Chlorination of Pyrrole. *N*-Chloropyrrole: Formation and Rearrangement to 2- and 3-Chloropyrrole[1]

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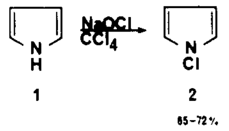
Received November 20, 1981

N-Chloropyrrole (**2**) was formed in 65–72% yield when pyrrole (**1**) in CCl_4 was chlorinated with aqueous NaOCl. This intermediate rearranged in methanol to give chloropyrroles by two distinct reactions: a thermal rearrangement which gave 2-chloropyrrole (**3**) and an acid-catalyzed intermolecular reaction which gave 2-chloropyrrole (**3**), 3-chloropyrrole (**4**), and 2,5-dichloropyrrole (**5**). Nucleophilic attack on the N–Cl bond of **2** was demonstrated by reactions in the presence of CN^- and SCN^-. In the latter case, 2-(thiocyano)pyrrole was formed.

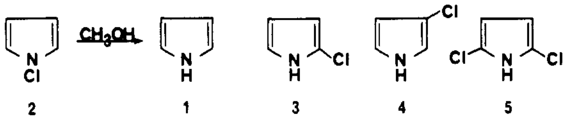
Nearly 100 years ago the chlorination[3,4] of pyrrole (**1**) with NaOCl under homogeneous conditions was reported to give polychlorinated and oxidized products.[5] We have reported the N-chlorination of indoles[6] and carbazole[7] with aqueous NaOCl under heterogeneous conditions. It is of interest to study the chlorination of pyrrole under the same conditions which led to the formation of the *N*-chloro derivatives of indole and carbazole. The controlled chlorination[3] of pyrrole and its derivatives is usually effected with SO_2Cl_2.[8] Recently successful chlorinations with *N*-chlorosuccinimide have been reported.[9] This paper describes the chlorination of pyrrole with NaOCl and some reactions of the initially formed *N*-chloro intermediate.

Preparation of *N*-Chloropyrrole. The *N*-chlorination of pyrrole occurred in 65–72% yield when a solution of pyrrole (**1**) in CCl_4 was stirred for 2–3 h with an aqueous solution of NaOCl (pH 13) at 0 °C (Scheme I). This reaction was exothermic, and the resulting solutions were lachrymatory. The intermediate present in CCl_4 oxidized the iodide ion. Its spectral properties clearly demonstrated N-substitution: IR (CCl_4) no N–H stretching frequency; ^1H NMR (CCl_4) two apparent triplets[10] at 6.60 (2 H) and 6.08 ppm (2 H); ^{13}C NMR (CCl_4) 124.0 ($C_{2,5}$) and 109.3 ppm ($C_{3,4}$).

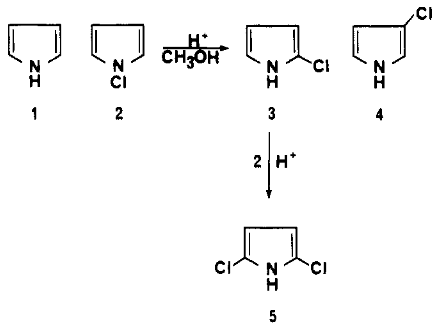
Scheme I



Scheme II



Scheme III



Rearrangement of *N*-Chloropyrrole. A solution of **2** in CCl_4 was combined with an equal volume of methanol, refluxed for 2 h, and analyzed by GC. The products were identified (see below) as: pyrrole (**1**), 2-chloropyrrole (**3**), 3-chloropyrrole (**4**), and 2,5-dichloropyrrole (**5**). The mixture was analyzed by GC–MS, and spectra were obtained which were identical with those observed when authentic samples of pyrrole, 2-chloropyrrole,[8a,11] and 2,5-dichloropyrrole[8a] were analyzed under the same conditions. Another compound was present whose mass spectrum (M^+, 101) indicated it was an isomer of 2-chloropyrrole. This product was isolated by column chromatography on silica gel (*n*-hexane/$CHCl_3$, 1:1, v/v) and purified by molecular distillation to give a short-lived liquid whose ^1H NMR agreed with that previously reported for 3-chloropyrrole.[12] Pyrrole was isolated by distillation from reactions run in the presence of K_2CO_3 (see the following section). This is the first study in which 3-chloropyrrole (**4**) has been identified as a product of the chlorination of pyrrole (**1**;[12] Scheme II).

The data summarized in Table I and Figure 1 indicated that the chloropyrroles were formed in two processes: a thermal rearrangement which gave 2-chloropyrrole (**3**) and an acid-catalyzed intermolecular reaction which gave **3**, **4**, and **5**. Chloropyrroles **4** and **5** almost disappeared when the reaction was run in the presence of the basic ion-exchange resin[13] Amberlyst A-21 (Figure 1b). These reactions

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[1] Presented in part at the 8th International Congress of Heterocyclic Chemistry, Graz, Austria, Aug 1981.

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[3] For a review on the chlorination of pyrroles, see Jones, R. A.; Bean, G. P. "The Chemistry of Pyrroles"; Academic Press: New York, 1977, pp 129–133.

[4] For reviews on the electrophilic substitution reactions of the pyrrole ring, see the following: (a) Reference 3, Chapter 4. (b) Marino, G. *Adv. Heterocycl. Chem.* **1971**, *13*, 235. (c) Marino, G. *Chim. Ind.* (*Milan*) **1973**, *55*, 349.

[5] Ciamician, G.; Silber, P. *Chem. Ber.* **1884**, *17*, 1743. Ciamician, G.; Silber, P. *Ibid.* **1885**, *18*, 1763. Ciamician, G.; Silber, P. *Gazz. Chim. Ital.* **1884**, *14*, 356. Ciamician, G.; Silber, P. *Ibid.* **1886**, *16*, 39.

[6] (a) De Rosa, M. *J. Chem. Soc., Chem. Commun.* **1975**, 482. (b) De Rosa, M.; Triana Alonso, J. L. *J. Org. Chem.* **1978**, *43*, 2639. (c) De Rosa, M.; Carbognani, L.; Febres, A. *Ibid.* **1981**, *46*, 2054. (d) De Rosa, M.; Carbognani, L.; Fernandez, M. R.; Febres, A. "Abstracts of Papers", 178th National Meeting of the American Chemical Society: Washington, DC, Aug 1979; American Chemical Society: Washington, DC, 1979; ORGN 183.

[7] De Rosa, M.; Triana Alonso, J. L. 174th National Meeting of the American Chemical Society: Chicago, IL, Sept 1977; American Chemical Society: Washington, DC, 1977; ORGN 155.

[8] For some examples, see the following. (a) Cordell, G. A. *J. Org. Chem.* **1975**, *40*, 3161. (b) Motekaitis, R. J.; Heinert, D. H.; Martell, A. E. *Ibid.* **1970**, *35*, 2504. (c) Reference 3.

[9] (a) Gilow, H. M.; Burton, D. E. *J. Org. Chem.* **1981**, *46*, 2221. (b) Aiello, E.; Dattolo, G.; Cirrincione, G.; Almerico, A. M. 8th International Congress of Heterocyclic Chemistry: Graz, Austria, Aug 1981.

[10] Jones, R. A.; Mcl. Spotswood, T.; Cheuychit, P. *Tetrahedron* **1967**, *23*, 4469.

[11] Cordell, G. A. *Spectrosc. Lett.* **1975**, *8*, 983.

[12] Photolysis of 3-chloropyridine *N*-oxide yielded 3-chloropyrrole. Bellamy, F.; Streith, J.; Fritz, H. *Nouv. J. Chim.* **1979**, *3*, 115.

Table I. Reactions of *N*-Chloropyrrole in Methanol

reaction conditions[a]		product yields,[b] %			
base/nucleophile	time	pyrrole	2-chloropyrrole	3-chloropyrrole	2,5-dichloropyrrole
	2 h	30	31	13	16
K_2CO_3[c]	10-15 min	85-90[d]			
KCN	*e*	92-94[d]			
Amberlyst A-21	10-12 h	59	37	3	0.5
anisole[g]	2 h	32	29	19	12
furan[h,i]	2 h	33	28	15	13
N-methylpyrrole[h]	2 h	86	6	5	

[a] A 5.0-mL solution of 2 in CCl_4 was combined with 5.0 mL of CH_3OH, base (nucleophile) was added, and the mixture refluxed. [b] Except where noted, yields are base on percent of total area (±1-3%). [c] Two grams of K_2CO_3.. [d] Method of internal standard (naphthalene). [e] Reaction was over on mixing solutions (60 s). [f] Two grams of Amberlyst A-21. [g] Molar ratio of anisole to 2 was 15:1. [h] Molar ratio 5:1 with respect to 2. [i] No change in product distribution was noted when the the reaction was run at 55 °C.

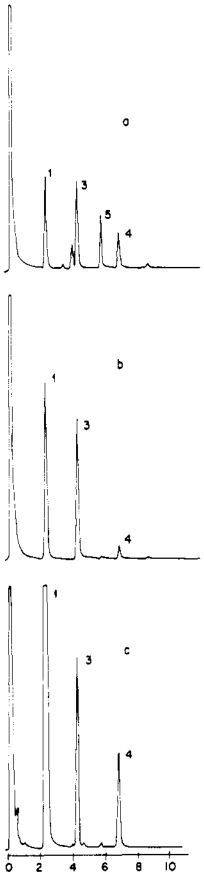
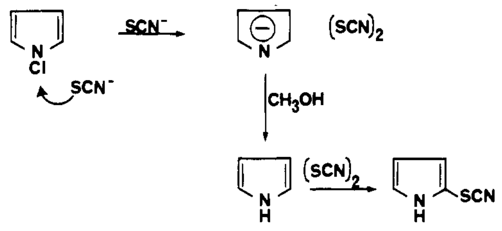


Figure 1. (a) Reaction in CCl_4–CH_3OH (1:1, v/v), (b) reaction in the presence of Amberlyst A-21, (c) reaction in the presence of added pyrrole (ratio of pyrrole to *N*-chloropyrrole 5:1).

were also slower. The intermolecularity of the acid-catalyzed reaction was demonstrated by the results in the presence of added pyrrole (Figure 1c) and *N*-methylpyrrole (Table I).[14] The relative proportion of monochloropyrroles **3** and **4** to that of 2,5-dichloropyrrole (**5**) increased from 2.8:1 to 99:1 when pyrrole was added. In the presence of *N*-methylpyrrole the yields of all the chloropyrroles decreased. Clearly, 2-chloropyrrole (**3**) was formed in a slow, acid-independent step and also in a faster, acid-catalyzed reaction (Scheme III).

Scheme IV



The products obtained in the presence of acid[16] indicated that pyrrole underwent electrophilic attack by Cl^+ or its equivalent. Thermal rearrangement of **2** was slower than this acid-catalyzed reaction; therefore, the results obtained in the presence of excess pyrrole should be indicative of the relative reactivity of the α and β positions of pyrrole toward a source of Cl^+. The ratio[17] of 2-chloro- to 3-chloropyrrole was 1.9:1 under these conditions. Similar ratios have been previously reported for the nitration,[18] protodedeuteration,[19] and acetylation[20] of pyrrole. The conjugate acid of *N*-chloropyrrole (**2**) was the most likely source of Cl^+.

Electrophilic substitution reactions of pyrrole are characterized by low positional selectivity and high relative reactivity.[4] No significant change was noted in the total yield of chloropyrroles when either anisole or furan was present in the reaction mixture. This and the low α to β ratio were in accord with these trends.[4] Thermal rearrangement of **2** to give 2-chloropyrrole (**3**) was analogous to the thermal rearrangement of *N*-acetylpyrrole.[21,22]

Dechlorination of *N*-Chloropyrrole. It was observed (Table I) that reactions in K_2CO_3/CH_3OH were faster than with just CH_3OH, and much faster than when Amberlyst A-21 was present. This suggested the possibility that

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[13] Amberlyst A-21 (The Rohm and Hass Co.) is a weakly basic macrorecticular ion exchange resin. It was dried prior to use by azeotropic distillation with benzene. The resin was then air-dried and washed repeatedly with CH_3OH. The product obtained in CH_3OH was combined with the resin and refluxed for 16 h. No selective absorption of any of the pyrroles was noted. When triethylamine or tri-*n*-butylamine was used as the base, similar changes in the product distribution were noted. A number of new products were also observed.

[14] *N*-Methylpyrrole[15] (99.8%) was obtained by preparative GC.

[15] Heaney, H.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1973**, 499.

[16] Reactions in methanol produced acid. HCl vapors were detected in reactions run in a closed system at room temperature.

[17] A mixture containing the chloropyrroles was refluxed for 16 h. Decomposition occurred as evidenced by change in peak heights in the gas chromatogram. The relative proportions of 1 and 3 were affected the most. The ratio determined by GC (assuming equal detector response) is most likely a minimum value.

[18] Cooksey, A. R.; Morgan, K. J.; Morrey, D. P. *Tetrahedron* **1970**, *26*, 5101. Fournari, P.; Tirouflet, J. *Bull. Soc. Chim. Fr.* **1963**, 484. Anderson, H. J. *Can. J. Chem.* **1957**, *35*, 21.

[19] Schwetlick, K.; Unverferth, K. *J. Prakt. Chem.* **1972**, *314*, 603. Muir, D. M.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1316. Bean, G. P.; Wilkinson, T. J. *Ibid.* **1978**, 72.

[20] Reference 4b, Table XI.

[21] Reference 3, pp 157-158 and 252.

[22] Kutscher, W.; Kaluza, G. *Chem. Ber.* **1966**, *99*, 3712. Patterson, J. M.; Bruser, D. M. *Tetrahedon Lett.* **1973**, 2959 (see footnote 8).

carbonate was participating in the dechlorination process. Nucleophilic attack on the chloro group of the N–Cl bond of **2** was demonstrated by reactions run in the presence of CN^- and SCN^-. Dechlorination of **2** with CN^- took less than 60 s and a 92–94% yield of pyrrole was observed. Reactions run in the presence of SCN^-, at room temperature, were over in 60 min. A residue was isolated whose spectral properties indicated that it was essentially pure 2-(thiocyano)pyrrole.[23] A 12–15% yield of pyrrole was detected by GC 60 s after the reaction with SCN^- was initiated. Less than 5% of pyrrole could be detected at the end of the reaction. Reductive dechlorination gave the pyrrole anion and $(SCN)_2$.[24] The anion abstracted a proton to give pyrrole, which subsequently reacted with $(SCN)_2$ (Scheme IV).

It would be expected that the ratio of pyrrole (**1**) to 2,5-dichloropyrrole (**5**) should be 1 in reactions run under conditions where the acid-catalyzed process predominated. The yields of **1** were always greater than that of **5**. It is likely that the heterolysis of the N–Cl bond was a favorable process even in the absence of any added nucleophile. Assistance by CH_3OH was probable.

The results of this study can be contrasted with similar studies on indole. Initially, an *N*-chloro derivative was formed, but base (K_2CO_3) was found to promote the rearrangement of *N*-chloroindole to 3-chloroindole.[6b] No evidence for dechlorination was detected. Studies on the chlorination of pyrroles and similar heteroaromatic amines are continuing.

Experimental Section

Infrared spectra were taken on a Perkin-Elmer 567 spectrophotometer. A Varian T-60 was used for recording ^1H NMR spectra and a Brucker WP-80 for ^{13}C NMR spectra. GC analysis was carried out on a Hewlett Packard 5850A gas chromatograph, using a 6 ft × 0.25 in. glass column packed with Degs (10%) on a Gas Chrom Q column with temperature programming. The reaction was followed by standard iodometric methods. Pyrrole was distilled prior to use from zinc dust. Solutions of NaOCl were prepared by passing Cl_2 through a solution of NaOH, and the resulting solutions were ca. 1 M and pH 13. **Caution**: Solutions of *N*-chloropyrrole are lachrymatory.

N-Chlorination of Pyrrole. To a vigorously stirred solution containing 1.34 g (20.0 mmol) of pyrrole in 50.0 mL of carbon tetrachloride at 0 °C was added 100 mL of a cold aqueous solution of NaOCl. The mixture was stirred for 2–3 h at 0 °C and the organic layer was separated and dried by passing it through a short column containing anhydrous potassium carbonate. A 65–72% yield (iodometric analysis) of *N*-chloropyrrole was obtained: IR (CCl_4) no N–H stretching frequency; ^1H NMR (CCl_4) δ 6.60 (t, 2 H), 6.08 (t, 2 H); ^{13}C NMR (CCl_4) δ 124.0 ($C_{2,5}$), 109.3 ($C_{3,4}$).

The fresh solution was pink and faded to yellow in the presence of light or during storage. It could be stored for up to 2 weeks at 0 °C over K_2CO_3 with little alteration.

Rearrangement of *N*-Chloropyrrole. To 5.0 mL of CCl_4 containing *N*-chloropyrrole (**2**) was added 5.0 mL of methanol and the mixture was refluxed for 2 h. The reaction mixture was analyzed by GC, and the following were identified as products of the reaction: pyrrole (30%), 2-chloropyrrole (31%), 3-chloropyrrole (13%), and 2,5-dichloropyrrole (16%). The mixture was analyzed by GC–MS, and mass spectra were obtained which were identical with those observed when authentic samples of pyrrole (mass spectrum, *m/e* (relative intensity) 67 (M, 100), 41 (M − CN, 44), 40 (M − HCN, 61)); 2-chloropyrrole (mass spectrum,[11] *m/e* (relative intensity) 103 (M + 2, 36), 101 (M + 2, 100), 74 (M − HCN, 28), 66 (M − Cl, 19)); and 2,5-dichloropyrrole (mass spectrum, *m/e* (relative intensity) 139 (M + 4, 10), 137 (M + 2, 57), 135 (M, 100), 100 (M − Cl, 17), 74 (M − Cl − CN, 17), 73 (M − Cl − HCN, 81)] were analyzed under the same conditions. The mass spectrum of 3-chloropyrrole [mass spectrum, *m/e* (relative intensity) 103 (M + 2, 30), 101 (M, 100), 74 (M − HCN, 16), 66 (M − Cl, 15)] was quite similar to that of 2-chloropyrrole (**3**). 3-Chloropyrrole was isolated as follows. A solution containing 8.90 g (0.13 mol) of pyrrole in 300 mL of CCl_4 was stirred with 300 mL of NaOCl at 0 °C for 2 h and **2** was isolated as described above. The solution containing **2** was combined with 300 mL of methanol and refluxed for 3.5 h. The solvent was partially removed by evaporative distillation at reduced pressure. To the cooled residue was added 10 g of silica gel G-60 (Merck) and the remaining solvent was removed at reduced pressure. The dry silica gel containing the product mixture was transferred to the top of a column packed with 500 g of silica gel and eluted with *n*-hexane–$CHCl_3$ (1:1, v/v), and 100-mL fractions were collected. Fractions 4–6 contained 2,5-dichloropyrrole and fractions 10–14 contained 3-chloropyrrole. These later fractions were combined, and the solvent was removed by evaporative distillation at reduced pressure. The residue was distilled in a short-path distillation apparatus at 40–42 °C (0.2 mm). A short-lived liquid was obtained which quickly turned blue. Its mass spectrum (see above) and ^1H NMR (CCl_4) [δ 6.00–6.18 (m, 1 H), 6.52–6.70 (m, 2 H)] indicated the formation of 3-chloropyrrole (**4**).

Acknowledgment. This investigation was supported in part by Grant No. 32-26-S1-0641 from the Consejo Nacional de Investigaciones Cientificas y Tecnologicas (CONICIT). We thank Dr. J. D. Medina, Lic. M. Gomez, and Lic. C. Cabello of the Instituto Venezolano de Investigaciones Cientificas (IVIC) for the gas chromatography/mass spectroscopy and Professors A. Rojas and B. Mendez of the Universidad Central de Venezuela for the ^{13}C NMR spectra.

Registry No. **1**, 109-97-7; **2**, 80263-41-8; **3**, 56454-22-9; **4**, 69624-11-9; **5**, 56454-23-0.

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(23) Gronowitz, S.; Hornfeldt, A. B.; Gestblom, B.; Hoffman, R. A. *J. Org. Chem.* **1961**, *26*, 2615. Matteson, D. S.; Snyder, H. R. *Ibid.* **1957**, *22*, 1500.

(24) Methoxide ion has been reported to effect the dechlorination of *N*-chloro and *N,N*-dichloro derivatives of some phosphinic amides (Harger, M. J. P.; Stephen, M. A. *J. Chem. Soc., Perkin Trans 1* **1980**, 705). Reductive dechlorination of 3-chloro-3*H*-indoles with SCN^- has been reported to give 6-thiocyanoindoles by a mechanism analogous to that proposed in this work (Tamura, Y.; Chun, M. W.; Nishida, H.; Ikeda, M. *Heterocycles* **1977**, *8*, 313).

(25) The reaction mixture also contained an unidentified compound (retention time 4.03 min) whose mass spectrum indicated that it did not contain chlorine.