Lactim Ether Chemistry. Cyclic β-Enamino Ester Synthesis

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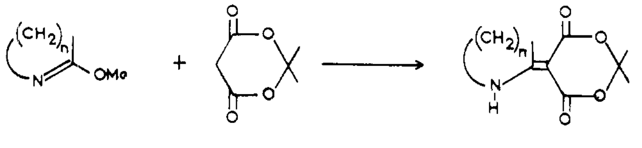
Several methods for the synthesis of two cyclic enamino esters 1, n = 3 and 4, have been described in the literature[1-5] but generally with low yields (about 20% from 2-pyrrolidinone and 2-piperidone). We report a facile and versatile three-step synthesis of the enamino esters 1, n = 3–5, in yields of 30–57%.

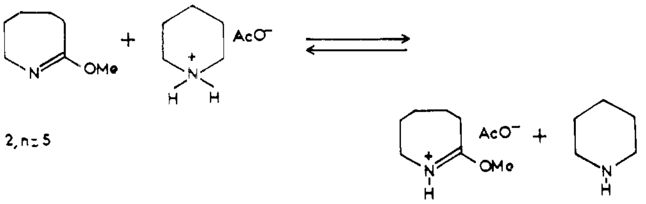
Under mild conditions[1,2,6-8] active methylene compounds, except malonates, react with lactim ethers 2.



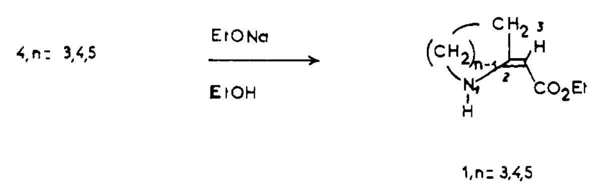
2, n=3,4,5 3 4

Compounds 4, n = 3 and 4, were obtained by reaction of 2, n = 3 and 4, in the presence of triethylamine,[1] with isopropylidene malonate (3): pK_a = 5.1;[9] no reaction occurred with 2, n = 5.

However, O-methylcaprolactim (2, n = 5) reacted in the presence of piperidinium acetate as catalyst to give 4, n = 5, in 58% yield. An equilibrium between lactim ether and piperidinium acetate shows the increasing reactivity of 2 as below:



Acidic[10] and nonacidic alcoholyses[11] were inefficient to open cyclic esters 4, n = 3–5, but enamino esters 1, n = 3–5, could be prepared by reaction with sodium ethoxide (70% yield).



Stereochemical assignments are based on IR, ^{1}H NMR, and ^{13}C NMR data and on ^{1}H NMR shift reagent studies, using tris(dipavalomethanato)europium(III) or Eu(DPM)$_3$. With Eu(DPM)$_3$ no larger deshielding effects were observed for C-3 hydrogens of β-enamino esters 1, n = 3–5, indicating all to be Z isomers.

Experimental Section

General Procedure for Reactions of 2, n = 3 and 4, with 3. Lactim ether 2[7,2] (0.2 mol), isopropylidene malonate[9] (28.8 g, 0.2 mol), and triethylamine (5 mL) were refluxed overnight in benzene (200 mL). After evaporation of benzene, the products were isolated as usual.

Isopropylidene α-(Tetrahydro-2-pyrrolidene)malonate (4, n = 3): yield 29 g, recrystallized from ethanol (94%); mp 171 °C; IR (CHBr$_3$) 3260, 1695, 1645, 1570 cm^{-1}; NMR (CDCl$_3$) δ 1.67 (s, 6 H), 2.16 (m, 2 H), 3.41 (m, 2 H), 3.80 (m, 2 H), 9.84 (s, 1 H); MS m/e 211 (53), 154 (67), 109 (100), 43 (85).

Anal. Calcd for $C_{10}H_{13}NO_4$: C, 56.86; H, 6.20; N, 6.63. Found: C, 56.61; H, 6.10; N, 6.61.

Isopropylidene α-(Hexahydro-2-pyridinylidene)malonate (4, n = 4): yield 34 g, recrystallized from ethanol (76%); mp 116 °C; IR (CHBr$_3$) 3200, 1695, 1635, 1600 cm^{-1}; NMR (CDCl$_3$) δ 1.67 (s, 6 H), 1.80 (m, 4 H), 3.20 (m, 2 H), 3.55 (m, 2 H), 11.50 (s, 1 H); MS m/e 225 (1), 168 (41), 167 (56), 123 (100).

Anal. Calcd for $C_{11}H_{15}NO_4$: C, 58.65; H, 6.71; N, 6.22. Found: C, 58.51; H, 6.84; N, 6.41.

Isopropylidene α-(Hexahydro-2-azepinylidene)malonate (4, n = 5). O-Methylcaprolactim[12] (6.2 g, 0.05 mol), isopropylidene malonate (7.2 g, 0.05 mol), acetic acid (4 mL), and piperidine (2 mL) were refluxed overnight in benzene (70 mL). After evaporation, the crude product was recrystallized from methanol to give 4, n = 5: yield 6.9 g (58%); mp 147 °C; IR (CHBr$_3$) 3200, 2950, 1700, 1650, 1600 cm^{-1}; NMR (CDCl$_3$) δ 1.70 (s, 6 H), 1.80 (m, 6 H), 3.35–3.70 (m, 4 H), 11.50 (s, 1 H): MS m/e 239 (25), 182 (51), 181 (92), 137 (100).

Anal. Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.28; H, 7.05; N, 6.08.

General Procedure to Open Cyclic Esters 4. Sodium ethoxide (0.1 mol) in ethanol (200 mL) and 4 (0.1 mol) were refluxed overnight. After evaporation of solvent, under vacuum, water (150 mL) and then hydrochloric acid (10%) were added until the pH was 6. The resulting mixture was extracted with chloroform (3 × 30 mL) and dried on sodium sulfate, and then the solvent was removed.

Ethyl α-(Tetrahydro-2-pyrrolidinylidene)acetate (1, n = 3): yield 14.1 g, recrystallized from hexane (91%); mp 62 °C (lit.[1] mp 63 °C).

Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 61.72; H, 8.60; N, 9.00.

Ethyl α-(Hexahydro-2-pyridinylidene)acetate (1, n = 4): yield 10.2 g (60%), distilled under vacuum; bp 92 °C (0.1 mm) (lit.[2] bp 104 °C (2 mm)); n^{22}_{D} = 1.5243.

Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.11; H, 9.06; N, 8.37.

Ethyl α-(Hexahydro-2-azepinylidene)acetate (1, n = 5): yield 15 g, recrystallized from methanol (82%); mp 49 °C; IR (CHBr$_3$) 3280, 2950, 1620, 1574 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.22 (t, 3 H, J = 7 Hz), 1.70 (m, 6 H), 2.25 (m, 2 H), 3.35 (m, 2 H), 4.08 (q, 2 H, J = 7 Hz), 4.45 (s, 1 H), 8.83 (s, 1 H); ^{13}C NMR (CDCl$_3$) δ 14.74 (CH$_2$CH$_3$), 26.57 (C-5), 30.21 (C-4), 30.52 (C-6), 35.13 (C-3), 44.29 (C-7), 58.30 (CH$_2$CH$_3$), 80.81 (=CH), 168.42 (C-2), 170.85 (CO$_2$Et); MS m/e 183 (58), 138 (65), 111 (100).

Anal. Calcd for $C_{10}H_{17}NO_2$: C, 65.54; H, 9.35; N, 7.64. Found: C, 65.45; H, 9.35; N, 7.76.

Registry No. 1 (n = 3), 35150-22-2; 1 (n = 4), 25654-24-4; 1 (n = 5), 70912-51-5; 2 (n = 3), 5264-35-7; 2 (n = 4), 5693-62-9; 2 (n = 5), 2525-16-8; 3, 2033-24-1; 4 (n = 3), 70912-52-6; 4 (n = 4), 70912-53-7; 4 (n = 5), 70912-54-8.

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