INTRAMOLECULAR VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN IN 3-NITROCHLOROACETANILIDES. A SYNTHESIS OF OXINDOLE DERIVATIVES

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Abstract - 3-Nitrochloroacetanilides were treated with a strong base to form the \( \alpha \)-chlorocarbanions, which enter intramolecular reaction with the nitroaromatic rings producing nitrooxindoles.

The vicarious nucleophilic substitution of hydrogen (VNS) is a general method for nucleophilic alkylation,\(^1\) hydroxylation,\(^2\) and amination\(^3\) of nitroarenes. We have also reported an intramolecular variant of this process for \( N \)-nitroaryl- and \( N \)-nitrobenzylchloromethanesulfonamides.\(^4\) In this paper we would like to report an intramolecular VNS reaction of chloroacetanilide derivatives leading to 5-membered heterocyclic systems, nitrooxindoles. Although there are no reported examples of an intermolecular VNS reaction of chloroacetamide derivatives with nitroarenes, there is a reasonable supposition that it should proceed satisfactorily in analogy to \( \alpha \)-halonitriles and \( \alpha \)-haloesters.\(^5\) Indeed, in a few preliminary experiments we have found that \( N,N \)-diethylchloroacetamide carbanion reacted with \( p \)-chloronitrobenzene replacing \( \text{ortho} \)-hydrogen to the nitro group to give \( N,N \)-diethyl-5-chloro-2-nitrophenylacetamide. Conventional nucleophilic replacement of the halogen was not observed in these experiments.

Since the VNS reaction proceeds in positions \( \text{ortho} \) and \( \text{para} \) to the nitro group, \( N \)-chloroacetyl- and \( N \)-\( \alpha \)-chloropropionyl \( m \)-nitroanilines (1a-f) were chosen as the starting materials. They were prepared \textit{via} acylation of \( N \)-propyl-3-nitro- and 2-fluoro-5-nitroanilines, and \( N \)-methyl-2-methoxy-5-nitroaniline with chloroacetyl and \( \alpha \)-chloropropionyl chlorides. The corresponding substituted \( N \)-alkyl- nitroanilines were prepared according to known procedures: reductive \( N \)-propylation with propionaldehyde or \( N \)-methylation of the \( N \)-formyl derivative followed by hydrolysis. After some preliminary experiments we have found that the intramolecular VNS reactions of 1a-f proceeded satisfactorily when carried out in the presence of an excess of \( t \)-BuOK in DMF. Results of these reactions are given in Scheme.

\(^{*} \text{Dedicated to Professor Alan R. Katritzky on the occasion of his 65th birthday} \)
It is rather surprising that the reaction proceeded exclusively ortho to the nitro group even with the tertiary carbanions of 1d-f. We were unable to find other isomers in all these experiments. Tendency for the ortho substitution was observed previously in the intramolecular reactions of chlorosulfonamides, however, in those cases the products of the para substitution were also isolated and characterized. As in other cases of the VNS reactions of halonitrobenzenes with α-chlorocarbanions we observed strong preference for the VNS of hydrogen over S_Ar of halogen even fluoride (1b and 1e).

The reported reaction offers a new and simple method for synthesis of substituted oxindoles. It is in principle a process analogous to the Friedel-Crafts type cyclization of chloroacetanilide derivatives proceeding with the same stoichiometry but reverted polarity.

EXPERIMENTAL
Melting points are uncorrected. 1H-Nmr spectra were recorded on Varian Gemini 200 spectrometer in CDCl3 or C6D6 with TMS as a reference. Chemical shifts are given in ppm, coupling constants J in Hertz. High-resolution mass spectra were measured on AMD 604 spectrometer. For column chromatography silica gel 240-400 mesh (Merck) and hexane-ethyl acetate as eluent were used.

2-X-Nitro-N-propylanilines (X=H,F,MeO) were prepared via reductive propylation of the corresponding commercial anilines with propionaldehyde according to the lit. and converted to the α-chloroacyl derivatives (1a-f) via acylation with chloroacetyl chloride and α-chloropropanoyl chloride in the presence of 10% aqueous NaOH in benzene (1a,c,d,f) or NaH in DMF (1b,e).

1a: yield 64%, mp 48-49.5°C. 1H Nmr (CDCl3): 0.64 (t, J=7.4, 3H, CH3), 1.06-1.28 (m, 2H, CH2), 3.30 (s, 2H, CH2), 6.52-6.66 (m, 2H), 7.59-7.67 (m, 2H). Hrms Calcd for C11H9N2O2Cl: 256.0615. Found 256.0614.

1b: yield 66%, mp 73-75°C. 1H Nmr (CDCl3): 0.63 (t, J=6.8, 3H, CH3), 1.04-1.26 (m, 2H, CH2), 3.35 (s, 2H,
**N,N-Diethyl-(5-chloro-2-nitrophenyl)acetamide.** A solution of p-chloronitrobenzene (3.2 g 20 mmol) and N,N-diethylchloroacetamide (3.0 g 20 mmol) in dry DMF (20 ml) was added at -20°C to a stirred solution of t-BuOK (11.2 g, 100 mmol), in dry DMF (30 ml). After 25 min the addition was completed and blue mixture was stirred for an additional hour at -20°C, and poured into cold hydrochloric acid (200 ml). After extraction with AcOEt (3 x 30 ml) and evaporation of the solvent the residue was chromatographed (AcOEt-hexane 1:8) to give the product 4.6 g, yield 85% oil. 1H Nmr (CDCl3): 1.11 (t, J=7.1, 3H, CH3), 1.29 (t, J=7.1, 3H, CH3), 3.31-3.48 (m, 4H, 2 x CH2), 4.03 (s, 2H, CH2), 7.31 (d, J=2.3, 1H), 7.38 (dd, J=3.7, 2.3, 1H), 8.03 (d, J=8.7, 1H). Hrms (m/z): 270.0771 (M+Cl, C12H13N2O2Cl, calcd 270.0772). Anal. Calcd for C12H13N2O2Cl: C, 53.24; H, 5.58; N, 10.35. Found: C, 52.99; H, 5.70; N, 10.35.

**1-Alkyl-4-Nitro-7-Oxindoles.**

1a: yield 77%, mp 149-151°C. 1H Nmr (CDCl3) of rotamers): 1.41 and 1.46 (2 x d of rotamers, J=6.4, 3H, CH3), 2.79 and 2.83 (2 x s of rotamers, 3H, NCH3), 2.93 and 2.97 (2 x s of rotamers, 3H, OCH3), 3.81 and 3.94 (2 x q of rotamers, J=6.4, 1H, CH3), 5.83 and 5.92 (2 x d of rotamers J=9.2, 1H, H-5), 7.78 (d, J=9.2, 1H, H-6), 8.13 (d, J=1.8, 1H, H-2). Hrms Calcd for C17H14N2O2Cl: 273.0564. Found 273.0564.

<table>
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2a: yield 62%, mp 112-113°C (96% EtOH). 1H Nmr (CDCl3) 0.99 (t, J=7.4, 3H, CH3), 1.72 (sext, J=7.4, 2H, CH2), 3.73 (t, J=7.4, 2H, CH2), 4.01 (s, 2H, CH2), 7.12 (d, J=7.9, 1H), 7.47 (dd, J=8.4, 7.9, 1H), 7.85 (d, J=7.9, 1H). Hrms (m/z): 220.0851 (M+, C11H12N2O3, calcd 220.0847). Anal. Calcd for C11H12N2O3: C, 59.99; H, 5.50; N, 12.72. Found: C, 59.85; H, 5.49; N, 12.42.

2b: yield 64%, mp 116-117°C (96% EtOH). 1H Nmr (CDCl3): 0.89 (t, J=7.5, 3H, CH3), 1.62 - 1.82 (m, 2H, CH2), 3.86 (dt, J=7.5, 1.6, 2H, CH2), 4.05 (s, 2H, CH2), 7.19 (d apparent t, J=9.3, 7.2, 1H), 7.84 (dd, J=9.3, 3.9, 1H). Hrms (m/z): 238.2175 (M+, C11H11N2O4F, calcd 238.2179). Anal. Calcd for C11H11N2O4F: C, 55.46; H, 4.65; N, 11.76. Found: C, 55.30; H, 4.68; N, 11.50.


\[ **NO_2** - position 1 for all assignment of H in the aromatic rings. \]
for C₁₉H₁₉N₂O₄: C, 54.06; H, 4.54; N, 12.61. Found: C, 53.97; H, 4.41; N, 12.62.

2d: yield 68%, mp 72-72.5°C (96% EtOH) ¹H Nmr (CDCl₃): 0.97 (t, J=7.4, 3H, CH₃), 1.52 (d, J=7.4, 3H, CH₃), 1.72 (sex, J=7.4, 2H, CH₂), 3.61 and 3.84 (m, 2H, CH₂), 4.03 (q, J=7.4, 1H, CH), 7.13 (d, J=7.8, 1H, H₄), 7.45 (apparent t, J=7.8, 1H, H₅, 7.81 (dd, J=8.4, 0.9, 1H, H₆). Hrms (m/z): 234.1002 (M⁺, C₁₉H₁₉N₂O₄, calc. 234.1004). Anal. Calcd for C₁₉H₁₉N₂O₄: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.52; H, 6.00, N, 11.74.

2e: yield 57%, mp 96-97°C (96% EtOH). ¹H Nmr (CDCl₃): 0.96 (t, J=7.5, 3H, CH₃), 1.53 (d, J=7.4, 3H, CH₃), 1.62-1.90 (m, 2H, CH₂), 3.81-3.91 (m, 2H, CH₂), 4.07 (dq, J=7.4, 0.6, 1H, CH), 7.20 (ddd, J=10.5, 9.2, 0.6, 1H, H₅), 7.83 (dd, J=9.2, 3.9, 1H, H₆). Hrms (m/z): 252.0908 (M⁺, C₁₂H₁₄N₂O₂F, calc. 252.0910). Anal. Calcd for C₁₂H₁₄N₂O₂F: C, 57.17; H, 5.20; N, 11.11. Found: C, 57.07; H, 5.24; N, 11.22.

2f: yield 37%, mp 166-167°C (96% EtOH). ¹H Nmr (CDCl₃): 1.50 (d, J=7.4, 3H, CH₃), 3.51 (s, 3H, NCH₃), 3.97 (s, 3H, OCH₃), 4.02 (q, J=7.4, 1H, CH), 6.93 (d, J=9.2, 1H, H₅), 7.83 (d, J=9.2, 1H, H₆). Hrms (m/z): 236.0790 (M⁺, C₁₁H₁₂N₂O₄, calc. 236.0797). Anal. Calcd for C₁₁H₁₂N₂O₄: C, 55.96; H, 5.12; N, 11.87. Found: C, 55.69, H, 5.04; N, 11.63.

REFERENCES

Received, 20th October, 1993