Studies on Pyrrolidones. Synthesis and *N*-Alkylation of β-Enaminoesters Derived from Pyroglutamic Acid

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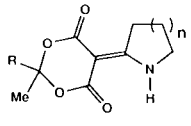
Received December 16, 1991

The condensation of iminoether **7**, derived from pyroglutamic acid (**4**), with active methylene reagents such as Meldrum's acid or methyl cyanoacetate, lead to β-enaminoesters **2**. Solid-liquid phase transfer *N*-alkylation of these compounds is described.

J. Heterocyclic Chem., **29**, 1285 (1992).

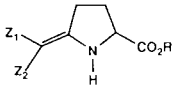
β-Enaminoesters **1** and **2**, derived respectively from lactams **3** and pyroglutamic acid (**4**) are precursors of products such as alkaloids [1-5], carbapenams [6,7], semicorrins [8], or pyrroles [9]. Some of these compounds exhibit bactericidal [10], herbicidal [11] and psychotropic [12] properties. These observations and our interest in pyroglutamic acid chemistry, prompted us to develop a versatile and easy method for the preparation of β-enaminoesters **2** derived from pyroglutamic acid (**4**); interestingly, related acids **2j** have recently been described in a context of penams synthesis [13].

Figure 1



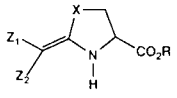
1a-d

1a n = 1, R = Me
1b n = 2, R = Me
1c n = 3, R = Me
1d n = 1, R = iPr



2a-i

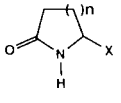
R = Me, Et



2j

X = O, S

Z_1, Z_2 = electron withdrawing groups

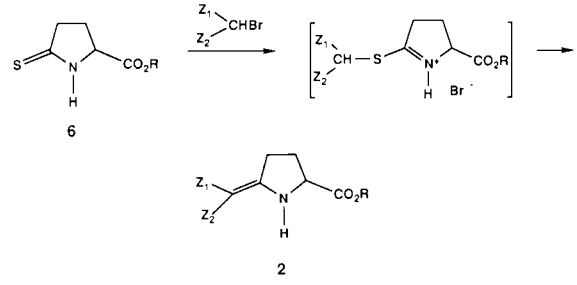


3-5

3 n = 1-3, X = H
4 n = 1, X = CO_2H
5a n = 1, X = CO_2Me
5b n = 1, X = CO_2Et

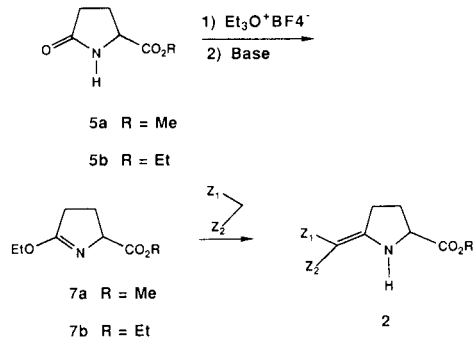
It is already known that, in the pyroglutamic acid series, Eschenmoser's method can be used for the synthesis of β-enaminoesters **2** [14]. In that way, the sulfide contraction of thiolactams **6** gives alkylidenepyrrolidines **2** [6,15-18] (Scheme 1), however, this method requires the synthesis of thiolactams **6** [6,16,19-21].

Scheme 1



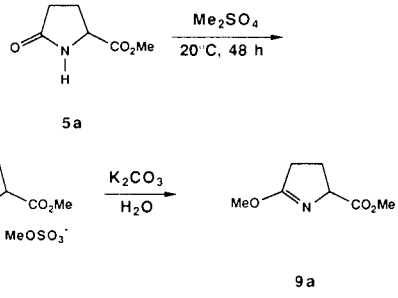
Another general method for the synthesis of β-enaminoesters in the condensation of ethyliminoethers with active methylene reagents [14,22-26]. In that way, some compounds **2** have been prepared from iminoethers **7a-b** [8,27] (Scheme 2), but the synthesis of these iminoethers requires the preparation of triethyloxonium fluoborate [28] and the use of expensive reagents and of great amounts of solvents [28-30].

Scheme 2



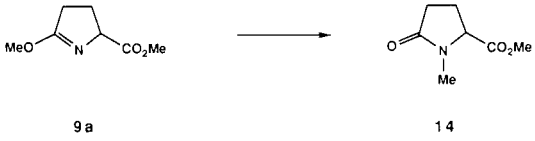
During the course of our study, Nagasaka [7] reported the *O*-methylation of methyl pyroglutamate (**5a**), at room temperature, with a slightly deficient amount of dimethyl sulfate, and in the absence of solvent; in this method, the iminoether salt **8a** was neutralized by using an aqueous solution of potassium carbonate (Scheme 3).

Scheme 3



These conditions were chosen by the authors because iminoether **9a** is a heat sensitive compound, whose Chapman's transposition [21-33] leads to methyl *N*-methylpyroglutamate (**14**) [27] (Scheme 4).

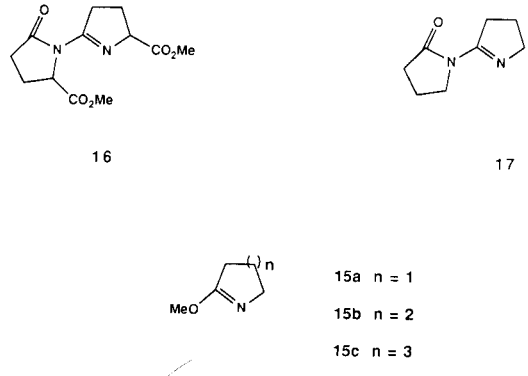
Scheme 4



This transposition was caused by a *N*-methylation of the nucleophilic iminoether, catalyzed by traces of alkylating reagent [34]. Indeed, we have checked that the reaction of iminoether **9a** with a catalytic amount of dimethylsulfate yields 67% of methyl *N*-methylpyroglutamate (**14**). We have also found that iminoether salt **8a** is a stable compound, and that the *O*-methylation reation of methyl pyroglutamate (**5a**) can be achieved at 60° (12 hours) with a slight excess of dimethyl sulfate, giving a near quantitative yield of iminoether salt **8a**. Iminoether **9a** is not a very basic compound and, by addition of triethylamine to the crude mixture, iminoether salt **8a** is neutralized, while the excess of dimethylsulfate is destroyed. An ether extraction then yielded 74% of pyroglutamic iminoether **9a**. In the same way, iminoether **9b** can be prepared from ethyl pyroglutamate (**5b**).

The complete and instantaneous destruction of dimethyl sulfate by triethylamine avoids the catalytic transposition of iminoether **9a** and the formation of methyl *N*-methylpyroglutamate (**14**); however, after a few weeks at 6°, precipitation of a small amount of dimer **16** was observed (this dimer **16** can also be obtained by reacting methyl pyroglutamate (**5a**) and phosphorus oxychloride [35a]). It is interesting to note that the *O*-methylation of lactam **3** (n = 1) with dimethyl sulfate afforded the expected iminoether **15a** as well as the dimer **17** [35b].

Figure 2



We have studied the condensation of these iminoethers **7a**, **9a-b** with acyclic active methylene reagents, without solvent (Scheme 5). The reaction did not occur at room temperature, but β-enaminoesters **2a-f** can be obtained in average yield by heating the mixture at 85°, without catalyst [36], or with triethylamine [37] or nickel acetylacetonate [38] as a catalyst (see Table 1).

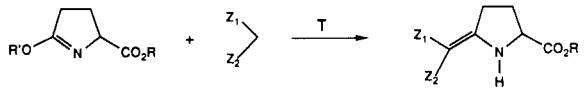
A previous synthesis of compound **2g** has been described by Nagasaka [7], following the general method of Lhommet (benzene, triethylamine, 1 equivalent, reflux) [39]. We have found that, contrasted with the acyclic ones, cyclic active methylene compounds react very easily with iminoether **9a**. Thus, the reaction can be performed at room temperature, without solvent or catalyst, and β-enaminoesters, such as Meldrum's derivative **2g**, are obtained in good yields; these conditions are quite general and can be used with iminoethers **15a-c** (Scheme 5, Table 1).

These operating conditions have been optimized in order to obtain β-enaminoesters **2a-b** and **2g** on a large-scale, without isolating intermediates **8a-b** and **9a-b**. At the end of the reaction, addition of water to the crude mixture allowed the precipitation of products in very good overall yields (Scheme 6) [9].

It was also interesting to prepare the *N*-methyl derivatives **10** of β-enaminoesters **2**; classical preparations of such compounds are the condensation of active methylene reagents with activated forms of *N*-substituted lactams such as lactam acetals **11** [23,40], iminoether salts **12a** [40], thioiminoether salts **12b** [41] or iminium chloride **12c** [42].

It is not convenient to use pyroglutamic acid derivatives **12a-c** mainly because this needs the preparation of thiopyroglutamic derivatives or the use of phosgene or of triethyloxonium fluoborate; indeed, the salt **13** cannot be used, because an equilibrium between **13** and **14** was obtained by reacting methyl *N*-methylpyroglutamate (**14**) [43] with dimethyl sulfate (70% nmr yield of salt **13**). The condensation of this crude mixture with methyl cyanoacetate occurred, but the yield of **10d** did never exceed 41% (Scheme 7).

Scheme 5

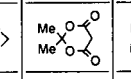
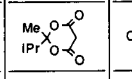
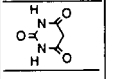


7a R = Me, R' = Et

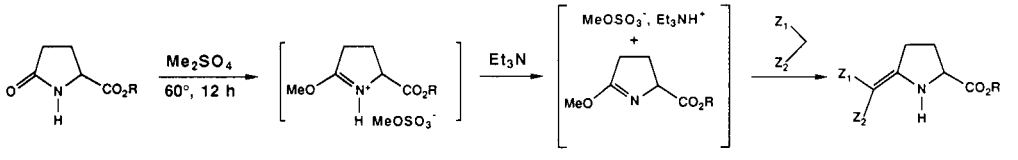
9a R = R' = Me

9b R = Et, R' = Me

2a-i

	2a	2b	2c	2d	2e	2f	2g	2h	2i
Z_1 / Z_2	NC / MeO_2C	NC / MeO_2C	NC / EtO_2C	NC / H_2NOC	MeO_2C / MeOC	MeOC / MeOC			
R	Et	Me	Me	Me	Me	Me	Me	Me	Me
T(°C)	80	80	80	80	80	80	20	20	40

Scheme 6



5

8a R = Me

8b R = Et

9

2a-b, 2g

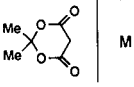
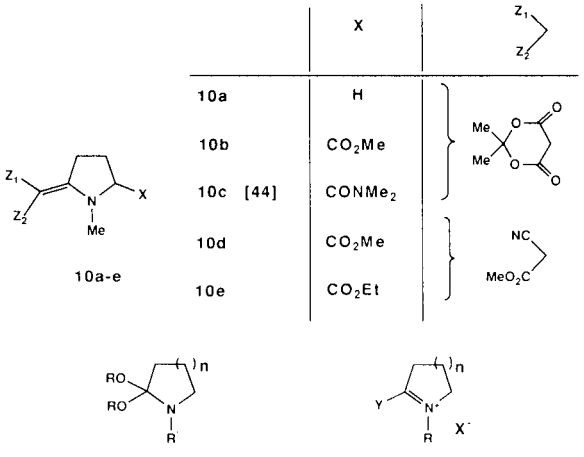
	Z_1 / Z_2	R	yield (%)
2a	NC / MeO_2C	Et	80
2b	NC / MeO_2C	Me	82
2g		Me	83

Figure 3



	X	Z_1 / Z_2
10a	H	
10b	CO_2Me	
10c [44]	$CONMe_2$	
10d	CO_2Me	
10e	CO_2Et	

10a-e

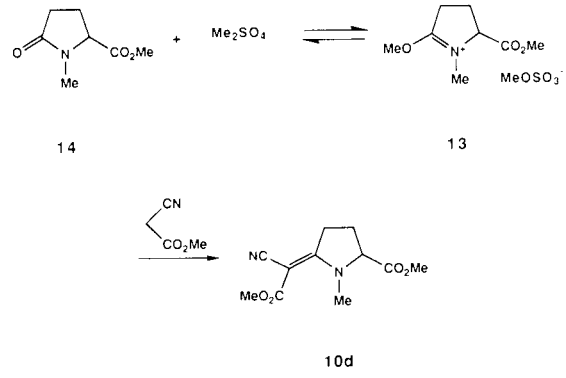
11

12a Y = OEt, X^- = BF_4^-

12b Y = SR, X^- = Br^-

12c Y = Cl, X^- = Cl^-

Scheme 7



14

13

10d

We have previously reported a new method for the *N*-alkylation of methyl pyroglutamate (**5a**) in solid-liquid phase transfer conditions [43]. β-Enaminoesters **2** are vinylogs of **5a**, so we reacted compounds **2** in the same way as for methyl pyroglutamate (**5a**). β-Enaminoester **2**, potassium carbonate and the phase transfer agent (Me-

Table 1

Preparation of β-Enaminoesters **1a-d** and **2a-i**

Compound No.	Catalyst (%)	Temperature (°C)	Reaction Time	Yield (%)	Literature Yield (%)
1a		20	12 hours	76	66 [38]
1b		20	4 hours	81	57 [38]
1c		20	24 hours	60	58 [38]
1d		20	15 minutes	60	
2a		85	1.5 hours	53	
2b		85	1.5 hours	75 [a]	
		80	14 hours	90 [b]	
2c		80	6 hours	70	
2d		20	2 hours	0	
	Et_3N (5)	20	2 hours	0	
	Et_3N (5)	80	8 hours	65	
2e	Et_3N (18)	85	11 days	47	
	AcacNi (3)	85	11 days	38	
2f	Et_3N (100)	85	11 days	32	
2g		20	12 hours	85	73 [7]
2h		20	7 hours	100	
2i		40	10 hours	52	

[a] From iminoether **9a**. [b] From iminoether **7a**.

OSO_3-Et_3MeN^+ prepared *in-situ*) were vigorously stirred by a polytron-type apparatus while adding dimethyl sulfate (the temperature was carefully maintained at 40°) (Scheme 8). In that way, the *N*-methyl β-enaminoesters **10a-e** were obtained in 70-90% yield (Table 3).

The antitumor effects of these compounds were tested *in-vivo* against P-388 leukemia in mice, according to a typical NCI protocol [45]. These compounds have no activity under the testing conditions.

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded on a Perkin Elmer 700 spectrometer and the nmr spectra on a Hitachi Perkin Elmer R-600 at 60 MHz, using tetramethylsilane as an internal reference. Elemental analyses were performed by the Central Microanalytical Department of CNRS in Vernaison, France.

2-Methoxy-5-methoxycarbonyl-1-pyrroline (**9a**).

A mixture of dimethyl sulfate (330 ml, 3.5 moles) and methyl pyroglutamate (**5a**) (400 g, 2.8 moles) was stirred at 60° for 12 hours. The resulting iminoether salt **8a** was slowly dropped into an ice cooled solution of triethylamine (500 ml, 3.6 moles) in ether (400 ml). Iminoether **9a** was extracted with ether (3 x 1250 ml). After addition of ether, the mixture was vigorously stirred with a polytron-type apparatus and the organic layer was separated. Evaporation of the ether yields 74% of colourless iminoether **9a** whose nmr spectrum is identical with the one of an authentic sample [7].

Methyl 2-[2-(Methoxycarbonyl)-5-pyrrolidinylidene]cyanoacetate (**2b**).

From Iminoether **9a**.

A mixture of iminoether **9a** (157 g, 1 mole) and methyl cyanoacetate (99 g, 1 mole) was stirred at 80° during 1.5 hours. The solid, which precipitated after cooling and addition of water, was filtered, washed with water and recrystallized from water, yield 75% (see Table 2).

From Iminoether **7a**.

A mixture of iminoether **7a** [44] (40 g, 0.234 mole) and methyl cyanoacetate (34.75 g, 0.351 mole) was stirred at 80° for 14 hours. After cooling, compound **2b** was filtered and recrystallized from water, yield 90%.

From Methyl Pyroglutamate (**5a**).

Iminoether salt **8a** was prepared as usual. After neutralization of this salt with triethylamine, methyl cyanoacetate (1 equivalent) was added and the mixture was stirred at 80° for 1.5 hours. After cooling and addition of water, compound **2b** precipitated. The solid was filtered, washed with water and dried, yield 82%.

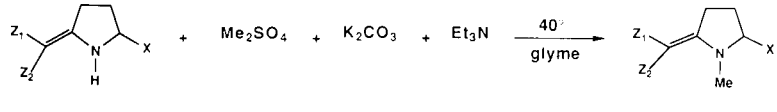
Ethyl 2-[2-(Methoxycarbonyl)-5-pyrrolidinylidene]cyanoacetate (**2c**).

A mixture of iminoether **7a** [44] (40 g, 0.234 mole) and ethyl cyanoacetate (39.7 g, 0.351 mole) was stirred at 80° for 6 hours. After cooling, compound **2c** was filtered and recrystallized from a mixture ether/methylene chloride, yield 70%.

Methyl 2-[2-(Ethoxycarbonyl)-5-pyrrolidinylidene]cyanoacetate **2a**.

Iminoether salt **8b** was prepared as usual from ethyl pyroglutamate (1214.8 g, 7.737 moles) and neutralized with triethylamine

Scheme 8



1a, 2b,g,k 10a-e

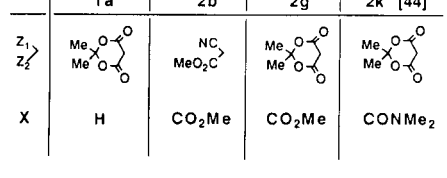


Table 2

Physical Data of β-Enaminoesters **1d** and **2a-i**

No.	Mp °C solvent	^{1}H NMR (ppm)	IR (Nujol) cm^{-1}	Molecular Formula	Analysis (%) Calcd./Found C	H	N	O
1d	126 Et_2O/Me_2CO	($CDCl_3$): 1-1.11 (d, 6H), 1.58 (s, 3H), 1.80-2.48 (m, 3H), 3.20-4 (m, 4H)	3290 (N-H), 1700 (C=O) 1655 (C=O), 1575 (C=C), 1240 (C-O)	$C_{12}H_{17}NO_4$	60.24 60.03	7.16 6.62	5.85 5.83	26.75 [a] 26.80
2a	86 Et_2O/CH_2Cl_2	($CDCl_3$): 1.30 (t, 3H), 1.9-2.6 (m, 2H), 2.6-3.2 (m, 2H), 3.73 (s, 3H), 4.24 (q, 2H), 4.3-4.8 (m, 1H), 9.05 (s, 1H)	3300 (N-H), 2200 (C≡N), 1750 (C=O), 1675 (C=O), 1590 (C=C), 1200 (C-O)	$C_{11}H_{14}N_2O_4$	55.46 55.58	5.92 5.94	11.76 11.45	26.86 27.03
2b	120 H_2O	($CDCl_3$): 2-2.6 (m, 2H), 2.7-3.2 (m, 2H), 3.70 (s, 3H), 3.73 (s, 3H), 4.3-4.7 (m, 1H), 9 (s, 1H)	3310 (N-H), 2210 (C≡N), 1750 (C=O), 1670 (C=O), 1580 (C=C), 1215 (C-O)	$C_{10}H_{12}N_2O_4$	53.57 53.86	5.36 5.44	12.50 12.32	28.57 28.48
2c	119 Et_2O/CH_2Cl_2	($CDCl_3$): 1.31 (t, 3H, J = 7.2 Hz), 2-2.7 (m, 2H), 2.8-3.2 (m, 2H), 3.78 (m, 2H), 3.78 (s, 3H), 4.23 (q, 2H, J = 7.2 Hz), 4.3-4.7 (m, 1H), 9.1 (s, 1H)	3400 (N-H), 2200 (C≡N), 1735 (C=O), 1655 (C=O), 1585 (C=C), 1150 (C-O)	$C_{11}H_{14}N_2O_4$	55.46 55.47	5.92 5.88	11.76 11.77	26.86 26.89
2d	142 EtOH	($CDCl_3$): 2-2.6 (m, 2H), 2.7-3.15 (m, 2H), 3.75 (s, 3H), 4.3-4.7 (m, 1H)	3400 (N-H), 2200 (C≡N), 1730 (C=O), 1640 (C=O), 1570 (C=C)	$C_9H_{11}N_3O_3$	51.67 51.78	5.30 5.38	20.08 19.84	22.94 23.29
2e	79 EtOH	($CDCl_3$): 2-2.5 (m, 5H), 3-3.4 (m, 2H), 3.7 (s, 3H), 3.75 (s, 3H), 4.3-4.7 (m, 1H), 9 (s, 1H)	3200 (N-H), 1750 (C=O), 1690 (C=O), 1600 (C=C), 1560 (C=C), 1215 (C-O)	$C_{11}H_{15}NO_5$	54.76 54.98	6.27 6.38	5.80 6.00	33.16 32.95
2f	97 EtOH	($CDCl_3$): 2-2.25 (m, 8H), 2.8-3.3 (m, 2H), 3.77 (s, 3H), 4.28-4.59 (m, 1H), 9.2 (s, 1H)	3200 (N-H), 1750 (C=O), 1640 (C=O), 1590 (C=C) 1530 (C=C), 1205 (C-O)	$C_{11}H_{15}NO_4$	58.66 58.60	6.71 6.79	6.22 6.31	28.41 28.15
2g [7]	140 H_2O	($CDCl_3$): 1.7 (s, 6H), 2.2-2.7 (m, 2H), 3.2-3.7 (m, 2H), 3.7 (s, 3H), 4.4-4.9 (t, 1H), 10.1 (s, 1H)	3300 (N-H), 1745 (C=O), 1720 (C=O), 1660 (C=C), 1210 (C-O)	$C_{12}H_{15}NO_6$	53.53 53.46	5.61 5.59	5.20 5.39	35.65 35.92
2h	oil	($CDCl_3$): 0.99-1.11 (s, 6H), 1.58 (s, 3H), 2-2.4 (m, 1H), 2.1-2.68 (m, 2H), 3.1-3.6 (m, 2H), 3.75 (s, 3H), 4.4-4.8 (m, 1H), 7.1-7.6 (m, 1H)						
2i	>260 DMF	(DMSO d_6): 1.8-2.6 (m, 2H), 2.95-3.45 (m, 2H), 3.65 (s, 3H), 4.35-4.6 (m, 1H), 10.26-11.1 (m, 3H)	3220 (N-H), 1760 (C=O), 1720 (C=O), 1670 (C=O), 1630 (NCO), 1540 (C=C)	$C_{10}H_{11}N_3O_5$	47.43 47.18	4.32 4.32	16.59 16.54	31.59 31.96

[a] Best analysis obtainable.

Table 3

Physical Data of *N*-Alkyl β-Enaminoesters **10a-e**

No.	T [a] hours	Yield (%)	Mp °C solvent	^{1}H NMR ($CDCl_3$) (ppm)	IR (Nujol) cm^{-1}	Molecular Formula	Analysis (%) Calcd./Found C	H	N	O
10a	11	73	161 EtOH	1.70 (s, 6H), 1.92-2.42 (m, 2H), 3.15 (s, 3H), 3.42 (t, 2H, J = 8 Hz), 3.80 (t, 2H), J = 8 Hz)	1700 (C=O), 1665 (C=O), 1570 (C=C), 1285 (C-O)	$C_{11}H_{15}NO_4$	58.66 58.52	6.71 6.57	6.22 6.24	28.41 28.46
10b	8.5	72	160 EtOH	1.71 (s, 6H), 2.1-2.7 (m, 2H), 3.13 (s, 3H), 3.25-3.65 (m, 2H), 3.83 (s, 3H), 4.3-4.6 (m, 1H)	1730 (C=O), 1705 (C=O), 1660 (C=O), 1560 (C=C)	$C_{13}H_{17}NO_6$	55.12 55.16	6.05 6.03	4.94 4.91	33.88 33.80
10c [44]	3.5	71	207 EtOH	1.66 (s, 6H), 2-2.5 (m, 2H), 2.97 (m, 3H), 3.03 (s, 3H), 3.2-3.65 (m, 2H), 4.6-4.95 (m, 1H)	1700 (C=O), 1660 (C=O), 1560 (C=C), 1280 (C=O)	$C_{14}H_{20}N_2O_5$	56.75 56.90	6.80 6.90	9.45 9.37	26.99 26.90
10d	16	92	104 H_2O	1.8-2.6 (m, 2H), 2.7-3.6 (m, 2H), 3.41 (s, 3H), 3.73 (s, 3H), 3.80 (s, 3H), 4.1-4.5 (m, 1H)	2200 (C≡N), 1740 (C=O), 1710 (C=O), 1570 (C=C), 1210 (C-O)	$C_{11}H_{14}N_2O_4$	55.46 55.33	5.92 6.08	11.76 11.95	26.86 26.82
10e	7	98	86 EtOH	1.31 (t, 3H), 1.9-2.6 (m, 2H), 2.7-3.6 (m, 2H), 3.42 (s, 3H), 3.73 (s, 3H), 4.25 (m, 1H), 4.25 (q, 2H)	2200 (C≡N), 1750 (C=O), 1675 (C=O), 1590 (C=C), 1200 (C-O)	$C_{12}H_{16}N_2O_4$	57.13 56.91	6.39 6.54	11.10 11.08	25.37 25.53

[a] T = Reaction time.

(1.345 ℓ, 9.66 moles). Iminoether **9b** was not separated from the triethylammonium salt; ^{1}H nmr: 1.29 (t, 3H, J = 7.2 Hz), 1.9-2.7 (m, 4H), 3.86 (s, 3H), 4.20 (q, 2H, J = 7.2 Hz), 4.4 (m, 1H).

Methyl cyanoacetate (683 ml, 7.74 moles) was dropped into iminoether **9b** in 1.5 hours at 85° and the resulting mixture was stirred for an hour. After cooling and addition of water (1.4 ℓ), the solid was filtered, washed with water and recrystallized from a mixture ether/methylene chloride, yield 53%.

General Procedure for the Preparation of β-Enaminoesters **2d-f**.

One equivalent of iminoether **9a**, one equivalent of active methylene compound and 3-100% of catalyst (triethylamine or Nickel acetylacetonate) were stirred at 85°. The β-enaminoester which precipitated after removing methanol and cooling was filtered and recrystallized from ethanol. The yields and physical data of β-enaminoesters **2d-f** prepared in this way are reported in Tables 1 and 2.

Isopropylidene-(2-methoxycarbonyl-5-pyrrolidinylidene)malonate (**2g**).

From Methyl Pyroglutamate (**5a**).

After neutralization of iminoether salt **8a** (2 moles) with triethylamine (362 ml, 2.6 moles), Meldrum's acid (288 g, 2 moles) was added and the mixture was stirred at room temperature for 24 hours; the β-enaminoester was filtered and recrystallized from water, yield 83% in white compound **2g** whose physical data are identical with those of an authentic sample [7].

From Iminoether **9a**.

A mixture of isopropylidene malonate (410 g, 2.85 moles) and iminoether **9a** (447 g, 2.85 moles), was stirred at room temperature overnight. The solid was filtered and washed with ether, yield 85%.

β-Enaminoesters **1a-c**.

The above procedure was used for the preparation of β-enaminoesters **1a-c** from iminoethers **15a-c** and isopropylidenemalonate. The yields are reported in Table 1 and physical data of these compounds are identical with those of authentic samples [38].

β-Enaminoesters **1d** and **2h**.

In a same way, iminoethers **9a** and **15a** reacted with 2-methyl-2-isopropyl-1,3-dioxan-4,6-dione. The yields and the physical data of these compounds are reported respectively in Table 1 and 2.

5-[2-(Methoxycarbonyl)-5-pyrrolidinylidene]malonylurea (**2i**).

A mixture of iminoether **9a** (20 g, 0.13 mole) and barbituric acid (13 g, 0.13 mole) in 50 ml of ether was stirred under reflux for 10 hours. After cooling, the solid was filtered, washed with hot dimethylformamide, yield 52%. Physical data are reported in Table 2.

Methyl *N*-Methylpyroglutamate (**14**).

A solution of iminoether salt **8a** (40 g, 0.15 mole) in 80 ml of tetrahydrofuran was refluxed under nitrogen atmosphere. Triethylamine (20.7 ml, 0.15 mole) was dropped and then dimethyl sulfate (1.4 ml, 0.015 mole) was added. The resulting mixture was stirred at 80° for 4 hours. After cooling, water and toluene were added; the organic layer was separated and dried with sodium sulfate. After removing the solvent, methyl *N*-methylpyroglutamate (**14**) was obtained, yield 67%, whose physical data are identical with those of authentic sample [43].

Methyl 2-[1-Methyl-2-(methoxycarbonyl)-5-pyrrolidinylidene]cyanoacetate (**10d**).

A mixture of β-enaminoester (**2b**) (620.5 g, 2.77 moles), triethylamine (18.7 ml, 0.13 mole), potassium carbonate (483 g, 3.5 moles) and 1,2-dimethoxyethane (2.3 ℓ) was stirred vigorously with a polytron-type apparatus. Dimethyl sulfate (343 ml, 3.63 moles) was slowly added at 40° and the stirring was carried on for 16 hours. The excess of dimethyl sulfate was neutralized with 18.7 ml of triethylamine. The solid was filtered and washed with 1,2-dimethoxyethane (2 x 1.2 ℓ) with vigorous stirring. The solvent was evaporated under vacuum, and the residual solid was washed with water and dried. Ester **10d** was obtained in 92% yield. The yields and physical data of the β-enaminoesters **10a-e** prepared in the same way are reported in Table 3.

REFERENCES AND NOTES

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[1] S. Danishefsky and J. Etheredge, *J. Org. Chem.*, **39**, 3430 (1974).

[2] H. W. Pinnick and Y. H. Chang, *J. Org. Chem.*, **43**, 4662 (1978).

[3] Y. Yamada, K. Hatano, and M. Matsui, *Agr. Biol. Chem.*, **34**, 1536 (1970).

[4] A. S. Howard, G. C. Gerrans, and J.-P. Michael, *J. Org. Chem.*, **45**, 1713 (1980).

[5] M. Haddad, J.-P. Célérier, and G. Lhommet, *Heterocycles*, **26**, 2335 (1987).

[6] M. D. Bachi, R. Breiman, and H. Meshulam, *J. Org. Chem.*, **48**, 1439 (1983).

[7] T. Nagasaka, A. Tsukada, and F. Hamaguchi, *Heterocycles*, **24**, 2015 (1986).

[8] H. Fritschi, U. Leutenegger, and A. Pfaltz, *Angew. Chem.*, **98**, 1028 (1986).

[9] B. Rigo and D. Fasseur, French Patent demandé, FR 2,650,588 (1991); *Chem. Abstr.*, **116**, 128653w (1992).

[10] V. J. Lee, P. F. Fabio, and M. F. Reich, 12th International Congress of Heterocyclic Chemistry, Poster Session, Jerusalem, Israël, 1989.

[11] J. L. Huppatz, J. N. Philipps, and B. M. Rattigam, *Agr. Biol. Chem.*, **45**, 2769 (1986).

[12] Teikoku Chemical Industry Co., Ltd. Japan 80 02649 (1980); *Chem. Abstr.*, **93**, 71453k (1980).

[13] Z. Huang and M. Wang, *Synth. Commun.*, **21**, 1177 (1991).

[14] M. Roth, P. Dubs, E. Göschi, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 710 (1971).

[15] K. Shiosaki and H. Rapoport, *J. Org. Chem.*, **50**, 1229 (1985).

[16] J. S. Petersen, G. Fels, and H. Rapoport, *J. Am. Chem. Soc.*, **106**, 4539 (1984).

[17] A. M. P. Koskinen and H. Rapoport, *J. Med. Chem.*, **28**, 1301 (1985).

[18] M. H. Howard, F. J. Sardina, and H. Ropoport, *J. Org. Chem.*, **55**, 2829 (1990).

[19] A. Kleeman, J. Martens, and K. Drauz, *Chem. Ztg.*, **105**, 266 (1981).

[20] T. P. Andersen, P. B. Rasmussen, I. Thomsen, S. O. Lawesson, P. Jorgensen, and P. Lindhardt, *Liebigs Ann. Chem.*, 269 (1986).

[21] C. Larsen, H. Kragh, P. B. Rasmussen, T. P. Andersen, and A. Sennig, *Liebigs Ann. Chem.*, 819 (1989).

[22] S. Petersen and E. Tietze, *Chem. Ber.*, **90**, 909 (1857).

[23] V. A. Azimov, V. G. Granik, R. G. Glushkov, and L. N. Yakhontov, *Chem. Heterocyclic Comp.*, 289 (1978).

[24] P. Brunerie, J.-P. Célérier, H. Petit, and G. Lhommet, *J. Heterocyclic Chem.*, **23**, 1183 (1986).

[25] G. Lhommet, M.-G. Richaud, and P. Maitte, *J. Heterocyclic*

Chem., **19**, 431 (1982).

[26] P. Singh, M. S. Batra, and H. Singh, *Synth. Commun.*, **14**, 533 (1984); H. Singh, M. S. Batra, and P. Singh, *Indian J. Chem.*, **23B**, 1176 (1984).

[27] B. Rigo, Thesis No. 617, Lille, France, 1984.

[28] H. Meerwein, *Org. Synth.*, **46**, 113 (1966).

[29] N. M. Kolocouris, Thesis No. 247, Lille, France, 1971; N. M. Kolocouris, *Bull. Soc. Chim. France*, 1053 (1973).

[30] M. Lee and J. W. Lown, *J. Org. Chem.*, **52**, 5717 (1987).

[31] R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948).

[32] A. W. Chapman, *J. Chem. Soc.*, 569 (1929).

[33] S. Kano, T. Yokomatsu, S. Hibino, K. Imamura, and S. Shibuya, *Heterocycles*, **6**, 1319 (1977).

[34] J. W. Ralls and C. A. Elliger, *Chem. Ind. (London)*, 20 (1961).

[35a] K. Drauz, A. Kleeman, J. Martens, P. Scherberich, and F. Effenberger, *J. Org. Chem.*, **51**, 3494 (1986); [b] T. Yamasaki, K. Matoba, M. Yajima, M. Nagata, and R. N. Castle, *J. Heterocyclic Chem.*, **12**, 973 (1975).

[36] A. E. Wick, P. A. Bartlett, and D. Dolphin, *Helv. Chim. Acta*, **54**, 513 (1971).

[37] Z. I. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.*, **17**, 2230 (1969).

[38] J.-P. Célérier, E. Deloisy-Marchalant, G. Lhommet, and P. Maitte, *Org. Synth.*, **67**, 170 (1988).

[39] J.-P. Célérier, E. Deloisy, G. Lhommet, and P. Maitte, *J. Org. Chem.*, **44**, 3089 (1979).

[40] Y. Shuo and H. Shaman-Atidi, *J. Am. Chem. Soc.*, **91**, 6683 (1969).

[41] M. M. Gugelchuk, D. J. Hart, and Y. M. Tsai, *J. Org. Chem.*, **46**, 3671 (1981).

[42] J.-P. Célérier, G. Lhommet, and M.-G. Richaud, *Synthesis*, 195 (1983).

[43] P. Cauliez, B. Rigo, D. Fasseur, and D. Couturier, *J. Heterocyclic Chem.*, **28**, 1143 (1991).

[44] The preparation of the β-enaminoester **2k**, precursor of the β-enaminoester **10c** will be described in a next paper.

[45] M. R. Boyd, *Principles Practices Oncol.*, **3**, 1 (1989).