Different Behaviour of Secondary and Primary Amines towards 1-Alkyl-3,4-dinitropyrroles

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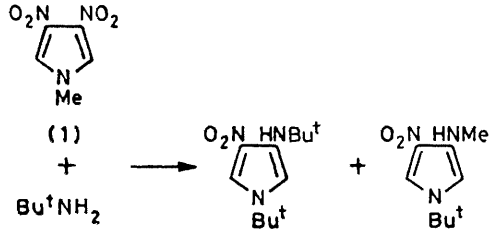
Summary The reaction of 1-alkyl-3,4-dinitropyrroles with secondary amines gives nucleophilic aromatic *cine* substitution (formation of 1-alkyl-2-amino-4-nitropyrroles), whereas the reaction with primary amines follows a more complicated pattern, involving mainly a multistep ring-opening and ring-closure process, and also yielding the product of formal direct substitution, but not that of *cine* substitution

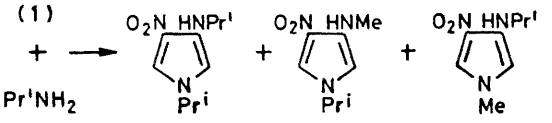
WE have recently described the formation of the product of either direct or *cine* substitution[1] upon base or, respectively, acid promoted decomposition of *trans*-1-alkyl-4,5-dimethoxy-3-nitro-2-pyrrolines, formed from 1-alkyl-3,4-dinitropyrroles and methoxide ion in methanol.[2] Here we describe the behaviour of 1-alkyl-3,4-dinitropyrroles towards secondary and primary amines in MeCN.

Secondary amines give mainly nucleophilic aromatic *cine* substitution. Thus, 1-methyl-3,4-dinitropyrrole (0.024 M) (**1**) reacts with two equiv. of piperidine in refluxing MeCN (30 h) to yield (90% of the reaction products) 1-methyl-2-piperidino-4-nitropyrrole, m.p. 102.5—103.5 °C, M^+ 209 *m/e*. Characterizing features of this product are two doublets (J 2.25 Hz) in the low field region of the ^{1}H n.m.r. spectrum (CCl_4), at δ 6.0 and 7.1, and of the ^{13}C n.m.r. spectrum ($CDCl_3$), at δ 118.9 and 92.0 p.p.m., with coupling constants, 193 and 178 Hz, respectively, showing coupling with hydrogen atoms at the α and β positions,[3] the u.v. spectrum, λ_{max} (MeOH) 281 and 358 nm (log ε 3.86 and 3.58) is very similar to that of 2-methoxy-1-methyl-4-nitropyrrole[1] [λ_{max} (MeOH) 280 and 359 (log ε 3.84 and 3.62)]. 2,3-Dinitro-1,4-dipiperidino-buta-1,3-diene (**2**), is formed in small yield (3%) upon ring-opening. This is the only product obtained when 3,4-dinitrothiophen reacts with piperidine in methanol.[4] Because of the concomitant presence of secondary amines and NO_2^- ions, carcinogenic *N*-nitrosoamines are formed during these reactions. So far, the reaction of piperidine or other secondary amines is the first *cine* substitution of 1-alkyl-3,4-dinitropyrroles.



SCHEME 1

In contrast with secondary amines, primary amines do not give *cine* substitution products but yield 1-alkyl-3-*N*-alkylamino-4-nitropyrroles (Schemes 1 and 2). Also a product formed from direct substitution may be detected (only in very small amounts, with, for instance, isopropylamine).



SCHEME 2

3-Alkylamino-4-nitro derivatives were characterized by ^{1}H n.m.r. spectra (coupling constants larger than in 2,4-disubstituted pyrroles) and u.v. spectra. Owing to the possibility of ionization and tautomerization of *N*-alkylamino derivatives, they were converted into *N*,*N*-dialkylaminopyrroles with MeI. Thus, while the former display absorption maxima at 310—320 and 430—440 nm, the corresponding tertiary amines show only one maximum, at 310—315 nm. Also 3-alkoxy-1-alkyl-4-nitropyrroles display only one absorbance maximum, at nearly 300 nm.[1] In a typical experiment (**1**) (0.04 M) reacted with t-butylamine (100 equiv.) in refluxing MeCN (20 h) to yield (Scheme 1) 1-t-butyl-3-(*N*-t-butylamino)-4-nitropyrrole, 15%, m.p. 137.5—139 °C, M^+ 239 *m/e*, δ (CCl_4) 1.32 (s, 9H), 1.55 (s, 9H), 5.5 (broad, 1H), 6.02 (d, 1H, J 3 Hz), 7.34 (d, 1H, J 3 Hz), and 23% of 1-t-butyl-3-(*N*-methylamino)-4-nitropyrrole (**3**), m.p. 91—92 °C, M^+ 197 *m/e*, δ (CCl_4) 1.55 (s, 9H), 2.81 (s, 3H), 5.91 (broad, 1H), 5.94 (d, 1H, J 3 Hz), and 7.32 (d, 1H, J 3 Hz). These products were isolated after evaporation of the solvent and extraction with CCl_4. They were separated from each other and unreacted (**1**) by chromatography on silica-gel with C_6H_6–$MeCO_2Et$ 95/5. Methylation of (**3**) with MeI in Me_2SO yielded 1-t-butyl-3-(*NN*-dimethylamino)-4-nitropyrrole, m.p. 44.5—45.5 °C, M^+ 211 *m/e*, δ (CCl_4) 1.55 (s, 9H), 2.66 (s, 6H), 6.18 (d, 1H J 3 Hz), and 7.48 (d, 1H, J 3 Hz), λ_{max} (MeOH) 310 nm (log ε 3.97).

Reaction of 1-t-butyl-3,4-dinitropyrrole (0.024 M) with an excess of Me_2NH (25 equiv.), in MeOH–MeCN, at 80 °C (sealed tube) afforded the isomeric *cine* substitution product, 1-t-butyl-2-(*NN*-dimethylamino)-4-nitropyrrole, m.p. 69.5—70 °C, M^+ 211 *m/e*, δ (CCl_4) 1.65 (s, 9H), 2.61 (s, 6H), 6.41 (d, 1H, J 2.25 Hz), and 7.19 (d, 1H, J 2.25 Hz), λ_{max} (MeOH) 280 and 336 nm (log ε 3.85 and 3.72).

A wider range of products (Scheme 2), including the formal product obtained from direct substitution, was obtained from (**1**) and the less bulky isopropylamine (40 equiv. in refluxing MeCN for 2.5 h).

The different behaviour of secondary and primary amines had already been recognized in the reaction of some *ortho* dinitrobenzene derivatives. Thus, 2,3-dinitrophenyl alkyl ethers undergo *cine* substitution with secondary amines,[5] but direct substitution with primary amines (at position 2),

2,3-dinitrophenol gives *cine* substitution with secondary amines, whereas primary amines do not react at all [5] Other *cine* substitutions reported so far with amines involved secondary amines [6] The reasons for the different behaviour of primary and secondary amines have not yet been investigated

The reaction with primary amines where the nitrogen atom initially bearing the alkyl group finally becomes exocyclic, whereas the nitrogen atom of the nucleophile is incorporated in the ring, is analogous to the amination of six-membered aza- and poly-aza heteroaromatic compounds with NH_2^- ion in liquid ammonia, involving addition of the nucleophile, ring-opening, and ring-closure, as recognized by van der Plas [7] However this kind of mechanism is novel for the pyrrole system The ready ring-closure of (**2**) with primary amines to yield 1-alkyl-3-(*N*-alkylamino)-4-nitropyrroles gives valid support to this pathway [8] A ring-opening, ring-closure reaction has also been observed in the reaction of pyrroles with nitrenes [9] It is possible also that the observed direct substitution involves the ring-opening ring-closure route, instead of the addition–elimination mechanism

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