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Intramolecular Cycloadditions of Photogenerated Azaxylylenes with Oxadiazoles Provide Direct Access to Versatile Polyheterocyclic Ketopiperazines Containing a Spiro-oxirane Moiety

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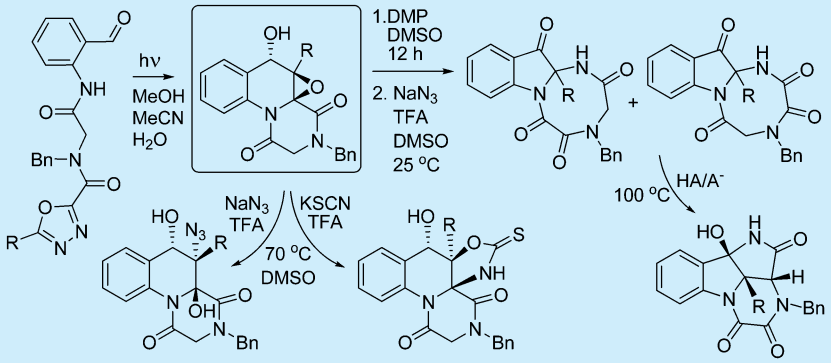
Supporting Information



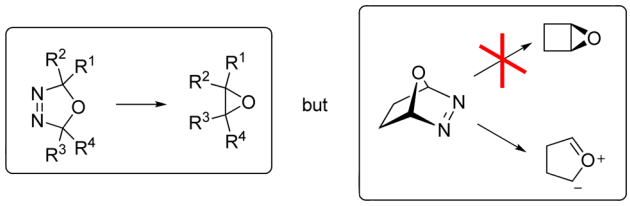
ABSTRACT: Photogenerated azaxylylenes undergo intramolecular cycloadditions to 1,3,4-oxadiazole pendants, which are accompanied by concomitant release of dinitrogen, yielding functionalized ketopiperazinoquinolinols containing an oxirane moiety fused to the quinolinole moiety while spiro-connected to diketopiperazine. These primary photoproducts are reactive versatile intermediates which can be further derivatized under nucleophilic S_N1- or S_N2-like ring opening of the oxirane moiety. The oxidized quinolinones undergo new rearrangements under the conditions of the Schmidt reaction, leading to unprecedented triazacanoindolinones.

1,3,4-Oxadiazoles react with *alkynes* in a hetero-Diels–Alder fashion with subsequent aromatization-driven extrusion of molecular nitrogen to yield substituted furans.[1] Similar reactions with *alkenes*, where aromatization upon nitrogen extrusion is not attainable, produce useful intermediates—cyclic carbonyl ylides. Boger recognized this early and developed an intramolecular tandem [4 + 2]/[3 + 2] cycloaddition cascade, where carbonyl ylides are intramolecularly trapped by nucleophilic alkenes to yield a "stereochemically rich pentacyclic core." This powerful methodology was successfully utilized in total syntheses of a spectacular array of alkaloids, including minovine, (−)-aspidospermine, (−)-spegazzinine, (+)-*N*-methylaspidospermidine, (−)-vindorosine, (−)-vindoline, and many other natural targets.[2,3]

Extrusion of molecular nitrogen from less strained monocyclic oxadiazolines yields oxiranes, Scheme 1.[4] This mode of action is not known for bicyclic oxadiazolines, plausibly because cycloaddition reactions of oxadiazoles producing such bicyclic intermediates were explored primarily in the hetero-Diels–Alder, i.e., [4 + 2] context, thus restricting the topology of oxadiazoline intermediates to a particularly strained oxadiazabicyclo[2.2.1] core, where the formation of 5-oxabicyclo[2.1.0]pentanes is not feasible.

We have been developing a novel photoassisted synthetic methodology based on intramolecular cycloadditions of azaxylylenes, photogenerated via excited state intermolecular proton transfer (ESIPT) in aromatic amino ketones, to unsaturated heterocyclic pendants such as furan, thiophene, or pyrrole. Depending on photoprecursors, both [4 + 2] and [4 + 4] cycloadditions were observed, with the [4 + 4] photoproducts shown to be predominant in the case of furoyl pendants.[5] We hypothesized that an intramolecular [4 + 4] photocycloaddition of azaxylylenes to 1,3,4-oxadiazolyl pendants could conceivably produce less strained oxadiazoline intermediates incorporated within the more accommodating bicyclo[4.2.1] scaffold, with likely formation of oxiranes as a

Scheme 1. Nitrogen Extrusion from Oxadiazoles of Mono- vs Bicyclic Topology



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result of photoinduced extrusion of molecular nitrogen. In this paper, we demonstrate that this is indeed the case. Moreover, as our approach allows for expeditious access to complex polyheterocyclic molecular architectures, the incorporation of oxirane moiety via a photochemical approach under neutral mild conditions might be the only way to synthesize these versatile and reactive synthons suitable for subsequent postphotochemical transformations.

We now report that azaxylylenes generated from photoprecursors **1a−e**, containing oxadiazole pendants, undergo intramolecular [4 + 4] cyclization accompanied by extrusion of molecular nitrogen to yield diketopiperazinoquinolinols **2a−e** possessing an oxirane moiety fused to quinolinol but spiro-connected to the diketopiperazine fragment, Scheme 2.[6]

Scheme 2. Rapid Photoassisted Access to Diketopiperazino-Oxiranoquinolinols

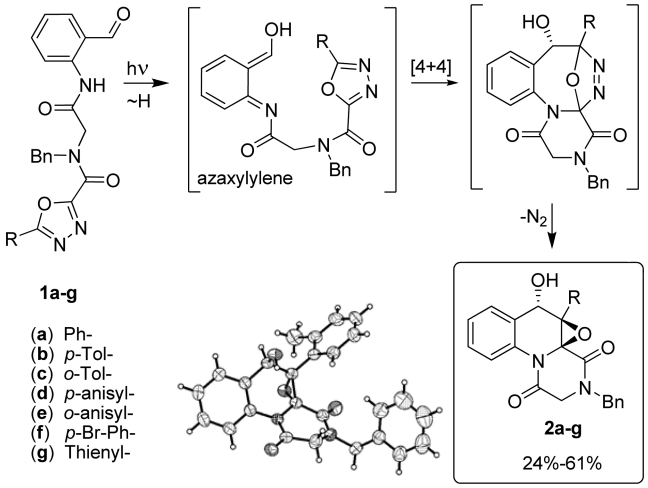


Table 1. Irradiation Conditions and Yields of Oxiranes 2

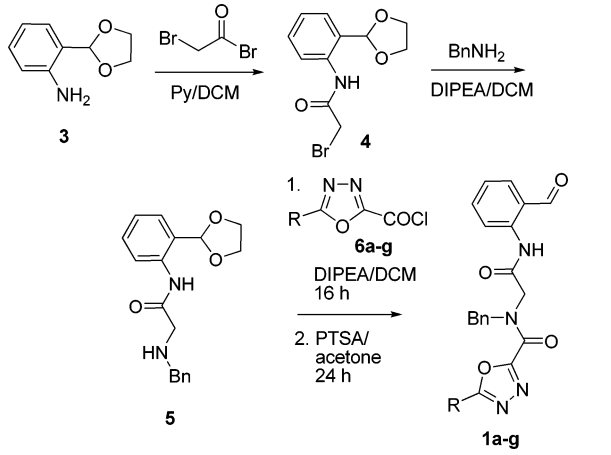
	R	solvent[a]	time (h)	yield[b] (%)
a	Ph-	A	48	61
b	*p*-Tol-	A	6	53
c	*o*-Tol-	A	35	52
d	*p*-anisyl-	A	9	58
e	*o*-anisyl	A	9	57
f	*p*-BrPh-	B	40	24
g	2-thienyl	C	12	43

[a]A: MeOH, 20 v/v % CH_3CN, 5 v/v % H_2O. B: DMSO. C: MeOH,+ 5 v/v % H_2O. [b]Isolated yields of oxiranes **2**.

As in our initial work,[5a] the modular "assembly" of photoprecursors **1a−e** is based on the peptoid synthesis inspired approach involving (i) acylation of the photoactive core, i.e., the aromatic *o*-aminoketone (or protected aldehyde) with bromoacetyl bromide to yield bromoacetanilide **4**, (ii) subsequent treatment with benzylamine to access *N*-benzylglycine **5**, and (iii) acylation with the substituted oxadiazolecarboxylates, Scheme 3. Theoretically, this modular approach allows for a minimum of three diversity inputs and thus qualifies for a diversity-oriented synthetic methodology.

Conditions and yields for irradiation of photoprecursors **1a−g** are summarized in Table 1. The oxiranes **2a−g** were isolated after column chromatography in moderate to good yields, except for *p*-bromophenyl derivative **2f**, which required DMSO

Scheme 3. Peptoid Synthesis Inspired Modular Assembly of Photoprecursors 1a−e

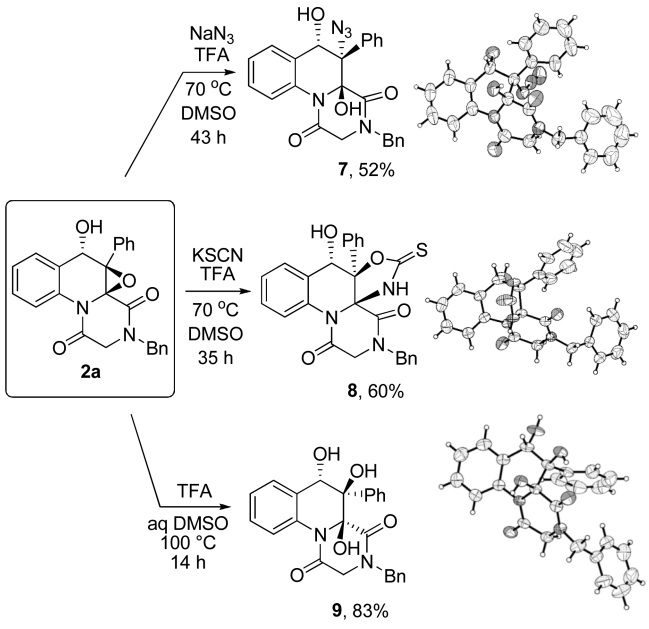


as the irradiation solvent. The latter affected the yield due to a challenging workup.

Oxiranes **2** belong to a small group of stable heterocyclic synthons containing a three-membered reactive heterocycle. A representative recent example is Yudin's versatile aziridino-*fused* ketopiperazines[7] obtained from aziridine aldehyde dimers.[8] In piperazinoquinolinols **2**, the oxirane moiety is fused to the quinolinol core, but it is *spiro*-linked to the diketopiperazine moiety, which potentially allows for nucleophile introduction both in the position 2 of quinolinol (i.e., the diketopiperazine ring) or position 3.

We first explored oxirane ring opening in **2a** under both S_N1 and S_N2 nucleophilic conditions as shown in Scheme 4 and

Scheme 4. Oxirane Ring Opening with Nucleophiles



found that an S_N2-like reaction of sodium azide produces azidodiol **7** with the anti attack of the azido group in position 3 of the quinolinol moiety. In contrast, under the S_N1 conditions, the protonated oxirane ring opens to form a more stable iminium, not benzylic, cation, which traps thiocyanate at the "hard" terminus, nitrogen, in a syn fashion. The syn

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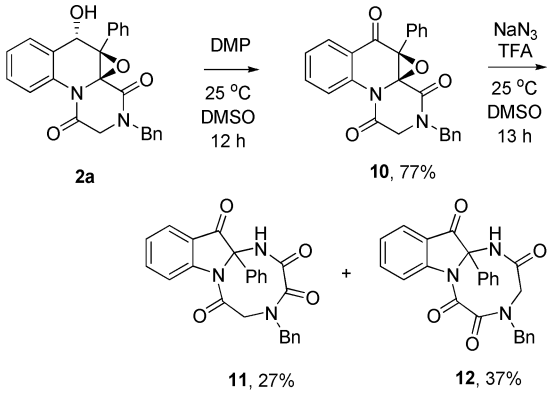
stereochemistry is possibly due to the phenyl group blocking the nucleophile's approach to the *anti*-face.

The initially formed *cis*-hydroxy isocyanate spontaneously cyclizes under the reaction conditions to form oxazoline-2-thione **8**, in keeping with what was previously reported in the literature.[9] In the absence of strong nucleophiles in wet DMSO, a similar S_N1 process results in *trans,cis*-triol **9**.[10] Structures of products **7**–**9** are unambiguously determined by X-ray crystallography.

Our rationale for the two different mechanisms of nucleophilic substitution is based on the pK_a values of HN_3 (4.72), HSCN (−1.86), and TFA (−0.25). As the nucleophile is taken in 3–5-fold excess of TFA, the ring opening by the azide anion is expected to proceed via the S_N2 mechanism with general acid catalysis by HN_3, whereas the formation of **8** (and **9**) most likely occurs via specific acid catalysis by TFA via the S_N1 mechanism, i.e., the formation of a transient iminium cation.

The primary photoproduct epoxy alcohol **2a** is readily oxidized with Dess–Martin periodinane (DMP) into epoxy ketone **10** as exemplified in Scheme 5. Under Schmidt reaction conditions, however, ketone **10** undergoes an extensive rearrangement into triketotriazacanoindolinones **11** and **12**.

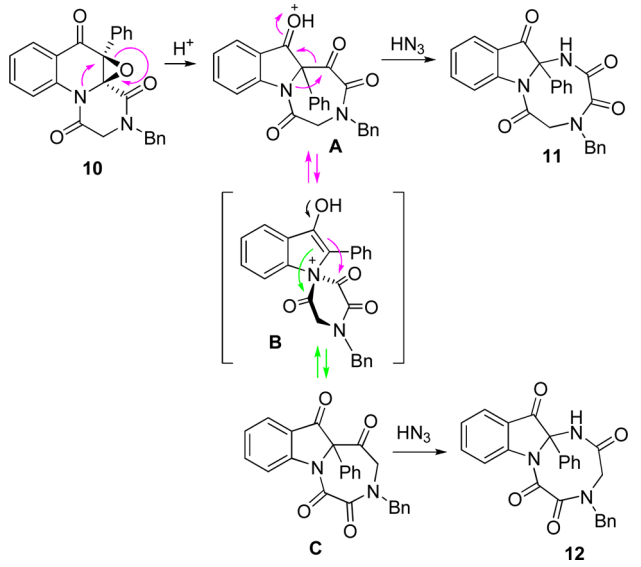
Scheme 5. Oxidation of Alcohol 2a into Ketone 10 and Its Rearrangement into Triazacanoindolinones under the Schmidt Conditions



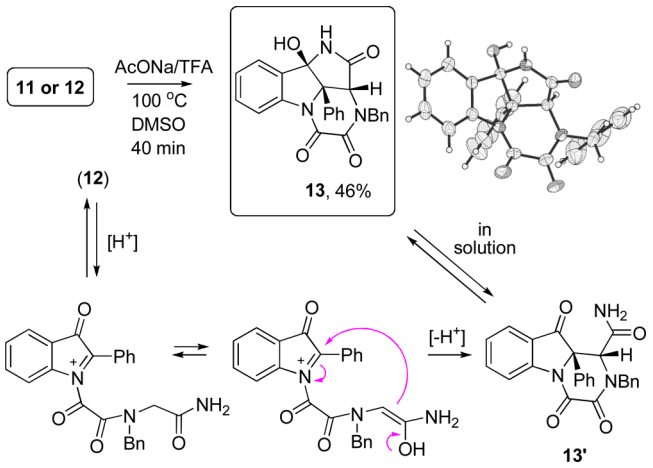
We hypothesize that the formation of triazacanes **11** and **12**, Scheme 6, involves acid-catalyzed ring opening of the oxirane ring accompanied by the quinolinol nitrogen atom migration to form diazepinoindolinones **A**. It is likely that the subsequent Schmidt reaction occurs with the azide anion attacking the aliphatic, not aromatic ketone, leading to **11**. The triazacanes **11** and **12** differ only by the position of one carbonyl group at the benzylated nitrogen atom, which suggests that isomer **12** could plausibly be a product of a similar Schmidt reaction of a diazepine intermediate **C**, pseudosymmetric to **A**. From this, we inferred that intermediates **A** and **C** are equilibrated via a spiro-ammonium intermediate **B**, i.e., via reversible acyl shifts between positions 1 and 2 of the indolinone moiety.[11]

Triazocanes **11** and **12** are stable at ambient temperature and could be crystallized (their structures are determined by x-ray crystallography). However, upon continued heating under the Schmidt conditions in DMSO they both cleanly rearranged into hemiaminal **13**, Scheme 7. The azide anion in the rearrangement serves as a general base. Sodium acetate, which has similar basicity, promotes the same rearrangement.

Scheme 6. Plausible Mechanism of Formation of Triazacanoindolinones 11 and 12



Scheme 7. Rearrangement of 12 into Hemiaminal 13



We did not detect any equilibration between **11** and **12** in solution under acid or base catalysis. However, when purified and separately treated with the acetate buffer in DMSO at 100 °C, each triazacane yielded the same tetracyclic piperazinoindolinone **13**.

The same formation of the sole product **13** was also achieved in one step from keto-oxirane **10** under the Schmidt conditions at 100 °C.

The mechanistic rationale for this transformation of aminal **12**, shown in Scheme 7, involves recapture of the key iminium intermediate by the enol form of the eliminated glycine amide moiety with diastereospecific formation of a new C–C bond completed with the aminal ring closure. NMR analysis of the product shows that tetracyclic hemiaminal **13**, observed in the solid state, exists in equilibrium with the open keto-amide **13′** present at 15–20% in solution. The mechanism of formation of **13** from the second triazacane **11** is currently under investigation.

To summarize, we have shown that intramolecular [4 + 4] cyclization of photogenerated azaxylylenes and 1,3,4-oxadiazole pendants occurs under mild irradiation conditions and is accompanied by extrusion of molecular nitrogen to yield

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diketopiperazinoquinolinols containing reactive oxirane, fused to quinolinol, and spiro-connected to the diketopiperazine moiety. Several examples of subsequent transformations presented in this paper attest to the synthetic utility of primary photoproducts **2** as versatile synthons for rapid access to novel polyheterocyclic molecular architectures. The modular assembly of photoprecursors from simple building blocks via well-established coupling reactions gives additional advantage to this photoassisted synthetic methodology, especially in the context of diversity-oriented synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(6) For all experimental procedures, see the Supporting Information.

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(10) An alternative explanation for the stereochemistry of triol **9** involves intramolecular epoxide ring opening by the benzylic OH forming an isomeric hydroxy epoxide which, in turn, hydrolytically opens in an *anti*-fashion to yield *trans*−*cis* triol **9**. While feasible, the formation of the isomeric epoxide does not offer rationale for stereochemistry of oxazoline-2-thione **8**. We therefore prefer the S_N1 mechanism with the iminium ion as an intermediate for both **8** and **9**.

(11) We were unable to isolate intermediates **A** or **C** shown in Scheme 6: in the absence of sodium azide epoxide **10** is stable with TFA, plausibly indicating that the first step in the rearrangement requires nucleophilic catalysis. In the presence of NaN_3 the Schmidt rearrangement occurs faster than the first step, preventing isolation of **A** (or **C**).

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