Cycloaddition

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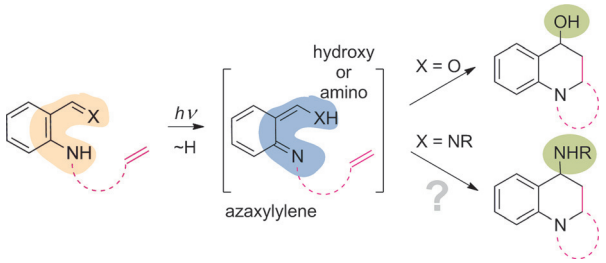
Amino Azaxylylenes Photogenerated from *o*-Amido Imines: Photoassisted Access to Complex Spiro-Poly-Heterocycles**

*Olga A. Mukhina, Dmitry M. Kuznetsov, Teresa M. Cowger, and Andrei G. Kutateladze**

Abstract: *Upon irradiation, cyclic imines containing o-amido groups are shown to produce reactive intermediates, amino azaxylylenes, which undergo intramolecular cycloadditions to tethered unsaturated pendants to yield complex N,O-heterocycles having an additional spiro-connected nitrogen heterocyclic moiety. Modular assembly of the photoprecursors allows expeditious increase of the complexity of the target poly-heterocyclic scaffolds with a minimal number of experimentally simple reaction steps. The photocyclization and subsequent postphotochemical transformations are accompanied by an increase of Lovering's fsp3 factor, thus producing unprecedented three-dimensional molecular architectures, and offering extended sampling of chemical space.*

Earlier we demonstrated that hydroxyl azaxylylenes, generated by excited-state intramolecular proton transfer (ESIPT) within aromatic *o*-aminoketones, are capable of intramolecular cycloadditions yielding novel poly-heterocyclic molecular architectures possessing quinolinol (shown) or benzazacane cores [Scheme 1; (X = O)].[1]

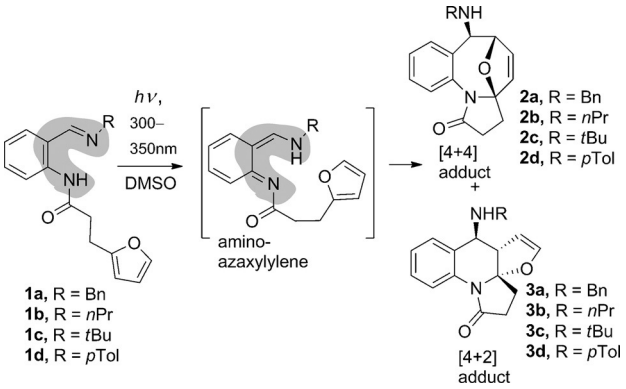


Scheme 1. Photogeneration of azaxylylenes and their intramolecular photocyclizations.

Direct incorporation of an amino functionality into such poly-heterocyclic scaffolds through cycloadditions of amino-substituted azaxylylenes derived from imines [Scheme 1; (X = N)] is appealing from a synthetic standpoint. However, despite being isoelectronic to the thoroughly studied carbonyl compounds, imines have rarely been the subjects of photochemical studies.[2] Such studies on imines are mostly limited to geometrical isomerization[3] with an occasional account of photochromism,[4] photoinduced electrocyclizations,[5] and cycloadditions.[6] The synthetic potential of imines in photochemical reactions is severely limited by the fast rotational dissipation of excitation energy. Given that ESIPT is known to occur in a number of hydrogen-bond donor–acceptor pairs, especially in *ortho*-substituted aromatic compounds, including imines,[7] we rationalized that such proton transfer must be happening at least on the same time scale if not faster than the rotational dissipation of excitation, and we attempted intramolecular trapping of imine-derived amino azaxylylenes. We now report that such photoassisted intramolecular transformations do indeed occur for imines, thus offering rapid access to novel poly-heterocyclic molecular architectures.

For the initial proof of concept we performed relative quantum yield (QY) experiments on the NMR scale, and demonstrated that several acyclic imine photoprecurors (**1a–d**; Scheme 2), which are readily available by the reaction of *o*-amido benzaldehydes and primary amines, yielded both the [4+2] and [4+4] photoproducts. The relative QY was highest in the case of benzylimine **1a** (Table 1). This could also be more practical as benzyl is a useful protecting group which can be readily removed.

The preparative scale irradiation of **1a** furnished the cycloadducts **2a** (45%) and **3a** (24%) after column separa-



Scheme 2. Photogeneration of amino azaxylylenes and their intramolecular photocyclizations (**2b–d** and **3b–d** were observed by ^{1}H NMR spectroscopy but not isolated). DMSO = dimethylsulfoxide.

Table 1: Relative quantum yields for **1a–d**.

	1a	1b	1c	1d
ϕ	(1.0)	0.83	0.65	0.05

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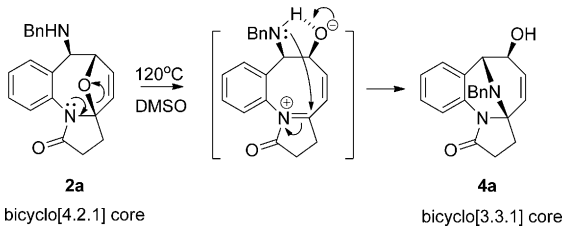
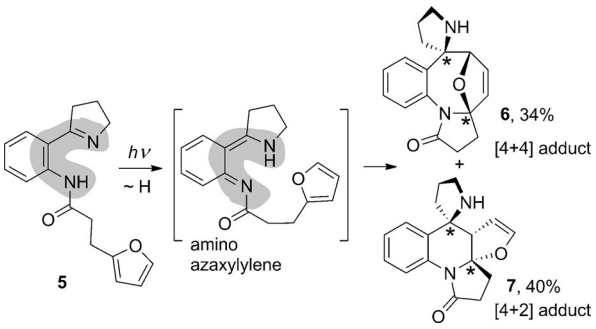
tion (Scheme 2). It is instructive that upon heating in DMSO, the [4+4] cycloadduct **3a** undergoes the same quantitative [4.2.1]→[3.3.1] rearrangement previously observed for the aldehyde-derived products,[11f,8] thus offering a simple approach to diversifying the heterocyclic core Scheme 3.



Scheme 3. The [4.2.1]→[3.3.1] rearrangement of **2a**.

We next examined cyclic imine photoprecursors and established that they are photoactive as well (note that the competing rotational relaxation channel is not available to cyclic imines in their excited state). Cyclic imines were expected to yield spiro-connected nitrogen heterocycles, which have attracted considerable interest in recent years[9] as their distinct three-dimensional structure arguably "furnishes access to denser, more rigid substructures"[10] and ostensibly allows probing vast areas of previously unexplored chemical space. They have been targets of several creative synthetic studies.[11] Herein we report a general method of the cyclic-imine-based photoassisted synthesis of complex nitrogen poly-heterocycles containing one or two spiro-connections.

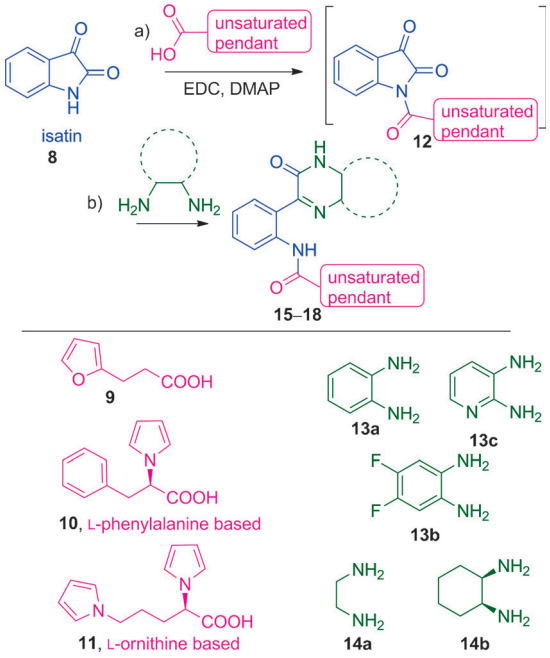
The model photoprecursor **5**,[12] outfitted with a pyrroline ring *ortho* to the amido moiety (see the Supporting Information for synthetic details) was irradiated in a broadband ($\lambda =$ 300–400 nm) Rayonet irradiator to yield the products of [4+2] and [4+4] cycloadditions (Scheme 4). In the photoproducts **6** and **7** the upper pyrrolidine is spiro-connected to a benzazacane and quinoline core, respectively. It is also easy to recognize that the lower pyrrolidone moiety, derived from the propanamide linker and fused to either quinoline or benzazacane cores, is also spiro-connected to the dihydrofuran (DHF) fragment.



Scheme 4. Photocyclization of the pyrroline photoprecursor **5**.

Encouraged by this result with a simple cyclic imine we surveyed methods for rapid modular assembly of photoprecursors possessing a cyclic imine moiety, with the goal of accessing more complex and diverse targets. As N-acylated isatins are known to ring-open with various nucleophiles and dinucleophiles,[13] we modified the Schreiber and Munoz synthetic procedure[14] for the synthesis of amidophenyl quinoxalinones to probe whether the imine moiety in quinoxalinones and their saturated counterparts is capable of initiating the photoinduced proton transfer and generating amino azaxylylenes, and to assess whether these amino azaxylylenes are cycloaddition-competent.

As shown in Scheme 5, the quinoxalinone photoprecursors **15a–c** and **16a,b** were synthesized by a) N-acylating the isatin **8** with carboxylic acids (**9–11**), carrying unsaturated pendants, under EDC/DMAP coupling conditions, and b) subsequent isatin ring opening with either the diamines **13** or **14**, that is, either aromatic *o*-phenylenediamines or aliphatic cyclohexane- or ethylene-1,2-diamine. Such simple and straightforward modular assembly of photoprecursors allows for at least three diversity inputs (including the potentially substituted isatins) and is consistent with the philosophy of diversity-oriented synthesis.[15]



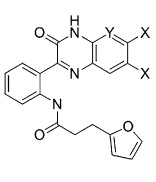
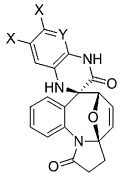
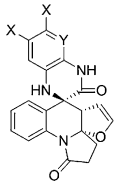
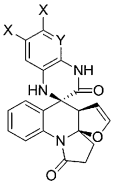
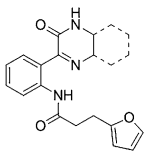
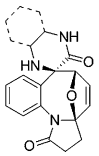
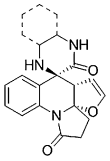
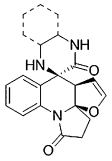
Scheme 5. Fast modular assembly of quinoxalinone photoprecursors from building blocks (*cis*-**14b** is used as a racemic mixture). EDC = [3-(dimethylamino)propyl]carbodiimide, DMAP = *N*,*N*-(dimethylamino)-pyridine.

Quinoxalinones bearing a carbonyl group conjugated to the imine were intentionally chosen for two reasons: 1) cycloadditions of photogenerated azaxylylenes with electron-rich unsaturated pendants were expected to proceed faster, reminiscent of inverse electron demand Diels–Alder reactions, and 2) this strategically placed carbonyl group allowed for utilization of either the oxophilic titanium- or lithium-based Lewis acids to further polarize and activate the azaxylylenes. We found that the photoinduced cyclization of

quinoxalinone-derived azaxylylenes in the presence of $Ti(OR)_4$ is accelerated by at least one order of magnitude, and potentially offers an opportunity to utilize chiral titanium chelators to induce enantioselective photocyclizations.[16]

The azaxylylene precursors **15** and **16** (see Table 2) have a broad UV absorption with a maximum at around 360 nm. Irradiations were carried out with Nichia 365 nm UV LEDs (for experimental details see the Supporting Information) in dichloromethane or DMSO. Optimization of irradiation conditions revealed that addition of one equivalent of a Lewis acid accelerates the reaction, with $Ti(OiPr)_4$ being particularly suitable because of its high solubility in dichloromethane. Irradiation proceeded smoothly, thus giving [4+4] and [4+2] cycloaddition products. The results of irradiation of the compounds **15a–c** and **16a,b** are summarized in Table 2.

Table 2: Photoinduced cyclizations of the quinoxalinones **15** and **16**.[a]

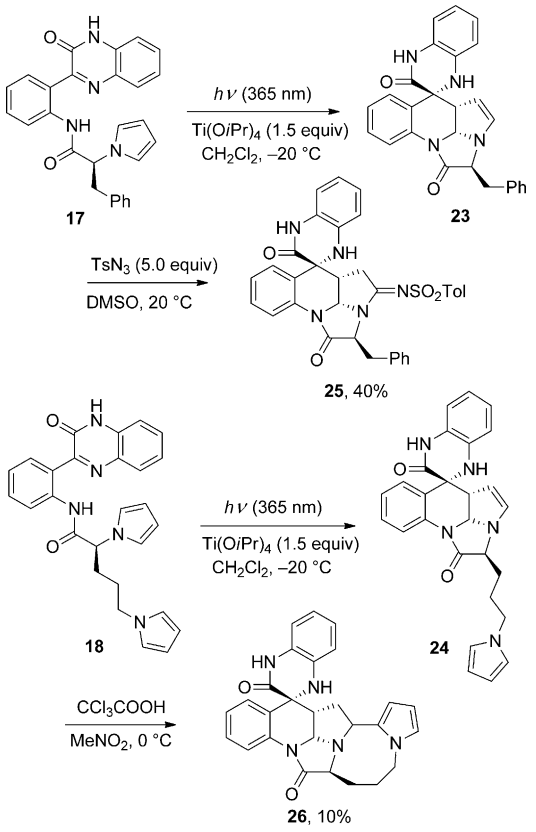
Photoprecursor	[4+4]	*anti*-[4+2] adduct	*syn*-[4+2] adduct
			
15a X = H, Y = CH	**19a** 31 %	*anti*-**20a** 18 %	*syn*-**20a** 8 %
15b X = F, Y = CH	**19b** 34 %	*anti*-**20b** 25 %	*syn*-**20b** 11 %
15c X = H, Y = N	**19c** 39 %	*anti*-**20c** 26 %	*syn*-**20c** –
			
16a, (based on **14a**)	**21a** 12 %	*anti*-**22a** –	*syn*-**22a** –
16b, (based on **14b**)	**21b**, (26 % + 23 %)[b]	*anti*-**22b**, (12 % + 15 %)[b]	*syn*-**22b** –

[a] Reaction conditions: 365 nm LED, CH_2Cl_2, 1–2 equiv $Ti(OiPr)_4$. Yield is that of the product isolated after column chromatography. [b] Diastereomers resulting from stereocenters in cyclohexanediamine.

The structures of the products were unambiguously determined by X-ray analysis (5 structures). The major products are the *syn*-[4+4] and *anti*-[4+2] adducts, where *syn* and *anti* describe relative stereochemical arrangement of the newly formed (benzylic) amino group and the oxygen atom of the dihydrofuran moiety. In several cases two [4+2] isomers are produced, with the *anti* adduct remaining the major product. Stereochemistry of the major product is supported by the ^{13}C NMR spectra: the chemical shift of the benzylic (spiro) carbon atom is within 1 ppm ($\delta = 59.8$–60.6 ppm) for all products regardless of stereochemistry, whereas the chemical shift of the neighboring bridgehead carbon atom changes from $\delta = 51$–53 ppm for the *anti* isomer to 57–58 ppm for the *syn*-isomer, that is, for the *anti* isomers: $\Delta\delta = 7.6$–8.6 ppm, while for the *syn*-isomers: $\Delta\delta = 2.9$ ppm.

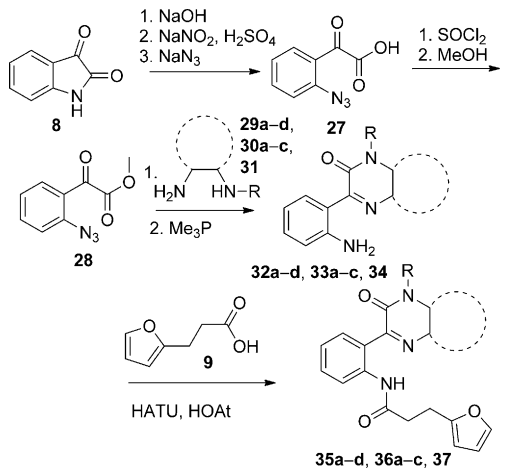
The reaction is not limited to aromatic imines, as exemplified by the ethylenediamine-based **16a** and *cis*-1,2-cyclohexanediamine-based precursor **16b** undergoing the same cycloaddition with moderate yields (Table 2). In the case of **16b**, both [4+4] and [4+2] products are formed as mixtures of diastereomers.

The photoactive core of quinoxalinones is reactive toward pyrrole-based unsaturated pendants. When pyrrole-containing carboxylic acids based on L-phenylalanine and L-ornithine are used for the acylation of isatin, the photoprecursors **17** and **18**, respectively, are obtained (Scheme 6). Both were found to be photoactive and yielded reactive synthones, pyrrolines **23** and **24**, resulting from stereoselective [4+2] cycloaddition. These enantiopure pyrrolines are further modified by post-photochemical transformations into sulfonylamidines (**25**) or diazacanes (**26**) containing a spiroquinoxalinone moiety and a total of five stereogenic centers. The yields of the products isolated after column chromatography are modest, yet these complex enantiopure molecular architectures are accessed in a two-step one-pot reaction from readily available precursors.



Scheme 6. Photoinduced cyclizations with pyrrole-containing amino-acid-based pendants yield complex enantiopure nitrogen heterocycles (yields for products isolated after two steps).

To further probe the scope of these photoinduced intramolecular cyclizations we also synthesized their derivatives with N-alkyl substituents on the quinoxalinone ring. Scheme 7



Scheme 7. Synthesis of N-substituted quinoxalinones. (for experimental details see the Supporting Information). HATU = *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, HOAt = 1-hydroxy-7-azabenzotriazole.

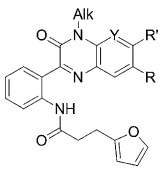
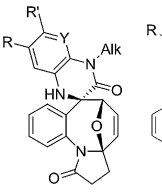
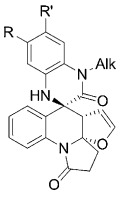
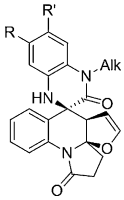
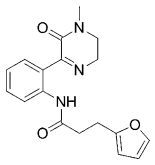
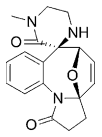
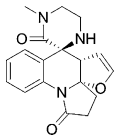
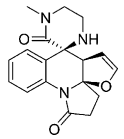
shows that in this case the methyl *o*-azidophenylglyoxalate **28**, which is readily available from isatin, was the key intermediate. While it adds two extra steps to the synthesis of the photoprecursors, these are high-yielding steps, with the anilines **32**–**34** synthesized in 0.5 gram quantities which can be stored for subsequent modification with various unsaturated substituents [Scheme 7, furanpropanoic acid (**9**) is shown].

Table 3 summarizes the photoinduced cyclizations in the N-substituted series. The formation of the [4+4] adduct proceeds with complete diastereoselectivity, thus yielding only the *syn* product. The pathway leading to the [4+2] adduct is complicated in some cases by the formation of two diastereomers, *syn* and *anti*. The second isomer (*syn*) proved difficult to isolate, and was sufficiently stable only in two cases: *syn*-**41b** and *syn*-**41c**. Similar to the N-H quinoxalinones, *syn* and *anti* isomers can be distinguished by ^{13}C NMR spectroscopy. Additionally, we were able to obtain X-ray structures for a number of [4+2] adducts (*anti*-**39a–d** as well as *syn*-**41c**), and they were critical for structure assignment.

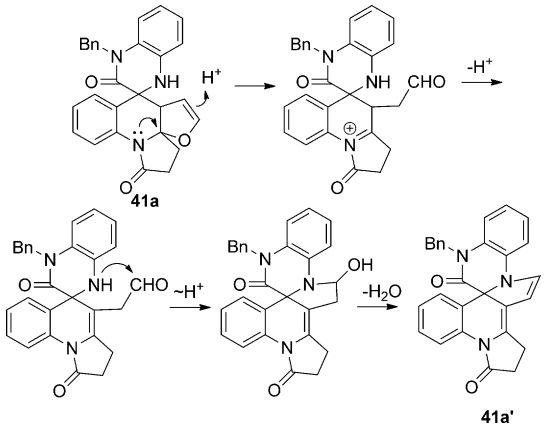
Generally, the 2,3-dihydrofuran, that is, [4+2] products, are more reactive and acid-sensitive than their [4+4] counterparts. In the case of **41a** we observed dihydrofuran (DHF) ring-opening and re-cyclization into the polyheterocycle **41a′**, which possesses an unprecedented piperazino-pyrrolino-quinoline core (Scheme 8). The structure of the product is confirmed by the agreement between the experimental and calculated ^{1}H and ^{13}C NMR chemical shifts and proton spin–spin coupling constants.[17]

In conclusion, upon irradiation of cyclic imines containing *o*-amido groups reactive intermediates, amino azaxylylenes, are produced and they are capable of intramolecular cycloadditions to tethered unsaturated pendants to yield complex N,O-heterocycles with additional spiro-connected nitrogen heterocyclic moiety. Modular assembly of photoprecursors allows expeditious growth of the complexity of the target poly-heterocyclic scaffolds and is achieved with a minimal number of experimentally simple reaction steps. The photocyclization and subsequent post-photochemical transformations are accompanied by the increase of Lovering's fsp^3 factor,[18] producing unprecedented three-dimensional molecular architectures and thus offering extended sampling of chemical space.

Table 3: Photoinduced cyclizations of N-alkylated quinoxalinones.

Photoprecursor	[4+4]	*anti*-[4+2] adduct	*syn*-[4+2] adduct
			
Alk = Me, Y = CH			
35a R = R′ = H	**38a** 42%	*anti*-**39a** 18%	*syn*-**39a** –
35b R = Me, R′ = H	**38b** 42%	*anti*-**39b** 19%	*syn*-**39b**[b]
35c R = OMe, R′ = H	**38c** 33%	*anti*-**39c** 13%	*syn*-**39c**[b]
35d R = Cl, R′ = H	**38d** 32%	*anti*-**39d** 18%	*syn*-**39d** –
Alk = Bn			
36a Y = CH, R = R′ = H	**40a** 33%	**41a′**[a] 12%	
36b Y = CH, R = R′ = Me	**40b** 27%	*anti*-**41b** 24%	*syn*-**41b** 20%
36c Y = N, R = R′ = H	**40c** 17%	*anti*-**41c** 35%	*syn*-**41c** 13%
			
37	**42** 39%	*anti*-**43** 35%	*syn*-**43**

[a] Reaction conditions: 365 nm LED, CH_2Cl_2, 1–2 equiv $Ti(OiPr)_4$. See Scheme 8. [b] Observed by NMR spectroscopy and not isolated.



Scheme 8. The DHF to pyrroline rearrangement.

Keywords: cycloaddition · heterocycles · photochemistry · spiro compounds · synthetic methods

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