I_2/O_2-Enabled N−S Bond Formation to Access Functionalized 1,2,3-Thiadiazoles

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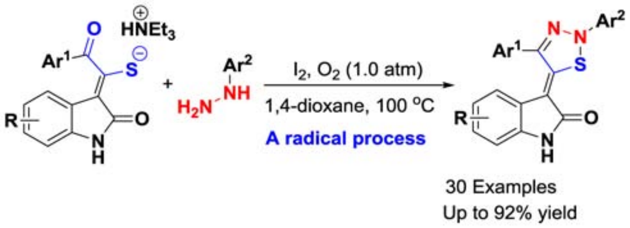
Ⓢ *Supporting Information*

ABSTRACT: A new, metal-free intermolecular formal [3 + 2] heterocyclization between triethylammonium thiolates and aryl hydrazines has been established by using the combination of I_2 and O_2 as efficient oxidation sources, allowing a concise and low-cost access to new densely functionalized 1,2,3-thiadiazoles with good to excellent yields. The reaction showed a broad scope of substrates of both reactants and attractive characteristics consisting of eco-friendly oxidants, flexible structural modification, broad functional group compatibility, and mild reaction conditions.



Owing to increasing concerns about environmental protection and waste generation, more efforts have been made toward finding alternative sustainable methodologies for constructing privileged structures of chemical and pharmaceutical interest.[1] Among them, direct cross-dehydrogenative coupling (CDC) has become a powerful and applicable methodology for the formation of functionalized compounds,[2] with the advantage of atom economy[3] and green chemistry.[4] Although metal-catalyzed CDCs have been occupying a dominant position in organic synthesis,[5] the use of transition metals for reactions would be arguably considered to be environmentally unfriendly.[6] Therefore, the exploration of metal-free versions is more desirable.[7] Recently, the versatility of an I_2/O_2 catalytic system has been reported as an alternative to access privileged structures.[8] However, to the best of our knowledge, the utilization of domino strategy combined with I_2/O_2-enabled N−S bond formation for the creation of functionalized 1,2,3-thiadiazoles through formal [3 + 2] heterocyclization has not been documented so far.

Meanwhile, 1,2,3-thiadiazoles have been widely used as plant inducers, represented by thidiazuron (TDZ),[9] acibenzolar (BTH),[10] and tiadinal (TDL)[11] (Figure 1). They exhibit a wide spectrum of interesting pharmacological properties, such as anti-HIV-1,[12] antitumor,[13] antithrombotic,[14] and antiviral.[15]

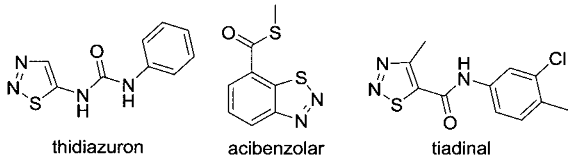
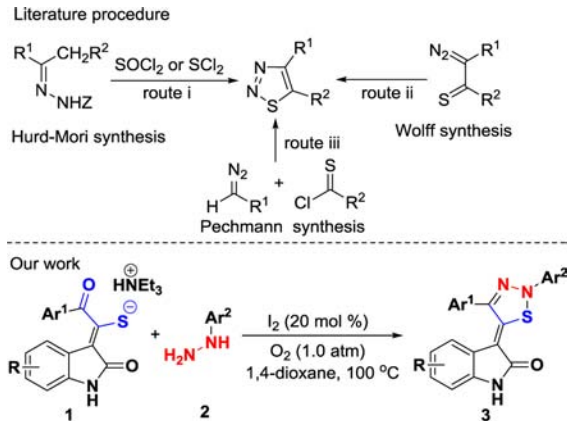


Figure 1. Several Representative Plant Inducers.

Moreover, they have been widely serving as versatile precursors for heterocyclic syntheses. Several methods have been developed to build 1,2,3-thiadiazole frameworks including: (a) reactions of hydrazones of cyclic ketones with thionyl chloride (Hurd−Mori synthesis, Scheme 1, route i);[16] (b) generation and concomitant cyclization of α-diazothiocarbonyl compounds (Wolff synthesis, Scheme 1, route ii);[17] (c) the reaction of diazo compounds with thioyl chloride (Pechmann synthesis, Scheme 1, route iii),[18] and other methods.[19] However, these methods require highly reactive reagents such as $SOCl_2$, SCl_2, or diazo compounds which have safety concerns. Therefore, the development of a safe and environ-

Scheme 1. Several Strategies toward 1,2,3-Thiadiazoles



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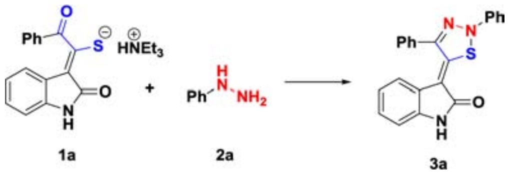
mentally benign protocol toward the formation of these compounds would be needed. Herein, we report a novel I_2/O_2-enabled cross-dehydrogenative coupling between the preformed triethylammonium thiolates **1** and simple arylhydrazines **2**, allowing the direct N−S bond formation to access functionalized 1,2,3-thiadiazoles **3** with good to excellent yields.

In our previous report, triethylammonium thiolates **1** were easily prepared through the reaction of α-thiocyanate ketones with indoline-2,3-diones in ethyl acetate in the presence of stoichiometric Et_3N at room temperature.[20] As a continuation of our project on radical transformations,[21] we reasoned that under oxygen conditions the preformed triethylammonium thiolates **1** preferentially react with molecular iodine to form an S−I bond followed by its homolysis to give sulfur radical, which is trapped by other radical acceptors to generate new sulfur-containing compounds due to the combination of I_2 and O_2 acting as a useful radical catalytic system.[8] We thus attempted to perform the reaction of triethylammonium thiolate **1a** with phenylhydrazine (**2a**) in EtOH at 80 °C using 20 mol % of I_2 as a catalyst under oxygen conditions. Pleasantly, the expected product **3a** was obtained, albeit with a low 23% yield (Table 1, entry 1). Encouraged by this result, we then investigated the solvent effect on this transformation with the use of various polar solvents, such as 1,2-dichloroethane (DCE), ethyl acetate (EA), MeCN, tetrahydrofuran (THF), and 1,4-dioxane. The use of 1,2-dichloroethane (DCE) generated a slightly lower yield (entry 2). Ethyl acetate (EA) completely compressed the reaction (entry 3). When the reaction was performed in MeCN, a higher 58% yield was obtained (entry 4). THF and 1,4-dioxane were found to be more efficient than other solvents (entries 1−4 vs entries 5 and 6). Among the latter two, 1,4-dioxane was superior to THF to give a slightly higher yield (entry 6). Next, we adjusted the reaction parameter including loading of iodine and temperatures. The yield of **3a** leveled off when the loading of iodine was increased to 30 mol % (entry 7), whereas lowering the loading of iodine led to a lower yield (70%) (entry 8). Moreover, reaction temperatures remarkably affected reaction efficiency.

Table 1. Optimization Conditions[a]



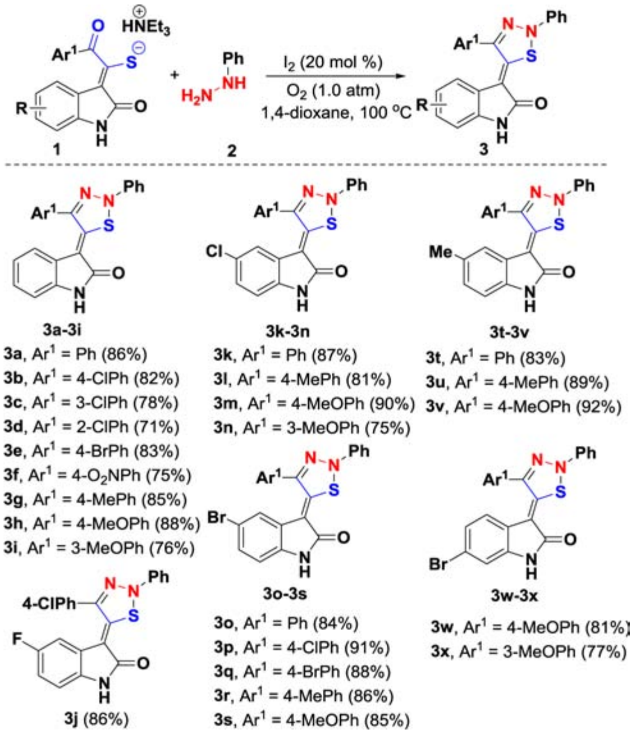
entry	cat. (mol %)	solvent	temp (°C)	yield[b] (%)
1	I_2 (20)	EtOH	80	23
2	I_2 (20)	DCE	80	19
3	I_2 (20)	EA	80	trace
4	I_2 (20)	MeCN	80	58
5	I_2 (20)	THF	80	71
6	I_2 (20)	1,4-dioxane	80	75
7	I_2 (30)	1,4-dioxane	80	75
8	I_2 (10)	1,4-dioxane	80	70
9	I_2 (20)	1,4-dioxane	100	86
10	I_2 (20)	1,4-dioxane	110	84
11	I_2 (20)	1,4-dioxane	100	80[c]
12		1,4-dioxane	100	ND[d]

[a] Reaction conditions: all of the reactions were performed with **1a** (1.0 mmol), **2a** (1.5 mmol), and solvent (2.0 mL) in a sealed reaction tube under O_2 (1.0 atm) conditions. [b] Isolated yield is based on **1a**. [c] Under air conditions. [d] ND (Not Detected)

Adjusting the reaction temperature to 100 °C proved more efficient, delivering the expected product **3a** in 86% yield (entry 9). Further increasing reaction temperatures to 110 °C did not significantly change the yield (entry 10). The same reaction performed under air conditions resulted in a decreased yield (80%) (entry 11). Without I_2 catalyst, no expected product **3a** was observed (entry 12), confirming that I_2 is essential for the success of this transformation.

With the established optimal conditions, we then set out to explore the scope of this reaction by allowing a variety of structurally diverse triethylammonium thiolates **1** to react with phenylhydrazine **2a**; the results are summarized in Scheme 2.

Scheme 2. Substrate Scope for Synthesis of 3a−x



[a] Reaction conditions: all reactions were performed with **1** (1.0 mmol), **2** (1.5 mmol), I_2 (0.2 mmol), and 1,4-dioxane (2.0 mL) in a sealed reaction tube at 100 °C under O_2 (1.0 atm) conditions for 24 h. Isolated yield is based on **1**.

The influence of substituents in the phenyl ring (Ar^1 moiety) of triethylammonium thiolates **1** was first investigated. The variants of substituents did not hamper the reaction process. This I_2-catalyzed formal [3 + 2] annulation tolerated substrates **1** bearing both electron-donating and electron-withdrawing groups under the optimized conditions. Substituents residing at different positions on the phenyl ring (Ar^1), such as Cl, Br, Me, and MeO, were found to be compatible. For instance, the more sterically demanding *o*-chloro substituent was successfully engaged in this reaction. Even a challenging case in which a strong electron-withdrawing effect NO_2 exists on the *para*-position was well-suited for this present transformation, converting into the corresponding product **3f** in a 75% yield. Next, we turned our attention to investigation of the electronic properties of the indolin-2-one moiety (R). Substrates **1** carrying both electron-rich and electron-poor groups all worked

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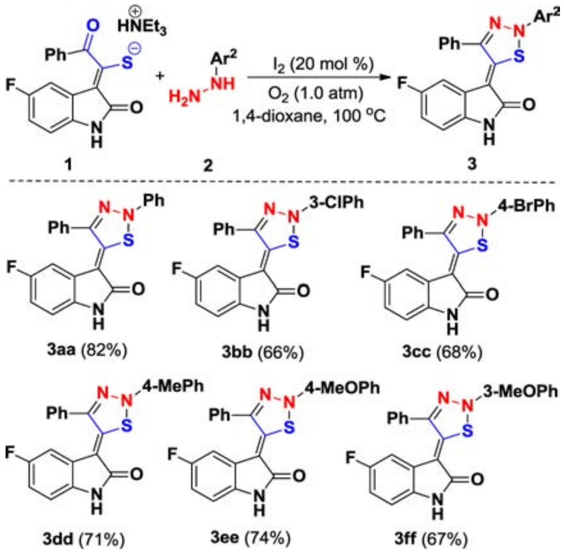
well to provide the desired products **3j−x** in yields ranging from 75% to 92%. Functional groups like fluoride, chloride, bromide, and methyl situated in the 5- or 6-position of the indolin-2-one ring were well tolerated.

After the successful utilization of various triethylammonium thiolates **1**, we next extended our investigation to the scope of aryl hydrazide (Ar^2) (Scheme 3). As F-containing compounds can improve pharmacological properties compared to their nonfluorinated analogues, we decided to use their 5-fluoro-substituted counterpart **1** to expand its synthetic utility. Similarly, the variation of the electronic properties of substituents on the phenyl ring (Ar^2) have no significant effect on this transformation. A variety of functional groups like chloro, bromo, methyl, and methoxy enabled the reaction to occur smoothly, resulting in good yields (66%−82%) of products **3aa−ff**. The structural elucidation of the products was determined by the analysis of IR, NMR, and HRMS spectra. In the case of **3j**, the structure was unequivocally confirmed by X-ray analysis (Figure 2).

Scheme 3. Substrate Scope for Synthesis of 3aa−ff



[a] Reaction conditions: all reactions were performed with **1** (1.0 mmol), **2** (1.5 mmol), I_2 (0.2 mmol), and 1,4-dioxane (2.0 mL) in a sealed reaction tube at 100 °C under O_2 (1.0 atm) conditions for 24 h. Isolated yield is based on **1**.

To understand the mechanism, several control experiments were carried out (Scheme 4). When triethylammonium thiolate **1a** was treated with phenylhydrazine **2a** in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or butylhydroxytoluene (BHT) (2.0 equiv) under the standard conditions (Scheme 4a), the reaction gave complex mixtures without observation of the desired product **3a**, suggesting a possible radical process. The desired product **3a** was not observed under argon conditions (Scheme 4b), indicating that O_2 plays a key role in the success of this reaction.

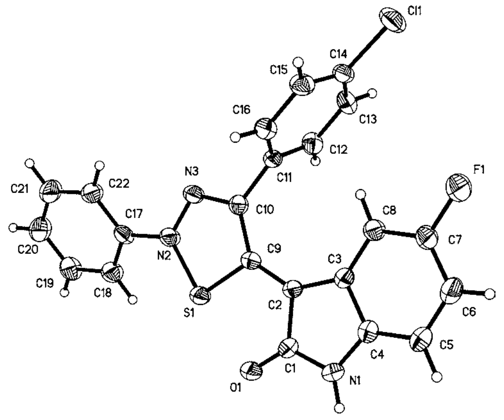
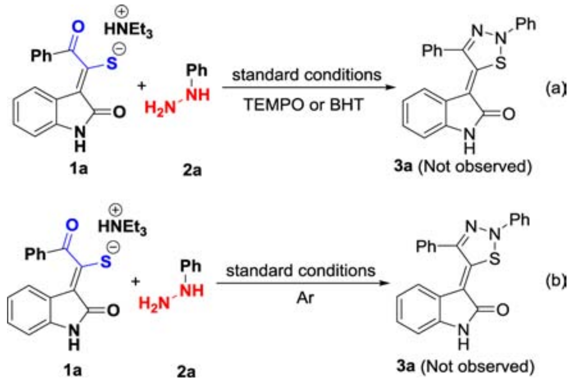
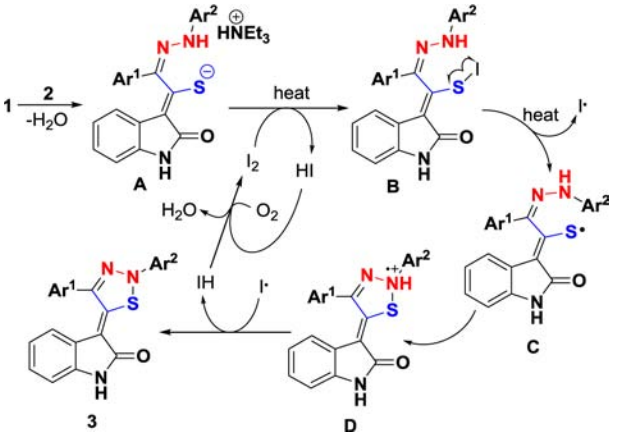


Figure 2. ORTEP drawing of **3j**.

Scheme 4. Control Experiments



Scheme 5. Proposed Mechanism for Formation of 3



On the basis of the above analysis and literature survey,[7,8] a reasonable mechanism is outlined in Scheme 5. Triethylammonium thiolates **1** are reacted with aryl hydrazines **2** to give access to aryl hydrazones **A**, which undergo an S−I bond formation to generate intermediates **B**, followed by homolysis of S−I bond of intermediates **B** to yield radical intermediates **C**. The intramolecular radical coupling/cyclization between the sulfur radical and nitrogen atom of aryl hydrazines occurs, providing radical cations **D**, which undergo a single-electron transfer (SET) process[22] in the presence of I radical and subsequent deprotonation to access the final 1,2,3-thiadiazoles **3**. I_2 is regenerated by reaction with iodine anion and molecular O_2.[8]

In summary, we have developed a new I_2/O_2-enabled N−S bond formation that offers efficient construction of densely functionalized 1,2,3-thiadiazoles via a metal-free formal [3 + 2] annulation of triethylammonium thiolates with aryl hydrazines. The reaction pathway involved a hydrazone formation/radical coupling/SET sequence, allowing us to access blocks of 1,2,3-thiadiazoles with a wide diversity of substituents in a successive

C−N and N−S bond-forming process. Eco-friendly oxidants, flexible structural modification, and broad functional group compatibility as well as mild reaction conditions make this strategy highly viable for future applications.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00079.

Experimental procedures and spectroscopic data for all new compounds **3a−y,aa−ff** (PDF)
X-ray crystallographic data for **3j** (CIF)

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Notes

The authors declare no competing financial interest.

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