Studies on Pyrrolidones. Synthesis and Reactivity of β-Enaminomonoesters and β-Enaminomononitriles Derived from Pyroglutamic Acid

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In the pyroglutamic acid series, β-enaminoesters **3** were formed in the 2-position by opening of the corresponding Meldrum's derivative **6**, and β-enaminonitriles **4** were obtained by treating carbamate vinylogous **5** by trimethylsilyl iodide. Alkylation and acylation of β-enaminoester **3a** was briefly examined.

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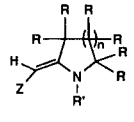
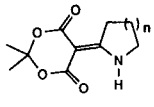
The chemistry of β-enaminoesters and -nitriles **1** has been of a great interest for many research groups, because they are useful intermediates for the synthesis of natural compounds [1-6]. They have been mainly synthesized by one of the following methods: reaction of lactam acetals with cyanoacetic acid [7] or aromatic methyl ketones [8], treatment of (methylthio)-alkylideniminium salts with active methylene compounds [9], Eschenmoser sulfide contraction of thiolactams [10], Wittig reaction of *N*-tosyl lactams [11], or ring opening of Meldrum's derivative **2** (by an alcoholate [12] or thermolysis in the presence of alcohols [13]).





2a : n = 1
2b : n = 2
2c : n = 3

	Z	R'	R	n
1a	CN	H	H	1
1b	CN	Me	H	
1c	CO_2R	H	H	
1d	COAr	H	H	
1e	CO_2R	H	H, Me	
1f	CN	H	H, Me	
1g	$CONR_1R_2$	H	H	1-3

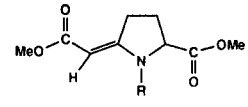
Figure 1

In the pyroglutamic series, β-enaminoesters **3** and -nitriles **4** have been less studied than other compounds **1**, nevertheless, they have been used as precursors of carbapenams [14], corrins [15], or anatoxins [16]. They were prepared by the Eschenmoser's method [16], by treatment of tertiobutyl esters **5a** with an acid [15], or by reaction of β-enaminoesters **6** with a Lewis acid in an alcoholic medium [14].

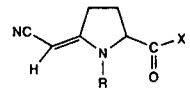
The aim of this paper is to report some aspects on the synthesis and the reactivity of β-enaminoesters **3** and -nitriles **4** which possess a vinylic hydrogen.

Formation of β-Enaminoesters **3a**.

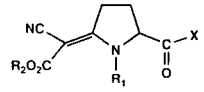
We have previously described a versatile synthesis of Meldrum's derivative **6a** [18]; in an attempt to open the



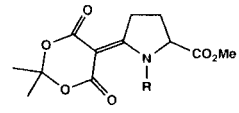
3a : R = H
3b : R = Me



4a : X = OMe, R = H
4b : X = OMe, R =Me
4c : X = NMe_2, R = H
4d : X =NMe_2, R = Me



Cpd	X	R_1	R_2
5a	OMe	H	tBu
5b		H	Et
5c		Me	Et
5d		H	Me
5e		Me	Me
5f	NMe_2	H	Me
5g		Me	Me
5h	OtBu	Me	Me



6a : R = H
6b : R = Me

Figure 2

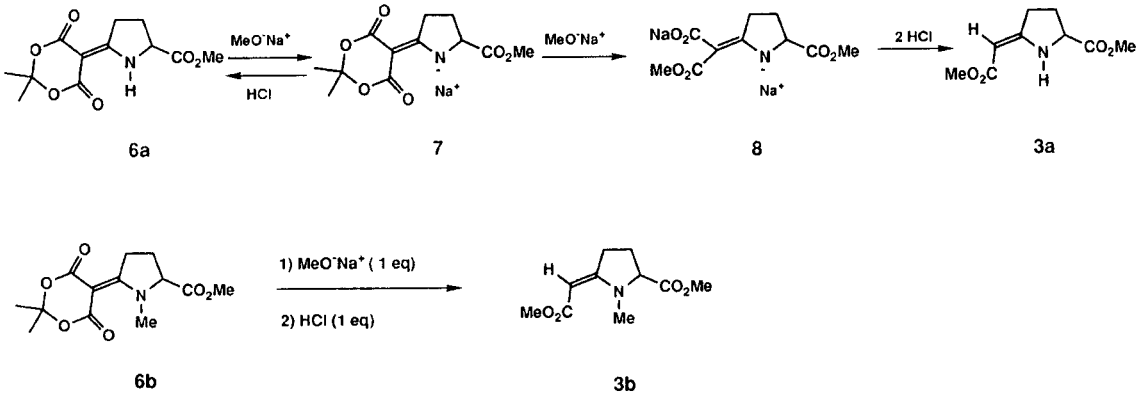
Meldrum's ring of this ester, we used sodium methylate [19] (Lhommet's method [12]): equimolar amounts of compound **6a** and sodium methylate were refluxed in methyl alcohol for 48 hours; after neutralization, the starting material was entirely recovered. However, by using two equivalents of sodium methylate, a quantitative yield of crude β-enaminoester **3a** was obtained.

On the other hand, for the preparation of *N*-methyl β-enaminoester **3b**, only one equivalent of sodium methylate was required; this suggests that the methoxycarbonyl group of **6a** increases the acidity of the nitrogen atom, leading to the formation of salt **7**, thus another equivalent of alcoholate was necessary to open the Meldrum's ring (Scheme 1).

The 5-methoxycarbonyl functionality of pyroglutamic acid derivatives proves to be very sensitive to hydrolytic conditions, thus it is very important to neutralize the sodium salt **8** with the exact amount of hydrochloric acid.

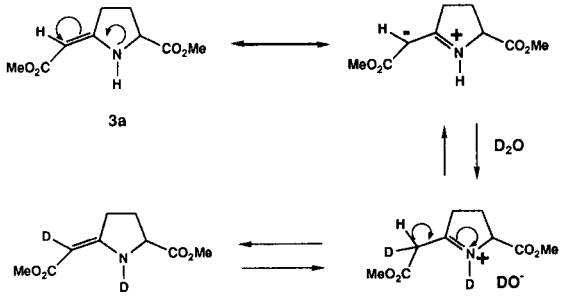
As for other enamines **1b** [17] and **1e-f** [20], the vinylic hydrogen of compound **3a** can be exchanged with deu-

Scheme 1



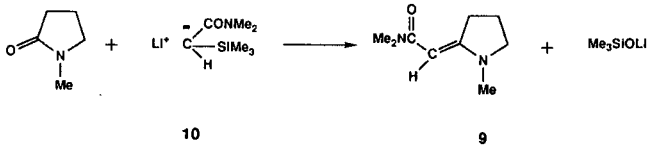
terium oxide. Interestingly this feature involving the donating effect of the nitrogen lone pair was not altered by the withdrawing effect of the methoxycarbonyl group (Scheme 2).

Scheme 2



The synthesis of β-enaminoamides **9** derived from lactams has been carried out by reaction of *N*-methylpyrrolidone with the lithium salt **10** (Scheme 3) [21] or by thermolysis of β-enaminoesters **2a-c** in the presence of amines [13].

Scheme 3

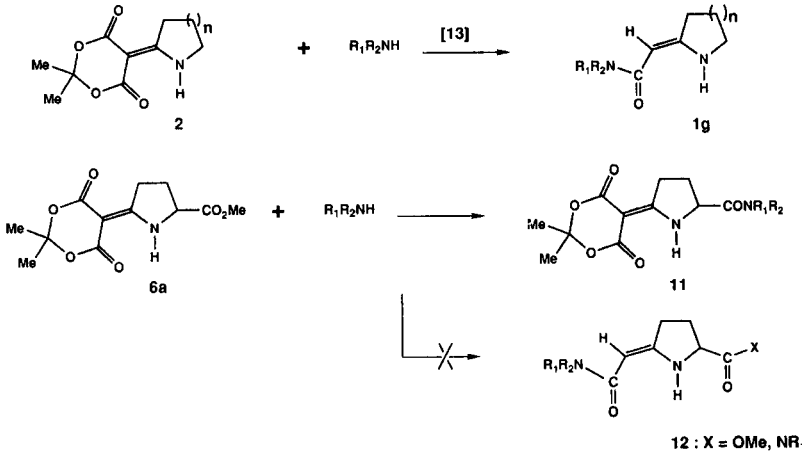


In contrast with the β-enaminodiesters **2** case, reaction of compound **6a** with an excess of amines afforded only the amides **11** [22] and did not yield the expected products **12** (Scheme 4).

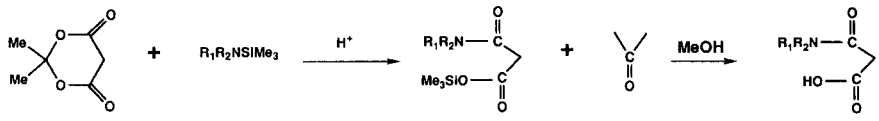
We recently described a very easy ring opening of Meldrum's acid at room temperature, by silylated amines under acidic catalysis [23] (Scheme 5).

We used unsuccessfully these conditions with β-enaminoester **6b**. It was possible to observe by nmr the disappearance of the silylated amine and to detect the formation of a small amount of β-enaminoamides **13**. Unfortunately, we were unable to isolate these compounds. We think that the Meldrum's ring of product **6b** is less reac-

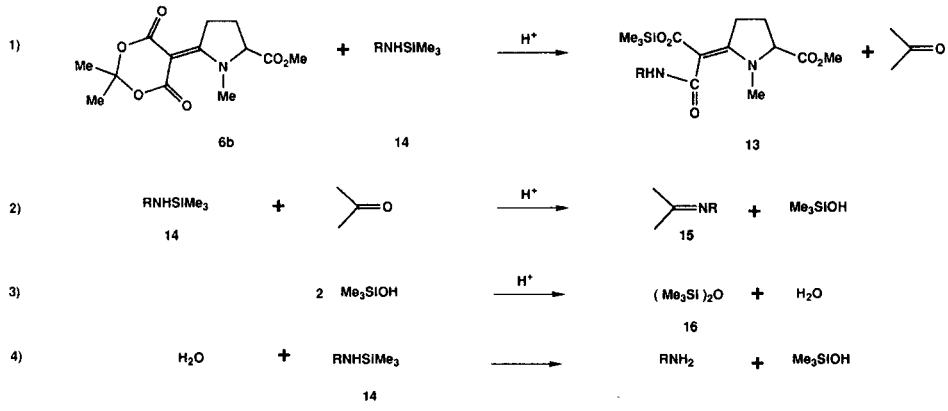
Scheme 4



Scheme 5



Scheme 6



tive than isopropylidene malonate towards silylated amines and that compounds **14** react more easily with the produced acetone (Scheme 6, eq. 1), giving rise to an imine **15** and trimethylsilanol (Scheme 6, eq. 2). Condensation of two molecules of silanol affords hexamethyldisiloxane (**16**) and the resulting water (Scheme 6, eq. 3) decomposes the silylated amine **14** (Scheme 6, eq. 4). (It was checked by nmr that the 5-methoxycarbonyl group of compound **6b** remained unaltered during these experiments).

To decrease the rate of the reaction between the silylated amine **14** and the ketone, the same reactions were carried out with β-enaminoester **17** [18] (Figure 3); unfortunately, the steric hindrance of methyl isopropyl ketone could not prevent the above described decomposition of silylated amines **14** (Scheme 6, eq. 2).

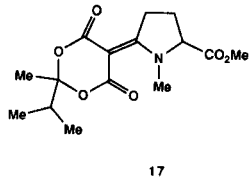


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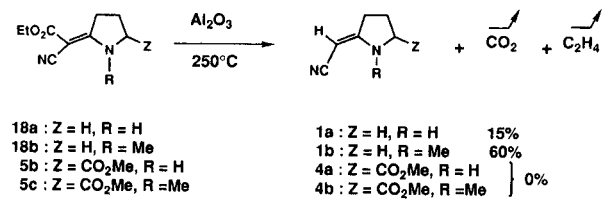
Figure 3

Formation of β-Enaminonitriles **4**.

We have recently reported that the decarboxyethylation of β-enaminoesters **18a-b** by aluminum oxide at 210° leads to the β-enaminonitrile **1a-b** and that this reaction was not successful in pyroglutamic series because of the withdrawing effect of the 5-methoxycarbonyl group [17] (Scheme 7).

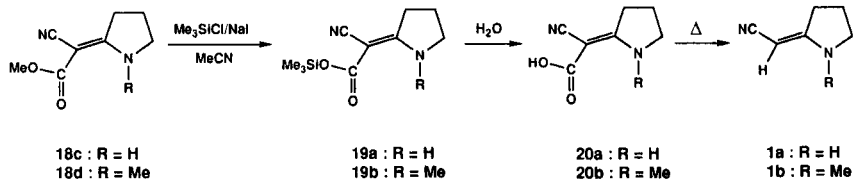
Scheme 7



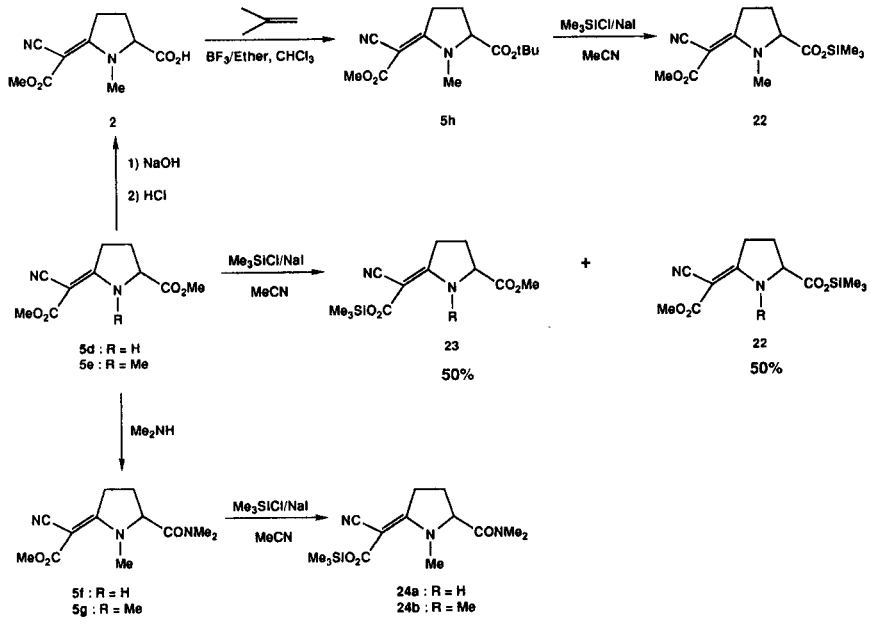
Due to these limitations, we thought to obtain nitriles **4** by applying to the carbamate vinylogous **5** the trimethylsilyl iodide cleavage of carbamates [31], and we tested this reaction by refluxing β-enaminoesters **18c-d** with a sodium iodide/trimethylsilyl chloride/acetonitrile mixture [34]. The reaction was slower than for carbamates, and a 48 hours reaction time was necessary to obtain the silylesters **19a-b** in a quantitative nmr yield. These products can be purified by distillation, and water hydrolysis gives then a 80-90% yield of β-enaminonitriles **1a-b**. It is interesting to note that, by avoiding heating during the hydrolysis step, it is possible to isolate compounds **20a-b** which are vinylogous of carbamic acids (Scheme 8).

In order to obtain some insight on this reaction, the β-enaminoesters **5a-h** were submitted to the action of *in-situ* generated trimethylsilyl iodide. It was then observed that products **24** were formed in a quantitative nmr yield and that the two esters groups of compounds **5d-e** reacted equally with this iodide; as for the tertiobutyloxycarbonyl function of product **5h**, it reacts even faster; thus an ester group does not remain unaltered in position 5 during this trimethylsilyl ester exchange (Scheme 9).

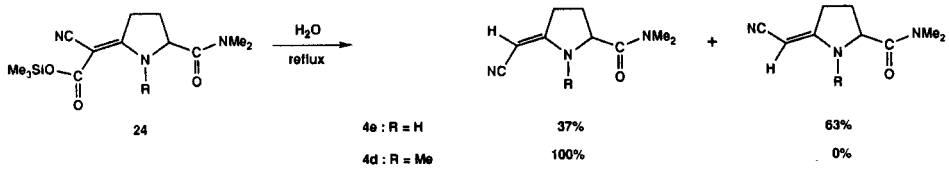
Scheme 8



Scheme 9



Scheme 10



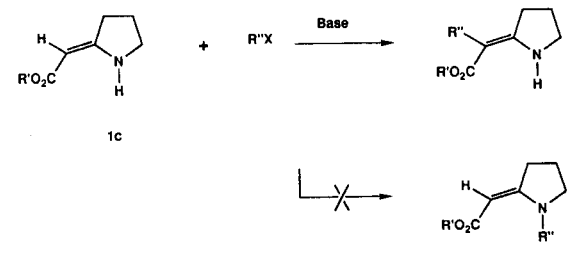
Water hydrolysis of silylesters **24** yields nitrile **4c** as an *E*/*Z* isomeric mixture and amide **4d** as a single isomer (Scheme 10).

Alkylation and Acylation of β-Enaminoester **3a**.

There are two nucleophilic positions (NH and CH vinylic carbon) in the structure of compounds **3**. In a next part of this work, the reactivity of β-enaminoester **3a** with alkylating and acylating reagents was compared with the one of Meldrum's derivatives **6a** and with the reactivity of model compounds **1c**.

Alkylation reaction of β-enaminoesters **1c** in the presence of a base such as sodium hydride [24] or LDA [25] has been previously described; only *C*-alkylation products were obtained (Scheme 11).

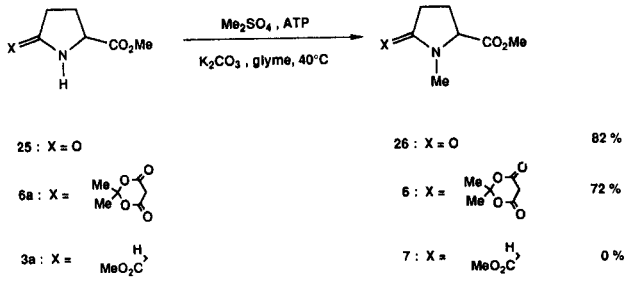
Scheme 11



N-Alkylation reactions of methyl pyroglutamate (**25**) [26] and of β-enaminoester **6a** (vinylogous with **25**) under solid-liquid phase transfer conditions were already reported (Scheme 12) [18]. Thus, we reacted compound **3a** in the same way. Dimethyl sulfate was added at 40° into a vigorously stirred (polytron-type apparatus) mixture of β-en-

aminoester **3a**, potassium carbonate and a phase transfer agent (triethylmethylammonium methylsulfate prepared *in-situ* or tetrabutylammonium bisulfate monohydrate). However, under these conditions, the starting material was recovered unaltered.

Scheme 12



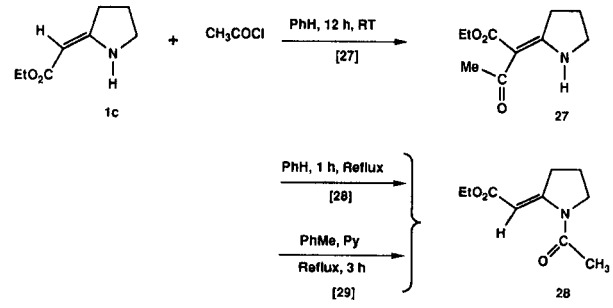
It was interesting to note this difference between compound **3a** and esters **6a** or **25**, showing that compound **3a** possessing only one vinylic ester group lost a part of this vinylogous feature towards lactam **25**.

This study has been discontinued because *N*-methyl β-enaminoester **3b** could be easily obtained by opening of the Meldrum's ring of compound **6b** by sodium methylate in methanol (Scheme 1).

The reaction of β-enaminoester **1c** derived from pyrrolidone (Z = CO_2Et) with acetyl chloride or acetic anhydride leads to the formation of either the *N*-acylated β-enaminoester **27** or the *C*-acylated product **28**, according to the experimental conditions. At room temperature, the kinetic compound **27** was obtained [27], whereas the thermodynamic compound **28** was isolated when the reaction was carried out in refluxing benzene [28] or in refluxing toluene with pyridine as a catalyst [29] (Scheme 13).

In the pyroglutamic series, reaction of β-enaminoester **3a** with acetyl chloride in toluene (90°, 20° or 0°) yielded *C*-acylated product **29** which was identical to a sample prepared by condensation of iminoether **30** and methyl acetylacetate [18]. It is to be noted that compound **6a** does not react with acetyl chloride under these conditions (Scheme 14).

Scheme 13



The antitumor effects of compound **3a** were tested *in-vivo* against P-388 leukemia in mice, according to a typical NCI protocol [30]. This compound has 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 Service Central de Microanalyse of CNRS in Vernaison, France.

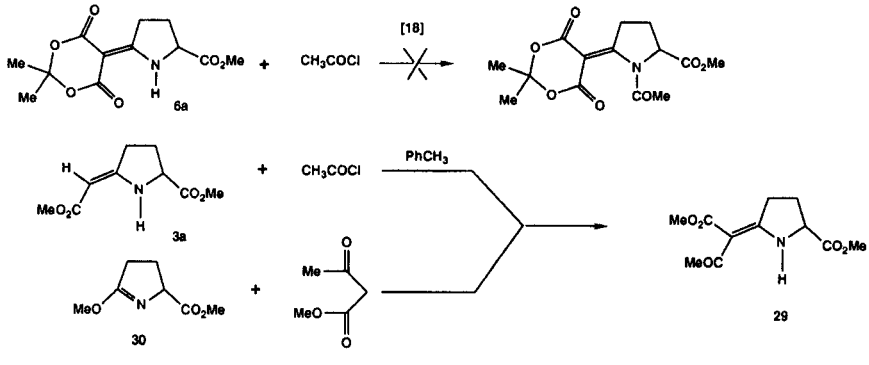
Methyl (5-Methoxycarbonyl-2-pyrrolidinylidene)acetate (**3a**).

A mixture of β-enaminoester **6a** (5.4 g, 20 mmoles) and sodium methoxyde (30% in weight in methanol, 7.2 g, 40 mmoles) in 30 ml of methanol was refluxed during 48 hours under inert atmosphere. The sodium salts were neutralized with concentrated hydrochloric acid (3.3 ml, 40 mmoles). The inorganic salts were filtered and the methanol removed under vacuum. The residue was dissolved in 50 ml of methylene chloride, the organic layer was washed with water (3 x 50 ml), dried over sodium sulfate, filtered and evaporated. The β-enaminoester **3a** yielded 85% and was recrystallized from water, mp 93°; ir (nujol): ν cm^{-1} 3300 (N-H), 1745 (C=O), 1650 (C=O), 1600 (C=C), 1200 (C-O); ^1H nmr (deuteriochloroform): δ ppm 2-2.8 (m, 4H), 3.63 (s, 3H), 3.75 (s, 3H), 4.25-4.7 (m, 2H), 8.1 (s, 1H).

Anal. Calcd. for $C_9H_{13}NO_4$: C, 54.26; H, 6.58; N, 7.03; O, 32.13. Found: C, 53.90; H, 6.68; N, 7.16; O, 32.30.

Methyl (*N*-Methyl-5-methoxycarbonyl-2-pyrrolidinylidene)acetate (**3b**).

Scheme 14



A mixture of *N*-methyl β-enaminoester **6b** (5 g, 18 mmoles) and sodium methoxyde (30% in weight in methanol, 3.4 g, 18 mmoles) in 30 ml of methanol was refluxed during 30 hours under an inert atmosphere. After cooling, the sodium salt was neutralized by concentrated hydrochloric acid (1.5 ml, 18 mmoles). The inorganic salts were filtered and the methanol removed under vacuum. The residue was dissolved in 50 ml of methylene chloride, the organic layer was washed with water (3 x 50 ml), dried over sodium sulfate, filtered and evaporated. The crude *N*-methyl β-enaminoester **3b** yielded 65%, mp 42°; ir (nujol): ν cm^{-1} 1740 (C=O), 1690 (C=O), 1600 (C=C); ^1H nmr (deuteriochloroform): δ ppm 2-2.4 (m, 2H), 2.8 (s, 3H), 3-3.4 (m, 2H), 3.60 (m, 2H), 3.75 (s, 3H), 4-4.3 (m, 1H), 4.6 (m, 1H).

Anal. Calcd. for $C_{10}H_{15}NO_4$: C, 56.26; H, 7.09; N, 6.57; O, 30.01. Found: C, 56.16; H, 7.06; N, 6.62; O, 29.82.

2-(α-Cyanomethylene)-*N*-methylpyrrolidine (**1b**).

A mixture of β-enaminoester **18b** (1.9 g, 10 mmoles), sodium iodide (4.5 g, 30 mmoles) and trimethylsilyl chloride (2.2 g, 20 mmoles) in 13 ml of acetonitrile was refluxed for 48 hours under an inert atmosphere. The solvent was removed under vacuum and 50 ml of water was added to the residue. The solution was refluxed and extracted with methylene chloride (3 x 30 ml). The organic layer was washed with water (3 x 50 ml), dried over sodium sulfate, filtered and evaporated. The crude β-enaminonitrile **1b** was distilled to give 82% of a yellow liquid, bp 95° (0.25 mm); ir (potassium bromide): ν cm^{-1} 2200 (C=N), 1615 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.65-2.4 (m, 2H), 2.79 (s, 3H), 2.87 (t, J = 7 Hz, 2H), 3.60 (m, 2H), 3.5 (t, J = 6 Hz, 2H), 3.63 (s, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_7H_{10}N_2$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.52; H, 8.21; N, 23.00.

2-(α-Cyano-α-carboxymethylene)pyrrolidine (**20a**).

A mixture of β-enaminoester **18c** (1.4 g, 10 mmoles), sodium iodide (4.5 g, 30 mmoles) and trimethylsilyl chloride (2.2 g, 20 mmoles) in 10 ml of acetonitrile was refluxed for 48 hours under an inert atmosphere. The silyl ester **19a** was characterized by ^1H nmr (deuteriochloroform): δ ppm 0.31 (s, 9H), 1.9-2.4 (m, 2H), 2.7-3.1 (m, 2H), 3.5-3.9 (m, 2H), 8.5-9.0 (bs, 1H).

The solvent was removed under vacuum. After addition of 50 ml of water to the residue, the compound **20a** was precipitated and filtered, 90%, mp 157-158°; ir (potassium bromide): ν cm^{-1} 3270 (N-H), 3040-2700 (O-H), 2210 (C=N), 1650 (C=O), 1590 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.9-2.4 (m, 2H), 2.7-3.1 (m, 2H), 3.5-3.9 (m, 2H), 8.7-9 (bs, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41; O, 21.83. Found: C, 56.16; H, 5.69; N, 18.12; O, 15.72. Due to thermal instability of the β-enaminoacid **20a**, the values found for carbon and oxygen are not good.

2-(α-Cyanomethylene)pyrrolidine (**1a**).

β-Enaminoacid **20a** (1.0 g, 6.6 mmoles) was refluxed in 50 ml of water for 10 minutes. The solution was extracted with methylene chloride (2 x 30 ml). The organic layer was dried on sodium sulfate, filtered and evaporated. The β-enaminonitrile **1a** was obtained in a quantitative yield and recrystallized from hexane, mp 73°; ^1H nmr (deuteriochloroform): δ ppm 1.8-2.3 (m, 2H), 2.4-3.0 (m, 2H), 3.3-3.65 (m, 2H), 3.7 (s, 0.5 H, deuterium oxide exchangeable), 4.0 (s, 0.5 H, deuterium oxide exchangeable), 5.6 (bs, 1H, deuterium oxide exchangeable).

This mixture of *Z*/*E* isomers is identical to a sample obtained following the literature [1,32,33].

2-(α-Cyano-α-methoxycarbonylmethylene)-5-*N*,*N*-dimethylcarbamoylpyrrolidine (**5f**).

A solution of ester **5d** (37.5 g, 0.17 mole) in 100 ml of methanol was saturated by dimethylamine and the mixture was stirred at room temperature for 9 days. The solid was filtered and washed with methanol. The amide **5f** yielded 91% and was recrystallized from water, mp 170°; ir (potassium bromide): ν cm^{-1} 3230 (N-H), 2200 (C=N), 1690 (C=O), 1650 (C=O), 1600 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.9-2.5 (m, 2H), 2.9-3.4 (m, 2H), 3.73 (s, 3H), 4.3-4.7 (m, 1H), 9.0 (s, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{11}H_{15}N_3O_3$: C, 55.69; H, 6.37; N, 17.71; O, 20.23. Found: C, 55.57; H, 6.28; N, 17.63; O, 20.22.

2-(α-Cyano-α-methoxycarbonylmethylene)-5-*N*,*N*-dimethylcarbamoyl-1-methylpyrrolidine (**5g**).

A solution of ester **5a** (10 g, 42 mmoles) in 100 ml of methanol was saturatd by dimethylamine and the mixture was stirred at room temperature for 9 days. the solid was filtered and washed with methanol. The amide **5g**, yield 90% was recrystallized from water, mp 131°; ir (potassium bromide): ν cm^{-1} 2200 (C=N), 1700 (C=O), 1650 (C=O), 1565 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.7-2.3 (m, 2H), 2.3-3.0 (m, 2H), 2.95 (s, 3H), 3.02 (s, 3H), 4.64 (s, 3H), 4.45-4.7 (m, 1H).

Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72; O, 19.10. Found: C, 57.22; H, 6.94; N, 16.51; O, 19.27.

t-Butyl 5-(α-Cyano-α-methoxycarbonylmethylene)-1-methylprolinate (**5h**).

A solution of boron trifluoride/ether (20 ml, 0.15 mole) was added to carboxylic acid **21** (22.4 g, 0.1 mole) in 250 ml of chloroform. This solution was saturated with isobutene at 0° and then stirred at room temperature for 5 days. The mixture was poured in water containing potassium carbonate. The aqueous solution was extracted with methylene chloride (3 x 100 ml). The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was washed with alkaline water and recrystallized from ether, yield 80%, mp 121°; ir (potassium bromide): ν cm^{-1} 2200 (C=N), 1740 (C=O), 1710 (C=O), 1570 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.49 (s, 9H), 1.9-2.3 (m, 2H), 3.0-3.4 (m, 2H), 3.41 (s, 3H), 3.73 (s, 3H).

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99; O, 22.83. Found: C, 59.81; H, 7.23; N, 9.99; O, 22.78.

5-(α-Cyanomethylene)-2-*N*,*N*-dimethylcarbamoylpyrrolidine (**4c**).

A mixture of β-enaminoester **5f** (2.4 g, 10 mmoles), sodium iodide (4.5 g, 30 mmoles) and trimethylsilyl chloride (2.2 g, 20 mmoles) in 15 ml of acetonitrile was refluxed for 48 hours under an inert atmosphere. The solvent was removed under vacuum and 50 ml of water was added to the residue. The solution was refluxed and extracted with methylene chloride (3 x 20 ml). The organic layer was dried over sodium sulfate, filtered and evaporated. The crude β-enaminonitrile **4c** was recrystallized from water, yield 88%, mp 129-130°; ir (potassium bromide): ν cm^{-1} 3275 (N-H), 2190 (C=N), 1650 (C=O), 1600 (C=C); ^1H nmr (deuteriochloroform): δ ppm 1.7-2.5 (m, 2H), 2.5-3.1 (m, 2H), 3.0 (s, 3H), 3.1 (s, 3H), 3.8 (s, 0.37 H, deuterium oxide exchangeable), 4.12 (s, 0.63 H, deuterium oxide exchangeable), 4.47 (m, 1H), 6.0-6.2 (bs, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45; O, 8.93.

Found: C, 60.21; H, 7.20; N, 23.17; O, 8.93.

5-(α-Cyanomethylene)-2-*N*,*N*-dimethylcarbamoyl-1-methyl-1-pyrrolidine (**4d**).

A mixture of β-enaminoester **5g** (2.5 g, 10 mmoles), sodium iodide (4.5 g, 30 mmoles) and trimethylsilyl chloride (2.2 g, 20 mmoles) in 15 ml of acetonitrile was refluxed for 48 hours under inert atmosphere. The solvent was removed under vacuum and the silyl ester **24** was characterized by ^{1}H nmr (deuteriochloroform): δ ppm 0.31 (s, 9H). Water (50 ml) was added to the silyl ester, the solution was refluxed and extracted with methylene chloride (3 x 20 ml). The organic layer was dried over sodium sulfate, filtered and evaporated. The residue was purified by chromatography (silica gel, dichloromethane/methanol, 95/5). The oil was obtained in a yield of 85%; ir (potassium bromide): ν cm^{-1} 2200 (C=N), 1600 (C=O), 1610 (C=C); ^{1}H nmr (deuteriochloroform): δ ppm 1.7-2.2 (m, 2H), 2.5-3.2 (m, 2H), 2.74 (s, 3H), 2.97 (s, 3H), 3.05 (s, 3H), 3.73 (s, 1H), 4.4-4.6 (m, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 62.15; H, 7.82; N, 21.74; O, 8.28. Found: C, 62.10; H, 7.83; N, 21.73; O, 8.33.

Methyl 5-(α-Acetyl-α-methoxycarbonylmethylene)prolinate (**29**).

A stirred solution of β-enaminoester **3a** (2 g, 10 mmoles) and acetyl chloride (0.7 ml, 10 mmoles) in toluene (25 ml) was heated at 90° for 90 minutes. The toluene solution was washed with water, aqueous potassium carbonate solution, then water. After drying (sodium sulfate) and evaporation, the residue was kept at −20° until the precipitation of a solid which was recrystallized from ethyl alcohol, yield 54%, mp 79°; ir (nujol): ν cm^{-1} 3200 (N-H), 1750 (C=O), 1690 (C=O), 1600 (C=C), 1560 (C=C); ^{1}H nmr (deuteriochloroform): δ ppm 2.0-2.5 (m, 5H), 3.0-3.4 (m, 2H), 3.70 (s, 3H), 3.75 (s, 3H), 4.3-4.7 (m, 1H), 9 (s, 1H).

Anal. Calcd. for $C_{11}H_{15}NO_5$: C, 54.76; H, 6.27; N, 5.80; O, 33.16. Found: C, 54.98; H, 6.38; N, 6.00; O, 32.95.

REFERENCES AND NOTES

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