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Letter

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

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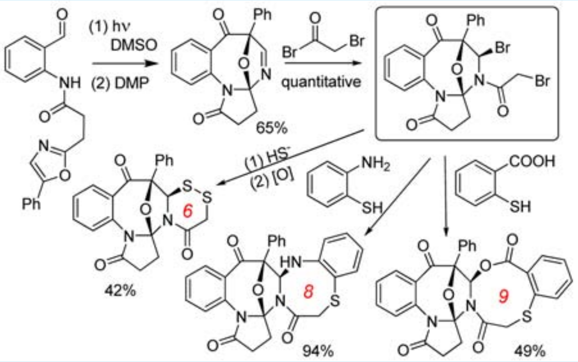
Supporting Information

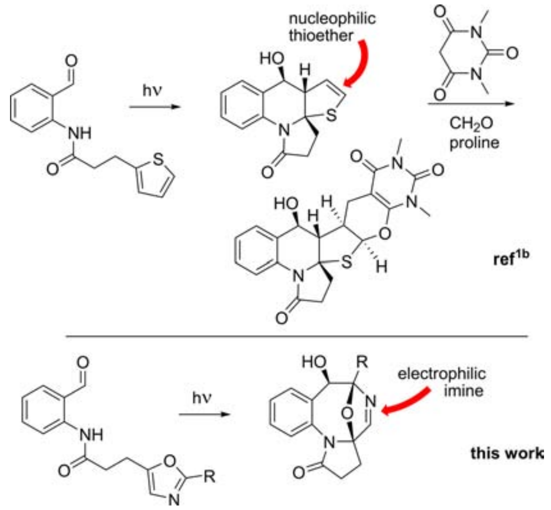
ABSTRACT: Photogenerated aza-*o*-xylylenes undergo intramolecular cycloaddition reactions to tethered oxazoles, with primary photoproducts featuring a reactive cyclic imine moiety suitable for multicomponent postphotochemical transformations. For example, the reaction of these imine photoproducts with 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).



Intramolecular 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.[1] 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[1b] (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).

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)



In this Letter, we report that *oxazoles*,[2] 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 cyclizations, 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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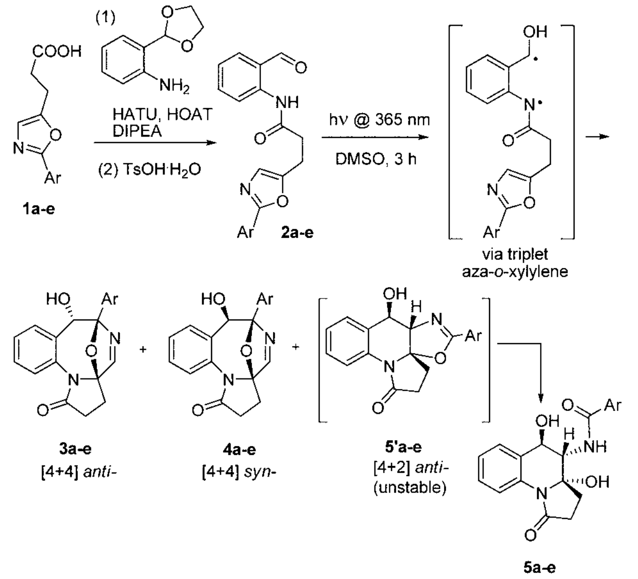
as described in the literature[3] and outfitted with photoactive *o*-aminobenzaldehyde cores to yield photoprecursors **2a–e** as shown in Scheme 2. Upon UV-irradiation with 365 nm UV LEDs, oxazoles **2** underwent ESIPT-mediated [4 + 4] and [4 + 2] formal photocyclizations to form primary photoproducts **3–5**. As we reported earlier,[1f] 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.

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



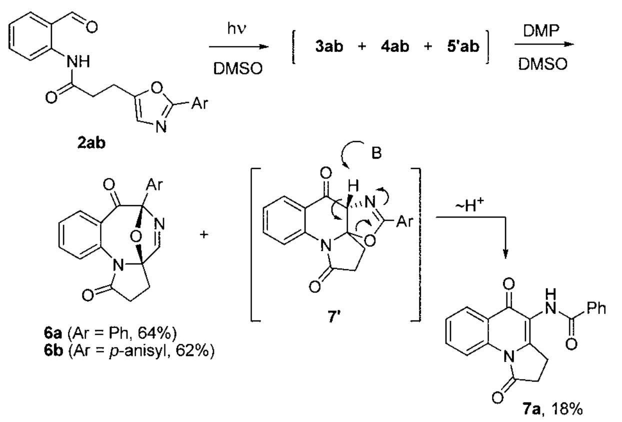
The combined isolated yield of the diastereomers of the major [4 + 4] photoproducts was 60–70%. As we were aiming to introduce the newly formed cyclic imine functionality into postphotochemical transformations, we elected to oxidize the reaction mixture before isolation of the [4 + 4] product to convert benzylic alcohol into the keto group. This helps avoid complications in subsequent transformations, prevents retro-cyclization, and reduces the number of diastereomers to just one. As Scheme 3 illustrates, the one-pot irradiation/oxidation 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.[4]

Table 1. Isolated Yields for Primary Photoproducts in the Reaction of 5-Tethered Oxazoles

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

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

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



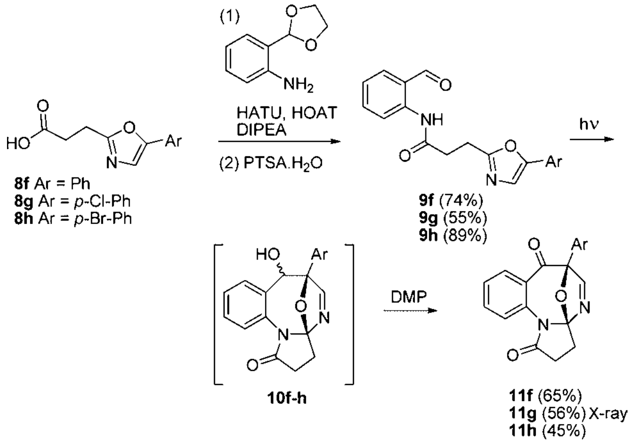
Photoprecursors **9** possessing the oxazole pendants tethered through position 2 (i.e., not 5) are also readily "assembled" in a modular fashion. Their photochemistry is similar to that of 5-substituted oxazoles **2**, although they do not form the [4 + 2] photoproducts, only [4 + 4], conceivably because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

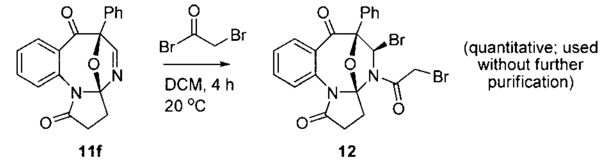
At this point it was abundantly clear that this new photoinduced cycloaddition reaction of aza-*o*-xylylenes with oxazole pendants is rather general in its scope. We therefore surveyed known multicomponent reactions of imines suitable for postphotochemical diversification of the polyheterocyclic imine-containing 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.[5] 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.[6]

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



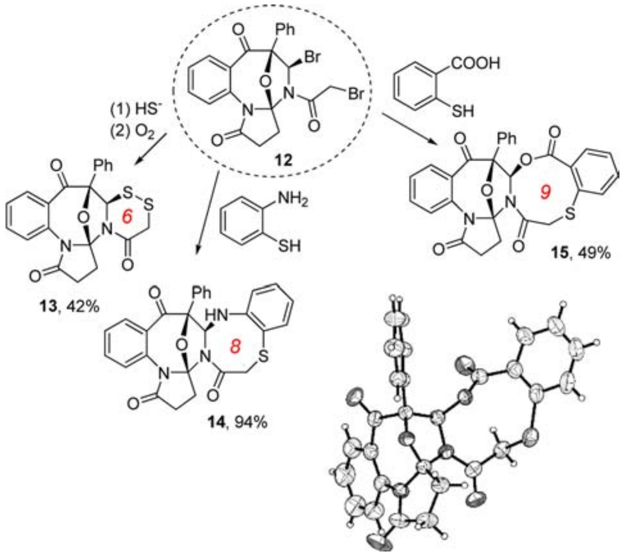
Scheme 5. *In Situ* Generation of 1,4-Dibromo Synthon 12



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[7] (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 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 1,4-dielectrophilic species, α,α'-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.

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



■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.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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(2) Photoinduced electrocyclizations and [4 + 2] cycloadditions of oxazoles are precedented in the literature, but to the best of our knowledge, oxazoles are not known to undergo [4 + 4] cyclizations: (a) Šagud, I.; Faraguna, F.; Marinić, Ž.; Šindler-Kulyk, M. *J. Org. Chem.* **2011**, *76*, 2904. (b) Šagud, I.; Božić; Marinić, Ž.; Šindler-Kulyk, M. *Beilstein J. Org. Chem.* **2014**, *10*, 2222. (c) Šagud, I.; Antol, I.; Marinić, Ž.; Šindler-Kulyk, M. *J. Org. Chem.* **2015**, *80*, 9535.

(3) (a) Synthesized from commercial aminolevulinic methyl ester: Suzuki, K.; Yamaguchi, T.; Tamura, A.; Nishizawa, T.; Yamaguchi, M. PCT Int. Appl. 2010, WO2010004972. (b) **1b** is also reported in: Siegel, C.; Bastos, C. M.; Harris, D. J.; Dios, A.; Lee, E.; Silva, R.; Cuff, L. M.; Levine, M.; Celatka, C.; Vinick, F. et al. PCT Int. Appl. 2008, WO 2008150486.

(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.

(5) Similar reactions of chloroacetyl chloride with imines are known: (a) Golding, B. T.; Hall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1975**, *13*, 1302. (b) Lidert, Z.; Gronowitz, S. *Synthesis* **1980**, *1980*, 322. (c) Venkov, A.; Nikolova, M.; Mollov, N. *Synthesis* **1982**, *1982*, 216. (d) Schwarze, W.; Drauz, K.; Martens, J. *Chemiker-Zeitung* **1987**, *111*, 149.

(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 ^{1}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_N1-like substitution at the iminium carbon.

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