Coupled Flavin-Iodine Redox Organocatalysts: Aerobic Oxidative Transformation from *N*-Tosylhydrazones to 1,2,3-Thiadiazoles

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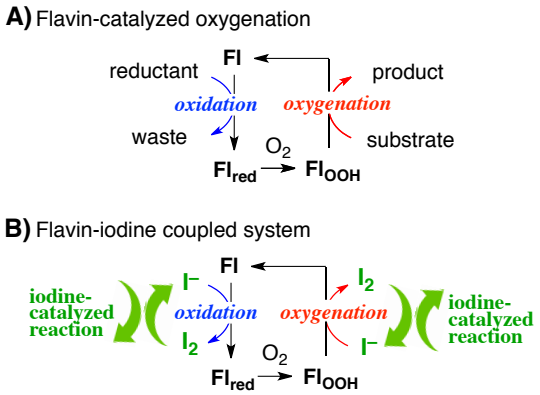
ABSTRACT: A bioinspired two-component redox organocatalyst system using 1,10-bridged flavinium and NH_4I was developed to perform environmentally friendly aerobic oxidative ring formation of 1,2,3-thiadiazoles from *N*-tosylhydrazones and sulfur. The redox organocatalysis of the flavinium promoted the iodine-catalyzed system without the use of any sacrificial reagents, except for environmentally benign molecular oxygen.

KEYWORDS: *redox organocatalyst*, *flavin*, *iodine*, *aerobic oxidation*, *thiadiazole*

The development of aerobic oxidative transformations is a major, but highly rewarding, challenge in modern chemistry because such reactions utilize ambient molecular oxygen as an easily available, inexpensive, and minimally polluting oxidant.[1] For providing environmentally friendly aerobic oxidations that fulfill the requirement of green chemistry, construction of biomimetic dual or multiple catalytic systems is recognized as one of the most promising approaches despite the difficulty.[2] Flavin catalysts, which have been developed by mimicking the functions of flavin-dependent monooxygenases, have received increasing attention as unique biomimetic redox organocatalysts that promote metal-free catalytic oxygenations through the activation of molecular oxygen.[2-4] Thus, the use of flavin-catalyzed systems is an attractive strategy for designing green and sustainable oxidative transformations using molecular oxygen as the terminal oxidant. However, examples of such strategies remain limited in spite of the potential applications evidenced by the versatile functions of flavoproteins.[4-6] Moreover, biomimetic aerobic oxygenation of various substrates generally requires sacrificial reductants (*e.g.*, hydrazine,[4a,4c,4h] zinc,[4b,4d] ascorbic acid,[4f] Hantzsch's ester,[4e] and formic acid[4g]) to convert the flavin catalyst (**Fl**) to reduced flavin ($\mathbf{Fl_{red}}$), which then generates the oxidatively active flavin hydroperoxide ($\mathbf{Fl_{OOH}}$) via O_2 activation (Scheme 1A), and a novel approach without sacrificial reductants remains a challenge.

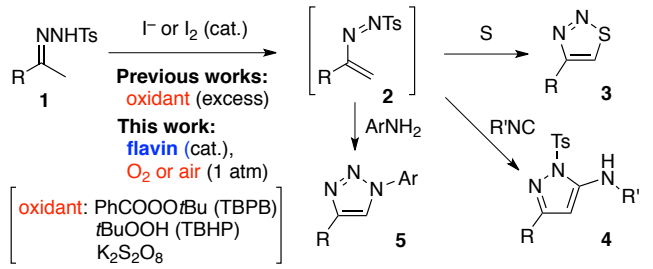
Iodine catalysts have recently drawn considerable attention as nontoxic and readily available redox organocatalysts for diverse oxidative transformations.[7] Among a series of iodine-catalyzed reactions, metal-free oxidative transformations of *N*-tosylhydrazones (**1**) with nucleophiles through azoalkene intermediates (**2**) have been demonstrated as a useful tool for the synthesis of pharmacologically important nitrogen-containing heterocyclic compounds (**3**–**5**, Scheme 2).[8] For example, the TBAI-catalyzed oxidative cyclization of **1** with sulfur in the



Scheme 1. Flavin-Catalyzed (A) Aerobic Oxygenation of Substrate Using Reductant and (B) Aerobic Oxidative Transformation of I^- to I_2

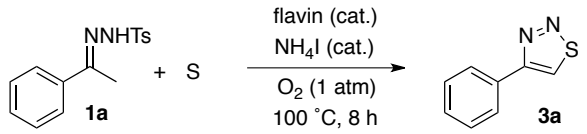
presence of $K_2S_2O_8$ gave 1,2,3-thiadiazoles (**3**),[8c] which are not only key structural moieties with bioactive and pharmacological properties,[9] but also a great source of reactive intermediates for the synthesis of diverse sulfur-containing compounds.[9a,10] Because I_2 is employed to mediate the oxidative transformations of **1** to **2**, this catalytic system requires an excess amount of oxidants, such as TBHP, TBPB, and $K_2S_2O_8$, to reoxidize *in situ* generated I^- to I_2, which is a relatively expensive process and/or generates copious amounts of waste (Scheme 2).[8] The development of a novel strategy is required to provide eco-friendly iodine-catalyzed reactions that use molecular oxygen as the terminal oxidant. We anticipated that the flavin-catalyzed aerobic oxygenation system could be applied to these iodine-catalyzed reactions to replace the stoichiometric oxidants with molecular oxygen, thus providing novel bioinspired dual catalytic system for environmentally friendly aerobic oxidative transformations (Scheme 2). As a result, green catalytic conversion from I^- to I_2 would occur without the use of any sacrificial reagents, except for molecular oxygen, by the flavin-catalyzed aerobic transformation. In this

case, flavin catalysis would provide I_2 efficiently in both the oxidation and oxygenation steps (Scheme 1B). In other words, I^- plays the dual role of reductant in the oxidation step and substrate in the oxygenation step.



Scheme 2. Previous and Present Approaches to Iodine-Catalyzed Oxidative Transformations of 1

Table 1. Screening of Flavin Catalysts[a]



entry	flavin	sulfur (equiv)	yield (%)[b]
1	**6a**	10	46
2	**6b**	10	42
3	**7•TfO**	10	48
4	**8•Cl**	10	63
5	**8•TfO**	10	37
6[c]	**8•Cl**[d]	1.2	82
7[c,e]	**8•Cl**[d]	1.2	18
8[c]	None	1.2	7

[a]Reactions of **1a** were carried out in DMAc-pyridine (0.2 M, 49:1, v/v) in the presence of flavin (10 mol%), NH_4I (20 mol%), and sulfur at 100 °C for 8 h under O_2 (1 atm). [b]Yields were determined by ^1H NMR spectroscopy using 1,1,2,2-tetrachloroethane as an internal standard. [c]DMAc-pyridine (0.5 M, 19:1, v/v) and NH_4I (10 mol%) were used as the solvent and iodine source, respectively. [d]5 mol%. [e]Under N_2.

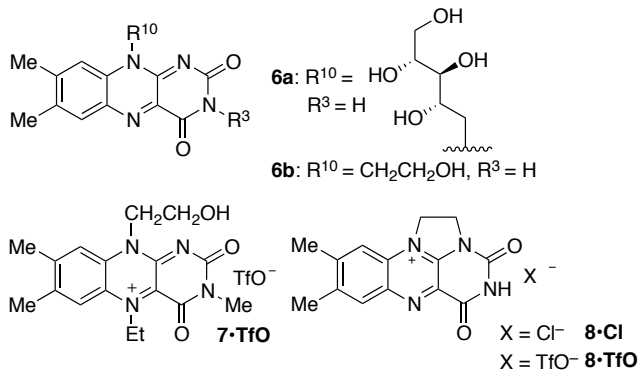


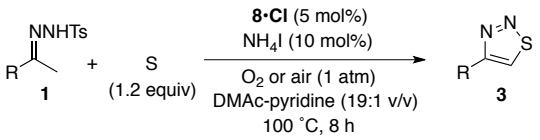
Chart 1. Structures of Flavin Catalysts

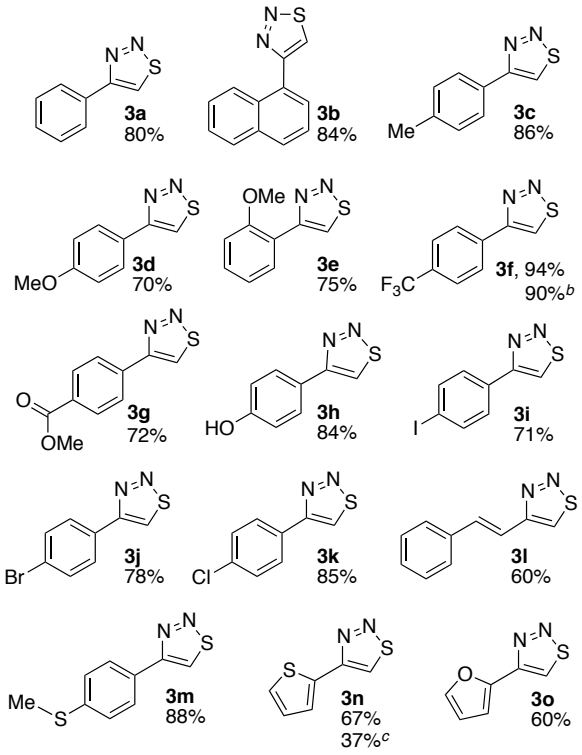
We initially investigated the catalytic activity of various flavins for the reaction of acetophenone tosylhydrazone (**1a**) with sulfur in the presence of NH_4I in DMAc under molecular oxygen (1 atm) at 100 °C for 8 h. Novel 1,10-bridged alloxazinium chloride and triflate (**8•Cl** and **8•TfO**) were readily synthesized through the reaction of $SOCl_2$ and **6b**, which can be prepared from commercially available riboflavin (**6a**) via two steps (Chart 1, Supporting Information).[4g] All of the flavins (**6**–**8**) were tolerated under these reaction conditions and successfully promoted aerobic oxidative ring formation to give the desired 1,2,3-thiadiazole (**3a**) in 42–63% yields (Table 1, entries 1–4). Among them, we chose the 1,10-bridged alloxazinium salt (**8•Cl**) as the best from the viewpoint of catalytic efficiency. An examination of 10 solvents (Supporting Information, Table S1) revealed the best efficiency in DMAc-pyridine (49:1, v/v). Attempts using various iodine sources revealed that NH_4I gave the highest yield, whereas no reaction occurred without an iodine source (Table S1). Further optimization of the reaction conditions revealed that the present flavin-iodine-catalyzed system was successful with only 1.2 equiv of sulfur in the presence of 5 mol% of **8•Cl** and 10 mol% of NH_4I in DMAc-pyridine (19:1, v/v, entry 5). Presumably, the slow generation of the oxidatively active peroxide (**Fl$_{OOH}$**) results in an atom-economical process because it circumvents the problems of sulfur consumption and/or easily oxidizable reaction intermediates, which occur in conventional processes using a stoichiometric amount of oxidant. Control experiments were performed to gain additional insight into the mechanism. Reactions under a N_2 atmosphere or in the absence of the flavin catalyst gave poor yields (entries 6 and 7, respectively), indicating that flavin-catalyzed O_2 activation plays an essential role in the reaction.

Given these results, we next explored the substrate scope of tosylhydrazones using the optimized reaction conditions (Table 2). A variety of tosylhydrazones were found to display comparable reactivity and afforded good yields of 1,2,3-thiadiazoles. The oxidative ring formation was applicable for substrates bearing both electron-donating and electron-withdrawing groups on the phenyl ring (**3c**–**3f**), and ring formation under air (1 atm) also proceeded smoothly. The reaction tolerated a range of functional groups such as ester, hydroxy, iodo, bromo, and chloro groups to produce **3g**–**3k**. The reaction of tosylhydrazone bearing an alkene functionality also occurred without transformation of the alkene, giving the corresponding product **3l** in 60% yield. Interestingly, the thio functionality was well-tolerated; that is, **3m** was produced in 88% yield even though sulfides are known to be easily converted to sulfoxides under oxidative conditions.[11] Apparently, oxygenation of I^- occurs preferentially to that of the thio functionality, leading to intriguing chemoselectivity.[12] 1,2,3-Thiadiazoles bearing thienyl and furanyl groups (**3n** and **3o**) were isolated in 67 and 60% yields, respectively, whereas the stoichiometric reaction of **1n** with I_2 (1.2 equiv) gave **3n** in a relatively lower 37% yield.

The flavin-catalyzed aerobic oxidation of I^- was then investigated by following the absorption spectral changes of HI in DMAc at 80 °C under air (Supporting information, Figure S1). In the presence of **8•TfO**, which has better solubility than **8•Cl**, the absorption signals centered at approximately 296 and 366 nm increased with time. We assign these signals to I_3^- species generated from I_2 through the dynamic equilibrium between I_2 and I_3^- (Figure S1 (a, b, and d–h)).[13] A similar spectral change was observed during the stoichiometric oxidation of I^- with

Table 2. Substrate Scope of the Flavin-Iodine-Catalyzed System.[a]



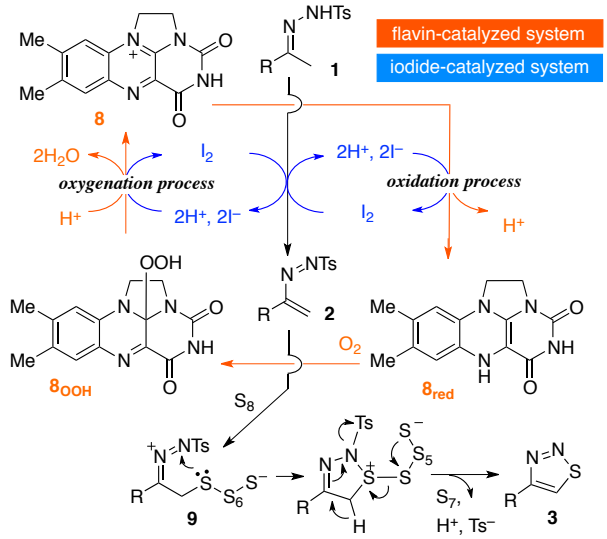


[a]Reactions of **1** were performed in DMAc-pyridine (0.5 M, 19:1, v/v) in the presence of **8•Cl** (5 mol%), NH_4I (10 mol%), and sulfur (1.2 equiv) at 100 ˚C for 8 h under O_2 (1 atm). [b]Under air (1 atm). [c]Reaction was performed in DMAc-pyridine (0.5 M, 19:1, v/v) in the presence of I_2 (1.2 equiv) and sulfur (1.2 equiv) at 100 ˚C for 8 h under N_2.

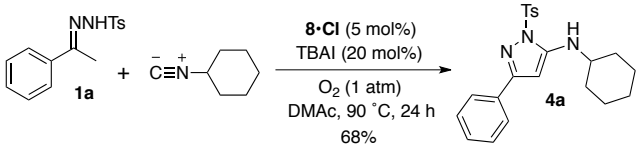
TBHP (Figure S2). In contrast, hardly any spectral changes occurred in the absence of **8•TfO** (Figure S1 (b and c)).

Based on these experimental results and previous reports,[8] a plausible mechanism for flavin-iodine-catalyzed aerobic oxidative ring formation of 1,2,3-thiadiazoles from tosylhydrazones is proposed in Scheme 3. In the presence of I_2, tosylhydrazone **1** is oxidatively converted to give corresponding azoalkene **2**, H^+, and I^- through α-iodation of **1** and subsequent HI elimination of α-iodo hydrazine. After the addition of S_8, which is a main allotrope of molecular sulfur, to **2**, cyclization of zwitterionic **9** and subsequent elimination of S_7 and TsH give the desired product, 1,2,3-thiadiazole **3** product.[8c] Flavin catalyst **8** facilitates the oxidation of I^- to give I_2 and reduced flavin $\mathbf{8}_{red}$, which activates molecular oxygen to give hydroperoxyflavin $\mathbf{8}_{OOH}$. Then, catalytically generated $\mathbf{8}_{OOH}$ participates in the oxygenation of I^- to give I_2, **8**, and environmentally benign H_2O via the generation of IO^-.[14,15] Thus, I_2 can be efficiently regenerated by both oxidation and oxygenation of I^-, which is mediated by the flavin-catalyzed system through the use of molecular oxygen as the terminal oxidant.

In one final example, we show that the present flavin-iodine-catalyzed system is capable of realizing cross-coupling of **1a** and isocyanide to yield 5-aminopyrazole **4a** (Scheme 4),[16] which was previously achieved using a stoichiometric amount of TBHP as a terminal oxidant (Scheme 2).[8b] Although the reaction efficiency was moderate, this preliminary



Scheme 3. Proposed Mechanism for the Flavin-Iodine-Catalyzed Aerobic 1,2,3-Thiadiazole Ring Formation



Scheme 4. Flavin-Iodine-Catalyzed Aerobic Cross-Coupling of 1a and Isocyanide

result clearly suggests the potential versatility of the present flavin-iodine-catalyzed system.

In conclusion, we have developed a unique flavin-iodine-catalyzed system for chemoselective, metal-free aerobic oxidative ring formation of 1,2,3-thiadiazoles bearing various functionalities from *N*-tosylhydrazones and sulfur. The present aerobic two-component organocatalyst system is applicable not only to diverse iodide-catalyzed transformations that have conventionally required stoichiometric oxidants, but also for the development of unprecedented green transformations utilizing molecular oxygen. Further studies using this strategy are currently underway in our laboratory.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and NMR spectra of novel compounds and products

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(11) The flavin-catalyzed system is also known to promote the oxidation of sulfides to sulfoxides, see refs. 3.

(12) The chemoselectivity was also supported by the fact that the reaction of **1a** in the presence of methylphenylsulfide (1 equiv) gave **3a** in 71% yield without the generation of methylphenylsulfoxide (Scheme S2, Supporting Information).

(13) Because the spectral changes were measured during the initial stage of the reaction (<10% yield) where an excess amount of I^- exists, the generated I_2 was almost quantitatively converted to I_3^- through the dynamic equilibrium between I_2 and I_3^-. (a) Awtrey, A. D.; Connick, R. E. *J. Am. Chem. Soc.* **1951**, *73*, 1842-1843; (b) Gottardi, W. *Arc. Pharm.* **1999**, *332*, 151-157; (c) Gottardi, W. In *Iodine Chemistry and Applications*; Kaiho, T. Ed.; John Wiley & Sons, Inc.: New Jersey, 2015, p 375.

(14) The stoichiometric oxygenation of I^- to I_3^- via IO^- with the analogous hydroperoxyflavin has been reported. Bruice, T. C.; Noar, J. B.; Ball, S. S.; Venkataram, U. V. *J. Am. Chem. Soc.* **1983**, *105*, 2452-2463.

(15) There may be another possibility; Through the dynamic equilibrium, $\mathbf{8_{OOH}}$ forms **8** and H_2O_2 which may also participate in the oxygenation of I^- to give I_2. The contribution of the in-situ generated H_2O_2 could not be thoroughly ruled out, although the oxidation ability of flavin hydroperoxide is 10^4 times stronger than H_2O_2 (ref. 14). In fact, H_2O_2 promoted the present ring formation in the absence of the flavin catalyst although the yield was moderate (Scheme S3, Supporting Information).

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