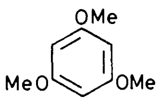
Boron Trichloride as a Selective Demethylating Agent for Hindered Ethers

Christopher F. Carvalho and Melvyn V. Sargent*

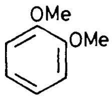
Department of Organic Chemistry, University of Western Australia, Nedlands, W.A. 6009, Australia

Boron trichloride has been found to be an efficient reagent for the selective cleavage of sterically hindered methoxy groups in methoxyarenes; the scope and utility of this reaction are explored.

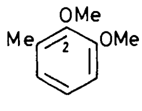
The cleavage of aryl methyl ethers, in spite of the numerous methods available, still commands the attention of synthetic organic chemists.[1] In phenolic chemistry, boron trichloride is generally used for the selective cleavage of methoxy groups in an *ortho*-relationship to carbonyl groups.[2] Although isolated instances of other types of selective demethylation have been noted with this reagent, the underlying generalities of the regioselectivity have not been appreciated.[3] The conditions are mild and the reaction times are short. Nevertheless boron trichloride is capable of cleaving the methoxy group of anisole[4] but the rate of reaction is presumably slower than that of boron tribromide on account of the reduced nucleophilicity of chloride, so that boron tribromide is the reagent of choice for complete demethylation of polymethoxyarenes.



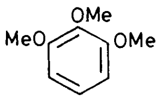
(1)



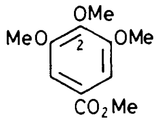
(2)



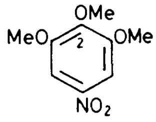
(3)



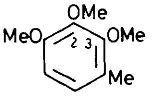
(4)



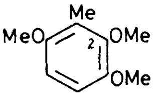
(5)



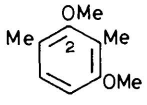
(6)



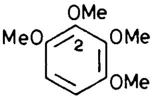
(7)



(8)



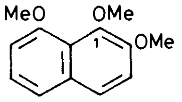
(9)



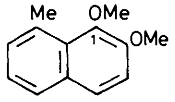
(10)

Table 1. Cleavage of methoxybenzene compounds with boron trichloride C(*n*)O-Me → C(*n*)O-H.

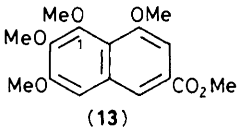
Substrate	BCl_3 (equiv.)	Reaction time/h	% Product(s) C(*n*)OH
(1)	1	20	C(1) (50); C(1), C(3) (8); Substrate (40)
(2)	1	4	C(1) (86); C(1), C(2) (9)
(3)	1.1	26	C(2) (90)
(4)	1.1	3	C(2) (90)
	1	41	C(2) (47); C(1), C(2) (43)
(5)	2.2	5	C(2) (95)
(6)	2.2	22	C(2) (72)
(7)	1.1	2.5	C(2) (78); C(2), C(3) (20)
(8)	1.1	4.75	C(2) (90)
(9)	2.2	23	C(2) (90)
(10)	1.1	2.25	C(2) (85)



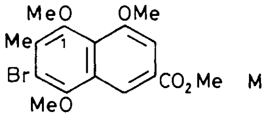
(11)



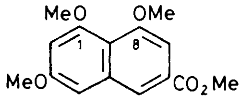
(12)



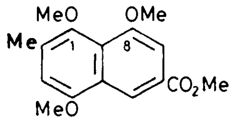
(13)



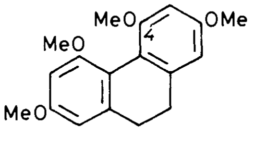
(14)



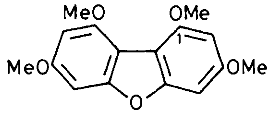
(15)



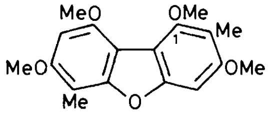
(16)



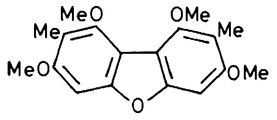
(17)



(18)



(19)



(20)

Table 2. Cleavage of methoxyarenes (**11**)—(**20**) with boron trichloride C(*n*)O-Me → C(*n*)O-H.

Substrate	BCl_3 (equiv.)	Reaction time/h	% Product(s) C(*n*)OH
(**11**)	1.1	3.5	C(1) (80)
(**12**)	1.1	0.75	C(1) (95)
(**13**)	6	1	C(1) (80)
(**14**)	5	1	C(1) (90)
(**15**)	5	7.25	C(8)(11) C(1),C(8) (70)
(**16**)	5	3.5	C(1),C(8) (90)
(**17**)	4	3	C(4) (90)
(**18**)	5	7.5	C(1) (90)
(**19**)	5	2	C(1) (90)
(**20**)	5	1	C(1) (95)

It appeared likely to us that the reduced nucleophilicity of chloride might enable boron trichloride to be used in the selective demethylation of polymethoxyarenes. Consequently we have studied the demethylation of a number of methoxyarenes; the reagents were mixed in dichloromethane at −10 or 0 °C and allowed to warm to room temperature. The results are recorded in Tables 1 and 2.

Whilst the selectivity is not great in the case of tri-*O*-methylphloroglucinol (**1**) it is markedly enhanced in the cases of veratrole (**2**) and 3-methylveratrole (**3**) as compared with boron tribromide.[5] We have also found that boron trichloride exhibits a high degree of selectivity in the cleavage of sterically hindered methoxy groups, *e.g.* (**4**)—(**10**). The classical examples are those of tri-*O*-methylpyrogallol (**4**) and its derivatives. The usual explanation of this effect is that the central methoxy group is out of the plane of the benzene ring so that this oxygen is more basic than its neighbours;[6] boron trichloride would therefore co-ordinate preferentially at this centre hence leading to demethylation. In the cases of compounds (**5**) and (**6**) it was necessary to use two equivalents of boron trichloride to cause demethylation to occur at an appreciable rate since one equivalent of the reagent is presumably co-ordinated to the nitro or ester substituent. In the case of the unsymmetrical compound (**7**) the methoxy group that is cleaved is the one flanked by two methoxy groups; no trace of the compound resulting from demethylation of the methoxy group flanked by a methyl group and a methoxy group could be detected. The buttressing effect of a methoxy group and a methyl group, or of two methyl groups provides sufficient steric effect for demethylation to occur as shown by the examples of compounds (**8**) and (**9**).

We have also studied a number of *peri*-methoxynaphthalenes and dibenzofurans. Again the most sterically hindered *peri*-methoxy group is cleaved at short reaction times but at longer reaction times further cleavage of *peri*-methoxy groups may occur. The tetramethoxy-9,10-dihydrophenanthrene (**17**) also undergoes selective demethylation.

These results display the syntheses of phenolic compounds which are not easily obtained by other methods and the method herein should be of use in the synthesis of natural products.

Received, 24th October 1983; Com. 1401

References

1 M. V. Bhatt and S. U. Kulkarni, *Synthesis*, 1983, 249.
2 F. M. Dean, J. Goodchild, L. E. Houghton, J. A. Martin, R. B. Morton, B. Parton, A. W. Price, and N. Somvichien, *Tetrahedron Lett.*, 1966, 4153.
3 D. H. R. Barton, L. Bould, D. L. J. Clive, P. D. Magnus, and T. Hase, *J. Chem. Soc. C*, 1971, 2204.
4 W. Gerrard and M. F. Lappert, *J. Chem. Soc.*, 1952, 1486.
5 E. H. Vickery, L. F. Pahler, and E. J. Eisenbraun, *J. Org. Chem.*, 1979, **44**, 4444.
6 C. F. Wilcox, Jr., and M. A. Seager, *J. Org. Chem.*, 1969, **34**, 2319.