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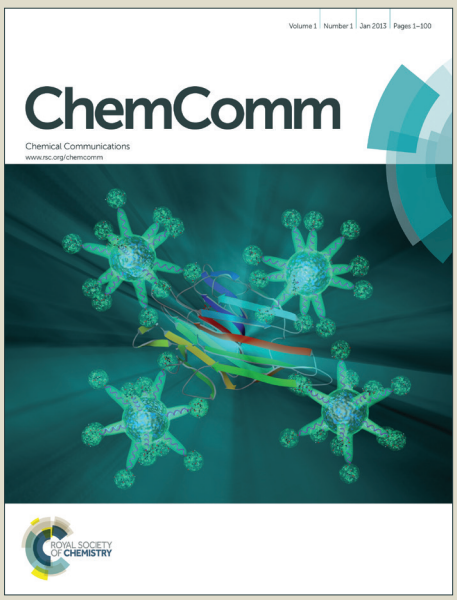

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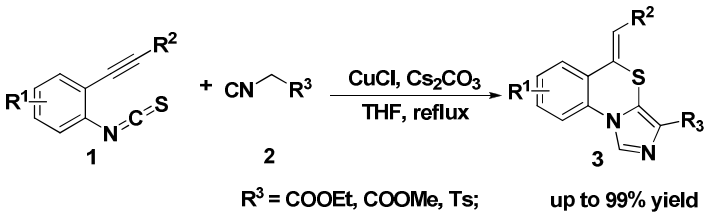

Wenyan Hao, Jiangbo Zeng, Mingzhong Cai*

An efficient route to 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines has been developed by copper(I)-catalyzed tandem reaction of *o*-alkynylphenyl isothiocyanates with isocyanides in THF with Cs_2CO_3 as base.

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Copper(I)-catalyzed tandem reaction of *o*-alkynylphenyl isothiocyanates with isocyanides: a rapid synthesis of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines

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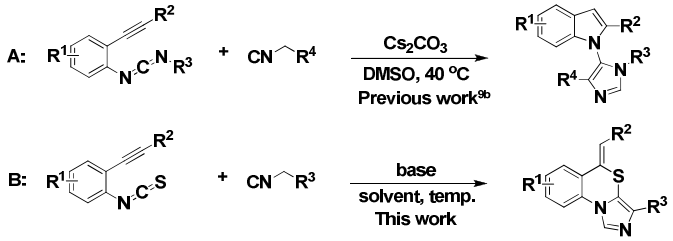
Wenyan Hao, Jiangbo Zeng and Mingzhong Cai*

An efficient route to 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines has been developed by copper(I)-catalyzed tandem reaction of *o*-alkynylphenyl isothiocyanates with isocyanides in THF with Cs_2CO_3 as base. The present tandem process allows the assembly of a variety of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines in good to excellent yields.

Development of efficient methods for preparation of *N*-heterocyclic compounds in the field of chemical genetics was a continuing target pursued by chemists.[1] Benzo-1,3-thiazines are very important sulfur-containing *N*-heterocyclic compounds since benzo-1,3-thiazine scaffold is present in a plethora of biological relevant molecules displaying a variety of pharmaceutical properties.[2] Benzo-1,3-thiazine derivatives are widely applied in pharmaceutical and biochemical fields and have attracted significant attention because of their interesting chemical properties[3] and synthetic methods.[4] By far the prevalent strategies for constructing benzo-1,3-thiazine derivatives are the transition-metal-catalyzed tandem *6-exo-dig* cyclization reactions of 2-ethynylanilines with isothiocyanates.[5] For instance, Wu and co-workers[5c] reported the synthesis of 2,4-dihydro-1*H*-benzo[*d*][1,3]thiazines via a silver-catalyzed tandem addition-cyclization reaction of 2-alkynylbenzenamines with isothiocyanates. On the other hand, imidazo-1,3-thiazine derivatives rank among the most representative compounds of chalcogen-containing *N*-heterocyclic molecules. They have aroused considerable attention due to their unique biological activity such as benzodiazepine substitutes and anti-inflammatory agents.[6] Many methods for the synthesis of these heterocyclic compounds have been reported, most of which based on alkylations of cyclic thioureas by appropriate 1,2- or 1,3-dielectrophiles[7] and condensations of thiazines with 1,2- or 1,3-difunctionalized units, such as α,β-unsaturated esters or lactam acetals.[8] However, to our surprise, the synthesis of polycyclic skeleton 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines has not been reported until now. As our continuous interest for the expeditious synthesis of biologically relevant heterocyclic compounds through tandem reaction strategy,[9] herein, we wish to report our recent effort for the generation of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines via copper(I)-catalyzed cascade reaction of *o*-alkynylphenyl isothiocyanates with isocyanides.



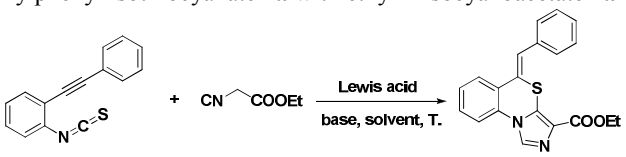
Scheme 1 Our strategy (working hypothesis)

Isocyanides, which are often recognized as powerful and versatile C1 building blocks, have been widely used in organic synthesis due to their unique properties.[10] Apart from their traditional multicomponent reactions,[11] isocyanide-based cycloaddition reactions offer great potential for the synthesis of various *N*-containing heterocycles.[12-14] Very recently, we reported a tandem reaction of *N*-[2-(1-alkynyl)phenyl]carbodiimides with isocyanides to obtain indolyl imidazole derivatives (Scheme 1, A).[9b] Considering the structural similarities between *o*-alkynylphenyl isothiocyanates and *N*-[2-(1-alkynyl)phenyl]carbodiimides, we conceived that 5*H*-benzo[*d*]-imidazo[5,1-*b*][1,3]thiazine scaffolds could be constructed via a cascade reaction of *o*-alkynylphenyl isothiocyanates with isocyanides (Scheme 1, B). To validate the feasibility of this hypothesis, we started to explore the possibility of this transformation.

The starting *o*-alkynylphenyl isothiocyanates were prepared from 2-iodoanilines with terminal alkynes via Sonogashira coupling,[15] followed by the treatment with thiophosgene[16] in good yields. At the outset, we used *o*-phenylethynylphenyl isothiocyanate **1a** and ethyl 2-isocyanoacetate **2a** as the substrates in a model reaction to optimize the conditions, and the results are summarized in Table 1. The reaction was carried out in the presence of AgOTf (10 mol%), and Cs_2CO_3 (2.0 equiv.) in anhydrous CH_3CN at 80 °C for 3 h. To our delight, the desired product **3a** was successfully isolated in 88% yield (Table 1, entry 1). Other Lewis acids as the catalyst in the reaction were then screened (Table1, entries 1-7). Copper (I) sources were found to be equally effective as silver salts and CuCl gave the best result (Table 1, entry 5). A blank experiment indicated that the Lewis acid was necessary because the desired compound **3a** was obtained in only 35% yield after 24 h without addition of a Lewis

acid as catalyst (Table 1, entry 8). We next examined the base effect on the reaction. Lower yields were observed when other inorganic bases such as K_3PO_4, Na_2CO_3 or $NaHCO_3$ were employed, whereas DBU and DABCO failed to promote the reaction and *t*-BuOK was less effective (Table 1, entries 9-14). It is worth noting that no reaction took place in the absence of base (Table 1, entry 15). These results indicated that the combination of a Lewis acid catalyst and a base is indispensable to afford the target product with high yield. Additionally, we realized that THF was the most optimal solvent for the reaction, giving rise to the desired product in 99% yield (Table 1, entries 16-20). Furthermore, we found that the reaction was also affected by the temperature. Reducing the reaction temperature resulted in a diminished yield (Table 1, entries 21-23).

Table 1 Initial studies for the tandem reaction of *o*-phenylethynylphenyl isothiocyanate **1a** with ethyl 2-isocyanoacetate **2a**[a]



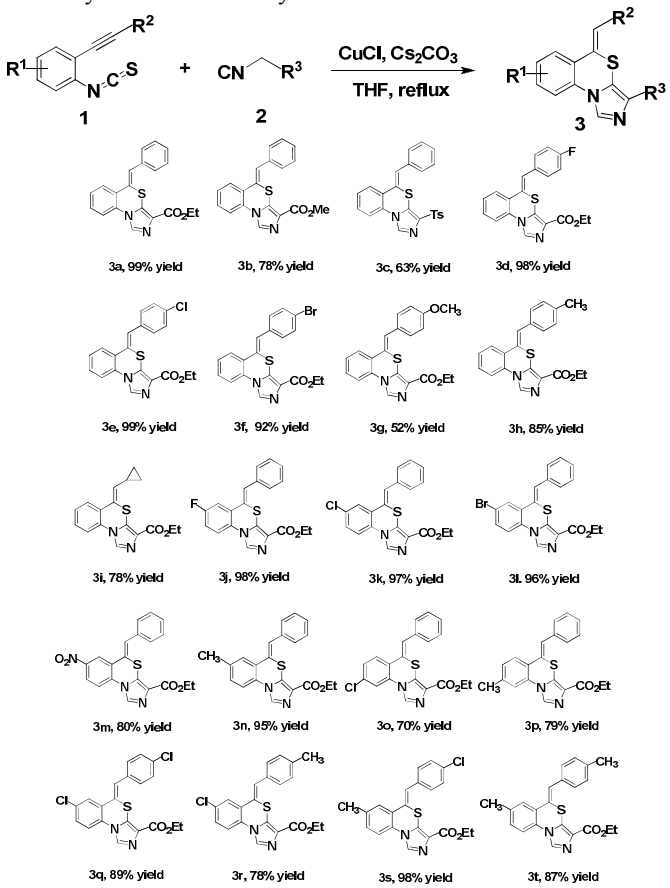
1a **2a** **3a**

Entry	Lewis acid	Base	Solvent	T (°C)	Yield[b] (%)
1	AgOTf	Cs_2CO_3	CH_3CN	80	85
2	Ag_2CO_3	Cs_2CO_3	CH_3CN	80	75
3	$Pd(OAc)_2$	Cs_2CO_3	CH_3CN	80	55
4	$PdCl_2$	Cs_2CO_3	CH_3CN	80	45
5	CuCl	Cs_2CO_3	CH_3CN	80	89
6	CuBr	Cs_2CO_3	CH_3CN	80	87
7	CuI	Cs_2CO_3	CH_3CN	80	85
8[c]	–	Cs_2CO_3	CH_3CN	80	35
9	CuCl	K_3PO_4	CH_3CN	80	78
10	CuCl	Na_2CO_3	CH_3CN	80	61
11	CuCl	$NaHCO_3$	CH_3CN	80	60
12	CuCl	DBU	CH_3CN	80	trace
13	CuCl	DABCO	CH_3CN	80	trace
14	CuCl	*t*-BuOK	CH_3CN	80	31
15	CuCl	–	CH_3CN	80	NR
16	CuCl	Cs_2CO_3	DCE	80	90
17	CuCl	Cs_2CO_3	Toluene	80	80
18	CuCl	Cs_2CO_3	DMF	80	65
19	CuCl	Cs_2CO_3	DMSO	80	83
20	CuCl	Cs_2CO_3	THF	70	99
21	CuCl	Cs_2CO_3	THF	r.t.	30
22	CuCl	Cs_2CO_3	THF	40	62
23	CuCl	Cs_2CO_3	THF	50	75

[a] Reaction was performed with **1a** (0.2 mmol), **2a** (0.4 mmol), Lewis acid (0.02 mmol), base (0.4 mmol) in solvent (2 mL) for 3 h. [b] Isolated yield based on *o*-phenylethynylphenyl isothiocyanate **1a.** [c] The reaction time was 24 h.

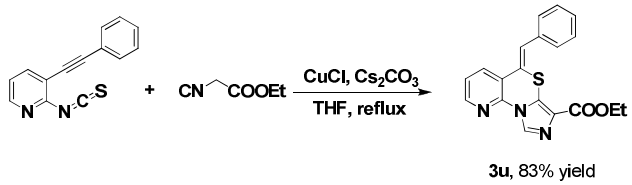
With the optimal conditions established, we turned our attention to explore the substrate scope with different *o*-alkynylphenyl isothiocyanates and various isocyanides and the results are summarized in Table 2. All reactions proceeded smoothly, leading to the desired 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines in good to excellent yields. For example, when methyl 2-isocyanoacetate or 1-isocyanomethanesulfonyl-4-methylbenzene was employed in the reaction, the corresponding products **3b** and **3c** were isolated in 78% and 63% yields, respectively. The substituents on R^2 position of *o*-alkynylphenyl isothiocyanates showed obvious electronic effects on the reaction. When R^2 group in the substrates **1** was an electron-deficient aryl, such as *p*-FC_6H_4, *p*-ClC_6H_4, *p*-BrC_6H_4, the reactions with **2a** proceeded smoothly to afford the corresponding products **3d-3f** in excellent yields. It was found that the reactions of substrates **1** with an electron-rich aryl group such as *p*-$MeOC_6H_4$, *p*-MeC_6H_4 at the R^2 position afforded the corresponding products **3g** and **3h** in only 52% and 85% yields, respectively. The structure of **3h** was further confirmed by X-ray diffraction analysis (see Figure 1 in the supporting information). Reaction of ethyl 2-isocyanoacetate (**2a**) and compound **1** bearing a cyclopropyl group attached on the R^2 position gave rise to the corresponding product **3i** in 78% yield. Surprisingly, no desired products were obtained when R^2 group in the substrate *o*-alkynylphenyl isothiocyanates **1** was an alkyl group, such as *n*-butyl, *n*-hexyl, or cyclopentyl. It may be due to the fact that the alkyl group cannot conjugate with acetylenic bond and activate it.

Table 2 Synthesis of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines via copper(I)-promoted tandem reaction of *o*-alkynylphenyl isothiocyanates **1** with isocyanides **2**[a]



[a] Reaction was performed with *o*-alkynylphenyl isothiocyanate **1** (0.2 mmol), isocyanide **2** (0.4 mmol), Cs_2CO_3 (0.4 mmol), CuCl (0.02 mmol) in THF (2 mL) under reflux for 3 h.

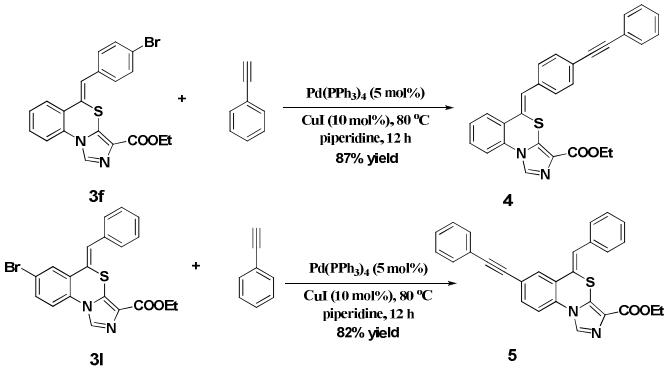
In addition, the reactions of *o*-alkynylphenyl isothiocyanates bearing various substituents such as fluoro, chloro, bromo, nitro and methyl groups on the aryl rings, regardless of their electronic properties and substitution positions, gave the desired products **3j**–**3t** in good to excellent yields. All products were uniformly formed as the *Z*-isomer, which might be due to a kinetic reason according to Baldwin's rules.[17] In order to further expand the substrate scope, we examined the reaction of 2-isothiocyanato-3-(phenylethynyl)pyridine with **2a** at the standard condition (Scheme 2), the corresponding product (*Z*)-ethyl 5-benzylidene-5*H*-imidazo[5,1-*b*]pyrido[2,3-*d*][1,3]-thiazine-7-carboxylate **(3u)** was obtained in 83% yield.



3u, 83% yield

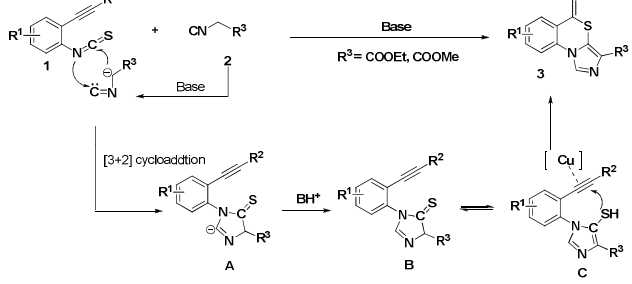
Scheme 2 The reaction of 2-isothiocyanato-3-(phenylethynyl)-pyridine with **2a**

With these 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines **3** in hand, we envisaged that some molecules could be further functionalized. Thus, Sonogashira cross-coupling reactions of compounds **3f** and **3l** with phenylacetylene were explored (Scheme 3). As expected, the reactions proceeded smoothly to afford the corresponding coupling products **4** and **5** in good yields, respectively.



Scheme 3 Sonogashira cross-coupling reactions of compounds **3f** and **3l** with phenylacetylene

A possible mechanism was proposed, which is shown in Scheme 4. We reasoned that in the presence of a base, the formal [3 + 2] cycloaddition of 2-isocyanoacetate **2** to an isothiocyanate moiety in compound **1** would occur first to produce intermediate **A**. Intermediate **A** could then undergo protonolysis and isomerization to afford intermediate **C**. Finally, an intramolecular cyclization of intermediate **C** promoted by copper(I) would happen to give the target product **3.**



Scheme 4 A possible mechanism for the reaction of *o*-alkynyl-phenyl isothiocyanate with 2-isocyanoacetate**.**

In summary, we have described a highly efficient method for the synthesis of 5*H*-benzo[*d*]imidazo[5,1-*b*][1,3]thiazines via copper(I)-catalyzed tandem reaction of *o*-alkynylphenyl isothiocyanates with isocyanides. The reactions generated a variety of 5*H*-benzo[*d*]-imidazo[5,1-*b*][1,3]thiazines in good to excellent yields under mild conditions. Different functional groups could be compatible in this transformation and a [3+2] cycloaddition mechanism was involved. More transformations incorporating isothiocyanates and isocyanides for the synthesis of biologically interesting heterocycles are ongoing in our laboratory.

Notes and references

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