Original Research Article

Synthesis of dihydropyridines and quinoxaline derivatives using 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride as a new, reusable and efficient Brønsted acidic ionic liquid catalyst

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Quinoxaline derivatives
Solid acid
Ionic liquid
Green chemistry

ABSTRACT

In this work, the efficiency, generality and applicability of new silica supported Brønsted acidic ionic liquid (BAIL) 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride as heterogeneous and green catalyst for organic transformations are studied. Herein, the following one-pot multi-component reactions in the presence of [Msei]Cl are investigated: (i) the synthesis of quinoxaline derivatives from phenylendiamine and 1,2-diketones in EtOH and under mild conditions (room temperature), (ii) the preparation of 1,4-dihydropyridines from one-pot multi component condensation of 1,3-dicarbonyl compounds (2 equiv.), NH₄OAc (1.5 equiv.) and aldehydes (1 equiv.) under solvent-free conditions at moderate temperature (90 °C). High yields, relatively short reaction times, efficiency, generality, clean process, simple methodology, low cost, easy work-up, ease of preparation and regeneration of the catalyst and green conditions (in the synthesis of the quinoxaline derivatives) are advantages of the application of [Msei]Cl as catalyst in the above organic reactions.
Introduction

In recent years, the search for environmentally benign chemical processes or methodologies has received much attention. Green chemistry is an approach to the synthesis, processing, and use of chemicals that aims to reduce the risks to humans and the environment [1]. Over the last few years, ionic liquids (ILs) have been popularly used as solvents for organic synthesis, catalysis, and also been used as media for extraction processes. Ionic liquids have received much attention due to their unique properties such as non-volatility, non-flammability, reusability and great potential as environmentally benign media. Some of the ionic liquids have been proved to act as catalysts because of their high polarity and the ability to solubilize both \( z \) and organic compounds, which can result in the enhancement of the rate of the reaction [2].

The advantages of homogeneous catalysts, high activity and selectivity, heterogeneous catalysts, easy catalyst separation, long catalytic life, easy catalyst regenerability, thermal stability and recyclability [3-5].

Quinoxaline derivatives are an important class of nitrogen-containing heterocyclic in medicinal chemistry. Among the various classes of heterocyclic compounds, quinoxalines form an important component of pharmacologically active compounds. In the recent past, there has been an enhanced interest in the synthesis of quinoxaline derivatives due to their potential application in various
antibiotics, such as levomycin, echinomycin and actinoleutin that are known to inhibit growth of gram positive bacteria and are active against various transplantable tumors [6, 7]. Its derivatives have been used as anti-viral [8], anti mycobacterial [9], anticancer agents [10]. In addition, they are used in dyes [11] and building blocks for the synthesis of organic semiconductors [12], applied for metal cations extraction [13, 14], cavitands [15], DNA cleaving agents [16]. The most several method for their preparation relies on the condensation of an aryl o-phenyldiamine with a 1,2-dicarbonyl compound. moreover, there are various synthetic routes toward quinoxalines including Bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines [17], heteroannulation of nitroketene N,S-aryliminoacetals [18] and etc. Various reagents have been used for the synthesis of derivatives quinoxaline, which include iodine [19], silica sulfuric acid [20], Ni-nanoparticles [21], cerium ammonium nitrate [22], InCl₃ [23], microwave irradiation [24, 25], ionic liquid [26] as catalysts. The preparation of 1,4-dihydropyridines and its derivatives plays an important role in organic synthesis. It derivatives is one of the main pharmaceutical structures with various biological and pharmacological effects. One of the most significant effects of them is regulatory effect on calcium channels which lead to wide spectrum use of these compounds in cardiovascular disease management. New researches has been proved broad and important role of these compounds including the anti tuberculosis and anti convulsion effects. Some examples for pharmaceutical using of these compounds include: anti malaria, vasodilator, anesthetic, antidiabetic, and antimutagenic, dyes, additives as antioxidant, agrochemicals as well as veterinary and also in qualitative and quantitative analysis [27, 28]. Numerous synthetic methods have been reported for the preparation of 1,4-dihydropyridine derivatives under classical or modified conditions [29, 30]. However, many of these methods suffer from certain drawbacks including longer reaction times, unsatisfactory yields, low efficiency, long time period for completing these reactions, harsh reaction conditions, and using poisonous and expensive catalyst materials.

Herein, we report a new method and efficient one-pot synthesis of 1,4-dihydropyridine and quinoxaline derivatives using bronsted acidic ionic liquid 1-methyl-3-(2-(sulfoxoxy)ethyl)-1H-imidazol-3-ium chloride ([Msei]Cl) as a new catalyst. [Msei]Cl as a solid acid was introduced by Wu et al. (Scheme 1 and Figure 1) and used it for the regioselective conversion of synthesis of 2,4,5-triaryl-5H-chromeno[4,3-b]pyridines under microwave radiation [31]. The reactions are typically carried out in an inert atmosphere N₂. The formed ionic liquid is immiscible with the starting materials, and it forms a dense phase on the bottom of a reaction flask. This reaction was easy and clean, because HCl gas was evolved from the reaction vessel immediately (Figure 2).
This simple method is important from both environmental and economic viewpoints as it produces little waste and also the catalyst can be recovered from the reaction mixtures and reused. In contrast to other acids, storage and handling of this compound do not need special precautions and it can be stored on the bench top for weeks without losing its catalytic activity.

The simple experimental procedure, non-corrosive, eco-friendly, solvent-free reaction conditions, non-toxicity of the reagent, utilization of an inexpensive and readily available catalyst, short period of conversion and excellent yields are the advantages of the present method.

![Scheme 1. Preparation of 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride](image)

**Experimental**

**Materials and methods**

The products were separated and purified by different chromatographic techniques and were identified by the comparison of their IR, Melting Point and NMR with those reported for the authentic samples. IR spectra of the compounds were obtained on a Perkin Elmer spectrometer version 10.03.06 using a KBr disk. ¹H NMR Spectra were recorded on an 400 MHz FT NMR Spectrometer in CDCl₃ as a solvent and chemical shift values are recorded in units δ (PPM) relative to tetramethylsilane (Me₄Si) as an internal standard. The purity of the substrate and reaction monitors were accompanied with TLC on silica-gel polygram SILG/UV 254 plates. All reagents were purchased from Merck or Aldrich Fine Chemicals and were used without further purification.

**General procedure for the synthesis of quinoxaline Derivatives**

A solution of aromatic o-phenylenediamine (1 mmol) and a 1,2-dicarbonyl compound (1 mmol) in EtOH (10 mL) was stirred at room temperature in the presence of catalytic amount of [Msei]Cl (3 mol %, 0.014 g) for the result reported in Table 3. The progress of the reaction was monitored by TLC (n-Hexane/EtOAc, 20:1). After completion of the reaction, the catalyst was filtered off. Afterward, H₂O (25 mL) was added to the reaction mixture, and was allowed to stand at room temperature for 30 minute. This period, crystals of the crude product formed which were collected by filtration, and recrystallized from EtOH to give the pure product.
General Procedure for the Preparation of 1, 4-dihydropyridine Derivatives

A mixture of 1,3-dicarbonyl (2 mmol, 0.2 g), aromatic aldehyde (1 mmol), NH₄OAc (1.5 mmol) in the presence of catalytic amount of [Msei]Cl (1 mol %, 0.3 g), under solvent-free conditions at moderate temperature (90 °C). The progress of the reaction was monitored by TLC (n-Hexane/EtOAc, 8:2). After completion of the reaction, ethyl acetate (5 mL) was added to the reaction mixture, and was allowed to stand at room temperature for 5 minutes. The catalyst was filtered off. The filtrate was successively diluted with 5% NaHCO₃ (10 mL). The filtrate was concentrated under vacuum and the residue was recrystallized from EtOH to produce 1,4-dihydropyridine derivatives as pure crystalline products in 80-99% yields. The results are shown in Table 6.

Scheme 2. Synthesis of quinoxaline derivatives using [MSEI]Cl

Results and discussion

Recently, with an objective to develop environmentally benign reaction conditions and media for organic reactions with excellent efficiency and selectivity ionic liquid has been shown to be a useful solvent. In this article, we report the synthesis of 1,4-dihydropyridine and quinoxaline derivatives using bronsted acidic ionic liquid 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride {[Msei]Cl} as a new acidic ionic liquid catalyst (Schemes 2 and 3).
IR spectrum showed the characteristic peak of O-H group at 3200-3600 cm\(^{-1}\), C=C (1440. 1579 cm\(^{-1}\)), S=O (1019 cm\(^{-1}\)), S-O (623 cm\(^{-1}\)).

The reaction of o-phenylenediamines with various diketones was also examined in different solvents such, acetonitrile, chlorophorm, water, and methanol water. Higher yields and shorter reaction times were obtained when the reaction was carried out in EtOH. Thus, EtOH was selected and used as reaction media for all reactions (Table 1).

The effect of catalyst loading on the condensation reaction between diketones and o-phenylenediamines was also studied. To determine the role of 1-methyl-3-(2-(sulfooxy)ethyl)-1H-imidazol-3-ium chloride, the model reaction was carried out in the absence of catalyst at room temperature under solvent-free condition (Table 2). As it can be seen in Table 2 excellent yield and shorter reaction time were obtained when the reaction was carried out in the presence of 3 mol% of the catalyst. It is notable that when 20 mol% of catalyst was used, the yield of the desired product decreased dramatically.

This is presumably due to the considerable protonation of o-phenylenediamines nitrogen atoms by acidic protons on the catalyst surface which decreases their nucleophilic activity towards the carbonyl group of diketone. Thus, under the optimized reaction conditions, this reaction was effected using various diketones and o-phenylenediamines and the results were summarized in Table 3.

The results listed in Table 3 show that various o-phenylenediamines (electron-donating and electron-withdrawing groups) react smoothly with diketones to afford the products quinoxaline in good to excellent yields, on the other hand, some of 1,2-diketones were subjected for condensation reaction and the desired products were obtained in excellent yields (Table 3, 3a, 3d and 3h).

![Figure 2. Comparison FT-IR spectrum of ionic liquid 3, Bronsted acidic ionic liquid 4](image-url)
Synthesis of dihydropyridines and quinoxaline derivatives using...  

Scheme 3. Synthesis of 1,4-dihydropyridines using [MSEI]Cl

After evaporation of solvent, also showed excellent reusability in these reactions. The catalyst was recovered in excellent yields (99, 95 and 91%, Figure 3) and used in the reactions three times; it showed the same activity as fresh catalyst without any significant loss of its activity.

Table 1. The solvent effect for synthesis of quinoxalines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (10 ml)</th>
<th>Time (min)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl3</td>
<td>80</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>MeCN</td>
<td>85</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>H2O</td>
<td>185</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>EtOH</td>
<td>10</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>EtOH/H2O (1/1)</td>
<td>120</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>EtOH/H2O (4/1)</td>
<td>150</td>
<td>95</td>
</tr>
<tr>
<td>7</td>
<td>EtOH/H2O (9/1)</td>
<td>165</td>
<td>91</td>
</tr>
<tr>
<td>8</td>
<td>EtOH/H2O (6/4)</td>
<td>115</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>EtOH/H2O (3/7)</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>EtOH/H2O (7/3)</td>
<td>140</td>
<td>92</td>
</tr>
</tbody>
</table>

a o-Phenylenediamine (1.0 mmol), diketone (1.0 mmol) reacted at room temperature

b Yield of isolated products

Recent developments in 1,4-dihydropyridine chemistry and our continued interest in the development of efficient and environmentally friendly procedures for the synthesis of heterocyclic compounds, prompted us to study the conversion of dimedone into fused 1,4-dihydropyridines in the presence of 1-methyl-(2-([sulfooxy]ethyl)-1H-imidazol-3-ium chloride. As summarized in Table 6, several different aromatic aldehydes (1 equiv), 1,3-dicarbonyl compounds (2 equiv) and NH4OAc (1.5 equiv) in presence of Bronsted acidic ionic liquid (BAIL) under solvent-free conditions and thermal 90 °C (Scheme 2).

In recent years, solvent-free organic reactions have caused great interests, which have many advantages such as excellent yield, selectivity, simplicity of reaction, simple experimental procedure, separation and purification, mild reaction conditions, and to benefit industry as well as environment. The effect of temperature was also studied by carrying out the model reaction in the presence of [MSEI]Cl (1 mol%) To find the optimal conditions the synthesis of 1,4-dihydropyridine
Table 2. Catalyst's optimization in synthesis of quinoxaline

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (%)</th>
<th>Time (min)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>750</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>0.01</td>
<td>130</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>0.03</td>
<td>10</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>0.05</td>
<td>75</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
<td>60</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>0.20</td>
<td>120</td>
<td>87</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yield of isolated products

Table 3. Synthesis of quinoxaline derivatives catalyzed by [MSEI]Cl using different o-phenylenediamines and 1,2-diketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (h:min)</th>
<th>Yield(%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>M.P. (°C) [Lit.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Product 1" /></td>
<td>00:10</td>
<td>99</td>
<td>124-126 [16]</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2.png" alt="Product 2" /></td>
<td>03:53</td>
<td>96</td>
<td>187-189 [17]</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3.png" alt="Product 3" /></td>
<td>00:30</td>
<td>95</td>
<td>259-260 [32]</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4.png" alt="Product 4" /></td>
<td>03:20</td>
<td>98</td>
<td>137-139 [32]</td>
</tr>
<tr>
<td>5</td>
<td><img src="image5.png" alt="Product 5" /></td>
<td>00:30</td>
<td>95</td>
<td>225-226 [32]</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Product 6" /></td>
<td>04:05</td>
<td>91</td>
<td>243-245 [32]</td>
</tr>
<tr>
<td>7</td>
<td><img src="image7.png" alt="Product 7" /></td>
<td>05:52</td>
<td>94</td>
<td>243-245 [32]</td>
</tr>
</tbody>
</table>
was used as a model reaction (see Table 4). In the absence of [Msei]Cl, the products were obtained in low yield and long reaction times 860 minute. Next, was carried out under the previously mentioned conditions using different quantities of catalyst at 90 °C.
Table 4. Optimization of temperature for 1, 4-dihydropyridine synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>120</td>
<td>70</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>100</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>90</td>
<td>30</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>100</td>
<td>35</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>110</td>
<td>33</td>
<td>92</td>
</tr>
</tbody>
</table>

Table 5. Optimization of catalyst for 1, 4-dihydropyridine synthesis

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (%)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>860</td>
<td>89</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>0.05</td>
<td>125</td>
<td>73</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>0.1</td>
<td>65</td>
<td>80</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>120</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>1.0</td>
<td>30</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>30</td>
<td>90</td>
<td>90</td>
</tr>
</tbody>
</table>

Table 6. [MSEI]Cl Catalyzed the synthesis of 1,4-dihydropyridine derivatives via Hantzsch reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Time (h:min)</th>
<th>Yield (%)</th>
<th>M.P. (°C) [Lit.]</th>
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</thead>
<tbody>
<tr>
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<td><img src="image.png" alt="Image" /></td>
<td>00:55</td>
<td>90</td>
<td>115-117 [34]</td>
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</tbody>
</table>
Synthesis of dihydropyridines and quinoxaline derivatives using...

2.  
\[
\begin{align*}
\text{MeOC} & \quad \text{COMe} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
2b

01:45  95  179-182 [35]

3.  
\[
\begin{align*}
\text{MeOC} & \quad \text{COMe} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
3c

00:55  89  196-197 [35]

4.  
\[
\begin{align*}
\text{MeOC} & \quad \text{COMe} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
4f

03:00  89  220-222 [35]

5.  
\[
\begin{align*}
\text{MeOC} & \quad \text{COMe} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
5i

01:40  99  151-153 [34]

6.  
\[
\begin{align*}
\text{MeOC} & \quad \text{COMe} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
6j

01:15  83  193-194 [35]

7.  
\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{CO}_2\text{Et} \\
\text{Me} & \quad \text{Me} \\
\text{N} & \quad \text{H} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]
7

01:45  88  152-154 [35]
8
\[ \text{EtO}_2\text{C} \text{Me} \text{Et}_2\text{CO}_2\text{Et} \]
\[ \text{Me} \text{Me} \text{N} \text{H} \text{CO}_2\text{Et}_2\text{Et} \]
\[ \text{7p} \]
01:30 92 161-163 [36]

9
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\[ \text{Me} \text{Me} \text{N} \text{H} \text{CO}_2\text{Et}_2\text{Et} \]
\[ \text{7q} \]
01:25 95 130-131 [37]

10
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\[ \text{Me} \text{Me} \text{N} \text{Br} \text{H} \text{CO}_2\text{Et}_2\text{Et} \]
\[ \text{7s} \]
02:15 93 139-141 [37]

11
\[ \text{EtO}_2\text{C} \text{Me} \text{Et}_2\text{CO}_2\text{Et} \]
\[ \text{Me} \text{Me} \text{N} \text{Br} \text{H} \text{CO}_2\text{Et}_2\text{Et} \]
\[ \text{7t} \]
02:35 90 144-146 [37]

12
\[ \text{EtO}_2\text{C} \text{Me} \text{Et}_2\text{CO}_2\text{Et} \]
\[ \text{Me} \text{Me} \text{N} \text{H} \text{CO}_2\text{Et}_2\text{Et} \]
\[ \text{7u} \]
02:00 92 156-158 [37]
Synthesis of dihydropyridines and quinoxaline derivatives using... 13

![Chemical structure of compounds 7v and 7w]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>Octanol-water partition coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>7v</td>
<td>02:50</td>
<td>97</td>
<td>146-148 [37]</td>
</tr>
<tr>
<td>7w</td>
<td>01:45</td>
<td>95</td>
<td>230-231 [37]</td>
</tr>
</tbody>
</table>

*a Yield of isolated products

Figure 3. Reusability of catalyst

Acknowledgments

We gratefully acknowledge funding from the National Elites Foundation of Iran for this research.

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