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A FACILE CLEAVAGE OF BENZYLIDENE ACETALS WITH DIISOBUTYLALUMINUM HYDRIDE

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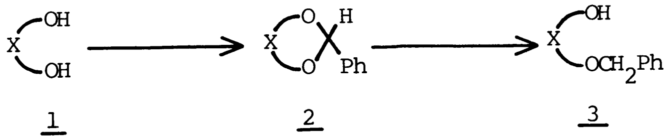
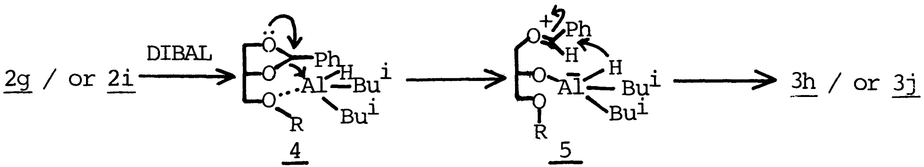
Benzylidene acetals of 1,2- and 1,3-glycols are easily cleft by diisobutylaluminum hydride in a toluene solution at 0 °C - room temperature to give the corresponding monobenzyl ethers of the glycols. In general the reaction proceeds excellently in regio-selective manner depending on the stereochemical environment.

Selective monobenzylation of glycols is one of important protection steps in organic synthesis. Besides direct monoalkylation using a benzyl halide, one efficient method for monoprotection known is reductive cleavage of a benzylidene derivative of a glycol by hydrogenolysis using a mixture of lithium aluminum hydride and aluminum chloride in ether$^{1)}$ (Scheme 1). This procedure has been successfully employed in the recent syntheses of some biologically important natural products, such as mitosenes,$^{2)}$ sugars,$^{3)}$ platetet-activating glycerols,$^{4)}$ and carbapenem antibiotics,$^{5)}$ by several workers. We describe here a facile and efficient cleavage of the benzylidene acetals 2 using diisobutylaluminum hydride in toluene in place of using a mixture of lithium aluminum hydride and aluminum chloride in ether. There has been reported a reductive cleavage of some aliphatic ketals with diisobutylaluminum hydride at higher temperature,$^{6)}$ however facile hydrogenolysis of benzylidene acetals using diisobutylaluminum hydride has not been reported so far. The reaction is easy to carry out using 2.5 equivalents of the reducing agent in a toluene solution at 0 °C - room temperature to give the corresponding monobenzyl ethers 3 in good yields with one exception (entry 10). In most cases, the cleavage occurs selectively at less hindered site of the molecule with two exceptions (entries 7 and 8) in which cleavage occurs at more

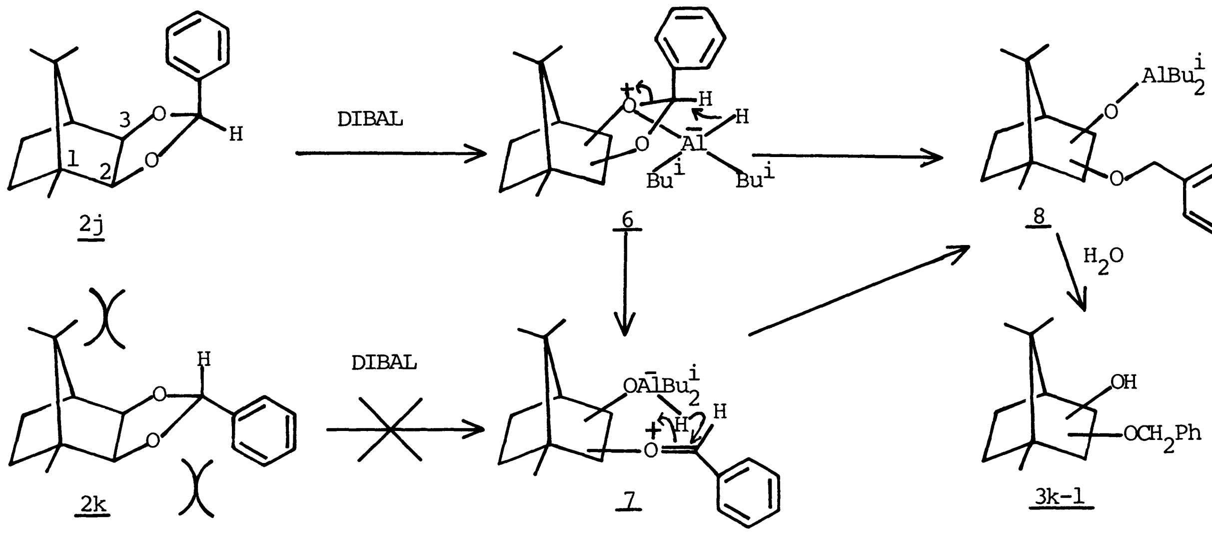


Scheme 1.

hindered position in major extent. In these exceptions the observed regioselectivity can be explained in terms of participation of three oxygen atoms in the molecule which directs the cleavage of acetal group by complex formation with the organoaluminum reagent as shown in Scheme 2. Although the cleavage is presumed to occur through internal delivery of hydride, an external pathway is also conceivable since more than two equivalents of the organoaluminum reagent are generally required to give satisfactory yields under the conditions. It is also of interest to note that the reduction is highly affected by stereochemical environment of the molecule. Thus, of two isomers 2j and 2k, only the former can be cleft facily under the conditions to give a mixture (ca. 2:1) of the monobenzyl ethers 3k and 3l in 88% total yield, while the latter is virtually inert under the same conditions. Preferential formation of 3k over 3l in the former may be brought about by the steric effect of the methyl group at C-1 center which shields the oxygen at C-2 center more extent in forming a complex 6 with the organoaluminum. When a mixture (1:1) of two isomers 2j and 2k is subjected under the same reaction conditions, only the former is reacted to give a mixture of the benzyl ethers 3k and 3l accompanied by the latter completely intact. These suggest that only the former 2j is able to form an aluminum complex at the less hindered *endo* face of the molecule allowing reductive cleavage to form the benzyl ethers 3j and 3k via a four-center transition state 6 or an acylium intermediate 7, while the latter 2k is unable to form an aluminum complex at both *endo* and *exo* faces owing to steric congestion (Scheme 3).

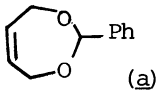
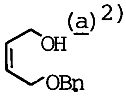
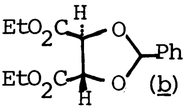
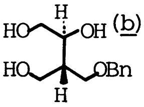
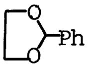
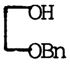
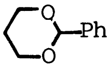
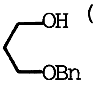
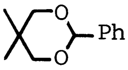
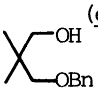
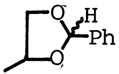
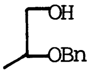
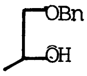
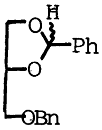
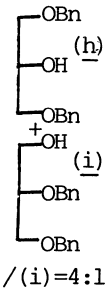
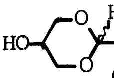
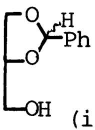
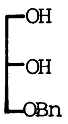


Scheme 2.



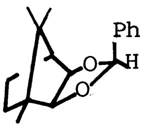
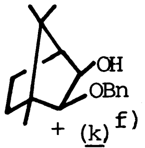
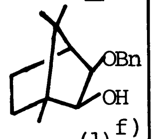
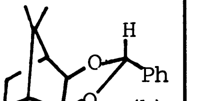
Scheme 3.

Table 1.

Entry	Acetal (2) a)	Reaction time (h) b)	Product (3)	Bp or mp	Yield /%	^{1}H-NMR (δ) ppm g)
1	 (a)	4	(a) 2) 	Bp 114-120 °C/ 0.4 mmHg	84	2.23(1H,bs,exchangeable), 4.06(4H,m), 4.45(2H,s), 5.70(2H,m), 7.23(5H,s)
2	 (b)	5	(b) 3) 	mp 60-63 °C	77	2.65 (3H,bs,exchangeable), 3.41-4.16(6H,m), 4.65(2H,ABd, J=11 Hz), 7.33(5H,s)
3	 (c)	4	(c) 	Bp 70 °C/0.3 mmHg (lit.1a) 135 °C/ 13 mmHg)	82	2.33(1H,bs,exchangeable), 3.60(4H,m), 4.53(2H,s), 7.30(5H,s)
4	 (d)	22	(d) 	Bp 110 °C/0.1 mmHg (lit.1a) 110 °C/ 0.5 mmHg)	85	1.88(2H,q,J=6 Hz), 2.50 (1H,bs,exchangeable), 3.55(2H,d,J=6 Hz), 3.72 (2H,m), 4.47(2H,s), 7.23(5H,s)
5	 (e)	7	(e) 	Bp 120 °C/0.1 mmHg	82	0.90(6H,s), 2.65(1H, bs,exchangeable), 3.32 (2H,s), 3.45(2H,bs), 4.48(2H,s), 7.28(5H,s)
6	 (f) c)	5	 (f)  (g) (f)/(g)=4:1	Bp 90 °C/0.2 mmHg e)	78	1.15(3H,dd,J=5.4 Hz, J=1.6 Hz), 2.28(1H,bs, exchangeable), 3.57 (3H,m), 4.55(2H,d, J=2.4 Hz), 7.30(5H,s), [acetate:1.20(3H,d, J=9 Hz), 2.03(3H,s), 3.43-3.97(1.2H,m), 4.08(1.6H,s), 4.57 (2H,s), 4.93-5.47(0.2H, m), 7.27(5H,s)]
7	 (g) c)	5	 (h) + (i) (h)/(i)=4:1	Bp 150 °C/0.2 mmHg e)	86	2.51(1H,bs,exchangeable), 3.57(5H,m), 4.51(4H,s), 7.27(5H, s), [acetate:2.02(3H, s), 3.63(1.8H,d,J=5 Hz), 4.20(0.4H,m), 4.50(4H, s), 5.22(0.8H,quint, J=5 Hz), 7.27(10H,s)]
8	 (h) d) +  (i)	14	(j) f) 	(lit.7) 110-120 °C/ 0.15 mmHg)	69	2.93(1H,bs,exchangeable), 3.25(1H,bs,exchangeable), 3.33(2H,d,J=4 Hz), 3.42 (2H,d,J=6 Hz), 3.77(1H, m), 4.47(2H,s), 7.25(5H, s)

(continued)

Table 1 (continued)

9	 (j)	1	 + (k)[f]  (l)[f]	(lit.[8] oil)	88 (58) + (30)	0.72(3H,s), 0.89(3H,s), 1.03(3H,s), 0.80-1.93 (5H,m), 2.88(1H,d,exchangeable), 3.40(1H, d,J=7 Hz), 3.80(1H,dd, J=7 Hz), 4.60(2H,s), 7.30(5H,s) 0.82(3H,s), 0.96(3H,s), 1.13(3H,s), 0.90-1.83 (4H,m), 1.93(1H,m), 2.95(1H,bd,exchangeabl), 3.62(2H,bd), 4.61(2H, ABd,J=11 Hz) 7.27(5H,s)
10	 (k)	24	very slow			
11	(j) / (k)[c]	0.1	(k)[f] + (l)[f] + (2k)[f]		88 (33) + (9) + (46)	

a) Acetals 2 except 2j are prepared from benzaldehyde with the corresponding glycols 1 in the presence of p-toluenesulfonic acid in refluxing benzene. The acetal 2j is prepared from an equivalent amounts of the aldehyde and the glycol at room temperature in the presence of p-toluenesulfonic acid and anhydrous magnesium sulfate. In entry 2, 6.5 equivalents of the reducing agent is used. Satisfactory elemental analyses for all the newly synthesized compounds were obtained. b) Reaction is carried out at room temperature. c) Obtained as an inseparable mixture of two diastereomers (ca. 1:1). d) Obtained as an inseparable mixture of two pairs of diastereomers (ca. 1:1:1:1). e) Obtained as an inseparable mixture (4:1). f) Separated by silica gel chromatography. g) Measured in deuteriochloroform. bs=broad singlet, bd=broad doublet.

A typical procedure for the formation of 2-benzyloxyethanol 3c is as follows : To a stirred solution of 2-phenyldioxolane 2c 1.68 g (11.2 mmol) in toluene (10 ml) is added diisobutylaluminum hydride (1.5 mol in toluene) 17 ml (25.5 mmol) dropwise at 0 °C. After stirring for 5 h at rt, to the mixture is added methanol, followed by 10% aq NaOH and the organic layer is separated, and the aqueous layer is extracted with ether. Combined organic layer is washed with sat. aq NaCl and dried over MgSO$_4$. The solvent is evaporated in vacuo and the residue is distilled under vacuum to give 2-benzyloxyethanol 3c, 1.37g (82%): bp 70 °C (0.3 mmHg).

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