A General Procedure for the Efficient Synthesis of (Alkylamino)naphthoquinones

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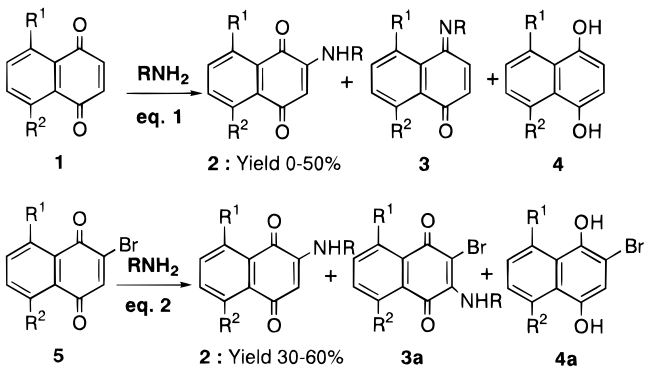
Alkylamino derivatives of naphthazarine, juglone, and naphthoquinone have been synthesized via their corresponding bromo-analogues, in high yields, especially in the case of naphthazarins.

The synthesis of simple alkylamino derivatives of naphthoquinones and related compounds is of considerable interest, since they exhibit potent antitumor[1] and antimalarial[2] activities. In addition, due to their functional properties they have found wide industrial applications in color chemistry[3] and hair dying,[4] as well as photostabilizers.[5] Furthermore, the aminonaphthoquinone moiety is a component of the molecular framework of several natural products (e.g. rifamycins,[6] kinamycins,[7] rifampicins,[8] streptovaricins,[9] etc.) and has been used as a synthetic key intermediate for the construction of several biologically important compounds.[10]

The hitherto reported general methods for their preparation can be classified in two groups: one which involves a direct 1,4-type addition of amines to the quinone moiety of naphthoquinones[2,11] **1** (Scheme 1, eq 1), while the other involves the nucleophilic displacement of the readily obtained halo-derivatives[12] **5** (eq 2).

Scheme 1



However, both methods are tedious and usually give very low yields and many byproducts, especially with primary amines. These drawbacks, in conjunction with the difficulties encountered during their chromatographic purification,[13] makes these methods synthetically unattractive.

The variety of compounds obtained via eqs 1 and 2 originate from the redox properties of naphthoquinone, which leads to the formation of the inert diol **4** (or **4a**), and the existence of four electrophilic centers of comparable reactivity, leading to the formation of 1,2- and 1,4-addition adducts, **3** and **3a**, as well as bis-adducts.

Recently, D. H. R. Barton[14] has reported an efficient nucleophilic substitution reaction of α-bromo-ketones with amines in a high yield fashion. These findings prompted us to reinvestigate the nucleophilic substitution of naphthoquinones. As substrate for our study we have chosen bromonaphthoquinone **5**[15−18] which can be easily reduced to compound **6** (Scheme 2). The latter is in equilibrium between the enol-form **6a** and the keto-form **6b**, the position of the equilibrium being dependent on

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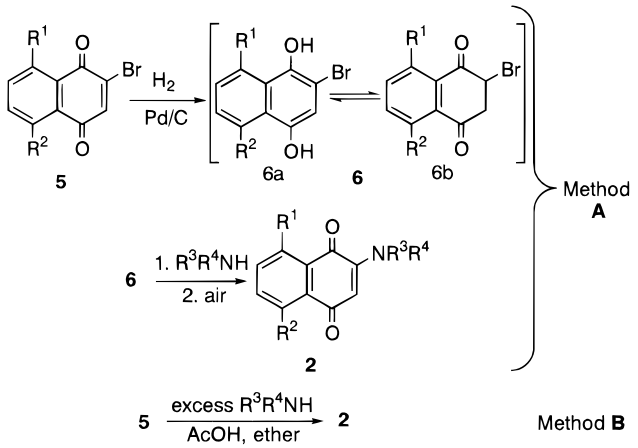
Scheme 2



the substitution pattern.[19] In contrast to the oxidized state **5**, compound **6b** possesses a simple very reactive electrophilic carbon, i.e. the bromo-substituted one.

Accordingly, after treatment of **5** with H_2 over Pd/C catalyst and subsequent addition of a solution of an amine (Scheme 2, method A), a fast and clean substitution took place. Presumably, additional exposure of the reaction mixture to atmospheric oxygen[20] afforded the observed amino derivative **2**. Overall this reactions sequence is very efficient, as the isolation and purification of the product in most cases is performed merely by recrystallization.

Table 1 summarizes the products and chemical yields obtained by the above procedure (method A). For comparison purposes, the same products were prepared by method B, which is an adaptation of the literature reports for this transformation.[12] Based on the rationale with which this new method was developed, it is not surprising that it works best with naphthazarin (Table 1, entries 1−6), since the equilibrium **6a** ↔ **6b** is shifted toward the keto-form **6b**.[19] In the case of juglone (entries 7−11), this equilibrium is more balanced and, as a consequence, the substitution is slower.[21] Nevertheless, our approach gives better yields and higher regioselectivity than the reported procedures.[22] Finally, naphthoquinone (entries 12 and 13), which exists almost exclusively in the enol-form **6a**, requires longer reaction times.

The applicability of the present procedure for the preparation of new naphthazarine derivatives is currently under investigation.

Experimental Section

The ^{1}H NMR spectra (200 MHz) were recorded in $CDCl_3$. Infrared (IR) spectra were obtained in accordance with the KBr disk technique. Microanalytical data were provided by the Microanalytical Service Laboratory of NRC "Democritos". Mass spectra were recorded operating in electron impact (EI) mode. Melting points were uncorrected. Column (flash) chromatography was performed on silica gel (32−63 nm), and TLC analyses were carried out using glass precoated silica gel plates.

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(20) The reaction time of the oxidation dependent upon the substitution of the aromatic ring.

(21) Both regioisomers of aminojuglone derivatives were independently prepared according to the literature (ref 11b) and found to be identical with those prepared following our method.

(22) The yield of compound **2g** seems to depend strongly on the time of air-oxidation and workup manipulations. Extension of the oxidation period beyond 10 min dramatically decreases the yield.

Table 1. Comparison of Methods A and B for the Synthesis of (Alkylamino)naphthoquinones

Entry	Naphthoquinones **5** R^1	R^2	$-NR^3R^4$	Product **2a-o**	Method A Yield %	Method B Yield %
1	OH	OH	—NHMe	**2a**	71	4[a]
2	OH	OH	—NHEt	**2b**	83	11[a]
3	OH	OH	—NH^{i}Pr	**2c**	79	12[a]
4	OH	OH	—NMe_2	**2d**	74	38[a]
5	OH	OH	—N⟨⟩	**2e**	89	66[a]
6	OH	OH	—N⟨⟩O	**2f**	77	68[a]
7	H	OH	—N⟨⟩O	**2g**	69[a]	20[a]
8	H	OAc	—NH^{i}Pr	**2h**	51[a]	33[a]
9	H	OMe	—N⟨⟩O	**2k**	-[b]	-[b]
10	OH	H	—NH^{i}Pr	**2l**	81	72[a]
11	OH	H	—N⟨⟩O	**2m**	87	65[a]
12	H	H	—NH^{i}Pr	**2n**	48[a]	92
13	H	H	—N⟨⟩O	**2o**	80	79

[a] chromatographic purification
[b] many byproducts, compound **2k** formed in less than 5% yield

General Experimental Procedures. Method A: In dry ethyl ether (or ethyl acetate) the respective bromonaphthoquinone derivative **5** and 15% (by weight of **5**) of 10% Pd/C were stirred under H_2 atmosphere for 1−3 h. After the color of the reaction had turned pale yellow, a solution of 1.2 equiv of the amine was added, and the reaction mixture was stirred for an additional 10−50 min period under hydrogen. The reaction mixture was then acidified with 1 N HCl, stirred for 5−30 min in open air, filtered through a Celite pad, and extracted once with 1 N HCl. The organic layer was subsequently washed with water to neutrality, dried over $MgSO_4$, and evaporated under reduced pressure. Crystallization afforded the desired amino adduct in analytically pure form.

Method B: To an ice-cold solution of the respective bromonaphthoquinone derivative **5** in dry ethyl ether was added an ethereal solution of amine (7 equiv) and acetic acid (6.5 equiv). Then the reaction was allowed to warm to room temperature and stirred for an additional 4 h. The end of the reaction was detected by TLC, and the product was isolated as in method A. The product was purified either by crystallization or by column chromatography.

5,8-Dihydroxy-2-(methylamino)-1,4-naphthoquinone (2a). Following the general method A, 3 equiv of methylamine was used. Crystallization of the residue with ethyl ether−hexane gave **2a** as a dark red solid: mp 218−220 °C; IR (KBr) 3325, 2905, 1562, 1400 cm^{-1}; ^{1}H NMR δ 13.32 (s, 1H), 11.84 (s, 1H), 7.29 (d, 1H, J = 8.7 Hz), 7.12 (d, 1H), 6.10 (bs, 1H), 5.67 (s, 1H), 3.00 (d, 3H, J = 4.5 Hz); MS (m/z) 219 (M^+). Anal. Calcd for $C_{11}H_9O_4N$ (219.053): C, 60.26; H, 4.14; N, 6.39. Found: C, 60.30; H, 4.27; N, 6.24.

5,8-Dihydroxy-2-(ethylamino)-1,4-naphthoquinone (2b). Following the general method A, 3 equiv of ethylamine was used. Crystallization of the residue with ethyl ether−hexane gave **2b** as a dark red solid: mp 161−165 °C; IR (KBr) 3260, 2910, 1570, 1505, 1445 cm^{-1}; ^{1}H NMR δ 13.36 (s, 1H), 11.84 (s, 1H), 7.26 (d, 1H, J = 9.3 Hz), 7.09 (d, 1H), 6.59 (s, 1H),

6.02 (bs, 1H), 3.26 (m, 2H), 1.35 (t, 3H, $J = 3.5$); MS (m/z) 233 (M^+). Anal. Calcd for $C_{12}H_{11}O_4N$ (233.069): C, 61.78; H, 4.76; N, 6.01. Found: C, 61.87; H, 4.97; N, 5.84.

5,8-Dihydroxy-2-(isopropylamino)-1,4-naphthoquinone (2c). Following the general method A, 3 equiv of isopropylamine was used. Crystallization of the residue with ethyl acetate−hexane gave **2c** as a dark red solid: mp 120−122 °C; IR (KBr) 3375, 2920, 2850, 1580, 1510, 1435 cm^{-1}; ^1H NMR δ 13.32 (s, 1H), 11.84 (s, 1H), 7.23 (d, 1H, $J = 9.4$ Hz), 7.10 (d, 1H), 5.98 (bs, 1H) 5.68 (s, 1H), 3.67 (dsep, 1H, $J = 8.4$ Hz), 1.18 (d, 6H); MS (m/z) 247 (M^+). Anal. Calcd for $C_{13}H_{13}O_4N$ (247.084): C, 63.14; H, 5.30; N, 5.67. Found: C, 63.18; H, 5.33; N, 5.53.

5,8-Dihydroxy-2-(dimethylamino)-1,4-naphthoquinone (2d). Crystallization of the residue with ethyl ether−hexane gave **2d** as a dark red solid: mp 140−142 °C; IR (KBr) 3450 (bd), 2935, 1605, 1550, 1450 cm^{-1}; ^1H NMR δ 13.29 (s, 1H), 12.10 (s, 1H), 7.17 (d, 1H, $J = 9.1$ Hz), 7.03 (d, 1H), 5.72 (s, 1H), 3.26 (s, 6H); MS (m/z) 233 (M^+). Anal. Calcd for $C_{12}H_{11}O_4N$ (233.069): C, 61.78; H, 4.76; N, 6.01. Found: C, 61.75; H, 4.63; N, 5.81.

***N*-(5,8-Dihydroxy-1,4-naphthoquinon-2-yl)piperidine (2e).** Crystallization of the residue with ethyl acetate−hexane gave **2e** as a dark red solid: mp 107−110 °C; IR (KBr) 3400 (bd), 2925, 2850, 1600, 1560, 1445 cm^{-1}; ^1H NMR δ 13.08 (s, 1H), 12.19 (s, 1H), 7.17 (d, 1H, $J = 9.4$ Hz), 7.02 (d, 1H), 5.92 (s, 1H), 3.48 (m, 4H), 1.70 (s, 6H); MS (m/z) 273 (M^+). Anal. Calcd for $C_{15}H_{15}O_4N$ (273.100): C, 65.91; H, 5.54; N, 5.13. Found: C, 65.68; H, 5.37; N, 4.94.

***N*-(5,8-Dihydroxy-1,4-naphthoquinon-2-yl)morpholine (2f).** Crystallization of the residue with ethyl ether−hexane gave **2f** as a dark red solid: mp 178−180 °C; IR (KBr) 3450, 2958, 2880, 1625, 1475 cm^{-1}; ^1H NMR δ 13.90 (s, 1H), 12.18 (s, 1H), 7.18 (d, 1H, $J = 9.5$ Hz), 7.02 (d, 1H), 5.90 (s, 1H), 3.80 (t, 4H, $J = 3.6$ Hz), 3.48 (t, 4H); MS (m/z) 275 (M^+). Anal. Calcd for $C_{14}H_{13}O_5N$: C, 61.07; H, 4.76; N, 5.09. Found: C, 60.83; H, 4.83; N, 4.74.

***N*-(5-Hydroxy-1,4-naphthoquinon-2-yl)morpholine (2g).** The residue after column chromatography purification (using hexane−ethyl acetate 9:1 as eluant) and crystallization with ethyl acetate−hexane afforded **2g** as a dark red solid: mp 190−195 °C; IR (KBr) 3420, 2920, 1625, 1565, 1400 cm^{-1}; ^1H NMR δ 11.85 (s, 1H), 7.60 (m, 2H), 7.02 (m, 1H), 6.10 (s, 1H), 3.88 (t, 4H, $J = 3.4$ Hz), 3.50 (t, 4H); MS (m/z) 259 (M^+). Anal. Calcd for $C_{14}H_{13}O_4N$ (259.084): C, 64.84; H, 5.06; N, 5.40. Found: C, 64.88; H, 5.27; N, 5.34.

5-(Acetyloxy)-2-(isopropylamino)-1,4-naphthoquinone (2h). The residue after column chromatography purification (using hexane−ethyl acetate 9:1 as eluant) and crystallization with ethyl acetate−hexane afforded **2h** as a yellow solid, mp 118−122 °C; IR (KBr) 3380, 2980, 1775, 1685, 1610 cm^{-1}; ^1H NMR δ 8.10 (d, 1H, $J = 8.0$ Hz), 7.74 (t, 1H), 7.25 (d, 1H), 5.79 (bs, 1H), 5.72 (s, 1H), 3.62 (sep, 1H, $J = 4.4$), 2.46 (s, 3H), 1.28 (d, 6H); MS (m/z) 273 (M^+). Anal. Calcd for $C_{15}H_{15}O_4N$ (273.100): C, 65.91; H, 5.54; N, 5.13. Found: C, 65.84; H, 5.37; N, 4.94.

5-Hydroxy-3-(isopropylamino)-1,4-naphthoquinone (2l). Crystallization of the residue with ethyl acetate−hexane afforded **2l** as a dark red solid: mp 111−114 °C; IR (KBr) 3485, 3310, 2900, 1585 cm^{-1}; ^1H NMR δ 11.53 (s, 1H), 7.62 (m, 3H), 6.00 (bs, 1H), 5.45 (s, 1H), 3.45 (dsep, 1H, $J = 3.6$ Hz), 1.28 (d, 6H); MS (m/z) 231 (M^+). Anal. Calcd for $C_{13}H_{13}O_3N$ (231.090): C, 67.51; H, 5.67; N, 6.06. Found: C, 67.43; H, 5.57; N, 5.84.

***N*-(5-Hydroxy-1,4-naphthoquinon-3-yl)morpholine (2m).** Crystallization of the residue with ethyl acetate−hexane afforded **2m** as an dark orange solid: mp 150−154 °C; IR (KBr) 3425, 2925, 1620, 1555, 1465 cm^{-1}; ^1H NMR δ 12.54 (s, 1H), 7.43 (m, 2H), 7.15 (m, 1H), 5.83 (s, 1H), 3.85 (t, 4H, $J = 3.4$ Hz), 3.47 (t, 4H); MS (m/z) 259 (M^+). Anal. Calcd for $C_{14}H_{13}O_4N$ (259.084): C, 64.84; H, 5.06; N, 5.40. Found: C, 64.96; H, 5.11; N, 5.21.

2-(Isopropylamino)-1,4-naphthoquinone (2n). The residue after column chromatography purification (using hexane−ethyl acetate 8:1 as eluant) and crystallization with ethyl acetate−hexane afforded **2n** as a yellow solid: mp 68−70 °C; IR (KBr) 3355, 2990, 1675, 1600, 1505 cm^{-1}; ^1H NMR δ 8.08 (m, 2H), 7.62 (d, 2H), 5.79 (bs, 1H), 5.72 (s, 1H), 3.62 (sep, 1H, $J = 3.6$ Hz), 1.28 (d, 6H); MS (m/z) 215 (M^+). Anal. Calcd for $C_{13}H_{13}O_2N$ (215.095): C, 72.53; H, 6.09; N, 6.51. Found: C, 72.48; H, 6.08; N, 6.72.

***N*-(1,4-naphthoquinon-2-yl)morpholine (2o).** Crystallization of the residue with ethyl ether−hexane gave **2o** as a yellow orange solid: mp 134−135 °C; IR (KBr) 3450, 2980, 1680, 1595 cm^{-1}; ^1H NMR δ 8.08 (m, 2H), 7.65 (m, 2H), 6.02 (s, 1H), 3.88 (t, 4H, $J = 3.5$ Hz), 3.52 (t, 4H); MS (m/z) 243 (M^+). Anal. Calcd for $C_{14}H_{13}O_3N$ (243.090): C, 69.11; H, 5.39; N, 5.76. Found: C, 68.80; H, 5.51; N, 5.64.

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