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Iminoxyl Radical-Promoted Dichotomous Cyclizations: Efficient Oxyoximation and Aminooximation of Alkenes

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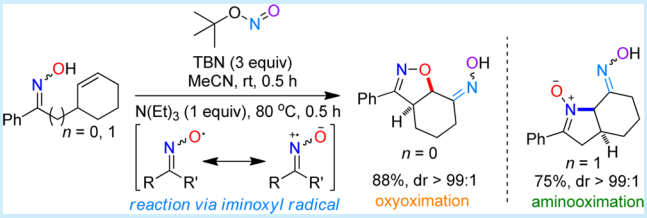
Supporting Information

ABSTRACT: A novel iminoxyl radical-involved metal-free approach to vicinal oxyoximation and aminooximation of unactivated alkenes is developed. This method utilizes the dichotomous reactivity of the iminoxyl radical to furnish a general difunctionalization on alkenes using simple *tert*-butyl nitrite (TBN) as the iminoxyl radical initiator as well the carbon radical trap. By using this protocol, oxime featured 4,5-dihydroisoxazoles and cyclic nitrones were facilely prepared from *β,γ*- and *γ,δ*-unsaturated ketoximes, respectively.

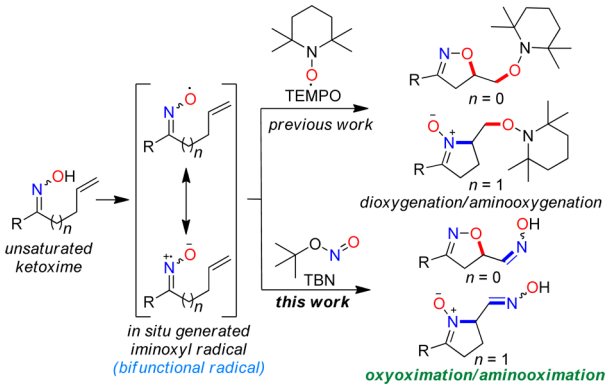


Heteroatom-centered radical cyclizations have been extensively studied, and they have wide applications in the synthesis of heterocyclic compounds.[1] However, most of those studies are focused on single-heteroatom-centered radicals, whereas the cyclization involving heteroatom-centered radicals with spin density located on two heteroatoms is rarely reported. Different from the former, the cyclization of heteroatom-centered radicals with spin density located on two heteroatoms can not only provide a facile method for the synthesis of double-heteroatom-containing heterocycles but also take advantage of the dichotomous reactivity of both heteroatoms depending on the position of the tethered alkenes.[2]

Iminoxyl radicals are fascinating heteroatom-centered radicals which possess the electronic structure where the single electron spin is delocalized on both the O- and N-atom.[3] Very recently, we have demonstrated that the readily prepared *β,γ*- and *γ,δ*-unsaturated ketoximes can be initiated to the corresponding iminoxyl radicals which behave as the oxygen-centered radicals as well as the N-centered radicals. Consequently, both the O- and N-atom 5-*exo*-trig radical cyclizations can take place to yield carbon-centered radicals depending on the position of the carbon−carbon double bond. The interception of the thus formed carbon centered radicals by TEMPO delivers isoxazolines and cyclic nitrones in a way that both the dioxygenation and aminooxygenation of alkenes can be realized (Scheme 1).[2a]

To develop more efficient iminoxyl radical-promoted dichotomous cyclizations for synthetic purposes, we hypothesized that the commercially available *tert*-butyl nitrite (TBN) could be used as an iminoxyl radical initiator as well as a nitric oxide source.[4] Previous studies have shown that TBN is an effective reagent for the nitration[5] and nitrosation (oximation)[6] of alkenes. We hoped that by applying TBN to the cyclization of *β,γ*- and *γ,δ*-unsaturated ketoximes, the nitroso incorporated isoxazolines and cyclic nitrones would be obtained. The latter would subsequently tautomerize to the corresponding stable oxime incorporated isoxazolines and cyclic nitrones. Thus, both the vicinal oxyoximation and aminooximation of the unactivated alkenes could be realized as the novel types of the oxyamination and diamination[7] (Scheme 1).

Scheme 1. Iminoxyl Radical-Promoted Difunctionalization of Alkenes



These oxime attached isoxazolines and cyclic nitrones not only are useful synthetic intermediates but also exhibit attractive biochemical and pharmaceutical properties.[8]

We commenced our studies by stirring *β,γ*-unsaturated ketoxime **1a** to TBN in MeCN at room temperature under an argon atmosphere. A colorless precipitate, which was confirmed by a single-crystal X-ray diffraction study as **2a** (Scheme 2), was formed within 0.5 h in 96% yield. Apparently, the desired reaction took place, generating NO trapped 4,5-dihydroisoxazole **2a′** which immediately dimerized to the product **2a**. Heating compound **2a** in MeCN at 80 °C in the presence of 1

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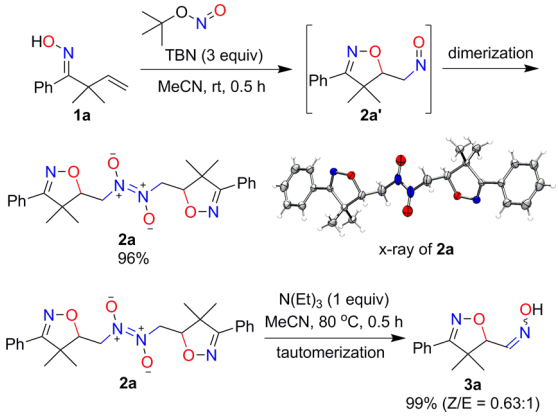
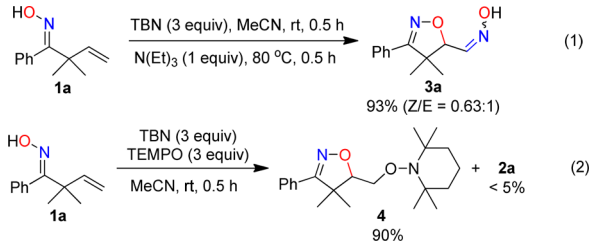
Scheme 2. Iminoxyl Radical-Promoted Oxyoximation of Alkenes



equiv of triethylamine delivered isoxazoline carbaldehyde oxime **3a** quantitatively (Scheme 2). In this way, a one-pot process for the synthesis of isoxazoline carbaldehyde oximes was developed by the reaction of **1a** with TBN in MeCN following facile in situ workup with $N(Et)_3$ (eq 1).

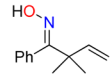
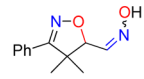
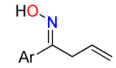
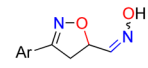
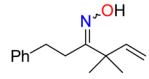
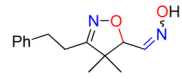
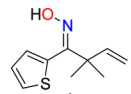
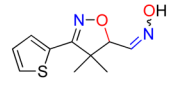
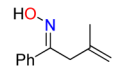
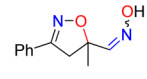
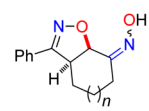


To confirm that the reaction was initiated by the generation of the iminoxyl radical rather than the radical addition of TBN and/or NO to alkenes, TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) was used as the carbon-centered radical scavenger under the same reaction conditions as those shown in eq 2. The reaction gave TEMPO trapped isoxazoline **4** in 90% yield, accompanied by less than 5% of **2a**. This result demonstrated clearly that the initiation step is the generation of the iminoxyl radical because TEMPO is a more efficient scavenger than TBN for the cyclized carbon radical.

To examine the scope of the present protocols, a variety of *β,γ*-unsaturated ketoximes were subjected to the standard reaction conditions outlined in eq 1. The results are summarized in Table 1. Terminal alkenes participated in the oxyoximation process very well, giving rise to isoxazoline carbaldehyde oximes **3a**−**3h** in good to excellent yields. Both aromatic and aliphatic substituted ketoximes were tolerated (Table 1, entries 1−6). Thiophen incorporated ketoxime **1g** was also transformed to the desired product **3g** in excellent yield (Table 1, entry 7). Oxyoximation involving 1,2-disubstituted alkenes was also successful, as demonstrated in the reaction of substrate **1h** (Table 1, entry 8). When the alkene moiety was incorporated in a ring, as in the cases of **1i** and **1j**, the reactions afforded isoxazoline fused cyclopentanone oxime **3i** and cyclohexanone oxime **3j** in 82% and 88% yield, respectively (Table 1, entries 9 and 10). Notably, the reaction can also be easily carried out in a gram scale without difficulty, thereby delivering **3d** in excellent yield.

Besides the importance of the isoxazoline scaffold in pharmacophores and organic synthesis,[8a,b] the formation of compounds **3** involves oxyoximation of alkenes and features an

Table 1. Iminoxyl Radical-Promoted Oxyoximation of Alkenes for the Synthesis of Isoxazolines[a]

entry	substrate	product	% yield[b,c]
1	 **1a**	 **3a**	93 (0.63:1)
2	 Ar = Ph, **1b**	 Ar = Ph **3b**	91 (0.71:1)
3	4-MeOPh **1c**	4-MeOPh **3c**	90 (0.8:1)
4	4-ClPh **1d**	4-ClPh **3d**	83[d] (0.6:1)
5	4-CNPh **1e**	4-CNPh **3e**	86 (0.55:1)
6	 **1f**	 **3f**	88 (0.75:1)
7	 **1g**	 **3g**	89 (0.96:1)
8	 **1h**	 **3h**	86 (0.19:1)
9	 *n* = 0, **1i**	 *n* = 0, **3i**, >99:1 dr	82 (0.24:1)
10	*n* = 1, **1j**	*n* = 1, **3j**, >99:1 dr	88 (0.11:1)

[a]All reactions run 0.1 M in MeCN using ketoximes **1** (0.5 mmol) and TBN (1.5 mmol) at room temperature under Ar. [b]Yields of isolated product after $N(Et)_3$ workup. [c]Ratio in parentheses indicates the *Z*/*E* isomers. The determination of the ratio of *Z*/*E* isomers is based on ^1H NMR (see Supporting Information for the detail). [d]10 mmol scale of substrate was used.

oxime motif which is of great synthetic value in multi-transformations for important organic intermediates. As in the case of **3d**, the aldoxime moiety can be transformed to the cyano group after dehydration by treating with MsCl (methanesulfonyl chloride) and pyridine at room temperature, delivering 3-phenyl-4,5-dihydroisoxazole-5-carbo-nitrile **5** in 98% yield. In addition, **3d** can be transformed to 3-phenyl-4,5-dihydroisoxazole-5-carboxamide **6** in 67% yield through Beckman rearrangement using a catalytic amount of $In(NO_3)_3$. Moreover, **3d** can also be converted to a 1,3-dipole by treatment with NCS (*N*-chloro-succinimide) and $N(Et)_3$, which can further react with methyl propiolate to give compound **7** in 96% yield (Scheme 3).

Having successfully achieved the O-atom 5-*exo*-trig radical cyclization of *β,γ*-unsaturated ketoximes,[9] we moved on to extend the protocol to *γ,δ*-unsaturated counterparts to see if the latter could also undergo the N-atom 5-*exo*-trig radical cyclization to form cyclic nitrones, as we previously observed.[2a] Indeed, as shown in Table 2, oxime incorporated cyclic nitrones **8** were obtained in high yields accompanied by the intramolecular aminooximation of alkenes in all cases. On the other

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Scheme 3. Follow-up Transformation of Isoxazoline Carbaldehyde Oximes

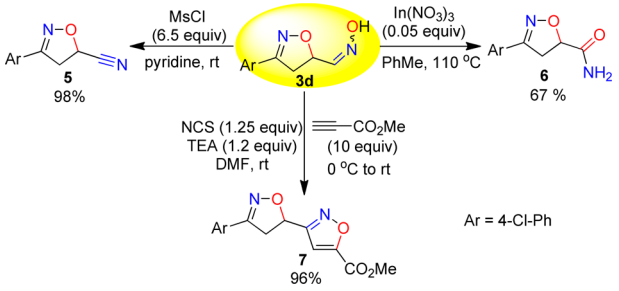
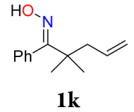
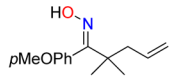
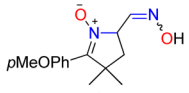
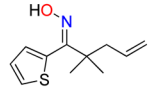
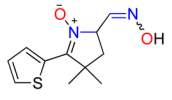
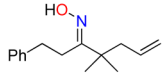
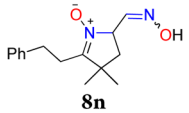
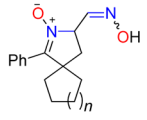
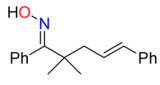
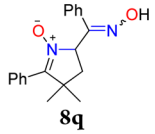
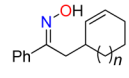
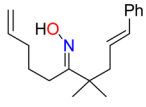
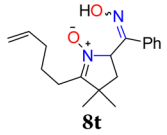


Table 2. Iminoxyl Radical-Promoted Aminooximation of Alkenes for the Synthesis of Cyclic Nitrones[a]

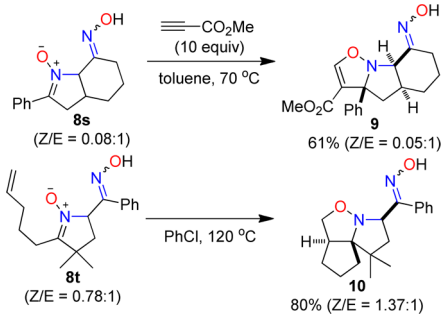
entry	substrate	product	% yield[b,c]
1	 **1k**	 **8k**	82 (0.52:1)
2	 **1l**	 **8l**	84 (0.54:1)
3	 **1m**	 **8m**	85 (1:0.89)
4	 **1n**	 **8n**	82 (0.50:1)
5	 *n* = 1 **1o**	 *n* = 1 **8o**	86 (0.49:1)
6	*n* = 2 **1p**	*n* = 2 **8p**	83 (0.76:1)
7	 **1q**	 **8q**	91 (0.87:1)[d]
8	 *n* = 0 **1r**	 *n* = 0 **8r**, >99:1 dr	73 (0.09:1)[d]
9	*n* = 1 **1s**	*n* = 1 **8s**, >99:1 dr	75 (0.08:1)
10	 **1t**	 **8t**	97 (0.78:1)[d]

[a]All reactions run at 0.1 M in MeCN using ketoximes **1** (0.5 mmol) and TBN (1.5 mmol) at room temperature under Ar. [b]Yields of isolated product after $N(Et)_3$ workup. [c]Ratio in parentheses indicates the *Z*/*E* isomers. The determination of the ratio of *Z*/*E* isomers is based on ^{1}H NMR (see Supporting Information for the detail). [d]*Z*/*E* isomers were separated.

hand, the O-atom-involved 1,5-H shift, which occurs under other circumstances,[10] was not observed in the present cases, because it is much less favored than the N-atom-involved 5-*exo*-trig cyclization. Unsaturated ketoxime incorporated terminal olefins were transformed to cyclic nitrone carbaldehyde oximes in good yields (Table 2, entries 1−6). When ketoximes **1o** and **1p** were utilized in the reaction, cyclic nitrones were formed as spiro-compounds in excellent yields (Table 2, entries 5 and 6). For compound **1q**, which incorporates a styryl moiety, the reaction afforded **8q** in 91% yield (Table 2, entry 7). The structures of **Z-8q** and **E-8q** were confirmed by single-crystal X-ray diffraction studies. When the alkene moiety was incorporated in a ring, as in the cases of **1r** and **1s**, the reaction also afforded cyclic nitrone fused cyclopentanone oxime **8r** and cyclohexanone oxime **8s** in 73% and 75% yield, respectively. Reaction of **1t** afforded the desired product **8t** in 97% yield, demonstrating the compatibility of the mild, efficient, radical-chain protocol with additional olefin groups susceptible to nitration.

Cyclic nitrones have attracted great attention due to their multiple uses in pharmacy[8c,d] and as 1,3-dipoles in organic synthesis.[11] In this context, the oxime incorporated cyclic nitrones could also be used as 1,3-dipoles (Scheme 4). When

Scheme 4. Inter- and Intramolecular [3 + 2] Cycloadditions of Oxime Attached Cyclic Nitrones



compound **8s** was treated with methyl propiolate, it could give formal [3 + 2] cycloaddition product **9** as a single diastereoisomer in 61% yield. In addition, intramolecular [3 + 2] cycloaddition could also take place when compound **8t** was involved, delivering complex product **10** as a single diastereomer in 80% yield.

In conclusion, we have developed a mild, convenient, and efficient method for the synthesis of functionalized 4,5-dihydroisoxazoles and cyclic nitrones from *β*,*γ*-unsaturated and *γ*,*δ*-unsaturated ketoximes. This protocol employs the simple TBN as the radical initiator, which can readily convert the ketoximes to iminoxyl radicals. TBN also acts as a radical trap in this reaction to capture the carbon radicals generated from the C−O and C−N forming 5-*exo*-trig cyclizations of unsaturated iminoxyl radicals, and thus the novel oxyoximation and aminooximation of unactivated alkenes can be realized.[12] To the best of our knowledge, the present study represents the first example of using TBN to generate iminoxyl radicals as well as the first example of vicinal oxyoximation and amino-oximation of unactivated alkenes. Further studies on the iminoxyl radical promoted reaction are in progress in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and spectral data for all new compounds are provided. 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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(12) See Scheme S1 in the Supporting Information for the plausible mechanism for the TBN-initiated iminoxyl radical-involved process.