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Cleavage of epoxides into halohydrins with elemental iodine and bromine in the presence of 2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene (BABMB) as catalyst

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Abstract—The ring opening of epoxides with elemental iodine and bromine in the presence of 2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene as a new catalyst affords vicinal iodo alcohols and bromo alcohols in high yields. This new procedure occurs regioselectively under neutral and mild conditions in various aprotic solvents even when sensitive functional groups are present. © 2002 Elsevier Science Ltd. All rights reserved.

There is a continued interest in the regioselective ring opening of oxiranes to the corresponding vicinal halohydrins. Although a variety of new and mild procedures to effect this transformation have been reported, most of them have some limitations.[1] The reaction is typically performed with hydrogen halides, but the harsh reaction conditions and the low observed regioselectivity in the opening of unsymmetrical epoxides have prompted a search for more selective and milder procedures.[1b] Recently, it has been found that epoxides can be converted into halohydrins by means of elemental halogen,[2] but this method has limitations such as low yield, long reaction times, low regioselectivity and formation of acetonide byproducts in addition to the expected iodoadduct. Furthermore, iodination does not occur in aprotic solvents other than acetone.

In conjunction with ongoing work in our laboratory on the synthesis and formation of complex heterocyclic compounds containing donor nitrogen atoms, with neutral molecules such as iodine and bromine,[3] we found out that 2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene (BABMB) efficiently catalyzed the addition of elemental iodine and bromine to epoxides under mild reaction conditions with high regioselectivity. Recently, we prepared[4] BABMB and used it as a starting diamine material for the preparation of corresponding macracyclic diamides. In this study, we wish to report the results of the reactions of some epoxides with elemental iodine and bromine in the presence of a sub-stoichiometric amount of BABMB (Scheme 1, Table 1).

As shown in Table 1, in each case, cleavage of the epoxide ring occurs and upon thiosulfate workup, the corresponding iodohydrins and bromohydrins are obtained. The yields obtained with this methodology are good to excellent and the reaction times are very short. The optimum amount of catalyst was found to be 0.1 mol for 1 mol of epoxide and halogen. As indicated in entries 9 and 10 in which only the *anti*-isomer is obtained, the reactions are completely *anti*-stereoselective. As for the regioselectivity, an attack of the nucleophile preferentially occurs at the less-substituted oxirane carbon. An anti-Markovnikov-type[5,6] regioselectivity is generally observed in these reactions. In many cases, this type of regioselectivity appears to be the opposite of that observed in ring opening of the same epoxides with aqueous hydrogen halides under classic acidic conditions.[7]

On the basis of our study on the complexation of BABMB and other work reported on different ligands[8–14] with elemental halogen, it seems that in these reactions trihalide ion, X_3^-, is formed and used as the nucleophile. The electronic absorption spectra of the related addition of BABMB to iodine shows a strong band at 364 nm and a strong band at 272 nm in addition of BABMB to bromine, presumably due to the complex formation of this ligand with I_2 and Br_2. In contrast, none of the initial reactants show any measurable absorption in these regions. It should be noted that the bands of 364 and 272 nm are characteristic for the formation of I_3^- and Br_3^- ions, respectively, in the process of complex formation of different electron pair donor ligands with iodine[10–12] and bromine.[13,14] In order to ascertain the effect of the nature of solvent, the reactions with styrene oxide in various aprotic solvents were carried out. The

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Keywords: epoxide; halohydrin; catalyst.

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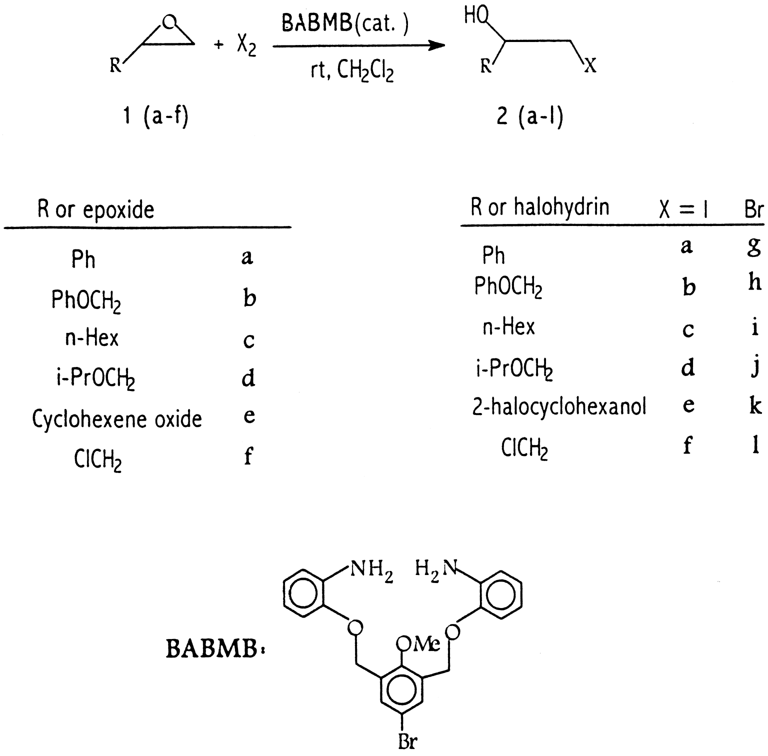
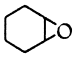
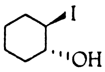
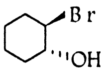


R or epoxide	
Ph	a
$PhOCH_2$	b
n-Hex	c
i-$PrOCH_2$	d
Cyclohexene oxide	e
$ClCH_2$	f

R or halohydrin	X = I	Br
Ph	a	g
$PhOCH_2$	b	h
n-Hex	c	i
i-$PrOCH_2$	d	j
2-halocyclohexanol	e	k
$ClCH_2$	f	l

Scheme 1.

Table 1. Reaction of various epoxides with iodine and bromine in the presence of BABMB catalyst in CH_2Cl_2 at room temperature

Entry	Substrate	Halogenation (X_2)	Product	Reaction time (h)	Yield[a] (%)
1	**1a**	I_2	**2a**	0.17	97
2	**1a**	Br_2	**2g**	0.25	95
3	**1b**	I_2	**2b**	6.5	94
4	**1b**	Br_2	**2h**	5.5	95
5	**1c**	I_2	**2c**	6.0	93
6	**1c**	Br_2	**2i**	0.67	87
7	**1d**	I_2	**2d**	5.75	80
8	**1d**	Br_2	**2j**	1.5	85
9		I_2		2.5	90
10	**1e**	Br_2		0.67	91
11	**1f**	I_2	**2f**	10.0	82
12	**1f**	Br_2	**2l**	3.75	80

[a] Yield of isolated product.

Table 2. Halogenation reaction of styrene oxide in the presence of 0.1 mol of BABMB in various solvents

Entry	Solvent	Time (h)		Yield[a] (%)	
		Bromination	Iodination	Bromination	Iodination
1	CH_2Cl_2	0.33	0.75	>95	>95
2	$CHCl_3$	0.5	1.5	>95	91
3	C_6H_6	1	2	86	90
4	CH_3CN	1	2	87	85
5	CH_3COCH_3	1.5	3	77	62
6	THF	1.5	3	63	51

[a] GC yield.

results are shown in Table 2. The reactions were largely dependent on the nature of solvent.

In conclusion, this new method appears to be highly competitive with the other methods reported in the literature. The reaction occurs in neutral and mild conditions on the acid-sensitive substrates and vicinal halohydrins were obtained in high yields and regioselectivity. In addition, in comparison with our previous methods,[3] BABMB is cheaper, less step need for preparation, and overall yield is higher.

1. General procedure for cleavage of epoxides with elemental halogens

Epoxide (1 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of BABMB catalyst (0.1 mmol) in CH_2Cl_2 (5 mL) at room temperature. Next, a solution of elemental halogen (1 mmol) in CH_2Cl_2 (5 mL) was added portion-wise (15 min) to the above mixture. The progress of the reaction was monitored by GLC and TLC. After complete disappearance of the starting material, the reaction mixture was washed with 10% aqueous $Na_2S_2O_3$ (2×10 mL) and water (2×10 mL). The aqueous layer was extracted with CH_2Cl_2 (2×10 mL).The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to give crude alcohol–catalyst. The crude products were purified on a column of silica gel. The solvent was evaporated and pure halohydrin was obtained. The halohydrins obtained throughout this procedure were identified by comparison, where possible, with authentic samples prepared in accordance with literature procedures.[2,3,15–18]

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