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Regioselective reduction of 4,6-*O*-benzylidenes using triethylsilane and $BF_3 \cdot Et_2O$

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Abstract

The 4,6-di-*O*-benzylidene acetals of glucose, mannose, glucosamine, and galactose were regioselectively reduced by triethylsilane in the presence of $BF_3 \cdot Et_2O$ to yield the 6-*O*-benzyl ethers in good to excellent yields.

Carbohydrates are by now well recognized as important participants in cellular communication events such as chemotaxis, neutrophil recruitment, fertilization, host-pathogen recognition, and both random and non-random metastasic distributions of malignancies.[1] With this understanding of the vital roles played by carbohydrate recognition elements has come an increased need for efficient synthetic strategies for the preparation of carbohydrate-based materials. Successful oligosaccharide synthesis relies heavily on efficient methodology for the selective protection/deprotection of carbohydrate hydroxyl groups. A commonly utilized protecting group in this regard is the benzylidene acetal, which provides selective protection of the 4- and 6-hydroxyl moieties of, among other species, the pyranoses of glucose, galactose, and mannose.[2,3] Adding greatly to the utility of this group are methodologies for the regioselective reductive cleavage of the benzylidene acetal, allowing selective formation of a benzyl ether at either the C4 or C6 hydroxyl groups.

Methodology for the regioselective reduction of 4,6-*O*-benzylidene acetals to the corresponding 4-hydroxyl-6-*O*-benzyl ether has been in place since 1981.[4] The most commonly used protocol for this transformation uses $NaCNBH_3$ in the presence of hydrogen chloride gas. The procedure suffers from low yields and requires scrupulously dry conditions. Other reported conditions for the reduction of benzylidene acetals make use of stronger hydride sources, such as $LiAlH_4$–$AlCl_3$ or DIBAL, reagents incompatible with many other protecting groups.[3]

In the course of our studies towards *C*-glycosyl serine derivatives, we carried out the deoxygenation of disaccharide **1** with triethylsilane and $BF_3 \cdot Et_2O$. These conditions effected the simultaneous reduction of the benzylidene, providing the fully reduced disaccharide **2** in 73% yield (Scheme 1).[5] The reduction showed complete regiospecificity, producing only the 6′-*O*-benzyl disaccharide.

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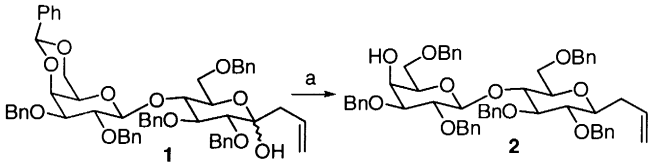
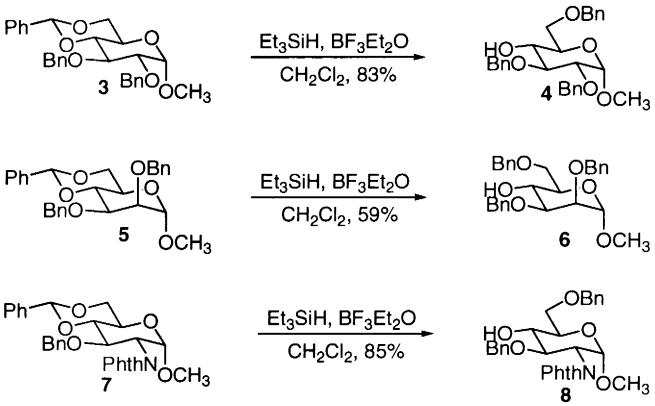


Scheme 1. Reduction of galactose-derived benzylidene and anomeric hydroxyl using TES/$BF_3 \cdot Et_2O$

A survey of the literature yielded only one other example of the use of triethylsilane for the reduction of benzylidene acetals. In this case the reaction was promoted only by a large excess (5.4 equivalents) of trifluoroacetic acid, conditions incompatible with many functional groups.[6] Additionally, the transformation was successful only for glucose-derived benzylidenes; galactose derivatives were either unreactive or decomposed.

To examine the generality of benzylidene reduction with TES/$BF_3 \cdot Et_2O$, the 4,6-di-*O*-benzylidenes of glucose **3**, mannose **5**, and glucosamine **7** were subjected to the reduction conditions.[7] In each instance the benzylidene was smoothly reduced to the 6-*O*-benzyl ether in unoptimized yields ranging from 59% to 85% (Scheme 2). No 4-*O*-benzyl products were detectable by NMR, demonstrating the complete regioselectivity of the reaction. Gray and co-workers have previously reported the use of a large excess of TES/$BF_3 \cdot Et_2O$/TFA for the reductive cleavage of a variety of glycosides.[8] Here, no glycosidic bond cleavage was detectable in any of the reactions.



Scheme 2. Reduction of glucose-, mannose-, and glucosamine-derived monosaccharides

In a typical procedure, methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside **7** (49.5 mg, 0.098 mmol) was dried under high vacuum for 15 hours prior to use. To a solution of **7** in CH_2Cl_2 (0.1 M, 1.0 mL) at 0°C was added Et_3SiH (12 equiv., 0.188 mL) and $BF_3 \cdot Et_2O$ (2 equiv., 25 μL). The reaction was warmed to 25°C over 4 hours. The mixture was diluted with CH_2Cl_2 (30 mL), washed with satd $NaHCO_3$ (1×40 mL), dried, and concentrated. Purification via flash chromatography eluting with a gradient of 2:1 to 1:1 petroleum ether:EtOAc provided **8** (42.2 mg, 85%) as a film.[9]

In conclusion, we have reported a robust facile procedure for the regioselective reductive cleavage of the 4,6-di-*O*-benzylidene group to the corresponding 6-*O*-benzyl ether. The methodology is experimentally straightforward and utilizes reaction conditions compatible with most common carbohydrate protecting groups.

Acknowledgements

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