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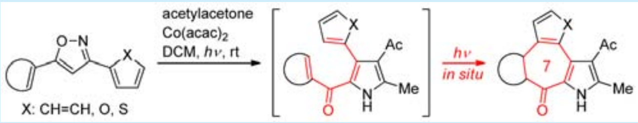
A Light-Induced Vinylogous Nazarov-Type Cyclization

Stefan Pusch, Dieter Schollmeyer, and Till Opatz*

Institute of Organic Chemistry, Johannes Gutenberg University, Duesbergweg 10-14, 55128 Mainz, Germany

Supporting Information

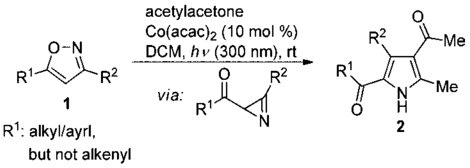
ABSTRACT: The first examples of a photochemically induced vinylogous Nazarov-type cyclization forming a cycloheptadienone core are described. The reaction can be included in a three-step cascade consisting of a photochemical isoxazole−azirine ring contraction, cobalt(II)-catalyzed ring expansion, and the photochemical cyclization. Furthermore, the first representative of the hitherto unknown 1-azatricyclo[2.2.0.0^{2,6}]hexanes has been identified as a side product of the azirine formation.



The Nazarov cyclization[1] is a well-known example of a 4π-electrocyclization enabling the synthesis of cyclopentenones. Besides the well-known Lewis acid catalyzed variant, photochemical cyclizations have also been reported for this reaction type.[2] The formal replacement of the carbonyl group with a C=C double bond allowed for "vinylogous" Nazarov cyclizations catalyzed by Sc^{III}, thus yielding alkylidenecyclopentenes, but in this case, the reaction took place on a cross-conjugated system again involving four electrons.[3] The preparation of cyclohexenones from vinyl cyclopropyl ketones has been reported as a homo-Nazarov cyclization.[4] Furthermore, many Nazarov-like cyclizations can be found in the literature[5] while a vinylogous variant furnishing seven-membered rings has not been reported to the best of our knowledge.[6]

In a recent, nonrelated study,[7] we were able to transform isoxazoles **1** into 2,4-diacylpyrroles **2** (Scheme 1). This process includes the photochemical *in situ* generation of acylazirines and a subsequent cobalt(II)-catalyzed condensation reaction.

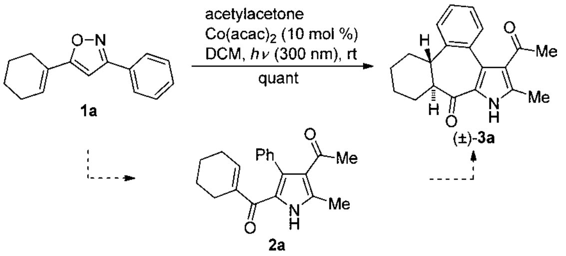
Scheme 1. One-Pot Preparation of Pyrroles from Isoxazoles (Pusch and Opatz, 2016)



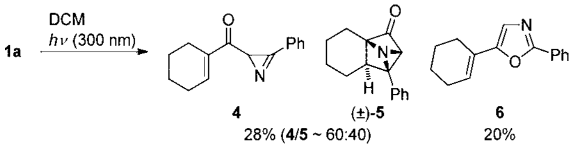
If isoxazole **1a** was subjected to the same reaction conditions, the unexpected product **3a** was isolated instead (Scheme 2). The structures of compounds **1a** and **3a** could be confirmed by NMR spectroscopy and X-ray crystallography (see the Supporting Information for details). Presumably, the reaction occurs via the formation of intermediate **2a**.

To test this hypothesis, pure isoxazole **1a** was irradiated with 300 nm UV light (Scheme 3). Besides small amounts (9%) of recovered isoxazole **1a**, an inseparable mixture of the expected acylazirine **4** and the tetracyclic amine **5** was isolated along with oxazole **6**, an expected product of a second photochemical ring transformation on **4**.[8]

Scheme 2. One-Pot Photoisomerization−Condensation−Photocyclization Cascade



Scheme 3. Photoisomerization of the Isoxazole Starting Material



The structure of the tetracycle **5**, apparently formed by an intramolecular [2 + 2] cycloaddition from azirine **4**, was deduced from NMR experiments including [^{1}H,^{13}C]-1,1-ADEQUATE.[9] Additionally, the ^{13}C chemical shifts of this compound calculated using DFT are in excellent agreement with the experimental data (see the Supporting Information). This represents the first example of a 1-azatricyclo[2.2.0.0^{2,6}]-hexane, a ring system for which only scattered reports on carbacyclic analogues exist.[10]

The mixture of compounds **4** and **5** was then reacted with acetylacetone in the presence of a cobalt(II) catalyst in the dark (Scheme 4). The expected pyrrole **2a**, formed in almost quantitative yield with respect to the amount of azirine, could now be isolated and separated from the tetracycle **5**. The fused

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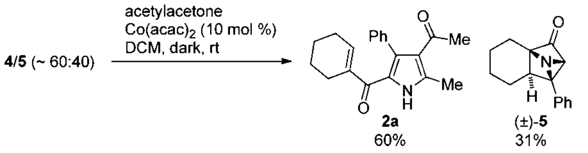
Scheme 4. Pyrrole Synthesis from the Azirine Precursor

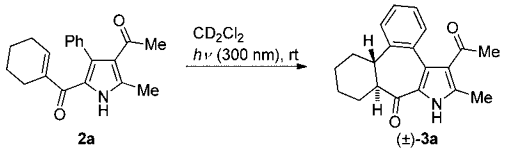


and bridged azetidinone **5** has a characteristic carbonyl stretch frequency of 1773 cm^{-1} and a chemical shift of 187.4 ppm for the carbonyl carbon. After several crystallization attempts, single crystals could be obtained and the structures of compounds **2a** and **5** were ultimately confirmed by X-ray crystallography (see the Supporting Information for details).

Compound **5** does not yield pyrrole **3a** if irradiated in the presence of acetylacetone and Co(acac)$_2$. Therefore, the Co^{II}-catalyzed condensation which traps the azirine **4** formed *in situ* during the one-pot procedure from Scheme 2 must be faster than the formation of tetracycle **5** from intermediate **4** and must also be faster than the (presumably irreversible[8]) formation of oxazole **6** from **4**.

Pyrrole **2a** can be transformed into **3a** solely by irradiation with UV light (Scheme 5; see the Supporting Information for the photochemical cyclization followed by NMR).

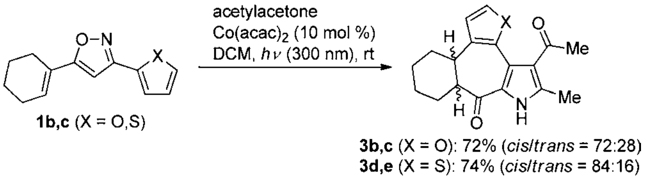
Scheme 5. Photochemical Cyclization



No Lewis acid or transition metal catalyst seems to be required in this case. In particular, no cyclization could be observed if compound **2a** was stirred with BF$_3$·OEt$_2$ in dichloromethane in the dark. Probably, a thermal disrotatory electrocyclization would require an unfavorably shaped π system with a low degree of conjugation and hence involve a high energy barrier.

Only the (racemic) *trans*-fused isomer of pyrrole derivative **3a** was observed in the light-induced reaction. In contrast, both the *cis* and *trans* isomers were produced in the one-pot reaction of isoxazoles **1b** and **1c** (Scheme 6).

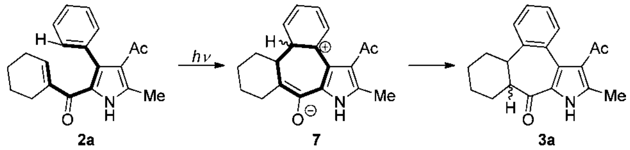
Scheme 6. One-Pot Pyrrole Synthesis with a Furanyl or Thienyl Isoxazole



Here, the *cis* isomers were formed predominantly. For the furan derivative, the isomers **3b** and **3c** could be separated by RP-HPLC and both structures were confirmed by X-ray crystallography (see Supporting Information for details).

Formally, the photocyclization described above can be considered as a conrotatory 6π electrocyclization from an electronically excited state of **2a** to intermediate **7**, followed by a hydrogen shift yielding **3a** (Scheme 7).

Scheme 7. Putative Reaction Mechanism for the Electrocyclization



The first process is photochemically allowed according to the Woodward–Hoffmann rules.[11] The thermal electrocyclization of heptatrienyl cations has already been studied in silico.[12] To gain an approximate impression of the energy profile of the new cyclization, (TD-)DFT calculations were performed on model compound **8** lacking the acetyl and methyl groups (Figure 1).

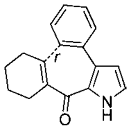


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Figure 1. Model compound for the (TD-)DFT calculations.

Relaxed surface scans with incremental shortening of the distance *r* at the ωB97XD/6-31+G(d) level with IEFPCM solvation for CH$_2$Cl$_2$ (Figure 2)[13] showed that a thermal conrotatory cyclization is indeed unfavorable due to a high activation barrier.

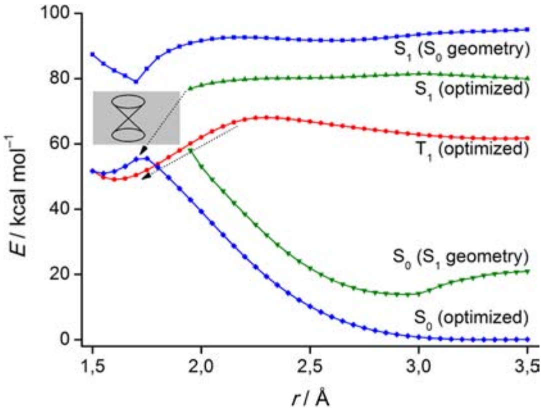

Figure 2. Potential energy scans for the cyclization of model compound **8**.

On the other hand, no significant barrier was found for a scan of the optimized S$_1$ geometries. The optimzation of the S$_1$ structures failed for short distances (*r*) due to transition energies very close to zero. The discontinuous derivative of the potential energy curve (for the vertical absorption) at *r* = 1.7 Å and the low gap between S$_1$ and S$_0$ states suggests a conical intersection[14] (or seam of conical intersections) to be present in this area (marked in gray in Figure 2).[15]

Alternatively, the reaction could proceed via a triplet state, as intersystem crossing rates are usually high for carbonyl compounds. As expected, a low activation barrier was predicted for this process. Indeed, the reaction is slowed down significantly by the addition of 4 equiv of *trans*-piperylene or triplet oxygen (see the Supporting Information).[16] In the latter case, the formation of byproducts resulting from oxidation was observed while the cyclization proceeded very cleanly under complete exclusion of oxygen. This observation indicates that the cyclization of **2a** to **3a** at least partly occurs through the T_1 state.

Intermediate **7** might also be represented as a singlet biradical (see the Supporting Information for details), which could in turn yield *trans*-**3a** via a suprafacial hydrogen shift. In contrast, a zwitterionic intermediate should be favored for the cyclization of **1b** and **1c** due to stabilization by the heteroatom, resulting in a mixture of *cis* and *trans* pyrroles after a proton transfer.

To summarize, a one-pot cascade reaction based on an isoxazole–azirine photorearrangement followed by a cobalt-catalyzed condensation reaction and finally a photochemical 6π electrocyclic ring closure was described. The latter process is the first example of a photochemical vinylogous Nazarov-type cyclization, which should proceed via either an excited singlet or triplet state. While higher level calculations (ideally using multireference methods) are still required to investigate the reaction in detail, the presented cyclization represents a new opportunity for the construction of seven-membered ring structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01449.

Experimental procedures, analytical data, NMR spectra, crystallographic data for compounds **1a**, **2a**, **3a–c**, and **5**, and computational chemistry (PDF)[17]

X-ray crystal structure data for **1a** (CIF)

X-ray crystal structure data for **2a** (CIF)

X-ray crystal structure data for **3a** (CIF)

X-ray crystal structure data for **3b** (CIF)

X-ray crystal structure data for **3c** (CIF)

X-ray crystal structure data for **5** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: opatz@uni-mainz.de.

Notes

The authors declare no competing financial interest.

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