Cascade Reaction

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Cascade Nitration/Cyclization of 1,7-Enynes with *t*BuONO and H_2O: One-Pot Self-Assembly of Pyrrolo[4,3,2-*de*]quinolinones**

*Yu Liu, Jia-Ling Zhang, Ren-Jie Song, Peng-Cheng Qian, and Jin-Heng Li**

Abstract: *Here we describe the one-pot construction of the pyrrolo[4,3,2-de]quinolinone scaffold by a cascade nitration/cyclization sequence of 1,7-enynes with tBuONO and H_2O. The cascade proceeds through alkene nitration, 1,7-enyne 6-exo-trig cyclization, C–H nitrations, and redox cyclization, and exhibits excellent functional group tolerance. The mechanism was investigated using in situ high-resolution mass spectrometry (HR-MS).*

Pyrrolo[4,3,2-*de*]quinolinone represents an essential part of the scaffold of numerous natural compounds and pharmaceuticals with remarkable biological and medicinal properties (Figure 1) and is widely used as a valuable functional intermediate.[1,2] For these reasons, considerable efforts have been devoted to the development of new and simple methods for the total synthesis of pyrrolo[4,3,2-*de*]quinolinone and its derivatives.[3–5] Generally, these methods proceed either by construction of the quinoline system followed by elaboration of the pyrrole ring,[3] or by construction of the indole scaffold followed by the piperidine ring.[4] However, in all cases the construction of the pyrrolo[4,3,2-*de*]quinolinone scaffold requires several steps with rather low overall yields.[3–5] Thus, it would be highly desirable to exploit new routes and especially one-pot strategies toward these structures.

Cascade reactions have proven to be a powerful shortcut for the assembly of complex ring systems in organic synthesis.[6] Among these processes, the cyclization of 1,*n*-enynes is a particularly effective and atom-economical step for constructing the ring systems.[6,7] Herein, we report an unprecedented cascade nitration/cyclization of *N*-(2-(ethynyl)aryl)acrylamides (**1**) with *t*BuONO and H_2O for the one-pot synthesis of pyrrolo[4,3,2-*de*]quinolinone architectures under metal-free conditions (Scheme 1);[8] this is realized through a cascade of alkene nitration, 1,7-enyne 6-*exo*-trig cyclization, C–H nitrations, and redox cyclization, representing the first example of a one-pot assembly of the pyrrolo-[4,3,2-*de*]quinolinone scaffold.

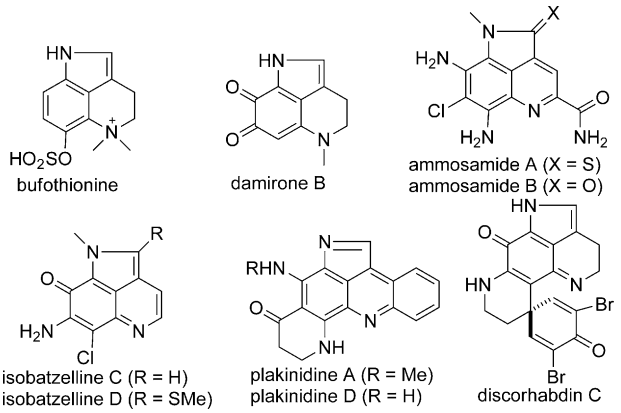
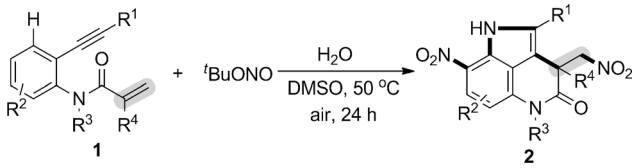


Figure 1. Examples of important pyrrolo[4,3,2-*de*]quinolinones.



Scheme 1. Cascade nitration/cyclization of 1,7-enynes.

We commenced our studies by exploring the reaction between *N*-methyl-*N*-(2-(phenylethynyl)phenyl)methacrylamide (**1a**) with *t*BuONO to optimize the reaction conditions (Table 1). After extensive screening of different reaction parameters, the desired pyrrolo[4,3,2-*de*]quinolinone **2a** was formed with the highest yield from the reaction of 1,7-enyne **1a** with 4 equiv *t*BuONO in dimethyl sulfoxide (DMSO) at 50 °C for 24 h (entry 1). Encouraged by these results, we examined the effect of the reaction temperature (entries 1–3): whereas at a reaction temperature of 50 °C product **2a** was isolated in 78 % yield (entry 1), the yield decreased to 63 % when the temperature was increased to 80 °C (entry 2), and to 45 % at a reaction temperature of 30 °C (entry 3). It has been reported that 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO), a radical initiator, proved beneficial in some nitration reactions using *t*BuONO.[8] However, the presence of TEMPO suppressed the current reaction (entries 4 and 5): the yield of product **2a** decreased from 78 % to 67 % with 20 mol % TEMPO and to 53 % with 100 mol % TEMPO. Notably, a good yield was even achieved under N_2 atmosphere when DMSO was purged with N_2 (entry 6). This suggests that

[*] Y. Liu, J.-L. Zhang, Dr. R.-J. Song, P.-C. Qian, Prof. Dr. J.-H. Li
State Key Laboratory of Chemo/Biosensing and Chemometrics
College of Chemistry and Chemical Engineering
Hunan University, Changsha 410082 (China)
E-mail: jhli@hnu.edu.cn
Prof. Dr. J.-H. Li
State Key Laboratory of Applied Organic Chemistry Lanzhou University
Lanzhou 730000 (China)

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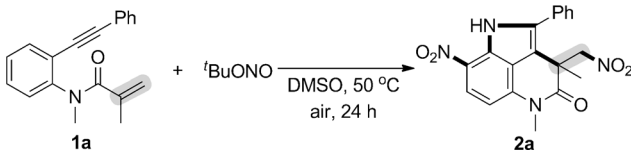
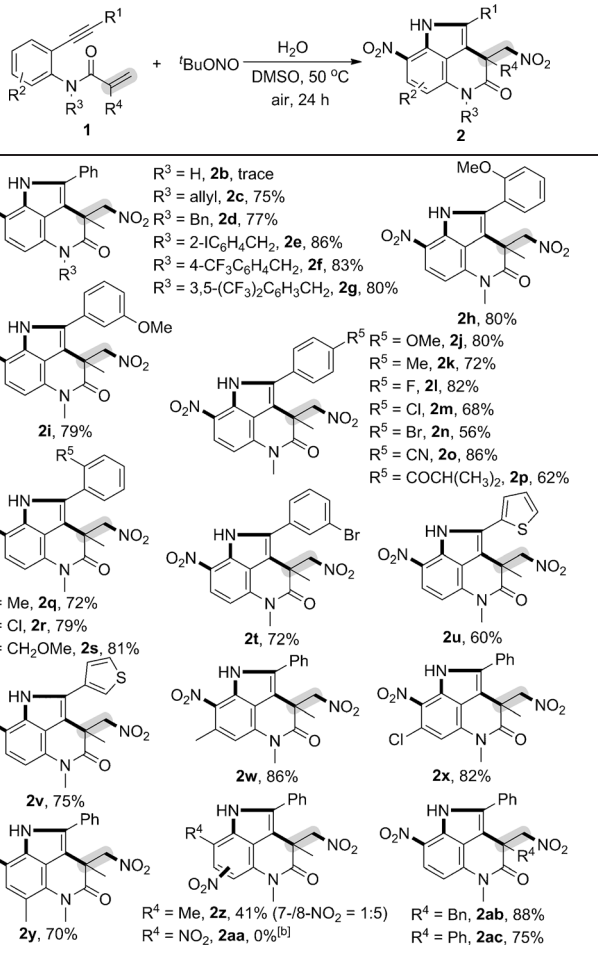
Table 1: Screening of the reaction conditions.[a]



Entry	Variation from the standard conditions	Yield [%][b]
1	none	78
2	at 80 °C	63
3	at 30 °C	45
4	TEMPO (20 mol %)	67
5	TEMPO (100 mol %)	53
6[c]	DMSO purged with N_2	75
7	MeCN instead of DMSO	19
8	DMF instead of DMSO	31
9	CH_2ClCH_2Cl instead of DMSO	26
10	toluene instead of DMSO	16
11	0.9 mmol H_2O in anhydrous DMSO	76
12	2.8 mmol H_2O in anhydrous DMSO	65
13[d]	none for 72 h	76

[a] Reaction conditions: **1a** (0.2 mmol), *t*BuONO (4 equiv), and DMSO (3 mL) at 50 °C under air atmosphere for 24 h. DMSO contains about 0.5 % w/w H_2O (about 0.92 mmol H_2O in 3 mL DMSO). [b] Yield of the isolated product. [c] Under N_2 atmosphere. [d] **1a** (1 g, 3.64 mmol).

Table 2: Nitration/cyclization of 1,7-enynes (**1**) with *t*BuONO.[a]



[a] Reaction conditions: **1** (0.2 mmol), *t*BuONO (4 equiv), and DMSO (3 mL) at 50 °C under air atmosphere for 24 h. [b] More than 95 % of substrate **1aa** was recovered.

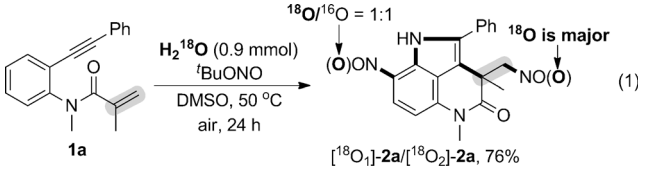
the presence of O_2 only slightly affects the reaction in terms of yield (entry 1 versus entry 6). A series of solvents, including MeCN, DMF, CH_2ClCH_2Cl, and toluene, were also tested, and the results showed that they were less effective than DMSO (entry 1 versus entries 7–10). We found that the amount of H_2O had a fundamental influence on the reaction (entry 1 versus entries 11 and 12): a good yield was still achieved at a loading of 0.9 mmol H_2O using anhydrous DMSO, but the yield decreased from 78 % to 65 % when the amount of H_2O was increased to 2.8 mmol. It is noteworthy that the reaction could also be performed in good yield at a scale of 1 g (3.64 mmol) 1,7-enyne **1a** (entry 13).

With the optimized reaction conditions in hand, a variety of 1,7-enynes **1** were reacted with *t*BuONO to investigate the scope of this nitrative cyclization protocol (Table 2). Initially, the effect of substituents on the nitrogen atom was examined (products **2b–g**). Whereas substrate **1b** with a free N–H bond was not viable for this nitrative cyclization reaction (product **2b**), substrates **1c–g**, having an allyl or a substituted benzyl group on the nitrogen atom, were successfully converted into the corresponding pyrrolo[4,3,2-*de*]quinolinones **2c–g** in good yields. The results showed that several substituents, including MeO, Me, F, Cl, Br, CN, $COCH(CH_3)_2$, and CH_2OMe, on the aryl ring at the alkyne were well-tolerated under the optimized conditions, and the substituents at the *ortho*-, *meta*-, or *para*-position have no distinct influence on the reaction. For example, substrates **1h–j** with a MeO group were transformed into products **2h–j** with similar yields. Importantly, halogen functional groups, F, Cl, and Br, were compatible with the optimized reaction conditions, thereby enabling subsequent modifications at the halogenated positions (products **2e**, **2l–n**, **2r**, and **2t**). Application of substrates **1o** and **1p** with an electron-withdrawing group, delivers the desired products **2o** and **2p** in good yields. Heteroaryl alkynes **1u** and **1v** were also suitable for this nitrative cyclization transformation, giving products **2u** and **2v** in 60 % and 75 % yield, respectively. Unfortunately, aliphatic alkynes were not viable for this reaction.

Several substituents on the aromatic ring of the *N*-phenyl moiety, including Me and Cl, were also compatible with the optimized reaction conditions (products **2w–aa**). Treatment of substrates **1w** or **1x**, bearing a Me or a Cl group at the 5-position, with *t*BuONO and H_2O afforded the corresponding products **2w** and **2x** in high yield. The bulky substrate **1y** with a Me group at the 5-position was successfully transformed into product **2y** in 70 % yield. Substrate **1z** having a Me group on the 4-position of the *N*-phenyl moiety gave two regioselective nitration isomers **2z** in 41 % yield; however, substrate **1aa** with a NO_2 group showed no reactivity (product **2aa**). Gratifyingly, this nitrative cyclization protocol could also be applied to substrates **1ab** and **1ac** with a Bn or a Ph group at the 2-position of the acrylamide moiety, providing products **2ab** and **2ac** in 88 % and 75 % yield, respectively.

As can be seen in Table 1, the amount of H_2O had an effect on the reaction, suggesting that the oxygen atoms in two NO_2 groups may be from H_2O. To verify this, we

conducted an ^{18}O-labeling experiment with $H_2{}^{18}O$ [Eq. (1)].[9] The results showed that a mixture of product [$^{18}O_1$]-**2a** containing one oxygen atom and and product [$^{18}O_2$]-**2a** containing two oxygen atoms was observed with a 1:1 ratio.

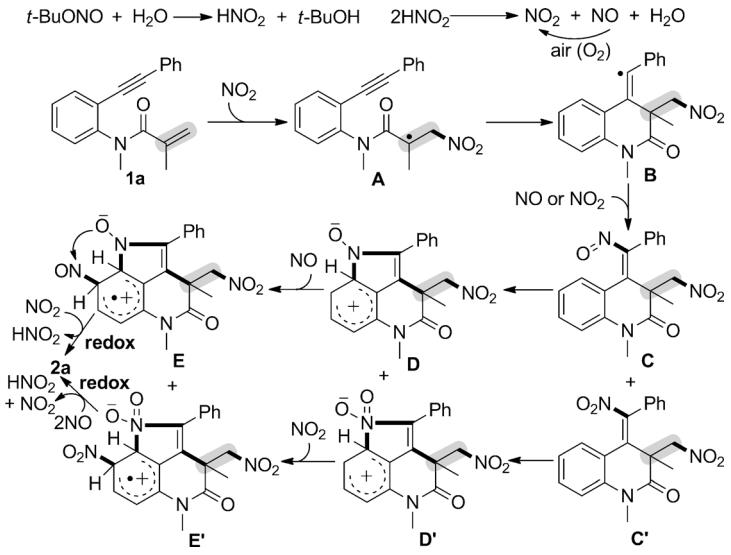


(1)

This suggests that nitration at the 4-position of the *N*-phenyl moiety is crucial for the described reaction, and that H_2O is not the sole source of the oxygen atoms of the nitro groups.

To understand the mechanism, three radical inhibitors (4 equiv), TEMPO, hydroquinone, and butylhydroxytoluene (BHT), were added to the reaction, leading to its inhibition. With $PhNO_2$ as the radical inhibitor, the yield of product **2a** decreased from 78% to 69%.[10] This implies that the reaction proceeds via a radical intermediate, which is also supported by the intermolecular kinetic isotope effect experiment ($k_H/k_D = 1$).[9]

Proposed reaction mechanisms based on the above results[9] and previous reports[6–8,11,12] are shown in Scheme 2. Initially, addition of NO_2, which is generated in situ from ^{t}BuONO,[8,11,12] to the carbon–carbon double bond of the 1,7-enyne **1a** gives alkyl radical intermediate **A**, which cyclizes to form intermediate **B**. The reaction of intermediate **B** with NO or NO_2 affords the corresponding intermediates **C** and **C′**, which was supported by HRMS analysis.[9] Cationic intermediates **D** and **D′** are formed by electrophilic addition of the N=O group to the phenyl ring in intermediates **C** and **C′**. Subsequently, treatment of the cationic intermediates **D** and **D′** with NO or NO_2 selectively provides cationic radical intermediates **E** and **E′**. Finally, the redox reaction of the cationic radical intermediates **E** and **E′** gives product **2a**.



Scheme 2. Possible mechanisms.

Within the redox process, the oxygen atom of the nitro group on the aryl ring can be derived from ^{t}BuONO and H_2O, which is the reason why this reaction can be performed without addition of O_2 (entry 6 versus entry 1; Table 1).

In summary, we have developed a novel metal-free cascade reaction for the synthesis of pyrrolo[4,3,2-*de*]quinolinone derivatives from readily available *N*-(2-(ethynyl)aryl)-acrylamides and ^{t}BuONO in good yields. In this cascade, which proceeds through alkene nitration, 1,7-enyne 6-*exo*-trig cyclization, C–H nitrations, and redox cyclization, two nitro groups and an amine group are incorporated into the product. This method provides a valuable one-pot shortcut for the assembly of pyrrolo[4,3,2-*de*]-quinolinone derivatives and exhibits a broad enyne scope with excellent functional group tolerance. Detailed studies on the mechanism and the extension of this cascade method are currently underway in our laboratory.

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[9] Detailed data on the ^{18}O-labeling experiment (Figure S1), the intermolecular kinetic isotope effect experiment (Figure S2), and the in situ HRMS analysis of the reaction of substrate **1a** and *t*BuONO (Figure S3) are summarized in the Supporting Information.

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