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Note

A highly regio- and chemoselective synthesis of vicinal bromohydrins by ring opening of terminal epoxides with dibromoborane–dimethyl sulfide ☆

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Abstract

Dibromoborane–dimethyl sulfide ($BHBr_2$–SMe_2) displays high degrees of chemo- and regioselectivity during the brominative cleavage of the epoxy group into vicinal bromohydrins in the presence of alkene, alkyne, allene, ether, acetal and acetonide, besides its hydroborating ability. Several reducible functional groups, such as chloride, aldehyde, ketone, azide, ester, nitrile and *tert*-amino ester, have been successfully accommodated during the epoxide opening process.

Keywords: Epoxides; Bromohydrin; Dibromoborane–dimethyl sulfide; Regioselectivity; Chemoselectivity

1. Introduction

Vicinal halohydrins serve as valuable synthetic intermediates [1] which have found wide applications in the synthesis of halogenated marine products (laurenyne and isodactylyne) and other biologically useful substances (thienamycin and immunosuppressant ISP-1) [2]. The most common and practical method for the synthesis of β-halohydrins is the halogenative cleavage of epoxides. Although numerous methods and reagents have been developed to effect such transformations, they are not always fully satisfactory, especially with structurally complex organic molecules bearing sensitive functional groups [3]. Due to their high reactivity and Lewis acidity of *B*-haloboranes (BX_3), a number of structurally modified monofunctional *B*-haloboranes, such as, Me_2BBr [4a,4b], Ph_2BBr [4c] and $(Me_2N)_2BBr$ [4d] of diminished reactivity, have been synthesized and tested for the regio- and chemoselective ring opening of epoxides.

We have developed several new boron-based reagents, such as, Ipc_2BX (*B*-halodiisopinocampheylboranes) [5a,5b], Ter_2BX (*B*-haloditerpenylboranes) [5c], $(MeO)_2BX$ [5d,5e] that have proven to be highly effective in the regio-, chemo-, and enantioselective halogenative ring opening of epoxides. Encouraged by the report on the chemoselective cleavage of epoxide using BH_2Cl–SMe_2 by Bovicelli et al. [6], we exploited the synthetic utility of commercially available reagents, BH_2Br–SMe_2 and $BHBr_2$–SMe_2, as highly regioselective reagents for the conversion of epoxides into vicinal bromohydrins [7]. Since both bromine and hydrogen atoms in these reagents are transferable, it is of great interest to explore the chemoselectivity of these reagents in the ring opening of epoxides. Recently, we systematically investigated the regio- and chemoselective cleavage of terminal epoxides using BH_2Br–SMe_2 [8]. As expected, 1,2-epoxyoct-7-ene underwent 30–35% hydroboration at 0 °C. Also, the partial reduction of aromatic aldehydes

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

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and ketones was observed. Later, these problems were overcome by conducting the reactions at −25 °C, especially for alkenes and ketones. Considering the reactivity of BH_2Br–SMe_2 towards alkenes, aldehydes and ketones, it was of considerable interest to explore another commercially available reagent, which might regio- and chemoselectively cleave the epoxy moiety into bromohydrins in the presence of alkenes, ketones and other reactive functionalities, preferably at ambient temperature. Besides being an excellent hydroborating agent [9a], $BHBr_2$–SMe_2 has also been utilized in (a) deoxygenation of sulfoxides [9b] and (b) syntheses of 3-*O*-carboranylcarbenes and metal isocyanoborohydrides [9c]. Accordingly, we undertook a systematic study of the chemoselective ring opening of epoxides in the presence of a variety of reactive functional groups utilizing $BHBr_2$–SMe_2. In this note, we wish to report the regio- and chemoselective synthesis of vicinal bromohydrins from terminal epoxides utilizing the commercially available (Aldrich) reagent, $BHBr_2$–SMe_2.

2. Results and discussion

2.1. Regioselective ring opening of terminal epoxides

Dibromoborane–dimethyl sulfide very readily cleaved three representative terminal epoxides (entries 1–3) in 15 min at room temperature (Chart 1, Table 1). Dibromoborane–dimethyl sulfide ($BHBr_2$–SMe_2) cleaved 1,2-epoxydodecane **1** (entry 1) to the corresponding regioisomeric bromohydrins (**2** and **3**) in excellent chemical yield (90%) with regioselectivity (primary bromide **2**/secondary bromide **3** = 9/1) in CH_2Cl_2 in 0.25 h at room temperature (Scheme 1). Except for styrene oxide, the transfer of bromine was observed at the less hindered carbon (C-1), by S_N2'-type mechanism, in the cases of terminal substrates. In the case of styrene oxide **7** (entry 3), bromine is transferred at C-2 carbon (benzylic position) by following an apparent S_N1-type mechanism. The cleavage of C–O bond in 2-methyltetrahydrofuran was observed to be comparatively slow, but yielded primary bromide as a major product (total yield: 90%; regioselectivity: 71/29).

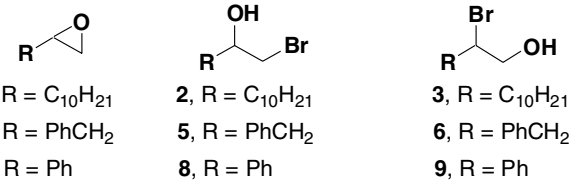
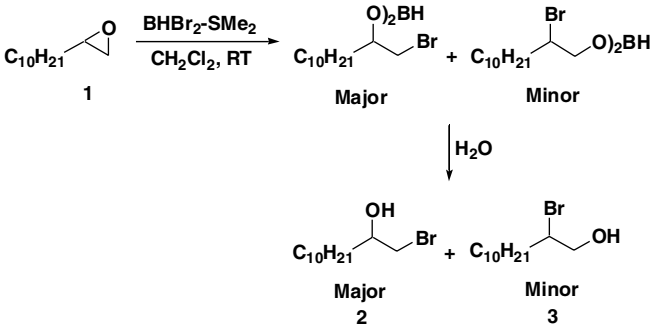


Chart 1. Representative epoxides and product bromohydrins.



Scheme 1. Regioselective cleavage of 1,2-epoxydodecane with $BHBr_2$–SMe_2 in CH_2Cl_2.

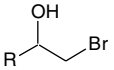
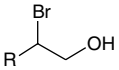
2.2. Chemoselective ring opening of 1,2-epoxyoct-2-ene *10*

First, we reexamined the chemoselective ring opening of 1,2-epoxyoct-7-ene **10**, which cleanly underwent brominative cleavage (87–90% yield, regioisomeric ratios (**11** & **12**) = 83/17, major primary bromide) at room temperature, without hydroborating the terminal alkene (Scheme 2). In the case of BH_2Br–SMe_2, the partial hydroboration of the terminal double bond was observed at both 0 °C and RT. Therefore, $BHBr_2$–SMe_2 should be preferred over BH_2Br– SMe_2 while conducting such a reaction on complex unsaturated target molecules.

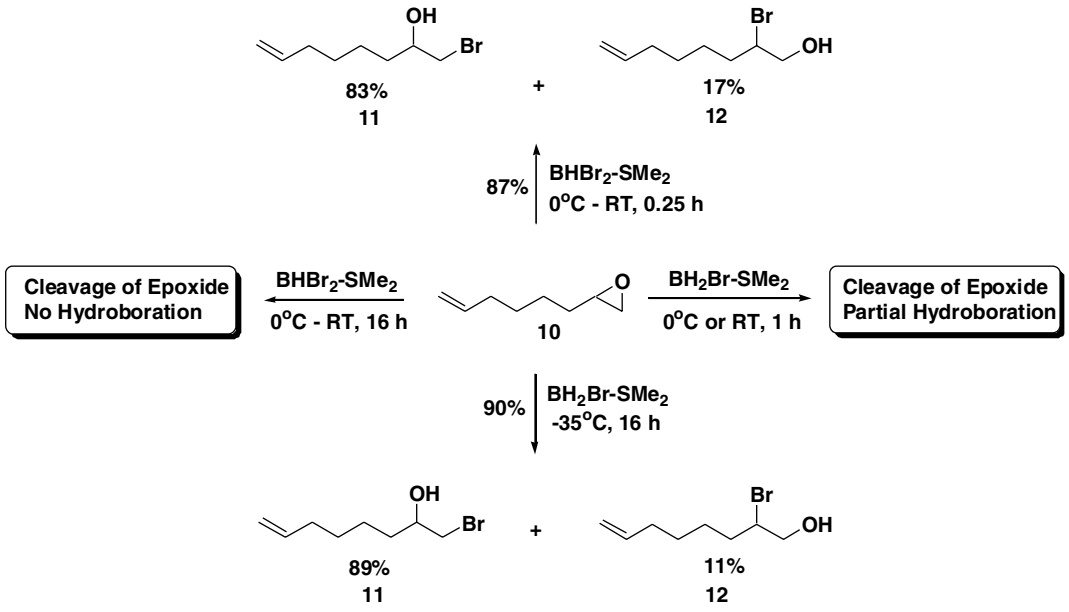
2.3. Chemoselective ring opening of 1,2-epoxydodecane *1*

After establishing the reaction conditions, we investigated the chemoselective cleavage of the 1,2-epoxydodecane **1** in the presence of few representative alkenes and alkynes at room temperature. This reagent preferentially reacts with the epoxy group in the presence of alkenes (entries 4–6), alkyne (entry 8) and allene (entry 7) (Scheme 3, Table 2). It was interesting to observe the chemoselective cleavage of ethereal C–O bond of the epoxy group in the presence of allyl-, aryl- and benzyl ethers (entries 4, 5 and 18), at room temperature.

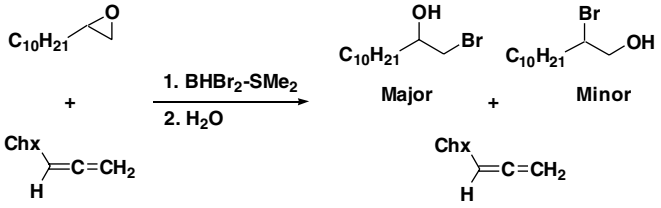
Table 1
Brominative cleavage of terminal epoxides with $BHBr_2$–SMe_2 in CH_2Cl_2 solvent

Entry		Reaction conditions[a]			Isolated yield[b,c] (%)
1	$C_{10}H_{21}$	RT/0.25 h	90	10	90
2	$PhCH_2$	RT/0.25 h	89	11	95
3	Ph	RT/0.25 h	07	93	83

[a] 1.10 equiv. of reagent used.
[b] Isolated yields.
[c] Combined yield.



Scheme 2. Chemoselective cleavage of 1,2-epoxyoct-7-ene with BH_2Br–SMe_2 and $BHBr_2$–SMe_2 in CH_2Cl_2.



Scheme 3. Chemoselective cleavage of 1,2-epoxydodecane with $BHBr_2$–SMe_2 in the presence of an allene, propa-1,2-dienylcyclohexane in CH_2Cl_2.

Acetals, ketals, and orthoesters are very useful synthetic intermediates, but they are very labile, especially in the presence of Lewis acids. Consequently, we examined the cleavage of 1,2-epoxydodecane in the presence of 1,2:3,5-di-*O*-isopropylidene-D-xylofuranose and glucopyranoside (entries 10 and 11). No cleavage of xylofuranose or glucopyranoside was observed at −25 °C. These structures are the integral parts of sugars and related molecules that are highly sensitive to such Lewis acids. No reduction of the azido group (entry 9) was observed during the epoxide opening reaction, under the present experimental conditions. Dichloroborane–dimethyl sulfide, $BHCl_2$–SMe_2 [10] is known to reduce organyl azides to the corresponding amines (Scheme 4). Bromohydrins were obtained in excellent yields with high regioselectivity and the recovery of most of the added "reactive" compounds was essentially quantitative.

Knowing the reducing ability of $BHBr_2$–SMe_2, the epoxide opening reactions were carried out with $BHBr_2$–SMe_2 in the presence of an equivalent amount of other compounds bearing reducible functionalities, such as, chloride, aldehyde, ketone, ester, and nitrile. In the cases of aromatic aldehydes (entries 12 and 13), considerable amounts of reduction products were observed at 0 °C, which were suppressed at −25 °C (Scheme 5). Again, considerable amounts of reduction of acetophenone and 4-cyanoacetophenone were observed at 0 °C with BH_2Br–SMe_2. No reduction of ketones, acetophenone and 4-acetylbenzonitrile (entries 14 and 15), were observed even at room temperature (with $BHBr_2$–SMe_2). Other reducible functional groups, such as, chloro, ester and nitrile (entries 12 and 16–18) were found to be unreactive even at room temperature during the epoxide opening process. The scope and generality of this chemoselective transformation is illustrated with various reactive functional groups and the results are summarized in Table 2.

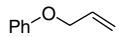
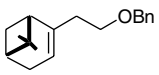
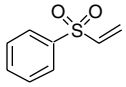
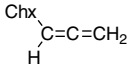
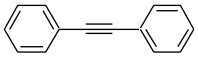
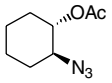
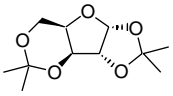
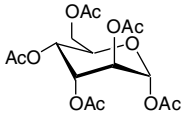
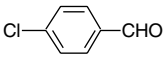
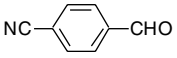
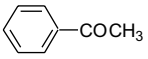
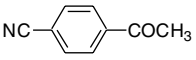
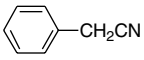
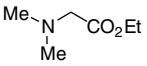
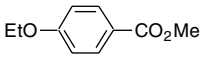
In summary, $BHBr_2$–SMe_2 chemoselectively cleaves the epoxy moiety in the presence of many other reactive alkenes, alkynes, and carbon–oxygen bonds, such as alkyl-, allyl-, aryl-, benzyl ethers, pyranylacetal, and ketal. This reagent has accommodated 1,2:3,5-di-*O*-isopropylidene-D-xylofuranose during the epoxide cleavage, which is very useful in the synthesis of carbohydrates and other marine natural products. Several reducible functional groups, such as aldehyde, ketone, nitrile, azide, chloro, and esters, remain unaffected during the reaction. This reagent has many advantages over currently available methodologies because of its simple reaction conditions, high regio- and chemoselectivity, and also commercial availability, which should make it synthetically more useful and valuable.

3. Experimental

3.1. General

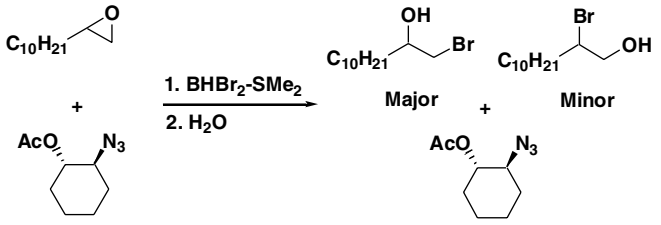
Manipulations and reactions with air-sensitive compounds were carried out under nitrogen atmosphere. ^1H, ^{13}C, and ^{11}B NMR spectra were recorded on

Table 2
Chemoselective cleavage of 1,2-epoxydodecane with $BHBr_2$–SMe_2 in the presence of various reactive compounds

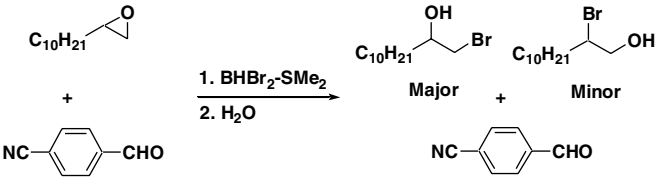
Entry	Reactive compound	Reaction conditions[a]	Bromohydrins yield[b] (%)	Recovered reactive compound[b] (%)
4		RT/0.25 h	98	99
5		RT/0.25 h	98	99
6		RT/0.25 h	95	90
7		RT/0.25 h	95	85
8		RT/0.25 h	95	95
9		0 °C/0.5 h	95	95
10		−25 °C/3 h	85	95
11		−25 °C/3 h	80	95
12		−25 °C/3 h	95	98
13		−25 °C/3 h	95	98
14		RT/0.25 h	95	99
15		RT/0.25 h	95	99
16		RT/0.25 h	95	98
17		RT/0.25 h	85	85
18		RT/0.25 h	98	99

[a] 1.0 equiv. of reagent used.
[b] Yields of the product bromohydrins and the recovered reactive compounds were determined by ^{1}H NMR using biphenyl as an internal standard.

Varian-Gemini 300 MHz multinuclear NMR spectrometer. The ^{11}B NMR chemical shifts are in δ relative to BF_3–OEt_2. All the starting materials (epoxides and other reactive compounds used for chemoselectivity study) were purchased from Aldrich Chemical Co. Glucosepentaacetate was gifted by Dr. P. Mathivanan, Purdue University. *trans*-1-Acetoxy-2-azidocyclohexane was prepared by the cleavage of *meso*-cyclohexene oxide with sodium azide and subsequent acetylation of *trans*-2-azidocyclohexan-1-ol. Regioselectivity of the reaction was determined by integrating and comparing the selected signals (either –C*H*Br and –CH_2Br protons or –C*H*OH and CH_2OH protons) of the regioisomers by ^{1}H NMR spectroscopy. The error in determining the regio- and chemoselectivity (using biphenyl as an internal standard) using integration method by ^{1}H NMR spectroscopy should be within ±5%.



Scheme 4. Chemoselective cleavage of 1,2-epoxydodecane with $BHBr_2$–SMe_2 in the presence of *trans*-1-acetoxy-2-azidocyclohexane in CH_2Cl_2.



Scheme 5. Chemoselective cleavage of 1,2-epoxydodecane with $BHBr_2$–SMe_2 in the presence of 4-cyanobenzaldehyde in CH_2Cl_2.

3.2. A representative procedure for the regioselective cleavage of 1,2-epoxydodecane **1**

$BHBr_2$–SMe_2 (1.1 ml, 1.1 mmol, 1.0 M in CH_2Cl_2) was added slowly to a stirred methylene chloride solution (5 ml) of 1,2-epoxydodecane **1** (2.0 mmol) at room temperature under nitrogen atmosphere. After 0.25 h, the intermediate dialkoxyborane species was treated with water (5 ml) and the resulting bromohydrins were extracted with CH_2Cl_2 (3×25 ml), dried over anhydrous $MgSO_4$, and concentrated. The % chemical transformation of the regioisomeric bromohydrins (**2** and **3**) was determined by comparing the integrations of selected proton signals using ^{1}H NMR spectroscopy after adding biphenyl (0.25 mmol) as an internal standard (Table 1). The major regioisomers were also purified on silica gel column and the chemical yields were determined. All the bromohydrins are well characterized in the literature.

3.2.1. 1-Bromododecan-2-ol **2** [3h]

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.70 (m, 1H, –C*H*OH), 3.50 (dd, 1H, –CH_2Br), 3.35 (dd, 1H, –CH_2Br), 2.10 (d, 1H, –CHO*H*), 1.60–1.10 (m, 18H, –CH_2–), 0.88 (t, 3H, –CH_3) (the minor isomer 2-bromododecan-1-ol **3** shows distinct characteristic peak at δ 4.15 (m, –C*H*Br)).

3.2.2. 1-Bromo-3-phenylpropan-2-ol **5** [3a]

^{1}H NMR (300 MHz, $CDCl_3$): δ: 7.35–7.10 (m, 5H, Ar*H*), 3.95 (m, 1H, –C*H*OH), 3.19 (ddd, 2H, –CH_2Br), 2.80 (d, 2H, PhCH_2–), 2.20 (d, 1H, –CHO*H*) (the minor isomer 2-bromo-3-phenylpropan-1-ol **6** shows relevant characteristic peak at δ 4.10 (m, –C*H*Br)).

3.2.3. 2-Bromo-2-phenylethanol **9** [3b]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43–7.30 (m, 5H, Ar*H*), 5.06 (dd, 1H, –C*H*Br–), 4.06 (dd, 1H, –CH_2OH), 3.96 (dd, 1H, –CH_2OH), 2.09 (s, 1H, –CH$_2$O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.2, 128.9, 128.8, 127.9, 67.5, 56.9 (the minor isomer 2-bromo-1-phenylethanol **8** shows characteristic peaks at δ 4.90 (m, PhC*H*(OH)–) and 3.60 (dd, –CH_2Br)).

3.2.4. 1-Bromooct-7-en-2-ol **11**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.60 (m, 1H, CH_2=C*H*–), 5.00 (m, 2H, CH_2=CH–), 3.80 (m, 1H, –C*H*OH–), 3.55 (dd, 1H, –CH_2Br), 3.40 (dd, 1H, –CH_2Br), 2.20 (m, 3H, –CH_2–, –CHO*H*), 1.70–1.20 (m, 6H, –CH_2–); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.6, 114.5, 71.0, 40.6, 34.9, 33.5, 28.7, 25.0.

3.2.5. 2-Bromooct-7-en-1-ol **12**

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.80 (m, 1H, CH_2=C*H*–), 5.00 (m, 2H, CH_2=CH–), 4.15 (m, 1H, –C*H*Br–), 3.80 (m, 2H, –CH_2OH), 2.10–1.40 (m, 9H, –CH_2– and CHO*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5, 114.7, 67.2, 59.9, 34.7, 33.4, 28.2, 26.9.

3.3. General procedure for the chemoselective cleavage of 1,2-epoxydodecane in the presence of propa-1,2-dienylcyclohexane

$BHBr_2$–SMe_2 (1 ml, 1.0 mmol, 1.0 M in CH_2Cl_2) was added slowly to a stirred methylene chloride solution (5 ml) of 1,2-epoxydodecane **1** (1.0 mmol) and propa-1,2-dienylcyclohexane (1.0 mmol) at room temperature under nitrogen atmosphere. After 0.25 h, the intermediate dialkoxyborane species was treated with water (5 ml) and the resulting bromohydrins were extracted with CH_2Cl_2 (3×25 ml), dried over anhydrous $MgSO_4$, and concentrated. The chemical conversion of the regioisomeric bromohydrins and the % recovery of the added allene, were calculated by comparing the integrations of selected proton signals using ^{1}H NMR spectroscopy after adding biphenyl (0.25 mmol) as an internal standard (Table 2).

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