Efficient and Regioselective Conversion of Epoxides into Vicinal Chloroesters with $TiCl_4$ and Imidazole in Ethyl Acetate†

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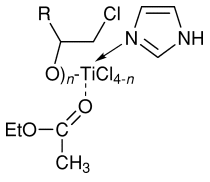
Epoxides can be cleaved easily in EtOAc with $TiCl_4$ in the presence of imidazole to afford β-chloroesters with excellent yields and regioselectivity.

Regioselective ring-opening of epoxides to β-halohydrins is a subject of interest in organic synthesis.[1] Although this matter has been widely studied in recent years, the conversion of epoxides into β-chloroesters as important derivatives of halohydrins has been rarely studied. Formation of β-chloroacetates from olefins and epoxides has been reported with acetyl chloride in the presence of chromyl chloride,[2,3a] with low regioselectivity, or hexaalkylguanidium chloride.[3b] A similar transformation with benzoyl chloride has also been studied in the presence of $Bu^n_2SnCl_2$–PPh_3[4] and $CoCl_2$.[5]

Reports on the application of $TiCl_4$ for the formation of halohydrins[6] from epoxides and our observations on the ring opening of epoxides with heteronucleophiles[7] catalysed with Lewis acids led us to explore the possibility of using $TiCl_4$ for such a transformation. Thus we report here that epoxides can react with ethyl acetate in the presence of $TiCl_4$ and imidazole to afford vicinal chloroacetates in high yields (Table 1).

GC and ^{1}H NMR analysis of the crude products showed the excellent regioselectivity with the formation of, mostly, one isomer. The presence of different substituents on the epoxide ring and the absence of side reactions showed the chemoselectivity of this transformation (Scheme 1).

In the absence of imidazole, the reactions are not complete even after 24 h and the products that are formed are mostly chlorohydrins. The presence of imidazole greatly accelerates the reaction, possibly through interaction with β-chloroalkoxytrichlorotitanate(IV) which can be formed as an intermediate in the reaction with ethyl acetate (**4**).



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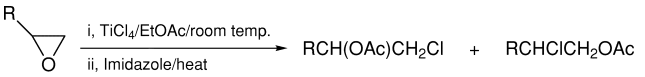
Other bases, such as triethylamine, diethylamine, pyridine and DABCO, also enhance the reaction, but imidazole is the most efficient. The stereochemistry of the cyclic products was determined by different procedures.[8]

These results show that this method is very suitable for the direct conversion of epoxides into β-chloroacetates. High yields, high regio- and chemoselectivities, easy work-up and the availability of the reagents can be considered as advantages of this method.



1a R = Ph
b R = Bu^n
c R = $CH_2{=}CHCH_2OCH_2$
d R = $(CH_3)_2CHOCH_2$
e R = $ClCH_2$
f cyclohexene oxide
g cyclopentene oxide
h cyclooctene oxide

Scheme 1

Experimental

Products were characterized by comparison of their physical data, IR, NMR and mass spectra with those reported in the literature. The IR spectra were recorded on a Perkin Elmer IR-157 G and a Perkin Elmer 781 spectrophotometer. The NMR spectra were recorded on a Bruker Avance DPX-250. Mas spectra were recorded on a Shimadzu GCMS-QP 1000 EX instrument.

General Procedure for Reaction of Epoxides with $TiCl_4$ in EtOAc.—In a round-bottomed flask equipped with a condenser and magnetic stirrer, the epoxide (1 mmol) was added dropwise to a solution of $TiCl_4$ 91.5 mmol, 0.285 g) in EtOAc (8 ml) at room temperature. The reaction mixture was then stirred vigorously for 10 min. Subsequently, imidazole (3.0 mmol, 0.204 g) was added to the reaction mixture in small portions over a period of time shown in Scheme 1. The reaction progress was monitored with TLC or GLC. After completion of the reaction, solvent was evaporated and water (10 ml) was added to the residue. β-Chloroacetate was extracted with $CHCl_3$ (3×15 ml) and dried with anhydrous Na_2SO_4. The product was obtained in 80–95% yield after chromatography on a short column of silica-gel. Spectral data of the products are as follows: **2a**: bp 100 °C (0.3 mmHg[3b]), δ_C ($CDCl_3$), 20.2, 58.8, 67.08, 126.6, 127.6, 127.7, 136.8, 169.6; *m/z* (70 eV) 163 (M – Cl, 0.1), 139 (M – OAc, 1.2%); **2b**: δ_H ($CDCl_3$), 1.0 (3 H, t, *J* 5.5 Hz), 1.26–1.7 (6 H, m), 2.1 (3 H, s), 3.6 (2 H, partially resolved doublet), 5.1 (1 H, q); *m/z* (70 eV) 143 (M – OAc, 1.8%); **2c**: δ_H ($CDCl_3$), 2.1 (3 H, s), 3.6–3.8 (2 H, m), 3.9–4.15 (2 H, partially resolved doublet), 4.2–4.4 (1 H, m), 4.9–5.25 (2 H, m), 5.7–6 (1 H, m); δ_C ($CDCl_3$), 21.2, 43.06, 68.4, 72.07, 72.68, 117.7, 134.5, 170.5;

Table 1 Reaction of epoxides with $TiCl_4$[a] in EtOAc in the presence of imidazole[b]

Epoxide	Time (h)	Yield (%)[c]	Products	**2**:**3**[d]
1a	3.5	95	**2a**+**3a**	96:4
1b	2	89	**2b**+**3b**	80:20
1c	7	93	**2c**+**3c**	95:5
1d	2.5	94	**2d**+**3d**	91:9
1e	1.5	80	**2e**+**3e**	90:10
1f	1	92	**2f**[e]	—
1g	2	87	**2g**[f]	—
1h	2.5	95	**2h**[g]	—

[a]1.5 Molar equivalents of $TiCl_4$ were used. [b]3 Molar equivalents of imidazole were used. [c]Isolated yield after chromatography. [d]The ratio of compounds **2** and **3** was determined by GC and ^{1}H NMR analysis. [e]*trans*-1-Chloro-2-acetoxycyclohexane. [f]*trans*-1-Chloro-2-acetoxycyclopentane. [g]*trans*-1-Chloro-2-acetoxycyclooctane.

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m/*z* (70 eV) 133 (M–OAc, 1.2), 98 (M − 133 − Cl, 4.2%); **2d**: δ_H ($CDCl_3$), 1.05 (6 H, d, *J* 6 Hz), 2.01 (3 H, s), 3.4–3.8 (5 H, complex), 4.9 (1 H, m); δ_C ($CDCl_3$), 20.58, 21.64, 42.62, 65.78, 71.68, 72.13, 169.86; *m*/*z* (70 eV) 159 (M − Cl, 1.8), 135 (M − OAc, 3.9%); **2e**: δ_H ($CDCl_3$) (3 H, s), 3.6–3.8 (4 H, m), 5.1–5.4 (1 H, m); δ_C ($CDCl_3$), 20.57, 40.80, 66.12, 169.09, *m*/*z* (70 eV) 101 (M − 2Cl, 18.9%); **2f**: (*trans*-1-chloro-2-acetoxycyclohexane) δ_H ($CDCl_3$), 1–1.5 (4 H, m), 1.5–1.8 (4 H, m), 2.01 (3 H, s), 3.65–4.1 (1 H, m), 4.6–4.9 (1 H, m); δ_C ($CDCl_3$), 23.01, 25.91, 26.54, 32.74, 36.8, 62.69, 77.82, 172.1; *m*/*z* (70 eV) 141 (M − Cl, 10.7%), 117 (M − OAc, 1.9%); **2h**: (*trans*-1-chloro-2-acetoxycyclooctane) δ_H ($CDCl_3$) 1.4–1.9 (8 H, complex), 2.1 (3 H, s), 1.96–2.2 (4 H, m), 4.16 (1 H, m), 5.1 (1 H, m); δ_C ($CDCl_3$), 19.8, 22.2, 23.9, 24.2, 24.3, 29.8, 30.3, 63.01, 77.4, 168.8; *m*/*z* (70 eV) 169 (M − Cl, 1.8%), 145 (M − OAc, 1.8%); **2g**: (*trans*-1-chloro-2-acetoxycyclopentane) δ_H ($CDCl_3$), 1–1.5 (2 H, m), 1.5–1.8 (4 H, m), 2.05 (3 H, s), 3.6–4.05 (1 H, m), 4.5–4.85 (1 H, m), *m*/*z* (70 eV) 127 (M − Cl, 8.5%), 103 (M − OAc, 1.4%).

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8 The stereochemistry of the cyclic products were determined according to the following procedures: (*a*) the corresponding *trans*-halohydrins which are formed as intermediates from the reaction of epoxides with $TiCl_4$ in the absence of imidazole were separated and their physical data were compared with the data reported in the literature.[9] (*b*) The acetate or benzoate derivatives of the obtained cyclic chlorohydrins were also prepared and their physical data were compared with those reported in the literature.[10] (*c*) The spectral data obtained from the acetate derivative of halohydrins in procedure (*b*) were found to be identical with those obtained with our method.

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