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LETTERS

V_2O_5–H_2O_2: a convenient reagent for the direct oxidation of acetals to esters

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Abstract—Both cyclic and acyclic acetals were deprotected to give the corresponding aldehydes in acetonitrile, and are transformed to methyl esters in methanol, on treatment with a catalytic quantity of V_2O_5 and H_2O_2. Under identical conditions acid-sensitive alcohol protecting groups, such as tetrahydropyranyl and *tert*-butyldimethylsilyl ethers, were cleaved regenerating the corresponding alcohols. © 2002 Elsevier Science Ltd. All rights reserved.

Amongst the plethora of groups typically employed for protecting aldehydes, acetals enjoy a cardinal position, as exemplified by the numerous methods devised for their attachment and removal.[1] Direct conversion of cyclic and acyclic acetals to esters is a useful synthetic methodology in organic chemistry and numerous methods using a variety of reagents and conditions have been developed. A comprehensive list of reagents for the one-step transformation of an acetal to ester has been compiled by Larock.[2] These include O_2, O_2 under photochemical conditions in the presence of Na_2SO_3, O_3, H_2O_2 in the presence of $FeSO_4$, ROOH, $(^tBuO)_2$–$K_2Cr_2O_7$, ^{t}BuOOH, 3,3-dimethyldioxirane, NBS and N_2O_4. Other reagents are also effective for this type of transformation including peracetic acid,[3] DDQ,[4] ^{t}BuOOH-Pd(II) catalyst,[5] sodium perborate,[6] oxone,[7] Co(II) catalyst,[8] $VO(OAc)_2$,[9] H_2O_2 and HCl in alcohol,[10] electrochemical oxidation,[11] $PPh_3^+BF_3^-$,[12] MTO–H_2O_2.[13] With a few exceptions, most of the methods suffer from disadvantages such as ease of operation, drastic conditions, long reaction times, use of excess and expensive reagents. Furthermore, some methods suffer from drawbacks like unsatisfactory yields in the case of aromatic aldehydes bearing an electron-withdrawing substituent in the aromatic ring, polymerisation of 2-furfural and an ineffective for aldehydes containing double bonds.

We have been studying the activation of V_2O_5 using hydrogen peroxide for different oxidation reactions.[14] The peroxo-vanadium species generated upon treatment of oxides of vanadium with hydrogen peroxide is a stronger oxidant than either hydrogen peroxide or V_2O_5 and oxidises a variety of organic substrates.[15] Recently, we have utilised it for the oxidative transformation of aldehydes to esters,[14b] in which, in order to accelerate the reaction, a catalytic quantity of perchloric acid was added to the reaction medium. However, the inherent acidity[14a] generated in the reaction medium by the reaction of V_2O_5 and H_2O_2 was apparently enough to bring about the esterifications although the reaction rates were slow. We decided to test whether the intrinsic acidity originating from V_2O_5–H_2O_2 is sufficient to deprotect acid-sensitive protecting group like acetals and to see if the resulting carbonyl compound, in an alcoholic medium, could be converted into the ester. In this letter, we describe a mild and efficient method for the transformation of both cyclic and acyclic acetals to carbonyl compounds when acetonitrile was used as solvent, and to esters when alcohol was used. We also describe deprotection of other acid-sensitive protecting groups such as THP and TBDMS ethers under similar conditions.

As a test substrate for the oxidative transformation of acetal to ester, benzaldehyde diethyl acetal **1** was chosen. The reaction was performed by dissolving acetal (1 mmol) in methanol (3 mL) to which was added a solution of V_2O_5 (0.04 mmol) dissolved in 30% H_2O_2 (4 mmol) under ice-cold conditions. The reaction times are indicated for each substrate in Table 1.

In most previous cases of acetal to ester transformation, the ester corresponding to the starting acetal were obtained. However, in H_2O_2–HCl-mediated reactions,[10] esters corresponding to solvent alcohol were obtained via a transesterification mechanism. In our case, esters

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Table 1. Oxidative transformation of acetal to methyl ester with V_2O_5–H_2O_2

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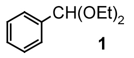
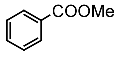
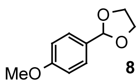
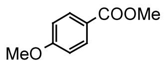
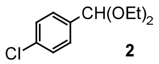
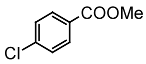
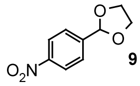
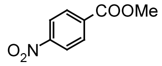
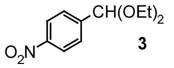
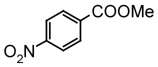
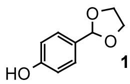
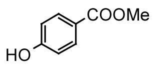
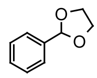
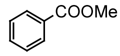
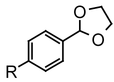
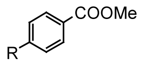
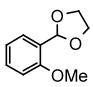
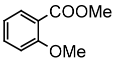
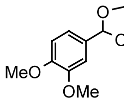
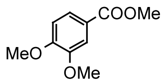
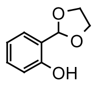
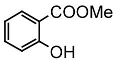
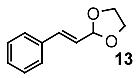
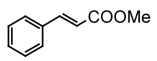
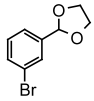
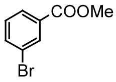
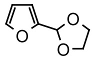
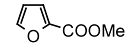
 **1**	4.00		91	 **8**	3.00		95
 **2**	5.00		90	 **9**	0.50		83[c,d]
 **3**	2.00		96[c]	 **10**	3.50		95
 **4**	4.00		92	 **11** R=NHCOCH$_3$	1.50	 R=NHCOCH$_3$	98
 **5**	7.00		93	 **12**	7.00		87[d]
 **6**	5.00		87	 **13**	2.50		94
 **7**	6.00		82[d]	 **14**	9.00		82[d]

[a] Reactions were monitored by TLC, GC. [b] Confirmed by comparison with IR and ^{1}H NMR of the authentic sample. [c] 10 equiv. of 30% H_2O_2 and the reaction was performed at reflux. [d] The balance is aldehyde.

derived only from the solvent, but not by a transesterification path. As expected, the acetal is first deprotected to the corresponding carbonyl compound and the resultant aldehyde is subsequently esterified by a mechanism similar to that proposed earlier.[14b]

Treatment of a wide variety of acetals with V_2O_5–H_2O_2 in methanol gave the corresponding methyl esters in high to excellent yields under mild reaction conditions. Acyclic acetals **1** and **2** were converted to the corresponding methyl esters, however acetal **3** and **9** containing an electron-withdrawing group were reluctant to yield the ester, probably due to difficulty in regeneration of the aldehyde, and also a high activation energy for esterification.[14b] However, good yields were achieved using a 10-fold excess of 30% H_2O_2 under reflux conditions. Cyclic 1,3-dioxolanes **4**–**12** were converted to the corresponding methyl esters in good yields. Double-bond-containing substrate **13**, which is problematic and requires drastic conditions by other methods, yielded an ester by this method. Esterification of 2-furaldehyde in good yields further demonstrates the efficacy of the methodology.

In all the cases examined, reaction times were much longer than in our earlier methodology.[14b] The present one is a two-step process involving a deprotection step followed by an esterification. The pH values recorded at the beginning and after completion of the reaction were ca. 1.86 and 2.06, respectively. In our earlier methodology, the reaction times were relatively shorter, because esterification was directly from the aldehyde. In addition, external acid was also added to the medium because under acidic conditions, peroxo-vanadium species, the active oxidising agent is stable and active.[15a] An acidic medium also prolongs the lifetime of the peroxo species of $MeReO_3$ against reversible decomposition.[13] One of the drawbacks of the previous methodology was over-oxidation of some of the aldehydes giving acids instead of esters. By the present methodology aldehyde is slowly generated in situ from the acetal, and no over-oxidised products were detected.

Since aldehyde generated in the reaction medium and in the presence of methanol is converted to methyl ester, we reasoned that by changing the solvent to acetonitrile it should be possible to isolate the aldehyde. With this objective, acetals (1 mmol) of various aldehydes in acetonitrile (3 mL) were treated with a solution of V_2O_5 (0.04 mmol) dissolved in 30% H_2O_2 (4 mmol) under ice-cold conditions. Aldehydes were regenerated from both cyclic and acyclic acetals in less than 10 min. The results are shown in Table 2. It is interesting to note that the resultant aldehydes do not oxidised further under this conditions, however, after a longer period of time, aldehydes tended to be oxidised to the corresponding acids.

All the acetals described to this point were symmetrical and we thought it interesting to test the oxidation of

Table 2. Deprotection of acetals to aldehydes and THP and TBDMS ethers to corresponding alcohols with V_2O_5–H_2O_2

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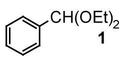
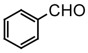
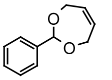
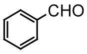
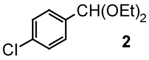
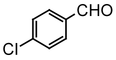
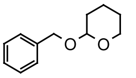
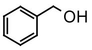
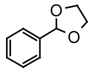
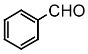
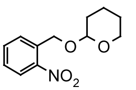
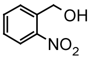
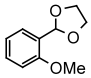
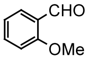
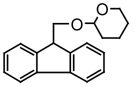
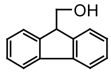
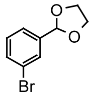
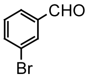
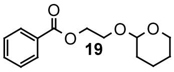
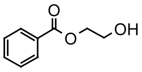
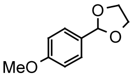
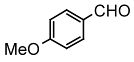
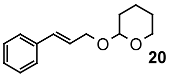
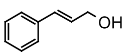
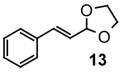
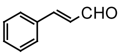
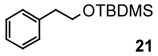
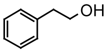
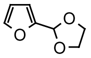
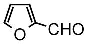
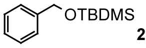
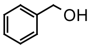
 1	0.16		95	 15	2.00		94
 2	0.16		94	 16	0.25		92[c]
 4	0.16		94	 17	0.25		97[c]
 5	0.16		91	 18	0.25		88[c]
 7	0.16		94	 19	0.25		99[c]
 8	0.16		96	 20	0.25		91[c]
 13	0.16		92	 21	2.00		96
 14	0.16		93	 22	3.50		80[d]

[a]Reactions were monitored by TLC, GC. [b]Confirmed by comparison with IR and ^1H NMR of the authentic sample. [c]The reaction was performed at reflux. [d]The balance is aldehyde.

unsymmetrical acetals such as tetrahydropyranyl derivatives of alcohols. It has been reported that THP ethers when treated with neutral or basic oxidising agents gave rise exclusively to the hydroxy esters[2,6] while treatment with other acidic oxidants[7,16] gave oxidative deprotection. When tetrahydropyranyl ethers of various alcohols were treated under identical conditions with V_2O_5–30% H_2O_2 very poor yields of alcohols were obtained. However, refluxing the reaction mixture can accelerate the deprotection as shown for different tetrahydropyranyl ethers in Table 2. This observation shows that tetrahydropyranyl ethers are more stable compared to either cyclic or acyclic acetals. We further extended this methodology for the deprotection of other acid-sensitive protecting groups such as *tert*-butyldimethylsilyl (TBDMS) ethers. When TBDMS ethers **21** and **22** were treated with a solution of V_2O_5–30% H_2O_2, under ice-cold conditions, alcohols were regenerated in good yields. Surprisingly in the latter case along with the benzyl alcohol some benzaldehyde was also detected, which could originate from the over oxidation of the resultant benzyl alcohol. The present study indicates that TBDMS ethers are more labile compared to THP ethers under acidic conditions, which is consistent with our earlier observation.[17]

In conclusion, the present method represents a simple, rapid way to oxidise acetals to esters and to deprotect THP and TBDMS ethers. The reagent, V_2O_5, is used in catalytic quantity and hydrogen peroxide is a cheap and relatively safe oxidant, which produces only water as the side product. Acetals can be converted to other esters using different primary alcohols. Although procedures already exist for conversion of aldehydes to esters, the simplicity and low cost of our procedure allow it to compete as a practical alternative.

(a) General procedure for the transformation of acetal to ester:

Vanadium pentoxide (7.24 mg, 0.04 mmol) was added to a 30% aq. solution of hydrogen peroxide (0.45 mL, 4 mmol) and left stirring at 0°C until all the vanadium pentoxide dissolved and the solution became reddish brown in colour (approx. 10 min). This was then added to an ice-cold and stirred solution of acetal (1 mmol) in methanol (3 mL). The resulting solution was stirred at ~5°C until TLC and GC detected no starting material. The solvent was removed in vacuo and the residue redissolved in ethyl acetate (20 mL). The organic layer was first washed with 5% aq. sodium bicarbonate solution (5 mL) then with water (5 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate) to afford the product.

(b) General procedure for deprotection of tetrahydropyranyl and TBDMS ethers to alcohols:

The reddish brown V_2O_5 solution obtained as described above was added to a solution of tetrahydropyranyl ether (1 mmol) in acetonitrile (3 mL). The resulting solution was refluxed for 0.25 h. The solvent was removed in vacuo and the residue redissolved in ethyl acetate (20 mL). The organic layer was first washed with 5% aq. sodium bicarbonate solution (5 mL), then with water (5 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, hexane:ethyl acetate) to afford the product.

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