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Regiocontrolled Opening of 2-Methyltetrahydrofuran with Various Boron Reagents*

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Regiocontrolled halogenative cleavage of 2-methyltetrahydrofuran with various *B*-bromoboranes, by a predominantly S_N2-type mechanism favouring the formation of primary bromide, is described. A comparative study of the relative reactivities of $BH_2Br{\cdot}SMe_2$, $BHBr_2{\cdot}SMe_2$, BBr_3, $(MeO)_2BBr$, and $MeOBBr_2$ revealed that the newly synthesized $(MeO)_2BBr$ is a highly promising regioselective reagent, especially at lower temperatures.

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Regioselective cleavage of unsymmetrical ethers is a highly promising transformation in organic synthesis. 1-Bromo-4-pentanol appears to be a very useful synthetic intermediate in natural product syntheses.[1] It can be achieved directly by the regiocontrolled brominative cleavage of 2-methyltetrahydrofuran by taking advantage of the different steric environments of the two ethereal C–O bonds. Several reagents including $MgBr_2/Ac_2O$,[2] RCOX/Pd^{II}/R_3SnX,[3] RCOX/Pt^{II},[4] MeCOCl/NaI,[5] ROCl/$ZnCl_2$,[6] PhCOCl/Hg/Al,[7] and ROCl/$BiCl_3$,[8] are available for the selective *O*-acylative ring opening of 2-methyltetrahydrofuran and subsequent trapping of carbo-cations with halides, leading to the formation of predominantly secondary alkyl halides. Primary halides have also been obtained by the regioselective cleavage of 2-methyltetrahydrofuran using $(n\text{-}C_4H_9)_4N^+Br^-$ or I^-/BF_3 etherate,[9] $AlCl_3$/NaI,[10] Me_3SiCl/NaI,[11] and *tert*-BuCOCl/NaI.[5] Boron halides and *B*-Br-9-BBN are well recognized as ether-cleaving reagents.[12] The BBr_3-assisted halogenative cleavage of 2-methyltetrahydrofuran yielded bromohydrins in a non-regioselective fashion. Guindon et al.[13] achieved the regiocontrolled ring opening of 2-methyltetrahydrofuran in a 3.5 : 1 regioisomeric ratio of 1-bromopentan-4-ol and 4-bromopentan-1-ol with dimethylboron bromide (Me_2BBr) at 0°C. Our longstanding interests in developing new boron-based reagents for organic synthesis persuaded us to synthesize the structurally modified *B*-bromoboranes $(MeO)_2BBr$ **4** and $MeOBBr_2$ **5**. Considering the synthetic importance of 1-bromo-4-pentanol and its ester derivatives, we undertook a comparative study of the regioselective brominative cleavage of 1-methyltetrahydrofuran with various *B*-bromoboranes. The preliminary results of this study with newly synthesized reagents $(MeO)_2BBr$ and $MeOBBr_2$, along with the commercially available $BH_2Br{\cdot}SMe_2$, $BHBr_2{\cdot}SMe_2$, and BBr_3, are described in this Communication.

Dimethoxyboron bromide, $(MeO)_2BBr$ **4**,[14] and methoxyboron dibromide, $MeOBBr_2$ **5**, were prepared by treating trimethylborate, $(MeO)_3B$, with boron tribromide, BBr_3 **3**, in appropriate ratios in either CH_2Cl_2 or *n*-pentane at −78 or 0°C (Scheme 1). The ^{11}B NMR spectrum showed a sharp peak at δ_B 22.6 (>95% chemical purity) for $(MeO)_2BBr$ in CH_2Cl_2 solvent, with the complete disappearance of BBr_3 (δ_B 41.0) and $(MeO)_3B$ (δ_B 18.0). A sharp ^{11}B NMR signal was seen at δ_B 26.0 for $MeOBBr_2$.

First, the regioselective cleavage of 2-Me-THF **6** was studied with the commercially available reagent $BH_2Br{\cdot}SMe_2$ **1**. The cleavage of **6** with **1** provided a mixture of regioisomeric bromohydrins (yield 80%), 1-bromopentan-4-ol **7**, and 4-bromopentan-1-ol **8** (3:1) in CH_2Cl_2 at room temperature in 24 h (Scheme 1, Table 1). No significant cleavage (<5%) occurred at −35°C for 24 h. The replacement of a hydrogen atom with an electronegative bromine atom ($BHBr_2{\cdot}SMe_2$ **2**) resulted in an enhanced reactivity of the reagent, but slightly lower regioselectivity (7:3). Boron tribromide, which is highly reactive, afforded a mixture of **7** and **8** (3:2) under identical reaction conditions (as for $BH_2Br{\cdot}SMe_2$ and $BHBr_2{\cdot}SMe_2$). The ^{11}B NMR study revealed that the cleavage of 2-Me-THF **6** with BBr_3 was complete in 0.5 h in CH_2Cl_2 at room temperature.

Next, we proceeded to test the effectiveness of these two newly synthesized *B*-bromoboranes, $(MeO)_2BBr$ **4** and $MeOBBr_2$ **5**, in the regioselective cleavage of cyclic ether **6**. During our study on regio- and chemoselective ring opening of epoxides,[14,15] $(MeO)_2BBr$ displayed relatively

* This paper is dedicated to the memory of my mentor, the late Professor Herbert C. Brown (1912–2004). The work described herein was carried out at Purdue University during my stay as a post-doctoral research associate (1995–2001).

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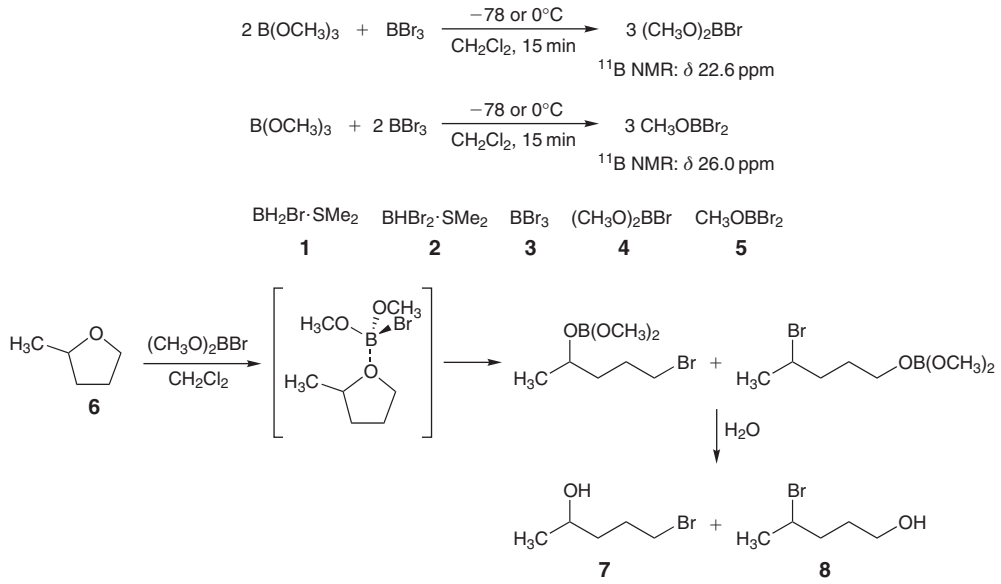

Scheme 1. Regiocontrolled brominative cleavage of 2-methyltetrahydrofuran with $(MeO)_2BBr$.

Table 1. Regiocontrolled cleavage of 2-methyltetrahydrofuran with various bromoboranes

Entry	Reagent	Reaction conditions[A]	OH / Br (7)	Br / OH (8)	Yield [%][B]
1	$BH_2Br{\cdot}SMe_2$	0°C → RT, 24 h	76	24	80
2	$BH_2Br{\cdot}SMe_2$	−78°C → RT, 18 h	76	24	55
3	$BH_2Br{\cdot}SMe_2$	−35°C, 24 h	–	–	<5
4	$BHBr_2{\cdot}SMe_2$	0°C → RT, 24 h	69	31	88
5	$BHBr_2{\cdot}SMe_2$	−78°C → RT, 16 h	72	28	88
6	$BHBr_2{\cdot}SMe_2$	0°C, 21 h	71	29	80
7	BBr_3	RT, 1.75 h	55	45	95
8	BBr_3	−78°C → RT, 18 h	62	38	93
9	$(MeO)_2BBr$	RT, 0.25 h	71	29	85
10	$(MeO)_2BBr$	−78°C → RT, 16 h	80	20	91
11	$(MeO)_2BBr$	−25°C, 21 h	76	24	83
12	$(MeO)_2BBr$	−78°C, 5 h	88	12	20
13	$(MeO)_2BBr$	−43°C, 20 h	85	15	90
14	$MeOBBr_2$	−78°C → RT, 16 h	67	33	90

[A] 1.20 equiv. of reagent used.
[B] Regioselectivity and chemical yields were determined by ^1H NMR spectroscopy using biphenyl as an internal standard.

higher reactivity by cleaving 7-oxanorbornane into *trans*-4-bromocyclohexan-1-ol in 1 h at −78°C, but Me_2BBr took 4 h at 0°C. ($BH_2Br{\cdot}SMe_2$ **1** failed even after 4 h at −78°C; it could only cleave at room temperature in 16–24 h.) As expected, this new reagent **4** very efficiently cleaved cyclic ether **6** in less than 15 min at room temperature. The observed lower regioselectivity (2.4:1) can be attributed to such higher reactivity of this reagent. An optimal chemical yield (90%) with regioselectivity (5.65:1) was achieved when the reaction was conducted at −43°C for 20 h. The cleavage was slow at −78°C (only 18–20% conversion after 5 h). Finally, the cleavage of 2-Me-THF **6** was studied with the new reagent **5** under identical conditions (at −78°C, 12 h, then slow warming, 12 h), which provided a regioisomeric mixture of **7** and **8** (2:1) in comparison with $(MeO)_2BBr$ **4** (3.7:1).

In conclusion, *B*-bromoboranes react with unsymmetrical cyclic ether 2-methyltetrahydrofuran in a regiocontrolled fashion by a predominantly S_N2-type reaction pathway, affording primary bromide. The temperature of the reaction has a strong effect on the regioselectivity, especially with dimethoxyboron bromide **4**. Dimethoxyboron bromide appears to be the reagent of choice. The simple and convenient method of preparation of these reagents, shorter reaction times, high reactivities, and simple workup procedures should make these reagents highly practical in synthetic organic

chemistry. Further studies into the use of these new and other structurally modified reagents will be reported.

Experimental

Manipulations and reactions with air-sensitive compounds were carried out under nitrogen. Glassware was oven-dried, assembled while hot, and cooled in a stream of dry nitrogen gas. ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded on a Varian–Gemini 300 MHz multinuclear NMR spectrometer. The ^{11}B NMR chemical shifts are reported as δ relative to $BF_3{\cdot}OEt_2$. The starting substrate, 2-methyltetrahydrofuran **6**, $BH_2Br{\cdot}SMe_2$ **1**, $BHBr_2{\cdot}SMe_2$ **2**, BBr_3 **3**, and $B(OCH_3)_3$ were purchased from Aldrich. Dichloromethane (CH_2Cl_2) was distilled over P_2O_5 and stored under nitrogen.

*Preparation of Methoxyboron Dibromide **5***

The new reagent, methoxyboron dibromide **5**, was prepared by mixing trimethyl borate (1.0 equiv.) with boron tribromide (2.0 equiv.) in either dichloromethane or *n*-pentane at −78 or 0°C under nitrogen. The ^{11}B NMR spectrum showed a sharp peak at δ_B 26.0 (>95% chemical purity) for $MeOBBr_2$ in CH_2Cl_2 with the complete disappearance of BBr_3 (δ_B 41.0) and $(MeO)_3B$ (δ_B 18.0).

*Regioselective Cleavage of 2-Methyltetrahydrofuran **6** with $(MeO)_2BBr$ **4***

To a cooled stirred solution of $(MeO)_2BBr$ **4** (6.0 mmol) in anhydrous CH_2Cl_2 (20 mL) at −43°C under nitrogen atmosphere, was slowly added neat 2-methyltetrahydrofuran **6** by syringe. The resulting reaction mixture was stirred at −43°C for 20 h, and then treated with water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), organic extracts were combined, dried (Na_2SO_4), filtered, and evaporated under vacuum. The regioselectivity (**7**:**8** 5.65:1) was determined on the basis of ^{1}H NMR spectroscopic data by integrating and comparing the protons attached to either –OH or –Br present in both regioisomers. The chemical yield (90%) was determined by ^{1}H NMR spectroscopy using biphenyl as an internal standard. **7** and **8**: δ_H ($CDCl_3$) 4.15 (m, C*H*OH), 3.85 (m, CHBr), 3.65 (t, CH_2OH), 3.45 (t, CH_2Br), 2.10–1.80 (m, CH_2CH_2CH_2), 1.73 (d, CH(OH)CH_3), 1.70–1.50 (m, CH_2CH_2CH_2), 1.21 (d, CH(Br)CH_3).

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