



An efficient route to 2,3-disubstituted indoles via reductive alkylation using H₂ as reductant

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ABSTRACT

An efficient route to 2,3-disubstituted indoles was developed via reductive alkylation of 2-substituted indoles using hydrogen as a clean and atom economic reductant under ambient pressure.

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Substituted indoles are important structures due to their wide distribution in nature products and biologically active molecules.¹ Among them, 2,3-disubstituted indole, bearing substitutes at both C-2 and C-3 positions, is a particular subclass of substituted indoles, which are the core nucleus of many promising therapeutic agents.² Considering the significance of this kind of compounds, a variety of synthetic methods have been developed over the past hundred years. For example, the venerable Fischer indole synthesis was discovered as early as 1883,³ and recently various transition-metal-catalyzed transformations were developed.⁴ Despite the progress achieved, continual emergence of novel biologically active indole-containing natural products promotes the development of new and convenient access to 2,3-disubstituted indoles.⁵

Among the numerous methods developed, the most direct and divergent method to 2,3-disubstituted indoles is via C-3 Friedel–Crafts alkylation reaction of simple and commercially available 2-substituted indoles with aldehydes or ketones.⁶ Nevertheless, the products are 3-(α -hydroxyalkyl) indoles and an extra step of reduction has to be performed to obtain 3-alkyl substituted indoles. Reductive alkylation that is based on tandem Friedel–Crafts alkylation and removing of hydroxyl could occur under mild condition, thus C-3 alkyl substituted indoles can be attained in one pot (Scheme 1). Due to its high efficiency in the synthesis of C-3 substituted indoles, reductive alkylation has been studied by several groups. Steele,⁷ Mahadevan,⁸ Campbell,⁹ and Zhang¹⁰ have em-

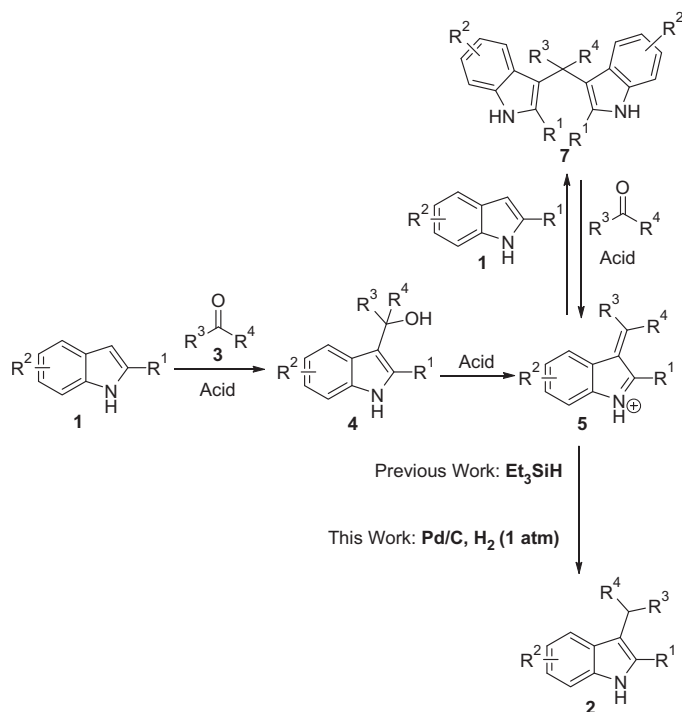
ployed this method to get the desired compounds using triethylsilane as the reductant. Though triethylsilane is efficient, its atom economy is low and the further purification is relatively complex. Meanwhile, hydrogen gas is considered as a clean reductant and its application in indoles' reductive alkylation has not been reported up to now despite the operational simplicity and atom economy. Herein, we described an efficient route to 2,3-disubstituted indoles via reductive alkylation of simple 2-substituted indoles with aldehydes or ketones using H₂ as a clean and atom economy reductant under ambient pressure.

As we know, benzylic alcohol can be conveniently reduced by Pd/C–H₂ system in the presence of acid.¹¹ We envisaged that the dehydration reduction of Friedel–Crafts reaction products, 3-(α -hydroxyalkyl) indoles **4**, might be feasible under Pd/C–H₂ system. So, dehydration reduction of 3-(α -hydroxyalkyl) indoles **4** was investigated using Pd/C as a catalyst in the presence of a weak acid (PhCO₂H) with H₂ (1 atm). To our delight, the desired products **2** were obtained in excellent yields (Scheme 2). Encouraged by these results, direct reductive alkylation of 2-substituted indoles with aldehydes or ketones in one pot was investigated using hydrogen gas as reductant in the presence of Brønsted acid.

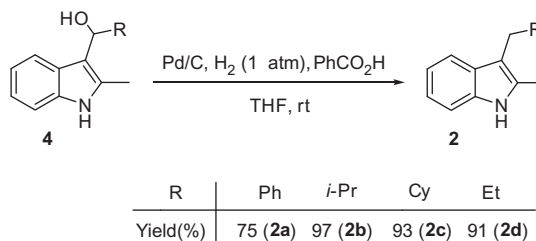
Initial studies were conducted using 2-methylindole and benzaldehyde (1.1 equiv) as a model reaction with H₂ (1 atm) as the reductant (Table 1). Firstly, the reaction was carried out in THF using PhCO₂H as the acid under room temperature. The mixture was stirred for 4 h and to our disappointment no desirable reaction occurred (Table 1, entry 1). In principle, strong acid and low temperature facilitate the Friedel–Crafts reaction,^{7–10} but poor results were still obtained when the reaction was carried out in THF (Table 1, entries 2 and 3). Then, the effect of solvent on the reactivity was

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Scheme 1. Reductive alkylation of indoles.



Scheme 2. The reduction of 2-methyl-3-(α -hydroxyalkyl)indoles **4** under Pd/C–H₂ system.¹²

examined. CH₂Cl₂ was found to be the most effective among the solvents tested, this may attribute to CH₂Cl₂ facilitated Friedel–Crafts reaction, and the yield of the desired product was sharply increased to 95% (Table 1, entry 5). In addition to TFA, we compared the effect of several other Brønsted acids such as TsOH, CSA, and PhCO₂H. PhCO₂H failed to deliver the product (Table 1, entry 6), TFA showed the best catalytic reactivity. Thus, the optimized condition was established as: Pd/C–H₂ (1 atm)/CH₂Cl₂/TFA/0 °C.

With the optimized conditions in hand, we turned our attention to an investigation of the scope of this transformation. The results are summarized in Table 2. As expected, various aldehydes worked well under the standard reaction conditions. Particularly, aliphatic aldehydes were also good reaction partners, moderate to excellent yields were obtained (Table 2, entries 2–4). Remarkably, the transformation is also tolerant of *ortho*-substitution in aromatic aldehydes, and the steric hindrance had no effect on the reaction (Table 2, entries 5 and 7). The effect of the electronic properties of the substituents on the phenyl ring of the aryl aldehydes was also investigated. Generally, substrate bearing electron-donating substituents showed high reactivity and 2-methoxy-benzaldehyde gave the highest yield (Table 2, entry 7), whereas an electron-withdrawing group decreased the efficiency. Take 4-fluoro-benzaldehyde for example, the yield was dramatically decreased to 68%

Table 1
Optimization of reaction condition of reductive alkylation^a

Entry	Solvent	Temp (°C)	Acid ^b (1.5 equiv)	Yield ^c (%)
1	THF	25	PhCO ₂ H	<5
2	THF	25	TFA	<5
3	THF	0	TFA	<5
4	Toluene	0	TFA	29
5	DCM	0	TFA	95
6	DCM	0	TsOH·H ₂ O	62
7	DCM	0	CSA	83
8	DCM	0	PhCO ₂ H	<5

^a Conditions: **1a** (1.0 mmol), **3a** (1.1 mmol), acid (1.5 mmol), 5% Pd/C (15 mg).

^b TFA: trifluoroacetic acid; TsOH·H₂O: *p*-toluenesulfonic acid monohydrate; CSA: camphorsulfonic acid.

^c Isolated yields based on **1a**.

Table 2
Reductive alkylation of indoles with various aldehydes and ketones^a

Entry ¹³	R ¹	R ²	R ³	R ⁴	Yield ^b (%)
1	Me	H	Ph	H	95 (2a)
2	Me	H	<i>i</i> -Pr	H	96 (2b)
3	Me	H	Cy	H	89 (2c)
4	Me	H	<i>n</i> -Pentyl	H	81 (2e)
5	Me	H	2-MeC ₆ H ₄	H	95 (2f)
6	Me	H	4-MeC ₆ H ₄	H	92 (2g)
7	Me	H	2-MeOC ₆ H ₄	H	99 (2h)
8	Me	H	3-MeOC ₆ H ₄	H	93 (2i)
9	Me	H	4-MeOC ₆ H ₄	H	83 (2j)
10	Me	H	4-FC ₆ H ₄	H	68 (2k)
11	Me	5-F	Ph	H	72 (2l)
12	Ph	H	Ph	H	94 (2m)
13	H	H	–(CH ₂) ₅ –	H	62 (2n)
14	Me	H	–(CH ₂) ₅ –	H	95 (2o)
15 ^c	Me	H	Ph	Me	29 (2p)
16 ^d	Me	H	Ph	Me	82 (2p)

^a Conditions: **1** (2.0 mmol), **3** (2.2 mmol), 5% Pd/C (30 mg), CF₃CO₂H (3.0 mmol), 0 °C.

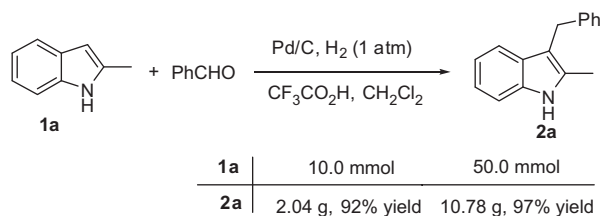
^b Isolated yields based on **1**.

^c The reaction was carried out at 0 °C.

^d The reaction was carried out at 40 °C.

(Table 2, entry 10). Various substituted indoles reacted smoothly, affording the products in moderate to excellent yields. The electron-withdrawing group (5-F) of the indole core gave a slight decreased yield, and steric hindrance (2-Ph) had no obvious influence on the outcome of the reaction (Table 2, entries 11 and 12). Notably, ketones were also compatible in this reaction. When cyclohexanone was employed, 95% yield was obtained (Table 2, entry 14). However, when acetophenone reacted with 2-methylindole, only 29% conversion was obtained. Fortunately, increasing the reaction temperature to 40 °C, yield of **2p** was increased to 82% (Table 2, entries 15 and 16).

It is noted that the reductive alkylation of indole **1a** also could be carried out in an enlarged scale with Pd/C–H₂ (1 atm) system.



Scheme 3. Scale up of reductive alkylation of indole **1a**.

As illustrated in **Scheme 3**, the desired product **2a** was obtained in 92% yield at 10 mmol scale and in 97% yield at 50 mmol scale, respectively.

In summary, we have developed an efficient and facile approach to 2,3-disubstituted indoles via reductive alkylation of simple 2-substituted indoles with aldehydes or ketones using hydrogen as a clean and atom economic reductant under ambient pressure. The main advantages of this route are excellent yields, simple operation, and purification procedures.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2011.03.099](https://doi.org/10.1016/j.tetlet.2011.03.099).

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- General procedure from 2-methyl-3-(α -hydroxyalkyl)-indoles 4 to 2,3-disubstituted indoles 2*: compound **4** (2.0 mmol) was dissolved in 10 mL THF, and PhCO₂H (0.2 mmol), 5% Pd/C (30 mg) was added. The mixture was stirred at room temperature under H₂ (1 atm, hydrogen balloon) atmosphere for 12 h, then the product was purified by flash chromatography on silica gel using EtOAc/hexanes (1:5) as eluent.
- General procedure from 2-substituted indole 1 to 2,3-disubstituted indoles 2*: a solution of 2-substituted indole **1** (2 mmol) and the aldehyde or ketone **3** (2.2 mmol) in CH₂Cl₂ (10 mL) was added dropwise to a stirred, ice-cold solution of TFA (3.0 mmol) and 5% Pd/C (30 mg) in CH₂Cl₂ (5 mL) under H₂ (1 atm, hydrogen balloon) atmosphere. The mixture was stirred at 0 °C and monitored by TLC until completed (4–8 h). After evaporation of the solvent under reduced pressure, the product was purified by flash chromatography on silica gel using EtOAc/hexanes (1:5) as eluent.