

Halogenated Cleavage of Epoxides into Halohydrins in the Presence of a Series of Diamine Podands as Catalyst with Elemental Iodine and Bromine

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The ring opening of epoxides with elemental iodine and bromine in the presence of three diamine podands 7-9 as new catalysts 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 presented.

Key Words : Diamine, Epoxide, Halohydrin, Catalyst

Introduction

Epoxides are one of the most versatile intermediates in organic synthesis, and a large variety of reagents are known for the ring opening of these compounds.^{1,3} Among the numerous transformations already reported,⁴ opening of the epoxide ring to the corresponding vicinal halohydrins was typically performed with hydrogen halides, but the harsh reaction conditions and the low observed regioselectivity in the opening of asymmetrical epoxides have prompted a search for more selective and milder procedures.¹ A great effort has been made in the last few years to find new mild procedures for converting epoxides into halohydrins. For example, silyl halides can be added to epoxides to give halohydrins.⁵ In these cases, however, the primary reaction products are the O-silyl protected derivatives.⁵ Other methods require the use of a halogen and triphenyl phosphine,⁶ or disubstituted borane halogenides,⁷ β -bromo bis-(dimethyl-amino) borane,⁸ monochloro borane-dimethyl sulfide,⁹ $\text{Li}_n\text{M}_n\text{X}_n$ ($\text{M} = \text{Ni}, \text{Cu}, \text{Ti}$)^{2,10} and MBr_n .^{11,12} Recently, it has been found that epoxides can be converted into halohydrin by means of elemental halogen,^{13a} but this method has some limitations such as low yield, long reaction times, low regioselectivity and formation of acetone by-product in addition to the expected iodo-adduct in acetone solution. Furthermore, iodination does not occur in CH_2Cl_2 , CHCl_3 , C_6H_6 , CH_3CN , and THF solvents.

The properties of cyclic crown ethers are approximated by acyclic neutral ligands (podands). Variations of the endo-polarophilicity/exo-lipophilicity balance, complex stability, ion selectivity can often be accomplished more easily, with greater versatility, and at less expense with acyclic polyether than with their cyclic counterparts; complexation and de-complexation are generally faster in acyclic systems; and the pseudocavity usually has greater conformational flexibility.^{13b} In conjunction with on-going 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,¹⁴ we found out that diamine podands 7-9 efficiently catalyzed the addition of elemental iodine and bromine to epoxides under mild reaction conditions with high regioselectivity. In this study, we wish to report the results of the reactions of some epoxides with elemental iodine and bromine in the presence of catalytic amount of diamine podands 7-9.

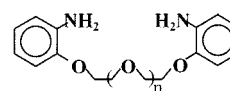
Results and Discussion

Aromatic amines are widely used as intermediates for dyes, photographic materials, pharmaceutical and agricultural chemicals and as antioxidants. Also, diamines are used as starting materials for the synthesis of polymers, azacrowns, and macrocyclic diamides.

The diamino podands 7-9 (Scheme 1) were obtained according to the literature.¹⁴

Epoxides of convenient volatility to allow GC analysis were chosen for study. The results of the reactions of styrene oxide with elemental iodine and bromine in the presence of the diamine 7-9 are summarized in Table 1. In each case, cleavage of epoxide ring occurs and upon thiosulfate workup, the corresponding iodohydrin and bromohydrin were obtained. In comparison, the cleavage behaviour of styrene oxide with elemental iodine and bromine in the absence of catalyst is given in entries 1, 2 and 7.

As shown in Table 1, yields for both iodination and bromination with this methodology are quite good and catalyst 8 is the most effective one (Table 1, entries 5, 9). However, iodination of styrene oxide with an excess of elemental iodine in the absence of catalyst did not occur


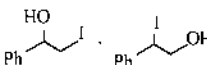



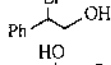



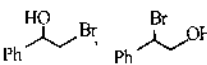
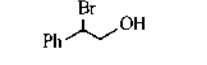




n = 0	7
n = 1	8
n = 2	9

Scheme 1

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Table 1. Reaction of styrene oxide with elemental iodine and bromine in the presence of representative catalysts

Entry	Catalyst	Conditions	Time (h)	Yield (%) ^a	Products	Ref.
1	–	I ₂ , rt	2	83		13a
2	–	CH ₂ Cl ₂ /I ₂ (excess)	–	–	No R.	13a
3	–	LiI, AcOH, THF, rt	1.3	87(1:2)		11
4	7	I ₂ , rt/CH ₂ Cl ₂	1	80		
5	8	I ₂ , rt/CH ₂ Cl ₂	0.75	>95		
6	9	I ₂ , rt/CH ₂ Cl ₂	1.5	>95		
7	–	Br ₂ , rt/CH ₂ Cl ₂	1	31		13a
8	7	Br ₂ , rt/CH ₂ Cl ₂	0.5	91		
9	8	Br ₂ , rt/CH ₂ Cl ₂	0.33	>95		
10	9	Br ₂ , rt/CH ₂ Cl ₂	0.66	89		
11	–	n-Bu ₄ N ⁺ Br ⁻ /Mg(NO ₃) ₂ , CHCl ₃	5	78(5:1)		15
12	–	(Me ₂ N) ₂ 3Br/CH ₂ Cl ₂ , N ₂ atm	12	75(1:4.5)		8
13	–	HBr, CHCl ₃	0.25	>99		16a
14	–	HI, CHCl ₃	0.25	>99		16a

^aGC Yield.

even under reflux and extension of reaction time to several days, and unreacted styrene oxide was completely recovered. In addition, the yield of the bromination reactions is very low in the absence of catalyst.

The results obtained with some representative epoxides in the presence of diamine **8** as catalyst are summarized in Table 2 and are compared with the corresponding results obtained in the reaction of the same epoxides in the absence of catalyst (Table 2, entries 2, 4, 6, and 12). When epoxides were allowed to react in the presence of a catalyst, an increase in the yields and regioselectivities were observed in all of the reactions studied. Generally, the optimum amounts of the catalyst were found to be 0.1 mol for 1 mol of epoxide and halogen.

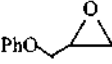
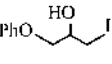
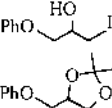
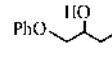
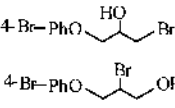
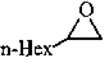
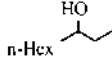
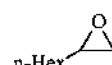
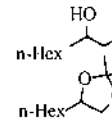
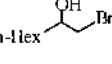
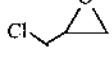
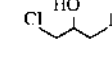
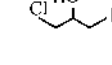

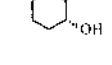
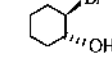
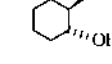
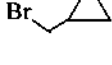
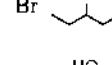
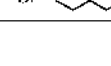
However, the following factors can influence the yield and regioselectivity of the reactions: (1) the steric hindrance of epoxides, (2) the rate of admixing the reagents, (3) the order in which the reagents are combined, and (4) the nature of

solvent. In cases of the rate and order in which the reagents are combined, for example, if bromine before the catalyst is added to epoxide, two isomeric bromo alcohols are produced. However, if the epoxide is added to the catalyst, and then bromine is added dropwise over a period of time, only one isomer is formed. Furthermore, the rapid addition of bromine reduced the regioselectivity.

The results of a halogenative cleavage of styrene oxide with iodine and bromine by catalyst **8** in various aprotic solvents are reported in Table 3. The iodination and bromination reactions proceed most cleanly in CH₂Cl₂, CHCl₃, CH₃CN, and benzene solution, while those done in THF and acetone lead to a lower yield of halohydrins.

As shown in Table 2 (entries 10, 11), in which only the trans isomer is obtained, the reactions are completely stereoselective. As for the regioselectivity, an attack of the nucleophile preferentially occurs at the less-substituted oxirane carbon. An anti-Markovnikov-type¹⁷ regioselectivity is

Table 2. Reaction of epoxides with elemental iodine and bromine in the presence of representative catalyst **8**

Entry	Epoxide	Catalyst	Conditions	Time (h)	Yield ^a (%)	Product (s)	Ref.
1		8	I ₂ , r.t., CH ₂ Cl ₂	10	90		
2	"	—	I ₂ , r.t., acetone	—	94(1:1)		13a
3	"	8	Br ₂ , r.t., CH ₂ Cl ₂	6	90		
4	"	—	Br ₂ , r.t., CH ₂ Cl ₂	—	88(5:1)		13a
5		8	I ₂ , r.t., CH ₂ Cl ₂	1	>95		
6		—	I ₂ , acetone	—	79(1:4)		13a
7	"	8	Br ₂ , r.t., CH ₂ Cl ₂	0.33	>95		
8		8	I ₂ , r.t., CH ₂ Cl ₂	3	75		
9	"	8	Br ₂ , r.t., CH ₂ Cl ₂	2	70		
10		8	I ₂ , r.t., CH ₂ Cl ₂	0.5	90		
11	"	8	Br ₂ , r.t., CH ₂ Cl ₂	0.33	>95		
12	"	—	LiBr, AcOH, THF, r.t.	5	90		11
13		8	I ₂ , r.t., CH ₂ Cl ₂	2.5	75		
14	"	8	Br ₂ , r.t., CH ₂ Cl ₂	2.5	70		

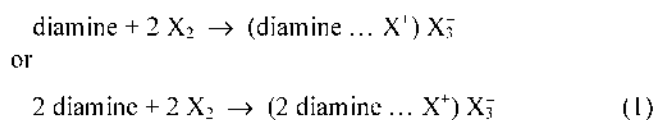
^aGC yield.

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 (entries 14 and 15, Table 1).

Halogenative cleavage of epoxides occurs according to the following four-step mechanism:¹⁴

The first step involves the formation of a 1 : 2 or 1 : 1 molecular complex between diamine and elemental halogen,

in which halogen ion (X₃⁻) exists as a contact ion pair:



In the second step this complex is further decomposed to release X₃⁻ ion into solution as

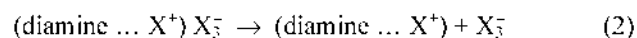
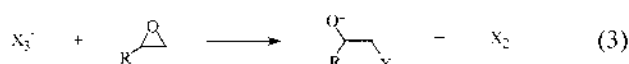


Table 3. Halogenation reaction of styrene oxide in the presence of 0.1 mol of catalyst **8** in various solvents

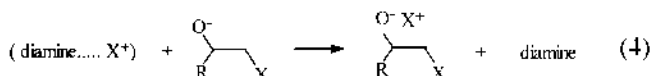
Entry	Solvent	Time (h)		Yield ^a (%)	
		bromination	iodination	bromination	iodination
1	CH ₂ Cl ₂	0.33	0.75	95	95
2	CHCl ₃	0.5	1.5	95	90
3	C ₆ H ₆	1	2	88	91
4	CH ₃ CN	1	2	89	87
5	CH ₃ COCH ₃	1.5	3	76	60
6	THF	1.5	3	64	50

^aGC yield.

Therefore, in this way, molecular iodine or bromine is converted to a nucleophilic halogen species in the presence of a suitable diamine and, in the third step, this ion participates in the ring opening reaction of epoxides:

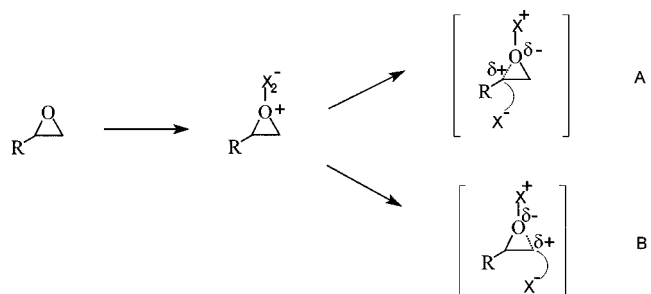


Finally, the catalyst is regenerated in step 4.



These steps occur continuously until all of the epoxides and halogen are consumed, and after workup, the catalyst can be recovered easily.

On the other hand, when catalyst is not present, cleavage of epoxides can occur *via* two limiting mechanistic pathways, either electrophilic attack by molecular halogen, behaving as Lewis acid, giving the more stable carbonium ion-like transition state (A), or *via* nucleophilic attack by halide ion on the epoxide or epoxide-halogen complex, giving the more stable transition state (B):



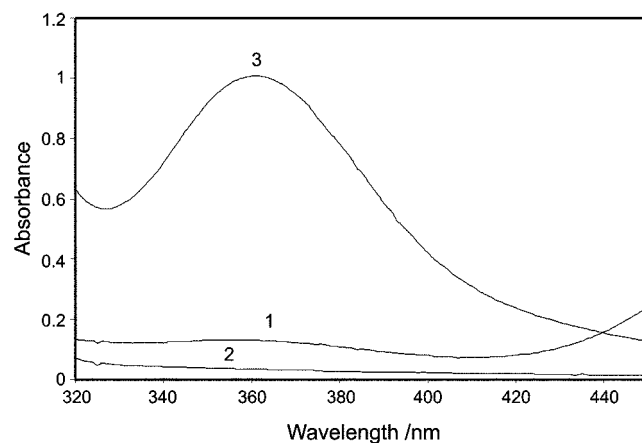
Most Lewis acidic compounds, such as titanium halides, foster electrophilic opening of the epoxide ring to yield transition state A. When weaker Lewis acids are employed, namely bromine or iodine, nucleophilic attack, by the halide ions generated should be fostered and transition state B may be expected to be lower in energy. In this case, the cleavage leads to a mixture of secondary alcohol and primary alcohol products.¹⁸

The variation in yield and rate of cleaving epoxides by elemental iodine or bromine in the presence of these catalysts (7-9) can be rationalized in terms of the suggested mechanism. The diamine **8** is the most active catalyst in these reactions.

In support of this mechanism, the electronic absorption spectra of iodine (1), catalyst **8** (2) complex formation between iodine and catalyst **8** (3) and complex formation of iodine

with all of the used diamine podants in dichloromethane solution at 25 °C are shown in Figures 1 and 2 respectively. As can be seen from Figure 1, while none of the initial reactants show any measurable absorption in the 320-440 nm region, the addition of diamine podand **8** to iodine results in strong absorption band at 364 nm, presumably due to the complex formation of iodine with diamine podand **8**. It should be noted that the band of 364 nm is characteristic for the formation of the triiodide ion, I₃⁻, in the process of complex formation between iodine and different electron-pair donor ligands.^{19a-f} As shown in Figure 2, in all cases a characteristic band in 364 nm is well known to be specific for the formation of triiodide ion, I₃⁻. In the case of catalyst **8**, this band appeared immediately and clarified the much faster complexation of iodine with this catalyst.¹⁹⁻²²

The decrease in regioselectivity that results by merely reversing the order of mixing of epoxide and halogen, namely the slow addition of bromine to epoxide, before catalyst was added, can be readily understood from the model. When the initial epoxide was introduced (in the absence or presence of catalyst), it would encounter an excess amount of bromine: electrophilic attack by bromine can then occur, giving the transition state A, and bromine anions will attack the more substituted carbon. On the other hand, slow addition of bromine to the mixture of catalyst and epoxide fosters the four-step mechanism presented above in which all of the elemental bromine is converted to Br₃⁻ by the catalyst and it then attacks the less substituted carbon selectively.

**Figure 1.** Absorption spectra of: (1) iodine; (2) catalyst **8**; (3) complex of catalyst **8** with iodine in dichloromethane solution

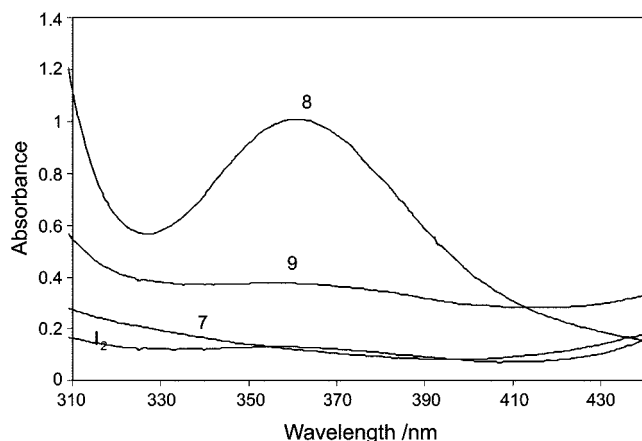


Figure 2. Absorption spectra of complexes between iodine and the used diamine podands in dichloromethane solution. Spectra from bottom to top refer to iodine, diamines **7**, **8** and **9**; iodine complex.

In conclusion, we have found that suitable diamino compounds can catalyze the regioselective ring opening of epoxides by elemental iodine and bromine under neutral conditions with a variety of sensitive functional groups, as well as the convenience of this procedure, which make this synthetic technique highly useful.

Experimental Section

IR spectra were obtained on an Impact 400 D Nicolet FTIR spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX-250 (90 MHz) in pure deuterated solvents. UV Vis spectra were obtained with a Philips PU8750 spectrometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument at 70 eV. The purity determination of the substrates and reactions monitoring were accomplished by TLC on silica gel polygram SILG/UV 254 plates or GLC on a Shimadzu GC-10A instrument with a flame ionization detector using a column of 15% carbowax 20 M chromosorb W acid washed 60-80 mesh. Column chromatography was carried out on short columns of silica gel 60 (230-400 mesh) in glass columns (2-3 cm diameter) using 15-30 g of silica gel per 1 g of crude mixture. Melting points were determined in open capillary tubes in a Buchi-510 circulating oil melting point apparatus. Epoxides, and other chemical materials were purchased from Merck and Fluka in high purity and were used without further purification.

General Procedure for Halogenative Cleavage of Epoxides. Epoxide (1 mmol) in CH_2Cl_2 (5 mL) was added to a stirred solution of 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 portionwise (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 $\text{Na}_2\text{S}_2\text{O}_3$ (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 by 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.^{11,13,24-26}

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