

## Highly Efficient, and Fast Solid State Deprotection of 1,3-Dithianes and 1,3-Dithiolanes using Mercury(II) Nitrate Trihydrate

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**Abstract:** A variety of 1,3-dithianes and 1,3-dithiolanes are deprotected in the solid state to the corresponding parent carbonyl compounds in excellent yields using mercury(II) nitrate trihydrate in a mild, efficient and fast method.

**Keywords:** 1,3-Dithiane; 1,3-Dithiolane; Mercury(II); Deprotection; Carbonyl compounds; Solid-state.

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### Introduction

1,3-Dithiane and 1,3-dithiolane derivatives are versatile intermediates in the synthesis and interconversion of monocarbonyl and 1,2-dicarbonyl compounds. Thioacetals are often used as protecting groups for carbonyl compounds, particularly in multistep natural product synthesis [1-2], due to their stability towards both acidic and basic conditions. Many procedures are available in the literature for preparing thioacetals [3], but their deprotection to the parent carbonyl compounds is not always an easy process. In recent years various hydrolytic [4] or oxidative methods [5-6] have been reported for dethioacetalizations and in the last two decades or so numerous reagent combinations have

been documented for deprotection of thioacetals, including clay supported ammonium ion [7], ferric or cupric nitrates [8], zirconium sulfonyl phosphonate [9], oxides of nitrogen [10], air/bismuth(III) nitrate [11],  $\text{Fe}(\text{phen})_3(\text{PF}_6)_3$  [12], DDQ [13],  $\text{SeO}_2/\text{AcOH}$  [14],  $\text{hv}/\text{pyrylium}/\text{O}_2$  [15], N-fluoro-2,4,6-trimethylpyridinium triflate-water system [16], methylene green/visible  $\text{hv}$  [17],  $\text{SbCl}_5/\text{N}_2$  [18],  $\text{GaCl}_3/\text{H}_2\text{O}$  or  $\text{GaCl}_3/\text{MeOH}/\text{O}_2$  [19],  $(\text{CF}_3\text{CO}_2)_2\text{IPh}$  [20], *m*- $\text{ClC}_6\text{H}_4\text{CO}_3\text{H}/\text{CF}_3\text{CO}_2\text{H}$  [21],  $\text{NaNO}_3/\text{aqueous solution}$  ( $\text{NO}^+$ ,  $\text{H}_2\text{ONO}^+$ ,  $\text{ClNO}$ ) or *t*-butyl hypochlorite ( $\text{Cl}^+$ ) in anhydrous  $\text{CCl}_4$  [22], *t*-butyl bromide (or iodide)/DMSO [23], DMSO/HCl/ $\text{H}_2\text{O}$  [24], TMSI (Br)/DMSO [25],  $\text{LiN}(\text{I-C}_3\text{H}_7)_2/\text{THF}$  [26],  $\text{HgO}/35\%$  aqueous  $\text{HBF}_4$  [27], benzeneseleninic anhydride [28], periodic acid [29], isoamyl nitrite [30], *O*-mesitylenesulfonyl hydroxylamine [31],  $\text{Et}_3\text{O}^+\text{BF}_4^-$  [32], MeI in moist acetone [33] or in 96% methanol [34], ceric ammonium nitrate (CAN) in aqueous  $\text{CH}_3\text{CN}$  [35],  $\text{HgO-BF}_3/\text{H}_2\text{O-THF}$  [35], N-chloro-*p*-toluenesulphonamide (chloroamine-T) [36], 1-chlorobenzotriazole [37], N-halosuccinimide [38],  $\text{CuCl}_2/\text{CuO}$  [39] and benzyltriphenylphosphonium peroxymonosulfate [40].

Many of these methods, however, suffer from one or more of the following disadvantages: long reaction times, vigorous reaction conditions, the occurrence of side reactions, unavailability of the reagents, poor yields of the desired product and furthermore, they usually often involve solvents. Consequently, there is a need for a simple, less expensive, fast, and efficient method for deprotection of thioacetals and thioacetals.

In recent years, there has been an increasing interest in reactions that proceed in the absence of solvents due to their reduced pollution, low costs and simplicity in process and handling. Because of our interest in photochemical and thermal reactions of inorganic mercury compounds [41], we now report the use of mercury(II) nitrate trihydrate as a highly efficient, fast and selective reagent for the deprotection of thioacetals (1,3-dithiolanes and 1,3-dithianes) to the corresponding carbonyl compounds at solid state. This is the first report for solid-state deprotection of 1,3-dithiolanes and 1,3-dithianes with this reagent.

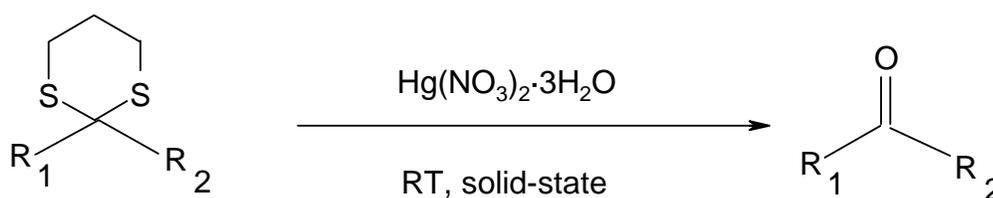
## Results and Discussion

Deprotection of thioacetals and thioacetals with mercury (II) nitrate trihydrate proceeds readily under solid-phase conditions. Initially, we decided to explore the role of both the hydrated and anhydrous mercury (II) nitrate in a solventless system for the deprotection of 2-(3-nitrophenyl)-1,3-dithiane used as a model compound. In the absence of mercury (II) nitrate trihydrate no dethioacetalization of the model compound was observed, even after prolonged reaction times. Since deprotection of the model compound failed in the absence of mercury(II) nitrate trihydrate, the effect of mercury(I) nitrate dihydrate,  $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$  was also investigated. Surprisingly,  $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$  was effective, but required longer reaction times (30min.) and gave a lower yield (70%) in the solid state. We assume that the reason that  $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$  did not work as well as  $\text{Hg}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  is because mercury(I) has less affinity towards the sulfur atoms of 1,3-dithio compounds than mercury(II). Deprotection of thioacetals with mercury(II) nitrate trihydrate was also investigated in

solution phase and the results showed that the reaction was complete in 20 min. Mercury(II) chloride did not initiate the reaction in solid phase nor in the solution. Deprotection of thioacetals did not proceed with mercury (II) acetate in the solid phase but it was complete after ca. 45 min. in an aqueous acetonitrile. An optimum 1:2 molar ratio of thioacetal to mercury (II) nitrate trihydrate was established for complete deprotection of thioacetals to carbonyl compounds in solid phase.

In this method, deprotection of a thioacetal or thioketal is achieved by grinding together a mixture of the substrate with mercury (II) nitrate trihydrate in the solid state (Scheme 1). The reaction time is usually between 1-4 minutes. The carbonyl compounds were isolated by washing the reaction mixtures with solvent followed by filtration. Evaporation of the filtrate under vacuum followed by flash chromatography often produces pure carbonyl compounds in high yields (Table 1).

**Scheme 1**



This method therefore offers a simple, mild, and efficient solid-state route for converting thioketals and thioacetals to the corresponding carbonyl compounds. As evident from the results presented in Table 1, the presence of functional groups such as  $\text{NO}_2$  and  $\text{MeO}$  affects the reaction times. This could be the consequence of complexation between these functional groups and the mercury(II) nitrate. Notably, aldehydes did not undergo further oxidation to their carboxylic acids under the reaction conditions. To demonstrate the utility of the procedure, a ten-fold scale reaction was carried out under solid-state conditions for the deprotection of 2-(3-nitrophenyl)-1,3-dithiane to afford 3-nitrobenzaldehyde in 95% yield. It should also be noted that no exotherm or other safety problems were observed during mixing of the starting materials and the reactions themselves.

We have proposed the possibility of formation of a complex between the dithioacetals and the mercury in the reaction mixture. Reaction conditions suggest a non-solvolytic reaction in which oxygen of mercury(II) nitrate acts as a nucleophilic species. A similar conclusion and mechanism has also been proposed by Ley for deprotection of S,S-thioacetals using seleninic anhydride [28]. These observations prompted us to also study dethioacetalization of 1,3-dithiolanes and 1,3-dithianes by  $\text{Hg(NO}_3)_2 \cdot 3\text{H}_2\text{O}$  and  $\text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ . The color of  $\text{Hg(NO}_3)_2 \cdot 3\text{H}_2\text{O}$  changed from white to dark brown and then to white. Our studies showed that the rate of the reactions in the solid phase follows the sequence:  $\text{Hg(NO}_3)_2 \cdot 3\text{H}_2\text{O} > \text{Hg}_2(\text{NO}_3)_2 \cdot 2\text{H}_2\text{O}$ .

**Table 1.** Deprotection of 1,3-dithiolanes, and 1,3-dithianes with  $\text{Hg}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  in a solventless system with (1:2 molar ratios, 100% conversion).

Entry	R <sub>1</sub>	R <sub>2</sub>	Time/min	Yields/% <sup>a</sup>
1	2-MeOC <sub>6</sub> H <sub>4</sub>	H	3	90
2	4-BrC <sub>6</sub> H <sub>4</sub>	Me	2	92
3	4-ClC <sub>6</sub> H <sub>4</sub>	H	2	90
4	Ph	Ph	3	90
5	4-PhC <sub>6</sub> H <sub>4</sub>	Me	4	88
6	4-BrC <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> Br	4	91
7	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	2	95
8	2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	2	95
9	4-ClC <sub>6</sub> H <sub>4</sub>	Ph	3	92
10	C <sub>6</sub> H <sub>13</sub>	H	1	96

<sup>a</sup> Yields refer to isolated products; entries 1, 3, 7, 8 and 10= dithianes, entries 2, 4, 5, 6 and 9 = dithiolanes

In order to show the usefulness of the procedure, we have compared the results of deprotection of thioacetals by our method with some of those previously reported in the literature (Table 2). As shown in Table 2, the yields of the products in two of the three cases examined are better with the present method, whereas in all three cases the reaction times are substantially shorter compared to the reported methods. Overall the results showed that mercury (II) nitrate trihydrate in the solid state is seen to be superior to the reported reagents in terms of higher yields, shorter reaction times, mild conditions and very easy work up.

**Table2.** Comparison of deprotection of 1,3-dithanes by our method with some of those reported in the literature.

R <sub>1</sub>	R <sub>2</sub>	Yield (%)/Time (min)		
		I <sup>a</sup>	II <sup>b</sup>	III <sup>c</sup> (our method)
4-Cl-C <sub>6</sub> H <sub>4</sub>	H	93/16	92/120	90/2
3-O <sub>2</sub> N-C <sub>6</sub> H <sub>4</sub>	H	88/20	88/60	95/2
4-Br-C <sub>6</sub> H <sub>4</sub>	CH <sub>2</sub> Br	86/15	80/45	91/4

<sup>a</sup> Ref. [40], <sup>b</sup> Ref. [6], <sup>c</sup> our method

## Conclusions

In this study, we have introduced a new application of  $\text{Hg}(\text{NO}_3)_2 \cdot 3\text{H}_2\text{O}$  as an effective reagent for solid-state deprotection of 1,3-dithiolanes and 1,3-dithianes. Although it offers no “green chemistry” advantages, it is important to note that most of the reported methods for the deprotection of 1,3-dithianes and 1,3-dithiolanes use toxic reagents but this method has the advantages of very short reaction time (1-4 min.), no side reactions, excellent yields, mild reaction conditions, a solid state reaction and simple extraction of the products. In the other hand, those methods which might be classified as “green chemistry” typically suffer from other disadvantages such as long reaction times, and low yields of the products. Consequently this methodology represents a good addition to list of methods already available for this purpose.

## Experimental

### General

All of the products were characterized by a comparison of their spectral (IR,  $^1\text{H-NMR}$  and TLC) and physical data (melting and boiling points) with those of known samples [42]. All yields refer to isolated products. NMR spectra were recorded on a Bruker AW 80 MHz in  $\text{CDCl}_3$  relative to TMS as an internal standard. IR spectra were run on a Shimadzu IR-435 spectrophotometer. Mass spectra were recorded on an AMD 604 spectrometer, EI-mode at 70 eV, FT-mode at 0.005 V. The purity of the substances and the progress of the reactions were checked by TLC on silica gel or with a Shimadzu GC-16A Gas Chromatograph instrument equipped with a flame ionization detector. All of the reactions were carried out in the absence of solvent at room temperature in a fume hood with strong ventilation. The carbonyl derivatives were prepared from the corresponding carbonyl compounds and 1,3-propanedithiol according to the reported procedures [3,7b].

*Typical procedure for solid phase deprotection of thioacetals with mercury(II) nitrate trihydrate: reaction of 2-(3-nitrophenyl)-1,3-dithiane.*

Mercury(II) nitrate trihydrate (0.757g, 2 mmol) was added to 2-(3-nitrophenyl)-1,3-dithiane (0.235g, 1 mmol) placed in a mortar. The reaction mixture was ground by pestle at room temperature under solvent-free condition for 1-4 minutes. After the disappearance of starting material as monitored by TLC, the mixture was washed at once with ethanol or acetonitrile (5 mL) and filtered. The filtrate was evaporated under reduced pressure and the resulting crude material was purified by flash chromatography on  $\text{SiO}_2$  (eluent:  $\text{CH}_2\text{Cl}_2$ ) to afford 3-nitrobenzaldehyde (95%); m.p = 42°C; IR(KBr):  $\nu = 3050(\text{m}), 2950(\text{m}), 1685(\text{s}), 1610(\text{m}), 1570(\text{m}), 828(\text{m}), 760(\text{m}) \text{ cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 80MHz):  $\delta = 7.9 (\text{s}, 1\text{H}), 8.0-8.4 (\text{m}, 4\text{H})$  ppm; MS: m/e=151.

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*Sample Availability:* Available from the authors.