Synthesis of Pyrroles via Ethyl *N*-(3-Oxo-1-alkenyl)glycinates

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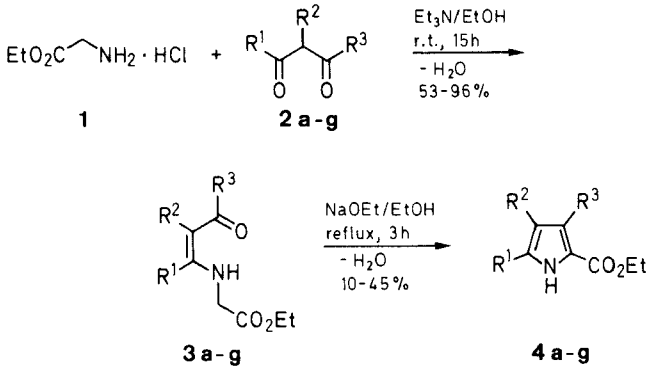
The reaction of ethyl glycinate hydrochloride (**1**) with 1,3-dicarbonyl compounds **2a–g** in presence of triethylamine leads to the formation of ethyl *N*-(3-oxo-1-alkenyl)glycinates **3a–g**. These compounds are easily converted to the pyrroles **4a–g** by base-catalyzed intramolecular Knoevenagel condensation.

The Paal–Knorr method or the Paal procedure,[1,2] which involves the condensation of β-keto esters with α-amino ketones, are well established procedures[2] in pyrrole syntheses, but they often give low yields. Though α,β-unsaturated β-amino ketones are useful starting materials in the synthesis of many heterocyclic compounds,[3–5] pyrrole syntheses rarely make use of them, despite the fact this method offers a great variation in substitution pattern of the pyrrole ring.[6–9] Treibs and Ohorodnik[6] demonstrated, that pyrroles and β-hydroxypyrroles can be prepared by base-catalyzed reaction of glycinates with β-diketones or β-keto esters, respectively. Moreover Tashiro and co-workers[8] showed that pyrroles can be obtained by reaction of ethyl glycinate hydrochloride with 1,3-dicarbonyl compounds in boiling dimethylformamide, but the method fails or gives poor yields for nonaromatic ketones. Recently, Breitmaier and Walizei[9] reported the synthesis of pyrroles starting from glycinates and alkoxyacroleins. This caused us to present here our own results in pyrrole synthesis with ethyl glycinates, which we have obtained in the course of our work on porphyrin synthesis. Especially pyrroles unsubstituted at position-5 are valuable starting materials in porphyrin and bile-pigment syntheses,[10] but the preparation of 3,4-dialkyl substituted systems by known procedures is often difficult. Even the method of Breitmaier et al. is not applicable to these systems, due to the starting materials which allow only the introduction of one alkyl group at position-4 of the pyrrole ring.

We now report a convenient synthesis of 2-pyrrole carboxylates, alternatively alkyl substituted at positions 3 and 4 or 3, 4 and 5 starting from 1,3-dicarbonyl compounds, which is outlined in the scheme.



1 **2a-g** **3a-g** **4a-g**

2–4	R^1	R^2	R^3
a	Me	Me	Me
b	Me	H	Me
c	H	Me	Et
d	H	Me	Pr
e	H	Et	Pr
f	H	$-(CH_2)_3-$	
g	H	$-(CH_2)_4-$	

Table 1. Ethyl *N*-(3-Oxo-1-alkenyl)glycinates **3a–g** Prepared

Product	Yield (%)	mp (°C)[a] (EtOH)	Molecular Formula[b] or Lit. mp (°C)	MS (70 eV)[c] *m/z* (%)	IR (KBr)[d] ν (cm^{-1})	^{1}H-NMR (CD_3OD/TMS) δ, *J* (Hz)
3a	70	79–81	$C_{10}H_{17}NO_3$ (199.24)	199 (M^+, 48), 126 (100)	1730, 1600	1.37 (t, 3H, *J* = 7.10), 1.97 (s, 3H), 2.10 (s, 3H), 2.20 (s, 3H), 4.25 (s, 2H), 4.34 (q, 4H, *J* = 7.10)
3b	85	64–65	$C_9H_{15}NO_3$ (185.22)	185 (M^+, 67), 112 (100)	1741, 1616	1.38 (t, 3H, *J* = 7.11), 2.05 (s, 3H), 2.10 (s, 3H), 4.27 (s, 2H), 4.34 (q, 2H, *J* = 7.11), 5.15 (s, 1H)
3c	85	56–58	$C_{10}H_{17}NO_3$ (199.24)	199 (M^+, 55), 170 (100)	1740, 1650	1.10 (t, 3H, *J* = 7.57), 1.30 (t, 3H, *J* = 7.10), 1.66 (s, 3H), 2.55 (q, 2H, *J* = 7.57), 4.12 (s, 2H), 4.24 (q, 2H, *J* = 7.10), 5.13 (br s), 7.58 (s, 1H)
3d	73	51–52	$C_{11}H_{19}NO_3$ (213.33)	213 (M^+, 65), 170 (100)	1740, 1640	1.01 (t, 3H, *J* = 7.40), 1.37 (t, 3H, *J* = 7.00), 1.70 (tq, 2H, *J* = 6.30, 7.40), 1.76 (s, 3H), 2.60 (t, 2H, *J* = 6.30), 4.11 (s, 1H), 4.30 (q, 2H, *J* = 7.00), 7.60 (s, 1H)
3e	96	86–87	$C_{12}H_{21}NO_3$ (227.29)	227 (M^+, 48), 184 (100)	1737, 1625	1.03 (t, 3H, *J* = 7.50), 1.37 (t, 3H, *J* = 7.10), 1.70 (m, 2H), 2.35 (t, 2H, *J* = 7.50), 2.55 (t, 2H, *J* = 7.35), 4.10 (s, 2H), 4.30 (q, 2H, *J* = 7.10), 7.50 (s, 1H)
3f	85	45–46	$C_{10}H_{15}NO_3$ (197.13)	197 (M^+, 31), 124 (100)	1730, 1640	1.35 (t, 3H, *J* = 7.21), 1.97 (m, 2H), 2.33 (t, 2H, *J* = 7.80), 2.58 (t, 2H, *J* = 7.30), 4.08 (s, 2H), 4.27 (q, 2H, *J* = 7.21), 7.23 (s, 1H)
3g	53	oil	$C_{11}H_{17}NO_3$ (211.31)	211 (M^+, 31), 138 (100)	1741, 1645	1.37 (t, 3H, *J* = 7.20), 1.82 (m, 4H), 2.35 (m, 4H), 4.15 (s, 2H), 4.30 (q, 2H, *J* = 7.20), 7.62 (s, 1H)

[a] Uncorrected, measured with a Büchi 510 apparatus.
[b] Satisfactory microanalyses obtained: C ±0.19, H ±0.08, N ±0.10.
[c] Obtained on a VG-Analytical VG 70: 250 E spectrometer.
[d] Recorded on a Shimadzu IR-435 Infrared spectrophotometer.
[e] Obtained on a Varian EM 90 spectrometer.

Condensation of the diketo compounds **2a–g** with ethyl glycinate hydrochloride **(1)** in ethanol in presence of triethylamine at room temperature gives ethyl *N*-(3-oxo-1-alkenyl)glycinates **3a–g** in 45–96% yield (Table 1). Compounds **3a–g** were converted into the corresponding pyrroles **4a–g** without further purification by treatment with sodium ethoxide in refluxing ethanol.

The prepared pyrroles were characterized by their MS, ^{1}H-NMR and ^{13}C-NMR spectra (Table 2). Interestingly in the ^{13}C-NMR spectra C-3 is the most downfield shifted atom (δ = 127–138) undoubtedly due to the electron-withdrawing ester moiety at position 2.[15] The presented method based on a procedure described by Treibs and Ohorodnik[6] for the synthesis of β-hydroxypyrroles and trialkylsubstituted 2-pyrrolecarboxylates. As mentioned above, our variant allows also the synthesis of 5-unsubstituted pyrroles by use of β-keto aldehydes. The synthesis of 5-alkyl substituted 2-pyrrolecarboxylates by established procedures, like Kleinspehn's variant[12] of the Knorr method, in some cases gives a better yield than the reported method. Nevertheless for the synthesis of 5-unsubstituted 2-pyrrolecarboxylates our method is an interesting alternative to existing procedures. It is characterized by its great flexibility with regard to the substitution pattern of the pyrrole ring system and starting 1,3-dicarbonyl compounds are easily available by standard procedures.[16] Furthermore the method is easily transferable to the synthesis of 2-cyanopyrroles by using glycinonitrile hydrochloride instead of ethyl glycinate hydrochloride.[17]

Ethyl *N*-(3-Oxo-1-alkenyl)glycinates 3a–g; General Procedure:
Ethyl glycinate hydrochloride **(1)** (0.1 mol, 1 equiv) and triethylamine (0.1 mol, 1 equiv) are carefully added to a solution of the required 1,3-dicarbonyl compound **2a–g** (0.1 mol, 1 equiv) in

Table 2. Pyrroles **4a–f** Prepared

Product	Yield (%)	mp (°C)[a] (Et_2O/pentane)	Molecular Formula[b] or Lit. mp (°C)	MS (70 eV)[c] *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[d] δ, *J*(Hz)	^{13}C-NMR ($CDCl_3$)[e,f] δ
4a	27	125–126	$C_{10}H_{15}NO_2$ (181.2)[11]	181 (M^+, 100), 151 (80)	1.35 (t, 3H, J = 7.1), 1.89 (s, 3H), 2.20 (s, 3H), 2.21 (s, 3H), 4.29 (q, 2H, J = 7.1), 9.30 (s, 1H)	8.8 (C-4α), 10.6 (C-3α), 11.4 (C-5α), 14.6 ($OCH_2\underline{C}H_3$), 59.6 (OCH_2), 116.6 (C-2), 117.1 (C-4), 127.4 (C-3), 129.4 (C-5), 161.8 (CO)
4b	28	123–124	124–125[12]	167 (M^+, 100), 138 (31)	1.35 (t, 3H, J = 7.2), 2.20 (s, 3H), 2.22 (s, 3H), 4.30 (q, 2H, J = 7.2), 5.80 (s, 1H), 9.31 (br, 1H)	10.8 (C-5α), 13.1 (C-3α), 14.6 ($OCH_2\underline{C}H_3$), 59.7 (OCH_2), 111.3 (C-2), 117.8 (C-4), 128.9 (C-5), 132.3 (C-3), 161.7 (CO)
4c	45	74–75	75[13]	181 (M^+, 100), 152 (20)	1.20 (t, 3H, J = 7.5), 1.35 (t, 3H, J = 7.2), 1.95 (s, 3H), 2.70 (q, 2H, J = 7.5), 4.30 (q, 2H, J = 7.2), 6.60 (d, 1H, J = 3.0), 8.80 (br, 1H)	9.8 (C-3β), 14.5 ($OCH_2\underline{C}H_3$), 15.1 (C-4α), 18.2 (C-3α), 59.8 (OCH_2), 118.6 (C-2), 119.8 (C-4), 120.2 (C-5), 133.1 (C-3), 161.6 (CO)
4d	16	67–70	$C_{11}H_{17}NO_2$ (195.3)	195 (M^+, 63), 165 (100)	0.95 (t, 3H, J = 7.3), 1.35 (t, 3H, J = 7.1), 1.50 (tq, 2H, J = 7.7, J = 7.3), 2.03 (s, 3H), 2.71 (t, 2H, J = 7.7), 4.30 (q, 2H, J = 7.2), 6.67 (d, 1H, J = 2.9), 8.79 (br, 1H)	9.9 (C-3γ), 14.5 ($OCH_2\underline{C}H_3$), 14.9 (C-4α), 23.9 (C-3β), 26.9 (C-3α), 59.7 (OCH_2), 119.1 (C-2), 120.2 (C-5), 126.9 (C-4), 131.5 (C-3), 161.6 (CO)
4e	32	38–40	$C_{12}H_{19}NO_2$ (209.3)	209 (M^+, 53), 180 (100)	0.96 (t, 3H, J = 7.3), 1.18 (t, 3H, J = 7.6), 1.35 (t, 3H, J = 7.2), 1.53 (tq, 2H, J = 6.0, J = 7.3), 2.44 (q, 2H, J = 7.6), 2.71 (t, 2H, J = 6.0), 4.31 (q, 2H, J = 7.2), 6.67 (d, 1H, J = 2.9), 8.90 (br, 1H)	14.3 (C-4β), 14.4 (C-3γ), 14.5 ($OCH_2\underline{C}H_3$), 24.3 (C-3β), 26.9 (C-3α), 59.7 (OCH_2), 119.1 (C-5), 127.2 (C-4), 130.8 (C-3), 161.6 (CO)
4f	10	98–99	$C_{10}H_{13}NO_2$ (179.2)	179 (M^+, 100), 150 (35)	1.34 (t, 3H, J = 7.2), 2.30–2.40 (m, 2H), 2.64 (t, 2H, J = 7.1), 2.83 (t, 2H, J = 7.1), 4.28 (q, 2H, J = 7.1), 6.60 (d, 1H, J = 2.7), 8.83 (br, 1H)	14.6 ($OCH_2\underline{C}H_3$), 24.9 (C-4α, Cα), 26.3 (C-3β), 31.1 (C-3α), 59.8 (OCH_2), 114.7 (C-2), 115.1 (C-5), 132.7 (C-4), 138.5 (C-3), 161.7 (CO)
4g	42	75–76	$C_{11}H_{15}NO_2$ (193.2)	193 (M^+, 81), 164 (100)	1.34 (t, 3H, J = 7.1), 1.70–1.75 (m, 4H), 2.50–2.60 (m, 2H), 2.80–2.90 (m, 2H), 4.30 (q, 2H, J = 7.1), 6.65 (d, 1H, J = 2.9), 8.90 (br, 1H)	14.6 ($OCH_2\underline{C}H_3$), 21.9 (C-4β), 23.1 (C-4α), 23.3 (C-3β), 23.4 (C-3α), 59.8 (OCH_2), 117.7 (C-2), 118.6 (C-5), 122.1 (C-4), 128.1 (C-3), 161.7 (CO)

[a] Uncorrected, measured with a Büchi 510 apparatus.
[b] Satisfactory microanalysis obtained: C ±0.30, H ±0.07, N ± 0.05.
[c] Obtained on a VG-Analytical VG 70: 250 E spectrometer.
[d] Obtained on a Varian XL 200 spectrometer (200 MHz).
[e] 50.0 MHz; 25°C.
[f] Assignment was made by 2D-INADEQUATE and long range heteronuclear correlation spectroscopy[14] **(4a, 4c, 4f)**.

EtOH (200 mL). The mixture is stirred at r.t. for 15 h. The solvent is evaporated and the residue is poured into water (100 mL), CH_2Cl_2 (50 mL) is added, the organic layer is separated and the water phase is extracted with CH_2Cl_2 (3 × 50 mL). The organic layers are combined, washed with water (50 mL), and dried (Na_2SO_4). The solvent is evaporated under reduced pressure and the remaining crude product is directly converted to the pyrroles or is recrystallized from EtOH.

Pyrroles 4a–g; General Procedure:
Ethyl *N*-(3-oxo-1-alkenyl)glycinate **3a–g** (0.1 mol, 1 equiv) is added under vigorous stirring and heating to 50 °C to a solution of NaOEt (0.1 mol, 1 equiv) in absolute EtOH (200 mL). The mixture is refluxed for 3 h, poured into water (500 mL) and extracted with Et_2O (3 × 100 mL). The combined organic layers are successively washed with water (50 mL), 0.1 M HCl (50 mL) and water (50 mL), and dried (Na_2SO_4). The solvent is evaporated under reduced pressure yielding an oily residue. This crude product is chromatographed on a silica gel column (60 × 2 cm, 70–230 mesh) using CH_2Cl_2 as eluent. After evaporation of the solvent the pyrroles were obtained as colorless crystals. Recrystallization from Et_2O/pentane affords analytically pure products.

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