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Photoassisted Synthesis of Complex Molecular Architectures: Dearomatization of Benzenoid Arenes with Aza-o-xylylenes via the Unprecedented [2+4] Reaction Topology

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Abstract

A new method for photoinduced dearomatization of arenes via an intramolecular cycloaddition with aza-o-xylylenes generated by the excited-state intramolecular proton transfer (ESIPT) in the readily available photoprecursors is developed. The topology of this cycloaddition, [2+4], is unprecedented for photo-dearomatizations of benzenoid aromatic carbocycles. It provides rapid access to novel heterocycles, cyclohexadieno-oxazolidino-quinolinols, as valuable synthons for a broad range of *postphotochemical* transformations.

Graphical Abstract

Synthesis of complex heterocycles via photoassisted dearomatization of benzenoid aromatics

Keywords

photochemistry; dearomatization; aza-o-xylylenes; polyheterocycles

Dearomatization of aryls provides an appealing preparative shortcut from the ubiquitous aromatic hydrocarbons to complex sp^3 -rich molecular topologies (see an excellent review by Porco¹), offering access to the vast areas of underexplored chemical space.² Dearomatization of electron-rich heterocycles such as indoles,³ furans,⁴ and pyrroles⁵ is precedented in the literature, including our own recent contributions.^{6,7}

In contrast, the options for ground state dearomatization of *carbocyclic benzenoid arenes* are limited,⁸ with the predominance of phenolic oxidation⁹ or transition metal-assisted dearomatization.¹⁰ <u>Photocycloadditions</u> to arenes complement nicely these methods leading to diverse products topology, Scheme 1.¹¹ Among these, the [3+2] reactions¹² were often used as key steps in the synthesis of natural products,¹³ while the [2+2],¹⁴ [4+2],¹⁵ and

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 $[4+4]^{16}$ cycloadditions of arenes remain somewhat underutilized. Furthermore, [2+4] photocycloadditions – with arene acting as a 2π "dienophile" – are unknown.¹⁷ Instructively, such [2+4] reactions in the ground state are very rare.¹⁸

We now report a new photo-dearomatization of arenes via the missing [2+4] topology, resulting in the formation of unique cyclohexadiene-fused heterocycles as primary photoproducts, amenable for further growth of framework complexity via straightforward *postphotochemical* transformations.

As we shown recently, cycloadditions of the ESIPT-generated azaxylylenes involve triplet species.^{6d} The reaction is initiated by the electrophilic N-centered radical, with the overall process resembling a formal inverse electron demand Diels-Alder reaction. We hypothesized that a similar initial step should occur with donor-substituted benzenoid arenes. This indeed was the case: a readily available anilide of phenoxyacetic acid (**1a**) proved cycloaddition-competent, furnishing cyclohexadieno-quinolinol **4a** upon irradiation with 365nm LEDs, Scheme 2.

The scope of this cycloaddition was assessed with a matrix of amides comprised of three photoactive cores, *o*-amino-benzaldehyde 1, aminoacetophenone 2, and aminotetralone 3, and twelve aromatic pendants: derivatives of phenoxyacetic- $(\mathbf{a}-\mathbf{h})$, phenylpropanoic- $(\mathbf{i}-\mathbf{k})$ acids, and biphenyl l, Figure 1.

Optimization of reaction conditions and solvent led to DMSO as a solvent of choice. The products resulting from irradiations of **1a–1c**, **1h**, **1j**, **2d**, **3d**, **3e**, **3j** are summarized in Figure 2. For aldehyde-based precursors **1a–1c** the sole *syn*-diastereomer was observed, where "*syn*" refers to the relative position of the benzylic OH and the newly formed cyclohexadiene ring. The stereochemical assignment was based on the analysis of proton spin-spin coupling constants (SSCC) and their comparison with the values calculated with our *relativistic force field (rff), DU8c*, method,¹⁹ Table S1.

Phenylpropanoic derivatives, such as **1j**, gave two regioisomers *syn*-**4j** and *syn*-**4j**' in the ratio ca. 2:1.

The reaction scope is not limited to photoprecursors derived from benzaldehyde. Compounds **2d**, **3d**, **3e** and **3j** containing acetophenone and tetralone-based photoactive cores were also cycloaddition-competent. The stereo- and regiochemistry of cycloaddition for compounds *anti*-6d,e,j and j' as well as *syn*- and *anti*-5d was unambiguously confirmed by x-ray analysis.

In several cases the methoxy-cyclohexadiene moiety in the primary photoproducts underwent hydrolysis into cyclohexenone. This reaction can be spontaneous as in the case of *syn*-4g, or happen during the chromatography as in the case of *anti*-6d, Scheme 3.

A special case of interrupted postphotochemical hydrolysis is represented by *syn*-products **4**, YR=OMe or NHAc, Scheme 4 and Figure 3. After protonation of the vinyl ether moiety, the methoxyallyl cation is trapped by the benzylic hydroxy-group yielding cyclic ketal **9**.

In this context, reaction of the aldehyde-based photoprecursor **1d** presents a special case, Scheme 5. The initially formed *syn*- and *anti*-**4d** are unstable on the column. Upon addition of tosic acid *anti*-**4d** hydrolyzes to enone *anti*-**10d**. The *syn*-**4d** initially undergoes cyclic ketalization to form **9d**, but its hydrolysis could be driven further to enone *syn*-**10d**, with subsequent acid-catalyzed nucleophilic capture of the benzylic hydroxyl group by the α , β unsaturated ketone, producing stable ether **11d**. The structure of ether **11d** was initially assigned based on the analysis of its NMR, with the *rff*-calculated SSCCs matching experimental data with high accuracy (rmsd = 0.09 Hz), and later was also proved by x-ray analysis.

Synthetically appealing *postphotochemical* modifications to diversify and grow complexity of the resulting core scaffolds are not limited to ketalization. The primary photoproducts possess a reactive cyclohexadiene fragment that can be readily engaged in [4+2] cycloadditions, for example, hetero Diels-Alder reactions with *in situ* generated benzoylnitroso compounds, Scheme 6.

Another prominent postphotochemical transformation is a reaction with singlet oxygen yielding endoperoxides, such as **14** and **15**, Scheme 6. Peroxides are ubiquitous in natural products,²⁰ many possessing antitumor, antibacterial, and antimalarial activity. Additionally, these endoperoxides can be ring-opened with urea or bases, offering rapid access to complex pentasubstituted cyclohexenes fused to oxazolidino-quinolinol cores, for example ketal **16**, triol **17**, or enone **18**, Scheme 7.

In conclusion, we developed a new method for dearomatization of benzenoid arenes, with the arene reacting as the 2π component – an unprecedented topology for a photochemical reaction of benzenoid aromatics. The primary photoproducts are cyclohexadieno-quinolinol fused heterocycles which can be engaged in experimentally simple *postphotochemical transformations* to further grow scaffold diversity and complexity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Unsaturated benzenoid pendants and linkers



Figure 1. Substrate matrix.

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Figure 2.

Primary photoproducts from anilides **1a–1c**, **1h**, **1j**, **2d**, **3d**, **3e**, **3j**; isolated yields after chromatographic separation of diastereomers; ^a7% of **anti-4j**' was additionally isolated

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Figure 3.

Formation of cyclic ketals. Conditions for ketal formation: (^a) spontaneous; (^b) HCl in ether, (^c) *p*-TsOH•H₂O



Scheme 1.

Molecular topologies accessible through *photochemical* dearomatization of benzenoid arenes.



Scheme 2. A typical [2+4] cycloaddition of **1a**.







Scheme 4. Ketal Formation from the *syn*-Photoproduct.



Scheme 5.

Acid-catalyzed postphotochemical transformations.

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Scheme 6. Hetero-Diels-Alder reaction of primary photoproducts

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18, 29% (x-ray)



anti-6d

Scheme 7.

Reaction of primary photoproducts with singlet oxygen (isolated yields for compounds 16-18 were calculated over two steps).

15, 56%

(x-ray)

TEA

DCM