# A Convenient Oxidative Dethioacetalization of 1,3-Dithiolanes and 1,3-Dithianes with Iron(III) Nitrate and Montmorillonite K10 in Hexane

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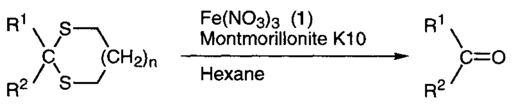
The efficient and experimentally simple oxidative cleavage of cyclic thioacetals to regenerate the carbonyl compounds using a solid-solution biphasic system is described.

The protection of certain functional groups and the deprotection of the protected derivatives constitute important processes in the synthetic chemistry of polyfunctional molecules including the total synthesis of natural products. Thus large numbers of protective groups have been developed along with numerous methods for their removal.[1-4] Cyclic thioacetals and ketals have been widely used as carbonyl protecting groups and, indeed, considerable effort has been made for the development of new methods for their introduction and removal.[5] Of the many dethioacetalization methodologies, chemical procedures are generally more accessible for synthetic chemists than others based on photolytic and electrolytic processes and, indeed, they have been widely used. However, chemical methods often require the use of heavy metal reagents[1,3] such as $Hg^{2+}$, $Ag^{+}$, $Tl^{3+}$, $Cd^{2+}$, $Se^{4+}$ which are inherently toxic and/or expensive to use. In view of economical, practical, and recent environmental[6] demands, we saw significant advantage in using a nontoxic and inexpensive metal salt, such as iron(III) nitrate (**1**). Some early success in the use of nitrosonium and nitronium ion sources[7-11] for regenerating carbonyl compounds from protected derivatives under various conditions may support this idea. In continuation of our investigations on new cleaner chemical processes,[12,13] we report here our results from work undertaken to establish an economically and environmentally acceptable procedure for the deprotection of *S*,*S*-acetals based on the use of this salt.

In order to simplify the method, to increase reagent utility, and to avoid nonselective hydrolysis, a method based on dry conditions has been developed to convert *S*,*S*-acetals efficiently into the parent carbonyl compounds by simply adding an inorganic support material to a reaction mixture in an aprotic solvent. The efficiency of a heterogeneous system based upon iron(III) nitrate oxidation has been proved by earlier investigations.[13] For example, upon stirring dithiolane **2a** or dithiane **3a** derived from nonan-2-one (**4a**), with **1** and Montmorillonite K10 in hexane at 50 °C, **4a** was regenerated in 95 and 96 % yield, respectively, after 10 minutes. The reaction advantages are reminiscent of those of supported reagents,[14] whereby the mixture is easily worked up by filtration and the product isolated by removal of the solvent. It should be pointed out that in the absence of the clay, the reaction was sluggish and, more seriously, molten ferric nitrate and/or its degradation product(s) adhered to the walls of the reaction vessel forming an intractable solid mass, which made the isolation of carbonyl compounds considerably difficult and led to erratic results. Indeed, when no clay was added the conversion of **2a** and the yield of **4a** were only 58 and 52 %, respectively, under otherwise similar conditions to those described above. Clearly, the clay aided the reproducible and high activity of iron(III) nitrate.



(4)

(2) (n = 0)

(3) (n = 1)

| 2–4 | $R^1$ | $R^2$ | 2–4 | $R^1$ | $R^2$ |
|---|---|---|---|---|---|
| **a** | $C_7H_{15}$ | Me | **l** | 3-$MeC_6H_4$ | H |
| **b** | –$(CH_2)_5$– | | **m** | 4-$MeC_6H_4$ | H |
| **c** | –$(CH_2)_{11}$– | | **n** | 4-$ClC_6H_4$ | H |
| **d** | Ph | Me | **o** | 2-$BrC_6H_4$ | H |
| **e** | Ph | Et | **p** | 3-$BrC_6H_4$ | H |
| **f** | Ph | Ph | **q** | 4-$BrC_6H_4$ | H |
| **g** | see Table | | **r** | 4-$O_2NC_6H_4$ | H |
| **h** | $C_7H_{15}$ | H | **s** | 3,4-$(OCH_2O)C_6H_3$ | H |
| **i** | Ph | H | **t** | PhCH=CH | H |
| **j** | 4-$MeOC_6H_4$ | H | **u** | 1-naphthyl | H |
| **k** | 2-$MeC_6H_4$ | H | | | |

**Scheme**

The applicability of the current solid-solution biphasic procedure was tested using typical aliphatic, alicyclic, aromatic, and unsaturated substrates. The reaction conditions indicated in the Table have been optimized (see also Scheme). Thus the parent ketones **4a–g** and aldehydes **4h–u** can be regenerated in a rapid and high-yielding manner. As exemplified by a benzaldehyde series **4i–s**, substituents and their positions on the benzene ring do not cause significant changes in the rate or in the product yield, although both are strongly influenced by the substituents in other reaction systems.[15] The anhydrous conditions described here favor the conversion of *S*,*S*-acetals having the hydrolytically labile methylenedioxy linkage, **2s** and **3s**, to restore piperonal (**4s**), an important fragrance and a synthetic precursor of Dopa. The utility of the method for *S*,*S*-acetals of the unsaturated aldehyde **4t** and substrates with fused ring skeletons, **4g** and **4u**, is also apparent.

**Table.** Deprotection of *S,S*-Acetals with Iron(III) Nitrate and Montmorillonite K10 in Hexane

| Product | | From **2** | | From **3** | | mp (°C) or bp (°C)/Torr | |
|---|---|---|---|---|---|---|---|
| | | Time/min | Yield[a] (%) | Time/min | Yield[a] (%) | found | reported[b] |
| **4a** | $C_7H_{15}COMe$ | 10 | 96 | 10 | 95 | 74-76/12 | 75-77/12 |
| **4b** | cyclohexanone | 3 | 91 | 3 | 91 | 62-64/12 | 67/15 |
| **4c** | cyclododecanone | 10 | | 10 | 91 | 60-61 | 61 |
| **4d** | PhCOMe | 30[c] | 82 | 30[c] | 84 | 65-67/5 | 67/5 |
| **4e** | PhCOEt | 40[c] | 84 | 30[c] | 91 | 89-90/12 | 84-85/8 |
| **4f** | PhCOPh | 10 | 94 | 10 | 98 | 48-50 | 48.5-49 |
| **4g** | 5α-cholestan-3-one | 10 | 74 | 10 | 81 | 127-129 | 128-130[d] |
| **4h** | $C_7H_{15}CHO$ | 10 | 95 | 10 | 98 | 70-72/20 | 72/20 |
| **4i** | PhCHO | 10 | 95 | 10 | 96 | 65-68/12 | 62/10 |
| **4j** | $4\text{-}MeOC_6H_4CHO$ | 5 | 89 | 5 | 93 | 133-135/12 | 134-135/12 |
| **4k** | $2\text{-}MeC_6H_4CHO$ | 10 | 94 | 10 | quant | 69-71/6 | 68-72/6 |
| **4l** | $3\text{-}MeC_6H_4CHO$ | 10 | 90 | 10 | quant | 89-90/15 | 93-94/17 |
| **4m** | $4\text{-}MeC_6H_4CHO$ | 10 | quant | 10 | quant | 113-115/12 | 106/10 |
| **4n** | $4\text{-}ClC_6H_4CHO$ | 10 | 92 | 10 | 95 | 46-48 | 47 |
| **4o** | $2\text{-}BrC_6H_4CHO$ | 10 | 97 | 10 | 93 | 117-118/12 | 118-119/12 |
| **4p** | $3\text{-}BrC_6H_4CHO$ | 10 | 98 | 10 | 98 | 66-68/2 | 66-68/2 |
| **4q** | $4\text{-}BrC_6H_4CHO$ | 10 | 98 | 10 | 94 | 58-60 | 59-60 |
| **4r** | $4\text{-}O_2NC_6H_4CHO$ | 10 | quant | 10 | quant | 104-106 | 106 |
| **4s** | piperonal | 10 | 87 | 10 | 87 | 36-37 | 37 |
| **4t** | PhCH=CHCHO | 10 | 86 | 10 | 93 | 120-122/12 | 130/20 |
| **4u** | 1-naphthaldehyde | 10 | 98 | 10 | quant | 160-161/12 | 150/9 |

[a] Isolated yield based on **2**. [b] From Ref 19. [c] Reaction carried out at 40 °C. [d] From Ref 20.

The method described here can be favorably compared to those based on the supported reagents Montmorillonite K10 supported iron(III) (Clayfen) and copper(II) nitrates (Claycop),[8] and silica gel supported $Cu(NO_3)_2$[9] in terms of shorter reaction periods and removing the need for an independent preparation of a supported reagent prior to reactions. It therefore provides an improved version of reported procedures.[8,9] On environmental and economical grounds, use of hexane as the solvent offers an additional advantage, since it should be preferable to chlorinated hydrocarbons such as dichloromethane,[11] chloroform,[16] and carbon tetrachloride[9,10] which have been frequently employed in conventional heterogeneous systems. Clearly, the present system constitutes a simple and practical procedure for high-yielding deprotection of *S,S*-acetals, which also meets many economical and environmental requirements.

All carbonyl compounds are available from commercial sources. Montmorillonite K10 was purchased from Aldrich and was used as received. Commercial $Fe(NO_3)_3 \cdot 9H_2O$ (Koso Chemical, Tokyo, Japan) was highly hygroscopic and was thus finely ground in a dry box. Hexane was dried, distilled, and stored over molecular sieves. 1,3-Dithiolane **2g** and -dithiane **3g** of 5α-cholestan-3-one **(4g)** (Aldrich) were synthesized and purified according to Fieser's method.[17] The other *S,S*-acetals, **2** and **3**, were prepared from the corresponding carbonyl compounds and 1,2-ethanedithiol and 1,3-propanedithiol, respectively, in chloroform in the presence of $ZnCl_2$, according to the standard method.[18] The isolated carbonyl compounds were identified by spectroscopic ($^1H$ NMR and IR) and physical (either mp or bp) comparisons with literature data.[19,20]

**Dethioacetylation: Benzophenone (4f); Typical Procedure:**

A 30 mL two-necked round-bottom flask, equipped with a 2 cm Teflon-coated stirrer bar, a 25 cm reflux condenser and a glass tubing connected to an argon-filled balloon, was arranged for conducting the reaction under inert and dry conditions by connecting the top of the condenser to a liquid paraffin trap. The flask was charged with hexane (10 mL), Montmorillonite K10 (1 g), finely ground $Fe(NO_3)_3 \cdot 9H_2O$ (0.404 g, 1 mmol) and **3f** (0.272 g, 1 mmol) in that order. After gently passing argon stream through the reaction system, the resultant cloudy mixture was vigorously stirred at 50 °C for 10 min. The cooled mixture was filtered through a sintered glass funnel and the filter cake was washed thoroughly with portions of anhyd $Et_2O$ (*in toto* 50 mL). The combined clear solvent was removed on a rotary evaporator. GC analysis of the crude material showed that **4f** was regenerated quantitatively (4-chlorobenzophenone as an internal standard). Chromatography on a silica gel column [Merck, Silica gel 60 (70–230 mesh); hexane/EtOAc], afforded pure ($^1H$ NMR, GC, and TLC) **4f**; Yield: 0.179 g (98 %); mp 48–50 °C (Lit.[19] mp 48.5–49 °C).

Dethioacetalization of the other *S,S*-acetals was carried out as above, specific reaction conditions (reaction time and temperature) of which were determined on the basis of reactivity of the substrate and yield of the carbonyl compound (Table).

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