Highly Regioselective Preparation of 1,3-Dioxolane-4-methanol Derivatives from Glycerol Using Phosphomolybdic Acid

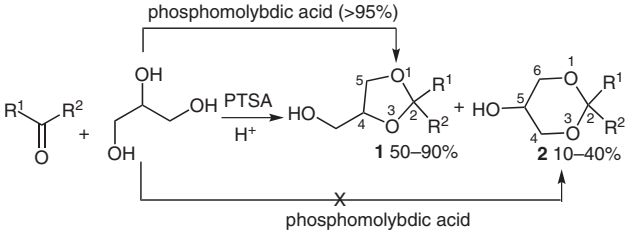
Nitin Wasantrao Fadnavis,* Gowri Sankar Reddipalli, Gadupudi Ramakrishna, Mithilesh Kumar Mishra, Gurrala Sheelu

Biotransformations Laboratory, Discovery Block, Indian Institute of Chemical Technology, Uppal Road, Habsiguda, Hyderabad 500007, India
Fax +91(40)27160512; E-mail: fadnavis@iict.res.in; E-mail: fadnavisnw@yahoo.com
Received 12 September 2008

Abstract: Phosphomolybdic acid (PMA) forms a blue-colored complex with glycerol in a 1:10 molar ratio. The glycerolato complex catalyzes conversion of glycerol into 1,3-dioxolane-4-methanol derivatives with complete regiospecificity in high yields (>95%) and the catalyst can be recycled up to ten times without loss of activity or regiospecificity.

Key words: glycerol, phosphomolybdic acid, complexation, regiospecificity, 1,3-dioxolane-4-methanol

Glycerol is the main byproduct obtained during the production of biodiesel from vegetable oils and about 10 wt% of glycerol is produced during the transesterification process. Increasing biodiesel production around the world is causing a substantial glut in the market for glycerol. Value addition by developing new processes/product lines from glycerol would help the biodiesel industry. Several products, such as surfactants, fuel additives, acrolein, glycerol carbonate, etc., are being produced using glycerol as a platform chemical.[1,2] These are, however, low-value products. Products such as 2,2-dimethyl-1,3-dioxolane-4-methanol (**1a**, solketal) are of relatively high value and are useful as plasticizers, solubilizing and suspending agents in pharmaceutical preparations, lubricants,[3] and fuel additives.[4] Enantiomerically pure forms of 1,3-dioxolane-4-methanol compounds are used in the synthesis of β-blockers, glycerophospholipids, PAF (platelet aggregating factor), (aryloxy)propanolamines, and other products used in the treatment of epilepsy and hypertension.[5] Preparation of such derivatives directly from glycerol is traditionally carried out using a homogeneous acid catalyst (H_2SO_4 or PTSA) and the ketone in large excess.[6] However, glycerol is a triol and its ketalization leads to a mixture of two products, a compound ketalized between positions 1 and 2 (product **1**) and a compound ketalized between positions 1 and 3 (product **2**), which is difficult to separate (Scheme 1).[7] In addition, recovery of the product from the homogeneous catalyst increases costs and produces unnecessary effluent. A reusable, solid acid heterogeneous catalyst with high regiospecificity would be highly desirable for such a reaction.



Scheme 1 Ketalization of glycerol with various ketones in presence of an acid catalyst (PTSA) vs phosphomolybdic acid

Heteropoly acids, such as phosphomolybdic acid (PMA), are commercially inexpensive and environmentally friendly catalysts that exhibit high activity and selectivity.[8] It has been reported that heteropoly acids are several times more active than sulfuric acid, 4-toluenesulfonic acid, boron trifluoride–diethyl ether complex, and zinc chloride[9] and, they can be supported on a solid matrix such as silica gel and recycled several times.[10] Silica gel supported phosphomolybdic acid has been used as an acid catalyst for the chemoselective hydrolysis of acetonides of carbohydrates.[10e] Herein, we report on the feasibility of preparing 1,3-dioxolane derivatives directly from glycerol and ketones using phosphomolybdic acid as a catalyst. The reactions proceed smoothly to give only the five-membered 1,3-dioxolane derivative **1** without side products. All the unconsumed reagents are easily recovered and recycled, the catalyst can be reused several times without loss of activity or regiospecificity, and the overall process is highly environmentally friendly producing very little effluent (Scheme 1).

Phosphomolybdic acid is sparingly soluble in most solvents including water. However, it was found to dissolve in glycerol on heating and form a deep blue complex. The formation of glycerolato complexes between glycerol and metal ions such as zinc, cobalt, and nickel has been previously reported.[11] However, they have been reported to be insoluble in most solvents and have, indeed, been crystallized from water. The glycerol–phosphomolybdic acid complex is found to be fairly soluble in excess glycerol. Elemental analysis of the isolated glycerol–phosphomolybdic acid complex indicates complexation of ten glycerol molecules with one phosphomolybdic acid molecule along with two molecules of water. The infra red spectrum of commercial phosphomolybdic acid exhibits bands in the range 3200–3400 cm^{-1} due to ν(O–H) and ν(H–O–H)

SYNTHESIS 2009, No. 4, pp 0557–0560
Advanced online publication: 09.01.2009
DOI: 10.1055/s-0028-1083319; Art ID: P09808SS

for water of crystallization and constitutional water present in the heteropoly acid. The other major peaks at 1064, 960, and 783 cm^{-1} are due to (P–O_i–Mo), (Mo–O_t), and (Mo–O_b–Mo), where O_i, O_t, and O_b are the inner, terminal, and bridging oxygen atoms, respectively, in the Keggin framework. These bands are shifted to 1090, 980, and 827 cm^{-1} due to complexation with glycerol. The UV-visible spectrum of the glycerol–phosphomolybdic acid complex in acetonitrile shows absorption maxima at 288 and 302 nm due to ligand-to-metal charge-transfer transitions associated with the octahedrally coordinated Mo^{6+} unit and a broad shoulder at 700 nm.[12] Thermogravimetric analysis of the complex shows a loss of 1% in weight up to 110 °C, a major weight loss of 12.9% up to 260 °C, and a further weight loss of 8.5% between 260 °C and 380 °C. This behavior is consistent with loss of water of hydration (1.3%) and carbon (13%).

Direct ketalization of glycerol by various ketones, such as acetone, butan-2-one, cyclopentanone, and cyclohexanone, catalyzed by 4-toluenesulfonic acid gave the desired five-membered dioxolanes **1a–d** with 80–90% selectivity along with 20–10% of six-membered dioxane **2a–f** as a side product. In the case of acetophenone, **1e** was formed with only 50% selectivity. Several other products were also formed in this case and isolation of the desired product was quite tedious. In comparison, preparation of the dioxolanes using glycerol–phosphomolybdic acid complex as catalyst gave dioxolane derivatives **1a–f** with complete regiospecificity.

In a typical experiment, phosphomolybdic acid (0.92 g, 0.5 mmol) and commercial glycerol (11 g, 85% purity, 0.1 mol) were placed in a two-necked round-bottomed flask fitted with a magnetic stirrer and Dean–Stark assembly. Toluene (100 mL) was added and the reaction mixture was refluxed with stirring. Water present in the glycerol was removed as an azeotrope over two hours. The glycerol–phosphomolybdic acid complex was formed in the flask as a deep blue complex. In case of high boiling ketones such as acetophenone, the ketone (0.1 mol) was then added to the reaction flask and the contents were further refluxed with simultaneous azeotropic removal of water. The conversion of ketone into the ketal was followed by GC analysis. After complete conversion, the reactants were cooled to room temperature and the clear toluene layer containing the product was decanted. The insoluble viscous catalyst layer was washed with toluene (2×10 mL) and the combined toluene layers were concentrated on a rotavapor. The ketal was obtained as an oil (>97% pure by GC analysis, yield 96% based on ketone). In the case of relatively low boiling ketones such as acetone and butan-2-one, toluene was decanted after azeotropic removal of excess water from the glycerol–phosphomolybdic acid mixture, and the ketone itself was used as a solvent. Water formed during ketalization was removed via a soxhlet extractor loosely packed with 4 Å molecular sieves. After completion of the reaction (followed by GC), the low boiling solvent was recovered by distillation and the product was extracted from the oily catalyst with toluene. Removal of toluene gave the ketal in 93–95% yield (based on glycerol). The ketals **1a–f** were then further purified by flash chromatography over silica gel for characterization.

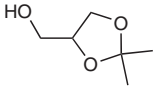
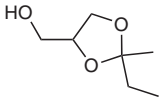
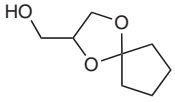
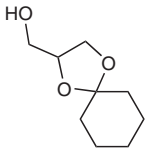
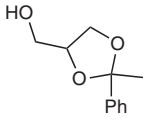
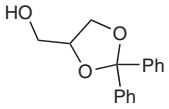
The structure of the product was determined from the ^1H NMR and ^{13}C NMR spectra. The signals in ^1H NMR spectra mostly appear as multiplets due to partial merging of the signals due to the α- and β-isomers that are present in approximately equal concentrations. Similarly, in the ^{13}C NMR spectra, two closely spaced signals are obtained for the same carbon atom. In spite of this, it was easy to distinguish between the five- and six-membered ring products. In ^1H NMR, H4 of the five-membered **1a** (Scheme 1) resonates as a multiplet at δ = 4.18 while H5 of the six-membered **2a** resonates at δ = 3.55. Integration of the proton resonating at δ = 4.18 gave the concentration of five-membered ketal **1a** as 100%. In ^{13}C NMR spectra of the ketals **1a–f**, C4 of the five-membered acetonide resonated around δ = 75–76 while C5 in the six-membered ring resonated at δ = 64 (between the signals of CH_2OH and C5 carbon). Absence of the signal at δ = 64 in the ^{13}C NMR spectra of all the compounds **1a–f** confirmed that phosphomolybdic acid catalyzed ketalization is regiospecific and gives exclusively the five-membered ketals. The results are summarized in Table 1.

The catalyst residue obtained after product extraction with toluene consisted mainly of the catalyst and some unreacted glycerol, which was recycled without isolation or purification with a fresh batch of glycerol and the ketone in the same pot. In the case of solketal **1a**, recycle studies for ten recycles on a 100-gram product scale showed that the catalyst can be reused at least ten times without loss of activity or regioselectivity.

In conclusion, phosphomolybdic acid can be used as an efficient regiospecific catalyst for the preparation of ketals of glycerol in high yields. A molar ratio of 1:200 of catalyst to substrate is enough to carry out the reaction within 6–20 hours depending on the ketone. Additionally, it is not necessary to support the catalyst on a solid surface. At the end of reaction, the toluene soluble product is separated from insoluble heavy catalyst by simple decantation and the catalyst is reused for several recycles without removal from the reactor or any purification.

Commercially available chemicals were reagent grade and were redistilled before use. ^1H NMR spectra were recorded with a Bruker Avance DPX 300 spectrometer at 300 MHz using TMS as an internal standard. ^{13}C NMR spectra were recorded on the same instrument at 75 MHz and are referenced against the central line of the solvent signal ($CDCl_3$ triplet at δ = 77.0). IR spectra were obtained with a Bio-Rad FTS 3000MX. Mass spectra were recorded with a Finnigan Mat 1210 spectrometer. Elemental analyses (C, H, N) were performed with a Perkin Elmer 2400 Series II CHNS/O Analyzer. GC analysis was carried out on Shimadzu 2010 GC unit using DB-5 capillary column (J & W Scientific, 30 m, 0.25 mm ID). Analysis conditions were as follows: injector temperature: 300 °C; detector temp. 310 °C, column pressure 100 kPa. Analysis program: inject 100 °C, hold 1 min, ramping 5 °C/min up to 150 °C; hold 2 min; ramping 10 °C/min up to 250 °C, hold for 7 min.

Table 1 Phosphomolybdic Acid Catalyzed Preparation of 1,3-Dioxolane-4-methanol Derivatives from Glycerol and Ketones

Substrate	Product		Solvent	Time (h)	Isolated yield (%)
acetone	**1a**		acetone	6	95
butan-2-one	**1b**		butan-2-one	6	94
cyclopentanone	**1c**		toluene	6	93
cyclohexanone	**1d**		toluene	6	95
acetophenone	**1e**		toluene	18	96
benzophenone	**1f**		toluene	18	96

2,2-Dimethyl-1,3-dioxolane-4-methanol (1a); Typical Procedure

Phosphomolybdic acid (PMA) (9.2 g, 5 mmol) and commercial glycerol (110 g, 1 mol based on 85% purity) were placed in a 2-L 2-necked round-bottomed flask fitted with a mechanical stirrer and Dean–Stark assembly. Toluene (300 mL) was added and the mixture was refluxed with stirring at 100 rpm. H_2O present in glycerol was removed as an azeotrope over 2 h. The glycerol–PMA complex was formed in the flask as a deep blue viscous slurry. The flask was cooled to r.t. and toluene was decanted. The side arm of the Dean–Stark assembly was loosely packed with 4 Å molecular sieves, acetone (1 L) was then added, and the mixture was refluxed with stirring. The reaction was followed by GC analysis of the acetone layer. When the reaction was complete (6–8 h), acetone was recovered by distillation and collected from the side arm. Toluene (200 mL) was added, the contents were stirred for 5 min, the layers were allowed to separate, and the toluene layer was decanted. The procedure was repeated twice to extract the product into the toluene layer. Removal of toluene gave the acetonide **1a**. The catalyst slurry was reused for the next cycle without removing it from the flask. The catalyst was recycled 10 times without losing activity or selectivity. In each run 105–110 g of product (93–95% yield based on 85% pure glycerol) was obtained; GC: t_R = 3.02 (**1a**), 3.17 (**2a**) min.

IR ($CHCl_3$): 3430 (br), 2986, 2937, 2887, 2363, 1376, 1254, 1214, 1156, 1051, 973, 843 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.18 (m, 1 H), 4.00 (dd, *J* = 8.31, 6.80 Hz, 1 H), 3.76 (dd, *J* = 8.31, 6.80 Hz, 1 H), 3.68 (dd, *J* = 11.33, 3.78 Hz, 1 H), 3.54 (dd, *J* = 11.33, 5.29 Hz, 1 H), 1.80 (br s, 1 H), 1.38 (s, 3 H), 1.20 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.28 (C2), 76.11 (C4), 65.66 (C5), 62.86 (CH_2OH), 26.54 and 25.11 (Me).

MS: *m*/*z* = 133 (M + 1).

2-Ethyl-2-methyl-1,3-dioxolane-4-methanol (1b)

GC: t_R = 4.0 (**1b**), 3.26 (**2b**) min.

IR ($CHCl_3$): 3434 (br), 2977, 2937, 2885, 1378, 1338, 1191, 1135, 1077, 936, 877 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.28–4.11 (m, 1 H), 4.05–3.95 (m, 1 H), 3.85–3.70 (m, 2 H), 3.51–3.61 (m, 1 H), 1.85 (br s, 1 H), 1.76–1.60 (m, 2 H), 1.30 and 1.36 (2 s, 3 H), 1.0–0.90 (m, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 111.53 and 111.21 (C2), 76.53 and 75.84 (C4), 65.8 (C5), 63.08 and 62.90 (CH_2OH), 32.51 and 31.59 (CH_2CH_3), 24. 13 and 23.08 (Me), 8.42 and 8.15 (CH_3CH_2).

MS: *m*/*z* =147 (M + 1).

1,4-Dioxaspiro[4.4]nonane-2-methanol (1c)

GC: t_R = 7.34 (**1c**), 7.89 (**2c**) min.

IR ($CHCl_3$): 3438 (br), 2957, 2877, 1336, 1204, 1107, 1041, 973, 860 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.19–4.10 (m, 1 H), 3.98–3.92 (m, 1 H), 3.78–3.66 (m, 3 H), 3.60–3.52 (m, 1 H), 1.90–1.70 (m, 8 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 110.4 (C2), 72.42 (C4), 65.31 (C5), 62.99 (CH_2OH), 38.34 and 23.21 (cyclopentyl).

MS: *m*/*z* = 159 (M + 1).

1,4-Dioxaspiro[4.5]decane-2-methanol (1d)

GC: t_R = 9.25 (**1d**), 10.22 (**2d**) min.

IR ($CHCl_3$): 3443 (br), 2935, 2862, 1161, 1103, 1043, 932 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 4.23–4.13 (m, 1 H), 4.04–3.96 (m, 1 H), 3.78–3.64 (m, 2 H), 3.58–3.45 (m, 1 H), 2.10 (br s, 1 H), 1.66–1.20 (m, 10 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 109.93 (C2), 75.71 (C4), 65.33 (C5), 63.08 (CH_2OH), 36.35, 34.72, 25.06, 23.94, 23.71 (cyclohexyl).

MS: m/z = 173 (M + 1).

2-Methyl-2-phenyl-1,3-dioxolane-4-methanol (1e)
GC: t_R = 12.42 and 12.56 (**1e**), 16.06 and 16.22 (**2e**) min.

IR ($CHCl_3$): 3358 (br), 2925, 2358, 1216, 1042 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.22 (m, 5 H), 4.39–4.29 (m, 1 H), 4.20–4.01 (m, 1 H), 3.90–3.55 (m, 3 H), 1.80 (br s, 1 H), 1.60 and 1.65 (2 s, 3 H).

^{13}C NMR(75 MHz, $CDCl_3$): δ = 142.98, 128.20, 127.88, 125.21 (C_{Ph}), 109.63 (C2), 75.96 (C4), 66.19 and 65.69 (C5), 63.35 and 62.82 (CH_2OH), 28.09 and 27.95 (CH_3).

MS: m/z = 195 (M + 1).

2,2-Diphenyl-1,3-dioxolane-4-methanol (1f)
IR ($CHCl_3$): 3436 (br), 3059, 2939, 2888, 1262, 1207, 1088, 1027, 995 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.56–7.23 (m, 10 H), 4.37–4.27 (m, 1 H), 4.06–3.96 (m, 2 H), 3.84–3.76 (m, 1 H), 3.68–3.58 (m, 1 H), 1.80–1.75 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.94, 128.17, 126.18, 125.97 (C_{Ph}), 110.04 (C2), 76.36 (C4), 66.19 (C5), 63.08 (CH_2OH).

MS: m/z = 257 (M + 1).

PMA–Glycerol Complex
The dark blue PMA–glycerol complex recovered after the reaction with acetone was washed with a large excess of boiling acetone (2 ×) and the blue-black powder was dried under vacuum at 60 °C for 12 h (13 g, 95%). Elemental analysis indicates complexation of 10 glycerol molecules and 2 H_2O molecules with one PMA molecule.

Anal. Calcd for $C_{30}H_{67}Mo_{12}O_{72}P$: C, 13.03; H, 2.42; Mo, 41.71; P, 1.12. Found: C, 13.01; H, 2.51; Mo, 35.3; P, 1.14.

Due to inherent nature of heteropoly acids, the phosphorus/molybdenum ratio is not exact.

Acknowledgment

We thank the Council of Scientific and Industrial Research (CSIR), New Delhi and the University Grants Commission (UGC) for financial support.

References

(1) (a) Pagliaro, M.; Ciriminna, R.; Kimura, H.; Rossi, M.; Pina, C. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4434. (b) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411. (c) Armaroli, N.; Balzani, V. *Angew. Chem. Int. Ed.* **2007**, *46*, 52. (d) Chheda, J. N.; Huber, G. W.; Dumesic, J. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 7164.
(2) (a) Klepacova, K.; Mravec, D.; Kaszonyi, A.; Bajus, M. *Appl. Catal., A* **2007**, *328*, 1. (b) Ott, L.; Bicker, M.; Vogel, H. *Green Chem.* **2006**, *8*, 214. (c) Chai, S.-H.; Wang, H.-P.; Liang, Y.; Xu, B.-Q. *Green Chem.* **2007**, *9*, 1130.
(3) Walsh, R. H. US 5268007, **1993**.
(4) Seemuth, P. D. US 4457763, **1984**.
(5) Jurczac, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
(6) He, D. Y.; Li, Z. J.; Liu, Y. Q.; Qiu, D. X.; Cai, M. S. *Synth. Commun.* **1992**, *22*, 2653.
(7) (a) Kazumasa, H.; Furukawa, Y. US 6143908, **2000**. (b) Kazumasa, H.; Furukawa, Y. US 6124479, **2000**.
(8) (a) Kozhevnikow, I. V. *Chem. Rev.* **1998**, *98*, 171. (b) Mizuno, N.; Misono, M. *Chem. Rev.* **1998**, *98*, 199. (c) Misono, M.; Ono, K.; Aoshima, G. A. *Pure Appl. Chem.* **2000**, *72*, 1305.
(9) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.
(10) (a) Izumi, Y.; Hasebe, R.; Urabe, K. *J. Catal.* **1983**, *84*, 402. (b) Yadav, J. S.; Satyanarayana, M.; Balanarsaiah, E.; Raghavendra, S. *Tetrahedron Lett.* **2006**, *47*, 6095. (c) Nagaiah, K.; Sreenu, D.; Srinivasa Rao, R.; Vashishta, G.; Yadav, J. S. *Tetrahedron Lett.* **2006**, *47*, 4409. (d) Abd El-Wahab, M. M. M.; Said, A. A. *J Mol. Catal. A: Chem.* **2005**, *240*, 109. (e) Yadav, J. S.; Raghavendra, S.; Satyanarayana, M.; Balanarsaiah, E. *Synlett* **2005**, 2461.
(11) (a) Radoslovich, E. W.; Raupach, M.; Slade, P. G.; Taylor, R. M. *Aust. J. Chem.* **1970**, *23*, 1963. (b) Taylor, R. M.; Brock, A. J. US 4544761, **1985**.
(12) Tsigdinos, G. A.; Hallada, C. J. *Inorg. Chem.* **1968**, *7*, 437.