Cyclization

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Oxime Radical Promoted Dioxygenation, Oxyamination, and Diamination of Alkenes: Synthesis of Isoxazolines and Cyclic Nitrones**

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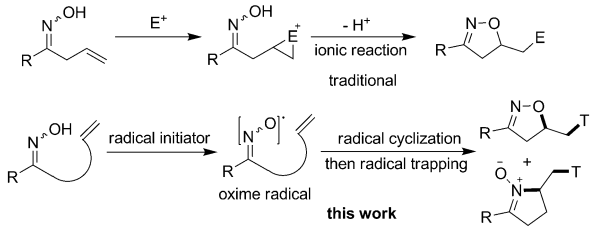
In memory of Jay K. Kochi

Oximes are fascinating molecules which are used widely in both organic chemistry and biochemistry.[1] The cyclization of β,γ-unsaturated oximes constitutes a general synthetic approach toward isoxazolines which are structurally important in organic synthesis. So far the strategies employed for this purpose involve the activation of carbon–carbon double bonds by running the reaction under ionic conditions in the presence of strong electrophilic reagents[2] or using palladium as the catalyst;[3] methods of initiating the reactions from the oxime side have not been reported. The free radical cyclization reactions have found wide applications in the synthesis of carbo- and heterocyclic compounds.[4] In this context, it is reasonable to expect that the oxime radical (iminoxyl radical) involved in the intramolecular addition to a carbon–carbon double bond should provide a convenient method for the synthesis of isoxazolines. However, to the best of our knowledge the participation of an oxime radical in reactions has not been reported so far. This situation is a little bit surprising considering that oxime radicals have been known for a long time, and their analogues, aminoxyl radicals such as TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy), have found wide applications in organic synthesis.[5]

Oxime radicals were first identified by Thomas using EPR spectroscopy as early as 1964,[6] and Ingold et al. isolated and studied the di-*tert*-butyliminoxyl radical in 1971.[7] The physical properties such as structure, stability, and spectroscopy of oxime radicals have been extensively studied since then.[8] Given our continued interest in the aminoxyl radical mediated reactions,[9] we report herein the first 5-*exo*-trig cyclization of β,γ-unsaturated oximes involving an oxime radical, a reaction which was initiated by commercially available TEMPO or DEAD (diethyl azodicarboxylate). The reactions afforded 4,5-dihydroisoxazoles with dioxygenation and oxyamination at the alkene moiety. In addition, when γ,δ-unsaturated ketoximes were subjected to the reaction conditions, cyclic nitrones were generated as the result of the 5-*exo*-trig N–C bond-forming cyclization promoted by oxime radicals (Scheme 1).



Scheme 1. Oxime radical 5-*exo*-trig cyclization. T = trap.

At the beginning of this study, we first chose TEMPO to initiate the free radical cyclization of β,γ-unsaturated oximes. Previous studies indicate that the O–H bond in an oxime has a relatively low bond dissociation energy (BDE, an average of about 83 kcal mol^{-1}).[10] We anticipated that TEMPO might convert oximes into oxime radicals by a hydrogen atom abstraction (HAT) process. The formed oxime radicals would then undergo a 5-*exo*-trig cyclization to give the corresponding carbon-centered radicals which could be trapped immediately by TEMPO to produce isoxazoline derivatives. With this in mind, we set out by treating a mixture of the β,γ-unsaturated ketoxime **1a** with TEMPO (3 equiv) in toluene at 80 °C under argon. As expected, the desired reaction took place, thus generating the TEMPO-trapped 4,5-dihydroisoxazole **2a** in 71 % yield (Scheme 2).

While this result verified our initial hypothesis, the yield of **2a** was unsatisfactory to us. To improve the yield, we turned our attention to dialkyl azodicarboxylates such as DEAD and DIAD (diisopropyl azodicarboxylate), which are known to react with NHPI (*N*-hydroxyphthalimide) and TEMPOH to afford the PINO (phthalimido-*N*-oxyl) radical and TEMPO, respectively.[11] Very recently, Alexanian et al. reported that DIAD could be used to generate hydroxamic acid radicals from hydroxamic acids which are analogues of NHPI.[12] To our delight, when DEAD (1 equiv) was used as the oxime radical initiator, and TEMPO (2 equiv) was used as the carbon radical trapping agent, the same product **2a** was obtained in 93 % yield along with a tiny amount of the DEAD-trapped by-product isoxazoline **3a** (Scheme 3, con-

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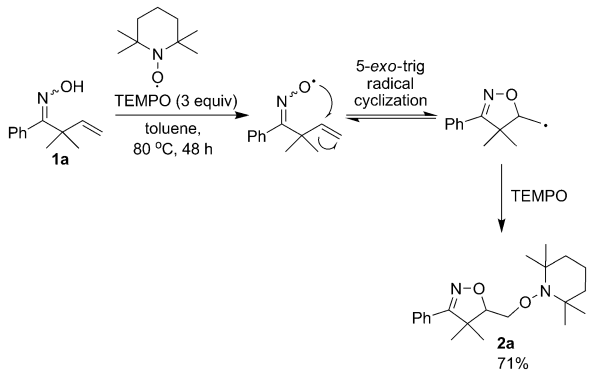
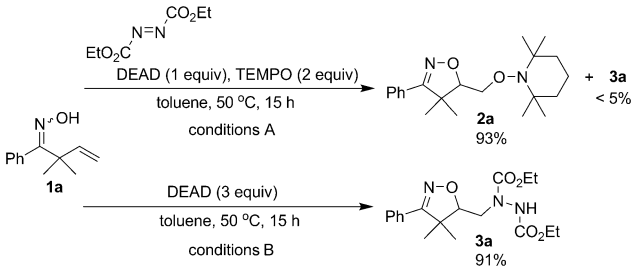


Scheme 2. TEMPO-initiated oxime radical 5-*exo*-trig cyclization.



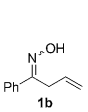
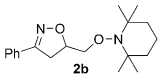
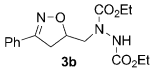
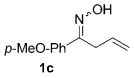
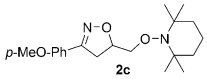
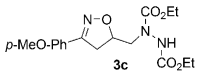
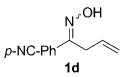
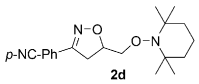
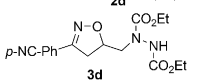
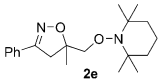
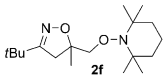
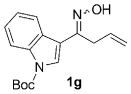
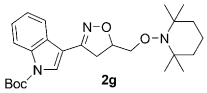
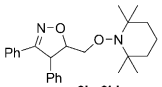
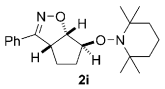
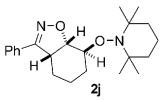
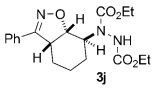
Scheme 3. DEAD-initiated oxime radical 5-*exo*-trig cyclization.

ditions A). In contrast, when DEAD (3 equiv) was used in the absence of TEMPO under the same reaction conditions, the compound **3a** was obtained in 91% yield (Scheme 3, conditions B). This result demonstrates clearly that DEAD could serve as an oxime radical initiator as well as carbon radical trapping agent in the reaction.[13]

Besides the importance of the isoxazoline structure motif, the formation of compounds **2a** and **3a** involves dioxygenation and oxyamination, respectively, of unactivated alkenes, and these are two types of reactions which are of synthetic significance.[14] To examine the scope of the present protocols, a variety of β,γ-unsaturated ketoximes were subjected to the reaction conditions as shown in Scheme 3. The results are summarized in Table 1. Compounds **1b–j** reacted very well under both sets of reaction conditions, thus giving rise to the corresponding dioxygenation and oxyamination products **2** and **3**, respectively, in good to excellent yields. Both aromatic- and aliphatic-substituted ketoximes were tolerated (Table 1, entries 1–5). Indole-containing ketoxime **1g** was also transformed into the desired product in excellent yield (Table 1, entry 6). When compound **1h** was used as the substrate, the product was formed as a mixture of diastereoisomers (Table 1, entry 7). When the alkene moiety was incorporated into a ring, as in the cases of **1i** and **1j**, the reaction afforded the *trans* dioxygenation and oxyamination products with high stereoselectivity. Apparently, the trapping of the cyclization-derived carbon radicals was more favored from the less hindered exo direction (Table 1, entries 8 and 9). Notably, the reaction could also be easily carried out in a gram scale without difficulty, thereby delivering **2b** and **3b** in excellent yield.

The reductive cleavage of 4,5-dihydroisoxazoles constitutes a highly effective method for the synthesis of β-hydroxy

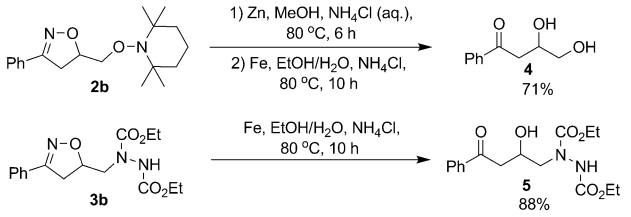
Table 1: Oxime radical promoted dioxygenation and oxyamination of alkenes to synthesis of isoxazolines.[a]

Entry	Substrate	Conditions[b]	Product	*t* [h]	Yield [%][c]
1	 1b	A	 2b	20	90[d]
		B	 3b	20	88[d]
2	 1c	A	 2c	15	96
		B	 3c	15	88
3	 1d	A	 2d	15	90
		B	 3d	15	86
4	 1e	A	 2e	15	93
5	 1f	A	 2f	24	77
6	 1g	A	 2g	24	90
7	 1h	A	 2h+2h'	48	80 59:41[e]
8	 1i	A	 2i	36	90 95:5[e,f]
9	 1j	A	 2j	36	90 95:5[e,f]
		B	 3j	36	88 95:5[e,f]

[a] All reactions run at 0.5 M toluene using oxime **1** (0.5 mmol) under Ar at 50 °C. [b] Conditions A: DEAD (0.5 mmol) and TEMPO (1.0 mmol); Conditions B: DEAD (1.5 mmol). [c] Yield of isolated product. [d] On a gram scale 5 mmol oxime was used. [e] Diastereomeric ratios determined by ^{1}H NMR spectroscopy of crude reaction mixtures. [f] The configuration of diastereomer was confirmed by NOE and coupling constants from ^{1}H NMR spectroscopy.

ketones. Following the reported procedure,[14d,15] the dioxygenation product **2b** can be reduced to the synthetically useful compounds, the β,γ-diol **4**, in good yield. Compound **3b** was reduced in the same way to give β-hydroxy-γ-diethyl hydrazine-1,2-dicarboxylate ketone (**5**) in excellent yield (Scheme 4).

Having successfully achieved the 5-*exo*-trig radical cyclization of β,γ-unsaturated ketoximes, we moved on to extend



Scheme 4. Reductive cleavage of 4,5-dihydroisoxazoles.

the protocol to γ,δ-unsaturated ketoximes to see if the latter compounds could undergo 6-*exo*-trig cyclization to form 5,6-dihydro-4*H*-1,2-oxazines. However, when **6a** was used as the substrate, the expected 6-*exo*-trig cyclization product was not formed. Instead, we obtained the cyclic nitrones **7a** and **8a** as the products under reaction conditions A and B, respectively (Table 2, entry 1). Apparently, 5-*exo*-trig C–N bond-forming cyclization of the oxime radical is more favored than the 6-*exo*-trig C–O bond-forming cyclization for compound **6a**. Although this result seemed surprising at first, that is, the DIAD-promoted cyclization of γ,δ-unsaturated hydroxamic acids proceeding in the 6-*exo*-trig C–O bond-forming fashion,[12] it is consistent with the pattern of single-electron distribution in oxime radicals. The previous EPR studies revealed that oxime radicals should be represented by resonance structures **A** and **B** (Figure 1).[6,8a–e] Later computational studies showed that the single-electron spin densities are located on the O atom (0.54–0.58) and on the N atom (0.45–0.47) in oxime radicals.[10] Our own computational study also gave the similar spin densities on O and N atoms in the ketoxime radical **C**. It means that oxime radicals can behave as nitrogen-centered radicals as well as oxygen-centered radicals in the reaction. This result also proves that oxime radicals are σ radicals rather than π radicals.[10]

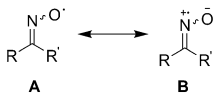
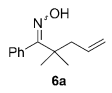
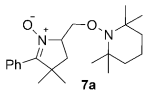
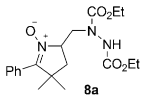
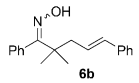
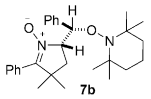
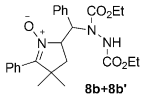
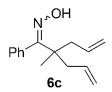
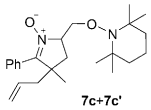
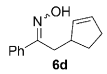
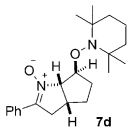
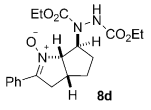


Figure 1. Resonance structures **A** and **B** exist for oxime radicals.

Theoretical calculations on the energy profile for the cyclization processes of **C** indicates that the C–N bond-forming 5-*exo*-trig cyclization via **TS1** is more favored than the C–O bond-forming 6-*exo*-trig cyclization via **TS2** by 3.8 kcal mol^{-1} in terms of free energy of activation (Figure 2).[16] Such an energy difference explains why the reaction of compound **6a** failed to deliver the 6-*exo*-trig cyclization products. In fact, numerous studies have shown that the 5-*exo*-trig cyclization of nitrogen- or oxygen-centered radicals is generally a facile process, but the 6-*exo*-trig cyclization is seldom reported.[4a,b]

The same product, **7a**, was also obtained in 70% yield when TEMPO (3 equiv) was used as the radical initiator in the absence of DEAD, thus demonstrating that the formation of the cyclic nitrone **7a** from **6a** is unambiguously a free radical process (Scheme 5).

Table 2: Oxime radical promoted oxyamination and diamination of alkenes to synthesis of cyclic nitrones.[a]

Entry	Substrate	Conditions[b]	Product	*t* [h]	Yield [%][c]
1	 6a	A	 7a	72	80[d]
		B	 8a	72	75[d]
2	 6b	A	 7b	48	90 90:10[e]
		B	 8b+8b'	48	71 64:36[e]
3	 6c	A	 7c+7c'	48	83 50:50[e]
4	 6d	A	 7d	30	75 >99:1[e,f]
		B	 8d	48	68 >99:1[e,f]

[a]–[f] See Table 1.

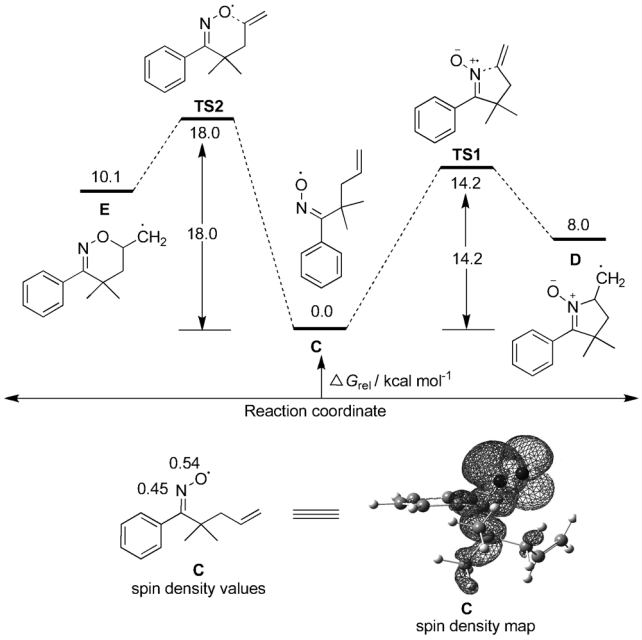
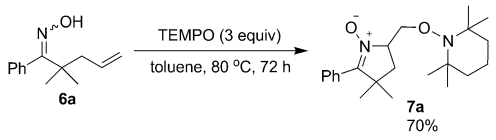


Figure 2. a) Energy profiles for the 6-*exo*-trig cyclization (O atom) and 5-*exo*-trig cyclization (N atom) of the ketoxime radical **C**; the relative energies are given in kcal mol^{-1}. b) The calculated Mulliken spin density values for the O and N atoms and the spin density map of the ketoxime radical **C**. Gridline indicates regions of positive spin density.



Scheme 5. TEMPO-initiated oxime radical N-atom 5-*exo*-trig cyclization.

The procedures were then applied to several other γ,δ-unsaturated ketoximes. As shown in Table 2, in all these cases, cyclic nitrones were obtained in good yields. Compound **6b** was transformed under reaction conditions A into **7b** and its diastereoisomer **7b′**, in a combined yield of 90% (Table 2, entry 2). The ratio of **7b** to **7b′** was 90:10. The structure of compound **7b** was confirmed by a single-crystal X-ray diffraction study.[17] The observed stereoselectivity can be explained with the model shown in Figure 3. In this model, the carbon radical generated from **6b** reacts with TEMPO

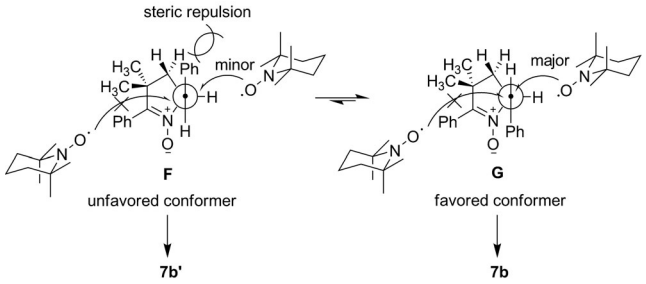
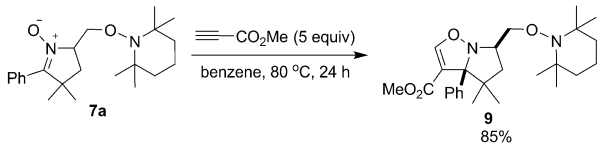


Figure 3. Rationalization of the high selectivity for the formation of **7b.**

through either conformer **F** or conformer **G**, with **G** being lower in energy than **F**. TEMPO is expected to attack the carbon radical from the direction away from the nitrone ring to avoid the steric repulsion. The formation of **7b**, which resulted from the trapping of conformer **G** by TEMPO, is preferred according to the Curtin–Hammett principle.[18] In contrast, the stereoselectivity is much lower for the reaction of **6b** under reaction conditions B, probably because DEAD is not as sterically demanding as TEMPO. The reactions of compound **6d** afforded either **7d** or **8d** in good yield and excellent stereoselectivity, similar to the reactions of **1i** and **1j** as mentioned previously (Table 2, entry 4).

Cyclic nitrones have attracted great attention because of their multiple uses in pharmaceuticals[19] and as spin-trapping reagents.[20] In addition, the [3+2] cycloaddition of nitrones with dipolarophiles are important transformations in organic synthesis.[21] In this context, **7a** reacted with methyl propiolate through a [3+2] cycloaddition to form the product **9** in excellent yield (Scheme 6).



Scheme 6. The [3+2] cycloaddition of cyclic nitrone with methyl propiolate.

In conclusion, we have demonstrated that the reactions involving an oxime radical could be of great synthetic value. Oxime radicals can be conveniently prepared from ketoximes by using commercially available TEMPO or DEAD as the radical initiator. By using this protocol, simple methods were developed for the synthesis of 4,5-dihydroisoxazoles and cyclic nitrones from β,γ-unsaturated and γ,δ-unsaturated ketoximes, respectively, through C–O bond-forming and C–N bond-forming 5-*exo*-trig cyclizations. TEMPO and DEAD act as carbon radical scavengers as well in the reactions, and consequently, the dioxygenation, oxyamination, and diamination of unactivated alkenes can be realized. Furthermore, this work gives direct evidence for the notion that single-electron spin densities are delocalized on both the O atom and N atom in the oxime radicals. Further studies on the oxime radical promoted reaction are in progress in our laboratory.

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[16] See the Supporting Information for details of the theoretical study.

[17] CCDC 880616 (**7b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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