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## A Facile and Eco-friendly Synthesis of Bis(indolyl)methanes Using Montmorillonite K-10 Impregnated with Bismuth Nitrate in the Solid State

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### ABSTRACT

Montmorillonite impregnated with bismuth nitrate has been found to be an excellent reagent for the synthesis of bis(indolyl)methanes in the solid state. This methodology involves the electrophilic condensation of indole with a wide range of aldehydes.

**Keywords:** Montmorillonite K-10, Bismuth nitrate, Bis(indolyl)methane, Indole, Aldehyde, Solid state

### INTRODUCTION

Bis(indolyl)methanes and their derivatives are attracting much attention due to their synthetic as well as biological applications [1]. These compounds are active cruciferous substances for promoting beneficial estrogen metabolism and inducing apoptosis in human cancer cells [2-4]. Bis(indolyl)methanes are also a drug of choice for breast cancer prevention [5,6].

Numerous methods for the synthesis of bis(indolyl)methanes have been reported in literature using Lewis and Bronsted acids [7-10], PPA/SiO<sub>2</sub> [11], silica sulphuric acid [12], In(OTf)<sub>3</sub> [13], I<sub>2</sub> [14], PCl<sub>5</sub> [15], ionic liquid [16,17], citric acid [18] and cellulose perchloric acid [19]. Recently amberlyst-15 [20] and bismuth triflate have been used for the synthesis of these compounds [21]. However, many of these methods involve excess amount of catalyst, long reaction time, tedious work up and low yield of products.

Surface mediated organic syntheses are investigated extensively now a days because of their eco-friendly nature [22]. Bismuth nitrate is an inexpensive, easy to handle and commercially available [23,24]. Montmorillonite K-10 has a substantially higher surface area. Moreover, the supported bismuth nitrate is easier to handle, readily separable from the products by simple filtration, recyclable and requires milder reaction conditions. Therefore, in the present study, bismuth nitrate impregnated on montmorillonite K-10 is employed as a useful catalyst for the synthesis of bis(indolyl)methanes in the solid state at room temperature.

### EXPERIMENTAL SECTION

All the reagents were purchased from Merck, Fluka, Aldrich and Sigma and used without purification. Melting points were recorded by a capillary melting point apparatus and were uncorrected. All experiments were monitored by Thin Layer chromatography (TLC). Fourier Transform Infra-Red (FTIR) spectra were recorded on Perkin Elmer FTIR-1600 spectrophotometer as KBr disc. Nuclear Magnetic Resonance (<sup>1</sup>H and <sup>13</sup>C-NMR) spectra (400 MHz, 100 MHz) were recorded on a Bruker Advance DRX-400 spectrophotometer. HRMS were recorded on a Thermo Fischer Scientific LTQ Orbitrap-XL mass spectrometer.

#### General procedure for the synthesis of bis(indolyl)methanes

A mixture of aldehyde (1 mmol), indole (2 mmol) and Bi(NO<sub>3</sub>)<sub>3</sub>-Mont. K-10 were grinded in a pestle mortar and continued until reaction was completed. Progress of the reaction was monitored by TLC (Ethylacetat: n-hexane, 2:8). After completion of the reaction, reaction mixture was extracted with ethyl acetate in a soxhlet apparatus. This was then crystallized with aqueous ethanol to get the pure product.

#### Spectra data of the products

**3,3'-(Phenylmethylene)bis(1H-indole) (3a):** IR<sub>v</sub> (cm<sup>-1</sup>) (KBr): 3410, 3055, 3022, 2928, 2852, 1599, 1455. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>), δ=5.88(s, 1H), 6.63 (d, J=2.4 Hz, 2H), 7.00 (dd, J=7.9 Hz, 2H), 7.17 (dd, J=7.9 Hz, 2H), 7.21 (m, 1H), 7.27 (m, 2H), 7.33(d, J=8.0 Hz, 4H), 7.38 (d, J=8.0 Hz, 2H), 7.87 (br, s, 2H). <sup>13</sup>C-NMR: 144, 136.9, 128.7, 127.1, 126.2, 123.6, 121.9, 119.9, 119.7, 119.3, 111.0, 40.2.

**3,3'-[(4-Chlorophenyl)methylene]bis(1H-indole) (3b):** IR<sub>v</sub> (cm<sup>-1</sup>) (KBr): 3417, 1637, 1486, 1455, 1416, 1338, 1092, 743. <sup>1</sup>H-NMR (400 MHz, DMSO), δ=10.86 (s, 2H), 7.39-7.33 (m, 4H), 7.31 (d, J=8.5 Hz, 2H), 7.27(d, J=7.9 Hz, 2H), 7.04 (t, J=7.5 Hz, 2H), 6.87 (t, J=7.5 Hz, 2H), 6.83

(s, 2H), 5.87 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ), 136.7, 130.1, 128.1, 126.8, 123.5, 122, 119.8, 119.4, 119.3, 111, 39.8  
HRMS, m/z: 357( $\text{M}+\text{H}^+$ ).

**3,3'-(2-Bromophenyl)methylene]bis(1H-indole) (3c):** IR $\nu$  ( $\text{cm}^{-1}$ ) (KBr): 3416, 1637, 1457, 1416, 1339, 1094, 1017, 743.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ =7.88(s, 2H), 7.46-7.27 (m, 5H), 7.19 (s, 1H), 7.15 (d, J = 5.8 Hz, 1H), 7.13-7.06 (m, 2H), 7.05-7.00 (m, 1H), 6.95 (t, J=7.5 Hz, 2H), 6.56 (s, 2H), 6.27 (s, 1H). HRMS (EI), m/z Calcd. For  $\text{C}_{23}\text{H}_{16}\text{BrN}_2$  [M-H] 399.05023 found 399.05086.

**3,3'-(4-Nitrophenyl)methylene]bis(1H-indole) (3d):** IR $\nu$ ( $\text{cm}^{-1}$ )(KBr): 3455, 1637, 1506, 1456, 1414, 1341, 1101, 744.  $^1\text{H-NMR}$  (400 MHz, DMSO),  $\delta$ =10.95 (s, 2H), 8.15 (d, J=8.7 Hz, 2H), 7.61(d, J=8.7 Hz, 2H), 7.38 (d, J=8.1 Hz, 2H), 7.30 (d, J=7.9 Hz, 2H), 7.06 (t, J=7.5 Hz, 2H), 6.96-6.78 (m, 4H), 6.04 (s, 1H).

$^{13}\text{C-NMR}$  (100 MHz, DMSO),  $\delta$ =153.61, 176.26, 137.10, 129.93, 124.35, 123.87, 121.58, 119.39, 118.91, 112.07, 40.66, 40.45, 40.24, 40.03, 39.83, 39.62, 39.41. HRMS (EI), m/z Calcd. For  $\text{C}_{23}\text{H}_{16}\text{O}_2\text{N}_3$ , [M-H] 366.12480, Found: 366.12896.

**3,3'-(4-Methylphenyl)methylene]bis(1H-indole) (3e):** IR $\nu$  ( $\text{cm}^{-1}$ ) (KBr): 3421, 1635, 1512, 1454, 1416, 1339, 1095, 742.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ =7.91 (s, 2H), 7.39 (dd, J=8.0 Hz, 2H), m 7.35 (d, J=8.1 Hz, 2H), 7.22 (d, J=7.9 Hz, 2H), 7.16(t, J=7.5 Hz, 2H), 7.08 (d, J=7.7 Hz, 2H), 7.00 (t, J=7.5 Hz, 2H), 6.66 (s, 2H), 22.31 (s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ =136.7, 128.9, 127.1, 123.5, 121.9, 119.9, 119.2, 110, 55.9, 39.8.

**3,3'-(3-Nitrophenyl)methylene]bis(1H-indole) (3f):** IR $\nu$  ( $\text{cm}^{-1}$ ) (KBr): 3411, 1637, 1508, 1456, 1417, 1339, 1094, 744.  $^1\text{H-NMR}$  (400 MHz, DMSO- $d_6$ ),  $\delta$ =10.94 (s, 2H), 8.17 (s, 1H), 8.07 (d, J=8.0 Hz, 1H), 7.84 (d, J=8.0 Hz, 1H), 7.58 (t, J=8.4, 16.0, 7.6 Hz, 1H), 7.37 (d, J=8.0 Hz, 2H), 7.30 (d, J=8 Hz, 2H), 7.06 (t, J=7.2, 14.8, 7.6 Hz, 2H), 6.88 (m, 4H), 6.07(s, H).

**3,3'-(4-Bromophenyl)methylene]bis(1H-indole) (3g):** IR $\nu$  ( $\text{cm}^{-1}$ ) (KBr): 3417, 2918, 2849, 1618, 1482, 1455, 1414, 1199, 1033, 742.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ =7.78 (s, 1H), 7.391 (m, 2H), 7.33 (d, J=8.8 Hz, 1H), 7.20 (t, J=8.2 Hz, 2H), 7.04 (t, J=8.2 Hz, 1H), 6.56 (s, 1H), 5.85 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ =143.2, 136.7, 131.4, 130.5, 126.9, 123.7, 123.0, 122.1, 120.0, 119.9, 119.4, 119.1, 111.2, 39.8.

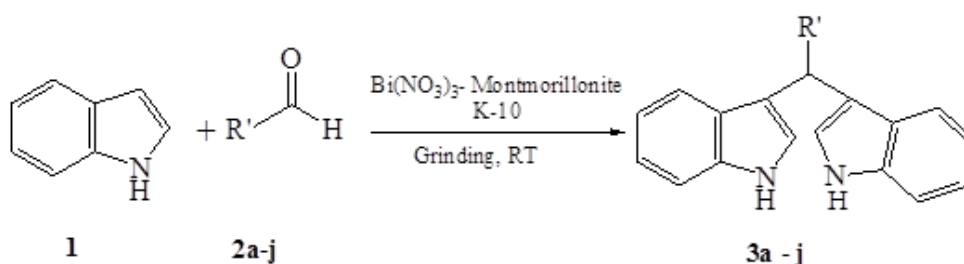
**3,3'-(2-Nitrophenyl)methylene]bis(1H-indole) (3h):** IR $\nu$  ( $\text{cm}^{-1}$ ) (KBr): 3419, 1636, 1560, 1523, 1454, 1417, 1352, 1096, 744.  $^1\text{H-NMR}$  (400 MHz, DMSO),  $\delta$ =10.93 (s, 2H), 7.88 (d, J=7.9 Hz, 1H), 7.56 (t, J=7.5 Hz, 1H), 7.46 (t, J=7.3 Hz, 1H), 7.40 (d, J=7.7 Hz, 1H), 7.36 (d, J=8.1 Hz, 2H), 7.21 (d, J=8.0 Hz, 2H), 7.06 (t, J=7.5 Hz, 2H), 6.89 (t, J=7.4 Hz, 2H), 6.78 (s, 2H), 6.40 (s, 1H).

**3,3'-(4-Methoxyphenyl)methylene]bis[1H-indole] (3i):** IR $\nu$  ( $\text{cm}^{-1}$ ) (KBr): 3412, 1636, 1564, 1509, 1455, 1417, 1340, 1250, 1175, 1095, 107, 744.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ =7.90(s, 2H), 7.38 (d, J=8.0 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 7.24 (d, J=7.9 Hz, 2H), 7.16 (t, J=7.4 Hz, 2H), 7.00 (t, J=7.3 Hz, 2H), 6.81 (d, J=8.6 Hz, 2H), 6.63 (s, 2H), 5.83 (s, 1H), 3.77(s, 3H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ),  $\delta$ =136.7, 136.2, 127.1, 123.5, 121.9, 120, 119.9, 119.4, 119.2, 113.6, 110.9, 55.2, 38.6.

**3,3'-(2-Chlorophenyl)methylene]bis(1H-indole) (3j):** IR $\nu$  ( $\text{cm}^{-1}$ ) (KBr): 3414, 1627, 1458, 1417, 1338, 1093, 744.  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ),  $\delta$ =7.93 (s, 2H), 7.64(d, J=7.8 Hz, 1H), 7.44 (d, J=7.9 Hz, 2H), 7.38 (d, J=8.1 Hz, 2H), 7.23 (s, 1H), 7.21 (s, 1H), 7.17 (s, 2H), 7.14-7.10 (m, 1H), 7.06 (d, J=15.0 Hz, 2H), 6.62 (s, 2H), 6.34 (s, 1H).

## RESULTS AND DISCUSSION

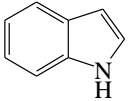
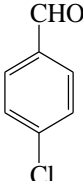
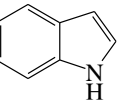
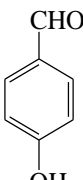
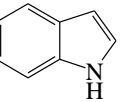
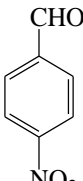
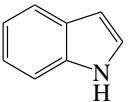
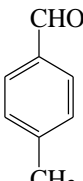
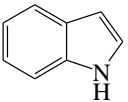
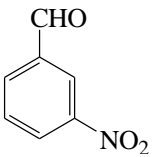
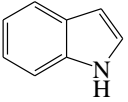
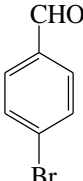
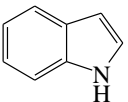
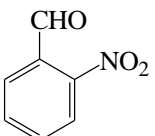
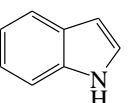
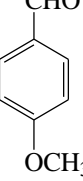
The procedure involved the reaction between indole (1) and aldehydes (2a-j) using bismuth nitrate-montmorillonite K-10 catalyst by grinding in a pestle mortar at 25-28°C. After the completion of the reaction, the reaction mixture was extracted with ethyl acetate. The pure compounds were obtained by column chromatography on silica gel. To gauge the scope of this methodology, a variety of aldehydes (2a-j) were reacted with indole (1) in the presence of the catalyst to produce the corresponding bis(indolyl)methanes (Table 1). The nature of substitution on the aromatic ring showed some effect on product yields and reaction times. Aromatic aldehydes having electron withdrawing groups at o- and p- position provided products in excellent yields with shorter reaction times. Substrates with electron donating group took longer time with moderate yields. Heterocyclic aldehydes reacted smoothly with indole to give the corresponding product in excellent yield (Scheme 1).

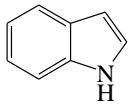
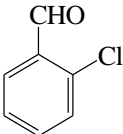


Scheme 1: Condensation of indole with aldehydes using  $\text{Bi}(\text{NO}_3)_3$  montmorillonite K-10

Table 1:  $\text{Bi}(\text{NO}_3)_3$ -Montmorillonite K-10 catalyzed synthesis of bis(indolyl)methanes

Entry	1	2	3	Tim (min)	Yield (%)	M.p. (°C)
A			3a	10	88	125

B			3b	08	87	76-78
C			3c	22	80	105
D			3d	10	83	215
E			3e	15	78	95
F			3f	09	83	255
G			3g	12	85	108
H			3h	10	80	141
I			3i	20	83	190

J			3j	15	85	72
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This methodology has several advantages like shorter reaction times, reusability of the catalyst and easy work up procedure.

### CONCLUSION

This communication describes Bi(NO<sub>3</sub>)<sub>3</sub>-montmorillonite K-10 mediated efficient eco-friendly and rapid synthesis of bis(indolyl)methanes from indole and substituted aldehydes in excellent yield at room temperature in the solid state. Bismuth nitrate impregnated on montmorillonite K-10 acts as a green media for the reaction making this method cheaper, simple and environment friendly.

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