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A FACILE ONE-STEP SYNTHESIS OF ETHYL 2-(1,1-DIALKYL AND ARYLMETHYL) MALONATES

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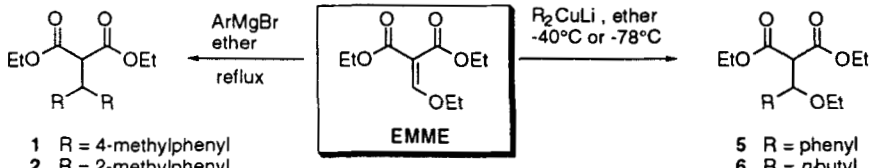
Abstract: Diethyl ethoxymethylenemalonate (EMME) is unexpectedly converted into diethyl 2-(1,1-dialkyl and diarylmethyl) malonate derivatives by a classical Grignard reaction. Addition of organocuprates to EMME gave diethyl 2-(1-ethoxyalkyl) malonate derivatives. The yields range from 42-63%.

Diethyl ethoxymethylenemalonate (EMME) is an extremely valuable starting material for the synthesis of quinolones.[1] Our continuing interest in model studies aimed at discerning the mode of action of quinolone anti-bacterials[2] led us to prepare several arylidene malonic acids derivatives. These compounds (**1-7**) were prepared by



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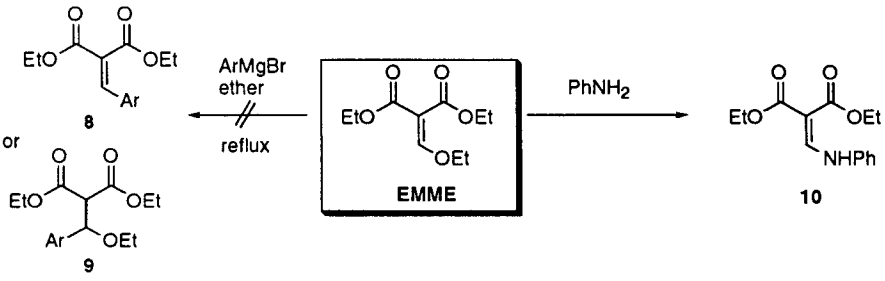
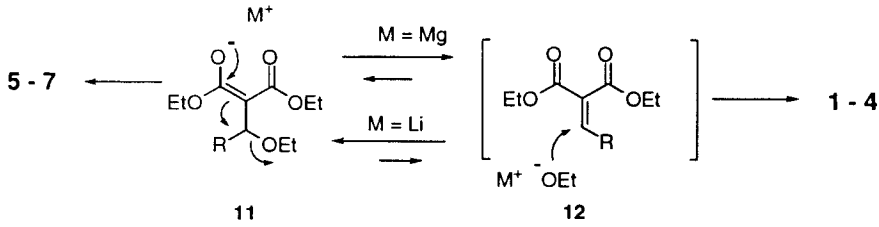
reaction of EMME with the appropriate Grignard reagent. In previous studies a method to protect the amino moiety in amino acids using EMME was reported[3] but most of these compounds were prepared by conjugate addition of amine derivatives to EMME.[4] The products of this latter reaction were the corresponding diethyl β-amino-methylene



malonates. There have also been reports of the conversion of EMME to benzo[b]quinolizines via reaction with oxoquinolinyl acetates[5] and into pyrido[2,3-d]pyrimidines by reaction with oxopyrimidines.[6] In contrast to these previous reports, we found that reaction of EMME with Grignard reagents or organocuprates leads to 2-(1,1-diarylmethyl) malonates **1-4**, and 1-ethoxy-1-arylmethyl (or 1-alkylmethyl) malonate derivatives, **5-7**, in moderate yield. Previous work suggested that a Grignard reagent would react with EMME to give an α,β-unsaturated diester (**8**) or a derivative such as **9** since aniline reacted with EMME to give **10**.[4] The proton NMR spectra of **1-4** did not show the expected vinylic hydrogen peak but rather two doublet peaks near 5.2-4.3 ppm. Mass spectrometry confirmed these compounds to be **1-4**. The appropriate Grignard reagent was prepared by the reaction of magnesium with 2-bromotoluene, 4-bromotoluene, 3-fluoro-1-bromobenzene, or benzyl bromide in diethyl ether.

It was known that reaction of enones containing β-leaving groups with organocuprates gave β-alkylated substitution products by a formal addition-elimination sequence.[7] In contrast to this work, we found that phenyl, *n*-butyl, *t*-butyl organocuprates reacted with EMME to give the corresponding 1-ethoxy-1-arylmethyl or

1-ethoxy-1alkylmethyl malonate, **5-7**. Formation of **6** is analogous to Yamaguchi's report,[8] in which the reaction of EMME with a lithium enolate gave a 1,4-addition product that retained the ethoxy group.



Although it has been suggested that single electron transfer occurs between cuprates and enones,[9] the exact mechanism of this reaction is not thoroughly understood. A possible explanation for the difference in behavior between Grignard reagents and organocuprates may be the stability of metal alkoxide as a leaving group. It may be that the magnesium associated ethoxide obtained with organomagnesium reagents, see **12** (M = Mg), which is more stable (less nucleophilic) than the lithium ethoxide obtained with lithium cuprates (see **11**, M = Li), whichis more nucleophilic. Furthermore, lithium ion seems to be coordinated more tightly in activated enolate **11** (M = Li), than in the magnesium associated enolate, **11** (M = Mg). Since magnesium is not expected to coordinate as tightly with the oxygen in enolate **11** (M = Mg), expulsion of the ethoxy group to give **12** (M = Mg) is more facile. Once **12** is formed, a second molecule of Grignard reagent could attack via conjugate addition to give **1-4**.

The reaction with organocuprates can be explained in two ways. If **11** (M = Li) is generated LiOEt is formed (see **12**, M = Li), and conjugate addtion of ethoxide to **12** will give **5-7**. Alternatively, formation of **11** (M = Li) can simply be protonated to give **5-7**. It is not clear which of these two plausible mechanisms are operative.

In conclusion, this method gave 1,1-dialkyl or 1,1-diarylmethyl malonate derivatives. The organocuprte reaction, however, gave the 1-ethoxy-1-substituted

malonate derivative, and provides one of the few methods available for adding a group to a conjugated acceptor bearing a leaving group at the β-position, without elimination of that leaving group.

Experimental Section

Melting points were taken on a Haake Buchler melting point apparatus and are uncorrected. Infrared spectra were recorded with a BOMEN model FT-IR M100-C15 and recorded in reciprocal centimeters. ^{1}H NMR and ^{13}C NMR spectra were determined in a solution of d-chloroform using a Brüker AM 300 FT-NMR (300 MHz) and reported in ppm downfield form tetramethylsilane as an internal standard. Mass spectra were measured on an KRATOS MS 25 RFD (70 eV, EI). Column chromatography was performed with silica gel 60(70-230 mesh) from E. Merck.

Diethyl 2-(1,1-bis(4-methylphenylmethyl) Malonate, 1: A flame dried three-neck round bottom flask fitted with pressure equalizing addition funnel, magnetic stirrer and reflux condenser was charged with 0.08 g (3.32 mmol) of magnesium turnings. Slow addition of solution of dry diethyl ether (5 mL) and 4-bromotoluene (0.57 g, 3.32 mmol), initiated formation of the Grignard reagent. A solution of EMME (0.553 g, 2.556 mmol) in 3 mL of diethyl ether was added, dropwise, and the solution was refluxed for 3 hr. After hydrolysis with saturated aqueous ammonium chloride, filtration and drying ($MgSO_4$), the solvents were evaporated. The crude malonate product was purified by chromatography on silica gel (R_f = 0.38; 20% diethyl ether in hexane) to give **1** (0.44 g, 1.24 mmol, 49%) as a clear oil: ^{1}H NMR ($CDCl_3$): δ 7.5-7.3 (8H, m), 4.9 (1H, d), 4.5 (1H, d), 4.18 (q, 4H), 2.5 (s, 6H), and 1.25 (t, 6H) ppm; ^{13}C NMR ($CDCl_3$): δ 167.7, 138.6, 136,2, 129.1, 127.5, 61.3, 57.5, 50.4, 20.9, and 13.7 ppm; IR (film): 3200-2800, 1741, 1512, 1456, 1369, 1254, 1163, 1031, and 810 cm^{-1}; MS: m/z (Rel. Intensity): 354 (25, P^{+}), 309 (5), 308 (4), 280 (45), 263 (5), 235 (29), 208 (22), 195 (100), 180 (15), 165 (19), 145 (10), 115 (18),

91(12), and 84 (28). HRMS. Calcd. for $C_{22}H_{26}O_4$, m/z 354.1831. Found. 354.1823 (± 1.8 mmu).

Diethyl 2-(1,1-bis(2-methylphenylmethyl) Malonate, 2: Reaction of 0.04 g (1.76 mmol) of Mg and 0.3 g (1.76 mmol) of 2-bromotoluene in 3 mL of diethyl ether, as above, was followed by treatment with 0.45 g (2.1 mmol) of EMME and this was refluxed for 3 hours. Work-up as described for **1** and purification by column chromatography (R_f = 0.4 , 20% diethyl ether in hexane) gave 0.35 g (1.01 mmol, 49 %) of **2**: ^{1}H NMR ($CDCl_3$): δ 7.3-7.0 (10H, m), 5.20 (1H, d), 4.30 (1H, d), 3.96 (4H, q), 2.36 (6H, s), and 0.94 (6H, t) ppm; IR (neat): 3200-2800, 1741, 1224, 1445, and 1370 cm^{-1}; Mass Spectrum (m/z, Rel. Intensity): 263 (17, P^+), 235 (28), 217 (95), 195 (82), 179 (65), 171 (33), 144 (90), 115 (100), 73 (42), and 45 (40). HRMS. Calcd. for $C_{22}H_{26}O_4$, m/z 354.1831. Found. 354.1827 (± 1.8 mmu).

In addition, 0.08 g (0.38 mmol, 22%) of EMME was recovered.

Diethyl 2-(1,1-bis(3-fluorophenylmethyl) Malonate, 3: Reaction of 0.12 g (5.10 mmol) of Mg and 0.88 g (5.10 mmol) of 1-bromo-3-fluorobenzene in 2 mL of diethyl ether was followed by treatment with 0.85 g (3.92 mmol) of EMME. The resulting slurry was refluxed for 3 hours. Work-up as described for **1** and purification by column chromatography (R_f = 0.38, 20% diethyl ether in hexane) gave 0.59 g (1.64 mmol, 42 %) of **3**: ^{1}H NMR ($CDCl_3$): 7.29-6.79 (8H, m), 4.70 (1H, d), 4.35 (1H, d), 4.11-3.84 (4H, q), and 1.22-1.0 (6H, t) ppm; IR (neat): 3200-2800, 1740, 1510, 1456, 1370, 1250, 1160, and 1028 cm^{-1}; Mass Spectrum (m/z, Rel. Intensity): 362 (20, P^+), 317 (5), 288 (43), 260 (6), 243 (30), 216 (25), 203 (100), 183 (20), 149 (15), 121 (12), 103 (21), and 73 (20). HRMS. Calcd. for $C_{20}H_{20}O_4F_2$, m/z 362.1330. Found. 362.1341 (± 1.8 mmu).

In addition, 0.24 g (1.10 mmol, 28 %) of EMME was recovered.

Diethyl 2-(1-benzyl-2-phenylethyl) Malonate, 4: Reaction of 0.06 g (2.52 mmol) of Mg and 0.43 g (1.94 mmol) of benzyl bromide in 2 mL of diethyl ether was

followed by treatment with 0.42 g (1.94 mmol) of EMME. The resulting slurry was refluxed for 3 hours. Work-up as described for **1** and purification by column chromatography (R_f = 0.37 , 20% diethyl ether in hexane) gave 0.32 g (0.88 mmol, 46 %) of **4**: ^{1}H NMR ($CDCl_3$): δ 7.23-7.10 (10H, m), 4.12 (4H, q), 3.3 (1H, d), 2.8-2.6 (5H, m), and 1.2 (6H, t) ppm; ^{13}H NMR ($CDCl_3$): δ 168.9, 140.0, 129.2, 128.3, 126.1, 61.1, 53.0, 42.8, 37.2, and 14.0 ppm; IR (neat): 3200-2800, 1735, 1495, 1453, 1372, 1256, 1100, 1032, and 748 cm^{-1}; Mass Spectrum (m/z, Rel. Intensity): 354 (21, P^+), 309 (5), 281 (14), 263 (5), 235 (20), 208 (18), 195 (74), 263 (5), 235 (20), 208 (18), 195 (74), 180 (10), 161 (15), 115 (16), 91 (25), 84 (100), and 49 (85). HRMS. Calcd. for $C_{22}H_{26}O_4$, m/z 354.1831. Found. 354.1836 (± 1.8 mmu).

In addition, 0.15 g (0.69 mmol, 36 %) of EMME was recovered.

Diethyl 2-(1-ethoxy-1-phenylmethyl) Malonate, 5: Freshly distilled diethyl ether (7 mL) was added to 0.65 g of copper (I) iodide (3.44 mmol) in a flame dried, three-necked 25 mL flask equipped with an Ar inlet and a mechanical stirrer. This solution was cooled to -78°C and 3.82 mL of phenyllithium (1.8M in hexane, 6.88 mmol) was added with stirring over a 2 min period. A solution of EMME (0.37 g, 1.72 mmol) in 3 mL of ether was transferred by syringe to the reaction mixture and stirring continued for 30 min at - 78°C. The mixture was warmed to room temperature and stirred for 1 hr, then cooled to 0°C and cautiously hydrolyzed with 2 mL of H_20. The two layers were separated, and the aqueous layer was washed with two 15 mL portions of ether. The combined organic phase was filtered through Celite, and dried with $MgSO_4$. Purification by column chromatography (R_f = 0.4; 20 % diethyl ether in hexane) gave 0.31 g (1.10 mmol, 63 %) of **5**: ^{1}H NMR ($CDCl_3$): δ 7.39-7.24 (5H, m), 4.9-4.87 (1H, d), 4.3-4.2 (2H, q), 3.85-3.95 (2H, q), 3.75 (1H, d), 3.35 (2H, q), 1.30 (3H, t), 1.11 (3H, t), and 1.0 (3H, t) ppm; IR (neat): 3100-2800, 1742,

1740, 1454, 1370, and 1201 cm^{-1}; MS (m/z, Rel. Intensity): 294 (1, P^+), 265 (25), 249 (3), 221 (2), 179 (5), 149 (7), 135 (100), 107 (52), and 79 (28).

In addition, 0.1 g (0.36 mmol, 21 %) of EMME was recovered.

Diethyl 2-(1-ethoxypentyl) Malonate, 6: A solution of lithium-di-*n*-butyl cuprate solution was prepared by adding 2.75 mL of *n*-butyllithium (2.5 M in hexane, 6.89 mmol) via syringe to a suspension of 0.65 g (3.44 mmol) of cuprous iodide in 2 mL of anhydrous ether at -40°C, as described for **5**. A solution of EMME (0.37 g, 1.72 mmol) in 2 mL of ether was added, dropwise via syringe, over a period of 2 min. The mixture was stirred for 30 min at -40°C, for 3 hr at 0°C, and then quenched with 2 mL of water. Filtration and drying ($MgSO_4$) was followed by evaporation of solvents and purification by column chromatography ($R_f = 0.4$; 20 % diethyl ether in hexane) gave 0.25 g (0.92 mmol, 63 %) of **6**: ^1H NMR ($CDCl_3$): δ 4.2-4.1 (4H, q,q), 3.9-3.8 (1H, m), 3.5-3.4 (2H, q), 3.5 (1H, m), 1.5 (1H, m), 1.4-1.25 (6H, m), 1.26 (6H, t), 1.09 (3H, t), and 0.84 (3H, t) ppm; ^{13}C NMR ($CDCl_3$): δ 167.6, 167.4, 77.9, 66.1, 61.3, 61.2, 57.1, 32.4, 27.1, 22.7, 15.4, 14.1, 14.0, and 13.9 ppm; IR (neat): 3200-2800, 1744, 1473, 1393, 1295, 1215, 1156, 1091, and 1034 cm^{-1}; MS (m/z, Rel. Intensity): 275 (22, P^+), 229 (8), 217 (15), 171 (10), 161 (5), 141 (15), 115 (72), 103 (8), 99 (5), 85 (55), 83 (63), 77 (18), 59 (100), and 43 (30).

Diethyl 2-(1-ethoxy-2,2-dimethylpropyl) Malonate, 7: A solution of lithium-di-*t*-butyl cuprate solution was prepared by adding 5.18 mL of *t*-butyllithium (1.2 M in hexane, 6.8 mmol) via syringe to a suspension of 0.65 g (3.44 mmol) of cuprous iodide in 2 mL of anhydrous ether at -40°C. A solution of EMME (0.37 g, 1.72 mmol) in 2 mL of ether was added, dropwise via syringe, over a period of 2 min. The mixture was stirred for 30 min at -40°C, for 3 hr at 0°C, and then quenched with 2 mL of water. Filtration and drying ($MgSO_4$) was followed by evaporation of solvents and purification by column chromatography ($R_f = 0.14$; 20 % diethyl ether in hexane) gave 0.29 g (1.064 mmol, 62 %) of **7**: ^1H NMR ($CDCl_3$): δ 4.2-4.09 (4H, *q*), 3.7

(1H, d), 3.69-3.47 (m, 3H), 1.26-1.20 (6H, t), 1.14 (1H, m), 1.06 (3H, t), and 0.86 (9H, s) ppm; ^{13}C NMR ($CDCl_3$): δ 169.0, 168.8, 84.8, 69.0, 61.3, 54.8, 36.4, 31.0, 29.0, 25.7, 15.3, 14.0, and 13.9 ppm; IR (neat): 3200-2800, 1743, 1459, 1371, 1133, 1035, and 864 cm^{-1}; MS (m/z, Rel. Intensity): 275 (5, P^+), 229 (5), 217, 20), 161 (5), 155 (7), 145 (12), 115 (100), 103 (65), 99 (43), 87 (22), 71 (39), and 51 (60).

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