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.

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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 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.
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 nitroalonaldehyde when ring transformation proceeds according to our prediction.
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-thiouracil 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.

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). 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. However, this method suffers from competitive reaction of the eliminated nitroacetamide with unreacted pyridone 2 leading to adduct 12. This problem is solved by use of 1-methyl-5-nitro-2-pyrimidinone instead of pyridone 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.

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Base</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEt</td>
<td>COOEt</td>
<td>a NEt₃</td>
<td>97</td>
</tr>
<tr>
<td>Me</td>
<td>COMe</td>
<td>b NEt₃</td>
<td>80</td>
</tr>
<tr>
<td>OEt</td>
<td>H</td>
<td>c NaOEt</td>
<td>44</td>
</tr>
</tbody>
</table>
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. In the case of 13c, the strong base is necessary because the formation of the second enolate 16 does not proceed easily.

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). In this reaction, dinitropyridone 2 serves as the synthetic equivalent of nitromalonaldehyde.

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

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.

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>Solv.</th>
<th>Temp./°C</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>OEt</td>
<td>COOEt</td>
<td>a</td>
<td>Pyridine</td>
<td>50</td>
</tr>
<tr>
<td>OEt</td>
<td>H</td>
<td>b</td>
<td>Pyridine</td>
<td>70</td>
</tr>
<tr>
<td>Me</td>
<td>H</td>
<td>d</td>
<td>DMF</td>
<td>70</td>
</tr>
<tr>
<td>COOEt</td>
<td>H</td>
<td>e</td>
<td>Pyridine</td>
<td>110</td>
</tr>
</tbody>
</table>

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). 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. 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.

<table>
<thead>
<tr>
<th>R^1</th>
<th>R^2</th>
<th>Ketone</th>
<th>Temp./°C</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>-(CH_2)_3-</td>
<td>19a</td>
<td>100</td>
<td>21a</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>-(CH_2)_3-</td>
<td>19b</td>
<td>100</td>
<td>21b</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>20a</td>
<td>120</td>
<td>22a</td>
<td>6</td>
</tr>
</tbody>
</table>

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). 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.

<table>
<thead>
<tr>
<th>Solv.</th>
<th>AcOH/equiv.</th>
<th>Yield/%</th>
<th>Recovery of 1/%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>22a</td>
<td>23a</td>
</tr>
<tr>
<td>MeOH</td>
<td>0</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>MeOH</td>
<td>1</td>
<td>40</td>
<td>56</td>
</tr>
<tr>
<td>MeOH</td>
<td>4</td>
<td>22</td>
<td>59</td>
</tr>
<tr>
<td>MeOH-AcOH (3:1)</td>
<td>24</td>
<td>9</td>
<td>21</td>
</tr>
<tr>
<td>AcOH&lt;sup&gt;a&lt;/sup&gt;</td>
<td>---</td>
<td>65</td>
<td>14</td>
</tr>
</tbody>
</table>

<sup>a</sup> 3 days

Next, the TCRT of pyrimidinone 1 with other aromatic ketones 20 was studied (Table 5). Six p-substituted acetonaphthones 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-Nitroacetonaphthone 20h showed similar reactivity to afford pyridone 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 methoxyacetonaphthones 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. Pyridylpyrimidines 22n and 22o were predominantly formed in cases of acetylpyridines 20m 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.

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield/%</th>
<th>Ratio of 22/23</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-NH₂C₆H₄</td>
<td>b</td>
<td>trace 47</td>
</tr>
<tr>
<td>4-AcNH₂C₆H₄</td>
<td>c</td>
<td>7</td>
</tr>
<tr>
<td>4-MeO₃C₆H₄</td>
<td>d</td>
<td>20</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>e</td>
<td>25</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>a</td>
<td>49</td>
</tr>
<tr>
<td>4-ClC₆H₄</td>
<td>f</td>
<td>37</td>
</tr>
<tr>
<td>4-NO₂C₆H₄</td>
<td>g</td>
<td>52</td>
</tr>
<tr>
<td>3-NO₂C₆H₄</td>
<td>h</td>
<td>38</td>
</tr>
<tr>
<td>2-NO₂C₆H₄</td>
<td>i</td>
<td>0</td>
</tr>
<tr>
<td>3-MeO₂C₆H₄</td>
<td>j</td>
<td>27</td>
</tr>
<tr>
<td>2-MeO₂C₆H₄</td>
<td>k</td>
<td>30</td>
</tr>
<tr>
<td>2,4-(MeO)₂C₆H₅</td>
<td>l</td>
<td>19</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>m</td>
<td>44</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>n</td>
<td>44</td>
</tr>
<tr>
<td>2-Pyridyl</td>
<td>o</td>
<td>49</td>
</tr>
<tr>
<td>2-Pyrolyl⁺</td>
<td>p</td>
<td>0</td>
</tr>
<tr>
<td>3-Pyrolyl⁺</td>
<td>q</td>
<td>0</td>
</tr>
<tr>
<td>2-Thienyl⁺</td>
<td>r</td>
<td>0</td>
</tr>
<tr>
<td>2-Furyl</td>
<td>s</td>
<td>13</td>
</tr>
</tbody>
</table>

A plausible mechanism for this TCRT is shown in Scheme 10. 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, nitopyridine 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

<sup>7</sup> days
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.

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

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeOC₆H₄</td>
<td>d</td>
</tr>
<tr>
<td>4-MeC₆H₄</td>
<td>e</td>
</tr>
<tr>
<td>C₆H₅</td>
<td>a</td>
</tr>
<tr>
<td>4-NO₂C₆H₄</td>
<td>g</td>
</tr>
</tbody>
</table>
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). In cases of cyclopentanone 19b and cyclohexanone 19a, cycloalka[dl]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.

![Reaction Scheme](image)

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

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Solv.</th>
<th>Yield/%</th>
<th>Ratio 21/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 19b</td>
<td>MeOH</td>
<td>85</td>
<td>0</td>
</tr>
<tr>
<td>2 19a</td>
<td>MeOH</td>
<td>71</td>
<td>0</td>
</tr>
<tr>
<td>3 19c</td>
<td>MeOH</td>
<td>11</td>
<td>79</td>
</tr>
<tr>
<td>3 19c</td>
<td>AcOH</td>
<td>90</td>
<td>0</td>
</tr>
<tr>
<td>4 19d</td>
<td>MeOH</td>
<td>67</td>
<td>17</td>
</tr>
</tbody>
</table>

**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).16 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-aminopyridines 31.

<table>
<thead>
<tr>
<th>R^2</th>
<th>R^1</th>
<th>Yield/%</th>
<th>31</th>
<th>14</th>
</tr>
</thead>
<tbody>
<tr>
<td>COOEt</td>
<td>H</td>
<td>d</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>COOMe</td>
<td>H</td>
<td>f</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>COOPr</td>
<td>H</td>
<td>g</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>COO(2-Pentyl)</td>
<td>H</td>
<td>h</td>
<td>81</td>
<td>12</td>
</tr>
<tr>
<td>COOMe</td>
<td>Me</td>
<td>i</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>COOMe</td>
<td>MeO</td>
<td>j</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>CONH₂</td>
<td>H</td>
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<td>COMe</td>
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<td>45</td>
</tr>
</tbody>
</table>
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.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Enamine</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R&lt;sup&gt;1&lt;/sup&gt;</td>
<td>R&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>OEt</td>
<td>Pr</td>
</tr>
<tr>
<td>OEt</td>
<td>i-Pr</td>
</tr>
<tr>
<td>OEt</td>
<td>4-MeOC&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>OEt</td>
<td>Pr</td>
</tr>
<tr>
<td>Me</td>
<td>Pr</td>
</tr>
<tr>
<td>Ph</td>
<td>Pr</td>
</tr>
<tr>
<td>OEt</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
</tr>
<tr>
<td>OEt</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;CHMeOH</td>
</tr>
<tr>
<td>OEt</td>
<td>CHMeCH&lt;sub&gt;2&lt;/sub&gt;OH</td>
</tr>
<tr>
<td>OEt</td>
<td>CMe&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
</tr>
</tbody>
</table>

Scheme 13. Preparation of β-functionalized enamines 37.


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<sup>3</sup>. When pyridone 2 was reacted with cyclohexanone 19a in the presence of ammonia, cyclohexa[8]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 acetonaphone 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.

![TCRT reaction diagram]

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>-(CH$_2$)$_4$-</td>
<td>19a</td>
<td>40a</td>
</tr>
<tr>
<td>-(CH$_3$)$_3$-</td>
<td>19b</td>
<td>40b</td>
</tr>
<tr>
<td>H</td>
<td>Ph</td>
<td>20a</td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>20t</td>
</tr>
</tbody>
</table>

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 acetonaphone 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-nitroacetonaphone 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 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.

<table>
<thead>
<tr>
<th>NH$_4$OAc /equiv.</th>
<th>Time/h</th>
<th>Yield/%</th>
<th>Ratio of 41a/42a</th>
<th>Ratio of exo-42a/endo-42a</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>24</td>
<td>19</td>
<td>61</td>
<td>24/76</td>
</tr>
<tr>
<td>5</td>
<td>24</td>
<td>43</td>
<td>46</td>
<td>48/52</td>
</tr>
<tr>
<td>10</td>
<td>24</td>
<td>64</td>
<td>25</td>
<td>72/28</td>
</tr>
<tr>
<td>15</td>
<td>24</td>
<td>79</td>
<td>0</td>
<td>100/0</td>
</tr>
<tr>
<td>5$^a$</td>
<td>7</td>
<td>92</td>
<td>5</td>
<td>95/5</td>
</tr>
<tr>
<td>15$^a$</td>
<td>5</td>
<td>90</td>
<td>0</td>
<td>100/0</td>
</tr>
</tbody>
</table>

$^a$Microwave heating was used.

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 $41\text{a}$.

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 $20\text{g}$, larger amounts of ammonium acetate (longer reaction time) were necessary for the efficient TCRT, and small amount of $42\text{g}$ was detected. Similar tendency was also observed when heteroaromatic ketones $20\text{m-s}$ 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.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>NH$_2$OAc/ equiv.</th>
<th>Yield%</th>
<th>$41$</th>
<th>$42$</th>
<th>$41+42$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ar</td>
<td>R</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C$_6$H$_5$</td>
<td>H a</td>
<td>5</td>
<td>43</td>
<td>46</td>
<td>89</td>
</tr>
<tr>
<td>C$_6$H$_5$</td>
<td>H a</td>
<td>15</td>
<td>79</td>
<td>0</td>
<td>79</td>
</tr>
<tr>
<td>4-MeOC$_6$H$_4$</td>
<td>H d</td>
<td>$5^{a,b}$</td>
<td>95</td>
<td>0</td>
<td>95</td>
</tr>
<tr>
<td>3-MeOC$_6$H$_4$</td>
<td>H j</td>
<td>10</td>
<td>97</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>2-MeOC$_6$H$_4$</td>
<td>H k</td>
<td>5</td>
<td>94</td>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td>4-MeC$_6$H$_4$</td>
<td>H e</td>
<td>5</td>
<td>88</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>4-ClC$_6$H$_4$</td>
<td>H f</td>
<td>10</td>
<td>96</td>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>4-NO$_2$C$_6$H$_4$</td>
<td>H g</td>
<td>15</td>
<td>93</td>
<td>2</td>
<td>95</td>
</tr>
<tr>
<td>4-Pyridyl</td>
<td>H n</td>
<td>15</td>
<td>66</td>
<td>33</td>
<td>99</td>
</tr>
<tr>
<td>3-Pyridyl</td>
<td>H m</td>
<td>15</td>
<td>97</td>
<td>0</td>
<td>97</td>
</tr>
<tr>
<td>2-Pyridyl</td>
<td>H o</td>
<td>15</td>
<td>80</td>
<td>12</td>
<td>92</td>
</tr>
<tr>
<td>2-Pyrrolyl$^p$</td>
<td>H p</td>
<td>10</td>
<td>87</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>2-Thienyl$^q$</td>
<td>H r</td>
<td>10</td>
<td>85</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>2-Furyl</td>
<td>H s</td>
<td>5</td>
<td>87</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>C$_6$H$_5$</td>
<td>Me t</td>
<td>$15^{a,c}$</td>
<td>98</td>
<td>0</td>
<td>98</td>
</tr>
<tr>
<td>C$_6$H$_5$</td>
<td>Pr u</td>
<td>$15^{a,c}$</td>
<td>97</td>
<td>0</td>
<td>97</td>
</tr>
</tbody>
</table>

$^a$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 tri-substituted 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.**

<table>
<thead>
<tr>
<th>Ketone</th>
<th>NH$_2$OAc/ equiv.</th>
<th>Temp./°C</th>
<th>Time/h</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-MeOC$_6$H$_4$</td>
<td>H 51a</td>
<td>15</td>
<td>80(^{°})</td>
<td>4</td>
</tr>
<tr>
<td>4-ClC$_6$H$_4$</td>
<td>H 51b</td>
<td>30</td>
<td>65</td>
<td>24</td>
</tr>
<tr>
<td>H</td>
<td>H 51c</td>
<td>30</td>
<td>80(^{°})</td>
<td>4</td>
</tr>
<tr>
<td>Me</td>
<td>Me 51d</td>
<td>30</td>
<td>65</td>
<td>24</td>
</tr>
<tr>
<td>2,6,6-trimethylcyclohexenyl</td>
<td>H 51f</td>
<td>30</td>
<td>80(^{°})</td>
<td>6</td>
</tr>
</tbody>
</table>

\(^{a}\)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.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>a 87</td>
</tr>
<tr>
<td>Et</td>
<td>b 80</td>
</tr>
<tr>
<td>Me,Si</td>
<td>c 54c 24/54d 60*</td>
</tr>
</tbody>
</table>

*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. 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.

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

![Chemical structure](image)

<table>
<thead>
<tr>
<th>R</th>
<th>NH$_2$OAc equiv.</th>
<th>Yield/%</th>
<th>Recovery of 2/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et</td>
<td>a 5</td>
<td>26</td>
<td>66</td>
</tr>
<tr>
<td>Et</td>
<td>a 10</td>
<td>75</td>
<td>20</td>
</tr>
<tr>
<td>Et</td>
<td>a 15</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>Et</td>
<td>a 15</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>Me</td>
<td>b 15</td>
<td>52</td>
<td>0</td>
</tr>
<tr>
<td>i-Pr</td>
<td>c 15</td>
<td>71</td>
<td>16</td>
</tr>
<tr>
<td>PhCH$_3$</td>
<td>d 15</td>
<td>34</td>
<td>21</td>
</tr>
<tr>
<td>t-Bu</td>
<td>e 15</td>
<td>29</td>
<td>63</td>
</tr>
<tr>
<td>t-Bu</td>
<td>e 15</td>
<td>68</td>
<td>0</td>
</tr>
<tr>
<td>Ph</td>
<td>f 15</td>
<td>47</td>
<td>44</td>
</tr>
<tr>
<td>Ph</td>
<td>f 15</td>
<td>75</td>
<td>0</td>
</tr>
</tbody>
</table>

*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](image)

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). 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 (R1, R2=-(CH2)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>
<thead>
<tr>
<th>Ketone</th>
<th>Time/h</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>19a</td>
<td>24</td>
<td>66a</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>1”</td>
<td></td>
<td>97</td>
</tr>
<tr>
<td>19b</td>
<td>24</td>
<td>66b</td>
<td>67</td>
</tr>
<tr>
<td></td>
<td>2”</td>
<td></td>
<td>87</td>
</tr>
<tr>
<td>19c</td>
<td>24</td>
<td>66c</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>1”</td>
<td></td>
<td>91</td>
</tr>
<tr>
<td>19d</td>
<td>24</td>
<td>66d</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>1”</td>
<td></td>
<td>95</td>
</tr>
<tr>
<td>19e</td>
<td>24</td>
<td>66e</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>2”</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>19f</td>
<td>24</td>
<td>66f</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>3”</td>
<td></td>
<td>89</td>
</tr>
<tr>
<td>19g</td>
<td>24</td>
<td>66g</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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. 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.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Yield/%</th>
<th>R1</th>
<th>R2</th>
<th>65</th>
<th>62</th>
<th>62'</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>a</td>
<td>50</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>a</td>
<td>83</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>b</td>
<td>51</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et</td>
<td>H</td>
<td>c</td>
<td>66</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>i-Pr</td>
<td>H</td>
<td>d</td>
<td>58</td>
<td>0</td>
<td>31</td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td>H</td>
<td>e</td>
<td>83</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Et</td>
<td>Et</td>
<td>f</td>
<td>67</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pr</td>
<td>Pr</td>
<td>g</td>
<td>74</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C6H5</td>
<td>Pr</td>
<td>h</td>
<td>62</td>
<td>24</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>C6H5</td>
<td>C6H5</td>
<td>i</td>
<td>8</td>
<td>81</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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
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.

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Amine</th>
<th>Product</th>
<th>Yield/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>R2</td>
<td>R3</td>
<td>R4</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>58a</td>
<td>Pr</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>58a</td>
<td>Pr</td>
</tr>
<tr>
<td>Me</td>
<td>Me</td>
<td>58a</td>
<td>Et</td>
</tr>
<tr>
<td>Et</td>
<td>H</td>
<td>58c</td>
<td>Pr</td>
</tr>
<tr>
<td>Et</td>
<td>H</td>
<td>58c</td>
<td>Pr</td>
</tr>
<tr>
<td>Pr</td>
<td>H</td>
<td>58e</td>
<td>Pr</td>
</tr>
<tr>
<td>Pr</td>
<td>H</td>
<td>58e</td>
<td>Pr</td>
</tr>
<tr>
<td>Pr</td>
<td>H</td>
<td>58f</td>
<td>Pr</td>
</tr>
<tr>
<td>Pr</td>
<td>H</td>
<td>58f</td>
<td>Pr</td>
</tr>
<tr>
<td>C6H5</td>
<td>Pr</td>
<td>58h</td>
<td>Pr</td>
</tr>
<tr>
<td>C6H5</td>
<td>C6H5</td>
<td>58i</td>
<td>Pr</td>
</tr>
</tbody>
</table>
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 (R3 and R4).

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 aza-heterocyclic 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
