Synthesis of Substituted Nitrooxindoles via Intramolecular Oxidative Nucleophilic Substitution of Hydrogen in \textit{m}-Nitroacylanilides

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Received 30 April 2002; revised 10 July 2002

Abstract: A simple method of the synthesis of substituted nitrooxindoles via intramolecular oxidative nucleophilic substitution of hydrogen is described.

Key words: nucleophilic aromatic substitution, oxindoles, nitroacylanilides

The indole ring system is present in many natural products, pharmaceuticals, agrochemicals, etc. Thus, there is a continuous quest for efficient methods of synthesis of indole derivatives.\(^1\) Of great interest are also methods of synthesis of oxindoles.\(^2\) Amongst numerous methods applicable for construction of the indole ring, we are particularly interested in those based on nucleophilic substitution of hydrogen in nitroarenes.\(^3\) These methods use two principal approaches. One of them consists in the introduction of substituents \textit{ortho} to the nitro group via vicarious nucleophilic substitution (VNS) or oxidative nucleophilic substitution of hydrogen (ONS\(\text{H}\)). After further transformations of the products, including reduction of the nitro group, the indole ring is formed.\(^4,5\) Alternative approach use \textit{m}-nitroaniline as the basic starting material, its further transformations including the key process of nucleophilic substitution of hydrogen with proper carbanions, leads to nitroindoles in which the nitrogen atom of the amino groups is found in the indole ring.\(^6\) Perhaps the most attractive variant of the latter approach is the recently reported synthesis of nitroindoles via direct condensation of \textit{m}-nitroaniline with enolates of ketones.\(^7\) Nitrooxindoles were prepared via intramolecular VNS reaction of \textit{m}-nitroanilides of \(\alpha\)-halocarboxylic acids.\(^8\)

In this paper, we report that nitrooxindoles can be readily obtained from simpler starting materials, \textit{m}-nitroanilides of carboxylic acids via intramolecular ONS\(\text{H}\) reaction. The reaction consists in the treatment of \textit{m}-nitroanilides of alkanoic acids with a strong base, which abstracts a proton from the acyl moiety. The generated carbanions add intramolecularly to the nitroaromatic ring \textit{ortho/para} to the nitro group giving anionic \(\sigma^\text{II}\) adducts that are subsequently oxidized to form the oxindole ring. Since acidity of NH hydrogen of the \textit{m}-nitroanilides is similar or even higher than that of \(\alpha\)-methyl or \(\alpha\)-methylene protons of the acyl moieties, for the reaction to proceed the NH proton should be replaced by a substituent, for instance, a methyl group. Thus, \(N\)-methyl \textit{m}-nitroanilinides were used in our studies. Amongst a few base-solvent systems typically used for generation of carbanions, \(t\)-BuOK/DMSO at room temperature was found to give the best results. It should be mentioned that formation of oxindoles via the intramolecular ONS\(\text{H}\) reaction of \textit{m}-nitroanilinides is accompanied with a deep blue or red coloration of the reaction mixture because highly colored \(o\)- and \(p\)-nitrobenzylcarbanions are produced. The process and results are presented in Scheme 1 and Table 1.

Intramolecular substitutions of hydrogen in the nitroaryl ring, which proceeds in the vicinity of the amide moiety, can take place in two positions: \textit{ortho} and \textit{para} in relation to the nitro group giving two isomeric 4- and 6-nitrooxindoles \(2\) and \(3\), respectively. In all cases of the \textit{m}-nitroacylanilides studied there was strong preference for the reaction to occur in the more sterically hindered position \textit{ortho} to the nitro group to give \(4\)-nitrooxindoles \(2\) as the main products. Tendency for such orientation was already observed in inter- and intramolecular VNS reactions \(^9\) and also in the synthesis of nitroindoles via the reaction of ketones with \textit{m}-nitroaniline.\(^7\) The intramolecular reaction of carbanions generated from 6-chloro-3-nitroanilinides can proceed via ONS\(\text{H}\) at position 2 to produce 7-chloro-4-nitrooxindoles or by conventional nucleophilic substitution of the halogen (S\(\text{N}\)Ar) to give 6-nitrooxindoles. Although in the reaction of anilides \(1\text{e-h}\) two nitrooxindoles are formed: expected 7-chloro-4-nitrooxindoles and products which do not contain the halogen, the latter were identical to the main products obtained from anilides \(1\text{a-d}\), thus were obviously produced not via intramolecular S\(\text{N}\)Ar of the halogen but via dehalogenation proceeding during the reaction. A similar dehalogenation process was observed in the synthesis of indoles via direct condensation of enolates with 2-chloro-5-nitroaniline.\(^7\) This observation provides additional support to the general rule that nucleophilic addition of carbanions to nitroaromatic rings proceeds usually faster in positions occupied with hydrogen than in those, similarly activated, occupied with halogens.\(^10\) It appears that the anionic \(\sigma^\text{II}\) adducts produced via intramolecular addition of the carbanion of nitroanilinides are oxidized by air oxygen always present in the system. When the reaction of \(1\text{b}\) was carried out in meticulously deoxygenated system, the oxindole was not
formed; on the other hand bubbling of oxygen in the reaction mixture does not change the results.

**Table 1** Substituted Nitrooxindoles 2 (and 3) Prepared

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>R</th>
<th>No</th>
<th>Products, Yield (%)</th>
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<td>8h</td>
<td>Cl</td>
<td>Ph</td>
<td>2h</td>
<td>2d</td>
</tr>
</tbody>
</table>

*Three equivalents of r-ButOK were used.

**Scheme 1**

Commercial DMSO and DMF were distilled over CaH₂ and stored over molecular sieves. Column chromatography was performed using Merck Kieselgel 60. ¹H NMR and ¹³C NMR were recorded on Varian Gemini (200 MHz) and Varian Mercury (400 MHz) spectrometers. Chemical shifts (δ) are given in ppm downfield from TMS. Coupling constants are given in Hz. MS were measured on AMD 604 spectrometer.

Starting materials: 3'-nitroacetanilide, 2'-chloro-5'-nitroacetanilide, N-methyl-3'-nitroacetanilide (1a), N-methyl-2'-chloro-5'-nitroacetanilide (1e) and N-Methyl-2'-chloro-5'-nitroacetanilide (1c) were prepared according to reported procedures. Compounds 1b-d were prepared via acylation of N-methyl-3-nitroanilide with appropriate acyl chlorides, whereas 1f-h were prepared via methylation of appropriate 2'-chloro-5'-nitroanilanilides.

It was observed that ¹H and ¹³C NMR spectra of compounds 1a-h some signals were broadened or doubled. This is caused by restricted internal rotation of N-(C=O) bond and is often observed in the NMR spectra of amides.¹³

**N-Methyl-3-nitropropionanilide (1b): Typical Procedure**

To a solution of N-methyl-3-nitroanilne (4.26 g, 28 mmol) in anhyd toluene (60 mL) were added a solution of propionyl chloride (2.98 g, 32 mmol) in toluene (5 mL) and Et₃N (3.4 g, 33.6 mmol). The mixture was stirred for 3 h at r.t. and treated with H₂O (150 mL) and EtOAc (100 mL). The organic layer was separated washed and dried. The solvents were evaporated and the residue recrystallized from hexane–toluene to give 1b; yield: 4.95 g (85%); mp 64 °C.

¹H NMR (200 MHz, CDCl₃): δ = 1.11 (t, 3 H, J = 7.4 Hz), 2.16 (br, 2 H), 3.34 (s, 3 H), 7.55–7.68 (m, 2 H), 8.08–8.12 (m, 1 H), 8.17–8.24 (m, 1 H).

¹³C NMR (CDCl₃): δ = 9.41, 27.70, 37.37, 122.21, 130.41, 133.32, 145.24, 148.89, 173.40.

MS (EI): m/z (%) = 208 (M⁺, 14), 152 (100), 106 (14), 57 (32).

Anal. Calcd for C₁₀H₁₄N₂O₃: C, 59.45; H, 6.35; N, 12.6. Found: C, 57.33; H, 6.05; N, 13.27.

N-Methyl-3-nitrobutyranilide (1c)

Yield: 87%; mp 51°C (hexane–toluene).

¹H NMR (400 MHz, CDCl₃): δ = 0.88 (br, 3 H), 1.45 (m, 2 H), 2.1 (br, 2 H), 3.34 (s, 3 H), 7.56–7.66 (m, 2 H), 8.09 (m, 1 H), 8.20 (m, 1 H).


MS (EI): m/z (%) = 222 (M⁺, 13), 152 (100), 106 (16), 71 (42), 43 (61).


N-Methyl-3-nitrophenylacetanilide (1d)

Yield: 75%; mp 70–72 °C (hexane–toluene).

¹H NMR (400 MHz, acetone-d₆): δ = 3.22 (br, 3 H), 3.58 (br, 2 H), 7.1 (br, 1 H), 7.16–7.26 (m, 2 H), 7.7–7.78 (m, 3 H), 8.12 (br, 1 H), 8.21 (br, 1 H).

¹³C NMR (CDCl₃): δ = 37.61, 41.67, 96.6, 127.25, 128.99, 131.39, 136.39, 146.21, 149.62.

MS (EI): m/z (%) = 270 (M⁺, 22), 152 (50), 118 (36), 91 (100).


(2')-Chloro-5-nitroacetanilide

Yield: 86%; mp 160 °C (EtOH).

¹H NMR (200 MHz, CDCl₃): δ = 2.28 (s, 3 H), 7.51 (d, 1 H, J = 8.8 Hz), 7.65 (br s, 1 H), 7.86–7.92 (m, 1 H), 9.3 (br s, 1 H).

¹³C NMR (CDCl₃): δ = 24.86, 96.1, 116.27, 118.97, 128.37, 129.49, 135.47, 147.17, 168.33.

MS (EI): m/z (%) = 214 (M⁺, 18), 179 (25), 172 (100), 126 (20), 90 (17), 43 (79).

Anal. Calcd for C₁₁H₁₂ClN₂O₂: C, 44.76; H, 3.36; Cl, 16.59; N, 13.06.

(2')-Chloro-5-nitro)propionanilide

Yield: 71%; mp 124–125 °C (hexane–toluene).

Synthesis 2002, No. 15, 2203–2206 ISSN 0039-7881 © Thieme Stuttgart · New York
1H NMR (200 MHz, CDCl3): δ = 1.3 (t, 3 H, J = 7.5 Hz), 2.54 (q, 2 H, J = 7.5 Hz), 7.54 (d, 1 H, J = 8.8 Hz), 7.77 (s, 1 H), 7.9 (dd, 1 H, J = 8.8, 2.7 Hz), 9.35 (d, 1 H, J = 2.7 Hz).
13C NMR (CDCl3): δ = 9.25, 30.91, 116.16, 118.77, 128.36, 129.43, 135.5, 147.19, 172.06.

MS (EI): m/z (%): 228 (M+2, 25), 193 (22), 126 (17), 90 (22), 57 (100).

Anal. Caled for C9H5ClN: C, 49.61; H, 4.71; Cl, 14.73; N, 11.54. Found: C, 49.61; H, 4.71; Cl, 14.72; N, 11.48.

N-Methyl-(2-chloro-5-nitro)butyranilide (1g)

Yield: 90%; mp 46–47 °C (heptane).

1H NMR (200 MHz, CDCl3): δ = 0.85 (t, 3 H, J = 7.3 Hz), 1.56–1.72 (m, 2 H), 1.90–2.00 (m, 2 H), 3.23 (s, 3 H), 7.74 (d, 1 H, J = 8.6 Hz), 8.18–8.24 (m, 2 H).
13C NMR (CDCl3): δ = 13.69, 18.34, 35.66, 35.85, 124.17, 125.19, 131.5, 140.60, 142.36, 147.18, 172.25.

MS (EI): m/z (%): 221 (M+2, 69), 188 (32), 186 (100), 140 (12), 71 (81), 43 (99), 41 (19).

Anal. Caled for C9H7ClN2O: C, 51.47; H, 5.1; Cl, 13.81; N, 10.91. Found: C, 51.23; H, 5.26; Cl, 13.98; N, 10.77.

N-Methyl-(2-Chloro-5-nitro)phenylacetanilide (1h)

Yield: 88%; mp 164 °C (hexane–EtOAc).

1H NMR (400 MHz, CDCl3): δ = 2.34 (s, 3 H, J = 3.3, 1 H, J = 15 Hz), 3.51 (d, 1 H, J = 15 Hz), 6.92–6.96 (m, 2 H), 7.18–7.23 (m, 3 H), 7.68 (d, 1 H, J = 8.8 Hz), 7.89 (s, 1 H, J = 2.7 Hz).

13C NMR (CDCl3): δ = 36.10, 41.72, 124.22, 125.80, 127.04, 128.51, 128.71, 131.32, 134.05, 140.64, 141.83, 146.86, 170.36.

MS (EI): m/z (%): 304 (M+2, 4), 269 (54), 213 (12), 186 (19), 118 (45), 91 (100).

Anal. Caled for C10H12ClN2O: C, 59.12; H, 4.3; Cl, 11.63; N, 9.19. Found: C, 58.92; H, 4.23; Cl, 11.55; N, 8.98.

1,3-Dimethyl-4-nitrooxindole (2b)

Typical Procedure

To a stirred solution of 2-buOK (170 mg, 1.5 mmol) in anhyd DMSO (50 mL) was added dropwise a solution of 1b (208 mg, 1 mmol) in DMSO (5 mL) during 20 min at rt. The dark blue mixture was stirred for 40 min, treated with dil. HCl (100 mL) and extracted with EtOAc. The combined organic extracts were washed, dried, the solvent evaporated and the residue purified by column chromatography on silica gel using hexane–EtOAc as eluent to give 2b.

Yield: 64%; mp 148–150 °C (hexane–EtOAc).

1H NMR (400 MHz, CDCl3): δ = 1.52 (d, 3 H, J = 7.5 Hz), 3.27 (s, 1 H), 4.03 (q, 1 H, J = 7.5 Hz), 7.12 (d, 1 H, J = 7.8 Hz), 7.47 (m, 1 H), 7.82 (m, 1 H).

13C NMR (CDCl3): δ = 14.9, 26.64, 41.83, 113.07, 117.38, 126.67, 129.07, 144.94, 146.32, 177.74.

MS (EI): m/z (%): 206 (M+2, 100), 189 (17), 160 (35), 117 (38).


1-Methyl-4-nitrooxindole (2a)

Yield: 35%; mp 149–151 °C (hexane–EtOAc).

1H NMR (400 MHz, CDCl3): δ = 3.28 (s, 3 H), 4.03 (s, 2 H), 7.12 (d, 1 H, J = 7.7 Hz), 7.49 (m, 1 H), 7.87 (dd, 1 H, J = 9.6, 0.8 Hz).

13C NMR (CDCl3): δ = 26.61, 37.02, 113.10, 117.03, 121.25, 129.16, 144.31, 147.24, 173.85.

MS (EI): m/z (%): 192 (M+2,100), 175 (35), 147 (38), 117 (31), 91 (28).

Anal. Caled for C5H4N2O2: C, 56.25; H, 4.2; N, 14.58. Found: C, 56.02; H, 4.26; N, 14.41.

3-Ethyl-1-methyl-4-nitrooxindole (2c)

Yield: 95%; mp 114–115 °C (hexane–EtOAc).

Synthesis 2002, No. 15, 2203–2206 ISSN 0039-7881 © Thieme Stuttgart · New York
3-Ethyl-1-methyl-6-nitrooxindole (3e)

Yield: 9%; mp 117 °C (hexane–EtOAc).

1-Methyl-6-nitro-3-phenyloxindole (3d)

Anal. Calcd for C15H12N2O3: C, 67.16; H, 4.51; N, 10.44. Found: C, 59.84; H, 5.41; N, 12.55.

7-Chloro-1-methyl-4-nitro-3-phenyloxindole (2h)

Yield: 32%; mp 165–166 °C (hexane–EtOAc).

HRMS: m/z (%) = 302 (M⁺, 100), 285 (28), 268 (65).

Acknowledgement

This work was supported by State Committee for Scientific Research Grant No. PBZ 6.01.

References