Tetrahedron Letters,Vol.24,No.37,pp 3969-3972,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

DIMETHYLBORON BROMIDE AND DIPHENYLBORON BROMIDE. ACETAL AND KETAL CLEAVAGE. CLEAVAGE OF MEM, MOM AND MTM ETHERS.

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ABSTRACT: A general and efficient procedure for the cleavage of acetals and ketals by the use of dimethylboron bromide or diphenylboron bromide is described. Under similar reaction conditions, MEM, MOM and MTM ethers also react to afford the parent alcohols in excellent yields.

Ketals and acetals are one of the most useful functionalities in organic chemistry. They find application, for instance, in the protection of carbonyl groups (e.g. dimethyl ketals, 1,3-dioxolanes), alcohols (e.g. methoxymethyl ethers, 2-methoxyethoxymethyl ethers) and diols (e.g. isopropylidene ketals). As such they are an important constituent of the available "repertoire" of protecting groups[1] used in organic syntheses. The most often used approach for the cleavage of acetals or ketals and the subsequent regeneration of the parent carbonyl compound involves treatment with acids or Lewis acids.[1] For example, cyclic acetals and ketals are traditionally cleaved using acid-catalyzed exchange ketalization (e.g. H_2SO_4-acetone[3]; pTsOH-acetone[4]; pyr-pTsOH-acetone[5]), acid catalyzed hydrolysis (e.g. 2N HCl-THF;[6] $LiBF_4$,H_2O-CH_3CN[7]), or oxidative cleavage (e.g. $Ph_3C^+BF_4^-$,CH_2Cl_2).[8] In some cases, the use of strong acids, depending on the stability or sensitivity of a given polyfunctional substrate to acidic media is a severe limiting factor. Recently, trimethylsilyl iodide, the most reactive organosilicone reagent[9] has been shown to convert acyclic ketals to ketones in good yield.[10] However, cyclic ketals decompose under these reaction conditions.[10]

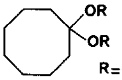
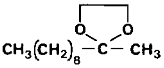
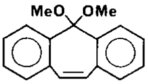
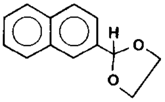
We are reporting, herein, on a new, efficient and versatile approach to cleave acetals and ketals under non-acidic and aprotic conditions using either dimethylboron bromide or diphenylboron bromide. This work is part of our studies on monofunctional organoborane reagents of general formula R_2BBr of which Me_2BBr has been reported recently to be a very efficient reagent for the cleavage of a variety of ethers[2] (alkyl, aryl alkyl, cyclic).

Table 1 summarizes some of the results we have obtained. It is to be noted that both cyclic and acyclic ketals or acetals are efficiently cleaved at -78°C to give, after aqueous work-up, the corresponding ketones or aldehydes in excellent yield.

Acetals derivatives such as MOM[11] (methoxymethyl ether), MEM[12] (2-methoxyethoxymethyl ether) and MTM[13] (methylthiomethyl ether) are used for the protection of the hydroxyl functionality. One will remember that the cleavage of MOM ethers requires strong acidic conditions (e.g. HCl,THF;[12] PhSH,BF_3.Et_2O[14]). In the MEM case, mild Lewis acids ($ZnBr_2$[12], $TiCl_4$[12]) were reported to affect the cleavage of the acetal to give the parent alcohol.[15] In some instances however stronger conditions had to be used (e.g. n-BuLi;[16] TFA;[17] HF[18]). MTM ethers are usually removed using Ag^+salts.[13]

We have studied the cleavage of MOM, MEM and MTM ethers with the disubstituted boron bromide reagents. Under our experimental conditions we have found that these protecting groups cleave smoothly at -78°C to give the corresponding alcohols in very high yields as illustrated in Table 2.

TABLE 1

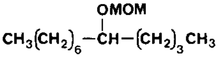
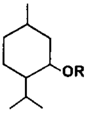
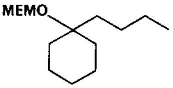
ENTRY	SUBSTRATE	REAGENT[a]	YIELD[b](%)
1	 R=Me	Me_2BBr	93
2	" R= $-(CH_2)_2-$	Me_2BBr	92
3	" R= $-CH_2-C(CH_3)_2CH_2-$	Me_2BBr[c]	91
4	 $CH_3(CH_2)_8-C-CH_3$	Me_2BBr	97
5	"	Ph_2BBr	90
6		Me_2BBr	93
7		Me_2BBr	95
8	$CH_3(CH_2)_7CH(OMe)_2$	Me_2BBr	91

[a] All reactions were carried out at a concentration of 0.1 M using 2 equiv. of reagent at -78° C for 1 hr.

[b] Isolated yields of aldehyde or ketones. All products were identifed by comparison with authentic samples.

[c] 3 equiv. of reagent were used.

TABLE 2

ENTRY	SUBSTRATE	REAGENT[a]	YIELD[b] (%)
1	$Ph(CH_2)_2CH_2OMEM$	Me_2BBr	87
2	"	Ph_2BBr	87
3	 $CH_3(CH_2)_6-CH(OMOM)-(CH_2)_3CH_3$	Me_2BBr	93
4	 R=MOM	Me_2BBr	90
5	" R=MEM	Me_2BBr	91
6		Me_2BBr[c]	94
7	$CH_3(CH_2)_{10}CH_2OMTM$	Me_2BBr[d]	95

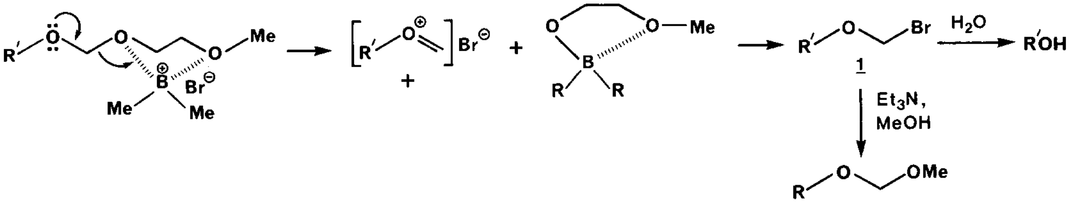
[a] All reactions were carried out at a concentration of 0.1 M using 3 equiv. of reagent at -78° C for 1 hr.

[b] Isolated yields of alcohols. All products were identified by comparison with authentic samples.

[c] 0.1 equiv. of Et_3N was added as an acid scavenger.

[d] 4 equiv. of reagent were used. After 1 hr. at -78°C the reaction mixture was warmed to 0°C for 1 hr.

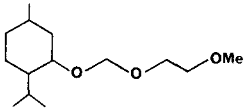
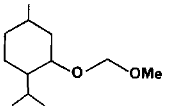
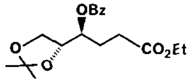
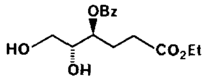
The following is a mechanistic view of the cleavage reaction as applied to MEM ethers.



The presence of the intermediate 1 is reinforced by the fact that, when Et_3N and MeOH were added at -78°C to the reaction mixture (prior to the aqueous work-up), a methoxymethyl ether derivative was isolated and characterized. Furthermore, under conditions in which the hydrolysis of 1 was not complete we have isolated and identified the product of reaction of the desired alcohol and the proposed bromo intermediate 1.[19] This conversion of a MEM to a MOM ether can be made into a preparative reaction as illustrated in entry 1, Table 3.

Ketal derivatives such as isopropylidene are also used to protect diols.[1] Usually harsh acidic conditions are used to regenerate the diol. It is of interest to note that dimethylboron bromide cleaves this functionality at -78°C to give the parent diol in good yield as illustrated in Table 3, entry 3.[20]

TABLE 3

ENTRY	SUBSTRATE	REAGENT	PRODUCT	YIELD[a]%
1		Me_2BBr[b]		95
2	$MEMOCH_2(CH_2)_6CH_2OMe$	Me_2BBr[c]	$HOCH_2(CH_2)_6CH_2OMe$	91
3		Me_2BBr[d]		79

[a] Isolated yields. Products were identified by comparison with authentic samples.
[b] 3.0 equiv. of Me_2BBr was added at -78° C for 1 hr., then Et_3N (3.3 equiv.) in MeOH was added at -78° C and warmed to room temperature.
[c] 3 equiv. of reagent used, at -78°C for 1 hr.
[d] 6 equiv. of reagent used, at -78°C for 1 hr.

The chemoselectivity of Me_2BBr should prove of considerable utility. Thus we have previously shown that ethers can be cleaved at 0°C to 25°C in good to excellent yield in the presence of common protecting groups such as acetates,[2] and silylethers[2] to yield the corresponding alcohol. Of interest is the fact that acetals derivatives such as MEM ethers, because of their intrinsic reactivity could be cleaved selectively at -78°C in the presence of a methyl ether as exemplified by the cleavage of 8-methoxy-1-octanol-MEM ether to the corresponding methoxy alcohol in 91% yield (entry 2, Table 3).

In summary, dimethylboron bromide[21] and diphenylboron bromide[21] can be used efficiently under non-acidic conditions to regenerate a carbonyl group from its corresponding cyclic or acyclic acetal or ketal in excellent yield. They can also be used to cleave MEM, MOM and MTM ethers. The usefulness of dimethylboron bromide to cleave the isopropylidene function in order to liberate the corresponding diol is also exemplified. In the present work diphenylboron bromide works as well as dimethylboron bromide in the cases studied.[22] Variations and differences in the use, and selection of these and other disubstituted boron bromide reagents are under study.[23]

Experimental A typical example follows. To a cold (-78°C), stirred solution of menthol MEM ether (0.97 mmol), in 8.1 mL dry methylene chloride, under argon, was added dropwise, a solution of dimethylboron bromide (1.78 M, 1.63 mL) in 1,2-dichloroethane. After 1 h the reaction mixture was cannulated into a vigorously stirred mixture of tetrahydrofuran[24] (10 mL) and saturated aqueous sodium bicarbonate (5 mL). The reaction vessel and cannula were rinsed with a additional 5 mL of methylene chloride. After a few minutes ether was added, the organic layer separated and washed successively with brine (3 mL), 10% aqueous sodium bisulphate (3 mL), and brine (3 mL). The aqueous layers were extracted with ether (10mL) and the organic layers combined. After drying (Na_2SO_4), the resultant solution was concentrated and subjected to flash chromatography to afford after distillation (air-bath) pure menthol (91%).

Acknowledgement

A Natural Sciences and Engineering Research Council of Canada industrial research fellowship (to H.E.M.) is gratefully acknowledged. The authors thank Dr. J. Rokach for his constant support and collaboration.

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15. In our hands the use of anhydrous $ZnBr_2$[12] for the cleavage of MEM ethers proved to be less efficient. Better results were obtained using wet $ZnBr_2$. For example, treatment of menthol-MEM ether with 5 equiv. wet $ZnBr_2$ in CH_2Cl_2 for 17 h at r.t. gave menthol in 68% yield (compared to 52% using 15 equiv. anhydrous $ZnBr_2$ at r.t. for 30 h).
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19. Reaction of menthol-MEM ether with Me_2BBr gave, after quenching with sat. aq. sodium bicarbonate in the absence of tetrahydrofuran (see Experimental), a mixture of menthol and formaldehyde-dimenthol ketal in 61 and 15% yield, respectively.
20. We have previously cleaved this acetonide using HCl(5N)-EtOH at 60°C for 1 h in yields ranging from 50 to 70%. Y. Guindon, R. Zamboni, C.K. Lau and J. Rokach, Tetrahedron Lett., 739 (1982).
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22. No systematic effort was undertaken to study all substrates with both reagents.
23. We have also found that 9-BBN bromide readily cleaves MEM ethers at -78°C. However the use of this reagent is somewhat less convenient, since the borate biproducts require careful chromatographic separation.
24. In the cleavage of acetals and ketals tetrahydrofuran was omitted from the work-up procedure.

(Received in USA 1 June 1983)