Halogenation Using Quaternary Ammonium Polyhalides. XX.[1] Bromination of Phenols with Polymer-Bound Benzyltrimethylammonium Tribromide

Takaaki KAKINAMI,* Hiroyuki SUENAGA, Tadashi YAMAGUCHI, Tsuyoshi OKAMOTO, and Shoji KAJIGAESHI*,†
Department of Industrial Chemistry, Ube Technical College, Tokiwadai, Ube 755
†Department of Industrial Chemistry, Faculty of Engineering, Yamaguchi University, Tokiwadai, Ube 755
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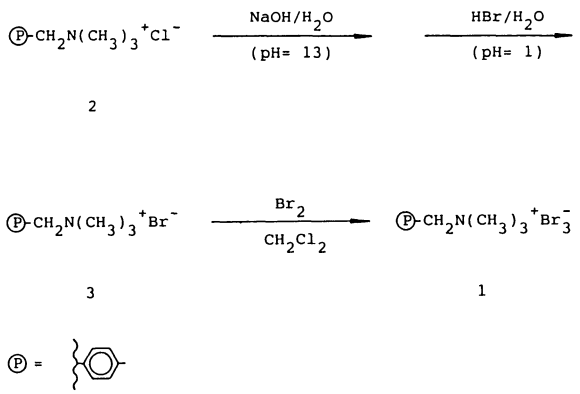
Synopsis. Bromo-substituted phenols were obtained quantitatively by passing a solution of phenols in dichloromethane-methanol through a column packed with styrene polymer-bound benzyltrimethylammonium tribromide.

Subsequent to Merrifield's report of the solid-phase peptide synthesis in 1963,[2] a number of functional polymers have been found, and the development of the regeneratable polymers as support is even now an interesting subject regarding organic synthesis. During the course of our investigation on the bromination of aromatic compounds with benzyltrimethylammonium tribromide (BTMA Br_3),[3] we happen to think of the use of polymer-bound BTMA Br_3 (Ⓟ-BTMA Br_3) (**1**) as a brominating agent.

Cacchi et al. have already reported the α-bromination of ketones by the use of a polymeric brominating agent (Amberlyst A 26-Br_3^- form).[4] However, their bromination method was carried out by mixing ketones with the insoluble polymeric agent in a solvent in the usual way. In this paper we wish to report on a facile bromination of phenols by the use of a column packed with **1**.

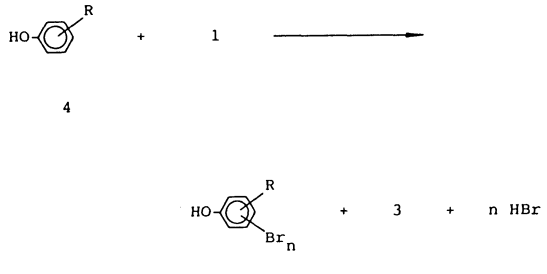
Results and Discussion

Our polymeric agent **1** (orange red) was readily prepared from AGl-X_2 (**2**) (100—200 mesh, chloride form), which was a commercially available (Bio-Rad Laboratories, USA) anion exchange resin containing a quaternary ammonium group, as shown in Scheme 1:



Scheme 1.

Passing a solution of phenols (**4**) in dichloromethane-methanol through a column packed with **1** at room temperature gave bromo-substituted phenols (**5**) in quantitative yields (Scheme 2). As shown in Scheme 2, polymer **1** is transformed into a colorless



Scheme 2.

Ⓟ-BTMA Br^- (**3**) which can be easily regenerated to the original **1** by passing a solution of bromine in dichloromethane through the column. Still, $CaCO_3$ powder was used for the bromination of phenols bearing electron-attracting groups, because $CaCO_3$ should activate these inactive aromatic ring by the formation of the phenolate ion. The results are summarized in Table 1.

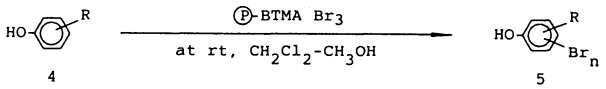
We have already prepared **5** by the reaction of **4** with BTMA Br_3, a soluble reagent in dichloromethane-methanol, at room temperature.[5] However, the procedure using **1** thus provides a facile method of obtaining bromo-substituted products from the corresponding aromatic compounds, owing to the ease of the operation and the capability of regeneration of the reagent. We believe that this method using **1** may be satisfactorily applied for the industrial production of bromo-substituted aromatic compounds.

As a limitation of the procedure, the selective bromination of phenols is difficult since this method cannot be carried out stoichiometrically. Furthermore, attempts at the bromination of a more reactive **4**, such as 4-methoxyphenol, 5-methyl-1,3-benzenediol, 1,3,5-benzenetriol, 1-naphthol, and 2-naphthol, were unsuccessful because these substrates underwent oxidation by **1**.

Experimental

Preparation of Styrene Polymer-Bound BTMA Br_3 (1): To a stirred suspension of AGl-X_2 (**2**) (100 g) in water (300

Table 1. Bromination of Phenols **4** with Ⓟ-BTMA Br_3 (**1**)



4 5

Substrate (**4**) R		Product (**5**)		Yield[a] %	Mp/°C Found	Mp/°C Reported
H	(**4a**)[b]	2,4,6-Br_3	(**5a**)	97	94—95	95[6]
2-Me	(**4b**)	2,4-Br_2-6-Me	(**5b**)	98	57—58	56.5—57.6[7]
3-Me	(**4c**)	2,4,6-Br_3-3-Me	(**5c**)	99	82—83	81[8]
4-Me	(**4d**)	2,6-Br_2-4-Me	(**5d**)	97	46—47	49[9]
4-t-Bu	(**4e**)	2,6-Br_2-4-*t*-Bu	(**5e**)	99	70—71	70—71[10]
2,3-Me_2	(**4f**)	4,6-Br_2-2,3-Me_2	(**5f**)	96	68—69	67—68[5]
2,5-Me_2	(**4g**)	4,6-Br_2-2,5-Me_2	(**5g**)	99	78—79	79[8]
2,6-Me_2	(**4h**)	4-Br-2,6-Me_2	(**5h**)	99	78	80—81[11]
3,4-Me_2	(**4i**)	2,6-Br_2-3,4-Me_2	(**5i**)	96	39—40	39—40[8]
3,5-Me_2	(**4j**)[c]	2,4-Br_2-3,5-Me_2	(**5j-2**)	91	79—80	72—73[12]
4j		2,4,6-Br_3-3,5-Me_2	(**5j-3**)	97	167—168	166[13]
2-MeO	(**4k**)	4,6-Br_2-2-MeO	(**5k**)	91	66—67	64—65[14]
3-MeO	(**4l**)[c]	4,6-Br_2-3-MeO	(**5l-2**)	94	67—68	73—75[15]
4l	[b]	2,4,6-Br_3-3-MeO	(**5l-3**)	97	106—107	105[15]
2-Cl	(**4m**)[b]	4,6-Br_2-2-Cl	(**5m**)	97	78—79	76[16]
3-Cl	(**4n**)[b]	2,4,6-Br_3-3-Cl	(**5n**)	99	106—107	105—106[17]
4-Cl	(**4o**)[b]	2,6-Br_2-4-Cl	(**5o**)	97	88—89	92[18]
2-Br	(**4p**)[b]	2,4,6-Br_3	(**5a**)	96	93—94	95[6]
3-Br	(**4q**)[b]	2,3,4,6-Br_4	(**5q**)	97	113—114	113[19]
4-Br	(**4r**)[b]	2,4,6-Br_3	(**5a**)	99	92—93	95[6]
3-Me-4-NO_2	(**4s**)[b]	2,6-Br_2-3-Me-4-NO_2	(**5s**)	98	134.5—135	134[20]
4-Me-2-NO_2	(**4t**)[b]	6-Br-4-Me-2-NO_2	(**5t**)	99	68—68.5	68—69[21]
2-NO_2	(**4u**)[b]	4,6-Br_2-2-NO_2	(**5u**)	97	118	118[22]
3-NO_2	(**4v**)[b]	2,4,6-Br_3-3-NO_2	(**5v**)	97	87—88	89—90[23]
4-NO_2	(**4w**)[b]	2,6-Br_2-4-NO_2	(**5w**)	99	143	144[24]
2-COOH	(**4x**)[b]	4,6-Br_2-2-COOH	(**5x**)	98	220	228[25]
2-COOMe	(**4y**)[b]	4,6-Br_2-2-COOMe	(**5y**)	97	147—148	149[26]
2-COOEt	(**4z**)[b]	4,6-Br_2-2-COOEt	(**5z**)	98	101—102	101[26]
4-COOMe	(**4a′**)[b]	2,6-Br_2-4-COOMe	(**5a′**)	95	124.5—125	125[27]
4-COOEt	(**4b′**)[b]	2,6-Br_2-4-COOEt	(**5b′**)	97	108—108.5	108[27]
3-OH	(**4c′**)	2,4,6-Br_3-3-OH	(**5c′**)	95	111—112	111[8]
2-Me-3-OH	(**4d′**)	4,6-Br_2-2-Me-3-OH	(**5d′**)	99	101—102	102[28]

a) Yield of isolated product. b) $CaCO_3$ powder was used. c) This run was done in dichloromethane without methanol.

ml) we added 1-M aqueous sodium hydroxide (1M=1 mol dm^{-3}) at room temperature until the pH of the solution was indicated at about 13. The obtained precipitate was filtered and washed with water until it was neutral; a suspension of the above-mentioned powder in water (300 ml) was made sufficiently acidic (pH=1) with 1-M hydrobromic acid under stirring for 1 h at room temperature. The solid residue was then filtered and washed with water until neutral to give polymer-bound BTMA Br (**3**) as a white polymer; 47.2 g.

A dilute solution of bromine in dichloromethane was slowly added into a stirred suspension of **3** in dichloromethane (300 ml) until the color of bromine in the solution did not fade. The mixture was stirred overnight at room temperature; the obtained solid was filtered, washed with dichloromethane and dried under vacuum at room temperature to give a stable, orange red polymer **1**: yield 61.2 g; mp 210 °C.

2,4,6-Tribromo-3-methylphenol (5c); Typical Procedure: Compound 3-methylphenol (0.54 g, 5 mmol) in dichloromethane (20 ml)-methanol (20 ml) was adsorbed on **1** (50 g) packed in a column. The developing solvent (dichloromethane-methanol (3 : 1)) was passed through the column at a rate of 7 ml/10 min. In this case, the upper part of **1**, which reacted with the substrate, was completely decolorized. The obtained eluate (200 ml) was concentrated and treated with 5% aq solution of $NaHSO_3$ (10 ml); the mixture was then extracted with ether (40 ml×4). The ether solution was dried over $MgSO_4$ and concentrated in vacuo to give **5c** as a colorless crystals; yield 1.70 g (99%); mp 82—83 °C (lit,[8] mp 81 °C).

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