Dimethoxyboron bromide – a new, efficient, regio- and chemoselective reagent for the conversion of terminal epoxides into bromohydrins

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Dimethoxyboron bromide, $(MeO)_2BBr$, easily prepared in excellent yield from boron tribromide and trimethyl borate, is a new, efficient, regio- and chemoselective reagent useful for the halogenative cleavage of compounds containing epoxy groups into vicinal bromohydrins in the presence of ether, acetal, ketal, *N*-oxide, and sulfoxide groups, at low temperatures (–78°C).

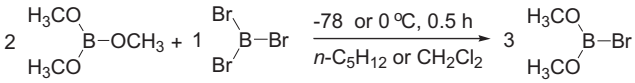
Keywords: dimethoxyboron bromide, epoxide, bromohydrin, regioselectivity, chemoselectivity

Vicinal halohydrins serve as very important precursors of a wide variety of functional groups.[1] These β-halohydrins are also key intermediates in the syntheses of halogenated marine natural products (Laurenyne, Aplysiapyranoid A) and many other medicinally valuable products (Immunosuppressant ISP-1, Thienamycin, Antiviral Nucleosides).[2,3] They are also very useful in ring contraction, ring expension, and molecular rearrangement reactions.[4,5] Therefore, there is a continued interest in developing simple, mild, and convenient procedures for the regiospecific conversion of epoxides into β-halohydrins. Although a number of reagents have been introduced for the ring opening of epoxides to vicinal halohydrins, they are not always fully satisfactory and suffer from certain disadvantages, such as a corrosive nature, low regioselectivity, high reactivity, acidity, *in situ* preparation and handling of the reagent, longer reaction times, skeletal rearrangement, and byproduct formation.[6] Recently, there have been several new procedures reported on the regioselective ring opening of epoxides into halohydrins using cerium(III) chloride, lithium halides/β-cyclodextrin, LiX/AcOH, X_2/2,6-bis[2-(*o*-aminophenoxy)methyl]-4-bromo-1-methoxy-benzene (BABMB) catalyst, $(CH_3O)_3B$-MX, X_2/isoniazide, and X_2/thiourea catalyst.[7]

Haloboranes (BX_3) are highly reactive reagents for the cleavage of carbon–oxygen bonds.[8] A number of structurally modified haloboranes (R_2BX) of diminished reactivity have been prepared which have proven to be promising reagents for the regio-, chemo- and enantioselective ring opening of oxiranes to the corresponding halohydrins.[9] It is evident from the literature that there is a need for a non-aqueous source of "soft" nucleophilic halide ion that would open an epoxy moiety with high degrees of regio-, chemo-, and stereoselectivity without attacking other acid- and base-sensitive functional groups. In 1998, we reported our preliminary study on the ring opening of epoxides with *B*-haloboranes, especially with *B*-bromoboranes and successfully demonstrated their synthetic utilities in the regio- and stereocontrolled cleavage of epoxides.[10] We now report that dimethoxyboron bromide, readily prepared from $(MeO)_3B$ and BBr_3, reacts very efficiently with terminal epoxides to give the corresponding β-bromohydrins in high regioisomeric purity and high chemical yield. The quantitative recovery of compounds bearing reactive C–O bonds, such as, allyl ether, acetals, and ketals during the ring cleavage process clearly demonstrates the functional group tolerance (chemoselectivity) by this new reagent.

The reagent, dimethoxyboron bromide, $(MeO)_2BBr$, is prepared by mixing trimethyl borate (2.0 equiv) with the corresponding boron tribromide (1.0 equiv) in either dichloromethane or *n*-pentane at 0°C (Scheme 1). The ^{11}B NMR spectrum shows a sharp peak at δ 22.6 ppm (>95% chemical purity) for $(MeO)_2BBr$ in CH_2Cl_2 with the complete disappearance of BBr_3 (δ 41.0 ppm) and $(MeO)_3B$ (δ 18.0 ppm).

When 1,2-epoxydodecane is reacted with dimethoxyboron bromide at room temperature, only 60% 1-bromo-2-alkanol is formed along with 40% 2-bromo-1-alkanol (Scheme 2). An improved regioselectivity (90% 1-bromoalkan-2-ol) is

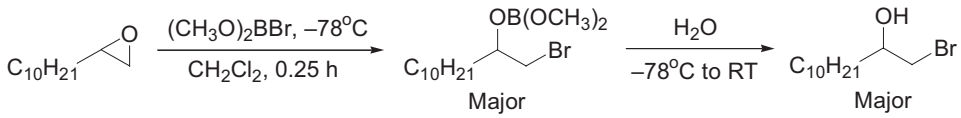


Scheme 1 Preparation of dimethoxyboron bromide.

Table 1 Regioselective cleavage of 1,2-epoxydodecane with $(MeO)_2BBr$[a] in dichloromethane or *n*-pentane at different temperatures

Entry	Epoxide (R)	Solvent/temp/time	% $RCH(OH)CH_2Br$[b]	% $RCH(Br)CH_2OH$	% Yield[c]
1	$C_{10}H_{21}$	*n*-C_5H_{12}/RT/0.25 h	60	40	90
2	$C_{10}H_{21}$	*n*-C_5H_{12}/0 °C/1 h	66	33	95
3	$C_{10}H_{21}$	*n*-C_5H_{12}/–78 °C/3.5 h	89	11	90
4	$C_{10}H_{21}$	CH_2Cl_2/0 °C/0.25 h	66	33	95
5	$C_{10}H_{21}$	CH_2Cl_2/–78 °C/0.25 h	81	19	93 (88)[d]

[a]1.0 Equiv of the reagent used. [b,c]Regioselectivities and the chemical yields (isolated yields after reaction workup) were determined by 300 MHz ^1H NMR spectroscopy using biphenyl as an internal standard. [d]Isolated yield is given in the parentheses after column chromatography.



Scheme 2 Reaction of dimethoxyboron bromide with 1,2-epoxydodecane.

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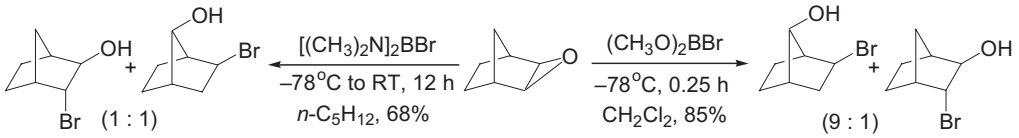
Table 2 Regioselective cleavage of representative terminal epoxides with $(MeO)_2BBr$[a] in CH_2Cl_2

Entry	Epoxide (R)	Temp/time	% $RCH(OH)CH_2Br$[b]	% $RCH(Br)CH_2OH$	% Yield[c,d]
1	$C_{10}H_{21}$	–78°C/0.25 h	81	19	93 (88)
2	$PhCH_2$	–78°C/0.25 h	92	8	97 (91)
3	$ClCH_2$	–78°C/0.25 h	98	2	93 (85)
4	$BrCH_2$	–78°C/0.25 h	90	10	93 (88)
5	Ph	–78°C/0.25 h	4	96	75 (70)
6	$H_2C=CH(CH_2)_4$	–78°C/0.25 h	85	15	98 (90)
7	$PhOCH_2$	–78°C/0.25 h	95	5	90 (86)
8	$(CH_3)_2CHOCH_2$	–78°C/0.25 h	95	5	93 (88)
9	$CHF_2CF_2OCH_2$	–78°C/0.25 h	95	5	98 (92)

[a]1.0 Equiv of the reagent used. [b,c]Regioselectivities and the chemical yields (isolated yields after reaction workup) were determined by 300 MHz ^1H NMR spectroscopy using biphenyl as an internal standard. [d]Isolated yields are given in the parentheses after column chromatography.



Scheme 3 Reaction of *exo*-2,3-norbornene oxide with $(MeO)_2BBr$ and $(Me_2N)_2BBr$.

observed at –78°C. Reversal of addition of the reagent has very little effect on product regioselectivity. In the case of dimethoxyboron bromide, the solvent polarity has very little or no effect on product regioselectivity whereas *B*-bromobis (dimethylamino)borane showed a complete reversal of product regioselectivity in CH_2Cl_2 (87% secondary bromide) and *n*-pentane (89% primary bromide).[9b] The results are summarised in Table 1.

Dimethoxyboron bromide readily reacts with a variety of epoxides even at –78°C to afford the corresponding bromohydrins in excellent chemical yields with high regioselectivity, as shown in Table 2. The nature of the side chain has a considerable effect on regioselective outcome. An increased proportion of primary bromides is observed with the glycidic ethers. In the case of styrene oxide, the secondary bromide predominates. The observed product distribution is in good agreement with the electrophile-assisted cleavage of epoxide following a "borderline S_N2" reaction pathway, except for the styrene oxide which appears to react by following an S_N1-type mechanism. It is interesting to observe that dimethoxyboron bromide reacts with *exo*-2,3-norbornene oxide to afford a mixture of products, the minor product being the expected β-bromohydrin, 2-*endo*-bromonorbornan-3-*exo*-ol (10–15%) and the major product being a carbocationic rearranged 2-*exo*-bromonorbornan-7-*syn*-ol (85-90%). On the other hand, *bis*-(dimethylamino)boron bromide yielded a 55 : 45 mixture of the expected β-bromohydrin and an isomeric rearranged bromoalcohol (Scheme 3). The results are summarised in Table 2.

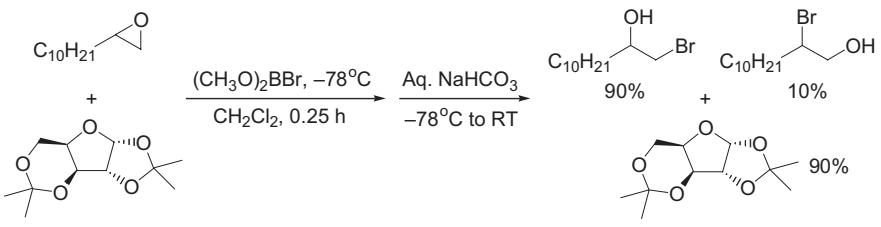
In order to explore further the chemoselectivity of this reagent, the epoxide opening reactions were carried out with dimethoxyboron bromide in the presence of an equivalent amount of other compounds bearing reactive functionalities, such as, alkyl-, allyl-, aryl ethers, pyranylacetal, and ketal (Table 3). The epoxy moiety was chemoselectively cleaved without affecting the reactive carbon–oxygen bonds. It was also interesting to note that 2,6-dimethyl-4-nitropyridine *N*-oxide and dibenzyl sulfoxide were quantitatively (>95%) recovered without any deoxygenation.

To understand the reactivity of the dimethoxyboron bromide, $(MeO)_2BBr$, 7-oxanorbornane, a cyclic ether, was reacted with $BH_2Br{\cdot}SMe_2$ and $(MeO)_2BBr$ at –78°C for 3 h, under similar reaction conditions. The reagent, $(MeO)_2BBr$ very efficiently cleaved the 7-oxanorbornane into the *trans*-4-bromocyclohexan-1-ol in >95% chemical yield whereas no ether cleavage product was observed with $BH_2Br{\cdot}SMe_2$

Table 3 Reaction of $(MeO)_2BBr$[a] with 1,2-epoxydodecane in the presence of various reactive compounds: chemoselectivity

Entry	Reactive compound	Solvent/temp/time	Bromohydrins /%[b]	Recovery of reactive compd/%[b]
1	Allyl phenyl ether	CH_2Cl_2/–78°C/4 h	88	89
2	1,3-Benzodioxole	CH_2Cl_2/–78°C/4 h	91	96
3	Dibenzyl sulfoxide	CH_2Cl_2/–78°C/0.25 h	90	98
4	4-Nitro-2,6-dimethylpyridine *N*-oxide	CH_2Cl_2/–78°C/0.25 h	90	95
5	1,2: 3,5-Di-*O*-isopropylidene-D-xylofuranose	CH_2Cl_2/–78°C/0.25 h	87	90

[a]1.0 Equiv of the reagent used. [b]Chemical yields (%) of the bromohydrins and the recovered reactive compounds after reaction workup were determined by 300 MHz ^1H NMR spectroscopy using biphenyl as an internal standard.



Scheme 4 Chemoselective cleavage of 1,2-epoxydodecane in presence of 1,2: 3,5-di-*O*-isopropylidene-D-xylofuranose.

(as seen by ^{1}H NMR of the crude product). In fact, >90% cleavage occurred within an hour with $(MeO)_2BBr$. This clearly demonstrates that $(MeO)_2BBr$ is a much more reactive reagent than $BH_2Br{\cdot}SMe_2$.

In summary, dimethoxyboron bromide $(MeO)_2BBr$, is a new, highly regio- and chemoselective reagent for the efficient cleavage of epoxides to vicinal bromohydrins even at low temperatures. Many other reactive ethereal carbon–oxygen bonds, such as alkyl, allyl and aryl ethers, pyranylacetals, and ketals at –78°C in 0.25 h and 1,2: 3,5-Di-*O*-isopropylidene-D-xylofuranose, a valuable intermediate in the carbohydrate chemistry, have been successfully accommodated during the cleavage of the epoxy moiety. This reagent complements the currently available methodologies due to its high regioselectivity and the compatibility with various sensitive functional groups.

Experimental

Except 1,2 : 3,5-Di-*O*-isopropylidene-D-xylofuranose (gifted by Dr. Mathivanan, Purdue University), all starting materials were purchased from the Aldrich Chemical Company. All products are known compounds (1,3-dibromo-2-propanol from Agroorganics); they were identified by comparison of their spectroscopic data with those of authentic samples.[6]

Preparation of dimethoxyboron bromide and its reaction with 1,2-epoxydodecane

The reagent, $(MeO)_2BBr$ (3.0 mmol, 0.5 M in CH_2Cl_2 or *n*-pentane) was prepared by adding BBr_3 (1.0 mmol) slowly to a stirred solution of trimethyl borate $(MeO)_3B$ (2.0 mmol) in CH_2Cl_2 or *n*-pentane (cooled at –78 or 0°C) under a nitrogen atmosphere. After 0.25 h, the ^{11}B NMR spectrum showed a sharp singlet peak at 22.6 ppm. The reagent $(MeO)_2BBr$ (3.0 mmol, 0.5 M in CH_2Cl_2 or *n*-pentane) was cooled to –78°C and the neat 1,2-epoxydodecane (2.80 mmol) was added dropwise. The reaction mixture was allowed to react for 0.25 h at –78°C. The intermediate boron species (^{11}B: δ 18.0 ppm) was treated with water (5 ml) at –78°C and the reaction mixture was allowed to warm up slowly (0.25 h). The resulting bromohydrin was extracted with CH_2Cl_2 (3 × 25 ml), dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The regioselectivity and the chemical yields were determined by ^{1}H NMR spectroscopy using biphenyl (0.25 mmol) as internal standard. These vicinal bromohydrins were also purified by column chromatography on silica gel using 2–5% EtOAc in hexanes and characterised by spectroscopic means (Table 2).

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