1-(3, 4-dichlorobenzensulfonyl)-3-methyl-1H-imidazolium chloride: An efficient catalyst for the synthesis of 1, 8-dioxo-octahydroxanthenes under microwave irradiation

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Abstract

The reaction of 5,5-dimethyl-1,3-cyclohexanedione with various aromatic aldehydes to give corresponding 1,8-dioxo-octahydroxanthenes in aqueous medium has been reported. These reactions were carried out under microwave irradiation and catalyzed by 1-(3, 4-dichlorobenzensulfonyl)-3-methyl-1H-imidazolium chloride. A plausible mechanism for the synthesis of 1,8-dioxo-octahydroxanthenes catalyzed by [3, 4-dcbsmim][Cl] in water has been given.

Keywords: Aldehydes, 1-(3, 4-dichlorobenzensulfonyl)-3-methyl-1H-imidazolium chloride ([3,4-dcbsmim][Cl]), 5,5-dimethyl-1,3-cyclohexanedione, 1,8-dioxo-octahydroxanthenes, Microwaves, Water.

1. INTRODUCTION

Xanthenes constitute an important class of biologically active compounds because of its wide range of biological and pharmaceutical properties such as anti-inflammatory, antidepressants and antimalarial agents [1]. They act as sensitizers in photodynamic therapy (PDT) for destroying the tumor cells [2]. Xanthenes are also used in the dye industry [3], in cosmetics and pigments [4], in laser technology because of their spectroscopic properties [5], etc. Xanthenes based dyes are extracted naturally from soil and plants such as Indigofera longeracemosa [6]. They are used as pH sensitive fluorescent materials for the visualization of biomolecular assemblies [7] and also as antagonists for the paralyzing action of zoxazolamine [8].

Due to their biological and pharmacological importance, several methods have been reported for the synthesis of Xanthenes employing Lewis acids as catalysts to accelerate the condensation reaction of aldehydes with 5,5-dimethyl-1,3-cyclohexanediol in the presence of 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate) [9], montmorillonite K10 [10], ZrOCl₂·8H₂O [11], heteropolyacid supported MCM-41 [12], nanosized MCM-41-SO₄H [13], nano CuCl [14], nanoSO₄²⁻/xFe-Zr-O [15], silica bonded N-propyl sulfamic acid [16], Zn[LProline]₂ [17], [Bmim][HSO₄] [18], [Hmim][TFA] [19], [TMPSA][HSO₄] [20], [DDPA][HSO₄] [21], [Et₃N-SO₂H][Cl] [22], [Bmim][BF₄] [23], [Et₃NH]H₂PO₄ [24], [Et₃NH][HSO₄] [25], TMGT [26], p-dodecylbenzensulphonic acid [27], trichloroacetic acid [28], silica sulfuric acid [29], alumina-sulfuric acid [30], trimethylsilyl chloride [31], NaHSO₄·SiO₂ [32], ZnO-acetyl chloride [33], CAN [34], Amberlyst-15 [35], Dowex-50W [36], PMA-SiO₂ [37], PPA-SiO₂ [38], as catalysts and also in ionic liquid [Bmim][BF₄] as solvent catalysed by FeCl₃·6H₂O [39], InCl₃·4H₂O [40], and NaHSO₄ [41], Mg(BF₄)₂ doped in [Bmim][BF₄] [42] and LiBr [43], SmCl₃ [44] etc. All the methods have their own advantages with some disadvantages such as low yields, requirement of organic solvents, use of expensive catalysts, tedious workup procedure, etc.

In recent years, ionic liquids are of considerable interest as they can serve as catalysts, green reaction media in organic synthesis and also due to their properties such as non-volatility, non-flammability, ionic conductivity [45-48]. Recently a variety of ionic liquids have been demonstrated as practical alternative to organic solvents as well as catalysts in organic reactions/transformations [49]. Recently, 1-(Benzensulfonyl)-3-methyl-1H-imidazolium chlorides catalyzed electrophilic substitution reactions of indoles with various carbonyl compounds for an efficient one pot synthesis of...
bis(indolyl)methanes have also been reported by our group\cite{50}. Also the use of microwave irradiation for carrying out organic reactions has been well established in recent years\cite{51-52} as it is an environmentally friendly method for the organic synthesis. herein, we report the catalytic application of 1-(3, 4-dichlorobenzenesulfonyl)-3-methyl-1H-imidazolium chlorides for the synthesis of 1,8-dioxo-octahydroxanthenes by the condensation of aromatic aldehydes with 5,5-dimethyl-1,3-cyclohexanedione using easily available, reusable ionic liquid as catalyst under microwave irradiation in aqueous media.

2. EXPERIMENTAL

All solvents and reagents were commercial and used without further purification. Melting points were uncorrected. Nuclear magnetic resonance spectra were obtained on a Bruker AMX spectrophotometer in CDCl$_3$ at 300 MHz. Chemical shifts were obtained in parts per million (δ) and were measured using tetramethyl silane (TMS) as reference. IR spectra were recorded on a Shimadzu FT-IR-8400S spectrophotometer using KBr pellets and were reported as wave numbers (ν cm$^{-1}$). The synthesis was carried out using modified household microwave oven (Frigidaire).

2.1. Preparation of [3,4-dcbsmim][Cl]

1-Methyl-1H-imidazole (2.0 mmol) was taken in a dry round bottomed flask at 0°C. To this 3,4-dichlorobenzenesulfonyl chloride (2.0 mmol) was added slowly and the reaction mixture stirred for 3-4 min to obtain a light yellow precipitate. The product was washed with petroleum ether, dried and stored in cool place. The compound was obtained in 95-96 % yield.\cite{50}

2.2. General procedure for the microwave synthesis of 1,8-dioxo-octahydroxanthenes:

A mixture of aldehyde (5.0 mmol) and 5,5-dimethyl-1,3-cyclohexanedione (10 mmol), 1- (3, 4-dichlorobenzenesulfonyl)-3-methyl-1H-imidazolium chloride ( [3,4-dcbsmim][Cl] ) (0.5 mmol) and 5 mL of water was taken in a closed teflon vessel. The mixture was irradiated with microwaves for a given time (Table 2). The reaction was monitored by TLC. After completion of the reaction, the product was filtered out from the water media and then recrystallized from ethanol. Further, the filtrate (water) was vacuum evaporated to dryness to recover the catalyst [3,4-dcbsmim][Cl] and the resulting catalyst was reused directly for the next run. The products were characterized by melting points, IR, NMR & Mass spectra and compared with those reported for the authentic samples.

2.3. Spectral Data for the few compounds

2.3.1. 9-phenyl-3,3,6,6-tetramethyl-1,2,3,4,6,7,8-octahydroxanthen-1,8-dione (3a)

White solid; m.p=205-207°C. IR (KBr) (ν max/cm$^{-1}$): 2972,1670,1360,1196. $^1$HNMR(CDCl$_3$300MHz):δ=0.97(s,6H),1.08(s,6H),2.15-2.26(q, 4H),2.48(s,4H),4.72(s, 1H),7.07-7.14(m,1H),7.16-7.26(m,2H),7.36(m,2H). $^{13}$CNMR (CDCl$_3$100MHz): δ=27.2, 29.2, 31.9, 32.0, 41.3, 50.3, 114.6, 126.3, 128.0, 128.3, 144.0, 163.2, 195.0. MS (EI) m/z 270 (M$^+$).

2.3.2. 9-(4-chlorophenyl-3,3,6,6-tetramethyl-1,2,3,4,6,7,8-octahydroxanthen-1,8-dione (3b)

White solid; m.p=229-232°C. IR (KBr) (ν max/cm$^{-1}$): 2960,1660,1350,1191. $^1$HNMR(CDCl$_3$300MHz):δ=0.99(s,6H),1.08(s,6H),2.14-2.26(q, 4H),2.46(s,4H),4.70(s, 1H),7.16-7.42(m,4H). $^{13}$CNMR (CDCl$_3$100MHz): δ=27.2, 28.1, 30.8, 31.9, 32.1, 40.7, 50.6, 115.1, 128.1, 129.0, 129.6, 142.6, 162.4, 196.3. MS (EI) m/z 385 (M$^+$).

2.3.3. 9-(4-hydroxyphenyl-3,3,6,6-tetramethyl-1,2,3,4,6,7,8-octahydroxanthen-1,8-dione (3f)

White solid; m.p=245-248°C. IR (KBr) (ν max/cm$^{-1}$): 3303,2954,1650,1360,1191. $^1$HNMR(CDCl$_3$300MHz):δ=0.99(s,6H),1.09(s,6H),2.14-2.20(q, 4H),2.47(s,4H),4.63(s, 1H),5.72(s,1H),7.16-7.02(m,4H). $^{13}$CNMR (CDCl$_3$100MHz): δ=27.2, 29.1, 30.2, 31.4, 32.1, 40.6, 50.6, 115.1, 128.0, 129.0, 139.4, 140.6, 162.4, 195.3. MS (EI) m/z 366 (M$^+$).

3. RESULTS AND DISCUSSION

Initially, the catalyst [3,4-dcbsmim][Cl] was prepared as previously explained. In order to optimize the green reaction conditions, we firstly investigated the greener solvents on the reaction rate as well as yields of the products (Table 1). In a typical experimental procedure, the reaction of 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol) and benzaldehyde (0.5 mmol) catalyzed by [3,4-dcbsmim][Cl] (0.5 mmol) in different solvent media was investigated under microwaves. Water is found as an ideal solvent because it is inexpensive, non-flammable, abundant and environmentally benign.

To determine the optimum concentration of catalyst, we have investigated the model reaction of benzaldehyde (10.0 mmol) with 5, 5-dimethyl-1, 3-cyclohexanedione (20.0 mmol) carried out at 1, 5, 10, and 20 mol% of [3,4-dcbsmim][Cl] in water under microwave irradiation. The products were obtained in about 90, 92, 94 and 94 % yield, respectively in 3min. This indicates that 10 mol% of [3,4-dcbsmim][Cl] is sufficient for the best yield. Subsequently, all the
Table - 1: Effect of solvent in the preparation of 3,3,6,6-tetramethyl-9-phenyl-3,4,6,7-tetrahydro-2H-xanthene-1,8(5H,9H)-dione catalyzed by [3,4-dcbsmim][Cl].

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Catalyst (mol %)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile(3mL) + [Bmim][Cl] (7 mL)</td>
<td>10</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile (10 mL)</td>
<td>10</td>
<td>4</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>[Bmim][Cl] (10 mL)</td>
<td>10</td>
<td>4</td>
<td>93</td>
</tr>
<tr>
<td>4</td>
<td>Water (10 mL)</td>
<td>10</td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>Neat</td>
<td>10</td>
<td>4</td>
<td>90</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: benzaldehyde (0.5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol), Microwaves in different solvents; *b* Isolated yield.

Table - 2: [3,4-dcbsmim][Cl] catalyzed microwave synthesis of 1,8-dioxo-octahydroxanthenes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>Product 3</th>
<th>Time (min)</th>
<th>Yield* (%)</th>
<th>Melting point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzaldehyde</td>
<td>3a</td>
<td>3</td>
<td>94</td>
<td>205-207</td>
</tr>
<tr>
<td>2</td>
<td>4-Chlorobenzaldehyde</td>
<td>3b</td>
<td>4</td>
<td>95</td>
<td>229-232</td>
</tr>
<tr>
<td>3</td>
<td>2-Chlorobenzaldehyde</td>
<td>3c</td>
<td>5</td>
<td>94</td>
<td>225-227</td>
</tr>
<tr>
<td>4</td>
<td>4-Bromobenzaldehyde</td>
<td>3d</td>
<td>5</td>
<td>90</td>
<td>240-242</td>
</tr>
<tr>
<td>5</td>
<td>4-Fluorobenzaldehyde</td>
<td>3e</td>
<td>5</td>
<td>91</td>
<td>226-228</td>
</tr>
<tr>
<td>6</td>
<td>4-Hydroxybenzaldehyde</td>
<td>3f</td>
<td>5</td>
<td>92</td>
<td>245-248</td>
</tr>
<tr>
<td>7</td>
<td>2-Hydroxybenzaldehyde</td>
<td>3g</td>
<td>4</td>
<td>89</td>
<td>202-206</td>
</tr>
<tr>
<td>8</td>
<td>4-Methoxybenzaldehyde</td>
<td>3h</td>
<td>5</td>
<td>90</td>
<td>240-242</td>
</tr>
<tr>
<td>9</td>
<td>3-Methoxybenzaldehyde</td>
<td>3i</td>
<td>5</td>
<td>95</td>
<td>178-180</td>
</tr>
<tr>
<td>10</td>
<td>4-Nitrobenzaldehyde</td>
<td>3j</td>
<td>3</td>
<td>92</td>
<td>224-226</td>
</tr>
<tr>
<td>11</td>
<td>3-Nitrobenzaldehyde</td>
<td>3k</td>
<td>5</td>
<td>93</td>
<td>170-172</td>
</tr>
<tr>
<td>12</td>
<td>4-Tolualdehyde</td>
<td>3l</td>
<td>4</td>
<td>90</td>
<td>208-209</td>
</tr>
<tr>
<td>13</td>
<td>2,4-Dichlorobenzaldehyde</td>
<td>3m</td>
<td>5</td>
<td>91</td>
<td>247-249</td>
</tr>
<tr>
<td>14</td>
<td>Cinnamaldehyde</td>
<td>3n</td>
<td>4</td>
<td>90</td>
<td>178-180</td>
</tr>
<tr>
<td>15</td>
<td>4-Hydroxy-3-methoxybenzaldehyde</td>
<td>3o</td>
<td>5</td>
<td>85</td>
<td>226-228</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: aromatic aldehyde (0.5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol), [3,4-dcbsmim][Cl] (0.5 mmol), Microwave irradiation, in aqueous medium; *b* Isolated yield.
Scheme - 2: Plausible mechanism for the synthesis of 1,8-dioxooctahydroxanthenes catalyzed by [3, 4-dcbsmim][Cl] in water.

Table - 3: Recycling of the catalyst.

<table>
<thead>
<tr>
<th>Run</th>
<th>Time(min)</th>
<th>Yield b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>85</td>
</tr>
</tbody>
</table>

a Reaction conditions: 4-nitro benzaldehyde (0.5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol), [3,4-dcbsmim][Cl] (0.5 mmol), Microwaves, in aqueous medium; b Isolated yield.

In order to demonstrate the reusability of [3,4-dcbsmim][Cl] the experiment was performed using 4-nitrobenzaldehyde as a model substrate under aqueous condition. The product was recrystallized from 95% ethanol to obtain the desired product in pure form. The water layer consisted of [3,4-dcbsmim][Cl] along with some residual reactants and byproducts, and vacuumed to get catalyst with impurities. The resulting catalyst was directly used in subsequent runs without further treatment (Table 3).
Table - 4: Comparison of ionic liquids used as catalyst for the synthesis of 1,8-dioxo-octahydroxanthene.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic liquid</th>
<th>Conditions</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Bmim] HSO₄</td>
<td>100 °C</td>
<td>25</td>
<td>93</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>TMGT/TFA</td>
<td>75 °C</td>
<td>20-30</td>
<td>92</td>
<td>26</td>
</tr>
<tr>
<td>3</td>
<td>[Et₃NH][H₂PO₄]</td>
<td>100 °C</td>
<td>5</td>
<td>96</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>Mg(BF₄)₂ doped in [Bmim][BF₄]</td>
<td>80 °C</td>
<td>30</td>
<td>97</td>
<td>42</td>
</tr>
<tr>
<td>5</td>
<td>[Et₃NH][HSO₄]</td>
<td>100 °C</td>
<td>20</td>
<td>94</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>No Catalyst</td>
<td>Water, MW</td>
<td>7</td>
<td>80</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>[3,4-dcbsmim][Cl]</td>
<td>Water, MW</td>
<td>3</td>
<td>94</td>
<td>Present work</td>
</tr>
</tbody>
</table>

a Reaction conditions: benzaldehyde (0.5 mmol), 5,5-dimethyl-1,3-cyclohexanedione (1.0 mmol) at different conditions; b Isolated yield.

4. CONCLUSION

In conclusion, 1-(3,4-dichlorobenzenesulfonyl)-3-methyl-1H-imidazolium chloride [3,4-dcbsmim][Cl] has proven to be an efficient and recyclable catalyst for the synthesis of xanthene derivatives under microwave irradiation. The method is simple, clean, and green. The recycled ionic liquid can be reused for 3-4 cycles without loss in catalytic activity.

Acknowledgements:
The authors are thankful to Bangalore University, Bangalore, for the financial support through YRB-BUIRF. We also thank NMRC, IISc., Bangalore for NMR spectral analysis and Department of Organic Chemistry IISc., Bangalore for mass spectral analysis.

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