4.1.1 Introduction

Quinoxaline and its derivatives have been received much attention because of their wide range of pharmacological and therapeutic properties.\(^1\)\(^-\)\(^5\) They have also been found application in organic semiconductors,\(^6\) dyes,\(^7\) electroluminescent materials,\(^1\) cavitands,\(^8\) building blocks for the synthesis of anion receptors\(^9\) and DNA cleaving agents.\(^9\) Quinoxaline ring moiety constitute part of the various antibiotics such as Echinomycin, Levomycin and Actinoleutin\(^10,\)\(^11\) that are known to inhibit growth of Gram positive bacteria and are active against various transplantable tumors.\(^12\)

The *ideal synthesis* should lead to the desired product in as few steps as possible, in good yield and by using environmentally compatible reagents (*Figure 1*).\(^13\) The synthetic variables that have to be optimized are time, cost, yield and simplicity of procedure, safety and environmental acceptability.

![Figure 1. The chemical ideal synthesis.](image)

In multistep synthesis the temporal and preparative complexity increases in proportion to the number of steps in a first approximation. It is reflected in many isolation and purification procedures such as crystallization, extraction, distillation or chromatography. Besides the multistep, sequential synthesis of a target molecule, the desired product can also be obtained in one-step reactions of three or more starting compounds. In the past decades, the development of effective
multicomponent based synthesis has played an important role to achieve high atom economy and sustainable chemistry.

Large and important classes of MCRs are the isocyanide multicomponent reactions (ISMCRs). Isocyanides, formerly known as isonitriles are compounds with extraordinary functional group. Isocyanides are the only class of stable organic compounds with a divalent carbon. The chemistry of isocyanide began in 1859 (When Lieke had prepared allylisocyanide from allyl iodide and silvercyanide). The classical synthesis of isocyanides were developed in 1867 by Gautier. In 1958, Ugi et al. introduced various methods to form isocyanides by dehydrating formylamines. Subsequently, the variable preparative four component one-pot reaction of the isocyanides (U-4CR) was introduced and these one-pot reactions required generally much less work and form higher yields of product than the usual multistep synthesis.

In 1950 Rothe et al. discovered the first naturally occurring isocyanide in Penicillium notatum Westling. This was latter used as the antibiotic xanthocillin and in 1956 the 0,0'-dimethylxanthocillin was prepared from the diformylamine in the presence of phenylsulphonylchloride and pyridine.

In 1990 a review of isocyanide chemistry appeared which marked the new era of isocyanide chemistry. A new period of isocyanide chemistry began when Bossio et al. introduced new syntheses of unusual molecules by new types of isocyanides MCRs and reactivated the interest of many colleagues in this chemistry.

One of the classical themes in the chemistry of isocyanides is heterocycles synthesis. The name of Schollkopf and van Leusen stand for many pioneering developments in this field. Among others imidazoline, oxazoline, thiazoline, pyrrole, imidazole, oxazole and thiazole synthesis.

Shaabani et al. have been developed a novel isocyanide based three component synthesis of 3,4-dihydroquinoxalin-2-amines. In this protocol 3,4-dihydroquinoxalin-2-amines synthesized by condensation of o-phenylenediamines ketones and isocyanides in the presence of p-toluenesulphonic acid (Scheme 1).
Shaabani et al. J. Comb. Chem. 2008, 10, 323

Scheme 1. Reaction conditions: (i) p-TsOH, EtOH, rt, 2-5 h, 75-95%.

Jian et al.30 reported CAN catalyzed synthesis of 3,4- dihydroquinoxalin-2-amine derivatives based on isocyanide starting from readily available o-phenylenediamines, ketones and isocyanides (Scheme 2).


Scheme 2. Reaction conditions: (i) CAN (5 mol%), EtOH, rt, 62-95%.

Recently, Lee et al.31 have been described synthesis of 3,4- dihydroquinoxalin-2-amine derivatives based on isocyanide starting from readily available o-phenylenediamines, ketones and isocyanides in the presence of EDTA as a catalyst (Scheme 3).

Lee et al. Tetrahedron Lett. 2010, 66, 8938

Scheme 3. Reaction conditions: (i) EDTA (20 mol%), H2O, 80 °C, 1-12 h, 20-95%.

The great potential of room temperature ionic liquids as environmentally benign media for catalytic processes, much attention have currently been focused on organic reactions catalyzed by ionic liquids, several organic reactions catalyzed by ionic liquids have been reported with high performance. Numerous literature material is available which shows the importance of ILs e.g. a number of excellent books32 and recent general reviews33 as well as those covering specific topics such as catalysis (including biocatalysis) in ionic liquids,34 synthesis of organometallic complexes in ionic liquids,35 biphasic systems and supported ionic liquids.36

155
ionic liquids with fluorine containing anions,\textsuperscript{38} analytical applications of ionic liquids,\textsuperscript{39} chiral ionic liquids,\textsuperscript{40} electrochemistry in ionic liquids\textsuperscript{41} and physical properties of ionic liquids are available.\textsuperscript{42} In addition, a number of special issues\textsuperscript{43,44} have appeared covering a range of topics including ionic liquids as green solvents,\textsuperscript{45} physical and thermodynamic data\textsuperscript{46} and organometallic chemistry in ionic liquids.\textsuperscript{47}
4.1.2 Present work

In our present work, we have developed a one-pot three-component condensation of o-phenylenediamines 1, ketones 2 and isocyanides 3 at ambient conditions using “green” room temperature imidazolium ionic liquid, [Hbim]BF$_4$ as reaction media as well as promoter in the absence of any added catalyst respectively to affords the corresponding 3,4-dihydroquinoxalin-2-amine derivatives in excellent yields (Scheme 4). We have compared the reaction times and yields for the p-TSA$^{29}$ catalyzed synthesis of 3,4-dihydroquinoxalin-2-amines. It is noteworthy that the products, 3,4-dihydroquinoxalin-2-amines 4, were isolated in excellent yields in short reaction times employing simple workup procedures and the non-volatile IL could be efficiently recovered and reused and the process does not need any additional acidic catalyst.

![Scheme 4. Ionic liquid: as efficient, recyclable and green catalyst for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives.](image)
4.1.3 Results and discussion

In the beginning, a model reaction was carried out by condensing o-phenylenediamine 1a (1 mmol), cyclohexanone 2a (1 mmol) and tert-butylisocyanide 3a (1 mmol) in the IL, 1-n-butylimidazolium tetrafluoroborate ([Hbim]BF$_4$), when mixture of o-phenylenediamine, cyclohexanone, tert-butylisocyanide and [Hbim]BF$_4$ was stirred at room temperature, it afforded the desired product N-tert-butyl-1’H-spirocyclohexane-1,2’-quinoxalin]-3’-amine 4a in 92% yield (Scheme 5).

![Scheme 5. Reaction conditions: (i) [Hbim]BF$_4$ (2 mL), rt, 2.5 h, 92%.](image)

At the next stage, we examine the model reaction (Scheme 5) from the viewpoint of time, yield and recyclability of catalyst. We found that [Hbim]BF$_4$ is an effective catalyst for this reaction in terms of yield and recyclability in compared with other catalysts and recently reported methods (Table 1).

To illustrate the need of [Hbim]BF$_4$, reaction of o-phenylenediamine 1a, cyclohexanone 2a and tert-butylisocyanide 3a was studied in the absence of [Hbim]BF$_4$. The yield of product was only 12% (Entry 1, Table 1). Hence, [Hbim]BF$_4$ is an important component of the reaction.

One of the advantages of ILs is their ability to function as a recyclable reaction media. We were able to separate IL from the reaction media easily and reused it for subsequent reactions (Entry 8, Table 1). Furthermore, the stability of the IL after recycle batches was investigated by recording the $^{19}$F NMR spectra of the IL recovered after the reaction (Figure 2) as such before the reaction (Figure 3). The $^{19}$F NMR spectra of the IL were recorded neat with an external lock of D$_2$O and using trifluoroacetic acid as an internal standard. The $^{19}$F NMR spectra were identical and no changes were observed indicating the stability of the IL under these conditions (Figure 2).
In order to investigate the scope and generality of this process, a series of aryl-1,2-diamines, acyclic/cyclic ketones and isocyanides were subjected to condensation using the IL, [Hbim]BF$_4$ as reaction media as well as promoter at room temperature (Table 2). All products were characterized by IR, $^1$H NMR, $^{13}$C NMR, EA and mass spectroscopy.$^{29-31}$

Table 1. Model reaction in the presence of different catalysts

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Conditions</th>
<th>Time (h)</th>
<th>Yield$^a$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>rt</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>$p$-TsOH</td>
<td>CH$_3$OH/rt</td>
<td>4</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>CAN</td>
<td>CH$_3$OH/rt</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>EDTA</td>
<td>H$_2$O/80 °C</td>
<td>1</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>FeCl$_3$</td>
<td>CH$_3$OH/rt</td>
<td>7</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>ZrOCl$_2$</td>
<td>CH$_3$OH/rt</td>
<td>8</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>InCl$_3$</td>
<td>CH$_3$OH/rt</td>
<td>7</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>[Hbim]BF$_4$</td>
<td>rt</td>
<td>2.5</td>
<td>92 (92, 90, 90)$^b$</td>
</tr>
</tbody>
</table>

$a$ Yield of pure, isolated product.

$b$ The same ionic liquid was used for each of the three runs.

Figure 2. $^{19}$F spectrum of [Hbim]BF$_4$ recovered after reaction.
Ionic liquid: as efficient, recyclable and green catalyst for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives

Figure 3. $^{19}$F spectrum of [Hbim]BF$_4$ before reaction.

Table 2. Synthesis of 3,4-dihydroquinoxalin-2-amine derivatives (4a-4l)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine 1</th>
<th>Ketone 2</th>
<th>Isocyanide 3</th>
<th>Product 4</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Amine 1" /></td>
<td><img src="image2" alt="Ketone 2" /></td>
<td><img src="image3" alt="Isocyanide 3" /></td>
<td><img src="image4" alt="Product 4" /></td>
<td>2.5</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td><img src="image5" alt="Amine 2" /></td>
<td><img src="image6" alt="Ketone 2" /></td>
<td><img src="image7" alt="Isocyanide 3" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>2.0</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td><img src="image9" alt="Amine 3" /></td>
<td><img src="image10" alt="Ketone 2" /></td>
<td><img src="image11" alt="Isocyanide 3" /></td>
<td><img src="image12" alt="Product 4" /></td>
<td>2.5</td>
<td>95*</td>
</tr>
<tr>
<td>4</td>
<td><img src="image13" alt="Amine 4" /></td>
<td><img src="image14" alt="Ketone 2" /></td>
<td><img src="image15" alt="Isocyanide 3" /></td>
<td><img src="image16" alt="Product 4" /></td>
<td>1.5</td>
<td>93</td>
</tr>
</tbody>
</table>

Continued on next page…
The plausible mechanism for the formation of products 4a-4l is shown in **Scheme 6**. The role of the IL may be postulated in terms of the Brønsted acidity of the –NH proton of the imidazolium cation, leading its interaction through hydrogen bonding with the carbonyl oxygen atom of ketone. This increases the electrophilicity of carbonyl carbon, there by facilitating the attack of nucleophilic
Ionic liquid: as efficient, recyclable and green catalyst for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives

nitrogen and facilitates the formation of iminium cation A. Then nucleophilic addition of isocyanide 3 followed by an intramolecular nucleophilic attack by the NH$_2$ group on the B could result in the generation of C, which then finally should be isomerized to final product 4.

Scheme 6. Suggested mechanism for the preparation of 3,4-dihydroquinoxalin-2-amine derivatives (4a-4l).
4.1.4 Conclusions

In conclusion, we have developed a novel one-pot synthesis of 3,4-dihydroquinoxalin-2-amine derivatives in excellent isolated yields at ambient conditions using ionic liquid [Hbim]BF$_4$ as a reaction medium cum promoter. For this process, there was no need for any additional catalyst, which is generally required in the methodologies reported so far. The ambient reaction conditions, absence of a catalyst and recyclability of the non-volatile ILs makes this an environment friendly methodology amenable for scale up.
4.1.5 Experimental

4.1.5.1 General procedure for the synthesis of 3,4-dihydroquinoxalin-2-amines

A mixture of aryl-1,2-diamine 1 (1 mmol), ketone 2 (1 mmol) and isocyanide 3 (1 mmol) in 1-n-butylimidazolium tetrafluoroborate (2 mL) was stirred at room temperature for the appropriate time as mentioned in Table 2. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into ice cold water and stirred for 5 min. The solid was filtered and washed with water and dried. The crude product further purified by column chromatography on silica gel (ethyl acetate/n-hexane) to afford the pure product.

The aqueous layer consisting of the IL was subjected to distillation at 80 °C under vacuum for 2.5 h to remove water, leaving behind the IL [Hbim]BF₄ (recovery 96%), which was recycled.

4.1.5.2 Characterization data of representative compounds (4k and 4l)

\[
\text{N-tert-butyl-7'-nitro-1'H-spiro[cyclopentane-1,2'-quinoxalin]-3'-amine (4k)}
\]

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>125-128 °C</td>
</tr>
<tr>
<td>Yield</td>
<td>93%</td>
</tr>
<tr>
<td>IR (KBr, cm⁻¹)</td>
<td>1347, 1535, 1617, 2887, 2915, 3300.</td>
</tr>
<tr>
<td>(^1)H NMR (300 MHz, CDCl₃)</td>
<td>δ = 1.42 (s, 9H), 1.68-1.97 (m, 8H), 3.90 (s, 1H), 4.63 (s, 1H), 6.78 (d, J = 8.6 Hz, 1H), 7.23 (s, 1H), 7.79 (d, J = 8.5 Hz, 1H).</td>
</tr>
<tr>
<td>(^13)C NMR (75 MHz, CDCl₃)</td>
<td>δ = 23.00, 32.00, 46.00, 52.50, 60.00, 76.98, 103.30, 108.50, 110.64, 128.00, 143.48, 146.00, 152.30.</td>
</tr>
<tr>
<td>Elemental analysis</td>
<td>C₁₆H₂₂N₄O₂</td>
</tr>
<tr>
<td></td>
<td>Calcd. C 63.55, H 7.33, N 18.53%.</td>
</tr>
<tr>
<td></td>
<td>Found C 63.19, H 7.40, N 18.18%.</td>
</tr>
</tbody>
</table>
Ionic liquid: as efficient, recyclable and green catalyst for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives

N-cyclohexyl-7'-nitro-1'H-spiro[cyclopentane-1,2'-quinoxalin]-3'-amine (4l)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Solid</td>
</tr>
<tr>
<td>Melting point</td>
<td>210-115 °C</td>
</tr>
<tr>
<td>Yield</td>
<td>92%</td>
</tr>
<tr>
<td>IR (KBr, cm(^{-1}))</td>
<td>1352, 1542, 1609, 2868, 2923, 3305.</td>
</tr>
<tr>
<td>(^1)H NMR (300 MHz, CDCl(_3))</td>
<td>δ = 1.13-1.29 (m, 8H), 1.53-1.81 (m, 10H), 2.50 (s, 1H), 3.66-3.73 (m, 1H), 5.63 (s, 1H), 6.7 (d, (J = 8.5) Hz, 1H), 7.23 (s 1H), 7.50 (d, (J = 8.3) Hz, 1H).</td>
</tr>
<tr>
<td>(^{13})C NMR (75 MHz, CDCl(_3))</td>
<td>δ = 23.79, 24.30, 25.50, 31.69, 31.86, 38.59, 38.88, 39.15, 39.43, 39.70, 39.97, 40.26, 48.92, 50.23, 60.65, 108.98, 110.06, 110.45, 126.00, 144.01, 147.00, 150.09.</td>
</tr>
<tr>
<td>Elemental analysis</td>
<td>C(<em>{18})H(</em>{24})N(_4)O(_2)</td>
</tr>
<tr>
<td></td>
<td>Calcd. C 65.83, H 7.37, N 17.06%</td>
</tr>
<tr>
<td></td>
<td>Found C 65.49, H 7.40, N 17.23%</td>
</tr>
</tbody>
</table>
Figure 4. $^1$H NMR spectra of $N$-tert-butyl-7'-nitro-1'H-spiro[cyclopentane-1,2'-quinoxalin]-3'-amine (4k).
Figure 5. $^{13}$C NMR spectra of $N$-tert-butyl-7'-nitro-1'H-spiro[cyclopentane-1,2'-quinoxalin]-3'-amine (4k).
Figure 6. $^1$H NMR spectra of $N$-cyclohexyl-7'-nitro-1'H-spiro[cyclopentane-1,2'-quinoxalin]-3'-amine (41).
Figure 7. $^{13}$C NMR spectra of $N$-cyclohexyl-7'-nitro-1'H-spiro[cyclopentane-1,2'-quinoxalin]-3'-amine (4l).
4.1.6 References

5. (a) Badran, M. M.; Botros, S.; El-Gendy, A. A.; Abdou, N. A.; El-Assi, H.;
   Kushner, J.; Paluch, J.; White, K.; Edelstein, M.; Palomino, E.; Corbett, T. H.;
   Kushner, J.; White, K.; Bourugeois, N. M.; Crantz, B.; Palomino, E.; Corbett, T. H.;
14. *Carbon monoxide, which is isolobal with isocyanides, also contains a formally
divalent carbon. The carbon atom in carbenes is also divalent. However, most
carbenes are extremely short-lived compounds.*
Ionic liquid: as efficient, recyclable and green catalyst for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives


Ionic liquid: as efficient, recyclable and green catalyst for the synthesis of 3,4-dihydroquinoxalin-2-amine derivatives