A Simple Synthesis of Pyrroles

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A new, convenient procedure is described for the synthesis of pyrroles by cyclocondensation of 2-amino-1-alkenyl ketones with α-aminocarbonyl compounds.

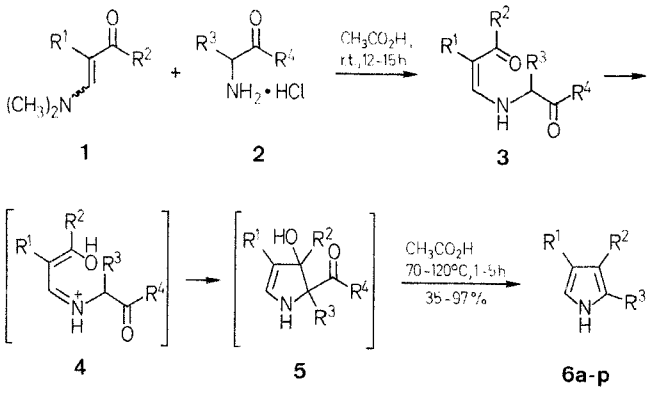
We describe here a novel and simple method for the preparation of pyrroles unsubstituted in positions 1 and 5. This method complements known procedures for the synthesis of pyrrole-2-carboxylic esters and analogs prepared by the condensation of dicarbonyl compounds with aminocarbonyl compounds or their precursors.[1-5]

We have found that 2-amino-1-alkenyl ketones **(1)** react with α-aminocarbonyl compounds **(2)** (R^1 and R^3 are electron-withdrawing groups) to form the pyrroles **6** having alkoxycarbonyl, aminocarbonyl, or cyano groups at C-2, aryl, acyl, or alkoxycarbonyl groups at C-4, and alkyl groups at C-3. (Table 1).

Table. Preparation and Properties of Pyrroles **6**

Compound **1**		Compound **2**		Product **6**	Reaction Conditions (°C, h)	Yield[a] (%)	m.p. (°C)[b] (solvent)	Molecular Formula[c] or m.p. (°C) reported	^{1}H-NMR (DMSO-d_6/TMS)[d] δ (ppm)
R^1	R^2	R^3	R^4						
C_2H_5OOC	CH_3	$CONH_2$	NH_2	**a**	100, 3	95	239–240 (ethyl acetate)	$C_9H_{12}N_2O_3$ (196.2)	1.26 (t, 3H); 2.48 (s, 3H); 4.17 (q, 2H); 7.14 (s, 2H); 7.43 (s, 1H); 11.69 (s, 1H)
C_2H_5OOC	CH_3	CN	NH_2	**b**	70, 5	37[e]	123–124 (diisopropyl ether)	135[15]	1.28 (t, 3H); 2.33 (s, 3H); 4.21 (q, 2H); 7.67 (s, 1H); 12.63 (s, 1H)
C_2H_5OOC	CH_3	$COCH_3$	CH_3	**c**	120, 3	55[e]	120 (ethyl acetate/ diisopropyl ether)	117[15]	1.27 (t, 3H); 2.41 (s, 3H); 2.55 (s, 3H); 4.20 (q, 2H); 7.50 (s, 1H); 12.15 (s, 1H)
CH_3CO	CH_3	$COOC_2H_5$	CH_3	**d**	90, 5	56[f]	94 (diisopropyl ether)	$C_{10}H_{13}NO_3$ (195.2)	1.31 (t, 3H); 2.36 (s, 3H); 2.50 (s, 3H); 4.26 (q, 2H); 7.76 (s, 1H); 12.09 (s, 1H)
CH_3CO	CH_3	$CONH_2$	NH_2	**e**	70, 4	73	225–226 (ethyl acetate/ 2-propanol)	$C_8H_{10}N_2O_2$ (166.2)	2.33 (s, 3H); 2.48 (s, 3H); 7.17 (s, 2H); 7.68 (s, 1H)
CH_3CO-	CH_3	CN	NH_2	**f**	90, 3	94	213–214 (ethyl acetate)	$C_8H_8N_2O$ (148.2)	2.32 (s, 3H); 2.36 (s, 3H); 7.91 (s, 1H)
C_6H_5CO-	CH_3	$COOC_2H_5$	CH_3	**g**	80, 3	55[f]	130–132 (diisopropyl ether)	$C_{15}H_{15}NO_3$ (257.3)	1.33 (t, 3H); 2.58 (s, 3H); 4.30 (q, 2H); 7.25 (s, 1H); 7.61 (m, 5H); 12.25 (s, 1H)
C_6H_5CO-	CH_3	$CONH_2$	NH_2	**h**	90, 3	86	251–252 (2-propanol)	$C_{13}H_{12}N_2O_2$ (228.3)	2.54 (s, 3H); 7.21 (s, 2H); 7.21 (s, 1H); 7.60 (m, 5H); 11.81 (s, 1H)
C_6H_5CO-	CH_3	CN	NH_2	**i**	90, 3	71	220–221 (ethyl acetate)	$C_{13}H_{10}N_2O$ (210.2)	2.39 (s, 3H); 7.60 (m, 6H); 12.75 (s, 1H)
C_6H_5	CH_3	$COOC_2H_5$	CH_3	**j**	90, 2	54[f]	94 (diisopropyl ether)	$C_{14}H_{15}NO_2$ (229.3)	1.32 (t, 3H); 2.40 (s, 3H); 4.27 (q, 2H); 7.27 (m, 6H); 11.72 (s, 1H)
C_6H_5	CH_3	$CONH_2$	NH_2	**k**	120, 2	95	224 (ethyl acetate)	$C_{12}H_{12}N_2O$ (200.2)	2.38 (s, 3H); 7.20 (m, 8H); 11.66 (s, 1H)
C_6H_5	CH_3	CN	NH_2	**l**	100, 1	97	175–176 (diisopropyl ether)	$C_{12}H_{10}N_2$ (182.2)	2.26 (s, 3H); 7.34 (m, 6H); 12.21 (s, 1H)
C_6H_5	C_2H_5	CN	NH_2	**m**	120, 4	92	130 (diisopropyl ether)	$C_{13}H_{12}N_2$ (196.3)	1.11 (t, 3H); 2.68 (q, 2H); 7.30 (m, 6H)
C_2H_5OOC	C_3H_7	$CONH_2$	NH_2	**n**	120, 2.5	74	203–204 (ethyl acetate/ 2-propanol)	$C_{11}H_{16}N_2O_3$ (224.3)	0.87 (t, 3H); 1.26 (t, 3H); 1.48 (m, 2H); 3.01 (t, 2H); 4.16 (q, 2H); 7.14 (s, 2H); 7.42 (br. s, 1H); 11.80 (br. s, 1H)
$C_2H_5OOC-CO-$	CH_3	$CONH_2$	NH_2	**o**[g]	90, 5	38	177–178 (ethyl acetate)	$C_{10}H_{12}N_2O_4$ (224.2)	1.30 (t, 3H); 2.49 (s, 3H); 4.31 (q, 2H); 7.32 (s, 2H); 7.71 (s, 1H); 12.11 (br. s, 1H)
C_2H_5OOC	C_6H_5	$CONH_2$	NH_2	**p**	120, 5	35[e]	217–218 (ethyl acetate)	$C_{14}H_{14}N_2O_3$ (258.3)	1.01 (t, 3H); 3.97 (q, 2H); 7.29–7.51 (m, 5H + 1H + 2H); 12.19 (s, 1H)

[a] Yield of isolated product.
[b] Uncorrected.
[c] Satisfactory microanalyses obtained: C ±0.36, H ±0.35, N ±0.36.
[d] Obtained on a BRUKER AC 250 spectrometer.
[e] Isolated and purified by column chromatography on silica gel, using trichloromethane/methanol (98 : 2) as eluent.
[f] Isolated and purified by column chromatography on silica gel, using cyclohexane/ethyl acetate (70 : 30) as eluent.
[g] ^{13}C-NMR (DMSO-d_6): δ = 11.34 ($\underline{C}H_3$); 13.88 ($CH_2\underline{C}H_3$); 61.64 ($\underline{C}H_2O$); 119.02, 124.27, 125.81, 130.66 (pyrrole); 162.37 ($\underline{C}ONH_2$); 163.85 (CO–$\underline{C}OO$); 181.18 ppm ($\underline{C}O$–COO).



The reaction is simply carried out by stirring equimolecular mixtures of compounds **1** and **2** in acetic acid at room temperature for 12–15 hours to first afford the intermediates **3** via a nucleophilic displacement reaction. Heating of the mixture then effects ring closure of **3** with elimination of acetic acid or carbamic acid, respectively, to give the pyrroles **6**. In some cases, the intermediates **3** can be isolated from the reaction mixture by filtration ($R^3 = CN$, $CONH_2$; $R^4 = NH_2$), general, however they were converted into pyrroles **6** without previous purification.

A study of the cyclocondensation of a variety of α-aminocarbonyl compounds (type **2**) with 2-amino-1-alkenyl ketones to investigate the scope of the method revealed that the best leaving groups -CO-R^4 are acetyl and aminocarbonyl, while the alkoxycarbonyl, benzoyl, or cyano group showed little tendency to split off. Thus, condensation of ethyl 2-aminoacetoacetate (**2**, $R^3 = CH_3$, $R^4 = OC_2H_5$) with e.g., **1d** or **1g** gave almost exclusively the pyrrole-2-carboxylic esters **6d** and **6g**, respectively.

The starting materials and reagents are readily available. The β-aminoenones **1** are readily obtained by reaction of dimethylformamide dimethyl acetal with alkyl ketones and the α-aminocarbonyl compounds **2** are prepared from the oximino precursors by catalytic reduction.

In conclusion, the present method is a useful alternative to known syntheses of substituted pyrroles because of the simple and mild conditions (one-pot operation) and the high yields. Further, the procedure can be used for large-scale preparations. Pharmacological evaluation of the products showed no cardiotonic activity.

The following starting materials were prepared according to literature procedures, except for **2b** which is commercially available.

2-Amino-1-alkenyl Ketones (**1**):
Ethyl 2-(dimethylaminomethylene)-3-oxobutanoate (**1a**),[6] 3-(dimethylaminomethylene)-2,4-pentanedione (**1d**),[7] 2-(dimethylaminomethylene)-1-phenyl-1,3-butanedione (**1g**),[8] 4-dimethylamino-3-phenyl-3-buten-2-one (**1j**),[9] ethyl 2-(dimethylaminomethylene)-3-oxo-3-phenylpropanoate (**1p**).[10]

α-Aminocarbonyl compounds (**2**):
Aminomalonic diamide (**2a**),[11] α-aminocyanoacetamide (**2b**),[12] 3-amino-2,4-pentanedione (**2c**),[13] ethyl 2-amino-3-oxobutanoate (**2d**).[14]

Pyrroles (6); General Procedure:
A mixture of the 2-amino-1-alkenyl ketone **1** (10 mmol) and the α-aminocarbonyl compounds **2** (12 mmol) in acetic acid (40 ml) is stirred at room temperature for 12–15 h. The mixture is then heated at 70–120°C for 1–5 h, cooled to ambient temperature, and concentrated using a Rotavapor; the residue is taken up in dichloromethane (100 ml) and neutralised with sodium hydrogen carbonate. The organic layer is dried with sodium sulfate, filtered, and evaporated under reduced pressure to afford the product **6**. Final purification is accomplished either by crystallization or column chromatography on silica gel using chloroform or cyclohexane as eluent. All products were further characterized by microanalyses and NMR spectrometry.

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(1) Fischer, H., Fink, E. *Z. Physiol. Chem.* **1944**, *280*, 123.
(2) Kleinspehn, G.G. *J. Am. Chem. Soc.* **1955**, *77*, 1546.
(3) Johnson, A.W., Markham, E., Price, R., Shaw, K.B. *J. Chem. Soc.* **1958**, 4254.
(4) Paine, J.B., Dolphin, D. *J. Org. Chem.* **1985**, *50*, 5598.
(5) Patterson, J.M. *Synthesis* **1976**, 281.
(6) Meerwein, H., Florian, W., Schön, N., Stopp, G. *Liebigs Ann. Chem.* **1961**, *641*, 1.
(7) Kölle, U., Kolb, B., Mannschreck, A. *Chem. Ber.* **1980**, *113*, 2560.
(8) Clark, B.P., Ross, W.J., Todd, A. *German Patent (DOS)* 3012 584 (1980), Lilly Ind. Ltd.; *C. A.* **1981**, *94*, 121322.
(9) Lin, Y., Lang, S. *J. Heterocycl. Chem.* **1977**, *14*, 345.
(10) Breaux, E.J., Zwikelmaier, K.E. *J. Heterocycl. Chem.* **1981**, *18*, 183.
(11) Cheeseman, G.W.H. *J. Chem. Soc.* **1960**, 242.
(12) Commercially available from E. Merck, Darmstadt, West Germany.
(13) Hoy, K.L., Hartung, W.H. *J. Org. Chem.* **1958**, *23*, 967.
(14) Iida, H., Hayashida, K., Yamada, M., Takahashi, K., Yamada, K. *Synth. Commun.* **1973**, 225.
(15) Fischer, H., Wiedemann, O. *Z. Physiol. Chem.* **1926**, *155*, 52.