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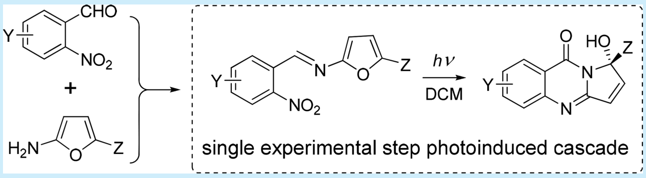
Photoinitiated Cascade for Rapid Access to Pyrroloquinazolinone Core of Vasicinone, Luotonins, and Related Alkaloids

D. Sai Reddy and Andrei G. Kutateladze*

Department of Chemistry and Biochemistry, University of Denver, Denver, Colorado 80208, United States

Supporting Information

ABSTRACT: Furylimines of aromatic *o*-nitro aldehydes undergo a photoinduced cascade transformation offering rapid atom- and step-economical access to complex polyheterocyclic scaffolds possessing a privileged pyrroloquinazolinone core.



The recent renaissance in photoredox catalysis—and synthetic photochemistry in general—speaks volumes about the ability of photoinduced reactions to access complex molecular architectures in a minimal number of steps.[1] Combining more than one step in a photoinitiated cascade improves step-normalized growth of complexity, while simplifying and streamlining experimental procedures.[2] In our own work we demonstrated that extended polyheterocyclic scaffolds, rivaling the complexity indices[3] of complex natural products, could be assembled in 2−4 experimentally simple steps from ubiquitous chemical feedstock utilizing a photochemical cascade as the key step.[4]

In our search for new photoinduced cascade transformations to access complex heterocycles, we realized that some well-known photoinduced rearrangements are absent from the toolbox of synthetic chemistry. One of these reactions—a photoinduced hydrogen atom transfer from the benzylic sp^3 carbon in *o*-nitrobenzyl systems—is widely used in photoremovable protecting groups (PPGs) chemistry, but rarely used in synthesis, with a notable exception of photochemical synthesis of indazolones recently reported by Kurth and coworkers.[5] Another variation on this theme is the well-known intramolecular redox disproportionation in *o*-nitrobenzaldehyde, which is initiated by hydrogen atom abstraction from the sp^2 carbon, resulting in the formation of *o*-nitrosobenzoic acid. This reaction has been widely used for UV actinometry in the 280−410 nm range of the UV spectrum.[6]

We note that nitroso compounds exhibit a wealth of synthetically useful reactivity, from aldol-like condensations to nitroso Diels−Alder reactions yielding cyclic hydroxylamines,[7] which are often reduced or undergo N−O bond scission either photochemically or under thermal activation. In this work, we developed a photoinduced cascade which involves a photochemical generation of transient aryl nitroso species, its intramolecular Diels−Alder reaction with a furan moiety to furnish an oxazabicyclo[2.2.1]heptane core possessing the labile N−O moiety with subsequent rearrangement into the target pyrroloquinazolinone in a single step. The pyrrolo- or pyrrolidino-quinazolinone core is a prominent feature in many biologically active natural products, including alkaloids vasicinone,[8] tryptanthrin,[9] and luotonins[10] shown in Figure 1.

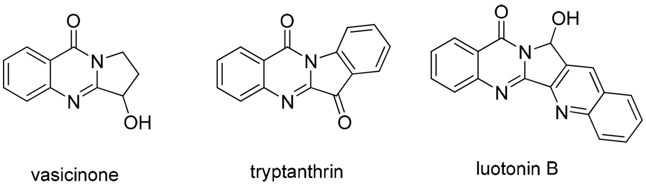


Figure 1. Vasicinone, tryptanthrin, and luotonin B.

A number of ground state reactions to access alkaloids containing a pyrroloquinazolinone core are known which include the following: synthesis of luotonins via a radical cascade;[11] synthesis of vasicinone and related heterocycles from (i) *o*-azidobenzoic acid derivatives by reductive cyclization[12] or (ii) condensation of anthranylamide and acetoxysuccinic anhydride[13] or other derivatives of succinic acid;[14] access to the quinazolinone core in the luotonin synthesis via reaction of anthranylamide with acyl chlorides[15] or with quinolin-carboxaldehyde.[16] Several of these ground state syntheses of pyrroloquinazolinones are nicely summarized in ref 17.

Our photoinduced cascade offers a much milder option for construction of pyrroloquinazolinone cores. Scheme 1 illustrates the typical reaction of methyl 5-aminofuran-2-carboxylate **2a** and 3-nitropyridine-2-carbaldehyde **1d** providing expeditious access to the pyrrolo-aza-quinazolinone framework. Imines are formed under standard conditions. The subsequent photoinduced cascade is carried out in dichloromethane (DCM), Scheme 1.

Overall, this approach gives rapid access to complex polyheterocyclic scaffolds in an experimentally simple atom- and step-economical way from readily available starting materials. In this context, not unimportant is the fact that

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Scheme 1. Typical Furylimine Formation and Subsequent Photoinduced Cascade Furnishing a Fused Pyrimidone

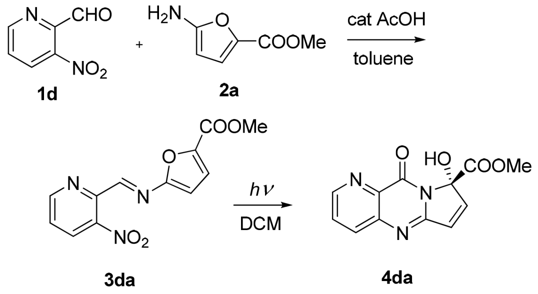
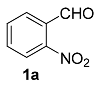
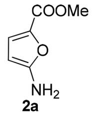
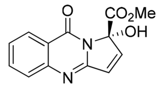
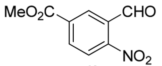
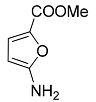
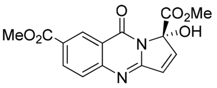
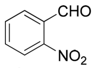
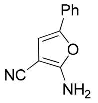
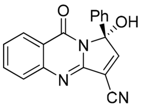
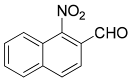
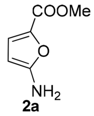
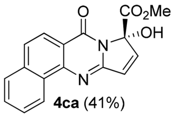
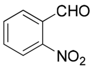
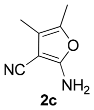
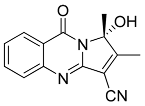
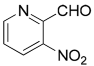
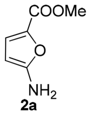
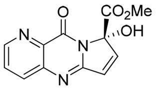
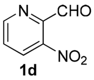
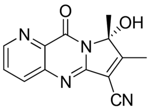
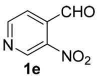
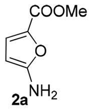
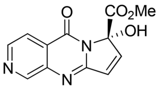
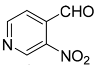
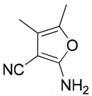
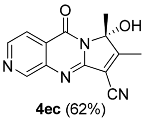
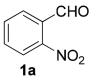
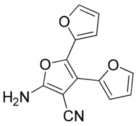
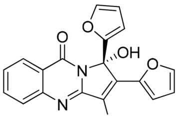


Table 1. Pyrroloquinazolinone Products and Isolated Yields

aldehyde	aminofuran	product
 **1a**	 **2a**	 **4aa** (77%) *x-ray*
 **1b**	 **2a**	 **4ba** (69%) *x-ray*
 **1a**	 **2b**	 **4ab** (65%) *x-ray*
 **1c**	 **2a**	 **4ca** (41%)
 **1a**	 **2c**	 **4ac** (74%)
 **1d**	 **2a**	 **4da** (69%)
 **1d**	 **2c**	 **4dc** (73%)
 **1e**	 **2a**	 **4ea** (76%)
 **1e**	 **2c**	 **4ec** (62%)
 **1a**	 **2d**	 **4ad** (53%)

the recent developments in sustainable chemistry point to a number of furan-based semiproducts as a viable biomass-derived chemical feedstock.[18]

The simplicity of the experimental procedure is a prominent feature of this short photoassisted synthetic sequence. As many aromatic *o*-nitro aldehydes and acceptor-substituted furanamines are readily available from commercial sources, we tested the scope of this reaction sequence and found that the procedure is broadly applicable. Examples with isolated yields are presented in Table 1 below. Notice that hemiaminals **4** are racemic.

Structures of pyrroloquinazolinones **4aa**, **4ba**, and **4ab** were established with X-ray crystallography. The rest of the products were characterized by solution NMR, with the *DU8+* computations[19] of NMR chemical shifts and spin−spin coupling constants supporting the structure assignment. For details of these computations and rmsd values matching ^{1}H, ^{13}C NMR chemical shifts and proton spin coupling constants, see the Supporting Information.

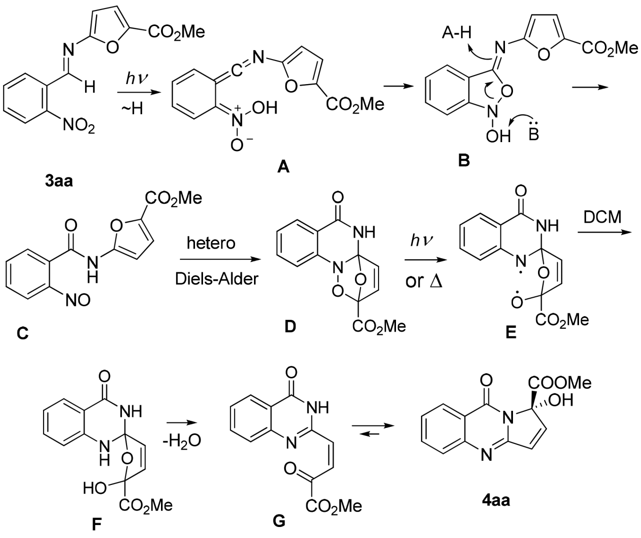
Our mechanistic rationale for this cascade is shown in Scheme 2. It involves intramolecular hydrogen atom abstraction by the *ortho*-nitro group in benzaldimine **3aa** followed by oxygen transfer via cycloaddition/fragmentation. This leads to the formation of nitroso amide **C**, which undergoes the intramolecular hetero Diels−Alder reaction to form **D**. Cyclic hydroxylamine **D** undergoes homolytic fragmentation with the N,O-diradical **E** being reduced via H-abstraction, presumably from the solvent (CH_2Cl_2). The dehydrated open form **G** of the resulting hemiacetal **F** then spontaneously cyclizes into the hemiaminal product **4aa**. Since the vicinal protons of the double-bond in the open form **G** are expected to have very different chemical shifts and spin−spin coupling constants from **4aa**, we could confidently corroborate that there is no open form **E** in the NMR spectrum of the reaction mixture.

Monitoring the reaction by NMR reveals the intermittent appearance of the NH proton belonging to nitroso amide **C**. The Diels−Alder intermediate **D** was not isolated, although very small olefinic peaks with $J = 5.9$ Hz observed in the reaction mixture are consistent with the heterobicyclo[2.2.1]-heptene $CH{=}CH$ moiety and may belong to this transient.[20]

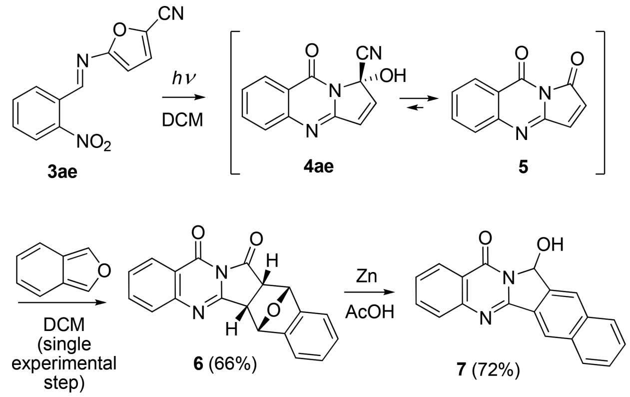
Utilization of *o*-nitrobenzaldimine of 5-cyanofuranamine (**3ae**) offers an atom- and step-economical pathway to the *carba*-analog of luotonin B (**7**) as shown in Scheme 3. The primary product of the photoinduced cascade in this case is cyanohydrin **4ae** which is expected to lose HCN and act as dienophile **5**[21] in the postphotochemical step, i.e. Diels−Alder reaction with isobenzofuran (readily available as described before[22]). After this experimentally simple photoinitiated one-pot sequence, the reaction mixture in acetic acid is treated with Zn powder.

This last step accomplishes two goals: aromatization of the oxabenzobicyclo[2.2.1]heptane moiety in **6** and selective

Scheme 2. Plausible Mechanistic Rationale for the Photoinduced Cascade 3aa →4aa



Scheme 3. Atom- and Step-Economical Synthesis of the *Carba*-Analog of Luotonin B (7)



reduction of the butyrolactam moiety into hemiaminal, furnishing the *carba*-analog of luotonin B (**7**).

In conclusion, we developed a new experimentally simple atom- and step-economical approach to diverse pyrroloquinazolinones via a photoinitiated cascade starting from a readily available feedstock. The cascade is initiated by the synthetically underutilized photoinduced benzylic hydrogen transfer in *o*-nitroaromatics which sets up [4 + 2] cycloaddition of the transient nitroso arenes. As a diverse library of imines **3xe** could be assembled in a modular fashion from various (hetero)aromatic nitroaldehydes and furanamines, our approach allows for rapid access to complex polyheterocycles in a minimal number of steps. Experimentally simple postphotochemical transformations of the primary photoproducts allow for further growth of the diversity and complexity of the target heterocyclic scaffolds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00858.

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for all compounds, computational details, and calculated NMR chemical shifts and constants (PDF)

Accession Codes

CCDC 1894983−1894985 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: akutatel@du.edu.

ORCID

D. Sai Reddy: 0000-0003-3471-8339
Andrei G. Kutateladze: 0000-0003-3066-517X

Notes

The authors declare no competing financial interest.

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