The Michael Reaction of Methanetricarboxylic Esters. A Simple Method for Two-Carbon Chain Elongation

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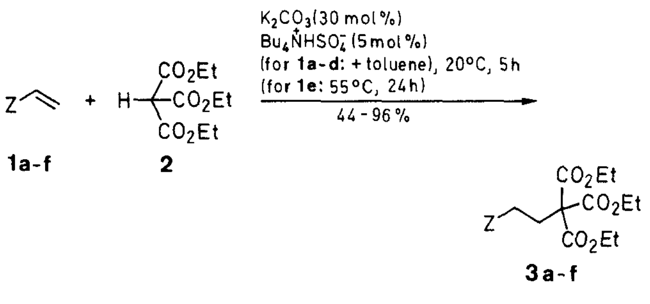
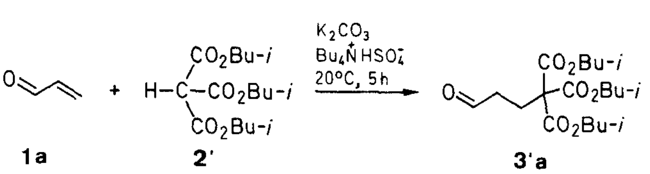
The conjugate addition of triethyl methanetricarboxylate to various Michael acceptors proceeds readily under solid-liquid phase-transfer catalysis conditions. The reaction scope and limitations have been elaborated.

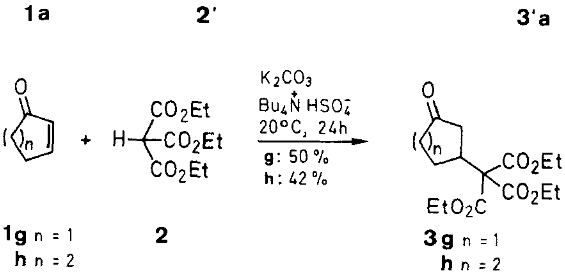
The reaction of dialkyl malonates with Michael acceptors is one of the most fundamental methods of chain elongation by two carbon atoms.[1,2] However, the utility of this method is often hampered by the undesired addition of a second acceptor molecule because of the high acidity of the resulting dialkyl alkylmalonates. This side reaction becomes particularly pronounced with reactive acceptors so that monofunctionalized products cannot be obtained in this case.[2] As a general solution for this problem, we propose the use of trialkyl methanetricarboxylates, where the second acidic H-atom of a malonic ester is replaced by an alkoxycarbonyl group. A similar approach has been applied to by-pass difficulties in the classical malonic ester synthesis;[3] anyhow, the easily available methanetricarboxylic esters[4] are hithero almost unused as Michael donors.[5] However, methanetricarboxylic esters have been used for radical-initiated two-carbon elongations of 1-alkenes.[11]

We report here an efficient method for the conjugate addition of triethyl methanetricarboxylate (**2**) to Michael acceptors **1**. These reactions proceed smoothly under solid-liquid phase-transfer catalysis (PTC) conditions both in the presence or absence of toluene as solvent and the products can be easily isolated. Various Michael acceptors were studied in order to investigate scope and limitations of the method.



1, 3	Z	1, 3	Z
a	CHO	**d**	COMe
b	CO_2Me	**e**	SOPh
c	–CN	**f**	SO_2Ph





The reactions of the functionally substituted ethylenes **1b-f** gave good to high yields of **3** whereas with acrolein (**1a**) some oligomeric side products were obtained. In this case, the use of KF/Al_2O_3[6] as catalyst and/or a reaction temperature of 0 °C did not lead to an improvement, but performing the reaction with triisobutyl methanetricarboxylate (**2'**) substantially increased the yield of the corresponding Michael adduct **3'a**. Cyclic acceptors, namely 2-cyclopentenone (**1g**) and 2-cyclohexenone (**1h**), also gave resonable yields in the reaction. The example of crotonaldehyde (**1i**) illustrates the advantage of the present method over the classical methods: cf. 90% of **3i**, 36% yield of **5** from **1i** and diethyl malonate (**4a**), and 45% yield of **5** from **1i** and diethyl acetylmalonate (**4b**). The latter donors **4a** and **4b** gave the same product **5** because, under the conditions used, diethyl acetylmalonate (**4b**) underwent β-keto ester cleavage prior to the addition.

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Table. Michael Adducts **3** and **5** Prepared

Product	Reaction Time (h)	Reaction Temperature (°C)	Yield[a] (%)	mp (°C)[b] (solvent) or bp (°C)/Torr	GC[c] (min/°C)	TLC[d] (eluent) R_f	Molecular Formula[e]	IR (film)[f] ν (cm^{-1})	^1H-NMR ($CDCl_3$/TMS)[g] δ, J(Hz)
3a	5	20	44	109–112/0.5	14.3/160 (DEGS)	0.45 (i-$Pr_2O/CHCl_3$, 10 : 3)	$C_{13}H_{20}O_7$ (288.3)	2985, 2936, 2906, 2830, 2724, 1735, 1250, 1092	1.29 (t, 9H, $J = 7$), 2.62 (m, 4H, AA'BB'), 4.27 (q, 6H, $J = 7$), 9.76 (t, 1H, $J = 1$)
3'a	5	20	68	oil	12/180 (DEGS)	0.70 (i-$Pr_2O/CHCl_3$, 10 : 3)	$C_{19}H_{32}O_7$ (372.4)	2964, 2876, 2820, 2730, 1756, 1736, 1256	0.90 (d, 18H, $J = 6.5$), 1.94 (m, 3H), 2.30–2.88 (m, 4H, AA'BB'), 3.95 (d, 6H, $J = 6.5$), 9.74 (s, 1H)
3b	12	20	77 (85)	117–120/0.5	24/160 (DEGS)	0.67 (i-Pr_2O/EtOAc, 4 : 1)	$C_{14}H_{22}O_8$ (318.3)	2990, 2950, 2910, 1740, 1215, 1065	1.29 (t, 9H, $J = 7$), 2.54 (m, 4H, AA'BB'), 3.69 (s, 3H), 4.28 (q, 6H, $J = 7$)
3c	5	20	80 (91)	119–120/0.5	25/160 (DEGS)		$C_{13}H_{19}NO_6$ (285.3)	2990, 2945, 2910, 2250, 1733, 1215, 1085	1.23 (t, 9H, $J = 7$), 2.55 (m, 4H, AA'BB'), 4.23 (q, 6H, $J = 7$)
3d	12	20	96 (100)	117–119/0.5	22.4/160 (DEGS)	0.47 (i-$Pr_2O/CHCl_3$, 10 : 3)	$C_{14}H_{22}O_7$ (302.3)	2988, 2945, 2910, 1736, 1180, 1094	1.29 (t, 9H, $J = 7$), 2.15 (s, 3H), 2.59 (m, 4H, AA'BB'), 4.27 (q, 6H, $J = 7$)
3e	24	55	55	oil		0.38 (i-Pr_2O/EtOAc, 4 : 1)	$C_{18}H_{24}O_7S$ (384.4)	3060, 2980, 2940, 2905, 1736, 1046	1.25 (t, 9H, $J = 7$), 2.80 (m, 4H, AA'BB'), 4.23 (q, 6H, $J = 7$), 7.57 (m, 5H)
3f	5	20	77	37–38 (MeOH)		0.58 (i-Pr_2O/EtOAc, 4 : 1)	$C_{18}H_{24}O_8S$ (400.4)	3065, 2984, 2940, 2906, 1732, 1306, 1164, 1088	1.23 (t, 9H, $J = 7$), 2.96 (m, 4H, AA'BB'), 4.21 (q, 6H, $J = 7$), 7.50–8.00 (m, 5H)
3g	24	20	50 (52)	oil	30/150 (QF-1)	0.56 (i-Pr_2O/EtOAc, 4 : 1)	$C_{15}H_{22}O_7$ (314.3)	2984, 2952, 2920, 1734, 1050	1.29 (t, 9H, $J = 7$), 1.85–2.54 (m, 6H), 3.12 (m, 1H), 4.28 (q, 6H, $J = 7$)
3h	24	20	42 (48)	oil	26/180 (DEGS) 26/160 (QF-1)	0.55 (i-Pr_2O/EtOAc, 4 : 1)	$C_{16}H_{24}O_7$ (328.4)	2983, 2940, 2905, 1744, 1715, 1190, 1050	1.29 (t, 9H, $J = 7$), 1.45–2.58 (m, 9H), 4.27 (q, 6H, $J = 7$)
3i	12	20	90 (93)	120–122/0.5	8.7/180 (DEGS)		$C_{14}H_{22}O_7$ (302.3)	2990, 2955, 2908, 2820, 2720, 1740, 1220, 1065	1.17 (d, 3H, $J = 7$), 1.30 (t, 9H, $J = 7$), 2.26–3.30 (m, 3H), 4.28 (q, 6H, $J = 7$), 9.78 (dd, 1H, $J_1 = 2$, $J_2 = 0.6$)
3j	24	20	78	32–34 (pentane)	20.7/180 (QF-1)		$C_{22}H_{36}O_{10}$ (460.5)	2984, 2940, 2905, 1736, 1168	1.28 (t, 9H, $J = 7$), 1.46 (s, 18H), 2.81 (d, 2H, $J = 5$), 3.44 (t, 1H, $J = 5$), 4.24 (q, 6H, $J = 7$)
5	12 12	20 20	36[h] 45[i]	105/0.5	14.7/160 (DEGS)	0.55 (i-$Pr_2O/CHCl_3$, 10 : 3)	$C_{11}H_{18}O_5$ (230.2)	2980, 2940, 2905, 2820, 2718, 1730, 1750, 1160, 1035	1.08 (d, 3H, $J = 6.8$), 1.29 (t, 6H, $J = 7$), 2.77 (m, 3H), 3.42 (d, 1H, $J = 6.8$), 4.23 (q, 4H, $J = 7$), 9.80 (dd, 1H, $J_1 = 1.7$, $J_2 = 0.9$)

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[a] Yield of isolated products based on Michael acceptors. Yield determined by GC of crude product is shown in parentheses.

[b] Uncorrected; measured with a Boëtius hot-stage apparatus.

[c] Performed on a Perkin-Elmer F-11 gas chromatograph operating with FID and equiped with a 1 m × 4 mm column packed with 6% QF-1 on Gas-Chrom Q and a 1 m × 4 mm column packed with 2% DEGS on Chromosorb G, N_2 flow rate 50 mL/min.

[d] Obtained on silica gel-60 precoated plates (Merck).

[e] Satisfactory microanalyses: C ±0.30, H ±0.20, N ±0.10, S ±0.30.

[f] Recorded on a Specord M-80 spectrophotometer.

[g] Measured using a Tesla 100 MHz spectrometer.

[h] With diethyl malonate.

[i] With diethyl acetylmalonate.

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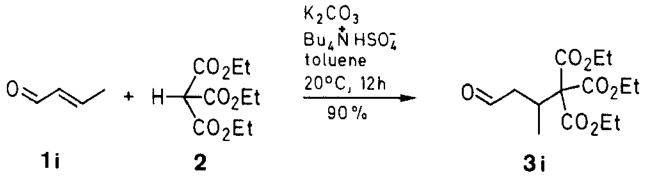
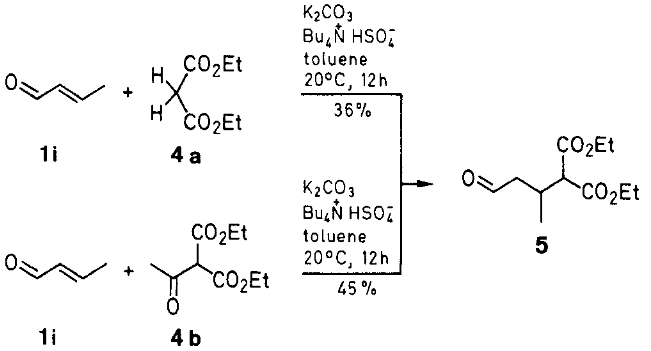
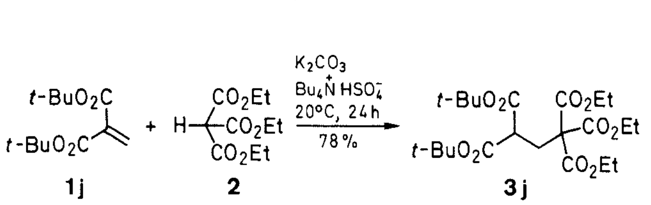




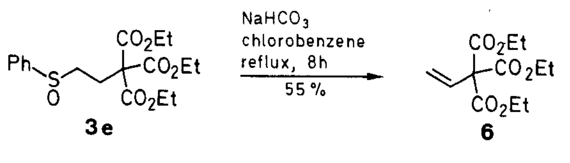
The only moderate yields of product **5** (36 and 45%) obtained under the phase-transfer conditions used by us were higher though than the yields reported for the usual methods.[7]

Methyl crotonate and methyl methacrylate are not reactive enough as acceptors and failed to give adducts under the conditions used by us. The same applies to phenyl-substituted acceptors such as ethyl cinnamate, cinnamaldehyde, and ω-nitrostyrene.

The readily available di-*tert*-butyl methylenemalonate[8] (**1j**) reacts with **2** to give the expected triethyl 3,3-bis(*tert*-butoxycarbonyl)propane-1,1,1-tricarboxylate) (**3j**) in 78% yield, whereas the reported[5] conjugate addition of trimethyl methanetricarboxylate gives only 12% of the corresponding pentamethyl ester.



The adducts **3** are suitable for a variety of further functionalizations; thus, the easy removal of the ethoxycarbonyl group[9] creates a new reactive site in the molecule. The sulfoxide **3e** is particularly interesting as a synthetic building block. This compound is relatively thermally stable and it needs eight hours boiling in chlorobenzene to be converted into triethyl 2-propene-1,1,1-tricarboxylate (**6**).



In summary, the Michael reaction of methanetricarboxylic esters renders possible an easy two-carbon chain elongation and provides a simple access to useful 1,4- and 1,5-difunctional synthetic intermediates.[10] Further work on the applicability of adducts **3** is under way in our laboratory.

Michael Addition of Triethyl Methanetricarboxylate (2), Triisobutyl Methanetricarboxylate (2′), Diethyl Malonate (4a), and Diethyl Acetylmalonate (4b) to Michael Acceptors 1; General Procedure:

A mixture of the Michael acceptor **1** (14 mmol) and the Michael donor **2** (3.4 mL, 16 mmol), **2′** (5.06 g, 16 mmol), **4a** (2.56 g, 16 mmol), or **4b** (3.24 g, 16 mmol), K_2CO_3 (0.58 g, 4.2 mmol), and $Bu_4N\ HSO_4^-$ (0.24 g, 0.7 mmol) [in the cases **1a–d, i**, toluene (3 mL) is also added] is stirred at 20°C or 55°C for the time given in the Table. The reaction is then quenched with H_2O (5 mL) and the mixture extracted with Et_2O (2 × 5 mL). The combined extracts are washed with brine (5 mL), dried (Na_2SO_4), and evaporated. The crude products are purified by distillation (**3a–d, i** and **5**), crystallization (**3f, j**), or flash chromatography on silica gel (**3e, g, h** and **3′a**).

Triethyl 2-Propene-1,1,1-tricarboxylate (6):

A solution of triethyl 3-(phenylsulfinyl)propane-1,1,1-tricarboxylate (**3e**; 1.43 g, 3.72 mmol) in chlorobenzene (15 mL) containing suspended $NaHCO_3$ (0.62 g, 7.4 mmol) is refluxed with stirring for 8 h. The cooled mixture is washed with H_2O (3 mL), sat. $NaHCO_3$ solution (3 mL), and brine (3 mL). It is then dried (Na_2SO_4) and the solvent is removed under reduced pressure. The crude product is column-chromatographed on silica gel using a mixture of hexane/i-Pr_2O (1:1) as eluent; yield: 0.49 g (41%; 55% by GC of the crude product); oil; TLC: R_f 0.46 (hexane/i-Pr_2O, 1:1); GC retention time: 2.3 min (170°C/DEGS).

$C_{12}H_{18}O_6$	calc.	C 44.70	H 5.63
(322.4)	found	44.51	5.75

IR (film): ν = 3095, 2980, 2940, 2906, 1736, 1640, 1240, 1066 cm^{-1}.

^1H-NMR ($CDCl_3$/TMS): δ = 1.23 (t, 9H, J = 7 Hz), 4.23 (q, 6H, J = 7 Hz), 5.20–5.48 (m, 2H), 6.22 (dd, 1H, J_{trans} = 18.5 Hz, J_{cis} = 9.5 Hz).

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