

# Silica Supported Synthesis of Bis(Indolyl) Methane Derivatives Under Microwave Irradiation

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**ABSTRACT:** In this communication, we report an efficient synthesis of bis-(indolyl)methane derivatives from indole on reaction with aromatic aldehydes in silica gel support under microwave irradiation under solvent free condition.

**KEYWORDS:** solid phase synthesis, bis-(indolyl)methane, microwave irradiation, solvent free

## I. INTRODUCTION

Indole moieties are featured in a variety of pharmalogically and biologically active compounds<sup>1</sup> which makes it the current interest of organic synthesis. Particularly, bis-(indolyl)methanes are known to enhance estrogen metabolism in humans and is likely to be drug of choice for breast cancer and also it exhibits antibacterial activities.<sup>2-4</sup> A wide range of applications of bis(indolyl)methane derivatives has grown interest among chemist to develop their synthetic methods since long back.

## II. RELATED WORK

Numerous methods for synthesis of this has been developed including use of Lewis acid<sup>5</sup>, protic acid<sup>6</sup>, PPA/SiO<sub>2</sub><sup>7</sup>, silica sulfuric acid<sup>8</sup>, In(OTf)<sub>3</sub><sup>9</sup>, I<sub>2</sub><sup>10</sup>, PCl<sub>5</sub><sup>11</sup>, I<sub>2</sub><sup>12</sup>. However, many of the reported procedures have significant drawbacks such as requirement of stoichiometric amount of catalyst, long reaction time, expensive catalyst, low yield, harsh reaction condition, cumbersome workup procedure and use of environmentally toxic reagents. Although some drawbacks were overcome to some extent by recently reported green methods under solvent free condition or using ionic liquids<sup>13</sup> as reaction medium but the demand for increasingly efficient and clean chemical synthesis still continues for both economic and environment points of view.

During the past two decades many publications have described successful combination of microwave irradiation<sup>14</sup> as a non-classical source of energy with alternative reaction medium. Here we report the efficient method for the synthesis of bis-(indolyl)methanes derivatives under microwave irradiation in an environmentally free conditions within a short period giving better yield.

## III. PROPOSED WORK, RESULT & DISCUSSION

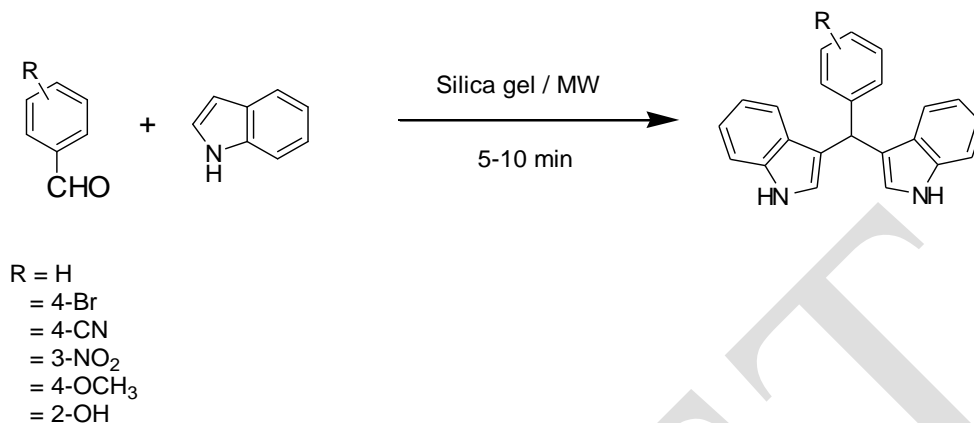
The electrophilic substitution reaction of indole with aldehydes in presence of silica gel under microwave irradiation afforded the corresponding bis-(indolyl)methane derivatives within few minutes (Scheme 1). The experimental procedure for these reactions is very ease to handle and does not require an inert atmosphere. This method respond well for a wide variety of aromatic aldehydes (Table 1). Prior to studies on bis-coupling reaction on silica surface under

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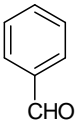
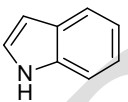
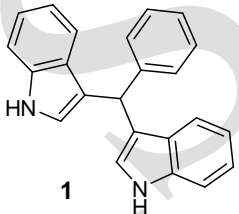
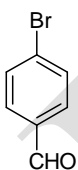
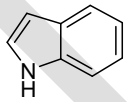
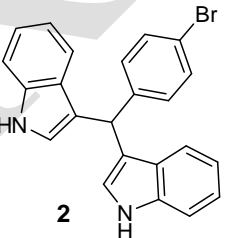
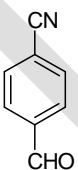
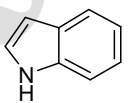
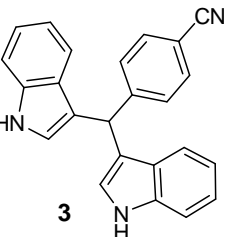
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Scheme 1



**Table-1:** Microwave irradiated bis-(indolyl)methane derivatives on silica gel

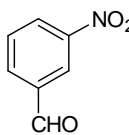
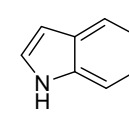
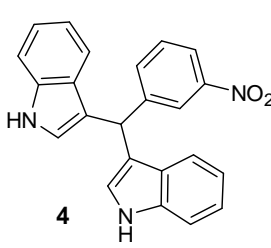
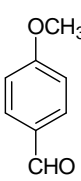
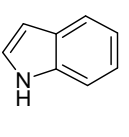
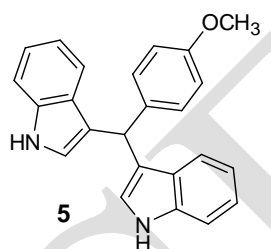
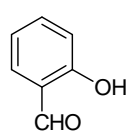
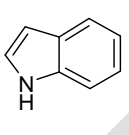
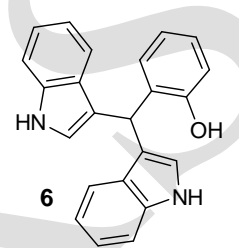
entry	aldehyde	Indole	Product	Time	Yield (%) <sup>a</sup>	M.P (°C)
1.				5 min	95	140-143
2.				5 min	80	108-110
3.				5 min	85	209-211

continue.....

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entry	aldehyde	Indole	Product	Time	Yield (%) <sup>a</sup>	M.P (°C)
4.			 4	5 min	90	256-259
5.			 5	9 min	70	185-189
6.			 6	8 min	80	191-194

<sup>a</sup>Yields are reported on the basis of pure isolated product, checked by TLC.

microwave irradiation, we attempted the same reaction at room temperature under stirring. But, unfortunately we could not find any new spot on TLC plate. Electron withdrawing group in aromatic ring increases the yield of the reaction (entries 3 and 4) and the electron donating group decreases the rate of reaction (entries 2, 5, and 6).

To check the reusability of silica gel, when the reaction of indole with carbonyl compound was over the product was extracted with chloroform and the silica gel was filtered. It was washed with chloroform repeatedly, dried and reused for the reaction of indole with same and different aldehydes. It was found that silica gel can be recycled for at least four cycles without any change in activity.

On standing for several weeks the colour of these bis-(indolyl) compounds changed to reddish from colourless. Further inspection through TLC it was learned that the compound started to degrade to a high polar compound. Spectral data indicates the oxidation product of bis(indolyl)methane derivatives.

## IV. COMPARATIVE STUDY

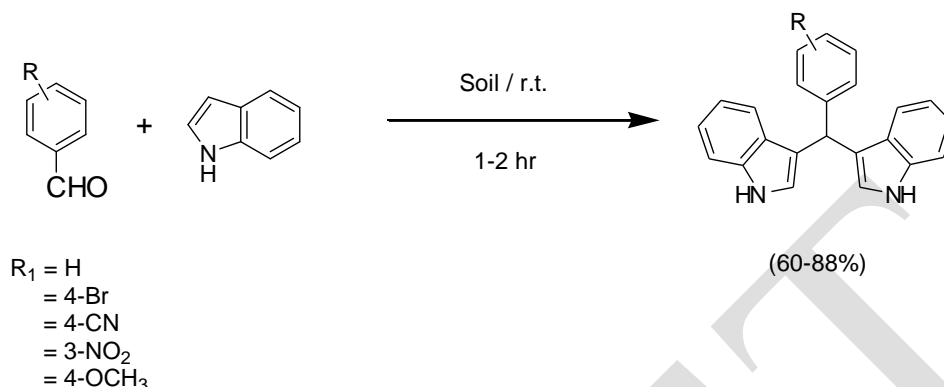
A comparative study on bis-(indolyl)methane derivatives synthesis was also done in a much greener way with soil (collected from north-eastern region of India, pH 5-6) in place of silica gel under constant stirring at room temperature (Scheme-2). The reaction was preceded with moderate yields but needs longer duration of time (Table 2).

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Scheme-2


**Table 2:** Comparative study on the synthesis of bis-(indolyl)methane derivatives in silica gel under microwave with the same in soil at room temperature

Entry	aldehyde	Silica gel (microwave)		Soil	Yield(%)
		Time(min)	Yield(%)		
1.	benzaldehyde	5	95	1	80
2.	<i>p</i> -cyano benzaldehyde	5	85	1	82
3.	<i>m</i> -nitro benzaldehyde	5	90	1	88
4.	<i>p</i> -bromo benzaldehyde	5	80	1	79
5.	anisaldehyde	9	70	2	60

## V. EXPERIMENTAL RESULT

### General Remarks

All starting material and silica gel were obtained from best known commercial supplier. Thin layer chromatography were performed on silica gel coated glass plate and spots were detected in iodine chamber. Petroleum ether refers to the fraction of boiling point 60-80 °C. Silca gel (60-120 mesh) was used in column chromatography. Evaporation of all steps were conducted at room temperature in fume hood. All melting points are uncorrected. Spectral data (IR, <sup>1</sup>H-NMR, MS) of all compounds were recorded both in IISc, Banglore and Kalyani University, Kalyani, North Bengal Univesity, Darjeeling, West Bengal.

### General procedure for the synthesis of bis(indolyl)methane derivatives:

The grinding mixture of *p*-cyanobenzaldehyde (131 mg, 1.0 mmol), indole (234 mg, 2.0 mmol), and silica gel (1.0 gm) taken in a round bottom flask fitted with a guard tube was subjected to microwave irradiation for a specified period. The reaction was monitored by TLC. On completion of reaction (checked by TLC) chloroform (10 mL) was added and the reaction mixture was then filtered. Removal of excess solvent resulted crude material, which was then purified through column using silica gel (60-120 mesh) to afford compound **3** as a white solid. The compound **3** was characterized by spectral methods. The spectral data are summarized below:

Yield: 85%, m.p. 209-211 °C; IR (KBr): 3428.2, 3363.9, 2917.2, 2848.9, 2223.6, 1601.6, 1488.2, 1454.9, 1212.9, 1089.0, 791.8, 737.8 cm<sup>-1</sup>; <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz): δ 5.94 (s, 1H, Ar-CH), 6.65-6.66 (d, *J* = 1.5 Hz, 2H), 6.99-7.04 (t, 2H), 7.16-7.21 (t, 2H), 7.31-7.39 (q, 4H), 7.43-7.46 (d, *J* = 7.8 Hz, 2H), 7.55-7.57 (d, *J* = 8.4 Hz, 2H), 7.99 (br.s., 2H, NH); MS (m/z): 347 (M<sup>+</sup>); Cal. mass of oxidized form: 346 (M+H), 369 (M+Na)<sup>+</sup>;

Compounds **(1)**-**(6)** were prepared using similar procedures as mentioned in Table 1.

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3,3'-Bis(indolyl)phenylmethane (**1**): Yield: 95%, m.p. 140-143 °C; IR (KBr): 3410.7, 3058.4, 2924.1, 2854.0, 1615.9, 1519.8, 1456.47, 1423.9, 1262.9, 1210.6, 1012.1, 745.3, 700.6 cm<sup>-1</sup>; MS (m/z): 322 (M<sup>+</sup>); Cal. mass of oxidized form: 321 (M+H)<sup>+</sup>;  
3,3'-Bis(indolyl)-4-bromophenylmethane (**2**): Yield: 80%, m.p. 108-110 °C; IR (KBr): 3402.7, 3058.0, 2924.4, 2854.0, 1617.8, 1457.9, 1010.9, 743.3 cm<sup>-1</sup>; MS (m/z): 402 (M<sup>+</sup>); Cal. mass of oxidized form: 401 (M+H)<sup>+</sup>;  
3,3'-Bis(indolyl)-3-nitrophenylmethane (**4**): Yield: 90%, m.p. 256-259 °C; IR (KBr): 3414.5, 3057.4, 1616.9, 1526.6, 1457.1, 1359.6, 1095.0, 743.8 cm<sup>-1</sup>; MS (m/z): 367 (M<sup>+</sup>), 390 (M+Na); Cal. mass of oxidized form: 366 (M+H)<sup>+</sup>;  
3,3'-Bis(indolyl)-4-methoxyphenylmethane (**5**): Yield: 70%, m.p. 185-189 °C; IR (KBr): 3411.1, 1685.5, 1676.5, 1604.9, 1578.9, 1305.6, 1264.2, 1027.5, 743.3 cm<sup>-1</sup>; MS (m/z): 352 (M<sup>+</sup>); Cal. mass of oxidized form: 351 (M+H)<sup>+</sup>;  
3,3'-Bis(indolyl)-2-hydroxyphenylmethane (**6**): Yield: 80%, m.p. 191-194 °C; IR (KBr): 3422.3, 2927.4, 2854.1, 1654.1, 1647.7, 1638.3, 745.0 cm<sup>-1</sup>; MS (m/z): 338 (M<sup>+</sup>), 361 (M+Na)<sup>+</sup>; Cal. mass of oxidized form: 335 (M<sup>+</sup>);

## VI. CONCLUSION

In summary, we have developed an efficient way to synthesize bis-(indolyl)methane derivatives on treatment of indole with aldehydes in good yields. The procedure offers several advantages, including mild reaction conditions, greener approach, surface reusability and simple experimental and isolation procedures.

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