Riboflavin-Based Photocatalysis for Aerobic Oxidative S–N Bond Formation of Thiols and Amines

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A novel organophotocatalytic process using riboflavin derivatives, which allows for aerobic oxidative multistep S–S, S–N, and S–O bond formations of thiols and amines, is presented herein. The reaction proceeded under mild metal-free conditions using air (1 atm) as an environment-friendly oxidant, yielding sulfinamides and sulfonamides.

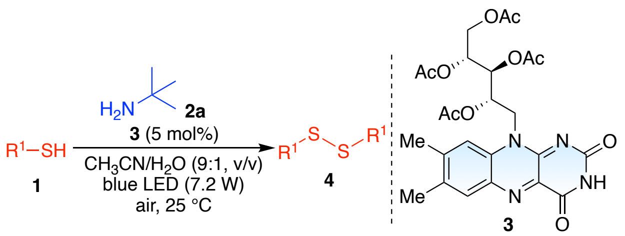
Keywords: S–N bond formation, Flavins, Photocatalysis

Riboflavin, commonly known as vitamin B_2, and its derivatives function as unique redox organocatalysts that facilitate diverse catalytic oxidations, and are thus attractive tools for designing green and sustainable transformations.[1,2] In recent years, photocatalytic oxidation, which does not proceed thermally, has also received significant attention. Photocatalysis by riboflavin analogs have been reported to efficiently promote the oxidation of toluenes,[3] alcohols,[4] amines,[5] and others[6] under visible-light irradiation to afford the corresponding products.[7] In higher plants, riboflavin acts as a functional center of blue-light sensitive photoreceptor called phototropin, which controls blue-light responses, such as a stem bending toward light.[8] By mimicking the reaction process of phototropin, we recently developed a strategy for the aerobic photooxidative heterocoupling of two thiols to synthesize unsymmetrical disulfides catalyzed by a simple riboflavin derivative.[9] The selective S–S bond formation efficiently occurs under visible-light irradiation by the consumption of molecular oxygen (air, 1 atm), which is an ideal oxidant with environmental and economic advantages. Because disulfides are useful synthetic intermediates,[10] this system is expected to be applicable to multistep reactions that enable further bond-forming reactions between sulfur and other atoms using in-situ-generated disulfides and flavin catalysis.

Sulfinamides and sulfonamides are widely found in pharmaceuticals, agrochemicals, and other functional molecules because of their abundant biological activity and chemical and metabolic stability.[11] The classical method for synthesizing sulfinamides and sulfonamides is the reaction of sulfinyl or sulfonyl chlorides with amine nucleophiles.[12] However, sulfinyl and sulfonyl chlorides are toxic and require pre-preparation with oxidant and chlorinating reagents. In contrast, the oxidative coupling of thiols and amines is promising for atom- and step-economical synthesis, providing the desired products briefly and efficiently from simple starting materials. Therefore, various approaches using transition metal catalysts,[13] iodine and oxidants,[14] and electrochemical methods have been reported.[15] Herein, we report a novel photocatalytic protocol using riboflavin, which proceeds via aerobic oxidative S–N bond formation between thiols and amines to afford sulfinamides and sulfonamides. In this system, the riboflavin-based photocatalyst not only promoted the formation of disulfides by the aerobic oxidation of thiols but also catalyzed the subsequent S–N and S–O bond formation. Various oxidative transformations using flavin photocatalysts have been developed; however, to the best of our knowledge, no successful example of S–N bond formation between thiols and amines has been reported.

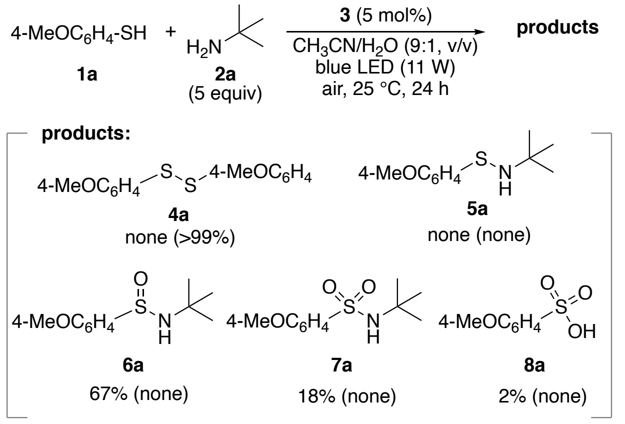
First, 4-methoxybenzenthiol (**1a**) was oxidized in the presence of *tert*-butylamine (**2a**, 5 equiv) using riboflavin tetraacetate (**3**) as a photocatalyst in CH_3CN/H_2O (9:1, v/v) in air (1 atm, balloon) and blue LED irradiation at 25 °C (Table 1). Consequently, the corresponding disulfide **4a** was obtained in only 5 min (entry 1). In the absence of **2a**, the reaction barely proceeded, affording **4a** in 9% yield (entry 2). Addition of a primary amine enhanced the conversion of **1a**. Unsubstituted benzenethiol (**1b**), electron-deficient 4-chlorobenzenethiol (**1c**), and alkanethiol **1d** were also efficiently converted to the corresponding disulfides in 67–94% yields over 5–60 min (entries 3-5). In contrast, the oxidation of **1b** and **1d** was suppressed under dark conditions, yielding the corresponding disulfides in yields of 24% and 5%, respectively (entries 6 and 7). Although the oxidation of thiols also occurred slightly under dark conditions, the reaction was greatly enhanced by flavin photocatalysis. Interestingly, when the reaction time was extended to 6 h, disulfide **4a** was further converted (entry 8). Analysis of the products revealed that a reaction time of 24 h for **1a** and **2a** yielded the corresponding sulfinamide **6a** and sulfonamide **7a** in 67% and 18% yields, respectively, which were possibly formed by the oxidative S–N bond formation of **4a** with **2a** (Scheme 1). The formation of the corresponding sulfenamide **5a** and sulfuric acid **8a** was minimal, affording yields of 0% and 2%, respectively. However, only disulfide **4a** was obtained under dark conditions without further conversion to **5a–8a**. This suggests that light irradiation is crucial for the oxidative S–N bond formation, yielding **6a** and **7a** (Scheme 1).

Table 1. Aerobic oxidation of thiols **1a–1d** in the presence of amine **2a**.[a]



Entry	1	2a (equiv)	Time (min)	Yield of 4 (%)
1	4-$MeOC_6H_4SH$ (**1a**)	5	5	>99
2	**1a**	–	5	9
3	PhSH (**1b**)	5	5	94
4	4-ClC_6H_4SH (**1c**)	5	5	88
5	$C_8H_{17}SH$ (**1d**)	5	60	67
6[b]	**1b**	5	5	24
7[b]	**1d**	5	60	5
8	**1a**	5	360	0

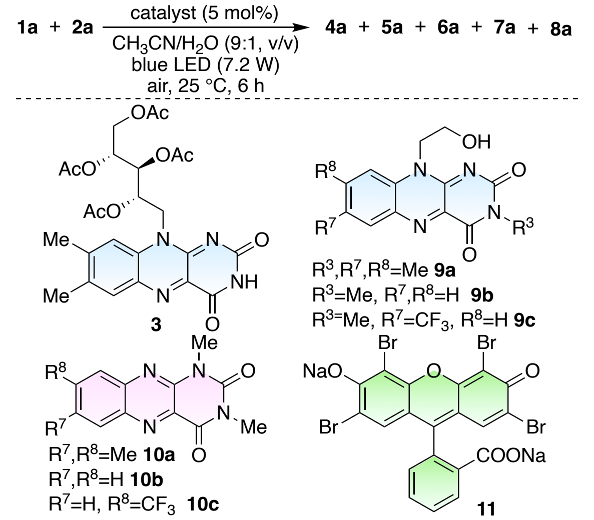
[a] Conditions: **1** (0.025 M), **2a** (0.125 M), **3** (5 mol%), and CH_3CN/H_2O (9:1, v/v) with blue LED (7.2 W) in air (1 atm, balloon) at 25 °C. The yield was determined by GC and ^1H NMR using tetraethylene glycol dimethyl ether and 1,1,2,2-tetrachloroethane, respectively, as an internal standard. [b] Under dark conditions.



Scheme 1. Flavin-catalyzed aerobic oxidative transformation of **1a** and **2a** to **4a–8a** under visible-light irradiation. The values within parentheses are the results obtained when the reaction was conducted under dark condition for 6 h.

We investigated the catalytic activity of various neutral flavin compounds (**3**, **9**, and **10**) in the reaction of **1a** in the presence of **2a** to elucidate the effect of flavin catalysis on the multistep conversion of **1a** (Table 2). Isoalloxazines **3** and **9** and alloxazine **10** bearing various substituents efficiently catalyzed the conversion of **1a** in 6 h (entries 1–7). The relatively electron-rich isoalloxazines **3** and **9a** and electron-rich alloxazine **10a** further enhanced the oxidative conversion of **4a** to **6a** and **7a** in comparison with the corresponding compounds **9b**, **9c**, **10b**, and **10c** with a relatively electron-deficient π-conjugated system. Among these, riboflavin tetraacetate (**3**), which can be easily synthesized by one-step acetylation from inexpensive riboflavin (vitamin B_2),[16] exhibited the best catalytic activity for multistep oxidation; the total yields of **6a** and **7a** were 81% (entry 1). Depending on the flavin compound, different results support their catalytic effect on the oxidative transformation of **4a**. When eosin Y (**11**) was used as the photocatalyst in the present reaction, no conversion to **5a**–**7a** was observed, although **4a** was obtained (entry 8). This may be explained by the difference in the reduction potentials in the excited states of **3** (E^*_{red}= 1.67 V vs. SCE)[17] and **11** (E^*_{red}= 0.83 V vs. SCE).[18]

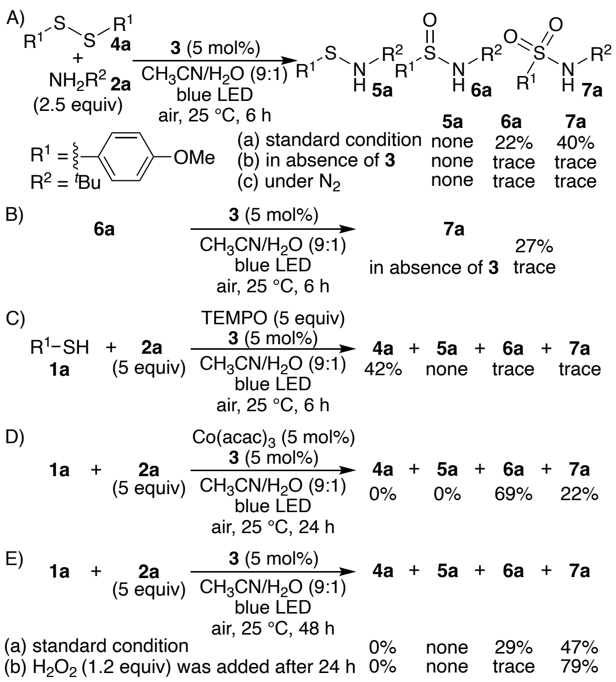
Table 2. Effect of photocatalysis for the aerobic oxidative reaction of **1a** and **2a**.[a]



Entry	Catalyst	Conv. of 1a (%)	Yield of 4a (%)	Total yield of 6a and 7a (%)
1	**3**	>99	0	81
2	**9a**	>99	0	76
3	**9b**	>99	6	48
4	**9c**	>99	77	8
5[b]	**10a**	>99	0	76
6[b]	**10b**	>99	3	41
7[b]	**10c**	>99	0	64
8[c]	**11**	>99	87	1

[a] Conditions: **1a** (0.025 M), **2a** (0.125 M), catalyst (5 mol%), and CH_3CN/H_2O (9:1, v/v) with a blue LED (7.2 W) in air (1 atm, balloon) at 25 °C for 6 h. The yield was determined by GC using tetraethylene glycol dimethyl ether as an internal standard. [b] Purple LED was used. [c] Green LED was used.

Control experiments were performed to gain insight into the reaction mechanism. We first performed the reaction using disulfide **4a** as the starting material under standard conditions to confirm that **4a** is the reaction intermediate for the conversion to **6a** and **7a** (Scheme 2Aa). Indeed, **4a** was converted to the corresponding sulfinamide **6a** and sulfonamide **7a** in 22% and 40% yields, respectively, indicating that oxidative S–N bond formation proceeded after the S–S bond formation of thiols. In the absence of the flavin catalyst or under nitrogen conditions, products with S–N bond, **5a–7a**, were not obtained (Schemes 2Ab and c). In previously reported examples, the coupling between thiols and amines proceeded by the nucleophilic attack of amines on in-situ-generated disulfides, thus forming sulfenamides.[15,19] However, in this flavin-catalyzed system, the formation of sulfenamides **5** was not detected, although disulfides **4** were formed. Sulfinamides **6** were formed directly from disulfides **4** without undergoing oxidation of **5**. In contrast, **6a** was converted to sulfonamide **7a** under standard conditions, whereas **7a** was not obtained in the absence of the flavin catalyst **3**. These transformations from **4a** and **6a** to **6a** and **7a**, respectively, occurred without additives (Schemes 2Aa and B), suggesting that the flavin catalyst functions as a photosensitizer, promoting radical-mediated processes. When 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), a radical inhibitor, was added under the reaction conditions, the formation of **6a** and **7a** was prevented, although **4a** was obtained in 42% yield (Scheme 2C). In contrast to the S–S bond formation that yielded **4a** from **1a**, the subsequent oxidative S–N bond formation to **6a** and **7a** may have proceeded through a radical process. To investigate the effect of singlet oxygen on this reaction, $Co(acac)_3$ was added to the reaction condition as a singlet oxygen quencher (Scheme 2D).[20] Since the yields of **6a** and **7a** did not change whether $Co(acac)_3$ was added or not (Schemes 1 and 2D), singlet oxygen is unlikely to be involved in this reaction. We also carried out an experiment in which the blue light source was switched on/off during the reaction of **1a** and **2a** (Figure 1). The products **6a** and **7a** were formed only under light irradiation, and the reaction did not proceed under dark condition, suggesting that the possibility of the radical chain process in this reaction is negligible.



Scheme 2. Control experiments.

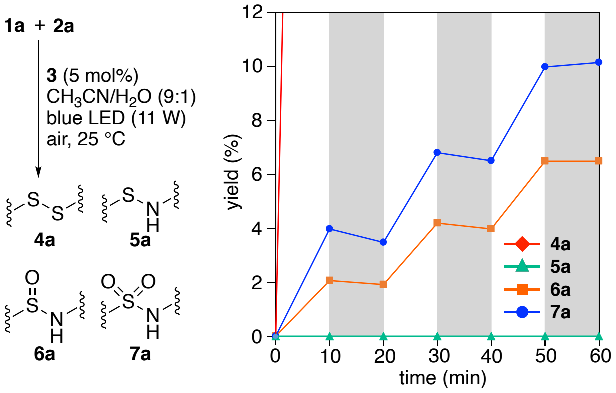
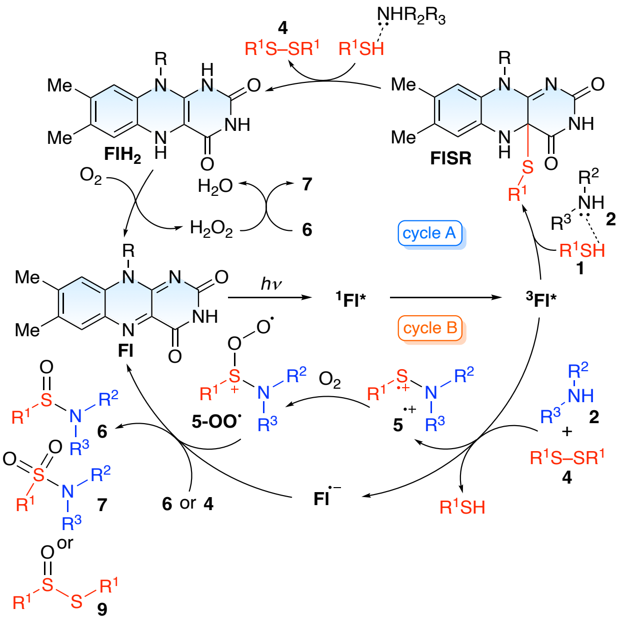


Figure 1. Light on/off experiment of the reaction of **1a** and **2a**. The blue LED was turned on and off every 10 min, starting from the on state. The gray areas represent the time when the light was turned off.

Based on the experimental results and previous literature, a plausible reaction mechanism was proposed (Scheme 3). Through "cycle A," **Fl** is excited by visible-light irradiation to afford **^{3}Fl*** via **^{1}Fl***; **^{3}Fl*** then reacts with thiol **1** to form flavin-thiol adducts (**FlSR**).[9] In the presence of basic amine **2**, thiol **1** is nucleophilically activated, which promotes the nucleophilic attack on **FlSR** and yields disulfide **4** and reduced flavin (**FlH_2**). The generated **FlH_2** reacts with molecular oxygen and reverts to the initial **Fl** along with the formation of H_2O_2.[21] Furthermore, **^{3}Fl*** reacts with **2** and **4** to form the radical cation intermediate **5**$^{\bullet+}$, which immediately reacts with molecular oxygen to form intermediate **5-OO**$^{\bullet}$

(cycle B).[20,22] The oxidatively active **5-OO**$^{\bullet}$ is converted to the desired **6** through the transfer of oxygen atom to **6** or **4**, affording **7** or **9**. The **Fl**$^{\bullet-}$ generated from ^{3}**Fl*** was converted to initial **Fl** possibly through electron transfer to radical cations formed during the reaction of **5-OO**$^{\bullet}$ with **6** or **4**. For investigating the effect of the H_2O_2 produced in cycle A, 1.2 equiv of H_2O_2 was added to the reaction solution produced by the 24-h reaction of **1a** and **2a** under standard conditions (Scheme 2E). Consequently, the oxidation of **6a** was enhanced; thus, **7a** was obtained in 79% yield, although both **6a** and **7a** were obtained in 29% and 47% yields, respectively, without the addition of H_2O_2. This suggests that the in-situ-generated H_2O_2 also promotes the oxygenation of **6** to **7**. The addition of H_2O_2 is useful for the chemoselective synthesis of sulfonamides. Thus, in the present system, the flavin catalyst plays multiple roles in S–S, S–N, and S–O bond formation, thus enabling the multistep synthesis of sulfinamides and sulfonamides from simple thiols and amines with the consumption of air.



Scheme 3. Proposed catalytic cycle.

In summary, we developed a new strategy for the synthesis of sulfinamides and sulfonamides via S–N bond formation by coupling thiols and amines using flavin photocatalysts. The flavin-photocatalyzed oxidation of thiols to disulfides is facilitated in the presence of amines. The flavin catalyst also acts as a photosensitizer under visible-light irradiation to promote S–N and S–O bond formation (oxygenation). At this stage, only primitive findings on novel catalysis have been obtained. However, we believe that this will provide practical organic synthetic methods by further examining and improving the selectivity between sulfinamides and sulfonamides, substrate scope, and catalyst design.

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Graphical Abstract

Textual Information

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Authors' Names(required)	Marina Oka, Aki Takeda, and Hiroki Iida

Graphical Information