Synthesis of quinolinequinone derivatives and related carbocyclic compounds

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ABSTRACT

Palladium-catalyzed Buchwald-Hartwig aminations of various quinolinequinone derivatives give excellent yields of novel 6-arylamino derivatives of the disubstituted quinolinequinones and 3-arylamino derivatives of the corresponding naphthoquinones. The precursor quinolinequinones are prepared in a three-step sequence from 8-hydroxyquinoline. The transition-metal-catalyzed arylations of 6,7-dibromo-5,8-quinolinequinone, 6,7-dichloro-5,8-quinolinequinone and 2,3-dichloro-1,4-naphthoquinone are reported for the first time and offer fast and easy access to their derivatives.

INTRODUCTION

Quinolinequinones **1** are bicyclic heterocycles and quinone derivatives consisting of a pyridine ring and a quinone. For a long time, they have been in the focus of a large number of studies because of their wide spectrum of biological activities, which include potent antifungal, antibacterial [1], antimalarial [2] and antineoplastic [3] properties.

They are also an important structural moiety in a number of more complex antibiotic agents such as streptonigrin **2** [4], streptonigrone **3** [5] and lavendamycin **4** [6] as they play an important role in determining their biological activities [7]. The general structure of quinolinequinones **1** has been modified at various positions, and the synthesis and biological activities of various substituted quinolinequinones have been reported, often prepared by the regioselective nucleophilic substitution of 6,7-dichloro-5,8-quinolinequinone with arylamines (Figure 1).

In 1994, Ryu and Kim prepared and investigated 6-(*N*-arylamino)-7-chloro-5,8-quinolinedione derivatives and found that these compounds exhibit potent antifungal and antibacterial activities [8]. In another development, the synthesis and biological activities of several disubstituted quinoline-5,8-diones were reported [9]. The majority of these compounds were prepared by regioselective nucleophilic substitution of quinolinequinone and naphthoquinone with arylamines.

Herein we report on the synthesis of some novel derivatives of 6,7-dibromo-5,8-quinolinequinone, using a transition-metal-based approach, in order to reveal easier routes by which a number of novel derivatives of quinolinequinones can be prepared.

The Buchwald-Hartwig amination is a palladium-catalyzed cross-coupling reaction of an aryl halide or pseudo-halide with an amine together with a strong base [10]. The formation of C-N bonds is the major focus of this research, coupling aryl halides as key intermediates with anilines. We have used various anilines in this research to demonstrate easier routes for the preparation of new quinolinequinones using a transition-metal-based approach. The Buchwald-Hartwig reaction is initiated by an oxidative addition of the aryl halide to the palladium, which is followed by coordination of the amine. The strong base then abstracts a proton from the amine, which attacks the palladium with the halide acting as a leaving group. Reductive elimination then produces the final aryl amine product and regenerates the catalyst [11, 12].

RESULTS AND DISCUSSION

The yields in the synthesis of target molecules using the Buchwald-Hartwig reaction depend largely on the reaction conditions and on the type of ligands used. Several ligands had been employed in C-N cross-coupling processes. Also several palladium sources have been used. We started our investigations using the combination of palladium(II) acetate and triphenylphosphine, but these conditions only provided traces of the desired coupling products. Following the discovery of Huang et al. [13] that biaryl dialkylphosphines are excellent ligands in C-N bond formation, we exchanged triphenylphosphine with the advanced ligands Xphos and Brettphos in the reaction while still maintaining palladium(II) acetate as the palladium source. These gave very encouraging outcomes as

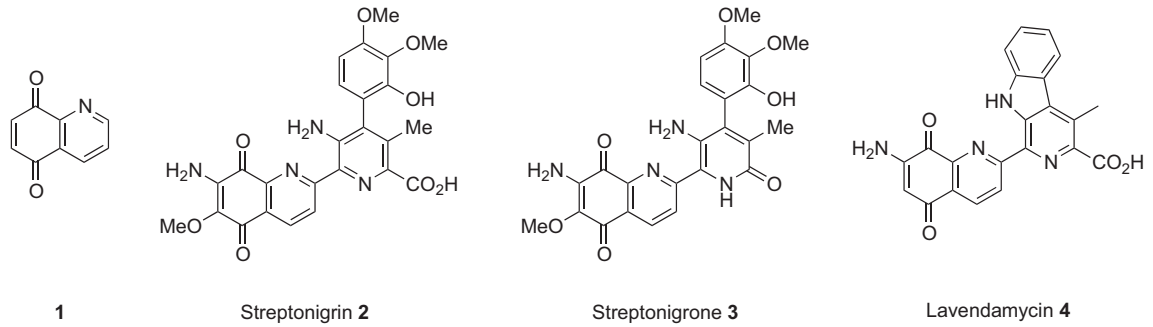
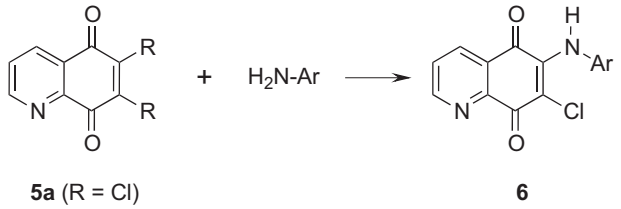


Figure 1. Quinolinequinone derivatives.

the yields and reaction times were greatly improved (Table 1, entry 2). This finding agrees with the discovery made by Galardon et al. [14] that the use of bulky ligands accelerates the elimination step in palladium-catalyzed reactions. We then realized the work of Brett et al. [15], describing a procedure that maximizes the efficiency of biaryl dialkylphosphine ligands. They discovered that a highly active catalyst can be generated by heating palladium(II) acetate (1 mol%), water (4 mol%) and Xphos (3 mol%) for 1 min at 80 °C in 1,4-dioxane, which can be monitored visually by a colour change. We adopted the procedure with little variation and received the most encouraging outcome. Under these reaction conditions, the reactions were completed much faster and with similar efficiency (Table 1, entry 3; Scheme 1).

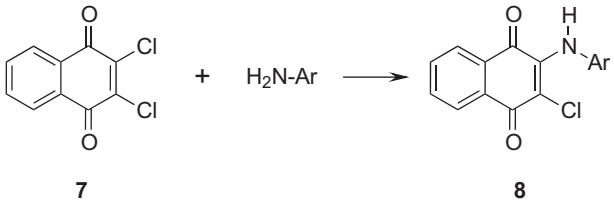


Scheme 1. Amination of 6,7-dichloro-5,8-quinolinequinone 5a.

The reaction on the quinolinequinone **5** is typically at the 6-position through the involvement of the electron-donating nitrogen atom leading to compounds of type **6** [16]. In Table 2 the optimized reaction conditions have been employed for the rapid synthesis of several novel quinolinequinone derivatives. Both 6,7-dichloro- and 6,7-dibromo-5,8-quinolinequinones **5a** and **5b** have been employed in the reaction, the dibromo derivative showing slightly higher reactivity in the reaction.

Table 1. Optimization of reaction conditions for the amination of disubstituted-5,8-quinolinequinone.

Entry	Reaction conditions	Yield (%)	Reaction time (h)
1	$Pd(OAc)_2/PPh_3$	Trace	28–48
2	$Pd(OAc)_2$/BrettPhos or XPhos	>80	12–24
3	$Pd(OAc)_2$/XPhos, water activation	>80	1–3



The same reaction conditions were subsequently used to functionalize 2,3-dichloro-1,4-naphthoquinone with similar efficiency as shown in Table 3.

In summary, we have developed an efficient protocol for the synthesis of different novel monosubstitued and disubstituted quinolinequinones and naphthoquinones as potential core structures for the development of biologically active molecules.

EXPERIMENTAL

General

Melting points were determined with a Fisher-John apparatus and are uncorrected. Ultraviolet and visible spectra were recorded on a Unico-UV2102 PC spectrophotometer using matched 1-cm quartz cells using methanol and DMSO as solvents. The absorption maxima are given in nanometers and the figures in parenthesis are dimethyl sulphoxide values. The nuclear magnetic resonance (NMR) spectra were recorded on Bruker DPX-250, Bruker DPX-400, Bruker DPX-500 or Oxford 300. Chemical shifts are reported in ppm values relative to tetramethylsilane (TMS) as an internal standard. Elemental analyses were obtained on Heraeus CHN-O rapid analyser.

6,7-Dichloro-5,8-quinolinequinone 5a

The synthesis of this compound followed the same procedure as that described for **5b**; in the last step, HBr and $KBrO_3$ were replaced with HCl and $KClO_3$ (m.p. 243–245 °C).

Table 2. Amination of 6,7-disubstituted-5,8-quinolinequinones with different aniline derivatives.

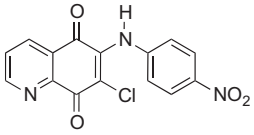
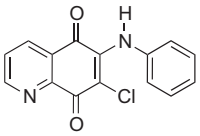
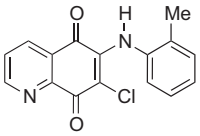
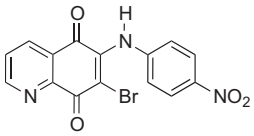
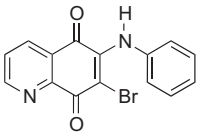
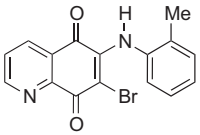
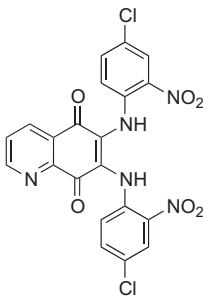
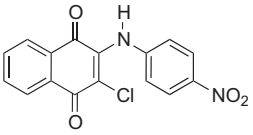
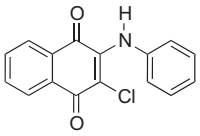
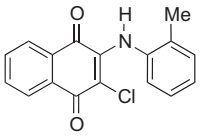
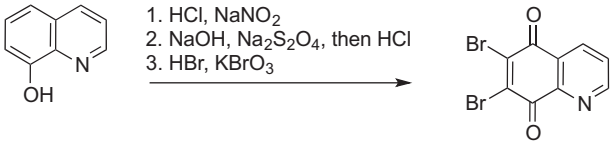
Entry	Quinolinequinone	Aniline	Product 6	Reaction time (min)	Yield (%)
1	**5a** (R = Cl)	4-NO_2-C_6H_4-NH_2	 **6a**	80	84
2	**5a** (R = Cl)	C_6H_5-NH_2	 **6b**	170	85
3	**5a** (R = Cl)	2-Me-C_6H_4-NH_2	 **6c**	70	85
4	**5b** (R = Br)	4-NO_2-C_6H_4-NH_2	 **6d**	75	86
5	**5b** (R = Br)	C_6H_5-NH_2	 **6e**	60	90
6	**5b** (R = Br)	2-Me-C_6H_4-NH_2	 **6f**	90	90
7	**5a** (R = Cl)	2-NO_2-4-Cl-C_6H_3-NH_2	 **6g**	1680	85
8	**5b** (R = Br)	2-NO_2-4-Cl-C_6H_3-NH_2	**6g**	190	85

Table 3. Amination of 2,3-dichloro-1,4-naphthoquinone with different aniline derivatives.

Entry	Aniline	Product 8	Reaction time (min)	Yield (%)
1	4-NO_2-C_6H_4-NH_2	 **8a**	130	84
2	C_6H_5-NH_2	 **8b**	120	90
3	2-Me-C_6H_4-NH_2	 **8c**	130	80
4	2-NO_2-4-Cl-C_6H_3-NH_2	–	480	0

6,7-Dibromo-5,8-quinolinequinone 5b



5b

The synthesis of this compound was carried out in three steps reactions from 8-hydroxyquinoline with concentrated hydrochloric acid followed by the addition of sodium nitrite at 0 °C for 1 h. The mixture was allowed to stand overnight at 0 °C, washed and dried to give 8-hydroxy-5-nitrosoquinoline hydrochloride, a bright yellow solid (m.p. 179–181; lit. 180 °C) [9].

8-Hydroxy-5-nitrosoquinoline hydrochloride (0.216 mol, 40 g) was added to a mixture of water (160 mL) and 5 N NaOH (260 mL) and heated to 40 °C. $Na_2S_2O_4$(1.28 mol, 95 g) was added to the reaction mixture and then the temperature was increased to 75 °C. The reaction mixture was cooled to 50 °C and 12 N HCl (250 mL) was added. Then the reaction mixture was cooled to 0 °C and filtered to give 5-amino-8-hydroxyquinoline dihydrochloride (34 g, 91%) [9].

Addition of 5-amino-8-hydroxyquinoline dihydrochloride (55.6 mmol, 9 g) to hydrobromic acid (81 g); the reaction mixture was heated to 60 °C and $KBrO_3$ (27 mmol, 4.5 g) was added. The reaction mixture was stirred for 30 min at 50 °C, filtered and recrystallized twice from butanol to yield 6,7-dibromo-5,8-quinolinequinone as a yellow precipitate (15.8 g, 90%) (m.p. 239–241; lit. 243–245 °C) [9].

General procedures for the Buchwald-Hartwig amination

Procedure A: BrettPhos (0.94 μmol, 0.5 mg, 0.15 mol%) and $Pd(OAc)_2$ (0.05 mol%, 0.1 mg, 0.05 mol%) were placed in a 25 mL three-neck round-bottom flask. After purging with nitrogen for 30 s, 1 mL water and 5 mL EtOH were added and the solution was heated for 60 s to 80 °C; the preactivation could be followed by a colour change. Then 6,7-dihalo-5,8-quinolinequinone, aniline derivative, base and 5 mL EtOH were added. The reaction mixture was heated at reflux with vigorous stirring for the indicated time. The completion of the reaction was monitored by thin-layer chromatography (TLC), then cooled, filtered and recrystallized with water and acetone.

Procedure B: XPhos (0.0032 mmol, 1.5 mg, 1 mol%) and $Pd(OAc)_2$ (0.0095 mmol, 2.1 mg, 3 mol%) were placed in a 25 mL three-neck round-bottom flask. After purging with nitrogen for 30 s, 1 mL water and 5 mL EtOH were added and the solution was heated for 60 s to 80 °C; the preactivation could be followed by a colour change. Then the 6,7-dihalo-5,8-quinolinequinone, aniline derivative, base and 2 ml dioxane were added. The reaction mixture was heated at reflux with vigorous stirring for the indicated time. The completion of the reaction was monitored by TLC, then cooled, filtered and recrystallized with water and acetone.

7-Chloro-6-[(4-nitrophenyl)amino]quinoline-5,8-dione 6a

Procedure A. 6,7-Dichloro-5,8-quinolinequinone **5a** (0.88 mmol, 200 mg), 4-nitroaniline (3.52 mmol, 486 mg), NaO*t*-Bu (1.06 mmol, 101 mg, 1.2 eq), 80 min. The product (red solid) m.p. 318–320 °C was obtained in 244 mg (0.74 mmol); yield: 84%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0127), 620 (0.088), 630 (0.071), 640 (0.057); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.1 (d, *J* = 3.6 Hz, 1H), 8.4 (dd, *J* = 1.6, *J* = 8 Hz, 1H), 8.2 (dd, 2H), 7.6 (dd, *J* = 4.8, *J* = 8.4 Hz, 2H), 7.1 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.44 (C = O(C-5)), 172.38 (C = O(C-8)), 160.87 (C-1), 153.90 (C-7), 151.34 (C-10), 147.15 (C-3), 133.82 (C-13), 133.65 (C-4 & C-2), 132.13 (C-12 & C-14), 106.508 (C-11 & C-15) ppm; IR 1670 (C = O), 1496 (NO_2) cm^{-1}; MS 283.27, 328.02; Anal. Calcd. (found) for $C_{15}H_8ClN_3O_4$: C, 54.65 (54.70); H, 2.45 (2.40); N, 12.75 (12.70); Cl, 10.75 (10.66).

7-Chloro-6-(phenylamino)quinoline-5,8-dione 6b

Procedure A. 6,7-Dichloro-5,8-quinolinequinone **5a** (0.88 mmol, 200 mg), aniline (0.86 mmol, 80 mg), NaO*t*-Bu (1.06 mmol, 101 mg, 1.2 eq), 170 min. The product (dark red solid) m.p. 314–316 °C was obtained in 173 mg (0.608 mmol); yield: 85%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0.039), 620 (0.015), 630 (0.013), 640 (0.010); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.8 (d, *J* = 4 Hz, 1H), 8.4

(d, *J* = 6.8 Hz, 1H), 7.7 (dd, *J* = 4.8, *J* = 7.6 Hz, 1H), 7.2 (dd, 2H), 7.1 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.51 (C = O(C-5)), 153.89 (C-1), 151.33 (C-7), 1136.31 (C-9), 136.12 (C-10), 133.82 (C-3), 128.02 (C-14 & C-12), 125.58 (C-11 & C-15), 113.41 (C-13), 112.36 (C-6) ppm; IR 1558 (C = O), 1512 (NH) cm^{-1}; MS 284.04, 285.04; Anal. Calcd. (found) for $C_{15}H_9ClN_2O_2$: C, 63.28 (63.33); H, 3.19 (3.20); N, 9.84 (9.93); Cl, 12.45 (12.70).

7-Chloro-6-(*o*-tolylamino)quinoline-5,8-dione 6c

Procedure B. 6,7-Dichloro-5,8-quinolinequinone **5a** (0.44 mmol, 100 mg), *o*-toluidine (0.53 mmol, 57 mg), K_2CO_3 (0.62 mmol, 86 mg, 1.4 eq), 70 min. The product (dark red solid) m.p. 316–318 °C was obtained in 112 mg (0.373 mmol); yield: 85%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (1.099), 620 (0.819), 630 (0.727), 640 (0.654); IR 1678 (C = O), 1504 (N-H), 1307 (CH_3), 3250br cm^{-1}; MS 298.05, 263.08; Anal. Calcd. (found) for $C_{16}H_{11}ClN_2O_2$: C, 64.33 (64.30); H, 3.71 (3.64); N, 9.38 (9.32); Cl, 11.87 (11.68).

7-Bromo-6-[(4-nitrophenyl)amino]quinoline-5,8-dione 6d

Procedure A. 6,7-Dibromo-5,8-quinolinequinone **5b** (0.63 mmol, 200 mg), 4-nitroaniline (2.52 mmol, 348 mg), NaO*t*-Bu (0.76 mmol, 73 mg, 1.2 eq), 75 min. The product (red solid) m.p. 238–240 °C was obtained in 203 mg (0.54 mmol), yield: 86%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (2.697), 620 (2.7), 630 (2.282) 640 (2.389); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.0 (dd, *J* = 1.6, *J* = 4.8 Hz, 1H), 8.4 (dd, *J* = 1.6, *J* = 7.6 Hz, 1H), 8.2 (m, 2H), 7.6 (dd, *J* = 4.8, *J* = 8.0 Hz, 2H), 7.1 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 206.4 (C = O(C-7)), 207.0 (C = O(C-4)), 161.2 (C-6), 153.9 (C-1), 149.2 (C-8), 114.6 (C-9 & C-13), 134.0 (C-10 & C-12), 136.3 (C-11), 136.2 (C-3), 128.0 (C-15), 127.6 (C-14), 112.4 (C-5) ppm; IR 1712 (C = O), 1419 (NO_2) cm^{-1}; MS 371.94, 328.00, 239.04 (M^+); Anal. Calcd. (found) for $C_{15}H_8BrN_3O_4$: C, 48.15 (48.18); H, 2.16 (2.15); N, 11.23 (11.20); Br, 21.36 (21.30).

7-Bromo-6-[phenylamino]quinoline-5,8-dione 6e

Procedure A. 6,7-Dibromo-5,8-quinolinequinone **5b** (0.63 mmol, 200 mg), aniline (0.76 mmol, 71 mg), NaO*t*-Bu (0.76 mmol, 73 mg, 1.2 eq), 60 min. The product (dark red solid) m.p. 254–256 °C was obtained in 187 mg (0.568 mmol); yield: 90%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0.045), 620 (0.019), 630 (0.010) 640 (0.009); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.8 (dd, *J* = 2, *J* = 4.8 Hz, 1H), 8.4 (dd, *J* = 1.6, *J* = 8 Hz, 1H), 7.7 (dd, *J* = 4.8, *J* = 8 Hz, 1H) 7.3 (dd, 2H), 7.1 (m, 3H) ppm; IR 1550 (C = O), 1516 (NH); 2600br cm^{-1}; MS 329.0, 331.0 (M^+); Anal. Calcd. (found) for $C_{15}H_9BrN_2O_2$: C, 54.74 (54.80); H, 2.76 (2.81); N, 8.51 (8.57); Br, 24.28 (24.22).

7-Bromo-6-(*o*-tolylamino)quinoline-5,8-dione 6f

Procedure B. 6,7-Dibromo-5,8-quinolinequinone **5b** (0.32 mmol, 100 mg), *o*-toluidine (0.38 mmol, 41 mg), K_2CO_3 (0.62 mmol, 86 mg, 1.4 eq), 90 min. The product (red solid) m.p. 216–218 °C was obtained in 98 mg (0.284 mmol); yield: 90%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0.393), 620 (0.272), 630 (0.249), 640 (0.233); IR 1739 (C = O), 1373 cm^{-1}; MS 143.14, 239.12, 313.15, 341.06 (M^-); Anal. Calcd. (found) for $C_{16}H_{11}BrN_2O_2$: C, 56.00 (56.30); H, 3.23 (3.19); N, 8.16 (8.21); Br, 23.28 (23.17).

6,7-Bis[(4-chloro-2-nitrophenyl)amino]quinoline-5,8-dione 6g

Procedure A. 6,7-Dibromo-5,8-quinolinequinone **5b** (0.63 mmol, 200 mg), 4-chloro-2-nitroaniline (2.52 mmol, 435 mg), NaO*t*-Bu (0.76 mmol, 73 mg, 1.2 eq), 190 min. The product (red solid) m.p. 286–288 °C was obtained in 268 mg (0.536 mmol); yield: 85%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0.043), 620 (0.017), 630 (0.008) 640 (0.007); ^{1}H NMR (400 MHz, MeOH): δ = 8.92 (dd, *J* = 1.6, *J* = 4.8 Hz, 1H), 8.91 (s, 2H), 8.36 (ddd, *J* = 1.6, *J* = 7.6 Hz, 1H), 8.32 (m, 2H), 7.60 (dd, *J* = 4.8, *J* = 8 Hz, 1H), 7.58 (s, 2H), 7.56 (m, 2H) ppm; IR 1700 (C = O), 1500 (NO_2), 2600 cm^{-1}; MS 130.99; 501.97 (M^+); Anal. Calcd. (found) for $C_{21}H_{11}Cl_2N_5O_6$: C, 50.42 (50.71); H, 2.22 (2.14); N, 14.00 (14.03); Cl, 14.17 (14.23).

2-Chloro-3-((4-nitrophenyl)amino)naphthalene-1,4-dione 8a

Procedure B. 2,3-Dichloro-1,4-naphthoquinone (0.88 mmol, 200 mg), 4-nitroaniline (1.10 mmol, 152 mg), K_2CO_3 (1.23 mmol, 170 mg, 1.4 eq), 130 min. The product (dark red solid) m.p. 318–320 °C was obtained in 243 mg (0.74 mmol); yield: 84%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0.082), 620 (0.039), 630 (0.035), 640 (0.018); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.2 (dd, 2H), 7.28 (dd, 2H), 7.23 (dd, 2H), 7.2 (s, 1H), 6.7 (d, 2H) ppm; IR 1712 (C = O), 1419 (NO_2), 663 (C = C in ring) cm^{-1}; MS 264.98, 298.03, 313.98, 328.02; Anal. Calcd. (found) for $C_{16}H_9ClN_2O_4$: C, 58.46 (58.41); H, 2.76 (2.82); N, 8.52 (8.61); Cl, 10.78 (10.93).

2-Chloro-3-(phenylamino)naphthalene-1,4-dione 8b

Procedure A. 2,3-Dichloro-1,4-naphthoquinone (0.88 mmol, 200 mg), aniline (1.10 mmol, 102 mg), NaO*t*-Bu (1.06 mmol, 101 mg, 1.2 eq), 120 min. The product (dark red solid) m.p. 314–316 °C was obtained in 225 mg (0.793 mmol); yield: 90%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0.366), 620 (0.276), 630 (0.252), 640 (0.214); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.1 (dd, 2H), 8.1 (dd, 2H), 7.7 (dd, 2H), 7.6 (dd, 4H) ppm; IR 1739 (C = O), 2340br cm^{-1}; MS 144.04, 248.07, 283.04, 285.04, M^+; Anal. Calcd. (found) for $C_{16}H_{10}ClNO_2$: C, 67.74 (67.70); H, 3.55 (3.51); N, 4.94 (4.89); Cl, 12.50 (12.37).

2-Chloro-3-(*o*-tolylamino)naphthalene-1,4-dione 8c

Procedure B. 2,3-Dichloro-1,4-naphthoquinone (0.44 mmol, 100 mg), *o*-toluidine (0.53 mmol, 57 mg), K_2CO_3 (0.61 mmol, 85 mg, 1.4 eq), 130 min. The product (dark red solid) m.p. 316–318 °C was obtained in 105 mg (0.352 mmol); yield: 80%.

The ultraviolet maximum absorption bands in methanol: nm (logE), 600 (0.031), 620 (0.022), 630 (0.024), 640 (0.017); IR 1674 (C = O), 1508 (NH), 1477 cm^{-1}; MS 121.02, 161.05, 191.02, 297.93 M^+; Anal. Calcd. (found) for $C_{17}H_{12}ClNO_2$: C, 68.58 (68.70); H, 4.06 (4.00); N, 4.70 (4.71); Cl, 11.91 (11.98).

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COMPETING INTERESTS

The authors declare no competing interests.

PUBLISHING NOTES