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Rapid Photoassisted Access to N,O,S-Polyheterocycles with Benzoazocine and Hydroquinoline Cores via Intramolecular Cycloadditions of Photogenerated Azaxylylenes

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o-Azaxylylenes have been known for half a century,^[1] but remained in relative synthetic obscurity until a decade ago, when in this journal Corey reported their first preparation under simple mild conditions via base-induced elimination of hydrogen chloride from derivatives of *o*-chloromethylaniline,^[2] noting that “Surprisingly, simplest method possible for *o*-azaxylylene production [...] has never been reported.”

Given that synthetically useful reactions of *o*-xylylenes (i.e. all-carbon *o*-quinodimethanes) are plentiful,^[3] and their generation via intramolecular photoinduced hydrogen abstraction in aromatic *o*-alkyl ketones is well documented,^[4] it was surprising for us to realize that the equally simple photogeneration of *o*-azaxylylenes from *o*-aminoketones via excited state intramolecular proton transfer (ESIPT)^[5] has never been utilized in synthetic chemistry either.

It is conceivable that such implementation was attempted but failed due to the fast back proton transfer successfully competing with bimolecular cycloadditions. Intramolecular proton transfers from one heteroatom to another (and back) are fast: a typical example is the much studied photophysics of salicylaldehyde or *o*-hydroxyacetophenone, although the elusive tautomeric form is not impossible to characterize.^[6] We, however, found that the *intramolecular* cycloaddition reactions of *o*-azaxylylenes *photogenerated* via excited state proton transfer can successfully compete with the back proton transfer. In this Communication, we report the first example of [4+2] and [4+4] cycloaddition reactions of photogenerated azaxylylenes with unsaturated pendants, offering expeditious access to a diverse array of N,S,O-polyheterocycles with mostly unprecedented topologies (Scheme 1).

As the azaxylylenes are expected to act as acceptors in the inverse electron demand cycloaddition reactions, we synthesized photoactive azaxylylene precursors **1** and **4** by coupling *o*-aminoketones with furan- or thiophenepropionic acid chlorides.^[7] These *o*-acylamido precursors have broad UV absorption with a maximum at 340–350 nm. Irradiations were carried out with a Rayonet broadband 300–400 nm UV source or Nichia

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365 nm UV LEDs and gave stable polyheterocycles **2-3,5** possessing unprecedented doubly fused furo[2,3-b]quinoline and pyrrolo[1,2-a]quinoline motif in case of the [4+2] photoadducts **3,5** and the O-bridged pyrrolo[1,2-a]benzazocine core for the [4+4] photoadducts **2**, (Scheme 2, for experimental details refer to SI).

Chemoselectivity: as follows from Scheme 2, the furan-based photoprecursors yielded both [4+4] and [4+2] cycloadducts **2** and **3**. Their ratios were generally ranging from 1:1 to 2:3 (see also Table 1, which summarizes isolated yields, chemo-, and stereo-selectivities). In contrast, the thiophene derivatives **4a,b** undergo mostly [4+2] cycloaddition forming dihydrothiophenes **5a,b** (major) and **5'a** (a minor OH-epimer observed for R=H). Cycloadditions of thiophenes, especially in the acetophenone series (**b**, R=Me), most efficiently occur upon heating the reaction mixture during irradiation.

Diastereoselectivity, i.e. the *syn/anti* configuration of OH (relative to the heteroatom in the annelated ring or the bridge) was high in this series, with the predominant formation of *anti*-[4+2] and *syn*-[4+4] diastereomers, as shown. In some cases, benzaldehyde derivatives produced a small amount of minor OH-epimer (denoted with a prime). Ketones always reacted to yield exclusively the *anti*-isomer in the [4+2] case and the *syn*-isomer in the [4+4] case.

Mechanistically, this last example with tetralone **1d**, which lacks a rotatable carbonyl group, pointed to the *endo*-transition state (or *endo*-intermediate) in both [4+2] and [4+4] cycloadditions (Scheme 3). Our hypothesis is that benzaldehyde or acetophenone-derived azaxylylene also react with furan or thiophene pendants via a similar *endo*-transition state (or intermediate). In these cases, where the carbonyl group is rotatable, the minor OH-epimers potentially result from the *out*-OH conformer of azaxylylene (at this point, however, we do not know whether the mechanism is concerted or stepwise – *vide infra*).

While the detailed photophysical mechanistic study of these cycloadditions is ongoing and will be reported elsewhere, we suggest that these are excited state reactions, not the ground state additions of photo pre-generated azaxylylenes. All photoprecursors possess two characteristic emission bands in their fluorescence spectra: the 400 nm fluorescence from the initial amide form and the 540-550 nm band with a remarkably large Stokes shift, attributable to excited state intramolecular proton transfer (ESIPT) – in this particular case the emission from the S₁ state of azaxylylene. Conceivably this band can be used in a fluorescence quenching assay for high throughput screening/optimization of reaction conditions, similar to a report by Porco and Jones^[8] for 3-hydroxyquinolines.

At this point, it was clear that we have uncovered a powerful photoassisted reaction which offers expeditious access to topologically unique N,O,S-polyheterocycles. (Preparative potential of similar *all-carbon* [4+4] photoinduced cycloadditions of pyran-2-ones and pyridones to tethered furans accessing cyclooctane cores is exemplified in the elegant synthetic work of West,^[9] and Sieburth.^[10]) We evaluated the utilization of several simple and high-yielding reactions as candidates for the rapid “assembly” of photoprecursors and implemented them as shown below. First, we have developed a modular approach, suitable for combinatorial synthesis with several diversity inputs, based on a bromoacetyl bromide linker, inspired by the readily automated peptoid synthesis.^[11] The overall sequence is exemplified using protected *o*-aminobenzaldehyde (**7**) or unprotected *o*-aminoacetophenone (**6b**) in Scheme 4.

First, the reaction with bromoacetyl bromide yielded bromoacetamides **8, 9b** nearly quantitatively, which were used without further purification and served as key intermediates in accessing monoketo- and diketopiperazino-fused quinolines and benzazacines **16-26**. In

the left series shown in Scheme 4, bromoacetamides **8**, **9b** were reacted with benzylamine and subsequently acylated with 2-furoyl, thienyl, or pyrroloyl chlorides to furnish photoprecursors **10-12**.

Chemoselectivity: Azaxyllylenes photogenerated from these precursors, where the heteroyl pendant has a conjugated carbonyl, revealed considerable bias toward [4+4] cycloaddition (Table 1) especially in polar solvents (*cf.* MeCN *vs.* toluene or benzene). The pyrroloyl photoprecursor **12a** form [4+4] diketopiperazines **18a** exclusively; no [4+2] product was observed.

Diastereoselectivity was high in the [4+4] reactions, with the benzylic OH group positioned predominantly in the *syn* configuration to the endocyclic O, N, or S bridge. Non-polar solvents not capable of hydrogen bonding (benzene, toluene) afforded higher *d.r.* (diastereomeric ratio) values. Reactions were faster in acetonitrile, but at the expense of somewhat reduced diastereoselectivity at ambient temperature. Lowering the temperature to 0°C generally improves the *d.r.* values. The reactions are further accelerated in acetonitrile in the presence of up to 5 vol % of HMPA. We attribute this to longer lifetimes of excited azaxyllylenes hydrogen-bonded to HMPA, by analogy to the reported effect of HMPA on lifetimes of all-carbon xylylenes.^[4]

An alternative mode of the peptoid-inspired modular assembly of photoprecursors from bromoacetamides **8**, **9b** (refer to the right column in Scheme 4) involved the reaction with furfuryl amine and subsequent acylation with acyl chlorides or sulfonylation with benzenesulfonyl or dimethyl sulfamoyl chlorides (as the last diversity input) furnishing photoprecursors **13-15**. In this series the furan or thiophene pendant is tethered via a CH₂-bridge, not via a carbonyl group as in **10-12**. This appears to have a noticeable effect on chemoselectivity: the [4+4] to [4+2] ratio is decreased.

Diastereoselectivity of photoinduced cycloadditions in the aminoketones' series, i.e. the *syn:anti* ratio for the [4+4] cycloadducts and *anti:syn* ratio for the [4+2] adducts, is generally higher than benzaldehyde's. On the contrary, as a rule the relative quantum yields of cycloaddition are higher for the aldehyde. Table 1 lists the isolated yields of the products after column chromatography and also NMR-based ratios pertaining to the regioand stereochemical outcomes.

Both [4+4] and [4+2] cycloadducts shown in Scheme 4 are relatively stable and can be purified chromatographically, with the exception of pyrrole-based **18a**, which degraded on silica gel. The irradiations were carried out to quantitative conversion. For the preparative runs listed in Table 1 converting 100-300 mg of photoprecursor normally requires 2-4 hours of irradiation for benzaldehyde and tetralone derivatives, and up to 12 hours for the slower reacting acetophenone-alkenyl dyads. The latter can be accelerated to under 2-3 hours by carrying out the irradiation in refluxing toluene (conditions "B").

Enantiomerically pure photoprecursor **27a** was synthesized from bromoacetamide **8** with optically active (R)-(+)- α -phenylethylamine in a procedure similar to the synthesis of **10a**. However, as shown in Scheme 5, this chiral auxiliary did not transfer chirality as both [4+4] diastereomeric cores in cycloadducts **28-29** formed with little stereoselectivity, i.e. the **28:29** ratio was nearly 2:1.

Conceivably, this lack of chirality transfer is due to the fact that the chiral auxiliary is peripherally attached to the nitrogen atom of the tether linking the photoactive pendant with the furan moiety, and therefore has little effect on the folding of the tether in the transition state. As to *syn*-selectivity, it was expectedly high: only *syn*-epimers **28a** and **29a** were

observed at 0°C in acetonitrile. Irradiation at 25°C or in the presence of HMPA yielded small amounts of *anti*-epimers **28'a** and **29'a** (structures determined by xray crystallography).

We hypothesized that the incorporation of a cyclic amino acid such as L-proline or L-thiaproline into the tether should have a more pronounced effect on stereocontrol of the photocyclization (and, at the same time, can serve as another diversity input). Photoprecursors **32** were therefore synthesized by acylating L-proline or L-thiaproline with furoyl chloride, and coupling it to a photoactive pendant as shown in Scheme 6. At 0°C photocyclization of **32** occurred exclusively via the [4+4] pathway and gave adducts **33** (major) and their OH-epimers **33'** with *d.r.* of 12.5:1 for "C" and 4:1 for "S". The minor epimers **33'** are conceivably due to the rotatable formyl group in **32**, generating a small amount of the *out*-OH azaxylylene. Note, however, that unlike the reaction of **27a**, the polyheterocyclic core in **33/33'** is formed in a stereospecific fashion (i.e. for the given stereochemistry of L-proline, the bridgeheads have S,S not R,R configuration) indicating full stereochemical control of the tether's "folding" in the transition state by the (thia)proline moiety with 100% chirality transfer.

This example involves a modular assembly of photoprecursors **32** via two trivial high yielding amide bond formations – the acylation of an amine with an acyl chloride. This was followed by a photochemical step yielding **33** as the major product – an enantiomerically pure polyheterocycle with four stereogenic centers, one of which is quaternary.

To evaluate the scope of the photoassisted reactions of azaxylylenes, we also outfitted aminoketones (and amino-benzaldehyde) with *alkenyl pendants*. Irradiation of these photoprecursors **34**, **36**, and **37** yielded the products of [4+2] cycloaddition (Scheme 7).

The [4+2] reactions shown in Scheme 7 are accelerated at elevated temperatures, which is critical for the acetophenone derivatives (R=Me), where high yields are achieved in refluxing solvent within 3 hours of irradiation. Reactions with the aldehyde precursors (R=H) are much faster and proceed at ambient temperature, or at 0°C. Benzophenone derivatives (**f**) reacted very slowly with alkenes.

Cycloaddition in acetophenone-based **34b** (cyclopentenylacetic pendant) showed moderate diastereoselectivity: *d.r.* value of 3:1 was observed for the benzylic epimers **35b** and **35'b**, whereas *benzaldehyde*-derived **35a** and **35'a** formed in nearly equal amounts.

In most cases, the stereochemistry of the major diastereomers is unambiguously established by xray analysis (see SI). The structure of the minor products was inferred from NMR spectra and – in the benzaldehyde series – confirmed by PCC oxidation of epimeric alcohols **35a** and **35'a**, which both gave the same ketone **40**. The tetracyclic alcohol **38a** gave ketone **41**. Xray structures were obtained for both ketones **40** and **41**.

Although the formation of two epimers of alcohol **35** is observed in Scheme 7, a *concerted* mechanism is still a possibility. Such concerted cycloaddition can be rationalized invoking both *OH-in* and *OH-out* rotamers of azaxylylene. Alternatively, it may proceed via two different facial approaches of the cyclopentene moiety, resulting in the *endo*- and *exo*-transition states.

However, in the reactions of photoprecursors **34a,b** and **36** at 20°C we isolated aminorals **42a,b** and **43f** (up to 30%), Scheme 9, indicating that the excited state [4+2] cycloadditions of azaxylylenes to alkenes, which are formally not allowed by the orbital symmetry rules, may not be concerted at all.

Our mechanistic rationale for the amination formation, which is in keeping with the hypothesis of a non-concerted cycloaddition, is shown in Scheme 10. It involves N-attack of the excited azaxylylene (alternatively depicted as a 1,4-diradical) on the double bond to form the initial 1,6-diradical, which can (i) recombine to form both **35a** and **35'a**, or (ii) disproportionate by H-abstraction to form benzylic alcohol with an N-acyl enamine moiety, which undergoes subsequent ground state or photoinduced intramolecular alcohol addition to yield amination **42a**.

The formation of aminals **42** and **43** is fully suppressed at elevated temperatures (irrad. + reflux), i.e. the amination formation as a side product in slower reactions at 20°C can be readily rectified and therefore is not an issue from the preparative standpoint. However, it provides useful indirect evidence for the non-concerted pathway. It is also possible that a triplet state is involved in product formation.

In view of these findings it is conceivable that the additions to the heterocyclic furanyl, thienyl, or pyrrolyl pendants may also occur via a non-concerted singlet or triplet mechanism. Studies are under way in our laboratory to elucidate the detailed mechanism of these reactions.

In conclusion, we have discovered new cycloaddition reactions of *o*-azaxylylenes, generated via ESIPT from *o*-amido-substituted aldehydes or ketones, which provide rapid access to conformationally constrained fused N,O,S-polyhetero-cycles with benzoazocine or hydroquinoline cores. The photo precursors for these reactions can be readily assembled via simple coupling reactions, making the overall sequence amenable to high throughput diversity-oriented synthesis.

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Scheme 1.
Photogeneration of azaxylylenes and their intramolecular photocyclizations.

Scheme 2.

[4+2] and [4+4] cycloadditions of photogenerated azoxylylenes to the furan and thiophene pendants; **5'a** denotes the minor OH-epimer in the thiophene [4+2] cycloadduct. Isolated yields are shown; NMR-determined ratios are found in Table 1.

Scheme 3.

Diastereoselective photocyclization of amidotetralone **1d**. Xray structures of the [4+2] and [4+4] adducts are shown.

Scheme 4.

Peptoid synthesis-inspired modular assembly of azaxilylene precursors and their cyclizations. ^aAcetal hydrolysis step is required only in the “a” (i.e. benzaldehyde) series; ^bmajor diastereomer is shown, the minor OH-epimer (not shown) is denoted with a prime, **16'a** etc.

Scheme 6.

Photoassisted synthesis of fused ketopiperazines in the L-proline and L-thiaproline series.

Scheme 7.

[4+2]-Cycloadditions to alkenyl pendants. Irradiations of photoprecursors **b** (R=Me) were carried out in refluxing solvent.

Scheme 8.
Oxidation of epimeric alcohols led to the same ketone.

Scheme 9.
Aminals formed at lower temperatures.

Scheme 10. Mechanistic rationale for the formation of amins **42**.

Table 1

Isolated yields, conditions, chemoselectivity and stereoselectivity of cycloadditions.

Photo Precursor	Conditions ^a	Isolated yields ^b	Ratios by NMR	
			[4+4]:[4+2]	d.r. ^c [4+2] [4+4]
1a	C	2a , 25%; 3a , 55%	1:1	>30:1 >30:1
1b	C	2b , 30%; 3b , 53%	0.7:1	>30:1 >30:1
1c	A	2c , 53%; 3c , 23%	2.1:1	>30:1 >30:1
1d	A	2d , 43%; 3d , 46%;	1:1	>30:1 >30:1
1e	A	2e , 38%; 3e , 44%;	1.2:1	>30:1 >30:1
4a	A	5a , 64%	1:9	>30:1 >30:1
4b	B	5b , 60%	-	2:1 -
10a	A	16a , 47%; 16'a , 33%; 19a , 9%	12:1	1.5:1 >30:1
11a	F	17a/17'a , 26%	>30:1	- 0.55:1
12a	D	18a ^d	>30:1	- >30:1
13a	A	21a , 32%; 21'a , 8%; 23a , 33%	1.1:1	>30:1 4.3:1
13b	A	21b , 59%; 23b ^e	4.6:1	>30:1 >30:1
14b	A	22b , 57%; 24b , 28%	2.6:1	>30:1 >30:1
15a	A	25a , 46%; 25'a , 7%; 26a , 29%	1.9:1	>30:1 1:1.3
15b	A	25b , 45%; 26b , 36%	1.4:1	>30:1 >30:1
32C	E	33C , 53%	>30:1	- 9:1
32S	E	33S , 61%; 33'S , 11%	>30:1	- 8:1
34a	C	35a , 30%; 35'a , 26% ^f	-	1:1 -
34b	C	35b , 38%; 35'b , 13% ^g	-	3:1 -
36a	C	38a , 87%	-	>30:1 -
36b	C	38b , 85%	-	>30:1 -
36f	C	38f , 47% ^h	-	>30:1 -
37a	C	39a , 70%	-	>30:1 -

^a Conditions (100-300 mg loading): "A" – acetonitrile, 20°C; "B" – toluene, reflux; "C" – benzene, 20°C; "D" – acetonitrile, 0°C, 2 eq HMPA; "E" – acetonitrile, 0°C, 5 vol% HMPA; "F" – acetonitrile, reflux

- b* isolated yields after column chromatography
- c* *anti:syn* for [4+2] and *syn:anti* for [4+4]
- d* quantitative by NMR (see SI); decomposes during chromatography
- e* the [4+4] and [4+2] cycloadducts are not separable
- f* at 20°C animals **42ab**, **43f** were also formed; isolated yields: **42a** (17%)
- g* at 20°C animals **42ab**, **43f** were also formed; isolated yields: **42b** (30%)
- h* at 20°C animals **42ab**, **43f** were also formed; isolated yields: **43f** (30%)