

## Substituted Pyrroles

N. Zh. Mamardashvili\*, M. E. Kluyeva and O. A. Golubchicov

Institute of Solution Chemistry of the Russian Academy of Sciences, 153045 Academicheskaya, 1, Ivanovo, Russia

E-mail: ngm@ihnr.polytech.ivanovo.su

\* Author to whom correspondence should be addressed.

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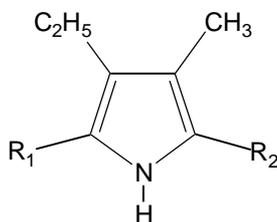
**Abstract:** A stepwise synthesis of  $\alpha$ -unsubstituted pyrroles with desired substituents in the  $\beta$ -positions of the ring has been devised.

**Keywords:** pyrroles,  $\beta$ -substituted.

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### Introduction

Pyrrole synthesis depends strongly on the nature and relative position of the substituents in the molecule. The methods permitting the synthesis of comparatively simple pyrroles are found to be useful for more complex structures. This paper describes the synthesis of a series of pyrrole derivatives (1-5).



**Figure 1.** R<sub>1</sub> = CH<sub>3</sub> (1, 6), COOC<sub>2</sub>H<sub>5</sub> (2-5); R<sub>2</sub> = COOCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub> (1, 2), COOH (3), I (4), H (5), COOC<sub>2</sub>H<sub>5</sub> (6).

Relatively accessible  $\alpha$ -ethoxycarbonylpyrroles are obtained by the condensation of the corresponding alkylpentanediones with nitrosoacetoacetic ester in acetic acid with the reduction [1-8]. However  $\alpha$ -unsubstituted pyrroles – the desired product of the synthesis - have a great disadvantage: they contain large substituents in adjacent  $\beta$ -positions responsible for extra restrictions during condensation. We now report a method that allows the synthesis of structures with these large substituents in the desired positions while excluding the steric factor influence on pyrrole reactivity.

## Results and Discussion

2,4-Dimethyl-3-ethyl-5-benzyloxycarbonylpyrrole (**1**) was prepared by reaction of 2,4-dimethyl-3-ethyl-5-ethoxycarbonylpyrrole (**6**) with benzyl alcohol. 2-Ethoxycarbonyl-3-ethyl-4-methyl-5-benzyloxycarbonylpyrrole (**2**) was prepared by oxidizing the  $\alpha$ -methyl group of (**1**) with sulfuryl chloride and treatment with ethanol. Reduction of (**2**) with hydrogen over palladium catalyst yields 2-ethoxycarbonyl-3-ethyl-4-methyl-5-carboxypyrrole (**3**). Decarboxylation was carried out in two stages. At first the carboxy-group was substituted by iodine to form 2-ethoxycarbonyl-3-ethyl-4-methyl-5-iodopyrrole (**4**) and then the iodine was removed with  $\text{SnCl}_2$ . This sequence gives 2-ethoxycarbonyl-3-ethyl-4-methylpyrrole (**5**) in adequate yield. (**6**) is the key compound in the synthesis of many di- and tetra-pyrrole compounds of linear and cyclic structure.

To confirm the molecular structures the IR spectra of the synthesized pyrroles were investigated (Table 1). Together with NMR data, in most cases they reliably prove the presence of the functional groups in the molecules.

## Experimental

### General Methods and Materials

$^1\text{H}$  nuclear magnetic resonance spectra were recorded on a Bruker AC-500 spectrometer operating at 600 MHz with HMDS as internal standard in deuteriochloroform. IR spectra were obtained on a Speord M80 spectrophotometer in KBr tablets. 2,4-Dimethyl-3-ethyl-5-ethoxycarbonylpyrrole (**6**) was synthesized by a known method [2].

### *2,4-Dimethyl-3-ethyl-5-benzyloxycarbonylpyrrole (1)*

2,4-Dimethyl-3-ethyl-5-ethoxycarbonylpyrrole (**6**, 10 g) in benzyl alcohol (50 mL) were placed into a flask equipped with a distilling column, Liebig condenser and dropping funnel. The solution was heated to boiling temperature and then a solution of sodium (0.2 g) in benzyl alcohol (100 mL) was added to the flask. After all the ethanol was distilled off the reaction mixture was cooled, diluted with water (200 mL) and then acidified with acetic acid. The resulting precipitate was isolated by filtration and recrystallized from ethanol. Yield 87%, melting point 166-168 $^\circ\text{C}$ , NMR: 8.89 (s, 1H, NH), 7.34

(m, 5H, C<sub>6</sub>H<sub>5</sub>), 4.22 (m, 2H, OCH<sub>2</sub>Ph), 2.27 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.21 (s, 3H, 2-CH<sub>3</sub>), 2.09 (s, 3H, 4-CH<sub>3</sub>), 0.84 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>)

#### *2-Ethoxycarbonyl-3-ethyl-4-methyl-5-benzyloxycarbonylpyrrole (2)*

Freshly distilled sulfonyl chloride (8.9 mL) was added to a solution of 2,4-dimethyl-3-ethyl-5-benzyloxycarbonylpyrrol (**1**, 9g) in dry ether (100 mL) while the reaction mixture temperature was kept below 20°C. The mixture was kept overnight at room temperature and then the ether was evaporated. Ethanol (150 mL) was added to the residuum. After 1 hour the solution was diluted with water (200 mL). The organic phase was extracted with ether and washed with water. The ether was evaporated and the resulting product was recrystallized from ethanol. Yield 92%, melting point 51-53°C, NMR: 8.88 (s, 1H, NH), 7.36 (m, 5H, C<sub>6</sub>H<sub>5</sub>), 4.32 (m, 2H, OCH<sub>2</sub>Ph), 4.13 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.69 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.24 (s, 3H, 4-CH<sub>3</sub>), 1.27 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 0.84 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>).

#### *2-Ethoxycarbonyl-3-ethyl-4-methyl-5-carboxypyrrole (3)*

Hydrogen was passed through a stirred mixture of 2-ethoxycarbonyl-3-ethyl-4-methyl-5-benzyloxycarbonylpyrrole (**2**, 10 g), activated 10% Pd/C (2g), tetrahydrofuran (200 mL) and triethylamine (2 mL) over 6 hours. Then the solution was evaporated down to 50-mL residual volume and methanol (100 mL) was added. After evaporating the remaining tetrahydrofuran the methanol solution was cooled. The resulting precipitate was isolated by filtration and washed with methanol, then ether and hexane. Yield 96%, melting point 186-188°C, NMR: 9.38 (s, 1H, NH), 4.17 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.69 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 2.24 (s, 3H, 4-CH<sub>3</sub>), 1.32 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 0.87 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>).

#### *2-Ethoxycarbonyl-3-ethyl-4-methyl-5-iodopyrrole (4)*

A solution of sodium bicarbonate (4.5 g) in water (80 mL) was added dropwise to a stirred solution of 2-ethoxycarbonyl-3-ethyl-4-methyl-5-carboxypyrrole (**3**, 5g) in ethanol (100 mL). Then the solution was filtered and a solution of iodine (4.6 g) and KI (5.9 g) in water (50 mL) was added to the filtrate with stirring at 60°C. Stirring was continued for another 10 minutes and then the reaction mixture was diluted with water (100 mL). The resulting precipitate was isolated by filtration. Yield 86%, melting point 119-120°C, NMR: 8.90 (s, 1H, NH), 4.21 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.67 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.90 (s, 3H, 4-CH<sub>3</sub>), 1.28 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 0.86 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>).

#### *2-Ethoxycarbonyl-3-ethyl-4-methylpyrrole (5)*

Hydrochloric acid (100 mL) was added to a boiling solution of 2-ethoxycarbonyl-3-ethyl-4-methyl-5-iodopyrrole (**4**, 5g), SnCl<sub>2</sub> (8.5 g) and KI (0.8 g) in ethanol (350 mL). The organic phase was extracted with ether and washed with water. The ether was evaporated under vacuum at room tempera-

ture. Yield 87%, melting point 22-24°C, NMR: 8.94 (s, 1H, NH), 4.20 (q, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.68 (q, 2H, CH<sub>2</sub>CH<sub>3</sub>), 1.94 (s, 3H, 4-CH<sub>3</sub>), 1.29 (t, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 0.87 (t, 3H, CH<sub>2</sub>CH<sub>3</sub>)

**Table 1.** Infrared spectra of pyrroles (**1-5**), cm<sup>-1</sup>.

<b>1</b>	$\gamma$ (NH)	$\gamma$ (CH)	$\delta$ (CH)	$\gamma$ (CH)	C-C	C=O	C-O
<b>6</b>	3456	-	1379	1022	1348, 1510	1664	1290
<b>1</b>	3450	3100, 3138	1380	1010	1360, 1530	1670	1280
<b>2</b>	3451	3100, 3140	1380	1015	1338, 1514	1690	1287
<b>3</b>	3450	-	1377	1090	1328, 1517	1685	1273
<b>4</b>	3462	-	1384	1116	1390, 1517	1687	1268
<b>5</b>	3450	3112	1382	1000	1357, 1578	1680	1295

## References and Notes

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*Samples Availability:* available from the authors and MDPI.