Articles

Efficient Synthesis of Aminonaphthoquinones and Azidobenzohydroquinones: Mechanistic Considerations of the Reaction of Hydrazoic Acid with Quinones. An Overview

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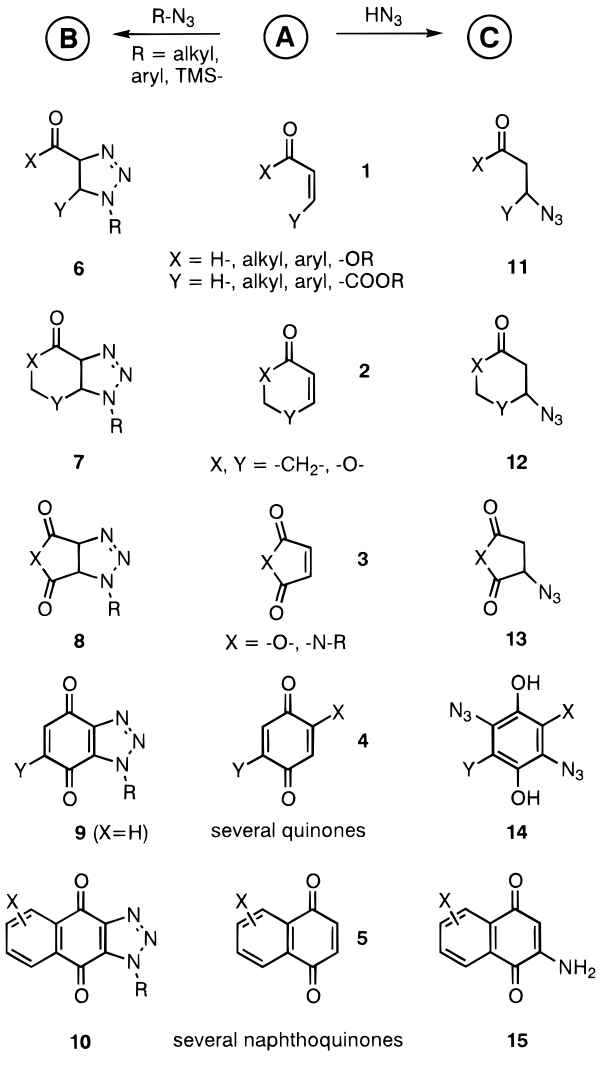
Parameters useful to predict and control the reaction outcome of conjugate addition of hydrazoic acid to quinones have been studied, and the optimum conditions for the efficient synthesis of aminonaphthoquinones and azidobenzohydroquinones are reported. The application of this reaction for the efficient formal synthesis of dephostatin is also presented.

Conjugate addition reactions of azides to α,β-unsaturated carbonyl compounds is a very useful synthetic method in organic chemistry, providing efficient access to a variety of natural products or compounds with pronounced biological activity.[1] While alkyl (or silyl) azides react in a straightforward fashion with α,β-unsaturated carbonyl and dicarbonyl substrates (Scheme 1, compounds **1**−**5**) furnishing the corresponding triazoles **6**−**10** in high yields,[2] hydrazoic acid affords diverse products.[3,4] Open-chain or cyclic α,β-unsaturated ketones **1** and **2** as well as anhydrides and imides **3** yield the expected β-azido adducts (**11**−**13**).[5] On the contrary, with quinone-type substrates the products depend strongly on experimental conditions, substituents, and stability of intermediates. Thus, reaction of benzoquinones **4** with hydrazoic acid furnishes 2,5-diazido-1,4-benzohydroquinones **14**.[6] These compounds, which originally were thought to be the 2-azido derivatives,[7] may further be transformed to the corresponding 2-aminobenzoquinones. However, in the case of naphthoquinones **5** the corresponding 2-amino derivatives **15** were isolated directly (without

Scheme 1. Products B and C from the Reaction of α,β-Unsaturated Carbonyl Compounds A, with Azides and Hydrazoic Acid



[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

(1) Scriven, E. F.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 351.

(2) (a) Benati, L.; Montevecchi, P. C.; Spagnolo, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 71. (b) Sha, C.-K.; Ouyang, S.-L.; Hseih, D.-Y.; Chang, R.-C.; Chang, S.-C. *J. Org. Chem.* **1986**, *51*, 1490. (c) Liu, J.-M.; Young, J.-J.; Li, Y.-J.; Sha, C.-K. *J. Org. Chem.* **1986**, *51*, 1120. (d) Schultz, A. G.; McMahon, W. G. *J. Org. Chem.* **1984**, *49*, 1676. (e) Barnish, I. T.; Gibson, M. S. *J. Chem. Res., Synop.* **1992**, 208. (f) Al-Kazwini, A. T.; O'Neil, P.; Cundall, R. B.; Adams, G. E.; Junito, A.; Maignan, J. *Tetrahedron Lett.* **1992**, *33*, 3045. (g) Washburne, S. S.; Peterson, W. R.; Berman, D. A. *J. Org. Chem.* **1972**, *37*, 1738.

(3) These compounds are relatively stable except naphthoquinones, which can easily be transformed to the corresponding 2-enaminones; see refs 2a and 20.

(4) Only reaction of hydrazoic acid with alkynones furnished triazines; see: Olivieri-Mandala, E. *Mem. Accad. Lincei (VI)* **1926**, *2*, 132.

(5) (a) Boyer, J. H. *J. Am. Chem. Soc.* **1951**, *73*, 5248. (b) Olivieri-Mandala, E. *Gazz. Chim. Ital.* **1941**, *71*, 182. (c) Awad, W. J.; Omran, S. M. A. R.; Nagieb, F. *Tetrahedron* **1963**, *19*, 159.

(6) Moore, H. W.; Shelden, H. R.; Shellhamer, D. F. *J. Org. Chem.* **1969**, *34*, 1999 and references therein.

(7) (a) Olivieri-Mandala, E.; Calderao, E. *Gazz. Chim. Ital.* **1915**, *45*, 307. (b) Olivieri-Mandala, E. *Gazz. Chim. Ital.* **1915**, *45*, 120.

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the need of a reduction step) in good to marginal yields.[8] In most cases the mechanism of the above transformation was described as an overall intramolecular oxidation−reduction, and the role of the reactant ratio, the pH of the medium, and the presence of atmospheric oxygen were not studied thoroughly. Furthermore, as was originally pointed out by Moore during his extensive studies in this field,[6] the literature abounds with contradictory reports and diverse yields.[7,8]

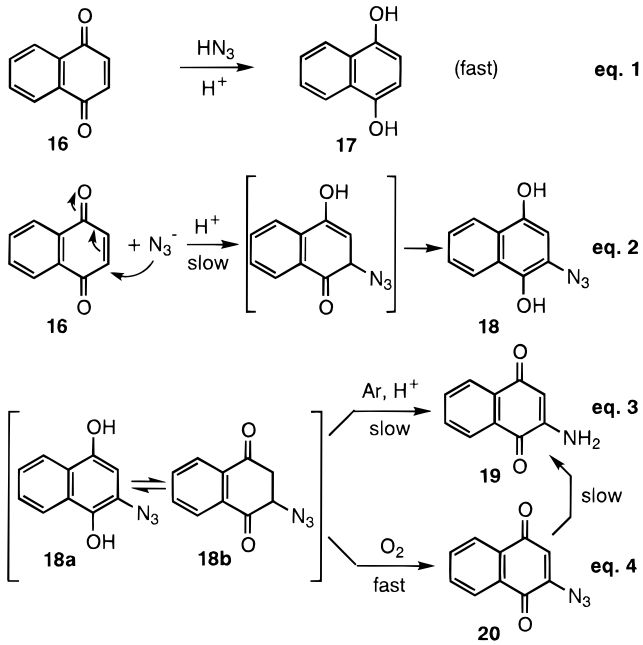
As a consequence, this reaction is not considered to be a reliable synthetic tool, and aminoquinone derivatives, which are important building blocks in the synthesis of a variety of natural products and medicinal compounds,[9] are usually prepared by alternative, multistep synthetic pathways.[9,10]

We have a long-standing interest in the study of Michael additions to unsaturated cyclic ketones and quinones and their use for the synthesis of natural products and compounds with biological interest.[11] Therefore, this particular reaction has captured our interest. The obvious need for a convenient and high yielding synthetic method for the preparation of various azido and amino quinones has prompted us to reinvestigate more systematically the various aspects of this reaction.

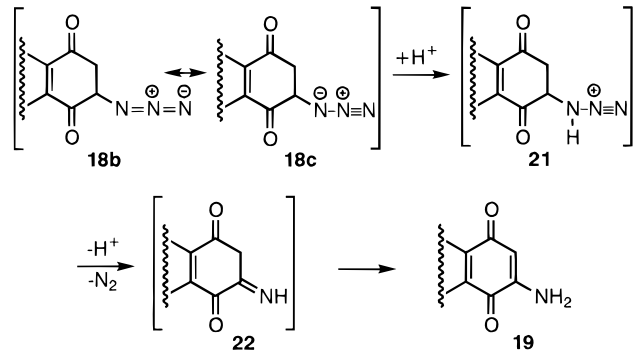
Results and Discussion

In order to elucidate the reaction mechanism and to determine the optimal conditions for the addition of hydrazoic acid to various naphthoquinones, we examined the reaction of a methanolic solution of naphthoquinone (**16**) with hydrazoic acid (generated *in situ* from sodium azide and acid). Our findings are summarized in Scheme 2. When naphthoquinone is treated with hydrazoic acid at 0 °C for 5−15 min, it is first reduced by hydrazoic acid to the corresponding hydroquinone **17** (Scheme 2, eq 1), which is the only detectable product (by TLC). Longer reaction times and/or higher temperature results in the simultaneous formation of 2-azidohydroquinone (**18**), suggesting that the rate of formation of the azido adduct is slower (Scheme 2, eq 2). 2-Azidohydroquinone, which is in equilibrium with its keto form (**18a** ↔ **18b**), is unstable and is converted to 2-aminonaphthoquinone (**19**) or 2-azidonaphthoquinone (**20**), depending on the reaction conditions. Thus, when the reaction is conducted under air at 0 °C with an excess of hydrazoic acid, intermediate **18** is oxidized to 2-azidonaphthoquinone **20**, which is isolated as the main product (Scheme 2, eq 4). Prolonged reaction times at room temperature, however, resulted

Scheme 2



Scheme 3



in its partial transformation to 2-aminonaphthoquinone (**19**). In order to obtain a quantitative conversion to compound **19** (Scheme 2, eq 3), which is the product usually reported in the literature, the reaction should be carried out under an inert atmosphere using a large excess of hydrazoic acid (6 equiv) and a pH around 4. Formation of 2-aminonaphthoquinone (**19**) under these acidic reducing conditions can be rationalized as shown in Scheme 3. According to this mechanism, **18c** under acidic conditions is converted to imino intermediate **22** by loss of dinitrogen. Compound **22** is then readily transformed to the stable tautomeric form of 2-aminonaphthoquinone (**19**).[12] Our findings and the proposed mechanism are reminiscent of the previous known conversion of 2-azido ketones to 2-amino-α,β-unsaturated ketones.[13]

Benzoquinones also follow the above scenario (Scheme 3) with minor variations attributed to (1) the difference in oxidation potential of benzoquinones *vs* naphthoquinones, which indicates that azidobenzohydroquinones are

(8) (a) Fieser, L. F.; Hartwell, J. L. *J. Am. Chem. Soc.* **1935**, *57*, 1482. (b) Parker, K. A.; Sworin, M. E. *J. Org. Chem.* **1981**, *46*, 3218. (c) Forrester, A. R.; Ingram, A. S.; John, I. C.; Thomson, R. H. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1115.

(9) (a) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782. (b) Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5790. (c) Renault, J.; Giorgi-Renault S.; Baron, M.; Mailliet, P.; Paoletti, C.; Cros, S.; Voisin, E. *J. Med. Chem.* **1983**, *26*, 1715. (d) Kende, A. S.; Ebetino, F. H. *Tetrahedron Lett.* **1984**, *25*, 923. (e) Thomson, R. H. *Naturally Occurring Quinones*, 2nd. ed.; Academic Press: New York, 1971. (f) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (g) Lancini, G.; Zanichelli, W. In *Antibiotics*; Perlman, D., Ed.; Academic Press: New York, 1971; pp 531−600.

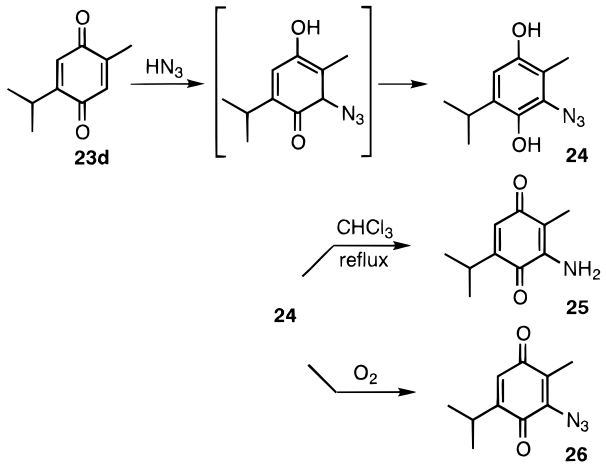
(10) (a) Moore, H. W.; Shelden, H. R.; Deters, D. W.; Wikholn, R. J. *J. Am. Chem. Soc.* **1970**, *92*, 1675. (b) Kuo, H. S.; Yoshina, S. *Yakugaku Zasshi* **1977**, *97*, 827.

(11) (a) Georgiadis, M. P.; Couladouros, E. A. *J. Heterocycl. Chem.* **1991**, *28*, 1325. (b) Apostolopoulos C. D.; Couladouros, E. A.; Georgiadis, M. P. *Liebigs Ann. Chem.* **1994**, *8*, 781. (c) Couladouros, E. A.; Apostolopoulos, C. D. *Synlett* **1996**, 341. (d) Couladouros, E. A.; Plyta, Z.; Papageorgiou V. *J. Org. Chem.* **1996**, *61*, 3031.

(12) A mechanism similar to the one in Scheme 3 may also be proposed for the reaction of various haloquinones with hydrazoic acid, since 2-azidohydroquinone is the common intermediate. In this way the diverse results usually reported,[9a−c] can also be rationalized.

(13) (a) Ermolaev, K. M.; Mainind, V. I. *Zh. Org. Khim.* **1969**, *5*, 1218; *Chem. Abstr.* **1969**, *71*, 101374w. (b) Ermolaev, K. M. *Zh. Org. Khim.* **1972**, *8*, 1828; *Chem. Abstr.* **1973**, *78*, 29291s. (c) Effenberger, F.; Beisswenger, T.; Az, R. *Chem. Ber.* **1985**, *118*, 4869. (d) Effenberger, F.; Beisswenger, T. *Chem. Ber.* **1984**, *117*, 1497.

Scheme 4

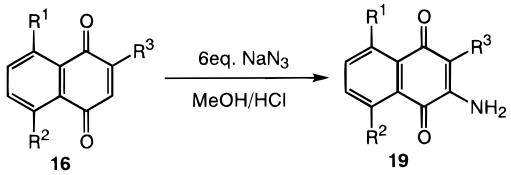


less liable to oxidize, (2) the negligible enol−keto equilibrium, and (3) the electronic influence of the substituents, which is more pronounced in benzoquinones. Thus, when thymoquinone **23d** is treated with hydrazoic acid under an inert atmosphere, the corresponding azidobenzohydroquinone **24** is formed as the main product (Scheme 4). The latter upon exposure to atmospheric oxygen is easily oxidized to quinone **26**. The same product **26** is formed when the reaction is carried out under air from the beginning. In this example, as well as with the other studied benzoquinones, the rate of formation of the amino derivative (like **25**) is extremely slow. However, as Moore has originally reported,[14] intermediate **24** when refluxed in chloroform, under argon, was quantitatively transformed to the corresponding aminoquinone **25**, presumably by the same reaction sequence described above for naphthoquinones.

In summary, azidohydroquinones, depending on the reaction conditions, behave either as normal aryl azides or as α-azido ketones.[15]

In light of these new findings, we were able to optimize the reaction conditions. Thus, when aminonaphthoquinones are desired, the use of a stronger acid than acetic acid, which is usually used, along with an inert atmosphere, a polar solvent, and a sufficient excess of sodium azide are essential in order to obtain the desired compounds under mild conditions and avoid the side reactions. These specific experimental conditions were effective for a variety of substrates, and in each case the yield was considerably improved (Table 1).[8a,b,20,21] The regioselectivity of the addition when applied on nonsymmetric substrates (compounds **16e,f**) is also improved in comparison to previous reports.[8b,20,21a]

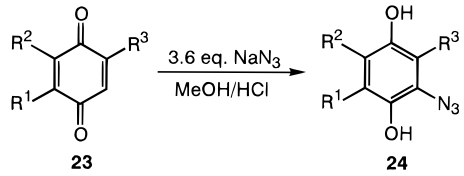
Table 1. Addition of Hydrazoic Acid to 1,4-Naphthoquinones



substrate	R^1	R^2	R^3	time (h)	*T* (°C)	yield (%)	reported yields (%)
a	H	H	H	15	rt	97	92[g]−81[d,f]
b	H	H	SPh	15	rt	82	68[g]
c	H	H	CH_3	36	50	59[a]	70[f]−0[d]
d	OH	OH	H	20	50	75	78[g]
e	H	OH	H	6	rt[b]	97	91[f]−27[e]
f	OMe	H	H	12	rt	58[a,c]	40[e]−8[f]

[a] Column chromatography purification. [b] pH = 1. [c] 12% of the other regioisomer was also isolated. [d] See ref 8a. [e] See ref 8b. [f] See ref 22. [g] See ref 21a.

Table 2. Addition of Hydrazoic Acid to 1,4-Benzoquinones



substrate	R^1	R^2	R^3	time (h)	*T* (°C)	yield (%)
a	H	H	H	0.5	−78	88[a]
b	H	SPh	H	0.75	−78	79
c	H	CH_3	H	0.75	−78	67
d	^{i}Pr	H	CH_3	5[b]	rt	52[a,c]

[a] Column chromatography purification. [b] 6 equiv of HN_3. [c] 20% of starting material and 14% of quinone **26** were also isolated.

In the case of benzoquinone substrates, the targeted aminobenzoquinones are relatively unstable, with 2-aminobenzoquinone itself being an unknown species.[22] Thus, we preferred to explore the formation of azidobenzohydroquinones that are often used as masked aminobenzoquinones, and their general direct synthesis has not been reported previously. When the reaction was performed under an inert atmosphere at −78 °C with an excess of hydrazoic acid, we were able to avoid the formation of diazido or amino derivatives and prepare the desired azidobenzohydroquinones[23] as the exclusive products (Table 2).

We believe that the reaction of hydrazoic acid with quinones is now a reliable synthetic tool, and as an example of this methodology, we present a formal synthesis of dephostatin **29**, a naturally occurring tyrosine

(14) Moore, H. W.; Shelden, H. R. *J. Org. Chem.* **1968**, *33*, 4019.

(15) It is well known that while aryl azides and open chain vinyl keto azides are quite stable,[16] their saturated analogs (i.e., α-azido ketones) are readily transformed to enamino ketones.[17−19]

(16) To the best of our knowledge there is only in one example where a 2-azido α,β-unsaturated ketone, after heating under oxidative conditions (I_2), is partially transformed to the enamino analog; see: Henn, L.; Hickey, D. M. B.; Moody, C. J.; Rees, C. W. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189.

(17) (a) Patonay, T.; Hoffman, R. V. *J. Org. Chem.* **1994**, *59*, 2902 and references therein. (b) DeWald, H. A.; Heffner, T. G.; Jaen, J. C.; Lustgarten, D. M.; McPhail, A. T.; Meltzer, L. T.; Pugsley, T. A.; Wise, L. D. *J. Med. Chem.* **1990**, *33*, 445. (c) Yasuda, N.; Tsutsumi, H. Takaya, T. *Chem. Lett.* **1985**, 31. (d) Bashyal, B. P.; Chow, H.; Fleet, G. W. J. *Tetrahedron Lett.* **1986**, *27*, 3203. (e) Sant Van K.; South M. S. *Tetrahedron Lett.* **1987**, *28*, 6019.

(18) (a) Patonay, T.; Hoffman, R. V. *J. Org. Chem.* **1995**, *60*, 2368. (b) Magnus, P.; Barth, L. *Tetrahedron* **1995**, *51*, 11075. (c) Takeuchi, H.; Yanagida, S.-I.; Ozaki, T.; Hagiwara, S.; Eguchi, S. *J. Org. Chem.* **1989**, *54*, 431. (d) VanSant, K.; South, M. S. *Tetrahedron Lett.* **1987**, *28*, 6019.

(19) (a) Forster, M. O.; Fietz, H. E. *J. Chem. Soc.* **1905**, *87*, 826; (b) **1907**, *91*, 867.

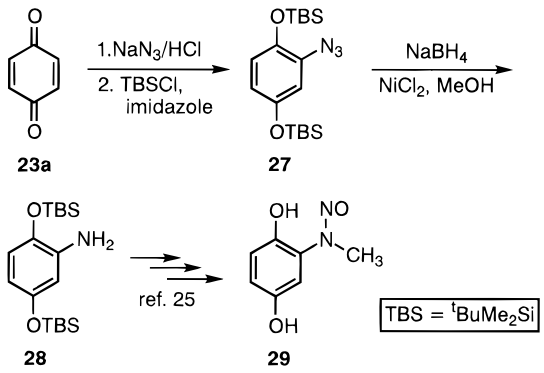
(20) Husu, B.; Kafka, S.; Kadunc, Z.; Tisler, M. *Monatsh. Chem.* **1988**, *119*, 215.

(21) (a) Bittner, S.; Lempert, D. *Synthesis* **1994**, 917. (b) Podrebarac, E. G.; Cheng, C. C. *J. Org. Chem.* **1970**, *35*, 281. (c) Dudley, K. M.; Miller, J. W.; Schneider, P. W.; McKee, R. L. *J. Org. Chem.* **1969**, *34*, 2750.

(22) Ott, R.; Pinter, E.; Kajtna, P. *Monatsh. Chem.* **1980**, *11*, 813.

(23) When the reaction was performed in the presence of air, a mixture of 2-azidobenzohydroquinone and 2-azidobenzoquinone was obtained.

Scheme 5



kinase inhibitor[24] (Scheme 5). Thus, starting from benzoquinone **23a**, compound **27** was readily prepared and then converted efficiently to amine **28** upon treatment with $NaBH_4/NiCl_2$ with 62% total yield for three steps *vs* 12% of the recently reported procedure.[25]

In conclusion, we can state that the azide anion addition to naphthoquinones and benzoquinones is an interesting reaction that provides direct access to aminonaphthoquinones and azidobenzohydroquinones, respectively. In this report, the mechanism and various aspects of this reaction are investigated, and a method of general applicability for their high-yield synthesis under mild experimental conditions is provided.

Experimental Section

General Procedures. Reaction progress was monitored with analytical TLC on 0.25 mm silica gel precoated glass plates with fluorescent indicator UV_{254} (Merck). Flash chromatography was conducted with Merck silica gel 32−63 mm packing. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were obtained in accordance with the KBr disk technique. ^{1}H NMR spectra were recorded at 200 MHz in $CDCl_3$ using TMS as internal standard. Mass spectra were acquired by electron impact at 70 eV. Solvents and commercial reagents were purchased as analytical reagent grade and used without any further purification. Starting quinones were purified by crystallization or sublimation, since the reaction yields depend strongly on their purity.

General Procedure for the Synthesis of 2-Amino-1,4-naphthoquinones. To a stirred solution of naphthoquinone (1.8 mmol) in 15 mL of methanol under argon was added a solution of sodium azide (10.6 mmol) in 5 mL of water, acidified to pH 4 (with 1 N HCl). The reaction was stirred at rt (or 50 °C) and monitored by TLC (the exact times and temperatures are depicted in Table 1), and then the mixture was extracted twice with EtOAc and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was crystallized from an ether−hexane mixture.

2-Amino-1,4-naphthoquinone (19a). Following the general procedure, 280 mg (1.79 mmol) of naphthoquinone (**16a**) afforded 297 mg (97%) of **19a** as an orange powder: mp 202−204 °C (lit.[21a] 204−205 °C); IR ν 3392, 1685, 1618 cm^{-1}; ^{1}H NMR δ 8.07 (m, 2H), 7.68 (m, 2H), 6.01 (s, 1H), 5.14 (s, 2H); MS *m*/*z* 173 (M^+, 89), 146 (52), 145 (25), 117 (15), 105 (74), 104 (40), 76 (100), 50 (42).

2-Amino-3-(phenylthio)-1,4-naphthoquinone (19b). Following the general procedure, 280 mg (1.05 mmol) of 2-(phenylthio)-1,4-naphthoquinone (**16b**) afforded 242 mg (82%) of **19b** as a dark red powder: mp 168−170 °C (lit.[21a] mp 170−171 °C); IR ν 3435, 3323, 3288, 1685 cm^{-1}; ^{1}H NMR δ 8.14 (m, 2H), 7.72 (m, 2H), 7.23 (s, 5H), 6.01 (s, 2H); MS *m*/*z* 281 (M^+, 61), 264 (5), 248 (16), 165 (5), 121 (100), 104 (15), 89 (16).

2-Amino-3-methyl-1,4-naphthoquinone (19c). Following the general procedure, 280 mg (1.63 mmol) of 2-methyl-1,4-naphthoquinone (**16c**) afforded, after chromatographic purification using 30% EtOAc/hexane as eluent, 180 mg (59%) of **19c** as a red powder: mp 158−159 °C (lit.[21a] mp 157−158 °C); IR ν 3450, 3338, 1667, 1615 cm^{-1}; ^{1}H NMR δ 8.20 (m, 2H), 7.78 (m, 2H), 5.15 (s, 2H), 2.19 (s, 3H); MS *m*/*z* 187 (M^+, 100), 160 (44), 130 (72), 104 (35), 76 (72), 54 (53).

2-Amino-5,8-dihydroxy-1,4-naphthoquinone (19d). To a stirred solution of 5,8-dihydroxy-1,4-naphthoquinone (**16d**) (80 mg, 0.42 mmol) in 80 mL of methanol under argon was added a solution of sodium azide (220 mg, 3.37 mmol) in 5 mL of water, acidified to pH 4 (with 1 N HCl). The reaction mixture was stirred at 50 °C for 20 h. Then the mixture was extracted with EtOAc, and the organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was crystallized from ether−hexane to afford 65 mg (75%) of **19d** as a dark red powder: mp 254−255 °C (lit.[21a] mp >250 °C); IR ν 3410, 3140, 1655, 1575 cm^{-1}; ^{1}H NMR δ 11.90 (s, 1H), 10.95 (s, 1H), 7.25 (d, J = 10.9 Hz, 1H), 7.12 (d, J = 10.9 Hz, 1H), 5.90 (s, 1H), 5.30 (br, 2H); MS *m*/*z* 205 (M^+, 100), 178 (15), 136(9), 123 (17), 108 (8), 53 (10).

3-Amino-5-hydroxy-1,4-naphthoquinone (19e). Following the general procedure, 280 mg (1.61 mmol) of 5-hydroxy-1,4-naphthoquinone (**16e**) afforded 295 mg (97%) of **19e** as a red powder: mp 253−254 °C (lit.[21a] mp >250 °C); IR ν 3398, 1600, 1580 cm^{-1}; ^{1}H NMR δ 11.57 (s, 1H), 7.64 (m, 2H), 7.18 (d, J = 7.2 Hz, 1H), 5.98 (s, 1H), 5.18 (s, 2H); MS *m*/*z* 189 (M^+, 100), 162 (52), 132 (20), 121 (29), 92 (31), 63 (21).

2-Amino-5-methoxy-1,4-naphthoquinone (19f). Following the general procedure, 280 mg (1.49 mmol) of 5-methoxy-1,4-naphthoquinone (**16f**) afforded, after chromatographic purification using 50% EtOAc/hexane as eluent, 175 mg (58%) of **19e** as a yellow powder: mp 156−158 °C (lit.[21a] 157−158 °C); IR ν 3420, 3315, 1610, 1560 cm^{-1}; ^{1}H NMR δ 7.80 (d, J = 7.3 Hz, 1H), 7.72 (tr, J = 8 Hz, 1H), 7.22 (d, J = 7.3 Hz, 1H), 5.95 (s, 1H), 5.29 (br, 2H), 4.05 (s, 3H); MS *m*/*z* 203 (M^+, 25), 189 (8), 149 (23), 84 (55), 69 (77), 55 (73), 43 (100).

2-Azido-1,4-naphthoquinone (20).[10a] To an ice-cold (0 °C) solution of naphthoquinone (40 mg, 0.25 mmol) in 2.5 mL of methanol was added a solution of sodium azide (98 mg, 1.5 mmol) in 1 mL of water, acidified (with 1 N HCl) to pH 4. The reaction mixture was stirred at 0 °C for 1 h and then extracted with EtOAc, washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed using 5% Et_2O/hexane, yielding 27 mg (45%) of **20** as an amorphous solid: IR ν 2100, 1674, 1645, 1592, 1570 cm^{-1}; ^{1}H NMR δ 8.08 (m, 2H), 7.75 (m, 2H), 6.45 (s, 1H).

General Procedure for the Synthesis of Azido-1,4-benzohydroquinones. To a dry ice−acetone (−78 °C) stirred solution of benzoquinone (2.6 mmol) in 10 mL of methanol under argon atmosphere was added a solution of sodium azide (9.4 mmol) in 10 mL of methanol/water (2:3 vol/vol), acidified (with 1 N HCl) to pH 4. The mixture was stirred at −78 °C for 1 h, concentrated, and partitioned between CH_2Cl_2 and water. The organic layer was evaporated under reduced pressure and chromatographed using 25% EtOAc/hexane, yielding the azido-1,4-benzohydroquinone product.

2-Azido-1,4-benzohydroquinone (24a). Following the general procedure, 280 mg (2.59 mmol) of benzoquinone (**23a**) afforded 344 mg (88%) of **24a** as a pink powder: mp 97−99 °C; IR ν 3320, 2105 cm^{-1}; ^{1}H NMR δ 6.79 (d, J = 10.7 Hz, 1H), 6.72 (s, 1H), 6.57 (m, 1H), 4.95 (s, 1H), 4.68 (s, 1H); MS *m*/*z* 151 (M^+, 29), 123 (19), 110 (100), 109 (29), 95 (52), 82 (29), 68 (39), 53 (39). Anal. Calcd for $C_6H_5O_2N_3$: C, 47.69; H, 3.33; N, 27.80. Found C, 47.55; H, 3.12; N, 28.01.

2-Azido-5-(phenylthio)-1,4-benzohydroquinone-(24b).[14] Following the general procedure, 280 mg (1.30 mmol) of 2-(phenylthio)benzoquinone (**23b**) afforded 265 mg (79%) of **24b** as an ivory powder: mp 99−101 °C; IR ν 3350, 2075 cm^{-1}; ^{1}H NMR δ 7.22 (m, 6H), 6.85 (s, 1H), 6.25 (s, 1H), 4.95 (s, 1H);

(24) (a) Imoto, M.; Kakeya, H.; Sawa, T.; Hayashi, C.; Hamada, M.; Takeuchi, T.; Umezawa, K. *J. Antibiot.* **1993**, *46*, 1342. (b) Kakeya, H.; Imoto, M.; Takahashi, Y.; Naganawa, H.; Takeuchi, T.; Umezawa, K. *J. Antibiot.* **1993**, *46*, 1716.

(25) Hamel, P.; Girard, Y. *Tetrahedron Lett.* **1994**, *35*, 8101.

MS *m/z* 259 (M^+, 16), 231 (23), 202 (50), 186 (63), 77 (67), 68 (91), 51 (100).

2-Azido-5-methyl-1,4-benzohydroquinone (24c).[14] Following the general procedure, 280 mg (2.29 mmol) of 2-methylbenzoquinone (**23c**) afforded 269 mg (71%) of **24c** as an ivory powder: mp 96−98 °C; IR ν 3210, 2110 cm^{-1}; ^1H NMR δ 6.88 (s, 1H), 6.70 (s, 1H), 5.00 (br, 1H), 4.63 (br, 1H), 2.37 (s, 3H); MS *m/z* 165 (M^+, 7), 137 (8), 109 (58), 80 (35), 69 (68), 53 (46), 45 (60), 39 (100).

3-Azido-2-methyl-5-isopropyl-1,4-benzohydroquinone (24d). To a stirred solution of thymoquinone **23d** (280 mg, 1.7 mmol) in 10 mL of methanol under argon was added a solution of 663 mg (10.2 mmol) sodium azide in 5 mL of water, acidified (with 1 N HCl) to pH 4. The reaction was stirred at room temperature for 5 h, and then the mixture was extracted twice with EtOAc and the combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed using 10% EtOAc/hexane to give 184 mg (52%) of **24d** as a pink powder: mp 90−91 °C (lit.[10a] mp 91−93 °C); IR ν 3440, 2110, 1590 cm^{-1}; ^1H NMR δ 6.39 (s, 1H), 4.98 (s, 1H), 4.28 (br, 1H), 3.03 (sept, J = 7.7 Hz, 1H), 2.15 (s, 3H), 1.10 (d, J = 7.7 Hz, 6H). In addition, we have isolated 49 mg (14%) of 3-azido-2-methyl-5-isopropyl-1,4-benzoquinone (**26**) and 57 mg (20%) of 2-methyl-5-isopropyl-1,4-benzohydroquinone.

2-Azido-1,4-[(*tert*-butyldimethylsilyl)oxy]benzene (27). To an ice-cold (0 °C) solution of 2-azidohydroquinone **24a** (30 mg, 0.20 mmol) in 0.5 mL of DMF under an argon atmosphere were added TBDMSCl (105 mg, 0.69 mmol) and imidazole (47.3 mg, 0.69 mmol). The reaction was allowed to reach room temperature and stirred for 2 h. Then, the reaction mixture was partitioned between water and EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography eluting with 5% EtOAc/hexane gave 61 mg (95%) of compound **27** as a clear oil: IR ν 2980, 2960, 2115, 1490 cm^{-1}; ^1H NMR δ 6.65 (m, 1H), 6.48 (s, 1H), 6.42 (dd, J= 9, 0.8 Hz, 1H), 0.99 (s, 9H), 0.95 (s, 9H), 0.19 (s, 6H), 0.15 (s, 6H). Anal. Calcd for $C_{18}H_{33}O_2N_3Si_2$: C, 56.95; H, 8.76; N, 11.07. Found C, 56.71; H, 8.82; N, 11.01.

2-Amino-1,4-[(*tert*-butyldimethylsilyl)oxy]benzene (28).[25] To an ice-cold (0 °C) stirred solution of compound **27** (60 mg, 0.17 mmol) in methanol were added $NaBH_4$ (64 mg, 1.69 mmol) and $NiCl_2 \cdot 6H_2O$ (81 mg, 0.34 mmol). After 15 min of stirring, the reaction mixture was extracted twice with EtOAc. The combined organic layers were washed with water and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography, eluting 10% EtOAc/hexane to yield 44.7 mg (80%) of **28**: mp 36−37 °C; IR ν 3478, 3375, 2950, 2922, 2880, 2850, 1610, 1500, 1460, 1250, 1215 cm^{-1}; ^1H NMR δ 6.62 (m 1H), 6.29 (m 1H), 6.14 (m 1H), 3.62 (s 2H), 1.02 (s, 9H), 0.98 (s, 9H), 0.23 (s, 6H), 0.19 (s, 6H); MS *m/z* 353 (M^+, 28), 338 (5), 297 (17), 296 (100), 280 (5), 238 (14), 210 (6), 164 (25).

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