An Efficient Synthesis of Nitrated Cycloalka[*b*]pyridines

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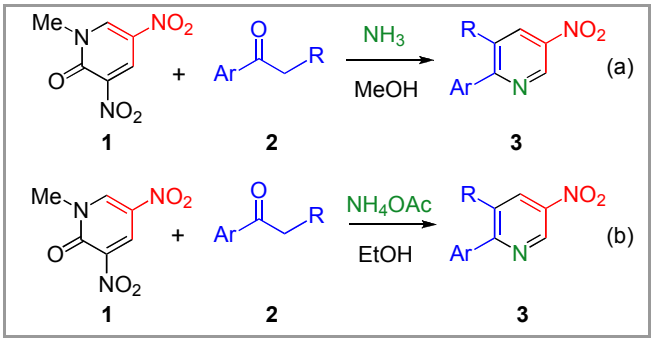
Abstract: The three-component ring transformation of 1-methyl-3,5-dinitro-2-pyridone with cycloalkanones of different ring sizes in the presence of ammonium acetate afforded the corresponding nitrated cycloalka[*b*]pyridines in high yields. Furthermore, a double bond could be easily introduced to the product by changing the cycloalkanone to a cycloalkenone.

Keywords: pyridines, multicomponent reaction, ketones, heterocycles, bicyclic compounds, and ring transformation.

Nitro compounds are important organic compounds that are widely used in organic syntheses because of diverse reactivities.[1] We have reported a synthetic method for the arylated nitropyridines **3** by the three-component ring transformation (TCRT) of dinitropyridone **1** with aromatic ketones **2** in the presence of ammonia,[2] in which dinitropyridone **1** serves as the synthetic equivalent of unstable nitromalonaldehyde (Scheme 1, method a).[3] Recently, other research groups also reported the TCRT of **1** with ketones using ammonia as the nitrogen source.[4] Although these methods easily provide nitropyridine derivatives via a single step, they suffer from low yields of the products because of the competitive ammonolysis of the substrate **1**.[5] Furthermore, methanolic ammonia should be prepared in advance, which is also troublesome.

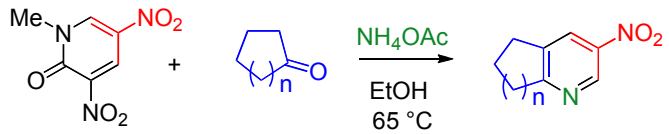
These disadvantages were overcome by using less nucleophilic ammonium acetate (NH_4OAc) instead of ammonia.[6] The reaction of dinitropyridone **1** with aromatic ketones **2** in the presence of NH_4OAc afforded the nitropyridines **3** in good to excellent yields (Scheme 1, method b).[7] This TCRT is advantageous in terms of the use of solid NH_4OAc compared to gaseous ammonia, and extra NH_4OAc can be easily removed from the reaction mixture by thermal decomposition. The successful results of our study prompted us to extend the substrate scope of this method to a series of cyclic ketones **4**. Thus, nitrated cycloalka[*b*]pyridines **5** could be successfully obtained and further used as useful intermediates for the synthesis of metacyclophanes,[4] pharmacophores,[8] and biologically active compounds.[9]



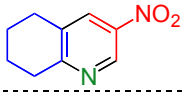
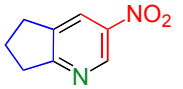
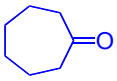
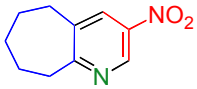
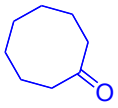
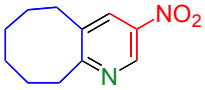
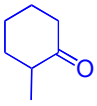
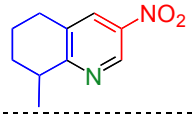
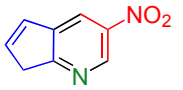
Scheme 1. Synthetic methods for 2-arylated-5-nitropyridines **3** by TCRT of dinitropyridone **1** with aromatic ketones **2** in the presence of a nitrogen source.

The reaction of the dinitropyridone **1** with cyclohexanone **4a** in the presence of 5 equiv. NH_4OAc at 65 °C for 24 h afforded nitrated cyclohexa[*b*]pyridine **5a**[2b,4b,10] in a moderate yield, because of the shortage of the nitrogen source due to the competitive thermal decomposition of NH_4OAc (Table 1, entry 1).[7] This problem was easily solved by increasing the amount of NH_4OAc, and the yield of **5a** could be increased to 95% (entries 2 and 3). When microwave heating was used, nitropyridine **5a** was afforded efficiently within 1 h (entry 4). Cyclopentanone **4b** was less reactive than **4a**, thus affording cyclopentapyridine **5b**[2b,10] in only 67% yield under the same reaction conditions used for **4a** (entry 5). In such a case, microwave heating was effective, and the reaction was completed within a short time under microwave heating (entries 6 and 7). In contrast, larger cycloalkanones **4c** and **4d** underwent the TCRT efficiently to afford the corresponding cyclohepta- and cyclooctapyridines **5c**[10] and **5d**,[4b,10] respectively (entries 8−11). When unsymmetrical 2-methylcyclohexanone **4e** was employed, 8-methylated tetrahydroquinoline **5e** was obtained efficiently (entries 12 and 13). This reaction was also applied to unsaturated cyclic ketone **4f**, thus affording 7,8-dihydroquinoline **5f** even though microwave heating was necessary for efficient TCRT (entries 14−16). On the other hand, cylopentenone **4g** did not undergo the TCRT even though microwave heating was used (entry 17).

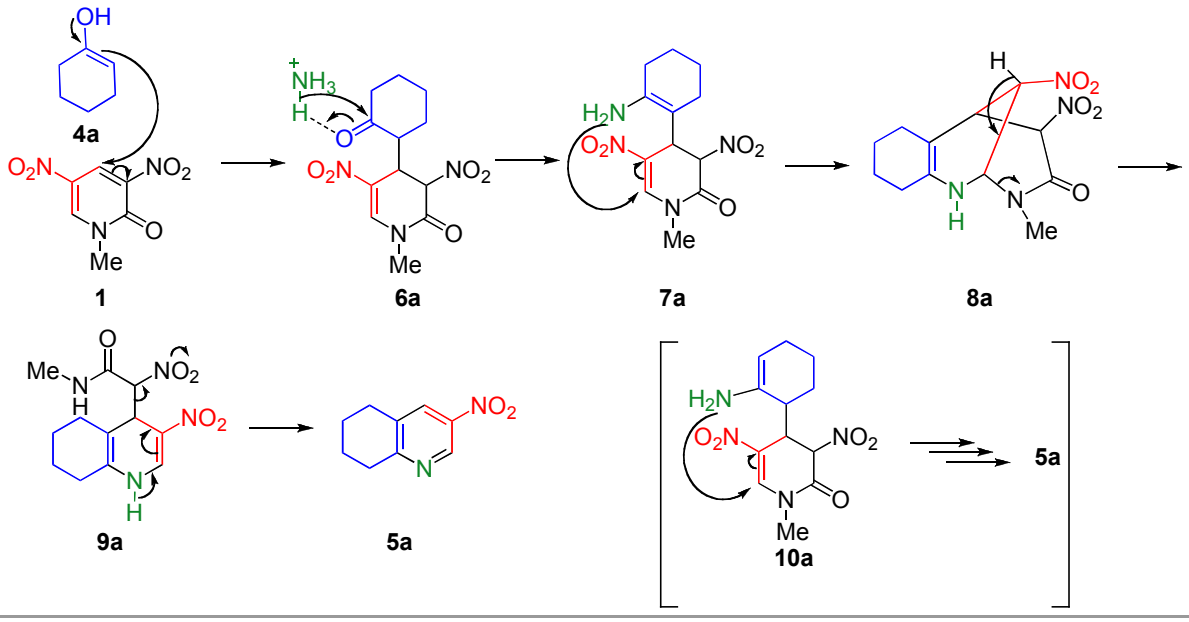
Table 1. Synthesis of cycloalka[*b*]pyridines **5** by TCRT.



1 **4** **5**

Entry	n	Ketones		NH_4OAc (equiv.)	Time (h)	Product		Yield (%)
1	2		**4a**	5	24		**5a**	56
2				10	24			88
3				15	24			95
4				15	1[a]			97
5	1		**4b**	15	24		**5b**	67
6				15	2[a]			87
7				15	1[a]			70
8	3		**4c**	15	24		**5c**	94
9				15	1[a]			91
10	4		**4d**	15	24		**5d**	85
11				15	1[a]			95
12	2		**4e**	15	24		**5e**	83
13				15	2[a]			86
14	2		**4f**	15	24		**5f**	59
15				15	3[a]			89
16				15	1[a]			40
17	1		**4g**	15	4[a]		**5g**	0

a: Microwave heating was used.



Scheme 2. A plausible mechanism for the formation of the condensed nitropyridine **5a**.

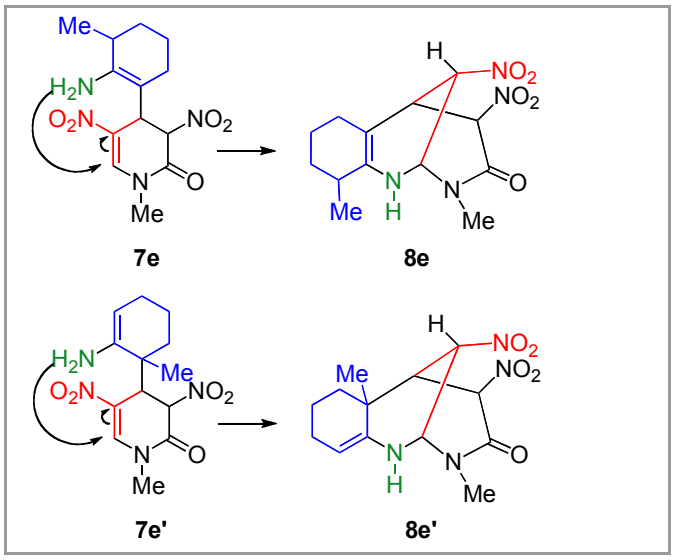


Figure 1. Two plausible intermediates derived from 1-methylcyclohexanone **4e**.

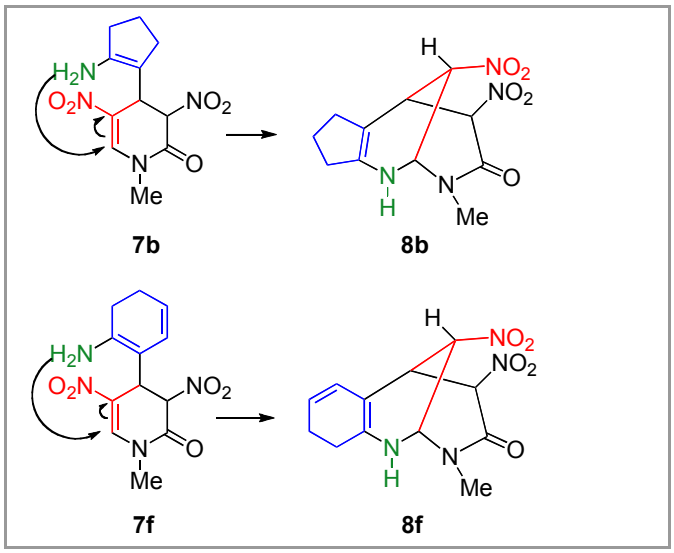


Figure 2. The intermediate **7b** and **7f**.

A plausible mechanism for this TCRT is shown in Scheme 2. After the addition of the enol form of **4a** to the 4-position of **1**, the resulting adduct **6a** is transformed to enanine **7a** by reacting with ammonium ion. The intramolecular attack of the amino group at the 6-position affords tricyclic intermediate **8a**, from which nitroacetamide is eliminated to afford nitropyridine **5a** after the aromatization of intermediate **9a**. Although another reaction path via enamine **10a** can be considered, the same product **5a** is formed. In the case of unsymmetrical 2-methylcyclohexanone **4e**, two kinds of intermediates **8e** and **8e'** are possible (Figure 1), however, the latter intermediate cannot afford aromatized product. Therefore, only **5e** is formed via the intermediate **8e**. In the reactions using cyclopentanone **4b** and cyclohexenone **4f**, the loss of the flexibility of **7b** and **7f** makes the formation of tricyclic intermediates **8b** and **8f** more difficult (Figure 2). To the contrary, cyclopentenone **4g** did not afford ring transformed product **5g** because formation of a sterically restricted intermediate is necessary.

In summary, nitrated cycloalka[*b*]pyridines **5** were efficiently synthesized by the TCRT of dinitropyridone **1** with saturated and unsaturated cyclic ketones **4** in the presence of NH_4OAc. Because the method requires only simple manipulations and mild reaction conditions, it has great potential for the synthesis of [*b*]-condensed pyridine frameworks.

Experimental Section

The melting points were determined on a Yanaco micro-melting-points apparatus, and were uncorrected. The ^1H NMR spectra were measured on a Bruker Ascend-400 at 400 MHz with TMS as an internal standard. The ^{13}C NMR spectra were measured on a Bruker Ascend-400 at 100 MHz, and assignment was performed by DEPT experiments. The IR spectra were recorded on a JASCO FT/IR-4200 spectrometer. The high resolution mass spectrum was measured on a JEOL JMS-DX303HF. Microwave heating was performed using Anton-Paar Microwave 300. All the reagents and solvents were commercially available and were used as received.

General procedure of TCRT. To a solution of the dinitropyridone **1** (50 mg, 0.25 mmol) in ethanol (5 mL), cyclohexanone **4a** (26 μL, 0.25 mmol) and NH_4OAc (289 mg, 3.75 mmol) were added, and the resultant mixture was heated at 65 °C on the oil bath for 24 h. After removal of the solvent, the residue was washed with benzene (3 × 10 mL) to afford 5,6,7,8-tetrahydro-3-nitroquinoline (**5a**) (42 mg, 0.24 mmol, 95%) as a yellow powder. The reactions of the dinitropyridone **1** with other ketones **4b-g** were performed in a similar way. When the reaction was conducted using microwave heating, the experiment was conducted in a similar way.

6,7-Dihydro-3-nitro-5*H*-cyclopenta[*b*]pyridine (5b).[2b,10]

Yellow powder.

Yield: 43 mg, 97%.

6,7,8,9-Tetrahydro-3-nitro-5*H*-cyclohepta[*b*]pyridine (5c).[10]

Yellow powder.

Yield: 36 mg, 87%.

5,6,7,8,9,10-Hexahydro-3-nitro-cycloocta[*b*]pyridine (5d).[4b,10]

Yellow powder.

Yield: 49 mg, 95%.

5,6,7,8-Tetrahydro-8-methyl-3-nitroquinoline (5e).[10]

Yellow powder.

Yield: 41 mg, 86%.

7,8-Dihydro-3-nitroquinoline 5f.

Yellow powder; mp 57-59 °C.

Yield: 40 mg, 89%.

IR (KBr, cm^{-1}) 1261, 1577, 1509.

^1H NMR ($CDCl_3$) δ = 2.49 (ddt, J = 2.8, 4.0. 8.4 Hz, 2H), 2.99 (t, J = 8.4 Hz, 2H), 6.57 (dt, J = 4.0, 8.0 Hz, 1H), 6.74 (ddt, J = 0.8, 2.8, 8.0 Hz, 1H), 8.16 (dd, J = 0.8, 2.8 Hz, 1H), 9.19 (d, J = 2.8 Hz, 1H).

^{13}C NMR ($CDCl_3$) δ = 22.6 (CH_2), 26.5 (CH_2), 128.9 (CH), 129.3 (CH), 131.3 (C), 139.1 (CH), 141.1 (C), 143.3 (CH), 158.8 (C).

HRMS (EI, magnetic field) Calcd for $C_9H_8N_2O_2$: 176.0586. Found: 176.0586.

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