Synthesis Of Thiophene Isoxazolines In Ionic Liquid
[Bmim][BF₄]

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Abstract: [BMIM][BF₄] was used as an efficient ionic liquid for the synthesis of thiophene isoxazolines through the cyclocondensation of α,β-unsaturated thiophene ketones with hydroxylamine hydrochloride in ionic liquid/water/acetic acid biphasic system at 80°C temperature. The methodology puts forward several rewards such as exceptional yields, easy work-up and mild conditions.

Keywords: Thiophene isoxazolines, [BMIM][BF₄], biphasic system, α,β-unsaturated thiophene ketones

I. Introduction

Isoxazoles are well known five membered heterocyclic compounds, receiving considerable importance both in advance organic material¹ and biological applications in medicinal² and material science³. Isoxazole derivatives are a promising structural moiety for drug designing, which are reported to possess antibacterial, anticonvulsant, antipsychotic, anti-inflammatory, antitumor, analgesic, insecticidal, antioxidant, anti depressant and anti microbial activities.⁴⁻¹²

The most representative synthetic strategies for the construction of isoxazoles nucleus including (i) reaction of hydroxylamine with 1,3dicarbonyl compounds¹³ (ii) [3 + 2] cycloaddition of alkynes/alkenes and nitrile oxides¹⁴ (iii) intermolecular cyclization of oximes with C=C double/triple bonds¹⁵. However; these synthetic strategies generally require harsh reaction condition including strong bases, strong mineral acids, or high temperatures or provide modest regioselectivity and neither economic nor eco-friendly.

Ionic liquids (ILs) have been extensively promoted as well-designed replacements of volatile organic solvents; however limiting their use to conventional solvents restrict their potential. The impact of Ionic liquids in chemistry is associated to their exceptional properties as non-molecular solvents: a negligible vapor pressure associated to a high thermal stability. The emergent significance of ionic liquids (ILs) has resulted in an exponentially increasing invention of synthetic and analytical applications.

Ionic liquids (ILs) have been accepted as a new green chemical revolution which excited both the academia and the chemical industries. This new chemical group can reduce the use of hazardous and polluting organic solvents due to their unique characteristics as well as taking part in various new syntheses. The terms room temperature ionic liquid (RTIL), nonaqueous ionic liquid, molten salt, liquid organic salt and fused salt have all been used to describe these salts in the liquid phase¹⁶. ILs are known as salts that are liquid at room temperature in contrast to high-temperature molten salts. They have a unique array of physico-chemical properties which make them suitable in numerous applications in which conventional organic solvents are not sufficiently effective or not applicable. Researchers have discovered that ILs are more than just green solvents and they have found several applications such as replacing them with volatile organic solvents, making new materials, conducting heat effectively, supporting enzyme-catalyzed reactions, hosting a variety of catalysts, purification of gases, homogenous and heterogeneous catalysis, biological reactions media and removal of metal ions¹⁷. [bmim][BF₄], hydrophilic ionic liquid is well known for its capability in various catalytic applications. Particularly, hydrophilic media possessing tetra fluoroborate [BF₄] anions have a multitude of usages in different biochemical and chemical reactions.¹⁸ Chaban and Prezhdo¹⁹ et al investigated the volatility of the imidazolium-based RTILs/ACN mixtures on the basis of precision simulations of liquid/vapor interfaces over a wide composition range and observed noticeable decrease in the volatility of ACN, and hence, reduced hazards.

Kumar V. Srinivasan et al ²⁰ described an improved and rapid one-pot synthesis of 2,4,5-triaryl imidazoles in a room temperature ionic liquid, which does not need any added catalyst.

We embarked on the synthesis of thiophene isoxazoles via the cyclocondensation of α,β-unsaturated thiophene carbonyl compounds with hydroxylamine hydrochloride. A number of solvent systems have been investigated to set the reaction conditions of these compounds. In the said synthesis, we have chosen 3-(thiophen-2-yl)-1-p-tolylprop-2-en-1-one (1a), as a starting material. We have made efforts in making a library
of isoxazolines using different concentration of [BMIM][BF_4], in biphasic solvent system and our observations prompted us to explore the potential use of [BMIM][BF_4], /water solvent system.

II. Materials and Methods

Material and Methods:

Chemicals used were of analytical reagent grade. All the solvents were dried and freshly distilled prior to use. Thin layer chromatographic analysis was performed on precoated silica gel plates (Alugram® SIL G/UV 254, 0.2mm thickness). Melting points were recorded by open capillary method and are uncorrected. Infrared (IR) spectra were recorded on FT-IR Spectrometer. Proton magnetic resonance (¹H-NMR) spectral data were recorded on a Bruker 400MHz spectrometer in DMSO-d₆ solution. The chemical shifts are reported in δ (ppm) relative to internal standard tetramethylsilane (TMS) and coupling constant J is given in Hz. Mass spectrometry was conducted using WATERS Q-TOF MICROMASS.

General Procedure:

A conventional method: A mixture of differently substituted chalcones (1a-e), 3-(thiophen-2-yl)-1-(p-substituted)prop-2-en-1-ones (10mmol) were dissolved in 20 ml of ethanol along with hydroxylamine hydrochloride (10mmol) in acetic acid were refluxed for 6 hours. The reaction mixture was then poured into ice cold water with stirring and left over night at room temperature. The progress of the reaction was monitored by TLC. The precipitate obtained was filtered, washed and dried. The products 3-cyclopropyl-5-(p-substituted)-4,5-dihydroisoxazole (3a-e) were recrystallized using ethanol. Similar procedure was followed for various chalcones.

Preparation of 3-(thiophen-2-yl)-5-(p-tolyl)-4,5-dihydroisoxazole: 3a: C₆H₁₅NOS

A mixture of (E)-1-cyclopropyl-3-(p-tolyl) prop-2-en-1-one, (10mmol) 1a and hydroxylamine hydrochloride (10mmol) was introduced into a vigorously stirred [bmim][BF₄] (10 mmol) and water (10 mmol)/acetic acid (10mmol) biphasic solvent system at room temperature for 2 h. The temperature of the reaction mixture was maintained at 80°C. TLC was not feasible as the reaction mixture contained ionic liquid. After completion, the reaction was quenched with water (5mL) and the product was separated out by extracted with diethyl ether (10 mLx3). The ionic liquid [bmim][BF₄] layer was dried over the anhydrous CaCl₂ in a desiccator and later on it was oven dried with prior to use. The organic layer was dried over anhydrous Na₂SO₄ and then concentrated in vacuo to afford pure 3-cyclopropyl-5-(p-tolyl)-4,5-dihydroisoxazole 3a. The product was recrystallized from ethanol. The oven dried ionic liquid has been reused for next reaction without noticeable effect on the reaction. C₆H₁₅NOS: Yield:95% ,Melting Point:123°C, IR (KBr, λ_max/cm⁻¹): 1657(C=N),1804 (N-O), 1040(Ar-H), 1097 (C-O), 2466(CHO) / DMSO/CHCl₃ cm⁻¹, ¹H NMR(400 MHz, CDCl₃/DMSO-d₆): δ(ppm) 2.35 (s, 3H, Ar-CH₃), 3.20-3.86, 8.36Hz, H₀; 1.87-1.95 (dd, 1H, J=1.72, H₁, 7.00-7.02 (dd, 1H, J=3.56-3.6, H₂); 7.13-7.28 (m, 3H, Thiophene ring); 7.32-7.57 (m, 4H, phenyl ring). ¹³C NMR (200MHz CDCl₃): δ 21.48, 42.84, 83.08, 124.21, 125.31, 127.94, 129.99, 137.02, 139.00, 161.99; Mass Spectrum: m/z 243 M⁺, 228, 160, 152, 91, 83 ; CHN calculated: C 69.11, H 5.39, N 5.76; CHN found: C 69.09, H 5.37, N 5.74

Preparation of 5-(4-bromophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole: 3b: C₆H₈BrNOS

Yield: 92%, Melting Point: 117°C, IR (KBr, λ_max/cm⁻¹): 1650(C=N),1798 (N-O), 1040(Ar-H), 1068 (C-O), 2467(CHO) / DMSO/CHCl₃ cm⁻¹, ¹H NMR(400 MHz, CDCl₃/DMSO-d₆): δ(ppm) 2.99-3.07 (dd, 1H, J=8.36,11.48Hz, H₁a); 1.21-2.20(dd,1H, J=8.28,11.36Hz, H₁b); 6.80-6.99 (m, 1H, H₂); 7.03-7.22(m,3H, Thiophene ring); 7.31-7.71 (m, 4H, phenyl ring). ¹³C NMR (200MHz CDCl₃): δ 42.28, 83.48, 121.83, 124.16, 125.47, 127.33, 131.89,141.65, 163.05, Mass Spectrum: m/z 308 M⁺; CHN calculated: C 50.66, H 3.27, N 4.54, CHN found: C 50.64, H 3.25, N 4.52

Preparation of 5-(4-chlorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole: 3c: C₆H₈ClNOS

Yield: 95%, Melting Point: 127°C, IR (KBr, λ_max/cm⁻¹): 1652(C=N), 1797 (N-O), 1045(Ar-H), 1095(C-O), 2468(CHO) / DMSO/CHCl₃ cm⁻¹, ¹H NMR(400 MHz, CDCl₃/DMSO-d₆): δ(ppm) 2.74-2.81 (dd, 1H, J=8.28,11.6 Hz,H₁); 1.87-1.95 (dd, 1H, J=8.28,11.6Hz,H₂); 6.84-6.91 (m, 1H, H₂); 6.97-7.13 (m, 3H, Thiophene ring); 7.16-7.42 (m, 4H, phenyl ring). ¹³C NMR (200MHz CDCl₃): δ 42.99, 83.34, 124.21, 124.99, 126.85, 127.91, 129.42, 134.00, 140.00, 164.11, Mass Spectrum: m/z 263 M⁺; CHN calculated: C 59.20, H 3.82, N 5.31, CHN found: C 59.18, H 3.80, N 5.29

Preparation of 5-(4-fluorophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole: 3d: C₆H₈FNO

Yield: 95%, Melting Point: 161°C, IR (KBr, δ_max/cm⁻¹): 1657(C=N), 1798(N-O), 3051(Ar-H), 1094(C-O), 2441(CHO) / DMSO/CHCl₃ cm⁻¹, ¹H NMR(400 MHz, CDCl₃/DMSO-d₆): δ(ppm) 3.90-3.97 (dd, 1H, J=8.16,11.56Hz,H₁);
Preparation of 5-(4-nitrophenyl)-3-(thiophen-2-yl)-4,5-dihydroisoxazole: 3e: C13H10N3O5S
Yield: 90%. Melting Point: 118°C, IR (KBr, λmax/cm⁻¹): 1674(C=O), 1109 (C-O), 2450(CH₂ iso)cm⁻¹, 1H NMR(400 MHz, CDCl₃) δ(ppm): 2.49-2.56 (dd, 1H, J=8.16, 11.32Hz,H₂:2): 2.03-2.10(dd, 1H, J=8.2, 11.24Hz, H₃); 7.05-7.09 (d, 1H, J= 12.44Hz, H₄); 7.3-7.9 (m, 3H, Thiophene ring); 7.82-8.29 (m, 4H, phenyl ring). ¹³C NMR (200 MHz, CDCl₃): δ: 115.55, 123.0, 127.99, 129.50, 146.55, 148.22, 164.21, Mass Spectrum: m/z 275M⁺, CHN calculated: C 63.14, H 4.08, N 5.66, CHN found: C 63.12, H 4.06, N 5.64

Results and Discussion

III. Results and Discussion

Primarily 1a was desired as a model substrate. We have optimized the reaction conditions in a variety of solvents at diverse time intervals. 1a was subjected to reaction with hydroxylamine hydrochloride to afford 3-(thiophen-2-yl)-5-p-tolyl-4,5-dihydroisoxazole (3a). (Scheme 1, Table 1)

**Table 1: Optimization of the reaction conditions for the synthesis of 3-(thiophen-2-yl)-5-p-tolyl-4,5-dihydroisoxazole (3a)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent (S₁)</th>
<th>Temp</th>
<th>% of isolated yield at time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH (S₁)</td>
<td>reflux</td>
<td>1 h      2 h    3 h    4 h    5 h    6 h</td>
</tr>
<tr>
<td>2</td>
<td>AcOH/water (S₂)</td>
<td>reflux</td>
<td>25 40 50 62 70 80</td>
</tr>
<tr>
<td>3</td>
<td>DMF (S₃)</td>
<td>reflux</td>
<td>15 25 35 40 45 45</td>
</tr>
<tr>
<td>4</td>
<td>DMF/water (S₄)</td>
<td>reflux</td>
<td>11 20 30 35 35 35</td>
</tr>
<tr>
<td>5</td>
<td>[bmim][BF₄] (S₅)</td>
<td>reflux</td>
<td>80 30 50 60 70 75 90</td>
</tr>
<tr>
<td>6</td>
<td>[bmim][BF₄]/water (S₆)</td>
<td>80°</td>
<td>20 40 50 65 80 90</td>
</tr>
<tr>
<td>7</td>
<td>[bmim][BF₄]/AcOH (S₇)</td>
<td>80°</td>
<td>50 60 95 95 95 95</td>
</tr>
</tbody>
</table>

We have executed the optimization model, which was earlier reported in the synthesis of pyrimidine-isoxazolines in our laboratory by K. Lanjewar et al. The reaction of 1a and hydroxylamine hydrochloride in ethanol with S₁ at reflux was complete within 6 h, giving 3a in 80% isolated yield. The progress of the reactions was checked in every one hour ranging from 1 to 6 h. TLC was not feasible as the reaction mixture contained ionic liquid. The reaction time was vigilantly controlled to avoid the breakup of products and formation of byproducts. It was examined that the reaction did not proceed well by addition of a small amount of water, the yield was reduced to 72%. The efficacy of the reaction was noticeably influenced by the nature of solvents, when we increased the hydrophilicity of the reaction mixture S₂ which reduced the outcome of the product. Additionally, reaction in DMF S₃ and DMF/water S₄ at reflux for 6 h reduced the yield drastically. In S₅ and S₆, the yield obtained was highly reduced, this suggested that the reaction rate may enhanced in proptoic solvents. Furthermore, the reactions in ionic liquid [bmim][BF₄] S₇, [bmim][BF₄]/water S₈, [bmim][PF₆]wares under various time intervals. The reaction takes place at 70°C in ionic liquids S₇-S₈. The use of [bmim][BF₄]/water/AcOH S₉ demonstrated in much elevated reaction rates than those performed with S₇-S₈ solvent systems. Remarkably, it was observed that the reaction of 3a proceeds better in all ionic liquids as compared to common organic solvents S₁-S₆. Reaction in S₇ conclusively proved the utmost level of efficacy and atom economy when compared to solvents S₁-S₆, on top of use of AcOH/water as the secondary solvents in S₇ illustrated the enhance productivity of the reaction. As a result, the reaction exercised well in acidic and protic solvents, additionally the use of ionic liquid augmented the outcome of the reaction. Table 1. summarizes our results, clearly showing the superiority of ionic liquid/AcOH/water biphasic system over organic solvent-water system.

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The track of the reaction was monitored by TLC but we found that for all early experiments, TLC or HPLC was not an optimal choice for evaluation of yields or for a quantitative in-process assay; the viscous solution containing water and ionic liquids was not conductive to TLC. We resorted to quenching the reaction by adding little amount of water and moreover the product was isolated by extraction with Et\textsubscript{2}O in 4 installments. The ionic liquid was kept over at CaCl\textsubscript{2} in the dessicator and furthermore it was oven dried prior to reuse for next cycle of reaction. The elemental analysis was conducted on isolated compounds and yields were calculated on purified compounds. We searched our investigation to new substrates by varying the substituents on ring B Table 2.

**Table: 2** Characterization and physical conant of 3-(thiophen-2-yl)-5-p-tolyl-4,5-dihydroisoxazole (3a-e)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compd.</th>
<th>R</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>CH\textsubscript{3}</td>
<td>95</td>
<td>123</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>Br</td>
<td>92</td>
<td>117</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>Cl</td>
<td>95</td>
<td>127</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>F</td>
<td>95</td>
<td>161</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>NO\textsubscript{2}</td>
<td>90</td>
<td>118</td>
</tr>
</tbody>
</table>

In Table 2, it was observed that, the incorporation of electron withdrawing substituents at the para position of ring B (Scheme 1) (entries 4b-e) did not exhibited any noticeable change in yield.

To authenticate the effect of concentration of [bmim][BF\textsubscript{4}] on the efficiency of the reaction, we progressively increased the concentration of [bmim][BF\textsubscript{4}]/water from 1 mmol-15 mmol keeping 10 mmol of water and acetic acid constant at 80°C for 3 h. It was observed that as the concentration of [bmim][BF\textsubscript{4}] in water/acetic acid increased, the efficiency of the reaction also increased. On completion, variations in yields were observed, encouraged us to repeat this procedure a number of times; proving that variations in yield were not attributable to work-up losses. Beyond 10 mmol of [bmim][BF\textsubscript{4}] the efficiency was decreased, suggesting that the acidic, polar and hydrophilic environment was conducive to the reaction and excess amount of ionic liquid may interfere the reaction mechanism. Reasonable hydrophobic-hydrophilic solvent interactions have been observed.

A plausible explanation of the reaction mechanism\textsuperscript{21} in ionic liquid-water biphasic system is as follows: 1-butyl-3-methyl imidazolium tetra fluoroborate [bmim][BF\textsubscript{4}] is hydrophilic and miscible with water. One of the reactants 3a is hydrophobic while hydroxylamine hydrochloride is hydrophilic in nature. Non polar end of the ionic liquid may show affinity towards hydrophobic moiety which enhances the rate of the reaction. Different solvation affinities of these two reactants may be resoluted at in situ solvent system. Solvent system provides a platform in which the non polar organic counterpart [bmim]\textsuperscript{+} easily makes 3a soluble; [BF\textsubscript{4}]\textsuperscript{-} water counterpart makes hydroxylamine hydrochloride soluble. The hydroxylamine hydrochloride in aqueous phase is transported to ionic liquid phase where reaction occurs at the end of the ionic liquid may show affinity towards hydrophobic moiety in situ solvent system Figure 1. This suggests that IL biphasic system effectively delivers the products in homogeneous solvent system.

![FIGURE 1 A plausible mechanism in ionic liquid-water biphasic system\textsuperscript{21}](image)

On completion of the reaction, we have optimized the extraction and isolation of the resulting product in ionic phase by using various solvents such as diethyl ether, di-chloromethane, ethyl acetate and n-hexane; the best results were obtained with diethyl ether and this was the solvent of choice for further experiments. Inorganic salts, formed as byproduct dissolved in water. The separated ionic liquid was flushed out with diethylether. The excess amount of water was removed by keeping the ionic liquid in CaCl\textsubscript{2} dessicator. The oven dried ionic liquid was reused for next cycle, without diminution of the yields up to the 10 cycle but there is noticeable drop in yield after 10\textsuperscript{th} cycle suggested that the catalyst may have contaminated or degraded or
exhausted. This procedure has the merit of being environmentally benevolent possessing effortless operation, expedient work-up, reduced time and proceeding in good yields.

For elucidation of the structure 3a-e, in Table 2 the IR spectra showed a peak at 1657 cm⁻¹ due to C=O stretching of pyrazoline ring, peak at 1097 cm⁻¹ because of C-O stretching of isoxazoline ring respectively. Furthermore, ¹H NMR spectra of compounds 3a-e showed a singlet of 3 protons at 2.45 due to Ar-CH₃ protons. In isoxazoline ring, there are three types of hydrogens, one attached to C₆ carbon ie H₂ and (H₁ and H₂) two at C₄ carbon of isoxazoline ring. The two hydrogens attached to C₃ position are juxtaposed cis and trans H₁ and H₂. The ¹H NMR spectra showed for H₃, dd at δ 7.00-7.02 due to H₂ proton and H₁, H₂ coupled with both H₁ and H₂ to give a dd at δ 2.50-2.51. The dd at δ 2.35-2.40 due to H₁ and H₂ proton, confirmed the structure of isoxazoline ring. The ¹³C NMR spectra also support the structure; signals at δ 21, 42, 83, 124 and 161 indicate the presence of isoxazoline ring. Compounds 3a-e gave satisfactory elemental analysis; mass spectra also lend credence to the structures.

Stereochemical aspects: To reveal the steriospecificity of the compounds, they were tested for specific rotation. It was observed that all the compounds were found to be optically inactive with no specific rotation. Thus we have not attempted to resolve the chiral centres: this was referred to later date pending obtainment of the results.

The purity of the compounds was monitored by TLC and the structures of all the derivatives 3a-e were supported by spectral data. The IR, ¹H NMR, ¹³C NMR, Mass spectra and elemental analytical data are in agreement with the proposed structures. Physical and analytical data of the synthesized compounds are reported in Table 2.

IV. Conclusion

In conclusion, the ionic liquid [bmim][BF₄]/AcOH/water proved to be an remarkably proficient solvent system for the synthesis of isoxazolines at ambient temperature within 3 h. The reaction is influenced by [bmim][BF₄]/water/AcOH biphasic system which stabilizes the hydrophobic reactant, and water/AcOH stabilizes hydroxylamine hydrochloride: the reaction presumably occurs at homogeneous phase. The study was finally completed by performing their in-vitro anti-fungal activities of all compounds.

V. Acknowledgements

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References


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