

Visible-Light-Mediated Iminyl Radical Generation from Benzyl Oxime Ether: Synthesis of Pyrroline via Hydroimination Cyclization

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Supporting Information

ABSTRACT: The treatment of an *O*-(4-methoxybenzyl) oxime ether bearing an olefin substituent and 1-chloroan-thraquinone (1-Cl-AQN) catalyst in 2-butanone under visible-light irradiation affords pyrroline via an iminyl radical intramolecular hydroimination. Mechanistic studies indicate that iminyl radical generation mainly proceeds by hydrogen abstraction of the photocatalyst from the benzyl position of the oxime. Moreover, the hydrogen atom was identified in circulation from the benzylic position of the substrates between AQN and 2-butanone to quench the carbon radical without requiring any additional reagents.

N itrogen-centered radicals (NCRs) are valuable active species for constructing nitrogen-containing heterocyclic skeletons, which are included in many bioactive substances.¹⁻³ Notably, iminyl radicals are useful radical species in NCRs that enable the embedding of the imine group for easy molecular conversion in a cyclic skeleton.⁴ A typical method for generating iminyl radicals is the homolysis of the N-O bond of oxime. The cleavage of the N-O bond is commonly engaged under harsh reaction conditions, such as high temperature or UV irradiation (Scheme 1A).⁵ Recently, the groups of Yu, Leonori, and Studer reported methods for producing iminyl radicals via a photoredox reaction using a photocatalyst (Scheme 1B).⁶ In these methods, the cleavage of the oxime's N-O bond underwent single-electron transfer (SET) between the photoredox catalyst and the substrate to afford iminyl radicals under moderate reaction conditions. However, the photoredox pathway required re-oxidation reagents or hydrogen donor reagents, such as aryl disulfide or 1,4-cyclohexadiene, to regenerate the photocatalyst. Thus, a novel and economical method for generating iminyl radicals under mild conditions is required.

Hydrogen atom transfer (HAT) is a molecularly activated mode that abstracted a hydrogen atom from a weak C–H bond of a substrate.⁷ The HAT catalyst activates the reagent and acts as a hydrogen donor if the hydrogenated catalyst passes along a hydrogen atom to the substrate.⁸ Iminyl radical generation methods via hydrogen abstraction have been reported; however, they have been only applied to basic experiments.⁹ No generation method in the HAT pathway has been reported.

With this perspective, we have reported anthraquinone (AQN) catalytic benzylic selective oxidation,¹⁰ wherein a benzyl radical, generated by hydrogen abstraction from the excited AQN, was thought to be a plausible reaction intermediate. Thus, a novel iminyl radical evolution method







can be developed using regioselective HAT. We assumed that an iminyl radical was produced in two steps (Scheme 1C): (1)

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excited AQN abstracts the hydrogen atom from benzyl oxime ether 1 and (2) generated benzyl radical 2 immediately undergoes β -scission to produce an iminyl radical 3 and an aldehyde. Herein, we report new synthesis pathways of pyrrolines via the intramolecular cyclization of an iminyl radical generated from an *O*-(4-methoxybenzyl) oxime ether under visible-light irradiation.

Since hydrogen abstraction with AQN from benzyl ether has not been reported yet, the generation of a benzyl radical was confirmed using the oxidation reaction of the preceding example.¹⁰ After identifying hydrogen abstraction at the benzylic position (Table S1), we attempted a pyrroline formation reaction using an arylmethyl oxime ether possessing an olefin moiety to confirm the iminyl radical production (Scheme 2). At first, *O*-benzyl oxime ether (1c) afforded the



^{*a*}Reaction conditions: A solution of 1 (0.15 mmol), 2-Cl-AQN (0.1 equiv) and in 2-butanone (2 mL) was irradiated with a fluorescent lamp (23 W \times 4) under an argon atmosphere and stirred for 20 h. ^{*b*}¹H NMR yields. The isolated yield is shown in parentheses.

corresponding pyrroline **5a** in 13% yield in the presence of 2chloro-AQN in 2-butanone under visible light irradiation using a 23 W fluorescent lamp. As hypothesized, the electron density of the aryl group affected benzylic selective hydrogen abstraction¹⁰ and β -scission. The oxime with an electrondeficient aryl group did not afford the corresponding product (**1a**, **1b**); however, electron-rich aryl groups (**1d**, **1e**), particularly 4-methoxybenzyl (PMB) group **1d**, afforded the corresponding pyrroline **5a**. When a more electron-rich aryl group (**1e**) was used, substrate was not completely consumed.

Thus, we used O-PMB oxime ether 1d as the model substrate and tuned the reaction conditions (Table 1). As a photocatalyst, AQNs generally showed good reactivity. This reaction could be performed using 2-butanone. Among our examinations, a combination of 2-butanone and 1-Cl-AQN (1chloroanthraquinone) afforded a good result due to its solubility and low nucleophilicity (entries 1-6). In contrast, a large amount of starting material remained unreacted when eosin Y was used as the photocatalyst (entry 7). This reaction did not proceed without the photocatalyst (entry 8). Furthermore, additive K₂CO₃ accelerated the reaction slightly against the inert effect of an acid (entries 1, 9, and 10). After finely tuning the reaction conditions, 72% of 5a was obtained when 0.1 equiv of 1-Cl-AQN was used as the photosensitizer, 1.0 equiv of K₂CO₃ as the additive, and 5 mL of 2-butanone as the solvent under visible-light irradiation (entry 11). Upon diluting the substrate concentration, the permeability of the visible light improved.

Table 1. Optimization of the Reaction Conditions a,b

PMP Ph 1d (0.15 mmol)		photocatalyst (0.1 equiv) additive solvent (2 mL) rt, 20 h visible light		Ph 5a
entry	photocatalyst	additive	solvent	yield (%)
1	2-Cl-AQN	K ₂ CO ₃	2-butanone	52
2	2-Cl-AQN	K_2CO_3	acetone	7
3	2-Cl-AQN	K_2CO_3	EtOAc	8
4	2-Cl-AQN	K_2CO_3	MeOH	0
5	2-Cl-AQN	K ₂ CO ₃	DMSO	0
6	1-Cl-AQN	K ₂ CO ₃	2-butanone	68
7	eosin Y	K_2CO_3	2-butanone	0
8		K_2CO_3	2-butanone	0
9	1-Cl-AQN	AcOH	2-butanone	45
10	1-Cl-AQN		2-butanone	58
11 ^c	1-Cl-AQN	K ₂ CO ₃	2-butanone	72

^{*a*}Reaction conditions: A solution of **1d** (0.15 mmol), photocatalyst (0.1 equiv), and additive (1.0 equiv) in solvent (2 mL) was irradiated with fluorescent lamp (23 W \times 4) under an argon atmosphere and stirred for 20 h. ^{*b*1}H NMR yields. ^{*c*}2-Butanone (5 mL).

With the optimized reaction conditions in hand, we then studied the scope and limitation of the reaction (Scheme 3). Oxime 1d afforded the corresponding pyrroline 5a in 78%



^{*a*}Reaction conditions: A solution of 1 (0.15 mmol), 1-Cl-AQN (0.1 equiv), and K_2CO_3 (1.0 equiv) in 2-butanone (5 mL) was irradiated with a fluorescent lamp (23 W × 4) under an argon atmosphere and stirred for 20 h. ^{*b*}Isolated yields. ^{*c*}1-Cl-AQN (0.05 equiv). ^{*d*}1-Cl-AQN (0.15 equiv). ^{*f*}dr = 3:1.

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isolated yield in the presence of 0.05 equiv of the catalyst. In general, the substituent at the aryl group on the main chain of the oxime did not affect the reactivity of the substrate. For example, the oximes with an aryl group possessing electrondonating groups (1f-h) afforded the corresponding products (5f-h) in good yields. Halogen substituents did not affect this reactivity considerably, and the corresponding products (5im) could be obtained in good yields regardless of the ortho-, meta-, and para-positions. The cyano group, an electronwithdrawing group, also afforded the product 5n in good yields. Furthermore, the substrate with the pyridine moiety could be applied to this reaction to produce the corresponding product (50) in 32% yield. If an oxime with an alkyl chain instead of an aryl group 1p was used, the yield of product 5p decreased and a nitrile byproduct 6p, which was thought to be generated by the fragmentation of iminyl radical,¹¹ was detected. When tetralin oxime 1q was used, tricyclic product 5q was obtained in 81% yield. We examined substrate 1r and expected to observe an increase in the yield due to the Thorpe-Ingold effect; however, the yield of 5r remained moderate. The oxime ether possessing trisubstituted internal olefin 1s was also converted to the corresponding pyrroline 5s in moderate yield.

To further investigate the primary reaction mechanism, several controlled experiments were conducted (Table 2).



When O-PMB oxime 1d was exposed under an atmospheric condition, a primary alcohol 7a,^{6b} generated by trapping molecular oxygen with the terminal carbon radical, was detected via ¹H NMR spectroscopy without any desired product (entry 1). Inhibition of this reaction using a radical scavenger, such as TEMPO (1.0 equiv), suggested that the pyrroline formation involved a radical pathway (entry 2). The desired pyrroline product was not detected under dark reaction conditions (entry 3). Furthermore, the time-course experiment with intermittent light intervals showed that the cleavage of the N-O bond only occurred upon irradiation with a fluorescent lamp (Scheme S1). This indicates that the excited AQN by visible-light irradiation was involved in the hydrogen abstract reaction and that this reaction does not progress through a radical-chain pathway where the carbon radical 5' abstracts the hydrogen atom from the benzylic position of the substrate instead of excited AQN. Subsequently, we considered the mechanism of the benzyl radical production. In addition to the hydrogen abstraction, the photoexcited AQN acted as a singleelectron oxidizing agent.¹² With this substrate, the same benzyl radical species could be generated via single-electron oxidation at the electron-rich aryl group and deprotonation by base at the benzylic position. Therefore, by measuring oxidationreduction potentials of the substrate, it was confirmed that the generation of the radical species via a proton concerted electron transfer (PCET) mechanism was possible.¹³ Thus, the oxidation potential of the substrate 1d was +1.28 V vs FC/FC⁺, whereas the oxidation potential of 1-Cl-AQN was +1.9 V vs FC/FC⁺. This indicates that the benzyl radical generation using PCET was possible. Furthermore, the success of the iminyl radical generation via PCET was experimentally confirmed using 9,10-dicyanoanthracene, known as a single-electron oxidizing agent (Table 2, entry 4). Thus, the progress of the reaction could be confirmed; therefore, it is expected that the benzyl radical was generated by the concerted progress of two mechanisms, namely hydrogen abstraction and PCET.

We conducted several deuterium-labeling experiments to identify the hydrogen donor source and found that the deuterated substrate at the benzylic position $[D_2]1d$ rarely afforded the deuterated product (Scheme 4A). However,





deuterated 2-butanone was detected by ²H NMR spectroscopy (Figure S1). When the reaction was performed in acetone- d_6 , a deuterated product was detected, although this hydroimination reaction progressed to low yield in acetone (Table 1, entry 2, and Scheme 4B).

On the basis of the above results, we proposed a plausible pathway (Scheme 5). At first, the photoexcited 1-Cl-AQN (1-

Scheme 5. Plausible Mechanism



Cl-AQN*), excited by visible-light irradiation, abstracted the hydrogen atom at the benzylic position or oxidized the PMP group via SET in conjunction with the proton transfer to afford benzyl radical intermediate 2. We assumed that the basic conditions promoted the PCET. Benzyl radical intermediate 2 was then immediately transformed into iminyl radical species 3

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and *p*-anisaldehyde 4 through N–O bond cleavage. 5-*exo-trig*-Cyclization of iminyl radical 3 produced the 5' carbon radical, which trapped the hydrogen atom from 2-butanone to afford the corresponding pyrroline. AQN was presumably regenerated by offering the hydrogen from AQH[•] to butanone, thereby completing the catalytic cycle.

In conclusion, we developed a synthesis pathway of pyrrolines using an unprecedented method of iminyl radical generation from an O-PMB oxime ether using visible light and a photocatalyst. We were unable to conclude that the reaction proceeded only through the HAT pathway; however, this approach conclusively afforded the iminyl radical generation method under mild conditions using visible-light energy. The previous iminyl radical method with a photoredox catalyst required an additional hydrogen donor and oxidant to quench the carbon radical, which was generated by the iminyl radical cyclization. In contrast, our proposed method was highly atom efficient as no additional reagent was used due to the circulation of the hydrogen atom abstracted from the benzylic position of the substrate between the AQN and 2-butanone. Furthermore, this is the first report on a photoredox method using a readily prepared O-PMB oxime ether and is thought to contribute significantly to the knowledge of iminyl radical chemistry.

ASSOCIATED CONTENT

S Supporting Information

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Experimental details and NMR spectra (PDF)

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Notes

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