報 文

Preparation of 1,3-Dioxolanes from Epoxides and Carbonyl Compounds under Neutral Conditions

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Lithium halides catalyzed the reaction of epoxides with carbonyl compounds in a polar aprotic solvent to give 1,3-dioxolane derivatives. 2,4-Disubstituted-1,3-dioxolanes from unsymmetrically substituted epoxides (1-chloro-2,3-epoxypropane, 1,2-epoxypropane and 1,2-epoxybutane) and benzaldehyde were found to be mixtures of stereoisomers in which 2- and 4-substituents were in the *cis*- and *trans*-conformations. The *cis/trans* ratio of the resulting 1,3-dioxolanes was dependent on the type of catalyst. In the Lewis acid catalyzed reaction, the *cis*-isomer was preferentially formed, conversely the lithium halide catalyst offered the *trans*-isomer preferentially.

1 Introduction

1,3-Dioxolanes are very important compounds in organic synthesis as intermediates^{1),2)} or protecting compounds³⁾ and for preparing easily hydrolyzable surfactants⁴⁾. These compounds are usually prepared by the reaction of diols⁵⁾ or epoxides⁶⁾ with carbonyl compounds using mineral acids, *p*-toluenesulfonic acid, tin tetrachloride and boron trifluoride as catalyst. Recently, we reported that aluminum chloride catalyzed the reaction of epoxides with aldehydes or ketones⁷⁾. From the limitation of the synthetic procedures under acidic conditions, we investigated the synthetic method under neutral conditions.

There is only one paper to our knowledge describing a synthesis of 1,3-dioxolanes in neutral conditions⁸⁾. The method, reported by Nerdel, involves the reaction of ethylene oxide with aldehydes using a quarternary ammonium salt. A high temperature, usually 170~220°C, is required to produce 1,3-dioxolanes and the reaction has not been studied in detail.

In this paper, we report a mild and facile synthetic procedure for preparing 1,3-dioxolanes under neutral conditions by the reaction of epoxides with carbonyl compounds, and the dependence of distribution of the stereoisomers on the type of catalyst.

2 Experimental

Reaction of 1-chloro-2,3-epoxypropane (ECH) with benzaldehyde

To a stirred solution of LiBr (0.6 g, 6 mmol), dried *in vacuo* prior to use, in hexamethylphosphoric triamide (HMPA, 10.7 g, 60 mmol) was added 6.4 g (60 mmol) of benzaldehyde, followed by dropwise addition of 5.6 g (60 mmol) of ECH. After being stirred at 120°C for 7.5 h, 5.6 g (60 mmol) of ECH was added to the mixture and the mixture was heated at 120°C for an additional 7.5 h. The cooled solution was then diluted with brine and extracted with diethyl ether. The organic layer was dried over anhydrous Na₂SO₄ and distilled. Unreacted benzaldehyde (1.5 g, 24%) was recovered, and the product (**1**) (6.2 g, 54%) was obtained. bp 93~94°C/2 mmHg. IR (neat): 1230, 1090, 1070, 970, 760, and 700 cm⁻¹. Anal. Calcd. for C₁₀H₁₁ClO₂: C, 60.46; H, 5.58; Cl, 17.85. Found: C, 60.18; H, 5.82; Cl, 18.0. ¹H NMR (CCl₄, δ) (**1a**): 3.3~3.8 (3 H, m, ClCH₂CH), 4.18 (2 H, d, *J*=4.5 Hz, OCH₂), 5.82 (1 H, s, HC<O), 7.3~7.6 (5 H, m, C₆H₅). (**1b**): 3.4~4.5 (5 H, m, ClCH₂CHCH₂O), 6.02 (1 H, s, HC<O), 7.1~7.6 (5 H, m, C₆H₅). Mass spectrum (30 eV): (**1a**); *m/e* 197 (ra 100), 106

(47), 199 (31), 198 (M^+ , 26), 79 (26), 92 (25), 78 (21), 121 (11), 76 (10), and 200 (9). (**1b**); m/e 197 (ra 100), 106 (43), 79 (32), 199 (33), 198 (M^+ , 28), 78 (23), 121 (17), and 149 (11).

In the other runs of the reactions under various conditions, the recovery of benzaldehyde and the yield of (**1**) were determined by GLC using standard mixtures of benzaldehyde, (**1**), and internal standard (methyl decanoate).

Reaction of ECH with cyclohexanone

To a stirred solution of LiBr (0.6 g, 6 mmol) in HMPA (10.7 g, 60 mmol) was added 5.9 g (60 mmol) of cyclohexanone, followed by dropwise addition of 5.6 g (60 mmol) of ECH. After being stirred at 120°C for 8 h, 5.6 g (60 mmol) of ECH was added to the mixture and the mixture was heated at 120°C for an additional 7 h. The reaction mixture was treated by the method described above, and 3.8 g (64%) of cyclohexanone was recovered. The product (**2**) (1.4 g, 12%) was obtained. bp 89~91°C/4 mmHg.

IR (neat): 1285, 1165, 1100, 1050, 930, 850, and 760 cm^{-1} . Anal. Calcd. for $\text{C}_9\text{H}_{15}\text{ClO}_2$: C, 56.69; H, 7.93; Cl, 18.59. Found: C, 56.26; H, 7.74; Cl, 18.8. ^1H NMR(CCl_4 , δ): 1.2~1.7 (10 H, m, CH_2), 3.1~4.3 (5 H, m, $\text{ClCH}_2\text{CHCH}_2$). Mass spectrum (30 eV): m/e 148 (ra 100), 150 (33), 56 (23), 162 (11), 134 (10), 76 (9), and 190 (M^+ , 8).

In the other runs of the reactions, the recovery of cyclohexanone and the yield of (**2**) were determined by GLC using standard mixtures of cyclohexanone, (**2**) and internal standard (methyl decanoate).

Reaction of 1,2-epoxypropane (PO) and 1,2-epoxybutane (BO) with benzaldehyde

To a solution of LiBr (0.5 g, 5 mmol) in HMPA (9.0 g, 50 mmol) were added 5.3 g (50 mmol) of benzaldehyde and 3.5 g (60 mmol) of PO. The mixture was heated in a sealed tube at 120°C for 8 h and treated according to the procedure described above. After removal of ethyl ether, the residue was distilled at reduced pressure and 1.1 g (21%) of benzaldehyde was recovered. The product (**3**) (4.3 g, 53%) was obtained. bp 87~88.5°C/4 mmHg.

IR (neat): 1220, 1090, 1065, 1030, 980, 760, and 700 cm^{-1} . Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{O}_2$: C, 73.15; H, 7.37. Found: C, 72.99; H, 7.57. ^1H NMR(CCl_4 , δ): 1.26 (3 H, d, $J=6.0$ Hz,

CH_3), 3.2~4.3 (3 H, m, $\text{MeCH}(\text{O})\text{CH}_2\text{O}$), 5.61 (s, $\text{HC}=\text{O}$ *cis*), 5.77 (s, $\text{HC}=\text{O}$ *trans*), 7.1~7.4 (5 H, m, C_6H_5). Mass spectrum (20 eV): m/e 163 (ra 100), 106 (93), 164 (M^+ , 83), 79 (52), 88 (40), 92 (34), 60 (28), and 91 (25).

To a stirred solution of LiBr (1.6 g, 15 mmol) in HMPA (26.9 g, 150 mmol) was added 15.9 g (150 mmol) of benzaldehyde, followed by dropwise addition of 10.8 g (150 mmol) of BO. After being stirred at reflux (95~117°C) for 7 h, 10.8 g (150 mmol) of BO was added to the mixture. The mixture was heated at reflux for an additional 8 h. The resulting solution was treated by the procedure described above and 3.2 g (20%) of benzaldehyde was recovered. The product (**4**) was obtained by distillation (17.3 g, 65%). bp 143~145°C/3 mmHg. IR (neat): 1230, 1115, 1090, 1070, 1030, 980, 960, 920, 760, and 700 cm^{-1} . Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_2$: C, 74.13; H, 7.92. Found: C, 73.97; H, 8.07. ^1H NMR(CCl_4 , δ): 0.93 (3 H, t, $J=6.0$ Hz, CH_3), 1.3~1.8 (2 H, m, CH_2), 3.2~4.1 (3 H, m, $\text{EtCH}(\text{O})\text{CH}_2\text{O}$), 5.60 (s, $\text{HC}=\text{O}$ *cis*), 5.76 (s, $\text{HC}=\text{O}$ *trans*), 7.0~7.4 (5 H, m, C_6H_5). Mass spectrum (30 eV): 177 (ra 100), 106 (45), 56 (45), 178 (M^+ , 43), 92 (41), 79 (26), 123 (19), and 78 (19).

3 Results and Discussion

Reaction of 1-chloro-2,3-epoxypropane (ECH) with benzaldehyde

The reaction of ECH with benzaldehyde at 120°C in the presence of LiBr in HMPA gave 4-(chloromethyl)-2-phenyl-1,3-dioxolane (**1**). The product was a mixture of stereoisomers in which the substituent group at 2-C and 4-C were in *cis* (**1a**)- and *trans* (**1b**)- configuration. The structures of *cis*- and *trans*-isomers were estimated on the basis of chemical shifts of the H-2 protons in NMR spectra. The closer proximity of the 4-(chloromethyl) group and H-2 proton in the *trans*-2,4-disubstituted dioxolane should lead to mutual deshielding and therefore, to a shift of the H-2 signal to lower field than for the *cis*-isomer, similar to that reported for the diastereoisomeric 4-(acetoxymethyl)-2-pentadecyl dioxolanes^{9,10} and 4-

(halomethyl)-2-methyl dioxolanes¹¹⁾. Actually, the chemical shift for H-2 in (1a) was found to be 5.82 ppm and the corresponding signal of (1b) was shifted to lower field (6.02 ppm).

In order to optimize the synthetic conditions and to get information regarding the reaction mechanism, we examined the effect of solvent and catalyst on the yield of 1,3-dioxolane. In the reaction in nonpolar solvent, such as benzene and carbon tetrachloride, whole amount of benzaldehyde was recovered. However, the addition of a small amount of HMPA to benzene resulted in the formation of (1), as shown in Table-1. In the reaction in *N,N*-dimethyl-

Table-1 Reactions of ECH with benzaldehyde in various solvents in the presence of LiBr.

Solvent	Reaction conditions		Recovery of benzaldehyde (%)	Yield of (1) (%)
	Temp. (°C)	Time (h)		
HMPA	120	5	27	52
DMF	120	5	69	17
DMA	120	5	55	27
NMP	120	5	50	24
Benzene*	85	5	65	13
THF*	85	5	67	14

* A combination of LiBr/HMPA (1 : 1) was used as a catalyst.

formamide (DMF), *N,N*-dimethylacetamide (DMA) and *N*-methylpyrrolidone (NMP), dioxolane (1) was obtained in a lower yield (Table-1). HMPA was the most suitable solvent and may act not only as a solvent but also specifically solvate the lithium ion to enhance the nucleophilicity of the resulting "naked" halide ion¹²⁾. Among lithium halides, LiCl and LiBr were suitable catalysts. The yield of dioxolane, however, was low when lithium iodide was employed as a catalyst, which may be due to its low solubility. The situation was the same for tetraethylammonium bromide (TEAB) and the yield was low due to its low solubility

(Table-2). The yield of (1) increased with increasing temperature up to 120°C. Above 140°C, however, the reaction led to the formation of dark resinous matter.

Table-2 Reactions of ECH with benzaldehyde in HMPA in the presence of various salts.

Catalyst	Reaction temp. (°C)	Recovery of benzaldehyde (%)	Yield of (1) (%)
LiCl	120	39	53
LiBr	120	27	52
LiBr	90	50	33
LiI	120	74	9
TEAB	120	72	16

Reaction time: 5 h.

Reaction of ECH with cyclohexanone

The reaction of ECH with cyclohexanone in HMPA in the presence of LiBr at 140°C gave 1,4-dioxo-2-(chloromethyl)spiro[4,5]decane (2) in the yield of 17%. In the presence of LiCl and TEAB, the yield of (2) was 12% and 3%, respectively.

Reaction of 1,2-epoxypropane (PO) and 1,2-epoxybutane (BO) with benzaldehyde

The reaction of PO and BO with benzaldehyde in HMPA in the presence of LiBr gave 53% yield of 4-methyl-2-phenyl-1,3-dioxolane (3) and 65% yield of 4-ethyl-2-phenyl-1,3-dioxolane (4), respectively. Dioxolanes (3) and (4) were obtained as mixtures of stereoisomers in which 2-phenyl and 4-alkyl groups were in the *cis*- and *trans*-configuration. None of the stereoisomers was isolated, but the presence of the *cis*- and *trans*-isomers was confirmed by occurrence of two kinds of H-2 signals in ¹H NMR spectrum. [5.61 and 5.77 ppm in (3), and 5.60 and 5.76 ppm in (4).]

Effect of catalyst on the isomer ratio of 2,4-disubstituted 1,3-dioxolanes

The reaction of unsymmetrically substituted epoxides with benzaldehyde gave the mixtures of isomeric 1,3-dioxolanes in which the configuration of 2- and 4-substituents was *cis* and *trans*. The *cis/trans* ratio determined by the measurement of signal areas of H-2 in ^1H NMR spectra was dependent on the type of catalyst. The result is summarized in **Table-3**. In the Lewis acid catalyzed reactions, the *cis*-isomer was preferentially formed, conversely the lithium halide catalyst offered the *trans*-isomer preferentially.

Table-3 Effect of catalyst on the *cis/trans* ratio of 1,3-dioxolanes from epoxide and benzaldehyde.

Epoxide	Catalyst	Reaction temp. (°C)	Reaction time (h)	<i>cis</i> (%)	<i>trans</i> (%)
ECH	LiBr	120	15	26	74
ECH	LiCl	120	5	30	70
ECH	$\text{AlCl}_3^{\text{a)}$	66	5	67	33
PO	$\text{LiBr}^{\text{b)}$	120	8	23	77
BO	LiBr	Reflux	15	25	75
BO	$\text{AlCl}_3^{\text{a)}$	75	4	63	37
ECH	$\text{BF}_3\text{OEt}_2^{\text{c)}$	40	5	58	42

a) The AlCl_3 catalyzed reactions were carried out in the absence of solvent.

b) The reaction of PO was carried out in a sealed tube.

c) The BF_3 catalyzed reaction was carried out in CCl_4 .

The difference in the isomer ratio between Lewis acid and lithium halide catalysts may be explain by the following reaction scheme. In the Lewis acid catalyzed reaction, the initiation of the reaction might be the attack of aldehyde oxygen to the ring carbon of Lewis acid coordinated epoxide (oxonium ion), in a similar manner to that suggested by Blackett^{6g)}. The attack of aldehyde on the unsubstituted carbon of epoxide ring is advantageous owing to steric effect. From the observation of cpk model, the rotations of C-C bond and C-O bond in the shift of transition state (b) to (c) may be restricted to the direction illustrated in **Scheme-1** because of the steric effect of R' , H' and H'' . Thus Lewis acid catalyst offered the *cis*-isomer preferentially.

Conversely, the lithium halide catalyzed reac-

Scheme-1

tion may proceed by the attack of halohydrin alkoxide ion, which is formed by the nucleophilic attack of halide ion on the ring carbon of epoxide, on the aldehyde carbon and lead to the preferential formation of the *trans* isomer because of steric effect. (**Scheme-2**)

Scheme-2

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エポキシドとカルボニル化合物からの中性条件下での 1,3-ジオキソランの合成

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エポキシドとカルボニル化合物を極性非プロトン溶媒中、ハロゲン化リチウム触媒で反応させることにより 1,3-ジオキソラン誘導体が得られた。非対称エポキシド（1-クロロ-2,3-エポキシプロパン, 1,2-エポキシプロパン及び 1,2-エポキシブタン）とベンズアルデヒドから得られた 2,4-ジ置換-1,3-ジオキソランは、2-と 4-置換基がシスとトランスの配置をした立体異性体の混合物であることがわかった。得られた 1,3-ジオキソランのシス/トランス比は触媒のタイプに依存した。すなわち、ルイス酸接触反応ではシス異性体が優先して生成し、逆にハロゲン化リチウム触媒はトランス異性体を優先して生成した。