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Synthesis of some novel fluoro isoxazolidine and isoxazoline derivatives using *N*-benzyl fluoro nitrone via cycloaddition reaction in ionic liquid

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Abstract. 1-Butyl-3-methylimidazolium-based ionic liquids are found to accelerate significantly the intermolecular 1,3-dipolar cycloaddition of *N*-benzyl-fluoro nitrone derived *in situ* from 2,6-difluoro benzaldehyde and *N*-benzylhydroxylamine, with activated alkenes and electron deficient alkynes to afford enhanced rates and improved yields of novel isoxazolidines and isoxazolines.

Keywords. *N*-Benzyl fluoro nitrone; cycloaddition reaction; fluoro isoxazolidine and isoxazolines; ionic liquid; 1,3-amino alcohol; aldehyde/ketone synthesis.

1. Introduction

The 1,3-dipolar cycloaddition reactions represent a favourite method for the construction of five-membered heterocycles, important frameworks of various natural products.[1] In particular, the 1,3-dipolar cycloaddition reaction of nitrones with alkenes and alkynes afford isoxazolidines and isoxazolines which are interesting intermediates for the synthesis of β-amino alcohols and alkaloids.[2,3] Isoxazolines possess medicinal activities such as antibacterial, anticonvulsant, antibiotic, antitubercular and antifungal activities.[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 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]

It is known that introduction of fluorine atom into specific position of organic molecule may cause significant changes in the stability, lipophilicity and biological activities of the resulting molecules.[11] This has been attributed to high electronegativity of the halogen, strong C–F bond and similar size of halogen and hydrogen atoms. The presence of a fluoro group due to a low polarizability and high lipophilicity induces a relative metabolic stability and improves the bioavailability of the modified heterocycles compared to its hydrocarbon analogues.[12,13]

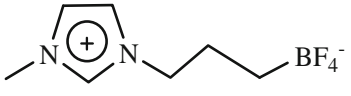
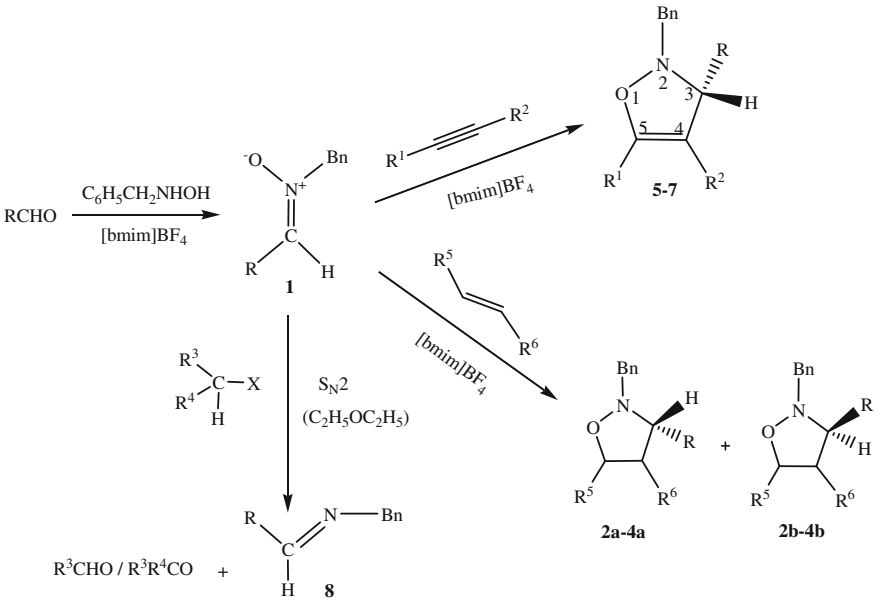


Figure 1. Chemical structure of ionic liquid used in this study.

*For correspondence



R = 2,6 difluro benzene; Bn = $C_6H_5CH_2$
R^1 = Ph; R^2 = $COOCH_3$
R^1 = R^2 = $COOCH_3$
R^1 = R^2 = COOH
R^3 = Et; Ph; R^4 = H etc
R^3 = R^4 = Ph; R^3 = Me; R^4 = Ph
R^5, R^6 = -CONPhCO-; -CONMeCO-; -CONCyCO-

Scheme 1. Synthesis of fluoro isoxazoline and isoxazolidine derivatives using fluoro nitrone and application of the nitrone in atom-efficient aldehyde and ketone synthesis.

In continuation of our effort to establish green methodologies in nitrone cycloaddition reactions,[14–18] herein, we wish to report the use of ionic liquid as recyclable solvent for 1,3-dipolar cycloaddition reactions of *N*-benzyl fluro nitrone (having vast synthetic potentials) with active alkenes and electron deficient alkynes to produce fluoro isoxazolidine and isoxazoline derivatives with vast biological activity in a one-pot operation (scheme 1, table 1). Compared to conventional conditions, cycloaddition reactions performed in ionic liquids are much faster and selective.

Table 1. Physicochemical data of synthesized compounds **2a**–**4a**; **2b**–**4b** and **5**–**7**.

Entry	Nitrone	Dipolarophile[a]	Time (min)	Cycloadduct[b], m.p.(°C), **2a**–**4a**: *cis*; **2b**–**4b**: *trans*	*Cis*/*trans* ratio (%)	Yield[c] (%)
1	*N*-benzyl fluoro nitrone	*N*-phenyl maleimide	26 (12 h)	**2a**: White crystals, 128 **2b**: White crystals, 102	**2a**: 66 **2b**: 22	88 (68)
2	*N*-benzyl fluoro nitrone	*N*-methyl maleimide	30 (13 h)	**3a**: White solid, 135 **3b**: White solid, 120	**3a**: 65 **3b**: 21	86 (66)
3	*N*-benzyl fluoro nitrone	*N*-cyclohexyl maleimide	36 (13 h)	**4a**: Yellow crystals, 142 **4b**: Yellow crystals, 113	**4a**: 63 **4b**: 22	85 (66)
4	*N*-benzyl fluoro nitrone	Methyl phenyl propiolate	26 (17 h)	**5**: Dark red thick liquid		88 (67)
5	*N*-benzyl fluoro nitrone	Dimethyl acetylene dicarboxylate	30 (19 h)	**6**: Red viscous liquid		86 (65)
6	*N*-benzyl fluoro nitrone	Acetylene dicarboxylic acid	32 (18 h)	**7**: Colourless thick liquid		86 (66)

[a]Reaction conditions: nitrone (1 mmol), dipolarophile (1 equivalent), [bmim]BF_4 (2 mL), N_2 atmosphere, RT
[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 by conventional methods

2. Experimental

2.1 *General procedures*

^{1}H nuclear magnetic resonance (NMR) spectra were recorded with a Bruker DRX 300 spectrometer (300 MHz, FT NMR) using tetra methyl silane (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. Mass spectroscopy (MS) spectra were recorded with a Jeol SX-102 (FAB) instrument. Elemental analyses (C,H,N) were performed with a Perkin-Elmer 2400 series CHN analyser. All the reactions were monitored by thin-layer chromatography (TLC) using 0.25 mm silica gel plates (Merck 60F_{254} UV indicator), while column chromatography was performed with silica gel (E Merck India) 60–200 mesh. Starting materials and reagents used in the reactions (*N*-benzylhydroxylamine, 2,6 difluoro benzaldehyde) were obtained commercially from Aldrich, Lancaster, and were used without purification, unless otherwise indicated. All other reagents and solvents were purified after receiving from commercial suppliers.

2.1a *General procedure of synthesis of N-benzyl fluoro nitrone (1) in ionic liquid*: 2,6-Difluoro benzaldehyde (1 mmol) and *N*-benzylhydroxylamine (1 equivalent) was added to [bmim]BF_4 (2 mL) in a 10 mL conical flask, mixed thoroughly and stirred at room temperature for 60 min. The formation of nitrone was monitored by TLC (R_f = 0.40). After completion of reaction, the reaction mixture was washed with diethyl ether (3 × 10 mL) and the combined ether extract was concentrated *in vacuo* to obtain nitrone (**1**) as white crystalline solid (m.p 42°C, uncorrected). As the nitrone decomposes at room temperature, *in situ* reactions were performed with alkene and alkynes.

2.1b *Spectroscopic data of nitrone **1***: UV λ_{max} 238 nm; IR (KBr): υ_{max} 3025 (m), 2235 (m), 1680 (m), 1610 (s), 1440 (m), 1154 (m), 784 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.96–7.79 (m, 3H, $C_6H_3F_2$), 7.67–7.35 (m, 5H, $C_6H_5CH_2$), 6.98 (s, 1H,–CH=N^+), 3.37 (s, 2H, $C_6H_5CH_2$). ^{13}CNMR ($CDCl_3$): δ 142.04 (CH=N^+), 134.80, 134.34, 134.12, 133.93 (phenyl carbons), 131.60, 130.00, 129.55, 129.46, 128.67, 128.22 (2,6 difluoro phenyl carbons).

2.1c *General procedure of synthesis of novel diastereomeric fluoro isoxazolidine derivatives (**2–4**) in ionic liquid*: *N*-phenyl maleimide (1 equivalent) was added *in situ* at the time of development of nitrone **1** and the reaction mixture was further stirred at room temperature for an appropriate time (table 1). After completion of reaction, as indicated by TLC (R_f = 0.58, 0.64), the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extracts were concentrated *in vacuo* and the resulting product mixture was directly charged on silica gel column and eluted with a mixture of ethyl acetate:n-hexane (1:8) to afford pure fluoro isoxazolidines **2a** and **2b** (88%, entry 1, table 1, scheme 1). 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. Same methodology was adopted for the synthesis of other novel fluoro isoxazolidine derivatives (entries 2 and 3).

2.1d *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**2a**)*: White crystals. Yield 66%; R_f = 0.58; IR (KBr): υ_{max} 3020 (m), 2920 (m), 2835 (m), 1758 (s), 1690 (s), 1480 (m), 1346 (m), 805 (s), 770 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.74–7.68 (m, 3H, $C_6H_3F_2$), 7.12–6.83 (m, 2 × 5H, C_6H_5 protons), 5.84 (d, 1H, J = 6.70 Hz, C_5H), 3.40 (dd, 1H, J = 6.06, 6.18 Hz, C_4H), 3.54 (s, 2H, $C_6H_5CH_2$), 2.95 (d, 1H, J = 6.32 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 173.42, 173.10 (carbonyl carbons), 138.10, 138.06, 138.02, 137.97, 136.86, 136.81, 136.78, 136.75 (phenyl carbons), 134.34, 134.14, 134.06, 133.76, 133.65 (2,6 difluoro phenyl carbons), 85.22 (C_5), 77.20 (C_3), 58.46 (C_4), 39.55 ($\underline{CH_2}C_6H_5$); FAB-MS: m/z 420 (M^+, 100%), 343, 329, 306, 252, 216 (B.P.), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66 %. Found: C, 68.44; H, 4.19; N, 6.52.

2.1e *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-phenyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**2b**)*: White crystals. Yield 22 %; R_f = 0.64; IR (KBr): υ_{max} 3010 (m), 2915 (m), 2830 (m), 1764 (s), 1685 (s), 1486 (m), 1340 (m), 864 (s), 783 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.70–7.66 (m, 3H, $C_6H_3F_2$), 7.30–7.12 (m, 2 × 5H, C_6H_5 protons), 5.76 (d, 1H, J = 2.24 Hz, C_5H), 3.63 (dd, 1H, J = 2.26, 2.08 Hz, C_4H), 3.28 (s, 2H, $C_6H_5CH_2$), 3.06 (d, 1H, J = 3.04 Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 172.40, 172.24 (carbonyl carbons), 137.80, 137.74, 137.72, 137.57, 137.36, 136.34, 136.26, 136.18 (phenyl carbons), 134.80, 134.60, 134.44, 134.22, 134.13 (2,6 difluoro phenyl carbons), 80.65 (C_5), 76.52 (C_3), 57.90 (C_4),

41.24 ($\underline{CH_2}C_6H_5$); FAB-MS: m/z 420 (M^+, 100%), 343, 329, 306, 216 (B.P.), 113, 91, 77; Anal. Calcd. for $C_{24}H_{18}O_3N_2F_2$: C, 68.57; H, 4.28; N, 6.66%. Found: C, 68.49; H, 4.17; N, 6.50.

2.1f *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-methyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**3a**)*: White solid. Yield 65%; $R_f = 0.54$; IR (KBr): υ_{max} 3005 (m), 2935 (m), 2820 (m), 1760 (s), 1675 (s), 1465 (s), 1340 (m), 814 (s), 778 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.89–7.86 (m, 3H, $C_6H_3F_2$), 7.64–7.46 (m, 5H, C_6H_5 protons), 6.56 (d, 1H, $J = 6.10$ Hz, C_5H), 3.89 (s, 2H, $C_6H_5CH_2$), 3.79 (dd, 1H, $J = 6.00$, 5.90 Hz, C_4H), 3.49 (s, 3H, N–CH_3), 2.95 (d, 1H, $J = 6.76$ Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 170.58, 170.50 (carbonyl carbons), 136.44, 136.40, 136.32, 136.25 (phenyl carbons), 132.70, 132.64, 132.51, 132.43, 132.18 (2,6 difluoro phenyl carbons), 82.98 (C_5), 76.66 (C_3), 59.70 (C_4), 39.60 ($\underline{CH_2}C_6H_5$), 37.54 (N–CH_3); FAB-MS: m/z 358 (M^+, 100%), 345, 267, 252, 244, 154 (B.P.), 113, 91; Anal. Calcd. for $C_{19}H_{16}O_3N_2F_2$: C, 63.68; H, 4.46; N, 7.82 %. Found: C, 63.49; H, 4.36; N, 7.57.

2.1g *2-Benzyl-3-(2,6-difluorophenyl)-dihydro-5-methyl-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**3b**)*: White solid. Yield 21 %; $R_f = 0.60$; IR (KBr): υ_{max} 3015 (m), 2905 (m), 2828 (s), 1760 (s), 1680 (s), 1460 (s), 1355 (m), 820 (s), 783 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.88–7.84 (m, 3H, $C_6H_3F_2$), 7.60–7.49 (m, 5H, C_6H_5 protons), 6.52 (d, 1H, $J = 3.22$ Hz, C_5H), 3.84 (s, 2H, $C_6H_5CH_2$), 3.76 (dd, 1H, $J = 1.96$, 2.12 Hz, C_4H), 3.47 (s, 3H, N-CH_3), 2.96 (d, 1H, $J = 1.96$ Hz, C_3H); ^{13}C NMR ($CDCl_3$): δ 171.34, 171.27 (carbonyl carbons), 135.98, 135.94, 135.82, 135.75 (phenyl carbons), 133.12, 133.04, 132.91, 132.83, 132.77 (2,6 difluoro phenyl carbons), 84.08 (C_5), 73.80 (C_3), 54.95 (C_4), 41.42 ($\underline{CH_2}C_6H_5$), 39.05 (N–CH_3); FAB-MS: m/z 358 (M^+, 100%), 345, 267, 252, 154 (B.P.), 113, 91, 77; Anal. Calcd. for $C_{19}H_{16}O_3N_2F_2$: C, 63.68; H, 4.46; N, 7.82%. Found: C, 63.42; H, 4.32; N, 7.62.

2.1h *2-Benzyl-5-cyclohexyl-3-(2,6-difluorophenyl)-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**4a**)*: Yellow crystals. Yield 63%, $R_f = 0.50$; IR (KBr): υ_{max} 3015 (m), 2900 (s), 2840 (m), 1760 (s), 1674 (br, s), 1470 (s), 1330 (m), 805 (s), 786 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.60–7.56 (m, 3H, $C_6H_3F_2$), 7.17–7.06 (m, 5H, C_6H_5 protons), 6.30 (d, 1H, $J = 6.74$ Hz, C_5H), 3.60 (s, 2H, $C_6H_5CH_2$), 3.42 (dd, 1H, $J = 6.20$, 6.10 Hz, C_4H), 2.83 (d, 1H, $J = 6.76$ Hz, C_3H), 1.95–1.52 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 168.54, 168.50 (carbonyl carbons), 131.66, 131.60, 131.55, 131.50 (phenyl carbons), 129.15, 129.06, 128.80, 128.73, 128.68 (2,6 difluoro phenyl carbons), 83.60 (C_5), 74.55 (C_3), 58.24 (C_4), 38.78 ($\underline{CH_2}C_6H_5$), 27.40, 27.29, 26.87, 26.70, 26.58, 26.46 (cyclohexyl carbons); FAB-MS: m/z 426 (M^+, 100 %), 343, 335, 312, 252, 222 (B.P.), 113, 91, 83; Anal. Calcd. for $C_{24}H_{24}O_3N_2F_2$: C, 67.60; H, 5.63; N, 6.57 %. Found: C, 67.46; H, 5.35; N, 6.37.

2.1i *2-Benzyl-5-cyclohexyl-3-(2,6-difluorophenyl)-dihydro-2H-pyrrolo[3,4-d]isoxazole-4,6(5H,6 a-H)-dione (**4b**)*: Yellow crystals. Yield 22 %, $R_f = 0.62$; IR (KBr): υ_{max} 3010 (m), 2905 (s), 2835 (m), 1764 (s), 1675 (s), 1466 (s), 1336 (m), 815 (s), 783 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.52–7.85 (m, 3H, $C_6H_3F_2$), 7.25–7.14 (m, 5H, C_6H_5 protons), 6.14 (d, 1H, $J = 1.88$ Hz, C_5H), 3.55 (s, 2H, $C_6H_5CH_2$), 3.38 (dd, 1H, $J = 2.08$, 2.04 Hz, C_4H), 2.80 (d, 1H, $J = 1.80$ Hz, C_3H), 1.90–1.38 (m, 11H, cyclohexyl protons); ^{13}C NMR ($CDCl_3$): δ 169.88, 169.83 (carbonyl carbons), 130.54, 130.49, 130.45, 130.32 (phenyl carbons), 128.77, 128.68, 128.56, 128.53, 128.48 (2,6 difluoro phenyl carbons), 80.44 (C_5), 77.50 (C_3), 58.97 (C_4), 37.05 ($\underline{CH_2}C_6H_5$), 25.30, 25.22, 25.17, 25.06, 24.88, 24.76 (cyclohexyl carbons); FAB-MS: m/z 426 (M^+, 100 %), 343, 312, 252, 222 (B.P.), 113, 91, 83, 77; Anal. Calcd. for $C_{24}H_{24}O_3N_2F_2$: C, 67.60; H, 5.63; N, 6.57%. Found: C, 67.37; H, 5.40; N, 6.33.

2.1j *General procedure of synthesis of novel fluoro isoxazoline derivatives (**5–7**) in ionic liquid*: Methyl phenyl propiolate (1 equivalent) was added *in situ* at the time of development of nitrone **1** and the reaction mixture was further stirred at room temperature for an appropriate time (table 1). After completion of reaction, as indicated by TLC ($R_f = 0.66$), the reaction mixture was washed with diethyl ether (3 × 10 mL). The combined ether extract was concentrated *in vacuo* and the resulting crude product was directly charged on silica gel column and eluted with a mixture of ethyl acetate:*n*-hexane (1:8) to afford pure fluoro isoxazoline **5** (88%, entry 4, table 1, scheme 1). 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. Same methodology was adopted for the synthesis of other novel fluoro isoxazoline derivatives (entries 5 and 6).

2.2 *Methyl-2-benzyl-3-(2,6-difluorophenyl-2,3-dihydro-5-phenylisoxazole-4-carboxylate (**5**)*

Dark red thick liquid. Yield 88%; $R_f = 0.66$; IR (KBr): υ_{max} 3010 (m), 2246 (m), 1740 (s), 1710 (s), 1690 (s), 1610 (s), 1480 (s), 1324 (s), 1215 (s), 810 (m), 782 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87–7.80 (m, 3H, $C_6H_3F_2$), 7.68–7.31 (m, 2 × 5H, C_6H_5), 3.38 (s, 3H, –$COOCH_3$), 2.68 (s, 2H, $C_6H_5CH_2$), 1.25 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 168.52 (–$\underline{CO}OCH_3$), 137.20, 137.04, 136.87, 136.66, 135.65, 135.48, 135.20, 134.93 (aromatic carbons), 132.77, 132.35, 132.08, 131.78, 130.80, 129.90 (2,6 difluoro phenyl carbons), 88.16 (C_5), 73.60 (C_3), 58.45 (C_4), 45.17 (–$COO\underline{CH_3}$), 36.80 (benzylic carbon); FAB-MS (*m*/*z*): 407 ($\overline{M^+}$), 330, 294, 211 (B.P.), 203, 113, 105, 91, 77. Anal. Calcd. for $C_{24}H_{19}O_3F_2N$: C, 70.76; H, 4.66; N, 3.43. Found: C, 70.63; H, 4.61; N, 3.35%.

2.2a *Dimethyl-2-benzyl-3-(2,6-difluorophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylate (**6**)*: Red viscous liquid. Yield 86%; $R_f = 0.60$; IR (KBr): υ_{max} 3015 (m), 2250 (m), 1725 (s), 1685 (s), 1610 (s), 1440 (s), 1260 (s), 1225 (s), 805 (m), 780 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.44–7.36 (m, 3H, $C_6H_3F_2$), 7.10–6.98 (m, 5H, C_6H_5), 3.30 (s, 3H, –$COOCH_3$), 3.24 (s, 3H, –$COOCH_3$), 2.55 (s, 2H, $C_6H_5CH_2$), 1.72 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 169.74, 169.58 (–$\underline{CO}OCH_3$, carbonyl carbons of the ester group), 135.80, 135.73, 135.54, 135.47 (aromatic carbons), 133.30, 133.28, 133.24, 133.15, 133.12, 133.05 (2,6 difluoro phenyl carbons), 85.25 (C_5), 77.80 (C_3), 56.90 (C_4), 45.74, 44.82 (–$COO\underline{CH_3}$, methyl carbons of the ester methyl group), 39.23 (benzylic carbon); FAB-MS (*m*/*z*): 389 (M^+), 358, 330, 302, 276, 271 (B.P.), 185, 113, 91, 77; Anal. Calcd. for $C_{20}H_{17}O_5F_2N$: C, 61.69; H, 4.37; N, 3.59. Found: C, 61.58; H, 4.26; N, 3.35%.

2.2b *2-Benzyl-3-(2,6-difluorophenyl)-2,3-dihydroisoxazole-4,5-dicarboxylic acid (**7**)*: Colourless thick liquid. Yield 66%; $R_f = 0.66$; IR (KBr): υ_{max} 3010 (m), 2995 (br), 2246 (m), 1760 (s), 1610 (s), 1480 (s), 1324 (s), 1215 (s), 1105 (s), 800 (m), 782 (s) cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.02 (s, 2H, 2XCOOH), 7.90–7.87 (m, 3H, $C_6H_3F_2$), 7.66–7.44 (m, 5H, C_6H_5), 2.91 (s, 2H, $C_6H_5CH_2$), 2.88 (s, 1H, C_3H); ^{13}C NMR ($CDCl_3$): δ 173.69, 172.04 (carboxyl carbons), 138.50, 138.44, 138.37, 138.26 (aromatic carbons), 135.44, 135.40, 135.28, 134.93, 134.87, 134.75 (2,6 difluoro phenyl carbons), 88.20 (C_5), 74.43 (C_3), 58.60 (C_4), 37.87 (benzylic carbon); FAB-MS (*m*/*z*): 361 (M^+), 344, 316, 288, 271 (B.P.), 248, 157, 113, 91, 77. Anal. Calcd. for $C_{18}H_{13}O_5F_2N$: C, 59.83; H, 3.60; N, 3.87. Found: C, 59.75; H, 3.40; N, 3.58%.

3. Results and discussion

As an example, the reaction between **1** and alkynes, afforded cycloaddition derivative **5** after 17 h in CH_2Cl_2 in 67% yield and 88% yield (entry **4**) in [bmim]BF_4 at room temperature after 26 min, respectively. In a typical procedure, 1 mmol of nitrone was mixed with 1 equivalent of alkynes/alkenes in [bmim]BF_4 (2 mL) under stirring, at room temperature. After the development of nitrone (monitored by TLC), 1 mmol of dipolarophile was added *in situ* and 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. 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 out many more times. Excellent diastereofacial selectivity and faster reaction reaction rates have been observed when the reaction of nitrone **1** with activated alkenes (maleimides) are carried out in room temperature ionic liquids (RTILs). For example, the reaction between **1** with *N*-phenyl maleimide, afforded cycloaddition derivatives **2a** and **2b** after 12 h in CH_2Cl_2 in 68% yield and 88% yield (entry 1) in [bmim]BF_4 at room temperature after 26 min, respectively. The addition of nitrone **1** to maleimides results in a mixture of diastereomer **2a**–**4a** and **2b**–**4b** (almost 65:25 ratio in all cases) and generation of as many as three chiral centres in a single step. Studies of organic reactions in ionic liquid show

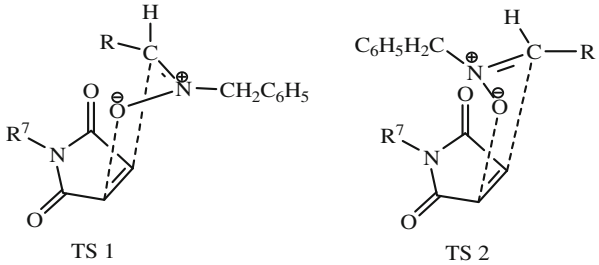
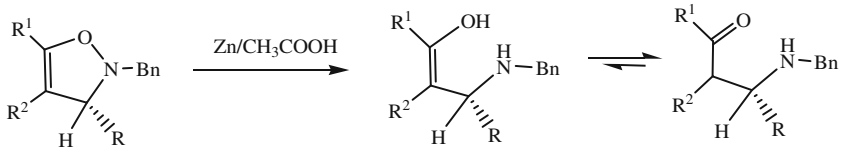


Figure 2. *Exo/endo* approach of nitrone to maleimides in cycloaddition reactions.



Scheme 2. Synthesis of 1,3 amino alcohol from isoxazoline derivatives.

that there is a higher probability of the formation of mixture of diastereomers when ionic liquid is used as solvent rather than conventional organic solvents. These results can be rationalized by an *exo* approach of nitrone **1**, which has *Z*configuration for the formation of major cycloadducts **2a**–**4a** (transition state 1, figure 2).[19] Minor cycloadducts **2b**–**4b** are formed by the *endo* approach of *Z* nitrone (transition state 2, figure 2).[19] The mixture of diastereomers is identified by considering the multiplicity of the proton signals at 3-H and 4-H along with their coupling constant values.[20,21] The most significant differences in the ^{1}H NMR data for the diastereomers is the position and multiplicity of the 3-H signal. In the major adducts **2a**–**4a**, coupling constant between 3-H and 4-H has been measured as $J_{3,4} \sim 6.26$ Hz implying a *cis* relationship between H-3 and H-4, while for minor adducts **2b**–**4b**, $J_{3,4}$ is ~2.26 Hz implies a *trans* relationship between H-3 and H-4.[20,21]

Several butylmethylimidazolium based ionic liquids (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 (88%) and reaction time (26 min) as compared with [bmim]PF_6 (84%; 43 min; entry 4). For optimizing 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. We examined the reaction 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 reaction (table 1).

All the novel fluoro cycloadducts are stable and prominent molecular ion peak, base peaks are obtained in the mass spectrum as expected. In case of fluoro isoxazoline derivatives (**5**–**7**), we have also obtained expected fragmentation peaks 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. Expected signals in ^{1}H NMR, ^{13}C NMR, Fourier transformer infrared spectroscopy (FT-IR) were obtained for all the isoxazolidine and isoxazoline derivatives (**2**–**7**). Satisfactory elemental analysis values were also obtained for all the novel cycloadducts.

Furthermore, synthetic potential of the novel fluoro isoxazoline derivatives (**5**–**7**) are tremendous as they could be converted into 1,3 difunctional amino alcohols (scheme 2). Studies are in progress.

Synthetic potentiality of nitrone **1** has been tested successfully as an oxidizing reagent in the conversion of alkyl halides to aldehydes and ketones (scheme 1) following a pattern of atom efficient reactions reported by our group.[14] Studies are in progress at present in our laboratory. We have already reported synthesis of various aldehydes and ketones from alkyl halides using α-chloro nitrones in atom-efficient reactions.[14,22]

4. Conclusion

In conclusion, we have shown that 1,3-dipolar cycloadditions of fluoro nitrones with activated alkenes and electron deficient alkynes may be conveniently carried out in RTIL's by obtaining corresponding novel fluoro isoxazolidines and isoxazolines in good conversions and yields with tremendous synthetic potentiality. The ionic liquid may be recycled several times without loss of activity or selectivity.

Supporting Information

The electronic supporting information can be seen in www.ias.ac.in/chemsci.

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