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Transition-metal-free visible light-promoted photoredox oxidative dehydrogenative cyclization: expeditious approach to 1,2,4-thiadiazoles

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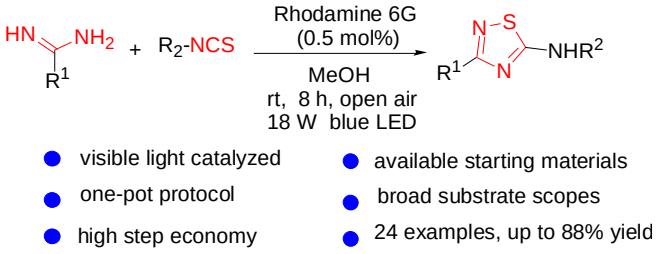
Abstract

A novel visible-light-catalyzed oxidative N-S bond formation for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles has been developed. This protocol features a metal-free approach, green oxidant, room temperature process, broad substrate scope, good functional group tolerance, excellent yields and a one-pot reaction without the isolation of the intermediates.



Keywords: Metal-free, photoredox, oxidative S-N bond formation, 1,2,4-thiadiazole

Introduction

Thiadiazoles are an important class of five-membered heterocyclic motifs containing two nitrogen atoms and a sulfur atom, that are associated with a broad spectrum of biological and pharmacological activities.[1-3] Among them, the 1,3,4-thiadiazoles have emerged as an important structural moiety present in a large number of functionalized molecules with a broad range of biological activities, such as anticancer,[4-5] antimicrobial,[6] anticonvulsant,[7] fungicidal,[8] antihepatitis B virus,[9] and anti-HIV activity.[10] Moreover, they are also found in valuable pharmaceuticals, including sitagliptin,[11] maraviroc,[12] trizaolam,[13] deferasirox,[14] and cefozopran[15] (Figure 1).

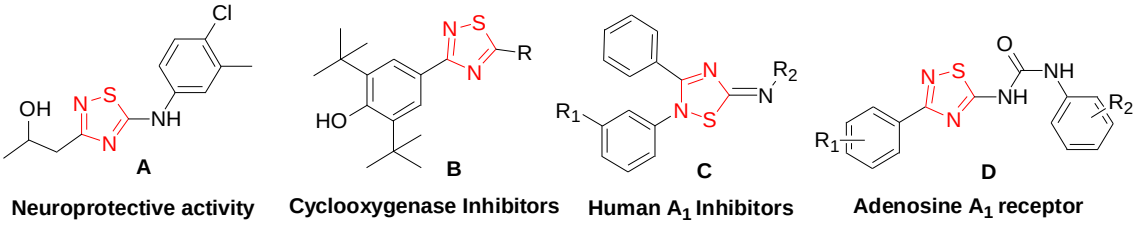
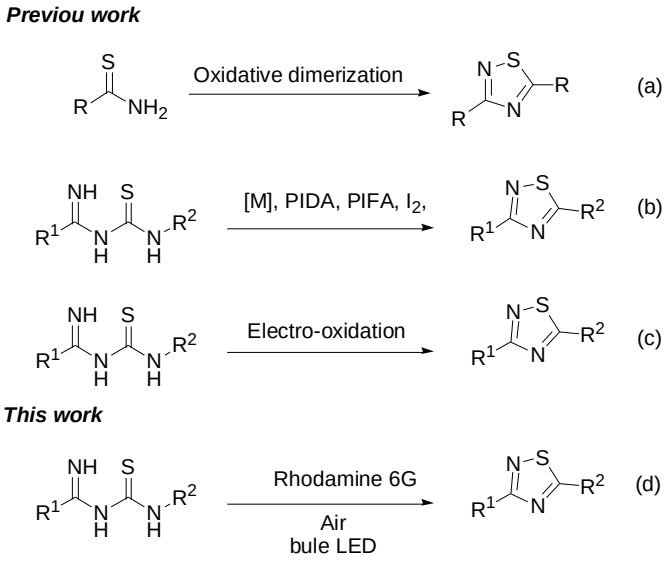


Figure 1. Selected bioactive molecules that contain 1,3,4-thiadiazole skeletons.

Therefore, the synthesis of 1,2,4-thiadiazole derivatives has received considerable attention. The traditional method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles relies on the oxidative dimerization reaction of thioamides using various oxidants (Scheme 1, a).[16-23] Recently, alternative methods were developed through intramolecular oxidative dehydrogenative cyclization by employing transition-metal or stoichiometric amount of oxidants such as hypervalent iodine (III), I_2, or O_2 (Scheme 1, b).[24-31] Most recently, an elegant protocol has been published via the electro-oxidative intramolecular dehydrogenative N-S bond formation of imidoyl thioureas (Scheme 1, c).[32] Despite major progress in the field, the use of transition-metal catalysts or oxidants is still standard, which affects atom economy and environmental issues. Therefore, it is desirable to develop a more pratical and environmentally friendly method for the synthesis of 3,5-disubstituted 1,2,4-thiadiazoles.



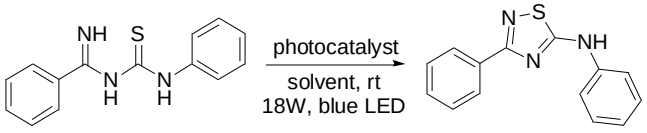
Scheme 1. Different approaches to functionalized1,2,4-thiadiazoles.

In recent years, visible-light photoredox catalysis has emerged as a powerful synthetic tool for mild and environmentally benign organic transformations.[33-39] These attractive synthetic reactions are mainly spurred by exogenous photocatalysts to facilitate the conversion of visible light into chemical energy under exceptionally mild conditions. A variety of elegant photocatalyzed reactions for the construction of C-C and C-heteroatom bonds have been well established using visible-light using transition metal complexes or organic dyes as photoredox catalysts.[40-48] Meanwhile, the application of photoredox catalysis for heteroatom-heteroatom bond formation has attracted a lot of attention and has become a promising green approach to produce final products.[49-52] Herein we report a direct and environmentally friendly method for the synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles using Rhodamine 6G as an organophotoredox catalyst irradiated with blue LED light under an air atmosphere at room temperature (Scheme 1, d).

Results and Discussion

We initiated our studies by choosing *N*-(phenylcarbamothioyl)benzimidamide (**1a**) as a model substrate in the presence of 0.5 mol % of *fac*-Ir(bpy)$_3$ in CH_3OH at room temperature under air atmosphere. After 8 h of irradiation with a 18 W blue LED light, the desired dehydrogenative cyclization product **2a** was obtained in 63% yield (Table 1, entry 1). Encouraged by this promising result, we next surveyed a range of photocatalysts under the same conditions (Table 1, entries 2-7). We found that the Ru(bpy)$_3$Cl$_2$ photocatalyst can slightly improve the efficiency for generation of **2a** (71%, Table 1, entry 2). To develop a metal-free protocol, we then examined various organic dyes including eosin Y, methylene blue, rose bengal, 3DPAFIN (1,3-dicyano-2,4,5,6-tetrakis(diphenylamino)benzene), and Rhodamine 6G (Table 1, entries 3-7). These results showed that the organic photocatalyst rhodamine 6G provided the best result (87%, Table 1, entry 7). We then screened the reaction in various solvents such as CH_3CN, DMF, CH_2Cl_2, CH_3CH_2OH, and 1,4-dioxane (Table 1, entries 8-12). Interestingly, we found that these solvents can promote this reaction in good yield and that CH_3OH was found to be the best choice. The reaction time was examined and the yield did not improve (88%, Table 1, entry 13). The amount of the photocatlayst was also investigated, and it was found that 0.5 mol % catalyst loading was sufficient to furnish the product in excellent yields (Table 1, entries 14 and 15). Performing the reaction under oxygen atmosphere did not improve the product yield (Table 1, entry 16). Control experiments showed that the presence of the photocatalyst, air, and the light source is necessary for this transformation to proceed (Table 1, entries 17-19). Finally, we attempted to carry out the nucleophilic addition and oxidative cyclization in a one-pot fashion. To our delight, the desired product **2a** was also obtained in similar yield when the imidoyl thiourea **1a** was formed in a preceding step from an aryl isocyanate in the same reaction vessel without isolation and under the optimal reaction conditions (Table 1, entry 20).

Table 1. Screening of optimal reaction conditions[a,b,c]



1a **2a**

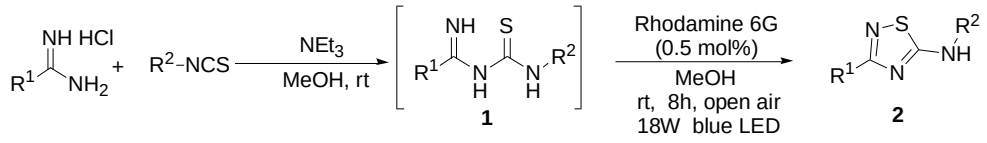
Entry[a]	Photocatalyst	Solvent	Yield (%)[b]
1	*fac*-Ir(bpy)$_3$	CH_3OH	63
2	Ru(bpy)$_3$Cl$_2$	CH_3OH	71
3	Eosin Y	CH_3OH	72
4	Methylene blue	CH_3OH	68
5	Rose bengal	CH_3OH	23
6	3DPAFIN	CH_3OH	79
7	Rhodamine 6G	CH_3OH	87
8	Rhodamine 6G	CH_3CN	81
9	Rhodamine 6G	DMF	57
10	Rhodamine 6G	CH_2Cl_2	65
11	Rhodamine 6G	CH_3CH_2OH	73
12	Rhodamine 6G	1,4-dioxane	71
13[c]	Rhodamine 6G	CH_3OH	88
14[d]	Rhodamine 6G	CH_3OH	78
15[e]	Rhodamine 6G	CH_3OH	89
16[f]	Rhodamine 6G	CH_3OH	88
17[g]	Rhodamine 6G	CH_3OH	0
18[h]	Rhodamine 6G	CH_3OH	trace
19[i]	Rhodamine 6G	CH_3OH	trace
20[j]	Rhodamine 6G	CH_3OH	87

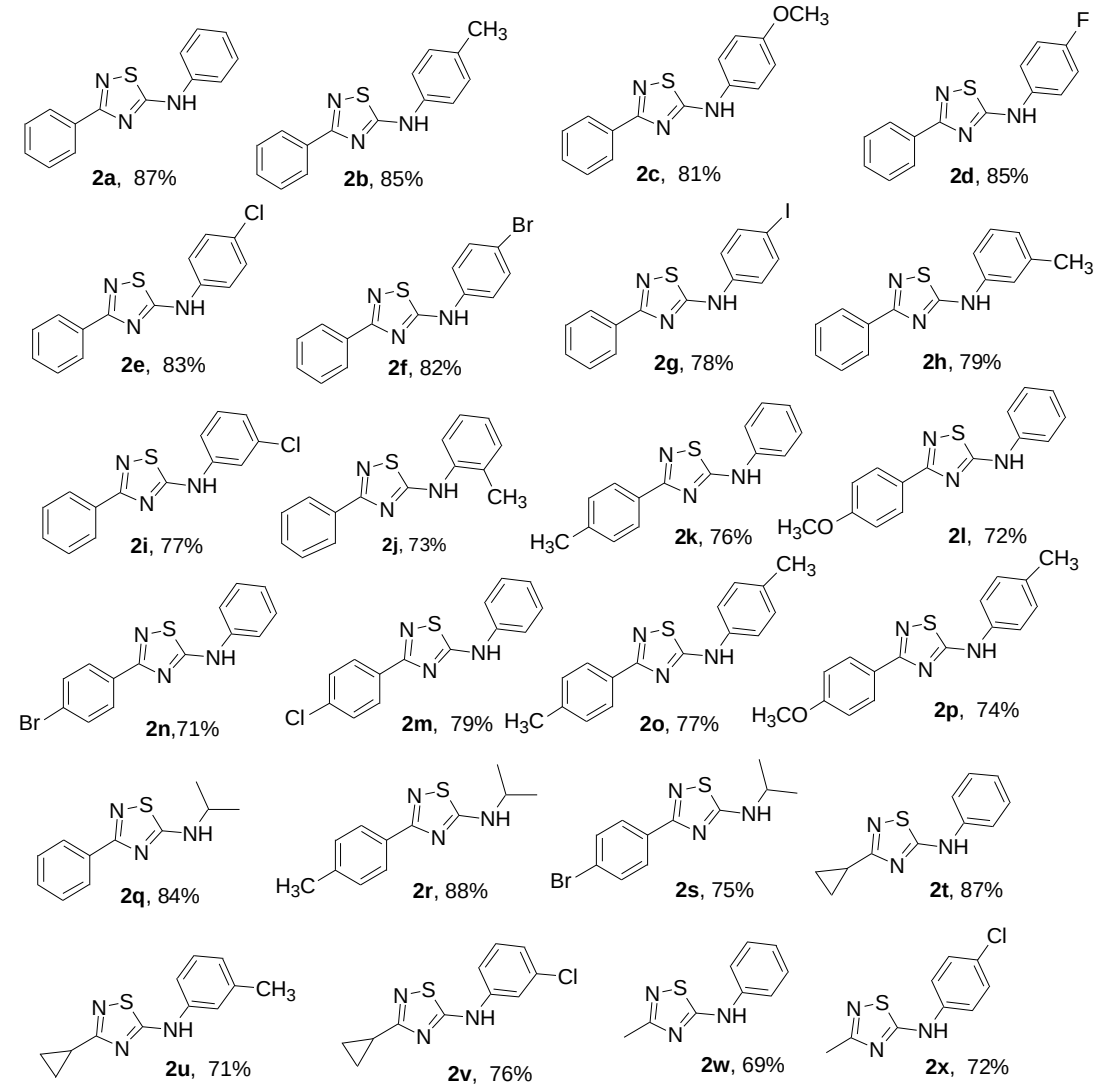
[a]Reaction conditions: imidoyl thiourea (**1a**, 0.2 mmol), and photocatalyst (0.5 mol %) in solvent (2 ml) were irradiated with 18W blue LEDs at room temperature in the open air for 12 h. [b]Isolated yields. [c]Reaction time for 12h. [d]Photocatalyst (0.25 mol %); [e]Photocatalyst (1.0 mol %); [f]The reaction was conducted under O_2. [g]The reaction was performed in the dark. [h]The reaction was conducted under N_2. [i]Reaction was performed without a catalyst. [j]One-pot protocol. 3DPAFIN = 1,3-dicyano-2,4,5,6-tetrakis(diphenylamino)benzene.

With the optimal conditions (Table 1, entry 7) in hand, we next probed the scope and generality of this intramolecular oxidative S-N bond formation approach to a variety of 3-substituted-5-amino-1,2,4-thiadiazoles

in a one-pot fashion and the results are summarized in Scheme 2. First, we investigated the scope of the R substituent on aryl isothiocyanates. Various electron-donating and -withdrawing substituents including *p*-Me, *p*-OMe, *p*-F, *p*-Cl, *p*-Br, *p*-I, *m*-Me, and *m*-Cl, were well-tolerated, affording the corresponding 1,2,4-thiadiazoles in good to excellent yields (**2a**-**2i**). Meanwhile, the *o*-methyl substituted isothiocyanates **1j** had little influence on the reaction and afforded the desired product **2j** in 73% yield.

Table 2. One-pot synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles *via* in situ generated Imidoyl Thiourea[a,b]





[a]Reaction conditions: imidoyl thiourea (**1a**, 0.2 mmol), and rhodamine 6G (0.5 mol %) in CH_3OH (2 ml) were irradiated with 18W blue LEDs at room temperature in the open air for 8 h. [b]Isolated yields.

Next, we investigated the scope of the R substituent on phenyl amidines. A range of substrates bearing electron-donating or electron-withdrawing group-substituted aromatic rings all underwent the oxidative dehydrogenative cyclization smoothly and gave the desired products in very good yields (**2k**-**2m**). Moreover, both various substituted amidines and isothiocyanates could provide the desired products in 77% and 74% yield (**2o** and **2p**), respectively. Furthermore, alkyl isothiocyanates such as isopropyl isothiocyanate were compatible with the optimized conditions as well, affording the desired products **2q**-**2s** in excellent yields. Interestingly, alkyl amidines such as cyclopropyl and methyl amidine reacted smoothly, affording the desired products **2t**-**x** in very high yields.

Conclusions

In conclusion, we have developed a metal-free, visible-light induced organophotoredox-catalyzed dehydrogenative cyclization protocol for the intramolecular N-S bond formation using rhodamine 6G as a photocatalyst under aerobic reaction conditions. A broad range of 3-substituted 5-amino-1,2,4-thiadiazole derivatives are conveniently synthesized in good to excellent yields with good functional group tolerance, Further investigation for other heterocyclic syntheses based on this photocatalytic protocol is underway in in our laboratory.

Experimental Section

General procedure for 3,5-disubstituted 1,2,4-thiadiazoles 2. In an oven-dried single-necked bottle (10 mL) equipped with a stir bar, amidine hydrochloride (0.2 mmol), isothiocyanate **2** (0.2 mmol), NEt_3 (0.4 mmol), and CH_3OH (2 mL) were added and stirred at room temperature until the conversion was completed as indicated by TLC. Then, rhodamine 6G (0.5 mol %) was added, the reaction mixture was open to the air and stirred at room temperature under the irradiation of a 18 W LED lamp for 8 h. After completion of the reaction, the resulting mixture was extracted with EtOAc and the organic phase was then removed under vacuum. The residue was purified by flash column chromatography using a mixture of petroleum ether and ethyl acetate as eluent to give the desired products **2**.

Compounds **2a-x** are known compounds and their spectral data are in agreement with those reported in the literature (see also the Supplementary Material file)

Acknowledgements

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Supplementary Material

Copies of 1H NMR spectra of compounds **2a-x** are given in the supplementary material file associated with this paper.

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