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Regioselective Conversion of Unsymmetrical Terminal Epoxides into Vicinal Chlorohydrins Using Dimethoxyboron Chloride*

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A highly regioselective synthesis of chlorohydrins by chlorinative cleavage of unsymmetrical epoxides utilizing dimethoxyboron chloride is described. Except for styrene oxide, all the terminal epoxides were regioselectively cleaved following a predominantly S_N2-type reaction pathway favouring the formation of primary chlorides. In the case of styrene oxide, a benzylic epoxide, $(MeO)_2BCl$ transfers the chlorine at the benzylic position, by following an apparent S_N1-type mechanism.

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Halohydrins are highly valuable and versatile intermediates which have found broad applications in the syntheses of halogenated marine natural products and pharmaceuticals.[1–4] Therefore, there is a continued interests in developing new simple, mild, practical, environmentally benign, efficient, and highly selective methods for the preparation of these halohydrins.[5–7] Among the methodologies known in literature, the most common method appears to be the ring opening of epoxides using various halogenating agents.[2] Boron halides are well recognized as ether cleaving reagents.[8] We[9] and others[10] have developed several structurally modified *B*-haloorganoboranes which have proven to be highly promising reagents in the regio-, chemo-, and enantioselective cleavage of carbon–ethereal bonds, especially epoxides. Although significant advances[11] have been made in the areas of ring opening of epoxides into chlorohydrins, it is highly desirous to develop new reagents and methods to effect such transformations. In view of the synthetic importance of chlorohydrins, we undertook the preparation of monofunctional *B*-chloroorganoborane, dimethoxyboron chloride, and explored its synthetic potential in the regioselective ring opening of few representative terminal epoxides, and the preliminary results of such study are described in this communication.

Dimethoxyboron chloride, $(MeO)_2BCl$,[12] was conveniently prepared by the exchange reaction between trimethylborate, $(MeO)_3B$, and boron trichloride, BCl_3, in appropriate ratio (2/1) in *n*-pentane/*n*-hexanes mixture at −78°C, as shown in Scheme 1. The ^{11}B NMR spectrum showed a new sharp peak at δ_B 23.5 ppm (>95% chemical purity) for $(MeO)_2BCl$ with complete disappearance of BCl_3 and (MeO_3B) signals.

$$BCl_3 + 2B(OMe)_3 \xrightarrow[-78 \text{ to } 0^\circ C,\ 0.5\ h]{n\text{-Pentane}/n\text{-Hexanes}} 3(MeO)_2BCl,\ \delta_B\ 23.5\ ppm$$

Scheme 1. Preparation of dimethoxyboron chloride, $(MeO)_2BCl$.

First of all, we examined the ring opening of 1,2-epoxydodecane with $(MeO)_2BCl$ at 0°C for 0.5 h which produced a mixture of primary and secondary chlorides (77/23) in high chemical yield (90%). The shorter reaction time and lower regioselectivity indicated that $(MeO)_2BCl$ is more reactive than $BH_2Cl{\cdot}SMe_2$. The regioselectivity (90/10) of the reaction was significantly improved when the reaction was conducted at −78°C for 3.5 h. After optimizing the reaction conditions, few representative unsymmetrical epoxides of varied side chain, were subjected to ring opening reactions with $(MeO)_2BCl$. Except for styrene oxide, all the representative epoxides underwent chlorinative cleavage favouring primary chloride by regioselective chlorine transfer at the less hindered carbon of the epoxy group following an electrophilic borderline S_N2-type mechanism (Scheme 2). Based on mechanistic and stereochemical results, a similar reaction pathway involving a four-centred transition state, preceded by boron complexation with oxygen lone pair, and resulting in the cleavage of C–O bond, has been proposed by Brown et al.[9c,9d] for the asymmetric ring opening of *meso*-epoxides with $^dIpc_2BX$ (X = Cl, Br, I). In the case of styrene oxide, a benzylic epoxide, the reaction apparently occurs via S_N1-type mechanism, providing benzylic chloride as a

* 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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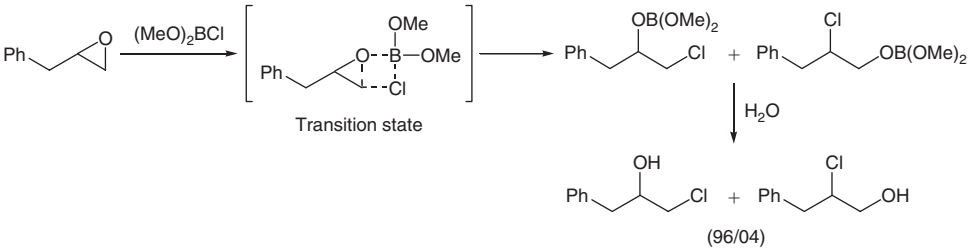
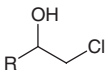
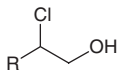


Scheme 2. Regioselective cleavage of (±)-(2,3-epoxypropyl)benzene with $(MeO)_2BCl$.

Table 1. Regioselective cleavage of terminal epoxides with $(MeO)_2BCl$

Entry		Conditions[A]			Yield [%][B]
1	$C_{10}H_{21}$	0°C, 0.5 h	77	23	90
2	$C_{10}H_{21}$	−78°C, 3.5 h	90	10	93
3	$PhCH_2$	−78°C, 3.5 h	96	04	90
4	Ph	−78°C, 3.5 h	05	95	50
5	$CH_2{=}CH(CH_2)_4$	−78°C, 3.5 h	89	11	95
6	$PhOCH_2$	−78°C, 3.5 h	95	05	90
7	$(CH_3)_2CHOCH_2$	−78°C, 3.5 h	95	05	88
8	$CHF_2CF_2OCH_2$	−78°C to RT, 4.0 h	95	05	50
9	$CHF_2CF_2OCH_2$	−78 to −50°C, 23 h	95	05	93

[A] 1.20 equiv of reagent used, in solvents *n*-pentane (16–18 mL)/CH_2Cl_2 (1 mL).
[B] Regioselectivity and the chemical yields were determined by ^1H NMR spectroscopy using biphenyl as an internal standard.

major product (05/95), possibly due to the more stabilized carbocation character of the benzylic carbon.

Halohydrins, derived from glycidic ethers, can serve as valuable intermediates in the synthesis of biologically active amino alcohols, which are known as β-blockers and as muscle relaxants. Consequently, few glycidic ethers were also selected for such a regioselectivity study (Table 1). All the three glycidic ethers bearing phenyl, isopropyl, and tetrafluoroethyl groups readily and regioselectively cleaved into chlorohydrins, affording predominantly primary chloride (95/05). The only observation worth noting is that the cleavage of epoxy group of 2-[(1,1,2,2-tetrafluoroethoxy)methyl]oxirane was relatively slow (only 50% conversion after 4 h at −78°C). When the reaction was carried out at −78 to −50°C for 23 h, 92% chemical yield of chlorohydrins was obtained. The lower yield of halohydrins, obtained from styrene oxide, is due to the volatile nature of the halohydrins.

Finally, the results achieved from the regioselective ring opening of styrene oxide with $(MeO)_2BCl$ is compared with some of the existing methods known in the literature, to substantiate the effectiveness of this reagent. The ratios of $PhCH(OH)CH_2Cl/PhCH(Cl)CH_2OH$ with various chlorinating agents, such as, $PhCOCl/Bu_2SnCl_2$ (product ratio 33/67),[2b] $R'COCl/CoCl_2$ (04/96),[2c] Li_2CuCl_4 (25/75),[2d] $BH_2Cl{\cdot}SMe_2$ (06/94),[11a] $NH_4Cl/LiClO_4$ (45/55),[2e] $NH_4Cl/Mg(ClO_4)_2$ (25/75),[2e] phosphaferrocene/Me_3SiCl (27/73),[11b] Silica gel/LiCl/H_2O (21/79),[11c] $SiCl_4$/HMPA (5.5/94.5),[11d] $CeCl_3$ (08/84),[11g] $BHCl_2{\cdot}SMe_2$ (09/91),[9d] $POCl_3$ or PCl_3/DMAP (0/100),[11h] [AcMIm]X (100/0),[6] and $(MeO)_2BCl$ (05/95) clearly demonstrate that $(MeO)_2BCl$ is a highly effective reagent in comparison with many existing methods.

To conclude, we have demonstrated the synthetic potential of dimethoxyboron chloride in the regioselective cleavage of few representative epoxides. This new reagent very readily and efficiently cleaves unsymmetrical terminal epoxides in a highly regioselective manner. Although there are several procedures available for such transformations, we believe the present method should make valuable contribution in organic chemistry, complementing the current existing methodologies, due to its simple preparation, high regioselectivity, efficiency, and convenient handling as well as easy workup.

Experimental

Manipulations and reactions with air-sensitive compounds were carried out under nitrogen atmosphere. ^1H, ^{13}C, and ^{11}B NMR spectra were recorded on Varian Gemini 300 MHz multinuclear NMR spectrometer. The ^{11}B NMR chemical shifts are relative to $BF_3{\cdot}OEt_2$. Starting materials were purchased from Aldrich.

Preparation of Dimethoxyboron Chloride

Dimethoxyboron chloride, $(MeO)_2BCl$, was synthesized by the exchange reaction between boron trichloride (2.0 mmol in *n*-hexanes) and trimethyl borate (4.0 mmol) in *n*-pentane (16 mL) at −78°C for 0.5 h under nitrogen atmosphere. After 0.5 h, the reaction mixture was allowed to warm up to 0°C. An aliquot was transferred into a NMR tube under nitrogen atmosphere and the ^{11}B NMR spectrum was recorded which showed a sharp peak at δ_B 23.5 (>95% purity). The reagent solution was again cooled to −78°C and dry CH_2Cl_2 (1 mL) was added (for solubility reason). This in situ prepared reagent (~6.0 mmol) is ready for the regioselective reaction.

Regioselective Cleavage of (±)-(2,3-Epoxypropyl)benzene with Dimethoxyboron Chloride

To a cooled stirred solution of $(MeO)_2BCl$ (6.0 mmol) in *n*-pentane/CH_2Cl_2 (19–20 mL) at −78°C under nitrogen atmosphere, was added (±)-(2,3-epoxypropyl)benzene (5.0 mmol) via syringe. The resulting reaction mixture was stirred at −78°C for 3.5 h, and then treated with water (15 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL), the combined organic extracts were dried (Na_2SO_4), filtered, and evaporated to dryness in vacuo. The regioselectivity was determined using ^{1}H NMR spectroscopic data by either integrating and comparing the protons attached to –OH or –Br present in both regioisomers (96:04). The chemical yield (90%) was determined by ^{1}H NMR spectroscopy using biphenyl as an internal standard. Finally the major regioisomer was purified on silica gel column and characterized by ^{1}H and ^{13}C NMR spectroscopic data. 1-Chlorododecan-2-ol,[11b] 2-chlorododecan-1-ol,[11b] 2-chloro-1-phenylethanol,[11b] 2-chloro-2-phenylethanol,[11b] and 1-chloro-3-phenoxypropan-2-ol[11c] are well characterized.

1-Chloro-3-phenylpropan-2-ol: δ_H ($CDCl_3$) 7.40–7.10 (5H, m, Ar*H*), 4.00 (1H, m, C*H*OH), 3.70–3.40 (2H, ddd, CH_2Cl), 2.88 (2H, d, ArCH_2), 2.22 (1H, d, CHO*H*). δ_C ($CDCl_3$) 136.9 (ArC1), 129.3 (Ar*C*3, *C5*), 128.7 (Ar*C*2, *C6*), 126.8 (Ar*C*4), 72.2 (C2), 49.1 (C1), 40.6 (C3).

1-Chloro-3-isopropoxypropan-2-ol: δ_H ($CDCl_3$) 3.90 (1H, m, C*H*OH), 3.70 (3H, m, C*H*O and CH_2O), 3.50 (2H, d, CH_2Cl), 2.65 (1H, d, O*H*), 1.17 (6H, d, $(CH_3)_2$CH). δ_C ($CDCl_3$) 72.4 (*C*2), 70.4 (C3), 68.6 (C4), 45.9 (C1), 22.0 (C5), 21.9 (C6).

1-Chloro-3-(1,1,2,2-tetrafluoroethoxy)propan-2-ol: δ_H ($CDCl_3$) 6.00–5.50 (1H, m, C*H*F_2), 4.10 (3H, m, C*H*O and CH_2O), 3.66 (2H, m, CH_2Cl), 2.42 (1H, d, O*H*). δ_C ($CDCl_3$) 117.2 (*C*4), 107.6 (C5), 69.2 (C2), 64.7 (C3), 45.4 (C1).

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