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Short Communication

Synthesis of Benzylidene-Protected Dihydroxyacetone

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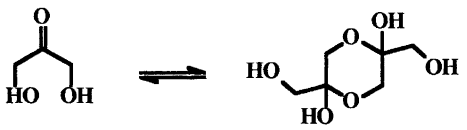
A potentially useful C_3-synthon is 1,3-dihydroxyacetone. However, the compound is unstable, as it, e.g., exists in an equilibrium with its dimer (Scheme 1). It has found



Scheme 1.

synthetic application, e.g., in the synthesis of carbohydrates,[1] of heterocycles[2] and serinol derivatives.[3] The value of dihydroxyacetone is particularly associated with reactivity at the carbonyl group. Thus, the α-carbons may be subject to alkylation and functionalization, or the carbonyl group may undergo carbonyl group transformation. However, to do this, the hydroxy groups need to be blocked. Protection of the hydroxy functions will hinder dimer formation and eliminate the possibility of rearrangement reactions, e.g., formation of pyruvaldehyde[4] or lactic acid.[5] This can be accomplished by acetal or ketal formation. Syntheses of ketals[6] and acetals[7] of dihydroxyacetone have been reported, and synthetic use was reported by, e.g., Enders *et al.*, who used dihydroxyacetone acetonide in conjunction with chiral auxiliaries for enantioselective alkylation.[8]

The reason for dihydroxyacetone not having found more extensive synthetic use may be ascribed to the fact that the desired acetals and ketals have not been generally available. Synthesis of, e.g., 1,3-di-*O*-benzylidenedihydroxyacetone, **3**, in reasonable yield has not yet appeared in the literature. We here report a convenient and inexpensive procedure for the large-scale preparation of **3** starting from glycerol and benzaldehyde.

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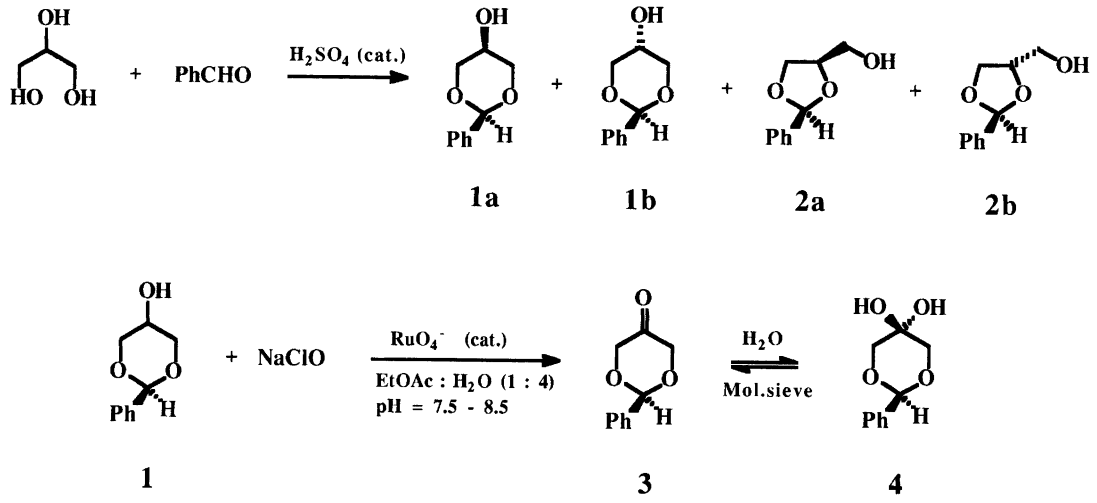
Results and discussion

Using a modification of the method previously described by Hibbert *et al.*,[9] glycerol and benzaldehyde were reacted in the presence of catalytic amounts of sulfuric acid, yielding a mixture of the 1,3-dioxanes **1** and 1,3-dioxolanes **2**, Scheme 2. Formation of the undesired five-membered products could not be suppressed. Typically the ratio of **1**:**2** was about 5:4. The *cis*-compound **1a** was the predominant product. The composition was measured by GLC analysis or by integration of the characteristic. ^{1}H NMR spectral peaks, (**1a**, δ 5.54; **1b**, δ 5.39; **2a**, δ 5.95; **2b**, δ 5.81). This was in good agreement with the composition reported by Serdarevich.[10] The structures of the **1**-isomers and their spectroscopic properties have been discussed by a number of groups.[11]

Compounds **1** were isolated by crystallization of the crude product from diethyl ether at −25 °C, yielding 21% of **1** (better than 90% pure by GLC, containing 6–7% of **2**). Compound **1a** was the predominant product, and was obtained pure after one additional crystallization from diethyl ether. By this procedure the desired 1,3-dioxanes were separated from the mixture of products. To improve the overall yield of **1**, the mother liquor was then concentrated, and further **1** was obtained after acid-catalyzed equilibration and subsequent crystallization. The isomerization of analogous 1,3-dioxolanes to the corresponding 1,3-dioxanes has been studied by Aksnes *et al.*[12] It was noted that 1,3-dioxane formation was favored at low temperature. The continuous recycling of the reaction mixture through the equilibration/crystallization procedure made it possible to transform most of the material into product **1**. The combined yield after two cycles was 46%.

The mixture of 2-phenyl-5-hydroxy-1,3-dioxanes, **1**, was next oxidized to the benzylidene-protected dihydroxyacetone, **3**. A number of oxidation reagents were tested (Ag-picolinate,[13] PCC, Swern oxidation, sodium hypochlorite).[14] However, the most convenient method was oxidation with sodium hypochlorite in the presence of a Ru-catalyst, (e.g., $RuO_2 \cdot H_2O$), Scheme 2. The re-



Scheme 2.

action was carried out using a 1:4 mixture of ethyl acetate–water as the solvent and keeping the pH in the range 7.5–8.5. At this pH, the active Ru-species in the catalytic oxidation was assumed to be mainly perruthenate, RuO_4^-, and, we believe, to some extent also ruthenium tetraoxide, RuO_4. At higher pH the ruthenate anion, RuO_4^{2-}, predominates.[15] Under these conditions **3** was obtained in good yield as the exclusive product. The starting alcohol contained varying amounts (4–7%) of the five-membered alcohols, **2**. However, this had no effect on the purity of the products, as compounds related to **2** were not observed. This was attributed to an oxidative degradation of **2**, hence relatively crude samples of **1** may be used. Pure **3** was obtained after recrystallization, either as the free ketone or the stable hydrate, **4**.

Experimental

^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX400 FT NMR instrument in $CDCl_3$ using tetramethylsilane, TMS, as the internal standard. IR spectra were obtained using a Nicolet 20-SXC FT-IR spectrometer. Mass spectra were recorded on an AEI MS-902 spectrometer at 70 eV (IP) and 200°C inlet temperature. GLC analyses were performed on a Varian 3700 gas chromatograph equipped with BP-1 or BP-5 capillary columns (25 m). Melting points are uncorrected.

5-Hydroxy-2-phenyl-1,3-dioxane, **1**. A mixture of glycerol (10.85 mol, 1000 g) and benzaldehyde (9.53 mol, 1000 g) and catalytic amounts of concentrated sulfuric acid (1.0 ml) was stirred at room temperature for 4 h and then heated at 40–45°C under reduced pressure (10 mmHg). The water formed during the condensation reaction was removed by distillation as an azeotrope with benzaldehyde, which at intervals was reintroduced into the reaction mixture. After ≈4 h no more water was formed and the mixture then appeared as a clear, slightly yellow solution, which was cooled to room temperature, and stirred for a further 1 h. Diethyl ether (1.5 l) was then added, the resulting solution was washed with a 10% sodium carbonate solution (2 × 0.3 l), brine (0.3 l), dried over anhydrous sodium sulfate (to which was added 10 g of anhydrous potassium carbonate) and filtered. GLC analysis and ^1H NMR spectral measurements indicate that the crude product was typically composed of **1a** (31%), **1b** (22%), **2a** (22%) and **2b** (19%) together with 7% benzaldehyde. 1.0 l of diethyl ether was then added and the solution placed overnight in a freezer at −25°C. The precipitate was isolated by filtration, yielding 365 g of a white crystalline product which was identified as mainly **1a** (90%) together with **1b** (3%) and 6% **2**.

The mother liquor, which typically contained 13% **1a**, 24% **1b**, 24% **2a**, 21% **2b** and 15% benzaldehyde (by GLC), was then concentrated under reduced pressure. The crude mixture was treated with 100 ml of dry glycerol and sulfuric acid (1 ml, conc.), and stirred for 4 h at room temperature. At this point the mixture contained 33% **1a**, 22% **1b**, 14% **2a**, 13% **2b** and 18% benzaldehyde. The product mixture was treated with diethyl ether (2.0 l), extracted with 10% sodium carbonate solution (2 × 0.2 l), and brine (0.2 l), dried over anhydrous sodium sulfate (to which was added 5 g of anhydrous potassium carbonate) and filtered. The organic solution was then placed overnight in a freezer at −25°C. The precipitate was isolated by filtration, yielding 430 g of a mixture containing 82% **1a**, 10% **1b** and 8% **2**.

The combined yield of **1** was 795 g, 46% after drying *in vacuo*. Crystallization this product from diethyl ether gave pure **1a** as a white crystalline product with m.p. 82–83°C and the following spectroscopic properties, (product **1a**): ^1H NMR (400 MHz, $CDCl_3$): δ 3.15 (d, J = 10.0 Hz, 1 H, OH), 3.58 (brd, J = 10.0 Hz, 1 H), 4.09 (dd, J = 12.0 and 1.5 Hz, 2 H), 4.17 (dd, J = 12.0 Hz and 1.5 Hz, 2 H), 5.54 (s, 1 H), 7.36 (m, 3 H), 7.49 (m, 2 H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 64.0, 72.3, 101.7, 125.9, 128.3, 129.1, 137.9 ppm; IR (KBr): 3285 and 3190 (brd), 2987, 2920, 2855, 1452, 1391, 1340, 1279, 1239, 1231, 1156, 1089, 1017, 996, 977, 948, 930, 831, 808, 741 cm^{-1}; MS [*m/z* (% rel. int.)]: 180 (71, M^+), 179 (68), 149 (8), 108 (10), 107 (100), 106 (16), 105 (65), 103 (17), 91 (21), 79 (38), 78 (10), 77 (46), 57 (12), 51 (14).

2-Phenyl-1,3-dioxan-5-one, **3**. A slurry of ruthenium dioxide hydrate (254 mg, 1.7 mmol) in water (10 ml) was oxidized with aqueous sodium hypochlorite solution (12%). Ethyl acetate (100 ml), water (400 ml) and **1** (18.0 g) (82.4% pure, containing 6% **2** and 1% benzaldehyde as impurities) were then added. Sodium hypochlorite (12%) was added to the well stirred reaction mixture at a rate of 6.0–6.5 ml min^{-1}. During the reaction the pH was maintained at 7.5–8.5 by addition of sodium hydroxide solution (20%) using an automatic pH-stat. After approx. 30 min the reaction ceased and the addition of sodium hypochlorite was stopped. The reaction mixture was then extracted with ethyl acetate (5 × 100 ml), the organic phase was dried over anhydrous magnesium sulfate, together with 1 g of cellulose powder to remove oxidizing ruthenium species, and the solvent was then evaporated off under reduced pressure. GLC analysis indicated **3** to be the exclusive product. Recrystallization from (wet) diethyl ether (300 ml), gave pure **4**. The yield was 12.3 g, 76%. Pure **3** was best obtained by treatment of a solution of **4** in diethyl ether with molecular sieves (3 Å), but was in general formed in anhydrous solutions. The products exhibited the following properties.

2-Phenyl-1,3-dioxan-5-one, **3**. M.p. 35–36°C. ^{1}H NMR (400 MHz, dioxane-d_8): δ 4.43 and 4.48 (AB-pattern, J_{AB} = 17.6 Hz, 2 H), 5.85 (s, 1 H), 7.36 (m, 3 H), 7.47 (m, 2 H); ^{13}C NMR (100 MHz, dioxane-d_8): δ 72.8, 99.0, 126.5, 128.4, 129.2, 138.2, 204.1; IR (neat): 3035, 2977, 2825, 1741, 1454, 1420, 1388, 1214, 1125, 1048, 986, 971, 926, 744, 697 cm^{-1}; MS [*m/z* (% rel.int.)]: 178 (44, M^+), 177 (9), 148 (61), 120 (37), 119 (30), 107 (8), 106 (42), 105 (100), 92 (22), 91 (36), 90 (45), 89 (20), 77 (38), 51 (21).

2-Phenyl-5,5-dihydroxy-1,3-dioxane, **4**. M.p. 85–87°C. ^{1}H NMR (400 MHz, dioxane-d_8), 10% D_2O): δ 3.75 and 3.86 (AB-pattern, J_{AB} = 11.0 Hz, 2 H), 5.43 (s, 1 H), 7.33 (m, 3 H), 7.45 (m, 2 H); ^{13}C NMR (100 MHz, dioxane-d_8, 10% D_2O): δ 74.9, 87.0, 101.6, 127.0, 128.5, 129.2, 139.0; IR (KBr): 3238 (brd), 3061, 2963, 2863, 1451, 1387, 1321, 1289, 1239, 1213, 1168, 1103, 1073, 1034, 985, 964, 932, 818, 742, 696 cm^{-1}; MS [*m/z* (% rel.int.)]: Identical with the mass spectrum of **3**.

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