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Sustainable and practical semi-heterogeneous photosynthesis of 5-amino-1,2,4-thiadiazoles over WS_2/TEMPO

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ABSTRACT

An eco-friendly and practical method for the clean preparation of 5-amino-1,2,4-thiadiazoles was developed. With WS_2 as the semiconductor photocatalyst, both TEMPO and O_2 (in air) as the redox catalysts, a variety of thiadiazoles were semi-heterogeneously formed in high to quantitative yields and could be easily collected by CPME extraction and rinsing. Furthermore, the catalytic system can be reusable for at least 5 reaction runs.

Visible-light induced catalysis has emerged as an efficient tool in green chemistry, which provides mild and eco-friendly conditions for promoting various functional-group transformation [1–4]. During the past decades, significant achievements have been made in both homogeneous [5,6] and heterogeneous photocatalysis [7–9]. Compared to homogeneous counterparts [10–20], heterogeneous photocatalysts [21–27] have many advantages, such as the easy separation and good recyclability, but suffer from low catalytic performance, therefore, the homogenization of heterogeneous catalysts is expected to be the key to improve catalytic performance and the merger of homogeneous and heterogeneous photocatalysis would be the optimal one. Tungsten disulfide (WS_2), as inexpensive and readily available poly semiconductor photocatalysts, possessing virtues such as excellent chemical stability and good reusability [28,29]. However, the fast recombination of photogenerated carriers has a significant influence on its catalytic activity. Recently, redox catalyst mediated semiconductor photocatalysis has shown the potential in solving the problem above [30–34]. Despite the concerted catalysis strategy can effectively improve the photocatalytic performance of semiconductor photocatalyst, examples of redox catalyst mediated photocatalysis are still limited.

The 1st principle of Anastas' Green Chemistry is that it is better to prevent waste than to treat or clean up waste after it has been created [35]. However, the organic reactions often require tedious chromatographic separations to remove side-products and impurities, thus lengthening the synthetic sequence and producing organic wastes, contravening this principle. In 2020, Zimmerman and Anastas proposed that the material- and energy-consuming isolation and purification of the synthesized products is one of the core principles of future green chemistry [36]. Considerable efforts have been made to design and develop novel eco-friendly synthetic methods in line with the above-mentioned principles in recent years [37–39].

Thiadiazoles represent a class of five-membered *N*-heterocycles which are present in numerous natural products, small-molecule drugs and functional materials [40,41]. Among various thiadiazole derivatives, 5–amino-1,2,4-thiadiazoles have attracted great attention since they exhibit interesting biological and pharmacological functions. The classical one-step synthetic methods to such molecules depend on the homogeneous oxidative [3 + 2] annulation of amidine hydrochlorides with isothiocyanates (Scheme 1) [42,43]. From an eco-friendly and economic point of view, those procedures suffer from some drawbacks, such as the use of transition metal catalysts, high reaction temperature, excessive reactants, and tedious purification procedures. Therefore, developing environmentally friendly and practical synthetic methods for 5–amino-1,2,4-thiadiazoles is highly desirable. As part of our ongoing efforts in developing green synthesis chemistry [44–49], we herein report the semi-heterogeneous photosynthesis of 5–amino-1,2,4-thiadiazoles from amidine hydrochlorides with isothiocyanates over WS_2/TEMPO. Notably, the desired products can be

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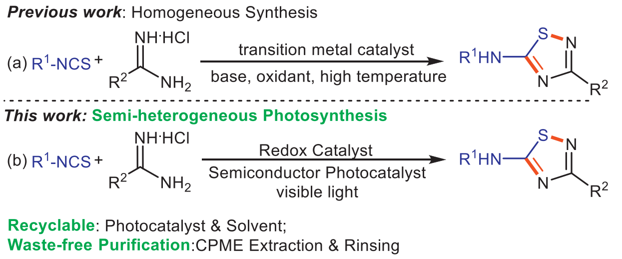
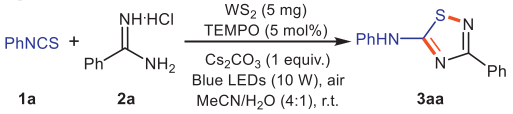


Scheme 1. The synthesis of 5–amino-1,2,4-thiadiazoles.

Table 1
Optimization of reaction conditions.[a]



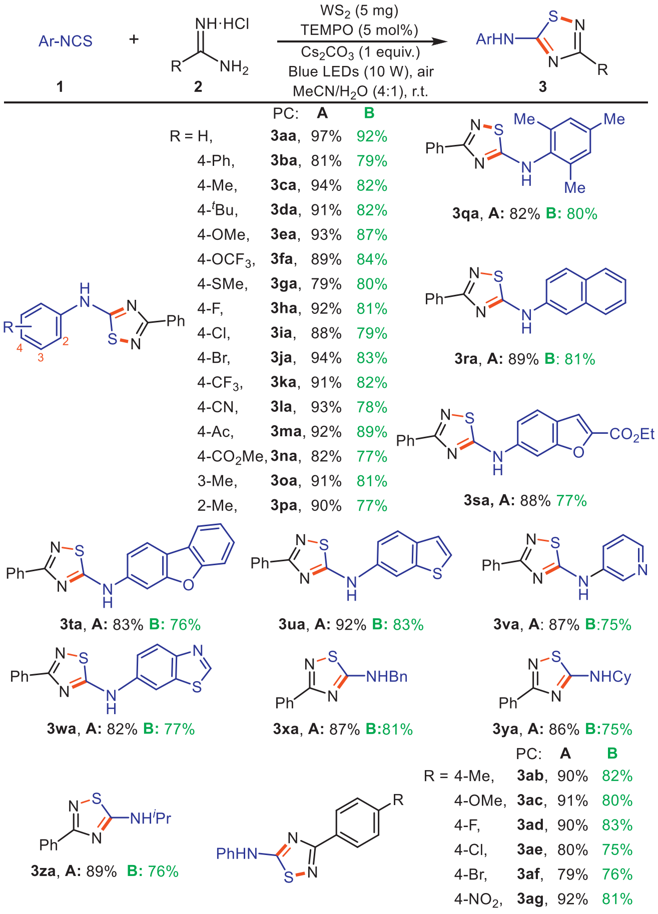
Entry	Variation from the standard reaction conditions	Yield (%)[b]
1	None	99
2	g-C_3N_4, α-Fe_2O_3, CdS instead of WS_2	56, 64, 70
3	WO_3, WSe_2, WC_2 instead of WS_2	83, 72, 41
4	Without semiconductor photocatalyst	Trace
5	NHPI, NPh_3 instead of TEMPO	67, 39
6	KI instead of TEMPO	21
7	Without redox catalyst	33
8	Purple LED instead of blue LED	68
9	Green LED instead of blue LED	74
10	White LED instead of blue LED	77
11	LEDs (6 W), LEDs (8 W) instead of LEDs (10 W)	41, 68
12	$MeCN/H_2O$ (3:1) instead $MeCN/H_2O$ (4:1)	67
13	$MeCN/H_2O$ (5:1) instead $MeCN/H_2O$ (4:1)	75
14	MeCN instead $MeCN/H_2O$ (4:1)	62
15	N_2 instead of air	Trace
16	Without light	Trace

[a] Conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), WS_2 (5 mg), TEMPO (5 mol%), Cs_2CO_3 (0.2 mmol), $MeCN/H_2O$ (4:1, 4 mL) under irradation with 10 W Blue LEDs in air for 14 h.

[b] Yield estimated by GC with dodecane as the internal reference.

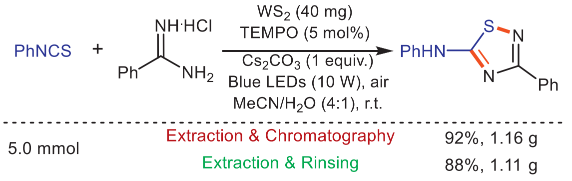
easily collected by CPME extraction and rinsing without chromatographic purification.

Initially, phenyl isothiocyanate (**1a**) and benzimidamide hydrochloride (**2a**) were chosen as the template substrates to optimize the reaction conditions. Upon investigating various reaction parameters, the best results were obtained by performing the semi-heterogeneous reaction of **1a** and **2a** with WS_2 as the semiconductor photocatalyst, TEMPO as the redox catalyst, Cs_2CO_3 as the base and $MeCN/H_2O$ (4:1) as the solvent in air at ambient temperature under the irradiation of 10 W blue LEDs. In this case, the desired thiadiazole **3aa** was generated with a quantitative GC yield (Table 1, entry 1). Varying the semiconductor photocatalysts did not provide the improved yield of **3aa** (entries 2 and 3). In the absence of any semiconductor photocatalyst, trace amount of **3aa** was detected (entry 4). Replacing TEMPO with other redox catalysts led to inferior reaction efficiencies (entry 5). Conducting the reaction with KI as the redox catalyst only gave 21% yield of **3aa** and most of the starting materials were un-reacted (entry 6). Without any redox photocatalyst, a 33% yield of **3aa** was formed (entry 7). Performing this transformation with other visible-light sources, such as purple LEDs, green LEDs and white LEDs gave lower yield of **3aa** (entries 8–10). Reducing the power of the blue LEDs to a decreased yield of **3aa** (entry 11). Varying the volume ratio of MeCN aqueous solution or conducting the reaction with anhydrous MeCN resulted in reduced reaction efficiencies (entries 12–14). No reaction occurred under a nitrogen atmosphere or in the absence of visible light (entries 15 and 16).



Scheme 2. Substrate scope. Conditions A: **1** (0.4 mmol), **2** (0.4 mmol), WS_2 (5 mg), TEMPO (5 mol%), Cs_2CO_3 (0.4 mmol), $MeCN/H_2O$ (4:1, 7 mL) under irradiation with 10 W Blue LEDs in air, isolated yields by chromatographic separations. Conditions B: **1** (0.4 mmol), **2** (0.4 mmol), WS_2 (5 mg), TEMPO (5 mol%), Cs_2CO_3 (0.4 mmol), $MeCN/H_2O$ (4:1, 7 mL) under irradiation with 10 W Blue LEDs in air, isolated yields by CMPE extraction and rinsing.

With the optimal reaction conditions in hand (Table 1, entry 1), the scope of our method was tested by investigating various isothiocyanates and benzimidamide hydrochlorides. As shown in Scheme 2, no matter whether the benzene ring of phenyl isothiocyanate was substituted with either neutral, electron-rich, electron-deficient or sterically hindered groups, all of them gave the target products in excellent yields (**3aa**-**3pa**). Both bulky mesityl isothiocyanate and naphthyl isothiocyanate were also well tolerated to provide the desired products (**3qa** and **3ra**) in high yields. It was worth noting that the isothiocyanate substrates with *O*-, *S*-, *N*-heterocyclic ring were also compatible with this process, generating the target products (**3sa**-**3wa**) in 82%–92% yields. In addition, the present method could also be applied for benzylic and aliphatic isothiocyanates yielding thiadiazoles (**3xa**-**3za**) with excellent yields. No desired product was observed when butylamidine hydrochloride was used as the substrate. Next, a series of benzimidamides reacted with **1a** to afford the desired products in high yields. Both electron-rich and electron-deficient groups on the aromatic ring of **2** were compatible under same reaction conditions. All the reported synthetic methods for thiadiazole require tedious and somewhat complicated column chromatographic purification, resulting in the inevitable formation of large amounts of chemical waste. In addition, column chromatographic purification could be difficult to scale up as well as be cost-prohibitive to perform on a large scale. To demonstrate the practicality of the developed protocol, the semi-heterogeneous reactions were performed

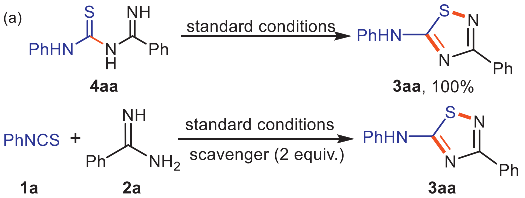


Scheme 3. Large-scale synthesis of **3aa**.

in 0.4 mmol scale. To our delight, in the 0.4 mmol-scale synthesis, the pure thiadiazoles can be easily obtained by eco-friendly cyclopentyl methyl ether (CPME) extraction and rinsing.

To further prove the utility of this method, both the gram-scale synthesis and the catalytic system circulation experiment were carried out. Firstly, the template reaction was scaled up to 5 mmol, and 1.16 g of **3aa** was readily collected (Scheme 3). Second, the reusability of catalytic system was investigated. After completion of the catalytic process, the product was extracted by CPME and the mixture of **1a**, **2a**, TEMPO and Cs_2CO_3 were freshly added into the mother liquor for the next catalytic cycle. Upon 5 successive reaction runs, comparable yields were still maintained, as shown in Fig. 1a. By comparison of XRD data between WS_2 before (black line) and after (red line) reaction with standard data of WS_2 (blue line), it was found that there was basically no difference before and after reaction (Fig. 1b). In addition, the reactions were conducted with a range of wavelengths of LEDs. The results suggested that there was no linear relationship between the wavelength of LEDs and the reaction efficiency (Supporting information).

To probe the mechanism of the semi-heterogeneous photocatalytic reaction, a series of control experiments was performed. Since the imidoyl thiourea (**4aa**) was detected at the beginning of the photocatalytic reaction, we envisioned that **4aa** might be the crucial intermediate of this reaction. When **4aa** was subjected to the standard conditions, we obtained **3aa** as the sole product in 100% GC yield (Scheme 4a), which further confirmed that **4aa** was the crucial intermediate of the present reaction. When the template reaction was conducted in the presence of radical scavengers (TEMPO and BHT), no desired product formation was observed (Schemes 4b and c). With 1,4-benzoquinone as the superoxide radical anion ($O_2^{\cdot-}$) scavenger, only a trace amount of **4aa** was observed (Scheme 4d), providing strong evidence for the essential role of $O_2^{\cdot-}$. In contrast, the addition of hydroxyl radical ($HO^\cdot$) scavenger (isopropanol), singlet oxygen ($^1O_2$) scavenger (DABCO) and peroxide radical ($HOO^\cdot$) scavenger ($FeSO_4$,) had almost no influence on the reaction (Scheme 4e-g). When hole (h^+) scavenger (NH_4COOH, Scheme 4h) or electron (e^-) scavenger ($AgNO_3$, Scheme 4i) was added to the standard reaction system, the formation of **4aa** was significantly suppressed, confirming that both h^+ and e^- were critical for this reaction. This reaction was totally suppressed when the $CuCl_2$ (SET scavenger) was added to the reaction system (Scheme 4j), supporting the involvement of a single electron transfer (SET) process in the semi-heterogeneous annulation. In addition, the light irradiation on-off experimentsand the quantum efficiency ($\Phi = 1.2\%$) indicated that this reaction was driven by visible light, and a radical chain process might be ruled out (see Supporting information for details).



	Scavenger	Active Species	3aa
(b)	TEMPO	radical	trace
(c)	BHT	radical	trace
(d)	1,4-benzoquinone	$O_2^{\cdot-}$	trace
(e)	Isopropanol	$HO^\cdot$	82%
(f)	DABCO	$^1O_2$	79%
(g)	$FeSO_4$	$HOO^\cdot$	72%
(h)	NH_4COOH	Hole	trace
(i)	$AgNO_3$	e^-	trace
(j)	$CuCl_2$	SET	19%

Scheme 4. Radical-capturing experiments.

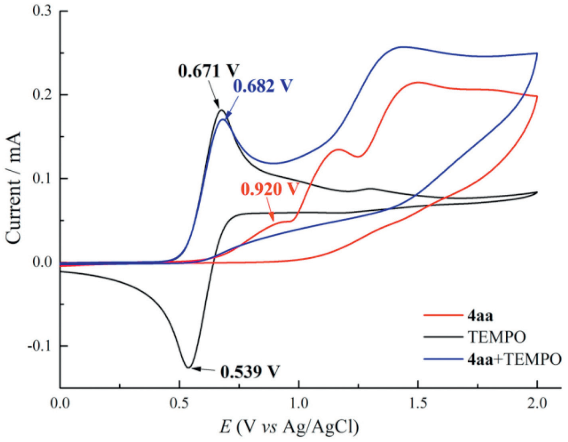


Fig. 2. Cyclic voltammetry experiment.

To gather more information about the mechanism, the cyclic voltammetry studies were carried out. As shown in Fig. 2, TEMPO displayed a distinct oxidation peak at 0.671 V and reduction peak at 0.539 V *vs.* Ag/AgCl, whereas **4aa** presented a higher oxidation peak at 0.920 V Ag/AgCl. The experimental results indicating that TEMPO could be oxidized preferentially by the h^+. An obvious oxidation potential of 0.682 V and a complete disappear of reduction current was detected in the mixture of TEMPO and **4aa**, suggesting

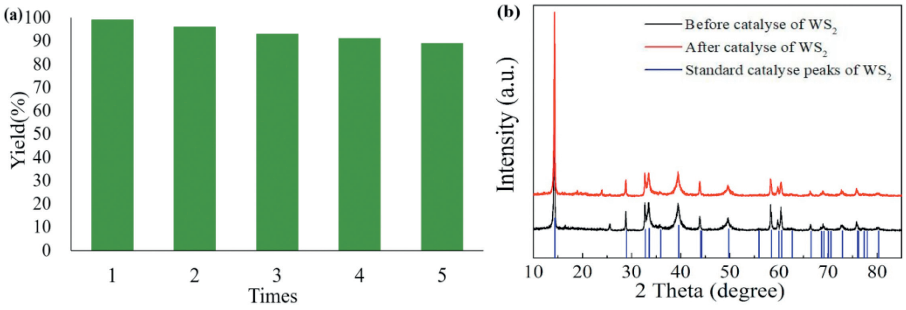
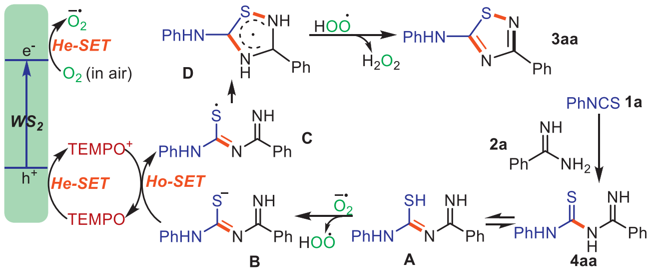


Fig. 1. The reusability of catalytic system (a) and the XRD of WS_2 (b).



Scheme 5. Proposed reaction mechanism.

that a homogeneous electron transfer occurred between oxidation state TEMPO and **4aa** [50].

According to the above-mentioned results and previous reports [51,52], a plausible mechanism was devised (Scheme 5). After blue light illumination, WS_2 was excited to yield a separation of the photo-generated electron-hole pairs, which then could trigger the redox reaction. The photo-generated electron reduced molecular oxygen (in air) into the higher active excited $O_2^{\cdot-}$ by a heterogeneous single electron transfer (He-SET) process. The $O_2^{\cdot-}$ then abstracted a hydrogen atom from thiolene **A** (tautomer of the *in situ* generated **4aa**) to produce the $HOO^{\cdot}$ and the anion intermediate **B**. At the same time, a heterogeneous single electron transfer (He-SET) from TEMPO to the photo-generated hole to generate the oxidation state $TEMPO^+$, which oxidized intermediate **B** to yield the sulfur-centered radical **C**, followed by an intramolecular cyclization to ring closure radical intermediate **D**. Finally, the terminal thiadiazole **3aa** was formed through the dehydrogenation and aromatization under the assistance of $HOO^{\cdot}$.

The present manuscript highlights a practical and sustainable method for the preparation of 5–amino-1,2,4-thiadiazoles. With WS_2 semiconductor as the photocatalyst, both TEMPO and air as the redox catalysts, a broad range of thiadiazoles were semi-heterogeneously synthesized in high to quantitative yields with excellent functional group tolerance. Importantly, the pure products can be easily collected by CPME rinsing. The photo-generated electron heterogeneously reduced O_2 into $O_2^{\cdot-}$, which abstracted a hydrogen atom from thiolene to produce the thiolene anion. Another heterogeneous SET process simultaneously occurred between the photo-generated hole and TEMPO delivering the oxidation state $TEMPO^+$, which oxidized the thiolene anion to yield the radical intermediate through a homogeneous SET process. Through this strategy, the fast recombination of photo-generated carers in WS_2 can be sharply decreased. In addition, both the photocatalyst and solvent can be readily reusable for at least 5 successive reaction runs without significant loss of catalytic activity. We believe this strategy can be in conformity with the “prevent waste” principle and meet the requirement of material- and energy-consuming isolation and purification.

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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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109514.

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