A Useful and Environmentally Benign Synthetic Protocol for Dethiolization by Employing Vanadium Pentoxide Catalyzed Oxidation of Ammonium Bromide by Hydrogen Peroxide

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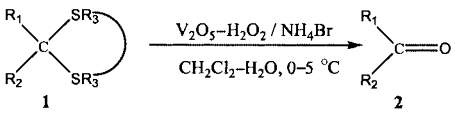
A wide variety of thioacetals and thioketals can be cleaved chemoselectively in presence of olefin and aromatic ring as well as other protecting groups to carbonyl compounds by employing V_2O_5 catalyzed oxidation of ammonium bromide by H_2O_2 in CH_2Cl_2–H_2O solvent system; mild conditions, high selectivity, good yield, and no side products such as bromination or oxidation are some of the major advantages.

Thioacetals and thioketals are widely used as carbonyl protecting groups in complex natural product synthesis due to their robustness towards hydrolytic cleavage in both acidic as well as basic conditions.[1] Among various dithioacetals, diethyldithioacetal is extensively used as a protecting group mainly in carbohydrate chemistry to prepare open chain aldosugars.[2] Though a large number of reagents and methods have already been developed[3] for regeneration of carbonyl functionality, still many of them are not straightforward. The usual deprotection procedures are i) by using heavy metals[4] such as mercury or other heavy metals,[5] which are inherently toxic and expensive; ii) by employing Fe(III) salts;[6] iii) by utilizing some non metallic reagents such as oxides of nitrogen;[7] iv) by using some halonium ion sources.[8] Unfortunately, the methods particularly based on halonium ion sources have certain drawbacks such as use of a molar excess reagents, also requires expensive silver salts in case of olefinic compounds as well as to obtain better yield,[8a] relatively drastic reaction conditions, long reaction time and inert atmosphere,[8b] requirement of hazardous reagents molecular bromine and HBr as well as harmful chemical pyridine for the preparation of pyridinium bromide perbromide.[8c] Therefore, it seems that there is still a greater scope for development of newer methods, which proceed under mild, economically much cheaper and environmentally favorable conditions.

Taking cues from the discovery of vanadium bromoperoxidase (VBrPO),[9a] a vanadium enzyme which catalyzes the oxidation of bromide by hydrogen peroxide[9b] as well as our earlier results,[10] we wish to report a catalytic and an environmentally acceptable deprotection protocol of dithioacetals and ketals involving V_2O_5, ammonium bromide and H_2O_2 (Scheme 1). The catalyst V_2O_5 is used for oxidation of bromide by H_2O_2 and all these chemicals are environmentally acceptable.



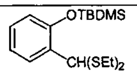
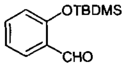
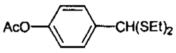
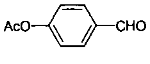
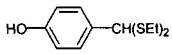
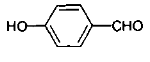
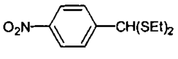
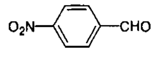
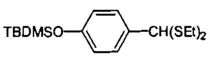
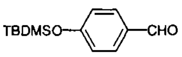
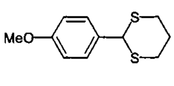
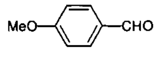
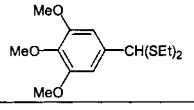
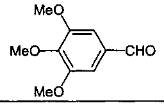
1 2

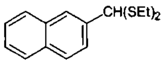
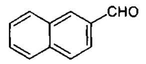
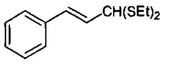
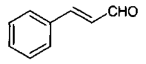
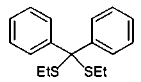
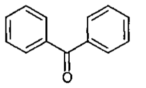
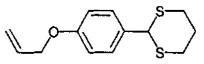
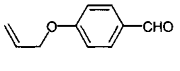
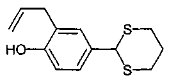
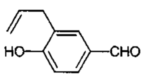
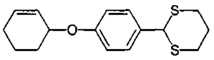
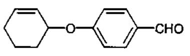
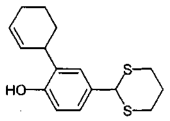
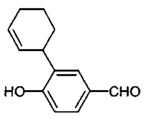
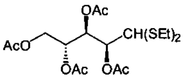
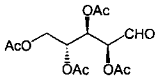
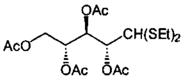
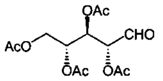
R_1 = aryl, alkyl, sugar residue
R_2 = H, aryl; R_3 = Et, -$(CH_2)_3$-

Scheme 1.

Subsequently, we have attempted for optimization of the reaction conditions for deprotection of dithioacetals and ketals to obtain the desired carbonyl compounds. We have observed that (1:1:0.1:10) substrate / ammonium bromide / vanadium pentoxide / hydrogen peroxide in dichloromethane–water solvent (5:1, 6 mL per mmol of substrate) give best results. We have also noticed that the same reaction will be completed within a shorter period if only the amount of ammonium bromide is increased from 1 to 3 equivalents and V_2O_5 from 0.1 to 0.25 equivalents. Following the above typical reaction procedure,[11] the compound 2-*tert*-butyldimethylsilyloxybenzaldehyde diethyldithioacetal (**1a**) reacts smoothly to give deprotected compound 2-*tert*-butyldimethylsilyloxybenzaldehyde (**2a**) in a high yield. Similarly, various protected dithioacetals and ketals **1b–1o** gave smoothly carbonyl compounds **2b–2o** in good yields under identical reaction conditions. The results are summarized in table 1 and the deprotected products are analyzed by recording IR and compare with the authentic sample spectra as well as ^1H NMR and elemental analyses. In this method, direct oxidation of sulfur is not possible which has already been investigated by others.[12] Interestingly, we did not notice any bromination in the double bond or allylic position (entries **l–o**) and in the aromatic ring.

Table 1. Cleavage of various thioacetals and ketals using V_2O_5 catalysed oxidation of ammonium bromide by H_2O_2

Entry	Substrate (1)	Time in h	Product (2)[a]	Yield[b] / %
a		1.75		94
b		1.5		75
c		2.0		65
d	$CH_3(CH_2)_{10}CH(SEt)_2$	1.75	$CH_3(CH_2)_{10}CHO$	80
e		2.0		96
f		1.5		95
g		2.0		90
h		1.5		94

i		1.75		95
j		1.5		90
k		2.0		95
l		2.0		83
m		1.75		67
n		1.5		80
o		2.0		78
p		2.5		75
q		2.5		70

[a] Products have been characterized by comparison of IR with the authentic compounds, ^{1}H NMR and elemental analyses of the samples. [b]Isolated yields.

This method has been further extended for the preparation of open chain aldehydic compounds **2p** and **2q** from compound **1p** and **1q**, respectively. The probable mechanism for the cleavage of thioacetals can be explained as follows. Vanadium pentoxide reacts with H_2O_2 to generate reactive peroxovanadate (V) intermediates,[13] which oxidize bromide (Br^-) to the Br^+. The reactive bromonium ion can undergo further oxidation to Br_2 or Br_3^-, which might exist in solution. Then the reactive species Br^+ reacts with dithioacetals to form bromosulfonium complex, which is finally hydrolyzed by water to the parent carbonyl compound.

In conclusion, we have devised a simple and useful catalytic method for the regeneration of parent carbonyl compounds from their corresponding dithioacetals or ketals chemoselectively using ammonium bromide, V_2O_5 and H_2O_2 under very mild conditions. It is significant to note that neither olefin and allylic position, nor aromatic ring is brominated under the experimental conditions. Due to its operational simplicity, generality, efficacy, and cost effective, this method is expected to have much wider applicability for the cleavage of thioacetals chemoselectively. A similar deprotection reaction also might be possible by using other alkali metal bromide, which is under investigation.

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11 A typical deprotection procedure: Into a stirred solution of vanadium pentoxide (0.018 g, 0.1 mmol) in water (1.0 mL) is added 30% hydrogen peroxide solution (0.6 mL, 5 mmol) at 0–5 °C and stirring is continued. The color of the solution is changed to the clear dark brown-red after 25 min, and ammonium bromide (0.1 g, 1.0 mmol) is added into it. After 10 min of stirring at the same temp, the substrate 4-nitrobenzaldehyde diethyldithioacetal (**1e**) (0.257 g, 1 mmol) is added slowly by dissolving in dichloromethane (5 mL). Stirring is continued further and 50% conversion is over within 30 min as monitored by TLC. Then further 0.6 mL (5 mmol) of H_2O_2 is added and the reaction is completed within another 55 min. The reaction mixture is finally extracted with CH_2Cl_2 (20 mL × 2) and the organic layers are dried over anhydrous Na_2SO_4. The organic extract is concentrated in vacuo to give crude product, which is finally purified by column chromatography on silica gel (eluent: hexane/EtOAc, 9:1). The product **2e** is obtained as light yellowish crystalline solid 0.145 g (96%), m.p. 105–106 °C (lit. 104–106 °C).

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