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Preferential hydrolysis of benzylic/allylic dithianes and dithiolanes using *o*-iodoxybenzoic acid (IBX) in DMSO containing traces of water

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Abstract—Dithianes and dithiolanes at benzylic or allylic carbons can easily be hydrolyzed by IBX in DMSO, whereas non-activated dithianes/dithiolanes are much more stable under these conditions. © 2002 Elsevier Science Ltd. All rights reserved.

Compared with their oxygen-counterparts, thioacetals/thioketals, especially dithianes/dithiolanes, are much easier to form and remarkably more stable under acidic as well as basic conditions.[1] Nevertheless, they can still be cleaved cleanly to release free carbonyl groups under essentially neutral conditions by using e.g. a proper oxidant[2] or visible light.[3] Thus, it is possible to cleave selectively[4] thioacetals/thioketals in the presence of acetals/ketals and vice versa. These properties make thioacetals/thioketals excellent protecting groups in synthesis. In addition, the 1,3-dithianes formed from aldehydes can form carbanions on treatment with a strong base, which easily react with various electrophiles to afford thioketals, representing a useful means of carbon–carbon bond formation.[5] It is therefore not surprising that dithianes/dithiolanes are of great importance in synthesis. However, the deprotection of thioacetals/thioketals is not always facile. In some cases it can be an extremely difficult task. This is presumably the main impetus for the lasting efforts to develop new deprotection protocols, which had resulted in more than 60 procedures[6] in the literature by the mid-1990s.

It is interesting to note that amongst the numerous methods[6] for converting thioacetals/thioketals to the corresponding carbonyl compounds documented over the last half-century, there is essentially none that shows a substantial difference in cleavage rate for different types of dithianes/dithiolanes. To our knowledge only one[7] procedure, which uses $Tl(NO_3)_2 \cdot 3H_2O$ as the reagent, has been reported to be able to cleave selectively an allylic dithiolane in the presence of another dithiolane at a non-allylic position. However, the reactions using $Tl(NO_3)_2 \cdot 3H_2O$ proceed rather fast, which inevitably makes it difficult to control the reaction and thus greatly discourages further exploration of this reagent in selective deprotection. Throughout the 20 years since this first report,[7] only one[8] among the numerous documented applications has involved selective deprotection. No one seems to have exploited the effects of subtle structural differences between different types of dithianes/ditholanes on their cleavage/hydrolysis. Herein, we wish to report the first systematic study on the type-selective dithianes/ditholanes cleavage and the first reagent that shows large differences in reaction rates for different types of dithianes/ditholanes.

Our deprotection of ‘activated’ dithianes/ditholanes (e.g. those at benzylic and allylic positions) was realized by treatment of the substrate with *o*-iodoxybenzoic acid[9,10] (IBX) in DMSO containing traces of added water. At ambient temperatures, the dithianes/ditholanes at benzylic, or allylic positions were easily cleaved to give the corresponding carbonyl compounds whereas those at non-activated positions remained intact unless subjected to prolonged exposure to the cleaving conditions.[11] The yields are generally high for activated substrates. As shown in Table 1, the activated thioacetals are rather liable to the IBX cleavage conditions. In most cases, the sulfur protecting groups at benzylic and allylic positions can be removed cleanly within 30 minutes, whilst non-activated ones remained

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Keywords: activated dithianes; activated dithiolanes; selective hydrolysis; IBX.

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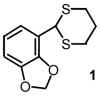
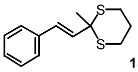
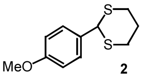
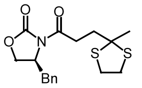
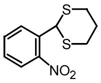
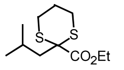
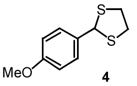
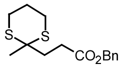
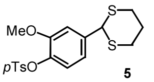
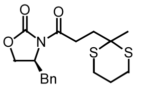
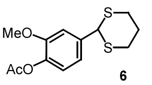
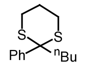
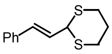
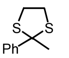
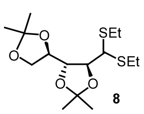
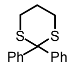
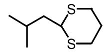
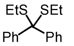
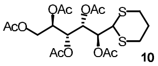
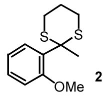
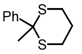
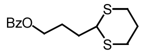
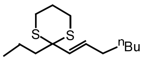
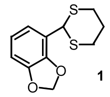
Table 1. IBX mediated cleavage of thioketals/thioacetals into the corresponding carbonyl compounds[a]

Substrate	Conditions	Yield	Substrate	Conditions	Yield[b]
 **1**	0.5 h / 22 °C	88%	 **13**	16 h / 22-32 °C	74%
 **2**	0.5 h / 15 °C	91%	 **14**	10 h / 7-13 °C	(No reaction)[c]
 **3**	0.5 h / 15 °C	92%	 **15**	9 h / 27-34 °C 26 h / 27-34 °C	(No reaction)[c] (90% of **15** recovered)
 **4**	0.5 h / 22 °C	70%	 **16**	18 h / 28 °C	(No reaction)[c]
 **5**	0.5 h / 20 °C	91%	 **17**	9 h / 8-17 °C 60 h/ 8-17 °C	(No reaction)[c] 50%
 **6**	0.5 h / 20 °C	91%	 **18**	9 h / 25°C	79%
 **7**	0.75 h / 25 °C	91%	 **19**	9 h / 20 °C	61%
 **8**	10 h / 15-25 °C 22 h / 25 °C	(No reaction)[c] (80% of **8** recovered)	 **20**	2 h / 18 °C	93%
 **9**	1 h / 11-18 °C 5 h / 11-18 °C	(No reaction)[c] (89% of **9** recovered)	 **21**	4 h / 25 °C	88%
 **10**	1 h / 25 °C	(97% of **10** recovered)	 **22**	9 h / 22-32 °C	81%
 **11**	6 h / 22-32 °C	92%	 **24**	1 h / 25 °C	(90% of **24** recovered)[d]
 **12**	12 h / 22-32 °C	68%	 **1**	1 h / 25 °C	93%[d]

[a] Cf ref. 11. [b] Isolated yields. [C] As shown by TLC. [D] Intermolecular competition test starting with equimolar amounts of **1** and **24** in the same flask under the otherwise the same conditions in ref 11.

intact under the same conditions for many hours, even days. The deprotection of dithianes prepared from aromatic ketones proceeds more slowly, often requiring a few hours to drive the reaction to completion. However, the large rate difference between activated (benzylic/allylic) and non-activated ketone-derived dithianes remains. Dithiolanes appear to be more difficult to cleave than the corresponding dithianes, as observed under other dethioacetalization conditions.

To have a closer comparison of the selectivity between the activated and non-activated substrates we carried out competition tests. Thus, an equimolar mixture of **17** and **22** was treated with 1.5 molar equiv. of IBX at 22–26°C (ambient temperature)[11] for 9 h (Scheme 1, Box A). The resulting reaction mixture was worked up and further treated with $NaBH_4$ to reduce the resulting aromatic ketone (because **22a** had the same R_f as that of **22** on TLC) into the corresponding alcohol **23**. Column chromatographic separation gave **23** and the unreacted starting **22** in 70% and 86% yields (with some loss of material during the work-up), respectively. Similar selectivity was also found between dithianes prepared from aldehydes (Scheme 1, Box B).

It is noteworthy that pollution of the reaction mixture by *traces*[12] of an iron salt could dramatically speed up the cleavage processes and lead to drastic decreases in the rate differences between the activated and the non-activated species. Further investigation into this unexplained phenomenon is still ongoing in our group.

Acknowledgements

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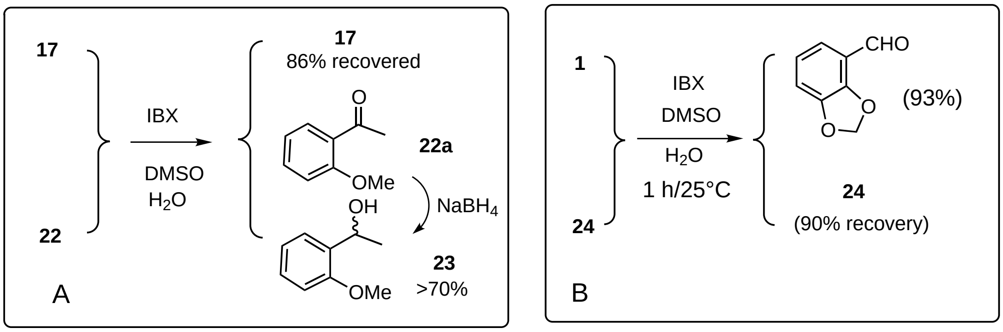

Scheme 1.

(CAS), and the Life Science Special Fund of CAS Supported by the Ministry of Finance (Stz 98-3-03).

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6. See, e.g.: *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W.; Wuts, P. G. M., Eds.; John Wiley and Sons: New York, 1999.
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10. See, e.g.: Wirth, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2812–2814.
11. General experimental procedure. The dithiane or dithiolane (1.0 mmol) was dissolved in DMSO (5.0 mL) containing a small amount (ca. 0.09 mL) of added H_2O. IBX (1.5 mmol) was then introduced. The mixture was stirred (preferably under N_2 or argon) at ambient temperature for 15 min–12 h (depending on the structure of the substrate). When TLC showed completion of the reaction, water (10 mL) was added. The white precipitates were filtered off (washing with ether). The combined filtrate/washings were washed with water and brine, and dried over Na_2SO_4. The residue after removal of the solvent was chromatographed on silica gel (eluting with petroleum ether/ethyl acetate) to give the pure product.
12. For a rapid yet indiscriminate thioketal/thioacetal cleavage using 6 molar equiv. of $FeCl_3$, see: Kamal, A.; Laxman, E.; Reddy, P. S. M. M. *Synlett* **2000**, 1476–1478.