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Conversion of epoxides into halohydrins with elemental halogen catalyzed by thiourea

Hashem Sharghi* and Mohammad Mehdi Eskandari

Department of Chemistry, College of Science, Shiraz University, Shiraz 71454, I. R. Iran

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Abstract—A highly regioselective method for the synthesis of β-iodohydrins and β-bromohydrins by the direct ring opening of epoxides with elemental halogen in the presence of thiourea is described. This method occurs under neutral and mild conditions with high yields in various solvents even when sensitive functional groups are present.
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1. Introduction

Epoxides are versatile intermediates in organic synthesis and a large variety of reagents are known for the ring opening of these compounds.[1,2] The most common method for the synthesis of 1,2-halohydrins from epoxides is their ring opening either with hydrogen halides or with hydrohalogenic acid.[3] However, these procedures are limited when protic acid sensitive substrates are used. 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.[4] In these cases, however, the primary reaction products are the *O*-silyl protected derivatives.[4] Other methods require the use of a halogen and triphenylphosphine,[5] or disubstituted borane halogenides,[6] β-bromo bis-(dimethylamino) borane,[7] monochloro borane–dimethylsulfide,[8] $Li_nM_nX_n$ (M=Ni, Cu, Ti)[9] and MX_n.[10] It has been found that epoxides also can be converted into halohydrins by means of elemental halogen,[11] but this method has some limitations such as low yield, long reaction times, low regioselectivity and formation of acetonides as by-products in addition to the expected iodo adduct in acetone solution. Furthermore, iodination does not occur in other aprotic solvents. In relation with our pervious work on the use of pyridine-containing macrocyclic compounds,[12] we introduce a very simple, mild, cheap, available and efficient method for the conversion of epoxides into halohydrins. We found that thiourea catalyzed the addition of elemental halogen to epoxides under mild reaction conditions with high regioselectivity. In this paper we describe our successful results that led to a novel and extremely simple method for the transformation of epoxides into halohydrins with elemental iodine and bromine in the presence of catalytic amount of thiourea.

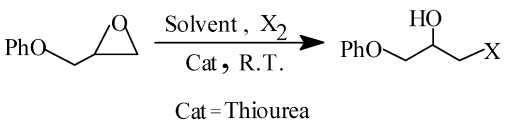
2. Result and discussion

In order to optimise the reaction conditions, we first examined the effects of elemental halogens in the presence of different amounts of thiourea on 1,2-epoxy-3-phenoxypropane as a model in various solvents (Table 1 and Scheme 1).

Table 1. Addition of iodine (1 mmol) and bromine (1 mmol) to 1,2-epoxy-3-phenoxypropane (1 mmol) catalysed by different amounts of thiourea in various solvents at 25°C

Entry	Solvent	Catalyst (mmol)	Iodination		Bromoniation	
			Time (h)	Yield[a] (%)	Time (h)	Yield[a] (%)
1	CH_3CN	0.2	2.5	70	1.5	75
2	CH_3CN	0.1	2.5	70	1.5	75
3	CH_3CN	0.05	2.5	50	1.5	60
4	CH_3CN	0.025	2.5	30	1.5	40
5	THF	0.1	2.5	55	1.5	60
6	Et_2O	0.1	2.5	40	1.5	45
7	CH_2Cl_2	0.1	2.5	30	1.5	50
8	$CHCl_3$	0.1	2.5	33	1.5	35
9	DMSO	0.1	2.5	25	1.5	35
10	HMPA	0.1	2.5	30	1.5	40
11	Dioxane	0.1	2.5	50	1.5	60

[a] Isolated yield.



Cat = Thiourea

Scheme 1.

Keywords: thiourea; epoxide; halohydrins.
* Corresponding author. Tel.: +98-711-2287600; fax: +98-711-2280926; e-mail: shashem@chem.susc.ac.ir

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Table 2. Reaction of various epoxides with iodine and bromine in the presence of thiourea catalyst in CH_3CN at room temperature

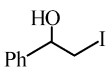
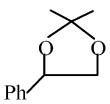
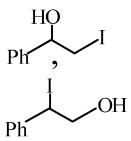
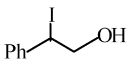
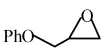
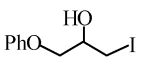
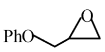
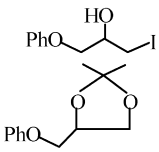
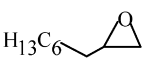
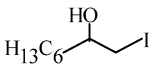
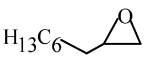
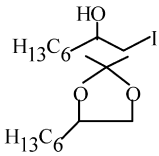
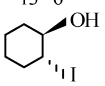
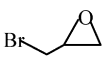
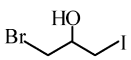
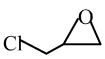
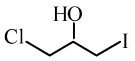
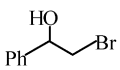
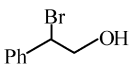
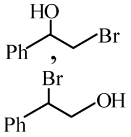
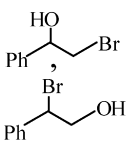
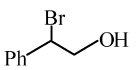
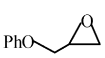
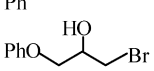
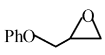
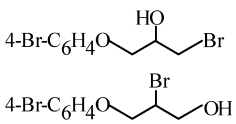
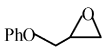
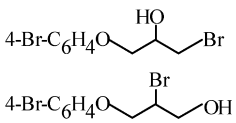
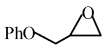
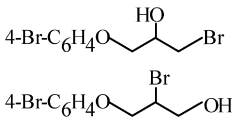
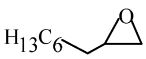
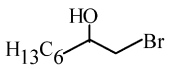
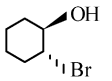
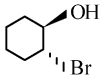
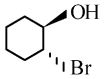
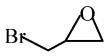
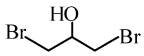
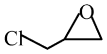
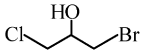
Entry	Epoxide	Catalyst	Reaction condition	Product	Reaction time (h)	Yield[a] (%)	Reference
1		Thiourea	$I_2/CH_3CN/25°C$		0.83	90	
2		–	I_2 (excess)/CH_2Cl_2/reflux	No reaction	Several days	–	11
3		–	I_2 (excess)/CH_3CN	No reaction	Several days	–	11
4		–	I_2/acetone/25°C		2	83	11
5		–	LiI/AcOH/THF/rt		1.3	87 (1:2)	10a
6		–	$HI/CHCl_3$		0.25	>99	15
7		Thiourea	$I_2/CH_3CN/25°C$		2.5	70	
8		–	I_2/acetone/25°C		–	94 (1:1)	11
9		Thiourea	$I_2/CH_3CN/25°C$		3	70	
10		–	I_2/acetone/25°C		–	79 (1:4)	11
11		Thiourea	$I_2/CH_3CN/25°C$		1.15	80	
12		Thiourea	$I_2/CH_3CN/25°C$		5.5	58	
13		Thiourea	$I_2/CH_3CN/25°C$		5.5	63	
14		Thiourea	$Br_2/CH_3CN/25°C$		0.33	95	
15		–	$Br_2/rt/CH_2Cl_2$		1	33	11
16		–	*n*-$Bu_4NBr/Mg(NO_3)_2/CHCl_3$		5	78 (5:1)	33
17		–	$(Me_2N)_2BBr/CH_2Cl_2/N_2$		12	75 (1:4.5)	7
18		–	$HBr/CHCl_3$		0.25	>99	15
19		Thiourea	$Br_2/CH_3CN/25°C$		1.5	75	

Table 2 (*continued*)

Entry	Epoxide	Catalyst	Reaction condition	Product	Reaction time (h)	Yield[a] (%)	Reference
20		–	Br_2/CH_3CN		–	66 (1:2)	11
21		Thiourea	$Br_2/CH_3CN/25°C$		0.75	80 (4.5:1)	
22		–	$Br_2/rt/CH_2Cl_2$		–	88 (5:1)	11
23		Thiourea	$Br_2/CH_3CN/25°C$		0.75	75	
24		Thiourea	$Br_2/CH_3CN/25°C$		0.66	87	
25		–	Br_2/CH_2Cl_2		–	44	11
26		–	LiBr/AcOH/THF/25°C		5	90	10a
27		Thiourea	$Br_2/CH_3CN/25°C$		0.83	65	
28		Thiourea	$Br_2/CH_3CN/25°C$		0.83	75	

[a] Isolated yield.

As shown in Table 1, yields of both iodination and bromination with this methodology are quite good. The optimum amount of catalyst was found to be 0.1 mol for 1 mol of epoxide and halogen.

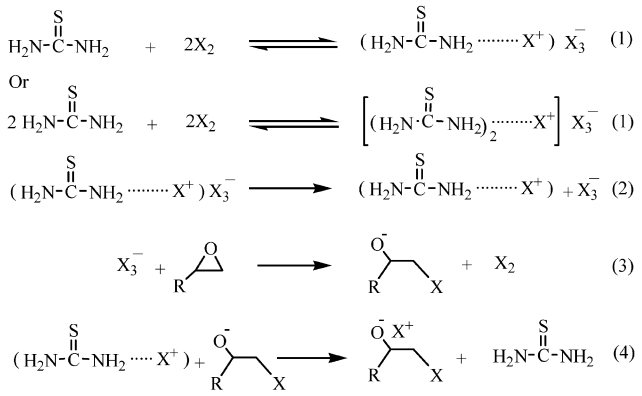
The results obtained with some representative epoxides in the presence of thiourea as catalyst are summarized in Table 2 and are compared with the corresponding results obtained in the reaction of the same epoxides in the absence of catalyst (Table 2, entries 2, 3, 4, 8, 10, 15, 20, 22, 25). On the other hand, for comparison, some other methods for conversion of epoxides to the corresponding halohydrins are given in Table 2, entries 5, 6, 16, 17, 18 and 26. When epoxides were allowed to react in the presence of catalyst, increases in yield and regioselectivity were observed in all of the reactions studied. The increase appeared to be largely dependent on the nature of solvent and amount of catalyst (Table 1).

However, other factors can exert a controlling influence, such as: (1) steric hindrance of epoxides, (2) the rate of admixing the reagents and (3) the order in which the reagents are combined. Each can have pronounced effect on the observed ratio of halohydrin isomers and overall yield.

A comparison of the reaction of epoxides with elemental bromine or iodine in the presence of thiourea catalyst indicates that an increase in steric hindrance at the epoxide ring results in a general decrease in the rate of halohydrin formation (for example, compare Table 2, entry 1 with entry 11).

The order and rate in which the reagent are combined were found to exert a subtle influence on yield and regioselectivity in both bromohydrin and iodohydrin formation. For example, if bromine is added to epoxide before catalyst is added, two bromohydrin isomers are produced, but if the epoxide is added to catalyst and then bromine is added dropwise over a period time, only one isomer is formed. Furthermore, fast addition of bromine reduced regioselectivity, too (Table 2, entry 21).

As shown in Table 2 (entries 11 and 24) in which only the *trans* isomers were detected, the reactions are completely *trans*-stereoselective. A contra-Markovnikov-type[13,14] of regioselectivity is generally observed in these reactions. In one case, this type of regioselectivity appears to be opposite to that observed in the ring opening of the same epoxides with aqueous hydrohalogenic acids, under classic conditions[15] (entries 6 and 18). The regiochemical mode of epoxide cleavage by elemental iodine or bromine in the presence of thiourea catalyst can be viewed as occurring via nucleophilic attack by halide ion on the less sterically hindered epoxide carbon. This mechanism closely



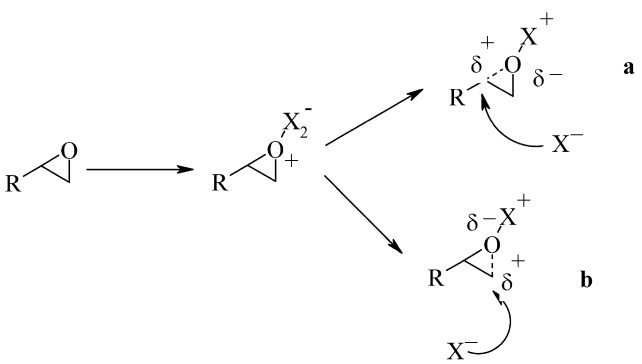
Scheme 2.

resembles the S_N2 model for aliphatic nucleophilic displacement. On the basis of our study on the complexation of thiourea and other work reported on the different ligands[11,16] with elemental halogen, halogenative cleavage of epoxides occurs according to the following four-step mechanism (Scheme 2).

The first step involves the formation of a 1:2 or 1:1 molecular complex between thiourea and elemental halogen, in which halogen ion (X_3^-) exists as a contact ion pair. In the second step this complex is further decomposed to release X_3^- ion into solution. Therefore, in this way, molecular iodine or bromine is converted to a nucleophilic halogen species in the presence of a thiourea and, in the third step, this ion participates in the ring opening reaction of epoxides. These steps occur continuously until all of the epoxides and halogen are consumed.

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–halogen complex, giving the more stable transition state **b** (Scheme 3).

The regiochemistry of the cleavage can be selective depending on the choice of Lewis acid and reaction conditions. The reaction conditions providing the most Lewis acidic, namely with titanium halides, foster electrophilic opening of the epoxide ring to yield transition state **a**. Conversely, when weaker Lewis acids are employed, such as molecular halogen, nucleophilic attack by the halide ions



Scheme 3.

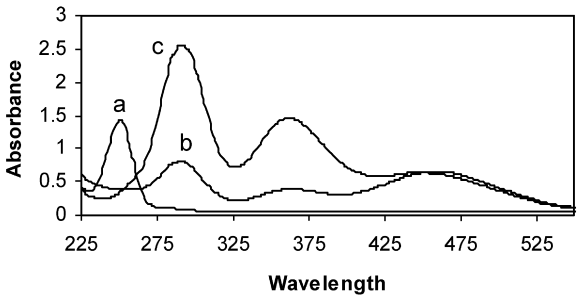


Figure 1. Absorption spectra in CH_3CN solution: (a) Thiourea. (b) I_2. (c) Thiourea–I_2.

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.[14]

The variation in yield and rate of cleaving epoxides by elemental iodine or bromine in the presence of thiourea can be satisfactory rationalized in terms of the suggested mechanism.

In support of this mechanism, reaction of thiourea with iodine was followed by UV spectroscopy (Fig. 1). Figure 1 shows the characteristic UV band at 364 nm. This band is well known to be specific for the formation of triiodide ion, I_3^-, in the complex formation process between iodine and different electron-pair-donating ligands.[17–19] The decrease in regioselectivity that results by merely reversing the order of mixing of epoxide and halogen, namely the slow addition of epoxide to bromine or fast addition of bromine to epoxide, before catalyst was added, can readily be 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 Br_3^- by the catalyst and it then attacks the less substituted carbon selectively.

In conclusion, thiourea appears to be an efficient catalyst for ring opening of the epoxides with elemental halogens under mild conditions. In addition, the advantages such as high regio- and stereoselectivity of the reactions, stability, commercially available and cheapness of the catalyst, high yield and ease of workup make this method a useful addition to the present methodologies in organic syntheses.

3. Experimental

Yields refer to isolated yields, NMR spectra were recorded in $CDCl_3$ on a Bruker Advanced Dpx-250 (^1H NMR 250 MHz and ^{13}C NMR 62.9 MHz) spectrophotometer using TMS as internal standard. UV–vis spectra were obtained with a Philips PU8750 spectrometer. GC spectra were recorded on a Shimadzu GC-14A. Infrared spectra were recorded on a Perkin–Elmer IR-157G and a

Perkin–Elmer 781 spectrometer. Chromatography was carried out on silica gel 60 (70–230 mesh).

3.1. General procedure for conversion of epoxides into halohydrins

Epoxide (1 mmol) in CH_3CN (5 mL) was added to a stirred solution of catalyst (0.1 mmol) in CH_3CN (5 mL) at room temperature. Next, a solution of elemental halogen (1 mmol) in CH_3CN (5 mL) was added portionwise (15 min) to the above mixture. The reaction was monitored by GLC+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 (3×10 mL). The combined organic layer was dried over anhydrous $MgSO_4$ and evaporated to give crude halohydrin. The crude product(s) was purified by column chromatography. The halohydrins were identified by comparison with authentic samples prepared in accordance with literature procedures.[9c,10,11,20,22]

3.1.1. 2-Iodo-1-phenylethanol. White crystal; mp 33–35°C (lit.,[21] 34°C). Yield=90%; spectroscopic data identical to that reported in the literature.[12]

3.1.2. 2-Bromo-1-phenylethanol. Liquid; bp 110–111°C (4.2 mm) (lit.,[22] 120–123°C (5 mm). Yield=95%; spectroscopic data identical to that reported in the literature.[12]

3.1.3. 1-Bromo-2-octanol. Liquid; bp 115–117°C (15 mm) (lit.,[23] 111–112°C (10 mm). Yield=75%; spectroscopic data identical to that reported in the literature.[20]

3.1.4. 1-Iodo-2-octanol. Yellow liquid. Yield=70%; spectroscopic data identical to that reported in the literature.[20]

3.1.5. 2-Iodocyclohexanol. White crystal; mp 41.5–43°C (lit.,[24] 41.5–42.5°C). Yield=80%; spectroscopic data identical to that reported in the literature.[20]

3.1.6. 2-Bromocyclohexanol. Liquid; bp 84–86°C (10 mm) (lit.,[25] 88–90°C (7 mm). Yield=87%; spectroscopic data identical to that reported in the literature.[20]

3.1.7. 1-Bromo-3-phenoxy-2-propanol. Odourless liquid; bp 160–161°C (15 mm) (lit.,[26] 167–169°C (16 mm). Yield=75%; spectroscopic data identical to that reported in the literature.[12]

3.1.8. 1-Iodo-3-phenoxy-2-propanol. Odourless liquid; bp 176–180°C (16 mm) (lit.,[26] 177–181°C (16 mm). Yield=70%; spectroscopic data identical to that reported in the literature.[12]

3.1.9. 1,3-Dibromo-2-propanol. Yellow liquid; bp 103–106°C (15 mm) (lit.,[27] 105°C (16 mm). Yield=65%; spectroscopic data identical to that reported in the literature.[28]

3.1.10. 1-Bromo-3-chloro-2-propanol. Liquid; bp 96–98°C (15 mm) (lit.,[29] 95–98°C (15 mm). Yield=75%; spectroscopic data identical to that reported in the literature.[30]

3.1.11. 1-Bromo-3-iodo-2-propanol. Yellow liquid. Yield=58%; spectroscopic data identical to that reported in the literature.[31]

3.1.12. 1-Chloro-3-iodo-2-propanol. Liquid; bp 53–55°C (0.2 mm) (lit.,[32] 52–54°C (0.2 mm). Yield=63%; spectroscopic data identical to that reported in the literature.[31]

3.1.13. 2,2-Dimethyl-4-phenyl-1,3-dioxolane. Liquid. Yield=83%; spectroscopic data identical to that reported in the literature.[34]

3.1.14. 2-Iodo-2-phenylethanol. Yield=58%; spectroscopic data identical to that reported in the literature.[35]

3.1.15. 2,2-Dimethyl-4-(phenoxymethyl)-1,3-dioxolane. Liquid. Yield=44%; spectroscopic data identical to that reported in the literature.[34]

3.1.16. 4-Hexyl-2,2-dimethyl-1,3-dioxolane. Liquid. Yield=64%; spectroscopic data identical to that reported in the literature.[11]

3.1.17. 2-Bromo-2-phenylethanol. White crystal; mp 36–37°C (lit.,[36] 38°C). Yield=33%; spectroscopic data identical to that reported in the literature.[35]

3.1.18. 1-Bromo-3-(4-bromophenoxy)-2-propanol. Yield=22%; spectroscopic data identical to that reported in the literature.[11]

3.1.19. 2-Bromo-3-(4-bromophenoxy)-1-propanol. Yield=44%; spectroscopic data identical to that reported in the literature.[11]

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