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Ionic liquids/H_2O systems for the reaction of epoxides with NaN_3: a new protocol for the synthesis of 2-azidoalcohols

J. S. Yadav,* B. V. S. Reddy, B. Jyothirmai and M. S. R. Murty

Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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Abstract—Oxiranes undergo ring opening rapidly with sodium azide in a [bmim]BF_4/H_2O or [bmim]PF_6/H_2O (2:1) solvent system, under mild and neutral reaction conditions to afford the corresponding 2-azidoalcohols in high to quantitative yields. The remarkable features of this procedure are improved yields, enhanced reaction rates, high regioselectivity and ease of recyclability of ionic liquids (ILs). The recovered ionic liquid can be reused for four to five times but with gradual decrease in activity.

2-Azidoalcohols are important precursors for the synthesis of β-aminoalcohols,[1] some of which are of significance as β-adrenergic blocking agents, as highly effective antagonists for the treatment of cardiovascular diseases, cardiac failure and asthma, and are also useful as chiral auxiliaries in asymmetric synthesis.[2] They are also useful intermediates for the synthesis of amino sugars and carbocyclic nucleosides.[3] The simple and the most straightforward synthetic method for the preparation of 2-azidoalcohols involves the regioselective ring opening of oxiranes with sodium azide under various reaction conditions.[1] These epoxide opening reactions are, however, generally carried out under either acidic or basic conditions[1,3,4] and they usually require high temperatures and/or long reaction times, and side reactions, such as isomerization, epimerization and rearrangements may be induced by the alkaline conditions. Furthermore, high temperatures are not only detrimental to certain functional groups, but also to the control of regioselectivity. A variety of activators or promoters have been reported to assist epoxide ring-opening reactions with sodium azide under mild conditions.[5–7] Since 2-azidoalcohols have become increasingly useful and important in drugs and pharmaceuticals, the development of simple, efficient and environmentally friendly processes for their synthesis is desirable.

In recent years, ionic liquids have emerged as alternative reaction media for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[8] They are solvents with unique properties such as tunable polarity, high thermal stability, immiscibility with a number of organic solvents, negligible vapour pressure and ease of recyclability. 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 the organic cation (Fig. 1).

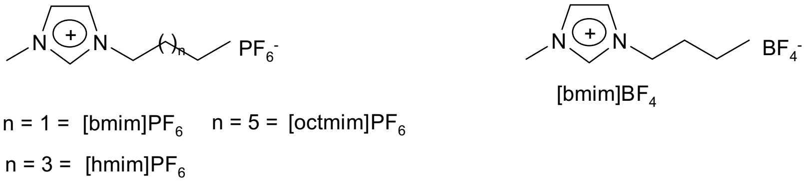

Figure 1. Chemical structure of the ionic liquids.

Keywords: Ionic liquids (ILs); Oxiranes; Azidoalcohols.

* Corresponding author. Fax: +91 40 27160512; e-mail: yadavpub@iict.res.in

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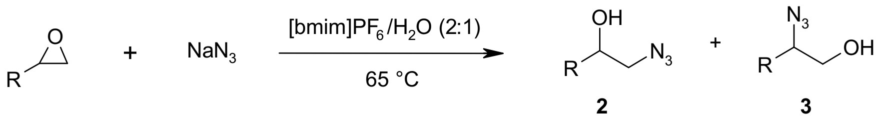


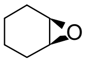
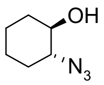
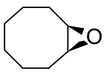
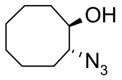
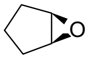
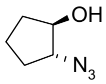
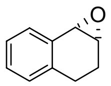
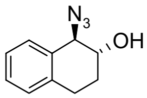
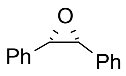
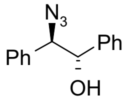
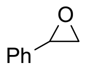
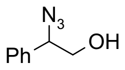
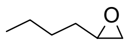
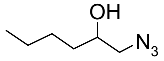
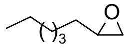
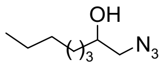
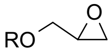
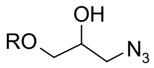
Scheme 1.

These structural variations offer flexibility to the chemist to find the best solvent, catering to the needs of any particular process. 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]

In this article, we report the use of ionic liquids as novel and recyclable reaction media for the synthesis of 2-azidoalcohols from oxiranes and sodium azide under mild and neutral conditions (Scheme 1).

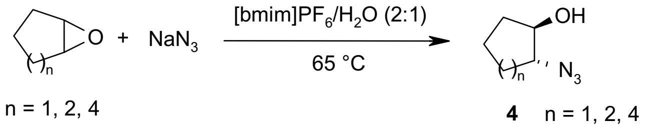
Treatment of 3-phenoxy-1,2-epoxypropane with sodium azide in a 1-butyl-3-methylimidazolium hexafluorophosphate/water (2:1) solvent system for 3 h afforded the corresponding 2-azidoalcohol **2** (R = $PhOCH_2$) in 95% yield. The product was isolated by simple extraction with diethyl ether. The rest of the ionic liquid was washed further with ether and reused in successive runs without further purification. Encouraged by the results obtained with 3-phenoxy-1,2-epoxypropane, we examined several other epoxides (Table 1). Various 3-aryloxy-1,2-epoxypropanes and aliphatic oxiranes reacted

Table 1. Synthesis of 2-azidoalcohols in 1-butyl-3-methylimidazolium ionic liquids

Entry	Epoxide		Product[a]		[bmim]PF_6–H_2O		[bmim]BF_4–H_2O	
					Time (h)	Yield (%)[b]	Time (h)	Yield (%)[b]
a				**4a**	3.0	95	4.5	89
b				**4b**	5.0	87	6.0	81
c				**4c**	3.5	90	5.5	85
d				**4d**	4.0	94	5.0	87
e				**5e**	3.5	93	4.5	88
f				**3f**	3.0	91(5)	5.5	84(11)
g				**2g**	4.5	90(8)	6.0	87(9)
h				**2h**	4.0	89(9)	4.5	85(12)
								
i	R = phenyl		R = phenyl	**2i**	3.0	95	5.0	89
j	R = *p*-Cl-phenyl		R = *p*-Cl-phenyl	**2j**	4.5	93	6.0	85
k	R = benzyl		R = benzyl	**2k**	5.0	90	6.5	87
l	R = *p*-MeO-phenyl		R = *p*-MeO-phenyl	**2l**	4.0	94	5.5	82
m	R = *p*-Me-phenyl	**1m**	R = *p*-Me-phenyl	**2m**	3.5	96	4.0	85
n	R = *p*-isopropylphenyl	**1n**	R = *p*-isopropylphenyl	**2n**	4.0	92	5.5	89
o	R = 2-naphthyl	**1o**	R = 2-naphthyl	**2o**	5.0	90	7.0	84

[a] All the products have been reported previously.[12]

[b] Yields refer to isolated pure products after purification by column chromatography. Yields in parentheses refer to the other regioisomer as determined by GLC analysis.



Scheme 2.

smoothly with sodium azide under similar reaction conditions to produce the corresponding 2-azidoalcohols in excellent yields. Styrene epoxide and tetrahydronaphtho-[1,2-*b*]oxirane underwent cleavage with sodium azide with preferential attack at the benzylic position to give the corresponding azidohydrins in 94% and 91% yields, respectively[10] (Table 1, entries d and f). The stereochemistry of the product **4d** was found to be trans based on the ^{1}H NMR coupling constants. The ^{1}H NMR coupling constants of **4d** are δ 4.41 (d, $J = 7.1$ Hz, 1H) for (–CHN$_3$). The large coupling constant values are in accordance with trans stereochemistry. The product **5e** (Table 1, entry e) obtained from *cis*-stilbene was the *anti*-isomer based on the ^{1}H NMR coupling constants δ 4.50 (d, $J = 6.5$ Hz, 1H) for (–CHN$_3$) and δ 4.65 (d, $J = 6.5$ Hz, 1H) for (–CHOH). Bicyclic oxiranes such as cyclopentene, cyclohexene and cyclooctene epoxides also underwent cleavage with sodium azide to produced 2-azidoalcohols **4** in high yields (Scheme 2).

Except for the reactions of styrene oxide, hexene oxide and octene oxide, which produced minor amounts of the other regioisomer (5%, 8% and 9%), the reactions of other epoxides were found to be highly regioselective affording a single product in high to quantitative yield. The stereochemistry of the ring-opened products from bicyclic epoxides was found to be trans from the coupling constants of the ring hydrogens as has been observed in most epoxide ring-opening reactions.[5–7] The direction of ring opening is that characteristically observed for terminal epoxides under S$_N$2 conditions, probably dictated by steric and electronic factors. In the absence of the ionic liquid, the reactions were very slow in water, resulting in low yields. The addition of ionic liquid significantly improved the reaction rates and yields. This is probably due to activation of the epoxide by the acidic nature of the ring hydrogen of the imidazole moiety. Thus, the combination of ionic liquid and water as solvent system (2:1) was found to be an effective reaction media for this conversion. The cleavage of epoxides with sodium azide was performed in both hydrophilic [bmim]BF$_4$ and hydrophobic [bmim]PF$_6$ ionic liquids, the latter being superior in terms of conversion. The main advantage of the use of ionic liquids is that these molten salts can be easily recovered on work-up. Since the products were fairly soluble in the ionic liquids, they could be easily separated by simple extraction with ether. The remaining ionic liquid was thoroughly washed with ether and reused for four to five subsequent runs, but with a gradual decrease in activity. For example, treatment of 3-phenoxy-1,2-epoxypropane with sodium azide in [bmim]PF$_6$ afforded the 2-azidoalcohol in 95%, 90%, 87%, 83% and 79% yields over five runs. Even though, the yields decreased gradually in runs performed using recovered ionic liquid, the products obtained were of the same purity as in the first run. In terms of efficiency and selectivity, this procedure has advantages over either protic or Lewis acid catalyzed procedures. The scope and generality of this process is illustrated with respect to various epoxides and sodium azide[11] and the results are presented in Table 1.

In summary, an ionic liquid/water solvent system was proved to be an effective reaction medium for the synthesis of 2-azidoalcohols from epoxides by playing the dual role of solvent as well as promoter. The epoxides showed a significant increase in reactivity thereby reducing the reaction times and improving the yields substantially. Simple experimental and product isolation procedures combined with ease of recovery and reuse of this reaction media is expected to contribute to the development of green strategy for the preparation of 2-azidoalcohols.

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11. Experimental procedure: Epoxide (1 mmol) and sodium azide (1.5 mmol) in 1-butyl-3-methylimidazolium hexafluorophosphate/water (2:1, 3 mL) were stirred at 65 °C for an appropriate time (Table 1). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3×10 mL). The combined ether extracts were concentrated in vacuo and the resulting product was directly charged onto a small silica gel column and eluted with a mixture of ethyl acetate/*n*-hexane (2:8) to afford the pure 2-azidoalcohol. The remainder of the ionic liquid was washed with ether and recycled in subsequent runs. The azidoalcohols thus obtained were identified by comparison of their NMR, IR Mass, TLC, mixed TLC analysis and physical data with authentic samples. The spectral data of all the products were identical with those of the authentic samples.[12]
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