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A novel method for regioselective ring-opening reduction of 4,6-*O*-benzylidene hexopyranoside derivatives using $CoCl_2$ and BH_3·THF

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Abstract—A novel and facile reductive ring-opening reaction for 4,6-*O*-benzylidene acetal derivatives of hexopyranosides using $CoCl_2/BH_3$·THF gave the corresponding 4-*O*-benzyl-6-OH derivatives selectively in good yields. This convenient method should allow large-scale synthesis at low cost.
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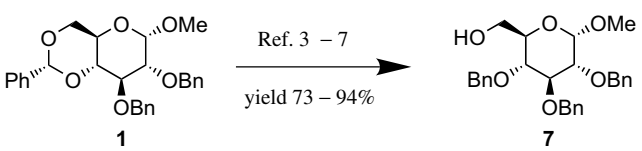
Regioselective protection of hydroxyl groups in polyhydroxy compounds such as glycoside plays an important role in the synthesis of natural products, including carbohydrates. Benzylidene acetal is often used for protection of 1,3-diol compounds, because of the possibility of further transformation into a benzoyl or benzyl group by ring-opening oxidation or reduction.[1,2] In particular, regioselective reduction of 4,6-*O*-benzylidene acetal derivatives of hexopyranosides, giving the corresponding 4-*O*-benzyl derivatives, is an important reaction in the carbohydrate field and has been the subject of much investigation by researchers. Methyl 2,3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (**1**) has been often used as a model compound in these studies (Scheme 1). Regioselective reductions of this compound using $LiAlH_4/AlCl_3$,[3] DIBAL-H,[4] $Me_2NH{\cdot}BH_3/BF_3{\cdot}OEt_2$,[5] $V(O)(OTf)_2/BH_3$·THF,[6] and Bu_2BOTf/BH_3·THF[7] gave the corresponding 4-*O*-benzyl derivative **7** in 90%, 88%, 73%, 94%, and 82% yields, respectively. Various other conditions for reductive cleavage of 4,6-*O*-benzylidene-protected pyranosides have also been reported.[8–15] $LiAlH_4/AlCl_3$ and DIBAL-H are of limited use due to their effects on acyl groups, which are often used in carbohydrate chemistry. The other reagents mentioned above, and also $Et_3SiH/PhBCl_2$,[15] do not affect acyl groups, but are mostly too expensive for use in large-scale processes.



1 **7**

Scheme 1. Reported reductive ring-opening of 4,6-*O*-benzylidene acetal.

Here, we report a novel facile method for regioselective ring-opening reduction of benzylidene acetals using $CoCl_2/BH_3$·THF. This newly developed method is suitable for use with substrates containing acetyl groups in large-scale synthesis at room temperature.

Methyl 4,6-*O*-benzylidene-α-D-gluco-, D-galacto-, and D-mannopyranoside derivatives **1**–**3**, **5**, **6** and phenyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside derivative **4** were used as substrates (Table 1, entries 1–6). The general procedure is as follows: To a stirred solution of the appropriate 4,6-*O*-benzylidene acetal hexopyranoside derivative in THF solution (3.0 equiv, 1 M BH_3 solution in THF), anhydrous $CoCl_2$ (3.0 equiv) was added at room temperature. The reaction was completed within 10 min. After disappearance of the starting material was observed by TLC, the blue reaction mixture was diluted with an excess volume of EtOAc, and the undissolved cobalt salt was recovered by filtration

Keywords: Carbohydrates; Reductive benzylidene ring-opening; Cobalt chloride; Borane.
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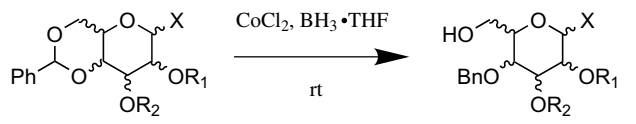
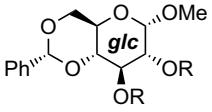
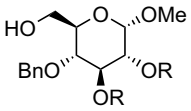
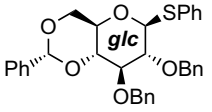
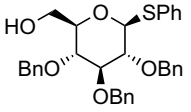
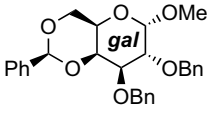
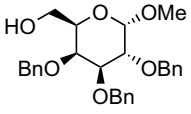
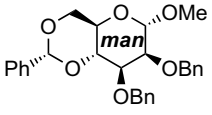
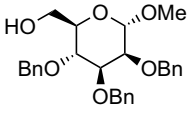
Table 1. Synthesis of 4-*O*-benzyl derivatives from 4,6-*O*-benzylidene acetals[a,f]



Entry	Substrate	Product[b]	Yield[c] (%)
			
1	**1**: R = Bn	**7**: R = Bn	quant
2	**2**: R = Ac	**8**: R = Ac	91[d]
3	**3**: R = H	**9**: R = H	85[d]
4	 **4**	 **10**	quant
5	 **5**	 **11**	quant
6	 **6**	 **12**	85[e]

[a] All reactions were carried out at room temperature using $CoCl_2$ (3 equiv) and BH_3·THF (3 equiv).
[b] The NMR data of all products were identical with those reported previously: **7** and **12**, Ref. 14; **8**, Ref. 15; **9**, Ref. 16; **10**, Ref. 17; **11**, Ref. 18.
[c] Isolated yield.
[d] The corresponding 4,6-di-OH derivatives were obtained as side products in 5% (entry 2) and 12% (entry 3) yields, respectively.
[e] The corresponding 6-*O*-benzyl derivative was obtained in 10% yield.
[f] Three abbreviations are used: *gluco*- (*glc*), *galacto*- (*gal*), and *manno*- (*man*).

in a form suitable for reuse. The filtered solution was treated with aq $NaBH_4$ (0.2 equiv) by stirring in a two-phase condition, and the resulting black precipitate was filtered off. The organic layer was washed with aq $NaHCO_3$ and water, dried with anhydrous $MgSO_4$, and evaporated to give the appropriate 4-*O*-benzyl derivative with high selectivity. The product was purified on a column of silica gel (EtOAc–hexane), if necessary. The reaction results are summarized in Table 1. All substrates gave the corresponding 4-*O*-benzyl derivatives in good yields. In particular, the 2,3-di-*O*-benzyl derivatives (entries 1, 4, and 5) gave the products quantitatively. Most of the yields obtained by this method were better than those obtained by reported methods.[3–15] A large-scale synthesis was also examined (entry 2) by using 50.1 g of the substrate, affording 43.6 g of the corresponding product (87% yield).

The present study is the first example of facile, regioselective cleavage of 4,6-*O*-benzylidene acetals using $CoCl_2/BH_3$·THF. We believe this procedure will be of great utility in the field of carbohydrate synthesis. Similar experiments on reductive ring-opening in a variety of other benzylidene acetal substrates with different protecting groups, and investigation of the mechanisms of these reactions, are now in progress.

Acknowledgments

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