Title

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# Green Aerobic Oxidation of Thiols to Disulfides by Flavin–Iodine Coupled Organocatalysis

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air (O$_2$)   H$_2$O   I$_2$
R—SH  →  flavin catalysis  →  iodine catalysis  →  R—S—S—R
t-BuOH, 26 °C, 6-24 h        up tp 98% yield
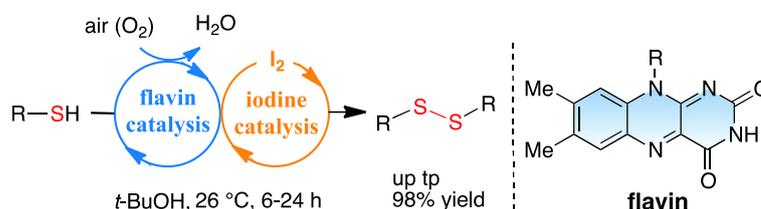
**flavin**

**Abstract** A coupled catalysis was performed using a riboflavin-derived organocatalyst and molecular iodine, which successfully promoted the aerobic oxidation of thiols to disulfides under metal-free mild conditions. The activation of molecular oxygen occurred smoothly at room temperature through the transfer of electrons from the iodine catalysis to the biomimetic flavin catalysis, which formed the basis of the green oxidative synthesis of disulfides from thiols.

**Key words** oxidation, thiols, disulfides, flavin, iodine

A major challenge in organic synthesis is the development of efficient catalytic systems for aerobic oxidations that are carried out under environmentally friendly conditions.[1] Because molecular oxygen is an oxidant that is atom economical, readily available, and minimally polluting, significant effort has been devoted to achieving catalytic O$_2$-activations for implementing oxidations and oxidative transformations. However, most catalytic O$_2$-activations have required transition-metal catalysts, harsh conditions, additional reagents that generate copious amounts of waste, or a combination thereof. Therefore, the development of a green and facile approach under metal-free mild conditions remains an ongoing challenge.

Flavin catalysts, which were developed by mimicking the catalytic function of flavoenzymes,[2] have been attracting increasing attention as organocatalysts[3] and photocatalysts[4] that enable O$_2$ activation.[5] Taking inspiration from enzymatic multiple catalytic systems, we recently developed a novel strategy for performing green aerobic oxidative transformations using coupled flavin and iodine catalysis.[6] This metal-free dual catalytic system was successfully applied to oxidative C-S and C-N bond formations (such as those observed during the sulfenylation[7] and azolation of indole analogues[8]) as well as oxidative heteroaromatic ring formations through dual or multi-step

aerobic oxidations.[9] In this flavin–iodine coupled system, thiols are converted into disulfides; however, the in-situ generated disulfide intermediates are immediately consumed by successive transformations.[7a] Consequently, a flavin–iodine catalysis system has never been applied to the practical synthesis of disulfides, although the dual catalytic system would be expected to provide green and efficient aerobic oxidation of thiols under metal-free mild conditions.

Disulfides are used as synthetic intermediates and reagents in organic synthesis;[10] they are also important in biological[11] and materials chemistry.[12] Among the diverse approaches used for the synthesis of symmetrical and unsymmetrical disulfides,[13] aerobic oxidative coupling of simple thiols is recognized as an ideal atom-economical and green approach.[13b,14] Furthermore, we recently reported the photocatalytic synthesis of symmetrical and unsymmetrical disulfides via aerobic oxidative coupling of thiols under visible light irradiation by using riboflavin tetraacetate (**1a**) as the photo-organocatalyst, which can be readily derived from inexpensive and commercially available riboflavin (vitamin B$_2$) (Scheme 1A).[15] Herein, we report the novel aerobic oxidation of thiols via a dual catalytic system by using **1a** and iodine, thus providing a facile synthesis procedure for disulfides under metal-free mild conditions without the need for light irradiation (Scheme 1B).

Scheme 1  Riboflavin-catalyzed aerobic oxidation of thiols. (A) Photocatalysis with **1a**. (B) **1a**-iodine coupled catalysis.



Figure 1  Structures of flavin and flavinium catalysts.

First, we investigated the effects of various flavin catalysts, iodine sources, and solvents on the oxidation of 1-octanethiol (**2a**) under air (1 atm, balloon) in MeOH at 26 °C for 4 h (Tables 1, S1, and S2). Among the various neutral flavins (**1** and **4**, Figure 1, 5 mol%)[16] and cationic flavinium salts (**5–7**)[17,18] tested in the presence of $I_2$ (5 mol%), **1a**, which was easily prepared by the acetylation of riboflavin (**1c**),[16] successfully promoted the oxidation of **2a** to afford the corresponding disulfide **3a** in 86% yield (entry 1, Table 1). Commercially available riboflavin tetrabutyrate (**1b**) showed comparable catalytic activity, whereas the poor solubility of the non-protected riboflavin (**1c**) resulted in only a modest yield (entries 2 and 3). Although alloxazines bearing an electron-deficient $CF_3$ group have been reported for the photocatalyzed dehydrogenation of alcohols,[19] the electron-deficient alloxazine **4** afforded **3a** in only 14% yield (entry 4). Poor yields were generally obtained from cationic flavinium salts **5–7** (entries 5–7), which are known to function as efficient organocatalysts for oxygenations.[5a] The most efficient oxidation was carried out in the presence of $I_2$ in *t*-BuOH (entry 8).

We next investigated the substrate scope of the aerobic oxidation of thiols under the optimized reaction conditions (Scheme 2). The oxidations of primary and secondary alkanethiols **2a** and **2b** successfully furnished the corresponding disulfides **3a** and **3b** in 97% and 91% yield, respectively. The cyclic disulfide **3c** was obtained through the intramolecular cyclization of 1,4-butanedithiol (**2c**). The reactions of alkanethiols bearing hydroxyl and ester groups also occurred smoothly (**3d** and **3e**). Phenylmethanethiol **2f** and the related methanethiols bearing furyl and thiophenyl groups **2g** and **2h** also gave the desired disulfides **3f–3h** in 92–94% yield. Moreover, arylthiols bearing either electron-donating or electron-withdrawing groups **2i–2n** could be oxidized to the corresponding disulfides **3i–3n** in high yield, although the poor solubility of **2n** afforded a relatively low yield for **3n**. The previously reported **1a**-catalyzed photooxidation system required basic conditions (Scheme 1A); thus, acidic substrates such as **2q** and **2r** could not be used.[15] To our delight, however, the flavin–iodine-catalyzed reaction could tolerate a variety of functional groups to produce **3o–3r**, which not only included basic amino groups but also acidic hydroxy and carboxyl groups.

Table 1  Optimization of reaction conditions for the aerobic oxidation of **2a**[a]



| Entry | Flavin | $I_2$ (mol%) | Yield (%) |
|---|---|---|---|
| 1 | **1a** | 5 | 86 |
| 2 | **1b** | 5 | 82 |
| 3 | **1c** | 5 | 23 |
| 4 | **4** | 5 | 14 |
| 5 | **5•TfO** | 5 | 24 |
| 6 | **6•TfO** | 5 | 72 |
| 7 | **7•TfO** | 5 | 20 |
| 8[b] | **1a** | 5 | 91 |
| 9 | None | 5 | 10 |
| 10 | **1a** | None | 2 |
| 11[c] | **1a** | 5 | 17[d] |

[a] Conditions: **2a** (0.5 M), flavin (5 mol%), and $I_2$ (5 mol%) in MeOH, under air (1 atm, balloon) and in the dark at 26 °C for 4 h. The yield was determined by GC using biphenyl as an internal standard. [b] Using *t*-BuOH as the solvent. [c] Under $N_2$. [d] Average of two runs.

**Scheme 2** Aerobic oxidation of thiols catalyzed by **1a**. [a] Conditions: **2** (0.5 M), **1a** (5 mol%), and $I_2$ (5 mol%) in *t*-BuOH under air (1 atm, balloon) and in the dark at 26 °C. [b] **1b** was used as the catalyst. [c] Isolated as the corresponding methyl ester after esterification with trimethylsilyldiazomethane.

We performed a series of control experiments to gain insights into the reaction mechanism. In the absence of flavin **1a**, $I_2$, or molecular oxygen, the aerobic oxidation of **2a** barely occurred, thereby suggesting that the reaction is promoted by an aerobic process catalyzed by both the flavin and iodine catalysts (entries 9–11 of Table 1). Subsequently, the effect of light irradiation on the catalytic activity was investigated; however, no difference was observed between the reactions that occurred in the dark and under ambient light (Scheme 3Aa,b). When the reaction was carried out in the absence of $I_2$ and under the strong visible light irradiation of a white LED, poor yield and selectivity were observed (Scheme 3Ac). Unlike the previously reported photocatalysis of **1a,** which was performed for the aerobic oxidation of thiols under basic conditions,[15] this study was carried out under neutral conditions and was not significantly influenced by photocatalysis.



**Scheme 3** Control experiments to elucidate the effect of light irradiation and in-situ generated $H_2O_2$.
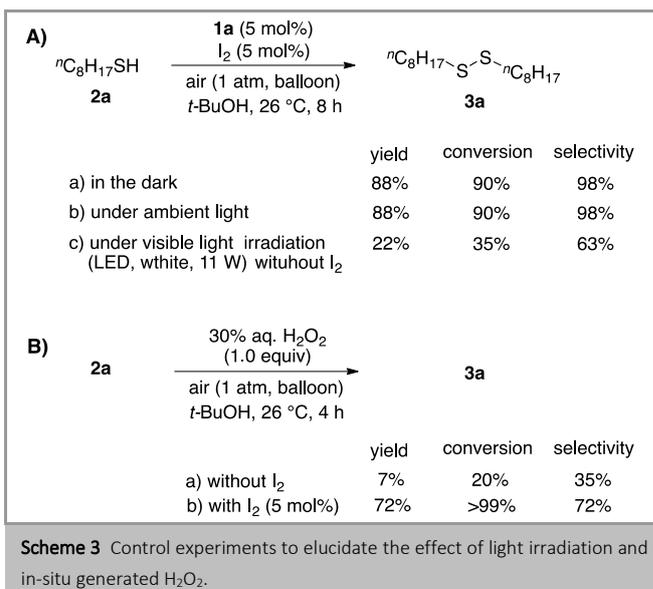
Based on the experimental results of this study and previous reports, we proposed a plausible catalytic cycle for the flavin–iodine-catalyzed aerobic oxidation of thiols, as shown in Scheme 4. Thiols are oxidized to disulfides though the formation of sulfenyl iodide (RS-I) by using $I_2$, which is accompanied by the formation of $I^-$.[20,21] Although the cationic flavinium catalyst with its relatively higher oxidation ability could directly oxidize the thiols to disulfides,[7a] the neutral flavin **1a** did not play an important role in the oxidation of thiols without $I_2$ (entry 10 of Table 1).[22] In this system, the neutral flavin **1a** functions as a redox catalyst that regenerates $I_2$ by oxidizing $I^-$ and is converted to the reduced flavin **1a$_{red}$**.[6] The in-situ generated **1a$_{red}$** is known to react with molecular oxygen and retransforming to flavin **1a** through the formation of hydroperoxyflavin **1a$_{OOH}$**, which is followed by the generation of $H_2O_2$.[23] To investigate the effect of $H_2O_2$, oxidation of **2a** using $H_2O_2$ as an oxidant was examined. In the absence of $I_2$, $H_2O_2$ could directly oxidize **2a**; however, the yield (7%) and selectivity (35%) were low (Scheme 3Ba). In contrast, the oxidation of **2a** occurred smoothly with $H_2O_2$ in the presence of a catalytic amount of $I_2$ (Scheme 3Bb). This indicates that the $H_2O_2$ generated in-situ via the flavin catalysis also participates in the oxidation of $I^-$ to give $I_2$. Thus, the present system requires only atmospheric air and discharges environmentally benign $H_2O$ as a sole byproduct, resulting in a green and selective oxidation system.



**Scheme 4** Proposed catalytic cycle for the aerobic oxidation of thiols.
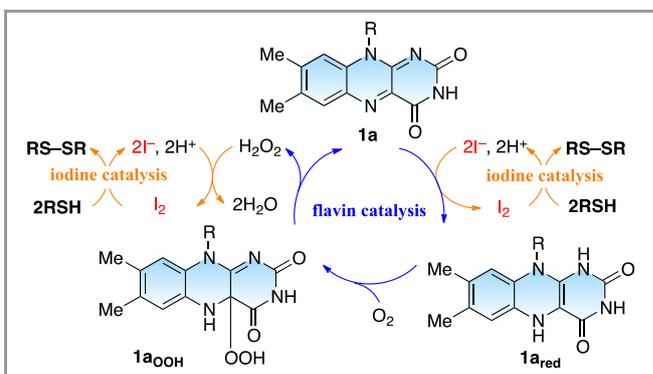
In summary, by taking advantage of flavin–iodine-coupled organocatalysis, we achieved facile and green synthesis of disulfides through the aerobic oxidation of thiols catalyzed by $I_2$ and a neutral flavin catalyst, such as readily preparable **1a** or commercially available **1b**.[24] Flavins **1a** and **1b** efficiently catalyzed the oxidative transformation of $I^-$ to $I_2$ through the activation of molecular oxygen, which promotes the oxidation of thiols to disulfides. While the previously reported **1a**-catalyzed photooxidation of thiols was carried out by visible light irradiation under basic conditions, the combination of **1a** with $I_2$ enabled the oxidation of thiols to not only proceed without light irradiation, but also be independent of the acidity of the reaction conditions; therefore, this approach could be applied to diverse thiols including those bearing amino and carboxyl groups. Furthermore, this facile and versatile methodology could be applicable to the multi-step and multi-component synthesis of diverse sulfur-containing compounds that are of importance in biological and medicinal chemistry. It would be also applicable to other chalcogenides such as selenium and tellurium.

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## Supporting Information

Yes

## Primary Data

No

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(24) **Typical Procedure for the Catalytic Aerobic Oxidation of 2a.** A mixture of **2a** (73.1 mg, 0.50 mmol), **1a** (13.6 mg, 0.025 mmol), $I_2$ (6.35 mg, 0.025 mmol), and *t*-BuOH (1.0 mL) was stirred at 26 ℃ (water bath) for 8 h under air (1 atm, balloon) in the dark. The solvent was removed using evaporation and the residue was purified via column chromatography ($SiO_2$, chloroform) to obtain **3a** (70.7 mg, 97%) as a colorless oil; the results have been summarized in Scheme 2. Characterization data of the products are described in the Supporting Information.