Iminoxyl Radical-Promoted Oxycyanation and Aminocyanation of Unactivated Alkenes: Synthesis of Cyano-Featured Isoxazolines and Cyclic Nitrones

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S *Supporting Information*

ABSTRACT: A novel and facile approach to vicinal oxycyanation and aminocyanation of internal unactivated alkenes is developed. This method utilizes the dichotomous reactivity of iminoxyl radical derived from the initiation of β,γ- and γ,δ-unsaturated ketoximes to provide the general difunctionalization of internal alkenes using *tert*-butyl hydroperoxide (TBHP)

as the environmentally friendly oxidant, CuCN as the commercially available cyanating reagent, and pentamethyldiethylene-triamine (PMDETA) as the ligand. By using this protocol, a series of useful cyano-featured isoxazolines and cyclic nitrones were efficiently prepared.

The cyano group as an important functional group not only can undergo manifold valuable transformations[1] but also exists widely in bioactive natural products and pharmaceuticals.[2] In particular, the cyano-featured five-membered heterocycles have found various applications as fine chemicals.[3] For example, compounds **I** and **II** are synthetic molecules with antibacterial activity.[4,5] Compound **III** is an important intermediate for the synthesis of amathaspiramides (Figure 1).[6]

Figure 1. Bioactive molecules with cyano substituted heterocycle unit.

Thus, the efficient introduction of cyano group into organic molecules has drawn much attention from chemists and pharmacologists.[7] Over the past decades, studies in this line are mainly focused on the nucleophilic substitution of primary alkyl halides with cyanides[8] and transition metal catalyzed $C(sp^2)-H$ and $C(sp^3)-H$ bond cyanation,[9,10] while investigations on direct cyanation of alkenes are relatively less reported.[11]

Considering that alkenes are broadly available chemicals, the vicinal oxycyanation and aminocyanation of alkenes are attractive strategies to introduce the CN group as well as the O/N atom into organic molecules.[12] Recently, a few radical-mediated approaches have been reported based on these strategies. For instance, in 2013 Alexanian's group developed an amidoxyl radical promoted intra-/intermolecular oxycyanation of unactivated alkenes (Scheme 1a).[12b] Very recently, Liu et al. disclosed an amide radical-involved asymmetric intermolecular

Scheme 1. Radical Mediated Oxycyanation and Aminocyanation of Alkenes

aminocyanation of aryl alkenes.[12c] Despite these elegant studies toward this end, however, the advancement is far from meeting the synthetic demand, and there are still much that remains to be explored.

In continuation of our research on the difunctionalization of alkenes,[13] herein we present a new and efficient iminoxyl radical-promoted protocol[14] for the oxycyanation and amino-cyanation of internal unactivated alkenes by using β,γ- and γ,δ-unsaturated ketoximes as readily available substrates, CuCN as the cyanating reagent, and TBHP as the oxidant. Consequently, the structurally important cyano-featured isoxazolines and cyclic nitrones were facilely synthesized. This strategy not only presents the first example of iminoxyl radical-participated vicinal oxycyanation and aminocyanation of unactivated alkenes but also attains a direct radical cyclization leading to structurally important cyano-featured isoxazolines and cyclic nitrones.

We commenced our study by stirring 2,2-dimethyl-1-phenylbut-3-en-1-one oxime (**1a**) with CuCN (2.5 equiv) in acetonitrile using TBHP (3.0 equiv) as the oxidant and diamine L1 (2.5 equiv) as the ligand at room temperature for 12 h under Ar. To our delight, the desired oxycyanation product **2a** was obtained in 62% yield (Table 1, entry 1). Screening other
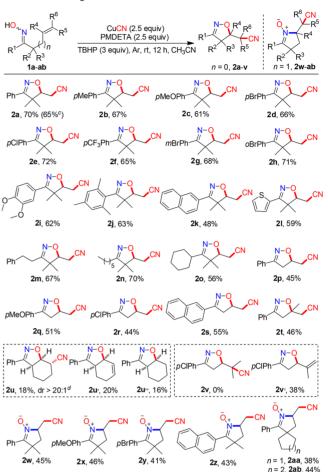
Table 1. Optimization of the Reaction Conditions[a]

entry	CN source	ligand	solvent	yield (%)[b]
1	CuCN (2.5 equiv)	L1	CH₃CN	62
2	**CuCN (2.5 equiv)**	**L2**	**CH₃CN**	**70**
3	CuCN (2.5 equiv)	L3	CH₃CN	47
4	CuCN (2.5 equiv)	L4	CH₃CN	3
5	CuCN (2.5 equiv)	L5	CH₃CN	8
6	CuCN (2.5 equiv)	L2	DMF	33
7	CuCN (2.5 equiv)	L2	DMSO	34
8	CuCN (2.5 equiv)	L2	toluene	trace
9[c]	CuCN (3.0 equiv)	L2	CH₃CN	61
10[d]	CuCN (2.5 equiv)	L2	CH₃CN	44
11[e]	CuCN (2.0 equiv)	L2	CH₃CN	64
12[f]	CuCN (2.5 equiv)	L2	CH₃CN	53
13[g]	TMSCN (2.5 equiv)	L2	CH₃CN	17
14[h]	TsCN (2.5 equiv)	L2	CH₃CN	12

[a]All reactions were carried out by using **1a** (0.3 mmol), CN source, ligand (2.5 equiv), TBHP (70% aqueous, 3.0 equiv), solvent (2 mL) at rt under Ar (1 atm) for 12 h, except as noted. [b]Isolated yield. [c]L2 (3.0 equiv) and TBHP (3.5 equiv) were used. [d]L2 (3.0 equiv) was used. [e]L2 (2.0 equiv) and TBHP (2.5 equiv) were used. [f]L2 (2.0 equiv) was used. [g]Cu(OAc)₂ (0.2 equiv), L2 (0.2 equiv), and TBHP (2.0 equiv) were used. [h]Cu(OAc)₂ (0.2 equiv), L2 (0.2 equiv), and TBHP (1.5 equiv) were used.

ligands such as triamine L2, tetraamine L3, 1,1′-bipyridine L4, and 1,10-phen L5 revealed that L2 was the best ligand and the yield of **2a** was further improved to 70% (Table 1, entries 2−5). No better yield of **2a** was obtained when other solvents such as DMF, DMSO, and toluene were used (Table 1, entries 6−8). A further increase or decrease of the usage amount of CuCN, L2, and TBHP did not provide a better result (Table 1, entries 9−12). In addition, other cyanating reagents such as TMSCN and TsCN were also tested in the reaction under Cu(OAc)₂ catalyzed conditions, but they were found to be inferior compared with CuCN (Table1, entries 13−14). Other catalytic systems by using a variety of copper salts, CN-sources, and oxidants were explored as well; however, no positive result was obtained (see Supporting Information for detail).

With the optimized conditions in hand (Table 1, entry 2), the scope of the reaction with various β,γ- and γ,δ-unsaturated ketoximes was investigated, and the result is summarized in Scheme 2. First, aryl and alkyl substituted β,γ-unsaturated ketoximes **1a−v** were explored. Phenyl substituted ketoximes with a range of electronic properties participated well in the reaction, affording the oxycyanation products **2a−j** in good yields. The structure of **2c** was confirmed by single-crystal X-ray analysis (see SI). Notably, the tandem reaction could be easily carried out on a gram scale without difficulty, as demonstrated

Scheme 2. Scope of Unsaturated Oximes[a,b]

[a]All reactions run in CH₃CN (2 mL) using **1** (0.3 mmol), CuCN (0.75 mmol), L2 (0.75 mmol), and TBHP (0.9 mmol) at rt under Ar (1 atm) for 12 h. [b]Isolated yields are shown. [c]**1a** (8 mmol) was used, and the corresponding product **2a** was obtained in 1.112 g. [d]The configuration of diastereomer was determined by coupling constants of ¹H NMR and NOE.

in the case of **2a**. Naphthalenyl- and thiophene-substituted ketoximes were also suitable for the process, providing the corresponding products **2k** and **2l** in good yields. Alkyl such as phenethyl, n-hexyl, and cyclohexyl incorporated ketoximes were also good candidates for the transformation, which can be converted into the desired products **2m−o** in 56−70% yields. In addition, aryl substituted β,γ-unsaturated ketoximes without a gem-dimethyl group were also examined in the reaction, and the corresponding products **2p−s** were obtained in moderate to good yields. Significantly, this oxycyanation approach is applicable to 1,1-disubstituted alkenes, as demonstrated in the case of **2t**. When the cyclohexene moiety was incorporated in the β,γ-unsaturated ketoxime, as in the case of **1u**, the reaction gave the oxycyanation product **2u** in 18% yield, accompanied by the isoxazoline-fused cyclohexene **2u′** and cyclohexane **2u″** in 20% and 16% yields, respectively. When the ketoxime **1v** was used as the substrate, however, the reaction did not yield the expected oxycyanation product **2v**; instead, compound **2v′** was obtained in a yield of 38%. Obviously, the secondary and tertiary carbon-centered radicals were inclined to undergo elimination and gave the corresponding olefins in this circumstance.[15] Next, we shifted our attention to γ,δ-

unsaturated counterparts to see if the latter could also undergo aminocyanation through a N atom 5-*exo*-trig cyclization[16] as displayed in our previous work.[13a−d] Gratifyingly, a series of aryl substituted γ,δ-unsaturated ketoximes participated smoothly in the reaction, delivering the desired aminocyanation products **2w−ab** in moderate yields.

To further investigate the applicability of this protocol, other cuprous salts such as CuCl, CuBr, and CuI were also allowed to react with **1a**, and the corresponding oxyhalogenation products **3−5** were obtained in 71−74% yields (Scheme 3). Moreover,

Scheme 3. Oxyhalogenation of Unactivated Alkenes[a,b]

[a]All reactions run in CH₃CN (2 mL) using **1a** (0.3 mmol), CuX (0.75 mmol), L2 (0.75 mmol), and TBHP (0.9 mmol) at rt under Ar (1 atm) for 12 h. [b]Isolated yields. [c]Cu(OAc)₂ (0.2 equiv), L2 (0.3 equiv), KSCN (2.5 equiv), and TBHP (2.0 equiv) were used.

when **1a** reacted with KSCN utilizing Cu(OAc)₂ as the catalyst, the desired thiocyano substituted isoxazoline **6** was also acquired in 30% yield along with **7** in 23% yield.

The cyano group is a versatile functional group that can be exploited in synthetically useful transformations. In this context, products **2** serve as precursors for other isoxazoline derivatives. For instance, compound **2a** could be easily converted to the carboxylic acid **8** and amide **9** in excellent yields by treatment with an acid and a base, respectively (Scheme 4).

Scheme 4. Follow-up Transformations of 2a

To confirm that the iminoxyl radical was involved in the reaction, the control experiments were conducted as shown in Scheme 5. When the radical scavenger 2,2,6,6-tetramethyl-1-

Scheme 5. TEMPO Scavenging and Radical Probe Experiments

piperidinyl-oxy (TEMPO) was added in the reaction system, the oxycyanation was almost completely inhibited and the TEMPO-trapped isoxazoline **10** was obtained in 95% yield (Scheme 5, eq 1). When ketoxime **11** was subjected to the standard conditions, the anticipated ring-opening cyanation product **12** was obtained in 31% yield along with the ring-opening/elimination product 1,3-diene **13** in 25% yield

(Scheme 5, eq 2).[15a] These results demonstrated clearly that the initiation step is the generation of the iminoxyl radical which is involved in the subsequent oxycyanation and aminocyanation process.

Based on the experimental results and the aforementioned control experiments, a proposed mechanism for the iminoxyl radical-promoted oxycyanation and aminocyanation is drawn in Figure 2. First, TBHP reacts with Cu[I] species **A** to produce Cu[II]
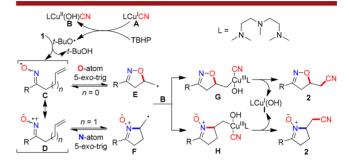

Figure 2. Proposed mechanism.

species **B** and *t*-BuO radical, and the latter then initiates oxime **1** to an iminoxyl radical via a hydrogen atom abstraction (HAT) process. The formed iminoxyl radical possesses an electronic structure with the single-electron spin density delocalized on both the O- and N-atom (resonance structures **C** and **D**),[13a−d] and thus it can undergo dichotomous O- and N-atom 5-*exo*-trig radical cyclization depending on the position of the tethered alkene, yielding the formed C-centered radicals **E** and **F**, respectively. Subsequently, the C-centered radical **E** or **F** reacts with Cu[II] species **B** to form Cu[III] intermediate **G** or **H**.[10h,11e] Finally, intermediate **G** or **H** undergoes reductive elimination to furnish the desired cyanation product **2** and the cuprous species **I**.

In conclusion, a novel, facile, and efficient approach for the oxycyanation and aminocyanation of unactivated alkenes has been successfully developed. This method features easily accessible substrates, commercially available and inexpensive reagents, and mild conditions. By using this protocol, structurally important cyano-substituted isoxazolines and cyclic nitrones can be readily synthesized from unsaturated ketoximes. To the best of our knowledge, the present study represents the first example of iminoxyl radical-promoted oxycyanation and aminocyanation of unactive alkenes. Further studies on the cyanation of alkenes and more iminoxyl radical-involved reactions are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00826.

> Detailed experimental procedures and spectral data for all products (PDF)
> Crystallographic data for the compound **2c** (CIF)

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Notes

The authors declare no competing financial interest.

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