Oxidative Halogenation of Substituted Pyrroles with Cu(II). Part I. Bromination of some 3-Acetylpyrroles

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3-Acetylpyrroles are brominated with copper(II) bromide. The reaction afforded almost quantitatively only nuclear monobromination. Evidence for the structures of final compounds was by mass spectrometry, ^{1}H-nuclear magnetic resonance, ir, and elemental analysis.

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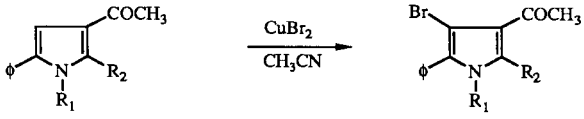
In previous investigations, we studied the oxidative processes of substituted pyrroles [1-5]. Copper(II) halogenation is now selected as a possible model for these oxidations. This reaction has been applied to a variety of substrates (saturated and unsaturated ketones, phenol) [6,7], and very interesting results are reported by King and Ostrum [8] who obtained selective monobromination on side-chain of hydroxyacetophenones with copper bromide. There is no indication of nuclear bromination.

The literature reports only two cases of halogenation of pyrrole derivatives with copper(II). Monobromopyrroles were isolated in low yields in the halogenation of methyl-2-pyrrolecarboxylate [9]. A complex mixture of polybromopyrroles had been obtained in the halogenation of 1-methylpyrrole [10].

Scheme 1



R_1 = H, CH_3, C_6H_5, $C_6H_5CH_2$
R_2 = CH_3, C_6H_5

The notheworthy biological activity of several halogenated derivatives of pyrrole stimulated our interest to examine closely the behaviour of copper(II) halides on pyrrolic substrates.

We report here the results of the halogenation of some 3-acetylpyrroles with cooper(II) bromide, using acetonitrile as the solvent at room temperature. We obtained under our experimental conditions only nuclear monobromination with very high yields. The structure of the products of reaction were confirmed by elemental analysis and spectroscopic data (ir, mass, ^{1}H nmr).

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 EM-360 A Varian spectrometer in deuteriochloroform unless otherwise noted, 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 a H.P. 185 B CHN analyzer.

General Procedure for the Halogenation with Copper(II) Bromide.

The appropriate pyrrole (0.01 mole) was dissolved in 30 ml of acetonitrile and 0.02 mole of copper(II) bromide was added and allowed to stir at room temperature until the starting material disappeared (6-8 hours). The reaction was monitored by tlc. The mixture was poured into about 50 ml of water, made alkaline with 20% aqueous ammonia, extracted with ether and dried with anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue in the case of pyrroles **IX**, **X**, and **XIII**, was chromatographed on silica gel deactivated with water (15%). The product was collected with petroleum ether 50-70°/ethyl acetate 8:2. The pyrroles **VIII**, **XI**, **XII** and **XIV** were recrystallized from ethanol.

General Procedure for the Preparation of Pyrroles **I-IV**.

3-Acetyl-1-phenyl-1,4-pentandione (0.01 mole), 20 ml of acetic acid and *ca.* 0.04 mole of the appropriate amine were refluxed for 1 hour. The reaction mixture was then allowed to stand at room temperature for 1 hour, poured into ice-cold water (200 ml), and neutralized with 20%, aqueous ammonia. The residue was purified by chromatography on a column of silica gel deactivated with water (15%). The eluting solvent was petroleum 50-70°/ethyl acetate 8:2.

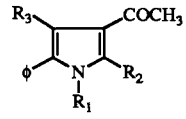
Synthesis of 2,5-Diphenyl-3-acetylpyrrole (**V**).

Magnesium turnings (0.48 g, 0.020 mole) were suspended in 200 ml of dry ether and 2.4 g (0.022 mole) of ethyl bromide was added dropwise. After all of the magnesium reacted, 4.38 (0.020 mole) of 2,5-diphenylpyrrole dissolved in dry ether was added dropwise, and the reaction mixture was refluxed for 1 hour. After cooling, 1.5 g of acetyl chloride was added and the mixture was allowed to stir at room temperature for 1 hour. The ether layer was allowed to stand and a solid was collected by pouring the mixture into a 0.1 *M* ammonium chloride solution. The residue collected after standing overnight was recrystallized from ethanol, mp 175-176°, yield 70%.

Synthesis of 1-Methyl-2,5-diphenyl-3-acetylpyrrole (**VI**).

Compound **V** (2.6 g) was suspended in 50 ml of dry toluene and 1.27 g of potassium *t*-butylate, *ca.* 0.5 ml of tris[2-(2-methoxyethoxy)ethyl]amine (TDA-1), and 0.6 ml of methyl iodide were added. The mixture was kept at 40° for 30 minutes with stirring. The solvent was removed under reduced pressure and the residue was purified by chromatography following the same pro-

Table 1



Compound	Molecular Formula (M^+)	Analyses Calcd./Found % C	H	N	R_1	R_2	R_3	Yield %	Mp (°C)	IR ν (cm^{-1})
I	$C_{13}H_{13}NO$	78.36	6.58	7.03	H	CH_3	H	70	180-181	3200 (NH), 1630 (CO)
	(199)	78.51	6.69	6.89						
II	$C_{14}H_{15}NO$	78.84	7.09	6.57	CH_3	CH_3	H	65	89-90	1650 (CO)
	(213)	79.05	7.28	6.82						
III	$C_{20}H_{19}NO$	83.01	6.62	4.84	$C_6H_5CH_2$	CH_3	H	60	oil	1660 (CO)
	(289)	82.84	6.48	4.65						
IV	$C_{19}H_{17}NO$	82.88	6.22	5.09	C_6H_5	CH_3	H	80	102-103	1660 (CO)
	(275)	83.01	6.06	5.20						
V	$C_{18}H_{15}NO$	83.73	5.79	5.36	H	C_6H_5	H	70	175-176	3200 (NH), 1620 (CO)
	(261)	82.91	5.94	5.41						
VI	$C_{19}H_{17}NO$	82.88	6.22	5.09	CH_3	C_6H_5	H	90	oil	1650 (CO)
	(275)	83.07	6.38	5.27						
VII	$C_{25}H_{21}NO$	85.44	6.02	3.99	$C_6H_5CH_2$	C_6H_5	H	47	79-80	1650 (CO)
	(351)	85.21	6.16	4.12						
VIII	$C_{13}H_{12}BrNO$	56.13	4.35	5.04	H	CH_3	Br	95	149-150	1660 (CO)
	(277)	56.31	4.28	5.21						
IX	$C_{14}H_{14}BrNO$	57.55	4.83	4.79	CH_3	CH_3	Br	80	97-98	1645 (CO)
	(291)	57.41	4.98	4.96						
X	$C_{20}H_{18}BrNO$	65.22	4.93	3.80	$C_6H_5CH_2$	CH_3	Br	85	oil	1655 (CO)
	(367)	65.34	5.07	3.92						
XI	$C_{19}H_{16}BrNO$	64.42	4.55	3.95	C_6H_5	CH_3	Br	95	145-146	1645 (CO)
	(353)	64.29	4.68	4.10						
XII	$C_{18}H_{14}BrNO$	63.54	4.15	4.12	H	C_6H_5	Br	96	168-169	3160 (NH), 1650 (CO)
	(339)	63.72	3.98	4.25						
XIII	$C_{19}H_{16}BrNO$	64.42	4.55	3.95	CH_3	C_6H_5	Br	85	148-149	1660 (CO)
	(353)	64.69	4.79	4.20						
XIV	$C_{25}H_{20}BrNO$	69.77	4.68	3.25	$C_6H_5CH_2$	C_6H_5	Br	92	114-115	1670 (CO)
	(429)	69.98	4.85	3.42						

Table 2

^{1}H-NMR Data of Compounds I-XIV δ (ppm), (deuteriochloroform)

Compound	
I	2.45, 2.60 (6H, s, 2 CH_3), 6.70 (1H, d, J = 4.8 Hz, CH), 7.10-7.70 (5H, m, C_6H_5), 9.30 (1H, s broad, NH)
II	2.40, 2.62 (6H, s, 2 CH_3), 3.50 (1H, s, N-CH_3), 6.53 (1H, s, CH), 7.20-7.60 (5H, m C_6H_5)
III	2.45, 2.49 (6H, s, 2 CH_3), 5.10 (2H, s, CH_2), 6.60 (1H, s, CH), 7.10-7.60 (10H, m, 2 C_6H_5)
IV	2.50, 2.56 (6H, s, 2 CH_3), 6.76 (1H, s, CH), 6.95-7.60 (5H, m, C_6H_5)
V [a]	2.28 (3H, s, CH_3), 7.08 (1H, d, J = 4.8 Hz, CH), 7.18-8.00 (10H, m, C_6H_5), 11.95 (1H, s, broad, NH)
VI	2.10 (3H, s, $COCH_3$), 3.34 (3H, s, N-CH_3), 6.77 (1H, s, CH), 7.20-7.70 (10H, m, C_6H_5)
VII	1.97 (3H, s, CH_3), 4.90 (2H, s, CH_2), 6.73 (1H, s, CH), 6.93-7.50 (15H, m, C_6H_5)
VIII	2.51, 2.58 (6H, s, 2 CH_3), 7.33-7.70 (5H, m, C_6H_5), 9.28 (1H, s, broad, NH)
IX	2.59, 2.67 (6H, s, 2 CH_3), 3.40 (3H, s, N–CH_3), 7.30-7.65 (5H, m, C_6H_5)
X	2.40, 270 (6H, s, 2 CH_3), 4.97 (2H, s, CH_2), 7.10-7.70 (10, m, C_6H_5)
XI	2.34, 2.68 (6H, s, 2 CH_3), 7.02-7.27 (10, m, C_6H_5)
XII [a]	2.20 (3H, s, CH_3), 7.15-8.06 (10, m, C_6H_5), 12.16 (1H, s, broad, NH)
XIII [a]	2.00 (3H, s, $COCH_3$), 3.20 (3H, s, N–CH_3), 7.40-7.75 (10H, m, C_6H_5)
XIV [a]	2.03 (3H, s, CH_3), 5.02 (2H, s, CH_2), 6.43-7.70 (15H, m, C_6H_5)

[a] DMSO-d_6 as solvent.

cedure as for pyrroles **I-IV**, yield 90%.

Synthesis of 1-Benzyl-2,5-diphenylpyrrole.

1,4-Diphenylbutane-1,4-dione, (4.76 g, 0.020 mole) and 11.7 g (0.01 mole) of benzylamine were dissolved in acetic acid (20 ml) and refluxed for 1 hour at 120°. After cooling water was added and the residue obtained after filtration was recrystallized from ethanol, mp 144°, yield 80%; ^{1}H-nmr: δ 5.20 (2H, s, CH_2), 6.37 (2H, s, 2 CH), 6.50-7.50 (15H, m, C_6H_5).

Synthesis of 1-Benzyl-2,5-diphenyl-3-acetylpyrrole (**VII**).

1-Benzyl-2,5-diphenylpyrrole (3.09 g, 0.01 mole) was dissolved in 1,2-dichloroethane anhydrous (50 ml) was added dropwise to a solution of 1.7 g of anhydrous aluminumchloride and 0.78 g of acetyl chloride in anhydrous 1,2-dichloroethane (50 ml). After standing overnight the mixture was poured into about 250 ml of water and a little crushed ice. The water was then removed and the organic layer, dried over anhydrous sodium sulphate, was evaporated under reduced pressure. The residue was purified by chromatography on a column of silica gel deactivated with water (15%) using petroleum ether 50-70°/ethyl acetate (95:5) as the eluent. The column afforded two main fractions: starting material not reacted (1.2 g) and the desired acetylpyrrole (1.4 g), mp 80°, yield 40%.

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