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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<sub>2</sub>/DMSO or I<sub>2</sub>/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 I2-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-2H-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 2aminothiophenol 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 stoichiometric 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

\* Corresponding authors. E-mail addresses: hxqqxh2008@163.com; shenguodong33@163.com; bingyu@zzu.edu.cn the reaction time in terms of sustainability. We herein report an efficient condition-controlled reaction between arvl methyl ketones and disulfanediyldianilines under microwave-assisted conditions, which would generate bibenzo[b][1,4]thiazines or 2acylbenzothiazoles as the main products in only 15 min, respectively (Scheme 1).



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

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<sub>2</sub> (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-2H,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<sub>2</sub> 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<sub>2</sub> 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<sub>3</sub>, -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(4chloroaniline) 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.

Table 1 Optimization of the reaction conditions.<sup>a</sup>



DMSO <sup>a</sup> Reaction conditions: 1a (0.25 mmol) and 1b (0.525 mmol) in solvent (2 mL) at 150 W for 15 min.

DMSO

DMSO

120

110

125

0

0

0

86

80

85

The yield was determined by <sup>1</sup>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.

<sup>c</sup> The reaction time was 10 min.

<sup>d</sup> The reaction time was 20 min.

 $I_2(0.16)$ 

 $I_2(0.16)$ 

 $I_2(0.16)$ 

<sup>e</sup> 1b is 0.45 mmol.

 $18^{e}$ 

19

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Scheme 2. Scope of synthesis of bibenzo[b][1,4]thiazines. Reaction conditions: I<sub>2</sub> (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<sub>2</sub>O<sub>3</sub>) based on **a**.

Next, we evaluated the substrate scope for the synthesis of 2acylbenzothiazoles **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 electrondonating 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<sub>3</sub>, –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<sup>1</sup>. 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**).



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**.

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 <sup>1</sup>H NMR and GC-MS (Scheme 4). When the radical scavenger 2,2,6,6-

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



Scheme 4. Control experiments.

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 thivl radical 1aa was generated from 1a under the irradiation of microwave. When DMSO was applied as the solvent, **1b** was transformed into  $\alpha$ iodoacetophenone 1ba in presence of I2, 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 product 1d. On the other hand, when the reaction was conducted in CH3CN 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<sub>2</sub> loading was probably due to the low efficiency of the regeneration process.



In summary, we have developed an efficient microwaveassisted 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<sub>2</sub>/MeCN or I<sub>2</sub>/DMSO) without the involvement of explosive oxidants and additional activating reagents.

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## **Graphical Abstract**

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

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A condition-controlled strategy to selectively synthesize nitrogen-sulfur heterocycles through microwave-assisted high-efficiency protocol has been proven. This method can selectively synthesize five-membered ring and six-membered ring benzoheterocyclic compounds through the control of solvents and the consumption of iodine in high yields.

## **Declaration of interests**

 $\boxtimes$  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.