JOC*Note*

One-Pot Synthesis of 1- and 2-Substituted Naphtho[2,3-*d*][1,2,3]triazole-4,9-diones

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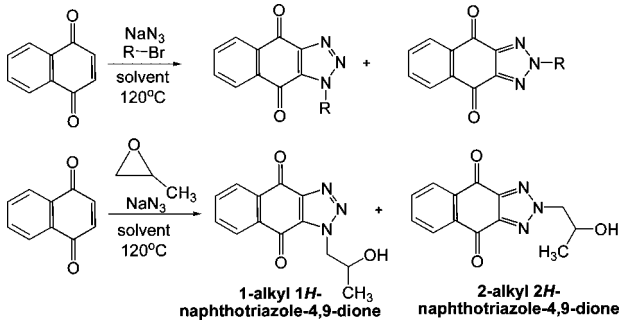
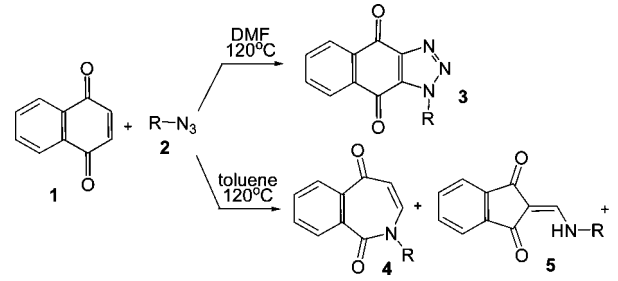


A one-pot three-component [2+3] cycloaddition for the synthesis of 1-alkyl 1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione and 2-alkyl 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione has been developed. By taking the advantage of difference in basicity, both products can be obtained in good purity. The unique heterocyclic scaffolds of these two products could exert interesting chemical and biological properties. The synthetic protocol is concise and suitable for scale-up synthesis of the desired products.

Heterocyclic compounds bearing 1,2,3-triazole have long been the focus of synthetic chemistry due to their broad spectrum of applications in biological, pharmaceutical, and material areas.[1] Recent resurgence in the use of 1,3-dipolar cycloaddition has further corroborated the interest in azido compounds and led to the development of novel synthetic methodologies in the preparation of 1,2,3-triazole derivatives.[2,3] Numerous efforts have also been devoted to simplify the synthetic protocol by conducting the cycloaddition in a one-pot design. For example, the "click" chemistry has been accomplished in one-pot fashion by using sodium azide, alkynes, Cu(I) catalyst, and appropriate aryl halides,[4] alkyl halides,[5] or epoxide.[6]

SCHEME 1



1,3-Dipolar cycloaddition can be conducted without using Cu(I) catalyst as well. We have recently discovered that cycloaddition of naphthoquinone, **1**, with azido compounds in the absence of Cu(I) under thermodynamic control offers 1-alkyl 1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **3** (Scheme 1).[7] Upon changing the solvent from DMF to toluene, a mixture of biologically interesting benzazepine-1,5-dione, **4**,[9] and 2-aminomethylene-1,3-indanedione, **5**,[9] besides compound **3** was obtained under the same condition. Compound **3** resembles anthraquinone, which has unique redox properties and, thus, may exert applications in medicinal and material areas.[8] The synthesis of similar compounds containing the structural features of **3**, **4**, and **5** has been reported via a multiple step process.[1,10] Reactions between quinones and azides have also been documented.[11] Nonetheless, one-pot synthesis with quinones, sodium azide, and appropriate alkyl halides has not been noted.

Our initial attempts using naphthoquinone, sodium azide, and alkyl bromides in DMF successfully provided the expected products, **3**, as the major products. Nevertheless, we have also noticed the formation of a byproduct with various yields. To our surprise, the byproduct upon further investigation was determined to be 2-alkyl 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **7**, that has decreasing yields, in general, as the chain length of alkyl group increases (Table 1). A similar one-pot reaction with formaldehyde and alkynes instead of alkyl halides and naphthoquinone has been reported to form both 1- and 2-substituted 1,2,3-triazoles.[12] A metal-mediated three-compo-

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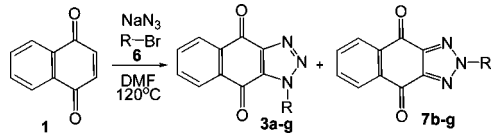
TABLE 1. One-Pot Synthesis of 1-Alkyl 1*H*-Naphtho[2,3-*d*][1,2,3]-triazole-4,9-dione



entry	alkyl bromides	isolated yield (%)		ratio of **3/7**[a]
1	benzyl bromide (**6a**)	**3a**,[7] 96%		100/0
2	butyl bromide (**6b**)	**3b**, 50%	**7b**, 25%	3.0/1
3	pentyl bromide (**6c**)	**3c**, 41%	**7c**, 12%	4.7/1
4	octyl bromide (**6d**)	**3d**, 52%	**7d**, 10%	8.2/1
5	dodecayl bromide (**6e**)	**3e**, 64%	**7e**, 4%	10.0/1
6	hexadecayl bromide (**6f**)	**3f**, 68%	**7f**, 4%	14.8/1
7	6-hydroxyhexyl bromide (**6g**)	**3g**, 58%	**7g**, 5%	8.1/1

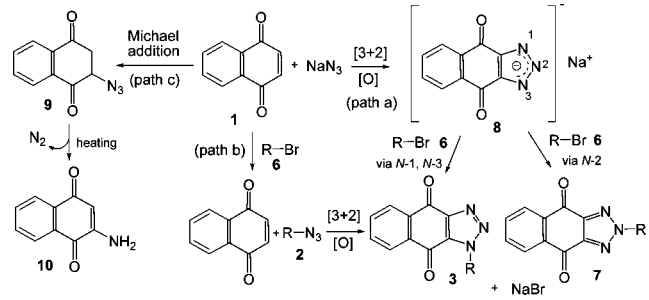
[a] The ratio of **3/7** was determined based on the integral ratio of ^{1}H NMR from the mixture of **3** and **7**.

nent method has also been shown to selectively offer 1- and 2-substituted 1,2,3-triazoles.[13] Both reports, however, do not have the structural scaffold of naphthoquinone fused with 1,2,3-triazole that resembles **3** or **7**. Molecules with the integration of quinone or naphthoquinone scaffolds are of particular interest due to their capability of disrupting the redox process of ubiquinone leading to their potential uses as antimicrobial and anticancer agents.[8] Multistep syntheses for the structural scaffold that is close to compound **3** have been reported.[10] To our knowledge, we only noticed a compound similar to **7**, 2-amino 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, in the literature, which was also prepared via a multistep fashion.[14] Therefore, our method offers an unique and simple syntheses of not only compound **3** but also the unusual compound **7**.

Although our one-pot protocol provided a convenient access to both compounds **3** and **7**, a potential problem emerged. In all cases, we encountered difficulty in the separation of **3** and **7**, which displayed almost identical R_f values on TLC and were mostly inseparable with use of silica gel-based column chromatography when eluted with commonly used organic solvents. An interesting study on the tautomerism of 1,2,3-triazoles has reported that 1-methylbenzotriazole is more basic than 2-methylbenzotriazole.[15] Thus, we speculated that compounds **3** and **7** should exert different basicity, which could be used as means to achieve their separation. To our delight, a mixture of **3** and **7** can be easily separated and purified by using column chromatography eluted with a slightly acidic solution of hexane/CH_2Cl_2/HOAc.

Naphthoquinone can react with azido compounds via a [2+3] cycloaddition,[11b,c] or with various nucleophiles through a Michael addition and/or oxidation process.[11c,16] Judging from the structure of azide,[17] and the isolated products, we favor the cycloaddition mechanism. The formation of compounds **3** and **7** occurred likely through an initial cycloaddition of azide (NaN_3) with naphthoquinone followed with an oxidation by excess naphthoquinone leading to the formation of an ionic pair

SCHEME 2. Proposed Routes for the Formation of 3 and 7



intermediate, sodium naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **8** (path a, Scheme 2). An S_N2 nucleophilic substitution via either N-1/N-3 or N-2 of **8** toward the corresponding alkyl bromides yields products **3** or **7**, respectively. In a different route, alkyl azide can be formed first via an S_N2 nucleophilic substitution of azide (N_3^-) and then offer *only* product **3** according to our previously reported cycloaddition/oxidation process[7] (path b, Scheme 2). Finally, a Michael addition of azide with naphthoquinone under prolonged reaction and higher temperature can lead to the formation of 2-amino-1,4-naphthoquinone, **10** (path c, Scheme 2).[11a,c]

Potential electrophiles that can be used in our one-pot protocol were also examined. These electrophiles include epoxides (**11**−**13**), 4-mesylated *N*-*tert*-butoxycarbonylpiperidine (**14**),[7] 1-chloroadamantane (**15**), methyl bromoacetate (**17**), ethyl bromoacetate (**18**), diethyl 2-bromoethylphosphonate (**19**), and 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide, **20** (Table 2).

Among the three epoxides tested, only propylene oxide **11** provided the expected products (entries 1−3, Table 2). When compound **14**[7] was employed, both 1- and 2-alkyl 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones, **3k** and **7k**, were obtained (entry 4). However, the yield was much lower than other examples we examined in Table 1. The reason could be attributed to the slower rate of nucleophilic substitution of the secondary mesylated group as compared to that of the primary alkyl bromides, which led to the decomposition of the ionic intermediate **8** and, hence, the lower yields. For the same reason, when 1-chloroadamantane, **15**, was employed, no reaction was noticed (entry 5). Nevertheless, 1-azidoadamantane, **16**, can still react with naphthoquinone and form 1-adamantyl 1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **3*l***, with 52% yield by using our previously reported method.[7] These results imply that cycloaddition of azide (N_3^-) and naphthoquinone (path a, Scheme 2) should occur much faster than the S_N1 nucleophilic substitution of azide (N_3^-) or **8** toward 1-chloroadamantane.

Surprisingly, when compounds **17** and **18** were used, we did not obtain the expected products from alkyl α-azidoacetate generated in situ (entries 6 and 7). Rather, the products isolated were determined to be 1-methyl 1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **3m**, and 2-methyl 2*H*-naphtho-[2,3-*d*][1,2,3]triazole-4,9-dione, **7m**, generated from **17**, and 1-ethyl 1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **3n**, and 2-ethyl 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **7n**, produced from **18**. The ionic intermediate **8** can be viewed as a "soft" nucleophile.[20,21] The ester function group of **17** and

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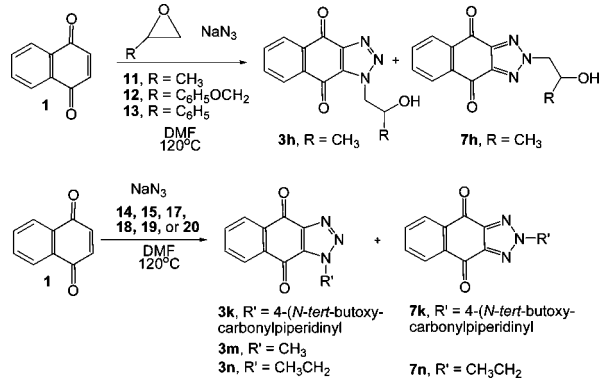
(17) Pauling, L.; Brockway, L. O. *J. Am. Chem. Soc.* **1937**, *59*, 13–20.
(18) Although no expected products were obtained, we did isolate 1,4-bis((2-hydroxy-3-phenoxy)propoxy)naphthylene, **21**, as the major component. Please refer to the SI for spectroscopic data of this compound.
(19) Similar to entry 2, we isolated 1,4-bis((2-hydroxy-2-phenyl)ethoxy)naphthylene, **22**, as the major component. Please refer tothe SI for spectroscopic data of this compound.

TABLE 2. Cycloaddition with Other Electrophiles



entry	electrophiles	isolated product (yield, %)		ratio of **3/7**
1	**11**	**3h**, 28%	**7h**, 28%	1/1
2	**12**[18]	no expected product		
3	**13**[19]	no expected product		
4	**14**[7]	**3k**,[7] 16%	**7k**, 12%	1.3/1
5	**15**	no reaction		
6	**17**	**3m**, 45%	not isolated	24.2/1[a]
7	**18**	**3n**, 22%	**7n**, 37%	1/1.44
8	**19**	**3n**, 53%	**7n**, 32%	1.64/1
9	**20**	no reaction		
10	ethyl acetate	no reaction		

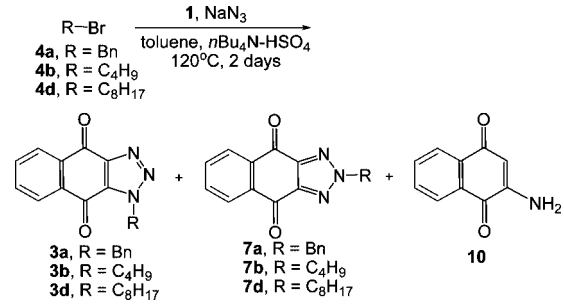
[a] The presence of **7m** can be observed from the ^{1}H NMR of the mixture of **3m** and **7m**. However, the amount of **7m** was too scarce to be isolated.

18 clearly behaves as a leaving group. The ester group, by comparison to the α-bromo group, acts as a "softer" leaving group, which could explain the formation of the isolated products. Although the results are unexpected, this outcome can be a useful alternative method in preparing compounds **3** and **7** with small alkyl groups since small molecules of alkyl halides and alkyl azides could be too volatile or unstable to handle. When ethyl acetate was used, no product was obtained (entry 10). Apparently, the inductive effect of the bromo group on α-bromoacetyl group is crucial.

When diethyl 2-bromoethylphosphonate, **19**, was used, **3n** and **7n** were obtained (entry 8). Again, the phosphonate group acts as a "soft" leaving group that gives rise to the isolated products, **3n** and **7n**. Since no expected 1-alkylated or 2-alkylated 1,2,3-triazoles were produced from azido compounds via a nucleophilic substitution of azide (N_3^-) toward the alkyl bromides in **17**, **18**, and **19**, the results concurred with our previous conclusion that cycloaddition of azide (N_3^-) should occur much faster than the nucleophilic substitution of azide. Using ethyl and methyl esters for *N*-alkylation can be uncommon, since we have only noticed one similar alkylation of triazole derivatives using dialkyl phosphonates in the literature.[22]

Finally, our attempt of using 2,3,4,6-tetra-*O*-acetyl-D-glucopyranosyl bromide, **20**, failed to provide any products (entry 9). It is likely that a fast cycloaddition of azide (N_3^-) with naphthoquinone prevents the formation of glucopyranosyl azide.

TABLE 3. One-Pot Synthesis in Toluene



entry	alkyl bromides	isolated yield (%)			ratio of **3/7**
1	benzyl bromide (**4a**)	**3a**, 21%		**10**, 51%	100/0
2	butyl bromide (**4b**)	**3b**, 44%	**7b**, 21%	**10**, 34%	1.45/1
3	octyl bromide (**4d**)	**3d**, 53%	**7d**, 43%	**10**, 14%	1.37/1

In the mean time, the intermediate **8** could not react with a relatively "hard" electrophilic anomeric carbon of compound **20**, and consequently, no expected products were obtained.

On the basis of a similar analysis, we can now propose a possible reason for the results obtained in Table 2 involving epoxides **11**, **12**, and **13**. A fast cycloaddition/oxidation converted all the azide to **8** and, in the same process, yielded 1,4-dihydroxynaphthalene from the reduction of naphthoquinone. This process also prevented the ring-opening of epoxides from azide, which is a step analogous to path b in Scheme 2. However, intermediate **8** could not undergo nucleophilic ring-opening of epoxides **12** and **13** likely due to their steric hindrance and "hardness". Thus, the isolated products came from the nucleophilic ring-opening of epoxides from the hydroxyl groups on 1,4-dihydroxynaphthalene.[18,19] In the case when less hindered propylene oxide, **11**, was used, intermediate **8** could still undergo nucleophilic ring-opening of epoxide leading to the formation of **3h** and **7h** (path a).

In our prior study, we have noticed a dramatic solvent effect in dictating the product formation.[7] Therefore, one-pot synthesis was also conducted in toluene with phase-transfer catalyst (nBu$_4$N-HSO$_4$). The products were determined to be **3** and/or **7** in addition to 2-amino-1,4-naphthoquinone, **10**[11a,c] (Table 3). Curiously, for the one-pot reactions carried out in toluene, no products bearing the scaffolds of benzazepine-1,5-dione, **4**, and 2-aminomethylene-1,3-indanedione, **5**, were obtained. Two possible reasons can account for the observation. First, since we obtained compounds **4** and **5** by using alkyl azides, it is likely that the nucleophilic substitution of azide (N_3^-) to form alkyl azide (path b in Scheme 2) was inhibited when the one-pot reactions were conducted in toluene. Second, the cycloaddition of azide (N_3^-) and the subsequent nucleophilic substitution (path a, Scheme 2) occur much faster than the alkyl azide formation (path b) in toluene as well. On the basis of the ratio of **3/7** it appears that toluene favors the production of more **7** although compound **3** is still the major product. Since **7** can be formed only via path a, the higher yield of **7** is consistent with our speculation that path b is suppressed in toluene.

The above analysis, however, is inapplicable to results generated from benzyl bromide (entry 1, Table 1, and entry 1, Table 3). Benzyl bromide can undergo nucleophilic substitution via either S_N1 or S_N2 mechanism. Thus, it is possible that the formation of benzyl azide via path b occurs much faster than the formation of **8** via path a leading to the formation of only 1-alkylated triazole (**3a**). Nevertheless, such hypothesis requires further investigation. The formation of **10** can be explained as

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proposed in the literature (path c, Scheme 2).[11c] Interestingly, we did not observe the formation of **10** when cycloaddition occurred in DMF.

In conclusion, our one-pot protocol shows a drastic difference in product formation, which leads to the unexpected but facile synthesis of 1-alkyl 1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **3**, and 2-alkyl 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-dione, **7**. From our prior study, compound **3** has been shown to have unique anticancer activity.[7] The investigation of anticancer activity for **7** is currently being carried out. An efficient purification protocol for separating these two adducts has also been established making our one-pot protocol an ideal method for large-scale synthesis of compounds **3** and **7** of interest.

From the mechanistic perspective, our results imply that the [2+3] cycloaddition of azide (N_3^-) and naphthoquinone occurs much faster than the nucleophilic substitution of azide. Since the ionic intermediate **8** may degrade in prolonged heating, electrophiles like alkyl halides that are more reactive toward nucleophilic substitution, in general, provide better yields of compounds **3** and **7**. However, the match of hardness and softness between the nucleophile **8** and the corresponding electrophiles is also important in dictating the site of nucleophilic substitution and the product formation. The Michael addition of azide to naphthoquinone may occur. Nevertheless, this reaction should be the slowest event under our synthetic protocol. With the exception of benzyl bromide, the rate of reaction for the proposed routes in our one-pot protocol carried out in DMF has the tendency as follow: path a > path b ≫ path c. In contrast to our previous study,[7] we observed no solvent effect in favoring the formation of benzazepine-1,5-dione, **4**, and 2-aminomethylene-1,3-indanedione, **5**, although decreased ratio of **3/7** was noted.

Our results prove that cycloaddition between naphthoquinone and azides can be a versatile reaction for providing structurally diverse molecules for various applications. Despite being studied extensively, many mechanistic details and governing factors regarding the formation of each individual class of products remain elusive. The intriguing results reported herein have prompted our further investigation on the factors that control the product formation and mechanistic insights.

Experimental Section

General Procedure for One-Pot Cycloaddition of Naphthoquinone. A solution of alkyl bromides (ca. 0.1 g), NaN_3 (2 equiv), and naphthoquinone (2 equiv) in DMF or in toluene (5 mL) with nBu$_4$N-HSO$_4$ (1 equiv) was stirred at 120 °C for 2 days. The solvent was evaporated and the crude product was purified by column chromatography (eluted from hexane:EtOAc = 100:0 to 50:50) to afford a mixture containing both 1-alkyl and 2-alkyl 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones. The mixture was purified again with a smaller column (eluted from hexane:CH_2Cl_2:AcOH = 100:0:0 to hexane:CH_2Cl_2:AcOH = 45:50:5) to achieve the separation of 1-alkyl and 2-alkyl 2*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones. The collected fractions of each product were concentrated and redissolved in ether, and then passed through a short column packed with layers of Celite, silica gel, and $NaHCO_{3(s)}$ to neutralize the residual acid. More ether was used to elute the column and the products can be recrystallized from a solution of ether and hexane.

Acknowledgment. We acknowledge the support from Department of Chemistry and Biochemistry, Utah State University. We also thank Prof. Vernon Parker of the Department of Chemistry and Biochemistry for valuable discussion.

Supporting Information Available: ^{1}H, ^{13}C, and related spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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