A practical and efficient synthesis of bis(indolyl)methanes in water, and synthesis of di-, tri-, and tetra(bis-indolyl)methanes under thermal conditions catalyzed by oxalic acid dihydrate

Ramin Ghorbani-Vaghei · Hojat Veisi · Hassan Keypour · Ahmad Ali Dehghani-Firouzabadi

Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, 65174 Hamadan, Iran

A. A. Dehghani-Firouzabadi
Department of Chemistry, Faculty of Science, Yazd University, 89195-741 Yazd, Iran

Received: 3 December 2008 / Accepted: 27 April 2009 / Published online: 16 May 2009
© Springer Science+Business Media B.V. 2009

Abstract A simple, clean, and highly efficient green protocol has been developed for synthesis of bis(indolyl), di(bis-indolyl), and tris-indolyl methanes by the reaction of indole with aldehydes and ketones in the presence of oxalic acid dihydrate [(CO$_2$H)$_2$·2H$_2$O] and N-cetyl-N, N, N-trimethylammonium bromide (CTAB) in water. Also, tri(bis-indolyl) and tetra(bis-indolyl)methanes as new bis(indolyl)methanes were prepared under thermal conditions.

Keywords Di-, tri-, and tetra(bis-indolyl)methanes · Oxalic acid dihydrate · CTAB · Water

Introduction

Bis(indolyl)methanes, indole and its derivatives are known as an important class of heterocyclic compounds and bioactive intermediates in R & D and pharmaceutical industry [1]. Bis(indolyl)methanes are found in cruciferous plants and are known to promote beneficial estrogen metabolism and induce apoptosis in human cancer cell [2]. Therefore, there is great interest in the synthesis of these compounds [3,4]. Synthetically, the reaction of 1H-indole with aldehydes or ketones produces azafulvenium salts that react further with a second 1H-indole molecule to form bis(indol-3-yl)methanes [5]. In recent years, synthesis of this class of molecules under mild conditions have been reported with promoters, such as Montmorillonite clay K-10 [6], trichloro-1,3,5-triazine [7], AlPW$_{12}$O$_{40}$ [8], sodium dodecyl sulfate (SDS) [9], ZrCl$_4$ [10], H$_2$NSO$_3$H [11], I$_2$ [12], zeolites [13], bentonite [14], In(OTf)$_3$/ionic liquid [15], CuBr$_2$ [16], Dy(OTf)$_3$/ionic liquid [17], HClO$_4$–SiO$_2$ [18], InCl$_3$ [19], MW/Lewis acids (FeCl$_3$, BiCl$_3$, InCl$_3$, ZnCl$_2$, CoCl$_2$) [20], NaHSO$_4$ and Amberlyst-15 [21], sulfated zirconia [22], ZrOCl$_2$/SiO$_2$ [23], silica sulfuric acid (SSA) [24], TiO$_2$ [25], (NH$_4$)$_2$HPO$_4$ [26], acidic ionic liquid [27], NaBF$_4$ [28], metal hydrogen sulfates [29], tetrabutylammonium tribromide [30], superacid SO$_4^{2-}$/TiO$_2$ [31], NBS [32], Ph$_3$CCl [33], H$_3$PW$_{12}$O$_{40}$ [34], LiClO$_4$ [35], and Bi(NO$_3$)$_3$·5H$_2$O [36]. However, most of the existing methods involve toxic metal ions and solvent, high cost, and cumbersome work-up procedures. Consequently, new procedures that address these drawbacks are desirable.

Performing organic reactions in aqueous media has attracted much attention because water would be considerably safe, non-toxic, environmentally friendly, and cheap compared to organic solvents [37]. Moreover, when a watersoluble catalyst is used, the insoluble products can be separated by simple filtration and the catalyst system can be recycled. Therefore, development of a catalyst system that is not only stable in water but also completely soluble in it is highly desirable.

Experimental section

Synthesis of bis(indolyl)methanes in water catalyzed by (CO$_2$H)$_2$·2H$_2$O/CTAB: general procedure

A mixture of indole (2.0 mmol), aldehyde or ketone (1.0 mmol), CTAB (5 mol %), and (CO$_2$H)$_2$·2H$_2$O (50 mol %) in water (3 mL) was stirred at room temperature for the appropriate time (Table 1). The progress of the reaction was
### Table 1  Solvent effect on the reaction between indole and benzaldehyde

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>3.5</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>CCl₄</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>CH₃CN</td>
<td>3.5</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>CH₃Cl₂</td>
<td>4</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>MeOH</td>
<td>3.5</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>EtOH-H₂O (1:1)</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>H₂O</td>
<td>2.5</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>H₂O-5 mol% CTAB</td>
<td>1.5</td>
<td>98</td>
</tr>
<tr>
<td>11</td>
<td>H₂O-5 mol% CTAB&lt;sup&gt;+&lt;/sup&gt;</td>
<td>6</td>
<td>10</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction condition: indole (2 mmol), PhCHO (1 mmol), oxalic acid dihydrate (50 mol%), solvent (3 mL), r.t.;<sup>b</sup> Isolated yield;<sup>c</sup> Non-catalyst monitored by TLC (n-hexan/acetone 4:1). After completion of the reaction, the resulting solid (crude product) was filtered and then recrystallized from ethanol–water to afford pure product.

**Synthesis of tri(bis-indolyl)methanes in DMSO catalyzed by (CO₂H)₂ · 2H₂O**

A mixture of indole (6.0 mmol), aldehyde (IV) (1.0 mmol), and catalyst (CO₂H)₂ · 2H₂O (75 mol%) in DMSO (5 mL) was heated in an oil bath to 100 °C. The reaction mixture was filtered after 25 min. The residue was washed with EtOH (5 mL). Then, water (30 mL) was added to the filtrate, and the product was precipitated and filtered. The product was purified by washing with cold EtOH (2 × 5 mL).

**Synthesis of tetra(bis-indolyl)methanes in DMSO catalyzed by (CO₂H)₂ · 2H₂O**

A mixture of indole (8.0 mmol), aldehyde (VI or VII) (1.0 mmol), and catalyst (CO₂H)₂ · 2H₂O+ (90 mol%) in DMSO (5 mL) was heated in an oil bath to 100 °C. The reaction mixture was filtered after 30 min. The residue was washed with EtOH (5 mL). Then, water (30 mL) was added to the filtrate, and the product was precipitated and filtered. The product was purified by washing with cold EtOH (2 × 5 mL).

**Preparation of 1,2,4,5-tetrakis(bromomethyl)benzene**

Durene (13.4 g, 0.1 mol), N-bromosuccinimide (75 g, 0.42 mol), and dibenzoylperoxide (~ 50 mg) were dissolved in CCl₄ (300 mL) and refluxed under irradiation by a 250 W lamp for 16 h. The solution was then cooled and the succinimide was filtered off and washed with CCl₄. The filtrate was washed with saturated sodium carbonate solution, water, and then dried (MgSO₄). The volume was reduced to ~ 75 mL and was placed in the freezer and the resulting solid was filtered off. This process was repeated several times and the crops of oily solid were combined. This material was then carefully recrystallized in CCl₄. The product was obtained as cubic crystal colorless. Yield: 21.6 g (48%); m.p. = 161–163 °C; <sup>1</sup>H NMR (CDCl₃, ppm): δ<sub>H</sub> 4.60 (8H, s, CH₂), 7.37 (2H, s, aryl); <sup>13</sup>C NMR (CDCl₃, ppm): δ<sub>C</sub> 28.7, 133.7, 137.7.

**Preparation of tetra-aldehydes**

A solution of NaOH (1.6 g, 40 mmol) in H₂O (15 mL) was added to a solution of 2-hydroxybenzaldehyde or 4-hydroxybenzaldehyde (4.9 g, 40 mmol) in ethanol (100 mL). The solution was stirred and heated for 1 h, then an ethanolic solution of 1,2,4,5-tetrakis(bromomethyl)benzene (4.5 g, 10 mmol, 200 mL) was added and refluxed for 12 h. The reaction mixture was cooled to room temperature and the white solid was filtered off, washed with cold ethanol and dried.

**Spectra data of 1,2,4,5-tetrakis(4-formylphenoxy)methyl benzene**

Yield: 5.2 g (84%), m.p.: 203–204 °C. IR (KBr disc): ν(C=O) 1692 cm<sup>−1</sup>. <sup>1</sup>H NMR (CDCl₃): δ<sub>H</sub> 5.27 (s, 8H), 7.08 (d, 8H), 7.68 (s, 2H), 7.76 (d, 8H), 9.86 (s, 4H). <sup>13</sup>C NMR: δ<sub>C</sub> 67.82, 115.16, 130.10, 130.84, 132.11, 135.15, 163.24, 190.55. Anal. Calcd. for C₃₈H₃₀O₈·H₂O: C, 72.14; H, 5.10. Found: C, 72.00; H, 5.00.

**Spectra data of 1,2,4,5-tetrakis(2-formylphenoxy)methyl benzene**

Yield: 5.0 g (82%), m.p.: 232–233 °C. IR (KBr disc): ν(C=O) 1682 cm<sup>−1</sup>. <sup>1</sup>H NMR (CDCl₃): δ<sub>H</sub> 5.49 (s, 8H), 7.65 (m, 18H), 10.33 (s, 4H). <sup>13</sup>C NMR: δ<sub>C</sub> 67.70, 114.32, 121.46, 124.88, 128.11, 128.61, 135.57, 136.68, 160.70, 189.44. Anal. Calcd. for C₃₈H₃₀O₈·H₂O: C, 72.14; H, 5.10. Found: C, 71.99; H, 4.96.

**Analytical data for compound V**

Light red solid, m.p.: 208–210 °C. IR (KBr): 3421, 2950, 2900, 1635, 1506, 1457, 1377, 1216, 1173, 1082, 742 cm<sup>−1</sup>. <sup>1</sup>H NMR (300 MHz, DMSO-d₆): δ<sub>H</sub> (ppm) 5.01 (s, CH₂ benzyllic, 6H), 5.72 (s, CH, 3H), 6.74–7.50 (m, CH aromatic, 18H), 118.82, 119.58, 121.25, 123.87, 127.05, 129.66, 137.03, 137.73, 138.15, 156.91. Anal. Calcd for C₇₈H₆₀N₆O₄: C, 82.95; H, 5.35; N, 7.44. Found: C, 82.52; H, 5.21; N, 7.36.