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A new route to the synthesis of isoxazoline derivatives from dihydropyran via cycloaddition reaction in ionic liquid

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ABSTRACT

A new approach to the synthesis and 1,3-dipolar cycloadditions of nitrones has been described from 2,3-dihydro-4*H*-pyran and various hydroxylamines, with electron-deficient alkynes for the synthesis of isoxazoline derivatives. Significant rate acceleration and improved yields of exclusively *exo* isoxazolines in 1-butyl-3-methylimidazolium based ionic liquids have been observed. Novel isoxazolines may be used as a precursor for the synthesis of variety of peptides.

Nitrones are effective 1,3-dipoles and can undergo readily cycloaddition reaction with various alkynes to produce substituted isoxazolines.[1] Moreover, nitrones can be used as potential oxidizing reagents in the conversion of various alkyl halides into aldehydes and ketones with atom-efficiency.[2,3] They are also versatile intermediates for the synthesis of natural products and many biologically interesting molecules.[4] Owing to the labile nature of the N–O bond under mild reducing conditions, isoxazolines provide easy access to a variety of fascinating 1,3-difunctional amino alcohols.[5] Despite their potential utility, many of these procedures require high temperatures and prolonged reaction times (drastic experimental conditions) and also suffer from poor regioselectivity, and lack of simplicity. In a few cases, the yields and selectivities reported are far from satisfactory due to the occurrence of several side reactions.[6]

The use of ionic liquids (ILs)[7] as support for organic synthesis, in particular in cycloaddition reactions, has been described in some recent publications.[8] In recent years ionic liquids have received a good deal of attention, since classical organic reactions can be performed in these media with great advantages (yield and selectivity) as compared with conventional conditions. Taking into account the advantages offered by ILs, we have combined our past experience in the field of cycloadditions with the versatile properties of ILs[9] with the aim to find new routes for efficient isoxazoline synthesis.

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 enhance reaction rates. As a result of their green credentials and potential to enhance reaction rates and selectivities, ionic liquids are finding increasing applications in organic synthesis[10] with an ever-increasing quest for exploration of newer reactions in ionic liquids.[11] There are many reports concerning the applications of ionic liquids as solvents and catalysts in 1,3-dipolar cycloadditions.[12,13] Several butylmethylimidazolium based ILs, [bmim]X, with varying anions ($X = PF_6^-, Br^-, BF_4^-$) were screened for this reaction. After a detailed study, [bmim]BF_4 was found to be superior in terms of yield (91%) and reaction time (35 min) as compared with [bmim]PF_6 (87%; 40 min; entry 1).[14,15] These reagents are safe, easy to handle, environmentally benign, and present fewer disposal problems. Therefore, we thought [bmim]BF_4 could be an excellent solvent for the employment of our proposed reactions (Fig. 1).

In continuation of our effort to establish green methodologies in nitrone cycloaddition reactions,[16,17] herein, we wish to report a new route to the synthesis and 1,3-dipolar cycloaddition reactions of dihydropyran derived nitrones (having vast synthetic potentials)

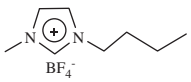

Figure 1. The chemical structure of the ionic liquid used in this study.

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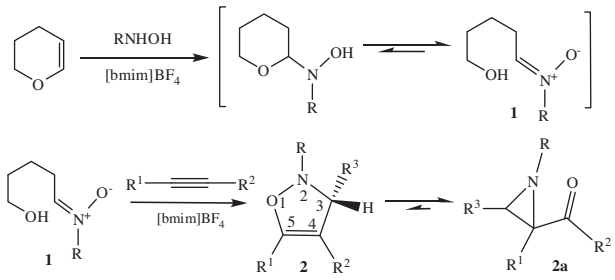


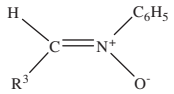
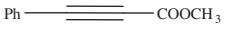
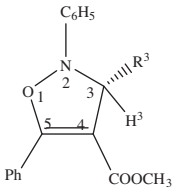
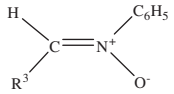
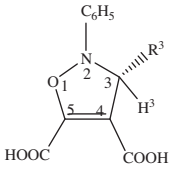
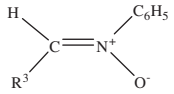
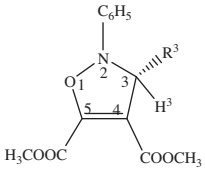
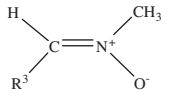
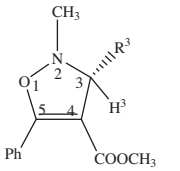
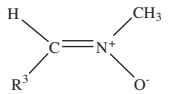
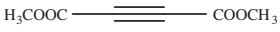
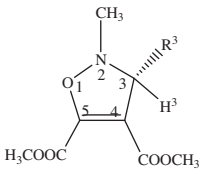
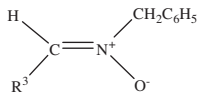
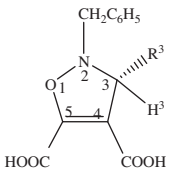
R = CH_3/C_6H_5/C_6H_{11}/ $C_6H_5CH_2$/4-HOC_6H_4/2-HOC_6H_4
R^1 = Ph ; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = -$(CH_2)_4OH$

Scheme 1.

with electron-deficient alkynes to produce novel isoxazoline derivatives (**2**) in an one pot operation (Scheme 1). Diastereoselective synthesis of novel isoxazolidine derivatives using nitrone **1** has been recently successfully tested with various maleimides.[18]

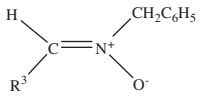
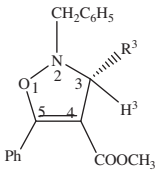
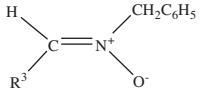
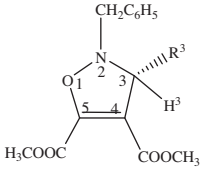
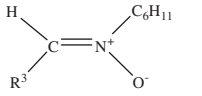
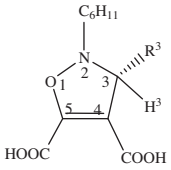
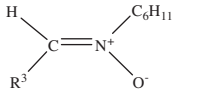
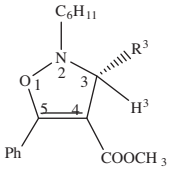
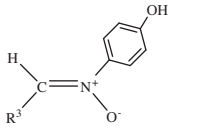
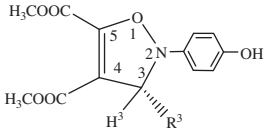
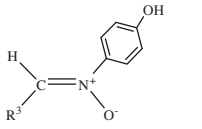
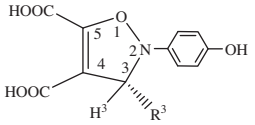
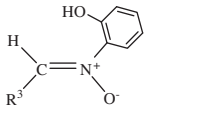
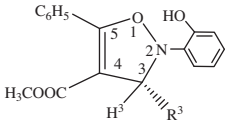
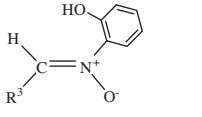
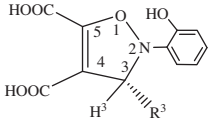
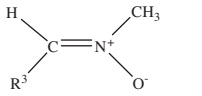
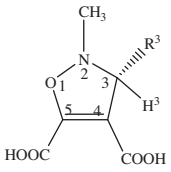
Compared to conventional conditions, the cycloaddition reactions performed in ionic liquids are much faster and selective. As an example, the reaction between nitrone **1** and alkynes, afforded cycloaddition derivative **2** at room temperature after 21 h in 62% yield in CH_2Cl_2 and after 35 min 91% yield in [bmim]BF_4 (entry 1) respectively. In a typical procedure 1 mmol of nitrone was mixed with 1 equiv of alkynes in [bmim]BF_4 (2 mL) under stirring, at 40 °C for the synthesis of novel isoxazoline derivatives (**2**). After the completion of reaction, the rest of the viscous ionic liquid was further washed with diethyl ether and dried at 80 °C under reduced pressure to retain its activity in subsequent runs and was reused up to five times without loss of activity or selectivity after five cycles. We have intentionally stopped the recycle at the fifth cycle, however we are convinced that this process may be carried on many more times. For optimizing the conditions, we used the substrates in different ratios. It was found that best results were obtained using 1:1 reactant ratio. The reaction in [bmim]BF_4 was also conducted at elevated temperatures (60–80 °C) for optimizing the conditions but no significant improvements were observed in yields and reaction times. For example, reaction of nitrone **1** (R = C_6H_5; $CH_2C_6H_5$) with methyl phenyl propiolate and dimethyl

Table 1
1,3-Dipolar cycloaddition reaction of dihydropyran derived nitrones with alkynes in ionic liquid

Entry	Nitrone[a]	Alkyne	Product[b] (**2**)	Time[c] (min)	Yield (%)
1				35 (1260) 35 (70 °C)	91 (62) 90 (70 °C)
2				36 (1200)	87 (60)
3				36 (1200)	85 (60)
4				35 (1230)	83 (59)
5				35 (1230)	81 (60)
6				36 (1200)	81 (58)

(*continued on next page*)

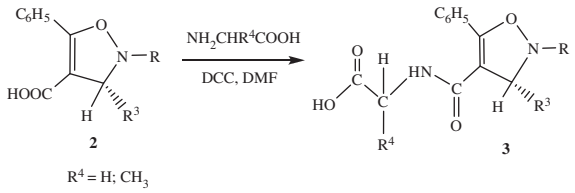
Table 1 (*continued*)

Entry	Nitrone[a]	Alkyne	Product[b] (**2**)	Time[c] (min)	Yield (%)
7				32 (1230)	80 (56)
8				30 (1200) 30 (65 °C)	80 (52) 81 (65 °C)
9				34 (1200)	78 (56)
10				36 (1380)	76 (57)
11				32 (1230)	84 (55)
12				30 (1200)	80 (53)
13				32 (1230)	82 (52)
14				32 (1200)	80 (58)
15				33 (1260)	78 (54)

[a] Reaction conditions: nitrone (1 mmol), alkynes (1 equiv), [bmim]BF_4 (2 ml), N_2 atmosphere.
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR, and MS spectral data.
[c] Isolated yield after purification. Figures in parentheses indicate reactions performed in conventional methods.

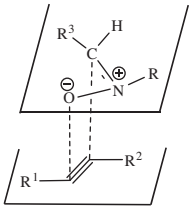
acetylene dicarboxylate was studied at 70 °C and 65 °C respectively but no such improvement was observed as far as the yield of the reactions is concerned (Table 1, entry 1 and 8). We examined the reactions under neat condition also, without using IL, to demonstrate catalytic ability of [bmim]BF_4. This result clearly indicates that [bmim]BF_4 has a significant catalytic role in these reactions (Table 1). The reaction of nitrone **1** with various alkynes follows the general mechanistic pattern of 1,3-dipolar cycloaddition reactions as found in the literature.[4,19] The addition of nitrone **1** to alkynes can be rationalized by an *exo* approach of the nitrone which has the Z configuration (transition state **I**).[20]

All the cycloadducts are found to be moderately stable and have prominent molecular ion peak and base peaks in the mass spectrum as expected. But while keeping for a longer period, the isoxazoline derivatives (**2**) undergo 'Baldwin rearrangement' to furnish corresponding aziridine derivatives (**2a**). Therefore, like other isoxazoline derivatives reported in the literature,[4,21,22] we have also obtained expected fragmentation peaks due to the development



Scheme 2.

of different aziridine derivatives. Base peaks are obtained due to loss of PhCO for phenyl methyl propiolate, $COOCH_3$ for dimethyl acetylene dicarboxylate, and COOH for acetylene dicarboxylic acid cycloadducts respectively. Hence it is confirmed that during mass fragmentation, the cycloadducts underwent rearrangement to aziridine derivatives.



TS **I**

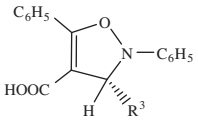
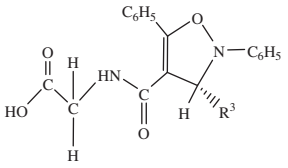
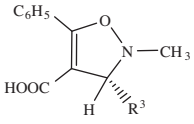
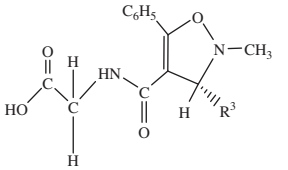
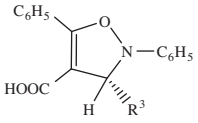
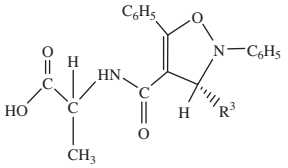
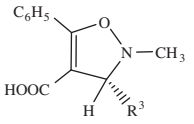
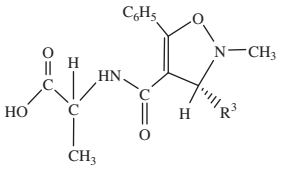
Furthermore, the novel isoxazoline derivatives (**2**) are found to have vast synthetic potential as they could be used as precursor for the synthesis of variety of novel peptides (**3**) with potential biological activity and thereby showing their importance in peptide chemistry as well (Scheme 2). All the novel peptides (**3**; Table 2, entries 1–4) have been found to be very effective against gram positive and gram negative organisms which gives an opportunity to develop new broad spectrum antimicrobial agents. Screening studies (SEM and TEM) on these novel peptides are going on at present. Initial studies on the synthesis of peptides have been successfully conducted with glycine and alanine using isoxazoline derivatives **2** (entry 1) in DMF. Studies in detail are in progress.

To explore the potential of this procedure we have extended the protocol, to N-substituted nitrones (with hydroxy derivatives in phenyl ring also) for the synthesis of exclusively *exo* isoxazoline derivatives (Table 1).

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. Enhanced reaction rates, excellent yields, and high selectivity are the features observed in these ionic solvents. All the products were characterized by ^1H NMR, ^{13}C NMR, IR, and MS spectroscopic data.[23]

In conclusion, we have reported a new methodology for the synthesis of nitrones and isoxazolines from dihydropyran (an unusual source for the synthesis of nitrone, because nitrones are usually synthesized from either aldehydes or ketones or their derivatives) via 1,3-dipolar cycloaddition reactions and also shown that these cycloadditions may be conveniently carried out in RTIL's with the obtainment of corresponding novel isoxazolines in good conversions and yields[24,25] with high synthetic potentials and selectivities. We have also introduced a new approach to the synthesis of peptides from isoxazolines. The ionic liquid may be recycled several times without loss of activity or selectivity.

Table 2
Synthesis of Peptides from isoxazoline derivatives in DMF

Entry	Isoxazoline[a] (**2**)	Amino acid	Peptide[b] (**3**)	Time[c] (min)	Yield (%)
1		Glycine		180	71
2		Glycine		180	70
3		Alanine		200	66
4		Alanine		200	61

[a] Reaction conditions: isoxazoline (1 mmol), amino acid (1 equiv), DMF (10 ml).
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR, and MS spectral data.
[c] Isolated yield after purification.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.159.

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24. *Representative experimental procedure for nitrone and isoxazoline synthesis (Table 1, entry 1):* 2,3-dihydro 4*H*-pyran (1 mmol) and *N*-phenylhydroxylamine (1 equiv) were added to [bmim]BF_4 (2 ml) in a 10 ml conical flask, mixed thoroughly, and stirred at 40 °C for 60 min. The formation of nitrone was monitored by TLC (R_f = 0.36). Methyl phenyl propiolate (1 mmol) was added at the time of development of nitrone and the reaction mixture was further stirred at 40 °C for an appropriate time (Table 1). After completion of reaction, as indicated by TLC (R_f = 0.52), 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 silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:8) to afford pure isoxazoline **2** (Table 1, entry 1, 91%) as dark red gelatinous mass. 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. Spectroscopic data for nitrone **1** (*R* = C_6H_5): UV λ_{max} 235 nm. IR (KBr): ν_{max} 3520 (br), 3015 (m), 1614 (s), 1430 (m), 1205 (m), 788 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.73–7.28 (m, 5H, C_6H_5), 6.45 (t, 1H, *J* = 5.00 Hz, –CH=N^+), 5.12 (br s, 1H, –OH, exchangeable in D_2O), 3.46 (dt∼m, 2H, CH_2 protons of –CH_2–$(CH_2)_3$OH), 2.04 (m, 6H, CH_2 protons). ^{13}CNMR (75 MHz, $CDCl_3$): δ 143.22 (CH=N^+), 131.56, 131.43, 131.22, 131.06 (aromatic carbons), 30.25, 30.17, 30.08, 29.96 (CH_2 carbons). Spectroscopic data for isoxazoline **2** (Table 1, entry 1): IR (KBr): ν_{max} 3545 (br), 3012 (m), 2250 (m), 1820 (s), 1770 (s), 1685 (m), 1610 (s), 1485 (s), 1320 (s), 1230 (m), 1125 (s), 985 (m), 784 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.86–7.20 (m, 2 × 5H, C_6H_5), 4.79 (br s, 1H, –OH, exchangeable in D_2O), 3.79 (t, 1H, *J* = 4.06 Hz, C_3H), 3.38 (s, 3H, –$COOCH_3$), 3.20 (dt∼m, 2H, CH_2 protons of –CH_2–$(CH_2)_3$OH), 1.73–1.30 (m, 6H, CH_2 protons). ^{13}C NMR ($CDCl_3$): δ 171.70 (–$COOCH_3$), 133.65, 133.60, 133.53, 133.46, 130.24, 130.18, 130.14, 130.08 (aromatic carbons), 85.60 (C_5), 76.92 (C_3), 64.28 (–CH_2OH), 59.32 (C_4), 44.10 (–$COOCH_3$), 32.16, 32.04, 31.93 (CH_2 carbons). FAB-MS (*m*/*z*): 353 (M^+), 294, 276, 203 (BP), 77, 73. Anal. Calcd for $C_{21}H_{23}O_4N$: C, 71.35; H, 6.55; N, 3.96%. Found: C, 71.12; H, 6.38; N, 3.64%.
25. *Representative experimental procedure for peptide synthesis (Table 2, entry 1)*: A mixture of hydrolyzed isoxazoline (1 mmol), glycine (1 equiv), and DCC (1 equiv) were added to DMF (10 ml). The mixture was heated with constant stirring at 80 °C for 180 min. After the completion of reaction as monitored by TLC (R_f = 0.46), the precipitated dicyclohexylurea was collected off and the filtrate was poured into ice-cold water. The solid that separated out was collected to afford **3** (Table 2, entry 1) as white crystals (yield 71%, mp 86 °C). Spectroscopic data for peptide **3** (Table 2, entry 1): IR (KBr): ν_{max} 3420–3405 (br), 3328 (m), 3150 (br), 2990 (br), 1722 (s), 1665 (s), 1423 (m), 1345 (s), 1180 (s), 851 (m), 786 (s), 680 (s) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 10.12 (s, 1H, COOH), 9.80 (s, 1H, –NH, D_2O exchangeable), 7.54–7.32 (m, 2 × 5H, C_6H_5 protons), 5.38 (br s, 1H, –OH, D_2O exchangeable), 4.33 (t, 1H, *J* = 2.74 Hz, C_3H), 4.22 (s, 2H, –CH_2), 3.24 (dt∼m, 2H, CH_2 protons of –CH_2–$(CH_2)_3$OH), 1.80–1.43 (m, 6H, CH_2 protons). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.55 (–COOH), 167.14 (–CONH), 137.80, 137.74, 136.95, 136.88, 132.32, 132.28, 132.23, 132.18 (aromatic carbons), 85.06 (C_5), 76.13 (C_3), 64.24 (CH_2OH), 55.24 (C_4), 26.12, 25.86, 25.70, 25.66 (CH_2 carbons). LC–MS (*m*/*z*): 396.2 $[M+H]^+$. Anal. Calcd for $C_{22}H_{24}O_5N_2$: C, 66.63; H, 6.09; N, 7.07. Found: C, 66.54; H, 6.10; N, 6.96.