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CATECHOL BORON HALIDES: MILD AND SELECTIVE REAGENTS FOR CLEAVAGE OF COMMON PROTECTING GROUPS

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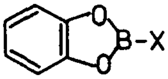
Abstract: Catechol boron halides (**1**,X=Cl,Br) cleave certain ether, ester and carbamate protecting groups under mild conditions. The scope and selectivity of these readily available reagents has been examined.

As synthetic targets increase in complexity, the requirements for mild and selective methods to introduce and remove protecting groups from highly sensitive multifunctional systems increases. The boron halides among other Lewis acids have long been recognized as effective reagents for ether cleavage.[1] However, the corrosive nature of these reagents present handling problems, and their high reactivity limits their utility.[2] More recently, derivatives of boron halides have been investigated in several laboratories in an effort to improve both selectivity and compatibility in multifunctional systems.[3] In this paper, we wish to report our related studies of the catechol boron halides (**1**,X=Cl,Br) which are mild and selective reagents for cleavage of certain ether, ester and carbamate protecting groups.



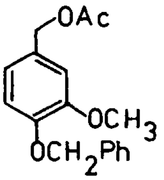
1 X=Br,Cl

The reagents **1** are readily prepared from the appropriate boron halide (1.1 equiv) and catechol (1 equiv) and are isolable by distillation as moisture sensitive low melting solids.[4] Typically, the reagents are more easily stored and dispensed as ~0.2M solutions in CH_2Cl_2. Solutions of this sort are stable for a period of months if properly protected from moisture.

We have examined the relative reactivity of **1** (X=Cl,Br) with a number of typical protecting groups. As expected, the bromide reagent is more reactive. For example, methyl and ethyl phenyl ether are quantitatively cleaved in CH_2Cl_2 at room temperature (36h) with 2 equiv of **1** (X=Br), but are inert to the corresponding chloride reagent. More readily cleavable ethers such as t-Butyl, allyl, and benzyl react completely at room temperature with 1 equiv of **1** (X=Br) over 18h. However, allyl phenyl ether is cleaved to the extent of only ~30% at room temperature with **1** (X=Cl) in 72h, and benzyl and t-Butyl phenyl ether require 24-48h at room temperature for complete reaction with **1** (X=Cl). Thus, when higher selectivity is required use of **1** (X=Cl) may be advisable.

A series of competition experiments were performed to ascertain the relative rate of cleavage of various commonly employed protecting groups by **1** (X=Br). These experiments were performed with 0.5 equiv of **1** (X=Br) and 0.5 equiv of each of two protected derivatives for 18h at room temperature and the consumption of starting materials was monitored by VPC.[5] The results sugest the following tentative order of reactivity: MOMOR ≈ MEMOR > tBOC > CBZ ≈ tBuOR > PhCH$_2$OR > CH$_2$=CHCH$_2$OR > tBuO$_2$CR ≈ 2°alkylOR > PhCH$_2$O$_2$CR ≈ 1°alkylOR >> alkylO$_2$CR.

A selection of typical mono and difunctional examples is given in Table 1. Examination of these cases indicates that selective cleavages are feasible in many instances, and that the reagents seem particularly effective for the cleavage of MEM and MOM ethers, groups which have occasionally proven particularly resistant to cleavage in the past.[3] Cleavage of CBZ groups is generally efficient although the products must be freed of reactive halides immediately upon workup or problems with N-alkylation will be encountered. There are limitations encountered when groups of comparable reactivity are present in multifunctional systems from which product mixtures sometimes result. For example, attempted cleavage of the benzyl ether in **2** and the MOM ether in **3** afforded mixtures of products with one equivalent of the reagent **1** (X=Br) under the usual conditions. The latter case is a particularly difficult one due to the extreme lability of OSiR$_3$ groups when adjacent to a carbonyl.[6] Furthermore, in multifunctional cases involving coordinating groups, excess reagent generally must be used.



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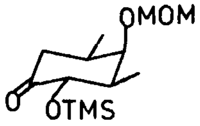
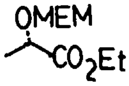
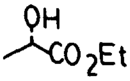
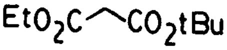
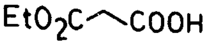
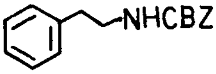
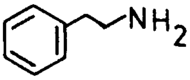
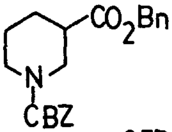
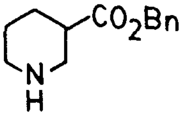
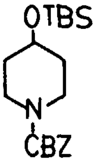
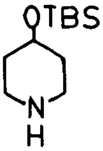
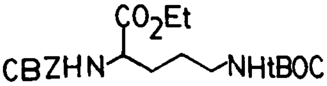
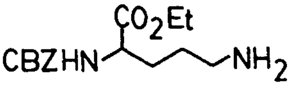
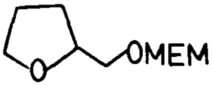
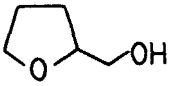
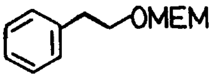
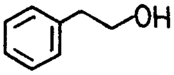
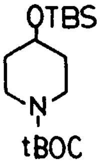
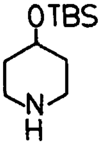
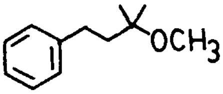
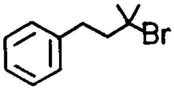


3

A general experimental procedure is as follows: a solution of the substrate (0.5 mmol) in 2mL of dry CH$_2$Cl$_2$ was treated dropwise with the appropriate stoichiometry of **1** (0.2M in CH$_2$Cl$_2$), 1 equiv for ethers and esters or 2 equiv for carbamates, dropwise at room temperature. After stirring at room temperature for the indicated period, the reacton mixture was treated with 2mL of H$_2$O, stirred 20 min, then diluted with an additional 30mL of CH$_2$Cl$_2$, and washed successively with 2 portions (15mL) of 10% NaOH solution and once with 15mL of saturated salt solution. The organic phase was dried (MgSO$_4$) and concentrated to afford the crude products which can then be further purified by distillation or chromatography as required. The purification procedure for amines, particularly water soluble amines involves acidification of the organic phase with anh HCl, concentration in vacuo, washing the residue with pentane to remove the halide, and basification with Et$_3$N in CH$_2$Cl$_2$. Note, isolation of phenols generally requires chromatographic removal of the catechol .

Table 1

Case	Substrate	Stoichiometry[a]	Conditions	Yield[b]	Product(s)
1		1	rt;18h	82%	
2		1	rt;18h	~100%	
3		2	rt;2h	83%	
4		2	rt;2h	54%	
5		2	rt;2h	75%	
6		2	rt;2h	53%	
7		1	rt;0.25h	70%[c]	
8		1	rt;0.25h	~100%[c]	
9		2	rt;0.5h	94%	
10		1	rt;4h	92%	

a) All reactions were conducted in CH_2Cl_2 using the indicated stoichiometry of **1**(X=Br).

b) Yields cited are isolated yields of purified products.

c) Yield determined by VPC.

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   b) Williams, D.R.; Sakdarat, S. Tetrahedron Lett.**1983**,24,3965;
   c) Guindon, Y.; Yoakim, C.; Morton, M. Tetrahedron Lett.**1983**,24,3969;
   d) Guindon, Y.; Yoakim, C.; Morton, M. Tetrahedron Lett.**1983**,24,2969.

4. Gerrard, W.; Lappert, M.F.; Mountfield, B.A. J.Chem.Soc.**1959**,1529.

5. Cleavage of carbamates generally requires 2 equiv of the reagent. The product amines can be isolated by neutralizion during the workup by addition of base. It is important to free the amine of the halide by-product rapidly to prevent alkylation especially when a reactive halide such as benzyl bromide is involved.

6. Experience in these laboratories has indicated that silyl ethers of α ketols are extraordinarily labile, presumably due to neighboring group participation in the protonation of the ether oxygen or complexation of the ether oxygen with Lewis acids.

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