Heterocycles

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Efficient and Economical Access to Substituted Benzothiazoles: Copper-Catalyzed Coupling of 2-Haloanilides with Metal Sulfides and Subsequent Condensation**

Dawei Ma, Siwei Xie, Peng Xue, Xiaojing Zhang, Jinhua Dong, and Yongwen Jiang**

Substituted benzothiazoles are one of the most important classes of heterocycles for pharmaceutical purposes; they exist in numerous bioactive molecules such as the clinically used drug zopolrestat (**1**, for the treatment of diabetes; Figure 1),[1] selective fatty acid amide hydrolase inhibitor **2**,[2] aldose reductase inhibitor **3**,[3] antitumor agents 5F203 (**4**)[4] and PMX 610 (**5**),[5] as well as fatty acid oxidation inhibitor (*R*)-CVT-3501 (**6**).[6] Additionally, benzothiazole moieties have been found frequently in other molecules such as a rariometric fluorescent pH indicator,[7] an iminocoumarin-based zinc sensor,[8] a bioluminogenic substrate,[9] some cleavage agents for soluble oligomers[10] of amyloid β-peptides, and ligands for catalytic reactions.[11]

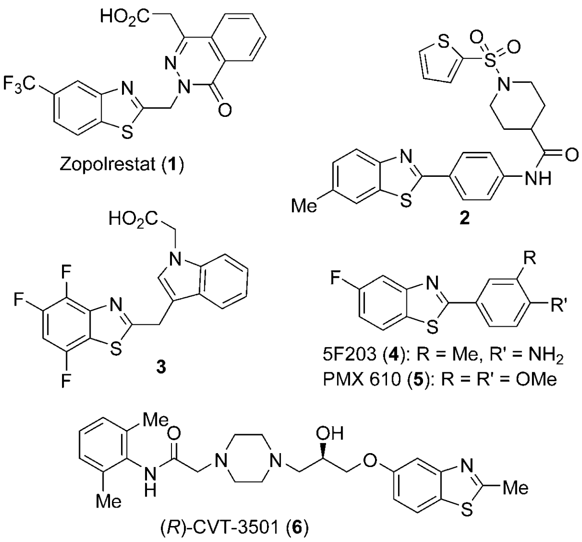


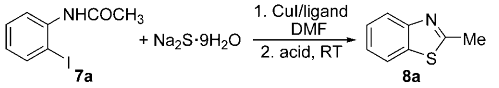
Figure 1. Structures of bioactive substituted benzothiazoles.

The common methods for the assembly of benzothiazoles are based on the condensation of 2-aminothiophenols with carboxylic acids or aldehydes,[4,7,11,12] but such methods suffer from difficulties in the preparation of readily oxidized 2-aminothiophenols. An alternative approach starts from 2-haloanilides,[13] however, in most cases the conversion of the amides into the corresponding thioamides using P_4S_{10} or Lawesson's reagent is required, but is generally not feasible for substrates comprised of ketone, ester, and amide moieties. To overcome this drawback, Itoh and Mase developed a novel and practical synthesis of benzothiazoles by using a palladium-catalyzed thiol cross-coupling reaction of 2-haloanilides and 2-ethylhexyl 3-mercapto-propionate.[14] The disadvantage of this method lies in the considerable costs for both the catalyst and the thiol reagent.

In the course of our studies on new methods for heterocycle synthesis through copper-catalyzed coupling reactions of 2-haloanilides with nucleophiles,[15,16] we attempted to use some metal sulfides as coupling partners. We were pleased to find that their coupling with 2-haloanilides worked well to give benzothiazoles after an acidic workup. To the best of our knowledge, this is the first successful example for the use of metal sulfides as coupling partners in a metal-catalyzed arylation.[17,18] Herein we disclose the details of our results.

As indicated in Table 1, we started our studies by conducting a CuI/L-proline catalyzed coupling reaction of *N*-(2-*i*odophenyl)-acetamide (**7a**) with $Na_2S{\cdot}9H_2O$ (Table 1, entry 1). It was found that after 12 hours at 80 °C, **7a** was completely consumed; the reaction mixture was then treated

Table 1: Screened reaction conditions for formation of benzothiazole **8a**.[a]



Entry	T [°C]	Acid	Yield [%][b]
1	80	HCl	67[c]
2	80	HCl	67
3	80	HCl	83[d]
4	80	CF_3CO_2H	83[d]
5	60	–	–
6	80	HCl	15[d]

[a] Reaction conditions for the coupling step: **7a** (1 mmol), $Na_2S{\cdot}9H_2O$ (2 mmol), CuI (0.1 mmol), DMF (2 mL). [b] Yield of isolated product. [c] 0.2 mmol of L-proline was added. [d] Used 3 mmol of $Na_2S{\cdot}9H_2O$.

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[*] Prof. Dr. D. Ma, P. Xue, Dr. Y. Jiang
State Key Laboratory of Bioorganic & Natural Products Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (China)
Fax: (+86) 21-6416-6128
E-mail: madw@mail.sioc.ac.cn
jiangyw@mail.sioc.ac.cn

S. Xie, Prof. Dr. X. Zhang, J. Dong
Shenyang Pharmaceutical University
103 Wenhua Lu, Shengyang 110016 (China)

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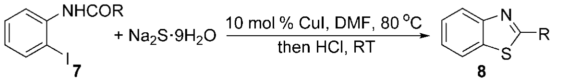
with 12 N HCl to afford benzothiazole **8a** in 67% yield. A similar result was obtained in the absence of L-proline (Table 1, entry 2), indicating that a ligand is not required in the coupling step. A better yield was obtained by increasing the amount of $Na_2S{\cdot}9H_2O$ to three equivalents (Table 1, entry 3). Changing the acid to CF_3CO_2H had no influence on this process (Table 1, entry 4), and coupling did not occur when the reaction temperature was lowered to 60 °C (Table 1, entry 5). CuI was found to be crucial, as evidenced by the fact that only 15% of **8a** was isolated in the absence of this catalyst (Table 1, entry 6).

Having the optimized the reaction conditions, we examined a series of 2-haloanilides to establish the scope and limits of this process. As summarized in Table 2, by using the present method, a considerable number of functional groups could be introduced into the 2-position of the benzothiazoles, including simple and functionalized alkyl groups (Table 2, entries 1–3), protons (Table 2, entry 4), substituted aryl groups (Table 2, entries 5–11), as well as heterocycles (Table 2, entries 12–14). For the formation of **8d**, **8e**, and **8o**, anhydrous potassium sulfide was employed as the coupling partner (Table 2, entries 3, 4, and 14). In these cases, $Na_2S{\cdot}9H_2O$ gave low yields of the products because of the competing amide of amide hydrolysis. Notably, benzothiazole **8h** has been reported to have potent tyrosine kinase inhibition and antitumor activity,[19] whereas compounds **8l**–**8n** could be used for the assembly of an antitumor agent,[20] an antiparasitic agent,[21] and an analogue of aldose reductase inhibitor **3**,[3] respectively.

Table 2: Assembly of 2-substituted benzothiazoles from aryl iodides.[a]

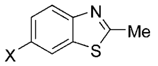
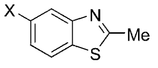
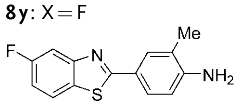
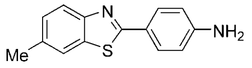
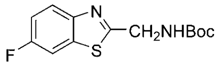
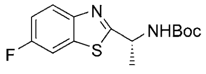
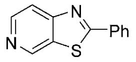


Entry	R	Product	Yield [%][b]
1	*i*Pr	**8b**	82
2	Bn	**8c**	72
3	CH_2NHBoc	**8d**	71[c]
4	H	**8e**	68[c]
5	Ph	**8f**	90
6	4-$CF_3C_6H_4$	**8g**	60
7	4-$NH_2C_6H_4$	**8h**	68
8	2-HOC_6H_4	**8i**	85
9	4-$MeOC_6H_4$	**8j**	88
10	4-HOC_6H_4	**8k**	87
11	4-HO-3-$MeOC_6H_3$	**8l**	85
12	2-pyridinyl	**8m**	72
13	2-((1H-indol-3-yl)methyl	**8n**	74[d]
14	2-furanyl	**8o**	84[c]

[a] Reaction conditions: **7** (1 mmol), $Na_2S{\cdot}9H_2O$ (3 mmol), CuI (0.1 mmol), DMF (2 mL), 12 h, then added 0.8 mL of 12 N HCl, RT, 5–10 h. [b] Yield of isolated product. [c] K_2S was used. [d] Used 0.2 mmol CuI.

A number of disubstituted benzothiazoles could be elaborated from trisubstituted aryl iodides (Table 3). The scope of this process was broad because of the following aspects: firstly, it seems that the electronic nature of the additional substituent has little influence on the reaction process, as both aryl iodides having electron-withdrawing and electron-donating groups gave the corresponding products in good yields (Table 3, entries 1–10). Secondly, several functional groups, such as fluoro, bromo, nitro, ketone, methoxy, and amido groups, are well-tolerated under these reaction conditions. These functional groups would allow additional transformations to give more complex benzothiazoles. In the case of an ester-substituted aryl iodide, the formation of the benzothiazole was accompanied by hydrolysis of the ester moiety, leading to the isolation of acid **8t** (Table 3, entry 5). Thirdly, both 2,5- and 2,6-disubstituted benzothiazoles and a pyridine-fused benzothiazole (Table 3, entry 16) could be elaborated from the corresponding aryl iodides. By taking advantage of this, antitumor agent 5F203 (**4**) (Table 3, entry 12),[4] and some known key intermediates for bioactive molecules, including compounds **8x** (Table 3, entry 9; for fatty acid oxidation inhibitor **6**[6]), **8z** (Table 3, entry 13; for fatty acid amide hydrolase inhibitor **2**[2]), and **8ab** (Table 3, entry 15; for synthesizing fungicide[22]), were effectively prepared.

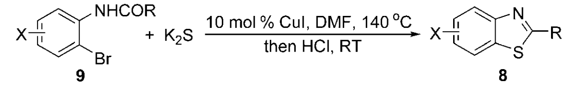
Table 3: Synthesis of disubstituted benzothiazoles from aryl iodides.[a]

Entry	Product	Yield [%][b]
		
1	**8p**: X=F	75
2	**8q**: X=Br	78
3	**8r**: X=NO_2	64
4	**8s**: X=$COCH_3$	71[c]
5	**8t**: X=CO_2H	82[d]
6	**8u**: X=Me	81
7	**8v**: X=OMe	73
8	**8w**: X=$NHCOCH_3$	81
		
9	**8x**: X=OMe	78
10	**8y**: X=F	77[c]
12	 **4**	69
13	 **8z**	55
14	 **8aa**	51
15	 **8ab**	81[c]
16	 **8ac**	76

[a] Reaction conditions: **7** (1 mmol), $Na_2S{\cdot}9H_2O$ (3 mmol), CuI (0.1 mmol), DMF (2 mL), 80 °C, 12 h, then added of 0.8 mL of 12 N HCl, RT, 5–10 h. [b] Yield of isolated product. [c] K_2S was used. [d] 3-acetamido-4-iodobenzoic methyl ester was employed as the starting material.

We next explored the possibility of employing aryl bromides as substrates and found that their reaction with K$_2$S under our standard conditions is sluggish. However, when the reaction temperature was raised to 140 °C, a satisfactory conversion was achieved to give benzothiazoles in moderate to good yields (Table 4). Notably, a 2,4,6-trisubstituted benzothiazole was obtained in 66 % yield from *N*-(2-*b*romo-4,6-dimethylphenyl)acetamide (Table 4, entry 5), thus further demonstrating the enormous potential of our method for the assembly of polysubstituted benzothiazoles.

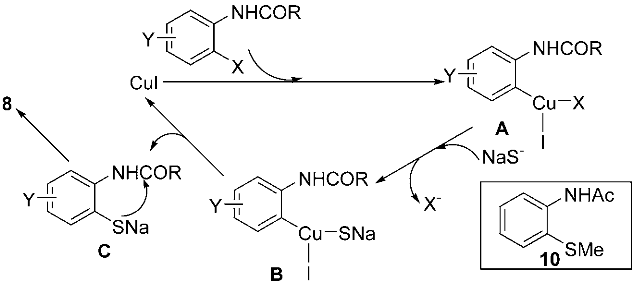
Table 4: Assembly of substituted benzothiazoles from aryl bromides.[a]



Entry	R	X (for **8**)	Product	Yield [%][b]
1	Ph	H	**8 f**	88
2	4-NH$_2$-3-MeC$_6$H$_3$	H	**8 ad**	78
3	Me	4,6-dimethyl	**8 ae**	66
4	Me	5-methoxy	**8 x**	41
5	Ph	6-fluoro	**8 af**	86
6	2-pyridinyl	H	**8 m**	63

[a] Reaction conditions: **9** (1 mmol), K$_2$S (3 mmol), CuI (0.1 mmol), DMF (2 mL), 140 °C, 12 h, then added 0.8 mL of 12 N HCl, RT, 5–10 h. [b] Yield of isolated product.

Although a detailed mechanistic investigation of this process awaits additional experimentation, a tentative proposal is outlined in Scheme 1. After an oxidative addition of CuI to the aryl halide to form complex **A**, a ligand exchange with sodium sulfide might provide complex **B**, which could then undergo reductive elimination to give intermediate **C** and regenerate CuI. The intramolecular condensation of **C** would furnish benzothiazoles **8**. The formation of **C** was confirmed by isolation of **10** (26 % yield, together with some unidentified side products) after trapping the coupling mixture with iodomethane. Additionally, it was found that the amido group was essential for the coupling step, presumably because of an *ortho*-substituent effect directed by this group[23] or the capability for subsequent condensation.



Scheme 1. Putative catalytic cycle for the S arylation.

In conclusion, we have developed a novel method for the synthesis of substituted benzothiazoles, which relies on an unprecedented CuI-catalyzed coupling reaction of aryl halides with metal sulfides. This approach can compliment many of the other existing methods for producing substituted benzothiazoles and in many cases would have definite advantages in terms of the scope and the conditions of the reaction. Thus, it can find numerous applications in organic synthesis. Additionally, the successful application of metal sulfides as coupling partners will stimulate studies on metal-catalyzed S-arylation by employing these inexpensive reagents.

Experimental Section

Typical procedure: A mixture of CuI (19 mg, 0.1 mmol), *o*-iodobenzamide (1 mmol), and Na$_2$S·9H$_2$O (or K$_2$S) (3 mmol) in DMF (2 mL) was stirred at 80 °C for 12 h. The reaction mixture was cooled to RT and then 0.8 mL of conc. HCl was added and the reaction mixture stirred for 5–10 h. After adding 10 mL saturated aq. NaHCO$_3$, it was extracted with ethyl acetate and then purified by silica gel chromatography to furnish the desired product.

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