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Cobalt(II)chloride catalyzed chemoselective thioacetalization of aldehydes

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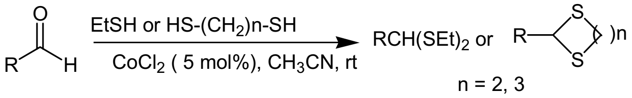
Abstract—A mild and chemoselective dithioacetalization procedure for the protection of various aldehydes in the presence of catalytic amount of cobalt(II)chloride is described.

The protection of carbonyl functionality as a dithioacetal[1] is a common practice in organic chemistry, as they are quite stable under basic or mildly acidic conditions.[2] The dithioacetals are also utilized as masked acyl anions[3] or masked methylene functions[4] in carbon–carbon bond forming reactions. Generally, they are prepared by condensation of carbonyl compounds with thiols or dithiols employing strong acid catalysts such as HCl,[5] PTSA,[6] $BF_3{\cdot}OEt_2$,[7] $AlCl_3$,[8] $TiCl_4$,[9] $Mg(OTf)_3$,[10] and $LaCl_3$.[11] A large number of these methods require long reaction times, reflux temperature, and stoichiometric amount of catalyst and provide low yields. Most recently, some methods employing LiBr,[12] $LiBF_4$,[13] $InCl_3$,[14] $Sc(OTf)_3$,[15] I_2[16] have been reported. Interestingly, only a few of these methods have demonstrated for chemoselective protection of aldehydes in the presence of ketones. Some methods are incompatible with other protecting groups such as TBS ethers[7b,12b,13b,16b] and fail to protect deactivated aromatic substrates.[15] Therefore, there is still a need to develop a simple and efficient method for chemoselective protection of aldehydes.

In my ongoing research program to develop new synthetic methodologies[17] for protection and deprotection of carbonyl compounds, I have found that cobalt(II)chloride, which acts as a mild Lewis acid, can be used for thioacetalization of carbonyl compounds. In this letter, I wish to report a simple and efficient method for chemoselective protection of various aldehydes as 1,3-dithianes, 1,3-ditholanes, and dithiols using a catalytic amount of cobalt(II)chloride (5 mol %) in good to excellent yields (Scheme 1). Treatment of 4-methoxybenzaldehyde with 1,3-propanedithiol in the presence of cobalt(II)chloride (5 mol %) in acetonitrile at room temperature afforded the desired 2-(4-methoxyphenyl)-1,3-dithiane. Similarly, several activated and deactivated aromatic aldehydes and aliphatic aldehydes underwent the protection reactions to give the corresponding carbonyl derivatives (Table 1). Acetonitrile is the solvent of choice as the best results were obtained. The experimental procedure is very simple,[18] more convenient, and also the method has ability to tolerate a variety of other protecting groups such as benzyl, allyl, and TBS ether.

It is noteworthy that ketones did not produce the corresponding thioacetals under the same reaction conditions. This result prompted me to explore the chemoselective protection of aldehydes in the presence of ketones. For example, when an equimolar mixture of 4-methoxybenzaldehyde and 4-methoxyacetophenone was allowed to react with 1,2-ethanedithiol in the presence of catalytic amount of cobalt(II)chloride only the 1,3-ditholane derivative of the 4-methoxybenzaldehyde was obtained (Scheme 2).

In conclusion, I have developed a simple and efficient method for chemoselective dithioacetalization of various aldehydes in the presence of a wide range of



Scheme 1.

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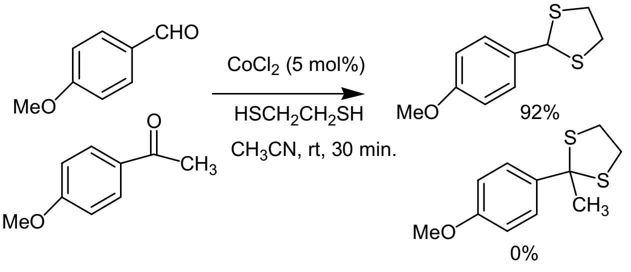
Table 1. Cobalt(II)chloride catalyzed protection of aldehydes as dithianes, dithiolanes, or diethyldithioacetals at room temperature

Entry	Substrate	Reagent	Time (h)	Yield [a](%)
1	Benzaldehyde	$HSCH_2CH_2CH_2SH$	1	91
2	4-Methoxybenzaldehyde	$HSCH_2CH_2CH_2SH$	0.5	92
3	4-Chlorobenzaldehyde	$HSCH_2CH_2CH_2SH$	0.5	88
4	4-Nitrobenzaldehyde	$HSCH_2CH_2CH_2SH$	4	78
5	Furfural	$HSCH_2CH_2CH_2SH$	1	85
6	4-Benzyloxybenzaldehyde	$HSCH_2CH_2CH_2SH$	1.5	89
7	Cinnamaldehyde	$HSCH_2CH_2CH_2SH$	0.5	87
8	2-Naphthaldehyde	$HSCH_2CH_2CH_2SH$	5	79
9	Thiophene 2-carboxaldehyde	$HSCH_2CH_2CH_2SH$	1	91
10	4-Hydroxybenzaldehyde	$HSCH_2CH_2CH_2SH$	2.5	80
11	2-Nitrobenzaldehyde	$HSCH_2CH_2CH_2SH$	5	76
12	4-Methylbenzaldehyde	$HSCH_2CH_2CH_2SH$	1	89
13	4-Allyloxybenzaldehyde	$HSCH_2CH_2CH_2SH$	0.5	91
14	Hexaldehyde	$HSCH_2CH_2CH_2SH$	5	79
15	4-TBSO-benzaldehyde	$HSCH_2CH_2CH_2SH$	1.5	83
16	1-Octanal	$HSCH_2CH_2CH_2SH$	1	75
17	Butyraldehyde	$HSCH_2CH_2CH_2SH$	2	71
18	Decylaldehyde	$HSCH_2CH_2CH_2SH$	2	77
19	Benzaldehyde	$HSCH_2CH_2SH$	2.5	89
20	4-Methoxybenzaldehyde	$HSCH_2CH_2SH$	2	93
21	4-Bromobenzaldehyde	$HSCH_2CH_2SH$	2	89
22	Hexaldehyde	$HSCH_2CH_2SH$	5	78
23	Benzaldehyde	$HSCH_2CH_3$	5	89
24	4-Methoxybenzaldehyde	$HSCH_2CH_3$	4	91
25	4-Chlorobenzaldehyde	$HSCH_2CH_3$	4	79
26	2-Naphthaldehyde	$HSCH_2CH_3$	12	74

[a] Yields refer to pure isolated products, characterized by IR, ^{1}H NMR, and MS.



Scheme 2.

other protecting groups using a catalytic amount of $CoCl_2$. Moreover, highly deactivated aromatic aldehydes can be converted to their corresponding dithioacetals without any difficulty.

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18. A Typical Procedure: To a stirred mixture of 4-methoxybenzaldehyde (681 mg, 5 mmol) and 1,3-propanedithiol (645 mg, 6 mmol) in acetonitrile (15 mL) was added $CoCl_2$ (30 mg, 5 mol%) at room temperature. The reaction mixture was stirred for 30 min. (TLC monitored) then concentrated in vacuo. The residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford pure 2-(4-methoxyphenyl)-1,3-dithiane (92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86–1.99 (m, 1H), 2.10–2.18 (m, 1H), 2.85–2.95 (m, 2H), 2.98–3.11 (m, 2H), 3.80 (s, 3H), 5.12 (s, 1H), 6.86 (d, $J = 8.5$ Hz, 2H), 7.40 (d, $J = 8.5$ Hz, 2H).