DEMETHYLATION OF ARYL METHYL ETHERS BY
BORON TRIBROMIDE

J. F. W. McOmie, M. L. Watts and D. E. West
School of Chemistry, The University, Bristol, England


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.

\[
\begin{align*}
\text{ArOMe} + \text{BBr}_3 & \rightarrow \left[ \begin{array}{c}
\text{Me} \\
\text{Ar} \quad \hat{\text{O}} \\
\text{BBr}_3
\end{array} \right] \\
& \rightarrow \text{ArOBBr}_2 + \text{MeBr}
\end{align*}
\]

\[
\text{ArOBBr}_2 + 3\text{H}_2\text{O} \rightarrow \text{ArOH} + \text{H}_3\text{BO}_3 + 2\text{HBr}
\]

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>
<thead>
<tr>
<th>No.</th>
<th>Compound</th>
<th>Solvent</th>
<th>Time</th>
<th>Starting Temp °C</th>
<th>BBr₃:Comp</th>
<th>Yield %</th>
<th>Footnotes</th>
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<tbody>
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<td>1</td>
<td>1-Methoxynaphthalene</td>
<td>CH₂Cl₂</td>
<td>24</td>
<td>-80</td>
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<td>13.5</td>
<td>a</td>
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<td>C₆H₆</td>
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<td>4</td>
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<td>C₆H₆</td>
<td>7 days</td>
<td>20</td>
<td>3:7:1</td>
<td>1.5</td>
<td>b</td>
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<tr>
<td>5</td>
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<td>C₆H₆</td>
<td>7 days</td>
<td>20</td>
<td>3:7:1</td>
<td>31</td>
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<td>6</td>
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<td>CH₂Cl₂</td>
<td>24</td>
<td>-80</td>
<td>2:1:1</td>
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<td>-80</td>
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<td>10</td>
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<td>n-pentane</td>
<td>10</td>
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<td>2:1</td>
<td>11</td>
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<td>18</td>
<td>-80</td>
<td>2:1</td>
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<td>CH₂Cl₂</td>
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<td>90</td>
<td>20</td>
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<td>-80</td>
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<td>77</td>
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<tr>
<td>18</td>
<td>2,2'-Di-iodo-4,4'-dimethoxy-3,5,3',5'-tetramethylibiphenyl</td>
<td>CH₂Cl₂</td>
<td>24</td>
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<td>CH₂Cl₂</td>
<td>24</td>
<td>-80</td>
<td>6:5:1</td>
<td>64*</td>
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<td>-80</td>
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<td>21</td>
<td>Di-isohomogenol (α-racemate)</td>
<td>C₆H₆</td>
<td>16.5</td>
<td>20</td>
<td>2:5:1</td>
<td>86</td>
<td>a</td>
</tr>
</tbody>
</table>

* The product was isolated as its tetra-acetate.

a This paper.  
b Reference 9.  
d Reference 10.  
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-dibenzylxoy-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 boron tribromide has been used by other workers 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.  

**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 CH₂Cl₂ (benzene or n-pentane) is added at room temp to a soln of BBr₃ (for amount see below) in 5 to 10 times its volume of CH₂Cl₂. The mixture, protected from ingress of moisture by means of a drying tube filled with CaCl₂, 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 BBr₃ 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-Di-hydroxybenzyl cyanide.** A soln of BBr₃ (0.015 mole) in dry CH₂Cl₂ (14.5 ml of a soln containing 11.4 g BBr₃ in 40 ml CH₂Cl₂) was added to a soln of 3,5-dimethoxy benzyl cyanide (0.885 g, 0.005 mole) in dry CH₂Cl₂ (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-di-hydroxy benzyl cyanide (0.505 g; 65%) which on crystallization from benzene formed blades, m.p. 148–149°. (Found: C, 64.15; H, 4.9. C₈H₁₈NO₂ requires: C, 64.4%; H, 4.7%)

**3,5,3′,5′-Tetrahydroxybiphenyl.** 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. C₁₄H₁₈O₄ requires: C, 68.3%; H, 5.7%)

**Demethylation of 2,2′-di-iodo-5,5′-dimethoxybiphenyl (17).** Use of 3 equivs BBr₃ gave 5,5′-di-hydroxy-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 C₁₂H₁₇I₂O₂ requires: C, 32.9; H, 1.8%). When only 0.9 equiv BBr₃ 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 C₁₂H₁₇I₂O₂ requires: C, 34.5; H, 2.2%) and the di-hydroxy compound (22%).

No demethylation of 17 occurred with BCl₃ even when it was refluxed for 2 hr with 8 equivs of the reagent in CH₂Cl₂.

**Demethylation of 2,2′-di-iodo-4,4′-dimethoxy-3,5,3′,5′-tetramethylbiphenyl (18).** The demethylation gave 4,4′-di-hydroxy-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. C₁₆H₁₆I₂O₂ requires: C, 38.9; H, 3.2%). This dihydroxy biphényl gave the corresponding diacetate when warmed with Ac₂O 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 diacetoxybiphenyl11 (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. C₂₉H₂₉I₂O₄ requires: C, 41.5; H, 3.5%). The ethanolic mother liquors were concentrated and several recrystallizations
gave 4,4'-diacetoxy-2-ido-3,5,3',5'-tetramethylbiphenyl (16 g, 24%) as crystals m.p. 184–185°. (Found: C, 53·3; H, 4·7. C₂₀H₂₁IO₄ 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 I₂/AgNO₃ were unsuccessful.

**Demethylation of 2,2'-di-iodo-4,5,4',5'-tetramethoxybiphenyl (19).** BBr₃ (0·5 ml) in CH₂Cl₂ (10 ml) was added to tetramethoxybiphenyl² (0·43 g) in CH₂Cl₂ (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 CH₂Cl₂ layer could be made to crystallize so they were united and warmed on a water-bath for 30 min with Ac₂O (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. C₂₀H₁₆I₂O₈ requires: C, 37·6; H, 2·7%.)

Metanethol obtained by demethylation of metanethole.¹³ Compound 20 was remethylated with Me₂SO₄ 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-isohomogenol¹³ (1·5 g) in benzene was treated with a soln of BBr₃ (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. C₁₈H₂₀O₄ requires: C, 72·0; H, 6·7%).

**REFERENCES**