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Facile and regioselective conversion of epoxides into β-chlorohydrins using $ZrCl_4$

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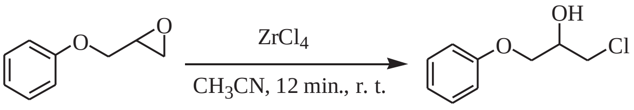
Epoxides were efficiently converted into the corresponding β-chlorohydrins in good yields by treatment with $ZrCl_4$ in acetonitrile.

Keywords: epoxides, β-chlorohydrins, zirconium (IV) chloride

Vicinal-halohydrins have attained great significance in the synthesis of halogenated marine natural products[1] and they can be utilised for some useful synthetic transformations.[2] They are generally prepared by ring opening of epoxides with hydrogen halides, a method which suffers from various disadvantages such as unwanted byproducts and low regioselectivity.[3] A variety of other reagents have been reported to convert epoxides into halohydrins including elemental halogens,[4] Lewis acids such as BF_3,[5] chlorosilanes,[6] haloboranes,[7] pyridine–HCl,[8] metal halides such as LiX,[9] $TiCl_4$–LiX,[10] $FeCl_3.6H_2O$ supported on SiO_2,[11] tin (II) halides,[12] dilithium tetrachlorocuprate,[13] $CeCl_3.7H_2O$–NaI,[14] recently a pyrrolidone/$SOCl_2$ complex[15] and hydrogen and lithium halides in the presence of β-cyclodextrin[16] and a few others.[17] All of these methods, while offering some advantages, also suffer from disadvantages such as the use of expensive reagents, a requirement of excess reagent or a co-reagent, longer reaction times (up to several days in some cases), refluxing conditions and low yield. Accordingly the development of a mild and efficient methodology for the conversion of epoxides into β-halohydrins is desired.

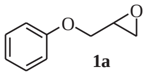
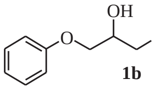
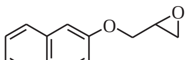
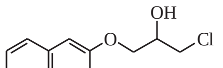
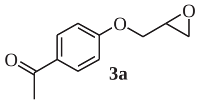
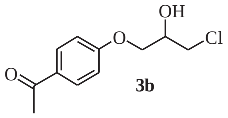
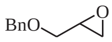
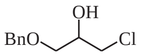
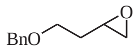
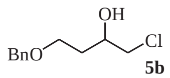
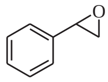
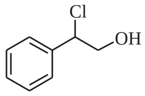
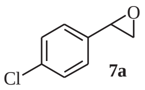
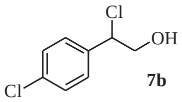
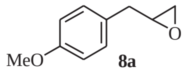
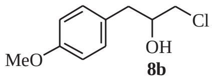
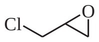
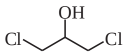
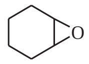
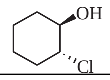
Recently, we have been engaged in the development of new methodologies using zirconium(IV) chloride ($ZrCl_4$) as a mild and efficient Lewis acid catalyst[18] and in this context we have investigated an expeditious method for the conversion of epoxides to β-chlorohydrins. Here, we report a highly regioselective and efficient ring opening of epoxides with $ZrCl_4$ in acetonitrile at room temperature to afford the corresponding β-chlorohydrins in good yields within a very short reaction time (Scheme 1).

The scope and generality of this conversion is illustrated with different epoxides and the results are summarised in the Table. In the first case, phenyl glycidyl ether was reacted with 0.4 equivalents of $ZrCl_4$ in acetonitrile at room temperature. Complete conversion was achieved within 12 minutes to afford 1-chloro-3-phenoxy-2-propanol in 94% yield (entry 1). Similarly, naphthyl, 4-acetylphenyl and benzyl glycidyl ethers also gave the corresponding β-chlorohydrins in 92, 93 and 90% yields respectively (entries 2, 3 and 4). This demonstrates the predominant attack of the reagent on the less hindered carbon of the epoxides. As expected in the case of styrene oxide substrates, 2-chloro-2-phenylethanols were obtained, suggesting that the preferential cleavage of the benzylic carbon–oxygen bond provides a stabilised cation species during the reaction (entry 6 and 7). Other substrates, benzyloxybutene oxide (entry 5) and epoxides having chloro and methoxy groups (entry 8 and 9) also underwent smooth cleavage of epoxide under the reaction conditions. The cyclohexene epoxide opening reaction was anti-stereoselective giving only the trans-isomer in 88% yield (entry 10).



Scheme 1

Table 1 Conversion of epoxides into β-chlorohydrins using $ZrCl_4$

Entry	Epoxide	Time/min	Product[a]	Yield/%[b]
1	 **1a**	12	 **1b**	94
2	 **2a**	12	 **2b**	92
3	 **3a**	15	 **3b**	93
4	 **4a**	10	 **4b**	90
5	 **5a**	8	 **5b**	92
6	 **6a**	5	 **6b**	92
7	 **7a**	6	 **7b**	91
8	 **8a**	8	 **8b**	94
9	 **9a**	10	 **9b**	86
10	 **10a**	12	 **10b**	88

[a]All the products were obtained as liquids and characterised by ^1H NMR, IR and mass spectrometry
[b]Isolated yields after purification.

In conclusion, we have developed a mild and efficient method for the regioselective conversion of epoxides into β-chlorohydrins using $ZrCl_4$ in acetonitrile. The advantages of the method are: (i) no co-reagents; (ii) a simple experimental procedure (anhydrous or dry atmosphere conditions are not required); (iii) high yields; and (iv) short reaction times. We feel the method will find important applications into organic synthesis.

Experimental

Crude products were purified by column chromatography on silica gel of 60–120 mesh. ^1H and ^{13}C NMR spectra were obtained on Gemini-200 spectrometer in $CDCl_3$. Chemical shifts are given in ppm with respect to internal TMS, and *J* values are quoted in Hz. IR spectra were obtained neat, and only the most significant absorptions in cm^{-1} are indicated. Mass spectra were recorded on a Finnegan

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MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer. ZrCl$_4$ and epoxides (**1a**, **6a**, **7a**, **9a** and **10a**) were purchased from Aldrich chemicals and used without further purification. Other epoxides **2a** to **4a**,[19a] **5a**[19b] and **8a**[19c] were prepared using literature procedures.

General procedure for the conversion of epoxides into β-chlorohydrins: To a stirred solution of epoxide (1 mmol) in acetonitrile (5 ml), ZrCl$_4$ (0.4 mmol) was added and the reaction mixture was stirred at room temperature for the given time (Table 1). After completion of the reaction (TLC), the solvent was removed under reduced pressure and the crude residue was extracted with EtOAc, washed with 10% aq. NaHCO$_3$, water and brine. After drying over Na$_2$SO$_4$ and evaporation of the solvent, the crude product was purified by column chromatography to give the corresponding β-chlorohydrin in excellent yields.

Spectroscopic and analytical data of the new products:
2b: Colourless oil; ^{1}H NMR (CDCl$_3$): δ 2.59 (d, *J*=5.2 Hz, 1H), 3.7–3.75 (m, 2H), 4.2–4.26 (m, 3H), 7.06–7.75 (m, 7H); ^{13}C NMR (CDCl$_3$): 45.8, 68.5, 69.7, 122.2, 127.4, 128.7, 133.2, 134.5, 156.1; IR (Neat): 3426, 1492, 1072 cm^{-1}; MS (*m/z*): 236 (M$^+$). Anal. Calcd for $C_{13}H_{13}ClO_2$: C, 65.97; H, 5.54. Found: C, 65.92; H, 5.52.

7b: Colourless oil; ^{1}H NMR (CDCl$_3$): δ 2.82 (br s, 1H), 3.8–3.92 (m, 2H), 4.92 (t, *J*=6.8 Hz, 1H), 7.23–7.4 (m, 4H); ^{13}C NMR (CDCl$_3$): 64.7, 67.8, 127.4, 128.7, 133.7, 138.9; IR (Neat): 3383, 1453, 1067 cm^{-1}; MS (*m/z*): 190 (M$^+$). Anal. Calcd for $C_8H_8Cl_2O$: C, 50.29; H, 4.22. Found: C, 50.26; H, 4.21.

Products **1b** & **3b**,[16] **4b**,[19d] **5b**,[19e] **6b**,[9a] and **8b** to **10b**.[16] ^{1}H NMR, IR and mass spectral data of these known compounds were identical with the reported data.

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