# Antimony(III) Sulfate Catalyzed Condensation Reaction of Indoles with Carbonyl Compounds

Aswathanarayana Srinivasa<sup>1</sup>, Putta Prabhakar Varma<sup>1</sup>, Vijaykumar Hulikal<sup>2</sup>, and Kittappa M. Mahadevan<sup>1,\*</sup>

<sup>1</sup> Department of Post Graduate Studies and Research in Chemistry, School of Chemical Sciences, Kuvempu University, Shankaraghatta, Karnataka, India

<sup>2</sup> BioOrganics and Applied Materials Pvt. Ltd., Peenya, Bangalore, India

Received March 27, 2007; accepted (revised) April 16, 2007; published online November 16, 2007 © Springer-Verlag 2007

**Summary.** Antimony sulfate was found to be on effective catalyst for the condensation reaction of indoles with carbonyl compounds at room temperature. This catalyst is inexpensive, easily available and it was also found that this catalyst could be recovered quantitatively and reused without much loss of catalytic activity.

**Keywords.** Antimony sulfate; Indoles; Aldehydes; Bis(indolyl)methanes; 3-Indolyl ketones.

## Introduction

Bis(indolyl)alkanes and their derivatives are attractive compounds as the bioactive metabolites of terrestrial and marine origin [1]. Vibrindole A has been demonstrated for the first time to exhibit antibacterial activity against Staphylococcus aureus, S. albus, and B. subtilis; gentamycin is in use as a standard drug [2]. Consequently, numerous methods have been reported for the preparation of bis(indolyl)methanes. Of these methods, the acid-catalyzed condensation of indoles with carbonyl compounds is one of the most common and straightforward approaches for the synthesis of bis(indolyl)methanes. The acids utilized in this type of reaction are protic acids [3] and Lewis acids [4], usually used in excess and require long hours for the completion of the reaction. Generally, these Lewis acid catalysts are

moisture sensitive and get easily decomposed or deactivated in the presence of even trace amounts of water and are thus difficult to handle. Further disposal of these acids leads to environmental pollution. The other catalysts used for this condensation are hexamethylene-bromine [5], trichloro-1,3,5-triazine [6],  $PPh_3 \cdot HClO_4$  [7].

With the rapid development in the field of catalytic and synthetic chemistry, researchers have started to pay more attention to develop eco-friendly and reusable catalysts to avoid or minimize these harmful environmental pollution problems. Particularly, the condensation of indoles and carbonyl compounds has been carried out successfully using catalysts like, KHSO<sub>4</sub> [8], I<sub>2</sub> [9], ion exchange resin [10], *NBS* [11], NaHSO<sub>4</sub> · SiO<sub>2</sub> [12], montmorillonite K-10 clay [13], ionic liquids [14], and rare earth catalysts [15]. However, some of the reported methods have the following drawbacks: for example use of expensive reagents [4c, g, 15], excess of catalyst [3a, e], long reaction time [3b, c, 4g, 10], low yield of product [3a], and use of additional microwave [4d].

To circumvent the environmental problems and limitations of the above-mentioned catalysts, we thought of using a *Lewis* acid, which is efficient as a catalyst, stable under the reaction conditions, and insoluble in common organic solvents. Since it will be insoluble in common solvents, it can be filtered off after the reaction and is suited for recycling.

<sup>\*</sup> Corresponding author. E-mail: mady\_kmm@yahoo.co.uk





Antimony salts are stable and insignificantly soluble in common organics solvents. We expected their catalytic activity to be similar to bismuth salts as both bismuth and antimony are positioned in the same group in the periodic table. Bismuth salts have been extensively used in various organic syntheses and found to be versatile catalysts in some organic reactions [16]. There are only few reports where antimony salts are used as catalysts, antimony chloride in particular has been used in Friedel-Crafts acylation [17]. Hence, we planned to explore the possibility of using various antimony salts in the synthesis of bis(indolyl)alkanes. The results of these experiments using various antimony salts as catalysts in the condensation reaction between indoles and carbonyl compounds are described in this paper.

#### **Results and Discussions**

Initial studies were aimed at the investigation of various antimony salts in the model reaction of indole with benzaldehyde (Scheme 1) for their catalytic activity in methanol. The results are shown in Table 1. Among the antimony salts used in this re-

**Table 1.** Effect of catalysts in the reaction of indole with benzaldehyde in *Me*OH at room temperature

Entry	Amount of catalyst	Time/h	Yield/% <sup>a</sup>
1	5% SbPO <sub>4</sub>	16.00	60
2	10% SbPO <sub>4</sub>	12.00	65
3	20% SbPO <sub>4</sub>	12.00	72
4	2.5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	2.30	88
5	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	1.30	96
6	10% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	0.50	97
7	5% SbCl <sub>3</sub>	3.00	55
8	10% SbCl <sub>3</sub>	2.00	65
9	5% Sb(NO <sub>3</sub> ) <sub>3</sub>	2.30	75
10	10% Sb(NO <sub>3</sub> ) <sub>3</sub>	1.45	88
11	5% SbF <sub>3</sub>	3.00	60
12	10% SbF <sub>3</sub>	1.50	68

<sup>a</sup> Isolated yields

action between indole and carbonyl compounds,  $Sb_2(SO_4)_3$  gave good results (Table 1, entry 5). Further it was noticed that 5 mol% of the catalyst gave the best result, though increasing the concentration of catalyst resulted in marginal increase in the yield without significant reduction in the reaction time (Table 1, entry 6).

Encouraged by this result, we further examined the catalytic activity of Sb<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> in different reaction media to investigate the solvent effect on reaction. The results are summarized in Table 2 and show that polar solvents such as *Me*OH and *Et*OH are better solvents than non-polar ones. Although the reaction proceeds in water, the isolated yields are low (60%) (Table 2, entry 11). Also, we examined the reaction in an alcohol/water system. Remarkably, the condensation proceeded smoothly in *Me*OH/H<sub>2</sub>O (3/1, *v*/*v*), *Et*OH/H<sub>2</sub>O (3/1, *v*/*v*) system and afforded the desired product in good yield (90%) (Table 2, entries 12, 13). However, methanol was found to be

 Table 2. Screening of the catalytic activity of antimony sulfate for the synthesis of bis(indolyl)methane at room temperature

Entry	Solvent	Amount of catalyst	Time/ h	Yield/% <sup>a</sup>
1	МеОН	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	1.30	96
2	<i>Et</i> OH	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	1.30	88
3	$CH_2Cl_2$	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	1.30	82
4	Toluene	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	2.00	78
5	CH <sub>3</sub> CN	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	1.30	86
6	DMF	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	2.30	72
7	THF	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	3.45	60
8	MeOH	2.5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	2.30	88
9	MeOH	10% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	0.50	94
10	MeOH	5% $Sb_2(SO_4)_3$	1.30	$(96, 90, 85)^{b}$
11	$H_2O$	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	4.00	60
12	$MeOH/H_2O$	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	1.50	90
13	$EtOH/H_2O$	5% Sb <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub>	1.50	90

<sup>a</sup> Isolated yields

<sup>b</sup> The same catalyst recovered and reused for each of the three runs





the best for the catalytic reaction at room temperature in terms of yield and reaction time.

As expected, antimony sulfate could be easily recovered by filtration and recycled without significant decrease in the activity of the catalyst (Table 2, entry 10, 1<sup>st</sup> run 96%, 2<sup>nd</sup> run 88%, and 3<sup>rd</sup> run 82%).

Having established the optimum reaction conditions, various aromatic and aliphatic aldehydes and ketones were reacted with indole to investigate the scope of the reaction (Scheme 2) and several representative results are summarized in the Table 3.

In all these cases, the condensation reaction of indoles with aromatic aldehydes proceeded smoothly at room temperature to produce the corresponding

 
 Table 3. The synthesis of bis(indolyl)methanes using antimony sulfate at room temperature

Product	$R^1$	$R^2$	<i>R</i> <sup>3</sup>	Time/ h	Yield/ %
3a	Н	Ph	Н	1.30	96
3b	Н	4-MeOPh	Н	1.10	95
3c	Н	4-HOPh	Н	1.20	93
3d	Η	$4-NO_2Ph$	Н	2.00	88
3e	Н	4-ClPh	Н	1.30	92
3f	Н	$4-N(Me_2)Ph$	Н	1.15	96
3g	Me	Ph	Н	1.30	94
3h	Н	2-furyl	Н	2.00	85
3i	Me	2-furyl	Н	2.20	82
3j	Ph	Ph	Н	3.00	85
3k	Н	2-hydroxynaphthyl	Н	1.50	90
31	Н	$C_3H_7$	Н	3.00	92 <sup>b</sup>
3m	Н	$C_3H_7$	Н	3.00	90
3n	Н	$C_{5}H_{11}$	Н	3.30	$90^{b}$
30	Н	$C_{5}H_{11}$	Н	3.30	85
3p	Н	PhCH=CH	Н	1.10	95
3q	Н	Ph	Me	8.00	80
3r	Η	$-C_5H_{10}-$		9.00	75
3s	Н	Ph	Me	5.00	84 <sup>b</sup>
3t	Η	Me	Me	5.00	78

<sup>a</sup> Isolated yields

<sup>b</sup> 10 mol% catalyst was loaded

bis(indolyl)methanes in good yield in short reaction time. It was observed that the electronic properties of the aromatic ring have an effect on the rate of the condensation reaction. The rate is accelerated if an electron-donating group is present on the aromatic ring compared to electron-withdrawing group. Thus anisaldehyde and hydroxybenzaldehyde (Table 3, 3b, 3c) reacted faster compared to nitrobenzaldehyde (Table 3, 3d) and also gave better yields. In addition, *n*-butanal and *n*-hexanal (Table 3, 3l, 3n) reacted with indoles to afford the product in good yield with prolonged reaction time. In the case of ketones (Table 3, 3q, 3r, 3t), the isolated yields are less compared to those for aldehydes. The indoles reacted with cinnamaldehyde (Table 3, 3p) in a relatively short reaction time to produce the corresponding bis(indolyl)methanes with high yields.

It is reported that, contrary to  $\alpha,\beta$ -unsaturated aldehydes,  $\alpha,\beta$ -unsaturated ketones undergo a 1,4addition reaction with indoles in presence of acid catalysts (protic and *Lewis* acid) [18] to yield indolyl ketones. These indolyl ketones have received a lot of interest for more than a century, as a number of their derivatives occur in nature and possess a variety of biological activities [19]; especially 3-indolyl ketones are very interesting.

As expected, in the presence of  $10 \mod\% \text{Sb}_2(\text{SO}_4)_3$ , the indoles underwent 1,4-addition with  $\alpha,\beta$ -unsaturated ketones (Scheme 3) to afford 3-indolyl ketones. The results are represented in the Table 4.

In conclusion, the condensation reaction of indole with carbonyl compounds were successfully carried out in presence of a catalytic amount of reusable  $Sb_2(SO_4)_3$  at room temperature in methanol. This method offers several significant advantages such as high conversions, easy handling, cheaper catalyst, cleaner reaction profiles, short reaction time, and the reaction conditions are environmental friendly and might be amenable for upscaling.





**Table 4.** Antimony sulfate catalyzed 1,4-addition of indoles with ketones at room temperature

Product	$R^1$	$R^4$	$R^5$	Time/h	Yield/% <sup>a</sup>
5a	Н	Ph	Ph	9.00	85
5b	Н	Ph	Ph	10.00	$80^{\mathrm{b}}$
5c	Н	Н	Me	8.00	90
5d	Н	Me	Ph	9.00	82
5e	Н	-C	$_{3}H_{6}-$	12.00	68
<b>5f</b>	Н	-C	$_{2}H_{4}-$	12.00	76
5g	Me	Ph	Ph	9.00	86
5h	Me	$-C_{2}$	$_{2}H_{4}-$	12.00	78
5i	Me	Me	Ph	6.00	84
5j	Me	Ph	Me	9.00	86
5k	Me	Η	Me	6.00	90

<sup>a</sup> Isolated yields

<sup>b</sup> 7.5 mol% catalyst was loaded

## Experimental

All melting points were recorded in open capillaries. The purity of the compounds was checked by TLC on silica gel and they were purified by column chromatography. <sup>1</sup>H 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. The compounds **3a** [3d], **3b** [10], **3c** [5], **3d** [10], **3e** [4f], **3f** [5], **3g** [3d], **3h** [3d], **3i** [3d], **3l** [5], **3n** [10], **3p** [5], **3q** [5], **3r** [4c], **3t** [10], **5c** [18e], **5d** [18i], **5e** [18e], **5f** [18i], **5g** [18i], **5h** [18i], **5i** [18i], **5j** [18i], and **5k** [18e] are known, their identities were proven by means of IR, NMR, and mass spectra. Herein we give melting points and spectral data for **3j**, and **3k**, which could not be found in literature.

General Procedure for the Synthesis of Bis(indolyl)methanes **3** Sb<sub>2</sub>(SO<sub>4</sub>)<sub>3</sub> (0.05 mmol) was added to a mixture of 2.0 mmol indole and 1.0 mmol aldehyde or ketone in 2 cm<sup>3</sup> methanol. The reaction mixture was stirred at room temperature for the appropriate time. After completion, the reaction mixture was quenched with 20 cm<sup>3</sup> H<sub>2</sub>O and extracted with  $3 \times 10 \text{ cm}^3$  ethyl acetate. The combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by column chromatography on SiO<sub>2</sub> with an ethyl acetate and petroleum ether mixture as eluent to afford the bis(indolyl)methanes.

3,3'-Bis(2-phenylindolyl)phenylmethane (**3j**, C<sub>35</sub>H<sub>26</sub>N<sub>2</sub>) Mp 266–268°C; IR (KBr):  $\bar{\nu}$  = 3425, 3099, 2955, 1645, 1600, 1480, 750 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.945 (br s, 2H, NH), 7.23–7.28 (m, 4H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.01–7.14 (m, 13H), 6.91 (d, *J* = 8.0 Hz, 2H), 6.75 (t, *J* = 7.2, 2.8 Hz, 2H), 6.05 (s, 1H) ppm; MS: m/z = 474 (M<sup>+</sup>).

3,3'-Bisindolyl(2-hydroxynaphthyl)methane (**3k**, C<sub>27</sub>H<sub>20</sub>N<sub>2</sub>O) Yellow solid; mp 203–205°C; IR (KBr):  $\bar{\nu}$  = 3415, 3020, 1605, 1460, 1290, 1068, 1004, 750 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 12.2 (s, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 8.06 (br s, 2H, NH), 7.83 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.3– 7.45 (m, 7H), 7.2 (t, *J* = 7.2 Hz, 2H), 7.02 (t, *J* = 7.6 Hz, 2H), 6.82 (s, 1H), 6.76 (s, 1H), 6.5 (s, 1H, CH) ppm; MS: *m*/*z* = 388 (M<sup>+</sup>).

General Procedure for the Synthesis of 3-Indolyl ketones 5  $Sb_2(SO_4)_3$  (0.1 mmol) was added to a mixture of 1.0 mmol indole and 1.0 mmol  $\alpha,\beta$ -unsaturated ketone in 2 cm<sup>3</sup> methanol. The reaction mixture was stirred at room temperature for appropriate time. After completion, the reaction mixture was quenched with 20 cm<sup>3</sup> water and extracted with 3 × 10 cm<sup>3</sup> ethyl acetate. The combined organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated, and purified by column chromatography on SiO<sub>2</sub> with an ethyl acetate and petroleum ether mixture as eluent to afford the 3-indolyl ketones.

## Acknowledgements

The authors are thankful to the 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 Indian Institute of Science, Bangalore, and CDRI, Lucknow, for spectral data.

#### References

- a) Osawa T, Namiki M (1983) Tetrahedron Lett 24: 4719; b) Porter JK, Bacon CW, Robbin JD, Himmelsbach DS, Higman HC (1977) J Agric Food Chem 25: 88; c) Garbe TR, Kobayashi M, Shimizu N, Takesue N, Ozawa M, Yukawa H (2000) J Nat Prod 63: 596
- [2] Hong C, Firestone GL, Bjeldanes LF (2002) Biochem Pharmacol 63: 1085
- [3] a) Kamal A, Qureshi A (1963) Tetrahedron 19: 513;b) Gregorovich BV, Liang K, Clugston M, Macdonald S

(1968) Can J Chem **46**: 3291; c) Roomi M, Macdonald S (1970) Can J Chem **48**: 139; d) Auria M (1991) Tetrahedron **47**: 9225; e) Pankajkumar RS, Devendrapratap US, Shriniwas DS (2005) Synth Commun **35**: 2133

- [4] a) Chatterjee A, Manna S, Benerji J, Pascard C, Prange T, Sghoolery J (1980) J Chem Soc Perkin Trans 1: 553;
  b) Babu G, Sridhar N, Perumal PT (2000) Synth Commun **30**: 1609; c) Yadav JS, Reddy BVS, Murthy VSR, Kumar GM, Madan C (2003) Synthesis 783; d) Xia M, Wang S-B, Yuan W-B (2004) Synth Commun **34**: 3175;
  e) Nagawade RR, Shinde DB (2005) Bull Korean Chem Soc **26**: 1962; f) Mo L-P, Ma Z-C, Zhang Z-H (2005) Synth Commun **35**: 1997
- [5] Bandagar BP, Bettigeri SV, Joshi NS (2004) Monatsh Chem 135: 1265
- [6] Sharma GVM, Reddy JJ, Lakshmi PS, Krishna PR (2004) 45: 7729
- [7] Nagarajan R, Perumal PT (2004) Synth Commun 32: 105
- [8] Nagarajan R, Perumal PT (2004) Chem Lett 33: 288
- [9] Bandgar BP, Shaikh KA (2003) Tetrahedron Lett 44: 1959
- [10] Feng X-L, Guan C-J, Zhao C-X (2004) Synth Commun 34: 487
- [11] Koshima H, Matsuaka W (2002) J Heterocyclic Chem 39: 1089
- [12] Ramesh C, Baneree J, Pal R, Das B (2003) Adv Synth Catal 345: 557
- [13] Chakrabarty M, Ghosh N, Basak R, Harigaya Y (1996) Tetrahedron Lett 37: 4467

- [14] Yadav JS, Reddy BVS, Sunitha S (2003) Adv Synth Catal **345**: 349
- [15] a) Wang L, Han J, Tian H, Sheng J, Fan Z, Tung X (2005) Synlett 2: 337; b) Mi X-L, Luo S-Z, He J-Q, Cheng J-P (2004) Tetrahedron Lett 45: 4567; c) Chen D, Yu L, Wang PG (1996) Tetrahedron Lett 37: 4467
- [16] a) Samajdar S, Becker FF, Banik BK (2000) Tetrahedron Lett 41: 8017; b) Samajdar S, Becker FF, Banik BK (2002) Synth Commun 32: 1917; c) Srivastava N, Banik BK (2003) J Org Chem 68: 2109
- [17] Olah GA, Nishimura J (1974) J Am Chem Soc 16: 2214
- [18] a) Szmuskovicz J (1957) J Am Chem Soc 79: 2819;
  b) Christofers J (1998) Eur J Org Chem 1259: 9; c) Babu LR, Perumal PT (2000) Aldricchim Acta 33: 16; d) Manabe K, Mori Y, Wkabayashi T, Nagayama S, Kobayashi S (2000) J Am Chem Soc 122: 7202; e) Bartoli G, Bartolacci M, Bosco M, Foglia G, Giuliani A, Marcantoni E, Sambari L, Torregiani E (2003) J Org Chem 68: 4594; f) Srivastava N, Banik BK (2003) J Org Chem 68: 2109; g) Singh DU, Singh PR, Samant SD (2006) Synth Commun 36: 1265; h) Zhang H-B, Liu L, Liu Y-L, Chen Y-J, Wang J, Wang D (2007) Synth Commun 37: 173; i) Bandini M, Cozzi GP, Glacomini M, Melchiorre P, Selva S, Umani-Ronchi A (2002) J Org Chem 67: 3700; j) Poupaert HJ, Bukuru J, Gozzo A (1999) Monatsh Chem 130: 929
- [19] Sunberg RJ (1996) The Chem of Indoles. Academic Press, New York, p 113