Communication

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Visible-Light-Mediated Synthesis of Amidyl Radicals: Transition Metal-Free Hydroamination and N-Arylation Reactions.

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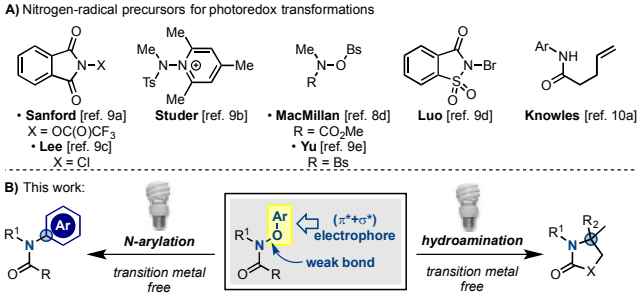
Supporting Information Placeholder

ABSTRACT: The development of photoredox reactions of aryloxy amides for the generation of amidyl radicals and their use in hydroamination–cyclization and N-arylation reactions is reported. Owing to the ease of SET reduction of the aryloxy amides, the organic dye eosin Y was used as the photocatalyst, which results in fully transition metal-free processes. These transformations exhibit a broad scope, tolerant to several important functionalities and have been used in the late-stage modification of complex and high-value N-containing molecules.

Nitrogen-containing compounds form the structural basis of almost all pharmaceuticals, agrochemicals and materials.[1] As a result, the development of new methodologies that allow the selective formation of C–N bonds under mild conditions and in complex molecular settings are of great relevance. Amidyl radicals represent a very useful class of reactive intermediates with potentially broad applications in the preparation of amides and carbamates.[2] However, their implementation in synthesis is somewhat limited by (i) their available precursors, which are often difficult-to-make and highly reactive, and (ii) the reaction conditions required for their generation, which often preclude the presence of many functional groups.[2a] Pioneering studies from Ingold revealed that amidyl radicals display remarkably high electrophilic character and this offers the advantage of an umpolung reactivity complementing the nucleophilic character of *N*-species in classical polar reaction modes.[3,4] However, as detailed by Newcomb, the amidyl radical electrophilicity also means that both inter and intra-molecular H-atom abstraction reactions are very favorable and this frequently thwarts the development of C–N bond-forming processes.[5]

Recent progress towards the generation and use of N-radicals has involved the use of photoredox catalysis[6] as an enabling tool for mild and selective single-electron transfer (SET)[7] processes.[8] Of relevance to this work are the reports of Sanford,[9a] Studer,[9b] Lee,[9c] Luo,[9d] and Yu,[9e] which developed the photoredox generation of *N*-radicals and used them in *N*-arylation reactions. These methodologies involve the use and introduction of substrate-specific and difficult-to-modify *N*-groups. More recently Knowles[10a] and Xu[10b] reported two elegant hydroamination reactions of amidyl radicals by using oxidative photoredox and electrochemical approaches respectively (Scheme 1A). These processes require the use of *N*-aryl-amides and therefore cannot be used in a general sense for the synthesis of N-containing molecules.

SCHEME 1. Amidyl radicals.

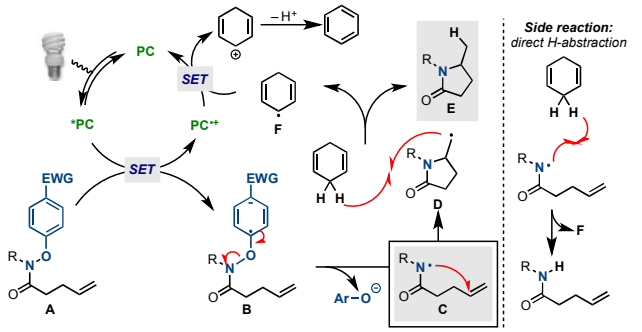


We have recently developed a transition metal-free photoredox cyclization of iminyl radicals derived from aryloximes.[11] We decided to evaluate whether this activation mode could be applied to the generation of amidyl radicals and use it as a general platform for the synthesis of N-containing molecules. We reasoned that electron poor aryloxy-amides

would be ideal amidyl radical precursors owing to the aryloxy motif serving as a ($\pi^*+\sigma^*$)-electrophore[7b] that should facilitate a photoredox SET reduction–fragmentation cascade *en route* to the amidyl radical. We were particularly keen to explore whether this methodology had the potential to solve the challenge of generating *any* amidyl radical *independently from the nature of its N-substituents* and therefore decided to focus our attention on (i) substrates and substitution patterns that go far beyond the limits of current methodologies and (ii) on providing access to highly functionalized, high-value N-containing compounds. In this paper we report the development of transition metal-free photoredox hydroamination-cyclization and *N*-arylation reactions of amidyl radicals and their use in the late stage functionalization of compounds with therapeutic applications.

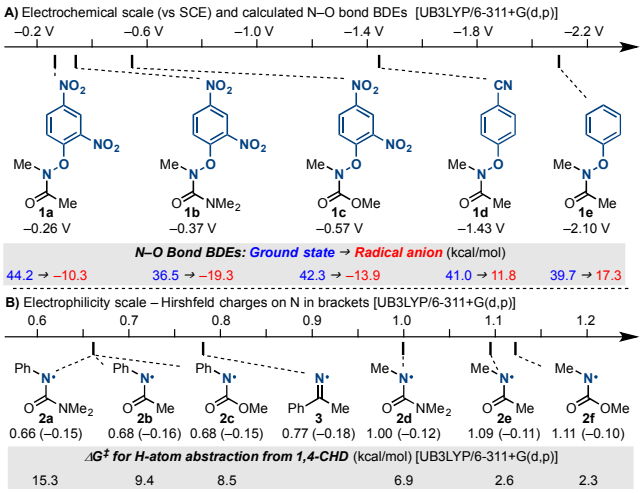
Our proposed catalytic cycle for the photoredox cyclization of aryloxyamides **A** is described in Scheme 2. We reasoned that upon photocatalyst (PC) excitation by visible light irradiation, SET reduction of the aryl unit of **A** would occur delivering the radical anion **B** and $PC^{\bullet+}$. At this point, N–O bond fragmentation would form the amidyl radical **C**, which would produce **D** after *5-exo-trig* cyclization. H-atom abstraction from 1,4-cyclohexadiene (1,4-CHD) would form the product **E** and generate the radical **F**, which would close the photoredox cycle by SET with $PC^{\bullet+}$. As aforementioned, a major element of concern was the high tendency of **C** to undergo preferential H-atom abstraction from 1,4-CHD over the desired 5-*exo-trig* cyclization.[12] This situation would be particularly problematic in our case as (i) 1,4-CHD has a dual role as both a H-atom donor and SET reductant in two distinct but sequential event of the catalytic cycle and (ii) direct H-atom abstraction would form **F**, which would close the catalytic cycle and eventually consume **A**.

SCHEME 2. Proposed photoredox cycle for the hydroamination-cyclization reaction.



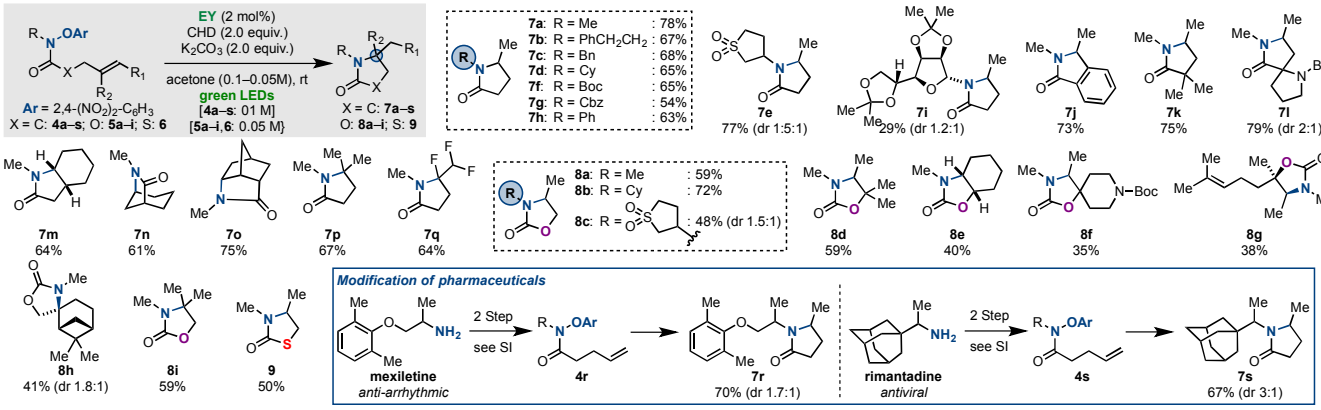
We started our investigation by performing cyclic voltammetry studies on model precursors **1a–e** (Scheme 3A). All of the substrates tested displayed irreversible reduction profiles and the nitro-containing compounds (**1a–c**) fell well inside the range for SET reduction by the excited state of the organic dye eosin Y [$E_{1/2}^{red}$ = –1.11 V (vs SCE)].[13] DFT calculations aimed at evaluating the N–O bond dissociation energies (BDEs) revealed that all substrates **1a–e** have N–O BDEs ≈ 40 kcal/mol. However, upon SET reduction a dramatic weakening of the N–O bond takes place, which makes the fragmentation process thermodynamically driven and essentially immediate in the case of the nitro-substituted derivatives **1a–c**.[14] Since a major element of concern in the development of our approach is the tendency of amidyl radicals to undergo H-atom abstraction, we were surprised by the high reactivity displayed by the N-Ar-amidyl radicals reported by Knowles[10a] and Xu.[10b] We performed further DFT studies to evaluate how the N-substitution pattern would impact the radical electrophilicity and, as a result, its ability to undergo H-atom abstraction. As described in Scheme 3B, local electrophilicity index-values (ω^{+}_{rc})[15a] and Hirshfeld charges[15b] for various radicals were calculated. This study revealed a remarkable modulation of the radical electrophilicity that is offered by the *N*-Ar substituent. According to our scale, Ar-amidyl radicals (**2a–c**) are significantly less electrophilic than alkyl-amidyl radicals (**2d–e**). They are even less electrophilic than iminyl radicals (e.g. **3**) and this might be the reason for their low tendency to abstracting H-atoms.[14] To further corroborate this scenario, we have calculated the barrier for H-atom abstraction ($\Delta G^{\ddagger}$) for the reaction between radicals **2a–f** and 1,4-CHD. As described in Scheme 3B, N-Ph substituted radicals **2a–c** displayed higher barriers for H-abstraction compared with the more electrophilic N-alkyl radicals **2d–f**.[14] These results clearly show the relevance and challenges that are associated with the development of photoredox reactions of amidyl radicals with alkyl and carbonyl-containing substitution patterns.

SCHEME 3. Electrochemical and DFT studies.



We started the optimization of our proposed process using the di-nitro-substituted amide **4a** due to its synergistic (i) ease of synthesis, (ii) ease of SET reduction and (iii) very favorable N–O bond fragmentation (Scheme 4).[11] Our optimized reaction conditions required the use of eosin Y as the PC, 1,4-CHD as the H-atom source, and K_2CO_3 as the base. Acetone was found to be the best reaction medium and in terms of the light source, we found that green LEDs (λ = 530 nm) gave the best results. Under these reaction conditions **7a** was obtained in 78% yield.[14] With these optimized reaction conditions in hand, we evaluated the scope of this photoredox cyclization reaction. Pleasingly, our protocol enabled the generation and the use of amidyl radicals with broad N-substitution patterns, as shown by the use of a primary alkyl group (**7b–c**) as well as the hindered cyclohexyl (**7d**) and a redox-active sulfone[16]-containing heterocycle (**7e**). More remarkably, we were able to generate and implement *N*-Boc and *N*-Cbz-protected amidyl radicals (**7f** and **7g**). The success of these cyclizations is noteworthy owing to the high electrophilicity of these radicals (ω^{+}_{rc} = 1.3).[14] To the best of our knowledge, the generation and the use of these amidyl radicals have never been reported in the literature.

SCHEME 4. Scope of the photoredox hydroamination-cyclization reaction.

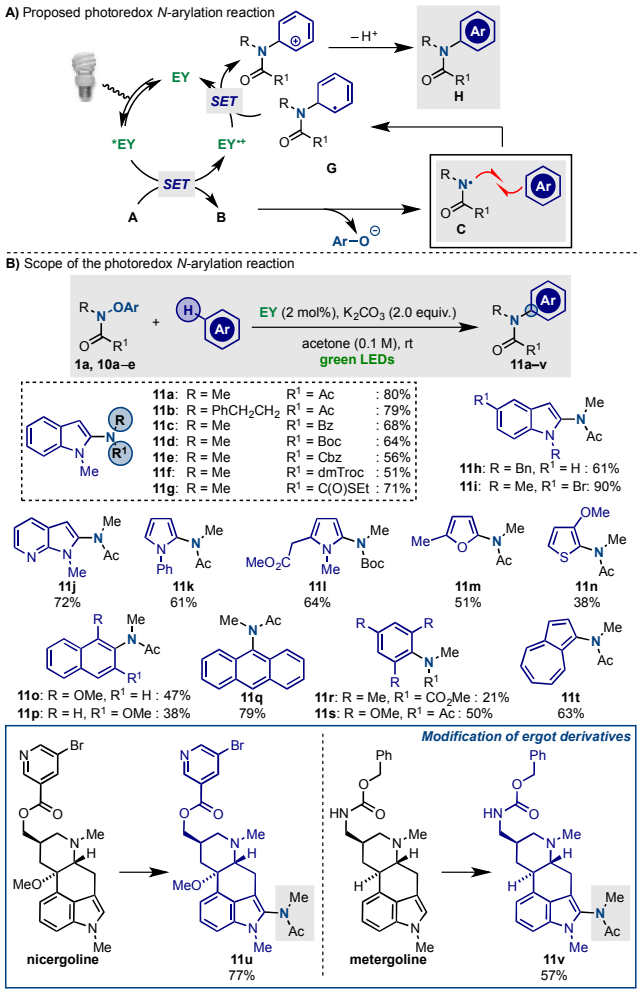


We then showcased our method by preparing more complex products, including **7i** which contained a sugar-like moiety as *N*-substituent, and bicyclic (**7j**,**k**,**n**), tricyclic (**7o**) and spirocyclic (**7l**) molecules. Cyclization to form a fully substituted carbon centre was possible (**7p**), and we succeeded in using a trifluoro substituted olefin substrate (**7q**). We then extended this chemistry to the synthesis of cyclic carbamates. However, in this case the reaction conditions had to be adjusted because the competing H-atom abstraction became significantly more problematic owing to the increased radical electrophilicity (see Scheme 3B). Nevertheless, we were able to use a range of differentially substituted substrates without the need for a stabilizing *N*-aromatic group (**8a–f**). We then used our methodology for the modification of the terpenes (–)-linalool (**8g**) and (–)-myrtenol (**8h**) as well as performing a cyclization that produced a cyclic thiocarbamate (**9**). Finally, as many therapeutic molecules contain alkyl-substituted amino groups, we showcased the applicability of our methodology with the late-stage modification of the blockbuster drugs mexiletine and rimantadine, which gave **7r** and **7s** in high yields.

Having developed a photoredox transition-metal free hydroamination process, we decided to evaluate whether our method could be used to achieve intermolecular *N*-arylation reactions (Scheme 5A).[17] Mechanistically, we envisaged that upon photoredox amidyl radical generation (**A**→**C**) and in the presence of an electron rich aromatic partner, an intermolecular reaction[18] would take place to forge the C–N bond in **G**. This species would then close the photoredox cycle and provide the product **H**. Related reactions have been reported in the literature (Scheme 2A),[9] however they do not allow structural modification of the N-radical and they require a large excess of the aromatic partner (normally 5/10-fold excess). We

hoped that our substrates and activation mode would address these two major limitations and provide a general platform for the arylation of *N*-molecules. As described in Scheme 5B, by simply exposing **1a** to *N*-Me-indole (2.0 equiv.), EY and K_2CO_3 in acetone under green LEDs irradiation, the coupled product **11a** was obtained in high yield.[14] Gratifingly, our approach enabled us to easily modify the N-substitution pattern as shown by the implementation of substrates that contain a *N*-alkyl chain (**11b**), a *N*-Bz (**11c**), the most commonly used *N*-protecting groups: *N*-Boc (**11d**), *N*-Cbz (**11e**) and *N*-dimethyl-Troc (**11f**), and a thiocarbamate (**11g**). The compatibility of the *N*-dimethyl-Troc group is noteworthy as the X–CCl_3 motif is frequently used as photoredox SET acceptor.

SCHEME 5. Photoredox *N*-arylation reaction.



We then looked at the aromatic unit and extended the scope of this reaction to *N*-Bn and 5-Br-*N*-Me-indole (**11h–i**) azaindole (**11j**), pyrroles (**11k–l**), furan (**11m**), thiophene (**11n**), naphthalenes (**11o–p**), anthracene (**11q**), mesitylene (**11r**), trimethoxybenzene (**11s**) and azulene (**11t**). As electron rich heteroaromatics constitute the core of many natural products and pharmaceutical agents[1] we decided to evaluate whether our method could be used as a late-stage amination protocol. We were intrigued by the idea of modifying the core structure of lysergic acid, a molecule that has been a source of interest and imagination in both chemistry and pop-culture.[19] We were delighted to see that, upon exposure of the therapeutically active ergot derivatives nicergoline and metergoline to our reaction conditions the C-2 amino-functionalised products **11u** and **11v** were obtained in good yields. We believe that these examples showcase the power of our arylation manifold owing to the high structural complexity and the number of functional groups that are tolerated, which includes an unprotected carbamate. In fact, the excited state of a photoredox catalyst could potentially oxidize the piperidine ring N-atom and reduce the electron poor pyridine ring. As an example, when the reaction on nicergoline was repeated by using $Ir(ppy)_3$ as the PC, we obtained a complex mixture, which was possibly due to the stronger redox properties of its excited state.

In conclusion, we have identified a class of easy-to-make and highly reactive aryloxyamides that were used in the first photoredox transition metal-free generation of amidyl radicals. This activation mode represents a general strategy for the implementation of intramolecular hydroamination reactions as well as intermolecular N-arylation processes. The methodology reported here displays high functional group tolerance, which is illustrated by the late-stage modification of terpenes, blockbuster drugs and complex ergot derivatives.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, ^1H and ^{13}C NMR spectra, DFT calculations (PDF).

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