CLEAVAGE OF CYCLIC ETHERS WITH BORON BROMIDE. A CONVENIENT ROUTE TO THE BROMOSUBSTITUTED ALCOHOLS, ALDEHYDES AND KETONES†

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Abstract - Cyclic ethers are readily cleaved by BBr_3 under mild conditions, providing the corresponding ω-bromoalkylborates (1). Redistribution of 1 with methanol affords ω-bromoalcohols (2). Oxidation of 1 with pyridinium chlorochromate forms the corresponding ω-bromoaldehydes (3). Under these conditions, epoxides yield first the borates of the corresponding bromohydrins, with subsequent oxidation of the intermediate (without isolation), giving the α-bromoketones in high purity and satisfactory yield.

Heterobifunctional alkanes play an important role in organic synthesis. In the preparation of unsaturated straight-chain compounds via the Wittig reaction, ω-haloaldehydes or alcohols serve as useful intermediates. For example, ω-bromoalcohols are valuable starting materials in the synthesis of some insect pheromones[1,2] and prostaglandins.[3] However, a systematic study of the preparation of such compounds from simple precursors has not been reported in the literature. We wish to report a convenient and general approach for the preparation of such derivatives from the readily available cyclic ethers.

The use of boron halides as ether cleavage reagents is well-documented in the literature.[4] Lately, boron bromide (BBr_3) has become the reagent of choice for such reactions.[5] It is more effective than boron chloride (BCl_3) and reacts cleanly and quantitatively under mild conditions. Consequently, we undertook to examine the cleavage of cyclic ethers with BBr_3 as a potential synthetic route to ω-bromoalcohols, ω-bromoaldehydes, and α-bromoketones.

Representative cyclic ethers react smoothly with BBr_3. The ether was added to a solution of BBr_3 in CH_2Cl_2 at 0°C in order to avoid any possible polymerization of the cyclic ether. After the initial exothermic reaction subsided, the mixture was heated for 1 h under reflux (40°C), forming the ω-bromoalkylborate (1) quantitatively (^{11}B nmr: δ 18 ppm, typical of borate esters) (Eq 1).

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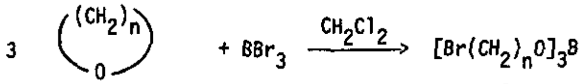
† Dedicated to Professor Herbert C. Brown in recognition of his fascinating contributions to chemistry.



1 (1)

Redistribution of 1 with excess of methanol provides the corresponding ω-bromoalcohol (2), which can be distilled following removal of methanol and methyl borate under aspirator vacuum (Eq 2).

$$\underset{1}{} + 3\ CH_3OH \xrightarrow{\Delta} \underset{2}{Br(CH_2)_nOH} + B(OCH_3)_3 \qquad (2)$$

In view of our recent findings that borate esters, like alcohols, can be directly oxidized to aldehydes and ketones,[6] we undertook to prepare ω-bromoaldehydes from 1. Indeed, the oxidation of 1 with pyridinium chlorochromate ($Pyr \cdot HCl \cdot CrO_3$, PCC)[7] does provide the desired aldehydes (3) in satisfactory yields (Eq 3).

$$1 + Pyr \cdot HCl \cdot CrO_3 \xrightarrow{CH_2Cl_2} \underset{3}{Br(CH_2)_{n-1}CHO} \qquad (3)$$

The oxidation reaction is operationally simple, involving the addition of 1 to a suspension of PCC in CH_2Cl_2, followed by heating the mixture under reflux for 1 h. The usual workup[6,7] provides the desired ω-bromoaldehydes (3) in good yields (Table I).

TABLE I. Preparation of ω-Bromoalcohols and ω-Bromoaldehydes From Cyclic Ethers

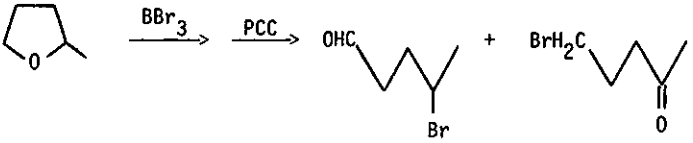
Ether	Product[a,b]	Yield[c] %	bp °C/mm	n^{20}_D
Tetrahydrofuran	4-Bromo-1-butanol	66	68-72/0.2	1.5035
	4-Bromobutanal	70	66-68/18	1.4763
Tetrahydropyran	5-Bromo-1-pentanol	86	72-74/0.2	1.4875
	5-Bromopentanal	72	87-89/12	1.4762
Oxepane	6-Bromo-1-hexanol	82	74-76/0.25	1.4852
	6-Bromohexanal	62	72-75/1.5	1.4753

[a] ^1H nmr spectra were consistent with the structures.

[b] Most of the products are unstable and tend to turn into dark viscous materials after some time; therefore, nmr spectra and $n^{20}D$ are recorded immediately following distillation.

[c] Yields of isolated products.

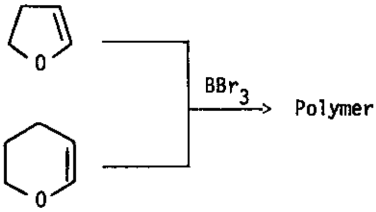
The success with simple symmetrical ethers encouraged us to examine the cleavage of unsymmetrically substituted cyclic ethers. Unfortunately, 2-methyltetrahydrofuran and 2-methyltetrahydropyran form an approximately 1:1 mixture of the two possible cleaved products. These can be estimated by ^{1}H nmr spectral methods upon oxidation with PCC (Eq 4).



(4)

Lowering the temperature of reaction with BBr_3 had no significant effect upon the isomer distribution.

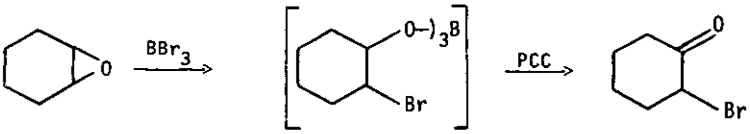
Unsaturated cyclic ethers, such as 2,3-dihydrofuran and 2,3-dihydropyran, undergo polymerization in the presence of BBr_3 (Eq 5).



(5)

Such polymerization was rapid, even at lower temperatures.

α-Haloketones are highly useful synthetic intermediates. They have been prepared via a variety of methods.[8] We investigated the cleavage of representative epoxides by boron bromide, followed by PCC oxidation of the product (without isolation) as a new approach to α-bromoketones (Eq 6) (Table II).



(6)

Indeed, 7-oxabicyclo[2.2.1]heptane afforded 4-bromocyclohexanone in 80% yield. Other epoxides reacted similarly.

TABLE II. Preparation of Bromoketones From Epoxides

Epoxide	Bromoketone[a]	Yield[b] %	bp °C/mm
Cyclopentene oxide	2-Bromocyclopentanone	77	50-51/1.2
Cyclohexene oxide	2-Bromocyclohexanone	82	60-61/2.4
Cyclooctene oxide	2-Bromocyclooctanone	67	81-83/1.0
7-Oxabicyclo[2.2.1]heptane	4-Bromocyclohexanone	80	65-68/3.0

[a] ^1H nmr spectra are consistent with the assigned structure.

[b] Isolated yields.

The following procedure for the preparation of 5-bromo-1-pentanol is representative: To a well-stirred solution of BBr_3 (1.92 ml, 20 mM) in CH_2Cl_2 (25 ml) taken in a 100-ml reaction flask[9] equipped with a reflux condensor, was added tetrahydropyran (5.87 ml, 60 mM) dropwise at 0°C, under nitrogen. Following completion of the addition, the reaction mixture was heated under reflux for 1 h; 1 formed completely (^{11}B nmr: δ 18). The solvent was removed and the residue was heated with 10 ml of methanol under reflux for 1 h. The volatile materials, methanol and methyl borate, were removed under reduced pressure and 8.7 g (86% yield) of 5-bromo-1-pentanol was obtained by distillation: bp 72-74°/0.2 mm, $n^{20}D$ 1.4875.

For the preparation of 5-bromopentanal, the CH_2Cl_2 solution of 1 was added to PCC (17.3 g, 80 mM) in CH_2Cl_2 (150 ml) and heated under reflux for 1 h. Dilution with Et_2O (150 ml), filtration through Florisil, followed by distillation, provided 7.1 g (72% yield) of 5-bromopentanal (Table I). The bromoketones were prepared from the borates of the bromohydrins by similar procedures.

In conclusion, cleavage of cyclic ethers with BBr_3 is an efficient method for the preparation of ω-bromoalcohols. Oxidation of the intermediate borate ester with pyridinium chlorochromate provides the corresponding ω-bromoaldehydes. Epoxides, when treated likewise, provide α-bromoketones in high yields. This represents an operationally simple, one-pot synthesis of such heterobifunctional organic compounds from readily available cyclic ethers.

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