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DEMETHYLATION OF ARYL METHYL ETHERS BY BORON TRIBROMIDE

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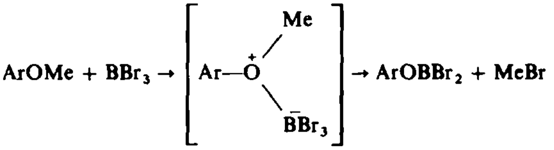
Abstract—The use of boron tribromide for effecting complete demethylation of aryl methyl ethers at, or below, room temperature is described.

Demethylation of aryl methyl ethers can be effected by a variety of reagents[1] but usually it is necessary to employ fairly high temperatures, e.g. by boiling the compound with a solution of hydrogen bromide in acetic acid. However, as mentioned in a preliminary publication[2] aromatic ethers can be cleaved at or below room temperature by means of boron tribromide. The results of our experiments are shown in the Table. The yields quoted are generally derived from a single experiment and could doubtless be improved by altering the reaction conditions. In every case complete demethylation occurred. The successful demethylation of the di-iodo compounds (**17–19**) is noteworthy since attempts to effect the demethylation of 2,2'-di-iodo-5,5'-dimethoxybiphenyl (**17**) with hydrogen bromide or with aluminium bromide in benzene caused extensive deiodination and decomposition although 3,3'-dimethoxy biphenyl was smoothly demethylated by both these reagents.

The reaction probably proceeds via a complex formed between the reagent and the ethereal oxygen atom.



$$\mathrm{ArOMe} + \mathrm{BBr_3} \rightarrow \left[\mathrm{Ar{-}\overset{+}{O}} \begin{array}{l} \diagup \mathrm{Me} \\ \diagdown \overset{-}{\mathrm{B}}\mathrm{Br_3} \end{array} \right] \rightarrow \mathrm{ArOBBr_2} + \mathrm{MeBr}$$

$$\mathrm{ArOBBr_2} + 3\mathrm{H_2O} \rightarrow \mathrm{ArOH} + \mathrm{H_3BO_3} + 2\mathrm{HBr}$$

It is advisable, therefore, to use one mole of boron tribromide per ether group together with an extra mole of reagent for each group containing a potentially basic N or O (e.g. —CHO, —CN, —CO_2H). This was not always done in our earlier experiments and may partly account for the low yields obtained in a few cases. For catechol dimethyl ethers (e.g. compounds **7** and **21**) it is likely that demethylation can proceed stepwise and that one mole of reagent suffices for each catechol group since a cyclic borate can be formed.

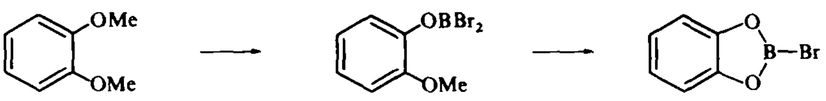


TABLE 1. COMPLETE DEMETHYLATION OF ARYL METHYL ETHERS

No.	Compound	Solvent	Time hr	Starting Temp °C	Mols BBr_3:Comp	Yield %	Footnotes
1	1-Methoxynaphthalene	CH_2Cl_2	24	−80	1:1	13·5	*a*
2	2-Methoxynaphthalene	CH_2Cl_2	24	−80	1:1	67	*a*
3	2,3,4,5-Tetrabromoanisole	C_6H_6	36	20	1·7:1	93	*b*
4	2,3,4,5-Tetrabromo-6-nitroanisole	C_6H_6	7 days	20	3·7:1	1·5	*b*
5	2,3,5,6-Tetrabromo-4-nitroanisole	C_6H_6	7 days	20	3·7:1	31	*b*
6	4-Methoxybenzoic acid	CH_2Cl_2	24	−80	2·3:1	92	*a*
7	4,5-Dimethoxybenzoic acid	CH_2Cl_2	24	−80	2·1:1	90	*a*
8	Orcinol dimethyl ether	n-pentane	24	−80	2:1	63	*c*
9	3,5-Dimethoxybenzoic acid	C_6H_6	44	20	2·2:1	31	*a*
10	1-(3,5-Dimethoxyphenyl)heptan-2-ol	n-pentane	10	−80	2:1	11	*d*
11	1-(3,5-Dimethoxyphenyl)heptan-2-one	CH_2Cl_2	18	−80	2:1	10	*e*
12	3,5-Dimethoxybenzyl cyanide	CH_2Cl_2	3	20	3:1	68	*a*
13	3,3'-Dimethoxybiphenyl	CH_2Cl_2	24	−80	1·7:1	77	*a*
14	4,4'-Dimethoxybiphenyl	CH_2Cl_2	24	−80	1·6:1	86	*a*
15	3,4,3',4'-Tetramethoxybiphenyl	CH_2Cl_2	24	−80	4·6:1	85	*a*
16	3,4,3',4'-Tetramethoxybibenzyl	C_6H_6	90	20	4·5:1	35	*a*
17	2,2'-Di-iodo-5,5'-dimethoxybiphenyl	CH_2Cl_2	24	−80	3:1	77	*a*
18	2,2'-Di-iodo-4,4'-dimethoxy-3,5,3',5'-tetramethylbiphenyl	CH_2Cl_2	24	−80	2·2:1	78	*a*
19	2,2-Di-iodo-4,5,4',5'-tetramethoxybiphenyl	CH_2Cl_2	24	−80	6·5:1	64*	*a*
20	Metanethole	CH_2Cl_2	3	−80	2·1:1	12	*a*
21	Di-isohomogenol (α-racemate)	C_6H_6	16·5	20	2·5:1	86	*a*

* The product was isolated as its tetra-acetate.

[a] This paper. [b] Reference 9. [c] A. B. Turner, Ph.D. thesis, Bristol, 1960. [d] Reference 10. [e] B. K. Bullimore, Ph.D. thesis, Bristol, 1963.

The reaction is conveniently carried out by mixing the reagents in an inert solvent at −80° and then allowing the mixture to warm up to room temperature overnight. Under these conditions isoeugenol and 4,5-dibenzyloxy-propenylbenzene gave no isolable products (polymerization probably occurred).

As well as the compounds listed in the Table we have demethylated a number of di- and tetra-methoxybiphenylenes in 30–60% yield. These will be reported in forthcoming papers on biphenylenes. Since our original publication[2] boron tribromide has been used by other workers[3–7] for demethylations, and boron trichloride has recently been shown to be a powerful, but selective reagent for the demethylation of OMe groups which are situated *ortho* to a CO group.[8]

EXPERIMENTAL

The compounds obtained by demethylation of the phenol ethers (**1–21**) were identified by m.p., mixed m.p., and by their IR spectra. New compounds were analysed (see below).

General method for demethylation. A soln or suspension of the MeO compound (x g; 1 equiv) in 20 to 30 times x ml of CH_2Cl_2 (benzene or n-pentane) is added at room temp to a soln of BBr_3 (for amount see below) in 5 to 10 times its volume of CH_2Cl_2. The mixture, protected from ingress of moisture by means of a drying tube filled with $CaCl_2$, is kept overnight. The mixture is then shaken with water to hydrolyse excess reagent and boron complexes and the phenolic product collected by extraction into ether.

If a milder procedure is required, the reactants can be mixed at −80° and allowed to warm up to room temp overnight.

We recommend the use of at least 1 equiv of BBr_3 for each MeO group or other group containing an "electron-donor" element, e.g. 3 equivs for a compound containing two MeO and one CN group.

3,5-*Dihydroxybenzyl cyanide.* A soln of BBr_3 (0·015 mole) in dry CH_2Cl_2 (14·5 ml of a soln containing 11·4 g BBr_3 in 40 ml CH_2Cl_2) was added to a soln of 3,5-dimethoxy benzyl cyanide (0·885 g, 0·005 mole) in dry CH_2Cl_2 (15 ml) at room temp. After 3 hr, water (25 ml) was added then ether (150 ml) and the ppt was removed by filtration. The ether layer was extracted with 2N NaOH and the alkaline extract was then acidified with dil HCl. Extraction with ether gave 3,5-*dihydroxy benzyl cyanide* (0·505 g; 65%) which on crystallization from benzene formed blades, m.p. 148–149°. (Found: C, 64·15; H, 4·9. $C_8H_7NO_2$ requires: C, 64·4; H, 4·7%.)

3,5,3',5'-*Tetrahydroxybibenzyl* was obtained from its tetra methyl ether (**16**) as prisms, m.p. 255–256°, after crystallization from water. (Found: C, 68·4; H, 5·9. $C_{14}H_{14}O_4$ requires: C, 68·3; H, 5·7%.)

Demethylation of 2,2'-*di-iodo*-5,5'-*dimethoxybiphenyl* (**17**).[11] Use of 3 equivs BBr_3 gave 5,5'-*dihydroxy*-2,2'-*di-iodobiphenyl* (77%) as chunky crystals, m.p. 186–187° from benzene–petroleum (b.p. 80–100°). (Found: C, 32·5; H, 2.2 $C_{12}H_8I_2O_2$ requires: C, 32·9; H, 1·8%.) When only 0·9 equiv BBr_3 was used, starting material (23%) was recovered. The phenolic material was separated on a silica-gel column using benzene as eluant thereby giving 5-*hydroxy*-2,2'-*di-iodo*-5'-*methoxybiphenyl* (37%) m.p. 152–153°. (Found: C, 34·9; H, 2·2. $C_{13}H_{10}I_2O_2$ requires: C, 34·5; H, 2·2%) and the di-hydroxy compound (22%).

No demethylation of **17** occurred with BCl_3 even when it was refluxed for 2 hr with 8 equivs of the reagent in CH_2Cl_2.

Demethylation of 2,2'-*di-iodo*-4,4'-*dimethoxy*-3,5,3',5'-*tetramethylbiphenyl* (**18**).[11] The demethylation gave 4,4'-*dihydroxy*-2,2'-*di-iodo*-3,5,3',5'-*tetramethylbiphenyl* as crystals, m.p. 244–245° from benzene–petroleum (b.p. 80–100°). (Found: C, 39·1; H, 3·55. $C_{16}H_{16}I_2O_2$ requires: C, 38·9; H, 3·2%.) This dihydroxy biphenyl gave the corresponding diacetate when warmed with Ac_2O and NaOAc. The diacetate, m.p. 209–211°, did not depress the m.p. of an authentic specimen.

Iodination of 4,4'-*diacetoxy*-3,5,3',5'-*tetramethylbiphenyl.* Iodine (40·6 g) was added to a soln of the diacetoxybiphenyl[12] (62·5 g) in AcOH (1500 ml) and the mixture was heated to 100°. Iodic acid (100 g) in water (150 ml) was added to the stirred soln at 30 min intervals over a period of 12 hr and the mixture was heated under reflux for a further 12 hr. The cooled mixture was poured into a stirred soln of sodium metabisulphite (10 g) in water (3 l). The resulting ppt was collected and crystallized (charcoal) from EtOH. The first crop of crystals was recrystallized from EtOH and gave 4,4'-*diacetoxy*-2,2'-*di-iodo*-3,5,3',5'-*tetramethylbiphenyl* (42·5 g, 35%) as a powder m.p. 211–212°. (Found: C, 42·0; H, 3·9. $C_{20}H_{20}I_2O_4$ requires: C, 41·5; H, 3·5%.) The ethanolic mothers liquors were concentrated and several recrystallizations gave *4,4'-diacetoxy-2-iodo-3,5,3',5'-tetramethylbiphenyl* (16 g, 24%) as crystals m.p. 184–185°. (Found: C, 53·3; H, 4·7. $C_{20}H_{21}IO_4$ requires: C, 53·1; H, 4·6%.)

Hydrolysis of the diacetoxy-di-iodobiphenyl with NaOH in aqueous EtOH give the corresponding dihydroxy biphenyl (96%), m.p. alone or mixture with the product from demethylation of the corresponding dimethoxy compound (see above) was 244–245°.

Attempts to iodinate 4,4'-dihydroxy-3,5,3',5'-tetramethylbiphenyl with ICl or with $I_2/AgNO_3$ were unsuccessful.

Demethylation of 2,2'-di-iodo-4,5,4',5'-tetramethoxybiphenyl (**19**). BBr_3 (0·5 ml) in CH_2Cl_2 (10 ml) was added to tetramethoxybiphenyl[11] (0·43 g) in CH_2Cl_2 (70 ml) at −80°. Next day the mixture was shaken with water (30 ml). Neither the white ppt nor the gum obtained by evaporating the CH_2Cl_2 layer could be made to crystallize so they were united and warmed on a water-bath for 30 min with Ac_2O (5 ml) and NaOAc (0·5 g). The product was crystallized from EtOH giving *4,5,4',5'-tetra-acetoxy-2,2'-di-iodobiphenyl* (0·33 g, 64%) as needles, m.p. 177–178°. (Found: C, 37·6; H, 2·5. $C_{20}H_{16}I_2O_8$ requires: C, 37·6; H, 2·7%.)

Metanethol, obtained by demethylation of metanethole.[13] Compound **20** was remethylated with Me_2SO_4 and KOH in EtOH. The metanethole (50%) formed prisms, m.p. and mixed m.p. 132–133°, showing that demethylation and remethylation had occurred without change of configuration.

Demethylation of α-di-isohomogenol (**21**). A soln of α-di-isohomogenol[13] (1·5 g) in benzene was treated with a soln of BBr_3 (2·6 g) also in benzene (14 ml). The mixture was kept at room temp for 16·5 hr then hydrolysed by addition of water. The ppt was recrystallized from aqueous EtOH and gave the α-racemate of *3-ethyl-5,6-dihydroxy-2-methyl-1-(3',4'-dihydroxyphenyl) indane* as flaky crystals, m.p. 65–66° with solidification and remelting at 133–134°. (Found: C, 71·4; H, 6·6. $C_{18}H_{20}O_4$ requires: C, 72·0; H, 6·7%.)

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