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One-pot tandem synthesis of 2, 3-unsubstituted indoles, an improved Leimgruber-Batchoindole synthesis

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A concise, fast and efficient one-pot methodology has been developed for preparing 2, 3-unsubstituted indoles from 2-nitrotoluenes and dimethylformamide dimethyl acetal. Compared with the classical Leimgruber-Batcho reaction, such one-pot process simplified the operation procedures, generated less by-products and chemical residues, and resulted in higher overall yields in a shorter reaction time.

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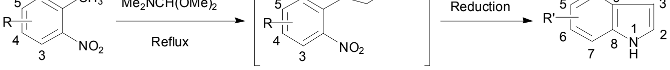
Introduction

The indole ring system is a significant structural component of a great number of biologically active natural and synthetic compounds, and it exists in plenty of pharmaceutical agents, dyestuffs, and pharmaceutical or agrochemical intermediates.[1] Despite numerous methods for the construction of indole ring have been developed in the past decades,[2] organic chemists are still to search for more straightforward, economical and green ways to make various substituted indoles, such as the transition-metal-catalyzed synthesis [3] and multistep one-pot synthesis [4].

The Leimgruber-Batcho indole synthesis is an important and efficient method of synthesizing substituted indoles, especially for the preparation of 2, 3-unsubstituted indoles. The classical Leimgruber-Batchoindole synthesis involves two steps reaction process, including the condensation of an appropriately substituted *o*-nitrotoluene with dimethylformamide dimethyl acetal (DMF-DMA) to give intermediate *o*-nitrophenylacetaldehyde enamine, and the subsequent reductive cyclization to furnish the substituted indoles.[5] Due to the fact that the starting material *o*-nitrotoluene derivatives are easily prepared and both two steps proceed under mild reaction conditions, this method has enjoyed widespread applications from laboratory to industry owing to the high functional group compatibility.[2d, 6] Nevertheless, there are also some drawbacks including relatively prolonged reaction time and cumbersome isolation procedures of enamine intermediates.[7] Some modification of this reaction has been developed, including the variation of the applied base, the reducing reagents, and the available acetals of dimethylformamide [8] as well as microwave-assisted synthesis [7b], *etc*..



Scheme 1. One-pot tandem synthesis of 2, 3-unsubstituted indoles.

Here, a concise, fast and efficient method was reported to synthesize indoles via the Leimgruber-Batcho reaction, which is a one-pot reaction directly from *o*-nitrotoluene derivatives to corresponding indole products (Scheme 1) without separation of enamine intermediates. The method was more concise and obtained higher yields with a much shorter reaction time compared with the conventional Leimgruber-Batcho indolization routes.

Results and discussion

We began our study by examining the one-pot reaction of 4-chloro-2-nitrotoluene (**1b**) and DMF-DMA (Scheme 1; R = Cl) as the standard reaction (Table 1). Gratifyingly, the expected product **3b** was obtained when the reaction was carried out in DMF, which was usually used in the first step in the classic Leimgruber-Batcho indole synthesis (Table 1, entry 1). It means that the one-pot synthesis of indoles *via* Leimgruber-Batcho reaction method is feasible. However, the total yield of **3b** was relatively low, just 36% within 10 h. According to the reaction process, the influence factors on this one-pot reaction are including solvent, additive, reducing agent, catalyst, and temperature. Thus, we thoroughly studied these influence factors on the one-pot reaction.

From Table 1, it was noted that the solvent had a great influence on both the yield and the rate of the reaction. The solvent screening showed that dioxane was the best option (Table 1, entries 1-5), and then following toluene, THF, DMF and methanol, respectively. DMF was unsuitable to this one-pot synthesis, due to the inhibition effect of DMF on Raney Ni and Pd/C in catalytic hydrogenation reaction.[9] In THF, because of its lower reflux temperature (about 66 ℃) in the reaction, the one-pot synthesis rate and yield were both lower than those in dioxane. The yield was only 13% when methanol was used (Table 1, entry 5). We supposed that, with methanol as a solvent, the formation of the intermediate carbanion **B** was probably suppressed and so the reaction was inhibited (Scheme 2).

The presence of pyrrolidine, as an additive, especially excess amount of pyrrolidine could greatly promote the reaction (Table 1, entries 4, 6, and 10), which could be predicted from the reaction mechanism presented in Scheme 2. We thought that excess amount of pyrrolidine could not only promote step a to generate compound **A** with a much higher reactivity than DMF-DMA, but also would be advantageous to *o*-nitrotoluene deprotonation (step b) to generate carbanion **B** as a proton acceptor. Additionally, the influence of other nitrogenous nucleophilic reagents, such as diethylamine,

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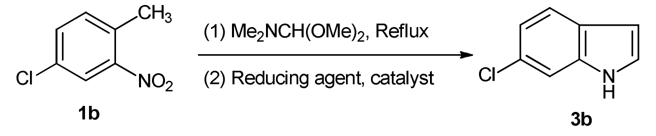
piperazine, morpholine, were also investigated. Nevertheless, all results were inferior compared with pyrrolidine (Table 1, entries 7-9).

Table 1. Optimization of the one-pot synthesis.[a]



1b **3b**

Entry	Solvents	Additives	Reducing agents	T/℃[b]	t/h	Y/%[c]
1	DMF	Pyrrolidine	85% N_2H_4	45	10	36
2	THF	Pyrrolidine	85% N_2H_4	45	10	65
3	Toluene	Pyrrolidine	85% N_2H_4	45	10	72
4	Dioxane	Pyrrolidine	85% N_2H_4	45	5.5	90
5	MeOH	Pyrrolidine	85% N_2H_4	45	10	13
6	Dioxane	Pyrrolidine (1.2 equiv)	85% N_2H_4	45	18	57
7	Dioxane	Diethylamine	85% N_2H_4	45	24	22
8	Dioxane	Piperazine	85% N_2H_4	45	15	trace[e]
9	Dioxane	Morpholine	85% N_2H_4	45	15	trace[e]
10	Dioxane	—	85% N_2H_4	45	32	trace[e]
11	Dioxane	Pyrrolidine	85% N_2H_4 （6 equiv）	45	9	63
12	Dioxane	Pyrrolidine	85% N_2H_4 （2 equiv）	45	15	28
13	Dioxane	Pyrrolidine	60% N_2H_4	45	6.5	82
14	Dioxane	Pyrrolidine	30% N_2H_4	45	7.5	77
15[d]	Dioxane	Pyrrolidine	85% N_2H_4	45	14	35
16[e]	Dioxane	Pyrrolidine	85% N_2H_4	45	14	8[f]
17	Dioxane	Pyrrolidine	85% N_2H_4	20	5.5	70
18	Dioxane	Pyrrolidine	85% N_2H_4	60	5.5	76
19[g]	Dioxane	Pyrrolidine	85% N_2H_4	45	10	46
20	Dioxane	Pyrrolidine	H_2	45	5.5	85

[a] Reaction conditions (unless otherwise stated): **1b** (4 mmol), DMF-DMA (4.8 mmol), additive (5 equiv), hydrazine (10 equiv), catalyst: 200 mg Raney nickel, in solvent (50 ml), under nitrogen atmosphere. [b] Reduction temperatures. [c] Isolated yields. [d] Catalyst: 40 mg 5%Pt/C. [e] Catalyst: 40 mg 5%Pd/C. [f] Examined by GC/MS. [g] Catalyst: 40 mg Raney nickel.

The yield of product **3b** reached 85% within 5.5 h when hydrogen gas was used as the reducing agent. If considering the safety and the large scale of the reactions, we thought that H_2 was also a good reducing agent compared with hydrazine hydrate (Table 1, entries 4 and 20). Additionally, the yields of **3b** reduced from 90% to 77% (entries 4 and 14) as the concentration of hydrazine hydrate decreased from 85% to 30%, which maybe because such decreased concentration of hydrazine hydrate produced a small amount of 1-hydroxindoles as by-product at the expense of indoles **3**.[10] Also, the decreased amount of hydrazine hydrate resulted in both lower yields and reaction rate (Table 1, entries 4, 11 and 12). We also examined the reactions with different catalysts (Ni, Pt, Pd). The results showed that the reaction catalyzed by Raney nickel worked much better than others (Table 1, entries 4, 15, and 16). When the amount of Raney nickel was reduced to 40 mg, the yield of **3b** decreased to 46%, meanwhile, the reaction time was prolonged to 10 h (Table 1, entry 19).

Besides, the reaction temperatures in the reduction procedure were also evaluated. The yields were both reduced whether the reaction was performed at 20 ℃ or 60 ℃ (Table 1, entries 4, 17-18), in which some enamine intermediates were still present in one-pot reaction at 20 ℃, however, some hydrodechlorinated products were formed at 60 ℃ according to the analysis of GC-MS.

After optimizing the reaction conditions, that the reaction proceeded in dioxane at the presence of pyrrolidine (5 equiv), using 85% hydrazine hydrate (10 equiv) as reducing agent, catalyzed by Raney nickel (200 mg) at 45 ℃ was selected to be an optimal condition for such one-pot synthesis of indole derivatives **3**.

To explore the generality of one-pot methodology, the optimized reaction condition was applied to synthesize a series of differently substituted indoles summarized in Table 2. The results suggested that all the *o*-nitrotoluene derivatives with various substituents could be performed smoothly, producing desired products, of which the reaction rates were greatly increased compared with those reported in literature [7a] (Table 2, entries 2-4). It was also noted that the developed one-pot protocol provided higher yields than the conventional Leimgruber-Batcho routes (Table 2, entries 2-4). Especially, the yield of **3b** was up to 90%, while the overall yield *via* the conventional routes was only 30% (Table 2, entry 2). However, the synthesis for 7-methylindole (**3l**) obtained a relatively low yield even with prolonged heating for 22 h or longer (Table 2, entry 12) and the similar results could be seen in the literature [7a]. The low yields of **3l** as well as **3j** probably resulted from steric effect.

As shown in Table 2, both the variety and position of substituents have a significant influence on the reaction. As for the same substituent group, the *o*-nitrotoluene derivatives substituted in 4 and 5 positions resulted in both better yields and higher reaction rate compared with those substituted in 3 and 6 positions (Table 2, entries 2-12). Additionally, the substituted *o*-nitrotoluenes with an electron-withdrawing group on the aromatic ring moiety showed higher reaction rate than the unsubstituted *o*-nitrotoluene, which were also faster than those having an electron-donating group (Table 2, entries 1-9, 11-12). The synthesis of **3j** was an exception with higher reaction rate than unsubstituted **3a** with the lowest yield

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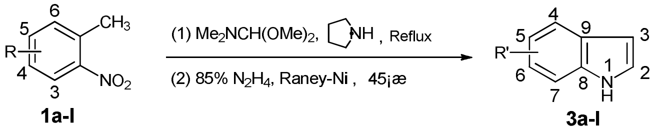
instead (Table 2, entries 1 and 10). Also, as to *o*-nitrotoluenes substituted at the same position, *o*-nitrotoluenes with an electron-withdrawing group afforded higher yields than those with an electron-donating group (Table 2, entries 5-7, 9-12). It was concluded that electron-withdrawing group substituted *o*-nitrotoluenes exhibited higher reactivities than those electron-donating group substituted *o*-nitrotoluenes, which was consistent with the reaction mechanism presented in Scheme 2 suggesting that electron-withdrawing groups involving halogenatoms with stronger electronegativity could accelerate step b to generate carbanion **B** due to the inductive effect.

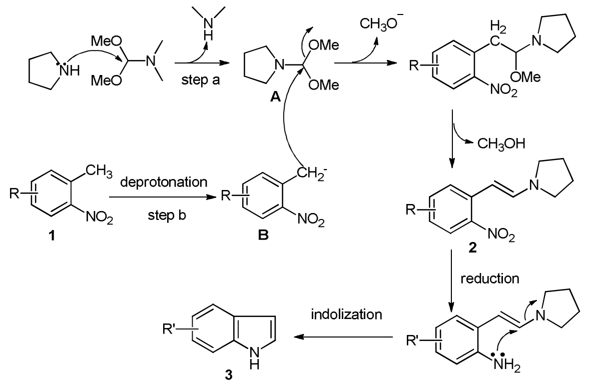
Table 2. One-pot synthesis of indole derivatives **3**.



1a-l **3a-l**

Entry	R	1	t/h	R'	3	Y/%[a]
1	H	**1a**	10	H	**3a**	71
2	4-Cl	**1b**	5.5, 24[b]	6-Cl	**3b**	90, 30[b]
3	4-Br	**1c**	3.5, 31[b]	6-Br	**3c**	82, 37[b]
4	4-NO_2	**1d**	5	6-NH_2	**3d**	52, 35[b]
5	5-CH_3	**1e**	14	5-CH_3	**3e**	65
6	5-CN	**1f**	2.5	5-CN	**3f**	71
7	5-Cl	**1g**	6	5-Cl	**3g**	74
8	4,5-Cl	**1h**	5	5,6-Cl	**3h**	92
9	6-Cl	**1i**	9	4-Cl	**3i**	55
10	6-NH_2	**1j**	6.5	4-NH_2	**3j**	34
11	3-Cl	**1k**	9	7-Cl	**3k**	70
12	3-CH_3	**1l**	22	7-CH_3	**3l**	53

[a] Isolated yields. [b] Data reported for the classic Leimgruber-Batcho routes.[7a]



Scheme 2. The reaction mechanism from *o*-nitrotoluenes to indoles.

On the basis of these preliminary results, the reaction mechanism was hypothesized as shown in Scheme 2, DMF-DMA is initially attacked by pyrrolidine via nucleophilic substitution to produce compound **A**, which could be subsequently attacked by carbanion **B** generated by deprotonation from *o*-nitrotoluene derivatives to produce enamine intermediate **2**. The intermediate **2** then undergoes reduction by hydrogen coming from hydrazine hydrate under the catalysis of Raney nickel, followed by cyclization to obtain the expected product **3**. According to the mechanism, we can infer that both excess amounts of pyrrolidine and electron-withdrawing groups on the aromatic ring moiety could promote step b to generate carbanion **B** and thus lead to quicker reaction rates.

Experimental

General Procedure for One-Pot Reaction from *O*-nitrotoluenes

A 100 mL three-necked flask equipped with magnetic stir bar and a condenser was charged with *o*-nitrotoluenes (4 mmol), DMF-DMA (4.8 mmol), pyrrolidine (20 mmol), and dioxane (50 mL) at 102 ℃ under nitrogen atmosphere for 2.5-22 h. The progress of the reaction was monitored by TLC. After the reaction was cooled to 45 ℃, 0.2 g of Raney nickel was added followed by 0.8 g of 85% hydrazine hydrate. Vigorous gas evolution was observed. An additional 0.8 g of 85% hydrazine hydrate was added after 30 min and again 30 min later. The temperature was maintained at 45 ℃. After completion of the reaction, the mixture was cooled to room temperature and the catalyst was filtered off and washed carefully with 5×10 ml dichloromethane or acetone. The filtrate was evaporated under reduced pressure, and the residue thus obtained was then purified by column chromatography on silica gel using a mixture of dichloromethane and petroleum ether as eluent to afford the desired product **3**.

Conclusions

In conclusion, we developed a simple and efficient one-pot tandem methodology to synthesize 2, 3-unsubstituted indoles from *o*-nitrotoluenes which was derived from the Leimgruber-Batcho reaction. Compared with the conventional Leimgruber-Batcho indole synthesis, not only would such one-pot process eliminate the need for isolation of the potentially unstable enamine intermediates, but also it would decrease the amounts of by-products and chemical wastes generated. Furthermore, it has been shown that the overall yields for one-pot procedures were higher (about twice) in a shorter reaction time than those of step-by-step processes. Additionally, it was found that the electron-withdrawing groups substituted *o*-nitrotoluenes exhibited higher reactivities and yields than those electron-donating groups substituted *o*-nitrotoluenes.

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Notes and references

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