A Simple Synthesis of 1,3-Cyclopentanedione

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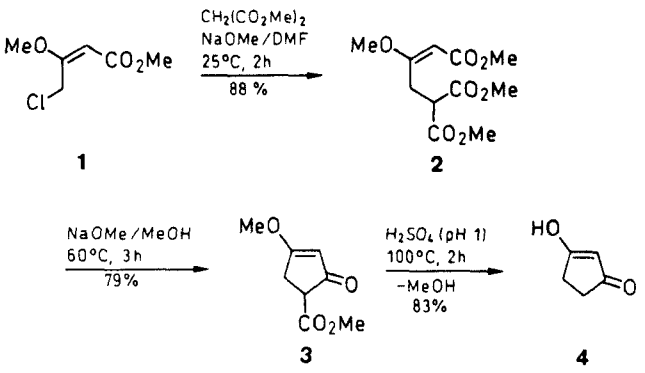
1,3-Cyclopentanedione was prepared by a simple procedure from methyl (*E*)-4-chloro-3-methoxy-2-butenoate via trimethyl (*E*)-3-methoxy-3-butene-1,1,4-tricarboxylate.

Despite its appeal as a building block for biologically active substances such as prostaglandins,[1] antibiotics,[2] fragrances,[3] and herbicides,[4] 1,3-cyclopentanedione (**4**) has not been produced industrially. The most simple laboratory syntheses, based on norborn-2-ene[5] or D-glucono-1,5-lactone,[6] involve consecutive low temperature ozonolyses in the former case, and a high dilution reaction in the latter.

Noyori's kinetic resolution of (±)-4-hydroxy-2-cyclopentenone,[7] forms **4** in 61% yield. This route appears to be economically feasible for the synthesis of (*R*)-4-hydroxy-2-cyclopentenone, however it is too expensive solely for the production of **4**. We now report on an extremely simple synthesis, suitable for an industrial production of **4**, based on methyl (*E*)-4-chloro-3-methoxy-2-butenoate (**1**).

Reaction of dimethyl malonate with **1** under basic conditions in dimethylformamide yields cleanly trimethyl (*E*)-3-methoxy-3-butene-1,1,4-tricarboxylate (**2**). The use of dimethylformamide avoids precocious ring closure to methyl 4-methoxy-2-oxo-3-cyclopentenecarboxylate (**3**), before all of the electrophile **1** has reacted. When the substitution reaction is carried out in alcoholic solvents, a variety of side products resulting from further alkylation of **3** are observed.



Scheme

The crude triester **2** is cyclized in methanol with an equivalent of sodium methoxide. The initial cyclization product reacts immediately with the methoxide present to form the sodium salt of **3** and dimethyl carbonate. The formation of the stabilized anion provides the driving force for the reaction. When ethanol is used as solvent, partial exchange of the 3-methoxy group occurs. The extent of exchange depends on the reaction time, but is of no consequence for the following reaction. 2-Oxo-3-cyclopentenecarboxylates such as **3** are very useful building-blocks in their own right for alkylated cyclopentenones.[10]

The hydrolysis and decarboxylation of **3** can be sequentially carried out under basic followed by acidic aqueous conditions, or simultaneously in the presence of mineral acid.

Dimethyl malonate and methyl (*E*)-4-chloro-3-methoxy-2-butenoate[8] (purity > 98%) are Lonza products. DMF, MeOH and NaOMe were purchased from the Fluka Chemical Co. Microanalyses were obtained using a Perkin-Elmer 240C analyser. IR spectra were obtained using a Nicolet SXB20 spectrophotometer. Mass spectra were obtained using a Finnegan 4021 (70 eV) spectrometer, with DEI ionisation ^{1}H NMR spectra were obtained using a Nicolet NT 300 MHz spectrometer. Melting points were taken using a Büchi 535 apparatus and are uncorrected.

Trimethyl (*E*)-3-Methoxy-3-butene-1,1,4-tricarboxylate (2):
To a stirred solution of dimethyl malonate (66 g, 500 mmol) in DMF (250 mL) at 20°C was added NaOMe (27.8 g, 500 mmol), followed 10 min later by methyl (*E*)-4-chloro-3-methoxy-2-butenoate (**1**; 41.6 g, 250 mmol). The suspension was stirred for 2 h. The solvent was distilled off at 45°C/20 mbar, the residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (120 mL). After neutralization of the aqueous phase with HCl (32%), the organic phase was separated and evaporated to dryness. The residue was distilled at 176 to 180°C/20 mbar. Yield: 58.8 g (88%) of the title product with a purity (GC) of 98%.

$C_{11}H_{16}O_7$	calc.	C 50.76	H 6.19
(260.2)	found	50.92	6.23

GC-MS (EI): *m/z* (%) = 260, 228, 197, 196, 169 (100), 141.

IR (KBr): ν = 1743, 1708, 1624, 1436, 1428, 1385, 1353, 1287, 1262, 1239, 1196, 1150, 1052, 1017 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 3.40 (d, $J_{4,5}$ = 7.8 Hz, 2 H, CH_2-4), 3.61 (s, 3 H, OCH_3), 3.68 (s, 3 H, CO_2CH_3-1), 3.73 (s, 6 H, CO_2CH_3-6,7), 3.75 (t, 1 H, $J_{4,5}$ = 7.8 Hz, CH-5), 5.08 (s, 1 H, CH-2).

Methyl 4-Methoxy-2-oxo-3-cyclopentenecarboxylate (**3**):
Na (14.1 g, 613 mmol) was added under Ar in portions over a period of 30 min to MeOH (0.71 L). The solution was heated to 60°C and trimethyl (*E*)-3-methoxy-3-butene-1,1,4-tricarboxylate (**2**; 80 g, 300 mmol) was added dropwise during 30 min. The suspension so-formed was stirred at 60°C for 3 h and then AcOH (37 mL) was added. The MeOH was evaporated and the residue was partitioned between CH_2Cl_2 (300 mL) and H_2O (400 mL). After phase separation, the H_2O phase was further extracted with CH_2Cl_2 (2 × 120 mL). The CH_2Cl_2 was evaporated and the product distilled at 116–120°C/7 mbar.

Yield: 42.5 g (79%), 97% purity (GC).

$C_8H_{10}O_3$	calc.	C 56.46	H 5.92
(170.2)	found	56.35	5.90

GS-MS (EI): *m/z* (%) = 170, 142, 139, 127, 112, 111, 110, 95, 83, 69 (100).

IR (KBr): ν = 1734, 1697, 1603, 1585, 1440, 1431, 1371, 1348, 1251, 1219, 1156, 987 cm^{-1}.

^{1}H NMR ($CDCl_3$/TMS): δ = 2.80 (dd, 1 H, J_{ab} = 18.0 Hz, $J_{5,1}$ = 7.6 Hz, CH-5b), 3.05 (m, 1 H, J_{ab} = 18.0 Hz, $J_{5,1}$ = 3.1 Hz, CH-5a), 3.55 (dd, 1 H, $J_{5b,1}$ = 7.6 Hz, $J_{5a,1}$ = 3.1 Hz, CH-1), 3.78 (s, 3 H, CO_2CH_3), 3.90 (s, 3 H, OCH_3), 5.30 (s, 1 H, CH-3).

1,3-Cyclopentanedione (4):
Compound **3** (112.1 g, 575 mmol) was added at 50°C to (336 g) H_2SO_4 (0.5 N). The solution was heated to 100°C for 2 h while MeOH was distilled off. At the end of the reaction the residual MeOH was removed under vacuum. The mixture was cooled to 20°C and brought to pH 2.5 with NaOH (50%). The product was isolated by continuous extraction with *i*-PrOAc (250 mL). The extract was evaporated to dryness and the residue was suspended in CH_2Cl_2 (100 mL), filtered and dried. Yield: 50 g (83%), purity 96% (HPLC) mp 145–147°C (Lit.[6] mp 149–151°C, after sublimation).

^{1}H NMR (DMSO-d_6/TMS): δ = 2.37 (s, 4 H), 5.10 (s, 1 H), 11.7–12.5 (br s, 1 H).

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