Polymer-supported analogues of t-butyl hypohalites. Preparation and applications in synthetic organic chemistry

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Crosslinked polymer-supported analogues of t-butyl hypochlorite and t-butyl hypobromite were prepared and developed as a new class of recyclable solid-phase oxidizing and halogenating reagents. The preparation of these new reagents involved a three-step polymer-analogous reaction starting from styrene–divinylbenzene crosslinked polymer. A ketone functional group was introduced into the copolystyrene–2% divinylbenzene resin beads by a Friedel–Crafts reaction with bromoacetone. This functional group was then converted to a tertiary alcoholic function on the polymer support by a Grignard reaction with methylmagnesium iodide. The treatment of this tertiary alcohol resin with sodium hypochlorite or sodium hypobromite yielded the polymeric t-butyl hypochlorite or hypobromite. These hypohalites were estimated iodometrically. These reagents were found to oxidize primary and secondary alcohols to the corresponding carbonyl compounds in high yields. They were also found to be suitable for halogenation of carbonyl compounds and amides. The spent polymeric reagent after the oxidation or halogenation step can be easily removed by filtration and can be regenerated many times by treating with the sodium hypohalite without any loss of capacity.

(Keywords: t-butyl hypohalites; solid-phase organic synthesis; polymeric reagents)

INTRODUCTION

Polymer-supported solid-phase organic synthesis utilizes reactive residues attached to insoluble crosslinked polymeric supports as reagents for effecting functional group conversions. The separation of reactants from catalysts and products is the step in a chemical synthesis where many losses take place. Purification procedures like distillation, recrystallization and chromatography are never 100% efficient and are time-consuming. The field of immobilizing chemical reagents on crosslinked polymer supports has received wide application in recent years[1-5] after the introduction of the solid-phase peptide synthesis by Merrifield[6]. Polymers and polymeric reagents are easily separable from low-molecular-weight compounds; with crosslinked insoluble polymers simple filtration is usually sufficient; ultrafiltration or selective precipitation removes soluble polymers. This feature enables one to use a large excess of either the soluble low-molecular-weight substrate or the polymeric reagent in order to increase the reaction rates and yields. The crosslinked polymer can be easily cleaned of soluble reactants and products. This permits the polymeric reagent to be used in either columns or batch processes, and it may be regenerated several times. The attachment to the insoluble macromolecular matrix can also solve the problems of lability, toxicity or odour, often experienced with low-molecular-weight reagents. In addition, the polymeric matrix can be so selected or tailor-made to provide a specific microenvironment that may induce some specificity at the reaction site[7].

An attempt towards the realization of the advantages of polymeric reagents in the design and development of crosslinked polymer-supported analogues of t-butyl hypohalites forms the subject matter of this paper. t-Butyl hypochlorite, t-butyl hypobromite and t-butyl hypoiodite are versatile reagents used for effecting a vast number of synthetic reactions in laboratory and industrial organic synthesis[8]. These low-molecular-weight reagents are generally volatile, very sensitive to temperature and light, hazardous and have very short shelf-life unless stored at low temperatures[9,10]. It occurred to us that these undesirable characteristics of these versatile reagents can be to some extent minimized by incorporating the corresponding reagent functions into the crosslinked styrene–divinylbenzene polymer matrix without appreciable loss of reactivity. A major consideration in the present approach is the regeneration of the polymeric reagent via a single chemical step after its use in a synthetic transformation. This feature will lend versatility to the reagent via a single chemical step after its use in a synthetic regeneration on columns.

RESULTS AND DISCUSSION

Preparation and characterization of crosslinked polystyrene-supported t-butyl hypochlorite and t-butyl hypobromite

The solid-phase analogue of t-butyl hypochlorite was prepared by a three-step polymer-analogous reaction starting from styrene–divinylbenzene crosslinked polymer. In the present work commercially available 2% crosslinked polystyrene was used as the support because of its favourable physical characteristics and ease of functionalization. The reaction sequence is depicted in

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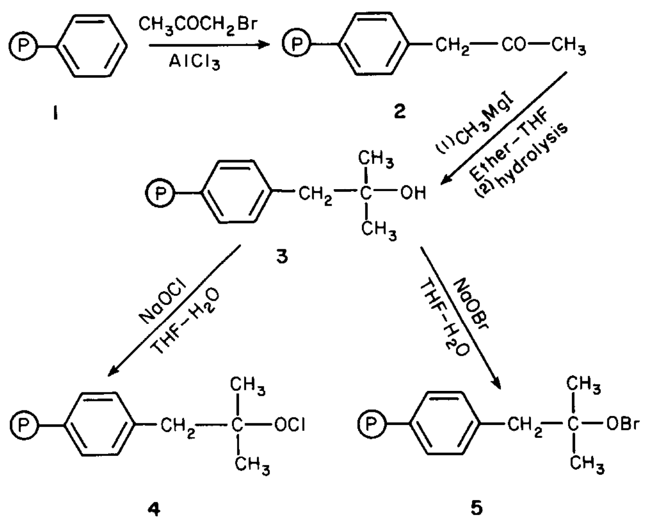


Figure 1 Preparation of polymer-bound t-butyl hypochlorite and t-butyl hypobromite

Figure 1. A ketone functional group CH_3COCH_2– was introduced into copolystyrene–2% divinylbenzene resin beads (**1**) by a Friedel–Crafts reaction with bromoacetone using Lewis acid catalyst. The ketone-incorporated resin (**2**) showed an intense carbonyl absorption at $1725\,cm^{-1}$ in the i.r. spectrum. This functional group was then converted to a tertiary alcoholic function by Grignard reaction with methylmagnesium iodide and hydrolysis. The absorption band at $1725\,cm^{-1}$ disappeared completely at this stage. The t-alcoholic resin (**3**) was allowed to react with sodium hypochlorite or sodium hypobromite in tetrahydrofuran–water mixture to afford the polymer-supported t-butyl hypochlorite (**4**) or the polymer-supported t-butyl hypobromite (**5**).

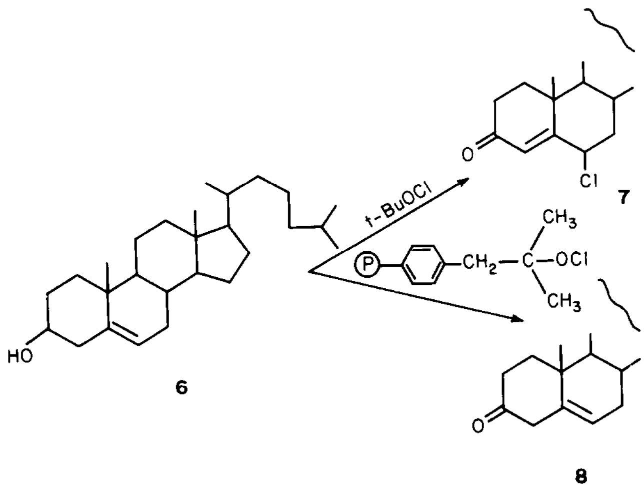
In all these steps of polymer-analogous conversions on the crosslinked macromolecular matrix, a remarkable dependence of the extent of conversions on the nature of the solvent and the extent of swelling was observed. Thus, in the Friedel–Crafts reaction step, the capacity of the resin **2** with respect to the CH_3COCH_2– group could be increased to about 2-fold when the starting resin was allowed to preswell in carbon tetrachloride for about 12 h. Similarly, the conversion of the keto group in the resin **2** to the alcoholic group by the Grignard reaction occurred more readily in a THF–ether solvent mixture than in pure ether. In the case of the preswollen resin the reaction was more facilitated. The extent of hypochlorite or hypobromite formation from the t-alcohol resin **3** was considerably enhanced when THF–water mixture was used as the solvent instead of pure water. These observations point to the role of the organic solvents in the swelling of the hydrophobic polystyrene matrix and thereby permitting the soluble reactants to diffuse into the crosslinked macromolecular matrix for effective reaction[11].

The polymer-supported t-butyl hypohalites retain the bead form characteristic of styrene–divinylbenzene copolymers prepared by suspension copolymerization[12]. They are easily filterable through sintered glass filters. The new resins undergo efficient swelling in carbon tetrachloride, chloroform or methylene chloride. The hypochlorite or hypobromite content of these resins can be varied at will by controlling the duration of the functionalization steps. The halogen content was determined by iodometric titration and verified by total halogen elemental analysis. The resins investigated in the present study contained 0.6 to 2.4 mmol of chlorine or bromine per gram of the resin. Qualitatively the hypochlorite or hypobromite function was detected from the evolution of iodine when treated with an acidified solution of 10% potassium iodide.

Oxidation of alcohols using polymer-bound t-butyl hypochlorite (4)

The t-butyl hypochlorite resin **4** was observed to be capable of oxidizing primary and secondary alcohols to the corresponding carbonyl compounds. Primary alcohols are converted to aldehydes and the secondary alcohols to ketones in isolated yields ranging from 80 to 98%. The oxidation conditions involve stirring of the alcohol with a 2-fold molar excess of the hypochlorite function in the resin in solvents like chloroform or methylene chloride at 50–60°C. The work-up of the reaction mixture involves just filtration of the spent residue, washing and removal of the solvent from the combined filtrate and washings to afford the oxidized product. The different alcohols which were oxidized using this procedure, the yield and conditions of oxidation are presented in *Table 1*.

Some striking differences in the oxidation process were observed when compared with the low-molecular-weight t-butyl hypochlorite oxidations in the case of some substrates. Thus, in the case of cholesterol (**6**), the low-molecular-weight reagent has been found to effect both oxidation and chlorination, yielding 6β-chloro-Δ^4-cholesten-3-one (**7**)[13]. When the oxidation was carried out with the new polymer-supported hypochlorite **4**, the product was Δ^5-cholestenone and no product of oxidation and subsequent chlorination was formed. A number of other cases of oxidation–chlorination have also been reported with the low-molecular-weight reagent[14,15].



In contrast to the above observation of only oxidation in the case of solid-phase polymer-supported hypochlorite, instead of oxidation–chlorination with the low-molecular-weight soluble analogue, in the case of benzoin both oxidation and chlorination occurred to 2,2′-dichlorobenzil with the polymer-supported reagent under identical conditions. Thus the absence of chlorination in the case of cholesterol appears to be due to the steric requirement of the crosslinked macromolecular matrix

Table 1 Oxidation of alcohols with polymer-supported t-butyl hypochlorite resins

Alcohol	Resin[a]	Duration of reaction (h)[b]	Product[c]	Isolated yield (%)	B.p. (M.p.) (°C)
η-Butyl alcohol	**4**	40	Butyraldehyde	90[d]	65
Benzyl alcohol	**4**	44	Benzaldehyde	98[e]	177
Cyclohexanol	**4**	42	Cyclohexanone	89	151
Cholesterol	**4**	40	Δ^5-Cholestenone	98	(127)
Cholesterol	**11**	96	Δ^5-Cholestenone	81	(127)
Menthol	**4**	43	Menthone	83[f]	207
Benzoin	**4**	40	2,2′-Dichlorobenzil	77	(121)

[a] 1.5-fold molar excess
[b] Includes preswelling also
[c] Characterized by comparison with authentic specimen
[d] 2,4-DNP derivative (70%)
[e] 2,4-DNP derivative (48%)
[f] Semicarbazone (69%)

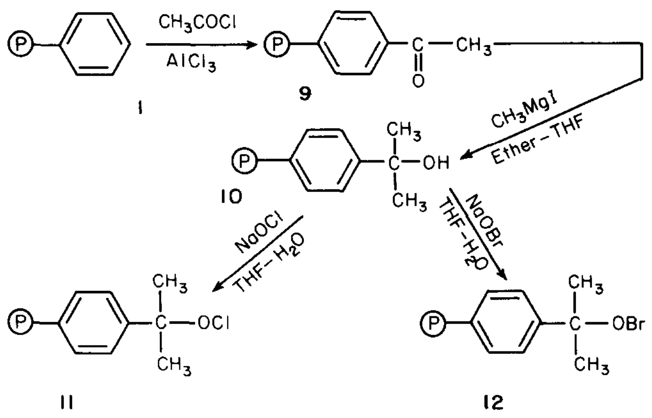


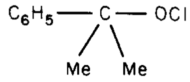
Figure 2 Synthesis of hypohalite resins with hypohalite functions adjacent to the polymer matrix

relative to the soluble reagent in approaching the rather rigid steroid substrate. In the case of the comparatively flexible benzoin substrate, such steric hindrance might be comparatively less and both oxidation and chlorination occur with the polymer-supported reagent as in the low-molecular-weight analogue. However, studies on well-defined model systems are required to draw definite conclusions in this regard.

Effect of the proximity of the functional group with the crosslinked matrix on the extent of the polymer-analogous conversions and oxidations

When the hydroxyl functional group was attached to the carbon nearest to the crosslinked styrene–divinylbenzene polymer matrix, a drastic reduction in the extent of the polymer-analogous conversion was observed in the hypochlorite and hypobromite formation steps. The speed of the oxidation step was also drastically reduced in the case of these resins. Thus, the maximum capacity achievable in the case of the hypochlorite resin (**11**) and the hypobromite resin (**12**), prepared as depicted in *Figure 2*, was 1.23 mmol g^{-1} and 1.11 mmol g^{-1} respectively even after 120 h of treatment with the corresponding hypohalite. But in the case of the resin **4** or **5** the capacity after 24 h of reaction was in the range 2.1–2.3 mmol g^{-1}. The oxidation reaction using the resin **11** was also found to be considerably slower than with the resin **4**. Thus for 81% conversion of cholesterol the resin **11** took 96 h in contrast to 40 h in the case of the resin **4** for 98% conversion.

This observation of the effect of a spacer methylene grouping between the polymer matrix and the reaction site in drastically changing the reactivity of the polymeric reagent is not surprising when one considers the reported increase in the catalytic activity of the systematic insertion of increasing methylene units between the polystyrene backbone and the catalytic centre[16–18]. Heterogeneous phase-transfer catalysts, such as phosphonium salts and crown ethers, immobilized on a polystyrene matrix, show an increase in activity approaching that of the corresponding non-immobilized catalysts, when they are bonded with long spacer chains to the polymeric support[16,17]. The effects of the insertion of one, two or three methylene units between the polystyrene backbone and the catalytic centre in such phase-transfer reactions have also been found to be very significant[18]. Such spacers allow the reaction site to protrude into the solution so that it is more solvated due to hydrophilic–hydrophobic balance and the approach by the soluble substrate is more facilitated. We are currently investigating the effect of the systematic insertion of a number of spacer groupings between the polystyrene matrix and the hypohalite sites in the reactions of the new resins. The reactivity of



$$C_6H_5—\underset{Me\;\;Me}{C}—OCl$$

a better model for the polymer, is a point to be considered in this connection in assessing the relative reactivities. In the light of the observed effect with just one spacer in the present case, it is expected that the reactivity could be substantially increased by further separating the heterogeneous matrix and the reaction site by suitable spacers.

Halogenations with the polymer-supported t-butyl hypohalites

The resins **4** and **5** were found to halogenate carbonyl compounds and amides in high yields. Thus, the t-butyl hypochlorite resin **4** chlorinates benzil to give 2,2′-dichlorobenzil and the hypobromite resin **5** brominates acetone, ethyl methyl ketone and acetophenone to the corresponding α-brominated products. Phthalimide and benzamide were observed to undergo *N*-chlorination on treatment with the hypochlorite resin in 78 and 82% yields respectively. In contrast to observation with the

Table 2 Halogenation of ketones and amides using polymer-supported hypohalite resins

Substrate	Resin[a]	Duration of reaction (h)[b]	Product[c]	Isolated yield (%)	M.p. (B.p.) (°C)
Acetophenone	5	38	Bromoacetophenone	48	51 (142)
Ethyl methyl ketone	5	40	1-Bromo-2-butanone	54	(129)
Acetone	5	40	Bromoacetone	Not isolated[d]	–
Benzoin	4	40	2,2′-Dichlorobenzil	77	121
Phthalimide	4	44	*N*-Chlorophthalimide	82	212
Benzamide	4	44	*N*-Chlorobenzamide	78	117

[a] 1.5-fold molar excess
[b] Includes preswelling also
[c] Characterized by comparison with authentic specimen
[d] Decomposed immediately

non-polymeric t-butyl hypochlorite reagent, cholesterol did not undergo oxidation–chlorination with the polymer-supported reagent, but only oxidation (see above). The details of the halogenation reaction with the two resins are presented in *Table 2*.

Recyclability of the spent resins for further reactions

The spent polymeric reagents from the oxidation or halogenation step can be regenerated in a single step without any loss of activity for subsequent reactions. The spent reagent can be freed effectively from soluble reagents or products by washing with solvents. The procedure for regeneration of the reagent functions is treatment with the sodium hypohalite in THF–water mixture. The capacity of the resins can be varied at will in the regeneration step just as in the original incorporation of the hypohalite functions. In the present study, the resins were recycled up to four times without any loss in capacity. The physical nature, filterability and swelling characteristics were found to be retained under these recycling conditions.

The foregoing investigations indicate that the essential requirements for a solid-phase polymeric reagent can be achieved in the design of crosslinked polystyrene-supported t-butyl hypohalites for organic oxidations and halogenations. The advantages of these new reagents include operational simplicity and recyclability. The reduction in reactivity compared to the non-polymeric analogue, characteristic of polymer-supported heterogeneous reactions, can be exploited to advantage in providing selectivity to the reactions. The styrene–divinylbenzene crosslinked support system selected in this case is more well defined and at the same time amenable to structural variations for studying the effect of crosslink density, functional group capacity and effect of spacers in the solid-phase oxidations or halogenations. In this context, these new resins are in contrast to the soluble *N*-chloronylons which have been introduced as polymeric oxidizing reagents by Schulz and coworkers[19–21] and the *N*-bromopolymaleimide introduced as brominating agent by Yaroslavsky *et al.*[22] The investigations on the effects of varying crosslink density, functional group capacity, different types of spacer groups and substrate–structure correlations are expected to shed much light on the nature of these solid-phase reactions and might eventually lead to the design of regio- and/or stereospecific oxidizing and halogenating agents. Studies along these lines are in progress.

EXPERIMENTAL

General

Infra-red spectra were taken on a Perkin–Elmer spectrometer with KBr pellets. Solvents were purified and dried following literature procedures. The resin support used was styrene–2% divinylbenzene prepared by suspension copolymerization or purchased from Fluka (Switzerland). Unless otherwise stated, all the low-molecular-weight substrates used were commercially available samples purified by distillation or crystallization. Bromoacetone was prepared by bromination of acetone following the literature procedure[23].

Friedel–Crafts reaction of bromoacetone with crosslinked polystyrene (1): preparation of 2-oxopropyl resin (2)

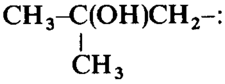
Styrene–2% divinylbenzene (200–400 mesh) beads were thoroughly washed with benzene, methylene chloride and carbon tetrachloride. The resin (9.8 g) was allowed to preswell in carbon tetrachloride (30 ml) for 12 h. Bromoacetone (20 g) was taken in a 500 ml round-bottomed flask fitted with a reflux condenser and cooled in an ice-bath. Anhydrous $AlCl_3$ (20 g) was added in small portions over a period of 10–15 min to the bromoacetone with stirring. After the addition was over, the preswollen polymer was gradually added to the reaction mixture with occasional shaking and continuous stirring. The mixture was heated under reflux (80°C) for 5 h and kept overnight at room temperature. The reaction mixture was poured into aqueous ethanol to break the Lewis acid complex. The resin particles were then collected on a glass filter and washed with water, ethanol, carbon tetrachloride, methylene chloride and methanol. The resin was dried *in vacuo* to constant weight. Yield: 11.8 g. CH_3COCH_2– capacity of the resin: 170 mg/g of the resin (2.98 mequiv/g). The resin showed a strong carbonyl absorption band at 1725 cm^{-1} in the i.r. spectrum (KBr).

When the reaction was conducted with the resin (not preswollen) for 2 h duration under the same conditions as above, the capacity of the resulting resin was only 93 mg/g corresponding to 1.63 mequiv CH_3COCH_2 per gram of the resin.

From a series of experiments, the procedure described above with the preswollen resin was chosen as the optimal conditions for obtaining the high-capacity resin.

Grignard reaction of 2-oxopropyl resin (2) with CH_3MgI: preparation of the t-alcohol resin (3)

Methyl iodide (6 ml) was added gradually to a suspension of magnesium turnings (2.5 g) and a crystal of iodine in dry ether (75 ml). When all the magnesium was dissolved, a suspension of the preswollen keto resin (2) (2.98 mequiv of CH_3COCH_2/g; 8 g) in tetrahydrofuran (75 ml) was added in small portions to the freshly prepared methylmagnesium iodide with constant stirring. The reaction mixture was heated in a water bath for 3 h. The resin was filtered, washed with alcohol, dilute H_2SO_4, THF–water, THF and methanol and dried *in vacuo* to afford the t-alcohol resin (3). Yield: 7.8 g. The polymer so obtained showed no carbonyl absorption in the i.r. spectrum. Capacity with respect to



$CH_3\text{–}\underset{\displaystyle CH_3}{\underset{|}{C}}(OH)CH_2\text{–}$: 2.86 mequiv/g.

Treatment of the t-alcohol resin (3) with sodium hypochlorite: preparation of polymer-supported t-butyl hypochlorite (4)

The t-alcoholic resin (3) (5 g) was allowed to swell in THF (100 ml) for 12 h. To this a 2 M solution of sodium hypochlorite (70 ml) was added with cooling in an ice-bath and stirring. The reaction mixture was stirred for 24 h at room temperature. The resin was filtered, washed with water, THF, methylene chloride and chloroform and dried *in vacuo* to constant weight. Yield: 4.6 g. Analysis: Cl 8.3%; capacity of the resin: 2.33 mequiv Cl/g.

Estimation of the hypochlorite function in the resin 4

The resin (100 mg) was suspended in 20 ml of glacial acetic acid and stirred for 12 h. The suspension was warmed gently with 10 ml of 2 N H_2SO_4 and 10 ml of 10% KI solution were added. The liberated iodine was titrated against standard thiosulphate solution using starch as indicator. From the titre value the equivalent of chlorine in the resin was calculated. Capacity of the resin obtained in the treatment of t-alcohol resin with aqueous NaOCl: 0.56 mequiv Cl/g; capacity of the resin obtained in the treatment of the t-alcohol resin (preswollen in THF for 12 h) with NaOCl in aqueous THF: 2.33 mequiv Cl/g.

Preparation of polymer-supported t-butyl hypobromite (5)

The t-butyl alcohol resin (3) (2 g) was treated with sodium hypobromite under identical conditions as in the preparation of the hypochlorite resin (4). Yield: 1.85 g. Analysis: Br 18.7%. The capacity of the resin was also determined by an iodometric procedure described in the case of the hypochlorite resin (4). Capacity: 2.33 mequiv Br/g.

Oxidation of alcohols with the hypochlorite resin (4): general procedure

The alcohols (~1 g) dissolved in chloroform (20 ml) was stirred with a 1.5-fold molar excess of the polymeric t-butyl hypochlorite. The reaction was followed by thin-layer chromatography. After the completion of the reaction, the resin was filtered and washed with chloroform. The combined filtrate and washings on evaporation of the solvent afforded the corresponding carbonyl compounds. The details of the individual oxidations are presented in *Table 1*. The products were identified and characterized by comparison (m.p. and i.r.) with authentic specimens.

Halogenation of ketones and N*-chlorination of amides with the hypohalite resins*

The experimental procedure followed was exactly analogous to the oxidation procedures. The details of the individual reactions are presented in *Table 2*.

Recycling of the spent hypohalite resins

The spent hypochlorite resin (3 g) from different oxidation reactions was washed successively with chloroform, methylene chloride, THF and chloroform (20 ml each; three times) and dried *in vacuo*. The dried resin was allowed to preswell in THF. This was treated with a 2 M solution of sodium hypochlorite in aqueous THF as described earlier. The regenerated resin was found to have a capacity of 2.30 mmol Cl/g.

The spent hypobromite resin was also regenerated analogously.

Acetyl polystyrene resin (9)

Polystyrene resin (10 g) was treated with acetyl chloride (20 g) and anhydrous aluminium chloride (20 g) in carbon tetrachloride analogous to the preparation of the resin 2 (see above). Yield: 12.0 g. Capacity: 167 mg acetyl groups/g of the resin corresponding to 3.88 mequiv of CH_3CO/g.

t-Alcoholic resin (10)

The ketoresin **9** (10 g) was treated with methylmagnesium iodide freshly prepared from methyl iodide (6 ml) and magnesium turnings (2.5 g) analogous to the preparation of the resin **3**. Yield: 9.7 g.

Hypochlorite resin (11)

The alcoholic resin **10** (5 g) was treated with the sodium hypochlorite solution. The duration of the reaction had to be increased to 96 h to achieve maximum capacity of 1.23 mmol of Cl/g.

Hypobromite resin (12)

The alcoholic resin **10** (4 g) was treated with sodium hypobromite as in the preparation of the resin **5** for 96 h to obtain the hypobromite resin **12** with capacity 1.11 mequiv/g.

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