Green Protocol for the Synthesis of *vicinal*-Halohydrins from Oxiranes Using the [Bmim]PF_6/LiX Reagent System

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Epoxides undergo rapid ring-opening with lithium halides in [bmim]PF_6 or [bmim]BF_4 ionic liquids under mild and neutral conditions to afford the corresponding *vic*-halohydrins in high to quantitative yields. The epoxides show enhanced reactivity in ionic liquids thereby reducing reaction times and improving the yields significantly. The recovered ionic liquid can be reused in three to four subsequent runs with consistent activity.

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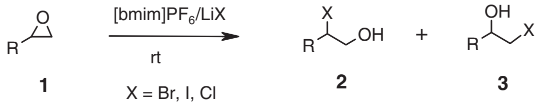
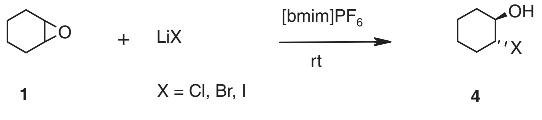
vic-Halohydrins have found wide spread application in organic synthesis. They are key intermediates in the synthesis of several halogenated marine natural products[1] and also in various useful synthetic transformations.[2] The most common method for the preparation of halohydrins involves ring-opening of epoxides either by hydrogen halides or by hydrohalogenic acids. These procedures are generally associated with by-products such as *vic*-dihalides and 1,2-diols.[3] Substantial efforts have been made in the last few years to develop new procedures for converting epoxides into halohydrins under mild conditions.[4] In this direction, many reagents such as halosilanes, haloboranes, and metal halides such as LiX–AcOH, LiX–SiO_2, LiX–TiX_4, NaX–$InCl_3$, and NaX–$CeCl_3$ have been reported for the conversion of epoxides to halohydrins.[5,7] Among these reagents, lithium halides are versatile because of their high reactivity and ready availability at low cost and also facilitate the ring-opening under mild conditions. However, the use of stronger Lewis acids or protic acids often results in low yields of halohydrins when applied to epoxides bearing acid sensitive functionalities. Subsequently, elemental halogens have also been employed for the conversion of epoxides into halohydrins, however, this method suffers from low conversions, prolonged reaction times and poor regioselectivity and also the formation of acetonide as reaction by-product in addition to the expected halohydrins.[8] Furthermore, many of these reagents always demand aqueous work-up for their separation or recycling or disposal. Since β-halohydrins have become increasingly useful and important in drugs and pharmaceuticals, the development of simple, efficient and environmentally benign processes are desirable.

Recently, ionic liquids have gained recognition as possible environmentally benign alternatives to more volatile organic solvents. Ionic liquids possess many interesting properties such as wide liquid range, negligible vapor pressure, high thermal stability, and good solvating ability for a wide range of substrates and catalysts.[9] Their non-voltile nature can reduce the emission of toxic organic compounds and facilitate the separation of products and/or catalysts from the reaction mixture. Furthermore, ionic liquids are being used as green solvents for the immobilization of transition metal based catalysts, Lewis acids and enzymes.[10a] The hallmark of such ionic liquids is our ability to alter their properties as desired by manipulating their structure with respect to the choice of organic cation or anion and side chain attached to organic cation. These structural variations offer flexibility to the chemist to devise the most idealized solvent, catering for the needs of any particular process. Their unprecedented ability to solvate a broad spectrum of substrates of organic and inorganic nature has widened the horizon of their applicability. However, there are no examples of the use of ionic liquids as reaction medium for the synthesis of *vic*-halohydrins.

In view of recent surge in the use of ionic liquids in organic synthesis, we herein report for the first time the use of ionic liquids as recyclable solvents for the regioselective ring-opening of epoxides with lithium halides to produce halohydrins under mild and neutral conditions (Scheme 1). Accordingly, treatment of styrene oxide with lithium bromide in 1-butyl-3-methylimidazolium hexafluorophosphate [bmim]PF_6 for 1.5 h at 27 °C afforded the corresponding bromohydrin **2** in 85% yield along with the other regioisomer **3** in 12% yield. The reaction proceeds rapidly at room temperature without the need of any additional acid catalyst. Owing to the low solubility of the product in ionic medium, it could be easily separated by simple extraction with diethyl ether. The remaining ionic liquid was further washed with diethyl ether and reused several times without further purification. Styrene oxide underwent cleavage by lithium halides in a regioselective manner with preferential attack at the benzylic carbon. Similarly, lithium chloride and lithium iodide reacted efficiently with styrene oxide to produce the corresponding 2-chloro- and 2-iodohydrins. These results prompted us to extend this process to other epoxides. Interestingly, various epoxides such as 3-aryloxy-1,2-epoxy propanes and alkyl oxiranes underwent cleavage smoothly with lithium halides in ionic liquids to afford 1-halohydrins **3** in excellent yields. Aryloxy-1,2-epoxy propanes and alkyl epoxides afforded the ring-opened products **3** resulting from terminal attack of the halide ion. Furthermore, cyclohexene oxide also underwent cleavage by lithium halides in a regioselective manner to give *vic*-halohydrins **4** in high yields (Scheme 2). Except for the reactions of styrene oxide and octene oxide which produce a minor amount of the other regioisomer, the reactions of other epoxides were found to be highly regioselective affording a single product in excellent yields. In the case of cyclohexyl epoxide, the stereochemistry of the ring-opened products 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 reactions are very



Scheme 1.



Scheme 2.

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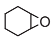
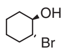
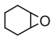
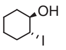
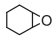
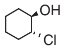
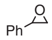
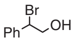
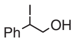
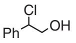
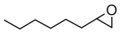
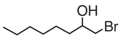
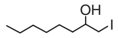
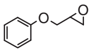
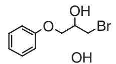
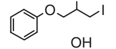
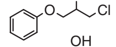
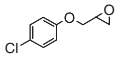
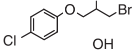
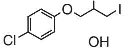
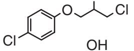
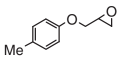
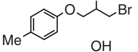
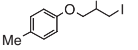
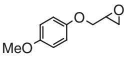
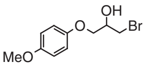
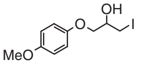
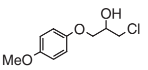
clean and highly regioselective, affording halohydrins in excellent yields and no side products or decomposition of the products were observed under the reaction conditions. In the absence of ionic liquid, the reaction was sluggish and most of the unreacted starting material was recovered. The main advantage of the use of ionic liquids is that they can be easily recovered while work-up and reused for three to four runs with consistent in activity. For instance, treatment of 3-phenoxy-1,2-epoxy propane with lithium iodide in [bmim]PF_6 ionic liquid afforded the corresponding iodohydrin in 96, 95, 94, and 95% yields over four cycles. Moreover, the products thus obtained were of the same purity as in the first run. Furthermore, the recovery and reuse of [bmim]PF_6 is facilitated by its hydrophobic nature.[12] Although, similar results were obtained using [bmim]BF_4, longer reaction times are required to achieve complete conversion. In order to compare the efficiency of ionic liquids, the reactions were also performed in organic solvents such as acetonitrile and tetrahydrofuran.

In these organic solvents, the epoxides were unreacted even after long reaction times (6–10 h). In contrast to conventional solvents, enhanced reaction rates, improved yields and high regioselectivity are the features obtained by ionic liquids. Owing to the activation of the epoxide by the acidic hydrogen of imidazole, the ring-opening of epoxides is facilitated by ionic liquids. This type of ionic environment cannot be achieved by conventional organic solvents. Furthermore, ionic liquids induce the ring-opening of epoxides by lithium halides without the need of any additional acid catalyst. Both PF_6^- and BF_4^- ionic liquids were obtained from Fluka and used as such without any further purification. The scope and generality of this process is illustrated with respect to various epoxides and lithium halides and the results are presented in Table 1.

Table 1. Synthesis of halohydrins from epoxides using [bmim]PF_6/LiX reagent system

Entry	Epoxide	LiX	β–Halohydrin[a]	Yield/%[b]	Time/h
a		LiBr		91	2.0
b		LiI		93	1.5
c		LiCl		89	3.0[c]
d		LiBr		85(12)	1.5
e	"	LiI		87(15)	1.0
f	"	LiCl		82(10)	2.0
g		LiBr		81(13)	3.5
h	"	LiI		84(10)	3.0
i		LiBr		93	3.0
j	"	LiI		96	2.5
k	"	LiCl		90	4.0[c]
l		LiBr		89	3.0
m	"	LiI		91	2.5
n	"	LiCl		87	4.0[c]
o		LiBr		91	3.0
p	"	LiI		93	2.5
q		LiBr		90	2.5
r	"	LiI		92	2.0
s	"	LiCl		89	3.0[c]

[a] All products were characterized by ^{1}H NMR, IR and mass spectroscopy.

[b] Yield in paranthesis indicates other regioisomer.

[c] Reactions were carried out at 65 °C.

In conclusion, this paper demonstrates the successful use of ionic liquids as novel and recyclable solvents for the synthesis of *vic*-halohydrins by regioselective ring-opening of epoxides with lithium halides. Ionic liquids play a dual role of solvent as well as the promoter thereby avoiding the use of additional acid catalyst to promote reaction. The epoxides show a significant increase in reactivity, thus reducing the reaction times and improving the yields significantly. The simple experimental and product isolation procedures combined with ease of recovery and reuse of this novel reaction media is expected to contribute to the development of green strategies for the preparation of *vic*-halohydrins.

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11 Experimental procedure: A mixture of epoxide (1 mmol) and lithium halide (1.2 mmol) in [bmim]PF_6 or [bmim]BF_4 (3 mL) was stirred at room temperature for the appropriate time (see Table). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with diethyl ether (3 × 10 mL). The combined organic 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 (1:9) to afford pure halohydrin. The rest of the ionic liquid was further washed with diethyl ether and recycled in subsequent runs. The halohydrins thus obtained were identified by comparison of their NMR, IR, Mass, TLC analysis, and physical data with authentic samples. The spectral data of all the products were identical with those of authentic samples.[6,7]

12 The continual reuse of [bmim]PF_6 may cause the liberation of most hazardous HF. Therefore, PF_6 based ionic liquid should be recycled with the utmost care. R. P. Swatloski, J. D. Holbrey, and R. D. Rogers, *Green Chem.*, **5**, 361 (2003).

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