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An Efficient Preparation of 2, 3-Disubstituted Indole Derivatives Induced by Low-valent Titanium

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Abstract: An efficient synthesis of 2, 3-disubstituted indole derivatives through low-valent titanium induced reductive cyclization of acylamido carbonyl compounds is described.

Keywords: Indole derivatives, low-valent titanium, reductive cyclization process.

Indole and its derivatives have captured the imagination of organic chemists for more than a century. Early works in this area mainly focused on the preparation of dyestuffs containing indole nucleus. However, since the isolation of indole alkaloids as the active principles from medicinal plants (*i.e.* antibiotics, anti-inflammatory, antihypertensive and antitumor agents), the indole nucleus has taken on considerable pharmacological importance. Therefore, it is not surprising that up to now many methods have already been developed for the synthesis of this kind of heterocyclic system[1]. However, due to the unavailability of some patterns of indole substitution using classic methods and the need for efficient ways to synthesize more elaborate structures possessing biological activity, the development of novel and convenient methods for the preparation of indole derivatives still remains an active research area.

The titanium-induced coupling of carbonyl compounds to alkenes is a particularly useful tool for the formation of carbon-carbon bonds and has witnessed its potential in the preparation of natural products and the formation of strained olefins and carbocycles. Recently, this transformation has been extended to the synthesis of heterocycles. Thus, on treatment with titanium on graphite[2], suitably substituted acylamido carbonyl compounds were smoothly cyclized to indole derivatives in good to excellent yields, although amides were hitherto considered to be essentially inert towards low-valent titanium[3]. Unfortunately, this process necessitates the using of hazardous compound such as metallic potassium or potassium-graphite laminate (C_8K) to prepare the active titanium species. What is more, as much as 6 equiv of metallic potassium, 50 equiv of graphite laminate relative to 1 equiv of substrate must be employed to get the desired

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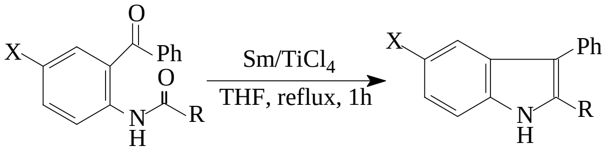
product in reasonable yield. Besides $TiCl_3/C_8K$, low-valent titanium reagent prepared from $TiCl_3/Zn$ system has also been reported as an efficient promoter in this coupling process[4~6]. But this method still has the disadvantage of needing excessive reagents. In fact, as many as 2~3 equiv of $TiCl_3$ and 4~8 equiv of zinc dust must be involved for a complete conversion of 1 equiv of substrate. On the other hand, we have reported that low-valent titanium reagent could also be prepared from Cp_2TiCl_2-Sm[7a] or $TiCl_4$-Sm[7b] system and the low-valent titanium reagent so formed has been successfully used in various reductive coupling processes. Herein, we wish to report that low-valent titanium reagent prepared from metallic samarium and $TiCl_4$ can efficiently promote acylamido carbonyl compounds (**1**) to undergo intramolecular reductive cyclization to give indole derivatives (**2**) in moderate to good yields under mild reaction conditions. The results were listed in **Scheme 1** and **Table 1**.

Scheme 1



1 **2**

Table 1 Preparation of indole derivatives through Sm/$TiCl_4$ induced intramolecular reductive coupling of acylamido carbonyl compounds

Entry	X	R	Yield (%)[a]
a	H	C_6H_5	89
b	H	4-$CH_3C_6H_4$	91
c	H	4-FC_6H_4	94
d	H	CH_3	83
e	H	CH_3CH_2	81
f	Cl	C_6H_5	90
g	Cl	4-$CH_3C_6H_4$	86
h	Cl	4-ClC_6H_4	83
i	Cl	4-FC_6H_4Ph	88
j	Cl	CH_3	78

a) Isolated yields based on **1**.

In a typical experimental procedure, titanium tetrachloride (0.22 mL, 2 mmol) was added to a stirred suspension of samarium powder (0.33 g, 2.2 mmol) in THF at room temperature under a nitrogen atmosphere. After completion of the addition, the mixture was refluxed for 2 h. Suspension of the low-valent titanium reagent so formed was cooled to room temperature and a solution of 2-benzamidobenzophenone (**1a**, 1 mmol) in anhydrous THF (2 mL) was added. Then, the mixture was refluxed for an hour. During this period of time, the deep dark color of the solution gradually changed into a brownish red. At completion, the reaction was quenched with dilute HCl and extracted with ether (3 × 20 mL). The combined extract was washed with saturated brine (15 mL) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the resulting crude product was purified by preparative TLC using ethyl acetate and cyclohexane (1:7) as eluant. Other 2, 3-disubstituted indoles were obtained in a similar manner.

In summary, we have found that low-valent titanium reagent derived from metallic samarium and $TiCl_4$ can efficiently promote acylamido carbonyl compounds to undergo intramolecular reductive cyclization to give indole derivatives in fair yields. Several merits of our method are worth to be mentioned here. Firstly, in contrast with the process reported in the literatures[2, 4~6], in which excess reagents relative to the substrates should be employed, 2 equiv of metallic samarium and titanium tetrachloride is enough to push the reductive cyclization to be completed with our process. Secondly, both substrates bearing electron donating groups and substrates bearing electron withdrawing groups undergo smoothly reductive cyclization process and give the desired products with equally fair yields. It means that this method may afford a general method for the preparation of 2,3-disubstituted indole derivatives with good yields under mild reaction conditions.

Acknowledgments

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