

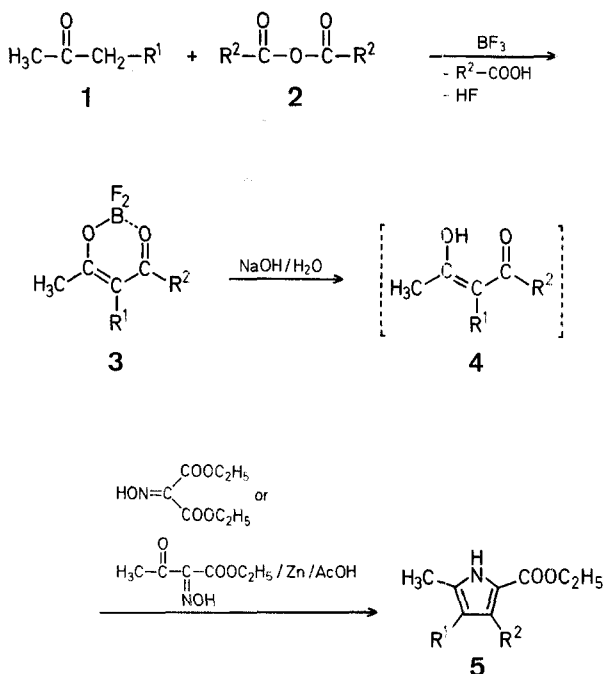
## A Convenient Synthesis of Pyrrole Precursors for Octaalkylporphyrins

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3,4-Diethyl-2-ethoxycarbonyl-5-methylpyrrole (**5d**,  $R^1 = R^2 = C_2H_5$ ) is an important precursor for the synthesis of octaethylporphyrin<sup>1</sup> and other related compounds that are widely used in porphyrin chemistry. The currently favored route to pyrrole **5d** from ethyl 3-oxopentanoate, a not readily available material, is rather long and expensive<sup>2,3</sup>. We wish to report here a simple method by which pyrrole **5d** and other long-chain 3,4-dialkylpyrroles (**5**) can be obtained in high yield.

The boron trifluoride-catalyzed reaction<sup>4,5</sup> of 2-pentanone (**1**,  $R^1 = C_2H_5$ ) with propanoic anhydride (**2**,  $R^2 = C_2H_5$ ) led directly to condensation at the more substituted  $\alpha$ -C atom. The crystalline boron difluoride complex **3d** ( $R^1 = R^2 = C_2H_5$ ) was isolated and then hydrolyzed with methanolic sodium hydroxide to afford the 1,3-diketone **4d**. For the purpose of pyrrole synthesis, isolation of the diketone **4d** was not necessary; the alkaline hydrolysate was simply mixed with excess acetic acid and used directly in the condensation with diethyl hydroxyiminomalonate<sup>6</sup>. It is interesting that the Knorr reaction gave exclusively the 3,4-diethyl-5-methylpyrrole **5d**; no trace of the possible isomeric 4,5-diethyl-3-methylpyrrole was found, presumably because the first step of such condensation was the formation of a Schiff base at the less-hindered carbonyl of the  $\beta$ -diketone **4d**.



This route of pyrrole synthesis can be a general method leading to various 3,4-substituted pyrroles (**5**). The special merit of this method is that it is economic, operationally simple, and suitable for large scale preparations. When combined with a modified octaethylporphyrin synthesis<sup>1</sup> (see experimental), the expensive porphyrin can be obtained readily with a minimum cost.

### 3-Ethyl-2,4-hexanedione-BF<sub>2</sub> Complex (**3d**):

Boron trifluoride gas is slowly bubbled through a mixture of 2-pentanone (43 g, 0.5 mol) and propanoic anhydride (130 g, 1.0 mol) in such a manner that the temperature of the mixture is kept below 50°. After the absorption of boron trifluoride has ceased the mixture is poured into ice/water (500 ml). The solid product is collected by filtration and recrystallized from methanol; yield: 85 g (89 %); m.p. 75–77°.

$C_8H_{13}BF_2O_2$  calc. C 50.57 H 6.90  
(190.0) found 50.43 6.95

M.S. (70 eV):  $m/e = 190$  ( $M^+$ ).

<sup>1</sup>H-N.M.R. ( $CDCl_3$ ):  $\delta = 1.08$  (t, 3H,  $J = 8$  Hz); 1.22 (t, 3H,  $J = 8$  Hz); 2.32 (s, 3H); 2.33 (q, 2H,  $J = 8$  Hz); 2.60 ppm (q, 2H,  $J = 8$  Hz).

<sup>13</sup>C-N.M.R. ( $CDCl_3$ ):  $\delta = 9.39$ ; 14.20; 19.40; 22.15; 28.12; 190.48; 194.04 ppm.

### 3-Ethyl-2,4-hexanedione (**4d**):

3-Ethyl-2,4-hexanedione-BF<sub>2</sub> complex (**3d**; 11 g) is dissolved in methanol (50 ml). This solution is brought to pH ~9 by adding 50 % aqueous sodium hydroxide. The mixture is refluxed on a steam bath for 15 min, methanol is removed in a rotary evaporator, and the residue is taken up in ether (50 ml). The solution is dried with sodium sulfate, the ether evaporated, and the residue distilled; yield: 6.5 g (80 %); b.p. 191–193° (Ref. <sup>6</sup>, b.p. 192–193°).

I.R. (neat):  $\nu_{max} = 1735, 1705, 1600$   $cm^{-1}$ .

<sup>1</sup>H-N.M.R. ( $CDCl_3$ ):  $\delta = 0.87$  (t, 3H,  $J = 7$  Hz); 1.02 (t, 3H,  $J = 7$  Hz); 1.80 (t, 2H,  $J = 7$  Hz); 2.08 (s, 3H); 2.44 (q, 2H,  $J = 7$  Hz); 3.52 (t, 1H,  $J = 7$  Hz); 16.3 ppm (s, broad, ~15 % of 1H).

<sup>13</sup>C-N.M.R. ( $CDCl_3$ ):  $\delta = 7.56$ ; 12.08; 21.84; 28.82; 35.76; 69.39; 204.22; 206.83 ppm.

The lines of the enol form were not clearly observed.

### 3,4-Diethyl-2-ethoxycarbonyl-5-methylpyrrole (**5d**), directly from **3d**:

3-Ethyl-2,4-hexanedione-BF<sub>2</sub> complex (**3d**; 36 g) is dissolved in methanol (100 ml) and the solution brought to pH ~9 by adding 50 % aqueous sodium hydroxide. The mixture is refluxed for 30 min and methanol is removed. The residue is mixed with acetic acid (200 ml) and placed in a 3-necked round bottom flask, equipped with a mechanical stirrer. Zinc dust (50 g) and diethyl hydroxyiminomalonate<sup>7</sup> (70 g) are added in portions so as to maintain the temperature at 90–95°. The mixture is heated under reflux for 1 h and then decanted into water. The solid product is collected by filtration and then dissolved in dichloromethane which causes the water present to separate. The crude pyrrole is obtained by evaporation of the organic phase; it is recrystallized from methanol to give colorless needles; yield: 23.5 g (62 %); m.p. 74–76° (Ref. <sup>3</sup>, m.p. 74–75°).

<sup>1</sup>H-N.M.R. ( $CDCl_3$ ):  $\delta = 1.05$  (t, 3H,  $J = 7.5$  Hz); 1.12 (t, 3H,  $J = 7.5$  Hz); 1.32 (t, 3H,  $J = 7.5$  Hz); 2.17 (s, 3H); 2.33 (q, 2H,  $J = 7.5$  Hz); 2.67 (q, 2H,  $J = 7.5$  Hz); 4.21 (q, 2H,  $J = 7.5$  Hz); 8.52 ppm (broad, 1H).

<sup>13</sup>C-N.M.R. ( $CDCl_3$ ):  $\delta = 11.29$ ; 14.52; 15.95; 17.11; 18.44; 59.49; 96.15; 116.08; 123.05; 129.60; 133.49; 161.76 ppm.

### Octaethylporphyrin:

3,4-Diethyl-2-ethoxy-5-methylpyrrole (**5d**) is first converted to the 5-diethylaminomethyl derivative via the 5-bromomethyl derivative before the cyclocondensation<sup>3</sup>. To a stirred solution of dry crystalline **5d** (20.9 g, 0.1 mol) in dry ether (500 ml) is added at room temperature, dropwise, a solution of bromine (16.2 g, >0.1 mol) in dichloromethane (50 ml) over a period of 15 min. The solution is refluxed for 5 min and then stirred with diethylamine (30 ml) for 15 min. The mixture is washed with 5 % aqueous potassium hydroxide and evaporated to dryness under vacuum. The residue is dissolved in 95 % ethanol (100 ml), a solution of potassium hydroxide (10 g) in water (20 ml) is added, and the mixture is

Table. 2,4-Diketones (4) and 3,4-Dialkyl-2-ethoxycarbonyl-5-methylpyrroles (5)

	R <sup>1</sup>	R <sup>2</sup>	Diketone 4			Pyrrole 5		
			Yield [%]	b.p./torr	Lit. b.p./torr	Yield [%] from 3	m.p.	Lit. m.p.
a	CH <sub>3</sub>	CH <sub>3</sub>	78	168°/760	77–79°/30 <sup>9</sup>	52	126°	128° <sup>10</sup>
b	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	70	186°/760	78–81°/20 <sup>9</sup>	48	97°	97° <sup>11</sup>
c	C <sub>2</sub> H <sub>5</sub>	CH <sub>3</sub>	68	185°/760	62°/25 <sup>12</sup>	52	92°	95–96° <sup>13</sup>
d	C <sub>2</sub> H <sub>5</sub>	C <sub>2</sub> H <sub>5</sub>	72	191–193°/760	192–193° <sup>6</sup>	62	75°	74–75° <sup>3</sup>
e	n-C <sub>5</sub> H <sub>11</sub>	CH <sub>3</sub>	68	124°/20	112–113°/15 <sup>9</sup>	55	71°	<sup>a</sup>
<sup>a</sup> C <sub>14</sub> H <sub>23</sub> NO <sub>2</sub> (237.4)			calc. C 70.85 found 70.79	H 9.77 9.72	N 5.90 5.94			

heated on a steam bath for 2 h. The mixture is then diluted with water (100 ml), and acetic acid (250 ml) is added. This mixture is heated on a steam bath while air is bubbled through it until the liquid has been evaporated almost to dryness. Methanol (200 ml) is then added, the insoluble porphyrin collected by filtration, and recrystallized from toluene; yield: 4–6 g (30–40 %); m.p. 323–324° (Ref. <sup>8</sup>, m.p. 324–325°).

C<sub>36</sub>H<sub>46</sub>N<sub>4</sub> calc. C 80.85 H 8.67 N 10.48  
(534.8) found 80.80 8.63 10.30

<sup>1</sup>H-N.M.R. (CDCl<sub>3</sub>): δ = 1.09 (t, 24 H, J = 7.5 Hz); 2.40 ppm (q, 16 H, J = 7.5 Hz).

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