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Highlight Article (Invited)

Pyrroloquinolines, a New Platform for Developing Organic Photosensitizers: When Synthetic Methodology Meets Photophysics[†]Zacharias Amara* 

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ABSTRACT

New molecular architectures with triplet sensitization properties can have a big impact on photochemistry and photobiology. In their recent work, de Bonfils *et al.* have tackled this challenge in a very systematic way using a powerful synthetic strategy. This consists of an elegant yet practical organocatalyzed cyclization/oxidation rearrangement sequence which they now apply to the synthesis of pyrroloquinolines, a new scaffold for photosensitizers. However, beyond this new class of compounds, the strategy has potential to produce a myriad of compact organic chromophores with promising photoinduced intersystem crossing properties. The study therefore provides interesting clues to serve the rational design of biocompatible molecular photosensitizers but also raises puzzling questions on the intriguing excited state reactivity of these molecular architectures.

INTRODUCTION

Photosensitization of triplet to singlet oxygen (¹O₂) has been known for decades and continues to be a very active research field, especially given the increased interests in the development of antimicrobial and antitumor materials (1). There is therefore a continuous need for discovering new photosensitizers and understanding their structural relationships with their excited states properties (2,3) Coeffard *et al.* (4) have recently developed a generic synthetic approach which has a fantastic potential as it could transform the way chemists conceive and explore new chromophores. The idea of the team of organic chemists from Nantes University is to apply a cyclization/oxidation sequence to aromatic building blocks to make chromophores with singlet to triplet intersystem conversion and singlet oxygen production under UV/Visible light irradiation. As a bonus, the synthesis looks user-friendly as it relies on a single-pot multi-step sequence, thereby making it useful to many laboratories across

the world. The new compounds present some important advantages such as the combination of a relatively high fluorescence and singlet oxygen quantum yields. In addition, the structures are flanked with nonplanar functional groups which could serve for further modifications and one can easily envisage many applications such as covalent attachment to proteins or surfaces or improving solubility and other physical parameters with low risks in affecting photochemical properties.

SYNTHESIS

The synthetic strategy lies on a key step consisting in an organocatalyzed cyclization between an aromatic unit and a cinnamaldehyde derivative which was previously applied by the same group (5). The newly created aromatic building block displays a low-lying π - π^* transition and is a relatively good fluorophore (here $\Phi_F = 0.358$ in acetonitrile). Following on this, the authors apply an oxidative rearrangement (6) to switch the chromophore unit into a fully conjugated α,β -unsaturated ketone which unlocks the triplet manifold (7). The success of this general approach has led to the conception of two new classes of photosensitizers, one of these (the pyrroloquinoline family) being described in this issue.

In their previous work, the authors used this approach to discover a way to red shift phenalenone absorption to the visible region of the electromagnetic spectrum (see Scheme 1A below) (8). Phenalenone is a reference in photochemistry as it has a quantum yield in singlet oxygen (Φ_Δ) which is close to unity, but its absorption is in the UV range making it less useful for biological applications. The new phenalenone derivatives from Coeffard *et al.* are red-shifted thanks to the introduction of appropriate substituents on the naphthalene unit.

In the present work, the group uses the same synthetic methodology to produce pyrroloquinolines with relatively high singlet oxygen quantum yields upon excitation in the UV/Vis region (see Scheme 1B below). The compounds are obtained *via* a mechanistically closely related organocatalyzed tandem alkylation/cyclization step followed by an oxidative rearrangement. Halogen substituents are required to introduce a spin-orbit coupling effect in order to efficiently reach the triplet state of the photosensitizer.

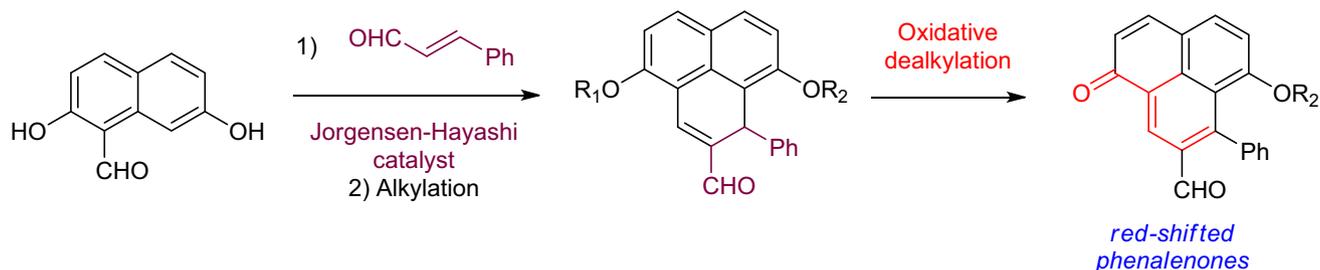
The resulting general synthetic strategy is the following: firstly, the indole ring is obtained *via* an elegant Bartoli synthesis between

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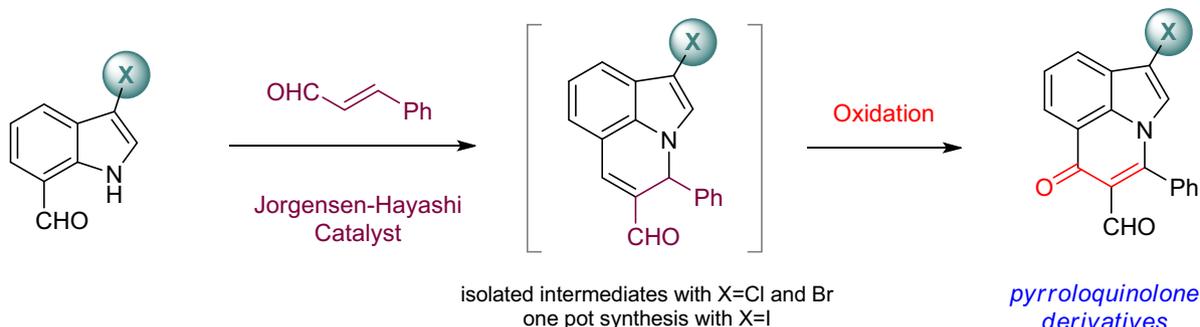
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A) Previous work: synthesis of visible-light active phenalenones (ref 8)



B) This work: synthesis of UV or visible-light active pyrroloquinolones



Scheme 1. General strategy developed by Coeffard *et al.* on the preparation of tricyclic aromatic compounds with potential photochemical activities: (A) The first approach enables to construct phenalenone derivatives; (B) The second approach enables the synthesis of halogenated pyrroloquinolines.

a nitro-aromatic and vinyl magnesium bromide; then, a site-selective halogenation (Cl, Br, I) is performed on position 3, and, finally, the organocatalyzed/oxidation sequence comes into play.

EXCITED STATE PROPERTIES AND RELAXATION PATHWAYS

Interestingly, the cyclized indole intermediates (X = Cl) exhibit a large fluorescence with a quantum yield of $\Phi_F = 0.358$ and a first excited singlet state lifetime of 6.4 (air) to 6.9 ns (Ar). This short-excited state lifetime is presumably incompatible with the utilization as a photosensitizer, but it surprisingly turns out that, in this case, the singlet oxygen quantum yield is equal to 0.273 in acetonitrile. This is weaker than the pyrroloquinoline products, which are produced *via* oxidative rearrangement (*vide infra*), but the combination of an effective radiative relaxation and a relatively high singlet oxygen production is relatively rare and therefore remarkable (9,10). Such intermediate could therefore serve as a fluorescent probe and as a singlet oxygen generator upon illumination and provide new tools to photobiologists.

In the pyrroloquinolines series, intersystem crossing is found to be less efficient compared to the phenalenones derivatives (8). The authors therefore decided to improve spin-orbit coupling by adding halogens on the position 3 of the indole ring. Three halogenated intermediates are thus obtained (Cl, Br and I) and the photophysical properties assessed by state-of-the-art spectroscopy. Centered around 370 nm, the typical $\pi-\pi^*$ transition exhibits a $10^4 \text{ M}^{-1} \text{ cm}^{-1}$ molar extinction coefficient and a weak solvatochromism. As correlated to the high singlet oxygen generation activity, a weak fluorescence was detected at around 460 nm.

More intriguingly, additional time-course absorption experiments demonstrated that the final oxidized compounds were unstable upon irradiation. This turned out to be a valuable result

as the yet unknown degradation products are believed to produce more singlet oxygen than the parent pyrroloquinolines. Indeed, singlet oxygen quantum yields measurements showed a marked increase after 15 min irradiation at 365 nm.

CONCLUSIONS

This inspirational work demonstrates how innovative strategies in organic synthesis can find valuable applications in photochemistry and photobiology. The use of modular approaches to synthetic organic chromophores is indeed a way to expand chemical libraries for photochemical applications. The work of Coeffard and his colleagues reveals how fundamental it is to develop synthetically accessible and low in cost approaches to bring this to reality. One of the highlights of this work is the discovery of a fluorescent compound with high singlet oxygen quantum yield and structural similarity with natural products (11,12) and bioactive compounds (13). This is a relatively rare feature of relevance to the development of theranostic molecular tools. It is also to be hoped that the photochemical instability of pyrroloquinolines will be eventually understood and that the molecular structures of the photoproducts resulting from light irradiation will be elucidated to help the discovery of new theranostic agents. Lastly, another interesting perspective of this work is the structural analogy of the synthesized compounds with halogenated alkaloids (14), a vast family of natural products which should be more systematically investigated as potential photosensitizers as they could exhibit potentially interesting photophysical properties.

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