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Metal-Free, Site-Selective Addition to Ynones: An Approach to Synthesize Substituted Quinoline Derivatives

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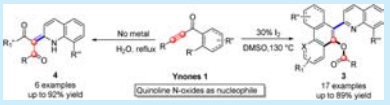
Supporting Information

ABSTRACT: An efficient two component cycloaddition reaction to synthesize various substituted quinoline derivatives was developed. Ynone **1** was functionalizated by *N*-oxide attacking the C3-oxetium site and C3-site regioselectively to give **3** and **4**. Analogues **3k** and **4v** have a high binding constant with Hg^{2+} in CH_3CN.



Regioselective addition reactions are useful tools in modern organic synthesis. For instance, the regioselective 1,2- and 1,4-addition to enone is a well-established method that has been successfully employed in the synthesis of important units of natural products.[1] Likewise, ynone is an electron-deficient alkyne that the C−C triple bond is polarized substantially by the carbonyl group, which causes the end distal of ynone to be significantly more electron-deficient than the proximal end, therefore inviting preferential attack by the approaching nucleophiles (Scheme 1A).[2,3,8] The regioselective addition on the end distal carbon site of ynone has been used for assembly of enone compounds, although the products are mixtures of double bond geometric isomers.[4] We thought that the development of efficient and regioselective addition to ynone with predictably site-selectivity would be worthwhile since this moiety is widely used as an intermediate in the construction of a variety of heterocyclic scaffolds.[5] Recently, pyridine/quinoline *N*-oxide, just as an oxygen donor, was employed in gold catalyzed oxidation of alkyne for the generation of α-oxo gold-carbene/carbenoid intermediates to synthesize various useful molecules.[6] To further develop ynone as a useful synthon, we envisioned that *N*-oxide, as a nucleophile, might attack the ynone **1** on C3-site to give **4** through an intermolecular cascade cycloaddition/ring opening process.[7] Meanwhile, ynone **1** might form the oxetium intermediate[8] in the presence of iodine followed by *N*-oxide attacking the C3-oxetium site selectively through internal tandem cycloaddition/oxidation/N−O bond cleavage/C−O and C−C bonds formation to afford the polycyclic compound **3**. Herein, we report an efficient two-component cycloaddition to substituted quinoline derivatives from ynone and *N*-oxide. This approach is metal-free, atom economic, and site regioselective for addition to ynones with *N*-oxides as the nucleophile (Scheme 1B).

Scheme 1. (A) Regioselective Addition to Ynones with Nucleophiles; (B) Our Design: Regioselective Addition to Ynones with *N*-Oxides

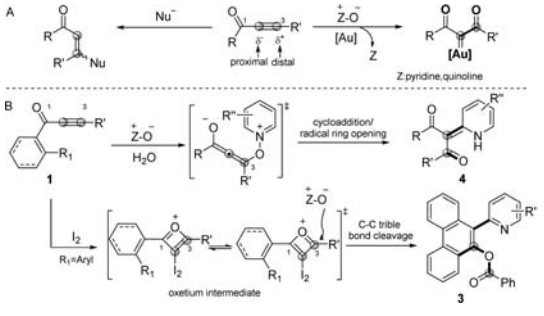
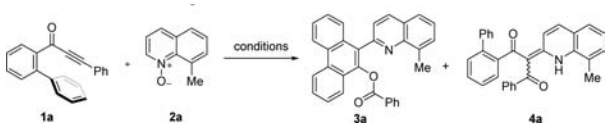


Table 1. Screening Conditions[a]



					yield (%)[b]	
entry	**2a** (equiv)	solvent	temp (°C)	additive (mol %)	**3a**	**4a**
1	1.5	DMSO	130	I_2 (10)	38	49
2	1.5	DMSO	130	I_2 (20)	78	10
3	1.5	DMSO	130	I_2 (30)	89	<2
4	1.5	DMSO	120	I_2 (30)	85	<3
5	1.5	DMSO	100	I_2 (30)	<5	53
6	1.2	DMSO	130	I_2 (30)	80	<2
7	2.0	DMSO	130	I_2 (30)	89	<2
8[c]	0	DMSO	130	I_2 (30)	0	0
9	1.5	DMF	130	I_2 (30)	0	75
10	1.5	DMSO	130	_	0	89
11[d]	1.5	H_2O	reflux	_	0	90

[a][**1a**] = 0.05 M, and the reaction time is 2 h. [b]Isolated yield. [c]90% of SM was recovered. [d]The ratio of *Z*/*E* is 3:2 and was determined by ^{1}H NMR.

At the outset, using *o*-phenyl ynone **1a** and quinoline 1-oxide, **2a**, as the nucleophile, the results of the optimization studies are shown in Table 1. Initially, iodine (10 mol %) was employed as the catalyst and *N*-oxide, **2a** (1.5 equiv), as the nucleophile, and the reaction was carried out in dimethyl sulfoxide (DMSO) at 130 °C for 5.5 h. To our delight, the

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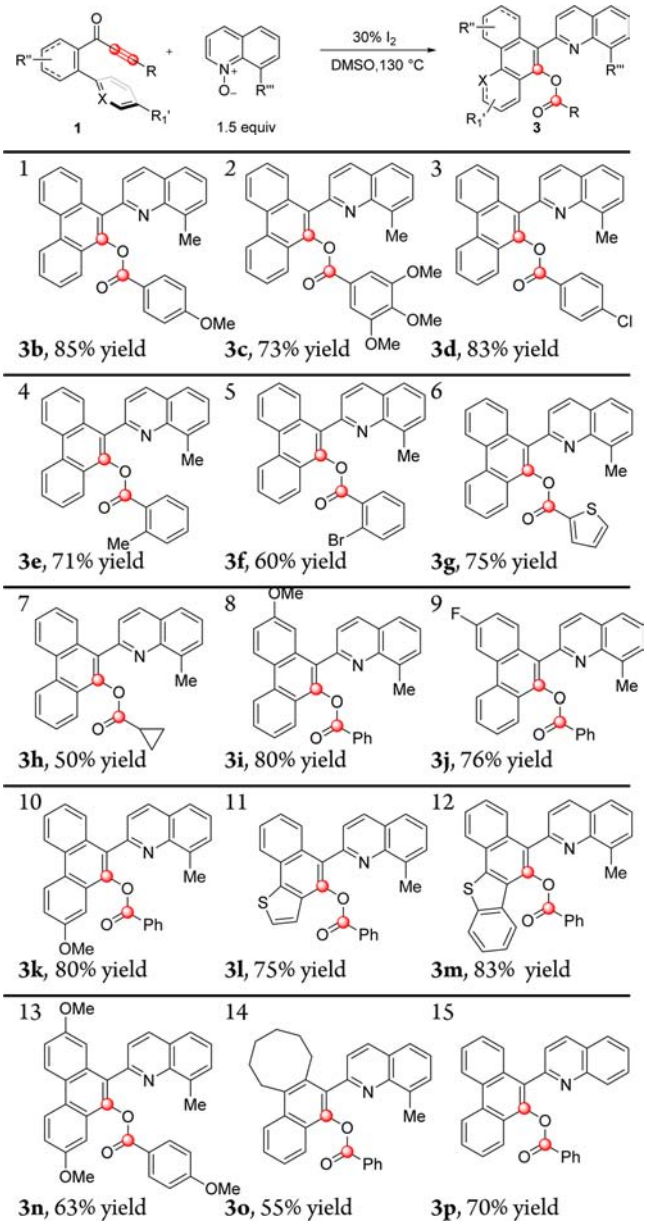
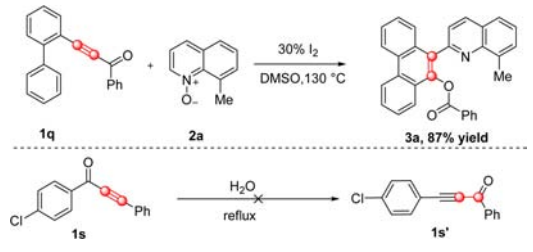
Table 2. Reaction Scope[a,b]



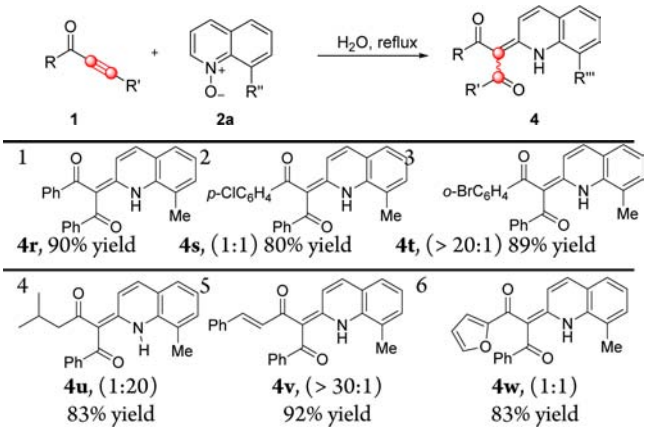
[a]The reactions were run in a vial without exclusion of air and moisture, and the substrate concentration was 0.05 M. [b]Yields of isolated products are reported.

Scheme 2. Additional Experiment



desired 10-(8-methyl quinolin-2-yl)phenanthren-9-yl benzoate **3a** was obtained in 38% isolated yield, along with a mixture of 1-([1,1′-biphenyl]-2-yl)-2-(8-methylquinolin-2(*1H*)-ylidene)-3-phenylpropane-1,3-dione **4a** in 49% yield (entry 1). The relative configuration of the product **3a** was unambiguously

Table 3. Reaction Scope[a,b]



[a]The reactions were run in a vial without exclusion of air and moisture, and the substrate concentration was 0.05 M. Yields of isolated products are reported. [b]The *E*/*Z* ratios of the products were determined by ^{1}H NMR.

assigned by X-ray crystallography (see Supporting Information (SI)).[9] By increasing the iodine catalyst loading to 20 mol %, a 78% yield of desired product **3a** was observed after 3.0 h with a trace amount of **4a** (entry 2). We noticed that it was a competitive reaction and the iodine can promote the reaction to give product **3a** with the *N*-oxide regioselectively attacking the ynone. For this, we tried a higher iodine catalyst loading (30 mol %), and fortunately, a slightly higher yield of desired product **3a** was observed after a shorter time and almost no **4a** was observed (entry 3). In seeking to additionally improve this reaction, we investigated the parameters of temperature and loading of *N*-oxide of **2a**, but no superior results were observed even after a longer time (compare entries 4−9, Table 1). It was found that only a trace of amount of **3a** was observed when the reaction was carried out at 100 °C for 12 h along with a 53% yield of **4a** which demonstrated that a high temperature is necessary to achieve **3a** by *N*-oxide regioselective addition to ynone (entry 5). Solvents, such as *N*,*N*-dimethylformamide (DMF), were also tested, but no desired product of **3a** was observed and only 75% of **4a** was isolated which showed that DMSO might play the role of oxidant in the synthesis of **3a** (entry 9). The reaction was also attempted in the absence of iodine; only **4a** was observed which indicated that iodine is the key factor in the synthesis of **3a** (entries 10−11). Interestingly, the reaction was carried out at reflux condition in water in the absence of iodine, and a 90% yield of **4a** was isolated with a 3:2 ratio of the geometric isomers.

With the optimized reaction conditions given in Table 1, entry 3, the scope of the transformation to **3** in the presence of iodine was first examined with various *o*-phenyl ynones as shown in Table 2. Thus, a tandem predictably site regioselective addition to ynones **1a−o** with 8-methylquinoline 1-oxide proceeded smoothly to provide corresponding products **3a−o** in moderate to good yield. The reaction works well with aromatic R groups. Various electron-donating and -withdrawing R groups were tolerated (**1b−1d**). For the ynones **1b** and **1d**, a *para*-methoxy and a *para*-chloro substitution on the benzene ring was inconsequential and corresponding **3b** and **3d** were obtained in 85% and 83% yield, separately. The substrate **1c** with trimethoxy substitutions on the benzene ring gave the corresponding **3c** in a slighter lower yield. The steric effect of R aryl groups was also considered, and the *o*-methyl aryl group

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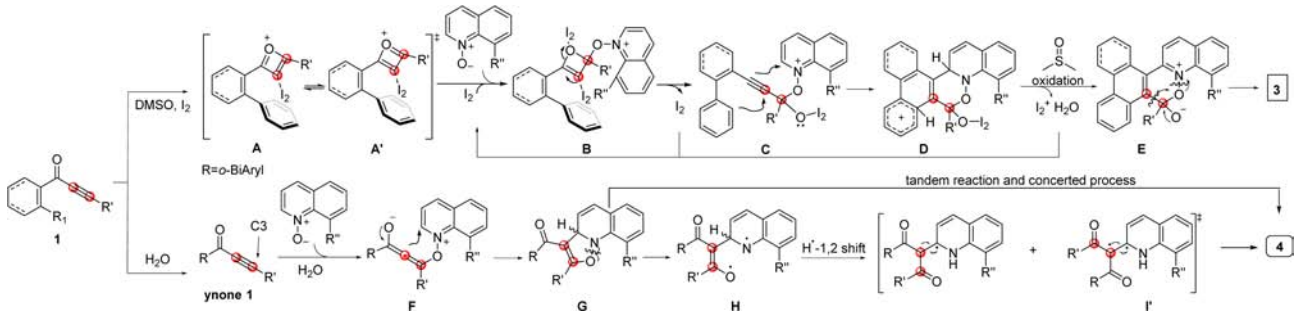
Scheme 3. Proposed Mechanism



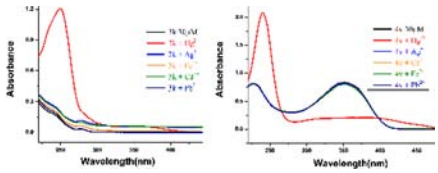


Figure 1. Changes in UV−vis spectra of **3k** and **4v** (30 μM) upon the addition of various metal ions (10 equiv) in CH_3CN.

showed a better yield than the *o*-bromide aryl group by installing the methyl and bromide group on the *ortho* position (**1e** vs **1f**). *O*-Phenyl ynone **1g** with a heteroaromatic R group afforded the desired product **3g** in 75% yield. Furthermore, a substrate like **1h** with an aliphatic R group can also give the desired product **3h** in an acceptable yield. Ynones such as **1i−j** with a different R′′ group were also studied, and the substrates with different electron-donating and -withdrawing R′′ groups proceeded smoothly to provide corresponding products **3i−j** in moderate yield. Other ynones such as **1k−n** with a different R′ group were also investigated. A substrate like **1k** with the methoxy R′ group on the *para*-position gave the corresponding product **3k** in 80% yield. However, if the *para*-methoxy R′ group was replaced by an electron-withdrawing *para*-fluoro R′ group, the reaction would not be clean. Interestingly, instead of *o*-phenyl ynones, the ynones **1l−m**, with a heteroaromatic group such as thiophene and benzo[*b*]thiophene on the *ortho*-position, were also functionalized selectively to afford the corresponding products **3l−m** in good yield. A more electron-rich ynone by installing three methoxy substitutions on different positions, such as **1n**, also gave the desired product **3n** in moderate yield. Considering other synthetically useful transformations, an ynone such as **1o**, with an aliphatic group, was also tested and the reaction worked well to afford **3o** in acceptable yield. Quinoline 1-oxide **2b** was used as a nucleophile, the reaction proceeded smoothly to provide corresponding product **3p** in moderate yield. Other *N*-oxides, like pyridine 1-oxide, were also investigated in this reaction; unfortunately, no desired product was obtained which demonstrated that the motif of quinolone is necessary. In order to gather additional experimental evidence for the mechanism, we examined the direct conversion of ynone **1q** with 8-methylquinoline 1-oxide **2a** under the standard conditions. Much to our delight, this reaction worked well and afforded corresponding product **3a** in 87% yield (Scheme 2). However, an additional experiment with ynone **1a** and iodine in DMSO at 130 °C was investigated, but no desired ynone **1q** was observed from proton NMR which demonstrated that ynones **1** did not undergo a 1,3-oxygen transposition reaction[10] in the presence of I_2.

Furthermore, to expand the scope of this reaction, we also investigated 1,3-diphenylprop-2-yn-1-one, **1r**, with iodine as the catalyst; unfortunately, no desired product was observed. But, to our delight, ynone **1r** was transferred smoothly to give corresponding product **4r** in excellent yield in reflux water in the absence of iodine. The relative configuration of the product **4r** was unambiguously assigned by X-ray crystallography (for details, see SI).[11] Thus, a tandem C3-site regioselective addition to ynones **1s−1w** with 8-methylquinoline 1-oxide was examined in reflux water as shown in Table 3 and proceeded smoothly to provide corresponding products **4s−w** in good to excellent yield. All the reactions proceeded with efficiencies and showed excellent regioselectivities, although the products **4** are mixtures of double bond geometric isomers. The reaction works well with aromatic, aliphatic, and heteroaromatic groups, and various R and R′ groups were tolerated (entries 2−6). A substrate like **1v** with the styrene R group gave the corresponding product **4v** in 92% yield with the ratio of geometric isomers being over 30:1.

In order to gather experimental evidence for the mechanism, the ynone **1s** was tested in reflux water, but no **1s′** was observed which ruled out the 1,3-O transposition process and indicated that the geometric isomers might be formed in the ring opening process (Scheme 2).

On the basis of the above observations, we propose the following plausible mechanisms for this cascade transformation (Scheme 3). (1) In the presence of iodine, *o*-phenyl ynone **1** was activated by iodine to afford oxetium intermediate **A** which remained in equilibrium with oxetium intermediate **A′**. (2) *N*-Oxide attacked the C3-oxetium site of intermediate **A′** selectively to give intermediate **B**, and then iodine activated the oxygen atom of intermediate **B** with a C−O bond cleavage and C−C triple bond formation to give intermediate **C**. (3) Intermediate **C** underwent internal tandem cycloaddition to afford intermediate **D**, followed by DMSO oxidation to intermediate **E**, releasing the iodine. (4) The oxygen ion of intermediate **E** underwent back electron transfer to cause an aryl group to migrate to the oxygen of the oxylammonium intermediate selectively to afford product **3** through the C−C, N−O bond cleavage process. For the synthesis of product **4**, (5) ynone **1** was regioselectively attacked by *N*-oxide on the distal end to give the zwitterionic complex **F** which then cyclizated to afford intermediate **G**. (6) Intermediate **G** might be through a radical ring opening process by N−O bond cleavage to afford radical intermediate **H**. (7) Radical intermediate **H** occurred from 1−2 H radical migration to the nitrogen atom to afford radical intermediate **I** and **I′**, and then two radicals gave a C−C double bond to **4**.[13] Alternately, intermediate **G** might be transferred to give product **4** via a tandem process which is a concerted process.

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In order to find more useful application of these compounds, we investigated the UV absorption of quinoline analogues **3k** and **4v** with various cations by adding 10 equiv of different metal cations in acetonitrile at a concentration of 30 μM (Figure 1); they have a high binding constant with Hg^{2+} in CH_3CN.[12]

In summary, we have described an efficient strategy to construct substituted quinoline derivatives through two-component cycloaddition from ynone and quinoline *N*-oxide. In the presence of iodine, ynone **1** was functionalized by *N*-oxide attacking the C3-oxetium site through internal tandem cycloaddition/oxidation/N−O bond cleavage/C−O and C−C bonds formation to afford the polycyclic compound **3**, during which the C−C triple bond of ynone underwent fracture and recombination. Meanwhile, in the absence of iodine, ynone **1** was selectively attacked on the C3-site to give **4** in good to excellent yield in water through the intermolecular cascade cycloaddition/ring opening process. This approach is metal-free, atom economic, and site regioselective for addition to ynones with *N*-oxides as nucleophiles. Quinoline analogues **3k** and **4v** have a high binding constant with Hg^{2+} in CH_3CN.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02813.

^{1}H and ^{13}C NMR spectra, HRMS, and crystal data for **3a** and **4r** (PDF)

X-ray crystallographic data for **3a** (CIF)

X-ray crystallographic data for **4r** (CIF)

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Author Contributions

‡These authors contributed equally.

Notes

The authors declare no competing financial interest.

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(9) The cif file has been deposited at the Cambridge Crystallographic Data Centre (CCDC number is 1501107).

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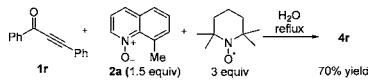
(13) According to the reviewer's advice, we tried reacting **1r** with *N*-oxide, **2a**, and TEMPO, and the desired product of **4r** was isolated in 70% yield. The proton NMR and ESI-MS showed that no TEMPO captured radical product was observed.



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