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An efficient ecofriendly protocol for the synthesis of novel fluoro isoxazoline and isoxazolidines using *N*-benzyl fluoro nitrone via cycloaddition reactions

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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 nitrones derived in situ from aldehydes and benzylhydroxylamine, with electron deficient alkynes to afford enhanced rates and improved yields of isoxazolines while with enals exclusively *endo* isoxazolidines are obtained with high selectivity. Synthetic potentiality of the novel isoxazolines and nitrones has also been tested successfully.

The 1,3-dipolar cycloaddition reactions represent the favourite method for the construction of five-membered heterocycles, the important frameworks of various natural products.[1] In particular the 1,3-dipolar cycloadditions of nitrones with alkenes and alkynes afforded isoxazolidines and isoxazolines which are interesting intermediates for the synthesis of β-amino alcohols and alkaloids.[2,3] Isoxazoline and isoxazolidines possess medicinal activities such as antibacterial, anticonvulsant, antibiotic, antitubercular and antifungal.[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 (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 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 a 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 the high electro negativity of the halogen, the strong C–F bond and the similar size of the

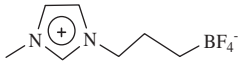

Figure 1. Chemical structure of ionic liquid.

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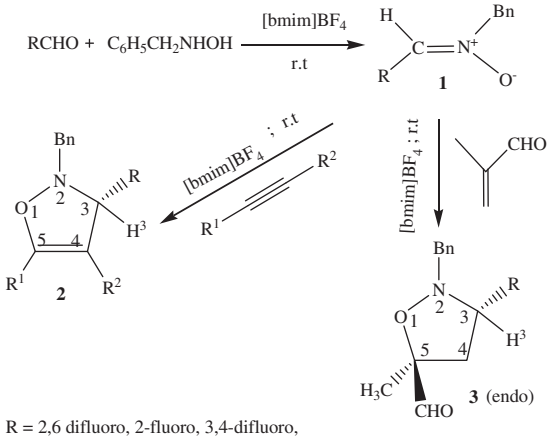
halogen and hydrogen atoms. For these reasons great efforts have been placed on the development and evaluation of biologically active fluorinated materials.[12] The biological properties of multifluorine containing compounds have been recently investigated. Owing to their unique properties, such as high thermal stability and lipophilicity, fluoro-organic compounds have been frequently used as biorelated material, medicine and agrochemicals.[13] The presence of a fluoro group (C–F group) due to low polarizability and high lipophilicity induces a relative metabolic stability and improves the bioavailability of the modified heterocycles compared to its hydrocarbon analogues.[14,15]

In continuation of our effort to establish green methodologies in nitrone cycloaddition reactions,[16–20] herein we wish to report the use of ionic liquids as recyclable solvents for 1,3-dipolar cycloaddition reactions of *N*-benzyl fluoro nitrone (having vast synthetic potentials) with electron deficient alkynes and alkenes (enals) to produce novel isoxazoline and isoxazolidine derivatives in a one-pot operation (Scheme 1).

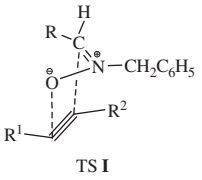
Compared to conventional conditions the cycloaddition reactions performed in ionic liquids are much faster and selective. As



R = 2,6 difluoro, 2-fluoro, 3,4-difluoro,
4-fluoro, 2-hydroxy, 4-hydroxy benzene/ phenyl
$R^1 = C_6H_5$; $R^2 = COOCH_3$
$R^1 = COOCH_3$; $R^2 = COOCH_3$
$R^1 = R^2 = COOH$
Bn = Benzyl

Scheme 1.

an example, the reaction between **1** and alkynes, afforded the cycloaddition derivative **2** after 17 h in CH_2Cl_2 in 67% yield and 93% yield (entry 1) in $[bmim]BF_4$ at room temperature after 26 min 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 room temperature. After the development of nitrone (monitored by TLC), 1 mmol of dipolarophile was added 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. 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. 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 (93%) and reaction time (26 min) as compared with $[bmim]PF_6$ (84%; 43 min; entry 1). 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. We examined the reaction under neat condition also, without using IL, to demonstrate the catalytic ability of $[bmim]BF_4$ This result clearly indicates that $[bmim]BF_4$ has significant catalytic role in this reaction (Table 1). The addition of nitrone **1** to alkynes and alkenes (enals) can be rationalized by an *exo* and *endo* approach of the nitrone which has the Z configuration (transition state **I** and **II**).[21]



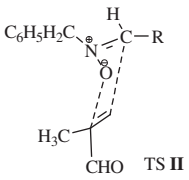
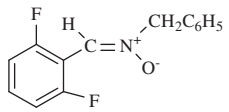
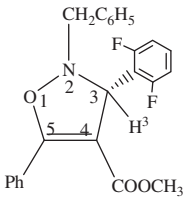
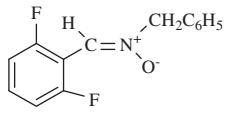
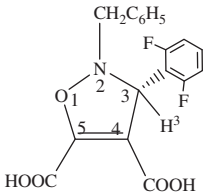


Table 1
1,3-Dipolar cycloaddition reactions of *N*-benzyl fluoro nitrone with alkynes in ionic liquid.

Entry	Nitrone[a]	Alkyne	Product[b] (**2**)	Time (min)	Yield[c] (%)
1				26 (1020)	93 (67)
2				35 (1080)	91 (64)