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New sterically unhindered benzoquinonemonoimines

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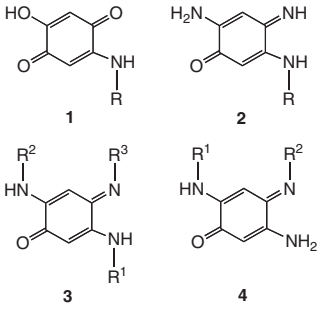
ABSTRACT

We accidentally found that the F→OH conversion by direct hydroxylation of electron deficient aryls above 150 °C allows the isolation of the precursors of novel quinonemonoimines **9**, previously unknown.

The synthesis of molecules exhibiting a quinoid structure continues to spur active investigations because of their implication in many areas of chemistry and biology.[1] More specifically, benzoquinones of type **1** are of major importance as bioinhibitors by analogy with closely related C-substituted derivatives[2–10] owing to the presence of acidic hydrogens that might interact with the ATP binding site through H-bonds.[2] Accordingly, the access to low molecular weight analogues is obviously a promising approach for the development of alternative anticancer agents.[2] Curiously, quinonemonoimine analogues **2** are hitherto unknown whereas their closely related structure should not only be very attractive in biology—as a potential new class of bioinhibitors by analogy with **1**[2–10]—but also in color[11] and coordination[12] chemistry as acidochromes and ligands, respectively. It is noteworthy that only N-substituted molecules of type **3**[13,14] and **4**[15] have been reported in the literature for biochemistry[14] or hair colorant[15] applications whereas **2**—unsubstituted in the 'upper' part—appears much more attractive due to the presence of additional H-donor sites and/or possible further functionalization of the nitrogen atoms. Therefore, the development of a versatile route that would give access to such molecules (**2**) would be very useful to enlarge the scope of this family of compounds. In the course of this study, the possible displacement of halogens by hydroxide anion on electron poor aromatic rings was envisaged although this transformation is often difficult[16a,b] without any cationic catalyst,[16c–e] oxidative processes[16f] or sigmatropic rearrangements.[16g]



Herein, we wish to report the synthesis of unprecedented aminoquinonemonoimines of type **2**. These molecules (**8**) were obtained from electron deficient diaryl intermediates (**7**) that could be isolated from a F→OH conversion above 150 °C.

We recently reported a straightforward synthesis of the azacalix[4]arene precursor **7a** by condensation of 1,3-diaminobenzene **5a** with the commercially available electron deficient aryl **6** in refluxing EtOH (Scheme 1, route i).[17] When the reaction was performed in wet DMSO at room temperature (rt), **7a** was obtained in 51% yield (Scheme 1, route ii). By studying this reaction in more detail, we have now found—accidentally—that the same reaction at 160 °C affords instead the hydroxy analogue **8a** in 35% yield (Scheme 2).[18]

Its IR spectrum shows a strong vibration band at 1252 cm^{-1} and its ^1H NMR reveals the lack of J_{H-F} coupling and an additional resonance at 10.93 ppm by comparison with **7a**.

These observations are in agreement with the replacement of the F atom in **7a** (soluble in DMSO) by an OH group in **8a** (Scheme

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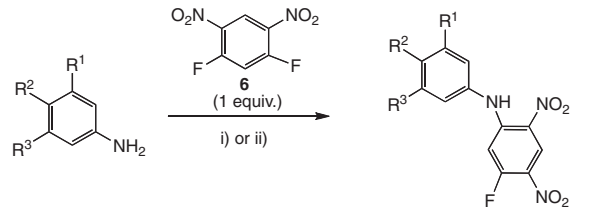
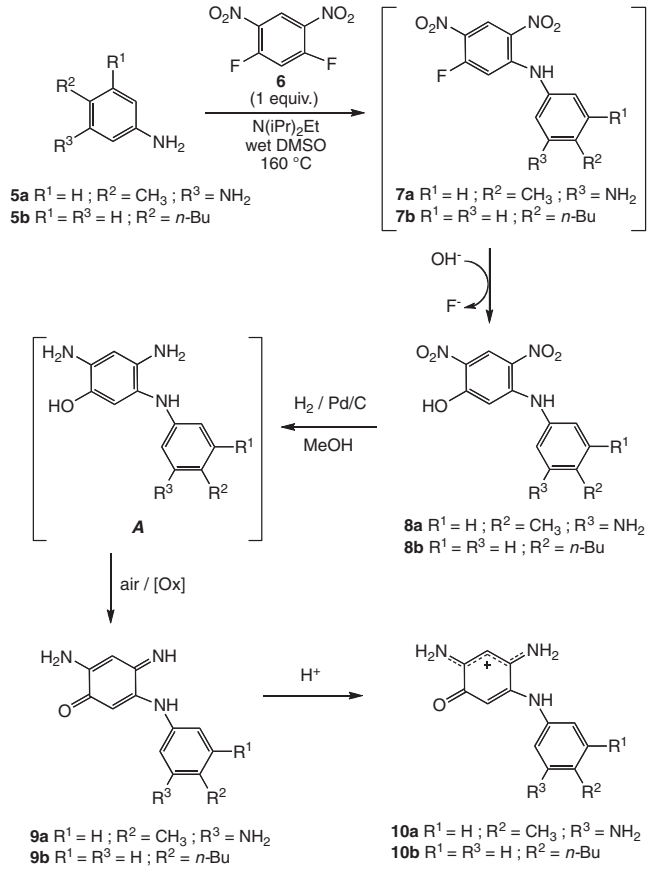


Scheme 1. Synthesis of N(H)-bridged diaryls **7**. Reagents and conditions: (i) $N(iPr)_2Et$/EtOH/reflux; (ii) Na_2CO_3/DMSO/rt.



Scheme 2. Synthesis of new benzoquinonemonoimines.

2). This hypothesis was further confirmed by X-ray analysis[19] which clearly established for **8a** the presence of the OH group involved in an intramolecular H-bonding interaction between the O(13)–H proton and O(17) [d(O(13)–H···O(17)) = 1.914 Å] (Fig. 1). The structure determination of **8a** revealed also the formation of a single regioisomer for which the CH_3 group on the phenyl ring is located in the *para*-position with respect to the NH bridge. This structure determination would suggest that the formation of **8a** is controlled by steric effects.

Similarly, the N(H)-bridged diaryls **7b** and **8b** could be prepared by condensation between *p*-*n*Bu–C_6H_4–NH_2 **5b** and **6** in 25% yield in refluxing EtOH and 62% yield in DMSO at 160 °C, respectively.[18]

The formation of **8a** and **8b** resulting from a Swern-type mechanism[20] (nucleophilic attack of DMSO on the C–F carbon) could be excluded since the use of refluxing wet DMF (T = 153 °C) instead of DMSO furnished also the OH derivatives **8**. In contrast, when the same reaction was performed in refluxing wet CH_3CN or EtOH,

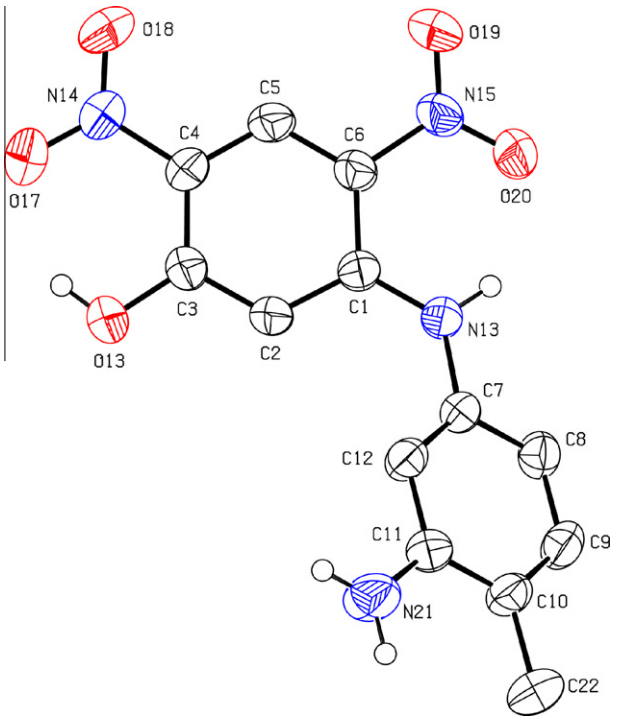


Figure 1. ORTEP view of the crystal structure of **8a**. Displacement parameters include 50% of the electron density. Selected bond distances (Å) and angles (°): N(13)–C(1) 1.353(2), C(1)–C(6) 1.434(3), C(6)–N(15) 1.444(3), C(1)–C(2) 1.399(3), C(3)–O(13) 1.338(3), N(13)–C(7) 1.419(2), C(1)–C(6)–N(15) 122.21(18), C(1)–C(6)–C(5) 121.66(18), N(13)–C(1)–C(2) 122.61(17), C(2)–C(3)–C(4) 118.87(18), C(3)–C(4)–N(14) 121.98(19).

the F→OH transformation could not be observed. These observations clearly established the displacement of the F halogen by direct hydroxylation of **7a** and **7b** (which do not precipitate in DMSO or DMF) above 150 °C. This transformation is facilitated by the presence in **6** of two electron-withdrawing nitro groups (positioned *ortho* and *para* to the substitution site) and by the electron-withdrawing *ipso* group (fluoride).

Then, the hydrogenation of **8a** and **8b** on Pd/C furnished the corresponding amino species **A** (not isolated) which under air (i.e., upon oxidation) sacrifice their aromatic character in favor of the target quinones **9a** and **9b** in 65% and 43% yield, respectively (Scheme 2).[21] Their NMR data are consistent with a quinoid form as shown for instance by the resonance of the carbonyl group at 180.89 and 180.99 ppm for **9a** and **9b**, respectively.

The UV–vis spectrum of molecules **9** is characterized by one strong absorption at 352 nm and by the presence of a weaker broad band at 496 nm (Fig. 2). Upon protonation in acetone with HCl, the absorption spectrum revealed two absorption bands at 369 nm and 612 nm. In both cases, the main absorptions can be attributed to the π–π^* transition of the quinoid skeleton, whereas the weak absorption band corresponds to a $n\pi^*$ transition originating at the nitrogen lone pair.[22] The observed bathochromic effect (i.e., drastic color change from red to green) can be explained by the protonation of the imine function leading to the iminium salt **10** in which the positive charge is stabilized by intramolecular delocalization, as already shown on related analogues (Scheme 1).[11]

In summary, the temperature controlled reactivity places **5** and **6** at the cross-roads of a new versatile strategy for the preparation of two different categories of N(H)-bridged diaryls **7** and **8**. The F→OH conversion in electron poor diaryls (**7**) occurs above 150 °C by replacement of the F halogen by the hydroxide anion. This reaction allows the isolation of the precursors (**8**) of unprecedented quinonemonoimines **9** for which the molecular structure

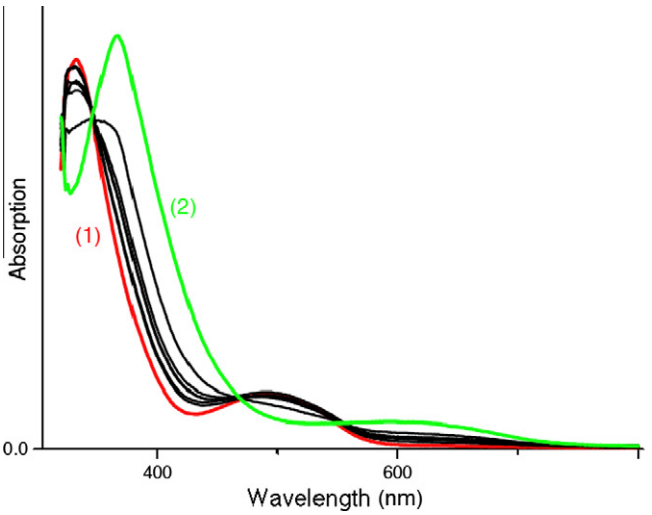


Figure 2. UV–vis spectrum of quinonemonoimines in neutral medium (**9**, red) and upon protonation (**10**, green).

opens new perspectives in different fields ranging from biochemistry (as bioinhibitors)[2–10] to color (as acidochrome)[11] and coordination chemistry (as N_3O donor ligands).[12]

Acknowledgments

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18. *Synthesis of* **7b**: To a solution of 4-butylaniline (97 μL, 0.98 mmol, 1 equiv), diisopropylethylamine (0.34 mL, 1.96 mmol, 2 equiv) in EtOH were added 200 mg (0.98 mmol, 1 equiv) of 1,5-difluoro-2,4-dinitrobenzene. The mixture was stirred for 30 min at room temperature then was refluxed for 1 h. The obtained precipitate was isolated by filtration and washed with water affording **7b** as a yellow solid (40 mg, 25% yield). Mp = 97 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.96 (t, J = 7.30 Hz, 3H), 1.40 (m, 2H), 1.64 (m, 2H), 2.67 (t, J = 7.79 Hz, 2H), 6.79 (d, $^3J_{HF}$ = 13.41 Hz, 1H, aromatic H), 7.18 (d, J_{ortho} = 8.22 Hz, 2H, aromatic H), 7.32 (d, J_{ortho} = 8.38 Hz, 2H, aromatic H), 9.17 (d, $^4J_{HF}$ = 7.85 Hz, 1H, aromatic H), 9.91 (br s, 1H, NH). MS (ESI)$^+$: $[M+H]^+$ m/z = 334, $[M+NH_4]^+$ m/z = 351, $[M+Na]^+$ m/z = 356, $[M+K]^+$ m/z = 372. Anal. Calcd for $C_{16}H_{16}FN_3O_4{\cdot}3/2H_2O$: C, 53.33; H, 5.31; N, 11.66. Found: C, 53.69; H, 4.86; N, 12.14.
Synthesis of **8a**: A mixture of 1,5-difluoro-2,4-dinitrobenzene (200 mg, 0.98 mmol, 1 equiv), 2,3-diaminotoluene (120.5 mg, 0.98 mmol, 1 equiv) and Na_2CO_3 (258 mg, 2.43 mmol, 2.5 equiv) was dissolved in 20 mL of DMSO and heated at 160 °C for 4 h. The solution was then poured into 40 ml of a mixture of 40 mL of HCl (1 M) and 50 mL of ethyl acetate and extracted with ethyl acetate (5 × 100 mL). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (5:5, R_f = 0.38) to give **8a** as a red solid (100 mg, 34% yield). ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.20 (s, 3H, CH_3), 3.81 (s, 2H, NH_2), 6.57 (m, 1H, aromatic H), 6.59 (s, 1H, aromatic H), 6.60 (d, J_{meta} = 2.04 Hz, 1H, aromatic H), 7.13 (d, J_{ortho} = 7.66 Hz, 1H, aromatic H), 9.17 (s, 1H, aromatic H), 9.77 (s, 1H, NH), 10.93 (s, 1H, OH). MS (MALDI-TOF)$^+$, $[M]^+$ m/z = 304.1. Anal. Calcd for $C_{13}H_{12}N_4O_5{\cdot}1/4C_6H_{12}$: C, 53.54; H, 4.65; N, 17.22. Found: C, 53.17; H, 4.36; N, 16.86. IR: ν_{C-OH} = 1258 cm^{-1}.
Synthesis of **8b**: A mixture of 1,5-difluoro-2,4-dinitrobenzene (400 mg, 1.96 mmol, 1 equiv), *n*-butylaniline (0.31 mL, 1.96 mmol, 1 equiv), and Na_2CO_3 (519.3 mg, 4.9 mmol, 2.5 equiv) was dissolved in 20 mL of DMSO and was heated at 160 °C for 4 h. The solution was then poured into a mixture of 40 mL of HCl (1 M) and 100 mL of ethyl acetate for extraction (5 times). The combined organic layers were dried over $MgSO_4$, evaporated and purified by column chromatography on silica gel using cyclohexane/ethyl acetate (9:1, R_f = 0.43) to give **8b** as a red solid (400 mg, 62% yield). Mp = 107 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.96 (t, J = 7.36, 3H), 1.40 (m, J = 7.55, 7.36 Hz, 2H), 1.64 (m, 2H), 2.67 (t, J = 7.73 Hz, 2H), 6.54 (s, 1H, aromatic H), 7.20 (d, J_{ortho} = 8.30 Hz, 2H, aromatic H), 7.31 (d, J_{ortho} = 8.50 Hz, 2H, aromatic H), 9.18 (s, NH), 9.84 (s, OH). MS (ESI)$^+$: $[M+H]^+$ m/z = 332. Anal. Calcd for $C_{16}H_{17}N_3O_5{\cdot}6/5C_6H_{12}$: C, 64.45; H, 7.32; N, 9.72. Found: C, 64.13; H, 7.28; N, 9.26.
19. *Crystal data for* **8a**: monoclinic, space group $P21/c$ with a = 5.3179(2), b = 17.5462(6), c = 14.6185(5), α = 90, β = 103.455(2), γ = 90 at 293(2) K with Z = 4, R_1 = 0.0582, GOF = 1.141. Crystallographic data for structure **8a** have been deposited at the Cambridge Crystallographic Data Centre (CCDC 785955). Copy of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +40(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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21. *General procedure for the synthesis of* **9a** and **9b**: A solution of **8** (80 mg) and palladium on carbon 5% in 20 mL of methanol was stirred under 60 bar of hydrogen for 24 h at room temperature, the catalyst was filtered off over celite and the filtrate was concentrated under vacuum and purified by column chromatography on silica gel affording **9a** and **9b**.
Compound **9a**: elution in AcOEt/MeOH (9:1, R_f = 0.42) (34 mg 53% yield). Mp = 175 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 2.14 (s, 3H, CH_3), 3.70 (s, 2H, NH_2), 4.76 (s, 2H, NH_2), 5.53 (s, 1H, aromatic H), 6.01 (s, 1H, aromatic H), 6.59 (m, 2H, aromatic H), 7.03 (d, J_{ortho} = 7.68 Hz, 1H, aromatic H), 8.40 (s, 1H, NH), 9.16 (s, 1H, NH). ^{13}C NMR (62 MHz, $CDCl_3$) δ = 16.41, 96.65, 97.04, 108.31, 112.43, 118.98, 130.63, 136.21, 143.20, 144.85, 162.38, 180.89. MS: (ESI)$^+$: $[M+H]^+$ m/z = 243. Anal. Calcd for $C_{13}H_{14}N_4O{\cdot}4/15AcOEt$: C, 63.57; H, 6.12; N, 21.08. Found: C, 64.06; H, 6.14; N, 20.63.
Compound **9b**: elution in AcOEt (R_f = 0.40) (105 mg, 43% yield). Mp = 172 °C. ^{1}H NMR (250 MHz, $CDCl_3$) δ = 0.99 (t, J = 7.24 Hz, 3H), 1.39 (m, J = 7.61, 7.51 Hz, 2H), 1.65 (m, J = 7.60, 7.78 Hz, 2H), 2.65 (t, J = 7.80 Hz, 2H), 4.97 (s, 1H, aromatic H), 5.60 (s, 1H, aromatic H), 6.00 (br s, 2H, aromatic H), 7.22 (d, J = 1.40 Hz, 2H, aromatic H), 9.10 (s, NH). ^{13}C NMR (62 MHz, $CDCl_3$) δ = 13.54, 21.90, 33.17, 34.72, 96.59, 97.17, 122.57, 128.98, 135.12, 139.88, 149.36, 162.48, 180.99; MS (ESI)$^+$: $[M+H]^+$ m/z = 270.1. Anal. Calcd for $C_{16}H_{19}N_3O{\cdot}1/5C_6H_{12}{\cdot}2/5AcOEt$: C, 70.25; H, 7.71; N, 13.07. Found: C, 70.09; H, 7.84; N, 13.21.
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