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Highlight Article (Invited)

Cyanine Modification Tuned for Amine Photorelease

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ABSTRACT

Cyanines are emerging as useful agents for photoreleasing biological compounds because of their capability of utilizing near-infrared (NIR) light. Another benefit is their ability to self-sensitize to produce singlet oxygen for the release of aryl amines, a process that has not been as feasible in the past. Here, we highlight the paper by Schnermann *et al.* (https://doi.org/10.1111/php.13090), which reports on a cyanine conjugate for heterolytic photocleavage of aryl amines. This paper is timely—delving into a photorelease mechanism involving a domino rearrangement and β-elimination triggered by NIR light.

COMMENTARY

A β-elimination strategy following cyanine photooxidation has resulted in an amine photorelease reaction. A cyanine conjugate designed for aryl amine photorelease conducted by Schnermann *et al.* (1) provides insight into this very reaction.

Their study is reported in *Photochemistry & Photobiology* (1) and describes the synthesis of cyanine conjugates that could be photooxidized to trigger a β-elimination for subsequent amine release. One such cyanine conjugate (CI-β-Cou) is shown in Fig. 1. They have designed the photorelease to be able to utilize NIR light for the amine to dissociate from the cyanine, where it can react with biological receptors.

Schnermann's incorporation of NIR activation into his system provides benefits for photorelease compared to reactions that use, for example, UV light. Such reliance on UV light has been found to be problematic due to limited capabilities for deep tissue penetration. It is worth noting that other researchers have made inroads in photorelease mechanisms with visible light (2–4), 2-photon activation (5,6) and photoinduced electron transfer techniques (7,8). Another problem that arises is the limited number of options for amine photorelease mechanisms. The complication relates to heterolytic bond-cleaving reactions because amines are strong bases and thus poor leaving groups (9–13). Amine photorelease can be accomplished with 4-hydroxyphenacyl compounds (14). Additionally, direct carbon–nitrogen (C–N)

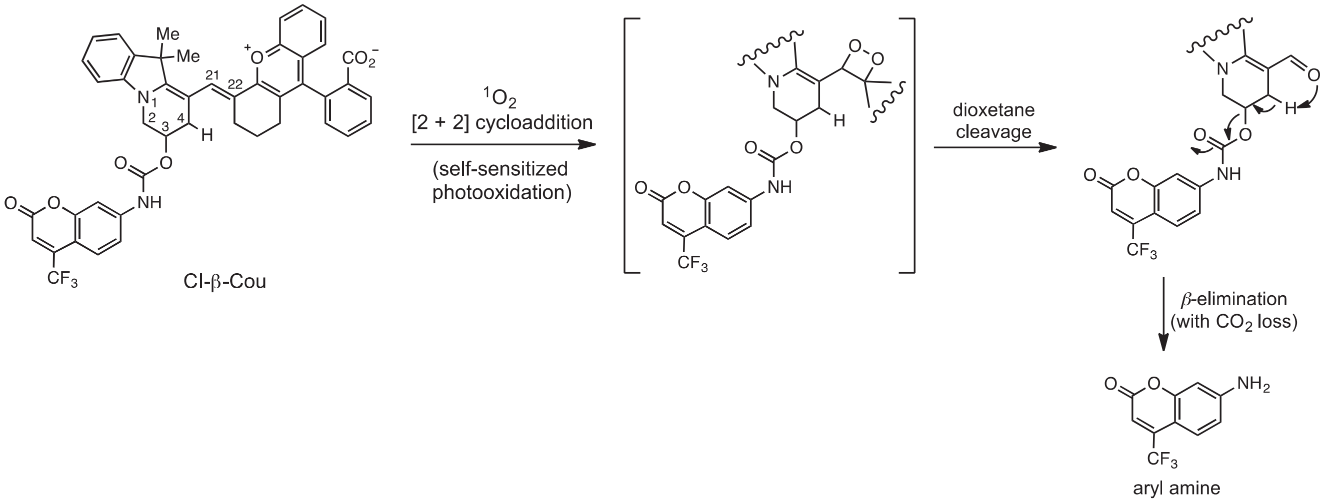

Figure 1. Cyanine designed and photochemically primed for amine photorelease. The first step is light and O_2 dependent, wherein the cyanine conjugate produces singlet oxygen via self-sensitization, which attacks the C(21)=C(22) bond. The formed dioxetane is unstable and cleaves to a pair of carbonyls. The amine-bearing carbonyl product undergoes a domino intramolecular rearrangement and β-elimination to release the aryl amine.

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*Corresponding author email: agreer@brooklyn.cuny.edu (Alexander Greer) bond (15,16) and nitrogen–nitrogen (N–N) bond photocleaving reactions can be used (17,18). In the latter case, photohomolysis of the N–N bond in nitrosamines to release aminyl radical only converts to the amine product after H-atom scavenging, and this causes low product yields and complex reaction mixtures. Thus, there is the potential to design the amine photorelease not only for NIR activation (19–22), but with carbamates linkers so that a β-elimination ensues (23–25).

Schnermann *et al.* (1) have incorporated both NIR and amine photorelease in their study. They used a three-step sequence as shown in Fig. 1. First, a self-sensitized formation of $^1O_2$ led to the regioselective [2 + 2] cycloaddition of $^1O_2$ at the cyanine C (21)=C(22) bond. Second, the dioxetane intermediate is cleaved by simultaneous C–C and O–O fragmentation to a pair of carbonyl compounds. Third, domino intramolecular rearrangement continues with the carbonyl segment bearing the amine undergoing a β-elimination. The inherent speed of the final decarboxylation is of note. This reaction heterolytically cleaves the amine along with a 1,3-cyclohexadiene and CO_2 as by-products.

Despite the utility of this aryl amine photorelease reaction, there are facets that remain to be elucidated further. For example, can the photoreleased amine provide protection as stabilizers (26) from unwanted photooxidation of cyanine, that is, nonselective reactions elsewhere than the C(21)=C(22) bond? Furthermore, does the amine product ability to physically quench $^1O_2$ (27–30) hinder this reaction sequence thus leading to diminishing returns in the photorelease process?

There is still a way to go before simple amines can be efficiently photoreleased. The work of Schnermann *et al.* (1) is a key initial step with the advent of NIR-absorbing cyanine conjugates to photorelease aryl amines. It has been shown that the reaction involves the photorelease of anilines, but it is conceivable that new cyanine conjugates will serve as a pathway to the photorelease of other amine compounds. Such endeavors with NIR light could enable amine photodelivery *deep* in biological tissues; indeed, just as the work of Schnermann and colleagues has provided *deep* insight to photochemists.

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