Indian Journal of Chemistry
Vol. 47B, September 2008, pp 1402-1406

A mild and versatile synthesis of bis(indolyl)methanes and tris(indolyl)alkanes catalyzed by antimony trichloride

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Received 22 November 2007; accepted (revised) 9 April 2008

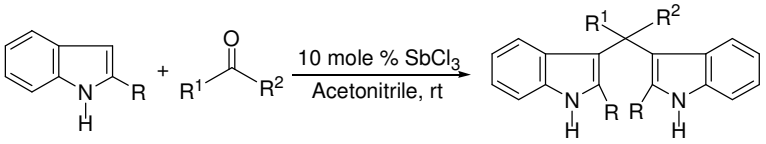
Antimony trichloride is found to be a mild and efficient catalyst for electrophilic substitution reaction at 3-position of 3-unsubstituted indole derivatives with a variety of carbonyl compounds in acetonitrile to afford the corresponding bis(indolyl)methanes in excellent yields. α, β-Unsaturated carbonyl compounds give tris(indolyl)alkanes under the same reaction conditions. The versatility of this method has been proved with a wide range of aromatic aldehydes with various stereo-electronic factors. This method shows much better selectivity between aldehydes and ketones as well as greater reactivity towards the electron deficient over the electron rich aromatic aldehydes, which are in contrast to the existing methods.

Keywords: Antimony trichloride, indoles, bis(indolyl)methane, α,β-unsaturated aldehyde, tris(indolyl)alkane

Indole and their derivatives are well known due to their potent biological activity and are used as antibiotics in the field of pharmaceuticals[1]. Bis-(indolyl)alkanes has received considerable attention because of occurrence in bioactive metabolites of terrestrial and marine origin[2]. Therefore, the synthesis of these moieties has become interesting target to synthetic organic chemists. The reaction of indole with carbonyl compound produces azafulvenium salts which can undergo further addition of a second molecule of indole to afford bis(indolyl)methane promoted by either protic acid[3] or Lewis acid[4]. Many of these method suffer from limitations such as the requirement of stoichiometric amount of Lewis acid, expensive and toxic catalyst, long reaction time and harsh acidic conditions, which are often incompatible with other sensitive functional groups present in the substrates. Moreover, many Lewis acids are deactivated or sometimes decomposed by nitrogen containing reactants. However, these problems were overcome to some extent by recently developed procedure of using catalytic amount of Lewis acid etc. Particularly, the condensation of indoles with carbonyl compounds has been carried using $LiClO_4$[5a], Montmorillonite clay[5b-c], NBS[5d], molecular iodine[5e], $In(OTf)_3$ in ionic liquid[5f], $Dy(OTf)_3$ in ionic liquid[5g], $KHSO_4.SiO_2$[5h], Zeolite-HY[5i], $Zr(OTf)_3$[5j], $TiCl_4$[5k]. Very recently trichloro-1, 3, 5-triazine (TCT)[6a], rare earth catalyst such as $La(PFO)_3$, (ref. 6b) and tetrabutyl ammonium bromide (TBATB)[6c] has also been reported.

Results and Discussion

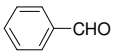
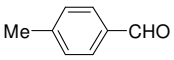
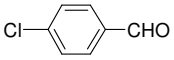
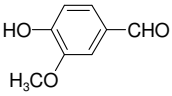
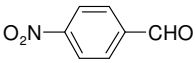
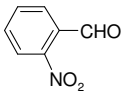
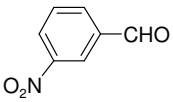
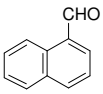
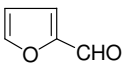
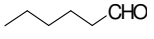
Hence the development of new efficient, clean, highly selective synthetic methods of indole derivatives is still desirable. In continuation to our effort of exploring antimony trichloride ($SbCl_3$, ref. 7) as a mild and efficient catalyst, we wish to report herein the synthesis of various bis(indolyl)methanes and tris(indolyl)alkane by reaction of indole derivatives with a variety of carbonyl compounds using antimony trichloride as a selective catalyst at room temperature (**Scheme I**) with excellent yield. To the best of our knowledge there is no report of the use of $SbCl_3$ as a catalyst for these types of reactions. As a representative example we carried out the reaction of indole **1a** with benzaldehyde **2a** was carried out in the presence of $SbCl_3$ (10 mole%) under refluxing condition in dry acetonitrile to furnish bis(indolyl)methane **3a** in 96% yield. Thus a series of aldehydes with various stereo-electronic effect were subjected to $SbCl_3$-catalyzed electrophilic substitution reactions with indole or 2-methyl indole and the results are summarized in **Table I**. The reaction is applicable to various aromatic as well as aliphatic aldehydes[1a].



Scheme I

Table I — Antimony trichloride catalyzed efficient synthesis of bis(indolyl)methanes[a]

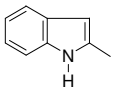
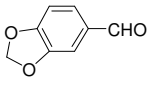
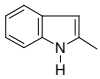
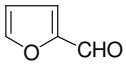
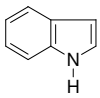
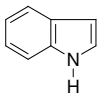
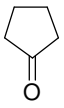
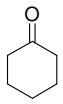
Reactions of indole derivatives with carbonyl compounds

Entry	Indole derivative	Carbonyl compound	Product[b]	Time (hr)	Yield (%)[c]	Ref
1			**3a**	0.5	96	6c
2			**3b**	0.5	98	5a
3			**3c**	1.0	95	6c
4			**3d**	1.0	98	6c
5			**3e**	2.5	97	
6			**3f**	0.3	96	
7			**3g**	1.0	97	
8			**3h**	0.75	94	
9			**3i**	0.25	96	
10			**3j**	0.5	97	
11			**3k**	0.5	93	5a

—Contd

Table I — Antimony trichloride catalyzed efficient synthesis of bis(indolyl)methanes[a]—*Contd*

Reactions of indole derivatives with carbonyl compounds

Entry	Indole derivative	Carbonyl compound	Product[b]	Time (hr)	Yield (%)[c]	Ref
12			3l	0.25	93	
13			3m	0.25	89	
14			3n	11	95	
15			3o	24	26d	5a
16			3p	4.0	92	5a

[a] All reaction were carried out using 10 mole % $SbCl_3$ in acetonitrile at room temperature.
[b] All products were characterized by their physical and spectroscopic data and are agreement with literature value.
[c] Yield refers to pure isolated products.
[d] Reaction remain incomplete after 24 hr.

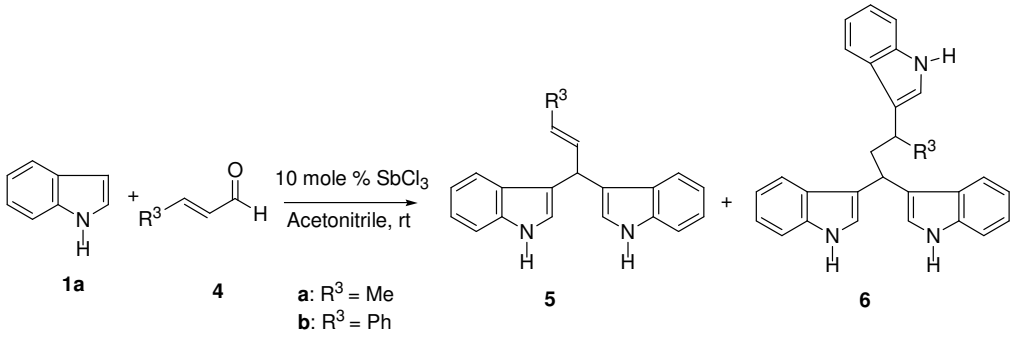
In all cases, reaction with aromatic aldehydes proceeds almost quantatively, and the nature of the substituents on the aromatic ring showed profound effect on this transformation than the aliphatic aldehydes. The electron withdrawing substituents in the aromatic ring such as NO_2 (entry 6-8, **Table I**) reduced the reaction time than the corresponding electron donating substituents (OH, OMe) with comparable yields, which are surprisingly different from the reported literature[5f,6b]. Reaction of indole with aliphatic aldehyde such as hexanal (entry 11) proceeds smoothly to afford 93% yield of bis(indolyl)methane in 30 min. The aliphatic ketones (entry 14-16) reacted slowly whereas the aromatic ketones such as acetophenone and benzophenone did not respond at all under the reaction conditions. The reaction was performed in various organic solvents but acetonitrile was found to be the best one in all respects.

With these encouraging results, the methodology using α,β-unsaturated aldehydes such as *trans*-croton-aldehyde and *trans*-cinnamaldehyde (**Scheme II**) was extended. In case of crotonaldehyde the reaction-mixture was stirred at room-temperature for 3 hr to afford only tris(indolyl)alkane **6a** in 94% isolated yield. The product was characterized from the spectroscopic data, which are in good agreement with the literature value[8]. In case of cinnamaldehyde, tris(indolyl)alkane **6b** is obtained in 85% yield, when stirred at room temperature for 8 hr in acetonitrile. Similarly, 2-cyclohexen-1-one **7** underwent the electrophilic addition with 3.6 equivalents of indole **1a** at room temperature for 12 hr to furnish tris(indolyl)alkane as the only product **8** in 87% yield (**Scheme III**). The product has been characterized with the reported literature[5j].

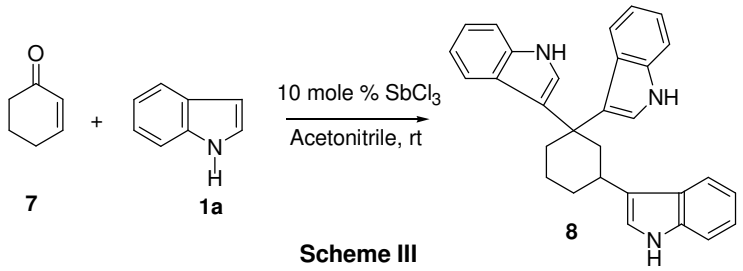
In comparison to the existing catalysts, $SbCl_3$ was found to be the better one in terms of cost, handling, remarkably operational simplicity, products isolation and reduced reaction-time specially for α,β-unsaturated carbonyl compounds[5j,8]. Moreover, it showed much better selectivity between aldehydes and ketones as well as greater reactivity towards the electron deficient over the electron rich aromatic aldehydes which are in contrast to the existing methods. The reactions were very clean and products were obtained in excellent yields without the formation of side products.

In conclusion, a mild, selective and excellent method for the synthesis of bis(indolyl)methanes and tris(indolyl)alkanes by the electrophilic addition of indoles to the carbonyl compounds in the presence of a catalytic amount of $SbCl_3$ have been developed.

All other compounds were characterized by NMR and HRMS analysis and comparing the data with authentic samples.



Scheme II



Scheme III

Experimental Section

Typical procedure[1a]: To a stirred solution of indole **1a** (468 mg, 4 mmole) and vanillin **2e** (304 mg, 2 mmole) in acetonitrile (3 mL) was added $SbCl_3$ (46 mg, 0.2 mmole) and the mixture was stirred for 2.5 hr at room temperature. After completion of the reaction (monitored by TLC) the reaction was quenched with water (4 mL) and extracted with chloroform (3 × 20 mL), washed with water (2 × 5 mL) and finally dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the residue obtained was purified by column chromatography over silica gel (60-120 mesh) using 20-30% ethyl acetate-petroleum ether (60-80°C) to afford **3e** as a crystalline solid (712 mg, 97%); m.p. 222°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (s, 3H), 5.82 (s, 1H), 6.66 (s, 2H), 6.82-6.86 (m, 2H), 6.89 (s, 1H), 7.01 (t, *J* = 7.5 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), (brs, 2H), 8.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.0, 56.0, 111.2, 111.5, 114.1, 119.3, 120.1, 121.4, 122.0, 123.7, 127.2, 136.2, 136.8, 143.9, 146.5; HRMS Calcd. for [$C_{24}H_{20}N_2O_2$ + Na^+]: 391.1422. Found: 391.1404.

Spectral data for 3f: m.p. 226°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.00 (s, 1H), 6.69 (s, 2H), 7.03 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 8.02 (brs, 2H), 8.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.6, 111.7, 118.5, 120.0, 120.0, 122.8, 124.0, 127.0, 129.9, 137.1, 152.2; HRMS Calcd. for [$C_{23}H_{17}N_3O_2$ + Na^+]: 390.1218. Found: 390.1434.

Spectral data for 3g: m.p. 144°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.67 (s, 1H), 6.68 (s, 2H), 7.02 (t, *J* = 7.7 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 2H), 7.32-7.43 (m, 7H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.96 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.8, 111.3, 117.6, 119.6, 119.7, 122.3, 124.0, 124.4, 126.8, 127.3, 131.3, 132.5, 136.7, 138.1, 149.8; HRMS Calcd. for [$C_{23}H_{17}N_3O_2$ + Na^+]: 390.1218. Found: 390.0044.

Spectral data for 3h: m.p. 125°C-30°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.01 (s, 1H), 6.70 (s, 2H), 7.03 (t, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.4 Hz, 2H), 7.34-7.41 (m, 4H), 7.45 (t, *J* = 7.9 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 8.02 (brs, 2H), 8.09 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 40.0, 111.4, 118.2, 119.5, 121.5, 122.3, 123.6, 123.8, 126.7, 129.2, 134.9, 136.8, 146.4, 148.5; HRMS Calcd. for [$C_{23}H_{17}N_3O_2$ + Na^+]: 390.1218. Found: 390.1213.

Spectral data for 3i: m.p. 252°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.58 (s, 2H), 6.67 (s, 1H), 7.00 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.5 Hz, 2H), 7.25-7.47 (m, 8H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 8.7 Hz, 1H), 7.91 (brs, 2H), 8.17 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.8, 111.0, 119.3, 119.4, 119.8, 121.9, 124.3, 124.4, 125.2, 125.5, 125.8, 126.2, 126.9, 127.1, 128.6, 131.9, 134.0, 136.8, 139.5; Anal. Calcd. for $C_{27}H_{20}N_2$: C, 87.07; H, 5.41; N, 7.52. Found: C, 87.02; H, 5.36; N, 7.50%.

Spectral data for 3j: m.p. 325°C; I.R. (KBr, cm^{-1}): 3411, 3305, 2976, 2871, 1620, 1456, 1338, 1008, 742; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.95 (s, 1H), 6.06 (d, *J* = 3.0 Hz, 1H), 6.30-6.31 (m, 1H), 6.89 (s, 2H), 7.04 (t, *J* = 7.4 Hz, 2H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.35-7.38 (m, 3H), 7.48 (d, *J* = 7.9 Hz, 2H), 7.98 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.5, 107.0, 110.5, 111.5, 117.5, 119.7, 122.0, 122.3, 123.5, 127.1, 136.9, 141.6, 157.5; Anal. Calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 80.71; H, 5.10; N, 8.92%.

Spectral data for 3l: m.p. 217°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.07 (s, 6H), 5.92 (s, 3H), 6.68-6.77 (m, 2H), 6.87 (t, *J* = 7.4 Hz, 2H), 7.01-7.06 (m, 4H), 7.23-7.26 (m, 3H), 7.74 (brs,2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4, 39.0, 100.7, 107.9, 109.8, 110.0, 113.5, 119.1, 119.3, 120.6, 121.9, 128.9, 131.8, 135.0, 137.9, 145.7, 147.5; HRMS Calcd. for [$C_{26}H_{22}N_2O_2$ + H^+]: 395.1754. Found: 395.1719.

Spectral data for 3m: m.p. 218°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.16 (s, 6H), 5.91 (s, 2H), 6.31 (m, 1H), 6.91 (t, *J* = 7.4 Hz, 2H), 7.02-7.08 (m, 4H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.41 (m, 1H), 7.76 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.0, 33.3, 107.5, 110.0, 110.3, 111.8, 118.9, 119.3, 120.7, 128.4, 131.6, 135.0, 141.0, 156.8; HRMS Calcd for [$C_{23}H_{20}N_2O$+ Na^+]: 363.1473. Found: 363.1460.

Spectral data for 3n: m.p. 162°C**;** I.R. (KBr, cm^{-1}); 3406, 2960, 1620, 1456, 1332, 1099, 744; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (s, 6H), 6.87 (t, *J* = 7.1 Hz, 2H), 6.98 (d, *J* = 2.4 Hz, 2H), 7.06 (t, *J* = 7.1 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 7.77 (brs, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0, 35.0, 111.2, 118.7, 120.6, 121.3, 121.4, 125.5, 126.4, 137.1; Anal. Calcd. for $C_{19}H_{18}N_2$: C, 83.18; H, 6.61; N, 10.21. Found: C, 83.11, H, 6.58; N, 10.15%.

Preparation of 6a: The reaction was carried out using the same procedure as described for **3e** by using indole **1a** (351 mg, 3.0 mmole), crotonaldehyde (70 mg, 1.0 mmole) in acetonitrile (1.5 mL) and $SbCl_3$ (23 mg, 0.1 mmole) to afford **6a** as a crystalline solid (379 mg, 94%); m.p. 109-110°C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (d, *J* = 6.9 Hz, 3H), 2.36-2.45 (m, 1H), 2.60-2.70 (m, 1H), 2.98-3.05 (m, 1H), 4.50 (t, *J* = 7.5 Hz, 1H), 6.58 (brs, 1H), 6.62 (brs, 1H), 6.68 (brs, 1H), 7.01-7.47 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.0, 29.0, 31.9, 43.8, 111.3, 111.3, 111.4, 119.0, 119.0, 119.7, 119.8, 120.1, 120.2, 120.4, 121.7, 121.8, 121.8, 122.4, 127.0, 127.1, 136.5, 136.6, 136.6; HRMS Calcd for [$C_{28}H_{25}N_3$ + K^+]: 442.1685. Found: 442.1681.

Acknowledgement

One of the authors (PK) thanks Jadavpur University, Kolkata and Government of West Bengal for awarding the Junior Research Fellowship.

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