Synthesis of Cyclic Oxoenaminoesters

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Ammonia and primary amines react with dimethyl 3-oxo-1,ω-alkanedioates to give cyclic *N*-acylated enaminoesters.

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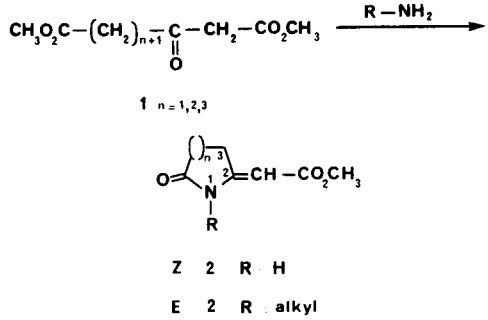
Cyclic *N*-acylated enaminoesters **2** are versatile intermediates for the synthesis of natural products like bile pigments [1,2]. Recent synthesis of enaminoesters have been described by reaction of Meldrum's acid with chloroimidates [3], or by opening of oxirane with sodium azide in the presence of ammonium chloride [4]. We would now like to report a convenient synthesis of acylated enaminoesters from easy prepared dimethyl 3-oxo-1,ω-alkanedioates **1**.

The β-ketoesters **1**, prepared from carbomethoxy alkanoyl chlorides [5,6] were treated with ammonia in methanol at 140° (method A) or with primary amines with removal of the water produced by azeotropic distillation. The enaminoesters intermediates were then cyclized with sodium hydride at room temperature (method B). The results are reported in Tables I and II.



The stereochemistry of these compounds could be established as *Z* for **2a** and as *E* for **2b-f** by the comparison of the 3-H chemical shifts which are either affected or not affected by the anisotropic effect of the carbonyl function.

In contrast to the Orr synthesis [4], this reaction is a one-step synthesis of acylenaminoesters utilizing an intramolecular stereospecific amidification. The stereochemistry is fixed by the substitution of the amine involved during the cyclization.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded on a Beckman IR 20 spectrophotometer. The nmr spectra were obtained on a Varian A 60 A spectrophotometer with tetramethylsilane as internal reference using deuteriochloroform or carbon tetrachloride as solvent. Chemical shifts are reported in parts per million (δ) and signals are quoted as: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). The presence of exchangeable protons was confirmed by use of deuterium oxide.

Ketoesters **1**. General Procedure.

Dimethyl 3-oxohexanedioate **1** (n = 1) was prepared as described [5] by condensation of Meldrum's acid with carbomethoxypropionyl chloride [7,8].

Dimethyl 3-oxoheptanedioate **1** (n = 2) was obtained by the same procedure from carbomethoxybutanoyl chloride [1,9], yield 70%, bp 120°/0.5 torr (lit [1] bp 120°-121°/0.2 torr); ir (neat): 1740, 1680 cm^{-1} (C=O); nmr (carbon tetrachloride): 1.70-2.90 (m, 6H), 3.45 (s, 2H), 3.67 (s, 3H), 3.75 (s, 3H).

Table I

Cyclic Oxoenaminoesters **2a-f**

Formula Number	n	R	Method	Yield (%)	bp (°C)/torr or (and) mp (°C)/solvent	Molecular formula or Lit mp (°C)	Analyses % Calcd./Found C	H	N
2a	1	H	A	56	160°/0.01 58°/EtOH	57-58° [1]	–	–	–
2b	1	C_6H_5-CH_2	B	62	109°/EtOH	$C_{14}H_{15}NO_3$	68.55 68.41	6.16 6.08	5.17 5.83
2c	1	*i*-C_3H_7	B	35	78°/EtOH	$C_{10}H_{15}NO_3$	60.89 61.07	7.67 7.54	7.10 7.02
2d	1	*n*-C_4H_9	B	40	62°/EtOH	$C_{11}H_{17}NO_3$	62.54 62.77	8.11 8.02	6.63 6.51
2e	1	CH_2=CH-CH_2	B	49	135°/0.05	$C_{10}H_{13}NO_3$	61.52 61.38	6.71 6.82	7.18 7.04
2f	2	C_6H_5-CH_2	B	54	90°/EtOH	$C_{15}H_{17}NO_3$	69.48 69.41	6.61 6.50	5.40 5.62

Table II

IR and NMR Spectral Data of Compounds **2a-f**

Compound	IR, cm^{-1}	NMR, (deuteriochloroform), (ppm)
2a	1740, 1680 1630	2.20-3.10 (m, 4H), 3.68 (s, 3H), 4.95 (s, 1H), 8.80-9.60 (broad s, 1H)
2b	1730, 1700 1620	2.40-3.50 (m, 4H), 3.65 (s, 3H), 4.72 (s, 2H), 5.22 (s, 1H), 7.10-7.45 (m, 5H)
2c	1700, 1680 1610	1.38 (d, J = 7 Hz, 6H), 2.20-3.35 (m, 4H), 3.57 (s, 3H), 4.00-4.55 (m, 1H), 5.18 (s, 1H)
2d	1725, 1700 1610	0.95 (m, 3H), 1.05-1.80 (m, 4H), 2.35-3.75 (m, 6H), 3.70 (s, 3H), 5.22 (s, 1H)
2e	1720, 1695 1610	2.25-3.25 (m, 4H), 3.55 (s, 3H), 4.05 (d, J = 5 Hz, 2H), 4.95-6.05 (m, 4H)
2f	1700, 1680	1.65-2.15 (m, 2H), 2.68 (t, J = 7 Hz, 2H), 3.24 (t, J = 7 Hz, 2H), 3.58 (s, 3H), 4.95 (s, 2H), 5.24 (s, 1H), 6.95-7.45 (m, 5H)

Dimethyl 3-oxooctanedioate **1** (n = 3) was prepared in the same way from carbomethoxypentanoyl chloride [10], yield 65%, bp 140°/0.1 torr; ir (neat): 1740, 1710 cm^{-1} (C=O); nmr (carbon tetrachloride): 1.40-1.80 (m, 4H), 2.00-2.70 (m, 4H), 3.36 (s, 2H), 3.63 (s, 3H), 3.72 (s, 3H).

Acyl Enaminoesters **2**.

Method A.

Ketodiester **1** (n = 1) (4.7 g, 0.025 mole) in methanol (20 ml) containing ammonia (2.4 g) were treated at 140° for 8 hours in an autoclave. The solvent was then evaporated and the residual product **2a** distillated.

Method B.

Ketodiester **1** (n = 1) (4.7 g, 0.025 mole) and 0.025 mole of primary amine were refluxed in toluene (75 ml), the water formed being removed by azeotropic distillation. This crude solution was added to a suspension of sodium hydride (0.025 mole) in toluene (25 ml). The mixture was stirred overnight at room temperature. Then water (100 ml) and 10% hydrochloric acid were added drop by drop; the later until *p*H = 6 was reached. The toluene layer was separated and the water layer extracted with chloroform (2 x 50 ml). The joined organic layers were dried with sodium sulfate and evaporated. The residual crude product was distilled or recrystallized from ethanol.

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