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

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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 treatment of epilepsy and hypertension.5 Preparation of such derivatives directly from glycerol is traditionally carried out using a homogeneous acid catalyst (H2SO4 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.

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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 chloride9 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 v(O–H) and v(H–O–H)

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

[Diagram showing ketalization reactions]
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 (\(P\text{–}O\text{–}Mo\), (Mo–O), (Mo–O\(_2\)–Mo), where \(O\), \(O\(_2\)\), and \(O\(_3\)\) 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–phosphomolydbic 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, the dioxolanes using glycerol–phosphomolydbic acid complex as catalyst gave dioxolane derivatives 1a–f with complete regiospecificity.

In a typical experiment, phosphomolydbic 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–phosphomolydbic 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 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.

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, phosphomolydbic 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 was easy to distinguish between the five- and six-membered ring products. In ¹H NMR, H4 of the five-membered ketal 1a (Scheme 1) resonates as a multiplet at \(\delta = 4.18\) while H5 of the six-membered 2a resonates at \(\delta = 3.55\). Integration of the proton resonating at \(\delta = 4.18\) gave the concentration of five-membered ketal 1a as 100\%. In ¹³C NMR spectra of the ketals 1a–f, C4 of the five-membered acetonedie resonated around \(\delta = 75–76\) while C5 in the six-membered ring resonated at \(\delta = 64\) (between the signals of CH\(_2\)OH and C5 carbon). Absence of the signal at \(\delta = 64\) in the ¹³C NMR spectra of all the compounds 1a–f confirmed that phosphomolydbic acid catalyzed ketalization is regiospecific and gives exclusively the five-membered ketals. The results are summarized in Table 1.

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. ¹³C 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 \(\delta = 77.0\)). 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 CHN/SO 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.
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. H2O 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: tR = 3.02 (1a), 3.17 (2a) min.

IR (CHCl3): 3430 (br), 2986, 2937, 2887, 2363, 1376, 1254, 1214, 1156, 1051, 973, 843 cm–1.

1H NMR (300 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): δ = 109.28 (C2), 76.11 (C4), 65.66 (C5), 62.86 (CH2OH), 26.54 and 25.11 (Me).

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

2-Ethyl-2-methyl-1,3-dioxolane-4-methanol (1b)
GC: tR = 4.0 (1b), 3.26 (2b) min.

IR (CHCl3): 3434 (br), 2977, 2937, 2885, 1378, 1338, 1191, 1135, 1077, 936, 877 cm–1.

1H NMR (300 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): δ = 111.53 and 111.21 (C2), 76.53 and 75.84 (C4), 65.8 (C5), 63.08 and 62.90 (CH2OH), 32.51 and 31.59 (CH2CH3), 24.13 and 23.08 (Me), 8.42 and 8.15 (CH3CH2).

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

1,4-Dioxaspiro[4.4]nonane-2-methanol (1c)
GC: tR = 7.34 (1c), 7.89 (2c) min.

IR (CHCl3): 3438 (br), 2957, 2877, 1336, 1204, 1107, 1041, 973, 860 cm–1.

1H NMR (300 MHz, CDCl3): δ = 4.19–4.10 (m, 1 H), 3.98–3.92 (m, 1 H), 3.78–3.66 (m, 3 H), 3.58–3.45 (m, 1 H), 1.90–1.70 (m, 8 H).

13C NMR (75 MHz, CDCl3): δ = 110.4 (C2), 72.42 (C4), 65.31 (C5), 62.99 (CH2OH), 38.34 and 23.21 (cyclopentyl).

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

1,4-Dioxaspiro[4.5]decane-2-methanol (1d)
GC: tR = 9.25 (1d), 10.22 (2d) min.

IR (CHCl3): 3443 (br), 2935, 2862, 1161, 1103, 1043, 932 cm–1.

1H NMR (300 MHz, CDCl3): 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).

13C NMR (75 MHz, CDCl3): δ = 110.4 (C2), 72.42 (C4), 65.31 (C5), 62.99 (CH2OH), 38.34 and 23.21 (cyclohexyl).

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

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

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetone</td>
<td>1a</td>
<td>acetone</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>butan-2-one</td>
<td>1b</td>
<td>butan-2-one</td>
<td>6</td>
<td>94</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>1c</td>
<td>toluene</td>
<td>6</td>
<td>93</td>
</tr>
<tr>
<td>cyclohexanone</td>
<td>1d</td>
<td>toluene</td>
<td>6</td>
<td>95</td>
</tr>
<tr>
<td>acetonaphone</td>
<td>1e</td>
<td>toluene</td>
<td>18</td>
<td>96</td>
</tr>
<tr>
<td>benzophenone</td>
<td>1f</td>
<td>toluene</td>
<td>18</td>
<td>96</td>
</tr>
</tbody>
</table>

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