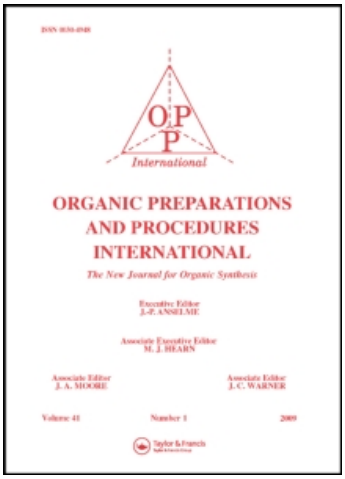

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

IMPROVED PREPARATION OF AMINOMETHYLENEMALONIC ACID DERIVATIVES BY TIN-PROMOTED ADDITION OF DIETHYL MALONATES TO NITRILES

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To cite this Article Nicolini, Marco and Citterio, Attilio(1993) 'IMPROVED PREPARATION OF AMINOMETHYLENEMALONIC ACID DERIVATIVES BY TIN-PROMOTED ADDITION OF DIETHYL MALONATES TO NITRILES', Organic Preparations and Procedures International, 25: 2, 229 — 231
To link to this Article: DOI: 10.1080/00304949309457951
URL: http://dx.doi.org/10.1080/00304949309457951

ORGANIC PREPARATIONS AND PROCEDURES INT., 25 (2), 229-258 (1993)

OPPI BRIEFS

IMPROVED PREPARATION OF AMINOMETHYLENEMALONIC ACID DERIVATIVES BY TIN-PROMOTED ADDITION OF DIETHYL MALONATES TO NITRILES

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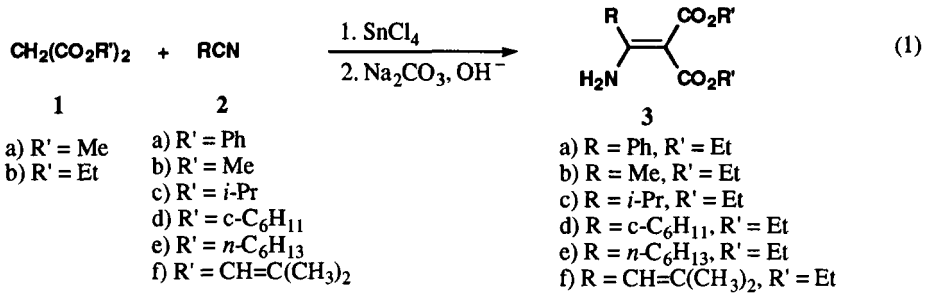
β-Aminomalonic acid derivatives **4** are intermediates for the preparation of β-amino acid derivatives **5**[1] with potential biological activity and were required as part of several ongoing studies. A general procedure for the synthesis of these compounds involves the tin-promoted addition of methylmalonate **1a** to nitriles **2** to yield aminomethylenemalonic acid derivatives **3** (Eq. 1)[2] which could then be converted to **5** (Eq. 2).

The drawback of the first step (Eq. 1) is that it affords only modest yield (17-55%) of **3** in a complex and a work-up procedure which cannot be generalized. Our attempts to solve these



(1)

1

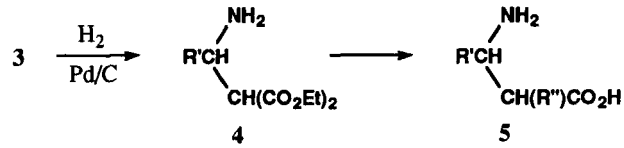
a) R' = Me
b) R' = Et

2

a) R' = Ph
b) R' = Me
c) R' = *i*-Pr
d) R' = c-C_6H_{11}
e) R' = *n*-C_6H_{13}
f) R' = CH=C(CH_3)$_2$

3

a) R = Ph, R' = Et
b) R = Me, R' = Et
c) R = *i*-Pr, R' = Et
d) R = c-C_6H_{11}, R' = Et
e) R = *n*-C_6H_{13}, R' = Et
f) R = CH=C(CH_3)$_2$, R' = Et



(2)

4 **5**

problems were directed at identifying conditions useful to improve this promising methodology. The procedure reported herein consists of the use of the esters of malonic acid higher than methyl

(mainly diethyl esters) and in a modification of the hydrolysis step. Some representative examples are reported in TABLE 1.

TABLE 1. Synthesis of Dialkyl β-Aminomalonates **3** by Tin(IV) Promoted Addition of Malonates **1** to Nitriles **2**

Entry	1	2	3	Yields (%)	mp. (°C)
1	**1b**	**2a**	**3a**	91	104-105
2	**1b**	**2b**	**3b**	91	oil
3	**1b**	**2c**	**3c**	50	oil
4	**1b**	**2d**	**3d**	87	60-61
5	**1b**	**2e**	**3e**	98	92-93
6	**1b**	**2f**	**3f**	80	48-49

EXPERIMENTAL SECTION

^{1}H NMR spectral data were obtained in $CDCl_3$ on a Bruker AM-250 NMR spectrometer. Chemical shifts (δ) are expressed in ppm, downfield from internal TMS. Mass spectra were determined on a RMU 6 spectrometer operating at 70 eV with an all glass inlet system. The purity of compounds **3** was checked by gas chromatography using a DANI 86.10 instrument equipped with a 25 m x 0.22 mm i.d. df=0.15 m/u CPIL 5CBcapillary column.

General Procedure.- Diethyl malonate (5.0 g, 0.038 mol), the nitrile (0.038 mol), 1,2-dichloroethane (20 mL) were placed in a 100 mL round-bottom flask equipped with a reflux condenser, a magnetic stirring bar, a serum cap and maintained under N_2 atmosphere. Stirring was started and $SnCl_4$ (21.7 g, 0.0836 mol) was added via a syringe in 10 min. The resulting mixture was heated at reflux for 2 hrs, then cooled at 20 and the solvent evaporated under reduced pressure (30 mmHg). The crude residue was dissolved in the minimum amount of acetone (80-100 mL) and a saturated aqueous Na_2CO_3 solution was added with vigorous stirring until the pH was 9-10. The white precipitate was collected through a sintered glass filter and washed with CH_2Cl_2 (4 x 50 mL). The combined solutions were dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified by recrystallization from 9:1 or 8:2 *n*-hexane-ethyl acetate, or by short path distillation. The purity of compounds **3a-3f** was checked by GLC and found to be higher than 98%.

Diethyl 2-Phenylaminomethylenemalonate (3a), white solid, ^{1}H NMR ($CDCl_3$): δ 7.4 (m, 5H), 8.95 (s broad, 1H), 5.15 (s broad, 1H), 4.24 (q, 2H, *J* = 6.5Hz), 3.82 (q, 2H, *J* = 6.5Hz), 1.30 (t, 3H, *J* = 6.5Hz), 0.80 (t, 3H, *J* = 6.5Hz). MS m/e (rel. int.): 263 (M^+; 26), 218 (35), 191 (45), 116 (30), 109 (100), 104 (81), 77 (33).

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.87; H, 6.51; N, 5.32. Found: C, 63.70; H, 6.70; N, 5.20

Diethyl 2-Methylaminomethylenemalonate (3b), ^{1}H NMR ($CDCl_3$): δ 8.94 (s broad, 1H), 5.14 (s broad, 1H), 4.20 (q, 2H, *J* = 7.0Hz), 4.16 (q, 2H, *J* = 7.0Hz), 2.12 (s, 3H), 1.30 (t, 3H, *J* = 7.00Hz), 1.26 (t, 3H, *J* = 7.00Hz).MS m/e (rel. int.):201 (M^+;36), 156 (92), 155 (47), 129 (44), 128 (50), 91

(55), 83 (38), 68 (19), 57 (58), 42 (100).

Anal. Calcd. for $C_9H_{15}NO_4$: C, 53.73; H, 7.46; N, 6.96. Found: C, 53.60; H, 7.90; N, 7.20

Diethyl 2-Isopropylaminomethylenemalonate (3c), ^{1}H NMR ($CDCl_3$): δ 8.84 (s broad, 1H), 5.08 (s broad, 1H), 4.22 (q, 2H, *J*= 7.0Hz), 4.15 (q, 2H, *J* = 7.0Hz), 2.98 (m, 1H), 1.30 (t, 3H, *J* = 7.0Hz), 1.26 (t, 3H, *J* = 7.0Hz), 1.18 (d, 6H, *J* = 7.0Hz). MS m/e (rel. int.): 229 (M^+, 13), 184 (43), 183 (37), 137 (58), 133 (39), 115 (60), 111 (37), 88 (26), 68 (34), 43 (100).

Anal. Calcd. for $C_{11}H_{19}NO_4$: C, 57.64; H, 8.30; N, 6.11. Found: C, 57.30; H, 8.50; N, 5.90

Diethyl 2-Cyclohexylaminomethylenemalonate (3d), white solid, ^{1}H NMR ($CDCl_3$): δ 8.81 (s broad, 1H), 5.08 (s broad, 1H), 4.20 (q, 2H, *J* = 6.7Hz), 4.12 (q, 2H, *J* = 6.7Hz), 2.63 (m, 1H), 1.5-2.0 (m, 10H), 1.30 (t, 3H, *J* = 6.7Hz), 1.21 (t, 3H, *J* = 6.7Hz). MS m/e (rel. int.): 269 (M^+, 23), 224 (49), 223 (51), 214 (28), 177 (69), 151 (28), 150 (28), 149 (49), 133 (38), 115 (56), 96 (26), 88 (23), 54 (23), 43 (100).

Anal. Calcd. for$C_{14}H_{23}NO_4$: C, 62.45; H, 8.55; N, 6.11. Found: C, 62.20; H, 8.70; N, 6.00

Diethyl 2-Hexylaminomethylenemalonate (3e), white solid, ^{1}H NMR ($CDCl_3$): δ 8.86 (s broad, 1H), 5.09 (s broad, 1H), 4.21 (q, 2H, *J* = 7.5Hz), 4.16 (q, 2H, *J* = 7.5Hz), 2.32-2.44 (m, 2H), 1.16-1.76 (m, 14H), 0.88 (t, 3H, *J* = 7.0Hz). MS m/e (rel. int.): 271 (M^+, 19), 225 (51), 213 (42), 200 (100), 167 (50), 129 (69), 96 (38), 83 (34), 57 (44).

Anal. Calcd. for $C_{14}H_{25}NO_4$: C, 61.99; H, 9.22; N, 5.17. Found: C, 62.00; H, 9.30; N, 5.30

Diethyl 2-Isopropenylaminomethylenemalonate (3f), pale yellow solid, ^{1}H NMR ($CDCl_3$): δ 8.76 (s broad, 1H), 5.16 (m, 1H), 5.10 (m, 1H), 5.08 (s broad, 1H), 4.18 (q, 2H, *J* = 6.75Hz), 4.13 (q, 2H, *J* = 7.0Hz), 2.0 (dd, 3H, *J* = 1.0Hz, 1.5Hz), 1.20 (t, 3H, *J* = 7.0Hz), 1.16 (t, 3H, *J* = 7.0Hz). MS m/e (rel. int.): 217 (M^+; 44), 198 (35), 182 (73), 154 (50), 152 (50), 109 (100), 83 (47), 80 (35), 68 (85).

Anal. Calcd. for$C_{12}H_{19}O_4N$: C, 59.75; H, 7.88; N, 5.81. Found: C, 59.60; H, 7.90; N, 5.70

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