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Communication

TEMPO visible light photocatalysis: The selective aerobic oxidation of thiols to disulfides

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Graphical abstract $2 R^{SH} + O_2$ TEMPO, EtOH 460 nm blue LEDs $R^{S}S^{R} + H_2O$ $R^{SH} + HS + O_2$ TEMPO, EtOH $R^{SH} + HS + O_2$ $R^{S}S^{S}S^{S} + H_2O$

Disulfides were obtained in a facile and efficient manner with very high isolated yields by TEMPO visible light photocatalysis in ethanol. A complex formed between TEMPO and thiols during the reaction course underpins the visible light activity.

ARTICLE INFO	ABSTRACT
Article history:	TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) is well-established in orangocatalysis that
Received 28 September 2019	usually work in synergy with transition-metal catalysis or semiconductor photocatalysis.
Received in revised form 12 October 2019	Here, TEMPO was turned into a visible light photocatalyst to conduct the selective
Accepted 16 October 2019	aerobic oxidation of thiols into disulfides. With O ₂ as an oxidant, a mild and efficient
Available online	protocol for the selective oxidation of thiols into disulfides including symmetrical and
Keywords:	unsymmetrical ones with 5 mol% of TEPMO as the photocatalyst was developed at room temperature under the irradiation of 460 nm blue LEDs. It was found that a complex
Radical	formed between TEMPO and thiols underpinned the visible light activity and disulfides
Visible light	were obtained in very high isolated yields. This work suggests that TEMPO takes diverse
TEMPO	roles in opening up the avenue for photocatalytic selective oxidative transformations with
Aerobic oxidation	O_2 as the oxidant.
Disulfides	

Disulfides are relatively stable products of thiol oxidation and play important roles in determining the secondary, tertiary, and quaternary structures of proteins [1]. Moreover, disulfides are abundantly existed in the natural products and have wide applications in the various industrial levels, which is mainly linked with their outstanding redox chemical characteristics [2]. The superiority on redox sensitivity has made the disulfide bond bridge highlight its vital value in drug delivery program [3]. In the field of physiology, the disulfide bonds are crucial building scaffolds for the stabilization of the folded form of proteins [4,5] and for the control of enzymes activity [6]. Moreover, thiols exhibit serious negative effects on human health and natural environment because of their high toxicity and pollution [7,8]. Thus, the oxidation of thiols is also of environmental significance.

Due to the importance of disulfides in both biological and chemical systems, the synthesis of them received much attention. For its application on organic synthesis, on one hand, the disulfides are used as the available reagents to realize the sulfenylation of some organic compounds [9-11] with few negative effects; on the other hand, as the protection group of thiols, disulfides are more stable in some conversions [12], and they are not foul smelling just as the thiol ones. With the benefits from the above, various methods of synthesis of disulfides have been reported in the past few decades, but the oxidation of thiols to disulfides is still the most common strategy [13]. In order to alleviate the negative issue that the thiols were prone to be over oxidized [14,15], extensive types of oxidants, including H_2O_2 [16], halogens and derivatives [17], KMnO₄/CuSO₄ [18] and sulfoxide [19], had been taken to implement the control oxidation tests. The target disulfides could be obtained efficiently, but those methods commonly held the main drawback: Toxic oxidant input and waste output all in stoichiometric amounts. Fortunately, O_2 or aerial O_2 was emerged as the optimal oxidant from the cost-efficient and eco-friendly perspective and had gained great achievements on this type of transformation.

 TiO_2 is one of the most famous semiconductor photocatalysts [20]. However, it needs UV light rather than visible light illumination to overcome its band gaps. Visible light, served as an easily available energy source to motivate and split organic molecules into highly active radicals in reactions [21-25], has widely extended its application in laboratory. When it came to the issue of oxidation of thiols to disulfides, this method has brought significant achievements and turned out to be one of the most promising strategies [26-28]. Apart

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from the classical approach which fulfils the transformation from thiols to disulfides (Scheme S1, Supporting information), accompanying by the consumption of reduction species with extra sacrificial reagent, CdSe QDs (quantum dots) exhibited considerable efficiency under visible light irradiation at room temperature without any additives [29], and the strategy highlighted on releasing hydrogen as the exclusive byproduct. But actually, more substantial efforts were made toward the themes of exploiting green oxidant O₂ and metal-free catalysis in the photocatalysis category. Recently, rose bengal, an organic dye, had successfully induced the oxidation coupling of thiols to disulfides with catalytic amounts under white light-emitting diodes (LEDs) at room temperature by using an efficient micro-flow reaction device [30]. With the similar reaction conditions, the dye Eosin Y could also photocatalyze the transformation with excellent product yields and scope, but equilmolar of additive tetramethylethylenediamine (TMEDA) was essential to short reaction time [31].

In this contribution, we would like to report a more facile and efficient test on the TEMPO-mediated selective oxidation of thiols into disulfides including symmetrical and unsymmetrical ones. Employing O_2 as the terminal oxidant and TEMPO as the photocatalyst, this protocol was demonstrated with an extraordinarily high efficiency and disulfides could be obtained in high isolate yields ($\geq 86\%$) at room temperature without any additives, along with excellent reaction selectivity, substrate scope as well as functional groups compatibility. This work demonstrates the versatile role of TEMPO that could potentially play in visible light-promoted selective organic transformations.

This research was commenced with our previous two studies regarding the selective aerobic oxidation of sulfides into sulfoxides by cooperative photocatalysis with TEMPO [32,33]. Beforehand, it was plausible because TEMPO is a very good hydrogen abstraction agent which can be viewed as a simple extension of our previous studies. To this hypothesis, we employed 4-methylbenzenthiol (1b) as the probe substrate under conditions quite similar to our previous studies. With alizarin red S-sensitized TiO₂ (ARS-TiO₂) as the photocatalyst, selective oxidation of 4-methylbenzenethiol into disulfides proceeded well (entry 1, Table 1). Adding TEMPO could considerably promote the yield of disulfide (entry 2, Table 1). These results were very promising at the early stage which might validate our hypothesis. Thereafter, we further our rigorous control experimental process. Quite unexpectedly, without the presence of ARS-TiO₂, the corresponding disulfide 2b could yield 44% (detected by gas chromatography) smoothly in methanol (MeOH) after dropping 5 mol% of TEMPO into the reaction mixture excited by 460 nm blue LEDs (entry 3, Table 1), suggesting TEMPO itself can be a photocatalyst for this specific reaction. Even though these results indicate that our previous cooperative photocatalysis with TEMPO does not reign for selective oxidation of thiols, we were quite happy to uncover the hitherto unknown photocatalytic activity of TEMPO. Motivated by this result, we were pleased to discover that ethanol (EtOH) acted as much better solvent than CH₃OH and CH₃CN for this photocatalytic reaction (entries 3-5, Table 1). Moreover, EtOH is a bio-compatible solvent which is also advantageous for the application of this protocol in bio-related scenario. Metal-free photocatalysis is particularly suitable to bio-friendly conditions [34]. We did more investigations on the photocatalytic selective oxidation reactions. Concluded from entries 6-8 of Table 1, we confirmed that the visible light, O2 and TEMPO made up the necessary components for the photocatalytic synthesis of disulfides. Low pressure O₂ (0.1 MPa) for a closed Pyrex reactor was selected to prevent the emitting of odor of thiols. Note that the reaction can proceed smoothly with aerial O2.

Table 1 Control experiments for the	visible light photocatalytic selective aerobic	c oxidation of 4-methylbenzenethiol by TEMPO ^a .
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² SH 1b	+ $1/2 O_2 \xrightarrow{\text{TEMPO, EtOH}} 460 \text{ nm blue LEDs}$	S S 2b	+ H ₂ O
Entry	Reaction conditions	Conv. (%) ^b	Sel. (%) ^b
1	ARS-TiO ₂	46	>99
2	ARS-TiO ₂ , TEMPO	93	>99
3	TEMPO	44	> 99
4	CH ₃ CN, TEMPO	95	> 99
5	EtOH, TEMPO	99	> 99
6	Dark, TEMPO	19	> 99
7	N ₂ , TEMPO	12	> 99
8	No TEMPO	16	> 99

^a Reaction conditions: 4-methylbenzenethiol (0.6 mmol), TEMPO (0.030 mmol), 460 nm blue LEDs (3 W \times 4), solvent (1 mL, MeOH for entries 1-3, CH₃CN for entry 4, EtOH for entries 5-8), O₂ (0.1 MPa), 25 min.

^b Determined by gas chromatography-flame ionization detector (GC-FID) using chlorobenzene as the internal standard, conversion of 4-methylbenzenethiol, selectivity of the corresponding disulfide.

After the establishment of TEMPO as a photocatalyst for the selective aerobic oxidation of thiols, we subsequently did some additional screening experiments to make more evident its importance. As such, we evaluated the influence of different kinds and amounts of TEMPO on the photocatalytic aerobic oxidation reaction which were summarized in Table S1 and Table S2 (Supporting information). Known from Table S1, TEMPO would be preferred as the photocatalyst from the views of efficiency and commercial cost. From the results in Table S2, it was reasonable to employ 5 mol% of TEMPO (30 μ mol) as the optimized initiator. Finally, we would like to continue the reaction with optimized conditions: 0.6 mmol of thiol, 5 mol% of TEMPO photocatalyst, 460 nm blue LED irradiation, EtOH solvent and 0.1 MPa of O₂.

The scope of thiols was further investigated under the optimal reaction conditions. As showed in Table 2, we first examined the aerobic oxidation of benzenethiol and this transformation was accomplished in 45 min (detected by thin-layer chromatography) with an isolated yield of 90% (entry 1, Table 2). When the substrates bearing electron donating groups on the *para*-substituted benzene ring (entries 2-5, Table 2) were tested, it was found that the reaction rate, according to the reaction time, had a positive correlation with the ability of electron donation of substrate. Additionally, the *ortho*-substituted thiol **1g** (entry 7, Table 2) needed much longer irradiation time than the *para*- and *meta*-substituted species (entries 5 and 6, Table 2) to accomplish the oxidation coupling. This sluggish performance could ascribe mainly to its unique steric hindrance. Analogously, the disubstituted **1h** (entry 8, Table 2) also suffered a long reaction time. Subsequently, after some other attempts on substrates bearing electron donating groups (entries 9-12, Table 2), we summarized that they needed much longer irradiation time than those ones possessing electron donating groups. From a view of electronic effect, it could be concluded that the electron donating group makes a positive contribution to stabilizing the radical intermediates generated in the conversion. Conveniently, these attempts showed a tolerance to various functional groups (F, Cl, Br, CF₃). The reaction strategy was also suitable for the hetero- and poly-aromatic thiols (entries 13 and 14, Table 2).

Table 2 Visible light photocatalytic selective aerobic oxidative synthesis of disulfides by TEMPO a

	SH + 1/2 O ₂	$\frac{\text{TEMPO, EtOH}}{460 \text{ nm blue LEDs}} R$	S.	S R	+ H ₂ O
Entry	Substrate	Product	T (min)	Yield (%) ^b	
1	SH Ia		45	90	
2	SH 1b	S S S	25	94	
3	Et Ic		25	90	
4	t-Bu Id	s s s s s s s s s s s s s s s s s s s	30	93	
5	MeO Ie	MeO 2e OMe	20	92	
6	MeO SH	MeO S S OMe	30	90	
7	OMe SH 1g	OMe S S 2g OMe	150	89	
8	MeO SH MeO 1h	MeO S S OMe MeO 2h	150	90	
9	F II	F 2i	30	91	
10	CI IJ		90	97	
11	Br Ik	Br 2k	105	97	
12	F ₃ C SH	F ₃ C 21	180	91	
13	SH Im		40	94	

14	SH In	S-S	75	90
15	SH 10	S-S-S-	60	0

^a Reaction conditions: thiol (0.6 mmol), 460 nm blue LEDs (3 W \times 4), EtOH (1 mL), O₂ (0.1 MPa). ^b Isolated yields of corresponding disulfides, see Supporting information for the NMR and HRMS data.

This visible light photocatalytic protocol was inadequate to convert the aliphatic thiol into disulfide (entry 15, Table 2), suggesting aliphatic thiol should be stable under the standard condition. Opportunity arises for the synthesis of unsymmetrical disulfides. Different from the symmetrical disulfide, the unsymmetrical one had its inherent challenge in synthesis with high selectivity. But the present method could get around the drawback and achieve the unsymmetrical disulfide with excellent isolated yield in a more facile and efficient manner when 3.0 equivalent of thiol **3** was added into the mixture at the initial stage (Scheme 1). Taking the synthesis of product **4b** as a model, this unsymmetrical synthesis occurred smoothly in 3 h irradiation and obtained a 92% isolated yield. This method was tolerated to various functional groups and influenced slightly by electronic effect (**4e**, **4j** and **4k**). Hetero- (**4m**) and ploy-aromatic (**4n**) thiols were also underwent this protocol to disulfides successfully.





After gathering the optimized conditions and affirming the generality this visible light photocatalytic protocol, we wanted to elucidate the underlying mechanistic insights regarding this TEMPO mediated process. For a photocatalytic reaction, it should be wavelength dependent. Thus, we carried out the selective oxidation reaction with different emitting maximum wavelength (λ_{max}). Table S3 (Supporting information) shows that 460 nm blue LEDs (the light-emitting spectrum, Fig. S1 in Supporting information) give the best results, indicating that the absorption of the visible light should be centered on this range.

In appearance, TEMPO is red-orange which means that it can directly absorb visible light around 460 nm range. However, absorption of TEMPO disappears in EtOH due to solvatochromism phenomena. Therefore, we assumed that there should be other pivotal spices involved to capture visible light. The trapping sulfur radical by TEMPO accounts for the photocatalytic oxidative synthesis of symmetrical disulfide. We did some further investigations on the course. During the trial, the optimization of application amount of TEMPO, we increased the TEMPO to 0.5 equivalent and 0.6 mmol of 4-methylbenzenethiol and 0.3 mmol of TEMPO were combined in a 10 mL Pyrex vessel with 1 mL of EtOH dissolved. Subsequently, O_2 was injected into the sealed vessel to reach 0.1 MPa of pressure. Then the reaction mixture was magnetically stirred at 1500 rpm and simultaneously illuminated 25 min. We released the reaction pressure and purified the crude product with column chromatograph (petroleum ether:ethyl acetate = 80:1, v:v), then the target products **2b** and **5b** (see photocatalytic experiments 3.7, Supporting information) were obtained. Complex **5b** formed by 4-methylbenzenethiol and TEMPO is reddish which can absorb visible light and can be excited by 460 nm blue LEDs for the activation of O_2 . We successfully trapped the radical intermediate **5b** in 17% isolated yield, together with the product **2b** in 81% yield (Eq. S1, Supporting information). This observation indicated directly the sulfur-center radical was involved in the visible light-induced process.

Furthermore, kinetic studies were carried out in an effort to understand the mechanism. As for the unsymmetrical aspect, we recorded the concentrations of main components (**1b**, **2b**, and **4b**) by GC during the synthesis of **4b**, and summarized as follows (Fig. S2, Supporting information): The product **2b** was afforded sharply at the initial 20 min from **1b**, then it suffered gentle consumption until it was depleted. Whilst the product **4b** began to increase dramatically after the mixture was irradiated 20 min, and received an excellent yield at the end. From the observations, we concluded that: i) The substrate **1b** was more prone to transform into **2b** at the initial stage; ii) the intermediate product **2b** was not stable in the identical reaction conditions with thiol **3** presence, and it would be forced to transform into the unsymmetrical disulfide **4b** *via* a radical pathway motivated by visible light. This hypothesis was reinforced by an assistant test, which implemented in dark and gave a 45% conversion of **1b**, 34% yield of **2b**, and 11% yield of **4b**.

Based on the above evidences, we would like to propose a plausible mechanism for the visible light photocatalytic selective aerobic oxidation of thiols into disulfides by TEMPO (Scheme 2). First, the key intermediate TEMPO-SR was obtained after the TEMPO attacked the substrate thiol, along with the generation of H[•]. The active H[•] was prone to combine with TEMPO to give TEMPOH. For the newly and stable TEMPO-SR, it was motivated by visible light to form TEMPO-SR^{*} in an excited state. Subsequently, the TEMPO-SR^{*} was treated by thiol and O₂ to afford the symmetrical disulfide, superoxide anion radical O₂⁻⁻ and TEMPOH. Then, the photocatalytic reaction cycle could be finished after the TEMPOH combined with O₂⁻⁻ to regenerate TEMPO, taking the H₂O₂ as the exclusive byproduct. Moreover, the visible light photocatalytic synthesis of unsymmetrical disulfide includes two sequential reactions. The selective oxidation of benzenethiol into symmetrical disulfide occurred beforehand and aliphatic thiol **3** was intact during this stage. Then, the formed symmetrical disulfide underwent a homolytic cleavage in the presence of TEMPO to react with aliphatic thiol **3**, affording the corresponding unsymmetrical disulfides in the end. Meanwhile, O₂ acts as acceptor for proton and electron.



Scheme 2. A plausible mechanism for the selective aerobic oxidation of thiols into disulfides by TEMPO visible light photocatalysis.

In summary, we have serendipitously disclosed a visible light photocatalytic protocol for the oxidation thiols into disulfides including symmetrical and unsymmetrical ones by employing TEMPO as photocatalyst at room temperature. Besides, EtOH was selected the solvent and O_2 was chosen as the terminal oxidant. Importantly, no additives and transition-metals were needed during the reaction process. A complex *in situ* formed between thiol and TEMPO has been identified to be central in implementing the photocatalytic activation of O_2 . This reaction strategy had been identified by a wide scope of thiols, and the results showed excellent yields, selectivity and functional groups compatibility.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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