Solvent Free Condensation Reactions between Diketone, Aromatic Aldehydes and A Nitrogen Source- A Green Chemical Approach - One Pot and Three Component Synthesis

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A B S T R A C T

The parameters like selectivity and overall yield, raw material, time, human resources, energy requirements, as well as the toxicity and hazard of the chemicals and the protocols involved are considered to be very important yard sticks for a neat and efficient organic synthesis. The development of multicomponent reactions (MCRs) in the presence of task-specific ionic liquids (ILs), used not only as environmentally benign reaction media, but also as catalysts, is a new approach that meet with the requirements of sustainable chemistry. Here, we propose the multicomponent condensation reaction of dimedone, aromatic aldehydes, and an aromatic amine under solvent-free conditions using the ionic liquid [Et$_2$NH]$_2$[BF$_4$]. Short reaction time (40-55 min), good to high yields (90-95 %), not using the organic solvents and simple work-up procedure and the recyclability of the ionic liquid are some of the advantages of this method. The same reaction was carried out in other ionic liquids in order to prove that the proposed ionic liquid is more efficient than them.

1. Introduction

In the context of sustainable chemistry [1] the design and development of sequences allowing highly selective access to elaborated molecular scaffolds while combining structural diversity [2], with eco-compatibility [3], are great challenges for organic chemists. Thanks to their ability to build one product in a single operation from three or more reactant molecules with good to high atom-economy[4] and multiple-bond-forming efficiency [5], multicomponent reactions (MCRs)[6], are now well-established approaches to reach this near ideal goal. Developing the cheap and best synthetic routes for Nitrogen containing heterocyclic systems is an important task in organic Chemistry. Multi-component reactions (MCRs) [7-9] are significant tools for the rapid and efficient synthesis of a wide variety of organic compounds. These reactions have been investigated extensively in organic, and diversity oriented syntheses, primarily due to their ability to complex molecular functionality from simple starting materials via one-pot reactions. In recent years, extensive research on the synthesis of tricycle compounds containing acridine derivatives, has been reported. Acridine derivatives have been found to possess useful biological activities such as antitumor properties, carcinogenic activity[10], anti-malarial activity [10] and heart defibrillation[10]. Due to its planar structure, acridine chromophore moiety sometimes has excellent DNA binding properties. Recently, the synthesis of polycyclic compounds, as potential bio-intercalating agents [11] has been extensively studied. Moreover, new acridine (naphthalene-quinolines) skeleton fused with a five or six-membered ring yields polycyclic derivatives, which also play important roles as some DNA-intercalating anticancer drugs [12]. Thus, the synthesis of acridine derivatives is an important and principal task in organic chemistry. Some methods are available in the literature for the synthesis of acridine derivatives from dimedone, aldehydes and different nitrogen sources like urea [13], methyl amine [14], ammonium acetate [15] and etc. It can be synthesized also under microwave irradiation [16], using ionic liquids [17-19] and some nano materials [20]. A very few reports are available in the literature on the synthesis of acridine derivatives mediated by ionic liquids with respect to different aldehydes. In continuation of our interest we are going to use the ionic liquid, [Et$_2$NH]$_2$[BF$_4$]; having solvent cum catalytic activity to synthesize the acridine derivatives with different aldehydes. To the best of our knowledge, the acridine derivatives were not prepared still using this ionic liquid.

2. Experimental Methods

2.1 Materials, Chemicals

All chemicals were obtained from Merck, Aldrich and SD fine chemicals. IR spectra were recorded from KBr disk using an FT-IR Bruker Tensor 27 instrument. 1H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer using TMS (Tetramethyl silane) as an internal standard. Chemical shift values are given in ppm (δ). Mass spectral measurements were performed by E1 method on a Jeol JMS-300 Spectrometer at 70 eV. Melting points were measured by using the capillary tube method with an electro thermal 9200 apparatus.

2.2 Synthesis of Ionic Liquid

The ionic liquid, [Et$_2$NH]$_2$[BF$_4$] was prepared according to the reference [21].

2.2.1 General Method for the Preparation of Acridine Derivatives

A mixture of dimedone (1 mmol), aromatic aldehyde (2 mmol), and aromatic amine (3 mmol) was taken in a 100 mL RB. To this 3 mL of ionic liquid was added and the mixture was heated at 70 °C for a particular time (40-55 min). The progress of the reaction was monitored by TLC. Upon completion, the reaction mixture was cooled to room temperature and copious amount of water was added. A mixture of products containing water soluble catalyst and water insoluble products. The product (maximum of yellow in colour) was then collected by simple filtration, dried and recrystallized from methano to give pure compounds scheme 1.

2.2.2 Procedure for Recycling and Reusing of the Ionic Liquid

Due to the fact that the catalyst was soluble in water, it could therefore be recycled by simply evaporating the filtrate. The separated catalyst was washed with ethyl acetate and dried at 60 °C under vacuum for 2 h and was reused in subsequent reaction. The catalyst could be used at least four times without significant loss of activity.

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3. Spectral Data

4a. Yellow solid, mp – 235-238°C
IR (KBr): 1652 [C=O (cm

4b. Yellow solid, mp – 212-214°C
IR (KBr): 1631 [C=O (cm

4c. Yellow solid, mp – 255-257°C
IR (KBr): 1611 [C=O (cm

4d. Yellow solid, mp – 242-245°C
IR (KBr): 1642 [C=O (cm

4e. Yellow solid, mp – 201-202°C
IR (KBr): 1644 [C=O (cm

4f. Brown solid, mp – 208-210°C
IR (KBr): 1642 [C=O (cm

4g. Orange solid, mp – 182-184°C
IR (KBr): 1663 [C=O (cm

4h. Orange solid, mp – 188-189°C
IR (KBr): 1639 [C=O (cm

4i. Brown solid, mp – 162-164°C
IR (KBr): 1654 [C=O (cm

4j. Yellow solid, mp – 189-190°C
IR (KBr): 1661 [C=O (cm

MASS: m/z 455 [M]+; C20H13N3

4k. Yellow solid, mp – 172-174°C
IR (KBr): 1647 [C=O (cm

MASS: m/z 515 [M]+; C20H13N3

4l. Yellow solid, mp – 177-178°C
IR (KBr): 1673 [C=O (cm

MASS: m/z 516 [M]+; C20H13N3

3. Results and Discussion

3.1 Selection of Ionic Liquid

The chosen ionic liquids such as [Et₅NH][BF₄] – [Et₅NH][HSO₄] and [TBA][AMPS] were prepared as per the available literature [21]. Using these ionic liquids, the condensation reaction was conducted by the dimedone 1, Benzaldehyde 2, and aniline 3. The results vividly demonstrate that [Et₅NH][BF₄] is more efficient than the other two ionic liquids chosen for the study Table 1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ionic liquid</th>
<th>Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Et₅NH][HSO₄]</td>
<td>80°C, 2 hrs</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>[TBA][AMPS]</td>
<td>80°C, 2 hrs</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>[Et₅NH][BF₄]</td>
<td>80°C, 2 hrs</td>
<td>94</td>
</tr>
</tbody>
</table>

3.2 Optimization of Volume of Ionic Liquid, [Et₅NH][BF₄]

After the selection of the ionic liquid, the same condensation reaction for at least half a dozen time was performed with [Et₅NH][BF₄] to ascertain the optimal volume of the chosen ionic liquid for the best results. The results show that 3 mL of the ionic liquid is suitable and ideal volume to carry out this condensation reaction Table 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Volume of ionic liquid in mL</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>94</td>
</tr>
</tbody>
</table>

Aldehyde-Benzaldehyde; Temp; 70 °C; Time; 40 min.

Table 3 Recycling and Reusing of the ionic liquid.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>94</td>
</tr>
</tbody>
</table>

Aldehyde-Benzaldehyde; Temp; 70 °C; Time; 40 min.

The one pot three component condensation reaction of dimedone 1, Aromatic aldehydes 2, and a nitrogen source (aromatic amine) 3 in an ionic liquid, [Et₅NH][BF₄] at 70 °C for a period of time (40-55 min) resulted in the formation of yellow to pale yellow solid of acridine diones 4. 4 shows good to high yields (90-95%). The product was collected by filtration using 10 mL of distilled water. The filtrate containing the ionic liquid was then recovered for reuse after drying at 60 °C in a vacuum for 2 h. The ionic liquid was recovered and reused for four times. Even in the fourth run the yield of the product is fairly good (Table 3).

In the scope of this one-pot three component condensation reaction for the synthesis of phenyl polyhydroxyacridine derivatives is illustrated by conducting the reaction with aromatic aldehydes having electron donating as well as electron withdrawing substituents on
benzene ring. It appears that the reactions were independent regarding the substituents on the benzene ring as well as the positions of the substituents (Table 4).

Table 4 One-pot three component synthesis of phenyl polyhydro acridine diones in an ionic liquid [Et3NH][BF4] medium.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde(s)</th>
<th>Product</th>
<th>Reaction Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzaldehyde</td>
<td>3</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>p-Methoxy benzaldehyde</td>
<td>4</td>
<td>40</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>2-Nitro benzaldehyde</td>
<td>5</td>
<td>50</td>
<td>91</td>
</tr>
<tr>
<td>4</td>
<td>4-Nitro benzaldehyde</td>
<td>5</td>
<td>50</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>2-Hydroxy benzaldehyde</td>
<td>5</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>4-Hydroxy benzaldehyde</td>
<td>5</td>
<td>45</td>
<td>94</td>
</tr>
<tr>
<td>7</td>
<td>2-Chloro benzaldehyde</td>
<td>5</td>
<td>40</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>4-Chloro benzaldehyde</td>
<td>5</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>9</td>
<td>p-Dimethylamino benzaldehyde</td>
<td>5</td>
<td>50</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>3,4,5-trimethoxy benzaldehyde</td>
<td>5</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>11</td>
<td>4-Hydroxy-3-Methoxy-5-Nitro benzaldehyde</td>
<td>5</td>
<td>50</td>
<td>92</td>
</tr>
<tr>
<td>12</td>
<td>3-Ethoxy-4-hydroxy benzaldehyde</td>
<td>5</td>
<td>45</td>
<td>91</td>
</tr>
<tr>
<td>13</td>
<td>Anthraaldehyde</td>
<td>5</td>
<td>50</td>
<td>93</td>
</tr>
<tr>
<td>14</td>
<td>Naphthaldehyde</td>
<td>5</td>
<td>55</td>
<td>92</td>
</tr>
<tr>
<td>15</td>
<td>Furfuraldehyde</td>
<td>5</td>
<td>55</td>
<td>90</td>
</tr>
</tbody>
</table>

α - isolated yield.

The structures of all the products have been established on the basis of analytical and spectroscopic data (UV-Vis, IR, 1H NMR and Mass). This ionic-liquid mediated reaction has advantages of easier work-up, favourable reaction conditions, high yields and an environmentally benign procedure and the ionic liquid (catalyst) is reusable.

3.3 Plausible Mechanism for This Condensation Reaction:

Initial formation of imine from aldehyde and amine:

Further steps involved in the mechanism:

The formation of 4 could be explained by the proposed plausible mechanism. The reaction occurs via an initial formation of the imine 5 from the condensation of aromatic aldehyde 2 and aniline 3, which suffers nucleophilic attack by dimedone 1 and loses amine to give the intermediate 6. Condensation of another molecule of dimedone 1 with aniline 3 gives another intermediate enamine 7. Then, the Michael
addition, cyclization and dehydration between intermediates 6 and 7 will take place to give the final product 4, Fig. 1.

4. Conclusion

In conclusion, we have developed a method for the condensation reaction between the dimerone, aldehydes, and a nitrogen source using [Et$_3$N][BF$_4$] as an efficient catalyst for the condensation of acridine derivatives under solvent-free conditions. Shorter reaction times, very good to high yields, simple workup procedure, and eco-friendly conditions are the main merits of this method. Further, the ionic liquid (catalyst) was recycled and reused for the same reactions for four times without significant loss in its activity. The wide scope of this three-component ionic liquid mediated reaction is that it tolerates the presence of electron with drawing as well as electron releasing groups on benzene ring. Thus, we believe that this simple and green methodology will be a practical alternative to the existing procedures.

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