THREE-COMPONENT RING TRANSFORMATION USING AMMONIUM ACETATE AS A NITROGEN SOURCE

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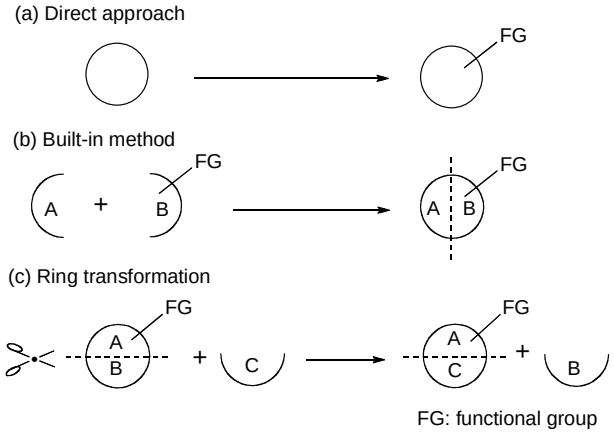
Abstract. *The ring transformation is a powerful protocol for preparing polysubstituted or polyfunctionalized compounds that are not easily available by alternative procedures. Nitropyrimidinone and dinitropyridone are excellent substrates for the nucleophilic-type ring transformation. The reaction of these substrates and a ketone in the presence of ammonium acetate undergoes the three-component ring transformation (TCRT) to afford azaheterocyclic compounds and nitro compounds. In these reactions, nitropyrimidinone serves as the synthetic equivalent of activated diformylamine or α-nitroformylacetic acid, and dinitropyridone serves as that of unstable nitromalonaldehyde.*

Contents

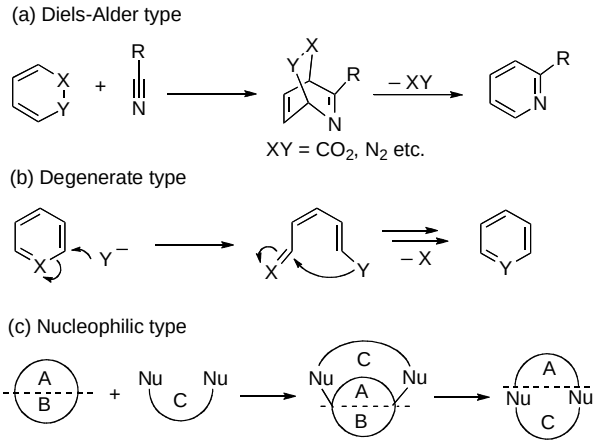
1. Introduction

A great number of heterocyclic compounds have been employed for functional materials such as medicines, agricultural chemicals, dyes, organic electroluminescence and so on. It is necessary to construct a large compound library for effective research of developing new functional materials. Heterocyclic compounds having a functional group are especially useful for the present purpose because they are also used as the key synthetic intermediates leading to versatile compounds. Direct functionalization of the heterocyclic framework is the best way if possible. While it is relatively easy to modify the electron-sufficient heterocyclic compounds such as pyrrole, direct modification of the electron-deficient heterocyclic compounds such as pyridine is rather difficult. Thus, supplementary protocols for modification of heterocyclic compounds should be developed (Scheme 1). The built-in method is one of the convenient procedures for preparation of functionalized heterocyclic compounds, in which a building block having a functional group is condensed with another component to construct a new ring system. As another supplementary protocol, the ring transformation is also often employed, in which the partial structure (B) of the substrate (A+B) is transferred to the reagent (C) to form a new ring system (B+C) accompanied by elimination of the leaving group (A). This method has served as a useful synthetic tool for polyfunctionalized compounds that are not easily available by alternative methods.



Scheme 1. Three preparative methods for functionalized heterocyclic compounds.

There are three kinds of ring transformations (Scheme 2). Among them, the most commonly used method is the Diels-Alder-type ring transformation, of which substrates have good leaving group as a partial structure such as carbon dioxide and nitrogen molecule.[1] Degenerate-type ring transformation was energetically studied by van der Plas and his co-workers, which proceeds via ANRORC (addition of nucleophile-ring opening-ring closure) mechanism.[2] As another type of reaction, nucleophilic-type ring transformation is also known, which includes the bicyclic intermediate resulting from addition of a dinucleophilic reagent to the substrate. Compared with the former two ring transformations, nucleophilic-type ring transformation has not been well studied.[3,4] Such situation prompted us to study this ring transformation to use as a general synthetic tool in organic syntheses.



Scheme 2. Different types of ring transformation.

For causing the nucleophilic ring transformation, the substrate requires high electron-deficiency such as nitropyridine derivatives. However, when these compounds are used as a substrate, employment of somewhat severe conditions, such as strong base and high temperature, are necessary to destroy the aromaticity of the pyridine nuclei. Thus, electron-deficient compounds with low aromaticity are required as a substrate. Furthermore, effective ring transformation is surely realized if the substrate has a good leaving group as the partial structure. On the basis of these consideration, we focused on 3-methyl-5-nitro-4-pyrimidinone (**1**) and 1-methyl-3,5-dinitro-2-pyridone (**2**) (Figure 1). The electron-withdrawing nitro and carbonyl groups and ring nitrogen atoms diminish the electron density of these compounds. As shown in resonance form, pyrimidinone **1** and pyridone **2** exhibit aromaticity, but it is easily destroyed because of small contribution of the betain resonance structure. In addition, the partial structure can be easily eliminated as a stable anion of nitroacetamide. Thus, these compounds are considered to be suitable substrates for nucleophilic-type ring transformation because of these structural features. It is considered that pyrimidinone **1** serves as a synthetic equivalent of activated diformylamine, and pyridone **2** serves as that of unstable nitroamlonaldehyde[5] when ring transformation proceeds according to our prediction.

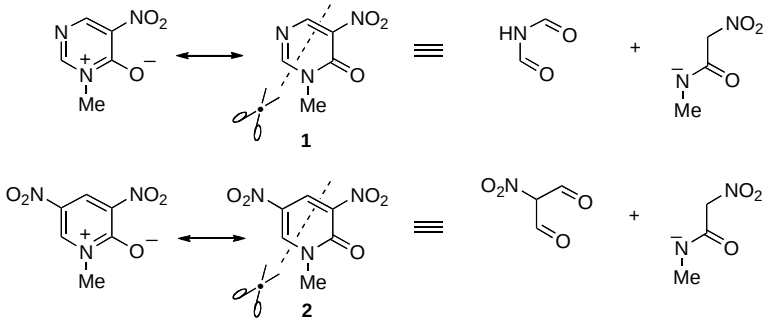
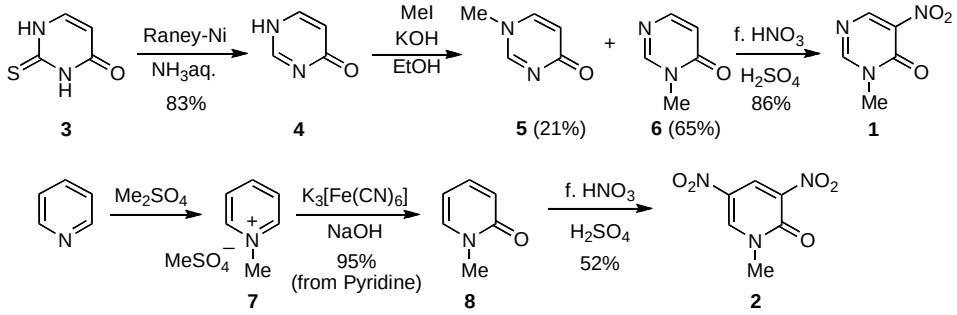


Figure 1. Nitropyrimidinone **1** and dinitropyridone **2**.

2. Past studies on nucleophilic-type ring transformation

2.1. Preparation of nitropyrimidinone 1 and dinitropyridone 2

Substrates **1** and **2** were readily prepared with a few steps as illustrated in Scheme 3. Nitropyrimidinone **1** was prepared from commercially available 2-thiouracil with three steps, namely, reduction, methylation, and nitration. In the reduction of 2-thyouracil **3** by Raney-nickel, aqueous ammonia was used as a solvent because of the low solubility of the starting material **3**. The succeeding methylation of pyrimidinone **4** by methyl iodide afforded two isomeric products, 1-methylated and 3-methylated pyrimidinones **5** and **6**. After separation by column chromatography, 3-methyl-4-pyrimidinone **6** was nitrated by fuming nitric acid with sulfuric acid to afford nitropyrimidinone **1**. Dinitropyridone **2** was prepared from pyridine with three steps. After conversion of pyridine to *N*-methylpyridinium salt **7** by dimethyl sulfate, oxidation with ferricyanide under alkaline conditions was conducted in one pot, which afforded 1-methyl-2-pyridone **8** in 95% yield. The following nitration by fuming nitric acid with sulfuric acid furnished dinitropyridone **2**.



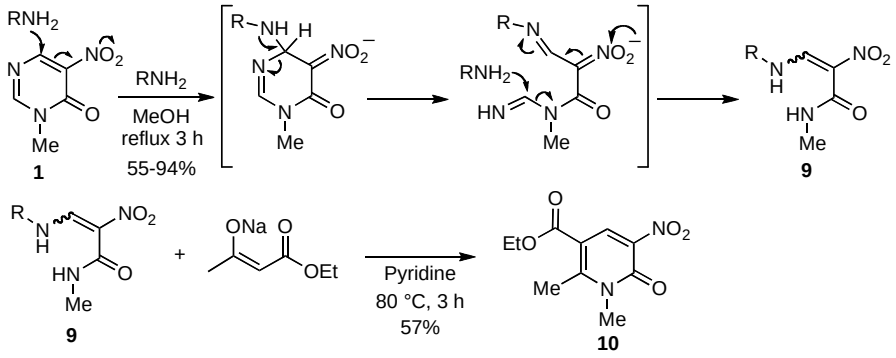
Scheme 3. Preparation of substrates **1** and **2**.

2.2. Aminolysis of the substrates

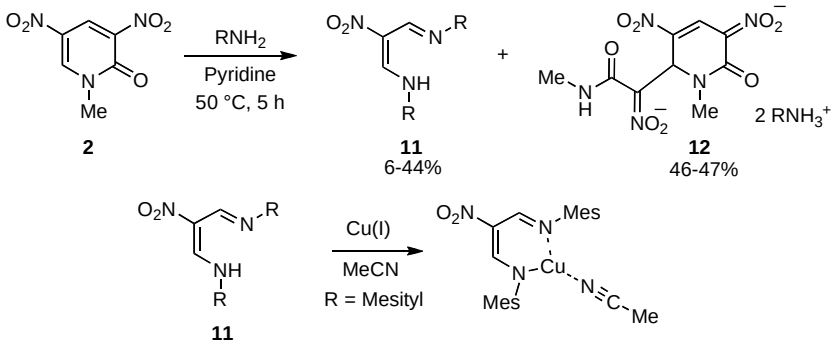
The electrophilicity of the prepared substrates **1** and **2** was evaluated by conducting aminolysis. As a result, both compounds easily reacted with amines to cause the ring opening reactions, which means that substrates **1** and **2** are electron-deficient enough for undergoing the ring transformation.

When nitropyrimidinone **1** is heated with an amine in methanol, the aminolysis proceeded to afford carbamoylnitroenamine **9** in moderate to high yields (Scheme 4).[6] Although nitroenamine is widely used as a building block for versatile frameworks because of the push-pull property, functionalized derivative is not common reagent because of poor accessibility. Hence, this aminolysis can be used as a synthetic method for functionalized nitroenamine. Indeed, nitroenamine **9** serves as a precursor of polyfunctionalized pyridone **10** upon treatment with sodium enolate of ethyl acetoacetate in pyridine (Scheme 4).

On the other hand, reaction of dinitropyridone **2** with amines furnished azadienamine having a nitro group **11**, which serves as an excellent ligand forming diverse metal complexes (Scheme 5). From this viewpoint, this aminolysis can be used as a preparative method for azadienamine **11**,[7] however, this method suffers from competitive reaction of the eliminated nitroacetamide with unreacted pyridone **2** leading to adduct **12**.[8] This problem is solved by use of 1-methyl-5-nitro-2-pyrimidinone instead of pyridone **2**.[7]



Scheme 4. Aminolysis of nitropyrimidinone **1**.

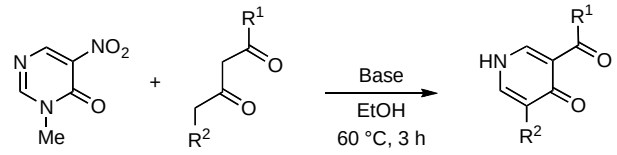


Scheme 5. Aminolysis of dinitropyridone **2**.

2.3. Reaction with 1,3-dicarbonyl compounds

The prepared nitropyrimidinone **1** was subjected to 1,3-dicarbonyl compounds **13** (Table 1).[9]

Table 1. Synthesis of 3,5-difunctionalized 4-pyridones **14**.

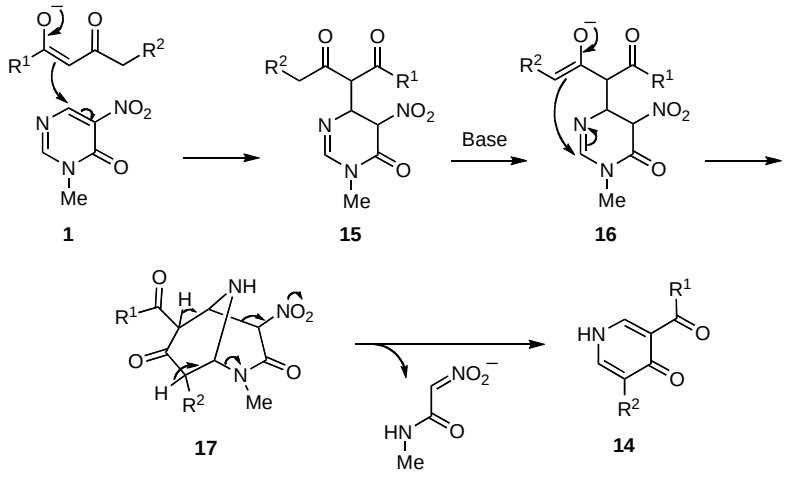


1 **13** **14**

R^1	R^2		Base	Yield/%
OEt	COOEt	**a**	NEt_3	97
Me	COMe	**b**	NEt_3	80
OEt	H	**c**	NaOEt	44

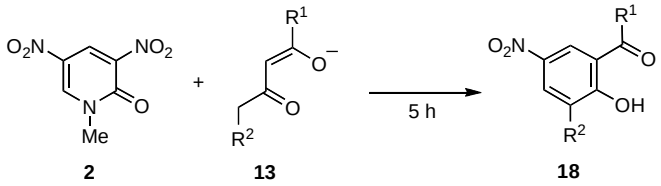
When nitropyrimidinone **1** was reacted with diethyl acetonedicarboxylate **13a** in the presence of triethylamine, the ring transformation proceeds under mild conditions to afford 3,5-difunctionalized 4-pyridone **14a** in an excellent yield. In this reaction, pyrimidinone **1** serves as the synthetic equivalent of activated diformylamine. It was also possible to introduce two acetyl groups into the 4-pyridone framework by using 2,4,6-heptatrione **13b**. In the case of ethyl acetoacetate **13c**, more basic sodium ethoxide was necessary to undergo the ring transformation.

A plausible mechanism for this reaction is illustrated in Scheme 6. The enolate ion attacks at the 6-position to afford adduct intermediate **15**, and the regenerated enolate **16** at the other side attacks at the 2-position leads to bicyclic intermediate **17**. The stable anionic nitroacetamide eliminates from this intermediate **17** to furnish ring transformed product **14**.[10] In the case of **13c**, the strong base is necessary because the formation of the second enolate **16** does not proceed easily.



Scheme 6. A plausible mechanism for the formation of 4-pyridones **14**.

On the other hand, dinitropyridone **2** also underwent the similar ring transformation with sodium enolate of 1,3-dicarbonyl compounds **13** to afford functionalized nitrophenols **18** in moderate to good yields (Scheme 7 and Table 2).[11] In this reaction, dinitropyridone **2** serves as the synthetic equivalent of nitromalonaldehyde.

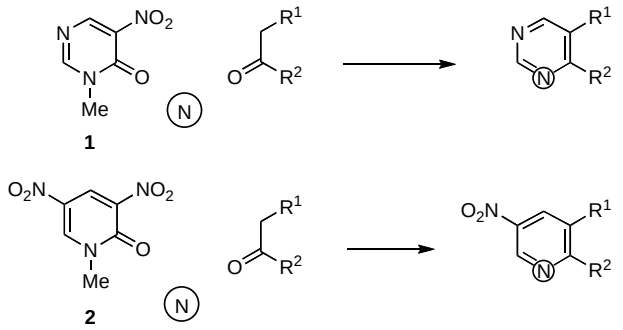


Scheme 7. Ring transformation of dinitropyridone **2** with sodium enolate of 1,3-dicarbonyl compounds **13**.

Table 2. Ring transformation of dinitropyridone **2** with sodium enolate of 1,3-dicarbonyl compounds **13**.

R^1	R^2		Solv.	Temp./°C	Yield/%
OEt	COOEt	**a**	Pyridine	50	91
OEt	H	**b**	Pyridine	70	61
Me	H	**d**	DMF	70	53
COOEt	H	**e**	Pyridine	110	42

To our expectation, both nitropyrimidinone **1** and dinitropyridone **2** revealed high reactivity to be used as the substrate in the nucleophilic-type ring transformation using 1,3-dicarbonyl compounds **13**. 1,3-Dicarbonyl compounds **13** can be surely used as excellent dinucleophilic reagents. However, diversity of the available 1,3-dicarbonyl compounds is not so large, which only afford several kinds of products. If simple ketones can be used instead of **13**, the synthetic utility of the ring transformation should be surely improved. In such case, it is necessary to use nitrogen source, because the ketone is a mononucleophilic reagent. Namely, it is a three-component ring transformation (TCRT) (Scheme 8).



Scheme 8. A concept of three component ring transformation (TCRT).

3. Three-component ring transformation (TCRT) of nitropyrimidinone

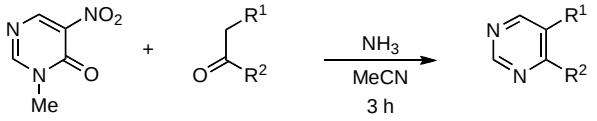
3.1. Using ammonia as a nitrogen source

According to the consideration mentioned above, we conducted TCRT of nitropyrimidinone **1** using ammonia as a nitrogen source (Table 3).[12] To a solution of nitropyrimidinone **1** in acetonitrile, cyclohexanone **19a** and methanolic ammonia was added, and the resultant mixture was heated at 100 °C for 3 h in a sealed tube. From the reaction mixture, cyclohexa[*d*]pyrimidine **21a** was obtained in 85% yield.

A large number of synthetic methods for pyrimidine derivatives have been developed. Among these synthetic methods, condensation of a C-C-C (e.g., malonaldehyde, malononitrile, diethyl malonate) and N-C-N (e.g., urea, guanidine) units is most commonly used.[13] On the other hand, the present TCRT constructs the pyrimidine framework by combination of C-N-C, C-C and N units, which is a hitherto unknown mode; hence, this method is an alternative method for the synthesis of 4,5-disubstituted pyrimidines. However, this TCRT suffers from narrow scope. In the case of cyclopentanone **19b**, the yield of pyrimidine **21b** was 31%.

When acetophenone **20a** was used, the yield of **22a** was only 6% even though severe reaction conditions were employed.

Table 3. TCRT of nitropyrimidinone **1** with ketone **19** in the presence of ammonia.

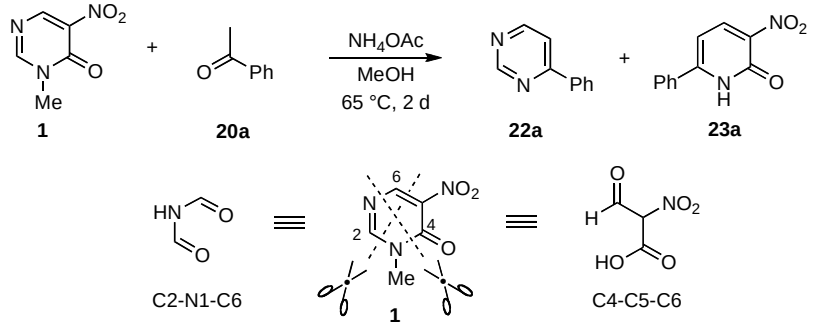


R^1 R^2	Ketone	Temp./°C	Product	Yield/%
-$(CH_2)_4$-	**19a**	100	**21a**	85
-$(CH_2)_3$-	**19b**	100	**21b**	31
H Ph	**20a**	120	**22a**	6

In the presence of TCRT, small amount of nitroenamines **9** (R=H, Me) were isolated (Scheme 4), which means competitive ammonolysis of pyrimidinone **1** as mentioned in Section 2.2 is one of the reasons for the low efficiency. This fact means that ammonia is not a suitable nitrogen source, lowering the yields of pyrimidines **21** and **22**. In order to avoid this problem, less nucleophilic ammonium acetate was employed as a nitrogen source instead of ammonia.

3.2. With aromatic ketones in the presence of ammonium acetate

Nitropyrimidinone **1** was reacted with acetophenone **20a** in the presence of ammonium acetate (Scheme 9).[14] As a result, TCRT proceeded to give 4-phenylpyrimidine **22a** in a considerably improved yield under milder conditions compared with the yield in the reaction using ammonia. In addition to pyrimidine **22a**, 3-nitro-2-pyridone **23a** was also isolated as yellow needles.



Scheme 9. Two kinds of TCRT of nitropyrimidinone **1** with acetophenone **20a**.

Pyrimidine **22a** is formed by the TCRT between the 2- and the 6-positions of **1**, and nitropyridone **23a** is formed by TCRT between the 4- and the 6-positions of **1**. Pyrimidinone **1** serves as a synthetic equivalent of activated diformylamine in the former case, and serves as that of α-formylacetic acid in the latter case.

Because of the biologically active potential, both pyrimidine **22** and 3-nitro-2-pyridone **23** are useful frameworks. So, it is important to control the selectivity between **22** and **23**, which improves the synthetic utility of the present TCRT. As a result of surveying counter anion of the ammonium salt, solvent and reaction conditions, addition of acetic acid is found to affect the selectivity (Table 4). Namely, addition of small amount of acetic acid somewhat increased the yield of **23a**. Contrary to this, the formation of **23a** was suppressed when a mixed solvent of methanol and acetic acid (3:1) was used. Dramatic change for the selectivity was observed in the reaction conducted in acetic acid, which afforded pyrimidine **22a** as a main product.

Table 4. The effect of acetic acid for the selectivity of two kinds of TCRT.

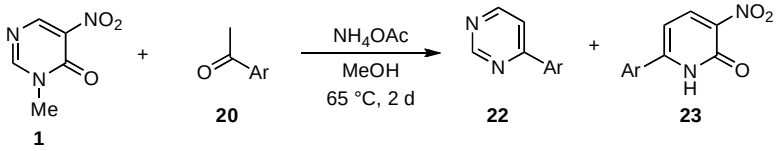
Solv.	AcOH/equiv.	Yield/%		Recovery of **1**/%
		22a	**23a**	
MeOH	0	49	51	0
MeOH	1	40	56	0
MeOH	4	22	59	0
MeOH-AcOH (3:1)		24	9	21
AcOH[a]	––	65	14	0

[a] 3 days

Next, the TCRT of pyrimidinone **1** with other aromatic ketones **20** was studied (Table 5). Six *p*-substituted acetophenones **20b-g** efficiently underwent the TCRT except for the reaction using **20b**, which was somewhat complicated with side reactions caused by the amino group. The ratio of **22**/**23** markedly varied with electronic properties of the substituent on the benzene ring. While pyridones **23** were mainly produced in reactions of **1** with electron-rich ketones **20b-e**, the ratio of **22**/**23** was inverted in the case of electron-poor ketone **20g**. 3-Nitroacetophenone **20h** showed similar reactivity to afford pyrimidine **22h** as the major product, however no reaction was observed upon treatment of **1** with 2-nitro derivative **20i** because of steric hindrance besides strong electron-withdrawing ability of the nitro group. On the other hand, all four methoxyacetophenones **20d** and **20j-l** afforded the corresponding products in good yields. It is noteworthy that the reactivity of these ketones is almost the same, although 3-methoxy group only serves as the electron-withdrawing group for the carbonyl group. Hence, the electron density on the benzene ring is more influential rather than that on the carbonyl group.

Similar tendency was also observed when heteroaromatic ketones were employed.[15] Pyridylpyrimidines **22n** and **22o** were predominantly formed in cases of acetylpyridines **20n** and **22o** having a more electron-poor acetyl group. When electron-sufficient heterocyclic ketones **20p-s** were employed, exclusive formation of pyridones **23p-r** was realized to our expectation.

Table 5. TCRT of pyrimidinone **1** with substituted acetophenones **20**.

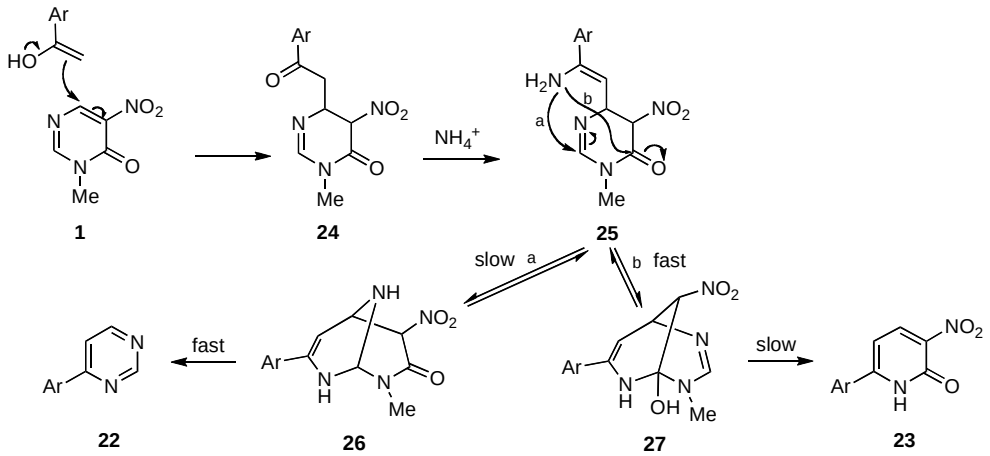


Ar		Yield/%		Ratio of **22**/**23**
		22	**23**	
4-$NH_2C_6H_4$	**b**	trace	47	>1/99
4-$AcNHC_6H_4$	**c**	7	61	10/90
4-$MeOC_6H_4$	**d**	20	63	24/76
4-MeC_6H_4	**e**	25	75	25/75
C_6H_5	**a**	49	51	49/51
4-ClC_6H_4	**f**	37	41	47/53
4-$NO_2C_6H_4$	**g**	52	10	77/23
3-$NO_2C_6H_4$	**h**	38	25	60/40
2-$NO_2C_6H_4$	**i**	0	0	––
3-$MeOC_6H_4$	**j**	27	54	34/66
2-$MeOC_6H_4$	**k**	30	52	37/63
2,4-$(MeO)_2$ C_6H_3	**l**	19	58	25/75
3-Pyridyl	**m**	44	38	54/46
4-Pyridyl	**n**	44	9	84/16
2-Pyridyl	**o**	49	1	98/2
2-Pyrrolyl[a]	**p**	0	47	0/100
3-Pyrrolyl[a]	**q**	0	68	0/100
2-Thienyl[a]	**r**	0	72	0/100
2-Furyl	**s**	13	60	18/82

[a]7 days

A plausible mechanism for this TCRT is shown in Scheme 10.[16] The enol form initially attacks to the 6-position of pyrimidinone **1** to afford adduct intermediate **24**. While an electron-rich ketone easily approaches to the electron-poor **1**, an electron-poor ketone cannot approach easily, which results in the difference of the reaction efficiency. Then adduct intermediate **24** is converted to enamine **25** by ammonium ion. Another route is also acceptable which involve the enamine formed in situ attacks the 6-position of **1**. When the amino group attacks the 2-position, pyrimidine derivative **22** is formed via bicyclic intermediate **26** accompanied by elimination of nitroacetamide (route a). On the other hand, when the amino group attacks the carbonyl group at the 4-position, nitropyridone **23** is formed via bicyclic intermediate **27** accompanied by elimination of amidine (route b). There is equilibrium between two bicyclic intermediates **26** and **27**. Although **27** is less stable than **26**, it is formed fast because of the lower electron density of the

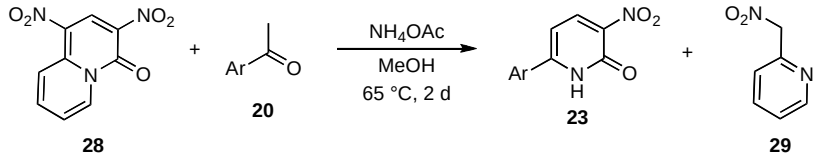
carbonyl group in **25**. However, the following aromatization proceeds slowly because amidine is not easily eliminated compared with nitroacetamide. Thus, more reactive enamine derived from electron-rich ketone undergoes the reaction via the route b to afford nitropyridone **23** efficiently. On the other hand, less reactive enamine derived from electron-poor ketone affords **22** via the route a.



Scheme 10. A plausible mechanism for formation of **22** and **23**.

In order to synthesize 3-nitro-2-pyridone **23** selectively, we conducted the TCRT using dinitroquinolizinone **28** as a substrate, of which the C1-C2-C3 moiety is considered to serve as a synthetic equivalent of α-formylacetic acid (Table 6).[17] Although the desired products **23** were obtained, the yields were moderate because eliminated 2-nitromethylpyridine **29** caused side reactions.

Table 6. TCRT of dinitroquinolizinone **28** with aromatic ketones **20**.



Ar		Yield/%
4-$MeOC_6H_4$	**d**	49
4-MeC_6H_4	**e**	41
C_6H_5	**a**	47
4-$NO_2C_6H_4$	**g**	35

3.3. With alicyclic ketones in the presence of ammonium acetate

The TCRT of nitropyrimidinone **1** with cycloalkanones **19** in the presence of ammonium acetate was studied (Table 7).[18] In cases of cyclopentanone **19b** and cyclohexanone **19a**, cycloalka[*d*]pyrimidines **21b** and **21a** were obtained in good yields without any detectable nitropyridines **30**. On the other hand, cycloheptanone **19c** showed quite different reactivity to afford condensed pyridone **30c** predominantly.

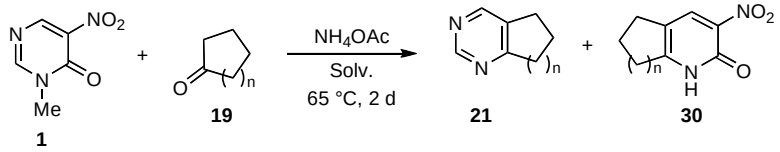
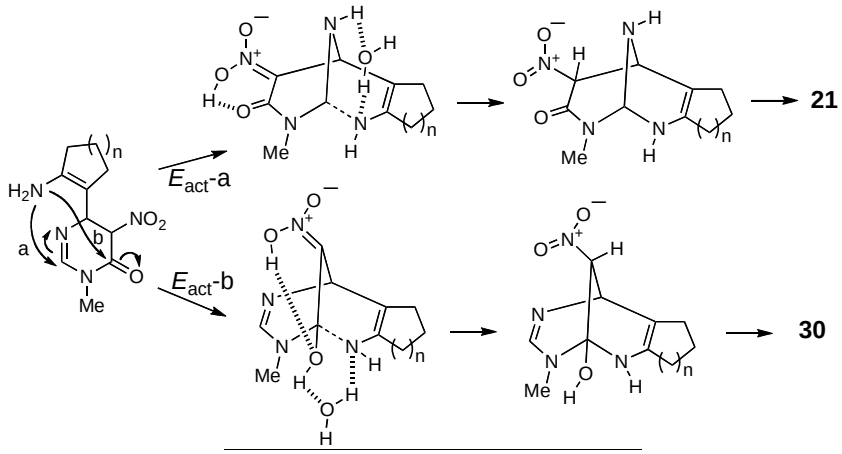


Table 7. TCRT using cycloalkanones **19**.

Ketone		Solv.	Yield/%		Ratio
n			**21**	**30**	**21**/**30**
1	**19b**	MeOH	85	0	100/0
2	**19a**	MeOH	71	0	100/0
3	**19c**	MeOH	11	79	12/88
3	**19c**	AcOH	90	0	100/0
4	**19d**	MeOH	67	17	80/20



n	E_{act}/kcal•mol^{-1}	
	a	b
2	23.44	25.75
3	26.38	26.30
4	21.34	34.31

Scheme 11. Transition states for forming bicyclic intermediates and calculated activation energies.

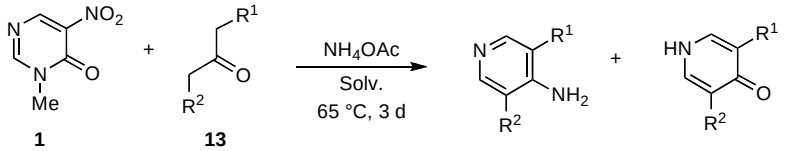
The selectivity was dramatically inverted leading to **21c** by using acetic acid as a solvent instead of methanol. When cyclooctanone **19d** was used, pyrimidine **21d** was obtained as a major product together with small amount of pyridone **30d**.

In order to realize the dramatic change of the selectivity, activation energy for forming a bicyclic intermediate was calculated by DFT method using B3LYP/6-31++G** (Scheme 11). Although two tautomeric enamines, the 5-nitro and the 5-nitronic acid forms, were employed as starting structures, all calculations could give no reasonable transition state structures. This problem was settled by adding one water molecule in the transition state with hydrogen bonds. Indeed, the solvent used for TCRT is not dried, thus enough water would present in the reaction mixture. In cases of cyclohexanone **19a** and cyclooctanone **19c**, E_{act}-a are smaller than E_{act}-b, which indicates the attack of the amino group to 2-position (route a) is more advantageous. On the other hand, the energy difference between E_{act}-a and E_{act}-b was quite small, which indicates the reaction path is readily changed when reaction conditions are varied.

3.4. With 1,3-dicarbonyl compounds in the presence of ammonium acetate

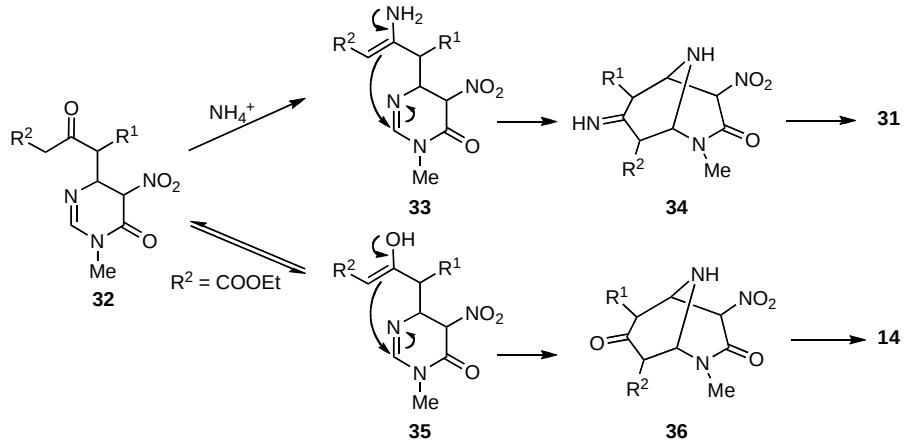
When nitropyrimidinone **1** was treated with 1,3-dicarbonyl compounds **13** in the presence of ammonium acetate, different type of TCRT was found to proceed leading to functionalized 4-aminopyridines **31** (Table 8).[19] In the reaction of **1** with ethyl acetoacetate **13d**, 4-aminopyridine-3-carboxylate **31d** was formed in an excellent yield. In this case, nitropyrimidinone **1** serves as a synthetic equivalent of activated diformylamine, however, nitrogen source was not built-in the ring. When the alkoxy group is sterically hindered, functionalized 4-pyridones **14g** and **14h** were additionally obtained.

Table 8. Synthesis of functionalized 4-aminopyrdines **31**.



R^1	R^2		Yield/%	
			31	**14**
COOEt	H	**d**	97	0
COOMe	H	**f**	87	0
COOPr	H	**g**	57	7
COO(2-Pentyl)	H	**h**	81	12
COOMe	Me	**i**	97	0
COOMe	MeO	**j**	97	0
$CONH_2$	H	**k**	31	0
Cl	H	**l**	17	0
COOEt	COOEt	**a**	0	88
COMe	COMe	**b**	0	45

The substituent R^2 is not necessary to be a hydrogen, and unsymmetrical trisubstituted aminopyridines **31i** and **31j** could be prepared efficiently. This TCRT was applicable to other active methylene compounds such as acetoacetamide **13k** and chloroacetone **13l** to afford the corresponding **31k** and **31l**, respectively. On the other hand, tricarbonyl compounds **13a** and **13b** having two active methylene groups only afforded **14a** and **14b**. Both products **31** and **14** are considered to form as illustrated in Scheme 12. Adduct intermediate **32** is a common intermediate for both products. Then, the ammonium ion converts **32** to enamine **33**, of which the β-carbon attacks the 2-position to afford aminopyridine **31** via bicyclic intermediate **34**. On the other hand, when enolization of **32** to **35** occurs prior to formation of enamine **33**, nitropyridone **14** is formed via bicyclic intermediate **36**. The bulky alkoxy group of **13g** and **13h** prevents the conversion of **32** to **33**, which results in small amounts of formation of **14g** and **14h**. In cases of **13a** and **13b**, there is an additional acidic methylene group, thus enol **35a** and **35b** are easily formed, which affords pyridone **14a** and **14b**, respectively (Scheme 12).

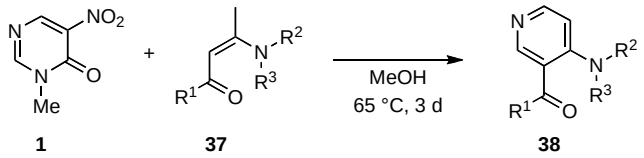


Scheme 12. A plausible mechanism for formation of **31** and **14**.

Taking the mechanism into our consideration, we considered enamines **37** could be used as a nucleophile for the ring transformation of nitropyrimidinone **1** (Table 9).[20]

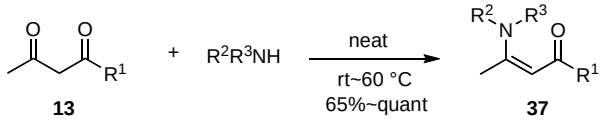
Enamines **37** are readily prepared by heating 1,3-dicarbonyl compounds **13** and amines without solvent. When enamine **37a** was reacted with pyrimidinone **1** (Scheme 13), *N*-modified 4-aminopyridine-3-carboxylate **38a** was obtained in high yield. It was easily achieved to introduce a substituent on the amino group by only changing an amine used for preparation of **37**. Enamines **37g-j** derived from amino alcohols were also usable for this reaction to afford the corresponding aminopyridines **38g-j** without observation of any influence of the hydroxy group. While α-branched enamine **37i** efficiently underwent the ring transformation as well as β-branched enamine **37h**, the reactivity of α,α-doubly branched enamine **37j** is significantly diminished. The vicinal functionality of the obtained aminopyridine-3-carboxylate **38g** facilitates the synthesis of [*c*]-fused bicyclic pyridine **39** in a quantitative yield upon heating with sodium hydride (Scheme 14).

Table 9. Synthesis of *N*-modified 4-aminopyridine-3-carboxylate **38**.



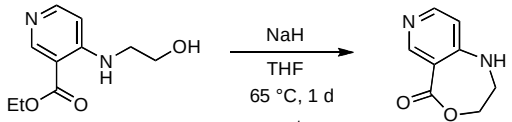
1 **37** **38**

Enamine				Yield/%
R^1	R^2	R^3		
OEt	Pr	H	**37a**	88
OEt	*i*-Pr	H	**37b**	79
OEt	4-$MeOC_6H_5$	H	**37c**	59
OEt	Pr	Pr	**37d**	73
Me	Pr	H	**37e**	28
Ph	Pr	H	**37f**	21
OEt	CH_2CH_2OH	H	**37g**	80
OEt	$CH_2CHMeOH$	H	**37h**	70
OEt	$CHMeCH_2OH$	H	**37i**	82
OEt	CMe_2CH_2OH	H	**37j**	14



13 **37**

Scheme 13. Preparation of β-functionalized enamines **37**.



38g **39**

Scheme 14. Synthesis of [*c*]-fused bicyclic pyridine **39**.

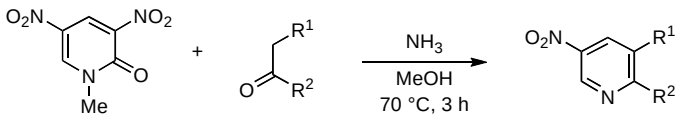
4. Three component ring transformation (TCRT) of dinitropyridone

4.1. Using ammonia as a nitrogen source

As mentioned in the last chapter, nitropyrimidinone **1** serves as an excellent substrate for the TCRT (Table 10). In consideration with these results, dinitropyridone **2** is considered to serve as an excellent substrate for the TCRT similarly.[3] When pyridone **2** was reacted with cyclohexanone **19a** in the presence of ammonia, cyclohexa[*b*]pyridine **40a** was obtained in high yield. However, this method suffers from the narrow scope of the ketones, which is similar problem observed in the TCRT of pyrimidinone **1** using ammonia (Section 3.1.). When other ketones were used under the same conditions, the yields of the products

were low except for the reaction using acetophenone **20a**. This is due to the competitive ammonolysis of the substrate **2**. In order to overcome this disadvantage, larger amounts of ammonia (140 equiv.) in autoclave under the severe conditions were used, which underwent the reaction efficiently. Conversion of the ketone to more reactive enamine was also effective. However, these methods are somewhat troublesome. Furthermore, it is necessary to prepare an ammonia solution beforehand.[21]

Table 10. TCRT of pyridone **2** with ketones in the presence of ammonia.



2 **19** or **20** **40** or **41**

Ketone			Product	
R^1	R^2			Yield/%
-$(CH_2)_4$-		**19a**	**40a**	83
-$(CH_2)_3$-		**19b**	**40b**	27
H	Ph	**20a**	**41a**	44
Me	Ph	**20t**	**41t**	10

4.2. With aromatic ketones in the presence of ammonium acetate[22]

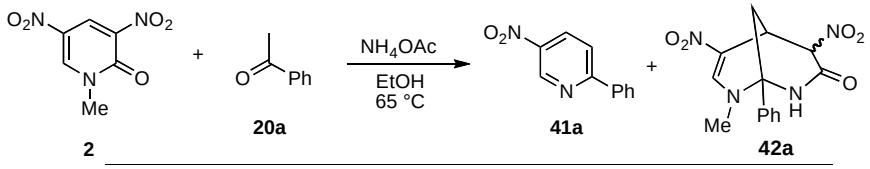
In order to avoid the undesired ammonolysis of dinitropyridone **2**, less nucleophilic ammonium acetate was used as a nitrogen source instead of ammonia (Table 11).

When pyridone **2** was allowed to react with acetophenone **20a** in the presence of three equivalents of ammonium acetate, nitropyridine **41a** was obtained although the yield was low. In this reaction, the main product was 2,8-diazabicyclo[3.3.1]non-3-ene derivative **42a**, which corresponds to the structure formed by insertion of **20a** and a nitrogen atom between N1 and C2 positions of **2**. The structure of **42a** was finally determined by X-ray single crystal analysis using product **42g**, which is derived from 4-nitroacetophenone **41g**. The isomeric structure of **42a** was assigned by NOESY spectrum (Figure 2).

A plausible mechanism for the formation of both products **41a** and **42a** is shown in Scheme 15. The reaction was initiated by the addition of enol form of **20a** to the 4-position of pyridone **2**. Then adduct intermediate **43** is converted into enamine **45** as a result of the reaction with ammonium ion. The enamine **45** serves as a common intermediate for products **41a** and **42a**. When the amino group attacks at the 6-position (path A), nitropyridine **41a** is formed via bicyclic intermediate **46** accompanied by elimination of nitroacetamide. On the other hand, when the amino group attacks the carbonyl group at the 2-position (path B), bicyclic intermediate **48** is formed, however, it easily undergoes the ring opening reaction because of the instability. This reaction mechanism is similar to that of TCRT using nitropyrimidinone **1** as illustrated in Scheme 10. In the case of TCRT of pyrimidinone **1**, the ring-opened product has an amidine moiety, which is easily eliminated accompanied by aromatization to afford nitropyridone **23**. Contrary to this, the

substituent is connected by a C-C bond in the case of ring-opened product **49**, which is not easily eliminated. Thus, the amino group attacks the C6 position of the tautomer **50** to afford bicyclic product **42a**.

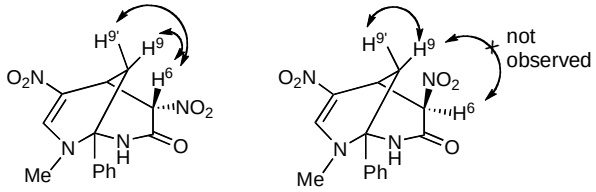
Table 11. TCRT of pyridone **2** with acetophenone **20a** using different amounts of ammonium acetate.



2 **20a** **41a** **42a**

NH_4OAc /equiv.	Time/h	Yield/%		Ratio of	Ratio of
		41a	**42a**	**41a**/**42a**	*exo*-**42a**/*endo*-**42a**
3	24	19	61	24/76	56/44
5	24	43	46	48/52	59/41
10	24	64	25	72/28	70/30
15	24	79	0	100/0	––
5[a]	7	92	5	95/5	60/40
15[a]	5	90	0	100/0	––

[a]Microwave heating was used.



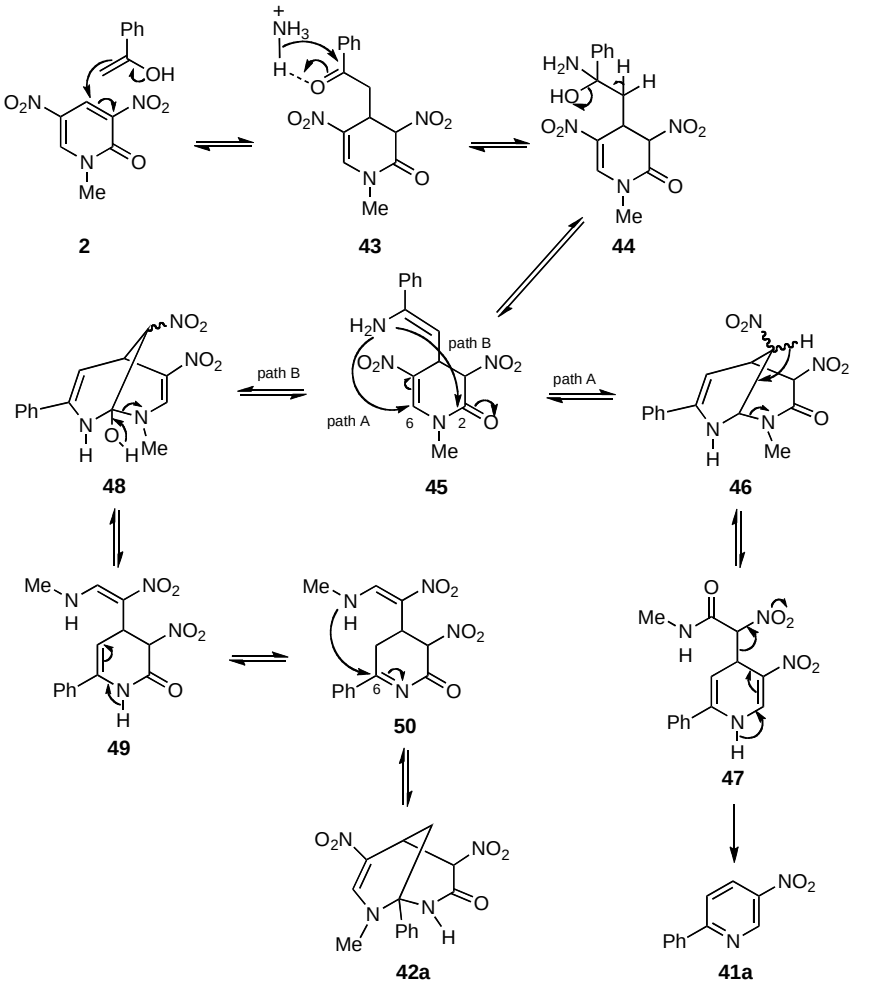
exo-**42a** *endo*-**42a**

Figure 2. Correlations between H6, H9 and H9' of isomers of **42a** in the NOESY spectra.

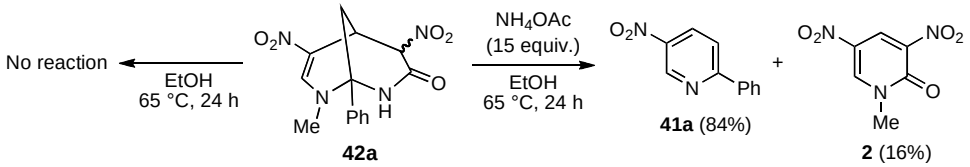
The selectivity of **41a** and **42a** was considerably affected by the amount of ammonium acetate (Table 11). The yield of nitropyridine **41a** increased up to 79% accompanied by a decrease in the yield of bicyclic product **42a** when the amount of ammonium acetate was increased greatly. Microwave heating was found to be effective for this reaction, which considerably reduced the reaction time and increased the yield of **41a**. In addition, although the bicyclic product **42a** is intact in an ethanol solution at 65 °C, it is converted into the aromatized **41a** and **1**, in 84% and 16% yields, respectively, in the presence of ammonium acetate (Scheme 16). This result indicates that there is equilibrium between **41a** and **42a** via enamine intermediate **45**.

On the basis of these results, the selectivity of **41a** and **42a** is realized as follows. In the enamine intermediate **45**, carbonyl group at the 2-position is more electrophilic, which facilitates the predominant attack of the amino group leading to bicyclic product **42a** via path B in the earlier stage of the reaction; **42a** is a kinetically controlled product. When the reaction mixture is heated for a longer time, the bicyclic product **42a** is converted to the intermediate **45** under the equilibrium, leading to stable aromatic product **41a** via path A; nitropyridine **41a** is a thermodynamic controlled product. In the present TCRT, competitive

thermal decomposition of ammonium acetate also occurs, and ammonia gas is evolved from the reaction mixture.



Scheme 15. A plausible mechanism for the formation of products **41a** and **42a**.

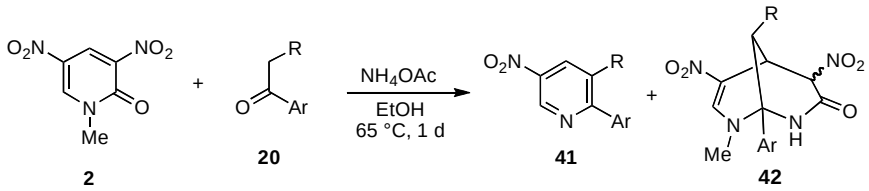


Scheme 16. Conversion of bicyclic compound **42a** into nitropyridine **41a** and dinitropyridone **2**.

When all ammonium acetate is consumed by the TCRT or has decomposed, the TCRT could not proceed anymore because it lacks a nitrogen source. Hence, further increasing ammonium acetate prolongs the real reaction time, which consequently increases the yield of **41a**.

Other aromatic ketones **20** were used for this TCRT (Table 12). As a result, electronic property of the ketone was found to affect the selectivity of the products **41** and **42**. When electron-rich ketones were used, the TCRT efficiently proceeded to afford the corresponding nitropyridines **41** in high yields without the detectable bicyclic products **42**. On the other hand, electron-poor ketone **20g**, larger amounts of ammonium acetate (longer reaction time) were necessary for the efficient TCRT, and small amount of **42g** was detected. Similar tendency was also observed when heteroaromatic ketones **20m-s** were used. The electron-deficiency of pyridone **2** prevents the approach of electron-poor ketone, which diminishes the efficiency of the TCRT. After addition, the formed enamine intermediate **45** cannot attack the 6-position because of the low nucleophilicity derived from electron-poor ketone.

Table 12. TCRT of pyridone **2** with other aromatic ketones **20**.



Ketone			NH_4OAc/	Yield/%		
Ar	R		equiv.	**41**	**42**	**41+42**
C_6H_5	H	**a**	5	43	46	89
C_6H_5	H	**a**	15	79	0	79
4-$MeOC_6H_4$	H	**d**	5[a,b]	95	0	95
3-$MeOC_6H_4$	H	**j**	10	97	0	97
2-$MeOC_6H_4$	H	**k**	5	94	0	94
4-MeC_6H_4	H	**e**	5	88	0	88
4-ClC_6H_4	H	**f**	10	96	0	96
4-$NO_2C_6H_4$	H	**g**	15	93	2	95
4-Pyridyl	H	**n**	15	66	33	99
3-Pyridyl	H	**m**	15	97	0	97
2-Pyridyl	H	**o**	15	80	12	92
2-Pyrrolyl[a]	H	**p**	10	87	0	87
2-Thienyl[a]	H	**r**	10	85	0	85
2-Furyl	H	**s**	5	87	0	87
C_6H_5	Me	**t**	15[a,c]	98	0	98
C_6H_5	Pr	**u**	15[a,c]	97	0	97

[a]Microwave heating was used. [b]For 6 h. [c]At 80 °C for 2 h

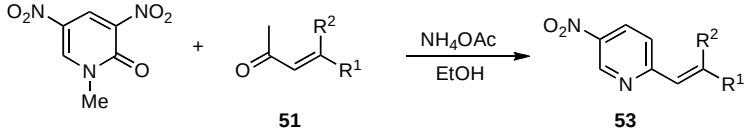
Consequently, the bicyclic products **42** are predominantly formed. Furthermore, ketones **20t** and **20u** having a longer alkyl chain were also usable for this TCRT, which afforded trisubstituted pyridines **41t** and **41u**, respectively, by using somewhat severe conditions. As shown here, various kinds of aryl groups can be introduced into the nitropyridine framework by only changing a ketone **20**, hence, this TCRT will be a metal-free supplementary method for the Suzuki reaction.

4.3. With α,β-unsaturated ketones in the presence of ammonium acetate

In the presence of TCRT, versatile nitropyridine derivatives can be synthesized by only changing the starting ketones. An alkenyl or an alkynyl group can be also introduced into the nitropyridine framework when α,β-unsaturated ketones **51** or **52** were employed.[23]

When alkenylketones **51** were used, the TCRT similarly proceeded to afford the corresponding alkenylpyridines **53** (Table 13), although large amounts of ammonium acetate were necessary, which substantially prolonged the reaction time. Microwave heating was found to be effective than conventional heating to increase the yield of **53** within shorter time. Among three styryl ketones **51a-c**, **51b** revealed higher reactivity because electron-rich **51b** can easily approach to the electron-deficient pyridone **2**. In the case of vinyl ketone **51d**, alkenylpyridine **53d** was not detected. Aliphatic ketone **51e** also afforded a complex mixture, from which alkenylpyridine **53e** was isolated in low yield because of the side reactions and the instability of the product **53e**. These problems were settled by employing a bulkier group to afford alkenylpyridine **53f** in high yield.

Table 13. Synthesis of 2-alkenyl-5-nitropyridines **53**.

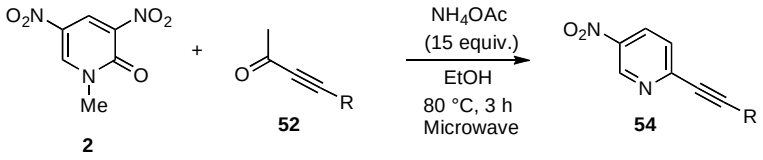


Ketone			NH_4OAc/	Temp./°C	Time/h	Yield/%
R^1	R^2		equiv.			
Ph	H	**51a**	15	80[a]	4	82
4-$MeOC_6H_4$	H	**51b**	30	65	24	94
4-ClC_6H_4	H	**51c**	30	80[a]	4	75
H	H	**51d**	30	65	24	0
Me	Me	**51e**	15	80[a]	2	25
2,6,6-trimethylcyclohexenyl	H	**51f**	30	80[a]	6	79

[a]Microwave heating was used.

The TCRT also facilitated alkynylation of nitropyridine framework by using alkynyl ketones **52** (Table 14). Both aromatic and aliphatic alkynyl ketones **52a** and **52b** underwent the TCRT leading to alkynylpyridines **54a** and **54b** in good yield, respectively. When trimethylsilylethynyl ketone **52c** was used, desilylation also occurred to afford a mixture of **54c** and **54d** with high total yield.

Table 14. Synthesis of 2-alkynyl-5-nitropyridines **54**.



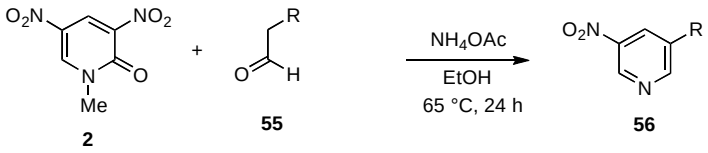
R		Yield/%
Ph	**a**	87
Et	**b**	80
Me_3Si	**c**	**54c** 24/**54d** 60[a]

[a]Desilylated product **54d** (R = H) was also obtained.

4.4. With aldehydes in the presence of ammonium acetate

So far, TCRT of dinitropyridone **2** with ketones has been mentioned. If aldehydes **55** are usable, the synthetic utility of the present TCRT will be improved, which affords 3,5-disubstituted pyridines **56**.[4] However, since the reactivity of an aldehyde is higher than that of a ketone, suppressing the side-reactions will be a problem to be addressed.[24]

Table 15. TCRT of pyridone **2** with aldehydes **55** in the presence of ammonium acetate.



R		NH_4OAc/equiv.	Yield/%	Recovery of **2**/%
Et	**a**	5	26	66
Et	**a**	10	75	20
Et	**a**	15	86	0
Et	**a**	15	24	65
Me	**b**	15	52	0
i-Pr	**c**	15	71	16
$PhCH_2$	**d**	15	34	21
t-Bu	**e**	15	29	63
t-Bu	**e**	15[a]	68	0
Ph	**f**	15	47	44
Ph	**f**	15[a]	75	0

[a]Microwave heating was used.

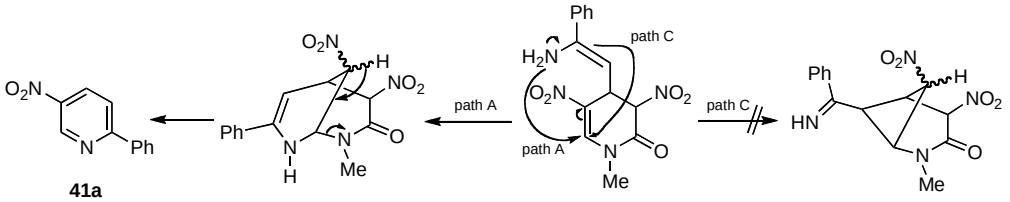
When dinitropyridone **2** was allowed to react with butanal **55a** in the presence of ammonium acetate, TCRT proceeded to afford 3-ethyl-5-nitropyridine **56a**, however, the yield of **56a** was low because of the side reactions such as the aldol reaction and the Chichibabin reaction affording a trialkylpyridine. This problem was solved by using two equivalents of aldehyde **55a** (Table 15). The larger amount of ammonium acetate was, the higher the yield of **56a** was, which prolonged the actual reaction time because ammonium acetate competitively decomposes. In order to reduce the reaction time, microwave heating was used, which was effective for the TCRT with ketones. However, the yield of **56a** was lower because the abovementioned side reactions were also accelerated.

Other aldehydes **55b-f** were subjected to the TCRT under the conditions optimized for **55a**. The TCRT using propanal **55b** proceeded well to afford **56b** in 52% yield, although the reaction was diminished by the competitive self-condensation of the aldehyde **55b**. Self-condensation was avoided when bulkier aldehyde **55c** was used, resulting in 3-isopropylpyridine **56c** recovered in 71% yield. In the case of more sterically hindered aldehyde **55d** and **55e**, the corresponding yields of nitropyridines **56d** and **56e** were significantly lower, highlighting the reduced efficiency of the TCRT decreased. This disadvantage was overcome with microwave heating, which improved the yield of **56e** to 68%. It was also possible to introduce a phenyl group to the pyridine ring by employing phenylacetaldehyde **55f** to afford **56f**.

4.5. With aliphatic ketones in the presence of ammonium acetate

4.5.1. Discussion on the basis of the reaction mechanism

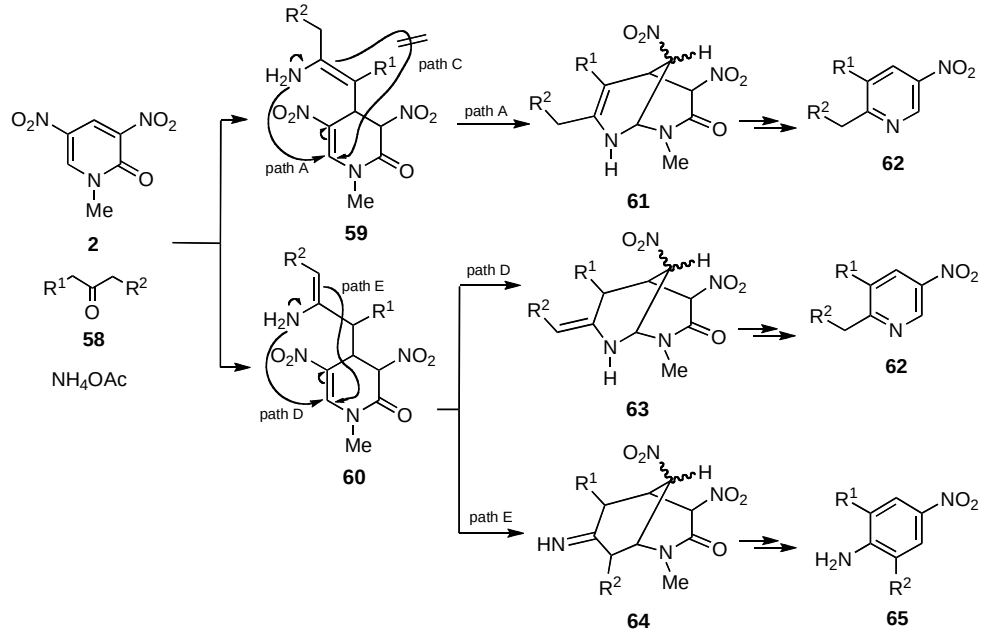
The TCRT of dinitropyridone **2** with aromatic ketones **20**, α,β-unsaturated ketones **51** and **52**, and aldehydes **55** can be used as supplementary methods for palladium catalyzed Suzuki, Heck and Sonogashira reactions, which afford only 3-nitropyridine derivatives as a product of the TCRT. This is because the β-carbon of enamine intermediate **45** cannot attack the 6-position through the path C, which forms sterically strained bicyclic intermediate **57** (Scheme 17). Hence, only attack of the amino group of the enamine occurs through the path A leading to nitropyridine **41a**.



Scheme 17. Two reaction paths from enamine intermediate **45**.

In the TCRT of pyridone **2** with aliphatic ketones **58** two kinds of enamine intermediates **59** and **60** can be formed (Scheme 18). In the case of enamine **59**, the TCRT proceeds through the path A only to afford 2,3-disubstituted 5-nitropyridines **62** due to the same reason mentioned above. On the other hand, in the case of enamine **60**, both the amino group and the β-carbon can attack the 6-position, both of which form a six membered ring. When the amino group of **60** attacks the 6-position through the path D, nitropyridine **62** is also obtained via bicyclic intermediate **63**. Contrary to this, when the TCRT proceeds through the path E,

2,6-disubstituted 4-nitroaniline **65** will be formed via bicyclic intermediate **64**. On the basis of this consideration, we studied the TCRT of pyridone **2** with cyclic and acyclic aliphatic ketones **19** and **58** in the presence of ammonium acetate.

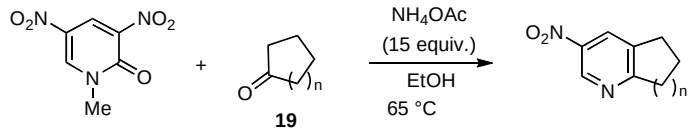


Scheme 18. A predicted reaction mechanism of the TCRT using aliphatic ketones **58**.

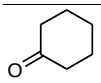
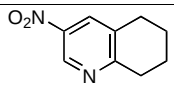
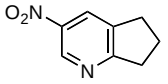
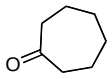
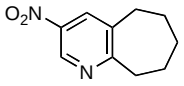
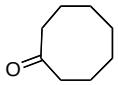
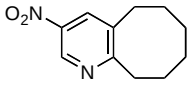
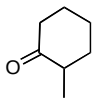
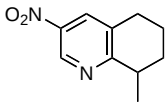
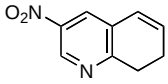
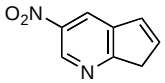
4.5.2. Reactions with cyclic ketones

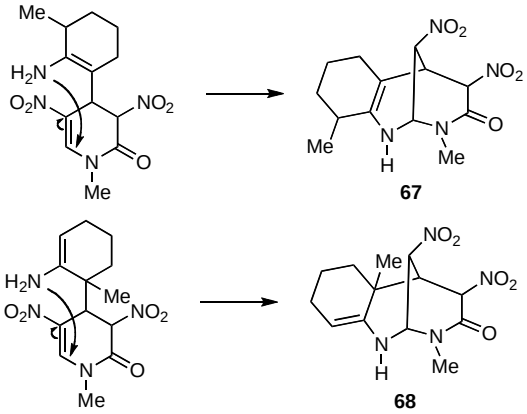
At first, the TCRT of pyridone **2** with cycloalkanones **19** was studied (Table 16).[25] In each case, somewhat larger amounts of ammonium acetate were necessary to avoid the shortage by thermal decomposition. In the case of cyclohexanone **19a**, the TCRT underwent efficiently to afford cyclohexa[*b*]pyridine **66a** in 95% yield. In this reaction, nitroaniline derivative **65** (R^1, R^2=-$(CH_2)_3$-) was not detected because the product is highly strained. Microwave heating was effective in this case to complete the reaction within one hour. Although cyclopentanone **19b** revealed lower reactivity leading to **66b** in only 67% yield under the same conditions, using microwave heating increased the yield of **66b** up to 87% within a short time. In contrast, larger cycloalkanones **19c** and **19d** underwent the TCRT efficiently to afford the corresponding cyclohepta- and cyclooctapyridines **66c** and **66d**, respectively. When unsymmetrical 2-methylcyclohexanone **19e** was employed, 8-methylated tetrahydroquinoline **66e** was obtained efficiently. In this case, two bicyclic intermediates **67** and **68** are possible; however, the latter intermediate **68** cannot afford aromatized product (Scheme 19). Therefore, only **66e** is formed via intermediate **67**. The reaction conditions were also applied to unsaturated cyclic ketone **19f**, thus affording 7,8-dihydroquinoline **66f**, although microwave heating was again necessary for the efficient TCRT.

Table 16. Synthesis of cycloalka[*b*]pyridines **66**.



2 **66**

Ketone		Time/h	Product	Yield/%
	**19a**	24 1[a]	 **66a**	95 97
	**19b**	24 2[a]	 **66b**	67 87
	**19c**	24 1[a]	 **66c**	94 91
	**19d**	24 1[a]	 **66d**	85 95
	**19e**	24 2[a]	 **66e**	83 86
	**19f**	24 3[a]	 **66f**	59 89
	**19g**	4[a]	 **66g**	0



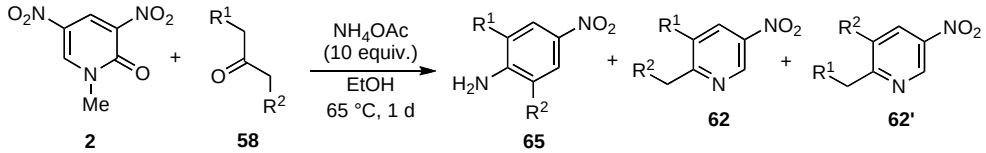
Scheme 19. Two plausible intermediates **67** and **68** derived from 2-methylcyclohexanone **19e**.

In contrast, cyclopentanone **19g** did not undergo the TCRT despite the application of microwave heating because the formation of sterically restricted intermediate is necessary.

4.5.3. Reactions with acyclic ketones[26]

According to the reaction mechanism as illustrated in Scheme 18, 2,6-disubstituted 4-nitroaniline **65** should be formed when aliphatic ketone **58** is used for the TCRT with dinitropyridone **2**. Generally, 2,6-disubstituted 4-nitroanilines **65** are prepared from the corresponding anilines by nitration under harsh conditions, wherein protection and deprotection of the amino group are necessary.[27] However, the preparation of 2,6-disubstituted anilines is restricted because of the following limitations of the Friedel-Crafts alkylation; (1) the monoalkylated product undergoes further alkylation to afford polyalkylated products, (2) it is difficult to introduce two different alkyl groups, (3) primary alkyl groups longer than the ethyl group cannot be introduced, (4) a phenyl group cannot be introduced, (5) aminated and nitrated benzenes do not facilitate the alkylation. We considered that the TCRT will overcome these disadvantages of the Friedel-Crafts alkylation and facilitate the synthesis of various 2,6-disubstituted 4-nitroanilines **65** only by using appropriate ketone **58** (Table 17).

Table 17. TCRT of pyridone **2** with acyclic ketones **58**.



Ketone			Yield/%		
R^1	R^2		**65**	**62**	**62'**
Me	Me	**a**[a]	50	44	––
Me	Me	**a**	83	13	––
H	H	**b**	51	47	––
Et	H	**c**	66	10	8
i-Pr	H	**d**	58	0	31
Pr	H	**e**	83	9	6
Et	Et	**f**	67	24	––
Pr	Pr	**g**	74	22	––
C_6H_5	Pr	**h**	62	24	13
C_6H_5	C_6H_5	**i**	8	81	––

[a]5 equivalents of ammonium acetate were used.

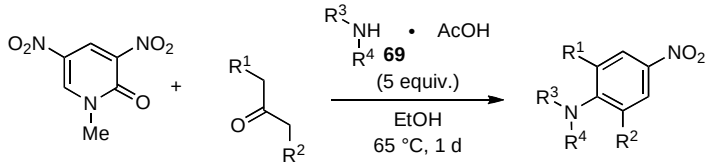
When dinitropyridone **2** was allowed to react with 3-pentanone **58a** in the presence of 5 equivalents of ammonium acetate, nitroaniline **65a** and nitropyridine **62a** were obtained in 50% and 44%, respectively, resulting from two kinds of TCRT. When 10 equivalents of ammonium acetate were used, the ratio of **65a** to

62a increased considerably without decrease in the total yield; this indicates the presence of an equilibrium between intermediates **64** and **63**, which are thermodynamically and kinetically controlled intermediates, respectively (Scheme 18).

This TCRT was applied to other ketones **58b-i** under the same conditions. In the case of acetone **58b**, two kinds of TCRT occurred to afford nitroaniline **65b** and nitroaniline **62b** in almost similar yields. It was possible to modify the 2- and 6-positions of the nitroaniline framework by only changing ketone **58**. Notably, this TCRT facilitates the introduction of a propyl or a phenyl group into the benzene ring, which cannot be achieved by the Friedel-Crafts reaction. As a result, symmetrical and unsymmetrical nitroanilines **65c-i** were easily prepared; however, the yield of **65i** was low, presumably because steric repulsion by the phenyl groups prevents the formation of intermediate **64i**.

As so far, ammonium acetate serves both as a nitrogen source and as an activator of ketone **58**. We considered that a combination of amine **69** and acetic acid, used instead of ammonium acetate, can carry out these roles, thus achieving the modification of the benzene ring as well as the amino group of the nitroaniline framework (Table 18).

Table 18. TCRT of pyridone **2** with aliphatic ketones **58** with a mixture of amine **69** and acetic acid.



2 **58** **70**

Ketone			Amine			Product	Yield/%
R^1	R^2		R^3	R^4			
Me	Me	**58a**	Pr	H	**69A**	**70Aa**	99
Me	Me	**58a**	-$(CH_2)_4$-		**69B**	**70Ba**	98
Me	Me	**58a**	Et	Et	**69C**	**70Cc**	98
Et	H	**58c**	Pr	H	**69A**	**70Ac**	83
Et	H	**58c**	-$(CH_2)_4$-		**69B**	**70Bc**	68
Pr	H	**58e**	Pr	H	**69A**	**70Ae**	77
Pr	H	**58e**	-$(CH_2)_4$-		**69B**	**70Be**	87
Pr	H	**58e**	Et	Et	**69C**	**70Ce**	51
i-Pr	H	**58d**	Pr	H	**69A**	**70Ae**	83
Et	Et	**58f**	Pr	H	**69A**	**70Af**	69
Et	Et	**58f**	-$(CH_2)_4$-		**69B**	**70Bf**	68
Pr	Pr	**58g**	Pr	H	**69A**	**70Ag**	81
Pr	Pr	**58g**	-$(CH_2)_4$-		**69B**	**70Bg**	59
C_6H_5	Pr	**58h**	Pr	H	**69A**	**70Ah**	80
C_6H_5	C_6H_5	**58i**	Pr	H	**69A**	**70Ai**	32

In this case, only nitroaniline **70** will be formed as a TCRT product, because the aromatization of the intermediate, which is required for the formation of nitropyridines, is prevented by the *N*-substituents (R^3 and R^4).

Propylamine **69A** was added to a solution of dinitropyridone **2**, 3-pentanone **58a**, and acetic acid in ethanol, and the resulting solution was heated at 65 °C for one day. From the reaction mixture, *N*-propylnitroaniline **70Aa** was obtained in 99% yield. This method was applied to the secondary amines, pyrrolidine **69B** and diethylamine **69C**, to afford *N*,*N*,2,6-tetrasubstituted 4-nitroanilines **70Ba** and **70Ca**, respectively, in excellent yields. Methyl ketones **58c-e** also underwent this TCRT by use of either propylamine **69A** or pyrrolidine **69B** with acetic acid to afford the corresponding nitroanilines **70** in moderate to excellent yields. Moreover, these reactions could induce modifications at the 2- and the 6-positions by use of ketones **58g-i**, with which a propyl or a phenyl group could be introduced to the nitroaniline framework.

5. Conclusions

Nitropyrimidinone **1** and dinitropyridone **2** are shown to serve as an excellent substrate for nucleophilic ring transformation, in which pyrimidinone **1** serves as the synthetic equivalent of activated diformylamine and α-formylacetic acid, and pyridone **2** serves as that of unstable nitromalonaldehyde. The TCRT of these substrates with simple ketones in the presence of ammonium acetate affords versatile azaheterocyclic compounds and nitro compounds efficiently. The modification of the products is easily achieved by only changing the ketones. Furthermore, each reaction proceeds under mild conditions. The reaction and work-up are conducted with simple experimental manipulations, which is advantageous from the viewpoint of practical use. These features facilitate the construction of a library of compounds that are not easily available by other methods. Especially, compounds having both electron-donating and electron-withdrawing groups (push-pull system) are useful framework for developing a novel functional materials such as medicines, agrochemicals, non-linear optical materials and so on. Hence, the present TCRT will provide a new synthetic tool for researchers studying in these fields.

References

1. (a) Kirkham, J. D.; Butlin, R. J.; Harrity, J. P. A. *Angew. Chem. Int. Ed.* **2012**, *51*, 6402; (b) Sabot, C.; Oueis, E.; Brune, X.; Renard, P. Y.; *Chem. Commun.* **2012**, *48*, 768; (c) Anderson, E. D.; Boger, D. L. *Org. Lett*. **2011**, *13*, 2492; (d) Delaunay, T.; Genix, P.; Es-Sayed, M.; Vors, J. P.; Monterio, N.; Balme, G. *Org. Lett.* **2010**, *12*, 3328; (e) Wu, C.; Fang, Y.; Larock, R. C.; Shi, F. *Org. Lett*. **2010**, *12*, 2234; (f) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun*. **2009**, 1470; (g) Yoshino, Y.; Kurahashi, T.; Matsubara, S.-J. *J. Am. Chem. Soc.* **2009**, *131*, 7494; (h) Xie, H.; Zu, L.; Oueis, H. R.; Li, H.; Wang, J.; Wang, W. *Org. Lett.* **2008**, *10*, 1923.
2. (a) Bonacorso, H. G.; Navarini, J.; Porte, L. M. F.; Pittaluga, E. P.; Junges, A. F.; Mayer, A. R.; Martins, M. A. P.; Zanatta, N. *J. Fluorine Chem*. **2013**, *151*, 38; (b) Koutentis, P. A.; Koyioni, M.; Michaelidou, S. S. *Org. Biomol. Chem.* **2013**, *11*, 621; (c) Rykowski, A.; Wolinska, E.; Branowska, D.; van der Plas, H. C. *ARKIVOC* **2004**, *5 (iii)*, 74; (d) Hajós, G.; Riedl, Z.; Kollenz, G. *Eur. J. Org. Chem.* **2001**, 3405; (e) van der Plas, H. C. *J. Heterocycl. Chem.* **2000**, *37*, 427.
3. Recent papers: (a) Schultz, T.; Turner, S. C.; Braje, W. M. *Synthesis* **2010**, 1339; (b) Sagitullina, G. P.; Garkushenko, A. K.; Vinokurova, Y. O.; Nyrkova, V. A.; Atavin, E. G.; Sagitullin, R. S. *Russ. J. Org.*

Chem. **2009**, *45*, 1045; (c) Guiadeen, D.; Kothandaraman, S.; Yang, L.; Mills, S. G.; MacCoss, M. *Tetrahedron Lett.* **2008**, *49*, 6368; (d) Shah, U.; Lankin, C. M.; Boyle, C. D.; Chackalamannil, S.; Greenlee, W. J.; Neustadt, B. R.; Cohen-Williams, M. E.; Higgins, G. A.; Ng, K.; Varty, G. B.; Zhang, H.; Lachowicz, J. E. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4204.

4. (a) Henry, C.; Haupt, A.; Turner, S. C. *J. Org. Chem.* **2009**, *74*, 1932; (b) Kelly, M. G.; Kaub, C. J.; Kincaid, J.; Janagani, S.; Wu, G.; Wei, Z.-L.; Sahasrabudhe, K.; Duncton, M.; Upasani, R. B.; Fang, Y.; Cox, M. *PCT Int. Appl.* 2007100758, **2007**.
5. (a) Nishiwaki, N.; Hirao, S.; Sawayama, J.; Saigo, K. *Heterocycles* **2012**, *84*, 115; (b) Nakaike, Y.; Kamijo, Y.; Mori, S.; Tamura, M.; Nishiwaki, N.; Ariga, M. *J. Org. Chem.* **2005**, *70*, 10169; (c) Nishiwaki, N.; Ogihara, T.; Takami, T.; Tamura, M.; Ariga, M. *J. Org. Chem.* **2004**, *69*, 8382; (d) Fanta, P. E. *Chem. Rev.* **1960**, *60*, 261.
6. (a) Nishiwaki, N.; Mizukawa, Y.; Terai, R. ; Tohda, Y. ; Ariga, M. *ARKIVOC* **2000**, *1 (ii)*, 103; (b) Nishiwaki, N.; Mizukawa, Y.; Ohta, M.; Terai, R.; Tohda, Y.; Ariga, M. *Heterocycl. Commun.* **1996**, *2*, 21.
7. (a) Takaichi, J.; Ohkubo, K.; Sugimoto, H.; Nakano, M.; Usa, D.; Maekawa, H. ; Fujieda, N.; Nishiwaki, N. ; Seki, S.; Fukuzumi, S.; Itoh, S. *Dalton Trans.* **2013**, *42*, 2438; (b) Shimokawa, C.; Tachi, Y.; Nishiwaki, N.; Ariga, M.; Itoh, S. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 118; (c) Shimokawa, C.; Yokota, S.; Tachi, Y.; Nishiwaki, N.; Ariga, M.; Itoh, S. *Inorg. Chem.* **2003**, *42*, 8395; (d) Yokota, S.; Tachi, Y.; Nishiwaki, N.; Ariga, M.; Itoh, S. *Inorg. Chem.* **2001**, *40*, 5316; (e) Nishiwaki, N.; Tohda, Y.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1996**, *69*, 1997.
8. Tohda, Y.; Ariga, M.; Kawashima, T.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 201.
9. Nishiwaki, N.; Tohda, Y.; Ariga, M. *Synthesis* **1997**, 1277.
10. Matsumura, E.; Tohda, Y.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 2413.
11. (a) Ariga, M.; Tohda, Y.; Matsumura, E. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 393; (b) Matsumura, E.; Tohda, Y.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2174.
12. Nishiwaki, N.; Matsunaga, T.; Tohda, Y.; Ariga, M. *Heterocycles* **1994**, *38*, 249.
13. Brown, D. J. Evans, R. F.; Cowden, W. B.; Fenn, M. D. *The Chemistry of Heterocyclic Compounds*, vol *52*. Wiley, New York (**1994**).
14. (a) Nishiwaki, N.; Adachi, T.; Matsuo, K.; Wang, H.-P.; Matsunaga, T.; Tohda, Y.; Ariga, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 27; (b) Nishiwaki, N.; Wang, H.-P.; Matsuo, K.; Tohda, Y.; Ariga, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2261.
15. Nishiwaki, N.; Yamashita, K.; Azuma, M.; Adachi, T.; Tamura, M.; Ariga, M. *Synthesis* **2004**, 1996.
16. Nishiwaki, N.; Ariga, M. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 882.
17. Nishiwaki, N.; Ohtomo, H.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *Heterocycles* **2001**, *55*, 1581.
18. Nishiwaki, N.; Sugimoto, R.; Saigo, K.; Kobiro, K. *Tetrahedron Lett.* **2013**, *54*, 956.
19. Nishiwaki, N.; Azuma, M.; Tamura, M.; Hori, K.; Tohda, Y.; Ariga, M. *Chem. Commun.* **2002**, 2170.
20. Nishiwaki, N.; Nishimoto, T.; Tamura, M.; Ariga, M. *Synlett* **2006**, 1437.
21. (a) Tohda, Y.; Kawahara, T.; Eiraku, M.; Tani, K.; Nishiwaki, N.; Ariga, M. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2176; (b) Tohda, Y.; Eiraku, M.; Nakagawa, T.; Usami, Y.; Ariga, M.; Kawashima, T.; Tani, K.; Watanabe, H.; Mori, Y. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2820.
22. Le, S. T.; Asahara, H.; Kobiro, K.; Sugimoto, R.; Saigo, K.; Nishiwaki, N. *Asian J. Org. Chem.* **2014**, *3*, 297.
23. Le, S. T.; Asahara, H.; Nishiwaki, N. *Chem. Lett.* **2015**, *44*, 776.
24. Le, S. T.; Asahara, H.; Nishiwaki, N. *J. Org. Chem.* **2015**, *80*, 8856.
25. Le, S. T.; Asahara, H.; Nishiwaki, N. *Synthesis* **2014**, *46*, 2175.

26. Le, S. T.; Asahara, H.; Nishiwaki, N. *Eur. J. Org. Chem.* **2015**, 1203.
27. (a) Carver, F. J.; Hunter, C. A.; Livingstone, D. J.; McCabe, J. F.; Seward, E. M. *Chem. Eur. J.* **2002**, *8*, 2848; (b) Al-Khafaji, S.; Cardinale, N.; Hanson, J. R. *J. Chem. Res. Synop.* **2003**, *388*, 701.