Synthesis of bis(indolyl)methanes using silica gel as an efficient and recyclable surface

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The indole unit forms the basis for general bis- and tetra(indolyl)methanes, which are widely present in bioactive metabolites of numerous compounds isolated from natural sources.1,2 Even the structurally prosaic bis(3-indolyl)methane (BIM), a metabolite of naturally occurring indole-3-carbinol, was effective in cancer chemotherapy.3,4 It induces unique responses such as growth inhibition, apoptosis, and antiangiogenic activities in various cancer cell lines and tumors.3 1,1-Bis(3-indolyl)-1-(p-bromophenyl)methane, in its turn, inhibits colon cancer cell and tumor growth.4

Due to their biological and pharmacological activities, there is a plethora of synthetic methods described for the selective synthesis of BIM derivatives, the most common of them involving the acid-promoted electrophilic substitution of indoles with carbonyl compounds.5 These reactions are highly atom-efficient, but the use of toxic and expensive reagents and volatile solvents are drawbacks that limit the scale-up of most of these procedures. Recently, greener approaches on the preparation of bis(indolyl)methanes have been described by us6 and others.7 These comprise the use of FeCl3-based ionic liquid7a modified zirconia,7b ZnO,7c oxalic acid,7d trityl chloride,7e and catalytic [bmim][MeSO4]7f under solvent-free conditions, glycerin/CECL3 7H2O,7g dodecylsulfonic acid in water,7h and PEG-supported sulfonic acid.7i HBF4/SiO2,7j CeCl3 7H2O/Nal/SiO2,7k HClO4/SiO2,7l and AlCl3/SiO2 7m were successfully used as heterogeneous, silica-supported catalytic systems for the selective synthesis of a series of BIM derivatives.

In the last years, the use of silica gel to promote organic synthesis has drastically increased.8–10 Because it is easily available, inexpensive, nontoxic, and separable from the product without difficulty, due to its insolubility in organic solvents, silica gel is a green alternative to organic reactions that are catalyzed or mediated on solid surface. Used as solid support8–10 or alone,9 silica gel has migrated over the years from the ending, purification step, to the reaction step in the synthesis.8 Except for four works using SiO2 as a solid support,7i–l to the best of our knowledge, the use of silica gel alone as a solid surface in the synthesis of bis(indolyl)methanes was not explored.

Because of our interest in the development of greener protocols for fine chemical synthesis,11 we decided to explore the viability of using silica gel to promote the electrophilic substitution of indoles with carbonyl compounds, specifically targeting the preparation of bis(indolyl)methanes (Scheme 1).

Our initial studies were focused on the development of an optimum set of reaction conditions for the synthesis of BIMs (Scheme 1). Firstly, indole 1a (1.0 mmol) was reacted with benzaldehyde 2a (0.6 mmol) on silica gel (10 mg) for 2 h at 100 °C in open atmosphere. Under these conditions, the desired product 3a was obtained in 87% (Table 1; entry 1). In a search for an even higher yield, we varied the amount of silica gel and, gratifyingly, a 99% yield of 3a was obtained when 50 mg was used (Table 1, entry 3). Finally, the reaction was performed at different temperatures.
Table 1
Optimization studies using indole 1a and aldehyde 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>SiO₂ (mg)b</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield of 3a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>100</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>100</td>
<td>2</td>
<td>93</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>100</td>
<td>1</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>r.t.</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>50</td>
<td>1</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>75</td>
<td>1</td>
<td>89</td>
</tr>
</tbody>
</table>

a Reactions performed with aldehyde 2a (0.6 mmol), indole 1a (1.0 mmol), and silica gel at the indicated temperature.
b Silica gel for column chromatography Acros Organics, 0.060–0.200 mm, 60 Å.
c Determined by GC, based on the amount of indole 1a.

Table 2
Scope and generality in the synthesis of bis(indolyl) methanes 3a–l using indoles 1a–c and carbonyl compounds 2a–j

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Carbonyl Compound</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>CHO</td>
<td>1.0</td>
<td>3a</td>
<td>99</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>2b</td>
<td>1.0</td>
<td>3b</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>2c</td>
<td>1.0</td>
<td>3c</td>
<td>96</td>
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<tr>
<td>4</td>
<td>1a</td>
<td>2d</td>
<td>2.5</td>
<td>3d</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>1a</td>
<td>2e</td>
<td>3.0</td>
<td>3e</td>
<td>96</td>
</tr>
</tbody>
</table>

(continued on next page)
At room temperature, a significant decrease in the yield of 3a was observed after 2 h (Table 1, entry 4). When the reaction was carried out at 50 and 75 °C, the product was also obtained in low yields comparable to the reaction performed at 100 °C (Table 1, entries 5–6 vs. entry 3). Thus, the best condition for the reaction was the use of silica gel (50 mg), indole 1 (1.0 mmol), and aldehyde 2 (0.6 mmol) at 100 °C under air atmosphere (Table 1, entry 3).

In order to demonstrate the efficiency of this protocol, we explored the generality of our methodology reacting other aldehydes and cyclohexanone 2b–j with different indoles 1a–c (Table 2). For all the studied examples, the BIMs were obtained in good to excellent yields after stirring at 100 °C for 1 to 9 h. When aldehydes were used, the respective products were obtained in slightly higher yields (Table 2, entries 1–9 and 11–12). For aromatic, vinyl, and heteroaromatic aldehydes, the bis(indolyl)methanes 3a–h were obtained in excellent yields after stirring for 1 to 3 h (Table 2, entries 1–8). However, when aliphatic aldehyde 2i and cyclohexanone 2j were reacted, the corresponding BIMs 3i and 3j were obtained in 88% and 72% yields, respectively (Table 2, entries 9 and 10). When substituted 5-bromo-1H-indole 1b was reacted with benzaldehyde 2a, the indole derivative 3k was obtained in high yield (Table 2, entry 11). It is worth mentioning that the indolic nitrogen need not be protected. Thus, we performed the reaction with 1-tosylindole 1c and benzaldehyde 2a and the corresponding product 3l was obtained in 81% yield after 9 h (Table 2, entry 12).

Furthermore, a study regarding the recovering and reusing of the silica gel was also performed. The silica gel can be successfully reused up to ten times without any pre-treatment with excellent results (Fig. 1). Thus, after the completion of the reaction of indole 1a and benzaldehyde 2a, product 3a was simply extracted with ethyl acetate. The solid phase was separated and dried under vacuum; the recovered silica gel was reused directly in a new reaction.

### Table 2 (continued)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Indole</th>
<th>Carbonyl Compound</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1a</td>
<td>2f</td>
<td>1.5</td>
<td>3f</td>
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</tr>
<tr>
<td>7</td>
<td>1a</td>
<td>2g</td>
<td>3.0</td>
<td>3g</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>1a</td>
<td>2h</td>
<td>3.0</td>
<td>3h</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>1a</td>
<td>2i</td>
<td>4.0</td>
<td>3i</td>
<td>88</td>
</tr>
<tr>
<td>10</td>
<td>1a</td>
<td>2j</td>
<td>8.0</td>
<td>3j</td>
<td>72</td>
</tr>
<tr>
<td>11</td>
<td>1b</td>
<td>2a</td>
<td>4.5</td>
<td>3k</td>
<td>91</td>
</tr>
<tr>
<td>12</td>
<td>1c</td>
<td>2a</td>
<td>9.0</td>
<td>3l</td>
<td>81</td>
</tr>
</tbody>
</table>

* Conditions: indole 1 (1.0 mmol), carbonyl compound 2 (0.6 mmol) on silica gel (50 mg) at 100 °C under air atmosphere.

* Yields of pure products isolated by column chromatography (hexanes/EtOAc) and identified by GC–MS and 1H and 13C NMR.
cycle, maintaining its good level of efficiency even after being reused ten times. The product 3a was obtained in yields between 99% and 92% after successive cycles (Fig. 1). \(^{13}\)

Finally, the chemoselectivity of the reaction was also investigated. Thus, a mixture of benzaldehyde 2a (0.6 mmol), cyclohexanone 3j (0.6 mmol), and indole 1a (1.0 mmol) was subjected to reaction on silica gel for 8 h at 100 °C. The only product obtained was 3a, derived from benzaldehyde 2a, in 97% yield, while cyclohexanone was recovered (Scheme 2). This result shows the high chemoselectivity of our method.

In conclusion, silica gel has proved to be an effective and recyclable solid surface for the synthesis of bis(indolyl)methanes. The method is simple, chemoselective, general, and the products were obtained in good to excellent yields after stirring for a few hours. Another benefit of the described procedure is the possibility of direct reuse of the silica gel for several cycles that, together with the solvent-free conditions, is particularly relevant considering the green chemistry concepts.

Acknowledgments

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References and notes

12. General procedure for the synthesis of BIMs: A mixture of carbonyl substrate (0.6 mmol), indole (1.0 mmol), and silica gel (Silica gel for column chromatography Acros Organics, 0.060–0.200 mm, 60 Å–50 mg) was stirred at 100 °C and after complete consumption of indole (1–9 h, see Table 2) the reaction mixture was cooled to room temperature. Then, the silica gel was filtered off and washed with ethyl acetate (3 × 10 mL). The organic layer was dried over anhydrous MgSO4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent. Spectral data of selected compounds: 3α[16]. 1H NMR (CDCl3, 200 MHz): δ 5.90 (s, 1H); 6.65 (s, 2H); 7.01 (t, J = 6.8 Hz, 2H); 7.14–7.41 (m, 11H); 7.89 (br s, 2H). 13C NMR (CDCl3, 100 MHz); δ (ppm): 31.6, 110.9, 111.9, 118.4, 119.5, 121.2, 124.0, 126.3, 127.1, 128.5, 128.6, 137.0, 145.2. MS (relative intensity, %) m/z: 322 (M+, 39), 245 (33), 207 (100), 122 (10). IR (KBr) cm−1: 3408, 3055, 3024, 1719, 1594, 1464, 1414, 1334, 1240, 1215, 1092, 1009, 747, 700, 596; 3b[15]. 1H NMR (CDCl3, 200 MHz): δ 2.31 (s, 3H); 5.84 (s, 1H); 6.62 (dd, J = 2.22, 0.9 Hz, 2H); 7.33 (d, J = 8.04 Hz, 2H); 7.39 (d, J = 7.79 Hz, 2H); 7.86 (br s, 2H). 13C NMR (CDCl3, 100 MHz); δ (ppm): 21.0, 39.9, 111.0, 119.1, 119.9, 121.8, 123.5, 127.2, 128.6, 128.9, 135.4, 136.8, 141.1. MS (relative intensity, %) m/z: 336 (M+, 100), 245 (49), 218 (30), 117 (14). IR (KBr) cm−1: 3408, 2918, 2856, 1701, 1650, 1412, 739; 3d[16]. 1H NMR (CDCl3, 200 MHz): δ 3.84 (s, 3H); 5.90 (s, 1H); 6.64–7.65 (m, 14H); 7.80 (br s, 2H). 13C NMR (CDCl3, 100 MHz); δ (ppm): 39.7, 55.6, 111.5, 114.0, 119.6, 120.4, 120.4, 122.3, 123.9, 127.5, 130.0, 136.7, 137.1, 158.3. MS (relative intensity, %) m/z: 352 (M+, 100), 245 (34), 235 (27), 117 (10). IR (KBr) cm−1: 3393, 2924, 1597, 1508, 1452, 1258, 1244, 1009, 739. 3e[17]. 1H NMR (CDCl3, 200 MHz): δ 5.41 (d, J = 7.1 Hz, 1H); 6.54 (d, J = 15.7 Hz, 1H); 6.80 (dd, J = 15.7, 7.1 Hz, 1H); 6.71 (s, 2H); 7.04 (t, J = 7.0 Hz, 2H); 7.18 (t, J = 7.0 Hz, 2H); 7.24–7.28 (m, 3H); 7.35–7.38 (m, 4H); 7.60 (d, J = 7.4 Hz, 2H); 7.94 (br s, 2H). 13C NMR (CDCl3, 100 MHz); δ (ppm): 43.1, 111.3, 117.4, 118.7, 120.0, 121.8, 122.2, 123.6, 126.8, 127.2, 128.4, 129.3, 134.3, 136.7. MS (relative intensity, %) m/z: 348 (M+, 100), 271 (19), 245 (48), 230 (65), 77 (16). IR (KBr) cm−1: 3408, 2922, 1719, 1597, 1545, 1464, 1244, 1094, 741, 700. 3f[18]. 1H NMR (CDCl3, 200 MHz): δ 1.50–1.65 (m, 6H); 2.44–2.55 (m, 4H); 6.83–6.90 (m, 4H); 6.99–7.20 (m, 4H); 7.53 (d, J = 7.9 Hz, 2H); 7.62 (br s, 2H). 13C NMR (CDCl3, 100 MHz); δ (ppm): 22.9, 26.7, 36.7, 39.5, 111.1, 118.5, 121.2, 121.5, 122.1, 123.7, 126.4, 137.1. MS (relative intensity, %) m/z: 314 (M+, 76), 271 (100), 197 (5), 117 (10). IR (KBr) cm−1: 3408, 3389, 2930, 2853, 1456, 1414, 1335, 1242, 1101, 1015, 816, 743, 582. 3g[19]. 1H NMR (DMsol, 400 MHz): δ 5.86 (s, 1H); 6.89 (d, J = 2.14 Hz, 2H); 7.14–7.34 (m, 9H); 7.43 (s, 2H); 10.98 (br s, 2H). 13C NMR (DMsol, 100 MHz); δ (ppm): 41.1, 110.7, 113.3, 117.5, 121.0, 123.2, 125.0, 127.5, 128.0, 128.2, 131.5, 144.1. MS (relative intensity, %) m/z: 482 [M+4]+ (50), 480 [M+2]+ (100), 478 (M+, 50), 403 (40), 323 (15), 204 (47) IR (KBr) cm−1: 3418, 2856, 2370, 1718, 1500, 1441, 1217, 1099, 872, 709, 704.

13. Use of silica gel: The aforementioned procedure was used with indole 1a (1.0 mmol), benzaldehyde 2a (0.6 mmol), and silica gel (50 mg). After the reaction was complete, the silica gel was separated by filtration, dried under vacuum, and reused in further reactions without previous purification.