Bis-Chlorodibutyltin Oxide as a New Reagent for a Mild, Versatile and Regioselective Ring-Opening of Epoxides

Claudio J. Salomon

Departamento Farmacia, IQUIOS (CONICET), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 531, 2000, Rosario, Argentina

E-mail: salomon@citynet.net.ar

Received 14 September 2000

Abstract: A convenient and efficient procedure for the ring-opening of epoxides by means of alcohols and bis-chlorodibutyltin oxide is described. The cleavage of the oxiranes is found to proceed regioselectively under mild reaction conditions. Thus, several haloalkanols, useful intermediates toward biological active molecules, are easily obtained in very good yields.

Key words: bis-chlorodibutyltin oxide, epoxides, regioselective, haloalkanols, β-chlorohydrin

Epoxides are among the most useful synthetic intermediates towards the synthesis of many biologically active compounds.[1] Due to their particular polarity and strain of their three member ring, they undergo facile, regio- and stereoselective ring-opening reactions with a wide variety of nucleophiles, providing a powerful strategy for organic synthesis.[2,3]

These transformations are generally promoted by different types of Lewis acid, which induce the nucleophilic attack over the position that can best accommodate the positive charge.[4] Many organotin reagents acting as Lewis acids have been used for the regiospecific conversion of epoxides into 1,2-amino[4]- 1,2-halo[5]-, 1,2-alkoxy[6]- and 1,2-azido[7]- alcohols. However, some of the drawbacks are the long reaction times,[8] low chemo-, regio- and stereoselectivity,[9] and the strong reaction conditions that promote extensive polymerization.[7]

For the past ten years, we have been involved in the development of efficient methods for esterification, transesterification and deesterification mediated by organotin oxides.[10] Recently, we have demonstrated that bis-tributyltin oxide and bis-chlorodibutyltin oxide, are effective reagents for the regio- and stereoselective ring-opening of *R*-(-)-styrene oxide.[11]

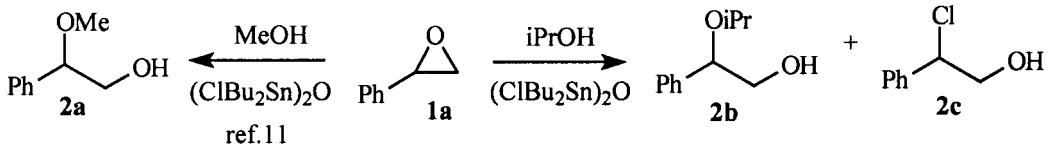
In view of the great utility of epoxides as synthetic intermediates in organic chemistry, it is worthwhile to explore the versatility of the bis-chlorodibutyltin oxide as Lewis acid on the epoxide-opening reactions with a variety of O-nucleophiles. In the present communication we report the results that successfully led to the development of a novel, simple method for the cleavage of epoxides in presence of several alcohols.

We reported the cleavage of styrene oxide (**1a**) with MeOH assisted by $(ClBu_2Sn)_2O$. Thus, 2-Methoxy-2-β-Phenylethanol (**2a**) was isolated as single isomer in 88% yield.[11] When the reaction was carried out in presence of *i*-PrOH, the corresponding 2-isopropoxy-2-phenylethanol (**2b**) was isolated in 53% yield. Surprisingly, a minor product was detected by TLC, isolated and characterized as the β-chlorohydrin **2c** (30%) (Scheme 1). In the presence of *t*-BuOH, **2c** was isolated in 51% yield, after 72 h.

Fluorine substituted organic compounds gain a growing interest because of their unique properties due to the influence of the electronegative fluorine substituent on the neighboring positions. However, the preparation of fluorohydrins from epoxides has always been a difficult transformation in fluorine chemistry,[12] therefore we first investigated the ring-opening of styrene oxide (**1a**) with 2-fluoroethanol in presence of bis-chlorodibutyltin oxide. The fluorophenylethanol **2d** was easily obtained as a single regioisomer in 88% yield.

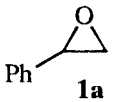
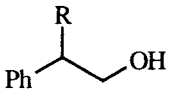
Treatment of styrene oxide with 2-chloroethanol and $(ClBu_2Sn)_2O$ afforded the aromatic chloroalcohol **2e** regioselectively in 87% yield. The bromophenylethanol **2f** was obtained in 83% yield when 2-bromoethanol cleaved regiospecifically styrene oxide in presence of the organostannane. (Table 1)

In order to study the reactivity of the aliphatic epoxides and the regioselectivity of the ring opening with $(ClBu_2Sn)_2O$, **1b** was reacted with MeOH, and surprisingly, two compounds were formed. The corresponding 1-methoxy-arylalcohol **2g** was obtained in very low yield (15%), and the unexpected β-chlorohydrin **2h** was isolated in high yield (84%). In the presence of *i*-PrOH, **2h** was

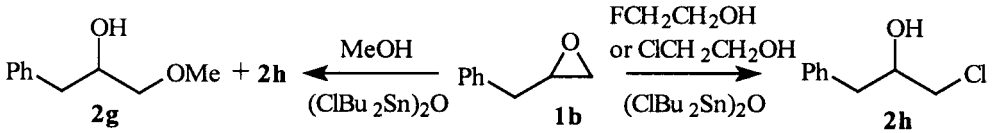


Scheme 1

Table 1 Ring-opening of Styrene Oxide (**1a**) with Alcohols in the Presence of $(ClBu_2Sn)_2O$, at 90 °C

Entry	Epoxide	Alcohol[a]	Time (h)	Product[b]	Yield (%)[c]		Ref.
1		MeOH	1		**2a**, R=OMe	88	11
2		i-PrOH	48		**2b**, R=OiPr	65[d]	11
3		t-BuOH	72		**2c**, R=Cl	51[e]	8
4	**1a**	FCH_2CH_2OH	16		**2d**, R= OCH_2CH_2F,	88	13a
5		$ClCH_2CH_2OH$	3		**2e**, R= OCH_2CH_2Cl	87	13b
6		$BrCH_2CH_2OH$	10		**2f**, R= OCH_2CH_2Br	83	13c

[a] As nucleophile and solvent. [b] Identified by ^1H, and ^{13}C NMR, and M.S. [c] Isolated yields. [d] The β-chlorohydrin **2c** was isolated in 30%. [e] Styrene oxide (**1a**) was recovered in 10-15%.



Scheme 2

obtained in moderate yield as single isomer. Interestingly, when the oxirane **1b** reacted with 2-fluoroethanol, the only compound isolated was the chlorohydrin **2h** in 78% yield. The ring opening of **1b** with $(ClBu_2Sn)_2O$ using 2-chloroethanol afforded the chlorohydrin **2h** in excellent yield (93%). (Scheme 2).

The ring-opening of **1c** with MeOH and $(ClBu_2Sn)_2O$ afforded the β-chlorohydrin **2i** in 87% yield isolated yield with no formation of the other regioisomer. In presence of *i*PrOH the same chlorohydrin was obtained in 70% yield.

Furans have been proven to be useful precursor to cyclic or acyclic functionalized compounds having a framework of four carbon atoms.[14] The mildness of bis-chlorodibutyltin oxide allowed the chemo- and regioselective opening of the 2-substituted epoxyfuran **1d** with MeOH, providing 1-Chloro-3-furfuryloxy-propan-2-ol (**2j**), in 62% yield, and the β-methoxy alcohol **2k**, in 27% yield. The reaction of **1d** with *i*PrOH afforded exclusively the polioxygenated β-chlorohydrin **2j** in 64% yield. The preparation of **2j** under mild non-hydrolytic conditions is a valuable alternative to those methods using NaOH or H_2SO_4.[15] (Table 2).

The highly regioselective ring-opening of epoxides with $(ClBu_2Sn)_2O$, by means of halogenated primary alcohols (entries 4-6, 9 and 10), as well as the moderate yields observed when *iso*-propanol is the nucleophile (entries 2, 8, 13, and 15), could be a consequence of the particular arrangement of tin and chloro atoms disclosed by Otera et al. They described that 1,3-disubstituted tetraalkyldistannoxanes have a dimeric structure, therefore, it might be possible that a chemical reaction carried out by one tin atom, can be influenced by the other tin atom.[17]

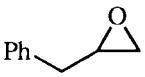
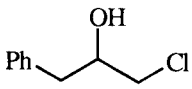
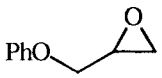
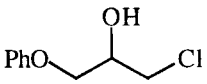
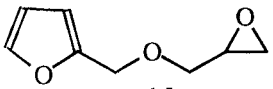
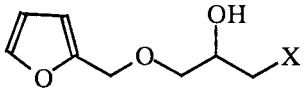
Based on a similar mechanisms,[18] we postulate that the unexpected formation of the β-chlorohydrins (entries 2, 8, 13 and 15) might be due to the coordination of the alcohol toward the tin atom, followed by a coordination of the oxygen atom of the epoxide at one of the tin atoms of the organometallic reagent. Then, a nucleophilic attack by the halide ion formed in situ, at one of the carbon atom of the epoxide, affords the β-chlorohydrin.

The regiochemical mode of the epoxide cleavage by the alcohols in the presence of $(ClBu_2Sn)_2O$ can be viewed as occurring via nucleophilic attack by the chloride or bromide ion on the less sterically hindered epoxide carbon. As expected, in the case of styrene oxide (**1a**), the nucleophile regiospecifically attacked the more substituted carbon of the oxirane. These results clearly suggested that a preferential cleavage of the benzylic C-O bond provided stabilized benzylic cation species during the reaction.

In conclusion, $(ClBu_2Sn)_2O$ can be regarded as a useful reagent for the oxirane ring-opening by means of different alcohols. The fluoro-, chloro- and bromoalcohol derivatives (**2d**, **2e**, and **2f**) easily obtained by this procedure provide a series of interesting intermediates of practical importance. The synthetic utility of the unexpected formation of β-chlorohydrins is shown by the easy preparation of the chloroalkanols **2h**, useful precursor of compounds with antiinflammatory activity,[19] and **2i**, key intermediate toward the synthesis of atenolol and other related drugs for the treatment of hypertension and angina.[20]

Due to the ease in handling and inertness towards several other functional groups $(ClBu_2Sn)_2O$ is recommended when chemoselectivity is crucial.[17] It is particularly noteworthy that we have recently developed an easy protocol

Table 2 Ring-opening of Aliphatic Epoxides with Alcohols in the Presence of $(ClBu_2Sn)_2O$, at 90 °C

Entry	Epoxide	Alcohol[a]	Time (h)	Product[b]	Yield (%)[c]		Ref.
7	 **1b**	MeOH	24		**2h**, X=Cl	84[d]	20
8		i-PrOH	72		**2h**,	62[e]	
9		FCH_2CH_2OH	48		**2h**,	78	
10		$ClCH_2CH_2OH$	18		**2h**,	93	
11	 **1c**	MeOH	24		**2i**	87	8
12		i-PrOH	72		**2i**	70	
13	 **1d**	MeOH	48		**2j**, X=Cl	62	16a
					2k, X=OMe	27	16b
14		i-PrOH	50		**2j**	64	

[a] As nucleophile and solvent. [b] Identified by ^1H, and ^{13}C NMR, and M.S. [c] Isolated yields. [d] 1-Methoxy-3-phenyl-2-propanol (**2g**) was isolated in 10%. [e] Epoxide **1b** was recovered in 15%.

for the disposal of organotin residues.[21] Thus the use of $(ClBu_2Sn)_2O$ could be valuable given the increasing demand for environmentally benign technology.[22] Finally, the present method offers considerable advantages in terms of simplicity, high efficiency and very mild conditions. Further studies toward a general application of this novel method are in progress in our laboratory.

General procedure: To a solution of the epoxide (1 mmol) in alcohol (2 mL) was added $(ClBu_2Sn)_2O$ (1 mmol).[23] The reaction mixture was magnetically stirred at 90 °C under N_2 atmosphere, monitoring the consumption of starting material by TLC (hexane:ethyl acetate, 4:1). The solvent was removed under vacuum and the residue was chromatographed on a silica-gel column eluted with hexane (50 mL), and hexane-ethyl acetate (3×40 mL:10 mL) to provide pure compounds (see Tables 1 and 2).

Experimental Section

Alcohols were purified by distillation and stored under molecular sieves. Epoxides and $(ClBu_2Sn)_2O$ are commercially available from Aldrich Chemical Comp, Inc. Flash column chromatography was carried out according to the standard literature method using silica gel 60 Merck (230-400 mesh). NMR spectra were measured in $CDCl_3$ and C_6D_6 at 200 MHz for ^1H and 20.15 MHz for ^{13}C, and recorded on a Bruker AC-200 spectrometer with TMS as internal standard. Mass spectra were obtained with MAT 8200 spectrometer.

Acknowledgement

The author is very grateful to Consejo Nacional de Investigaciones Técnicas y Científicas (CONICET), Agencia para la Promoción Científica y Tecnológica, Fundación Antorchas, and the National University of Rosario for the financial support.

References and Notes

(1) (a) Erden, I. *In Comprehensive Heterocyclic Chemistry*, 2nd ed,: Padwa, A., Ed.; Pergamon Press: Oxford **1996**; (b) Bartók, M.; Lang, K. L. *In The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York **1985**; Vol. 42, Part 3, p 1.c) Finney, N., *Chemistry and Biology* **1998**, 4, R73. (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, 53, 2861.

(2) a) Nugent, W. A. *J. Am. Chem. Soc.* **1992**, 114, 2768. b) Tokunaga, M., Larrow, J. F., Kakiuchi, F., Jacobsen, E. N. *Science* **1997**, 277, 936. For a recent reviews see: a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, 52, 14361. b) Hanson, R. M. *Chem. Rev.* **1991**, 91, 347.

(3) For reviews see: (a) Bonini, C.; Righi, G. *Synthesis* **1994**, 225. (b) Smith, J. G. *Synthesis* **1984**, 629. (c) Yamada, J.; Yumoto, M.; Yamamoto, Y. *Tetrahedron Lett.* **1989**, 30, 4255.

(4) Fiorenza, M.; Ricci, A.; Taddei, M.; Tassi, D. *Synthesis* **1983**, 640.

(5) Einhorn, C.; Luche, J.-L. *J. Chem. Soc. Chem. Commun.* **1986**, 1368

(6) (a) Otera, J.; Niibo, Y.; Tatsumi, N.; Nozaki, H. *J. Org. Chem.* **1988**, 53, 275. (b) Otera, J.; Yoshinga, Y.; Hirakawa, K. *Tetrahedron Lett.* **1985**, 25, 3219. (c) Niibo, Y.; Nakata, T.; Otera, J.; Nozaki, H., *Synlett* **1991**, 97 (d) Moberg, Ch.; Rákos, L.; Tottie, L. *Tetrahedron Lett.* **1992**, 33, 2191.

(7) Saito, S.; Yamashita, S.; Nishikawa, T.; Yokoyama, Y.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, 30, 4153.

(8) Kotsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Tetrahedron* **1988**, 54, 2709

(9) Konaklieva, M. I.; Dahi, M. L.; Turos, E.; *Tetrahedron Lett.* **1992**, 33, 7093

(10) (a) Salomon, C. J.; Mata, E. G. and Mascaretti, O. A. *Tetrahedron Lett.* **1991**, 32, 4239. (b) Salomon, C. J.; Mata, E. G. and Mascaretti, O. A. *Tetrahedron* **1993**, 49, 3691. (c) Salomon, C. J.; Mata, E. G. and Mascaretti, O. A. *J. Org. Chem.* **1994**, 59, 7259. (d) Salomon, C. J.; Mata, E. G. and Mascaretti, O. A. *J. Chem. Soc. Perkin 1*. **1996**, 995 (e) Furlán, R. L.; Mata, E. G. Mascaretti, O. A. J. *Chem. Soc. Perkin*

Trans. 1 **1998**, 355. (f) Mascaretti, O. A.; Furlán, R. L.; Salomon, C. J. and Mata, E. G. *Phosphorus, Sulfur and Silicon* **1999**, 150, 9

(11) Salomon, C. J.; Laborde, M. A, Gonzalez Sierra, M. and Mascaretti, O. A. *Main Group Metal Chemistry* **1998**, 21, 617.

(12) (a) Surya Prakash, G. K.; Yudin, A. K. *Chem. Rev.* **1997**, 97, 757. (b) Yoshida, M.; Suzuki, D.; Iyoda, M. *J. Chem. Soc. Perkin Trans. 1* **1997**, 643

(13) (a) **2-Phenyl-2-(2-fluoroethoxy)-ethanol (2c):** ^{1}H NMR δ 2.42 (1H, s); 3.67-3.75 (4H, m); 4.41-4.46 (2H, m); 4.68 (1H, m); 7.30-7.35 (5H, m); ^{13}C NMR d 67.90; 69.56; 81.45; 125.90; 128.01; 128,90; 136,77; MS (70eV) m/z 184 (M, 2%), 153 (100%), 121 (6%), 107 (50%), 79 (40%).
(b) **2-Phenyl-2-(2-chloroethoxy)-ethanol (2d):** ^{1}H NMR δ 2.42 (1H, s); 3.63-3.67 (6H, m); 4.48 (1H, dd, *J* = 6.0 and 4.4 Hz); 7.31-7.35 (5H, m); ^{13}C NMR δ 67.23; 68.95; 83.45; 126.66; 128.22; 128,51; 137,87. MS (70eV) m/z 200 (M, 4%), 169 (100%), 121 (16%), 107 (62%), 79 (71%).
(c) **2-Phenyl-2-(2bromoethoxy)-ethanol (2e):** ^{1}H NMR δ 2.44 (1H, dd, *J* = 8.5 and 4.4 Hz); 3.46-349 (2H, m); 3.52-3.83 (4H, m); 4.47 (1H, dd, *J* = 5.8 and 4.2 Hz); 7.30-7.37 (5H, m); ^{13}C NMR δ 67.23; 68.73; 83.39; 126.63; 128.20; 128,47; 137,85. MS (70eV) m/z 244 (M, 2 Br isotopes, 2%), 213 (72%), 133 (18%), 121 (17%), 105 (100%), 77 (72%).

(14) (a) For an accounts see: Ciufolini, M. A.; Hermann, C. Y.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 108. (b) D'Onofrio, F.; Piancatelli, G.; Nicolai, M. *Tetrahedron* **1995**, 51, 4083.

(15) Stankyavichene, L. M. M.; Raizhene, D. I. L.; Vizas, V. K.; Stankyavichus, A. P.; Terent'ev, P. B.; *Pharm. Chem. J.* (Engl. Transl.); **1986**, 20, 323.

(16) (a) **1-Methoxy-3-furfuryloxy-propan-2-ol (2h):** ^{1}H NMR δ 2.64 (1H, m); 3.36-3.51 (7H, m); 3.96 (1H, m); 4.49 (2H, s); 6.33-638 (2H, m); 7.40-7.42 (1H, m); ^{13}C NMR δ 59.04; 65.05; 69.21; 70.99; 73.57; 109.36; 110.14; 142,74; 151,31. MS (70eV) m/z 186 (M, 48%), 145 (5%), 97 (76%), 81 (100%).
(b) **1-Chloro-3-furfuryloxy-propan-2-ol (2i):** ^{1}H NMR δ 2.56 (1H, dd, *J* = 8.5 and 4.4 Hz); 3.56-3.62 (4H, m); 3.95-3.98 (1H, m); 4.51 (2H, s); 6.34-635 (2H, m); 7.40-7.42 (1H, m); ^{13}C NMR δ 69.21; 70.65; 71.99, 74.34; 109.36; 110.14; 142,74; 151,31. MS (70eV) m/z 190 (M, 26%), 137 (5%), 97 (43%), 81 (100%), 53 (34%).

(17) (a) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem.* **1991**, 56, 5307. (b) For a review see: Otera, J. *Chem. Rev.* **1993**, 93, 1449. (c) Orita, A.; Mitsutome, A.; Otera, J. *J. Org. Chem.* **1998,** 63, 2420.

(18) (a) Oriyama, T.; Ishiwata, A.; Hori, Y.; Yatabe, T.; Hasumi, N.; Koga, G. *Synlett* **1995**, 1004. (b) Thijs, L.; Cillisen, P. J. M.; Zwanenburg, B. *Tetrahedron* **1992**, 48, 9985. (c) Shibata, I.; Baba, A.; Matsuda, H. *Tetrahedron Lett.* **1986**, 27, 3021.

(19) Barron, D. I.; Bysenth, P. T.; Clarke, R. W.; Copley, A. R.; Stephenson, O.; Vallance, D. K.; Wild, M. *J. Med. Chem.* **1968**, 11, 1139.

(20) Kitaori, K; Takehira, Y.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Chem. Pharm. Bull.* **1998**, 46, 505.

(21) Salomon, C. J.; Danelon, G.O.; Mascaretti, O. A. *J. Org. Chem*. **2000**, in press.

(22) Nicklin, S.; Robson, M. W. *Appl. Organomet. Chem* **1988**, 2, 487.

(23) When the reaction was carried out using 0.1 equiv of $(ClBu_2Sn)_2O$, the product was isolated in very low yield, recovering the starting epoxide in 30-50%.

Article Identifier:
1437-2096,E;2001,0,01,0065,0068,ftx,en;S06100ST.pdf