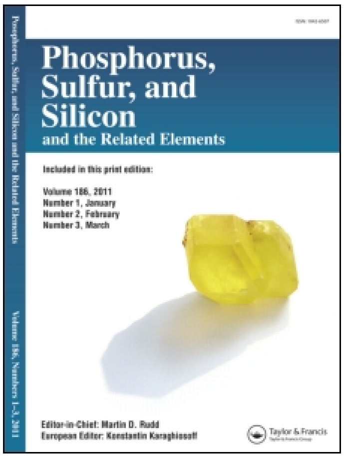

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Antimony Trichloride Catalyzed Condensation of Indole and Carbonyl Compounds: Synthesis of Bis(indolyl)methanes

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To cite this Article Srinivasa, A. , Nandeshwarappa, Belakatta P. , Kiran, Balaji M. and Mahadevan, Kittappa M.(2007) 'Antimony Trichloride Catalyzed Condensation of Indole and Carbonyl Compounds: Synthesis of Bis(indolyl)methanes', Phosphorus, Sulfur, and Silicon and the Related Elements, 182: 10, 2243 — 2249

To link to this Article: DOI: 10.1080/10426500701418265

URL: http://dx.doi.org/10.1080/10426500701418265

Phosphorus, Sulfur, and Silicon, 182:2243–2249, 2007
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ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701418265

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A mild and efficient condensation reaction of indoles with various aldehydes and ketones under catalysis of antimony trichloride ($SbCl_3$) afforded biologically important bis(indolyl)methanes in good yield. The structures of all the newly synthesized compounds were elucidated on the basis of IR, ^1H NMR and mass spectral data.

Keywords Aldehydes; antimony trichloride; ketones; bis(indolyl)methanes; indoles

INTRODUCTION

Bis(indolyl)alkanes and their derivatives are more attractive compounds as the bioactive metabolites of terrestrial and marine origin.[1] Vibrindole A was demonstrated for the first time to exhibit antibacterial activity against *Staphylococcus aureus, S. albus, and B. subtilis* and gentamycin is used as the standard drug.[2] Consequently, numerous methods have been reported for the preparation of bis(indolyl)methanes. Of these methods, the acid-catalyzed condensation reaction of indoles with carbonyl compounds is one of most simple and straightforward approaches for the synthesis of bis(indolyl)methanes. A variety of reagents such as $InCl_3$,[3]

Received February 25, 2007; accepted April 9, 2007.

The authors are thankful to Professor and Chairman, Department, of Post Graduate Studies and Research in Chemistry and Industrial Chemistry, Kuvempu University, Shankaraghatta, for providing laboratory facilities. The authors are also thankful to the Head, RSIC, Indian Institute of Science, Bangalore and CDRI, Lucknow for spectral data.

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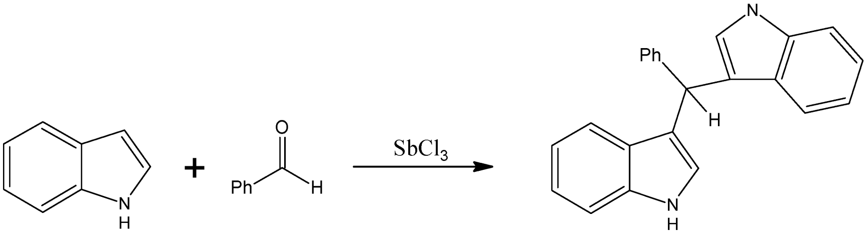
$Dy(OTf)_3$,[4] $ZrCl_4$,[5] InF_3,[6] $La(PFO)_3$,[7] CAN,[8] $LiClO_4$,[9] $FeCl_3$,[10] NBS,[11] $In(OTf)_3$,[12] $NaHSO_4{\cdot}SiO_2$,[13] $Ln(OTf)_3$,[14] hexamethylenetetraamine-bromine,[15] ion-exchange resin,[16] acetic acid,[17]sulphamic acid,[18] $H_3PMo_{12}O_{40}$. x H_2O,[19] $CuBr_2$,[20] zeolites,[21] $KHSO_4$,[22] I_2,[23] have been employed to accomplish this transformations. However, some of the reported methods have the following drawbacks: for example use of expensive reagents,[4,6,7,12,14] excess of catalyst,[17,18] long reaction time,[4,6,14,16] low yield of product,[5] and use of additional microwave.[10]

Although protonic and Lewis acids–catalyzed reaction of indoles with carbonyl compounds have long been known, so for there are no reports on the use of antimony trichloride ($SbCl_3$) as catalyst. Hence in our present work, we have demonstrated the synthesis of bis(indolyl)methanes using $SbCl_3$as catalyst in CH_2Cl_2.

RESULTS AND DISCUSSIONS

First, we examined the $SbCl_3$ in the model reaction of indole with benzaldehyde (Scheme I) in different reaction media to investigate the solvent effect on reaction. The results are summarized in the Table I and show that non-polar solvents such as CH_2Cl_2 and CH_3CN are better solvents than polar ones. However, the CH_2Cl_2 was found to be best for the catalytic reaction at room temperature in terms of yield, reaction time and product isolation.

Further, the minimum activity concentration of catalyst was also tested. It was observed that in the presence of 10 mol% of $SbCl_3$ the reaction afforded 94% yield of corresponding bis(indolyl)methane **3a**. However, smaller catalyst loading could results only in a marginal drop of the reaction time Table I, and increase in the amounts of catalyst did not gave better yield but reduced the reaction time Table I. As a comparative study, herein we have mentioned only few reported



1a **2a** **3a**

SCHEME 1 Screening of the reaction conditions for the synthesis of 3a.

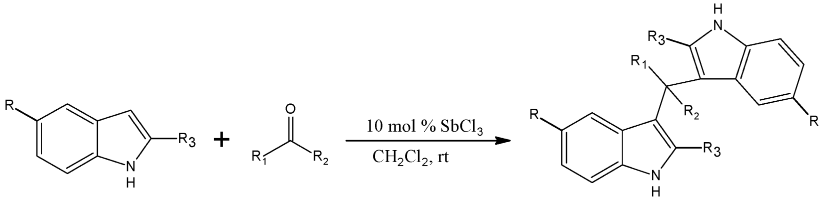
TABLE I Screening of the Reaction Conditions for the Synthesis of 3a

Entry	Solvent	Catalyst	Time (h)	Yield (%)[a]
1	CH_2Cl_2	10% $SbCl_3$	1.10	94
2	EtOH	10 % $SbCl_3$	3.00	58
3	CH_3CN	10% $SbCl_3$	2.00	88
4	EtOAc	10% $SbCl_3$	2.00	68
5	MeOH	10% $SbCl_3$	1.30	65
6	DMF	10% $SbCl_3$	2.30	68
7	THF	10% $SbCl_3$	3.45	75
8	CH_2Cl_2	5% $SbCl_3$	2.30	92
9	CH_2Cl_2	20% $SbCl_3$	0.25	94
10	EtOH/H_2O	10% $Dy(OTf)_3$[4]	12.00	95
11	CH_3CN	5% $ZrCl_4$[5]	0.35	91
12	CH_2Cl_2	resin[16]	24.00	92
13	MeOH	50% H_2NSO_3H[18]	3.00	90
14	CH_3CN	5% $CuBr_2$[20]	0.30	94
15	CH_2Cl_2	zeolite [21]	1.00	85

[a] Isolated yields.

catalysts Table I, which produced almost comparable results with our catalyst.

Having established reaction conditions, indoles **1** were reacted with various aldehydes and ketones **2** to investigate the reaction scope (Scheme 2) and several representative results are summarized in Table II. In all cases, the condensation reaction of indoles with aldehydes could proceed smoothly at room temperature to produce the corresponding bis(indolyl)methanes in good yield in relatively shorter reaction time. Whereas in the case of ketones, isolated yields are less compared to

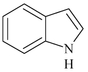
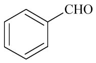
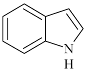
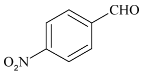
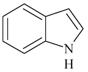
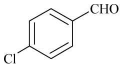
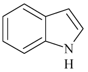
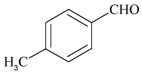
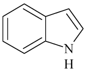
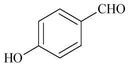
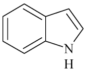
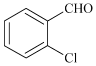
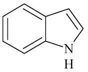
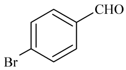
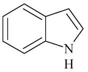
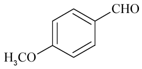
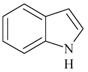
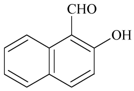
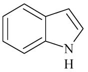
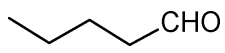
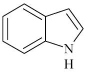
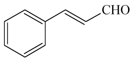
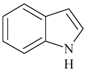
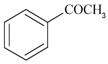
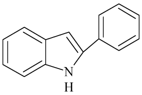
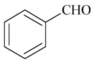
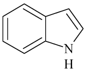
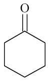
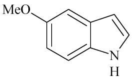
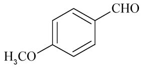
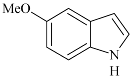
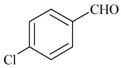


1 **2** **3**

R = H, OCH_3
R_3 = H, Ph

SCHEME 2 Synthesis of bis(indolyl)methanes catalyzed by $SbCl_3$.

TABLE II The Reactions of Indoles with Aldehydes or Ketones Catalyzed by $SbCl_3$

Product	Indole	Aldehyde/Ketone	Time (h)	Yield (%)[a]
3a			1.10	94
3b			0.45	95
3c			1.15	90
3d			1.45	88
3e			1.55	92
3f			1.50	88
3g			1.10	96
3h			1.50	88
3i			1.40	92
3j			3.30	85
3k			1.00	96
3l			8.00	42
3m			1.15	96
3n			9.00	78
3o			1.30	90
3p			2.00	84

[a] Isolated yields.

aldehydes and unreacted ketones and indole are remained. It has been observed that the electronic properties of the aromatic ring have the effect on the rate of the reaction. The rate is accelerated if an electron-withdrawing group is present on the aromatic ring.

In summary, the condensation reaction of indole with aldehydes and ketones was successfully carried out in presence of catalytic amount of $SbCl_3$ at room temperature. This method offers several significant advantages such as high conversions, cheaper catalyst, cleaner reaction profiles, short reaction time, and the reaction conditions are amenable to scaling.

EXPERIMENTAL

All the melting points were recorded in open capillary and were compared with the literature.[5,15] The purity of the compounds was checked by TLC on silica gel and were purified by column chromatography. ^1H NMR spectra were recorded on a Bruker-400 Hz spectrometer using TMS as an internal standard. IR spectra were obtained using a FTS-135 spectrometer instrument. Mass spectra were recorded on a JEOL SX 102/DA-6000 (10 kV) FAB mass spectrometer.

GENERAL PROCEDURE

$SbCl_3$ (0.2 mmol) was added to a mixture of indole (2.0 mmol) and aldehydes or ketones (1.0 mmol) in dichloromethane (5 mL) taken in 50-mL round bottom flask. The reaction mixture was stirred at room temperature and progress of the reaction was monitored by TLC. After the completion, the reaction mixture was filtered to remove the catalyst; the clear dichloromethane layer evaporated under reduced pressure to get residue and purified by column chromatography on SiO_2 with an ethyl acetate and petroleum ether mixture to afford bis(indolyl)methanes.

3,3′-Bis-indolyl(phenyl)methane (3a)

Pink solid; m.p. 124–125°C; IR (KBr) 3415, 3025, 1631, 1380, 1265, 1008, 734 cm^{-1}; ^1H NMR ($CDC1_3$) δ ppm: 7.89 (brs, 2H, NH), 7.38 (d, $J=7.8$ Hz, 2H), 7.33–7.35 (m, 4H), 7.19–7.30 (m, 5H), 7.00 (m, 2H), 6.64 (d, $J=1.1$ Hz, 2H), and 5.88 (s, 1H); MS: m/z 322 (M^+).

4-Chlorophenyl-3,3′-bis(indolyl)methane (3c)

Pink solid; m.p. 78–80°C; IR (KBr): 3411, 3055, 2923, 2848, 1617, 1417, 1327, 1013, 743 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 7.93 (brs, 2H, NH), 7.26–7.38 (m, 8H), 7.18 (t, $J = 7.8$ Hz, 2H), 7.02 (t, 2H, $J= 7.6$ Hz, 2H), 6.65 (s, 2H), and 5.86 (s, 1H); MS: m/z 356 (M^+).

4-Methoxyphenyl-3,3′-bis(indolyl)methane (3h)

Pinkish solid; m.p. 192–193°C; IR (KBr): 3392, 3055, 2933, 2838, 1610, 1507, 1320, 1023, 743 cm^{-1}; ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): δ ppm: 7.93 (brs, 2H, NH), 7.26–7.38 (m, 8H), 7.18 (t, $J= 7.8$ Hz, 2H), 7.02 (t, 2H, $J= 7.6$ Hz, 2H), 6.65 (s, 2H), 5.86 (s, 1H); 3.77 (s, 3H); MS: m/z 352 (M^+).

1-(di-1H-indol-3-ylmethyl)-2-naphthol (3i)

Yellow solid; m.p. 203–205°C; IR (KBr): 3415, 3020, 1605, 1460, 1290, 1068, 1004, 750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ ppm: 12.2 (s, 1H), 8.15 (d, $J=$ 8.6 Hz, 1H), 8.06 (brs, 2H, NH), 7.83 (d, $J= 8.0$ Hz, 1H), 7.73 (d, $J= 8.0$ Hz, 1H), 7.3–7.45 (m, 7 H), 7.2 (t, $J= 7.2$ Hz, 2H), 7.02 (t, $J= 7.6$ Hz, 2H), 6.82 (s, 1H), 6.76 (s, 1H), and 6.5 (s, 1H, CH); MS: m/z 388 (M^+).

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