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CLEAVAGE OF CARBON-OXYGEN BONDS. DIMETHYLBORON BROMIDE. A NEW REAGENT FOR ETHER CLEAVAGE

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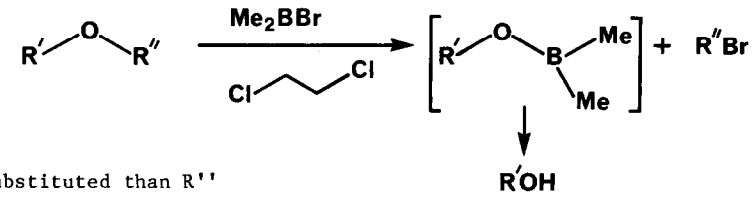
Abstract: A general and efficient procedure for the cleavage of aliphatic, aromatic and cyclic ethers by the use of dimethylboron bromide is described.

Recently a large "repertoire" of ether cleaving reagents has received considerable attention[1]. This has been given impetus by the growing need to develop reagents and methodologies that will permit the regeneration of a parent alcohol from its methyl ether in order to make possible the use of this functionality as a viable protecting group in organic synthesis. Three classes of excellent reagents have been highlighted: a) organosilicon[2] (TMSI, thiosilanes), b) thiol-Lewis acid[3] and c) boron halides[4], of which the last seem to be the most reactive[4c]. Boron tribromide, for instance, readily cleaves aryl methyl ethers to give the corresponding phenols in very good yield. Unfortunately, boron halides present some limitations as one considers the alkyl methyl ether and cyclic ether series. For instance, in the case of alkyl methyl ethers, the formation of alkyl halides is favored as illustrated by the conversion of β-dihydrocholesterol 3-methyl ether to 3-β-chlorocholestane by BCl_3[5]. In the cyclic ether series, when 2-methyltetrahydrofuran was treated with boron tribromide, nonregiocontrolled ring opening of the ring resulted (no yield reported)[6]. Thus competing SN_1 versus SN_2 mechanisms are inherent problems linked to the boron halides, which restricts their usefulness.

Nonetheless, attracted by the very potent oxygenophilic character of boron, we decided to look at monofunctional reagents of the general formula R_2BBr. On the one hand, the monofunctional reagent was expected to be more selective in reactivity and thus allow better control of reaction conditions. In addition, the electronic and steric nature of R could be varied in order to produce a more pronounced SN_1 or SN_2 character as desired, thus altering the overall reactivity of a given reagent. Herein, we would like to report that Me_2BBr[7] is a very efficient and mild reagent for the cleavage of the carbon-oxygen bond of a variety of ethers.

The overall reaction can be illustrated as follows:



R' more substituted than R''

R' and R'' could be part of a cycle

The following table summarizes the results

Of note is the fact that when β-dihydrocholesterol 3-methyl ether (entry 1) was treated with Me_2BBr in 1,2-dichloroethane, at room temperature, β-dihydrocholesterol was obtained in excellent yield (92%), with only a trace amount (4%) of 3-bromocholestane being formed. Primary (entries 4,5) and secondary methyl ethers (entries 1,6,7) could also be cleaved in good to excellent yield. The only tertiary methyl ether examined led to the corresponding bromide (entry 8). Aryl methyl ethers (entries 9,10) are cleaved to give the corresponding phenols, although as expected, more vigorous conditions are required. The reagent also cleaves benzyl ethers efficiently as illustrated by the conversion of the benzyl ether of β-dihydrocholesterol to the corresponding alcohol (entry 2).

Of particular interest is the fact that dimethylboron bromide also smoothly cleaves the carbon-oxygen bond of a cyclic ether at room temperature to give the corresponding bromo-alcohol in excellent yield (entry 11). In this context, although organosilanes and thiol-Lewis acid couples have been used successfully to cleave aryl and alkyl methyl ethers, their usefulness is somewhat restricted when the opening of cyclic ethers is considered[8]. To our knowledge only two examples have been reported, where TMSBr[9] and TMSI[2a] affect the ring opening of tetrahydrofuran, and no comments were made on the reactivity or the regioselectivity of these reagents in the case of substituted ring systems.

Of interest is the fact that in our case, dimethylboron bromide reacts smoothly and in a regiocontrolled manner with 2-methyltetrahydrofuran (entry 12) to give 1-bromo-4-pentanol as the major product in excellent yield.

The chemoselectivity of Me_2BBr should prove of considerable utility in organic synthesis. Thus the common protecting groups such as acetate (entry 3) and silyl ethers (entry 11) are unaffected, and alcohols are recovered unchanged[10], (in contrast, TMSI[11,12] reacts with both acetates and alcohols).

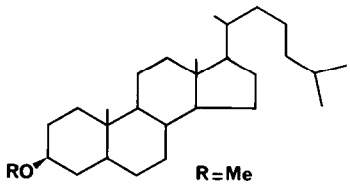
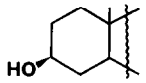
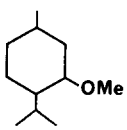
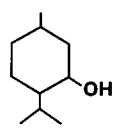
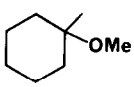
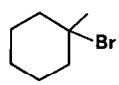
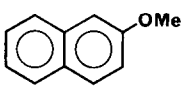
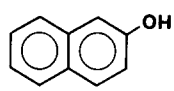
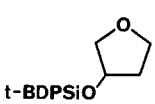
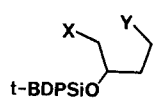
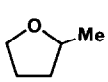
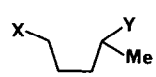
In summary, dimethylboron bromide is an effective and versatile reagent for the cleavage of C-O bonds of a variety of ethers (alkyl, arylalkyl and cyclic). In contrast to other boron halides, this reagent reacts by a preponderantly SN_2 mechanism, thus allowing for the regeneration of an alcohol from its methyl ether and for better regiocontrol in the cleavage of substituted cyclic ethers.

Further studies into the utility of reagents of general formula R_2BBr are currently underway.

Experimental

A typical experimental procedure follows. To a cold (0°C), stirred solution of 1-methoxydodecane (1.03 mmol) and triethylamine (0.21 mmol, to neutralize traces of free

TABLE 1

ENTRY	SUBSTRATE	REAGENT[a] (equiv.)	Δt (°C)	REACTION TIME (h)	PRODUCT[b]	YIELD[c] (%)
1	 R=Me	3.0	0 - 25	18		93
2	R=$C_6H_5CH_2$	3.0	0 - 25	16	as above	92
3	R=Ac	3.0	0 - 25	24	starting material	100
4	$C_6H_5(CH_2)_2CH_2OMe$	1.3	0 - 25	4	$C_6H_5(CH_2)_2CH_2OH$	93
5	$CH_3(CH_2)_{10}CH_2OMe$	1.3	0 - 25	3	$CH_3(CH_2)_{10}CH_2OH$	89
6	$CH_3(CH_2)_6CH(CH_2)_3CH_3$ (OMe)	1.3	0 - 25[d]	5	$CH_3(CH_2)_6CH(CH_2)_3CH_3$ (OH)	69[e]
7		1.3	0 - 25[d]	3		75[f]
8		1.6	0 - 25	6		49
9	C_6H_5OMe	4.0	70	30	C_6H_5OH	72
10		4.0	70	36		96
11		1.3	0 - 25	16	 i) X=OH, Y=Br ii) X=Br, Y=OH i:ii=1:1	87[g]
12		1.3	0 - 25[d]	16	 i) X=Br, Y=OH ii) X=OH, Y=Br i:ii=3.5:1	83[h]

[a] Unless otherwise stated all reactions were carried out at a concentration of 0.2-0.3M and included (except for entries 9 and 10) 10-15% Et_3N/equivalent of Me_2BBr as an acid scavenger. No reaction resulted when 3-phenyl-1-propanol methyl ether was treated with a 1:1 mixture of Et_3N/Me_2BBr at room temperature for 24h.

[b] All products were identified by comparison with authentic samples.

[c] Isolated yields.

[d] This reaction was carried out at 0.02M.

[e] 5-Bromododecane was also isolated in 26% yield.

[f] The corresponding bromide was formed in less than 10% yield.

[g] The ^1H NMR spectrum was consistent with the assigned structures. The product ratios were determined by a GCMS analysis.

[h] In this case the 2-methyltetrahydrofuran was added to a cold (0°C) mixture of Me_2BBr and Et_3N in 1,2-dichloroethane. The ^1H NMR spectrum of the product mixture fully corroborated the assigned structures: the methyl group of the secondary alcohol i (X=Br, Y=OH) gives rise to a doublet at δ 1.26 (J=6Hz) whereas the corresponding methyl group of the bromide ii (X=OH, Y=Br) was found at δ 1.75 (J=7.5Hz) in a ratio of 3.5 : 1 respectively.

acid) in 4.1 mL of dry 1,2-dichloroethane, under argon, was added a solution of dimethylboron bromide (1.34M, 0.99 mL) in 1,2-dichloroethane. The cooling bath was then removed and the resultant solution stirred at room temperature for 3 h. The reaction mixture was then cooled to 0°C, quenched with saturated aqueous sodium bicarbonate (2 mL) and diluted with ether (30 mL). The organic layer was separated, washed with saturated sodium bicarbonate (2 mL), water (2 mL) and brine (2 mL). The aqueous washings were extracted with ether and the organic layers combined. After drying, the resultant solution was concentrated and subjected to flash chromatography to provide pure 1-dodecanol (89%).

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