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An Alternative Synthetic Approach to 3-Alkylated/Arylated 5-Nitropyridines

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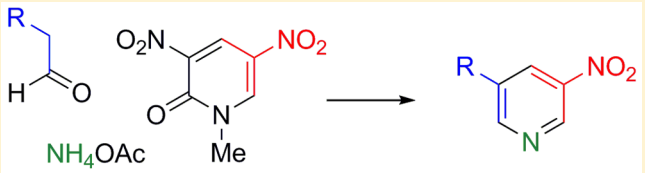
Supporting Information

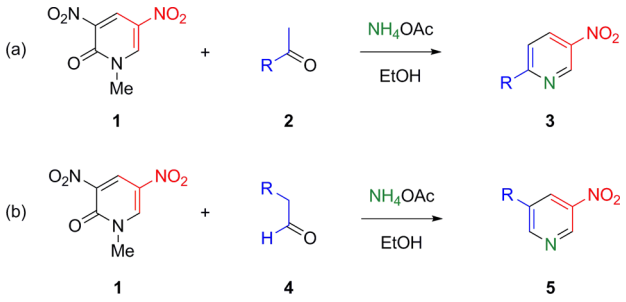
ABSTRACT: An alternative method for the synthesis of 3-alkylated/arylated 5-nitropyridines was developed involving a three-component ring transformation of 3,5-dinitro-2-pyridone on treatment with aldehyde in the presence of ammonium acetate. This method facilitates the modification of the substituent at the 3-position by changing the precursor aldehyde. The use of solid ammonium acetate instead of ammonia as the nitrogen source renders the synthetic method more practical and user-friendly.



3-Alkylated/arylated 5-nitropyridines are widely used as synthetic intermediates in the preparation of biologically active compounds, such as cytokine inhibitors for the treatment of various diseases,[1] Wnt β-catenin signaling pathway inhibitors,[2] HIV integrase inhibitors,[3] and dihydroorotate dehydrogenase (DHODH) inhibitors.[4] Despite these varied and useful applications, the versatile 3-alkylated/arylated 5-nitropyridine structures required for proper screening are not readily available due to difficulty of β-alkylation/arylation of the pyridine framework. Thus, only a few direct β-alkylation methods are currently known. One strategy, reported by Giam et al., involves destroying the aromaticity of the pyridine ring, achieving direct alkylation of pyridine via conversion to tetrakis(dihydropyridyl)aluminate with lithium aluminum hydride.[5] Tsuge et al. have succeeded in benzylation via a 1,4-disilyl intermediate.[6] Direct phenylation was only recently realized after considerable effort, although the methods still suffer from harsh conditions or low regioselectivity.[7] Additionally, 3-bromopyridine has been used as a substrate for alkylation using organometallic reagents/catalysts.[8] Although β-alkylation/arylation with this method was successful, the subsequent nitration step suffers from the low reactivity of the alkylated pyridine framework.

Meanwhile, ring transformation has been shown to have good synthetic utility in obtaining nitrated compounds. Diels–Alder-type ring transformations have been widely used, exemplified by the successful synthesis of 3-nitro-5-phenylpyridine by van der Plas et al. from nitropyrimidine and an enamine.[9] Alternatively, since its report by Ariga et al., nucleophilic ring transformation using 1-methyl-3,5-dinitro-2-pyridone (**1**) has also been employed.[10] In particular, the three-component ring transformation (TCRT) of pyridone **1** with ketones **2** in the presence of a nitrogen source (NH_3) is an excellent method to synthesize 2-substituted or 2,3-disubstituted 5-nitropyridines **3** used by researchers[11] and pharmaceutical companies.[12] However, this method requires prior preparation of NH_3 solution, and competing ammonolysis of pyridone **1** is sometimes observed. In order to solve these problems, we recently demonstrated a TCRT for the synthesis of nitropyridines **3**[13] and nitroanilines[14] using easy-to-handle solid NH_4OAc as the nitrogen source instead of NH_3 (Scheme 1, method a). With regard to the TCRT of **1** with aldehydes **4** in the presence of NH_3, only a few examples are known,[15] presumably due to side reactions of the reactive aldehydes **4**. We considered that 3-substituted 5-nitropyridines would be accessible with our NH_4OAc protocol via TCRT of pyridone **1** with aldehyde **4** in the presence of NH_4OAc (Scheme 1, method b).

Scheme 1. TCRT of Dinitropyridone 1



Dinitropyridone **1** was reacted with butanal (**4a**) in the presence of NH_4OAc (5 equiv) in ethanol at 65 °C for 24 h. After removal of the solvent, the residue was extracted with benzene (3 × 10 mL) to afford nitropyridine **5a**[15c] in a near-pure form, but with just 26% yield (Table 1, entry 1). It was noted that thermal decomposition of NH_4OAc was a competing reaction, consuming a quantity of the nitrogen source required for the TCRT to proceed.[13,14] Thus, using larger amounts of NH_4OAc in the reaction increased both the

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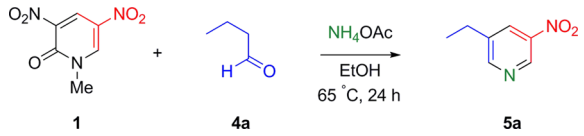
Table 1. TCRT of 1 with Butanal (4a) and NH_4OAc



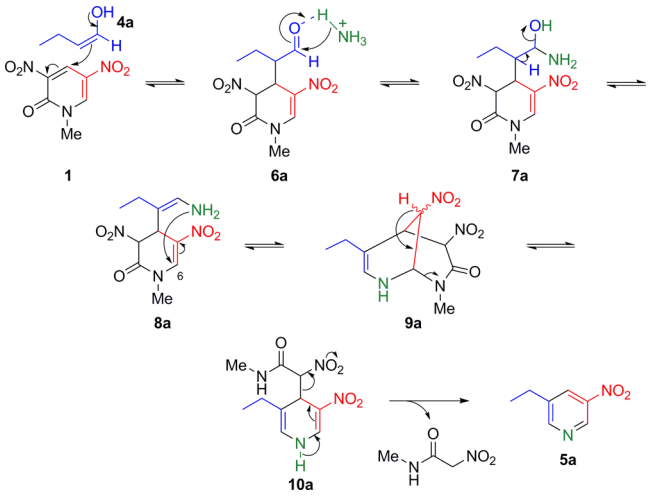
entry	NH_4OAc (equiv)	yield (%)	recovery of **1** (%)
1	5	26	66
2	10	75	20
3	15	86	0
4[a]	15	24	65

[a]Reaction was conducted using a microwave reactor (Anton Paar, Monowave 300) with measuring the reaction temperature by an IR external sensor.

actual reaction time and yield of nitropyridine **5a** (entries 2 and 3). In order to reduce the reaction time, microwave heating proved efficient for the TCRT of **1** with ketone **2**. However, the yield of **5a** was lower because the more reactive aldehyde **4a** caused side reactions such as aldol and Chichibabin[16] reactions, resulting in a complex reaction mixture (entry 4).

This TCRT is considered to proceed as illustrated in Scheme 2. The enol form of **4a** attacks the 4-position of **1**, giving adduct

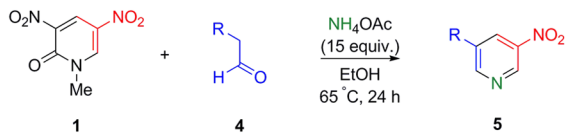
Scheme 2. Plausible Mechanism for TCRT of Dinitropyridone 1



6a, which reacts with an ammonium ion to form enamine **8a**. Nucleophilic attack at of the 6-position by the amino group gives bicyclic intermediate **9a**, which then undergoes ring-opening and subsequent aromatization with elimination of a stable nitroacetamide leaving group to give nitropyridine **5a**.

To expand the scope of this method, the reactions of **1** with various aldehydes **2b–f** were performed under the optimized conditions (Table 2). The TCRT using propanal (**4b**) proceeded well to afford 3-methyl-5-nitropyridine (**5b**)[17] in 52% yield, although the reaction was diminished by the competitive self-condensation of the aldehyde (entry 1). Self-condensation was avoided when bulkier aldehyde **4c** was used, resulting in 3-isopropylpyridine (**5c**)[15c] recovered in 71% yield (entry 2). In the case of more sterically hindered aldehydes **4d** and **4e**, the corresponding yields of nitropyridine products **5d**[18] and **5e**[19] were significantly lower, highlighting the reduced efficiency of the TCRT decreased (entries 3 and 4). This disadvantage was overcome with microwave heating, which

Table 2. TCRT of 1 with Various Aldehydes 4 and NH_4OAc



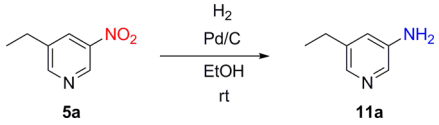
entry	R		yield (%)	recovery of **1** (%)
1	Me	**b**	52	
2	*i*-Pr	**c**	71	16
3	$PhCH_2$	**d**	34	21
4	*t*-Bu	**e**	29	63
5[a,b]	*t*-Bu	**e**	68	
6	Ph	**f**	47	44
7[a,b]	Ph	**f**	75	

[a]Reaction was conducted using a microwave reactor (Anton Paar, Monowave 300) with measuring the reaction temperature by an IR external sensor. [b]For 6 h.

improved the yield of **5e** to 68% (entry 5). It was also possible to introduce a phenyl group to the pyridine ring by employing phenylacetaldehyde **4f** to afford **5f**[9] (entries 6 and 7).

We then studied the conversion of nitropyridine **5a** to aminopyridine **11a**. Aminopyridines are widely used as synthetic intermediates for biologically active compounds because the amino group facilitates further chemical conversion.[20] 5-Amino-3-ethyl-5-nitropyridine **11a**[21] was obtained in 82% yield by hydrogenation of **5a** in the presence of Pd/C catalyst at room temperature (Scheme 3).

Scheme 3. Synthetic Application of Synthesized Nitropyridine 5a



In summary, we have successfully developed the first facile and efficient method for the synthesis of 3-substituted 5-nitropyridines tolerating a range of alkyl and aryl substituents. This method requires only simple manipulations in a one-step reaction with mild conditions. Furthermore, changing the alkyl/aryl group introduced at the 3-position requires only the use of a different aldehyde. These features improve the synthetic value of this method and provide an alternative approach to 3-substituted 5-nitropyridine frameworks.

EXPERIMENTAL SECTION

General Procedure of TCRT. To a solution of the dinitropyridone **1** (50 mg, 0.25 mmol) in ethanol (5 mL) were added butanal (**4a**) (46 μL, 0.5 mmol) and ammonium acetate (289 mg, 3.75 mmol), and then the resultant mixture was heated at 65 °C for 24 h. After removal of the solvent, the residue was extracted with benzene (3 × 10 mL) to afford almost pure nitropyridine **5a** (33 mg, 0.22 mmol, 86%) as a yellow powder. The TCRT reactions of the dinitropyridone **1** with other aldehydes **4b–f** were performed in a similar way.

3-(1,1-Dimethylethyl)-5-nitropyridine (5e) (Table 2, Entry 5).[19] Yellow powder (31 mg, 0.17 mmol, 68%), mp 248–250 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44 (s, 9H), 8.46 (dd, *J* = 2.4, 2.4 Hz, 1H), 8.97 (d, *J* = 2.4 Hz, 1H), 9.27 (d, *J* = 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.8 (CH_3), 34.1 (C), 127.8 (CH), 142.1 (CH), 144.2 (C), 147.5 (C), 152.8 (CH); IR (KBr, cm^{-1}) 1353, 1532. HRMS (EI, double focusing) Calcd for $C_9H_{12}N_2O_2$ 180.0899, Found 180.0899.

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The Conversion of 3-Ethyl-5-nitropyridine (5a) to 5-Amino-3-ethylpyridine (11a). To a solution of nitropyridine **5a** (70 mg, 0.46 mmol) in ethanol (5 mL) was added Pd/C powder (5 wt % Pd, 50 mg), and the reaction was carried out at room temperature for 40 h under a hydrogen atmosphere. After removal of Pd/C powder and solvent by filtration and vacuum pressure, respectively, the residue was extracted with chloroform (3 × 10 mL) to give 5-amino-3-ethylpyridine (**11a**)[21] (46 mg, 0.38 mmol, 82%) as a yellow powder.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01391.

^{1}H and ^{13}C NMR spectra for compounds **5a**−**f** and **11a** (PDF)

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Notes

The authors declare no competing financial interest.

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