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Ionic Liquid as Reagent. A Green Procedure for the Regioselective Conversion of Epoxides to *Vicinal*-Halohydrins Using [AcMIm]X under Catalyst- and Solvent-Free Conditions

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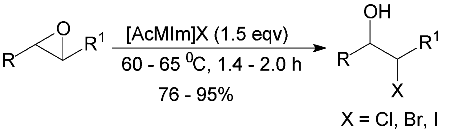
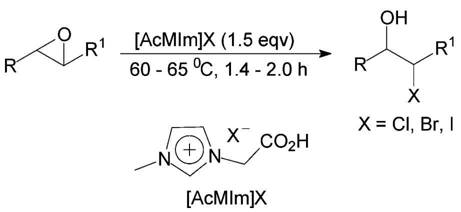


A variety of structurally diverse epoxides undergo facile cleavages by ionic liquid, [AcMIm]X without any catalyst and solvent to produce the corresponding *vicinal* halohydrins in high yields. The cleavages are considerably fast and highly regioselective.

The vicinal halohyrins are very useful synthetic intermediates and have found wide applications in organic transformations and in the synthesis of marine natural products.[1,2] The conventional reagents for epoxide ring opening to halohydrins are hydrogen halides and hypohalite−water.[3] However, these procedures are associated with the disadvantages of intolerance to acid-sensitive moieties and byproduct formation.[4] A variety of other reagents[5] such as ammonium halides in the presence of metal salts,[5a] halosilanes,[5b] haloboranes,[5c,d] and particularly halides of different elements such as P,[6] Al,[7] Fe,[8] Cu,,[9] Ni,[10] Sn,[11] and Li[12] are also available for this transformation. Among these reagents lithium halides in combination with various Lewis acids such as Li_2CuCl_4,[13] Lix−TiX_4,[14] Lix−[Bmim]PF_6[15] are reported to be more convenient and efficient. However, the presence of strong Lewis acid and protic acid in these Lix combined reagent systems often leads to low yields of halohydrins. As there is a continued interest in the selective ring opening of epoxides to give halohydrins a milder, more efficient, and environmentally friendly methodology would be highly desirable.

SCHEME 1. Synthesis of Halohydrins



The ionic liquids have been the subject of considerable current interest as environmentally benign reaction media in organic synthesis because of their unique properties of nonvolatility, nonflammability, and recyclability, among others.[16,17] However, the ability of ionic liquid as a clean catalyst[18] and reagent[19] has not been explored to any great extent although it is of much importance in the context of green synthesis. As a part of our continuous drive[20] to avoid organic solvent, toxic catalysts, and reagents, we have initiated a new program to explore the use of ionic liquid as efficient catalyst, reagent, as well as reaction media for useful organic transformations. We report here a novel use of an ionic liquid, acylmethylimidazolium halide ([AcMIm]X),[21] for the cleavage of epoxides to halohydrins without requirement of any other catalyst and solvent (Scheme 1). Thus, [AcMIm]X acts as reagent as well as solvent for this reaction.

The experimental procedure is very simple. A mixture of epoxide and [AcMIm]X was heated at 65 °C with stirring for 1.5−2.0 h (TLC). The reaction mixture was then quenched with brine and extracted with ether.

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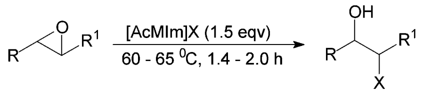
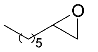
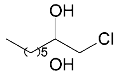
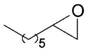
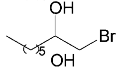
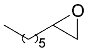
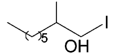
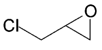
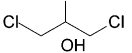
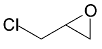
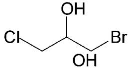
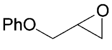
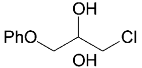
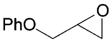
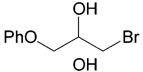
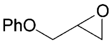
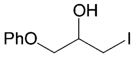
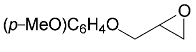
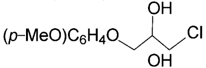
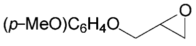
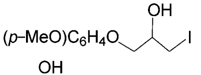
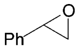
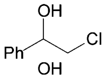
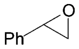
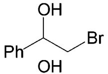
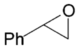
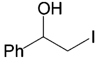
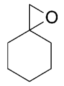
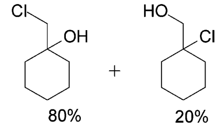
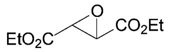
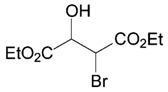
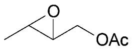
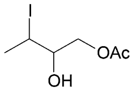
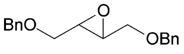
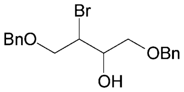
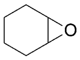
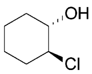
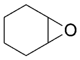
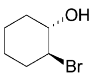
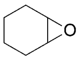
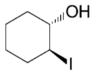
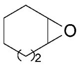
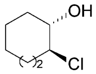
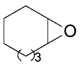
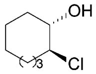
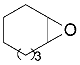
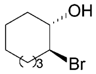
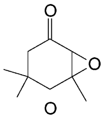
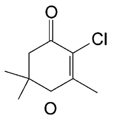
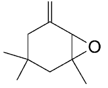
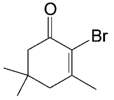
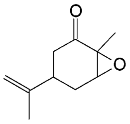
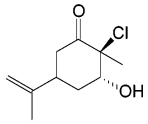
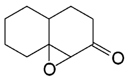
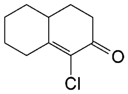
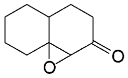
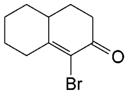
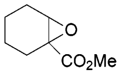
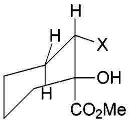
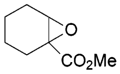
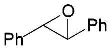
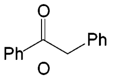
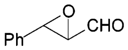
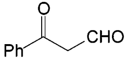
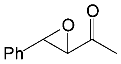
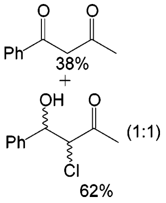
TABLE 1. Synthesis of β-Halohydrins from 1,2-Epoxides with [AcMIm]X



X = Cl, Br, I

entry	epoxide	product(s)	time(h)	yield(%)[a]	ref
1			1.5	95	23
2			1.5	95	15
3			1.4	95	15
4			1.4	80	24
5			1.5	80	24
6			1.8	78	15
7			1.6	80	15
8			1.5	82	15
9			1.8	78	15
10			1.6	80	15
11			1.5	87	15
12			1.4	90	15
13			1.4	90	15
14			1.6	80	5(a)
15			1.5	76	25
16			1.5	80	26
17			1.6	80	12
18			1.5	85	15
19			1.5	86	15
20			1.4	86	15
21			1.9	80	27
22			2.0	80	28
23			1.9	82	28
24			1.5	94	29
25			1.5	95	30
26			1.5	90	31
27			1.5	90	32
28			1.5	92	32
29		 29. X = Cl 30. X = Br	1.5	85	
30			1.5	85	
31			1.5	85	33
32			1.6	80	34
33			1.6	80	33 35

[a] Yields refer to those of pure isolated products characterized by IR and ^{1}H and ^{13}C NMR spectroscopic data and elemental analysis.

Usual workup followed by short column chromatography produced the pure product.

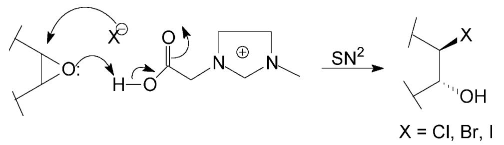
A wide range of structurally diverse epoxides underwent cleavages by this ionic liquid to produce the corresponding halohydrins. Chloro, bromo, and iodo groups can be introduced with similar efficiency by use of the corresponding chloride, bromide and iodide derivatives of the [AcMIm]X. The results are summarized in Table 1. The cleavages are, in general, regio- and stereoselective going through an S_N2 addition path. In case of open chain terminal epoxides (entries 1−10) less substituted ends were halogenated. The cyclic epoxides (entries 18−22) always produced *trans* halohydrins as indicated by the observed coupling constants of the ring hydrogens in their

^{1}H NMR spectra. In α-keto epoxides (entries 24−26), halogenation occurs at the epoxide juncture α to keto carbonyl. The β-trisubstituted keto epoxides (entries 27, 28), however, underwent simultaneous dehydration to give α,β-unsaturated ketones. Interestingly, α-carbomethoxy epoxides (entries 29 and 30) leads to halogenation at the β-position producing a single trans stereoisomer as indicated by the coupling constants of 8.7 Hz (entry 29) and 10.0 Hz (entry 30) due to C2−C3 diaxial H-interactions and 4.5 Hz (entry 29) and 5.4 Hz (entry 30) due to C2−C3 axial equatorial H-interactions in their ^{1}H NMR spectra. Phenyl-substituted epoxides (entries 11−13) also underwent facile ring cleavages to provide the corresponding halohydrins. However, diphenyl epoxide (entry 31) underwent rearrangement to give 2-phenylacetophenone. Similar rearrangement was also observed in phenyl-substituted α-carbonyl epoxides (entries 32 and 33). However, the exact reason for the formation of chlorohydrin as major product in entry 33 is not very clear to us. Very interestingly, in all of these phenyl-substituted epoxides only hydride migration occurs in contrast to Lewis acid catalyzed rearrangements[22] where phenyl migration takes place.

Very recently, a synthesis of halohydrins from oxiranes using LiX in ionic liquid [bmIm]PF$_6$ has been reported by Yadav and co-workers.[15] However, our work is essentially different from theirs as they carried out the reaction using a conventional halide reagent LiX in ionic liquid as the reaction medium, whereas in the present work, the particular ionic liquid, [AcMIm]X, is utilized as a reagent as well as reaction medium without requiring any other metal halide for the reaction.

In general, the reactions are considerably fast, clean, and high yielding, leading to the synthesis of halohydrins. Several functional groups, such as Cl, CO$_2$R, OAc, OCH$_2$Ph, and OCH$_3$, remain unaffected under the present reaction conditions. Presumably, due to the activation of the epoxide by the acidic hydrogen of imidazole moiety, epoxide ring cleavage is facilitated and is then promoted by the counter halide ion (X$^-$) of [AcMIm]X as depicted in Scheme 2.

SCHEME 2. Mechanism of Epoxide Cleavage



Conclusion

In summary, this procedure provides a novel and green protocol for epoxide ring cleavage leading to halohydrins by a simple and inexpensive ionic liquid, [AcMIm]X, which itself works as reagent, catalyst, and reaction medium. To the best of our knowledge, we are not aware of any such use of ionic liquid for epoxide cleavage. The other significant advantages offered by this method are operational simplicity, considerably fast reaction (1−2 h), mild reaction conditions, general applicability to a wide variety of substrates, regio- and stereoselectivity, and high isolated yields of products, and thus, it provides a better and practical alternative to the existing procedures.[3−16] Moreover, this strategy opens up a new area for further applications of ionic liquid in green synthesis.

Experimental Section

General Experimental Procedure for the Synthesis of Halohydrins by Ring Cleavage of Epoxide with [AcMIm]X. Representative Procedure for 1-Chloro-2-octanol. A mixture of 2-hexyloxirane (128 mg, 1 mmol) and [AcMIm]Cl (225 mg, 1.3 mmol) was heated at 65 °C with stirring for 1.5 h (TLC). The reaction mixture was quenched with saturated brine and extracted with ether (3 × 10 mL). Evaporation of ether left the crude product which was purified by column chromatography over silica gel (hexanes−Et$_2$O 80:20) to provide the pure 1-chloro-2-octanol as a colorless liquid (155 mg, 95%) whose spectroscopic data (IR, ^{1}H and ^{13}C NMR) are in good agreement with those of authentic sample. All of the products except two are known compounds and are easily identified with their appropriate stereoconfiguarion (whereever applicable) by comparison of their NMR spectra with those of authentic samples. The purity of all compounds was checked by GC, ^{1}H and ^{13}C NMR spectra, and elemental analysis.

Acknowledgment. S.B. is thankful to CSIR, New Delhi, for the fellowship.

Supporting Information Available: General experimental requirements and spectroscopic (IR, ^{1}H NMR, and ^{13}C NMR) data and elemental analysis of the products listed in entries 29 and 30 of Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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