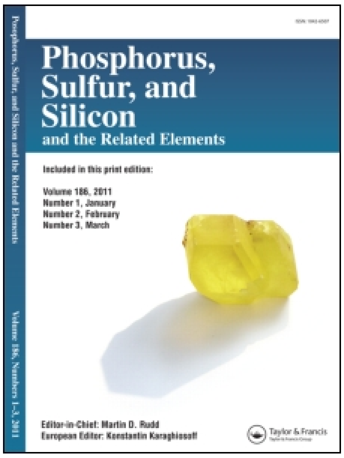

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CONVERSION OF EPOXIDES INTO 2-HYDROXYETHYL THIOCYANATES WITH NH_4SCN IN THE PRESENSE OF 2,6-BIS[2-(*O* -AMINO PHENOXY)METHYL]-4-BROMO-1-METHOXYBENZENE (BABMB) AS CATALYST

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CONVERSION OF EPOXIDES INTO 2-HYDROXYETHYL THIOCYANATES WITH NH_4SCN IN THE PRESENSE OF 2,6-BIS[2-(*O*-AMINO PHENOXY)METHYL]-4-BROMO-1-METHOXYBENZENE (BABMB) AS CATALYST

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*A convenient and efficient procedure for the ring-opening of 1,2-epoxyethanes with ammonium thiocyanate in the presence of 2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxybenzene (BABMB) is described. In this study, a reagent and conditions have been discovered with which the individual 2-hydroxyethyl thiocyanates can be synthesized in high yield and with more than 90% regioselectivity. Thus, several 2-hydroxyethyl thiocyanates, useful intermediates toward biological-active molecules, are easily obtained in very good yields.*

Keywords: Ammonium thiocyanate; catalyst; epoxide; podand diamine; thiocyanohydrin

Thiocanates are important intermediates in agricultural and pharmaceutical chemistry. 2-Hydroxyethyl thiocyanates represent an interesting subclass having multiple modes of reactivity. Synthetic access by oxirane ring opening with thiocyanate has been limited by a further reaction to give thiiranes.[1,2] The formation of thiiranes from the reaction of epoxides and thiocyanate ion has been proposed to occur through the intermediacy of the corresponding β-hydroxy thiocyanate, but this intermediate has not been isolated due to its rapid conversion to the corresponding thiirane.[2–4] There are two methods reported in the literature for the synthesis of 2-hydroxyethyl thiocyanates. In one method, 2-hydroxyethyl thiocyanates are prepared by the opening of a cyclic

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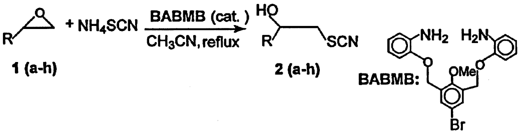


R 1 (a–h)		2-Hydroxyethyl thiocyanate 2 (a–h)
Ph	a	A
$PhOCH_2$	b	B
Cyclohexene oxide	c	C
$CH_3(CH_2)_3$	d	D
Indene oxide	e	E
$i\text{-}PrOCH_2$	f	F
$CH_2{=}CHCH_2OCH_2$	g	G
$ClCH_2$	h	h

sulfate with NH_4SCN to form the corresponding β-sulfate, which is hydrolyzed to the 2-hydroxyethyl thiocyanates. A second method employs an addition to the 1,2-epoxyethanes of thiocyanic acid generated in situ at low temperature.[5] For these syntheses, it has been reported that the presence of some hydroquinone or DDQ is required to stabilize the produced 2-hydroxyethyl thiocyanates, and to inhibit its conversion to thiirane.[3,6] Although reagents, such as [$Ti(O\text{-}^iPr)_4/NH_4SCN$],[7] $Ph_3P(SCN)_2$,[8] [$TiCl_3$(or $ZnCl_2$)/KSCN],[9] [$Pd(PPh_3)_4/NH_4SCN$],[10] and TMSNCS (Cat. TBAF),[11] are useful, they are limited to specific oxiranes, and are not applicable as versatile reagents in the preparation of 2-hydroxyethyl thiocyanates.[11]

The properties of cyclic crown ethers are approximated by acyclic neutral ligands (podands). Variation 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 decomplexation are generally faster in acyclic system and the pseudocavity usually has greater conformational flexibility.[12] In conjunction with the ongoing work in our laboratory on the synthesis and formation of complex heterocyclic compounds containing donor nitrogen atoms, with different molecules,[13,14] we found that podand diamine {2,6-bis[2-(*o*-aminophenoxy) methyl]-4-bromo-1-methoxybenzene} (BABMB) efficiently catalyzed the addition of ammonium thiocyanate to epoxide to form 2-hydroxyethyl thiocyanate. Recently, we prepared[13e,14] BABMB and used it as a new catalyst for the conversion of epoxide into halohydrins with elemental iodine and bromine. In this study, I wish to report the results of the reactions of some epoxides with ammonium thiocyanate in the presence of a substoichiometric amount of podand diamine BABMB (1).

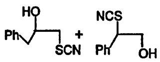
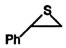
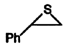
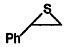
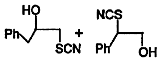
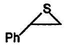
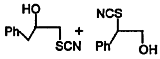
RESULTS AND DISCUSSION

Aromatic amines are used widely 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.

Epoxides of convenient volatility to allow GC analysis were chosen for the study. The results of the reactions of styrene oxide with thiocyanate ion in the presence of BABMB are summarized in Table I. In each case, cleavage of epoxide ring occurs and upon thiosulfate workup, the corresponding thiocyanohydrin was obtained. In comparison, the cleavage behavior of styrene oxide with ammonium thiocyanate in the absence of the catalyst is given in entry 3 of Table I.

As shown in Table I, yields of thiocyanation with this new methodology were quite good, and the reaction times were very short. However, the reaction of the styrene oxide with an excess of ammonium thiocyanate in the absence of the catalyst afforded the corresponding thiirane in 35% yield when the reaction mixture was refluxed for 3.5 h. An alternative preparation of 2-hydroxyethyl thiocyanate by

TABLE I Reaction of Styrene Oxide with NH_4SCN in the Presence of the Representative Catalyst

Entry	Catalyst	Reaction conditions	Product(s)	Reaction time (min)	Yield%[a]
1	BABMB	NH_4SCN/CH_3CN 70°C		10	91 (4:1)
2	BABMB	$KSCN/CH_3CN$ 70°C		120	10
3	—	NH_4SCN/CH_3CN 70°C		210	35
4	$Pd(PPh_3)_4$	NH_4SCN/N_2 THF/Reflux		120	35
5	Ti(o-iPr)$_4$	NH_4SCN/THF Reflux		240	30
6	$ZnCl_2$	KSCN/THF Reflux		180	60
7	DDQ	NH_4SCN/CH_3CN Reflux		50	91(1:8)

[a] Determined by GC.

TABLE II Thiocyanative Cleavage of Styrene Oxide with NH_4SCN in the Presence of BABMB as Catalyst in Different Solvents under Reflux Condition

Entry	Solvent	Time (min)	Yield[a](%)
1	CH_3CN	10	91
2	CH_3CN	200[b]	[c]
3	C_6H_6	120	<20
4	t-BuOH	60	54
5	EtOH	60	39
6	THF	60	35
7	CH_2Cl_2	60	<20
8	1,4-dioxane	60	40

[a] Determined by GC.

[b] In the presence of excess of NH_4SCN.

[c] 35% of the corresponding thiirane was obtained.

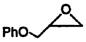
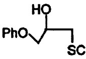
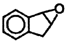
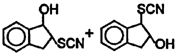
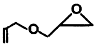
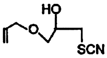
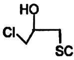
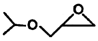
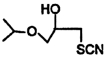
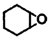
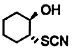
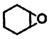
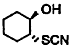
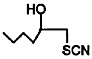
the reaction of styrene oxide with KSCN was examined. This route, however, is not a good one for the synthesis of 2-hydroxyethyl thiocyanates and gave a 10% yield of the corresponding thiirane (Table I, entry 2).

The results of the ring opening of styrene oxide in the presence of BABMB using various solvents are summarized in Table II. Thiocyanation reactions proceed very cleanly employing CH_3CN, while those performed in C_6H_6, t-BuOH, THF, EtOH, 1,4-dioxane and CH_2Cl_2 led to a lower yield of the thiocyanohydrins.

To ascertain the scope and limitation of the present reaction, several oxiranes were examined; these results are summarized in Table III. By comparison, a number of methods[7–10] for the conversion of oxiranes to the corresponding 2-hydroxyethyl thiocynates are given in entries 4–7 (Table I), and entry 7 (Table III). When epoxides were allowed to react in the presence of BABMB, the yield and regioselectivity, were higher than that observed in all of the reactions conditions studied. Generally, the optimum amount of catalyst was found to be 0.1 mmol for 1 mmol of epoxide and NH_4SCN. However, other factors can exert a controlling influence, such as (1) steric hindrance of epoxides, (2) the nature of solvent, and (3) electron-donating or withdrawing groups bonded to the epoxide. Each one can have a pronounced effect on the observed ratio of 2-hydroxyethyl thiocyanate isomers and the overall yield.

As shown in Table III (entry 6), in which only the trans isomer is given, the reactions are completely *anti* stereoselective. As for the regioselectivity, an attack of the nucleophile preferentially occurs at the

TABLE III Reaction of Epoxides with NH_4SCN in the Presence of BABMB Catalyst

Entry	Epoxide	Reaction conditions	Product(s)	Reaction time (min)	Yield%[a]
1		NH_4SCN/CH_3CN 70°C		45	90
2		NH_4SCN/CH_3CN 70°C		110	90 (4:1)
3		NH_4SCN/CH_3CN 70°C		70	83
4		NH_4SCN/CH_3CN 70°C		75	78
5		NH_4SCN/CH_3CN 70°C		65	79
6		NH_4SCN/CH_3CN 70°C		40	92
7		H_2Q^b(cat.) $KSCN/H_3PO_4$ H_2O/Et_2O		—	48[5a]
8		NH_4SCN/CH_3CN 70°C		90	81

[a] Determined by GC.

[b] Hydroquinone has been used to stablize 2-hydroxycyclohexyl thiocyanate (see Van Tamelen[5a]).

less-substituted oxirane carbon. An *anti*-Markovnikov-type[15] regioselectivity is generally observed in these reactions, except for the reactions of styrene oxide (Table I, entry 1), and indene oxide (Table III, entry 2), which produced 17% and 20% of their regioisomer, respectively, and only one isomer was obtained. In these reactions 5–10% of the corresponding thiiranes were also formed, which could easily be isolated by column chromatography.

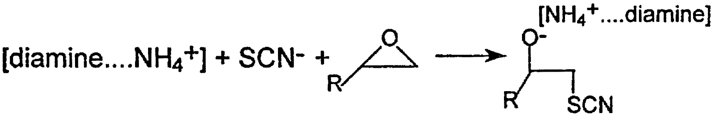
The regiochemical mode of epoxide cleavage by ammonium thiocyanate in the presence of BABMB can be viewed as occurring via nucleophilic attack by thiocyanate ion on the less sterically hindered epoxide carbon. This mechanism closely resembles the S_N2 model for aliphatic nucleophilic displacement. On the basis of our previous study on macrocyclic diamides and other works on the complexation of crown ethers, azophenol-dyed crown ethers and podand diamines with elemental halogens, alkaline metal ions, ammonium cation, and alkylamine,[13–18] conversion of epoxide to 2-hydroxy thiocyanate occurs according to the following four-step mechanism: The first step involves the formation of a 1:1 molecular complex between BABMB and NH_4SCN in which the thiocyanate ion (SCN^-) exists as a contact ion pair:

$$\text{diamine} + NH_4SCN \rightleftharpoons [\text{diamine}\ldots NH_4^+]SCN^- \qquad (1)$$

In the second step, this complex is further decomposed to release SCN^- ion into the solution as:

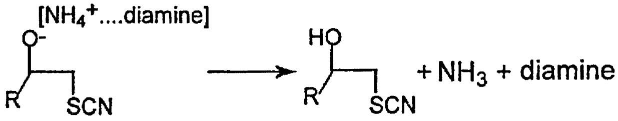
$$(\text{diamine}\ldots NH_4^+)SCN^- \rightarrow [\text{diamine}\ldots NH_4^+] + SCN^- \qquad (2)$$

Therefore, in this way, SCN^- ion is produced as a nucleophilic species in the presence of BABMB, and in the third step, this ion participates in the ring-opening reaction of epoxides:



(3)

Finally, the catalyst is regenerated in step 4:



(4)

These steps occur continuously until all of the epoxides and ammonium thiocyanate are consumed. The variation in yield and rate of epoxide ring opening by SCN^- in the presence of BABMB can be rationalized in terms of the suggested mechanism.

In support of this mechanism, interaction of BABMB with NH_4SCN was followed by UV spectroscopy (Figure 1). This figure shows the electronic absorption spectra of NH_4SCN, BABMB catalyst, and BABMB catalyst in the presence of NH_4SCN in CH_3CN solution. As we can see, addition of NH_4SCN to BABMB catalyst results in the appearance of a new absorption maximum at 290 nm. As is obvious, BABMB/NH_4SCN interaction will result in a strong absorption shift of about 20 nm toward longer wavelengths.

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 thiocyanohydrins were obtained in high yields and regioselectivity. In addition, in comparison with our previous methods,[13e] BABMB is less expensive, has fewer steps needed for the preparation, and has a higher overall yield.

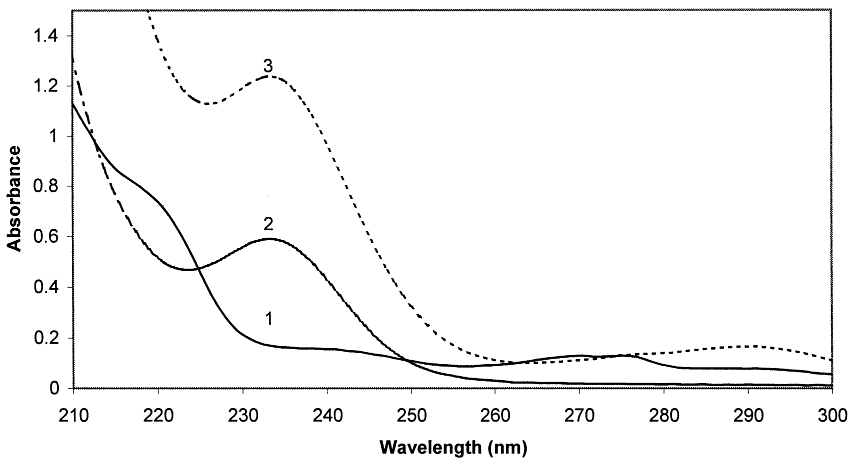


FIGURE 1 Absorption spectra from bottom to top refer to NH_4SCN (1), BABMB (2), and BABMB in the presence of NH_4SCN (3), in CH_3CN solution.

EXPERIMENTAL

General

Some 1,2-epoxyethanes and other chemical materials were purchased from Fluka and Merck in high purity. Products were characterized by comparison of their physical data with those of authentic samples. The nmr spectra were recorded on a Bruker Avance DPX instrument (250 MHz). IR spectra were recorded on a Shimadzo 450 spectrophotometer. Melting points were determined in open capillaries with a Galen-Kamp melting point apparatus. TLC accomplished the purity determination of the substrates and reaction monitoring on silica gel polygram SILG/UV 254 plates.

General Procedure for the Conversion of 1,2-Epoxyethanes to 2-Hydroxyethyl Thiocyanate Using BABMB as a Catalyst

To a mixture of epoxide (10 mmol) and NH_4SCN (10 mmol, 0.76 g) in acetonitrile (30 mL) was added a solution of the catalyst (1 mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred and heated in an oil bath at 70°C for 10–90 min. The reaction was monitored by TLC or GC. After completion of the reaction, the mixture was filtered and the solvent was evaporated. Chromatography of the crude product was performed on a column of silica gel eluted first with n-hexane for the separation of thiirane, followed by using C_6H_{14}/CH_2Cl_2 (1:1) for the separation of 2-hydroxyethyl thiocyanate as a pale yellow liquid. The 2-hydroxyethyl thiocyanates obtained throughout this procedure were identified by comparison, where possible, with authentic samples prepared in accordance with literature procedures.[3,8,11,13e]

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