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Polymer supported reagents containing pendant quaternary ammonium species for the α-halogenation of ketones

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The use of recyclable polymer supported benzyltriethylammonium dichloroiodate and tetrachloroiodate reagents in the α-halogenation of ketones by batch technique is described. The reagents were prepared by polymer analogous conversions using polystyrene crosslinked with ethyleneglycol dimethacrylate as the carrier matrix. Tetrachloroiodate reagent was found to have higher reactivity compared to dichloroiodate reagent. The effect of reaction conditions such as nature of the solvent, temperature and effective molar concentration of the reagent were investigated. © 1997 Elsevier Science Ltd. All rights reserved.

(Keywords: functionalized polymers; polymeric reagents; polystyrene supports)

INTRODUCTION

When the functional polymer itself reacts to transform a low molecular weight substrate to a product, it is coined as a polymeric reagent. It has been established that the nature of the polymer support material has a significant role in directing the course of the reactions with soluble substrates[1–5]. The reactivity of a support material is also dependent on the type of porous structure and size of the material. A change in the reactivity and specificity of a functionalized polymer is due to various physico-chemical effects arising due to intrinsic polymeric properties[6–11]. It has also been found that polarity of the support, degree of crosslinking, and the topographical nature of the gel network can affect the overall reactivity of a functional polymer[12,13]. The facile removal of the insoluble spent resin by simple filtration, regenerability and recyclability all contributed to the persistent popularity of supported reagents[14]. In the past few decades, a considerable amount of research has been aimed at gaining a better understanding of the structure–reactivity correlation of polymers. The aim of this paper is to illustrate the basic framework of functionalized polymer with their reactivities in chemical modification and in application in organic synthesis in an attempt to achieve more selectivity. This paper describes the preparation and synthetic application of some insoluble polymer supported polyhalide reagents containing pendant quaternary ammonium species for the α-halogenation of ketones.

EXPERIMENTAL

General

Solvents were purified and dried following standard procedures. The resin used was 2% EGDMA crosslinked polystyrene prepared by suspension copolymerization[15]. All the low molecular weight substrates used were commercially available samples purified by distillation or crystallization. Chloromethyl polystyrene was prepared by chloromethylation of the polystyrene support following standard procedures[16,17]. Microanalyses were performed at the Regional Sophisticated Instrumentation Centre at IIT Madras and CDRI Lucknow. Melting points were determined on a hot stage melting point apparatus. I.r. spectra were recorded on a Perkin–Elmer 397 spectrometer using KBr pellets and FT far i.r. spectra on a Bruker IFS 66V spectrometer using polyethylene pellets. Thin layer chromatography (t.l.c.) was performed on precoated silica gel plates.

Preparation of benzyltriethylammonium chloride resin

Chloromethyl polystyrene resin (10 g), preswollen in dioxan (30 ml), was refluxed with triethylamine (25 ml) in carbon tetrachloride at a temperature of 60°C for 80 h. The product was collected by suction filtration. The resin particles were Soxhlet extracted with ethanol for 15 h and finally washed with chloroform, acetone (30 ml × 3 each) and dried to constant weight. Yield = 13.1 g; capacity = 3.89 meq g^{-1}.

Preparation of benzyltriethylammonium dichloroiodate reagent

Polystyrene based benzyltriethylammonium chloride resin (12 g), preswollen in dichloromethane (25 ml) for 10 h, was cooled to 0°C. A solution of iodine monochloride in glacial acetic acid (0.5–1 M, 50 ml) was added to the cold suspension and stirred at a temperature of 0°C for 3 h. Stirring was continued for a further 6 h at room temperature. The resin particles were collected by suction filtration, washed with glacial acetic acid, chloroform and dried. Yield = 14.5 g; capacity = 1.31 meq g^{-1}.

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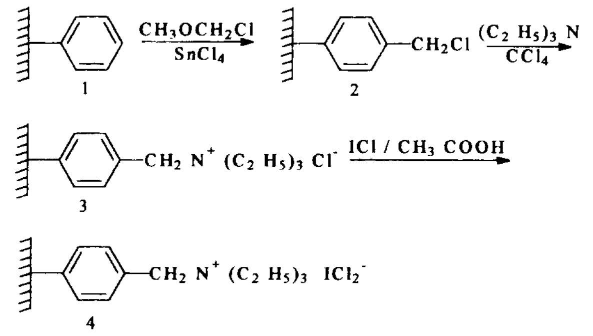


Scheme 1 Preparation of polystyrene based benzyltriethylammonium dichloroiodate reagent

Preparation of benzyltriethylammonium tetrachloroiodate reagent

The benzyltriethylammonium chloride resin (12 g), was suspended in chloroform (50 ml) for 10 h and cooled to 0°C. A solution of iodine trichloride in glacial acetic acid (0.5–M, 50 ml) was slowly added to the cold suspension with efficient shaking and stirred at a temperature of 0°C for 3 h. Stirring was continued for a further 6 h at room temperature. The resin particles were collected, washed repeatedly with glacial acetic acid and chloroform and dried to constant weight. Yield = 16.3 g; capacity = 1.1 meq g^{-1}.

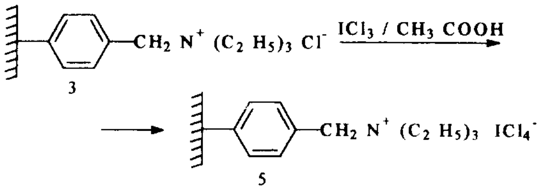
Halogenation of ketones

The ketone (3 mmol), dissolved in chloroform (20 ml), was stirred with a two-fold molar excess of the polymer supported polyhalide reagent. The reaction was followed by t.l.c. After the reaction, the partially spent resin was filtered and washed with chloroform. The combined filtrate and washings were concentrated. The residue obtained was treated with 1% $NaHSO_3$ solution and extracted with $CHCl_3$; evaporation of the solvent afforded the corresponding α-halo derivatives. The products were purified and characterized by comparison (m.p./b.p. and i.r. values) with authentic samples.

RESULTS AND DISCUSSION

Two percent ethyleneglycol dimethacrylate (EGDMA) crosslinked polystyrene beads (200–400 mesh) were functionalized to give polymer bound benzyltriethylammonium dichloroiodate by a three step reaction. The reaction sequence is depicted in *Scheme 1*.

Crosslinked polystyrene beads were converted to chloromethyl polystyrene resin using chloromethyl methyl ether as the electrophilic source and anhydrous stannic chloride as Lewis acid catalyst[16,17]. The resin (**2**) on reaction with excess triethylamine afforded the polymer bound benzyltriethylammonium chloride resin (**3**). Polystyrene-based benzyltriethylammonium dichloroiodate resin (**4**) was prepared by adding a solution of iodine monochloride in glacial acetic acid to a suspension of quaternized polymer beads in dichloromethane. The functional group conversions were monitored by i.r. spectral and analytical data. The i.r. spectra of the chloromethyl polystyrene resin showed absorption bands at 1260 cm^{-1} (CH_2Cl str) and 700 cm^{-1} (C–Cl str). When the chloromethyl resin was converted to the quaternized resin, the i.r. bands corresponding to CH_2Cl group almost disappeared. New bands corresponding to 1170 cm^{-1} (C–N str) and 2880 cm^{-1} (CH_2-methyl CH str) was found to occur. The dichloroiodate resin gave strong absorption bands at 215 cm^{-1} and 120 cm^{-1} characteristic of ICl_2^- species in the far i.r. spectrum, ascertaining the formation of polyhalide anion species.



Scheme 2 Preparation of polystyrene based benzyltriethylammonium tetrachloroiodate reagent

The resin (**3**) gave the qualitative test for chloride ions proving its ionic nature. The capacity of the resins (**2**) and (**3**) were determined by Volhard's estimation of chloride ions and the functional group capacity of dichloroiodate resin (**4**) by the iodometric method. The formation steps were found to take place almost quantitatively as evidenced by the percentage of halogen and nitrogen contents. The capacity of the reagent was found to be 1.31 meq g^{-1} of dry resin.

Tetrachloroiodate anionic species was incorporated by the reaction between a solution of iodine trichloride in glacial acetic acid and the suspended resin (**3**) in chloroform (*Scheme 2*). The formation of tetrachloroiodate function was ascertained by absorption bands at 250 cm^{-1} (ICl_4^- species). A small shoulder around 220 cm^{-1} (ICl_2^- species) was also observed. This indicates the presence of some ICl_2^- species also. This is probably due to greater steric repulsion because of the large size of ICl_4^- molecules. The average functional group capacity was found to be 1.1 meq g^{-1}.

Halogenation of carbonyl compounds

The 2% EGDMA crosslinked polystyrene bound benzyltriethylammonium dichloroiodate and tetrachloroiodate resins were used as reagents for α-halogenation of ketones. The reagents effectively transformed carbonyl compounds to the respective α-chlorinated compounds. The reaction was carried out by suspending the reagent in chloroform containing the carbonyl compound to be halogenated and stirred at room temperature. After the reaction, the spent resin was collected. The course of the reaction was monitored by t.l.c. The filtrate was further treated with 1% $NaHSO_3$ solution and extracted with chloroform which on evaporation afforded the corresponding monohalogenated product. The crude product was further purified by recrystallization or distillation and characterized by comparison with authentic samples (m.p./b.p. and i.r. data). The details of individual halogenation reactions using dichloroiodate and tetrachloroiodate reagents are presented in *Table 1*.

Small molecules such as 2-butanone and acetone were found to react much faster. The higher reaction rate can probably be due to the fact that small molecules can diffuse easily and concentrate within the polymer domains where there is a high local concentration of the active species. The reaction of acetophenone using dichloroiodate reagent was completed in 12 h while for acetone it required only 5 h.

When unsymmetrical ketones were subjected to halogenation, the reaction occurred at the more highly

Table 1 Halogenation of carbonyl compounds using EGDMA crosslinked polystyrene based benzyltriethylammonium dichloroiodate and tetrachloroiodate reagents

	Reaction period[b] (H)			Isolated yield (%)		
Substrates[a]	4	5	Products[c]	4	5	m.p./b.p. (°C)
Acetophenone	12	9	2-Chloroacetophenone	82	82	56
2′-Hydroxyacetophenone	11	7	2-Chloro-2′hydroxyacetophenone	80	80	72
4′-Chloroacetophenone	20	15	2-Chloro-4′-chloroacetophenone	90	88	102
4′-Methoxyacetophenone	20	12	2-Chloro-4′-methoxyacetophenone	71	73	96
4′-Nitroacetophenone	24	20	2-Chloro-4′-nitroacetophenone	85	83	107
Cyclohexanone	9	8	2-Chlorocyclohexanone	77	75	(82/10 mm)
2-Butanone	11	10	3-Chloro-2-butanone	66	63	(115)
Benzylacetone	15	12	3-Chlorobenzylacetone	63	60	(227)
Acetone	5	-	Chloroacetone	Not isolated		

4, Dichloroiodate reagent; 5, tetrachloroiodate reagent

[a] Resin to substrate ratio, 2/1; solvent, $CHCl_3$; temperature, 30°C

[b] Includes preswelling time also

[c] Characterized by comparison (m.p./b.p. and i.r.) with authentic samples

substituted position. Thus 2-butanone on reaction with dichloroiodate reagent produced 3-chloro-2-butanone in 63% yield.

α-Halogenation reactions are usually catalysed either by an acid or a base. The purpose of the catalyst is to provide a small amount of enol or enolate[18]. In the present case the reaction is found to be an autocatalysed one. The reactivity of these reagents was found to be increased in the presence of small amounts of acid in the reaction mixture. It was also found that in the uncatalysed reaction, the addition of $CaCO_3$ almost stopped the reaction. This suggests that $CaCO_3$ neutralizes the acid produced in the course of the reaction which further inhibits the reaction by preventing the formation of enol.

The reaction efficiency of these polymeric reagents were compared with those of similar reactive functions attached to a divinylbenzene (DVB) crosslinked polystyrene matrix. Thus, the dichloroiodate function introduced into the DVB crosslinked polystyrene through similar polymer analogous reactions as detailed in the EGDMA crosslinked polystyrene resin was found to be less reactive. Under similar conditions, the time required for the halogenation of 4′-chloroacetophenone using EGDMA crosslinked polystyrene based dichloroiodate reagent was 20 h, whereas, the DVB crosslinked polystyrene based dichloroiodate reagent required 24 h. In both the supports, the tetrachloroiodate reagent required less time than the dichloroiodate reagents. The dichloroiodate reagent prepared on Amberylst A-26 has been reported to produce polychlorinated products[19]. Another closely related polymeric analogue, poly(styrene-*co*-4-vinyl pyridinium) dichloroiodate reagent reported by Sket *et al.* has been successful in preparing iodo derivatives from some cyclic ketones such as 1-indalone, diketones and enol acetates[20]. The low reactivity and high selectivity in the present case is attributed to the use of comparably low capacity resins. However, when compared to the similar low molecular weight reagent developed by Kajigaeshi *et al.*[21], the yield from the present polymeric resin was less. But here, the selectivity, operational simplicity and regenerability seem to provide additional advantages. The spent resin can be converted back to the original reagent by a simple process. The regenerated reagents were also capable of α-halogenation reactions. The capacities of the dichloroiodate reagent after recyclization steps have been found to be 1.31, 1.25, 1.17, 1.07 and 1.01 meq g^{-1} of the dry resin.

Table 2 Effect of solvent on α-halogenation of 4′-chloroacetophenone

	Reaction period (h)		Isolated yield (%)	
Solvent/solvent mixture	4a	4b	4a	4b
$CHCl_3$	24	20	88	90
CH_2Cl_2	24	20	85	87
CCl_4	24	20	63	65
CH_2Cl_2–MeOH (5/2 v/v)	20	15	88	90
$CHCl_3$–MeOH (5/2 v/v)	20	–	87	–
CCl_4–MeOH (5/2 v/v)	–	15	–	77
Cyclohexane	24	20	51	63

4a, 4b, DVB and EGDMA crosslinked polystyrene based dichloroiodate reagents respectively

Resin to substrate ratio, 2/1; temperature, 30°C

Effect of reaction parameters on the extent of halogenation reactions

Reactions using polymeric reagents are heterogeneous in nature as they are composed of solvated polymeric chains and a solvent phase containing the dissolved substrate. For effective interaction to occur, the reagent function attached to the support, the solvent phase and the substrate should be mutually compatible. Generally, this compatibility is very much dependent on the reaction parameters and by suitably adjusting the reaction conditions, the reaction rate and thereby yields can be increased. The reagent selected for the study was dichloroiodate and the substrate, 4′-chloroacetophenone. The experimental procedure adopted was similar to the earlier case. The amount of product formed after maximum conversion was noted in each case.

Effect of solvent

The solvent-swollen polymeric reagent behaves as a true gel which expands to a large extent in good solvents and the functional groups attached to the polymer are now exposed to the continuous phase. The halogenation reaction was carried out in solvents of varying polarity. The percentage conversions obtained are given in *Table 2*. In the present study, using dichloroiodate reagent, the conversion rate was low in nonpolar solvents like

Table 3 Effect of molar ratio on α-halogenation of 4′-chloroacetophenone

Molar ratio	Reaction period[a] (h)		Isolated yield (%)	
	4a	4b	4a	4b
1/1	24	20	41	39
2/1	24	20	88	90
3/1	22	18	90	92
4/1	21	17	92	95
5/1	19	12	95	96

4a, 4b, DVB and EGDMA crosslinked polystyrene based dichloroiodate reagents respectively
Solvent, $CHCl_3$; temperature, 30°C
[a] Includes preswelling time also

Table 4 Effect of temperature on α-halogenation of 4′-chloroacetophenone

Temperature (°C)	Reaction period (h)	Isolated yield (%)
20	24	60
30	24	88
40	20	89
50	16	89

4a, DVB crosslinked polystyrene based dichloroiodate reagent
Resin to substrate ratio, 2/1; solvent, $CHCl_3$

cyclohexane and carbon tetrachloride. These solvents can only swell the matrix, but cannot produce effective solvation at the reactive sites. The enhanced reaction rate in solvent mixtures may be due to the selective solvation effect as well as to the favourable ion–dipole interactions. The percentage yields were also found to be higher in chloroform solvent. The solvent mixture such as CH_2Cl_2–MeOH provided a better hydrophobic/hydrophilic balance to the backbone as evidenced by high product yield.

Effect of molar concentration of the reagent

As the effective molar concentration of the polymeric reagent was increased, α-halogenation reaction was found to be facilitated to a great extent. To study the dependence of the reactivity of the polystyrene based dichloroiodate reagent, the relative concentrations investigated were 1/1, 2/1, 3/1, 4/1 and 5/1. The studies revealed that when a high resin to substrate ratio was taken, maximum conversion was achieved in much less time. As the substrate to resin ratio was increased from 1/1 to 1/5, corresponding increase in the percentage yield was from 39 to 96%. Almost quantitative conversion was obtained when high molar concentration of the reagent was used in much reduced time. The results are presented in *Table 3*.

Effect of temperature

The dependence of temperature on the reactivity was studied in a range from 20°C to 50°C. The results are presented in *Table 4*. It was found that on increasing the reaction temperature, the amount of α-chloro-*p*-chloroacetophenone obtained increased gradually. At higher temperature the product obtained was exclusively the monochloro derivative.

The foregoing studies indicate that the recyclable polymer supported benzyltriethylammonium dichloroiodate and tetrachloroiodate reagents have high efficiency for α-halogenation of ketones in preparative levels. These reagents retained their physical form and have the desired advantages of solid phase reagents and stable for long periods.

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