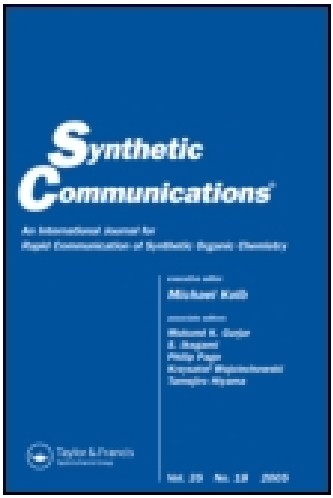


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Conversion of Epoxides to β-Chlorohydrins with Thionyl Chloride and β-Cyclodextrin in Water

K. Surendra [a] , N. Srilakshmi Krishnaveni [a] , Y. V. D. Nageswar [a] & K. Rama Rao [a]
[a] Organic Chemistry Division-1 , Indian Institute of Chemical Technology , Hyderabad, India
Published online: 18 Aug 2006.

Synthetic Communications®, 35: 2195–2201, 2005

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500182606

Conversion of Epoxides to β-Chlorohydrins with Thionyl Chloride and β-Cyclodextrin in Water

K. Surendra, N. Srilakshmi Krishnaveni, Y. V. D. Nageswar, and K. Rama Rao
Organic Chemistry Division-1, Indian Institute of Chemical Technology, Hyderabad, India

Abstract: Several epoxides are efficiently converted to the corresponding β-chlorohydrins in impressive yields with thionyl chloride in the presence of β-cyclodextrin using water as solvent at room temperature.

Keywords: β-Chlorohydrins, β-cyclodextrin, epoxides, thionyl chloride, water

Chlorohydrins and various other halohydrins are important class of organic compounds and versatile intermediates in the synthesis of a vast range of biologically active natural and synthetic products, unnatural aminoacids, and chiral auxiliaries for asymmetric synthesis.[1] They are also utilized in the synthesis of β-adrenergic blockers and are key intermediates in the preparation of homochiral β-blockers.[2]

Chlorohydrins are generally prepared by the ring opening of epoxides under electrophilic conditions with TMSCI,[3] polyvinylpyrrolidone/thionyl chloride,[4] hydrohalic acids,[5] Lewis acids such as BF_3[6] and chlorosilane,[7] metalhalides such as LiX,[8] haloboranes,[9] elemental halogens,[10] pyridine-HCl,[11] and so forth. Some more methods involve chloroallylboration of

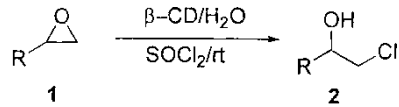
Received in India April 1, 2005
Address correspondence to K. Rama Rao, Organic Chemistry Division-1, Indian Institute of Chemical Technology, Hyderabad 500 007, India. Tel.: +91-40-27193164; Fax: +91-40-27160757; E-mail: drkrrao@yahoo.com

aldehydes,[12] cleavage of cyclic ketal acids with phosphorus pentachloride, thionyl chloride, and pivaloyl chloride,[13] and reaction of diol with dry HCl or chlorotrimethylsilane.[14] Although various recent advances have been made[15] there is still demand for developing newer methodologies, especially environmentally benign and highly efficient procedures for the effective transformation of epoxides to chlorohydrins. In continuation of our efforts to develop biomimetic approaches for chemical reactions involving cyclodextrins, we describe herein a novel method for the regioselective ring opening of oxiranes with thionyl chloride to form chlorohydrins under supramolecular catalysis involving β-cyclodextrin.

Cyclodextrins are cyclic oligosaccharides possessing hydrophobic cavities, which bind substrates selectively and catalyze chemical reactions with high selectivity. They catalyze reactions by supramolecular catalysis involving reversible formation of host–guest complexes by noncovalent bonding, as seen in enzymes. Complexation depends on the size, shape, and hydrophobicity of the guest molecule. Thus, mimicking biochemical selectivity, which is due to orientation of the substrate by complex formation positioning and only certain regions are for favorable attack, will be superior to chemical selectivity, which involves random attack because of intrinsic reactivity of the substrate at different regions. Our earlier expertise in the field of biomimetic modeling of organic chemical reactions involving cyclodextrins[16] prompted us to attempt the regioselective ring opening of oxiranes with thionyl chloride in the presence of β-cyclodextrin (β-CD), because this is one of the most useful synthetic transformations and has a variety of applications (Scheme 1).

The reactions were carried out by the in situ formation of β-cyclodextrin complex of oxirane (**1**) in water followed by the addition of thionyl chloride and stirring at room temperature to give corresponding chlorohydrins (**2**) in impressive yields (Table 1). The reactions did not proceed in the absence of β-CD. Although these reactions did occur with α-CD with the same regioselectivity, β-CD was preferred because of its inexpensive nature and accessibility. The complexes have been isolated and characterized by powder X-ray[17] and NMR studies in D_2O.[18]

The role of cyclodextrin was not only to activate the epoxide but to promote ring opening by inclusion complex formation with impressive regioselectivity. With the styrene epoxides (entries 8 and 9), the halide preferentially attacked the terminal carbon, whereas cyclohexene oxide gave only the *trans* isomer. A variety of epoxides such as styrene epoxides, cyclohexene epoxides,

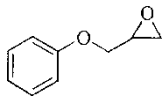
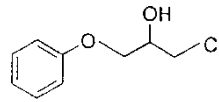
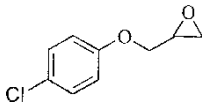
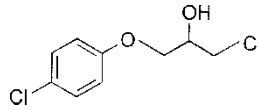
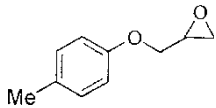
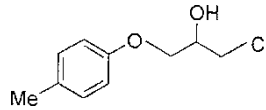
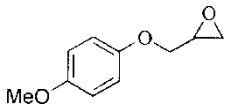
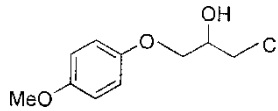
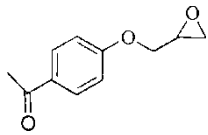
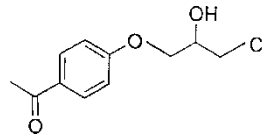
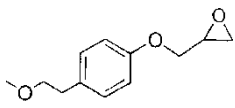
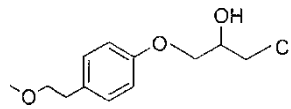
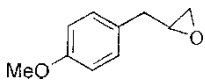
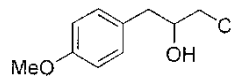
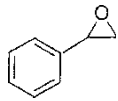
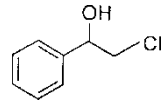
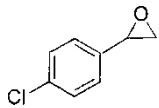
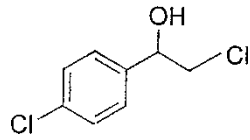


1 **2**

R=Aryloxy,Phenyl,Alkyl

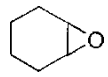
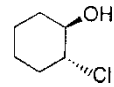
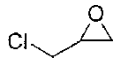
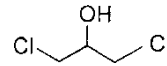
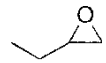
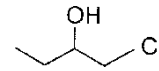
Scheme 1.

Table 1. Synthesis of β-chlorohydrins from epoxides and SO_2Cl in the presence of β-CD

Entry	Substrate	Product[a]	Yield[b] (%)
1			91[16a]
2			93[16a]
3			90
4			90
5			89[16a]
6			91
7			90[16a]
8			92[16a]
9			94[16a]

(*continued*)

Table 1. Continued

Entry	Substrate	Product[a]	Yield[b] (%)
10			88[16a]
11			84[16a]
12			84[16a]

[a]All the products were characterized by ^{1}H NMR, mass, and IR spectra data.
[b]Isolated yields.

epichlorohydrin, and phenoxy epoxides with different substituents such as chloro, methyl, methoxy, acetoxy, and metaprolol have been converted to corresponding chlorohydrins. All the compounds were characterized by the ^{1}H NMR, mass, and IR spectra or by comparison with the reported compounds.[15a]

In conclusion, the present methodology for conversion of epoxides to chlorohydrins is simple and efficient, and can be carried out in a biomimetic fashion from the easily accessible epoxides and thionyl chloride in the presence of β-CD.

EXPERIMENTAL

The β-cyclodextrin was purchased from Fluka. Epoxides were either purchased commercially or synthesized.[19] ^{1}H NMR spectra were obtained on a Varian 200- or Bruker 300-MHz spectrometer. IR spectra were recorded on a Nicolet FT-IR spectrometer. Mass spectra were observed on V.G. Auto Spectrometer. The reaction monitoring was accomplished by TLC on silica-gel plates.

General Method for Epoxidation

Phenol (9.4 g, 100 mmol) was dissolved in NaOH solution (1 N, 100 ml) and cooled to 5–10°C Then, epichlorohydrin (16 ml, 200 mmol) was added dropwise (1-h duration) to the reaction mixture and the reaction mixture stirred for 12 h, at room temperature. The product was extracted with CH_2Cl_2 and washed with 5% NaOH solution; the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under

reduced pressure. The product was purified by column chromatography using chloroform–hexane (40:60) as eluent.

General Procedure for the Conversion of Epoxides to Chlorohydrins

β-Cyclodextrin (1 mmol) was dissolved in water (15 ml) at 60°C; the epoxide (1 mmol) dissolved in acetone (1 ml) was slowly added at this temperature with stirring and the mixture was cooled to room temperature. Then, thionyl chloride (1.5 mmol) was added and stirring continued at room temperature for 10 h. After completion of the reaction the organic material was extracted with ethyl acetate; the organic phase was separated, filtered to remove any adhering CD particles, washed with brine, dried (Na_2SO_4), and concentrated. The crude product was purified by silica-gel column chromatography using ethyl acetate–hexane (2:8) as eluent.

Spectroscopic Data of New Compounds

1-Chloro-3-(4-methylphenoxy)-2-propanol (Table 1, entry 3): pale yellow oil, IR (neat): $\nu = 3510\,Cm^{-1}$; ^1H NMR ($CDCl_3$, 400 MHz,): $\delta = 2.30$ (s, 3H), 2.42 (d, 1H, $J = 3.2$ Hz), 3.66–3.80 (m, 2H), 4.00–4.10 (m, 2H), 4.12–4.20 (m, 1 H), 6.78 (d, 2H, $J = 8.0$ Hz), 7.05 (d, 2H, $J = 8.0$ Hz); mass (EI): m/z = 200; anal. calcd. for $C_{10}H_{13}O_2Cl$: C, 59.86; H, 6.53; Cl, 17.67; found: C, 59.95; H, 6.62; Cl, 17.67.

1-Chloro-3-(4-methoxyphenoxy)-2-propanol (Table 1, entry 4): pale yellow liquid; IR (neat): $\nu = 3525\,cm^{-1}$; ^1H NMR ($CDCl_3$, 200 MHz,): $\delta = 2.45$ (brs, 1H), 3.68–3.80 (m, 5H), 3.98–4.08 (m, 2H), 4.10–4.20 (m, 1H), 6.75–6.85 (m, 4H); mass (EI): $m/z = 216$; anal. calcd. for $C_{10}H_{13}O_3Cl$: C, 55.44; H, 6.05; Cl, 16.36; found: C, 55.36; H, 6.11; Cl, 16.42.

1-Chloro-3-[4-(2-methoxyethyl) phenoxy]-2-propanol (Table 1, entry 6): Colorless oil; IR (neat): $\nu = 3485\,cm^{-1}$; ^1H NMR ($CDCl_3$, 200 MHz,): $\delta = 2.56$ (brs, 1H), 2.80 (t, 2H, $J = 7.4$ Hz), 3.35 (s, 3H), 3.54 (t, 2H, $J = 7.4$ Hz), 3.68–3.80 (m, 2H), 4.00–4.09 (m, 2H), 4.12–4.10 (m, 1 H), 6.81 (d, 2H, $J = 7.6$ Hz), 7.12 (d, 2H, $J = 7.6$ Hz); mass (EI): $m/z = 244$; anal. calcd. for $C_{12}H_{17}O_3Cl$: C, 58.90; H, 7.00; Cl, 14.49; found: C, 58.98; H, 7.05; Cl, 14.41.

ACKNOWLEDGMENT

K.S. thanks Council of Scientific Research (CSIR), New Delhi, India, for the award of a research fellowship. IICT Communication No. 040911.

REFERENCES

1. (a) For a review, see Bartlett, P. A. *Asymmetric Synthesis*; Morrison, J. D., ed.; Academic: Orlando, FL, 1984 Vol. 3, p.411; (b) For review, see Moore, R. E. *Marine Natural Products*; Scheuer, P. J., ed.; Academic: New York, 1978 1, Chapter 2. (c) Fenical, W. *Marine Natural Products*; Scheuer, P. J., ed.; Academic: New York, 1980; Vol. 2, p. 174; (d) Tarasow, T. M. Preparation of (1R, 2S)- and (1S, 2R)-2-chloro-1,2-diphenylethanol and other β-halohydrins in enantiomerically pure form. *J. Org. Chem.* **1989**, *54*, 4966; (e) Erden, I. *Comprehensive Heterocyclic Chemistry*, 2nd ed.; Padwa, A., ed.; Pergamon: Oxford, 1996 Vol. 1A, Chapter 3.
2. (a) Berinakalti, H. S.; Banerji, A. A. Lipase catalysis in organic solvents. Application to the synthesis of (R)- and (S)-atenolol. *J. Org. Chem.* **1992**, *57*, 6003; (b) Bermudez, J. L.; Del Campo, C.; Salazar, H.; Takeda, H.; Achiwa, K. Efficient asymmetric hydrogenation of α-amino ketone derivatives. A highly enantioselective synthesis of phenylepinephrine, lecamisole, carnitine and propranolol. *Chem. Pharm. Bull.* **1995**, *43*, 738.
3. (a) Wang, L. S.; Hollis, K. T. Demonstration of a phosphozirconcene as a catalyst for the ring opening of epoxides with TMSCL. *Org. Lett.* **2003**, *5*, 2543; (b) Xu, L. W.; Li, L.; Xia, C. G.; Zhao, P. Q. Efficient synthesis of chlorohydrins: Ionic liquid–promoted ring-opening reaction of epoxide and TMSCL. *Tetrahedron Lett.* **2004**, *45*, 2435.
4. Tamami, B.; Ghazi, I.; Mahdavi, H. Polyvinyl pyrrolidone/thionyl chloride as a new polymeric reagent for facile conversion of epoxides to β-chlorohydrins. *Synth. Commun.* **2002**, *32*, 3725.
5. Stewart, C. A.; Vander Werf, C. A. Reaction of propylene oxide with hydrogen halides. *J. Am. Chem. Soc.* **1954**, *76*, 1259.
6. Coxon, J. N.; Harthson, M. P.; Rae, W. J. Reaction of epoxides—XXVI. The BF_3-catalyzed M rearrangement of 5, 6α-epoxy 6β-phenyl-5α-cholestan and a novel ketone rearrangement. *Tetrahedron* **1970**, *26*, 1091.
7. Andrews, G. C.; Grawford, T. C.; Contilio, L. G., Jr. Nucleophilic catalysis in the insertion of silicon halides into oxiranes: A synthesis of o-protected vicinal halohydroins. *Tetrahedron Lett.* **1981**, *22*, 3803.
8. (a) Bonini, C.; Righi, G. Regio- and chemoselective synthesis of halohydrins by cleavage of oxiranes with metal halides. *Synthesis* **1994**, 225; (b) Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujivara, S. Solvent-free organic reactions on silica-gel supports. Facile transformation of epoxides to β-halohydrins with lithium halides. *Tetrahedron* **1998**, *54*, 2709.
9. Joshi, N. N.; Srevnik, M.; Brown, H. C. Enantioselective ring cleavage of meso-epoxides with β-halodiisopinocamphenylboranes. *J. Am. Chem. Soc.* **1988**, *110*, 6246.
10. (a) Iranpoor, N.; Firouzabadi, H.; Chitsazi, M.; Jafari, A. Reactions of epoxides and episulfides with electrophilic halogens. *Tetrahedron* **2002**, *58*, 7037; (b) Iranpoor, N.; Firouzabadi, H.; Shekarize, M. Micellar media for the efficient ring opening of epoxides with CN^-, N_3^-, NO_3^-, NO_2^-, SCN^-, Cl^- and Br^- catalyzed with $Ce(OTf)_4$. *Org. Bio. Chem.* **2003**, *1*, 724; (c) Sharghi, H.; Eskandari, M. M. Conversion of epoxides into halohydrins with elemental halogen catalyzed by thiourea. *Tetrahedron* **2003**, *59*, 8509.
11. Loreto, M. A.; Pellacani, L.; Tardella, D. A. Pyridinium chloride in three-membered ring opening. Synthesis of chlorohydrins. *Synth. Commun.* **1981**, *11*, 287.

12. (a) Brown, H. C.; Racherla, U. S.; Liao, Y.; Khanna, V. V. Chiral synthesis via organoboranes. Simple procedures for the efficient recycling of the terpenyl chiral auxiliaries and convenient isolation of the homoallylic alcohols in asymmetric allyl- and crotylboration of aldehydes. *J. Org. Chem.* **1992**, *57*, 6608; (b) Jayaraman, S.; Hu, S.; Oehlschlager, A. C. Grntrymine B^1, the first quaternary isoquinoline alkaloid from *Ancistrocladus korupensis. Tetrahedron Lett.* **1995**, *36*, 4756.
13. Newman, M. S.; Chen, C. H. The reaction of cyclic α-ketal acids with phosphorus pentachloride. A new stereospecific route to esters of halohydrins. *J. Org. Chem.* **1973**, *38*, 1173.
14. Eras, J.; Mendez, J. J.; Balcells, M.; Canela, R. Chlorotrimethylsilane: A suitable reagent for the synthesis of chlorohydrin esters. *J. Org. Chem.* **2002**, *67*, 8631.
15. (a) Reddy, M. A.; Surendra, K.; Bhanumathi, N.; Rao, K. R. Highly facile biomimetic regioselective ring opening of epoxides to halohydrins in the presence of β-CD. *Tetrahedron* **2002**, *58*, 6003; (b) Ready, J. M.; Jacobsen, E. N. Asymmetric catalytic synthesis of α-aryloxyalcohols: Kinetic resolution of terminal epoxides via highly enantioselective ring opening with phenols. *J. Am. Chem. Soc.* **1999**, *121*, 6086; (c) Reymond, S.; Brunel, J. M.; Buono, G. New development in the enantioselective ring opening of meso-epoxides by various chloride ion silicon sources catalyzed by o-methoxyaryldiazaphosphonamide Lewis base. *Tetrahedron: Asymmetry* **2000**, *11*, 4441.
16. (a) Krishnaveni, N. S.; Surendra, K.; Rao, K. R. A simple highly selective biomimetic oxidation of alcohols and epoxides with N-bromosuccinimide in the presence of β-cyclodextrin in water. *Adv. Synth. Catal.* **2004**, *346*, 346; (b) Surendra, K.; Krishnaveni, N. S.; Nageswar, Y. V. D.; Rao, K. R. Highly regioselective ring opening of oxiranes with phenoxides in the presence of β-cyclodextrin in water. *J. Org. Chem.* **2003**, *68*, 4994.
17. Szejthi, T.; Osa, T. Comprehensive Supramolecular Chemistry; Pergamon: Oxford, U.K., 1996; Vol. 3, p. 253.
18. Demarco, P. V.; Thakkar, A. L. *Chem. Commun.* **1970**, 2.
19. Stephenson, O. The condensation of epichlorohydrin with monohydric phenols and with catechol. *J. Chem. Soc.* **1954**, 1571.