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Deblocking of Dithioacetals and Oxathioacetals Using Periodic Acid Under Mild Nonaqueous Conditions

Xiao-Xin Shi, Subhash P. Khanapure and Joshua Rokach*

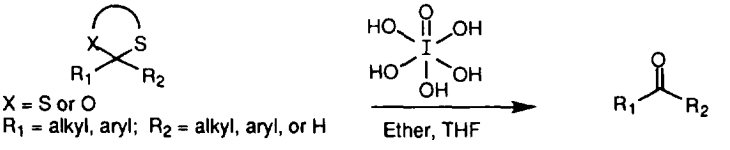
Claude Pepper Institute and Department of Chemistry, Florida Institute of Technology,
150 West University Boulevard, Melbourne, FL 32901, USA

Abstract: A novel method for the deblocking of the dithioacetals and oxathioacetals is described. Periodic acid under nonaqueous conditions has been used for the deprotection of the dithio- and oxathio-derivatives to the corresponding carbonyl compounds. This simple high-yield transformation is conveniently carried out in nonaqueous medium and works well with complex sensitive aldehydes and in the presence of other protective groups.

The importance of the 1,3-dithioacetals[1] and oxathioacetals[2,3,4] as versatile acyl anion equivalent reagents for carbon-carbon bond formation, as well as for protecting groups for carbonyl compounds, has been well documented.[5] The wide utility of the dithioacetals as protecting groups for carbonyl compounds is in part due to the multitude of various methods[5] available for the regeneration of carbonyl compounds from thioacetals. Earlier deprotection methods used conditions such as Raney Ni, isoamylnitrite[6] or chloromine-T.[7] The most frequently used methods involve mercuric chloride, NCS-$AgNO_3$,[8] and [bistrifluoroacetoxy]iodobenzene reagent.[9] New efficient methods for the transformations of dithioacetals and oxathioacetals to carbonyl compounds continue to be of considerable interest to organic chemists and have been described recently.[10] In connection with the synthesis of oxo-eicosanoids[11] we required a mild method for the deprotection of dithioacetals to obtain the corresponding carbonyl compounds. In addition, in several of our other projects, we needed a convenient deblocking method for the large-scale preparation of acid-sensitive aldehydes[12] **20a** and **20b** (Table 2).

We report here an efficient method to convert dithioacetals, oxathioacetals and sulfoxidothioacetals to the corresponding carbonyl compounds using periodic acid in nonaqueous solution under mild conditions (Scheme 1).

Scheme 1



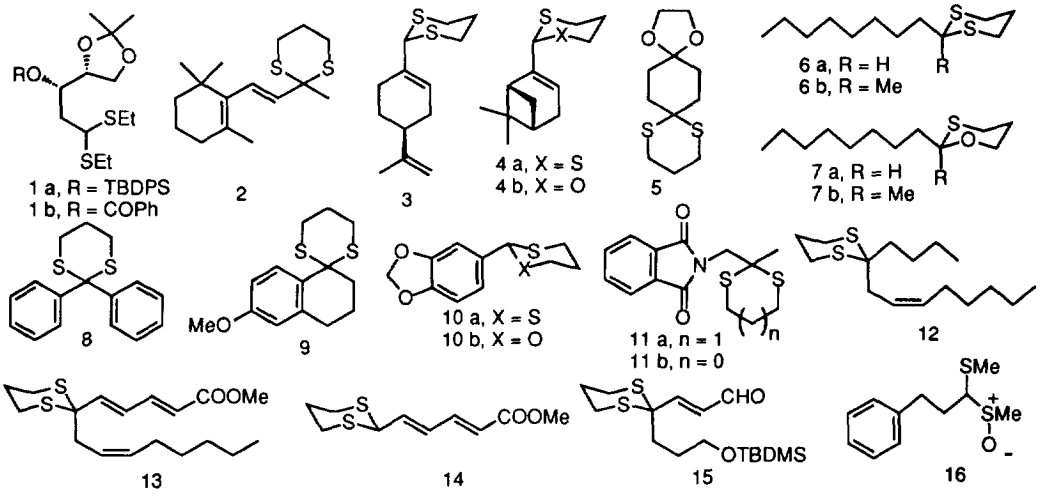
Aqueous periodic acid solution was used to deblock a steroidal dithioketal.[13] When we first examined the use of periodic acid for the deblocking of dithioacetal **1a** (Scheme 2) in THF : water (9 : 1),[14] we failed to observe any aldehyde product **20a** (Table 2), instead this reaction resulted in decomposition. We subsequently carried out the deblocking successfully using periodic acid in hydrate form in anhydrous solvent.[15]

The results were dramatic, as can be seen from Tables 1 and 2. We found that this method is generally applicable for deblocking dithioacetals as well as oxathioacetals to give ketones and aldehydes as shown in Table

1 and Table 2, respectively. When we treated dithioacetal **1a** with periodic acid in ether : THF (5 : 3) at 0 °C for 15 min, the aldehyde **20a** was obtained in 82% yield. This method is general and has been used for several thioacetals, thioketals, oxathioacetals, oxathioketals, and sulfoxidothioacetals. A notable advantage of this method is its simplicity and ease of the reaction work-up. In the case of ketone products, simple filtration through celite is enough to give the pure ketones. Another advantage is that after the reaction is finished, there is no smell of thiol, which makes this method very attractive, particularly for large-scale preparations.

As can be seen from Tables 1 and 2, we have incorporated some simple dithioacetals for good measure since some of these have been used in many of the known dithioacetal deprotection methods. Our major focus and interest over the years, however, has been on complex unsaturated mono- and bis-carbonyl compounds prepared from multiprotected carbohydrates. Aliphatic aldehydes clearly present another degree of complexity as these are much less stable under aqueous acidic, basic, and high-temperature neutral conditions than the aromatic aldehydes.

Scheme 2 **Substrates used**



Aromatic dithioketal **11a** or **11b** was cleaved to give the corresponding ketone without affecting the amide functionality (Table 1, entries 7 and 8). This method is versatile and has been applied to deblock oxathioacetals and oxathioketals to give the corresponding aldehydes or ketones (Table 1, entries 4 and 8; Table 2, entries 5, 7 and 9). In these cases, use of 1.1 equivalent reagent gave the best yields.

An interesting and noteworthy point to mention is the chemoselectivity of this method to selectively cleave the dithioacetal in **5** in the presence of the acid-sensitive ketal group (Table 1, entry 2). In fact, unlike their oxygen counterparts, the corresponding thioacetals are difficult to cleave under classical acidic hydrolytic cleavage. The cleavage of dithioketal **13** to give ketone **18** containing acid-sensitive dienyl ester and isomerizable double bond (Table 1, entry 10) indicates that this reaction can be applied to very acid-sensitive compounds. As can be seen from entry 11 (Table 1), the α,β-unsaturated aldehyde and the TBDMS group were not affected.

Table 1 : Deblocking of Dithioketals and Oxathioketals to Give Ketones.

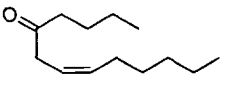
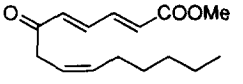
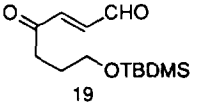
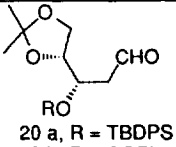
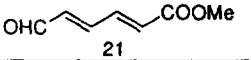
Entry	Substrate	Temperature	Time in min	Product	% Yield
1	2	room temp.	6	β-Ionone	93
2	5	- 10 °C	20	1,4-Cyclohexanedione monoethylene ketal	86
3	6b	room temp.	5	2-Decanone	94
4	7b	room temp.	10	2-Decanone	95
5	8	room temp.	2	Benzophenone	99
6	9	room temp.	6	6-Methoxytetralone	96
7	11a	room temp.	5	N-Acetonylphthalimide	98
8	11b	room temp.	8	N-Acetonylphthalimide	99
9	12	room temp.	10	 17	86
10	13	0 °C	15	 18	87
11	15	0 °C	15	 19	77

Table 2 : Deblocking of Dithioacetals and Oxathioacetals to Give Aldehydes.

Entry	Substrate	Temperature	Time in min	Product	% Yield
					
1	1 a	0 °C	15	20 a, R = TBDPS	82
2	1 b	0 °C	10	20 b, R = COPh	80
3	3	room temp.	5	(S)-Perillaldehyde	92
4	4a	room temp.	5	(R)-Myrtenal	95
5	4b	room temp.	5	(R)-Myrtenal	92
6	6 a	room temp.	5	Nonanal	91
7	7 a	room temp.	10	Nonanal	90
8	10a	room temp.	5	Piperonal	98
9	10b	room temp.	5	Piperonal	98
10	14	0 °C	15	 21	87

Natural product (S)-perillaldehyde was regenerated from the dithioacetal **3** (Table 2, entry 3), and (R)-myrtenal was regenerated from dithioacetal **4a** or oxathioacetal **4b** (Table 2, entries 4 and 5). We prepared sulfoxide **16** and found that it was deblocked to the corresponding aldehyde under the same conditions.

This is, to our knowledge, the first nonaqueous procedure for deblocking thioacetals, oxathioacetals and sulfoxidothioacetal. The oxygen incorporated in the final carbonyl products is provided by periodic acid, as no aqueous work up is required.

Typical General Procedure: To a 0 °C cooled solution of dithioacetal (10 mmol) or oxathioacetal (20 mmol) in anhydrous THF (20 mL) and ether (50 mL) was added drop-wise a solution of periodic acid (20 mmol) in anhydrous THF (10 mL) during a period of 3 min. The ice-bath was removed and the reaction mixture was stirred at room temperature for 2-15 min, during which time a white precipitate was formed. The reaction mixture was diluted with ether (100 mL) and quickly filtered through florisil/celite. The filtrate was evaporated at reduced pressure to give the corresponding carbonyl compounds. When necessary, a chromatographic purification was performed. In the case of aldehydes, washing with Na_2SO_3 solution improves the yields.

The combination of nonaqueous conditions, operational simplicity, short reaction time, ease of isolation of products, useful chemoselectivity, and versatility to deblock dithioacetals, oxathioacetals and sulfoxido-thioacetals, makes this method a significant addition to existing methodologies.

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