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A Facile Conversion of Epoxides to β-Halohydrins with Silica Gel-Supported Lithium Halides

Hiyoshizo Kotsuki* and Tomoyasu Shimanouchi

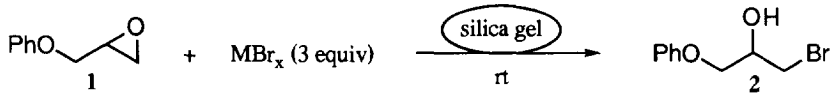
Department of Chemistry, Faculty of Science, Kochi University, Akebono-cho, Kochi 780, Japan

Abstract: A variety of epoxides are efficiently converted to the corresponding β-halohydrins with lithium halides supported on silica gel in dry media.

Epoxides are versatile intermediates in synthetic organic chemistry mainly due to their susceptibility to several nucleophiles[1] and availability in optically pure forms.[2] We have recently demonstrated that some epoxide opening reactions with amino acids and nitrogen heterocycles are efficiently catalyzed by silica gel in the absence of any solvent.[3] These facts encouraged us to continue further investigations to clarify the catalytic activity of silica gel for other nucleophiles.[4] In this communication we would like to describe our successful results that led to a novel and extremely simple method for the transformation of epoxides into β-halohydrins[5] using lithium halides supported on silica gel.

When treated at room temperature with 3 equiv of metal bromides adsorbed on silica gel (250 mg/mmol),[6] phenyl glycidyl ether (**1**) was converted into the corresponding bromohydrin **2**. The reaction appears to be significantly dependent upon the nature of the metal halide reagents as shown in Table 1.[7]

Table 1. Formation of Bromohydrin **2** from Phenyl Glycidyl Ether (**1**) and Metal Bromides.



Entry	MBr_x	Reaction Time, h	Yield, %[a]
1	LiBr	1	100
2[b]	LiBr	22	100
3[c]	LiBr	48	44[d]
4	NaBr	720	24 (73)
5	KBr	168	16 (59)[e]
6	CsBr	48	No reaction
7	$MgBr_2 \cdot 6H_2O$	3	100
8	$CuBr_2$	240	71 (19)

[a] Isolated yield. Yields in parentheses are the corresponding diol. [b] In CH_2Cl_2 solution. [c] Without using silica gel. [d] 25% recovery and 20% dimer. [e] 19% recovery.

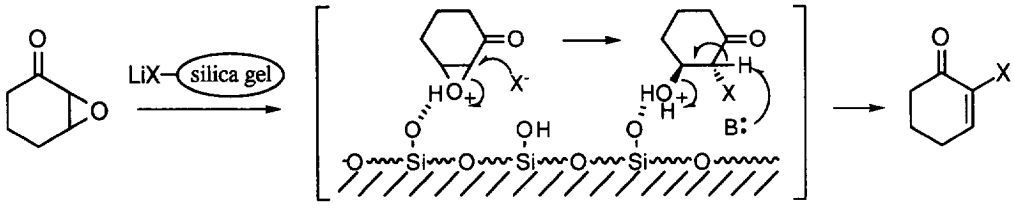
Thus, we found that the process using lithium bromide in a dry medium was the best and 2 was obtained quantitatively within only 1 h (entry 1). For comparison, the same reaction was also conducted in CH_2Cl_2 but it took 22 h for completion (entry 2). On the other hand, direct treatment of **1** with lithium bromide resulted in an incomplete reaction even after standing for 48 h at room temperature: **2** was isolated in 44% yield along with its dimer (20%) (entry 3). From these results we concluded that the supporting environment on silica gel played an essential role in facilitating this type of epoxide opening reaction.

Further extension of this procedure was exemplified as summarized in Table 2.[7] In many cases the reactions occurred smoothly to afford the desired halohydrins in high yields. In accordance with the previous observation[8] the reactivity of lithium halides definitely follows the order of LiI > LiBr >> LiCl (entries 1-3, 13, and 14, Table 2). Because of the minimal reactivity of lithium chloride, the reactions were usually accompanied by hydrolysis (entries 1 and 11, Table 2). In contrast, lithium iodide was most successful for the present purpose and the desired iodohydrins were rapidly formed in almost quantitative yields at room temperature. Unexpectedly, the reaction of 1-decene oxide toward lithium bromide was quite slow (entry 7, Table 2), implying the sluggish nature of movement of this epoxide on the silica gel surface.

For the terminal epoxides, ring opening reaction was highly regioselective in giving the corresponding 1-halo-2-alkanols, demonstrating the predominant attack of the reagents from the less hindered side of the epoxides. The only exception is the case of styrene oxide wherein 2-halo-2-phenylethanols were obtained as the major product, suggesting that the preferential cleavage of the benzylic C-O bond provided a stabilized benzylic cation species during the reaction (entries 1-3, Table 2). The proposed mechanism could also be rationalized by carefully dictating the reaction using (*R*)-(+)-styrene oxide (entry 4, Table 2): 2-bromo-2-phenylethanol, an S_N1-type adduct, showed only 32% ee by chiral HPLC analysis,[9] whereas a high optical purity of (*R*)-2-bromo-1-phenylethanol indicates a complete retention of an asymmetric character.[10]

Interestingly, 2-cyclohexenone oxide produced only 2-halocyclohexenones (entries 15 and 16, Table 2). The results can be explained by the mechanism depicted in Scheme 1: on the silica gel surface halide anions first

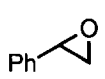
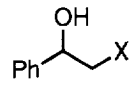
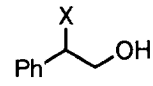
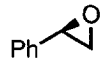
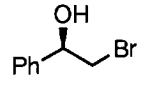
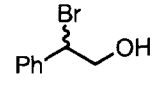
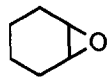
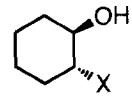
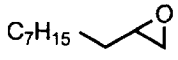
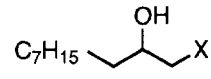
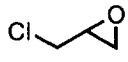
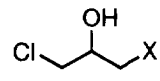
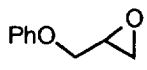
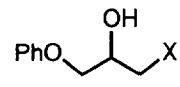
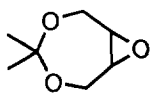
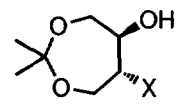
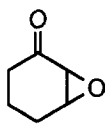
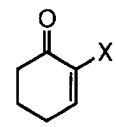
Scheme 1



attacked the α-carbon of the epoxide to produce the corresponding halohydrin intermediates which were then removed by water to afford the α-haloenone derivatives.[12] Unfortunately, all efforts to isolate the halohydrin intermediates were unsuccessful and no other products caused by reversed regioselective opening were detected. Since the starting epoxides are readily available from cycloalkenone precursors by simple epoxidation,[13] this method can serve as an alternative pathway to perform α-halogenation of these substrates.[14]

In conclusion, although there are several methods available for transformation of epoxides into the corresponding halohydrins, we believe that the present one offers considerable advantages in terms of simplicity, high efficiency, and very mild conditions.

Table 2. Reaction of Epoxides with Silica Gel-Supported Lithium Halides.[a]

Entry	Epoxide	LiX	Time	Product(s)		Yield, %[b]
						
1		LiCl	13 days	X = Cl (58 : 42)		52 (18)
2		LiBr	30 min	X = Br (38 : 62)		60
3		LiI	15 min	X = I (20 : 80)		83
4		LiBr	15 min	 (100% ee)[c]	 47 : 53 (32% ee)[c]	81
5		LiBr	30 min		X = Br	75
6		LiI	15 min		X = I	94
7		LiBr	19 h		X = Br	97
8		LiI	15 min		X = I	97
9		LiBr	1 h		X = Br	73
10		LiI	15 min		X = I	99
11		LiCl	22 days		X = Cl	50 (33)
12		LiI	15 min		X = I	96
13		LiBr	8 h		X = Br	80
14		LiI	15 min		X = I	90
15		LiBr	1 h		X = Br	61
16		LiI	15 min		X = I	61

[a]All reactions were performed using 3 equiv of LiX and silica gel (250 mg / mmol).

[b]Isolated yield. Yields in parentheses are the corresponding diol.

[c]Opical purity was determined by HPLC (DAICEL Chiralcel OB or OJ). See refs. 9 and 10.

General experimental procedure: To a mixture of epoxide (1.0 mmol) and lithium halide (3.0 mmol) in a few mL of CH_2Cl_2 was added silica gel (250 mg). After evaporation of most of the organic solvent, the residue was allowed to stand at room temperature for the reaction period shown in Tables 1 and 2. Then silica gel was thoroughly washed with AcOEt and concentrated. The residue was purified by preparative TLC or by silica gel column chromatography to afford the desired halohydrins.

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References and Notes

1. Parker, R. E.; Isaacs, N. S. *Chem. Rev.* **1959**, *59*, 737; Buchanan, J. G.; Sable, H. Z. *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley, 1972; Vol. 2, p 1; Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323; Smith, J. G. *Synthesis* **1984**, 629.
2. Sharpless, K. B. *Chem. Brit.* **1986**, *22*, 38; Pfenninger, A. *Synthesis* **1986**, 89; Hanson, R. M. *Chem. Rev.* **1991**, *91*, 437.
3. Kotsuki, H.; Shimanouchi, T.; Teraguchi, M.; Kataoka, M.; Tatsukawa, A.; Nishizawa, H. *Chem. Lett.* **1994**, 2159; Kotsuki, H.; Hayashida, K.; Shimanouchi, T.; Nishizawa, H. *J. Org. Chem.* in press. See also: Raubo, P.; Wicha, J. *Synlett* **1993**, 25; Bennett, F.; Patel, N. M.; Girijavallabhan, V. M.; Ganguly, A. K. *Synlett* **1993**, 703.
4. For general reviews in this area, see: McKillop, A.; Young, D. W. *Synthesis* **1979**, 401, 481; Clark, J. H.; Kybett, A. P.; Macquarrie, D. J. *Supported Reagents: Preparation, Analysis, and Application*, VCH, New York, 1992; *Solid Supports and Catalysts in Organic Synthesis*, Smith, K., Ed.; Ellis Horwood, New York, 1992.
5. Review: Bonini, C.; Righi, G. *Synthesis* **1994**, 225.
6. Wakogel C-300 was employed throughout this work.
7. Satisfactory spectral and analytical data were obtained.
8. Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1991**, *32*, 3021.
9. Although the absolute configuration of these products was undetermined, the retention time for each enantiomer was 38.8 min and 43.9 min, respectively, as determined by HPLC analysis (254 nm) using a Chiralcel OJ column with 10% *i*-PrOH in hexane as eluant at a flow rate of 0.5 mL/min.
10. This sample showed a single peak at 19.3 min using a Chiralcel OB column with 10% *i*-PrOH in hexane as eluant at a flow rate of 0.5 mL/min. The corresponding enantiomer had a retention time of 15.7 min. The absolute configuration was determined by the sign of the specific rotation: $[\alpha]_D^{24}$ -47 (*c* 1.0, $CHCl_3$) [lit.[11] $[\alpha]_D^{20}$ -39.0 (*c* 8, $CHCl_3$)].
11. Imuta, M.; Kawai, K.; Ziffer, H. *J. Org. Chem.* **1980**, *45*, 3352.
12. For a similar finding, see: Mandal, A. K.; Mahajan, S. W. *Tetrahedron* **1988**, *44*, 2293.
13. Larock, R. C. *Comprehensive Organic Transformations*, VCH, New York, 1989; pp 460-461.
14. Johnson, C. R.; Adams, J. P.; Braun, M. P.; Senanayake, C. B. W.; Wovkulich, P. M.; Uskokovic, M. R. *Tetrahedron Lett.* **1992**, *33*, 917 and references cited therein.

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