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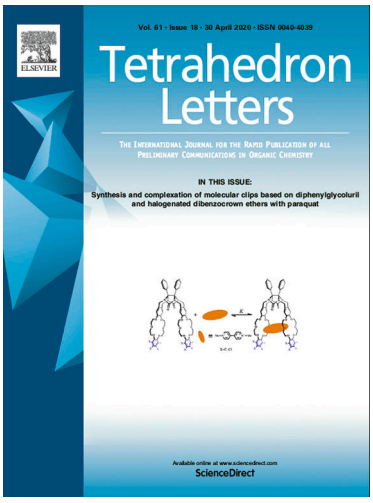

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Flavin/I_2 Catalyzed Aerobic Oxidative C-H Sulfenylation of Anilines

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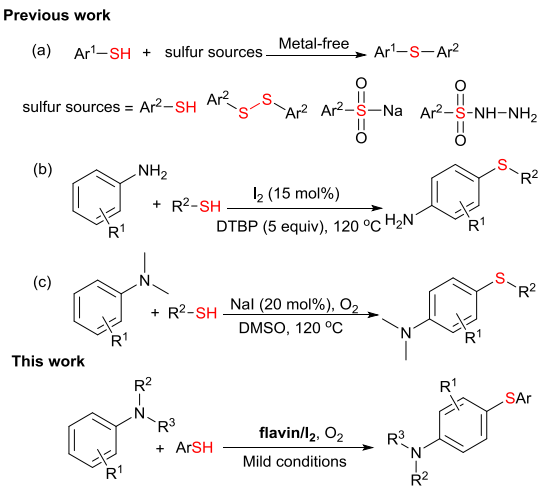
ABSTRACT

A flavin/I_2 catalyzed aerobic oxidative C-H sulfenylation of anilines with thiols under mild reaction conditions is presented for the first time. This metal-free reaction provides an atom-economic pathway to prepare various aryl sulfides with outstanding functional group compatibility. Moreover, it consumes molecular oxygen as the only terminal oxidant and produces environmentally-friendly H_2O as the only byproduct.

Introduction

Aryl sulfides are crucial building blocks that exist in pharmaceutical intermediates,[1] polymer materials,[2] and semiconductor material.[3] Therefore, the research on efficient construction of these valuable motifs has attracted extensive attention.[4] Traditionally, aryl sulfides have been synthesized by reacting stoichiometric organozinc[5] or Grignard reagents[6] with aryl halides, or cross-coupling of thiols/disulfides with aryl halides in the presence of catalysts of transition metals such as Fe,[7] Pd,[8] Co,[9] Cu,[10] Ni,[11] and Rh.[12] In recent times, direct C–H thiolation of arenes was also extensively explored to synthesize diaryl sulfides.[13] Despite abundant advantages, these methodologies still encounter certain limitations, including the need for arranging sophisticated setup for handling expensive/air-sensitive catalysts and harsh reaction conditions. Besides, owing to the low threshold residual tolerance of metals in the pharmaceutical industry and materials science,[14] there is an increasing demand for metal-free reactions for C-S bond formation. Recently, many disulfides,[15] sodium arylsulfinates,[16] and sulfonylhydrazides[17] have been developed for the sulfenylation of electron-rich arenes under metal-free conditions (Scheme 1a). Though direct dehydrogenative C-H/S-H cross-coupling is a more attractive approach for constructing a C-S bond, it is hindered by the vulnerable structure of sulfide which is prone to over-oxidization to sulfoxides/sulfones.[18] In 2015, Wang group [19] reported the formation of diaryl sulfides under the I_2/peroxides system (Scheme 1b). In 2017, Wang and co-workers[20] discovered that oxygen could be used as a green oxidant to furnish cross-coupling of *N*,*N*-dimethylanilines and aryl thiols with 20 mol% of NaI at 120 °C (Scheme 1c). In spite of such advantages, these protocols were still largely limited by excessive use of explosive peroxides, harsh reaction conditions and limited substrate scopes, such as amino group protected anilines. Hence, it is still a challenging task to develop a versatile protocol which fits in all the desired conditions for mild synthesis of diaryl sulfides via C-H/S-H cross-coupling of arene and aryl thiols. Inspired by Murahashi[21] and Iida's[22] pioneering work on flavin catalysts as well as our ongoing research on C-H functionalization and heterocyclic chemistry,[23] herein, we report a flavin/I_2 catalyzed system for aerobic oxidative C-H bond sulfenylation of anilines with thiols.



Scheme 1. Different protocols for the synthesis of diaryl sulfides.

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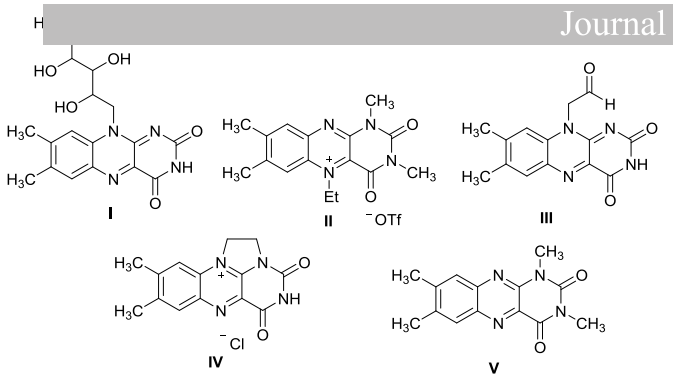


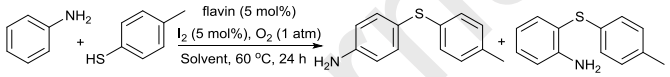
Fig 1. Structures of flavins and flavinium salts.

Results and discussion

Initially, aniline **1a** and 4-methylbenzenethiol **2a** were selected as the model substrates for optimizing the reaction conditions (Table 1). Action of different flavin catalysts were investigated under the oxygen atmosphere at 60 °C for 24 h with 5 mol % of iodine as cocatalyst and acetonitrile (0.5 mL) as the solvent (entries 1-5). Flavin II catalyzed the formation of 4-(*p*-tolylthio)aniline **3a** in 85% yield, with 9% of the corresponding *ortho*-substituted product **3a**' (entry 5). In the next phase of optimization of reaction conditions, different solvents such as DMSO, DMF, and TFE were screened, but all of those gave **3a** in lower yields (entries 6–8). Decreasing or elevating the reaction temperature did not enhance the yield (entries 9 and 10). Finally, iodide sources such as KI or NIS were also tested, but both gave inferior results (Table 1, entries 12 and 13). Thus, the optimized reaction conditions were established as: **1a** (1.0 mmol), **2a** (0.5 mmol), flavin II (5 mol %), and I_2 (5 mol %) in CH_3CN (0.5 mL) under O_2 atmosphere at 60 °C for 24 h.

With the optimized reaction conditions in hand, a range of thiophenols were employed for coupling with aniline, which yielded the corresponding products in moderate to excellent yields (Table 2). Thiophenols containing electron-donating (Me, MeO, Ph, and NH_2) and electron-withdrawing groups (F, Cl, and

Table 1.
Optimization of reaction conditions.



Entry[a]	catalyst	solvent	yield of **3a** (%)[b]	yield of **3a**' (%)[b]
1	I	CH_3CN	NR	NR
2	**II**	**CH_3CN**	**84 (85)[c]**	**9 (9)[c]**
3	III	CH_3CN	50	6
4	IV	CH_3CN	35	9
5	V	CH_3CN	NR	NR
6	II	DMSO	15	4
7	II	DMF	51	7
8	II	TFE	37	8
9[d]	II	CH_3CN	36	3
10[e]	II	CH_3CN	88	10
11[f]	II	CH_3CN	80	8
12[g]	II	CH_3CN	49	11
13[h]	II	CH_3CN	83	9

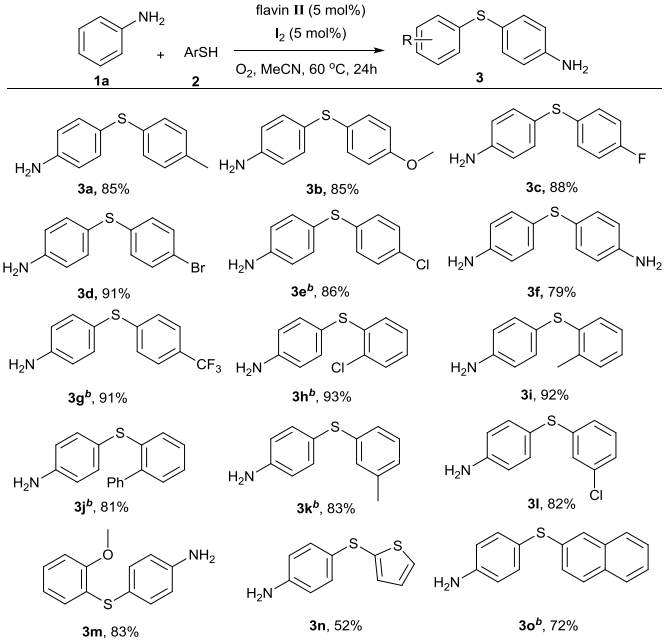
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), solvent (0.5 mL) at 60 °C for 24 h with O_2 atmosphere. [b] Yield determined by NMR with mesitylene as internal standard. [c] Isolated yield. [d] 40 °C. [e] 80 °C. [f] Under air. [g] KI instead of I_2. [h] NIS instead of I_2. NR = no reaction.

reacted smoothly with aniline **1a** to afford **3a**−**3m** in 79−93% yields. Notably, the brominated thiophenol gave the corresponding product **3d** in 91% yield, offering possibilities for further functionalization. Moreover, this reaction was not only limited to phenyl substrates, but heterocycles such as 2-thiophenethiol gave **3n** in 52% yield. The versatility of this reaction also displayed good functional group compatibility for 2-naphthalenethiol, furnishing **3o** in 72% yield.

In the next stage, the substituents on nitrogen were examined (**4a**-**4h** and **4s**, Table 3). When one of the hydrogens of the amino group was substituted by a single methyl group, the desired products **4a**-**4d** were obtained in good yields, disregarding the electronic property of the substituents on thiophenols. Besides, 2-thiophenethiol and 2-naphthalenethiol were also well-tolerated, giving the corresponding coupling products **4e** and **4f** in 67% and 85% yields respectively. In sharp contrast, acetyl aniline was ineffective in this reaction. The *N*,*N*-disubstituted anilines, however, gave the desired products **4g** and **4s** in slightly lower than expected yields. It is worth noting that the arythiation could occur at the *ortho* site of an amino group when the *para* position was occupied by a substituent, thereby giving the corresponding product in low yield (44%). This might be due to the steric hindrance effect at the *ortho* position. As for *ortho*-substituted anilines, the substrates containing electron-donating groups (Me, Et, and MeO) (**4j-4m**) showed higher reactivity than those with electron-withdrawing groups (**4n** and **4o**). To our delight, substrates with bulky substituents at *ortho*-site of an amino group (**1p** and **1s**) could also afford the corresponding products **4p** and **4s** in 80% and 64% yields, respectively. Moreover, $CONH_2$ and CO_2Et substituted anilines require longer reaction time owing to deactivated substrates caused by the substitution of electron withdrawing groups and gave the corresponding products **4t** and **4u** in 40% and 36% yields, respectively. Furthermore, NO_2 and CN substituted anilines were also tested, but did not afford the desired products.

To gain insight into the reaction mechanism, a series of

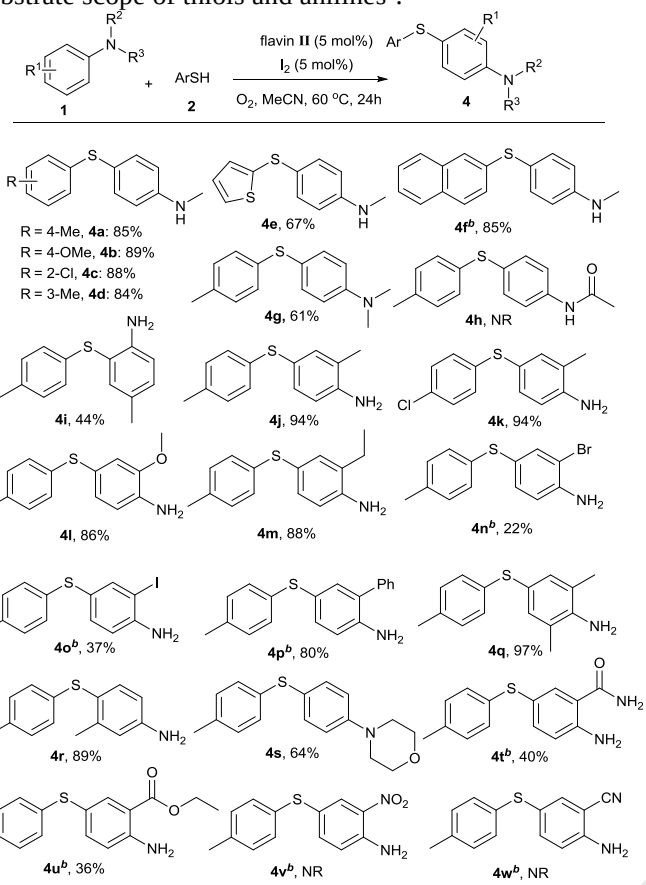
Table 2.
Substrate scope of thiols[a].



[a] Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), flavin **II** (5 mol%), I_2 (5 mol%), and MeCN (0.5 mL) at 60 °C for 24 h under O_2 atmosphere. [b] Reaction time (30 h).

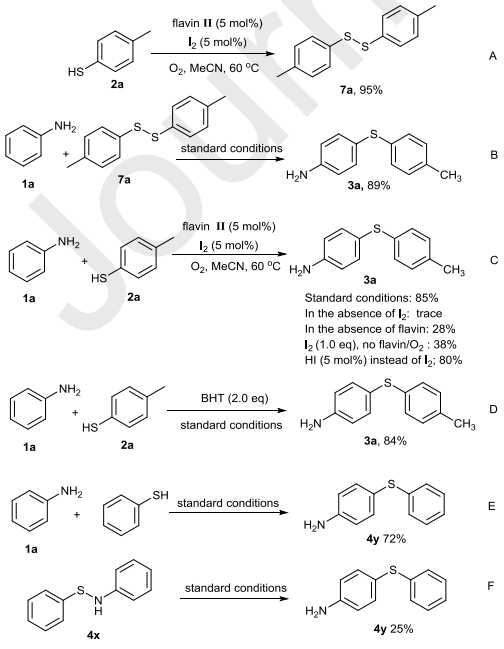
Tab

Substrate scope of thiols and anilines[a].

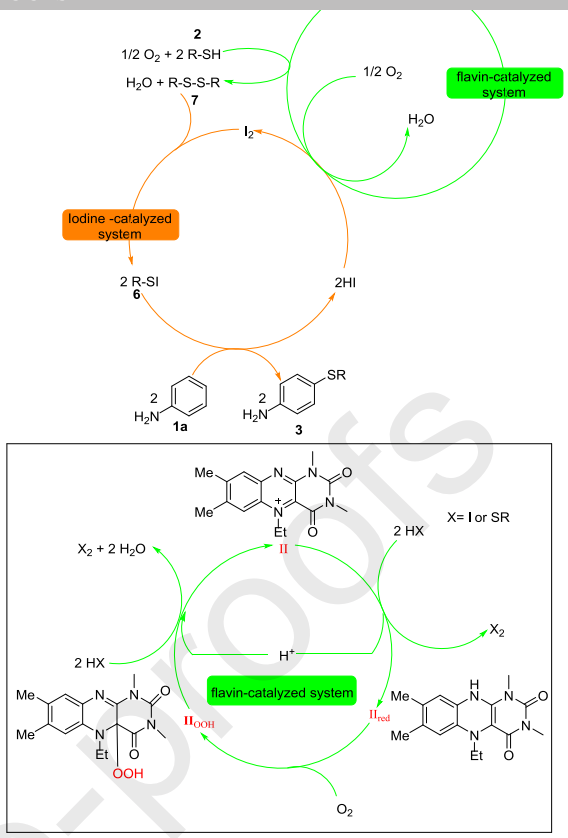


[a] Reaction conditions: **1** (1.0 mmol), **2** (0.5 mmol), flavin **II** (5 mol%), I_2 (5 mol%), and MeCN (0.5 mL), at 60 °C for 24 h under O_2 atmosphere. [b] Reaction time (30 h). NR = no reaction.

control experiments were conducted (Scheme 2). Firstly, 4-methylbenzenethiol **2a** could be easily oxidized by oxygen to diphenyl disulfide **7a** in the absence of aniline (Scheme 2A). Secondly, the reaction of **7a** and aniline **1a** forms the desired product **3a** in 89% yield under standard conditions (Scheme 2B). These results indicated that diphenyl disulfide might be the intermediate of this transformation. Thirdly, compared to the



Scheme 2. Control experiments



Scheme 3. Proposed mechanism for flavin/I_2 catalyzed aerobic oxidative C-H sulfenylation of anilines.

standard conditions, the reaction yield significantly decreased in the absence of either iodine, flavin catalyst**,** or oxygen. In addition, 38% of **3a** formed by using 1 equivalent of iodine without flavin and oxygen. When HI was used instead of iodine, the yield of **3a** slightly decreased to 80%. These results indicated that flavin/I_2 catalyst system played a significant role in this reaction (Scheme 2C). Moreover, addition of a radical scavenger butylated hydroxytoluene (BHT) to the reaction, gave the ideal product **3a** in 84% yield under standard conditions, which ruled out the likelihood of a radical mechanism (Scheme 2D). Thus, we concluded that an *in situ* generated sulfenyl iodide is the crucial intermediate in this reaction, and in the presence of flavin **II** catalyst, oxygen can continuously oxidize I^- to I_2 to complete the catalytic cycle. Last but not the least, sulfenyl iodide might first form arenesulfenanilides, which then underwent rearrangement to generate desired products according to theoretical calculation.[24] Arenesulfenanilide **4x** was then synthesized[25] and reacted under standard conditions to gave arrangement product **4x** in 25% yield, which is much lower than the 72% yield of reaction of aniline **1a** and thiophenol (Scheme 2E and 2F). In addition, *N*,*N*-disubstituted anilines could also produce the desired products (**4g** and **4s**) in moderate yields (Table 3). Therefore, we excluded the likelihood of arenesulfenanilide to be an intermediate of this reaction.

Based on the previous reports [26, 24]and the control experiments performed herein, a plausible mechanism for this reaction is proposed (Scheme 3). Initially, the thiophenol **2** is converted to diphenyl disulfide **7** by flavin-catalyzed oxidation reaction.[22b-d] Then, the aryl disulfide **7** reacts with I_2 to form aryl sulfenyl iodide **6**, which then undergoes attack by aniline **1a** to produce the desired product **3** and HI as the byproduct. The latter is subsequently oxidized by the flavin-catalyzed system when it enters the next catalytic cycle. In the flavin-catalyzed

syst 42

aerobic conditions to produce the disulfide and I_2 along with simultaneous generation of flavin $\mathbf{II_{red}}$. Next, the reductive flavin $\mathbf{II_{red}}$ is oxidized to hydroperoxyflavin $\mathbf{II_{OOH}}$ by oxygen. Finally, $\mathbf{II_{OOH}}$ could also promote the oxidation of thiol and HI, and at the same time, itself got reduced to flavin **II** to complete the cycle.[21] Therefore, the overall reaction consumes oxygen and produces H_2O as the only byproduct.

Conclusions

In conclusion, we report an aerobic oxidative C-H sulfenylation of anilines with thiols catalyzed by flavin/I_2 for the first time. This metal-free reaction uses molecular oxygen as the only terminal oxidant and produces environmentally-friendly H_2O as the only byproduct. Furthermore, the reaction was performed successfully under mild conditions with high atom-economy and excellent functional group compatibility. Further research on the practical applications of this method is in progress in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal

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the work reported in this paper.

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

conditions.

2. It consumes oxygen as the terminal oxidant and produces H_2O as the byproduct.
3. It features broad functional group tolerance and good to excellent yields.

Graphical Abstract

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1. A flavin/I_2 catalyzed C-H

Flavin/I_2 Catalyzed Aerobic Oxidative C-H Sulfenylation of Anilines

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Xinpeng Jiang, Zhifeng Shen, Cong Zheng, Liyun Fang, Keda Chen, and Chuanming Yu*