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Debenzylation of Complex Oligosaccharides Using Ferric Chloride

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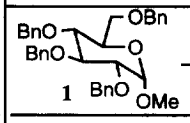
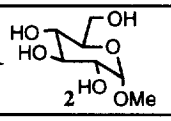
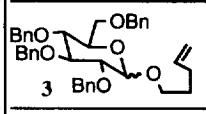
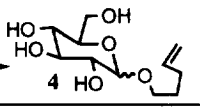
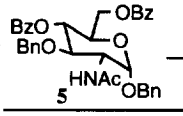
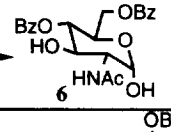
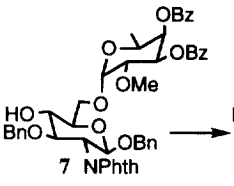
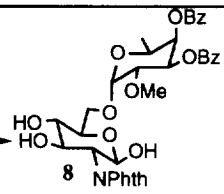
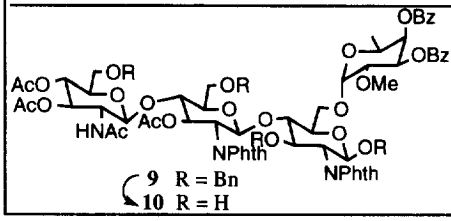
Abstract: Anhydrous $FeCl_3$ in CH_2Cl_2 at room temperature and 0 °C has been used to debenzylate monosaccharides and oligosaccharides in yields generally greater than 70%. Notably, alkenes, acetates, benzoates, phthalimides, acyl amides, and sensitive glycosidic linkages are unaffected by the reaction conditions. Copyright © 1996 Elsevier Science Ltd

Benzyl ethers are widely used as protecting groups for hydroxylic compounds due to their stability towards a wide variety of reaction conditions and their relatively easy removal through hydrogenolysis.[1] However, this procedure can be unpredictably problematic with multifunctional substrates such as those in the preparation of complex oligosaccharides where reductive cleavage is usually one of the final synthetic steps. During our recent synthetic studies on nodulation factors[2], we needed a method to remove benzyl groups on a late tetrasaccharide intermediate where survival of an alkene was desired. Although $FeCl_3$ has been utilized for the anomerization of glycosides [3] as well as the debenzylation of monosaccharides[4], this reagent has not been employed to cleave benzyl ethers on complex oligosaccharides containing numerous sensitive functional groups. Herein, we report the extension of anhydrous $FeCl_3$ under new reaction conditions to the debenzylation of such molecules.

In our initial studies on monosaccharides, we found that $FeCl_3$ was a highly efficient reagent for debenzylation both at room temperature and 0 °C (See Table I for results). In the cases of perbenzylated glycosides **1** and **3**, reaction with anhydrous $FeCl_3$ in CH_2Cl_2[5] afforded the tetraol products (**2** and **4**) in excellent yields at 25 and 0 °C, although the yields were slightly higher at 0 °C. Importantly, the terminal alkene in **3** survived the deprotection conditions. Glucosaminide **5** underwent cleavage of two benzyl groups in the presence of two benzoates without ester migration. The debenzylation of **5** was a little slower than for compounds **1** and **3** , and in some cases either monobenzylated product or a mixture with the expected diol was obtained.[6]

With the encouraging results with monosaccharides, we then sought to extend this methodology to complex oligosaccharides. Disaccharide **7** gave only modest yields of the desired product at 25 °C with $FeCl_3$, but reaction at a lower temperature provided the debenzylated disaccharide **8** in excellent yields. Notably, the benzoates, methyl ether, and the phthalimide all survived the reaction conditions, and no anomerization of either the intersaccharide bond or the reducing end sugar took place, since the product was recovered as the β anomer. Also, the extremely acid sensitive (1→6) fucosyl linkage was unaffected.[7,8] An even more impressive demonstration of this methodology was the deprotection of four benzyl groups on the complex tetrasaccharide **9** to afford **10** in 70% yield. Again, multiple functionalities withstood the reaction conditions and the desired product was a single anomer.

Table I $FeCl_3$ Debenzylations

Substrate	Product	Temp. (°C)	$FeCl_3$ (eq.)[a]	Time (h)	Yield (%)[b]
		25	12	0.5	80
		0	16	1.8	85
		25	12	0.5	75
		0	16	1.8	83
		25	4	0.5	76[c]
			8	0.8	84
		0	8	4.0	88[d]
			20	4.0	85
		25	4	0.5	44
			8	0.3	38
		0	8	2.3	70
			16	2.0	75
			24	1.8	64
		0	20	5.0	70

[a] Expressed as molar equivalents of $FeCl_3$.

[b] Isolated yields.

[c] The product was the monobenzylated sugar (anomeric hemiacetal).

[d] The recovered product was a 1:1 mixture of the monobenzylated sugar (anomeric hemiacetal) and the diol.

References and Notes

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4. a) Park, M.H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823 - 3824. b) Kartha, K.P. R.; Dasgupta, F.; Singh, P.P.; Srivastava, H.C. *J. Carbohydr. Chem.* **1986**, *5*, 437.
5. *Typical Procedure*: The substrate (10 - 150 mg) was dissolved in distilled CH_2Cl_2 under argon and anhydrous $FeCl_3$ added (see Table I for equiv.). Note, the reaction must be kept extremely dry for optimal yield. The reaction was quenched with H_2O (0.5 mL), and diluted with $CHCl_3$ (30 mL). The organic layer was extracted with brine (10 mL), and the aqueous layer was reextracted with $CHCl_3$:EtOAc (1:1, 2 x 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered, concentrated, and flash chromatographed on a silica column to give the desired product.
6. Slower reaction probably due to coordination of the $FeCl_3$ with the acetylamido group.
7. Kunz, H. ; Unverzagt, C. *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1697 - 1699 and references therein.
8. In control experiments, this disaccharide linkage was found to be stable to $FeCl_3$ up to 7 h at 0 °C.

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