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Expanding the Use of Benzothioxanthene Imides to Photochemistry: Eco-Friendly Aerobic Oxidation of Sulfides to Sulfoxides

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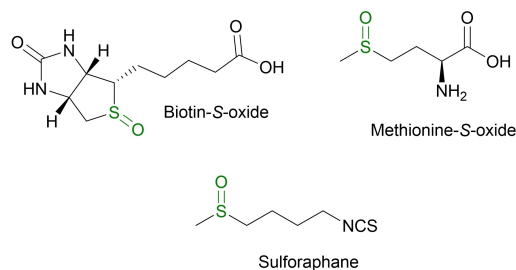
The sulfoxide moiety is one of the most commonly utilized groups in pharmaceutical and industrial chemistry. The need for sustainability and easy accessibility to sulfoxide moieties is deemed necessary, due to its ubiquity in natural products and potentially pharmaceutically active compounds. In this context, we report herein a sustainable, aerobic and environmentally friendly photochemical protocol based on the use of a

benzothioxanthene imide as the photocatalyst to selectively oxidize sulfides under mild irradiation (456 nm), in very low catalyst loading (0.01 mol%) and on water. In addition, to demonstrate the compatibility of our protocol with wide scope of substrates, the latter was successfully applied to the synthesis of the biologically-active Sulforaphane and Modafinil.

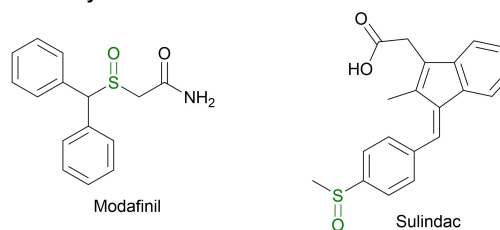
Introduction

The sulfoxide moiety has significantly influenced the fields of medicine and biology,^[1] with a range of natural and synthetic derivatives undergoing extensive investigation for their potential applications as pharmaceutical agents and/or synthetic reagents. For instance, Methionine-S-oxide, Biotin-S-oxide and Sulforaphane are prominent structures among natural sulfoxides (Scheme 1). Methionine, a natural amino acid, and its sulfoxide derivative have demonstrated noteworthy roles in biological functions, paralleling the significance observed for Biotin-S-oxide.^[2] Particularly impactful, Sulforaphane is a natural sulfoxide predominantly present in Brussels sprouts, broccoli, cabbage, and cauliflower. With anticancer and antioxidant properties, this molecule further underscores the consequential contributions of natural sulfoxides, both to medicinal and biological realms.^[3,4] The diverse biological activities associated with sulfoxides, akin to other sulfur-containing motifs, highlight their significance in drug design. Successful endeavors in the

Naturally occurring sulfoxides



Synthetically achievable sulfoxides



Scheme 1. Examples of bioactive sulfoxides.

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synthetic derivation of this functional group have afforded notable compounds, among which Modafinil and its derivatives stand out (Scheme 1). These compounds have demonstrated exemplary efficacy in addressing pathologies, such as narcolepsy and other sleep disorders.^[5] Additionally, Sulindac, an oral non-steroidal anti-inflammatory drug, has recently garnered considerable attention, due to its potential role in cancer chemoprevention (Scheme 1).^[6] These achievements highlight the fruitful exploration of synthetic sulfoxides in medicinal applications, with promising outcomes in drug development.

Synthetically speaking, the oxidation of sulfides is the most common method to prepare sulfoxides since its seminal report dating from 1865.^[7] Since then, a significant amount of documented published methods were hindered by the gener-

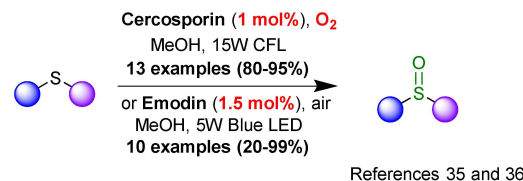
ation of extensive amounts of waste, primarily due to the utilization of the required oxidant in overstoichiometric amounts. More recently, a more environmentally sustainable approach, involving the use of hydrogen peroxide as the oxidant was introduced. However, its activation requires heat or the use of metal-based catalysts.^[6] Efforts to overcome this limitation involved the application of metal-free organocatalysts,^[9] flavins^[10] or activated ketones.^[11]

A pivotal juncture in organic synthesis was marked by the introduction of photochemistry by Giacomo Ciamician.^[12] Despite experiencing a century-long hiatus, photochemistry eventually gained full recognition and significantly impacted the scientific community after MacMillan, Stephenson and Yoon published pioneering investigations.^[13–15] Subsequently, photochemistry has evolved into a compelling instrument in organic synthesis, emerging as a method of choice for revitalizing previously reported reactions by imparting them with an environmentally benign nature.^[16–23] Additionally, it has been proven to be instrumental in accomplishing transformations that were previously unattainable. The seminal demonstration of photochemical oxidation of sulfides was reported by Schenck in 1962.^[24] Since that time, an array of methodologies has been documented, leveraging molecular oxygen as the oxidizing reagent.^[25] The attractiveness of employing molecular oxygen as an oxidizing agent lies not only in its natural presence in atmospheric air, but also in the diverse methods available for generating active oxygen species, which demonstrate exceptional efficacy across a broad spectrum of oxidation reactions.^[26] For instance, the oxidation of sulfides has emerged as a common and widely adopted process in photocatalytic protocols. Previous literature extensively and intensively features examples based on metal-based^[27–29] and/or heterogeneous photocatalysis.^[30–32] Despite the success demonstrated by metal-based photocatalysts, the emphasis should now shift towards adopting methods that align with eco-friendly principles. At this point, photoorganocatalytic systems seemed to be proper alternative, considering the increasing number of publications related to this subject. A variety of naturally occurring organic compounds has indeed been evaluated for this purpose, such as flavins by Cibulka^[33] and later from the Zhao group, who demonstrated enhanced catalytic properties through various substitutions.^[34] Natural compounds based on the anthraquinone scaffold have also been used as photosensitizers, such as Cercosporin^[35] or Emodin^[36] (Scheme 2, A).

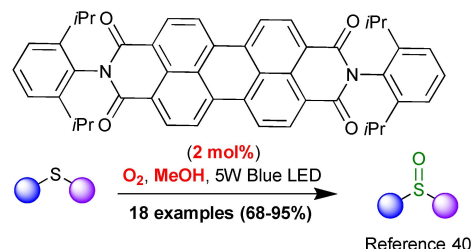
In parallel, a number of organic dyes have also been implemented in the oxidation of sulfoxides, like Rose Bengal^[37] or BODIPY dyes.^[38,39] In 2019, Zhang successfully experimented on the use of a perylene diimide as the photosensitizer, therefore adding another usable dye in the family of photocatalysts capable of oxidizing sulfides (Scheme 2, B). However, the use of an oxygen balloon was needed to afford the desired products.^[40]

On the fringe of these well-known class of compounds, various organic compounds have been used for this oxidation, either used as immobilized photocatalytic components^[41] or by themselves, like thioxanthone and its derivatives.^[42] The use of a system of CF₃SO₂Na and bis(2-butoxyethyl)ether as the photo-

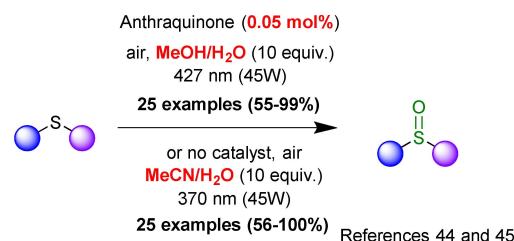
A) Natural Products based on the anthraquinone core as catalysts for the oxidation of sulfides



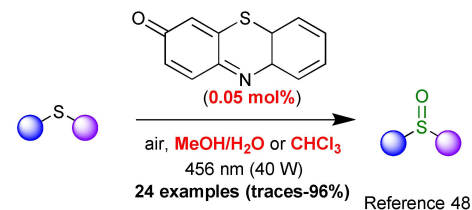
B) Photochemical oxidation of sulfides utilizing PDIs



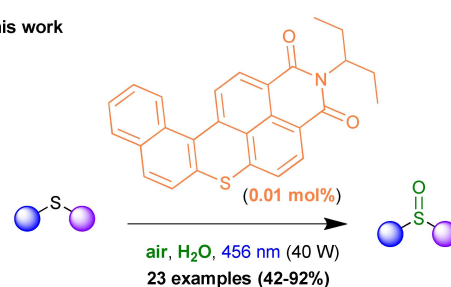
C) Our Previous photochemical aerobic oxidation of sulfides employing anthraquinone or catalyst-free conditions



D) Our previous photochemical aerobic oxidation of sulfides incorporating 3H-phenothiazin-3-one as a novel photocatalyst



E) This work



Scheme 2. Previous literature and this work on the photochemical aerobic oxidation of sulfides to sulfoxides.

catalyst and the solvent, respectively has also been reported.^[43] In 2022, the Kokotos group employed anthraquinone as an efficient photocatalyst at only 0.05 mol%, while reporting also a catalyst-free protocol, using irradiation at 370 nm (Scheme 2, C).^[44,45] A notable remark in all the previously mentioned protocols is the use of solely organic solvents or the

combination of them with water as an additive. Furthermore, in a number of cases in previously mentioned literature, the tested substrate scope was limited. Finally, a few more catalyst-free protocols were reported, such as a UV-irradiated one by Albin^[46] or, in 2021, by Sun and his coworkers utilizing blue LED irradiation in a methanol/water solvent system, however the substrate scope was limited to aryl-alkyl sulfides.^[47] More recently, the Kokotos group introduced a low catalyst loading protocol (0.05 mol%) under air and either in methanol/water or chloroform for the aerobic oxidation of sulfides (Scheme 1, D).^[48]

On the other hand, Cabanetos initiated an exploratory work on benzothioxanthene imide (BTI) derivatives. This class of rylene, initially prepared for textile industry, has been almost unnoticed by the scientific community. However, by pioneering the functionalization of the π -conjugated backbone,^[49–52] Cabanetos and coworkers unveiled unexpected properties.^[51,52] For instance, BTI (PC-1, Table 1) was found to be an impressive fluorophore, with a emission quantum yield reaching the unit, while its derivatives exhibit exceptional results, regarding the

generation of reactive singlet oxygen species ($^1\Delta_g$).^[50–52] Extending BTI's π -conjugated system, resulted in an amazing photosensitizer, namely the DBI (PC-2, Table 1), recently used in photodynamic therapy.^[52]

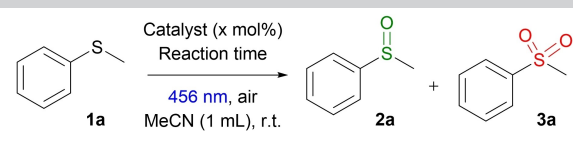
Considering that the Kokotos' research has been focused, over the past ten years, on developing novel and sustainable photochemical protocols, aiming at their implementation in the pharmaceutical industry,^[53–59] we embarked on a journey to combine this expertise with that of Cabanetos' groups (molecules with high quantum yield for the generation of singlet oxygen) to explore the potential of benzothioxanthene imides as photocatalysts.^[60] From this joint and common goal, we were able to develop an efficient, yet eco-friendly water-based protocol that uses oxygen as the only oxidizing agent.

Results and Discussion

Our initial experimental endeavors involved the use of thioanisole (**1a**) as the model substrate, in order to optimize reaction conditions (Table 1). The investigation encompassed the evaluation of four potential photocatalysts (Table 1, entries 2–10), concurrently exploring the lowest catalyst loading required to facilitate the oxidation process adequately. Notably, PC-1 and PC-2 performed excellently, but PC-2 emerged as the optimum catalyst, demonstrating superior performance at an exceptionally low loading of 0.01 mol% and reduced reaction time (Table 1, entry 8). In parallel, the oxidized version of PC-1 and PC-2 were also evaluated as the photocatalyst. It turned out that poor conversions were achieved, thus demonstrating the photostability of both PC-1 and 2 that might not undergo self-oxidization under these conditions and therefore impact the photoconversion of thioanisole into its sulfoxide/sulfone counterparts.

Following the obtained results, our investigation was extended by conducting sulfoxidation in different solvents (Table 2). Favorable outcomes were achieved in acetonitrile, chloroform or dichloromethane (Table 2, entries 1, 7 and 8). Notably, solvents with the capacity to form hydrogen bonds exhibited superior performances, specifically a variety of alcohols were tested that yielded comparable results (Table 2, entries 4–6), while the utilization of a solvent system comprising of acetonitrile and water exhibited commendable performance, resulting in a satisfactory yield of the desired product (Table 2, entry 3). Nevertheless, all tested solvents were outperformed, when water was implemented as the reaction medium, surpassing them not only in terms of yield, but also in selectivity for the desired sulfoxide over the overoxidized sulfone (Table 2, entry 2). On the other hand, the increased overoxidation of substrate **1a**, when the reaction was conducted in petroleum ether is also notable (Table 2, entry 9). Unfortunately, despite these conditions, complete oxidation to the corresponding sulfone could not be achieved. However, even without the access to sulfones, the use of a solvent, in which the reactants are not miscible gave us the opportunity to improve the green character of our protocol by transforming it to an "on-water" reaction. Ultimately, the pursuit of optimal

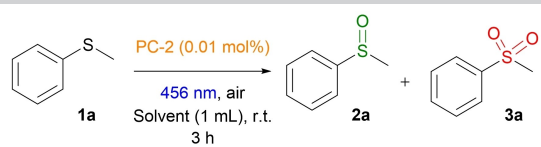
Table 1. Catalyst optimization and reaction time optimization studies.^[a]



Entry	Catalyst (mol%)	Reaction time (h)	Conversion (%) ^[b]		
			1a	2a	3a
1	–	18	88	12	0
2	PC-1 (0.5)	18	0	79	21
3	PC-2 (0.5)	18	0	58	42
4	PC-1 (0.05)	18	0	78	22
5	PC-2 (0.05)	18	0	90	10
6	PC-1 (0.01)	7	0	90	10
7	PC-2 (0.01)	5	0	86	14
8	PC-2 (0.01)	3	0	90	10
9	PC-3 (0.01)	3	95	5	0
10	PC-4 (0.01)	3	100	0	0

^a All reactions were carried out with **1a** (0.20 mmol) under blue LED irradiation. ^b Conversions were determined by ¹H-NMR.

Table 2. Solvent optimization study.^[a]



Entry	Solvent	Conversion (%) ^[b]		
		1 a	2 a	3 a
1	MeCN	0	90	10
2	H ₂ O	0	96	4
3	MeCN/H ₂ O	0	90	10
4	MeOH	0	92	8
5	EtOH	0	93	7
6	i-PrOH	0	92	8
7	CHCl ₃	0	90	10
8	CH ₂ Cl ₂	0	85	15
9	Petr. Ether	9	50	41
10	EtOAc	6	82	12
11	DMAc	82	18	0
12	DMF	0	90	10
13	Benzene	51	39	10

^a All reactions were carried out with **1 a** (0.20 mmol) under blue LED irradiation. ^b Conversions were determined by ¹H-NMR.

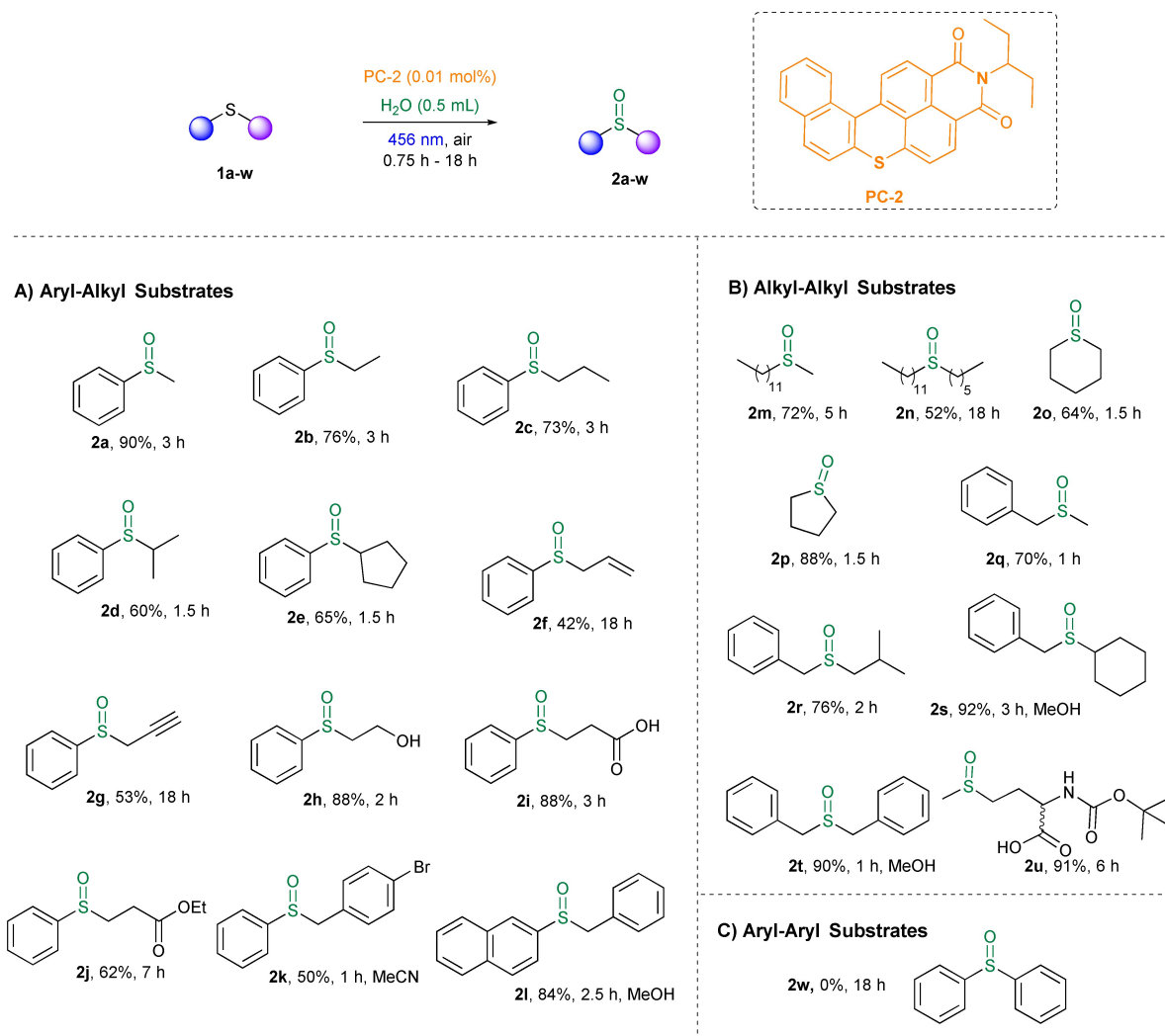
reaction conditions culminated in the identification of the most effective irradiation source.^[60] While employing CFL lamps as the irradiation source proved inadequate, the transition to LEDs resulted in a substantial enhancement in the yield of **2 a**.^[61] We deemed unnecessary performing the reaction at 370 nm or 390 nm, as the sulfoxidation can take place in the absence of a catalyst under these conditions.^[44,45] The optimal outcome was thus achieved, when the reaction mixture was carried out under 456 nm irradiation, while performing the reaction at 440 nm came as a close second. To sum up, we introduced an environmentally friendly water-based protocol for the oxidation of sulfides.

With these results in hand, we continued our journey to apply our suggested protocol in a variety of substrates that can be divided into three categories, *ie*, aryl-alkyl sulfoxides, alkyl-alkyl sulfoxides and aryl-aryl sulfoxides (Scheme 3). First, the investigation of aryl-alkyl sulfoxides was fruitful, since we obtained these products in satisfactory yields. Specifically, products containing simple aliphatic chains exhibited good yields (Scheme 3, **2 a–c**), while compounds with aliphatic chains that were connected to the sulfur atom with a secondary carbon atom reacted faster, but could not avoid the over-oxidation and performed slightly worse (Scheme 3, **2 d** and **2 e**). Furthermore, substrates decorated with functional groups, such as a carboxylic acid, alcohol or ester moiety, displayed excellent reactivity (Scheme 3, **2 h–j**). Note that compounds containing double or triple bonds produced a variety of by-products, leading to lower yields (Scheme 3, **2 f** and **2 g**). In the cases of **2 l** and **2 k**, a change in the reaction medium, *ie*, to methanol or

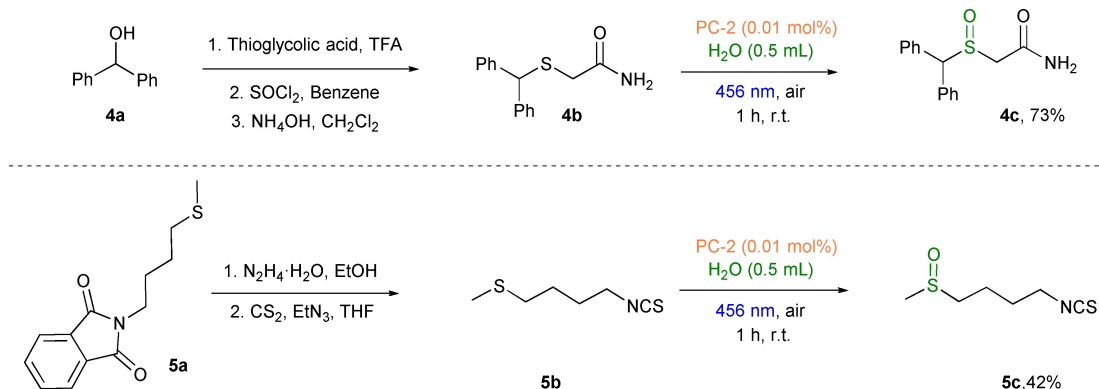
acetonitrile respectively, was required to achieve high photo-conversion, due to immiscibility of the catalyst with the substrates (Scheme 3). Afterwards, we initiated studies on alkyl-alkyl substrates and the results were equally noteworthy. In particular, substrates with lengthy aliphatic chains required extended reaction times to provide satisfactory results (Scheme 3, **2 m** and **2 n**). However, all other substrates required lower or equal reaction times to that of the standard conditions. Especially, compounds **2 o** and **2 p** were oxidized in a very short period of time and showcased excellent yields (Scheme 3). A minor change in the reaction medium was also required for the reaction with **2 s** or **2 t** and methanol was used, since the immiscibility of the substrates with PC-2 led to a zero yield, when the reaction was performed “on water”. In parallel, the oxidation of a natural amino acid was achieved, leading to sulfoxide **2 u** (Scheme 3). Sadly, studying the oxidation of aryl-aryl substrates proved to be sterile, due to the required mechanism for the oxidation of such compounds and the nature of the photocatalyst (a SET mechanism has to be followed and BTI is not capable of promoting this particular oxidation). Last but not least, we were delighted to synthesize and oxidize by our protocol two bioactive molecules, Modafinil (Scheme 4, **4 c**) and Sulforaphane (Scheme 4, **5 c**), providing us with adequate results.

To completely grasp the reaction mechanism that photocatalyst PC-2 follows, a series of control and quenching experiments, as well as UV-Vis and fluorescence studies were conducted. As a first control experiment, the reaction in the absence of oxygen was carried out, revealing that sulfoxide **2 a** was not detected upon irradiation of thioanisole in presence of photocatalyst PC-2. Moreover, the use of heat alone also proved to be ineffective.^[61] Thus, in order for our protocol to be productive, oxygen, irradiation and PC-2 have to be combined, while no specific thermal activation is required.^[61] Afterwards, reactive oxygen species quenchers were implemented, using thioanisole and dodecyl methyl sulfide as the model substrates to gain further insight into the reaction mechanism. Hence, 1,4-diazabicyclo [2.2.2]-octane (DABCO) and sodium azide were demonstrated as efficient quenchers for this reaction, since substantially lower synthetic yield were achieved, while fluorescence quenching studies showed that no interaction between the excited photocatalyst and the quenchers occurred (Figure 1, B).^[61] Therefore, we were hinted that a possible singlet oxygen mechanistic pathway occurs. Benzoquinone or cobalt (III) acetylacetonate were also tested and managed to quench the reaction, but fluorescence quenching studies established that both these quenchers were interacting with photocatalyst's PC-2 excited state, meaning that they were both deemed unsuitable.^[61] Lastly, 1,4-dimethoxybenzene was also implemented and the yield of both **2 a** and **2 m** remained unaffected, thus cancelling the possible mechanistic pathway of sulfide radical cation. On the other hand, we carried out hydrogen peroxide generation detection tests and proved that no H₂O₂ was generated in the reaction mixture under irradiation.^[61]

As depicted in Figure 1, A, the mixture of the model substrate and PC-2 showed no bathochromic shift in the UV-Vis spectrum, therefore verifying the absence of any interaction



Scheme 3. Substrate scope.

Scheme 4. Modafinil^[62] and Sulforaphane^[63] preparation under the developed photochemical aerobic oxidation.

between them. Moreover, the Stern-Volmer plots of the scavengers, model substrates and PC-2 (Figure 1, B) proved that no interaction occurs between them. This is to be expected, since the required redox potential for the single electron oxidation of the model substrates 1a and the unreactive 1w

are known to be +1.34 eV and +1.47 eV, respectively,^[48] while the reductive potential of the excited PC-2 seems not to be enough.^[61] Also, utilizing a recently published tool by Glorius,^[64] we were able to calculate the excited triplet energy of PC-2, which was found to be 52 kcal/mol. Using the same tool,^[64] the

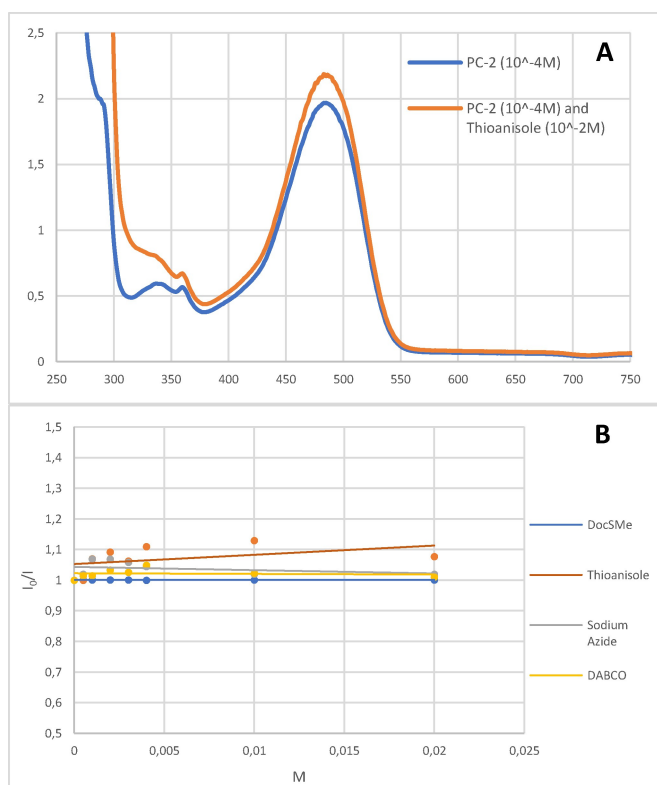
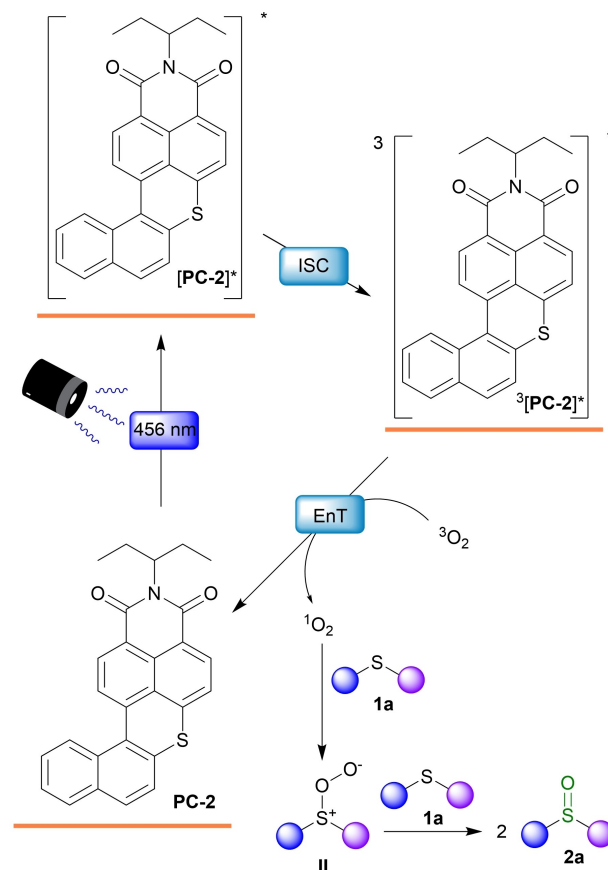


Figure 1. A) UV-Vis spectra of PC-2 and mixture of PC-2 and substrate **1a** in MeOH, B) Stern-Volmer plots of mixtures of PC-2 with various scavengers and substrates.

triplet energy of the model substrate **1a** was found to be 75 Kcal/mol, which is in agreement with literature reports, which state that the triplet energy of **1a** is between 68 and 84 kcal/mol.^[65] Hence, PC-2 does not possess the required energy to interact with **1a**. On the other hand, the required energy to promote oxygen to its singlet state is only 22 kcal/mol,^[66] something attainable for PC-2. To sum up, after evaluating those results, we were in a position to assume that the only reactive species formed from the irradiation of photocatalyst PC-2 was singlet oxygen, which is in line with literature results.^[52] PC-2 was indeed reported to exhibit a singlet oxygen quantum yield of ca 0.95 in CH₂Cl₂,^[52] while the quantum yield of the reaction^[67] was calculated to be 0.23.^[61]

With all this information in hand, we were able to suggest a plausible mechanism for our protocol (Scheme 5). Firstly, PC-2, via irradiation at 456 nm is promoted to its singlet excited state and then transitions to triplet excited state through efficient intersystem crossing, to finally interact with molecular oxygen to provide the reactive singlet oxygen species. Afterwards, a molecule of sulfide interacts with singlet oxygen to form the persulfoxide intermediate **II** that then reacts with a second molecule of sulfide, affording two molecules of the desired sulfoxide (Scheme 5).



Scheme 5. Proposed reaction mechanism.

Conclusions

In summary, we have introduced a photocatalytic oxidation process that provides ¹O₂ as the lone reactive oxygen species and does not involve a pathway that deviates from the EnT process. Therefore, the sulfide moiety was selectively oxidized to the vastly pharmaceutically and industrially desirable corresponding sulfoxides with a very low catalyst loading (0.01 mol%) under blue LED irradiation, while utilizing water as the reaction medium in relative short reaction times. Compared to the previously reported literature, we managed to increase the eco-friendly character of this reaction (lower catalyst loading, water as the solvent, short reaction times) and apply our protocol to synthesize the bioactive molecules sulforaphane and modafinil. We also investigated the nature of the benzothioxanthene imide as a potential photocatalyst and once again demonstrated its amazing upcycling capabilities (from a textile dye to a photocatalyst). These results have provided us with valuable information to apply, in the future, this catalytic system to a variety of oxidations, but not only.

Supporting Information

The authors have cited additional references within the Supporting Information.^[68–74]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Photochemistry · Oxidation · Aerobic · Sulfoxide · Benzothioxanthene imide

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reaction mediator and oxygen from the atmospheric air as the oxidant under blue LED irradiation to afford excellent yields in a variety of substrates.

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Expanding the Use of Benzthioxanthene Imides to Photochemistry: Eco-Friendly Aerobic Oxidation of Sulfides to Sulfoxides

