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Batool Akhlaghinia [a] & Ata Makarem [a]
[a] Department of Chemistry, Faculty of Sciences , Ferdowsi University of Mashhad , Iran
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Dithioacetalization of carbonyl compounds under catalyst-free condition

Batool Akhlaghinia and Ata Makarem*

Department of Chemistry, Faculty of Sciences, Ferdowsi University of Mashhad, Iran

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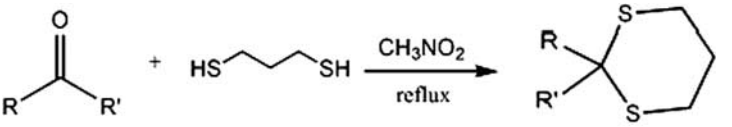
Protection of carbonyl compounds with 1,3-propanedithiol under a catalyst-free condition in nitromethane as a solvent has been described.



R : Ph , cinnamyl , alkyl ; R' : H ,Ph , alkyl

Keywords: aldehydes; ketones; carbonyl protection; 1,3-dithiane; 1,3-propanedithiol

1. Introduction

The protection of functional groups constitutes an important and essential process in the synthesis of polyfunctional molecules and complex natural products. Thioacetals play very important roles in organic syntheses since they are widely used as protecting groups for carbonyl compounds and applied as umpolung reagents in a diverse array of organic transformations (*1–4*). Thioacetals are relatively stable toward a wide variety of reagents and are also useful in organic synthesis as acyl carbanion equivalents in C−C bond-forming reactions (*5, 6*). Due to the resistance of thioacetals toward hydrolytic cleavage under ordinary acidic and basic conditions, the protection of carbonyl groups as their cyclic dithioacetals has long attracted considerable attention (*7*). To date, there are many approaches developed for the synthesis of thioacetals by the condensation of carbonyl compounds with thiols or dithiols using strong protic acids such as HCl (*8*) or Lewis acids such as $BF_3{\cdot}OEt_2$ (*9*) or $ZnCl_2$ (*10*) as catalysts. Other Lewis acids include $AlCl_3$ (*11*), WCl_6 (*5*), $InCl_3$ (*12*), P_2O_5/SiO_2 (*13*), and [bmim]HSO_4 (*14*).

*Corresponding author. Email: ata_makarem@yahoo.com

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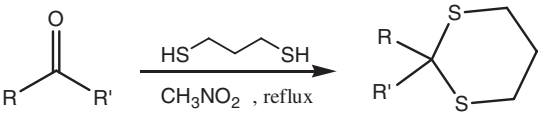
A number of milder procedures employing lithium salts (*15*), $NiCl_2$ (*16*), trichloroisocyanuric acid (*17*), NBS (*18*), I_2 (*19*) microwave (*20*), HBF_4-SiO_2 (*21*), $Y(OTf)_3$ (*22*), $VO(OTf)_2$ (*23*), $ScCl_3$ (*24*), and silica-functionalized sulfonic acid (*25*) have also been reported. Some of the methods mentioned above suffer from destroying the catalyst in the work-up procedure in which the Lewis acids may not be recovered and reused. Also, many of these procedures have some drawbacks including longer reaction times, low yields, involvement of expensive catalysts, difficult handling (*26*) and the requirement of the volatile organic solvent, dichloromethane. In an endeavor to change the current working practices to greener alternatives and to meet environmental demands for protecting carbonyl group, recently a catalyst-free dithioacetalization in glycerol (*27*) has been reported, but this method suffers from long reaction times. Herein, we report a novel and simple catalyst-free method for dithioacetalization of carbonyl compounds with 1,3-propanedithiol under mild conditions (Scheme 1).



R : Ph , cinnamyl , alkyl

R' : H ,Ph , alkyl

Scheme 1. Protection of carbonyl compounds with 1,3-propanedithiol.

The use of several solvents without the intervention of catalysts has been reported for various organic transformations. Watahiki *et al.* (*28*) reported the use of DMSO for cyanobenzoylation of aldehydes with benzyl cyanide. The combination of DMSO with hexane was employed for the cyanosilylation of aldehyde (*29*) as well as for the synthesis of silyl ethers from alcohols and *tert*-butyldimethylsilyl chloride (*30*). Similarly, Watahiki *et al.* (*31*) describe the synthesis of cyanohydrin carbonates in DMSO in the presence of molecular sieves. Kumamoto *et al.* (*32*) demonstrated the cyanation of acetal with trimethylsilyl cyanide in CH_3NO_2 at 60°C and high pressure. Recently Kadam and Kim (*33*) reported the synthesis of trimethylsilyl ethers from alcohols and HMDS in CH_3NO_2 without using a catalyst. In the course of our research program to develop better and newer synthetic methodologies (*34*) and considering the activity of HMDS in polar solvents, conversion of aldehydes and ketones into 1,3-dithianes under catalyst-free and almost neutral reaction conditions was investigated.

2. Results and discussion

The protection reaction of benzaldehyde in CH_3NO_2 was performed at room temperature with 0.5 ml of CH_3NO_2 to obtain 2-phenyl-1,3-dithiane in high yield (Entry 1, Table 1). Surprisingly, The reaction in refluxing CH_3NO_2, for different molar ratios of benzaldehyde/1,3-propanedithiol gives the desired product with excellent yields in short reaction times (Entries 2 and 3, Table 1). Refluxing enhanced the rate of the reaction and decreased the reaction time. For example, 0.5 ml of CH_3NO_2 and 2 mmol of 1,3-propanedithiol are sufficient for the completion of the protection reaction with 1 mmol of benzaldehyde at reflux in 10 min (Entry 3, Table 1).

The polar protic solvent CH_3OH at reflux produces a 10% yield of 2-phenyl-1,3-dithiane (Entry 5, Table 1). The polar aprotic solvents DMF and DMSO at 100°C give no product (Entries 8 and 9). Also, CH_3CN, THF, $CHCl_3$, 1,4-dioxane and *n*-hexane at reflux give no product (Entries 4, 6, 7, 10 and 11, Table 1).

Protection of aldehydes and ketones under catalyst-free conditions in nitromethane with 1,3-propandithiol exhibited high efficiency.

Various structurally diverse aldehydes and ketones **1**–**15** were converted to their corresponding dithioacetals in excellent yields within short reaction times with 100% conversion (Table 2). Aromatic aldehydes with electron-withdrawing groups require shorter reaction time compared with aromatic aldehydes with electron-donating groups. This result may indicate that the electron-donating ability of the substituent reduces the activity of carbonyl groups toward a nucleophile which decreases the reaction rate. It is very interesting to note that cinnamaldehyde **7** and croton-aldehyde **8** were protected within very short reaction times and gave high yields. Also because of lower reactivity of the carbonyl group connected to the α position of the naphthyl ring, protection of **10** required a longer reaction time (3.5 h). The protection reaction was also extended to aromatic ketones **14** and **15**. Acetophenone, in contrast to aliphatic ketones, could not be dithioacetalized completely. It gave the corresponding dithioacetal in a very low yield even after 72 h of reaction time. This may be due to the steric effect of the (Me) group in comparison to (H) in benzaldehyde. The aromatic sterically hindered ketone **15** fails to undergo protection with 1,3-propanedithiol even after 72 h of reaction time. This indicates that the steric effect is serious enough to prevent the reaction from taking place.

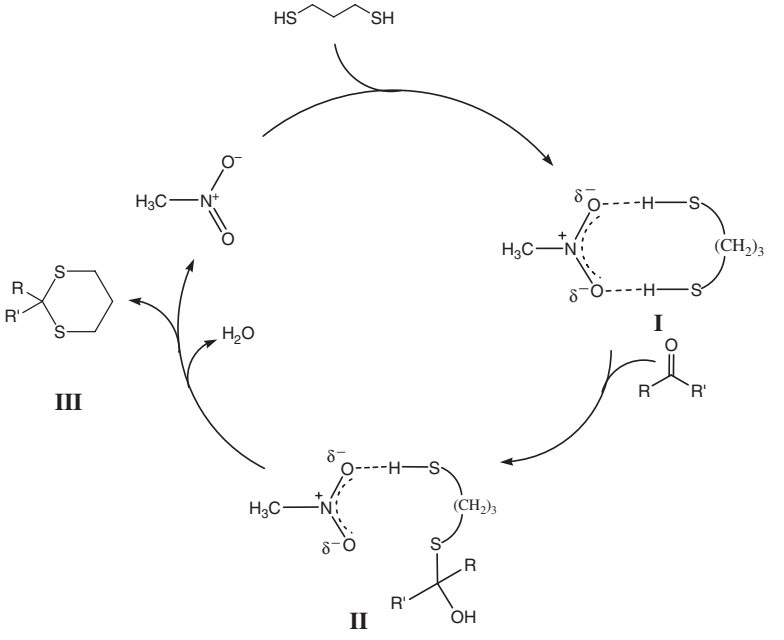
Table 1. Reaction of benzaldehyde with 1,3-propanedithiol under a catalyst-free condition.

Entry	Solvent	Temperature	Time (h)	Yield (%)[a]
1[b]	Nitromethane	Room temperature	50	90
2[c]	Nitromethane	Reflux	3.5	90
3[b]	Nitromethane	Reflux	10 (min)	91
4[d]	Acetonitrile	Reflux	2	0
5[d]	Methanol	Reflux	2	10
6[d]	1,4-Dioxane	Reflux	2	0
7[d]	THF	Reflux	2	0
8[d]	DMF	100°C	2	0
9[d]	DMSO	100°C	2	0
10[d]	Chloroform	Reflux	2	0
11[d]	*n*-Hexane	Reflux	2	0

Notes: [a]Isolated yield.
[b]Benzaldehyde/1,3-propanedithiol/nitromethane$_{ml}$: 1/2/0.5.
[c]Benzaldehyde/1,3-propanedithiol/nitromethane$_{ml}$: 1/1/0.5.
[d]In other solvents: benzaldehyde/1,3-propanedithiol/solvent$_{ml}$: 1/2/0.5.

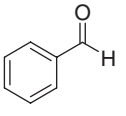
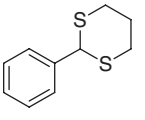
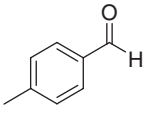
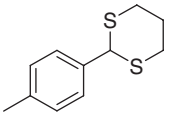
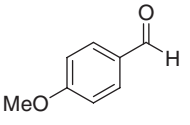
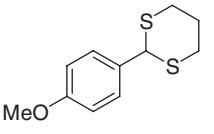
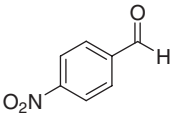
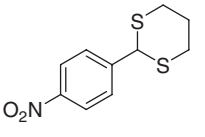
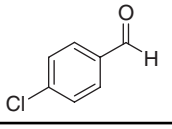
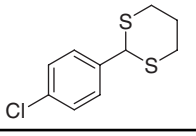
The basis of the dramatic effect of nitromethane in this protection is unclear at present. However, it is conceivable that the oxygen atom of heteroatom oxide can activate the protecting reagent (*32, 33*), through the hydrogen bonding with SH. Carbonyl groups react with the activated $HS(CH_2)_3SH\text{-}CH_3NO_2$ complex **I** to produce the C−S bond (**II**). An intermolecular nucleophilic attack in **II** with concomitant loss of a water molecule produces dithioacetals **III**. Regeneration of CH_3NO_2 initiates the second cycle. Nevertheless, at this time, there is no experimental evidence

for the existence of **I**, and the actual role of CH_3NO_2 and its clarification will require further study (Scheme 2).



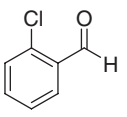
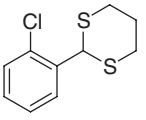
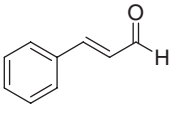
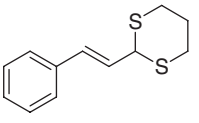
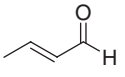
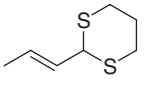
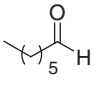
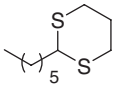
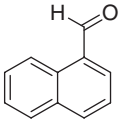
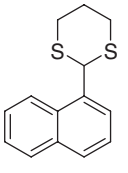
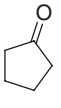
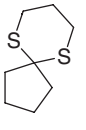
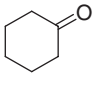
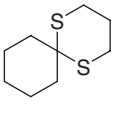
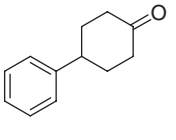
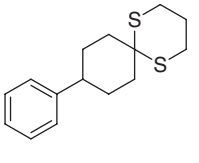
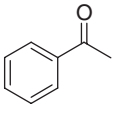
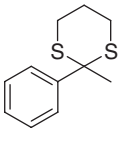
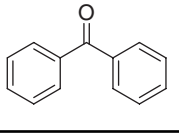
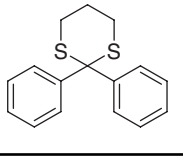
Scheme 2. Mechanism of the protection reaction.

Table 2. Dithioacetalization of various structurally diverse aldehydes and ketones in CH_3NO_2 under catalyst-free conditions.

Entry[a]	Substrate	Product[b]	Time (min)	m.p. (°C)	Yield (%)[c]
1			10	68–69, Lit (*35*):69–70	91
2			40	88–89, Lit (*36*):87	89
3			50	115, Lit (*19*):115–117	90
4			5	140–141, Lit (*11*):141–142	91
5			45	81, Lit (*37*):81–82	89

(*Continued*)

Table 2. Continued

Entry[a]	Substrate	Product[b]	Time (min)	m.p. (°C)	Yield (%)[c]
6			30	89, Lit (*38*):90–92	88
7			10	57–58, Lit (*39*):57–58	92
8			5	–	91
9			10	–	89
10[d]			3.5 (h)	145–147, Lit (*40*):145–146	90
11			25	–	90
12			15	38–39, Lit (*41*): 39–40	91
13[d]			60	106, Lit (*42*):107	90
14[d]			72 (h)	–	17
15[d]			72 (h)	–	0

Notes: [a]Substrate/1,3-propanedithiol/nitromethane$_{ml}$: 1/2/0.5.
[b]The products was identified by the comparison of its physical constants, IR and NMR spectral data with those of an authentic sample.
[c]Isolated yield.
[d]Substrate/1,3-propanedithiol/nitromethane$_{ml}$: 1/3/2.

3. Conclusion

A novel and efficient uncatalyzed method for the dithioacetalization of aldehydes and ketones has been developed. Aldehydes and ketones were protected in nitromethane as the solvent without the aid of a catalyst. The reaction proceeds very cleanly and the work-up procedure is very simple. The absence of a catalyst and mild reaction conditions are the advantages of the present study compared with other reported catalytic methods. Hence, it can be claimed that this method is the most economically convenient method for the protection of aldehydes and ketones.

4. Experimental section

4.1. *General remarks*

The completion of reactions were monitored by TLC on silicagel polygram STL G/UV 254 plates. Melting points were determined with an Electrothermal Type 9100 melting point apparatus. FT-IR spectra were recorded on an Avatar 370 FT-IR Therma Nicolet spectrometer. NMR spectra were recorded on a Brucker Avance instrument in $CDCl_3$.

Caution: Using of nitromethane may incur notable safety precautions. It is highly recommended to seek the Material Safety Datasheet.

4.2. *Experimental procedure for the dithioacetalization of benzaldehyde*

To a solution of benzaldehyde (1 mmol) in nitromethane (0.5 ml), 1,3-propanedithiol (2 mmol) was added and the mixture was refluxed. As monitored by TLC, benzaldehyde was consumed within 10 min. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The concentrated residue was dissolved in CH_2Cl_2 (5 cm^3) and washed with 10% NaOH (2 × 2 ml) and distilled water (5 ml). The combined organic extract was dried over anhydrous Na_2SO_4 and filtered. Removal of the solvent gave almost pure product, and further purification was performed by column chromatography on silica-gel using *n*-hexane/ethylacetate (10/1 v/v) as eluent (Entry 1, Table 2).

2-Phenyl-[1,3]dithiane(1): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.02 (m, 1H), 2.18–2.23 (m, 1H), 2.92–2.97 (m, 2H), 3.07–3.14 (m, 2H), 5.21 (s, 1H), 7.29–7.40 (m, 3H), 7.49–7.52 (m, 2H). IR (KBr): 2949, 2890, 1450, 1275, 1179, 726, 696 cm^{-1}.

2-(4-Methoxy-phenyl)-[1,3] dithiane(3): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.00 (m, 1H), 2.16–2.23 (m, 1H), 2.90–2.95 (m, 2H), 3.05–3.12 (m, 2H), 3.82 (s, 3H), 5.17 (s, 1H), 6.88–6.91 (d, 2H, J = 14.8 Hz), 7.41–7.44 (d, 2H, J = 14.4 Hz). IR (KBr): 2937, 2900, 1607, 1249, 1030, 775 cm^{-1}.

2-(Naphthalen-5-yl)-1,3-dithiane(10): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30–2.11 (m, 1H), 2.20–2.32 (m, 1H), 3.01–3.05 (m, 2H), 3.11–3.28 (m, 2H), 5.97 (s, 1H), 7.29–7.62 (m, 3H), 7.83–7.91 (m, 3H), 8.35 (d, 1H, J = 8.4). IR (KBr): 3045, 2930, 1596, 1506, 1419, 1273, 782, 546 cm^{-1}.

9-Phenyl-1,5-dithia-spiro[5.5]undecane(13): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.78–1.79 (m, 2H), 1.86–1.90 (m, 2H), 2.01–2.06 (m, 4H), 2.49–2.49 (m, 2H), 2.52–2.53 (m, 1H), 2.80–2.83 (m, 2H), 2.94–2.96 (m, 2H), 7.21–7.35 (m, 5H). IR (KBr): 3017, 2921, 1597, 1490, 1274, 760, 700, 535 cm^{-1}.

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