Ruthenium(III) Chloride-Catalyzed Thioacetalization of Carbonyl Compounds: Scope, Selectivity, and Limitations

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Abstract: A variety of carbonyl compounds can be easily and rapidly converted to the corresponding cyclic and acylic dithioacetals in the presence of a catalytic amount of ruthenium chloride in acetonitrile at room temperature. Some of the major advantages of this protocol are high chemoselectivity, operational simplicity, very short reaction times, high yields, and also compatibility with other protecting groups.

Keywords: aldehydes, chemoselectivity, dithioacetals, ketones, protecting groups; ruthenium chloride

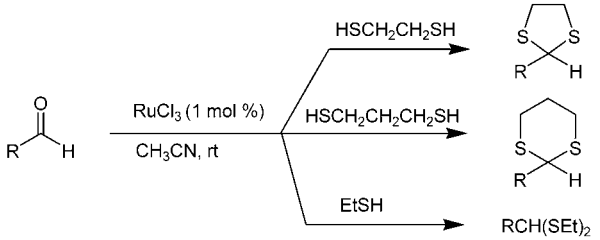
Introduction

In view of the tremendous versatility of thioacetals in organic synthesis as carbonyl protecting groups,[1] a large number of procedures has been reported for their preparation. The dithioacetals are also utilized as masked acyl anions[2] or masked methylene functions[3] in carbon-carbon bond forming reactions. In the literature there is quite a plethora of procedures reported for the protection of carbonyl compounds as dithioacetals employing HCl,[4] $BF_3 \cdot OEt_2$,[5] PTSA,[6] Bu_4NBr_3,[7] TMSOTf,[8] SO_2,[9] LiBr,[10] $LiBF_4$,[11] $AlCl_3$,[12] $TiCl_4$,[13] $ZrCl_4$,[14] 5 M $LiClO_4$,[15] $InCl_3$,[16] $Sc(OTf)_3$,[17] and I_2[18]as catalysts or as stoichiometric reagents. However, many of these methods have some drawbacks such as low yields of the products,[7] long reaction times,[14] harsh reaction conditions,[4,5,6] difficulties in work-up,[12,13] use of stoichiometric[5,9] and/or relatively expensive reagents,[7,8,14,15] and low yields when applied to ketones. Interestingly, only a few of these methods have demonstrated chemoselective protection of aldehydes in the presence of ketones. Some of the methods mentioned above are incompatible with other protecting groups such as TBS ethers[5b,10b,11b,18b] and fail to protect deactivated aromatic substrates.[17] Therefore, there is further scope to explore mild and efficient methods for thioacetalization of carbonyl compounds.

In this communication, I report a mild and efficient procedure for the conversion of carbonyl compounds into 1,3-dithiolanes, 1,3-dithianes, and diethyl dithioacetals using a catalytic amount of ruthenium chloride in acetonitrile at room temperature.

Results and Discussion

The reaction of 4-methoxybenzaldehyde with 1,2-ethanedithiol in the presence of 1 mol % of $RuCl_3$ in acetonitrile at room temperature afforded the desired 2-(4-methoxyphenyl)-1,3-dithiolane in 94% yield. Similarly, several activated and deactivated aromatic aldehydes and aliphatic aldehydes underwent the protection reaction rapidly to give the corresponding 1,3-dithiolanes, 1,3-dithianes, and diethyl dithioacetals (Scheme 1). The results shown in Table 2 clearly indicate the scope and generality of the reaction with respect to different aromatic, aliphatic, heterocyclic, unsaturated aldehydes. In order to find a suitable solvent system for the thioacetalization of aldehydes, several solvents were examined under the same reaction conditions. The results are summarized in Table 1. Acetonitrile was found to be the best solvent as it gave the best results (entry 1). Dichloromethane, tetrahydrofuran, 1,4-dioxane, toluene, benzene, ethyl acetate, and DMF can be used as alternative solvents, although longer reaction times were needed to complete the thioacetalization reaction.



Scheme 1.

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Table 1. Solvent effects in the thioacetalization of benzaldehyde with 1,2-ethanedithiol in the presence of a catalytic amount of $RuCl_3$.

Entry	Solvent	Reaction time	Yield [%][a, b]
1	Acetonitrile	10 min	92
2	Dichloromethane	1 h	81
3	Tetrahydrofuran	2 h	71
4	Benzene	2 h	61
5	1,4-Dioxane	4 h	58
6	Ethyl acetate	6 h	61
7	Toluene	6 h	62
8	DMF	6 h	40

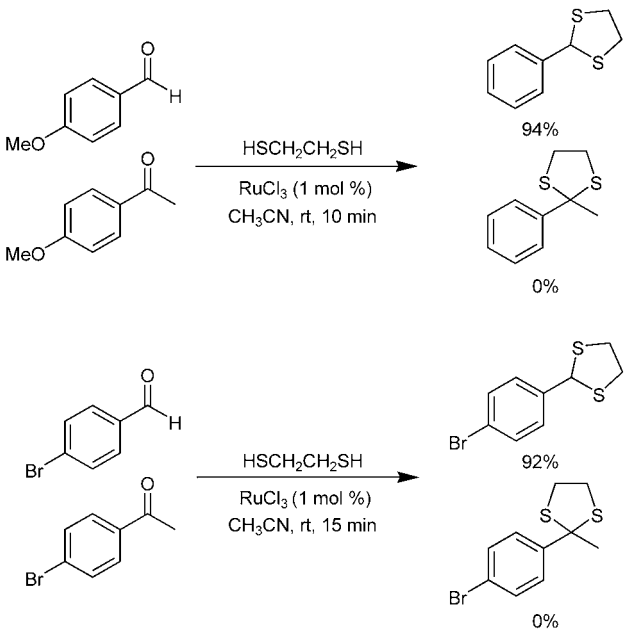
[a] NMR yield.
[b] 1 mmol benzaldehyde, 1.2 mmol 1,2-ethanedithiol, and 1 mol % $RuCl_3$ were used.

It is noteworthy that the conversion can be achieved in the presence of other protecting groups such as acetyl, benzyl, allyl, esters, and TBS ethers. The experimental procedure is very simple and convenient. Ketones also furnished excellent yields of the corresponding 1,3-dithiolanes in the presence of 20 mol % ruthenium chloride and 1,2-ethanedithiols, although after relatively longer reaction times (Table 2, entries 20–22). In contrast, many of the previously reported Lewis acid-catalyzed methods did not work well with ketones and only a few methods are available for the preparation of thioacetal derivatives which utilized stoichiometric amount of catalysts.[5,9] Cyclohexenone and alkynyl ketones reacted with 1,2-ethanedithol in the presence of $RuCl_3$ to give the corresponding 1,3-dithiolanes in moderate yields (entries 29 and 32,Table 2). The *p*-aminobenzaldehyde or *N,N*-dimethylaminobenzaldehyde due to strong deactivation of the carbonyl group did not give any satisfactory yields under these conditions, mostly starting materials were recovered. Alternatively, the amino group can coordinate to the ruthenium catalyst to deactivate the catalytic activity. In order to test this hypothesis, the thioacetalization reaction of an aldehyde

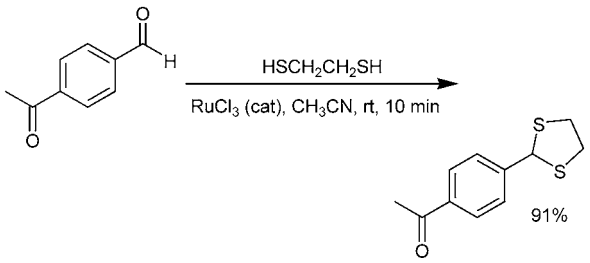
Table 2. Ruthenium(III) chloride-catalyzed protection of aldehydes as dithiolanes, dithianes or diethyl dithioacetals at room temperature.

Entry	Substrate	Reagent	Time	Yield [%][a]
1	Benzaldehyde	$HSCH_2CH_2SH$	10 min	92
2	4-Methoxybenzaldehyde	$HSCH_2CH_2SH$	10 min	94
3	4-Chlorobenzaldehyde	$HSCH_2CH_2SH$	10 min	88
4	4-Nitrobenzaldehyde	$HSCH_2CH_2SH$	28 min	79
5	Furfural	$HSCH_2CH_2SH$	10 min	85
6	4-Benzyloxybenzaldehyde	$HSCH_2CH_2SH$	12 min	89
7	Cinnamaldehyde	$HSCH_2CH_2SH$	10 min	82
8	3,4-Dimethoxybenzaldehyde	$HSCH_2CH_2SH$	35 min	76
9	Thiophene-2-carboxaldehyde	$HSCH_2CH_2SH$	15 min	90
10	4-Hydroxybenzaldehyde	$HSCH_2CH_2SH$	25 min	81
11	2-Nitrobenzaldehyde	$HSCH_2CH_2SH$	45 min	72
12	4-Carbomethoxybenzaldehyde	$HSCH_2CH_2SH$	20 min	85
13	4-Allyloxybenzaldehyde	$HSCH_2CH_2SH$	15 min	91
14	Hexaldehyde	$HSCH_2CH_2SH$	35 min	79
15	4-TBSO-benzaldehyde	$HSCH_2CH_2SH$	10 min	93
16	1-Octanal	$HSCH_2CH_2SH$	25 min	79
17	Butyraldehyde	$HSCH_2CH_2SH$	20 min	84
18	Decylaldehyde	$HSCH_2CH_2SH$	25 min	76
19	4-Acetyloxybenzaldehyde	$HSCH_2CH_2SH$	20 min	91
20	Acetophenone	HSCH2CH_2SH	25 h	75[b]
21	4-Methoxyacetophenone	HSCH2CH_2SH	16	78[b]
22	4-Chloroacetophenone	$HSCH_2CH_2SH$	22 h	70[b]
23	4-Benzoyloxybenzaldehyde	$HSCH_2CH_2SH$	30 min	90
24	4-Bromobenzaldehyde	$HSCH_2CH_2SH$	15 min	92
25	Benzaldehyde	$HSCH_2CH_2CH_2SH$	15 min	88
26	4-Methoxybenzaldehyde	$HSCH_2CH_2CH_2SH$	12 min	92
27	4-Chlorobenzaldehyde	$HSCH_2CH_3$	45 min	79
28	Benzaldehyde	$HSCH_2CH_3$	50 min	82
29	2-Cyclohexenone	HSCH2CH2SH	22 h	68[b]
30	4-*N,N*-Dimethylaminobenzaldehyde	$HSCH_2CH_2SH$	24 h	10[b]
31	4-Aminobenzaldehyde	$HSCH_2CH_2SH$	24 h	12[b]
32	4-Phenyl-3-butyn-2-one	$HSCH_2CH_2SH$	24 h	61[b]

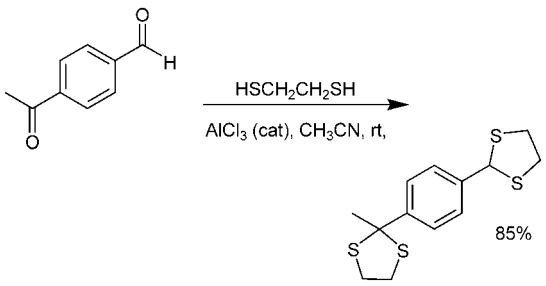
[a] Yields refer to pure isolated products.
[b] 20 mol % catalyst used.



Scheme 2.



Scheme 3.



Scheme 4.

was performed in the presence of dimethylaniline, which resulted in a dramatic effect with the thioacetalization reaction being almost completely suppressed. This result indicates the effect of coordination of the amino group to the ruthenium catalyst.

This method is highly chemoselective, providing selective protection of an aldehyde in the presence of a ketone. Therefore, a set of competitive protection reactions was conducted between aldehydes and ketones, the results of which are shown in Scheme 2. The aldehyde functionality of a keto-aldehyde was protected chemoselectively under identical condition (Scheme 3).

However, other Lewis acids such as $AlCl_3$ and $BF_3 \cdot OEt_2$ do not show any selectivity between an aldehyde and a ketone. The reaction of a keto-aldehyde with ethanedithiol in the presence of $AlCl_3$ yielded the bis-dithioacetal (Scheme 4). These results indicate that the present protocol is highly applicable for the chemoselective protection of aldehydes to the corresponding dithioacetals in the presence of ketone functions in multi-functional compounds.

Most recently, I have reported $Y(OTf)_3$,[19] $CoCl_2$,[20] and $Pr(OTf)_3$[21] as catalysts for the thioacetalization of aldehydes. In comparison with other catalysts such as $CoCl_2$, $Y(OTf)_3$, $Pr(OTf)_3$, $In(OTf)_3$, $Sc(OTf)_3$, $InCl_3$, $Bi(NO_3)_3$, which are recently reported in the thioacetalization of benzaldehyde, $RuCl_3$ employed here shows a more effective catalytic activity than the others in terms of the amount of catalyst, yields, and reaction times (Table 3). The efficacy of other Lewis acids such as $Nd(OTf)_3$, $Lu(OTf)_3$, and $Yb(OTf)_3$ was studied for this reaction. Among these catalysts, $RuCl_3$ was found to be superior in terms of conversion and reaction times (Table 3).

Table 3. Comparison of the effect of catalysts in thioacetalization of benzaldehyde with 1,2-ethanedithiol.

Catalyst	Catalyst load [mol%]	Time	Yield [%]
$Sc(OTf)_3$	4	10 min	85[17]
$Pr(OTf)_3$	5	30 min	89[21]
$Y(OTf)_3$	5	90 min	93[19]
$Nd(OTf)_3$	10	2 h	82
$Lu(OTf)_3$	20	3 h	75
$In(OTf)_3$	15	8 min	89[22]
$CoCl_2$	5	1 h	91[20]
$Bi(NO_3)_3$	10	5 h	78[23]
$RuCl_3$	1	10 min	92

Conclusion

In conclusion, I have demonstrated a very simple and convenient protocol for the protection of carbonyl compounds in the presence of a wide range of other protecting groups by using a catalytic amount of $RuCl_3$. Moreover, highly deactivated aromatic aldehydes can be converted to the corresponding dithioacetals without any difficulty. A high degree of chemoselectivity, considerably lower catalyst loading, very short reaction times, good to high yields, and operational simplicity make the present method a practical protocol for dithioacetalization processes.

Experimental Section

NMR spectra were recorded on Bruker 500 MHz or 300 MHz instruments for ^{1}H and 125 MHz or 75 MHz for ^{13}C in $CDCl_3$ solutions. Mass spectra were recorded on an Esquire LC 00066 mass spectrometer or a Finnigan 4000 mass spectrometer. All reagents and solvents were purchased as the highest grade available and used without further purification. Commercially available anhydrous $RuCl_3$ was used in all reactions.

General Procedure for Thioacetalization of Carbonyl Compounds

To a stirred solution of an aldehyde (5 mmol) and 1,2-ethanedithiol (6 mmol) in acetonitrile (10 mL) was added $RuCl_3$ (1 mol %) at room temperature. The reaction mixture was stirred at room temperature for an appropriate time (Table 1). After completion of reaction as indicated by TLC, the mixture was concentrated under vacuum and the crude residue was purified by silica gel column chromatography (eluted with hexane-ethyl acetate, 9/1) to afford the dithiolane in good yields.

Most of the products are known and were determined using comparison of their physical and spectral data with those reported in the literature.

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