Palladium-Catalyzed Amination of 2,3-Dichloro-1,4-naphthoquinone with Nitroarylamines

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Abstract: A convenient one-step synthesis of 2-[(nitroaryl)amino]-3-chloro-1,4-naphthoquinones is reported. The direct amination of 2,3-dichloro-1,4-naphthoquinone with nitro-substituted aryl amines is catalyzed by $PdCl_2$(dppf)/dppf[1] in the presence of *t*-BuONa as base to yield 2-[(nitroaryl)amino]-3-chloro-1,4-naphthoquinones, several of which were previously unavailable. Traces of the 2,3-di[(nitroaryl)amino]-1,4-naphthoquinones were detected as side products.

Key words: quinones, amines, catalysis, aminations, palladium

The amino naphthoquinone structure is common to numerous natural products (e.g., rifamycins,[2] damavaricins,[3] streptovaricins[4]) and has been used as a key synthetic intermediate for the construction of biologically important compounds associated with antitrypanosomal,[5] antimalarial,[6] antitumor[7] and antineoplastic[8] activities. In addition, they have found widespread industrial applications in color chemistry and hair dying,[9] and as photo stabilizers.[10] The classical routes to 2-amino-1,4-naphthoquinones are achieved either by the 1,4-type addition of amines with 1,4-naphthoquinone followed by air oxidation[11] or by nucleophilic addition–elimination on 2-halo-1,4-naphthoquinones.[12] High yields of the corresponding 2-aminonaphthoquinones can be obtained when primary and secondary aliphatic amines or anilines substituted with electron-donating groups are used; however, anilines substituted with strongly electron-withdrawing groups afford either poor yields of the corresponding aminonaphthoquinones or fail to react.[13] Thus, an alternative to the Michael addition protocols to prepare amino-substituted naphthoquinones with less nucleophilic amines and anilines would be useful to enhance the diversity of readily available amino-substituted naphthoquinones.

Although some 2-[(nitroaryl)amino]-3-chloro-1,4-naphthoquinones have recently been synthesized via a direct mixed acids nitration of 2-arylamino-3-chloro-1,4-naphthoquinones,[14] the yields and generality of the method are limited. In this letter we present an alternative strategy for the synthesis of 2-(nitroanilino)-3-chloro-1,4-naphthoquinones by the coupling of nitro-substituted aryl amines with 2,3-dichloro-1,4-naphthoquinone catalyzed by $PdCl_2$(dppf) in the presence of *t*-BuONa.[15] The results are summarized in Table 1.

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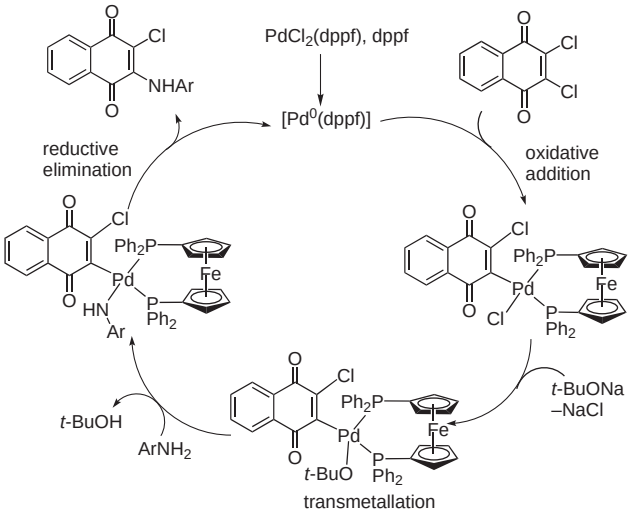


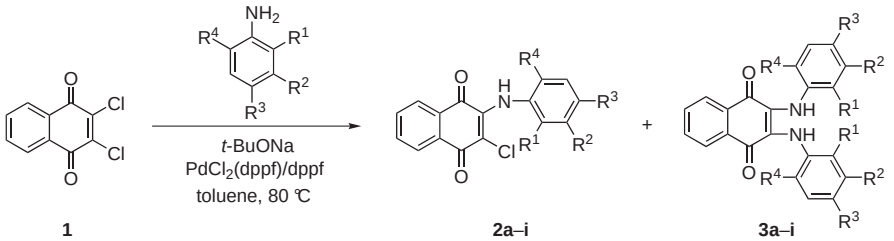
Scheme 1

In all of the coupling reactions, only a trace of 2,3-di[(nitroaryl)amino]-1,4-naphthoquinones **3** resulting from overamination of 2,3-dichloro-1,4-naphthoquinone can be detected as side products. To the best of our knowledge, these 2,3-dianilino-1,4-naphthoquinone derivatives have not been previously synthesized. After separation, compounds **3** were characterized by NMR spectroscopy.[16] As expected for such symmetrical compounds, the ^{1}H NMR spectra of **3** display four naphthalene protons with only two different chemical shifts and one set of aniline protons with double the integration. In the ^{13}C NMR spectra of **3**, fewer than ten aromatic carbon peaks and one carbonyl carbon peak can be detected further verifying the symmetrical structure of the 2,3-di[(nitroaryl)amino]-1,4-naphthoquinones.

As outlined in Scheme 1, we believe the catalytic cycle for this process is similar to that postulated for many palladium-catalyzed C–N bond forming reactions which involve an oxidative addition of the aryl halide, followed by transmetalation and reductive elimination.[17]

In conclusion, $PdCl_2$(dppf) has been found to catalyze the coupling of nitro-substituted arylamines with 2,3-dichloro-1,4-naphthoquinone. A variety of 2-[(nitroaryl)amino]-3-chloronaphthoquinones, some unattainable by any other procedure, are now available by a simple and mild method. An extension of this coupling methodology to synthesize nonsymmetrical diaminonaphthoquinones is currently in progress.

Table 1 Palladium-Catalyzed Amination of 2,3-Dichloro-1,4-naphthoquinone with Nitroanilines



2, **3**	R^1	R^2	R^3	R^4	Yield (%)[a]
a	H	H	NO_2	H	90
b	CF_3	H	NO_2	H	55
c	Cl	H	NO_2	Cl	45
d	H	NO_2	H	H	63
e	H	NO_2	CH_3	H	85
f	H	NO_2	OCH_3	H	64
g	H	NO_2	Cl	H	40
h	NO_2	H	H	H	42
i	NO_2	H	NO_2	H	64

[a] Isolated yield of compound **2** (average of two runs).

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References and Notes

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(15) **General Experimental Procedure.**
A mixture of 2,3-dichloro-1,4-naphthoquinone (200 mg, 0.88 mmol), nitroarylamine (0.97 mmol), *t*-BuONa (1.01 mmol), $PdCl_2$(dppf) (0.04 mmol), and dppf (0.04 mmol) in 5 mL toluene were stirred under a nitrogen atmosphere at 80 °C for 12 h, and then the reaction was concentrated and the products were purified by column chromatography (40–80% CH_2Cl_2–PE).
(16) ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Inova 500 MHz instrument.
Compound **2a**:[14] ^{1}H NMR ($CDCl_3$): δ = 8.22–8.25 (m, 3 H), 8.16 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.82 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.76 (dt, *J* = 7.5, 1.5 Hz, 1 H), 7.71 (s, 1 H), 7.08 (dd, *J* = 7.0, 2.0 Hz, 2 H).
Compound **3a**: ^{1}H NMR (DMSO-d_6): δ = 8.06 (dd, *J* = 5.5, 3.5 Hz, 2 H), 7.84 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.74 (dd, *J* = 7.5, 2.0 Hz, 4 H), 6.56 (t, 4 H). ^{13}C NMR (DMSO-d_6): δ = 181.61, 145.08, 140.32, 134.75, 131.83, 126.67, 126.30, 124.02, 119.06.

Compound **2b**: ^{1}H NMR ($CDCl_3$): δ = 8.57 (d, *J* = 2.5 Hz, 1 H), 8.39 (dd, *J* = 9.0, 2.5 Hz, 1 H), 8.23 (dd, *J* = 7.5, 1.0 Hz, 1 H), 8.17 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.87 (s, 1 H), 7.84 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.78 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.04 (d, *J* = 8.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ = 179.56, 177.18, 143.22, 141.38, 140.24, 135.44, 133.98, 131.95, 129.79, 127.59, 127.39, 126.89, 124.95, 123.85, 122.82, 122.78, 122.73, 122.69, 122.53, 122.28, 121.68, 121.52.

Compound **3b**: ^{1}H NMR ($CDCl_3$): δ = 8.40 (s, 2 H), 8.24 (m, 4 H), 8.13 (dd, *J* = 9.0, 2.0 Hz, 2 H), 7.85 (dd, *J* = 6.0, 3.5 Hz, 2 H), 6.56 (d, *J* = 9.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 180.55, 141.30, 139.97, 135.07, 130.50, 127.87, 127.37, 123.87, 122.76, 122.72, 122.67, 122.63, 121.68, 119.49, 118.47, 118.21.

Compound **2c**: ^{1}H NMR ($CDCl_3$): δ = 8.26 (s, 2 H), 8.18 (m, 1 H), 8.12 (m, 1 H), 7.80 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.74 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.28 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ = 178.88, 177.00, 145.36, 140.96, 140.00, 135.20, 133.57, 132.84, 131.99, 129.75, 127.31, 127.19, 123.44, 118.34.

Compound **2d**: ^{1}H NMR (DMSO-d_6): δ = 8.02–8.04 (m, 2 H), 7.90–7.92 (m, 2 H), 7.86 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.81 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.56 (t, *J* = 8.0, 1 H), 7.50 (dt, *J* = 8.0, 1.0 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ = 180.47, 177.77, 148.16, 143.42, 140.98, 135.48, 134.24, 132.39, 131.09, 129.91, 129.79, 127.28, 126.90, 118.91, 117.98, 117.79.

Compound **3d**: ^{1}H NMR (DMSO-d_6): δ = 8.05 (dd, *J* = 6.0, 3.0 Hz, 2 H), 7.82 (*J* = 6.0, 3.0 Hz, 2 H), 7.42 (dd, *J* = 8.5, 1.5 Hz, 2 H), 7.06–7.11 (m, 4 H), 6.72 (dd, *J* = 8.5, 2.0 Hz, 2 H). ^{13}C NMR (DMSO-d_6): δ = 181.58, 147.45, 139.23, 134.55, 131.89, 128.61, 126.53, 126.07, 124.88, 115.47, 114.24.

Compound **2e**:[14] ^{1}H NMR ($CDCl_3$): δ = 8.20 (dd, *J* = 7.5, 1.0 Hz, 1 H), 8.14 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.80 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.70–7.74 (m, 2 H), 7.63 (s, 1 H), 7.32 (d, *J* = 8.5 Hz, 1 H), 7.19 (dd, *J* = 8.0, 2.0 Hz, 1 H), 2.61 (s, 3 H).

Compound **3e**: ^{1}H NMR (DMSO-d_6): δ = 8.01 (dd, *J* = 5.5, 3.5 Hz, 2 H), 7.79 (dd, *J* = 5.5, 3.5 Hz, 2 H), 6.93 (d, *J* = 8.5 Hz, 2 H), 6.78 (d, *J* = 2.0 Hz, 2 H), 6.50 (dd, *J* = 8.0, 2.0 Hz, 2 H), 2.25 (s, 3 H). ^{13}C NMR (DMSO-d_6): δ = 181.52, 148.03, 136.95, 134.43, 131.88, 131.35, 126.42, 125.08, 124.78, 124.50, 115.79, 19.42.

Compound **2f**:[14] ^{1}H NMR (DMSO-d_6): δ = 8.04 (dd, *J* = 8.0, 1.0 Hz, 2 H), 7.88 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.82 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.68 (d, *J* = 3.0 Hz, 1 H), 7.46 (dd, *J* = 9.0, 3.0 Hz, 1 H), 7.32 (d, *J* = 9.0 Hz, 1 H), 3.93 (s, 1 H). ^{13}C NMR (DMSO-d_6): δ = 180.51, 177.53, 149.63, 143.83, 138.82, 135.53, 134.02, 132.50, 132.29, 130.90, 130.71, 127.24, 126.79, 120.91, 115.19, 114.44, 57.50.

Compound **3f**: ^{1}H NMR (DMSO-d_6): δ = 8.03 (dd, *J* = 5.5, 3.5 Hz, 2 H), 7.81 (dd, *J* = 5.5, 3.5 Hz, 2 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 6.74 (d, *J* = 2.0 Hz, 2 H), 6.63 (dd, *J* = 9.0, 2.0 Hz, 2 H), 3.77 (s, 6 H). ^{13}C NMR (DMSO-d_6): δ = 181.40, 147.50, 138.47, 134.34, 131.90, 131.19, 126.35, 126.17, 124.13, 116.39, 113.60, 57.51.

Compound **2g**: ^{1}H NMR (DMSO-d_6): δ = 8.04–8.07 (m, 2 H), 7.89 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.84 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.77 (d, *J* = 2.5 Hz, 1 H), 7.68 (d, *J* = 9.0 Hz, 1 H), 7.42 (dd, *J* = 9.0, 2.5 Hz, 1 H). ^{13}C NMR (DMSO-d_6): δ = 180.38, 177.77, 147.65, 143.20, 140.04, 135.47, 134.31, 132.30, 131.60, 131.10, 128.07, 127.29, 126.91, 119.50, 119.28, 119.18.

Compound **2h**: ^{1}H NMR ($CDCl_3$): δ = 9.49 (s, 1 H), 8.22 (dd, *J* = 6.5, 1.0 Hz, 1 H), 8.16–8.21 (m, 2 H), 7.81 (td, *J* = 8.0, 1.5 Hz, 1 H), 7.76 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.58 (td, *J* = 8.0, 1.5 Hz, 1 H), 7.20 (td, *J* = 6.0, 1.0 Hz, 1 H), 6.90 (m, 1 H). ^{13}C NMR ($CDCl_3$): δ = 179.71, 177.41, 140.54, 139.46, 135.06, 133.77, 133.62, 133.61, 131.99, 130.19, 127.39, 127.31, 125.95, 124.08, 123.26, 121.88.

Compound **3h**: ^{1}H NMR (DMSO-d_6): δ = 8.10 (dd, *J* = 5.5, 3.0 Hz, 2 H), 7.86 (dd, *J* = 5.5, 2.5 Hz, 2 H), 7.68 (dd, *J* = 8.5, 1.5 Hz, 2 H), 7.27 (m, 2 H), 6.78 (m, 4 H). ^{13}C NMR (DMSO-d_6): δ = 181.34, 137.02, 135.04, 134.42, 133.45, 131.66, 126.89, 125.66, 124.54, 122.33, 122.23.

Compound **2i**:[14] ^{1}H NMR (DMSO-d_6): δ = 8.86 (s, 1 H), 8.42 (d, *J* = 6.0 Hz, 1 H), 8.06–8.12 (m, 2 H), 7.90–7.95 (m, 2 H), 7.40 (d, *J* = 9.0 Hz, 1 H).

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