Visible light mediated metal-free thiol–yne click reaction†

Sergey S. Zalesskiy, Nikita S. Shlapakov and Valentine P. Ananikov*

The carbon–sulfur bond formation reaction is of paramount importance for functionalized materials design, as well as for biochemical applications. The use of expensive metal-based catalysts and the consequent contamination with trace metal impurities are challenging drawbacks of the existing methodologies. Here, we describe the first environmentally friendly metal-free photoredox pathway to the thiol–yne click reaction. Using Eosin Y as a cheap and readily available catalyst, C–S coupling products were obtained in high yields (up to 91%) and excellent selectivity (up to 60 : 1). A 3D-printed photoreactor was developed to create arrays of parallel reactions with temperature stabilization to improve the performance of the catalytic system.

Introduction

In recent decades, the thiol–yne coupling was established as a powerful and proven tool for carbon–sulfur bond formation.1 Currently, this process is of particular importance for the preparation of polymers,2 dendrimers,3 smart materials4,5 and functionalized surfaces.6,7 An important prerequisite for most of these applications is flexibility and efficient control with respect to reaction selectivity. Initially, the addition of thiols to alkynes was performed via a free-radical pathway.8 However, free-radical addition suffered from harsh conditions, low selectivity and extensive formation of by-products, which diminished the utility of this method in organic synthesis.8 The application of transitional metal catalysts improved the selectivity in favor of C–S bond formation;9 however, leaching of metal species10 and unavoidable contamination with biologically active metal-containing impurities makes the use of metal catalysts unacceptable for biomedical and pharma applications.

We propose a practical approach to access valuable S-functionalized products using a cheap and readily available alkyne made by the condensation of acetylene with acetone via the Favorskii reaction (Scheme 1). An atom-economic thiol–yne click reaction yields sulfonylated alkenes, which can be readily converted to dienes by known dehydration protocols in one step (Scheme 1). Sulfonylated dienes are universal building blocks for organic synthesis and polymer science.9 Their high reactivity in Diels–Alder reactions facilitates cycloaddition under mild conditions.10,11 The overall process is totally atom-economic and environmentally benign; the target product is formed from acetylene, acetone and thiol, releasing only one molecule of water. The key step of the overall process is the thiol–yne click reaction, which should be performed with high stereo- and regioselectivity and without a metal catalyst. It is important to exclude transition metal catalysts at this step because their avoidance decreases cost and eliminates the generation of toxic wastes. Thus, carrying out this transformation under metal-free, visible light-mediated conditions would provide an important advance in the synthetic methodology.

Herein, we present the first example of a metal-free photoredox thiol–yne click reaction. We have utilized the outstanding advantages of photocatalytic processes to render transformations of functionalized organic molecules.12 A special emphasis was placed on using organic catalysts13 to avoid metal contamination and to increase cost efficiency. To the best of our knowledge, no examples of metal-free photoredox thiol–yne coupling have been reported to date.14

Results and discussion

Initially, we evaluated the performance of various photoredox systems for the thiol–alkyne coupling (Table 1). Carrying out

Scheme 1 The key light-mediated thiol–yne click reaction for the synthesis of activated dienes from simple precursors.
selective transformation is challenging due to a number of parallel processes leading to products 3–6 (Scheme 2). The formation of 4a was eliminated by avoiding an excess of oxygen in the reaction mixture. The addition of pyridine to the reaction mixture allowed us to increase selectivity via suppression of the formation of the double addition products 5a and 6a. The absence of transition metal complexes excluded the formation of another regioisomer 7a,b.

Known ruthenium (entries 1 and 2, Table 1) and iridium-based (entry 3) photoredox systems gave good yields and E : Z selectivities of the desired product. Three different organic dyes demonstrated similar yields but afforded lower selectivity (entries 4–6, Table 1) relative to the Ir catalyst (entry 3, Table 1). Varying the solvent (entries 6–10, Table 1) allowed us to achieve 63% yield of 3a and 30 : 1 selectivity using Eosin Y as a photosensitizer (entry 10, Table 1). Although initial screening did not favor organic dyes as viable catalysts due to lower selectivities (cf. entries 3 and 10, Table 1), we developed this approach further to meet the requirements of cost-efficiency and avoiding metal contamination.

Variation of the amount of photocatalyst revealed a non-uniform trend (Table 2). Decreasing the amount of Eosin Y initially resulted in an increase in both the yield and selectivity (entries 1, 2 and 4, Table 2) but further lowering the amount of the dye led to a decrease in both parameters (entries 4 and 5, Table 2). It is very likely that the combination of two factors, namely excitation of only the surface layer of the solution due to increased optical density (because of the large amount of the dye in solution) and reaction stoppage due to degradation of Eosin Y (especially for very low dye loadings), is responsible for the observed behavior. Indeed, rapid degradation of the photocatalyst was clearly visible at low catalyst loadings, which resulted in discoloration of the solution.

We found that the dye degradation issues can be overcome by switching the reaction solvent to hexane (Table 2, entries 6 and 7). Eosin Y exhibits very low solubility in hexane, and at the beginning of the reaction, the majority of the Eosin Y remains undissolved. A low concentration of the dissolved catalyst results in a reaction mixture with optimal optical density and ensures uniform excitation of the reaction volume.

The dissolved photocatalyst slowly degrades during the course of the reaction, which makes the solution unsaturated. This naturally leads to the dissolution of subsequent portions of Eosin Y from the solid phase. This “saturation feedback” automatically maintains the concentration of the photocatalyst at the optimal level, thus compensating for the loss of active species. Under such self-regulating conditions, yields and E : Z selectivities as high as 85% and 50 : 1, respectively, were achieved (entry 7, Table 2).

Thus, a typical photoredox system with Eosin Y suffers from gradual photocatalyst degradation during the course of the reaction when all of the catalyst is dissolved in the reaction mixture (Fig. S1, ESI†). This degradation can halt the progress of the reaction at the middle or even initial stages of the reaction (entries 8 and 9, Table 2). In the developed approach, the low solubility of the photocatalyst increases the efficiency of light utilization by maximizing reactive excitations. The inevitable degradation of the photocatalyst is immediately compensated by the undissolved portion (Fig. S1†). It should be noted that when identical catalyst loadings were used in different solvents, namely DMSO and hexane (i.e., 2.1 mg of Eosin Y for 0.3 mol%), the reaction was governed by the solubility of the photocatalyst. Notably, the reaction in hexane proceeded with higher selectivity and yield than the reaction conducted in DMSO (entries 3 and 7, Table 2).

After establishing the optimal reaction conditions, efforts were focused toward performing thiol–yne click reactions with different substrates. The developed synthetic approach provides excellent opportunities for incorporating various sulfur

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**Scheme 2** Plausible products in the thiol–yne coupling process.

**Table 1** Search for the optimal catalyst for thiol–yne photoredox coupling

<table>
<thead>
<tr>
<th>#</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>LED</th>
<th>3a, %</th>
<th>E : Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ru(bpy)$_3$]$_2$[PF$_6$]$_2$</td>
<td>MeCN</td>
<td>465 nm</td>
<td>34</td>
<td>20 : 1</td>
</tr>
<tr>
<td>2</td>
<td>[Ru(bpy)$_3$]$_2$[PF$_6$]$_2$</td>
<td>MeCN</td>
<td>465 nm</td>
<td>40</td>
<td>30 : 1</td>
</tr>
<tr>
<td>3</td>
<td>Ir[ppy]$_3$</td>
<td>MeCN</td>
<td>530 nm</td>
<td>63</td>
<td>40 : 1</td>
</tr>
<tr>
<td>4</td>
<td>Fluorescein</td>
<td>MeOH</td>
<td>465 nm</td>
<td>60</td>
<td>27 : 1</td>
</tr>
<tr>
<td>5</td>
<td>Bengal rose</td>
<td>DMF</td>
<td>530 nm</td>
<td>53</td>
<td>25 : 1</td>
</tr>
<tr>
<td>6</td>
<td>Eosin Y</td>
<td>MeOH</td>
<td>530 nm</td>
<td>53</td>
<td>25 : 1</td>
</tr>
<tr>
<td>7</td>
<td>Eosin Y</td>
<td>DMF</td>
<td>530 nm</td>
<td>15</td>
<td>14 : 1</td>
</tr>
<tr>
<td>8</td>
<td>Eosin Y</td>
<td>MeCN</td>
<td>530 nm</td>
<td>56</td>
<td>27 : 1</td>
</tr>
<tr>
<td>9</td>
<td>Eosin Y</td>
<td>Et$_2$O</td>
<td>530 nm</td>
<td>20</td>
<td>20 : 1</td>
</tr>
<tr>
<td>10</td>
<td>Eosin Y</td>
<td>DMSO</td>
<td>530 nm</td>
<td>63</td>
<td>30 : 1</td>
</tr>
</tbody>
</table>

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**Table 2** Optimization of reaction conditions for the studied photoredox thiol–yne click reaction

<table>
<thead>
<tr>
<th>#</th>
<th>Eosin Y, mol%</th>
<th>Solvent</th>
<th>Yield, %</th>
<th>E : Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>DMSO</td>
<td>15</td>
<td>30 : 1</td>
</tr>
<tr>
<td>2</td>
<td>0.3</td>
<td>DMSO</td>
<td>38</td>
<td>30 : 1</td>
</tr>
<tr>
<td>3</td>
<td>0.3$^b$</td>
<td>DMSO</td>
<td>65</td>
<td>30 : 1</td>
</tr>
<tr>
<td>4</td>
<td>0.02</td>
<td>DMSO</td>
<td>46</td>
<td>45 : 1</td>
</tr>
<tr>
<td>5</td>
<td>0.001</td>
<td>DMSO</td>
<td>33</td>
<td>32 : 1</td>
</tr>
<tr>
<td>6</td>
<td>0.3</td>
<td>Hexane</td>
<td>70</td>
<td>37 : 1</td>
</tr>
<tr>
<td>7</td>
<td>0.3$^b$</td>
<td>Hexane</td>
<td>85</td>
<td>50 : 1</td>
</tr>
<tr>
<td>8</td>
<td>0.02</td>
<td>Hexane</td>
<td>11</td>
<td>10 : 1</td>
</tr>
<tr>
<td>9</td>
<td>0.001</td>
<td>Hexane</td>
<td>9</td>
<td>8 : 1</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 0.3 mol% catalyst loading, stirring under LED light for 4 h; see ESI for details. $^b$ Control experiments in the absence of photocatalyst were also performed; see ESI for details.
selectivity and reproducibility of photochemical reactions. An array of the custom-built photoreactors allowed us to execute a study of the substrate scope involving various substituents in a parallel fashion (Scheme 3). Four important advantages deserve particular attention: (i) the catalytic system showed excellent performance for various aryl thiols;² (ii) excellent stereoselectivity in the range of 60 : 1–25 : 1 was achieved; (iii) complete regioselectivity was maintained and the formation of another regioisomer (7a) was not observed; and (iv) the hydroxyl group remained intact during the reaction, which is a necessary prerequisite to access the diene backbone after dehydration (Scheme 1). The developed synthetic approach was tolerant toward electronic and steric effects of the substituents in the thiol moiety (Scheme 3). Even for thiols containing strongly electron-withdrawing substituents, such as CF₃ or COOMe, the desired products were formed in very high yield and high selectivity (i.e., 3e, 3g, 3h). We also tested aliphatic thiols in this reaction (R² = Alk); however, significantly lower selectivity was observed (<10 : 1). An important factor is the structure of the alkyne, where steric effect played a key role in obtaining high selectivity (see ESI†). Amazingly, high selectivity was observed for the alkyne bearing α-substituted carbon atom, which is required to implement the synthetic methodology proposed in the present study (Scheme 1). For the studied class of alkyynes the corresponding products 3a−3m were synthesized in good to high yields and excellent selectivity (Scheme 3) including sterically hindered alkyynes, where the products 3n−3p were formed in good yields (89−96%) and high selectivity (35 : 1−40 : 1).

A plausible mechanism for the photoredox thiol–yne click reaction is presented in Scheme 4A.³,⁵ A photoexcited molecule of Eosin Y (E*) undergoes oxidative quenching, furnishing a radical cation of arylthiol. Pyridine abstracts a proton from this species, yielding thyl radicals and preventing side reactions of ArSH⁺. In the next step, ArS⁺ is involved in the radical addition to the alkyne, giving the desired product 3 and regenerating ArS⁻ radicals. Within the mechanism the E-species

Fig. 2 Computer model of designed photoreactor (A) and ready to use assembled photoreactor (B).

Fig. 1 Comparison of the possible designs of the photoreactor: (A) side irradiation (LED strip); (B) bottom irradiation (LED matrix); (C) developed design with temperature stabilization.
of Eosin Y are regenerated upon interaction with molecular oxygen from ambient air. According to thermodynamic properties, single electron oxidation of benzenethiol by excited state of Eosin Y is a feasible process: the potential $E^*/E_0 = 1.18$ V vs. SCE is much higher as compared to $E_{PhSH/PhSH^+} = 0.95$ V vs. SCE.

Rather different stability of the primary and secondary intermediate radical species governs high regioselectivity (B) and stereoselectivity (C).

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Rather different stability of the primary and secondary intermediate radical species governs high regioselectivity (B) and stereoselectivity (C).

stability of the radical species linear (anti-Markovnikov type) products 3 were formed in the reactions, whereas formation of branched (Markovnikov type) products was not observed.

Steric effect of the substituent R provides the necessary control for stereoselectivity in the studied transformation (Scheme 4C). Decreasing steric bulk resulted in lower reaction selectivity or non-selective transformation (see ESI†). The presence of OH group and two other substituents at the $\alpha$-carbon atom in the developed concept (Scheme 1) perfectly matches the structure of the alkyne towards getting a high stereoselectivity.

Radical nature of the studied process was confirmed by performing a control experiment using a radical trap. Indeed, addition of $\gamma$-terpinene suppressed the reaction between the thiol and alkyne. Several other control experiments were also carried out to confirm the proposed mechanism and to demonstrate regeneration of the dye in the presence of oxygen (see ESI†).

Finally, as a proof of concept, we have prepared the target diene 8a using the industrially available starting materials acetylene, acetone and benzenethiol (Scheme 5). In the first step, alkyne 1a was prepared according to the published

### Scheme 3
The scope of the developed photocatalytic thiol–yne click reaction. (a) Isolated yields are given in parentheses, reaction time – 5 h. (b) Reaction time – 10 h. (c) Reaction time – 20 h.

### Scheme 4
The proposed mechanism (A) for the Eosin Y mediated thiol–yne photoredox coupling (Eosin Y is denoted with E), plausible origins of reaction regioselectivity (B) and stereoselectivity (C).

### Scheme 5
The synthesis of diene 8a using the developed approach.
procedure. Alkyne 1a was converted to vinyl sulfide 3a using the developed photochemical protocol. Dehydration of 3a under mild conditions furnished diene 8a in 94% isolated yield. Thus, a demanding S-functionalized 1,3-diene was prepared starting from simple precursors through a sequence of atom-economic addition reactions with the only release of water (Scheme 5).

Conclusions

To summarize, the use of cheap and commercially available Eosin Y as a photocatalyst provided an attractive and environmentally friendly protocol for thiol-yne coupling, furnishing valuable sulfur-functionalized products in good yields. The developed catalytic system demonstrated unprecedented selectivities (up to 60 : 1) considering the broad scope of substituted aryl thioles that could be used. The use of a custom-designed 3D-printed chemical photoreactor facilitated the rapid assessment of optimal reaction conditions to improve the performance of the catalytic system.

An efficient photocatalytic system was created using a combination of Eosin Y and hexane as solvent. Utilization of the “saturation feedback” approach described here to maintain the optimal concentration of the catalyst may substantially facilitate development of a variety of other photocatalytic transformations.

Experimental details

General procedures

Photochemical reactions were carried in 2 mL glass vials covered with aluminium tape. Magnetic stirrer bars were cleaned with boiling solution of alkali followed by boiling solution of aqua regia and further rinsing with distilled water to ensure that all traces of absorbed catalyst were removed. All reagents and catalysts were purchased from commercial sources and used without further purification. Solvents were purified by standard procedures. Flash chromatography was performed using Merck 60 μm silica. LC-MS-grade solvents (MeCN and DCM) for ESI-MS experiments were ordered from Merck and used as received. All samples (solutions in MeCN or DCM) for the ESI-MS experiments were prepared in 1.5 mL Eppendorf tubes. All plastic disposables (Eppendorf tubes and tips) used for sample preparation were washed with MeCN or DCM prior to use. 1H and 13C NMR data are referenced to TMS and residual solvent signal, respectively.

Formation of double addition products was observed in a few studied cases at a trace level. Purification was easily performed using a regular flash chromatography as described below.

High-resolution mass spectra were recorded on a Bruker maXis Q-TOF instrument (Bruker Daltonik GmbH, Bremen, Germany) equipped with electrospray ionization (ESI) ion source. The measurements were performed in a positive (+MS; +MS/MS) ion mode (HV capillary: 4500 V; HV end plate offset: −500 V) with a scan range m/z: 50–3000. External calibration of the mass spectrometer was performed using an electrospray calibrant solution (Fluka). A direct syringe injection was used for all of the analyzed solutions in MeCN or DCM (flow rate: 3 μL min−1). Nitrogen was used as the nebulizer gas (0.4 bar), dry gas (4.0 L min−1) and collision gas for all of the MS/MS analyses and experiments; the dry temperature was set at 180 °C. All of the recorded spectra were processed using the Bruker DataAnalysis 4.0 software package.

Synthesis of 3a–p

Alkyne (1 mmol), thiol (1.1 mmol), Eosin Y (0.003 mmol), pyridine (0.25 mmol) and 250 μL of hexane were placed into a 2 mL glass vial (covered with aluminium tape) equipped with a stirrer bar. The mixture was suspended with ultrasound. The vial was placed on a magnetic stirrer and fitted with the developed photoreactor reactor equipped with green LED (λmax = 533 nm). After completing the reaction, the solvent was removed under reduced pressure. The remaining viscous bright pink oil was purified with flash chromatography (petroleum ether/ethyl acetate/triethylamine = 4 : 1 : 0.075 elution) to obtain a pure product.

Synthesis of 8a

Vinylsulfide 3a (10.6 mg, 5.45 × 10−2 mmol) was dissolved in 2 mL of 1,4-dioxane, followed by addition of HCl (1 μL of 38% aqueous solution). The reaction mixture was stirred at room temperature for 4 hours. The reaction mixture was diluted with 10 mL of dioxane and the solvent was removed on a rotary evaporator. The water bath temperature should not exceed 30 °C during evaporation to avoid product decomposition. Product 8a was isolated as a slightly yellow oil and identified according to the published NMR data. Product yield – 9.3 mg (94%).

Acknowledgements

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Notes and references


9 Aryl derivatives (R = Ar) of sulfenylated dienes are particularly valuable due to their stronger S–C(sp²) bond and have more reliable applications in the synthesis of sulfur-functionalized compounds. Alkyl derivatives (R = Alk) are less stable due to a relatively weaker S–C(sp³) bond. For the difference in bond energy see: V. P. Ananikov, K. A. Gayduk, I. P. Beletskaya, V. N. Krustalev and M. Y. Antipin, *Chem.–Eur. J.*, 2008, 14, 2420.


