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Visible-Light Photoredox-Catalyzed Synthesis of Nitrones: Unexpected Rate Acceleration by Water in the Synthesis of Isoxazolidines

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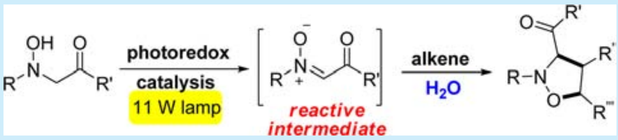
Supporting Information

ABSTRACT: A new oxidative [3 + 2] cycloaddition of *N*-substituted hydroxylamines with alkenes was established under visible light photoredox catalysis. This novel protocol provides a rapid, mild, and efficient access to valuable five-membered ring isoxazolidine heterocycles in a concise fashion.

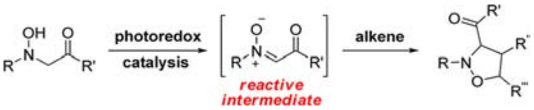


The development of highly efficient strategies for the preparation of isoxazolidines is of great importance since isoxazolidines represent an important class of versatile intermediates for a wide range of natural products and pharmaceuticals. Notably, these five-membered ring heterocycles can readily be converted into numerous useful functional groups such as amino acids, *β*-lactams, and 1,3-amino alcohols through reductive N−O bond cleavage. Therefore, it is not surprising that great efforts have been devoted to the development of new methods for the construction of isoxazolidine core. Among the different approaches available for the preparation of this structural motive, [3 + 2] cycloaddition of nitrones with alkenes is one of the most straightforward and convenient methods.[1] Since protocols based on the oxidative formation of nitrones from imines and amines employ harsh conditions and use excess amounts of oxidants, common strategies used to prepare nitrones are based on the alkylation of oximes, synthesis from nitro and nitroso compounds, and C═N bond formation, including condensation of *N*-substituted hydroxylamines with carbonyl compounds.[2] The oxidation of the corresponding hydroxylamines to nitrones is essentially the mildest oxidation method compared to the oxidative formation of nitrones from imines and amines.[3,4] However, previous reports on the oxidative formation of nitrones from the corresponding hydroxylamines require excess metal salts, oxides, or complex organic oxidants.[2,3,5]

Recently, visible-light has attracted significant interest being used as an inexpensive, readily available energy source for promoting organic transformations.[6] Visible light in combination with Ir(III)- and Ru(II)-based poly pyridyl complexes and organic dyes as single electron transfer catalysts have shown great potential to initiate oxidation reactions. In particular, tertiary amines can be oxidated to reactive iminium ions or azomethine ylides, while secondary amines can be oxidated to imine intermediates leading to reactive electrophiles.[7−11] Based on these previous reports on the photocatalyzed functionalization of tertiary and secondary amines,[6−12] we envisioned that *N*-alkyl-substituted arylhydroxylamines may be oxidated to nitrones by photocatalysis via single electron oxidation. This oxidation is difficult to be achieved, and different byproducts could be formed.

Thus, the successful accomplishment of such a reaction would not only be a new addition to the field of photoredox catalysis but, more importantly, would allow the preparation of otherwise sensitive nitrones in situ. Given that photoredox-catalyzed processes are typically mild and tolerant toward various functional groups, the in situ oxidation of hydroxylamines to reactive and less stable nitrone intermediates would be of broad applicability. We herein present the first visible-light photoredox oxidative [3 + 2] cycloaddition of *N*-alkyl-substituted hydroxylamines with alkenes (Scheme 1).

Scheme 1. Design of Visible-Light Photoredox Catalyzed Oxidative [3 + 2] Cycloaddition Reaction



We initiated our study on the photoredox-catalyzed oxidative [3 + 2] cycloaddition by using ethyl 2-(hydroxy(phenyl)amino)acetate **1a** as hydroxylamine substrate and ethoxyethene **2a** as dipolarophile in the presence of 1 mol % of $[Ir(ppy)_2bpy]PF_6$ as photoredox catalyst. Although the reaction proceeded slowly and the conversion was low, we were delighted to see that the desired product ethyl 5-ethoxy-2-phenylisoxazolidine-3-carboxylate **3a** was formed and isolated in 48% yield (Table 1, entry 1).

In order to increase the reactivity and improve the reaction yield, various reaction parameters were evaluated. Among the solvents tested, THF, DMF, and NMP gave only trace product (Table 1, entries 2, 6 and 7), and DCE, MeCN, and EtCN

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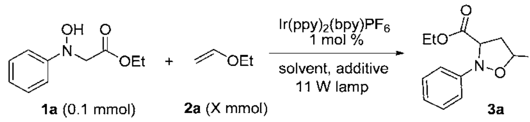
Table 1. Optimization of the Reaction Conditions for the Photoredox Oxidative [3 + 2] Cycloaddition[a]



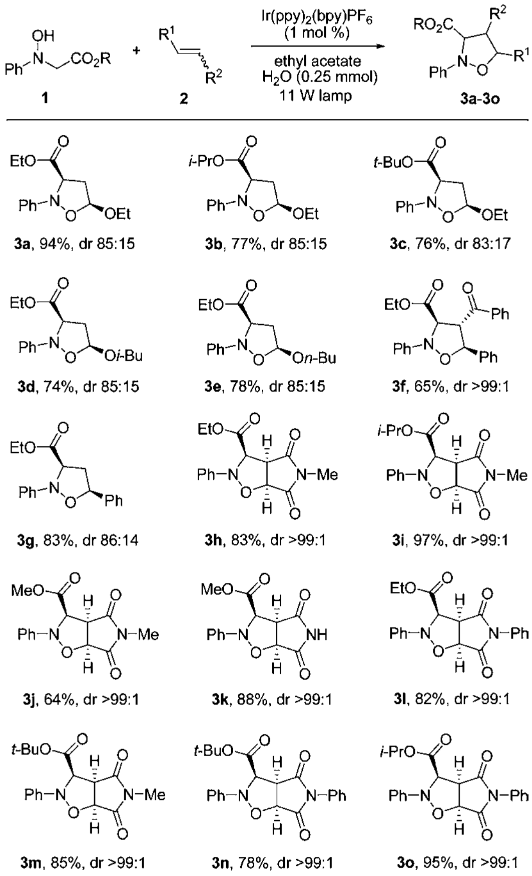
entry	2a (X mmol)	additive	solvent	time (h)	yield[b] (%)
1	0.3	none	toluene	48	48
2	0.3	none	THF	48	trace
3	0.3	none	DCE	48	39
4	0.3	none	MeCN	48	60
5	0.3	none	EtCN	48	53
6	0.3	none	DMF	48	trace
7	0.3	none	NMP	48	trace
8	0.3	none	EA	48	69
9	0.2	none	EA	36	52
10	0.15	none	EA	36	38
11[c]	0.3	none	EA	48	64
12	0.3	5% silica gel	EA	36	58
13	0.3	3 Å MS	EA	36	trace
14	0.3	NaOAc	EA	36	trace
15	0.3	H_2O (2.5 equiv)	EA	24	94
16	0.4	H_2O (2.5 equiv)	EA	24	94
17[d]	0.3	H_2O (2.5 equiv)	EA	24	trace
18[e]	0.3	H_2O (2.5 equiv)	EA	24	trace
19[f]	0.3	H_2O (2.5 equiv)	EA	24	11

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (X mmol), $[Ir(ppy)_2bpy]PF_6$ (1 mol %), 11 W fluorescent bulb irradiation, and solvent (1.0 mL). [b] Yield of the isolated product. [c] Reaction under oxygen atmosphere. [d] Reaction was carried out without catalyst. [e] Reaction was carried out in the dark. [f] Reaction under argon atmosphere. EA = ethyl acetate.

afforded the desired product **3a** in moderate yields (Table 1, entries 3–5). The best result was obtained in ethyl acetate as the solvent. By reducing the amount of **2a**, the reaction yield decreased (Table 1, entries 8–10). Next, different additives including silica gel, molecular sieves, NaOAc and H_2O were tested as well. When 5% silica gel was used, moderate conversion was observed and **3a** was isolated in 58% yield (Table 1, entry 12). Interestingly, only trace amounts of product were obtained when 3 Å molecular sieves and NaOAc were used (Table 1, entries 13 and 14). We were delighted to find that addition of 2.5 equiv of H_2O to the reaction mixture resulted in considerable faster reactions, and full conversion was observed in 24 h. Under these conditions, the corresponding product **3a** was isolated in 94% yield (Table 1, entry 15). Increasing the amount of alkene **2a** did not influence the reaction (Table 1, entry 16). Furthermore, only trace product was observed after 24 h in the absence of the photocatalyst and light (Table 1, entries 17 and 18). Water splitting by photoredox catalysts has been reported.[13] In order to elucidate its role during the course of our reaction, additional experiments were performed. However, increasing the amount of water did not improve the conversion of the reaction and performing the reaction for 24 h in the absence of oxygen, afforded the product in 11% yield (Table 1, entry 19). Based on these experiments, we concluded that water plays a decisive role after the photoredox cycle (vide infra).

With the best reaction conditions in hand, we started to examine the scope of this protocol by employing a large variety of *N*-alkyl-substituted phenylhydroxylamines **1** and different alkenes **2** (Scheme 2). In general, different glycine esters derived phenylhydroxylamines could be subjected to the reaction conditions yielding the corresponding products in moderate to excellent yields (Scheme 2, 64–97%). Different ester groups such as $-CO_2Me$, $-CO_2Et$, $-CO_2{}^iPr$, and $-CO_2{}^tBu$ were tolerated under our conditions. A variety of vinyl ethers, chalcone, *N*-substituted, and *N*-nonsubstituted maleimides were tested and proved to be compatible under the optimized conditions, giving the corresponding products in good to excellent yields.

Scheme 2. Evaluation of Different Ester Groups and Dipolarophiles in the Photoredox Oxidative [3 + 2]-Cycloaddition Reaction[a,b]

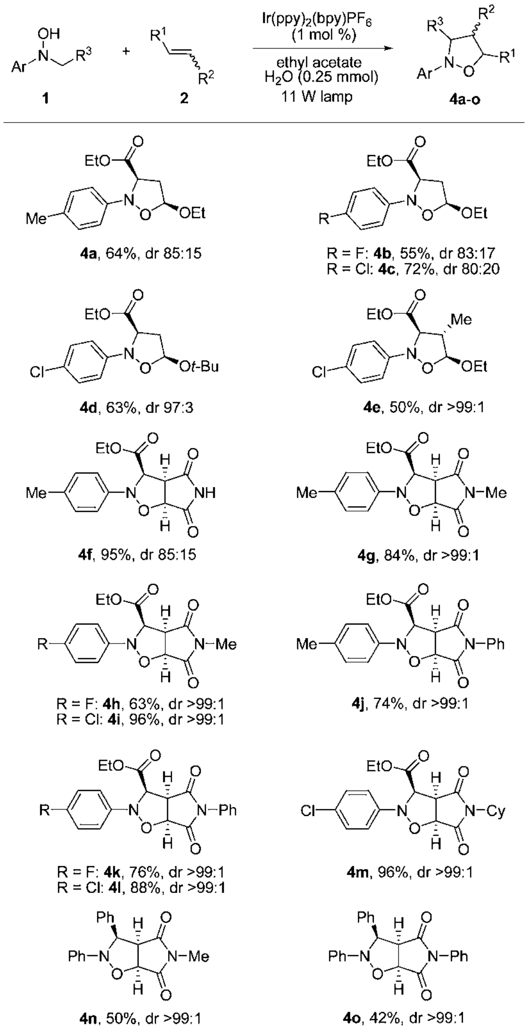


[a] Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), $[Ir(ppy)_2bpy]PF_6$ (1 mol %), 11 W fluorescent bulb, solvent (1.0 mL), 12–36 h. The diastereomeric ratio was determined by ^1H NMR spectroscopy when the minor diastereomer was observed in the ^1H NMR spectrum; otherwise it is reported as >99:1. [b] Yield of the isolated product.

The relative configuration of the product obtained in the reaction with vinyl ether was determined to be *cis* by correlation of **3g** with 1-(2,5-*cis*-diphenylisoxazolidin-3-yl)butan-1-one.[14]

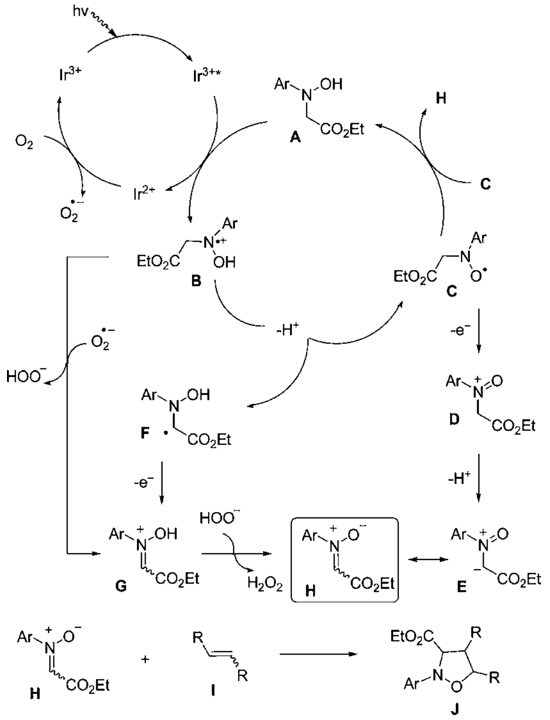
Furthermore, different electron-donating and electron-withdrawing groups on the aromatic ring of arylglycine ester derived hydroxylamines were tested and proved to be compatible as well (Scheme 3). Moreover, various *N*-substituted and *N*-non-substituted maleimides and vinyl ethers were tested under the standard conditions and gave the corresponding products in good to excellent yields. Different groups such as methyl, phenyl, and cyclohexyl on the *N* atom of maleimide were tested and gave the corresponding products in good to excellent yields. Notably, 1-ethoxyprop-1-ene was tested as well and gave the desired product ethyl 2-(4-chlorophenyl)-5-ethoxy-4-methylisoxazoli-

Scheme 3. Evaluation of Different Aryl Groups on the Hydroxylamine and Dipolarophiles in the Photoredox Oxidative [3 + 2] Cycloaddition[a,b]



[a] Reaction conditions: **1** (0.1 mmol), **2** (0.3 mmol), [Ir(ppy)$_2$bpy]PF$_6$] (1 mol %), 11 W fluorescent bulb, solvent (1.0 mL), 12–36 h. The diastereomeric ratio was determined by ^{1}H NMR spectroscopy when the minor diastereomer was observed in the ^{1}H NMR spectrum; otherwise it is reported as >99:1. [b] Yield of the isolated product.

Scheme 4. Proposed Mechanism for the Visible-light Photoredox Catalyzed Oxidative [3 + 2] Cycloaddition Reaction



dine-3-carboxylate **4e** in satisfactory yield (Scheme 3). To extend the substrate scope of the visible-light mediated oxidative [3 + 2] cycloaddition reaction for the isoxazolidines preparation, we switched from the glycine ester derivatives to *N*-benzyl-*N*-phenylhydroxylamine and 2-(hydroxy(phenyl)amino)-1-phenylethanone as substrates. To our great delight, *N*-benzyl-*N*-phenylhydroxylamine reacted with 1-phenyl-1*H*-pyrrole-2,5-dione and 1-methyl-1*H*-pyrrole-2,5-dione to give the corresponding products **4n** and **4o** in moderate yields (Scheme 3). The relative configuration of product **4n** was determined as cis/cis by X-ray single-crystal analysis.[15] Based on the above achievements, a catalytic cycle for this tandem transformation is proposed in Scheme 4. Upon irradiation, Ir^{III+} is excited to form Ir$^{III\bullet+}$ and then reductively quenched by hydroxylamine **A** to produce Ir^{II+} and ammonium radical cation **B** via SET oxidation. The Ir^{II+} is oxidated by O$_2$ to regenerate the catalyst Ir^{III+} and produce O$_2^{\bullet-}$. As mentioned above, water can be splitted by photoredox catalysts, providing active species which can promote or be involved in the reaction (HO$^\bullet$, HO$^-$, H$_2$O$_2$).[14] However, this seems not to be the major pathway in our case as increasing the amount of water did not improve the conversion and performing the reaction for 24 h in the presence of water, but absence of oxygen, afforded the product in 11% yield only.

Deprotonation of the ammonium radical cation **B** results in the formation of either C-radical **F** or O-radical **C**. Electron transfer from **F** affords intermediate **G**, which can be easily deprotonated by HOO$^-$ to yield nitrone **H**. Reaction of nitrone **H** with the dipolarophile **I** yields the [3 + 2] cycloaddition product **J**. The nitroxid **C** has an α-proton that can undergo disproportionation reaction to give hydroxylamine **A** and nitrone **H** (2**C** → **H** + **A**).[16] As a third possible alternative, nitroxide **C** can undergo electron and proton transfer to give nitrone **H**, which is essential for the cycloaddition reaction. We cannot rule out the eventuality that the cycloaddition reaction is also catalyzed by one of the species (e.g., H$_3$O$^+$, H$_2$O) present in the reaction mixture.

In conclusion, we have developed for the first time a visible-light mediated oxidative nitrone formation/[3 + 2] cycloaddition reaction for the preparation of isoxazolidines. This novel protocol provides a rapid, mild, and efficient access to important five-membered ring isoxazolidine heterocycles in a concise fashion. Notably, the aerobic oxidation of hydroxylamines to nitrones can be achieved through visible light photoredox catalysis under environmentally benign conditions, with low catalyst loading (1 mol %) and no additional oxidant. The application of this powerful system to the synthesis of natural products and pharmaceuticals is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, characterization data for products, and NMR spectra. 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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(15) CCDC-919398 contains the crystallographic data for **4n** (also available as Supporting Information). 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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