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MICROSCALE CLEAVAGE REACTION OF (PHENYL)BENZYL ETHERS BY FERRIC CHLORIDE

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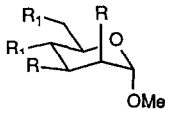
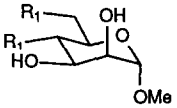
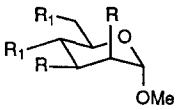
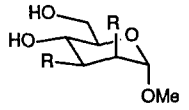
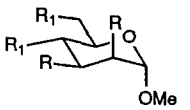
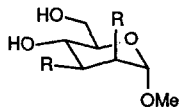
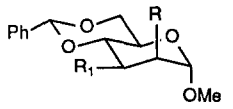
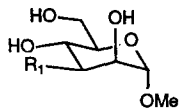
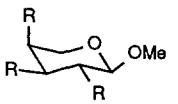
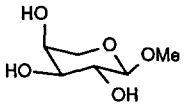
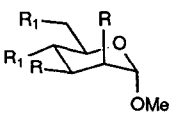
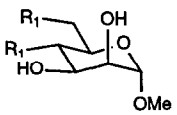
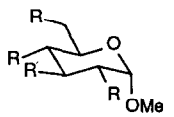
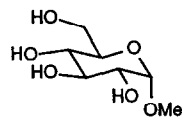
SUMMARY: Anhydrous $FeCl_3$ in CH_2Cl_2 cleaves benzyl and *p*-phenylbenzyl ethers of sugars in 15-30 minutes and 2-3 minutes, respectively, at room temperature in >70% yields; methyl ethers and acyl groups are not affected.

Benzyl ethers are commonly used as protecting groups for polyhydroxy compounds and carbohydrates because of their stability to both acids and bases. Although numerous methods are available for their removal[1], problems associated with reagent incompatibility, slow debenzylation rate, low yield in microscale reactions and acyl group migration[2] often arise in the presence of multiple functionalities. In connection with our microscale structure determination methods of oligosaccharides by the circular dichroic exciton chirality method[3,4], it was found that the following method using ferric chloride overcame these difficulties. Independent of these studies the cleavage of trityl ethers and benzylidene acetals[5], and the acetolysis of sugar benzyl ethers (5 min - 12 hr, 60 °C, 55-75% yield)[6] by ferric chloride have been reported recently.

We have found that anhydrous $FeCl_3$ in CH_2Cl_2 is highly efficient for the cleavage of benzyl and phenylbenzyl ethers at room temperature. Importantly, methyl ether, acetate and benzoate groups are not affected by the cleavage conditions. A typical procedure involves addition of anhydrous $FeCl_3$ (2 equiv or more) to a substrate (0.5-50 μmol.) solution in dry CH_2Cl_2 until the color of the reaction mixture changes to green-blue or brown in the case of *p*-phenylbenzyl ethers or benzyl ethers, respectively. This color change indicates the reaction end point and occurs in 2-3 minutes. The reaction is quenched by addition of water upon which the color usually disappears. Products are extracted with CH_2Cl_2. In the case of water-soluble products the solvents are evaporated, the residual mixture is treated with acetone to remove the $FeCl_3$, and the residue is purified by microflash chromatography in an appropriate solvent system.

The results obtained using various carbohydrate benzyl and *p*-phenybenzyl ethers are shown in the Table. The yields are usually higher than 70 %. The benzylate cleavage reactions presumably involve initial complexation of $FeCl_3$ to the ethereal oxygen atom and subsequent displacement with a proton to yield the free alcohols and benzyl chloride. Namely, $FeCl_3$ is reacting stoichiometrically[7]. This reaction does not proceed in protic or lone pair electron rich solvents such as alcohols, diethyl ether and acetone. The acids $FeCl_3 \cdot 6H_2O$, $ZnCl_2$ and $AlCl_3$ are not efficient but $SnCl_4$ was found to be as effective as $FeCl_3$.

Table. Deprotection of (phenyl)benzyl ethers of monosaccharides by $FeCl_3$

Entry	Substrate		Product	Time (min)	Yield (%)
1		R = OPhBn R_1 = OPhBz		3	82[a]
2		R = OPhBz R_1 = OPhBn		3	83[a]
3		R = OAc R_1 = OPhBn		4	68[b]
4		R = OPhBn R_1 = OCH_3		4	70[b]
5		R = OPhBn		3	73[b]
6		R = OBn R_1 = OPhBz		15	85[a]
7		R = OBn		30	71[b]

a) Yield was determined by UV (ε 47,800) after HPLC (0.3-0.5 μmol).

b) Isolated yield, SiO_2 column chromatography (50 μmol).

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