**171** with PhCOSH leads to the monothioamides (*R*,*S*)-**172** and (*S*,*S*)-**172**, respectively (Scheme 65). The

enantiomerically pure 4-benzyl-4-methyl-2-phenyl-1,3-thiazole-5(4*H*)-thiones (*R*)-**173** and (*S*)-**173** are obtained in 69% and 65% yield, respectively, *via* thionation and cyclization of (*R*,*S*)-**172** and (*S*,*S*)-**172** with *Lawesson* reagent in toluene.[121]

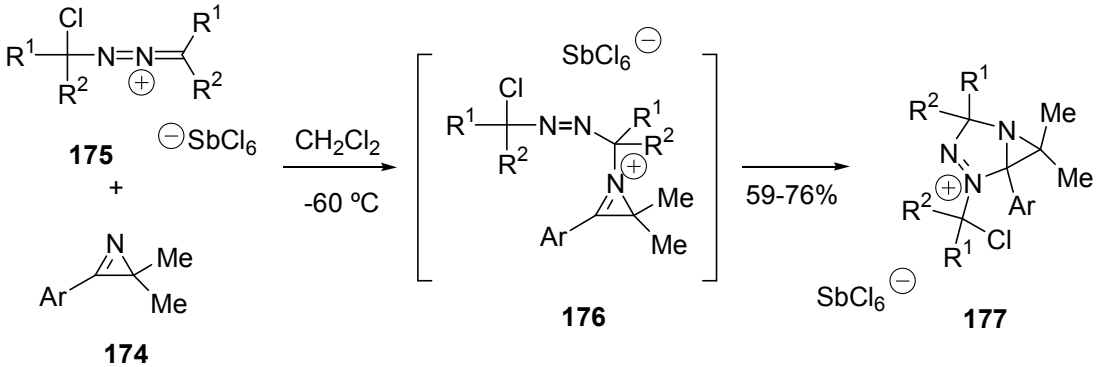


Scheme 64



Scheme 65

Ring expansion of azirines to five-membered heterocycles with three heteroatoms has been performed by addition of heterocumulenes to 2*H*-azirines. Heterocumulene salts **175** behave as cationic four-electron components undergoing intramolecular cycloaddition to multiple bonds as the azirine **174**, affording cycloadducts across the C-N double bond of the azirine **176** to furnish azirenotriazolium salts **177** (Scheme 66).[122]

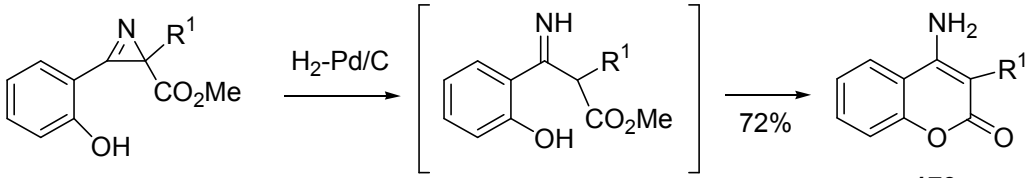


Scheme 66

Likewise, reaction of 3-dimethylamino-2,2-diphenyl-2*H*-azirine with *N*-sulfonylalkylamines provides 1,2,5-thiadiazoles. Whereas use of *N*-carbonylsulfonylamines primarily results in the formation of 1,2,3-oxathiazoles.[123]

2.2.4. Six-membered rings

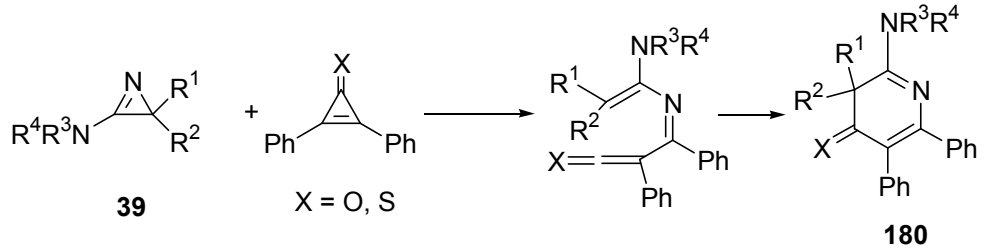
Azirine ring system has been used for the preparation of six-membered heterocycles by ring opening of the strained three-membered ring and expansion or dimerization. Only one case of six-membered ring with an oxygen atom has been reported. The synthesis was performed by catalytic hydrogenation of polyfunctionalised azirines **178** with palladium on carbon, and caused ring enlargement to 4-aminocoumarin derivatives **179** *via* cyclization and isomerization of the initially formed imino esters (Scheme 67).[124]



178 **179**

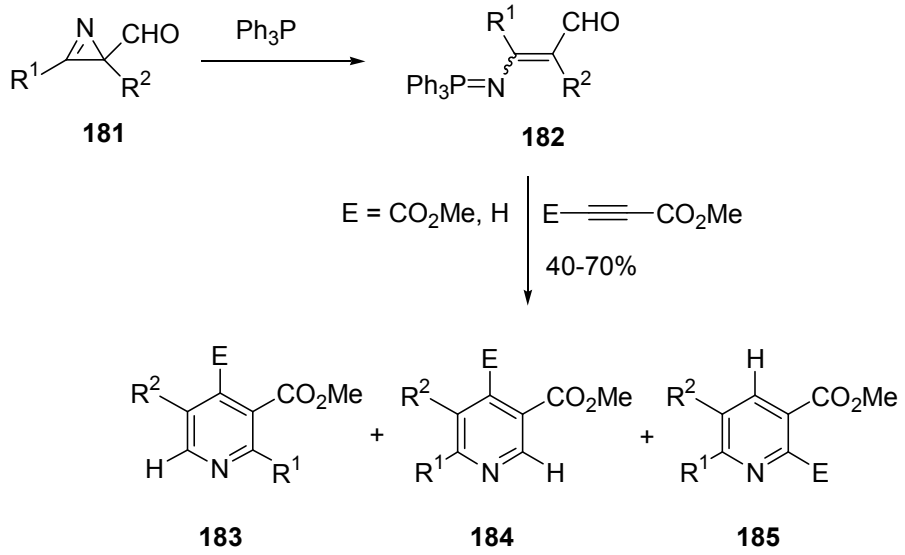
Scheme 67

However, 2*H*-azirines have been widely used for the preparation of nitrogen containing six-membered heterocycles. Thermal rearrangement of 2*H*-azirines having a cyclopropane ring at the 2-position is shown to give pyridines by participation of the cyclopropane ring in thermal ring enlargement reactions.[125] The reaction can be extended to 2-benzofurylazirines and tricyclic pyridines.[100] Three carbon atoms are formally inserted into the N-C2 bond of azirine when very reactive electrophilic reagents such as strained cyclopropenones react with 2,2-dialkyl-3-(dimethylamino)-2*H*-azirines **39** to afford good yields of the corresponding six-membered pyridin-4(3*H*)-one or -thione **180** (Scheme 68).[126]



39 X = O, S **180**

Scheme 68



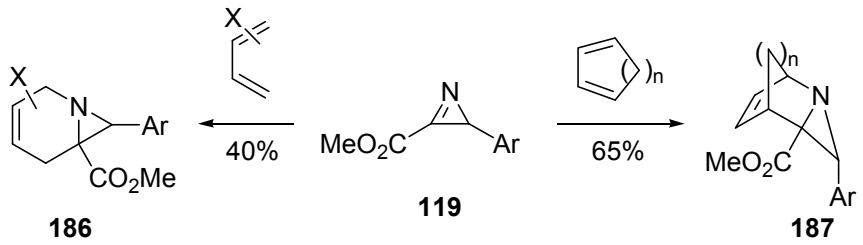
181 **182**

183 **184** **185**

Scheme 69

2*H*-Azirine carbaldehyde can be used for the preparation of nicotinate derivatives. The reaction of formyl-2*H*-azirine **181** with triphenylphosphine in refluxing toluene brings about the ring opening of azirine

to afford a conjugated phosphazene **182** (Scheme 69). This *N*-vinylic phosphazene[25a,127] can be used for the formation of substituted pyridines. The reaction of **182** with two equivalents of dimethyl acetylenedicarboxylate (DMAD) can be carried out in toluene at 140 ºC to give polysubstituted pyridines **183**-**185**.[24b] Methyl 2-aryl-2*H*-azirine-3-carboxylates **119** are good dienophiles and react with dienes such as cyclopentadiene, cyclohexa-1,3-diene, 2,3-dimethylbuta-1,3-diene and furans[128] at room temperature, and very reactive cyclic dienes such as tetrazines,[129] to give [4+2] bicyclic adducts **186** and **187** containing a six-membered heterocycle (Scheme 70). The cycloadditions are *endo* selective and the dienophile approach takes place from the less hindered face of the azirine.[130] Diels-Alder reactions of a chiral ester of 2*H*-azirine-3-carboxylic acid with cyclopentadiene are highly diastereoselective.[95]



186 **119** **187**

Scheme 70

3-Substituted 2*H*-azirines have also been employed as 2π components in Lewis acid-catalysed Diels-Alder reactions with electron-rich diene systems. Lewis acids are screened in the reaction between Danishefsky`s diene and 3-phenyl-2*H*-azirine **6** (R^1 = R^2 = H, R^3 = Ph) to give bicyclic adducts. The cycloadditions are found to proceed with *endo* selectivity providing a single diastereoisomeric product.[131] In a similar way, Diels-Alder cycloaddition of 3-(*t*-butyl carboxylate)-2*H*-azirine **6** (R^1 = R^2 = H, R^3 = CO_2t-Bu) with 1-methoxy-3-trimethylsilyloxybutadiene gives the corresponding bicyclic silyl enol ether derivative **188** (Scheme 71). This product decomposes at room temperature generating the corresponding seven-membered heterocyclic product **189** by ring expansion of the bicyclic nitrogen heterocycle **188**.[130b]

6

R^1 = R^2 = H, R^3 = Ph
R^1 = R^2 = H, R^3 = CO_2t-Bu

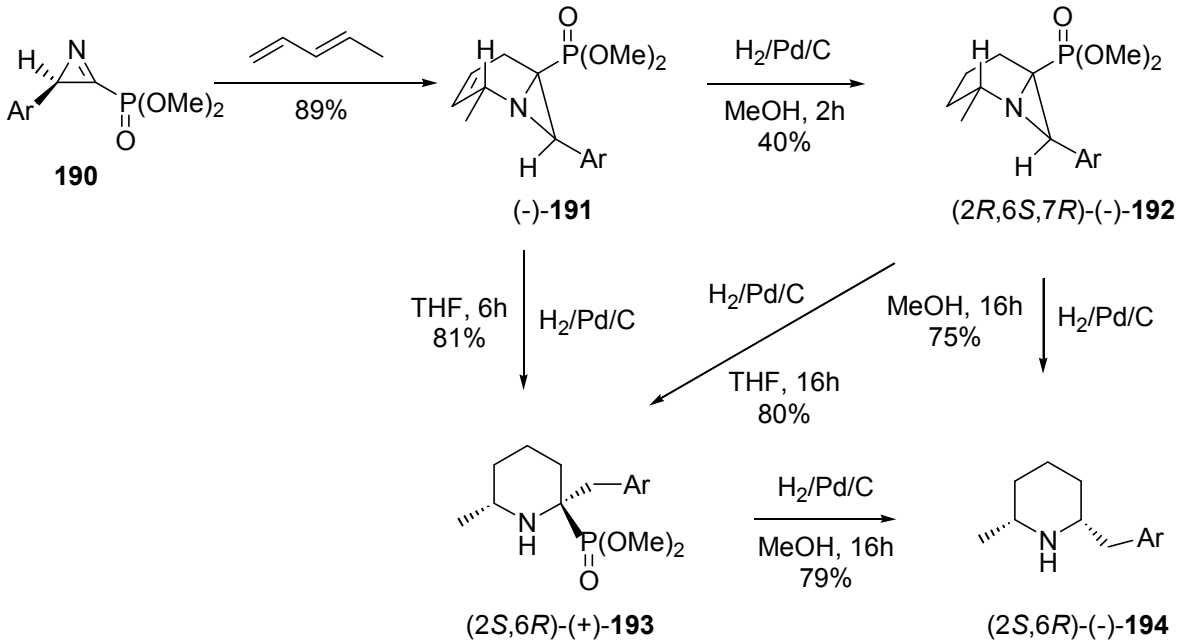
188 **189**

Scheme 71

Enantiomerically enriched 2*H*-azirine 3-phosphonates **190**, a new class of chiral iminodienophiles, can also give bicyclic aziridines **191** as Diels-Alder cycloadducts in good yields. Hydrogenation of these bicyclic aziridine adducts **191** results in a ring opening that affords the first examples of optically pure quaternary piperidine phosphonates **193** (Scheme 72).[132]

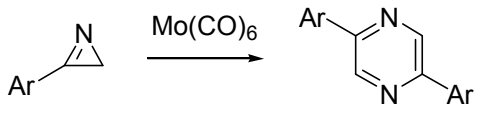
Azirines can also be used for the preparation of six-membered heterocycles with two nitrogen atoms. Dimerization reactions of 2*H*-azirines to pyrazines using several transition metal complexes have been studied.[67,133] Reaction of 3-aryl-2*H*-azirines **195** with an equimolar amount of a Group VI metal carbonyl gives 2,5-diarylpyrazines **196** in good yield (Scheme 73).

Likewise, polymeric materials with pyrazine groups are obtained using 2*H*-azirine as monomers.[134] Moreover, the preparation of pyrazine derivatives from reaction of 3-amino-2*H*-azirines with Lewis acid or carboxylic acid derivatives has also been reported for the preparation of six-membered heterocycles.[135] After activation by complexation with a Lewis acid ($BF_3 \cdot Et_2O$), 3-amino-2*H*-azirines react with the amino group of α-amino-acid esters to give 5-amino-3,6-dihydropyrazin-2(1*H*)-ones by ring enlargement.[136]



190 (-)-**191** (2*R*,6*S*,7*R*)-(-)-**192** (2*S*,6*R*)-(+)-**193** (2*S*,6*R*)-(-)-**194**

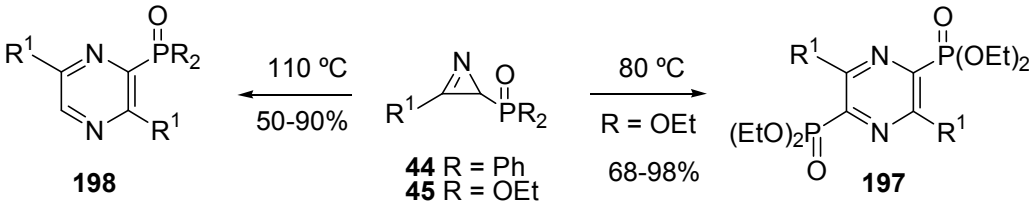
Scheme 72



195 **196**

Scheme 73

The synthesis of pyrazine phosphine oxide and phosphonate has been described. Tetrasubstituted pyrazines **197** containing two phosphonate groups in positions 2 and 5 and trisubstituted pyrazines **198** containing a phosphonate group or a phosphine oxide in 2-position are obtained by thermal treatment of 2*H*-azirine-2-phosphine oxide **44** or phosphonates **45** (Scheme 74).



198
R = OEt, R^1 = Ph
R = Ph, R^1 = Me, Et

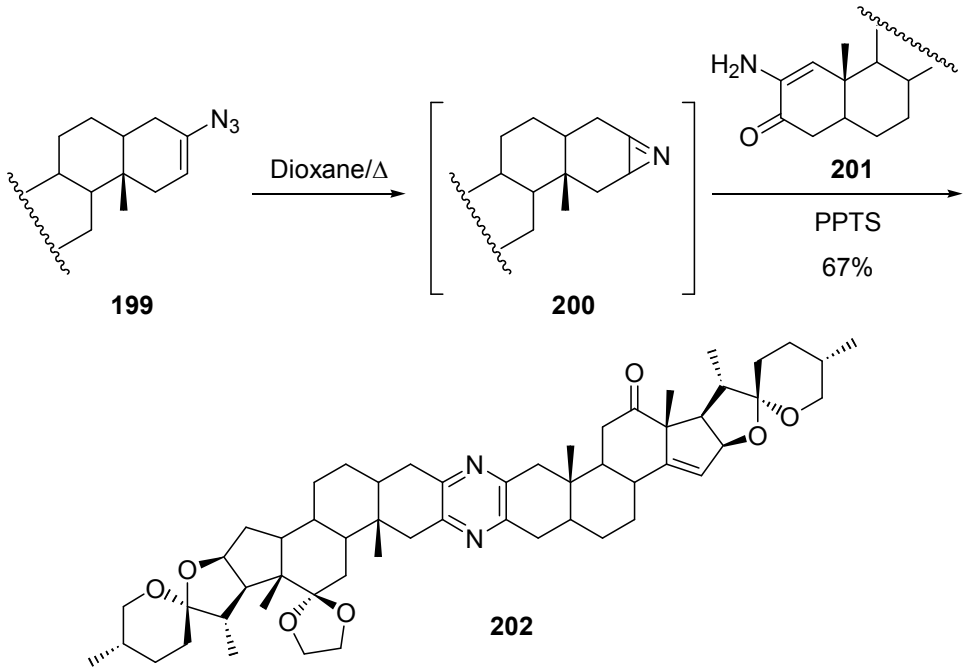
44 R = Ph
45 R = OEt

197

Scheme 74

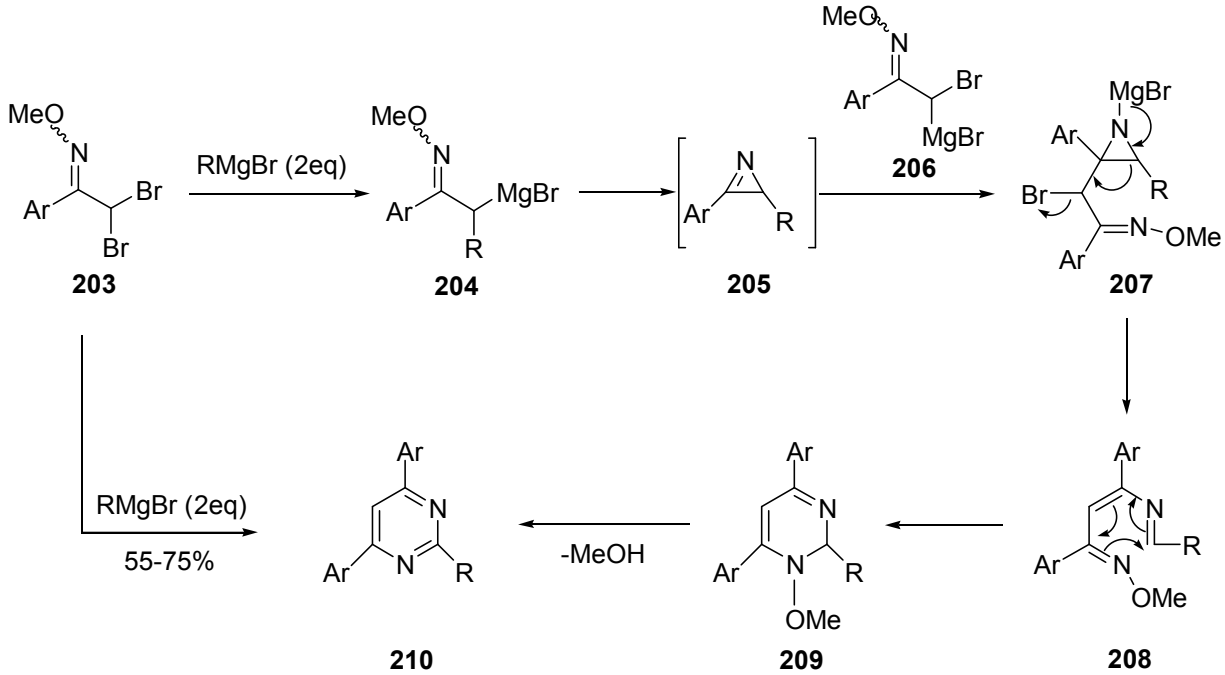
This process could imply thermal ring opening of 2*H*-azirines derived from phosphonates or phosphine oxides and dimerization of unstable nitrile ylide intermediates.[137] Bis(steroidal) pyrazines have also been

obtained by reaction of azirines with enamino ketones and a mild proton source.[138] Ring-fused azirine **200**, formed *in situ* from vinyl azide **199** in refluxing dioxane, react in the presence of pyridine-*p*-toluenesulfonate (PPTS) with enamino ketone **201** giving bis(steroidal) pyrazine **202** as shown in Scheme 75.



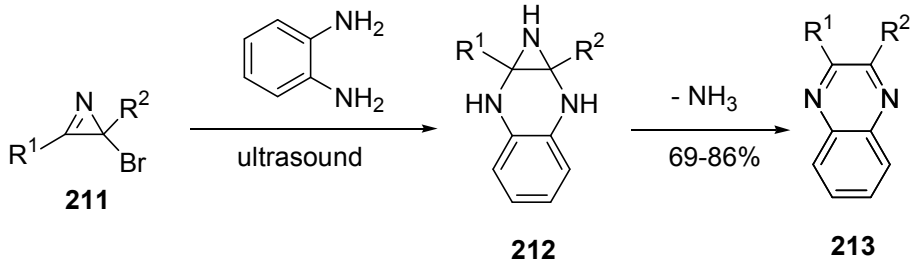
Scheme 75

Likewise, pyrimidines can also been prepared using 2*H*-azirines. The α,α-dibromo oxime ether **203** is alkylated with two equivalents of Grignard reagent to furnish **204**. α-Magnesiated oxime ether **204** undergoes Neber-type cyclization to provide a highly reactive azirine **205**. Reaction of azirine with **206** affords **207** which yields diimine **208** *via* ring opening. An electrocyclization of **208** provides pyrimidine **209** which is finally converted to pyrimidine **210** upon elimination of methanol (Scheme 76).[86]



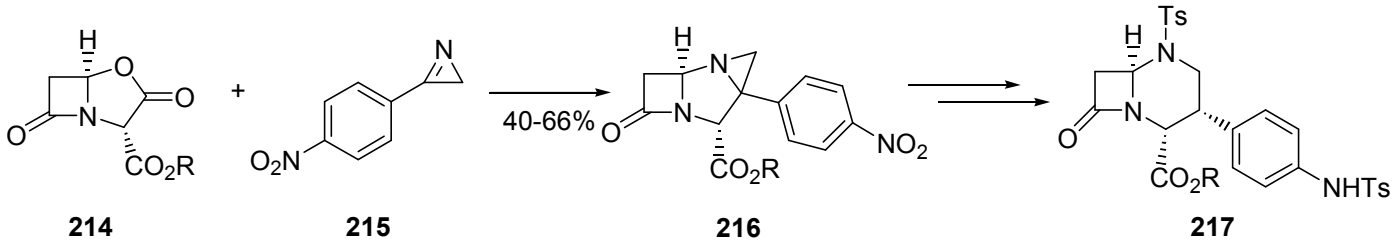
Scheme 76

Bicyclic heterocycles containing two nitrogen atoms such as quinoxalines **213** are obtained in high yield when the reaction of azirines **211** with 1,2-phenylenediamine is carried out in an ultrasound bath (Scheme 77). When the reaction is performed in the absence of the ultrasound bath the starting material is recovered. The process can be extended to other amines such as ethanolamine, when the reaction of 2*H*-azirine **211** (R^1 = Ph, R^2 = CO_2Et) is performed in the absence of water and using a large excess of ethanolamine, in an ultrasound bath, 2-amino-2*H*-[1,4]oxazine is obtained in 59% yield.[18a]



Scheme 77

Azirines can also be used for the preparation of functionalised β-lactames, given that the behaviour of 2*H*-azirines as 1,3-dipolarophiles provides 1-azacepham ring system. Thermolysis of 3-(4-nitrophenyl)-2*H*-azirine **215** in the presence of oxazolidinone **214** gives a single cycloadduct **216** (Scheme 78). Ring expansion of tricyclic β-lactames **216** gives the 3-substituted azacepham **217**.[139]



Scheme 78

Six-membered heterocycles with three nitrogen atoms have also been obtained by cycloaddition of azirines with heterocumulenes such as ketenes,[140] ketenimines, isocyanates,[141] isothiocyanates[142] and carbon disulfide.

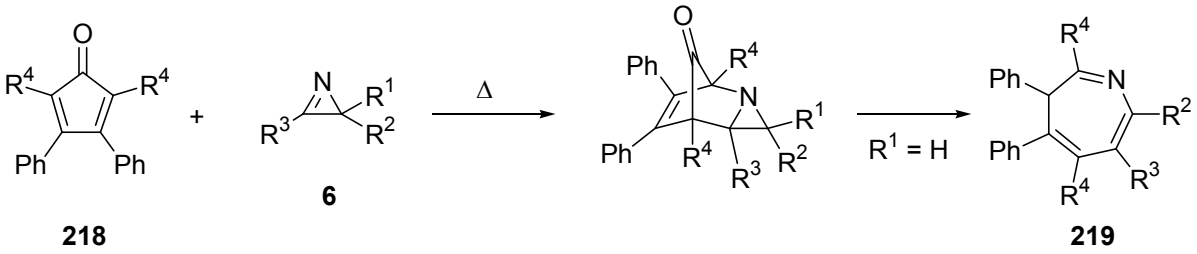
2.2.5. Larger heterocycles

Azirines are used for the synthesis of azepine derivatives taking into account that these three-membered heterocycles react as dienophiles with very reactive cyclic dienes such as tetrazines[129] or cyclone **218**.[26,109b,143] The first step of this latter reaction, between the azirine **6** and cyclopentadienone **218**, involves a [4+2] cycloaddition to give the *endo* adduct followed by chelotropic fragmentation of the adduct and isomerization to give the 3*H*-azepine ring **219** (Scheme 79).

However, a variety of five, six and seven-membered heterocyclic products are produced by the thermal reaction of azirines with tetrazines.[129] Likewise, Diels-Alder cycloaddition of *t*-butyl 2-azirinylcarboxylate to 1-methoxy-3-trimethylsilyloxybutadiene, gives cycloadducts that slowly decompose at room temperature to give azepinones.[130b]

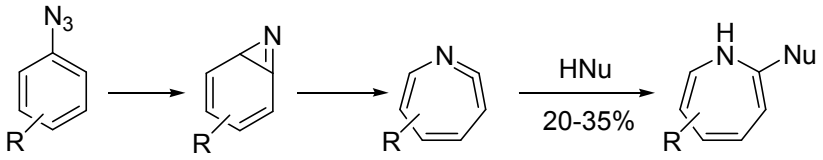
An alternative method for preparing 2-amino-3*H*-azepine utilizes the photolysis of aryl azides **220** or 1-naphthyl azide in the presence of diethylamine. The reaction pathway for the generation of a long lived

azirine intermediate **221**, is subsequently rearranged to the didehydroazepine intermediate **222** (Scheme 80). This species can be trapped with diethylamine to form azepine **223**.[144]



218 **6** **219**

Scheme 79

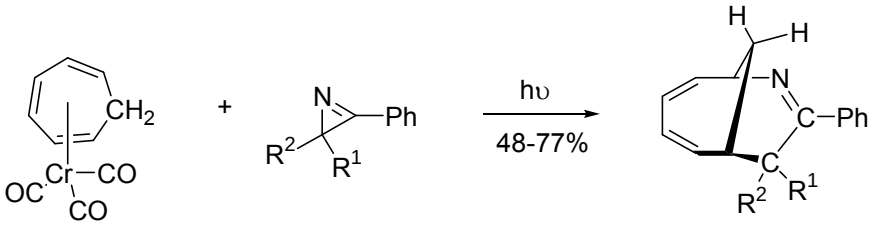


220 **221** **222** **223**

Scheme 80

Tetracyclic compounds containing a seven-membered ring can be prepared by thermolysis of 2*H*-azirines bearing aromatic substituents. Ring opening of the 2*H*-azirine followed by cyclization of the vinyl nitrene intermediate leads to the formation of tetracyclic azepines.[100]

Metal-mediated cycloadditions for the construction of bridged heterocycles have been reported. Thus, UV irradiation of tricarbonyl(cycloheptatriene)chromium (0) **224** and 3-phenyl-2*H*-azirines **96** (R^1 = H, Me, Ph, R^2 = H) at 0 °C gives 7-aza-8-phenylbicyclo[4.3.1]deca-2,4,7-trienes **225** *via* [6+3] cycloaddition of the 1,3-dipole generated by ring opening of the azirine to the cycloheptatriene ring[145] (Scheme 81).



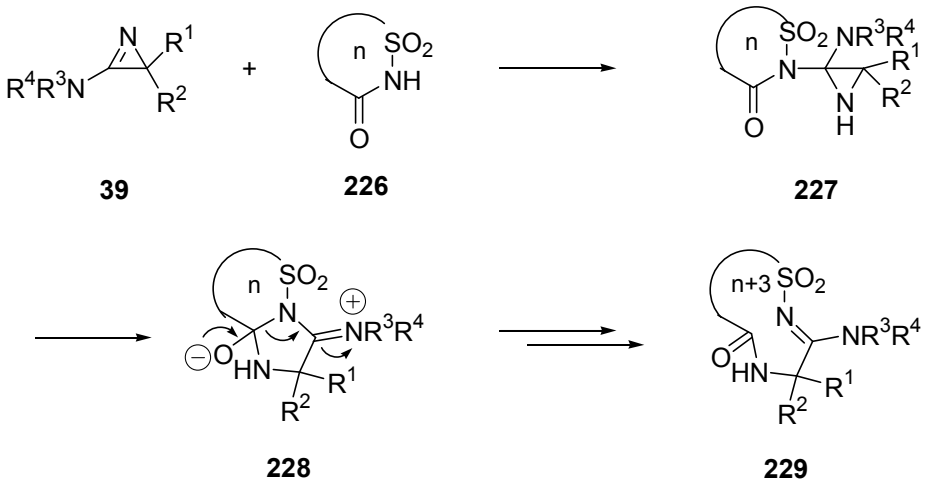
224 **96** **225**

Scheme 81

Heimgartner *et al*. have shown that nucleophilic addition of amides or hydrazides to 3-amino-2*H*-azirines **39** produces a variety of nitrogen heterocycles. Thus, reaction of **39** with salicylamide affords two imidazoles in a ratio which depends on reaction conditions.[146] Likewise, triazines as well as oxadiazoles have been obtained when hydrazides such as salicylhydrazide are treated with 3-amino-2*H*-azirines **39**.[147] This reaction can also be applied to NH-acidic heterocycles with $pK_a < 8$ to give ring enlarged heterocycles. Reaction of 1,2-thiazetidin-3-one 1,1-dioxides **226** (n = 4) with 3-amino-2*H*-azirines **39** affords 1,2,5-thiadiazepine derivatives[148] **229** (n = 4) (Scheme 82). A similar reaction has been observed with saccharin[149] and other 1,2-thiazol-3-one 1,1-dioxides,[150] yielding 1,2,5-thiadiazocine derivatives **229** (n = 5). With analogous six-membered derivatives, 1,2,5-thiadiazonin-6-one 1,1-dioxides **229** (n = 6) have been obtained[151] and with seven, eight and nine-membered, 1,2,5-benzothiadiazecinone 1,1-dioxides[152] **229** (n =

7), 1,2,5-thiadiazacycloundecen-6-one 1,1-dioxides **229** (n = 8) and 1,2,5-thiadiazacyclododecen-6-one 1,1-dioxides **229** (n = 9) have been synthesized[153] (Scheme 82). Other heterocyclic substrates which have reacted with 3-dimethylamino-2,2-dimethyl-2*H*-azirine and related azirines include imidazolidine-2,4-diones and the analogous imidazolidine-2,4,5-triones.[154]

Varying the substrate in reactions with other NH-acidic heterocycles demonstrates that the initial step in all these reactions is the protonation of 3-amino-2*H*-azirine **39**, since for substrates with $pK_a > 8$, the reaction no longer occurs. Subsequent nucleophilic attack onto the amidinium *C*-atom yields aziridine **227**, which undergoes a ring enlargement to give the zwitterionic intermediate **228**. After a second ring enlargement, the latter rearranges to the final product **229** (Scheme 82).



Scheme 82

In some cases the primary products cannot be isolated because of their further rearrangement under the reaction conditions. In this context, 3-amino-2*H*-azirines **39** react with hydantoins,[155] barbituric-acid derivatives,[156] 1,3-oxazol-5(4*H*)-ones,[157] and 1,3-oxazolidine-2,4-diones or 1,3-thiazolidine-2,4-dione[158] to give ring enlarged heterocycles, where the zwitterionic intermediate **228** rearranges in a different manner, and in some cases compound **229** can not be detected because of further rearrangement or transannular ring contraction.

3. Conclusions

This review offers an overview of the current synthetic uses of 2*H*-azirines as synthons for the preparation of a wide range of aliphatic nitrogen derivatives, as well as, for the construction of three-, four-, five-, six-, seven-, and larger heterocycles. Although considerable progress has been made in the chemistry of azirines over the last few years, the imaginative creation of new azirine architectures may yet bring about attractive advances in this field, especially their use as intermediates for the construction of biologically active compounds derived from nonproteinogenic aminoacids, peptides, and nitrogen containing heterocycles of different sizes.

Acknowledgements

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GAS-PHASE ION CHEMISTRY OF SIMPLE 1,4-BENZODIAZEPINES. PART I

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Abstract. *Gas-phase ion chemistry of 1,4-benzodiazepine derivatives is reviewed and presented here. The influence exerted by the nature and position of the substituents on gas-phase mono and bimolecular reactions are discussed. Different mass spectrometry methods have allowed to define correlation between the fragmentation patterns occurring inside a mass spectrometer and the structural features, and reactivity of this class of compounds.*

Contents

1. Introduction

Benzodiazepines are heterocycles of great interest in consequence of the wide range of their pharmacological activities.[1] As they act on the central nervous system with limited side effects, these drugs are widely employed as antipsychotics, anxiolytics, sedative hypnotics, anticonvulsants and muscle relaxants.[2-7] Changes in the benzodiazepine nucleus as well as in the nature and position of the substituents can modulate the drug activity, producing a fine-tuning of the biological effects.

Owing to the wide diffusion of such drugs, the development of reliable methods for the identification and quantitation of 1,4-benzodiazepines in complex matrices, such as body fluids, at low amounts, is needed. Several analytical techniques, such as nuclear magnetic resonance, and spectroscopic methods, together with immunological[8,9] and chromatographic approaches,[3,10,11] have been extensively employed for the characterization of benzodiazepines.[7]

Because of its high sensitivity and specificity, mass spectrometry, often coupled with gas and liquid chromatography, has been widely used for the detection and quantitation of 1,4-benzodiazepines in biological matrices,[12-28] and for the elucidation of their biotransformation pathways and pharmacokinetics.[29,30] On the other hand, only few mass spectrometry investigations have been devoted at studying their gas phase ion chemistry and reactivity.

Aimed at going deeply insight into the gas phase ion chemistry of 1,4-benzodiazepines, we wish to present here a critical review of papers published on this topic. Derivatives fused with other rings will be the subject of a second part of this review.[31]

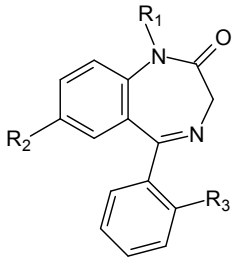
2. Gas-phase ion chemistry of 1,4-benzodiazepines

Different ionisation techniques, such as electron ionisation (EI), chemical ionisation (CI), fast atom bombardment (FAB), electrospray (ESI), and plasma desorption (PD) have been used for the characterization of 1,4-benzodiazepine derivatives. The study of metastable ions, the use of multiple collisional activation steps, high resolution measurements and the synthesis and study of labelled compounds have been carried out for the elucidation of their gas phase behaviour.

2.1. 5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives

5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives (**1**-**15**, Table 1) have been studied by mass spectrometry. Their electron ionisation mass spectra are characterized by abundant fragment ions due to consecutive losses of hydrogen, HCN and CO from the molecular ions.[32]

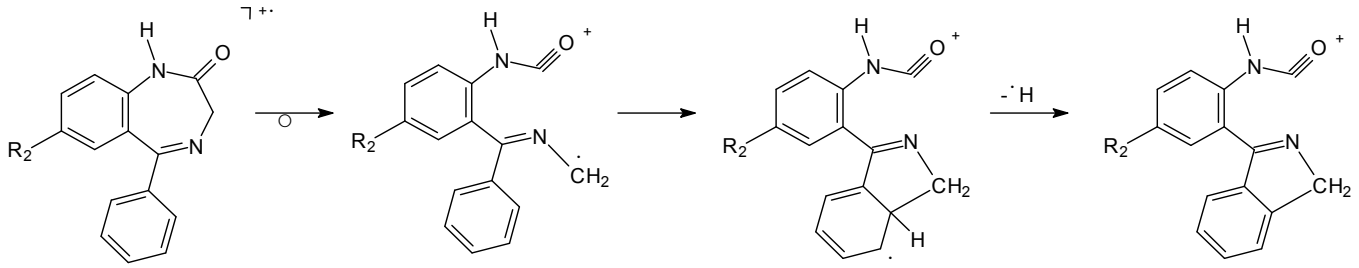
Table 1. Chemical structures of common 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones.



Compound	Commercial name	R_1	R_2	R_3
1		H	H	H
2	7-Aminonitrazepam	H	NH_2	H
3	7-Acetamidonitrazepam	H	$NHCOCH_3$	H
4	Nitrazepam	H	NO_2	H
5	Nordiazepam	H	Cl	H
6	*N*-desalkylflurazepam	H	Cl	F
7	Clonazepam	H	NO_2	Cl
8		CH_3	H	H
9	Nimetazepam	CH_3	NO_2	H
10	Diazepam	CH_3	Cl	H
11	7-Aminoflunitrazepam	CH_3	NH_2	F
12	Flunitrazepam	CH_3	NO_2	F
13	Prazepam	CH_2—◁	Cl	H
14	*N*-(2-hydroxyethyl)-flurazepam	CH_2CH_2OH	Cl	F
15	Flurazepam	$CH_2CH_2N(CH_2CH_3)$	Cl	F

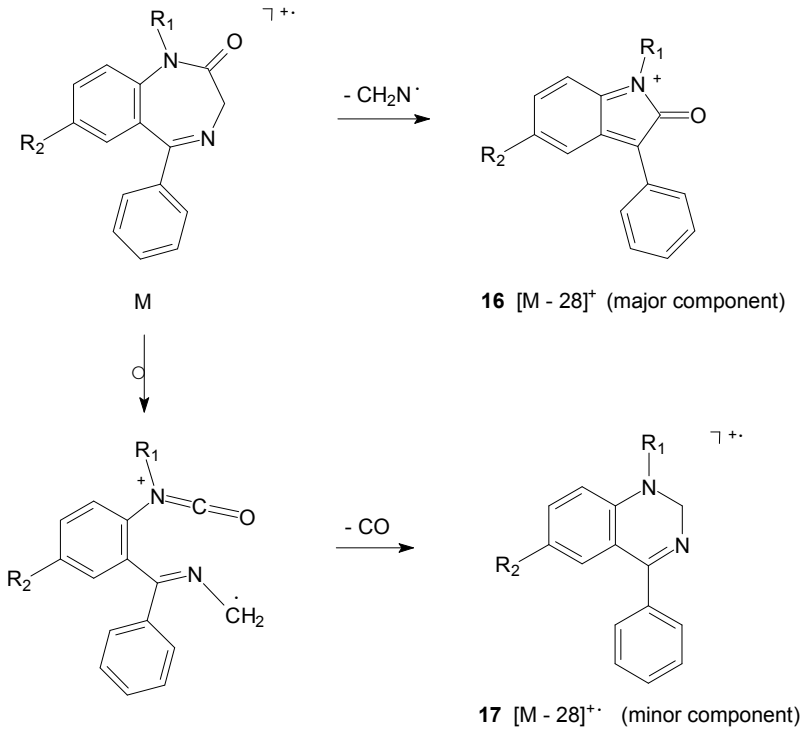
High resolution mass spectrometry,[29] study of metastable decompositions and deuterium labelling have been used for obtaining information about the formation of the ions $[M–H]^+$ from 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives.[33] Since the hydrogen radical is generally an unfavourable leaving

group, the high intensity of the ions corresponding to $[M–H]^+$ in the electron ionisation mass spectra of these compounds suggests efficient stabilization of the resulting ions.[33] From the examination of the molecular structure, it appears that a simple cleavage could not led to such an ion. It follows that there must be a rearrangement of the ring system accompanying this cleavage. One hydrogen might be eliminated from position 3, even if it has been found that it is involved only for a lesser extent (about 7%), from N(1) or from the aromatic rings. Although different mass spectrometric experiments do not allow to establish completely the origin of the hydrogen lost, a major pathway leading to the $[M–H]^+$ species has been proposed (Scheme 1). It involves a ring opening of the molecular ion followed by loss of hydrogen and a re-aromatisation effect that is the major driving force of the reaction.[33]



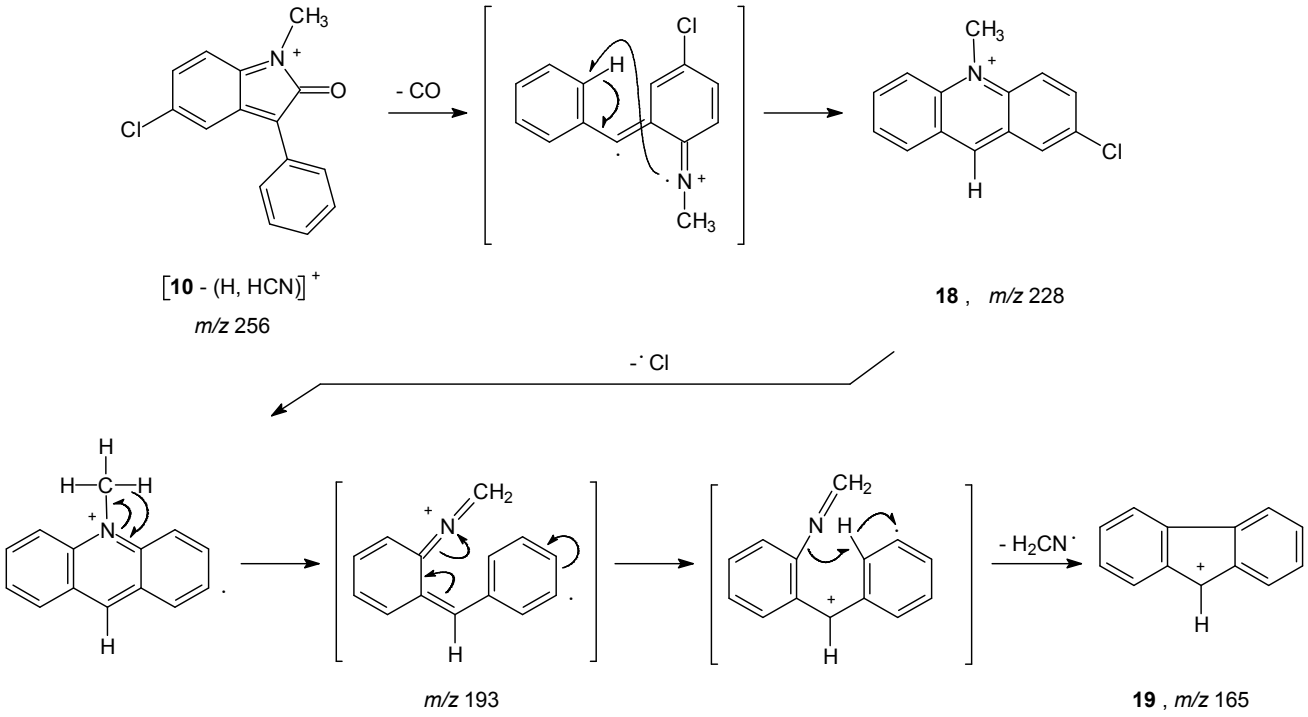
Scheme 1

Ions due to elimination of 28 and 29 u from the molecular ions are also observed in the mass spectra of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives.[32,33] Accurate mass measurements have shown that the $[M–28]^+$ ions are a doublet attributable to the isobaric $[M–CO]^{+\bullet}$ and $[M–(H, HCN)]^+$ species. In the case of **5**, the latter ion is about 20 times as intense than the former.[32] In both the fragmentation pathways, a contraction of the seven-membered ring occurs, yielding the indolone cation **16** and the quinazoline radical cation **17**, respectively (Scheme 2).



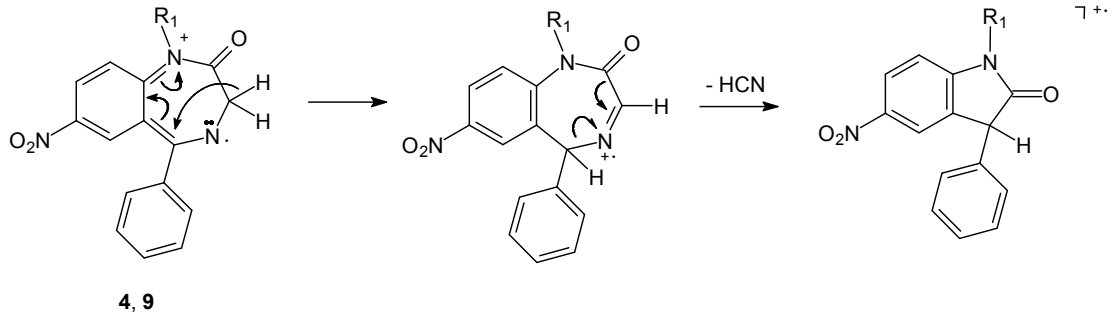
Scheme 2

Similarly to the gas phase behaviour of lactams,[34] the indolone **16** can eliminate CO, thus producing a four-membered ring system. However **16** can also rearrange to the highly stabilized acridine derivative **18** that, according to the fragmentation pathway reported in Scheme 3 for compound **10**, can yield the fluorene cation **19**.



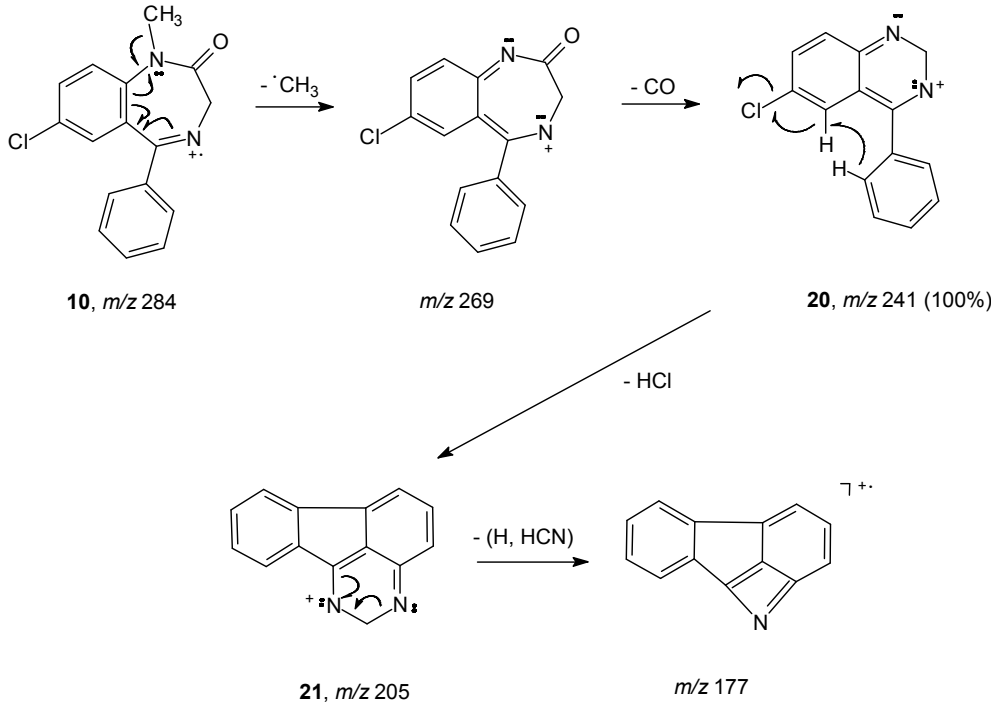
Scheme 3

The electron ionisation mass spectra of the 7-nitro derivatives **4** and **9** show a distinctive loss of HCN from the molecular ion, yielding intense peaks, whose relative intensities are 45 and 80% for **4** and **9**, respectively.[32] The ions $[M–HCN]^{+\bullet}$, that are not detected in the EI mass spectra of 7-amino derivatives **2** and **11**, may be produced by hydride migration from C(3) to C(5) (Scheme 4).



Scheme 4

A common fragmentation pathway for 3-unsubstituted-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones consists in the elimination of the substituent at N(1) followed by loss of CO. A possible rationalization for compound **10** is reported in Scheme 5.[32] Accurate mass measurements showed that the ions at *m/z* 241 are a doublet consisting of an ion with elemental composition $C_{14}H_{10}N_2Cl$ (**20**, Scheme 5) and of a smaller peak (1/6th of intensity) corresponding to $[C_{14}H_8NOCl]^{+\bullet}$ generated by loss of a methyl radical from the indolone **16**.



10, *m/z* 284 *m/z* 269 **20**, *m/z* 241 (100%)

21, *m/z* 205 *m/z* 177

Scheme 5

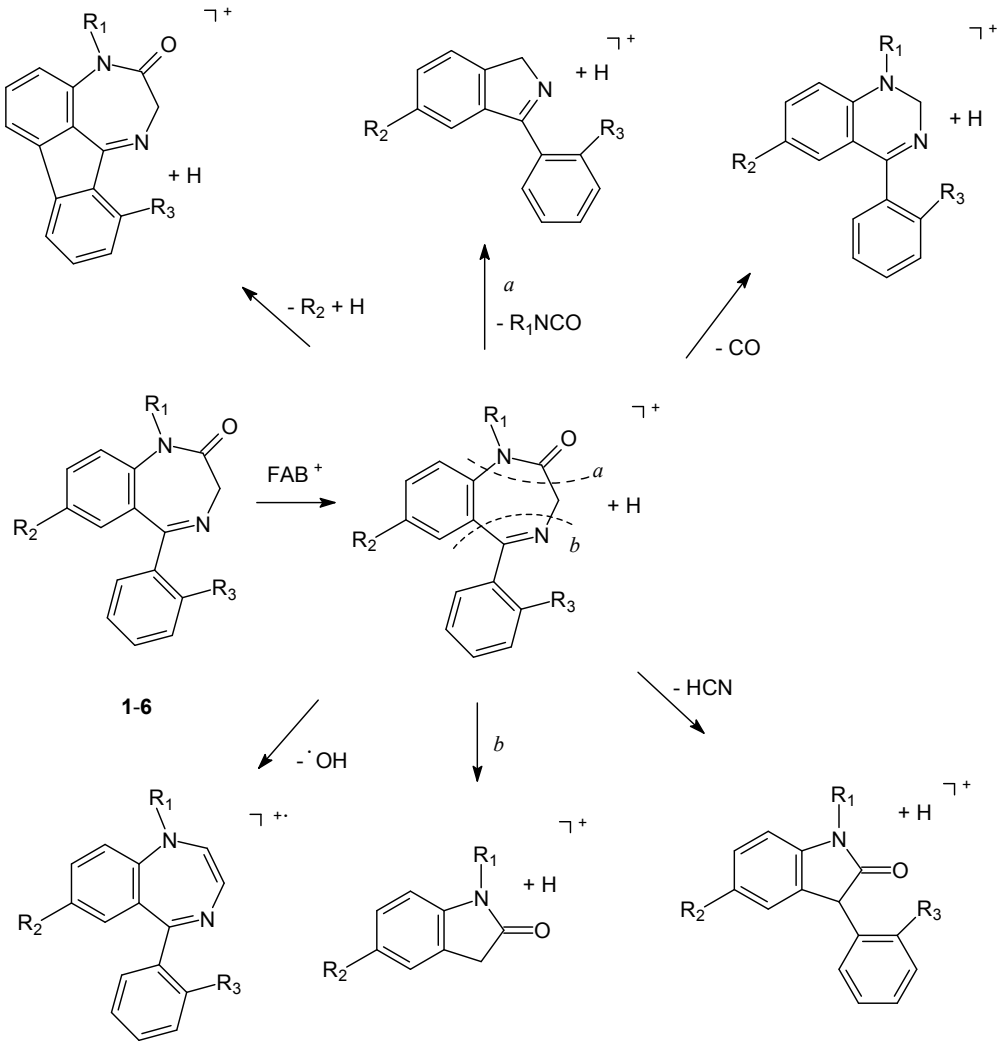
The species **20** (*m/z* 241), constituting the base peak of the mass spectrum of **10**, fragments by loss of HCl to the ions at *m/z* 205. This can be rationalized by formation of the fluorene **21** which then eliminates H and HCN to yield ions at *m/z* 177 (Scheme 5).[32] Interestingly, the loss of HCl could only be observed from an almost planar species and not from the intact benzodiazepines, in which the 5-phenyl ring is in another plane than the condensed benzene ring.[35]

Investigations based on the use of gas chromatography coupled with electron and chemical ionisation mass spectrometry have shown that thermal decomposition of benzodiazepines can occur. As an example, 7-nitro derivatives nitrazepam (**4**) and clonazepam (**7**) show thermal instability with the reduction of the nitro group to the corresponding amine, although the source of hydrogen is by no means clear.[36]

Aimed at avoiding any thermal decomposition, and at studying the effect of protonation on 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives, fast atom bombardment ionisation, both in positive and in negative mode, together with tandem mass spectrometry, has been used.[37] With this ionisation technique, abundant protonated $[M+H]^+$ or deprotonated $[M–H]^–$ molecules are produced whose fragmentation pathways (Scheme 6) resemble those followed by the corresponding radical cations produced under electron ionisation conditions. This suggests that the energy deposition under FAB ionisation is the same order of magnitude as that given in EI.[37] Most of the decomposition processes are related to cleavages of the diazepine ring that yield ring contraction. The loss of a radical OH, observed under FAB conditions, suggests that the protonation reaction could mainly occur at the oxygen atom of the carboxyl group. The use of FAB with negative ions produces a decrease of one order of magnitude in sensitivity, with few and scarcely abundant fragment ions.[37]

More recently, the gas phase behaviour of the benzodiazepine derivatives **5** and **10** has been studied by using atmospheric pressure ionisation techniques (Table 2).[38,39] It has allowed to investigate the behaviour of even-electron ions that are produced by these techniques. In the electrospray spectra of **5** and **10**, the protonated molecules $[M+H]^+$ produce the most intense peak. In source fragmentation is quite scarce, with

the exception of the ions due to $[MH–(CO, C_6H_5CN)]^+$ (*m/z* 140) in the mass spectrum of **5**, whose relative abundance is 76%.



Scheme 6

Collision induced dissociation (CID) MS/MS experiments, carried out in a triple quadrupole under low-energy regime, show a primary loss of CO from the protonated molecules of **5** and **10**. A competitive fragmentation pathway involves the primary loss of R_1-N=C=O. In the high-energy conditions, obtained in a double sector mass spectrometer, the CID MS/MS spectra are quite different from those obtained under the low energy regime. The only intense fragment ion is produced by a loss of a hydrogen atom, in competition with the elimination of elemental hydrogen or of hydrogen chloride. Ionisation due to particle bombardment (MeV ions or photons) (PDMS) produces $[M+H]^+$ ions with minor fragment ions attributable to $[MH–CO–H_2]^+$ and $[MH–CO–CH_4]^+$ (Table 2).

Electrospray ionisation, in conjunction with multiple collisional activation steps (MS^n), occurring in an ion trap, has been used for the characterization of 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones (Table 3).[38] Their decomposition pathways are depicted in Scheme 7. The loss of CO from the protonated species observed under MS^2 conditions is common to the fragmentation processes observed under electron ionisation and FAB by using quadrupole and double sector instruments, and it involves the seven-membered ring contraction. By selecting the $[MH–CO]^+$ ions, the MS^3 spectra show elimination of a chlorine atom, producing a resonance-stabilized radical cation (Scheme 7).

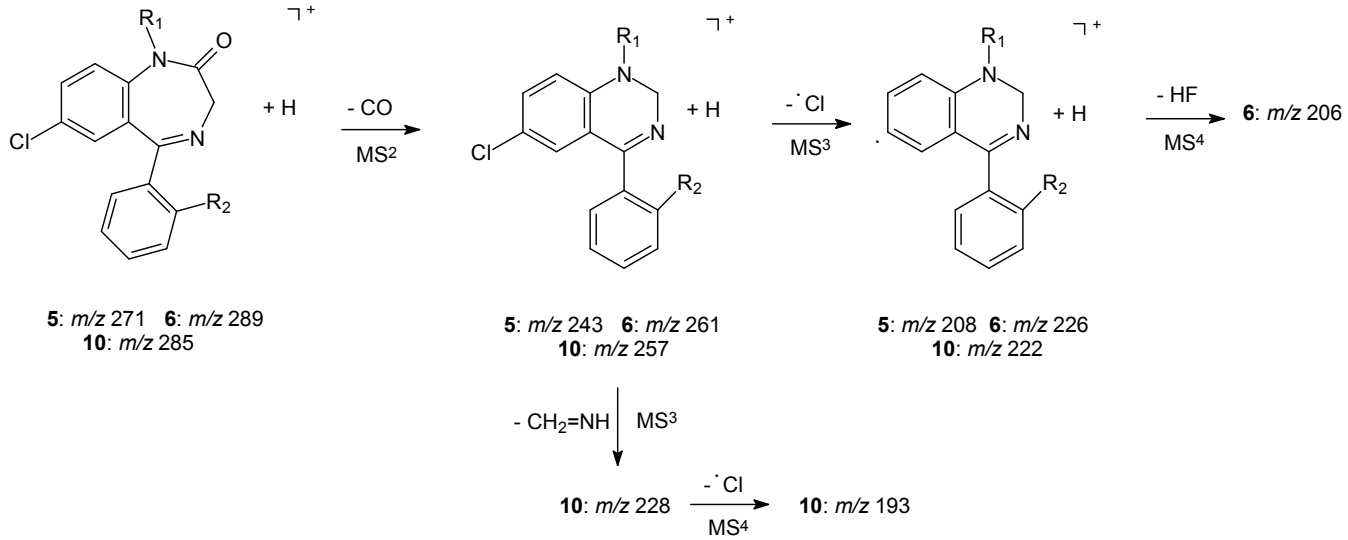
Table 2. Mass spectral data obtained by plasma desorption and electrospray ionisation for nordiazepam (**5**) and diazepam (**10**).

Ions	**Nordiazepam (5)**				**Diazepam (10)**			
	PDMS	**ESI-MS** [a]	**ESI-CID QqQ** [b]	**ESI-CID B/E** [c]	**PDMS**	**ESI-MS** [a]	**ESI-CID QqQ** [b]	**ESI-CID B/E** [c]
$[M+H]^+$	100	100	76	>> 100	100	100	45	>> 100
$M^{+\bullet}$	–	–	–	100	–	–	–	100
$[MH–H_2]^+$	–	–	–	30	–	–	–	8
$[MH–CO]^+$	–	12	14	–	–	16	17	–
$[MH–CO–H_2]^+$	16	–	–	9	22	–	2	8
$[MH–HCl]^+$	–	–	–	16	–	–	–	8
$[MH–CO–CH_4]^+$	–	–	–	–	6	–	12	3
$[MH–CO–H_2–HCN]^+$, $[MH–CH_3NCO]^+$	–	–	–	–	4	11	24	7
$[MH–NHCO–H_2]^+$	–	11	21	–	–	–	–	–
$[MH–CO–Cl]^+$	–	36	62	–	–	20	52	–
$[MH–NHCO–Cl]^+$	4	7	12	–	–	–	–	–
$[MH–CO–C_6H_6]^+$	15	38	81	4	–	–	–	–
$[m/z\ 228 – Cl]^{+\bullet}$	–	–	–	–	–	21	93	8
$[MH–CO–C_6H_5CN]^+$	10	76	100	9	2	27	100	2
m/z 105	–	7	7	–	–	–	–	–
m/z 91	–	31	19	–	–	–	–	–

[a] Cone voltage 50V

[b] QqQ=triple quadrupole analyser. Cone voltage 20V, collision energy 20eV

[c] B= magnetic analyser E= electrostatic analyser



Scheme 7

Table 3. MS^n CID decomposition data obtained by electrospray ionisation for 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones.

	Ions (*m/z*)				
Compound	**MS** $[M+H]^+$	**MS^2**	**MS^3**	**MS^4**	**MS^5**
7-Aminonitrazepam (**2**)	252	224, 121			
7-Acetamidonitrazepam (**3**)	294	207	180		
Nitrazepam (**4**)	282	236	207, 180		
Nordiazepam (**5**)	271	243	208		
N-Desalkylflurazepam (**6**)	289	261	226	206	
Diazepam (**10**)	285	257	228, 222	193	
7-Aminoflunitrazepam (**11**)	284	264	236	208	181
Flunitrazepam (**12**)	314	268	239	224	
N-(2-hydroxyethyl)flurazepam (**14**)	331	315	272	244	217
Flurazepam (**15**)	388	315	272	244	217

Diazepam (**10**) can follow an alternative fragmentation pathway that involves the loss of 29 u from the $[MH–CO]^+$ ions. This yields the species at *m/z* 228 that, in turn, lose a chlorine atom (Scheme 7). Ions at *m/z* 228 are produced also in the MS^2 spectra obtained with an ion trap by selecting the protonated molecules of **10** produced by chemical ionisation.[40] Ions $[MH–CO–Cl]^{+\bullet}$, produced by *N*-desalkylflurazepam (**6**), undergo loss of 20 u at the MS^4 stage that has been attributed to HF. As the C-F bond is quite strong (average bond energy 485 kJ mol^{-1}), it has been proposed that the driving force in this fragmentation is the large negative heat of formation of the ejected HF molecule ($\Delta H_f^0 = -271.1$ kJ mol^{-1}).[38]

7-Aminoflunitrazepam (**11**) has an extensive fragmentation in ESI-MS^n experiments (Figure 1). It is initiated by loss of HF from the protonated molecules (*m/z* 284), at the MS^2 stage (Scheme 8). Ions at *m/z* 264 are formed which, in turn, eliminate CO at the MS^3 stage, yielding a six-membered heterocyclic ring, also produced by fragmentation of protonated diazepam (**10**). A successive loss of 28 u, probably due to the NCH_2 radical (MS^4), produces a dismantling of the six-membered ring. At the MS^5 stage, elimination of HCN from the radical cation at *m/z* 208 produces the species at *m/z* 181 to which an aminophenyltropilium structure might be assigned (Scheme 8).[38]

When a large substituent is bound to N(1), it can be eliminated from the protonated molecule. It occurs in flurazepam (**15**), in which a diethylamine molecule is eliminated at the MS^2 stage from the diethylaminoethyl group bound to N(1) (Scheme 9).[38] The successive loss of 43 u (MS^3) has been tentatively assigned to HN=C=O with a consequent heterocyclic ring contraction. Alternatively, elimination of $^{\bullet}COCH_3$ should be also possible. In both cases, migration of an alkyl group is required. The successive collisional activation steps show losses of 28 (MS^4) and 27 u (MS^5), attributable to $^{\bullet}NCH_2$ and $^{\bullet}CH=CH_2$, respectively (Scheme 9).[38]

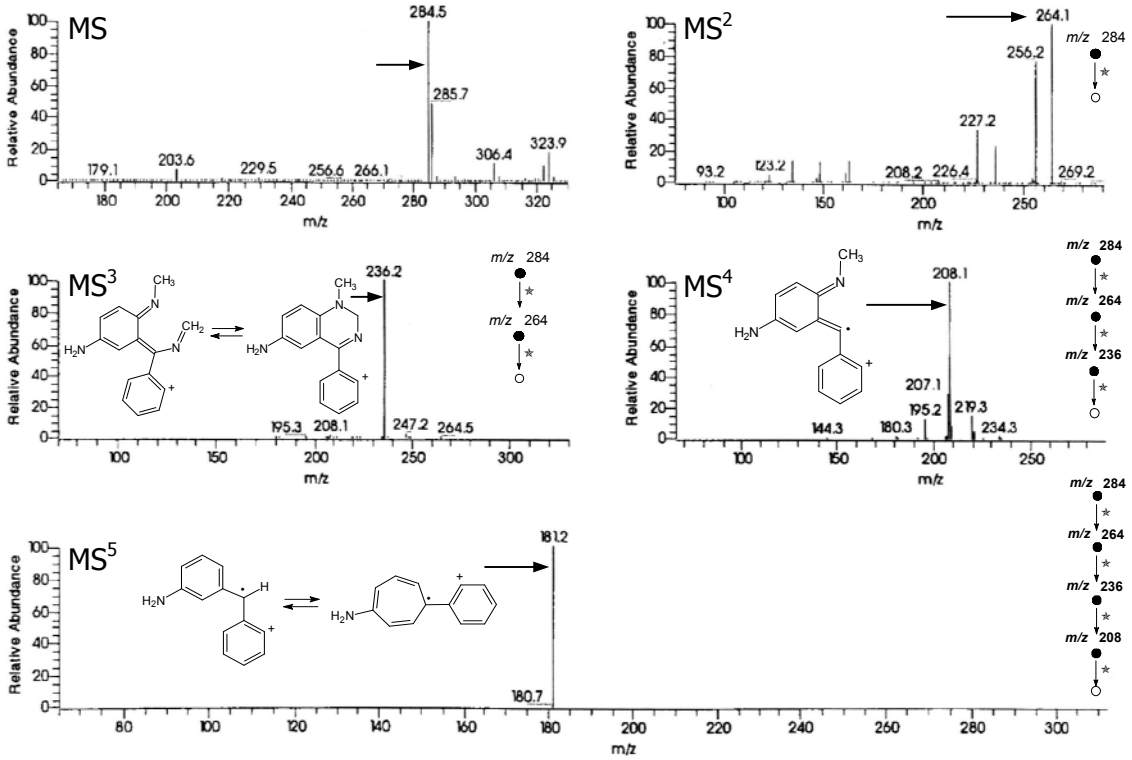
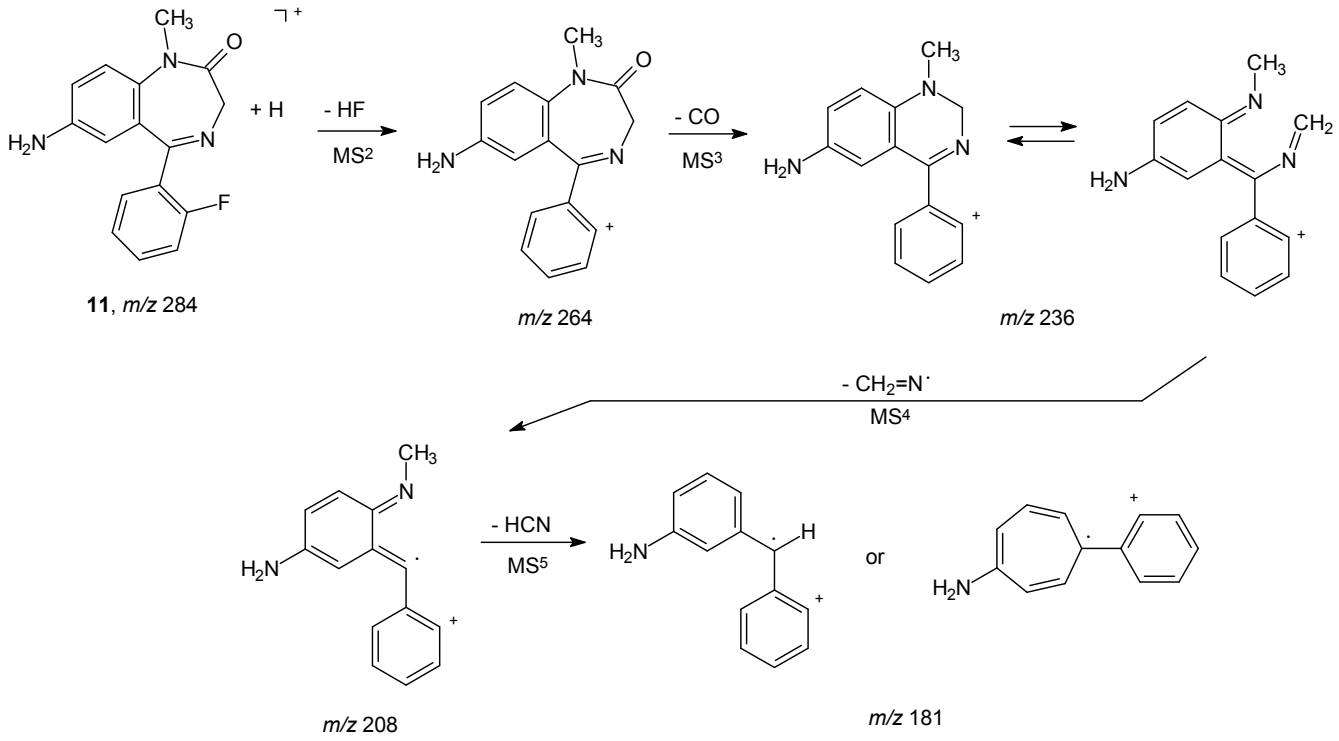


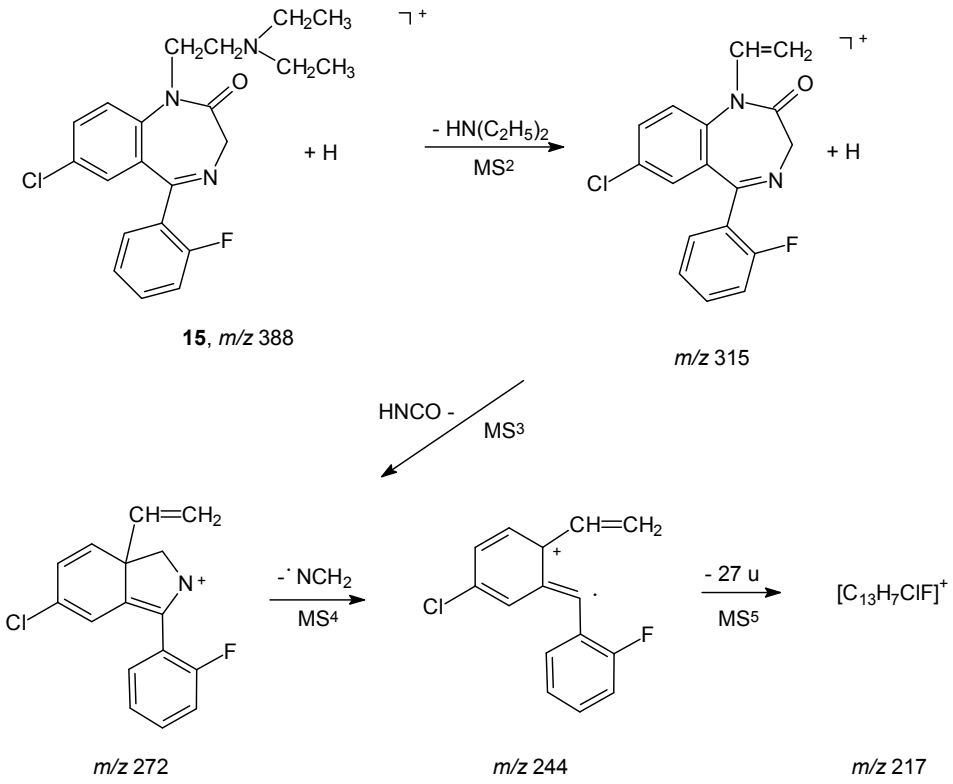
Figure 1. ESI-MS^n spectra of 7-aminoflunitrazepam (**11**). Adapted from ref. 38.



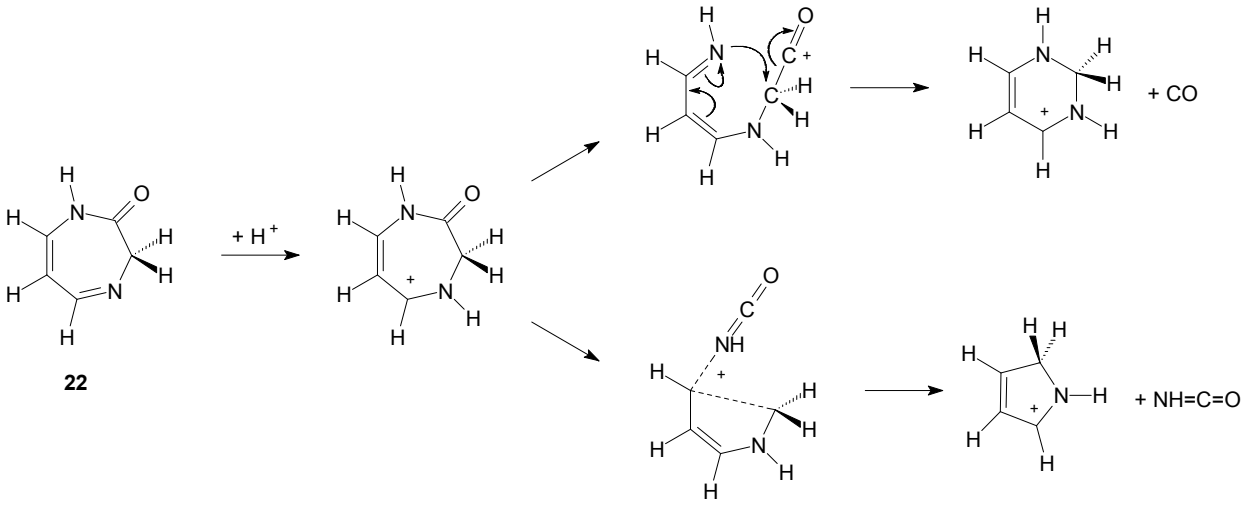
Scheme 8

Aimed at obtaining information about the site of protonation, different protonated forms of the 1,4-diazepine-2-one (**22**), chosen as a model compound, have been submitted to *ab initio* calculations. It resulted that the most stable cation is when protonation occurs at the imine function. The resulting structure is more stable of that produced by protonation at the oxygen atom (ΔE=113 kJ mol^{-1}) and of that protonated at N(1) (ΔE=189 kJ mol^{-1}).[39] Different ring opening mechanisms on both sides of the carbonyl group, and the great

stability of the final states explain the competitive elimination of CO and HN=C=O from $[M+H]^+$ (Scheme 10).



Scheme 9

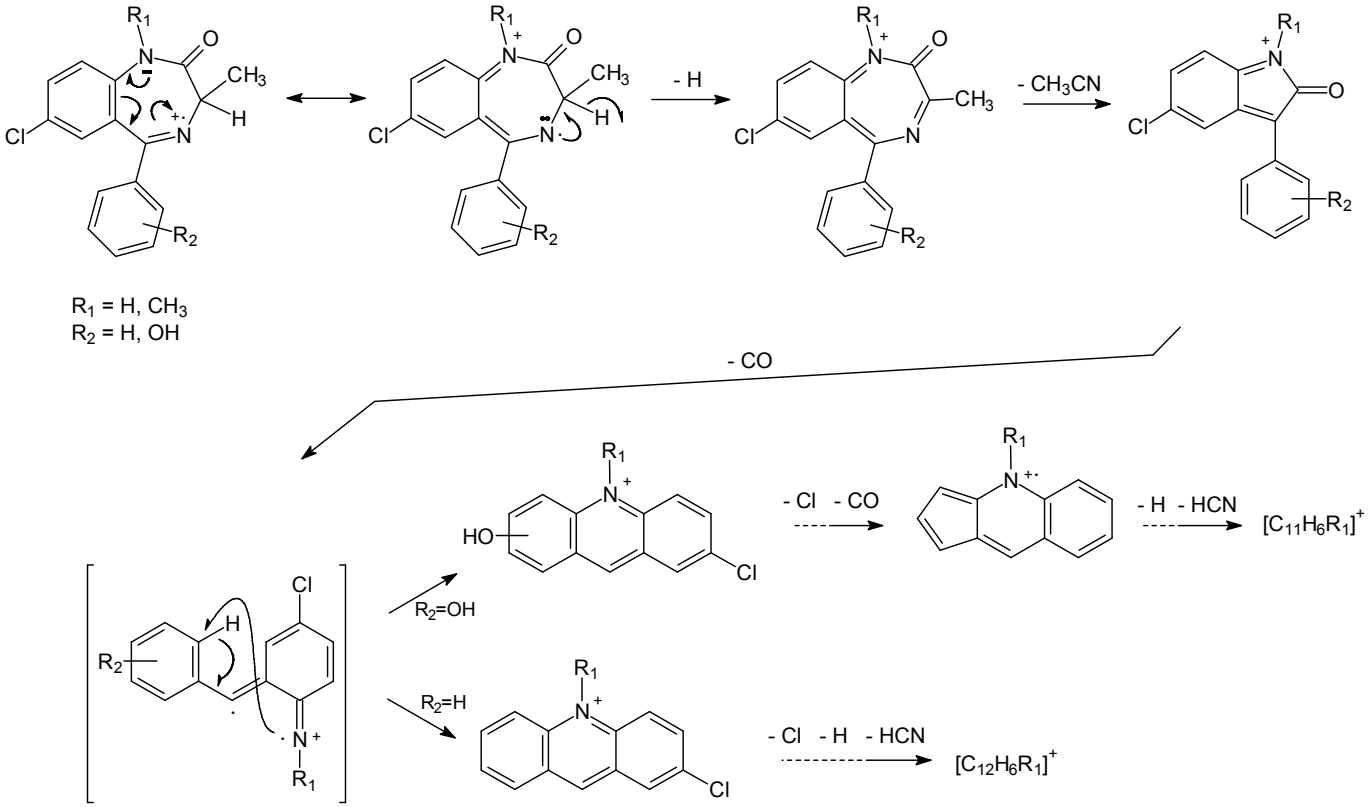


Scheme 10

2.2. 3-Alkyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones

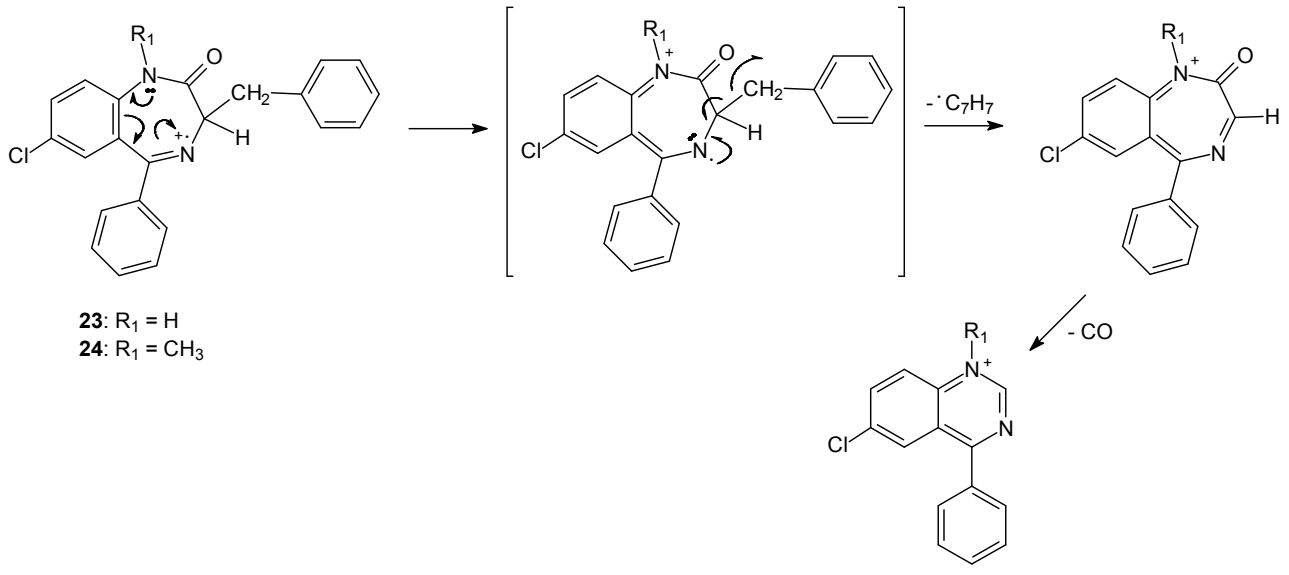
1,4-Benzodiazepines possessing a chiral centre at position 3, due to the substitution by an alkyl chain, have been synthesized and characterized by mass spectrometry. 3-Methyl derivatives of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-one have been studied by electron ionisation mass spectrometry and metastable ion analysis.[41] Their molecular ions have high abundance, generally higher than 60%. They show an initial loss of a hydrogen atom followed by elimination of CH_3CN (Scheme 11). These fragment ions, together with the

molecular ions, constitute the most abundant ions in their mass spectra. Other ionic species, produced by further losses of CO, Cl, HCN, have quite low relative intensity (generally <10%).[41]



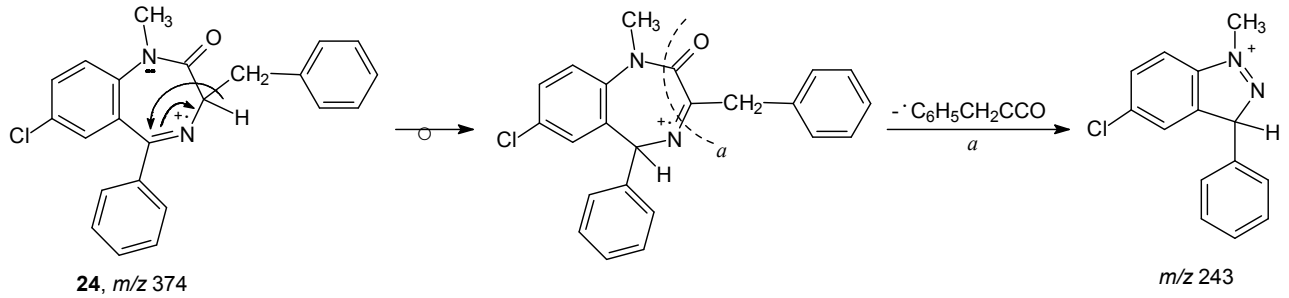
Scheme 11

The electron ionisation mass spectra of 3-benzyl derivatives **23** and **24** (Scheme 12) show that the base peaks are due to the elimination of the benzyl/tropilium radical.[41] Owing to a successive elimination of CO, a quinazolinium cation, commonly encountered in the fragmentation of 1,4-benzodiazepines unsubstituted at C(3), is formed (Scheme 12).



Scheme 12

Other abundant ions are due to a tropilium cation at *m/z* 91 and to the species at *m/z* 131, attributable to $[OCCCH_2C_6H_5]^+$ that contains both the C(2) and C(3) atoms. This latter species can be also eliminated as a radical from the molecular ion; in the case of compound **24**, ions at *m/z* 243 are produced (Scheme 13). A distinctive fragmentation pathway for **23** and **24**, confirmed by the presence of metastable ions, consists in the elimination of $^{\bullet}R_1NCOH$ from the molecular ion after a hydrogen transfer on the leaving group. This pathway is not observed for the molecular ions of 3-unsubstituted-1,4-benzodiazepine-2-ones.



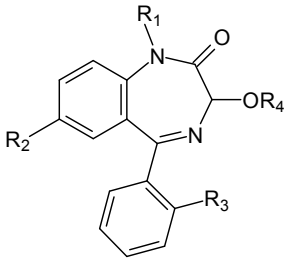
24, *m/z* 374

Scheme 13

2.3. 3-Hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one derivatives

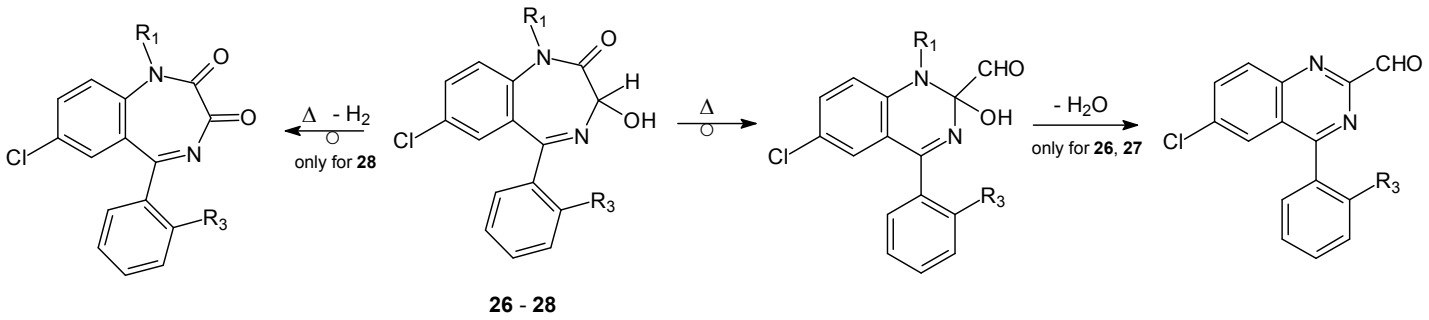
Different 3-hydroxy-1,4-benzodiazepines have been studied by mass spectrometry (Table 4). Some of them, and in particular derivatives **26-28** (Table 4), are known to be thermally unstable. The mechanism proposed for their thermal decomposition is a Frigerio-type rearrangement producing a ring contraction followed by a loss of water to form a stable aromatic structure (Scheme 14).[36]

Table 4. Chemical structures of 3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-3-ones.



Compound	Commercial name	R_1	R_2	R_3	R_4
25		H	NO_2	H	H
26	Oxazepam	H	Cl	H	H
27	Lorazepam	H	Cl	Cl	H
28	Temazepam	CH_3	Cl	H	H
29		H	NO_2	H	$COCH_3$
30		CH_3	Cl	H	$COCH_3$
31		CH_3	NO_2	H	$COCH_3$
32	3-Hydroxyflunitrazepam	CH_3	NO_2	F	H

The GC-MS analysis shows a partial decomposition of temazepam (**28**) producing two well-separated peaks. One should result by a rearrangement product due to the seven-membered ring contraction. The second peak has been attributed to an oxidized 2,3-diketo product with a molecular ion 2 u less than that of the parent compound (Scheme 14).[38]

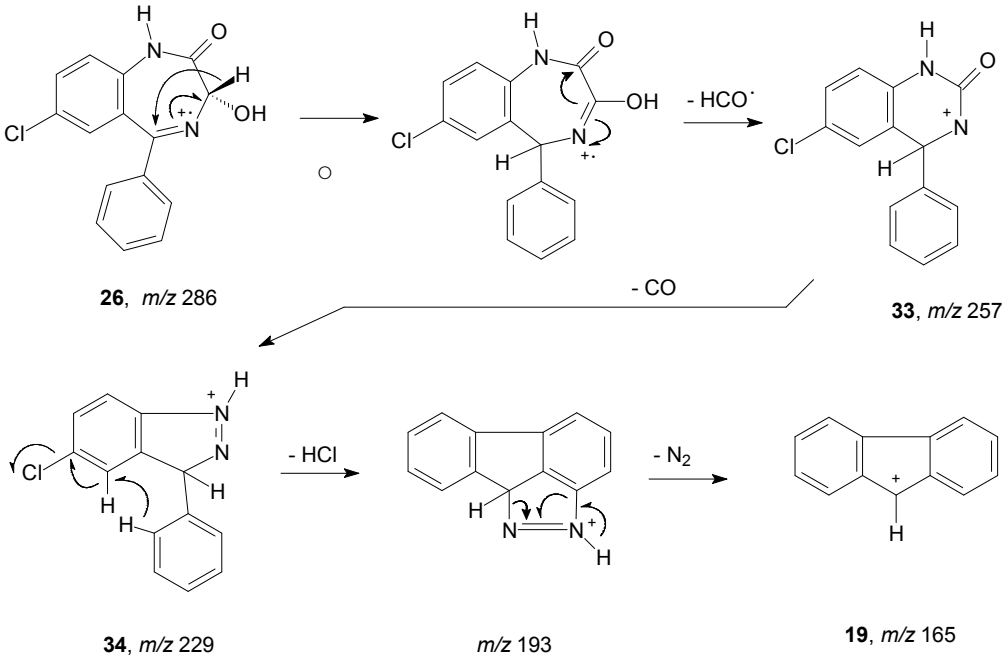


26 - **28**

Scheme 14

The electron ionisation mass spectra of 3-OH and 3-OAc derivatives are closely related. The molecular ions of 3-acetyl derivatives have a very small abundance (less than 5%), while the base peak is generally due to CH_3CO^+ at *m/z* 43. Accurate mass measurements and the study of metastable ions have been performed for elucidating the fragmentation pathways. The loss of ketene from the molecular ions of 3-acetyl derivatives produces the corresponding 3-hydroxy derivatives since further fragmentation is almost identical.

The fragmentation pathway proposed for the molecular ion of oxazepam (**26**) is reported in Scheme 15.[32] It consists in the losses of H, $^{\bullet}OH$ and H_2O. In most cases, the base peak of the mass spectrum is produced by the loss of a formyl radical (Scheme 15). According to the Author's interpretation, a hydride migration from C(3) to C(5) might occur before the loss of $HCO^{\bullet}$ that produces the quinazolinone **33**. The further loss of CO yields the indazole cation **34** at *m/z* 229 (Scheme 15). This latter can eliminate a chlorine atom, yielding ions at *m/z* 194.



26, *m/z* 286

33, *m/z* 257

34, *m/z* 229

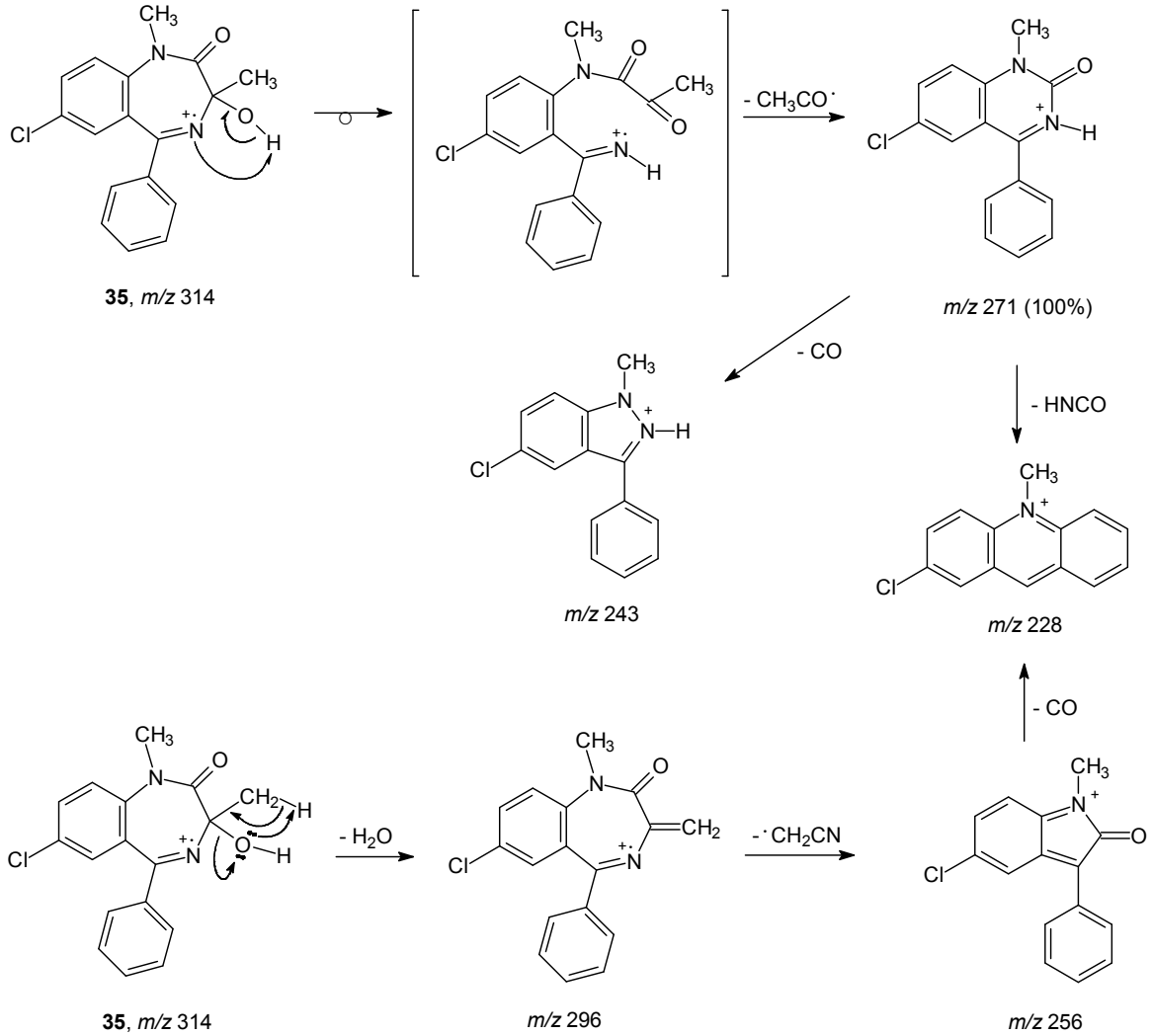
m/z 193

19, *m/z* 165

Scheme 15

Metastable ions and high resolution measurements revealed a further decomposition of the indazole **34** consisting in the loss of HCl followed by that of N_2 (Scheme 15). This fragmentation pattern has as a final product the fluorene **19**, also produced by 3-unsubstituted derivatives but by a different pathway (see Scheme 3). In addition, 3-hydroxy compounds show losses of H, HOCN yielding ions whose abundance is generally below 15%. These eliminations are analogues to that of HCN lost by 3-unsubstituted compounds.[32]

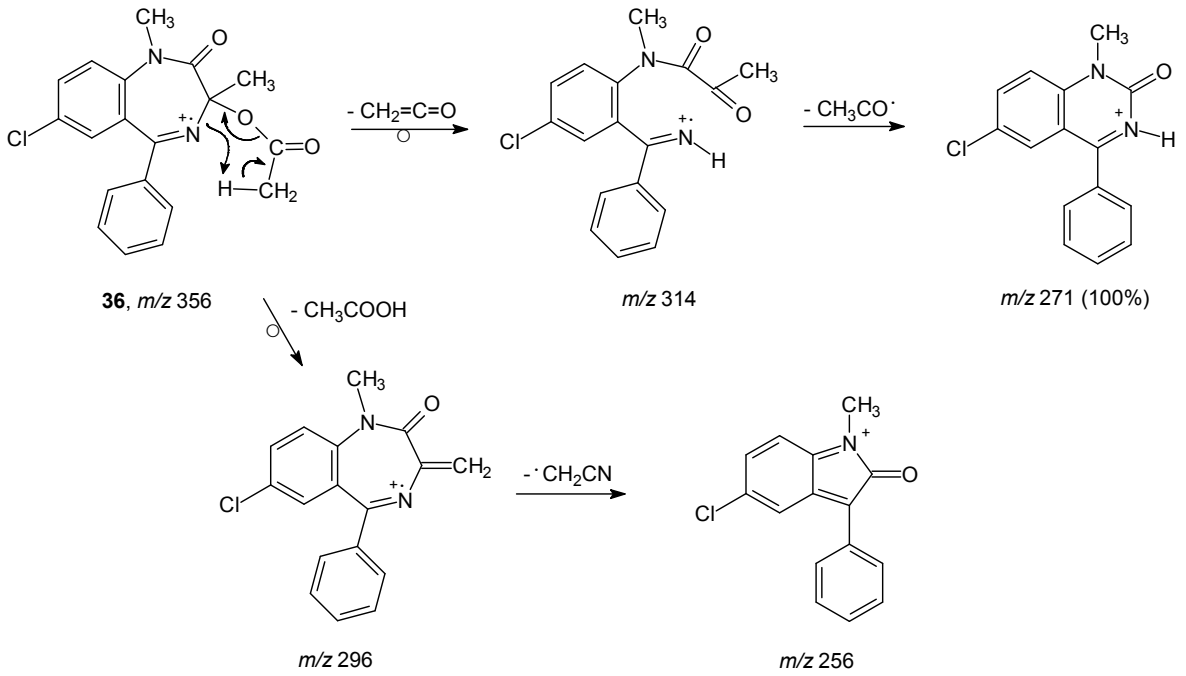
3-Hydroxy-1,4-benzodiazepine-2-ones, having a further alkyl group at position 3, have been synthesized and characterized by mass spectrometry.[41] The fragmentation pathway of **35** is characterized by the base peak due to elimination of $CH_3CO^{\bullet}$ from the molecular ion, whose relative abundance is 14%. According to the original paper,[41] this fragmentation is preceded by fission of the C(3)-N(4) bond with the consequent opening of the heterocyclic ring (Scheme 16).



Scheme 16

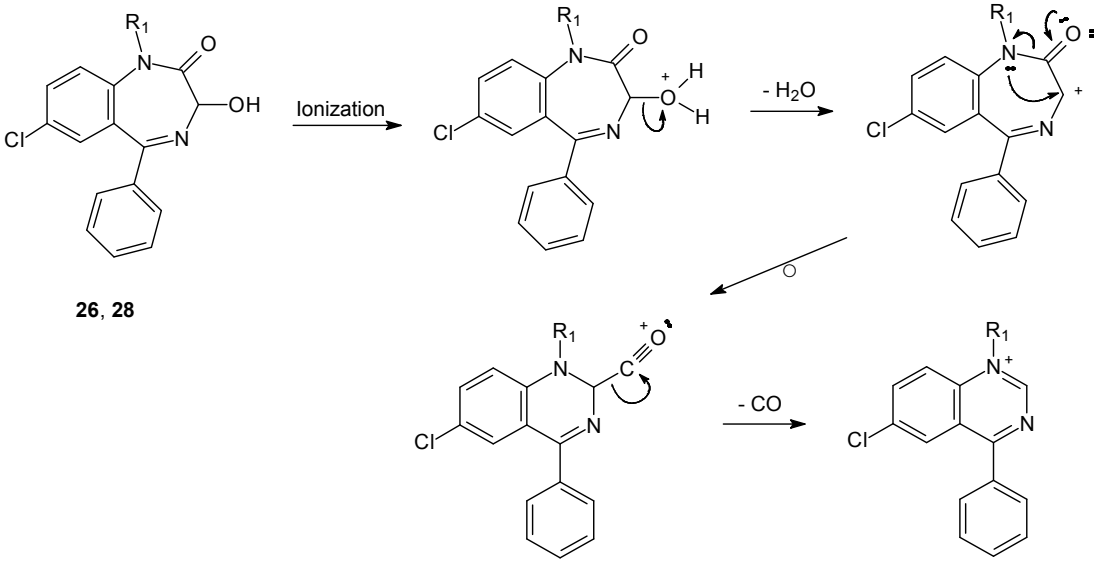
As the to elimination of $CH_3CO^{\bullet}$ from **35** is analogous to that of $HCO^{\bullet}$ from **26**, it is supposable that the same ring opening could occur in the fragmentation of the latter compound. Further loss of CO produces ions at *m/z* 243, while the elimination of HNCO yields the ions at *m/z* 228, possibly having an acridine structure. These latter ions could be also formed by an alternative fragmentation pathway starting with the elimination of H_2O from the molecular ion of **35**, followed by successive losses of $^{\bullet}CH_2CN$ and CO (Scheme 16).

3-Acetyl-3-hydroxy derivative **36** (Scheme 17) shows the loss of ketene from the molecular ion. The successive loss of $CH_3CO^{\bullet}$ yields ions at *m/z* 271 that, also for this compound, constitute the base peak of the electron ionisation mass spectrum. All the successive fragmentations are very scarce and resemble those of compound **35** (Scheme 16).[41] The study of metastable ions confirms the pathways proposed in Schemes 16 and 17.



Scheme 17

Under chemical ionisation conditions, followed by collisional activation, both protonated oxazepam (**26**) and temazepam (**28**) show losses of 18 and 46 u.[40] When the $[MH–18]^+$ fragment ions were collisionally activated, they dissociate exclusively by elimination of 28 u: This indicates that the loss of 46 u proceeds through a sequential mechanism involving successive losses of 18 and 28 u, this latter attributable to CO. The decomposition pathway proposed for the successive losses of water and CO from the protonated molecules of oxazepam (**26**) and temazepam (**28**) is reported in Scheme 18.[38]



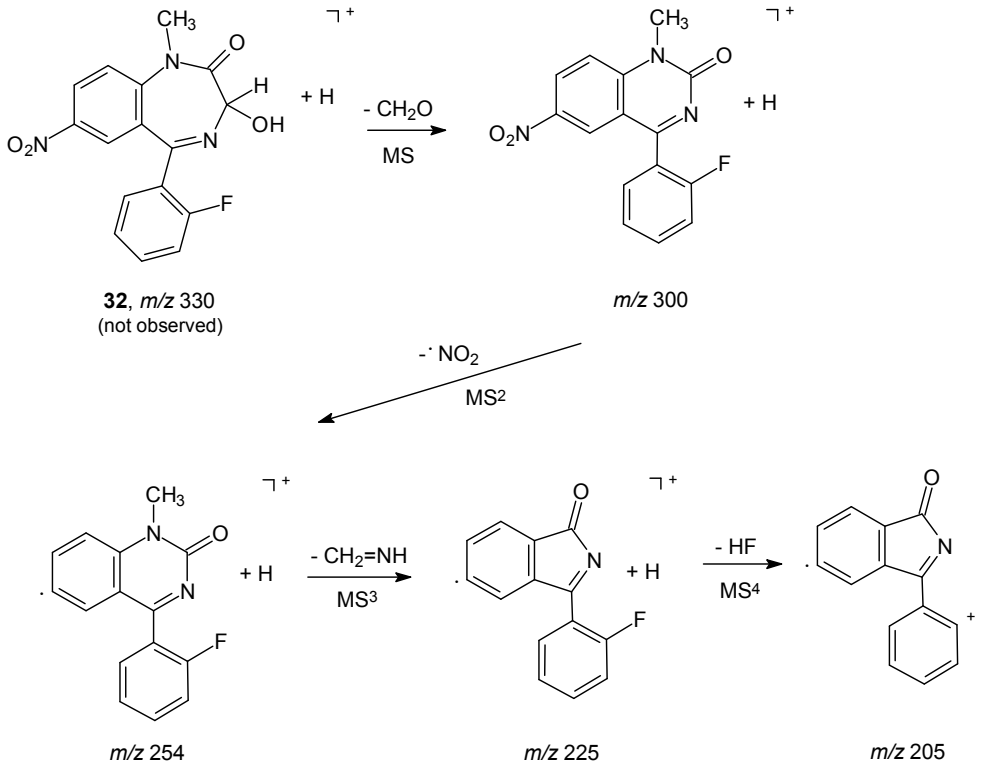
Scheme 18

Electrospray ionisation has been used for the characterization of 3-hydroxy derivatives of 1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones.[38] Their decomposition pathways determined by successive collisional activation steps are reported in Table 5.

Table 5. MS^n CID decomposition data obtained by electrospray ionisation for 3-hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones.

	Ions (*m/z*)			
Compound	**MS**	**MS^2**	**MS^3**	**MS^4**
Oxazepam (**26**)	287	269	241	163, 138
Lorazepam (**27**)	321	303	275	240, 205, 163
Temazepam (**28**)	301	283	255	
3-Hydroxyflunitrazepam (**32**)	300	254	225, 198	205

Owing to electrospray ionisation, the protonated molecule of 3-hydroxyflunitrazepam (**32**) completely decomposes by loss of a molecule of formaldehyde, producing ions at *m/z* 300, for which a ring contraction can be proposed, while $[M+H]^+$ is undetectable. Under collision induced dissociations, ions at *m/z* 300 lose $^{\bullet}NO_2$ (MS^3) followed by HF (MS^4) (Scheme 19).[38]



Scheme 19

Low energy collision-induced dissociations occurring in a triple quadrupole show the formation of intense peaks corresponding to a loss of water from the protonated molecules of oxazepam (**26**), lorazepam (**27**) and temaxepam (**28**). H/D exchange of labile hydrogen atoms showed that both hydrogens involved in the loss of water are labile. This fragmentation is followed by loss of CO, generally producing the base peak (Table 6).[39] At higher collision energy, the consecutive losses of H_2O and CO are in competition with the

elimination of 92, 56 and 73 u from protonated **26-28** (Table 6). [**27**+H]$^+$ eliminates two molecules of CO, or C_2O_2, and HCl to give the ions at *m/z* 229. [**26**+H]$^+$ loses C_2O_2 to give the species at *m/z* 231. Precursor-ion scans on *m/z* 231 yielded the only cation [**26**+H]$^+$, suggesting a one-step elimination of C_2O_2 instead of successive eliminations of two molecules of CO. The loss of 73 u from [**28**+H]$^+$ to give the ions at *m/z* 228 (no shifted at all after H/D exchange) might correspond either to a loss of HCN from [**28**+H–H_2O–CO]$^+$ (*m/z* 255) or to a direct elimination of $C_2H_3NO_2$ from the protonated molecule. Since no loss of HCN is observed in the CID spectra obtained by selecting the ions at *m/z* 255, a direct elimination of $C_2H_3NO_2$ is proposed.[39]

Table 6. Mass spectral data obtained by plasma desorption and electrospray ionisation for compounds **26-28**.

Ions	**Oxazepam (26)**				**Lorazepam (27)**				**Temazepam (28)**			
	PDMS	**ESI-MS**[a]	**ESI-CID QqQ**[b]	**ESI-CID B/E**[c]	**PDMS**	**ESI-MS**[a]	**ESI-CID QqQ**[b]	**ESI-CID B/E**[c]	**PDMS**	**ESI-MS**[a]	**ESI-CID QqQ**[b]	**ESI-CID B/E**[c]
$[M+H]^+$	100	96	–	>100	100	100	–	>100	100	55	2	>100
$M^{+\bullet}$	–	–	–	100	–	–	–	100	23	–	–	–
$[MH–H_2O]^+$	2	63	15	23	30	36	21	64	–	22	5	27
$[MH–Cl]^{+\bullet}$	–	–	–	–	–	–	–	20	–	–	–	–
$[MH–CO–H_2]^+$	19	–	6	4	17	–	–	–	29	–	–	–
$[MH–CO–CH_4]^+$	–	–	–	–		–	–	–	–	–	–	11
$[MH–H_2O–CO]^+$	9	100	100	5	34	62	100	9	48	100	100	24
$[MH–2CO]^+$	3	18	15	7	–	–	–	–	–	–	–	–
$[MH–2CO]^+$ or $[MH–OCCHOH]^{+\bullet}$	–	–	–	–	14	–	–	5	–	–	–	–
$[MH–2CO–HCl]^+$	–	–	–	–	25	18	31	11	–	–	–	–
$[MH–C_2H_2O_2]^+$	15	–	–	9	–	–	–	–	18	–	–	19
$[MH–C_2H_3NO_2]^+$	–	–	–	–	–	–	–	–	15	9	5	15
$[m/z\ 263–Cl]^{+\bullet}$	–	–	–	–	31	–	–	12	–	–	–	–
$[m/z\ 228–Cl]^{+\bullet}$	–	–	–	–	–	–	–	–	–	8	5	5
$[m/z\ 241–(C_6H_5,H)]^+$	–	–	7	–	–	–	–	–	–	–	–	–
$[m/z\ 231–(C_6H_5,H)]^+$	–	13	17	–	–	–	–	–	–	–	–	–
$[m/z\ 231–C_6H_5CN]^+$	–	34	25	–	–	–	–	–	–	–	–	–
$[C_6H_5CNH]^+$	–	–	38	–	–	–	–	–	36	5	2	5

[a] Cone voltage 50V

[b] QqQ=triple quadrupole analyser. Cone voltage 20V, collision energy 20eV

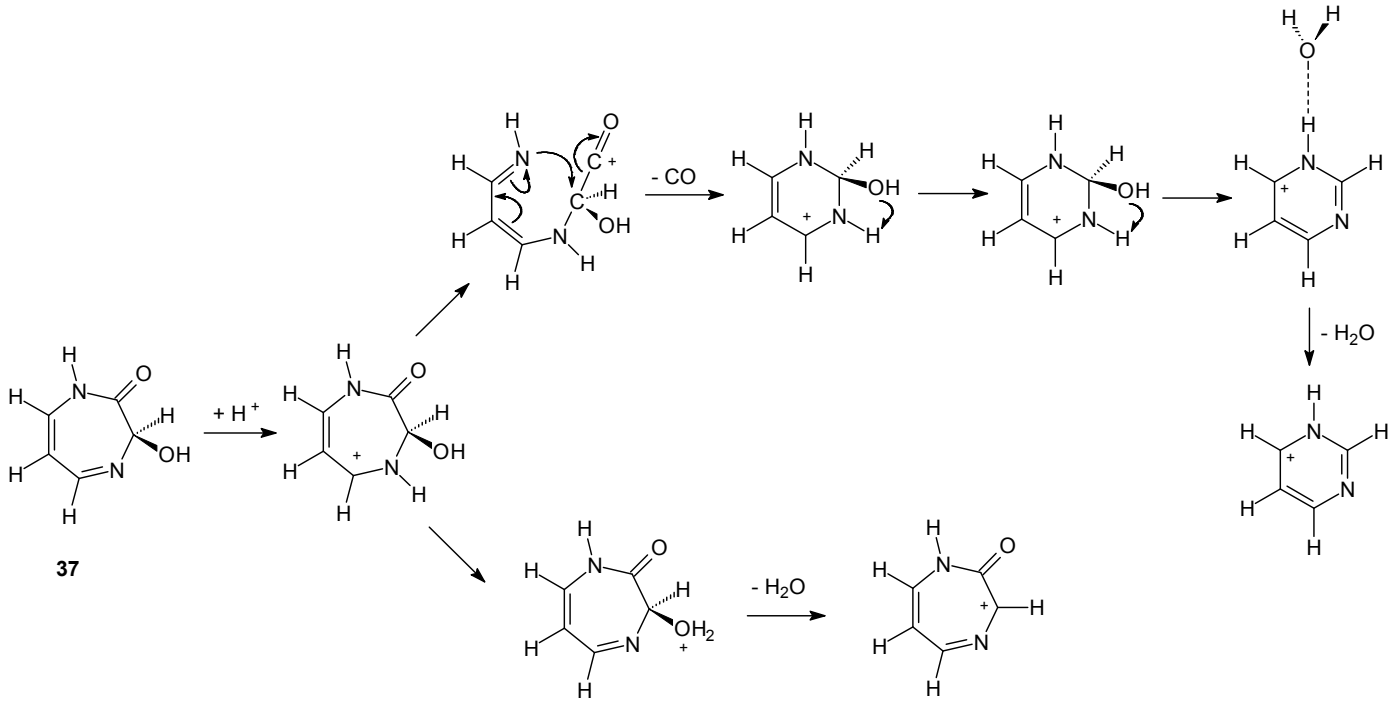
[c] B= magnetic analyser E= electrostatic analyser

Collision induced decompositions carried out in a high energy regime produce totally different MS/MS spectra. In these conditions, similarly to the behaviour of protonated nordiazepam (**5**) and diazepam (**10**) (see above), the decomposition of protonated molecules is dominated by the loss of a hydrogen atom. However

this decomposition is in competition with the elimination of water, which is the main decomposition process occurring in the low energy regime (Table 6).

Owing to ionisation by plasma desorption or laser desorption, the resulting mass spectra are characterized by scarce fragmentation. However, each compound (**26-28**) provides ions such as $[MH–CO]^+$, $[MH–CO–H_2]^+$ and $[MH–C_2H_2O_2]^+$ which are not observed either at low or at high collision energy. This suggests that a formation of these ions could involve a degradation, such as a CO loss, preceding the ionisation.[39]

In order to obtain further information on the gas phase behaviour of 3-hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-ones, theoretical calculations have been carried out on 3-hydroxy-1,3-dihydro-1,4-diazepin-2-one (**37**) chosen as a model compound. The most stable cation results when the protonation occurs at N(4) (Scheme 20).[39] Owing to opening of the seven-membered ring, a loss of CO can occur. After successive cyclisation, a molecule of water is lost. Alternatively, the protonated molecules can isomerise by transfer of a hydrogen atom from N(4) to the hydroxyl in position 3. From the resulting structure, a water molecule can be eliminated. (Scheme 20).[39] This last pathway, *i.e.* isomerisation and loss of water, is energetically unfavoured in respect to elimination of CO followed by that of water.

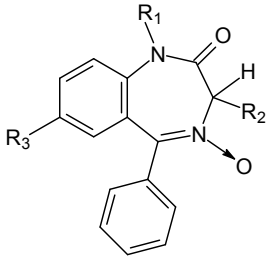


Scheme 20

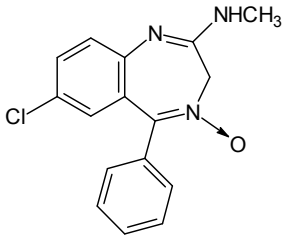
2.4. 5-Phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-N(4)-oxide derivatives

Electron ionisation mass spectra of different N(4)-oxide derivatives of 1,4-benzodiazepines (Table 7) have been obtained. As shown by NMR spectroscopy, the nitrone function in position 4 influences the electron structure of the seven-membered ring.[42] It follows that N(4)-oxides of 1,4-benzodiazepines should show a different gas phase behaviour in comparison with the other derivatives. Losses of H and CO occur under electron ionisation followed by a successive loss of an oxygen atom that yields a quinazoline cation (Scheme 21). In all EI mass spectra a loss of 17 u from the molecular ion is observed. Intense metastable ions supported the conclusion that the leaving group is an OH radical.[32]

Table 7. Chemical structures of common 5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepine-N(4)-oxides.

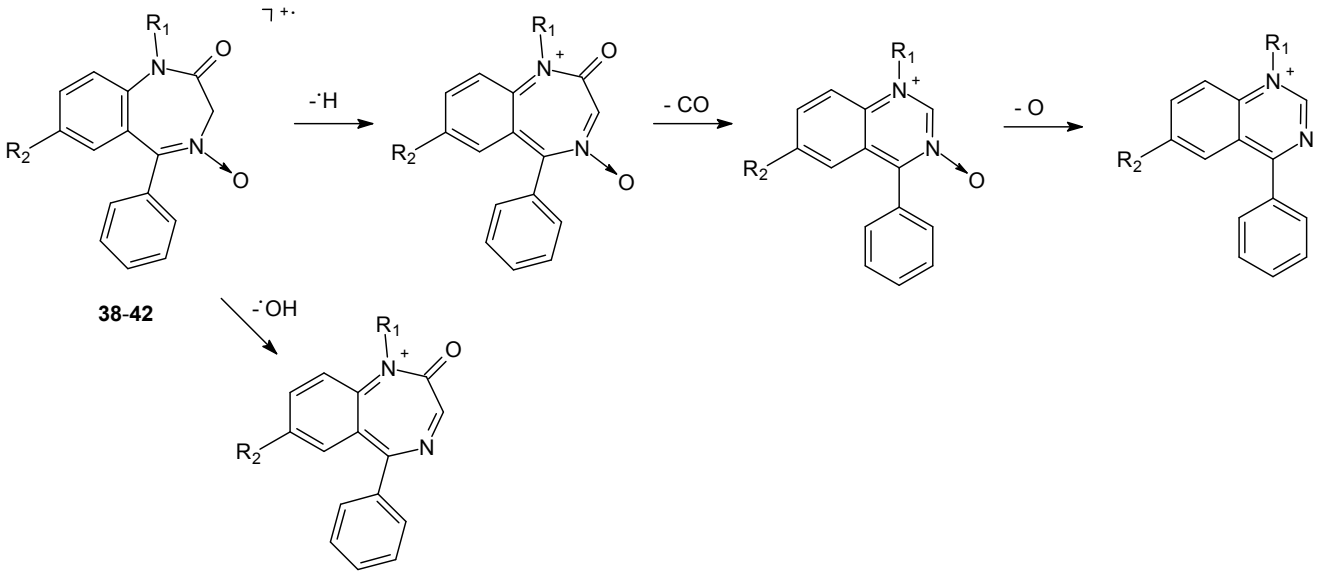


38-42



Chlordiazepoxide (**43**)

Compound	Commercial name	R_1	R_2	R_3
38	Demoxepam	H	H	Cl
39		H	H	NO_2
40		H	CH_3	NO_2
41		CH_3	H	Cl
42		CH_3	H	NO_2

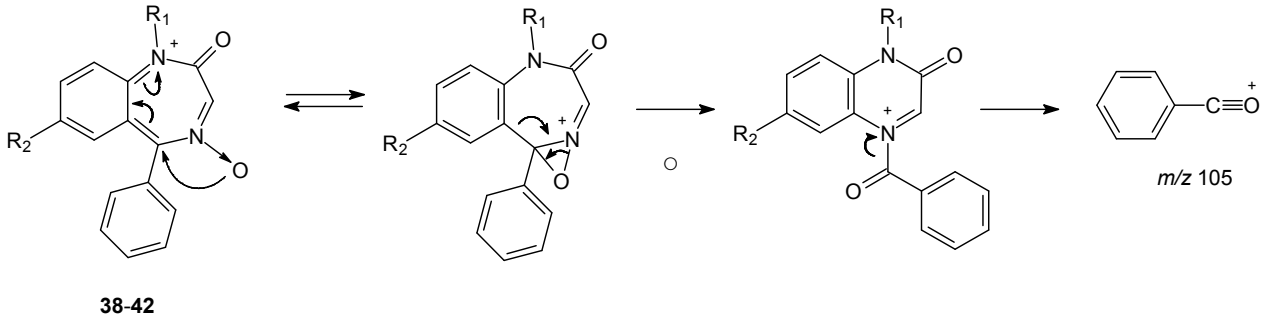


Scheme 21

The oxygen atom bound to N(4) might be orientated towards C(5), yielding a oxazirane derivative (Scheme 22).[32] An analogous photochemical reaction of chlordiazepoxide (**43**) to an oxazirane derivative, reversible upon heating, has been reported.[43] Owing to a rearrangement of the oxazirane, a 1,4-quinazolinone should be produced. This compound is analogous to that obtained by a Beckmann rearrangement. The mass spectra of all nitrones, chlorodiazepoxide (**43**) included, show a peak at *m/z* 105 with a relative abundance 14-21%, having formula C_7H_5O, undetected for all the other benzodiazepine derivatives. This ion might be produced from the 1,4-quinazolinone by cleavage of the exocyclic (O=)C-N bond (Scheme 22). 3-Methyl analogues show an analogous behaviour with successive eliminations of H, CO, O from the molecular ion.[41]

Owing to electrospray ionisation, $[M+H]^+$ ions are produced.[38,44] The protonated molecules produce under CID regime loss of 17 u, corresponding to the OH radical (Figure 2). At the MS^3 stage, this ion (*m/z* 283) yields three product ions at *m/z* 266, 255 and 227, the two former attributable to the loss of NH_3 and CH_2N, respectively. In MS^4 experiments, the ions at *m/z* 255 shows loss of 17 u, attributable to NH_3. As observed for all the other 1,4-benzodiazepine derivatives, the product ions observed in the MS^n spectra of

nitrones **38-43** appear to result from significant rearrangement of the heterocyclic ring, and it is very difficult to justify the resulting product ions from simple bond cleavage.[44]



38-42

Scheme 22

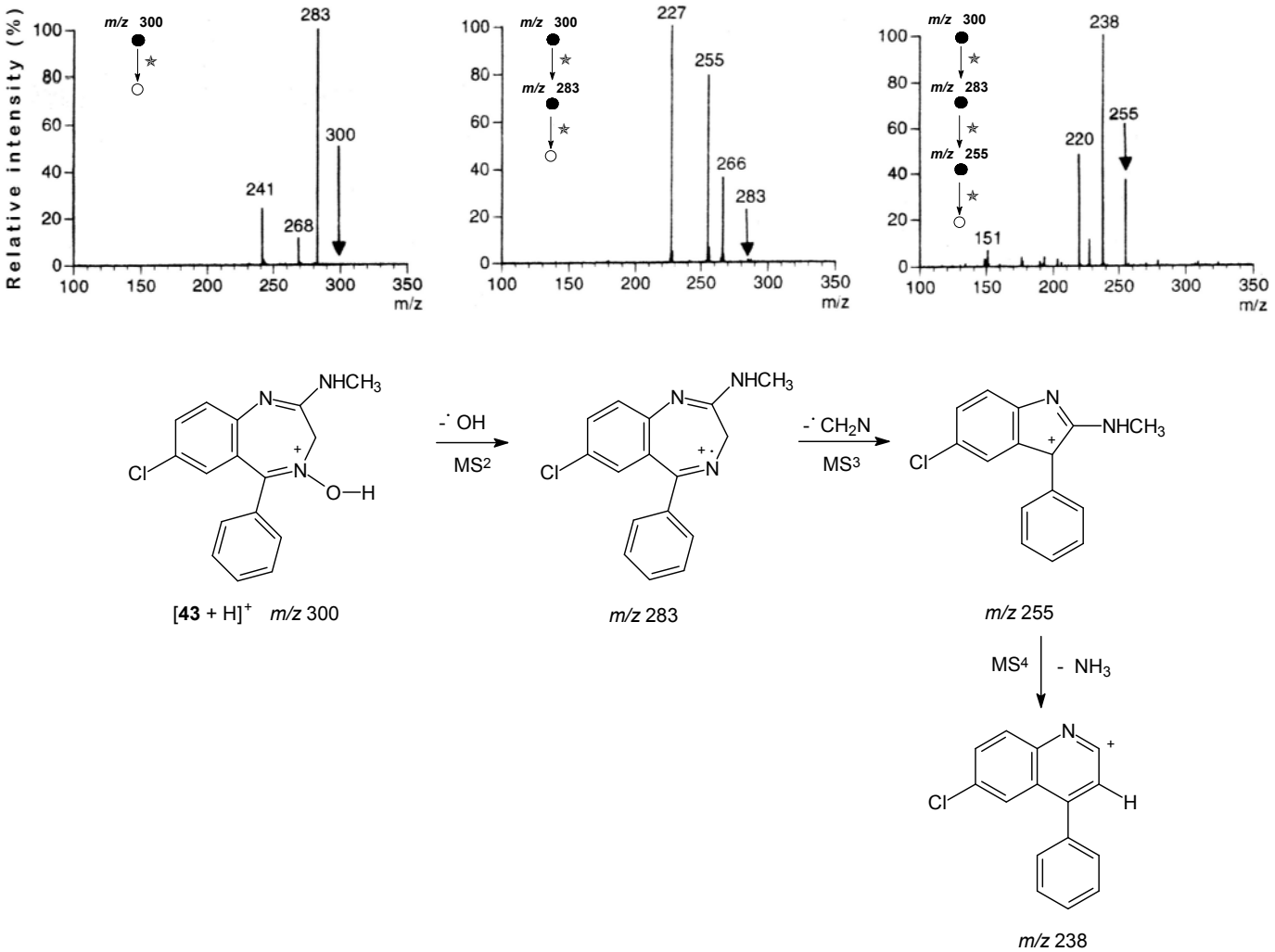
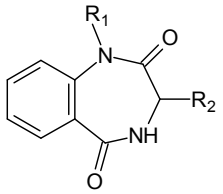


Figure 2. ESI-MS/MS spectra (*top*) of chlordiazepoxide (**43**) and proposed structures of product ions (*bottom*). Adapted from ref. 44.

2.5. 3,4-Dihydro-1*H*-1,4-benzodiazepine-2,5-diones

3,4-Dihydro-1*H*-1,4-benzodiazepine-2,5-diones are useful intermediates in the synthesis of pharmacologically active compounds.[45] A series of these derivatives (Table 8) has been obtained in good yields by reaction of the corresponding isatoic anhydride and amino acid in glacial acetic acid under reflux.[46]

Table 8. Chemical structure of 3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-dione derivatives.



Compound	R_1	R_2
44	H	H
45	CH_3	H
46	C_2H_5	H
47	C_6H_5	H
48	$CH_2C_6H_5$	H
49	H	CH_3
50	CH_3	CH_3
51	CH_3	$CH_2C_6H_5$
52	C_2H_5	CH_3

These compounds undergo facile cleavage of the diazepine ring under electron ionisation. The extent of fragmentation and its pathways are dependent on the nature of the substitution at the positions 1 and 3 of the diazepine ring.[46]

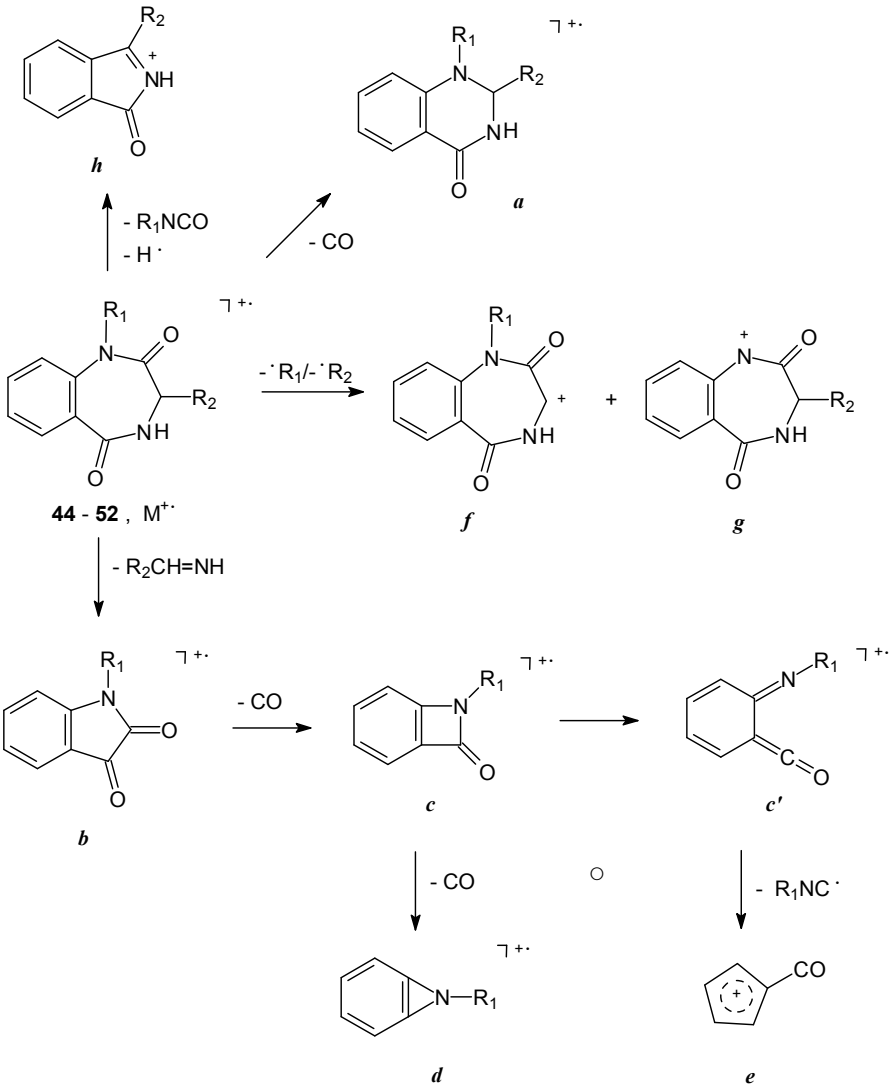
The electron ionisation mass spectra show the molecular ions having relative intensities ranging from 24 to 100%, their stability being generally reduced by the substitution of alkyl and/or phenyl groups at N(1) and/or C(3) (Table 9).[46]

Table 9. Partial EI mass spectral data (*m/z*, relative intensity (%)) of 3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-diones (**44**-**52**).[46]

Compound	$[M]^{+\bullet}$	*a*	*b*	*c*	*d*	*e*	*f*	*g*	*h*	*i*
44	176(100)	148(20)	147(48)	119(87)	91(17)	92(68)	175(3)	175(3)	–	120(67)
45	190(88)	162(17)	161(50)	133(41)	105(100)	92(11)	189(3)	–	132(13)	132(24)
46	204(95)	176(14)	175(43)	147(26)	119(100)	92(11)	203(4)	175(43)	132(41)	148(10)
47	252(41)	224(10)	223(9)	195(100)	167(23)	92(9)	–	–	–	196(19)
48	266(45)	–	237(4)	181(7)	–	–	–	175(5)	132(4)	209(4)
49	190(43)	162(6)	161(2)	–	–	–	–	–	–	119(54)
50	204(27)	176(<1)	161(100)	133(48)	105(82)	92(8)	–	–	146(4)	134(21)
51	280(5)	252(3)	161(100)	133(35)	105(46)	92(38)	189(38)	–	222(18)	134(22)
52	218(24)	190(<1)	175(100)	147(21)	119(97)	92(9)	–	–	146(20)	148(8)

The primary fragmentation is the loss of CO, also confirmed by metastable ions, yielding a dihydroquinazolinone ion ***a*** (Scheme 23). The abundance of this product ion depend upon the substitution at positions 1 and 3 of the diazepine ring, and this suggests that the loss of CO involves mainly C(2) instead of C(5). The other main fragmentation concerns the elimination of $R_2CH{=}NH$, giving an intense ion with an isatin structure (***b***, Scheme 23) from which a CO molecule can be eliminated. The resulting ion (***c***, Scheme

23) can rearrange to a ketimine structure and lose the R_1NC radical, yielding ions at *m/z* 92 (Scheme 23). Alternatively, ions ***c*** can eliminate CO. In the case of 1-benzyl- and 3-benzyl-3,4-dihydro-1*H*-1,4-benzodiazepine-2,5-diones, a prevailing fragmentation pathway consists in the loss of a benzyl/tropilium radical yielding intense ions (***f*** and ***g***, Scheme 23). Another fragmentation pathway yields an isoindolone cation ***h*** formed by consecutive losses of R_1NCO and H.



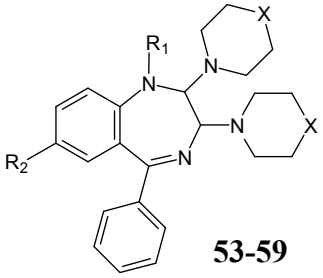
Scheme 23

2.6. Amino derivatives of 2,3-dihydro-1*H*-1,4-benzodiazepines

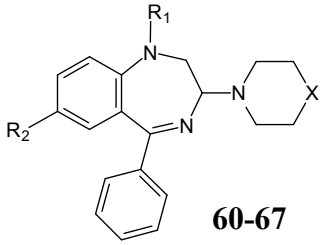
The gas phase behaviour of series of 2,3-diamino-2,3-dihydro-1*H*-1,4-benzodiazepines (**53-59**) and 3-amino-2,3-dihydro-1*H*-1,4-benzodiazepines (**60-67**) (Table 10) have been studied by electron ionisation mass spectrometry. Their fragmentation pattern have been elucidated with the aid of by deuterium labelled derivatives, high resolution mass measurements and metastable analysis performed by different techniques.[47] The most abundant ions produced in their electron ionisation mass spectra are reported in Table 11.

The fragmentation pattern of 2,3-diamino derivatives **53-59** is shown in Scheme 29. Their molecular ions are generally of low abundance, while the most intense ions are due to indole cations ***c*** (Scheme 24) whose elemental composition has been confirmed by high resolution mass spectrometry.

Table 10. Chemical structures of mono and diamino derivatives of 2,3-dihydro-1*H*-1,4-benzodiazepines.



53-59



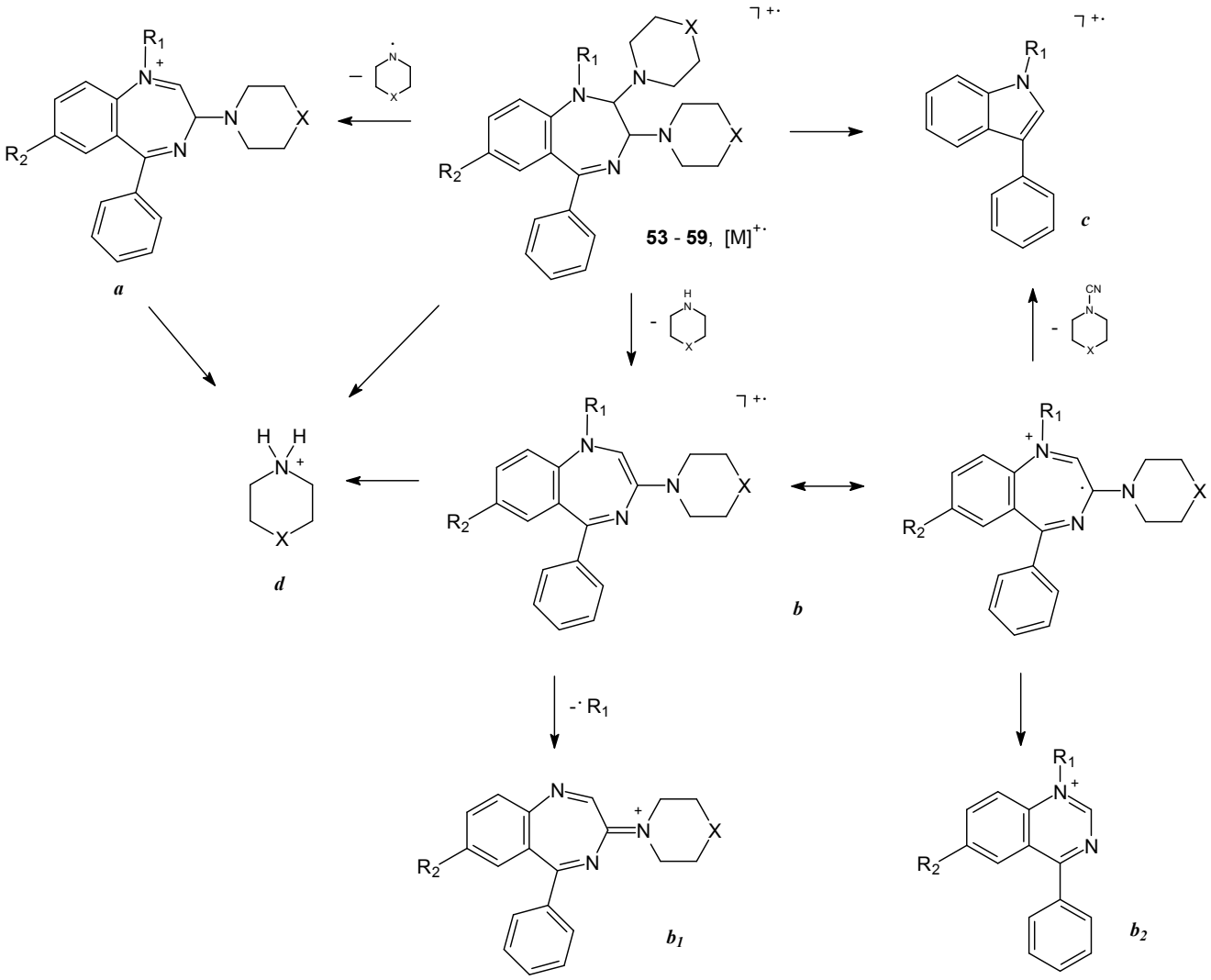
60-67

Compound	R_1	R_2	X	Compound	R_1	R_2	X
53	CH_3	NO_2	CH_2	**60**	H	NO_2	N-CH_3
54	CH_3	NO_2	O	**61**	H	Cl	CH_2
55	CH_3	NO_2	N-CH_3	**62**	H	Cl	O
56	CH_3	Cl	CH_2	**63**	H	Cl	N-CH_3
57	CH_3	Cl	O	**64**	CH_3	Cl	O
58	CH_3	Cl	N-CH_3	**65**	CH_3	Cl	N-CH_3
59	C^2H_3	Cl	O	**66**	^2H	Cl	CH_2
				67	^2H	Cl	O

Table 11. EI mass spectral data (*m/z*, relative intensity (%)) of 2,3-diamino-2,3-dihydro-1*H*-1,4-benzodiazepines (**53-59**).

Compound	$[M]^{+\bullet}$	*a*	*b*	b_1	b_2	*c*	*d*	*Other ions*
53	447(1)	363(2)	362(3)	347(6)	266(1)	252(18)	86(24)	84(100)
54	451(5)	365(26)	364(4)	349(5)	266(10)	252(100)	88(29)	86(20)
55	477(2)	378(21)	377(7)	362(5)	266(14)	252(87)	101(53)	99(66), 111(98), 83(39), 70(89), 58(100), 42(86)
56	436(4)	352(10)	351(3)	336(5)	255(15)	241(100)	86(27)	84(40)
57	440(7)	354(22)	353(5)	338(6)	255(28)	241(100)	88(64)	86(26)
58	466(8)	367(16)	366(11)	351(7)	255(24)	241(88)	101(59)	99(41), 111(78), 83(15), 70(54), 58(100), 42(85)
59	443(11)	357(33)	356(5)	338(4)	258(22)	244(100)	88(47)	86(16)

To ascertain the formation of these ions, different MS/MS measurements have been carried out. The mass analysed ion kinetic energy spectra obtained by selecting the molecular ion of compound **54** and its fragment ion $[M–C_4H_8NO]^+$ are reported in Figure 3. From a comparison of the two spectra it appears that ions ***c*** are produced mostly from the molecular ion and only in a very small amount from a two step pathways involving an intermediate ion (***b***, Scheme 24) produced by elimination of one amine moiety. The direct formation of ions ***c*** from $[M]^{+\bullet}$ requires extensive fragmentation and rearrangement involving the seven-membered ring contraction. However, the high abundance of ions ***c*** is probably due to its stability. In turn, ions ***b*** can eliminate the second amine residue and a carbon atom with the contraction of the heterocyclic ring to yield the quinazoline $\boldsymbol{b_2}$. Alternatively, the molecular ion can lose one amine radical to produce ion ***a***, while ions containing the amine moiety can be produced by different pathways (Scheme 24).



Scheme 24

Similarly to their 2,3-diamino analogues, 3-amino-2,3-dihydro-1*H*-1,4-benzodiazepine derivatives (**60**-**67**) show eliminations of an amine radical or an amine molecule from the molecular ion (ions ***a***, ***b*** Table 12, Scheme 25).[47] Both ions ***a*** and ***b*** lose HCN yielding the ion ***e*** and the indole cation ***c***, respectively. The deuterium labelling of H(1) of compounds having R_1=H has shown that the loss of HCN involves the deuterium atom at N(1) only for about one half of its extent. After elimination of HCN, the successive loss of the substituent at the benzene ring followed by that of R_1NCH produce stable fluorene ions. Ions ***f*** are distinctive for derivatives having R_1=H since its formation requires the presence of an hydrogen bound to N(1). In fact, a deuterium labelling of the hydrogen at N(1) produces a 1 u *m/z* shift in this fragment ion.[47]

2.7. 5-Phenyl-3*H*-1,4-benzodiazepine derivatives

2-Methoxy-5-phenyl-3*H*-1,4-benzodiazepine (**68**) and its related compounds produce intense rearrangement ions in their electron ionisation mass spectra (Table 13).[48]

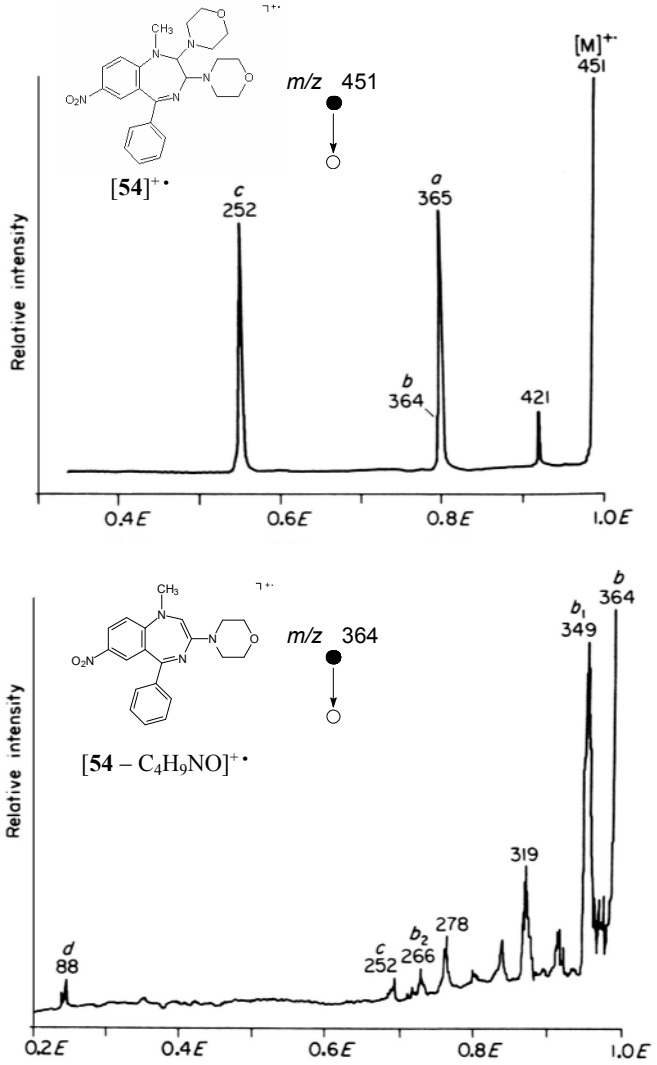
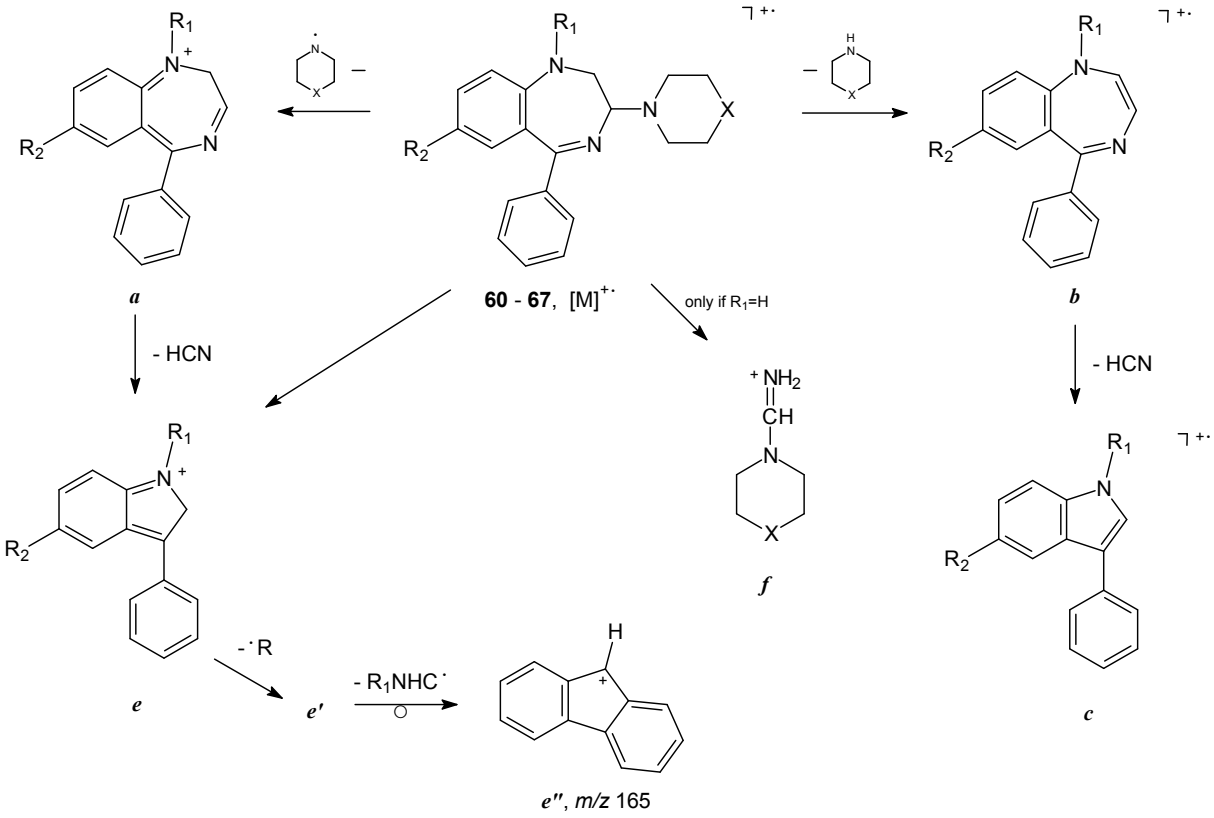


Figure 3. Mass-analysed ion kinetic energy spectra obtained by selecting the molecular ion of compound **54** (*top*) and its fragment ion $[M–C_4H_9NO]^+$ (*m/z* 364, *bottom*). Adapted from ref. 47.

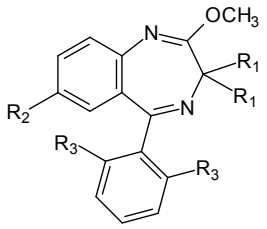
Table 12. EI mass spectral data (*m/z*, relative intensity (%)) of 3-amino-2,3-dihydro-1*H*-1,4-benzodiazepines (**60**-**67**).

Compound	$[M]^{+\bullet}$	*a*	*b*	*c*	*e*	e_1	e_2	*f*	*Other ions*
60	365(<1)	266(2)	265(3)	238(5)	239(3)	193(5)	165(7)	128(2)	111(5), 83(12), 70(32), 58(100), 42(69)
61	339(8)	255(9)	254(4)	227(19)	228(20)	193(22)	165(19)	113(100)	–
62	341(8)	255(12)	254(8)	227(30)	228(40)	193(36)	165(27)	115(100)	–
63	354(7)	255(16)	254(9)	227(32)	228(34)	193(32)	165(25)	128(55)	111(18), 83(83), 70(100), 58(98), 42(80)
64	355(11)	269(4)	268(1)	241(33)	242(100)	207(69)	165(20)	–	–
65	368(5)	269(5)	268(1)	241(100)	242(81)	207(84)	165(39)	–	111(8), 83(80), 70(80), 58(36), 42(57)
66	340(6)	256(5)	255(2)	227(11), 228(9)	229(22)	194(16)	165(4)	114(100)	–
67	342(11)	256(9)	255(5)	227(33), 228(29)	229(60)	194(34)	165(6)	116(100)	–



Scheme 25

Table 13. Electron ionisation mass spectral data of substituted 2-methoxy-5-phenyl-3*H*-1,4-benzodiazepines **68**-**76**.[48]

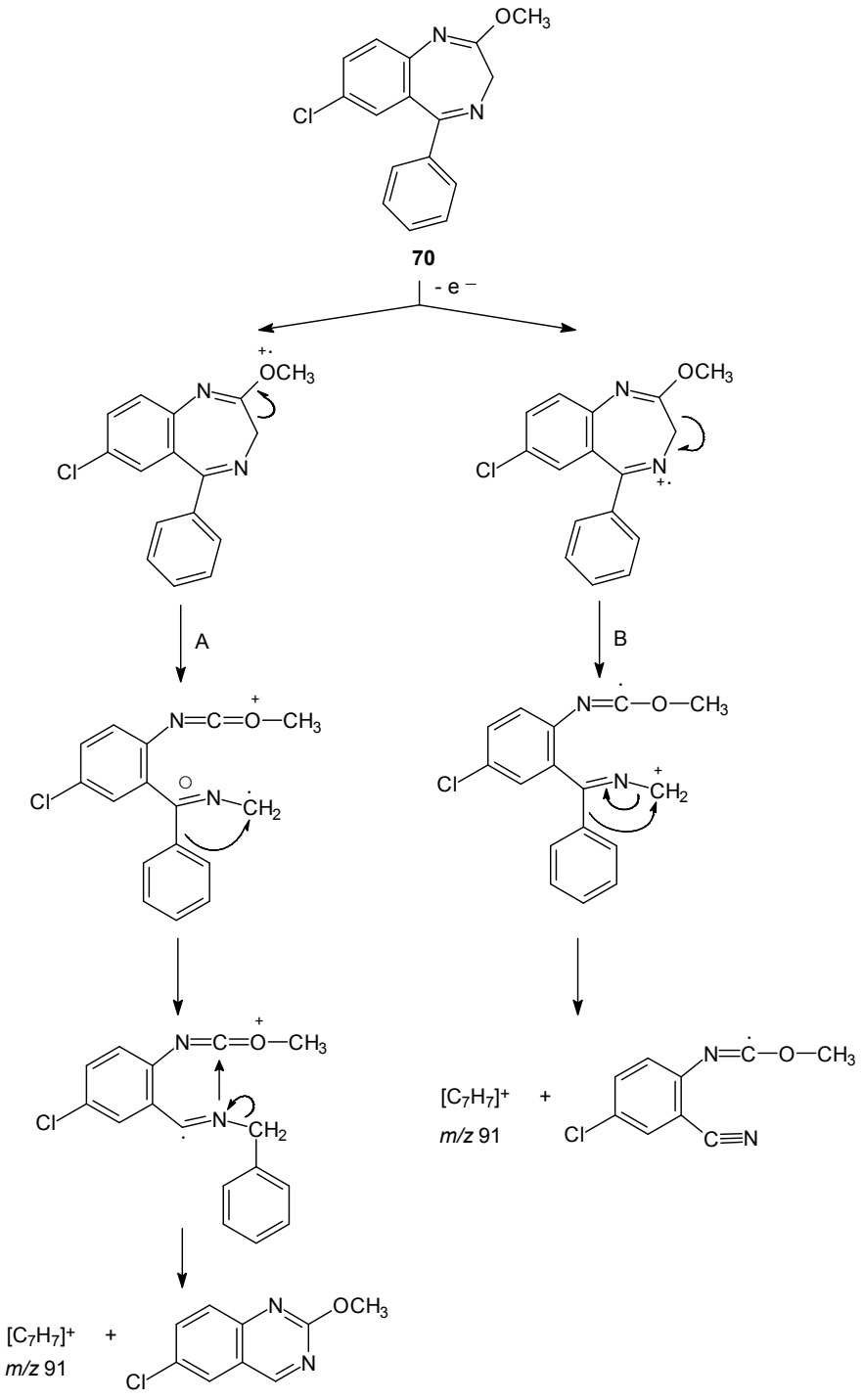


Compound	R_1	R_2	R_3	$[M]^{+\bullet}$	$[M–H]^+$	Rearrangement ion	Other ions
68	H	H	H	250(11)	249(20)	91(6)	77(2)
69	D	H	H	252(10)	251(20)	93(5)	250(3), 92(1), 91(1)
70	H	Cl	H	284(9)	283(15)	91(7)	249(2)
71	H	Cl	D	286(6)	285(4)	93(6)	284(12), 92(1), 91(<1)
72	H, CH_3	Cl	H	298(7)	297(14)	105(5)	283(2), 91(<1), 77(2)
73	H	NH_2	H	265(17)	264(21)	91(4)	249(3), 237(3)
74	H	OCH_3	H	280(10)	279(24)	91(5)	264(2), 252(3)
75	H	CH_3	H	264(10)	263(19)	91(7)	249(3)
76	H	NO_2	H	295(7)	294(11)	91(8)	278(2), 249(3), 248(8)

They are at *m/z* 91 for **68**, **70**, **73**-**76**. They are shifted at *m/z* 93 for **69** and **71**, while they are at *m/*z 105 for the 3-methyl derivative **72**. The abundance of these rearrangement ions is dependent upon the nature of

the substituent at position 7: it is greatest when the 7-substituent is NO_2, as it occurs in compound **76**, and the least when it is NH_2 (**73**).

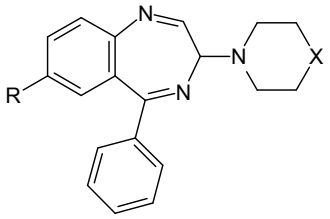
Ions at *m/z* 91 contain the 5-phenyl ring and the 3-CH_2 group. High resolution mass spectrometry and accurate mass measurements showed that they have elemental composition $[C_7H_7]^+$. Isotope labelling studies have allowed to propose the opening of the seven-membered ring and the migration of the phenyl ring from C(5) to C(3). Two possible mechanisms for the formation of ions at *m/z* 91 from **70** have been proposed (Scheme 26). Since theoretical calculations have shown that the charge is equally localized on the N(1)=C(2)-O group and on N(4)=C(5), two structures of the molecular ion have been proposed (Scheme 26).



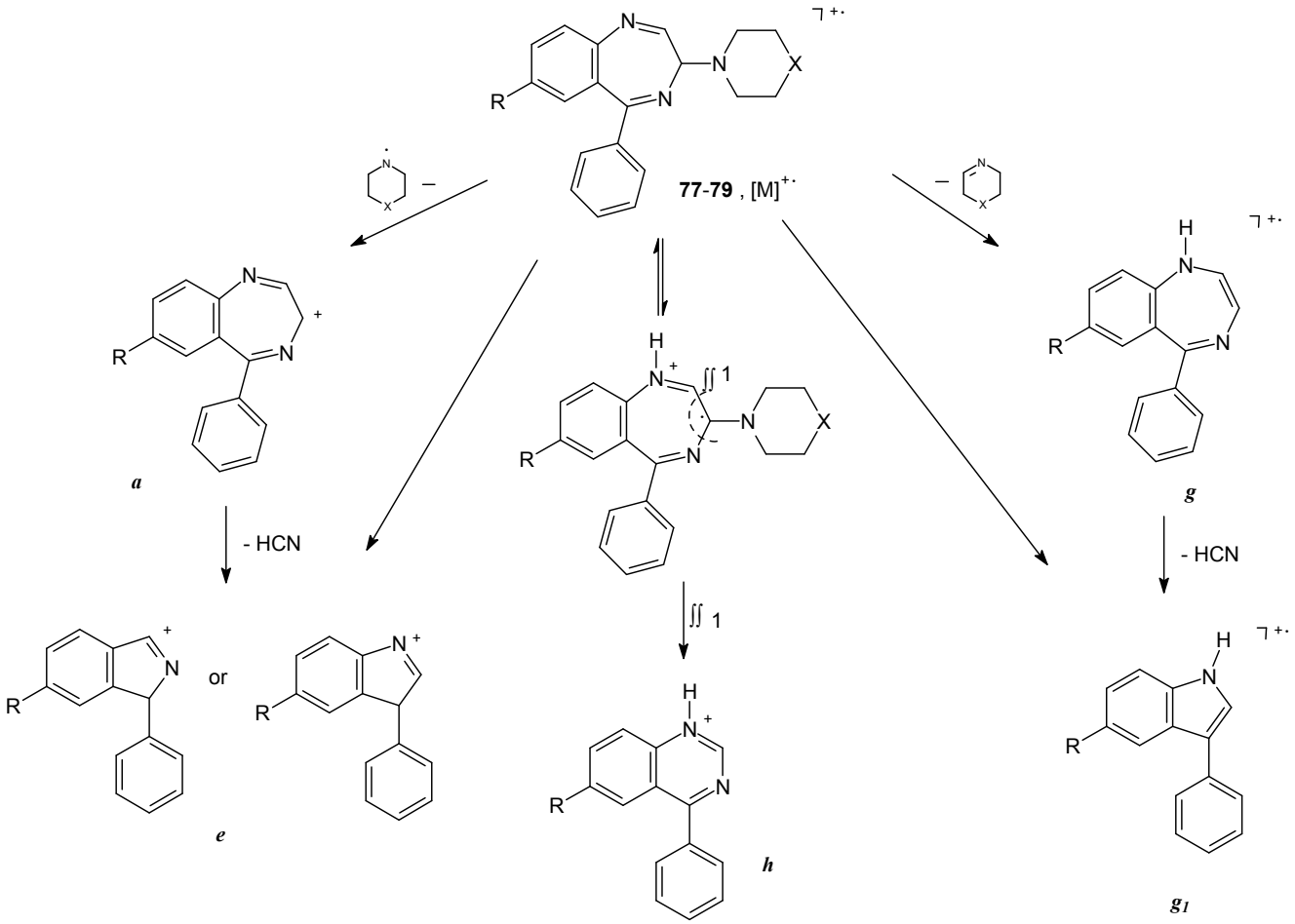
Scheme 26

According to pathway A, migration of the phenyl on the CH_2 group, having an unpaired electron, occurs after opening of the seven-membered ring by cleavage of the C(2)-C(3) bond. In pathway B, an analogous rearrangement is proposed but the CH_2 group carries a positive charge. This latter appears to be simpler and more favourable than pathway A.

Table 14. EI mass spectral data (*m/z*, relative intensity (%)) of 3-amino-3*H*-1,4-benzodiazepines (**77**-**79**)



Compound	R	X	$[M]^{+\bullet}$	*a*	*e*	*g*	g_1	*h*	*Other ions*
77	NO_2	N-CH_3	363(13)	264(6)	237(4)	265(13)	238(6)	252(7)	111(100), 84(40), 70(72), 58(88), 42(74)
78	Cl	N-CH_3	352(13)	253(13)	226(4)	254(14)	227(7)	241(20)	111(100), 83(32), 70(65), 58(42), 42(53)
79	H	O	305(19)	219(74)	192(16)	220(58)	193(16)	207(100)	



Scheme 27

Owing to their high degree of insaturation, the relative intensities of the molecular ions of 3-amino-3*H*-1,4-benzodiazepines (**77**-**79**) (Table 14) observed in the electron ionisation mass spectra are higher in respect to their saturated analogous (**53**-**67**).

The main fragmentation pathways consist in the elimination of an amine radical from $[M]^{+\bullet}$ and the subsequent loss of HCN. In addition, a distinctive fragmentation pathway characterizes the gas phase behaviour of these compounds. It involves the elimination of the amine residue with migration of an hydrogen atom from the amine to the benzodiazepine ring to give ions ***g*** (Scheme 27).

Probably the N(1)=C(2) double bond and the hydrogen in the α-position to the amine nitrogen atom are involved in a McLafferty-type rearrangement, in agreement the estimated distances from Dreiding models. Ions ***g*** can further lose HCN producing a substituted indole radical cation. Similarly with the previous two series of compounds, loss of the amine moiety with a carbon atom from the molecular ion and ring contraction of the seven-membered ring also occur.

3. Gas-phase ion-molecule reactions of 1,4-benzodiazepines

The use of a mass spectrometer as a chemical laboratory in the gas phase is more and more of interest. It allows to carry out ion-molecule reactions to evaluate the reactivity of a given molecular species towards different reagents and to identify and structurally characterize the ionic products.

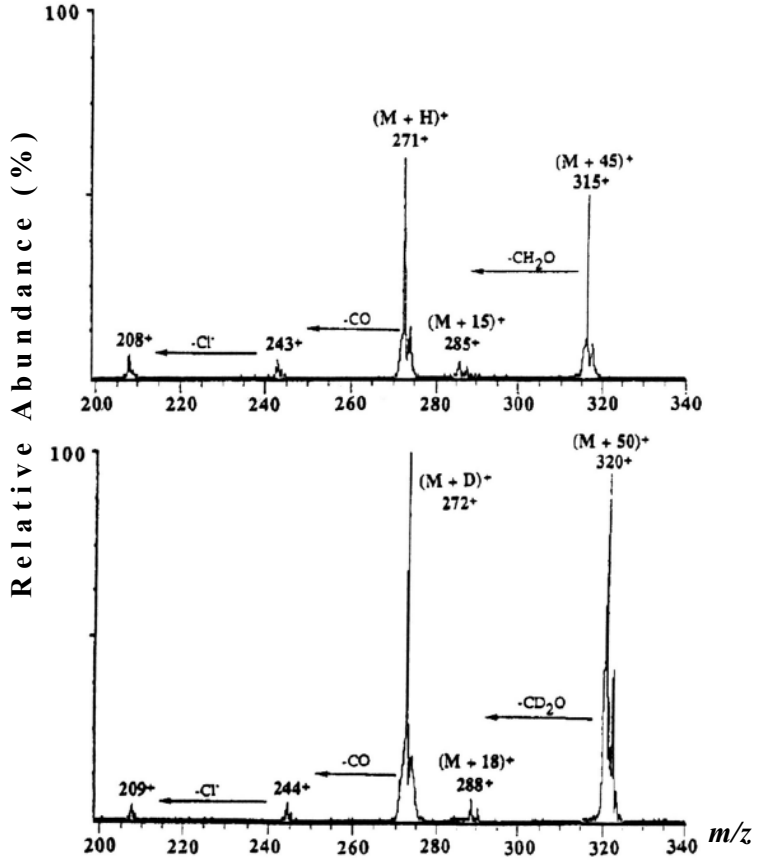


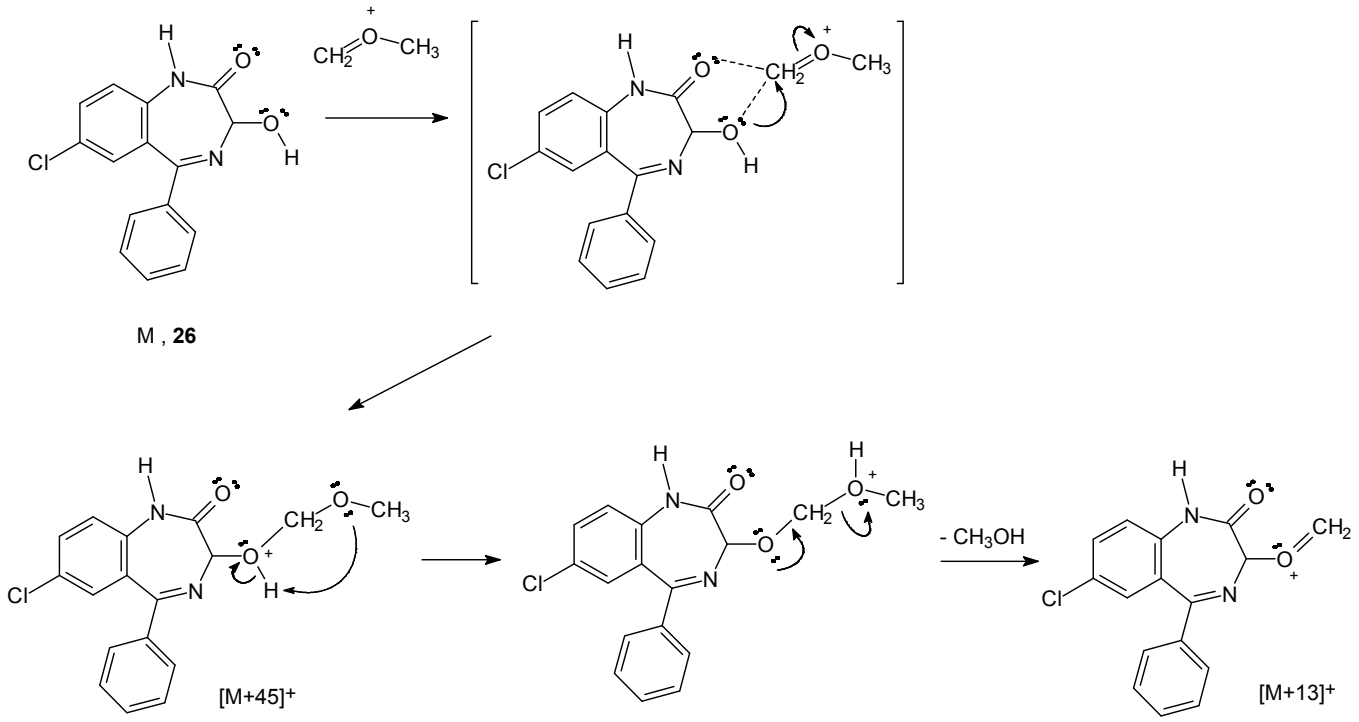
Figure 4. Chemical ionisation mass spectra of dimethyl ether (*top*) and dimethyl-d_6 ether (*bottom*) and nordiazepam (**5**). Adapted from Ref. 40.

Ion-molecule reactions have been performed between 1,4-benzodiazepines, *i.e.* nitrazepam (**4**), nordiazepam (**5**), diazepam (**10**), oxazepam (**26**), and temazepam (**28**), and dimethyl ether ions in a quadrupole ion trap mass spectrometer.[40] In these conditions, all the 1,4-benzodiazepine studied were

protonated, and all except temazepam (**28**) form $[M+45]^+$ adduct ions. The methoxymethylene ions of dimethyl ether selectively react with 3-hydroxy-1,4-benzodiazepines, oxazepam (**26**) and temazepam (**28**), to form $[M+13]^+$ adduct ions by methylene substitution.

On the contrary, 1,4-benzodiazepines without substituents at position 3 (**4**, **5** and **10**) react with the methoxymethylene ions to produce distinctive $[M+15]^+$ adducts by simple methyl cation transfer (Figure 4). These adducts are formed by elimination of methanol or formaldehyde, respectively, from $[M+CH_2OCH_3]^+$ ($[M+45]^+$) precursor ions. The selective formation of $[M+13]^+$ and $[M+15]^+$ products is useful since it allows differentiation of the two groups of 1,4-benzodiazepines.[40]

The use of dimethyl-d_6 ether, the study of the reactivity of model compounds together with CID-MS/MS measurements have allowed to obtain more information on these reactions and their mechanisms. The lack of formation of $[M+15]^+$ adducts for 3-hydroxy derivatives may signify that the formation pathway of these adducts is kinetically less favourable than the competitive formation pathway of the $[M+13]^+$ ions. In fact, S_N2 reactions, such as the methylation reaction, are typically slower than addition/elimination reactions, like the methylene addition reaction that yields $[M+13]^+$ ions.[40] It has been proposed than adducts $[M+13]^+$ are produced by elimination of methanol from those $[M+45]^+$ whose formation requires the necessity of two adjacent functional groups, *i.e.* hydroxyl and carbonyl groups, that can interact with the methoxymethylene ions (Scheme 28).



Scheme 28

4. Conclusion

Mass spectrometry and tandem mass spectrometry resulted powerful and suitable tools for the identification and structural characterization of 1,4-benzodiazepines. Different ionisation techniques, such as electron and chemical ionisation, as well as desorption techniques, such as fast atom bombardment, electrospray and plasma desorption have been used. The nature and position of substituents on the benzodiazepine nucleus influence their gas-phase behaviour producing selective and distinctive fragment

ions. This has let possible correlating fragmentation patterns to structural features of 1,4-benzodiazepines and their metabolites. Both simple cleavages and rearrangement reactions, most of them consisting in the contraction of the seven-membered ring, have been described and their rationalization can give useful information for structural characterization and differentiation of this wide series of compounds possessing important biological activity.

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SYNTHESIS AND CHEMICA PROPERTIES OF POLYNITRO- AND HALONITRO-DIHYDROTHIOPHENE 1,1-DIOXIDES

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Abstract. *The review is devoted to the analysis of literature data concerning synthetic methods, structure and chemical properties of polyfunctional heterocyclic deirvatives of the dihydrothiophene 1,1-dioxide series, such as polynitro- and halonitro- dihydrothiophene 1,1-dioxides. The reactions of these compounds with nucleophiles, resulting in the synthesis of new types of heterocyclic and linear compounds, and of organic complexes as well, are discussed. Great attention is paid to the specificity of chemical behavior of these substances, conditioned by the influence of the different functional groups present on the properties of an unsaturated heterocyclic system. In particular, the extensive reactivity of polynitrodihydrothiophene 1,1-dioxides and the easily-occurring halo- and prototropic transformations of bromonitrodihydrothiophene 1,1-dioxides are discussed.*

Contents

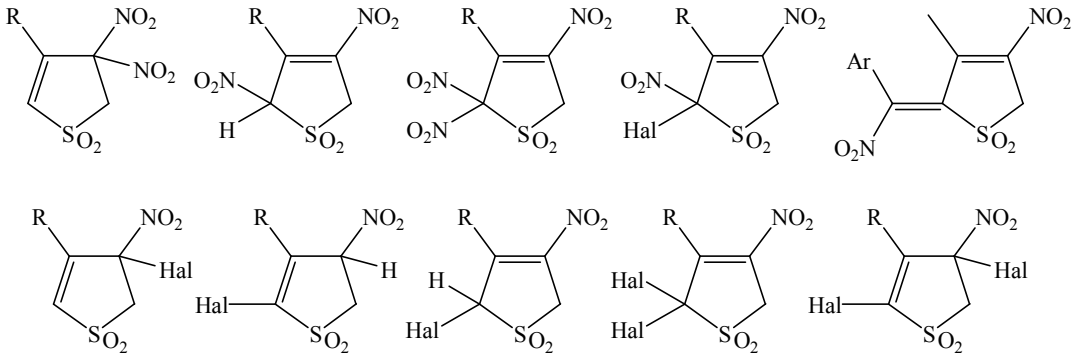
1. Introduction

Dihydrothiophene 1,1-dioxides are easily accessible heterocyclic compounds of interest for both theoretical and applicative aspects.[1-4] Nitro derivatives have proved to be special among substituted thiolene 1,1-dioxides. Their peculiar properties are mostly conditioned by the dominating influence of the nitro group. Nitrodihydrothiophene dioxides undergo reactions with nucleophilic, electrophilic, radical reagents and

heletropic transformations as well, an occurrence which makes such compounds highly reactive synthones, suitable for the preparation of otherwise barely accessible heterocyclic and dienic derivatives.[5,6] Besides that, nitrosulfolenes turned out to be useful models for studying theoretical problems such as competition between reaction centers,[5] oxime-nitron tautomerism,[7-9] allyl-vinyl isomerization,[5-10] conductivity of electron effects in sterically hindered, strongly fixed systems.[11] The introduction of additional nitro groups or of a halogen atom into the molecule of mononitrosulfolenes considerably widens their chemical potential and leads to the appearance of specific properties.

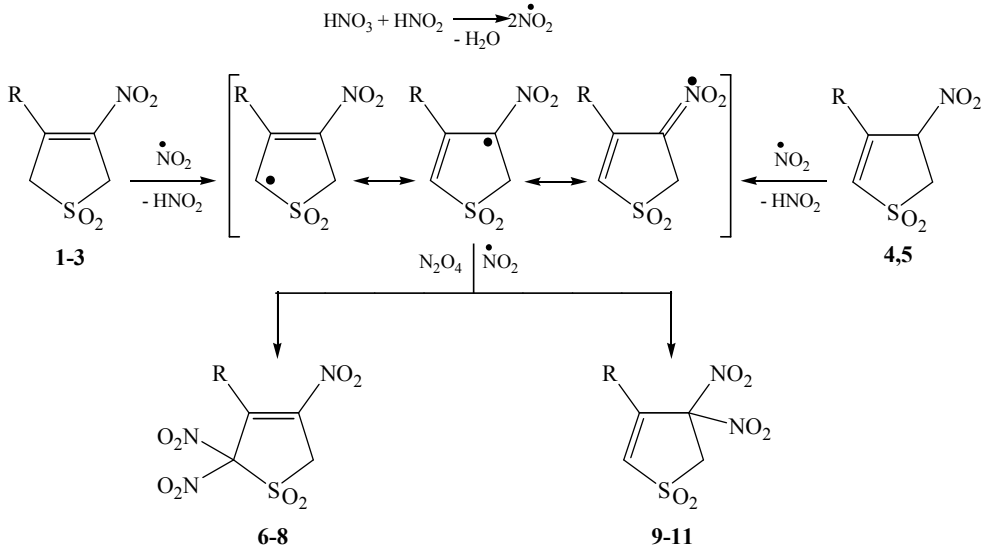
2. Synthesis of polynitro- and halonitro-dihydrothiophene 1,1-dioxides

Until recent years only 2,4(3,4)-dinitro-, and 2-bromo-3,4,5-trinitro-thiophenes,[12,13] were known among sulfur containing polynitro- and halonitro-heterocycles. Today, the wide reactivity of mononitrodihydrothiophene 1,1-dioxides towards radical and ionic reagents makes it possible to obtain various types of polynitro- and halonitro 1,1-dioxide derivatives differing for the combination of functional groups and for the structure (Scheme 1).



R = H, CH_3, Cl, NHAr

Scheme 1



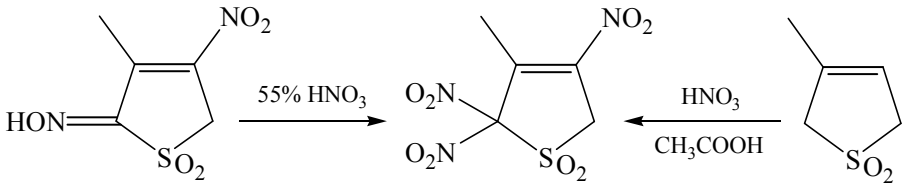
R = H (**1,6,9**), CH_3 (**2,4,7,10**), Cl (**3,5,8,11**)

Scheme 2

2.1. Synthesis of 2,2,4-trinitro-, 2,4-dinitro- and 2-halo-2,4-dinitro-2,5-dihydrothiophene 1,1-dioxides

Methods for the synthesis of polynitrothiolene 1,1-dioxides are based on the nitration of thiolene 1,1-dioxides and of their mononitro derivatives. The general method for the preparation of 2,2,4-trinitro-2,5-dihydrothiophene 1,1-dioxides **6-8** and 4,4-dinitro-3,4-dihydrothiophene 1,1-dioxides **9-11** is nitration of mononitrodihydrothiophene 1,1-dioxides **1-3** by dilute nitric acid.[14-17] These reactions are supposed to proceed along a homolitic pathway through heterocyclic allylic radicals formed from the isomeric Δ2- and Δ3-nitrodihydrothiophene 1,1-dioxides (Scheme 2).[5,14]

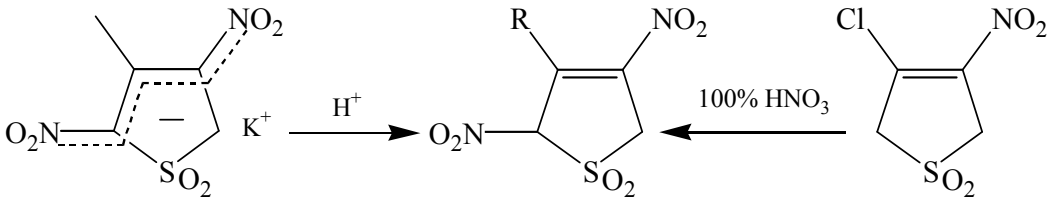
The methyl-substituted trinitrodihydrothiophene 1,1-dioxide **7** was also obtained by nitration of 2-hydroxyimino-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxide **12** or of 3-methyl-2,5-dihydrothiophene 1,1-dioxide **13**[15,17] by 55% nitric acid. The latter method is simpler, consisting of two consecutive nitrations that can be accomplished one-pot, without isolation of the intermediate **2** (Scheme 3).



12 **7** **13**

Scheme 3

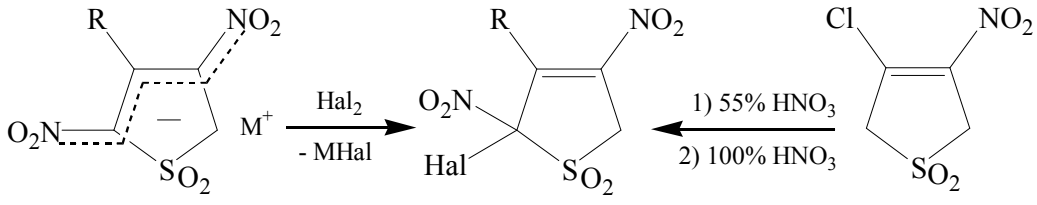
Neutralization of salt **14**, obtained from trinitrothiolene dioxide **7**,[18] led to the formation of 3-methyl-2,4-dinitrothiolene 1,1-dioxide **15**. 3-Chloro-2,4-dinitro-2,5-dihydrothiophene 1,1-dioxide **16** was obtained from the nitration of 3-chloro-4-nitro-2,5-dihydrothiophene 1,1-dioxide **3** with fuming nitric acid (Scheme 4).[19]



14 **15,16** **3**

R = CH_3 (**15**), Cl (**16**)

Scheme 4



14,17 **18-20** **3**

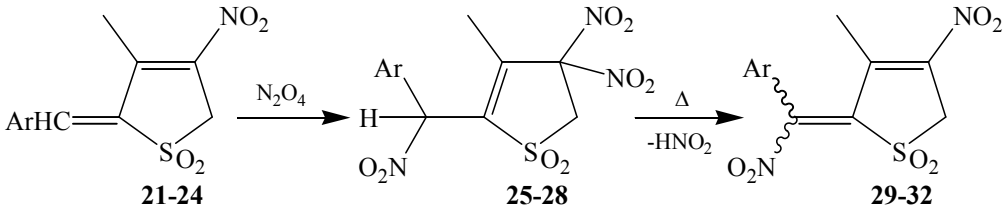
R = CH_3 (**14,18,19**), Cl (**17,20**); Hal = Cl (**18,20**), Br (**19**); M = K (**14**), Na (**17**)

Scheme 5

2-Halo-2,4-dinitrodihydrothiophene 1,1-dioxides **18-20** are easily obtained by halogenation of salts **14,17**.[19] Nitration of 3-chloro-4-nitro-2,5-dihydrothiophene 1,1-dioxide **3** also resulted in the formation of compound **20** (Scheme 5). This fact can be explained by the oxidative action of concentrated nitric acid leading to the decomposition of the starting dioxide **3** and promoting the formation of chlorinating reagents in the reaction mixture.[19]

2.2. Synthesis of dinitrobenzylidenethiolene 1,1-dioxides 2-(aryl-nitro-methylene)-3-methyl-4-nitro-3-thiolene 1,1-dioxides

Dinitrobenzylidenethiolene 1,1-dioxides 2-(aryl-nitro-methylene)-3-methyl-4-nitro-2,5-dihydro-thiophene 1,1-dioxides **29-32**, containing a fixed s-*trans*-1,4-dinitrodiene system with conjugated endo- and exocyclic double bonds, were obtained in two steps, namely nitration of 2-benzylidene-3-methyl-4-nitro-2,5-dihydrothiophene-1,1-dioxides **21-24** followed by elimination of nitrous acid from the initially formed trinitro derivatives **25-28** (Scheme 6).[20,21]



21-24 **25-28** **29-32**

Ar = C_6H_5 (**21,25,29**), $C_6H_4CH_3$-*p* (**22,26,30**), C_6H_4Cl-*p* (**23,27,31**), $C_6H_4NO_2$-*p* (**24,28,32**)

Scheme 6

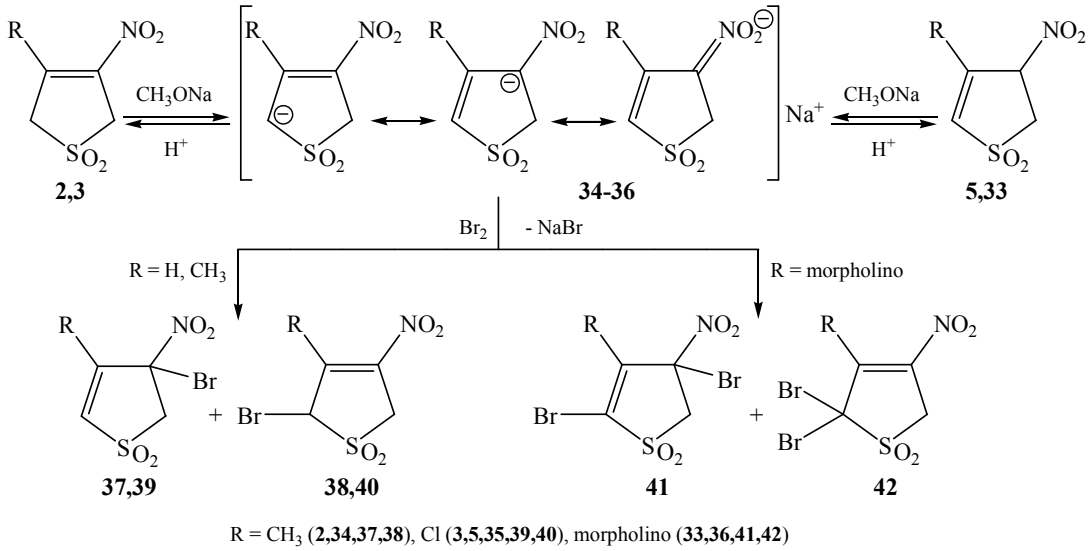
Actually, 2-(aryl-nitro-methylene)-3-methyl-4,4-dinitro-2,5-dihydrothiophene 1,1-dioxides **25-28** are easily formed as a result of the interaction of compounds **21-24** with N_2O_4 in CCl_4 at room temperature. The conditions for HNO_2 elimination from compounds **25-28** depend essentially on the nature of the substituent in the aromatic ring. Dinitrosulfodienes **29,31** are formed as a result of short-time heating of compounds **25,27** in polar solvents (methanol, acetone). The electrondonating effect of the methyl group of the *p*-tolyl fragment in compound **26** enforces more severe conditions for the formation of **30**. On the other hand, the presence of the nitro group in the aryl of **28** promotes its spontaneous transformation into dinitrodiene **32**.[21]

2.3. Synthesis of halonitrodihydrothiophene 1,1-dioxides

The synthesis of halonitrodihydrothiophene 1,1-dioxides includes two steps, namely the formation of salts of nitrodihydrothiophene 1,1-dioxides and their reaction with halogen. By means of chlorination, bromination and iodination of sodium 1,1-dioxo-2-thiolenyl-4-nitronates with different substituents at C(3) a series of various mono- and dihalonitrodihydrothiophene 1,1-dioxides were obtained.[22] The synthesis of bromo derivatives of 4-nitro-3,4- and 2,5-dihydrothiophene 1,1-dioxides **37-42** proceeds quite smoothly (Scheme 7).[23,24]

Interaction of Δ2- and Δ3-nitrodihydrothiophene 1,1-dioxides **2,3,5,33** with sodium methoxide resulted in the formation of sodium 1,1-dioxo-2-thiolenyl-4-nitronates **34-36**. Bromination of **34-36** proceeds under very mild conditions at room temperature in dry ether. The result of this process turned out to be depended on the nature of the substituent at C(3). In the case of the methyl- and chloro-substituted nitronates **34,35**

mixtures of isomeric 4-bromo-4-nitro-3,4- and 2-bromo-4-nitro-2,5-dihydrothiophene 1,1-dioxides **37,38** and **39,40** were formed as a result of electrophilic attack of bromine at C(2) or C(4) of resonance-stabilized nitroallyl anions. Such an outcome also occurs for the bromination of nitronate **36**, where, at the same time, due to the electrondonating effect of the morpholino nitrogen atom the reaction proceeds further, leading to the formation of a mixture of 2,4-dibromo-3-morpholino-4-nitro-3,4-dihydrothiophene and 2,2-dibromo-3-morpholino-4-nitro-2,5-dihydrothiophene 1,1-dioxides **41,42**.



R = CH_3 (**2,34,37,38**), Cl (**3,5,35,39,40**), morpholino (**33,36,41,42**)

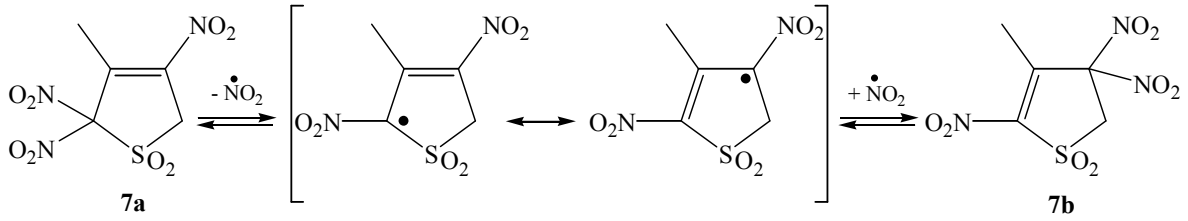
Scheme 7

The compounds synthesized were found to undergo halo- and prototropic rearrangements, which allowed broadening of the number of bromo derivatives of nitrodihydrothiophene 1,1-dioxide: such transformations will be described in chapter 4.3. Thus, for example, these reactions led to 2-bromo-3-methyl-4-nitro-3,4- and 2,4-dibromo-3-methyl-4-nitro-3,4-dihydrothiophene 1,1-dioxides **43,44** from 4-bromo-3-methyl-4-nitro-3,4- and 2-bromo-3-methyl-4-nitro-2,5-dihydrothiophene-1,1-dioxides **37,38**.[25,26]

3. Structure of polynitro- and halonitro-dihydrothiophene 1,1-dioxides

3.1. 2,2,4-Trinitro-, 2,4-dinitro- and 2-halo-2,4-dinitro-2,5-dihydrothiophene 1,1-dioxides

The homolitic route to trinitrodihydrothiophene dioxides **6-8** described above, provided by nitration of nitrodihydrothiophene dioxides by dilute nitric acid,[5] and the ease of allyl-vinyl isomerization of the starting nitrodihydrothiophene 1,1-dioxides,[10] made it possible to suppose that compounds **6-8** could be formed as a mixture of isomers (a) and (b) (Scheme 8).



Scheme 8

This hypothesis well agrees with theoretical calculations of structural, energetic and spectral characteristics of the isomeric (**7a**) and (**7b**). The calculations were done using the GAUSSIAN-98 package and showed little difference in energy values (Δ 0.56 kcal/mol) and in spectral parameters for the two alternative structures (**7a**) and (**7b**).[27]

It should be mentioned that the spectroscopic analysis of trinitrodihydrothiophene dioxides, both in solution and in the solid phase, was insufficient for a choice between the two isomeric structures **7a** or **7b**, although the former was found to be more appropriate for a description in solution.[27] By means of an X-ray powder diffraction crystal-structure determination, the methyl-substituted derivative was shown to exist in the solid phase as 3-methyl-2,2,4-trinitro-2,5-dihydrothiophene 1,1-dioxide **7a**.[27]

This method showed, for the heterocycle of **7a**, an envelope conformation with the sulfur atom being a little out of the plane; the nitro group at Csp^2 is involved in conjugation; and the nitro groups at Csp^3 are not equivalent and the two C-N bonds form a right angle. The interaction of the hydrogen atoms of the methylene group with one oxygen of the nitro group at Csp^2 is the shortest intermolecular contact.

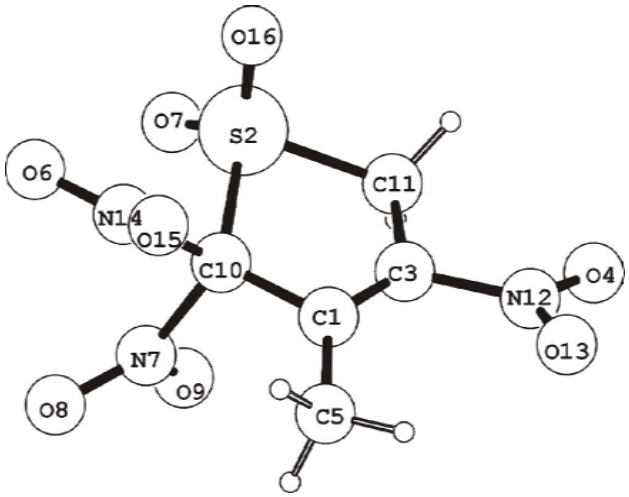


Figure 1. Geometry of **7a** according to X-ray powder diffraction data.

Spectral and geometric characteristics showed 2-halo-2,4-dinitro-2,5-dihydrothiophene 1,1-dioxides **18-20** and trinitro derivatives **6-8** to be close analogs.[19]

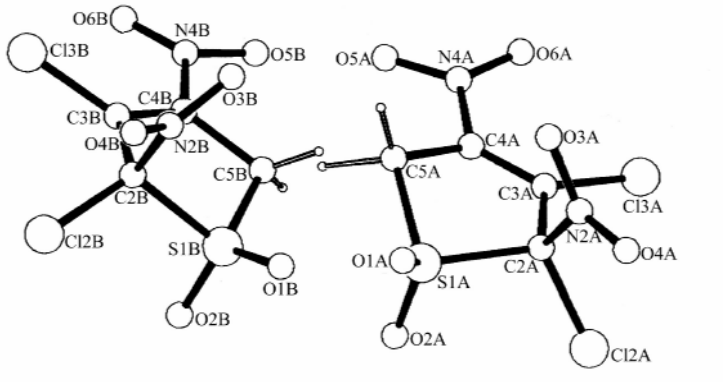


Figure 2. Geometry of **20a** and **20b** in the crystal.

Thus, according to X-ray data, the molecules of 2,3-dichloro-2,4-dinitro-2,5-dihydrothiophene 1,1-dioxide **20**, existing in the crystal as the enantiomeric **20a** and **20b** pair, also have an envelope conformation with the sulfur atom being out of the plane by 0.560(4) and -0.510(4) Å, respectively.

The packing of the molecules in the crystal is dependent on hydrogen bonds between the methylenic hydrogens and the oxygen atom of the conjugated nitro group of enantiomeric molecules.[19]

3.2. Dinitrobenzylidenedihydrothiophene 1,1-dioxides 2-(aryl-nitro-methylene)-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxides

In contrast with open chain aliphatic 1,4-dinitro-1,3-dienes,[28] more complex and fixed structures such as the dinitrosulfodienes moieties of the dihydrothiophene 1,1-dioxide series **29-32** cause substantial steric hindrance. These substances are formed as mixtures of *Z,E*- and *E,E*-isomers, although the former turned out to be the only isolable ones. By means of an X-ray analysis, the *Z,E*-isomer of compound **29a** was found to have an envelope conformation with the sulfur atom being out of the plane of the heterocycle.[21] The steric hindrance of this heterocycle is overcome by moving of the exocyclic nitro group and of the benzene ring out of the plane of the two conjugated double bonds. The packing of the molecules is mainly dependent on intermolecular hydrogen bonds between one oxygen atom of the exocyclic nitro group and the hydrogen atoms of the methylene group and of the phenyl ring.[21]

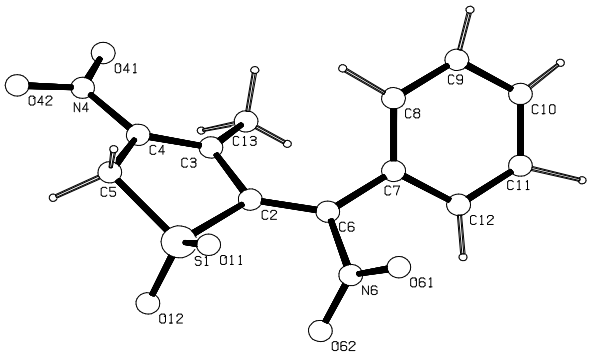


Figure 3. Geometry of **29a** in the crystal.

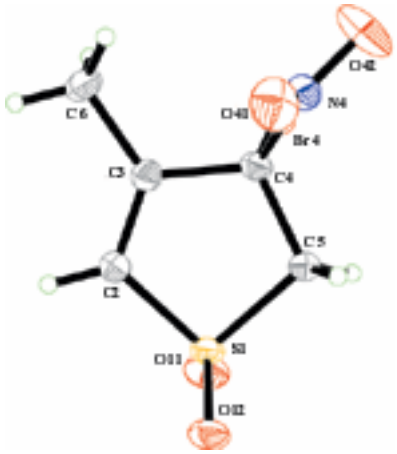


Figure 4. Geometry of **37** in the crystal.

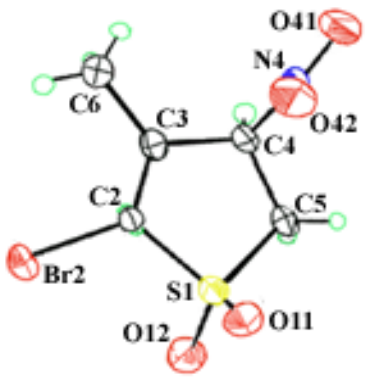


Figure 5. Geometry of **43** in the crystal.

3.3. Halonitrodihydrothiophene 1,1-dioxides

The structure of bromonitrodihydrothiophene 1,1-dioxides **37-44** was proved by spectral data. In particular, the structures of 4-bromo-3-methyl-4-nitro-3,4- (**37**) and 2-bromo-3-methyl-4-nitro-3,4-dihydrothiophene 1,1-dioxide (**43**) were studied by X-ray analysis.[24,26] These heterocycles were found to have an envelope conformation with the C(5) atom being out of the plane by 0.357(2) and 0.243(9) Å, respectively (Figures 4 and 5). Basic geometric parameters of **37** and **43** are close to the corresponding properties of the model aliphatic nitro compounds and nitro-dihydrotiophen-1,1-dioxides.[29,30]

The packing of the molecules in **43** depends on three weak hydrogen bonds, $C^5 - H^{51}\cdots O^{12}$, $C^4 - H^4\cdots O^{12}$, $C^4 - H^4\cdots O^{42}$, and on dipole-dipole interactions between Br^2 and O^{41} (Figure 6).[26]

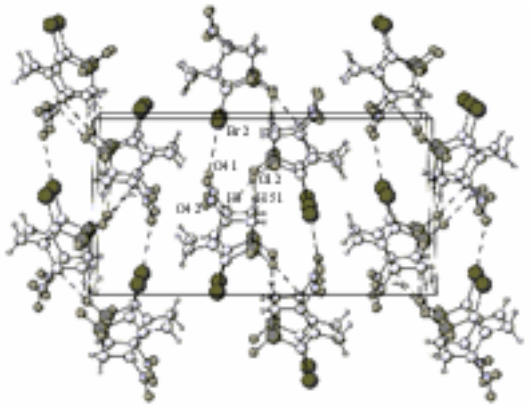
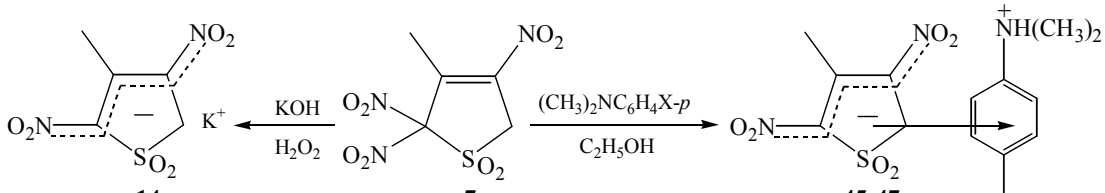


Figure 6. The cell of **43**.

4. Chemical properties of polynitrodihydrothiophene 1,1-dioxides

4.1. Peculiarities of the reactivity of 2,2,4-trinitro- and 2-halo-2,4-dinitro-2,5-dihydrothiophene 1,1-dioxides

The structure of trinitrodihydrothiophene dioxides **6-8** determines their chemical behaviour and, in particular, the possibility to react with nucleophiles by different routes. These compounds can actually react along three competitive pathways – elimination of nitronium cation (route **A**), elimination of HNO_2 (route **B**), and S_NVin at the chloronitrovinyl fragment, which is typical for compound **8** (route **C**).[22,31-33] The preference for a reaction route, as well as the specificity and extent of transformations of trinitrodihydrothiophene dioxides **6-8** were established to depend on the character of the substituent in the heterocycle and on the nature of the reagent, and specially on the reduction properties of the latter.[16-18,22,31-33] This makes 2,2,4-trinitro-2,5-dihydrothiophene 1,1-dioxides **6-8** and aliphatic trinitromethyl compounds similar.[34,35]

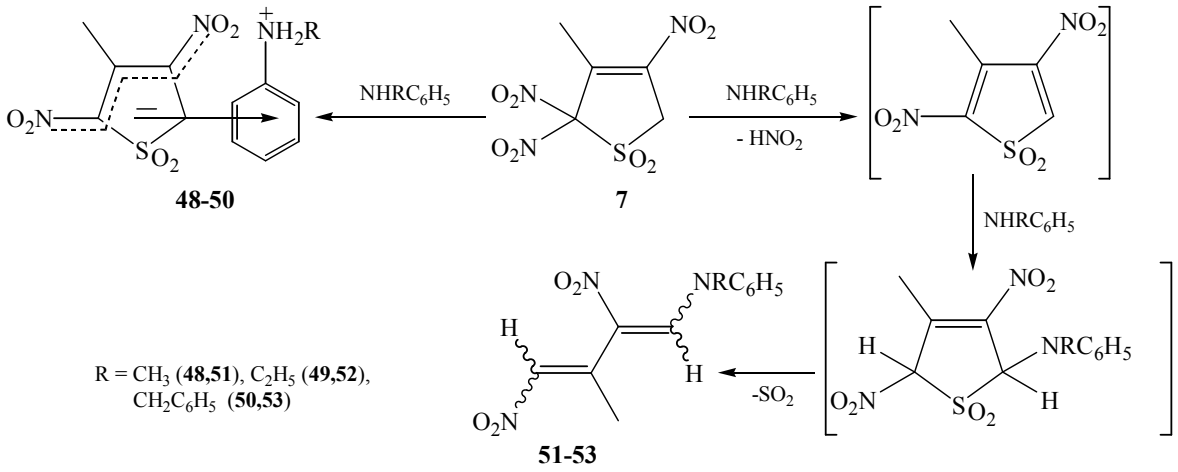


X = H (**45**), Br (**46**), C(O)H (**47**)

Scheme 9

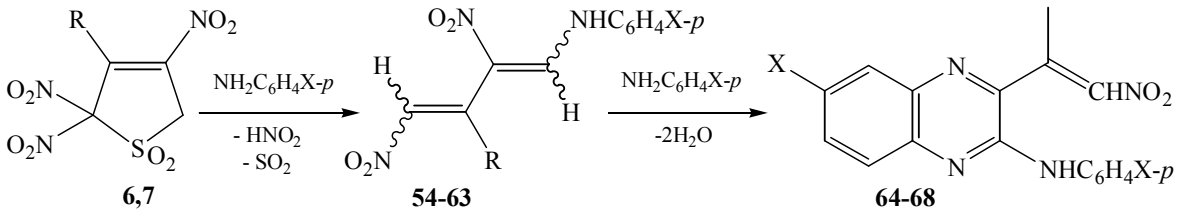
The reagents with low ionization potentials (hydroperoxide anion, tertiary arylamines) promote the selective reaction of trinitrodihydrothiophene 1,1-dioxide **7** by pathway **A** to form salts **14,45-47** (Scheme 9).[18,32,33] It should be mentioned that salts **45-47**, formed in reactions with tertiary arylamines, are characterized by additional donor-acceptor interactions.[32]

Secondary arylamines competitively react with trinitrodihydrothiophene 1,1-dioxide **7** along pathways **A** and **B** to form the salts **48-50** and 1-(*N*-alkyl)phenylamino-3-methyl-2,4-dinitro-1,3-butadienes **51-53**, respectively.[33,36] The formation of compounds **51-53** is the result of fast sequential transformations such as elimination of HNO_2, amination of dinitrothiophene 1,1-dioxide and elimination of sulfur dioxide (Scheme 10). It should be mentioned that these reactions proceed at room temperature. Such mild conditions of heletropic elimination of sulfur dioxide can be explained by the thermodynamic stability of the highly conjugated aminodinitrodienes which are formed.[36]



Scheme 10

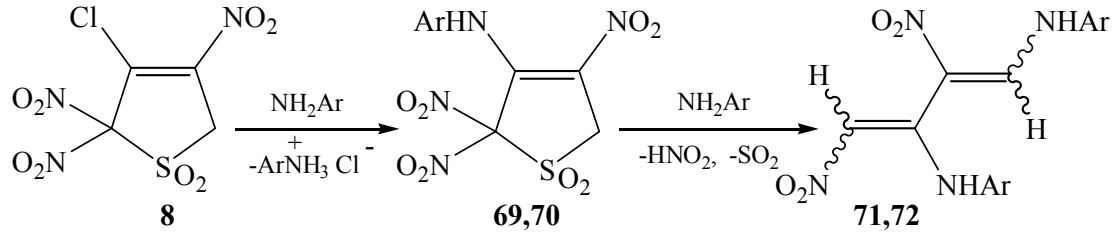
Under the action of primary arylamines, trinitrodihydrothiophene dioxides **6,7** undergo elimination of nitrous acid (route **B**) to form conjugated arylaminodinitrobutadienes **54-63**.[16,33,36,37] In some cases the interaction proceeds farther because of the addition of a second molecule of amine followed by intramolecular heterocyclization, resulting in the formation of quinoxaline derivatives **64-68** (Scheme 11).[33,38]



R = H (**6**): X = H (**54**), CH_3(**55**);
R = CH_3 (**7**): X = H (**56**), CH_3 (**57,64**), OH (**58**), OCH_3 (**59**), OC_2H_5 (**60**), Cl (**61,65**), Br (**62,66**), COOBu (**63,67**), NO_2 (**68**)

Scheme 11

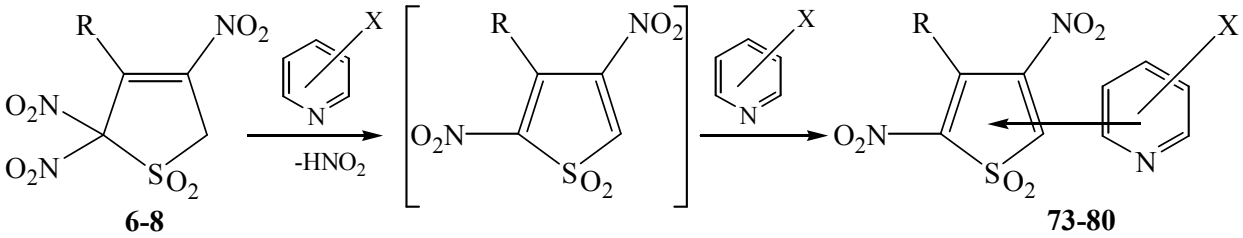
Trinitrodihydrothiophene dioxide **8**, containing a chloronitrovinyl fragment, reacts with primary arylamines along the S_NVin pathway (route **C**) to form arylaminotrinitrodihydrothiophene **69,70** and bis(arylamino)dinitrobutadienes **71,72** (Scheme 12).[17,22,33]



Ar = C_6H_5 (**69,71**), $C_6H_4CH_3$-*p* (**70,72**)

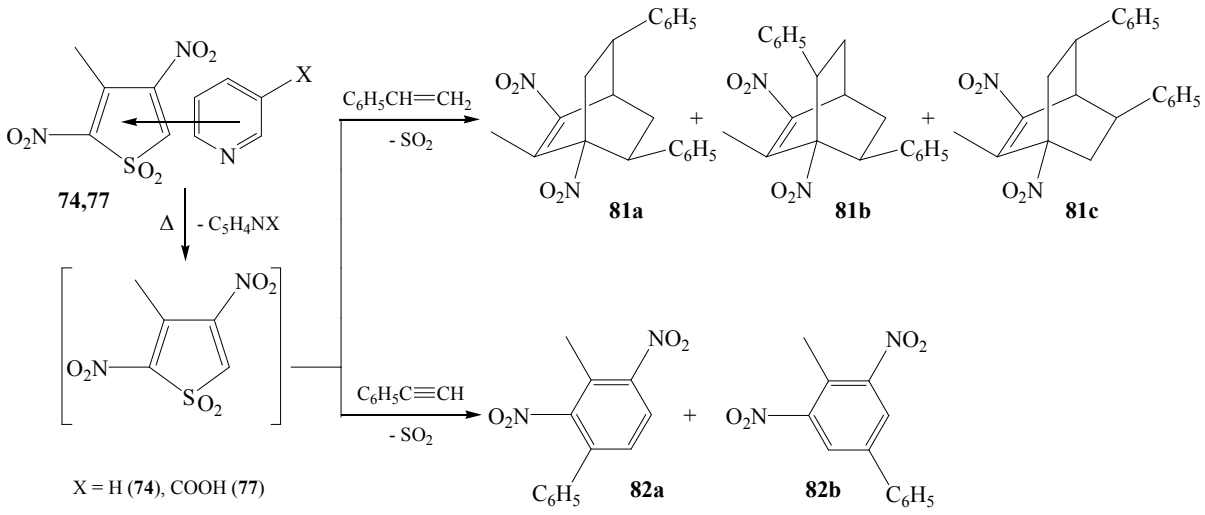
Scheme 12

The reaction of trinitrodihydrothiophene 1,1-dioxides **6-8** with pyridine and its analogs (substituted pyridines, quinoline) proceeds mainly along route **B**: the intermediate 2,4-dinitrothiophene 1,1-dioxide does not undergo nucleophilic addition and forms with pyridine and its analogs the stable molecular complexes **73-80**. In these complexes electron-deficient dinitrothiophene 1,1-dioxide is the acceptor while the nitrogen heterocycle is the donor (Scheme 13).[16,33,39]



R = H (**6**): X = H (**73**);
R = CH_3 (**7**): X = H (**74**), 2-CH_3 (**75**), 4-CH_3 (**76**), 3-COOH (**77**), 2-NH_2 (**78**), 4-NH_2 (**79**);
R = Cl (**8**): X = H (**80**)

Scheme 13



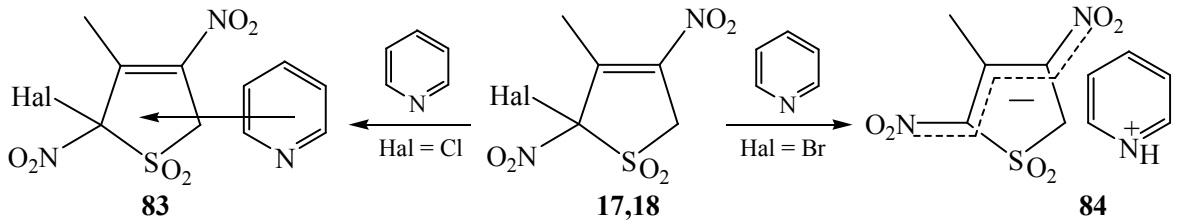
X = H (**74**), COOH (**77**)

Scheme 14

It should be mentioned that molecular complexes **73-80** can be used to stabilize and generate *in situ* the new and highly-reactive heterocyclic polynitro derivative 2,4-dinitrothiophene 1,1-dioxide. Molecular complexes **74,79** (R = CH_3) were shown to be able to generate an activated *s-cis*-fixed diene system in Diels-Alder reactions.[40] The interaction with styrene results in the formation of isomeric adducts of bis-addition

(**81a-c**). In the case of phenylacetylene the Diels-Alder process is followed by aromatization, leading to the formation of isomeric dinitro derivatives of diphenyl (**82a,b**) (Scheme 14).

Halodinitrodihydrothiophene 1,1-dioxides **15,16,18-20** have less synthetic possibilities than trinitrodihydrothiophene dioxides **7,8**. Compounds **18-20** do not undergo elimination of HNO_2 in contrast to trinitro derivatives **6-8**. For these substances oxidative processes are typical. Even reactions with the barely oxidable pyridine proceed along an electron-transfer pathway and can stop, depending on the strength of C–Hal bond, upon formation of the crystalline molecular complex **83**, or proceed further, resulting in elimination of a halogen cation and formation of pyridinium 3-methyl-4-nitro-1,1-dioxothiolenylnitronate **84** (Scheme 15).[41]



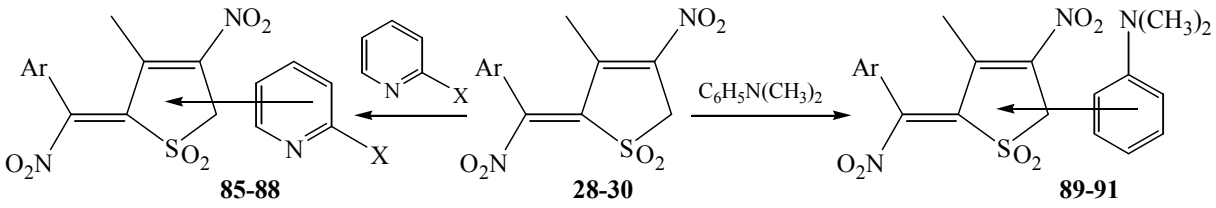
Hal = Cl (**17**), Br (**18**)

Scheme 15

4.2. Peculiarities of properties of dinitrobenzylidenedihydrothiophene 1,1-dioxides

Highly electron-deficient, strongly-fixed dinitrosulfodienes of the dihydrothiophene 1,1-dioxide series **29-32** can react actively with electron-donor reagents along two competitive pathways – electron transfer (route **A**) and nucleophilic reactions (route **B**), proceeding mainly according to vinyl substitution (S_NVin).[22]

Reagents with low ionization potential (NaOH, CH_3ONa, arylamines, arenethiols) exhibit donor properties while reacting with dinitrobenzylidenedihydrothiophene 1,1-dioxides **29-32**. Thus, reactions of *n*- and π-donors with low basicity (*N,N*-dimethylaniline, pyridine, 2-picoline) with compounds **29-31** stop upon formation of molecular complexes **85-91**, in which the strongly fixed structure of dinitrosulfodiene acts as an acceptor (Scheme 16).[42,43]



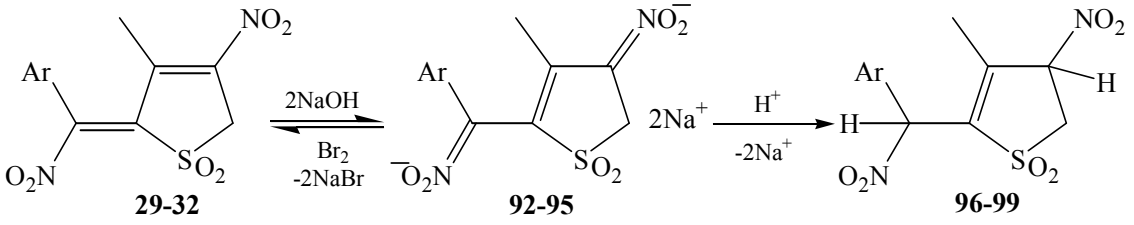
Ar = C_6H_5 (**28,85,86,89**), $C_6H_4CH_3$-*p* (**29,90**), C_6H_4Cl-*p* (**30,87,88,91**); X = H (**85,87**), CH_3 (**86,88**)

Scheme 16

Strong bases (NaOH, CH_3ONa) promote a deeper reduction process – the transformation of compounds **29-32** into the corresponding sodium bis(nitronate)s **92-95**. By treatment with an oxidant (Br_2) these dianions regenerate the initial dinitrosulfodienes **29-32**, while upon protonation turn into the corresponding dinitro derivatives **96-99** (Scheme 17).[43]

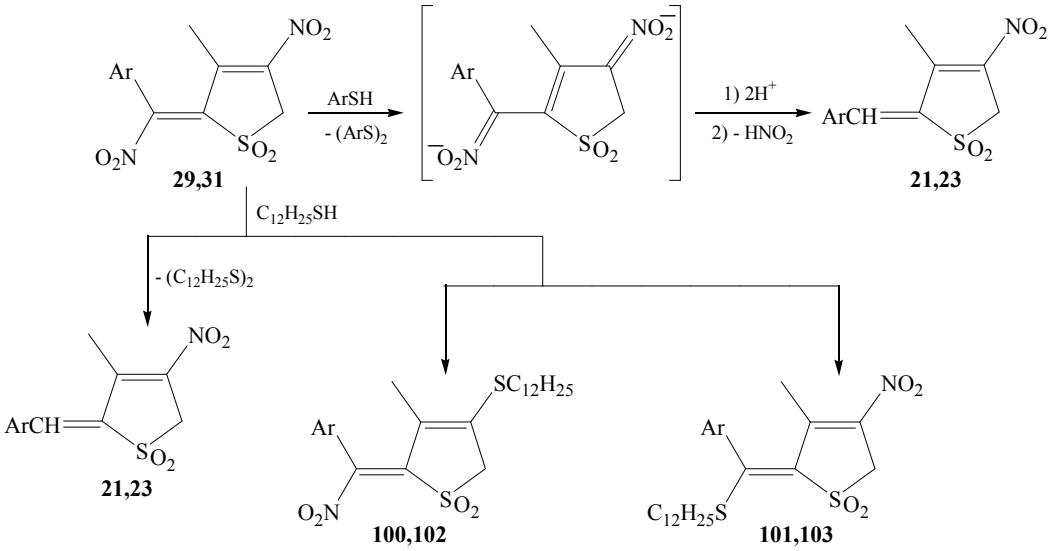
By reaction of dinitrosulfodienes **29,31** with easily oxidable nucleophiles such as aromatic thiols, electron-transfer processes proceed easier. In this case, arenethiols are oxidized to the corresponding diaryl

disulfides, while dinitrosulfodienes **29,31** lead to 2-benzylidene-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxides **21,23** (Scheme 18).[43] Reagents with stronger reducing properties promote dinitrosulfodienes to exhibit electrophilic properties. Thus, the interaction between compounds **29,31** and dodecanethiol proceeds mainly along a nucleophilic substitution (route **B**) at the endo- and exocyclic nitrovinyl fragments, resulting in the formation of a mixture of the isomeric thionitrosulfodienes **100-103** (Scheme 18).[43]



Ar = C_6H_5 (**29,92,96**), $C_6H_4CH_3$-*p* (**30,93,97**), C_6H_4Cl-*p* (**31,94,98**), $C_6H_4NO_2$-*p* (**32,95,99**)

Scheme 17



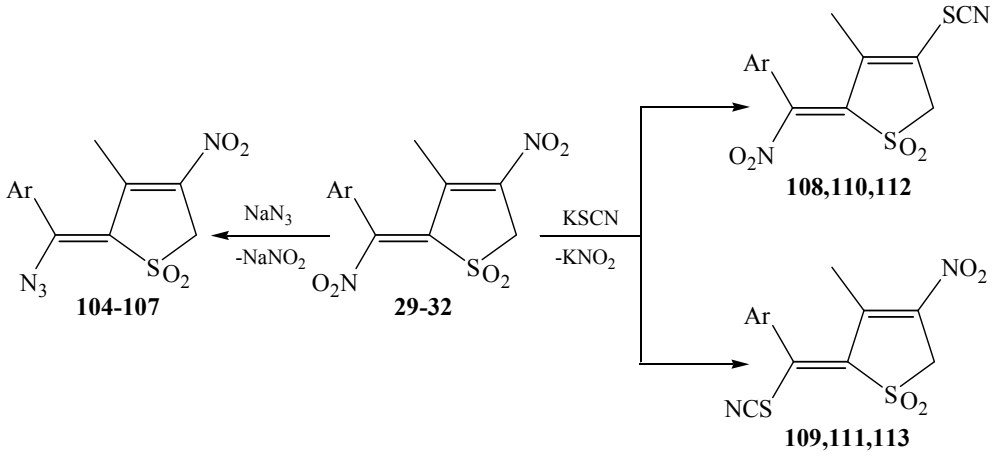
Ar = C_6H_5 (**21,29,100,101**), C_6H_4Cl-*p* (**23,31,102,103**)

Scheme 18

The reactions of the dinitrosulfodienes **29-32** with the hardly oxidable sodium azide and potassium thiocyanate proceed predominantly in accordance with the S_NVin mechanism and result in the formation of 2-(aryl-azido-methylene)-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxides **104-107**[22,43] and of the isomeric 2-(aryl-nitro-methylene)-3-methyl-4-thiocyanato- and 2-(aryl-thiocyanato-methylene)-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxides **108-113**, respectively (Scheme 19).[22]

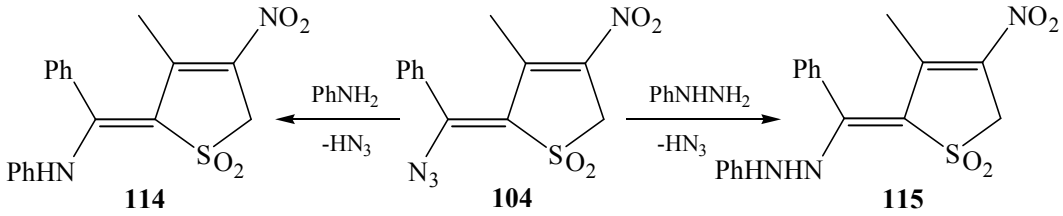
On the whole, the chemical behavior of dinitrosulfodienes of the dihydrothiophene 1,1-dioxide series **29-32**, including electron-transfer reactions and nucleophilic vinylic substitution, is quite close to that of aliphatic linear 1,4-dinitrodienes.[44] On the base of reactions of dinitrobenzylidenethiolene 1,1-dioxides **29-32** with nucleophilic reagents the methods for the synthesis of new classes of nitrosulfodienes of the dihydrothiophene 1,1-dioxide series, containing azido, thiocyanato, or alkylthio functionalities in the diene system, and of stable molecular complexes of dinitrosulfodienes with *N,N*-dimethylaniline and pyridines as

well, were worked out.[22,42,43] Aminonitrosulfodienes failed to be directly synthesized from dinitrodienes **29-32** because of the strong oxidative properties of the latter: therefore 2-(amino-phenyl-methylene)-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxides **114,115** were obtained by interaction of the less effective electron-acceptor azido derivative **104** with arylamines (Scheme 20).[45]



Ar = C_6H_5 (**29,104,108,109**), $C_6H_4CH_3$-*p* (**30,105**), C_6H_4Cl-*p* (**31,106,110,111**), $C_6H_4NO_2$-*p* (**32,107,112,113**)

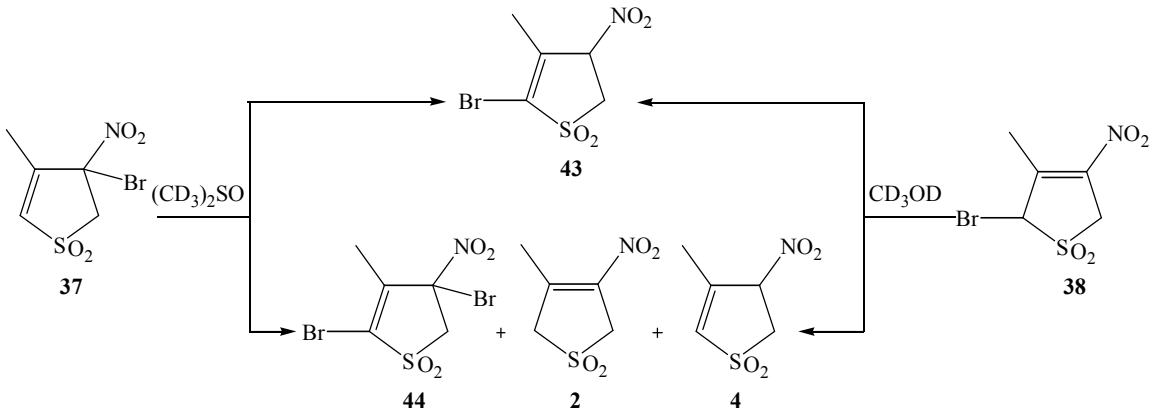
Scheme 19



Scheme 20

5. Halo- and prototropic rearrangements of bromonitrodihydrothiophene 1,1-dioxides

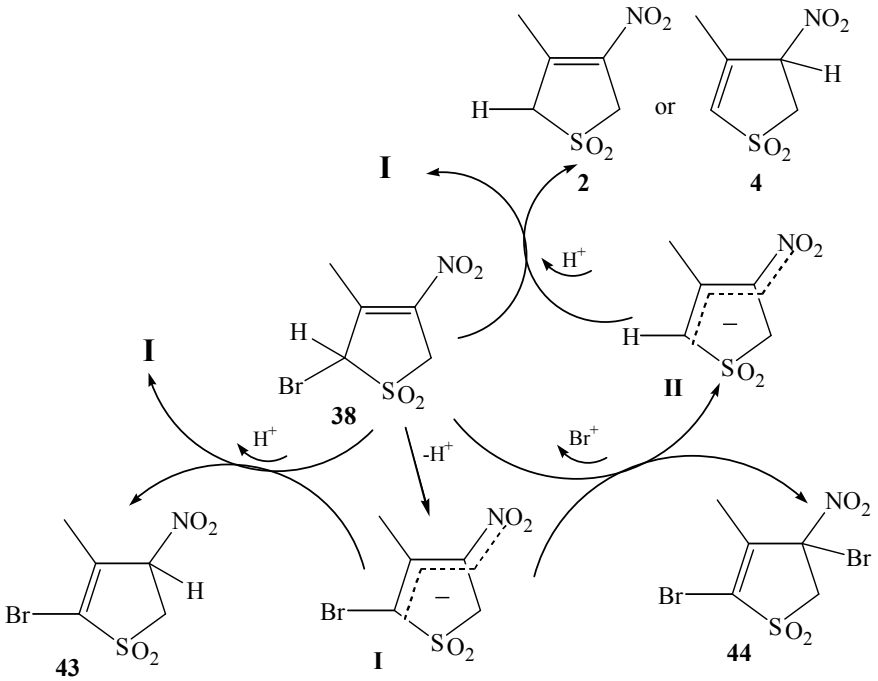
The mutual influence between functional groups (SO_2, NO_2) in the precursors of halonitrodihydrothiophene 1,1-dioxides, *i.e.* nitrodihydrothiophene 1,1-dioxides, was shown to activate substantially the CH-acidic properties of these heterocyclic nitro compounds, which undergo prototropic allyl-vinyl isomerization under very mild conditions, in polar solvents (DMSO, DMPA, alcohols) at room temperature and in the absence of bases.[10]



Scheme 21

The introduction of a halogen atom into the ring of nitrodihydrothiophene dioxide makes the double bond much more labile. Moreover, 4-bromo-3-methyl-4-nitro-3,4- and 2-bromo-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxides **37,38** contain two electropositive centers, *viz.* hydrogen and bromine, and therefore are able to undergo both halo- and prototropic rearrangements under the action of solvents. These transformations lead to the isomeric 2-bromo-3-methyl-4-nitro-3,4-dihydrothiophene 1,1-dioxide **43** and to disproportionation products such as 2,4-dibromo-3-methyl-4-nitro-3,4-dihydrothiophene 1,1-dioxide **44** and nitrodihydrothiophene dioxides **2,4** (Scheme 21).[22,25,26] It should be mentioned that the experimental conditions for the halotropy, reported in the bromonitrodihydrothiophene dioxides series for the first time, differ substantially from those required for literature examples of "halogen dance" or "halogen migration".[46,47] Carbo- and heterocyclic halo derivatives, which don't contain nitro group, undergo halogen cation migration only under the action of strong bases (KNH_2, BuLi and others).[46-48]

It is important to stress that the activity of bromonitrodihydrothiophene dioxides **37,38** in halo- and prototropic trasformations, as well as the conditions of these reactions depend on the substrate structure. The most labile isomer, 2-bromo-3-methyl-4-nitro-2,5-dihydrothiophene 1,1-dioxide **38**, undergoes such rearrangements either in methanol, acetonitrile or without any solvent with long endurance at room temperature. 4-Bromo-3-methyl-4-nitro-3,4-dihydrothiophene 1,1-dioxide **37**, which, in contrast to isomer **38**, does not have a mobile hydrogen atom, undergoes rearrangements in more polar media: in DMSO, in mixtures $(CD_3)_2SO/CD_3CN$ and in CD_3OD, containing catalytic quantity of pyridine-d_5. Such mild conditions of the rearrangements of these substances, are conditioned obviously by the high propensity of these compounds towards elimination of a positive polarized halogen and acidic hydrogen and by nucleophilic properties of cyclic resonance stabilized thiolenylnitronate anions **I,II** (Scheme 22).[22,25] By the example of compound **38** the processes observed can be shown as the following hypothetical scheme:



Scheme 22

On the whole, generalized and systematic literature data on the synthesis, structure and chemistry of polynitro and halonitrodihydrothiophene 1,1-dioxides prove the research line discussed to be very promising

and new. It can contribute to the development of the chemistry of nitro compounds and of functionalized sulfur-containing heterocycles to a significant extent.

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