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Communication

Microwave-assisted controllable synthesis of 2-acylbenzothiazoles and bibenzo[*b*][1,4]thiazines from aryl methyl ketones and disulfanediyldianilines

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ABSTRACT

A condition-controlled strategy for selectively synthesis of 2-acylbenzothiazoles and bibenzo[*b*][1,4]thiazines from aryl methyl ketones and disulfanediyldianilines was realized using I_2/DMSO or I_2/MeCN systems, respectively. The desired products were synthesized in only 15 min with moderate to excellent yields (50%-90%) under microwave-assisted, metal-free conditions. The strategy provides a great advantage for selective synthetic applications in the efficient synthesis of benzothiazoles and bibenzothiazines heterocycle compounds.

The direct functionalization of C–H bonds for the synthesis of heterocyclic compounds has emerged as an increasingly valuable tool for step-economical carbon-heteroatom bond-forming organic reactions [1-3]. Traditionally, transition metal complexes were generally used as efficient catalysts for the functionalization of C–H bonds, and a handful of eminent works have been disclosed [4,5]. Although these methods are very efficient, it often suffers from some drawbacks, such as the generation of waste, the use of expensive hazardous transition metals and ligands. With the development of green organic chemistry and enhancement of environmental protection consciousness of chemists [6,7], the application of a microwave-assisted strategy for the functionalization of C–H bonds to synthesize heterocyclic compounds under metal-free conditions is highly attractive.

2-Acylbenzothiazoles and bibenzo[*b*][1,4]thiazines are two classes of heterocyclic compounds containing both nitrogen and sulfur in the five- and six-membered ring, respectively, which could be used as multifunctional building units and valuable structural units in pharmaceutical chemistry, pesticides, industrial dyes and functional materials [8,9]. For example, benzothiazole is an important type of heterocyclic skeleton, which can be used for anticancer agents and enzyme inhibitors, and so on [10]. In recent years, some practical methodologies have been reported to synthesize benzothiazole compounds [11]. For instance, in 2012, Wu and co-workers reported an I_2-promoted oxidative cyclization reaction for the one-pot synthesis of 2-acylbenzothiazoles from methyl *o*-aminobenzenethiols and ketones [12]. In 2016, Wan *et al.* also developed a tunable procedure for the synthesis of benzothiazole-based vicinal diketones or 2-aroylbenzothiazoles from *o*-aminothiophenols [13]. For the preparation of thiazines, several synthesis protocols have been achieved. For example, the oxidative coupling of 3-phenyl-2*H*-1,4-benzothiazine with highly explosive picric acid [14]. Later, our group and Nguyen *et al.* found that bibenzo[*b*][1,4]thiazines can be constructed through a one-step reaction of readily available 2,2′-dithiodianiline or 2-aminothiophenol in the presence AIBN or TFA, respectively [15,16]. Some other methods require halogenated reagent, harsh reaction conditions, expensive catalysts, and additional ligands to proceed with the reactions, which accordingly would generate sto-

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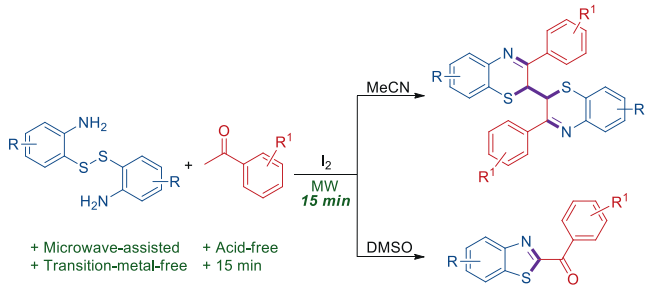
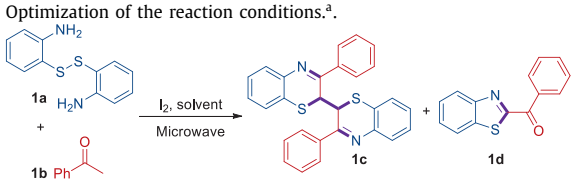


Scheme 1. Condition-controlled selective synthesis of 2-acylbenzothiazoles and bibenzo[*b*][1,4]thiazines.

Table 1
Optimization of the reaction conditions.[a].



Entry	I_2 (mmol)	Solvent (mL)	T (°C)	Yield (%)[b]	
				1c	**1d**
1	I_2 (0.12)	AcOH	120	56	0
2	I_2 (0.12)	DMF	120	69	0
3	I_2 (0.12)	MeCN	120	70	0
4	I_2 (0.12)	DMSO	120	0	72
5	I_2 (0.12)	Toluene	120	46	0
6	I_2 (0.12)	Dioxane	120	65	0
7	I_2 (0.25)	MeCN	120	72	0
8	I_2 (0.50)	MeCN	120	74	0
9	I_2 (0.75)	MeCN	120	74	0
10	I_2 (0.50)	MeCN	125	78	0
11	I_2 (0.50)	MeCN	130	78	0
12[c]	I_2 (0.50)	MeCN	125	70	0
13[d]	I_2 (0.50)	MeCN	125	78	0
14[e]	I_2 (0.16)	DMSO	120	0	88
15[e]	I_2 (0.20)	DMSO	120	0	87
16[c,e]	I_2 (0.16)	DMSO	120	0	82
17[d,e]	I_2 (0.16)	DMSO	120	0	86
18[e]	I_2 (0.16)	DMSO	110	0	80
19[e]	I_2 (0.16)	DMSO	125	0	85

[a] Reaction conditions: **1a** (0.25 mmol) and **1b** (0.525 mmol) in solvent (2 mL) at 150 W for 15 min.
[b] The yield was determined by ^{1}H NMR analysis of crude products using 1,3,5-trimethoxybenzene as the internal standard based on **1a** (for the yield of **1c**) or **1b** (for the yield of **1d**), respectively.
[c] The reaction time was 10 min.
[d] The reaction time was 20 min.
[e] **1b** is 0.45 mmol.

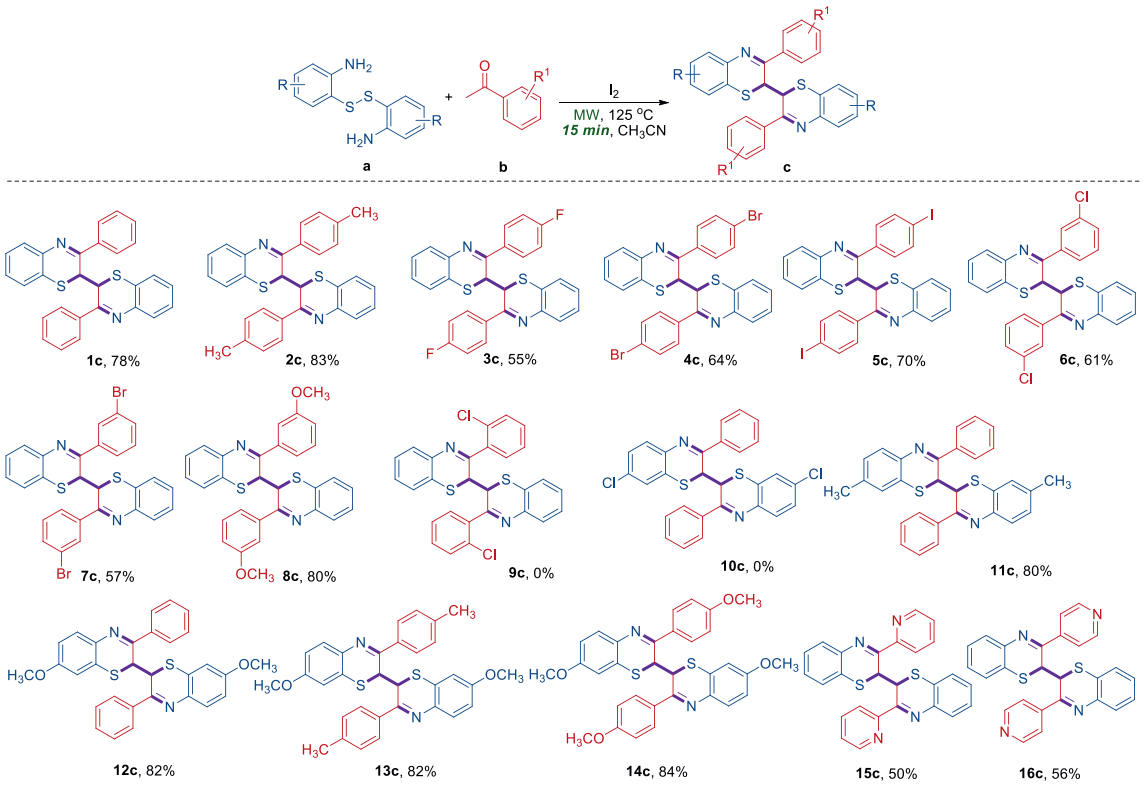
ichiometric amounts of waste after the reactions [17]. However, in the above-mentioned advances, most of the reactions need a long reaction time (up to 24 h) to get good yields. Thus, there is an incentive to develop efficient and green catalytic processes based on microwave technology to minimize the reaction time in terms of sustainability. We herein report an efficient condition-controlled reaction between aryl methyl ketones and disulfanediyldianilines under microwave-assisted conditions, which would generate bibenzo[*b*][1,4]thiazines or 2-acylbenzothiazoles as the main products in only 15 min, respectively (Scheme 1).

Initially, 2,2′-disulfanediyldianiline **1a** and acetophenone **1b** were selected to optimize the microwave-assisted reaction parameters (Table 1). We conducted the reaction with the conditions of I_2 (0.12 mmol), **1a** (0.25 mmol) and **1b** (0.525 mmol) in AcOH (2 mL) at 150 W/120 °C for 15 min, only 3,3′-diphenyl-2*H*,2′*H*-2,2′-bibenzo[*b*][1,4]thiazine **1c** was isolated in 56% yield (entry 1). Some other solvents, including DMF, MeCN, DMSO, toluene and dioxane were tested (entries 2–6), which disclosed that MeCN displayed the best efficiency for the synthesis of **1c** (entry 3). While the reaction performed in DMSO gave the sole product benzo[*d*]thiazol-2-yl(phenyl)methanone **1d** in 72% yield (entry 4). To further optimize the reaction conditions of product **1c**, the amount of I_2 was surveyed. It turns out that 2 equiv. of I_2 is the best loading for generating of **1c** (entries 7–9). Next, we checked the influence of the reaction temperature. The reaction yield did not increase when the reaction temperature was higher than 125 °C (entries 10 and 11). Moreover, changing the reaction time did not increase the yield of **1c** (entries 12 and 13). On the other hand, we also evaluated the reaction parameters including I_2 loading, reaction temperature, and reaction time for the synthesis of product **1d** (entries 14–19). From the above experimental results, it could be found that the application of DMSO as a solvent is critical for the formation of **1d**, which is similar with that of the reported case [18].

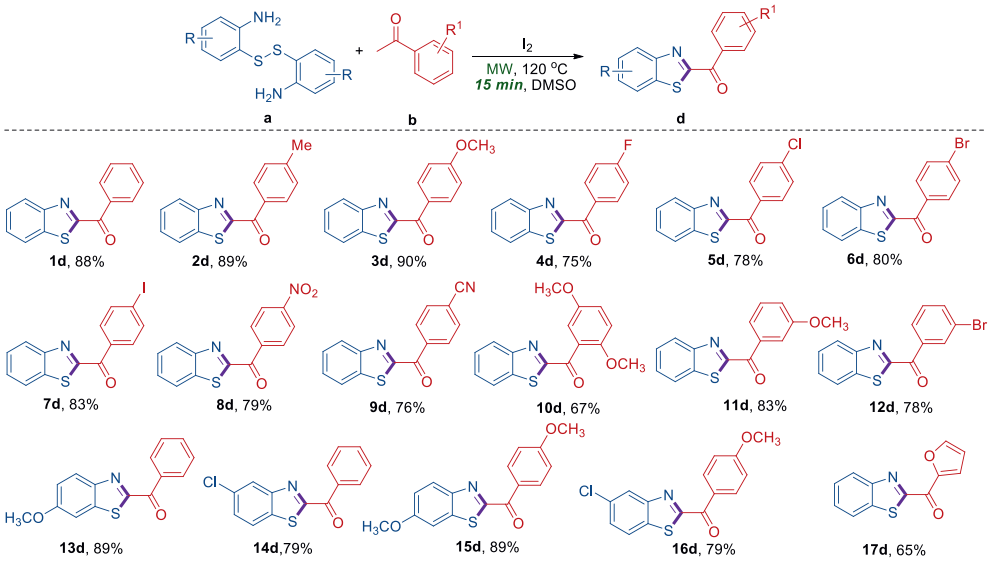
With the optimized reaction conditions, the scope of the substrates for the synthesis of bibenzo[*b*][1,4]thiazines was firstly investigated (Scheme 2). Initially, when aryl methyl ketones with electron-donating groups and electron- withdrawing groups in the *meta*- and *para*-position were used as reactants, and the corresponding products **1c**-**8c** could be obtained in moderate to good yields. Unfortunately, the *ortho*-position substituted aryl methyl ketone could not proceed in the reaction (**9c**) probably owing to the stereo-hindrance effect. The yields of the ketones bearing electron-donating groups (–CH_3, –OMe) (**2c** and **8c**) were better than those of substrates bearing electron-withdrawing groups (–F, –Cl, –Br, –I) (**3c**-**7c**). Next, the substituted 2,2′-disulfanediyldianilines were used to react with acetophenone (**10c**-**12c**). No product was detected when 2,2′-disulfanediylbis(4-chloroaniline) was used as the substrate (**10c**). The scope of the reaction was further explored by substituted dithiodianilines with substituted acetophenones bearing electron-donating groups, the products were isolated in good yields (**13c** and **14c**). From the above results, we found that the reaction was significantly influenced by both the electronic effect and stereo hindrance effect.

Next, we evaluated the substrate scope for the synthesis of 2-acylbenzothiazoles **d** after establishing the optimized reaction conditions. The procedure was extended to a variety of aromatic ketones for coupling with substituted dithiodianilines (Scheme 3, **1d**-**16d**). The reaction of aromatic ketones with both electron-donating and electron-withdrawing groups at *ortho*-, *meta*- and *para*-position of the phenyl group were suitable for obtaining the corresponding products in moderate to excellent yields (**1d**-**12d**). The reaction yields of the ketones bearing electron-donating groups at *para*-position (–CH_3, –OMe) (**2d** and **3d**) were slightly better than those of substrates bearing electron-withdrawing groups (–NO_2, –CN, –F, –Cl, –Br, –I) (**4d**-**9d**). The reaction yields were mainly influenced by the steric hindrance effect of group R^1. Relatively low yields were observed when *ortho*- and *meta*-substituted substrates were used (**10d**-**12d**). Notably, substituted 2,2′-disulfanediyldianilines reacted smoothly with **2a** to afford the desired corresponding products in good yields (**13d**-**16d**). Notably, the moderate yield could also be achieved when 2-acetylfuran was presented in the reaction (**17d**).

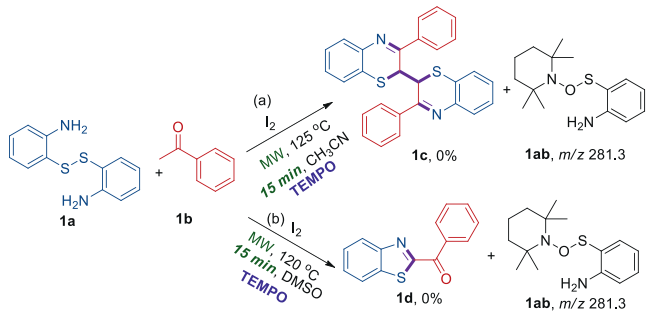
To clarify the mechanism of the two reactions, a series of control experiments were designed and conducted. The reaction intermediates were examined and monitored by ^{1}H NMR and GC–MS (Scheme 4). When the radical scavenger 2,2,6,6-tetramethylpiperidin-1-oxyradical (TEMPO, 1.0 mmol) was added to probe the radical nature of the two reactions, no corresponding products **1c** and **1d** were detected. While, the adduct **1ab** was observed by GC–MS in both reactions (Scheme 4 and Fig. S29 in Sup-



Scheme 2. Scope of synthesis of bibenzo[*b*][1,4]thiazines. Reaction conditions: I_2 (0.5 mmol), **a** (0.25 mmol) and **b** (0.525 mmol) in MeCN (2 mL) at 150 W/125 °C for 15 min. Isolated yield after flash chromatography (Al_2O_3) based on **a**.



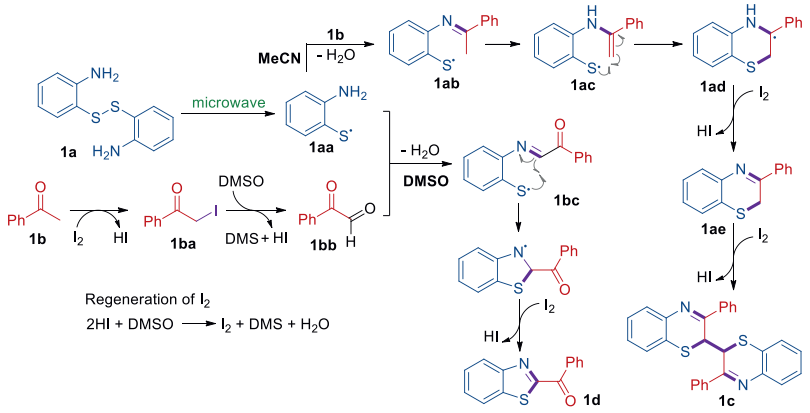
Scheme 3. Scope of the synthesis of 2-acylbenzothiazoles. Reaction conditions: **a** (0.25 mmol), **b** (0.45 mmol) and I_2 (0.16 mmol) in DMSO (2 mL) at 150 W/120 °C for 15 min. Isolated yields after flash chromatography based on **b**.



Scheme 4. Control experiments.

porting information), suggesting that the thiol radical was involved in the reaction.

On the basis of the above results and previous reports [12,15,19], the plausible reaction pathways are proposed for the synthesis of bibenzo[*b*][1,4]thiazines **c** and 2-acylbenzothiazoles **d**, respectively (Scheme 5). First, the thiyl radical **1aa** was generated from **1a** under the irradiation of microwave. When DMSO was applied as the solvent, **1b** was transformed into α-iodoacetophenone **1ba** in presence of I_2, which was further oxidized by DMSO to form **1bb** [20]. Then the condensation of **1aa** and **1bb** afforded the intermediate **1bc**. Subsequently, **1bc** underwent an intramolecular cyclization and hydrogen atom abstraction to afford the prod-



Scheme 5. Possible mechanisms.

uct **1d** On the other hand, when the reaction was conducted in CH_3CN the direct condensation of **1aa** and **1b** gave the intermediate **1ab**, which was converted into the corresponding isomer **1ac**. Then the intermediate **1ac** suffered from an intramolecular cyclization and hydrogen atom abstraction to generate the intermediate **1ae**, which was further dimerized into the desired product **1c** in the presence of I_2 (Scheme 5). On the other hand, I_2 could be regenerated from the reaction of HI and DMSO in the pathway of the generation of product **d** [12]. The reason of high I_2 loading was probably due to the low efficiency of the regeneration process.

In summary, we have developed an efficient microwave-assisted condition-controlled C(sp^3)-H activation strategy for the selective synthesis of 2-acylbenzothiazoles and bibenzo[*b*][1,4]thiazines from aryl methyl ketones and disulfanediyldianilines. In these reactions, a wide array of aryl methyl ketones were well compatible. The reaction was switchable by simply changing the reaction conditions (I_2/MeCN or I_2/DMSO) without the involvement of explosive oxidants and additional activating reagents.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.05.069.

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