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Fast and high-efficiency synthesis of *2*-substituted benzothiazoles via combining enzyme catalysis and photoredox catalysis in one-pot

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ABSTRACT

An efficient and green method, combining enzymatic and visible-light catalysis for synthesis of the widely applicable *2*-substituted benzothiazoles, has been developed. This method features a relay catalysis protocol consisting of biocatalytic promiscuity and visible-light-induced subsequent oxidization of *2*-phenyl benzothiazolines. The whole reaction process is very high-efficiency, achieving 99% yield in just 10 min, under an air atmosphere, nearly 100% atomic utilization, and the *2*-substituted benzothiazole products were obtained in good to excellent yields with a wide range of substrates. This reaction is the other example of combining the non-natural catalytic activity of hydrolases with visible-light catalysis for organic synthesis and the catalytic system does not require additional oxidants or metals, which is good for the environment.

1. Introduction

Enzyme is as an efficient, environmentally friendly and biodegradable catalyst in organic synthesis [1–3]. Compared with conventional chemical catalytic methods, enzymatic catalysis has many advantages, such as good selectivity, high catalytic efficiency, mild reaction conditions, fewer by-products production and fewer synthetic reaction steps [4–7]. In addition, some enzymes (especially hydrolases) have the ability to catalyze reactions that are completely different from those catalyzed in nature. This behavior is coined enzyme promiscuity, and it greatly enriches all types of enzymatic reactions [8,36–39]. In recent years, there have been more and more reports on enzymatic catalysis combining with other catalysis methods, such as photocatalysis, organometallic catalysis, and electrosynthesis [9–12]. Among them, the combination of photocatalysis and enzymes has become a very important point. Hyster and co-workers have reported the light-induced non-natural catalytic activity of NAD(P)-depended KRED with high stereoselectivity [13]. It illustrates how powerful the methods would be when combining light and enzymes.

Light energy, as a clean, inexpensive, sustainable, and environmentally friendly energy, has attracted wide attention [14,15]. Visible-light photoredox catalysis, refers to a type of catalysis that uses visible light energy to accelerate chemical reactions through a single-electron transfer (SET) process. In this catalytic method, the transition metal complex, organic dyes, semiconductor, and other photosensitive compounds are usually used as photoredox catalysts. As a powerful and sustainable chemical reaction method, photoredox catalysis has been revived in the past decade [16,17]. In fact, the earliest application of photoredox catalysis should be in nature, where saccharides are first constructed by CO_2 and H_2O through photosynthesis, and then are used as raw materials to generate other structures in the process of metabolism through enzymes [18]. This shows that the combination of photoredox catalysis activity and enzyme promiscuity can promote the synthesis of value-added chemicals and may reveal new catalytic functions of enzymes. In 2020, Zhao and co-workers reported a new-to-nature, visible-light-induced ene-reductase catalysed intermolecular radical hydroalkylation of terminal alkenes with readily available α-halo carbonyl compounds [19]. This method provides an efficient approach to various carbonyl compounds bearing a γ-stereocentre with excellent yields and enantioselectivities (up to 99% yield, 99% ee), which otherwise are difficult to access by chemocatalysis. This work further expands the reactivity repertoire of biocatalytic, synthetically-useful asymmetric transformations by the merger of photocatalysis and enzyme catalysis. In 2019, the Guan group reported a combination of photoredox catalysis and enzymatic catalysis for the direct asymmetric one-pot synthesis of *2*, *2*-disubstituted indol-*3*-ones [20]. In the same year, Wu studied demonstrated a new strategy of direct photoinduced KR of a-functionalized carboxylic acids by an engineered CvFAP without dependence on electron transfer by NADPH or prior preparation of esters, which are required in previous biocatalytic approaches [21,22].

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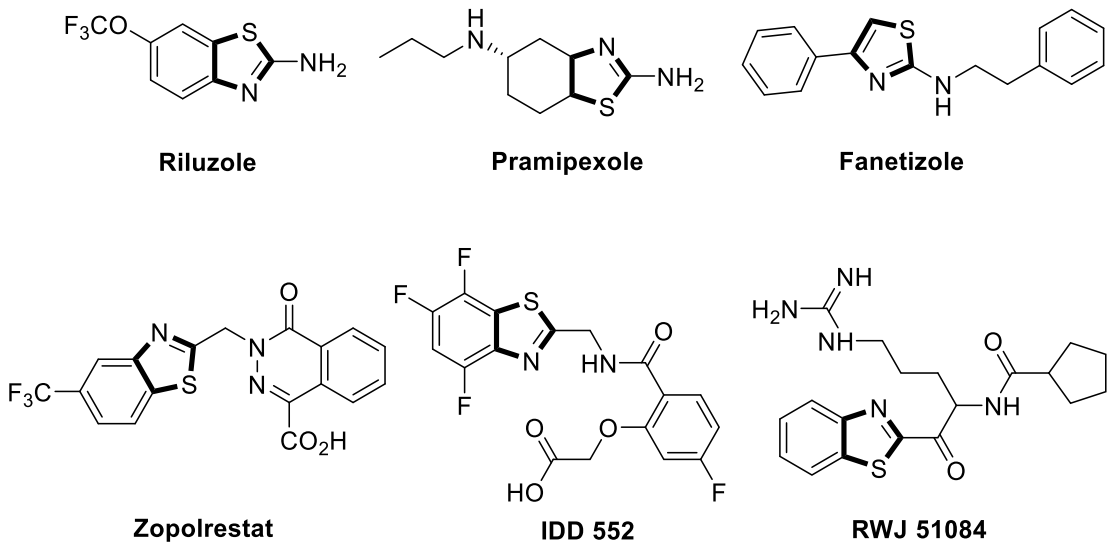


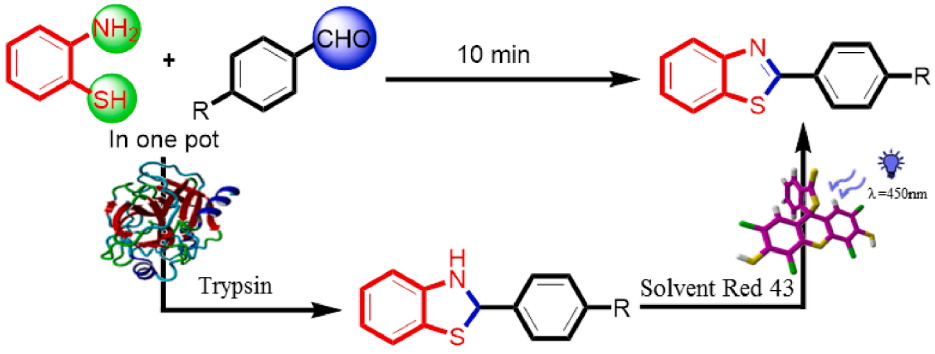
Fig. 1. Selected examples of benzothiazole derivatives embodied with biological activity and drugs.

This simultaneous photocatalytic and biocatalytic mode provides a gentle and effective strategy for the one-pot enantioselective synthesis of complex compounds. Therefore, combining photoredox catalysis and enzyme is worth developing with great potential. Initiating organic reactions using visible photoredox catalysis and enzyme promiscuity could be a green and powerful tool in synthetic organic chemistry.

Analogies and derivatives of benzothiazole compound have received extensive attention due to their good biological and pharmacological properties [23,24]. When biologists discovered the pharmacological characteristics of riluzole (*6*-trifluoromethoxy-*2*-benzothiazolamide) for the treatment of amyotrophic lateral sclerosis, they began to focus on this series of drugs (Fig. 1) [25], for example, IDD552 is a well-known aldolreductase inhibitor [26], RWJ-51084 is an effective cationic trypsin precursor and Fanetizole is an anti-inflammatory agent [27]. Therefore, synthesis of benzothiazole has attracted much attention due to its effective and significant biological activity and great pharmaceutical value. Although many strategies have been used to synthesize benzothiazole to date, the condensation reaction of *2*-aminobenzenethiol with carbonyl or cyano-containing substances is the most commonly used method. However, this method should be carried out under high temperature or metal catalyst conditions to ensure the smooth progress of the reaction [28,29]. Therefore, in order to overcome the above shortcomings, many new synthetic methods have been reported in recent years. For example, in 2010, Fan and co-workers reported that Ru(III) chloride is an effective catalyst for the formation of benzothiazole in (bmim)PF_6(ILs) medium [30]. In 2012, Wu's group reported I_2 promoted domino protocol and multipathway coupled domino strategy for synthesis of 2-acylbenzothiazoles [31,32]. In 2013, Siva S. Panda and his colleagues utilized microwave irradiation to form benzothiazoles [33]. In 2018, Maphupha and co-authors used laccase as a catalyst at room temperature for the synthesis of 2-arybenzothiazole erivatives [34]. Although these methods are very effective and satisfactory, they are also subject to some limitations in aspects of high temperature, long reaction time, low atomic economy, complex synthesis process and unfriendly environmental impact. Considering the medicinal value of benzothiazoles, the presence of metals should also be avoided in the catalytic system. Therefore, there is still a great need to find a gentle and applicable green synthesis method.

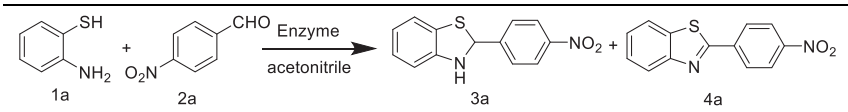
In recent years, our group has been committed to green enzyme catalysis methodology and some achievements have been made [35–39]. We were also attracted by the medicinal value of benzothiazoles, and considering the lack of green synthesis methods, we tried to synthesize benzothiazoles using enzyme-catalyzed methods. Unfortunately, the enzyme-catalyzed method can only obtain intermediate products. At this time, we thought of the same green photocatalytic oxidation method. When the two methods were combined, "one plus one is greater than two" was successfully realized.

Compared with the previously reported synthetic methods, this method is more efficient, green, convenient and does not require an additional oxidant or metal. The compatibility of trypsin and photocatalyst Solvent Red 43 in organic solvents under $\lambda = 450$ nm light irradiation, water content, amount of catalyst, and a series of experimental conditions were studied. The performance of the reaction system is promising, and under a variety of substrate conditions, a series of *2*-substituted benzothiazoles are obtained with good to excellent yields (up to 99%), under an air atmosphere, in just 10 min. After a simple



Scheme 1. Enzyme and visible light co-catalyzed a two-step reaction, in one pot.

Table 1
The catalytic effect of different commercial enzymes on the model reaction.[a]



1a 2a 3a 4a

Entry	Enzyme	3a Yield(%)[b]	4a Yield(%)[b]
1	Blank	10	Trace
2	Lipase from *Candida antarctia* B (CAL-B)	28	Trace
3	Lipase from Porcine pancreas (PPL)	33	Trace
4	Bovine serum albumin (BSA)	32	Trace
5	Lipase from *Mucor miehei* (MML)	50	Trace
6	Amano Lipase M from *Mucor javanicus* (MJL)	30	Trace
7	Trypsin (bovine pancreas)	72	Trace
8	Pepsin	57	Trace
9	Lipase from *Candida rugosa* (CRL)	65	Trace
10	Bovine pancreatic lipase (BPL)	58	Trace
11	Urea (200 mg)	8	Trace
12	Trypsin (pretreated with urea)	7[c]	Trace
13	$CuSO_4$ (39.9 mg)	5	Trace
14	Trypsin (pretreated with 250 mM Cu^{2+})	6[d]	Trace
15	Denatured Trypsin	9[e]	Trace

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), enzymes (5 mg), acetonitrile (1 mL) were added to 10 mL quartz tube, and at 200 rpm at λ = 450 nm 20 W for 10 min. [b]All yields were determined by HPLC. [c]Trypsin (10 mg) in urea solution (6.7 M) [urea (400 mg) in deionized water (1 mL)] was stirred at 25 °C for 24 h, and then water was removed by lyophilization before use. dTrypsin (10 mg) in Cu^{2+} solution (250 mM) [$CuSO_4$ (39.9 mg) in deionized water (1 mL)] was stirred at 25 °C for 24 h, and then water was removed by lyophilization before using. [e]Trypsin 120 °C for 24 h.

reaction conditions, only the target product and water are produced, which has high atom economy and environment-friendly. The combination of enzyme-catalysis and photoredox catalysis through cascade reaction for the synthesis of *2*-substituted benzothiazoles can be used as a supplement to current methods (Scheme 1).

2. Experimental section

2.1. Materials and analytical methods

All reagents were used without further purification unless otherwise noted. CRL (lipase from *Candida rugosa*), PPL (lipase from Porcine pancreas, 6.8 U/mg), BPL (lipase from Bovine pancreas, 15–35 u/g), MJL (Amano lipase from *Mucor javanicus*, 10,000 U/mg), CAL-B (lipase from *Candida antarctia* B, 2 U/mg), MML (lipase from *Mucor miehei* 1 U/mg), were purchased from Sigma-Aldrich and. Pepsin were purchased from Fluka. BSA (bovine serum albumin), trypsin (bovine pancreas), *2*-aminothiophenol, *p*-nitrobenzaldehyde, Solvent Red 43, Tris (*2*, *2*-bipyridyl) ruthenium (II) chloride hexahydrate, Rhodamine B, Fluorescein were purchased from Aladdin. The NMR spectra were obtained on an Agilent 400-MR DD2 spectrometer. The ^1H NMR (400 MHz) chemical shifts were measured relative to $CDCl_3$ or DMSO-d_6 as the internal reference. The ^{13}C NMR (100 MHz) chemical shifts were given using $CDCl_3$ or DMSO-d_6 as the internal standard. HPLC experiments were performed on Waters instrument (Waters e2695, 2998) using a C18 column with MeOH/water = 70:30 (v/v), 1 mL/min, λ max = 254 nm, and 30 °C. High resolution mass spectra (HR-MS) were obtained with a Waters-Q-TOF-Premier (ESI).

2.2. The typical procedure for synthesis of 2-substituted benzothiazoles.

2-aminothiophenol (0.2 mmol), *p*-nitrobenzaldehyde (0.2 mmol), Solvent Red 43 1% mol trypsin (10 mg), and toluene (2 mL) were added to 10 mL quartz tube, at 200 rpm and at λ = 450 nm, 20 W for 10 min. The reaction was completed by filtering the enzyme. The crude products were purified by silica gel column chromatography (200–300 mesh) with an eluent consisting of ethyl acetate-petroleum. Product-contained fractions were combined, concentrated, and dried to give respective product.

3. Results and discussion

3.1. Catalytic activity of different enzymes.

Initially, we chose the reaction of the substrates *2*-aminothiophenol (**1a**) and *p*-nitrobenzaldehyde (**2a**) in acetonitrile as the model reaction. In order to select a suitable enzyme to catalyze the synthesis of *2*-substituted benzothiazole compounds, the catalytic effect of different commercial enzymes on the model reaction was first studied, including routine, promiscuous activities, and some control experiments. The results are shown in Table 1. As shown in Table 1, all commercial enzymes cannot catalyze this reaction to form the final product, only the intermediate *2*, *3*-dihydro-*2*-(*4*-nitrophenyl) benzothiazole is produced (Figure S1A). Here, we mainly discuss the effect of different enzymes on the yield of intermediate. The catalytic activity of enzymes from different sources is quite different. The highest yield of 72% was achieved using trypsin (bovine pancreas) (Table 1, entry 7). Three kinds of enzymes like lipase from *Mucor miehei* (MML), showed moderate catalyst activity (Table 1, entries 6, 9–10). As for the four types of enzymes including lipase from *Candida antarctia* B (CAL-B), the catalytic yields are all around 30%, which is a bit lower than the highest yield, but it is still three times higher than the blank control reaction (Table 1, entries 2–4, 6). In order to prove the specific catalytic effect of trypsin on this reaction, a series of controlled experiments were carried out. We conducted a model reaction in the absence of trypsin and using thermally denatured trypsin. At the end of the reaction, only negligible products were observed (Table 1, entries 1 and 15), indicating that trypsin can initiate the reaction. In addition, trypsin was pretreated with urea as a denaturant and then used to catalyze the model reaction, producing only a very low yield (Table 1, entry 12). To determine the effect of urea on the model reaction, urea was used to catalyze the model reaction, and no product was observed in urea (Table 1, entry 11). These results indicate that after heat or urea denaturation, trypsin loses its natural structure and fails to complete the catalysis. Heavy metal ions can also inactivate enzymes by reacting with structural groups such as thiol groups, or with certain amino acid residues, causing tertiary structural changes. Therefore, Cu^{2+} was used for trypsin pretreatment, respectively. Similar to the denatured enzyme diagram below, after incubation with Cu^{2+}, the enzyme loses catalytic activity for the reaction (Table 1, entry 14). A blank reaction using only Cu^{2+} as the catalyst failed to obtain the product (Table 1, entry 13). The above control experiments showed that

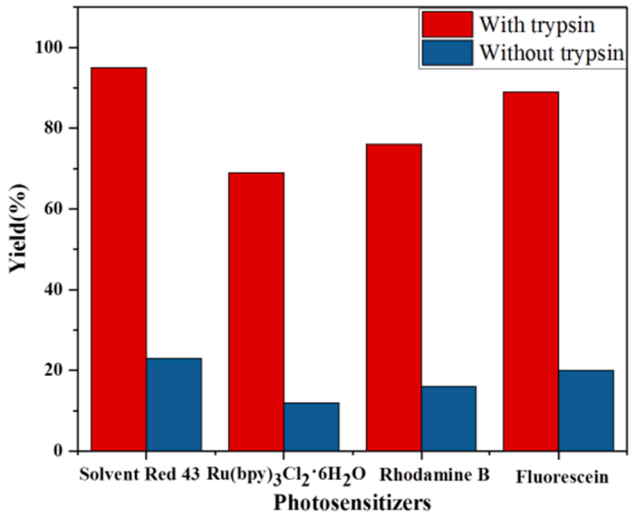
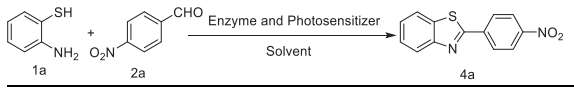


Fig. 2. Photosensitizers were screened in order to achieve the oxidation process. Reaction conditions: **1a** (0.1 mmol), **2a** (0.1 mmol), photosensitizer (1% mol), trypsin (5 mg) andacetonitrile (1 mL) were added to 10 mL quartz tube, and at 200 rpm at λ = 450 nm. All yields were determined by HPLC.

Table 2
Solvent screening.[a]



Entry	Solvents	Yield b (%)
1	Methanol	51
2	Ethylene glycol	55
3	DMF	78
4	THF	67
5	DMSO	51
6	Toluene	99
7	Trichloromethane	60
8	H_2O	24
9	CH_3CN	95

[a] Reaction conditions: 1a (0.1 mmol), 2a (0.1 mmol), Solvent Red 43 1% mol trypsin (5 mg) and solvent (1 mL) were added to 10 mL quartz tube, and at 200 rpm at λ = 450 nm, 20 W for 10 min. [b]All yields were determined by HPLC.

trypsin can catalyze a model reaction to produce intermediate.

3.2. Wavelength and photosensitizers screen

After determining the optimal enzyme, wavelength, and photosensitizers were screened in order to achieve the oxidation process. The results are shown in Table S1 and Fig. 2. Through Table S1, we determined that λ = 450 nm is the best catalytic wavelength. As illustrated in Fig. 2, it is worth noting that in the entries without trypsin, the yield was reduced by 70%. This shows that trypsin plays a vital role in this reaction among the four photosensitizers with enzymes, the reaction result of Solvent Red 43 is the best, the yield is greater than 95%. Compared with Solvent Red 43, the yield of Fluorescein also reached 89%. This may be related to the similar structure of the two photosensitizers. After all, they differ by only 4 bromine atoms. The worst reaction is Tris (*2*, *2*-bipyridyl) ruthenium (II) chloride hexahydrate, with only 69% yield. For items that do not contain trypsin, the situation is basically the same as that containing trypsin, with Solvent Red 43 giving the best response, followed by Fluorescein, and Tris (*2*, *2*-bipyridyl) ruthenium (II) chloride hexahydrate being the lowest yield. Therefore, we chose the Solvent Red 43 as the best photosensitizer to screen the subsequent reaction conditions.

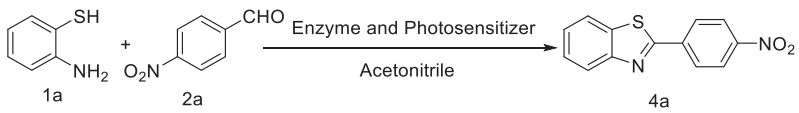
3.3. The influence of reaction medium

Since the reaction medium can directly or indirectly affect the photoenzymatic activity, the choice of the solvent for the photoenzymatic reaction is also one of the key factors for the reaction to be effective. We selected a series of solvents to examine their effects on the template reaction. The results are shown in Table 2. The results showed that the solvent played an important role in the model reaction. When water was used as the reaction solvent, only 24% target product was formed (Table 2, entry 8). This may be attributed to the poor solubility of organic compounds in water. In methanol, ethylene glycol and DMSO, the yield of the model reaction is about 50% (Table 2, entries 1, 2, 5). In DMF, THF and trichloromethane, the yield of model reaction achieved a moderate yield (Table 2, entries 3, 4, 7). Although a 95% yield has been achieved in acetonitrile (Table 3, entry 9), but in toluene, the yield is 99% (Table 2, entry 6). After determining the solvent, we explored the effect of different water content on the reaction, the results are shown in Figure S2. It can be seen from the figure that as the water content increases, the yield decreases in turn. This may be related to the solubility of the reactants in water. Therefore, we used toluene as the optimal reaction solvent for the photoenzymatic reaction.

3.4. The molar ratio, amount of enzyme and photocatalysis screen

Next, we further explored the effect of the molar ratio between *p*-

Table 3
Control experiments.[a]



Entry	Trypsin	λ = 450 nm	Solvent Red 43	4a Yield (%)[b]
1	+	+	+	95
2	–	+	+	23
3	+	–	+	Trace
4	+	+	–	Trace
5	–	–	+	0
6	+	–	–	Trace
7	–	+	–	0
8	–	–	–	0

[a] Reaction conditions: 1a (0.1 mmol), 2a (0.1 mmol), photosensitizer (1% mol), trypsin (5 mg) and acetonitrile (1 mL) were added to 10 mL quartz tube, and at 200 rpm at λ = 450 nm, 20 W for 10 min. [b]All yields were determined by HPLC.

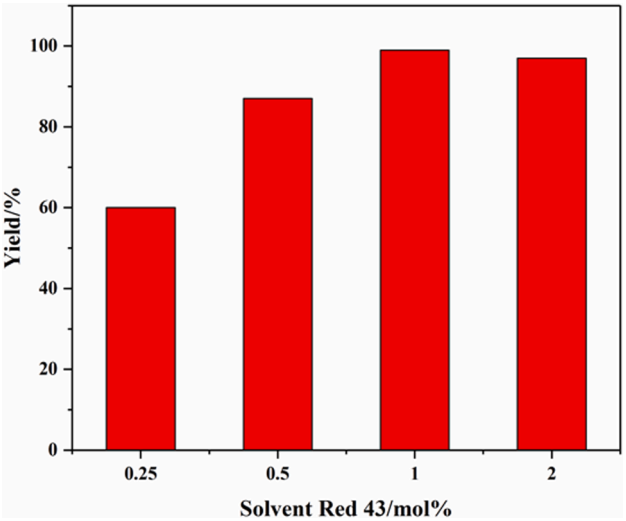


Fig. 3. The effect of the amount of Solvent Red 43 on the reaction. a)Reaction conditions: 1a (0.1 mmol), 2a (0.1 mmol), Solvent Red 43 0.25–2% mol, trypsin (5 mg), toluene (1 mL) were added to 10 mL quartz tube, and at 200 rpm at $\lambda = 450$ nm, 20 W for 10 min. All yields were determined by HPLC. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

nitrobenzaldehyde (**1a**) and *2*-aminothiophenol (**2a**) on the reaction. The results are shown in Figure S3. It can be observed that when *p*-nitrobenzaldehyde is excessive, the yield begins to decrease, and as the increment increases, the yield decreases. When *2*-aminothiophenol is excessive, it illustrated the same trend. When the molar ratio between the *p*-nitrobenzaldehyde and *2*-aminothiophenol is 1:1, the highest yield of 99% can be obtained. Therefore, we chose molar ratio **1a**:**2a** = 1:1 as the best molar ratio for subsequent studies.

Subsequently, we studied the effects of the amount of enzyme on the reaction, and the results are shown in Figure S4. It can be observed from Figure S4 that when the amount of the enzyme is increased from 0 mg to 30 mg, the yield of the target product is increased from 0% to 99%. When the enzyme amount is 5 mg, the yield reaches a maximum of 99%. However, as the amount of enzyme loading is further increased, the yield remains substantially unchanged. Therefore, we chose the most optimal reaction conditions with an enzyme content of 5 mg to carry out the subsequent reaction.

Similarly, the amount of photocatalysis also has a greater impact on the reaction. We investigated the effects of different amounts on the reaction, and the results are shown in Fig. 3. When the photocatalyst is 0.25%mol, the yield is only 60%. As the photocatalyst content increases, the yield increases. When the content increases to 2%mol, the yield no longer increases. Therefore, we chose 1%mol as the optimal reaction condition for the subsequent experiment. In the time curve (Figure S5), we found that the highest yield can be achieved within 10 min of this reaction.

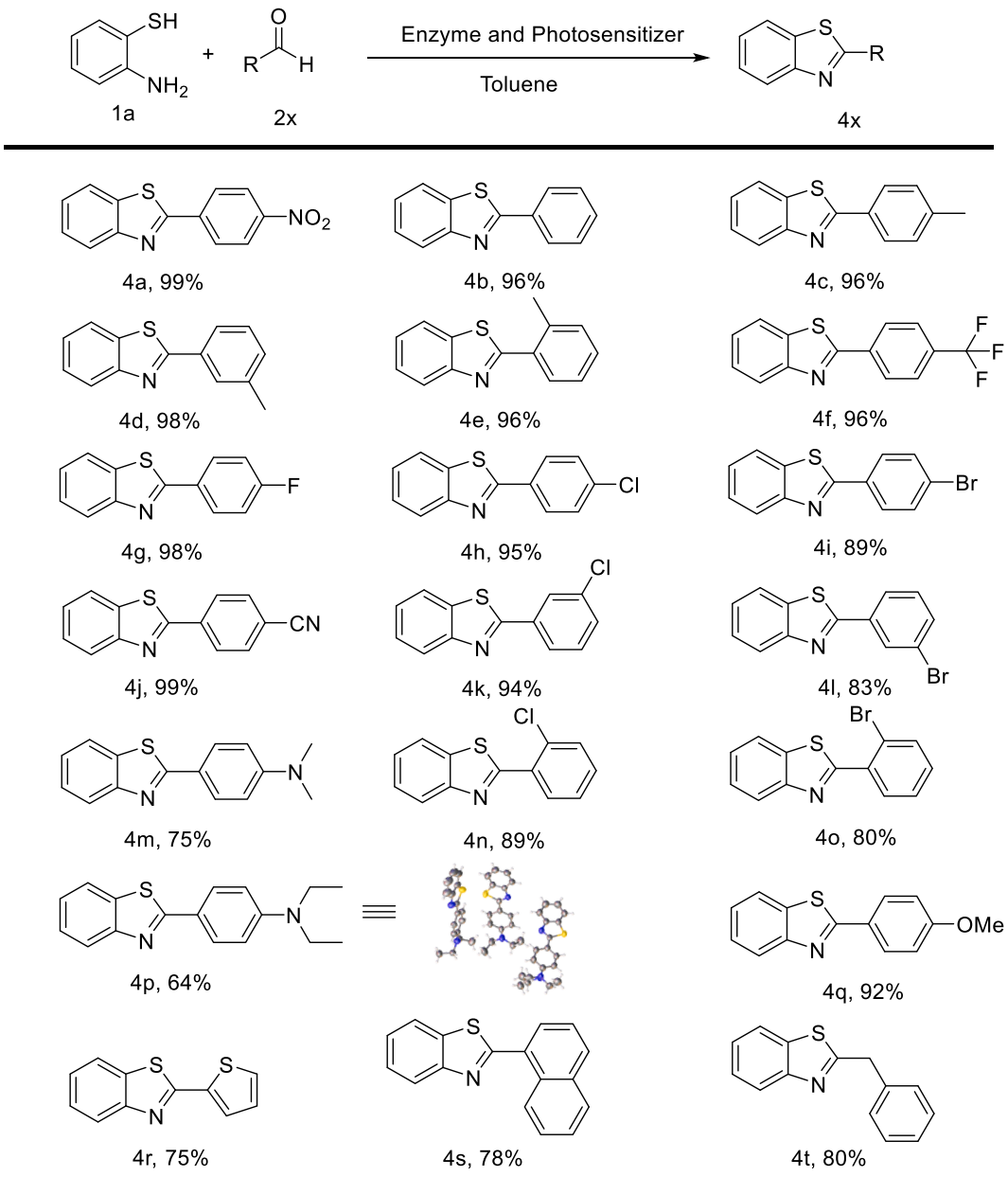
3.5. Substrate scope of the 2-substituted benzothiazoles

Based on the optimal reaction conditions for the above stencil reaction, we used a series of aromatic aldehydes for the conversion of this reaction. The results are shown in scheme 2. It can be seen from the table that the electronic effect on the substituents on the benzene ring imposes a great influence on the reaction. Although most electron-deficient or electron-rich aldehyde compounds can be smoothly converted to the corresponding products, the yields obtained are quite different. It can be observed from the table that aldehyde compounds containing electron-deficient like **4a**, **4g**, **4j** can obtain a good yield of 98–99%, while the electron-rich pair is like **4m**. The aldehyde compounds gave only a yield of 75%. When the electron-richness is further increased, the yield reduction is more obvious, only 64%, **4p** (single crystal X-ray diffraction analysis confirmed the structure, CCDC number: 2004038). The same can be seen in **4g**, **4h**, and **4i**. As the electron-richness of aldehyde compounds increases, the yield decreases in sequence, which are 98%, 95%, and 89%, respectively. For methyl-substituted benzaldehyde, the effect of steric hindrance on yield is negligible, which can be seen from **4c**, **4d**, and **4e.** When the benzaldehyde was replaced with a larger volume of 1-naphthaldehyde, the yield decreased significantly, only 78% **4s**, indicating that the steric effect is present in this reaction. On the contrary, when benzaldehyde is replaced by *2*-thenaldehyde, although the volume of *2*-thenaldehyde is small, **4r,** the electron-rich effect increases due to the presence of S atoms, and the yield decreases. Finally, when the reaction is carried out with phenylacetaldehyde **4t**, the yield is only 80%. The possible reason is that due to the increase of carbon atoms in the middle, it is difficult to conjugate the aldehyde group with the benzene ring, and the yield decreases.

3.6. Control experiments

To verify this photobiocatalytic concurrent reaction, some control experiments were conducted (Table 3, Fig. 4 and Scheme S1). Oxygen is crucial in the reaction process (Scheme S1). Even without photosensitizer and light, there is a small increase in yield in an oxygen environment. The reaction cannot continue under argon environment, which is consistent with the single enzyme yield. Under the reaction conditions that all three have, the model reaction gets 4a in 95% yield (Table 3, entry 1). In the absence of Trypsin, with Solvent Red 43 under light only a 23% yield was obtained (Table 3, entry 2). In the absence of light irradiation or Solvent Red 43, no reaction was observed (Table 3, entries 3 and 4). As expected, no reaction occurred in the absence of both photocatalyst and enzyme (Table 3, entry 5). Similarly, in the absence of the other two reaction conditions, the target product was not obtained (Table 3, entries 6 and 7). Not to mention reactions that do not have the three reaction conditions, the yield is 0% (Table 3, entry 8). These results indicated that light, trypsin, and Solvent Red 43 are indispensable for this photoenzymatic concurrent reaction.

In order to verify the effect of light irradiation, we conducted an on/off light experiment Fig. 4. In the absence of light, the reactions of **1a** and **2a** are very slow. Obvious acceleration was observed under light irradiation. In the first minute, the reaction rate is the fastest. With the consumption of A and B, the reaction rate gradually decreases, which conforms to the characteristics of reaction kinetics. The yield reached the maximum when the total reaction time was 18 min, was in good agreement with the reaction time curve (Figure S5).



Scheme 2. Synthesis of 2-substituted benzothiazoles under the optimal conditions. Reaction conditions: *2*-aminothiophenol (0.2 mmol), *p*-nitrobenzaldehyde (0.2 mmol), Solvent Red 43 1% mol trypsin (10 mg) and toluene (2 mL) were added to 10 mL quartz tube, at 200 rpm and at λ = 450 nm, 20 W for 10 min. The crude products were purified by silica gel column chromatography (200–300 mesh) with an eluent consisting of ethyl acetate-petroleum. Product-contained fractions were combined, concentrated, and dried to give respective product.

3.7. Proposed reaction mechanism

Based on the results of the reaction and similar transformations reported in the literature, we have reasonably speculated about the possible mechanism of action of this reaction, as shown in scheme 3. First, *p*-nitrobenzaldehyde (**2a**) enters the binding pocket of the enzyme and binds with the enzyme through hydrogen bonding. At this time, 2-aminothiophenol (**1a**) also enters the binding pocket and undergoes a nucleophilic addition reaction to the carbonyl carbon. Then one molecule of water is removed to form a Schiff base compound. The histidine residue in the enzyme takes the hydrogen from the thiol to generate sulfur anion. Sulfur anions attack carbon–nitrogen double bonds, nitrogen accepts electrons to generate nitrogen anions. The hydrogen ion of histidine residue is obtained by the nitrogen anion, the activity of the enzyme catalyst is restored, and the intermediate product **3a'** is generated. Subsequently, **SR 43** (Solvent Red 43) is excited to the excited state **SR 43*** under λ = 450 nm irradiation. A single electron oxidation of **3a** by the excited state **SR 43*** generated radical cation**3a'** and the reduced **SR 43•⁻** species. This charge-separated state species is oxidatively quenched by O_2 to produce **SR43** and superoxide. At last, deprotonation of **3a'** by superoxide followed by hydrogen atom abstraction by hydroperoxyl radical ($HOO^{\bullet}$) yields the desired benzothiazole **4a**.

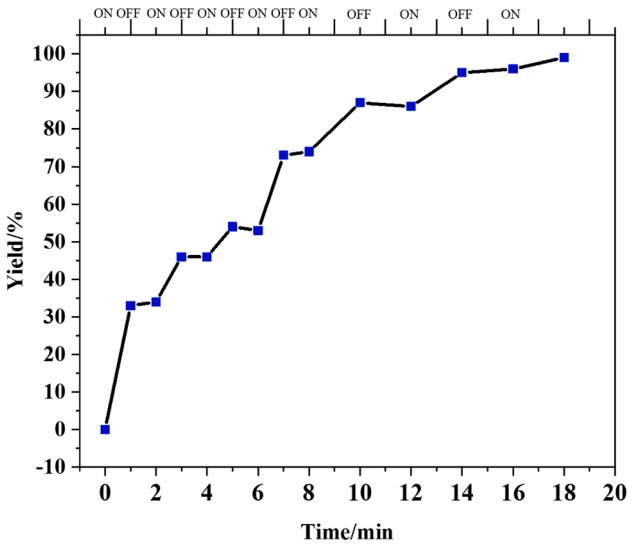


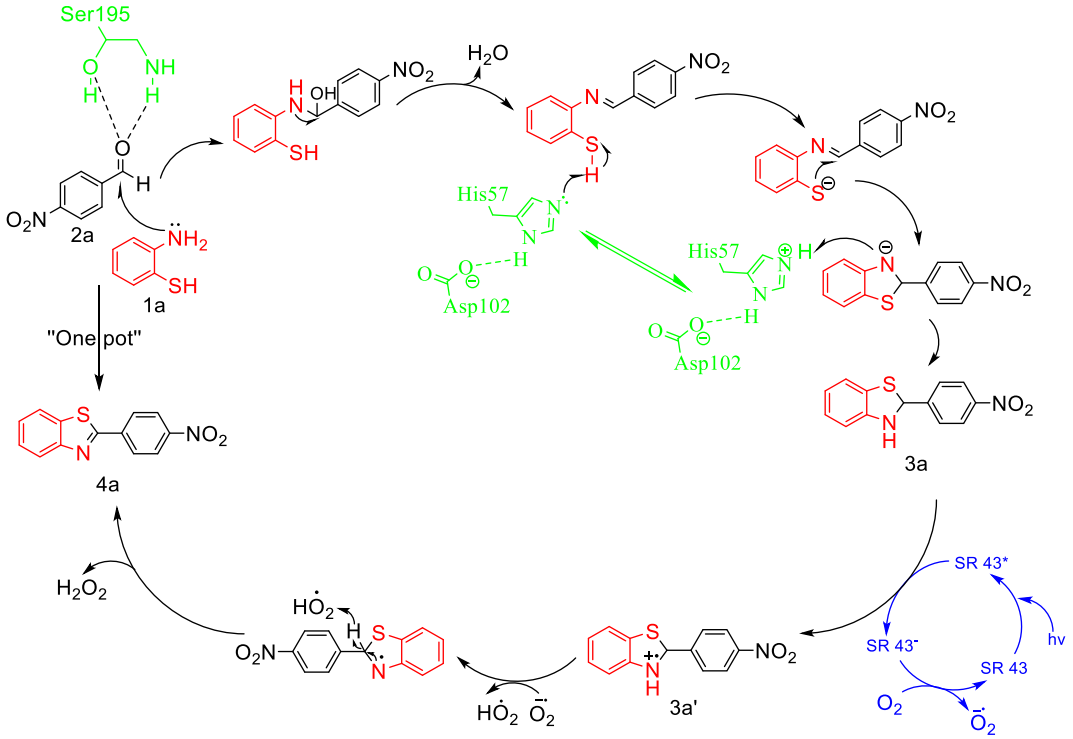
Fig. 4. ON/OFF light experiment. a)Reaction conditions: 1a (0.1 mmol), 2a (0.1 mmol), Solvent Red 43 1% mol, trypsin (5 mg), toluene (1 mL) were added to 10 mL quartz tube, and at 200 rpm at λ = 450 nm, 20 W. All yields were determined by HPLC. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Conclusion

In summary, this work combinated photoredox enzymatic and visible-light catalysis for synthesis of the widely applicable *2*-substituted benzothiazoles between a *2*-aminothiophenol(**1a**) and a series of aldehyde compounds in the first time. The optimal reaction conditions were obtained by investigating factors, such as types of enzymes, reaction solvent, molar ratio, enzyme amount, and reaction time. A series of substrates are expanded according to the optimal reaction conditions. Although the yield of a single target compound is low, the overall performance is medium to good, with a maximum yield of 99% in just 10 min. This novel method provides an example for the synthesis of target compounds using enzymes and light energy and explores an environmentally friendly, simple, and convenient synthetic route in organic chemical synthesis.

CRediT authorship contribution statement

Zeng-Jie Yang: Conceptualization, Methodology, Writing - original draft, Writing - review & editing, Validation. **Qing-Tian Gong:** Writing - review & editing, Formal analysis. **Yuan Yu:** Formal analysis, Writing - review & editing. **Wei-Fan Lu:** Writing - review & editing, Formal analysis. **Zhe-Ning Wu:** Writing - review & editing, Formal analysis. **Na Wang:** Writing - review & editing, Supervision, Visualization,



Scheme 3. Proposed mechanism of the reaction.

Resources. **Xiao-Qi Yu:** Funding acquisition, Project administration, Supervision, Visualization, Writing - review & editing, Conceptualization.

Declaration of Competing Interest

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bioorg.2020.104607.

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