An Efficient Method for One-Pot Reductive Cleavage of Acetals to Primary Alcohols Using a Bimetal Redox Couple $CoCl_2.6H_2O$-Zn

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Abstract: Acyclic or cyclic O,O-acetals and O,S-acetals underwent reductive cleavage to give primary alcohols efficiently on treatment with Zn-$CoCl_2.6H_2O$-bimetal redox system in dry tetrahydrofuran at ambient temperature to give good to excellent yields.

Keywords: Alcohols, acetals, bimetal redox system, deprotection, hydroxy ether, reductive cleavage.

INTRODUCTION

Acetals and thioacetals are extremely important intermediates in various synthetic routes. They are prepared as protecting groups of aldehydes [1] especially in the total synthesis of complex natural products, pharmaceuticals, phytopharmaceuticals, fragrances and also in lacquer industries as intermediates or as end products [2-8].

Although 1,2-diacetals have been known since 1938 [9], considerable interests in the application of these compounds have been received only in the recent years [10]. These are generally stable under acidic conditions. However, it may be noted here that benzylidene acetals have a special appealing feature of readiness to undergo reductive cleavage to regioselectively protected alcohols on manipulation of reaction condition [11]. Thus, it was revealed in subsequent studies that activation of different conventional reducing agents by Lewis acids favours chemo, stereo and regioselectivity in reductive cleavage of acyclic as well as cyclic acetals [12]. Facilitation by Lewis acids in such methodologies turned out to be especially fruitful in carbohydrate chemistry where reductive opening of acetals favours protective group manipulation.

Hydroxy ethers are important compounds as perfume chemicals or as raw materials for perfumes [13]. In order to have such specific compounds of commercial value and also for synthetic purposes, acetals or ketals are transformed into them through regioselective reductive cleavage using activated hydrides [14], $BF_3.Et_2O/Me_3SiH$ [11a], $Li/C_{10}H_8$/THF [15], activated zinc in methanol [16], silane-Rh-PPh_3 [17], CF_3COOH/triethyl silane [18], $Co(CO)_8$ under synthesis gas [19] etc. These reagents however are not effective to cleave the acyclic or cyclic O,O-acetals or O,S-acetals directly to the primary alcohols of the corresponding aldehydes. In our continued effort on chiral epoxidation of olefins [20], we were looking for an efficient system to have *trans*-2-buten-1-ol directly from *trans*-2-butenal diethyl acetal to prepare 2*S*,3*S*-epoxybutan-1-ol which is used as intermediate in the synthesis of erythromycin antibiotic. To our knowledge, there are no reports for direct preparation of primary alcohols of the corresponding aldehydes from their acetals, but to the hydroxy ethers only. The positive role of Lewis acid in activating different hydrides in the reductive cleavage of acetals tempted us to explore the reactivity of a Lewis acid in combination with a more electropositive metal which can form a bimetal redox couple in a suitable dry solvent to avoid expensive and explosive hydride reagents.

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RESULTS AND DISCUSSION

Bimetallic systems [21] are very attractive reagents for various syntheses of organic compounds. In our earlier studies [22] on selective reduction of aldehydes to primary alcohols, a bimetal redox couple Zn-$CoCl_2.6H_2O$ was developed. Although acetalization of aldehydes using anhydrous cobalt chloride is reported [23], regeneration of aldehydes or other carbonyls from their respective acetals using such reagents or to their corresponding reduced alcoholic form has not yet so far been reported.

When this system was applied consisting of Zn-$CoCl_2.6H_2O$ in 3:1 molar ratio [22] to *trans*-2-butenal diethyl acetal '1a', it straightway gave *trans*-2-buten-1-ol (**1b**, Table **1**) in very good yield (81%) without affecting the C=C bond. Accordingly a series of open chain O,O-acetals were treated with this redox couple under similar condition in dry THF. All these acetals were found to give primary alcohols in excellent yields (81-92%) (**1b-7b**, Table **1**) in 4-6 hours. After successful syntheses of primary alcohols directly from open chain acetals using Zn-$CoCl_2.6H_2O$ bimetal redox couple, the system was applied to a second series of cyclic acetals under similar condition. The system was also found to be effective in case of these cyclic O,O-diacetals to give their corresponding primary alcohols in 78-93% yields (**1b-8b**, Table **2**) at room temperature in 4-6 hours.

Finally the system was examined with a few cyclic O,S-diacetals in a similar manner, but at 60 °C and ended up with encouraging yields (77-91%) of primary alcohols in 3-6 hours (**1b-8b**, Table **3**) without any accompanying products

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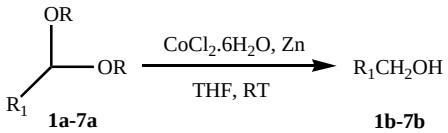
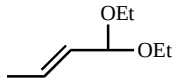
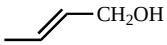
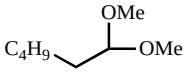
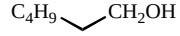
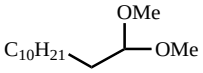
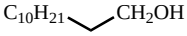
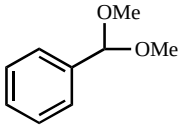
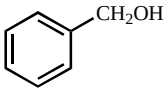
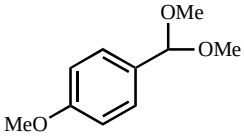
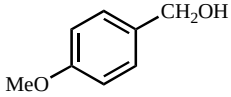
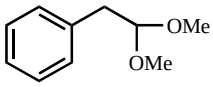
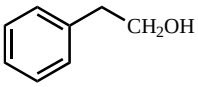
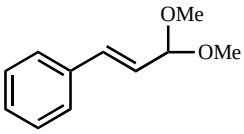
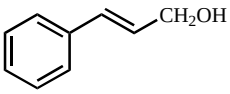
Table 1. *In-Situ* Formation of Alcohols by the Reductive Cleavage of Open Chain O,O-Acetals Using Cobalt Chloride Hexahydrate with Zinc Dust in Tetrahydrofuran at Room Temperature[a]

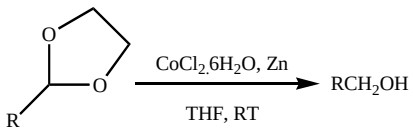


1a-7a **1b-7b**

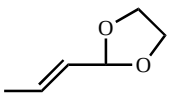
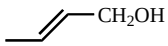
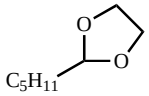
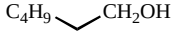
Entry	Substrates 1a-7a	Products[b] 1b-7b	Time (hours)	Yield[c] (%)	Reference
1			4	81	[26a]
2			6	83	[26b]
3			6	82	[26c]
4			4	90	[26d]
5			4	91	[26e]
6			4	92	[26f]
7			4	81	[26g]

[a]The reactions were run with the open chain O,O-acetals (8-10 mmol), cobalt chloride hexahydrate (2.37 g, 10 mmol), zinc dust (1.96 g, 30 mmol) at room temperature for 4-6 hours.
[b]The products were characterized from their respective IR, NMR and mass spectroscopic data and comparison with literature records.
[c]Isolated yields of products.

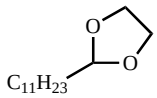
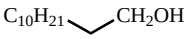
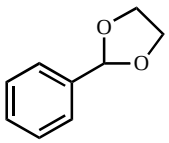
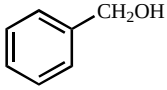
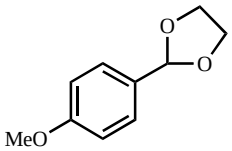
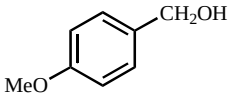
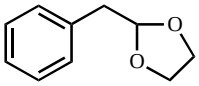
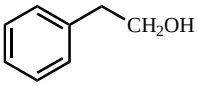
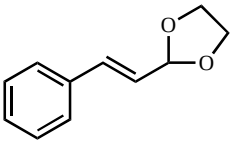
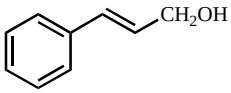
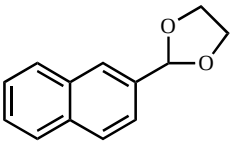
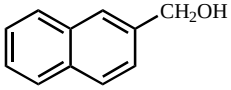
Table 2. *In-Situ* Formation of Alcohols by the Reductive Cleavage of Cyclic O,O-Acetals Using Cobalt Chloride Hexahydrate with Zinc Dust in Tetrahydrofuran at Room Temperature[a]



8a-15a **1b-8b**

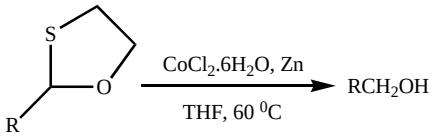
Entry	Substrates 8a-15a	Products[b] 1b-8b	Time (hours)	Yield[c] (%)	Reference
1			4	78	[26a]
2			5	83	[26b]

(Table 2). Contd…..

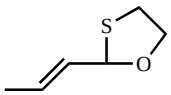
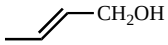
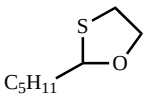
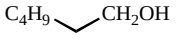
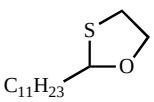
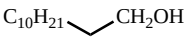
Entry	Substrates 8a-15a	Products[b] 1b-8b	Time (hours)	Yield[c] (%)	Reference
3			4	84	[26c]
4			4	93	[26d]
5			4	92	[26e]
6			4	88	[26f]
7			4	81	[26g]
8			6	80	[26h]

[a]The reactions were run with the cyclic O,O-acetals (8-10 mmol), cobalt chloride hexahydrate (2.37 g, 10 mmol), zinc dust (1.96 g, 30 mmol) at room temperature for 4-6 hours.
[b]The products were characterized from their respective IR, NMR and mass spectroscopic data and comparison with literature records.
[c]Isolated yields of products.

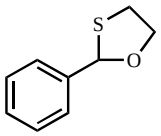
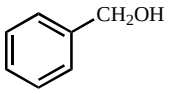
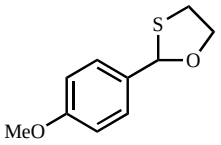
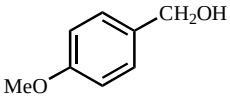
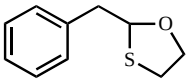
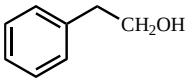
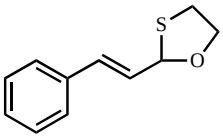
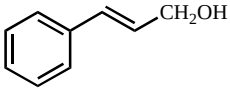
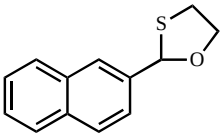
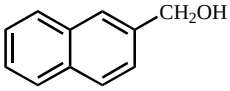
Table 3. *In-Situ* Formation of Alcohols by the Reductive Cleavage of Cyclic O,S-Acetals Using Cobalt Chloride Hexahydrate with Zinc Dust in Tetrahydrofuran at 60 °C[a]



16a-23a **1b-8b**

Entry	Substrates 16a-23a	Products[b] 1b-8b	Time (hours)	Yield[c] (%)	Reference
1			5	77	[26a]
2			5	83	[26b]
3			5	84	[26c]

(Table 3). Contd…..

Entry	Substrates 16a-23a	Products[b] 1b-8b	Time (hours)	Yield[c] (%)	Reference
4			4	91	[26d]
5			4	90	[26e]
6			4	88	[26f]
7			3	81	[26g]
8			6	81	[26h]

[a]The reactions were run with the cyclic O,S-acetals (8-10 mmol), cobalt chloride hexahydrate (2.37 g, 10 mmol), zinc dust (1.96 g, 30 mmol) at 60 °C for 3-6 hours.
[b]The products were characterized from their respective IR, NMR and mass spectroscopic data and by comparison with literature data.
[c]Isolated yields of products.

of hydroxy ethers. As observed earlier, the C=C double bond (**1a**, Table **1**) and the ether linkage (**5a**, Table **1**) were found to be resistant towards the system at room temperature. The hydrogen source for this reduction is believed to be from the water of crystallization [24] of $CoCl_2.6H_2O$.

To support this path, cobalt chloride hexahydrate was made anhydrous following standard procedure [25]. Anhydrous $CoCl_2$ with metallic zinc in dry THF, however, did not give any primary alcohol even after 30 hours from the corresponding aldehyde. This has clearly indicated the involvement of water of crystallization of cobalt chloride hexahydrate as the hydrogen source. The reaction proceeds initially *via* intermediacy of aldehyde (isolated in trace amount) from the acetal. The aldehyde formed was subsequently reduced to the corresponding primary alcohol by single electron transfer [22] from Co(0) generated *in situ* from Co(II) by Zn(0).

In conclusion, we have established a very mild, safe and efficient method for one pot reductive cleavage of open chain O,O-acetals as well as cyclic O,O and O,S-acetals directly to primary alcohols with very good yields. The method is believed to be an alternative of expensive and explosives hydride reagents.

TYPICAL EXPERIMENTAL PROCEDURE

In a 50 mL round bottomed flask, $CoCl_2.6H_2O$ (2.37 g, 10 mmol) and zinc powder (1.96 g, 30 mmol) were mixed together with subsequent addition of phenyl acetaldehyde-1,1-dimethyl acetal '**6a**' (1.66 g, 10 mmol) in dry tetrahydrofuran solvent (10 mL). The mixture was then stirred at room temperature for 4 hours. The progress of the reaction was monitored from time to time on TLC. At the end, the reaction mixture was filtered and washed the residue with THF (3 x10 mL). The filtrate containing the organic layer was concentrated in rotavapor and 20 mL of ethyl acetate was added to it. The organic layer was then sufficiently washed with $NaHCO_3$ solution (5%, 10 mL X 3) and the two layers were separated. The extract was dried over anhydrous Na_2SO_4 and then solvent was removed under reduced pressure. The pure alcohol 2-phenyl ethanol '**6b**' (1.1 g, 90% yield) was purified from the crude reaction mixture as colourless liquid by column chromatography using 5% ethyl acetate: hexane, ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.99 (b, 1H, CH_2OH), 2.82 (t, 2H, J = 6.63 Hz, $PhCH_2CH_2$), 3.79 (t, 2H, J = 6.63 Hz, CH_2CH_2OH), 7.19-7.32 (m, 5H, Ar-H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 38.86 ($PhCH_2CH_2$), 63.35 (CH_2CH_2OH), 126.18, 128.29, 128.42, 128.78, 129.05, 138.27 (6 X *C*, Ph). ν_{max} (neat/cm^{-1}): 3340, 3079, 3010, 2936, 2916. Anal. calcd. for $C_8H_{10}O$: C, 78.69; H, 8.19. Found C, 78.62; H, 8.21. MS (EI) *m/z* = 122 [M^+]. Applying the same procedure, all other acetals **1a-23a** were converted to their respective primary alcohols **1b-8b** at 25-60 °C in 3-6 hours and then characterized from their respective NMR, IR, CHN, GC and mass spectroscopic data.

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