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Microwave-assisted iodine-catalyzed oxidative coupling of dibenzyl(difurfuryl)disulfides with amines: a rapid and efficient protocol for thioamides†

Jinyang Chen,[a] Lan Mei,[a] Jialing Liu,[a] Chuntao Zhong,[a] Binfang Yuan*[a] and Qiang Li[b]

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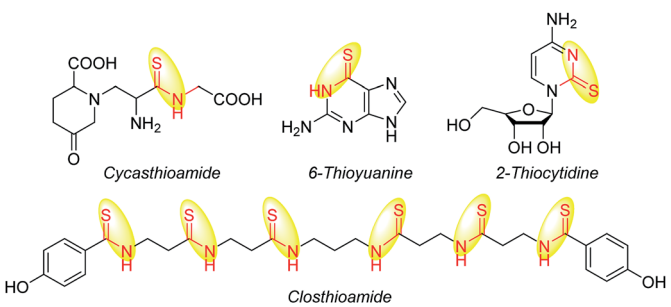
An efficient protocol for synthesis of thioamides was developed *via* the microwave-assisted iodine-catalyzed oxidative coupling of dibenzyl(difurfuryl)disulfides with amines. This process is scalable and tolerates a wide spectrum of amines to deliver the corresponding products in moderate to excellent yields in 10 minutes, providing a cheap and rapid approach to thioamides.

Thioamides have become an attractive synthetic goal in organic chemistry,[1] because thioamide skeletons are widely present in drugs and natural products,[2] such as cycasthioamide,[3] 6-thioyuanine,[4] 2-thiocytidine[5] and closthioamide[2a] (Scheme 1), and their application as useful precursors and versatile building blocks for construction of a range of heterocyclic compounds has also been studied.[1a,6] In addition, thioamides also can be used as a synthetic isostere for amides in peptide backbones,[7] and their application as directing groups has also been reported.[8,1c] Furthermore, the application of thioamides in developing novel a fluorophore/quencher pair for monitoring the unfolding of a small protein was also explored.[9]

Because of their wide application, efforts are devoted toward their generation.[10] The Willgerodt–Kindler reaction is a well-known method for construction of thioamides by using aldehydes and secondary amines as starting materials.[11] However, this thioamidation always suffers from the problems of low conversions and harsh conditions. Though, modified variations in Willgerodt–Kindler reaction were also reported,[1a,12] the use of excessive amounts of elemental sulphur makes it a less economical method. Lawesson's reagent was also used as common sulfur reagent for synthesis of thioamides,[13] however, this reaction was also occur under harsh conditions. Another thioamidation, where elemental sulfur was used as sulfur reagent, was also reported by Savateev's groups *via* a photo-initiated reaction (Scheme 2a).[11a] However, this transformation was only suitable for special thioamides with the same structure of amines. Thiols can also be used as sulfur reagent for construction of thioamides,[13b,c] but its pungent smell makes this reaction difficult to carry out (Scheme 2b). Recently, Nguyen's group described a novel process to thioamides by using sulfur as catalyst.[14] This method was suitable for a large range of amines for giving the corresponding products in good to excellent yields at 80 °C for a long time of 16 h.

Other methods for thioamides were also reported,[15] but challenges still exist in developing more convenient and efficient ways to these important scaffolds. In our previous work, thioamides were synthesized *via* the iodine-promoted thioamidation of several of amines.[16] However, this reaction must be performed under high temperature, for a long time (100 °C, 8.0 h), and 0.5 equiv. of I_2 must to be used to promote the thioamidation effectively (Scheme 2c).

As one of the efficient and clean procedures in modern synthetic organic chemistry, microwave-assisted organic synthesis (MAOS) has aroused wide interest among scientists, which are suited to the increased demands in industry with the advantages of short reaction times and expanded reaction range.[17] Herein, we reported an efficient method for synthesis of thioamides *via* the



Scheme 1 Structures of natural products bearing thiocarbonyl group.

[a]College of Chemistry and Chemical Engineering, Yangtze Normal University, Fuling, Chongqing, 408000, P. R. China. E-mail: 6781022@163.com

[b]Institution of Functional Organic Molecules and Materials, School of Chemistry and Chemical Engineering, Liaocheng University, No. 1, Hunan Street, Liaocheng, Shandong, 252059, P. R. China

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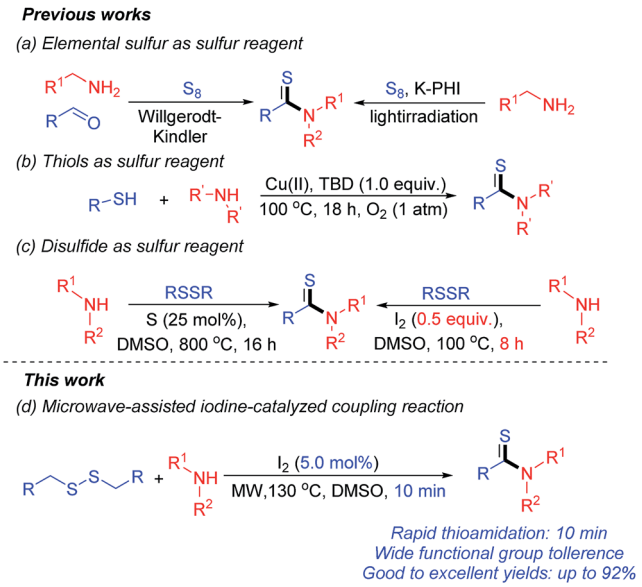


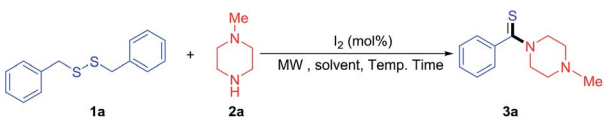
Scheme 2 General methods for synthesis of thioamides.

microwave-assisted iodine-catalyzed oxidative coupling of dibenzyl(furan-2-ylmethyl) disulfides with amines (Scheme 2d).

We initiated our studies with the reaction of dibenzyldisulfide (**1a**) with *N*-methylpiperazine (**2a**) catalyzed by 10 mol% of I_2 in DMSO under microwave radiation (100 °C) for 10 minutes, and the desired product (**3a**) was obtained in the yield of 36% (Table 1, entry 1). The reaction temperature affected the reaction obviously, and highest yield was obtained when the temperature was increased to 130 °C for 10 minutes (Table 1, entry 4). But no increase in yield was observed when the temperature was increased to 140 °C (Table 1, entry 5) and the reaction time to 15 minutes (Table 1, entry 8). Next, a series of solvents (such as DMSO, DMF, 1,4-dioxane, THF, CH_3CN, HOAc, chlorobenzene and toluene, or solvent-free) were also examined to promote the reaction (Table 1, entries 7–14), and results showed that DMSO is the best solvent, affording the desired product (**3a**) in the yield of 88% in 10 minutes (Table 1, entry 4). Then we explored the influence of the catalyst on the thioamidation, and results showed that the amount of 5.0 mol% of I_2 was enough to promote the reaction effectively (88%, Table 1, entry 15). The yield of desired product decreased to 73% and 78% respectively, even extending the reaction time to 15 minutes, when 3.0 mol% of I_2 was used. In addition, no increase in yield was observed, when the ratio of reactants (**2a**/**1a**) was increased to 3.0 (Table 1, entry 18). Only 18% of desired product was obtained, when the reaction was performed in the presence of 5.0 mol% of I_2 in DMSO at 130 °C for 10 minutes without microwave irradiation (Table 1, entry 18). After extensive screening, we were glad to find that the reaction of dibenzyldisulfide (**1a**) with *N*-methylpiperazine (**2a**) in DMSO catalyzed by 5.0 mol% of I_2 and assisted by microwave radiation provided the desired product (**3a**) with an excellent yield of 88% within 10 min (Table 1, entry 15).

With the optimal conditions in hand, the scope of the amines and disulfides were investigated, and results were summarized in Table 2. As shown in Table 2, we can see that

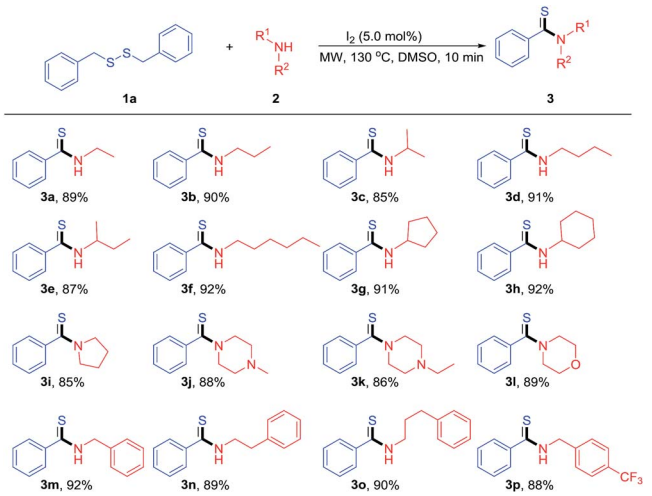
Table 1 Optimization of the reaction conditions[a]



Entry	I_2 (mol%)	Solvent	Temp. (°C)	Time (min)	Yield[b] (%)
1	I_2 (10 mol%)	DMSO	100	10	36%
2	I_2 (10 mol%)	DMSO	110	10	48%
3	I_2 (10 mol%)	DMSO	120	10	65%
4	I_2 (10 mol%)	DMSO	130	10	88%
5	I_2 (10 mol%)	DMSO	140	10	88%
6	I_2 (10 mol%)	DMSO	130	15	88%
7	I_2 (10 mol%)	DMF	130	10	74%
8	I_2 (10 mol%)	1,4-Dioxane	130	10	67%
9	I_2 (10 mol%)	THF	130	10	65%
10	I_2 (10 mol%)	CH_3CN	130	10	70%
11	I_2 (10 mol%)	HOAc	130	10	62%
12	I_2 (10 mol%)	Chlorobenzene	130	10	74%
13	I_2 (10 mol%)	Toluene	130	10	63%
14	I_2 (10 mol%)	Solvent-free	130	10	21%
15	**I_2 (5 mol%)**	**DMSO**	**130**	**10**	**88% (86%)[c]**
16	I_2 (3 mol%)	DMSO	130	10	73%
17	I_2 (3 mol%)	DMSO	130	15	78%
18[d]	I_2 (5 mol%)	DMSO	130	10	88%
19[e]	I_2 (5 mol%)	DMSO	130	10	18%

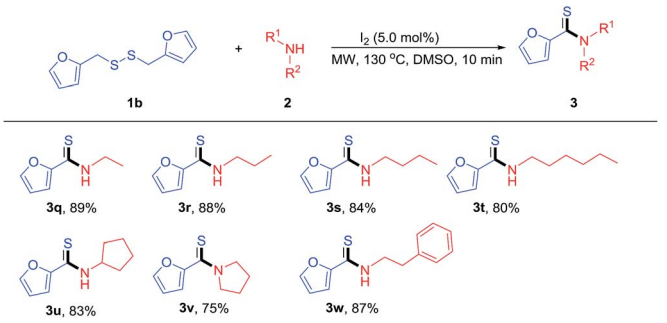
[a] Reaction conditions: dibenzyldisulfide **1a** (0.2 mmol), *N*-methylpiperazine **2a** (0.4 mmol), I_2, solvent (2.0 mL). [b] GC yields based on dibenzyldisulfide **1a**. [c] Isolated yields based on dibenzyldisulfide **1a**. [d] 0.6 mmol of *N*-methylpiperazine **2a** was used. [e] Without microwave radiation.

Table 2 Microwave-assisted iodine-catalyzed oxidative coupling of dibenzyl disulfide with amines[a,b]



[a] Reaction conditions: dibenzyldisulfide **1a** (0.5 mmol), amines **2** (1.0 mmol), I_2 (0.025 mmol), DMSO (2.0 mL), 130 °C, 10 min. [b] Isolated yields based on dibenzyldisulfide **1a**.

Table 3 Microwave-assisted iodine-catalyzed oxidative coupling of difurfuryl disulfide with amines[a,b]



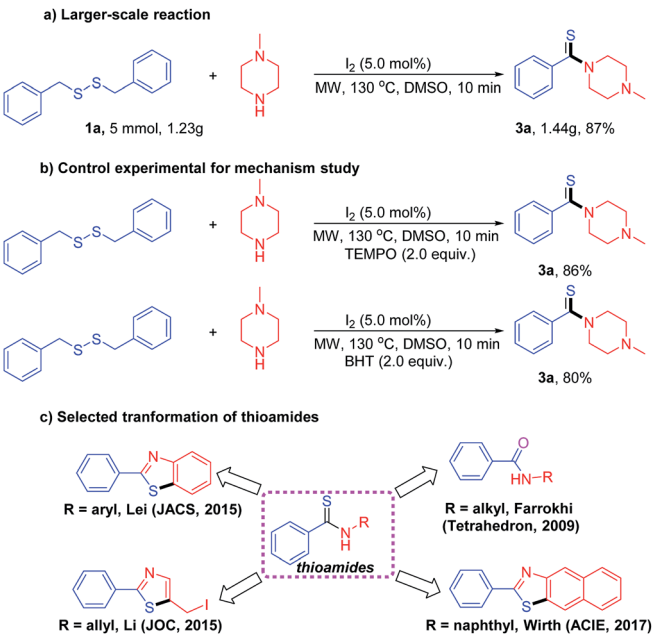
[a] Reaction conditions: difurfuryldisulfide (**1b**) (0.5 mmol), amines **2** (1.0 mmol), I_2 (0.025 mmol), DMSO (2.0 mL), 130 °C, 10 min. [b] Isolated yields based on difurfuryldisulfide (**1b**).

both aliphatic amines and aralkyl amines could efficiently undergo oxidative coupling effectively, affording corresponding products in good to excellent yields. The length and the steric hindrance of the alkyl affected the reactions slightly, and gave corresponding products with an excellent yield of 85–92% (**3a–3h**). The optimal conditions were also suitable for other N-containing heterocyclic amines (such as pyrrolidine, morpholine, 1-methylpiperazine and 1-ethylpiperazine), and corresponding products were obtained in the yield of 85–89% (**3i–3l**). Good yield was also obtained, when dibenzyldisulfide (**1a**) was treated with benzylamine (2-phenylethan-1-amine or 3-phenylpropan-1-amine) under the optimal conditions (**3m–3p**, 88–92%), and the strong electron-withdrawing group (CF_3) presenting at the ring of the benzyl amine affected the thioamidation slightly, giving the desired product **3p** in the yield of 88%.

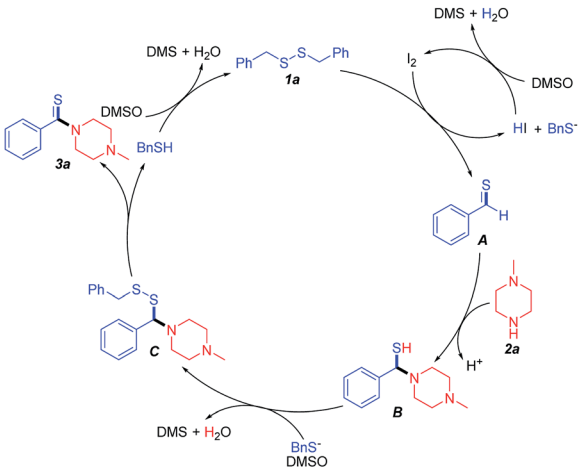
In subsequent studies, we examined the reaction of various amines with difurfuryl disulfide under the optimal conditions, and the results were summarized in Table 3. Analyzing Table 3, we can see that the thioamidation of difurfuryldisulfide with both alkylamines and heterocyclic amines gave desired products in moderate to good yields (**3q–3w**, 75–88%). And the steric hindrance (*n*-hexyl or cyclopentyl) of the aliphatic group affects the reaction slightly (**3t** and **3u**, 80% and 83%). To our delight, phenethyl amine was also prone to this thioamidation, for giving the desired product (**3w**) in the yield of 87%.

The thioamidation can also be carried out on a larger scale reaction, and the desired product (**3a**) were obtained in the yields of 87%, when 5 mmol of dibenzyldisulfide (**1a**) was treated with 10 mmol of *N*-methylpiperazine (**2a**) under the standard conditions (Scheme 3a). To shed light on the mechanism of the reaction, dibenzyldisulfide (**1a**) was treated with *N*-methylpiperazine (**2a**) under standard conditions by using 2.0 equiv. of TEMPO or BHT as radical scavengers (Scheme 3b), and desired product **3a** was obtained in the yields of 86% and 80% respectively, suggesting that no single-electron transfer process was involved through the whole reaction. In addition, thioamides have been used as important intermediates for the construction of heterocycles and other compounds containing both nitrogen and sulfur in their backbones (Scheme 3c).[18]

On the basis of the above experimental results and previous works,[16,19] a possible mechanism has been depicted in Scheme 4. The first step of the thioamidation is the generation of the intermediate **A** by the reaction of dibenzyldisulfide (**1a**) with I_2, with concomitant loss of HI and BnS^-. Then intermediate **A** react with *N*-methylpiperazine (**2a**) to yield intermediate **B**, which was converted to species **C** *via* coupling with BnS^- in the presence of



Scheme 3 (a) Larger-scale synthesis of **3a**. (b) Control experimental for mechanism study. (c) Selected transformation of thioamides.



Scheme 4 Proposed mechanism of the thioamidation.

DMSO. Finally, species **C** decomposed to desired product (**3a**) and BnSH, which was then converted to dibenzyldisulfide (**1a**) *via* oxidation reaction. During the whole reaction, the catalyst (I_2) was regenerated by the cycle of HI in the presence of DMSO, which catalyzed the thioamidation effectively.

Conclusions

In summary, we have developed a rapid and efficient protocol for the synthesis of thioamides *via* the microwave-assisted iodine-catalyzed oxidative coupling of dibenzyl(difurfuryl) disulfides with amines at 130 °C for 10 minutes. A broad range of amines were tolerated, and all the desired products could be obtained in good to excellent yields. Comparing with the previous methods, the present strategy has the advantages of high efficiency, simple operation, rapid reaction and less catalyst, providing a convenient way to thioamides, which are key intermediate for synthesis of other heterocycles compounds.

Conflicts of interest

There are no conflicts to declare.

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