Michael addition of nitromethane to isopropylidene 5-alkylidenemalonates

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The nitroethyl derivatives of isopropylidene malonate **2**, which were unknown, are synthesised by way of Michael addition of nitromethane to isopropylidene 5-alkylidenemalonates, among them 2,2-dimethyl-5-[1-(nitromethyl)cyclohexyl]-1, 3-dioxane-4,6-dione **2a**, which can be used as a new intermediate for synthesising Gabapentin.

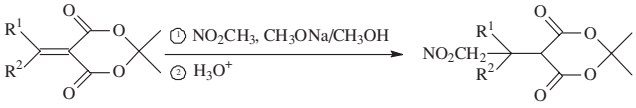
Keywords: isopropylidene 5-(2-nitroethyl)malonates, Michael addition, Meldrum's acid, nitromethane, isopropylidene alkylidenemalonates, gabapentin

As versatile reagents and important intermediates, Meldrum's acid (isopropylidene malonate) and its derivatives have been widely used in organic synthesis.[1-4] As α, β-unsaturated esters, isopropylidene 5-alkylidenemalonates are of high reactivity to many nucleophilic reagents. Up to now, however, Michael addition of nitromethane to isopropylidene 5-alkylidenemalonates has not been reported. Previously, we reported a cyanating addition to isopropylidene 5-alkylidenemalonates,[5] which provides a possible method for synthesising Gabapentin – an important drug which is very useful in the therapy of cerebral disorders such as certain forms of epilepsy, convulsant and other central nervous system diseases.[6] Although the procedure for synthesising Gabapentin is simpler than those reported earlier,[6,7] the use of poisonous and harmful cyanide is not desirable for considerations of safety. In the present investigation, we report a new procedure for synthesising the substituted 5-(2-nitroethyl)-Meldrum's acid which provides a simple and operationally safer way of synthesising Gabapentin.

Treatment of isopropylidene 5-alkylidenemalonates **1** with nitromethane in the presence of alkoxide at 0~10°C, gives Michael addition products **2**, as shown in Scheme 1.

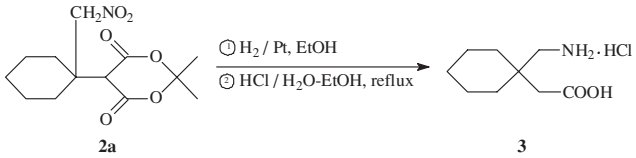
According to the literature,[1] we believed that the nitro derivatives of Meldrum's acid **2** could be hydrolysed to substituted γ-aminobutyric acids after reduction to their corresponding amines. In fact, the derivative of γ-aminobutyric acid, Gabapentin **3**, was readily prepared in one-pot using **2a** as starting material. This was catalytically hydrogenated using platinum as a catalyst and subsequently hydrolysed by hydrochloric acid (see Scheme 2).

In conclusion, we have introduced a new and efficient method for the synthesis of nitroethyl derivatives of isopropylidene malonate **2**, *via* one of which, **2a**, the anticonvulsant Gabapentin was obtained.



1		2	yield (%)
1a	R^1, R^2 = $(CH_2)_5$	2a	89
1b	R^1 = H, R^2 = phenyl	2b	85
1c	R^1 = H, R^2 = 4-methoxyphenyl	2c	86
1d	R^1 = H, R^2 = 3,4-dimethoxyphenyl	2d	85
1e	R^1 = H, R^2 = 4-chlorophenyl	2e	79
1f	R^1 = H, R^2 = 4-fluorophenyl	2f	78
1g	R^1 = H, R^2 = 4-hydroxyphenyl	2g	74
1h	R^1 = H, R^2 = ethyl	2h	87

Scheme 1



2a **3**

Scheme 2

Experimental

Melting points are uncorrected. ^{1}H NMR spectra were determined on a Brucker AC-80 instrument using TMS as an internal standard and $CDCl_3$ as solvent. IR spectra were recorded on a Perkin-Elmer 683 instrument. Mass spectra were obtained on an AEI MS-902 instrument. Elemental analyses were performed on a Carlo-Erba 1106 analytical instrument.

General procedure for the synthesis of ***2****:* To a stirred solution of **1** (5 mmol) and $NaOCH_3$ (5 mmol) in methanol (20 ml) was slowly added nitromethane (5 mmol) at 0–10°C. The mixture was stirred for 1 h at the same temperature and stood over night at room temperature. The reaction mixture was adjusted to pH 4 by adding 20% hydrochloric acid. After cooling, the precipitated crystals were collected by filtration, and washed successively with cooled methanol twice and water twice, and then dried to give a white crystalline powder **2** in good yield (see Scheme 1).

2a: M.p. 96–98 °C; ^{1}H NMR δ 5.22 (s, 2 H), 4.17 (s, 1 H), 1.73–2.18 (m, 10 H), 1.79 (s, 3 H), 1.64 (s, 3 H); IR (KBr, cm^{-1}) 1776, 1743, 1548, 1459, 1386, 875, 847; MS (%) 228 (2.13), 210 (5.85), 184 (1.16), 145 (4.41), 135 (7.69), 95 (96.41). Anal. calcd. for $C_{13}H_{19}NO_6$ C 54.73% H 6.71% N 4.91%, Found C 54.66% H 6.68% N 4.90%.

2b: M.p. 84–86 °C; ^{1}H NMR δ7.24–7.44 (m, 5 H), 5.15-5.41 (m, 2 H), 4.50–4.71 (m, 1 H), 3.88 (d, *J*=3.0Hz, 1 H), 1.73 (s, 3 H), 1.39 (s, 3 H); IR (KBr, cm^{-1}) 1779, 1740, 1554, 1385, 1330, 884; MS (%) 293 (0.54), 246 (0.42), 218 (3.29), 160 (13.22), 144 (5.95), 131 (8.30). Anal. calcd. for $C_{14}H_{15}NO_6$ C 57.34% H 5.16% N 4.78%, Found C 57.31% H 5.20% N 4.75%.

2c: M.p. 84–86 °C; ^{1}H NMR δ7.26 (d, *J*=8.8Hz, 2 H), 6.84 (d, *J*=8.8Hz, 2 H), 5.02–5.23 (m, 2 H), 4.49–4.71 (m, 1 H), 3.99 (d, *J*=3.0Hz, 1 H), 3.75 (s,3H), 1.72 (s, 3 H), 1.42 (s, 3 H); IR (KBr, cm^{-1}) 1789, 1749, 1555, 1378, 830; MS (%) 324 (0.83), 323 (4.54), 276 (1.35), 248 (2.29), 218 (3.94), 190 (52.62), 174 (22.67), 161 (29.05). Anal. calcd. for $C_{15}H_{17}NO_7$ C 55.73% H 5.30% N 4.33%, Found C 55.54% H 5.33% N 4.32%.

2d: M.p. 124–126 °C; ^{1}H NMR δ6.40–6.83 (m, 3 H), 5.09–5.30 (m, 2 H), 4.57–4.80 (m, 1 H), 4.00 (d, *J*=3.0Hz, 1 H), 3.856 (s, 3H), 3.850 (s, 3H), 1.72 (s, 3 H), 1.46 (s, 3 H); IR (KBr, cm^{-1}) 1781, 1747, 1556, 1467, 1379, 886, 853; MS (%) 354 (1.59), 353 (9.38), 306 (1.32), 278 (1.98), 251 (5.23), 248 (2.82), 220 (12.48), 204 (31.14), 191 (35.94). Anal. calcd. for $C_{16}H_{19}NO_8$ C 54.39% H 5.42% N 3.96%, Found C 54.57% H 5.45% N 3.91%.

2e: M.p. 90–92 °C; ^{1}H NMR δ7.36 (s, 4 H), 5.06–5.33 (m, 2 H), 4.49–4.68 (m, 1 H), 3.95 (d, *J*=3.0Hz, 1 H), 1.70 (s, 3 H), 1.52 (s, 3 H); IR (KBr, cm^{-1}) 1791, 1749, 1550, 1384, 1331, 890, 831; MS (%) 327 (0.23), 280 (0.41), 254 (0.84), 252 (2.32), 225 (1.23), 224 (3.93), 223 (3.58), 222 (10.54), 194 (28.41), 178 (24.70). Anal. calcd. for $C_{14}H_{14}ClNO_6$ C 51.31% H 4.31% N 4.27%, Found C 51.64% H 4.35 % N 4.27%.

2f: mp. 84–86 °C; ^{1}H NMR δ7.19–7.34 (m, 4 H), 5.10–5.32 (m, 2 H), 4.47-4.68 (m, 1 H), 3.96 (d, *J*=3.0Hz, 1 H), 1.70 (s, 3 H), 1.51 (s, 3 H); IR (KBr, cm^{-1}) 1795, 1778, 1555, 886, 839; MS (%) 311 (0.18), 264 (0.41), 236 (2.82), 206 (8.77), 178 (24.45), 162 (22.47),

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149 (17.27). Anal. calcd. for $C_{14}H_{14}FNO_6$ C 54.02% H 4.53% N 4.50%, Found C 54.19% H 4.55% N 4.57%.

2g: M.p. 146–148 °C; ^{1}H NMR δ7.14 (d, *J*=8.0Hz, 2 H), 6.74 (d, J=8.0Hz, 2 H), 5.09–5.31 (m, 2 H), 4.30–4.49 (m, 1 H), 2.51 (s, 1 H), 1.69 (s, 3 H), 1.49 (s, 3 H); IR (KBr, cm^{-1}) 3519, 1779, 1736, 1554, 891, 837; MS (%) 309 (0.45), 262 (0.37), 234 (1.08), 220 (0.81), 204 (0.74), 176 (15.34), 160 (6.96), 147 (9.30). Anal. calcd. for $C_{14}H_{15}NO_7$ C 54.37% H 4.89% N 4.53%, Found C 54.56% H 4.91% N 4.60%.

2h: M.p. 128-130 °C; ^{1}H NMR δ4.66–4.92 (m, 2 H), 3.89 (d, *J*=3.0Hz, 1 H), 3.10–3.32 (m, 1 H), 1.75 (s, 6 H), 1.50–1.75 (m, 2 H), 0.98 (t, 3H); IR (KBr, cm^{-1}) 1776, 1741, 1547, 1460, 1387, 1342, 913, 884, 636; MS (%) 246 (0.35), 218 (3.62), 188 (21.44), 171 (8.08), 160 (40.90), 145 (13.30), 144 (48.50), 115 (50.62). Anal. calcd. for $C_{10}H_{15}NO_6$ C 48.98% H 6.17% N 5.71%, Found C 49.54% H 6.09% N 5.65%.

One-pot procedure for the synthesis of Gabapentin

In an autoclave, **2a** (2g) in ethanol (30 ml) was hydrogenated (5 atm) for 4 h at 130 °C in the presence of the catalyst Pt (0.5g). The catalyst was filtered off and the filtrate was concentrated. The residue was mixed with 20% aqueous hydrochloric acid (20 ml), and the whole was refluxed for 5 h. The reaction mixture was cooled, and added to a mixture of water (30 ml) and methylene chloride (30 ml). The aqueous layer was separated and concentrated to dryness under reduced pressure, and the residue was mixed with acetone (30 ml). The white solid crystallised out upon standing, was collected by filtration, washed with acetone and dried to give 0.9 g **3**, yield 62%.

3: M.p. 122–124 °C (lit.[8]123–127 °C); Anal. calcd. for $C_9H_{18}NO_2Cl$ C 52.04% H 8.73% N 6.74%, Found C 51.84% H 8.85% N 6.65%.

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