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Samarium triiodide-catalyzed conjugate addition of indoles with electron-deficient olefins

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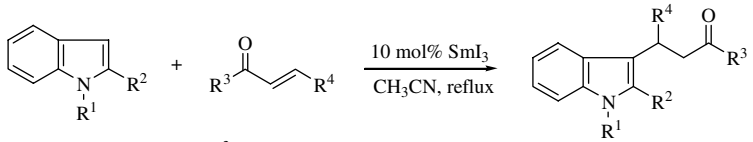
Abstract—The SmI_3-catalyzed reaction of indoles with electron-deficient olefins generated the corresponding Michael adducts in high yields. The substitution on the indole nucleus occurred exclusively at the 3-position and *N*-alkylation products have not been observed.

The development of new efficient synthetic methods leading to indole derivatives continues to receive much attention in organic synthesis because of their biological activities.[1] Various indole derivatives occur in many pharmacologically and biologically active compounds.[2] Among them 3-substituted indoles are important building blocks for the synthesis of biologically active compounds and natural products.[3] Therefore, a variety of methods have been reported for the preparations of this class of compounds.[4,5] The simple and direct method for the synthesis of 3-alkylated indoles involves the conjugate addition of indoles to α,β-unsaturated compounds in the presence of either protic[4] or Lewis acid.[5] However, the acid-catalyzed conjugate addition of indoles requires careful control of acidity to prevent side reactions such as dimerization or polymerization. Furthermore, many of these procedures involve strong acidic conditions, expensive reagents, low yields of products, and complex handling. Thus, a new efficient Lewis acid catalyst is desirable for conjugate addition of indoles to electron-deficient olefins.

Lanthanide ions are considered "hard" Lewis acids and form complexes with substantial ionic character because of poor overlap of the contracted 4f orbitals. Consequently, lanthanides preferentially coordinate to hard bases such as oxygen donor ligands and fluoride ion. Many lanthanides salts have been proved to be extraordinarily effective Lewis acids in various chemical transformations.[6,7b] Though samarium diiodide as a single electron reducing agent has played an important role in organic synthesis,[7] little work has been carried out on lanthanide salt, samarium triiodide used as a Lewis acid catalyst. This promoted us to investigate the use



R^1=H, $PhCH_2$ R^2=H, CH_3, Ph R^3=Ph, CH_3, Ph−CH=CH R^4=Ph, H R^3=R^4= $-(CH_2)_3-$

Scheme 1.

Keywords: Samarium triiodide; Indole; α,β-Unsaturated compounds; Michael reaction.
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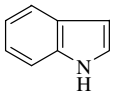
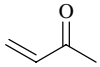
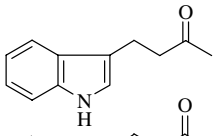
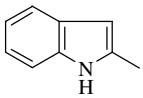
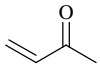
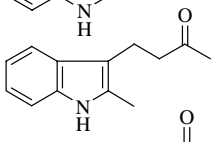
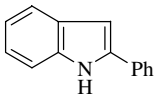
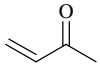
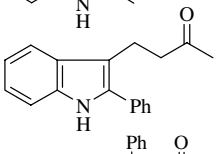
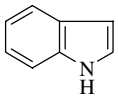
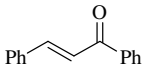
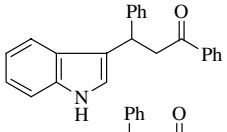
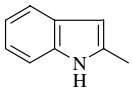
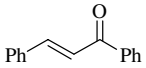
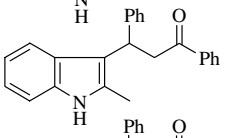
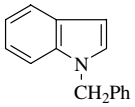
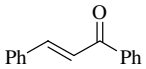
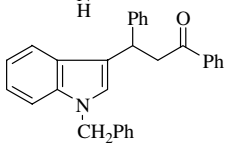
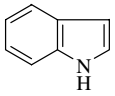
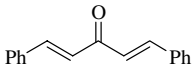
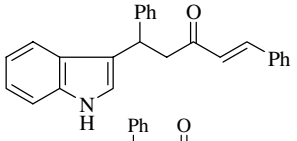
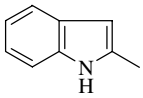
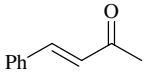
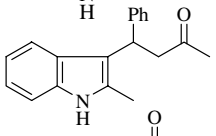
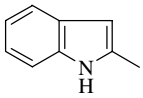
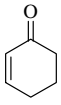
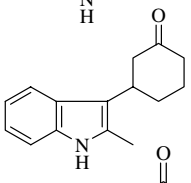
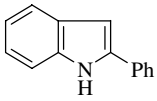
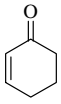
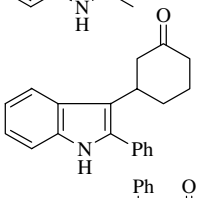
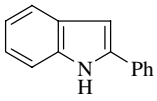
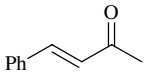
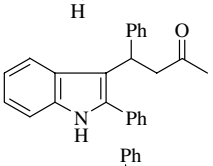
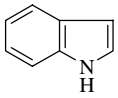
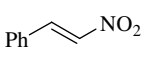
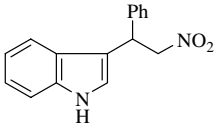
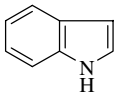
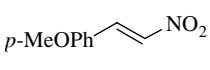
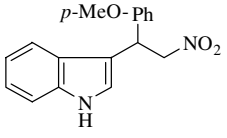
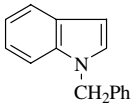
Table 1. Conjugate addition of indoles with electron-deficient olefins

Entry	Nucleophile	Electrophile	Product	Time (h)	Isolated yield (%)
1			**a** 	1	95
2			**b** 	1	95
3			**c** 	1	90
4			**d** 	6	85
5			**e** 	6	83
6			**f** 	6	75
7			**g** 	6	76
8			**h** 	6	75
9			**i** 	6	85
10			**j** 	6	90
11			**k** 	12	70
12			**l** 	1	95
13			**m** 	1	92
14			**n**	1	95

of samarium triiodide as a Lewis acid for conjugate addition of indoles to electron-deficient olefins. Herein, we report the remarkable catalytic activity of samarium triiodide in this Michael reaction (Scheme 1).

First, we carried out the reaction of indole with methyl vinyl ketone in the presence of catalytic amount of SmI_3 (10 mol%) in acetonitrile and obtained the corresponding 3-alkylated indole (product **a**, Table 1) in 95% yield. Then, various α,β-unsaturated compounds were reacted with indole, 2-methylindole, and 2-phenylindole to give the corresponding 3-alkylated products in high yields. The results are summarized in Table 1.[8] Electron-deficient olefins, such as methyl vinyl ketone, chalcone, benzalacetone, cyclohexenone, and dibenzylidene acetone, afforded the products in good to excellent yields. The treatment of β-nitrostyrene with indole produced the corresponding 3-alkylated indole in 92–95% yields (entries 12, 13). In comparison with 78% of product obtained via $InCl_3$-catalyzed reaction,[5e] SmI_3 was more efficient for the Michael addition of indole to β-nitrostyrene. Though 2-phenylindole was more hindered, its 3-position alkylation was proceeded in good to excellent yields (entries 3, 10, 11). The reactions were clean and the products were obtained in high yields without the formation of any side products such as *N*-alkylation product. This important result provided a remarkable contrast to similar reactions under palladium catalysis, where *N*-alkylation was predominant.[9] Furthermore, the indole nitrogen did not require prior protection and the avoidance of strong bases for deprotection permitted compatibility with a wide range of functional groups. The procedure did not require any acidic promoters or inert atmospheric condition.

In conclusion, samarium triiodide has been found to be a superior Lewis acid for the alkylation of indoles with electron-deficient olefins.

Acknowledgement

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References and notes

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8. Typical experimental procedure: a mixture of indole (1 mmol) or 2-methylindole (1 mmol) or 2-phenylindole (1 mmol), electron-deficient olefin (1 mmol) and SmI_3 (0.1 mmol) in CH_3CN (1 mL) was stirred at reflux condition. After completion of the reaction as indicated by TLC, the resulting mixture was diluted with H_2O (10 mL) and extracted with EtOAc (15 mL × 3). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (eluant: EtOAc: Petroleum ether = 1:6) to afford the corresponding 3-alkylated indole. All new compounds were fully characterized by ^1H NMR, ^{13}C NMR, MS, IR and elemental analysis.
3-(1-benzyl-1H-indol-3-yl)-1,3-diphenylpropan-1-one(f): 311 mg (75%). IR (film) υ_{max}: 3034, 1680, 1598, 1493 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.72 (dd, J = 7, 16.5 Hz, 1 H), 3.81 (dd, J = 7, 16.5 Hz, 1H), 5.09 (t, J = 7 Hz, 1H), 5.26 (s, 2H), 6.90–7.07 (m, 4H), 7.10–7.21 (m, 3H), 7.23–7.30 (m, 5H), 7.33–7.47 (m, 5H), 7.50–7.55 (m, 1H), 7.88–7.93 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 38.3, 45.3, 49.9, 109.7, 118.4, 119.1, 119.8, 121.9, 125.6, 126.3, 126.6, 127.3, 127.5, 127.8, 128.1, 128.4, 128.5, 128.7, 132.9, 137.0, 137.2, 137.6, 144.3, 198.6; ESI-MS: *m/z* (%) = 416 (88) [M+H$^+$], 438 (100) [M+Na$^+$]; Anal. Calcd for $C_{30}H_{25}NO$: C, 86.72; H, 6.06; N, 3.37. Found: C, 86.84; H, 6.05; N, 3.43.
3-(1-(4-methoxyphenyl)-2-nitro ethyl)-1H-indole(m): 272 mg (92%). IR (film) υ_{max}: 3412, 3058, 1610, 1548, 1509, 1373 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ = 3.79 (s, 3H), 4.91 (dd, J = 7.5, 12.5 Hz, 1H), 5.06 (dd, J = 7.5, 12.5 Hz, 1H), 5.15 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 8.5 Hz, 2H), 7.03 (s, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.26 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 7.5 Hz, 1H), 7.45 (d,

J = 7.5 Hz, 1H), 8.10 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 40.9, 55.2, 79.7, 111.3, 114.3, 114.8, 119.0, 119.9, 121.4, 122.7, 126.1, 128.8, 131.2, 136.5, 158.9; ESI-MS: m/z (%) = 297 (15) [M+H$^+$], 319 (100) [M+Na$^+$]; Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.91; H, 5.44; N, 9.45. Found: C, 68.80; H, 5.32; N, 9.46.

1-benzyl-3-(1-(4-methoxyphenyl)-2-nitro ethyl)-1H-indole (n): 367 mg (95%). IR (film) υ_{max}: 3027, 1606, 1548, 1501, 1373 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 3.53 (s, 3H), 4.66 (dd, J = 7, 11 Hz, 1H), 4.79 (dd, J = 7, 11 Hz, 1H), 4.93 (t, J = 7 Hz, 1H), 5.00 (s, 2H), 6.64–6.71 (m, 2H), 6.76–6.80 (m, 1H), 6.86–6.93 (m, 3H), 6.96–7.02 (m, 1H), 7.04–7.16 (m, 6H), 7.26–7.34 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 40.6, 49.6, 54.8, 79.5, 109.8, 113.6, 114.0, 119.0, 119.4, 122.2, 125.4, 126.4, 126.6, 127.4, 128.5, 128.6, 131.2, 136.7, 137.1, 158.6; ESI-MS: m/z (%) = 387 (100) [M+H$^+$], 409 (91) [M+Na$^+$]; Anal. Calcd for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.46; H, 5.73; N, 7.13.

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