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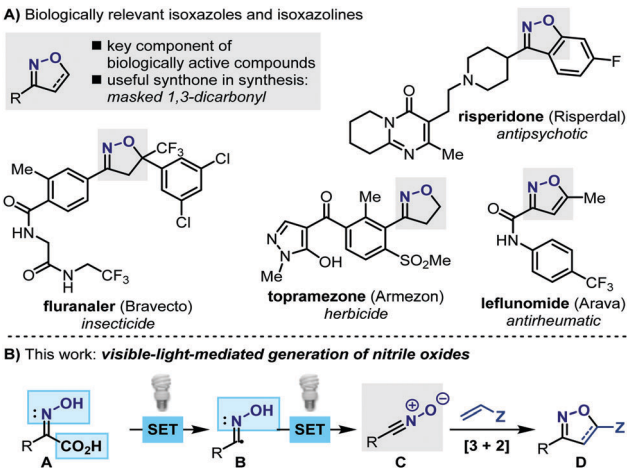
# Visible-light-mediated generation of nitrile oxides for the photoredox synthesis of isoxazolines and isoxazoles†

Thomas D. Svejstrup,‡[a] Wojciech Zawodny,‡[a] James J. Douglas,[b] Damon Bidgeli,[a] Nadeem S. Sheikh[c] and Daniele Leonori*[a]

**Visible-light photoredox catalysis enables the synthesis of biologically relevant isoxazolines and isoxazoles from hydroxyimino acids. The process shows broad functional group compatibility and mechanistic and computational studies support a visible-light-mediated generation of nitrile oxides by two sequential oxidative single electron transfer processes.**

Small nitrogen-containing heterocycles are among the most important building blocks for the synthesis of biologically active molecules.[1] Among this class of compounds, isoxazolines and isoxazoles are particularly relevant as they form the core structure of many currently used therapeutic agents, veterinary products and agrochemicals (Scheme 1A).[2] The continued interest in isoxazolines and isoxazoles is not limited to their biological properties but equally their routine use as masked 1,3-dicarbonyl functionalities.[3] Generally, these heterocycles are assembled *via* a [3+2]-dipolar cycloaddition of nitrile oxides, themselves typically prepared from sometimes unstable hydroxymoyl chlorides,[4] or by the dehydration of nitroalkanes[5] under frequently harsh conditions.[2c,6] Given the relevance of isoxazolines and isoxazoles in organic and medicinal chemistry, the development of new methods able to access them from simple and stable starting materials, and under mild reaction conditions is an important endeavour.

Visible light-photoredox catalysis has now been established as a powerful technique to perform single-electron transfer (SET)[7] reactions under very mild and user-friendly conditions.[8] While exploited for the formation of many C–C and C–X (X = heteroatom) bonds, photoredox catalysis has found a somewhat limited application in the synthesis of small ring heterocycles[9] *via* dipolar cycloaddition.[10] Xiao and co-workers developed a method for the synthesis of pyrroles and oxazoles involving the oxidation of 2H-azirines to aza-allenyl radical cations.[11] Rueping[12] and Xiao[13] reported the SET oxidation of tetrahydroisoquinolines as a key step in the generation of azomethine ylides and the subsequent preparation of pyrrole derivatives. Yoon has developed the photoredox cycloaddition of phenols and cyclopropyl ketones to access dihydrobenzofurans and saturated 5-membered ring heterocycles.[14] Furthermore, Tan,[15] Bissember[16] and Zhang[17] have recently disclosed the formation of α-amino radicals and their use in Povarov reactions. In this communication we describe the development of the first visible-light-mediated method for the generation of nitrile oxides and their utility in the synthesis of isoxazolines and isoxazoles (Scheme 1B).




Scheme 1 Isoxazoles and isoxazolines and current work.

At the outset of our work, we were keen to identify a class of nitrile oxide precursors that would be (i) easy-to-make, (ii) bench stable, and (iii) that would offer high structural modularity. We reasoned that hydroxyimino acids **A** would represent an ideal starting point owing to their simple preparation *via* condensation of α-ketoacids with hydroxylamine (Scheme 1B). Mechanistically,

[a] *School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK. E-mail: daniele.leonori@manchester.ac.uk*
[b] *AstraZeneca, Silk Road Business Park, Macclesfield SK10 2NA, UK*
[c] *Department of Chemistry, Faculty of Science, King Faisal University, Al-Ahsa 31982, Saudi Arabia*

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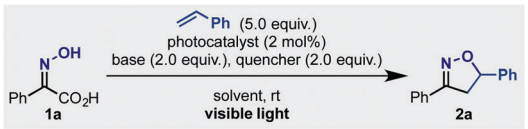
‡ These authors contributed equally.

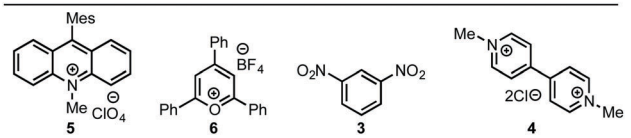
we were intrigued by the fact that these substrates contain two redox active functionalities (the carboxylic acid group and the N–OH system)[6c] that can sequentially serve as a duel photoredox electrophore *en route* to the nitrile oxide. According to our design plan, photoredox SET decarboxylation[18] would produce the acyl-like radical **B**, that upon a second SET oxidation would form the nitrile oxide **C**. Subsequent *in situ* [3+2] cycloaddition with a dipolarophile would furnish the targeted isoxazoline **D**.

To assess our hypothesis, we started by investigating the reaction of **1a** and styrene using various photoredox catalysts and terminal oxidants. As illustrated in Scheme 2, we were pleased to find that using eosin Y as the photoredox catalyst, $NaHCO_3$ as the base and air as the terminal oxidant in DMF under visible-light irradiation, **2a** was obtained in 6% yield (entry 1). We then evaluated different oxidants and found that by employing oxone the yield was improved to 38% (entries 2–5). By using $Ru(bpy)_3Cl_2$ as the photoredox catalyst, the efficiency of the process was further improved and **2a** was isolated in 75% yield (entry 7). Control experiments and light ON–OFF reaction analysis confirmed the requirement for light, photocatalyst and oxone.[19] Other bases, solvents and photoredox catalysts were evaluated but they generally provided **2a** with lower efficiency (entries 12–16).

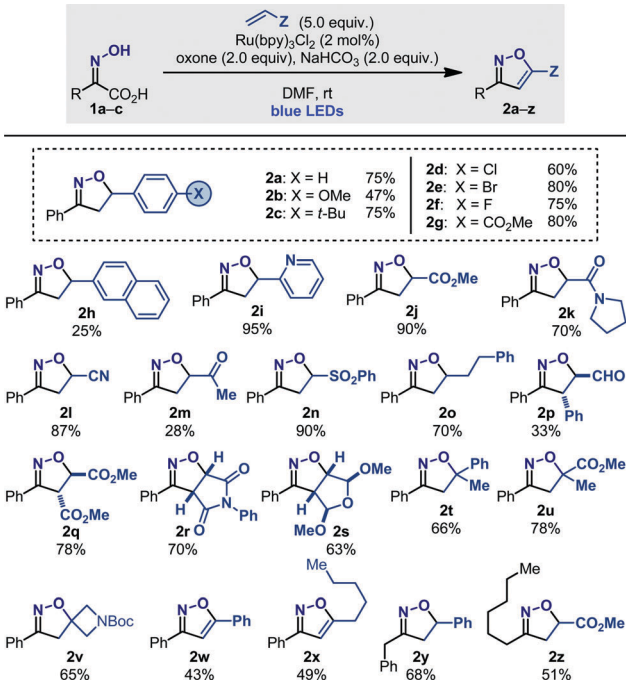
With the optimised reaction conditions in hand, we evaluated the scope of the process using hydroxyimino acid **1a** and a series of differentially *para*-substituted styrene partners (Scheme 3). The reaction tolerated both electron rich and electron withdrawing substituents as shown by the formation of substrates **2a–g** in good to high yields. We then expanded the scope to 2-vinyl-naphthalene and 2-vinyl-pyridine that successfully provided **2h** and **2i** in moderate and high yields respectively. We were keen




| Entry | Photocatalyst | Base | Quencher | Solvent | Light | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | EY | $NaHCO_3$ | air | DMF | 30W CFL | 6 |
| 2 | EY | $NaHCO_3$ | $BrCCl_3$ | DMF | green LEDs | 12 |
| 3 | EY | $NaHCO_3$ | **3** | DMF | green LEDs | traces |
| 4 | EY | $NaHCO_3$ | **4** | DMF | green LEDs | traces |
| 5 | EY | $NaHCO_3$ | oxone | DMF | green LEDs | 38 |
| 6 | $Ru(bpy)_3Cl_2$ | $NaHCO_3$ | oxone | DMF | 30W CFL | 41 |
| **7** | **$Ru(bpy)_3Cl_2$** | **$NaHCO_3$** | **oxone** | **DMF** | **blue LEDs** | **75** |
| 8 | – | $NaHCO_3$ | oxone | DMF | blue LEDs | traces |
| 9 | $Ru(bpy)_3Cl_2$ | $NaHCO_3$ | oxone | DMF | – | traces |
| 10 | $Ru(bpy)_3Cl_2$ | $NaHCO_3$ | oxone | MeCN | blue LEDs | 11 |
| 11 | $Ru(bpy)_3Cl_2$ | $NaHCO_3$ | oxone | DMSO | blue LEDs | traces |
| 12 | $Ru(bpy)_3Cl_2$ | $Cs_2CO_3$ | oxone | DMF | blue LEDs | 31 |
| 13 | $Ru(bpy)_3Cl_2$ | $(i\text{-Pr})_2NEt$ | oxone | DMF | blue LEDs | 18 |
| 14 | $Ir(ppy)_3$ | $NaHCO_3$ | oxone | DMF | blue LEDs | 16 |
| 15 | **5** | $NaHCO_3$ | oxone | DMF | 30W CFL | 3 |
| 16 | **6** | $NaHCO_3$ | oxone | DMF | 30W CFL | 63 |



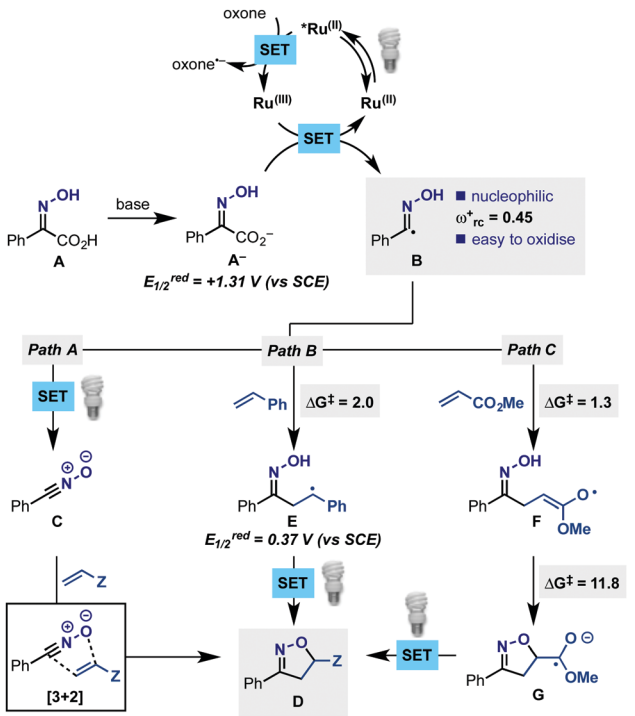

Scheme 2 Optimization of the visible-light-mediated synthesis of isoxazoline **2a** from hydroxyimino acid **1a**.




Scheme 3 Scope of the visible-light-mediated synthesis of isoxazolines and isoxazoles.

to explore the use of Michael acceptors as dipolarophiles in order to (i) evaluate the functional group compatibility of our process as well as (ii) obtaining molecules with handles for further manipulation. Pleasingly this photoredox manifold allowed reaction with a broad range of substrates such as carbonyl-based Michael acceptors (**2j**, **2k**, **2m**), acrylonitrile (**2l**) and a redox active vinyl-sulfone (**2n**).[20] Alkyl substituted olefins could also be engaged in the reaction (**2o**) as well as di-substituted olefins (**2p** and **2q**). Both electron rich and electron poor cyclic dipolarophiles reacted well allowing access to bicyclic frameworks (**2r** and **2s**). The formation of **2s** is noteworthy as the excited state of many photoredox catalysts are able to cleave highly electron rich functionalities by oxidative SET.[21] This methodology was also successful when *gem*-di-substituted olefins were employed as shown by the formation of **2t** and **2u** that contain a quaternary stereocentre and **2v** that shows that this method is suitable for the preparation of spirocycles By using alkynes, the aromatic isoxazoles **2w** and **2x** were obtained in moderate yield. Finally we extended our protocol using hydroxyimino acids **1b** and **1c** that generated benzylic and alkyl nitrile oxides and formed products **2y** and **2z** in good yields.

Having evaluated the scope of this photoredox transformation we decided to perform mechanistic and computational studies to investigate our proposed mechanism. As illustrated in Scheme 4, upon visible-light irradiation, the excited state of $Ru(bpy)_3^{2+}$ [$*Ru(bpy)_3^{2+}$] could be oxidised by oxone to $Ru(bpy)_3^{3+}$, a very strong oxidant [$E_{1/2}^{red}$ = 1.29 V (*vs.* SCE)], that can promote the oxidative decarboxylation of $\mathbf{1a}^-$.[18a] This event would deliver the acyl-like radical **B** and close the photoredox cycle. We have excluded a direct oxidative decarbocylation of $\mathbf{1a}^-$ by [$*Ru(bpy)_3^{2+}$] owing to (i) the high oxidation potential of




Scheme 4 Mechanistic pathways. DFT method: UB3LYP/6-31+G(d,p). The $\Delta G^{\ddagger}$ values are in kcal mol$^{-1}$.

**1a**$^{-}$ [$E^{ox}_{1/2}$ = 1.31 V (*vs.* SCE)] and (ii) Stern–Volmer analysis that revealed oxone and not **1a**$^{-}$ to quench [*Ru(bpy)$_3^{2+}$] (Scheme 4).[19]

From radical **B** three possible pathways can be envisaged. An additional SET oxidation would form the nitrile oxide **C** that upon [3+2] cycloaddition would deliver **D** (Path A). The oxidation potentials of many acyl radicals have been determined and they fell well in the range accessible by *Ru(bpy)$_3^{2+}$ thus supporting this scenario.[22] Alternatively, radical addition of **B** to the olefins (Pathways B and C) could deliver intermediates **E** and **F**. Indeed, DFT calculations revealed **B** to be an extremely nucleophilic radical (electrophilicity index[23] $\omega^{+}_{rc}$ = 0.45) and the addition reaction to both styrene and methyl acrylate to be very facile ($\Delta G^{\ddagger}$ = 2.0 and 1.3 kcal mol$^{-1}$ respectively).[19] From radical **E**, photoredox oxidation[24] would form a benzylic carbocation that upon cyclization would give **D**. In the case of Michael acceptors (Path C), photoredox oxidation of **F** is unlikely, and therefore a direct cyclization might take place giving ketyl radical **G** (calculated $\Delta G^{\ddagger}$ = 11.8 kcal mol$^{-1}$).[19] Final photoredox oxidation would form **D**.[25] In order to distinguish between these three Pathways, we performed Hammett analysis on the reaction between **1a** and *para*-substituted styrenes. This study gave a V-shaped Hammett plot that is consistent with the reaction going trough nitrile oxide **C** (Path A) and can be rationalised on the basis of a switch in frontier molecular orbitals interactions in the cycloaddition step going from electron rich to electron poor styrenes.[26]

In conclusion, we have developed the first visible-light mediated process that enables the generation of nitrile oxides and the easy synthesis of biologically relevant isoxazolines and isoxazoles. Future work will be aimed at expanding this double-oxidative approach to the generation of other dipoles.

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