Poly-*N*-haloacrylamides as polymeric solid phase synthetic reagents for α-halogenation of ketones

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Poly-*N*-bromoacrylamide (PNBA), poly-*N*-chloroacrylamide (PNCA) and poly-*N*-iodoacrylamide (PNIA) were prepared starting from commercially available polyacrylamide (PA) and were developed as new solid phase polymeric reagents for halogenation of ketones. PNBA was prepared by the bromination of polyacrylamide with bromine and potassium hydroxide in a suspension in carbontetrachloride. PNCA and PNIA were prepared by the reaction of *t*-butylhypochlorite and *t*-butylhypoiodite, respectively, on polyacrylamide. The active halogen contents of these reactive polymers, determined by iodometric titration, ranged from 3.8 to 7 meq g^{-1}. These insoluble, but swellable, reagents were found to effect preparative level conversion of ketones to α-haloketones. The spent reagents were regenerated and reused for five cycles of the halogenation reaction. The advantages of these polymeric halogenating agents include operational simplicity, longer shelf life, and the elimination of the hazardous nature characteristic of the analogous low molecular halogenating reagents like *t*-butylhypohalites. The reactivity of the PNBA was found to be much greater than the *N*-bromoamide function incorporated in a polystyrene matrix or the *t*-butylhypobromite function attached onto a polystyrene matrix. This points to the role of the polar polymeric matrix in facilitating the halogenation reaction by the *N*-haloamide function which is favoured in a polar environment.

(Keywords: poly-*N*-haloacrylamides; polymeric reagents; α-halogenation; ketones)

INTRODUCTION

A polymeric organic reagent can provide an effective alternative to its low-molecular weight counterpart if its design is such that it allows easier isolation of the desired product after the reaction, and if the polymeric by-product can be regenerated and recycled for further use. A number of reactive species have been attached to polymeric supports based on this idea and have been successfully used in organic synthesis[1-5]. The majority of the polymeric reagents prepared so far use crosslinked polystyrene as the support material on account of its commercial availability and ease of functionalization by a variety of substitution reactions in the aromatic ring[1]. It has been established that the nature of the polymeric support matrix has a significant role in the extent of swelling and hence on the course of the reactions on the soluble substrate[1,6-9]. The polarity of the support material is one of the most important features influencing the reactivity of the bound species with the substrate[10]. Thus, for example, the amino group in a crosslinked polystyrene matrix, crosslinked polyacrylamide matrix and in a soluble polyethylene oxide chain exhibits differing reactivity in synthetic transformations for the synthesis of peptides[11-13]. It has also been established that the degree of crosslinking and the topographical nature of the gel network affect the chemical reactivity of the attached functional groups[14]. The polyacrylamide support offers a contrast to the polystyrene matrix in terms of polarity. The polyacrylamide is extremely polar and hydrophilic whereas the polystyrene is non-polar and hydrophobic. The polyacrylamide-type gels have been widely used in affinity chromatography and gel electrophoresis of biological macromolecules on account of their polar nature. We thought of incorporating some simple reactive functions into the commercially available cheap polyacrylamide and comparing their reaction efficiency with similar systems attached to the non-polar hydrophobic polystyrene. Recently, we have reported the preparation of poly-*N*-bromoacrylamide and its application as an oxidizing reagent[15]. This reagent was found to have a much higher oxidizing efficiency compared with a *t*-butylhypobromite function attached to a polystyrene matrix[16]. The reaction duration required for the polystyrene-bound hypobromite function was found to be four to five times that for the polyacrylamide-based reagent. This paper describes the use of different poly-*N*-haloacrylamides for the α-halogenation of ketones. These polar polyacrylamide-based *N*-haloamides differ from the reagents supported on the polystyrene matrix[16] in that they have much higher capacity and require much less time for the halogenation reaction.

EXPERIMENTAL

*Preparation of poly-*N*-bromoacrylamide (I)*

Polyacrylamide (BDH, $\bar{M}_v = 5\,000\,000$, 5 g) was suspended in CCl_4 (75 ml) containing 5 ml of bromine in a

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Table 1 α-Halogenation of ketones using poly-*N*-haloamides[a]

Entry No.	Ketone	Reagent	Time (h)	Product[b]	Yield[c] (%)
1	Acetophenone	I	10	Phenacyl bromide	77
2	Acetophenone	II	12	Phenacyl chloride	30
3	Acetophenone	III	12	Phenacyl iodide	15
4	*p*-Methylacetophenone	I	8	p-Methyl phenacyl bromide	60
5	*p*-Methyl acetophenone	II	8	*p*-Methyl phenacyl chloride	25
6	*p*-Methyl acetophenone	III	8	*p*-Methyl phenacyl iodide	85
7	Cyclohexanone	I	9	2-Bromocyclohexanone	65
8	Cyclohexanone	III	12	2-Iodocyclohexanone	62
9	Acetone	I	8	Bromoacetone	Not isolated
10	Acetone	III	10	Iodoacetone	51
11	Methyl ethyl ketone	I	10	Bromomethyl ethyl ketone	58
12	Methyl ethyl ketone	III	12	Iodomethyl ethyl ketone	40
13	Acetophenone	VI	48	Phenacyl bromide	20

[a] All reactions were carried out in chloroform at 60°C using three to five times molar excess of the reagent

[b] Products were characterized by m.p (b.p), i.r., and n.m.r. analysis

[c] Isolated yield

250 ml round-bottom flask. Potassium hydroxide solution (25%, 25 ml) was slowly added to the suspension with stirring and cooling in ice. Stirring was continued for a period of 10 h. The insoluble product was filtered, washed with water (10 ml × 4 times) and methanol (10 ml × 2 times) and air-dried in an oven at 60°C to produce 5.5 g of poly-*N*-bromoacrylamide (orange granules). Capacity = 5.6 meq g^{-1}.

*Preparation of poly-*N*-chloroacrylamide (II)*

Polyacrylamide (3 g) was suspended in 50 ml CCl_4 containing 0.2 ml formic acid. *t*-Butylhypochlorite (10 ml) was added slowly with stirring and cooling in ice. After 10 h stirring, the product was filtered, washed with CCl_4 (10 ml × 4 times) and dried at 60°C. Yield = 3.5 g; capacity = 9.3 meq g^{-1}.

*Preparation of poly-*N*-iodoacrylamide (III)*

Polyacrylamide (3 g) was suspended in 60 ml CCl_4 containing 5 g iodine. *t*-Butylhypochlorite (8 ml) was added slowly with stirring. Stirring was continued for a period of 10 h. The product was filtered, washed with CCl_4 (till the washing was free of iodine) and dried at 60°C. Yield = 6.3 g; capacity = 5.3 meq g^{-1}.

*Preparation of *N*-bromoacetamido polystyrene (VI)*

Carboxymethyl polystyrene (IV), prepared from chloromethyl polystyrene by the method of Fréchet *et al.*[19] (5 g) was suspended in DMF (70 ml) and 5 ml $SOCl_2$ was added with stirring. Stirring at 70°C was continued for a period of 24 h. The product was filtered, washed free of $SOCl_2$ with DMF and then with methanol (10 ml × 3 times) and dried. The yield of the acid chloride was 5.1 g. I.r. (KBr): 1745 cm^{-1} (–COCl).

The above polymeric acid chloride (5 g) was again suspended in DMF (60 ml) and concentrated ammonia (25 ml) was added. The mixture was stirred at 70°C for 24 h and filtered, washed with DMF (10 ml × 3 times), water (10 ml × 5 times), methanol (10 ml × 3 times) and dried. Yield = 4.8 g. I.r. (KBr): 1670 (–CO) and 3400–3450 ($-NH_2$) cm^{-1}.

The polymeric amide was brominated by the same method described earlier for polyacrylamide. Yield = 4.2 g (starting with 4 g of the amide polymer); capacity = 0.8 meq g^{-1}; i.r. (KBr): 700, 1680, 3450 cm^{-1} (intensity decreased compared with the amide polymer, V).

*Determination of the capacity of the poly-*N*-haloamides by iodometric titration*

Poly-*N*-haloamide (100 mg) was suspended in water (20 ml) for 8 h. KI solution (10%, 10 ml) and 10% sulphuric acid (10 ml) were added to the suspension and the liberated iodine was titrated against standard thiosulphate solution using starch as indicator. From the titre value the amount of available halogen per gram of the polymer sample was calculated.

In the case of poly-*N*-iodoacrylamide no KI solution was used.

Halogenation of ketones: general procedure

Approximately 5 mmol of ketone was dissolved in 10 ml of $CHCl_3$. Three- to five-fold molar excess of the polymeric reagent, which was treated with 10% sulphuric acid, was added to the solution and the mixture was stirred at 60°C for the period indicated (*Table 1*). The reactions were followed by thin-layer chromatography (t.l.c.). After complete conversion, the polymer was filtered off and washed with a little solvent. The washings and the filtrate were combined and the solvent removed to obtain the product.

Recycling of the spent polymeric reagent

The spent polymer obtained from different halogenation reactions was combined and washed with $CHCl_3$ to remove any residual organic substrate or product. The washed polymer was dried and suspended in CCl_4 and halogenated as described earlier.

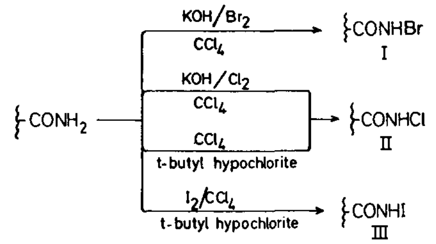
Table 2 Capacities of poly-*N*-bromoacrylamide after five cycles of regeneration

No. of cycles/regeneration	Capacity (meq g^{-1})
1	5.2
2	2.9
3	2.3
4	2.1
5	2.9

RESULTS AND DISCUSSION

Commercially available polyacrylamide was halogenated in CCl_4 by suitable reagents at 0°C to give the *N*-halogenopolymers. Potassium hypobromite was used for bromination, while *t*-butylhypochlorite and *t*-butylhypoiodite were used for chlorination and iodination, respectively (*Scheme 1*). The product polymers were washed free of the low-molecular weight reagents and unbound halogen. The *N*-halogenopolymers were insoluble in water in contrast to the starting polyacrylamide.

Scheme 1



The halogen contents of the product polymers were determined by iodometric titration. The poly-*N*-bromoacrylamide has a capacity of 5.2–5.7 meq g^{-1}; the values for the *N*-chloroderivative and the *N*-iododerivative were 8.6 and 5.1 meq g^{-1}, respectively. These values correspond to 78–90% conversion in the halogenation reaction.

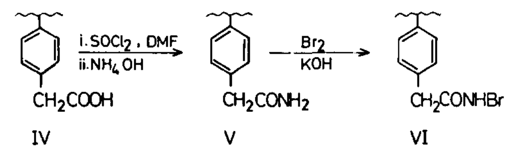
The infra-red (i.r.) spectra of the product polymers showed absorptions in the regions 3200–3500 (weak), 2940, 2870, 1690, 1455, 1375, 1200 and 760–780 cm^{-1}. In comparison with the i.r. spectrum of the starting polyacrylamide, the intensity of the broad band in the region 3200–3500 cm^{-1} in the case of the product poly-*N*-haloacrylamide decreased considerably. The solubility of the sample in deuterated solvents was too low for recording the nuclear magnetic resonance (n.m.r.) spectra. The *N*-halopolymers did not contain any amino group which could be formed by the possible Hoffmann-type degradation of amides on treatment with potassium hypohalites. This was confirmed by carrying out the sensitive ninhydrin colour reaction which detects amino groups up to a level of 0.1 μmol[17]. Gel permeation chromatography (g.p.c.) analysis of the poly-*N*-haloacrylamides before and after the halogenation reactions did not show any peak due to low-molecular weight fractions indicating the absence of any side reactions that degrade the polymer.

The *N*-halopolymers were used as reagents for α-halogenation of ketones. Both *N*-bromo and *N*-iodo polymers converted ketones to the corresponding α-haloketones (60–90% yield). But with *N*-chloro polymer the yields were comparatively less. The results of various halogenation reactions are presented in *Table 1*. The reagents were treated with 10% sulphuric acid prior to reaction. The polymeric derivatives act as halogen reservoirs and release the halogen into the solvent, which in turn reacts with the substrates. The low yields with poly-*N*-chloroacrylamide may be attributed to the fact that the chlorine released into the solvent during the course of the reaction was escaping as chlorine gas under the experimental conditions (60°C). The presence of free chlorine, bromine and iodine in the systems can be detected by the characteristic blue colouration with starch–KI paper for chlorine and bromine, and with starch paper for iodine.

The halogenation reactions were completed (as indicated by the complete disappearance of the substrate) in 8–12 h except in the case of chlorination. The reactions were monitored by t.l.c. At the end of the reaction the polymeric by-product was separated by filtration and the product was isolated by removal of the solvent.The spent reagents can be converted back to the original *N*-halogeno derivatives in a single step. These regenerated reagents were also capable of α-halogenation reactions. The capacities of the poly-*N*-bromoacrylamide after five cycles of regeneration are given in *Table 2*.

The capacity and reaction efficiency of these polymeric halogenating reagents were compared with those of similar reactive functions attached to the polystyrene matrix. Thus, an *N*-bromoamide function was introduced into the polystyrene matrix through the sequence of reactions shown in *Scheme 2*.

Scheme 2



The resulting polymer (VI) was found to have a capacity of 0.8 meq g^{-1}. All other conditions being the same, this reagent required 48 h for 20% bromination in the case of acetophenone. The reaction duration required for the halogenation using polystyrene-supported *t*-butylhypobromite under these conditions is 38 h for 48% conversion[16], whereas the poly-*N*-bromoacrylamide effected 77% conversion in 10 h. In contrast, bromination of ketones in near quantitative yields with polymeric pyridinium hydrobromide perbromide resins has been reported by Fréchet *et al.*[18]. It has been observed by these investigators that the bromination reactions occurred more smoothly in methanol than in chloroform or CCl_4 at room temperature, pointing to the role of the polarity of the solvent in promoting the reactions. The increase in the reaction efficiency in the present case compared with the polystyrene-supported reagent is attributable to the highly polar nature of the polyacrylamide matrix and its increased swelling behaviour which permits a more effective penetration of the soluble substrate into the polymer matrix. The efficiency could also arise from the fact that these polar polymers wet well with the acid and release halogen into the solvent. This observation is consistent with the results made on the polar pyridinium hydrobromide perbromide resins of Fréchet *et al.* In this connection, it is noteworthy that Fréchet's system does not use any acid.

In conclusion, poly-*N*-haloacrylamides reported here function as a new class of readily available and easy-to-use heterogeneous reagents for the preparative level α-halogenation of ketones. The advantages of these reagents include operational simplicity, longer shelf life and the elimination of the hazardous nature characteristic of the common low-molecular weight halogenating reagents like *t*-butylhypohalites. Comparison with similar systems attached to a hydrophobic polystyrene matrix points to the positive role of the polar polyacrylamide support in facilitating the halogenation reaction. Further studies with regard to the effect of crosslink density, effect of different solvents, temperature, etc., could throw much light on the course of these heterogeneous reactions occurring in the gel matrix. Studies along these lines are in progress.

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