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Cleavage Pattern of Alkoxy- or Aryloxymethyl Ethers Induced by Mixed Hydrides

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Hydrogenolysis of the 6-O-methylthiomethyl(MTM)-, 2-trimethylsilyl-ethoxymethyl(SEM)-, benzyloxymethyl(BOM)-, p-anisyloxymethyl(pAOM)- and ethoxymethyl(EOM)- derivatives of methyl 2,3,4-tri-O-benzyl-, (1) as well as of the 4-O-SEM, BOM, pAOM and EOM derivatives of methyl 2,3,6-tri-O-benzyl-α-D-glucopyranoside (2) was studied.

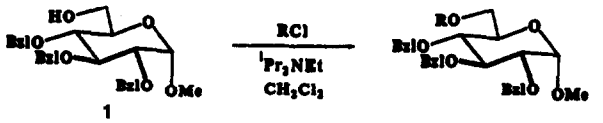
Protecting group strategy continues to play a vital role in the execution of multistep organic syntheses, most particularly in the case of complex oligosaccharides. Numerous alkoxy- and aryloxymethyl ether-type protecting groups have been worked out and emloyed for the temporary protection of primary or secondary hydroxyl groups: methoxymethyl[1] (MOM), methoxyethoxymethyl[2] (MEM), benzyloxymethyl[3] (BOM), 4-pentenyloxymethyl[4] (POM), p-anisyloxymethyl[5] (pAOM), guaiacyloxymethyl[6] (GuOM), 2-trimethylsilyloxymethyl[7] (SEM), tert-butyldimethylsilyloxymethyl[8] (TBDMSOM), thexyldimethylsilyloxymethyl[8] (TDSOM), methylthiomethyl[9] (MTM), 2,2,2-trichloroethoxymethyl[10] (TCEM), ethoxymethyl[11,12] (EOM), and tert-butoxymethyl[13]. The preparation of such ethers is well-established: in most cases the alcohol is simply reacted with alkoxy or aryloxymethyl chlorides in the presence of a base with low nucleophilicity, but in some cases more sophisticated methodology should be employed[14,17].

The removal of these protecting groups requires quite different conditions. The common feature of these groups is that they are sensitive in more or less extent to acids, but removal of some of these protecting groups can be effected by metal ions, hydrogenolysis or with F^- [2-15, 18-23, 26].

Albeit the above-mentioned groups are called ethers, they can also be considered as mixed methylene acetal derivatives; therefore they should be cleaved by mixed hydride reagents. In spite of the fact that cyclic methylene acetals react with the $LiAlH_4$-$AlCl_3$ reagent to give methyl ethers[24,25], this type of reagent system, to the best of our knowledge, was used only in the case of the MOM group[27].

In this paper we report on the cleavage of the MTM, BOM, EOM, SEM, and pAOM groups with mixed hydrides.

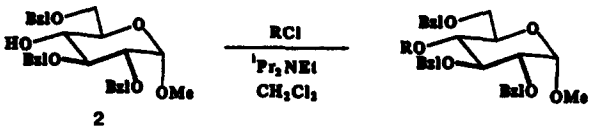
The known methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[28] (1) and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[29] (2) were used as starting compounds for our investigations. For the preparation of the employed substrates, 1 and 2 were treated with the selected alkyl or aryloxymethyl chloride[30] in the presence of diisopropyl-ethylamine (Hünig's base). The reaction conditions and yields are summarized on *Fig. 1.* and *Fig. 2.*



1

R	Yield	Conditions	
MTM	43%	1 day, reflux	3
SEM	83%	1 night, reflux	4
BOM	78%	1 hour, r.t.	5
pAOM	88%	3.5 hours, r.t.	6
EOM	86%	1 hour, r.t.	7

Fig. 1.



2

R	Yield	Conditions	
SEM	52%	1 day, reflux	8
BOM	66%	1 day, reflux	9
pAOM	70%	2 days, reflux	10
EOM	84%	2 hours, r.t.	11

Fig. 2.

The data show that the primary OH of 1 reacted smoothly with the chlorides even at room temperature. The only exception was the conversion into 3, which needed a little more drastic conditions. The yield of this reaction was rather low (43 %), and it could not be increased even by changing the base from iPr_2NEt to NaH.

The protection of the secondary OH group of compound 2 required elevated temperature and prolonged reaction time. Unfortunately, the reaction of 2 with MTMCl gave the acetal only in extremely low yield. We tried to improve this yield by using the dibenzoylperoxyde-dimethylsulfide[17] and also the DMSO-Ac_2O reagents[14], but both attempts failed.

The structure of all synthesized compounds was confirmed by ^1H and ^{13}C-n.m.r. spectroscopic methods, and their homogenity was proved by HPLC.

For the reduction of cyclic carbohydrate acetals into hydroxy/ethers, the $LiAlH_4$-$AlCl_3$, the $BH_3.NMe_3$-$AlCl_3$ and the $NaCNBH_3$-HCl systems have been succesfully employed. In the case of $LiAlH_4$-$AlCl_3$ one can "fine tune" the hydride donor ability *vs.* Lewis acid character of the system by simply changing the molar ratio of the two reagents. This reagent system is applicable when the target molecule does not contain base-labile functions, while the borane type reagents are compatible also with acyl groups.

Besides the chemical compatibility, an additional crucial question is the regioselectivity of the cleavage reaction. In our case, in principle, two products are expected to form: the starting compounds (1 and 2) or their *O*-methyl derivatives (methyl 2,3,4-tri-*O*-benzyl-6-*O*-methyl-α-D-glucopyranoside (12) and methyl 2,3,6-tri-*O*-benzyl-4-*O*-methyl-α-D-glucopyranoside (13), respectively).

We used five different reaction conditions for our investigation. The results of the cleavage (100 % conversion if not indicated otherwise) and the exact product distribution (determined by HPLC) are summarized in *Tables I* and *II*.

TABLE I.

Product distribution of the reductive hydrogenolysis in the case of methylene acetals at the primary (C-6) position

	AlH_2Cl		$AlHCl_2$		BH_3/THF		BH_3/toluene	
	1	**12**	**1**	**12**	**1**	**12**	**1**	**12**
MTM(3)	100	0	100	0	85[a]	15[a]	100	0
SEM(4)	0[b]	0[b]	100	0	100	0	100	0
BOM(5)	0[b]	0[b]	89	11	98	2	100	0
pAOM(6)	45	55	32	68	12	88	0	100
EOM(7)	0[b]	0[b]	100[c]	0[c]	0[d]	0[d]	100[e]	0[e]

[a] 24h, rt., 15% conversion. [b] 48 h, 40 °C, no reaction. [c] 24h, r.t., 40% conversion.

[d] 24 h, 70 °C, no reaction. [e] 5 h, r.t., 50% conversion.

TABLE II.

Product distribution of the reductive hydrogenolysis in the case of methylene acetals at the secondary (C-4) position

	AlH_2Cl		$AlHCl_2$		BH_3/THF		BH_3/toluene	
	2	**13**	**2**	**13**	**2**	**13**	**2**	**13**
SEM(8)	100[a]	0[a]	82	18	0[d]	0[d]	100	0
BOM(9)	100[b]	0[b]	90	10	0[d]	0[d]	100	0
pAOM(10)	0[c]	0[c]	0[c]	0[c]	0[d]	0[d]	0	100
EOM(11)	100[e]	0[e]	100[f]	0[f]	0[d]	0[d]	100[g]	0[g]

[a] 48 h, rt., 5% conversion. [b] 24 h, 5% conversion. [c] 48 h, 40 °C, no reaction.

[d] 24 h, 70 °C, no reaction. [e] 24 h, 40 °C, 20% conversion. [f] 24 h, 40 °C, 50% conversion.

[g] 5 h, r.t., 60% conversion.

AlH_3 did not react with the acetals, and also AlH_2Cl reacted sluggishly, or did not react at all (6-*O*-SEM, BOM, EOM and 4-*O*-p-AOM). $AlHCl_2$ cleaved each acetal except the secondary pAOM derivative **10**. The main products of all reactions were the starting compound **1** or **2**, but in the case of pAOM derivatives, the 6-*O*Me ether was found to dominate.

The $BH_3.NMe_3$-$AlCl_3$ reagent in THF cleaved all the primary acetals, except compound **7**, and the secondary acetals did not react under such conditions. A change of the solvent from THF to toluene had a dramatical effect on the outcome of the reaction: all of the model compounds reacted, producing the 6-*O* or 4-*O* unprotected sugar (**1**,**2**). The only exceptions were compounds **6** and **10**, where the 6-*O*- and 4-*O*-methyl ethers were formed exclusively as the result of the cleavage.

The above results demonstrate, that the most useful reagent for the cleavage of such type of protecting groups is the $BH_3.NMe_3$-$AlCl_3$ system in toluene. The reaction is clean, fast and it regenerates the OH-group. The only exceptions were

the pAOM protected derivatives. However, generalization of the above observations necessiates further, more detailed investigations.

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