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Synthesis of Isoxazoline-Functionalized Phenanthridines via Iminoxyl Radical-Participated Cascade Sequence

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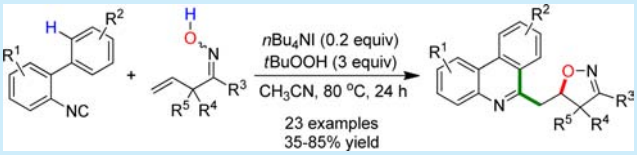
Supporting Information

ABSTRACT: Readily accessible β,γ-unsaturated ketoximes reacted with 2-arylphenylisonitriles under the conditions of *t*-BuOOH and *n*-Bu_4NI to give isoxazoline functionalized phenanthridines via tandem intramolecular/intermolecular C−O/C−C/C−C bond formation. The reaction involves the initial generation of iminoxyl radicals from the oxidation of β,γ-unsaturated ketoximes by *t*-BuOOH and *n*-Bu_4NI followed a cascade radical cyclization/addition/cyclization sequence.

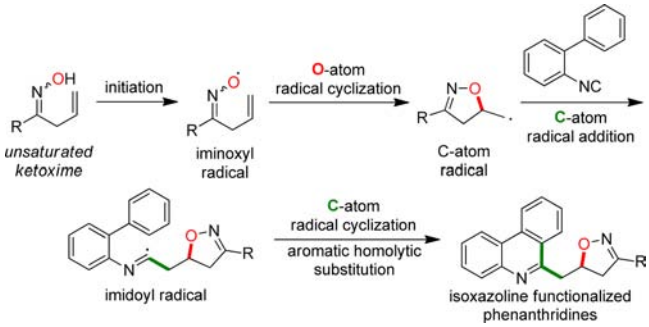


Free radical reactions have become important and effective tools in organic synthesis in the past decades.[1] Among a wide variety of radical-based synthetic methodologies, those taking advantage of the radical cascade reactions have proven to be highly valuable for the synthesis of complex polycyclic compounds due to their highly synthetic efficiency and lesser environmental impact.[2]

Iminoxyl radicals are fascinating heteroatom-centered radicals, and their structural properties have been extensively studied.[3] Recently, we have developed a series of cyclization reactions involving unsaturated iminoxyl radicals for the synthesis of isoxazolines and cyclic nitrones.[4] As a continuation of our interest in the iminoxyl radical-based reactions for synthetic purposes, we devised a cascade cyclization/addition/cyclization strategy for the preparation of isoxazoline-functionalized phenanthridines from readily accessible β,γ-unsaturated ketoximes and 2-arylphenylisonitriles. We envisioned that the carbon-centered radical derived from the O atom 5-*exo*-trig cyclization of the β,γ-unsaturated iminoxyl radical would undergo intermolecular addition to the isonitrile group of 2-arylphenylisonitrile to produce the imidoyl radical. Further intramolecular aromatic homolytic substitution[5] of the imidoyl radical would yield the isoxazoline-featured phenanthridine (Scheme 1). 2-Arylphenylisonitriles have been proven to be efficient radical acceptors,[6] and it was expected that the intermolecular radical addition in our synthetic design would proceed as well.[7]

The skeleton of phenanthridine widely exists in pharmaceutical and bioactive compounds. Phenanthridine derivatives possess important biological activities such as antibacterial, antitumoral, antileukemic, and cytotoxic activities.[8] They can also act as DNA inhibitor and intercalator.[9] On the other hand, isoxazoline derivatives not only are useful synthetic intermediates but also exhibit attractive biochemical and pharmaceutical properties.[10] Consequently, these two classes of compounds have attracted the interest of synthetic chemists. In this context, the present reaction provides an efficient approach for the synthesis of structurally novel isoxazoline featured phenanthridines which possess potential biochemical and pharmaceutical properties as well a tandem process for the intra-/intermolecular C−O/C−C/C−C bond formation.

Scheme 1. Iminoxyl Radical-Participated Cascade Cyclization/Addition/Cyclization Sequence



To test the hypothesis, we performed the reaction of 2-isocyanobiphenyl (**1a**, 0.2 mmol) with 2,2-dimethyl-1-phenylbut-3-en-1-one oxime (**2a**, 0.6 mmol) by using *t*-BuOOH (TBHP, 0.6 mmol) as the oxidant. TBHP is an effective reagent as the source of *t*-BuO radical, and the latter has been proved to be an effective initiator to convert oxime to the corresponding iminoxyl radical.[4b] To our delight, the iminoxyl radical promoted cascade sequence took place, and the desired product isoxazoline-functionalized phenanthridines **3aa** was obtained in 53% yield. The structure of **3aa** was confirmed by a single-crystal X-ray diffraction study (Figure 1). To improve the yield, various catalysts such as $FeCl_3$, $FeCl_2$, $Fe(acac)_2$, CuI, KI, and TBAI were tested, among which TBAI was found to be the most efficient (Table 1, entries 2−8). The reaction was also carried out in several other solvents such as toluene, DMF, DMSO, and 1,4-dioxane, but the results obtained under these conditions were less satisfactory (Table 1, entries 9−13).

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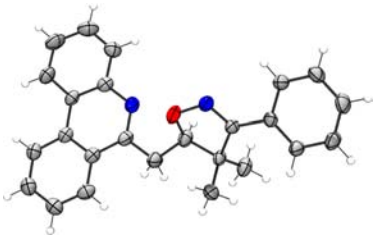
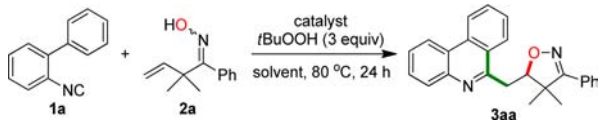


Figure 1. X-ray structure of **3aa** (thermals ellipsoids are shown with 30% probability).

Table 1. Optimization for the Cascade Sequence[a]

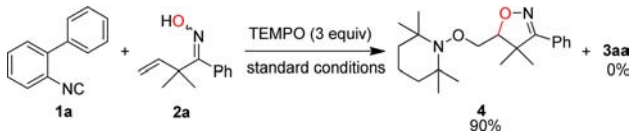


entry	catalyst (mol %)	solvent	%, yield[b]
1[c]		neat	53
2	$FeCl_2$/20	CH_3CN	31
3	$FeCl_3$/20	CH_3CN	42
4	$Fe(acac)_2$/20	CH_3CN	30
5	CuI/20	CH_3CN	49
6	KI/20	CH_3CN	48
7	TBAI/10	CH_3CN	68
8	**TBAI/20**	**CH_3CN**	**82**
9	TBAI/20	toluene	75
10	TBAI/20	DMF	53
11	TBAI/20	DMSO	50
12	TBAI/20	1,4-dioxane	70
13	TBAI/20	*n*-BuOAc	61

[a]All reactions run 0.2 M in MeCN using 2-isocyanobiphenyl **1a** (0.2 mmol), 2,2-dimethyl-1-phenylbut-3-en-1-one oxime **2a** (0.6 mmol), and TBHP 70% in water (0.6 mmol) at 80 °C under Ar. [b]Yields of isolated product. [c]At 100 °C.

To confirm that the generation of iminoxyl radical was the initial step, TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyl) was used as the carbon-centered radical scavenger under the indicated reaction conditions as shown in Scheme 2. The

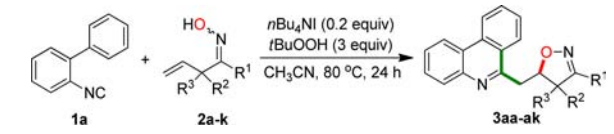
Scheme 2. Control Experiment

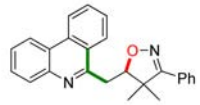
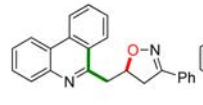
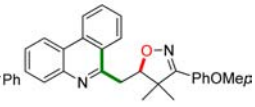
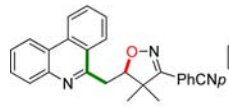
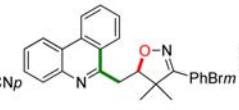
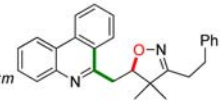
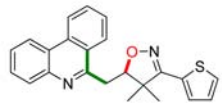
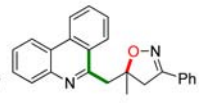
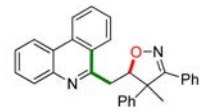
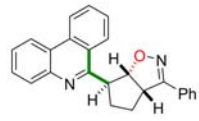
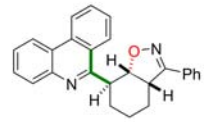


reaction gave TEMPO-trapped isoxazoline **4** in 90% yield with the desired product **3aa** undetected. This result demonstrated clearly that the initiation step is the generation of the iminoxyl radical (Scheme 2).

To assess the scope of this cascade sequence, a variety of *β,γ*-unsaturated ketoximes **2** were subjected to the optimized reaction conditions with 2-isocyanobiphenyl **1a**. The results are summarized in Table 2. *β,γ*-Unsaturated ketoximes bearing terminal alkenes participated in the cascade sequence very well, giving rise to isoxazolines featured phenanthridines **3aa**−**ai** in good to excellent yields. Both aromatic and aliphatic substituted *β,γ*-unsaturated ketoximes were tolerated (**3aa**−**af**). Thiophene incorporated ketoxime reacted as well with **1a** to afford **3ag** in good yield. The cascade sequence involving *β,γ*-unsaturated

Table 2. Scope of *β,γ*-Unsaturated Ketoximes[a]



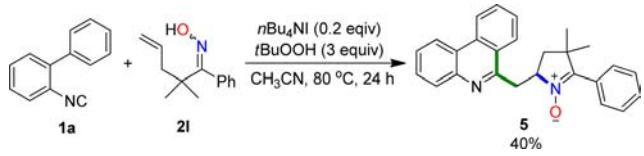
product, yield[b]	product, yield[b]	product, yield[b]
 **3aa**, 82%	 **3ab**, 52%	 **3ac**, 70%
 **3ad**, 73%	 **3ae**, 71%	 **3af**, 60%
 **3ag**, 74%	 **3ah**, 58%	 **3ai**, 76%, dr = 1.1:1
 **3aj**, 82%, dr > 95:5[c,d]	 **3ak**, 85%, dr > 95:5[c,d]	

[a]All reactions run 0.2 M in MeCN using 2-isocyanobiphenyl **1a** (0.2 mmol), *β,γ*-unsaturated ketoximes **2** (0.6 mmol), TBAI (0.04 mmol), and TBHP 70% in water (0.6 mmol) at 80 °C under Ar. [b]Yields of isolated product. [c]The determination of the ratio of diastereoisomer is based on ^{1}H NMR. [d]The configuration of diastereomer was confirmed by coupling constants of ^{1}H NMR and NOE.

ketoximes bearing 1,2-disubstituted alkenes was also successful, as demonstrated by the modest yield of **3ah**. When the cyclopentene or cyclohexene moiety was incorporated in the *β,γ*-unsaturated ketoxime, the reaction afforded the corresponding product **3aj** or **3ak** as a single diastereoisomer. Apparently, the trapping of the cyclization-derived carbon radical in these two cases was more favored from the less hindered *exo* direction.

When compound *γ,δ*-unsaturated ketoxime **2l** was allowed to react with 2-isocyanobiphenyl **1a**, the nitrone-tethered phenanthridine **5** was obtained in 40% yield (Scheme 3).

Scheme 3. *γ,δ*-Unsaturated Ketoxime-Participated Cascade Sequence with 2-Isocyanobiphenyl



This result is consistent with our previous findings that *γ,δ*-unsaturated ketoxime-derived iminoxyl radicals are susceptible to N atom 5-*exo*-*trig* cyclization rather than O atom 6-*exo*-*trig* cyclization.[4] Thus, the present protocol is also suitable for the preparation of nitrone-functionalized phenanthridine derivatives.

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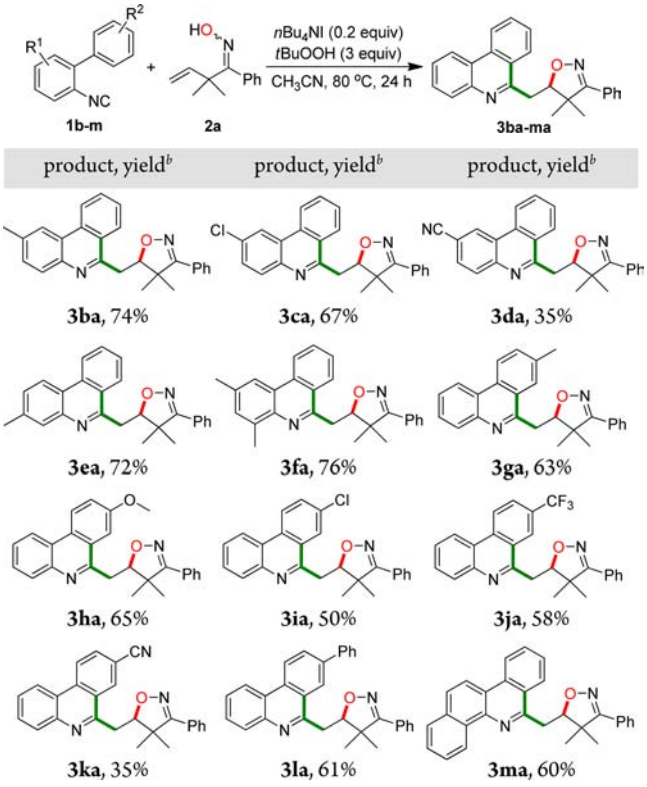
Having successfully achieved the cascade sequence with unsaturated ketoximes, we then turned our attention to explore the scope of 2-isocyanobiaryls **1**. A variety of biaryl isocyanides were also employed to react with 2,2-dimethyl-1-phenylbut-3-en-1-one oxime **2a** under the optimized reaction conditions. As shown in the examples in Table 3, a broad range of 2-

Table 3. Scope of 2-Isocyanobiaryls[a]



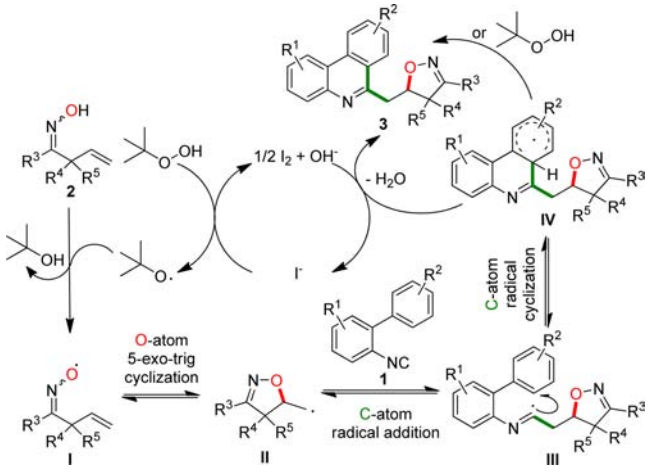
[a]All reactions run 0.2 M in MeCN using 2-isocyanobiaryls **1** (0.2 mmol), 2,2-dimethyl-1-phenylbut-3-en-1-one oxime **2a** (0.6 mmol), TBAI (0.04 mmol), and TBHP 70% in water (0.6 mmol) at 80 °C under Ar. [b]Yields of isolated product.

isocyanobiaryl compounds with electron-donating and -withdrawing groups reacted smoothly with **2a** to give the corresponding isoxazoline-featured phenanthridine derivatives **3ba**−**ma** in good yields.

To account for the process of the TBAI/TBHP-promoted cascade sequence, a plausible mechanism is proposed as shown in Scheme 4. *t*-BuOOH first reacted with *n*-Bu_4NI to produce I_2 and *t*-BuO radical;[11] the latter can initiate oxime **2** to iminoxyl radical **I** via a HAT (hydrogen atom abstraction) process. The iminoxyl radical then undergoes fast 5-*exo*-*trig* cyclization to yield the corresponding C-centered radical **II**. Intermolecular addition of the carbon-centered radical **II** to 2-isocyanobiaryl **1** produces the imidoyl radical **III**, which further cyclized to the adjacent phenyl ring to yield the cyclohexadienyl radical **IV**. Finally, further oxidative aromatization of the cyclohexadienyl radical **IV** by I_2 or TBHP gives the desired product **3**.

In conclusion, we have developed a novel, efficient, and practical iminoxyl radical-participated cascade cyclization/addition/cyclization sequence for the synthesis of isoxazoline-functionalized phenanthridines using 2-isocyanobiaryls and *β*,*γ*-unsaturated ketoximes as the easily available substrates and TBAI/TBHP as the catalytic oxidative system. To the best of our knowledge, the present study represents the first example

Scheme 4. Plausible Mechanism for the TBAI/TBHP-Promoted Radical Cascade Sequence



of using TBAI/TBHP as the catalytic oxidative system for the generation of iminoxyl radicals as well as the first example of iminoxyl radical-participated cascade cyclization/addition/cyclization sequence through a one-pot tandem intramolecular/intermolecular C−O/C−C/C−C bonds formation. Further studies on the iminoxyl radical promoted reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all products and X-ray data for compound **3aa** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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