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A Mild, Chemoselective Protocol for the Removal of Thioketals and Thioacetals Mediated by Dess–Martin Periodinane

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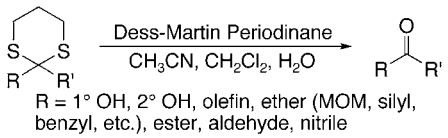
ABSTRACT



This paper describes the development of a useful procedure for the removal of thioacetals and thioketals using Dess–Martin periodinane (DMP) reagent. In contrast to existing methods, this protocol offers general reactivity, compatibility with a wide range of functional groups, and convenient reaction times. Also discussed are chemoselectivity experiments involving functionalities that may be subject to oxidation by DMP, qualitative effects of substrate on hydrolysis rate, and direct thioacetal to acetal conversions.

Acetals and ketals are widely used as protecting groups for carbonyl compounds due to their negligible susceptibility to nucleophilic attack, ease of preparation, and stability to reduction methods.[1] Thioacetals and thioketals are particularly attractive as carbonyl protecting groups in complex molecule synthesis because of their added stability to acidic conditions. Additionally, the lithium anions of 1,3-dithianes have found utility as nucleophiles[2] in alkylation and epoxide ring-opening reactions, thereby providing an umpoloung[3] approach to the synthesis of ketones or β-keto alcohols.

The use of cyclic thioacetals and thioketals in complex molecule synthesis, however, is often impeded by the lack of mild, general methods for their removal. Traditionally, cyclic thioacetal or thioketal cleavage has mainly been achieved through oxidative means or by the action of mercury(II) salts.[1a] However, these methods frequently result in competitive side reactions in the presence of olefins, aromatic rings, groups that are readily oxidized, and acid-sensitive functionalities.[4] In 1989, Stork and Zhao reported the removal of a series of 1,3-dithianes with bis(trifluoroacetoxy)iodobenzene (BTI).[5,6] This reagent affords the desired ketones, aldehydes, or acetals (in the presence of an alcohol) in good yield with reaction times of less than 10 min. The use of BTI for dithiane cleavage has greatly expanded the utility of these protecting groups. Indeed, in applications involving complicated substrates, BTI is frequently the reagent of choice.[2c,7]

As part of studies directed toward the synthesis of the natural product leucascandrolide A, we required an efficient method for the removal of a thioketal from the intermediate **1a** (eq 1). In our hands, reaction of **1a** with BTI resulted in

(1) (a) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999; pp 297−348. (b) Cordes, E. H.; Bull, H. G. *Chem. Rev.* **1974**, *74*, 581−603.

(2) (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075−1077. (b) Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643−7677. (c) Smith, A. B., III; Condon, S. M.; McCauley, J. A. *Acc. Chem. Res.* **1998**, *31*, 35−46. (d) Liu, P.; Panek, J. S. *Tetrahedron Lett.* **1998**, *39*, 6147−6150.

(3) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357−402.

(4) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366−367.

(5) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287−290.

(6) For the original BTI report, see: Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272−4276.

(7) For recent illustrative examples, see: (a) Nakatsuka, M.; Ragan, R. A.; Sammakia, T.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1990**, *112*, 5583−5601. (b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667−3670. (c) Paquette, L. A.; Duan, M.; Kanetzki, I.; Kempmann, C. *J. Am. Chem. Soc.* **2002**, 4257−4270.

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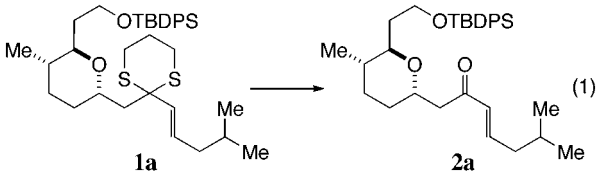
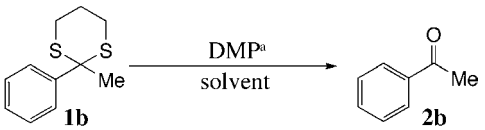
70% yield of the desired ketone **2a** in less than 5 min with significant loss of silicon protecting group. Various amounts (~20%) of multiple olefin isomers were obtained as additional side products.[8] Increased reaction time (10 min) resulted in larger amounts of undesired material.



Concerned by the prospect of significant material loss during scale-up procedures, we sought a more reliable method for dithiane removal. Based on an examination of the proposed mechanism for BTI-mediated dethioacetalization,[5] we postulated that Dess−Martin periodinane[9] (DMP) would affect the desired transformation in a milder manner. Indeed, it is well established that DMP tolerates a myriad of functional groups.[10] Additionally, DMP is commercially available.[11] Despite the widespread use of DMP in oxidative applications, there are no known reports of DMP-mediated thioacetal or thioketal removal.[12,13]

To evaluate this possibility, a series of conditions were investigated to affect the deprotection of 2-methyl-2-phenyl-1,3-dithiane **1b**. As shown in Table 1, clean conversion was generally achieved in polar solvents with the use of stoichiometric or multiple equivalents of DMP. In these experiments, a dramatic rate enhancement was observed using MeCN versus MeOH (entries 2 and 5), suggesting that nucleophilic attack of methoxide onto the presumed carbocation electrophile effectively competes with or precedes hydroxide attack. Interestingly, this observation indicates that direct acetal formation from thioacetals under anhydrous conditions may be possible. DMP reactivity in the presence of methanol also indicates that chemoselective dethioacetalization on substrates bearing hydroxyl groups may be possible. Importantly, commercially available DMP is effective in this reaction, although it reacts more slowly than freshly prepared DMP (entries 6 and 5, respectively).[14] Accordingly, the use of two equivalents of DMP in an 8:1:1 $CH_3CN/CH_2Cl_2/H_2O$ solvent mixture cleanly provides the desired ketone in a convenient 2 h reaction period (entry 5).

Table 1. Optimization of Thioketal Deprotection Conditions



entry	equiv of DMP	solvent (8:1:1)	time (h)	% conv[b]
1	1.0	$MeOH/CH_2Cl_2/H_2O$	68	90
2	2.0	$MeOH/CH_2Cl_2/H_2O$	18	>95 (91[c])
3	3.0	$MeOH/CH_2Cl_2/H_2O$	12	>95 (92[c])
4	1.0	$MeCN/CH_2Cl_2/H_2O$	18	>95 (81[c])
5	2.0	$MeCN/CH_2Cl_2/H_2O$	2	>95 (92[c])
6	2.0[d]	$MeCN/CH_2Cl_2/H_2O$	4	>95
7	2.0	H_2O only	48	>95
8	2.0	$THF/CH_2Cl_2/H_2O$	96	<50

[a] All reactions run at room temperature, with 1.0 mmol of **1b**, 0.2 M solvent concentration. [b] Reflects percent conversion (measured by ^1H NMR analysis of crude mixture after removal of solvents). [c] Isolated yield of **2b** after column chromatography. [d] Reaction using commercially available DMP (Aldrich).

To determine functional group compatibility and to investigate chemoselectivity in this reaction, a series of substrates were subjected to optimized deprotection conditions. As illustrated in Table 2, this protocol provides smooth, general removal of thioacetals and thioketals on substrates containing many different functional groups, including nitriles, esters, lactones, aldehydes, ethers, and olefins. The desired ketones and aldehydes are synthesized in good to excellent yield, with full conversion achieved in 0.5−18 h. Although primary methoxymethyl ethers (**1i**), primary TBDPS ethers (**1p**, **1a**), and secondary TBS ethers (**1p**) are stable to these slightly acidic conditions, primary TBS or TES ethers (**1n**) are subject to hydrolysis, yielding the hydroxy ketone as the major product. Additionally, acid-promoted epimerization of a chiral center adjacent to an emerging carbonyl in an aldehyde product has been observed under these conditions (entry 13). In most cases, however, no reaction with the functional groups illustrated is observed, even after prolonged reaction times.[15] It is also interesting to note that both primary (**1k**, **1m**) and secondary (**1l**) hydroxyl groups are tolerated[16] in this reaction without any observable oxidation to the undesired aldehyde or ketone.[17] Of principle interest to our current studies directed toward the synthesis of leucascandrolide A, **1a** is converted cleanly to the desired α,β-unsaturated ketone **2a** in 91% yield after

(8) Among multiple methods utilized, only BTI resulted in significant conversion to desired compound **2a**.

(9) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(10) (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549−7552. (c) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2584.

(11) Aldrich catalog number 27,462-3 (Dess−Martin periodinane).

(12) A recent report of benzylic/allylic dithiane removal using *o*-iodoxybenzoic acid (IBX) has come to our attention: Wu, Y.; Shen, X.; Huang, J.-H.; Tang, C.-J.; Liu, H.-H.; Hu, Q. *Tetrahedron Lett.* **2002**, *43*, 6443−6445.

(13) A literature search of articles citing refs 5 and 9 resulted in nine hits. Close inspection of the documents indicates that DMP oxidation has never been reported on a dithiane-containing substrate.

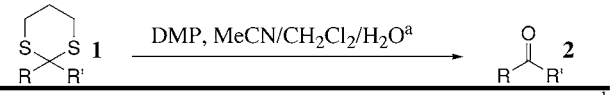
(14) This trend appears to be general. All reported yields in this publication are for DMP, freshly prepared as per ref 10a, and: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

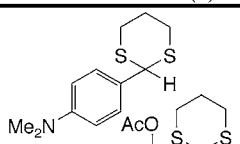
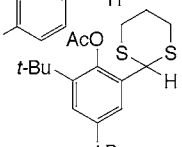
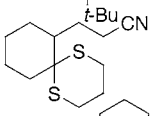
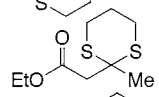
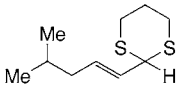
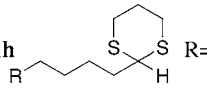
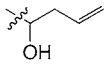
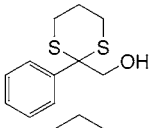
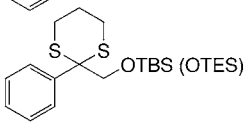
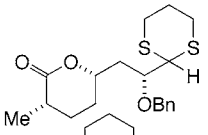
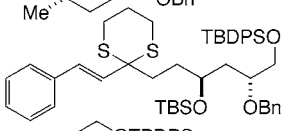
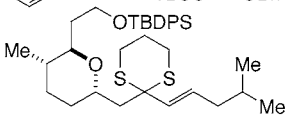
(15) When the *N*-tosyl hydrazone of **1j** was exposed to the conditions outlined in Table 2, the hydrazone was removed in 20 min, leaving unreacted thioacetal. For similar transformations using DMP, see: (a) Chaudhari, S. S.; Akamanchi, K. G. *Tetrahedron Lett.* **1998**, *39*, 3209−3212. (b) Chaudhari, S. S.; Akamanchi, K. G. *Synthesis* **1999**, 760−764. (c) Bose, D. B.; Narsaiah, A. V. *Synth. Commun.* **1999**, *29*, 937−941.

(16) Under these conditions, intramolecular attack of an unprotected β-hydroxyl onto a stabilized allylic carbocation has been observed, resulting in a mixture of heterocyclic compounds. This method is not recommended for unprotected alcohols where formation of an epoxide, furan, or pyran is possible.

(17) In two separate experiments, treatment of **1k** with 2 equiv and 8 equiv of DMP in 9:1 CH_3CN/CH_2Cl_2 (0.2 M) under strictly anhydrous conditions results in chemoselective conversion to aldehyde **2k** after aqueous workup, without observable alcohol oxidation.

Table 2. Examination of Substrate Compatibility



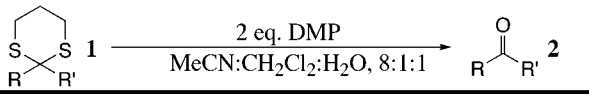
entry	thioacetal/thioketal (**1**)	time (h)	% yield(**2**)[b]
1	**1c** 	0.5	96
2	**1d** 	2	99
3	**1e** 	3.5	87
4	**1f** 	8	63[c]
5	**1g** 	12	70[c]
6	**1h**  R=CH_2OAc	2	91
7	**1i**	R=CH_2OMOM	5	89
8	**1j**	R=CHO	4	73[c]
9	**1k**	R=CH_2OH	2.5	82
10	**1l** 	R=	2	85
11	**1m** 	18	99
12	**1n** 	12	95[d]
13	**1o** 	12	68[e]
14	**1p** 	12	82
15	**1a** 	12	91

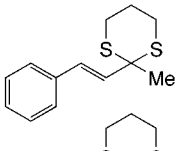
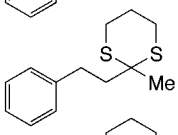
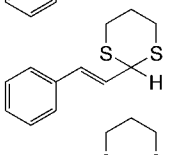
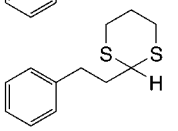
[a] Reaction at room temperature, using 0.8−2.0 mmol of **1**, 2 equiv of DMP in 8:1:1 MeCN/CH_2Cl_2/H_2O solvent mixture (0.2 M). [b] Isolated yield after column chromatography. [c] >95% conversion to **2**; yield reflects product volatility. [d] Isolated yield of hydroxy ketone (desilylated product). [e] Product epimerization observed by ^{1}H NMR analysis (15:1 thioacetal → 5:1 aldehyde).

12 h (entry 15). Gratifyingly, no detectable loss of the TBDPS ether or olefin isomerization occurs with the use of DMP. These results suggest that this protocol may be useful for late-stage formation of carbonyls in complex molecule synthesis, including targets containing both alcohol and ketone or aldehyde functionalities.

In our preliminary studies, a significant increase in hydrolysis rate was observed in unhindered substrates, benzylic or allylic dithianes, and in thioketals versus thioacetals. Although this protocol provides desired product in all cases examined, we felt that a brief analysis of the contributing electronic factors affecting rate would provide qualitative information regarding predictable reaction times. Accordingly, DMP-mediated hydrolysis was performed on a series of sterically similar cinnamaldehyde derived thioacetals and thioketals, and the reaction progress was closely monitored. As shown in Table 3, a general increase in rate

Table 3. Effect of Substrate on Hydrolysis Rate



entry	thioacetal/ thioketal	% conversion after indicated time[a] 15 min	30 min	1 h	2 h
1	 **1q**	92	>95[b]	>95	>95
2	 **1r**	55	90	>95[b]	>95
3	 **1s**	50	85	>95[b]	>95
4	 **1t**	<5	<5	5	29[c]

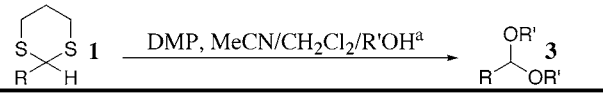
[a] Measured by ^{1}H NMR analysis of crude material, after filtration through a short $MgSO_4$ column and solvent removal. [b] Starting material no longer observable by ^{1}H NMR. [c] Complete conversion achieved in less than 8 h.

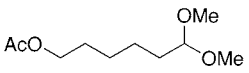
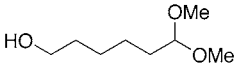
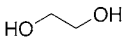
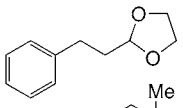
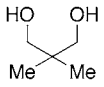
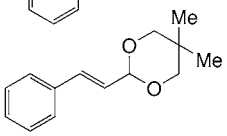
is observed for more electron rich allylic substrates (**1q**, **1s**) and for thioketals (**1q**, **1r**). Interestingly, the allylic substitution rate increase is similar in magnitude to that of the thioketal effect. We postulate that a stabilization of the carbocation in the α,β-unsaturated substrates provides a more stable electrophile, thereby enhancing the rate of hydrolysis. Importantly, the effects are cumulative, as shown in the rapid dethioketalization of **1q**, which reaches completion in less than 30 min. These observations imply that in some cases of unactivated thioacetals, DMP-mediated deprotection may be sluggish.

BTI-mediated thioacetal cleavage in the presence of an alcohol is known to form the corresponding acetal directly.[5] To determine if the analogous DMP-mediated transformation

is effective, a series of thioacetals were treated with anhydrous cleavage conditions as shown in Table 4. Interestingly, both cyclic and acyclic acetals are formed cleanly in good yield, with reaction rate displaying similar trends as the DMP/water-mediated process. Again, chemoselectivity is demonstrated, as there is no involvement of a primary alcohol (entry 2). This protocol should find general utility in cases where a direct thioacetal to acetal conversion would be advantageous, or where an aldehyde functionality would be problematic.

Table 4. Conversion of Thioacetals to Acetals



entry	R'OH	acetal product (**3**)	time (h)	% yield[b]
1	MeOH	 **3a**	9	91
2	MeOH	 **3b**	12	88
3		 **3c**	12	74
4		 **3d**	0.6	88[c]

[a] Reaction run at room temperature, using 2 equiv of DMP, 8:1:1 MeCN/CH_2Cl_2/R′OH solvent (0.2 M). [b] Isolated yield after column chromatography. [c] 2 equiv of DMP, 10 equiv of diol, 0.2 M CH_2Cl_2 solvent, rt.

In summary, we have developed a convenient procedure for the removal of thioacetals and thioketals mediated by Dess−Martin periodinane reagent. This protocol possesses enhanced functional group compatibility, displays milder yet generally effective reactivity, and is especially useful for the hydrolysis of more reactive allylic or benzylic dithianes. The use of this reagent has facilitated the smooth deprotection of the advanced leucascandrolide A thioketal intermediate **1a** and should find general applicability in other complex systems.[18]

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Supporting Information Available: General experimental procedures for thioacetal/thioketal formation, DMP-mediated hydrolysis, and DMP-mediated direct acetal formation. Spectroscopic characterization (IR, HRMS, $[\alpha]_D$, ^1H and ^{13}C NMR data) of selected novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) **Representative Experimental Procedure.** To a sample of **1b** (210 mg, 1.0 mmol) in 5.0 mL of 8:1:1 MeCN/CH_2Cl_2/H_2O (0.2 M) was added 424 mg of Dess−Martin periodinane (2.0 mmol) in one portion. The reaction mixture was stirred at room temperature, exposed to air, for 2 h until complete consumption of starting material as observed by TLC. The reaction was quenched with 20 mL of 50% aq $NaHCO_3$. The layers were separated, and the aqueous layer was extracted 3× into 50 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography (silica, 5% EtOAc/hexanes) affords 112 mg (92%) of desired ketone **2b**.