Reactions of Substituted Epoxides with Alkyl Chloroacetate

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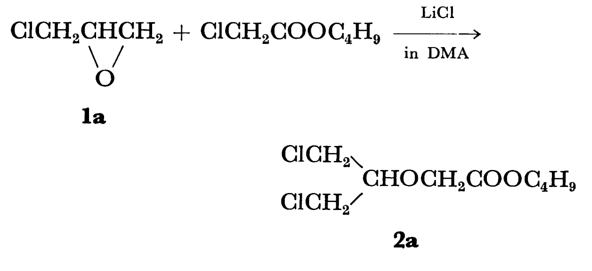
The reactions of substituted epoxides with alkyl chloroacetate in the presence of lithium salts, quarternary salts and zinc chloride were studied. The reaction of 1-chloro-2,3-epoxypropane (**1a**) with butyl chloroacetate (BCA) in the presence of any of these catalysts yielded exclusively butyl [2-chloro-1-(chloromethyl)ethoxy]acetate (**2a**) via the normal cleavage of **1a** followed by the reaction with the chloroacetate. On the other hand, the reaction of 1,2-epoxypropane(**1b**) with BCA yielded a mixture of isomeric products resulting from the normal and abnormal cleavages of **1b**, and the ratio of the normal and abnormal products is dependent on the type of the catalyst. Moreover, it was found that lithium salt alone catalyzed the insertion reaction in a polar aprotic solvent, whereas the reaction in aromatic solvent needed a suitable co-catalyst such as hexamethylphosphoric triamide and triphenylphosphine oxide.

Insertion of an epoxide into the carbon-halogen bond of an alkyl halide had not been investigated to any noticeable extent. In our previous papers, we reported the insertion of ethylene oxide into the carbon-halogen bond of benzyl chlorides[1)] and halooctanes[2,3)] using zinc halide as a catalyst. The reaction of ethylene oxide with benzyl chlorides and halooctanes in *N*,*N*-dimethylacetamide(DMA) gave 2-chloroethyl benzyl ethers and 1-(2-haloethoxy)octanes, respectively, while the reaction of ethylene oxide with secondary halooctanes in the absence of any solvent gave the mixture of 2-(2-haloethoxy)octane, 3-(2-haloethoxy)octane and 4-(2-haloethoxy)octane.

In this study, we obtained the novel insertion compounds from the reaction of substituted epoxides with butyl chloroacetate(BCA) and investigated the distribution of isomers of the insertion products. Moreover, we searched for more effective catalysts and reaction systems from the limitation of zinc halide hitherto used as a catalyst. It was found that the isomer distribution of the insertion product caused by the direction of ring opening was dependent on the substituent of the epoxide ring and the type of the catalyst and that lithium salt complexed with suitable co-catalyst was effective for the present insertion reaction.

Results and Discussion

*Reaction of 1-Chloro-2,3-epoxypropane(**1a**) with BCA.* The reaction of the epoxide **1a** with BCA in DMA in the presence of lithium chloride gave only product, butyl [2-chloro-1-(chloromethyl)ethoxy]acetate(**2a**), in the yield of 35.6%.



$$ClCH_2CHCH_2 + ClCH_2COOC_4H_9 \xrightarrow[\text{in DMA}]{\text{LiCl}} (ClCH_2)_2CHOCH_2COOC_4H_9$$

1a

2a

The structure of this novel compound **2a** could not be determined clearly by ^{1}H-NMR spectrum because the signals of methylene and methine proton between the chlorine and the ether oxygen of the normal and abnormal products, $(ClCH_2)_2CHO$– and $ClCH_2CH(Cl)CH_2O$–, would appear at similar chemical shifts. However, the presence of seven signals above 80.00 in ^{13}C-NMR unambiguously supported the structure of **2a**. Chemical shifts were assigned on the basis of Lindeman-Adams' equation,[4)] the substituent effect and off-resonance spectrum. The effect of catalyst on the yield of the product **2a** is shown in Table 1. Zinc chloride and triethylamine gave a small amount of **2a**. Lithium salts and tetraethylammonium bromide gave considerable amounts of **2a**. In the reaction of **1a** with BCA in DMA, a very small amount of dibutyl oxydiacetate(**3**) was detected by GLC analysis. This could be due to a trace amount of water in DMA. Thus, the reaction of **1a** with BCA was tried in benzene and toluene to avoid the formation of **3**. Lithium salt alone is insoluble in benzene and toluene, and refluxing a benzene or toluene solution of **1a** and BCA in the presence of lithium salt gave no reaction. However, by the addition of an equimolar amount of hexamethylphosphoric triamide(HMPA) to lithium salt the insertion reaction took place smoothly. These results suggest that DMA, added as a solvent in the former reaction, and HMPA, added as a co-catalyst in the latter reaction, may play the same role for the insertion reaction. DMA and HMPA act not only simply as solvents, but also specifically solvate the lithium ion to enhance the nucleophilicity of the resulting "naked" halide ion. It was reported by Rickborn[5)] that a 1:1 complex of LiBr–HMPA was an efficient catalyst for the rearrangement of epoxides, but the catalytic activity of the complex was quenched by the addition of a second

TABLE 1. EFFECT OF CATALYSTS ON THE YIELD OF **2a**[a)]

Catalyst	Recovery of BCA (%)	Yield of **2a** (%)[b)]
LiCl	43.3	33.0
LiBr	60.0	35.8
TEAB	61.0	28.6
TEA[c)]	79.5	4.9
$ZnCl_2$[d)]	73.3	8.2

a) Reaction temperature is 80 °C and other conditions are the same as those in the case of LiCl, described in Experimental Section. The reactions were carried out in homogeneous system. b) Based on BCA. c) Triethylamine. d) Reaction temperature is 100 °C.

Table 2. Catalysis by lithium salt-cocatalyst for the reaction of the epoxide **1a** with BCA in benzene[a]

Catalyst	Recovery of BCA (%)	Yield of **2a** (%)[b]
LiCl-HMPA	59.2	27.2
LiBr-HMPA	33.5	46.3
LiBr-4HMPA[c]	16.9	48.1
LiI-HMPA	38.3	33.9
LiCl-DMF[d]	87.8	9.9
LiCl-DMA	83.2	10.3
LiCl-NMP[e]	87.0	10.7
LiCl-DMSO[f]	92.4	1.7
LiBr-TMU[g]	95.0	3.3
LiCl-TPPO	66.6	15.9
LiBr-TPPO	31.4	51.0
LiBr-TBPO[h]	63.7	19.9
LiCl-$(EtO)_3PO$[i]	77.3	9.0
LiCl-$(PhO)_3PO$[j]	93.5	2.8
LiBr-12-Crown-4	95.6	4.3
LiBr-15-Crown-5	57.4	16.2
LiBr-18-Crown-6	95.0	0.4
LiBr-Dibenzo-18-crown-6	83.2	5.4

a) Reaction temperature is 90 °C and other conditions are described in Experimental section. The reaction mixtures were not clear solution because of the inadequate solubility of catalysts. b) Based on BCA. c) A mixture of 6 mmol of LiBr and 24 mmol of HMPA was used. d) *N*,*N*-Dimethylformamide. e) *N*-Methyl-2-pyrrolidone. f) Dimethyl sulfoxide. g) Tetramethylurea. h) Tributylphosphine oxide. i) Triethyl phosphate. j) Triphenyl phosphate.

equivalent of HMPA. Although such quenching was not observed in the present reaction, it was found that an equimolar amount of HMPA to lithium salt was sufficient to promote the insertion (Table 2). In DMA the yield of **2a** is not different regardless of the kind of lithium salts, as shown in Table 1, while in benzene the yield of **2a** by LiBr catalyst is higher than by LiCl catalyst. The difference in the catalysis may be ascribed to the difference in the solubility of these catalysts in DMA and benzene; both LiCl and LiBr are soluble in DMA, but LiBr is more soluble in benzene than LiCl.

The effectiveness of other polar aprotic additives, phosphates, phosphine oxides and crown ethers as promoting agents is shown in Table 2. Triphenylphosphine oxide (TPPO) was the best promoting agent except for HMPA. The best yield of **2a** was 57.6% in the reaction using LiBr–TPPO catalyst at 90 °C for 24 h. 15-Crown-5 was the most effective among the crown ethers inspected when used with lithium bromide. The effect of solvents on the yield of the insertion product **2a** is shown in Table 3. The yield of **2a** was lower in toluene at a higher temperature than in benzene at a lower temperature. This may be due to inadequate solubility of lithium bromide–HMPA in toluene. Tetrahydrofuran was effective at a lower temperature.

Table 3. Effect of solvents on the yield of **2a**[a]

Solvent	Recovery of BCA (%)	Yield of **2a** (%)[b]
Toluene[c]	41.6	29.2
Dioxane[d]	57.8	20.5
THF[e]	54.2	28.2

a) Lithium bromide and HMPA were used as a catalyst and a co-catalyst, respectively. The reaction mixture were not clear solutions because of the inadequte solubility of catalysts. b) Based on BCA. c) Reaction temperature is 110 °C. d) Reaction temperature is 90 °C. e) Reaction temperature is 70 °C.

Table 4. The reaction of **1a** with BCA in the presence oe quarternary salts[a]

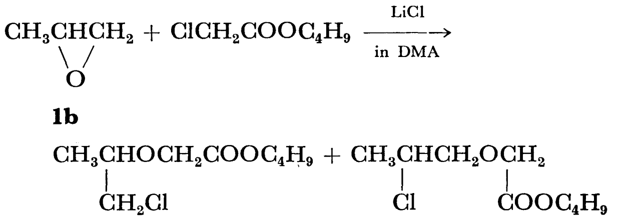
Catalyst	Recovery of BCA (%)	Yield of **2a** (%)[b]
TEAB-HMPA	90.8	6.0
TBAB-HMPA	42.8	30.1
TBAB	51.6	20.7
MTPPI-HMPA	63.1	23.3

a) A mixture of 6 mmol each of quarternary salt and HMPA, 60 mmol each of BCA and **1a** in 20 ml of benzene was stirred at 90 °C for 5 h. The reaction mixtures were clear solutions, except for TEAB-HMPA and MTPPI-HMPA. b) Based on BCA.

Quarternary salts were also effective for the insertion reaction in benzene (Table 4). Tetraethylammonium bromide (TEAB) and methyltriphenylphosphonium iodide (MTPPI) are not sufficiently soluble in benzene to cause reaction, unlike tetrabutylammonium bromide (TBAB). Thus, the former two quarternary salts were not effective in benzene in the absence of HMPA, whereas TBAB alone promoted the insertion in this nonpolar solvent. However, with TBAB the yield of **2a** increased upon addition of HMPA. This result suggests that the nucleophilicity of the halide ion of TBAB was enhanced by the addition of HMPA.

*Reaction of 1,2-Epoxypropane (**1b**) with BCA.* The reaction of the epoxide **1b** with BCA in DMA in the presence of lithium chloride gave a mixture of butyl [1-(chloromethyl)ethoxy]acetate (the normal isomer, **4a**) and butyl (2-chloropropoxy)acetate (the abnormal isomer, **4b**).

These novel compounds, the normal and abnormal isomers, were separated and isolated by GLC using DEGS liquid phase. ^{1}H-NMR spectrum of the isolated **4a** showed a characteristic doublet peak at δ 1.30 due to the methyl proton adjacent to the methine carbon.



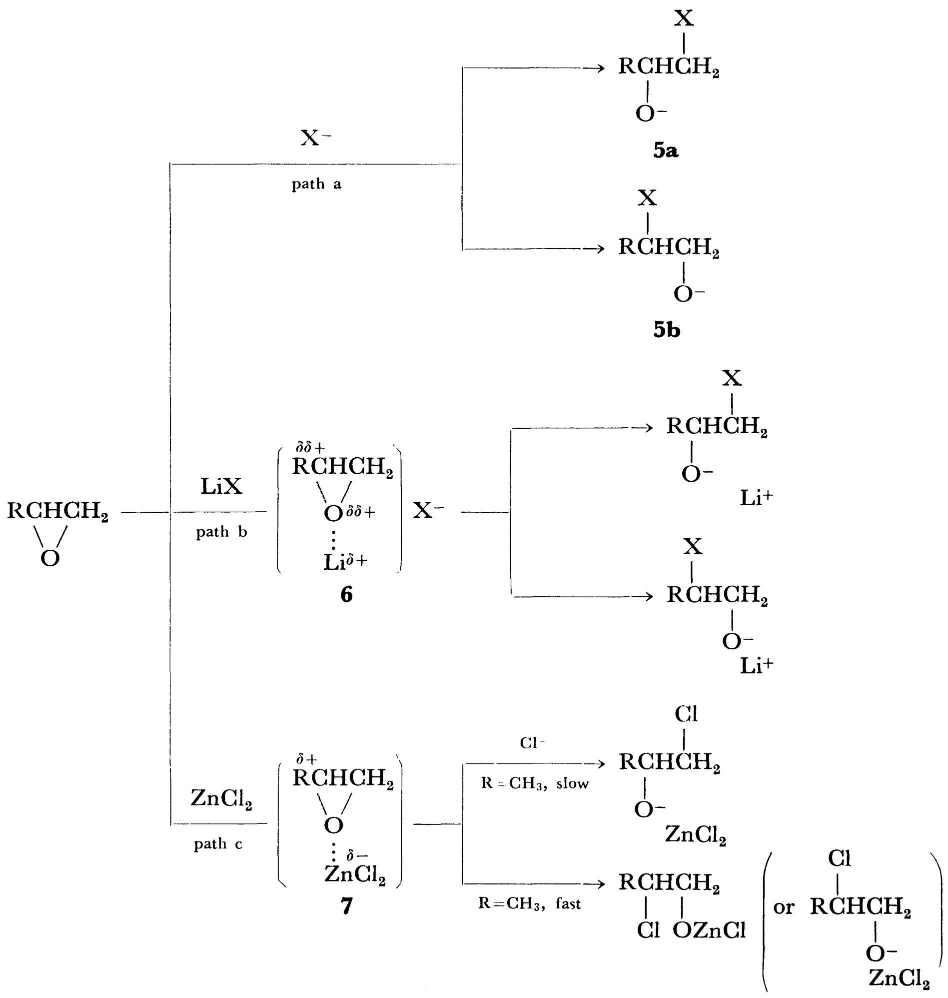
$$\underset{\text{O}}{CH_3CHCH_2} + ClCH_2COOC_4H_9 \xrightarrow[\text{in DMA}]{\text{LiCl}}$$

1b

$$\underset{CH_2Cl}{CH_3CHOCH_2COOC_4H_9} + CH_3\underset{Cl}{CH}CH_2O\underset{COOC_4H_9}{CH_2}$$

4a 41.2%

4b 58.8%



Scheme 1.

^{1}H-NMR spectrum of the isolated **4b** showed a characteristic doublet peak at 1.56 ppm due to the methyl proton adjacent to the methine carbon attached to the chlorine atom. In mass spectra, the normal isomer **4a** gave characteristic fragment peaks at *m/e* 159 and 103 based on the elimination of chloromethyl group and the abnormal isomer **4b** gave characteristic fragment peaks at *m/e* 172 and 71 based on dehydrochlorination. From these results the structures of the normal and abnormal isomers were confirmed.

Isomer Distribution and Probable Mechanism. The reaction of the epoxide **1a** with BCA exclusively gave the normal insertion product **2a**, regardless of the type of catalyst. However, the reaction of the epoxide **1b** with BCA gave the mixture of the isomeric products, **4a** and **4b**. The present reaction may proceed by the following mechanism, as shown in Scheme 1.

The exclusive formation of the normal isomer in the reaction of the epoxide **1a** may be explained by the inductive (electron-withdrawing) and large steric effects of chloromethyl group. The stability of a transition state such as **6** or **7** is disturbed by the electron-withdrawing power of chloromethyl group.

TABLE 5. ISOMER DISTRIBUTION OF THE REACTION PRODUCT OF BCA WITH THE EPOXIDE **1b**[a)]

Catalyst	Isomer distribution		Yield of **4a**+**4b**(%)[b)]
	4a(%)	**4b**(%)	
$ZnCl_2$	20.0	80.0	34.5
LiCl	41.2	58.8	31.5
LiCl+TEAB[c)]	44.8	55.2	44.2
TEAC[d)]	58.5	41.5	—
TEAB	60.0	40.0	21.0

a) A mixture of 0.5 mmol of catalyst, 5 mmol each of BCA and DMA, and 20 mmol of **1b** was stirred at 100 °C for 5 h. The reactions were carried out in homogeneous system. b) Based on BCA. c) A mixture of 0.5 mmol each of lithium chloride and tetraethylammonium bromide was used. d) Tetraethylammonium chloride.

On the other hand, the formation of the normal and abnormal isomers in the reaction of the epoxide **1b** can be attributable to the inductive (electron-donating) and steric effects of methyl group. The isomer distribution of the products from the reaction of the epoxide **1b** with BCA was dependent on the type of the catalyst. The results are summarized in Table 5. Use of tetraethylammonium salts resulted in a little preferential formation of the normal isomer. In this case, the nucleophilic attack by halide ion may an important role in the ring opening of epoxide. The isomer distribution may be ascribed to the steric effect of methyl group which is smaller than that of chloromethyl group (path a). Use of lithium halide led to a little preferential formation of the abnormal isomer. Lithium ion, solvated by (or complexed with) DMA, HMPA, or TPPO, would coordinate to the oxygen of the epoxide ring and polarize the C–O bond of the epoxide, thus facilitating the ring opening by nucleophilic attack by halide ion. The isomer distribution may be attributable to the inductive and steric effects of methyl group of the epoxide **1b** (path b). Zinc chloride highly preferentially gave the abnormal isomer. In this case, the chloride ion seems to be less nucleophilic, which is in accord with the fact that the reaction of **1a** is very slow as shown in Table 1. Zinc chloride would coordinate stronger to the oxygen of the epoxide ring. Predominant formation of **4b** can be explained by the attack (intramolecular or not) of the chloride ion on the highly polarized transition state like **7** or the secondary carbonium ion which is preferentially formed by the inductive effect of the methyl group (path c).

Experimental

^{1}H-NMR and ^{13}C-NMR spectra were recorded with JEOL JNM-MH-100 and JNM-FT-100 Spectrometers in carbon tetrachloride and deuterochloroform solution, respectively. Mass spectra were determined with a JEOL JMS-07 Spectrometer at an ionizing voltage of 30 eV.

*Reaction of 1-Chloro-2,3-epoxypropane (**1a**) with Butyl Chloroacetate (BCA) in* N,N-*Dimethylacetamide (DMA).* LiCl 0.13 g (3 mmol) was dried under vacuum prior to use and was dissolved in 5.2 g (60 mmol) of DMA. Then, 9.0 g (60 mmol) of BCA and 5.5 g (60 mmol) of **1a** were added to the solution and the mixture was stirred at 100 °C for 5 h. The resulting reaction mixture was extracted (Et_2O–H_2O), and the ethereal extract was washed with H_2O and dried with $MgSO_4$. 2.5 g of BCA was recovered by distillation and 5.5 g (37.5% based on BCA) of crude butyl 2-chloro-1-(chloromethyl)ethoxy acetate (**2a**, 95% purity by GLC) was obtaned. The product purified further by distillation had the following properties: Bp 108—109 °C/2 mmHg (1 mmHg=133.322 Pa). ^{13}C-NMR (excluding COO) δ 13.68 (Off-resonance decoupling; q, CH_3), 19.14 (t, $\underline{C}H_2CH_3$), 30.65 (t, $\underline{C}H_2C_2H_5$), 43.37 (t, $Cl\underline{C}H_2$), 65.00 (t, $COO\underline{C}H_2$), 68.02 (t, $O\underline{C}H_2COO$), 79.58 (d, $\underline{C}HO$). ^{1}H-NMR δ 0.98 (3H, t, J=7.5 Hz, CH_3), 1.30—1.70 (4H, m, CH_2), 3.70—3.72 (5H, m, $ClCH_2CHCH_2Cl$), 4.16 (2H, t, J=7.5 Hz, $COOCH_2$), 4.26 (2H, s, OCH_2COO). Found: C, 44.26; H, 6.37; Cl, 29.1%.[6] Calcd for $C_9H_{16}O_3Cl_2$: C, 44.46; H, 6.64; Cl, 29.16%.

*Reaction of **1a** with BCA in Benzene and Other Nonpolar Solvents.* A mixture of 6 mmol of lithium salt, dried prior to use, and co-catalyst (1.0 g in the case of crown ethers), and 60 mmol of BCA and **1a** in 20 ml of a solvent was stirred at 70—110 °C for 5 h. The yield of **2a** and the recovery of BCA, as shown in Tables 2 and 3, were determined by GLC.[7]

*Reaction of 1,2-Epoxypropane (**1b**) with BCA.* A mixture of 3.15 g (15 mmol) of tetraethylammonium bromide (TEAB), 13.1 g (150 mmol) of DMA, 22.6 g (150 mmol) of BCA and 17.4 g (300 mmol) of **1b** was heated in a glass autoclave at 100 °C for 5 h. The reaction product was isolated by the same procedure as in the case of **2a** and 4.5 g (14.4%) of the pure product was obtaned. Bp 65—66 °C/20 mmHg. Found: C, 51.53; H, 8.39; Cl, 17.1%; Mol. weight, 213.3.[8] Calcd for $C_9H_{17}O_3Cl$: C, 51.80; H, 8.21; Cl, 16.99%; Mol. weight, 208.5. This product contained the normal cleavage product **4a** and the abnormal cleavage product **4b**. Each isomer was isolated by GLC using DEGS 20%, 3 m column. **4a**: ^{1}H-NMR δ 0.93 (3H, t, J=6.5 Hz, terminal CH_3), 1.30 (3H, d, J=6.0 Hz, CH_3C–O–), 1.43—1.47 (4H, m, CH_2), 3.35—3.84 (3H, m, $ClCH_2$-CHO), 4.07—4.20 (4H, m, CH_2OCOCH_2O). **4b**: 0.98 (3H, t, J=6.5 Hz, terminal CH_3), 1.56 (2H, d, J=6.0 Hz, CH_3CCl), 3.57—3.77 (3H, m, OCH_2CHCl), 4.06—4.21 (4H, m, CH_2OCOCH_2O). The reactions using various catalysts were carried out in a 20 ml sealed tube. Product distribution was determined by GLC[9] using standard mixtures, and the overall yield of the insertion products was determined by GLC.[10]

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References

1) I. Ikeda, T. Takeda, and S. Komori, *J. Org. Chem.*, **35**, 2353 (1970).

2) T. Takeda, I. Ikeda, S. Yasuhara, and S. Masuyama, *Nippon Kagaku Kaishi*, **1974**, 1682.

3) T. Takeda and S. Yasuhara, *Nippon Kagaku Kaishi*, **1976**, 1579.

4) L. P. Lindeman and J. Q. Adams, *Anal. Chem.*, **43**, 1245 (1971).

5) B. Rickborn and R. M. Gerkin, *J. Am. Chem. Soc.*, **93**, 1693 (1971).

6) Content of chlorine was determined by a modified semimicro butanol–Na method. W. Kimura, *Kogyo Kagaku Zasshi*, **37**, 1310 (1934).

7) Silicon DC 550 10% on Shimalite, 3 m, 190 °C. By making a calibration curve between the isolated product and the internal standard, the yield based on BCA was determined. (Internal standard; methyl tetradecanoate)

8) Molecular weight was determined by the measurement of the depression of the freezing point of benzene.

9) DEGS 20% on Shimalite, 3 m, 170 °C.

10) Silicon DC 550 10% on Shimalite, 3 m, 170 °C.