Visible-Light Cascade Photooxygenation of Tetrahydrocarbazoles and Cyclohepta[b]indoles: Access to C,N-Diacylumion Ions

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In memory of Rolf Huisgen

Abstract: Tetrahydrocarbazoles and perhydrocyclohepta[b]indoles undergo a catalytic cascade singlet oxygenation in alkaline medium, which leads to chiral tricyclic perhydropyrrolo- and perhydroazepino[1,2-a]indoles in a single operation. These photooxygenation products are new synthetic equivalents of uncommon C,N-diacylumion ions and can be functionalized with the aid of phosphoric acid organocatalysis.

The selective oxidation of organic compounds by catalytic aerobic photooxidation has long been a key objective in sustainable synthetic and industrial chemistry. The rapid recent development of chemical photocatalysis with visible light consequently has fueled a growing interest in the development of new photooxygenation reactions with dioxygen, particularly by way of photoelectron transfer-induced and radical C-H oxidations. Photochemically produced organic peroxides have not only been utilized as key high-energy intermediates in the synthesis of natural products and functional carbon- and heterocyclic target structures, but they have also gained much attention as potential new antiparasitics, especially for combating malaria.

As part of our investigations in the photooxidation of N-heterocyclic compounds, we reexamined the dye-sensitized photooxygenation of tetrahydrocarbazoles and tetrahydro-β-carbolines, which initially generates the corresponding benzylic hydroperoxides by way of the singlet oxygen ene reaction (Scheme 1a). In the case of tetrahydrocarbazole, the C-4a hydroperoxide is relatively long-lived in pH-neutral solution, but exposure to Brønsted acids causes the rapid elimination of H₂O₂. The resulting benzylic cation rearranges to a C-1 cation, which can be intercepted with nucleophiles like anilines to give 1-aminotetrahydrocarbazoles, as reported by Klussmann et al. In the case of tetrahydro-β-carbolines, however, the benzylic hydroperoxide instantly undergoes C-C bond cleavage via its unstable 1,2-dioxetane congener. Chen and co-workers engaged the so-produced 2-acyl anilides in acid-mediated cyclocondensations with anilines to furnish aminated dihdydropyrrolo[3,4-b]quinolines.

We report here the cascade photooxygenation of tetrahydrocarbazoles and perhydrocyclohepta[b]indoles in alkaline medium, which leads to perhydropyrrolo- and perhydroazepino[1,2-a]indoles in a single operation (Scheme 1b). Contrary to the previous methods, the initially introduced oxygen is not expelled during a sequence leading back to aromatic products, but three oxygen atoms are permanently integrated into a chiral product structure. This multistep cascade can be regarded as a telescoped photochemical Witkop–Winterfeldt/C-C cleavage reaction, and the perhydropyrrolo- and perhydroazepino[1,2-a]indole products are highly useful synthetic equivalents of new and uncommon C,N-diacylumion ions.
In our initial experiment, we attempted the photooxidation of hexahydroxycehpta[b]indole (1a) under basic conditions, and found that alongside the 4-quinolone 2a, the valuable perhydroazepino[1,2-a]indole 3a was produced in a small amount. Consequently, we aimed to maximize the yield of 3a. We evaluated various photocatalysts and photosensitizers for the photooxygenation of 1a, and the reaction mixtures were analyzed by quantitative 1H NMR spectroscopy (Table 1). LED irradiation (460 nm blue) of 1a alone, in CD3OD solution in the presence of NaOD and under O2 atmosphere, led to 15% conversion after 14 h and the generation of only quinolone 2a in 14% yield. In the presence of 2 mol% of triphenylpyrylium cation (TPP+), a comparable result was obtained (entries 1 and 2). Using ruthenium(II) tris-bipyrazine and 9-mesityl-10-methylacridinium (Mes+-Acr) improved conversion of 1a to 60–77%, to give compound 2a in 24% and 59% yield, respectively, while the desired hemiaminal 3a was detected in small quantities of ca. 5%, exclusively as its ring-closed tautomer. However, 3a was also accompanied by the anthranilic dicarboxylate 4a in the form of its disodium salt (entries 3 and 4). When the xanthene dyes Eosin Y and Rose Bengal were utilized at the form of its disodium salt (entries 3 and 4). When the xanthene dyes Eosin Y and Rose Bengal were utilized at the form of its disodium salt (entries 3 and 4). When the xanthene dyes Eosin Y and Rose Bengal were utilized at the form of its disodium salt (entries 3 and 4).

Table 1: Cascade photooxygenation of cyclohepta[b]indole 1a.

| Entry | Cat./Sens. | λex [nm] | Conv. of 1a [%][b] | Yield [%][b] 1a : 2a : 3a : 4a |
|-------|------------|----------|-------------------|-----------------------------|
| 1     | none       | 460      | 15                | 14:0:0                      |
| 2     | TPP·BF4    | 460      | 12                | 11:0:0                      |
| 3     | Ru(bipy)3(PF6)2 | 460 | 60                | 24:5:2                      |
| 4     | Mes+-Acr·ClO4 | 460     | 77                | 59:6:2                      |
| 5     | Eosin Y    | 530      | 100               | 13:31:21                    |
| 6     | Rose Bengal| 530      | 100               | 0:20:53                     |
| 7     | 1,8-HOAQ   | 460      | 100               | 0:35:52                     |
| 8     | Rose Bengal, DMTU | 530 | 100               | 0:45:10                     |
| 9     | Rose Bengal, MnSO4 | 530 | 100               | 0:35:7                      |
| 10    | Rose Bengal, MnO2 | 530 | 100               | 0:55:54:11                   |
| 11    | 1,8-HOAQ, DMTU | 460 | 100               | 0:40:12                     |
| 12    | 1,8-HOAQ, MnSO4 | 460 | 100               | 0:38:10                     |
| 13    | 1,8-HOAQ, MnO2 | 460 | 100               | 0:32:2                      |
| 14    | 1,8-HOAQ, PhCH3 | 400–450 | 98         | 7:66:65:2                      |

All reactions performed at 0.05 M concentration and irradiated with 10 W LED. [a] Determined by 1H-NMR. [b] 1H NMR yield against 1,3,5-trimethoxybenzene standard. [c] Yield of isolated product from preparative run on 0.25 mmol scale and using KOh aq./MeOH. [d] PhCH3, cosolvent, c (1a) = 0.03 M, 2 mol % catalyst addition at 0, 5, 10 h, total duration 15 h, 36 W blue CFL lamps.

The anthranilic amide 4a was obviously formed by oxidative C–C cleavage of hemiaminal 3a.[12] and we hypothesized that hydrogen peroxide generated during the reaction sequence may be the main cause for this undesired degradation reaction. Therefore, we experimented with the addition of various H2O2 scavengers and disproportionation catalysts.[13] In the case of Rose Bengal, equimolar amounts of DMTU (1,3-dimethylthiourea)[14] or manganese salts significantly improved the selectivity (entries 8–10), up to 5:1 in favor of 3a over 4a when MnIV oxide was used,[15] and hemiaminal 3a could be isolated in 54% yield on a preparative scale (entry 10). When 1,8-HOAQ was used as the sensitizer, MnO2 largely decelerated the photooxidation, resulting in only 44% conversion of 1a (entry 13). Addition of DMTU or MnSO4 again led to an increased selectivity towards 3a, with yields of about 40% (entries 11 and 12).

In summary, we found that the use of Rose Bengal instead of Eosin Y led to a significant improvement in the selectivity of the reaction. However, the use of Rose Bengal also led to a decrease in the yield of the desired product 3a. Further optimization of the reaction conditions is necessary to achieve full conversion of the intermediate 4-quinolone 2a.

A variety of functionalized cyclohepta[b]indoles 1a–11 were subjected to the optimized reaction conditions and the scope of the cascade photooxygenation is depicted in Figure 1. Substrates 1b–e, 1i, and 11 were readily prepared by Fischer indolization of cycloheptanone with the corresponding aryl hydrazines. Cycloheptainoindoles with bromine substitution at C2 and C3 of the aromatic ring were further derivatized by Suzuki coupling reactions to give the C2- and C3-arylated and arylated derivatives 1f–h and 1j,k (see SI for details). All photooxygenation reactions were performed using 1,8-HOAQ (conditions a) as well Rose Bengal/MnO2 (conditions b). 1,8-HOAQ appeared to be the superior sensitizer in most cases (best results are shown in Figure 1). The cascade reaction was found to be sensitive with regard to the aromatic substituent. Compared to the reaction of 1a, both the halide-substituted perhydroazepino[1,2-a]indoles 3b–d and the donor-substituted derivative 3e were isolated with yields of 30–40%. The alkylated compounds 3f–i were again accessible in good yields between 50–61%, including the sensitive cyclopropane derivative 3h. The C2-arylated compound 3j was isolated in 48% yield while its C3-arygoester 3k was obtained in 40% yield, interestingly accompanied by product 3a (12% yield), apparently as the result of an unexpected C3-dearylation. In all examples 3, the intermediate 4-quinolones 2 were generally fully consumed when Rose Bengal was utilized; when 1,8-HOAQ was used, intermediates 2 were present in up to 15% yield after the reaction in several cases. Reacting the highly electron-deficient...
2-cyanocyclohept[a]indole 11 gave only low conversion and generated a mixture of products where compound 3l could be detected in trace amounts only.

Under the conditions established for cyclohepta[b]indoles, 1,2,3,4-tetrahydrocarbazole (1m) reacted much faster and the corresponding anthranilic amide 4m was formed quantitatively after 14 h reaction time, regardless of which sensitizer was used. To gain insight into the effect of ring size, we investigated the photooxygenation of the intermediate quinolones 2a and 2m by in situ 1H NMR spectroscopy, in oxygen-saturated CD$_3$OD/NaOD solution with 445 nm blue laser photoexcitation and using 2 mol% 1,8-HOAQ (Scheme 2).

Under these model conditions, conversion of the cyclohexane-fused quinolone 2a was comparably slow (65% after 5 h), the seven-membered hemiaminal 3a being the main product, accompanied by only ca. 10% of dicarboxylate 4a. Consistently, a reaction time of 42 h was needed in a preparative run aimed at converting quinolone 2a quantitatively into 4a (see SI). Photooxygenation of the five-membered-ring quinolone 2m, derived from tetrahydrocarbazol 1m, proceeded much faster, and the six-membered-ring hemiaminal 3m formed rapidly, but it was further converted into dicarboxylate 4m almost instantaneously. As a consequence, compound 3m could be isolated only in small amounts in preparative experiments. However, introduction of a gem-dimethyl group in the C3-position of tetrahydrocarbazole allowed for the isolation of the corresponding perhydropyrido[1,2-a]indoles with good yields, as exemplified by products 3n (52%) and 3o (60%) in Figure 1. Hence, in these examples, the gem-dimethyl group could stabilize the hemiaminals 3n and 3o against oxidative degradation.

The proposed mechanism of the cascade photooxgena-
improved in strongly alkaline medium, is depicted in Scheme 3. When either sensitizer is used, Rose Bengal or 1,8-HOAQ, singlet oxygen is the dominant reactive oxygen species (ROS) in the reaction sequence. This was verified by studying the influence of various ROS scavengers on the reactions 1a → 3a + 4a and 2a → 3a + 4a (Tables S1 and S2), and the O$_2$-quencher sodium azide (NaN$_3$) showed the most pronounced effect on the overall reaction rate and product distribution. The ene reaction of substrate 1 with O$_2$ initially gives hydroperoxide 5, which under basic conditions undergoes rapid C-C cleavage to keto amide 7 via the unstable 1,2-dioxetane 6. The enolate 8 cyclizes by aldol condensation (“Camps” cyclization[17]) to give 4-quinolone 2 as product of a photochemical Witkop–Winterfeldt[18]-type reaction. The singlet oxygenation of 2 followed by ring cleavage of a second dioxetane 9, via a charge-transfer-induced decomposition, [19] generates product 3. The oxidation of quinolones 2 is fast for

Figure 1. Scope of photooxygenation products. Reactions performed on 0.25 mmol scale, yields after chromatography. a) 1,8-HOAQ (3 × 2 mol%), O$_2$, hv 400–450 nm CFL (36 W), KOH aq., MeOH/PhCH$_3$, r.t., 14–20 h. b) Rose Bengal (2 mol%), O$_2$, hv 530 nm LED, MnO$_2$ (1 equiv), NaOH aq., MeOH, r.t., 14–20 h.

Photo-NMR study of the photooxygenation of quinolones 2a and 2m.

Scheme 2. Proposed mechanism.

Scheme 3. Proposed mechanism.
strained cyclopentane derivatives \((n = 1)\), while for cyclohexane derivatives \((n = 2)\), it becomes the rate-determining step. A conceivable second product-forming pathway involving addition of \(O_2\) to the enolate 8, to give the hydroperoxide 10 as a precursor to 3, can be ruled out as neither 10 nor related intermediates could be observed.[26] The \(C\cdots C\) cleavage of hemiaminal 3 to dicarboxylate 4 commences from the ring-opened 1,2-diketone tautomer 3' and can occur by photo-oxidation as well as by the attack of in situ generated hydrogen peroxide (see SI).

The perhydroazepino- and pyrido[1,2-\(a\)]indoles 3 are new precursors to \(N\)-acyl iminium ions,[23] and we attempted their activation by phosphoric acid organocatalysis.[22] Our preliminary results, shown in Scheme 4, indicated that strong Brønsted acids like \(N\)-triflyl phosphoramides[23] are required to effectively convert model compound 3a into the iminium ion 11. Moreover, a strong effect of solvent was observed in the arylation reaction with 1, and can occur by photo-oxidation as well as by the attack of in situ generated hydrogen peroxide (see SI).

Further investigations are currently underway in our laboratory and more results will be reported in due course.

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**Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** cascade reactions · indoles · \(N\)-acyliminium ions · photooxidation · singlet oxygen

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