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RING CLEAVAGE OF THP AND THF ETHERS USING DIMETHYLBORON BROMIDE[1]

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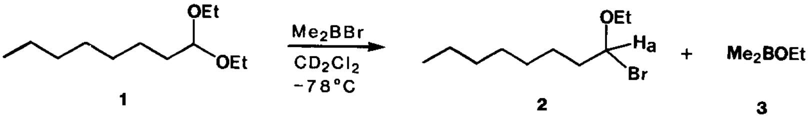
Summary: The reaction of dimethylboron bromide with THP and THF ethers was studied. Under conditions of kinetic control, these reactions proceed by selective cleavage of the ring carbon-oxygen bond to give acyclic α-bromo ethers. Treatment of these intermediates with a variety of nucleophiles gives ring-opened products.

Dimethylboron bromide (Me_2BBr) has recently been described by our laboratories as a mild and selective reagent for the cleavage of acetals and ketals (including MEM, MOM and MTM ethers) to the corresponding aldehydes, ketones or alcohols.[2a,b] While most simple acetals and ketals (including acetonides, MEM and MOM ethers) were cleaved efficiently at -78°C, tetrahydropyranyl (THP) and tetrahydrofuranyl (THF) ethers required more forcing conditions (8-18 h, room temperature) to generate the parent alcohol.[2b] The unexpected difference in reactivity between these classes of acetals has led us to re-examine these reactions and it is these results which we are now reporting.

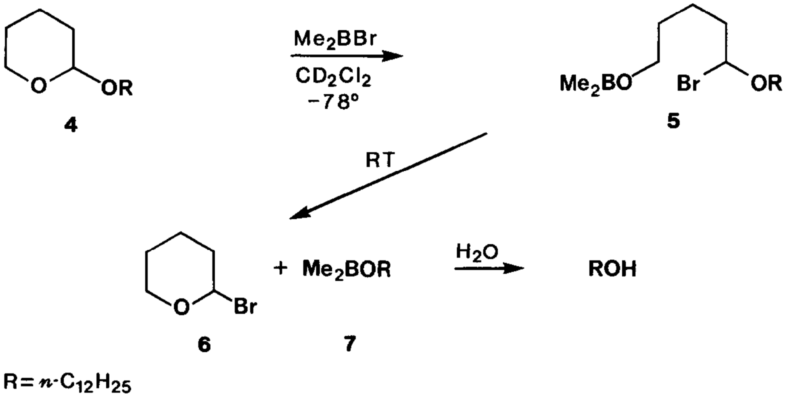
First, the reaction of Me_2BBr with a simple acetal (1), was studied by ^1H NMR (Scheme 1). When 1 was treated with Me_2BBr (2 eq.) in CD_2Cl_2 at -78°C, low-temperature ^1H NMR showed that the characteristic low-field signal for the acetal had immediately disappeared and was replaced by new a signal at 6.08 ppm (t, J = 5.2 Hz).[3] We attribute this new signal to H_a of the sensitive α-bromo ether 2.[4]

SCHEME 1



A similar low-temperature ^1H NMR experiment was then performed to study the reaction of Me_2BBr with the THP ether of dodecanol (4). We found, to our surprise, that this acetal also reacted instantly and completely at -78°C. The identity of the product was also of considerable interest as the ^1H NMR spectrum showed a new low-field signal at 6.10 ppm (t, J = 5.0 Hz). On the basis of the similarity in chemical shift and coupling constant of this signal with that from 2, we attribute this new signal to the ring-opened α-bromo ether 5 (Scheme 2). Upon warming the sample to room temperature, the signal at 6.10 ppm disappeared (over >25 h) and was replaced by a new signal at 6.78 ppm (br) corresponding to 2-bromotetrahydropyran (6).[5] Similar observations where made when the THF ether of dodecanol (8) was used in place of 4.

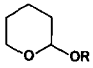
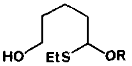
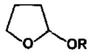
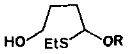
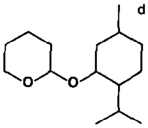
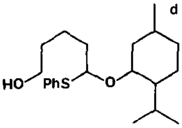
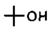
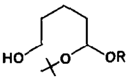
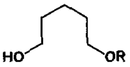
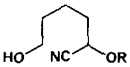
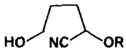
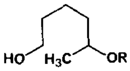
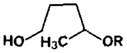
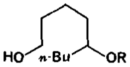
SCHEME 2



These results explain the anomalously slow cleavage of THP and THF ethers by Me_2BBr, as judged by production of the parent alcohol.[2b] In fact, Me_2BBr reacts very quickly at -78°C with THP and THF ethers, as it does with other acetals and ketals. The kinetic product (5), however, is that resulting from selective cleavage of the ring carbon-oxygen bond. Hydrolysis of 5, while giving some of the desired alcohol, also regenerates starting material (4) by cleavage of the boron-oxygen bond and recyclisation.[6] The kinetic product (5) is converted slowly at room temperature to the thermodynamic products (6 and 7). Hydrolysis of 7 generates the parent alcohol.

In order to provide further evidence for the ring-opened α-bromo ether and also to demonstrate the synthetic utility of this reaction, we have trapped the intermediate with a variety of nucleophiles to generate acyclic derivatives (Table). As can be seen from the table, THP ethers usually gave higher yields of ring-opened products than did the corresponding THF ethers.[7] Thiol nucleophiles reacted smoothly and generally afforded high yields of hydroxy-O,S-acetals (entries 1-3).[8] In the case of oxygen nucleophiles, low yields were obtained using methanol or methoxide under a variety of conditions, however, tert-butanol gave an excellent yield of the ring-opened hydroxy-acetal from THP ether 4 (entry 4).[9] Ring-opened reduction products were obtained when the α-bromo ether intermediate was treated with lithium triethylborohydride (entries 5 and 6). When silver cyanide was used, acyclic cyanoalkyl ethers were produced (entries 7 and 8). Excellent yields of ring-opened products were obtained from either THP or THF ethers using methylmagnesium bromide as nucleophile (entries 9 and 10). Higher alkyllithium or Grignard reagents however, gave complex product mixtures. These could be avoided by using lithium dialkyl cuprates (entry 11).[10]

RING OPENING OF THP AND THF ETHERS USING Me_2BBr[a]

ENTRY	SUBSTRATE	NUCLEOPHILE	PRODUCT[b]	YIELD[c]
1)	 4	EtSH		90%
2)	 8	EtSH		62%
3)	 [d]	PhSH	 [d]	90%
4)	4			87%
5)	4	$LiEt_3BH$		86%
6)	8	$LiEt_3BH$[e]		67%
7)	4	AgCN[e,f]		87%
8)	8	AgCN[e,f]		39%
9)	4	CH_3MgBr[e,g]		92%
10)	8	CH_3MgBr[e,g]		94%
11)	4	n-Bu_2CuLi[e,g]		89%

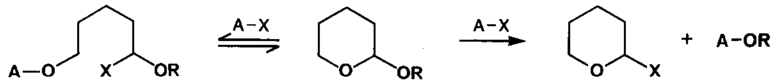
$R = n\text{-}C_{12}H_{25}$

a) UNLESS STATED OTHERWISE, ALL REACTIONS WERE CARRIED OUT IN CH_2Cl_2 USING A CONCENTRATION OF 0.1 M IN SUBSTRATE AND 2.0 eq. OF Me_2BBr AT -78°C FOR 30 MIN. N,N-DIISOPROPYLETHYLAMINE (2.5 eq.) AND NUCLEOPHILE (3.0 eq.) WERE THEN ADDED. b) ALL NEW PRODUCTS HAD SATISFACTORY SPECTRAL (NMR, IR AND MASS SPECTRA) AND ANALYTICAL (COMBUSTION ANALYSIS OR HIGH RESOLUTION MASS SPECTRUM) DATA. c) ISOLATED YIELDS OF PURIFIED PRODUCTS. d) DIASTEREOMER MIXTURE. e) NO N,N-DIISOPROPYLETHYLAMINE WAS USED. f) THE REACTION WAS WARMED TO -25°C AFTER ADDITION OF THE NUCLEOPHILE. g) ADDED AS A SOLUTION IN ETHER.

These results are also of interest from a mechanistic standpoint: While there exist in the literature isolated examples of similar transformations,[8,10-12] it is more often found that cleavage of the exocyclic carbon-oxygen bond is the favoured process when acetals of this type are treated with Brønstead or Lewis acids.[12-17] For example, studies on the acid catalysed hydrolysis of THP alkyl ethers suggest that these reactions proceed by formation of a cyclic oxonium ion.[13] Similarily, the reaction of TMSI or TMSBr with THF or THP ethers gives 2-halotetrahydrofurans or 2-halotetrahydropyrans respectively.[14,15]

More data will have to be collected before the unusual regioselectivity of Me_2BBr can be explained. At this stage, however, we would like to propose that, in non-participating solvents, acid catalysed cleavage of the ring carbon-oxygen bond of THP and THF ethers is the kinetically favoured process. The fact that ring-opened products are not observed in many reported cases may reflect the instability of the ring-opened intermediates (Scheme 3). With an acid reagent (Lewis or Brønstead) represented by the formula A-X, where for example, A is a H atom or TMS group, recyclisation of the ring-opened intermediate might be fast, even at -78°C, so that only the thermodynamic products are observed. When A is Me_2B, the deactivating nature of the boron-oxygen bond[18] slows the recyclisation down considerably so that the ring-opened intermediate is observed and can be trapped.

SCHEME 3



In summary, dimethylboron bromide reacts with THP and THF ethers to generate α-bromo ether intermediates resulting from selective cleavage of the ring carbon-oxygen bond. These intermediates can be trapped with a variety of nucleophiles to generate ring-opened products.

Notes and References

1. Presented in part at the 69th Canadian Chemical Conference, Saskatoon, Sask., June, 1986.
2. a) Y. Guindon, H.E. Morton, C. Yoakim, Tetrahedron Lett., (1983), 24, 3969. b) Y. Guindon, C. Yoakim, H.E. Morton, J. Org. Chem., (1984), 49, 4538. c) H.E. Morton, Y. Guindon, J. Org. Chem., (1985), 50, 5379.
3. This solution could be warmed to room temperature and α-bromo ether 2 could be isolated by evaporation of the excess Me_2BBr and postulated byproduct (Me_2BOEt). Some hydrolysis of 2 to the corresponding aldehyde occurred, but no significant change in the NMR spectrum of 2 was seen.
4. The intermediacy of an α-bromo ether in the reaction of Me_2BBr with an acetal had previously been inferred on the basis of trapping experiments.[2]
5. C.B. Anderson, D.T. Sepp, J. Org. Chem., (1967), 32, 607.
6. In one experiment, THP ether 4 was treated with Me_2BBr (2 eq.) for 30 min. at -78°C. Examination of the reaction mixture by TLC showed approximately equal amounts of starting material and dodecanol. Quenching the reaction at this stage, by pouring the solution into a mixture of 10% K_2CO_3 and THF, followed by aqueous workup and flash chromatography, gave more than 90% recovered THP ether 4.
7. Low-temperature ^1H NMR studies have shown that recyclisation of the acyclic α-bromo ether derived from a THF ether is faster than recyclisation of the corresponding intermediate derived from a THP ether.
8. Et_2AlSPh also gives ring-opened hydroxy-O,S-acetals from certain THP ethers: Y. Masaki, Y. Serizawa, K. Kaji, Chem. Lett., (1985), 1933.
9. The yield of hydroxy-acetal increased as the steric bulk of the oxygen nucleophile increased (ie. methanol < n-butanol < iso-propanol < tert-butanol).
10. $BF_3.Et_2O$ catalysed the reaction of $heptyl_2CuLi$ with 2-methoxytetrahydropyran to give exclusively the ring-opened product: A. Ghribi, A. Alexakis, J.F. Normant, Tetrahedron Lett., (1984), 25, 3075.
11. $BF_3.Et_2O$ also catalysed a rearrangement of the THP ether of allyl alcohol with ring opening: I.T. Kay, E.G. Williams, Tetrahedron Lett., (1983), 24, 5915.
12. The reaction of 2-alkoxytetrahydropyrans with PCl_3 gave mixtures of cyclic and acyclic α-chloro ethers: M.B. Gazizov, A.I. Razumov, I.Kh. Gizatullina, L.P. Ostanina, Zh. Obshch. Khim., (1980), 50(3), 687.
13. J.L. Jensen, W.B. Wuhrman, J. Org. Chem., (1983), 48, 4686.
14. T.H. Chan, S.D. Lee, Tetrahedron Lett., (1983), 24, 1225.
15. In accord with these reports, when we examined (by low-temperature ^1H NMR) the reactions of THP ether 4 with HBr and TMSBr, 2-bromotetrahydropyran (6) was the only product detected. No ring-opened products were observed, even at -78°C.
16. T. Tsunoda, M. Suzuki, R. Noyori, Tetrahedron Lett., (1980), 21, 71.
17. O. Takazawa, K. Kogami, K. Hayashi, Bull. Chem. Soc. Jpn., (1984), 57, 1876.
18. Overlap of the oxygen lone-pair electrons with the empty orbital on boron should decrease the oxygen nucleophilicity. For a similar use of the effect of the boron-oxygen bond on oxygen basicity see: J.E. McMurry, M.D. Erion, J. Amer. Chem. Soc., (1985), 107, 2712.

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