Phosphomolybdic Acid Supported on Silica Gel: An Efficient, Mild and Reusable Catalyst for the Chemoselective Hydrolysis of Acetonides

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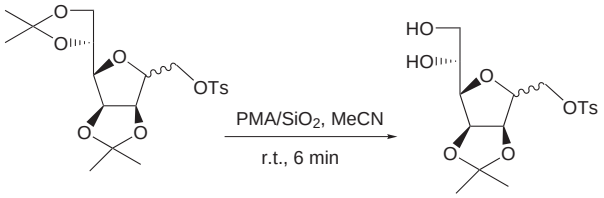
Abstract: Carbohydrate acetonides were chemoselectively cleaved to the corresponding diols by using environmentally benign phosphomolybdic acid ($H_3PMo_{12}O_{40}$) supported on silica gel (PMA–SiO_2) at ambient temperature in a short span of 5–7 minutes in acetonitrile. Acid-labile protective groups such as THP, TBS, TBDPS, MOM, OMe and PMB were found to be stable under the reaction conditions.

Key words: acetonides, phosphomolybdic acid, chemoselective hydrolysis, silica gel

Protecting groups play a very important role in the field of synthetic organic chemistry. Acetonide protection is one of the most frequently used techniques in the multistep synthesis of naturally occurring bioactive molecules for the protection of 1,2-and 1,3-diols.[1] Glucose diacetonide and mannose diacetonides are most extensively used as starting materials in Chiron approach.[2] Chemoselective deprotection of acetonides is an important transformation in the synthetic strategies of biologically active natural products, carbohydrates and nucleosides. Several mineral acid reagents, such as aq HCl,[3a] aq HBr,[3b] aq AcOH,[3c] 0.8% H_2SO_4 in MeOH,[3d] Dowex-H^+ in MeOH–H_2O (9:1),[3e] CF_3COOH,[3f] CSA,[3g] *p*-TsOH[3h] and Lewis acid-based reagents, $FeCl_3·6H_2O/SiO_2$,[4a] $CuCl_2·2H_2O$ in EtOH,[4b] $Zn(NO_3)_2·6H_2O$,[4c] $CeCl_3·7H_2O/(COOH)_2$[4d] and $BiCl_3$[4e] have been reported to cleave this terminal acetonide, but many of these methods suffer from disadvantages like strong acidic conditions, low yields, the need to employ a stoichiometric amount of reagents and long reaction times. Therefore, there is a need to develop a mild and high yielding protocol for the chemoselective hydrolysis of isopropylidene acetals.

Phosphomolybdic acid (PMA) belongs to the class of heteropoly acids (HPA). Catalysis with HPAs is a field of growing importance.[5] HPAs are commercially available, cheap and environmentally friendly catalysts. They exhibit high activities and selectivities and allow cleaner processing over conventional catalysts. HPAs have a very strong Brønsted acidity. In fact, it is reported that HPA has much higher activity than H_2SO_4, TsOH and $BF_3·OEt_2$.[6] Synthetically a variety of methods have been developed using HPAs as a catalyst which are being commercialized.[7] Fries rearrangement of phenyl acetate,[8] Friedel–Crafts acylation of phenols,[9] oxidation of alcohols[10] and regioselective opening of aziridines with nucleophiles have been reported using HPAs.[11]

Herein we wish to report phosphomolybdic acid supported on silica gel (PMA/SiO_2) as an efficient, mild and reusable catalyst for the deprotection of the acetonides. The hydrolysis was achieved by using 1 mol% of PMA/SiO_2 in acetonitrile at ambient temperature within a course of 5–7 minutes (Scheme 1).



Scheme 1

The deprotection proceeded efficiently in high yield with high chemoselectivity. From the blank experiments it was confirmed that the acetonides are stable to silica gel in the absence of PMA. The hydrolysis of acetonides took place even with 1 mol% PMA. For the reusability of the catalyst it has been supported on silica gel. The recovered catalyst was reused for six times without any appreciable loss in catalytic activity and presumably also yields of the products.

Having established the optimum reaction conditions, the deprotection of several representative acetonides was performed to demonstrate the versatility and uniqueness of the present reaction conditions. The acetonide group is selectively cleaved leaving other functional groups including olefins and ethers intact (Table 1). The method is highly chemoselective allowing deprotection of acetonides without effecting other hydroxyl protecting groups such as PMB, THP, MOM, TBS, TBDPS, allyl, propargyl, OBn, OAc, OMe, OTs groups. The systems containing 1,3- and 1,2-acetonide protection have also been investigated. Cleavage of 1,3-acetonides was observed over 1,2-acetonides selectively. The results are summarized in Table 2. The reaction proceeds smoothly and rapidly in commercial grade acetonitrile with the addition of 40 μL of water, which promotes the hydrolysis of acetonides.

In conclusion, we have developed a simple and efficient protocol for the chemoselective hydrolysis of acetonides

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using 1 mol% of PMA/SiO_2 as the catalyst. The advantage of this method is the simplicity of operation, low cost of the reagents, high yields of deprotected products and reusability of the catalyst. Moreover, its compatability with sensitive functionalities such as MOM, THP, MPM, TBS, TBDPS and double bonds with regard to economic and ecological consideration allows us to believe that this method represents a valuable alternative to the existing reagents reported in literature.

Table 1 PMA/SiO_2-Catalyzed Hydrolysis of Acetonides in Acetonitrile at Room Temparature[12]

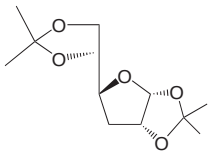
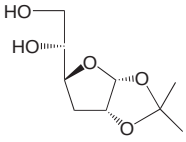
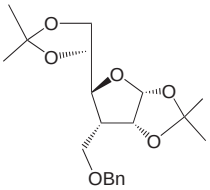
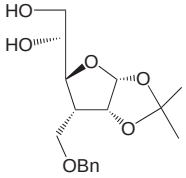
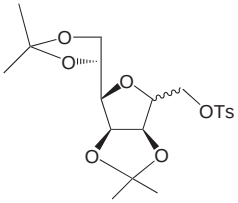
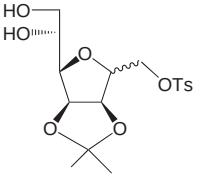
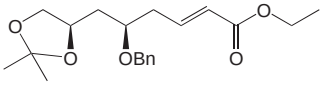
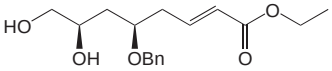
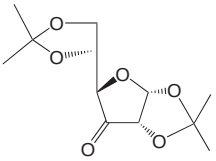
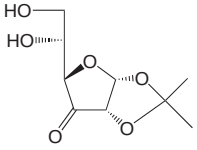
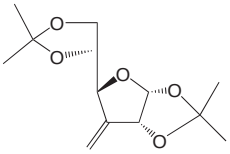
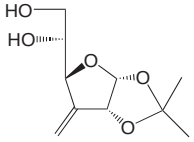
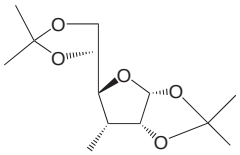
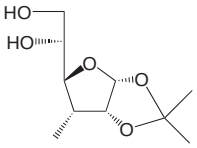
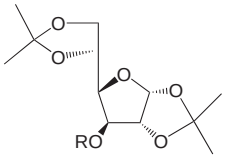
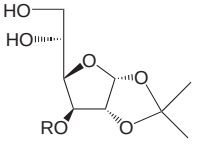
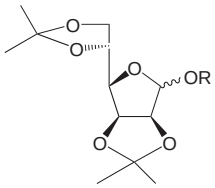
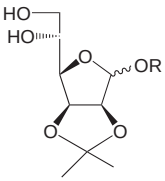
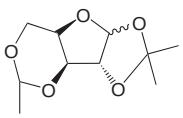
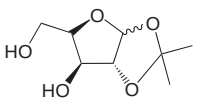
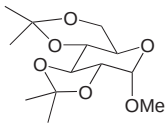
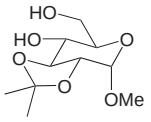
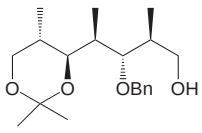
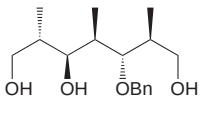
Entry	Substrate	Product[a]	Reaction time (min)	Yield (%)[b]
a			6	94
b			5	92
c			6	92
d			7	90
e			6	95
f			5	92
g			5	94
				
h	R = Ac	R = Ac	5	92
i	R = Bn	R = Bn	5	95
j	R = PMB	R = PMB	6	94

Table 1 PMA/SiO_2-Catalyzed Hydrolysis of Acetonides in Acetonitrile at Room Temparature[12] (continued)

Entry	Substrate	Product[a]	Reaction time (min)	Yield (%)[b]
k	R = All	R = All	5	90
l	R = Propargyl	R = Propargyl	5	90
m	R = MOM	R = MOM	5	93
n	R = TBDPS	R = TBDPS	7	94
o	R = Me	R = Me	5	92
p	R = TBS	R = TBS	7	90
				
q	R = Bn	R = Bn	6	93
r	R = MOM	R = MOM	4	91
s	R = THP	R = THP	5	95
t	R = Propargyl	R = Propargyl	5	90
u	R = All	R = All	4	94
v	R = TBS	R = TBS	5	90
w	R = TBDPS	R = TBDPS	5	89
x	R = Ac	R = Ac	5	92
y	R = PMB	R = PMB	5	90

[a] All products were characterized by ^{1}H NMR spectroscopy and mass spectrometry.
[b] Yield of isolated product.

Table 2 PMA/SiO_2-Catalyzed Hydrolysis of Acetonides in Acetonitrile at Room Temperature

Entry	Substrate	Product[a]	Reaction time (min)	Yield (%)[b]
i			4	90
ii			6	95
iii			5	92

[a] All products were characterized by ^{1}H NMR spectroscopy and mass spectrometry.
[b] Yield of isolated product.

Acknowledgment

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(12) **Typical Experimental Procedure.**
(a) **Preparation of PMA/SiO_2 Catalyst.**
PMA–SiO_2 catalyst was prepared following the published procedure.[11]
(b) **Preparation of Terminal Diols.**
To a solution of glucose diacetonide (260 mg, 1 mmol) in MeCN (2 mL) were added the 1 mol% PMA/SiO_2 (0.01 mmol, based on PMA) followed by 40 μL of H_2O, and the reaction mixture was stirred at ambient temperature for 5–7 min. After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure and the residue was dissolved in THF (2 mL) and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography (100–200 silica gel mesh) using hexane and EtOAc as solvent system to afford the pure diols. The filtered catalyst was reused without prior drying.
Spectral Data.
Entry b: $[\alpha]_D$ +6 (*c* 1.76, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.38 (s, 5 H), 5.75 (d, *J* = 3.8 Hz, 1 H), 4.64 (dd, $J_{1,2} = J_{2,3}$ = 3.7 Hz, 1 H), 4.54 (s, 2 H), 3.40–4.00 (m, 6 H), 2.00–2.40 (m, 1 H), 1.48 (s, 3 H), 1.29 (s, 3 H). MS–FAB: *m/z* = 325.
Entry c: $[\alpha]_D$ +2.8 (*c* 1, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 2 H), 7.38 (d, *J* = 8.0 Hz, 2 H), 4.83 (d, *J* = 7.0 Hz, 1 H), 4.15 (d, *J* = 5.5 Hz, 1 H), 4.05 (d, *J* = 5.5 Hz, 1 H), 3.90 (d, *J* = 5.0 Hz, 1 H), 3.52–3.70 (m, 2 H), 2.60 (br s, 1 H), 2.50 (s, 3 H), 2.00 (br s, 1 H), 1.50 (s, 3 H), 1.32 (s, 3 H). MS–FAB: *m/z* = 389 [M^+ + 1].
Entry d: $[\alpha]_D$ –16.2 (*c* 0.4, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 6.98–6.82 (m, 1 H), 5.85 (d, *J* = 15.6 Hz, 1 H), 4.69 (d, *J* = 11.1 Hz, 1 H), 4.46 (d, *J* = 11.1 Hz, 1 H), 4.18 (q, *J* = 7.4 Hz, 2 H), 3.86–3.78 (m, 2 H), 3.50 (dd, $J_{1,2}$ = 11.1, $J_{2,3}$ = 5.9 Hz, 1 H), 3.35 (dd, $J_{1,2}$ = 11.1 Hz, $J_{2,3}$ = 5.9 Hz, 1 H), 2.52 (t, *J* = 6.7 Hz, 2 H), 1.58–1.43 (m, 2 H), 1.28 (t, *J* = 7.4 Hz, 3 H). MS–FAB: *m/z* = 331 [M^+ + 23], 309 [M^+ + 1].