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Selective 6-O-Debenzylation of Mono- and Disaccharide Derivatives Using $ZnCl_2$-Ac_2O-HOAc

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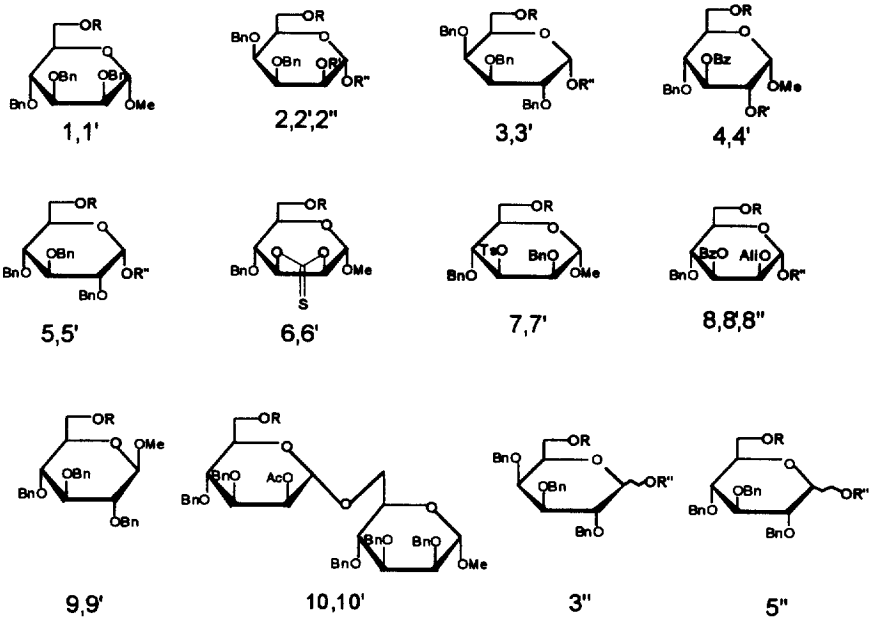
Abstract: Freshly fused $ZnCl_2$ in Ac_2O/HOAc at room temperature has been used for 6-O-debenzylation of mono- and disaccharide derivatives giving yields more than 80%. Notably, allyl, acetyl, benzoyl, tosyl, thiono groups are unaffected under the designated conditions.

Many important bioactive natural products contain 1 → 6 glycosidic linkages[1-6]. Selective 6-O-debenzylation of methyl glycoside derivatives is a very useful procedure for the synthesis of 1 → 6 linked oligosaccharides since it can substantially simplify the reaction pathway. Although the acetolysis of benzyl ethers initialized by Lewis acid or proton is well known, for example, by $FeCl_3/Ac_2O$[7], ZnI_2/Ac_2O[8], and H_2SO_4/Ac_2O[9], the selectivity and yield are not satisfactory. The direct 6-O-debenzylation using trimethylsilyl trifluoromethanesulfonate/acetic anhydride (TMSOTf/Ac_2O)[10] at -40 °C has been shown to be temperature dependent, and secondary benzyl ether linkages can also be cleaved as the temperature is raised. Iodotrimethylsilane is another catalyst for direct 6-O-debenzylation[11] giving moderate to good yield, but the secondary benzyl groups can also be cleaved as the reaction time is long. In our recent studies, we found that $ZnCl_2$ (7.5-10eq)-Ac_2O-HOAc was a highly efficient reagent for 6-O-debenzylation at room temperature. Compounds of diverse structure including methyl α - and β -D-glucopyranoside, methyl α -D-galacto, manno, talopyranoside and methyl 1 → 6 linked disaccharide were tried. Notably, allyl, acetyl, benzoyl, tosyl, thiono groups all survived under the reaction conditions, no anomerization and glycosidic bond breaking were observed (see Table I for results). Also, 6-O-debenzylation of monosaccharides having one free

hydroxy group (see **2** and **4**) was very successfully performed giving the products with two potential hydroxy groups capable of building branched oligosaccharides. It was also found that a large excess of freshly fused $ZnCl_2$ (20eq) and a long reaction time (4h) would simultaneously cleave the methyl glycosidic bond while the secondary benzyl groups were still not changed (see Table I for results). The typical procedure for selective 6-O-debenzylation is as follows: To a solution of 6-O-benzylated sugar (50—200mg) in 1 ml Ac_2O/HOAc (2:1) was added a solution of freshly fused $ZnCl_2$ (7.5—10 eq) in 1 ml Ac_2O/HOAc (2:1), the mixture was stirred at room temperature for 2h, TLC (3:1 petroleum ether-ethyl acetate) indicated that the reaction was complete. Water was added, and the mixture was extracted with dichloromethane three times, washed with saturated sodium carbonate, then water, dried with Na_2SO_4, and concentrated to give a syrup. Purification of the syrup by column chromatography (3:1 petroleum ether—ethyl acetate) yielded the pure product (yield >80%). The structures of most of the starting materials and products were simple, among which known compounds **1, 1'**[12], **2**[13], **3, 3'**, **3''**[14], **5, 5'**[15], **5''**[16], **7**[17], **9, 9'**[18], and **10, 10'**[19] were identified by comparison of their physical data to the reported values in literature, while new compounds were characterized by optical rotations, elemental analyses, and ^1H NMR spectrometry[20]. Compared to the starting materials, the products gave ^1H NMR spectra showing a downfield chemical shift of H-6 and upfield shift of the acetyl methyl signal. In summary here we report a very effective and facile method for selective 6-O-debenzylation and this method can be used in the synthesis of oligosaccharides.

Table I Results for selective 6-O-debenzylation using $ZnCl_2$-Ac_2O-HOAc

Compound	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
$ZnCl_2$ (eq)	7.5	10	7.5	10	7.5	10	10	10	7.5	10
Product	**1'**	**2'**	**3'**	**4'**	**5'**	**6'**	**7'**	**8'**	**9'**	**10'**
Yield	85%	90%	80%	86%	82%	88%	92%	94%	94%	81%
$ZnCl_2$ (eq)		20	20		20			20		
Product		**2''**	**3''**		**5''**			**8''**		
Yield		86%	90% α:β 4:1		87% α:β 6:1			92%		



1-10 R=Bn R'=H R"= Me

1'-10' R=Ac R'=Ac R"= Me

2",3",5",8" R=Ac R'=Ac R"=Ac

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20. All new compounds gave satisfactory elemental analysis results. Selected ^{1}H NMR ($CDCl_3$, Me_4Si as internal standard) data are as follows: **2'**. 7.36-7.24(m, 10H, Ph-*H*), 5.34(d, 1H, $J_{2,3}$ 1.7 Hz, H-2), 4.94, 4.75(AB_q, 2H, ^{2}J 11.7 Hz, PhCH_2), 4.80(s, 1H, H-1), 4.75, 4.67(AB_q, 2H, ^{2}J 11.7 Hz, PhCH_2), 4.40-4.18(m, 2H, H-6), 3.92-3.78(m, 3H, H-3,4,5), 3.32(s, 3H OCH_3), 2.10, 2.00(2s, 6H, 2COCH_3). **2''**. 7.38-7.24(m, 10H, Ph-*H*), 6.18(d, 1H, $J_{1,2}$ 0.9 Hz, H-1), 5.30(dd, 1H, $J_{2,3}$ 1.8 Hz, H-2), 4.92, 4.69(AB_q, 2H, ^{2}J 12.0 Hz, PhCH_2), 4.76, 4.56(AB_q, 2H, ^{2}J 12.0 Hz, PhCH_2), 4.32-3.32(m, 3H, H-3,4,5), 2.10, 2.08, 2.00(3s, 9H, 3COCH_3). **4'**. 8.04(d, 2H, *J* 8.9 Hz, Ph-*H* of Bz), 7.62-7.12(m, 8H, Ph-*H*), 5.85(t, 1H, $J_{3,4}$ 9.4 Hz, H-3), 5.05(dd, 1H, $J_{2,3}$ 9.4 Hz, H-2), 4.91(d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 4.56, 4.48(AB_q, 2H, ^{2}J 11.7 Hz, PhCH_2), 4.36(dd, 1H, $J_{6,6'}$ 12.5 Hz, $J_{5,6}$ 2.5 Hz, H-6), 4.20(dd, 1H, $J_{5,6'}$ 4.2 Hz, H-6'), 4.04-3.95(m, 1H, H-5), 3.76(t, 1H, $J_{4,5}$ 9.4 Hz, H-4), 3.43(s, 3H, OCH_3), 2.10, 1.96(2s, 6H, 2COCH_3). **6'**. 7.38-7.30(m, 5H, Ph-*H*), 5.08(t, $J_{3,4}$ 8.4 Hz, H-3), 5.06(s, 1H, H-1), 4.86, 4.60(AB_q, 2H, ^{2}J 11.4 Hz, PhCH_2), 4.76(d, 1H, $J_{2,3}$ 7.6 Hz, H-2), 4.34(dd, 1H, $J_{6,6'}$ 12.3 Hz, $J_{5,6}$ 1.9 Hz, H-6), 4.22(dd, 1H, $J_{5,6'}$ 4.8 Hz, H-6'), 3.88-3.79(m, 1H, H-5), 3.59(dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 3.40(s, 3H, OCH_3). 2.00(s, 3H, COCH_3). **7'**. 7.72(d, 2H, *J* 8.7 Hz, Ph-*H* of Ts), 7.52-6.81(m, 12H, Ph-*H*), 4.85(dd, 1H, $J_{2,3}$ 3.4 Hz, $J_{3,4}$ 8.9 Hz, H-3), 4.70-4.47(m, 5H, 2PhCH_2, H-1), 4.40-3.60(m, 5H, H-2,4,5,6), 3.32(s, 3H, OCH_3), 2.38(s, 3H, CH_3), 2.03(s, 3H, COCH_3). **8'**. 8.10(d, 2H, *J* 6.8 Hz, Ph-*H* of Bz), 7.60-7.28(m, 8H, Ph-*H*), 5.85-5.75(m, 1H, CH_2=C*H*), 5.50(dd, 1H, $J_{2,3}$ 3.3 Hz, H-3), 5.22(m, 1H, J_{trans} 15.0 Hz, ^{2}J 1.3 Hz, HC*H*=CH), 5.09(m, 1H, J_{cis} 8.3 Hz, *H*CH=CH), 4.76(d, 1H, $J_{1,2}$ 0.5 Hz, H-1), 4.73, 4.56(AB_q, 2H, ^{2}J 9.2 Hz, PhCH_2), 4.35(d, 2H, $J_{5,6}$ 2.7 Hz, H-6), 4.05-4.12(m, 2H, CH_2=CH-CH_2), 4.05(t, 1H, $J_{3,4}$ $J_{4,5}$ 8.7 Hz, H-4), 3.92(dd, 1H, $J_{2,3}$ 2.0 Hz, H-2), 3.40(s, 3H, OCH_3), 2.12(s, 3H, COCH_3). **8''**. 8.11(d, 2H, *J* 8.4 Hz, Ph-*H* of Bz), 7.66-7.12(m, 8H, Ph-*H*), 6.15(d, 1H, $J_{1,2}$ 1.8 Hz, H-1), 5.85-5.75(m, 1H, CH_2=C*H*), 5.51(dd, $J_{2,3}$ 4.2 Hz, H-3), 5.20(m, 1H, J_{trans} 16.3 Hz, ^{2}J 0.9 Hz, HC*H*=CH), 5.10(m, 1H, J_{cis} 9.8 Hz, *H*CH=CH), 4.74, 4.60(AB_q, 2H, ^{2}J 11.6 Hz, PhCH_2), 4.12(t, 1H, $J_{3,4}$ $J_{4,5}$ 9.3 Hz, H-4), 4.12-4.00(m, 3H, H-5, CH_2=CH-CH_2), 3.91(dd, 1H, $J_{2,3}$ 0.6 Hz, H-2), 2.14, 2.08(2s, 6H, COCH_3).

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