APPLICATIONS OF RING REARRANGEMENTS INVOLVING A PARTICIPATING SIDE CHAIN FOR THE SYNTHESIS OF FIVE-MEMBERED HETEROCYCLES

Andrea Pace,* Antonio Palumbo Piccionello, Ivana Pibiri, Angela Accardo, Nicolò Vivona and Silvestre Buscemi

Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche, Università degli Studi di Palermo, Viale delle Scienze Ed. 17, 90128 Palermo, Italy (e-mail: andrea.pace@unipa.it)

Abstract. *Heterocyclic rearrangements can be applied to the synthesis of a wide variety of heterocyclic systems. The number of heterocyclic precursors available from commercial sources may render the rearrangement strategy more accessible. In this review, we are presenting a critical overview of those rearrangements that can yield five-membered heteroaromatic targets, containing two or more heteroatoms, from easily accessible heterocyclic precursors and through synthetically satisfying protocols. In some of the presented examples the rearrangement approach represents an exclusive way of obtaining a desired heterocyclic target. This review has been organized based on the type of target heterocycle with the intention to provide an easily accessible guide containing straightforward information on which one is the more easily accessible heterocyclic precursor, the most appropriate rearrangement and the optimal reaction conditions.*

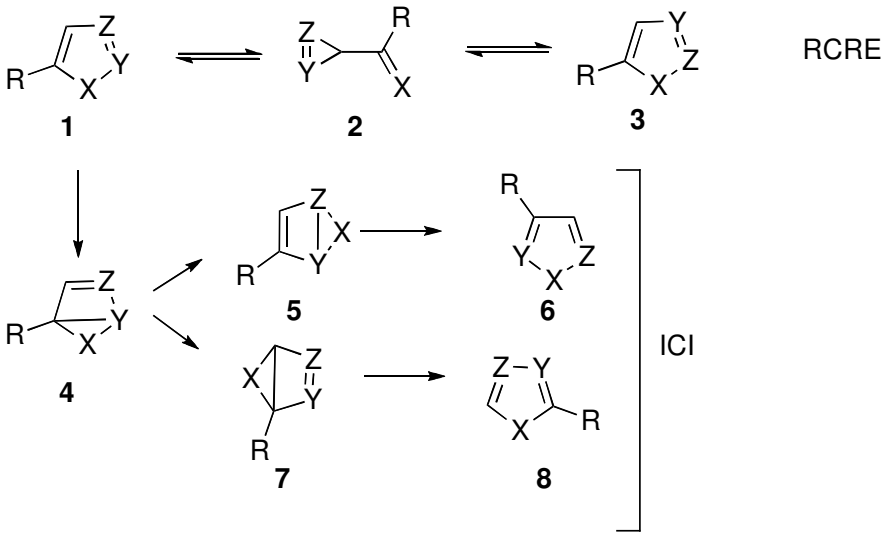
Contents

1. Introduction

Heterocyclic ring-rearrangements are a class of reactions, which has been largely investigated, especially in terms of mechanistic aspects. Additionally, these reactions can be synthetically very useful and

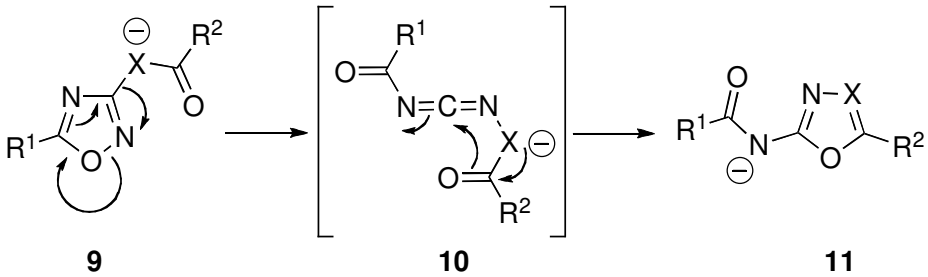
often may represent the preferred route to obtain target heterocycles starting from more easily accessible heterocyclic precursors. These rearrangements can involve either thermally or photochemically induced processes and are not easily and unequivocally classifiable. One type of classification, concerning monocyclic rearrangements of five-membered heterocycles, is based on the number of atoms of a side-chain linked to the starting heterocycle and involved in the formation of the final heterocyclic ring.[1]

According to this classification, photoinduced rearrangements consisting in the interchange of annular atoms of the starting ring would be considered as if they were involving zero atoms in the side-chain. Typically these occur through a *ring contraction-ring expansion* (RCRE) or an *internal cyclization-isomerization* (ICI) route (Scheme 1).[2]

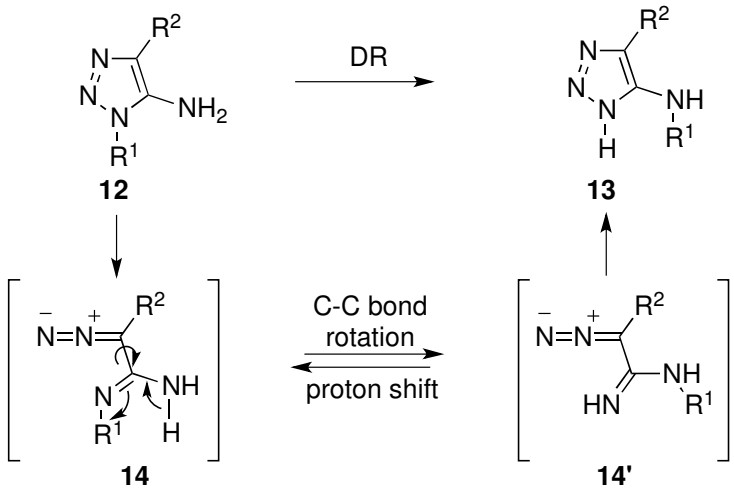


Scheme 1. General route for the ICI and RCRE rearrangements.

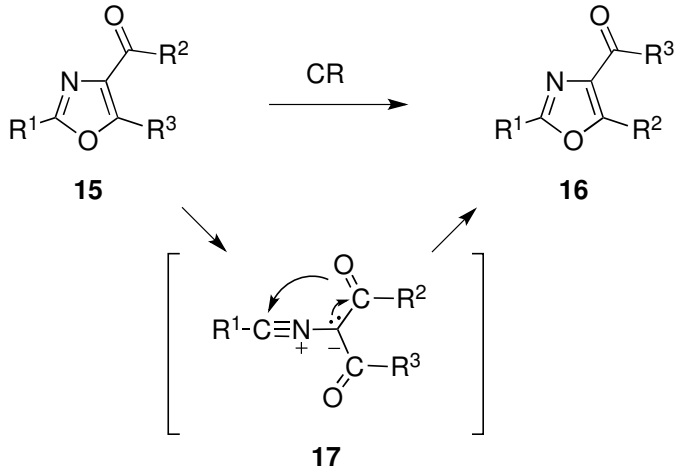
Similarly, rearrangements involving a *migration - nucleophilic attack - cyclization* (MNAC) sequence (Scheme 2)[3,4] as well as the more common *Dimroth rearrangement* (DR) (Scheme 3)[5] would be classified as rearrangements involving a one-atom participating side-chain. In turn, *Cornforth rearrangements* (CR),[6] typical for some 4-acyl-oxazoles, is proposed to proceed through an open-chain intermediate following a *ring opening-ring closing* (*RORC*) pathway and represents an example of a rearrangement involving a two-atom participating side-chain (Scheme 4). A wide variety of rearrangements involving a three-atom participating side-chain have been rationalized under the commonly accepted scheme of the *Boulton-Katritzky (BK) rearrangement*,[7] which is generally illustrated in Scheme 5.



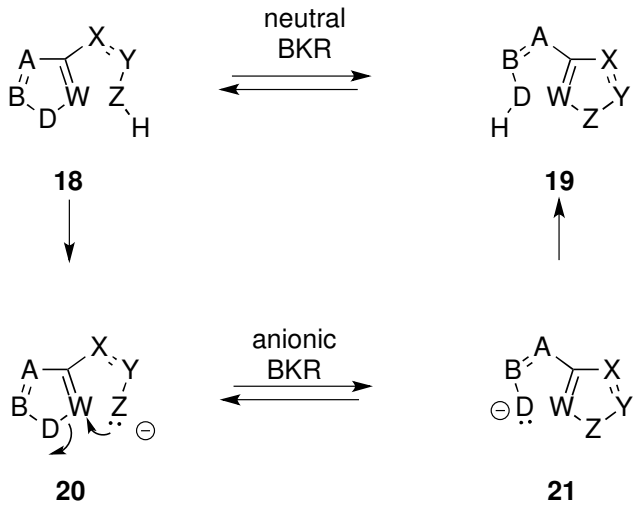
Scheme 2. General scheme of MNAC rearrangement of 1,2,4-oxadiazoles.



Scheme 3. A representative example of *Dimroth* rearrangement (DR) of 5-amino-1,2,3-triazoles.



Scheme 4. A representative example of a *Cornforth* rearrangement (CR) for 4-acyl-oxazoles.

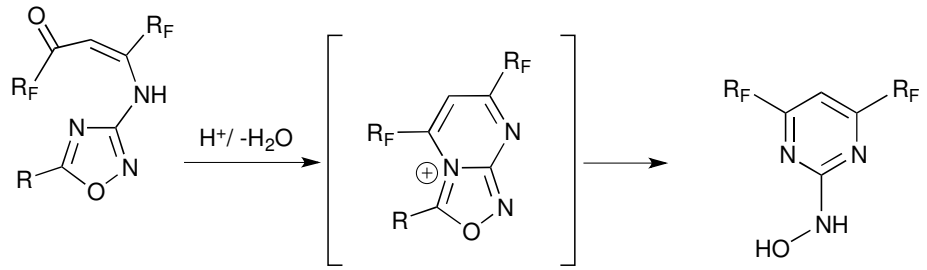


Scheme 5. General scheme of a *Boulton-Katritzky* Rearrangement.

In this type of rearrangement, the side-chain consists of a heteroallyl moiety conjugated to a heterocyclic ring containing an easily breakable bond. For these reason, the BK rearrangement is very

common among O-N bond containing azoles, such as isoxazoles, 1,2,4-oxadiazoles, 1,2,5-oxadiazoles (furazans), and 1,2,5-oxadiazole-*N*-oxides (furoxans), and involves the cleavage of the highly polarized O-N bond. These reactions have been also classified as internal nucleophilic substitutions usually involving a concerted ring closure - ring opening process around a nitrogen atom (W = N) as pivotal center, although examples are reported also with sulfur or carbon atoms as pivotal centers (W = S, C). The observed reactivity is strongly dependent on the nucleophilic charachter of the Z atom and on the *leaving group ability* of the A=B-D sequence, typical of the rearranging heterocycle (Scheme 5). These features justify the different tendency to rearrange of a given hetrerocycle as well as the possibility to take advantage of base catalysis, depending on the acidity character of the Z-H moiety.

Finally, an example of synthetically useful rearrangement involving a four-atom participating side-chain.[8] is represented by the reaction of fluorinated enaminoketone derivatives of 1,2,4-oxadiazole **22** which, depending on the chosen conditions, produces the corresponding six-membered heteroaromatic compounds (Scheme 6).



22 **23** **24**

Scheme 6. Rearrangements involving a four-atom participating side-chain.

Among all of the above mentioned ring-transformations, BK rearrangements have been reviewed also from a mechanistic point of view considering various parameters such as the the structure of the rearranging heterocycle, the nature of the side chain, the requirement of a basic or acid catalysis, the reaction medium and temperature.[9,10] However, the synthetic potential of these rearrangements has not been fully exploited. In this review, we are presenting a critical overview of those rearrangements that can yield five-membered heteroaromatic targets, containing two or more heteroatoms, from easily accessible heterocyclic precursors and through synthetically satisfying protocols.

Most of the reported examples of BK rearrangements concern O-N bond containing azoles as substrates however, significant examples of BK rearrangements around a sulfur atom pivotal center will be discussed. Furthermore, for the synthesis of oxazoles, thiazoles or 1,2,3-triazoles, an assay of synthetic strategies exploiting *Dimroth* and *Cornforth* rearrangements will be presented. Photoinduced heterocyclic rearrangements, which can be synthetically useful for the preparation of target heterocycles, have been recently reviewed and will not be reported here.[11]

Differently from heterocyclic reactivity reviews (organized based on the type of heterocyclic substrate) and mechanistic reports (organized upon types of reactions), this review has been organized based on the type of target heterocycle. It is our intention to offer to the synthetic chemist, aiming at obtaining a given heterocycle, an easily accessible guide containing straightforward information on which one is the more

easily accessible heterocyclic precursor, the most appropriate rearrangement and the optimal reaction conditions to achieve this goal.

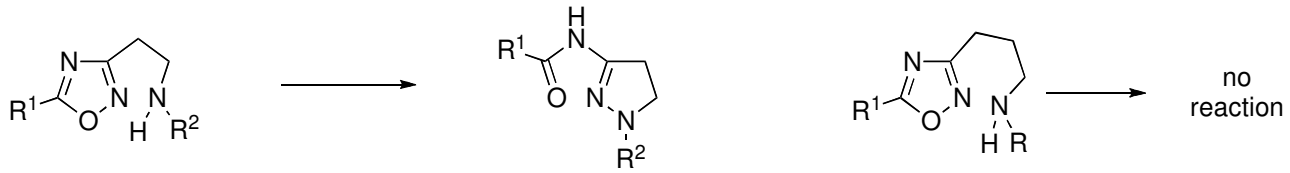
For a given heterocycle, the most significant and generally applicable examples will be presented, starting from accessible substrates and reporting a preparative-scale protocol. Mechanistic aspects will be commented only when necessary for better understanding of the presented reactions.

Aromatic substrates will be essentially considered; dihydro or tetrahydro species will be mentioned only when of particular interest in synthetic applications. As for terminology, the term *isoheterocyclic* or *ring-degenerate* will be used when rearrangement implies the same heterocyclic ring; when the starting and final product will be exactly identical, the term *fully-degenerate* will be used. As for the literature, this survey mostly covers articles issued after the 1993 review on heterocyclic rearrangement,[10] with efforts to present available recent results. Where appropriate, special cases from previous literature will be cited when of a general synthetic utility or to introduce recent applications.

2. Synthesis of five-membered heterocycles with two heteroatoms

2.1. Pyrazoles

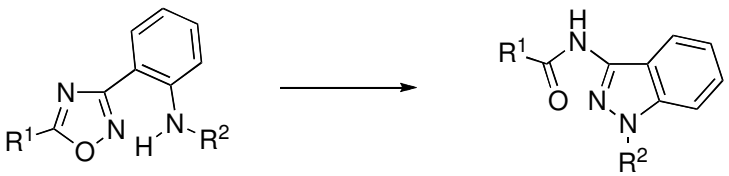
Examples of pyrazoles syntheses involving a BK rearrangement include: i) the synthesis of 3- acylamino-dihydropyrazoles **26** (possible precursors of the corresponding 3-amino derivatives) from 1,2,4-oxadiazoles **25** containing a saturated participating CCN side-chain (Scheme 7); ii) the annulation through a N-N bond formation leading to benzo-fused pyrazoles (indazoles) **29** (Scheme 8) or heterofused-pyrazoles **31** (Scheme 9) from the corresponding 1,2,4-oxadiazoles. These processes are of general applicability and some of them have been reviewed.[9,10,12]



25 **26** **27**

Scheme 7

On the other hand, annulations towards benzofused or heterofused pyrazoles **29** or **31** occur by heating in high boiling solvents such as xylene or DMF. Depending on the acidity of the side-chain NH moiety, the presence of a base may be required to observe the rearrangement. This is the case of systems containing an acylamino group **28** or **30** (R^2 = COMe, COPh) which rearrange easily in the presence of bases.

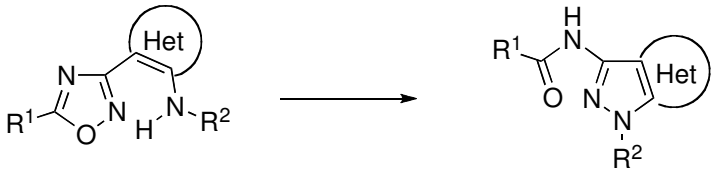


28 **29**

Scheme 8

Recently, this rearrangement of 3-(2-aminoaryl)-1,2,4-oxadiazoles into the corresponding 3-(acylamino)-1*H*-indazoles has been also achieved with good yields through MW irradiation with substrates containing various substituents on the aminoaryl moiety.[13]

In the case of heteroarylamino oxadiazoles, five- or six-membered heteroring moieties present in the the side-chain included pyrazole, pyrimidine, and pyridine (Scheme 9).

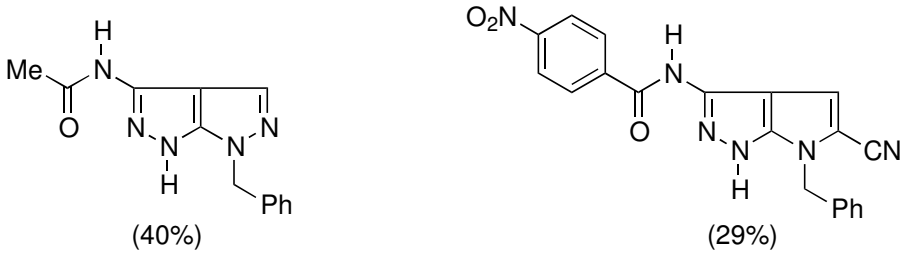


30 **31**

Scheme 9

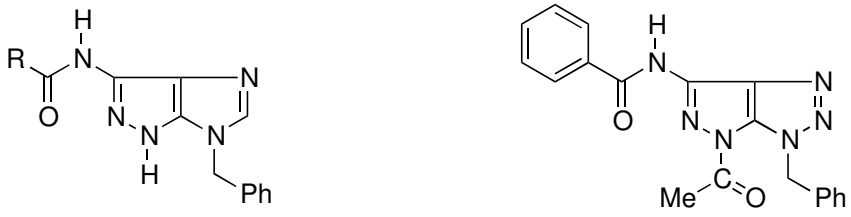
A recent application of this protocol regarded the synthesis of pyrazole[3,4-c]pyrazole **32** (40%), imidazo[4,5-c]pyrazoles **34a,b** (27-36%), pyrrole[2,3-c]pyrazole **33** (29%), and pyrazole[3,4-d]1,2,3-triazole **35** (42%) reached from the corresponding 1,2,4-oxadiazoles under thermal conditions promoted by sodium hydride in DMF or DMSO (Chart 1).[14]

The same annulation strategy was useful for the synthesis of 3-amino-6-(β-D-ribofuranosyl)-imidazo[4,5-c]pyrazole nucleoside **37**, a [5:5] fused analog of adenosine. The key rearrangement step at the oxadiazole moiety in **36** (easily obtained through the amidoxime route) is realized in 74% of yield by using sodium hydride in DMF; subsequent protecting-group interconversion procedures and hydrolysis of the acetylamino group produce the desired **37** (Scheme 10).[15] Another example of the same kind is represented by the synthesis of ribofuranosyl-pyrazolo[3,4-c]pyrazole analogs.[16]



(40%) (29%)

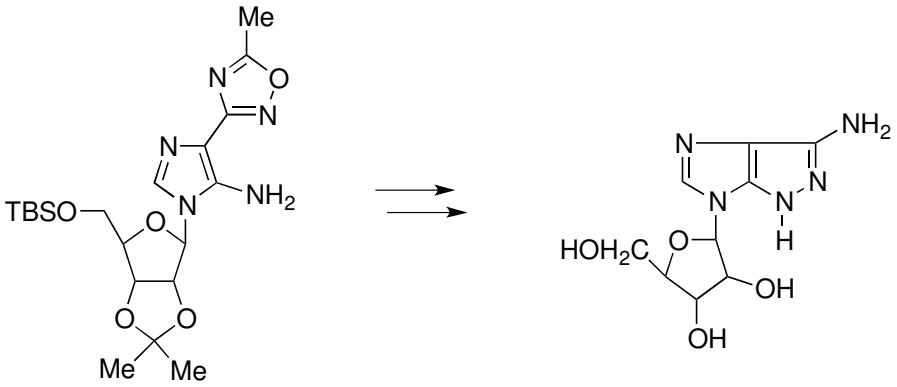
32 **33**



(27-36%) R = Me, Ph (42%)

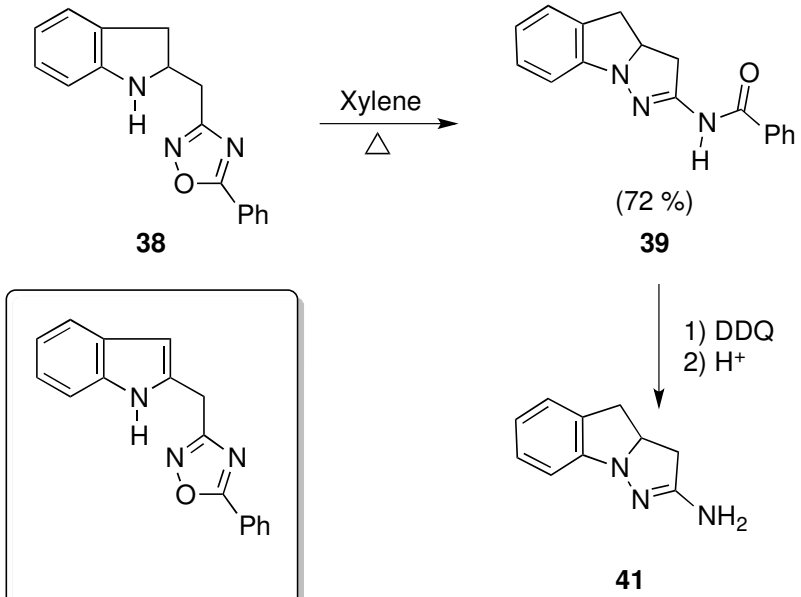
34 **35**

Chart 1



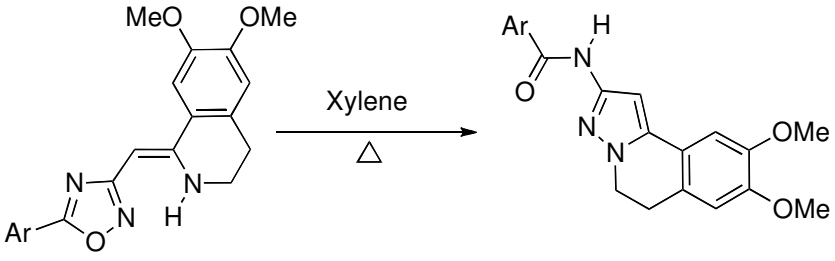
36 **37**

Scheme 10



38 **39** **40** **41**

Scheme 11



42 **43**

Ar = Ph; 4-$MeOC_6H_4$; 4-ClC_6H_4; 4-MeC_6H_4

Scheme 12

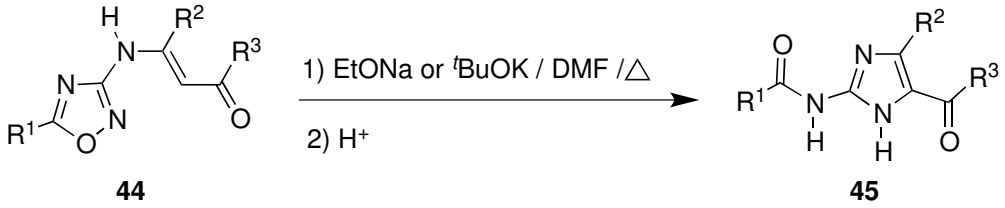
A different annulation through the N-N bond formation (involving an endocyclic nucleophilic nitrogen), regards the synthesis of 2-benzoylamino-[3,3a]-dihydro-4*H*-pyrazole[1,5-a]indole **39** which is

obtained in 72% of yields from **38** refluxed in xylene (Scheme 11).[17] The dihydro derivative **39** can be then transformed into the 2-amino-4*H*-pyrazolo[1,5a]indole **41** through a dehydrogenation with DDQ followed by hydrolysis of the benzoylamino group. Noteworthy, attempts to realize the BK-type N-N annulation on the indole derivative **40** to obtain the same amino compound **41**, failed, likely because of the poor nucleophilic character of the indole nitrogen atom.

Another annulation reaction occurring through this type of N-N bond formation is the synthesis of dihydroisoquinoline fused pyrazoles **43** (45-76%) obtained from oxadiazoles **42** refluxed in xylene (Scheme 12).[18]

2.2. Imidazoles

The first synthesis of imidazoles through a BK reaction lead to 2-acylamino-4(or 5)carbonyl imidazoles **45** from oxadiazolyl enaminoketons or enaminoesters **44**. These were easily obtained from 3-amino-1,2,4-oxadiazoles with β-diketones or β-ketoesters, respectively (Scheme 13).[19,20] The rearrangement is carried out in the presence of bases such as NaOEt or *t*-BuOK in DMF at 110°C. These conditions, in a polar aprotic solvent, enhance the nucleophilic character of the atom Z in the general BK scheme (see Scheme 5 above). The reaction is of general application and can be easily performed on a preparative scale. Nevertheless, some restrictions could arise for substrates having R^2 = H. In fact, the enaminoketone **44e** (R^1 = Ph; R^2 = H; R^3 = Me), upon heating with sodium hydride in DMF, produced a mixture of the corresponding imidazole **45e** (15%) and the pyrazole **46** (45%), the latter formed through a diazirine intermediate evolving into a carbodiimide species.[21] Recently, by using this strategy, some trifluoromethyl substituted imidazoles **45b-d** (51-75%) were obtained (Scheme 13). In this case, suitable trifluoromethylated β-dicarbonyl reagents were used to obtain the starting oxadiazoles.[22]



44 **45**

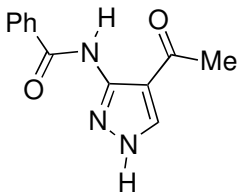
a: R^1 = Me, Ph; R^2 = Me; R^3 = Me, Ph, OEt

b: R^1 = Ph; R^2 = Me; R^3 = CF_3

c: R^1 = Ph; R^2 = R^3 = CF_3

d: R^1 = Ph; R^2 = CF_3; R^3 = OEt

e: R^1 = Ph; R^2 = H; R^3 = Me



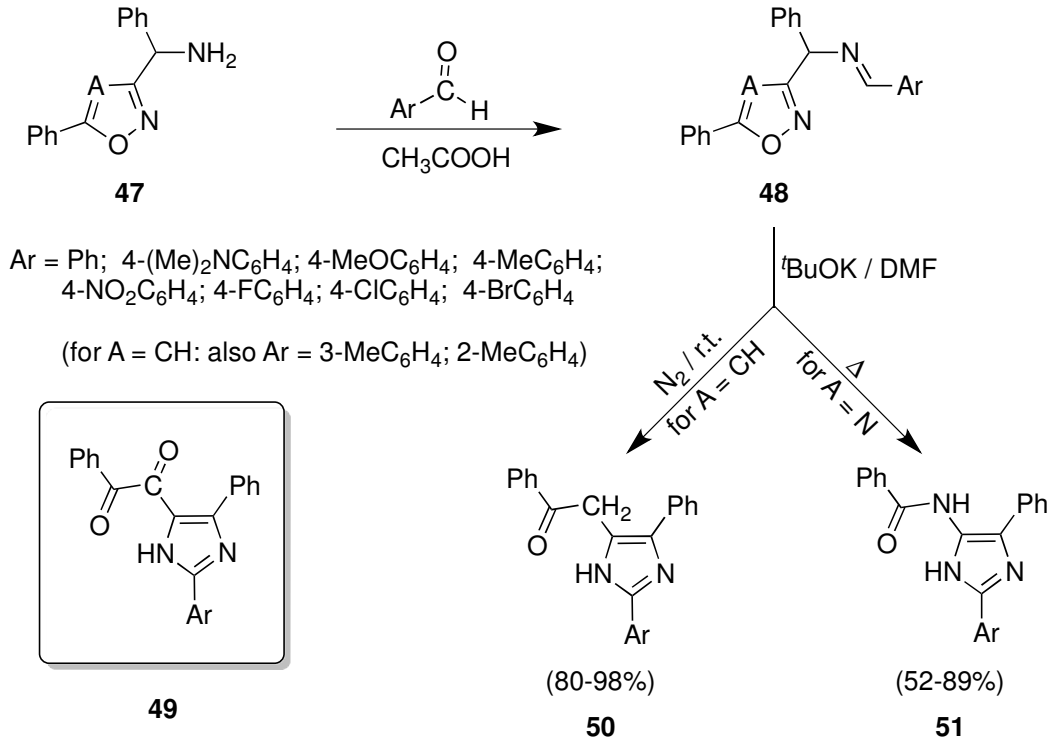
46

Scheme 13

Another generalizable synthesis of targeted imidazoles through a BK-type reaction regards the formation of 2-aryl-substituted 4(or 5)-benzoylaminoimidazoles **51** (52-89%)[23] or 4(or 5)-phenacylimidazoles **50** (80-98%)[24] by rearrangement of oxadiazoles **48** (A = N) or isoxazoles **48** (A = CH), respectively. In these reactions, a CNC-type side-chain is involved through a potentially nucleophilic

terminal carbon atom (Scheme 14). These rearranging substrates are easily accessible from the corresponding amino compounds **47** reacted with suitable aromatic aldehydes in acetic acid at room temperature. Interestingly, various aromatic aldehydes with a variety of electronic effects are well tolerated and can be used in the synthetic strategy. In turn, the ring-rearrangement of compounds **48** will be performed by using *t*-BuOK in refluxing DMF, in the case of oxadiazole derivatives **48** (A = N), or at r.t. and under nitrogen in the case of the isoxazole substrates **48** (A = CH) in order to prevent a base-promoted oxidation of the final phenacyl side-chain into the diketone **49**. Indeed, a representative rearrangement of isoxazoles **48** (Ar = Ph, 4-$MeOC_6H_4$) carried out in the presence of air, besides by-products from subsequent reactions, gave diketones **49** in 52 and 31%, respectively (Scheme 14).

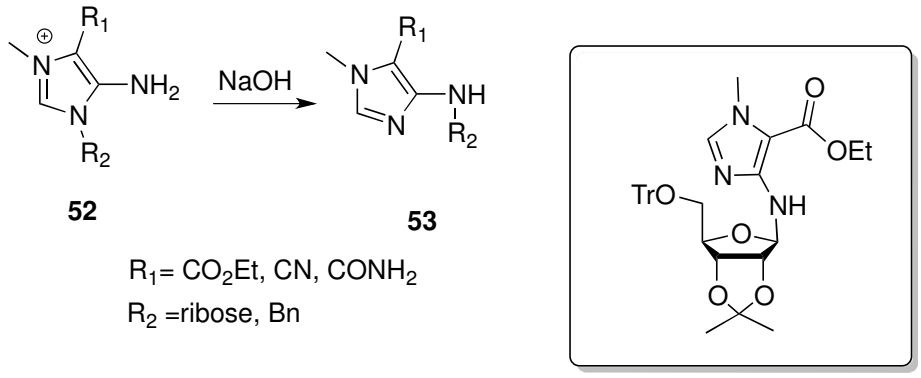
Since 4(5)-aminoimidazoles[25,26] and 4-acylaminoimidazoles[27-29] are key components in the synthesis of bioactive compounds, and considering the accessibility of their precursors, the observed rearrangement can be exploited as a valid approach towards target imidazoles. Conveniently, performing the rearrangement in the presence of oxygen favors further reactivity of isoxazole derivatives **48** (A = CH) into the preferential formation of oxidized compounds **49**.[24] This approach leads to functionalized imidazoles that can be further modified or used as building blocks for other heterocyclic syntheses.



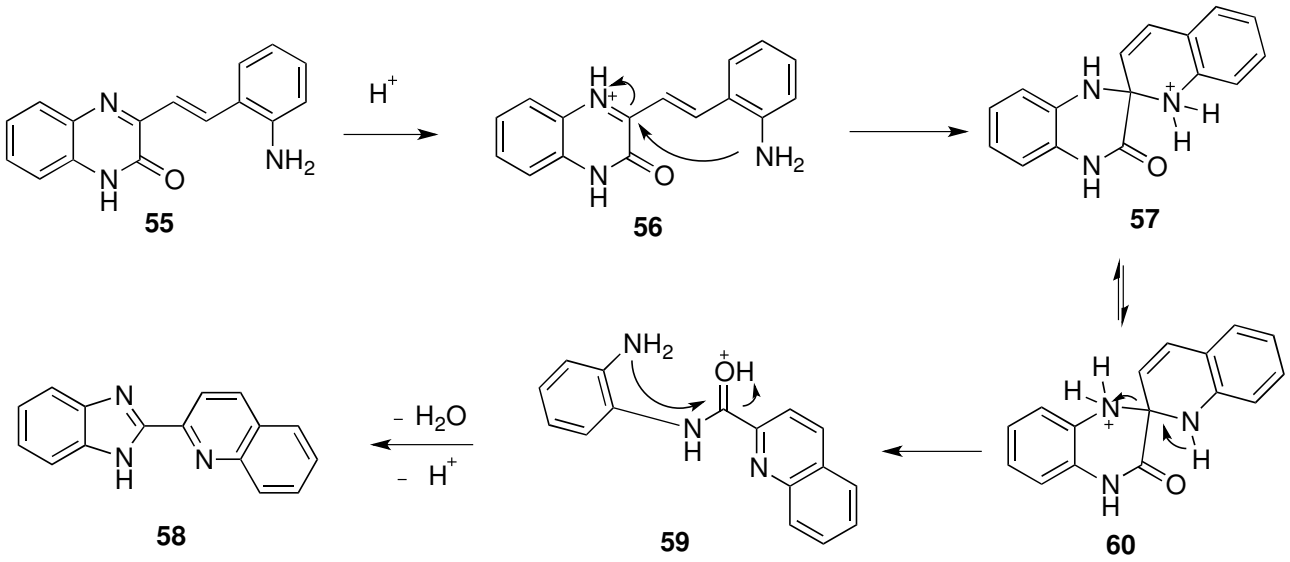
Scheme 14

Interestingly, a recent example of a base-catalyzed *Dimroth* rearrangement has been applied to imidazolium salts **52** leading to various 4-amino-imidazoles including the 4-β-D-ribofuranosyl-aminoimidazole nucleoside derivative **54** (Scheme 15).[30]

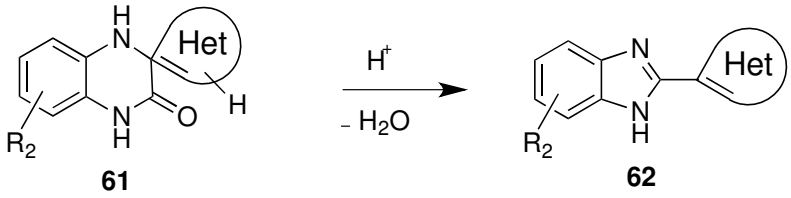
For the benzimidazole series, during the last decade Mamedov's group exploited an effcient method for the synthesis of benzimidazol-2-yl-quinolines **58** (Scheme 16).[31,32] This quinoxalinone–benzimidazole rearrangement has been recently applied to the synthesis of a series of benzimidazoles **62** directly linked to a heterocyclic moiety (Scheme 17).[33]



Scheme 15



Scheme 16



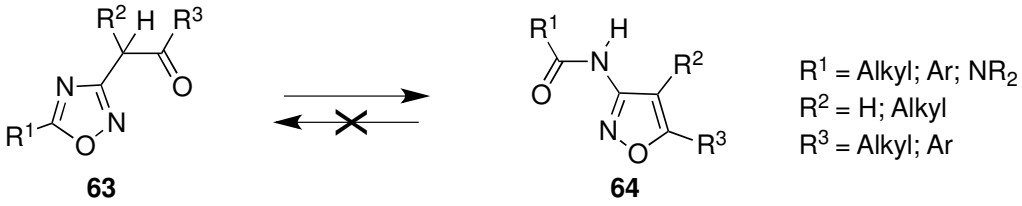
Scheme 17

2.3. Isoxazoles

Patented literature dedicated to the preparation of herbicides, reports that generalized 3-acyl-aminoisoxazoles **64** can be obtained by rearrangement of the corresponding oxadiazoles **63**. (Scheme 18).[34] In particular, isoxazole **64** (R^1 = NMe_2; R^2 = H; R^3 = CMe_3) is reported to be obtained quantitatively by acid treatment of the corresponding oxadiazole **63**, easily prepared from a Claisen-type reaction between the 3-methyl-5-dimethylaminooxadiazole and Me_3C-COOMe in the presence of LDA, the enolic form being the reacting side-chain in the BK scheme. On the other hand, 3-acylaminoisoxazoles **64** (R^1 = Me_2CH, cyclohexyl, $MeOCH_2$, Ph; R^2 =H; R^3 = Me) are reported to be obtained quantitatively by treatment of the corresponding 3-acetonyl-oxadiazoles with *t*-BuOK in THF or sodium methoxide in MeOH at r.t., the reacting side-chain being the enolate species (Scheme 18).[4,35] It is worth noting that even if the reversible

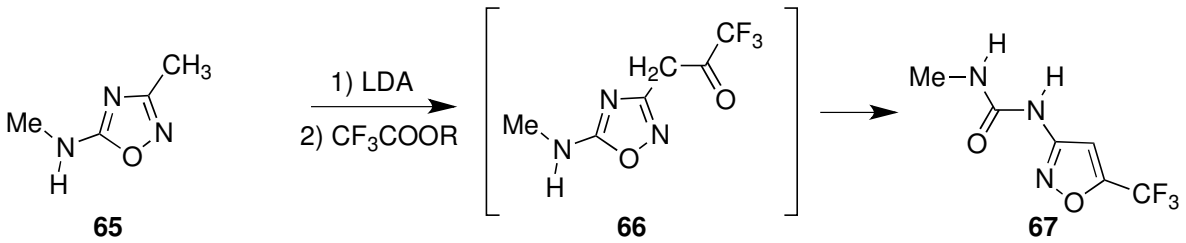
rearrangement should potentially lead to an equilibrium mixture since an O-N bond is formed and an O-N bond is cleaved in the process, the higher stability of the isoxazole nucleus compared to the oxadiazole leads to the quantitative formation of the isoxazole ring.

The above strategy has been also applied to the synthesis of (perfluoroalkyl)isoxazole derivatives having herbicidal activity. In particular, the formation of trifluoromethyl-substituted ureido-isoxazole **67** (38%) is reported from 3-methyloxadiazole **65** through the involvement of the rearranging oxadiazole intermediate **66** (Scheme 18).[36]



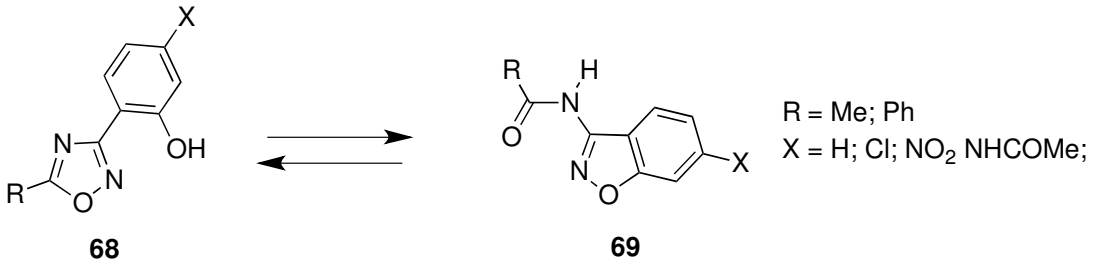
63 **64**

a: $R^1 = N(Me)_2$; R^2 = H; $R^3 = {}^t$Bu
b: $R^1 = {}^i$Pr; cyclohexyl; $-CH_2OMe$; Ph; R^2 = H; R^3 = Me

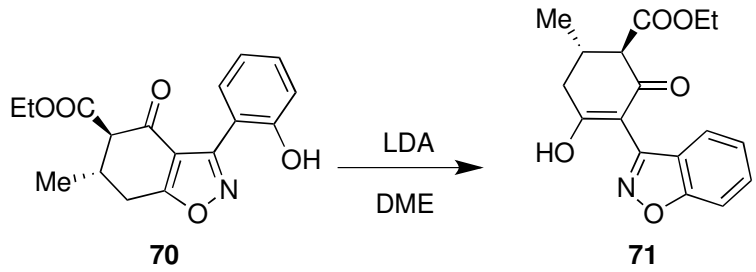


65 **66** **67**

Scheme 18



68 **69**

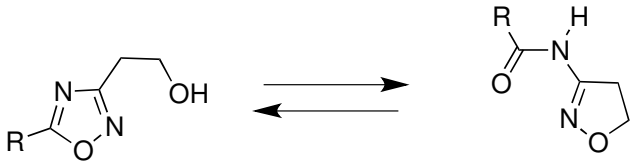


70 **71**

Scheme 19

As for annulated isoxazoles, it is worth remarking that 3-acylamino-benzisoxazoles **69** and 3-(*o*-hydroxyphenyl)-1,2,4-oxadiazoles **68** give rise to an equilibrium whose constant K=[**69**]/[**68**] depends on the type of substituents and reaction medium (Scheme 19).[9,10,37]

In particular, the equilibrium is essentially shifted towards the oxadiazole component by anionic bases, the driving force being the stabilization of the phenate species compared to the acylamino anion. In the context of a synthetic strategy towards polycyclic structures derived from the benzisoxazole compound **71**, the base promoted rearrangement of annulated isoxazole **70** into **71** has been reported in 35-45% yields, the driving-force being the stabilization of the enolate species in the final product and the formation of a benzofused heteroaromatic moiety (Scheme 19).[38] Finally, the synthesis of isoxazolines **73** (57-86%) was very recently achieved through the rearrangement of oxadiazoles **72** having a saturated CCO side-chain in DMSO at r.t. and in the presence of *t*-BuOK (Scheme 20).[39] In this case, even if the final product is not aromatic, the driving force in the rearrangement can be recognised in the stabilization of the amide moiety present in the side-chain of the final product.



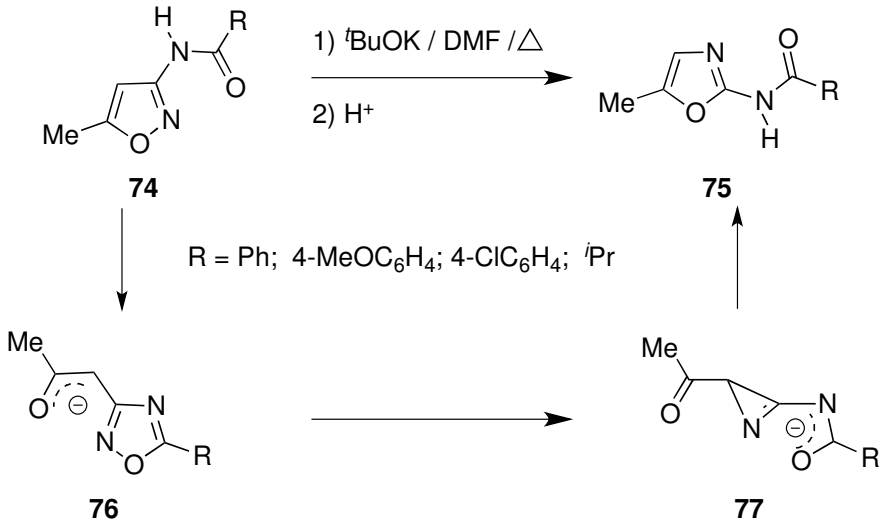
72 **73**

Scheme 20

2.4. Oxazoles

2-Acylaminooxazoles **75** can be obtained in good yields (74-80% %) by reacting 3-acylamino-isoxazoles **74** with *t*-ButOK in DMF at 110 °C (Scheme 21)[4,40] The reaction, which can be performed in preparative-scale and can be generalized for the synthesis of 2-amino-oxazoles, had been roughly explained through a ring contraction-ring expansion process at the isoxazole ring moiety involving an azirine species.[40]

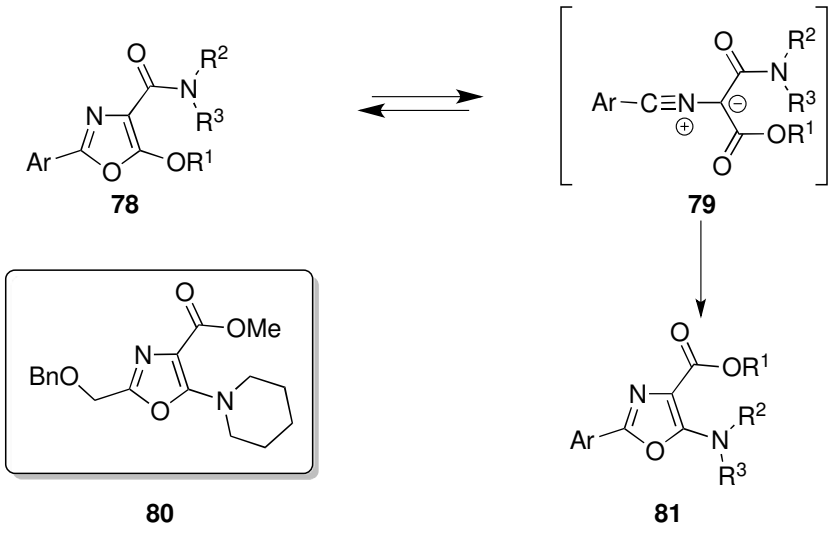
However, recent mechanistic and computational investigations evidenced a cascade reaction involving an initial reversible BK rearrangement of **74** into a labile oxadiazole intermediate **76** which then rearranges following a one-atom side chain pathway into the final product **75** through the azirine species **77** (Scheme 21).[4]



74 **75** **76** **77**

Scheme 21

Interestingly, valid syntheses of targeted functionalized oxazoles can be realized through ring-degenerate rearrangements of differently substituted oxazoles as precursors, following the *Cornforth* rearrangement route. This reaction consists of a *Ring-opening Ring-Closure* rearrangement of oxazole-4-(*N*-substituted) carboxamides **78** into 5-(*N*-substituted amino)-oxazole-4-carboxylates **81** through the open-chain intermediates **79** arising from the cleavage of the O(1)-C(5) bond. Subsequent closure of intermediates **79** will be entirely determined by the relative thermodynamic stabilities of starting 5-alkoxy substituted oxazoles **78** in one hand, and final 5-amino substituted oxazoles **81**, in the other (Scheme 22).[6,41-43] This transformation, which simply occurs in refluxing toluene with higher than 90% yields, is widely applicable to various *N*-mono and *N,N*-disubstituted amides. A recent application of this *Cornforth* strategy regards the synthesis of various 5-amino substituted oxazoles **81** (Ar = Ph; R_1 = Et) which can be obtained, with a variety of yields (23-99%) depending on the structure of the amide group in the rearranging substrate, by heating the accessible oxazole-4-carboxamides **78** (Ar = Ph; R_1 = Et) at 180 °C in trifluorotoluene under a high-speed microwave assisted procedure.[44] Recent examples regard the synthesis of 5-amino-oxazole-4-carboxylates as synthons for biologically active compounds.[45] It is interesting to remark the potential application of this strategy in the synthesis of substituted 5-aminooxazoles with a diverse array of functionality (the presence of different functional groups are tolerated by the work-up procedure) and of bioactive 5-aminooxazole derivatives such as the piperidin-oxazole **80**, a building block for the assembly of pseudomonic acid derived antibiotics.

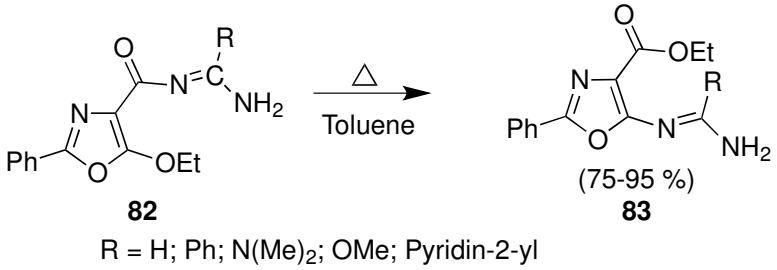


Scheme 22

The *Cornforth* strategy has been also applied to the synthesis of oxazoles **83** which are useful synthons for the cyclization into oxazolo[5,4-d]pyrimidines intermediates in the synthesis of purine and ipoxantine systems. To this aim, the precursors **82** are easily rearranged into desired **83** (75-95%) by simple refluxing in toluene (Scheme 23).[46] Interestingly from a synthetic point of view, the same rearrangement has been observed for the thiol ester **84** from which the corresponding 5-thiooxazole **85** (94%) can be produced.[41]

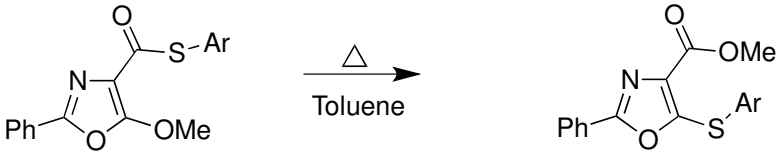
Besides other examples[47] of scarce synthetic utility, an interesting example of this strategy concerns the formation of disubstituted oxazolic derivatives **87** (47-84%) from the acylation reaction of the 2-(5-oxazolyl)-1,3-dithiane dianion **86**. The final products, at least formally, can be considered as the result

of the *Cornforth*-type rearrangement of the presumed, but not isolated, 4-acyloxazoles (Scheme 24). In some cases, mixtures of 4-acyl-oxazoles with the corresponding rearranged products could be isolated.[48]



82 **83**

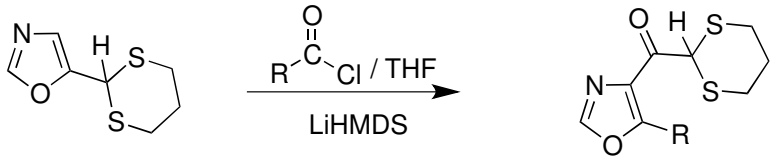
R = H; Ph; $N(Me)_2$; OMe; Pyridin-2-yl



Ar = 4-$CH_3C_6H_4$

84 **85**

Scheme 23



86 **87**

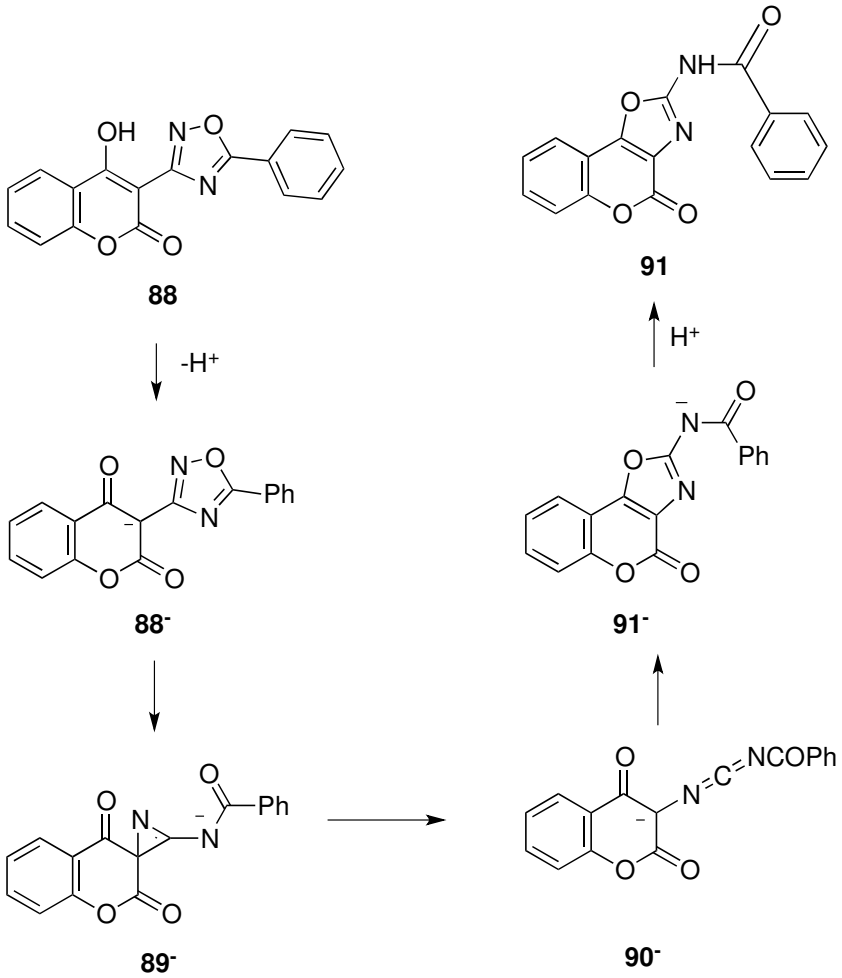
R = Ph; 4-ClC_6H_4; 2-Furanyl; 2-Benzothiophenyl

Scheme 24

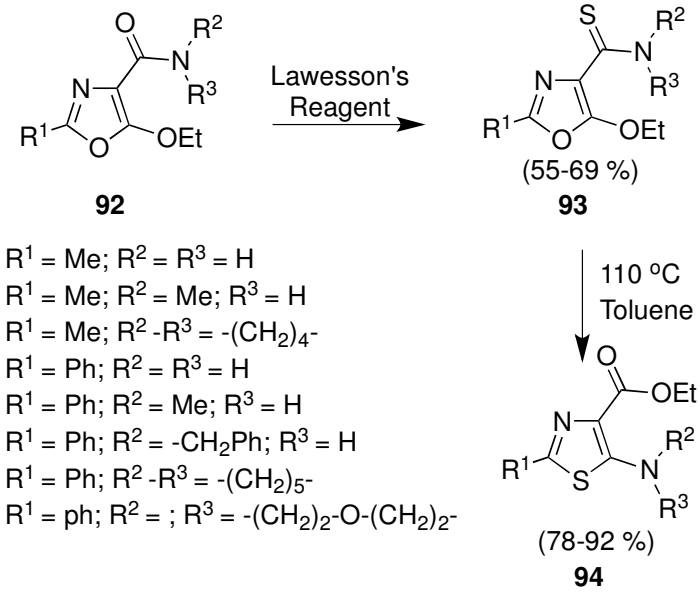
An interesting example of MNAC rearrangements has been applied at a preparative scale for the synthesis of oxazolic coumarine derivatives. The starting 1,2,4-oxadiazole substituted 4-hydroxycoumarine **88** (Scheme 25) can be converted, almost quantitatively into the corresponding 2-benzamido-4*H*-chromeno[3,4-d]oxazol-4-one **91** through the carbodiimide intermediate **90**.[49]

2.5. Thiazoles

An interesting ring interconversion leading to thiazoles **94** could be achieved through the *Cornforth*-like rearrangemet of the thiocarbonyl-oxazoles **93**, which is prepared in 55-69% yield upon sulfurization of the oxazole-amides **92** with Lawesson's reagent (Scheme 26).[50] The rearrangement of oxazoles **93** into thiazoles **94** takes place by simple refluxing in toluene, and final product are formed in 78-92% of yield. The reaction appears generally applicable to the synthesis of 2-alkyl and 2-aryl-5-alkylamino (5-dialkylamino) thiazoles. A restriction has been found in the synthesis of 5-arylamino derivatives, and this because the thiation reaction in preparing the corresponding oxazole precursors failed.



Scheme 25



Scheme 26

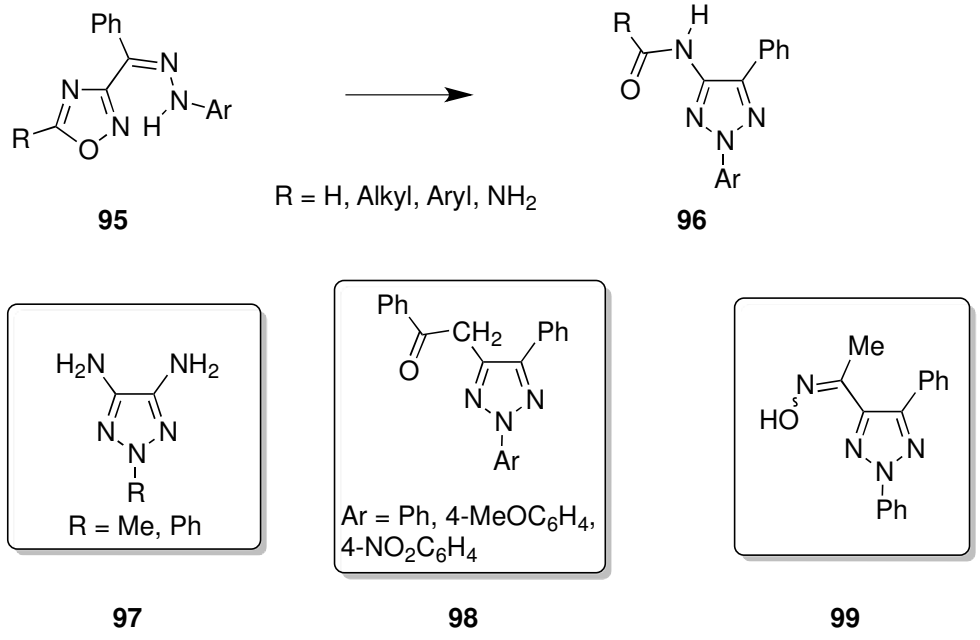
3. Synthesis of five membered heterocycles with three heteroatoms

3.1. 1,2,3-Triazoles

The synthesis of 2*H*-1,2,3-triazoles can be achieved through the BK rearrangement of the hydrazones of 3-acyl-1-oxa-2-azoles, a strategy that is classically represented in literature.[9,10] Typically, acylamino-

1,2,3-triazoles **96** can be obtained (generally in almost quantitative yield) from arylhydrazones of 3-acyl-1,2,4-oxadiazoles **95** by a thermal or base-induced reaction (Scheme 27).[9,10] This reaction appears rather generally applicable to a variety of substrates and allows to obtain the corresponding amino-triazoles by acid hydrolysis of the rearrangement products. This reaction has been used as a model for mechanistic studies, which considered the structural aspects of the reacting system: the mono- or poly-substitution at the hydrazonic aryl ring, the substitution at the C(5) of the oxadiazole ring, and the *E/Z* configuration of the hydrazone chain. Recent mechanistic studies for the thermal reaction[51] have accompanied also the mechanistic investigation on the photochemically induced reactivity of similar substrates.[52]

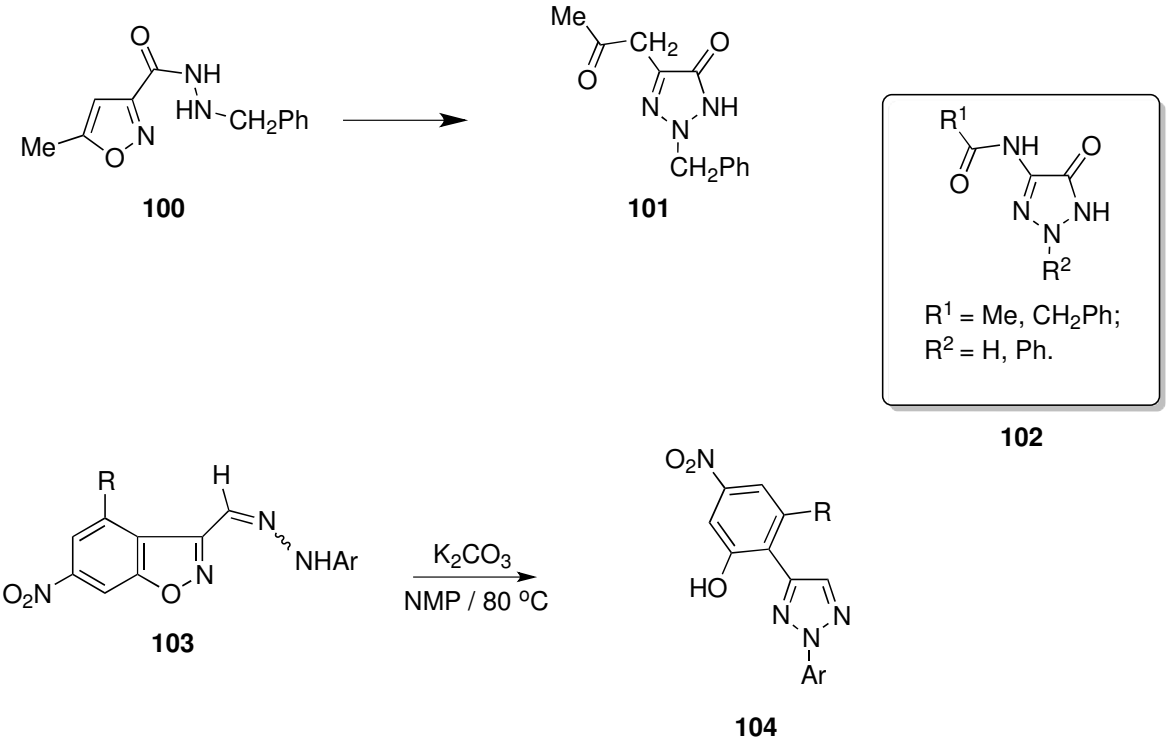
The above strategy has been productively used for the synthesis of different targeted 1,2,3-triazoles such as the diamino-compounds **97**, possible precursors for further heterocyclizations.[53] Additionally, a series of phenacyltriazoles **98** (from Z-arylhydrazones of 3-benzoyl-5-phenylisoxazole)[54-56] and *Z* (10%) and *E* (80%) triazolyl-ketone oximes **99** are similarly obtained through a base-promoted (in EtONa/EtOH) rearrangement reaction of both *E* and *Z* phenylhydrazones of 3-benzoyl-4-methylfurazan.[57]



Scheme 27

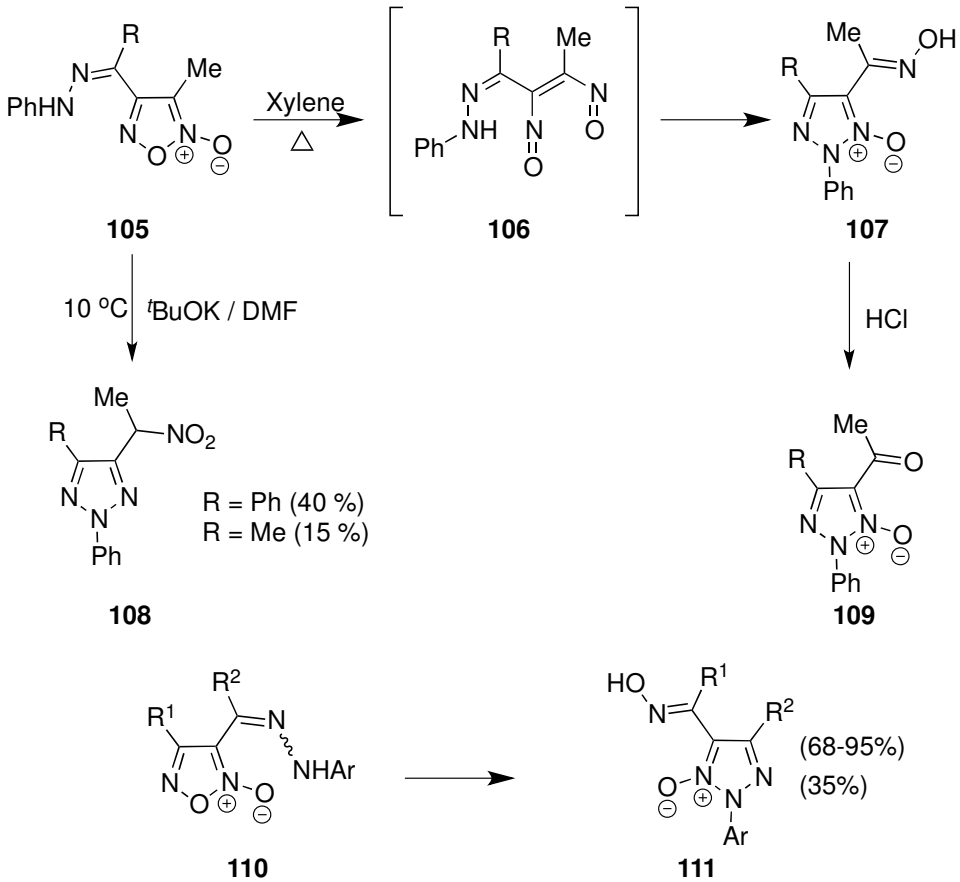
Similarly to the acylamino substituted triazolinones **102**, which were obtained by a thermal rearrangement of the corresponding oxadiazolyl-hydrazides,[58] the acetonyl substituted triazolin-5-one **101** has been recently reported (90% yield) from a thermal rearrangement of the isoxazolyl hydrazide **100** (Scheme 28).[59] Moreover, targeted 4-(*o*-hydroxyaryl)-1,2,3-triazoles such as **104** were prepared (30-73%) by rearrangement of arylhydrazones of benzo[d]isoxazole-3-carbaldehydes **103**, by using potassium carbonate in *N*-methylpyrrolidone (NMP) at 80 °C (Scheme 28).[60]

As for 1,2,3-triazole *N*-oxides derivatives, these can be obtained from suitable furazan-N-oxides (furoxans). For instance, N-oxides **107** is produced in in 48-67% yields by heating furoxan (*Z*)-phenyl-hydrazones **105** in *o*-xylene at 150 °C. The rearrangement can be explained through a *ring opening-ring closing* process involving the dinitroso derivative **106** as an intermediate (Scheme 29).[61]



R = NO_2, SPh, SCH_2Ph, cyclo-$C_6H_{11}S$; Ar = Ph, 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4

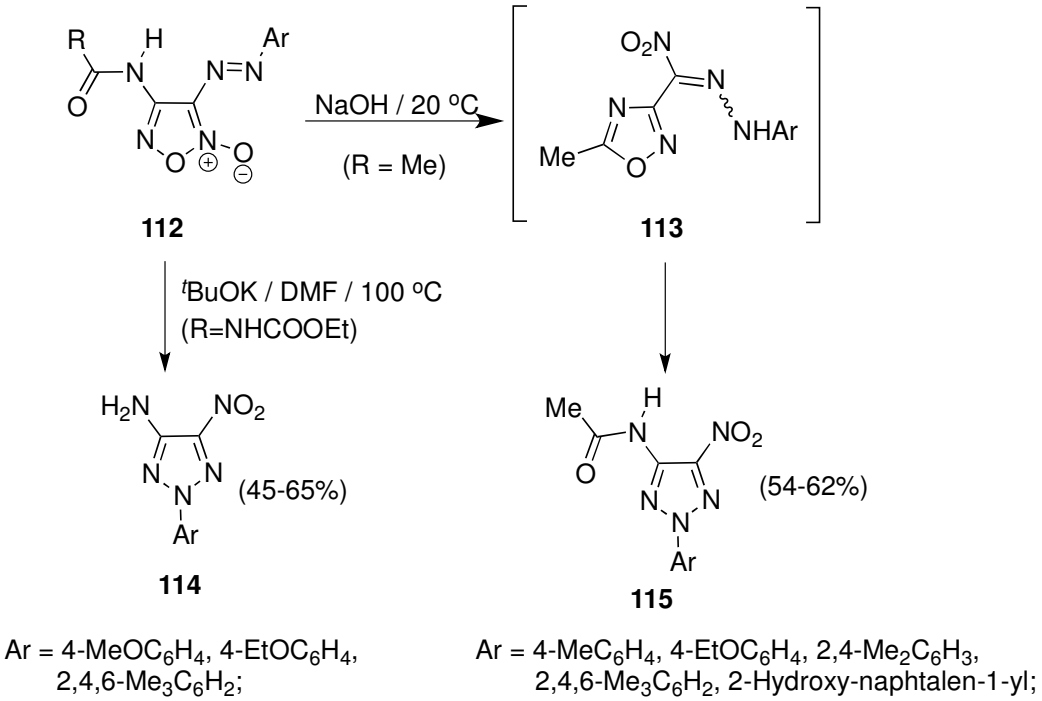
Scheme 28



a: R^1 = Ph; R^2 = H; Ar = Ph, 4-$NO_2C_6H_4$, 4-BrC_6H_4;
b: R^1 = NH_2; R^2 = Me; Ar = Ph

Scheme 29

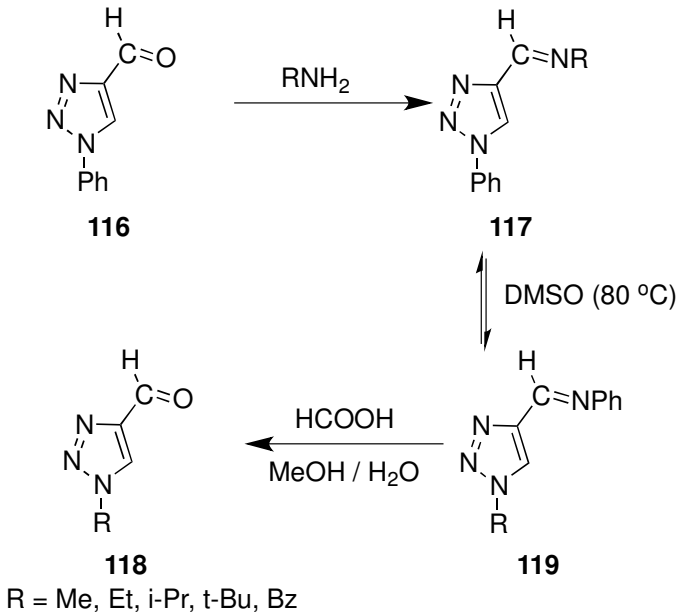
On the other hand, low to moderate yields of 5-(1-nitroethyl)-triazoles **108** (15-40%) are obtained when phenylhydrazones **105** are reacted in DMF/*t*-BuOK medium at 10 °C (Scheme 29).[61] Additionally, triazole N-oxides **111a** (68-95%) and **111b** (35%) are formed, through dinitroso intermediates, from furoxans **110a** in MeOH/KOH medium under reflux or from furoxan **110b** in refluxing *o*-xylene, respectively.[62] It is worth noting that, for the last furoxans substrates **110**, the N-oxide oxygen atom adjacent to the C(3) of the ring precludes a "pure" BK rearrangement by hindering the nucleophilic attack of the side-chain. The synthesis of nitro-triazoles **115** (54-62%) can be achieved from 4-acetylamino-3-arylazo-furoxans **112** by using aqueous (15%) NaOH. Here the reaction is explained through a cascade process (two subsequent BK reactions) involving the initial formation of the 1,2,4-oxadiazole intermediates **113** (Scheme 30).[63] A similar reaction, performed on the acetylaminofuroxan **112** (Ar = 4-acetamidofuroxan-3-yl) in $AcOH/Ac_2O$ mixture at 50 °C, produces the corresponding acetylamino-nitro-triazole **115** (Ar = 4-acetamidofuroxan-3-yl) in 65% of yield.[64] Similarly, the amino-nitro-triazoles **114** (45-65%) are directly obtained by treatment of 3-arylazo-4-(3-ethoxycarbonyl-ureido)furoxan **112** (R = NHCOOEt) with *t*-BuOK in DMF at 100 °C. The cascade process involving the oxadiazole species, is followed by the hydrolysis of the ureido group under the used experimental conditions (Scheme 30).[65]



Scheme 30

A synthetic strategy leading to 1*H*-1,2,3-triazoles considers the interconversion of suitable substituted 1*H*-1,2,3-triazoles through a *Cornforth*-like rearrangement. An illustrative example refers to the ring-degenerate process between differently substituted 1,2,3-triazoles **117** and **119** occurring by heating in DMSO at 80 °C and involving open-chain intermediate arising from the cleavage of the N(1)-N(2) bond. The equilibrium product distribution depends largely on the nature of the substituent R. In detail, when R is an electron rich or electron donating group such as alkyl or benzyl, the 1-alkyltriazoles **119** are essentially formed and isolated in 74-95% yield. Therefore, the ready accessibility of **116** (through a cycloaddition

reaction between phenylazide and propiolaldehyde), and the large variety of amines, which can be used, coupled with the easy procedure, make this strategy an excellent method leading to 1-alkyl-triazole 4-carbaldehydes **118** starting from the 1-phenyl substituted congener (Scheme 31). Importantly, this approach allows the synthesis of sterically hindered derivatives such as **118** (R = *i*-Pr; *t*-Butyl), which would be difficult to obtain from the cyclization of the corresponding alkyl-azide with propionaldehyde.[66]



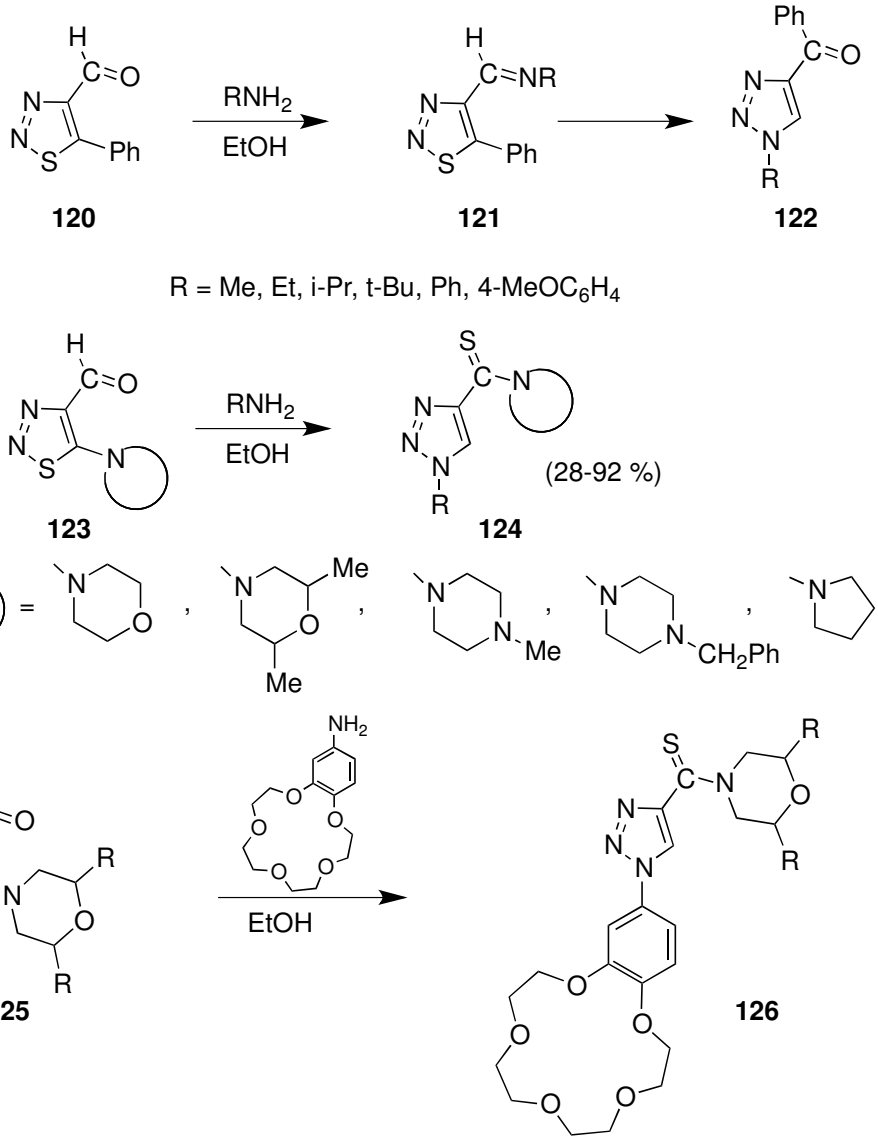
Scheme 31

By a similar strategy, 1*H*-1,2,3-triazoles can be also obtained by a rearrangement of 1,2,3-thiadiazole substrates through intermediates arising from cleavage of the S-N bond in a *ring opening-ring closure* route.[67-70] The representative synthesis of 4-benzoyl-triazoles **122** (42-62%) occurs through unisolated thiobenzoyl precursors **121** by reacting the 5-phenyl-1,2,3-thiadiazole-4-carbaldehyde **120** with various aliphatic or aromatic amines. Depending on the used amine, which affects the nucleophilic character of the intermediate iminic nitrogen, the reaction reaches completion in ethanol, at r.t. or under reflux, or in DMSO at 120 °C (Scheme 32).[71] Similarly, a broad range of 1,2,3-triazole-4-carbothioamides **124** are obtained in 28-92 % yield by reaction of 5-dialkylamino-substituted 1,2,3-thiadiazole-4-carbaldehydes **123** with primary aliphatic and aromatic amines, hydroxylamines, and *N*-substituted hydrazines (Scheme 32).[72] Furthermore, a recent application of this protocol refers to the synthesis of triazoles **126**, which are potential receptors for α-amino acids. These target triazoles are directly obtained in 63-77% yield by a simple reaction of the 1,2,3-thiadiazole-4-carbaldehyde **125** with 3-aminobenzo-15-crown-5 in ethanol at 20 °C (Scheme 32).[73]

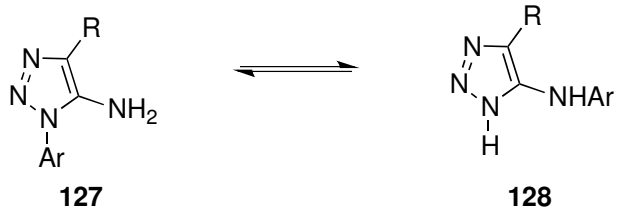
Synthesis of targeted 1*H*-1,2,3-triazoles can be also realized by the *Dimroth*-type rearrangement as in the case of the thermal or base-induced ring-degenerate rearrangement of 1-aryl-5-aminotriazoles **127** into the 5-arylaminotriazoles **128** (Scheme 33).

Dimroth rearrangements can occur in both five- and six-membered heteromonocycles as well as in annulated policyclic systems and have been largely reviewed.[74-76] Here we are considering DR of five-membered heteromonocycles reporting strategies directed to the synthesis of functionalized 1,2,3-triazoles. In this context, it is important to remark the easy accessibility of 5-amino triazoles starting material, which can be obtained regiospecifically by azides ($R\text{-}N_3$) cycloaddition to nitriles containing an activated

methylene group. Typically, the *Dimroth* rearrangement is a reversible process where the formation of the thermodynamically favoured compound is preferred. In the reaction illustrated in Scheme 33, electron-withdrawing groups at both 1- and 4-position favor the formation of the 1*H*-5-arylamino products **128**.



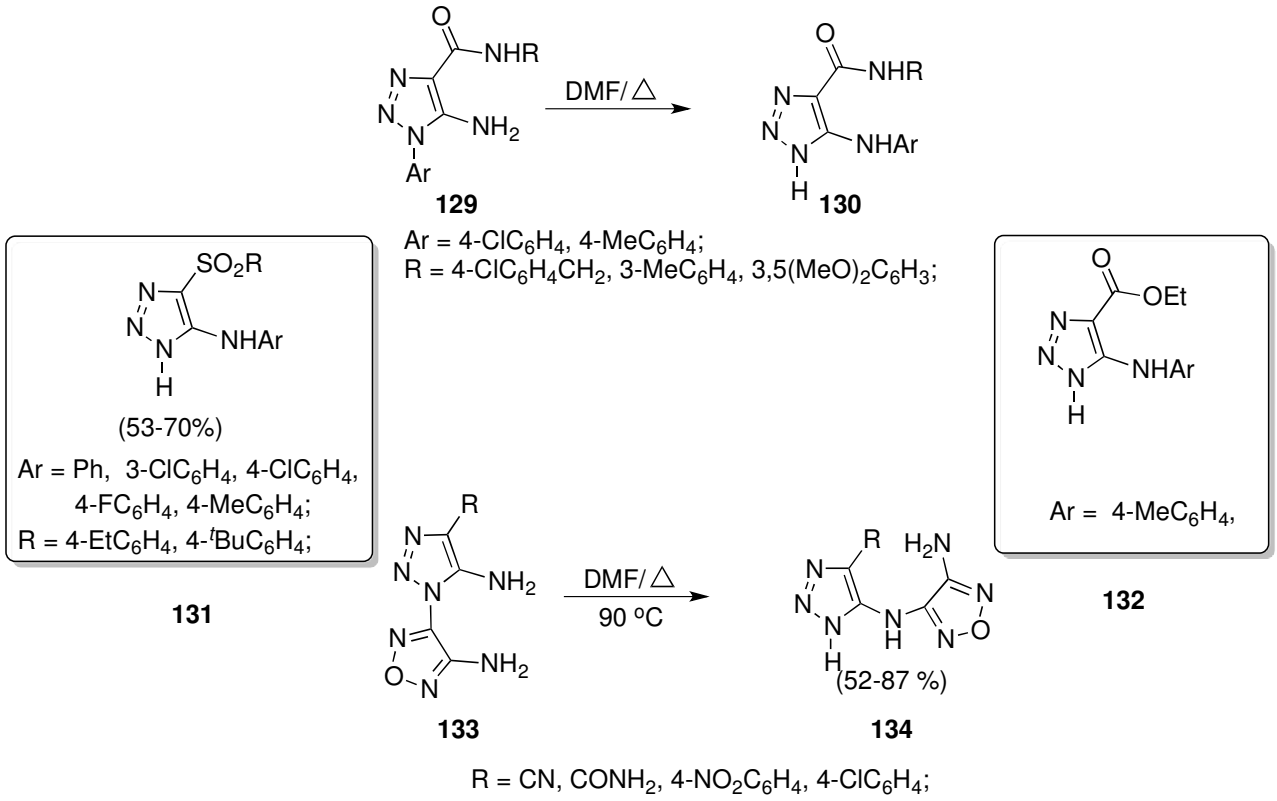
Scheme 32



Scheme 33

Besides other reported examples,[77,78] a recent synthesis of 4-carboxamido-5-arylamino triazoles **130** (61-72%) has been achieved from the corresponding 1-aryl-5-amino triazoles **129** by heating in DMF at 120-150 °C (Scheme 34).[79] Similarly, also 5-arylamino-4-carbethoxy-triazoles **132**[80] and 5-arylamino-4-

arylsulfonyl triazoles **131**[81] can be prepared in good yield. Moreover, 5-furazanylamino derivatives **134** (52-87%) can be easily obtained from 5-amino-1-furazanyl-triazoles **133** by simple heating in DMF a 90 °C.[82]



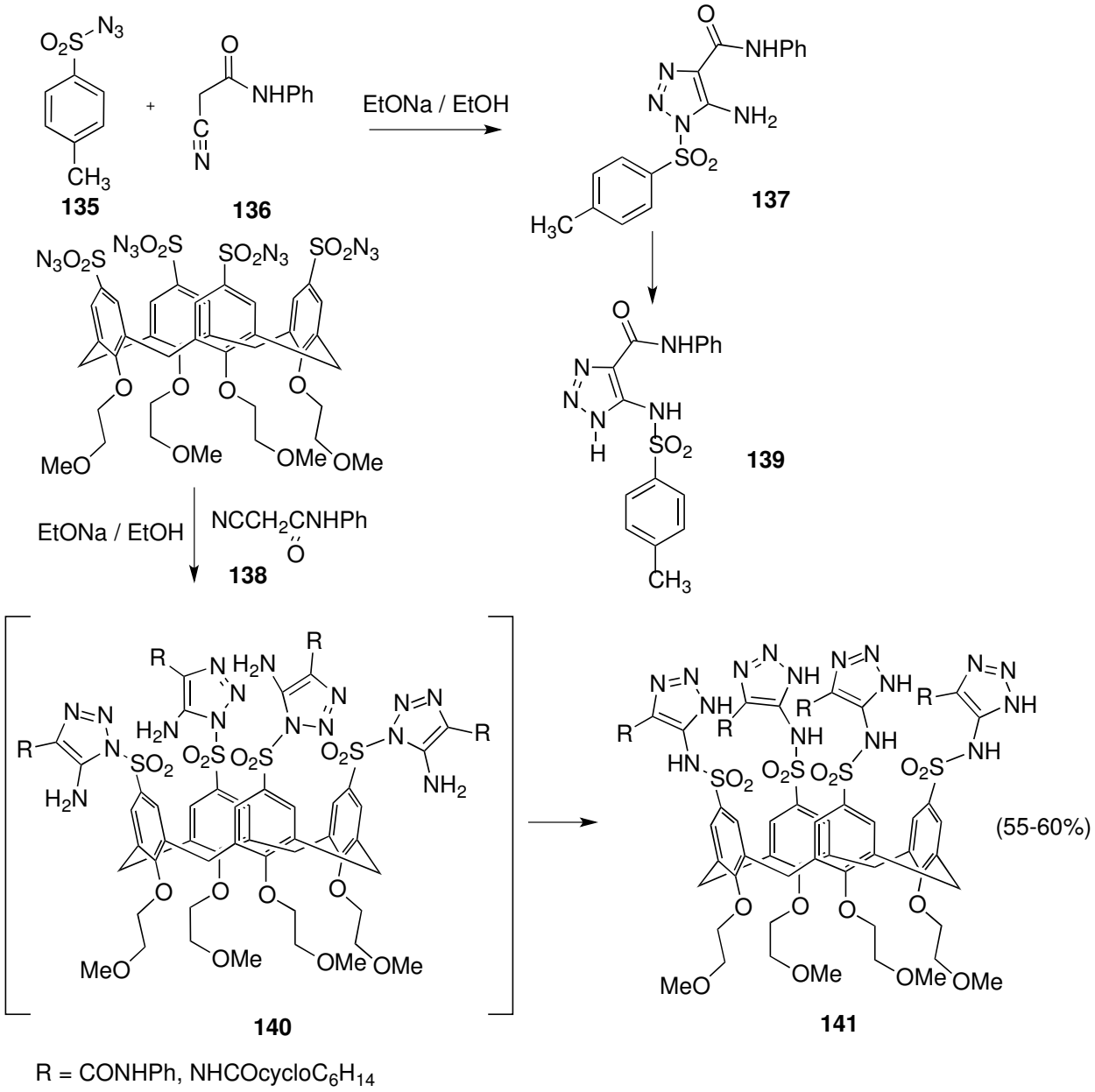
Scheme 34

From the reaction of tosylazide **135** with *N*-phenyl-2-cyanoacetamide **136** in EtOH/EtONa medium the rearranged 5-tosylamino-1,2,3-triazole **139** can be directly formed (Scheme 35).[83] Finally, in studying the synthesis of neutral anion receptors, a 5-aminotriazole moiety has been constructed in calix[4]arene structures by the reaction of the tetrakis-(azidosulphonyl)calix[4]arenes with *N*-substituted 2-cyano-acetamides in EtOH/EtONa medium. Rearrangement of the unisolated 5-amino-1-arylsulphonyl triazole moiety into the 5-arylsulphonylamino counterpart **141** takes place in situ producing the final product in 55-60% yield.[83] In a differently substituted calixarene, by refluxing the isolated 5-amino-1-arylsulphonyl triazole derivative in ethanol in the presence of triethylamine an 88% yield of the rearrangement step has been recorded.[84] Interestingly, it was observed that calixarenes containing the 5-amino-triazole moiety weakly chelates anions, while calixarenes containing the rearranged triazole moiety exhibits higher anionic complexation properties.

Dimroth rearrangements involving the interchange between exocyclic nitrogen and endocyclic sulfur atom can be also used for the synthesis of 1H-1,2,3-triazoles from 1,2,3-thiadiazoles.[68,70,85] In a general approach, 5-amino-(or substituted amino-) thiadiazoles **142** rearrange under the influence of a base into 5-mercaptotriazoles **143** which can further react, depending on the used conditions, thus precluding the possible reverse reaction (Scheme 36).

A synthetically useful reactivity of 5-halo-1,2,3-thiadiazoles, substituted at the C(4) with an electron-withdrawing group, with diamines such as diaminoethane or 1,2-phenylen-diamine, triggers cascade

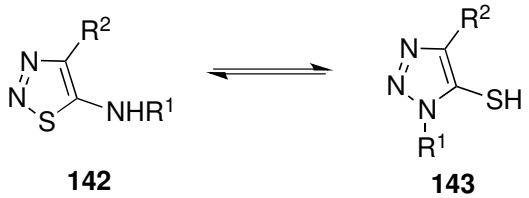
reactions involving *Dimroth* rearrangements.[86,87] An illustrative example of this strategy directed to the synthesis of thiadiazepines, is reported in the Scheme 37.



135 136 137 138 139 140 141

R = CONHPh, NHCOcycloC$_6$H$_{14}$

Scheme 35

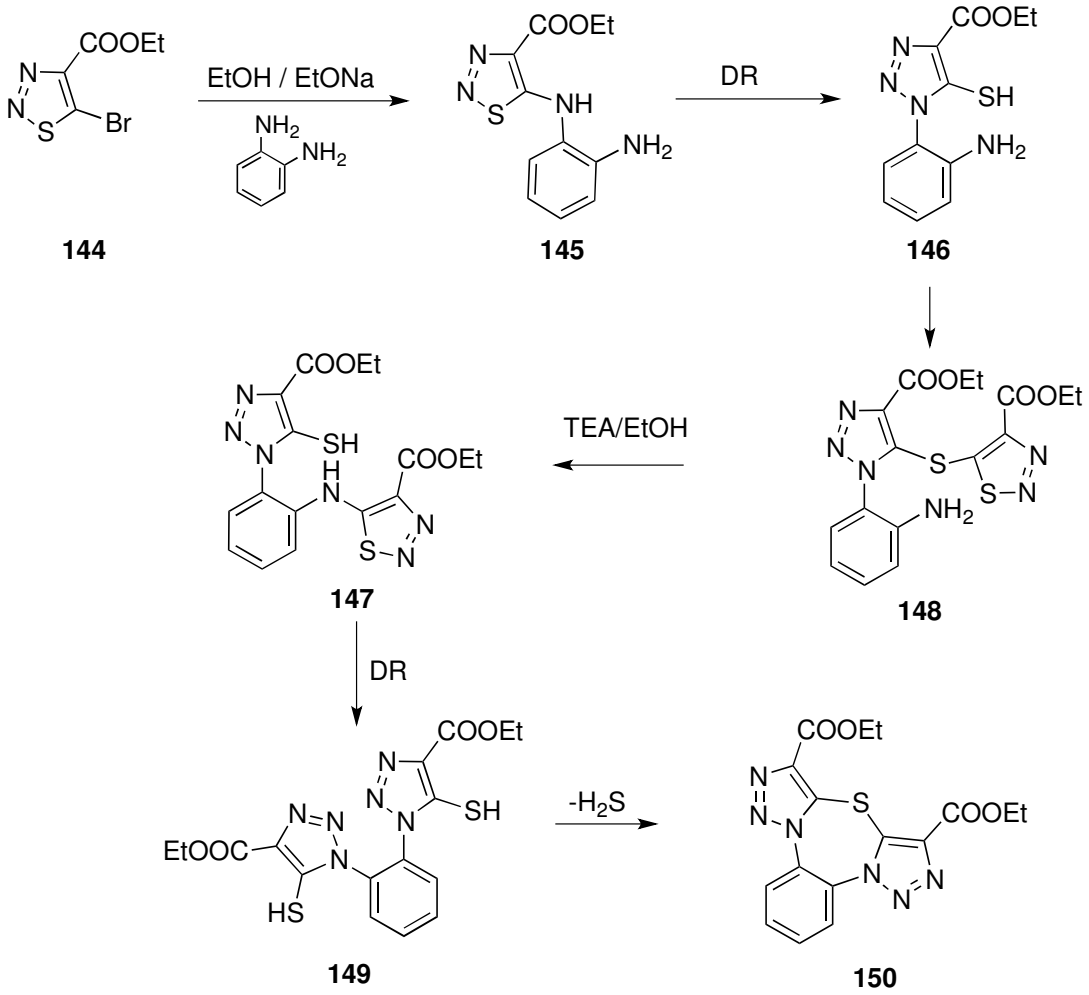


142 143

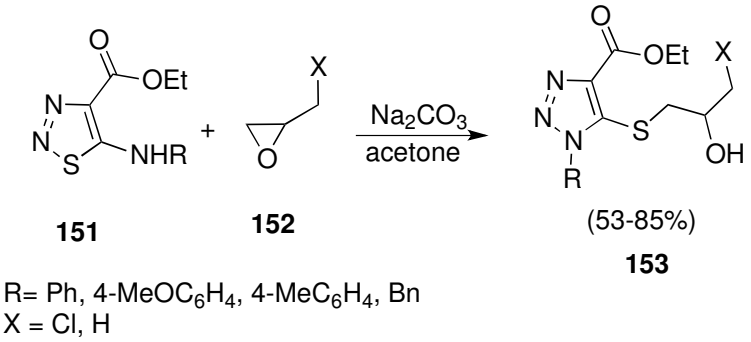
Scheme 36

In detail, the reaction of the 5-bromo-1,2,3-thiadiazole **144** with 1,2-phenylendiamine in EtOH/TEA produces compound **148** (93%) through a key *Dimroth* rearrangement of **145** into **146**. In turn, on heating in the presence of excess of base, compound **148** undergoes multistep subsequent transformations, including another *Dimroth* rearrangement between **147** and **149**, leading to the final cyclization into the thiadiazepine

150 (52%). Another recent example of 1,2,3-thiadiazole DR rearrangement was exploited for the synthesis of 5-(2-hydroxypropyl)sulfanyl-1,2,3-triazole fungicides **153** (Scheme 38).[88]



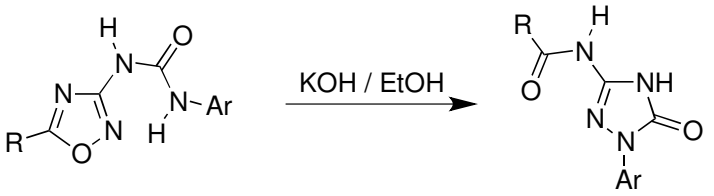
Scheme 37



Scheme 38

3.2. 1,2,4-Triazoles

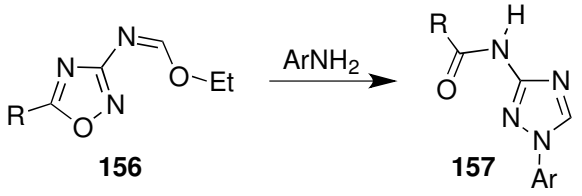
The synthesis of 1,2,4-triazoles through the BK rearrangement is widely presented in previous reviews.[9,10] Generally, 3-acylamino-1,2,4-triazolin-5-ones **155** are obtained through a base-induced rearrangement of 5-substituted 3-arylureido-1,2,4-oxadiazoles **154** (Scheme 39).[89,90]



154 **155**

a: R = Me; Ar = Ph

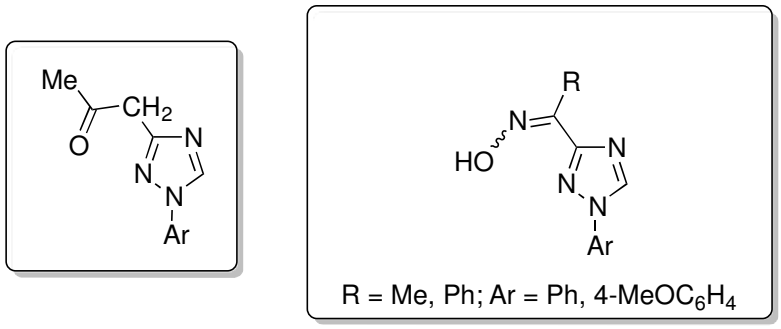
b: R = Ph; Ar = Ph; 4-$MeOC_6H_4$; 4-ClC_6H_4; 4-$NO_2C_6H_4$; 3-ClC_6H_4; 3-BrC_6H_4; 3-$NO_2C_6H_4$



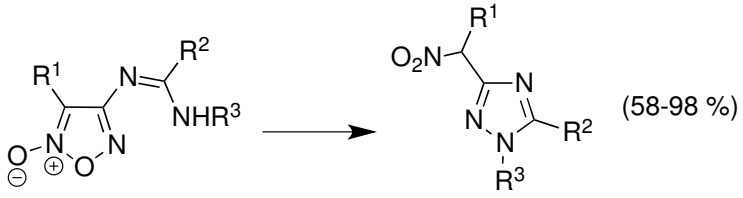
156 **157**

a: R = Me; Ar = Ph

b: R = Ph; Ar = Ph; 4-$MeOC_6H_4$; 4-ClC_6H_4; 4-$NO_2C_6H_4$; 3-ClC_6H_4; 3-BrC_6H_4; 3-$NO_2C_6H_4$



158 **159**



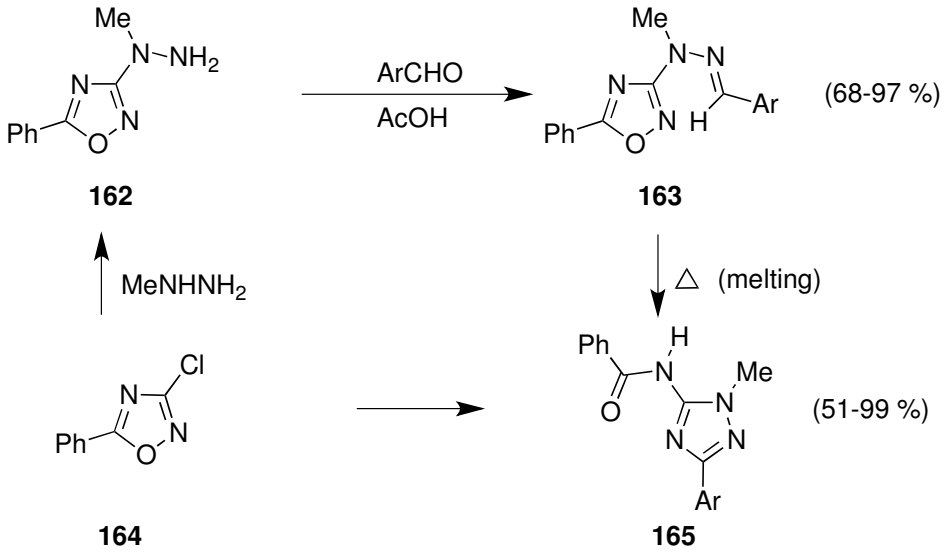
160 **161**

R^1 =Me, Ph, COOMe; R^2 = H, Me; R^3 = Me, 4-MeC_6H_4, 4-$EtOC_6H_4$

Scheme 39

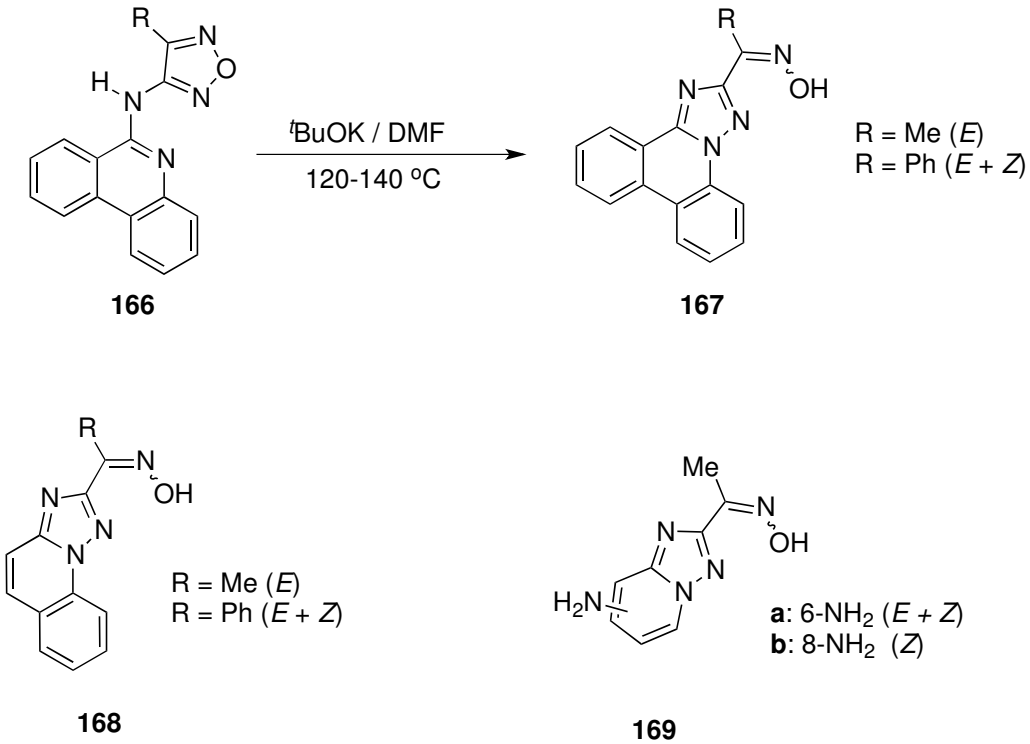
Moreover, 3-acylamino-1,2,4-triazoles **157** (70%) are directly produced from the corresponding 1,2,4-oxadiazole 3-arylformamidines upon melting. In this case, one-pot procedure by melting the ethoxyformylamino derivative **156** with anilines in the absence of solvent (at 120-170 °C) gives final products in 60-70% yields (Scheme 39).[91,92] Furthermore, 3-acetonyl-1,2,4-triazoles **158**[93] and triazolyl-ketone-oximes **159**[94] (60-80%) are similarly obtained from the corresponding isoxazoles or furazans, respectively. This approach has been extended to the synthesis of 3-(1-nitroalkyl)-1,2,4-triazoles **161** which can be obtained (58-98%) by the reaction of furoxan-amidines **160** with potassium methoxide in metanol at 20 °C (for **160**; R^3 = Ar) or with *t*-BuOK in DMF at 100 °C (for **160**; R^3 = Me).[95]

Novel 3-aryl-(hetaryl-) substituted 5-benzoylamino 1,2,4-triazole derivatives **165**, potential precursors of the corresponding 5-amino derivatives, have been recently achieved in 51-99% yield by a ring-transformation of *N*-1,2,4-oxadiazol-3-yl-*N*'-methyl-arylaldehyde hydrazones **163**, easily obtainable in high yields from the N-methylhydrazino derivative **162** reacted with various aromatic aldehydes in acetic acid (Scheme 40).[96]



Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-$NO_2C_6H_4$, 4-BrC_6H_4, 4-$CF_3C_6H_4$, 2-furanyl, 2-thiophenyl.

Scheme 40



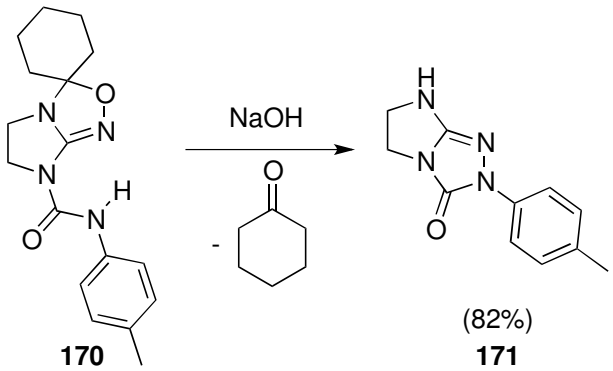
Scheme 41

Due to the lack of an acid hydrogen atom (ZH in the BK scheme) the process is not promoted by bases. It takes place upon heating at temperature at least 30 degrees higher than the corresponding melting

point, under solvent-free conditions. In our opinion, rather than a pure BK reaction involving a nucleophilic side-chain atom, a 6π electrocyclic ring closure ring opening process, followed by aromatization through a prototropic reaction, appears a better explanation. Nevertheless, the reaction appears of general application for the synthesis of various 3-aryl-(hetaryl-) substituted 5-amino-1,2,4-triazoles since various electronic effects in the Ar group are well tolerated. Moreover, the access to a variety of derivatives can be useful in the systematical study of the pharmacological activity of triazole derivatives.[97,98]

The BK rearrangement protocol has been also applied to the synthesis of annulated 1,2,4-triazoles. Thus, 1,2,4-triazolo[1,5-f]phenantridines **167** have been obtained in 90% yield from rearrangement of furazanylamino derivatives **166**, by treatment with *t*-BuOK in DMF at 120-140 °C (Scheme 41).[99] Here, the annular nitrogen of the phenantridine ring acts as the nucleophilic center in the N-N bond formation. Similarly, triazolo[1,5-a]quinolines **168** (66-70%) and triazolo[1,5-a]pyridines **169** (68-85%) have been obtained when suitable N-furazanyl-α–aminoquinoline or N-furazanyl-α-aminopyridine, respectively, were considered as starting substrate.[100]

Recently, the BK rearrangement of a dihydro-1,2,4-oxadiazolic systems, which was also studied from a theoretical point of view, has been applied also for the synthesis of imidazo[2,1-c][1,2,4]triazol-3-one **171** (Scheme 42).[101]



170 **171**

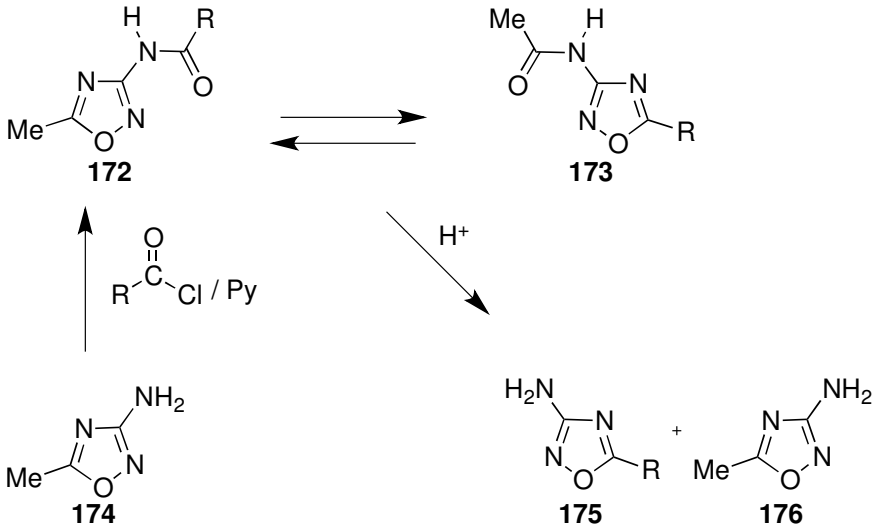
Scheme 42

3.3. 1,2,4-Oxadiazoles

The BK rearrangement strategy for the synthesis of 1,2,4-oxadiazoles is limited to target ring-degenerate compounds. In fact, due the high tendency to rearrange of this heterocycle, the 1,2,4-oxadiazole system usually represents the starting substrate rather than the final product.

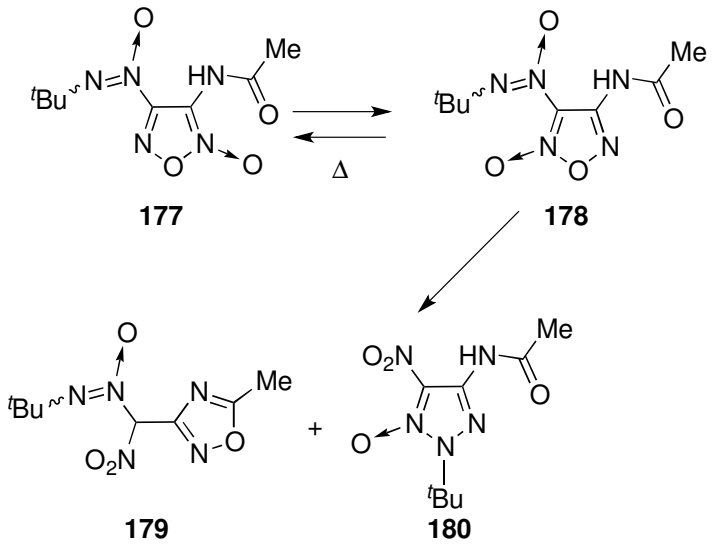
A significant example for synthetic application can be recognised in the synthesis of 3-amino-5-substituted-1,2,4-oxadiazoles **175** (Scheme 43)[102] exploiting the reversible (ring-degenerate) BK rearrangement of 3-acylamino-1,2,4-oxadiazoles.[103-105] This approach can be considered particularly useful to obtain 5- perfluoroaryl-, 5-heteroaryl- or 5-alkyl- substituted 3-aminooxadiazoles whose classical methodology through the acylcianamide route results troublesome.[106-110] Illustratively, 3-aroylamino compounds **172** (R = aryl), easily prepared from the 3-amino-5-methyloxadiazole **174**, undergo a thermally induced equilibration (by simply refluxing in ethanol) leading to a mixture of starting aroylamino derivative **172** and its 3-acetylamino counterpart **173**. When this mixture is hydrolized under acidic conditions, independently from the BK equilibrium composition, which is largely dependent on the electronic effects of substituents, the higher hydrolysis rate of the acetylamino derivative is coupled with the equilibrium shift,

synergically producing good yields of 3-amino-5-aryl- (polyfluoroaryl-, heteroaryl-)-oxadiazoles **175** (75-90%). The same methodology can be applied to the synthesis of 3-amino-5-alkyl-oxadiazoles **175** (R = alkyl) (Scheme 43). In this case, due to the ring-degenerate equilibrium between the alkanoylamino derivatives **172** (R = alkyl) and **173** (R = alkyl), yields of the final product cannot be higher than 50%.[102]



a: R = Ph; 4-$CF_3C_6H_4$; 3-$CF_3C_6H_4$; 2-$CF_3C_6H_4$; 2-$NO_2C_6H_4$; C_6F_5; 2,3,4-Trifluorophenyl; 2,3,4,5-Tetrafluorophenyl; 2-Furanyl; 2-Thiophenyl
b: R = Pr; ^{t}Bu; $C_{11}H_{23}$

Scheme 43



Scheme 44

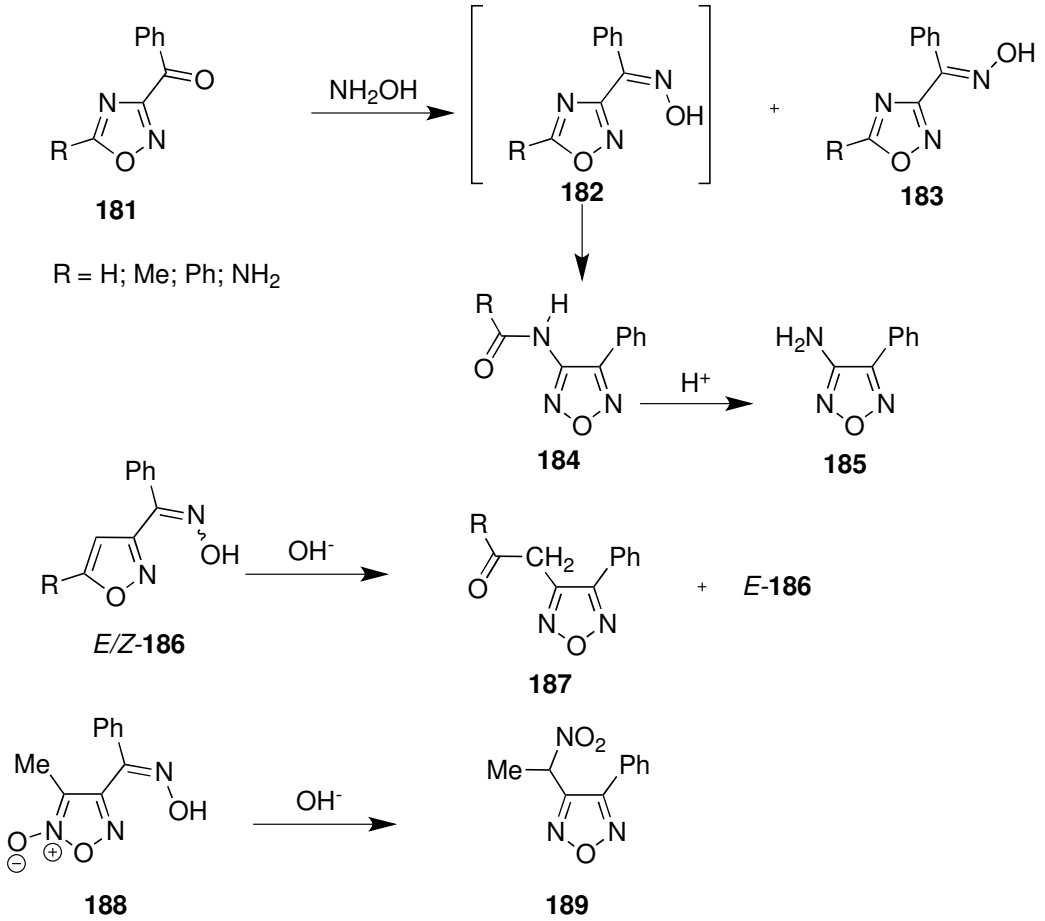
Interestingly, the first example of a BK rearrangement involving the participation of an azoxy lateral group (Scheme 44) was recently reported for the synthesis of 3-[(*t*-butyl-NNO-azoxy)(nitro)methyl]-5-methyl-1,2,4-oxadiazole in 50% yield together with triazole **180** (15%).[111]

3.4. 1,2,5-Oxadiazoles

An historical strategy directed toward the synthesis of 1,2,5-oxadiazoles (furazans) through a BK rearrangement considers the oximes of 3-acyl substituted 1,2,4-oxadiazoles and isoxazoles as rearranging

substrates (Scheme 45). These reactions have been critically reviewed, even regarding the influence of the functional group geometry on the rearrangement, and some discrepancies in the literature have been corrected.[10,112-114] Here we will only report examples which can be illustrative for synthetic scopes.

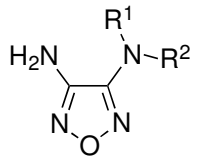
3-Acylaminofurazans **184** are formed directly (in about 50% yield) in the oximation reaction of 3- benzoyl-1,2,4-oxadiazoles **181** (R^1 = Ph, H, Me, NH_2) as a result of a spontaneous rearrangement of the *Z*- oximes component **182**. The *E*-oximes **183**, also formed in the oximation reaction, can be isolated (in about 35% yield) and subsequently rearranged by using experimental conditions (when tolerated) suitable for the *E/Z* isomerization. These conditions include melting, when acylaminofurazans are obtained, or heating with acids, when hydrolized 3-aminofurazans are produced (Scheme 45). Therefore the oximation of 3-aroyl-1,2,4-oxadiazoles followed by acid treatment of the resulting mixture can represent a valid methodology for the synthesis of 3-amino-4-arylfurazans.[9,115] A restriction to this general strategy could arise in the synthesis of 4-alkyl substituted aminofurazans due to the crucial *E* to *Z* isomerization step of the *E*-oximes preferentially formed in the oximation reaction of the corresponding 3-alkanoyl-1,2,4-oxadiazoles.



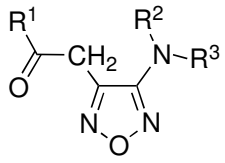
Scheme 45

By a similar strategy, furazanyl-ketones **187** are obtained by treatment with an aqueous base of the isolated *Z*-oximes of 3-benzoylisoxazoles **186** or of the crude oximation mixture containing both *E* (40%) and *Z*-isomers (60%). Under these conditions, the *E*-isomers remain unchanged.[113] Furthermore, the representative 3-(1-nitroalkyl)-furazan **189** is obtained by reacting the (*Z*)-furoxanoxime **188** with a base at room temperature.[116]

Several examples of targeted furazans which can be obtained from rearranging 1-oxa-2-azoles containing an amidoxime side-chain are reported extensively by Andrianov and coworkers.[117-120] The rearrangement reaction strictly depends on the crucial *E*/*Z* isomerization at the variously substituted amidoxime group. Illustrative targets regard: i) formation of diamino-furazans **190a-c** from suitably substituted 1,2,4-oxadiazoles;[117,118] ii) formation of the amino-furazans **191a-c** from suitably substituted isoxazoles (Chart 2).[114,119,120] Noteworthy, in the case of **191c** the 3-amino-4-methylfurazan will be the final product (40-46%) as a result of subsequent modification of functional groups under reaction conditions.[120]



190



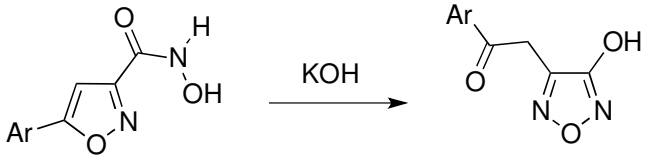
191

a: R^1-R^2 = -$(CH_2)_4$-
b: R^1 = H; R^2 = Alkyl; R^3 = NHCOOEt
c: R^1 = R^2 = H

a: R^1 = Ph; R^2 -R^3 = -$(CH_2)_5$-
b: R^1 = Ph; R^2 = R^3 = H
c: R^1 = R^2 = R^3 = H

Chart 2

Recently, a series of 4-aroylmethylen-1,2,5-oxadiazoles **193** (Ar = Ph, *p*-tolyl, 2,5-dimethylphenyl) was obtained also by rearrangement of 5-arylisoxazole-3-hydroxamic acids in aqueous KOH (Scheme 46).[121]



192 **193**

Scheme 46

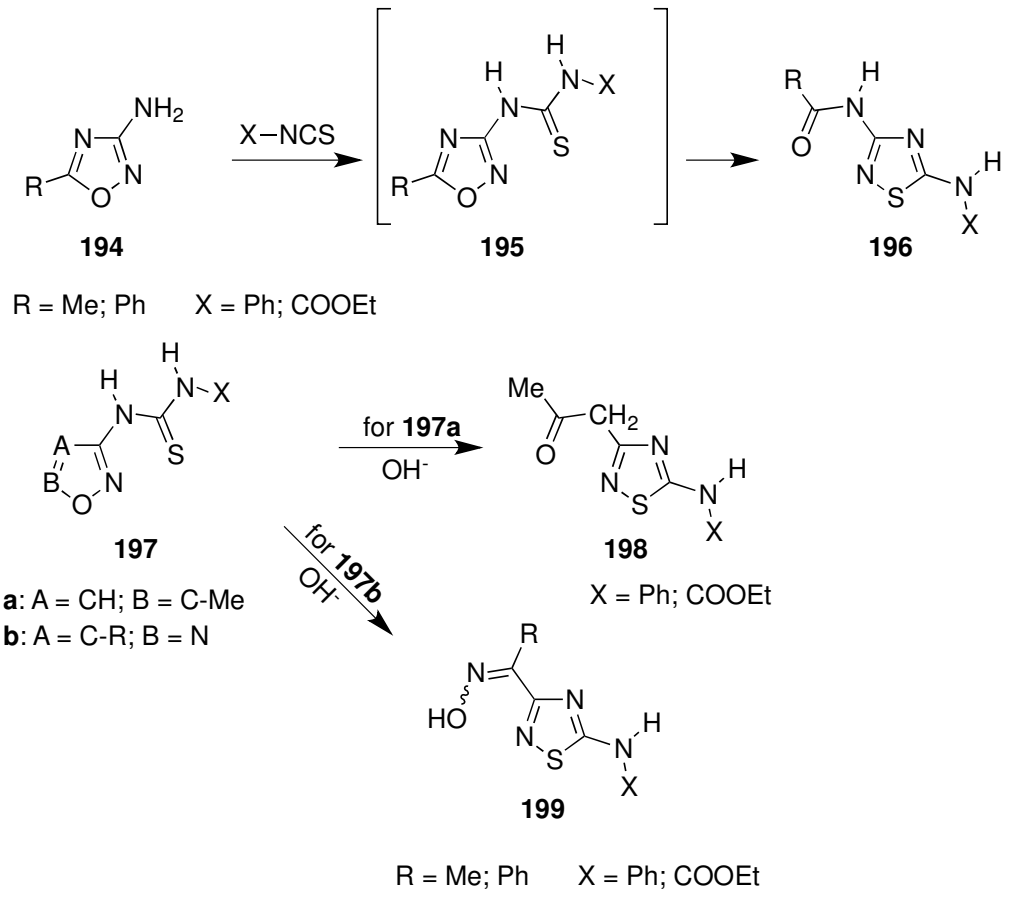
3.5. 1,2,4-Thiadiazoles

A rearrangement-strategy for the synthesis of 1,2,4-thiadiazoles considers substrates containing a thioureidic side-chain which can be easily reached from the reaction of 3-amino compounds and isothiocyanates (Scheme 47).[122,123] Due to the high nucleophilic character of the sulfur atom, the reaction between 3-amino-1,2,4-oxadiazoles **194** with isothiocyanates directly produces thiadiazoles **196** (50-70%). In turn, 3-acetonyl-thiadiazoles **198** (70%) and *Z*-oximes of 3-acylthiadiazoles **199** (60-80%) can be formed from thioureas **197a** and **197b**, respectively, treated with aqueous potassium hydroxide in ethanol at room temperature (Scheme 47).

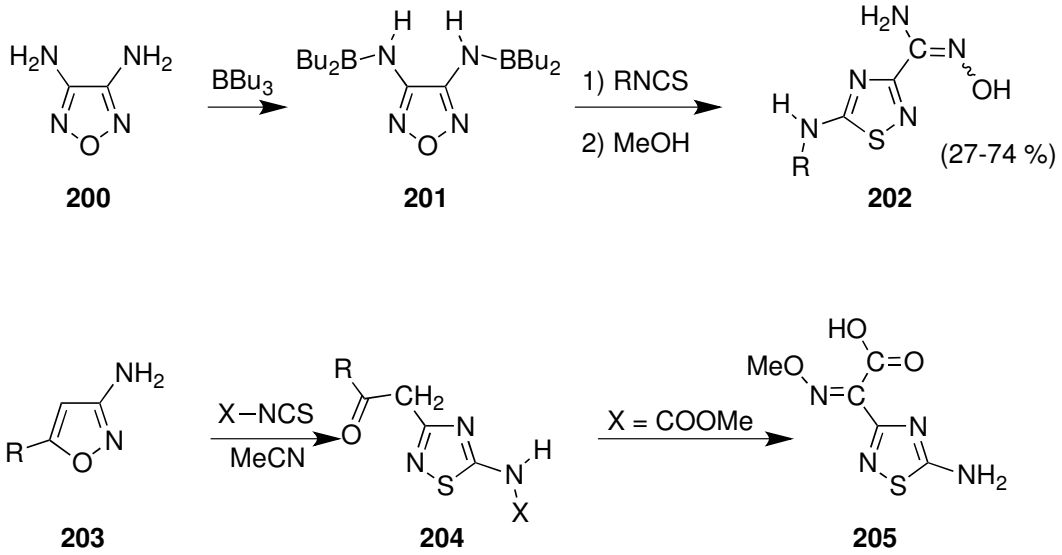
By following this strategy 1,2,4-thiadiazoles **202**, which contain an amidoxime functional group which can be used in further heterocyclic synthesis, are formed (27-74%) by using borylated 3,4-diaminofurazan as starting material for the reaction with isothiocyanates in the construction of the rearranging thioureido side-chain (Scheme 48).[115,124]

Furthermore, syntheses of thiadiazoles **204** (40-86%) from 5-substituted 3-aminoisoxazoles **203** was reported to occur by reaction with isothiocyanates, which were prepared *in situ* from chloroformates and

potassium thiocyanate in acetonitrile.[125-127] It is worth remarking that this successful strategy has been applied to the synthesis 5-amino derivative **205**, useful in the chemistry of cephalosporin antibiotics.



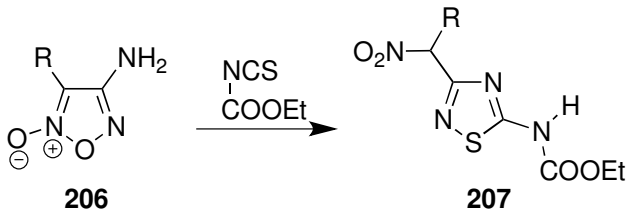
Scheme 47



Scheme 48

Starting from 3-amino-isoxazoles **203** (R = OMe, H), the rearrangement leads to derivatives **204** (R = OMe, H; X = COOMe).[126] Among the several steps involved, the skeleton rearrangement of starting

isoxazole into the thiadiazole one is the key step in the synthesis, subsequent reactions being routinary modification or formation of functional groups. This protocol has been extended to the synthesis of 3-(1-nitroalkyl)-thiadiazoles **207** (40-60%) obtained from the reaction of ethoxycarbonylisothiocyanate with 4-aminofuroxans **206** in refluxing ethyl acetate (Scheme 49). In the case of **206** (R = COMe) the final product was the thiadiazole **207** (R = H) due to an hydrolysis reaction during the work-up procedure.[129]

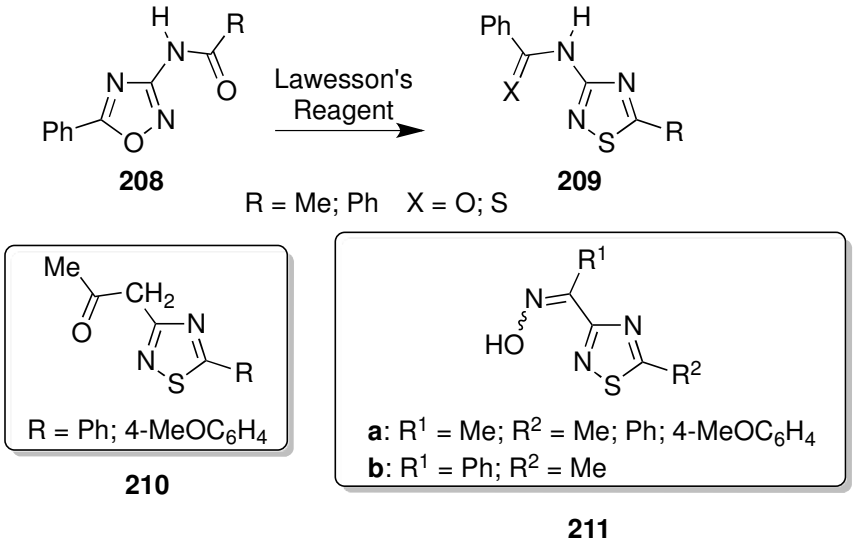


206 **207**

R = Me; Ph; COMe; -N=N-Ar (Ar = 4-MeOC$_6$H$_4$; 2,4,6-Trimethylphenyl)

Scheme 49

Differently targeted 1,2,4-thiadiazoles **209** are obtained by sulfurization of 3-acylamino-1,2,4-oxadiazoles **208** by using the Lawesson reagent in refluxing toluene (Scheme 50).[129]



208 **209**

R = Me; Ph X = O; S

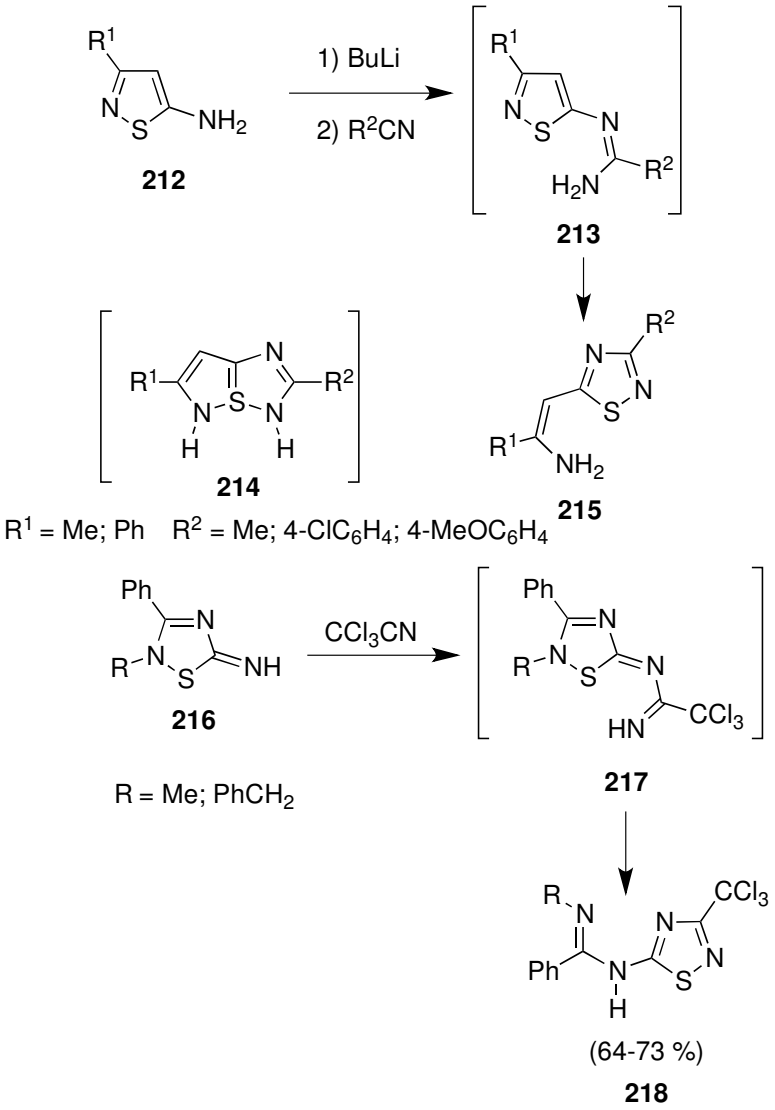
210

211

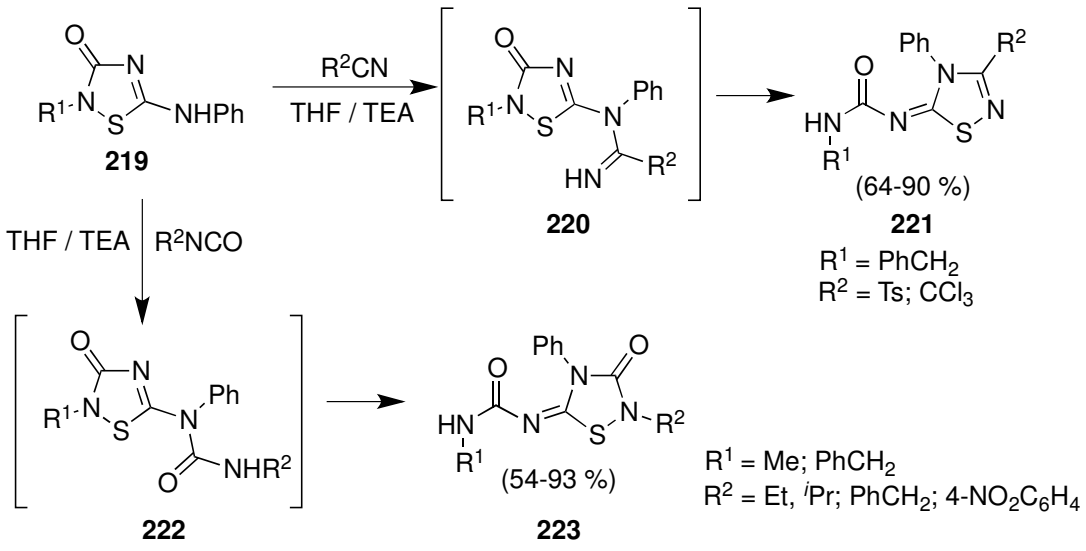
Scheme 50

Clearly, the reaction follows the initial formation of the corresponding thioamides where an high reactive NCS side-chain is operative; the amide **208** (R = Me; X = O) or the thioamide **209** (R = Ph; X = S) final products are formed in 40-50% isolated yields. Similarly, thiadiazolyl-ketones **210** can be obtained (45%) by sulfurization of 3-aroylamino-5-methylisoxazoles. In turn, thiadiazolylketone-oximes **211** are prepared from the corresponding 3-acylamino-4-R^1-substituted furazans, followed by an *in situ* treatment of the crude reaction mixture with aqueous sodium hydroxide. By this treatment, *E*-oximes **211** were isolated (50-60%) in the case of **211a** (R^1 = Me), whereas a mixture of *E* (45 %) and *Z* (10%) isomers was obtained in the case of **211b** (R^1 = Ph) (Scheme 50).[129]

Synthesis of 1,2,4-thiadiazoles can be also realized through rearrangements involving internal nucleophilic substitution at a pivotal sulfur atom in the starting ring by following the general BK rearrangement Scheme.



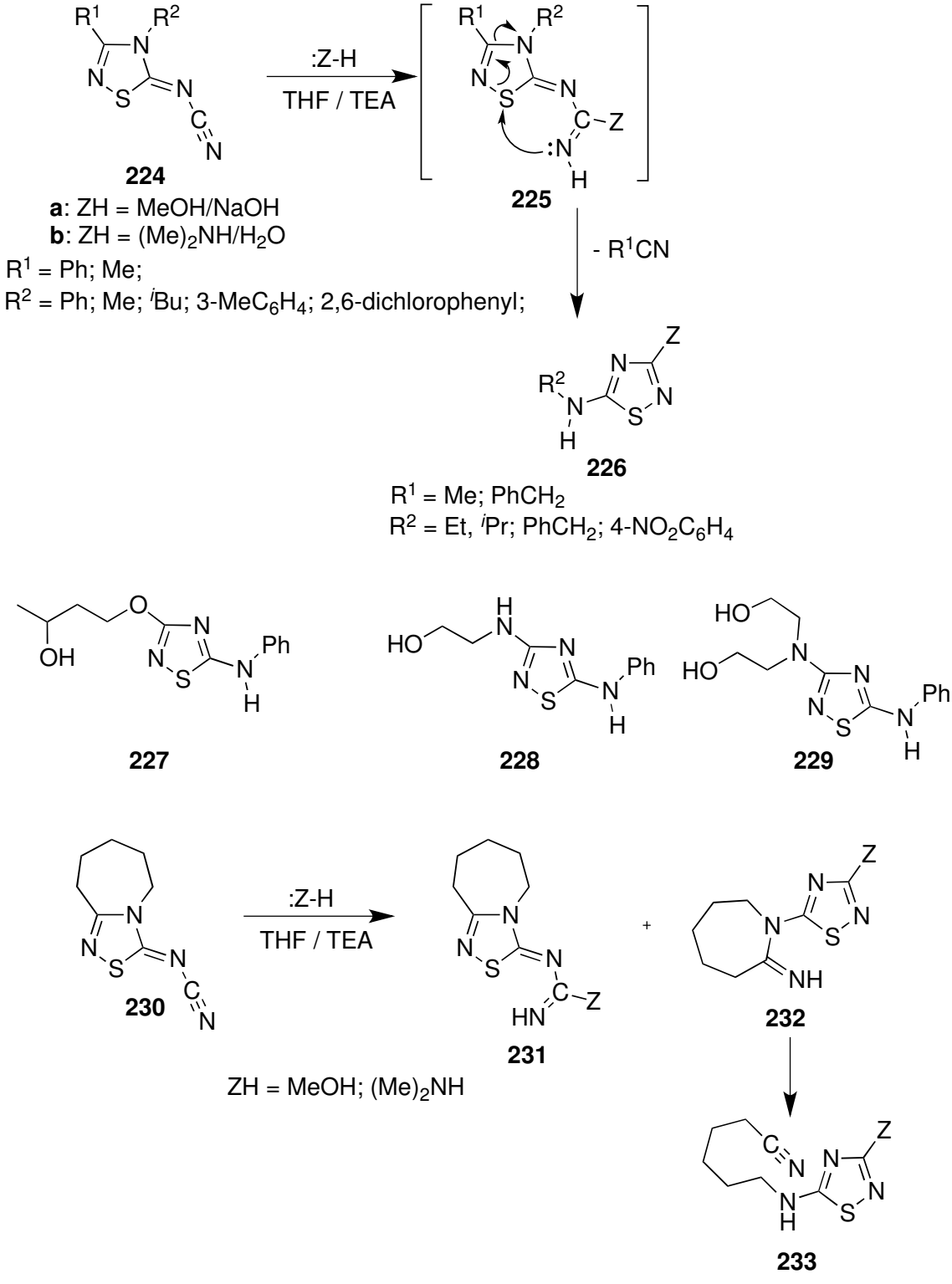
Scheme 51



Scheme 52

Typical examples of this addition-rearrangement process include: i) the synthesis of 1,2,4-thiadiazoles **215** from the reaction of 5-amino-isothiazoles **212** with nitriles or imidates, through the rearrangement of

unisolated amidines **213** involving the intermediacy of a sulfurane species **214** (Scheme 51); ii) the preparation of 5-amidino-3-trichloromethyl-1,2,4-thiadiazoles **218** (64-73%) from iminothiadiazoline **216** treated with trichloroacetonitrile (Scheme 51);[130] iii) the synthesis of thiadiazolines **221** (64-90%) from the reaction of thiadiazoline **219** with electrophilic nitriles in THF in the presence of TEA (Scheme 52);[131] iv) the formation of thiadiazolidines **223** (54-93%) through unisolated isomers **222** formed from the reaction of the same thiadiazoline **219** with isocyanates in THF/TEA medium (Scheme 52).[132]

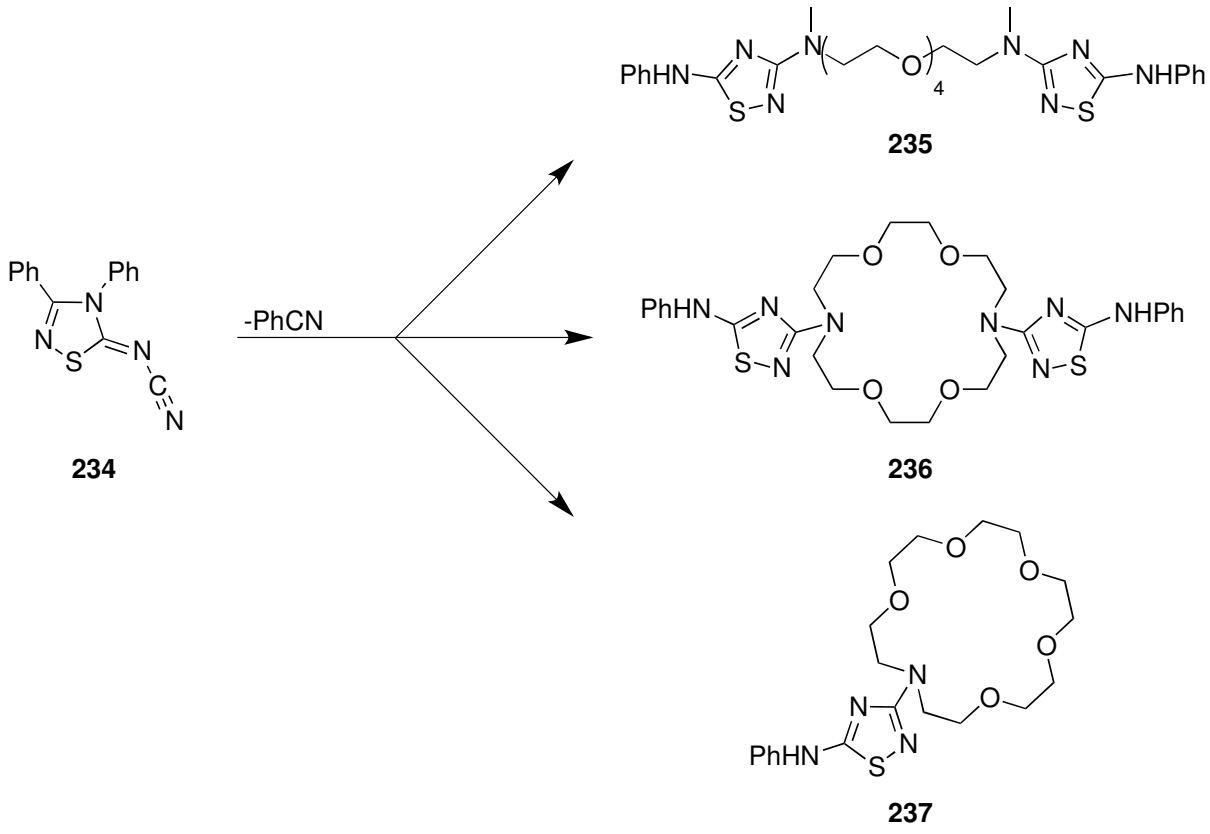


Scheme 53

Variously substituted thiadiazoles **226** (Z = OMe, NMe_2) are formed (54-96%) from the reaction of 5-(cyanoimino)thiadiazolines **224** with various nucleophiles (MeOH/NaOH or $HNMe_2/H_2O$ in dioxane, at room temperature) through the rearrangement of the non isolated addition intermediates **225** (Scheme 53).[133] In this scheme, the formation of the new ring in the BK model is coupled with elimination of the R^1CN species. Such a synthetic strategy can be generally applied to obtain C(3)-substituted thiadiazoles, depending on the used nucleophile.

Interestingly, the use of bidentate nucleophiles produces derivatives **227**-**229** in 55-86% yield. Interestingly, this reaction has been extended to the annulated *N*-cyano compound **230**, where the leaving nitrile species is still part of the final structure **233**.[133]

Other interesting examples of this strategy concern the synthesis of thiadiazolic derivatives as redox switchable ionophores for heavy and transition metal cations (Scheme 54).[134] The reaction of the 3,4-diphenyl-5-cyanimino-1,2,4-thiadiazoline **234** performed in refluxing toluene in the presence of the appropriate nucleophile leads to **235** (30%), **236** (41%), and to the bis adduct **237** (40%).



Scheme 54

4. Conclusions

It is important to remark that heterocyclic rearrangements can be applied to the synthesis of a wide variety of heterocyclic systems and product distribution may strongly depend on experimental conditions. In this context, the mechanistic studies of new rearrangements are crucial for assessing requirements for their exploitation in the synthetic field. Once mechanistic features are assessed, optimization of reaction conditions, including the use of novel techniques such as MW or UV irradiation or sanitation might improve yields and times thus favouring synthetic application. In some of the presented examples the rearrangement

approach represents an exclusive mean of obtaining a desired heterocyclic target. In other cases, despite average yields, the availability or easy accessibility of the rearranging substrate may play an important role in synthetic plans towards a target heterocyclic system. Moreover, the increased amount of readily available heterocyclic precursors from any commercial sources may today render the rearrangement strategy more accessible to avoid cumbersome *ab initio* preparation of heterocyclic scaffolds.

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