

# Three-component coupling reactions in ionic liquids: One-pot synthesis of isoxazolidines<sup>☆</sup>

J.S. Yadav<sup>\*</sup>, B.V.S. Reddy, P. Sreedhar, Ch.V.S.R. Murthy,  
G. Mahesh, G. Kondaji, K. Nagaiah

*Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500007, India*

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## Abstract

1-Butyl-3-methylimidazolium based ionic liquids are found to accelerate significantly the intermolecular 1,3-dipolar cycloaddition of nitrones derived in situ from aldehydes and phenyl hydroxylamine, with electron deficient olefins to afford enhanced rates and improved yields of isoxazolidines with high regio- and diastereoselectivity.

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## 1. Introduction

Performing three or more component coupling reactions in a single step operation by a catalytic process avoiding stoichiometric amounts of reagents or toxic reagents, expensive separation techniques, large volumes of solvents represents the target improvements of modern organic synthesis. 1,3-Dipolar cycloaddition reactions are among the most important synthetic routes for the construction of five-membered ring carbocycles and heterocyclic systems [1]. Particularly, nitrono cycloadditions are versatile for the construction of five-membered ring heterocycles [2]. Nitrones are effective 1,3-dipoles and they can undergo readily cycloaddition with electron-deficient olefins to produce substituted isoxazolidines. They are versatile intermediates for the synthesis of natural products and many biologically interesting molecules [3]. Owing to the labile nature of the N–O bond under mild reducing conditions, isoxazolidines provide easy access to a variety of fascinating 1,3-difunctional aminoalcohols [4]. Consequently, numerous methods have been reported for the construction of isoxazolidines by inter- and intramolecular nitrono cycloadditions

[5,6]. Despite their potential utility, many of these procedures require high temperature and prolonged reaction times and also suffer from poor regioselectivity and lack of simplicity. In few cases, the yields and selectivities reported are far from satisfactory due to the occurrence of several side reactions [5].

In recent times, ionic liquids have emerged as green solvents with desirable properties such as good solvating ability, wide liquid range, tunable polarity, high thermal stability, negligible vapour pressure and ease of recyclability [7]. They are referred to as ‘designer solvents’ as their properties such as hydrophilicity, hydrophobicity, Lewis acidity, viscosity and density can be altered by the fine-tuning of parameters such as the choice of organic cation, inorganic anion and the length of alkyl chain attached to an organic cation (Fig. 1).

These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering to the needs of any particular process. Since ionic liquids are entirely composed of non-coordinating ions, they can provide an ideal reaction medium for reactions that involve reactive ionic intermediates. Due to the stabilization of charged intermediates by ionic liquids, they can promote unprecedented selectivities and enhanced reaction rates. Consequently, ionic liquids are being used as recyclable solvents for the immobilization of transition metal based catalysts, Lewis acids and enzymes [8]. As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic

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<sup>\*</sup> Corresponding author. Tel.: +91 40 27160123x2659; fax: +91 40 27170512.  
E-mail address: [yadavpub@iict.res.in](mailto:yadavpub@iict.res.in) (J.S. Yadav).

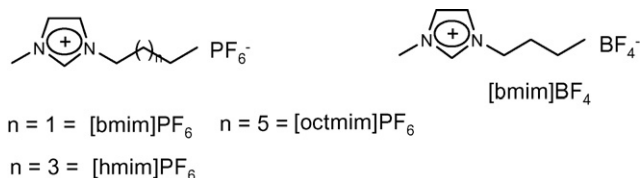


Fig. 1. Chemical structure of ionic liquid.

synthesis [9]. With an ever-increasing quest for exploration of newer reactions in ionic liquids [10].

## 2. Experimental

### 2.1. General methods

Melting points were recorded on a Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. <sup>1</sup>H NMR and <sup>13</sup>C spectra were recorded on Gemini-200 spectrometer and Bruker Avance (300 MHz) in CDCl<sub>3</sub> using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 60–120, mesh silica gel. All solvents were distilled, dried over CaH<sub>2</sub> and stored under nitrogen prior to use. Starting materials and reagents used in the reactions were obtained commercially from Aldrich, Lancaster, Fluka and were used without purification, unless otherwise indicated.

### 2.2. General procedure

Aldehyde (1 mmol), *N*-phenylhydroxyl amine (1 mmol), and acrylonitrile (1.2 mmol) in [bmim]PF<sub>6</sub> or [bmim]BF<sub>4</sub> (2 mL) were stirred at ambient temperature for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated *in vacuo* and the resulting product was directly charged on small silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:9) to afford pure isooxazolidine. The rest of the viscous ionic liquid was further washed with ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs.

#### 2.2.1. Spectral data for selected products

2.2.1.1. 4e. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): ( 1.70 (s, 3H), 2.20–2.28 (dd, *J* = 8.5, 4.2 Hz, 1H), 3.35–3.40 (dd, *J* = 8.4, 4.1 Hz, 1H), 3.6 (s, 3H), 4.75–4.85 (t, *J* = 6.9 Hz, 1H), 6.80–6.95 (d, *J* = 7.2 Hz, 3H), 7.10–7.25 (d, *J* = 7.2–Hz, 2H), 7.32–7.50 (m, 4H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 22.4, 49.6, 52.2, 68.9, 83.3, 114.7, 121.6, 127.9, 128.4, 129.0, 133.3, 139.9, 150.8, 173.2. EIMS: *m/z* (%): 332 (M<sup>+</sup>), 230, 164, 92, 77, 43.

2.2.1.2. 4f. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): ( 2.67–2.70 (ddd, *J* = 13.2, 5.4, 5.2 Hz, 1H), 3.12–3.25 (ddd, *J* = 13.0, 8.7, 2.8 Hz, 1H), 4.42–4.51 (dd, *J* = 8.0, 4.4 Hz, 1H), 4.92–4.51 (dd, *J* = 9.6, 5.3 Hz, 1H), 6.90–7.00 (d, *J* = 7.4 Hz, 2H), 7.00–7.10 (t, *J* = 7.0 Hz, 1H), 7.20–7.30 (t, *J* = 7.0 Hz, 2H), 7.40–7.52 (m, 2H),

7.60 (s, 1H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 44.1, 64.0, 67.6, 115.2, 117.1, 117.9, 124.4, 126.2, 129.0, 131.2, 132.4, 139.6, 148.0. EIMS: *m/z* (%): 319 (M<sup>+</sup>) 210, 176, 108, 91, 51.

2.2.1.3. 4k. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 2.60–2.75 (ddd, *J* = 13.1, 5.3, 5.1 Hz, 1H), 3.10–3.30 (ddd, *J* = 13.0, 8.6, 2.6 Hz, 1H), 4.30–4.45 (t, *J* = 6.5 Hz, 1H), 4.81–5.05 (ddd, *J* = 13.2, 5.1, 5.0 Hz, 1H), 6.0 (s, 2H), 6.80–6.85 (d, *J* = 7.2 Hz, 1H), 6.85–7.15 (m, 5H), 7.20–7.35, (t, *J* = 6.2 Hz, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>): δ 44.5, 64.0, 68.6, 101.0, 107.0, 109.1, 118.0, 118.9, 120.1, 121.0, 123.8, 124.0, 129.3, 133.6, 148.2. EIMS: *m/z* (%): 310 (M<sup>+</sup>).

## 3. Results and discussion

We wish to report the use of ionic liquids as recyclable solvents for 1,3-dipolar cycloaddition reactions of nitrones with electron deficient olefins to produce highly substituted isoxazolidines in a one-pot operation. Accordingly, treatment of C,*N*-diphenyl nitron with acrylonitrile in hydrophobic [bmim]PF<sub>6</sub> ionic liquid for 4.5 h gave the corresponding 5-substituted cycloadduct **4a** in 90% yield with excellent regio- and diastereoselectivity (Scheme 1). Likewise, methyl vinyl ketone also underwent 1,3-dipolar cycloaddition with diphenyl nitron to produce 5-substituted cycloadduct **4b** with the same regio- and distereoselectivity. In both cases, the products were obtained as a single diastereomer, the structure of which was determined by <sup>1</sup>H NMR and NOE experiments and also comparing their NMR spectrum with authentic sample [5,6]. Interestingly, methyl methacrylate also underwent smooth 1,3-dipolar cycloaddition with diphenyl nitron to produce product **4** as a single diastereomer with *trans*-selectivity (entries e, h, and I). However, the cycloaddition of ethyl acrylate with diphenyl nitron gave the corresponding cycloadduct as a mixture of 4 and 5 *m* in a ratio of 9:1 (entry m). These regioisomers could be easily separated by column chromatography on silica gel and also characterized by NMR, IR and mass spectroscopy. The cycloaddition was studied in both hydrophilic and hydrophobic ionic liquids. Interestingly, a similar success was also obtained by using hydrophilic [bmim]BF<sub>4</sub> ionic liquid and the results are presented in the Table 1. There are no considerable differences in reaction rates and yields either with [bmim]PF<sub>6</sub> or with [bmim]BF<sub>4</sub> solvent system. The anticipated 1,3-dipoles exhibit enhanced reactivity in ionic liquid thereby reducing the reaction times and improving the yields significantly. Furthermore, the ionic liquids were found to give better regioselectivity than organic solvents. For instance, treatment of C,*N*-diphenyl nitron with ethyl acrylate in [bmim]BF<sub>4</sub> gave the products **4m** and **5m** in 90% yield with the ratio of 9:1 over 4 h whereas the same reaction in refluxing benzene gave the desired products **4m** and **5m** in 68% with 2:1 ratio after 10 h. In addition, these molten salts could be easily recovered on work-up. Since the products are fairly soluble in ionic media; they could be easily extracted with ether. The rest of the ionic liquid was further washed with ether and recycled in three to four subsequent runs without loss of activity. The products were obtained of the same purity as

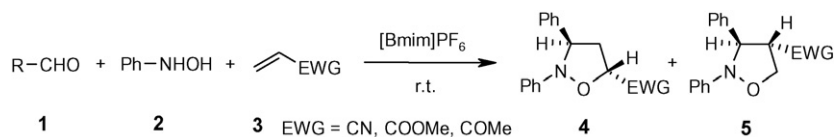
Table 1  
3-Dipolar cycloaddition of nitrones with olefins in ionic liquids

Entry	Nitron (1 + 2)	Alkene (3)	Product <sup>a</sup> (4)	[bmim]BF <sub>4</sub>		[bmim]PF <sub>6</sub>	
				Time (h)	Yield (%) <sup>b</sup>	Time (h)	Yield (%) <sup>b</sup>
a				4.0	92	4.5	90
b				4.5	89	5.0	86
c				4.0	93	4.5	92
d				4.5	87	5.0	85
e				5.0	85	6.0	83
f				5.0	86	5.5	84
g				4.5	87	5.0	82
h				5.0	85	6.0	80
i				4.0	92	4.5	87
j				5.0	86	6.0	80
k				4.5	85	5.0	83
l				5.0	87	6.0	81
m				4.0	90	4.5	86 <sup>c</sup>

<sup>a</sup> All products were characterized by <sup>1</sup>H NMR, IR and mass spectra.

<sup>b</sup> Isolated and unoptimized yields.

<sup>c</sup> Ten percent of other regioisomeric product was observed in <sup>1</sup>H NMR spectrum of crude product.



Scheme 1.

in the first run and no decrease in yields was obtained in runs carried out using recycled ionic liquid. For example, the treatment of C,N-diphenyl nitron with acrylonitrile in hydrophobic [Bmim]PF<sub>6</sub> gave 90%, 89% and 91% yields over three cycles.

The scope and generality of this process is illustrated with respect to various aldehydes and electron-deficient olefins and the results are presented in the Table 1. The use of recyclable ionic liquids as reaction media helps to avoid the use of high

temperature and environmentally unfavorable solvents like benzene thereby making the process economic and environmentally benign.

#### 4. Conclusion

In summary, we have described an efficient protocol for the preparation of isoxazolidines using ionic liquids as reac-

tion media. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green strategy for the preparation of isoxazolidines. Furthermore, the use of [bmim]PF<sub>6</sub> solvent system for this transformation avoids the use of toxic or corrosive reagents and high temperature reaction conditions and also it provides convenient procedure to carry out the reactions at ambient temperature.

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