Synthesis of β-Chlorohydrins in Water[1])

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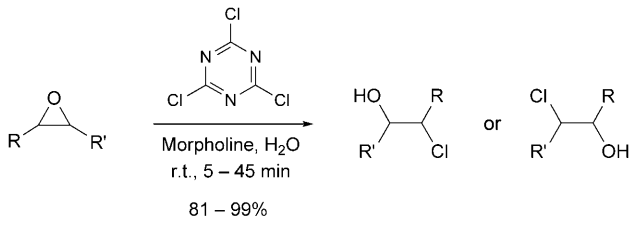
2,4,6-Trichloro-1,3,5-triazine (TCT, cyanuric chloride) was found to mediate the regio- and stereoselective ring opening of epoxides in H_2O in the presence of morpholine at room temperature to afford the corresponding β-chlorohydrins in excellent yields (*Table*). The transformation is very simple, fast, efficient, and ecologically beneficial.

Introduction. – The ring opening of epoxides by halide nucleophiles produces vicinal halohydrins, which are useful intermediates for the synthesis of halogenated marine natural products and various other bioactive compounds [1]. This transformation can be carried out with halogens, hydrogen halides, and metal halides in organic solvents such as MeCN or CH_2Cl_2 [2]. However, many of these methods are associated with several disadvantages, including harsh reaction conditions, unsatisfactory yields, and poor selectivity. Thus, an improved protocol for the conversion of epoxides into the corresponding vicinal halohydrins is essential.

Cyanuric chloride, *i.e.*, 2,4,6-trichloro-1,3,5-triazine (TCT), is a safe and inexpensive reagent being used in various chemical transformations in organic media [3]. In continuation of our work on the development of useful synthetic methodologies [4], we recently observed that the ring opening of epoxides can efficiently be carried out with TCT in the presence of morpholine in H_2O at room temperature to form the corresponding β-chlorohydrins (*Scheme 1*). Herein, we report the results and synthetic details of this useful transformation.

Scheme 1



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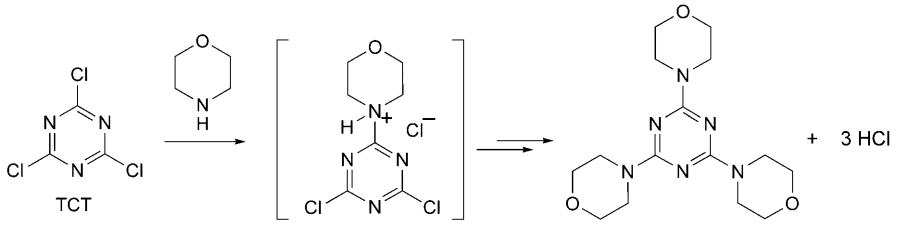
Results and Discussion. – As can be seen from the *Table*, chlorohydrin formation readily took place by simply stirring a mixture of TCT (2 mmol), morpholine (5 mmol), and epoxide (5 mmol) in H_2O at ambient temperature for 5–45 min. With styrene oxide (*Entry 1*), the reaction took only 5 min, affording 2-chloro-2-phenylethanol in 99% yield. The reaction was highly efficient, both for aromatic and aliphatic or alicyclic substrates. Even sterically hindered epoxides, derived from trisubstituted olefins (*Entry 8*), underwent the cleavage smoothly.

The conversion of epoxides into β-chlorohydrins took place with high regio- and stereoselectivity. In 2-aryl epoxides (*Entries 1* and *2*), nucleophilic attack of Cl^- occurred at the benzylic position. In contrast, 2-alkyl or 2-aryloxy epoxides gave rise to products derived by attack at the terminal 3-position. The ring opening of bicyclic epoxides (Entries *11* and *12*) occurred with *anti* selectivity to form the *trans*-configured products exclusively. The structures of the β-chlorohydrins were settled by spectroscopic (IR, ^{1}H-NMR), spectrometric (MS), and elemental analyses.

From a mechanistic point of view, the present conversion possibly takes place as follows. Reaction between morpholine and TCT liberates HCl *in situ*, as indicated by gas evolution upon mixing of these two components, before addition of H_2O (*Scheme 2*). Then, HCl protonates the epoxide O-atom, followed by nucleophilic ring opening. In the absence of morpholine, the reaction between epoxide and TCT in H_2O afforded a mixture of products, including β-chlorohydrins and 1,2-dihydroxy compounds. Note that morpholine derivatives have been used earlier together with TCT in other organic syntheses [3b].

Scheme 2



In conclusion, we have synthesized a number of β-chlorohydrins by regio- and stereoselective ring opening of epoxides applying cyanuric chloride (TCT) in the presence of morpholine in H_2O. The efficiency, and the economic and environmental benefits of this reaction are the notable features of our synthetic protocol.

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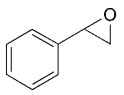
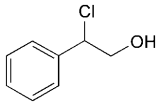
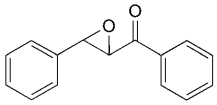
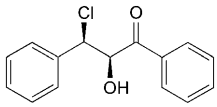
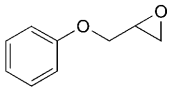
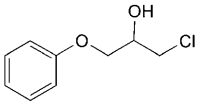
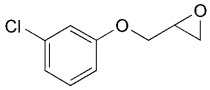
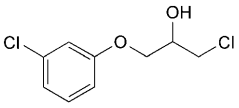
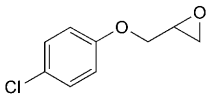
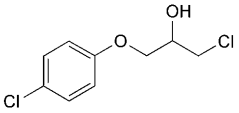
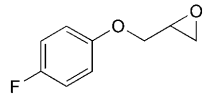
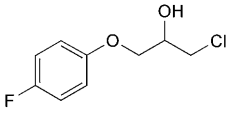
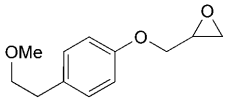
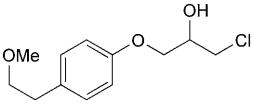
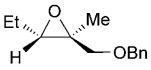
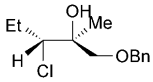
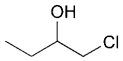
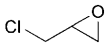
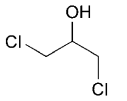
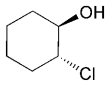
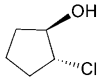
Experimental Part

General. IR Data are reported in cm^{-1}. ^{1}H-NMR Chemical shifts δ and coupling constants J are given in ppm (rel. to Me_4Si) and in Hz, resp. Mass-spectrometric (MS) data are reported in m/z.

Synthetic Procedure. To a mixture of TCT (2 mmol), morpholine (5 mmol), and an epoxide (5 mmol) was added H_2O (5 ml), and the mixture was stirred at r.t. (TLC control). After completion of the reaction,

Table. *Preparation of β-Chlorohydrins*

Entry	Epoxide	Time [min]	Product	Isolated yield [%]	Ref.
1		5		99	[2c]
2		15		87	[2f]
3		20		98	[2c]
4		30		97	–
5		25		98	[2e]
6		25		96	–
7		30		98	[2g]
8		45		81	–
9		25		92	[2d]
10		20		96	[2d]
11		15		98	[2d]
12		15		98	[2d]

H_2O (10 ml) was added, and the mixture was filtered. The filtrate was extracted with AcOEt (3×5 ml), dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was subjected to column chromatography (SiO_2, hexane/AcOEt) to afford the pure *β*-chlorohydrin. Selected anal. data are presented below.

1-Chloro-3-(3-chlorophenoxy)propan-2-ol (*Table*, *Entry 4*). Colorless liquid. IR (KBr): 3416, 1607, 1384. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.32 (*dd*, *J* = 8.0, 2.0, 1 H); 7.28–7.16 (*m*, 1 H); 6.97–6.86 (*m*, 2 H); 4.20 (*m*, 1 H); 4.18–4.05 (*m*, 2 H); 3.88–3.71 (*m*, 2 H); 2.65 (*d*, *J* = 6.5, 1 H). FAB-MS: 221/223/225 ($[M+H]^+$). Anal. calc. for $C_9H_{10}Cl_2O_2$: C 48.89, H 4.56; found: C 48.82, H 4.58.

1-Chloro-3-(4-fluorophenoxy)propan-2-ol (*Table*, *Entry 6*). Pale-yellow liquid. IR (KBr): 3414, 1618, 1491. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.22 (*d*, *J* = 8.0, 2 H); 6.83 (*d*, *J* = 8.0, 2 H); 4.15 (*m*, 1 H); 4.07–3.98 (*m*, 2 H); 3.74–3.67 (*m*, 2 H); 2.68 (br. *s*, 1 H). FAB-MS: 205/207 ($[M+H]^+$). Anal. calc. for $C_9H_{10}ClFO_2$: C 52.83, H 4.93; found: C 52.88, H 4.82.

(2S,3R)-1-(Benzyloxy)-3-chloro-2-methylpentan-2-ol (*Table*, *Entry 8*). Colorless liquid. IR (KBr): 3418, 1617, 1512, 1496. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.33–7.21 (*m*, 5 H); 4.54 (*s*, 2 H); 3.81 (*dd*, *J* = 11.0, 2.0, 1 H); 3.70 (*d*, *J* = 9.0, 1 H); 3.29 (*d*, *J* = 9.0, 1 H); 2.50 (br. *s*, 1 H); 2.12 (*m*, 1 H); 1.51 (*m*, 1 H); 1.16 (*s*, 3 H); 1.08 (*d*, *J* = 7.0, 3 H). FAB-MS: 243/245 ($[M+H]^+$). Anal. calc. for $C_{13}H_{19}ClO_2$: C 64.32, H 7.89; found: C 64.38, H 7.79.

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