

EFFECT OF HALOGEN ON THE REACTION OF 1-METHYLPYRROLE WITH N-HALOIMIDES.

Michael De Rosa* and Gustavo Cabrera Nieto

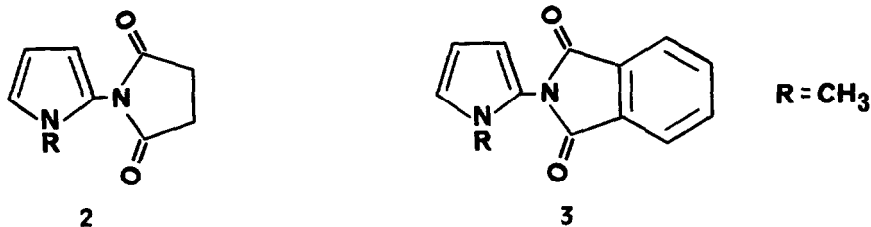
Departamento de Quimica, Universidad Simon Bolivar, Caracas, Venezuela 1080-A

Abstract: In the reaction of N-haloimides with 1-methylpyrrole, σ -substitution (addition-elimination) predominates over halogenation, when the halogen is chlorine.

Electrophilic aromatic substitution occurs because rearomatization of the initially formed σ -complex is faster than its reaction with a nucleophile. This has been attributed to a lower activation energy for the rearomatization step.¹ A number of examples exist in which addition to the aromatic nucleus is also observed.² Recently we reported that the reaction of 1-methylpyrrole with N-chloroacetanilide gave a product in which an acetanilide moiety was incorporated in the pyrrole ring.³ This is the first example of electrophilic substitution in pyrroles by addition-elimination (σ -substitution).⁴ Formation of this product was attributed to the nucleophilicity of the acetanilide anion in the initially formed ion pair and the effect of a 2-chloro substituent on the aromaticity of the pyrrole ring.³ A similar argument has been used to explain electrophilic substitution in furans by addition-elimination.⁵ Calculations have indicated that π -electron donors at C-2 increase the dienic character of the pyrrole ring.⁶ This enhanced dienic character should also be reflected in the energies of the transition states leading to the addition and substitution products and make addition competitive with substitution. σ -Substitution should also be observed when other nucleophilic anions are present and depend on the π -electron donating ability of the halogen. The results of this work are in accord with these suggestions.

Equimolar amounts of 1-methylpyrrole (1) and N-chlorosuccinimide (NCS) were combined in CHCl_3 (CDCl_3) containing NaHCO_3 and after 4 h no NCS could be detected iodometrically. There was obtained a 76% yield⁷ of imide 2 in

the presence of base and 33% without base. Base (NaHCO_3) suppresses the acid catalyzed chlorination of 1 to give chloropyrroles³.



Previously the reaction of 1-methylpyrrole (1) with NCS in THF has been reported to give only chloropyrroles.⁸ Reexamination of this reaction in THF indicated a trace (3%) of 2 in the absence of base; but 24% when NaHCO_3 was present. These results indicated that not only base but also solvent influence the yield of σ -substitution product. This was further demonstrated by carrying out the reaction between 1 and NCS in C_6D_6 , CH_2Cl_2 and CCl_4 (Table 1).

Table 1. Influence of Reaction Conditions on Yield of σ -Substitution Product

N-Halo Deriv. ^a	Solvent	% Yield ^b	
		Base ^c	No Base
NCS	CDCl_3	74	33
NCS	THF	24	3
NCS	C_6D_6	70	trace ^d
NCS	CH_2Cl_2	47	31
NCS	CCl_4	7	trace ^d
NBS	CDCl_3	0	0
NIS	CDCl_3	<5	0
NCP	CDCl_3	81	66
NBP	CDCl_3	0	0
NIP	CDCl_3	<5	0

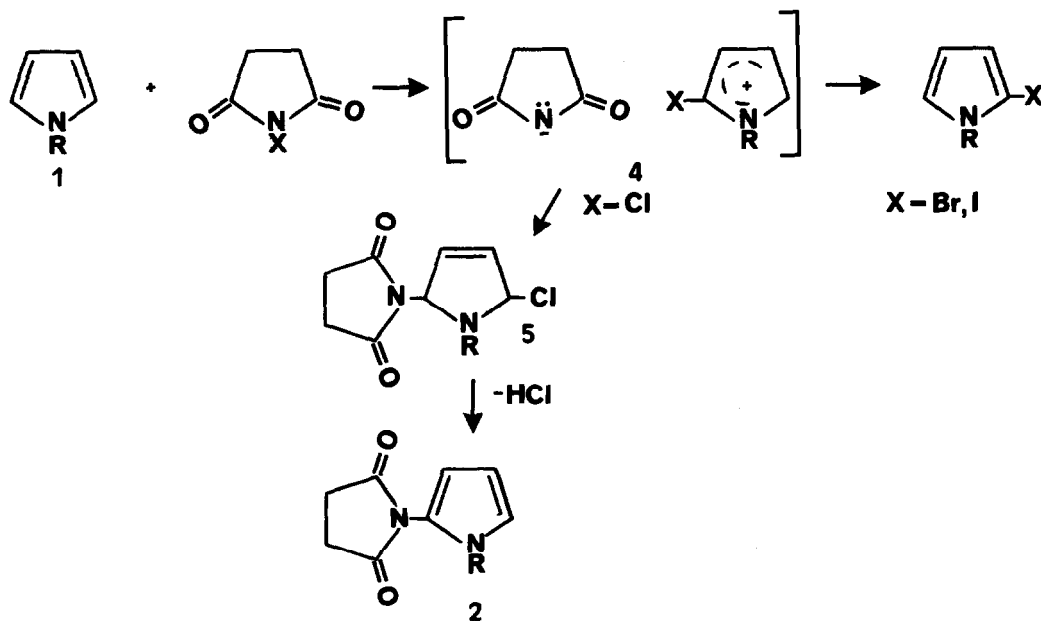
^aNCS, NBS and NIS are N-chloro-, N-bromo- and N-iodosuccinimide respectively. NCP, NBP and NIP are N-chloro-, N-bromo- and N-iodophthalimide respectively.

^bReactions run in 1.0 ml of solvent containing 0.2 mmole each of 1 and halogenating agent. Yields determined by ^1H NMR except in THF. In THF reactions run on a larger scale and product isolated. Preparative reactions run on a 5-10 mmolar scale.

^c NaHCO_3 . ^d<1%.

The halogen effect was determined by reacting 1 with *N*-bromosuccinimide (NBS) and *N*-iodosuccinimide (NIS) in $\text{CDCl}_3/\text{NaHCO}_3$. Only with NIS was a trace (<5%) of σ -substitution product observed (Table 1). When NBS was used only 2-bromo-1-methylpyrrole (57%) and 2,5-dibromo-1-methylpyrrole (16%) were formed and with NIS, 2-iodo-1-methylpyrrole (63%) and 2,5-diiodo-1-methylpyrrole (12%) were the principal products.⁹ To confirm these results the reaction of 1 with *N*-halophthalimides (Cl, Br and I)¹⁰ in $\text{CDCl}_3/\text{NaHCO}_3$ was studied. Only with the *N*-chloro derivative was an appreciable yield of the σ -substitution product obtained (Table 1) and a 81% yield of imide 3 was detected by ^1H NMR.⁷

The reaction of 1 and NCA must lead initially to an ion pair (4) composed of a σ -complex and the conjugate base of the imide (Scheme 1).³ The conjugate base can either deprotonate the σ -complex to give a halopyrrole or react with it to give adduct 5. Collapse of ion pair 4 to adduct 5 is favored in solvents of low to medium polarity where tight ion pairs are stable. Solvent separated ion pairs are favored in solvents of high polarity. The results (Table 1) indicate that this leads to deprotonation of the σ -complex to give chloropyrrole. Results in CCl_4 reflect the insolubility of NCS in this solvent.



In the reaction of N-haloimides (Cl, Br, I) with 1, the only difference in the initially formed ion pair 4 is the nature of the halogen (Scheme 1). Therefore the almost complete dichotomy between σ -substitution (Cl) and halogenation (Br, I) is a function of the halogen. This is attributed to the greater electron donating ability of chlorine¹¹ (as measured by σ_R). A chlorine atom would be expected to influence the aromatic character⁶ of the pyrrole ring to a greater extent than either bromine or iodine and thus favor collapse of the ion pair to the 2,5-adduct to a greater extent.

It is also possible that the dramatic difference in product distribution is caused by a difference in mechanism. The results of this study do not conclusively rule out this possibility.

References

1. L. Stock, "Aromatic Substitution Reactions", Prentice-Hall, Englewood Cliffs, NJ, 1968.
2. P. B. D. de la Mare, Acc. Chem. Res., 1974, 7, 361.
3. M. De Rosa and I. Brillembourg, J. Chem. Soc., Chem. Commun., 1986, 1585.
4. P. Kovacic and J. A. Levisky, J. Am. Chem. Soc., 1966, 88, 1000.
5. J. A. and G. F. Smith, "Heterocyclic Chemistry", Van Nostrand Reinhold, London, 1972, pp 189-190.
6. J. Kao, A. L. Hinde and L. Radom, Nouv. J. Chim., 1979, 3, 473.
7. Imide 2: ¹H NMR(CDCl₃) δ 6.78-6.65 (m, C5-H, $J_{3-5}=2.1$ Hz, $J_{4-5}=3.2$ Hz); 6.33-6.05 (m, C3-H and C4-H, $J_{3-4}=4.0$ Hz, $J_{3-5}=2.1$ Hz, $J_{4-5}=3.2$ Hz); 3.43 (s, 3H, NCH₃); 2.92 (s, 4H) ppm. Imide 3: ¹H NMR(CDCl₃) δ 8.10-7.67 (m, Arom. 4H); 6.80-6.65 (m, C₅-H); 6.30-6.13 (m, C₃-H and C₄-H); 3.52 (s, 3H, NCH₃) ppm.
8. H. M. Gilow and D. E. Burton, J. Org. Chem., 1981, 46, 2221.
9. Halopyrroles were isolated by column chromatography and identified by their respective ¹H NMR.
10. H. Zimmer and L. F. Audrith, J. Am. Chem. Soc., 1954, 76, 3856 (NCP). A. Kergomard, Bull. Soc. Chim. France, 1961 2360 (NBP). V. D. Vanker and G. Kumaravel, Tetrahedron Lett., 1984, 25, 233 (NIP by the same method authors used to prepare NIS).
11. J. Shorter, "Correlation Analysis in Organic Chemistry: An Introduction to Linear Free-Energy Relationships", Clarendon Press, Oxford, 1973, p 18.

(Received in USA 4 August 1987)