

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

Surya Kanta De

Department of Medicinal Chemistry and Molecular Pharmacology, School of Pharmacy, Purdue Cancer Center, Purdue University, West Lafayette, IN 47907, USA

Fax: (+1)-765-494-1414, e-mail: skd125@pharmacy.purdue.edu

Received: October 22, 2004; Accepted: January 24, 2005

Abstract: A variety of carbonyl compounds can be easily and rapidly converted to the corresponding cyclic and acyclic 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

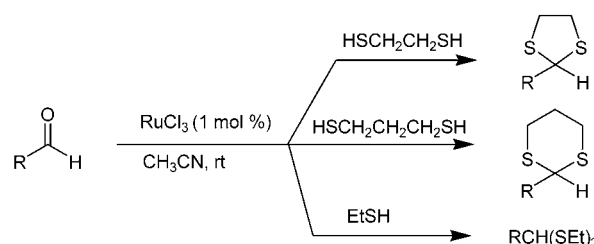
Introduction

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] BF₃·OEt₂,^[5] PTSA,^[6] Bu₄NBr₃,^[7] TMSOTf,^[8] SO₂,^[9] LiBr,^[10] LiBF₄,^[11] AlCl₃,^[12] TiCl₄,^[13] ZrCl₄,^[14] 5 M LiClO₄,^[15] InCl₃,^[16] Sc(OTf)₃,^[17] and I₂^[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 RuCl₃ 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.

Table 1. Solvent effects in the thioacetalization of benzaldehyde with 1,2-ethanedithiol in the presence of a catalytic amount of RuCl₃.

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 % RuCl₃ were used.

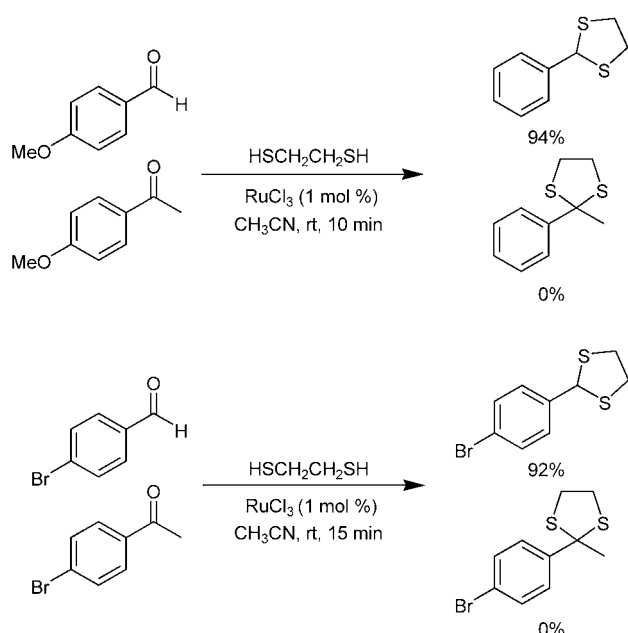
It is noteworthy that the conversion can be achieved in the presence of other protecting groups such as acetyl, benzyl, allyl, esters, and TBS ethers. The experimental

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-ethanedithiol in the presence of RuCl₃ 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

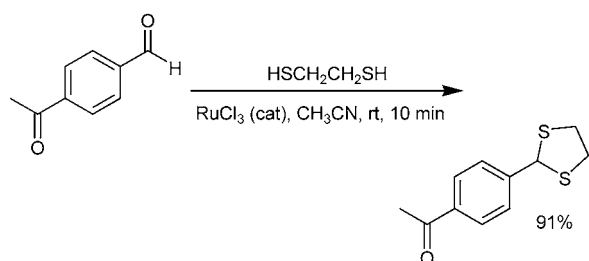
Table 2. Ruthenium(III) chloride-catalyzed protection of aldehydes as dithiolanes, dithianes or diethyl dithioacetals at room temperature.

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

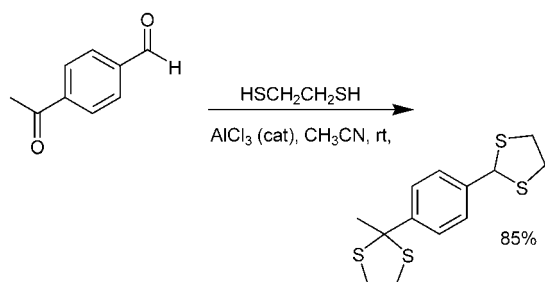
^[a] Yields refer to pure isolated products.^[b] 20 mol % catalyst used.



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 reac-

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

tions 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 AlCl₃ and BF₃·OEt₂ do not show any selectivity between an aldehyde and a ketone. The reaction of a keto-aldehyde with ethanedithiol in the presence of AlCl₃ 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] CoCl₂,^[20] and Pr(OTf)₃^[21] as catalysts for the thioacetalization of aldehydes. In comparison with other catalysts such as CoCl₂, Y(OTf)₃, Pr(OTf)₃, In(OTf)₃, Sc(OTf)₃, InCl₃, Bi(NO₃)₃, which are recently reported in the thioacetalization of benzaldehyde, RuCl₃ 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, RuCl₃ was found to be superior in terms of conversion and reaction times (Table 3).

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 RuCl₃. 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 ^1H 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.

References

- [1] a) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edn., Wiley, New York, **1999**, p. 329; b) P. J. Kocienski, *Protecting Groups*, 3rd edn., Thieme, Stuttgart, **2004**.
- [2] a) D. Seebach, *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 639; b) B. T. Grobel, D. Seebach, *Synthesis* **1977**, 357; c) P. C. Bulman Page, M. B. Van Niel, J. C. Prodger, *Tetrahedron* **1989**, 45, 7643.
- [3] G. R. Pettit, E. E. Van Tamelen, *Org. React.* **1962**, 12, 356.
- [4] J. W. Ralls, R. M. Dobson, B. Reigel, *J. Am. Chem. Soc.* **1949**, 71, 3320.
- [5] a) L. F. Fieser, *J. Am. Chem. Soc.* **1954**, 76, 1954; b) T. Nakata, S. Nagao, S. Mori, T. Oishi, T. *Tetrahedron Lett.* **1985**, 26, 6461.
- [6] C. Djerassi, M. Gorman, *J. Am. Chem. Soc.* **1953**, 75, 3704.
- [7] E. Mondal, P. R. Sahu, G. Bose, A. T. Khan, *Tetrahedron Lett.* **2002**, 43, 2843.
- [8] T. Ravindranathan, S. P. Chavan, S. W. Dante, *Tetrahedron Lett.* **1995**, 36, 2285.
- [9] B. Burezyk, Z. Kortylewicz, *Synthesis* **1982**, 832.
- [10] a) H. Firouzabadi, N. Iranpoor, B. Karimi, *Synthesis* **1999**, 58; b) M. Tandon, T. P. Begley, *Synth. Commun.* **1997**, 27, 2953.
- [11] a) J. S. Yadav, B. V. S. Reddy, S. K. Pandey, *Synlett* **2001**, 238; b) B. W. Metcalf, J. P. Burkhart, K. Jund, *Tetrahedron Lett.* **1980**, 21, 35.
- [12] B. S. Ong, *Tetrahedron Lett.* **1980**, 21, 4225.
- [13] V. Kumar, S. Dev, *Tetrahedron Lett.* **1983**, 24, 1289.
- [14] B. Karimi, H. Seradj, *Synlett* **2000**, 805.
- [15] V. G. Saraswathy, V. Geetha, S. S. Sankaraman, *J. Org. Chem.* **1994**, 59, 4665.
- [16] S. Madhuswamy, S. Arulananda Babu, C. Gunanatham, *Tetrahedron Lett.* **2001**, 42, 359.
- [17] A. Kamal, G. Chouhan, *Tetrahedron Lett.* **2002**, 43, 1347.
- [18] a) S. Samajdar, M. K. Basu, F. F. Becker, B. K. Banik, *Tetrahedron Lett.* **2001**, 42, 4425; b) A. R. Vaino, W. A. Szarek, *Chem. Commun.* **1996**, 2351.
- [19] S. K. De, *Tetrahedron Lett.* **2004**, 45, 2339.
- [20] S. K. De, *Tetrahedron Lett.* **2004**, 45, 1035.
- [21] S. K. De, Presented at the 227th National Meeting of the American Chemical Society, Anaheim, CA, March 2004, paper ORGN 160.
- [22] S. Muthusamy, S. A. Babu, C. Gunanatham, *Tetrahedron* **2002**, 58, 7897.
- [23] N. Srivastava, S. K. Dasgupta, B. K. Banik, *Tetrahedron Lett.* **2003**, 44, 1191.