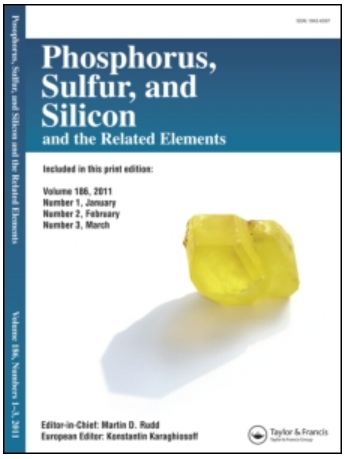

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MOLYBDENUM PENTACHLORIDE (MoC15) CATALYZES EFFICIENT DITHIOACETALIZATION OF CARBONYL COMPOUNDS AND TRANSDITHIOACETALIZATION OF O, O-ACETALS. THIS CATALYST ALSO CONDUCTS EFFICIENT NON-HYDROLYTIC DEPROTECTION OF DITHIOACETALS IN THE PRESENCE OF DRY DMSO. PART 2[1]

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MOLYBDENUM PENTACHLORIDE ($MoCl_5$) CATALYZES EFFICIENT DITHIOACETALIZATION OF CARBONYL COMPOUNDS AND TRANSDITHIOACETALIZATION OF O, O-ACETALS. THIS CATALYST ALSO CONDUCTS EFFICIENT NON-HYDROLYTIC DEPROTECTION OF DITHIOACETALS IN THE PRESENCE OF DRY DMSO. PART 2[1]

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Dithioacetalization of carbonyl compounds was performed efficiently in CH_2Cl_2 at room temperature in the presence of $MoCl_5$. Highly selective transdithioacetalization of acetals was also catalyzed efficiently by this catalyst. $MoCl_5$ performed non-hydrolytic deprotection of dithioacetals in the presence of dry DMSO.

Keywords: Molybdenum pentachloride; carbonyl compounds; dimethyl sulfoxide; deprotection; acetals; dithioacetalization; transdithioacetalization; dethioacetalization

INTRODUCTION

Protection of carbonyl groups as their thioacetals is an important transformation in the total synthesis of complex organic molecules.[2,3] Transformation of acetals to their thioacetals that often serve as precursors of acyl anion equivalent displaying a reactivity umpolung, and masked methylene functions and also high acid stability of S,S-acetals in comparison with O,O-acetals is a very important and useful functional group

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transformation[4,5] Regeneration of the carbonyl functionality from their thioacetals is a useful functional group transformation and a vast number of methods has been documented in the past two decades.[6]

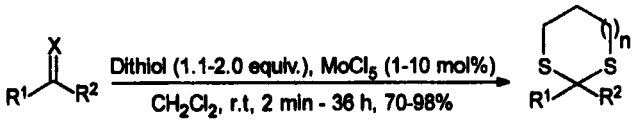
Recently, we have paid attention to explore some new applications of WCl_6 in organic synthesis[7] Along this line, we have found that this compound catalyzes deprotection of acetals, dithioacetalization of carbonyl compounds, transdithioacetalization of acetals, and promotes ring expansion-chlorination reactions of 1,3-dithiolanes and 1,3-dithianes. It also catalyzes acetalization of carbonyl compounds, and also conducts deoxygenative reaction of sulfoxides and reductive coupling of sulfonyl chlorides.[8–14]

Chromium, molybdenum and tungsten belong to group VIA of elements in the periodic table. Studies show that physical and chemical properties of these elements are quite versatile and different.[15]

Molybdenum pentachloride ($MoCl_5$) is a well-established compound that is commercially available and its handling does not need special precaution. In this paper, we report efficient catalytic activity of $MoCl_5$ for the protection reactions of carbonyl groups as their dithioacetals and transdithioacetalization of acetals. This catalyst also conducts efficient deprotection of dithioacetals in the presence of dry DMSO.

RESULTS AND DISCUSSION

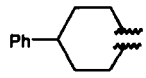
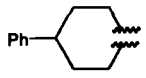
Preparation of 1,3-dithianes and 1,3- dithiolanes was successfully achieved from carbonyl compounds and also from open-chain and cyclic acetals in the presence of $MoCl_5$ (0.05–0.08 equiv.) and dithiols (1.1–2.0 equiv.) in good to excellent yields (**Scheme 1, Table I**).



R^1 = aryl, alkyl
R^2 = alkyl, H
Dithiol = 1,2-ethanedithiol, 1,3-propanedithiol
X = O, $(OMe)_2$, $(OEt)_2$, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$
n = 0, 1

SCHEME I

TABLE I Thioacetalization of Carbonyl Compounds and Transdithioacetalization of Acetals with $MoCl_5$

entry	R^1	R^2	*X*	*n*	*subst./ thiol* $MoCl_5$	*Time (min)*	*Yield*[a] [b] *(%)*
1	Ph	H	O	3	1:1.1:0.05	5	98
2	Ph	H	O	2	1:1.1:0.05	5	93
3	*p*-MeC_6H_4	H	O	3	1:1.1:0.05	7	96
4	*p*-ClC_6H_4	H	O	3	1:1 2:0.05	20	92
5	*p*-$MeOC_6H_4$	H	O	3	1:1.1:0.05	15	97
6	*p*-$NO_2C_6H_4$	H	O	3	1:1.5:0.08	5	92
7	PhCH=CH	H	O	3	1:1.1:0.05	5	98
8			O	2	1:1.5:0.05	20	90
9	Ph	Me	O	3	1:2:0.08	180	90
10	$PhCH_2CH_2$	Me	O	3	1:2:0.08	10	97
11	Ph	H	$(OMe)_2$	3	1:1.1:0.01	3	98
12	Ph	H	$(OEt)_2$	2	1:1.1:0.01	2	92
13	*p*-MeC_6H_4	H	$(OEt)_2$	3	1:1.1:0.01	5	97
14	*p*-ClC_6H_4	H	$(OEt)_2$	3	1:1.1:0.01	1	98
15	PhCH=CH	H	$(OEt)_2$	2	1:1.1:0.01	10	97
16			$(OEt)_2$	2	1:1.1:0.01	2	98
17	Ph	Me	$(OEt)_2$	3	1:1.2:0.01	5	95
18	*p*-ClC_6H_4	Me	$(OEt)_2$	3	1:1.2:0.01	5	98
19	$PhCH_2CH_2$	Me	$(OEt)_2$	3	1:1.1:0.01	2	96
20	*p*-ClC_6H_4	H	$-O(CH_2)_3O-$	3	1:1.1:0.05	36 h	70
21	Ph	Me	$-O(CH_2)_2O-$	3	1:2:0.1 1	36 h	80
22	*p*-MeC_6H_4	H	$-O(CH_2)_2O-$	3	1:1.1:0.05	36 h	75

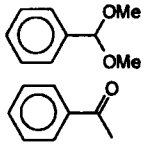
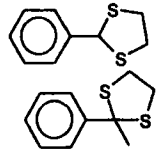
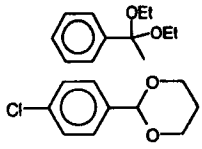
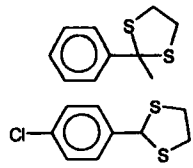
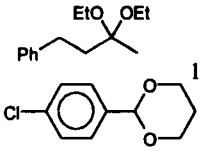
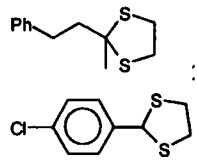
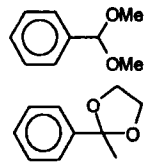
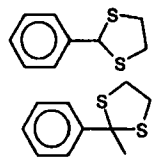
a. Isolated yields of pure products.
b. All reactions were performed at room temperature.

Dithioacetalization of ketones is a difficult task. However, this reaction in the presence of $MoCl_5$ proceeded smoothly and produced the desired S, S-acetals in excellent yields (**Table I**). We have found that WCl_6 was a failure catalyst for the dithioacetalization of ketones.[13]

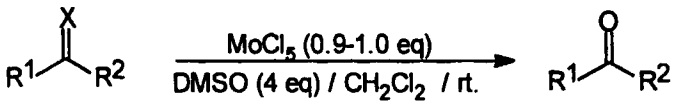
We have found that for the transformation of acetals to dithioacetals, $MoCl_5$ has the ability to differentiate between the open-chain acetals in comparison with their cyclic analogues. WCl_6 is a highly reactive catalyst and such selectivity has not been observed for the similar reactions conducted in its presence. Therefore, in light of this difference in reactivity, $MoCl_5$ is expected to find useful applications in organic synthesis. A series of competitive transdithioacetalization reactions were designed in order to show this chemoselectivity. The results are tabulated in **Table II**. To the best of our knowledge, this method represents the first example of the efficient and chemoselective dithioacetalization of open-chain acetals in the presence of their cyclic analogues.

Efficient regeneration of a masked carbonyl group under mild reaction conditions is a useful synthetic process[6]. Deprotection of S, S-acetals is not as easy as O, O-acetals deprotection and demands harsher reaction conditions. Usually hydrolytic reactions, in the presence of strong protic acids, are used for this process that is harmful to sensitive compounds. Lewis acids also used for this purpose, specially the highly toxic $Hg^{2+}$and other heavy metal cations have found general applicability for such functional group interconversion.[14,16] Therefore, it is of value to study and introduce new milder methods for such functional group transformation under non-aqueous conditions. In order to optimize the reaction condition, we first studied deprotection of 2-phenyl-1, 3-dithiolane, as a model compound, in the presence of $MoCl_5$ (0.9 equiv.) and dry DMSO (4 equiv.) in dry CH_2Cl_2 and the progress of the reaction was monitored by TLC. After 15 min the corresponding aldehyde was obtained in 85% yield. In order to show the general applicability of the method deprotection of various types of 1,3-dithiolanes and 1,3-dithianes of substituted benzaldehyde, cinnamaldehyde as well as benzophenone was also achieved in good yields without formation of polymeric materials (**Scheme 2, Table III, entries 2–7**). However, the yield of the aldehydes of acyclic thioacetals such as benzaldehyde diphenyl thioacetal was poor owing to the formation of diphenyl disulfide as a co-product (**Table I, entry 8**). DMSO addition in this method is obligatory and it transfers oxygen to the substrate to generate the carbonyl compound. We have suggested a mechanism in which the role of DMSO has been clarified (**Scheme 3**).

TABLE II Selective Transthioacetalization of Acetals in the Presence of $MoCl_5$

entry	*substrate*	*subst1/subst2/thiol /$MoCl_5$*	*product*	*time (min)*	*yield*[a] *(%)*
1		1:1:1.1:0.01		2	100 0
2		1:1:1.2:0.01			95 5
3		1:1:1.1:0.01		2	90 10
4		1:1:1.1:0.01		2	95 5

a. Yields based on GC and NMR.



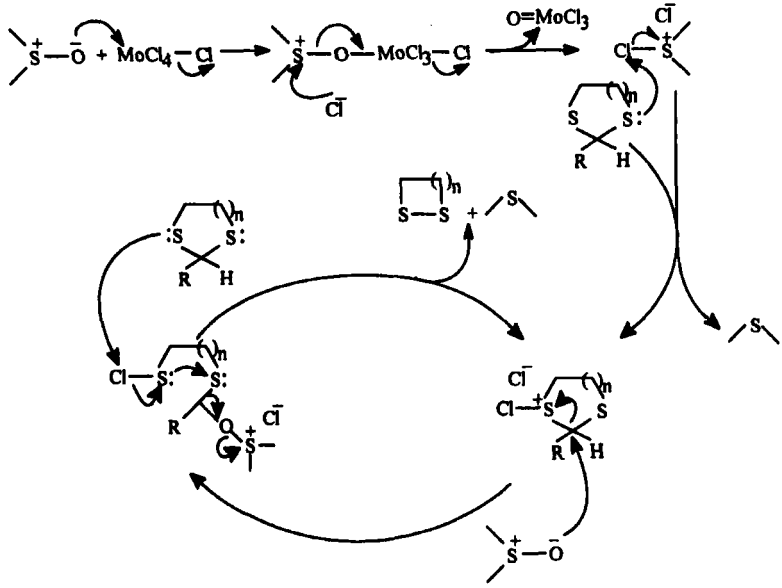
R^1 = Aryl
R^2 = H
X = $-S(CH_2)_3S-$, $-S(CH_2)_2S-$, PhS, $PhCH_2S$

SCHEME 2

TABLE III Deprotection of Thioacetals Derived from Aldehydes And Benzophenone with $MoCl_5$ in the Presence of Dry DMSO

Entry	R^1	R^2	*X*	*substr./$MoCl_5$/DMSO ratio*	*time (min)*	*yield[a] (%)*
1	Ph	H	$-S(CH_2)_2S-$	1:0.9:4	15	85
2	Ph	H	$-S(CH_2)_3S-$	1:0.9:4	3	91
3	p-ClC_6H_4	H	$-S(CH_2)_3S-$	1:0.9:4	4	95
4	p-MeC_6H_4	H	$-S(CH_2)_3S-$	1:0.8:3	5	92
5	p-$MeOC_6H_4$	H	$-S(CH_2)_3S-$	1:0.9:4	5	91
6	PhCH=CH	H	$-S(CH_2)_3S-$	1:0.9:4	30	80
7	PhCH=CH	H	$-S(CH_2)_2S-$	1:0.9:4	60	60
8	Ph	H	$(-SPh)_2$	1:1:3	20	30
9	Ph	Ph	$-S(CH_2)_3S-$	1:0.9:4	5	99

a. Yields refer to isolated products.



SCHEME 3

EXPERIMENTAL

General

Chemicals were either prepared in our laboratories or were purchased from Fluka and Merck Companies. Most of the products were purified by column chromatography or recrystallization from appropriate solvents and were identified by comparison of their mp, bp, IR, MS, NMR with those reported for the authentic samples. Progress of the reactions was followed by TLC using silica gel polygrams SIL G/UV 254 plates or by GC using a Shimadzu gas chromatograph GC-14A, equipped with a flame ionization detector and a 3 meters length glass column packed with DC-200 stationary phase and N_2 as the carrier gas.

Infrared spectra were recorded on a Perkin Elmer 781 spectrophotometer. NMR spectra were recorded by a Bruker Avance DPX 250 MHz instrument. Mass spectra were run on a Shimadzu GC MS-QP 1000 EX. Melting points were determined in open capillaries with a Galen-Kamp melting point apparatus.

General Procedure for Dithioacetalization of Carbonyl Compounds And Transdithioacetalization of Acetals Catalyzed with $MoCl_5$

To a solution of the carbonyl compound or *O,O*-acetal (5 mmol) and dithiol (5.5–10 mmol) in anhydrous CH_2Cl_2 (25 ml), $MoCl_5$ (0.25–0.5 mmol) was added at room temperature and the mixture was stirred for the appropriate time (5 min 24 h). The progress of the reaction was monitored by TLC or GC. After completion of the reaction the reaction was quenched with an aqueous solution of NaOH (10%, 25 ml), and the mixture was extracted with CH_2Cl_2 (2 × 25 ml). The organic layer was separated, washed with H_2O (2 × 15 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the almost pure dithioacetal. Further purification was performed by column chromatography on silica gel using petroleum ether as an eluent followed by bulb to bulb distillation or recrystallization to afford the desired product in good to excellent yield.

Dithioacetalization of Benzaldehyde to 2 – Phenyl –1,3-dithiolane Catalyzed with $MoCl_5$, a Typical Procedure

To a solution of benzaldehyde (0.531 g, 5 mmol) and 1,2-ethanedithiol (0.46 ml, 0.52 g, 5.5 mmol) in anhydrous CH_2Cl_2 (25 ml), $MoCl_5$ (68 mg,

0.25 mmol) was added at room temperature and the mixture was stirred for the appropriate time (5 min). The progress of the reaction was monitored by TLC or GC. After completion of the reaction the reaction was quenched with an aqueous solution of NaOH (10%, 25 ml), and the mixture was extracted with CH_2Cl_2 (2 × 25 ml). The organic layer was separated, and washed with H_2O (2 × 15 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the almost pure dithioacetal. Further purification was performed by column chromatography on silica gel using petroleum ether as eluent to afford pure 2-phenyl-1,3-dithiolane in excellent yield (0.85 g, 93%).

Transdithioacetalization of 2-phenyl-2-methyl-1,3-dioxolane to 2-phenyl-2-methyl-1,3-dithiolane Catalyzed with $MoCl_5$, a Typical Procedure

To a solution of 2-phenyl-2-methyl-1,3-dioxolane (0.82 g, 5 mmol) and 1,2-ethanedithiol (0.84 ml, 0.940 g, 10 mmol) in anhydrous CH_2Cl_2 (25–30 ml), $MoCl_5$ (0.137 g, 0.5 mmol) was added at room temperature and the mixture was stirred for the appropriate time (20 h). The progress of the reaction was monitored by TLC or GC. After completion of the reaction the reaction was quenched with an aqueous solution of NaOH (10%, 25 ml), and the mixture was extracted with CH_2Cl_2 (2 × 25 ml). The organic layer was separated, and washed with H_2O (2 × 15 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the almost pure dithioacetal. Further purification was performed by column chromatography on silica gel using petroleum ether as eluent to afford pure 2-phenyl-2-methyl-1,3-dithiolane in excellent yield (0.874 g, 89 %).

General Procedure for Deprotection of S,S-Acetals to Carbonyl Compounds with $MoCl_5$ in the Presence of Dry DMSO

To a solution of 1,3-dithiolane or 1,3-dithianes of substituted benzaldehyde or benzophenone (2 mmol), and dry DMSO (6–8 mmol), in dry CH_2Cl_2 (20 ml) was added $MoCl_5$ (1.6–1.8 mmol) and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC. After completion (3–60 min), the reaction was quenched with an aqueous solution of NaOH (10%, 25–30 ml), and

extracted with CH_2Cl_2 (3 × 25 ml). The organic extracts were washed successively with brine (15 ml), and water (2 × 10 ml). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to afford the almost pure product (s). Further purification was achieved by column chromatography on silica gel to give the desired product in good to excellent yields.

Deprotection of 2-Phenyl-1,3-dithiane to Benzaldehyde with $MoCl_5$ in the Presence of Dry DMSO, a Typical Procedure

To a solution of 2-phenyl-1,3-dithiane (393 mg, 2 mmol), and dry DMSO $MoCl_5$ (0.437 mg, 1.6 mmol) was added and the resulting solution was stirred at room temperature. The progress of the reaction was monitored by TLC (CCl_4 as eluent). After completion (5 min), the reaction was quenched with an aqueous solution of NaOH (10%, 25 ml), and extracted with CH_2Cl_2 (3 × 25 ml). The organic extracts were washed successively with brine (15 ml), and water (2 × 10 ml). The organic layer was separated and dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to afford the pure benzaldehyde (412 mg, 90% yield). The yield was also determined by the isolation of the 2,4-dinitrophenylhydrazine derivative.

Acknowledgements

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