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Graphical Abstract

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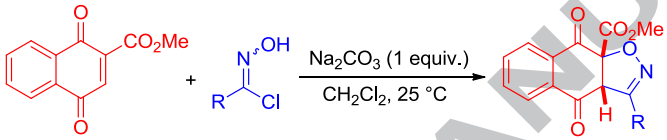

20 examples
up to 95% yield
up to >20:1 regioselectivity
up to >20:1 dr

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ABSTRACT

A base mediated 1,3-dipolar cycloaddition reaction of methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate with nitrile oxides *in situ* generated from *N*-hydroximoyl chlorides was achieved. With this developed protocol, a range of structurally diverse naphtho[2,3-*d*]isoxazole-4,9(3a*H*,9a*H*)-dione derivatives were smoothly obtained in high yields (up to 95%) with up to >20:1 regioselectivities and >20:1 diastereoselectivities under mild conditions. The promising applicability of the protocol was also demonstrated by the further transformations.

1. Introduction

Nitrogen- and oxygen-containing heterocyclic ring system represents a major structure type in a number of natural products and clinical pharmaceuticals.[1] In particular, isoxazolines and isoxazoles are an important class of heterocyclic compounds with remarkable biological activities including antibacterial,[2] anti-inflammatory,[3] antinociceptive,[4] anti-tubercular,[5] antithrombotic,[6] antiviral,[7] anticonvulsant[8] as well as anti-HIV properties.[9] Accordingly, developing efficient methodologies for the construction of various heterocyclic compounds containing isoxazoline or isoxazole framework has attracted the attention of the organic and medicinal chemists. And a variety of efficient strategies have been developed in this area.[10] Among the reported methods, 1,3-dipolar cycloaddition of nitrile oxides to suitable alkenes or alkynes belongs to the most straightforward approach and was widely used to access diverse interesting heterocyclic molecules.[11] However, the majority of these methods mainly afforded monocyclic compounds. In this context, it is still highly desirable to explore new and efficient methods to access isoxazolines or isoxazoles with polycyclic skeleton.

Naphthoquinones not only constitute the central skeleton of numerous natural products and pharmacologically important compounds,[12-14] but also have been studied for further synthetic purposes to access various dihydronaphthoquinones and their derivatives.[15] Particularly, naphthoquinones bearing electron-withdrawing substituents at C2-position have been widely used as dienophiles for cycloaddition reaction to construct various functionalized polycyclic compounds.[16] It's worth noting that most of the cycloaddition reactions of this type of naphthoquinones took place at C3- and O2′-position (Scheme 1 (1)). In stark contrast, only few examples have been reported as to the cycloaddition reactions occurring at the C=C bond (C3- and C2-position) of naphthoquinones (Scheme 1 (2)).[17] A survey of the literature revealed that the 1,3-dipolar cycloaddition reaction of C=C bond of methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate with nitrile oxides has not been reported, except one example of 1,3-dipolar cycloaddition of naphthoquinone with nitrile oxides gave the fused isoxalines with inferior regioselectivity.[18] We think that introduction of methyl ester into naphthoquinone will be helpful for the reactivity and regioselectivity, thus the reaction of methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate with nitrile oxides *in situ* generated from *N*-hydroximoyl chlorides should be achieved in high regioselectivity (Scheme 1 (3)). As part of our

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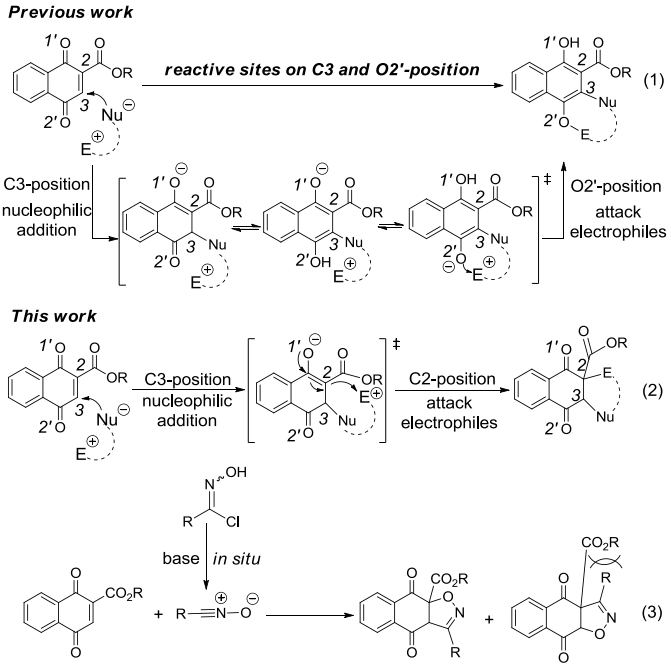
general interest in exploring creative methodologies for the synthesis of heterocyclic compounds,[19] herein we wish to report our recent research results on the 1,3-dipolar cycloaddition reaction of methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate with nitrile oxides for the synthsis of various dihydronaphthoquinone-containing polycyclic isoxazolines.

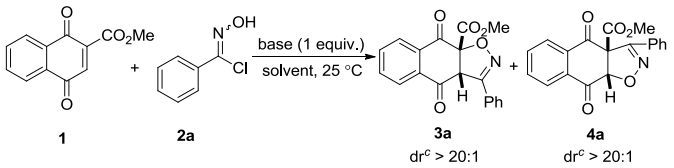


Scheme 1 Strategy for the synthesis of naphtho[2,3-*d*]isoxazole-4,9(3a*H*,9a*H*)-diones

2. Results and discussion

Initially, we commenced our investigation with the reaction of methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate **1** and nitrile oxide precursor **2a** in dichloromethane at 25 °C. As shown in Table 1, the reaction could occur in the absence of base and gave the corresponding cycloaddition product **3a** in 18% yield after 27 h (Table 1, entry 1). To our delight, the reaction proceeded smoothly with triethylamine (Et_3N) as the base and furnished product **3a** in 71% yield and excellent disastereoselectivity with good regioselectivity ratio after 1 h (Table 1, entry 2). Other bases such as DBU, $NaHCO_3$, Na_2CO_3, K_2CO_3 were also tested. Among them, Na_2CO_3 gave the best results and was selected as the suitable base for further optimization (Table 2, entries 3-6). Afterwards, a survey of various solvents, including $CHCl_3$, 1,2-dichloroethane (DCE), toluene, diethyl ether (Et_2O), THF, CH_3CN revealed that CH_2Cl_2 was the most suitable reaction media for this reaction and furnished 92% yield with >20:1 regioselectivity (Table 1, entry 5 *vs* entries 7-12). To further improve the yield, the substrate concentration was also examined. It was found that the yield was obviously improved and the product **3a** could be obtained in 95% yield within 3 h by increasing the substrate concentration (Table 1, entry 13). When the reaction was conducted on a 0.15 mmol scale, comparable result was obtained (Table 1, entry 13 *vs* 14). As a result, the following reaction conditions were recommended: 1.0 equiv. Na_2CO_3 with 0.1 M of substrate concentration in CH_2Cl_2 at 25 °C.

Table 1
Optimizing reaction conditions[a]

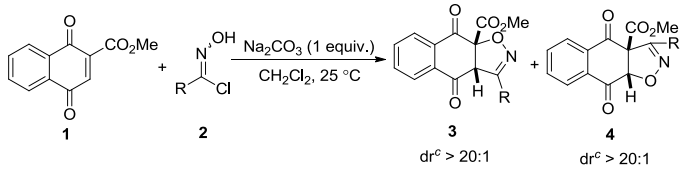


Entry	Solvent	Base	Time (h)	Yield (%)[b]	**3a**:**4a**[c]
1	CH_2Cl_2	/	27	18	nd
2	CH_2Cl_2	Et_3N	1	71	15:1
3	CH_2Cl_2	DBU	0.5	55	>20:1
4	CH_2Cl_2	$NaHCO_3$	5	90	14:1
5	CH_2Cl_2	Na_2CO_3	5	92	>20:1
6	CH_2Cl_2	K_2CO_3	5	86	>20:1
7	$CHCl_3$	Na_2CO_3	5	91	>20:1
8	DCE	Na_2CO_3	5	75	17:1
9	toluene	Na_2CO_3	5	90	>20:1
10	Et_2O	Na_2CO_3	8	50	13:1
11	THF	Na_2CO_3	3	86	>20:1
12	CH_3CN	Na_2CO_3	3	82	1.6:1
13[d]	CH_2Cl_2	Na_2CO_3	3	95	>20:1
14[e]	CH_2Cl_2	Na_2CO_3	3	94	>20:1

[a]Unless specified, the reactions were carried out with **1** (0.1 mmol), **2a** (0.15 mmol), and base (0.1 mmol) in 2.0 mL of solvent for the indicated time.
[b]Isolated yields of **3a** and **4a**.
[c]Determined by ^1H NMR analysis after isolation with column chromatography.
[d]1.0 mL solvent was used.
[e]The reaction was carried out using **1** (0.15 mmol), **2a** (0.225 mmol), and base (0.15 mmol) in 1.5 mL CH_2Cl_2. nd = no detection.

With the optimal conditions in hand, the substrate scope of this cycloaddition reaction was examined, and the results are summarized in Table 2. It was found that a series of *N*-hydroxybenzimidoyl chlorides **2**, either containing electron-withdrawing (**2b-k**) or electron-donating substituents (**2l-p**) on the different positions of benzene ring, were well tolerated and delivered their corresponding products **3b-p** in good yields (67-93%) and high to excellent regioselectivities (7:1->20:1) with excellent dr values (Table 2 entries 1-15). Generally, the *N*-hydroxybenzimidoyl chlorides **2** bearing electron-withdrawing groups (**2b-k**) furnished better regioselectivities than the electron-donating ones (Table 2, entries 1-10 *vs* 11-15). Notably, when two electron-donating methoxyl substitutents are incorporated into the phenyl ring of *N*-hydroxybenzimidoyl chloride **2q**, the corresponding product **3q** was obtained in excellent yield (95%) with acceptable regioselectivity (3.6:1) (Table 2, entry 16). Meanwhile, fused aromatic **2r** also reacted efficiently with **1**, giving product **3r** in 86% yield with 13:1 regioselectivity (Table 2 entry 17). Moreover, this protocol was also able to broaden to 2-thienyl substrate **2s**, and the reaction could be completed with good yield (87%) and regioselectivity (7.5:1) (Table 2, entry 18). Ultimately, an aliphatic substrate could also be applied in this transformation, but only 36% yield and 1:1 regioselectivity were achieved for product **3t** (Table 2, entry 19).

Table 2
Substrate scope for the 1,3-dipolar cycloaddition reaction[a]



Entry	R/**2**	Time (h)	**3**	Yield (%)[b]	**3**:**4**[c]
1	4-$NO_2C_6H_4$/**2b**	3	**3b**	76	13:1
2	4-CNC_6H_4/**2c**	3	**3c**	93	>20:1
3	4-FC_6H_4/**2d**	5	**3d**	78	13:1
4	4-ClC_6H_4/**2e**	5	**3e**	83	>20:1
5	4-BrC_6H_4/**2f**	5	**3f**	86	>20:1
6	3-BrC_6H_4/**2g**	3	**3g**	91	>20:1
7	2-ClC_6H_4/**2h**	5	**3h**	88	>20:1
8	2-BrC_6H_4/**2i**	3	**3i**	82	13:1
9	2-$CF_3C_6H_4$/**2g**	3	**3j**	73	>20:1
10	2-CNC_6H_4/**2k**	5	**3k**	87	>20:1
11	4-MeC_6H_4/**2l**	5	**3l**	67	10:1
12	4-$MeOC_6H_4$/**2m**	3	**3m**	90	7:1
13	3-MeC_6H_4/**2n**	5	**3n**	80	>20:1
14	3-$MeOC_6H_4$/**2o**	5	**3o**	82	15:1
15	2-MeC_6H_4/**2p**	5	**3p**	90	10:1
16	3,4-$(MeO)_2C_6H_3$/**2q**	3	**3q**	95	3.6:1
17	1-Naphthyl/**2r**	3	**3r**	86	13:1
18	2-Thienyl/**2s**	3	**3s**	87	7.5:1
19	Bn/**2t**	2	**3t**	36	1:1

[a]Unless specified, the reactions were carried out with **1** (0.15 mmol), **2** (0.225 mmol), and base (0.15 mmol) in 1.5 mL of CH_2Cl_2 for the indicated time.
[b]Isolated yield of **3a** and **4a**.
[c]Determined by ^{1}H NMR analysis after isolation with column chromatography.

In addition to the spectroscopic data (^{1}H, ^{13}C NMR, and mass spectrocopy analysis), the X-ray crystallography of the product **3a** was achieved (Figure 1), which unambiguously confirmed the structure of product **3a** from the C=C bond cycloaddition reaction of methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate.[20] The structures of the other products were assigned on the assumption of a uniform mechanistic pathway. The structure of all products in this paper is expressed as relative stereochemistry.[21]

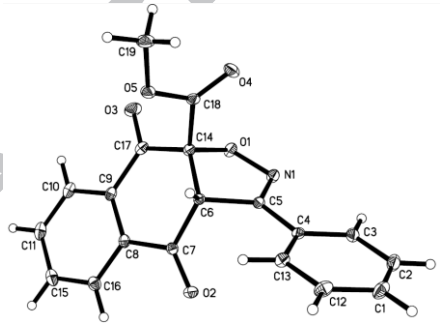
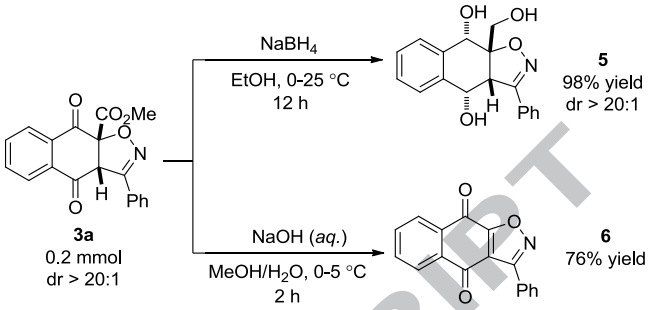


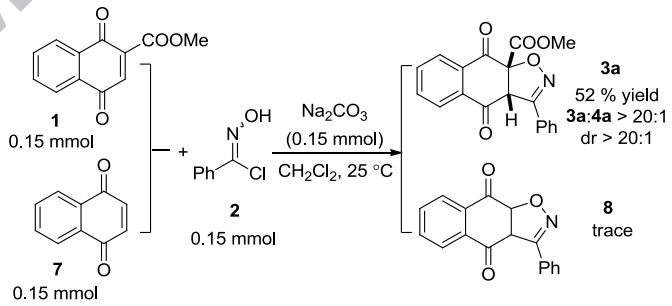
Figure 1 X-ray structure of product **3a**

In order to demonstrate the synthetic utility of this protocol, the conversions of the product **3a** into other functionalized and valuable compounds were performed. As shown in Scheme 2, cycloaddition product **3a** could be easily hydrogenated with sodium borohydride ($NaBH_4$) in ethyl alcohol (EtOH), and heterocyclic compound **5** containing multiple hydroxyl groups was obtained in excellent yield (98%) and diastereoselectivity (>20:1). The hydrogenated relative stereochemistry of **5** was confirmed by NOESY spectrum.[21] On the other hand, treatment of compound **3a** with NaOH could readily furnish naphthoquinone-containing polycyclic isoxazole **6** in 76% yield after 2 h via the hydrolyzation and decarboxylization processes.



Scheme 2 Transformation of the product **3a**

In order to gain insight into the influence of ester group on the reactivity between methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate and naphthalene-1,4-dione, we conducted a verified experiment (Scheme 3). We employed an equimolar mixture of methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate **1** and naphthalene-1,4-dione **7** reacting with equimolar nitrile oxide precursor **2a** under the optimal conditions. We found that product **3a** could be obtained in 52 % yield, but with trace compound **8**, when nitrile oxide precursor **2a** was completely consumed. This result suggested that 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate **1** had a reactivity higher than that of naphthalene-1,4-dione **7**, which could owe to the introduction of ester group into the naphthalene-1,4-dione.



Scheme 3 Verified experiment

3. Conclusion

In conclusion, we have developed a 1,3-dipolar cycloaddition reaction of nitrile oxides to methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate with Na_2CO_3 as base. A series of nitrile oxides generated *in situ* from *N*-hydroximoyl chlorides reacted smoothly with methyl 1,4-dioxo-1,4-dihydronaphthalene-2-carboxylate, affording a range of structurally diverse naphtho[2,3-*d*]isoxazole-4,9(3a*H*,9a*H*)-dione derivatives in high yields (up to 95%) with up to >20:1 regioselectivities and >20:1 diastereoselectivities. The usefulness of the protocol was successfully demonstrated by the additional transformation of the product into other novel polycyclic naphthoquinone derivatives.

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Supplementary data

Supplementary data (experimental details and ^{1}H, ^{13}C NMR spectra of compounds **3**) associated with this article can be found, in the online version, at https://doi.org/

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20. CCDC-1508911 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.
21. For detail, see supporting information.

Highlights:

(1) Various dihydronaphthoquinone-containing polycyclic isoxazolines were obtained in one step with this developed protocol.

(2) The introduction of ester group into naphthoquinone improved the reactivity.

(3) This developed protocol has overcome the problem of low regioselectivity of cycloaddition reaction.

(4) The product could be easily transformed into other novel polycyclic naphthoquinone derivatives.