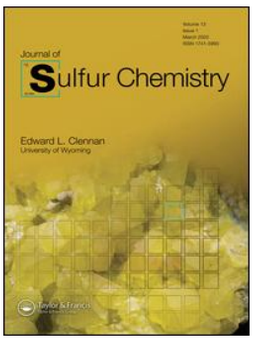

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SHORT COMMUNICATION

Mixed bases mediated synthesis of thioamides in water

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ABSTRACT

A mixed bases mediated protocol is developed to synthesize thioamides from *N*-aryl or *N*-alkylamide, aldehyde and elemental sulfur in water. This reaction requires no addition of external oxidant and avoids large excess of amides. Various functional groups and pharmaceutically interesting heteroaromatic rings could be introduced via this efficient procedure.

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Transition-metal-free; mixed bases mediated; thioamides; water as solvent; elemental sulfur

1. Introduction

Thioamides, as an important class of sulfur-containing compounds, are known as significant building blocks to furnish heterocyclic compounds in synthetic chemistry [1–7]. Thioamide motifs are also widely present in a large variety of biologically active compounds for pharmaceutical and agrochemical use [8,9]. For instance, ethionamide (ETH) and prothionamide (PTH) are generally used as second-line drugs in tuberculosis treatment [10]. Elesclomol has been proved to show anticancer activity by elevating oxidative stress and reactive oxygen species [11]. Extensive researches have been made to apply thioamides as ligands in organic chemistry and fluorescence quenching probes in material science [3,12–18].

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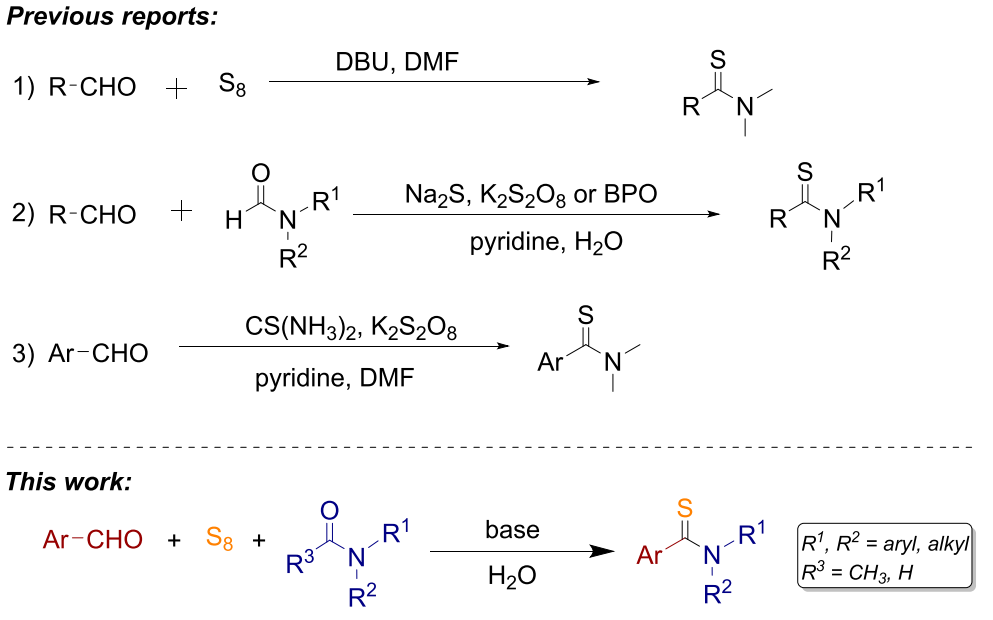
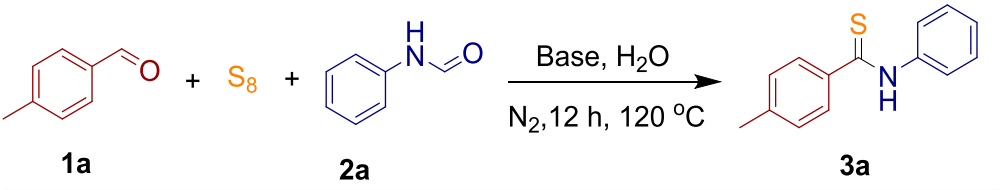


Figure 1. Synthetic strategies for thioamides.

Traditional methods toward the synthesis of thioamides used sulfur reagents, mostly Lawesson's reagent and P_2S_5 [19,20]. Both Lawesson's reagent and P_2S_5 have obvious drawbacks since they are sensitive to moisture. The Willgerodt–Kindler-type reaction of aldehydes (or ketones), amines and elemental sulfur is an alternative strategy [21–26]. Despite those classic methods, multicomponent coupling reactions have been proved to be step-economic and experimentally simple approaches to afford thioamide derivatives [27–36]. By using amides as nitrogen sources, Liu and co-workers reported a reaction of aldehyde or ketones with DMF (also as solvent) in the presence of elemental sulfur and DBU (Figure 1, Reaction 1) [37]. Later, Jiang *et al.* developed an aqueous procedure for the synthesis of alkyl and aryl thioamides (Figure 1, Reaction 2) [38]. This reaction of aldehydes, *N*-substituted formamides and sodium sulfide require the assistance of $K_2S_2O_8$ or benzoyl peroxide (BPO) as the oxidant. Bian's group reported that $K_2S_2O_8$ promoted aryl thioamides synthesis from aryl aldehydes with thiourea as the sulfur source in DMF (Figure 1, Reaction 3) [39]. Other methods to achieve thioamides with formamides as nitrogen source have been developed by altering various types of coupling partners. Recently, Cheng *et al* described a three-component reaction between quaternary ammonium salts and *N*-substituted formamides in aqueous solution of Na_2S_2 [40]. Liu's group accomplished thioamidation between alkynes and S_8 with amide as the solvent [41].

Despite their great advances, those methods are predominantly conducted with large excess of amides and require certain oxidants. Moreover, only *N*-alkylformamides (mostly DMF, DMAc or *N*-formylmorpholine) could be converted to the desired thioamide compounds. Hence, our research aimed at the development of a more versatile strategy using the green solvent while avoiding the usage of an external oxidant. In this article, we disclose a mixed bases mediated synthesis of thioamides from *N*-alkyl or *N*-arylamides, elemental sulfur and arylaldehydes in water.

Table 1. Optimal reaction screening[a].

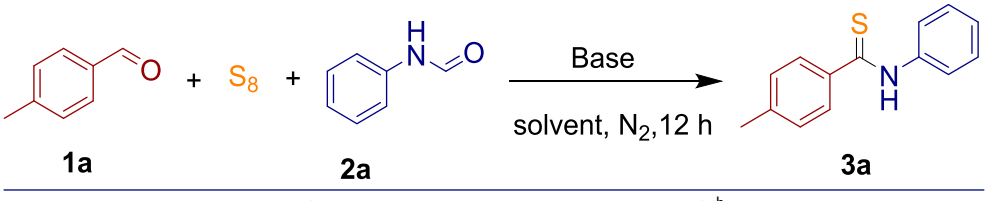


1a **2a** **3a**

Entry	Base	Yield[b] (%)
1	NaOH (3 eq.)	61
2	Na_2CO_3 (3 eq.)	70
3	K_3PO_4 (3 eq.)	59
4	DBU (3 eq.)	63
5	TEA (3 eq.)	62
6	TMDEA (3 eq.)	63
7	NaOH (1.5 eq.) + TEA (1.5 eq.)	72
8	Na_2CO_3 (1.5 eq.) + TEA (1.5 eq.)	90 (64[c], n.p.[d])
9	Na_2CO_3 (0.5 eq.) + TEA (0.5 eq.)	10
10	Na_2CO_3 (1 eq.) + TEA (1 eq.)	83
11	Na_2CO_3 (2 eq.) + TEA (2 eq.)	91
12	Na_2CO_3 (2 eq.) + TEA (1 eq.)	70
13	Na_2CO_3 (1 eq.) + TEA (2 eq.)	81

[a]Reaction conditions: **1a** (0.2 mmol), S_8 (0.2 mmol), **2a** (5 eq.), base, H_2O (1 mL), 120°C, sealed tube, N_2, 12 h. [b]Isolated yields. [c]Sealed tube, air. [d]No base.

Table 2. Reaction parameters screening for the synthesis of thioamides[a].



1a **2a** **3a**

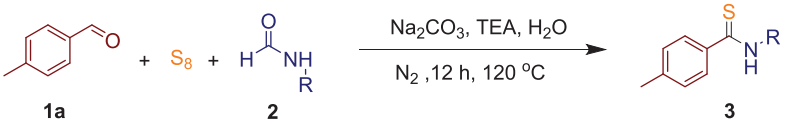
Entry	**2a** (eq.)	T(°C)	Solvent	Yield[b] (%)
1	5	80	H_2O (1 mL)	51
2	5	100	H_2O (1 mL)	88
3	5	130	H_2O (1 mL)	90
4	5	120	H_2O (0.5 mL)	90
5	5	120	H_2O (2 mL)	52
6	5	70	THF (1 mL)	trace
7	5	70	EtOH (1 mL)	n.p.
8	5	120	Toluene (1 mL)	n.p.
9	1	120	H_2O (1 mL)	20
10	2	120	H_2O (1 mL)	32
11	3	120	H_2O (1 mL)	57
12	4	120	H_2O (1 mL)	81
13	6	120	H_2O (1 mL)	91

[a]Reaction conditions: **1a** (0.2 mmol), S_8 (0.2 mmol), **2a** (x eq. of **1a**), Na_2CO_3 (1.5 eq.), TEA(1.5 eq.), solvent, 120°C, sealed tube, N_2, 12 h. [b]Isolated yields.

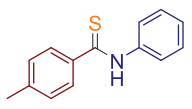
2. Results and discussion

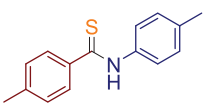
Our efforts to develop this reaction start with a model reaction between *p*-methylphenylaldehyde **1a** and *N*-phenylformamide **2a** with elemental sulfur as the sulfur source in water. Initially, various inorganic bases and organic bases were tested, as shown

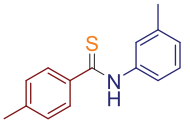
Table 3. Reaction of formamides with 4-methylbenzaldehyde[a].

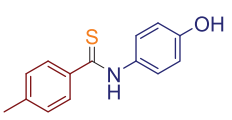


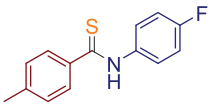
1a + S_8 + 2 → 3

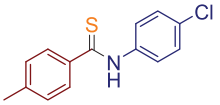

3a: 90%

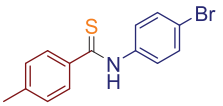

3b: 93%

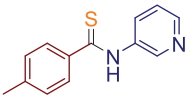

3c: 90%

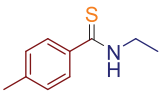

3d: 95%

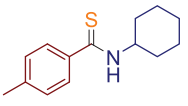

3e: 94%

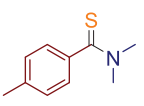

3f: 95%

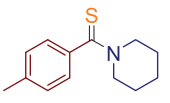

3g: 92%

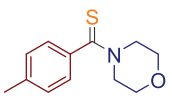

3h: 91%[b]

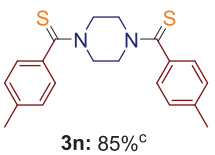

3i: 89%


3j: 95%


3k: 97%


3l: 85%

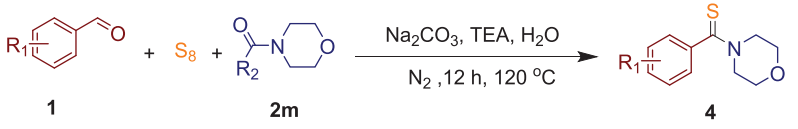

3m: 97%


3n: 85%[c]

[a]Reaction conditions: **1a** (0.2 mmol), S_8 (0.2 mmol), **2** (1 mmol), Na_2CO_3 (0.3 mmol), TEA (0.3 mmol), H_2O (1 mL), sealed tube, N_2, 120°C, 12 h. [b]Na_2CO_3 (0.3 mmol), TEA (0.6 mmol). [c]**1a** (0.4 mmol), S_8 (0.4 mmol), **2** (2 mmol), Na_2CO_3 (0.6 mmol), TEA (0.6 mmol).

in Table 1. While other bases exhibited not much difference in the desired transformation (Table 1, Entries 1, 3–6), Na_2CO_3 led to higher product yield (Table 1, Entry 2). Compared to the result of NaOH as the sole base (Table 1, Entry 1), we found that the combination of NaOH and triethylamine (TEA) could increase the product yield to 72% (Table 1, Entry 7). By keeping the total amount of mixed bases as 3 equivalents while the ratio of Na_2CO_3 to TEA as 1:1, the combination of Na_2CO_3 and TEA furnished the desired thioamide **3a** in 90% yield (Table 1, Entry 8). Variations from either the above-mentioned total amount or ratio led to similar or lower yields (Table 1, Entries 9–13). Control experiment performed under air atmosphere gave thioamide **3a** in 64% yield (Table 1, Entry 8). Moreover, no product was formed in the absence of base, indicating the necessity of base in the transition-metal-free thioamidation (Table 1, Entry 8). Other parameters, including ratio of **2a** against **1a**, base amount, solvent volume and reaction temperature, were evaluated as well (Table 2). The use of organic solvents (THF, EtOH and toluene) gave only trace amount or no product (Table 2, Entries 6–8).

Table 4. Reaction of aryl aldehydes with amides[a].

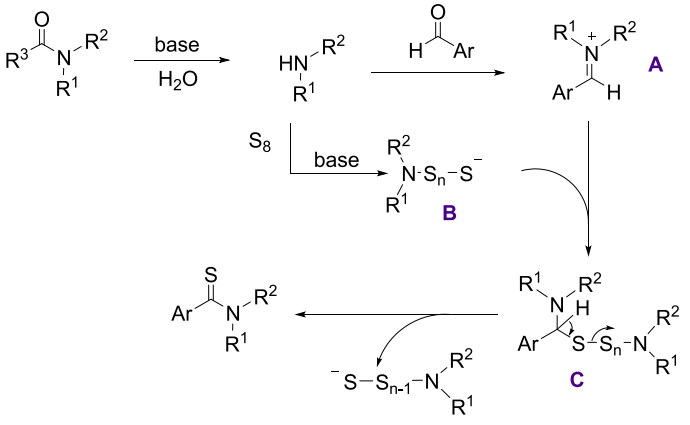


1 2m 4

4a	4b	4c	4d
R_2 = H 97%	R_2 = H 98%	R_2 = H 99%	R_2 = H 95%
R_2 = CH_3 95%	R_2 = CH_3 95%	R_2 = CH_3 95%	R_2 = CH_3 90%
4e	**4f**	**4g**	**4h**
R_2 = H 91%	R_2 = H 96%	R_2 = H 94%	R_2 = H 98%
R_2 = CH_3 90%	R_2 = CH_3 95%	R_2 = CH_3 91%	R_2 = CH_3 94%
4i	**4j**	**4k**	**4l**
R_2 = H 93%	R_2 = H 93%	R_2 = H 76%	R_2 = H 72%
R_2 = CH_3 90%	R_2 = CH_3 85%	R_2 = CH_3 25%	R_2 = CH_3 24%
4m	**4n**	**4o**	**4p**
R_2 = H 64%	R_2 = H 47%	R_2 = H 36%[b]	R_2 = H 45%[b]
R_2 = CH_3 n.p.	R_2 = CH_3 42%	R_2 = CH_3 28%[b]	R_2 = CH_3 40%[b]

[a]Reaction conditions: **1** (0.2 mmol), S_8 (0.2 mmol), **2 m** (1 mmol), Na_2CO_3 (0.3 mmol), TEA (0.3 mmol), H_2O (1 mL), sealed tube, N_2, 120°C, 12 h. [b]S_8 (0.4 mmol), **2 m** (2 mmol), Na_2CO_3 (0.6 mmol), TEA (0.6 mmol), H_2O (2 mL).

With the optimal reaction condition in hand, the scope of formamides was explored with 4-methylbenzaldehyde **1a** as a model substrate. A wide range of *N*-alkyl and *N*-arylamides could be smoothly converted to thioamides (Table 3). *N*-phenylformamides bearing electron-donating groups on the phenyl ring, such as methyl and hydroxyl or electron-withdrawing groups, such as halides, furnished thioamides **3a–g** in 90–95% yields. To be noticed, halide groups (Cl, Br) were well tolerated under this reaction condition, providing potential synthetic applications via conventional coupling reaction. *N*-(pyridin-3-yl)formamide could lead to thioamide **3h** in 91% yield while higher equivalent of TEA was needed. This transition-metal-free protocol is also compatible with primary and secondary *N*-alkylamides as substrates (**3i–n**). Piperazine-1,4-dicarbaldehyde containing two formamide motifs furnished the corresponding thioamide **3n** in good



Scheme 1. Proposed reaction mechanism.

yield, demonstrating the high efficiency of this aqueous compatible transition-metal-free method.

As part of an effort to expand the synthetic utility of this base-mediated thioamidation protocol, we investigated the substrate scope of arylaldehydes to react with *N*-formylmorpholine (Table 4). Aryl aldehydes bearing electron-donating groups, such as methyl (*para*- or *meta*-), isopropyl, hydroxyl, methoxy, and *N,N*-dimethylamino, or electron-withdrawing group, such as chloro, result in excellent yields (**4a–h**). Arylaldehyde with extended π-framework afford product **4i** in 93% yield. Noteworthy examples include the introduction of pharmaceutically interesting heteroaromatic rings such as thiophene, pyridine, pyrrole and imidazole to thioamides **4j–n**. Terephthalaldehyde and 4,4'-diformylbiphenyl could react with *N*-formylmorpholine to give product **4o** and **4p** in modest yields, respectively. The replacement of *N*-formylmorpholine with *N*-acetylmorpholine as the reaction partner in these examples did not affect the reaction outcome much in most cases, except for **4k–m**. In general, the product yields afforded by *N*-acetylmorpholine would be a little bit lower than they were in the situation of *N*-formylmorpholine. However, reactions of *N*-acetylmorpholine with aldehydes containing pyridine or pyrrole rings gave much lower yields (**4k, l**) or no product (**4m**) at all.

Based on previous reports [27,38,39], and our experimental results, the plausible reaction mechanism is proposed in Scheme 1. Initially, amine is formed by decarbonylation of formamide and undergoes nucleophilic attack to an aryl aldehyde, generating the iminium intermediate **A**. In the meantime, elemental sulfur undergoes nucleophilic attack by amine to form polysulfide **B**. Then, the iminium **A** react with polysulfide **B** to afford intermediate **C**. In the final step, elemental-sulfur-promoted oxidation of intermediate C releases the target product.

3. Conclusions

In conclusion, we have reported a mixed bases mediated thioamidation of aldehyde, amides and elemental sulfur in water. In contrast to other thioamidation strategies between aldehydes and *N*-alkylamides, there is no need for transition metal, external oxidant, large excess

of amides or organic solvent. This transition-metal-free protocol uses water as the solvent and is compatible with a wide range of *N*-aryl and *N*-alkylamides, while various functional groups (including Cl, Br) on the aromatic ring could be well tolerated. Noticeably, a series of pharmaceutically interesting heteroaromatic rings could be introduced in high efficiency via this aqueous compatible procedure.

4. Experimental

4.1. Typical procedure for the thioamides

A 25 mL Schlenk tube was charged with S_8 (51.2 mg, 0.2 mmol), TEA (30.4 mg, 0.3 mmol), Na_2CO_3 (31.8 mg, 0.3 mmol), **2** (121.1 mg, 1 mmol), **1** (24.1 mg, 0.2 mmol), H_2O (1 mL), and N_2, and then the resulting mixture was stirred at 120°C. After 12 h, the reaction mixture was extracted with dichloromethane (3 × 50 mL), and then dried over anhydrous sodium sulfate and filtered. After evaporation of the solvent under vacuum, the residue was subjected to flash column chromatography on silica gel to afford products **3a**–**3n**, **4a**–**4p**.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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