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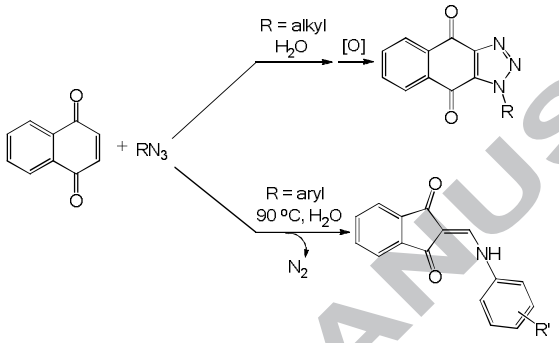

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Synthesis of bioactive 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones and *N*-aryl-2-aminomethylene-1,3-indanediones using water as the solvent

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ABSTRACT

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Through a [2+3] cycloaddition reaction, a new environmentally friendly method was developed to enable the synthesis of bioactive 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones and *N*-aryl-2-aminomethylene-1,3-indanediones using water as the solvent with good yields and minimum requirement of purification. This new green synthetic protocol is simple and suitable for scale-up synthesis.

Water has not been the common choice of solvent for organic reactions due to the solubility and reactivity problems of organic reactants in aqueous medium. Nevertheless, from the perspective of green chemistry, water is considered as a superior solvent for reactions because of its low cost, safety and lack of environmental concerns. For example, the pioneering work of Breslow in 1980 showed that Diels-Alder reactions could be achieved in aqueous medium.[1] Since then, more attention has been devoted to the investigation of conducting various organic reactions in aqueous medium.[2] In 2005, Sharpless and coworkers reported that several types of cycloaddition reactions could be accelerated in aqueous suspension without catalyst, even for water-insoluble substrates. Those reactions were conducted in a form of heterogeneous suspension that required vigorous stirring (so-called "on water reactions").[3] It was postulated that the hydrophobic effects[4] of the reactants in water could accelerate the reaction rates, and enhance the selectivity of reactions. Recent examples have also demonstrated the advantage of using water as solvents for improving the efficiencies of organic reactions. These include [2+3] cycloaddition of nitrones and allenolates without catalyst,[5] 1,3-dipolar cycloaddition reactions of hydrophobic nitrones[6] and 1,3-dipolar cycloaddition of azides with terminal and 1-iodoalkynes using copper(I) catalyst.[7]

1,4-Naphthoquinone and 2-methylene-1,3-indanedione are important structural units present in compounds that exert diverse biological and pharmaceutical applications (Figure 1).[8] For instance, plants containing a naphthoquinone scaffold are widely used in China and South American countries for treatment of malignant and parasitic diseases.[9] Several naphthoquinone derivatives have been employed as inhibitors against vitamin K dependent carboxylase.[10] Other examples include the use of 1,4-naphthoquinone derivatives as antibacterial,[11] antifungal,[12] and antitumor agents.[13] Furthermore, 1,4-naphthoquinone has also been noted to uncouple mitochondria oxidative phosphorylation leading to potential therapeutic applications.[14] Compounds bearing 2-methylene-1,3-indanedione or 2-methylene-4-cyclopentene-1,3-diones scaffold have been studied for their activity as antifungal agents,[15] anticancer agents[16] and therapeutic for hypotension.[17]

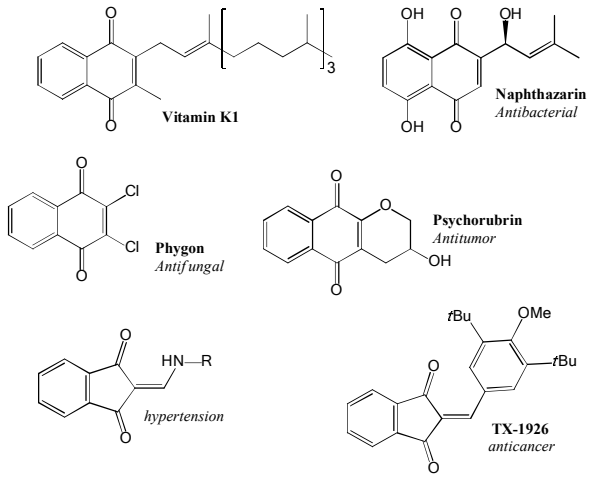

Fig. 1. Examples of molecules containing 1,4-naphthoquinone and 2-methylene-1,3-indanedione scaffolds

Our group has previously reported the synthesis of 1-alkyl-1*H*-naphthotriazole-4,9-diones, **3**, and *N*-glycosyl-2-aminomethylene-1,3-indanediones, **5** that show prominent

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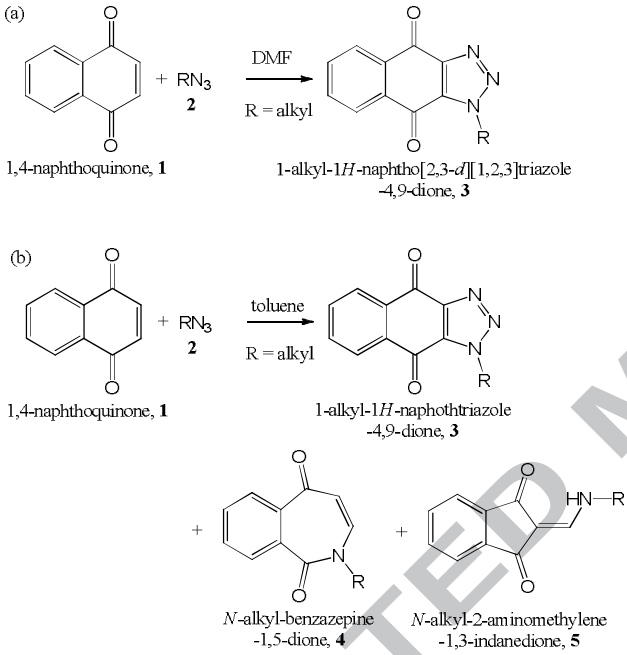
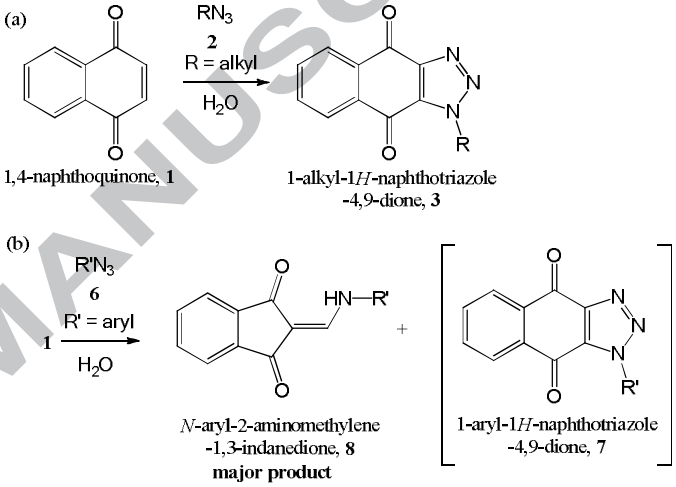
anticancer and antibacterial activities (Scheme 1).[18] The synthesis was carried out in organic solvents, such as DMF, dioxane and toluene, using a [2+3] cycloaddition of alkyl azides and 1,4-naphthoquinone followed with an oxidation *in situ*. We have noted that cycloaddition of alkyl azides and 1,4-naphthoquinone can lead to the formation of various heterocyclic compounds upon the manipulation of reaction conditions, such as temperature, solvent and the order of mixing reagents. In order to optimize the yield for the desired product, **3**, we have investigated several synthetic protocols.[18,19] For example, when conducting the reaction in polar organic solvent, such as DMF, the formation of by-products can be minimized (Scheme 1a). In contrast, when conducting the reaction in a less polar organic solvent like toluene, significant amounts of ring-expansion products (*N*-alkyl-benzazepine-1,5-dione, **4**) and ring contraction products (*N*-alkyl-2-aminomethylene-1,3-indanedione, **5**) were also obtained in addition to compound **3** (Scheme 1b).



Scheme 1. Synthesis of 1-alkyl-1*H*-naphthotriazole-4,9-dione and *N*-alkyl-2-aminomethylene-1,3-indanediones in organic solvent

In an effort to enable the production of compound **3** in an environmentally friendly process, we decided to investigate the feasibility of conducting the optimized protocol in aqueous medium (Scheme 2). To our delight, for most of the reactions examined, we obtained comparable yields and the reactions required minimum purification: no flash column chromatography was needed for most cases. A distinct difference associated with the type of azides employed was noted immediately. When alky azides were used as the substrates, only compound **3** was obtained in modest to good yields (Scheme 2a). However, when aryl azides, **6** were used, compound **8** (ring contraction product) were also obtained as the major by-products in several reactions (Scheme 2b).

The results from cycloaddition/oxidation of 1,4-naphthoquinone and alkyl azides using water as the solvent are summarized in Table 1 and the yields were compared with those conducted in DMF. We have noted that the higher reaction temperature may cause the formation of more by-products. Therefore, all these reactions were conducted at 70 °C instead of 110 °C. All the products were obtained in good purity without column chromatography purification. However, the yields varied depending largely on the chain length of the alky azides. Alkyl azides are immiscible with water and have lower density than water. Instead of forming a homogenous solution as the case in DMF, alkyl azides float on top of water during the reaction which will lead to the loss of azides through evaporation and, thus, lower the yields. As the length of alkyl chain increases, the boiling point of alkyl azide also increase and the yields improve, likely due to lowering the loss through evaporation. For example, for azides **2a-c,** the yields were lower than corresponding reactions in DMF. But when azides **2d-h** were used, the yields were very close to those conducted in organic solvent. As in the case of hexadecyl azide **2h,** the reaction could even be conducted in refluxing water and still achieved good yield as compared with the reaction carried out in DMF (entry 9, Table 1). In summary, we have demonstrated that water can be used as a medium for the cycloaddition/oxidation of 1,4-naphthoquinone and alkyl azides with comparable efficiency as those conducted in DMF.



Scheme 2. Synthesis of 1-alkyl-1*H*-naphthotriazole-4,9-dione, 1-aryl-1*H*-naphthotriazole-4,9-dione and *N*-aryl-2-aminomethylene-1,3-indanedione using water as the solvent

Table 1. Comparison of cycloaddition using alkyl azides in DMF and water[d]

Entry	Alkyl Azide	Product	Yield (%)[b]	
			DMF[a] at 110 °C	Water at 70 °C
1	$C_5H_{11}N_3$, **2a**	**3a**	40	21
2	$C_6H_{13}N_3$, **2b**	**3b**	49	26
3	$C_8H_{17}N_3$, **2c**	**3c**	62	32
4	$C_9H_{19}N_3$, **2d**	**3d**	38	34
5	$C_{10}H_{21}N_3$, **2e**	**3e**	54	37
6	$C_{11}H_{23}N_3$, **2f**	**3f**	47	52

7	$C_{12}H_{25}N_3$, **2g**	**3g**	51	55
8	$C_{16}H_{33}N_3$, **2h**	**3h**	68	63
9	$C_{16}H_{33}N_3$, **2h**	**3h**	68	72[c]

[a]Reference 19, 20. [b]Isolated yield. [c]Reflux.. [d]General condition: 0.2 g alkyl azide, 2 equiv. 1,4-naphthoquinone, 10 mL distilled water. The suspension was stirred vigorously overnight.

With this promising preliminary result in hand, we decided to study more alkyl azides with functional groups, such as hydroxy, ester and aryl, attached to alkyl chain (Table 2). When using water as the medium, all the tested azides offered comparable yields of the desired products with the exception of compound **2m**.

Table 2. Cycloaddition using substituted alkyl azides in DMF and water[c]

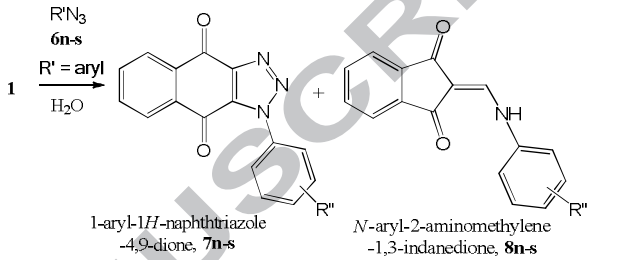
Entry	Azide	Yield (%) of **3i-m** Cycloaddition Product	
		DMF at 110 °C	Water at 70 °C[a]
1	methyl azidoacetate**, 2i**	51[b]	56
2	1,6-diazidohexane, **2j**	47[21]	54
3	6-azido-1-hexanol, **2k**	27[18b]	32
4	benzyl azide, **2l**	46[19]	33
5	anisyl azide, **2m**	81[21]	48

[a]Isolated yield. [b]This reaction was carried out at 80 °C. [c]General condition: 0.2 g alkyl azide, 2 equiv. 1,4-naphthoquinone, 10 mL distilled water. The suspension was stirred vigorously overnight.

To our surprise, when aryl azides were used as substrates for cycloaddition, we also isolated *N*-aryl-2-aminomethylene-1,3-indanediones, **8n-s** (ring contraction products) as the main by-products as well as the desired products, **7n-s** (cycloaddition products) (Table 3). However, these by-products were not observed when using alkyl azides as substrates (Tables 1 and 2). We believe temperature and solvent play the key roles here, so we ran the same reactions at 90 °C. At this temperature, reactions of aryl azides and 1,4-naphthoquinone provided the ring contraction products, *N*-aryl-2-aminomethylene-1,3-indanediones, **8n-s** as the dominant product with trace amount of cycloaddition product, 1-alkyl-1*H*-naphthotriazole-4,9-diones, **7n-s** in some cases. Interestingly, the ring contraction product was not observed when alkyl azides were employed. For example, cycloaddition using hexadecyl azide at reflux conditions on water gave exclusively the cycloaddition product (entry 9, Table 1). On the other hand, our group has also established an optimal protocol for the selective synthesis of cycloaddition product from aryl azides. When DMF was used as the solvent, conducting the cycloaddition at 60 – 65 °C offered only the cycloaddition products (Table 3, entry 2).[21] However, as the reaction temperature increased to 90 °C, a mixture of ring contraction product and cycloaddition products was obtained.

Since temperature can be a factor in controlling the product formation, we have further examined the effect of temperature by lowering the reaction temperature to 45 °C (Table 4). At this temperature, the formation of products was very slow as indicated by the low yields. Prolonged reaction time may help to increase the yields. However, more ring contraction product, **8n** was also obtained. Therefore, we conclude that the cycloaddition of aryl azides in aqueous medium is not selective for the formation of compound **7**. Nevertheless, selective formation of compound **7** can be achieved using DMF as the solvent.

Table 3. Cycloadditions using aryl azides[b]



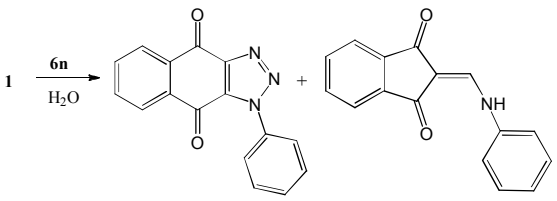
1-aryl-1*H*-naphthtriazole -4,9-dione, **7n-s**

N-aryl-2-aminomethylene -1,3-indanedione, **8n-s**

Entry	Azide	Temp.	Yield of **7**[a] (%)	Yield of **8** (%)
1	phenyl azide, **6n** (in H_2O)	60 °C	**7n**[21] (23)	**8n**[22] (34)
		90 °C	**7n** (trace)	**8n** (51)
2	phenyl azide, **6n** (in DMF)	60 °C	**7n** (27)	**8n** (trace)
		90 °C	**7n** (35)	**8n** (20)
3	4-azidotoluene, **6o** (in H_2O)	60 °C	**7o**[21] (35)	**8o**[23] (29)
		90 °C	**7o** (trace)	**8o** (48)
4	4-azidoanisole, **6p** (in H_2O)	60 °C	**7p**[21] (34)	**8p**[24] (28)
		90 °C	**7p** (trace)	**8p** (46)
5	*p*-azido-fluorobenzene , **6q** (in H_2O)	60 °C	**7q**[21] (22)	**8q**[25] (33)
		90 °C	**7q** (0)	**8q** (62)
6	*p*-azido-chlorobenzene , **6r** (in H_2O)	60 °C	**7r**[21] (21)	**8r**[26] (35)
		90 °C	**7r** (0)	**8r** (68)
7	1-azido-2,4-dimethoxy-benzene, **6s** (in H_2O)	60 °C	**7s** (54)	**8s**[24] (24)
		90 °C	**7s** (trace)	**8s** (52)

[a]The yields from reactions conducted at 60 °C were estimated based on the integration ratio from ^{1}H NMR. The yields from reaction conducted at 90 °C were isolated yields. [b]General condition: 0.2 g alkyl azide, 2 equiv. 1,4-naphthoquinone, 10 mL distilled water. The suspension was stirred vigorously overnight.

Table 4. Cycloaddition using phenyl azid in water[b]



1-aryl-1*H*-naphthotriazole -4,9-dione, **7n**

N-aryl-2-aminomethylene -1,3-indanedione, **8n**

Entry	Temp.	Time	Yield of **7n**[21] (%)[a]	Yield of **8n** (%)
1	45 °C	overnight	8	0
2	45 °C	1 day	10	6
3	45 °C	2 days	13	9
4	45 °C	4 days	25	13

[a]The yields were estimated based on the integration ratio from ^{1}H NMR. [b]General condition: 0.2 g alkyl azide, 2 equiv. 1,4-naphthoquinone, 10 mL distilled water. The suspension was stirred vigorously overnight.

In conclusion, we have demonstrated that [2+3] cycloaddition between 1,4-naphthoquinone and alkyl/aryl azides can be carried out in heterogeneous aqueous medium with good yield and minimum requirement of purification. There is an interesting difference between alkyl azides and aryl azides in terms of the major products isolated at different temperatures. When alkyl azides were used, 1-alkyl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones were the dominant products. When aryl azides were used, *N*-aryl-2-aminomethylene-1,3-indanediones could be the major products if the reactions were conducted at high temperature (90 °C). These two classes of compounds have been studied for their biological activities. Investigation of the antibacterial and antifungal activities of the synthesized compounds is being pursued. We are currently also exploring the conditions for the selective synthesis of 1-aryl-1*H*-naphtho[2,3-*d*][1,2,3]triazole-4,9-diones and *N*-alkyl-2-aminomethylene-1,3-indanediones in heterogeneous aqueous medium. Since the reactions conducted in aqueous medium can readily offer a large quantity, the developed protocols may expedite the discovery of practical products following the screen for biological activities.

General procedure for cycloaddition between 1,4-naphthoquinone and alkyl/aryl azides using water as the solvent. The alkyl/aryl azides (ca. 0.2 g) and naphthoquinone (2 equiv.) were added into a 50 mL round bottom flask containing distilled water (10 mL), and the reaction mixture was heated and stirred vigorously for overnight. After being cooled to room temperature, the solid was collected using Buchner funnel. The collected solid was stirred in 30 mL of ethyl ether for 2 hours to dissolve excess 1,4-naphthoquinone. The product was collected using Buchner funnel and washed with another 30 mL

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Supporting Data ^{1}H and ^{13}C spectra of the synthesized compound, and other experimental procedures can be found with the online manuscript.

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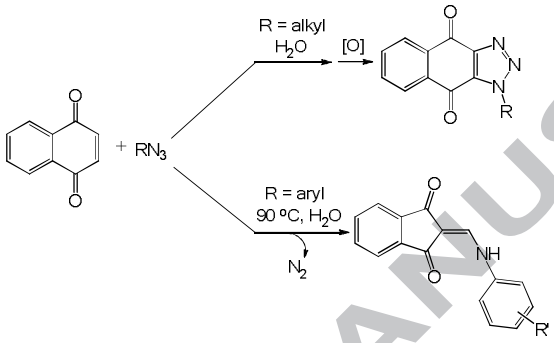

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