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## Solvent-controlled highly regio-selective thieno[2,3-b]indole formation under metal-free conditions

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An efficient three-component thieno[2,3-b]indole formation has been developed under metal-free conditions. The cascade cyclization was enabled by the acid-promoted annulation of indoles, ketones and sulfur powder, which provided modular synthesis of 2-substituted and 3thieno[2,3-b]indoles substituted with excellent regioselectivity and broad functional group tolerance. DMF solvent played an important role in the regioselectivity control.

Thienoindole derivatives are important fused heterocycles because they have potential biological activities with applications in agricultural chemistry and pharmaceutical industries.<sup>1</sup> Such as thienoindolin (Figure 1, A) isolated from the culture broth of Streptomyces albogriseolus (MJ 286-76F7) displays both growth promoting and inhibiting activities in rice seedlings.<sup>2</sup> Thienoindoles also widely used in organic electronics as novel are electroluminescence materials for designing light-emitting devices. For example, thieno[2,3-b]indole dyes (Figure 1, B-D) having a D- $\pi$ -A (Donor-p-bridge-Acceptor) structure, which have been evaluated in DSSCs and OSCs.<sup>3</sup> Accordingly, the development of efficient methods for the synthesis of thieno[2,3-b]indoles has attracted considerable interest. The current reported synthetic methods are mainly based on using functionalized indoles,<sup>4</sup> furans,<sup>5</sup> isatins<sup>6</sup> and thiophenes,<sup>7</sup> which require several steps to prepare. Therefore, the development of one-pot thieno[2,3-b]indoles fromation from readily available starting materials under simple conditions is highly desirable.

Multicomponent reactions (MCRs) constitutes one of the most efficient tools in modern synthetic organic chemistry. These reactions present a straightforward and atom-economic synthetic approach that offers highlighted advantages over conventional multistep reaction sequences.<sup>8</sup> The transition-metal-catalyzed MCRs is one of the most popular research topics in organic chemistry since its



Figure 1 Valuable thieno [2,3-b] indole-containing molecules.

high efficiency and chemical selectivity.<sup>9</sup> However, in view of the concerns about the influences of trace metals on human consumption drugs and the efficiency of organic electronic devices, the development of envionmentally benign synthetic methods with high selectivity under metal-free conditions is critical in modern organic synthesis, especially in the process of multicomponent reactions which selectivity control is always very challenging.

Previous work:



Scheme 1 New strategy for the synthesis of benzothieno[2,3-. b]indole.

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Elemental sulfur is widely distribute in nature, nontoxic and stable under normal conditions. Therefore, direct use of elemental sulfur as the sulfur source for the construction of sulfur-containing heterocycles is a direct, simple, and atom-economical approach.<sup>10</sup> Various methods have been developed to use elemental sulfur for the synthesis of sulfur-containing heterocycles.<sup>11</sup> Very recently, we benzothieno[2,3-b]indoles, reported various methods for phenothiazines, 1,2,4-thiadiazoles, and 2-arylbenzothiazoles formation from elemental sulfur base on multicomponent reactions.<sup>12</sup> Our previous research showed that palladium catalyst is necessary for the three-component benzothieno[2,3-b]indole formation (Scheme 1). As our continuing efforts on using readily available elemental sulfur to selective construct sulfur-containing heterocycles, herein we describe a general multicomponent reaction for thieno[2,3-b]indole formation from readily available indoles, ketones and sulfur powder. The reaction could be realized under metal-free conditions and the regioselectivity was well controlled by solvent and additive.

	+ 0 + + 88-	additive solvent	
1a	2a	3aa	4aa
Entry	Additive (mol %)	Solvent	Yield <b>(3aa/4aa</b> ) (%) <sup>b</sup>
1	HI (50)	chlorobenzene	19 (>99:1)
2	HI (50)	PhCF3	24 (>99:1)
3	HI (50)	anisole	26 (>99:1)
4	HI (50)	1,4-dioxane	33 (>99:1)
5	HI (50)	1,4-dioxane / PhCF <sub>3</sub> (3: 2)	43 (>99:1)
6 <sup>c</sup>	HI (50)	1,4-dioxane / PhCF <sub>3</sub> (3: 2	) 80 (>99:1)
7	HI (50)	DMF	12 (10:1)
8 <sup>d</sup>	HI (50)	DMF	61 (1:20)
9 <sup>d</sup>	HOAc (300)	DMF	64 (1:60)
10 <sup>d</sup>	HOAc (500)	DMF	69 (1:70)
11 <sup>d</sup>	HOAc (0.1 mL)	DMF	74 (1:75)
12 <sup>d,e</sup>	HOAc (0.1 mL)	DMF	83 (1:80)

 Table 1 Screening the reaction conditions<sup>a</sup>

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<sup>*a*</sup> Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), S (1.0 mmol), 130 °C, 4 h, under air. <sup>*b*</sup> GC yield based on **2a**. <sup>*c*</sup> *L*-Phenylalanine (0.5 mmol). <sup>*d*</sup> 150 °C, 16 h. <sup>*e*</sup> **1a** (0.2 mmol), **2a** (0.4 mmol), S (1.0 mmol), GC yield based on **1a**.

We commenced our investigation using 1-methyl-1*H*-indole (1a), acetophenone (2a) and sulfur powder as the model system (Table 1). To our delight, the desired product 3aa was generated exclusively in chlorobenzene at 130 °C when 50 mol% HI was used (entry 1). The yield of 3aa could be slightly increased when other solvents such as PhCF<sub>3</sub>, anisole and 1,4-dioxane were used (entries 2-4). The reaction yield could be slightly increased to 43% when a mixture of PhCF<sub>3</sub> and 1,4-dioxane were used (entry 5). The yield of 3aa could be further improved to 80% when L-phenylalanine (1 equiv.) was added to the reaction (entry 6). Interestingly, a small amount of 4aa was observed when DMF was used as the solvent (entry 7). The reaction yield of 4aa and the ratio of 4aa:3aa both could be improved when the reaction temperature was increased to 150 °C (entry 8). Further optimization of the reaction conditions showed that the use of HOAc was very effective (64% yield, 4aa:3aa = 60:1, entry 9). Delightedly, the reaction yield and regioselectivity of the product 4aa both

increased when the amount of HOAc increased (entries 10-11). The ratio of 1-methyl-1*H*-indole (1a) to acetophenone (2a) also affected the reaction yield profoundly and the reaction yield could be improved to 83% when the ratio of 1a: 2a was changed to 1: 2 (entry 11).

With the optimized conditions established, the scope and generality of the cyclization reaction were probed (Table 2). Various substituted acetophenones were examined under the optimized reaction conditions, as summarized in Table 2. The model reaction of 1a and 2a in the presence of sulfur powder afforded 3aa in 81% isolated yield. Similar yields were obtained for substrates with various functional groups (both electron-donating and electron-withdrawing groups) in the para position of the phenyl ring (3ab-3ai). The desired product 3ad was obtained in 83 % yield when a methoxy substituent was present. Halogen substituents on the benzene ring, including F, Cl, Br and I, were compatible for this kind of cyclization (3ae-3ah). The steric effect of the substituent was obvious since 1-(3-bromophenyl)ethanone (2n) and 1-(o-tolyl)ethanone (2q) gave **3an** and **3aq** in only 47% and 37% yield, respectively. Acetophenones 2t, 2u and 2v with two functional groups were also suitable substrates and gave the desired products in good yields (3at-3av). When 1-(naphthalen-2-yl)ethanone (2w) was used, the desired product 3aw was observed, albeit in 31% yield. To our surprise, 2,8-dimethyl-3-phenyl-8H-thieno[2,3b]indole 3ax was obtained in 91% yield when propiophenone (2x) was used as the substrate. However, 1,2-diphenylethanone (2y) was proved to be a less efficient coupling partner, which resulted in the desired product 3ay in only 33% yield.





<sup>&</sup>lt;sup>*a*</sup> Conditions: **1a** (0.6 mmol), **2** (0.5 mmol), S (1.0 mmol), HI (50 mol%), *L*-phenylalanine (1 equiv.), CF<sub>3</sub>Ph:1,4-dioxane = 2:3 (1.0 mL), 130  $^{\circ}$ C, 4 h, under air atmosphere. Isolated yield based on **2a**.

The influence of the substituents on the indole moiety was also evaluated and the results are presented in Table 3. The Please do not adjust margins Green Chemistry

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substituent position significantly affected the reaction yield and the reaction yields decreased dramatically when functional groups were presented at the C-4 position in indole (**3ba** and **3ca**). Better yields were obtained if the functional groups, such as methyl (**1d**, **1i** and **1l**), methoxy (**1e**), fluoro (**1f** and **1j**), chloro (**1g**) and bromo (**1h**) were located at C-5, C-6 and C-7 position. When free NH-indole (**1m**) was used as the substrate under the same conditions, **3ma** was obtained in 57% yield. It is noteworthy that other *N*-alkylindoles (**1n**, **1o** and **1p**) also suitable coupling partners to give the corresponding products in good yields.

Table 3 Substrate scope with respect to the indoles<sup>a</sup>



<sup>*a*</sup> Conditions: **1** (0.6 mmol), **2a** (0.5 mmol), S (1.0 mmol), HI (50 mol%), L-phenylalanine (1 equiv.), CF<sub>3</sub>Ph:1,4-dioxane = 2:3 (1.0 mL), 130 °C, 4 h, under air atmosphere. Isolated yield based on **2a**.

We next turned our attention to the development of the corresponding regioselective cyclization, which the substituent was located at C-2 position in the benzothieno[2,3-b] indole ring. When the reactions were performed in DMF, the regioselectivity of the cyclization process was switched (Table S5-S7). To further expand the scope of this direct cyclization reaction, we next sought to expand the scope of indoles and various substituted ketones, with the results shown in Table 4 and Table 5. Generally, aromatic acetophenones smoothly reacted to give the corresponding thieno[2,3-b]indoles in moderate to good yields (Table 4, 4ab-4au, 41-85%), regardless of the functional groups at the para-, meta-, or ortho-position. A large range of functional groups on the benzene ring such as alkyl (2b-2d, 2m, 2j and 2s), methoxy (2e, 2n and 2t), fluoro (2f, 2o and 2k), chloro (2g, 2p and 2u), bromo (2h and 2q), iodo (2i), and trifluoromethyl (2r) were all tolerated well under the given reaction conditions. To our delight, 1-(naphthalen-1yl)ethanone (2v) and 1-(naphthalen-2-yl)-ethanone (2w) also reacted well to give the corresponding products 4av and 4aw in 51 and 47% vield, respectively. Besides aromatic ketones, aliphatic ketones such as 3-methylbutan-2-one (2x) and 1-adamantyl methyl ketone (2y)also could couple with indole and sulfur to give the desired product in 37 and 43% yields, respectively.



<sup>*a*</sup> Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), S (1.0 mmol), HOAc (0.1 mL), DMF (0.3 mL), 150 °C, 16 h, under air atmosphere. Isolated yield based on **1a**.

To further examine the scope and limitations of the threecomponent regioselective cyclization, we tested various indoles for this kind of reaction (Table 5). Indoles bearing various substituents could smoothly couple with acetophenone (**2a**). When 5-methylindole was employed, the corresponding product **4ba** was obtained in 83% yield. Slightly lower yields were obtained when the methyl group was located at C-6 and C-7 position in the indole ring (**4ha** and **4ja**). Indoles with halogens were all accommodated well and furnished the desired





<sup>a</sup> Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), S (1.0 mmol), HOAc (0.1 mL), DMF (0.3 mL), 150 °C, 16 h, under air atmosphere. Isolated yield based on **1a**.

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products in good yields. Notably, unprotected 1H-indole (1k) participated well in this protocol to provide the corresponding product 4ka in 75% yield. We further tested this method with *N*-ethylindole (1l) and 1-isopropyl-1*H*-indole (1m), and the reaction proceeded smoothly to provide the desired products in good yields (4la-4ma)

The benzothieno[2,3-*b*]indole product **4aa** was obtained in 71% yield in a gram-scale reaction. We further evaluated the oxidative transformation of **4aa**. When **4aa** was treated with *m*-CPBA in CHCl<sub>3</sub> under an air atmosphere, the oxidized product 8-methyl-2-phenyl-8*H*-thieno[2,3-b]indole 1,1-dioxide (**4aa'**) was obtained in 87% yield (Scheme 2).



Scheme 2 Derivation of resultant benzothieno[2,3-b]indole.

To understand the mechanism of the reaction, we performed several control experiments (Scheme 3). When 1a reacted with 2a in the absence of sulfur powder, an intermediate 3a was obtained in 21% yield after 0.5 h (Scheme 3, a). The intermediate 3a could convert into the target benzothiophene 3aa with almost full conversation (Scheme 3, b). This result indicates that the reaction may proceed through [4+1] type synthetic route to 3-phenyl thieno[2,3-b]indole.<sup>13</sup> Treatment of 2a with sulfur powder under standard conditions without 1-methyl-indole (1a) gave the N,Ndimethyl-2-phenylethanethioamide (4a) in 63% yield (Scheme 3, c). Trace amount of desired product was obtained when 1-methyl-3styryl-1*H*-indole (5a) was treated with sulfur powder (Scheme 3, d). This observation implies that procedure of the product 4aa is different to the product 3aa pathway. Further treatment of 4a with 1methyl-indole (1a) afforded the desired product 4aa in 49% yield (Scheme 3, e). The product 3aa could be gained in 81% yield when using 2-phenylthiirane (6a) as the substrate with 1-methyl-indole (1a) (Scheme 3, f).



Figure 2 X-ray structure of 3ah and 4aa.

According to the above control experiments and related references, a proposed mechanism for 4aa is illustrated in Scheme 4. *N*,*N*dimethyl-2-phenylethanethioamide (4a) is generated from 2a with DMF and sulfur powder (Willgerodt-Kindler reaction).<sup>14</sup> Intermediate **4a** can be resonated to intermediate **A**. Then, 1-methylindole (**1a**) reacts with **A** to afford an intermediate **B**, which can be further converted into the desired product **4aa** under acidic conditions.<sup>15</sup> Solvent DMF plays an important role for the regioselectivity control for this kind cyclization.



Scheme 3 Control experiments under various conditions.



Scheme 4 Proposed mechanism of 4aa.

In summary, we have developed a simple, efficient and solvent-controlled *regio*-selective method for preparing thieno[2,3-b] indole derivatives from indoles, ketones, and

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sulfur powder under metal-free conditions. Cheap and readily available sulfur powder was acted as the sulfur source to selectively assemble the thieno-fused indole derivatives. Functional groups such as halogen, trifluoromethyl and cyano were well tolerated under the optimized reaction conditions. This three-component approach affords a facile route for the rapid synthesis of thieno[2,3-*b*]indoles. The detailed mechanism and synthetic application of this reaction are currently under investigation.

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# Solvent-controlled highly regio-selective thieno[2,3-*b*]indole formation under metal-free conditions

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Thieno[2,3-*b*]indole derivatives were selectively prepared from indoles, ketones and sulfur powder under metal-free conditions.