Direct Nitration of 3-Arylamino-2-chloro-1,4-naphthoquinones

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Abstract: A convenient two-step synthesis of mononitro and dinitro derivatives of the title compounds is reported. The Michael type addition of aromatic amines to 2,3-dichloro-1,4-naphthoquinone, is followed by mixed acids nitration to yield nitro aromatic quinones hard to get or unattainable before.

Key words: quinones, Michael additions, aromatic amines, nitroations, nitroquinones

1,4-Naphthoquinone derivatives in general, and those possessing an amino group in the 2-position in particular, have been long the subject of intensive research. They are of interest because many of them find use in a variety of medical and biological applications. Thus, they can act as antituberculars,1 antimalarials,2 antibacterial,3 antitumor agents,4 larvicides,5 lamoluscicides,5 herbicides,6 and fungicides.7 The synthesis of 2-aminoquinones, is usually accomplished via the Michael-type reaction of amines either with 1,4-naphthoquinone itself or with 2,3-dichloro-1,4-naphthoquinone. Primary and secondary aliphatic amines, cyclic amines and anilines substituted with electron-donating groups, are quite reactive and afford high yields of the corresponding aminooquinones.8,9 Only very poor yields are obtained, or no reaction at all is observed with aromatic amines, substituted with strong electron-withdrawing groups. Thus, the Michael addition does not allow the satisfactory preparation of nitro-substituted derivatives (e.g. 3a–h). The reported yield of the reaction of p-nitroaniline with 2,3-dichloro-1,4-naphthoquinone is lower than 3%10 and with 1,4-naphthoquinone only traces were obtained.11 Similarly, 2,4-dinitroaniline did not react with these quinones.

In the course of our work on anticancer quinones,12,13 we had to prepare and to test both the mononitro- and dinitrophenyl derivatives of naphthoquinone. As the classical route to such compounds was unfeasible, we developed an alternative two-step synthesis of such compounds. In the first step, 2-anilino-3-chloro-1,4-naphthoquinones were prepared by the classical Michael type addition-elimination reaction.8 In the second step, the phenyl group was nitratated via direct electrophilic aromatic substitution (Scheme 1). Under quite mild conditions (5–40 °C, dilute acids) we were able to obtain the mononitro derivatives 3a–f in moderate to good yield (35–65%). Under slightly more severe conditions (conc. acids) dinitration of the aromatic ring took place. The 2,4-dinitro derivative 3g and the 2,3-dinitro derivative 3h were obtained in very good yields (80 and 68%, respectively). The mononitro derivatives 3a–f and the dinitro derivatives 3g–h have not been previously described in the literature.

All products were identified by IR, 1H NMR, 13C NMR, MS, and UV/Vis spectral data. The infrared spectra of 3a–h exhibit typical strong quinonic carbonyl absorption between 1635 and 1680 cm−1. The NH stretching vibration appeared between 3237 and 3330 cm−1. In the 1H NMR spectra (CDCl3) of 3, four naphthalenic protons with different chemical shifts were observed, as expected from such non-symmetric systems.14,15 In the disubstituted compounds 3b–f, the three benzenic hydrogens appeared as doublet, double doublet, and doublet splittings. The position of the introduced nitro group was verified in the case of 3f by an X-ray diffraction study (Figure 1)16 and in

Scheme 1

<table>
<thead>
<tr>
<th>R</th>
<th>R¹</th>
<th>R²</th>
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<tr>
<td>a</td>
<td>NO²</td>
<td>H</td>
</tr>
<tr>
<td>b</td>
<td>CH₃</td>
<td>NO²</td>
</tr>
<tr>
<td>c</td>
<td>(CH₃)₃CH₅</td>
<td>NO²</td>
</tr>
<tr>
<td>d</td>
<td>OCH₃</td>
<td>NO²</td>
</tr>
<tr>
<td>e</td>
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<td>COOEt</td>
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<td>g</td>
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<tr>
<td>h</td>
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the other cases by analyzing chemical shifts and spin coupling constants of the $^1$H and $^{13}$C NMR data. The double nitration of \(2 (R = H)\) yielded the expected meta-dinitro compound \(3g\). However, double nitration of the methoxy compound \((2, R = OCH_3)\) produced the unexpected derivative \(3h\) in which the two nitro groups are ortho to each other. The proton NMR spectrum of \(3h\) showed two aromatic CH appearing as a double doublet at \(\delta = 7.72-7.78\) \((J = 9.1\) Hz). The methoxy hydrogens appeared as a singlet and the resonance of the naphthalene ring are highly distorted due to second-order effects. We do not have an explanation for this unusual orientation of the substitution.

The electronic absorption spectra showed the expected benzene and naphthoquinone bands in the UV region around 270–286 nm \((\lambda_1, \pi \rightarrow \pi^*\) electron transition) and at 336–344 nm \((\lambda_2)\). In addition, another lower energy band appeared in the visible region centered between 430–490 nm \((\lambda_3)\) which can be attributed to the n→\pi* transition. Comparing compounds \(3\) with the non-nitratd analogs showed that the values of \(\lambda_1\) and \(\lambda_2\) are not influenced by the introduction of the nitro group. On the other hand, this chromophore had a pronounced hypsochromic influence on the \(\lambda_3\) transition. Thus, in the case of mononitrated compounds the shift is between 10 to 20 nm and in the case of dinitrated compounds the shift is as large as 45 nm.

As can be seen from the crystal structure plot in Figure 1, the phenyl ring and the naphthoquinone ring system of \(3f\) do not lie in the same molecular plane. The dihedral angle between the two planes is 53.8°. This molecule is involved in an intramolecular hydrogen bond between the NH and one of the oxygens of the nitro group (N1–H1…O4, 2.103 Å). In typical amino substituted naphthoquinones, an intramolecular hydrogen bond exists between the NH and one of the quinonic oxygens. In the present case such an interaction is rather weak (2.173 Å) because of the non-planarity of the system.

**Figure 1** Crystal structure of compound \(3f\)

In conclusion, we have developed a route to the synthesis of mononitro and dinitro derivatives of 2-arylamino-1,4-naphthoquinones. Thus, we were able to prepare a variety of nitro aromatic quinones difficult to get or unattainable before. To the best of our knowledge, direct nitration of such quinones have not been reported before. The influence of the dinitro derivatives \(3g-h\) on the quinonic properties and on the ease of substitution of the second chlorine atom by nucleophiles is currently in progress.

IR spectra were recorded on a Nicolet 5ZDX FT-IR spectrometer. \(^1\)H and \(^13\)C NMR spectra were recorded on Bruker WP 200 SY and Bruker DMX 500 instruments. Mass spectra (CI in CH\(_4\)) were obtained on a Finnigan 4020 quadrupole spectrometer and LC-MS (APCI, atmospheric pressure chemical ionization) was performed using a Bruker esquire 3000\(^+\) (Bruker Daltonics, Germany). UV/Vis spectra were measured using HP 8452A diode array spectrophotometer. TLC was carried out on Merck 5554 pre coated silica gel 60. Mps were measured using a Thomas-Hoover capillary apparatus and are uncorrected. All chemicals, solvents and reagents were of commercial quality. X-ray analysis was done on a Nonius Kappa CCD diffractometer with MoK\(_\alpha\) radiation \((\lambda = 0.71073)\) with a graphite monochromer.

2-Arylamo-3-chloro-1,4-naphthoquinones 2; General Procedure

Preparation of \(2\) was performed according to literature procedures.\(^1\) The aromatic amine (13.2 mmol) was mixed with a solution of 2,3-dichloro-1,4-naphthoquinone (1: 1.0 g, 4.4 mmol) in EtOH (300 mL). Stirring the mixture at r.t. overnight caused the precipitation of the product. The precipitate was collected by filtration, washed with EtOH and recrystallized from EtOH–CHCl\(_3\) (5:1) to afford the pure 2-arylamino-3-chloro-1,4-naphthoquinones \(2\).

Nitrination of 2a–f; General Procedure

The appropriate 1,4-naphthoquinone \(2a-f\) (0.9 mmol) was added to a stirred mixture of 70% HNO\(_3\) (7 mL), 95% concd H\(_2\)SO\(_4\) (1.5 mL) and H\(_2\)O (3 mL) at 5 °C. The reaction mixture was allowed to warm to r.t. for \(2a-d\) and in all other cases was heated at 50 °C for 1 h. It was diluted with H\(_2\)O (100 mL) and the colored precipitate was collected by suction filtration. The crude product was washed with aq 5% NaHCO\(_3\) solution, with H\(_2\)O and cold EtOH.

2-Chloro-3-[(4-nitropheny)l]amino]-1,4-naphthoquinone (3a)

Recrystallized from CH\(_2\)Cl\(_2\) to afford orange crystals; yield: 64%; mp 288–289 °C.

IR (KBr): 3237, 2931, 1675, 1348 cm\(^{-1}\).

\(^1\)H NMR (200 MHz, DMSO-d\(_6\)): \(\delta = 9.7\) (br s, 1 H), 8.16 (d, \(J = 9.2\) Hz, 2 H), 8.04–8.07 (m, 2 H), 7.82–7.90 (m, 2 H), 7.22 (d, \(J = 9.2\) Hz, 2 H).

\(^13\)C NMR (200 MHz, DMSO-d\(_6\)): \(\delta = 177.6, 170.6, 147.1, 142.7, 141.9, 130.0, 133.8, 132.3, 126.8, 126.4, 124.7, 121.5, 104.9\).

HRMS (CI in CH\(_3\)OH): \(m/z\) calcd for C\(_{16}\)H\(_9\)ClN\(_2\)O\(_4\): 328.025085; found: 328.023509.

UV/Vis (CH\(_3\)OH): \(\lambda_{max}\) (log \(\epsilon\)) = 274 (4.18), 336 (4.18), 462 nm (3.68).

2-Chloro-3-[(4-methyl-2-nitrophenyl)amino]-1,4-naphthoquinone (3b)

Recrystallized from n-hexane–CH\(_2\)Cl\(_2\) (4:1) to afford orange crystals; yield: 36%; mp 243–245 °C.

IR (KBr): 3245, 2931, 1683, 1346 cm\(^{-1}\).

\(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta = 9.32\) (br s, 1 H), 8.18 (dd, \(J = 1.4, 7.7\) Hz, 2 H), 7.79 (d, \(J = 2.6\) Hz, 1 H), 7.77 (dt, \(J = 1.5, 7.4\) Hz, 2 H), 7.39 (dd, \(J = 2.6, 8.9\) Hz, 1 H), 6.81 (d, \(J = 8.6\) Hz, 1 H), 2.17 (s, 3 H).

\(^13\)C NMR (500 MHz, CDCl\(_3\)): \(\delta = 179.4, 177.0, 140.2, 139.2, 134.6, 134.0, 133.6, 133.2, 131.6, 130.5, 130.1, 129.7, 126.9, 125.4, 124.1, 119.9, 30.5.

ESI-MS: \(m/z\) = 342.0, 340.8 [C\(_{17}\)H\(_{11}\)ClN\(_2\)O\(_4\) (M – H)\(^+\)].
UV/Vis (CHCl₃): $\lambda_{\text{abs}}$ (log ε) = 276 (4.25), 344 (3.6), 466 nm (3.66).

2-Chloro-3-[(4-tetradeyl-2-nitrophenyl)amino]-1,4-naphthoquinone (3c)
Recrystallized from CHCl₃ to afford yellow crystals; yield: 45%; mp 178–180 °C.

IR (KBr): 3295, 2921, 1679, 1348 cm⁻¹.

HRMS (CI in CH₄): m/z = 524.2, 522.7 [C₁₀H₁₃ClN₂O₄ (M – H)⁻], 525.3 (M + H)⁺.

UV/Vis (CHCl₃): $\lambda_{\text{abs}}$ (log ε) = 246 (4.09), 286 (3.98), 342 (4.04), 440 nm (3.73).

Dinitro Derivatives 3g,h; General Procedure
A mixture of 70% HNO₃ (5.5 mL) and 95% concd H₂SO₄ (0.5 mL) was added to 2 (0.5 mmol) at 5 °C. The reaction mixture was allowed to stir at rt. for 2 h, diluted with H₂O (100 mL) and the precipitate was collected by filtration. The crude product was washed with aq NaHCO₃ solution, then with H₂O and with cold EtOH to give the desired compound.

2-Chloro-3-[(2,4-dinitrophenyl)amino]-1,4-naphthoquinone (3g)
Recrystallized from CH₃CO₂H to afford an orange solid; yield: 3%; mp 240–242 °C.

IR (KBr): 3286, 3091, 1666, 1353 cm⁻¹.

HRMS (CI in CH₄): m/z = 403.9 [C₁₇H₁₂ClN₃O₇, (M + H)⁺], 403.01, 401.8 [C₁₄H₁₀ClN₂O₆, (M – H)⁻].

UV/Vis (CHCl₃): $\lambda_{\text{abs}}$ (log ε) = 286 (4.47), 342 (3.8), 454 nm (3.82).

X-ray Crystal Data
Single crystal 3f was obtained by slow evaporation from CHCl₃, yellowish crystal, C₁₇H₁₂ClN₃O₆ (400.76); triclinic, P1, with a = 4.4690(9) Å, b = 6.7590(14) Å, c = 14.267(3) Å, α = 92.38(3)°, β = 91.47(3)°, γ = 91.47(3)°. V = 430.28(15) Å³. Z = 1. ρcalc = 1.547 Mg/m³, absorption coefficient 0.129 mm⁻¹ was performed at 120 K using graphite monochromated MoKα radiation ($\lambda = 0.71073$ Å), allowing indices $-$h ≤ 5, −8 ≤ k ≤ 8, 0 ≤ l ≤ 17, 0-range for data collection 2.86 to 26.37°, reflections measured 1727, unique reflections 1727 (Rint = 0.0000). Completeness to $\theta = 26.37°$ 98%, data/restraints/parameters 1727/3/258. The structure was solved by direct methods and refined by full-matrix least-squares on F² using SHELLX-97 program system. All non-hydrogen atoms were refined anisotropically and the position of the hydrogen atoms were calculated as a riding model. Goodness-of-fit on
Selected bond distances (Å) and bond angles (°): Cl(1)–C(10) 1.718(4); C(1)–N(1) 1.383(6); C(1)–C(2) 1.508(6); C(2)–O(1) 1.209(6); C(2)–C(3) 1.489(6); C(3)–C(8) 1.403(6); C(3)–C(4) 1.408(6); C(4)–C(5) 1.375(7); C(4)–H(4) 0.9300; C(9)–C(10) 1.221(6); N(1)–C(11) 1.390(6); C(11)–C(12) 1.406(6); C(12)–C(13) 1.370(6); C(16)–N(2) 1.461(5); C(10)–C(1)–N(1) 127.2(4); N(1)–C(1)–C(2) 111.8(4); O(1)–C(2)–C(3) 123.1(4); O(1)–C(2)–C(1) 119.0(4); C(1)–C(10)–Cl(1) 122.5(3); C(1)–N(1)–H(1) 109(3); C(11)–N(1)–C(16) 122.5(4); N(1)–C(11)–C(16) 118.7(4); N(1)–C(11)–C(12) 122.5(4); C(11)–C(12)–H(12) 119.1; C(15)–C(14)–H(17) 117.5(4).

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References

(16) Crystallographic data were deposited at Cambridge Crystallographic data Centre, 12 Union Road, Cambridge CB2 1EZ, UK and are available from there under the deposition number CCDC 255861.