Synthesis of Some 2,5-Disubstituted 5-Aryl-4-oxo-4,5-dihydropyrrole Derivatives from 2,5-Disubstituted 3-Ethoxycarbonyl-5-hydroxy-4-oxo-4,5-dihydropyrroles

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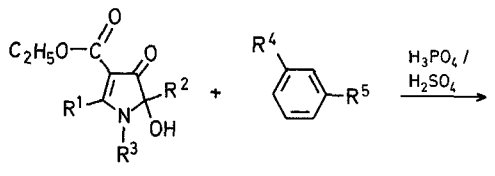
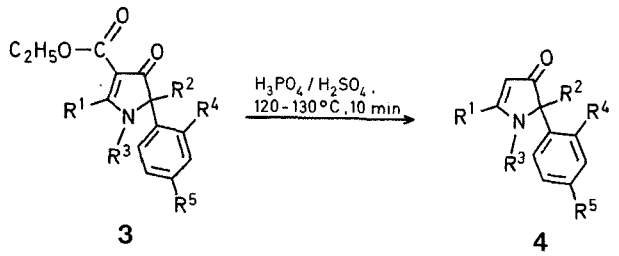
Although a variety of methods for the synthesis of 4-oxo-4,5-dihydropyrroles is given in the literature[1-6], the direct introduction of an aryl group into the 4-oxo-4,5-dihydropyrrole ring has not been reported. We now report that the 3-ethoxycarbonyl-5-hydroxy-4-oxo-4,5-dihydropyrroles **1**[7,8] condense with reactive aromatic compounds **2** such as resorcinol, phenol, or anisole, to afford the novel corresponding 5-aryl derivatives **3**. The use of acidic medium (15% concentrated sulfuric acid in 85% phosphoric acid) as the solvent and catalyst delivers **3** in a very clean and complete reaction.



1 **2**



3 **4**

In the case of phenol or anisole, the isomer distribution *ortho* to *para* appears to depend upon the nature of the R^3 substituent. The reaction yields largely the *ortho*-bonded products when $R^3 = H$, whereas, it leads to the *para*-derivatives with R^3 = alkyl (Table). The structural assignments of several pairs of isomeric compounds ($R^3 = H$) are based upon their ^{1}H-N.M.R. spectra. The *para*-disubstituted compounds **3d, 3f, 3h, 3j** are easy to recognize because of their symmetrical A_2B_2 pattern. In the case of the *N*-substituted derivatives **3l-n**, the R^5 substitution could not be unequivocally assigned on the basis of their spectral data. The *para* structure is supported by the *N*- or *O*-methylation of **3h** or **3m**, respectively, to give a product which is found spectroscopically identical to the compound **3n** prepared from **1** ($R^1 = CH_3$, $R^2 = CH_2C_6H_5$, $R^3 = CH_3$) and anisole.

When the compounds **3** are heated at 120-130 °C, in the same acidic medium (H_3PO_4/H_2SO_4), they rapidly decarboxylate giving rise to the corresponding derivatives **4.**

3-Ethoxycarbonyl-5-hydroxy-5-methyl-4-oxo-2-phenyl-4,5-dihydropyrrole (1; $R^1 = C_6H_5$, $R^2 = CH_3$, $R^3 = H$):

Prepared from 5-acetoxy-3-ethoxycarbonyl-5-methyl-4-oxo-2-phenyl-4,5-dihydrofuran and 28% aqueous ammonium hydroxide according to Ref.[7]; yield: 65%; m.p. 196 °C (CH_3CN).

$C_{14}H_{15}NO_4$	calc.	C 64.36	H 5.79	N 5.36
(261.3)	found	64.57	6.01	5.24

^{1}H-N.M.R. (DMSO-d_6): $\delta = 1.02$ (t, 3H); 1.33 (s, 3H); 4.0 (q, 2H); 4.80 (s, 1H, exch. with D_2O); 7.53 (s, 5H); 9.7 ppm (s, 1H, exch.).

I.R. (KBr): $\nu = 1700$, 1635 cm^{-1}.

2,5-Disubstituted 5-Aryl-3-ethoxycarbonyl-4-oxo-4,5-dihydropyrroles (3); General Procedure:

A mixture of **1** (10 mmol) and **2** (20 mmol) in 85% phosphoric acid (10 g) and concentrated sulfuric acid (1.5 g) is stirred at room temperature for 24 h. The reaction mixture is poured into crushed ice (100 g) with stirring.

Work up procedure for **3a-f, k-m** (R^4 or R^5 = OH): The solid that separates is filtered and washed with 5% aqueous sodium hydrogen carbonate solution and then water. Trituration of the crude product with 1:5 ethanol/ether (50 ml) gives, after filtration and drying, an essentially pure material which is recrystallized **(3a-c, e, k-m).** The isomer mixture **3c/3d** or **3e/3f** (0.5 g) is chromatographed through a column (3 cm × 40 cm) of silica gel (80 g) using ethyl acetate as eluent. Compound **3c** (0.34 g, 57%) or **3e** (0.38 g, 64%) is first eluted in the fraction 150 to 180 ml or 160 to 250 ml then the *para* isomer **3d** (0.10 g, 16%) or **3f** (0.08 g, 13%) is obtained from the 350 to 500 ml or 400 to 550 ml fraction.

Work up procedure for **3g-j, n** (R^4 or $R^5 = OCH_3$): The reaction mixture is extracted with chloroform (3 × 50 ml). The extracts are dried with sodium sulfate. The chloroform is evaporated and the residue triturated with ether (50 ml) to give a crystalline solid. Two fractional recrystallizations afford **3h** (acetonitrile; yield: 10%) or **3j** (methanol; yield: 5%). Pure *ortho* compound **3g** or **3i** is obtained from the **3g/3h** or **3i/3j** mixture (0.5 g) by chromatography through a column (3 cm × 40 cm) of silica gel (80 g) using ether as eluent: **3g** (0.12 g, 19%) or **3i** (0.28 g, 44%) in the fraction 800 to 1000 ml or 1000 to 1300 ml and then an isomeric mixture of **3g + 3h** or **ei + 3j.**

Methylation of 3h or 3m:

To a stirred solution of **3h** or **3m** (0.73 g, 2 mmol) in absolute ethanol (20 ml) containing sodium ethoxide (from 0.012 g of sodium) is added dropwise, dimethyl sulfate (0.30 g, 2.4 mmol). The mixture is then heated under reflux for 1 h, poured into water (50 ml), and extracted with chloroform. The extracts are dried and evaporated under reduced pressure. The residue is triturated with ether to give **3n**; yield: 0.46 g (61% from **3h**) or 0.53 g (70% from **3m**), which may be further recrystallized from acetonitrile.

2,5-Disubstituted 5-Aryl-4-oxo-4,5-dihydropyrroles (4); General Procedure:

A solution of **3** (5 mmol) in 85% phosphorus acid (5 g) and concentrated sulfuric acid (0.75 g) is heated with stirring in an oil bath at 120-130 °C for 10 min. The mixture is poured into crushed ice (100 g). The resulting precipitate is filtered, washed with 5% aqueous sodium hydrogen carbonate solution and then water. Crystallization from acetonitrile affords the pure compounds **4.**

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Table. 4-Oxo-4,5-dihydropyrroles **3** and **4**

Compound	R^1	R^2	R^3	R^4	R^5	Yield [%]	Molecular Formula[a]	m.p. [°C] (Solvent)	^{1}H-N.M.R. (DMSO-d_6/TMS) δ [ppm]
3a	CH_3	$CH_2C_6H_5$	H	OH	OH	82	$C_{21}H_{21}NO_5$ (367.4)	202° (CH_3CN)	1.14 (t, 3H, J=7 Hz); 2.29 (s, 3H); 3.35 and 3.41 (2 d, 2H, AB system, J_{AB}=13 Hz); 4.03 (q, 2H, J=7 Hz); 6.25 (q, 1H, J=2 Hz, J=8.5 Hz); 6.41 (d, 1H, J=2 Hz); 7.10 (d, 1H, J=8.5 Hz); 7.18 (s, 5H); 9.36 (br, 1H, exchangeable with D_2O); 9.96 (br, 1H exch.); 10.63 (br, 1H exch.)
3b	C_6H_5	CH_3	H	OH	OH	84	$C_{20}H_{19}NO_5$ (353.3)	260° (CH_3CN)	1.03 (t, 3H, J=7 Hz); 1.55 (s, 3H); 3.99 (q, 2H, J=7 Hz); 6.21–6.44 (m, 2H); 7.11–7.33 (m, 1H); 7.63 (s, 5H); 9.35 (br, 1H exch.); 9.76 (br, 1H exch.); 9.84 (br, 1H exch.)
3c	CH_3	$CH_2C_6H_5$	H	OH	H	84[b]	$C_{21}H_{21}NO_4$ (351.4)	224° (CH_3OH)	1.16 (t, 3H, J=7 Hz); 2.33 (s, 3H); 3.39 (s, 2H); 4.06 (q, 2H, J=7 Hz); 6.64–7.08 (m, 2H); 7.08–7.48 (m, 7H, with a singlet at 7.24); 10.11 (br, 1H exch.); 10.88 (br, 1H exch.)
3d	CH_3	$CH_2C_6H_5$	H	H	OH			260°[c]	1.13 (t, 3H, J=7 Hz); 2.34 (s, 3H); 3.10 and 3.31 (2 d, 2H, AB system, J_{AB}=13 Hz); 4.01 (q, 2H, J=7 Hz); 6.81 and 7.35 (2 d, 4H, A_2B_2 system, J_{AB}=9 Hz); 7.21 (s, 5H); 9.48 (br, 1H exch.); 10.05 (br, 1H exch.)
3e	C_6H_5	CH_3	H	OH	H	85[b]	$C_{20}H_{19}NO_4$ (337.4)	230° (CH_3OH)	1.04 (t, 3H, J=7 Hz); 1.65 (s, 3H); 4.00 (q, 2H, J=7 Hz); 6.76–7.04 (m, 2H); 7.24–7.54 (m, 2H); 7.61 (s, 5H); 9.83 (br, 1H exch.); 10.01 (br, 1H exch.)
3f	C_6H_5	CH_3	H	H	OH			224°	1.03 (t, 3H, J=7 Hz); 1.61 (s, 3H); 3.98 (q, 2H, J=7 Hz); 6.86 and 7.26 (2 d, 4H, A_2B_2 system, J_{AB}=9 Hz); 7.48–7.90 (m, 5H); 9.48 (br, 1H exch.); 10.14 (br, 1H exch.)
3g	CH_3	$CH_2C_6H_5$	H	OCH_3	H	80[b]	$C_{22}H_{23}NO_4$ (365.4)	192°[c]	1.33 (t, 3H, J=7 Hz); 2.34 (s, 3H); 3.30 and 3.41 (2 d, 2H, AB system, J_{AB}=13 Hz); 3.91 (s, 3H); 4.29 (q, 2H, J=7 Hz); 6.93–7.56 (m, 8H, with a singlet at 7.26); 7.71 (br, 1H exch.); 7.93–8.15 (m, 1H)[d]
3h	CH_3	$CH_2C_6H_5$	H	H	OCH_3			195° (CH_3CN)	1.21 (t, 3H, J=7 Hz); 2.49 (s, 3H); 3.36 (s, 2H); 3.76 (s, 3H); 4.13 (q, 2H, J=7 Hz); 6.84 and 7.50 (2 d, 4H, A_2B_2 system, J_{AB}=9 Hz); 7.16 (s, 5H); 8.31 (br, 1H exch.)[d]
3i	C_6H_5	CH_3	H	OCH_3	H	80[b]	$C_{21}H_{21}NO_4$ (351.4)	184°[c]	1.24 (t, 3H, J=7 Hz); 1.79 (s, 3H); 3.98 (s, 3H); 4.26 (q, 2H, J=7 Hz); 6.95–7.23 (m, 2H); 7.31–8.01 (m, 8H with 1H exch.)[d]
3j	C_6H_5	CH_3	H	H	OCH_3			205° (CH_3CN)	1.13 (t, 3H, J=7 Hz); 1.68 (s, 3H); 3.79 (s, 3H); 4.08 (q, 2H, J=7 Hz); 6.86 and 7.36 (2 d, 4H, A_2B_2 system, J_{AB}=9 Hz); 7.19–7.86 (m, 6H with 1H exch.)[d]

Table. (Continued)

Compound	R^1	R^2	R^3	R^4	R^5	Yield [%]	Molecular Formula[a]	m.p. [°C] (Solvent)	^{1}H-N.M.R. (DMSO-d_6/TMS) δ [ppm]
3k	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	OH	OH	90	$C_{28}H_{27}NO_5 \cdot C_2H_5OH$ (503.6)	196–198° (C_2H_5OH)	1.11 (t, 3H, J=7 Hz); 2.03 (s, 3H); 2.96 and 3.13 (2 lines, 1H, part of an AB system, J_{AB}=13 Hz); 3.65–4.18 (m, 3H); 4.78 and 4.86 (2d, 2H, AB system, J_{AB}=17 Hz); 6.11 (d, 1H, J=2 Hz); 6.25 (q, 1H, J=2 Hz, J=8.5 Hz); 7.16 (s, 10H); 7.38 (d, 1H, J=8.5 Hz); 9.28 (br, 1H exch.); 9.56 (br, 1H exch.)
3l	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	H	OH	60	$C_{28}H_{27}NO_4$ (367.4)	223° (CH_3CN)	1.11 (t, 3H, J=7 Hz); 2.09 (s, 3H); 3.03 and 3.19 (2 lines 1H, part of an AB system, J_{AB}=13 Hz); 3.75–4.18 (m, 3H); 4.78 and 4.95 (2 d, 2H, AB system, J_{AB}=17 Hz); 6.50–7.33 (m, 13H); 7.49–7.73 (m, 1H); 9.78 (br, 1H exch.)
3m	CH_3	$CH_2C_6H_5$	CH_3	H	OH	55	$C_{22}H_{23}NO_4$ (365.4)	201° (CH_3CN)	1.10 (t, 3H, J=7 Hz); 2.19 (s, 3H); 2.96 (s, 3H); 3.38 and 3.50 (2 d, 2H, AB system, J_{AB}=13 Hz); 3.99 (q, 2H, J=7 Hz); 6.71–7.44 (m, 8H with a singlet at 7.20); 7.44–7.71 (m, 1H); 9.06–10.16 (br, 1H exch.)
3n	CH_3	$CH_2C_6H_5$	CH_3	H	OCH_3	74	$C_{23}H_{25}NO_4 \cdot H_2O$ (379.4)	160° (CH_3CN)	1.29 (t, 3H, J=7 Hz); 2.26 (s, 3H); 2.93 (s, 3H); 3.41 and 3.64 (2 d, 2H, AB system, J_{AB}=13 Hz); 3.66 (s, 3H); 4.01–4.45 (m, 2H); 6.85–7.56 (m, 8H with a singlet at 7.24); 7.56–7.75 (m, 1H)[d]
4a	CH_3	$CH_2C_6H_5$	H	OH	OH	60	$C_{18}H_{17}NO_3 \cdot C_2H_5OH$ (341.4)	255° (C_2H_5OH)	2.03 (s, 3H); 3.20 and 3.33 (2 d, 2H, AB system, J_{AB}=13 Hz); 4.63 (s, 1H); 6.18 (q, 1H, J=2 Hz and 9 Hz); 6.31 (q, 1H, J=2 Hz); 6.99 (d, 1H, J=9 Hz); 7.18 (s, 5H); 9.24 (br., 2H, exch.); 11.95 (br, 1H, exch.)
4c	CH_3	$CH_2C_6H_5$	H	OH	H	60	$C_{18}H_{17}NO_2$ (279.3)	255° (CH_3CN)	2.05 (s, 3H); 3.21 and 3.41 (2 d, 2H, AB system, J_{AB}=13 Hz); 4.68 (s, 1H); 6.61–7.03 (m, 2H); 7.03–7.29 (m, 7H with a singlet at 7.18); 9.38 (br, 1H exch.); 12.13 (br, 1H exch.)
4e	C_6H_5	CH_3	H	OH	H	60	$C_{17}H_{15}NO_2$ (265.3)	192° (CH_3CN)	1.71 (s, 3H); 5.65 (s, 1H); 6.70–6.98 (m, 2H); 7.05–7.79 (m, 5H); 7.94–8.18 (m, 2H); 9.33 (br, 1H exch.); 11.28 (br, 1H exch.)
4k	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	OH	OH	60	$C_{25}H_{23}NO_3 \cdot H_2O$ (403.5)	210° (CH_3CN)	1.65 (s, 3H); 2.99 and 3.75 (2 d, 2H, AB system, J_{AB}=13 Hz); 4.48 (s, 1H); 4.71 (s, 2H); 6.16–6.29 (m, 2H); 6.49–7.36 (m, 11H); 9.19 (br, 1H exch.); 9.36 (br, 1H exch.)
4l	CH_3	$CH_2C_6H_5$	$CH_2C_6H_5$	H	OH	50	$C_{25}H_{23}NO_2 \cdot H_2O$ (387.5)	204° (C_2H_5OH)	1.70 (s, 3H); 3.09 and 3.85 (2 d, 2H, AB system, J_{AB}=13 Hz); 4.55 (s, 1H); 4.76 (s, 2H); 6.60–7.36 (m, 13H); 7.44–7.65 (m, 1H); 9.63 (br, 1H exch.)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.32; H, ±0.41; N, ±0.38.

[b] *Ortho/para* mixture: **3c/3d**: 78:22, **3e/3f**: 82:18 (estimated by column chromatography); **3g/3h**: 62:38, **3i/3j**: 78:22 (determined by ^{1}H-N.M.R.).

[c] Isolated by column chromatography.

[d] In $CDCl_3$. I.R. (KBr): $\nu_{C=O} \simeq 1620$–1670 cm^{-1} (β-amino-enone).

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