

# Visible-Light-Mediated 5-exo-dig Cyclizations of Amidyl Radicals.

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**Abstract:** The visible-light-mediated synthesis of 5-methylenepyrrolidinones is reported. This constitutes the first reported example of a *5-exo-dig* hydroamination reaction involving a nitrogen-centred radical.

#### Introduction

Nitrogen-centered radicals<sup>[1]</sup> (NCRs) are a versatile class of synthetic intermediates that can facilitate the preparation of molecules with therapeutic, agrochemical and materials properties.<sup>[2]</sup> As a result, the development of synthetic methodologies that streamline access to NCRs in an operationally simple, sustainable and cost-effective manner is of high relevance.

Despite the potential applications that one can envisage, the chemistry of NCRs has been somewhat limited by (i) the difficulties associated with the synthesis of their precursors and (ii) the harsh reaction conditions required to generate the radical species.<sup>[1]</sup> More recently, owing to the development of photoredox catalysis<sup>[3]</sup> as a powerful technique to perform single-electron transfer (SET)<sup>[4]</sup> events, the chemistry of NCRs has witnessed a remarkable resurgence.<sup>[5]</sup>

We have reported a novel class of electron poor *O*-aryl oximes and *O*-aryl-hydroxyamides and used them in hydroiminationand hydroamidation-cyclization reactions.<sup>[6]</sup> In both cases, the iminyl and amidyl NCRs were generated by a sequence of visible-light-mediated SET reduction and N–O bond fragmentation. Subsequent *5-exo-trig* cyclization constructed the pyrroline and pyrrolidinone heterocycles. Upon examination of the literature on NCR-cyclizations, we realized that while *5-exotrig* ring closures have been developed, the *5-exo-dig* mode has not experienced the same level of attention (Scheme 1). In fact, to the best of our knowledge, the use of amidyl radicals in

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hydroamination-cyclization reactions that provide access to 5methylenepyrrolidines has not been reported. This is very surprising given these compounds are readily functionalized and serve as versatile building block in complex molecular synthesis.<sup>[7]</sup>

We envisaged that a visible-light-mediated approach for amidyl radical generation<sup>[6b]</sup> would be compatible with *5-exo-dig* cyclizations and in this paper we describe the successful implementation of this process.



Scheme 1. 5-exo Radical cyclization of amidyl radicals and this work.

#### **Results and Discussion**

At the outset, we reasoned that our previously reported photoredox approach for amidyl radical generation and 5-exotria cyclization could be extended and applied in a 5-exo-dia setting.<sup>[6b]</sup> As described in Scheme 2A, visible-light excitation of the organic dye eosin Y (EY)<sup>[8]</sup> [ $E_{1/2}$ (EY<sup>\*+</sup>/\*EY) = -1.11 vs SCE] would enable the SET reduction of NCR precursor **A** ( $E_{1/2}^{red} = -$ 0.51 vs SCE).<sup>[9]</sup> This event would deliver the radical anion **B** that upon N–O bond fragmentation (calculated BDE for N–O bond in **B** = -10 kcal mol<sup>-1</sup>),<sup>[9]</sup> would form the amidyl radical **C**. At this 5-exo-dig cyclization would assemble the 5stage, methylenepyrrolidinone radical **D** that upon fast H-abstraction from 1,4-cyclohexadiene (C-H BDE = 73 kcal mol<sup>-1</sup>)<sup>[10]</sup> would give the desired product E and the radical F that would close the Photoredox cycle by SET with EY<sup>\*+</sup> (to give **G**). While feasible, this approach is not without concerns as amidyl radicals can undergo direct H-abstraction from 1,4-cyclohexadiene (to give H) in preference to 5-exo-type ring closure (Scheme 2B).<sup>[11]</sup> This is particularly evident when alkyl and acyl substituents are present at the N atom as they increase its electrophilic character.<sup>[6b]</sup> Furthermore, as radical 5-exo-dig cyclizations are slower than 5-exo-trig, this could result in significant quantity of unproductive H-atom abstraction.

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**Scheme 2.** A) Proposed photoredox mechanism for amidyl radical generation and *5-exo-dig* cyclization. B) Potential side reaction

We began our studies evaluating the ability of aryloxyamide 1a to undergo the proposed NCR generation-5-exo-dig sequence (Scheme 3A). To our delight, visible-light irradiation (30W CFL) of 1a in the presence of EY, 1,4-cyclohexadiene and K<sub>2</sub>CO<sub>3</sub> in acetone, gave the desired 5-methylenepyrrolidone 2a in 43% yield (entry 1). Interestingly, upon performing control experiments we realized that while the reaction was completely suppressed by the absence of visible-light (entry 2), EY was not required and 2a could be obtained in almost identical yield by simple irradiation of 1a in the presence of K<sub>2</sub>CO<sub>3</sub> and 1,4cyclohexadiene (entry 3). It is difficult at this stage to propose a mechanism for amidyl radical generation under this reaction conditions as preliminary mechanistic studies have not been conclusive.<sup>[9]</sup> The yield was then improved to 63% by running the reaction under more diluted conditions (entry 4). Other bases (entries 5 and 6) and solvents (entries 7-10) were evaluated but they generally provided inferior results. It is worth pointing out that the remaining mass-balance for all the reactions performed in acetone, CH<sub>3</sub>CN and DMSO is represented by the secondary amide 3a. This undesired product arises from the competitive Habstraction of the NCR C from 1,4-cyclohexadiene (Scheme 2B) and its formation can be somewhat controlled by adjusting the reaction concentration (Scheme 3B). We then confirmed the requirement for continuous visible-light irradiation by performing light-ON-OFF experiments although this does not eliminate the possibility of short-lived radical chains providing the majority of the productive conversion of 1a to 2a.<sup>[12]</sup> As shown in Scheme 3C, the reaction progression was evident only during the light-ON cycles and was suppressed when the reaction was run in the dark.



A) Screening of reaction conditions



 $\label{eq:scheme 3. A} \mbox{ Reaction optimization, B} \mbox{ Studies on concentration effects and C} \mbox{ Light ON-OFF experiments.}$ 

With reaction conditions in hand, we then carried experiments to evaluate the scope of this visible-light-mediated amidyl radical generation and *5-exo-dig* hydroamination-cyclization process.

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As described in Scheme 4A, a series of differentially substituted aryloxyamides were subjected to visible-light irradiation in the presence of  $K_2CO_3$  and 1,4-cyclohexadiene. Pleasingly, the reaction could be extended to the benzyl-protected amide **1b** that gave **2b** in similar yield. Surprisingly, the use of aryloxy amide **1c** resulted in lower yield and was accompanied by the formation of several by-products.





Scheme 4. Scope of the 5-exo-dig hydroamination via amidyl radicals.

A possible explanation for this result might be found in the ability of vinyl radicals to undergo intramolecular 1,5-H-atom abstraction.<sup>[13]</sup> As described in Scheme 4B, upon 5-exo-dig cyclization of NCR **Cc**, a very fast H-abstraction from the benzylic methylene group of **Dc** might take place thus providing the stable benzylic radical **H** that can undergo several side reactions. We then evaluated the use of substrates with sterically hindered *N-i*-Pr (**1d**) that gave access to **2d** in good yields. The  $\alpha$ -substituted amides **1e** and **1f** worked very well, benefitting from the Thorpe-Ingold effect,<sup>[14]</sup> and provided **2e** and **2f** in good yields. Finally, we extended this chemistry for the generation and the use of carbamate-type NCRs. In this case however, the increased electrophilicity of the NCR meant that a more facile direct H-atom abstraction takes place and therefore a more pronounced concentration effect was obtained. Nevertheless, we were able to expand this reaction to this class of substrates as demonstrated by the successful formation of methylene-oxazolidinones **2g** and **2h**.

As the reactivity of amidyl radicals in 5-exo-dig cyclizations has not been reported before, we decided to study the full reaction profile by DFT.<sup>[9]</sup> As reported in Scheme 5, both the direct Habstraction  $(\mathbf{C}_1 \rightarrow \mathbf{H}_1)$  and the 5-exo-dig cyclization  $(\mathbf{C}_1 \rightarrow \mathbf{D}_1)$  are exothermic, with the cyclization pathway requiring a lower activation energy (9.8 vs 13.1 kcal mol-1). The following Habstraction from the vinylic radical **D** is also exothermic with a barrier of 11.8 kcal mol<sup>-1</sup>. We then performed the same analysis for the direct H-abstraction  $(\mathbf{C}_{2-4} \rightarrow \mathbf{G}_{2-4})$  and 5-exo cyclization then H-abstraction  $(C_{2-4} \rightarrow D_{2-4} \rightarrow E_{2-4})$  for the propargylic carbamate radical C2, the amidyl radical C3 and the allylic carbamate radical C4. Salient conclusions drawn from our computational study include: 1) The more electrophilic propargylic carbamate radicals<sup>[6b]</sup> exhibit a slightly more facile direct H-abstraction  $(C_2 \rightarrow H_2)$ , which is in line with the requirement for more diluted reaction conditions for 1f-g. 2) Cyclization of carbamate radicals  $C_2$  and  $C_4$  require higher



Scheme 5. DFT studies for the 5-exo cyclization and direct H-atom abstraction of amidyl radicals [DFT method: UB3LYP/6-311+G(d,p)]].

energy barriers as compared to amidyl radicals C1 and C3 which is in line with the observed lower yields for the 5-exo-dig cyclizations. 3) Direct H-atom abstraction by the vinyl radical (D1 and **D**<sub>2</sub>) is more facile when compared with primary alkyl radicals (D<sub>3</sub> and D<sub>4</sub>) and it directly relates to the inherent radical reactivity and stability. 4) Plots of calculated reaction barrier height and reaction enthalpy for all the radical transformations studied here gave excellent correlations for both H-abstractions ( $C_{1-4} \rightarrow G_{1-4}$ and  $D_{1-4} \rightarrow E_{1-4}$ ). However, there was no apparent trend for the 5exo-trig/dig cyclizations ( $C_{1-4} \rightarrow D_{1-4}$ ), which suggests that the Evans-Polanyi rule does not hold for these reactions.<sup>[9, 15]</sup>

#### Conclusions

In conclusion, we have developed the first example of 5-exo-dig hydroamination-cyclization of an amidyl radical. The direct visible-light irradiation of electron poor aryloxyamides in the presence of K<sub>2</sub>CO<sub>3</sub> enabled the direct formation of the amidyl radical presumably via an EDA complex. As confirmed by DFT studies, 5-exo-dig cyclizations of amidyl radicals are less favorable than 5-exo-trig and this can explain the sometimes lower yields obtained.

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Visible-light irradiation of electron poor aryloxyamides in the presence of  $K_2CO_3$  leads to the formation of amidyl radicals that undergo *5-exo-dig* hydroamination-cyclization reactions.

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#### Nitrogen-Radicals\*

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