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Photocatalytic Generation of Nitrenes for Rapid Diaziridination

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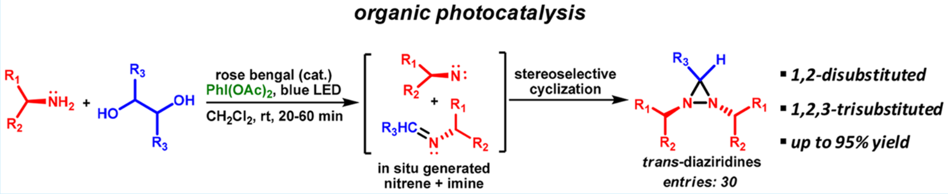
Supporting Information



ABSTRACT: A blue LED, an organic photocatalyst (rose bengal), and the Lewis acid like oxidant $PhI(OAc)_2$ were utilized to generate nitrene intermediates through reactions of 1,2-diols and aliphatic amines under mild reaction conditions. A versatile and rapid diaziridination strategy was established to construct functionalized 1,2-disubstituted diaziridines, diaziridines with chiral substituents, and 1,2,3-trisubstituted analogues with excellent reaction rates, yields, and stereoselectivities. Control and labeling experiments to elucidate the mechanism of this elegant metal-free photocatalyzed cyclization reaction were performed.

Cleavage and construction of bonds are powerful biochemical processes that occur frequently in nature in the syntheses of a wide range of natural products. Photocatalytic reactions inspire chemists and physicists to improve the efficiency of organic syntheses using inexpensive visible light. Several photoredox strategies for organic syntheses have been reported such as the direct excitation of substrates by highly energetic-ultraviolet light, abundant sunlight, and recently developed, energy-efficient, light-emitting diode (LED) sources.[1] Despite the great potential for using inexpensive and nonhazardous organic photocatalysis in synthesis, visible light-driven photocatalysis is still not a common tool for organic synthesis in either academia or industry. The limited usage of this strategy is due to drawbacks, including generally following radical mechanisms and slow reaction rates, and more importantly, the reactions typically do not pass through nitrenes or other common reaction pathways.[1e] Depending on their reduction potentials, conventional transition metal–ligand complexes are generally more effective for light absorption and for catalyzing light-induced electron-transfer reactions.[2] Organic photocatalysts are more attractive than their metal analogues because of their low cost, high solubility, simple handling procedures, and low environmental toxicity. Flavin, perylenediimide (PDI), rhodamine-6G, eosin Y, rose bengal, and a few other organic compounds[3] are receiving a substantial amount of attention as light absorbers in some photocatalytic reactions. The development of light-driven methods for generating widely used nitrene species is an ongoing challenge, and the successful development of such a method under mild, metal-free conditions would open up a new avenue for photocatalyzed synthetic chemistry beyond the existing radical approaches.

Diaziridine (1,2-diazacyclopropane) is one of the smallest privileged structures in organic chemistry, and its functionalized derivatives are often found in applications such as anticancer/antitumor agents, cytochrome P450 2B6/sterol-*O*-acetyltransferase inhibitors, pharmaceutical treatments for neurodegenerative disorders, neurotropic and antidepressant medicines,[4] rocket fuels, fragrance release mechanisms, and ultrafast spectroscopy techniques.[5] Diaziridines are frequently used as synthons for dipolar cycloadditions, ring expansions, alkylations, and the syntheses of carbenes and N-heterocycles.[6] In addition to the early reports on diaziridines,[7] modern syntheses are focused on hydroxylamine-*O*-sulfonic acid[8] or ethyl nosyloxycarbamate[9] mediated condensations of carbonyl compounds, amines, and ammonia/*N*-chloramines to generate primarily the 1,3-disubstituted diaziridines and its analogues. Most of the reported methods are limited by very slow reaction rates, the necessity of specially designed precursors, metal catalysts, and costly reagents. Direct syntheses of valuable 1,2-disubstituted diaziridines and diaziridines with chiral substituents are very rarely explored. To this end, Trapp reported an interesting route to diaziridines through 1,3-diamine formation, N–N coupling for enantioseparations,[10a] and sterodynamics of 1,2-dialkyldiaziridines.[10b−d] Direct C–N[11] and N–N[12] coupling reactions are attractive and challenging processes as they furnish a wide range of valuable N-bearing heterocycles and functional compounds. We communicate herein our preliminary results on blue LED-driven, metal-free photocatalysis for the in situ generation of nitrene and imine intermediates using inexpensive and readily available 1,2-diols, aliphatic amines, and hypervalent iodine for the construction of highly strained 1,2-disubstituted, diaziridines with chiral substituents, and 1,2,3-trisubstituted diaziridines and with excellent reaction rates and stereoselectivities.

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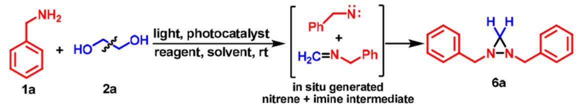
We envisioned the in situ generation of nitrene and imine intermediates through the treatment of amines and 1,2-diols with an efficient nonmetallic oxidant (Table 1). Several groups, including our own, have confirmed the strong Lewis acidity of λ^3-iodines,[13] so the use of a suitable analogue may efficiently furnish the desired nitrene intermediates under metal-free, photo-mediated conditions. On addition of PhI(OAc)$_2$ to a mixture of benzylamine (**1a**) and ethylene glycol (**2**) in toluene with rose bengal as the photocatalyst under irradiation by a blue LED, a new spot appeared by TLC. Characterization of the newly generated compound confirmed the formation of a diaziridine (**6a**) in moderate yield (68%, entry 1). Rose bengal and LED irradiation were essential in the catalytic cycle (entries 1−4), and rose bengal was found to be a more efficient photocatalyst than eosin Y (entry 5) or the commonly used metal catalyst Ir(PPy)$_3$ (entry 6).[2,3] The yield of the desired compound (**6a**) was lower (50−55%) when sunlight, a CFL, or a UV light were used as alternative light sources (entries 7−9). The reaction was almost halted by use of water as the reaction medium (entry 10). Polar organic solvents, such as MeCN and THF, afforded the desired product (**6a**) in moderate yield (60, 66%, entries 11 and 12). An excellent yield (95%) of **6a** was obtained when CH$_2$Cl$_2$ was used at ambient temperature (entry 13). The reaction between benzylamine (**1a**, 2 mmol), 1,2-diol (**2**, 0.5 mmol), and PhI(OAc)$_2$ (2 mmol) was rapid (20 min) in the presence of Rose bengal under irradiation by a blue LED. Although the nonmetallic oxidant PhI(OCOCF$_3$)$_2$ was effective for the transformation and afforded a comparable yield (entry 14), the reaction did not proceed in the presence of neutral PhIO or acidic HIO$_4$ (entries 15 and 16).

Table 1. Preliminary Observation of Photocatalytic Diaziridination

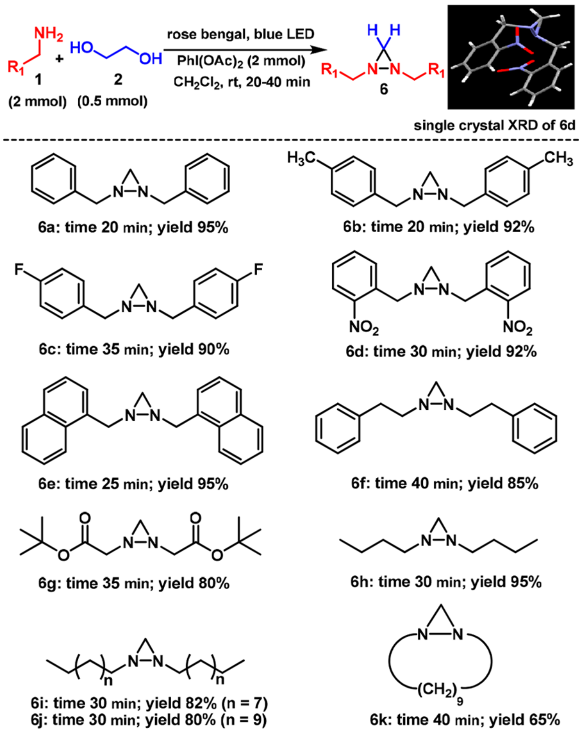


entry	reagent[a]	catalyst[b]	light	solvent[c]	time (h)	**6a**, yield[d] (%)
1	PhI(OAc)$_2$	RB[e]	LED[f]	PhCH$_3$	24	68
2	PhI(OAc)$_2$		LED[f]	PhCH$_3$	24	traces
3	PhI(OAc)$_2$	RB		PhCH$_3$	24	traces
4	PhI(OAc)$_2$			PhCH$_3$	24	traces
5	PhI(OAc)$_2$	Eosin Y	LED	PhCH$_3$	1	48
6	PhI(OAc)$_2$	Ir(PPy)$_3$	LED	PhCH$_3$	1	45
7	PhI(OAc)$_2$	RB	SunL[g]	PhCH$_3$	2	52
8	PhI(OAc)$_2$	RB	CFL[h]	PhCH$_3$	2	50
9	PhI(OAc)$_2$	RB	UV[i]	PhCH$_3$	2	55
10	PhI(OAc)$_2$	RB	LED	H$_2$O	24	traces
11	PhI(OAc)$_2$	RB	LED	MeCN	24	66
12	PhI(OAc)$_2$	RB	LED	THF	24	60
13	PhI(OAc)$_2$	RB	LED	CH$_2$Cl$_2$	0.3	95
14	PhIX$_2$[j]	RB	LED	CH$_2$Cl$_2$	1	85
15	PhIO	RB	LED	CH$_2$Cl$_2$	24	nd[k]
16	HIO$_4$	RB	LED	CH$_2$Cl$_2$	24	nd

[a] 2 mmol. [b] 1 mol %. [c] 5 mL. [d] Yield of the isolated product after purification through column chromatography. [e] Rose bengal. [f] 5 W blue LED, λ_{max} = 475 nm. [g] Sunlight. [h] 100 W CFL. [i] Ultraviolet light (30 W, λ_{max} = 365 nm). [j] X = OCOCF$_3$. [k] Not detected.

Following this initial success, the scope of the amine substrate that is used to trap the methylene group of the ethylene glycol for the direct syntheses of diaziridines was explored (Scheme 1). A wide variety of functional groups were well tolerated on the amines and afforded the desired diaziridines (**6a−k**). Aromatic residues such as phenyl groups (**6a**) bearing electron-donating (**6b**) or electron-withdrawing substituents (**6c,d**), naphthyl groups (**6e**), and benzyl groups (**6f**) were well tolerated. This mild process was also amenable to diaziridines bearing an aliphatic ester (**6g**) and long-chain hydrocarbons (**6h−j**). Interestingly, 1,9-diaminononane resulted in the most valuable structural architecture, a fused macrocyclic diaziridine (**6k**). This simple strategy furnished functionalized diaziridines in moderate to excellent yields (65−95%) in very short reaction times (20−40 min). We observed that secondary amines were not tolerated in the diaziridination reaction because they could not generate the nitrenes required to build the smallest dinitrogen-cyclic compound through the construction of new N−N and N−C bonds. When aromatic primary amines were used, the yields of the desired *N*-heterocycles were drastically reduced due to the rapid destruction of the PhI(OAc)$_2$ by the anilines. Formation of thermodynamically stable *trans*-diaziridines was confirmed by spectroscopic analyses (SI) and analyses of single-crystal X-ray diffraction data of the product **6d**.[14]

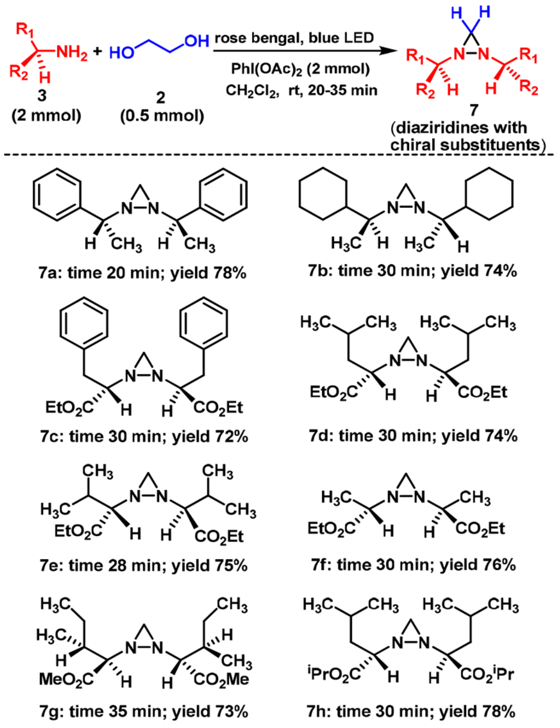
Scheme 1. Synthesis of Structurally Diverse Diaziridines



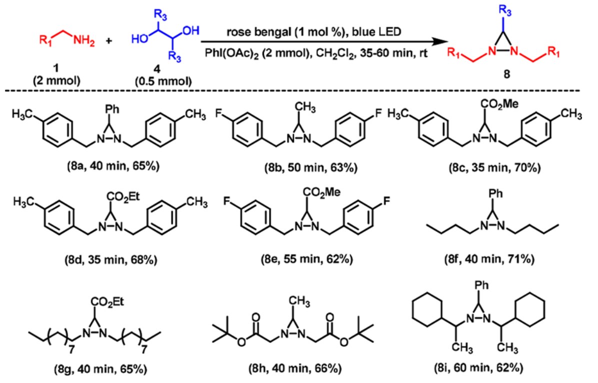
The substrate scope was also extended to chiral amines to synthesize optically active diaziridines (**7a-h**) under the developed mild-reaction conditions (**7**, Scheme 2). Substituted chiral amines as well as amino acid esters were rapidly transformed into the desired optically active 1,2-disubstituted diaziridines in high yields (72−78%). The special class of chiral diamino acid derivatives with strained heterocyclic structures (**7c−h**) will likely be present in materials required for future applications[15] such as in new drug development studies and as chiral synthons for total syntheses of functionalized *N*-heterocycles.

Next, we attempted to extend the strategy to the direct synthesis of 1,2,3-trisubstituted diaziridines (**8**, Scheme 3) utilizing 1,2-disubstituted-1,2-diols through the formation of

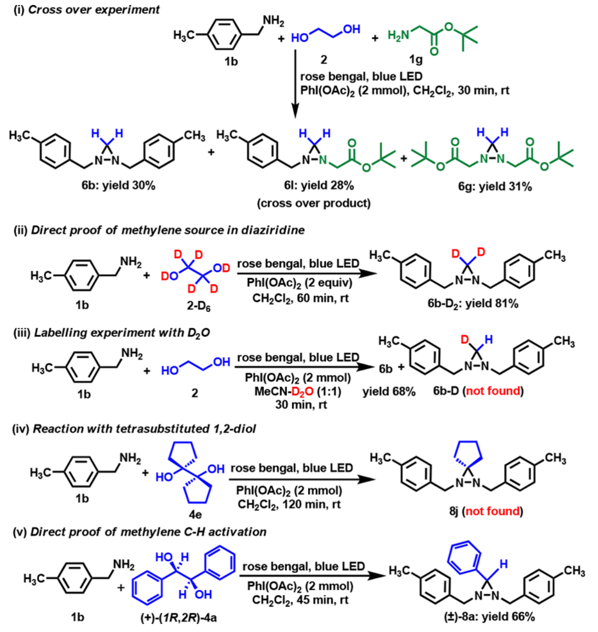
Scheme 2. Synthesis of Diaziridines Bearing Chiral Substituents



Scheme 3. 1,2,3-Trisubstituted Diaziridines from Substituted 1,2-Diol



Scheme 4. Control and Isotope-Labeling Experiments

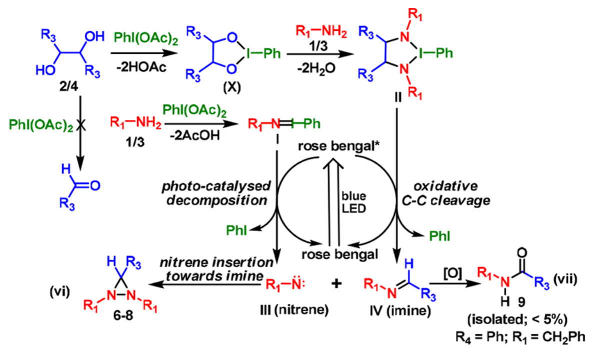


relatively crowded transition states. Dihydrobenzoin (**4a** for **8a**,**f**,**i**), butane-2,3-diol (**4b** for **8b**,**h**), dimethyl tartrate (**4c** for **8c**,**e**) and diethyl tartrate (**4d** for **8d**,**g**) were successfully employed with various types of amines for the rapid (35–60 min) production of the corresponding 1,2,3-trisubstituted diaziridines (**8a**–**i**, 62–71%).

To check the mechanism of the new reaction, some logical control experiments were performed. First, ethylene glycol was added to a mixture of two different amines **1b** and **1g** under the reaction conditions (eq i, Scheme 4). All three possible products [**6b**, **6l** (cross-over product), and **6g**] were isolated in comparable yields, which reveals that the reaction is intermolecular in nature and that the substituents on the amines do not have much influence on the reaction outcome. Ethylene glycol was found to be the methylene source for this aziridination since when **1b** and **2**-d_6 were allowed to react the corresponding diaziridine was isolated in 81% yield and characterized (eq ii and SI). However, incorporation of deuterium was not observed; the D-labeled diaziridine (**6b**-*d*) was not produced in the presence of D_2O (eq iii). [1,1′-Bicyclopentyl]-1,1′-diol was not reactive under the developed conditions (**4e**, eq iv). This indicates that the OH-attached carbon of the 1,2-diol should be sterically unhindered. In the other control experiment (eq v), optically inactive diaziridine **8a** was produced when optically pure (+)-1*R*,2*R*-dihydrobenzoin was used.

Thus, the control experiments and spectroscopic studies (NMR and ESI-MS) led us to propose a nitrene mechanism for the rapid construction of diaziridines (**6**–**8**, eq vi, Scheme 5). In contrast to the reported nitrene formation using a gold catalyst to afford aziridines,[16] the metal-free photocatalysis described herein allows the stereoselective synthesis of diaziridines. It is assumed that the 1,2-diol (**2** or **4**) and $PhI(OAc)_2$ combine to form an oxo-iodonium species (**X**) initially which, when combined with an aliphatic amine (**1** or **3**), rapidly transforms into another nitrogen-containing iodonium species (**II**). Simultaneously, another amine molecule (**1** or **3**) combines with $PhI(OAc)_2$ to produce iodonium ylide (**I**). Light-activated rose bengal converts this iodonium ylide (**I**) into a nitrene intermediate (**III**). On the other hand, the transient species **II** undergoes oxidative homolytic cleavage of the C–C bond to produce an imine (**IV**) through the reductive elimination of PhI in the presence of

Scheme 5. Possible Mechanistic Pathway



activated rose bengal. The desired diaziridine (**6**−**8**) has been produced via insertion of in situ generated nitrene (**III**) into imine (**IV**). It is important to note that although PhI(OAc)$_2$ often oxidizes 1,2-diols to aldehydes or acids,[17] the generation of aldehydes was not observed in this study. The formation of a benzamide derivative (**9**, eq vii, Scheme 5) from the dihydrobenzoin (**4a**) was detected by NMR and that product may be from the oxidation of the imine intermediate (**IV**). However, in the presence of benzaldehyde instead of dihydrobenzoin (**4a**) under the reaction conditions, product **9** was formed exclusively.

In conclusion, we have developed an unprecedented, nonmetallic, photocatalytic approach to the synthesis of diaziridines using blue LEDs, 1,2-diols, amines, rose bengal, and PhI(OAc)$_2$. This reaction proceeds through the generation of nitrene intermediates, which opens a new avenue of organic photocatalysis beyond the existing methods. Reactive nitrenes were efficiently exploited for rapid N−C/N−N-coupled cyclizations with generated imines to furnish functionalized 1,2-disubstituted diaziridines, diaziridines with chiral substituents, and 1,2,3-trisubstituted analogues. Several control experiments, namely, isotopic labeling and spectroscopic studies, were performed to explore the mechanism of this mild, rapid, and highly stereoselective photocatalytic strategy for the synthesis of strained 1,2-dinitrogen heterocycles.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02844.

Detailed experimental procedures; XRD and spectroscopic data (PDF)
X-ray data for **6d** (CIF)

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Notes

The authors declare no competing financial interest.

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