



Synthesis of functionalized 4-nitroanilines by ring transformation of dinitropyridone with enamines



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ABSTRACT

2-Functionalized 4-nitroanilines were readily synthesized by ring transformation using 3,5-dinitro-2-pyridone and enamines prepared from 1,3-dicarbonyl compounds and amines. Modification of the amino group and the *ortho*-position could be achieved by simply changing the enamines. Using this strategy, functional groups such as acetyl, benzoyl, and ethoxycarbonyl groups could be introduced into the nitroaniline framework.

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Ring transformation is one of the most powerful methods for constructing versatile ring systems. Besides the Diels-Alder-type¹ and degenerate-type² ring transformations, nucleophilic-type reactions have recently been recognized as the third type of ring transformation mechanisms.³ 1-Methyl-3,5-dinitro-2-pyridone (**1**) can be used as a suitable substrate for this type of reaction because of its high electrophilicity and the partial structure, nitroacetamide, which serves as a good leaving group.³ Indeed, pyridone **1** efficiently reacts with ketones and ammonium acetate in a three-component ring transformation to afford 4-nitroanilines **2**, which possesses alkyl/aryl groups at the 2- and 6-positions, in moderate to high yields (Scheme 1a).⁴ It was also possible to modify the amino group of nitroanilines by using a combination of amine and acetic acid instead of ammonium acetate (Scheme 1b).⁴

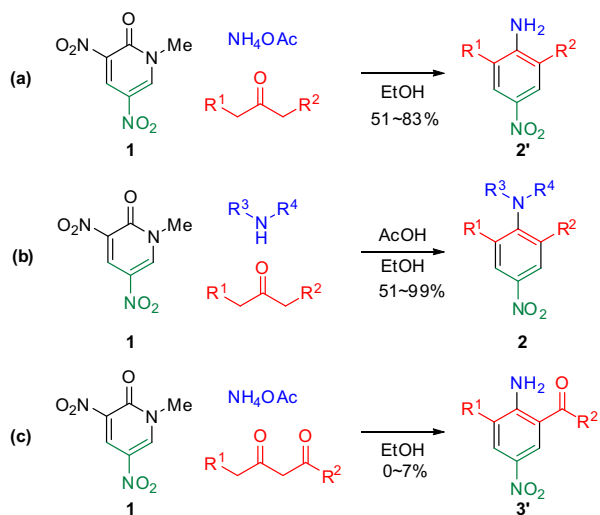
The presence of both the electron-donating amino group and the electron-withdrawing nitro group creates a biased electron density in the molecule, which sometimes shows intramolecular charge transfer. This electronic property plays an important role in nonlinear optical materials.⁵ Therefore, the above ring transformation is a useful protocol for the construction of a compound library of diverse nitroaniline derivatives that can be further utilized for the development of new functional materials. However,

only small amounts of the functionalized nitroanilines **3'** were obtained when 1,3-dicarbonyl compounds were used instead of ketones because of side reactions (Scheme 1c). These results prompted us to design a new ring transformation using dinitropyridone **1** and enamines **4** that are readily prepared from 1,3-dicarbonyl compounds and amines.

When a solution of **1** and **4a** in ethanol was heated at 80 °C for 1 day, a trace amount of the ring-transformed products, 2-ethanoyl-4-nitro-*N*-propylaniline (**3a**) and 4-nitro-*N*-propylaniline (**5a**), were detected in the reaction mixture (Table 1, Entry 1). It was confirmed that the latter product **5a** was not formed by the deacetylation of **3a**, as no reaction occurred upon treatment of isolated **3a** under the same reaction conditions. Several bases were used as the additive (Entries 2–10). Addition of propylamine accelerated the reaction and increased the yield of **3a** (Entry 2). Triethylamine also revealed a similar effect; it was found that the addition of 1 equiv. of the amine was sufficient and led to completion of the reaction (Entries 3 and 4). When the reaction time was prolonged to two days, pyridone **1** was completely consumed and the yield of **3a** had increased to 57% (Entries 5 and 6). No positive effect was observed when the bulkier tributylamine and less nucleophilic 2,6-lutidine were used (Entries 7 and 8). On the other hand, inorganic bases such as potassium carbonate and cesium carbonate decomposed pyridone **1** without the formation of any detectable ring-transformed products (Entries 9 and 10).

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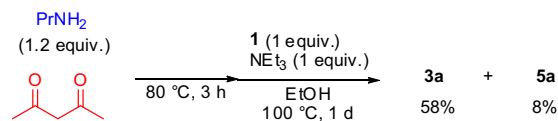
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Scheme 1. Three component ring transformations affording substituted 4-nitroanilines.

This reaction was also influenced to some extent by the choice of the solvent. The yield of the deacetylated product **5a** increased when the reaction was conducted in methanol (Entry 11). Although the less nucleophilic 2-propanol and hexafluoro-2-propanol (HFIP) solvents suppressed the side reactions, the yield of **3a** also decreased (Entries 12 and 13). A reaction temperature of 100 °C was rather effective in increasing the yield of **3a**, however, competitive decomposition of the substrates occurred at higher temperature (Entries 14 and 15).

The reaction could be conducted in one-pot without isolating of enaminone **4a**, which simplified the experimental manipulations (Scheme 2). After heating a mixture of propylamine and acetylacetone at 80 °C without a solvent for 3 h, the resultant mixture was



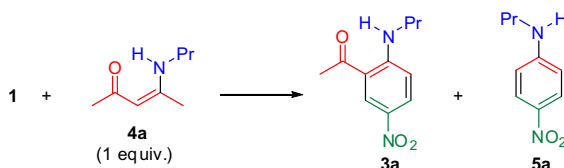
Scheme 2. One-pot synthesis of nitroaniline **3a**.

dissolved in ethanol. Then, dinitropyridone **1** and triethylamine were added, and the solution was heated at 100 °C for 1 day, which afforded nitroaniline **3a** in a comparable yield with the obtained from the reaction using isolated enaminone **4a**.

This synthetic protocol was also applicable to enaminone **4b**, which was derived from a diketone and a secondary amine. Although enaminone **4b** is not stabilized by an intramolecular hydrogen bond, it exhibited a higher reactivity than **4a** (Table 2). This reaction was also accelerated by adding diethylamine, and the yield of **3b** increased up to 85% when the reaction was conducted at 80 °C (Entries 1–3). The addition of triethylamine again revealed an accelerating effect (Entries 4–7). A one-pot reaction including the preparation of **4b** *in situ* was also possible, although the yield of **3b** decreased to 43%, which is presumably because the enaminone **4b** had not formed in a sufficient amount.

Under the optimized conditions, the synthesis of other types of nitroanilines **3** was studied by altering the enaminones **4** prepared by using other amines and 1,3-dicarbonyl compounds (Table 3). Bulky alkyl groups such as *sec*-butyl and *tert*-butyl and aryl groups such as phenyl and anisyl were introduced on the amino group of **3** (Entries 1–4). As shown in Table 2, enaminone **4b** derived from a secondary amine was also highly reactive. Indeed, the pyrrolidino-substituted enaminone **4g** efficiently reacted with dinitropyridone **1** to afford the corresponding nitroaniline **3g** in a high yield (Entry 5). The intramolecular hydrogen bond in enaminones derived from primary amines contributes to their stabilization, but might also diminish their reactivity for this reaction.

Table 1
Optimization of reaction conditions for the synthesis of nitroaniline **3a**.



Entry	Additive (1 equiv.)	Solv.	Temp. (°C)	Time (d)	Yield (%)	
					3a	5a
1	None	EtOH	80	1	1	2
2	PrNH ₂	EtOH	80	1	22	3
3	NEt ₃	EtOH	80	1	36	2
4	NEt ₃ ^a	EtOH	80	1	29	1
5	PrNH ₂	EtOH	80	2	52	2
6	NEt ₃	EtOH	80	2	57	7
7	NBu ₃	EtOH	80	2	45	7
8	2,6-Lutidine	EtOH	80	2	5	2
9	K ₂ CO ₃	EtOH	80	2	0	5
10	Cs ₂ CO ₃	EtOH	80	2	0	1
11	NEt ₃	MeOH	80	1	40	20
12	NEt ₃	<i>i</i> -PrOH	80	1	28	1
13	NEt ₃	HFIP ^b	80	1	6	1
14	NEt ₃	EtOH	100	1	63	9
15	NEt ₃	EtOH	120	1	56	8

^a 2 equiv.

^b Hexafluoro-2-propanol.

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