

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

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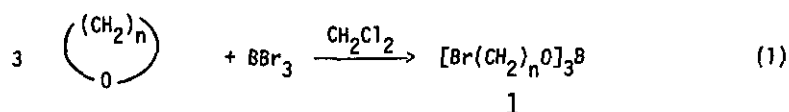
Abstract - Cyclic ethers are readily cleaved by BBr_3 under mild conditions, providing the corresponding ω -bromoalkylborates (1). Redistribution of 1 with methanol affords ω -bromoalcohols (2). Oxidation of 1 with pyridinium chlorochromate forms the corresponding ω -bromoaldehydes (3). Under these conditions, 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.

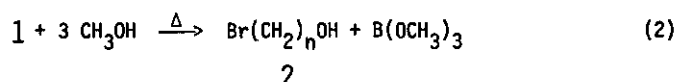
The use of boron halides as ether cleavage reagents is well-documented in the literature.⁴ Lately, boron bromide (BBr_3) has become the reagent of choice for such reactions.⁵ It is more effective than boron chloride (BCl_3) and reacts cleanly and quantitatively under mild conditions. Consequently, we 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).

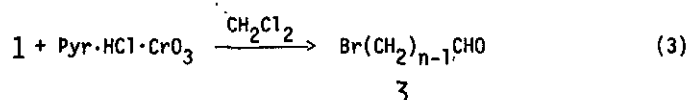
[†] Dedicated to Professor Herbert C. Brown in recognition of his fascinating contributions to chemistry.



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).



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·HCl·CrO₃, PCC)⁷ does provide the desired aldehydes (3) in satisfactory yields (Eq 3).



The oxidation reaction is operationally simple, involving the addition of 1 to a suspension of PCC in CH₂Cl₂, 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 _D ²⁰
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

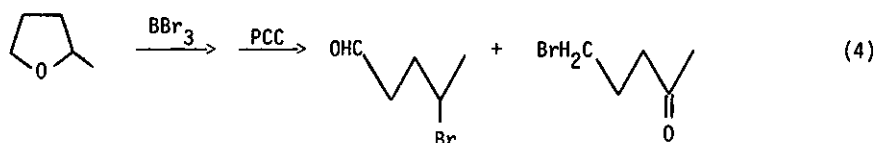
^a ¹H nmr spectra were consistent with the structures.

^b Most of the products are unstable and tend to turn into dark viscous materials after some time; therefore, nmr spectra and n_D²⁰ are recorded immediately following distillation.

^c Yields of isolated products.

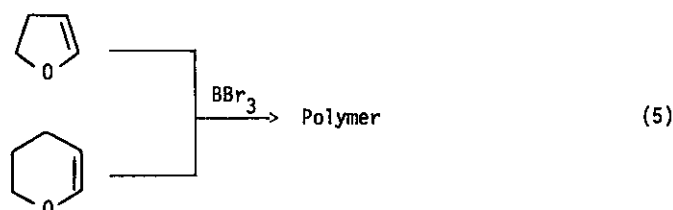
The success with simple symmetrical ethers encouraged us to examine the cleavage of unsymmetrically substituted cyclic ethers. Unfortunately, 2-methyltetrahydrofuran and 2-methyltetrahydropyran form an approximately 1:1 mixture of the two possible cleaved products. These can be

estimated by ^1H nmr spectral methods upon oxidation with PCC (Eq 4).



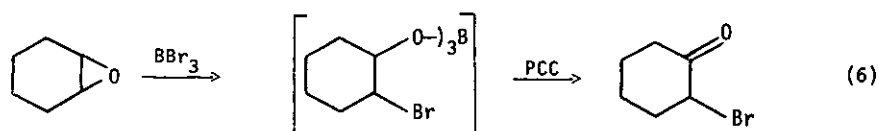
Lowering the temperature of reaction with BBr_3 had no significant effect upon the isomer distribution.

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



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).



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 BBr₃ (1.92 ml, 20 mM) in CH₂Cl₂ (25 ml) taken in a 100-ml reaction flask⁹ 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 (¹¹B 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_D^{20} 1.4875.

For the preparation of 5-bromopentanal, the CH₂Cl₂ solution of **1** was added to PCC (17.3 g, 80 mM) in CH₂Cl₂ (150 ml) and heated under reflux for 1 h. Dilution with Et₂O (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 BBr₃ 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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