

Selective *para*-Bromination of Phenols via a Regenerable Polymer-bound Tetraalkylammonium Tribromide

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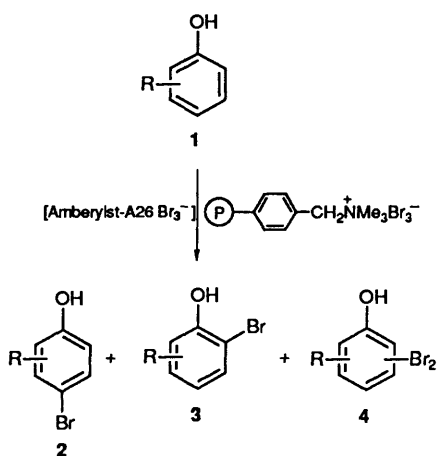
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Amberlyst-A26 resin in its tribromide form effects *para*-bromination of phenols with high yields and selectivity; the resin is easily recovered by filtration and can be reconverted into the tribromide form by addition of bromine.

The selective monobromination of phenols has always proved difficult as a result of the ease of polybromination. Therefore, it has been common practice to use more complex, multistage procedures to generate monobromophenols,¹ with all the attendant disadvantages. Our recent interest in the use of solids to catalyse and control organic reactions,² which has resulted in the discovery of a number of highly selective electrophilic aromatic substitution reactions,³ including bromination reactions,⁴ prompted us to consider the possibility of gaining control over the bromination of phenol by such means. We now report that the modified polystyrene ion-exchange resin, Amberlyst-A26,[†] in its tribromide form, is an excellent, regenerable reagent for selective *para*-bromination of phenols.

para-Bromination of phenols has previously been achieved by use of tetrabutylammonium tribromide in solution.⁵ This suggested the possibility of utilizing Amberlyst-A26 tribromide as a solid reagent for convenient *para*-bromination of phenols. Indeed, simply stirring a solution of phenol in dichloromethane with a slight excess of the resin tribromide, in the dark, for 24 h, resulted in the production of *para*-bromophenol in 86% yield with only 7% of the *ortho*-isomer.

The reaction was applied to a range of monosubstituted phenols (Scheme 1). In all cases the corresponding 4-bromo derivative was obtained in good to excellent yield (Table 1).



Scheme 1

The success of Amberlyst-A26 tribromide for selective *para*-bromination of phenols appears to be at variance with literature reports of polybromination of phenols with benzyltrimethyl-

Table 1 Yield of 4-bromophenol 2 and by-products according to Scheme 1

| R | t/h | Resin (mequiv) | Yield (%) ^a | | |
|-------|-----|----------------|------------------------|-------|-------|
| | | | 2 | 3 | 4 |
| H | 24 | 1.1 | 86 | 7 | trace |
| 2-MeO | 4 | 1.6 | 90(87) | 7(4) | trace |
| 2-Cl | 24 | 1.7 | 76 | 20 | trace |
| 2-Me | 5 | 1.1 | 85(74) | trace | trace |
| 3-Me | 3 | 1.1 | 60 | trace | 8 |

^a Determined by GC using an internal standard. Figures in parentheses indicate isolated yields.

ammonium tribromide either in solution⁶ or in a polymer-bound form.⁷ The difference appears to result largely from the use of methanol as a co-solvent in the literature procedures, which may lead to highly active methyl hypobromite as an intermediate brominating agent. Also, the passage of the phenols through a column of the polymeric reagent would maximize the availability of brominating agent, thereby favouring polybromination.

Even under the conditions used in this study polybromination can occur. For example, bromination of 3-methylphenol (*meta*-cresol) results in 8% of dibromo products, and this rises to 23% of dibromo products on attempted monobromination of 3,5-dimethylphenol with one molar equivalent of resin. Nevertheless, the good yields of 4-bromo products obtained from the monosubstituted phenols tried demonstrates that this is a powerful new synthetic method for the organic chemist.

For large scale work the cost of the resin might be a major disadvantage unless it could be recovered. We have therefore taken a sample of resin filtered off after a reaction and reconverted it into the tribromide by addition of bromine.⁸ Reuse of this resin in a further reaction with phenol gave results which were very comparable with those obtained using the original resin. Therefore, recycling of the resin appears to be a viable possibility.

The following procedure is representative. To a stirred solution of 2-methoxyphenol (0.174 g, 1.40 mmol) in dichloromethane (5 cm³), Amberlyst-A26 Br₃⁻ form (1.4 g, 1.6 mequiv.) was added at room temperature. The reaction mixture was stirred in the dark for 4 h. The decolorized resin was filtered off and washed well with dichloromethane. The filtrate and washings were concentrated under reduced pressure to yield a pale brown solid. Flash column chromatography [silica; hexane-ethyl acetate (4:1)] yielded 4-bromo-2-methoxyphenol (0.249 g, 87%) and 6-bromo-2-methoxyphenol (0.010 g, 4%). (NB. The commercial resin was washed with dichloromethane to remove impurities prior to use.)

[†] Purchased from Fluka.

Acknowledgements

We thank Amersham International plc for a studentship to D. M. J.

References

- 1 See, e.g., D. C. Huston and M. M. Ballard, *Org. Synth.*, Coll. Vol. II, 1943, 97; C. F. Koelsch, *Org. Synth.*, Coll. Vol. III, 1955, 132.
- 2 K. Smith, *Bull. Soc. Chim. Fr.*, 1989, 272; *Adv. Organobromine Chem.*, 1991, 1, 5; *Stud. Surf. Sci. Catal.*, 1991, 59, 55; K. Smith and K. B. Fry, *J. Chem. Soc., Chem. Commun.*, 1992, 187; K. Smith and D. Jones, *J. Chem. Soc., Perkin Trans. 1*, 1992, 407; K. Smith, ed., *Solid Supports and Catalysts in Organic Synthesis*, Ellis Horwood, Chichester, 1992.
- 3 Chlorination: K. Smith, M. Butters, W. E. Paget and B. Nay, *Synthesis*, 1985, 1155; K. Smith, M. Butters and B. Nay, *Synthesis*, 1985, 1157; *Tetrahedron Lett.*, 1988, 29, 1319. Nitration: K. Smith, K. Fry, M. Butters and B. Nay, *Synthesis*, 1989, 30, 5333.
- 4 A. G. Mistry, K. Smith and M. R. Bye, *Tetrahedron Lett.*, 1986, 27, 1051; A. G. Mistry, K. Smith and M. R. Bye, in *Bromine Compounds: Chemistry and Applications*, eds. D. Price, B. Iddon and B. J. Wakefield, Elsevier, Amsterdam, 1988, p. 277; K. Smith, D. M. James, A. G. Mistry, M. R. Bye and D. J. Faulkner, *Tetrahedron*, in the press.
- 5 S. Kajigaeshi, T. Kakinami, T. Okamoto, H. Nakamura and M. Fujikawa, *Bull. Chem. Soc. Jpn.*, 1987, 60, 4187; J. Berthelot, C. Guette, M. Ouchefoune, P. L. Desbene and J. J. Basselier, *J. Chem. Res. (S)*, 1986, 381.
- 6 S. Kajigaeshi, T. Kakinami, H. Tokiyama, T. Hirakawa and T. Okamoto, *Chem. Lett.*, 1987, 627.
- 7 T. Kakinami, H. Suenaga, T. Yamaguchi, T. Okamoto and S. Kajigaeshi, *Bull. Chem. Soc. Jpn.*, 1989, 62, 3373.
- 8 S. Cacchi and L. Caglioti, *Synthesis*, 1979, 64.

Paper 2/02740B

Received 26th May 1992

Accepted 5th June 1992