A Useful and Convenient Synthetic Procedure for Hydrolysis of Thioglycosides

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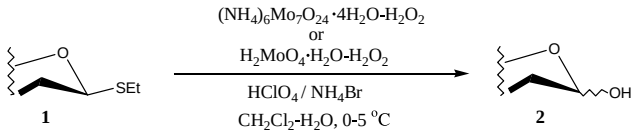
Various thioglycosides **1** are smoothly hydrolyzed chemoselectively to the corresponding 1-hydroxy sugars **2** in good yields at 0–5 °C by employing $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$-$H_2O_2$ or $H_2MoO_4\cdot H_2O$-H_2O_2 to promote oxidation of ammonium bromide in the presence of perchloric acid in CH_2Cl_2-H_2O solvent system. Mild conditions, good yields, no side reactions such as bromination either at the anomeric position or double bond, and even oxidation at the sulfur are some of the major advantages.

Suitably protected 1-hydroxy sugars are useful building blocks for the preparation of various glycosyl donors, which are extensively used for glycosylation reactions in carbohydrate chemistry.[1–5] The usual standard procedure for the preparation of protected 1-hydroxy sugars are as follows: i) they can be prepared, for instance **2a** and **2b**, from their corresponding 1,2,3,4,6-penta-*O*-acetyl sugars by selective hydrolysis of the acetate group at the anomeric position using hydrazine,[6] which is highly toxic; ii) they can also be obtained by acid catalyzed hydrolysis of benzylated methyl α-glycosides, for instance **2c**[7] and **2d,**[8] which are provided with relatively low yield; and iii) they can be easily accessed from their respective thioglycosides by hydrolysis.[9] The preparation of 1-hydroxy sugars starting from their corresponding thioglycosides is more convenient because of its excellent chemical stability, which provides efficient temporary protection at the anomeric position while carrying out the protecting group manipulations at the other positions.[10] On the other hand, thioglycosides are also valuable starting material for oligosaccharide synthesis.[11] In addition, the hydrolysis of 1-thioglycosides leads to the corresponding hemiacetals, which may either be converted into the better glycosyl donors such as trichloroacetimidates[12] or directly converted into the other stable protecting groups such as thexyldimethylsilyl (TDS), so that it is not involved in the glycosidation reactions when both acceptor and donor sugar units are armed 1-thioglycosides.[13] Hence, the hydrolysis of thioglycosides is very often encountered in preparing desired starting materials for oligosaccharide synthesis. The methods are available so far for hydrolysis of thioglycosides: i) by employing thiophilic reagents such as heavy metal salts,[14] which are inherently toxic ii) using N-bromosuccinimide[15] in acetone-H_2O iii) by utilizing a catalytic amount of trityl tetrakis(pentafluorophenyl)borate in combination with a Lewis acid catalyst and sodium periodate.[16] All these existing procedures have some drawbacks such as providing relatively low yield,[14] requiring molar excess of reagents, sometimes to be difficult to obtain hydrolyzed product if NBS is not recrystallized prior to use,[15] also requiring more expensive reagents and relatively harsh reaction conditions.[16] Therefore, what is needed is a methodology that is environmentally benign, mild, clean, and yet efficient.

Very recently we have reported the useful synthetic methods for deprotection of dithioacetals by employing V_2O_5-H_2O_2 catalyzed oxidation of ammonium bromide[17a] and bromination of various organic substrates by utilizing V_2O_5-H_2O_2 to promote oxidation of n-tetrabutylammonium bromide.[17b] Taking cues from the knowledge of the reactivity of diperoxomolybdate(VI) for oxidation of bromide,[18] we have now developed an environmentally acceptable protocol for hydrolysis of thioglycosides by employing ammonium heptamolybdate tetrahydrate or molybdic acid, hydrogen peroxide in the presence of perchloric acid, and ammonium bromide (Scheme 1). The promoter ammonium heptamolybdate or molybdic acid is used for the oxidation of ammonium bromide by H_2O_2 in the presence of perchloric acid and all these chemicals are environmentally acceptable.



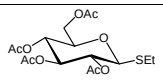
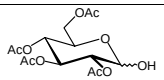
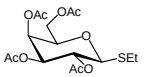
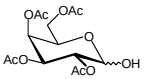
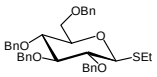
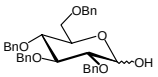
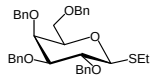
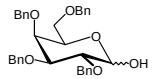
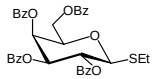
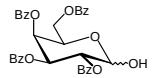
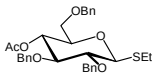
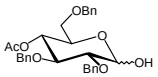
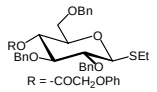
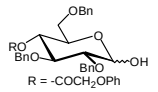
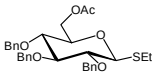
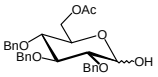
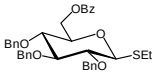
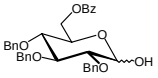
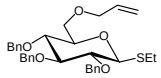
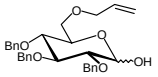
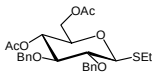
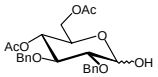
Scheme 1.

Subsequently, various reaction conditions were sampled, with the result that a (1 : 3 : 0.4 : 0.4 : 13) substrate/ammonium bromide/ammonium heptamolybdate/perchloric acid/hydrogen peroxide in dichloromethane-water solvent (2 : 1, 10 mL per mmol of substrate) gave best results (Method A). Interestingly, the similar hydrolysis could also be achieved by using molybdic acid instead of ammonium heptamolybdate with the same molar ratio of other reagents (Method B). By using the above typical reaction protocol,[19] the compound ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**1a**) reacted smoothly to give the hydrolyzed product 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**2a**) in 82% yield. The hydrolyzed product **2a** was also prepared from the compound **1a** in 87% yield by following the Method B. Likewise, various thioglycosides **1b-1k** were hydrolyzed easily to the desired compounds 1-hydroxy sugars **2b-2k** in good yields under identical reaction conditions. The results are summarized in the Table 1 and the hydrolyzed products are fully characterized by ^{1}H-NMR, ^{13}C-NMR, specific rotation and elemental analyses. In this procedure, direct oxidation of sulfur by hydrogen peroxide was not possible which had already been investigated by others.[20] It is noteworthy to mention that we have not noticed any bromination at the double bond or at the anomeric position.

The formation of the hydrolyzed products from their corresponding thioglycosides can be rationalized[18] as follows. Ammonium heptamolybdate or molybdic acid reacts with H_2O_2 in the presence of $HClO_4$ to generate diperoxomolybdate(VI), which oxidizes the bromide (Br^-) to Br^+ (which might also exist as Br_2 or Br_3^-). Then the reactive species Br^+ reacts with sulfur to form bromosulfonium complex, which is finally hydrolyzed by water to the corresponding 1-hyroxy sugars.

In summary, we have devised a simple and useful synthetic protocol for hydrolysis of thioglycosides to the corresponding 1-

Table 1. Hydrolysis of various thioglycosides using ammonium bromide promoted by $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$-$H_2O_2$ or $H_2MoO_4\cdot H_2O$-H_2O_2 in the presence of perchloric acid

Entry	Substrate (**1**)	Time in h	Product (**2**)[a]	Yield[b] / %
a		3.5[c] 5.5[d]		82 87
b		2.5[c]		75
c		5.5[c] 4.0[d]		81 84
d		0.75[c]		85
e		8.0[c] 5.0[d]		89 85
f		1.5[c]		82
g	 R = -$COCH_2OPh$	6.0[c]	 R = -$COCH_2OPh$	80
h		1.25[c]		70
i		6.0[c]		78
j		6.5[c]		75
k		7.0[c]		73

[a]Products have been characterized by ^{1}H-NMR, ^{13}C-NMR, mass spectra, elemental analyses, and specific rotation. [b]Isolated yield. [c]Method A. [d]Method B.

hydroxy sugar chemoselectively by using ammonium bromide, ammonium heptamolybdate or molybdic acid, H_2O_2 and perchloric acid under very mild conditions. It is interesting to note that neither olefinic double bond nor anomeric position was brominated under the experimental conditions. Due to its operational simplicity, generality, efficacy, and cost effectiveness, this method is expected to have much wider applicability for the hydrolysis of thioglycosides. Other thioglycosides can also be hydrolyzed using other alkali metal bromides under similar reaction conditions, which are under investigation.

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19 Method A: To a stirred solution of ammonium heptamolybdate tetrahydrate (0.124 g, 0.1 mmol) in water (0.5 mL), were added 30% hydrogen peroxide solution (360 μL, 3.2 mmol) and perchloric acid (0.1 mmol, 9 μL) at ice-bath temperature and stirring was continued. After 20 min, ammonium bromide (0.074 g, 0.75 mmol) was added in portion and immediately the colour changed into deep yellow from light pale yellow. Then, the substrate ethyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**1a**) (0.098 g, 0.25 mmol) was added by dissolving in dichloromethane (2 mL) to the above solution. The reaction was completed within a 3.5 h as monitored by TLC. The reaction mixture was finally extracted with CH_2Cl_2 (10 mL × 2) and the organic layers were dried over anhydrous Na_2SO_4. The organic extract was concentrated *in vacuo* to give the crude product, which was finally purified by column chromatography on silica gel (eluent: hexane/EtOAc, 1 : 1). The pure product 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (**2a**) was obtained 0.071 g (82%). Method B: The compound **2a** was also prepared from **1a** using molybdic acid following the identical procedure as above.
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