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BORON TRICHLORIDE AS A SELECTIVE DEMETHYLATING AGENT

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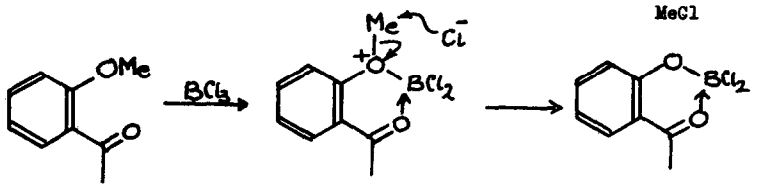
We report that boron trichloride readily demethylates methoxyl groups that stand ortho to a carbonyl group. Others are affected only slowly (1). We first used the reagent because, in combination with the aromatic aldehyde synthesis introduced by Rieche, Gross and Höft (2), it provides a convenient and efficient route to many derivatives of salicylaldehyde required for the synthesis of oxygen heterocyclic compounds. The examples in the Table illustrate these and other features.

Since boron trichloride has b.p. 12.5° we have usually cooled it to -70°, added the neat liquid to the reactant in cold methylene chloride, stoppered the vessel and kept it at laboratory temperature for the time stated in the

Table. The reagent is used in any convenient excess, but exposure to moisture is best kept to the minimum. The remaining reagent can be removed by evaporation or, except with carboxylic acids, destroyed by methanol. Most commonly, however, the methylene chloride solution is simply washed with plenty of water to free it from hydrochloric and boric acids and the product recovered by standard techniques. Compounds that possess methoxyl groups sensitive to acid hydrolysis may require the use of aqueous sodium acetate instead of water. Even with this modification, however, heteropeucenin methyl ether (I) gave a hydrochloride (II).

We think that selective dealkylation depends upon co-ordination of the boron atom with two oxygen atoms in a six-membered ring as shown in the following scheme or as found in the complexes formed by β-diketones (3):



These complexes are decomposed at once by water, whereas those from boron trifluoride (4) are relatively stable. A more important advantage over boron trifluoride is that Friedel-Crafts reactions and related condensations are avoided. On the other hand, the reagent is more selective than boron tribromide, perhaps because bromide ion is more strongly nucleophilic than chloride ion.

Factors that would be expected to impair the stability of the six-membered ring complex reduce the ease of demethylation. Thus acids are somewhat less quickly demethylated than aldehydes or ketones, which probably do not require the 5 minutes listed. In griseofulvin (III; R = Me) the carbonyl group is in a five-membered ring and therefore drawn away from the adjacent ether oxygen atom so that demethylation takes much longer than with other ketones. If a six-membered ring cannot be formed, demethylation is very slow indeed. Thus within the usual reaction periods there is little or no attack on the methoxyl group at position 3 in quercetin pentamethyl ether (IV; R = Me) on that at position 2' in griseofulvin (III; R = Me), or on that in 2-methoxy-1,4-naphthaquinone. As these methoxyl groups are sensitive to acid hydrolysis, the two methods are usefully complementary.

Demethylation of 1,3-dimethoxyxanthone is especially slow. As a six-membered ring can be formed, we attribute the observation to the relatively high basicity of the xanthone system which would greatly reduce the ability of the boron atom to attract electrons from a second oxygen atom.

From 2,2'-dimethoxybenzophenone one methyl group is lost rapidly and a second somewhat more slowly. The same boron atom cannot promote both losses for steric reasons, so we suppose that a dual complex (V) can be formed, one carbonyl oxygen atom becoming attached to two boron atoms. Such a dual complex cannot be formed by 2,6-dimethoxybenzaldehydes or -acetophenones, so these lose but one methyl group per carbonyl group. Again, both methyl groups are removed from 2,6-dimethoxybenzoic acid in the general conditions, though we think the loss actually occurs in two stages. Again it is possible to visualise a dual complex (VI), both oxygen atoms of the carboxyl group being employed despite the fact that one would not ordinarily be considered as a carbonyl oxygen atom.

It seems that benzyl groups are too easily removed by the reagent for selectivity to appear. On the other hand, the ethoxycarbonylmethyl group can be selectively removed

TABLE (con.)

Compound	Product	Time (Min.)	Yield %
Heteropeucenin dimethyl ether (I)	heteropeucenin 5-methyl ether hydrochloride (II)	5	90
Quercetin penta-methyl ether (IV; R = Me)	5-hydroxy-3,3',4',7-tetramethoxyflavone (IV; R = H)	30	86
1,3-Dimethoxy-xanthone	1-hydroxy-3-methoxyxanthone	120	90
β-2-Methoxy-6-methyl-benzoylacrylic acid	β-2-hydroxy-6-methyl-benzoylacrylic acid	5	81
Ethyl 2-acetyl-5-methoxyphenoxyacetate	2-hydroxy-4-methoxy-acetophenone	5	84
2,4-Dibenzyloxy-benzaldehyde	2,4-dihydroxy-benzaldehyde	30	75

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3. W. Dilthey, Ann., 344, 300 (1905); A. Rosenheim, W. Loewenstamm and L. Singer, Ber., 36, 1833 (1903); N.V. Sidgwick: The Chemical Elements and their Compounds, p. 408, Oxford University Press, London (1950); M.F. Hawthorne and M. Reintjes, J. Amer. Chem. Soc., 86, 5016 (1964).

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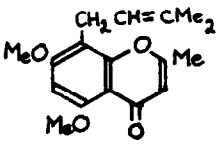
TABLE

Demethylations by Boron Trichloride

Compound	Product	Time (Min.)	Yield %
2,3-Dimethoxybenzaldehyde	2-hydroxy-3-methoxybenzaldehyde	5	93
2,4-Dimethoxybenzaldehyde	2-hydroxy-4-methoxybenzaldehyde	5	80
2,5-Dimethoxybenzaldehyde	2-hydroxy-5-methoxybenzaldehyde	5	72
2,4,6-Trimethoxybenzaldehyde	2-hydroxy-4,6-dimethoxybenzaldehyde	5	81
2,4,5-Trimethoxybenzaldehyde	2-hydroxy-4,5-dimethoxybenzaldehyde	5	50
4-Hydroxy-2,6-dimethoxyacetophenone	2,4-dihydroxy-6-methoxyacetophenone	30	74
2,4,6-Trimethoxy-1,3-diacetophenone	2,6-dihydroxy-4-methoxy-1,3-diacetophenone	20	72
2,3-Dimethoxybenzoic acid	2-hydroxy-3-methoxybenzoic acid	60	95
2,4-Dimethoxybenzoic acid	2-hydroxy-4-methoxybenzoic acid	60	70
2,6-Dimethoxybenzoic acid	2,6-dihydroxybenzoic acid	5	60
2,2'-Dimethoxybenzophenone	2-hydroxy-2'-methoxybenzophenone	30	80
	2,2'-dihydroxybenzophenone	8 hr.	97
8-Methoxy-2-propyl-1,4-naphthaquinone	8-hydroxy-2-propyl-1,4-naphthaquinone	30	90
2-Methoxy-1,4-naphthaquinone	no reaction	2 days	
Griseofulvin (III; R = Me)	4-demethylgriseofulvin (III; R = H)	8 hr.	80

without difficulty.

Chromatographic analysis showed that the following compounds were only slightly attacked during 30 min. : phloroglucinol trimethyl ether, 2,6-dimethoxyphenol, 3,4-dimethoxybenzaldehyde, 3,4-dimethoxyphenylacetic acid. The times and yields given in the Table are generally not optimal. Attention to individual cases could probably reduce some times of reaction and increase some yields. The reaction products were identified by comparison with authentic specimens or by analytical and spectroscopical methods and the preparation of derivatives.



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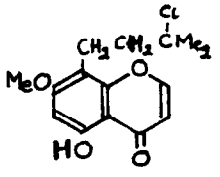

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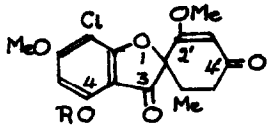

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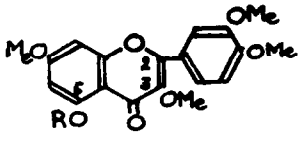

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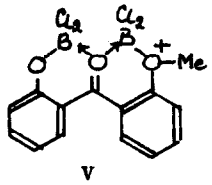

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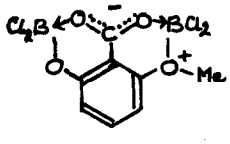

VI