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Visible-Light-Induced Photoaddition of *N*-Nitrosoalkylamines to Alkenes: One-Pot Tandem Approach to 1,2-Diamination of Alkenes from Secondary Amines

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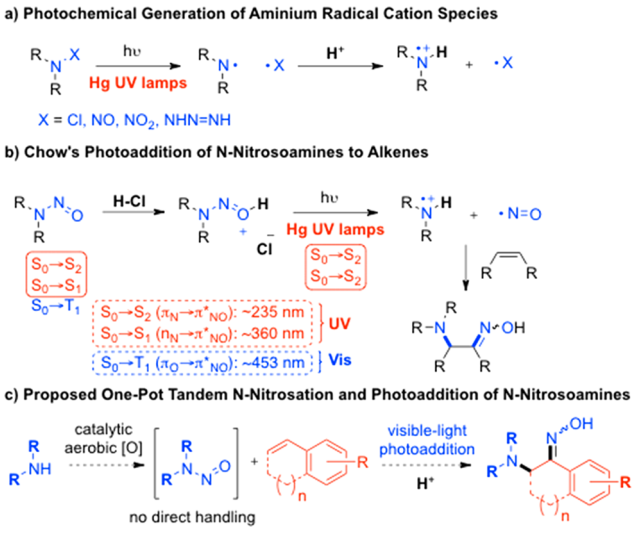
ABSTRACT: The generation of aminium radical cation species from *N*-nitrosoamines is disclosed for the first time through visible-light excitation at 453 nm. The developed visible-light-promoted photoaddition reaction of *N*-nitrosoamines to alkenes was combined with the *o*-NQ-catalyzed aerobic oxidation protocol of amines to telescope the direct handling of harmful *N*-nitroso compounds, where the desired α-amino oxime derivatives were obtained in a one-pot tandem N-nitrosation and photoaddition sequence.

The synthetic utility of nitrogen-centered radicals has been widely recognized in the functionalization of amine derivatives through new C−N bond formations.[1] In particular, the single-electron oxidation of amines to their corresponding aminium radical cations allows the facile addition to alkenes and alkynes,[2] and the recent development of photoredox catalysis amply demonstrates the synthetic powers of photoaddition of amines to C−C π bonds.[3] While N−X homolytic cleavage (X = Cl, NO, NO_2, or NHN═NH) in the presence of acids has been known as the best strategy for generating aminium radical cations upon UV irradiation (Scheme 1a),[2,4] the traditional photochemical experiment setups using mercury vapor pressure lamps in immersion-well reactors are not readily accessible for the majority of synthetic laboratories. In addition, the hazard associated with the use of strong UV lights often calls for special safety measures in conducting the photochemical reactions.[5] Among the photoinduced N−X cleavage reaction pathways, the *N*-nitrosoamines have received a great deal of attention from the scientific community after the initial reports of their biological function as potent nitric oxide donors, but with significant carcinogenic properties.[6] Because nitrosoamines are omnipresent in food, tobacco smoke, and drinking water, the removal of such contaminants under photolytic conditions has been the focus of intense investigation.[7] Nevertheless, no unified photochemical decomposition pathway of *N*-nitrosoamines has been established to date, and the growing concerns about *N*-nitrosoamine-contaminated pharmaceuticals still pose grave health risks to patients.[8]

Scheme 1. Photochemical Generation of Aminium Radical Cations from *N*-Nitrosoamines



The photochemistry of *N*-nitrosoamines was pioneered by the laboratory of Chow in 1965, where the N−NO bond was homoloytically cleaved by UV-light and added to alkenes (Scheme 1b).[9] The key to the successful generation of aminium radical cation species exclusively relied on the protonated form of the *N*-nitrosoamines using 1 equiv of HCl. Thus, under the typical photochemical reaction setup in an external cooling immersion-well reactor with a Hanovia UV lamp, a mixture of *N*-nitrosoamines and alkenes was irradiated at 254 nm (with a Vycor filter) to induce the photoaddition of

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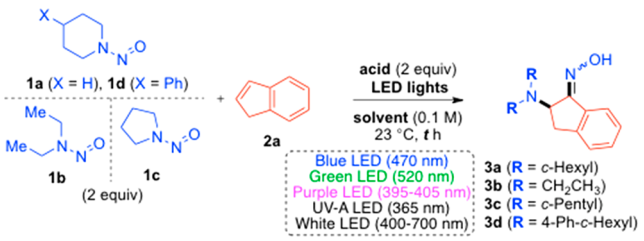
the aminium radical cation to alkenes to give the α-amino oxime derivatives. The photochemical behaviors of *N*-nitrosoamines have been studied in detail,[10] and the triplet and singlet excited-state energy transitions of *N*-nitrosoamines were identified as $S_0 \rightarrow S_2$ ($\pi_N \rightarrow \pi^*_{NO}$), $S_0 \rightarrow S_1$ ($n_N \rightarrow \pi^*_{NO}$), and $S_0 \rightarrow T_1$ ($\pi_O \rightarrow \pi^*_{NO}$).[11] The burning question of whether visible-light excitation of $S_0 \rightarrow T_1$ ($\pi_O \rightarrow \pi^*_{NO}$) at 453 nm could induce the homolytic cleavage of *N*-nitrosoamines to generate the aminium radical cations arises, given that the $S_0 \rightarrow S_2$ ($\pi_N \rightarrow \pi^*_{NO}$) and $S_0 \rightarrow S_1$ ($n_N \rightarrow \pi^*_{NO}$) transitions are related to the homolytic N−NO bond cleavage at 230 and 360 nm, respectively.[11a] The implication of such visible-light-induced aminium radical cation formation will be significant in understanding of photochemical pathways of *N*-nitrosoamines as well as the synthetic application of in situ-generated aminium radical cations. Herein, we disclose the generation of aminium radical cations from *N*-nitrosoamines under visible-light irradiation for the first time, and the subsequent reaction with alkenes to give the α-amino oxime derivatives (Scheme 1c).

The photochemical N−NO bond cleavage of *N*-nitrosoamines was investigated in the presence of indene **2a** (Table 1). Thus, the irradiation of *N*-nitrosopiperidine **1a** and **2a** using blue LED light did not promote the formation of the aminium radical cation (entry 1). The protonated form of **1a** with HCl failed to undergo the desired N−NO bond cleavage in the absence of a light source (entry 2). The use of visible light with blue LED light at 470 nm drastically changed the outcome of the reaction, where protonated **1a** smoothly underwent the photoinduced N−NO bond cleavage, and subsequently reacted with alkene **2a** to give the corresponding α-amino oxime **3a** as respective (*Z*) and (*E*) isomers in a combined yield of 93% (entry 3). The acidity−reactivity relationship of protonated **1a** was further examined using different acids (entries 4−10), and the employment of acids with pK_a values of no less than −0.44 was beneficial to the current visible-light-promoted photoaddition of *N*-nitrosopiperidine **1a** to alkene **2a** (TfOH pK_a = −14, Tf_2NH pK_a = −11.9, HCl pK_a = −8.0, MsOH pK_a = −2.6, TsOH pK_a = −0.51, HBF_4 pK_a = −0.44, HCOOH pK_a = 3.77, and $PhCO_2H$ pK_a = 4.2). Solvent screening also revealed that the current photoaddition reaction was not sensitive to the nature of solvents, providing good to excellent yields of **3a** in various organic solvents (entries 11−17). The wavelength of the applied light source significantly influenced the reaction rates (entries 18−21). Thus, the reaction under the green LEDs gave only 24% conversion within 48 h (entry 18), whereas the reactions under purple light and UV light significantly decreased the reaction time to 6 and 2 h, respectively (entries 19 and 20, respectively). The reaction could be also performed under white light without much change in the reaction time or chemical yield (entry 21). The use of 1 equiv of $TsOH{\cdot}H_2O$ or **1a** was tested, and the slightly reduced yields of **3a** were observed to be 77−78% (entries 22 and 23). As a result of the optimization process, the use of $TsOH{\cdot}H_2O$ was chosen to broaden the substrate scope due to the easy handling of the solid acid. Also, the current photoaddition reaction could be equally performed in laboratory grade EtOH, implying the beneficial effect of a nontoxic solvent.[12] The reaction of *N*-nitrosodiethylamine **1b** resulted in the formation of **3b** in 62% yield under purple LED light in 48 h (entry 24). The use of *N*-nitrosopyrrolidine **1c** and *N*-nitroso 4-phenylpiperidine **1d** also provided the desired α-amino oximes **3c** and **3d**, respectively,

Table 1. Optimization of Photoaddition of *N*-Nitrosoamines to Indene[a]



entry	1/acid	*hν*	solvent	yield (%)[b]
1	**1a**/−	Blue LED's	MeOH	0
2	**1a**/HCl	−	MeOH	0
3	**1a**/HCl	blue LEDs	MeOH	93
4	**1a**/TfOH	blue LEDs	MeOH	95
5	**1a**/$HNTf_2$	blue LEDs	MeOH	84
6	**1a**/MsOH	blue LEDs	MeOH	96
7	**1a**/TsOH	blue LEDs	MeOH	93 (92)
8	**1a**/HBF_4	blue LEDs	MeOH	82
9	**1a**/HCOOH	blue LEDs	MeOH	7
10	**1a**/$PhCO_2H$	blue LEDs	MeOH	0
11	**1a**/TsOH	blue LEDs	EtOH	88
12	**1a**/TsOH	blue LEDs	*i*-PrOH	80
13	**1a**/TsOH	blue LEDs	MeCN	39
14	**1a**/TsOH	blue LEDs	acetone	80
15	**1a**/TsOH	blue LEDs	EtOAc	49
16	**1a**/TsOH	blue LEDs	DMF	77
17	**1a**/TsOH	blue LEDs	DMSO	89
18[c]	**1a**/TsOH	green LEDs	MeOH	24
19[d]	**1a**/TsOH	purple LEDs	MeOH	89
20[e]	**1a**/TsOH	UV-A LEDs	MeOH	79
21[f]	**1a**/TsOH	white LEDs	MeOH	93
22[g]	**1a**/TsOH	white LEDs	MeOH	77
23[g,h]	**1a**/TsOH	white LEDs	MeOH	78
24[c]	**1b**/TsOH	purple LEDs	EtOH	62
25[c]	**1c**/TsOH	purple LEDs	EtOH	66
26[c]	**1d**/TsOH	purple LEDs	EtOH	72

[a]Reaction conditions: **1** (0.6 mmol), **2a** (0.3 mmol), and acid (0.6 mmol) in degassed solvent (0.1 M) under LED light at 23 °C for 16 h. [b]Yield determined by ^1H NMR using an internal standard (isolated yield in parentheses). [c]Reaction for 48 h. [d]Reaction for 6 h. [e]Reaction for 2 h. [f]Reaction for 15 h. [g]Reaction with 1 equiv of TsOH. [h]Reaction with 1 equiv of **1a**.

in 66−72% yields (entries 25 and 26, respectively). Thus, the conformation of *N*-nitrosoamines greatly influenced the photoaddition reactions of *N*-nitrosoamines.[13] It is noteworthy that the addition of aminium radical cations to **2a** was highly selective, resulting in the regioselective formation of α-amino oximes from the more stable benzylic radical intermediate species. This observation concurred with Chow's results.[9]

While the visible-light-promoted photoaddition of *N*-nitrosoamines to alkenes possesses high synthetic potential in the preparation of 1,2-diamine derivatives,[14] the toxicity associated with the *N*-nitrosoamines prompted the in situ generation of *N*-nitrosoamines through the aerobic oxidation of amines (Scheme 2). Thus, piperidine was aerobically oxidized to *N*-nitrosopiperidine **1a** in the presence of an *o*-naphthoquinone (*o*-NQ) catalyst.[15] The subsequent one-pot photoaddition reaction did not occur under white LED light (400−700 nm), although the use of UV-A LED light (365 nm) provided desired product **3a** in 60% yield (Scheme 2a). Because the

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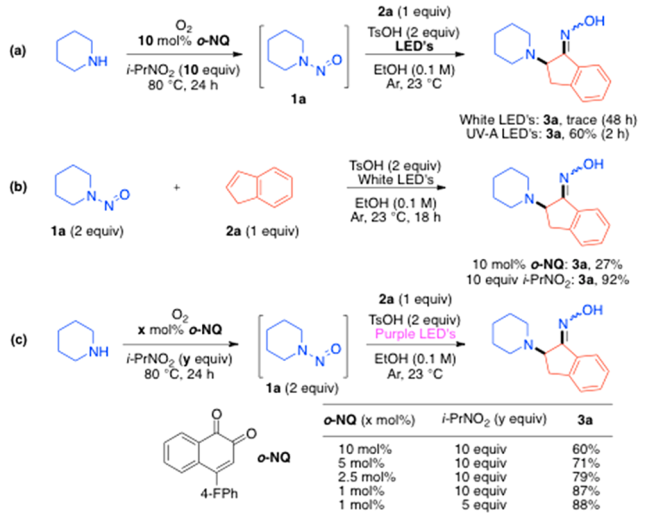
Scheme 2. One-Pot Tandem Functionalization

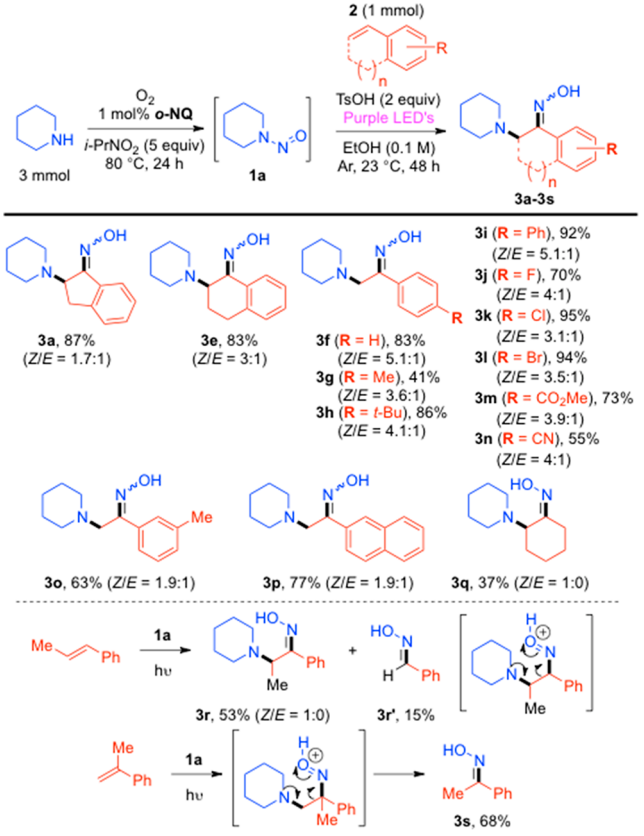


"NO" source, *i*-$PrNO_2$, was visible-light transparent, the *o*-NQ catalyst with a dark color was suspected for inefficient light transmission. Indeed, the control experiments with added *i*-$PrNO_2$ and *o*-NQ catalyst confirmed the significant interference of visible-light transmission by the *o*-NQ catalyst (Scheme 2b). Thus, to better transmit the visible light into the colored reaction solution, purple LED light (395 nm) was utilized. In addition, the amount of *o*-NQ catalyst in the aerobic N-nitrosation was decreased to 1 mol %, while employing 5 equiv of *i*-$PrNO_2$ (Scheme 2c).

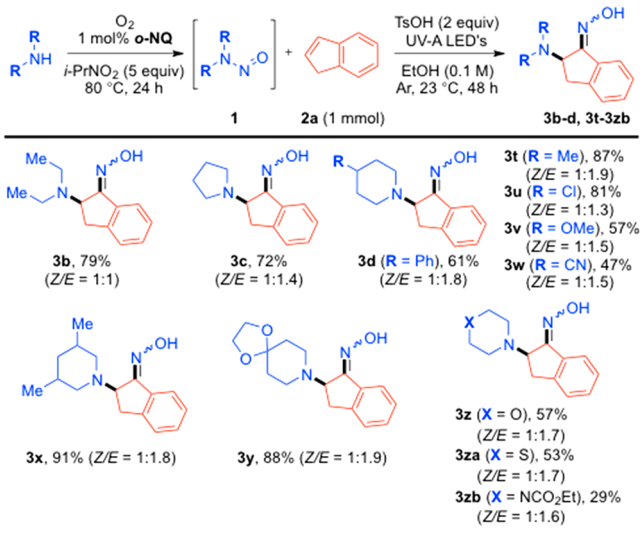
With the optimized one-pot tandem N-nitrosation and visible-light-promoted photoaddition reaction sequence, the alkene substrate scope on a 1 mmol scale was examined with in situ-generated *N*-nitrosopiperidine **1a** (Scheme 3). While the dark colored reaction mixture from the aerobic N-nitrosation required a more penetrating light source, the use of indene **2a** and 1,2-dihydronaphthalene **2b** in the one-pot tandem reaction sequence provided desired products **3a** and **3e** in 83−87% yields. The electronically diverse styrenes were also suitable under the current one-pot photoaddition reaction conditions, providing products **3f**−**3o** in 55−95% yields, with the exception of **3g** in a rather low yield of 41%. The reaction could also be applied to 2-vinylnaphthalene and cyclohexene, where desired products **3p** and **3q** were obtained in 77% and 37% yields, respectively. The subjection of *trans*-*β*-methylstyrene provided the corresponding *α*-amino oxime **3r** in 53% yield along with (*E*)-benzaldehyde oxime **3r′** in 15% yield through the carbon−carbon bond cleavage pathway instead of the tautomerization pathway to the oxime moiety.[9b] Likewise, the use of *α*-methylstyrene exclusively promoted the carbon−carbon bond cleavage pathway to give (*E*)-acetophenone oxime **3s** in 68% yield.

The one-pot tandem N-nitrosation and photoaddition sequence was further examined using various secondary amines (Scheme 4). In situ-generated *N*-nitrosodiethylamine **1b** from the aerobic N-nitrosation reaction was dark-colored and thus required the more penetrating light source, UV-A LED lights, to promote the photoaddition to furnish product **3b** in 79% yield. The tandem reaction sequence could be applied to *N*-nitrosopyrrolidine **1c** as well as *N*-nitrosopiperidine derivatives, where good functional group tolerance was demonstrated (**3c**−**3d** and **3t**−**3y**). In addition, the use of morpholine,

Scheme 3. Alkene Substrate Scope for the One-Pot Tandem N-Nitrosation and Photoaddition Sequence



Scheme 4. Amine Substrate Scope for the One-Pot Tandem N-Nitrosation and Photoaddition Sequence



thiomorpholine, and piperazine derivatives led to the corresponding *α*-amino oximes in 29−57% yields.

The current visible-light-promoted aminium radical cation formation from the direct excitation of the protonated *N*-nitrosoamine via the $S_0 \rightarrow T_1$ ($\pi_O \rightarrow \pi^*_{NO}$) transition greatly improved the practicality of photoaddition of *N*-nitrosoamines to alkenes. Thus, what appears to be a negligible absorption peak of the $S_0 \rightarrow T_1$ ($\pi_O \rightarrow \pi^*_{NO}$) transition at 450 nm was sufficient to induce homolytic N−NO bond cleavage under the

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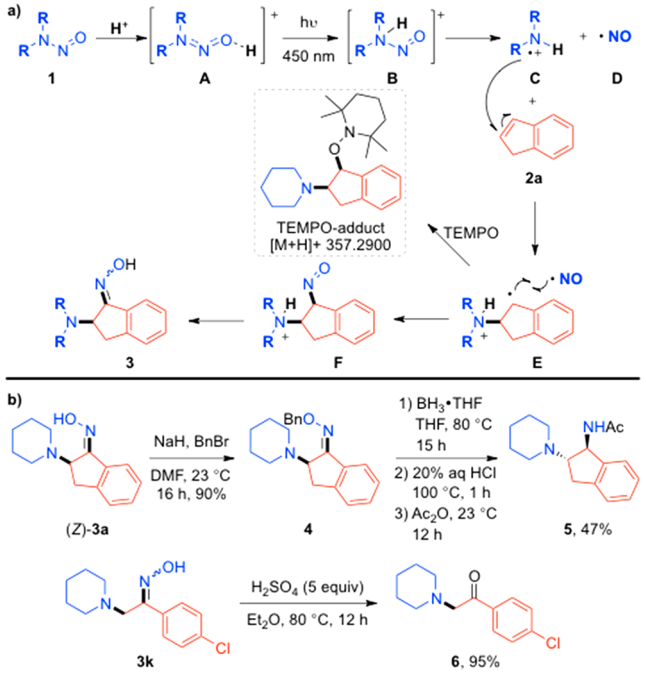
visible-light condition. The absorption peaks of *N*-nitrosoamines at 450 nm in various organic solvents were weak, and the intensity of the corresponding peaks did not change after the protonation (see the Supporting Information for UV−vis spectra). Previously, Chow and co-workers suggested that the triplet excited-state (T_1) of *N*-nitrosoamines do not lead to an irreversible chemical change because (1) when the $S_0 \rightarrow T_1$ transition band at 450 nm was excited at 77 K, the phosphorescence centered at 550 nm was observed and (2) no chemical reaction was observed in the presence of triplet sensitizers.[11a] However, a recent theoretical calculation contradicted the reactivity of the triplet excited state (T_1), estimating the homolytic and adiabatic N−NO bond dissociation of T_1 with 3.1 kcal/mol after excitation from S_0.[16] Thus, a plausible reaction mechanism for the visible-light-promoted photoaddition of *N*-nitrosoamines to alkenes is proposed on the basis of the photochemical decomposition of their triplet excited state of the N−NO bond (Scheme 5a). In this

Scheme 5. A Plausible Photoaddition Mechanism and Functionalization of α-Amino Oximes



scenario, protonated *N*-nitrosoamine **A** is photolytically transformed to *N*-nitrosoammonium ion **B** that is readily homolytically cleaved to give aminium radical cation **C** and nitric oxide **D**. Because aminium radical cation **C** is known to add to alkenes faster than it abstracts hydrogen from MeOH by a factor of 5000,[17] resulting carbon radical **E** is recombined with nitric oxide **D**. The tautomerization of **F** finally leads to α-amino oximes **3**. The involvement of carbon radical **E** was supported by the TEMPO adduct when the reaction was performed with a radical inhibitor. α-Amino oxime products **3** could be selectively transformed to *trans*-diamine **5** or hydrolyzed to the corresponding ketone **6** in good yields (Scheme 5b).

In summary, we have developed the one-pot tandem N-nitrosation of amines and photoaddition reaction to alkenes. The use of visible-light-promoted photoaddition of *N*-nitrosoamines to alkenes was disclosed for the first time through the unprecedented excitation of the triplet state (T_1) at 453 nm. Thus, the current method boasts the immersion photochemical apparatus-free visible-light-promoted photochemical reaction. In addition, the developed reaction sequence does not necessitate the handling of harmful *N*-nitroso compounds and also utilizes a nontoxic solvent, EtOH. Given that the decomposition pathways of *N*-nitroso compounds are of great interest to the scientific community, the current one-pot tandem N-nitrosation and photoaddition reaction sequence should stimulate considerable interest in the photochemical functionalization of *N*-nitrosoamines.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00786.

Experimental procedures, characterization data for all compounds, and NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds (*Z*)-**3a**−**3z**, (*E*)-**3a′**−**3z′**, and **4**−**6** (ZIP)

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Notes

The authors declare no competing financial interest.

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