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A Highly Regioselective Conversion of Epoxides to Halohydrins by Lithium Halides

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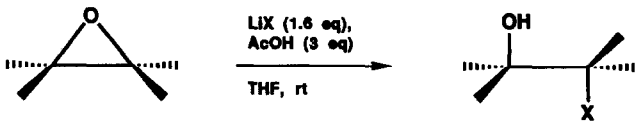
Key Words: Regioselective; epoxides; halohydrins; lithium; halides.

Abstract: *Lithium halides in the presence of an acid (pKa < 13) react with epoxides regioselectively to give vicinal halohydrins in high yields. The simplicity and convenience of this procedure makes it attractive for large scale synthesis.*

There is a continued interest in the regiospecific ring-opening of epoxides to give halohydrins. Although a variety of new and mild procedures to effect this transformation have been reported[1], most of them have some limitations. For example, in the presence of a suitable catalyst, chlorosilanes insert selectively into the less substituted C-O bond of 1-alkene oxides, affording O-silyl chlorohydrins[2]. Methods based upon hydrogen halides are not considered appropriate because they often lead to the formation of dihalides as reaction by-products[3]. Opening of unsymmetrically substituted epoxides with Br_2/PPh_3[4], BBr_3[5], Me_2BBr[6], $(Me_2N)_2BBr$[7], Me_3SiBr[8], Pyr.HCl[9], and $BF_3.Et_2O$/n-Bu_4NI[10] suffers from moderate regioselectively and/or the propensity to react with a range of nucleophilic functional groups. Recently, dilithium tetrabromonickelate (Li_2NiBr_4)[11] and dilithium tetrachlorocuprate (Li_2CuCl_4)[12] have been reported to be sources of "soft" nucleophilic bromide and chloride respectively which regioselectively convert epoxides to halohydrins under mild conditions. Many of the above cited procedures suffer from the limitation that they require preparations of the reagents *in situ* and no single procedure is suitable for the preparation of the three most useful halohydrins, the chloro-, bromo- and iodohydrins.

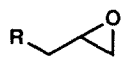
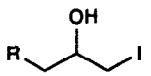
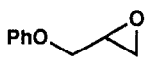
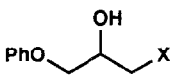
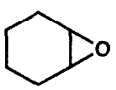
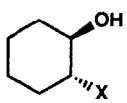
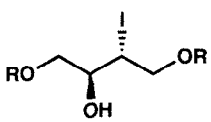
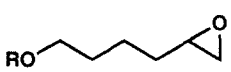
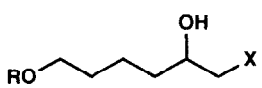
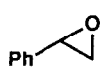
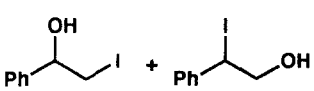


1 X = Cl, Br, I 2

Scheme 1

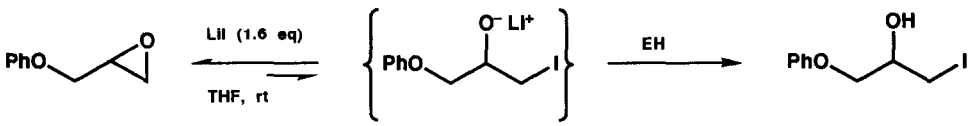
The use of lithium halides for opening of epoxides to give halohydrins, to the best of our knowledge, has not been reported[13]. On the contrary, lithium halides solublized with aprotic solvents (eg. DMF or HMPA) have been reported to be efficient catalysts for the rearrangement of epoxides to aldehydes and/or ketones[14]. We have reexamined this reaction and in this letter we report that lithium halides in the presence of acetic acid convert epoxides regioselectively to vicinal halohydrins (Scheme 1) in high yields under mild conditions even when sensitive functional groups are present.

Table 1. Reaction of Epoxides with Lithium Halides[a]

Entry	Epoxide	LiX	Reaction Time (h)	Halohydrin[b]	Yield[c] (%)
					
1	R = CN	LiI	0.25	R = CN	100
2	R = $PO(OCH_2Ph)_2$	LiI	0.25	R = $PO(OCH_2Ph)_2$	96
					
3		LiI	0.25	X = I	100
4		LiBr	5.0	X = Br	100
5		LiCl	24.0	X = Cl	100
					
6		LiI	0.3	X = I	97
7		LiBr	5.0	X = Br	90
					
8	R = Bn	LiI	5.0	R = Bn	100
9	R = TBDMS	LiI	48.0(24.0)[d]	R = TBDMS	100
10	R = THP	LiI	48.0	R = THP	100
					
11	R = MOM	LiI	1.0	R = MOM; X = I	92
12	R = MOM	LiBr	6.0	R = MOM; X = Br	90
13	R = Ac	LiI	0.75	R = Ac; X = I	92
					
14		LiI	1.3	34 : 66	87

[a]The reaction was carried out following the general procedure described in the text. [b]The products showed satisfactory IR, NMR and mass spectra. [c]Isolated yields based on the starting epoxide, purity > 95% by capillary GLC and ^{1}HNMR. [d]10 equiv. of LiI were used.

As the examples listed in Table 1 indicate, aliphatic terminal epoxides undergo highly regioselective attack by lithium halides to yield halohydrins with the halogen group at the less substituted carbon. Styrene oxide (entry 14), which is electronically prone to nucleophilic attack at the benzylic position, gives predominently the secondary halide. The reaction is also highly stereoselective as exemplified by the clean conversion of cyclohexene oxide to trans-2-halocyclohexanol (entries 6 and 7). It is worth noting that no skeleton rearrangement[14] of cyclohexene oxide took place under the reaction conditions. Entries 1-2 and 7-12 demonstrate that a variety of functional groups are stable to the reaction conditions. The reaction time can be significantly shortened by using a large excess of lithium halide (entry 9). Entry 11 is of particular interest since reaction of the methoxymethyl ether of 5-hexen-1-ol oxide with AcOH:KBr:THF (2:2:1) under various conditions is reported[7] to give only low yields of the expected bromohydrin. Entries 3-5 show that the reactivity of lithium halides towards epoxides follows the order LiI>LiBr>LiCl.



3 4 5

$pK_a \approx 16$

Scheme 2

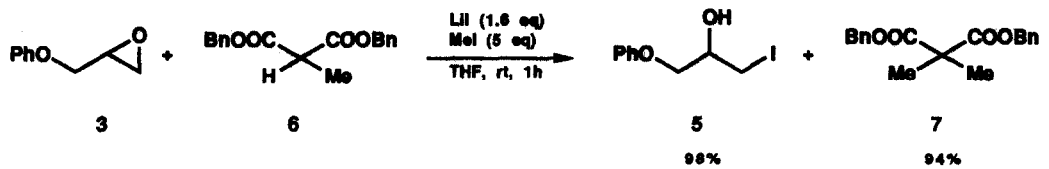
Table 2. The Effect of Different Electrophiles on the Reaction of LiI with Phenyl Glycidyl Ether **3**

Entry	Electrophile EH	pK_a[15]	Reaction Time (h)	Isolated Yield (%) of **5**
1	none	-	60.0	7
2	AcOH	4.6	0.25	100
3	PhOH	9.0	0.25	87
4	CH_3NO_2	11.0	1.0	89
5	$CH_3CH_2COCH_2COOEt$	11.0	0.25	95
6	$CH_2(COOMe)_2$	13.0	0.25	95

We next examined the effect of acetic acid in the opening of epoxides with lithium halides. It is quite clear that acetic acid plays an important role since almost all of the starting material is recovered (entry 1, Table 2), even after extended reaction time when it is not included in the reaction. It is proposed that the reaction involves a reversible epoxide ring opening by nucleophilic attack of a halide ion[14] (Scheme 2). The reaction is then driven to completion[16] by protonation of the intermediate alkoxide **4** by acetic acid (pK_a = 4.6). Since the alkoxides derived from secondary alcohols have pK_a of ≈16[15], acetic acid can in principle be replaced by any acid with pK_a <16. This is indeed the case as exemplified by the entries 3-6 in Table 2.

To further confirm that the acids listed in Table 2 are deprotonated by the alkoxide **4**, epoxide **3** (1 eq) was treated with 2-methyl dibenzylmalonate **6** (1 eq), LiI (1.6 eq) and an excess of MeI (5 eq) in dry THF at room

temperature (Scheme 3). The reaction was complete in 1h and the 1,2-iodohydrin **5** and 2,2-dimethyl dibenzylmalonate **7** were isolated in 98 and 94% yields respectively.



3 **6** **5** 98% **7** 94%

Scheme 3

In summary, our results indicate that unsymmetrically substituted epoxides are regio- and stereospecifically opened by the reaction of lithium halides in the presence of an acid ($pK_a < 13$) to yield vicinal halohydrins. The reaction conditions are mild and thus compatible with a variety of functional groups. The simplicity, convenience and versatility of this procedure makes it attractive for large scale synthesis.

General Procedure: To a solution of epoxide (1 mmol) and acetic acid (3 mmol) in dry THF (10 ml) was added anhydrous LiX and the reaction mixture was stirred at room temperature. After completion of the reaction (tlc monitoring), the reaction mixture was diluted with water and then extracted with ether. The organic layer was washed with water (and with 10% sodium thiosulfate solution in case of iodohydrins), dried ($MgSO_4$), and evaporated. The residue was dissolved in ether and passed through a small plug of silica gel to remove traces of inorganic salts. Evaporation of the filtrate afforded the product in >95% purity (by GLC and NMR).

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13 Lithium bromide has been reported to react sluggishly with 1-methylcyclohexene oxide giving a mixture of products, see reference 11.
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16. Acetic acid not only drives the reaction to completion but it also reduces the bascity of the halide ions which in some cases can lead to side products. For example, the reaction of 3,4-epoxybutanenitrile with LiI in the absence of acetic acid gives exclusively γ-hydroxycrotononitrile. See also reference 11.

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