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# Regioselective Addition of Organic Chlorides to Epoxides in the Presence of Quaternary Ammonium Chloride

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(Received July 9, 1986)

**Synopsis.** By a reaction of epoxides with organic chlorides in the presence of dodecyltrimethylammonium chloride as a catalyst, a series of 2-substituted 1-(chloromethyl)ethyl ethers were synthesized regioselectively in high yields under mild conditions.

Epoxides are useful materials in organic synthetic chemistry and industry based on its active epoxy ring, and many kinds of reactions with various reagents have been widely utilized. However, the reaction of epoxides with organic halides had not attracted much attention until the reaction with chloroacetate was reported, where the effect of a catalyst on this reaction was studied.[1] In the course of the investigation regarding the reactivity of epichlorohydrin under phase-transfer catalytic conditions,[2] we found that dodecyltrimethylammonium chloride is a very effective catalyst for the preparation of a wide variety of 2-substituted 1-(chloromethyl)ethyl ethers by the reactions of epoxides with various organic chlorides under mild conditions.

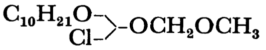
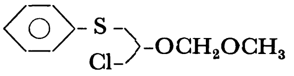
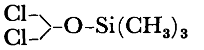
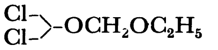
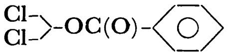
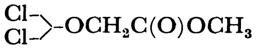
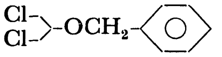
There are several reports concerning the application of 2-substituted 1-(chloromethyl)ethyl ethers. For example, 2-chloro-1-(chloromethyl)ethyl ethers can afford the corresponding azetidines by reactions with primary amines,[3] and are also used to modify the properties of rubber or cellulose.[4-7] At present, we found that 2-chloro-1-(chloromethyl)ethyl methoxymethyl ether (**3a**) is a very effective acetonylation reagent to convert a series of hydroxyl compounds to the corresponding acetonyl ethers.[8]

The reaction may proceed via the intermediate of 2-substituted 1-(chloromethyl)ethoxide as shown in Scheme 1, where $Q^+$ represents quaternary ammonium ion.

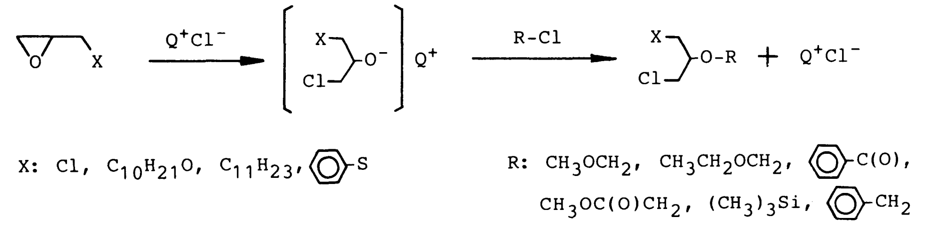
Several novel 2-substituted 1-(chloromethyl)ethyl ethers were synthesized in good yields using dodecyltrimethylammonium chloride as a catalyst. The synthetic conditions and results are shown in Table 1. Products are characterized by spectral and elemental analyses. In the mass spectra, all products gave the characteristic fragment peak based on the elimination of chloromethyl group, and no fragment peak based on dehydrochlorination appeared, showing that this addition reaction of organic chlorides to epoxide in the presence of dodecyltrimethylammonium chloride is regioselective, regardless of substitution group in the substrate epoxide within this experiment.

In the case of methallyl chloride with epichlorohydrin, no reaction proceeded at 85 °C. In the reaction of chloroacetone with epichlorohydrin, 2-chloro-1-(chloromethyl)ethanol was isolated in 57% yield as the main product rather than the anticipated 2-chloro-1-

Table 1. Synthesis of 2-Substituted 1-(Chloromethyl)ethyl Ethers

| Product | | Reaction conditions | | Yield[a)] |
|---|---|---|---|---|
| | | Temperature °C | Time h | % |
|  | **3a** | 30 | 20 | 93 |
|  | **3b** | 30 | 6 | 98 |
|  | **3c** | 30 | 6 | 78 |
|  | **3d** | 30 | 6 | 90 |
|  | **3e** | 10 | 3 | 91 |
|  | **3f** | 30 | 20 | 75 |
|  | **3g** | 80 | 3 | 90 |
|  | **3h** | 80 | 20 | 58 |
|  | **3i** | 100 | 20 | 30 |

a) Isolated yield. The catalyst used is commercial dodecyltrimethylammonium chloride without further purification.



Scheme 1.

(chloromethyl)ethyl acetonyl ether, possibly due to the too acidic methyl or methylene group of chloroacetone.

## Experimental

**General Procedure for Preparation of 2-Substituted 1-(Chloromethyl)ethyl Ethers. 2-Chloro-1-(chloromethyl)ethyl Methoxymethyl Ether (3a):** The mixture of chloromethyl methyl ether 24.6 g (0.30 mol), epichlorohydrin 31.4 g (0.36 mol) and dodecyltrimethylammonium chloride 3.9 g (0.015 mol) is stirred with a magnetic stirrer at 30 °C for 20 h. Then, by fractional distillation at reduced pressure, **3a** was obtained as a colorless liquid; yield: 48.3 g (93%); bp 94—95 °C/30 Torr (1 Torr=133.322 Pa). A GLC of the reaction product showed only one peak, except for excess epichlorohydrin. Another run of the same reaction was carried out at 50 °C for 3 h, yielding 74% of **3a**. Without the catalyst, the yield of **3a** was only 18%, even after a prolonged reaction time (48 h) at 30 °C. $^1$H NMR ($CDCl_3$) $\delta$=3.42 (s, 3H), 3.70—3.76 (d, 4H), 3.88—4.10 (m, 1H), 4.75 (s, 2H); MS, *m/z* (rel intensity) 173 ($M^{+}+1$), 171 ($M^{+}-1$), 123 (12), 75 (12), 45 (100); IR (neat) 2970, 1460, 1170, 1060, 923, 770 cm$^{-1}$. Found: C, 34.66; H, 5.98; Cl, 41.14%. Calcd for $C_5H_{10}Cl_2O_2$: C, 34.71; H, 5.83; Cl, 40.97%.

**1-(Chloromethyl)tridecyl Methoxymethyl Ether (3b):** Synthesized by the reaction of 1,2-epoxytetradecane (0.1 mol) and chloromethyl methyl ether (0.11 mol); bp 100 °C/0.05 Torr (Kugelrohr distillation). $^1$H NMR ($CDCl_3$) $\delta$=0.80—1.00 (t, 3H), 1.10—1.80 (m, 22H), 3.40 (s, 3H), 3.46—3.65 (d, 2H), 3.65—3.80 (m, 1H), 4.74 (s, 2H); MS, *m/z* (rel intensity) 243 (5), 45 (100); IR (neat) 2950, 1050 cm$^{-1}$. Found: C, 65.57; H, 11.52; Cl, 11.98%. Calcd for $C_{16}H_{33}ClO_2$: C, 65.61; H, 11.36, Cl, 12.10%.

**1-Chloromethyl-2-(decyloxy)ethyl Methoxymethyl Ether (3c):** Synthesized by the reaction of decyl glycidyl ether (0.1 mol) and chloromethyl methyl ether (0.11 mol); bp 115 °C/0.04 Torr. $^1$H NMR ($CDCl_3$) $\delta$=0.76—1.10 (t, 3H), 1.06—1.80 (m, 16H), 3.40 (s, 3H), 3.42—3.80 (m, 6H), 3.80—4.00 (m, 1H), 4.74 (s, 2H); MS, *m/z* (rel intensity) 294 (12), 57 (52), 45 (100); IR (neat) 2950, 1110, 1040 cm$^{-1}$. Found: C, 60.93; H, 10.87; Cl, 11.82%. Calcd for $C_{15}H_{31}ClO_3$: C, 61.10; H, 10.60; Cl, 12.02%.

**1-Chloromethyl-2-(phenylthio)ethyl Methoxymethyl Ether (3d):** Synthesized by the reaction of phenyl glycidyl sulfide (0.1 mol) and chloromethyl methyl ether (0.11 mol); bp 90 °C/0.01 Torr. $^1$H NMR ($CDCl_3$) $\delta$=3.10—3.30 (d, 2H), 3.40 (s, 3H), 3.60—3.80 (d, 2H), 3.80—4.00 (m, 1H), 4.78 (s, 2H); MS, *m/z* (rel intensity) 246 ($M^+$), 123 (61), 45 (100); IR (neat) 2950, 1590, 1460, 1440, 1160, 1110, 1040 cm$^{-1}$. Found: C, 53.52; H, 6.08%. Calcd for $C_{11}H_{15}ClO_2S$: C, 53.54; H, 6.13%.

**2-Chloro-1-(chloromethyl)ethyl Trimethylsilyl Ether (3e):** Synthesized by the reaction of epichlorohydrin (0.11 mol) and chlorotrimethylsilane (0.1 mol); bp 81 °C/20 Torr. $^1$H NMR ($CDCl_3$) $\delta$=0.10 (s, 9H), 3.40—3.60 (q, 4H), 3.80—4.00 (m, 1H); MS, *m/z* (rel intensity) 185 (24), 151 (47), 93 (100) 73 (62); IR (neat) 2950, 1250, 1100, 840 cm$^{-1}$. Found: C, 35.62; H, 7.03; Cl, 35.17%. Calcd for $C_6H_{14}Cl_2OSi$: C, 35.82; H, 7.01; Cl, 35.24%.

**2-Chloro-1-(chloromethyl)ethyl Ethoxymethyl Ether (3f):** Synthesized by the reaction of epichlorohydrin (0.11 mol) and chloromethyl ethyl ether (0.1 mol); bp 85 °C/20 Torr. $^1$H NMR ($CDCl_3$) $\delta$=1.14—1.26 (t, 3H), 3.56—3.90 (m, 6H), 3.90—4.12 (m, 1H), 4.80 (s, 2H); MS, *m/z* (rel intensity) 187 ($M^{+}+1$), 185 ($M^{+}-1$), 137 (14), 75 (14), 59 (100), 31 (32); IR (neat) 3000, 2900, 1450, 1140, 1060, 770 cm$^{-1}$. Found: C, 38.24; H, 6.47; Cl, 37.70%. Calcd for $C_6H_{12}Cl_2O_2$: C, 38.52; H, 6.47; Cl, 37.90%.

**2-Chloro-1-(chloromethyl)ethyl Benzoate (3g):** Synthesized by the reaction of epichlorohydrin (0.11 mol) and benzoyl chloride (0.1 mol); bp 89 °C/0.02 Torr. $^1$H NMR ($CDCl_3$) $\delta$=3.84—3.92 (d, 4H), 5.32—5.52 (m, 1H), 7.24—7.68 (m, 3H), 8.00—8.16 (m, 2H); MS, *m/z* (rel intensity) 234 ($M^+$), 232 ($M^+$), 123 (34), 122 (49), 105 (100); IR (neat) 1730, 1295, 1122, 730 cm$^{-1}$. Found: C, 51.48; H, 4.40; Cl, 30.20%. Calcd for $C_{10}H_{10}Cl_2O_2$: C, 51.53; H, 4.30; Cl, 30.40%.

**2-Chloro-1-(chloromethyl)ethyl Methoxycarbonylmethyl Ether (3h):** Synthesized by the reaction of epichlorohydrin (0.11 mol) and chloroacetic acid methyl ester (0.1 mol); bp 78 °C/0.02 Torr. $^1$H NMR ($CDCl_3$) $\delta$=3.72—4.00 (m, 8H), 4.30 (s, 2H); MS, *m/z* (rel intensity) 201 ($M^{+}+1$), 199 ($M^{+}-1$), 151 (46), 93 (100), 75 (45); IR (neat) 2975, 1760, 1440, 1230 cm$^{-1}$. Anal. Calcd for $C_6H_{10}Cl_2O_3$: C, 35.84; H, 5.01; Cl, 35.26%. Found: C, 36.06; H, 5.07; Cl, 35.07%.

**Benzyl 2-Chloro-1-(chloromethyl)ethyl Ether (3i):** Synthesized by the reaction of epichlorohydrin (0.12 mol) and benzyl chloride (0.1 mol); bp 80 °C/0.05 Torr. $^1$H NMR ($CDCl_3$) $\delta$=3.60—4.00 (m, 5H), 4.68 (s, 2H), 7.16 (s, 5H); MS, *m/z* (rel intensity) 220 ($M^+$), 218 ($M^+$), 91 (100); IR (neat) 2800, 1460, 1120, 1090, 760, 720 cm$^{-1}$. Found: C, 54.43; H, 5.70; Cl, 32.17%. Calcd for $C_{10}H_{12}Cl_2O$: C, 54.81; H, 5.52; Cl, 32.35%.

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