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## A green alternative approach for the preparation of bis-indolyl, tris-indolyl and di(bis-indolyl methanes) in aqueous media

Lachhireddy Venkataramana, Kuruva Chandra Sekhar, Valasani Koteswara Rao, Chamarthi Naga Raju\*  
 Department of Chemistry, Sri Venkateswara University, Tirupati - 517 502, (INDIA)

E-mail: rajuchamarthi10@gmail.com

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### ABSTRACT

A facile, efficient and green synthesis of bis-indolyl methanes, tris-indolyl methanes and di(bis-indolyl methanes) has been developed by one-pot condensation of indole with structurally diverse aldehydes and ketones in the presence of Me-SO<sub>3</sub>H in water medium as homogeneous and efficient catalyst at room temperature. © 2012 Trade Science Inc. - INDIA

### KEYWORDS

Green synthesis;  
 Indoles;  
 Tris-indolylmethanes;  
 Di(bis-indolylmethanes);  
 Me-SO<sub>3</sub>H catalyst;  
 Aqueous medium.

### INTRODUCTION

Indoles are important heterocyclic rings and many biologically active and natural products are 3-substituted indoles<sup>[1]</sup>. Indole forms an integral part of many natural products of therapeutic importance and possesses potentially reactive sites for a variety of chemical reactions to generate molecular diversity. Naturally occurring bis-indolyl alkanes consist of two indoles or substituted indole units in a molecule. Indole reacts with aromatic or aliphatic aldehydes and ketones to produce azafulvenium salt, which undergo further addition with a second molecule of indole to afford bis-indolyl alkane. Indolyl methanes have been isolated from terrestrial and marine natural sources such as tunicates and sponges<sup>[2]</sup>. Several bis (indo) alkaloids, which exhibit biological activity, have been isolated from the marine environment<sup>[3]</sup>. For example, vibrindole a (3,3'-diindolyl ethane) exhibits anti-bacterial activity and 3, 3'- diindolyl methane has potent anti-carcinogenic properties<sup>[4]</sup>. Strepindole is the first bacterial diindolyl methane metabolite possessing genotoxicity and DNA-damaging activities, which are

reputable in *Bacillus subtilis* cells<sup>[5]</sup>. Because of their wide occurrence as natural products and various biological activities, synthesis of these bis(indolyl) methanes have been attracted attention. 1,1-Bis(3'-indolyl)-1-(*p*-substituted phenyl) methanes containing *p*-trifluoromethyl (DIM-C-*p*-CF<sub>3</sub>Ph), *p*-*t*-butyl (DIM-C-*p*-*t*-BuPh), and *p*-phenyl (DIM-C-*p*-C<sub>6</sub>H<sub>5</sub>Ph) substituents has recently gained importance because of their antitumorigenic activity<sup>[6]</sup>. Synthetically, these compounds are obtained by the condensation of indoles with aldehydes/ketones in the presence of several bronsted<sup>[7]</sup> and Lewis acid catalysts such as LiClO<sub>4</sub><sup>[8]</sup>, In(OTf)<sub>3</sub><sup>[9]</sup>, Dy(OTf)<sub>3</sub><sup>[10]</sup>, Sc(OTf)<sub>3</sub><sup>[11,12]</sup>, CAN<sup>[13]</sup>, ZrOCl<sub>2</sub><sup>[14]</sup>, InCl<sub>3</sub><sup>[15]</sup>, and AIPW<sub>12</sub>O<sub>40</sub><sup>[16]</sup>, ionic liquids<sup>[17]</sup>, trichloro-1,3,5 triazine<sup>[18]</sup>, potassium hydrogen sulphate<sup>[19]</sup>. Recently sodium dodecyl sulfate was used to promote this reaction in water medium to afford bis(indolyl)methane<sup>[20]</sup> but requires cumbersome workup procedures.

However, many of these methods still suffer from some disadvantages such as use of expensive reagents<sup>[21-23]</sup> longer reaction times<sup>[24-27]</sup>, low yields of products in some cases<sup>[28]</sup>, high catalyst loading which cannot be recycled,

corrosive reagents, use of an additional microwave oven, large amounts of solid supports, which would eventually result in the generation of large amounts of toxic waste.

Therefore, a more efficient method to carry out this transformation, superior catalysts, which are cheap, less toxic, easily available, air stable and water tolerant are still sought.

Hence, we planned to explore the synthetic utility of methane sulfonic acid (Me-SO<sub>3</sub>H). We herein report an efficient and green method for the synthesis of bis(indolyl) alkanes with Me-SO<sub>3</sub>H in water medium with good to excellent yields. In addition, to best of our knowledge, there are no reports on the use of methane sulfonic acid as a catalyst for this conversion. This fact has prompted us to investigate Me-SO<sub>3</sub>H for the electrophilic substitution of indole with various aldehydes and ketones in a facile and practical manner.

## EXPERIMENTAL

All chemicals were obtained from Sigma-Aldrich, Merck and Lancaster, and used as such without further purification. Melting points were determined using a calibrated thermometer by Guna Digital Melting Point apparatus and are uncorrected. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded as solutions in DMSO-*d*<sub>6</sub> on a Bruker AMX 400 MHz spectrometer operating at 400 MHz for <sup>1</sup>H, 100 MHz for <sup>13</sup>C. The <sup>1</sup>H and <sup>13</sup>C chemical shifts were referenced to tetramethylsilane. LC Mass spectra were recorded on LCMS 2010A Shimadzu instrument.

### General procedure

A mixture of benzaldehyde (5 mmol) and indole (10 mmol) in water (20 ml) was stirred at room temperature in the presence of Me-SO<sub>3</sub>H (0.05 mmol) for an appropriate time (TABLE 1). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with water to get the pure product.

### General procedure for the synthesis of tris-indolyl and di(bis-indolyl methanes)

The catalyst was allowed to settle down, selective condensation of a dialdehyde i.e. terephthaldehyde to the corresponding bis-indolyl methane was achieved by controlling the molar ratio of indole (Scheme 1). The results showed that addition of 2 equivalents of indole to terephthaldehyde, gives (4a) in 97 % yield. Treatment of 4 equivalents of indole or substituted indoles

with terephthaldehyde gives the corresponding di(bis-indolyl methanes) (6a-d) in high yields at room temperature in water (Scheme 1).

### 3-((1H-Indol-3-yl) (phenyl) methyl)-1H-indole (3a)

Mp 141-143 °C. IR (KBr, cm<sup>-1</sup>): 3402, 3051, 1454. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 5.92 (1H, s, ArCH), 6.65 (2H, s), 7.16 (2H, t, *J* = 7.1 Hz), 7.18-7.26 (3H, m), 7.32-7.36 (2H, m), 7.39-7.44 (6H, m), 7.98 (2H, br, NH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 31.8, 111.8, 114.1, 119.4, 120.2, 122.3, 126.1, 126.7, 128.2, 129.2, 130.3, 138.0, 145.2; MS (m/z): 322 (M<sup>+</sup>).

### 3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (3b)

Mp 78-79 °C. IR (KBr, cm<sup>-1</sup>): 3422, 3056, 1489. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>), δ (ppm): 5.92 (s, 1H, Ar-CH), 6.62 (s, 2H), 7.01 (t, 2H, *J* = 8.2 Hz), 7.21-7.28 (m, 8H), 7.31 (d, 2H, *J* = 8.1 Hz), 7.85 (br, s, 2H, NH); MS (m/z): 356 (M<sup>+</sup>).

### 3-(Furan-2-yl(1H-indol-3-yl)methyl)-1H-indole (3k)

Mp 322-323 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.01 (1H, s, ArCH), 6.92 (2H, s), 7.06-7.23 (11H, m), 8.02 (2H, br, NH); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 34.2, 106.4, 111.8, 112.4, 113.3, 118.2, 120.1, 121.7, 121.9, 124.8, 126.6, 140.1, 141.2; MS (m/z): 312 (M<sup>+</sup>).

### 3-(1-(1H-Indol-3-yl)-1-phenylethyl)-1H-indole (3n)

Mp 164-166 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 2.44 (3H, s, CH<sub>3</sub>), 6.66 (2H, s), 6.98 (2H, t, *J* = 7.5 Hz), 7.19 (2H, t, *J* = 7.5 Hz), 7.28-7.41 (9H, m), 7.93 (2H, br, NH); MS (m/z): 367 (M<sup>+</sup>).

### 4-(Di(1H-indol-3-yl)methyl)benzaldehyde (4a)

Mp 257-259 °C. <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 6.08 (1H, s, ArCH), 6.67 (2H, s), 6.94-7.01 (4H, m), 7.21 (2H, d, *J* = 7.8 Hz), 7.34 (2H, d, *J* = 8.0 Hz), 7.43 (2H, d, *J* = 8.0 Hz), 7.60 (2H, d, *J* = 7.8 Hz), 8.02 (2H, br, NH), 9.68 (1H, s, O=CH); <sup>13</sup>C NMR (100 MHz, DMSO-*d*<sub>6</sub>): δ 36.1, 110.8, 112.4, 119.6, 120.0, 121.5, 124.7, 127.6, 130.0, 130.9, 134.8, 137.9, 146.7, 191.5; MS (m/z): 350 (M<sup>+</sup>).

### Tri (1H-indol-3-yl) methane (5b)

Mp 160-162 °C. IR (KBr, cm<sup>-1</sup>): 3422, 3050, 2832, 1612, 1458. <sup>1</sup>H NMR (300 MHz, DMSO-*d*<sub>6</sub>), δ (ppm): 6.02(s, 1 H, Ar<sub>3</sub>CH), 6.91 (s, 3H), 6.95 (t,

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3H,  $J = 7.4$  Hz), 7.11 (t, 3H,  $J = 7.2$  Hz), 7.33 (d, 3H,  $J = 7.2$  Hz), 7.54 (d, 3H,  $J = 7.5$  Hz), 10.73 (s, 3H, –NH; MS ( $m/z$ ): 361 ( $M^+$ ).

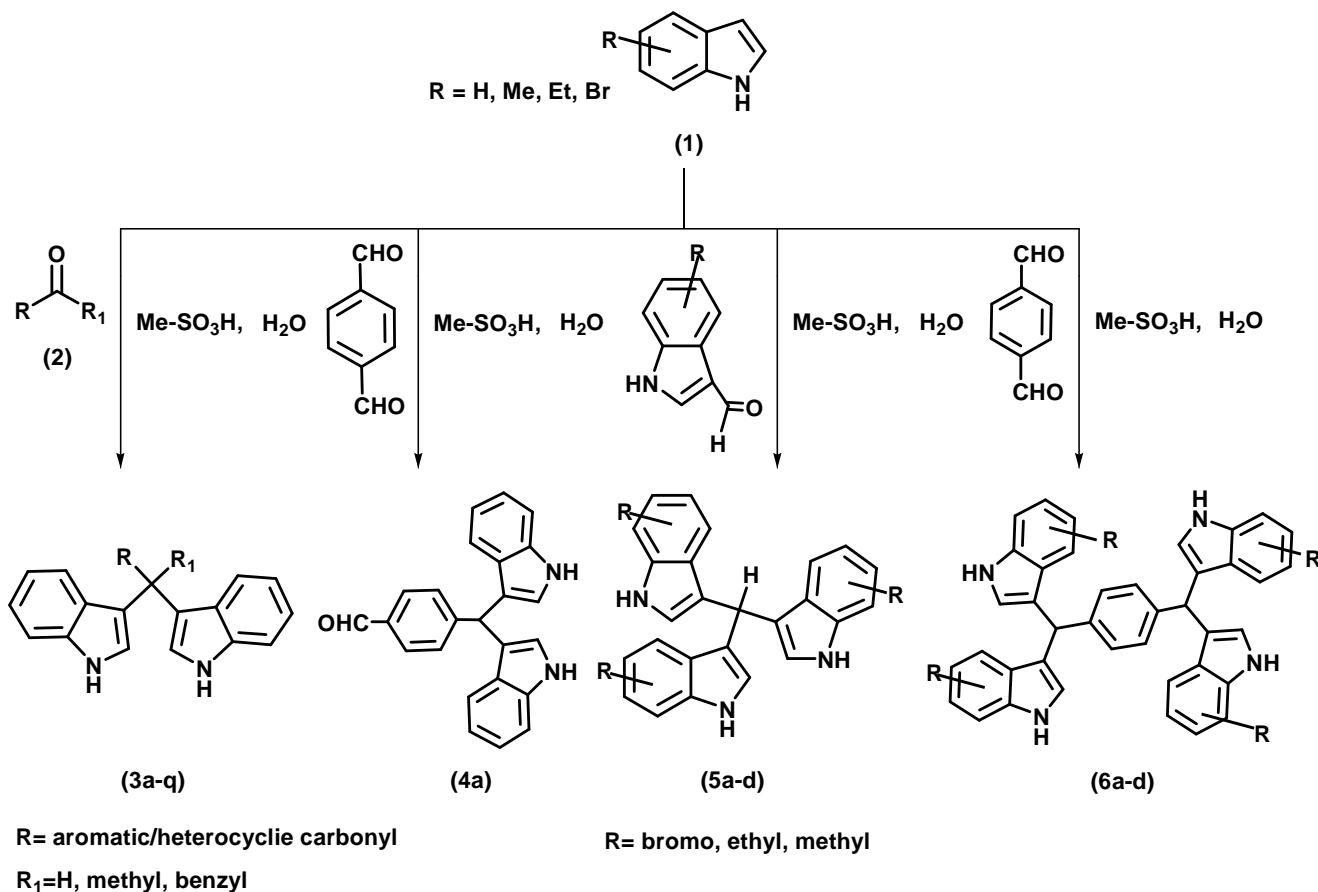
### 1,4-bis(di(1H-indol-3-yl)methyl)benzene (6a)

Mp 195–196 °C. IR (KBr,  $cm^{-1}$ ): 3412, 3058, 1628.  $^1H$ NMR (400 MHz, DMSO- $d_6$ ),  $\delta$  (ppm): 5.72 (s, 2 H, Ar–CH), 6.32 (s, 4H), 7.12 (t, 4H,  $J = 7.6$  Hz), 7.21 (t, 4H,  $J = 7.6$  Hz), 7.26–7.43 (m, 12H), 7.31 (br, s, 4H, NH; MS ( $m/z$ ): 566 ( $M^+$ ).

## RESULTS AND DISCUSSION

In our initial experiments the condensation of benzaldehyde and indole (mole ratio 1:2) was performed in the presence of catalyst Me-SO<sub>3</sub>H in THF. The catalyst facilitated the formation of bis(indolyl)alkanes in good yields but requires long time. Then it was decided to carry out the reaction in water medium proceeded smoothly in shorter reaction time with good yields. The results show that in water medium the catalytic activity of Me-SO<sub>3</sub>H was increased in all the cases (TABLE 1).

With the optimized conditions in hand to explore the generality of the reaction, we extended our study with different aromatic/heterocyclic aldehydes and ketones to prepare a series of bis-indolyl methanes, tris-indolyl methanes and di(bis-indolyl methanes) (TABLE 1). In all the cases the corresponding bis(indolyl)alkanes were obtained in good to excellent yields. However, with aromatic aldehydes with electron withdrawing groups as substituents the reaction time is shorter than those with electron donating groups. On the other hand reaction with substituted  $\alpha$ ,  $\beta$ -unsaturated aldehydes provided somewhat lower yields than those aromatic aldehydes (TABLE 1, entry (3n)). Encouraged by the results obtained for benzaldehyde and benzophenone, we have investigated a number of other aldehydes and ketones to probe their behavior under the current catalytic conditions. The results are listed in TABLE 1. A variety of carbonyl compounds reacted smoothly with indoles to produce bis-indolyl methanes under the present reaction conditions. The electron deficiency and the nature of substituents on the aromatic ring did not show any obvious effects on this conversion. Electron rich as well



Scheme 1

TABLE 1 : Preparation of bis-indolyl methanes from indoles and aldehydes or ketones in the presence of Me-SO<sub>3</sub>H at room temperature in water.

Entry	Indole	Carbonyl Compound	Product	Time (min)	Yield (%)	Entry	Indole	Carbonyl Compound	Product	Time (min)	Yield (%)
1			3a	5	97	14			3n	13	89
2			3b	9	95	15			3o	10	92
3			3c	9	95	16			3p	10	92
4			3d	10	91	17			3q	13	96
5			3e	6	96	18			4a	5	97
6			3f	12	93	19			5a	5	97
7			3g	16	96	20			5b	9	95
8			3h	18	94	21			5c	10	91
9			3i	12	95	22			5d	6	96
10			3j	11	90	23			6a	5	97
11			3k	8	94	24			6b	9	95
12			3l	5	96	25			6c	10	91
13			3m	8	86	26			6d	6	96

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as electron deficient aldehydes react with indoles with equal ease to give the products in excellent yields (TABLE 1), (3a-3q). Here aromatic and heterocyclic aldehydes (TABLE 1) are afforded the corresponding bis-indolyl methanes in high yields. In addition, the present methodology found to be efficient for the preparation of bis-indolyl methanes from less reactive aldehydes like 3-nitrobenzaldehyde and 4-nitrobenzaldehyde within 8 and 5 min respectively when compared to earlier reported methodology which takes longer times.

In order to show the accessibility of the present work in comparison with the reported results, we summarized some of the results for the preparation of bis(indolyl) alkanes in TABLE 1 which show the Me-SO<sub>3</sub>H is the most efficient catalyst with respect to the reaction time, temperature and exhibits broad applicability in terms of yield.

### CONCLUSION

In conclusion, we have developed a facile protocol for the synthesis of bis(indolyl)alkanes. The remarkable catalytic activity of Me-SO<sub>3</sub>H is superior to the reported other catalytic methods with respect to reduced reaction times, high yields and cost of the catalyst

The condensation of indole with carbonyl compounds was successfully carried out in presence of a catalytic amount of Me-SO<sub>3</sub>H at room temperature in water medium as an environmentally benign catalyst. The salient features of this procedure are short reaction time, improved yields.

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