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Z-Selective Synthesis of α-Sulfanyl Carbonyl Compounds from Internal Alkynes and Thiols via Photoredox Catalysis

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Abstract: A synthetically useful Z-selective cascade formal thiyl radical addition, 1,3-double bond isomerization, oxygen trapping reaction, can be promoted by Eosin B under visible light, leading to the construction of 2-aryl- and alkylthio enone derivatives in good yields. An accurate study on the reactivity of different thiols and the screening of the reaction conditions, allowed us to extend this reaction to a large number of substrates, showing a good functional groups tolerance while highlighting the limitations of this procedure. Background experiments and mechanistic studies were also. performed to rationalize this cascade process. The usefulness of this methodology was finally demonstrated via the transformation of a series of α-sulfanyl-enone adducts through selected oxidation reactions, stereoselective synthesis of cyclopropyl ketones, indanones, and pyrazole compounds.

Keywords: Alkynes; Photoredox catalysis; Thiyl radical; Cascade reaction

Introduction

The discovery of new synthetic protocols based on cascade reaction strategies, represents one of the preferred ways to achieve complex molecular architectures for drug discovery and/or technological applications with a high degree of sustainability and operational cost reduction.[1] In this regard, new photo-induced electron transfer (PET) procedures, have been explored as a valid alternative to conventional synthetic transformations.[2] In particular, protocols based on the simultaneous creation of new carbon-carbon and carbon-heteroatom bonds, constitute a fruitful research field.[3] In this context, alkyne-based synthetic platforms have emerged for their versatility, giving access to a variety of privileged molecular architectures from readily available starting materials.[4] Undoubtedly, one of the most studied reactions belonging to this class of compounds is represented by the formal radical addition of thiols to alkynes, more commonly known as thiol-yne reactions. These transformations

attracted the interest of both the academic and industrial scientific community because of their feasibility and wide range of applications (click chemistry) and in particular for their importance in polymer[5] and medicinal chemistry.[6] Many of these reactions have been developed mainly using terminal alkynes giving thiol-additions in high yield, stereo, and chemoselectivity[7] (Schemes 1a, 1b and 1c). On the other hand, literature on thiol-yne reactions involving internal alkynes are limited[8] (Scheme 1d). Recent advances in photocatalytic tandem reactions demonstrated that thiol-yne addition to acetylene dicarboxylic esters[9] and nitrogen-containing diarylacetylene derivatives[10] can be efficiently performed, giving access to a variety of privileged molecular architectures such as benzothiophene derivatives or 3-arylthio indoles (Scheme 1e, 1f). Moreover, the photooxidation of diarylalkynes carried out in the presence of aromatic thiols[11] or disulphides[12] as a source of thiyl radicals (RS•), has been investigated as a versatile method to access to 1,2-diaryl-ethane-1,2-dione derivatives in
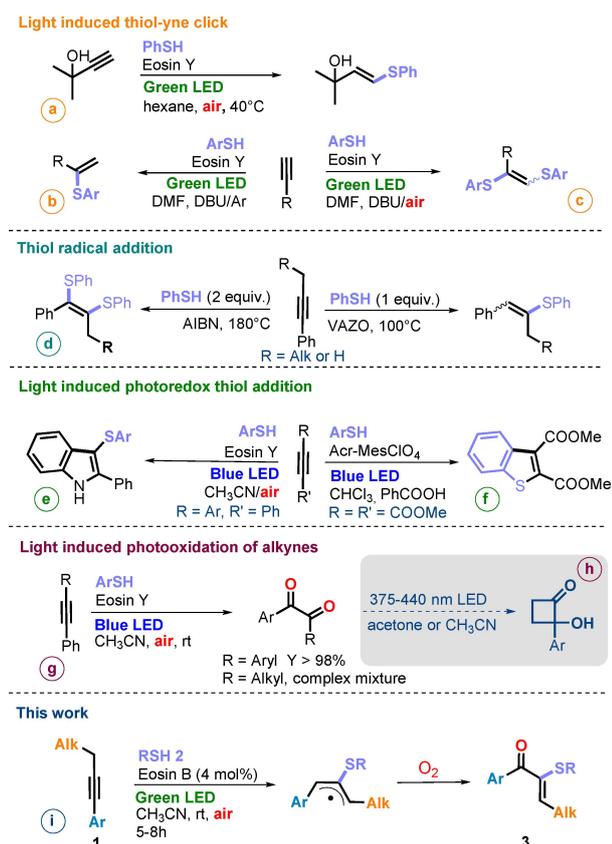
Scheme 1. Radical initiated transformation of alkynes involving thiol species.

satisfactory yields (Scheme 1g). In these reactions, RS$^\bullet$ undergoes reversible oxidation to peroxyl-radicals (RSOO$^\bullet$), which have been suggested as the principal oxidizing reagent of the alkyne triple bond.[11,13] On the other hand, attempts to oxidize aryl-alkyl derivatives failed, leading to the formation of complex mixtures of unidentified products.[11]

Very recently our research group developed a photochemical Norrish-Yang II (NYII) continuous flow process aimed at the synthesis of hydroxycyclo-butanones, starting from substituted α-diketones.[14] During this study, we noticed that alkyl diones would undergo rapid intramolecular cyclization reaction affording cyclobutanone adducts in excellent yields. However, long exposure of these strained four-membered ring compounds to light/O$_2$ (air), ended up in the formation of oxidation side products.

These results led us to think that, most likely, some alkynes photo-oxidation reactions failed due to the activation of secondary processes such as the Norrish-Yang photocyclization, thus leading to a general erosion of the chemical yields. In our mind, the development of a one-pot process that would allow us to obtain functionalized cyclobutanones in a single synthetic step starting from alkynes, appeared to be

very attractive.[15] Therefore, we planned a series of experiments in which 1-phenylbutyne **1a** was submitted to photo-oxidation reactions (440 nm) in the presence of 4-chloro-benzene thiol **2a** and Eosin B (EB) (Scheme 1g). In these experimental conditions, we observed the formation of a sulfanyl-butenone derivative **3aa** in non-negligible yields (12%) while the main reaction product was represented by a 90:10 $Z:E$ mixture of the alkene **4a** (37%). Nevertheless, the 1,2-diketone **6a** was detected only in traces. Not surprisingly, the cyclobutanone **7a**[14] was isolated in 10% yield together with the compound **5a** (10%) as reported in Scheme 2. Again, a consistent amount of 4-chlorophenyldisulphide was formed.

These experimental results led us to suppose that probably, two different reaction pathways were competing: one represented by the oxidation of the alkyne to 1,2-diketone species, and another independent process driven by a formal thiyl radical addition to the alkyne triple bond, leading to the formation of the sulfanyl-enone **3aa**. This meant that an appropriate tuning of the reaction conditions could promote the preferential formation of one of the identified products. Above all, the photocatalyzed synthesis of **3aa** had not been previously reported. In fact, this achievement would allow establishing a new visible light-driven synthetic strategy able to furnish in a single operation step, highly functionalized compounds from alkynes and thiols.[16] In particular, looking at the product **3aa**, a new cascade formal thiyl-radical addition, 1,3-isomerization, oxidation reaction, would take place with the establishment of two new C-heteroatom (C–S and C–O) bonds and the construction of a stereochemically defined α-sulfanyl-enone-unit.

Starting from this first evidence, we analysed the different reaction parameters involved in the reaction, including the nature of the solvents, the thiol concen-
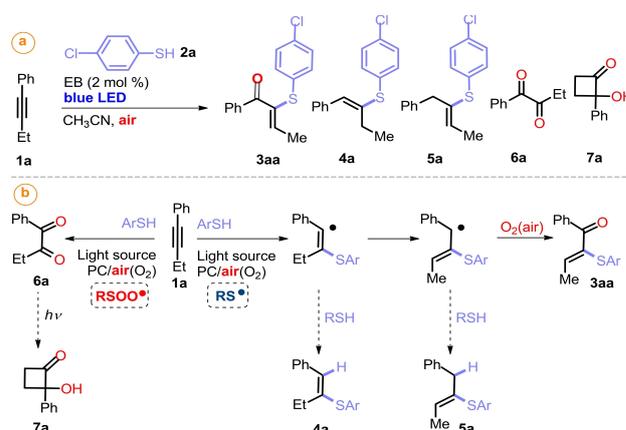
Scheme 2. [a] Photocatalytic reaction of thiol **2a** with **1a** in the presence of EB (2 mol%). Identification of the reaction products **3aa**, **4a**, **5a**, **6a**, **7a**. [b] First mechanistic hypothesis.

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tration, the role of O_2 and the airflow rates (mL/h), the light sources (LED emission spectra and photon flux) and the identification of appropriated catalyst. Herein we report the successful implementation of this procedure and the development of a new photocatalytic platform for the synthesis of functionalized enones.

Results and Discussion

Initial condition screening was performed using 1a (0.1 M in CH_3CN) and **2a** (2.0 equivalents). The experiments were performed in a 5 mL open vial, equipped with green LEDs (525 nm) placed around the flask. Reagents and catalyst were loaded together, and the resulting deep red suspension was irradiated (EB λ max: 527 nm)[17] for 12 hours. With this set-up, we were able to isolate the derivative **3aa** in a 15% yield. Moreover, the enol thioether **4a** was again the major product of the reaction, accompanied by diphenyldisulphide, along with traces of **5a** and **6a**. Interestingly, **7a** was not detected.[14,18]

Taking into consideration the fact that **4a** should be generated by the addition of a thiyl radical (Scheme 2b) followed by the abstraction of a hydrogen atom from a second molecule of thiophenol,[7] we performed the slow addition of **2a**, (2.0 equiv./4 h) to limit this process and drive the reaction towards the preferential formation of the adduct **3aa** (Scheme 2). This expedient allowed us to isolate the enone adduct in a 45% yield (Table 1, entry 1). Furthermore, having at our disposal an appreciable amount of product, we were then able to establish the stereochemistry of this compound by using a DPFGSE-NOESY1D NMR sequence, which indicated the predominant formation of the Z-isomer.

To further increase the chemoselectivity of this reaction, other photocatalysts including Eosin Y (EY), fluorescein, Rhodamine B (RB), (Mes-Acridine)ClO4 salts (Mes-Acr), DDQ, and tris(bipyridine)ruthenium (II) chloride [Ru(bpy)$_3$]Cl$_2$, were screened under the above-mentioned reaction conditions, confirming that EB acted as the best catalyst for this transformation when coupled with green LEDs (Scheme 3).

At this point, additional optimization experiments were performed in a reactor vessel closed with a suitably designed 3D-printed cap (a full reactor description and characterization is provided in the ESI). The device accommodates an easily changeable LED and is provided with a series of inlets that allow the introduction of both reagents and air. Also, using this reactor, we were able to control the reaction concentrations ($\triangle V < 5\%$ up to 6 h); in fact, in previous experiments, partial evaporation of the solvent was observed. At the same time, we were able to control both the amount of airflow and the reaction temperature (34 °C).

Table 1. Optimization of reaction conditions.[a,i]

Entry	equiv.	LEDs	3aa:4a:5a[g]	3aa yield %[h] (Z:E)
1[b]	2.0	3×3 W	50:9:2	45 (89:11)
2[c]	2.0	3 W	57:28:12	55 (91:9)
3[c]	1.5	3 W	65:20:8	60 (90:10)
4[d]	1.5	3 W	72:16:7	67 (88:12)
5[e]	1.5	3 W	79:10:2	72 (92:8)
6[f]	2.0	3 W	65:8:3	59 (91:9)

[a] Reactions were performed with **1a** (50 mg 0.35 mmol), **2a** (0.70 mmol), EB (2–4 mol%), solvent (3.0 mL), 34 °C; 3 or 3×3 W LED.
[b] Reactions were performed in an open vial.
[c] Reactions were performed in a closed vial, air flow rate 5 mL/h.
[d] Reactions were performed in a closed vial, air flow (10 mL/h) EB (3 mol%).
[e] Reactions were performed in a closed vial, air flow (10 mL/h) EB (4 mol%).
[f] Reaction were performed in a closed vial, air flow rate (20 mL/h).
[g] Reactions were followed by GC-MS.
[h] Isolated yield after flash chromatography.
[i] Photochemical reactor cartoon.

Scheme 3. [a] Reactions were performed with **1a** (0.35 mmol), **2a** (0.70 mmol), PC (2 mol%), solvent (3.0 mL), 30–35 °C, 3× 3Watt LED. [b] Isolated yield after flash chromatography.

Using this reactor (airflow of 5 mL/h), syringe pump addition of **2a** allowed us to convert **1a** into **3aa** in 57% (Table 1, entry 2).

An increase in air-flow rates to 10 mL/h, along with slow addition of **2a** (4 hours, 1.5 equiv.), afforded **3aa** in 65% conversion (Table 1, entry 3). However, during these trials, we noticed a slow and dramatic catalyst deactivation[19] (figure 1), with the consequent leveling of the reaction yields.[7a]

Fortunately, the yield of **3aa** could be increased when an additional fresh catalyst (1–2 mol%) was added to the reaction. It was therefore decided to opt

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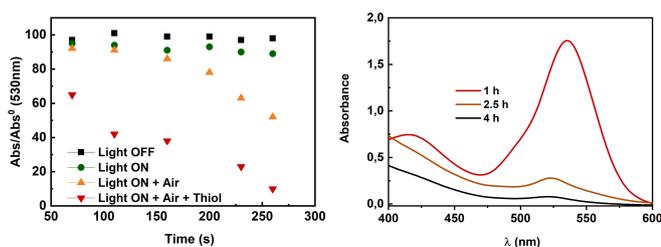
Figure 1. [a] Eosin B (EB) quenching plot in CH$_3$CN (dilution sample 1:100). Black: EB, Light OFF; green: EB, degassed CH$_3$CN, sealed vial, light ON (530 nm); orange: EB + air, light ON (525 nm); red: **2 a** + air, light ON (525 nm). [b] EB UV-Vis spectra recorded during the reaction of **1 a** with **2 a** in CH$_3$CN (3 mL), EB (2 mol%), air; light source: 5 Watt green LED (530 nm).

for a modified procedure in which the catalyst loading was increased from 2 to 4 mol% (72 and 79% conversion, entry 4 and 5). New experiments were carried out as follow: the catalyst (2 mol%) and **2 a** (1.5 equiv.) were dissolved in 2 mL of acetonitrile and added dropwise (4 hours) with a syringe pump to a **1 a** + EB (2 mol%) solution kept under stirring inside the reactor (light ON). We were delighted to see that, in these conditions, we could improve the **3 aa** conversion to 79% (entry 5). Further attempts to raise the reaction conversions by increasing the airflow rates to 20 mL/h, resulted in the isolation of lower amounts of **3 aa** (entry 6).

Satisfied with these results, we extended this reaction to other thiols in order to value the scope of this new transformation. For this reason, **1 a** was reacted with various substituted arylthiols bearing electron-withdrawing or donating groups. 4-Substituted benzenethiols such as **2 b** (p-CF$_3$), **2 c** (p-NO$_2$), and **2 d** (p-COOMe), gave the corresponding enones **3 ab–3 ad** in generally good yields and selectivity. Also, ortho- and meta-carboxymethyl benzene thiols (**2 e**, **2 f**) behave similarly (Scheme 4). On the other hand, reactions carried out with **2 h** (Ph), **2 i** (p-F), **2 l** (p-Me), and **2 m** (p-OMe) were unsatisfactory.[20] Taking into account a series of reports concerning the beneficial role of organic bases during the thiyl radicals (RS•) generation,[7a,20] we screened some base additives.

The use of 25 mol% of pyridine, turned out to be the winning choice, thus allowing us to react the thiols **2 h–i**, **2 l**, and **2 m** with **1 a** (see ESI for base screening), affording the corresponding enones **3** in satisfactory yields.

The same strategy led us to extend this procedure to aliphatic thiols like 2-methyl-2-propanthiol **2 n**, methyl-thioglycolate **2 o** and cyclohexylthiol **2 p** (Scheme 4).

However, an attempt to transfer this procedure modification to thiols **2 b–g** had a detrimental effect on both chemical yields and stereoselectivity (Table 2).
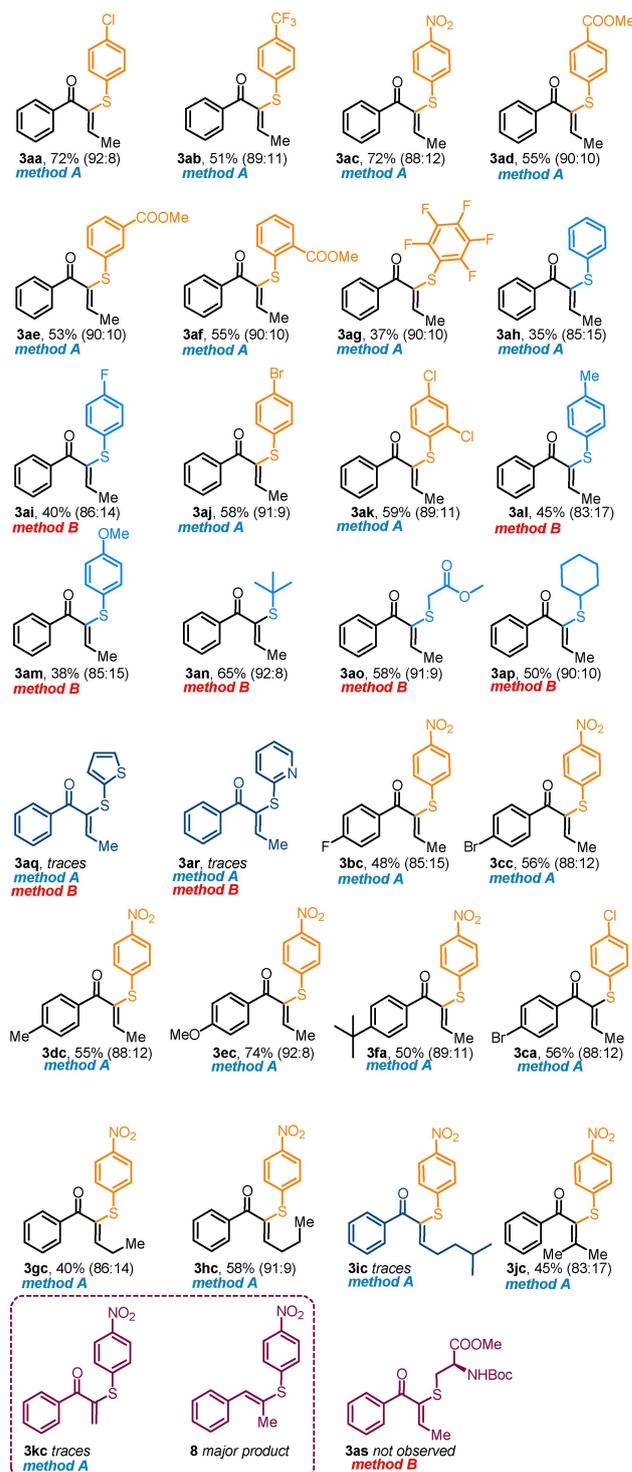
Scheme 4. Cascade thiyl radical-addition, [1,3]-double bond shift, oxidation reaction substrate scope.

Therefore, two methods were established: method A, which does not involve the use of a base additive (generally valid for functionalized arylthiols with electron-withdrawing groups), and method B, involving the use of a base, which was preferentially used for

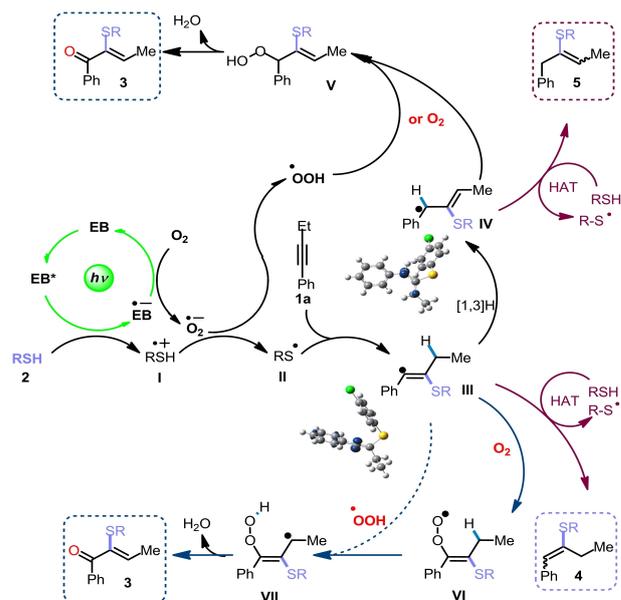**Table 2.** Reaction parameters optimization and comparison of methods A and B.[a]
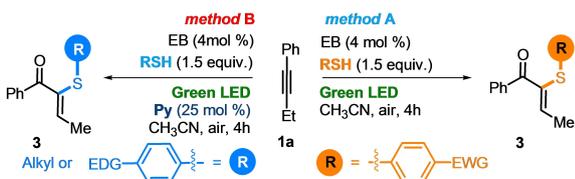
Entry	R	Method A, 3 yield % (*E*:*Z*)b	Method B, 3 yield % (*E*:*Z*)[b]
1	Ph	7 (nd)	35 (85:15)
2	4-MeC$_6$H$_4$	5 (nd)	45 (83:17)
3	4-MeOC$_6$H$_4$	2 (nd)	38 (85:15)
4	4-FC$_6$H$_4$	6 (nd)	40 (86:14)
5	*t*-Bu	–	65 (92:8)
6	CH$_2$COOMe	–	58 (91:9)
7	4-ClC$_6$H$_4$	72 (92:8)	45 (83:17)
8	4-NO$_2$C$_6$H$_4$	72 (88:12)	50 (84:16)

[a] Reactions were performed with **1a** (0.35 mmol), **2** (1.5 equiv.), EB (4 mol%), CH$_3$CN, rt.
[b] Isolated yield after flash chromatography.

Scheme 5. Proposed mechanism for the photocatalyzed synthesis of compounds **3**, **4** and **5**.

aliphatic thiols or functionalized arylthiols bearing electron-donating groups (Table 2). Further substrate scope investigations showed that thiols **2j** (*p*-Br), **2k** (2,4-dichloro) could be efficiently reacted with **1a**, leading to their enones in satisfactory yields using method A. Whereas, 2-mercapto thiophene **2q** and 2-mercapto pyridine **2r**, were unsatisfactory (regardless of the used method) and the corresponding adducts **3aq** and **3ar** were observed just in traces. On the other hand, reactions including the use of aryl-2-butynyl derivatives (**1b–f**) with **2a** performed well, leading to the isolation of both adducts **3bc** and **3fc** in good yields. Moreover, reactions carried out with other 1-phenyl-alkynes (**1g–h**, and **1j**) afforded the corresponding arylthio enones respectively in 40, 58 and 45% yield (Scheme 4). It is also useful to report that, during our experiments, we encountered some scope limitations, mainly correlated with the increase in the molecular complexity of the alkynyl-partners. Indeed, alkynes with longer aliphatic chains (>4 carbon atoms), turned out to be scarcely reactive under the developed reaction conditions. Whereas, reactions carried out with propinyl-benzene **1k**, allowed to obtain the enone **3kc** in traces, while the major product was represented by (2-phenylthio propenyl)-benzene **8**. Finally, attempts aimed at the synthesis of the cysteine derivative 3as were unsuccessful.

Back to our initial working hypothesis and combining all the observations collected during the development of this synthetic protocol, we worked out a rational reaction mechanism that could justify the formation of compounds **3** (Scheme 5). The EB photo-excitation underwent single electron-transfer oxidation

of benzenethiol species **2**, furnishing the arylthiol-radical cation (RSH$^{\bullet+}$) **I** by a SET process[7,21] Reduced EB (EB$^{\bullet-}$), can be oxidized back by molecular oxygen which, in turn, would be reduced to superoxide (O$_2^{\bullet-}$). This reactive species can abstract a proton from RSH$^{\bullet+}$ **I**, generating the thiyl-radical **II** (RS$^{\bullet}$) and the hydro-peroxyl radical (HOO$^{\bullet}$).[13]

The addition of **II** to **1a**, provides vinyl-sulfanyl radical species **III**, which can evolve by formal [1,3] hydrogen-shift to a more stable adduct **IV** (ΔE = 17 kcal/mol), in accordance with DFT calculations (see ESI). Then, hydrogen abstraction of a thiol hydrogen (HAT) by the radicals **III** and **IV**, gives access to the corresponding alkenes **4** and **5**.[7a,22]

On the other hand, the reaction of molecular oxygen with the adduct **IV** would promote the formation of compound **3**.[23] Alternatively, the intermediate **IV** might generate the peroxide **V** by its combination with the hydroperoxy-radical (HOO$^{\bullet}$) or molecular oxygen, furnishing the corresponding sulfanyl-enone[20] (Scheme 5). This first hypothesis is supported by our results obtained during the slow addition (4 h) of **2a** (Table 1, entries 4–7). Indeed, at low concentration, **2a** should not be available for HAT with the radical species **IV**.

Again, an increase of airflow from 5 to 10 mL/min would facilitate the formation of the adduct **V** and the consequent production of **3aa**. Nevertheless, a second pathway could be drawn, considering the reaction of **III** with an oxygen species (HOO$^{\bullet}$ or O$_2$) which would generate the radical intermediate **VI**. This allylic radical species would undergo 1,3 double-bond isomer-ization with the consequent formation of the adduct **3**.

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However, this sequence would not be able to explain the formation of alkene **5**. This mechanistic hypothesis was also corroborated by a series of control experiments summarized in Scheme 6. In more detail, the reaction of **1a** with thiol **2a** does not furnish the corresponding adduct **3aa** in experiments conducted in the dark. Also, in these conditions, the addition of **2a** to the triple bond occurs very slowly and without selectivity, providing a 50:50 mixture of the regioisomers **4a** and **8** (10% overall yield, Scheme 6, a).

A second experiment, carried out with bis(4-chlorophenyl)disulphide instead of **2a**, without changing the other operational conditions, did not lead to the formation of the adduct 3aa, indicating that no homolytic cleavage of the disulphide,[12] mostly generated during the photocatalytic process (Scheme 6, b) occurs. Then, to confirm whether enone **3aa** could be obtained directly by the oxidation of the alkenes **4** or **5**, a 50:50 mixture of these compounds was dissolved in acetonitrile and reacted in the operational conditions. However, after prolonged reaction (8 hours), no formation of **3aa** could be observed, both in the presence and in the absence of the thiol **2a** (Scheme 6, c), corroborating the hypothesis that enone **3aa** is the product of a specific cascade reaction as described in Scheme 5. Moreover, **4a** undergoes oxidative cleavage if submitted to green light, obtaining quantitative

amounts of benzaldehyde and thiopropionic acid S-phenyl ester **9**, but no traces of the enone **3aa** were detected (Scheme 6, d).

In order to investigate the possibility of synthesizing compound **3aa** via dione **6a**, the 1,2-diketone was submitted to the operating conditions. However, **3aa** was not observed after 12 hours reaction (Scheme 6, e). Furthermore, pure enone **3aa** was subjected to prolonged stirring under the reaction conditions, aiming to detect any oxidation reaction that could lead to the formation of **6a**. Even in this case, **3aa** was recovered unchanged (90%), accompanied exclusively by small amounts of the corresponding sulfone **10** (Scheme 6, f).

Inspired by the large number of molecular scaffolds accessible from enones **3**, we set out to perform the postfunctionalization of a series of these derivatives as shown in Scheme 7.

For this purpose, enone **3ac** was submitted to chemoselective oxidation of the sulfanyl-moiety, allowing to isolate the corresponding sulfone **11** in 88% yield by simple reaction with *m*-CPBA. Nevertheless, treatment of the same compound with sulfur ylides, allowed direct access to the cyclopropane derivative **12** in 65% yield and high stereoselectivity (98:2 *E:Z*-mixture of stereoisomers).[16] Then, indanone **13**, a
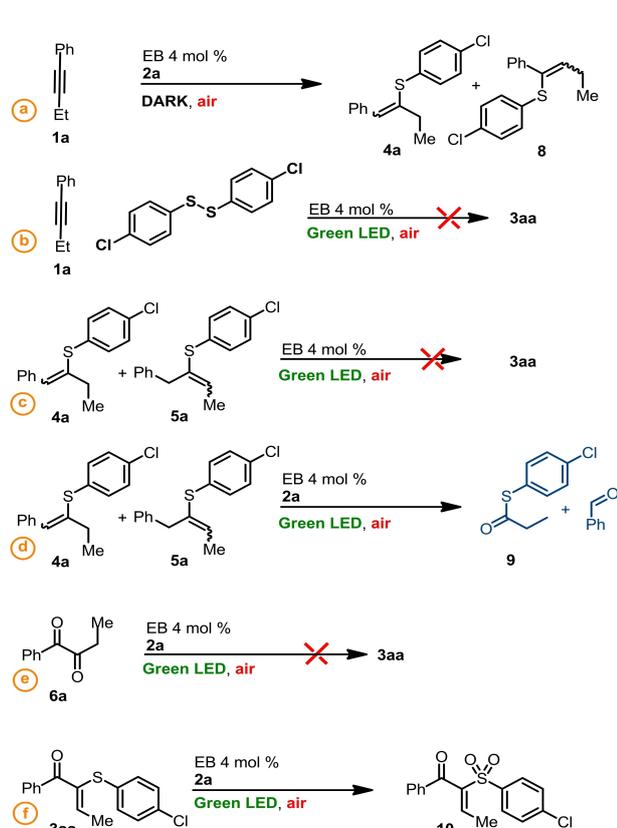
Scheme 6. Mechanistic investigation and background reactions.
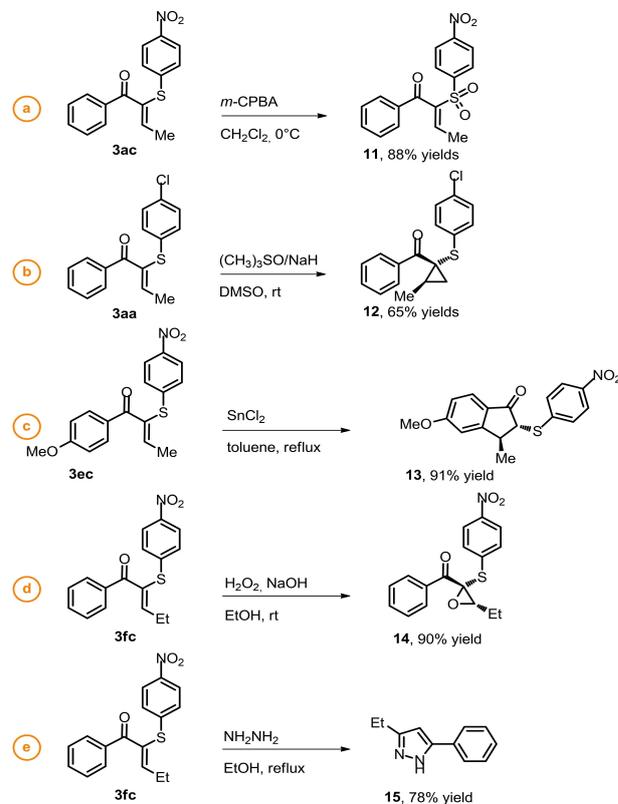
Scheme 7. Post functionalisation of enones **3aa**, **3ec** and **3fc** by single step reactions.

privileged structure in medicinal chemistry and natural products synthesis,[24] was obtained in excellent yield (91%) and high stereoselectivity (>99:1) by a Lewis acid catalysed intramolecular cyclization of enone **3ec**. Furthermore, pyrazole **15** was isolated in 78% yield by a simple reaction of **3fc** with hydrazine in ethanol at room temperature.[25] Finally, treatment of **3fc** with hydrogen peroxide in basic conditions furnished the keto-oxirane **14** in good chemical yields and high diastereoselectivity.[26]

Conclusion

We have developed a new photocatalytic process for the synthesis of aryl- and alkylthioenones through the direct reaction of readily available disubstituted alkynes and thiols. This process is promoted by Eosin B that, once irradiated with green light, triggers the conversion of selected thiols into thiyl radical species, which leads to the formation of α-sulfanyl-enone derivatives. Fine-tuning of thiols addition rate, the use of basic additives, as well as the airflow rates, allowed the establishment of a catalytic metal-free cascade process leading to the isolation of a large number of enones **3** with good to high chemo- and stereo-selectivity. To highlight the synthetic usefulness of this procedure, some of these derivatives were submitted to post functionalization showing rapid access to cyclo-propane and oxirane species, indanones, and pyrazole compounds. To the best of our knowledge, this is the first example of a direct regio- and chemoselective transformation of a disubstituted alkyne into unsatu-rated ketones through a formal thiyl addition reaction-1,3-isomerization-oxidation of alkynyl-aryl derivatives via photoredox catalysis. This cascade reaction shows a high tolerance towards a fair number of functional groups; however, some limits related to the nature of the alkyne aliphatic chain, probably due to steric hindrance, have been highlighted. This does not currently allow the extension of this method to alkynes with a more complex carbon skeleton. Studies aimed at solving this problem and further in-depth studies on mechanistic aspects are currently underway and will be reported in due course.

Experimental Section

Commercially available reagents were used as received unless otherwise noted. The alkynes **1a**, **1g**, **1h**, **1k** and thiols **2a–r** used in this work were purchased from Sigma Aldrich, FluoroChem or TCI and used as received. Alkyne derivatives **1** were prepared following the corresponding literature or by modification of previously published procedures. ^{1}H NMR spectra were recorded on a 500 MHz Varian spectrometers at 25 °C using CDCl$_3$ (ref. 7.26 ppm) as a solvent. ^{13}C NMR were recorded at 126 MHz (ref. CDCl$_3$ 77.16 ppm) using CDCl$_3$ as solvent. Chemical shifts (δ) are given in ppm. Coupling

constants (*J*) are reported in Hz. Low Mass Spectra Analysis were recorded on an Agilent-HP GC-MS (E.I. 70 eV). High Resolution Mass Spectra (HRMS) of compounds **1–15** were obtained using an High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode (ESI) acquired using a Bruker micrOTF–Q II or/and Agilent Q-TOF 6520. Melting points were determined with a Büchi M-560 (°C). Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merck 70–200 mesh silica gel. Yields refer to chromatography and/or spectroscopically pure materi-als. Acetone, acetonitrile, ethyl acetate were used as received (HPLC grade >99%) or distilled with the appropriate proce-dure. THF and toluene were distilled from sodium/ benzophe-none ketyl. UV-vis analysis were carried out with a Agilent-Cary 5000 UV-vis-NIR system. Florescence analysis were carried out with a Varian-Cary Eclipse Fluorescence spectrom-eter. LED diodes (3–5 W, royal blue (440 nm) or green (3 W, 530 nm) were purchased from SUIYANR. LEDs were charac-terized by using a power meter (Newport model 1918-C).

General Procedure for the Synthesis of enones 3 (**Method A**). In a 10 mL vial (A) equipped with a stirring bar, EB (2% mol) is suspended in CH$_3$CN (1 mL) and stirred at room temperature. In a second vial (B), EB (2 mol%) and 4-chlorobenzene thiol **2a** (0.57 mmol, 1.5 equiv.) are dissolved in 2 mL of CH$_3$CN. This solution is then drawn into a syringe and placed on a syringe pump. In the meantime, 1-phenil-1-butine **1a** (50 mg 0.38 mmol) is added to the vial A. The vial A is then closed with the 3D printed cap. Then the syringe needle of the EB+thiol **2a**/CH$_3$CN solution was inserted into one of the cap inlets. While the air is bubbled into the solution through a second needle connected to the air line. Finally, the LED light was switched on and both reagents and air were supplied. The reaction was followed by GC-MS. After 4–8 hours, CH$_3$CN was evaporated under reduced pressure. The crude product was loaded on a silica gel column to be purified by flash chromatography (eluents hexanes-Et$_2$O 7:1) to afford **3aa** as a yellow oil in 72% yield.

(**Method B**) In a 10 mL vial (A) equipped with a stirring bar, EB (2% mol) is suspended in CH$_3$CN (1 mL) and stirred at room temperature. In a second vial (B), EB (2 mol%) and 4-chlorobenzene thiol **2a** (0.57 mmol, 1.5 equiv.) are dissolved in 2 mL of CH$_3$CN. This solution is then drawn into a syringe and placed on a syringe pump. Then, 1-phenil-1-butine **1a** (50 mg 0.38 mmol) and pyridine (25 mol%) were added to the vial A. The vial A is closed with the 3D printed cap. The needle of the syringe containing the EB+thiol **2a**/CH$_3$CN solution was inserted into one of the inlets of the cap. While the air is bubbled into the solution through a second needle connected to the air line. Finally, the LED light was switched on and both reagents and air were supplied. The reaction was followed by GC-MS. After 4–8 hours, CH$_3$CN was evaporated under reduced pressure. The crude product was loaded on a silica gel column to be purified by flash chromatography (eluents hexanes-Et$_2$O 7:1).

Acknowledgements

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