A Short and Effective Synthesis of Dimethyl 2-Methoxycarbonyl-3-methylenesuccinate

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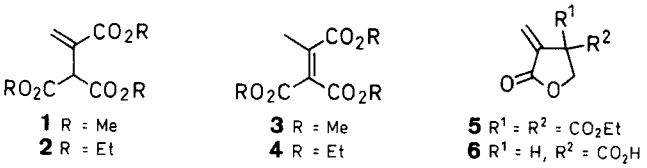
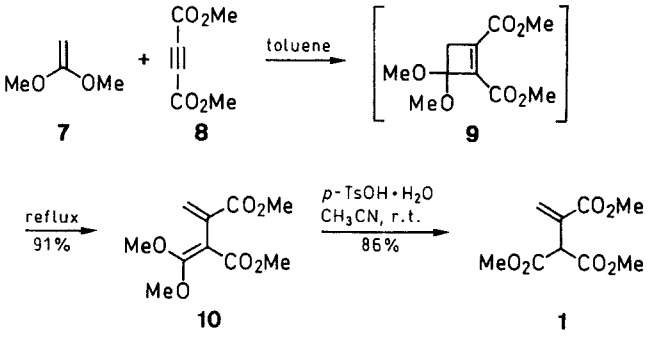
Cycloaddition of ketene dimethyl acetal (**7**) to dimethyl butynedioate (**8**) followed by electrocyclic ring opening yields diene **10**. This can be hydrolyzed readily to the title compound **1**.

The title compound **1** (also called trimethyl prop-2-en-1,1,2-tricarboxylate) represents an interesting and important synthetic intermediate, possessing versatile functionality including an electron deficient double bond and a malonic ester fragment. Although mentioned as a component of a mixture with its double bond isomer **3**,[1] **1** has not been described before. The respective triethyl ester **2** is known, but there is no satisfactory protocol for its selective synthesis. In a multistep procedure, a mixture of **2** and its isomer **4** is formed.[2-4] An additional sequence (deprotonation and kinetic reprotonation) is required to obtain exclusively **2**.[3,4] This compound has found broad use in enzymatic and enzyme model studies.[3-6] It may be converted readily into methylene lactones **5** and **6** (oxo analog of antitumor compound sarkomycin A) as well as into various succinic acid derivatives.[3,4,7] Furthermore, it was applied as a plant growth regulator.[8] Obviously the synthetic potential of **1** and **2** has been hardly tapped.



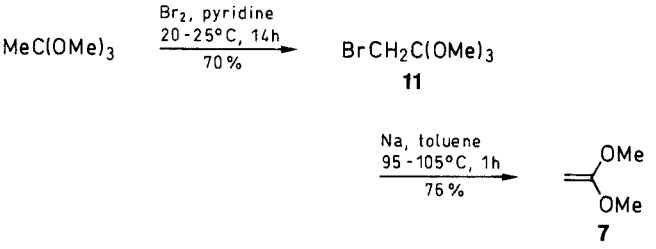
Scheme 1

Here we report on the selective, short and convenient synthesis of **1** (Scheme 2). It is known that diene **10** can be obtained by [2+2] cycloaddition of ketene dimethyl acetal (**7**) to dimethyl butynedioate (**8**), followed by ring cleavage.[9] Nevertheless, we have found, that the yield of diene **10** can be increased considerably – up to 91 % (as compared to 48 %[9]). To achieve this, the cycloaddition to give intermediate **9** is performed and completed at relatively low temperature.[10] Subsequent refluxing generates **10**. Mild hydrolysis of **10** gives the target triester **1**.



Scheme 2

Ketene dimethyl acetal (**7**) was obtained essentially according to the well-known procedure[11-13] (Scheme 3), but some improvements make this preparation slightly more efficient and convenient. In particular, the reduction of bromoorthoacetate **11** with sodium in toluene, followed by distillation, yields a toluene solution of **7**, which can be used directly for the cycloaddition (without prior isolation of **7**).



Scheme 3

Thus, such an approach to **1** comprises a number of synthetic advantages. It can be extended readily to the synthesis of **2** and other, including asymmetrical, esters of prop-2-ene-1,1,2-tricarboxylic acid as well as related derivatives substituted in the methylene moiety.

Trimethyl Bromoorthoacetate (11):[11,12]
Bromine (5.2 mL, 102 mmol) was added dropwise to a cooled (+5 °C) and stirred solution of trimethyl orthoacetate (12.6 mL, 100 mmol) in dry pyridine (8.2 mL, 100 mmol). During the addition, the temperature was maintained between 20 and 25 °C (ice/water bath). The mixture was set aside overnight at r.t. and then poured into 200 mL of vigorously stirred petroleum ether (bp 30–60 °C). The precipitate was filtered off and washed with petroleum ether (50 mL) and then with diethyl ether (2 × 50 mL). The combined organic phases were washed with sat. $NaHCO_3$ solution (30 mL) containing a small amount of $Na_2S_2O_3$, water (30 mL) and then dried (Na_2SO_4). Removal of solvents and distillation gave 14.1 g (70%) of **11**, bp 66–69 °C/9 Torr. (Lit. 74–75 °C/17 Torr.[11])

^1H NMR (60 MHz, $CDCl_3$): δ = 3.25 (s, 9H), 3.42 (s, 2H).

Ketene Dimethyl Acetal (7)[11,13] in Toluene:
Sodium (3.36 g, 146 mmol) in 57 mL of toluene was warmed to its melting point. A solution of **11** (14.13 g, 71 mmol) in 14 mL of toluene was added dropwise under stirring so as to maintain the temperature of this exothermic reaction between 95 and 105 °C. After the addition of all of **11**, the mixture was refluxed for 1 h under N_2 and then **7** was distilled off together with toluene (from 104 up to 109 °C). This solution (38.5 g) contained ca. 4.7 g (76%) of **7** (according to the integration of the corresponding NMR signals).

^1H NMR (80 MHz, $CDCl_3$): δ = 3.06 (s, 2H), 3.48 (s, 6H), 2.28, 7.13 (toluene, Me and Ph, respectively).

Dimethyl 2-(Dimethoxymethylene)-3-methylenesuccinate (10):
To the stirred toluenic solution of **7** mentioned above, **8** (7.53 g, 53 mmol) in 14 mL of toluene was added in one portion. When the temperature reached 35 °C, the mixture was cooled to 30 °C and then allowed to cool to the r.t. (ca. 2 h). After this it was placed into a water bath (28–32 °C), stirred for an additional 15 h[10] and then refluxed under nitrogen (3 h). Removal of toluene followed by a bulb-to-bulb distillation (110–120 °C/0.35 Torr) gave 11.13 g (91%) of **10**. The ^1H NMR spectrum was identical to that given in ref. 9.

Dimethyl 2-Methoxycarbonyl-3-methylenesuccinate (1):
A solution of *p*-TsOH · H_2O (0.23 g, 1.2 mmol) in 2.4 mL of water was added in one portion to the stirred solution of **10** (5.53 g, 24 mmol) in 24 mL of acetonitrile at r.t. After 1 h of stirring, the acetonitrile was removed, the residue was dissolved in 50 mL of Et_2O and washed with 5 mL of water, 1.1 mL of saturated aqueous $NaHCO_3$, then with 10 mL of water and dried (Na_2SO_4). Removal of solvent and distillation gave 4.47 g (86%) of **1**, bp 91–93 °C/0.45 Torr.

IR (film): ν = 3000, 2978, 1731, 1715, 1630, 1434, 1398 cm^{-1}.

^1H NMR (80 MHz, $CDCl_3$): δ = 3.77 (s, 6H), 3.79 (s, 3H), 4.65 (d, 1H, J = 0.9 Hz), 5.90 (d, 1H, J = 0.9 Hz), 6.51 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.5, 53.0 (2 OMe), 53.2, 129.2, 133.1, 165.8, 167.8 (2 CO).

MS (70 eV): m/z = 185 (12%), 157 (100), 153 (30), 125 (18), 98 (10), 59 (28).

Calc. for $C_9H_{12}O_6$: C 50.00, H 5.60%; found: C 49.84, H 5.78%.

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(10) NMR monitoring indicates the complete transformation of starting materials to **9** after 15 h at 28–30 °C. At this point **9** (90–93%) can be isolated (after removal of toluene) by a fast bulb-to-bulb distillation at 0.05–0.1 Torr.
^1H NMR (80 MHz, $CDCl_3$): δ = 2.82 (s, 2H), 3.41 (s, 6H), 3.77 (s, 6H). Further transformations of **9** are now being studied.
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