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A SIMPLE METHOD FOR SYNTHESIS OF THIOAMIDES AND APPLICATION IN SYNTHESIS OF 1,2,4-THIADIAZOLES

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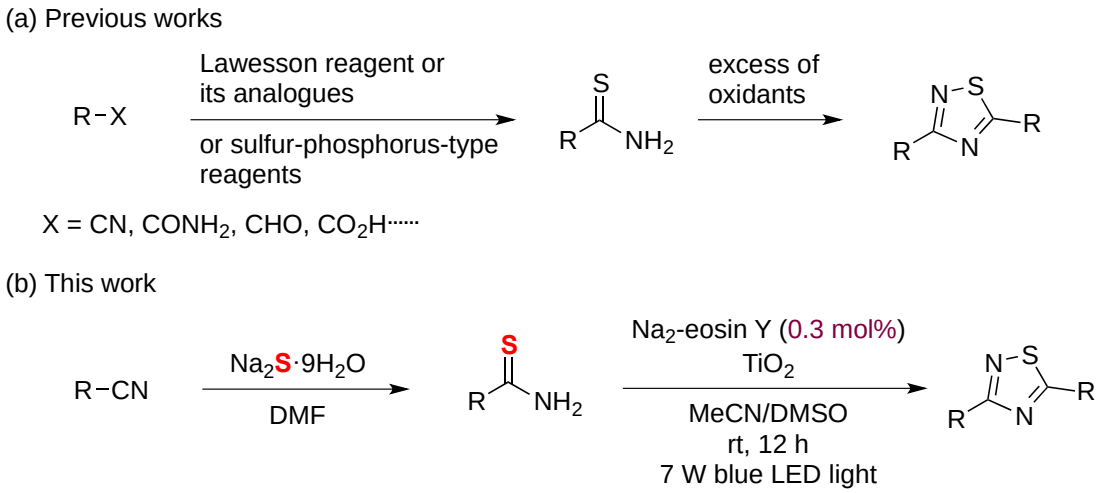
Abstract – A novel, simple protocol is disclosed for the synthesis of 1,2,4-thiadiazoles starting from thioamides with Na_2-eosin Y-sensitized titanium dioxide as catalyst through visible light irradiation (7 W blue LED light) and only 0.3 mol% catalysts were used. The raw material thioamides is prepared by aryl nitriles and sodium sulfide ($Na_2S·9H_2O$) in DMF and in this reaction, readily available, inexpensive inorganic salt ($Na_2S·9H_2O$) serves as the sulfur source and various functional groups of aryl nitriles were well and thioamides were synthesized successfully in gram-scale.

Thioamides and their derivatives are useful synthons in modern synthetic and medicinal chemistry due to their promising pharmaceutical and biological activity, and often found in vital medical molecules.[1] Consequently, a number of synthetic methods have been reported for the construction of these motifs using various reagents under diverse reaction conditions.[2-5] The general methods for the synthesis of thioamides use Lawesson's reagent and its analogues as sulfur sources (**Scheme 1**, a).[6,7] Similarly, sulfur–phosphorus-type reagents are applied to the synthesis of thioamides through nitriles or carboxylic acids and amides (**Scheme 1**, a).[8-10] Most of these reagents result in the formation of adverse by-products, not to mention some expensive reagents, and moreover, suffer from a narrow substrate scope. Accordingly, a simple method for the synthesis of thioamides is considered of high practical value.

Thioamides are applied broadly in the areas of synthesis of many significant sulfur-containing heterocycles as important building blocks, such as thiazolines, thiazoles, thiazolinones, thiadiazoles, tetrazoles, mesoionic rhodanine, betaines and other heterocyclic.[11] In particular, the 1,2,4-thiadiazoles which have a symmetrical core skeleton show a wide range of biological activities such as anti-cancer, anti-inflammatory, antituberculosis and antimicrobial activity.[12] Therefore, the synthesis of

1,2,4-thiadiazoles which have received extensive attention. The general synthetic route to synthesize 1,2,4-thiadiazoles involves the oxidative dimerization of thioamides by using various oxidants, such as $Cu(OTf)_2$, ceric ammonium nitrate (CAN), *t*-BuOCl, nitrous acid, oxone, pentylpyridinium tribromide, DDQ, organohypervalent iodine reagents, DMSO-electrophilic reagents and so on (**Scheme 1**, a).[13-18] However, many of these method suffer from limitations such as high temperature, large excess of reagents, harsh reaction conditions. Consequently, there is a need to develop a protocol that minimize the disadvantages enumerated above.

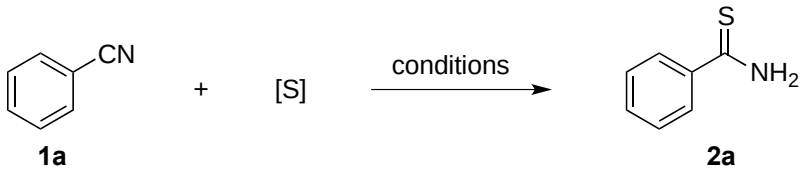
In view of this, herein, we would like to report a method for the synthesis of the thioamide via reaction of cheap, easily available sodium sulfide ($Na_2S·9H_2O$) and nitriles in DMF. Furthermore, a new route for the synthesis of 1,2,4-thiadiazoles by thioamides with Na_2-eosin Y-sensitized titanium dioxide as catalyst through 7 W blue light irradiation is presented (**Scheme 1**, b).



Scheme 1

Initially, the reaction conditions were optimized on simple benzonitrile (**1a**) (Table 1). Reaction of benzonitrile **1a** with S_8 in the presence of bases (entries 1-6) in different solvents. The expected product thiobenzamide **2a** was formed in absence of weak base Na_2CO_3 or K_2CO_3 in H_2O at 100 °C; however, the conversion was still incomplete after 12 h, giving product **2a** in low yields (Table 1, entres 1, 2). There are no the desired thiobenzamide **2a** by addition of organic base DBU in H_2O, DMF, or DMSO (entries 3, 5, 6), but the benzamide was obtained. AcOH as solvent could accelerate the reaction (entry 4) to give **2a** 52% yield. Then use of $Na_2S·9H_2O$ as sulfur source in solvents (entries 8-14), the product thiobenzamide **2a** were not found when the H_2O, DMSO or NMP as solvents. Further solvent screening (entries 10-14) suggested that DMF is the most effective media for this reaction. In general, the optimum conditions were 2.5 h at 130 °C in DMF.

Table 1. Optimization of the reaction conditions



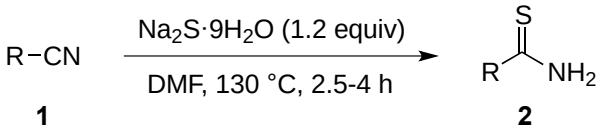
1a **2a**

Entry	S source	Base	Solvent	Yield[d] (%)
1[a]	S_8	Na_2CO_3	H_2O	56
2[a]	S_8	K_2CO_3	H_2O	54
3[a]	S_8	DBU	H_2O	0/51[e]
4[a]	S_8	DBU	AcOH	52
5[a]	S_8	DBU	DMSO	0/69[e]
6[a]	S_8	DBU	DMF	0/61[e]
8[b]	$Na_2S·9H_2O$	-	H_2O	0
9[b]	$Na_2S·9H_2O$	-	DMSO	0
10[b]	$Na_2S·9H_2O$	-	DMF	58
11[c]	**$Na_2S·9H_2O$**	**-**	**DMF**	**89**
12[c]	$Na_2S·9H_2O$	-	NMP	0
13[c]	$Na_2S·9H_2O$	-	DMAC	64
14[c]	$Na_2S·9H_2O$	-	PEG-400	0

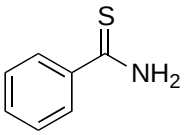
[a] Reaction conditions: **1a** 1.0 mmol, S_8 3.0 mmol, base 3.0 mmol, solvent 1 mL, 100 °C, 12 h; [b] Reaction conditions: **1a** 1.0 mmol, $Na_2S·9H_2O$ 1.2 mmol, solvent 1 mL, 100 °C, 2.5 h; [c] Reaction conditions: **1a** 1.0 mmol, $Na_2S·9H_2O$ 1.2 mmol, solvent 1 mL, 130 °C, 2.5 h; [d] Isolated yield; [e] Yield of benzamide.

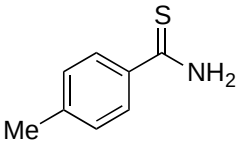
With the optimized reaction conditions established, a range of aromatic or heterocyclic nitriles substrates were then examined (Table 2). The experimental results showed that the substrates bearing electron-donating or electron-withdrawing groups underwent this reaction to generate thioamides in moderate to high yileds (65-90%). The substrate bearing the electron-donating groups Me, *t*-Bu, OMe reacted smoothly with yields of up to 90% (Table 2, **2b-e**). The substrate bearing the electron-withdrawing groups F, Cl, CF_3, also reacted well with yields of up to 72% (Table 2, **2f-i**). Naphthonitriles were successfully converted into the corresponding products with yields of up to 84% (Table 2, **2k**, **2l**). The coupling of heteroaryl nitriles with $Na_2S·9H_2O$ also performed well (Table 2, **2m-q**). In general, it can be concluded from the results that the system had broad applicability to substrates in this reaction.

Table 2. Substrate scope for the thioamides[a,b]

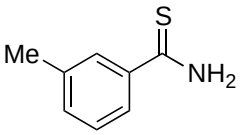


1 **2**

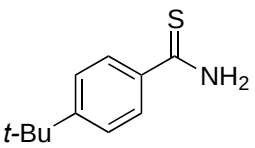

2a, 89%



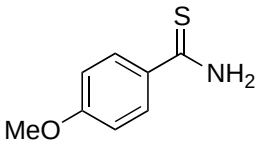
2b, 90%



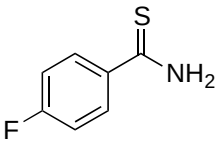
2c, 87%



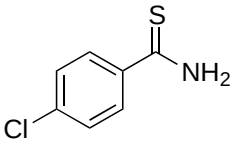
2d, 83%



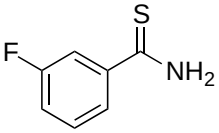
2e, 70%



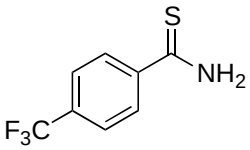
2f, 71%



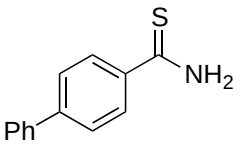
2g, 72%



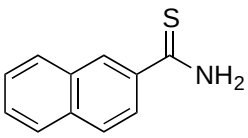
2h, 70%

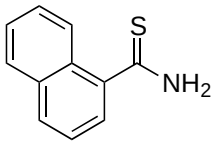


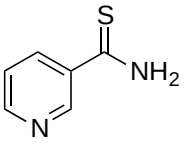
2i, 70%

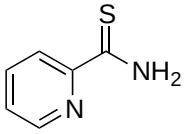


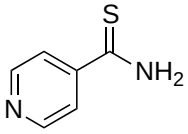
2j, 70%[c]

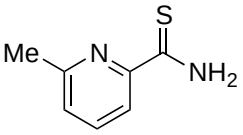

2k, 84%


2l, 68%[c]

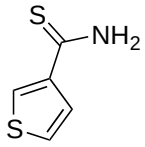

2m, 69%

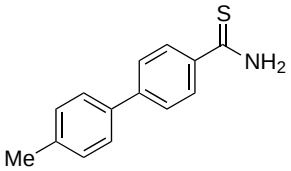

2n, 67%


2o, 70%



2p, 71%


2q, 82%

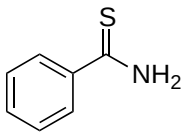


2r, 74%[c]

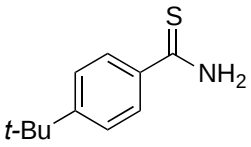
[a] Reaction conditions: **1** (1 mmol), $Na_2S·9H_2O$ (1.2 mmol), solvent 1 mL, 130 °C, 2.5 h; [b] Isolated yield; [c] Reaction time: 4 h.

In order to embody the application value of the method, the scalability of the reaction has been tested with five compounds (Table 3), and the results are encouraging.

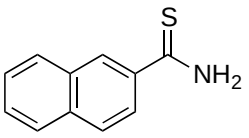
Table 3. Gram-Scale Synthesis[a,b]



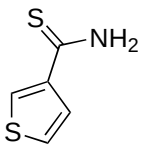
2a, 80%, 1.10 g



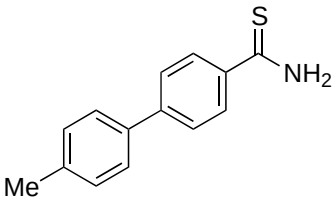
2d, 75%, 1.45 g



2k, 81%, 1.52 g



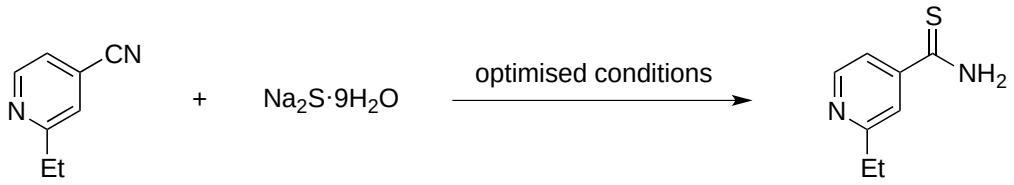
2q, 72%, 1.03 g



2r, 63%,[c] 1.43 g

[a] Reaction conditions: **1** (10 mmol), $Na_2S·9H_2O$ (12 mmol), solvent 1 mL, 130 °C, 2.5 h; [b] Isolated yield; [c] Reaction time: 4 h.

We next inspected the applicability of this method to synthesize ethionamide which is an antibiotic used to treat tuberculosis, and the synthesis of compound ethionamide was successful proceed under optimised conditions, and the target product was obtained in 67% yield.



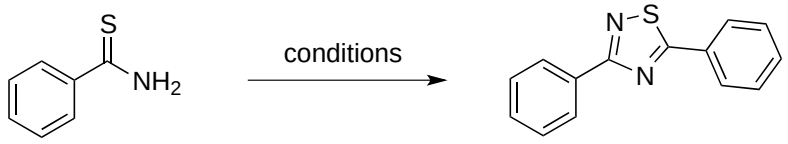
5.0 mmol

ethionamide
67%, 0.56 g

Scheme 2. Application of the reaction

With the effective method of thioamides in hand, the products were easily obtained as pure thioamides, which permit access to 1,2,4-thiadiazoles. The hypothesis was first examined using thiobenzamide **2a** as the model substrate. Initially, control experiments were performed in the dark or in the absence of the photoredox catalyst revealed that both the photoirradiation and catalyst are crucial for this reaction (Table 4, entries 1, 2). Then various solvents were screened upon irradiation by white LEDs in the presence of catalytic amount of Na_2-eosin Y-TiO_2 (0.3 mol%), affording the desired **3a** in low yields. We next examined the influence of blue LEDs in various solvents, the results showed that gave the highest yield (Table 4, 7-13), as well as identifying the mixture of MeCN (1.5 mL) and DMSO (0.5 mL) was the best.

Table 4. Optimization of the reaction conditions



2a **3a**

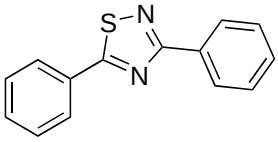
Entry	LEDs	Solvent	Yield[b] (%)
1	-	DMSO	0
2[c]	white	DMSO	0
3	white	DMSO	33
4	white	H_2O	trace
5	white	MeCN	36
6	white	DMF	30
7	blue	DMSO	52
8	blue	H_2O	trace
9	blue	DMF	37
10	blue	MeCN	55
11[d]	blue	DMSO/MeCN	60
12[e]	blue	DMSO/MeCN	63
13[f]	blue	DMSO/MeCN	70

[a] Reaction conditions: **2a** (0.25 mmol), Na_2-eosin Y-TiO_2 (8 mg, 0.3 mol% Na_2-eosin Y), solvent 2 mL, 7 W LEDs, rt, 12 h; [b] Isolated yield; [c] No catalyst; [d] MeCN 1.0 mL, DMSO 1.0 mL; [e] MeCN 1.2 mL, DMSO 0.8 mL; [f] MeCN 1.5 mL, DMSO 0.5 mL.

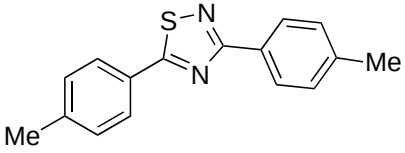
With the optimal reaction conditions in hand, we aimed to define the scope of this method. The experimental results showed that the substrates bearing electron-donating or electron-withdrawing groups underwent this reaction to generate 1,2,4-thiadiazoles in moderate yields (56-73%, Table 5). The methyl group increased the yield of up to 73%, while the *para*-substitution and *meta*-substitution had a little effect on the yield. The halogen groups, CF_3, OMe group decreased the yield. In addition, when 1-thionaphthamide **2l** and 2-thionaphthamide **2k** were employed as substrates, the corresponding product **3i** and **3j** could be obtained in 59% and 60% yields, respectively.

Table 5. Synthesis of 1,2,4-thiadiazoles[a,b]

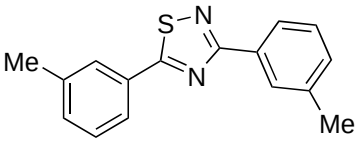
2 **3**



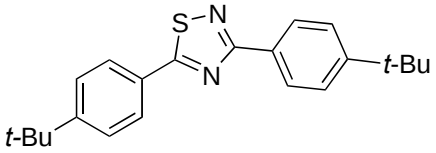
3a, 70%



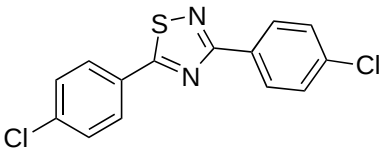
3b, 73%



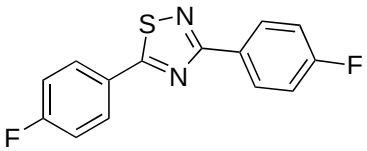
3c, 71%



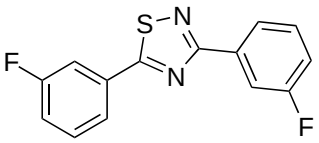
3d, 69%



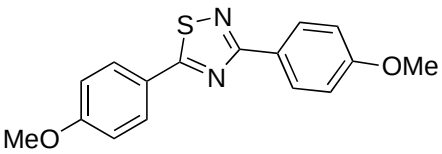
3e, 61%



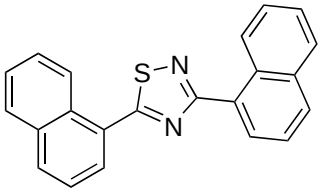
3f, 60%



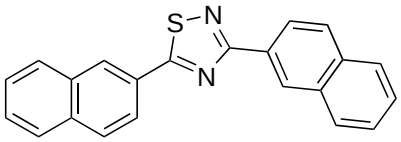
3g, 63%



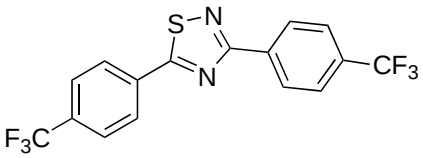
3h, 61%



3i, 59%



3j, 60%



3k, 56%

[a] Reaction conditions: **2** (0.25 mmol), Na_2-eosin Y-TiO_2 (8 mg, 0.3 mol% Na_2-eosin Y), MeCN 1.5 mL, DMSO 0.5 mL, rt, 12 h, 7 W blue LED light; [b] Isolated yield.

In summary, we have developed an efficient way to obtain thioamides by use aryl nitriles with $Na_2S·9H_2O$ as a conveniently available, inexpensive, and easy-to-handle sulfide surrogate, and the method can proceed well with gram-scale synthesis and highlights its potential application in organic

synthesis and pharmaceutical industry. Moreover, we used thioamides as raw material to synthesize 1,2,4-thiadiazoles through visible light irradiation (7 W blue light).

EXPERIMENTAL

The general procedure of preparing all thioamides: Benzonitrile **1a** (1 mmol), $Na_2S·9H_2O$ (1.2 mmol) and DMF (1 mL) were added into a 10 mL bottle. The reactor was placed in a heating magnetic stirrer at 130 °C. After 2.5 h, by adding about 3 mL H_2O after the reaction to disperse the solid product, the reaction mixture was extracted with EtOAc (3 x 3 mL), and the mixture was purified by column chromatography.

General procedure for preparation of 1,2,4-thiadiazoles: To a 10 mL bottle were added 0.25 mmol of arylthioamide and Na_2-eosin Y-TiO_2 (8 mg) in MeCN 1.5 mL and DMSO 0.5 mL. The reaction mixture was stirred at room temperature for 12 h. Next, by adding about 2 mL H_2O after the reaction to disperse the solid product, the reaction mixture was extracted with EtOAc, and the mixture was purified by column chromatography.

The Na_2-eosin Y-sensitized TiO_2 (rutile) catalyst was prepared accord with the literature[19]: Na_2-eosin Y (692 mg, 1 mmol) and anhydrous EtOH (120 mL) were added to a 250 mL round-bottom flask equipped with a stir bar. The flask was sealed with a rubber septum and sonicated for 10 min before TiO_2 (rutile) (10.0 g) was added to the flask. The flask was then sealed with a rubber septum and sonicated for another 10 min. The resulting mixture was stirred for 12 h at room temperature. The solvent was removed under reduced pressure, and the resulting red solid was dried at 40 °C in a vacuum oven for 12 h.

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