Tetrahedron Letters xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

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ARTICLE INFO

Article history:
Received 27 September 2017
Revised 29 October 2017
Accepted 2 November 2017
Available online xxxx

Keywords:
Ring transformation
Nitroaniline
Dinitropyridone
Enaminone
Bicyclic intermediate

ABSTRACT

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

Ring transformation is one of the most powerful methods for constructing versatile ring systems. Besides the Diels-Alder-type[1] and degenerate-type[2] 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 enaminones **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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https://doi.org/10.1016/j.tetlet.2017.11.003
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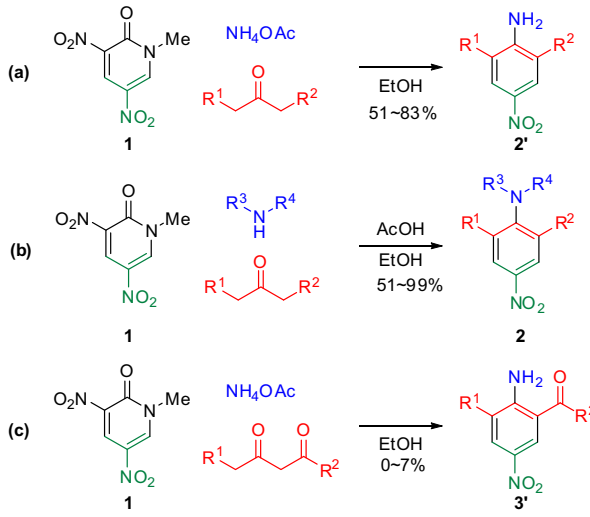
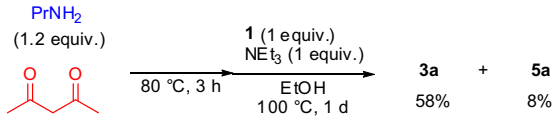


Scheme 1. Three component ring transformations affording substituted 4-nitroanilines.

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 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**.

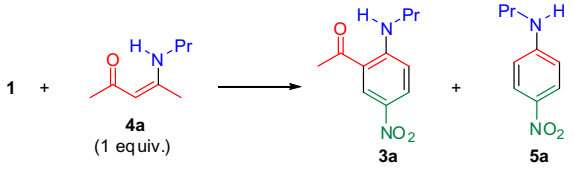


Scheme 2. One-pot synthesis of nitroaniline **3a**.

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.

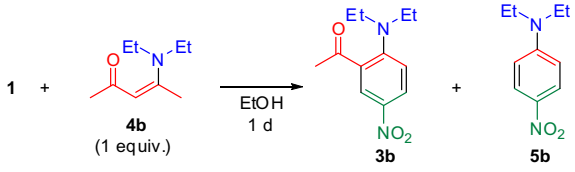
Table 1
Optimization of reaction conditions for the synthesis of nitroaniline **3a**.



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_2CO_3	EtOH	80	2	0	5
10	Cs_2CO_3	EtOH	80	2	0	1
11	NEt_3	MeOH	80	1	40	20
12	NEt_3	*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.

Table 2
Ring transformation using enaminone **4b**.

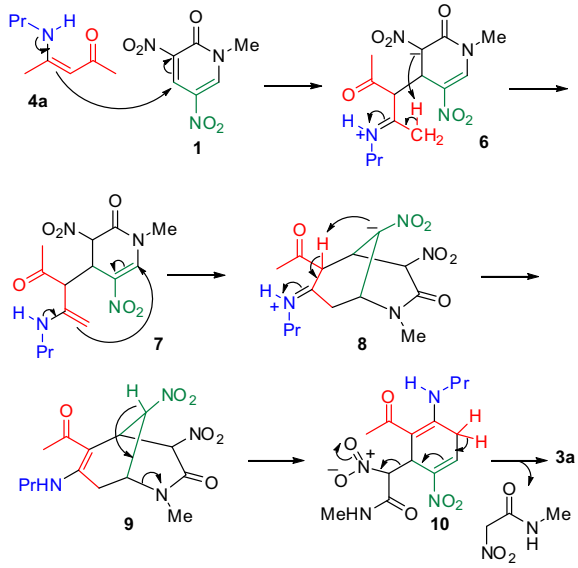


Entry	NEt_3 (equiv.)	Temp. (°C)	Yield (%)[a] 3b	5b
1	Et_2NH (1)	60	50	6
2	Et_2NH (2)	60	69	4
3	Et_2NH (1)	80	85 (80)[b]	3
4	NEt_3 (1)	80	63	4
5	NEt_3 (2)	80	75	10
6	NEt_3 (3)	80	75	6
7	NEt_3 (2)	100	68	6

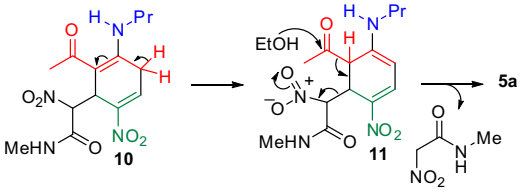
[a] Determined by ^1H NMR.
[b] Isolated yield.

It was also possible to introduce a benzoyl group at the *ortho*-position of the amino group by using benzoylacetone for preparation of enaminones **4h** and **4i** (Entries 6 and 7). Enaminones **4j–n** derived from keto esters were also used as substrates for the ring transformation (Entries 8–12). Furthermore, it was found that the reaction was not influenced by the presence of a hydroxy group on the amino group (Entry 9). In addition, it was not necessary for the substrate to have an acetyl group, as an alkyl group could also be introduced at the 6-position of 4-nitroaniline-2-carboxylate (Entry 12).

A plausible mechanism for this ring transformation is shown in Schemes 3 and 4. The reaction is initiated by the attack of enaminone **4a** on the 4-position of dinitropyridone **1** and enamine **7** is formed *via* the adduct intermediate **6**. The intramolecular attack of the enamine at the 6-position forms the bicyclic intermediate **8** and the subsequent proton transfer and ring opening reaction



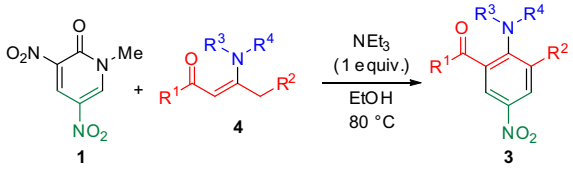
Scheme 3. A plausible mechanism for formation of **3a**.



Scheme 4. A plausible mechanism for formation of **5a**.

of **9** affords the 1,4-dihydrobenzene intermediate **10**, which is considered to serve a common intermediate for **3a** and **5a**. Nitroaniline **3a** is formed by aromatization of **10**, which is accompanied by the elimination of nitroacetamide. On the other hand, 1,2-dihydrobenzene **11** is formed when proton transfer occurs before the

Table 3
Scope and limitation of this protocol.



Entry	R^1	R^2	R^3	R^4		Time (d)	Yield (%)
1[a]	Me	H	*sec*-Bu	H	**c**	2	64
2	Me	H	*tert*-Bu	H	**d**	2	39
3	Me	H	Ph	H	**e**	2	23
4	Me	H	*p*-$MeOC_6H_4$	H	**f**	2	36
5	Me	H	$-(CH_2)_4-$		**g**	2	87
6	Ph	H	Pr	H	**h**	4	33
7	Ph	H	Et	Et	**i**	2	45
8	OEt	H	Pr	H	**j**	1	61
9	OEt	H	CH_2CH_2OH	H	**k**	1	45
10	OEt	H	Et	Et	**l**	1	57
11	OMe	H	H	H	**m**	1	31
12	OEt	Et	Pr	H	**n**	2	24

[a] At 100 °C.

elimination of nitroacetamide, and it is aromatized to nitroaniline **5a** by the elimination of both the acetyl group and nitroacetamide. When methanol is used as the solvent, its nucleophilic property might facilitate the deacetylation and lead to the formation of **5a**.

The reaction rate acceleration by the addition of amine can be explained as follows. At first, deprotonation of enaminone **4** by cleavage of the intramolecular hydrogen bond enhances the nucleophilicity of **4**. However, the added amine also plays another role because the reaction promotion effect was observed when enaminones derived from secondary amines were employed. A plausible secondary role of the amine is that it facilitates the formation of the enamine intermediate **7** from adduct **6** by deprotonation of the acetyl group. The amine might assist the ring opening of **8** and the aromatization of **9**.

In conclusion, a new ring transformation leading to functionalized nitroanilines **3** has been described. The modification of the nitroaniline framework **3** was easily achieved by altering enaminones **4**. Although many diverse functionalized nitroanilines are known, their preparative methods are relatively few. Among these methods, the amination of 2-halo-5-nitroacetophenone[6] and the derivatization of 4-nitroaniline-2-carboxylic acid[7] are the most commonly employed strategies. However, troublesome multi-step reactions are necessary for the preparation of the starting materials in previously reported methods. In contrast, the ring transformation methods described in this work reduces the number of reaction steps and makes the reaction practically applicable for the development of new functional materials.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.11.003.

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