



Synthesis of thiocyanohydrins from epoxides using quaternized amino functionalized cross-linked polyacrylamide as a new solid–liquid phase-transfer catalyst

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Abstract—Poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride resin was developed as a new polymeric phase-transfer catalyst. This quaternized polyacrylamide catalyzed the regioselective ring opening of epoxides by thiocyanate ion to give thiocyanohydrins in high yields under mild conditions. © 2002 Elsevier Science Ltd. All rights reserved.

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 Their electrophilic reactions with different nucleophilic anions have been an interesting subject in organic synthesis.² Of these anions, the reaction of thiocyanate ion with epoxides, in the absence or in the presence of a catalyst, has been widely studied and is a suitable method for the preparation of thiiranes.³ 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 due to its rapid conversion to the corresponding thiirane.^{3f–h,4,5}

There are only a few methods reported in the literature for the synthesis of β -hydroxy thiocyanates. In one method, thiocyanohydrins are prepared by the opening of a cyclic sulfate with NH_4SCN to form the corresponding β -sulfate, which is hydrolyzed to the thiocyanohydrin. A second method involves the addition of thiocyanic acid (generated in situ at low temperature) to an epoxide.⁶ Recently Sharghi reported the conversion of epoxides to β -hydroxy thiocyanates using NH_4SCN in the presence of phenol containing a macrocyclic diamine as a catalyst.⁷ In the first two of these methods, it has been reported that the presence of some hydroquinone or DDQ is required to stabilize the β -hydroxy thiocyanate and inhibit its conversion to a thiirane.^{4,8}

Phase-transfer catalysts (PTCs) facilitate reactions between water-soluble reagents and organic soluble substrates. The most important PTCs, which have been used widely in organic reactions, are quaternary ammonium and phosphonium salts, crown ethers, and cryptands.^{9–11} These catalysts are generally not recovered and this is a problem when the relatively expensive cryptands and crown ethers are used. On the other hand, some of the ammonium and phosphonium salts sometimes form stable emulsions. During the last few years much interest has been focused on the applications of functionalized polymers as PTCs,^{12,13} because they provide ease of separation of the catalyst and isolation of the product. A significant number of quaternary ammonium and phosphonium salts as well as crown ethers and cryptands bound to polystyrene type resins have been used in synthetic organic chemistry.^{12–16}

Polyacrylamide and its modified forms have been used as cosolvent-type catalysts for nucleophilic displacement reactions under biphasic and triphase conditions,¹⁷ as supports for the solid-phase synthesis of peptides,¹⁸ for metal complexation,^{19,20} and for the preparation of a number of polymer supported reagents.^{21–23} These supported systems, were found to have entirely different characteristics in terms of polarity, solvation, and reactivity compared to the commonly used polystyrene supported species.

Recently, we have reported the use of quaternized amino functionalized cross-linked polyacrylamide as an efficient polymeric PTC in the synthesis of halohydrins²⁴ and azidohydrins.²⁵ In this report, we

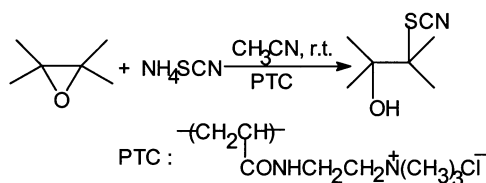
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describe the results that successfully led to the development of an efficient and simple method for the transformation of epoxides to β -thiocyanohydrins using quaternized amino functionalized cross-linked polyacrylamide as an efficient heterogeneous polymeric PTC.

Polyacrylamide cross-linked with divinylbenzene (2%) was prepared by free radical solution polymerization of the monomer mixture in ethanol using benzoyl peroxide as an initiator. Poly[*N*-(2-aminoethyl)acrylamide] was obtained by the transamidation reaction of cross-linked polyacrylamide with excess ethylene-diamine. Poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride was prepared by the reaction of poly[*N*-(2-aminoethyl)acrylamide] with an excess of methyl iodide in DMF at room temperature and subsequent exchange of the iodide anion with chloride.^{24,25}

To develop the synthetic utility of this modified polymer, it was examined in the reaction of epoxides with NH_4SCN , especially for the synthesis of β -thiocyanohydrins under phase-transfer conditions (Scheme 1). The effects of solvent and molar ratio of the polymer on the ring opening of epoxides were investigated. The reactions were carried out in wet tetrahydrofuran, chloroform, dichloromethane, ethyl acetate, acetonitrile and water. The best solvent was acetonitrile (Table 1). The optimum molar ratio of the polymeric catalyst to epoxide was found to be 0.15–0.2:1.

The reactions of different epoxides carrying electron-donating or withdrawing groups with NH_4SCN were performed in acetonitrile at room temperature in presence of 0.15–0.2 molar equiv. of the polymeric PTC. The corresponding β -thiocyanohydrins were obtained in very high yields without the formation of any of the corresponding thiranes (Table 2).



Scheme 1.

Table 1. The effect of the solvent on the reaction of styrene oxide with NH_4SCN using the polymeric PTC^a

Entry	Solvent	Time (h)	Conversion (%)
1	THF	6	5 ^b
2	CHCl_3	6	0
3	CH_2Cl_2	6	0
4	EtOAc	6	7 ^b
5	CH_3CN	1.5	100
6	H_2O	6	47

^a The molar ratio of the polymeric catalyst to styrene oxide was 0.2:1.

^b By GC.

Except for the reactions of styrene oxide (entry 1) and 1,2-butene oxide (entry 6) which produce a small percentage of the other regioisomer, the reactions of the epoxides were found to be highly regioselective and only one isomer was obtained. Also in the case of cyclic epoxides (Table 2, entries 7–8), *trans* products were obtained. Obviously, in these reactions, the attack appears to be largely, if not entirely, at the primary carbon atom of the epoxide ring. The direction of ring opening is that characteristically observed for reactions of monoalkyl-substituted epoxides under $\text{S}_{\text{N}}2$ conditions and is probably dictated by steric and electronic factors. In the reaction with styrene oxide, the thiocyanate ion attacks predominantly at the secondary carbon atom of the epoxide ring, a fact, which is reasonably well established.²⁶

As shown in our previous papers,^{24,25} the poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride resin in this transformation acts both as a catalyst for nucleophilic ring opening reactions as well as being a phase-transfer agent. It seems that this polymeric catalyst carrying the nucleophile has an activating effect on the epoxy substrate and the reaction proceeds smoothly in the vicinity of the catalyst. Probably the ring opening of the epoxide is facilitated by hydrogen bonding between the oxygen of the epoxide and the amidic hydrogen of the polymer.

In conclusion, poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium halide resin has proved to be a highly efficient polymeric PTC for the regioselective ring opening of epoxides to thiocyanohydrins by thiocyanate ion. It plays a special role as an electrophilic catalyst, as well, for such reactions. The resin has the inherent advantages of being a solid-phase-transfer catalyst, including operational simplicity, filterability, regenerability, and reuse. In particular, the workup of the reaction was very easy and the pure products could be isolated without any purification; the filtered polymeric catalyst could be recovered, and after changing it to the Cl^- form, it be used several times and used without any loss in its capacity and efficiency.

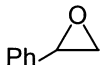
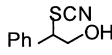
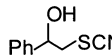
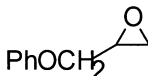
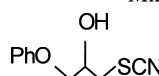
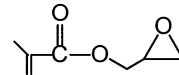
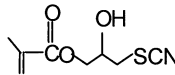
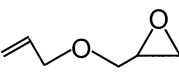
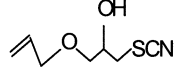
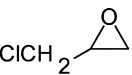
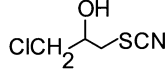
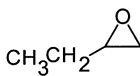
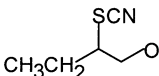
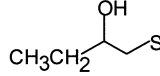

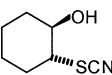
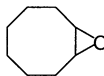
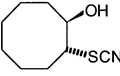
Reactions of epoxides with other nucleophiles under phase-transfer conditions, using this polymer and some other reactions such as reductions and the effect of parameters such as the nature of the alkyl groups on the quaternized site and the spacer length are currently under investigation.

Typical procedures:

(A) Poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium iodide resin was prepared as described in the our previous papers.^{24,25}

(B) Reactions of epoxides with NH_4SCN under PTCs: To a mixture of the epoxide (1.0 mmol) and NH_4SCN (3 mmol) in acetonitrile (20 ml), was added poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride (~0.1 g). The suspension was stirred at room tempera-

Table 2. Reaction of epoxides with NH₄SCN in presence of poly[N-(2-aminoethyl)acrylamido]trimethyl ammonium chloride resin as PTCs in CH₃CN^a

Entry	Epoxide	Time (h)	Product ^b	Yield % ^c
1		1.5	  Minor	90 ^d (89,11)
2		0.5		92
3		1		91
4		2.5		91
5		4		89
6		3	  Minor	90 ^d (18, 82)
7		1		89
8		6		86

a : All of the reactions were carried out at room temperature. Molar ratio of PTC to epoxide was 0.2: 1.

b : Structures and regiochemical ratios determined for the products by ¹H-NMR .

c : Yield refers to isolated product.

d : Two regioisomers were obtained and the yield refers to both isomers.

ture for the time shown in Table 2. The progress of each reaction was monitored by TLC, using CCl₄-ether (5:1) as eluent and/or GC. The polymer was removed by filtration. The organic solvent was dried with anhydrous Na₂SO₄ and the pure product was obtained upon evaporation of the solvent. The characterizations of products were performed using IR, ¹H and ¹³C NMR spectroscopy.

(C) Selected spectroscopic data: (a) 2-Hydroxycyclohexyl thiocyanate: IR (neat): ν SCN, 2163 cm⁻¹; ¹H NMR (DMSO), δ (ppm): 2.95 (1H, m), 2.36 (1H, m), 2.15 (1H, s), 1.8 (2H, m), 1.6 (2H, m), 1.2–1.5 (4H, m); ¹³C NMR (CCl₄), δ (ppm): 110.0, 72.2, 54.8, 34.9, 32.6, 30.6, 27.1; (b) 2-hydroxy-2-phenylethyl thiocyanate: IR (neat): ν SCN, 2160 cm⁻¹; ¹H NMR (DMSO), δ (ppm): 7.3 (5H, m), 4.9 (1H, dd), 3.95 (2H, m), 3.2 (1H, s); ¹³C NMR (DMSO), δ (ppm): 137.6, 129.1, 128.6, 126.4, 112.6, 71.3, 63.6.

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