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# UNUSUAL ORIENTATION IN VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN IN NITROPYRROLES[1]

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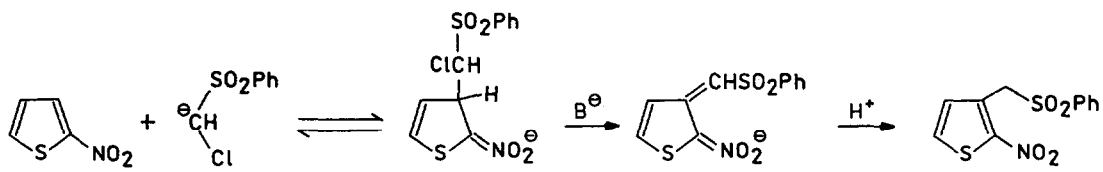
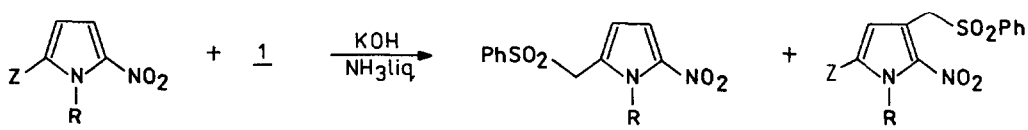
**Summary:** *The vicarious nucleophilic substitution of hydrogen in N-substituted 2-nitropyrrole with carbanion of chloromethyl phenyl sulfone occurs at position 5- or 3- depending upon electronic effects of the N-protecting group.*

In our preceding papers[2] we have reported the vicarious nucleophilic substitution of hydrogen[3] (VNS) in some nitro derivatives of five-membered heterocycles with chloromethyl phenyl sulfone (1) which, for example, with 2-nitrothiophene proceeds according to the following scheme.

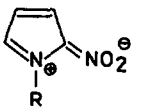


The position of the substituent entering into 2-nitrothiophene and 2-nitrofuran rings was established by means of NMR spectroscopy[4ab] and was unambiguously confirmed by chemical methods[2a]. Since 2-nitropyrrole is a strong NH-acid its N-methyl derivative 2 was used in this reaction to give a single product. On the basis of insufficiently diagnostic NMR data (the difference of values between $J_{H3-H4}$ and $J_{H4-H5}$ for substituted 2-nitropyrroles lies within the range of 1Hz[4c]), and mainly by analogy to nitrothiophene and nitrofuran, we have incorrectly claimed this product to be 1-methyl-2-nitro-3-phenylsulfonylmethylpyrrole 2b.[2a]

Recent detailed spectroscopic data[5] have raised doubts concerning this assignment, therefore the site of the substitution in 2 was determined by the reaction with 1-methyl-2-nitro-5-deuterio-pyrrole 3 prepared *via* nitration of 1-methyl-2,5-dideuteriopyrrole[6]; (due to some exchange[4d] during the nitration, 3 contained 40% of the isotopic label). The VNS reaction with 3 provided a product in which no deuterium was present, thus the product is 1-methyl-2-nitro-5-phenylsulfonylmethylpyrrole 2a; blank experiment has shown no significant isotope exchange under the VNS reaction conditions. Similarly N-*n*-propyl- and N-*iso*propyl-2-nitropyrrole 4 and 5 reacted with 1 only at C-5 to form 4a and 5a.



| | | | |
|---|---|---|---|
| Z = H; R = Me 2; *n*-Pr 4; *i*-Pr 5. | 2a 90%; 4a 93%; 5a 49% | – |
| D; Me 3; | 2a 88% | – |
| H; *p*-TolSO$_2$ 6 | – | 6b 72% |
| H; MeOCH$_2$ 7 | 7a 55% | 7b 12% |



2i

This dramatic difference in the VNS orientation between 2 (also 3, 4 and 5) and 2-nitrothiophene and furan can be rationalized by consideration of conjugation between the electron pair of the ring nitrogen atom and the nitro group, described by the resonance structure 2i[7], which would promote nucleophilic addition to C-5. A similar rationalization was proposed for the VNS orientation in dinitrophenols and nitroanilines[8].

Such a rationalization has been further supported by the VNS in 1-p-toluenesulfonyl-2-nitropyrrole 6, in which the strongly electron withdrawing substituent at the nitrogen atom eliminates such conjugation and therefore the substitution takes place at C-3 to give 6b. The methoxymethyl substituent in 7 occupies an intermediate position between alkyl and sulfonyl groups in terms of electronic effects, therefore the reaction yielded both isomeric products 7a and 7b in ratio 5:1.

The reported results are unique examples of direct chemical manifestation of the conjugative effects in pyrrole rings. As demonstrated it is thus possible to control the orientation of nucleophilic reactions in the nitropyrrole ring.

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## References and notes

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4. Comprehensive Heterocyclic Chemistry, Ed. A.R.Katritzky, Pergamon Press, 1984, Vol. 4; a)730; b) 558; c) 166; d) 206.
5. Coupling constants for the pyrrole ring protons (500 MHz, $^1$H NMR) $J_{3,4}$: for 2a = 4.2 Hz, 4a = 4.2 Hz, 5a = 4.1 Hz, 7a = 4.3 Hz; $J_{4,5}$ for: 6b = 3.55 Hz, 7b = 3.0 Hz.
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7. J.Kao, A.K.Hinde, L.Radom, *Nouv.J.Chem.*, 1979 , 3, 473.
8. M.Mąkosza, S.Ludwiczak, *J.Org.Chem.*, 1984, 49, 4562; S.Ludwiczak, Ph.D. Thesis, Warsaw Technical University, 1985.
9. A typical reaction procedure. To a stirred suspension of powdered KOH (0.02 mol) or $^t$BuOK (0.0075 mol) in liquid ammonia (25 mL) a solution of nitroaromatic compund (0.0025 mol) and the CH-acid (0.0025 mol) in THF (3 ml) was added dropwise. The intensively coloured mixture was stirred for 1 h. $NH_4Cl$ (1g) was added and the ammonia was evaporated. The residue was poured into diluted HCl, extracted with $CHCl_3$ and dried over $Na_2SO_4$. The products were separated by column chromatography on silica gel (various hexane/ethyl acetate mixtures as eluent) and purified by crystallization. Selected analytical data: Compound 2a; m.p.163.5-164.5°C (MeOH), $^1$H NMR ($CDCl_3$, δ ): 3.87(s,3H); 4.40(s,2H); 5.87(d,J=4.2Hz,1H); 7.10(d,J=4.2Hz,1H); 7.50-7.76(m,5H). Compound 4a; m.p.127-128°C ($CH_3OH$), $^1$H NMR ($CDCl_3$,δ): 0.9(t, J=7.0Hz,3H); 1.68(m,2H); 4.32(t,J=7.0Hz,2H); 4.48(s,2H); 5.91(d,J=4.2Hz,1H); 7.19(d,J=4.2Hz,1H); 7.62-7.90(m,5H). Compound 5a; m.p.108-109°C (MeOH) ,$^1$H NMR ($CCl_4$, δ): 1.47(d,J=7Hz,6H); 4.46(s,2H); 5.65-5.85(m,1H); 6.11(d,J=4.1,H); 6.88-7.85(m,6H). Compound 6b; m.p.173-176°C (EtOH), $^1$H NMR ($CDCl_3$, δ ): 2.52(s,3H); 4.80(s,2H); 6.56(d,J=3.55Hz,1H); 7.46-7.49(m,2H); 7.58(d,J=8.5Hz,2H); 7.60-7.66(m,3H); 7.85(d, J=3.55Hz,1H); 7.95(d,J=8.5Hz,2H). Compound 7a; m.p.96-98°C (MeOH), $^1$H NMR ($CDCl_3$, δ): 3.27(s,3H); 4.54(s,2H); 5.86(s,2H); 5.98 (d,J=4.3Hz,1H); 7.15(d,J=4.3Hz,1H); 7.54-7.58(m,2H); 7.68-7.72 (m,1H); 7.76-7.79(m,2H). Compound 7b; m.p.132-134°C (MeOH), $^1$H NMR ($CDCl_3$,δ): 3.28(s,3H); 4.80(s,2H); 5.56(s,2H); 6,50(d, J=3.0Hz,1H); 6.98(d,J=3.0Hz,1H); 7.47-7.49(m,2H); 7.59-7.63(m, 1H); 7.74-7.76(m,2H).

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