Green Synthesis of Bis(indolyl)methanes Catalysed by Salicylic Acid

Hoda Banari, Hamzeh Kiyani* and Alireza Pourali
School of Chemistry, Damghan University, 36719-41167 Damghan, Iran.
*Author for correspondence; e-mail: hkiyani@du.ac.ir

ABSTRACT
In this contribution, salicylic acid (SA) has been used to catalyze synthesis of a series of biologically relevant 3,3′-bis(indolyl)methanes (BIMs) via the electrophilic substitution of indole derivatives on aldehyde compounds. The optimum catalyst loading was observed at 15 mol%. The procedure is simple and the expected bis-heterocyclic compounds were isolated in good to high yields. The present protocol provides the advantages of convenience, mild reaction conditions, eco-friendliness, energy-saving, and no use of hazardous solvents.

Keywords: 3,3′-bis(indolyl)methanes, salicylic acid, indole, 2-methylindole, green

1. INTRODUCTION
3,3′-Bis(indolyl)methanes (BIMs) are an important class of heterocyclic compounds exhibiting a wide range of applications in industry and agrochemicals [1-2]. BIMs are significant drug candidates and has also been reported that possess various biological activities, including antibacterial [3], anti-inflammatory [3], antihyperlipidemic [4], anticancer [5], Leishmania donovani topoisomerase I inhibitory [6], analgesic [7], antifungal, and antileishmanial activity against Leishmania donovani promastigotes [8]. The structures of some biologically active BIMs are depicted in Figure 1. Heterocycles bearing bis(indolyl)methane units act as dietary supplements [9] and colorimetric chemosensors or pH indicators [10]. Therefore, there is a lot of interest for synthesis of these fascinating classes of compounds.

Figure 1. Some bioactive BIMs.
BIMs are commonly synthesized through Friedel-Crafts alkylation involving indoles and carbonyl compounds or other compounds such as benzyl alcohols and acetals. So far, several catalysts in different conditions are available in the literature for synthesis of BIMs, including diphenyl phosphate (DPP) in acetonitrile [5], sodium bisulphite in a mixture of methanol-water [7], Fe-pillared interlayered clay (Fe-PILC) in water [8], Indion Ina 225H resin in acetonitrile [11], benzoic acid on water [12], poly (ethylene-glycol) (PEG) supported sulfonic acid in methanol [13], iodine (I₂) in the presence of sodium dodecylsulfate (SDS) in aqueous solution [14], hybrid of heteropoly acid and polyvinylpyrrolidone [15], ethyl ammonium nitrate (EAN) ionic liquid [16], choline chloride/urea [17], fruit juice natural catalyst [18, 19], nano-iron(oxalate)-Fe₃O₄ in water [20], sodium triphenylphosphine-m-sulfonate/carbon tetrabromide (TPPMS/CBr₄) in acetonitrile [21], n-dodecylbenzene sulfonic acid (DBSA) in water [22], and triethylborane in 1,2-dichloroethane [23]. Furthermore, solid support SiO₂ under microwave irradiation in solvent-free conditions [24], ammonium niobium oxalate (ANO) under conventional heating (water, 50 °C) or under sonication (glycerol, 110 °C) [25], and Meldrum’s acid in water under ultrasonic conditions [26] are also valuable tools to the synthesis of these bis-heterocycles. Catalyst-free and solvent-free conditions for 10 min to 6 day have been used toward synthesis of BIMs [27]. Although methods to synthesis of BIMs have their merits, some reported methods suffer from one or more drawbacks, for example the utilization hazardous solvents, low product yields, longer reaction times, and the use of special techniques (microwave or ultrasound). Consequently, the development of simple and environmentally benign approach for synthesis of BIM scaffolds is always attractive.

The salicylic acid (SA) significantly increased superoxide dismutases, catalases, and peroxidase activity in fish [28]. The SA has been used as a catalyst for synthesis of homoallylic alcohols [29], 1,4-dihydropyridines and acridinediones [30]. However, to date, no reports have been published on the use of SA as a catalyst for synthesis of BIMs and this contribution is the first report about SA-catalyzed synthesis of BIM scaffolds.

![Scheme 1](image)

Scheme 1. SA catalyzed condensation of indoles (1a-b) with aldehydes (2) toward synthesis of BIMs (3a-s) in a mixture of H₂O-EtOH (1:1) solvent at room temperature (r.t.).

2. MATERIALS AND METHODS
2.1 Instruments and Characterization

All the reagents were obtained from commercial sources and used without further purification. Melting points were measured on a Büchi 510 melting point apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded at ambient temperature on a BRUKER AVANCE DRX-400 MHz spectrophotometer using
CDCl$_3$ as the solvent. The purity of synthesized compounds as well as the progress of the reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60F$_{254}$ aluminum sheets, visualized by UV light. All of the targeted products are reported in the literature and are characterized by comparison of their spectral and physical data on the basis of literature descriptions.

2.2 General Procedure for the Synthesis of Bis(indolyl)methanes (3a-u)

Indole derivative 1 (2 mmol), aldehyde 2 (1 mmol), and SA (15 mol%) were placed in a flask and H$_2$O-EtOH (1:1, 5 mL) was added. The reaction mixture was stirred at room temperature. After completion of the reaction (using TLC analysis), the solid was formed. The resulting solid product was filtered off, washed with small amounts of distilled water, dried, and recrystallized from hot ethanol to afford the targeted compounds. The filtrate containing the catalyst can be reused to carry out further testing on the model reaction. Spectral data for 3a and 3k as follows:

2.2.1 3, 32 -benzylidenebis(2-methyl-1H-indole) (3a)

IR (KBr, cm$^{-1}$): 3398, 3051, 2921, 2860, 1615, 1461, 1305, 1218, 746, 594; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.94 (s, 2H), 7.22-7.11 (m, 7H), 6.94 (t, $J$ = 6.8 Hz, 2H), 6.93 (d, $J$ = 8.4 Hz, 2H), 6.75 (t, $J$ = 7.6 Hz, 2H), 5.94 (s, 1H), 2.08 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 143.5, 134.9, 131.6, 128.9, 128.7, 128.1, 126.0, 120.4, 119.2, 119.1, 113.2, 110.0, 39.6, 12.5.

2.2.2 3, 3'-((phenylmethylene)bis(1H-indole) (3j)

IR (KBr, cm$^{-1}$): 3392, 3056, 2922, 2347, 1603, 1454, 1328, 1218, 1093, 1014, 748, 702, 595; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.07 (s, 2H), 7.37 (d, $J$ = 8.0 Hz, 2H), 7.34-7.13 (m, 9H), 6.99 (t, $J$ = 7.6 Hz, 2H), 6.65 (s, 2H), 5.90 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 144.1, 136.1, 128.7, 128.5, 127.2, 126.2, 124.1, 121.9, 119.8, 119.2, 118.9, 111.1, 40.2.

3. RESULTS AND DISCUSSION

In order to optimize the reaction conditions, the bisindolization of 2-methylindole (1a, 2 mmol) and benzaldehyde (2a, 1 mmol) was used as a model reaction, with the reaction carried out under diverse reaction parameters, such as different solvents and amounts of catalyst (Table 1). The model reaction was carried out using H$_2$O and a mixture of H$_2$O-EtOH (v:v, 1:1) solvents in the absence of catalyst at room temperature (r.t.), which leads to the formation of product (3a) in trace yields (Table 1, entries 1 and 2). The reaction in the presence of SA in H$_2$O gave 3a in 84% yield for 7 h (Table 1, entry 3). This result encourages us to examine other solvents using this amount of catalyst. For this purpose, the model reaction was investigated with different solvents, including EtOH, n-hexane, EtOAc, and CH$_2$Cl$_2$ to explore the efficacy of the SA catalyst (Table 1, entries 4-8). In this study, H$_2$O-EtOH (v:v, 1:1) was found to be the best choice. Implementation of the reaction under solvent-free conditions was not more efficient than using solvents (Table 1, entry 9). The effect of the amount of SA on the model reaction was then examined for different amounts, viz. 5, 10 and 20 mol% at r.t. (Table 1, entries 10-12). Using less than 15 mol% of catalyst, the product were formed in 75% and 80% isolated yields, respectively. However, no significant increase in the yield of the product was found upon further increasing the loading of SA beyond 15 mol%. The above results indicate that 15 mol% of SA was the optimum catalyst loading in terms of product
yield and reaction time. Satisfactory results were not achieved from the reactions at other temperatures. For this reason we have not mentioned in Table 1.

Table 1. Optimization of the reaction conditions for the synthesis of 3a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Time(^b) (h)</th>
<th>Yield(^c) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>H(_2)O</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>H(_2)O-EtOH (1:1, v:v)</td>
<td>24</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
<td>H(_2)O</td>
<td>7</td>
<td>84</td>
</tr>
<tr>
<td>4(^a)</td>
<td>15</td>
<td>H(_2)O-EtOH (1:1, v:v)</td>
<td>2</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>EtOH</td>
<td>7</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>n-Hexane</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>EtOAc</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>CH(_2)Cl(_2)</td>
<td>7</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>None</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>H(_2)O-EtOH (1:1, v:v)</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>H(_2)O-EtOH (1:1, v:v)</td>
<td>2</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>H(_2)O-EtOH (1:1, v:v)</td>
<td>2</td>
<td>92</td>
</tr>
</tbody>
</table>

\(^a\) Reaction were carried out with 2-methylindole 1a (2 mmol), benzaldehyde 2a (1 mmol), solvent (5 mL), and catalyst at room temperature.
\(^b\) Reaction progress was monitored with TLC analysis.
\(^c\) Isolated yield of product.
\(^d\) Optimized reaction conditions shown in bold.

The substrate scope of the reaction was successfully established with indoles (1a-b) and various aldehydes under the optimized reaction conditions and results are shown in Table 2. Substituted benzaldehydes with various functionalities in the phenyl group including -OH, -OCH\(_3\), -CH\(_3\), -(NCH\(_3\))\(_2\), and -Cl effectively formed the corresponding products (3b-g, 3k-p and 3s) in good isolated yields (Table 2, entries 2-7, 11-16 and 19). A strong electron-withdrawing group like -NO\(_2\) in the phenyl ring also successfully gave the corresponding BIMs (3h, 3q and 3t-u) in good yields (Table 2, entries 8, 17 and 20-21). Moreover, heterocyclic aldehydes like furfural also underwent the condensation with 2-methylindole (1a) and indole (1b) to afford the corresponding products (3i and 3r) in good yields (Table 2, entries 9 and 18). When the reaction was performed using
butyraldehyde (as an aliphatic aldehyde) and indoles (1a-b), only very small amounts of the products were formed even with prolonged reaction times. Implementation of reaction with ketones such as cyclohexanone and acetophenone is also not successful even after 24 hours.

Table 2. Synthesis of BIMs (3a-u) catalyzed by SA at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Indole</th>
<th>Product</th>
<th>Time (h)</th>
<th>Isolated yields (%)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C₆H₅CHO</td>
<td>1a</td>
<td>3a</td>
<td>2</td>
<td>90</td>
<td>245-247 (246-248)</td>
</tr>
<tr>
<td></td>
<td>4-HO-C₆H₄CHO</td>
<td>1a</td>
<td>3b</td>
<td>1.5</td>
<td>92</td>
<td>238-240 (239-241)</td>
</tr>
<tr>
<td></td>
<td>4-MeO-C₆H₄CHO</td>
<td>1a</td>
<td>3c</td>
<td>1.5</td>
<td>93</td>
<td>194-195 (195-196)</td>
</tr>
<tr>
<td></td>
<td>4-Me-C₆H₄CHO</td>
<td>1a</td>
<td>3d</td>
<td>1.5</td>
<td>94</td>
<td>237-239 (235-236)</td>
</tr>
<tr>
<td></td>
<td>4-Cl-C₆H₄CHO</td>
<td>1a</td>
<td>3e</td>
<td>2</td>
<td>92</td>
<td>174-175 (173)</td>
</tr>
<tr>
<td></td>
<td>4-NO₂-C₆H₄CHO</td>
<td>1a</td>
<td>3f</td>
<td>1</td>
<td>98</td>
<td>235-237 (238-239)</td>
</tr>
<tr>
<td></td>
<td>2-Cl-C₆H₄CHO</td>
<td>1a</td>
<td>3g</td>
<td>2</td>
<td>88</td>
<td>223-225 (218-222)</td>
</tr>
<tr>
<td></td>
<td>4-NO₂-C₆H₄CHO</td>
<td>1a</td>
<td>3h</td>
<td>1</td>
<td>92</td>
<td>238-240 (239-240)</td>
</tr>
<tr>
<td></td>
<td>Furfural</td>
<td>1a</td>
<td>3i</td>
<td>2</td>
<td>90</td>
<td>207-209 (208-212)</td>
</tr>
<tr>
<td></td>
<td>C₆H₅CHO</td>
<td>1b</td>
<td>3j</td>
<td>2</td>
<td>88</td>
<td>89-92 (89-91)</td>
</tr>
<tr>
<td></td>
<td>4-HO-C₆H₄CHO</td>
<td>1b</td>
<td>3k</td>
<td>2.1</td>
<td>90</td>
<td>114-116 (116-118)</td>
</tr>
<tr>
<td></td>
<td>4-MeO-C₆H₄CHO</td>
<td>1b</td>
<td>3l</td>
<td>2</td>
<td>88</td>
<td>187-189 (188)</td>
</tr>
<tr>
<td></td>
<td>3-MeO-C₆H₄CHO</td>
<td>1b</td>
<td>3m</td>
<td>2</td>
<td>89</td>
<td>176-179 (180)</td>
</tr>
<tr>
<td></td>
<td>4-Me-C₆H₄CHO</td>
<td>1b</td>
<td>3n</td>
<td>2</td>
<td>87</td>
<td>94-95 (93-95)</td>
</tr>
<tr>
<td></td>
<td>4-Cl-C₆H₄CHO</td>
<td>1b</td>
<td>3o</td>
<td>2</td>
<td>90</td>
<td>76-77 (75)</td>
</tr>
<tr>
<td></td>
<td>2-Cl-C₆H₄CHO</td>
<td>1b</td>
<td>3p</td>
<td>2</td>
<td>87</td>
<td>76-77 (75-76)</td>
</tr>
<tr>
<td></td>
<td>4-NO₂-C₆H₄CHO</td>
<td>1b</td>
<td>3q</td>
<td>1.5</td>
<td>87</td>
<td>215-218 (215-217)</td>
</tr>
<tr>
<td></td>
<td>Furfural</td>
<td>1b</td>
<td>3r</td>
<td>2.2</td>
<td>85</td>
<td>118-119 (117-118)</td>
</tr>
<tr>
<td></td>
<td>4-Me₃N-C₆H₄CHO</td>
<td>1b</td>
<td>3s</td>
<td>2</td>
<td>85</td>
<td>170-172 (169-171)</td>
</tr>
<tr>
<td></td>
<td>3-NO₂-C₆H₄CHO</td>
<td>1b</td>
<td>3t</td>
<td>1.5</td>
<td>88</td>
<td>220-222 (220)</td>
</tr>
<tr>
<td></td>
<td>2-NO₂-C₆H₄CHO</td>
<td>1b</td>
<td>3u</td>
<td>2.5</td>
<td>84</td>
<td>186-187 (188-190)</td>
</tr>
</tbody>
</table>

In all cases, the reaction medium can be reused for further reactions. Reusability of the reaction medium was implemented by use of the model reaction. After completion of the reaction, the resulting solid product was collected by filtration. To the filtrate that containing SA, 2-methylindole (1a) and benzaldehyde (2a) were added devoid of extra load of catalyst and the reaction mixture was stirred at room temperature for the required times to afford the corresponding product (Table 3).

Table 3. Study on the reuse of reaction medium.

<table>
<thead>
<tr>
<th>Run</th>
<th>Time (h)</th>
<th>Fresh</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>2</td>
<td>2.2</td>
<td>2.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Isolated yields (%)</td>
<td></td>
<td>90</td>
<td>90</td>
<td>80</td>
<td>70</td>
<td>55</td>
</tr>
</tbody>
</table>

Based on the proposed mechanism in the literature [16], a plausible reaction mechanism for the formation of BIMs (3a-u) catalyzed by SA is shown in Scheme 2. It can be assumed that the reaction starts with the activation of an oxygen atom of
the carbonyl group of the aldehyde by SA, followed by the nucleophilic attack of indole on activated aldehyde (4) and departure of water which led to the formation of alkene intermediate 7. The condensation of the second molecule of indole with the alkene intermediate 7 and then elimination of proton from bis-heterocyclic intermediate 8 leads to the formation of the desired BIMs (3a-u).

**Scheme 2.** A plausible reaction mechanism for the formation of BIMs (3a-u).

In order to demonstrate the advantages of using SA to bis(indolyl)methane synthesis, the results compared to a number of previously reported methods are presented in Table 4. This comparison clearly shows that it possesses several advantages, including relatively shorter reaction times, absence of heating, does not require the synthesis of the catalyst, avoiding the use of hazardous solvents, and lack of utilization of specific devices like ultrasound system.

**Table 4.** Comparison between SA and literature results for synthesis of 3q.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Reaction conditions</th>
<th>Time (h)</th>
<th>Yield (%) [ref]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe-PILC</td>
<td>H₂O, r.t.</td>
<td>6</td>
<td>72 [8]</td>
</tr>
<tr>
<td>2</td>
<td>Catalyst-free</td>
<td>Solvent-free, r.t.</td>
<td>6 day</td>
<td>58 [27]</td>
</tr>
<tr>
<td>3</td>
<td>Tamarind fruit juice</td>
<td>H₂O, 80 °C</td>
<td>2</td>
<td>93 [18]</td>
</tr>
<tr>
<td>5</td>
<td>Nano-Fe(ox)-Fe₃O₄</td>
<td>H₂O, reflux</td>
<td>1</td>
<td>92 [20]</td>
</tr>
<tr>
<td>6</td>
<td>Benzoic acid</td>
<td>H₂O, 80 °C</td>
<td>15</td>
<td>91 [12]</td>
</tr>
<tr>
<td>7</td>
<td>PEG-SO₃H</td>
<td>MeOH, r.t.</td>
<td>8</td>
<td>86 [13]</td>
</tr>
<tr>
<td>8</td>
<td>PVP-PWA</td>
<td>MeOH, r.t., under N₂</td>
<td>3</td>
<td>90 [15]</td>
</tr>
<tr>
<td>9</td>
<td>Choline chloride-urea</td>
<td>80 °C</td>
<td>4</td>
<td>98 [17]</td>
</tr>
<tr>
<td>10</td>
<td>TPPMS/CBr₄</td>
<td>MeCN, r.t.</td>
<td>4</td>
<td>91 [21]</td>
</tr>
<tr>
<td>11</td>
<td>Meldrum’s acid</td>
<td>H₂O, US</td>
<td>5</td>
<td>91 [26]</td>
</tr>
<tr>
<td>12</td>
<td>SA</td>
<td>H₂O-EtOH (1:1), r.t.</td>
<td>1.5</td>
<td>87 [this work]</td>
</tr>
</tbody>
</table>

Fe-PILC: Fe-pillared interlayered clay; Fe(ox): Iron(oxalate); PEG: Poly (ethylene-glycol); PVP-PWA: Polyvinylpyrrolidone-phosphotungstic acid; TPPMS/CBr₄: Sodium triphenylphosphine-ₘ-sulphonate/carbon tetrabromide; US: Ultrasound.
4. CONCLUSIONS

In conclusion, a series of bis(indolyl)methane derivatives as promising active biological compounds have been synthesized. This procedure involves the SA catalyzed condensation of indoles and aldehydes to give BIMs in good to high yields. This method provided an important additional technique to the existing procedures. Using a SA green protocol offers merits, such as the use of commercially available catalyst, no need for the synthesis of the catalyst, cost-effective, a more simple procedure, the avoidance of the hazardous solvents, as well as reusability of the reaction media.

ACKNOWLEDGEMENT

The authors are thankful to the Research Council of Damghan University.

REFERENCES


