Studies on Pyrrolidones. Reactivity of β-Enaminoesters Derived from Pyroglutamic Acid. Synthesis of Methyl Cyano[1-methyl-5-(5-methyl[1,3,4]oxadiazol-2-yl)pyrrolidin-2-ylidene]acetate

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The 5-methoxycarbonyl group of β-enaminoesters derived from methyl pyroglutamate was transformed into acids, amides and 1,3,4-oxadiazole.

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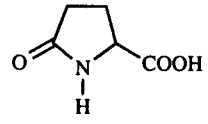
In previous papers from this series, we described the synthesis of β-enaminoesters **1** and **2** derived from pyroglutamic acid (**3**) [1,2], the reactivity of the β-enaminoester function (position 1) and of the vinylogous lactam function (position 2) [3]. We now describe the reactivity of the methoxycarbonyl group (position 3) toward nucleophiles and its transformation into 1,3,4-oxadiazoles (Figure 1).

Reaction of Compounds **1-2** with Sodium Hydroxide.

The first nucleophilic reaction we used was the saponification of the ester function. The methoxycarbonyl group of compounds **1** and **2** proved to be very sensitive toward transesterification and hydrolysis [1,4]. On the other hand, the β-enamine functionality of some compounds **1** and **2** is unstable toward concentrated acids and bases and some of the acids **5** are very soluble in water. Thus, the saponifi-

Figure 1



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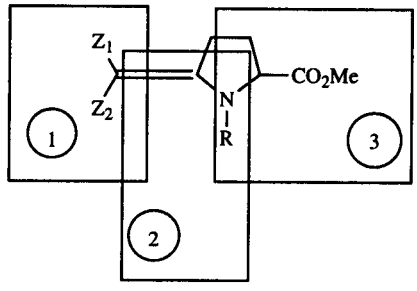
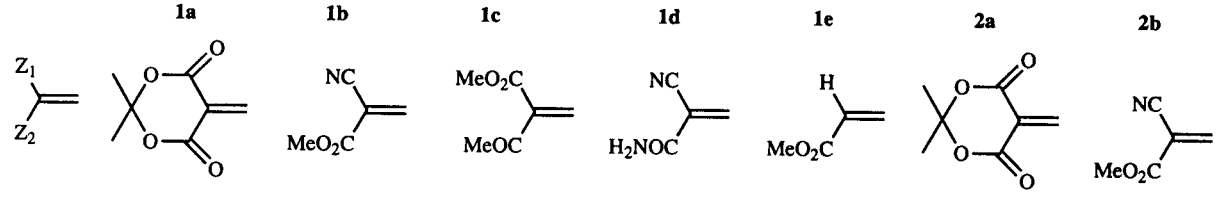
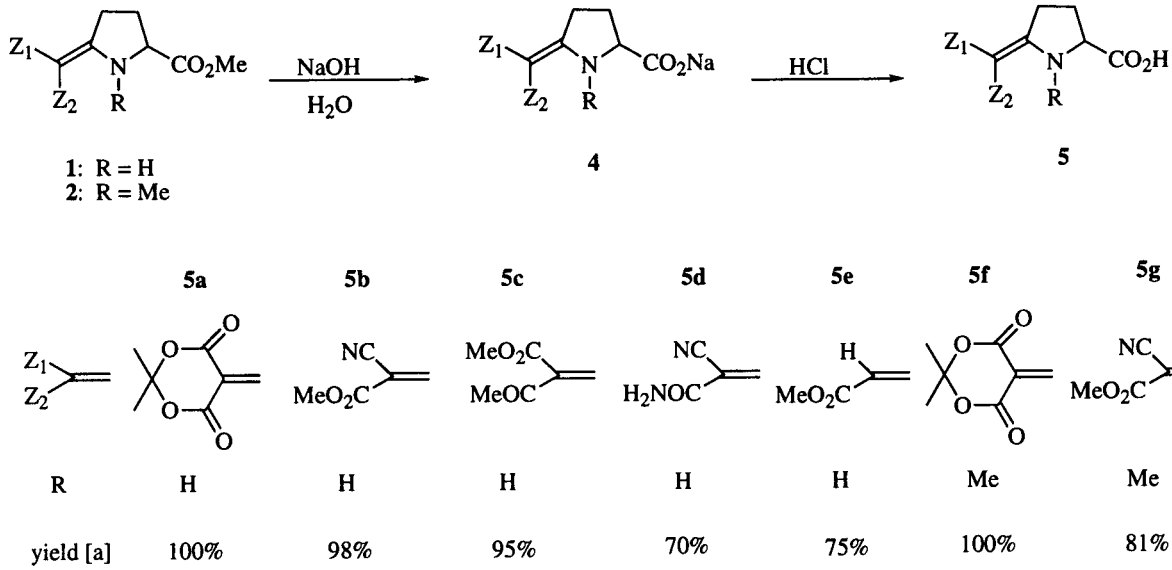


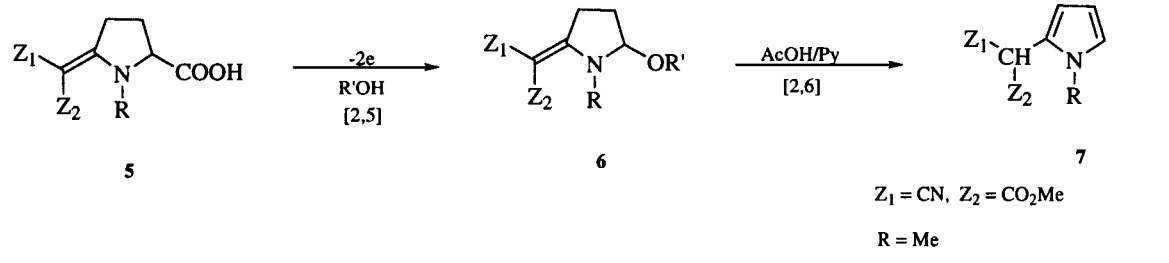


Scheme 1



[a] Crude products.

Scheme 2



cation of these esters was carried out under mild conditions: an exact amount of a concentrated solution of sodium hydroxide was added slowly dropwise at room temperature, into a suspension of the ester **1**, **2** in a small amount of water; after this addition, the solution was titrated with concentrated hydrochloric acid (Scheme 1). Acids **5** were then obtained crude in good yield and were recrystallized from water.

By using these conditions, we did not observe a decomposition of the enaminoester group. Acids **5** are stable compounds that can be transformed into vinylogs of *N*-acyl *N,O*-acetals **6** by anodic oxidation [2,5]; thus the availability of these acids has opened a new route to the synthesis of pyrroles **7** [2,6] (Scheme 2). The physical properties of acids **5** are reported in Table 1.

Reaction of Compounds **1a-b** and **2** with Amines and Hydrazine Hydrate.

It was interesting to prepare amides **8** because of their potential biological properties. Compounds **8a-b** were obtained by refluxing ester **1b** and **2b** with gaseous dimethylamine in methanol, and amides **8c-f** by refluxing ester **1a** with neat amines.The results are summarized in Scheme 3 and the physical data of amides **8** are reported in Table 2.

In the amidification reactions, we never observed any opening of the Meldrum's ring, although the preparation of the β-enaminoamides **10** by heating β-enaminoesters **9** in the presence of amines has been reported; in that case, the reaction was carried out 25° above the decomposition point of compounds **9** [7,8] (Scheme 4).

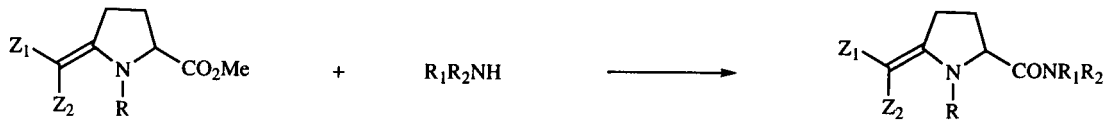
Hydrazine hydrate reacts even easier with esters **2**, yielding the hydrazides **11** at room temperature, always without opening of Meldrum's ring (Scheme 5).

The physical properties of compounds **11** are reported in Table 2.

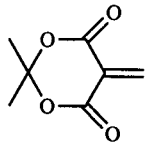
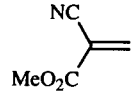
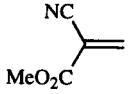
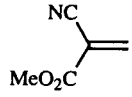
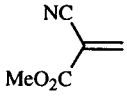
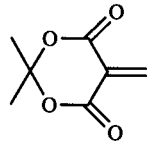
Preparation of 1,3,4-Oxadiazoles Derived from Compound **2**.

We already showed that heating of disilylated diacylhy-

Scheme 3



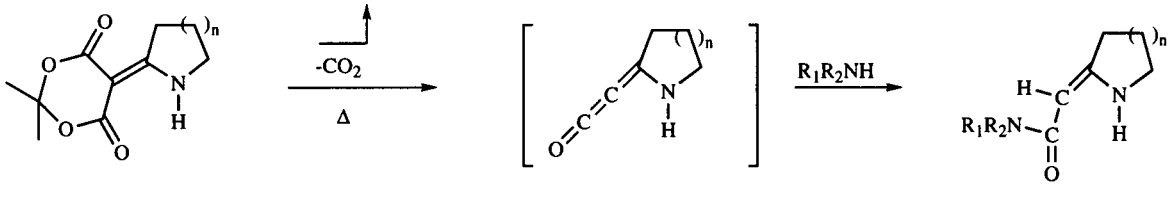
1a-b, 2b **8a-f**

		R			R
1a		H	**8a**		H
1b		H	**8b**		Me
2b		Me	**8c-f**		H

Compound	R_1	R_2	Yield [a]
8a	Me	Me	85%
8b	Me	Me	82%
8c	Me	Me	21% [b]
8d	H	Me_2CH	72%
8e	H	CH_2Ph	37% [c]
8f	H	*m*-CF_3Ph	19% [d]

[a] Recrystallized compound. [b] The transamidation was carried out in an aqueous solution of methylamine and the poor yield is due to the hydrolysis of the pyroglutamic ester function. [c] The poor yield reflects some difficulties observed during the crystallization of the amide **8e**. [d] The poor yield is due to the low nucleophily of the amine.

Scheme 4



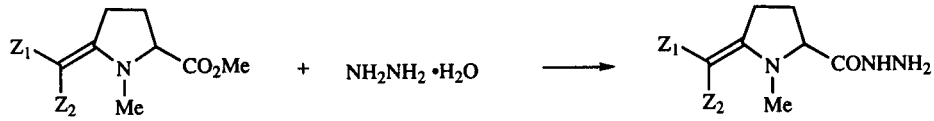
9 (n = 1-3) **10**

Table 1

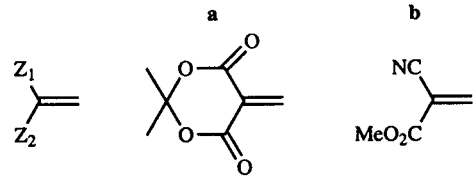
Physical Data of Compounds **5a-g**

	MP °C solvent	^{1}H NMR (δ ppm) solvent: D_2O + NaOD	IR (ν cm^{-1}) (nujol)	Molecular formula	Analysis (%) Calcd./Found C	H	N	O
5a	192	1.75 (s, 6H), 2-2.5 (m, 2H),	3450 (O-H), 3220 (N-H),	$C_{11}H_{13}NO_6$	51.76	5.13	5.49	37.61
	H_2O	3.3.4 (m, 2H), 4.3-4.8 (m, 1H)	1710 (C=O), 1660 (C=O), 1560 (C=C)		51.64	5.15	5.62	37.72
5b	168	1.5-2.6 (m, 2H), 2.6-3.2 (m, 2H),	3300 (O-H), 2200 (C≡N),	$C_9H_{10}N_2O_4$	51.43	4.80	13.22	30.45
	H_2O	3.74 (s, 3H), 4.25 (m, 1H)	1730 (C=O), 1650 (C=O), 1580 (C=C)		51.42	4.81	13.42	30.22
5c	158	1.4-2.1 (m, 2H), 2.32 (s, 3H), 2.7-3.4	3210 (N-H), 1720 (C=O),	$C_{10}H_{13}NO_5$	52.86	5.76	6.16	35.21
	H_2O	(m, 2H), 3.75 (s, 3H), 4.2-4.6 (m, 1H)	1690 (C=O), 1585 (C=C)		52.33	5.66	6.14	35.49
5d	> 260	1.5-2.7 (m, 2H), 2.7-3.1 (m, 2H),	3395 (O-H), 2200 (C≡N),	$C_8H_9N_3O_3$	49.23	4.65	21.53	24.59
	H_2O	4.2-4.5 (m, 1H)	1640 (C=O), 1600 (C=C), 1280 (C-O)		49.52	4.81	21.35	24.66
5e	93	1.6-2.8 (m, 4H), 3.6 (s, 3H),	3360 (N-H), 1710 (C=O),	$C_8H_{11}NO_4$	51.89	5.99	7.56	34.56
	H_2O	4.10-4.45 (m, 1H)	1640 (C=O), 1600 (C=C)		52.07	5.94	7.58	34.34
5f	129	1.70 (s, 6H), 2-2.4 (m, 2H), 3.05 (s, 3H),	3500 (O-H), 1720 (C=O),	$C_{12}H_{15}NO_6$,	50.17	5.96	4.87	38.98
	H_2O	2.7-3.15 (m, 2H), 4.45-4.7 (m, 1H)	1650 (C=O), 1570 (C=C), 1290 (C-O)	H_2O	50.43	5.90	4.90	38.89
5g	96	1.5-2.5 (m, 2H), 2.5-3.4 (m, 2H), 3.32	3490 (O-H), 2200 (C≡N),	$C_{10}H_{12}N_2O_4$,	49.58	5.83	11.56	33.02
	H_2O	(s, 3H), 3.71 (s, 3H), 4.1-4.5 (m, 1H)	1720 (C=O), 1680 (C=O), 1560 (C=C), 1210 (C-O)	H_2O	49.60	5.81	11.85	32.93

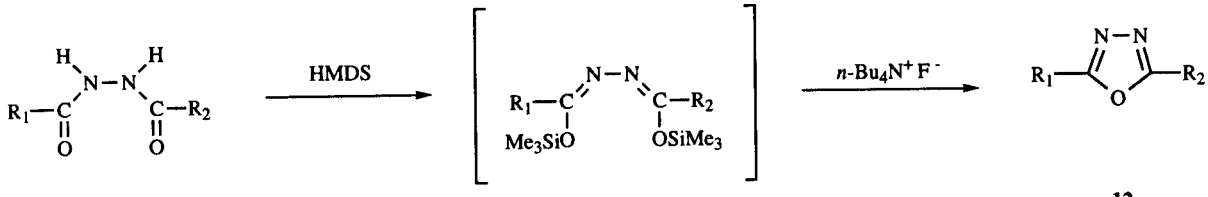
Scheme 5



2 **11**



Scheme 6



R_1, R_2 = alkyl or aryl groups

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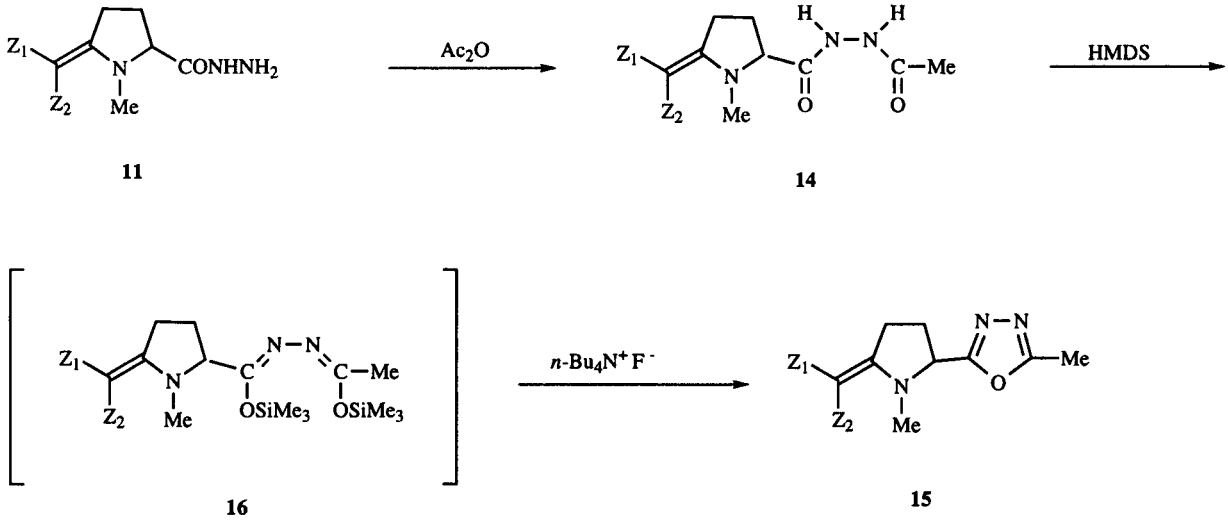
Table 2

Physical Data of Compounds **8a-f and 11a-b**

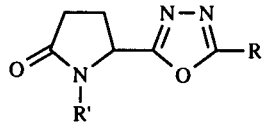
	MP °C solvent	^{1}H NMR (δ ppm)	IR (ν cm^{-1}) (nujol)	Molecular formula	Analysis (%) Calcd./Found C	H	N	O	F
8a	170 H_2O	$CDCl_3$: 1.9-2.5 (m, 2H), 2.9-3.4 (m, 2H), 3.73 (s, 3H), 4.3-4.7 (m, 1H), 9.0 (s, 1H)	3230 (N-H), 2200 (C≡N), 1690 (C=O), 1650 (C=O), 1600 (C=C), 1250 (C-O)	$C_{11}H_{15}N_3O_3$	55.69 55.57	6.37 6.28	17.71 17.63	20.23 20.22	
8b	131 H_2O	$CDCl_3$: 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)	3480 (N-Me), 2200 (C≡N) 1700 (C=O), 1650 (C=O), 1565 (C=C), 1240 (C-O)	$C_{12}H_{17}N_3O_3$	57.36 57.22	6.82 6.94	16.72 16.51	19.10 19.27	
8c	211 EtOH	$CDCl_3$: 1.64 (s, 6H), 2-2.5 (m, 2H), 2.95 (s, 3H), 3.05 (s, 3H), 3.4 (m, 2H), 4.6-5.0 (s, 1H), 10.18 (s, 1H)	3300 (N-H), 1710 (C=O), 1655 (C=O), 1595 (C=C), 1270 (C-O)	$C_{13}H_{18}N_2O_5$	55.31 55.55	6.42 6.48	9.92 9.73	28.34 28.53	
8d	196 EtOH	$CDCl_3$: 1-1.3 (d, 6H, J = 6 Hz), 1.69 (s, 6H), 2.05-2.6 (m, 2H), 3.1-3.6 (m, 2H), 3.7-4.2 (m, 1H), 3.7-4.65 (m, 1H)	3230 (N-H), 1710 (C=O), 1670 (C=O), 1640 (C=O), 1560 (C=C), 1270 (C-O)	$C_{14}H_{20}N_2O_5$	56.75 56.66	6.80 6.75	9.45 9.52	27.00 27.28	
8e	159 EtOH	$CDCl_3$: 1.60 (s, 6H), 2.26 (m, 2H), 3.4 (m, 2H), 4.2-4.65 (m, 3H), 6.55 (s, 1H), 10.25 (s, 1H)	3260 (N-H), 1705 (C=O), 1660 (C=O), 1570 (C=C), 1265 (C-O)	$C_{18}H_{20}N_2O_5$	62.78 62.78	5.85 5.85	8.13 8.11	23.23 23.33	
8f	223 Acetone	$CDCl_3$ + 5% DMSO-d_6: 1.7 (s, 6H), 2.1-2.7 (m, 2H), 3.2-3.65 (m, 2H), 4.5-4.9 (m, 1H), 7.6-7.9 (m, 4H)	3270 (N-H), 1700 (C=O), 1690 (C=O), 1560 (C=C)	$C_{18}H_{17}N_2O_5F_3$	54.27 54.34	4.30 4.41	7.03 6.99		14.32 14.25
11a	210 CH_2Cl_2	D_2O + NaOD: 1.73 (s, 6H), 2-2.5 (m, 2H), 3.00 (s, 3H), 3.1-3.5 (m, 2H), 4.24-4.58 (m, 1H)	3320 (N-H), 1710 (C=O), 1660 (C=O), 1545 (C=C), 1260 (C-O)	$C_{12}H_{17}N_3O_5$	50.88 50.80	6.05 6.05	14.83 14.83	28.24 28.48	
11b	228 EtOH	D_2O + NaOD: 1.5-2.3 (m, 2H), 2.73-3.44 (m, 2H), 3.21 (s, 3H), 3.70 (s, 3H), 3.9-4.3 (m, 1H)	3260 (N-H), 2200 (C≡N), 1680 (C=O), 1630 (C=O), 1560 (C=C)	$C_{10}H_{14}N_4O_3$	50.41 50.11	5.92 5.93	23.52 23.38	20.15 20.47	

Scheme 7



drazines with a small amount of catalyst is a very versatile way to obtain 1,3,4-oxadiazoles **12** [10] (Scheme 6), and we already used that reaction to convert pyroglutamic esters into 1,3,4-oxadiazoles **13** (Figure 2) [10,11].

Figure 2



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We applied this reaction scheme to the case of diacylhydrazines **14**: reaction of hydrazides **11** with acetic anhydride gives a quantitative crude yield of acetylhydrazides **14** and treatment of compound **14b** with hexamethyldisilazane and a catalytic amount of tetrabutylammonium fluoride gives the oxadiazole **15** in very good yields, without isolating intermediate **16** (Scheme 7).

The antitumor properties of amides **8c** and **8d** were tested according to a typical NCI protocol [9]. 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 "Service Central de Microanalyse" of CNRS in Vernaison, France.

Isopropylidene (5-Carboxy-2-pyrrolidinylidene)malonate (**5a**).

To a suspension of ester **1a** (2.7 g, 10 mmoles) in water (40 ml) was added a 1*M* solution of sodium hydroxide (10 ml, 10 mmoles). After dissolution in water, the organic salt was neutralized by 10 mmoles of concentrated hydrochloric acid. The organic acid **5a** precipitated. The yield of crude product **5a** was quantitative. The acids **5b-g** were obtained in the same way and the physical data are reported in Table 1.

Methyl Cyano-(5-dimethylcarbamoylpyrrolidin-2-ylidene)-acetate (**8a**).

A solution of ester **1b** (37.5 g, 170 mmoles) in 100 ml of methanol was saturated by gaseous dimethylamine and the mixture was stirred at room temperature for 9 days. The solid was filtered, washed with methanol, 91% yield, mp 170° (water).

The amide **8b** was prepared according to the same procedure. Physical properties (mp, ir, nmr) and the elemental analysis of amides **8a-b** are given in Table 2.

5-(2,2-Dimethyl-4,6-dioxo[1,3]dioxan-5-ylidene)pyrrolidine-2-carboxylic Acid Isopropylamide (**8d**).

A mixture of β-enaminoester **1a** (5.4 g, 20 mmoles) in isopropylamine (6.7 ml, 78 mmoles) was refluxed until the complete disappearence of the ester **1a** was observed by tlc. The amide precipitated and was filtered. The crude product was recrystallized from ethanol and the pure product was obtained in 72% yield.

The amides **8c** and **8e-f** were prepared according to the same procedure. Physical properties (mp, ir, nmr) and the elemental analyses of amides **8c-f** are given in Table 2.

Methyl Cyano-(5-hydrazinocarbonyl-1-methylpyrrolidin-2-ylidene)acetate (**11b**).

To a cooled (0°) solution of *N*-methyl-β-enaminoester **2b** (8.4 g, 35.3 mmoles) in methanol (25 ml) was added hydrazine hydrate (2.5 ml, 51 mmoles) and the mixture was stirred for 17 hours at room temperature. The hydrazide which precipitated was filtered and washed with methanol, 90% crude yield; the solid was washed with a hot mixture of ethanol/methylene dichloride.

The hydrazide **11a** was prepared from β-enaminoester **2a** by using the same procedure. The physical data of compound **11a-b** are reported in Table 2.

Methyl [5-(*N'*-Acetylhydrazinocarbonyl)-1-methylpyrrolidin-2-ylidene]cyanoacetate (**14b**).

A solution of acetic anhydride (7.7 ml, 80 mmoles) in methylene dichloride (20 ml) was cooled (0°) and hydrazide **11b** (5.7g, 24 mmoles) was added portionwise. Stirring was continued at room temperature for 24 hours. Compound **14b** was filtered and washed with ether, 90% crude yield, mp 244° (methanol); ir (nujol): ν cm^{-1}: 3290 (N-H), 2200 (C≡N), 1690 (C=O), 1610 (C=O), 1560 (C=C); ^1H nmr (sodium deuteroxide): δ ppm: 1.27-2.27 (m, 2H), 1.95 (s, 3H), 2.74-3.40 (m, 2H), 3.27 (s, 3H), 3.73 (s, 3H), 4.14-4.4 (m, 1H).

Anal. Calcd. for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99; O, 22.83. Found: C, 51.32; H, 5.90; N, 19.76; O, 22.91.

The above procedure was used for the preparation of diacylhydrazine **14a** from hydrazide **11a**, 90% crude yield, mp >260° (methanol); ir (nujol): ν cm^{-1} 3220 (N-H), 1670 (C=O), 1610 (C=O), 1580 (C=C); ^1H nmr (sodium deuteroxide): δ ppm 1.73 (s, 6H), 2.01 (s, 3H), 1.88-2.33 (m, 2H), 3.05 (s, 3H), 2.87-3.70 (m, 2H), 4.10-4.33 (m, 1H).

Anal. Calcd. for $C_{14}H_{19}N_3O_6$: C, 51.19; H, 5.88; N, 12.92; O, 29.51. Found: C, 51.41; H, 6.05; N, 12.73; O, 29.72.

Methyl Cyano-[1-methyl-5-(5-methyl[1,3,4]oxadiazol-2-yl)-pyrrolidin-2-ylidene]acetate (**15**).

A mixture of diacylhydrazine **14b** (3.66 g, 15.4 mmoles) and hexamethyldisilazane (10 ml, 47.5 mmoles) and a molar solution of tetrabutylammonium fluoride in tetrahydrofuran (0.2 ml, 0.2 mmole) was refluxed for 2 days. After cooling, methanol was added to hydrolyse any excess silylated diacetylhydrazine and the hexamethyldisiloxane formed was removed under vacuum. Methylene dichloride was added to the residue in order to precipitate the non-reacted diacylhydrazine which was filtered. The solvent was removed, the crude oxadiazole **15** obtained in 75% yield was recrystallized from an ether/methylene dichloride mixture, mp 82°; ir (nujol): ν cm^{-1} 2200 (C≡N), 1700 (C=O), 1560 (C=C); nmr (acetone-d_6): δ ppm 2.20-2.65 (m, 2H), 2.58 (s, 3H), 3.24-3.58 (m, 2H), 3.45 (s, 3H), 3.71 (s, 3H), 5.16-5.47 (m, 1H).

REFERENCES AND NOTES

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