Oxidative Halogenation of Substituted Pyrroles with Cu(II). Part III. Bromination and Chlorination of 2-Benzoylpyrrole

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The bromination of 2-benzoylpyrrole with copper(II) bromide in the homogeneous and the heterogeneous phase is described, giving 4- and 5-monobromo derivatives whose ratio decreases as the temperature is increased. The same reaction with copper(II) chloride in acetonitrile at 60° produces 5-chloro-2-benzoylpyrrole as the major product. 4,5-Dihalopyrroles in good yields are obtained with an excess of halogenating agent.

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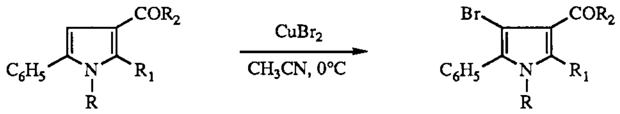
Introduction.

Recently [1,2] we have studied the oxidative bromination of some substituted pyrroles with copper(II) bromide. Our results have shown that the reaction carried out on compounds **I** affords with high yield nuclear monobromination as long as the experimental conditions are suitable (Scheme 1). A complex mixture of oxidation products from compounds **I** by the action of copper(II) chloride, under the same experimental conditions, are obtained [3].

To provide useful information on the direction of partial halogenation in pyrroles where more than one position is vacant, we have studied the bromination and chlorination of 2-benzoylpyrrole with copper(II) both in the heterogeneous and the homogeneous phase.

The previously reported halogenation of pyrrole derivatives bearing electron-withdrawing groups at the 2-position provides 4 and 5 isomers in a ratio that is dependent on the halogenating agent and on the experimental conditions [4-6].

Scheme 1



(I)

$R = H, CH_3, C_6H_5$
$R_1 = CH_3, C_6H_5$
$R_2 = CH_3, OH, OC_2H_5$

Results.

We have found that when 2-benzoylpyrrole was brominated in the heterogeneous phase (chloroform/ethyl acetate 1:1) using copper(II) bromide in a ratio of 1:2, the products of the reaction were the 4 and 5 isomers in a ratio that was 4:1 at room temperature and 2.5:1 at 60°. Similar results were obtained when the reaction was carried out in the homogeneous phase with acetonitrile under a nitrogen stream. By reaction of the 2-benzoylpyrrole with an excess (1:5) of the same halogenating agent the 4,5-dibromo derivative, with an almost quantitative yield, was obtained. The course of the reaction was quite different in the case of halogenation with copper(II) chloride. As a matter of fact, we did not observe any reaction in the heterogeneous phase and in the homogeneous phase at room temperature; at 60° in homogeneous phase the reaction proceeds very slowly to different products under various experimental conditions. After refluxing for 24 hours with copper(II) chloride (1:2 molar ratio), the 5-chloro and the 4-chloro derivatives, in a ratio of 2:1, together with a considerable amount of starting material, were isolated. We have observed the formation of the 4,5-dichloro and of the 4-chloro derivatives in a ratio of 2.25:1, when the reaction was carried out in the presence of an excess of the halogenating agent (1:5 molar ratio) until complete disappearance of the unreacted 2-benzoylpyrrole (72 hours) had occurred. Finally the complete conversion of the 4-chloro derivative into the 4,5-dichloro derivative may be obtained after seven days.

Conclusions.

As a result of our study we can state that when 2-benzoylpyrrole is reacted with a calculated amount (1:2) of copper(II) bromide the reaction affords primarily the 4-bromo derivative. Chlorination of the same pyrrole with copper(II) chloride gives results which are similar to the bromination results, except that chlorination is not as selective as bromination. This fact is consistent with an heterolytic halogenation occurring by attack of electrophilic species, probably the corresponding molecular halogens, on a pyrrole ring in which the presence of an electron-withdrawing group in the 2-position renders the 4- and 5-positions of comparable reactivity. Increasing the relative amount of copper(II) halogenides, raises the percentage of dihalogenated products and may produce almost a quantitative yield of it if desired.

EXPERIMENTAL

All melting points were determined on a Buchi-Tottoli micro melting point apparatus and are uncorrected. The ir spectra were recorded in Nujol mulls with a Perkin Elmer Infrared 137 E spectrophotometer. The ^{1}H nmr spectra were recorded on a Bruker SF 250 spectrometer in deuteriochloroform using TMS as the internal standard. Mass spectra were recorded on a Jeol-JMS-01-SG-2 spectrometer operating with an ionizing electrons beam at 75 eV. Elemental analysis for C,H,N were performed on an Hewlett Packard 185 B CHN analyzer. Chromatographic separations were performed on columns packed with silica gel 60 from Merck (70-230 mesh ASTM). All reactions were monitored by tlc on 0.2 mm x 20 cm x 20 cm silica gel 60 F-254 (Merck) plates using uv light for visualization.

Bromination of 2-Benzoylpyrrole in the Homogeneous Phase.

Reaction A.

2-Benzoylpyrrole (1.71 g, 0.01 mole) was dissolved in 100 ml of acetonitrile and 4.5 g (0.02 mole) of copper(II) bromide was added and allowed to stir at room temperature under a nitrogen stream. After 24 hours the reaction mixture was poured into 50 ml of 10% aqueous sulphuric acid solution and after stirring for 1 hour was extracted with ether. The organic phase, neutralized with saturated sodium hydrogen carbonate solution and dried over sodium sulphate was removed under reduced pressure. The residue was chromatographed on a silica gel column eluting with petroleum ether 50-70°/ethyl acetate (4:1). The following fractions were obtained:

5-Bromo-2-benzoylpyrrole.

This compound was obtained as pale yellow needles, 0.45 g, yield 18%, mp 115°, recrystallized from petroleum ether; ir: 3220 (NH), 1626 (CO) cm^{-1}; ms: m/z 249 (M$^+$); ^{1}H-nmr: δ 6.30 (1H, q, $J_{4,3}$ = 4 Hz, $J_{4,NH}$ = 2.5 Hz, exchange with deuterium oxide, d, J = 4 Hz, 4–H), 6.80 (1H, q, $J_{3,4}$ = 4 Hz, $J_{3,NH}$ = 2.5 Hz, exchange with deuterium oxide, d, J = 4 Hz, 3–H), 7.46-7.92 (5H, m, C_6H_5), 10.66 (1H, s broad, NH).

Anal. Calcd. for $C_{11}H_8BrNO$: C, 52.82; H, 3.22; N, 5.60. Found: C, 52.97; H, 3.30; N, 5.44.

4-Bromo-2-benzoylpyrrole.

This compound was obtained as pale yellow needles, 1.8 g, yield 72%, mp 158-159°, recrystallized from ethanol; ir: 3250 (NH), 1620 (CO) cm^{-1}; ms: m/z 249 (M$^+$); ^{1}H-nmr: δ 6.87 (1H, d broad, J = 2 Hz, exchange with deuterium oxide, s broad, 3–H), 7.15 (1H, d broad, J = 2 Hz, exchange with deuterium oxide, s broad, 5–H), 7.46-7.90 (5H, m, C_6H_5), 10.65 (1H, s broad, NH).

Anal. Calcd. for $C_{11}H_8BrNO$: C, 52.82; H, 3.22; N, 5.60. Found: C, 53.01; H, 3.35; N, 5.38.

Unreacted 2-benzoylpyrrole (0.12 g, 7%) was recovered.

Reaction B.

2-Benzoylpyrrole (1.71 g, 0.01 mole), 100 ml of acetonitrile and copper(II) bromide (4.5 g, 0.02 mole) were refluxed at 60° under a nitrogen stream for 2 hours. The reaction mixture was then allowed to stand at room temperature for 1 hour and treated as described in Reaction A. Eluting with petroleum ether 50-70°/ethyl acetate 4:1 the following fractions were obtained:

5-Bromo-2-benzoylpyrrole.

This compound had mp 115°, yield 18% (0.57 g) recrystallized from petroleum ether.

4-Bromo-2-benzoylpyrrole.

This compound had mp 158-159°, yield 57% (1.43 g) recrystallized from ethanol.

Unreacted 2-benzoylpyrrole (0.26 g, 15%) was recovered.

4,5-Dibromo-2-benzoylpyrrole.

2-Benzoylpyrrole (1.71 g, 0.01 mole) was dissolved in 100 ml of acetonitrile and 11.25 g (0.05 mole) of copper(II) bromide was added and allowed to stir at room temperature under a nitrogen stream. After 48 hours the reaction mixture was poured into 50 ml of 10% aqueous sulphuric acid solution and after stirring for 1 hour was extracted with ether. The organic phase was then neutralized with saturated aqueous sodium hydrogen carbonate, dried over sodium sulphate and removed under reduced pressure. The residue (2.8 g) was recrystallized from ethanol, pale yellow needles, mp 177°, yield 85%; ir: 3196 (NH), 1625 (C=O) cm^{-1}; ms: m/z 327 (M$^+$); ^{1}H-nmr: δ 6.89 (1H, s, 3–H), 7.48-7.93 (5H, m, C_6H_5), 11.21 (1H, s, broad, NH).

Anal. Calcd. for $C_{11}H_7Br_2NO$: C, 40.15; H, 2.14; N, 4.26. Found: C, 40.40; H, 2.26; N, 4.32.

General Procedure of Bromination in the Heterogeneous Phase.

2-Benzoylpyrrole (1.71 g, 0.01 mole) was dissolved in 50 ml of chloroform/ethyl acetate 1:1 and allowed to react with copper(II) bromide under the same experimental conditions as described for the reaction in the homogeneous phase. After filtering the copper(I) bromide formed, the solution was diluted with 150 ml of ether, neutralized with saturated aqueous sodium hydrogen carbonate and dried over sodium sulphate. The solvent was removed under reduced pressure and the residue was purified as precedently described.

Reaction A.

Chlorination of 2-Benzoylpyrrole with Copper(II) Chloride.

2-Benzoylpyrrole (1.71 g, 0.01 mole), 50 ml of acetonitrile and copper(II) chloride (2.70 g, 0.02 mole) were refluxed, under a nitrogen stream, for 24 hours at 60°. The reaction mixture was then allowed to stand at room temperature for 1 hour, poured into 50 ml of 10% aqueous sulphuric acid solution and treated as above described for the bromination. The residue was chromatographed eluting with petroleum ether 50-70°/methylene chloride/ethyl acetate (90:5:5). Two main fractions were obtained:

5-Chloro-2-benzoylpyrrole.

This compound was obtained as yellow needles, 0.9 g, yield 44%, mp 136-137°, recrystallized from ethanol; ir: 3220 (NH), 1630 (CO) cm^{-1}; ms: m/z 205 (M$^+$); ^{1}H-nmr: δ 6.20 (1H, q, $J_{4,3}$ = 4 Hz, J = $_{4,NH}$ = 2.5 Hz, 4–H), 6.82 (1H, q, $J_{3,4}$ = 4 Hz, $J_{3,NH}$ = 2.5 Hz, 3–H), 7.46-7.90 (5H, m, C_6H_5), 10.05 (1H, s broad NH).

Anal. Calcd. for $C_{11}H_8ClNO$: C, 64.24; H, 3.92; N, 6.81. Found: C, 64.37; H, 4.05; N, 6.90.

4-Chloro-2-benzoylpyrrole.

This compound was obtained as yellow needles, 0.43 g, yield 21%, mp 141-142°, recrystallized from ethanol; ir: 3255 (NH), 1625 (CO) cm^{-1}; ms: m/z 205 (M$^+$); ^{1}H-nmr: δ 6.81 (1H, d broad, J = 2 Hz, after exchange with deuterium oxide, s broad, 3–H), 7.10 (1H, d broad, J = 2 Hz, after exchange with deuterium oxide, s broad, 5–H), 7.46-7.89 (5H, m, C_6H_5), 10.36 (1H, s broad, NH).

Anal. Calcd. for $C_{11}H_8ClNO$: C, 64.24; H, 3.92; N, 6.81. Found: C, 64.46; H, 4.10; N, 6.95.

Unreacted 2-benzoylpyrrole (0.45 g , 26%) was recovered.

Reaction B.

2-Benzoylpyrrole (1.71 g, 0.01 mole), 50 ml of acetonitrile and copper(II) chloride (6.75 g, 0.05 mole) were refluxed, under nitrogen stream, for 72 hours at 60°. The reaction mixture was then treated as in Reaction A. Eluting with petroleum ether 50-70°/methylene chloride/ethyl acetate 90:5:5 two main fractions were obtained:

4,5-Dichloro-2-benzoylpyrrole.

This compound was obtained as pale yellow needles, 1.32 g, yield 55%, mp 190; recrystallized from ethanol; ir: 3200 (NH), 1625 (CO) cm^{-1}; ms: m/z 239 (M$^+$); ^{1}H-nmr: δ 6.83 (1H, s, 3-H), 7.47-7.90 (5H, m, C_6H_5), 10.99 (1H, s broad, NH).

Anal. Calcd. for $C_{11}H_7Cl_2NO$: C, 55.03; H, 2.94; N, 5.83. Found: C, 55.25; H, 3.08; N, 5.95.

4-Chloro-2-benzoylpyrrole.

This compound was obtained as pale yellow needles, 0.5 g, yield 24%, mp 141-142°, recrystallized from ethanol.

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