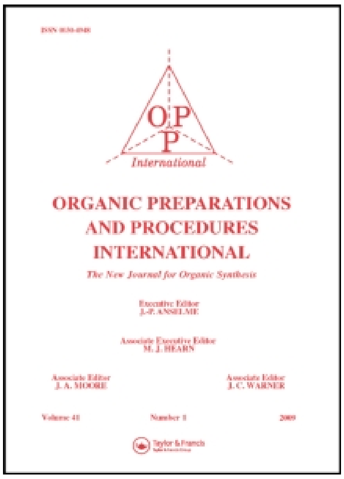

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REDUCTION CLEAVAGE OF AROMATIC CYCLIC ACETALS WITH ZIRCONIUM CHLORIDE-LITHIUM ALUMINUM HYDRIDE

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REDUCTION CLEAVAGE OF AROMATIC CYCLIC ACETALS WITH ZIRCONIUM CHLORIDE-LITHIUM ALUMINUM HYDRIDE

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The reductive cleavage of acetals and ketals to ethers or glycol monoethers in a synthetically useful process and a number of efficient reagents have been uncovered to effect such transformations, these include $LiAlH_4$-Lewis acid, Me_3SiH-Me_3SiOTf, Et_3SiH-acids, DIBAL, B_2H_6, H_2BCl, $NaBH_3CN$-HCl, $NaBH_4$-CF_3COOH, $Zn(BH_4)_2$-Me_3SiCl, Li-NH_3 and H_2-catalysts.[1] In addition, Ishihara and Kotsuki have applied such methodology to natural products syntheses.[2,3]

During a survey of the chemistry of $ZrCl_4$-$LiAlH_4$, we found that benzaldehyde ethylene acetal can be reduced selectively to the corresponding glycol monoether ($PhCH_2OCH_2CH_2OH$) in high yield on treatment with this reagent system in Et_2O at 30°. This prompted further investigation of the reductive cleavage of aromatic cyclic acetals with the new reductive system $ZrCl_4$-$LiAlH_4$, with regard to optimum reaction conditions (i. e. reactant ratios, temperature, time and solvent) and also the effect of ring substituents in aromatic cyclic acetals and the effect of the ring size of cyclic aromatic acetals. The results (Tables 1-4) indicate ether to be the optimum solvent for the reduction of the acetal to corresponding glycol monoether with the system ZrCl-$LiAiH_4$ and that the efficiency of the reduction of benzaldehyde ethylene acetal varies with the solvent. In addition, the yields and reduction products varied with the solvent. Thus in oxygen containing solvents (i. e. THF, EDME, Et_2O), the product of simple reduction ($PhCH_2OCH_2CH_2OH$) was obtained while in benzene, only toluene was formed. Overall, ether appears to be the most effective solvent (Table 1).

The effect of the reaction conditions on the reduction of benzaldehyde ethylene acetal is listed in Table 2. In general, the optimum molar ratio of substrate to $ZrCl_4$-$LiAlH_4$ was found to be relatively insensitive to changes as long as ratio was at least 1:1:5, 1:1:1, 1:2:1 or 1:1:2. The optimum reaction time was 12 hrs at 30° in ether. The reduction of substituted benzaldehyde ethylene acetals and various cyclic benzaldehyde acetals was also investigated and the results are given in Tables 3 and 4. Table 3 illustrates that the nitro group retards the reduction (and was reduced to the amine) while the strong electron-donating methoxy group promotes over-reduction to *p*-methoxytoluene. The results in Table 4 show that the five-membered ring cyclic acetals are more easily reduced than the corresponding six-membered acetals, and that with an unsymmetrical acetal, such as benzaldehyde 1,2-propylene acetal, the primary alcohol predominated over the secondary alcohol, indicating that the process probably does not involve carbocation intermediates.

EXPERIMENTAL SECTION

AR grade chemicals were used. $ZrCl_4$ was obtained from Aldrich Chemical Co. Inc. Et_2) was dried over sodium metal and then boiled under reflux. Acetals and ketals were prepared by the usual methods and dried before use. The reductive reaction of acetals and ketals were carried out under anhydrous conditions. The identity of all products was determined by gas chromatography using a HP5998 GC-MS instrument.

General Procedure for the Reductive Cleavage of Acetals with $ZrCl_4$-$LiAlH_4$. Reduction of Benzaldehyde Ethylene Acetal.- To a stirred suspension of $ZrCl_4$ (8 mmol) in anhydrous Et_2O (50 mL) was added $LiAlH_4$ powder (4 mmol) at room temperature under a nitrogen atmosphere. During the addition of $LiAlH_4$, hydrogen evolved vigorously and the reaction mixture became yellow. After stirring for 30 mins at room temperature, benzaldehyde ethylene acetal (4 mmol) was added and the mixture was heated at reflux for 12 hrs. Aqueous K_2CO_3(10%, 20 mL) was then added and after stirring for 10 mins, the organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was then removed on a rotary evaporator and the residue purified by column chromatography (SiO_2 as support; CH_2Cl_2-benzene as solvent) to provide the corresponding ether [0.54 g, 89% yield; bp 72-73° (1 mm Hg)]. All products were identified through mass spectra.

The same general procedure was used for the reductive cleavage of ketals and for the cleavage of benzaldehyde ethylene acetal to toluene. The following compounds were isolated.

$PhCH_2OCH_2CH_2OH$: bp. 72-73° (1 mm Hg) [lit.[4] bp. 135° (13 mm Hg)]; MS m/e: 152 (M), 107 ($M-CH_2CH_2OH$), 91 ($M-OCH_2CH_2OH$).

$4-ClC_6H_4CH_2OCH_2CH_2OH$: bp. 97-98° (16 mm Hg); MS m/e: 188 (M+2), 186 (M), 141 ($M-CH_2CH_2OH$), 127 ($M+2-OCH_2CH_2OH$), 125 ($M-OCH_2CH_2OH$).

$4-MeOC_6H_4CH_2OCH_2CH_2OH$: bp. 145-146° (5 mm Hg) [lit.[5] bp. 109° (0.5 mm Hg)]; MS m/e: 182 (M), 137 ($m-CH_2CH_2OH$), 121 ($m-OCH_2CH_2OH$).

$PhCH_2OCH_2CH_2CH_2OH$: bp. 88-89° (0.3 mm Hg) [lit.[4] mp. 110° (0.5 mm Hg)]; MS m/e: 166 (M), 107 ($M-CH_2CH_2CH_2OH$), 91 ($M-OCH_2CH_2CH_2OH$).

$PhCH_2OCH_2CH(CH_3)OH$: bp. 78-79° (0.25 mm Hg); MS m/e: 166 (M), 107 ($M-CH_2CH(CH_3)OH$), 91 ($M-OCH_2CH(CH_3)OH$), 45 ($MeCH=\overset{+}{O}H$, the characteristic peak of secondary alcohol).

$PhCH_2OCH(CH_3)CH_2OH$: bp. 100-101°(0.5 mm Hg); MS m/e: 166 (M), 148 ($M-H_2O$), 135 ($M-CH_2OH$). 108 ($M-CH_2=CH-CH_2OH$), 91 ($M-OCH(CH_3)CH_2OH$).

$PhCH(CH_3)OCH_2CH_2OH$: bp. 64-65° (16 mm Hg); MS m/e: 166 (M), 151 ($M-CH_3$), 121 ($M-CH_2CH_2OH$), 105 ($M-OCH_2-CH_2OH$).

$PhCH(Et)OCH_2CH_2OH$: bp. 74-75° (15 mm Hg); MS m/e: 180 (M), 151 (M-Et), 135 ($M-CH_2CH_2OH$), 119 ($M-OCH_2CH_2OH$).

TABLE 1. Reduction of Benzaldehyde Ethylene Acetal in Various Solvents

Solvent	Total yield (%)[b]	Product	Yield (%)
THF	12	$PhCH_2OCH_2CH_2OH$	42
		$PhCH_2OH$	58
EDME[c]	40	$PhCH_2OCH_2CH_2OH$	41
		PhMe	59
Et_2O	67	$PhCH_2OCH_2CH_2OH$	95
		$PhCH_2OH$	5
benzene	99	PhMe	100

a) All the reactions were conducted at refluxing temperature for 6 hrs. b) All the yields were determined by GC-MS and based on the substrate used. c) THF = tetrahydrofuran; EDME = ethylene glycol dimethyl ether.

TABLE 2. Effects of Reagent Ratio and Time on the Reduction of Benzaldehyde Ethylene Acetal

Molar ratio[b]	Reaction Time (hrs)	Total Yield[c] (%)	Product	Yield (%)
1:0:1	12	0	-	-
1:0.25:1	12	0	-	-
1:1:0.5	6	69	$PhCH_2OCH_2CH_2OH$	93
			PhMe	3
1:1:0.5	12	92	$PhCH_2OCH_2CH_2OH$	95
			PhMe	5
1:1:1	6	67	$PhCH_2OCH_2CH_2OH$	95
			$PhCH_2OH$	5
1:1:1	12	95	$PhCH_2OCH_2CH_2OH$	93
			$PhCH_2OH$	7
1:2:1	12	99	$PhCH_2OCH_2CH_2OH$	96
			$PhCH_2OH$	4
1:1:2	6	95	$PhCH_2OCH_2CH_2OH$	83
			PhMe	15
1:1:2	12	98	$PhCH_2CH_2OCH_2OH$	88
			PhMe	12
1:1:0	12		$PhCH_2OCH_2CH_2OH$	4

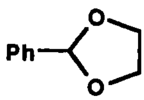
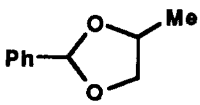
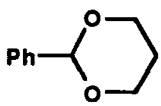
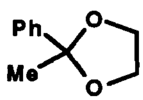
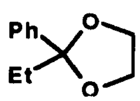
a) Reactions were conducted at 30° in Et_2O. b) Molar ratio is substrate-$ZrCl_4$-$LiAlH_4$. c) Yields were determined by GC-MS and based on the substrate used.

TABLE 3. Reduction of Substituted Benzaldehyde Ethylene Acetals in Et_2O

Substituent	Refluxing time (hrs)	Total Yield[b] (%)	Product	Yield (%)
p-NO_2	12	0	-	-
p-Cl	12	50	4-$ClC_6CH_2OCH_2CH_2OH$	81
			4-ClC_6H_4-CH_2OH	19
p-OMe	12	95	4-$MeOC_6H_4CH_2OCH_2CH_2OH$	45
			4-Methoxytoluene	55
p-OMe	7	97	4-$MeOC_6H_4CH_2OCH_2CH_2OH$	63
			p-Methoxytoluene	37

a) Substrate-$ZrCl_4$-$LiAlH_4$ = 1:1:1. b) All yields were determined by GC-MS and based on the substrate used.

TABLE 4. Reduction of Acetals from Benzaldehyde and Different Glycols[a]

Substrate	Total Yield[b] (%)	Product	Yield (%)
	95	$PhCH_2OCH_2CH_2OH$ $PhCH_2OH$	93 7
	83	$PhCH_2OCH(Me)CH_2OH$ $PhCH_2OCH_2CH(Me)OH$	69 31
	49	$PhCH_2OCH_2CH_2CH_2OH$ $PhCH_2OH$ PhMe	64 7 29
	99	$PhCH(Me)O(CH_2)_2OH$ PhCH(Me)OH	96 4
	97	$PhCH(Et)O(CH_2)_2OH$ PhCH(Et)OH	95 5

a) All the reactions were conducted at 30° in Et_2O for 12 hrs using the reagent system: substrate-$ZrCl_4$-$LiAlH_4$ = 1:1:1. b) All yields were determined by GC-MS and based on the substrate used.

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