Chemoselective Substitution Reaction of 2-Bromo-3-methoxy-1,4-naphthoquinone

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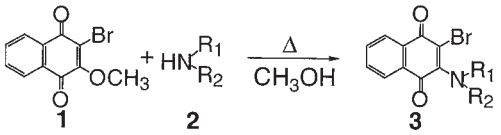
Chemoselective substitution reactions of 2-bromo-3-methoxy-1,4-naphthoquinone were studied here. In the reactions of 2-bromo-3-methoxy-1,4-naphthoquinone with a variety of alkylamines, 2-alkylamino-3-bromo-1,4-naphthoquinones resulted in high yields. Alkylthiols, on the other hand, were found to form 2-alkylthio-3-methoxy-1,4-naphthoquinones in their reactions with 2-bromo-3-methoxy-1,4-naphthoquinone in the presence of an amine.

The substitution of quinones has long been studied, partly because a quinone moiety is incorporated into various biologically important molecules of complex structure.[1] Starting with simple symmetrical 1,4-naphthoquinones such as 2,3-dichloro-1,4-naphthoquinone, for example, 2-alkylamino-3-chloro-1,4-naphthoquinones were successfully synthesized by choosing the stoichiometry of an alkylamine.[2] As of yet, however, there has not been a procedure established for introducing a particular substituent at the 2- and/or the 3-positions of 1,4-naphthoquinones in a regioselective manner when starting from 1,4-naphthoquinones lacking symmetry. In order to develop a method for regioselective substitution at the 2- and/or the-3-positions of 1,4-naphthoquinones, we studied the reaction of 2-bromo-3-methoxy-1,4-naphthoquinone (**1**) as an unsymmetrical starting 1,4-naphthoquinone. We found that a chemoselective substitution occurred upon applying appropriate conditions for the reaction. When alkylamines **2** were reacted with **1**,[3] substitution at the 3-methoxy group yielded 2-alkylamino-3-bromo-1,4-naphthoquinone derivatives **3** within a few hours. On the other hand, when alkylthiols **4** were reacted with **1** in the presence of an amine, substitution for the 2-bromine gave 2-alkylthio-3-methoxy-1,4-naphthoquinones **5** as the primary product. Depending upon the amount of amine as well as alkylthiol added, a second substitution resulted in the formation of 2,3-bis(alkylthio)-1,4-naphthoquinones (**6**) as the final substitution product.

A variety of alkylamines **2** were found to react with **1** in the dark, yielding 2-alkylamino-3-bromo-1,4-naphthoquinones **3** through a smooth substitution reaction at the 3-methoxy group (see Scheme 1). Methanol best served as the solvent for this substitution reaction. The rate of substitution was dependent upon the nature of amines. Primary amines reacted fast, whereas secondary amines afforded a substitution product rather slowly. In addition, the size of alkyl group was also found to influence the rate of substitution. Amines with bulky alkyl groups, in general, underwent the substitution reaction rather slowly. For these amines, a reaction at elevated temperatures was often found to effect the substitution process. Tertiary amines didn't lead to the formation of any substitution product with **1** even at elevated temperatures.[4]

Typically, **1** (0.1 mmol) was dissolved in methanol (20 mL). To this solution, an excess amount of an alkylamine **2** (0.2–0.5 mmol) was added in the dark. The color of the solution



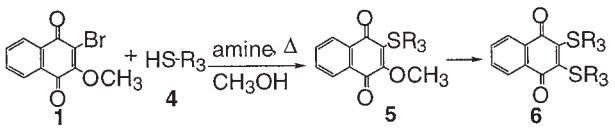
R_1-, R_2-: a) -H, $-CH_2CH_2CH_3$ b) -H, $-CH(CH_3)_2$
c) -H, $-CH_2CH_2CH_2CH_3$ d) -H, $-CH_2CH(CH_3)_2$
e) -H, $-C(CH_3)_3$ f) -H, $-CH(CH_2CH_3)_2$
g) $-CH_3$, $-CH_2CH_2CH_3$ h) $-CH_2CH_2CH_3$, $-CH_2CH_2CH_3$ i) $-CH_2CH_2CH_2CH_2CH_2-$
j) $-CH_2CH_2OCH_2CH_2-$

Scheme 1. Reaction of 2-Bromo-3-methoxy-1,4-naphthoquinone with Amine.

changed to dark red immediately upon the addition of amine to the solution of **1**. The reaction mixture was kept at room temperature for a few hours until the starting quinone was consumed. In order to complete the reaction of **1** with an amine **2** with bulky substituents, the reaction mixture was refluxed for a few hours. After the completion, the reaction mixture was concentrated in vacuo and purified on silica gel column with a mixed solvent such as pentane-ethyl acetate (95-5) as the eluent. 2-Alkylamino-3-bromo-1,4-naphthoquinones **3** were isolated as purple crystals in high yields. The structures of all products were supported by spectroscopic data such as MS, ^{1}H-NMR, ^{13}C-NMR, IR and UV.[5]

As described above, tertiary amines were found not to react with **1**. When an alkylthiol **4** was added to an unreacting mixture of **1** and a tertiary amine, an immediate color change of the reaction mixture was observed. In this reaction, an alkylthio group was first substituted for bromine at the 2-position, yielding 2-alkylthio-3-methoxy-1,4-naphthoquinone **5** (see Scheme 2). Depending upon the amount of amine added, a second substitution with the 3-methoxy group resulted in the formation of **6**.[6] In the absence of amine, an alkylthiol alone will not react with **1** even at an elevated temperature. Therefore, the formation of alkylthiolate ion in the equilibrium between alkylthiol and amine as a base was suggested to be critical for the observed substitution reaction. The reactivity of alkylthiol depends upon the alkyl group. Both primary alkyl thiols and secondary alkyl thiols were found to react effectively with **1**, whereas tertiary alkyl thiols did not react at a noticeable rate. Amines other than tertiary amine were also effective as the base for this substitution reaction. There was no product identified that would indicate an amine itself participated in the reaction as a nucleophile.

To a mixture of **1** (0.1 mmol) and an alkylthiol **4** (0.2–



R_3-: a) $-CH_2CH_2CH_3$ b) $-CH(CH_3)_2$

Scheme 2. Reaction of 2-Bromo-3-methoxy-1,4-naphthoquinone (**1**) with Thiol in the Presence of Amine.

0.5 mmol) in methanol (20 mL), for example, triethylamine (0.1 mmol) was added in the dark. The color of the reacting mixture immediately changed to deep orange. The reaction was completed in a few hours at room temperature. The purification of the mixture on silica gel column with an eluent mixture; pentane-ethyl acetate (95-5) gave 2-alkylthio-3-methoxy-1,4-naphthoquinones (**5**) as orange crystals. When **5** (0.1 mmol) were further reacted with alkylthiol **4** (0.2–0.5 mmol) in the presence of a catalytic amount of triethylamine[6] in methanol (20 mL) at room temperature, 2,3-bis(alkylthio)-1,4-naphthoquinones **6** were yielded in another few hours. **6** were also directly synthesized without isolating **5** when an excess amount of amine was added to a mixture of **1** and an alkylthiol **4**. **6** were obtained as orange crystals after purification on a silica gel column with a mixture of pentane-ethyl acetate (95-5) as the eluent. All products, **5** and **6**, were characterized by spectroscopic data such as MS, ^{1}H-NMR, ^{13}C-NMR, IR and UV.[7,8]

Clearly, the mechanisms involved in each substitution reaction are different. A nucleophilic attack of alkylthiolate ion is suggested to explain the substitution reaction at the 2-bromine with alkylthio group. On the other hand, an initial electron transfer process between an amine and **1** is hypothesized to explain the substitution of the 3-methoxy group with an alkylamino group.[4] Further study remains to disclose the mechanistic details.[9]

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References and Notes

1 For example, R. H. Thompson, ''Naturally Occurring Quinones, III,'' Chapman and Hall, New York (1986); ''The Chemistry of Quinonoid Compounds,'' 2nd ed., ed. by S. Patai, Wiley, New York (1988).

2 B. Prescott, *J. Med. Chem.*, **12**, 181 (1969); N. L. Agarwal and W. Schefer, *J. Org. Chem.*, **45**, 5139 (1980); E. M. Hodnett, *J. Med. Chem.*, **26**, 570 (1983).

3 L. F. Fieser and R. H. Brown, *J. Am. Chem. Soc.*, **71**, 3609 (1949).

4 Upon addition of tertiary amine such as triethylamine to methanolic solution of **1**, new broad absorption (λ_{max} at around 686 nm) was detected at room temperature, which would be ascribed to the formation of CT complex as the result of electron transfer process.

5 2-Bromo-3-propylamino-1,4-naphthoquionone (**3a**; R_1, R_2 = -H, -$CH_2CH_2CH_3$. Yield 98%). ^{1}H-NMR ($CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3H), 1.73 (sextet, J = 7.2 Hz, 2H), 3.85 (q, J = 7.2 Hz, 2H), 6.1 (br s, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 8.03 (d, J = 7.6 Hz, 1H), and 8.15 (d, J = 7.6 Hz, 1H). ^{13}C-NMR ($CDCl_3$) δ 11.1, 24.1, 46.9 126.8, 127.0, 129.7, 132.3, 134.8, and 180.1. IR (KBr) 1685, 1618 cm^{-1}. MS m/z 293, 291 (M^+-2H), 253, 251 (100%). 2-Bromo-3-isopropylamino-1,4-naphthoquinone (**3b**; R_1, R_2 = -H, -$CH(CH_3)_2$. Yield 91%). 2-Bromo-3-butylamino-1,4-naphthoquinone (**3c**; R_1, R_2 = -H, -$CH_2CH_2CH_2CH_3$. Yield 82%). 2-Bromo-3-isobutylamino-1,4-naphthoquinone (**3d**; R_1, R_2 = -H, -$CH_2CH(CH_3)_2$. Yield 55%). 2-Bromo-3-*tert*-butylamino-1,4-naphthoquinone (**3e**; R_1, R_2 = -H, -$C(CH_3)_3$. Yield 80%). 2-Bromo-3-(1-ethylpropyllamino)-1,4-naphthoquinone (**3f**; R_1, R_2 = -H, -$CH(CH_2CH_3)_2$. Yield 72%). 2-Bromo-3-N-methylylpropylamino-1,4-naphthoquinone (**3g**; R_1, R_2 = -CH_3, -$CH_2CH_2CH_3$. Yield 82%). 2-Bromo-3-dipropylamino-1,4-naphthoquinone (**3h**; R_1, R_2 = -$CH_2CH_2CH_3$, -$CH_2CH_2CH_3$. Yield 86%). 2-Bromo-3-piperidino-1,4-naphthoquinone (**3i**; R_1, R_2 = -$CH_2CH_2CH_2CH_2CH_2$-. Yield 85%). 2-Bromo-3-morpholino-1,4-naphthoquinone (**3j**; R_1, R_2 = -$CH_2CH_2OCH_2CH_2$-. Yield 91%).

6 The stoichiometric amount of amine was required for the first alkylthiolation to yield **5** in order to neutralize HBr formed through the substitution of bromine, whereas the second alkylthiolation, leading to **6**, required only a catalytic amount of amine.

7 2-Methoxy-3-propylthio-1,4-naphthoquinone (**5a**; R_3 = -$CH_2CH_2CH_3$. Yield 90%). 2-Isopropylthio-3-methoxy-1,4-naphthoquione (**5b**; R_3 = -$CH(CH_3)_2$. Yield 85%). ^{1}H-NMR ($CDCl_3$) δ 1.32 (d, J = 6.4 Hz, 6H), 4.09 (septet, J = 6.4 Hz, 1H), 4.19 (s, 3H), 7.69–7.72 (m, 2H), and 8.06–8.09 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ 23.6, 36.9, 61.2, 126.4, 126.6, 131.4, 132.2, 133.3, 133.6, 133.7, 158.7, 179.0, and 182.9. IR (KBr) 1661, 1590 cm^{-1}. HRMS calcd for $C_{14}H_{14}O_3S$ (M^+) m/z 262.066366, found 262.065404.

8 2,3-Bis(propylthio)-1,4-naphthoquinone (**6a**; R_3 = -$CH_2CH_2CH_3$. Yield 87%). 2,3-Bis(isopropylthio)-1,4-naphthoquionone (**6b**; R_3 = -$CH(CH_3)_2$. Yield 90%). ^{1}H-NMR ($CDCl_3$) δ 1.33 (d, J = 6.8 Hz, 12H), 4.27 (septet, J = 6.8 Hz, 2H), 7.70 (dd, J = 3.4, 6.0 Hz, 2H), and 8.06 (dd, J = 3.4, 6.0 Hz, 2H). ^{13}C-NMR ($CDCl_3$) d 23.8, 39.1, 126.9, 132.9, 133.5, 148.8, and 179.3. IR (KBr) 1668, 1592 cm^{-1}. HRMS calcd for $C_{16}H_{18}O_2S_2$ (M^+) m/z 306.074824, found 306.075455.

9 Preliminary semi-empirical calculation of electron density of **1** and electron spin density of the radical anion of **1** also supports our current hypothesis on the mechanistic details.