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Copper-catalyzed high selectively synthesis of 2-benzyl- and 2-benzylidene-substituted benzo[*b*]thiazinones from 2-iodophenyl cinnamamides and potassium sulfide

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An efficient and practical procedure for the synthesis of 2-benzyl- and 2-benzylidene-substituted benzo[*b*]thiazinones from easily available 2-iodophenylcinnamamides and potassium sulfide has been developed. In the presence of DBU, the reaction proceeds *via* electrophilic addition, followed dehydrogenation, and reduction to give 2-benzyl benzo[*b*]thiazinones. Furthermore, 2-benzylidenebenzo[*b*]thiazinones were obtained in moderate to good yields without addition of DBU.

Benzothiazines are a key functional molecules, and widely present in a myriad of natural products and biologically active compounds.[1] As an important derivative of benzothiazines, benzothiazinones show their good biological activities, such as antiarrhythmic,[2] antidiabetic,[3] anticonvulsant/antifungal,[4] antifungal activities,[5] antituberculosis activities (**Figure 1**).[6] Accordingly, much effort has been made towards the development of diverse synthetic methods for benzothiazinones. Conventional methods for the construction of benzothiazinones framework focus on (1) the condensation of 2-aminothiophenols with α,β-unsaturated carboxylic acids, β- ketoesters or epoxides;[7] (2) 2-chlorothiophenol reacted with chloroacetyl chloride and primary amines or mercaptoamides reacted with 2-halonitrobenzene *via* Smiles rearrangement;[8] (3) transition-metal-catalyzed C-S coupling reaction of thiols with 2-halonitrobenzene, chloroacetyl chloride, or 2-iodoaniline.[9] However, these methods suffer from difficulties in the preparation of readily oxidized thiophenols and thiols. So as to find some easily available materials and to develop simple and efficient methods for the synthesis of benzothiazinones are of great value.

In recent years, inorganic sulfides, as the stable and easily available sulfur source, have been widely used for the synthesis of sulfur-heterocycle compounds *via* the formation of double C-S bonds.[10] Among them, the construction of double C-S bonds *via* in situ generation of thiolate followed the addition of olefins is one of important strategies.[11] For example, Sekar and co-workers reported that 2-arylthiochromanones[12] and 2-acylbenzothiophene[13] have been synthesized from 2-halochalcones with xanthate *via* in situ incorporation of sulfur followed by copper-catalyzed addition cyclization. Meantime, our work indicated that benzothiophenes could be gained *via* direct S_NAr-type reaction, cyclization, and dehydrogenation process.[14] Recently, Ji group found that this strategy was used to obtain benzothiazines *via* a radical process.[15] Due to our continuous work to the synthesis of the sulfur-containing heterocyclic compounds using metal sulfides as sulfuration reagents,[16] we thought this strategy would apply to the synthesis of benzothiazinones from 2-iodophenyl cinnamamides and metal sulphide (**Scheme 1**). Herein, we wish to detail our results.

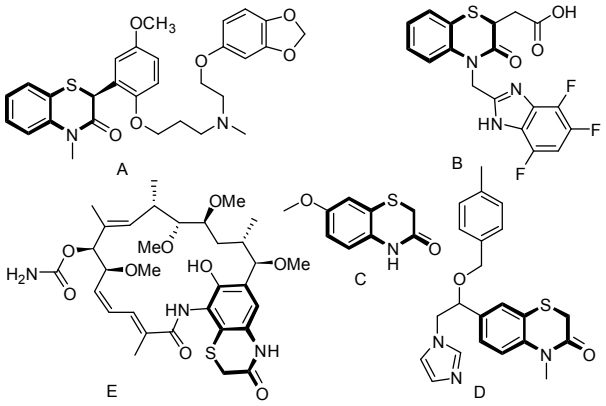
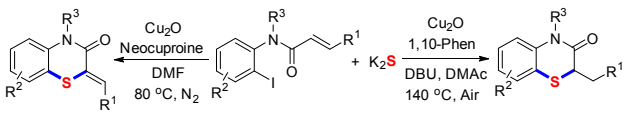


Figure 1. Bioactive 1,4-benzothiazine derivatives



Scheme 1. Selectively synthesis of 2-benzyl- and 2-benzylidene-substituted benzo[*b*]thiazinones

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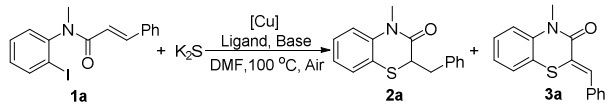
Initially, N-(2-iodophenyl)-N-methylcinnamamide (**1a**) and K_2S were selected as a model reaction to optimize the reaction conditions, and the results are summarized in **Table 1**. At first, **1a** reacted with K_2S in the presence of Cu_2O, 1,10-phenanthroline, and DBU in DMF at 100 °C for 6 h, to our delight, the desired product 2-benzyl-4-methyl-2H-benzo[*b*][1,4]thiazin-3(4H)-one (**2a**) could be obtained in 83% yield (entry 1). Several copper salts including CuCl, CuBr, CuI, CuOAc, $CuCl_2$, and $Cu(OAc)_2$ were examined (entries 2-7). The results indicated that the catalytic efficiency of monovalent copper salts were better than bivalent copper salts, and Cu_2O was still the best catalyst for this cycliation reaction. Subsequently, a series of ligands (including TEMED, L-proline, and DMEDA) were examined to improve the catalyst performance (entries 9−11), and 1,10-phenanthroline was found to be the best ligand, meanwhile, the yield of **2a** was also decreased when the reaction was performed in the absence of ligand (entry 8). However, trace amounts of product **2a** was observed when no base involved in this reaction and small amounts of **3a** was gained (entry 12), and the other bases, such as Et_3N, DMAP, and Cs_2CO_3, all gave lower yields of **2a** than DBU (entries 13−15), the results revealed that DBU played a significant role making for the formation of **2a**. In the examination of the solvents including DMF, DMSO, NMP, and DMAc, DMAc was proved to be the best solvent (entries 16−18). Finally, in order to improve the yield, the reaction temperature was evaluated, the yield of **2a** was increased along with the rise of the temperature. Thus, the optimized reaction conditions were as follows: **1a** (0.2 mmol), K_2S (0.6 mmol), Cu_2O (10 mol %), 1,10-phenanthroline (20 mol %), DBU (0.6 mmol), in DMAc (2 mL) under air atmosphere at 140 °C.

Table 1. Optimization of reaction condition[a]



1a 2a 3a

Entry	Catalyst	Ligand	Base	Yield 2a[b](%)	Yield 3a[b](%)
1	Cu_2O	1,10-Phen	DBU	83	0
2	CuCl	1,10-Phen	DBU	78	0
3	CuBr	1,10-Phen	DBU	82	0
4	CuI	1,10-Phen	DBU	72	0
5	CuOAc	1,10-Phen	DBU	53	0
6	$CuCl_2$	1,10-Phen	DBU	65	0
7	$Cu(OAc)_2$	1,10-Phen	DBU	58	0
8	Cu_2O	-	DBU	71	0
9	Cu_2O	TEMED	DBU	52	0
10	Cu_2O	L-proline	DBU	68	0
11	Cu_2O	DMEDA	DBU	53	0
12	Cu_2O	1,10-Phen	-	Trace	14
13	Cu_2O	1,10-Phen	Et_3N	4	55
14	Cu_2O	1,10-Phen	DMAP	Trace	48
15	Cu_2O	1,10-Phen	Cs_2CO_3	Trace	36
16[c]	Cu_2O	1,10-Phen	DBU	74	0
17[d]	Cu_2O	1,10-Phen	DBU	86	0
18[e]	Cu_2O	1,10-Phen	DBU	82	0
19[d,f]	Cu_2O	1,10-Phen	DBU	89	0
20[d,g]	Cu_2O	1,10-Phen	DBU	93	0

[a] Conditions: **1a** (0.20 mmol), K_2S (0.60 mmol), Cu catlyst (10 mol %), ligand (20 mol %), base (0.60 mmol), DMF (2 mL), air, at 100 °C for 6 h. [b] Isolated yield. [c] DMSO. [d] DMAc. [e] NMP. [f] 120 °C. [g] 140 °C.

With optimized reaction conditions in hand, we proceeded to investigate the substrate scope of the reaction. As shown in **Scheme 2**, the substituent of cinnamoyl was examined firstly, and the results demonstrated that both electron-donating groups such as methyl and methoxyl and electronic-withdrawing groups such halogen atoms (F, Cl, and Br), trifluoromethyl, and nitryl substituted cinnamamide could be smoothly transformed into the desired products. Especially, the steric effect of the substituents was not obvious to this reaction. For example, bearing of methyl and fluorine atom on the benzene ring at different positions of the cinnamamide (ortho-, meta-, and para-positions) showed almost equal efficiency (**2b**-**2d**, **2f**-**2h**). Unfortunately, nitryl-substituted 2-benzylbenzo[*b*]thiazinones **2l** was obtained in 27% yield only. Subsequently, we found that N-(2-iodophenyl)acrylamide could not give the target product.

To further examine the scope and limitation of the reaction, we tested the affects of substituents on the benzene ring of 2-iodoaniline. Different functional groups, including electronic-rich groups such as CH_3 and OCH_3 and electronic-deficient groups such as F and Cl on the benzene ring all tolerated well under the standard reaction conditions and achieved a moderate to good yields. For instance, N-(2-iodo-4-methylphenyl)cinnamamide can gave 88% yield of **2n**. On the other hand, the different substituents on the nitrogen atom were screened also. From the results showing, the electron-donating groups could promote the cyclization reaction, whereas the electron-withdrawing could inhibit the reaction. It is noteworthy that N-free 2-benzylbenzo[*b*]thiazinone **2t** was afforded in 85% yield, which could be used for further modification through amination reaction. Furthermore, the structure of **2v** was also unambiguously confirmed by single-crystal XRD analysis. However, when N-benzoyl substituted substrate was reacted with K_2S at optimized reaction conditions, the desired product could not be detected, and deacylated product **2t** was obtained with 32% yield. Finally, we also investigated the reactivity of N-(2-bromophenyl)-N-methylcinnamamide, but we only obtained **2a** in 43% yield.

During the optimizing the reaction conditions of synthesis of benzo[*b*]thiazinones, except 2-benzylbenzo[*b*]thiazinones, the product of 2-benzylidenebenzo[*b*]thiazinones were obtained. In order to achieve the single product of 2-benzylidenebenzo[*b*]thiazinones, we attempted to optimize the reaction conditions using N-(2-iodophenyl)cinnamamide (**1t**) with K_2S as the model reaction (see the **SI** for more details). After screening the reaction from copper-catalyst, ligands, and solvents, the optimized reaction condition were achieved as follows: **1t** (0.2 mmol), K_2S (0.6 mmol), Cu_2O (10 mol %), neocuproine (20 mol %), in DMF (2 mL) under nitrogen atmosphere at 80 °C, and the desired product **3t** was isolated in 91% yield. Furthermore, the structure of **3t** was also unambiguously confirmed by single-crystal XRD analysis. Subsequently, the substrate scope to the substituent of cinnamoyl were examined, as shown in **Scheme 3**, including the electron-donating groups such as -Me, -OMe and electron-donating groups such as fluorine atom were tolerated well and given the desired products in moderate to good yields. Similarly, the electronic effect of the substituents on the benzene ring of *o*-iodoaniline was also investigated, 4-methyl and 4-fluoro substituted substrate were provided the corresponding product **3tf** and **3tg** in 82% and 50% yield, respectively. At last, the N-methyl substituted **3a** was obtained in 58% yield with a slight condition change.

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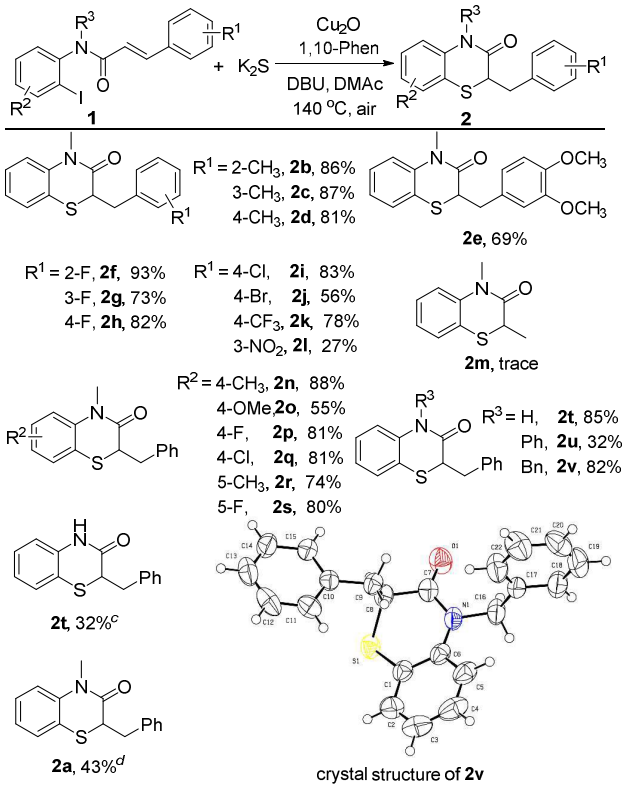
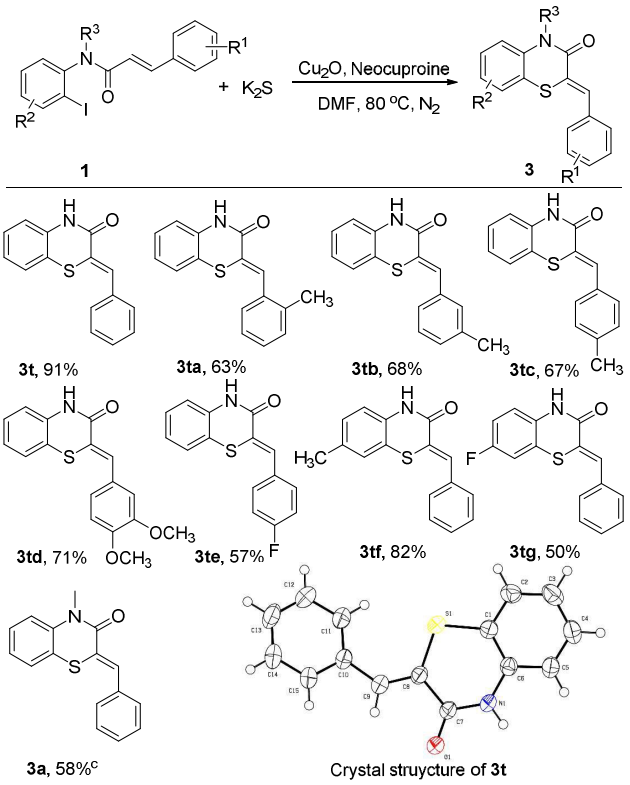


[a] Conditions: **1** (0.20 mmol), K_2S (0.60 mmol), Cu_2O (10 mol %), 1,10-Phen (20 mol %), DBU (0.6 mmol), DMAc (2 mL), air, at 140 °C for 6 h. [b] Isolated yield. [c] N-cinnamoyl-N-(2-iodophenyl)benzamide. [d] N-(2-bromophenyl)-N-methylcinnamamide.

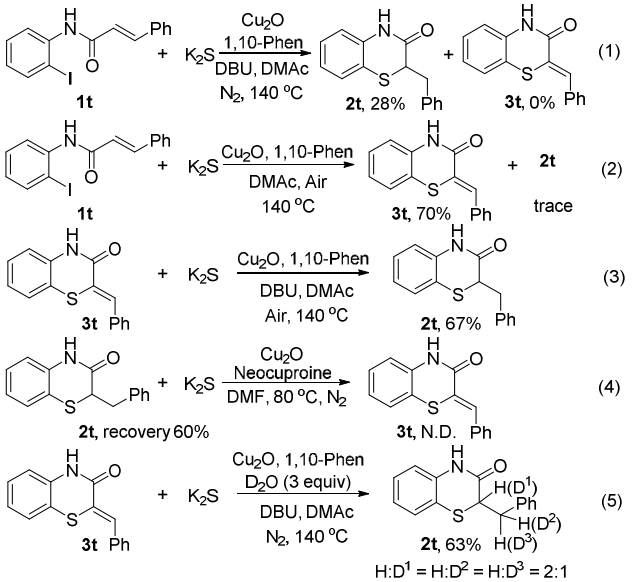
Scheme 2. Synthesis of 2-benzylbenzo[*b*]thiazinones[a,b]

To shed light on the mechanism of this reaction, several control experiments were carried out, as shown in **Scheme 4**. First of all, N-(2-iodophenyl)-N-methylcinnamamide (**1t**) was treated with K_2S under nitrogen atmosphere, and the desired product **2t** was afforded in 28% yield only (eq. 1). This result indicated the reaction underwent an oxidative process. Meantime, the model reaction was performed in the absence of DBU, to our surprise, 70% of **3t** was obtained and trace amounts of **2t** was observed (eq. 2). Then, we found that **3t** could transform into the desired product **2t** in 67% yield under standard reaction conditions (eq. 3). This significant result indicated that **3t** was an important precursor for the formation of benzothiazinones, and DBU played a significant role in terms of promoting the intermediate transformed into the desired product. And we knew that **2t** could not transform into the desired product **3t** under the secondly optimized reaction conditions (eq. 4). This result suggested that **2t** could not come into being directly through nucleophilic addition reaction during the reaction process. Finally, from the deuterated experiment, we could deduce that water acted as the hydrogen donor in the transformation, which possibly derived from the solvent (eq. 5).



[a] Conditions: **1** (0.20 mmol), K_2S (0.60 mmol), Cu_2O (10 mol %), Neocuproine (20 mol %), DMF (2 mL), N_2, at 80 °C for 12 h. [b] Isolated yield. [c] **1a** (0.20 mmol), K_2S (0.60 mmol), Cu_2O (10 mol %), 1,10-Phen (20 mol %), DMAc (2 mL), air, at 140 °C for 6 h.

Scheme 3. Synthesis of 2-benzylidenebenzo[*b*]thiazinones[a,b]



Scheme 4. Control experiments

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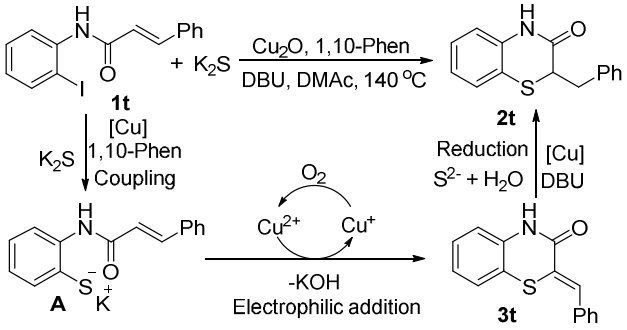
On the basis of the present experimental results and previous mechanisms reported,[12-17] a possible mechanism for the **1t** was proposed as outlined in **Scheme 5**. Initially, intermediate **A** was generated in situ by the reaction of N-(2-iodophenyl)cinnamamide (**1t**) with K_2S *via* the copper-catalyzed traditional coupling reaction. Then, intermediate **A** could transform into intermediate **3t** via oxidation, electrophilic addition and elimination in the presence of copper and oxygen. At last, following a sequential reduction of **3t**, the desired product **2t** was formed in the presence of DBU.



Scheme 5. Possible mechanism for the formation of **2t**

We have established a simple and practical method for the synthesis of 2-benzylbenzo[*b*]thiazinones and 2-benzylidenebenzo[b]thiazinones via a copper-catalyzed coupling reaction of 2-iodophenylcinnamamides and potassium sulfide. The experimental results showed that DBU as a switch of the reaction could control the selectivity of 2-benzylbenzo[*b*]thiazinones and 2-benzylidenebenzo[*b*]thiazinones. Further investigation on the synthetic application and mechanistic studies of DBU is currently ongoing in our laboratory.

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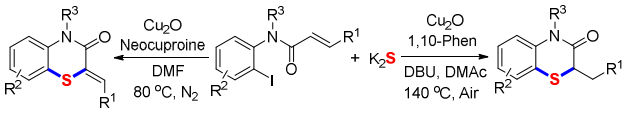
Copper-catalyzed high selectively synthesis of 2-benzyl- and 2-benzylidene-substituted benzo[*b*]thiazinones from 2-iodophenyl cinnamamides and potassium sulfide

Wenjuan Liu, Hao Min, Xiaoming Zhu, Guobo Deng* and Yun Liang*



An efficient and practical procedure for the synthesis of benzo[*b*]thiazinones from easily available 2-iodophenylcinnamamides and potassium sulfide has been developed. DBU as a switch could control the selectivity of the formation of 2-benzyl-substituted benzo[*b*]thiazinones and 2-benzylidenebenzo[*b*]thiazinones.