Eosin Y Catalyzed Visible-Light-Driven Aerobic Oxidative Cyclization of Thioamides to 1,2,4-Thiadiazoles

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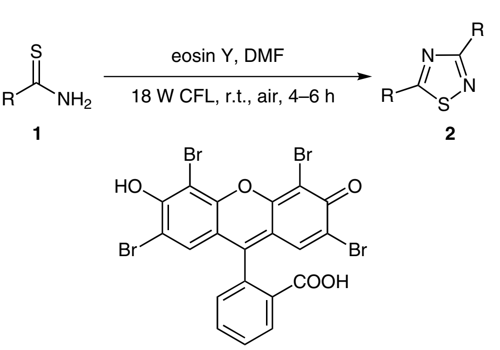
Abstract: A new approach for an efficient metal-free synthesis of 1,2,4-thiadiazoles from primary thioamides using visible light and air in the presence of eosin Y as a photoredox catalyst is reported. The protocol involves an aerobic oxidative cyclization of thioamides via the formation of C–N and C–S bonds to afford excellent yields of the products in a simple one-pot operation under mild conditions.

Key words: visible light, eosin Y, photoredox, thioamides, cyclization, thiadiazoles

During the last decade, visible-light photoredox catalysis has emerged as a promising tool for organic synthesis.[1] This is because of ready availability, ease of handling, nontoxicity, sustainability, and potential applications of visible light. However, owing to the inability of most organic molecules to absorb light in the visible region, generally photosensitizers or photocatalysts are required to induce visible-light-driven reactions.[2] Mostly, organometallic complexes such as $Ru(bpy)_3^{2+}$ and $Ir(ppy)_2(dtb\text{-}bpy)^+$ (where, bpy = 2,2′-bipyridine, ppy = 2-phenylpyridine, dtb-bpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) have been used as visible-light photoredox catalysts.[1] Following the seminal work of MacMillan et al.[3] and Yoon et al.,[4] several powerful methods for a number of chemical transformations in organic synthesis have been developed employing these photoredox catalysts.[1]

However, the main disadvantages of these metal-based methods are the high cost, potential toxicity, and low sustainability of the ruthenium and iridium complexes. Recently, metal-free organic dyes have been utilized as visible-light photoredox catalysts,[5] which are inexpensive, easy to handle, and eco-friendly, and provide a superior alternative to transition-metal photocatalysts. Importantly, these organocatalysts have great potential for applications in visible-light-mediated useful organic transformations

The literature records only a few reports on photocatalytic reactions involving a sulfur radical; including the oxidation of sulfides to sulfoxides,[6a] cyclization of thioamides to 2-substituted benzothiazoles[6b] using $Ru(bpy)_3^{2+}$ as a catalyst, and rose bengal catalyzed photochemical oxidation of thiobenzamides leading to 3,5-diphenyl-1,2,4-thiadiazoles in very poor yield (8%).[7] In continuation of our work on heterocyclization reactions[8] and intrigued by the fact that organosulfur compounds form radicals easily and have found wide applications in radical reactions, we proposed the present eosin Y catalyzed visible-light-mediated aerobic oxidative cyclodesulfurization of thioamides **1** to 1,2,4-thiadiazoles **2** as depicted in Scheme 1. We selected eosin Y as the photocatalyst for our present study on the basis of earlier observations and properties of organic dyes used as photoredox catalysts.[5,9]



Scheme 1 Synthesis of 1,2,4-thiadiazoles from primary thioamides

1,2,4-Thiadiazoles are an important class of biologically and pharmaceutically important compounds.[10–13] The antibiotic cefozopram[10] is a 1,2,4-thiadiazole drug, which is currently in clinical use. Besides this, the 1,2,4-thiadiazole scaffold is a key structural unit in many synthetic products with a broad range of biological activities as affecting the cardiovascular system, suppressing inflammation, antibiotic action, central nervous system activity, acetylcholinesterase inhibition, action on G-protein coupled receptors, and glycogen synthase kinase 3b inhibition.[11d] Various 1,2,4-thiadiazoles exhibit thiol-trapping properties and this has been reviewed.[12] Another review article has appeared on the synthesis and therapeutic applications of 1,2,4-thiadiazoles.[13] Most of the methods available for the synthesis of 1,2,4-thiadiazoles involve oxidative cyclization of primary thioamides with a variety of oxidizing agents such as hypervalent iodine,[14] DMSO/HCl,[15] and DMSO/2-chloro-1,3-dimethylimidazolium chloride.[16] IBX/TEAB,[17] methansulfonic acid derivative with benzenetellurinic acid,[18] telluroxide or selenoxide,[19] methyl bromocyanoacetate, and[20a] DDQ.[20b]

Molecular oxygen is the best oxidizing agent because of its easy availability, eco-friendliness, and sustainability,

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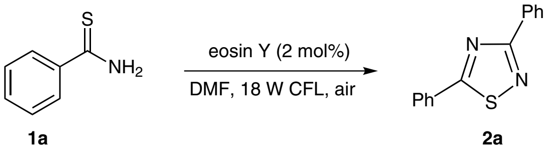
but it has never been used as oxidant in the synthesis of 1,2,4-thiadiazoles. Herein, we report an aerobic oxidative visible-light-initiated catalytic synthesis of 1,2,4-thiadiazoles. In a prototype reaction, benzothioamide (**1a**), in DMF solution and in the presence of 2 mol% eosin Y, was exposed to air (but no air bubbling) and to the light of a household 18 W fluorescent lamp at room temperature. Gratifyingly, the desired 1,2,4-thiadiazole **2a** was obtained in 91% yield (Table 1, entry 1). This result encouraged us to carry out a series of control experiments to show that in the absence of any one of the reagents/reaction parameters there was only trace or no product formation (Table 1, entries 2–5). The use of daylight in place of fluorescent light was also less effective (Table 1, entries 6–8). These results indicate that the reaction conditions (photocatalyst, visible light, and air) all are essential for the reaction and support the photocatalytic model for the reaction.

Table 1 Screening and Control Experiments[a]



Entry	Visible light	Eosin Y	Air	Time (h)	Yield (%)[b]
1	+	+	+	4	91
2	–	+	+	6	n.r.[c]
3	+	–	+	6	n.r.
4	+	+	–	6	n.r.
5	+	+	N_2	8	trace
6	+	+	+	8	13[d]
7	+	+	N_2	8	trace[d]
8	+	–	N_2	8	n.r.[d]

[a] Reaction conditions: **1a** (1.0 mmol), DMF (3 mL), 18 W CFL (compact fluorescent lamp; Philips, 6500 K, 1010 lm, 85 mA) irradiation under an air atmosphere at r.t.

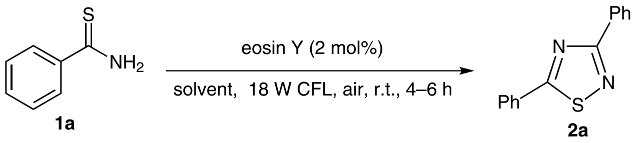
[b] Isolated yield of the product **2a**; n.r.= no reaction.

[c] The reaction was carried out in the dark.

[d] The reaction was carried out in daylight.

Next, we optimized the reaction conditions with respect to solvents and catalyst loading. It was noted that the reaction was not very sensitive to the reaction media because in all solvents tested (DMF, DMSO, MeCN, MeOH, EtOH, and THF) the yield was >50% (Table 2). The highest yield (91%) was in the case of DMF as solvent, and this was used as solvent in subsequent studies. The optimum catalyst loading was found to be 2 mol% (Table 2, entry 1). On lowering the catalyst loading from 2 mol% to 1 mol%, there was a significant decrease in the yield; while an increase in the catalyst loading from 2 mol% to 3 mol% did not improve the yield (Table 2, entries 1 and 7).

Table 2 Optimization of Reaction Conditions[a]



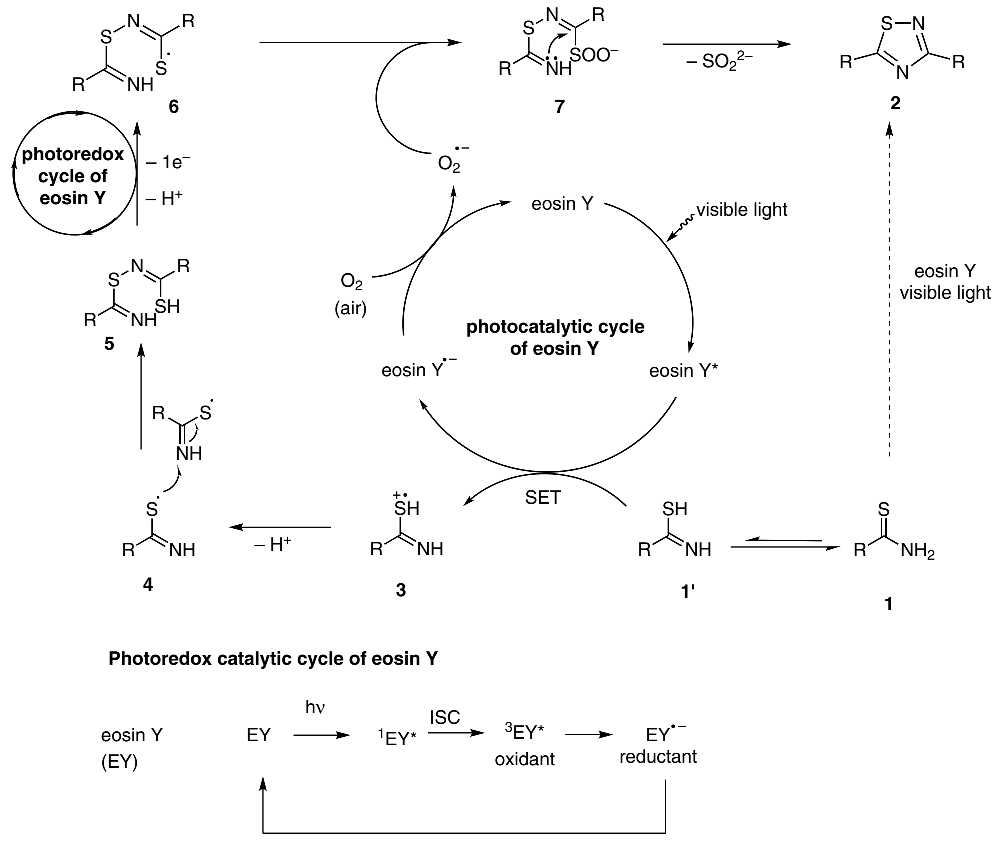
Entry[a]	Eosin Y (mol%)	Solvent[c]	Time (h)	Yield (%)[b]
1	2	DMF	4	91
2	2	DMSO	6	87
3	2	MeCN	8	76
4	2	MeOH	7	57
5	2	EtOH	7	55
6	2	THF	8	51
7	3	DMF	4	91
8	1	DMF	6	67

[a] Reaction conditions: **1a** (1.0 mmol), solvent (3 mL), 18 W CFL (compact fluorescent lamp; Philips, 6500 K, 1010 lm, 85 mA) irradiation under an air atmosphere at r.t.

[b] Isolated yield of the product **2a**.

With the optimized reaction conditions in hand, the functional-group compatibility and scope of the present photocatalytic protocol were demonstrated across a range of aromatic, heteroaromatic, and aliphatic primary thioamides (Table 3). The reaction is very mild and tolerates many functional groups. All the primary thioamides **1** afforded the desired products **2** in good to high yields (72–95%) regardless of differences in the electronic and steric properties of the substrates **1**. However, thioamides with an electron-donating substituent on the aromatic ring appear to react faster and afford higher yields in comparison to those bearing an electron-withdrawing substituent (Table 3, entries 2 and 3 vs. entries 6–10).

On the basis of our observations and literature reports,[9,21,22] a plausible mechanism for the formation of 1,2,4-thiadiazoles **2** from thioamides **1** is proposed in Scheme 2. The photoredox catalyst eosin Y (EY) is excited on absorption of visible light and its more stable triplet state ^{3}EY* undergoes single electron transfer (SET).[21] Both reductive and oxidative quenching are known for ^{3}EY*.[9] A SET from the thiolic form **1′** to ^{3}EY* generates the radical cation **3**, which forms a sulfur radical **4** after losing a proton. The cyclodesulfurization of **4** gives **5**, which forms the sulfur radical **6** following a similar path through which **1′** forms **4**. The sulfur radical **6** is oxidized with $O_2^{\bullet-}$, produced in the photoredox cycle of EY, to give peroxysulfenate **7**. An intramolecular nucleophilic attack of the imino nitrogen of **7** on the carbon containing SO_2^-

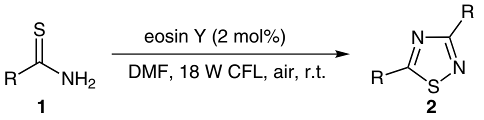


Scheme 2 Photoredox catalytic cycle of eosin Y for the oxidative cyclodesulfurization of thioamides to 1,2,4-thiadiazoles **2**

as a good leaving group affords the desired product **2** with the liberation of SO_2^{2-}.[22]

In summary, we have developed an efficient metal-free visible-light-initiated aerobic oxidative cyclization of primary thioamides to 1,2,4-thiadiazoles using molecular oxygen as an oxidant and eosin Y as the photoredox catalyst. This protocol is a superior alternative to the existing 1,2,4-thiadizole syntheses with the advantages of high efficiency, sustainability, and eco-friendly reagents, that is, visible light and air. Moreover, the reaction is performed in a simple one-pot operation under mild conditions and tolerates many functional groups.

Table 3 Visible-Light-Driven Aerobic Oxidative Conversion of Primary Thioamides into 1,2,4-Thiadiazoles[23]



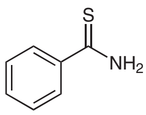
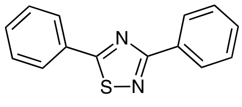
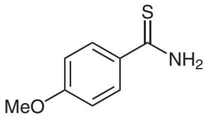
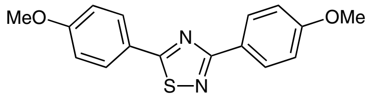
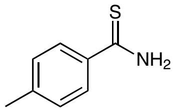
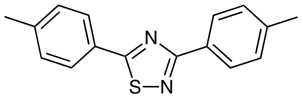
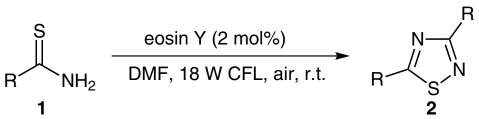
Entry	Substrate **1**	Product **2**[a]	Time (h)	Yield (%)[b]
1		 **2a**	4	91
2		 **2b**	4	95
3		 **2c**	4	93

Table 3 Visible-Light-Driven Aerobic Oxidative Conversion of Primary Thioamides into 1,2,4-Thiadiazoles[23] (continued)



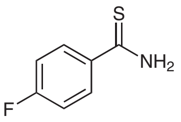
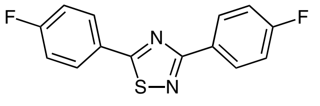
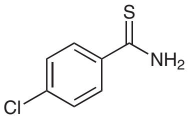
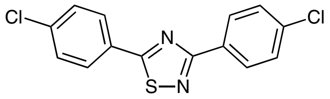
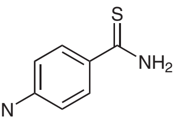
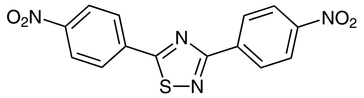
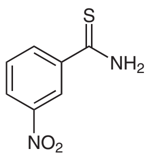
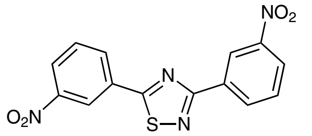
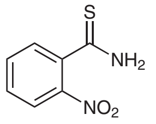
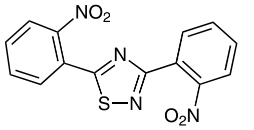
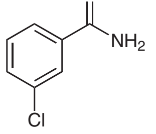
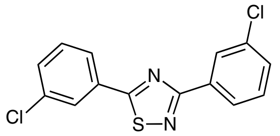
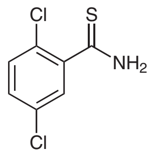
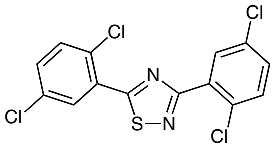
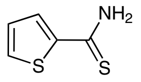
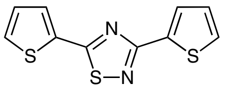
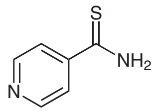
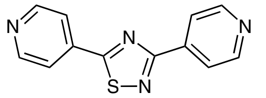
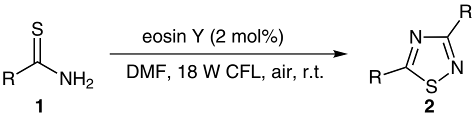
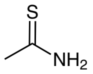
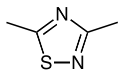
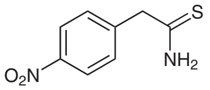
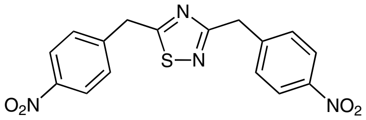
Entry	Substrate **1**	Product **2**[a]	Time (h)	Yield (%)[b]
4		 **2d**	6	86
5		 **2e**	6	88
6		 **2f**	6	75
7		 **2g**	6	80
8		 **2h**	6	72
9		 **2i**	6	90
10		 **2m**	6	74
11		 **2n**	4	92
12		 **2o**	6	76

Table 3 Visible-Light-Driven Aerobic Oxidative Conversion of Primary Thioamides into 1,2,4-Thiadiazoles[23] (continued)



Entry	Substrate **1**	Product **2**[a]	Time (h)	Yield (%)[b]
13		 **2p**	5	87
14		 **2q**	5	93

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[a] All the products are known compounds and were characterized by comparison of their mp and spectral data with those of reported in the literature.[20,24]

[b] Isolated yield of product **2**.

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References and Notes

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(23) **General Procedure for the Synthesis of 1,2,4-Thiadiazoles 2**
To a solution of thioamide **1** (1.0 mmol) in DMF (3 mL) was added eosin Y (2 mol%), and the mixture was irradiated with a household 18 W CFL (Philips, 6500 K, 1010 lm, 85 mA) with stirring under an air atmosphere (but no air bubbling) at r.t. for 4–6 h. After completion of the reaction (monitored by TLC), H_2O (3 mL) was added, and the mixture was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude product was purified by silica gel column chromatography using a gradient mixture of hexane–EtOAc as eluent to afford an analytically pure sample of **2**. All the products are known compounds and were characterized by the comparison of their melting points and spectroscopic data with those reported in the literature.[20,24]

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