An efficient method for synthesis of bis(indolyl)methane and di-bis(indolyl)methane derivatives in environmentally benign conditions using TBAHS

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Abstract: An efficient procedure for the synthesis of bisindolylmethanes from condensation of indole and aromatic aldehydes or ketones is described. The aromatic electrophilic substitution reactions of indole with aromatic aldehydes and ketones are achieved in the presence of tetrabutylammonium hydrogen sulfate as a mild and efficient solid acid catalyst. This methodology offers several advantages such as good yields, simple procedure, mild and environmentally benign conditions.

Subjects: Environmental Chemistry; Medicinal & Pharmaceutical Chemistry; Organic Chemistry

Keywords: bis(indolyl)methane; condensation; green synthesis; tetrabutylammonium hydrogen sulfate

1. Introduction

The indole ring system is present in many natural products, pharmaceuticals, and agrochemicals. These compounds bearing indole moiety have shown many pharmaceutical properties such as antimicrobial, antibacterial, antiviral, antifungal, antimetastatic, radical scavenging, analgesic, and anti-inflammatory activities (Bell, Carmeli, & Sar, 1994; Benabadji, Wen, Zheng, Dong, & Yuan, 2004; Fahy, Potts, Faulkner, & Smith, 1991; Irie et al., 1999; Kamal et al., 2009; Kobayashi et al., 1994; Kuethe, 2006; Shir, Zolfigol, Kruger, & Tanbakouchian, 2010; Sivaprasad, Perumal, Prabavathy, & Mathivanan, 2006; Sujatha, Perumal, Muralidharan, & Rajendran, 2009; Valeria & Ernesto, 1998). Numerous inhibitory activities are reported for bisindolylmethanes (BIMs) derivatives in different cancer including bladder cancer, lung cancer cells, colon cancer, prostate cancer, breast tumor cells (Ge, Fares, & Yannai, 1999; Gong, Firestone, & Bjeldanes, 2006; Gong, Sohn, Xue, Firestone, & Bjeldanes, 2006;)

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Ichite et al., 2009; Ling & Wan-Ru, 2004; Nachshon-Kedmi, Yannai, & Fares, 2004; Safe, Papineni, & Chintharlapalli, 2008; Sung et al., 2007. The oxidized forms of BIMs are utilized as dyes (Novak, Kramer, Klapper, Daasch, & Murr, 1976) and colorimetric sensors (He et al., 2006; Martinez, Espinosa, Tárraga, & Molina, 2008).

A simple and standard method for the synthesis of bis(indolyl)methanes is the Friedel–Crafts reaction between indoles and carbonyl compounds in the presence of an acid or base. Varieties of catalytic reagents used in the synthesis of BIMs have been reviewed (Shiri et al., 2010). Various Brønsted acids (Ramesh, Banerjee, Pal, & Das, 2003; Zahran, Abdin, & Salama, 2008), Lewis acids (Chen, Yu, & Wang, 1996; Kundu & Maiti, 2008; Qu et al., 2011), heterogeneous acidic catalyst (Firouzabadi, Iranpoor, & Jafari, 2006), ionic liquid (Kalantari, 2015; Veisi, Hemmati, & Veisi, 2009), and some other catalysts have been applied for this synthesis (Haghighi & Nikoofar, 2014; Hojati, Zeinali, & Nematdoust, 2013; Per, Desai, Thopate, & Wadgaonkar, 2006; Xie, Sun, Jiang, & Le, 2014). Although these protocols are valuable, most of them suffer from one or more drawbacks including long reaction times, low yields of products, harsh reaction conditions, corrosive reagents, and use of expensive and/or toxic catalysts and solvents. Moreover, many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants. It is clear that due to the biological activities and versatile application possibilities of BIMs, there is a continuous quest for more efficient, mild, and clean procedures for synthesis of these compounds. This prompted us to investigate the feasibility of less hazardous, solvent-free synthesis of aryl-3,3′-bis(indolyl)methane derivatives under modified experimental conditions.

Acidic tetrabutylammonium hydrogen sulfate (TBAHS) act as a phase transfer catalyst and performs many organic transformations under mild conditions. It has been used for dehydration and cyclization step in Hantzsch reaction (Tripathi, Tewari, & Dwivedi, 2004). TBAHS has been applied for one-pot synthesis of pyrano[2,3-c]pyrazoles via domino/Knoevenagel-hetero-Diels–Alder reaction (Parmar, Teraiya, Patel, & Talpada, 2011). It also has been used for synthesis of 3,4-dihydropyrimidin-2(1H)-ones (Shaabani, Bazgir, & Arab-Ameri, 2004), 1,8-dioxo-octahydroxanthenes (Karade, Sathe, & Kaushik, 2007), 5-substituted 1H-tetrazoles (Wang, Liu, & Cheon, 2015), and other heterocyclic compounds (Jóńczyk & Kulinski, 1993; Parmar, Teraiya, Barad, Sharma, & Gupta, 2013). TBAHS is an inexpensive, safe-handleable and thermally stable substance.

For unique catalyst features of TBAHS and in continuation of our efforts to develop green and mild methodologies for the synthesis of heterocycles (Bodaghifard, Solimannejad, Asadbegi, & Dolatabadifarrahani, 2016; MobiniKhaleedi, Foroughhifar, & Bodaghifard, 2011), herein we wish to report a mild, efficient, and green procedure for the synthesis of biologically interesting mono- and di-bisindolylmethane derivatives via the reaction of indole and aldehydes or ketones in the presence of TBAHS in solvent-free condition or using a little amount of solvent (Scheme 1).
2. Results and discussion

In order to determine the optimum reaction conditions, we examined the influence of the temperature, reaction time, and the amounts of TBAHS upon a model reaction between benzaldehyde (1 mmol) and indole (2 mmol) (Scheme 2). The best result was obtained with 0.1 mmol of TBAHS at 60°C using 1 mL EtOAc or in the absence of any solvent (Table 1, entry 5 and 6). Increasing the amount of catalyst to 0.2 mmol does not affect the product yield (Table 1, entry 10). Moreover, the catalyst is essential and in the absence of the catalyst, poor yield of the corresponding BIM is produced (Table 1, entry 7, 11).

Encouraged by these results, we studied the reaction of various aldehydes and ketones under optimized conditions to better understand the scope and generality of this simple procedure (Scheme 1).

A series of aromatic aldehydes and ketones underwent an electrophilic substitution reaction with indole smoothly, to afford a range of substituted bis(indolyl)methanes in good to excellent yields (Table 2, 3a–o). The results showed that the reaction proceeds very efficiently in all cases. This method is equally effective for aldehydes bearing electron withdrawing or donating groups in the aromatic rings. Furthermore, reactions of ketones with indole were satisfactorily performed by the current pathway but they need longer times and afforded lower yield of products than aldehydes due to lower reactivity of ketones. The products 3i and 3m are novel compounds and have been fully characterized by their elemental analysis, FT-IR and 1H and 13C NMR spectra. The results indicated that the method A need less time that can be related to more and faster interaction of starting materials in the presence of little amount of ethyl acetate. In the absence of ethyl acetate and solid-state manner (method B), the interaction slowed down and in longer time produced the desired products.

2.1. Experimental

All chemicals and solvents were obtained from commercial sources and used without further purification. All known organic products were identified by comparison of their physical and spectral data with those of authentic samples. Thin layer chromatography (TLC) was performed on UV-active pre-coated plates of silica gel (TLC Silica gel60 F254). The FTIR spectrum was recorded on a Shimadzu IR-470 spectrometer using KBr disks. The 1H and 13C NMR spectra were recorded on a Brucker Avance spectrometer operating at 400, 300 and 100, 75 MHz, respectively, in DMSO-d$_6$ or CDCl$_3$ with TMS as an internal standard. Coupling constants, J, were reported in Hertz units (Hz). Spin multiplicities are shown as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), and m (multiplet). Elemental analyses were performed by Vario EL equipment at Arak University.

2.1.1. General procedure for synthesis of bis(indolyl)methanes catalyzed by Bu$_4$NHSO$_4$

**Method A:** To a mixture of indole (2 mmol), aldehyde, or ketone (1 mmol) ethyl acetate (1 mL) as a solvent, Bu$_4$NHSO$_4$ (0.1 mmol) was added and the mixture stirred magnetically at 60°C. After complete conversion, as indicated by TLC (hexane/ethyl acetate 4:1), the reaction mixture was cooled to room temperature and crushed ice was added. The precipitate was filtered and dried under vacuum. The product was purified by recrystallization hexane-ethyl acetate (Table 2).
Method B: To a mixture of indole (2 mmol) and aldehyde or ketone (1 mmol), Bu4NHSO4 (0.1 mmol) was added and the mixture stirred magnetically at 60°C. After complete conversion, as indicated by TLC (hexane/ethyl acetate 4:1), the reaction mixture was cooled to room temperature and crushed ice was added. The precipitate was filtered and dried under vacuum. The product was purified by recrystallization from hexane–ethyl acetate (Table 2).

**Table 1. Optimization of reaction condition for synthesis of 3,3′-bis-indolyl phenylmethane**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mmol)</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu4NHSO4 (0.1)</td>
<td>EtOH</td>
<td>r.t.</td>
<td>24</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Bu4NHSO4 (0.1)</td>
<td>EtOH/H2O (3:1)</td>
<td>r.t.</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Bu4NHSO4 (0.1)</td>
<td>CH3CN</td>
<td>r.t.</td>
<td>24</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>Bu4NHSO4 (0.1)</td>
<td>EtOAc</td>
<td>r.t.</td>
<td>11</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>Bu4NHSO4 (0.1)</td>
<td>EtOAc</td>
<td>60</td>
<td>1</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>Bu4NHSO4 (0.1)</td>
<td>–</td>
<td>60</td>
<td>4</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>–</td>
<td>60</td>
<td>12</td>
<td>36</td>
</tr>
<tr>
<td>8</td>
<td>Bu4NHSO4 (0.1)</td>
<td>–</td>
<td>r.t.</td>
<td>12</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>Bu4NHSO4 (0.15)</td>
<td>–</td>
<td>r.t.</td>
<td>12</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>Bu4NHSO4 (0.2)</td>
<td>–</td>
<td>r.t.</td>
<td>12</td>
<td>86</td>
</tr>
<tr>
<td>11</td>
<td>–</td>
<td>–</td>
<td>r.t.</td>
<td>22</td>
<td>10</td>
</tr>
</tbody>
</table>

aBenzaldehyde (1 mmol), indole (2 mmol).

bIsolated yields.

**Table 2. Synthesis of bisindolylmethanes catalyzed by TBAHS**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde or ketone</th>
<th>Product</th>
<th>A&lt;sup&gt;a&lt;/sup&gt;</th>
<th>B&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Time (h)</td>
<td>Yield (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Time (h)</td>
</tr>
<tr>
<td>1</td>
<td>C6H5CHO</td>
<td>3a</td>
<td>1</td>
<td>95</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>4-Me-C6H4CHO</td>
<td>3b</td>
<td>1.5</td>
<td>93</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>4-Cl-C6H4CHO</td>
<td>3c</td>
<td>1</td>
<td>94</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4-OMe-C6H4CHO</td>
<td>3d</td>
<td>1</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>3-NO2-C6H4CHO</td>
<td>3e</td>
<td>1</td>
<td>91</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>4-NO2-C6H4CHO</td>
<td>3f</td>
<td>1</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>2,4-Cl2-C6H3CHO</td>
<td>3g</td>
<td>1</td>
<td>93</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>2-Cl-C6H4CHO</td>
<td>3h</td>
<td>1.2</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Isophthaldehyde</td>
<td>3i</td>
<td>1.5</td>
<td>88</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>Terphthaldehyde</td>
<td>3j</td>
<td>1.5</td>
<td>90</td>
<td>5</td>
</tr>
<tr>
<td>11</td>
<td>Acetone</td>
<td>3k</td>
<td>12</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>Cyclohexanone</td>
<td>3l</td>
<td>10</td>
<td>90</td>
<td>24</td>
</tr>
<tr>
<td>13</td>
<td>4-Me-cyclohexane</td>
<td>3m</td>
<td>10</td>
<td>87</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>Acetophenone</td>
<td>3n</td>
<td>12</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>15</td>
<td>Isatin</td>
<td>3o</td>
<td>2</td>
<td>93</td>
<td>6</td>
</tr>
</tbody>
</table>

<sup>a</sup>Method A: Bu4NHSO4 (0.1 mmol), 60°C, EtOAc (1 mL).

<sup>b</sup>Method B: Bu4NHSO4 (0.1 mmol), 60°C.

<sup>c</sup>Isolated yields.

<sup>e</sup>Novel product.
2.1.2. General procedure for synthesis of di-bis(indolyl)methanes
To a mixture of indole (4.5 mmol) and dialdehyde (1 mmol) Bu₄NHSO₄ (0.1 mmol) was added and the mixture stirred magnetically at 60°C. After complete conversion, as indicated by TLC (hexane/acetone 4:1), the reaction mixture was quenched by adding ice water (10 ml). The precipitate was filtered, evaporated, and the corresponding di-bis(indolyl)methanes were obtained in excellent yields and then recrystallized from hexane–ethyl acetate to afford pure products (Table 2, entry 9–10).

3. Conclusion
In summary, we have developed a novel, efficient, and environmentally benign method for the synthesis of pharmaceutically important bis(indolyl)methanes and di-bis(indolyl)methanes using tetrabutylammonium hydrogen sulfate in excellent yield. This new protocol has advantages over previously reported procedures such as cleaner reaction profiles, use of inexpensive catalyst, simple experimental and work-up procedure, high conversions, and high yield and chemoselectivity, hence believed to be superior over many existing synthetic methods. Also two novel BIM derivatives have been synthesized and characterized by spectroscopic data.

Supplementary material
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