SHORT PAPER

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Facile preparation of 2,3-disubstituted indole derivatives through low-valent titanium induced intramolecular reductive coupling reactions of acylamido-carbonyl compounds†

Xuesen Fan* and Xinying Zhang

School of Chemical and Environmental Sciences, Key Laboratory of Environmental Science and Engineering of Henan Education Department, Henan Normal University, Xinxiang 453002, P. R. China

An efficient synthesis of 2,3-disubstituted indole derivatives through low-valent titanium induced reductive cyclisation of suitably substituted acylamido-carbonyl compounds is described.

Keywords: 2,3-disubstituted indole derivatives, low-valent titanium, acylamido-carbonyl compounds

Indole and their derivatives have captured the imagination of organic chemists for more than a century.[1] Early works mainly focused on the preparation of dyestuffs containing the indole nucleus. However, since the isolation of the indole alkaloids as the active principals from medicinal plants (*i.e.* antibiotics, anti-inflammatory, anti-hypertensive and anti-tumor agents), the indole nucleus has taken on considerable pharmacological importance. It is not surprising that up to now many methods have already been developed for the synthesis of this kind of heterocyclic system.[2] Nonetheless, with the structural elucidation of increasingly complex indole alkaloids, new more efficient and practical methodology for assembly of the indole nucleus is still required.

The titanium-induced coupling of carbonyl compounds to alkenes (known as the McMurry reaction)[3] is a particularly useful tool for the formation of carbon–carbon bonds in many natural product syntheses, the formation of strained olefins and the preparation of carbocycles. Recently, this transformation has been extended to the formation of heterocycles. Thus, on treatment with titanium on graphite,[4] 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.[5] 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. Moreover, as much as 6 equiv of metallic potassium and 50 equiv of graphite laminate relative to 1 equiv of substrates must be employed to get the desired products in reasonable yields. Thus, this method seems to be unsuitable for up-scaling. On the other hand, it has been reported that a low-valent titanium reagent could also be prepared from the Cp_2TiCl_2–Sm[6] or $TiCl_4$–Sm[7] systems and the low-valent titanium reagent so formed has been used successfully in various reductive coupling processes. Here we report that the low-valent titanium reagent prepared from metallic samarium and $TiCl_4$ can promote efficiently acylamido-carbonyl compounds (**1**) to undergo intramolecular reductive cyclisation to give indole derivatives (**2**) in moderate-to-good yields under mild reaction conditions. The results were listed in Scheme 1 and Table 1.

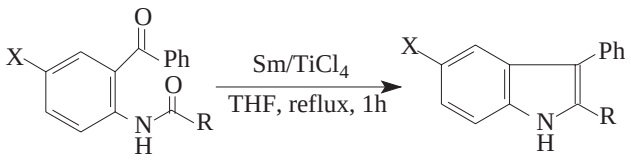
From Table 1, we found that when suitably substituted acylamido-carbonyl compounds **1** were treated with our Sm/$TiCl_4$ system, the corresponding indoles **2** were obtained in fair yields. Several aspects of this process are worth mentioning:

(i) This reductive process underwent smoothly and was completed within an hour under reflux conditions. It should be noted that both substrates derived from 2-aminobenzophones and aryl acyl chlorides and substrates derived from 2-aminobenzophones and alkyl acyl chlorides underwent the reductive coupling process almost equally well.

(ii) In contrast with the method reported in the literature,[4] in which excess reagents relative to the substrates should be employed, just 2 equiv of titanium reagent is enough to push the reductive cyclisation process to completion in our process. It makes our process more economical and ecologically benign, thus more practical for up-scaling.

(iii) The observation that intra-molecular keto-amide coupling completely overcome the inter-molecular diketone coupling contrasts with the previous experiences with low-valent titanium-induced reactions.

(iv) Both substrates bearing electron donating groups and substrates bearing electron withdrawing groups underwent smoothy reductive cyclisation and gave the desired products in



1 **2**

Scheme 1

Table 1 Synthesis 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 oxo amides.

* To receive any correspondence. E-mail: fanxs88@263.net

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fair yields. The absence of observable substituent effect and the chemo-selectivity in such reducible groups as chloride and fluoride suggests that this method may afford a general method for the preparation of 2,3-disubstituted indole derivatives.

In summary, we have found that a low-valent titanium reagent derived from metallic samarium and $TiCl_4$ can efficiently promote suitably substituted acylamido-carbonyl compounds to undergo intramolecular reductive cyclization to give indole derivatives in fair yields. With its mildness, convenience and environmental benignancy, the method presented above may be used as an attractive alternative to the previously reported methods for the preparation of indole derivatives. Studies to find new uses of the $Sm/TiCl_4$ system in the synthesis of heterocyclic compounds are now in progress in our laboratory.

Experimental

Tetrahydrofuran was distilled from sodium-benzophenone ketyl immediately prior to use. Melting points were uncorrected. Infrared spectra were recorded on a Bruker Vector 22 spectrometer with absorption in cm^{-1}. ^1H NMR spectra were determined on a Bruker AC-400 (400 MHz) spectrometer as $CDCl_3$ solutions. Chemical shifts were expressed in ppm downfield from the internal standard tetramethylsilane. Mass spectra were recorded on a HP 5989B mass spectrometer. Elemental analyses were carried out on a Carlo-Erba EA 1110 instrument.

General procedure for the preparation of 2,3-disubstituted indoles: Under anhydrous conditions, titanium tetrachloride (0.22 ml, 2 mmol) was added dropwise using a syringe to a stirred suspension of samarium powder (0.33 g, 2.2 mmol) in THF (10 ml) at room temperature under a dinitrogen atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was then cooled to room temperature and a solution of substrate **1** (1 mmol) in anhydrous THF (2 ml) was added. The mixture was refluxed for an hour, during which, the deep dark colour of the solution changed into a brownish red gradually. 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.

2a: *2,3-Diphenylindole*: colourless crystal, m.p.121–123°C (lit.[4] 122–124°C); IR (KBr) ν 3410, 1605, 1516, 1486 cm^{-1}; ^1H NMR δ 8.36 (s, 1H, NH), 7.83 (d, 1H, *J* = 8.4 Hz), 7.28–7.68 (m, 13H). MS *m/z* (%): 269 (M^+, 100).

2b: *2-(4-Methylphenyl)-3-phenylindole*: syrup, IR ν 3409, 1602, 1514, 1487 cm^{-1}; ^1H NMR δ 8.44 (s, 1H, NH), 7.85 (d, 1H, *J* = 8.0 Hz), 7.60 (d, 2H, *J* = 8.0 Hz), 7.30–7.53 (m, 7H), 7.21 (d, 2H, *J* = 8.0 Hz), 2.47 (s, 3H); ^{13}C NMR δ 21.4, 111.1, 114.7, 119.8, 120.6, 122.7, 126.4, 128.3, 128.7, 129.0, 129.9, 130.4, 134.5, 135.5, 136.0, 137.7; MS *m/z* (%): 283 (M^+, 100). Anal. Calcd for $C_{21}H_{17}N$: C 89.01, H 6.05, N 4.94; Found: C 88.90, H 6.15, N 4.88.

2c: *2-(4-Fluorophenyl)-3-phenylindole*: m.p. 133–135°C; IR (KBr) ν 3410, 3050, 1605, 1515, 1489 cm^{-1}; ^1H NMR, 8.20 (br s, 1H, NH), 7.66 (d, 1H, *J* = 8.0 Hz), 7.35–7.43 (m, 7H), 7.28–7.32 (m, 3H), 6.99–7.04 (m, 2H). ^{13}C NMR δ 111.0, 115.1, 115.7, 115.9, 119.7, 120.6, 122.8, 126.4, 128.6, 128.7, 128.8, 128.9, 129.9, 130.0, 130.1, 133.2, 135.0, 135.9, 161.1, 163.6; MS *m/z* (%): 287 (M^+, 100). Anal. Calcd for $C_{20}H_{14}FN$: C 83.60, H 4.91, N 4.87; Found: C 83.46, H 4.82, N 4.72.

2d: *2-Methyl-3-phenylindole*: colourless crystal, m.p. 56–57°C (lit.[4] 58–61°C); IR (KBr) ν 3405, 3038, 2965, 1603, 1556, 1489 cm^{-1}; ^1H NMR, 7.96 (s, 1H, NH), 7.78 (d, 1H, *J* = 8.0 Hz), 7.57–7.64 (m, 4H), 7.44–7.22 (m, 4H), 2.52 (s, 3H); MS *m/z* (%): 207 (M^+, 100).

2e: *2-Ethyl-3-phenylindole*: syrup, IR ν 3413, 3060, 2971, 1603, 1495 cm^{-1}; ^1H NMR, 7.93 (s, 1H, NH), 7.76 (d, 1H, *J* = 8.0 Hz), 7.53–7.61 (m, 4H), 7.36–7.42 (m, 2H), 7.18–7.29 (m, 2H), 2.92 (q, 2H, *J* = 7.6 Hz), 1.35 (t, 3H, *J* = 7.6 Hz). ^{13}C NMR δ 14.5, 19.8, 110.7, 113.9, 119.1, 120.1, 121.7, 126.1, 128.1, 128.7, 129.7, 135.4, 135.6, 137.5; MS *m/z* (%): 221 (M^+, 100). Anal. Calcd for $C_{16}H_{15}N$: C 86.84, H 6.83, N 6.33; Found: C 86.64, H 6.95, N 6.21.

2f: *5-Chloro-2,3-diphenylindole*: colourless crystal, m.p. 124–126°C; IR (KBr) ν 3438, 1601, 1505, 1460 cm^{-1}; ^1H NMR δ 8.62 (s, 1H, NH), 7.61 (d, 1H, *J* = 1.5 Hz), 7.37–7.14 (m, 12H); ^{13}C NMR δ 111.9, 119.1, 122.9, 126.1, 126.6, 128.0, 128.2, 128.7, 128.8, 129.9, 130.1, 132.3, 134.4, 134.6, 135.6; MS *m/z* (%): 305 (M^+ + 2, 34), 303 (M^+, 100). Anal. Calcd for $C_{20}H_{14}ClN$: C 79.07, H 4.65, N 4.61; Found: C 79.12, H 4.68, N 4.63.

2g: *5-Chloro-2-(4-methylphenyl)-3-phenylindole*: colourless crystal, m.p. 140–142°C; IR (KBr) ν 3411, 1602, 1514, 1489 cm^{-1}; ^1H NMR δ 8.14 (s, 1H, NH), 7.58 (d, 1H, *J* = 1.4 Hz), 7.37–6.98 (m, 11H), 2.36 (s, 3H); ^{13}C NMR δ 21.6, 111.6, 114.6, 119.2, 122.8, 126.1, 126.5, 128.0, 128.3, 128.6, 128.8, 129.8, 130.1, 132.5, 134.6, 134.8, 135.3; MS *m/z* (%): 319 (M^+ + 2, 34), 317 (M^+, 100); Anal. Calcd for $C_{21}H_{16}ClN$: C 79.36, H 5.07, N 4.41; Found: C 79.32, H 5.14, N 4.48.

2h: *5-Chloro-2-(4-chlorophenyl)-3-phenylindole*: colourless crystal, m.p. 161–162°C; IR (KBr) ν 3410, 1602, 1525, 1499 cm^{-1}; ^1H NMR δ 8.23 (s, 1H, NH), 7.60 (d, 1H, *J* = 1.4 Hz), 7.41–7.18 (m, 11H); ^{13}C NMR δ 112.1, 119.3, 123.3, 126.4, 126.9, 128.8, 129.1, 129.4, 129.9, 130.0, 130.7, 134.0, 134.1, 135.6, 136.0; MS *m/z* (%): 341 (M^+ + 4, 11), 339 (M^+ + 2, 66), 337 (M^+, 100). Anal. Calcd for $C_{20}H_{13}Cl_2N$: C 71.02, H 3.87, N 4.14; Found: C 71.20, H 3.75, N 4.20.

2i: *5-Chloro-2-(4-fluorophenyl)-3-phenylindole*: colourless crystal, m.p.146–148°C; IR (KBr) ν 3416, 1602, 1516, 1497 cm^{-1}; ^1H NMR δ 8.17 (s, 1H, NH), 7.62 (s, 1H), 7.41–7.18 (m, 9H), 7.03–7.99 (m, 2H); ^{13}C NMR δ 111.9, 114.8, 115.8, 116.0, 119.2, 123.1, 126.3, 126.7, 128.3, 128.4, 128.8, 129.8, 129.9, 130.0, 134.2, 134.3, 134.5, 161.3, 163.7; MS *m/z* (%): 323 (M^+ + 2, 34), 321 (M^+, 100). Anal. Calcd for $C_{20}H_{13}ClFN$: C 74.65, H 4.07, N 4.35; Found: C 74.52, H 4.21, N 4.26.

2j: *5-Chloro-2-methyl-3-phenylindole*: syrup, IR ν 3415, 3026, 2965, 1604, 1497 cm^{-1}; ^1H NMR, 7.86 (s, 1H, NH), 7.68 (d, 1H, *J* = 1.5 Hz), 7.50–7.52 (m, 4H), 7.36–7.39 (m, 1H), 7.19–7.13 (m, 2H), 2.45 (s, 3H). ^{13}C NMR δ 12.5, 111.5, 114.4, 118.3, 121.7, 125.7, 126.3, 128.8, 129.1, 129.4, 133.3, 133.7, 134.8; MS *m/z* (%): 243 (M^+ + 2, 32), 241 (M^+, 100). Anal. Calcd for $C_{15}H_{12}ClN$: C 74.53, H 5.00, N 5.79; Found: C 74.35, H 5.16, N 5.82.

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