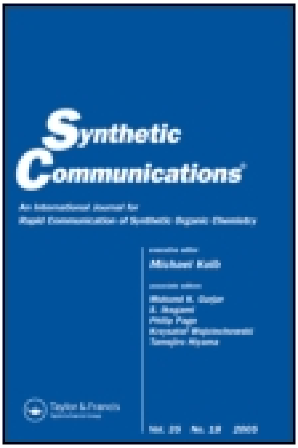

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PEG-SO_3H as Soluble Acidic Polymeric Catalyst for Regioselective Ring Opening of Epoxides: A High-Efficient Synthetic Approach to β-Hydroxy Thiocyanates

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Abstract: Poly(ethylene glycol)–bound sulfonic acid, PEG-SO_3H, was developed as an environmentally friendly and efficient homogeneous polymeric catalyst in organic synthesis. This polymeric phase-transfer catalyst catalyzed the regioselective ring opening of epoxides by thiocyanate ion to give thiocyanohydrins as key intermediates in agricultural and pharmaceutical chemistry in high yields.

Keywords: PEG-SO_3H, polymer support, regioselectivity, ring opening, thiocyanohydrine

Soluble polymeric supports offer certain advantages over insoluble polymers in terms of ease of analysis and monitoring and, most importantly, the establishment of homogeneous conditions, which are most conducive to bimolecular processes.[1] Polyethylene glycol (PEG) and its derivatives are known to be inexpensive, thermally stable, recoverable, toxicologically innocuous, and environmentally benign media for chemical reactions,[2] as well as having almost negligible vapor pressure.

The formation of thiiranes from the reaction of epoxides and thiocyanate has been proposed to occur through the intermediacy of the corresponding β-hydroxy thiocyanate, but this intermediate has not been isolated because of its rapid conversion to the corresponding thiirane.[3] The presence of some hydroquinone[4] or 2,3-dicyano-5,6-dichloro-1,4

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benzoquinone (DDQ)[5] is required to stabilize the produced β-hydroxy thiocyanate and to inhibit its conversion to thiirane. Although a few useful reagents, such as $Ph_3P(SCN)_2$,[6] $Ti(O\text{-}^iPr)_4$,[7] $TiCl_3$ (or $ZnCl_2$),[8] $Pd(PPh_3)_4$,[9] trimethylsilyl isothiocyanate (TMSNCS) (Cat. tetrabutylammonium fluoride [TBAF]),[10] crowns, and cryptants[11] have been reported for the ring opening of epoxide to the thiocyanohydrine, unfortunately some of these methods are not always fully satisfactory and suffer from disadvantages such as relatively long reaction times or low regioselectivity, or involve high-temperature reaction conditions to obtain ring-opened products. Consequently, it seems that there is still a need for development of newer methods that proceed under mild and economically appropriate conditions. Recently, applications of some metalloporphyrins,[12–15] polymeric phase-transfer catalyst,[16] and Selectfluor[17] as catalysts for regioselective conversion of epoxides to β-hydroxy thiocyanates were reported.

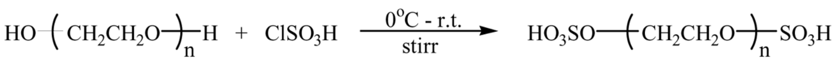
Keeping in mind these facts, we now describe our successful result that led to an efficient and simple method for the transformation of epoxides into the corresponding β-hydroxy thiocyanates using NH_4SCN in the presence of a catalytic amount of poly(ethylene glycol)-bound sulfonic acid, PEG-SO_3H, in high isolated yields.

PEG-SO_3H was prepared[18] by simple mixing of PEG-6000 and chlorosulfonic acid in CH_2Cl_2 (Scheme 1). The reaction is very clean, and the polymeric phase-transfer catalyst can be easily precipitated in ether.

Conversion of terminal hydroxyl groups of PEG to OSO_3H is confirmed by ^1H NMR spectroscopy. The ^1H NMR spectrum shows singlets at δ 12.85 and δ 4.23 ppm due to the proton of SO_3H and the methylene protons in polymer backbone, respectively.

In the first step, phenyl glycidyl ether was chosen as a model compound and reacted with NH_4SCN in CH_2Cl_2 and in the presence of PEG-SO_3H. Thin-layer chromatographic (TLC) analysis showed that the catalyst acted very efficiently, and only 0.1 molar equivalent of the catalyst was enough to convert phenyl glycidyl ether to its corresponding β-hydroxy thiocyanate in high isolated yield within 1 h (Table 1).

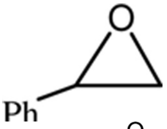
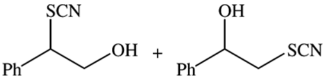
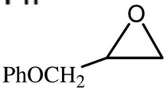
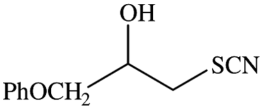
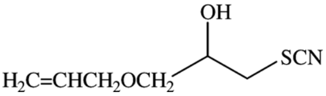
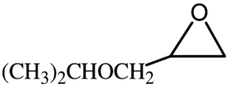
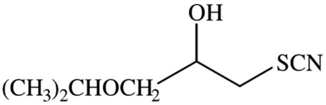
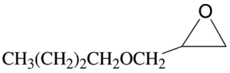
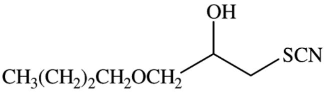
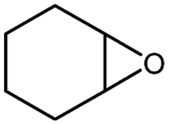
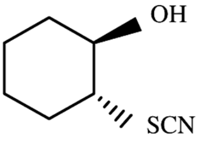
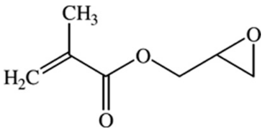
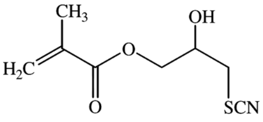
Different types of oxiranes, except styrene oxide, carrying activated and deactivated groups were cleanly, easily, and efficiently converted to the corresponding β-hydroxy thiocyanates as exclusive and virtually pure products according to TLC and ^1H NMR, in considerably short times



$$HO\left(CH_2CH_2O\right)_n H + ClSO_3H \xrightarrow[\text{stirr}]{0^{\circ}C\text{ - r.t.}} HO_3SO\left(CH_2CH_2O\right)_n SO_3H$$

Scheme 1. Preparation of poly(ethylene glycol)-bound sulfonic acid.

Table 1. Reaction of various epoxides with ammonium thiocyanate in the presence of PEG-SO$_3$H in CH$_2$Cl$_2$[a]

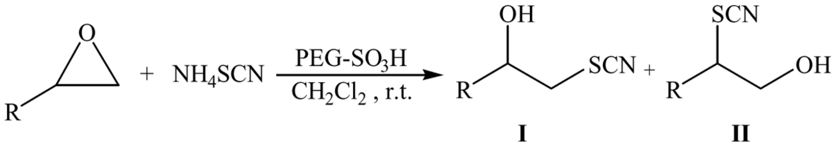
Entry	Substrate	Product (s)	Yields (%)
1			83 (96:4)[b]
2			88
3			91
4			88
5			84
6			85
7			90

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples.

[b] According to GC analysis.

and in high isolated yields. The scope and generality of this process is illustrated with several examples, and the results are summarized in Table 1. The structure of all the products were settled from their analytical and spectral (IR, ^{1}H NMR) data and by direct comparison with authentic samples.

It is noteworthy that no evidence for the formation of thiirane as by-product of the reaction was observed, and the products were obtained in pure form without further purification.



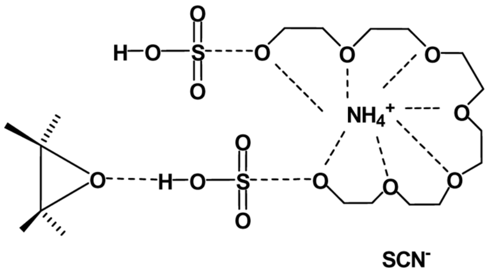
Scheme 2. Regioselective ring opening of epoxide in the presence of PEG-SO_3H.

The reaction of styrene oxide with NH_4SCN in the presence of PEG-SO_3H was completed in CH_2Cl_2 at room temperature after 1 h and produced 2-hydroxy-1-phenylethyl thiocyanate (II) as the major product and a trace amount of other regioisomer 2-hydroxy-2-phenylethyl thiocyanate (I). Epoxides carrying electron-withdrawing groups reacted under similar reaction conditions, and their corresponding β-hydroxy thiocyanates were produced in excellent yields and regioselectivity. In these cases, with the attack of the thiocyanate ion on the less substituted oxirane carbon, the regioselectivity was reversed and β-hydroxy thiocyanates (I) were obtained. It is shown that, for epoxides carrying electron-donating groups, it is the electronic factor that predominates, and the thiocyanate ion attacks predominantly at the secondary carbon atom of the epoxide ring, a fact that is reasonably well established.[19] In contrast, in epoxides carrying electron-withdrawing groups, it is the steric factor in that predominates and the nucleophilic attack of thiocyanate ion is strongly favored on the less substituted carbon of epoxides. Also in the case of cyclohexene oxide, the stereochemistry of the ring-opened product was found to be *trans*.

The efficiency of PEG-SO_3H in the conversion of epoxides to β-hydroxy thiocyanates was definitely confirmed by reaction of styrene oxide with NH_4SCN under similar reaction conditions, without adding PEG-SO_3H. In this case, the reaction did not complete after 5 h, and only a little thiirane was obtained. Also this reaction was examined in the presence of PEG instead of PEG-SO_3H. TLC analysis showed that the reaction did not complete after 5 h and only a trace amount of β-hydroxy thiocyanate was obtained. Any attempts to prepare thiocyanohydrin by ring opening of styrene oxide with thiocyanate anion in the presence of PEG and sulfuric acid were not successful, and polymerization reaction was occurred.

It seems that this polymeric catalyst forms a complex with cation, much like crown ethers, and this complex causes the anion to be activated. In addition, polymeric catalyst probably can be facilitated the ring opening of the epoxide by hydrogen bonding as shown in Scheme 3.

Compared to some previously reported methods with major or minor drawbacks, several noteworthy features of this reagent are apparent, such as easily workup procedure, operational simplicities, and use of inexpensive reagent.



Scheme 3. Anion activation by PEG-SO_3H.

In summary, we believe that the present procedure for regioselective ring opening of epoxides with ammonium thiocyanate using PEG-SO_3H provides an easy, mild, efficient, versatile, and general methodology for the preparation of β-hydroxy thiocyanates from different classes of epoxides, and we feel that it may be a suitable addition to methodologies already present in the literature.

EXPERIMENTAL

Some 1,2-epoxyalkanes and other chemical materials were purchased from Fluka and Merck in high purity. Poly(ethylene glycol)–bound sulfonic acid was prepared according to the previously reported procedure.[18] All of the thiocyanohydrin compounds were prepared by our procedure, and their spectroscopic and physical data were compared with those of authentic samples.

NMR spectra were recorded in $CDCl_3$ on a Bruker Advanced DPX 400-MHz instrument spectrometer using TMS as internal standard. IR spectra were recorded on a BOMEM MB-Series 1998 FT-IR spectrometer. The purity determination of the products and reaction monitoring were accomplished by TLC on silica-gel polygram SILG/UV 254 plates.

General Procedure for the Preparation of β-Hydroxy Thiocyanatesin CH_2Cl_2

To a mixture of epoxide (1 mmol) and NH_4SCN (3 mmol) in CH_2Cl_2 (10 mL), PEG-SO_3H (0.1 mmol, 0.6 g) was added, and the mixture was stirred at room temperature for 1 h. The progress of the reaction was monitored by TLC using CCl_4-ether (4:1). On completion of the reaction, the solvent was evaporated under reduced pressure. Water (10 mL) was added to the residue, and then the product was extracted with ether (3 × 10 mL). The solvent was dried over anhydrous calcium chloride and evaporated under reduced pressure. The desired thiocyanohydrines were obtained in good to excellent isolated yields (83–91%).

Representative Examples of Spectra Data of Thiocyanohydrin

3-Phenoxy-2-hydroxypropyl Thiocyanate[14]

IR (neat): ν SCN (2156 cm^{-1}). ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 7.27$ (2H, m), 7.01 (1H, m), 6.9 (1H, m), 4.29 (1H, m), 4.04 (2H, d), 3.78 (1H, s), 3.30 (1H, m), 3.16 (1H, m). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 158.5$, 129.9, 121.3, 114.6, 113.0, 69.5, 68.0, 37.4.

2-Hydroxycyclohexyl Thiocyanate[14,16]

IR (neat): ν SCN (2151 cm^{-1}). ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 3.34$ (1H, m), 3.14 (2H, m), 1.98 (2H, m), 1.69 (2H, m), 1.21–1.28 (4H, m). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 110.5$, 76.4, 52.6, 31.5, 30.5,25.1, 22.2.

3-Allyloxy-2-hydroxypropyl Thiocyanate[14]

IR (neat): ν SCN (2155 cm^{-1}). ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 5.86$ (1H, m), 5.19–5.29 (2H, m), 4.05 (3H, m), 3.53 (2H, m), 3.04–3.24 (3H, m). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 133.6$, 117.4, 113.0, 71.6, 70.7, 69.1, 37.3.

2-Hydroxy-3-thiocyanatopropyl Methacrylate

IR (neat): ν SCN (2157 cm^{-1}). ^{1}H NMR (CDCl$_3$, 400 MHz): $\delta = 6.06$ (1H, m), 5.55 (1H, m), 4.4 (3H, m), 3.40 (1H, m), 3.16 (1H, m), 3.03 (1H, m), 1.85 (3H, m). ^{13}C NMR (CDCl$_3$, 100 MHz): $\delta = 167.0$, 135.2, 126.5, 112.8, 68.0, 66.1, 37.3, 18.4.

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