SYNTHESIS OF ARYL SUBSTITUTED EPIHALOHYDRIN DERIVATIVES†

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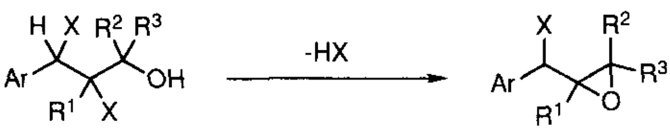
Abstract– Aryl substituted epihalohydrin derivatives were synthesized by the dehydrohalogenation of 2,3-dihalo-3-arylpropanol derivatives in the two phase solvent system of aqueous alkali solution and benzene with a phase transfer reagent such as benzyltrimethylammonium chloride.

Since 2-chloromethyloxirane (epichlorohydrin) possesses three adjacent reactive sites, the oxirane serves as a versatile C3-synthon in syntheses of an array of important molecules.[1,2] We have reported a synthesis of perhydrooxazinone and oxazolidinone derivatives with epichlorohydrin but those yields were not good.[2] If an aryl group attached to the chloromethyl carbon of epichlorohydrin, the chloromethyl group should be activated as a benzyl position, and hence the yields of the oxazinones would be improved and the syntheses of other heterocyclic compounds could be expected.

Aryl substituted epihalohydrins have only been reported on the synthesis of 2-halomethyl-3-phenyloxiranes from cinnamyl halides with peracid[3] and 2-chloromethyl-2-aryloxiranes from 1,3-dichloro-2-propanone[4] or 2,3-dichloropropanal[5] with Grignard reagents. Those aryl substituted epihalohydrins were not activated the halomethyl group. In this report, we wish to communicate a synthesis of 2-arylhalomethyloxiranes (**1**) of which the aryl group is attached to the halomethyl group.



2 **1**

Table 1. The Yield of 2-Arylhalomethyloxiranes (**1**)

	Ar	R^1	R^2	R^3	X	Yield (%)[a]	bp (mp) (°C / Torr)
1a	Ph	H	H	H	Br	71	120-121 / 2
1b	Ph	H	H	H	Br	33[b]	(34-36)
1c	Ph	H	H	H	Cl	24	90-93 / 1
1d	*p*-ClC_6H_4	H	H	H	Br	61	109-112 / 4
1e	Ph	Me	H	H	Br	86	110-113 / 2.5
1f	Ph	H	Me	H	Br	82[c]	112-114 / 1.5
1g	Ph	H	Me	Me	Br	85	(105-106)

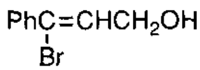
a) (*R**, *R**)-diastereomer b) (*R**, *S**)-diastereomer c) a mixture of diastereomers

A general procedure for the preparation of **1** is as follows: a mixture of 29% NaOH aqueous solution (17 ml, 123 mmol), benzyltrimethylammonium chloride (3.3 g, 18 mmol),[6] and 2,3-dibromo-3-arylpropanol (**2**, 50 mmol) in benzene (330 ml) was refluxed vigorously for 0.5 to 1 h. The organic phase was washed with water, dried with anhydrous sodium sulfate, and chromatographed on a silica gel column with benzene to give **1** as summarized in Table 1.

Those oxiranes were obtained diastereoselectively[7] except for **1f** due to using a diastereo mixture of the starting material. The *threo* (or *R**, *R**) type oxirane (**1a**) was prepared from *erythro*-2,3-dibromo-3-phenylpropanol (**2a**)[8] which was readily derived from *E*-cinnamyl alcohol with bromine. The *erythro* (or *R**, *S**) type one (**1b**) was also prepared from *Z*-cinnamyl alcohol but the yield was relatively low.

E-form

1a
(*R**, *R**)-form



3

$PhCH{=}CHBr$
4

$PhC{\equiv}CCH_2OH$
5

Table 2. Dehydrobrominations of 2,3-Dibromo-3-phenylpropanol (**2a**)

Base	Solvent	Temp.	Time (h)	Yield (%)			
				1a	**3**	**4**	**5**
aq. 29% NaOH[a)]	benzene	reflux	1	72	12		4
aq. 15% NaOH	benzene	reflux	5	22	20	13	
aq. 29% NaOH[b)]	benzene	reflux	2	2	63		
DBU	THF	room temperature	18		73		
KOBu-*t*	DMF	room temperature	2				98

a) Benzyltrimethylammonium chloride was used as a phase transfer reagent.

b) 18-Crown-6 was used as a phase transfer reagent.

In the dehydrobromination of **2a**, without any phase transfer reagents and/or dilution of the alkali solution caused a complicated reaction to give 3-bromo-3-phenyl-2-propenol (**3**)[9] and β-bromostylene (**4**) in poor yields, and hence the oxirane (**1a**) was obtained also in low yield as shown in Table 2. When 18-crown-6 was used as a phase transfer reagent in the reaction of **2a**, **3** was mainly obtained accompanied with **1a**. At the monophase reaction using miscible solvents such as THF and DMF with a strong base,[10] **3** and 3-phenyl-2-propynol (**5**)[9] were given selectively according to the polarity of the solvents and basicity of the used base.

Those observations indicate that the first attack with the base to **2** occurs at the hydroxy proton in the aqueous phase or on the interface between aqueous and organic phase. In the mono phase of an organic solvent, C-3 proton of **2** is first attacked to proceed the dehydrobromination to afford **3** and **5**. Because 18-crown-6 is more effective sodium cation transfer reagent than benzyltrimethylammonium hydroxide, the reaction may be conducted in the organic phase.

The presented 2-arylhalomethyloxirane synthesis could be recommended for mass production because those are readily available starting materials with simple operation.

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†Dedicated to Dr. M. Hamana on the occasion of his 75th birthday.

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6. The salt acts as benzyltrimethylammonium hydroxide.
7. Spectral data of the typical oxiranes were as follows; **1a**: Ir (neat) 1248 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ 2.75 (1H, dd, J = 4.5, 2.4 Hz), 2.69 (1H,dd, J = 4.5, 3.9 Hz), 3.57 (1H, ddd, J = 7.5, 3.9, 2.4 Hz), 4.62 (1H, d, J = 7.5 Hz), 7.30-7.48 (5H, m, ArH); ^{13}C nmr (75 MHz, $CDCl_3$) δ 49.1 (CH_2), 55.0 (CHBr), 55.7 (CH), 127.7 (*o*), 128.7 (*m*), 128.8 (*p*), 137.7 (C-1); ms (70 eV, rel. intensity) *m/z* 214 (M^+, 4), 212 (M^+, 4), 171 (12), 169 (12), 105 (100). **1b**: Ir (neat) 1254 cm^{-1}; ^{1}H nmr (300 MHz, $CDCl_3$) δ 2.73 (1H, dd, J = 4.8, 2.7 Hz), 3.00 (1H, dd, J = 4.8, 3.9 Hz), 3.58 (1H, ddd, J = 7.5, 3.9, 2.7 Hz), 4.65 (1H, d, J = 7.5 Hz), 7.29-7.46 (5H, m, ArH); ^{13}C nmr (75 MHz, $CDCl_3$) δ 48.4 (CH_2), 52.9 (CHBr), 54.9 (CH), 127.9 (*o*), 128.7 (*m*), 128.8 (*p*), 138.0 (C-1); ms (15 eV, rel. intensity) *m/z* 214 (M^+, 4), 212 (M^+, 4), 133 (M-Br,100).
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