Indian Journal of Chemistry
Vol. 53B, February 2014, pp 218-226

Synthesis of some novel class of isoxazoline and isoxazolidine derivatives in ionic liquid *via* 1,3-dipolar cycloaddition reaction of dihydropyran derived nitrones and their antimicrobial activities

Bhaskar Chakraborty*[a], Amalesh Samanta[b], Chiran Devi Sharma[a] & Nasima Khatun[b]

[a]Organic Chemistry Laboratory, Sikkim Government College, Gangtok 737 102, India

[b]Division of Microbiology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata 700 032, India

E-mail: bhaskargtk@yahoo.com

Received 9 April 2013; accepted (revised) 13 December 2013

1,3-Dipolar cycloaddition of dihydropyran derived nitrones synthesized from 2,3 dihydro 4*H*-pyran and various hydroxylamines, with electron deficient alkynes are found to have significant rate acceleration and improved yields of isoxazolines in 1-Butyl-3-methylimidazolium based ionic liquids while with enals exclusively *endo* isoxazolidines are obtained with high selectivity. Synthetic potentiality of the novel isoxazolines and nitrones have been also tested successfully in peptide and aldehyde synthesis. All the novel isoxazoline and isoxazolidine derivatives have been screened for antimicrobial activities and found to be active.

Keywords: Dihydropyran derived nitrones, cycloaddition reaction, novel isoxazolidine & isoxazolines, ionic liquid, peptides, aldehyde synthesis, antimicrobial activity

Nitrones are versatile synthetic intermediates and excellent spin trapping reagents[1]. Nitrones are prepared either by condensation of aldehyde and ketones with hydroxyl amines[1] or by oxidation of the corresponding *N*,*N*–disubstituted hydroxylamines[2]. The 1,3-dipolar cycloaddition reaction between a nitrone and olefins or alkynes represents the favourite method for the construction of five-membered heterocycles commonly called isoxazolidines and isoxazolines, important frameworks of various natural products[3]. Isoxazoline and isoxazolidines posses medicinal activities such as antibacterial, anticonvulsant, antibiotic, antitubercular and antifungal activity[4,5]. Despite their potential utility, many of these procedures require high temperature 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]. In recent times, ionic liquids have emerged as green solvents with desirable properties such as good solvating ability, wide liquidious range, tunable polarity, high thermal stability, negligible vapour pressure and ease of recyclability[7]. Therefore, classical organic reactions can be performed in these media with great advantages (yield and selectivity) as compared to conventional conditions. 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 (**Figure 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 synthesis[9] with an ever-increasing quest for exploration of newer reactions in ionic liquids[10].

In continuation of the efforts to establish green methodologies in nitrone cycloaddition reactions[11-16], herein is reported the use of ionic liquids as recyclable solvents for synthesis and 1,3-dipolar cycloaddition reaction of dihydropyran derived nitrones (having

vast synthetic potentials) with electron deficient alkynes and alkenes (enals) to produce novel isoxazoline and isoxazolidine derivatives in an one pot operation (**Scheme I**). Moderate selectivity in the cycloaddition reactions using nitrone **1** have been recently successfully tested with various maleimides[13]. In the present study a variety of hydroxylamines and dipolarophiles have been used to study the synthetic potentiality of nitrones **1** and selectivities found in cycloaddition reactions. At the same time the reactions were compared in conventional methods also as far as yields and selectivities are concerned. Compared to conventional conditions the cycloaddition reactions performed in ionic liquids are much faster and selective.

As an example, the reaction between nitrone **1** (R=Ph) and alkynes, afforded cycloaddition derivative **2a** after 25 hr in CH_2Cl_2 in 62% yield and 91% yield (**entry 1, Table I**) in [bmim]BF_4 at RT after 35 min respectively. In a typical procedure 1 mmol of nitrone was mixed with 1 equivalents of alkyne/alkenes in [bmim]BF_4 (2 mL) under stirring, at 40°C. After the development of nitrone (monitored by TLC), 1 mmol of dipolarophile were added *in situ* and the progress of the reaction was monitored by TLC. After completion of reaction, 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/ isoxazolidines. 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 nor 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.

Treatment of nitrone **1** with methacrolein in [bmim]BF_4 for 40 min gave the corresponding 5-substituted *endo* isoxazolidine (**entry 4**, **Table I**) in 88% yield with excellent regioselectivity. However, in the absence of ionic liquids, the reaction did not yield any product even after a long reaction time (42 hr). Under conventional conditions (CH_2Cl_2 as

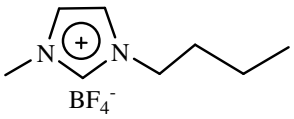
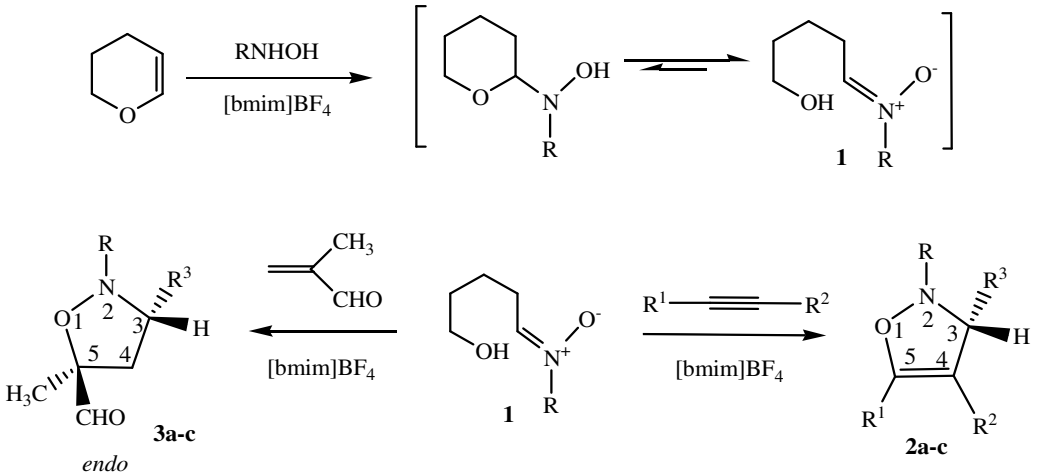


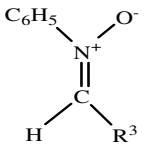
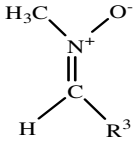
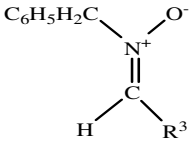
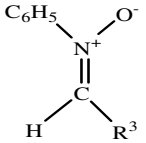
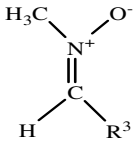
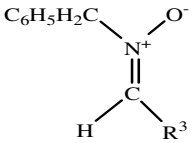
Figure 1 — The chemical structure of the ionic liquid used in this study



R = CH_3/C_6H_5/ $C_6H_5CH_2$
R^1 = Ph ; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = -$(CH_2)_4$OH

Scheme I — Synthesis of novel isoxazoline and isoxazolidine derivatives

Table I — Physicochemical data of synthesized compounds (**2a-c** and **3a-c**)

Entry	Nitrone	Dipolarophile[a]	Time (min)	Cycloadduct	Yield[b] (%)
1		Methyl phenyl propiolate	35 (1500)	**2a**: Red thick liquid	91 (62)
2		Dimethyl acetylene dicarboxylate	37 (1560)	**2b**: Colourless liquid	90 (63)
3		Acetylene dicarboxylic acid	35 (1560)	**2c**: Colourless liquid	90 (60)
4		Methacrolein	40 (2520)	**3a**: Colourless liquid	88 (58)
5		Methacrolein	44 (2400)	**3b**: Pale yellow liquid	86 (60)
6		Methacrolein	43 (2460)	**3c**: Colourless sticky liquid	85 (57)

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

solvent, 40-60°C, 42 hr), the products were obtained as a mixture of *endo* and *exo*-isomers (65:35) favouring the *endo*-diastereomer. Signals for the *endo* and *exo* diastereomers were assigned by ^{1}H NMR analysis[17,18]. Detailed study on cycloaddition reaction using methacrolein in conventional solvent (CH_2Cl_2/THF) is under progress.

Several butylmethylimidazolium based ILs, [bmim]X, with varying anions (X = PF_6^-, Br^-, BF_4^-) were screened for this reaction. Evidently, [bmim]BF_4 was found to be superior in terms of yield (91%) and reaction time (35 min) as compared with [bmim]PF_6 (84%; 45 min; **entry 1, Table I**). 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 for optimizing the conditions and no significant improvements were observed in yields and reaction times. The reaction was examined under neat condition also, without

using IL, to demonstrate catalytic ability of [bmim]BF_4. This result clearly indicates that [bmim]BF_4 has significant catalytic role in this reactions.

Nitrones bearing benzyl groups on the nitrogen atom are extremely valuable for applications in synthesis as these moieties act as versatile protecting groups. It has been found that the *N*-substituted nitrones afforded the expected *endo* substituted isoxazolidines **3** with high yields. 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. 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. Enhanced reaction rates, excellent yields, and high selectivity are the features observed in these ionic solvents.

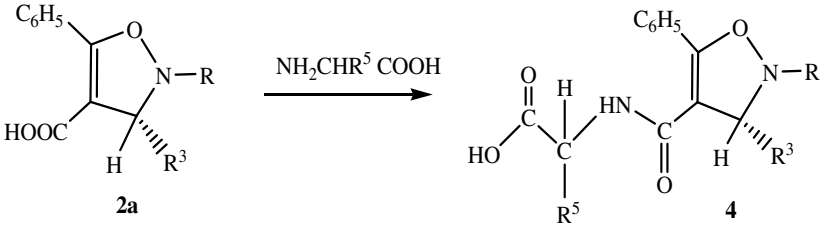
All the novel cycloadducts (isoxazoline and isoxazolidine derivatives) are stable and prominent molecular ion peaks and base peaks are obtained in the mass spectrum as expected. In case of isoxazoline derivatives **2a-c**, expected fragmentation peaks are also obtained due to the development of different 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 isoxazoline cycloadducts underwent rearrangement to aziridine derivatives. Structures of all the isoxazolidine and isoxazoline derivatives (**2a-c** and **3a-c**) have been confirmed on the basis of expected signals obtained in ^1H and ^{13}C NMR, MS and FT-IR spectra. Satisfactory elemental analysis values were also obtained for all the novel cycloadducts.

Furthermore, the novel isoxazoline derivatives **2a-c** are found to have vast synthetic potential as they could be used as precursor for the synthesis of various novel peptides with potential biological activity and thereby demonstrating their importance in peptide chemistry as well (**Scheme II**). Detailed studies are in progress.

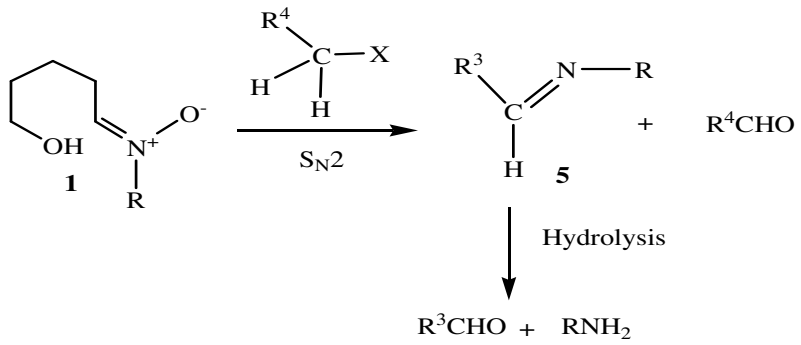
Synthetic potentiality of the nitrones **1** are also tremendous as they could be used as oxidizing reagent in the conversion of alkyl halides to aldehydes and ketones (**Scheme III**) following a pattern of atom efficient reactions reported by our group[16]. Synthesis of various aldehydes and ketones from alkyl halides using α-chloro nitrones in atom efficient reactions have been already reported[16,19].

Antimicrobial screening test

In vitro antimicrobial evaluation of all the synthesized novel compounds (**2a-c** and **3a-c**) were tested on fifteen (15) bacterial strains (depicted in



Scheme II — Synthesis of peptides using isoxazoline derivatives



Scheme III — Synthesis of aldehydes using nitrones

Table II — MIC values (μg/mL) of novel isoxazoline and isoxazolidines (**2a-c ; 3a-c**)

Organisms	Compd					
	2a	**2b**	**2c**	**3a**	**3b**	**3c**
Escherichia coli ATCC 25938	600	400	600	400	600	_
Salmonella.typhi 62	400	600	200	200	600	600
Vibrio cholerae 20	600	600	200	600	1000	600
Klebsiella pneumoniae 10031	600	600	_	600	_	_
Shigella dysentery 1	400	600	400	600	1000	_
Pseudomonas AMRI 100	800	600	400	600	_	_
Salmonella typhimurium NTCC 74	600	400	600	400	_	_
Staphylococcus aureus 29737	600	600	400	600	600	_
Bacillus cereus 11778	600	400	400	600	1000	_
Bacillus subtilis 6633	600	600	400	600	1000	_
Streptococcus epidermidis 1222	400	400	400	600	1000	_
Micrococcus luteus 10240	600	600	400	600	600	_
Pseudomonas aeruginosa 2561	600	400	400	400	_	_
Bacillus pumilus 14884	600	400	600	400	1000	_
Bordetella bronchiseptica NCTC 4617	400	600	400	600	_	_

'-' represents no antimicrobial activity of the compounds.

Table II) with amoxicillin as reference[20]. Nutrient agar was used as culture medium and the strains were grown at 37°C for 24 hr. The suspension was prepared by matching a 0.5 McFarland standard[21]. The compounds were dissolved in 4% dimethyl sulphoxide solution along with sterile distilled water for screening using Agar dilution[22]. The susceptible organisms were screened for minimum inhibitory concentration (MIC) using standard Cup plate assay method[23]. 0.1 mL of bacterial solution (2×10^6 CFU/mL) was transferred to nutrient agar plates and uniformly spread by a sterile glass spreader. The sensitivity was evaluated by measuring the presence of clear zone of inhibition on agar surface around the wells observed after 24 hr of incubation at 37ºC (Ref 24). From the antimicrobial study, the MIC values (**Table II**) of the synthesized novel compounds (**2a-c** and **3a-c**) and their corresponding zone of inhibition using amoxicillin as reference antimicrobial agent were obtained (**Table III**). Detailed study confirms that compound **3c** has its effect specifically on *Salmonella typhi* 62 and *Vibrio cholerae* 20 which gives an indication of new enteric drug. All the novel compounds (**2a-c** and **3a-c**) 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.

Experimental Section

^{1}H NMR spectra were recorded with a Bruker DRX 300 spectrometer (300 MHz, FT NMR) using TMS as internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz. The coupling constants (*J*) are given in Hz. IR spectra were obtained with a Perkin-Elmer RX 1-881 machine as film or as KBr pellets for all the products. MS spectra were recorded with a Jeol SX-102 (FAB) instrument. All the reactions were monitored by TLC using 0.25 mm silica gel plates (Merck $60F_{254}$ UV indicator) while column chromatography was performed with

Table III — Represents Zone of Inhibition of novel isoxazoline and isoxazolidines (**2a-c ; 3a-c**)

Organisms	Compd						
	2a	**2b**	**2c**	**3a**	**3b**	**3c**	Amoxicillin
Escherichia coli ATCC 25938	16	19	21	20	20	_	40
Salmonella.typhi 62	18	20	18	16	_	29	38
Vibrio cholerae 20	12	33	16	25	16	_	34
Klebsiella pneumoniae 10031	16	13	_	22	_	_	22
Shigella dysentery 1	18	22	25	20	24	30	27
Pseudomonas AMRI 100	10	11	18	21	_	_	21
Salmonella typhimurium NTCC 74	20	28	20	19	_	_	24
Staphylococcus aureus 29737	13	18	21	22	20	28	37
Bacillus cereus 11778	18	28	_	22	21	_	30
Bacillus subtilis 6633	12	30	24	23	24	_	40
Streptococcus epidermidis 1222	24	18	19	21	23	_	30
Micrococcus luteus 10240	24	20	14	19	13	31	42
Pseudomonas aeruginosa 2561	21	29	12	18	_	_	39
Bacillus pumilus 14884	38	21	18	20	12	30	41
Bordetella bronchiseptica NCTC 4617	30	24	23	23	_	_	40

'-' represents no measurable zone of diameter at MIC value of supplied compounds.

silica gel (E.Merck India) 60–200 mesh. All other reagents and solvents were purified after receiving from commercial suppliers. *N*-Benzylhydroxylamine, starting materials, reagents used in the reactions were obtained commercially from Aldrich, Lancaster and were used without purification, unless otherwise indicated. 1-Butyl-3-methylimidazoliumtetrafluoroborate ([bmim]BF_4) and 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) ionic liquids were prepared according to the procedures reported in the literature[25]. All the bacterial strains were obtained from the Division of Microbiology, Department of Pharmaceutical Technology, Jadavpur University, Kolkata, India

General procedure of synthesis of nitrone 1 (R = C_6H_5) in RTIL

2,3-Dihydro-4*H*-pyran (1 mmol) and *N*-phenylhydroxylamine (1 equivalent) was 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). The nitrone was isolated as pale yellow crystals which decomposed on standing. Similar procedure was adopted for the synthesis of other nitrones. As all the nitrones decomposes on keeping at room temperature, therefore, *in situ* reactions were performed with activated alkenes and alkynes.

Spectral data of nitrone 1 (R = C_6H_5)

UV (λ_{max}); 235 nm; IR (KBr): 3520 (br), 3015 (m), 1614 (s), 1430 (m), 1205 (m), 788 (s) cm^{-1}; ^{1}H 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), 2.04-1.25 (m, 8H); ^{13}C NMR (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).

General procedure of synthesis of isoxazoline derivatives using RTIL (Table I ; entry 1)

2,3-Dihydro-4*H*-pyran (1 mmol) and *N*-phenylhydroxylamine (1 equivalent) was 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 I**). 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 **2a** as red thick liquid (**Table I, entry 1**, 91%). 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. Similar procedure was adopted for other substrates (**entry 2** and **3**) depicted in **Table I**.

General procedure of synthesis of isoxazolidines (Table I ; entry 4)

2,3-Dihydro-4*H*-pyran (1 mmol) and *N*-phenyl-hydroxylamine (1 equivalent) was 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). Methacrolein (1 mmol) was added dropwise, by syringe, at the time of development of nitrone and the reaction mixture was further stirred at 40°C for an appropriate time (**Table I, entry 4**). After completion of reaction, as indicated by TLC (R_f = 0.44), the reaction mixture was washed with diethyl ether (3×10mL). 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 isoxazolidine **3a** as colourless liquid (**Table I, entry 4**, 88%). 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. Similar procedure was adopted for the cycloaddition reaction of other nitrones with methacrolein (**entry 5** and **6**) depicted in **Table I**.

Spectroscopic data of isoxazoline derivatives (2a-c)

(*R*)–Methyl 2,3 dihydro-3-(4-hydroxybutyl)-2,5-diphenylisoxazole-4-carboxylate, 2a

IR (KBr): 3545 (br), 3012 (m), 2250 (m), 1820 (s), 1770 (s), 1610 (s), 1485 (s), 1320 (s), 1230 (m), 1125 (s), 985 (m), 784 (s) cm^{-1}; ^{1}H 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,-$COOCH_3$), 1.82-1.22 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 171.70 (-*CO*OCH_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), 59.32 (C_4), 44.10 (-COO*CH*$_3$), 32.16, 32.04, 31.93, 31.86 (CH_2 carbons); FAB-MS: *m/z* 353 (M^+), 294, 276, 203 (B.P), 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%.

(*R*)–Dimethyl 2,3 dihydro-3-(4-hydroxybutyl)-2-methylisoxazole-4,5-dicarboxylate, 2b

IR (KBr): 3550 (br), 2238 (m), 1830 (s), 1764 (s), 1616 (s), 1480 (s), 1305 (s), 1235 (m), 1140 (m), 978 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 4.83 (br, s, 1H,-OH, exchangeable in D_2O), 3.30 (s, 2 × 3H,-$COOCH_3$), 2.85 (s, 3H, N-CH_3), 2.49 (t, 1H, *J* = 5.10 Hz, C_3H), 2.19-1.60 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 173.23, 173.16 (-*CO*OCH_3, carbonyl carbons), 88.40 (C_5), 75.18 (C_3), 57.90 (C_4), 42.78, 42.74 (-COO*CH*$_3$, ester carbons), 30.34, 30.30, 30.23, 30.16 (CH_2 carbons); FAB-MS: *m/z* 273 (M^+), 242, 186, 185 (B.P), 87, 73. Anal. Calcd for $C_{12}H_{19}O_6N$: C, 52.72; H, 7.00; N, 5.12. Found: C, 52.63; H, 6.68; N, 5.10%.

(*R*)–2-Benzyl-2,3-dihydro-3-(4-hydroxybutyl) isoxazole-4,5-dicarboxylic acid, 2c

IR (KBr): 3575 (br), 3050 (m), 1824 (s), 1760 (s), 1610 (s), 1464 (s), 1315 (s), 1230 (m), 1135 (m), 782 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 10.72 (br, s, 2H, 2 × COOH), 7.57-7.33 (m, 5H, C_6H_5), 5.10 (br, s, 1H,-OH, exchangeable in D_2O), 3.72 (t, 1H, *J* = 3.74 Hz, C_3H), 3.43 (s, 2H, $CH_2C_6H_5$), 1.59-0.85 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 174.72, 174.69 (-*CO*OH, carbonyl carbons), 129.80, 129.77, 129.73, 129.68 (aromatic carbons), 85.17 (C_5), 73.54 (C_3), 59.13 (C_4), 36.81 (-*CH*$_2$$C_6H_5$), 27.53, 27.37, 27.30, 27.25 (CH_2 carbons); FAB-MS: *m/z* 321 (M^+), 230, 157 (B.P), 91, 73. Anal. Calcd for $C_{16}H_{19}O_6N$: C, 59.79; H, 5.95; N, 4.36. Found: C, 59.66; H, 5.79; N, 4.31%.

Spectroscopic data of isoxazolidine derivatives (3a-c)

(*3R*)-3-(4-Hydroxybutyl)-5-methyl-2-phenyl isoxazolidine-5-carbaldehyde, 3a

IR (KBr): 3580 (br), 2995 (m), 1720 (s), 1615 (s), 1460 (m), 1320 (s), 1180 (s), 985 (m), 786 (s) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (s, 1H, CHO), 7.46-7.26 (m, 5H, C_6H_5), 5.45 (br, s, 1H,-OH, exchangeable in D_2O), 4.39 (dd, 1H, *J* = 3.36, 3.30 Hz, C_3H), 3.24 (dd, 1H, *J* = 6.06, 6.10 Hz, C_4H), 2.89 (dd, 1H, *J* = 5.12, 5.05 Hz, C_4H, *endo*), 2.15 (s, 3H,

CH_3), 1.80-1.25 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.58 (-CHO), 132.32, 132.28, 132.23, 132.18 (aromatic carbons), 83.50 (C_5), 72.40 (C_3), 56.70 (C_4), 25.15 (CH_3), 28.90, 28.86, 28.80, 28.76 (CH_2 carbons); FAB-MS: *m/z* 263 (M^+), 186, 175, 113 (B.P), 77, 73. Anal. Calcd for $C_{15}H_{21}O_3N$: C, 68.40; H, 8.03; N, 5.32. Found: C, 68.27; H, 7.89; N, 5.26%.

(*3R*)-3-(4-Hydroxybutyl)-2,5-dimethyl isoxazolidine-5-carbaldehyde, 3b

IR (KBr): 3562 (br), 2874 (m), 1718 (s), 1612 (s), 1485 (s), 1334 (s), 1205 (s), 970 (m) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.44 (s, 1H, CHO), 4.83 (br, s, 1H,-OH, exchangeable in D_2O), 3.31 (s, 3H, CH_3), 2.85 (dd, 1H, *J* = 4.22, 4.18 Hz, C_4H), 2.51 (s, 3H, N-CH_3), 2.48 (dd, 1H, *J* = 3.10, 3.08 Hz, C_4H, *endo*), 2.19 (dd, 1H, *J* = 4.06, 4.04 Hz, C_3H), 1.66-1.40 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.42 (-CHO), 84.33 (C_5), 77.12 (C_3), 57.80 (C_4), 30.54 (N-CH_3), 28.60 (CH_3), 24.48, 24.43, 24.38, 24.34 (CH_2 carbons); FAB-MS: *m/z* 201 (M^+), 185, 128, 113 (B.P), 97, 73. Anal. Calcd for $C_{10}H_{19}O_3N$: C, 59.66; H, 9.51; N, 6.96. Found: C, 59.57; H, 9.45; N, 6.79%.

(*3R*)-2-Benzyl-3-(4-hydroxybutyl)-5-methyl isoxazolidine-5-carbaldehyde, 3c

IR (KBr): 3560 (br), 3050 (s), 1715 (s), 1680 (s), 1445 (m), 1330 (s), 1210 (s), 1020 (m), 786 (s) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.25 (s, 1H, CHO), 7.57-7.33 (m, 5H, C_6H_5), 5.10 (br, s, 1H,-OH, exchangeable in D_2O), 3.72 (dd, 1H, *J* = 6.30, 6.36 Hz, C_4H), 3.43 (s, 2H, $CH_2C_6H_5$), 2.88 (s, 3H, CH_3), 2.36 (dd, 1H, *J* = 4.72, 4.68 Hz, C_4H, *endo*), 1.59 (dd, 1H, *J* = 4.00, 4.02 Hz, C_3H), 1.24-0.90 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 202.35 (-CHO), 135.28, 135.25, 135.23, 135.16 (aromatic carbons), 85.84 (C_5), 76.52 (C_3), 55.60 (C_4), 42.70 ($CH_2C_6H_5$), 27.96 (CH_3), 26.67, 26.64, 26.60, 26.56 (CH_2 carbons); FAB-MS: *m/z* 277 (M^+), 247, 204, 113 (B.P), 91, 77, 73. Anal. Calcd for $C_{16}H_{23}O_3N$: C, 69.27; H, 8.35; N, 5.05. Found: C, 69.18; H, 8.20; N, 4.95%.

Conclusion

In conclusion, we have shown that 1,3-dipolar cycloadditions of dihydropyran derived nitrones with alkene and alkynes may be conveniently carried out in RTIL's with the obtainment of corresponding novel isoxazoline and isoxazolidines in good conversions and yields with high synthetic potentials and selectivities. The ionic liquid may be recycled several times without loss of activity nor selectivity. Majority of the synthesized compounds have been found to have potential activity against both gram positive and gram negative organisms and thereby showing an opportunity to behave as broad spectrum antimicrobial agents.

Acknowledgements

The authors acknowledge the financial support from Department of Science and Technology, Government of India, New Delhi (grant no: SR/S1/OC-34/2011). Authours are also grateful to SAIF, CDRI, Lucknow for providing spectral data.

References

1 Breuer E, in *The Chemistry of Amino*, *Nitroso*, *Nitro Compounds*, edited by S Patai (John Wiley and Sons), **1982**, 459 and references cited therein.
2 Murahashi S I, Mitsui H, Watanabe T & Zenki S, *Tetrahedron Lett*, 24, **1983**, 1049 and references cited therein.
3 (a) Tufariello J J, in *1,3-Dipolar Cycloaddition Chemistry*, edited by A Padwa (Wiley, New York), **1984**; (b) Torssell K B G, *Nitrile Oxides*, *Nitrones and Nitronates in Organic Synthesis* (VCH, New York), **1988**; (c) Seerden J P G, Boeren M M M & Scheeren H W, *Tetrahedron*, 53 (3), **1997**, 11843; (d) Gothelf K V & Jørgensen K A, *Chem Rev*, 98, **1998**, 863.
4 Patterson W, Cheung P S & Ernest M J, *J Med Chem*, 35, **1992**, 507.
5 Wagner E, Becan L & Nowakowska E, *Bioorg Med Chem*, 12, **2004**, 265.
6 Confalone P N & Huie E M, *Org React*, 36, **1988**, Chapter 1, pp 1–173.
7 (a) Welton T, *Chem Rev*, 99, **1999**, 2071; (b) Wasserscheid P & Keim W, *Angew Chem Int Ed Engl*, 39, **2000**, 3772.
8 Sheldon R, *Chem Commun*, **2001**, 2399.
9 Gordon C M, *Appl Catal A: Gen*, 222, **2001**, 101.
10 (a) Yadav J S, Reddy B V S & Baishya G, *J Org Chem*, 68, **2003**, 7098; (b) Yadav J S, Reddy B V S, Reddy J S S & Srinivas Rao R, *Tetrahedron*, 59, **2003**, 1599.
11 Chakraborty B & Luitel G P, *Tetrahedron Lett*, 54, **2013**, 765.
12 Chakraborty B & Sharma P K, *Synth Commun*, 42, **2012**, 1804.
13 Chakraborty B, Sharma P K, Rai N & Sharma C D, *J Chem Sci*, 124, **2012**, 679.
14 Chakraborty B, Sharma P K, Rai N, Kafley S & Chhetri M S, *J Chem Res*, 34, **2010**, 147.
15 Chakraborty B, Sharma P K & Chhetri M S, *J Heterocycl Chem*, 49, **2012**, 1260.
16 Chakraborty B, Sharma P K & Kafley S, *Green Chem Lett Rev*, 6, **2013**, 141.
17 Deshong P, Li W, Kennington J W & Ammon H L, *J Org Chem*, 56, **1991**, 1364.
18 (a) Gandolfi R & Grunanger P, *The Chemistry of Heterocyclic Compounds* (Wiley Interscience), 49 (2), **1999**, 774; (b) Andrei B & Kundig P E, *Org Biomol Chem*, 10, **2012**, 114.
19 Chakraborty B, Sharma P K, Chhetri M S, Kafley S & Ghosh A R, *J Indian Chem Soc*, 88, **2011**, 245.

20 Sahu K B, Ghosh S, Banerjee M, Maity A, Mondal S, Paira R, Saha P, Naskar S, Hazra A, Banerjee S, Samanta A & Mondal N B, *Med Chem Res*, 22, **2013**, 94.
21 McFarland J, *J Am Med Assoc*, 14, **1907**, 1176.
22 Paira M K, Mondal T K, Ojha D, Slawin A M Z, Tiekink E R T, Samanta A & Sinha C, *Inorg Chim Acta*, 370, **2011**, 175.
23 Andrews J M, *J Antimicrobial Chemother*, 48, **2001**, 43.
24 National Committee for Clinical Laboratory Standards (NCCLS), Approved Standard M7-A3, 3rd Edn. NCCLS, Villanova, PA, **1993**.
25 (a) Park S & Kazlauskas R J, *J Org Chem*, 66, **2001**, 8395; (b) Bonhote P, Dias A P, Papageorgiou N, Kalyanasundaram K & Gratzel M, *Inorg Chem*, 35, **1996**, 1168.