Imidate Chemistry: A General and Versatile Synthesis of β-Enaminoesters, β-Ketoesters, and Methyl Ketones from Nitriles

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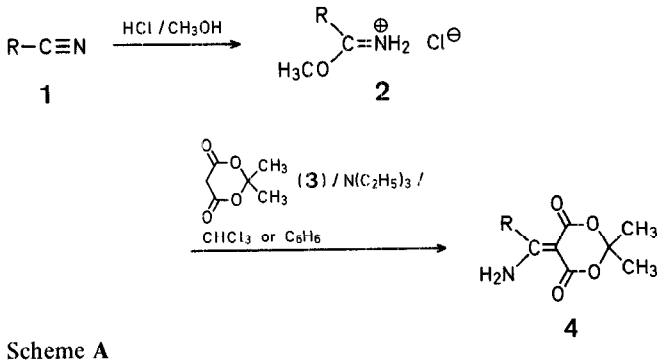
Since the first example of the Claisen condensation was discovered more than a century ago, β-ketoesters and derivatives have been important intermediates in organic synthesis[2]. In addition to the ammonolysis[3] of β-ketoesters, β-enaminoesters have been prepared in poor yields by the condensation of Grignard reagents with cyanoacetates[4]. We report here a general and versatile method based on the reactivity of Meldrum's acid[5] (**3**) with imidates **2**, as outlined in Scheme **A**. Under the same conditions, active methylene compounds such as malononitrile, ethyl or benzyl cyanacetate reacted with the imidate derived from acetonitrile, but no reaction occurred with acetylacetone, ethyl acetoacetate, or diethyl malonate. However, good yields were ob-



1 2 4

Scheme **A**

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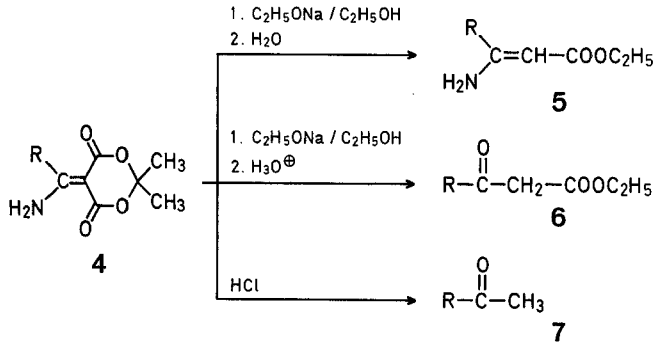
tained on reaction with Meldrum's acid (**3**), probably due to its high acidity (pKa = 5.1[5b]). The imidate hydrochlorides **2** were prepared by the classical Pinner synthesis[6]. The results are summarised in Table 1.

As it is known that acylated Meldrum's acids[7] are readily transformed into β-ketoesters by alcoholyses, the subsequent reactions of **4** represent the easy transformations of the β-enaminodiesters **4** to β-enaminoesters **5**, β-ketoesters **6**, or methyl ketones **7** as shown in Scheme **B**.

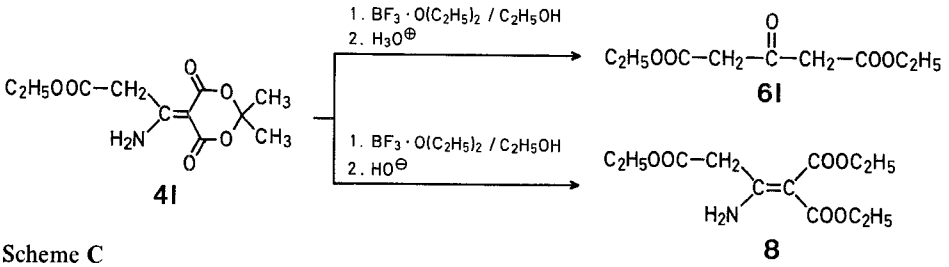


Scheme **B**

The ring of the β-enaminodiesters **4** may be opened by treatment with sodium ethoxide and variation of the acidity during the hydrolysis step permits the isolation of either β-enaminoester **5** at pH = 14 (Table 2) or β-ketoesters **6** at pH = 5–6 (Table 3). Finally, the use of drastic conditions (concentrated hydrochloric acid) may lead, after hydrolysis and decarboxylation, to the methyl ketones **7** (Table 4).

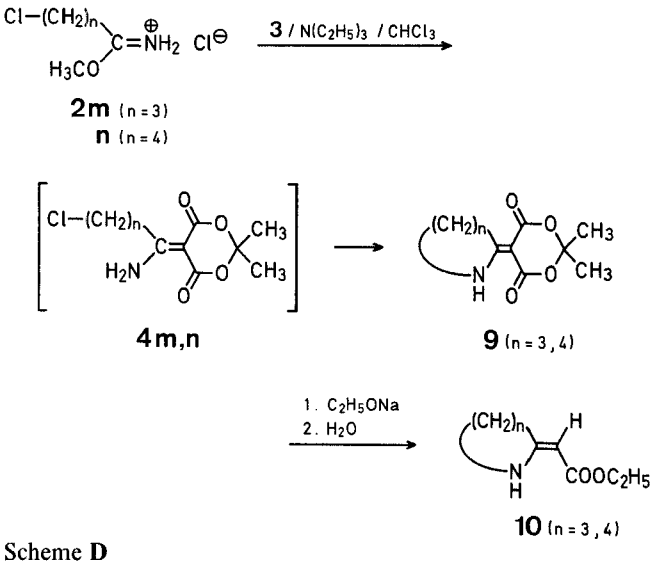
The methyl ketones **7m** and **7n** are of particular interest; **7m** is an important intermediate for the synthesis of nerolidol[18].

Compound **4l**, which contains acidic protons, was precipitated on treatment with sodium ethoxide in ethanol as a non-soluble sodium salt. However, **4l** was transformed by treatment with boron trifluoride etherate to diethyl 3-oxopentane-1,5-dioate (**6l**) at pH = 5–6, whereas basic hydrolysis did not result in further decarboxylation of the intermediate **8**, as shown in Scheme **C** (40% yield).



Scheme **C**

With the imidates **2m, n** in which R = Cl–(CH$_2$)$_n$–, on reaction with **3**, ring closure took place in chloroform leading to the cyclic β-enaminoesters **9** in yields of 24 and 26% yields, respectively (Scheme **D**); the difference in behavior in benzene and chloroform as solvent was due to the total solubility of triethylamine hydrochloride in chloroform. We have recently shown[19] that products (n = 3, 4), may be transformed by a similar process into compounds **10** (n = 3, 4).



Scheme **D**

β-Enaminodiesters 4; General Procedure:

Method A: in chloroform: The imidate hydrochloride **2** (0.1 mol), Meldrum's acid[5b] (**3**; 14.4 g, 0.1 mol) and triethylamine (16 ml, 0.115 mol) are heated under reflux overnight in chloroform (100 ml). The organic layer is washed with water (3 × 100 ml) until pH 7–8, dried with sodium sulfate, and then the solvent is removed. Trituration of the oily residue with ether gives a solid product which is recrystallised from an appropriate solvent (Table 1).

Method B: in benzene: The imidate hydrochloride **2** (0.1 mol), Meldrum's acid[5b] (**3**; 14.4 g, 0.1 mol) and triethylamine (16 ml, 0.115 mol) are heated under reflux overnight in benzene (200 ml). After evaporation of solvent under vacuum, water (150 ml) is added. The resulting mixture is extracted with chloroform (3 × 40 ml) and the extract dried with sodium sulfate. Trituration of the oily residue with ether gives a solid product which is recrystallised from an appropriate solvent (Table 1).

β-Enaminoesters 5; General Procedure:

The β-enaminodiester **4** (0.05 mol) and sodium ethoxide (3.74 g, 0.055 mol) in ethanol (55 ml) are heated under reflux overnight. After evaporation of the solvent, water (100 ml) is added. The resulting mixture is extracted with chloroform (3 × 40 ml), dried with sodium sulfate, and evaporated. The crude product is distilled or recrystallised (Table 2). With **4k**, a stoichiometric amount of sodium ethoxide is used and the mixture is heated under reflux for 10 h.

β-Ketoesters 6; General Procedure:

The β-enaminodiester **4** (0.05 mol) and sodium ethoxide (3.74 g, 0.055 mol) in ethanol (55 ml) are heated under reflux overnight. After evaporation of solvent, water (100 ml) and then hydrochloric acid (10%) are added until pH 5–6. The resulting mixture is extracted with chloroform (3 × 40 ml), dried with sodium sulfate, and evaporated. The crude product is distilled or recrystallised (Table 3). With **4j**, 0.1 mol of 10% hydrochloric acid is added.

Methyl Ketones 7; General Procedure:

The β-enaminodiester **4** (0.05 mol) is heated under reflux in concentrated hydrochloric acid (40 ml). Potassium carbonate is added until pH 7, the resulting mixture is extracted with chloroform (3 × 40 ml) and dried with sodium sulfate. The crude product is distilled (Table 4).

Diethyl 3-Oxopentane-1,5-dioate (6l):

The β-enaminodiester **4l** (25.7 g, 0.1 mol) and boron trifluoride etherate (50 ml, 0.3 mol) are heated under reflux for 48 h in ethanol (200 ml). Removal of the solvent under vacuum, addition of water (200 ml), and re-

Table 1. β-Enaminodiesters **4a–n**

Product No.	R	Yield [%] in C_6H_6	Yield [%] in $CHCl_3$	m.p. [°C] (solvent)	Molecular formula[a]		^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm] $>C(CH_3)_2$
4a	H	—	76	215° (dec) (acetone)	$C_7H_9NO_4$	(171.1)	1.65[b]
4b	CH_3	70	70	163° (C_2H_5OH)	$C_8H_{11}NO_4$	(185.2)	1.70
4c	C_2H_5	50	67	95° (i-C_3H_7OH)	$C_9H_{13}NO_4$	(199.2)	1.70
4d	n-C_3H_7	34	33	106° (C_2H_5OH)	$C_{10}H_{15}NO_4$	(213.2)	1.70
4e	n-C_4H_9	65	29	80° (ether)	$C_{11}H_{17}NO_4$	(227.2)	1.70
4f	n-$C_{17}H_{35}$	80	66	88° (ether)	$C_{24}H_{43}NO_4$	(409.6)	1.68
4g	i-C_3H_7	14	17	152° (C_2H_5OH)	$C_{10}H_{15}NO_4$	(213.2)	1.70
4h	c-C_3H_5	7	29	198° (acetone)	$C_{10}H_{13}NO_4$	(211.2)	1.70
4i	$C_6H_5CH_2$	65	47	166° (C_2H_5OH)	$C_{14}H_{15}NO_4$	(261.3)	1.65
4j	C_6H_5	22	22	164° (C_2H_5OH/H_2O)	$C_{13}H_{13}NO_4$	(247.2)	1.73
4k	4-O_2N—C_6H_4	—	49	227° ($CHCl_3$)	$C_{13}H_{12}N_2O_6$	(292.2)	1.70[b]
4l	C_2H_5O—CO—CH_2	92	60	111° (C_2H_5OH)	$C_{11}H_{15}NO_6$	(257.2)	1.70
4m	Cl—$(CH_2)_3$—	90	—	120° ($CHCl_3$/ether)	$C_{10}H_{14}ClNO_4$	(247.5)	1.68
4n	Cl—$(CH_2)_4$—	64	—	80° (ligroin)	$C_{11}H_{16}ClNO_4$	(261.5)	1.68

[a] Satisfactory microanalyses obtained (C ±0.40, H ±0.23, N ±0.22, Cl ±0.22); exception: **4e** C ±0.49.
[b] DMSO-d_6 solution.

Table 2. β-Enaminoesters **5a–k**

Product No.	R	Yield [%]	b.p. [°C]/torr or m.p. [°C] (solvent)	Molecular formula[a] or Lit. b.p. [°C]/torr		^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm] =CH—
5a	H	48	—[b]	$C_5H_9NO_2$	(115.1)	4.4–5.1
5b	CH_3	81	100°/10	101°/13[4]		4.50
5c	C_2H_5	63	75°/0.07	74°/2[4]		4.43
5d	n-C_3H_7	59	115°/5	88°/2[4]		4.55
5e	n-C_4H_9	89	108°/3	96°/2[4]		4.55
5f	n-$C_{17}H_{35}$	82	52° (ether)	$C_{22}H_{43}NO_2$	(353.6)	4.68
5g	i-C_3H_7	89	102°/4	$C_8H_{15}NO_2$	(157.2)	4.67
5h	c-C_3H_5	68	109°/3	$C_8H_{13}NO_2$	(155.2)	4.45
5i	$C_6H_5CH_2$	62	47° (C_2H_5OH)	$C_{12}H_{15}NO_2$	(205.2)	4.61
5j	C_6H_5	85	117°/0.1	141°/2[4]		4.87
5k	4-O_2N—C_6H_4	61	91° (ether)	$C_{11}H_{12}N_2O_4$	(236.2)	5.00

[a] Satisfactory microanalyses obtained (C ±0.31, H ±0.31, N ±0.22).
[b] Isolated by column chromatography of silica gel (Merck 60, 35–70 mesh), eluting with acetone.

Table 3. β-Ketoesters **6b–h, j, l**

Product No.	R	Yield [%]	b.p. [°C]/torr or m.p. [°C] (solvent) found	reported
6b	CH_3	85	80°/15	181°/760[8]
6c	C_2H_5	59	82°/7	75–78°/9[9]
6d	n-C_3H_7	41	104°/22	84–88°/11[10]
6e	n-C_4H_9	65	90°/0.05	110–112°/16[9]
6f	n-$C_{17}H_{35}$	64	48° (ether)	46°[10]
6g	i-C_3H_7	65	90°/15	86°/15[11]
6h	c-C_3H_5	41	70°/0.05	100°/11[12]
6j	C_6H_5	81	105°/0.02	119°/1[13]
6l	C_2H_5O—CO—CH_2	22	87°/0.3	146°/15[14]

moval of the inorganic residue by filtration leaves an aqueous layer which is extracted with chloroform (3 × 100 ml) and dried with sodium sulfate. After evaporation of the solvent, the crude product is distilled to give **6l**; yield: 4.5 g (22%); b.p. 87°C/0.3 torr (Lit.[14], b.p. 146°C/15 torr).

Diethyl 3-Amino-2-ethoxycarbonyl-2-pentene-1,5-dioate (8):
The β-enaminodiester **4l** (10.0 g, 0.04 mol) and boron trifluoride etherate (20 ml, 0.16 mol) are heated under reflux for 48 h in ethanol (200 ml).

Table 4. Methyl Ketones **7i, m, n**

Product No.	R	Yield [%][a]	b.p. [°C]/torr found	reported
7i	$C_6H_5CH_2$	53	93°/15	217°/760[15]
7m	Cl—$(CH_2)_3$	24	61°/15	71°/20[16]
7n	Cl—$(CH_2)_4$	73	45°/0.1	85°/16[17]

[a] Purity >99% by G.L.C. (SE 30, 1.5 m, 140°C).

The reaction mixture is then added drop-wise to a saturated solution of potassium carbonate (100 ml). The resulting solution is extracted with chloroform (3 × 75 ml) and dried with sodium sulfate. After evaporation of the solvent the crude product is distilled to give **8**; yield: 4.2 g (40%); b.p. 95°C/1 torr; n_D^{23}: 1.4557.

$C_{12}H_{19}NO_6$	calc.	C 52.74	H 7.01	N 5.13
(273.3)	found	52.90	7.03	5.31

I.R. (neat): ν = 3400, 2960, 1735, 1705, 1620 cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$): δ = 1.0–1.5 (m, 9H); 3.00 (s, 0.5H); 3.50 (q, 5H, J = 7 Hz); 3.80 (s, 1H); 3.9–4.4 (m, 1H); 5.15 (s, 0.5H); 9.50 ppm (s, 2H).

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