Tetrahedron Vol. 45, No. 14, pp. 4593 to 4598, 1989
Printed in Great Britain

0040-4020/89 $3.00+.00
Maxwell Pergamon Macmillan plc

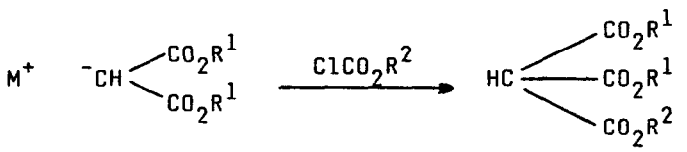
CARBON-ACYLATIONS IN THE PRESENCE OF MAGNESIUM OXIDE. A SIMPLE SYNTHESIS OF METHANETRICARBOXYLIC ESTERS

Jacek Skarżewski
Institute of Organic and Physical Chemistry, Technical University, 50-370 Wrocław, Poland

(*Received in UK 2 May* 1989)

Abstract- Magnesium oxide is an effective reagent for the carbon - acylation of malonates with either acyl chlorides or chloroformates. Various malonic esters (methyl, ethyl, isopropyl and isobutyl) were easily alkoxycarbonylated to give the corresponding methanetricarboxylic esters. The reaction scope and limitations have been elaborated.

Methanetricarboxylic esters are interesting building blocks for the synthesis of multiarmed ligands [1]. These triesters have already found many synthetic applications and their preparation as well as chemistry has recently been reviewed [2]. Generally, methanetricarboxylic esters are synthesized from malonic esters via C-acylation of the corresponding metal (preferably magnesium)[3] salts with alkyl chloroformate. The ethoxymagnesium salt advantageously employed in this reaction is generated by the use of metallic



magnesium in the presence of ethanol and the procedure requires strictly anhydrous conditions [4]. In order to avoid this inconvenience, we examined the ethoxycarbonylation of diethyl malonate using the alternative bases. The results are presented in Table 1. A well known solid-liquid PTC method, designed for the alkylation of diethyl malonate [5], did not lead to the C-acylated product. Also the procedure recently developed by Rathke and Cowan for acylation of diethyl malonate and ethyl acetoacetate with acid chlorides using tertiary amines and magnesium chloride [6] was unsuccessful. However, the reactions performed with a solid base, such as magnesium hydroxide or better magnesium oxide, gave triethyl methanetricarboxylate in quite reasonable yields. Additionally, less basic zinc oxide was ineffective and the substrates were recovered, while the application of calcium oxide, which

TABLE 1. Ethoxycarbonylation of diethyl malonate [a]

Entry	Base	Solvent	Temperature °C	Reaction time,h	Yield %
1	MgO	Toluene	80	5	58
2	MgO	Toluene	80	7	71
3	MgO	Toluene	80	7	59[b]
4	$Mg(OH)_2$	Toluene	80	7	56
5	K_2CO_3/Bu_4NCl	Toluene	80	7	3.6[c]
6	$MgCl_2 + 2Et_3N$	CH_3CN	20	10	5.3[c]
7	$MgCl_2 + 2C_5H_5N$	CH_2Cl_2	0 - 20	2.5	20

[a] Yield based on weight of distilled product; 1.3 : 1 : 2.5 ratio of diethyl malonate, ethyl chloroformate, solid base, 1:1:1 for $MgCl_2$ (entries 6 and 7).

[b] Yield for 1.5 : 1 : 1.5 ratio.

[c] Yield based on GC analysis.

is more basic than MgO, induced a violent decomposition of ethyl chloroformate.

Magnesium oxide has gained some attention of organic chemists [7] and recently catalytic properties of its surface have been exploited in the heterogeneous Wittig, Knoevenagel, and Wittig-Horner reactions [8]. Since it seemed worthy to extend further the utility of this inexpensive and convenient base, we examined a scope and limitations of the observed C-acylation. Various malonic acid esters were reacted with chloroformates and acid chlorides in the presence of MgO. The reactions were carried out under identical conditions and the yields were not optimized. The results are summarized in Table 2. Thus developed procedure offers simple and economic synthesis of methanetricarboxylic esters. In the case of different alkyl groups ($R^1 \neq R^2$), small amounts of the mixed side products were detected by gas chromatography. This may be due to the transesterification [9] or dealkoxycarbonylation [10] - acylation processes. Such side reaction was particularly pronounced for R^1 : Et, R^2 : $PhCH_2$ (entry 5) and R^1 : i-Pr, R^2 : Et (entry 9) and no pure product could be isolated in these cases. The tert-butyl esters were

TABLE 2. Acylation of malonates in the presence of magnesium oxide [a]

Entry	Malonate R^1 (R,R´)	Acylating agent	Yield (%) Main product	Other products
1	Et, Et	CH_3COOCl	(5.5)	(4.4) Ethyl acetoacetate
2		PhCOCl	62	16 Benzoic acid
3		EtOCOCl	71 (73)	
4		i-BuOCOCl	69 (71)	(1.5 and 2.7)[b]
5		$PhCH_2OCOCl$	an unresolved mixture	
6	Me, Me	EtOCOCl	52 (55)	(2 and 5)
7		i-BuOCOCl	47 (50)	(45) substrate
8	Et, t-Bu	EtOCOCl	(7.4) (2.4)[c]	and 16 Diethyl malonate, 51 substrate
9	i-Pr, i-Pr	EtOCOCl	(57)	(10 and 12)
10		i-BuOCOCl	49 (55)	(1.2 and 1.5)
11	i-Bu, i-Bu	EtOCOCl	41 (59)	(8 and 12)[d]
12		i-BuOCOCl	71 (74)	
13	t-Bu, t-Bu	EtOCOCl	(4)	91 substrate

[a] Reaction conducted on 0.2 or 0.05 mol scale, see Experimental. Yields based on weight of the distilled product and/or GC analysis (in parentheses).

[b] Identified as triethyl and ethyl diisobutyl methanetricarboxylate, respectively.

[c] Identified as triethyl methanetricarboxylate.

[d] Identified as diethyl isobutyl methanetricarboxylate and triisobutyl methanetricarboxylate, respectively.

not acylated because of the steric hindrance preventing an access to the surface of solid MgO. Diethyl malonate was easily benzoylated under these conditions, but the corresponding reaction with more reactive acetyl chloride gave only 5.5% of the desired product. This result may be attributed to the well known cleavage of β-keto esters to produce the anion of the strongest acid, i.e. a removal of the acetyl group in the case of diethyl acetylmalonate[3].

When the reaction of diethyl malonate with acetyl chloride was run for a shorter period of time (2 h instead of 7 h), more of the acetylated product was obtained. Also ethyl acetoacetate was treated with ethyl chloroformate in the presence of MgO for 2 h and the results were compared with those obtained by the use of the $MgCl_2$ - tertiary amine system[6] (Table 3). A comparison of two base systems shows that the consecutive cleavage of diethyl acetylmalonate is less important in the case of the later one. Additionally, the deethoxycarbonylation process was observed when $MgCl_2$-triethylamine in acetonitrile was applied for a prolonged time (Table 3, entry 3, 13% of ethyl acetoacetate)[11]. All these results suggest that the most satisfactory synthesis of diethyl acetylmalonate is that using $MgCl_2$- pyridine in methylene dichloride.

TABLE 3. Synthesis of diethyl acetylmalonate [a]

Entry	Base	Solvent	Temp. °C	Reaction time, h	Acylating agent	Yield (%)[b] Diethyl malonate	Diethyl acetylmalonate	ethyl acetoacetate
1	MgO	Toluene	80	2	CH_3COCl	59	21	3
2	MgO	Toluene	80	2	EtOCOCl	13	52	1
3	$MgCl_2$+2Et_3N	CH_3CN	20	12	CH_3COCl	14	71[c]	13
4	$MgCl_2$+2C_5H_5N	CH_2Cl_2	0-20	1	EtOCOCl	0.5	73	20

[a] Reactions carried out on 50 mmol scale. For entries 3 and 4 a 1:1:1 reagent ratio was used, for 1 and 2, see Table 1,2.
[b] Yields determined by GC analysis of the crude products; for the distilled main product the yields were 1-2% lower than given.
[c] The yield of 85% based on the distilled "bulb to bulb" product was reported by Rathke and Cowan[6].

An attempted ethoxycarbonylation of methyl cyanoacetate was not effective with either MgO (no product formed) or $MgCl_2$-pyridine (20% of product).

In conclusion, the developed C-acylation procedure extends the concept of using magnesium oxide as a base and presents a convenient way for a practical preparation of methanetricarboxylic esters.

Experimental

^1H NMR spectra were recorded in $CDCl_3$ on a Tesla 100 MHz spectrometer using TMS as internal standard. IR spectra were recorded on a Specord M-80 spektrophotometr in CCl_4. Gas chromatographic analyses were performed with a Perkin-Elmer F-11 and a Giede GCHF 18.3.6 gas chromatographs operating with FID and equipped with a 1m x 4mm column packed with 6% QF-1 on Gas-Chrom Q and a 1 m x 4 mm column packed with 2% DEGS on Chromosorb G.

All solvents used were anhydrous and freshly distilled. Triethylamine and pyridine were distilled over calcium hydride. Dimethyl and diethyl malonate, ethyl acetoacetate, methyl cyanoacetate, benzoyl and acetyl chlorides (commercial products) were purified by simple distillation. All chloroformates were reagent grade products purchased from Merck. Di-tert-butyl malonate was prepared according to a literature[12]. Tert-Butyl ethyl malonate[13] was synthesized from ethoxycarbonylacetic acid and tert-butanol using a DCC/DMAP

method[14]. Diisopropyl malonate[15] and diisobutyl malonate[16] were obtained by an azeotropic esterification of malonic acid in the catalytic presence of Dowex 50 W8 H^+-form. Anhydrous magnesium chloride was obtained by a literature method[17]. Magnesium hydroxide and magnesium oxide were analytical grade reagents from Reachim (USSR) and these solids were analysed by a thermogravimetric method (20-900 °C); $Mg(OH)_2$: % of weight-loss (water), calcd 30.9, found 30.5 at 380 °C; MgO : % of weight-loss found 3.7 at 320°C. Calcium oxide and zinc oxide were also analytical grade reagents.

General procedure. A flame dried 250 ml three neck flask equipped with thermometer, mechanical stirrer, reflux condenser and paraffin oil bubbler was filled with magnesium oxide (20.0 g, 0.50 mol), dry toluene (50 ml), diethyl malonate (40 ml, 0.26 mol) and ethyl chloroformate (20 ml, 0.20 mol). The mixture was stirred at 80±3°C for 7 h, then cooled to 5°C and at this temp. water was added dropwise until all the precipitate becomes granular or pasty. A solution was decanted, the precipitate was washed with ether (15 ml) which was added to the solution. The remaining solid was carefully treated with 5N HCl while cooling the flask with an ice bath. After the most of solid was dissolved, the aqueous suspension was extracted with ether (2 x 20 ml) and the extracts were combined with previous organic solution. The combined solutions were washed with 1N HCl, water, 5% NaHCO soln, brine and dried over Na_2SO_4 . Ether was evaporated and the crude product was distilled under reduced pressure using a 25 cm long Vigroux column to give 34.3 g (71%) of **triethyl methanetricarboxylate**, b.p. 135-137°/12 mm Hg, lit.[18] 135-137°/12 mm Hg; IR $\nu_{C=O}$ 1742, 1768, ν_{C-O} 1145; NMR 1.30 (t, 9H, J=7 Hz, CH_3CH_2-), 4.28 (q, 6H, J=7 Hz, CH_3CH_2-), 4.40 (s, 1H, HC≡, shifted to 4.51 in the presence of C_6D_6); GC (DEGS, 120°) 6.8 min, (QF-1, 120°) 6.6 min.

All other acylations with MgO were carried out in the same manner replacing diethyl malonate and/or ethyl chloroformate with the appropriate reagents (Table 2 and 3). When the reaction was run on 50 mmol scale, a 50 ml flask was used. For the acylation in the presence of $MgCl_2$, a literature procedure was followed strictly.

Diethyl acetylmalonate, b.p. 106°/12 mm Hg, lit.[19] 115-117°/17 mm Hg ; IR $\nu_{C=O}$ 1643,1720, $\nu_{C=C}$ 1600; NMR (60% of enol) 1.28, 1.30 (two t, 6H, J=7 Hz, CH_3CH_2-, enol and ketone), 2.19, 2.20, and 2.34 (three s, 3H, cis, trans-enol and ketone, CH_3-), 4.26, 4.29 (two q, 4H, J=7 Hz, CH_3CH_2-), 4.49 (s, 0.4H, HC≡), 13.40 (s, 0.6H enol OH); GC (DEGS, 120°) 7.4 min, (QF-1, 120°) 5.8 min, (QF-1, 100°) 7.5 min.

Diethyl benzylmalonate, b.p. 131-133°/0.5 mm Hg, lit.[19] 144-149°/0.8 mm Hg; IR $\nu_{C=O}$ 1680, 1720, 1741; NMR (13% of enol) 1.02, 1.22 and 1.33 (three t, 6H , J=7 Hz, CH_3-, nonequivalent), 3.98-4.42 (three q, 4H, J=7 Hz, CH_3CH_2- , nonequivalent), 5.35 (s, 0.87 H, HC≡), 7.39-7.99 (m, 5H, ArH), 13.44 (s, 0.13 H, enol OH).

Diethyl isobutyl methanetricarboxylate, b.p. 157-161°/15 mm Hg; IR $\nu_{C=O}$ 1740, 1767, ν_{C-O} 1149; NMR 0.94 (d, 6H, J=7 Hz, $-CH(CH_3)_2$), 1.28 (t, 6H, J=7 Hz, $-CH_2CH_3$), 1.98 (m, 1H, $-CH(CH_3)_2$), 3.55 (d, 2H, J=7 Hz, $-CH_2CH(CH_3)_2$), 4.21 (s, and q, 5H, J=7 Hz, HC≡ and $-CH_2CH_3$); GC (GC (QF-1, 120°) 12 min; Anal. calcd for $C_{12}H_{20}O_6$ (260.3) C 55.37, H 7.75, found C 55.41, H 7.69.

Ethyl dimethyl methanetricarboxylate, b.p. 132-135°/12 mm Hg, lit.[20] 138-139°/12 mm Hg; IR $\nu_{C=O}$ 1743, 1770, ν_{C-O} 1148; NMR 1.30 (t, 3H, J=7 Hz, CH_3CH_2-), 3.81 (s, 6H, $-OCH_3$), 4.27 (q, 2H, J=7 Hz, CH_3CH_2-), 4.44 (s, 1H, HC≡); GC (QF-1, 120°) 5.5 min.

Isobutyl dimethyl methanetricarboxylate, b.p. 149-151°/15 mm Hg; IR $\nu_{C=O}$ 1747, 1767, ν_{C-O} 1147; NMR 0.94 (d, 6H, J=7 Hz, $-CH(CH_3)_2$), 1.98 (m, 1H, $-CH(CH_3)_2$), 3.80 (s, 6H, $-OCH_3$), 4.00 (d, 2H, J=6.5 Hz, $-OCH_2CH(CH_3)_2$), 4.46 (s, 1H, HC≡); GC (QF-1, 120°) 12.5 min; Anal. calcd for $C_{10}H_{16}O_6$ (232.2) C 51.72, H 6.95, found C 51.58, H 7.21.

Isobutyl diisopropyl methanetricarboxylate, b.p. 159-161°/15 mm Hg, IR $\nu_{C=O}$ 1749, 1770, ν_{C-O} 1153; NMR 0.95 (d. 6H, J=7 Hz, $-CH_2CH(CH_3)_2$), 1.28 (d, 12 H, J=6.5 Hz, $-OCH(CH_3)_2$),

1.99 (m, 1H, $-CH_2CH(CH_3)_2$),3.99 (d, 2H, j=6.5 Hz, $-OCH_2CH\leq$), 4.35 (s, 1H, HC≡) , 5.11 (sep, 2H, J=6.5 Hz, $-OCH(CH_3)_2$); GC (QF-1, 110°) 27.7 min, (QF-1, 130°) 10.7 min; Anal. calcd for $C_{14}H_{24}O_6$ (288.3) C 58.31, H 8.39, found C 58.19, H 8.30.

Ethyl diisobutyl methanetricarboxylate, b.p. 105°/0.5 mm Hg, IR ν_{C-O} 1742, 1768, ν_{C-O} 1147; NMR 0.94 (d, 12 H, J=7 Hz, $-CH(CH_3)_2$), 1.30 (t, 3H, J=7 Hz, $-CH_2CH_3$), 1.98 (m, 2H, $-CH(CH_3)_2$), 4.00 (d, 4H, J=6.5 Hz, $-OCH_2CH\leq$), 4.26 (q, 2H, J=7 Hz,$-OCH_2CH_3$) 4.41 (s, 1H, HC≡); GC (QF-1, 130°), 13.5 min; Anal. calcd for $C_{14}H_{24}O_6$(288.3) C 58.31, H 8.39, found C 58.15, H 8.27.

Triisobutyl methanetricarboxylate, b.p. 106-108°/0.5 mm Hg, lit.[18] 142°/2 mm Hg, IR $\nu_{C=O}$ 1748, 1775, ν_{C-O} 1156; NMR 0.94 (d, 18 H, J=7 Hz, $-CH(CH_3)_2$); 1.99 (m, 3H, $-CH_2CH(CH_3)_2$), 4.00 (d, 6H, J=6.5 Hz, $-OCH_2-$), 4.43 (s, 1H, HC≡); GC (QF-1, 120°) 20.7 min.

Acknowledgment - The author is grateful to Prof. J.Młochowski for helpful discussions. This work was supported by Grant CPBP 01.13 from the Polish Academy of Sciences.

References

1. (a)Menger,F.M. Top.Curr.Chem. **1986**, 136, 1-15; (b) Newkome,G.R; Yao,Z.; Baker,G.R.; Gupta,V.K.; Russo,P.S.; Saunders,M.J. J.Am.Chem.Soc. **1986**, 108, 849-850; (c) Skarżewski, J.; Młochowski J J.Chem.Res. (S), **1988**, 64-65, (M), **1988**, 552-569.
2. Newkome,G.R.; Baker,G.R. Org.Prep.Proced.Int. **1986**, 18, 117-144.
3. (a) House,H.O. Modern Synthetic Reactions, 2nd ed. Benjamin Publ.,Menlo Park, **1972**, Chap. 11; (b) Henecka,H. Methoden der Organischen Chemie (Houben-Weyl), Thieme, Stuttgart, vol.VII/2a, **1973**, p.492-547.
4. (a) Lund,H.; Voigt,A. Org.Synth. **1943**, coll.vol.2, 594-596; (b) Reynolds,G.A.; Hauser, C.R. Org.Synth. **1950**, 30, 70-72.
5. Fedoryński,M.; Wojciechowski,K.; Matacz,Z.; Mąkosza,M. J.Org.Chem. **1978**, 43, 4682-4684.
6. Rathke,M.W.; Cowan,P.J. J.Org.Chem. **1985**, 50, 2622-2624.
7. Fieser,L.; Feiser,M. Reagents for Organic Synthesis, J.Wiley, New York, **1967**, 1,633-634; **1969**, 2, 256-257; **1979**, 7, 221.
8. Moison,H.; Texier-Boullet,F.; Foucaud,A. Tetrahedron **1987**, 43, 537-542.
9. Padgett,H.C.; Csendes.I.G.; Rapoport,H. J.Org.Chem. **1979**, 44, 3492-3496.
10. Krapcho,A.P. Synthesis **1982**, 805-822, 893-914.
11. Magnesium chloride is recommended as an effective deethoxycarbonylating agent, see: Tsuda,Y.; Sakai,Y. Synthesis **1981**, 119-120.
12. McCloskey, A.L.; Fonken,G.S.; Kluiber,R.W.; Johnson,W.S. Org.Synth. **1954**, 34, 26-29.
13. Strube, R.E. Org.Synth. **1957**, 37, 34-36.
14. Wiener,H.; Gilon.C. J.Mol.Catal. **1986**, 37, 45-52
15. Palomea,M.H.; Mikkila,I. Ber. **1942**, 75, 1659-1667.
16. Gallus,H.P.; Macbeth,A.K. J.Chem.Soc. **1937**, 1810-1812.
17. Pray,A.R. Inorg.Synth. **1957**, 5, 153-156.
18. Backer,H.J.; Lolkema,J. Rec.Trav.Chim. **1938**, 57, 1234-1248.
19. Tarbell,D.S.; Price,J.A. J.Org.Chem. **1957**, 22, 245-250.
20. Scholl,R.; Egerer,W. Ann. **1913**, 397, 301-366.