Synthesis of azidohydrins from epoxides using quaternized amino functionalized cross-linked polyacrylamide as a new polymeric 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 azide ion to give azidohydrins in high yield under mild conditions. © 2001 Elsevier Science Ltd. All rights reserved.

Problems associated with the phase separation of an inorganic reagent and an organic substrate can be overcome by the use of phase-transfer catalysts in both homogeneous and heterogeneous forms.[1,2] Polymer-supported catalysts are the most attractive types of polymer-supported species for applications in organic chemistry, because they provide great ease in separation and recycling of the catalyst and isolation of the product.[3,4] Although a polystyrene support has been widely used for the preparation of polymer-supported phase-transfer catalysts, its physicochemical incompatibility with solvents and substrates most often leads to low efficiency and reactivity.[5] The design of synthetic polar polymeric supports such as polyacrylamide is a significant advance. Polyacrylamide and its modified forms have been used as cosolvent-type catalysts for nucleophilic displacement reactions under biphase and triphase conditions,[6] as supports for the solid-phase synthesis of peptides,[7] for metal complexation,[8] and for the preparation of a number of polymer-supported reagents.[9] Also, modified polyacrylamide grafted onto the surface of a porous nylon capsule membrane was used as a phase-transfer catalyst.[10] These supported systems were found to have different characteristics in terms of polarity, solvation, and reactivity compared to commonly used polystyrene-supported species.[9c,11]

β-Azidoalcohols are an important class of organic compounds, and they serve as precursors in the synthesis of β-aminoalcohols, amino sugars and carbocyclic nucleosides.[12–14] The usual synthetic routes to these

compounds involve ring opening of 1,2-epoxides with azide anion. The reactions are often carried out under either alkaline or acidic conditions and several different methods have been devised in order to obtain the direct azidolysis of epoxides in the presence of sodium azide.[12,13,15] Usually these conditions require high temperatures and/or long reaction times, and as side reactions, isomerizations, epimerization, and rearrangements may be induced by the alkaline conditions of the reactions with alkali azides in these systems. Furthermore, in recent years several novel methods have been introduced for this kind of transformation, for example, it has been found that sodium azide impregnated on a calcium cation exchange Y-type zeolite (CaY) induced the nucleophilic ring opening of epoxides in aprotic solvents affording azidohydrins.[16] Other reported reagents are tributyltin azide without solvent and promoter,[17a] dibutyltin azide in DMF,[17b] triethylaluminum/hydrogen azide as a mild and efficient reagent for medium to large ring cyclic epoxides,[18a] diethylaluminium azide for the regio and stereoselective ring opening of 2,3-epoxyalcohols,[18b] trimethylsilylazide in the presence of a Lewis acid,[18c] and also trimethylsilylazide in presence of Cr (salen).[18d] In addition, it has been reported that simple salts, such as lithium or magnesium perchlorate, zinc or lithium triflate, and ammonium chloride can be used as efficient catalysts for the azidolysis of epoxides in acetonitrile.[19] Use of phase-transfer catalyst,[20a] and polymer-supported azide systems[20b] have also been reported for the preparation of azidohydrins. In most of these cases, the presence of a cation or a Lewis acid seems to be necessary to facilitate the cleavage of epoxides. However, the aforementioned methodologies are not without problems,

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such as difficulty in preparation and/or storage of reagents or catalysts, workup and isolation of products.

Recently we have reported the use of quaternized amino functionalized cross-linked polyacrylamide as an efficient polymeric phase-transfer catalyst in the synthesis of halohydrins.[21] In this report we describe the results that successfully led to the development of an efficient and simple method for the transformation of epoxides to β-azidohydrins using quaternized amino functionalized cross-linked polyacrylamide as an efficient heterogeneous polymeric phase-transfer catalyst.

Polyacrylamide cross-linked with divinylbenzene (2%) was prepared by free radical solution polymerization of the monomer mixture in ethanol using benzoylperoxide as an initiator and poly[*N*-(2-aminoethyl)acrylamide] was obtained by the transamidation reaction of cross-linked polyacrylamide with excess amounts of ethylenediamine.[8a,21] 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.

The synthetic utility of this modified polymer was explored by examining the reaction of epoxides with sodium azide for the preparation of β-azidohydrins using the polymer as a phase-transfer catalyst. The effects of solvent and molar ratio of the polymer on the ring opening reaction of epoxides were investigated. The reactions were carried out in wet tetrahydroforan, chloroform, dichloromethane, ethyl acetate, acetonitrile and water. The last two solvents proved to be the best (Table 1). The optimum molar ratio of the polymeric catalyst to epoxide was found to be 0.2:1.

The reactions of different epoxides with sodium azide were performed effectively and in high yields in water (Table 2, Scheme 1). The experimental results showed that acetonitrile can also be used as a solvent in this reaction, however, because of its toxicity, cost and environmental problems, water was preferred as the most suitable solvent.

Except for the reaction of styrene oxide (entry 1) and 1,2-butene oxide (entry 6) which produce a small per-

centage of the other regioisomer, the reaction of other epoxides were found to be highly regioselective and only one isomer was obtained. Also, in case of epichlorohydrin (entry 5), the diazido-alcohol product, and in cases 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 S_N2 conditions and is probably dictated by steric and electronic factors. In the reaction with styrene oxide, the azide ion attacks exclusively at the secondary carbon atom of the epoxide ring, a fact, which is reasonably well established.[15a,17b,18a,19a]

In order to get an insight into the role of poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride resin as a polymeric catalyst in this type of transformation, a series of reactions were performed on styrene oxide with NaN_3 in the presence of catalysts A–E (Table 3). Obviously, in the absence of any catalyst no reaction occurred. The reactions proceeded in the presence of all of these catalysts (entries 2–6), however, the rate of reaction was highest in the case of poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride resin E (entry 6).

In the case of poly[*N*(2-aminoethyl)acrylamide] (A), tetrabutylammonium bromide (C), and Amberlyst A-26 [Cl⁻ form] (D) (entries 2, 4, and 5), respectively, the rates were almost the same, but much lower than that of E (entry 6), and the rate when polyacrylamide (B) (entry 3) was used was very low. As for B, no quaternized site is present and the polymer is unable to act as a phase-transfer catalyst. Entry 7 shows that a combination of species A and C lowers the reaction time considerably compared to each one alone. All of these experimental facts lead us to believe that poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium halide resin (E) 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 attracting 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 epoxy molecule and amidic hydrogen of the polymer. This kind of catalytic activity is not possible in entries 4 and 5 where species C and D act only as phase-transfer catalysts.

In conclusion, poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium halide resin proved to be a highly efficient polymeric phase-transfer catalyst for regioselective ring opening of epoxides to azidohydrins by azide anion. It played a special role as an electrophilic catalyst, as well, for such reactions. The resin has the inherent advantages of a solid-phase transfer catalyst, including operational simplicity, filterability, regenerability, and reuse. In particular, workup of the reaction was very easy and pure products were isolated without any purification, and the
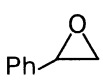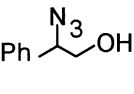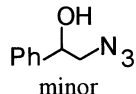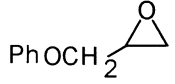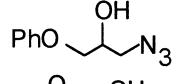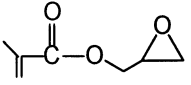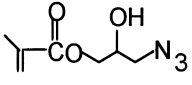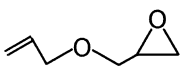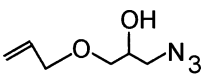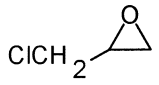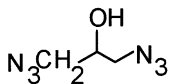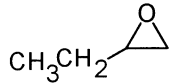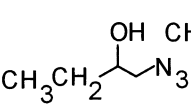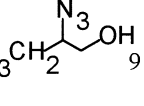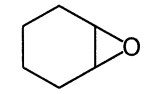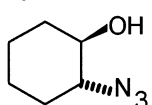
Table 1. The effect of the solvent on the reaction of styrene oxide with NaN_3 using the polymeric PTC[a]

Entry	Solvent	Time (h)	Conversion (%)
1	THF	6	8[b]
2	CHCl₃	6	0
3	CH₂Cl₂	6	0
4	EtOAc	6	5[b]
5	CH₃CN	3	100
6	H₂O	6	100

[a] The molar ratio of the polymeric catalyst to styrene oxide was 0.2:1.
[b] By GC.

Table 2. Reaction of epoxides with NaN_3 in the presence of poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride resin as PTC[a]

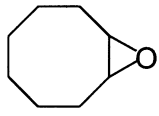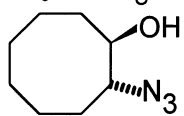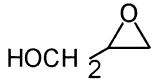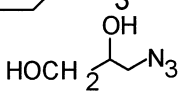| Entry	Epoxide	Solvent	Time (h)	Product[b]	Yield %[c]
1	Ph—epoxide	H_2O	6	Ph–CH(N_3)–CH_2OH ; Ph–CH(OH)–CH_2N_3 (minor)	95[d] (91,9)
2	PhOCH_2—epoxide	H_2O	12	PhO–CH_2–CH(OH)–CH_2N_3	94
3	CH_2=C(CH_3)C(O)O–CH_2—epoxide	H_2O	12	CH_2=C(CH_3)C(O)O–CH_2–CH(OH)–CH_2N_3	95
4	CH_2=CH–CH_2–O–CH_2—epoxide	H_2O	12	CH_2=CH–CH_2–O–CH_2–CH(OH)–CH_2N_3	92
5	ClCH_2—epoxide	H_2O	6	N_3CH_2–CH(OH)–CH_2N_3	90
6	CH_3CH_2—epoxide	H_2O	14	CH_3CH_2–CH(OH)–CH_2N_3 ; CH_3CH_2–CH(N_3)–CH_2OH (minor)	91[d] (81, 19)
7	cyclohexene oxide	H_2O	8	trans-2-azidocyclohexanol (OH, N_3)	89
8	cyclooctene oxide	H_2O/ CH_3CN	10	trans-2-azidocyclooctanol (OH, N_3)	87
9	HOCH_2—epoxide	H_2O	12	HOCH_2–CH(OH)–CH_2N_3	92

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 ratio determined for the products by proton-NMR .
c : Yield refers to isolated product.
d : Two regioisomers were obtained and the yield refers to both isomers.
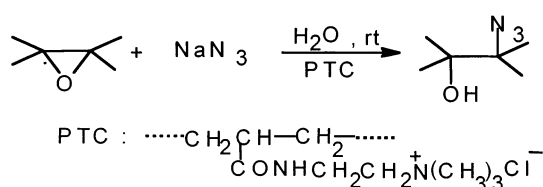
Scheme 1.

filtered polymeric catalyst could be recovered, and after changing to its Cl⁻ type 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 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) Preparation of poly[*N*-(2-aminoethyl)acrylamido]-

trimethyl ammonium iodide resin: poly[*N*-(2-amino-ethyl)acrylamide] was prepared as described in the literature.[8a,21] Poly[*N*-(2-aminoethyl)acrylamide] (5 g) was equilibrated in DMF (100 ml) for 12 h. Methyl iodide (20 ml, 320 mmol) and NaOH (1 g, 25 mmol) were added and the reaction mixture stirred at room temperature for 48 h. The quaternized polymer was collected by filtration, washed several times with water and methanol until the filtrate was free from CH_3I, as indicated by the absence of formation of AgI with $AgNO_3$. Finally the polymer was washed with ether and dried at 50°C under reduced pressure. Yield = 8.23 g (69%). Capacity = 3.06 mmol/g. The chloride form was obtained by exchange of the iodide in an aqueous solution of sodium chloride.

(B) Reaction of epoxide with sodium azide under PTC: To a mixture of epoxide (1.0 mmol) and sodium azide (5 mmol) in water (20 ml), was added poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride (~0.1 g). The suspension was stirred at room temperature for the lengths of time shown in Table 2. The progress of each reaction was monitored by TLC, using

Table 3. The reaction of styrene oxide with NaN_3 in water[a]

Entry	Catalyst[b]	Time (h)	Temp. (°C)	Conversion (%)
1	–	48	25	0
2	A	36	25	100
3	B	60	25	82
4	C	32	25	100
5	D	32	25	100
6	E	6	25	100
7	A+C	20	25	100

[a] The molar ratio of catalyst to epoxide was 0.2:1.
[b] The type of catalysts were: A: poly[*N*-(2-aminoethyl)acrylamide]; B: polyacrylamide; C: tetrabutylammonium bromide; D: Amberlyst A26; E: poly[*N*-(2-aminoethyl)acrylamido]trimethyl ammonium chloride.

CCl_4–ether (5:1) as eluent and/or GC. The polymer was removed by filtration. The products were obtained upon extraction with CH_2Cl_2. The organic solvent was dried with anhydrous Na_2SO_4 and the pure product was obtained upon evaporation of the solvent. Product characterization was performed using IR, ^1H and ^{13}C NMR spectroscopy.

Acknowledgements

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