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Nucleophilic Substitution Reactions Using Polyacrylamide-Based Phase Transfer Catalyst in Organic and Aqueous Media

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Dedicated to my dear friend and colleague Professor H. Forouzabadi on the occasion of his 65th birthday.

Poly [N-(2-aminoethyl) acrylamido] trimemethyl ammonium chloride was prepared and used as an effective heterogeneous phase-transfer catalyst. This modified polyacrylamide catalyzed nucleophilic displacement of alkyl halides for easy preparation of alkyl thiocyanates, alkyl cyanides, alkyl azides, and alkyl aryl ethers in high yields and short reaction times in organic and aqueous media under two-phase and triphase conditions. The catalyst can be recovered and reused several times.

Keywords: Heteronymous catalysis, Modified polyacrylamide, Phase transfer catalyst, Nucleophilic displacement

INTRODUCTION

Phase transfer catalysis is a widely accepted method in industry and organic synthesis as an effective synthetic tool by which liquid-liquid or liquid-solid phase-separated reactions are accelerated [1]. Extensive reviews both on chemistry and engineering viewpoints of phase transfer catalysts (PTC)s have been published in the last few decades [2]. PTCs are also widely used in manufacturing specialty chemicals [3]. Onium salts (ammonium, phosphonium and sulfonium salts), crown ethers and cryptands, and solvents and co-solvents have been widely used as PTCs [4]. These catalysts are generally not recovered and some of the ammonium and phosphonium salts form stable emulsions that lead to tedious work-up procedure. The concept of heterogeneous catalysis has been introduced to overcome these problems associated with the use of conventional soluble catalysts [5]. In this regard different kinds of polymer supported matrixes such as polystyrene based systems have been used with the nature of the matrix having a significant role in the success of the process [6-8]. Physiochemical incompatibility of the conventional polystyrene-supported species with solvents and substrates has led to the design of synthetic polymeric supports which are compatible with both aqueous and organic phases, such as polyacrylamide, polyvinylpyrrolidone, and poly ethylene glycol [9-11]. These supported systems were found to have different characteristics in terms of polarity, salvation, and reactivity compared to polystyrene-supported species.

Nucleophilic substitution reactions of different nucleophiles on alkyl halides in the presence of phase transfer catalysts are important and well-studied reactions in organic synthesis. Applying phase transfer catalysts for displacement reactions of alkyl halides in an organic phase with inorganic anions in an aqueous phase, that are inhibited because of phase separation was reported for the first time by Charles M. Starks in 1970 [12]. Since that time many papers on PTC and

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polymeric PTC assisted nucleophilic substitution reactions have been reported.

Thiocyanates are important sulfur-containing compounds for the synthesis of heterocycles [13]. They are reported as bactericide and also used in phytosanitary chemistry. Nucleophilic displacement of a leaving group with thiocyanate ion by use of different homogenous and especially heterogeneous phase transfer catalysts has been generally applied to the preparation of alkyl thiocyanates. Because of the problems in using homogenous PTCs much interest has been focused on the applications of heterogeneous PTCs. They especially provide easy separation of the catalyst and isolation of the thiocyanates. Polystyrene immobilized onium salts [6-8], polymeric cosolvents [14], and pseudo polymeric crown ethers [15] are among such heterogeneous systems. Many other various matrixes with different characteristics have also been used. Silica gel [16], polyethylene glycol [10], poly N-methyl-2-pyrrolidone [11], and poly pyridylthio group [17] are some examples. In almost all of these cases the reaction medium are organic or organic/water binary systems.

Nucleophilic displacement by cyanide ion on organic halides by using PTC which extends the carbon chain by one atom, providing an entry to carboxylic acid derivative, represents the most commonly used method for the preparation of nitriles. In addition to many homogeneous PTCs [18a,b], many heterogeneous polymeric PTCs such as onium salts immobilized on polystyrene resin [19], macrocylic polyethers and cryptands [20], and polymeric co-solvents [21] have been utilized in this regard with more or less success.

Alkyl azides are useful organic intermediate for synthesis of various nitrogen-containing compounds which are important in medicinal chemistry like heterocycles. They are also potential precursors of primary amines through reduction procedures. Quantitative conversion of halides to azides have been possible by using PTCs. Onium salts anchored to polystyrene matrix [7], PEG [22] and recently surfactant pillared clay materials [23] are some heterogeneous PTCs found in the preparation of azides.

Williamson synthesis is the most common procedure for the synthesis of ethers by substitution reaction of phenols or its derivatives on alkyl halides. PTCs are applied in these reactions to transfer phenoxides derivatives to the organic phase of alkyl halides. Solid phase co-solvents like polyamide and polyacrylamide [24], polyethylene glycol (PEG) [25], polystyrene resin-bound pyridinium salts [26], polymeric sulfoxide [27] and recently the pore surface of highly hydro thermally stable inorganic mesoporous materials [28] are the most common heterogeneous PTCs applied widely in Williamson synthesis.

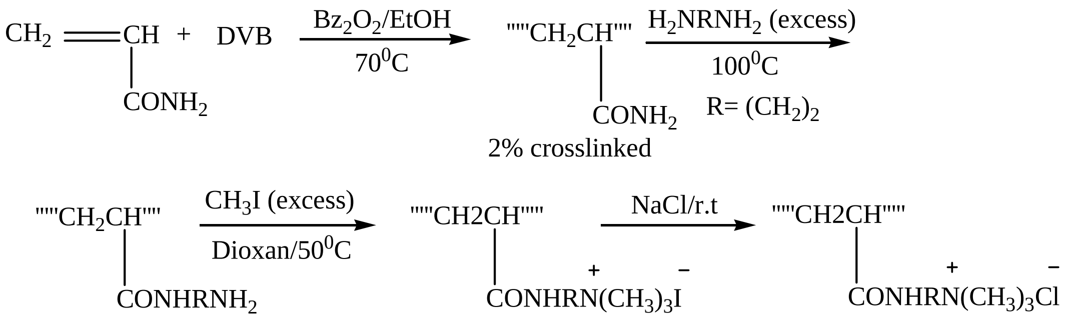
Organic reactions in water have recently attracted great interests [29a-c]. The substitution of organic solvent as reaction media by water minimizes the environmental impact, besides lowering the cost and decreasing operational danger. In addition to the economic and human aspects, water presents many physico–chemical properties that can be useful in the reactions, such as high polarity, ion solvating capacity, and the ability to form hydrogen bonds to form a structured liquid, and to aggregate apolar molecules dissolved in the water. Therefore, performing organic reactions in water may profit by these beneficial aspects. Most often the reaction medium for the nucleophilic displacement reactions are organic or organic/water binary systems. So, the concept of water mediated displacement reactions, as a green protocol, needs more attention.

In continuation of our studies on the use of modified polyacrylamide as a new heterogeneous phase transfer catalyst in organic synthesis [30] and as a new and more compatible polymeric catalyst for water mediated reactions [31], in this paper we report the use of polyacrylamide based phase transfer catalyst as an efficient heterogeneous PTC for preparation of alkyl thiocyanates, alkyl cyanides, alkyl azides and alkyl aryl ethers from alkyl halides in organic and aqueous media.

EXPERIMENTAL

Materials and techniques

crylamide (Fluka) was recrystallized from chloroform. Divinylbenzene (55%) (Fluka) was washed with sodium hydroxide solution (1%, 10 ml×2) and water (20 ml×3), to remove the inhibitor. Other reagents and solvents were used without further purification. Gas chromatography was recorded on a Shimadzu GC 14-A. IR spectra were run on a Perkin Elmer IR-157-G spectrophotometer. NMR spectra were recorded on a Bruker Avance DPX instrument (250 MHz). All products were characterized by comparison of their IR and NMR spectra and physical data with those of the authentic samples. All yields refer to the isolated products.



Scheme 1

Preparation of poly [N-(2-aminoethyl) acrylamido] trimethyl ammonium chloride

The polymeric catalyst was prepared as described in our previous papers [30a]. The capacity of the quaternized resin was determined both gravimetrically and by iodometric titration method. This was found to be 3.20 and 3.12 mmol per gram of the resin respectively.

Typical procedure

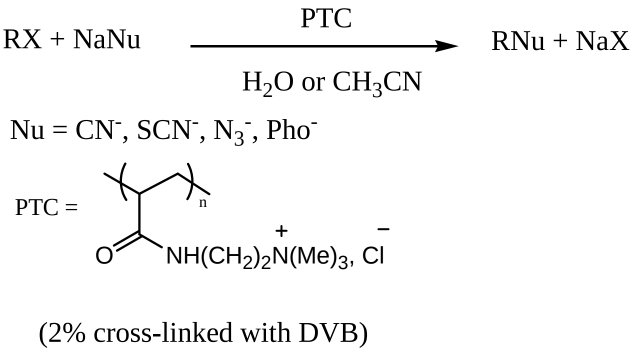
Preparation of alkyl thiocyanates, alkyl cyanides, alkyl azides, and alkyl aryl ethers under PTC in CH_3CN and H_2O:

To a mixture of alkyl halide and NaM (M=SCN, CN, N_3) in CH_3CN or $H_2O$was added poly [*N*-(2-aminoethyl) acrylamido] trimethyl ammonium chloride. The suspension was stirred under reflux condition for the lengths of time shown in Table 1. [For the preparation of alkyl aryl ethers PTC was added to a mixture of alkyl halides and phenol in aqueous NaOH solution (5%, 10 ml)]. Progress of the reaction was monitored by TLC, using *n*-hexane/ethyl acetate (7:3) as eluent and/or GC. After completion of the reaction polymeric catalyst and excess of salt were removed by filtration. The organic solvent was dried with anhydrous Na_2SO_4. The corresponding pure products were obtained upon evaporation of the solvent. In the case of water the product was obtained upon extraction with CH_2Cl_2. The characterization of products was performed by comparison of their FT-IR, ^{1}H-NMR, ^{13}C-NMR, and physical data with those of the authentic samples.

RESULTS AND DISCUSSIONS

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 ethylenediamine. 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 dioxane and subsequent exchange of the iodide anion with chloride [30] (Scheme1). The capacity of the quaternized resin was determined gravimetrically and by iodometric titration methods (titrated against AgNO3 using potassium chromate as end-point detection indicator) to be 3.12 and 3.20 mmol/g of the resin respectively.

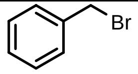
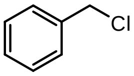
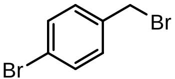
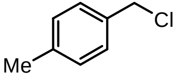
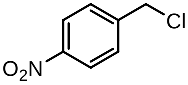
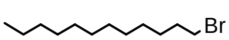
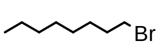
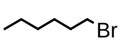
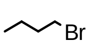
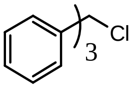
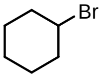
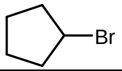
The synthetic utility of this modified polymer was studied by conversion of alkyl halides to their corresponding thiocyanates, cyanides, azides and alkyl aryl ethers (Scheme 2).



Scheme 2

Short reaction times with good to excellent yields express the effectiveness of the catalyst in accelerating the reactions.The effects of the solvent and molar ratio of the polymer to substrate on the substitution of alkyl halides were investigated. The reaction was carried out in different solvents

Table 1. Reaction of alkyl halides with nucleophiles in the presence of poly [N-(2-aminoethyl) acrylamido] trimethyl ammonium chloride resin as PTC in CH_3CN and H_2O [a]:

No	Substrates	Time: $CH_3CN(H_2O)$				Yields [b] (%): $CH_3CN(H_2O)$			
		SCN^-	CN^-	N_3^-	Pho^-	SCN^-	CN^-	N_3^-	Pho^-
1		5(10) min (5) min	2(3) h	1(2.30) h	-	95(93) (93)	95(90)	90(90)	-
2		15(30) min (10) min	5(6.30) h	1.30(3) h	-	92(90) (90)	92(88)	89(88)	-
3		5(10) min (5) min	2(3) h	45min(2h)	-	93(92) (90)	97(96)	96(96)	-
4		15(30) min (10) min	5(6) h	2(3) h	-	88(87) (85)	93(85)	87(85)	-
5		20(45) min (20) min	5(6) h	1.45(4) h	-	96(97) (90)	-	93(90)	-
6		2.5(5) h (2) h	4.30(-) h	10(-) h	-	89(88) (92)	85(-)	90(-)	-
7		2(4) h -(2) h	4.30(-) h	9(-) h		87(85) -(85)	85(-)	87(85)	
8		2(4) h (1.30) h	4(-) h	9(-) h	-	80(80) -(85)	80(-)	76(85)	
9		1.45(3) h (1.30) h	4(-) h	8(-) h	-	80(80) -(80)	75(-)	70(80)	
10		30mim(1h) -	2(2.30) h	30min(1.2h)		95(95[85,15])[c] -	93(92)	95(95)	
11		4(6) h -/2 h	10(-) h	12(-) h		84(80) (100)[d]	75(-)	83(-)	-
12		3(5) h (3.30) h	9(-) h	10(-) h	-	87(85) (70[80,20])[e]	87(-)	85(-)	-

a: All of the reactions were carried out under reflux condition. Molar ratio of PTC to alkyl halide was 0.1:1 for thiocyanates and 0.2:1 for cyanides and azides in CH_3CN and was .15:1 for thiocyanates, 0.25:1 for cyanides, 0.3:1 for azides.and 0.15:1 for alkyl aryl ethers in H_2O.

Products were identified by comparison of their IR and NMR spectra with those reported in the literature;

b: All products were obtained after 100% conversion and yields refer to the isolated products;

c: Structures and regiochemical ratios determined for the products by ^{13}C-NMR;

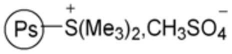
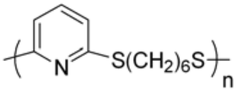
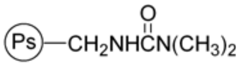
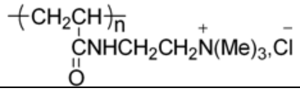
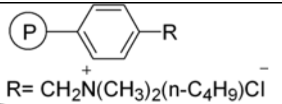
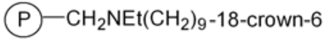
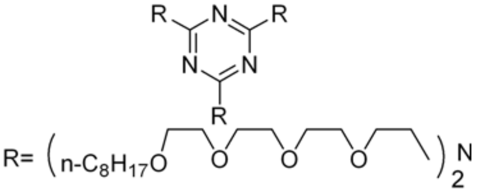
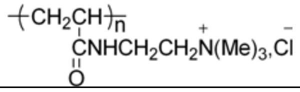
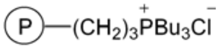
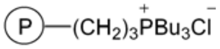
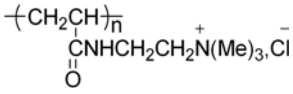
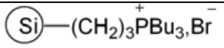
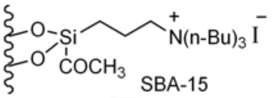
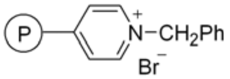
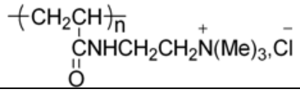
d: 100% conversion to cyclohexene (elimination product) by GC;

e: 70% conversion to substitution product (80%) and elimination product (20%) by GC.

such as EtOAc, THF, *n*-hexane, CH_2Cl_2, $CHCl_3$, H_2O, and CH_3CN. Acetonitile and water proved to be the best due to the polar nature of the catalyst and its compatibility with both organic and aqueous phases. Molar ratio of the polymeric catalyst to alkyl halide was optimized for each nucleophile in water and acetonitrile.

The corresponding alkyl thiocyanates were obtained in good to excellent yields in water and acetonitrile without the formation of any alkyl isothiocynates except in the case of ph_3ccl (Table 1). The characteristic ^{13}C-NMR and IR absorption bands for thiocyanates and isothiocyanates appeared at about 111 ppm, 2160 cm^{-1} (sharp), and 132 ppm, 1950-2100 cm^{-1} (broad) respectively.

Table 2. A comparison of the catalyst with some previous heterogeneous catalysts reported in the literature for nucleophilic substitution reaction on alkyl halides:

No	Catalyst	Product	Condition	Ref
	Preparation of *n*-octyl thiocyanates under different heterogeneous PTC			
1	Coated Silica Gel with KSCN	$C_8H_{17}SCN$	no solvent/30-80^oC/24h/97%	16
2	 $\text{Ps}-\overset{+}{S}(Me_3)_2,CH_3\overset{-}{SO_4}$	$C_8H_{17}SCN$	H_2O,T^a/100^oC/24h/80%	6
3		$C_8H_{17}SCN$	H_2O,T/100^oC/24h/64%	17
4	 $\text{Ps}-CH_2NH\overset{O}{\overset{\parallel}{C}}N(CH_3)_2$	$C_8H_{17}SCN$	H_2O,T/100^oC/24h/67%	21
5		$C_8H_{17}SCN$	H_2O/reflux/4h/85% or CH_3CN/ reflux/2h/87%	-
	Preparation of *n*-octyl cyanide under different heterogeneous PTC			
6		$C_8H_{17}CN$	Benzene,H_2O/110^oC/4h/92% or T,H_2O/110^oC/15h/98%	32
7	 $\text{P}-CH_2NEt(CH_2)_9\text{-18-crown-6}$	$C_8H_{17}CN$	H_2O,T/90^oC/7h/95%	33
8		$C_8H_{17}CN$	H_2O/80^oC/5h/48%	34
9		$C_8H_{17}CN$	CH_3CN/reflux/4.30h/85% or H_2O/reflux/10h/65%	-
	Preparation of alkyl azides under different conditions			
10	 $\text{P}-(CH_2)_3\overset{+}{P}Bu_3\overset{-}{Cl}$	PhN_3	H_2O/110^oC/1h/92%	7
11	 $\text{P}-(CH_2)_3\overset{+}{P}Bu_3\overset{-}{Cl}$	$C_5H_{11}N_3$	H_2O/110^oC/0.5h/63%	8
12	Surfactant pillared clay	PhN_3	H_2O,hexane/90-100^oC/6h/84%	23
13		PhN_3	H_2O/reflux/2.30h/90% or CH_3CN/reflux/1h/90%	-
	Preparation of alkyl aryl ethers using different heterogeneous PTCs			
14	 $\text{Si}-(CH_2)_3\overset{+}{P}Bu_3,\overset{-}{Br}$	$PhCH_2OPh$	CH_2Cl_2/25^oC/6h/97%	35
15	Polyacrylamide (PAA)	$C_7H_{17}OPh$	Dioxane,H_2O/75^oC/5h/75%	10
16		$PhCH_2OPh$	H_2O,T/70^oC/4h/98%	28
17		$PhCH_2OPh$	H_2O,Pho^-/100^oC/42%	26
18		C_4H_9OPh	H_2O,NaOH/reflux/1.30 h/ 80%	-

a: T: Toluene

Quantitative conversion of alkyl cyanides and alkyl azides were obtained in good to excellent yield in acetonitrile (Table 1). In aqueous media, benzylic alkyl halides were reacted readily, but conversion of aliphatic substrates to their corresponding nitriles and azides are not complete in acceptable times (Table 1). This is probably due to the lower nucleophilicity of cyanide and azide ion compared to thiocyanide and phenoxide ion.

The reaction of different alkyl halides with sodium phenoxide which is produced in situ during the reaction of phenol with aqueous solution of sodium hydroxide was performed effectively in high yields and in a short reaction time in aqueous media (Table 1). O-Alkylation has been predominated entirely in these reactions and no C-alkylation product has been observed. Primary alkyl halides give their corresponding ethers successfully, but secondary alkyl halides give also elimination product; Cyclohexyl bromide gives elimination product entirely and cyclopentyl bromide gives a mixture of substitution and elimination products. Tertiary alkyl halide failed to react due to the steric hindrance.

After completion of the substitution reactions the spent polymer was filtered, washed and dried. IR spectra and capacity of these polymers were the same as those of the original polymers. The polymer catalyst could be used as PTC for several times without considerable loss in their efficiency.

A comparison of the catalyst with some previous heterogeneous catalysts reported in the literature for nucleophilic substitution reaction on alkyl halides is shown in Table 2. In most of these cases the reaction medium for the displacement reactions are organic or organic/water binary systems. As seen the present method offers considerable advantages in terms of short reaction times, high yields, and green aqueous media in addition to inherent advantages of solid-liquid phase transfer catalyst.

CONCLUSION

In conclusion, utilizing this catalyst is cheap due to its recovery from reaction mixture and its preparation is easy. The resin could simply be recovered and reused several times without considerable loss in its capacity and efficiency. The workup of the reaction is very easy and the pure products can be isolated without any purification. Use of water as a green reaction media is the most important advantage of the present method.

ACKNOWLEDGMENT

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