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Cobalt(II)-catalyzed chemoselective synthesis of acetals from aldehydes

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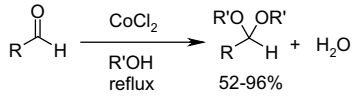
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Abstract—The acetalization of aldehydes has been studied with methanol, ethanol, and 2-propanol using $CoCl_2$ in high yields under reflux conditions. The reaction is simple, efficient, chemoselective and does not involve any other additive.
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Acetalization is one of the most widely used synthetic methods for protecting aldehydes and ketones in the course of the preparation of a variety of multifunctional complex organic molecules.[1] Generally, these reactions are carried out by treatment of carbonyl compounds with the alcohol and/or the corresponding orthoformate in the presence of an acid catalyst. Some methods for the formation of dimethyl acetals include dry HCl in MeOH,[2] $LaCl_3$/MeOH/$(MeO)_3CH$,[3] MeOH–$(COOH)_2$/DCC–$SnCl_4$,[4] $(MeO)_3CH$/*p*-TsOH,[5] Me_3SiOMe/Me_3SiOTf,[6] MeOH/$(MeO)_4Si$/dry HCl,[7] and MeOH/$PhSO_2NHOH$.[8] Fewer methods are known for the synthesis of diethyl acetals. These include $(EtO)_3CH$/HCl,[9] $(EtO)_3CH/FeCl_3$[10] in refluxing ethanol, $(EtO)_3CH$/Amberlyst,[11] DDQ[12] and $ZrCl_4$.[13] Some other methods that do not involve protic acid catalysis and operate under almost neutral conditions have also been reported.[14] Most of these existing methods, however, catalyze the acetalization of both aldehydes and ketones[1–12,14a–g] and little is known about a sufficiently selective as well as convenient acetalization method for aldehydes in the presence of the ketones.[13,14h]

Recently, we and others reported that $CoCl_2$ catalyzes efficiently the tosylation[15] and acylation[16] of alcohols in high yields. Since $CoCl_2$ is a mild Lewis acid, inexpensive, water tolerant and operates under nearly neutral conditions, its further exploration for other functional transformations will be quite useful. Herein we report the chemoselective acetalization in high yields of aldehydes without affecting ketones using 5 mol% of $CoCl_2$ (Scheme 1). This method is simple, efficient and does not involve either a halogenated solvent or an additive, which is important from the economical and environmental viewpoint. To the best of our knowledge no report is available in the literature using a metal salt as a catalyst for the selective acetalization of aldehydes with alcohols in presence of ketones without any other additive.

The acetalization of 2-nitrobenzaldehyde was first carried out with $CoCl_2$ in dry methanol. As expected the reaction took place and afforded the corresponding acetal in 91% yield when reaction was allowed to reflux for 4 h in the presence of 5 mol% $CoCl_2$ (Table 1).[17] This method was also effective with ethanol and 2-propanol affording the corresponding acetals in 84% and 52% yields, respectively. Similarly, the acetalization of 3- and 4-nitrobenzaldehydes was studied with methanol and ethanol and the corresponding acetals were obtained in 84–96% yields. It is noteworthy that the catalyst can be filtered and recycled without loss of activity after drying in an air-oven at 110 °C for 3 h.[18]



R=alkyl, aryl; R'=CH_3-, C_2H_5-, $(CH_3)_2CH$-

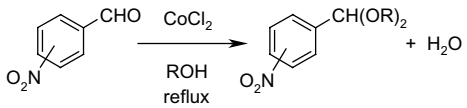
Scheme 1.

Keywords: Acetalization; Chemoselective; Aldehyde; Catalyst; Cobalt (II) chloride.

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Table 1. Acetalization of nitrobenzaldehydes with MeOH, EtOH, and ^{i}PrOH in the presence of $CoCl_2$



NO_2	R	Time (h)	Yield[a] (%)
Ortho	Me	4.0	91
	Et	7.0	84
	^{i}Pr	15.0	52
Meta	Me	3.5	95
	Et	4.0	84
Para	Me	2.0	96

[a] A mixture of aldehyde (1 mmol), $CoCl_2$ (5 mol %) and alcohol (4 mL) was refluxed for the appropriate time using a $CaCl_2$ guard tube.

To study the scope of this protocol, the acetalization of other aldehydes was performed with MeOH and EtOH (Table 2, entries 1–14).[17] Benzaldehyde was converted to the corresponding methyl and ethyl acetals in 78% and 73% yields, respectively. Likewise, 4-bromobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, 1-naphthaldehyde, geranial, cinnamaldehyde and heptanal were transformed to the respective acetals in 67–95% yields. The reactivities of the aromatic and allylic aldehydes were greater compared to heptanal.

The reactions were chemoselective. For example, when a mixture of benzaldehyde and acetophenone was subjected to acetalization with methanol using 5 mol % of $CoCl_2$, the aldehyde was chemoselectively converted to the corresponding acetal and no reaction was observed with acetophenone. A similar observation was noted with a cyclohexanone and heptanal mixture (Scheme 2). A separate experiment with cyclohexanone and methanol was also carried out and no reaction was observed even after 10 h refluxing. These studies clearly reveal that this method can be applied to the chemoselective acetalization of aldehydes in the presence of ketones.

Table 2. Chemoselective acetalization of aldehdyes with $CoCl_2$

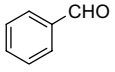
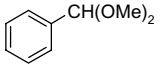
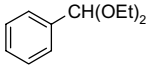
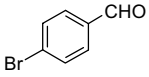
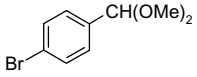
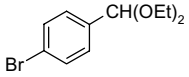
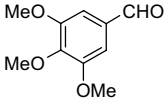
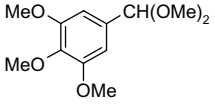
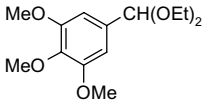
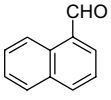
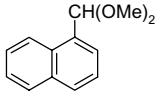
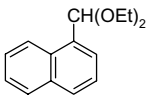
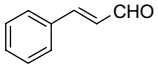
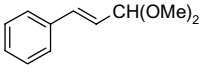
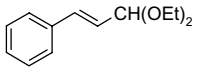
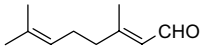
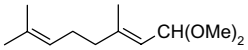
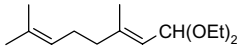
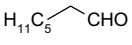
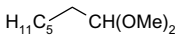
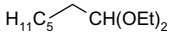
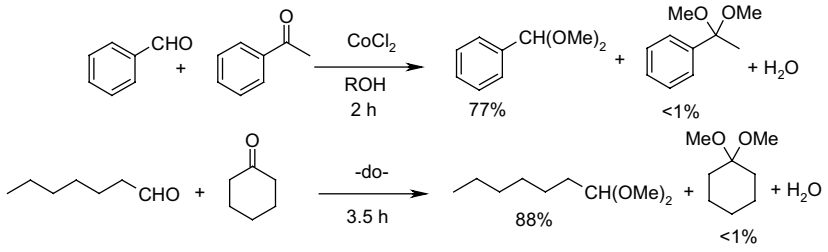
Entry	Aldehyde	Alcohol	Time (h)	Product	Yield[a,b] (%)
1		MeOH	2.0		78
2		EtOH	2.5		73
3		MeOH	1.0		95
4		EtOH	1.1		91
5		MeOH	4.0		78
6		EtOH	4.0		67
7		MeOH	0.4		73
8		EtOH	1.0		67
9		MeOH	0.3		79

Table 2 (*continued*)

Entry	Aldehyde	Alcohol	Time (h)	Product	Yield[a,b] (%)
10		EtOH	0.4		74
11		MeOH	0.3		75
12		EtOH	0.4		70
13		MeOH	3.5		90
14		EtOH	4.0		82

[a] A solution of $CoCl_2$ (5 mol%), aldehyde (1 mmol), and alcohol (4 mL) was refluxed for the appropriate time using a $CaCl_2$ guard tube.
[b] Isolated yield.



Scheme 2.

In conclusion, a simple, efficient, and eco-friendly protocol is described for the chemoselective acetalization of aldehydes with alcohols using the cheap and water tolerant $CoCl_2$ as a catalyst. It does not involve additives and the catalyst can be recycled without loss of activity. Removal of water is not warranted in these reactions.

Acknowledgements

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17. Typical acetalization procedure: A mixture of aldehyde (1 mmol), $CoCl_2$ (5 mol%, dried at 110 °C for 3 h prior to use) and dry alcohol (4 mL) was refluxed for the appropriate time (see Tables 1 and 2) using a calcium chloride guard tube. After the starting material was consumed (as indicated by TLC), the alcohol was evaporated under reduced pressure to afford a residue, which was treated with ethyl acetate (5 mL). The cobalt(II) salt was filtered and the filtrate was passed (after concentrating to 0.5 mL under reduced pressure) through a short pad of basic alumina using ethyl acetate and hexane (1:19) as eluent to provide analytically pure acetal, which was characterized by 400 MHz ^{1}H NMR and IR analysis.
18. The recovered cobalt(II) salt (>98%), after drying at 110 °C for 3 h, was investigated for the acetalization of 2-nitrobenzaldehyde with methanol and 90% of acetal was obtained.