Review

Synthesis of Nitroaromatic Compounds via Three-Component Ring Transformations

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Abstract: 1-Methyl-3,5-dinitro-2-pyridone serves as an excellent substrate for nucleophilic-type ring transformation because of the electron deficiency and presence of a good leaving group. In this review, we focus on the three-component ring transformation (TCRT) of dinitropyridone involving a ketone and a nitrogen source. When dinitropyridone is allowed to react with a ketone in the presence of ammonia, TCRT proceeds to afford nitropyridines that are not easily produced by alternative procedures. Ammonium acetate can be used as a nitrogen source instead of ammonia to undergo the TCRT, leading to nitroanilines in addition to nitropyridines. In these reactions, dinitropyridone serves as a safe synthetic equivalent of unstable nitromalonaldehyde.

Keywords: dinitropyridone; three-component ring transformation; nitropyridine; nitroaniline; bicyclic intermediate; nitromalonaldehyde

1. Introduction

1.1. Ring Transformation

Ring transformation is a powerful synthetic method that accompanies the “scrap and build” of cyclic compounds. The general concept of this method is shown in Scheme 1. When a substrate (A + B) is reacted with a reagent (C), the partial structure (A) of the substrate is transferred to the reagent to construct a new ring system (A + C), simultaneously eliminating the leaving group (B). This reaction facilitates the synthesis of functionalized compounds that are not easily afforded by alternative procedures.

Scheme 1. General concept of the ring transformation.

There are four types of ring transformations, namely, Diels–Alder-type, decarboxylative, degenerate, and nucleophilic-type ring transformations (Scheme 2). The most commonly used methods are Diels–Alder-type ring transformation (type a) [1–3] and decarboxylative ring transformation (type b) [4–6], wherein the substrates have a good leaving group as a partial structure (molecular nitrogen and carbon dioxide, respectively). Degenerated ring transformation was energetically studied by van der Plas [7]. This reaction proceeds through the addition of nucleophile–ring opening–ring closure (ANOROC) mechanism. The nucleophilic-type ring transformation has not been studied extensively as compared to the other three ring transformations [8–13].
1.2. Suitable Substrate for Nucleophilic-Type Ring Transformation

To cause the nucleophilic-type ring transformation, a substrate requires three conditions: (1) high electron deficiency, (2) low aromatic stabilizing energy, and (3) the presence of a good leaving group as the partial structure. Based on these considerations, 1-methyl-3,5-dinitro-2-pyridone (1) appears to be a suitable structure for this purpose (Figure 1). The electron-withdrawing nitro and carbonyl groups, besides the ring nitrogen atoms, diminish the electron density of this compound. As shown in the resonance form, though pyridone 1 exhibits aromaticity, it is easily destroyed because of the minimal contribution of the betaine resonance structure. In addition, the partial structure can be easily eliminated as a stable anion of nitroacetamide. When the ring transformation proceeds at the 4- and 6-positions accompanied by elimination of anionic nitroacetamide, the C4–C5–C6 moiety of pyridone 1 serves as the synthetic equivalent of nitromalonaldehyde (NMA-H). NMA-H is typically considered a synthon in retrosynthesis. However, NMA-H is too unstable to be isolated. Instead, its sodium salt (NMA-Na) has been widely used, although it should be handled carefully because of the explosive impurities [14]. Thus, it is necessary to develop a safe synthetic equivalent of NMA-H [15]. From this perspective, a nucleophilic-type ring transformation using pyridone 1 is a useful synthetic method for versatile nitro compounds because of its higher safety.

Figure 1. Resonance structure of dinitropyridone 1 and its partial structure.

Dinitropyridone 1 can be easily prepared from pyridine in three steps. After the conversion of pyridine to N-methylpyridinium salt 2 by dimethyl sulfate, oxidation with ferricyanide under alkaline conditions in one pot leads to the formation of 1-methyl-2-pyridone 3. The subsequent nitration of 3 by fuming nitric acid with sulfuric acid forms dinitropyridone 1 (Scheme 3).
2. Ring Transformation of 1 with Carbon Dinucleophiles

2.1. Aminolysis of Dinitropyridone 1

Dinitropyridone 1 serves as a suitable substrate for nucleophilic-type ring transformation, which can be confirmed through aminolysis. The ring opening reaction of 1 proceeds upon treatment with amine, leading to nitro-substituted azadienamine 4 and dianionic product 5 (Scheme 4) [16]. The latter is formed by the addition of anionic nitroacetamide to pyridone 1. This reaction is initiated by the addition of amines at the 4- and 6-positions. The subsequent cleavage of two C–C bonds furnishes azadienamine 4, which indicates that anionic nitroacetamide serves as a good leaving group. However, it also serves as a nucleophile to form adduct 5 (Scheme 4).

Azadienamine 4 can be used as an excellent ligand to form diverse metal complexes [17–19]. From the perspective of ligand preparation, this reaction is not suitable, as dinitropyridone 1 is consumed by eliminated nitroacetamide. This problem is overcome by using 1-methyl-5-nitro-2-pyrimidinone (6) instead of dinitropyridone 1, as the eliminated urea is less nucleophilic than nitroacetamide and can thus avoid the consumption of 6 (Scheme 5) [20].

2.2. Reaction of Dinitropyridone 1 with 1,3-dicarbonyl Compounds

The landmark work on nucleophilic-type ring transformation was achieved by Matsumura et al. (Table 1) [21,22]. When dinitropyridone 1 is allowed to react with sodium enolate of diethyl acetylatedicarboxylate 7a, the ring transformation can afford a high yield of 2,6-difunctionalized 4-nitrophenol 8a. This reaction can be applied to reagents 7b–d, each possessing one active methylene group, to afford the corresponding nitrophenols 8b–d.
Table 1. Synthesis of functionalized 4-nitrophenols by ring transformation.

| R¹   | R²    | Solv. | Temp./°C | Yield/% |
|------|-------|-------|----------|---------|
| OEt  | COOEt | a     | 50       | 91      |
| OEt  | H     | b     | 70       | 61      |
| Me   | H     | c     | 70       | 53      |
| COOEt| H     | d     | 110      | 42      |

A plausible mechanism for this reaction is illustrated in Scheme 6. The enolate ion 7b attacks the 4-position of pyridone 1 to afford adduct intermediate 9, and the regenerated enolate 10 attacks the 6-position of 1, leading to bicyclic intermediate 11, from which the stable anionic nitroacetamide is eliminated to furnish nitrophenol 8b; the bicyclic intermediate 11 can be isolated from the reaction mixture [21]. In addition, the reaction of nitropyrimidinone 6 and diethyl acetonedicarboxylate 7a also affords bicyclic product 12 in high yield because unstable anionic urea cannot eliminate [23] (Scheme 7). Based on these results, the ring transformation is considered to proceed via bicyclic intermediates.

Scheme 6. A plausible mechanism for the formation of 8.

Scheme 7. Synthesis of bicyclic compound 12.

3. Three-Component Ring Transformation (TCRT)

3.1. General Concept of TCRT

As mentioned previously, dinitropyridone 1 is highly reactive when used as the substrate in the nucleophilic-type ring transformation. The 1,3-dicarbonyl compounds 7 are excellent dinucleophilic reagents. However, the diversity of the available 1,3-dicarbonyl
compounds 7 is low, which only affords few products 8. If simple ketones can be used instead of 7, the synthetic utility of the ring transformation should be improved. In such cases, it is necessary to use a nitrogen source as ketone is a mononucleophilic reagent. This process is referred to as three-component ring transformation (TCRT) (Scheme 8).

Scheme 8. The general concept of TCRT.

3.2. TCRT Using Ammonia as the Nitrogen Source

Tohda et al. studied the reaction of dinitropyridone 1 with ketones in the presence of ammonia (Table 2) [24]. When a methanol solution of pyridone 1 is heated with cyclohexanone 13a in the presence of ammonia (20 equiv.) at 70 °C (condition A), cyclohexa[b]pyridine 14a is obtained in 83% yield. However, this method suffers from the narrow scope of ketones. The TCRT using cyclopentanone 13b under the same conditions forms cyclopenta[b]pyridine 14b in a considerably lower yield. When acetophenone 15a is allowed to react under the same conditions, TCRT proceeds similarly; however, the yield is low owing to the competitive ammonolysis of substrate 1. To overcome this disadvantage, it is important to employ severe conditions (heating with larger amounts of ammonia (140 equiv.) at 120 °C in an autoclave (condition B)). This reaction is applicable to other aromatic ketones 15b–h to afford the corresponding 2-(het)aryl-5-nitropyridines 16b–h, respectively. The ketone is not required to have an acetyl group, and propiophenone 15i undergoes the TCRT, leading to trisubstituted pyridine 16i. In the case of aromatic ketones 15a–i, employment of condition B is effective for obtaining pyridines 16a–i in better yields. In contrast, ketone 15j possessing an α’-proton forms pyridine 16j with better yield under condition A, as severe conditions cause side reactions. Indeed, pinacolone 15k without an α’-proton undergoes the TCRT more efficiently.

Table 2. TCRT using dinitropyridine 1, ketones, and ammonia, leading to nitropyridines.

| Ketone | Condition 1 | Product | Yield/% |
|--------|-------------|---------|--------|
| R1     | R2          |         |        |
| –(CH₂)₄– | 13a | A | 14a | 83 |
| –(CH₂)₃– | 13b | A | 14b | 27 |
| H      | Ph          | 15a     | A | 16a | 44 |
| H      | Ph          | 15a     | B | 16a | 81 |
| H      | 4-NH₂C₆H₄ | 15b     | B | 16b | 44 |
| H      | 4-MeOC₆H₄ | 15c     | B | 16c | 64 |
| H      | 4-MeC₆H₄  | 15d     | B | 16d | 30 |
| H      | 4-NO₂C₆H₄ | 15e     | B | 16e | 27 |
| H      | 2-pyridyl  | 15f     | B | 16f | 72 |
| H      | 2-furyl    | 15g     | B | 16g | 62 |
| H      | 2-thienyl  | 15h     | B | 16h | 56 |
| Me     | Ph          | 15i     | A | 16i | 10 |
| Me     | Ph          | 15i     | B | 16i | 37 |
| H      | i-Pr        | 15j     | A | 16j | 36 |
| H      | i-Pr        | 15j     | B | 16j | 21 |
| H      | tert-Bu     | 15k     | B | 16k | 69 |

1 Condition A: ketone (2 equiv.), ammonia (20 equiv.), heating at 70 °C for 3 h; Condition B: ketone (2 equiv.), ammonia (140 equiv.), heating at 120 °C for 3 h in an autoclave.
This TCRT efficiently proceeds under mild conditions (condition A) only when cyclohexanone 13a is used as the reagent. In other words, this protocol is an effective approach to [b]-fused 5-nitropyridines. This reaction is often employed for synthesizing biologically active compounds, medicines, and their synthetic intermediates.

Cyclohexa[b]pyridines 14c–f (Figure 2) are synthesized by TCRT using ammonia as a nitrogen source, in which functional groups such as carbamate, ester, and acetal are tolerated during the reaction [25–30]. Notably, multiple functionalities remain during the TCRT to afford a complex structure 14f. Piperidine-4-ones are usable as reagents in TCRT to produce 5,6,7,8-tetrahydro-1,6-naphthyridines 14g–m [31–37]. Not only N-alkylated derivatives 14g–i, but also N-aryl derivative 14j and N-acyl derivatives 14k–m are available. When unsymmetrical pieridine-3-one is used, two condensed pyridines are formed, including 1,5-naphthyridine 14n [38]. Tetrahydropyran-4-one can be used for this method, which makes pyranopyridines 14o and 14p available [39–41].

Figure 2. Nitropyridines condensed with a six-membered ring.

Cycloalkanones with different ring sizes can also be used as reagents in this TCRT (Figure 3). Cyclopenta[b]pyridine 14q, even though it has a complex structure, can be synthesized by altering the cyclopentanone to the corresponding one [42,43]. When pyrrolidine-3-one is used, 4-azaindole 14r is obtained [44].
Furthermore, cyclohepta[b]pyridine 14s can be synthesized upon treatment of pyridone 1 with cycloheptanone 13s [45,46]. When aza-containing cycloheptanone 13t and bridged cycloheptanone 13u are employed, cycloheptapyridine 14t [47] and tricyclic pyridines 14u [36] are formed. Nitropyridines condensed with a larger ring (from eight to eleven membered rings) can be prepared by only altering cycloalkanones [48,49].

3.3. Reaction Mechanism of TCRT

Two plausible mechanisms of TCRT are illustrated in Scheme 9. As mentioned in Section 2.1, both the 4- and 6-positions of dinitropyridone 1 are highly electrophilic, and are thus attacked by the enol form of 15a and ammonia to form adduct intermediate 17 (path a) [24]. The same product, 16a, is obtained when the ammonia and enol switch positions to attack. The amino group intramolecularly attacks the carbonyl group derived from 15a, leading to bicyclic intermediate 18, from which nitroacetamide is eliminated and accompanied by aromatization to afford nitropyridine 16a. Another possibility is that ketones are converted to enamines, which might serve as an actual nucleophile (path b) [50]. After adding the enamine to pyridone 1, the amino group intramolecularly attacks the 6-position to form bicyclic intermediate 20, and elimination of nitroacetamide leads to the formation of nitropyridine 16a.

3.4. TCRT Using Ammonium Acetate as the Nitrogen Source

This TCRT proceeds efficiently when reactive cycloalkanones 13 are employed as reagents. In other words, when less reactive ketones such as 15a are used, both electrophilic sites of 1 are attacked by ammonia, which undergoes ammonolysis to consume pyridone...
Le et al. mitigated this problem by using a less nucleophilic ammonium acetate as a nitrogen source instead of ammonia. When pyridone 1 is reacted with acetophenone 15a and three equivalents of ammonium acetate, nitropyridine 16a and a bicyclic product 21a are obtained (Table 3) [51]. The former is produced by TCRT, and the latter is formed by the insertion of 15a and nitrogen between the N1 and C2 positions of pyridone 1. Isolated 21a can be converted to 16a upon treatment with ammonium acetate, which indicates that there is equilibrium between these products. Thus, 16a is a thermodynamically controlled product, and 21a is a kinetically controlled product. The ratio of 16a increases as larger amounts of ammonium acetate or microwave heating are used. The use of larger amounts of ammonium acetate prolongs the actual reaction time, because it decomposes to gaseous ammonia and acetic acid upon heating.

Table 3. TCRT using pyridone 1 with different amounts of ammonium acetate.

| NH₄OAc /equiv. | Time/h | Yield/%  | Ratio of 16a/21a | Ratio of exo-21a/endo-21a |
|---------------|--------|----------|----------------|------------------------|
| 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          | —                      |
| 5¹            | 7      | 92/5     | 95/5           | 60/40                  |
| 15¹           | 5      | 90/0     | 100/0          | —                      |

¹ Microwave heating is used.

The formation of bicyclic product 21a is considered to proceed as shown in Scheme 10. After addition of an enol form of 15a to the 4-position of 1, the acyl moiety of 22 is converted to enamine 19 by the ammonium ion. When the amino group of 19 intramolecularly attacks at the 6-position (path c), nitropyridine 16a is formed via bicyclic intermediate 20, as illustrated in Scheme 9. In contrast, the amino group of 19 attacks the carbonyl group, and degenerated ring transformation proceeds to afford 24. After prototropy leading to 25, the methylenamino group attacks the imino functionality to afford bicyclic product 21a. However, the aminal structure of 21a is easily cleaved under acidic conditions to regenerate intermediate 19, which furnishes aromatized product 16a, predominantly under severe conditions.

Scheme 10. A plausible mechanism for the formation of bicyclic product 21a.
This method is applicable to other aromatic ketones 15a–q (Table 4). TCRT efficiently proceeds in reactions using both electron-rich and electron-poor ketones, among which electron-poor ketones reveal lower reactivity and require larger amounts of ammonium acetate (longer reaction time). In cases of electron-poor ketones 15e, 15f, and 15o, bicyclic products 21e, 21f, and 21o are obtained, respectively. The ketone is not required to have an acetyl group, and ketones 15i and 15q afforded the corresponding trisubstituted pyridines 16i and 16q in almost quantitative yields, respectively.

Table 4. TCRT with other aromatic ketones 15.

| Ketone | NH₄OAc/ equiv. | Yield/% | 16 | 21 | 16 + 21 |
|--------|----------------|---------|----|----|---------|
| Ph     | H a            | 15      | 79 | 0  | 79      |
| 4-MeOC₆H₄ | H c        | 5 1,2  | 95 | 0  | 95      |
| 3-MeOC₆H₄ | H l        | 10     | 97 | 0  | 97      |
| 2-MeOC₆H₄ | H m        | 5      | 94 | 0  | 94      |
| 4-MeC₆H₄  | H d        | 5      | 88 | 0  | 88      |
| 4-ClC₆H₄  | H n        | 10     | 96 | 0  | 96      |
| 4-NO₂C₆H₄ | H e        | 15     | 93 | 2  | 95      |
| 4-pyridyl | H o        | 15     | 66 | 33 | 99      |
| 3-pyridyl | H p        | 15     | 97 | 0  | 97      |
| 2-pyridyl | H f        | 15     | 80 | 12 | 92      |
| 2-furyl  | H g        | 5      | 87 | 0  | 87      |
| 2-thienyl | H h        | 10     | 85 | 0  | 95      |
| Ph     | Me i         | 15 1,3 | 98 | 0  | 98      |
| Ph     | Pr q         | 15 1,3 | 97 | 0  | 97      |

1 Microwave heating is used. 2 For 6 h. 3 At 80 °C for 2 h.

α,β- Unsaturated ketones 26 and 28 can also be used for the TCRT (Tables 5 and 6) [52]. These ketones are less reactive, requiring 15–30 equivalents of ammonium acetate. Among the three styryl ketones, electron-rich ketone 26b reveals higher reactivity, which facilitates the approach to electron-deficient pyridone 1. The reaction with alkynyl ketones 28 efficiently furnishes alkynylpyridines 29. When silylethynyl ketone 28c is used, the desilylated product 29d is also obtained.

Table 5. TCRT with alkenyl ketones.

| Ketone | NH₄OAc/ equiv. | Temp./°C | Time/h | Yield/% |
|--------|----------------|----------|--------|---------|
| R¹     | R²            |          |        |         |
| H      | Ph a          | 15       | 80 ¹   | 4       | 82      |
| H      | 4-MeOC₆H₄ b  | 30       | 65     | 24      | 94      |
| H      | 4-ClC₆H₄ c   | 30       | 80 ¹   | 4       | 75      |
| H      | H d           | 30       | 65     | 24      | 0       |
| Me     | Me e          | 15       | 80 ¹   | 2       | 25      |
| H      | 2,4,6-      | 30       | 80 ¹   | 6       | 79      |

¹ Microwave heating is used.
For the C–C bond formation on the pyridine framework, the Heck, Suzuki, Stille, and Sonogashira reactions are commonly used. However, these methods require the use of poisonous and expensive transition metals and a purification step to avoid metal contamination of the products. In addition, troublesome multistep reactions are necessary to prepare the substrates for these reactions (2-halo-5-nitropyridines). Thus, the TCRT is a metal-free supplementary method for the abovementioned reactions.

### 3.5. Preparation of 3-substituted 5-nitropyridines 31 by TCRT

When dinitropyridone 1 is allowed to react with aldehyde 30 and ammonia as a nitrogen source, TCRT does not occur at all. In such a case, the use of ammonia/ammonium acetate as a mixed nitrogen source is effective to undergo the TCRT. However, the yields of 31 are low, as highly reactive aldehyde 30 causes side reactions such as self-condensation [24,53]. Using only ammonium acetate helps the TCRT to afford the corresponding pyridines 31a–f in moderate to high yields (Table 7) [54]. This protocol facilitates the introduction of not only a bulky alkyl group such as a tert-butyl but also an aromatic group into the pyridine framework with simple experimental manipulations.

### Table 6. TCRT with alkynyl ketones 28.

| R  | Yield/% |
|----|---------|
| Ph | a 87    |
| Et | b 80    |
| Me3Si | c 29  |

1 Desilylated product 29d (R = H) is also obtained.

Microwave heating is used.

### 3.6. TCRT Using Cyclic Ketones 13

Dinitropyridone 1 undergoes TCRT with cycloalkanone 13 in the presence of ammonium acetate, leading to cycloalka[b]pyridines 14 (Table 8) [55]. Cycloalkanones 13 with various ring sizes efficiently react under conventional heating (Condition C) to afford the corresponding nitropyridines condensed with five-, six-, seven-, and eight-membered rings. The reaction time is considerably shortened by using microwave heating (Condition D). In this reaction, the unsymmetrical ketone, 2-methylcyclohexanone 13aa, which reacts at the 6-position not at the 2-position, as aromatization is prevented by a methyl group in the

### Table 7. TCRT with aldehydes 30.

| R  | Yield/% |
|----|---------|
| Me | a 52    |
| Et | b 86    |
| i-Pr | c 71 |
| t-Bu | d 68  |
| PhCH2 | e 34 |
| Ph | f 75    |

Microwave heating is used.
latter case, can also be used as a reagent. When 2-cyclohexenone 13ab is used, migration of the double bond is observed, which may occur after the addition of ketone 13ab to pyridone 1 and the subsequent conversion to dienamine 32ab, leading to the formation of dienamine 33ab (Scheme 11).

Table 8. TCRT with cycloalkanones 13.

| Substrate | Product | Condition C | Condition D |
|-----------|---------|-------------|-------------|
|           |         | Time/h      | Yield/%    | Time/h      | Yield/%    |
| 14b       | 14b     | 24          | 67          | 2           | 87         |
| 14a       | 14a     | 24          | 95          | 1           | 97         |
| 14s       | 14s     | 24          | 94          | 1           | 91         |
| 14w       | 14w     | 24          | 85          | 1           | 95         |
| 14aa      | 14aa    | 24          | 83          | 2           | 86         |
| 14ab      | 14ab    | 24          | 59          | 3           | 89         |

Scheme 11. A plausible mechanism for the double bond migration.

3.7. Reconsideration about the Reaction Mechanism of TCRT

As shown in Scheme 10, the TCRT is initiated by the addition of the enol form of a ketone to the 4-position of dinitropyridine 1, after which the acyl group of adduct 19 is converted to enamine 20 by the ammonium ion. Enamine has an ambident property, where β-carbon is generally more nucleophilic than the amino group. In the case of adduct intermediate 19 derived from aromatic ketone 15, N-attack (path c) forms a six-membered ring to afford bicyclic intermediate 20, from which nitropyridine 16 is obtained, accompanied by the elimination of nitroacetamide (Scheme 12). In contrast, if a C-attack (path e) occurs, sterically strained four-membered ring 34 is formed. Hence, nitropyridine 16 is formed as the sole product in this TCRT. In cases of α,β-unsaturated ketones 26 and
and aldehydes 30, a similar reactivity is observed, as these carbonyl compounds have only one kind of α-hydrogen.

Scheme 12. Plausible mechanism using aromatic ketone 15 and cycloalkanone 13.

In the case of aliphatic ketones 36, two types of enamines (37 and 38) are possibly formed (Scheme 13). While the intermediate 37 cannot cause a C-attack similar to 19, the intermediate 38 can cause both N- and C-attacks to furnish bicyclic intermediates 41 and 42, respectively. From bicyclic intermediates 40 and 41, nitopyridine 43 is formed. In contrast, 2,6-disubstituted 4-nitroaniline 44 should form when nitroacetamide is eliminated from bicyclic intermediate 42. Thus, two ring-transformed products (43 and 44) are yielded when aliphatic ketones 36 are used as reagents.

Scheme 13. Plausible mechanisms of TCRT when an aliphatic ketone 36 is employed as reagent.
In the reactions of pyridone 1 with cycloalkanone 13, only nitropyridine 14 is formed (Table 8). Although the adduct of 1 and cycloalkanone 13 can form two kinds of enamines, one enamine can form a six-membered ring as a result of C-attack, and the formed intermediate 35 is too strained to be formed (Scheme 12).

3.8. TCRT Using Aliphatic Ketones 36

When dinitropyridone 1 is subjected to a reaction with aliphatic ketones 36 in the presence of ammonium acetate, two types of TCRT occur to afford nitropyridines 43 and nitroanilines 44 (Table 9) [56]. Generally, 2,6-disubstituted 4-nitroanilines 44 are prepared from the corresponding anilines by nitration under harsh reaction conditions, wherein protection and deprotection of the amino groups are necessary [57]. Furthermore, the preparation of this compound suffers from the limitation of Friedel–Crafts alkylation. There are several limitations for the Friedel–Crafts alkylation, such as the following: (1) The monoalkylated product undergoes further alkylation, (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, and (5) nitrobenzene and aniline do not facilitate the alkylation. The TCRT overcomes these disadvantages.

Table 9. Two kinds of TCRT using aliphatic ketones 36.

| Ketone | Yield/% | 44 | 43 | 43' |
|--------|---------|----|----|-----|
| R1     | R2      |    |    |     |
| Me     | Me      | 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  | —  |
| C6H5   | Pr      | h  | 62 | 24  | 13 |
| C6H5   | C6H5    | i  | 8  | 81  | —  |

1 Five equivalents of ammonium acetate are used.

When dinitropyridone 1 is reacted with 3-pentanone in the presence of five equivalents of ammonium acetate, nitroaniline 44a and nitropyridine 43a are obtained at 50% and 44%, respectively, resulting from two types of TCRT. In contrast, the ratio of 44a to 43a increases significantly without a decrease in total yield, indicating the presence of an equilibrium between bicyclic intermediates 42 and 41 (Scheme 13). The substituents can be modified by altering only the ketones 36 (Table 9). Monoalkylated nitroanilines 44c–e and unsymmetrical nitroanilines 44h and 44i are available from the corresponding unsymmetrical ketones 36. Furthermore, it is easy to prepare nitroanilines 44g–i possessing a propyl or phenyl group, which cannot be introduced by the Friedel–Crafts alkylation. However, steric repulsion by the phenyl groups prevents the formation of bicyclic intermediate 42i.

A combination of propylamine 45A and acetic acid can be used as a reagent instead of ammonium acetate, which facilitates N-modification of the amino group as well as the benzene ring of nitroaniline 46 (Table 10). This method is applicable to secondary amines, pyrrolidine 45B and diethylamine 45C, to afford N,N,2,6-tetrasubstituted 4-nitroanilines 46B and 46C, respectively. This reaction also enables the introduction of a propyl or phenyl
group into the benzene framework, which cannot be introduced by the Friedel–Crafts reaction.

Table 10. Synthesis of N,N,2,6-tetrasubstituted 4-nitroanilines 46 by TCRT using aliphatic ketones 36 and dialkylammonium acetate 45.

| Ketone | Amine | Product | Yield/% |
|--------|-------|---------|---------|
| R^1    | R^2   | R^3     | R^4     |         |         |
| Me     | Me    | 36a     | Pr      | H       | 45A     | 99      |
| Me     | Me    | 36a     | Et      | (CH_2)_4^- | 45B    | 98      |
| Me     | Me    | 36a     | Et      | Et      | 45C     | 98      |
| Et     | H     | 36c     | Pr      | H       | 45A     | 83      |
| Et     | H     | 36c     | -(CH_2)_4^- | 45B   | 68      |
| Pr     | H     | 36e     | Pr      | H       | 45A     | 77      |
| Pr     | H     | 36e     | -(CH_2)_4^- | 45B   | 87      |
| Pr     | H     | 36e     | Et      | Et      | 45C     | 51      |
| Pr     | H     | 36d     | Pr      | H       | 45A     | 83      |
| Et     | Et    | 36f     | Pr      | H       | 45A     | 69      |
| Et     | Et    | 36f     | -(CH_2)_4^- | 45B   | 68      |
| Pr     | Pr    | 36g     | Pr      | H       | 45A     | 81      |
| Pr     | Pr    | 36g     | -(CH_2)_4^- | 45B   | 59      |
| C_6H_5 | Pr    | 36h     | Pr      | H       | 45A     | 80      |
| C_6H_5 | C_6H_5| 36i    | Pr      | H       | 45A     | 82      |

As shown in Scheme 13, the TCRT proceeds through the C-attack of the intermediately formed enamine 38. This means that functionalized nitroanilines 48 can be prepared if a similar structure is available via an alternative route. For this purpose, relatively stable enamines 47 prepared from 1,3-dicarbonyl compounds 7 and amine 45 are considered suitable. When dinitropyridone 1 reacts with enamine 47, nucleophilic-type ring transformation proceeds to afford 2-functionalized 4-nitroaniline 48 (Table 11) [58]. This protocol facilitates the modification of the functional group and amino group of 48 by altering 1,3-dicarbonyl compounds 7 and amine 45. Diketones 7c and 7e as well as keto ester 7b can be used as 1,3-dicarbonyl compounds. These reagents are not required to possess an acetyl group (R^1 = H), and 7f undergoes similar ring transformations. Bulky amines such as tert-butyamines 45D and 45E and less nucleophilic anilines 45F and 45G can be used as amines. Even though amines have a functional group, the corresponding nitroaniline 48Hb is obtained. Furthermore, cyclic and acyclic secondary amines 45B and 45C can be used for this reaction, which results in 2-functionalized N,N-dialkyl-4-nitroanilines 48Bc, 48Ca, and 48Ce.
Table 11. Synthesis of 2-functionalized 4-nitroanilines 48.

| 1,3-Dicarbonyl Compound | Amine | Time/d | Product | Yield/% |
|-------------------------|-------|--------|---------|---------|
| R¹ R² R³ R⁴             |       |        |         |         |
| H Me 7c Pr H           |       | 45A    | 2       | 48Ac 57 |
| H Me 7c sc-Bu H        |       | 45D    | 2       | 48Ca 64 |
| H Me 7c tert-Bu H      |       | 45E    | 2       | 48Ca 39 |
| H Me 7c C₆H₅           |       | 45F    | 2       | 48Ac 23 |
| H Me 7c 4-MeC₆H₄       |       | 45G    | 2       | 48Gc 36 |
| H Me 7c -(CH₂)₄-       |       | 45B    | 2       | 48Bc 87 |
| H C₆H₅ 7e Pr H         |       | 45A    | 4       | 48 Ae 33 |
| H C₆H₅ 7e Et Et        |       | 45C    | 2       | 48Ce 45 |
| H OEt 7b Pr H          |       | 45A    | 1       | 48 Ab 61 |
| H OEt 7b HOCH₂CH₂ H    |       | 45H    | 1       | 48Hb 45 |
| H OEt 7b Et Et         |       | 45C    | 1       | 48Cb 57 |
| Et OEt 7f Pr H         |       | 45A    | 2       | 48Af 24 |

4. Conclusions

When dinitropyridone 1 is subjected to a reaction with cycloalkanones 13 in the presence of ammonia, nucleophilic-type TCRT efficiently proceeds to afford nitrated cycloalka[8]pyridines 14. In this reaction, pyridone 1 serves as a synthetic equivalent of unstable NMA-H. However, this method is applicable only to cycloalkanones 13, as the competitive ammonolysis of 1 cannot be ignored in cases of other types of ketones.

This disadvantage is overcome by using the less nucleophilic ammonium acetate as a nitrogen source instead of ammonia. Aromatic ketones 15, alkenyl ketones 26, alkynyl ketones 28, and aldehyde 30 undergo TCRT to furnish the corresponding pyridines that are not easily available by alternative methods, including transition-metal-catalyzed coupling reactions. When acyclic aliphatic ketones 36 are used as the reagent, the TCRT proceeds in different modes to give 4-nitroaniline derivatives 44. In this reaction, a combination of amine and acetic acid is usable, leading to the synthesis of N,N₂,2,6-tetrasubstituted 4-nitroanilines 46. Furthermore, functionalized nitroanilines 48 are available using enaminoles 47 as a reagent.

In addition to the easy modification of the product framework, the reaction is conducted under mild conditions with simple experimental manipulations, which are more practical. These features facilitate the construction of a library of compounds that are not easily available by other methods. In particular, compounds possessing both electron-donating and electron-withdrawing groups (push–pull systems) are necessary for developing novel functional materials such as medicines, agrochemicals, and non-linear optical materials. Therefore, the TCRT will provide a new synthetic tool for researchers studying in this field.

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