A Green Protocol for Efficient Synthesis of 1,8-Dioxo-Octahydroxanthenes Using Ionic Liquid

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ABSTRACT
A clean, simple, efficient synthesis of 1,8-dioxo-octahydroxanthenes derivatives using ionic liquid 1-butyl, 3-methylimidazolium perchlorate ([bmim] ClO₄) has been developed. The method provides several advantages such as simple work up, environmental friendliness and excellent yields in short reaction time. The ionic liquid [bmim] ClO₄ used was recovered and reused for three times.

Keywords: 1,8-Dioxo-Octahydroxanthenes; Ionic Liquid; Aldehydes; Dimedone

1. Introduction
1,8-dioxo-octahydroxanthenes are important class of oxygen heterocycles in which a phenyl substituted pyran ring is fused on either side with two cyclohexanone rings. Presence of conjugated bis-dienone functionality makes these compounds sensitive to be attacked by nucleophiles and light energy. In the past decade, synthesis of xanthenes derivatives has been of considerable interest to organic chemists because they possess various biological and pharmaceuticals activities such as antiviral [1], antibacterial [2] and anti-inflammatory [3] properties. These are being utilized as antagonists for paralyzing action of zoxazolamine [4] and in photodynamic therapy [5]. Xanthenes and benzoanthenes derivatives are the parent framework used for the synthesis of xanthenediones involving the condensation of aromatic aldehydes with 1,3-cyclohexanedione or 5,5-dimethyl-1,3-cyclohexanedione. The various catalysts have been reported for synthesis of 1,8-dioxo-octahydroxanthenes: NSPVPD [18], [Et₃NH][HSO₄] [19], SiCl₄ [20], [Et₃NC₅SO₃H][HSO₄] [21], polyline p-toluenesulfonate [22], alumina-sulfuric acid [23], CAN [24], [BMIm][BF₄]-Mg(BF₄) [25], SnCl₃ [26], [Et₃N- SO₃H]Cl [27], DABCO [28], SmCl₃ [29], cellulose sulfuric acid [30], heteropolyacid-MCM-41 i.e. (H₃PW₁₂O₄₀) [31], [bmmim] HSO₄ [32], Fe(HSO₄)₃ [33], [Hbim]BF₄ [34], TBAHS [35] tetramethylguanidium trifluoracetate [36], [DDPA][HSO₄] [37], [TMPSA] HSO₄ [38], [Hmim] TFA [39], trichloro isocyanuric acid [40], SbCl₅/SiO₂ [41], SiO₂-R-SO₂H [42], InCl₃/P₂O₅ [43], p-dodecyl benzenesulfonic acid [44], triethyl benzyl ammonium chloride (TEBA) [45], dianmonium hydrogen phosphate [46], PPA-SiO₂ [47], montmorillonite K-10 [48], Fe⁺³-Montmorillonite.

There are a wide variety of methods for the preparation of the xanthenes having been reported and they are classified according to starting compounds which includes synthesis by cyclization of polycyclic aryl triflate esters [14], intra-molecular trapping of benzynes by phenols [15] and reaction of arloxy magnesium halides with triethyl orthoformate [16] as well as cyclo-condensation of 2-hydroxyln aromatic aldehyde with 2-tetralone [17]. One of the commonly used methods reported for the synthesis of xanthenedeones involves the condensation of aromatic aldehydes with 1, 3-cyclohexanedione or 5,5-dimethyl-1, 3-cyclohexanedione. The various catalysts have been reported for synthesis of 1,8-dioxo-octahydroxanthenes: NSPVPD [18], [Et₃NH][HSO₄] [19], SiCl₄ [20], [Et₃NC₅SO₃H][HSO₄] [21], polyline p-toluenesulfonate [22], alumina-sulfuric acid [23], CAN [24], [BMIm][BF₄]-Mg(BF₄) [25], SnCl₃ [26], [Et₃N- SO₃H]Cl [27], DABCO [28], SmCl₃ [29], cellulose sulfuric acid [30], heteropolyacid-MCM-41 i.e. (H₃PW₁₂O₄₀) [31], [bmmim] HSO₄ [32], Fe(HSO₄)₃ [33], [Hbim]BF₄ [34], TBAHS [35] tetramethylguanidium trifluoracetate [36], [DDPA][HSO₄] [37], [TMPSA] HSO₄ [38], [Hmim] TFA [39], trichloro isocyanuric acid [40], SbCl₅/SiO₂ [41], SiO₂-R-SO₂H [42], InCl₃/P₂O₅ [43], p-dodecyl benzenesulfonic acid [44], triethyl benzyl ammonium chloride (TEBA) [45], dianmonium hydrogen phosphate [46], PPA-SiO₂ [47], montmorillonite K-10 [48], Fe⁺³-Montmorillonite.

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In recent years, ionic liquids have emerged as a useful alternative to conventional organic solvents and catalysts due to their particular properties, such as negligible vapor pressure, chemical stability, excellent solvent power for organic and inorganic compounds, as well as the ease of recovery [37]. Recently, much attention has been paid to organic reactions carried out by using ionic liquids greater than ever importance in the context of green synthesis. Although ionic liquids were primarily introduced as an alternative green reaction medium, today they have progressed extremely beyond that, playing a significant role in controlling reactions as catalysts.

2. Experimental Procedure
All the chemicals were purchased from Sigma Aldrich and Merck chemicals. Melting points recorded on Veego melting point apparatus and were uncorrected. 1H NMR spectra were recorded on a Brucker Avance II 400 MHz spectrometer with TMS as internal standard. IR spectra were recorded on a Brucker Avance II 400 MHz spectrometer. The ionic liquid was synthesized according to ref. [58].

General Procedure for Synthesis of 1,8-Dioxo-Octahydroxanthenes Derivatives
To a mixture of aldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclohexanediene (2 mmol) and [bmim]ClO4 (4 mmol) was added in 50 ml round bottom flask and was stirred at 100°C on heating magnetic stirrer (Scheme 1). The progress of the reaction was monitored by TLC after completion of the reaction the reaction mixture was cooled to room temperature and water (5 ml) was added, solid separated was filtered. The crude product was recrystallized from ethanol to give the pure product. The [bmim]ClO4 was recovered by distillation and reused 3 times.

The comparison of various reported catalyst is summarized in (Table 1).

| 3,3,6,6-tetramethyl-9-(4-chloro-phenyl)-1,8-dioxo-octahydroxanthene (Entry 1) | IR (cm⁻¹): 3030, 2985, 2952, 1679, 1661, 1469, 1361, 1198, 1166, 1003, 852. 1H NMR: 7.17 - 7.24 (dd, 4H), 4.71 (s, 1H), 2.46 (s, 4H), 2.18 (q, 4H), 1.10 (s, 6H), 0.98 (s, 6H). 13C NMR: 191.10, 157.17, 137.45, 126.79, 124.53, 122.97, 110.03, 45.45, 35.61, 26.96, 26.22, 24.03, 22.05 m/z: 385.2 (M + 1), 773.5. |
| 3,3,6,6-tetramethyl-9-(4-methyl-phenyl)-1,8-dioxo-octahydroxanthene (Entry 2) | IR (cm⁻¹): 3036, 2959, 2873, 1663, 1623, 1359, 1197, 1164, 1139, 1000, 842. 1H NMR: 7.17 (d, 2H), 7.02 (d, 2H), 4.71 (s, 1H), 2.45 (4H), 2.24 (s, 3H), 2.18 (q, 4H), 1.07 (s, 6H), 0.99 (s, 6H). 13C NMR: 196.4, 162.0, 141.1, 135.7, 128.7, 128.2, 115.7, 50.7, 40.8, 32.2, 31.4, 29.2, 27.3, 21.0 m/z: 363.5 (M + 1), 773.5. |
| 9,9’-(1,4-phenylene)bis(3,3,6,6-tetramethyl-3,4,5,6,7,8-hexahydro-1H-xanthene-1,8(2H)-dione (Entry 4) | IR (cm⁻¹): 2957, 2871, 1665, 1620, 1365, 1201, 1167, 1144, 1005, 590. 1H NMR: 7.07 (s, 4H), 4.70 (s, 2H), 2.42 (s, 8H), 2.17 (s, 8H), 1.07 (s, 12H), 0.97 (s, 12H). m/z: 13C NMR: 196.4, 162.4, 141.7, 127.9, 115.7, 50.8, 40.8, 32.1, 30.1, 28.9, 27.7. m/z: 645.4 (M + Na), 773.5. |
| 3,3,6,6-tetramethyl-9-(4-hydroxy-3-methoxy-phenyl)-1,8-dioxo-octahydroxanthene (Entry 5) | IR (cm⁻¹): 3412, 3029, 2954, 1666, 1622, 1514, 1431, 1359, 1278, 1229, 1197, 1135, 1028, 624, 571. 1H NMR: 7.01 (s, 1H), 6.73 (d, 1H), 6.56 (dd, 1H), 5.49 (bs, 1H, -OH), 4.66 (s, 1H), 3.89 (s, 3H), 2.45 (s, 4H), 2.20 (q, 4H), 1.00 (s, 12H). 13C NMR: 196.6, 162.0, 145.8, 144.0, 136.4, 120.0, 115.8, 113.9, 112.2, 55.8, 50.7, 40.8, 32.2, 31.3, 29.3, 27.2. m/z: 396.47, 419.3 (M + Na), 773.5. |
| 3,3,6,6-tetramethyl-9-(4-methoxy-phenyl)-1,8-dioxo-octahydroxanthene (Entry 7) | IR (cm⁻¹): 3059, 2958, 2876, 1665, 1626, 1511, 1462, 1357, 1260, 1193, 1109, 1031, 841, 569. 1H NMR: 7.18 (d, 2H), 6.75 (d, 2H), 4.69 (s, 1H), 3.73 (s, 3H), 2.45 (s, 4H), 1.09 (s, 6H), 0.99 (s, 6H). 13C NMR: 196.5, 162.0, 157.9, 136.4, 129.3, 115.7, 113.4, 55.1, 50.7, 40.8, 32.2, 30.9, 29.2, 27.3. m/z: 381.2, 773.5. |

3. Result and Discussion
To a mixture of 4-chloro benzaldehyde (1 mmol) and 5,5-dimethyl-1,3-cyclohexanediene (2 mmol) and [bmim]ClO4 (4 mmol) was added in 50 ml round bottom flask and was stirred at 100°C on heating magnetic stirrer. The progress of the reaction was monitored by TLC. After completion of the reaction the reaction mixture was cooled to room temperature and water (5 ml) was added, solid separated was filtered and product was characterized by IR, NMR, 13C-NMR and mass.

The reaction between dimedone and 4-chloro benzaldehyde in the presence of [bmim]ClO4 was studied as a model reaction. To optimize the reaction conditions of reaction temperature we have tried the study of above model reaction from temperature 60-110°C in the gap of 10°C. The best result in terms of time and yield for the reaction has been observed at 100°C (Table 2).

Table 1. Comparison table with various reported catalysts.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst used</th>
<th>Time</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tetrachloro silane</td>
<td>3 hrs</td>
<td>CH₂Cl₂</td>
<td>60 - 70</td>
<td>92</td>
<td>[20]</td>
</tr>
<tr>
<td>2</td>
<td>SmCl₃</td>
<td>8 hrs</td>
<td>No solvent</td>
<td>120</td>
<td>98</td>
<td>[29]</td>
</tr>
<tr>
<td>3</td>
<td>Cellulose sulfonic acid</td>
<td>6 hrs</td>
<td>No solvent</td>
<td>110</td>
<td>95</td>
<td>[30]</td>
</tr>
<tr>
<td>4</td>
<td>Heteropoly acid supported MCM-41</td>
<td>5 hrs</td>
<td>Ethanol</td>
<td>90°C</td>
<td>90</td>
<td>[31]</td>
</tr>
<tr>
<td>5</td>
<td>[Bmim]HSO₄</td>
<td>3.5 hrs</td>
<td>No solvent</td>
<td>80°C</td>
<td>76 - 94</td>
<td>[32]</td>
</tr>
<tr>
<td>6</td>
<td>[Hbim]BF₄</td>
<td>45 min.</td>
<td>Methanol</td>
<td>Ultrasonic 25 - 30°C</td>
<td>85</td>
<td>[34]</td>
</tr>
<tr>
<td>7</td>
<td>Trimethyl silyl chloride</td>
<td>8 - 10 hrs</td>
<td>Acetonitrile</td>
<td>Reflux</td>
<td>72 - 84</td>
<td>[50]</td>
</tr>
<tr>
<td>8</td>
<td>[Bmim]ClO₄</td>
<td>40 - 90 min.</td>
<td>----</td>
<td>100°C</td>
<td>85 - 95</td>
<td>Present work</td>
</tr>
</tbody>
</table>

Table 2. Optimization of reaction temperature for synthesis of 1,8-dioxo-octahydroxanthenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (hrs.)</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>8 hrs</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>70</td>
<td>6 hrs</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>5 hrs</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>90</td>
<td>2.5 hrs</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>100</td>
<td>1 hr</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>110</td>
<td>1 hr</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 3. Green protocol for efficient synthesis of 1, 8-dioxoxanthenes using [bmim]ClO₄.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (min.)</th>
<th>Yield (%)</th>
<th>Mp. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-Chloro benzaldehyde</td>
<td>3a</td>
<td>60</td>
<td>94</td>
<td>215 - 217</td>
</tr>
<tr>
<td>2</td>
<td>4-Methyl benzaldehyde</td>
<td>3b</td>
<td>70</td>
<td>95</td>
<td>217 - 218</td>
</tr>
<tr>
<td>3</td>
<td>Benzaldehyde</td>
<td>3c</td>
<td>40</td>
<td>92</td>
<td>205 - 206</td>
</tr>
<tr>
<td>4</td>
<td>Terephthaldehyde</td>
<td>3d</td>
<td>90</td>
<td>88</td>
<td>&gt;300</td>
</tr>
<tr>
<td>5</td>
<td>Vanillin</td>
<td>3e</td>
<td>50</td>
<td>85</td>
<td>225 - 227</td>
</tr>
<tr>
<td>6</td>
<td>4-Fluro benzaldehyde</td>
<td>3f</td>
<td>50</td>
<td>92</td>
<td>232 - 233</td>
</tr>
<tr>
<td>7</td>
<td>4-Methoxy benzaldehyde</td>
<td>3g</td>
<td>60</td>
<td>95</td>
<td>241 - 243</td>
</tr>
<tr>
<td>8</td>
<td>3-Chloro benzaldehyde</td>
<td>3h</td>
<td>60</td>
<td>90</td>
<td>183 - 184</td>
</tr>
<tr>
<td>9</td>
<td>4-Bromo benzaldehyde</td>
<td>3i</td>
<td>60</td>
<td>90</td>
<td>222 - 224</td>
</tr>
<tr>
<td>10</td>
<td>4-Hydroxy benzaldehyde</td>
<td>3j</td>
<td>70</td>
<td>87</td>
<td>228 - 230</td>
</tr>
</tbody>
</table>

To evaluate the scope of this reaction a range of 1, 8-dioxo-octahydroxanthenes were prepared by the reaction of dimedone and aromatic aldehydes under optimized reaction conditions. The results are summarized in the table (Table 3). Various aromatic aldehydes with electron donating substituent’s reacted efficiently and quickly with dimedone to give cyclocondensation products in high yields over short reaction times. Similarly aldehydes with electron withdrawing substituent’s reacted efficiently to yield the corresponding 1,8-dioxo-octahydroxanthenes.

Study of reuse of the ionic liquid can be easily done up to 3 times with excellent yields without loss in the reactivity (as shown in graph/Figure 1). After 3rd cycle we observed sudden decrease in the 4th reuse of ionic liquid thus the ionic liquid used was recycled for 3 times. The structure of isolated products was assigned based on their spectral analyses as well as by matching with their melting point with reported analogous.
4. Conclusion

In summary, we have developed a high-yielding simple, convenient, straight-forward and practical one-pot procedure for the synthesis of different types of 1,8-dioxo-octahydroxanthenes derivatives using [bmim]ClO₄. The ionic liquid used can be easily recovered and reused 3 times without significant decrease in the yield of the product.

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