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

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Graphical abstract

Keywords

quinoxalinones; amino-azaxylylenes; [4+2] cycloaddition; [4+4] cycloaddition; polyheterocycles; photoassisted DOS

Earlier we demonstrated that *hydroxy*-azaxylylenes, generated via excited state intramolecular proton transfer (ESIPT) in aromatic *o*-aminoketones, are capable of intramolecular cycloadditions yielding novel polyheterocyclic molecular architectures possessing quinolinol (shown) or benzazacane cores, Scheme 1 (X=O).¹

Direct incorporation of an amino functionality into such polyheterocyclic scaffolds resulting from cycloadditions of amino-substituted azaxylylenes derived from imines (i.e. X = N) is appealing from the synthetic standpoint. However, despite being isoelectronic to the thoroughly studied carbonyl compounds, imines have rarely been subjects of photochemical studies,² which were mostly limited to geometrical isomerization³ with an occasional account of photochromism,⁴ photo induced electrocyclizations⁵, and cycloadditions.⁶ Their synthetic potential 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 H-bond donor-acceptor pairs, especially in *ortho*-aromatic compounds including imines,⁷ we

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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 attempted intramolecular trapping of imine-derived *amino*-azaxylylenes. We now report that such photoassisted intramolecular transformations indeed occur in imines, offering rapid access to novel polyheterocyclic architectures.

For the initial proof of concept we performed NMR-scale relative quantum yield (QY) experiments demonstrating that several acyclic imine photoprecursors **1a-d**, readily available via the reaction of *o*-amido benzaldehydes and primary amines, yielded both the [4+2] and [4+4] photoproducts. Relative QY was highest in the case of **1a** (R = Bn, Table 1), which could also be more practical, as benzyl is a useful protecting group, which can be readily removed when needed.

The preparative scale irradiation of **1a** furnished cycloadducts **2a** (45%) and **3a** (24%) respectively after column separation. It is instructive that upon heating in DMSO [4+4] cycloadduct **3a** undergoes the same quantitative [4.2.1]→[3.3.1] rearrangement previously observed for the aldehyde-derived products,^{1f,8} offering a simple approach to diversifying the heterocyclic core.

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 commanded considerable interest in recent years⁹ as their distinct three-dimensional structure arguably “furnishes access to denser, more rigid substructures”¹⁰ and ostensibly allows for probing vast areas of previously unexplored chemical space. They have been targets of several creative synthetic studies.¹¹ Here we report a general method of cyclic imine-based photoassisted synthesis of complex nitrogen polyheterocycles containing one or two spiro connections.

Model photo precursor **5**,¹² outfitted with a pyrroline ring *ortho* to the amido moiety (see SI for synthetic details) was irradiated in a broadband 300-400 nm Rayonet irradiator to yield the products of [4+2] and [4+4] cycloaddition (Scheme 4). In the photoproducts **6** and **7** the “northern” pyrrolidine is spiro-connected to benzazacane or quinoline cores. It is also easy to recognize that the south-bridged pyrrolidone moiety, derived from the propanamide linker and fused to quinoline or benzazacane cores, is also spiro-connected to the dihydrofuran (DHF) fragment.

Encouraged by this result with simple cyclic imine we have surveyed methods for rapid modular “assembly” of photo precursors 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 procedure¹⁴ 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, quinoxalinone photo precursors **15a-c** and **16a,b** were synthesized by (i) N-acylating isatin **8** with carboxylic acids **9-11**, carrying unsaturated pendants, under EDC/DMAP coupling conditions, (ii) subsequent isatin ring opening with a diamine **13** or **14**, i.e. either aromatic *o*-phenylenediamines or aliphatic cyclohexane- or ethylene-1,2-diamine. Such simple and straightforward modular assembly of photo precursors allows for at least three diversity inputs (including the potentially substituted isatins) and is consistent with the philosophy of diversity-oriented synthesis¹⁵.

Quinoxalinones bearing a carbonyl group conjugated to the imine were intentionally chosen for two reasons: (i) cycloadditions of photogenerated azaxylylenes with electron rich unsaturated pendants were expected to proceed faster, reminiscent of inverse electron demand Diels-Alder reactions, and (ii) this strategically placed carbonyl group allowed for utilization of 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, which potentially offers an opportunity to utilize chiral titanium chelators inducing enantioselective photocyclizations.¹⁶

Azaxylylene precursors **15** and **16** have broad UV absorption with a maximum at around 360 nm. Irradiations were carried out with Nichia 365 nm UV LEDs (for experimental details see SI) 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 due to its high solubility in dichloromethane. Irradiation proceeded smoothly giving [4+4] and [4+2] cycloaddition products. The results of irradiation of compounds **15a-c** and **16a,b** are summarized in Table 2.

The structures of the products were unambiguously determined by Xray analysis (total of 5 structures). The major products are the *syn*-[4+4] and *anti*-[4+2] 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 *anti*- remaining the major. Stereochemistry of the major product is supported by the ¹³C NMR spectra: chemical shift of the benzylic (spiro) carbon is within 1ppm (59.8-60.6 ppm) for all products regardless of stereochemistry, whereas chemical shift of the neighboring bridgehead carbon changes from 51-53 ppm for the *anti*-isomer to 57-58 ppm for the *syn*-; i.e., for the *anti*-isomers $\delta = 7.6$ -8.6 ppm, while for the *syn*-isomers $\delta = 2.9$ ppm.

The reaction is not limited to aromatic imines, as exemplified by ethylenediamine-based **16a** and *cis*-1,2-cyclohexanediamine-based precursor **16b** undergoing the same cycloaddition with moderate yields. 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 or L-ornithine are used for acylation of isatin, photoprecursors **17** and **18** are obtained. Both were found to be photoactive and yield reactive synthones, pyrrolines **23** and **24**, resulting from

stereoselective [4+2] cycloaddition. These *enantiopure* pyrrolines are further modified via post-photochemical transformations into sulfonylamidines (**25**) or diazacanes (**26**) containing a spiro-quinoxalinone moiety and a total of five stereogenic centers, Scheme 6.

The isolated yields after column chromatography are modest; yet these complex enantiopure molecular architectures are accessed via a two-step one-pot reaction from readily available precursors.

To further probe the scope of these photoinduced intramolecular cyclizations we also synthesized their derivatives with *N-alkyl* substitution in the quinoxalinone ring. Scheme 7 shows that in this case methyl *o*-azidophenylglyoxalate **28**, readily available from isatin, was the key intermediate.

While it adds two extra steps to the synthesis of photoprecursors, these are high-yielding steps, with anilines **32-34** synthesized in 0.5 gram quantities and stored to be subsequently outfitted with diverse unsaturated pendants (Scheme 7, furanpropanoic acid is shown).

Table 3 summarizes the photoinduced cyclizations in the N-substituted series. The formation of the [4+4] adduct proceeds with complete diastereoselectivity, 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**. Similarly to N-H quinoxalinones, *syn*- and *anti*- isomers can be distinguished by ¹³C NMR. Additionally, we were able to obtain Xray structures for a number of [4+2] adducts, **anti-39a-d** as well as **syn-41c**, which was critical for structure assignment.

Generally, the 2,3-dihydrofuran – i.e. [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 recyclization into polyheterocycle **41a'**, possessing unprecedented piperazino-pyrrolino-quinoline core, Scheme 8. The structure of the product is confirmed by the agreement between the experimental and calculated ¹H and ¹³C NMR chemical shifts and proton spin-spin coupling constants.¹⁷

In conclusion: upon irradiation, cyclic imines containing *o*-amido groups are shown to produce reactive intermediates, *amino*-azaxylylenes, capable of intramolecular cycloadditions to tethered unsaturated pendants yielding complex N,O-heterocycles with additional spiro connected nitrogen heterocyclic moiety. Modular assembly of photoprecursors allows for expeditious growth of complexity of the target polyheterocyclic scaffolds achieved with a minimal number of experimentally simple reaction steps. The photocyclization and subsequent postphotochemical transformations are accompanied by the increase of Lovering's fsp³ factor,¹⁸ producing unprecedented 3D molecular architectures and thus offering extended sampling of chemical space.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Mukhina OA, Kumar NNB, Arisco TM, Valiulin RA, Metzel GA, Kutateladze AG. *Angew Chem, Int Ed*. 2011; 50:9423. (b) Nandurkar NS, Kumar NNB, Mukhina OA, Kutateladze AG. *ACS Comb Sci*. 2013; 15:73. [PubMed: 23157463] (c) Kumar NNB, Mukhina OA, Kutateladze AG. *J Am Chem Soc*. 2013; 135:9608. [PubMed: 23789841] (d) Cronk WC, Mukhina OA, Kutateladze AG. *J Org Chem*. 2014; 79:1235. [PubMed: 24397435] (e) Kumar NNB, Kuznetsov DM, Kutateladze AG. *Org Lett*. 2015; 17:438. [PubMed: 25587772] (f) Mukhina OA, Kumar NNB, Cowger TM, Kutateladze AG. *J Org Chem*. 2014; 79(22):10956. [PubMed: 25370821] (g) Umstead WJ, Mukhina OA, Kutateladze AG. *Eur J Org Chem*. 2015 accepted.
2. (a) Pratt AC. *Soc Rev*. 1977; 6:63. (b) Padwa A. *Chem Rev*. 1977; 77:37.
3. (a) Belowich ME, Stoddart JF. *Chem Soc Rev*. 2012; 41:2003. [PubMed: 22310886] (b) Lehn JM. *Chem Eur J*. 2006; 12:5910. [PubMed: 16800010]
4. Amimoto K, Kawato T. *J Photochem Photobiol C*. 2005; 6:207.
5. Austin M, Egan OJ, Tully R, Pratt AC. *Org Biomol Chem*. 2007; 5:3778. [PubMed: 18004457]
6. for a recent example, see Sampedro D, Soldevilla A, Campos PJ, Ruiz R, Rodrigues MA. *J Org Chem*. 2008; 73:8331. [PubMed: 18826280] for a review, see: Nishio T. *CRC Handbook of Organic Photochemistry and Photobiology*. Horspool W. CRC Press Boca Raton 1995:841.
7. Gao F, Ye X, Li H, Zhong X, Wang Q. *ChemPhysChem*. 2012; 13:1313. [PubMed: 22344872]
8. Similar molecular skeleton was previously accessed by the reaction of quinazolines with 1,3-bis(silyl enol ethers) Karapetyan V, Mkrtchyan S, Schmidt A, Gutlein JP, Villinger A, Reinke H, Jiao H, Fischer C, Langer P. *Org Biomol Chem*. 2008; 6:2961. [PubMed: 18688489] Karapetyan V, Mkrtchyan S, Karapetyan G, Villinger A, Saghiyan A, Ghochikyan TV, Langer P. *Helv Chim Acta*. 2011; 94:2045.
9. (a) Marson CM. *Chem Soc Rev*. 2011; 40:5514. [PubMed: 21837344] (b) Zheng Y, Tice CM, Singh SB. *Bioorg Med Chem Lett*. 2014; 24:3673. [PubMed: 25052427]
10. Carreira EM, Fessard TC. *Chem Rev*. 2014; 114:8257. [PubMed: 25003801]
11. for recent examples see: Perry MA, Hill RR, Rychnovsky SR. *Org Lett*. 2013; 15:2226. [PubMed: 23594129] Kong K, Enquist HA Jr, Mc Callum ME, Smith GM, Matsumaru T, Menhaji-Klotz E, Wood JL. *J Am Chem Soc*. 2013; 135:10890. [PubMed: 23837485] Kotha S, Deb AC, Lahiri K. *Synthesis*. 2009:165.
12. for experimental details see Supporting Information.
13. (a) Franke A. *Liebigs Ann Chem*. 1982:794. (b) Viswanathan N, Joshi BS, Likhate MA. *Proc Indian Acad Sci (Chem Sci)*. 1984; 93:589. (c) Hellal M, Cuny GD. *J Org Chem*. 2010; 75:3465. [PubMed: 20394404]
14. Weiwer M, Spoonamore J, Wei J, Guichard B, Ross NT, Masson K, Silkworth W, Dandapani S, Palmer M, Scherer CA, Stern AM, Schreiber SL, Munoz B. *ACS Med Chem Lett*. 2012; 3:1034. [PubMed: 23256033]
15. Dow, M.; Marchetti, F.; Nelson, A. *Diversity-Oriented Synthesis of Natural Product-Like Libraries*, in *Diversity-Oriented Synthesis: Basics and Applications in Organic Synthesis, Drug Discovery, and Chemical Biology*. Trabocchi, A., editor. John Wiley & Sons, Inc.; Hoboken, NJ, USA: 2013.
16. The results of the experiments with chiral TADDOL ligands will be published elsewhere
17. Kutateladze AG, Mukhina OA. *J Org Chem*. 2015; 80:1021/acs.joc.5b00619 for the previous version of rff see Kutateladze AG, Mukhina OA. *J Org Chem*. 2014; 79:8397. [PubMed: 25158224]
18. for Lovering's fsp3 parameter see: Lovering F, Bikker H, Humblet C. *J Med Chem*. 2009; 52:6752. [PubMed: 19827778]

Scheme 1. Photogeneration of azaxylylenes and their intramolecular photocyclizations

Scheme 2.

Photogeneration of *aminoazaxylylenes* and their intramolecular photocyclizations (**2b-d** and **3b-d** were observed by ^1H NMR but not isolated).

Scheme 3. The [4.2.1] $\rightarrow$ [3.3.1] rearrangement of **2a**

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

Scheme 5.

Fast modular assembly of quinoxalinone photoprecursors from building blocks (cis-**14b** is used as a racemic mixture).

Scheme 6.

Photoinduced cyclizations with pyrrole-containing amino acid-based pendants yield complex enantiopure nitrogen heterocycles (isolated yields are over two steps).

Scheme 7. Synthesis of N-substituted quinoxalinones. (for experimental details see SI)

Scheme 8.
The DHF to pyrroline rearrangement.

Table 1Relative quantum yields of **1a-1d**.

	1a	1b	1c	1d
ϕ	(1.0)	0.83	0.65	0.05

Table 2

Photoinduced cyclizations of quinoxalinones **15** and **16**.^a

Photoprecursor	[4+4]	<i>anti</i> -[4+2]	<i>syn</i> -[4+2]

15a X=H, Y=CH	19a 31%	<i>anti</i> - 20a 18%	<i>syn</i> - 20a 8%
15b X=F, Y=CH	19b 34%	<i>anti</i> - 20b 25%	<i>syn</i> - 20b 11%
15c X=H, Y=N	19c 39%	<i>anti</i> - 20c 26%	<i>syn</i> - 20c --

16a , (based on 14a)	21a 12%	<i>anti</i> - 22a --	<i>syn</i> - 22a --
16b , (based on 14b)	21b , (26%+23%) ^b	<i>anti</i> - 22b , (12%+15%) ^b	<i>syn</i> - 22b --

^a Isolated yields after column chromatography are shown;^b diastereomers due to stereocenters in cyclohexanediamine – see text.

Table 3
Photoinduced cyclizations of N-alkylated quinoxalinones

Photoprecursor	[4+4]	<i>anti</i> -[4+2]	<i>syn</i> -[4+2]
<p>Alk=Me, Y=CH</p> <p>35a R=R'=H</p> <p>35b R=Me, R'=H</p> <p>35c R=OMe, R'=H</p> <p>35d R=Cl, R'=H</p> <p>Alk=Bn</p> <p>36a Y=CH, R=R'=H</p> <p>36b Y=CH, R=R'=Me</p> <p>36c Y=N, R=R'=H</p>	<p>38a 42%</p> <p>38b 42%</p> <p>38c 33%</p> <p>38d 32%</p> <p>40a 33%</p> <p>40b 27%</p> <p>40c 17%</p>	<p><i>anti</i>-39a 18%</p> <p><i>anti</i>-39b 19%</p> <p><i>anti</i>-39c 13%</p> <p><i>anti</i>-39d 18%</p> <p><i>anti</i>-41b 24%</p> <p><i>anti</i>-41c 35%</p>	<p><i>syn</i>-39a --</p> <p><i>syn</i>-39b^b</p> <p><i>syn</i>-39c^b</p> <p><i>syn</i>-39d --</p> <p>41a^a 12%</p> <p><i>syn</i>-41b 20%</p> <p><i>syn</i>-41c 13%</p>
<p>42 39%</p>	<p><i>anti</i>-43 35%</p>	<p><i>syn</i>-43</p>

^a see Scheme 8^b observed by NMR, not isolated