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## Metal-free dehydrosulfurization of thioamides to nitriles under visible light

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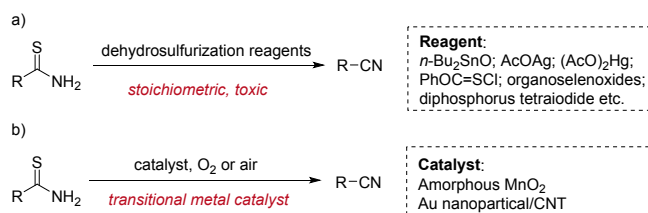
**A visible light mediated, metal-free dehydrosulfurization reaction of thioamides to nitriles is described. This reaction features the high yields, mild reaction conditions, and the use of a cheap organic dye as the photoredox catalyst and air as the oxidant.**

Nitriles are versatile intermediates in synthetic chemistry,<sup>1</sup> and also widespread structural motifs in pharmaceuticals, agricultural chemicals, herbicides, dyes and electronic materials.<sup>2-3</sup> One of the most classical methods for the synthesis of nitrile compounds involves the use of highly toxic inorganic and organic cyanides.<sup>4</sup> Over the past few years, considerable efforts to the synthesis of nitriles have been reported, using non-metallic cyano-group sources.<sup>5</sup> However, these methods often require transition metals and/or stoichiometric oxidants. Alongside these procedures, the dehydrosulfurization of thioamides to nitriles have become an attractive alternative method, as thioamides are easily accessible and widely used in organic synthesis.<sup>6</sup> Typically, the reported protocols for the preparation of nitriles from thioamides normally required stoichiometric dehydrosulfurization reagents to irreversibly convert thioamides to the key sulfide intermediates (Scheme 1a).<sup>7</sup> In contrast, catalytic approaches for dehydrosulfurization of primary thioamides are more desirable but rarely reported. So far, only two examples of catalytic dehydrosulfurization of thioamides to nitriles have been revealed recently, using amorphous MnO<sub>2</sub><sup>8</sup> and gold-carbon nanotube nanohybrid (AuCNT)<sup>9</sup> as the catalyst, respectively (Scheme 1b).

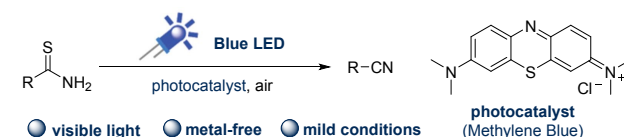
On the other hand, visible-light is an environmentally benign and renewable energy source for chemical reactions, and visible-light photoredox catalysis has emerged as a highly versatile tool for organic synthesis.<sup>10,11</sup> Despite these advances, a direct conversion of thioamides to nitriles by visible-light photocatalysis remains elusive so far. Herein, we report an unprecedented, visible light-mediated photocatalytic approach for dehydrosulfurization of thioamides to nitriles, by using an

organic dye (Methylene Blue, MB) as photocatalyst and molecular oxygen (air) as oxidant at room temperature (Scheme 1).

Previous work:



This work:



**Scheme 1** Synthesis of nitriles from thioamides and the visible light-mediated dehydrosulfurization in this work.

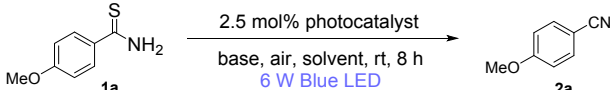
Initially, 4-methoxybenzothioamide **1a** was selected as the model substrate for optimization of the dehydrosulfurization conditions. When the reaction was conducted in CH<sub>3</sub>CN using Eosin Y as catalyst, DIPEA as base, with 6 W blue LED irradiation over 8 h under an air atmosphere (air balloon) at room temperature, the expected 4-methoxybenzothioamide **2a** was obtained in 50% yield, together with amide and several other side-products (Table 1, entry 1, for details, please see Scheme S1 in the supporting information). Light is crucial to this reaction, and in the absence of visible light irradiation, no reaction was observed (entry 2). Subsequently, different organic dyes including Mes-Acr<sup>+</sup>ClO<sub>4</sub><sup>-</sup>, Rose Bengal, Methylene Blue, Rhodamine B, Fluorescein, Methyl Orange, and Acid Red 51 were investigated as the photocatalyst (entries 3–9). Commercially available Acid Red 51 showed the highest selectivity to afford **2a** in 65% yield (entry 9). Lower yield was obtained when transition-metal-based catalyst [Ru(bpy)<sub>3</sub>]Cl<sub>2</sub>·6H<sub>2</sub>O was used (entry 10). Switching the solvent from CH<sub>3</sub>CN to CH<sub>2</sub>Cl<sub>2</sub>, 1,4-dioxane, DMSO, or THF led to lower yields (entries 11–14). In addition, different inorganic bases such as Na<sub>2</sub>CO<sub>3</sub> and K<sub>2</sub>CO<sub>3</sub> were examined, showing that the yield was increased as the basicity increase (Table 1, entries 15–16). Other organic bases, such as TMEDA, Et<sub>3</sub>N, and DBU, were also tested in the model reaction (entries 17–19). Pleasingly, the strong base DBU was found to give the best result with 93%

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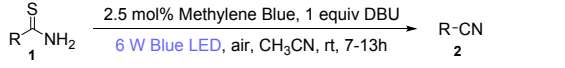
**Table 1** Optimization of Reaction Conditions<sup>a</sup>


Entry	Photocatalyst	Base	Solvent	Yield <sup>b</sup> (%)
1	Eosin Y	DIPEA	CH <sub>3</sub> CN	50
2 <sup>c</sup>	Eosin Y	DIPEA	CH <sub>3</sub> CN	n.r.
3	Mes-Acr <sup>+</sup> ClO <sub>4</sub> <sup>-</sup>	DIPEA	CH <sub>3</sub> CN	55
4	Rose Bengal	DIPEA	CH <sub>3</sub> CN	32
5	Methylene Blue	DIPEA	CH <sub>3</sub> CN	43
6	Rhodamine B	DIPEA	CH <sub>3</sub> CN	52
7	Fluorescein	DIPEA	CH <sub>3</sub> CN	58
8	Methyl Orange	DIPEA	CH <sub>3</sub> CN	50
9	Acid Red 51	DIPEA	CH <sub>3</sub> CN	65
10	[Ru(bpy) <sub>3</sub> ]Cl <sub>2</sub> •6H <sub>2</sub> O	DIPEA	CH <sub>3</sub> CN	49
11	Acid Red 51	DIPEA	CH <sub>2</sub> Cl <sub>2</sub>	57
12	Acid Red 51	DIPEA	1,4-dioxane	62
13	Acid Red 51	DIPEA	DMSO	36
14	Acid Red 51	DIPEA	THF	53
15	Acid Red 51	Na <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	23
16	Acid Red 51	K <sub>2</sub> CO <sub>3</sub>	CH <sub>3</sub> CN	26
17	Acid Red 51	TMEDA	CH <sub>3</sub> CN	61
18	Acid Red 51	Et <sub>3</sub> N	CH <sub>3</sub> CN	66
19	Acid Red 51	DBU	CH <sub>3</sub> CN	93
20	<b>Methylene Blue</b>	<b>DBU</b>	<b>CH<sub>3</sub>CN</b>	<b>96</b>

<sup>a</sup>Reaction conditions: **1a** (0.05 mmol), photocatalyst (2.5 mol%), base (1.0 equiv.) and solvent (0.05 mL) were irradiated with 6 W blue LEDs at room temperature under air for 8 h. <sup>b</sup>Determined by NMR using benzyl ether as an internal standard. DIPEA: *N,N*-Diisopropylethylamine. <sup>c</sup>Without light. n.r. = no reaction.

yield (entry 19). Finally, we tested several organic dye again with DBU, and glad to find that Methylene Blue could give a very clean reaction with the nearly quantitative yield (96%, entry 20).

With the optimized conditions in hand, the reaction scope of this new visible light-mediated dehydrosulfurization protocol was investigated using various structurally diverse aromatic, heteroaromatic, and aliphatic primary thioamides (Table 2). Gratifyingly, the aromatic thiobenzamide (**1a–1j**) which contain both electron-donating and electron-withdrawing substituents were well tolerated under the reaction conditions, affording the corresponding substituted benzonitrile derivatives **2a–2j** in high yields (Table 2, entries 1–10). An *ortho*-substituted substrate, 2-methoxybenzothioamide **1c** could also be converted to the corresponding nitrile **2c** in excellent yield (entry 3). Interestingly, halide substituted thiobenzamides are also suitable substrates, giving the corresponding benzonitriles (**2e–2g**) in excellent yields (entries 5–7). Notably, a range of functional groups such as methoxy (**1a** & **1c**), halide (**1f** & **1g**), and phenolic (**1d**) groups were compatible with the reaction conditions, and the corresponding products could be potentially further modified. Apart from thiobenzamides, heterocyclic thioamides (**1k–1p**) with nitrogen and sulfur atoms could also work well in this reaction to produce the desired nitriles (**2k–2p**) in excellent yields (entries 11–16). It is worth mentioning that, in most cases, we could observe a clean reaction by crude <sup>1</sup>H NMR analysis. Some isolated yields lower than 90% may be due to the product sublimation (visible on the evaporator) or its volatile nature.

**Table 2** Reaction Scope<sup>a</sup>


Entry	Substrate	Product	Entry	Substrate	Product
1	<b>1a</b>	<b>2a</b> , 94%	2	<b>1b</b>	<b>2b</b> , 80%
3	<b>1c</b>	<b>2c</b> , 91%	4	<b>1d</b>	<b>2d</b> , 88%
5	<b>1e</b>	<b>2e</b> , 86%	6	<b>1f</b>	<b>2f</b> , 87%
7	<b>1g</b>	<b>2g</b> , 89%	8	<b>1h</b>	<b>2h</b> , 87%
9	<b>1i</b>	<b>2i</b> , 85%	10	<b>1j</b>	<b>2j</b> , 95%
11	<b>1k</b>	<b>2k</b> , 87%	12	<b>1l</b>	<b>2l</b> , 95%
13	<b>1m</b>	<b>2m</b> , 93%	14	<b>1n</b>	<b>2n</b> , 86%
15	<b>1o</b>	<b>2o</b> , 81%	16	<b>1p</b>	<b>2p</b> , 90%
17	<b>1q</b>	<b>2q</b> , 91%	18	<b>1r</b>	<b>2r</b> , 62%

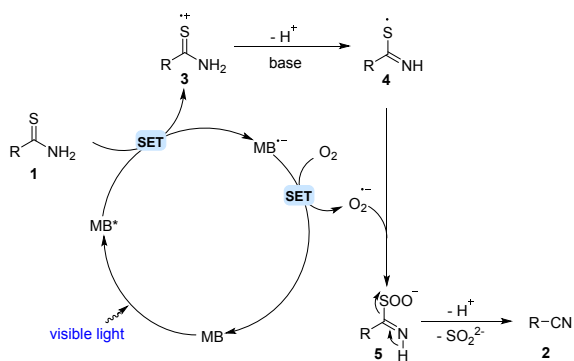
<sup>a</sup>Reaction conditions: **1** (0.3 mmol), Methylene Blue (2.5 mol%), DBU (1.0 equiv.) and CH<sub>3</sub>CN (3.0 mL) were irradiated with 6 W blue LEDs at room temperature under air for 7–13 h. <sup>b</sup>Isolated yield.

Moreover, not only aromatic thioamides but also aliphatic thioamides were amenable to undergo this dehydrosulfurization to furnish the corresponding nitrile **2q** in good yields (entry 17). In addition, thiocinnamamide **1r** can also be converted to the desired  $\alpha,\beta$ -unsaturated nitrile **2r** (entry 18).

On the basis of previous reports<sup>12,13</sup> and our observations, a plausible reaction pathway is outlined in Scheme 2. Initially, organic photoredox catalyst Methylene Blue (MB) is converted into the excited MB\* under visible-light irradiation. Next, a single electron transfer from **1** to MB\* affords the corresponding radical cation **3** and MB<sup>•-</sup> radical anion. Then, the radical cation **3** is deprotonated to give the stabilized sulfur radical **4** in the presence of base. Meanwhile, MB<sup>•-</sup> is oxidized by molecular oxygen (air) to regenerate the photocatalyst MB and concurrently affords O<sub>2</sub><sup>•-</sup>, which is subsequently coupled with the sulfur radical **4** to yield peroxysulfenate **5**. Finally,

deprotonation/elimination in the presence of base produces the desired final nitrile product **2**.

In summary, a visible light mediated dehydrosulfurization of thioamides to nitriles has been demonstrated for the first time. This new approach features the high reaction yield, good functional-group tolerance, and the use of a cheap organic dye (Methylene Blue) as the photocatalyst and air as the environmentally benign oxidant.



**Scheme 2** Proposed mechanism

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## Conflicts of interest

There are no conflicts to declare

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## Table of content entry:

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## Dehydrosulfurization under visible light:



R = aryl, alkyl

up to 95% yield

● *visible light*   ● *metal-free*   ● *mild conditions*

A visible light-mediated dehydrosulfurization of thioamides to nitriles is developed, using an organic dye as photocatalyst and air as oxidant.