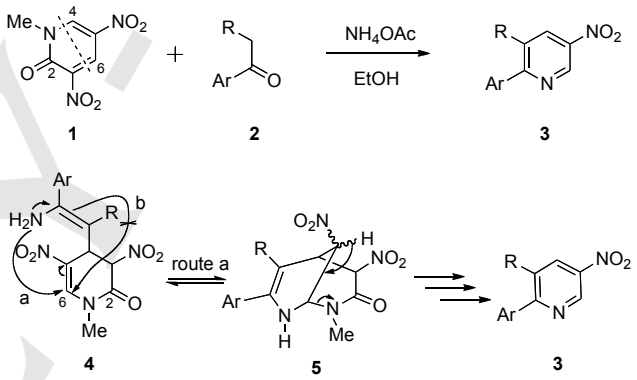
Tailor-made Synthesis of *N,N*,2,6-Tetrasubstituted 4-Nitroanilines by Three Component Ring Transformation of Dinitropyridone

Song Thi Le,[a] Haruyasu Asahara,[a,b] and Nagatoshi Nishiwaki[a,b]*

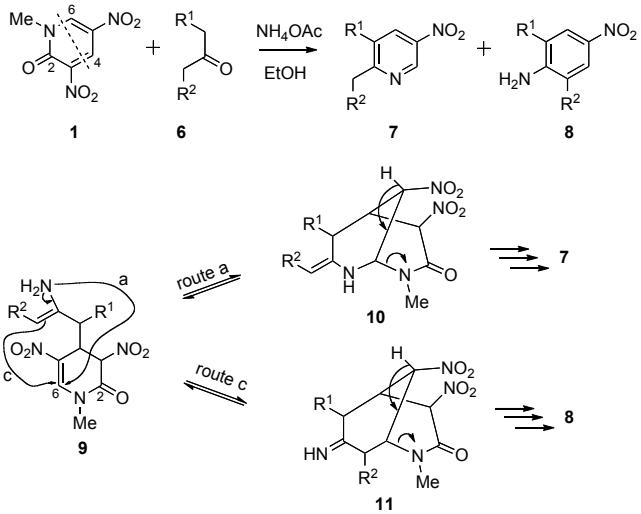
Abstract: The ring transformation of dinitropyridone afforded various kinds of 2,6-disubstituted-4-nitroanilines upon treatment with aliphatic ketones in the presence of ammonium acetate as a nitrogen source, wherein dinitropyridone behaved as the synthetic equivalent of unstable nitromaloaldehyde. The benzene ring as well as the amino group of the nitroaniline framework was easily modified by only changing a ketone and the nitrogen source, which afforded *N,N*,2,6-tetrasubstituted 4-nitroanilines in good to excellent yields.

Ring transformation reactions provide a unique method for the synthesis of functionalized heterocyclic compounds, which are not easily prepared by other methods.[1,2] We have reported an alternative method for the synthesis of nitropyridines **3** by the three component ring transformation (TCRT) of dinitropyridone **1** with aromatic ketones **2** in the presence of ammonium acetate (Scheme 1),[2] wherein dinitropyridone **1** serves as the synthetic equivalent of unstable nitromalonaldehyde.[3] This reaction is initiated by the nucleophilic attack of the enol form of **2** followed by conversion to enamine **4**. When the amino group of enamine **4** attacks the 6-position (route a), 2-arylated 5-nitropyridines **3** are formed via bicyclic intermediates **5** (Scheme 1).[4] However, the β-carbon of enamine **4** cannot attack the 6-position (route b) because it would form a sterically strained four membered ring. On considering this reaction mechanism, we predicted that another ring transformation would occur when aliphatic ketones **6** having two α-hydrogens, viz. α- and α‘-, are employed instead of aromatic ketones **2** (Scheme 2). In this ring transformation, both the amino group and the β-carbon can attack the 6-position in the case of enamine **9**, which leads to the formation of nitropyridines **7** (route a) or nitroanilines **8** (route c).

2,6-Disubstituted 4-nitroanilines **8** are useful synthetic intermediates for functional materials such as inhibitors of cholesterol acyl transferase,[5] and π-conjugated polymers[6] and are key intermediates for the synthesis of compounds with antimicrobial activities[7] and the β-diketiminate ligand.[8] Moreover, the push-pull electronic property is crucial for developing organic materials with potential for applications in nonlinear optics. Generally, 2,6-disubstituted 4-nitroanilines **8** are prepared from the corresponding anilines by nitration under harsh conditions, wherein protection and deprotection of the amino group are necessary.[9] However, the preparation of 2,6-disubstituted anilines is restricted because of the following limitations of the Friedel-Crafts alkylation:[10] 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) phenyl and vinyl groups cannot be introduced, and 5) aminated and nitrated benzenes do not facilitate the alkylation. We believe that our TCRT method will overcome these disadvantages of the Friedel-Crafts alkylation and facilitate the synthesis of 2,6-disubstituted 4-nitroanilines **8** by only changing ketones **6**.



Scheme 1. TCRT of dinitropyridone **1** with aromatic ketones **2** in the presence of ammonium acetate, leading to the formation of 6-arylated nitropyridines **3**.



Scheme 2. TCRT of dinitropyridone **1** with aliphatic ketones **6** in the presence of ammonium acetate, affording disubstituted nitropyridines **7** and nitroanilines **8**.

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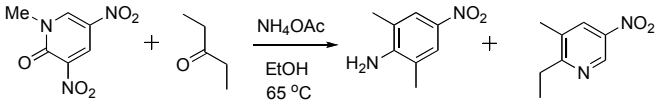
When dinitropyridone **1** was allowed to react, at 65 °C for 24 h, with 3-pentanone **6a** in the presence of 5 equiv. of ammonium acetate in ethanol, nitroaniline **8a**[11] and nitropyridine **7a**[11] were obtained in 50% and 44% yield, respectively, resulting from two kinds of TCRTs (Table 1, entry 1). When 10 equiv. of ammonium acetate were used, the ratio of **8a** to **7a** increased considerably without decreasing the total yield (entry 2); this indicates the presence of equilibrium between **10** and **11**, which are kinetically and thermodynamically controlled intermediates, respectively, that can interconvert via enamine **9**. In the present TCRT, the competitive thermal decomposition of ammonium acetate to ammonia, which was liberated from the reaction mixture as a gas, also occurred. When all the ammonium acetate was consumed, the TCRT could no longer proceed because of the lack of a nitrogen source. Thus, increasing the amount of ammonium acetate prolonged the actual reaction time, resulting in the predominance of nitroaniline **8a**. However, no additional change was observed on using larger amounts of ammonium acetate (entry 3). Also, it was found that heating for 24 h was necessary for the completion of the TCRT (entries 4-6).

Table 1. Optimization of reaction conditions for the TCRT



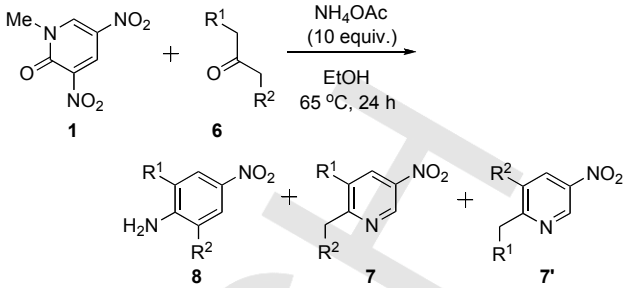
1 **6a** **8a** **7a**

Entry	NH_4OAc (Equiv.)	Time (h)	Yield (%)	
			8a	**7a**
1	5	24	50	44
2	10	24	83	13
3	15	24	86	13
4	10	18	70	14
5	10	12	64	13
6	10	6	55	13

This TCRT was applied to other ketones **6b-i** under the conditions optimizited for **6a** (Table 2). When acetone **6b** was used as a substrate, two kinds of TCRTs occurred, similar to **6a**, to afford nitroaniline **8b**[11] and nitropyridine **7b**[11] in 51% and 47% yields, respectively (entry 2). It was possible to modify the 2- and 6- positions of the nitroaniline framework by only changing ketone **6** (entries 3-9). Notably, this TCRT facilitates the introduction of a propyl or phenyl group into the benzene ring, which cannot be achieved by the Friedel–Crafts reaction. As a result, symmetrical and unsymmetrical nitroanilines **8f-i**[11] were easily prepared; however the yield of **8i** was low, presumably because steric repulsion by the phenyl groups prevents the formation of **11i** (entries 6-9).

As mentioned above, two kinds of TCRTs competitively occurred to form 5-nitropyridines **7** and 4-nitroanilines **8**. In these reactions, ammonium acetate serves as both a nitrogen source and an activator of ketone **6**. We believe that a combination of amine **12** 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. In this case, only nitroanilines **13** will be formed as a TCRT product, because the aromatization of the intermediate, which is required fort he formation of nitropyridines, is prevented by the *N*-substitutents (R^3 and R^4).

Table 2. Application of the TCRT to other aliphatic ketones **6**

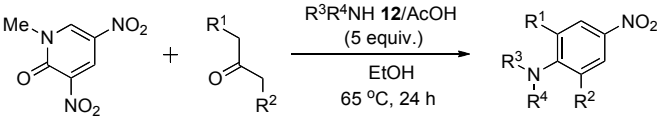


1 **6** **8** **7** **7'**

Entry	Ketone **6**			Yield (%)		
	R^1	R^2		**8**[11]	**7**[11]	**7'**[11]
1	Me	Me	**a**	83	13	0
2	H	H	**b**	51	47	0
3	Et	H	**c**	66	10	8
4	*i*-Pr	H	**d**	58	0	31
5	Pr	H	**e**	83	9	6
6	Et	Et	**f**	67	24	0
7	Pr	Pr	**g**	74	22	0
8	C_6H_5	Pr	**h**	62	24	13
9	C_6H_5	C_6H_5	**i**	8	81	0

Propylamine **12A** was added to a solution of dinitropyridone **1**, 3-pentanone (**6a**) and acetic acid in ethanol, and the resulting solution was heated at 65 °C for 24 h. After the usual work-up, 2,6-dimethyl-4-nitro-*N*-propylaniline (**13Aa**) was obtained in 99% yield (Table 3, entry 1). This method was applied to the secondary amines, pyrrolidine **12B** and diethylamine **12C**, to afford *N,N*,2,6-tetrasubstituted 4-nitroanilines **13Ba** and **13Ca**, respectively, in excellent yields (entries 2 and 3). Methyl ketones **6b-d** also underwent this TCRT using a combination of either propylamine **12A** or pyrrolidine **12B** with acetic acid to afford the corresponding nitroanilines **13** in moderate to excellent yields (entries 4-9). Moreover, these reactions could induce modifications at the 2- and 6-positions using ketones **6e-h**, by which a propyl or a phenyl group could be introduced to the nitroaniline framework (entries 10-15).

Table 3. TCRT of dinitropyridone **1** with aliphatic ketones **6** using the mixture of amine **12** and acetic acid.



1 **6** **13**

Entry	Ketone **6**			Amine **12**			Product	Yield (%)
	R^1	R^2		R^3	R^4			
1	Me	Me	**a**	Pr	H	**A**	**13Aa**	99
2	Me	Me	**a**	-$(CH_2)_4$-		**B**	**13Ba**	98
3	Me	Me	**a**	Et	Et	**C**	**13Ca**	98
4	Et	H	**b**	Pr	H	**A**	**13Ab**	83
5	Et	H	**b**	-$(CH_2)_4$-		**B**	**13Bb**	68
6	Pr	H	**c**	Pr	H	**A**	**13Ac**	77
7	Pr	H	**c**	-$(CH_2)_4$-		**B**	**13Bc**	87
8	Pr	H	**c**	Et	Et	**C**	**13Cc**	51
9	*i*-Pr	H	**d**	Pr	H	**A**	**13Ad**	83
10	Et	Et	**e**	Pr	H	**A**	**13Ae**	69
11	Et	Et	**e**	-$(CH_2)_4$-		**B**	**13Be**	68
12	Pr	Pr	**f**	Pr	H	**A**	**13Af**	81
13	Pr	Pr	**f**	-$(CH_2)_4$-		**B**	**13Bf**	59
14	C_6H_5	Pr	**g**	Pr	H	**A**	**13Ag**	80
15	C_6H_5	C_6H_5	**h**	Pr	H	**A**	**13Ah**	32

In summary, we have developed a new preparative method for 2,6-disubstituted 4-nitroanilines **8** and **13** by the TCRT of dinitropyridone **1** with aliphatic ketones **6** in the presence of ammonium acetates. In this reaction, a number of ketones **6** are usable as substrates, which facilitate the modification of the nitroaniline framework. In addition, this TCRT requires only simple experimental manipulations and mild reaction conditions, which is advantageous from the viewpoint of practical use. These features facilitate the construction of a libray of compounds that are not easily available by other methods. Furthermore, modification of the amino group was successfully achieved by using a combination of amine **12** and acetic acid. Consequently, the tailor-made synthesis of *N,N*,2,6-tetrasubstituted 4-nitroanilines **8** and **13** became possible on demand.

Experimental Section

To a solution of the nitropyridone **1** (50 mg, 0.25 mmol) in ethanol (5 mL), were added 3-pentanone (**6a**, 26 µL, 0.25 mmol) and ammonium acetate (96.3 mg, 1.25 mmol), and then the resultant mixture was heated at 65 ˚C for 24 h. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to remove unreacted ketone **6a**, which affords a mixture of the nitropyridine **7a** and the nitroaniline **8a**. The separation of products was performed by column chromatography on silica gel (hexane : ethyl acetate = 95 : 5) to afford **7a** (18.3 mg, 0.11 mmol, 44%) and **8a** (20.8 mg, 0.13mmol, 50%), respectively. The TCRT reaction of the dinitropyridone **1** with other ketones were performed in a similar way.

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Keywords: Nitroheterocycles • Multicomponent reaction • Ring transformation • Ketones • Synthetic method.

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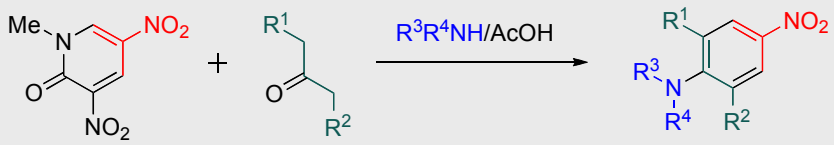

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