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s-Tetrazine: robust and green photo-organocatalyst for aerobic oxidation of *N,N*-disubstituted-hydroxylamines to nitrones

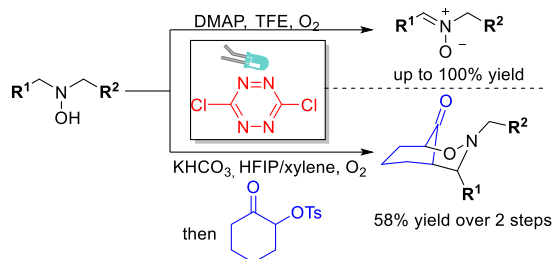
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Photocatalytic oxidation of hydroxamine



Photocatalytic one pot sequential (3+3) cycloaddition

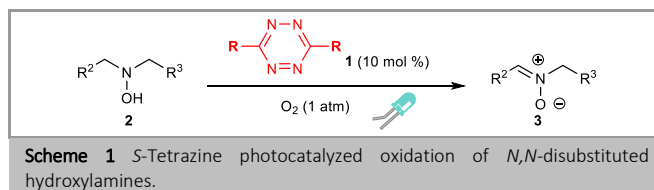
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Abstract: Efficient photocatalytic aerobic oxidative dehydrogenation reactions of *N,N*-disubstituted hydroxylamines to nitrones were developed with an *in situ* generated photocatalyst based on commercially available 3,6-dichlorotetrazine. This process affords a wide range of nitrones in high yields under mild conditions. In addition, an oxidative (3+3) cycloaddition between an oxallyl cation precursor and a hydroxylamine was also developed.

Key words s-Tetrazine, photo-organocatalyst, nitrones, sequential oxidative (3+3) cycloaddition.

Nitrones are an important class of functional group that have been extensively used as versatile intermediates in many organic reactions such as nucleophilic additions, radical additions, cycloaddition reactions, electrocyclization reactions etc.¹ In addition, nitrones such as α -phenyl *N*-tertiary-butyl nitrone (PBN) and 5,5-dimethyl-pyrroline *N*-oxide (DMPO) are widely used as spin-trapping reagents for the detection and identification of radicals formed in biological systems or chemical reactions.² Traditionally, nitrones are prepared by the condensation reaction between *N*-substituted hydroxylamines and carbonyl compounds in the presence of dehydrating agents.³ The alternative approach is the direct oxidation of easily available *N,N*-disubstituted-hydroxylamines⁴ to nitrones which avoids the manipulation of unstable aldehydes.⁵ However, although efficient, this latter oxidative procedure usually utilizes stoichiometric amounts of oxidants^{1e, 6} or catalytic amounts of toxic metals.⁷ To date, only one photocatalytic⁸ oxidation process using an expensive iridium complex has been reported.^{9a} Therefore, the development of efficient and more environmentally friendly synthesis of nitrones by oxidation of *N,N*-disubstituted hydroxylamines is still of great importance. Herein we communicate the first photo-organocatalytic aerobic oxidation of *N,N*-disubstituted-hydroxylamines, affording diverse nitrones in good yields under very mild reaction

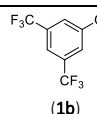

conditions using tetrazines, as cheap and easily available organic redox catalysts (Scheme 1).



As a part of our continuous interest in the development of photocatalytic and/or organocatalytic aerobic oxidation,¹⁰ we have recently disclosed a new class of photooxidants, 3,6-disubstituted *s*-tetrazines.¹¹ Their efficiency was successfully demonstrated by their ability to mediate oxidative C–S bond functionalizations under visible light irradiation.¹² We also found that 3,6-disubstituted *s*-tetrazines in their ground states were efficient organocatalysts for the aerobic oxidative nitroso-Diels-Alder (NDA) reaction of *N*-arylhydroxylamines with dienecarbamates.¹³ Based on our previous works,^{12,13} we envisioned that 3,6-disubstituted *s*-tetrazines could catalyze the oxidation of *N,N*-disubstituted-hydroxylamines to nitrones. To test our hypothesis, we examined the oxidation of *N,N*-dibenzylhydroxylamine **2a** in the presence of 3,6-bis(2,2,2-trifluoroethoxy)-1,2,4,5-tetrazine (10 mol %) as a photocatalyst **1a** and 2,6-lutidine (2.0 equiv) as a base under visible light irradiation (green LEDs) and oxygen atmosphere. Pleasingly, the desired nitrone **3a** was obtained in 62% yield (Table 1, entry 1). Reaction with other *s*-tetrazines **1b–1d** resulted in lower yields (entries 2–4). The effect of solvent was also examined, and protic solvents such as 2,2,2-trifluoroethanol (TFE), ethanol (EtOH) and hexafluoroisopropanol (HFIP) improved significantly the yield (entries 7–9). Subsequently, a series of bases were investigated, revealing that DMAP was best, affording **3a** in 95% yield (entry 10). Yield decreased by using 1.0 equiv of DMAP (entry 13).

Replacing oxygen gas by air atmosphere (entry 14) diminished significantly the reaction efficiency. Inspired by our previous work, we were interested to evaluate the possibility to generate *in situ* the active photocatalyst **1a** from commercially available 3,6-dichlorotetrazine **1d**. Gratefully, this protocol using 10 mol% of **1d** and 2 equivalents of DMAP delivered **3a** in same yield (entry 15). None or only trace of nitron was observed in the absence of photosensitizer **1**, DMAP or oxygen (entries 16-18). However, when the reaction was carried out in the dark, the desired product was isolated in 52% yield (entry 19). Although less efficient than at its excited state, **1a** in the ground state in TFE can oxidize the *N,N*-disubstituted-hydroxylamines **2**. Finally, the photocatalytic aerobic oxidation was successfully performed on 1 mmol scale to produce the corresponding nitron in 82% yield after 8 h and in 95% after 16 h (entry 20).

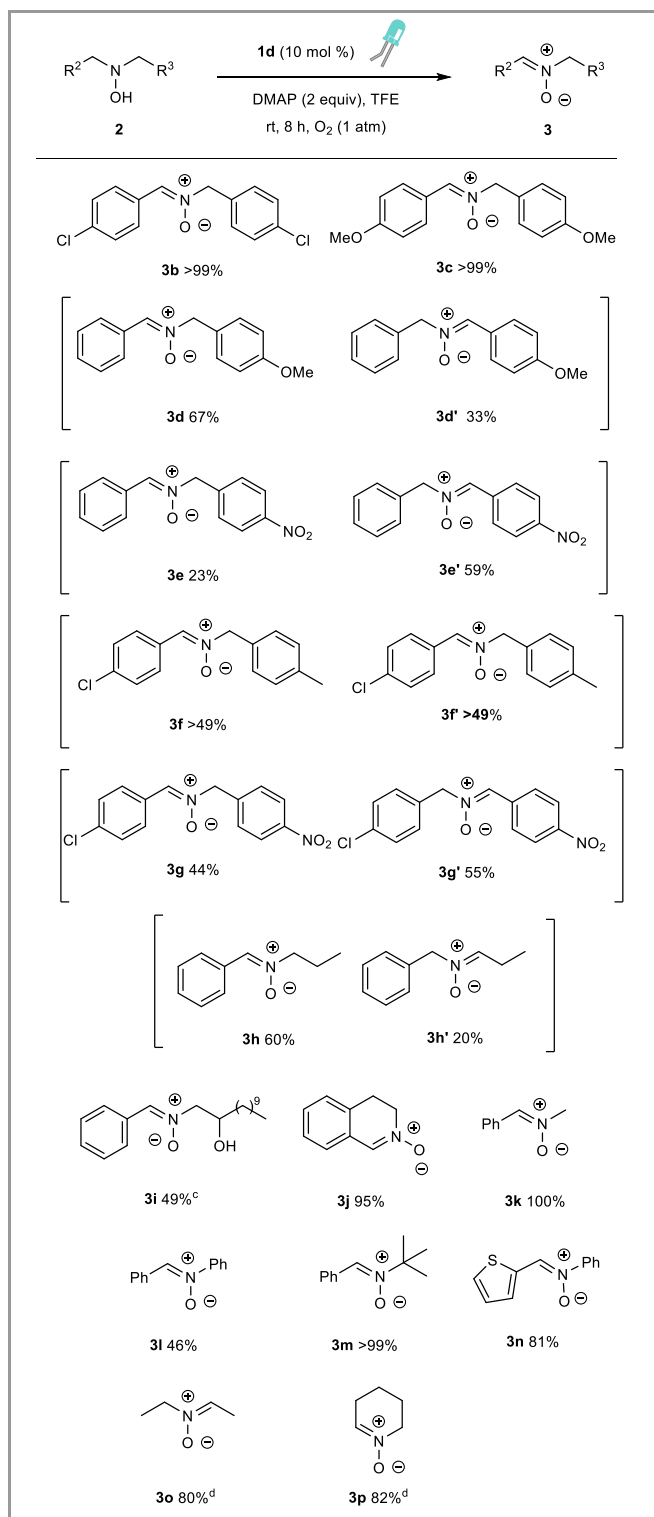
Table 1 Survey of reaction conditions for the photocatalyzed oxidation of **2a**.^a

Entry	R (1)	Base	Solvent	3a Yield (%) ^b
1	CF ₃ CH ₂ O- (1a)	2,6-lutidine	DCM	62
2	 (1b)	2,6-lutidine	DCM	55
3	 (1c)	2,6-lutidine	DCM	44
4	Cl (1d)	2,6-lutidine	DCM	38
5	1a	2,6-lutidine	CH ₃ CN	47
6	1a	2,6-lutidine	Toluene	24
7	1a	2,6-lutidine	EtOH	80
8	1a	2,6-lutidine	TFE	80
9	1a	2,6-lutidine	HFIP	78
10	1a	DMAP	TFE	95
11	1a	K ₂ CO ₃	TFE	71
12	1a	Cs ₂ CO ₃	TFE	58
13 ^c	1a	DMAP	TFE	49
14 ^d	1a	DMAP	TFE	65
15	1d	DMAP	TFE	95
16 ^e	1d	DMAP	TFE	trace
17	1d	-	TFE	26
18	-	DMAP	TFE	-
19 ^f	1d	DMAP	TFE	52
20 ^g	1d	DMAP	TFE	82(95) ^h

^a General conditions: *N,N*-dibenzylhydroxylamine **2a** (0.1 mmol), base (0.21 mmol), **1** (0.01 mmol), in solvent (1 mL) irradiated overnight with 7.2 W green LEDs ($\lambda = 535$ nm) at rt. ^b Yields refer to chromatographically pure products. ^c With 1.0 equiv of base. ^d Reaction conducted under air atmosphere. ^e Reaction conducted under argon atmosphere. ^f Reaction performed in the dark. ^g 1 mmol scale relative to **2a**. ^h After 16 h.

With the optimum conditions in hand, the scope of the photooxidation was next examined with different *N,N*-dibenzylhydroxylamines **3b-3g** in the presence of 3,6-dichlorotetrazine **1d** under green LEDs irradiation (Scheme 2).

As a result, all reactions provided the corresponding nitrones in excellent yields

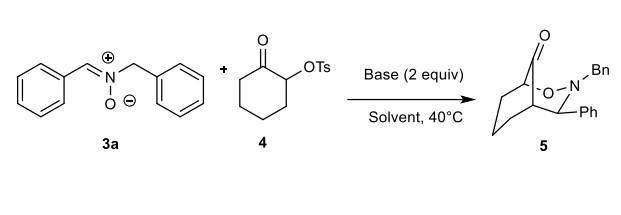


(>90%). Symmetric benzylhydroxylamines bearing electron-rich and -poor aromatic substituents reacted smoothly to give the corresponding nitrones **3b** and **3c** in nearly quantitative yields.

The oxidation of unsymmetrical dibenzylhydroxylamines afforded 82-100% yields of two easily separable regioisomeric nitrones (**3d-3h**) in a ratio going from 2:1 to 1:1. These results indicate that the electronic properties of aromatic rings have little effect on the regioselectivity in the nitron formation. On the other hand, the unsymmetrical mono-benzylated secondary hydroxylamines (**2k**) led to the regioselective synthesis of stabilized nitrones **3k** in excellent yield. In addition, the cyclic hydroxylamine **2j** worked well to afford a suitable precursor **3j** for the construction of isoquinoline alkaloids. It worth noticing that this photooxidative process was also compatible with free alcohol (**3i**). The *N*-phenyl hydroxylamine **2l** worked also well to form the corresponding nitron **3l** in moderate yield. The presence of heteroaromatic rings such as thiophene was also tolerated. The commonly used free-radical spin trapping agent, α -phenyl *N*-tertiary-butyl nitron (**3m**) was synthesized in quantitative yield from easily available *N*-benzyl-*N*-(tert-butyl)hydroxylamine (**2m**).¹⁴ Pleasingly, replacing DMAP with potassium hydrogenocarbonate as a base allowed the isolation of nitrones **3o-p** in good yields from symmetrically disubstituted *N,N*-dialkylhydroxylamines (**2o-p**).

To demonstrate the applicability of this photocatalytic oxidative reaction, we were interested to explore the feasibility of developing oxidative 1,3-dipolar (3+3)-cycloaddition between *N,N*-disubstituted hydroxylamines **2** and oxyallyl cations. In 2018, Archambeau¹⁵ and Rawal¹⁶ groups independently reported an efficient (3+3)-cycloaddition of nitrones and α -tosyl ketones as stable precursors of oxyallyl cations. Given that cycloadditions were carried out in presence of a base and protic solvents, we reasoned that this reaction could be compatible with our photooxidative process. Toward this end, we initially tested the cycloaddition of α -tosyl cyclohexanone **4** with preformed nitrones **3a** (Table 2). Using our optimized conditions for nitron formation, the desired 1,2-oxazinane **5** was isolated in 15% yield (entry 1). Variations of the base and the solvent revealed that the yield slightly increased from 15% to 35% using KHCO_3 in a mixture of HFIP/xylenes (entries 2-3).¹⁶ It was subsequently found that reaction with 3 equivalents of **4** improved the yield to 58% (entry 4).

Table 2 Survey of reaction conditions for the (3+3) cycloaddition.^a

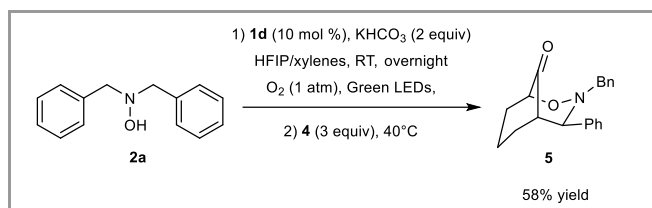


Entry	Base	Solvent	γ	5 Yield (%) ^b
1	DMAP	TFE	1.5	15
2	KHCO_3	TFE	1.5	26
3	KHCO_3	HFIP/xylenes (1:1)	1.5	35
4	KHCO_3	HFIP/xylenes (1:1)	3	58

^a General condition: **3a** (0.1 mmol), **4** ($\gamma \times 0.1$ mmol), base (0.2 mmol), in solvent (1 mL) for 15 h. ^b Yields refer to chromatographically pure products.

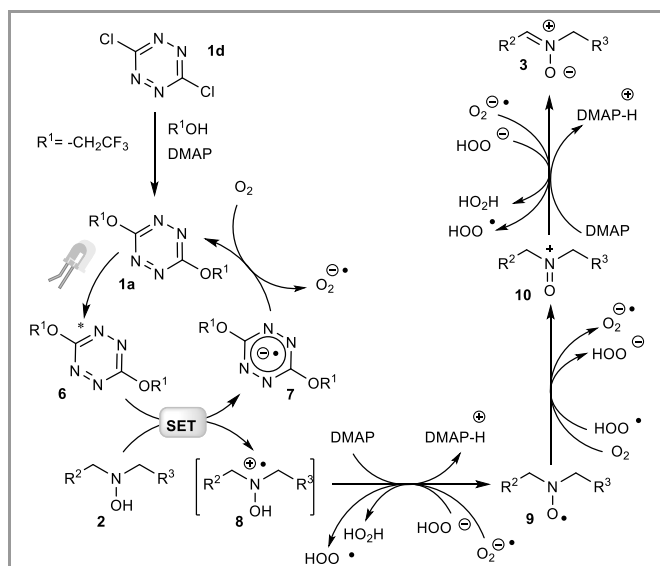
Encouraged by this result, the photocatalytic oxidative (3+3)-cycloaddition between **2a** and **4** with tetrazine **1d** was further

evaluated under these reaction conditions. While no reaction took place when the reagents were combined all together, a sequential one-pot two step oxidation/cycloaddition procedure afforded the desired 1,2-oxazinane **5** in 58% yield (Scheme 3).



Scheme 3 Tetrazine-catalyzed aerobic oxidative (3+3) cycloaddition.

The following control experiments were conducted to probe the mechanism. In the presence of the superoxide radical anion quencher TEMPO, the formation of nitron **3a** was inhibited, suggesting that superoxide radical anion ($\text{O}_2^{\bullet-}$) is involved in this reaction.¹⁷ Then, the oxidation potential of *N,N*-dibenzylhydroxylamine **2a** was determined by cyclic voltammetry as +0.14 V vs SCE in DCM (see supporting information). This data indicated that the oxidation of **2a** by excited 3,6-bis(2,2,2-trifluoroethoxy)-1,2,4,5-tetrazine (**1a**) ($E^0(1a^*/1a^{\bullet-})=1.59$ V vs SCE in DCM).^{12,13} is thermodynamically favorable. To confirm this, Stern-Volmer fluorescence quenching studies were performed with *s*-tetrazine **1a** (see supporting information). Fluorescence intensity dramatically decreased when hydroxylamine **2a** was introduced. These linear relationships mainly support that the excited organocatalyst is reductively quenched by hydroxylamine. On the basis of the above experiments and previous mechanistic studies,^{8,12,13} a plausible mechanism for visible-light-induced aerobic oxidation of hydroxylamines can be proposed (Scheme 4). Initial oxidation of hydroxylamine **2** by the visible-light-excited (*in situ* generated) photocatalyst **1a** produces the hydroxylammonium radical cation **8** and tetrazine anion-radical **7**. The ground state catalyst **1a** is regenerated by the reduction of oxygen generating the oxygen superoxide radical anion ($\text{O}_2^{\bullet-}$). Simultaneously, the radical hydroxylammonium cation-radical **8** undergoes deprotonation by DMAP, $\text{O}_2^{\bullet-}$ or HOO^{\bullet} to afford an *O*-centered radical **9**. This resulting radical is quickly further oxidized by either oxygen or any ROS like the hydroperoxide radical (HOO^{\bullet}) affording **10**. Finally, the base-mediated deprotonation of **10** leads to the desired nitron **3**. Another possible mechanism without light irradiation was proposed (See supporting information). In the dark, the tetrazine ($E^0(1a/1a^{\bullet-})=-0.58$ V vs SCE in DCM)^{12,13} in presence of DMAP¹⁸ could simultaneously oxidize and deprotonate the hydroxylamine (*via* a proton-coupled electron transfer (PCET)-type mechanism)¹⁹ to form the final nitron.¹³ Next, the reduced organocatalyst is oxidized by oxygen, thereby completing the catalytic cycle (See supporting information).



Scheme 4 Proposed mechanism for the aerobic photooxidation of hydroxylamines to nitrones.

In conclusion, we have devised a photo-organocatalytic protocol for the synthesis of nitrones through aerobic oxidation of *N,N*-disubstituted-hydroxylamines. The *in situ* formed 3,6-bis(2,2,2-trifluoroethoxy)-1,2,4,5-tetrazine was found to exhibit a high catalytic activity in forming these products. This catalytic transformation allowed atom economical and direct synthesis of nitrones. The reaction has a broad substrate scope affording various nitrones in excellent yields. We have also developed an oxidative (3+3) cycloaddition of an oxyallyl cation with a nitronium formed *in situ* from oxidation of a *N,N*-disubstituted-hydroxylamine.

Funding Information

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

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- (20) **Representative procedure for synthesis of compound 3:** In a flame-dried tube ($\emptyset = 10$ mm) were placed *N,N*-disubstituted hydroxylamine **2** (0.1 mmol, 1 equiv), 3,6-dichlorotetrazine **1d** (2 mg, 0.01 mmol, 0.1 equiv), DMAP (26 mg, 0.21 mmol, 2.1 equiv) and TFE (1 mL). The solution was flushed with a balloon of O₂ for 1 min. The balloon was left on the top of the tube to maintain the O₂ atmosphere and the reaction was stirred overnight under green light irradiation. After completion, TFE was removed under vacuum and the residue was purified by silica gel flash chromatography (PE/EtOAc 2:1). **3a**: ¹H NMR (300 MHz, CDCl₃) δ 8.21 (s, 2H), 7.47 (s, 2H), 7.40 (s, 7H), 5.06 (s, 2H).