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

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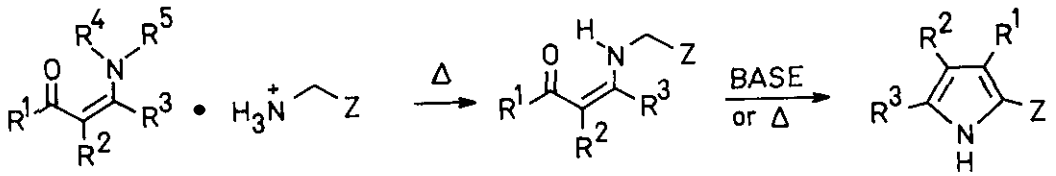
Abstract- β-Aminoenones react with ethyl glycinate, α-aminoacetonitrile and α-aminoacetamide hydrochlorides leading to 2-functionalized pyrroles. Although the transamination is a high-yield process, the transformation of the intermediate, in both basic or thermally induced conditions, affords the corresponding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

One of the most fruitfull 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 ketones[7] and 3-alkoxyacroleins,[8] have been condensed, in both acidic[1-6] or basic [8] media, with preformed[1,3] or in situ generated[4] diethyl aminomalonate, α-aminocarbonyl compounds[6] and glycine esters and aminoacetonitrile[8] 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 hydrochorides.[9,10]

The regioselectivity of the reaction is considerably high and it has been correlated with the structure of the enolized diketones[1] 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-O with ethyl glycinate hydrochloride 2a, aminoacetonitrile hydrochloride 2b and aminoacetamide hydrochloride 2c, leading to the preparation of 2-functionalized pyrroles 4Aa-Oc.



1A-O 2a-c 3Aa-Oc 4Aa-Oc

	R^1	R^2	R^3	R^4	R^5
1A	Me	H	Me	H	H
1B	Me	H	Me	Me	H
1C	Me	H	Me	$-(CH_2)_4-$	
1D	Et	H	Me	H	H
1E	i-Pr	H	Me	H	H
1F	$PhCH_2CH_2$	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_6H_4	H	Me	H	H
1L	p-$MeOC_6H_4$	H	Me	H	H
1M	p-$NO_2C_6H_4$	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

	Z
2a	$-CO_2Et$
2b	-CN
2c	$-CONH_2$

Table 1. Transamination of β-Aminoenones 1A-O 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-Ob to 3-Functionalized Pyrroles 4Aa-Ob.

		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, generaly low, depend on the functional group at the α-amino derivative 2; thus, the best results are obtained from α-aminoacetonitrile 2c and β-aminoenones 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.

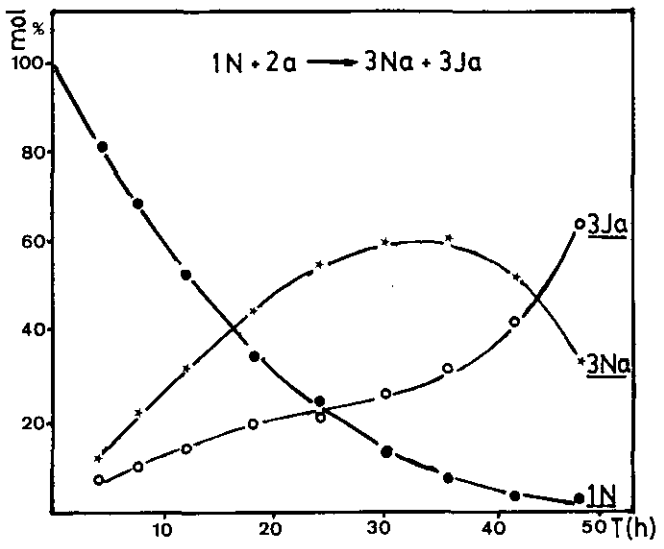
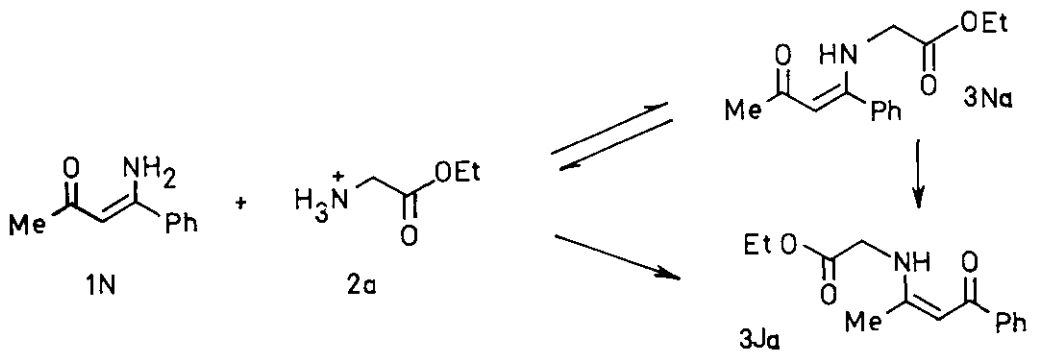


Figure 1

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 requeriments at R^1 and R^3 ($R^3 > R^1$ or R^3 = aryl and R^1 = 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 Brucker 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 analizer. Starting materials were comercially 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 ($CDCl_3$): 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($CDCl_3$): 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-d_6): 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/s(%): 156(M^+,57); 112(100). $C_7H_{12}N_2O_2$ 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 ($CDCl_3$): 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). $C_{10}H_{17}NO_3$ 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 ($CDCl_3$): 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). $C_8H_{12}N_2O$ 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-d_6): 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). $C_8H_{14}N_2O_2$ 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($CDCl_3$): 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). $C_{11}H_{19}NO_3$ 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($CDCl_3$): 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). $C_9H_{14}N_2O$ 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($CDCl_3$): 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). $C_9H_{16}N_2O_2$ 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($CDCl_3$): 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). $C_{16}H_{21}NO_3$ 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($CDCl_3$): 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). $C_{14}H_{16}N_2O$ 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 (CCl_4): 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($CDCl_3$): 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). $C_{10}H_{17}NO_3$ 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($CDCl_3$): 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). $C_{16}H_{21}NO_3$ 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($CDCl_3$): 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). $C_{14}H_{16}N_2O$ 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($CDCl_3$): 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($CDCl_3$): 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). $C_{12}H_{12}N_2O$ 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-d_6): 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). $C_{12}H_{14}N_2O_2$ 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($CDCl_3$): 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). $C_{15}H_{19}NO_4$ 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-d_6): 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). $C_{13}H_{16}N_2O_2$ 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($CDCl_3$): 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). $C_{15}H_{19}NO_4$ 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-d_6): 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). $C_{13}H_{16}N_2O_3$ 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($CDCl_3$): 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). $C_{14}H_{16}N_2O_5$ 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($CDCl_3$): 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 (3Oa) Colorless solid, mp 80-81°C(from ethanol). Nmr($CDCl_3$): 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). $C_{19}H_{19}NO_3$ 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 (3Ob) Colorless solid, mp 123-124°C(from ethanol). Nmr($CDCl_3$): 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). $C_{17}H_{14}N_2O$ 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 $MgSO_4$. The solvent was evaporated under vacuum and the residue was chromatographed on silica gel and CH_2Cl_2 (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(CCl_4): 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 (CCl_4): 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). $C_7H_8N_2$ 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($CDCl_3$): 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 (4Da) Colorless solid, mp 77-78°C(from methanol)(lit.,[15] 85-86°C). Nmr(Acetone-d_6): 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(CCl_4): 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). $C_8H_{10}N_2$ 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-pyrrolecarboxamide (4Dc) Colorless solid, mp 178-179°C(from methanol). Nmr ($CDCl_3$): 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). $C_8H_{12}N_2O$ 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-pyrrolecarboxylate (4Ea) Colorless solid, mp 56-57°C(from methanol). Nmr($CDCl_3$): 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). $C_{11}H_{17}NO_2$ 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(CCl_4): 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). $C_9H_{12}N_2$ 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-pyrrolecarboxamide (4Ec) Colorless solid, mp 150-151°C(from hexane-benzene). Nmr($CDCl_3$): 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). $C_9H_{14}N_2O$ 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-pyrrolecarboxylate (4Fa) Colorless solid, mp 104-105°C(from methanol). Nmr($CDCl_3$): 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). $C_{16}H_{19}NO_2$ 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(CCl_4): 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). $C_{14}H_{14}N_2$ 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-pyrrolecarboxylate (4Ga) Colorless solid, mp 74-75°C(from methanol),(lit.,[12] 74°C). Nmr(Acetone-d_6): 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-pyrrolecarboxylate (4Ia) Colorless solid, mp 125-126°C(from methanol). Nmr($CDCl_3$): 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). $C_{16}H_{19}NO_2$ 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 ($CDCl_3$): 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). $C_{14}H_{14}N_2$ 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-pyrrolecarboxylate (4Ja) Colorless solid, mp 131-132°C(from methanol),(lit.,[13] 134-135°C). Nmr (DMSO-d_6): 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($CDCl_3$): 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). $C_{12}H_{10}N_2$ 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-pyrrolecarboxylate (4Ka) Colorless solid, mp 158-159°C(from methanol).

Nmr(CCl_4): 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). $C_{15}H_{17}NO_2$ 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-pyrrolecarboxylate (4Kc) Colorless solid, mp 184-185°C(from hexane-benzene). Nmr($CDCl_3$): 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). $C_{13}H_{14}N_2O$ 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-pyrrolecarboxylate (4La) Colorless solid, mp 127-128°C(from methanol). Nmr(CCl_4): 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). $C_{15}H_{17}NO_2$ 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-pyrrolecarboxylate (4Ma) Colorless solid, mp 184-185°C(from methanol). Nmr(Acetone-d_6): 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). $C_{14}H_{14}N_2O_4$ 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-pyrrolecarboxylate (4Na) Colorless solid, mp 114-115°C (from methanol), (lit.,[13] 114-115°C). Nmr($CDCl_3$): 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-pyrrolecarboxylate (40a) Colorless solid, mp 135-136°C(from ethanol), (lit.,[13] 135-137°C). Nmr($CDCl_3$): 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($CDCl_3$): 6.57(d, J=2 Hz,1H); 6.90-7.70(m,10H); 12.20(broad,1H). Ms,m/z(%): 244(M^+,100). $C_{17}H_{12}N_2$ 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-pyrrolecarboxylate (4Pa) Colorless solid, mp 88-89°C(from methanol). Nmr ($CDCl_3$): 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). $C_{15}H_{15}NO_2$ requires: C, 71.68; H, 10.02; N, 5.57. Found: C, 71.59; H, 10.15; N, 5.68.

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