Nucleophilic Aromatic Substitution in the Pyrrole Ring

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SUMMARY 2,5-Dinitro-1-methylpyrrole undergoes nucleophilic aromatic substitution by piperidine and methoxide ion in mild conditions.

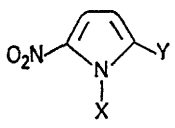
To date there have been no reports on bimolecular nucleophilic substitution in the pyrrole series. We now describe two examples of the reaction of 2,5-dinitro-1-methylpyrrole (I) with nucleophilic reagents.[1]

In Me_2SO compound (I) (0·11 M) reacts with piperidine (0·43 M) to give the substitution product (II). At room temperature the reaction, followed by t.l.c., is complete in nearly three days. The product (m.p. 79—80°C) is identified by its n.m.r. spectrum [τ (CCl_4) 3·12 (1H, d, J 4 Hz), 4·51 (1H, d, J 4 Hz), 6·32 (3H, s), 7·02—7·23 (4H, broad m), 8·37 (6H, m)] and mass spectrum (M^+ at m/e 209).

The displacement reaction on (I) proceeds even more rapidly with methoxide ion. When (I) (0·2 M) is treated with 0·2 M methoxide ion in methanol solution, at 40 °C, the reaction is complete within two minutes and yields 2-methoxy-1-methyl-5-nitropyrrole (III). This product (m.p. 120—121 °C) is identified by its n.m.r. spectrum [τ (CCl_4) 3·03 (1H, d, J 4 Hz), 4·67 (1H, d, J 4 Hz), 6·10 (3H, s), 6·27 (3H, s)] and mass spectrum (M^+ at m/e 156).

Presumably, a major contributing factor to the ease of

these reactions is the fact that the substrate bears an *N*-methyl group rather than an *N*-hydrogen atom. This avoids N-H ionization in the presence of strong bases and the consequent lowering of the ring reactivity.[2]



	X	Y
(I)	Me	NO_2
(II)	Me	NC_5H_{10}
(III)	Me	OMe
(IV)	CH_2-CH_2OH	COMe

The displacement is also assisted by the activating effect of nitro groups in conjugated positions and by the good-leaving character of the nitro group.[3] The reaction with the amine is favoured by the known accelerating effect of Me_2SO on aromatic substitution by neutral nucleophiles.[4]

The closest available example of nucleophilic aromatic substitution at the pyrrole ring involves the intramolecular displacement[5] of the nitro group from 2-acetyl-1-(2-hydroxyethyl)-5-nitropyrrole (IV) to give 5-acetyl-2,3-dihydropyrrolo[2,1-*b*]oxazole. This nucleophilic reaction on a pyrrole ring, which is presumably favoured by the entropic factor (five-membered ring cyclization), has been viewed[6] as a rather exceptional one. In fact, our results show that activated *N*-substituted pyrrole derivatives do undergo bimolecular nucleophilic substitution under mild conditions.

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[1] For preceding work in this field see F. De Santis and F. Stegel, *Tetrahedron Letters*, 1974, 1079.
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[6] A. Gossauer, 'Die Chemie der Pyrrole,' Springer, Berlin, 1974, p. 323.