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Borane/Bu_2BOTf: A Mild Reagent for the Regioselective Reductive Ring Opening of Benzylidene Acetals in Carbohydrates

Lu Jiang, Tak-Hang Chan*

Department of Chemistry, McGill University, Montréal, Québec H3A 2K6, CANADA

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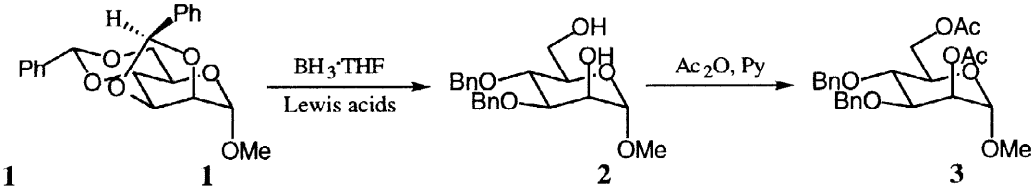
Abstract: *BH_3/Bu_2OTf is an effective reagent to reductively cleave 4,6-O-benzylidene acetals of various hexopyranosides to the corresponding 4-O-benzyl ethers. 4,6-O-Isopropylidene acetals can be similarly cleaved. Common protecting groups are stable to the reaction conditions.*

Selective protection of different hydroxy groups in a carbohydrate molecule is a key step in the chemical synthesis of complex carbohydrates. In this connection, the reductive ring opening of cyclic benzylidene acetals to the corresponding O-benzyl ethers, in a regioselective manner, is a useful strategy because of the ease of formation of the acetal as well as the well-established nature of the benzyl ether protection.[1] The regioselectivity in the reductive ring opening of 4,6-O-benzylidene acetals of hexopyranosides varies with the reagents and the solvents. For the preparation of the 6-O-benzyl derivatives, $NaBH_3CN$-HCl in THF gives the best results.[2] Other reagents such as Et_3SiH-trifluoroacetic acid,[3] $Me_3N{\cdot}BH_3$-$AlCl_3$ in THF[4] and $Me_2NH{\cdot}BH_3$-$BF_3{\cdot}OEt_2$ in CH_3CN[5] are also effective. On the other hand, there is a need for a mild and effective reagent for the regioselective reductive cleavage of 4,6-O-benzylidene acetals to the corresponding 4-O-benzyl ethers with the 6-hydroxy unsubstituted. The reagents so far reported in the literature for that purpose are either not chemoselective ($LiAlH_4$-$AlCl_3$ in THF),[1] not sufficiently regioselective ($Me_2NH{\cdot}BH_3$-$BF_3{\cdot}OEt_2$ in dichloromethane)[5] or give modest yield of the desired products ($Me_3N{\cdot}BH_3$-$AlCl_3$ in toluene).[4]



Scheme 1 **1** **2** **3**

Table 1. Reductive Opening of Benzylidene Acetal **1** with $BH_3{\cdot}THF$.

Entry	Lewis acid	Quantity (equiv.)	Temperature (°C)	Reaction Time(h)	Isolated Yield(%) of **3**
1	$BF_3{\cdot}OEt_2$	10	25	12	complex mixtures
2	1M Bu_2BOTf in CH_2Cl_2	1	25	1/12	83
3	1M Bu_2BOTf in CH_2Cl_2	0.5	0	1	97
4	2M TMSOTf in CH_2Cl_2	0.5	0	1	85
5	TfOH	0.5	0	1	75

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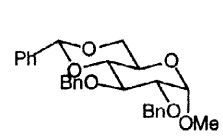
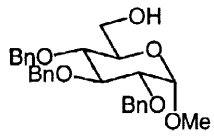
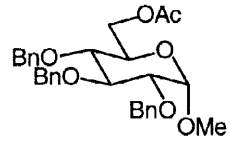
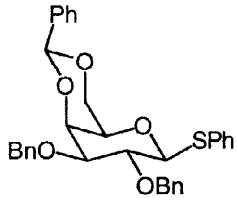
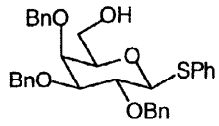
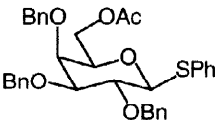
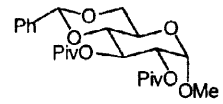
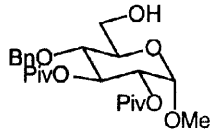
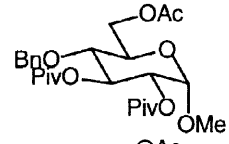
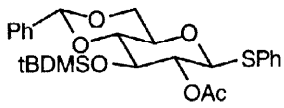
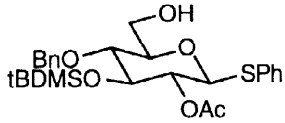
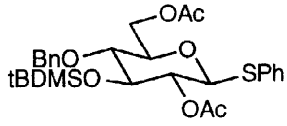
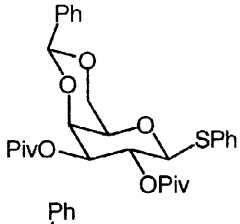
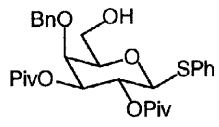
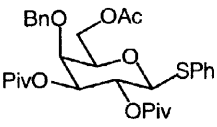
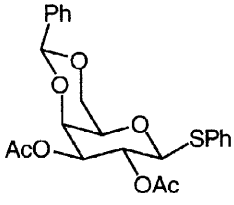
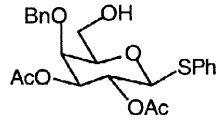
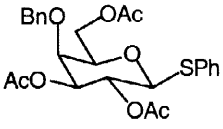
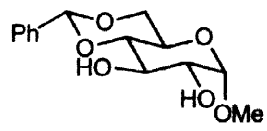
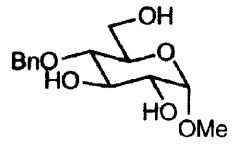
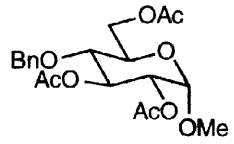
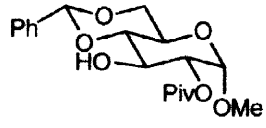
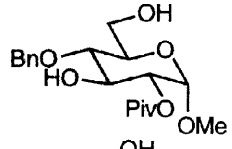
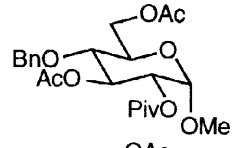
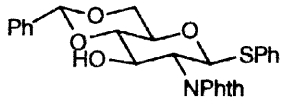
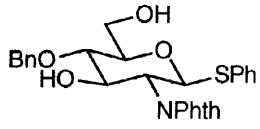
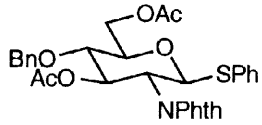
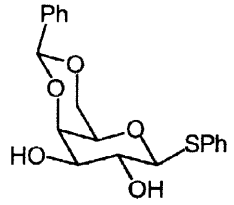
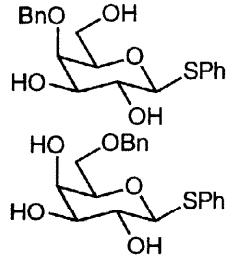
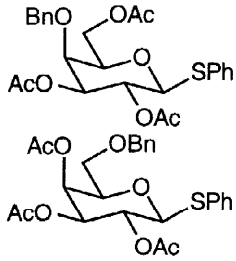
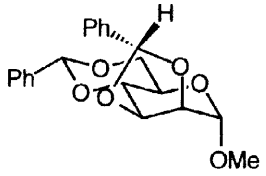
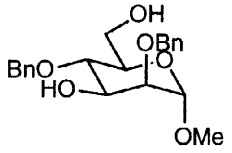
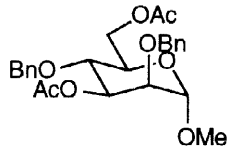
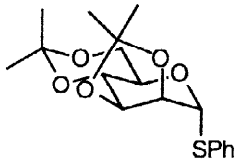
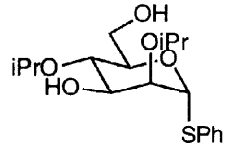
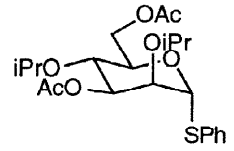
Although it is well known that simple acetals and ketals are reductively cleaved with BH_3·THF alone under mild conditions, benzylidene acetals of hexopyranosides are resistant to it. Using compound **1** as the common substrate,[6] we found that BH_3·THF in conjunction with Lewis acid is effective in reductive ring opening of such benzylidene acetals. The regioselectivity and the efficacy of the opening depend on the type of Lewis acid and the solvent (Table 1). As previously observed, BF_3 etherate in THF (entry 1, Table 1) gave a complex mixture of products due to non-regioselective opening. Triflic acid (entry 5) gave regioselectively, but with modest yield, the 3,4-di-O-benzyl derivative **2** which, for ease of characterisation, was converted to the 2,6-di-O-acetate **3**. Trimethylsilyl triflate (entry 4) was similarly regioselective and gave a better yield of **3** (85%). Among the Lewis acids tested by us, dibutylboron triflate gave the best result, with **3** as the exclusive product in 97% isolated yield. Since the reagent, 1M dibutylboron triflate in dichloromethane, is commercially available and gave the best result, we have examined further the scope of this Lewis acid in conjunction with BH_3·THF for the reductive ring opening of other cyclic acetals.

Table 2. Reductive Openings of Benzylidene and Isopropylidene Acetals of Hexopyranosides with BH_3·THF and Bu_2BOTf at 0 °C.

Entry	Substrate	Reduced Product	Acetylated Product	Isolated Yield(%)
1				87
2				95
3				88
4				81
5				90
6				70

7				91
8				86
9				72
10				89(1:1)
11				88
12				77

It seems that BH_3·THF-Bu_2BOTf is a mild and effective reagent for the regioselective reductive ring opening of 4,6-O-benzylidene acetals of hexopyranosides to the corresponding 4-O-benzyl ethers with the 6-hydroxy unsubstituted. Thus, methyl 2,3-di-O-benzyl-4,6-O-benzylidene-α-D-glucopyranoside (entry 1, Table 2) was converted efficiently to the corresponding 2,3,4-tri-O-benzyl derivative (again characterised as the acetylated product) in 87% isolated yield. Similarly, the phenyl 4,6-O-benzylidene-2,3-di-O-benzyl-1-thio-β-D-galactopyranoside (entry 2, Table 2) was reduced to the 2,3,4-tri-O-benzyl compound. In this case, the anomeric thiophenyl function was inert to the reductive conditions. Other commonly used protecting groups in carbohydrate chemistry are also inert to this reagent. Methyl 2,3-di-O-pivaloyl-4,6-O-benzylidene-α-D-glucopyranoside (entry 3, Table 2) was reduced to the 4-O-benzyl ether with the pivaloyl protection intact. Acetyl and t-butyldimethylsilyl protection are similarly compatible to the reaction conditions (entries 4, 5 and 6). Also, the phthalimide group (entry 9) which may have been sensitive to borane reduction survived the reaction conditions unchanged. Hydrolysis of the benzylidene acetals during reaction sometimes accounted for the low yield of reaction when $NaBH_3CN$-HCl in THF was used. Such undesirable hydrolysis would not occur in the present case since BH_3·THF reacts with water readily. On the other hand, the presence of free hydroxyl groups in the molecule may affect the regioselectivity of the reaction. In the case of 4,6-O-benzylidene acetal of glucopyranoside, the presence of one (entry 8 and 9) or even two (entry 7) free hydroxyl groups at the 2, 3-

positions appeared not to affect the yield or regioselectivity of the reductive ring opening. For the 4,6-O-benzylidene acetal of galactopyranoside, however, the presence of the two hydroxyl groups (entry 10) led to a loss of regioselectivity in the reduction, giving a 1:1 mixture of 4- and 6-O-benzyl ethers.

The reagent is also effective in the reductive ring opening of 2,3-O-benzylidene dioxolanes of mannosides. However, the regioselectivity of the ring opening depends on the stereochemistry of the phenyl substituent as observed by many others previously.[1] The exo-isomer **1** gave regioselectively the 3-O-benzyl ether **2** (entry 3, Table 1) whereas the endo isomer gave the 2-O-benzyl ether (entry 11, Table 2) in 88%. It appears that the dependence of regioselectivity of the ring opening on the stereochemistry of the phenyl substituent is independent of the reducing reagent. We note, however, that when stereochemistry of the dioxolane ring is not at issue as in the case of methyl 2,3:4,6-di-O-isopropylidene-α-D-mannopyranoside (entry 12, Table 2), reductive ring opening of the dioxolane occured regioselectively to give the 2-O-isopropyl (as well as the 4-O-isopropyl) ether.

In conclusion, the BH_3·THF-Bu_2BOTf reductive system regioselectively cleaves benzylidene and isopropylidene acetals rapidly under mild conditions. Benzyl, silyl, ester and phthaloyl protecting groups are compatible with the reaction conditions. This protection protocol should have utility in oligosaccharide synthesis.

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6. Benzylidene and isopropylidene acetals were prepared according to the procedures described in: Ferro, V.; Mocerino, M.; Stick, R. V.; Tilbrook, M. G. *Aust. J. Chem.* **1988**, *41*, 813.

7. Experimental procedures: A solution of 1M BH_3 in THF (10 mL) was added to a 50 ml dry flask containing 1 mmol of compound **1** at 0 °C and the solution was stirred for 5 minutes. A solution of of 1M Bu_2BOTf in CH_2Cl_2 (1 mL) was then added to the clear solution slowly. After 1 hour at 0 °C, TLC showed that the starting material had disappeared. Triethylamine (0.5 mL) was then added to the reaction flask followed by careful addition of methanol until the evolution of H_2 had ceased. The reaction mixture was codistilled with methanol three times before being put on the silica gel column. Elution with 1:1 hexanes and ethyl acetate gave the pure 3,4-dibenzyl derivative **2** which was converted to the 2,6-diacetate **3** by acetic anhydride and pyridine. In the case of the free hydroxy groups present in the substrates, 7 mL of 1M BH_3 in THF was used for every mmol of the substrate. For larger reaction scale (e.g. 10 mmol), the amount of borane required can be reduced to three fold excess.