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O-Perhalopyridin-4-yl Hydroxylamines: Amidyl-Radical Generation Scaffolds in Photoinduced Direct Amination of Heterocycles

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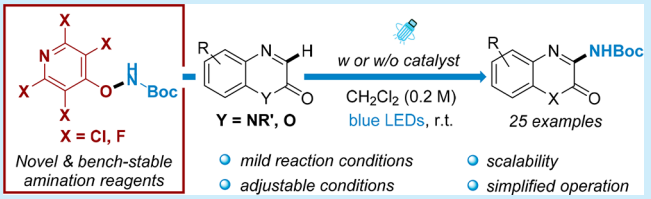
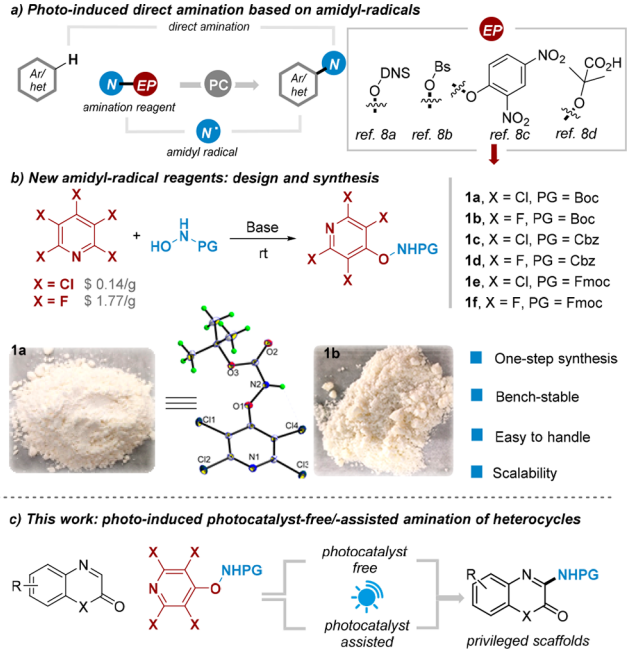
ABSTRACT: Reported herein is the design and synthesis of new *O*-perhalopyridin-4-yl hydroxylamines as shelf-stable and versatile amidyl-radical precursors. The novel amination reagents can be easily prepared via a single synthetic step from inexpensive commercially available starting materials using monoprotected $HONH_2$ as amino source. The synthetic potency of the developed reagents was well demonstrated by direct amination of a series of quinoxalin-2(1*H*)-ones and their analogues under photocatalytic conditions, even without any additive and photocatalysts.



Due to the wide presence of nitrogen-containing natural products, pharmaceuticals, and functionalized materials, facile accesses to the construction of C−N bond are intensively pursued.[1] In this context, direct amination to forge C−N bonds through N-centered radicals is progressively emerging as an efficient and straightforward pathway.[2] Notably, amidyl radicals, as versatile nitrogen-centered radical intermediates, are playing an important role in the fusion of various C−N bonds.[3] Traditionally, formation of amidyl radicals mainly relied on the homolysis of difficult-to-construct N−X bonds under harsh conditions,[4] which fundamentally precluded their wide implementation in synthetic community. Encouragingly, recent progress on visible-light-induced photocatalysis[5] provides fresh opportunities for the generation of various amidyl radicals under mild conditions. While direct cleavage of the strong N−H bond of the amide has been sparsely achieved to assemble various N-containing heterocycles,[2a,6] most present strategies dominantly count on the photoinduced N−heteroatom bond cleavage[6b,7] (Scheme 1a). Recently, various protected hydroxylamine derivatives have received particular attention, which have been prepared and applied as effective amidyl-radical precursors in the domain of visible-light photochemistry (Scheme 1a).[8] To cater for the redox potential of photocatalyst, a series of electrophores including dinitrophenylsulfonyl (DNs),[8a] benzenesulfonyl (Bs),[8b] *O*-2,4-dinitrophenyl,[8c] and α-amido-oxy acid[8d] pendents have been introduced onto the oxygen atom of hydroxylamines to facilitate the generation of amidyl radicals. Despite these encouraging advances, their applications are somewhat limited by the inherent drawbacks, including high cost of amination reagents, dependence on substrate redox potentials, and involvement of metal photocatalysts or sacrificial donors. As such, exploiting new and easily accessible amination reagents would overcome the present hurdles to extend the boundary of

Scheme 1. Visible-Light-Driven Photocatalytic Aminationbased on Amidyl Radicals



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the amidyl-radical chemistry, thus offering new synthetic opportunities for direct amination.

From the viewpoint of green chemistry, photocatalyst-free process in the visible-light photochemistry is especially attractive as a more eco-friendly strategy.[9] Mostly, electron donor−acceptor (EDA) complexes were usually observed in these processes,[10] where electron donor and electron acceptor were actively interacted. Up to now, a series of electron acceptors,[7f,11] including Umemoto's reagents,[11a] Katritzky pyridinium salts,[7f] phthalimide-derived esters,[11e] *etc.*, have been widely used in an impressive range of photocatalyst-free transformations. Realizing the fact that the amidyl-radical reagent is still rarely found in the EDA process, we sought to develop a new amidyl-radical precursor by rationally modulating the features of its electrophore to facilitate the exploitation of photocatalyst-free amination protocol. Very recently, our group identified perfluoropyridin-4-yl moiety as a novel activation module in the generation of nitrogen-centered radicals from cycloketone oximes.[12] Motivated by this work and given our long-standing interest in photochemistry,[13] we envisioned that this interesting scaffold might also possess the potential to serve as an ideal electrophore for facilitating the generation of amidyl radicals through an EDA process due to its intrinsic electronic properties. Following this rationale, we designed a set of *O*-perhalopyridin-4-yl hydroxylamines as amidyl-radical precursors, which could be conveniently prepared from inexpensive commercially available pentahalopyridines and monoprotected $HONH_2$ (Scheme 1b) over a single step. The structures of these prepared amination reagents were confirmed by X-ray as well as NMR analysis. By taking advantage of the newly developed amination reagents, direct amination of a variety of biologically relevant heterocycles were expected to realize under photocatalytic conditions without any additive and photocatalysts (Scheme 1c).

To verify our design, we first sought to test the direct amination of 1-methylquinoxalin-2(1*H*)-one(**2a**) by utilizing *tert*-butyl (perchloropyridin-4-yl)oxycarbamate (**1a**) (Figure 1,

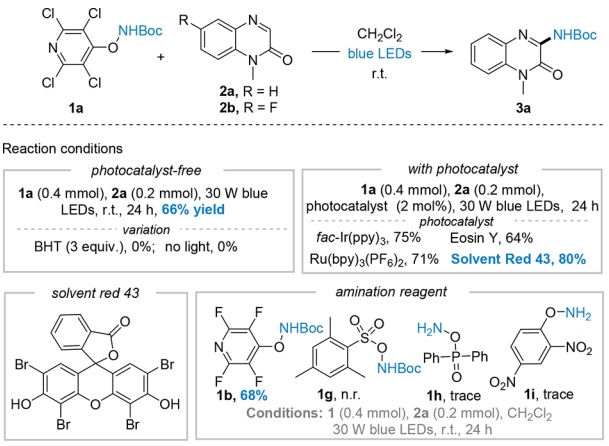

Figure 1. Optimization of the reaction conditions.

see the Supporting Information for details). Gratifyingly, the target product *tert*-butyl (4-methyl-3-*oxo*-3,4-dihydroquinoxalin-2-yl)carbamate (**3a**) was obtained in 66% yield under irradiation of 30 W blue LEDs without adding any photocatalyst. Notably, such nitrogen-containing heterocycles are widely encountered in natural products and pharmaceuticals with a range of biological activities.[14] To shed more light on the nature of the present reaction, further control experiments were launched. As expected, light was necessary to this transformation. Solvent screening demonstrated that CH_2Cl_2 was the optimal choice (Table S1, see the Supporting Information for details). Interestingly, addition of exogenous photocatalysts such as $Ru(bpy)_3(PF_6)_2$ or Solvent Red 43 could further improve the reaction efficacy. Simultaneously, various amination reagents bearing different electrophores were also investigated. Perfluoropyridin-4-yl reagent **1b** gave similar results, while other commercially available potential amination reagents **1g**−**1i** were unsuitable for the photocatalyst-free process (Figure 1).

At this stage, we preliminarily postulated that the photochemically active EDA complexes between **1a** and **2a** might be involved in this process. Subsequently, mixing **1a** with **2a** resulted in an obvious red shift in their UV−vis absorption spectra, which is likely attributed to the association of these two species (Figure 2a). The ^{19}F NMR signal of **2b** shifted

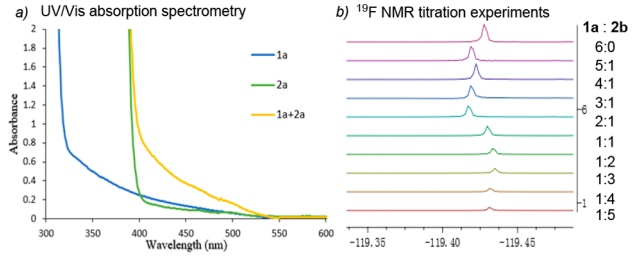

Figure 2. Mechanistic studies: (a) UV/vis absorption spectrometry; (b) ^{19}F NMR titration experiments.

downfield and upfield respectively, along with changing the ratio of **1a** and **2b** (Figure 2b). All the above observations essentially provide the evidence for the formation of EDA complex between **1a** and **2a**. The mass analysis of the reaction mixture in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenol (BHT) indicates the formation of amidyl-radical species (see Supporting Information for details). Electron paramagnetic resonance (EPR) experiments with DMPO were conducted to detect the radical species. However, the EPR signals for amidyl adduct were unable to be precisely identified due to their insufficient intensity. Instead, the EPR signals clearly indicate the involvement of carbon-centered radical (a^N = 14.33 G, a^H = 20.95 G, g = 2.002) (see Supporting Information for details). The on−off experiments support the involvement of a radical chain process (see Supporting Information for details), while the results of a quantum yield measurement (F = 2.78) cannot rule out an inefficient chain propagation pathway. Despite the complication of the mechanism for this transformation (see Supporting Information for details), a plausible EDA pathway is proposed in Figure 3. With blue LEDs irradiation, a SET process occurred within the EDA complex **A**, delivering the radical ion pair **B**. Irreversible fragment of **B** generated the radical cation **E** and amidyl radical **D**, with the release of $C_5Cl_4NO^-$ **C**. Subsequent radical cross coupling of **E** and **D** formed the intermediate **F**. Final deprotonation of **F** gave the corresponding product.

Next, the feasibility and reliability of the designed amidyl-radical precursors as well as the compatibility of the reaction conditions were comprehensively evaluated (Scheme 2).

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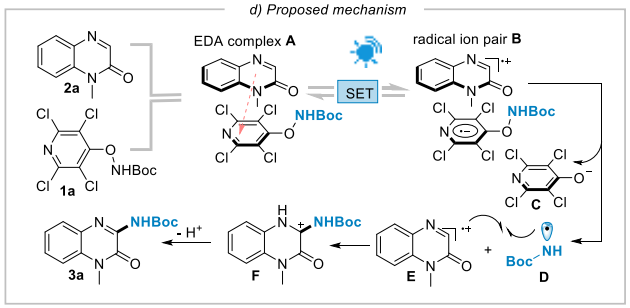
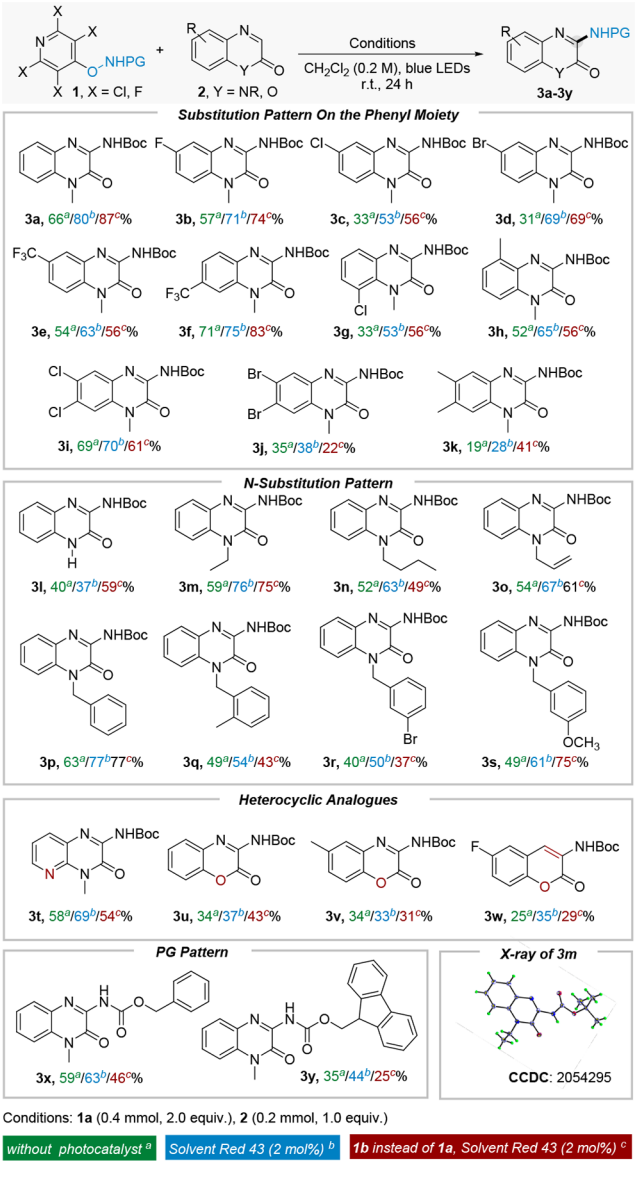


Figure 3. Proposed mechanism for photocatalyst-free conditions.

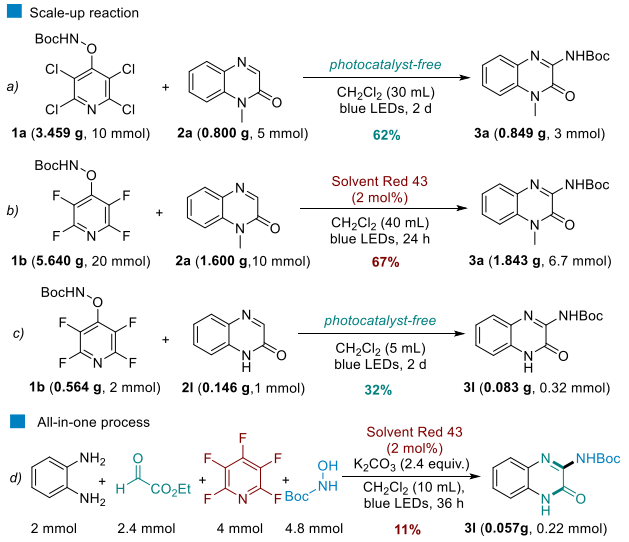
Scheme 2. Scope of the Photoinduced Amination Reaction



Generally, there was no obvious difference in the reactivity between perchloropyridin-4-yl and perfluoropyridin-4-yl reagents. In general, the photocatalyst-free process usually gave slightly lower yields than the photocatalyst-assisted process, which was possibly attributed to the inferior efficiency of absorption of photons for EDA complex than the photocatalyst. A wide range of quinoxalin-2(1*H*)-ones bearing different substituents and protecting groups were proven to be suitable reaction partners in this photoinduced process, delivering the desired aminated products **3a**−**3s** smoothly. Interestingly, unprotected quinoxalin-2(1*H*)-one also delivered the desired product **3l** in an acceptable yield. This photoinduced protocol was also amenable to the heterocyclic analogues such as 2*H*-benzo[*b*][1,4]oxazin-2-one and coumarins (**3t**−**3w**). However, other heterocyclic substrates including 1*H*-benzo[*d*]imidazole, benzo[*d*]thiazole, and quinolone were unable to give the desired products (see Supporting Information for details), presumably because of their incapacity for the formation of EDA or mismatching redox properties. Meanwhile, the protecting group on hydroxylamine could be changed to benzoxycarbonyl (Cbz) and 9-fluorenylmethyl (Fmoc) groups, albeit with lower reaction efficiency (**3x** and **3y**).

Ultimately, the scalability and practicality of this photoinduced process were evaluated (Scheme 3). Pleasingly, a

Scheme 3. Scalability and Practicality of the Photoinduced Process



scale-up reaction for the direct amination of quinoxalin-2(1*H*)-one **2a** was performed under both photocatalyst-free conditions and photocatalyst-assisted conditions, and the corresponding product **3a** was successfully isolated with mostly comparable yields (62%, Scheme 3a, 67%, Scheme 3b), respectively. The reaction for quinoxalin-2(1*H*)-one **2l** could also be easily scaled up with lower yield (Scheme 3c). Furthermore, an alternative four-in-one process by starting from *o*-phenylenediamine, ethyl glyoxalate, pentafluoropyridine, and *N*-Boc-hydroxylamine was also established to deliver the desired product **3l** in 11% yield, rendering this protocol more adjustable and industry-friendly (Scheme 3d).

To conclude, we have first designed and identified a new class of highly reactive, practical and easy-to-prepared *O*-perhalopyridin-4-yl hydroxylamines as effective amidyl-radical precursors, allowing the general and direct amination of various heterocycles under visible-light-driven conditions. It is noteworthy that this photoinduced transformation is able to proceed smoothly without adding any photocatalyst, metal catalyst, or additive. These salient features of this new type of reagents in photocatalytic transformation would offer intriguing opportunities for rapid expansion of nitrogen-containing

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molecular complexity. Further efforts are underway in our laboratory to utilize the newly developed precursors in other transformations, which will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00064.

Experimental details, characterization data, and mechanisms for new compounds, including EPR and NMR spectra, X-ray crystallographic data of **1a**, X-ray crystallographic data of **1d**, and X-ray crystallographic data of **3m** (PDF)

Accession Codes

CCDC 2054289, 2054293, and 2054295 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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