A New, Facile Synthesis of Methyltartronic Acid

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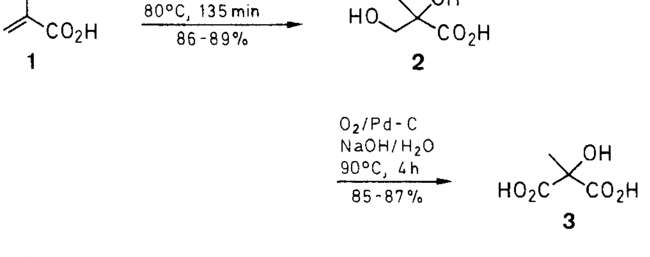
A simple two-step approach to methyltartronic acid (2-hydroxy-2-methylpropanedioic acid, **3**) from methacrylic acid (**1**) via α-methylglyceric acid (**2**) is described. It is based on the successive use of hydrogen peroxide and oxygen as oxidants in the same aqueous medium, in combination with tungstic acid and palladium on carbon as catalysts, respectively.

Methyltartronic acid (2-hydroxy-2-methylpropanedioic acid, **3**) is a valuable compound that is used as a soil-corrective,[2] for pickling and descaling metal surfaces,[3] as a food acidulant,[4] and for the manufacture of water-absorbent materials.[5] Besides, its alkyl esters find application as non-toxic plasticizers for polyvinyl chloride,[6] in the preparation of detergent builders,[7] and as intermediates for the synthesis of oxazolidine derivatives having analgesic or pesticidal activity.[8]

A number of methods for preparing methyltartronic acid (**3**) or its alkyl esters are known. They involve the addition of hydrogen cyanide to pyruvic acid,[9] isonitrosoacetone,[10] ketene,[11] or acetic anhydride[12] followed by acid hydro(alcoho)lysis[13] of the resulting cyano derivative, the oxidation of alkyl methylmalonates by potassium permanganate,[14] nitric acid,[15] or oxygen in the presence of a metal catalyst,[16] the rearrangement and hydrolysis of 2,3-dioxobutyrates in strong alkali,[17] and the treatment of α-bromo-α-methylmalonic acid with silver oxide[18] or aqueous barium hydroxide.[19] All these methods are either laborious, or provide low yields, or use expensive and/or toxic and hazardous reagents, or require large amounts of oxidants that cause waste and pollution problems.

We were interested in devising an inexpensive, safe, and non-polluting route to the title compound. Our continuing work on selective oxidative processes with hydrogen peroxide catalyzed by tungsten compounds[20–24] led us to consider a novel approach to **3** connected with this kind of chemistry and using methacrylic acid (**1**) as the starting material. Accordingly, dihydroxylation of **1**, via epoxidation–hydrolysis, with aqueous hydrogen peroxide catalyzed by tungstic acid would give α-methylglyceric acid (2,3-dihydroxy-2-methylpropanoic acid, **2**), which on further oxidation would afford the desired acid **3**.



The hydrogen peroxide/tungstic acid oxidizing system, however, while effective for the first step, was inadequate for the second one, as it was expected to cause C–C bond cleavage of **2**, a *vic*-diol.[22]

Among the few oxidizing agents known to selectively convert hydroxymethyl into carboxy groups in *vic*-diols with no appreciable cleavage,[25–27] dioxygen in the presence of a platinum-group metal catalyst in the liquid phase[26,27] looked the most attractive one, and its action on crude, isolated **2** was investigated. Accordingly, **2** was oxidized to **3** by oxygen over 5% palladium on carbon in alkaline medium. However, the oxidation was hardly reproducible, suggesting catalyst poisoning. This was found to be caused by the sodium sulfite[28] used in the workup of **2** to decompose unconverted hydrogen peroxide. We then tried to obtain **3** from **1** directly, without isolating **2**, by the successive use of hydrogen peroxide and oxygen oxidants with the respective tungstic acid and palladium catalysts in the same reaction medium. We were successful and could thus develop a simple, cheap, and efficient one-pot two-step synthesis of **3** from **1** via **2** at atmospheric pressure and under mild conditions.

The details of the synthesis are described in the experimental section. In brief, it consists in reacting very dilute (4–5%) aqueous hydrogen peroxide with a slight excess of **1** at 80 °C in the presence of catalytic amounts of tungstic acid, followed by passing oxygen through the olefin-free solution made strongly alkaline with sodium hydroxide and containing the palladium catalyst at 90 °C. Conventional workup of the basic solution affords analytically pure methyltartronic acid (**3**) in an overall yield of 75–77% based on hydrogen peroxide, with an 83–85% selectivity on the olefin. Under the experimental conditions adopted, oxidation of intermediate **2** to **3** was complete in 4 hours, whereas 135 minutes were required to perform dihydroxylation of **1**. Decomposition of unreacted hydrogen peroxide ($\sim$4%) in the basic medium occurred smoothly on addition of the palladium catalyst. The palladium catalyst could be used several times without reduction in yield and rate. Replacement of oxygen with air caused a substantial prolongation of the reaction time (15 hours instead of 4, with thrice the gasflow rate), while only a modest decrease (4–5%) in the yield and selectivity was observed.

A few points were found to be crucial to the success of the synthesis. Addition of hydroquinone (0.1%) to freshly distilled methacrylic acid (**1**) before use is recommended, otherwise olefin polymerization would take place to an appreciable extent, with negative effects on the yield and selectivity of the reaction. An efficient dispersion of oxygen into the solution is of great importance to achieve a fast oxidation of **2**. No attempt, however, was made to optimize this parameter. The temperature as well as the basicity of the medium also significantly affect the oxidation of **2** to **3**. The latter occurs satisfactorily at 60 °C, but long induction periods are observed,[29] which are readily done away with by working at 90 °C. Likewise, the presence of a large excess of alkali with respect to the amount required to neutralize the carboxy groups brings about a marked increase in the oxidation rate. The use of 4.3–4.4 equivalents of alkali per mole of **2** to be oxidized gave the best results. With lower ratios, ranging from 2.5 to 3.5:1, the reaction time was considerably longer.

To our knowledge, the conversion of **2** to **3** reported here represents the first example of a catalytic selective oxidation of a hydroxymethyl to carboxy group by oxygen carried out on a *vic*-diol containing a carboxy group β to the primary hydroxy function.

If desired, intermediate α-methylglyceric acid (**2**) can be isolated in 86–89% yield based on hydrogen peroxide and with a 96–97% selectivity on the olefin by a simple workup (see experimental section).[30]

Finally, the methyltartronic acid (**3**) so formed can directly be converted in situ into its alkyl esters.[31] Thus, analytically pure diethyl methyltartronate[32] was obtained from **1** in an overall yield of 65% based on hydrogen peroxide.

All reagents were of commercial quality from freshly opened containers. H_2O_2 (40% w/v) and 5% Pd–C were purchased from Fluka Chemical Co., whereas tungstic acid was obtained from Merck. Methacrylic acid (**1**, Fluka) was distilled before use and stabilized with hydroquinone (0.1%). All products prepared are known. Their identity was confirmed by microanalyses, spectral data, and comparison with authentic samples. GC analyses [after silylation of the product with *N,O*-bis(trimethylsilyl)acetamide] were performed on a Varian 3700 instrument equipped with a 30 m × 0.32 mm (i.d.) (0.25 µm film) SPB-5 bonded-phase fused silica capillary column, with column temperature programming. Melting points were taken on a Büchi melting point apparatus (oil bath) and are uncorrected.

Methyltartronic Acid (2-Hydroxy-2-methylpropanedioic Acid) (3):
A 200-mL, four-necked, conical glass flask fitted with mechanical stirrer, thermometer, and reflux condenser was charged with H_2WO_4 (0.25 g, 1 mmol), water (20 mL), and 40% w/v H_2O_2 (7.45 mL, 87.65 mmol). The mixture was heated to 50–60 °C until a clear solution was obtained, then water (35 mL) and methacrylic acid (**1**; 8.6 g, 100 mmol) were added. The resulting solution (initially brown-coloured) was brought to 80 °C under stirring and kept at this temperature for 135 min (~96% conversion of H_2O_2, iodometric titration), whereupon it was cooled to r.t. Et_2O (4 × 30 mL) was added and, after each addition, the two-phase mixture was stirred for a few minutes, then the upper organic layer was siphoned off. By evaporation of the combined, dried (Na_2SO_4) and filtered organic extracts, unreacted **1** (1.77 g, 20.56 mmol) was recovered. The aqueous solution was left into the flask, which was fitted with a fine-fritted glass gas inlet (7-mm diameter) and whose condenser was connected with a bubble-counter, and stripped of dissolved Et_2O. Then, a solution of NaOH (13.5 g) in water (10 mL) and 5% Pd–C (1.2 g) were added successively. The mixture was heated to 90 °C under vigorous stirring (900 rpm) and oxygen was bubbled through it (14–15 L/h) for 4 h (complete disappearance of intermediate **2** monitored by GC). The catalyst was filtered from the warm solution and washed with hot water, the filtrate was concentrated to ca. 10 mL at 40 °C (bath temperature) under water-pump vacuum using a rotary evaporator, acidified with 20% HCl (57 mL), and then evaporated to dryness. The solid residue was extracted (at reflux) with Et_2O (2 × 100 mL) and the extract was concentrated to afford **3** as a white solid; yield: 8.95 g (76%, based on H_2O_2 charged); purity: 99% (GC); mp 142 °C (MeCN, dec.) (Lit.[14] 141–142 °C).

Isolation of Intermediate α-Methylglyceric Acid [(±)-2,3-Dihydroxy-2-methylpropanoic Acid] (2):
At the end of the dihydroxylation reaction of **1** with H_2O_2 as described above, the aqueous solution, after recovery of the unreacted olefin by extraction with Et_2O (3 × 25 mL), was treated with 5% Pd–C (1 g) at 60 °C for 25 min to decompose all unreacted (~4%) H_2O_2. The filtrate was then evaporated to dryness at 40 °C under reduced pressure. The residue is stirred with MeCN (50 mL) for 10 min, then the extract was filtered and concentrated to give a thick syrup, which solidified on cooling. A small amount of MeCN (1–2 mL) was added, and the white crystalline diol **2** so obtained was filtered, washed with Et_2O (2 × 10 mL), and dried; yield: 9.27 g (88%, based on H_2O_2); purity: 99% (GC); mp 103–104 °C (MeCN) (Lit.[33] 103–104 °C).

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Even under basic conditions, tungstate-catalyzed oxidation of **2** by H_2O_2 did not lead to **3** but essentially to polymeric materials.

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(29) No induction period was observed when isolated **2** (see experimental section) was purified by recrystallization and then oxidised under the same reaction conditions.

(30) Curiously, whereas tungstate-catalyzed epoxidation of **1** by aq H_2O_2[34] as well as separate hydration to **2** of the resulting epoxide[35] have been reported, to the best of our knowledge the preparation of **2** by direct dihydroxylation of **1** with the above oxidizing system is not known. However, the direct addition of H_2O_2 with inorganic catalysts to water-soluble α,β-unsaturated acids to give the corresponding glycols has long been known.[36]

(31) The residue obtained from evaporation of the acidified filtrate was refluxed with the appropriate alcohol in the presence of conc H_2SO_4 as the catalyst.

(32) This compound is a useful intermediate in the preparation of ethyl 3-(3,5-dichlorophenyl)-5-methyl-2,4-dioxo-5-oxazolidinecarboxylate, an effective fungicide (Serinal®).[37]

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