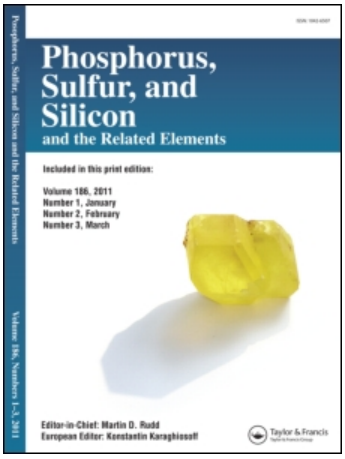

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A Mild and Chemoselective Dithioacetalization of Aldehydes in the Presence of Anhydrous Copper (II) Sulfate

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A Mild and Chemoselective Dithioacetalization of Aldehydes in the Presence of Anhydrous Copper (II) Sulfate

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Various aldehydes have been protected with different thiols as dithioacetals with excellent yields using anhydrous copper sulfate as a mild and chemoselective catalyst. The reaction is carried out in a solvent and/or under solvent-free conditions. The transthioacetalization of oxyacetals into dithioacetals was also achieved in an excellent yield.

Keywords Aldehydes; anhydrous copper (II) sulfate; dithioacetalization; protection; transthioacetalization

INTRODUCTION

The conversion of aldehydes and ketones to dithioacetals and dithioketals is a common practice in a multistep synthesis due to their stability under both acidic and basic conditions.[1] In addition, thioacetals are also used as masked acyl anions[2] and methylene functions[3] in carbon-carbon bond forming reactions. Commonly, these compounds are prepared by protic or lewis acid-catalyzed condensation of carbonyl compounds with thiols.[4] Lewis acid catalysts such as $ZnCl_2$,[5] $LnCl_3$,[6] $FeCl_3/SiO_2$,[7] $AlCl_3$,[8] $ZrCl_4/SiO_2$,[9] $TeCl_4$,[10] $SnCl_2$,[11] $SiCl_4$,[12] $TiCl_4$,[13] $BF_3 \cdot OEt_2$,[14] $LaCl_3$,[15] WCl_6,[16] $(CH_3)_3SiCl$,[17] 5 M $LiClO_4$,[18] $Mg(OTf)_3^{19}$, $CoCl_3$,[20] Molybdenyl acetylacetonate,[21] $In(OTf)_3$,[22] $NiCl_2$,[23] Yttrium triflate,[24] Bismuth nitrate,[25] etc. have been used for this purpose. Although many methods have been reported for the dithioacetalization of aldehydes and ketones, there still is a great demand for the introduction of mild, efficient, and chemoselective practical methods. Interestingly,

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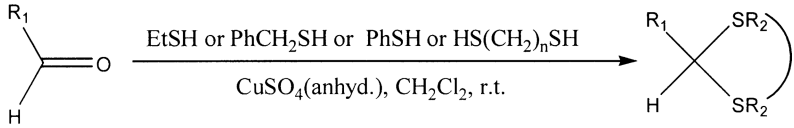
only a few methods are known in the literature for the chemoselective protection of aldehydes in the presence of ketons.[20,22–23] In general, the reported procedures are associated with certain limitations, such as low yields, harsh reaction conditions, longer reaction times, and costly reagents, as well as an inconvenience in handling reagents. Previously, copper (II) salts were used for the dithioketalization of ketones in boiling dry THF for several hours.[26] The method is not chemoselective, and drastic reaction conditions have been used (along reaction time, high temperature). Herein we report an efficient, clean, fast, and mild method for the chemoselective dithioacetalization of aldehydes in a solvent and/or under solvent-free conditions in the presence of anhydrous copper sulfate.

RESULTS AND DISCUSSION

In order to find the best reaction conditions, different variations were examined. At first, the reaction was carried out in different solvents. The reaction could be performed efficiently in $CHCl_3$, CH_2Cl_2, benzene, acetonitrile, and *n*-hexane. Due to the higher solubility of the substrates and higher rates of the reactions, CH_2Cl_2 was chosen as the suitable solvent. It should be pointed out that in the absence of anhydrous copper sulfate, the reaction did not proceeded in CH_2Cl_2 even after prolonged reaction times. In a typical procedure, benzaldehyde (2.5 mmol) with benzyl mercaptane (3 mmol) in the presence of anhydrous copper sulfate (3.5 mmol) at r.t. in CH_2Cl_2 afforded the desired dithioacetal in a 95% yield. Various thiols and dithiols (such as 1,2 and 1,3-dithiols) were used with different types of aldehydes (Scheme 1). Except for

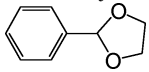
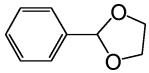
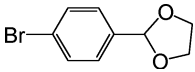
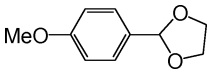


R_1 = aryl, alkyl, alkenyl
R2 = Et, $PhCH_2$, Ph, -$(CH2)_n$- n= 2,3

SCHEME 1

thiophenol, the other thiols and dithiols reacted efficiently with aldehydes in dichloromethane at r.t. in a short reaction time, and pure products were obtained in excellent yields by crystallization or PTLC. Results are summarized in Table I. All products were characterized by spectroscopic analysis and also by comparison of the data obtained with those

TABLE I Anhydrous Copper (II) Sulfate Catalyzed Protection of Aldehydes and Transthioacetalization of Oxyacetals at RT

Entry	Aldehyde	Thiol	Time (min)/ Yield (%)[a,b]	Time (min)/ Yield (%)[a,c]
1	Benzaldehyde	$PhCH_2SH$	5/95	5/95
2	4-Fluorobenzaldehyde	$PhCH_2SH$	5/97	5/96
3	4-Chlorobenzaldehyde	$PhCH_2SH$	5/97	5/96
4	4-Bromobenzaldehyde	$PhCH_2SH$	5/97	
5	4-Methoxybenzaldehyde	EtSH	5/94	
6	Benzaldehyde	EtSH	5/94	
7	4-Fluorobenzaldehyde	EtSH	5/95	
8	4-Chlorobenzaldehyde	EtSH	5/95	
9	Pentaldehyde	EtSH	5/94	
10	Benzaldehyde	$HSCH_2CH_2SH$	5/97	5/97
11	4-Methoxybenzaldehyde	$HSCH_2CH_2SH$	5/97	5/95
12	4-Chlorobenzaldehyde	$HSCH_2CH_2SH$	5/97	
13	4-Bromobenzaldehyde	$HSCH_2CH_2SH$	5/98	5/98
14	4-Nitrobenzaldehyde	$HSCH_2CH_2SH$	5/98	
15	4-Methylbenzaldehyde	$HSCH_2CH_2SH$	5/96	5/95
16	3,4-Dimethoxybenzaldehyde	$HSCH_2CH_2SH$	7/95	10/80
17	Furfural	$HSCH_2CH_2SH$	5/98	5/95
18	Cinnamaldehyde	$HSCH_2CH_2SH$	5/97	5/96
19	Hexaldehyde	$HSCH_2CH_2SH$	5/94	5/94
20	Hexaldehyde	$HSCH_2CH_2CH_2SH$	5/94	5/94
21	Benzaldehyde	$HSCH_2CH_2CH_2SH$	5/97	5/96
22	4-Methoxybenzaldehyde	$HSCH_2CH_2CH_2SH$	5/96	5/94
23	4-Chlorobenzaldehyde	$HSCH_2CH_2CH_2SH$	5/97	5/95
24	2-Nitrobenzaldehyde	$HSCH_2CH_2CH_2SH$	5/96	5/95
25	4-Nitrobenzaldehyde	$HSCH_2CH_2CH_2SH$	5/98	5/97
26	4-Methylbenzaldehyde	$HSCH_2CH_2CH_2SH$	5/97	
27	Benzaldehyde	PhSH	40/55	20/60
28	4-Methoxybenzaldehyde	PhSH	55/50	20/55
29		$HSCH_2CH_2CH_2SH$	50/94	30/90
30		$HSCH_2CH_2CH_2SH$	50/95	
31		$HSCH_2CH_2SH$	50/97	
32		$HSCH_2CH_2SH$	60/94	

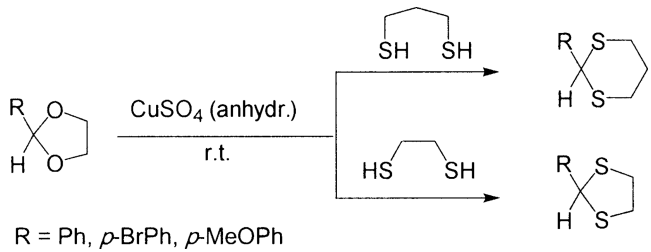
[a]All yields refer to isolated products, and all products were characterized by m.p., IR, and ^{1}H-NMR. Their physical data were similar to those reported in the literature.

[b]Dichloromethane as a solvent.

[c]Solvent-free conditions.

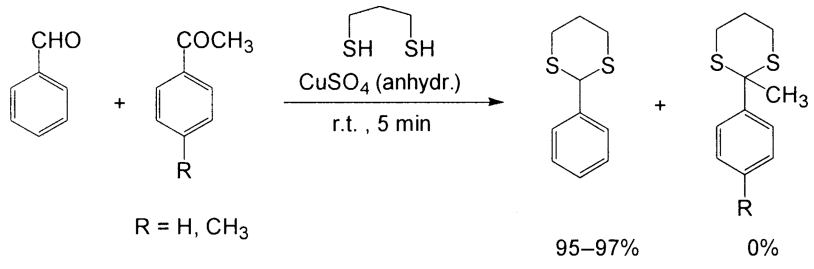
of authentic samples. We found that the reaction is almost independent of a substituent on aromatic aldehydes (entries 1, 2, 3, 5, 10, 11, 12, 21, 22, 23 in Table I). It also has been observed that the position of the substituent on the ortho or para positions of the aromatic ring does not alter the rate and yield of the reaction (entries 24 and 25 in Table I). Also the presence of two electron-donating substituents on the benzene ring of aldehyde has a slight decreasing effect on the relative rate of the reaction compared to benzaldehyde (entry 16, Table I). Aliphatic and α, β-unsaturated aldehydes were also dithioacetalized in excellent yields (entries 9, 18, 19, and 20 in Table I).

Transthioacetalization of oxyacetals in CH_2Cl_2 was also achieved efficiently in the presence of anhydrous copper sulfate to afford the corresponding dithioacetals in high yields (entries 29–32 in Table I). In this case, the time was longer (Scheme 2).



SCHEME 2

Interestingly, this procedure can also be extended for the chemoselective protection of an aldehyde in the presence of a ketone. For instance, when an equimolar mixture of benzaldehyde and acetophenone or *p*-methylacetophenone was allowed to react with 1,3-ethanedithiol in the presence of anhydrous copper sulfate, only the 1,3-dithiane derivative of the benzaldehyde was obtained in an excellent yield (Scheme 3).



SCHEME 3

We have also investigated the reaction under solvent-free conditions. The reaction proceeded at 40–50°C in very short reaction time (less than five minutes). The behavior of solvent-free conditions is similar to using dichloromethane as a solvent (Table I).

The anhydrous copper-sulfate support is prepared conveniently compared to other reported reagents. Also, this support is nonvolatile, nonflammable, eco-friendly, safe, clean, cheap, and recyclable.

In conclusion, aldehydes were protected chemoselectively as their thioacetals under mild reaction conditions in the presence of anhydrous copper sulfate. Transthioacetalization reactions of oxyacetals were also easily achieved by using this reagent. In addition, high chemoselectivity observed for functional group interconversions presents useful synthetic potentials of the method.

EXPERIMENTAL

Compounds gave satisfactorily all spectroscopic data. IR spectra were taken as thin films for liquid compounds and as KBr pellets for solids on a Nicolet spectrometer (Magna 550). A bruker (DRX-500 Avance) NMR was used to record the ^{1}HNMR spectra. All NMR spectra were determined in $CDCl_3$ at an ambient temperature. Melting points were determined on a Buchi B540 apparatus.

The Thioacetalization of Aldehydes and Transthioacetalization of Acetals in a Solvent

General Procedure

The dithiol (3 mmol) or thiol (5–6 mmol) was added to a stirring solution of aldehydes or acetals (2.5 mmol) in CH_2Cl_2 (15 mL). Then, anhydrous copper sulfate (3.5 mmol) was added, and the resulting mixture was stirred at r.t. for an appropriate time as required for completion of the reaction, which was monitored by TLC (petroleum ether:ethyl acetate, 4:1). After separation of the catalyst by filtration, the solvent was removed under reduced pressure. In all these cases, crude products were sufficiently pure (TLC and ^{1}H-NMR), and the further pure products were obtained by crystallization from petroleum ether (b.p. 100–140°C) or PTLC.

The Thioacetalization of Aldehydes in a Solvent-Free Condition

General Procedure

The dithiol (3 mmol) or thiol (5–6 mmol) and anhydrous copper sulfate (3.5 mmol) were added to a solution of aldehydes or acetals

(2.5 mmol) in diethyl ether (5 mL). After evaporation of the solvent under vacuum, the solid residue was heated at 40–50°C for an appropriate time as required for completion of the reaction, which was monitored by TLC. Then, CH_2Cl_2 (20 mL) was added, and a catalyst was separated. The remainder of the procedure is similar to that described in the previous section.

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