

THE REACTION OF β -AMINOENONES WITH α -AMINO DERIVATIVES.
SYNTHESIS OF 2-FUNCTIONALIZED PYRROLES

Angel Alberola*, José M. Andrés, Alfonso González, Rafael Pedrosa, and Martina Vicente

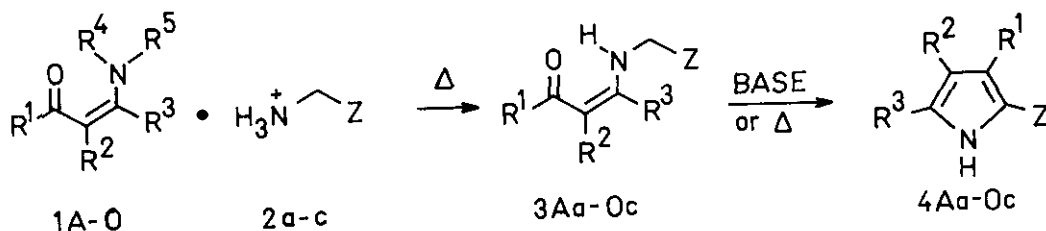
Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Valladolid.
Dr. Mergelina s/n, 47011-Valladolid, Spain

Abstract- β -Aminoenones react with ethyl glycinate, α -aminoacetonitrile and α -aminoacetamide hydrochlorides leading to 2-functionalized pyrroles. Although the transamination is a high-yield process, the transformation of the intermediate, in both basic or thermally induced conditions, affords the corresponding pyrroles in poor to moderate yields.

One of the most fruitful synthesis of pyrroles bearing different types of substituents and functionalities is the cyclization of 2-amino-1-alkenylcarbonyl derivatives. To this end, 1,3-dicarbonyl compounds,¹⁻⁵ β -aminoenones,⁶ β -chlorovinyl ketones⁷ and 3-alkoxyacroleins,⁸ have been condensed, in both acidic¹⁻⁶ or basic⁸ media, with preformed^{1,3} or in situ generated⁴ diethyl aminomalonate, α -aminocarbonyl compounds⁶ and glycine esters and aminoacetonitrile⁸ in a two-steps or one-pot preparation of pyrroles. On the other hand, we have recently reported a regioselective synthesis of 2- and 3-acylpyrroles from β -aminoenones and α -amino ketone hydrochlorides.^{9,10}

The regioselectivity of the reaction is considerably high and it has been correlated with the structure of the enolized diketones¹ or β -aminoenones,^{9,10} whereas the chemical yield and the rate of the process are also dependent on the protic or aprotic character of the solvent and, on the reaction temperature.^{9,10}

We report now our results on the reactivity of β -aminoenones **1A-0** with ethyl glycinate hydrochloride **2a**, aminoacetonitrile hydrochloride **2b** and aminoacetamide hydrochloride **2c**, leading to the preparation of 2-functionalized pyrroles **4Aa-0c**.



	R ¹	R ²	R ³	R ⁴	R ⁵	Z
1A	Me	H	Me	H	H	2a -CO ₂ Et
1B	Me	H	Me	Me	H	2b -CN
1C	Me	H	Me	-(CH ₂) ₄ -		2c -CONH ₂
1D	Et	H	Me	H	H	
1E	i-Pr	H	Me	H	H	
1F	PhCH ₂ CH ₂	H	Me	H	H	
1G	Me	H	Et	H	H	
1H	Me	Me	Me	H	H	
1I	Me	PhCH ₂	Me	H	H	
1J	Ph	H	Me	H	H	
1K	p-MeC ₆ H ₄	H	Me	H	H	
1L	p-MeOC ₆ H ₄	H	Me	H	H	
1M	p-NO ₂ C ₆ H ₄	H	Me	-(CH ₂) ₄ -		
1N	Me	H	Ph	H	H	
1O	Ph	H	Ph	H	H	
1P	t-Bu	H	t-Bu	H	H	

Table 1. Transamination of β -Aminoenones 1A-0 with α -Amino derivatives 2a-c.

Run	Compd.1	Compd.2	Time(h)/ solvent ^a	Product(%)	Run	Compd.1	Compd.2	Time(h)/ solvent ^a	Product(%)
1	1A	2a	1/M	3Aa(89) ^b	23	1I	2a	1/M	3Ia(94)
2	1A	2a	2/M	3Aa(85)	24	1I	2a	1.5/M	3Ia(96)
3	1A	2b	1/M	3Ab(84)	25	1I	2b	1/M	3Ib(86)
4	1A	2c	1/M	3Ac(57)	26	1J	2a	1/M	3Ja(54) ^b
5	1A	2c	3/M	3Ac(95)	27	1J	2a	3/M	3Ja(87)
6	1B	2a	1/M	3Aa(81) ^b	28	1J	2b	1/M	3Jb(82)
7	1C	2a	1/M	3Aa(96)	29	1J	2c	1/M	3Jc(50)
8	1D	2a	1/M	3Da(90) ^b	30	1J	2c	6/M	3Jc(89)
9	1D	2a	2/M	3Da(88)	31	1K	2a	1/M	3Ka(82) ^b
10	1D	2b	1/M	3Db(81)	32	1K	2a	3/M	3Ka(91)
11	1D	2c	3/M	3Dc(93)	33	1K	2c	6/M	3Kc(92)
12	1E	2a	1/M	3Ea(71) ^b	34	1L	2a	1/M	3La(92)
13	1E	2a	2/M	3Ea(92)	35	1L	2a	3/M	3La(96)
14	1E	2b	1/M	3Eb(87)	36	1L	2c	6/M	3Lc(88)
15	1E	2c	1/M	3Ec(58)	37	1M	2a	1/M	3Ma(5) ^b
16	1E	2c	4/M	3Ec(90)	38	1M	2a	24/E	3Ma(89)
17	1F	2a	1/M	3Fa(81) ^b	39	1N	2a	1/M	3Na(6) ^b
18	1F	2a	2.5/M	3Fa(96)	40	1N	2a	36/E	3Na(61) ^c
19	1F	2b	1/M	3Fb(89)	41	1O	2a	48/E	3Oa(74)
20	1G	2a	1/M	3Ga(56) ^b	42	1O	2b	16/M	3Ob(74)
21	1G	2a	2/M	3Ga(90)	43	1P	2a	54/E	4Pa(23)
22	1H	2a	1/M	3Ha(94)					

^a The reactions were carried out at reflux temperature of the corresponding solvent (M= methanol; E= ethanol).

^b Yields determined by nmr on the mixture of reaction.

^c From the reaction mixture, **3Ja** was isolated in 30 % yield.

The first step of the reaction is an addition-elimination process, leading to the transamination intermediate 3 and the results are summarized on Table 1; the rate of interchange decreases in the order α -aminoacetonitrile (2b) > ethyl glycinate (2a) > α -aminoacetamide (2c).

Otherwise, the rate of transamination decreases with the electron-withdrawing character of R^1 (compare runs 26, 31, 34 and 37 on Table 1), and the steric requirements of R^1 and R^3 ; in this respect, when both R^1 and R^3 are *tert*-butyl substituents (1P), the intermediate 3Pa can not be isolated and ethyl 2-(3,5-di-*tert*-butyl)pyrrolylcarboxylate 4Pa is obtained after a long period of reflux (run 43).

The cyclocondensation step of the intermediates 3 to pyrroles 4 was tested in different conditions including a base (sodium ethoxide or methoxide or pyridine) or thermally induced reactions (DMF at reflux), and data are summarized on Table 2.

Table 2. Cyclization of 3Aa-0b to 3-Functionalized Pyrroles 4Aa-0b.

Reaction Conditions					Reaction Conditions				
Run	Compd.	Base ^a / solvent ^b	Time(h)	Pyrrole(%)	Run	Compd.	Base ^a / solvent ^b	Time(h)	Pyrrole(%)
1	3Aa	EtONa/EtOH	3	4Aa(33)	17	3Ga	EtONa/EtOH	3	4Ga(23)
2	3Aa	DMF	58	4Aa(17)	18	3Ia	EtONa/EtOH	3	4Ia(19)
3	3Aa	pyridine	90	4Aa(10)	19	4Ib	DMF	13	4Ib(44)
4	3Ab	EtONa/EtOH	3	4Ab(12)	20	3Ja	EtONa/EtOH	6	4Ja(14)
5	3Ab	MeONa/MeOH	3	4Ab(9)	21	3Jb	DMF	96	4Jb(37)
6	3Ab	DMF	48	4Ab(37)	22	3Jc	EtONa/EtOH	3	-- ^c
7	3Ac	EtONa/EtOH	3	4Ac(32)	23	3Ka	EtONa/EtOH	3	4Ka(15)
8	3Ac	MeONa/MeOH	3	4Ac(22)	24	3Ka	DMF	100	-- ^d
9	3Da	EtONa/EtOH	3	4Da(17)	25	3Kc	EtONa/EtOH	3	4Kc(10) ^c
10	3Db	DMF	44	4Db(22)	26	3La	EtONa/EtOH	3	4La(10)
11	3Dc	EtONa/EtOH	3	4Dc(42)	27	3Lc	EtONa/EtOH	3	-- ^c
12	3Ea	EtONa/EtOH	3	4Ea(25)	28	3Ma	DMF	44	4Ma(23)
13	3Eb	DMF	50	4Eb(25)	29	3Na	EtONa/EtOH	3	4Na(24)
14	3Ec	EtONa/EtOH	3	4Ec(43)	30	3Oa	EtONa/EtOH	5	4Oa(30)
15	3Fa	EtONa/EtOH	6	4Fa(20)	31	3Ob	DMF	66	4Ob(41)
16	3Fb	DMF	72	4Fb(29)					

^a Molar ratio base:3 = 1:1 except for runs 15, 20 and 30 where molar ratio base:3 = 2:1.

^b The reactions were carried out at room temperature for runs 15, 20 and 30, and at reflux temperature of the given solvent for the others.

^c On the reaction mixture retrocondensation products (acetophenone, p-methylacetophenone and p-methoxyacetophenone) were isolated.

^d The products were 3Ka (50 %) and the corresponding diketone (50 %).

The cyclization of the intermediates is a regioselective reaction leading to 2-functionalized pyrroles, and chemical yields, generally low, depend on the functional group at the α -amino derivative 2; thus, the best results are obtained from α -aminoacetonitrile 2c and β -amino-enones 1A-E (R^1 = alkyl) (runs 7, 8, 11 and 14), while intermediates 3Jc-3Lc (R^1 = aryl) mainly

yield retrocondensation products. These results differ from previously reported^{9,10} for the reaction of β -aminoenones with phenacylamine hydrochloride, leading to 2- and/or 3-acylpyrroles in high yields, and it is a consequence of the regioselective cyclization of the intermediates 3, or one of their enolic forms, to the most stable aromatic pyrrole, instead of to the pyrrolidone derivative.

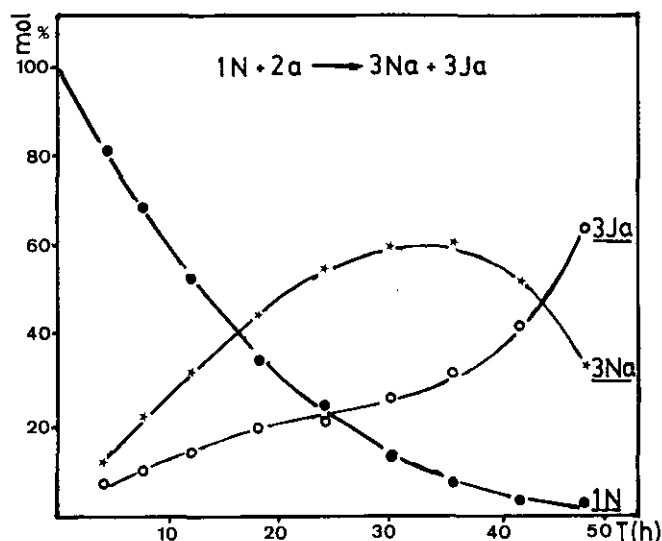
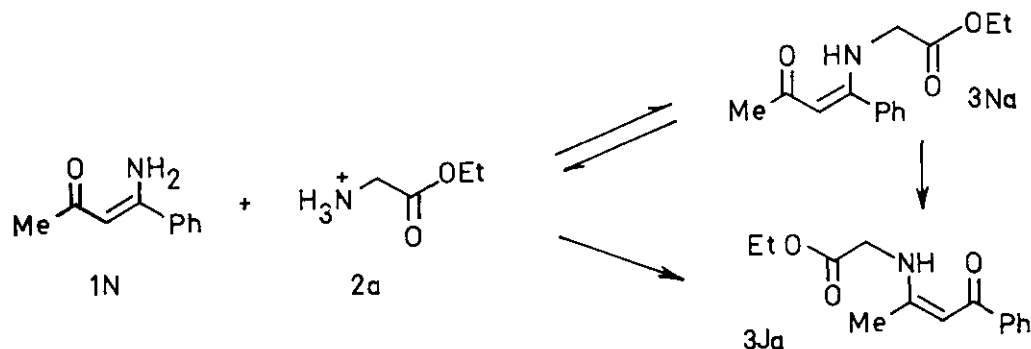


Figure 1

On the other hand, attempts to increase the chemical yields by increasing the reaction time and temperature failed because retrocondensation and isomerization processes. These are specially important for β -aminoenones with different steric or electronic requirements at R^1 and R^3 ($R^3 > R^1$ or $R^3 = \text{aryl}$ and $R^1 = \text{alkyl}$). We have investigated the regioselectivity of these transformation on intermediates 3Ja and 3Na obtained by reaction of 1J and 1N with 2a respectively. Thus, 3Na is completely transformed into its regioisomer 3Ja after heating in ethanol for 15 h with ethyl glycinate hydrochloride, while the inverse transformation does not

occur; moreover, 1N does not isomerize to 1J when heated for the same period of time with or without ammonium chloride, and benzoylacetone (the product of hydrolysis) can not be detected at any stage. Otherwise, on Figure 1, it has been represented the evolution of the amount of 3Na and 3Ja in the mixture of the reaction of 1N with 2a in refluxing ethanol. The data show that the highest yield for 3Na is obtained after 36 h, and that the regioisomer 3Ja appears early in the reaction mixture, being the major product after 44 h.



The scheme given above depicts the two mechanistic path as they would operate on the formation of the intermediates. The equilibrium leading to 3Na is an addition-elimination process, and 3Ja could be obtained by irreversible isomerization of 3Na or by an alternative 1,2-addition of ethyl

glycinate hydrochloride to the carbonyl group in **1N**. Although we have proved that **3Na** does isomerize to **3Ja**, we have been unable to discount a competing direct formation of the regioisomer by 1,2-addition.

EXPERIMENTAL

Mp's (uncorrected) were determined in an open capillary tube. Nmr were recorded on a Bruker AC80 or Varian T60 A, and chemical shifts are given in ppm downfield from TMS. Mass spectra were measured on a Hewlett-Packard 5988A mass spectrometer by Electronic Impact at 70 eV, and combustion analysis were determined on a Perkin-Elmer 140B analyzer. Starting materials were commercially available or synthesized as previously described.¹¹

Synthesis of the Intermediates 3. General procedure A mixture of 10 mmol of the corresponding β -aminoenone **1A-P** and 11 mmol of α -amino derivative **2a-c**, in anhydrous methanol or ethanol (30 ml) was refluxed for the time indicated on Table 1. The solvent was evaporated under vacuum and the residue was redissolved in THF; the salts were filtered off, the THF was eliminated under reduced pressure and the solid was recrystallized from an appropriate solvent. In this way, the following compounds were obtained:

Ethyl N-(1-Methyl-3-oxo-1-butenyl)glycinate (3Aa) Colorless solid, mp 65-66°C (from hexane) (lit.,¹⁶ 66-67°C). Nmr (CDCl₃): 1.27(t, J=6 Hz, 3H); 1.90(s, 3H); 2.00(s, 3H); 4.00(d, J=6 Hz, 2H); 4.20(q, J=7 Hz, 2H); 5.07(s, 1H); 10.90(broad, 1H). Ms, m/z(%): 185(M⁺, 49); 112(100).

N-(1-Methyl-3-oxo-1-butenyl)glycinonitrile (3Ab) Colorless solid, mp 109-110°C (from ethanol) (lit.,¹⁶ 112-113°C). Nmr(CDCl₃): 2.03(s, 6H); 4.24(d, J=7 Hz, 2H); 5.18(s, 1H); 10.70(broad, 1H). Ms, m/z(%): 138(M⁺, 31); 123(100).

N-(1-Methyl-3-oxo-1-butenyl)glycinamide (3Ac) Colorless solid, mp 177-178°C (from methanol). Nmr(DMSO-d₆): 1.87(s, 6H); 3.90(d, J=6 Hz, 2H); 4.97(s, 1H); 7.13(broad, 1H); 7.43(broad, 1H); 10.60(broad, 1H). Ms, m/z(%): 156(M⁺, 57); 112(100). C₇H₁₂N₂O₂ requires: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.77; H, 7.88; N, 17.82.

Ethyl N-(1-Methyl-3-oxo-1-pentenyl)glycinate (3Da) Colorless solid, mp 68-69°C (from methanol). Nmr (CDCl₃): 1.07(t, J=7 Hz, 3H); 1.27(t, J=7 Hz, 3H); 1.92(s, 3H); 2.26(q, J=7 Hz, 2H); 4.02(d, J=6 Hz, 2H); 4.23(q, J=7 Hz, 2H); 5.08(s, 1H); 10.90(broad, 1H). Ms, m/z(%): 199(M⁺, 31); 170(100). C₁₀H₁₇NO₃ requires: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.13; H, 8.68; N, 7.12.

N-(1-Methyl-3-oxo-1-pentenyl)glycinonitrile (3Db) Colorless solid, mp 63-64°C (from hexane). Nmr (CDCl₃): 1.05(t, J=7 Hz, 3H); 2.03(s, 3H); 2.28(q, J=7 Hz, 2H); 4.14(d, J=7 Hz, 2H); 5.18(s, 1H); 10.70 (broad, 1H). Ms, m/z(%): 152(M⁺, 9); 123(100). C₈H₁₂N₂O requires: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.02; H, 7.86; N, 18.49.

N-(1-Methyl-3-oxo-1-pentenyl)glycinamide (3Dc) Colorless solid, mp 150-151°C (from methanol). Nmr (DMSO-d₆): 1.05(t, J=7 Hz, 3H); 1.93(s, 3H); 2.22(q, J=7 Hz, 2H); 3.93(d, J=6 Hz, 2H); 5.06(s, 1H); 6.80(broad, 1H); 7.10(broad, 1H); 10.80(broad, 1H). Ms, m/z(%): 170(M⁺, 41); 141(100). C₈H₁₄N₂O₂ requires: C, 56.45; H, 8.29; N, 16.46. Found: C, 56.32; H, 8.39; N, 16.35.

Ethyl N-(1,4-Dimethyl-3-oxo-1-pentenyl)glycinate (3Ea) Colorless solid, mp 64-65°C (from hexane). Nmr(CDCl₃): 1.08(d, J=7 Hz, 2H); 1.25(t, J=7 Hz, 3H); 1.92(s, 3H); 2.43(m, 1H); 3.98(d, J=6 Hz, 2H); 4.21(q, J=7 Hz, 2H); 5.07(s, 1H); 10.90(broad, 1H). Ms, m/z(%): 213(M⁺, 19); 170(100). C₁₁H₁₉NO₃ requires: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.85; H, 8.76; N, 6.69.

N-(1,4-Dimethyl-3-oxo-1-pentenyl)glycinonitrile (3Eb) Colorless solid, mp 70-71°C (from hexane-benzene). Nmr(CDCl₃): 1.06(d, J=7 Hz, 6H); 2.05(s, 3H); 2.47(m, 1H); 4.15(d, J=7 Hz, 2H); 5.20(s, 1H); 10.80(broad, 1H). Ms, m/z(%): 166(M⁺, 9); 123(100). C₉H₁₄N₂O requires: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.11; H, 8.57; N, 16.76.

N-(1,4-Dimethyl-3-oxo-1-pentenyl)glycinamide (3Ec) Colorless solid, mp 134-135°C (from hexane-

benzene). Nmr(CDCl₃): 1.06(d, J=7 Hz, 6H); 1.93(s, 3H); 2.43(m, 1H); 3.93(d, J=6 Hz, 2H); 5.10(s, 1H); 6.70(broad, 2H); 10.90(broad, 1H). Ms, m/z(%): 184(M⁺, 15); 141(100). C₉H₁₆N₂O₂ requires: C, 58.68; H, 8.75; N, 15.20. Found: C, 58.79; H, 8.69; N, 15.14.

Ethyl N-(1-Methyl-3-oxo-5-phenyl-1-pentenyl)glycinate (3Fa) Colorless solid, mp 55-56°C (from hexane-benzene). Nmr(CDCl₃): 1.28(t, J=7 Hz, 3H); 1.87(s, 3H); 2.73(m, 4H); 3.97(d, J=6 Hz, 2H); 4.19(q, J=7 Hz, 2H); 5.00(s, 1H); 7.18(s, 5H); 10.96(t, J=6 Hz, 1H). Ms, m/z(%): 275(M⁺, 45); 170(100). C₁₆H₂₁NO₃ requires: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.71; H, 7.78; N, 5.16.

N-(1-Methyl-3-oxo-5-phenyl-1-pentenyl)glycinonitrile (3Fb) Colorless solid, mp 84-85°C (from hexane-benzene). Nmr(CDCl₃): 1.95(s, 3H); 2.74(m, 4H); 4.00(d, J=7 Hz, 2H); 5.13(s, 1H); 7.17(s, 5H); 10.63(broad, 1H). Ms, m/z(%): 228(M⁺, 11); 123(100). C₁₄H₁₆N₂O requires: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.73; H, 7.14; N, 12.21.

Ethyl N-(1-Ethyl-3-oxo-1-butenyl)glycinate (3Ga) Colorless solid, mp 43-44°C (lit.,¹² 41°C). Nmr(CCl₄): 1.10(t, J=7 Hz, 3H); 1.27(t, J=7 Hz, 3H); 1.93(s, 3H); 4.07(d, J=6 Hz, 2H); 4.20(q, J=7 Hz, 2H); 4.36(q, J=7 Hz, 2H); 4.98(s, 1H); 10.90(broad, 1H).

Ethyl N-(1,2-Dimethyl-3-oxo-1-butenyl)glycinate (3Ha) Colorless solid, mp 84-85°C (from hexane-benzene). Nmr(CDCl₃): 1.28(t, J=7 Hz, 3H); 1.87(s, 3H); 1.92(s, 3H); 2.12(s, 3H); 3.98(d, J=6 Hz, 2H); 4.20(q, J=7 Hz, 2H); 12.10(broad, 1H). Ms, m/z(%): 199(M⁺, 16); 108(100). C₁₀H₁₇NO₃ requires: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.37; H, 8.68; N, 7.11.

Ethyl N-(2-Benzyl-1-methyl-3-oxo-1-butenyl)glycinate (3Ia) Colorless solid, mp 88-89°C (from hexane-benzene). Nmr(CDCl₃): 1.25(t, J=7 Hz, 3H); 1.82(s, 3H); 2.05(s, 3H); 3.68(s, 2H); 4.02(d, J=6 Hz, 2H); 4.20(q, J=7 Hz, 2H); 7.20(s, 5H); 12.30(broad, 1H). Ms, m/z(%): 275(M⁺, 77); 91(100). C₁₆H₂₁NO₃ requires: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.86; H, 7.62; N, 5.16.

N-(2-Benzyl-1-methyl-3-oxo-1-butenyl)glycinonitrile (3Ib) Colorless solid, mp 120-121°C (from ethanol). Nmr(CDCl₃): 2.00(s, 3H); 2.08(s, 3H); 3.72(s, 2H); 4.16(d, J=7 Hz, 2H); 7.23(s, 5H); 12.03(broad, 1H). Ms, m/z(%): 228(M⁺, 29); 188(100). C₁₄H₁₆N₂O requires: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.71; H, 7.01; N, 12.33.

Ethyl N-(1-Methyl-3-oxo-3-phenyl-1-propenyl)glycinate (3Ja) Colorless solid, mp 82-83°C (from methanol) (lit.,¹² 84°C). Nmr(CDCl₃): 1.20(t, J=7 Hz, 3H); 1.92(s, 3H); 4.02(d, J=6 Hz, 2H); 4.15(q, J=7 Hz, 2H); 5.65(s, 1H); 7.20-8.00(m, 5H); 11.33(t, 1H).

N-(1-Methyl-3-oxo-3-phenyl-1-propenyl)glycinonitrile (3Jb) Colorless solid, mp 110-111°C (from ethanol). Nmr(CDCl₃): 2.08(s, 3H); 4.16(d, J=7 Hz, 2H); 5.85(s, 1H); 7.20-8.00(m, 5H); 11.30(broad, 1H). Ms, m/z(%): 200(M⁺, 80); 105(100). C₁₂H₁₂N₂O requires: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.09; H, 6.12; N, 13.91.

N-(1-Methyl-3-oxo-3-phenyl-1-propenyl)glycinamide (3Jc) Colorless solid, mp 212-213°C (from ethanol). Nmr(DMSO-d₆): 2.15(s, 3H); 4.20(d, J=6 Hz, 2H); 6.00(s, 1H); 7.40(broad, 2H); 7.40-8.30(m, 5H); 11.60(t, J=6 Hz, 1H). Ms, m/z(%): 218(M⁺, 11); 91(100). C₁₂H₁₄N₂O₂ requires: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.11; H, 6.46; N, 12.91.

Ethyl N-(1-Methyl-3-oxo-3-p-tolyl-1-propenyl)glycinate (3Ka) Colorless solid, mp 87-88°C (from ethanol). Nmr(CDCl₃): 1.25(t, J=7 Hz, 3H); 1.98(s, 3H); 2.35(s, 3H); 4.05(d, J=6 Hz, 2H); 4.23(q, J=7 Hz, 2H); 5.77(s, 1H); 6.88(d, J=9 Hz, 2H); 7.88(d, J=9 Hz, 2H); 11.45(broad, 1H). Ms, m/z(%): 277(M⁺, 65); 121(100). C₁₅H₁₉NO₄ requires: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.05; H, 6.99; N, 5.14.

N-(1-Methyl-3-oxo-1-propenyl-3-p-tolyl)glycinamide (3Kc) Colorless solid, mp 166-167°C (from ethanol). Nmr(DMSO-d₆): 2.10(s, 3H); 2.37(s, 3H); 4.08(d, J=6 Hz, 2H); 5.77(s, 1H); 7.10(broad, 2H); 7.56(d, J=8 Hz, 2H); 7.80(d, J=8 Hz, 2H); 11.40(broad, 1H). Ms, m/z(%): 232(M⁺, 21); 105(100). C₁₃H₁₆N₂O₂ requires: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.31; H, 7.06; N, 12.14.

Ethyl N-(1-Methyl-3-p-methoxyphenyl-3-oxo-1-propenyl)glycinate (3La) Colorless solid, mp 86-87°C (from ethanol). Nmr(CDCl₃): 1.23(t, J=7 Hz, 3H); 1.97(s, 3H); 3.75(s, 3H); 4.02(d, J=6 Hz, 2H);

4.20(q, J=7 Hz, 2H); 5.72(s, 1H); 6.88(d, J=9 Hz, 2H); 7.88(d, J=9 Hz, 2H); 11.45(broad, 1H). Ms, m/z(%): 277(M⁺, 65); 121(100). C₁₅H₁₉NO₄ requires: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.07; H, 6.99; N, 4.98.

N-(1-Methyl-3-p-methoxyphenyl-3-oxo-1-propenyl)glycinamide (3Lc) Colorless solid, mp 173-174°C (from ethanol). Nmr(DMSO-d₆): 2.13(s, 3H); 3.93(s, 3H); 4.15(d, J=6 Hz, 2H); 5.86(s, 3H); 7.07(d, J=8 Hz, 2H); 7.20(broad, 1H); 7.60(broad, 1H); 8.00(d, J=8 Hz, 2H); 11.40(broad, 1H). Ms, m/z(%): 248(M⁺, 17); 121(100). C₁₃H₁₆N₂O₃ requires: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.96; H, 6.42; N, 11.25.

Ethyl N-(1-Methyl-3-p-nitrophenyl-3-oxo-1-propenyl)glycinate (3Ma) Yellow solid, mp 107-108°C (from ethanol). Nmr(CDCl₃): 1.30(t, J=7 Hz, 3H); 2.07(s, 3H); 4.17(d, J=6 Hz, 2H); 4.27(q, J=7 Hz, 2H); 5.75(s, 1H); 7.98(d, J=9 Hz, 2H); 8.25(d, J=9 Hz, 2H); 11.70(broad, 1H). Ms, m/z(%): 292(M⁺, 46); 219(100). C₁₄H₁₆N₂O₅ requires: C, 57.53; H, 5.49; N, 9.56. Found: C, 57.62; H, 5.45; N, 9.66.

Ethyl N-(1-Butenyl-3-oxo-1-phenyl)glycinate (3Na) Colorless oil. Nmr(CDCl₃): 1.20(t, J=7 Hz, 3H); 2.05(s, 3H); 3.82(d, J=6 Hz, 2H); 4.13(q, J=7 Hz, 2H); 5.15(s, 1H); 7.35(s, 5H); 10.80(broad, 1H). Ms, m/z(%): 247(M⁺, 29); 105(100).

Ethyl N-(3-Oxo-1,3-diphenyl-1-propenyl)glycinate (30a) Colorless solid, mp 80-81°C (from ethanol). Nmr(CDCl₃): 1.20(t, J=7 Hz, 3H); 3.92(d, J=6 Hz, 2H); 4.15(q, J=7 Hz, 2H); 5.85(s, 1H); 7.20-8.00(m, 10 H); 11.40(broad, 1H). Ms, m/z(%): 309(M⁺, 47); 105(100). C₁₉H₁₉NO₃ requires: C, 73.77; H, 6.19; N, 4.53. Found: C, 73.71; H, 6.25; N, 4.64.

N-(3-Oxo-1,3-diphenyl-1-propenyl)glycinonitrile (30b) Colorless solid, mp 123-124°C (from ethanol). Nmr(CDCl₃): 4.04(d, J=7 Hz, 2H); 6.00(s, 3H); 7.30-8.20(m, 10 H); 11.17(broad, 1H). Ms, m/z(%): 262(M⁺, 29); 105(100). C₁₇H₁₄N₂O requires: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.93; H, 5.29; N, 10.74.

Cyclization of the Intermediates 3 to 2-Functionalized Pyrroles 4. General procedure. To a solution of sodium methoxide or ethoxide (10 mmol, or 20 mmol for runs 15, 20 and 30) in 5 ml of methanol or ethanol were added 10 mmol of the corresponding intermediate **3** in 10 ml of the same solvent, and the mixture was refluxed (or stirred at room temperature for runs 15, 20 and 30) for the time shown in Table 2. The mixture was cooled to room temperature and quenched with 10 g of ice in water; the aqueous layer was extracted with ether (3x20 ml), the ethereal phase was washed with water and brine and dried over anhydrous MgSO₄. The solvent was evaporated under vacuum and the residue was chromatographed on silica gel and CH₂Cl₂ (for 2-ethoxycarbonyl- and 2-cyanopyrroles) or ethyl acetate (for 2-carbamoylpyrroles) as eluents.

When pyridine or DMF were used as solvents, 10 mmol of compound in 10 ml of solvent were refluxed for the time indicated in Table 2. After this period, the solution was cooled to room temperature, the solvent was distilled under vacuum and the residue was chromatographed as above indicated. The physical and spectral properties of pyrroles **4** are as follows:

Ethyl 3,5-Dimethyl-2-pyrrolecarboxylate (4Aa) Colorless solid, mp 121-122°C (from ethanol), (lit.,¹³ 122-124°C). Nmr(CCl₄): 1.32(t, J=7 Hz, 3H); 2.20(s, 3H); 2.23(s, 3H); 4.23(q, J=7 Hz, 2H); 5.65(d, J=2 Hz, 1H); 10.70(broad, 1H). Ms, m/z(%): 167(M⁺, 94); 121(100).

2-Cyano-3,5-dimethylpyrrole (4Ab) Colorless solid, mp 71-72°C (from hexane). Nmr (CCl₄): 2.17(s, 3H); 2.22(s, 3H); 5.67(d, J=2 Hz, 1H); 9.60(broad, 1H). Ms, m/z(%): 120(M⁺, 67); 119(100). C₇H₈N₂ requires: C, 69.98; H, 6.71; N, 23.31. Found: C, 69.83; H, 6.80; N, 23.43.

3,5-Dimethyl-2-pyrrolecarboxamide (4Ac) Colorless solid, mp 162-163°C (from diethyl ether) (lit.,¹⁴ 163°C). Nmr(CDCl₃): 2.23(s, 3H); 2.30(s, 3H); 5.77(d, J=2 Hz, 1H); 6.00(broad, 2H); 9.90(broad, 1H). Ms, m/z(%): 138(M⁺, 100).

Ethyl 3-Ethyl-5-methyl-2-pyrrolecarboxylate (40a) Colorless solid, mp 77-78°C (from methanol) (lit.,¹⁵ 85-86°C). Nmr(Acetone-d₆): 1.20(t, J=8 Hz, 3H); 1.36(t, J=7 Hz, 3H); 2.28(s, 3H);

2.78(q, J=8 Hz, 2H); 4.35(q, J=7 Hz, 2H); 5.86(d, J=2 Hz, 1H); 9.45(broad, 1H). Ms, m/z(%): 181(M⁺, 80); 134(100).

2-Cyano-3-ethyl-5-methylpyrrole (4Db) Colorless oil. Nmr(CCl₄): 1.20(t, J=7 Hz, 3H); 2.23(s, 3H); 2.55(q, J=7 Hz, 2H); 5.73(d, J=2 Hz, 1H); 9.70(broad, 1H). Ms, m/z(%): 134(M⁺, 35); 119(100). C₈H₁₀N₂ requires: C, 71.61; H, 7.51; N, 20.87. Found: C, 71.50; H, 7.42; N, 20.96.

3-Ethyl-5-methyl-2-pyrrolicarboxamide (4Dc) Colorless solid, mp 178-179°C (from methanol). Nmr(CDCl₃): 2.20(t, J=7 Hz, 3H); 2.23(s, 3H); 2.72(q, J=7 Hz, 2H); 5.83(d, J=2 Hz, 1H); 6.23(broad, 2H); 10.20(broad, 1H). Ms, m/z(%): 152(M⁺, 100). C₈H₁₂N₂O requires: C, 63.13; H, 7.95; N, 18.41. Found: C, 63.20; H, 8.03; N, 18.32.

Ethyl 5-Methyl-3-isopropyl-2-pyrrolicarboxylate (4Ea) Colorless solid, mp 56-57°C (from methanol). Nmr(CDCl₃): 1.23(d, J=7 Hz, 6H); 1.35(t, J=7 Hz, 3H); 2.30(s, 3H); 3.55(m, J=7 Hz, 1H); 4.38(q, J=7 Hz, 2H); 5.96(d, J=2 Hz, 1H); 9.50(broad, 1H). Ms, m/z(%): 195(M⁺, 50); 134(100). C₁₁H₁₇NO₂ requires: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.74; H, 8.87; N, 7.11.

2-Cyano-5-methyl-3-isopropylpyrrole (4Eb) Colorless solid, mp 58-59°C (from hexane). Nmr(CCl₄): 1.22(d, J=7 Hz, 6H); 2.20(s, 3H); 2.90(m, J=7 Hz, 1H); 5.73(d, J=2 Hz, 1H); 9.80(broad, 1H). Ms, m/z(%): 148(M⁺, 29); 133(100). C₉H₁₂N₂ requires: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.86; H, 8.09; N, 18.89.

5-Methyl-3-isopropyl-2-pyrrolicarboxamide (4Ec) Colorless solid, mp 150-151°C (from hexane-benzene). Nmr(CDCl₃): 1.22(d, J=7 Hz, 6H); 2.20(s, 3H); 3.13(m, J=7 Hz, 1H); 5.83(d, J=2 Hz, 1H); 6.33(broad, 2H); 10.50(broad, 1H). Ms, m/z(%): 166(M⁺, 66); 134(100). C₉H₁₄N₂O requires: C, 65.03; H, 8.49; N, 16.85. Found: C, 65.12; H, 8.43; N, 16.71.

Ethyl 3-(β-Phenylethyl)-5-methyl-2-pyrrolicarboxylate (4Fa) Colorless solid, mp 104-105°C (from methanol). Nmr(CDCl₃): 1.32(t, J=7 Hz, 3H); 2.18(s, 3H); 2.87(m, 4H); 4.25(q, J=7 Hz, 2H); 5.68(d, J=2 Hz, 1H); 7.07(s, 5H); 10.00(broad, 1H). Ms, m/z(%): 257(M⁺, 44); 166(100). C₁₆H₁₉NO₂ requires: C, 74.69; H, 7.44; N, 5.44. Found: C, 74.78; H, 7.32; N, 5.56.

2-Cyano-5-methyl-3-(β-phenylethyl)pyrrole (4Fb) Colorless solid, mp 63-64°C (from hexane-toluene). Nmr(CCl₄): 2.17(s, 3H); 2.82(s, 4H); 5.65(d, J=2 Hz, 1H); 7.15(s, 5H); 9.60(broad, 1H). Ms, m/z(%): 210(M⁺, 17); 119(100). C₁₄H₁₄N₂ requires: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.89; H, 6.80; N, 13.21.

Ethyl 5-Ethyl-3-methyl-2-pyrrolicarboxylate (4Ga) Colorless solid, mp 74-75°C (from methanol), (lit., ¹² 74°C). Nmr(Acetone-d₆): 1.18(t, J=7 Hz, 3H); 1.27(t, J=7 Hz, 3H); 2.30(s, 3H); 2.63(q, J=7 Hz, 2H); 4.25(q, J=7 Hz, 2H); 5.82(d, J=3 Hz, 1H); 10.10(broad, 1H).

Ethyl 4-Benzyl-3,5-dimethyl-2-pyrrolicarboxylate (4Ia) Colorless solid, mp 125-126°C (from methanol). Nmr(CDCl₃): 1.30(t, J=7 Hz, 3H); 2.17(s, 3H); 2.22(s, 3H); 3.75(s, 2H); 4.28(q, J=7 Hz, 2H); 7.15(s, 5H); 9.30(broad, 1H). Ms, m/z(%): 257(M⁺, 100). C₁₆H₁₉NO₂ requires: C, 74.69; H, 7.44; N, 5.44. Found: C, 74.78; H, 7.57; N, 5.38.

4-Benzyl-2-cyano-3,5-dimethylpyrrole (4Ib) Colorless solid, mp 101-102°C (from hexane-benzene). Nmr(CDCl₃): 2.10(s, 3H); 2.18(s, 3H); 3.72(s, 2H); 6.80-7.40(m, 5H); 9.70(broad, 1H). Ms, m/z(%): 210(M⁺, 71); 133(100). C₁₄H₁₄N₂ requires: C, 79.97; H, 6.71; N, 13.32. Found: C, 80.09; H, 6.64; N, 13.23.

Ethyl 5-Methyl-3-phenyl-2-pyrrolicarboxylate (4Ja) Colorless solid, mp 131-132°C (from methanol), (lit., ¹³ 134-135°C). Nmr(DMSO-d₆): 1.13(t, J=7 Hz, 3H); 2.23(s, 3H); 4.10(q, J=7 Hz, 2H); 5.87(d, J=2 Hz, 1H); 7.00-7.60(m, 5H); 10.80(broad, 1H). Ms, m/z(%): 229(M⁺, 81); 183(100).

2-Cyano-5-methyl-3-phenylpyrrole (4Jb) Colorless solid, mp 147-148°C (from hexane-benzene). Nmr(CDCl₃): 2.30(s, 3H); 6.20(d, J=2 Hz, 1H); 7.20-7.80(m, 5H); 9.20(broad, 1H). Ms, m/z(%): 182(M⁺, 100). C₁₂H₁₀N₂ requires: C, 79.10; H, 5.53; N, 15.37. Found: C, 79.21; H, 5.44; N, 15.45.

Ethyl 5-Methyl-3-p-tolyl-2-pyrrolicarboxylate (4Ka) Colorless solid, mp 158-159°C (from methanol).

Nmr(CCl₄): 1.16(t, J=7 Hz, 3H); 2.30(s, 3H); 2.33(s, 3H); 4.20(q, J=7 Hz, 2H); 5.93(d, J=2 Hz, 1H); 7.07(d, J=8 Hz, 2H); 7.37(d, J=8 Hz, 2H); 10.10(broad, 1H). Ms, m/z(%): 243(M⁺, 67); 197(100). C₁₅H₁₇NO₂ requires: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.16; H, 7.12; N, 5.63.

5-Methyl-3-p-tolyl-2-pyrrolicarboxylate (4Kc) Colorless solid, mp 184-185°C (from hexane-benzene). Nmr(CDC₃Cl₃): 2.30(s, 3H); 2.37(s, 3H); 5.50-6.20(m, 3H); 7.17(d, J=8 Hz, 2H); 7.31(d, J=8 Hz, 2H); 10.50(broad, 1H). Ms, m/z(%): 214(M⁺, 54); 154(100). C₁₃H₁₄N₂O requires: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.76; H, 6.66; N, 13.19.

Ethyl 3-p-Methoxyphenyl-5-methyl-2-pyrrolicarboxylate (4La) Colorless solid, mp 127-128°C (from methanol). Nmr(CCl₄): 1.20(t, J=7 Hz, 3H); 2.30(s, 3H); 3.77(s, 3H); 4.20(q, J=7 Hz, 2H); 5.92(d, J=2 Hz, 1H); 6.80(d, J=9 Hz, 2H); 7.40(d, J=9 Hz, 2H); 10.00(broad, 1H). Ms, m/z(%): 259(M⁺, 67); 213(100). C₁₅H₁₇NO₂ requires: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.37; H, 6.74; N, 5.48.

Ethyl 5-Methyl-3-(p-nitrophenyl)-2-pyrrolicarboxylate (4Ma) Colorless solid, mp 184-185°C (from methanol). Nmr(Acetone-d₆): 1.23(t, J=7 Hz, 3H); 2.37(s, 3H); 4.31(q, J=7 Hz, 2H); 6.33(d, J=3 Hz, 1H); 8.00(d, J=9 Hz, 2H); 8.37(d, J=9 Hz, 2H); 10.10(broad, 1H). Ms, m/z(%): 274(M⁺, 100). C₁₄H₁₄N₂O₄ requires: C, 61.32; H, 5.14; N, 10.21. Found: C, 61.22; H, 5.25; N, 10.12.

Ethyl 3-Methyl-5-phenyl-2-pyrrolicarboxylate (4Na) Colorless solid, mp 114-115°C (from methanol), (lit., ¹³ 114-115°C). Nmr(CDC₃Cl₃): 1.33(t, J=7 Hz, 3H); 2.37(s, 3H); 4.33(q, J=7 Hz, 2H); 6.38(d, J=2 Hz, 1H); 7.20-7.80(m, 5H); 9.60(broad, 1H). Ms, m/z(%): 229(M⁺, 65); 183(100).

Ethyl 3,5-Diphenyl-2-pyrrolicarboxylate (40a) Colorless solid, mp 135-136°C (from ethanol), (lit., ¹³ 135-137°C). Nmr(CDC₃Cl₃): 1.13(t, J=7 Hz, 3H); 4.20(q, J=7 Hz, 2H); 6.57(d, J=3 Hz, 1H); 7.10-7.80 (m, 10H); 9.80(broad, 1H). Ms, m/z(%): 291(M⁺, 55); 217(100).

2-Cyano-3,5-diphenylpyrrole (40b) Colorless solid, mp 195-196°C (from methanol). Nmr(CDC₃Cl₃): 6.57(d, J=2 Hz, 1H); 6.90-7.70(m, 10H); 12.20(broad, 1H). Ms, m/z(%): 244(M⁺, 100). C₁₇H₁₂N₂ requires: C, 83.58; H, 4.95; N, 11.46. Found: C, 83.67; H, 5.06; N, 11.38.

Ethyl 3,5-Di-tert-butyl-2-pyrrolicarboxylate (4Pa) Colorless solid, mp 88-89°C (from methanol). Nmr(CDC₃Cl₃): 1.30(s, 9H); 1.40(s, 9H); 1.32(t, J=7 Hz, 3H); 4.32(q, J=7 Hz, 2H); 5.96(d, J=3 Hz, 1H); 9.70(broad, 1H). Ms, m/z(%): 251(M⁺, 27); 190(100). C₁₅H₁₅NO₂ requires: C, 71.68; H, 10.02; N, 5.57. Found: C, 71.59; H, 10.15; N, 5.68.

ACKNOWLEDGEMENTS

Authors thank to the Spanish DGICYT for financial support of this work (Project PB86-0145). One of us (J.M.A.) is also indebted to the Ministry of Education and Science of Spain for a grant (PFPI).

REFERENCES

1. a) J. B. Paine and D. Dolphin, *J. Org. Chem.*, **1985**, 50, 5598; b) J. B. Paine, J. R. Brough, K. K. Buller, and E. E. Erikson, *J. Org. Chem.*, **1987**, 52, 3986.
2. A. W. Johnson, E. Markham, R. Price, and K. B. Shaw, *J. Chem. Soc.*, **1958**, 4254.
3. J. M. Patterson, *Synthesis*, **1976**, 281.
4. G. G. Kleinspehn, *J. Am. Chem. Soc.*, **1955**, 77, 1546.
5. S. Umio, K. Kariyone, K. Tanaka, and T. Kishimoto, *Chem. Pharm. Bull.*, **1969**, 17, 576.
6. E. Cohen and R. Dewald, *Synthesis*, **1987**, 566.
7. S. Hauptmann and J. Weisflog, *J. Prakt. Chem.*, **1972**, 314, 353.
8. G. H. Walizei and E. Breitmaier, *Synthesis*, **1989**, 337.
9. A. Alberola, J. M. Andr s, A. Gonz lez, R. Pedrosa, and M. Vicente, *Heterocycles*, **1989**, 29,

1973.

10. A. Alberola, J. M. Andr  s, A. Gonz  lez, R. Pedrosa, and M. Vicente, Heterocycles, **1989**, 29, 1983.
11. A. Alberola, C. Andr  s, A. Gonz  lez, R. Pedrosa, and M. Vicente., An. Quim. (Madrid), **1987**, 83C, 55.
12. A. Treibs and A. Ohorodnik, Liebigs Ann. Chem., **1958**, 611, 139.
13. S. Mataka, K. Takahasi, Y. Tsuda, and M. Tashiro, Synthesis, **1982**, 157.
14. A. Houben and F. Fischer, Ber., **1931**, 64, 2639.
15. R. A. Nicolaus and R. Nicoletti, Ann. Chim. (Rome), **1957**, 47, 167.
16. C. A .C. Haley and P. Maitland, J. Chem. Soc., **1951**, 3155.

Received, 5th February, 1990