

# Photoassisted Diversity-Oriented Synthesis: Intramolecular Cycloadditions of Photogenerated Azaxylylenes with Oxazole Pendants, and Subsequent Postphotochemical Multicomponent Modifications

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Supporting Information

**ABSTRACT:** Photogenerated aza-*o*-xylylenes undergo intramolecular cycloaddition reactions to tethered oxazoles, with primary photoproducts featuring a reactive cyclic imine moiety suitable for multicomponent postphotochemical transformations. For example, the reaction of these imine photoproducts with bromoacetyl bromide leads to a key 1,4-dielectrophilic synthon, offering access to diverse polyheterocyclic molecular architectures. This reaction sequence is accompanied by rapid growth complexity in a very few simple synthetic steps, and is in keeping with the philosophy of diversity-oriented synthesis (DOS).

ntramolecular cycloadditions of aza-o-xylylenes photogenerated via excited state intramolecular proton transfer (ESIPT) in aromatic aminoketones is developing into a general methodology for photoassisted synthesis of complex polyheterocycles.<sup>1</sup> The scope of this reaction is rather broad: we have demonstrated that photoprecursors with unsaturated pendants from simple alkenes to dienic heterocycles such as furans, thiophenes, or pyrroles are cycloaddition-competent. In these cases, the initial photoproducts possess a newly installed electron-rich reactive double bond, amenable to postphotochemical transformations with electrophiles to further grow the complexity of primary photoproducts. For example, hetero-Diels-Alder or Povarov-type reactions offer rapid access to rather complex polyheterocyclic molecular architectures<sup>1b</sup> (Scheme 1, top, illustrates this point with the oxa-Diels-Alder modification of the initially formed reactive electron-rich dihydrothiophene moiety).

Whether or not the excited aza-o-xylylenes are capable of intramolecular cycloadditions to heterodienic unsaturated pendants with *two* heteroatoms (e.g., oxazoles) is an important question, as the primary photoproducts in this case are expected to contain *an electrophilic* reactive moiety, such as an imine (Scheme 1, bottom).

In this Letter, we report that *oxazoles*,<sup>2</sup> tethered to the photoactive core of aromatic amino-ketones, are indeed cycloaddition-competent with photogenerated aza-*o*-xylylenens, offering rapid photoassisted access to reactive photoproducts containing a cyclic imine moiety. The primary photoproducts are potentially suitable for a variety of subsequent *postphotochemical transformations*, including multicomponent cycliza-



Scheme 1. Intramolecular Cycloaddition of Aza-*o*-xylylenes Generated via ESIPT: Primary Photoproducts with the Newly Installed Reactive Nucleophilic Thioether (Top); vs Electrophilic Imine (Bottom)



tions, to further expand the diversity of resulting polyheterocyclic scaffolds.

3-(Oxazol-5-yl)propanoic acids **1a-e**, in which the oxazole moiety is tethered through position 5, were readily synthesized

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as described in the literature<sup>3</sup> and outfitted with photoactive *o*aminobenzaldehyde cores to yield photoprecursors 2a-e as shown in Scheme 2. Upon UV-irradiation with 365 nm UV

Scheme 2. Synthesis of Oxazole-5-yl Based Photoprecursors and Their Photoinduced Cyclization via ESIPT/Aza-oxylylene



LEDs, oxazoles 2 underwent ESIPT-mediated [4 + 4] and [4 + 2] formal photocyclizations to form primary photoproducts 3– 5. As we reported earlier,<sup>1f</sup> the cycloaddition reaction most likely occurs via the triplet aza-o-xylylenes, which are better represented by the 1,4-diradicaloid structure shown in Scheme 2. Unlike the outcome of similar reactions with tethered *furan*propanoyl pendants, the diastereoselectivity of photolysis of oxazoles 2 was low for the two isomeric [4 + 4] products, *syn-* (3) and *anti-* (4). Oxazoles 2 also yielded the minor products of [4 + 2] cycloaddition, oxazolino-quinolinols 5'. However, they were unstable and hydrolyzed during workup and chromatographic purification to amido-diols 5. Table 1 summarizes the isolated yields and gives legends for the aromatic substituents.

The combined isolated yield of the diastereomers of the major [4 + 4] photoproducts was 60–70%. As we were aiming to introduce the newly formed cyclic imine functionality into postphotochemical transformations, we elected to oxidize the

 Table 1. Isolated Yields for Primary Photoproducts in the

 Reaction of 5-Tethered Oxazoles

		yield <sup>a</sup> (%)		
	Ar	<b>3a–e</b> ( <i>anti-</i> )	4a–e ( <i>syn</i> -)	5a–e (diol) <sup>b</sup>
2a	Ph-	34	32	14
2b	p-anisyl-	27	34	15
2c	2-furyl-	39 <sup>c</sup>	31	17
2d	2-thienyl-	23	43	16
2e	5-oxazolyl-	62	_d	d

<sup>*a*</sup>Isolated yields of photoproducts. <sup>*b*</sup>The primary [4 + 2] products 5' are unstable and hydrolyze during workup and column purification via oxazoline ring opening to give isolable dihydroxy benzamides. <sup>*c*</sup>Structure is determined by X-ray crystallography; see Supporting Information <sup>*d*</sup>Minor 4e and 5e were not isolated; detected by NMR.

reaction mixture before isolation of the [4 + 4] product to convert benzylic alcohol into the keto group. This helps avoid complications in subsequent transformations, prevents retrocyclization, and reduces the number of diastereomers to just one. As Scheme 3 illustrates, the one-pot irradiation/oxidation

Scheme 3. Two-Step One-Pot Photocyclization-Oxidation Sequence



procedure worked nicely. For phenyl- or *p*-anisyl-oxazoles the yields of keto-imines **6** derived from the [4 + 4] photoproducts were 64% and 62% respectively, over the two steps. Oxidation of the minor [4 + 2] cycloadduct was accompanied by the oxazoline ring opening to yield benzamido-quinolone 7a. This is expected as the initial phenone produced by oxidation of the primary [4 + 2] photoproduct **5**' has an acidic enolizable proton and should be prone to elimination with subsequent oxazoline ring opening, as shown in Scheme 3. The minor quinolinone 7a is a peculiar diamidoenone and is photoactive itself.<sup>4</sup>

Photoprecursors **9** possessing the oxazole pendants tethered through position 2 (i.e., not 5) are also readily "assembled" in a modular fashion. Their photochemistry is similar to that of 5-substituted oxazoles **2**, although they do not form the [4 + 2] photoproducts, only [4 + 4], conceivably because the [4 + 2] photoproducts in this case are hemiaminals of aromatic aldehydes.

The two-step one-pot irradiation/oxidation procedure, starting with 9, gives imines 11 topologically similar to imines 6 except for the placement of the imine nitrogen atom in the diazacane ring, Scheme 4.

At this point it was abundantly clear that this new photoinduced cycloaddition reaction of aza-o-xylylenes with oxazole pendants is rather general in its scope. We therefore surveyed known multicomponent reactions of imines suitable for postphotochemical diversification of the polyheterocyclic imine-containing scaffolds **6** and **11**. This work is in progress, and the full account will be reported elsewhere. In this Letter we wish to report a new three-component reaction involving bromoacetyl bromide.

We have found that imine 6 or 11 reacts cleanly with bromoacetyl bromide producing reactive synthons, latent acyl iminium salts with two 1,4-electrophilic centers.<sup>5</sup> Scheme 5 shows the formation of dibromide synthon 12 from imine 11f (Ar = Ph). Under the optimized conditions (equimolar reagent, 4 h in dichloromethane at 20 °C), dibromide 12 is formed at a 95+% purity and does not require further purification.<sup>6</sup>

Scheme 4. Photocyclization/Oxidation Sequence in Oxazole-2-yl Tethered Photoprecursors 9







Synthon 12 is a versatile reactive 1,4-dibromide, which can be engaged by various dinucleophiles under mild conditions to append the pyrrolidino-benzodiazacane core of the primary [4 + 4] photoproducts with an additional heterolactam ring as large as one that is nine-membered, as in the case of thiosalicylic acid<sup>7</sup> (its X-ray structure is shown), Scheme 6.

To summarize, we have demonstrated that photogenerated aza-o-xylylenes are capable of intramolecular cycloadditions with tethered oxazole pendants. Unlike previously reported reactions with the furan-, thiophene-, or pyrrole-based unsaturated pendants, which give primary photoproducts containing reactive *nucleophilic* double bonds, the photoinduced

Scheme 6. Further Diversification of the Primary Photoproducts via the Reactions of 1,4-Dibromo Synthon 12 with Dinucleophiles; ORTEP Drawing of 15 Is Shown



reactions of oxazole pendants offer access to strained cyclic imines, i.e. reactive *electrophilic* moieties, potentially suitable for postphotochemical transformations via existing multicomponent reactions. Additionally, a new three-component reaction was developed, which involves *in situ* generation of 1,4dielectrophilic species,  $\alpha, \alpha'$ -dibromo amide **12**, upon treatment of the primary photoproducts with bromoacetyl bromide, and subsequent reaction with dinucleophiles to yield fused (hetero) lactams of varied ring sizes, further diversifying the resulting polyheterocyclic cores.

# ASSOCIATED CONTENT

#### **Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.5b03503.

Experimental details and NMR spectra (PDF) Crystallographic data for 3c (CIF) Crystallographic data for 11g (CIF) Crystallographic data for 15 (CIF)

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Notes

The authors declare no competing financial interest.

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(4) Photochemistry of minor diamidoenones 7 will be addressed elsewhere. In this Letter we will focus on the major photoproduct possessing a 1,3-diazacane core.

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(5) Similar reactions of chloroacetyl chloride with imines are known:
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(6) Stereochemical assignment in 12 (*exo*-Br vs *endo*-Br) was challenging as there are no useful proton-proton coupling constants which can be used for stereoassignment. We assigned the *exo*-Br stereochemistry based on DFT calculations: according to B3LYP/-631+G(d,p) the *exo*-isomer is 4.5 kcal/mol more stable than the *endo*-isomer. We hypothesize that there exists an *exo*-*endo* equilibration mechanism through ionization of the C-Br bond and formation of transient iminium ion. The experimental <sup>1</sup>H NMR spectrum does not show any evidence for the presence of the second stereoisomer, which is in keeping with the DFT results which would predict less than 0.05% of the minor *endo*-isomer.

(7) The *exo*-stereochemistry of the carboxylate, as clearly demonstrated by the X-ray structure, is also in keeping with the hypothesis of a transient acyliminium intermediate in an  $S_N$ 1-like substitution at the iminium carbon.