Michael Addition of Isopropylidene Malonate to Electrophilic Olefins under Phase-Transfer Conditions

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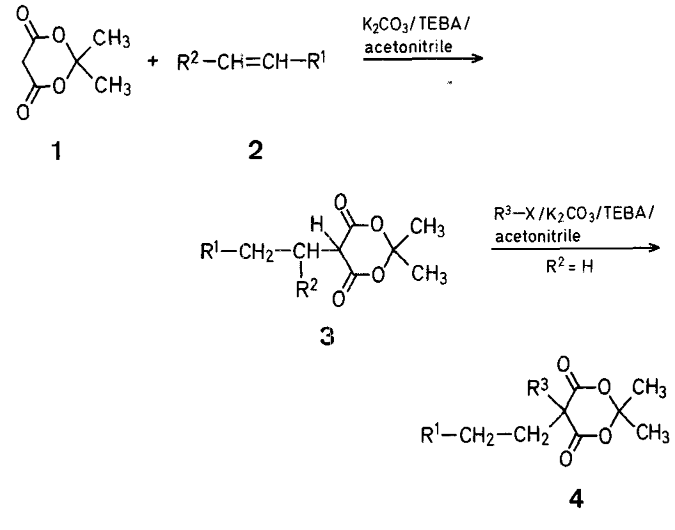
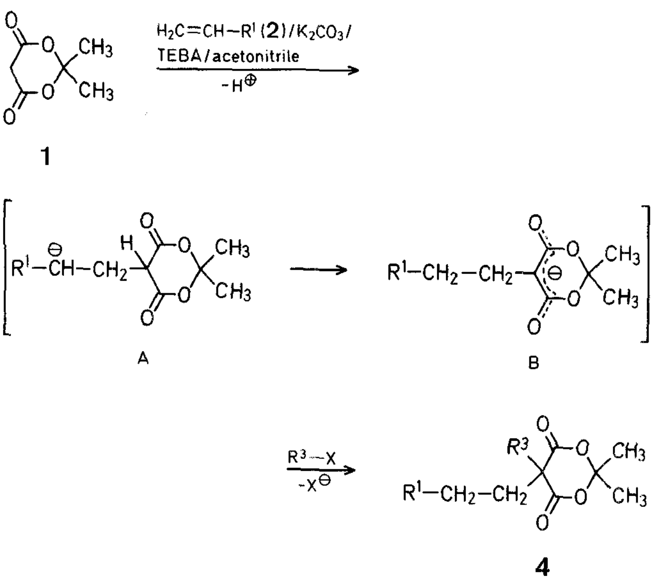
Isopropylidene malonate (**1**, Meldrum acid) is a versatile organic reagent[1]. We have recently reported several new methods for the synthesis of 5-substituted isopropylidene malonates[2-5]. Although the Michael addition is an important method for the alkylation of active methylene compounds[6,7] there are only few reports on the Michael addition of isopropylidene malonate to electrophilic olefins[8,9].

We have previously shown[4] that the alkylation of the highly acidic isopropylidene malonate (pK_a: 4.97) with alkyl halides takes place under solid-liquid phase-transfer conditions using solid potassium carbonate as a base. We report here the application of this technique to the Michael addition of isopropylidene malonate to electrophilic olefins. The reaction was accomplished by heating solid potassium carbonate, isopropylidene malonate (**1**), and the electrophilic olefin (**2**) in acetonitrile in the presence of benzyltriethylammonium chloride (TEBA) at 50–60°C (molar ratio $1/2/K_2CO_3/TEBA = 1/1.5/1/1$). The Michael addition products **3a–d** were thus obtained in high yields. Unlike the direct alkylation of isopropylidene malonate with alkyl halides which gives disubstituted derivatives, the Michael addition stops after monosubstitution, even if 3 equivalents of electrophilic olefin are used. This latter method is therefore general and convenient for the synthesis of monosubstituted isopropylidene malonates containing various functional groups such as cyano, acyl, and alkoxycarbonyl groups. The monosubstituted isopropylidene malonates (**3**) thus obtained can be alkylated with alkyl halides to give disubstituted isopropylidene malonates (**4**) (Method A).



We assume that the Michael addition of electrophilic olefins (**2**) to isopropylidene malonate (**1**) leads to the initial formation of an anion of the type A which then isomerizes to a stabler anion of the type B. Since anions B should be suitable substrates for alkylation with alkyl halides, we also prepared the disubstituted isopropylidene malonates **4** by a one-pot procedure according to the following scheme (Method B).



Since the substituted isopropylidene malonates are easily hydrolyzed to carboxylic acids[3,5,10] or converted into carboxylic esters[3,5,11], the method described here may also be considered as a new method for the synthesis of substituted glutaric acids, δ-ketocarboxylic acids, or their esters.

The structures of all products were confirmed by their microanalyses and I.R. and N.M.R. spectra (Table).

Monosubstituted Isopropylidene Malonates 3a-d; General Procedure: To a stirred solution of isopropylidene malonate (**1**; 1.44 g, 10 mmol) in acetonitrile (10 ml) is added finely powdered potassium carbonate (1.38 g, 10 mmol) and benzyltriethylammonium chloride (2.28 g, 10 mmol). The mixture is stirred for 15 min at room temperature and then a solution of the electrophilic olefin (**2**; 15 mmol) in acetonitrile (5 ml) is added. The resultant mixture is stirred for 8-10 h at 50-60 °C until T.L.C. analysis (silica gel G, chloroform) indicates complete disappearence of the starting material **1**. The mixture is cooled, water (50 ml) is added, the solution is washed with ether (10 ml), and acidified to pH 1-2 with 6 normal hydrochloric acid. The crude product **3** which precitates is isolated by suction. The filtrate is extracted with ether (3 × 15 ml). The combined ether solution is washed with water (10 ml) and dried with magnesium sulfate. After removal of the solvent, an additional small amount of crude product is obtained. The combined crude product **3** is purified by recrystallization from benzene/petroleum ether.

Table 1. Monosubstituted Isopropylidene Malonates (**3**) prepared

3	R^1	R^2	Yield [%]	m.p. [°C]	Molecular formula[a]
a	$-COOC_2H_5$	H	94	97-98°	$C_{11}H_{16}O_6$ (244.2)
b	$-CN$	H	93	123-124°	$C_9H_{11}NO_4$ (197.2)
c	$-CO-CH_3$	H	90	119-120°	$C_{10}H_{14}O_5$ (214.2)
d	$-COOC_2H_5$	$-COOC_2H_5$	70	117-118°	$C_{14}H_{20}O_8$ (316.3)

[a] Satisfactory microanalyses obtained: C, ±0.35; H, ±0.08.

Table 2. Disubstituted Isopropylidene Malonates (**4**) prepared

4	R^1	R^3-X	Method	Yield [%]	m.p. [°C]	Molecular formula[a]
a	$-CO-CH_3$	H_3C-J	A	76	72-73°	$C_{11}H_{16}O_5$
			B	70		(228.1)
b	$-COOC_2H_5$	$C_6H_5-CH_2-Cl$	A	82	100-101°	$C_{18}H_{22}O_6$
			B	74		(334.4)
c	$-CN$	H_3C-J	A	85	91-92°	$C_{10}H_{13}NO_4$
			B	72		(211.2)
d	$-CO-CH_3$	$C_6H_5-CH_2-Cl$	B	65	90-91°	$C_{17}H_{20}O_5$ (304.4)

[a] Satisfactory microanalyses obtained: C, ±0.35; H, ±0.11.

Table 3. Spectral Data of Compounds **3** and **4**

Compound	*I.R. (KBr)* ν [cm^{-1}]	*^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$)* δ [ppm]
3a	1800, 1756, 1742, 1400, 1390, 1185	1.30 (t, 3 H); 1.81 (s, 3 H); 1.89 (s, 3 H); 2.70-2.38 (m, 4 H); 4.01 (t, 1 H); 4.20 (q, 2 H)
3b	2358, 1794, 1755, 1390, 1362	1.74 (s, 3 H); 1.82 (s, 3 H); 2.41 (q, 2 H); 2.71 (t, 2 H); 3.61 (t, 1 H)
3c	1798, 1757, 1721, 1391, 1361	1.76 (s, 3 H); 1.83 (s, 3 H); 2.16 (s, 3 H); 2.30 (q, 2 H); 2.73 (t, 2 H); 3.86 (t, 1 H)
3d	1792, 1763, 1743, 1395, 1331, 1176	1.26 (t, 6 H); 1.78 (s, 6 H); 2.98 (d, 2 H); 3.7 (m, 1 H); 3.90-4.26 (m, 5 H)
4a	1793, 1747, 1723, 1393, 1377	1.55 (s, 3 H); 1.70 (s, 3 H); 1.78 (s, 3 H); 2.08 (s, 3 H); 2.30 (t, 2 H); 2.52 (t, 2 H)
4b	1777, 1743, 1731, 1384, 1348, 782, 710	0.64 (s, 3 H); 1.23 (t, 3 H); 1.57 (s, 3 H); 2.21-2.38 (m, 4 H); 3.23 (s, 2 H); 4.04 (q, 2 H); 7.18 (s, 5 H)
4c	2262, 1786, 1750, 1397, 1336, 1170, 765, 706	0.68 (s, 3 H); 1.59 (s, 3 H); 2.11 (s, 3 H); 2.23-2.60 (m, 4 H); 3.25 (s, 2 H); 7.22 (s, 5 H)

Disubstituted Isopropylidene Malonates (4); General Procedures:

Method A: To a stirred solution of a monosubstituted isopropylidene malonate (**3**; 5 mmol) in acetonitrile (10 ml) is added finely powdered potassium carbonate (0.69 g, 5 mmol), benzyltriethylammonium chloride (1.14 g, 5 mmol), and the alkyl halide (10 mmol). The resultant mixture is stirred for 4 h at 40-50 °C. Then water (25 ml) is added with vigorous stirring. The crude product **4** is collected by suction, washed with cold water, dried in air, and purified by recrystallization from benzene/petroleum ether.

Method B: To a stirred solution of isopropylidene malonate (**1**; 1.44 g, 10 mmol) in acetonitrile (10 ml) is added finely powdered potassium carbonate (1.38 g, 10 mmol) and benzyltriethylammonium chloride (2.28 g, 10 mmol). The mixture is stirred for 15 min. Then a solution of the electrophilic olefin (**2**; 15 mmol) in acetonitrile (5 ml) is added and stirring is continued for 8-10 h at 50-60 °C until the reaction is complete. Then, a solution of the alkyl halide (20 mmol) in acetonitrile (5 ml) is added. The resultant mixture is stirred for 4 h at 40-50 °C and then worked up as in Method A.

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