Preparation of Ethyl 3,5-Disubstituted Pyrrole-2-carboxylates from 1,3-Diketones and Ethyl Glycinate Hydrochloride

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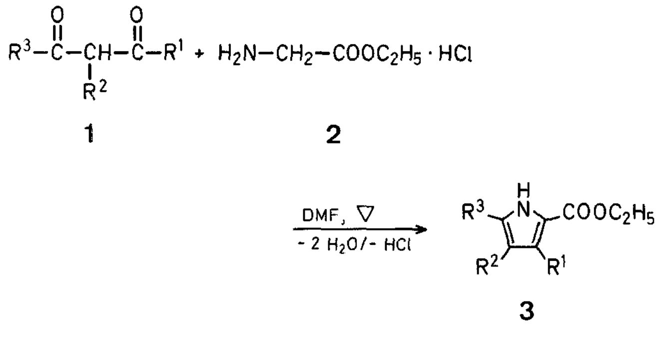
The synthesis of pyrroles from 1,4-diketones and primary amines, i.e., the Paal-Knorr method[1], has been extensively investigated. On the other hand, pyrrole syntheses using 1,3-diketones and C—N components as starting materials have been a subject of comparatively little interest. The reactions of acetylacetone with diethyl oximinomalonate[2] or 3-oximinobutanone[3] in the presence of zinc/acetic acid afford 4-substituted 3,5-dimethylpyrrole-2-carboxylic esters or tetramethylpyrrole, respectively, and the reaction of aroylacetones with ethyl aminomalonate gives enamines which, on treatment with sodium ethoxide or polyphosphoric ethyl ester, are converted into two isomeric pyrrolecarboxylates[4].

We report here a new convenient synthesis of ethyl pyrrole-2-carboxylates (**3**) by the reaction of 1,3-diketones (**1**) with ethyl glycinate hydrochloride (**2**) in boiling dimethylformamide.



The best yield (74%) is obtained for ethyl 3,5-diphenylpyrrole-2-carboxylate (**3a**) whereas pyrrole **3b**, obtained from benzoylacetone in 41% yield, is accompanied by trace amounts of the isomeric product **3c**. The reaction with 2,4-pentanedione affords only an 18% yield of **3d** and the reaction of 2-acetylcyclopentanone leads only to the formation of resinous material

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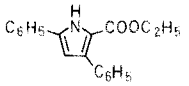
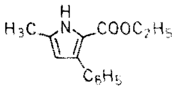
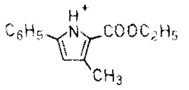
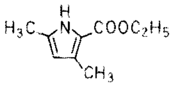
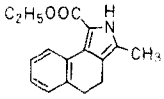
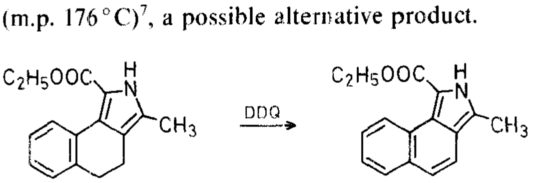
Table. Ethyl Pyrrole-2-carboxylates (**3**)

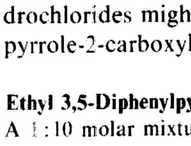
Product		Reaction time [h]	Yield [%]	m.p. [°C]	Molecular formula[a] or m.p. [°C] reported
3a		48	74	135–137°	140–144°[5]
3b		21	41	134–135°	133–134°[6]
3c		21	trace	114–115°	$C_{14}H_{15}NO_2$ (299.3)
3d		6	18	122–124°	124–124.5°[2]
3e		24	43	144.5–147°	$C_{16}H_{17}NO_2$ (255.3)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.23; H, ±0.14; N, ±0.34.

but not to the expected pyrrole. On the other hand, the expected ethyl 3-methyl-4,5-dihydro-2*H*-benzo[*e*]isoindole-1-carboxylate (**3e**) is obtained in 43% yield from 2-acetyl-1-tetralone; it may be oxidized with DDQ to give ethyl 3-methyl-2*H*-benzo[*e*]isoindole-1-carboxylate (**3f**; m.p. 190–191 °C) which is different from the known benzo[*g*]indole derivative **4** (m.p. 176 °C)[7], a possible alternative product.



3e **3f**



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Since many 1,3-diketones are easily accessible by various methods[8] the reaction of 1,3-diketones with glycine ester hydrochlorides might provide a convenient preparative route to pyrrole-2-carboxylic esters.

Ethyl 3,5-Diphenylpyrrole-2-carboxylate (1a):

A 1 : 10 molar mixture of dibenzoylmethane (**1a**; 500 mg) and ethyl glycinate hydrochloride (**2**; 3.11 g) in dimethylformamide (50 ml) is heated at reflux temperature for 24 h. Then, additional **2** (3.11 g) is added and heating is continued for 24 h. The mixture is poured into water (200 ml) and the resultant mixture allowed to stand overnight. The precipitated product **3a** is isolated by suction and recrystallized from hexane to give colorless prisms; yield: 478 mg.

Reaction of 1,3-Dioxo-1-phenylbutane (Benzoylacetone) with Ethyl Glycinate Hydrochloride (2):

A 1 : 10 molar mixture of benzoylacetone (**2b**; 500 mg) and ethyl glycinate hydrochloride (**2**; 4.30 g) in dimethylformamide (50 ml) is heated at reflux temperature for 21 h. The solvent is then removed in vacuo and the residue extracted with hot benzene (3 × 50 ml). The extract is evaporated in vacuo and the residue column-chromatographed on silica gel (Wako gel, C-300) using benzene as an eluent to afford **3c** and **3b**. Compound **3c** is recrystallized from hexane as colorless prisms; yield: 14 mg, and **3b** from hexane as colorless plates; yield: 285 mg.

Reaction of 2,4-Pentanedione (Acetylacetone) with Ethyl Glycinate Hydrochloride (2):

A 1 : 10 molar mixture of 2,4-pentanedione (**1d**; 300 mg) and ethyl glycinate hydrochloride (**2**; 4.18 g) in dimethylformamide (50 ml) is heated at reflux temperature for 6 h and then poured into water (200 ml). The resultant mixture is extracted with benzene (100 ml), the extract washed with water (6 × 250 ml), and dried with sodium sulfate. The solvent is removed in vacuo and the residual product recrystallized from methanol to afford **3d** as colorless plates; yield: 88 mg.

Ethyl 3-Methyl-4,5-dihydro-2*H*-benzo[*e*]isoindole-1-carboxylate (3e):

A 1 : 10 molar mixture of 2-acetyl-1-tetralone (**1e**; 10.0 g) and ethyl glycinate hydrochloride (**2**; 76.0 g) in dimethylformamide (250 ml) is heated at reflux temperature for 24 h, and then poured into water (1000 ml). The resultant mixture is extracted with benzene (500 ml), the extract washed with water (6 × 1000 ml), and dried with sodium sulfate. The solvent is removed in vacuo and the residue column-chromatographed on silica gel (Wako gel, C-300) using benzene as the eluent. Product **3e** is recrystallized from hexane to give pale yellow needles; yield: 6.04 g.

$C_{16}H_{17}NO_2$ (255.3)

M.S.: $m/e = 255$ (M^+).

I.R. (KBr): $\nu = 3340, 1662, 1650$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 1.38$ (t, 3H, $J = 7$ Hz, CH_3); 2.23 (s, 3H, CH_3); 2.55, 2.81 (each d.d, 4H, CH_2CH_2); 4.34 (q, 2H, $J = 7$ Hz, CH_2); 7.1–7.3 (m, 3H); 8.3–8.5 (m, 1H); 8.7 ppm (br s, 1H, NH).

Ethyl 3-Methyl-2*H*-benzo[*e*]isoindole-1-carboxylate (3f):

A 1 : 1.5 molar mixture of the dihydro derivative **3e** (245 mg) and DDQ (400 mg) in dry benzene (10 ml) is heated at reflux temperature for 2 h under a nitrogen stream. The precipitated DDQ-H_2 is filtered off and the filtrate is subjected to column chromatography on silica gel (Wako gel, C-300) using benzene as an eluent to give unreacted **3e**

(5 mg) and **3f**. Compound **3f** is recrystallized from ethanol to give violet needles: yield: 30 mg (12%); m.p. 190–191 °C.

$C_{16}H_{15}NO_2$	calc.	C 75.87	H 5.97	N 5.53
(253.3)	found	75.83	5.99	5.64

M.S.: $m/e = 253$ (M^+).

I.R. (KBr): $\nu = 3310, 1660$ cm^{-1}.

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 1.46$ (t, 3H, $J = 7$ Hz, CH_3); 2.67 (s, 3H, CH_3); 4.45 (q, 2H, $J = 7$ Hz, CH_2); 7.4–8.1 (m, 6H); 9.4 ppm (br s, 1H, NH).

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