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Regio- and chemoselective reductive cleavage of 4,6-*O*-benzylidene-type acetals of hexopyranosides using BH_3·THF–TMSOTf

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ABSTRACT

Benzylidene-type cyclic acetals of carbohydrates undergo efficient reductive ring opening using BH_3·THF and a catalytic amount of TMSOTf at room temperature. 4,6-*O*-Benzylidene-hexopyranosides afford the corresponding 4-*O*-benzyl ethers exclusively, in high yields. Other benzylidene-type acetals, such as naphthylmethylene and 4-methoxybenzylidene acetals are also cleaved with the same reagent. The conversions are highly regio- and stereoselective and afford benzyl-type ethers in excellent yields.

Regioselective protection of individual hydroxy groups of carbohydrates is an essential step for the synthesis of complex carbohydrates. Cyclic acetals are formed regioselectively and are commonly used for the 4,6-*O*-protection of hexopyranosides. In addition, the reductive ring opening of benzylidene-type acetals to the corresponding *O*-benzyl (or substituted benzyl) ethers, in a regioselective manner, allows release of any one of the two hydroxy groups, while providing the other as benzyl protected. Thus, these two steps constitute a very effective method for regioselective benzylation.

Various reagent systems have been introduced for the regioselective ring cleavage of benzylidene acetals to benzyl ethers.[1] For the preparation of 4-*O*-benzyl ethers these include: $LiAlH_4$–$AlCl_3$,[2] DIBAL-H,[2c,3] BH_3·NMe_3–$AlCl_3$,[4] BH_3·$HNMe_2$–BF_3·OEt_2,[5] BH_3·NMe_3–Me_2BBr,[6] Et_3SiH–$PhBCl_2$,[7] PS-DES™–$PhBCl_2$,[7a] polymethylhydrosiloxane (PMHS)–$AlCl_3$,[8] and BH_3·THF alone[2c] or in combination with Ph_2BBr,[9a] Bu_2BOTf,[9b,c] lanthanide triflates,[9d] $Cu(OTf)_2$,[9e] or $CoCl_2$.[9f] Alternatively, for the preparation of 6-*O*-benzyl ethers, $NaCNBH_3$–HCl,[10] $NaCNBH_3$-MsOH,[11] BH_3·NMe_3–$AlCl_3$,[4a] BH_3·$HNMe_2$–BF_3·OEt_2,[5a] or silanes, such as Et_3SiH[12] in combination with TFA,[12a] TfOH,[7a] or BF_3·OEt_2,[5b,12b] and Me_2EtSiH–$Cu(OTf)_2$[9e] have been reported.

The regioselectivities and the yields of the ring opening reactions using the above reagents are influenced by several factors. The regioselectivity often varies on changing the structure of the substrate and the steric bulk of neighboring substituents often has a directing effect.[2c] In most of the above methods, the choice of the reaction solvent is restricted, and the desired regioselectivity can only be obtained in a particular solvent. Changing the solvent sometimes not only results in loss, but also in reversal of the regioselectivity.[3b,4a,5a] Reaction temperature and even reagent concentrations have been reported to have a similar effect.[9c] Traces of water[13] and protic acids[9c] also influence the yields and reaction rates. Additionally, some of these reagents such as $LiAlH_4$–$AlCl_3$[2] and DIBAL-H[3] are not compatible with several of the common protecting groups, whilst other reagents, such as BH_3·NMe_3–$AlCl_3$ in toluene[4a] give only modest yields of products due to decomposition of the starting materials. In most of these methods, the hydride or Lewis acid have to be used in large excess. Some of the latter are quite hazardous and expensive, which limit their use in large-scale applications.

Hence, there is still the need for a generally applicable, regioselective, effective, and practical method for the reductive ring opening of 4,6-*O*-benzylidene-hexopyranosides to the corresponding 4-*O*-benzyl ethers. Here we report a new method for the ring opening of benzylidene-type acetals which provides *O*-benzyl and related ethers in excellent yields and regioselectivity.[14]

Using compound **1** as a common substrate we have studied the reductive ring cleavage using various borane complexes (BH_3·NMe_3, BH_3·SMe_2, and BH_3·THF) as hydride donors in combination with different Lewis acids. The results of the reactions with TMSOTf are summarized in Table 1.

Reaction with BH_3·NMe_3 in CH_2Cl_2 gave only the 6-*O*-benzyl derivative (as a ~1:1 mixture of **2a** and its trimethylsilyl derivative **2b**), BH_3·SMe_2 afforded 6-*O*- (**2a**) and 4-*O*-benzyl ethers (**3**) in ca.

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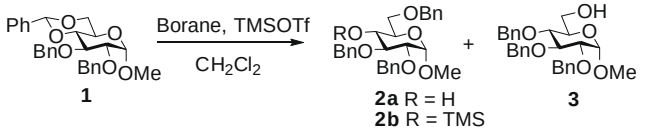
Table 1
Reductive ring opening of 4,6-*O*-benzylidene acetal **1** with different borane complexes and TMSOTf

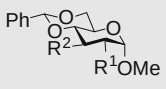
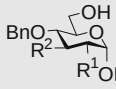
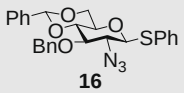
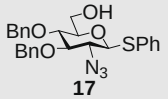
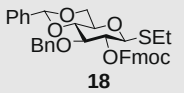
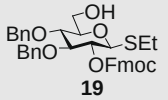
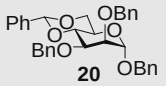
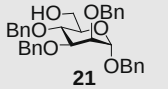
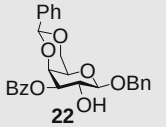
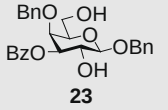
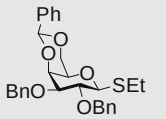
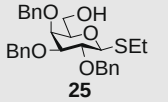
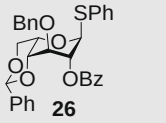
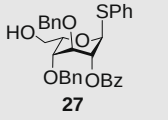


Entry	Borane complex	Amount of TMSOTf (equiv)	Reaction time (h)	Isolated yield (%)	
				6-*O*-Benzyl **2**	4-*O*-Benzyl **3**
1	$BH_3{\cdot}NMe_3$	1.5	7	84	0
2	$BH_3{\cdot}SMe_2$	0.15	1	48	40
3	$BH_3{\cdot}THF$	0.15	1	0	96

Table 2
Effect of Lewis acids on the reductive cleavage of **1** with $BH_3{\cdot}THF$

Entry	Lewis acid	Amount (equiv)	Reaction time (h)	Isolated yield of **3** (%)
1	TMSOTf	0.15	1	96
2	$Sc(OTf)_3$	0.15	6	96
3	ZnI_2	0.15	7	99
4	$AlCl_3$	1.15	24	99
5	$BF_3{\cdot}OEt_2$	3	240	91

Table 3
Reductive cleavage of 4,6-*O*-benzylidene-hexopyranosides with $BH_3{\cdot}THF$ and TMSOTf

Entry	Substrate	Product	Isolated yield (%)
1			
a	**1** R^1 = OBn, R^2 = OBn	**3** R^1 = OBn, R^2 = OBn	96
b	**4** R^1 = OBz, R^2 = OBz	**5** R^1 = OBz, R^2 = OBz	87
c	**6** R^1 = OBn, R^2 = OBz	**7** R^1 = OBn, R^2 = OBz	99
d	**8** R^1 = $NHCO_2Bn$, R^2 = OBn	**9** R^1 = $NHCO_2Bn$, R^2 = OBn	99
e	**10** R^1 = OBn, R^2 = OH	**11** R^1 = OBn, R^2 = OH	72
f	**12** R^1 = OAc, R^2 = OTBDMS	**13** R^1 = OAc, R^2 = OTBDMS	87
g	**14** R^1 = OTBDMS, R^2 = OAc	**15** R^1 = OTBDMS, R^2 = OAc	95
2	 **16**	 **17**	95
3	 **18**	 **19**	89
4	 **20**	 **21**	91
5	 **22**	 **23**	88
6	 **24**	 **25**	91
7	 **26**	 **27**	95

1:1 ratio. Using $BH_3{\cdot}THF$, however, only the 4-*O*-benzyl ether (**3**) was formed, which was isolated in excellent yield. Similar changes in the regioselectivity using the same borane complexes in combination with $AlCl_3$ have been published recently.[15]

These results suggest that the choice of the borane complex plays a decisive role in determining the regioselectivity. Next, the effect of various Lewis acids was studied in combination with $BH_3{\cdot}THF$ (Table 2).

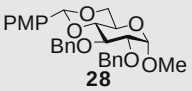
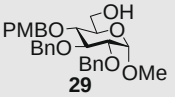
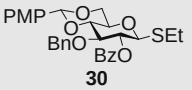
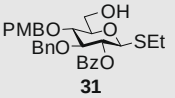
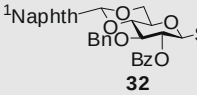
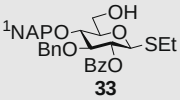
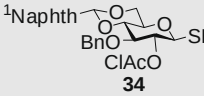
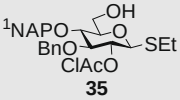
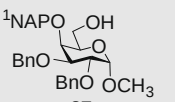
Irrespective of the Lewis acid used (TMSOTf, $Sc(OTf)_3$, ZnI_2, $AlCl_3$, and $BF_3{\cdot}OEt_2$), in all cases, the 4-*O*-benzyl ether was formed in excellent yield. On the other hand, the reaction rate was strongly influenced by the Lewis acid.

From the reagent combinations tested $BH_3{\cdot}THF$–TMSOTf[16] was selected for further investigations and a series of 4,6-*O*-benzylidene acetals were next reduced in CH_2Cl_2 (Table 3).[17]

In all cases, the cleavage reactions afforded the corresponding 4-*O*-benzyl ethers in high yields. The regioselectivity and the yields were unaffected by the nature and steric bulk of the O-3 substituents. Also, the regioselectivity was not influenced by the type of ring annelation, both trans- (entries 1–4) and cis-annelated systems (entries 5–7) gave the 4-*O*-benzyl ethers. In contrast to other methods,[3a,4a,5a] the regioselectivity was not affected by changing the solvent, essentially the same results were obtained by performing the reactions in THF instead of CH_2Cl_2.

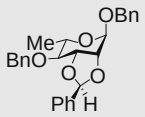
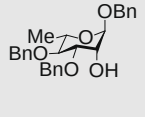
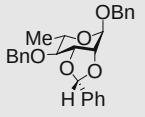
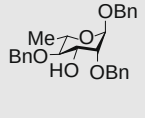
The reagent system is compatible with most common protecting groups, such as benzyl (entries 1–4, 6–7) and *tert*-butyldimethylsilyl ethers (entries 1f and 1g), acyl groups including benzoyl (entries 1b, 1c, 5, 7), acetyl (entries 1f and 1g), and chloroacetyl (see Table 4), as well as benzyloxycarbonyl (entry 1d) and fluorenylmethoxycarbonyl (entry 3) groups. Furthermore, the reactions could also be performed in the presence of free hydroxy (entries 1e and 5), azido (entry 2), and thioglycoside (entries 2, 3, 6, and 7) moieties. No undesired hydrolysis of the benzylidene acetals was observed as $BH_3{\cdot}THF$ reacts readily with water.

Table 4
Reductive cleavage of 4-methoxybenzylidene and 1-naphthylmethylene acetals using $BH_3{\cdot}THF$-TMSOTf

Entry	Substrate	Product	Isolated yield (%)
1	 **28**	 **29**	89[a]
2	 **30**	 **31**	76
3	 **32**	 **33**	90
4	 **34**	 **35**	84
5	 **36**	 **37**	84

PMB = *p*-methoxybenzyl; PMP = *p*-methoxyphenyl; ^{1}NAP = 1-naphthylmethyl; ^{1}Naphth = 1-naphthyl.
[a] The reaction was carried out using $BH_3{\cdot}THF$ without TMSOTf.

Table 5
Reductive cleavage of 1,3-dioxolane-type benzylidene acetals with BH_3·THF-TMSOTf

Entry	Substrate	Product	Isolated yield (%)
1	 **38**	 **39**	88
2	 **40**	 **41**	69

The BH_3·THF–TMSOTf reagent proved to also be effective for the ring opening of other benzylidene-type acetals. Reactions of *p*-methoxybenzylidene and 1-naphthylmethylene acetals afforded the *p*-methoxybenzyl (PMB) and 1-naphthylmethyl (^{1}NAP) ethers, respectively, in high yields and regioselectively (Table 4). In the case of reduction of *p*-methoxybenzylidene acetals, reactions could be performed using BH_3·THF without TMSOTf.

The reagent system is also applicable for the reductive cleavage of 1,3-dioxolane-type benzylidene acetals (Table 5). As with other reagents, the regioselectivity in this case was determined by the configuration of the acetal carbon.[10b,13,18]

In conclusion, BH_3·THF-TMSOTf is an effective and practical reagent which cleaves benzylidene, *p*-methoxybenzylidene, and naphthylmethylene acetals regioselectively under mild conditions to the corresponding 4-*O*-ethers in excellent yield. Furthermore the regioselectivity was not influenced by the type of ring annelation. The conversions are highly chemo- and regioselective and afford the corresponding ethers in excellent yields. This method should have utility in the preparation of complex carbohydrates.

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Supplementary data

Supplementary data (characterization data of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.194.

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16. TMSOTf is less expensive than the metal triflates[9d,9e] and organoboron compounds[9a–c] used in combination with BH_3·THF recently. In contrast to methods using Ph_2BBr,[9a] Bu_2BOTf[9b,c], and $CoCl_2$[9f] where an excess of the Lewis acid is required, the ring opening proceeds readily using only a catalytic amount of TMSOTf. An additional advantage is the relative safe handling of TMSOTf compared to the highly pyrophoric Bu_2BOTf.[9b,c]
17. *Typical experimental procedure*: To a solution of the acetal (1 mmol) in dry CH_2Cl_2 (10 mL) a 1 M solution of borane in THF (5 mL, 5 equiv) and TMSOTf (0.027 mL, 0.15 equiv) were added and the mixture was stirred under argon at room temperature. When TLC indicated the complete disappearance of the starting material (1–4 h), Et_3N (1 mL) was added, followed by careful addition of MeOH until the evolution of H_2 ceased. The mixture was concentrated, and the residue was coevaporated with MeOH (3×30 mL). Purification of the residue by silica gel column chromatography afforded the 4-*O*-benzyl ethers. Reactions on a larger scale (up to 0.05 mol) were also performed by reducing the excess of borane to 2 equiv giving the same results. All new compounds were analyzed and characterized by ^{1}H-, ^{13}C- NMR, and MS-spectroscopies.
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