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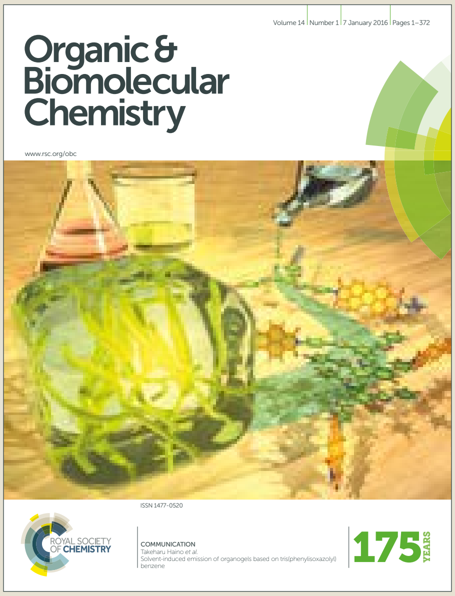

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COMMUNICATION

Copper-Catalyzed Synthesis of 2-Aminobenzothiazoles from 2-Iodophenyl Isocyanides, Potassium Sulfide and Amines

Hao Min, Genhua Xiao, Wenjuan Liu and Yun Liang*

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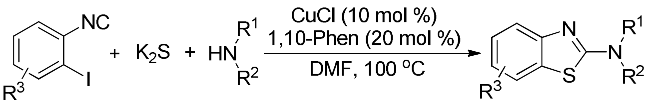
A simple and practical useful synthetic method for the synthesis of a variety of 2-aminobenzothiazoles was developed. This methodology could construct one C-N bond and two C-S bonds in a step reaction and provide the desired products in good to perfect yields.

Benzothiazoles are key structural motifs of numerous natural products and biologically active molecules.[1] As important benzothiazole derivatives, 2-aminobenzothiazoles show various biological activities such asubiquitin ligase inhibitors,[2] antitumor,[3] antirotavirus infections,[4] the adenosine receptor,[5] and the nuclear hormone receptor.[6] The rising use of these biologically significant 2-aminobenzothiazoles has stimulated considerable interest in developing their synthetic methods with enhanced generality, scope, and cost effectiveness. Accordingly, many efficient methods were developed for the synthesis of 2-aminobenzothiazoles.[7-12] Recently, four synthetic strategies based on the sulfur-containing substrate have been developed for the assembly of 2-aminobenzothiazoles. a) amination of benzothiazoles;[9] b) intra-molecular cycliaztion of thioureas or isothiocyanates;[10] c) inter-molecular cycliaztion of isothiocyanates with amines;[11] d) domino condensation/s-arylation/cyclization of CS_2 with amine and 2-iodoanilines.[12] Despite the significances, these reported methods suffer from the prefunctionalized sulfur-containing substrate which usually required several steps and harsh reaction conditions for their preparation. However, the usage of metal sulfides as a surrogate for the efficient construction of 2-aminobenzothiazoles is an important strategy from the viewpoints of operational simplicity, economic raw material, and assembly efficiency. For solving the problem of sulfur source, we successfully synthesized 2-aminobenzothiazoles from carbodiimides with sodium hydrosulfide *via* two C-S bonds formation.[13] Due to the difficulty in the preparation of carbodiimides, the synthetic method was limited yet. In order to disclose new approaches from more simple substrates, the strategy through multiple chemical bond formation is desired. Recently, we found three-component synthesis of benzothiazolethiones from *o*-iodoanilines, isocyanide, and potassium sulfide *via* one C-N bond and multiple C-S bonds formation in a step reaction.[14] Therefore, we thought the strategy would apply to the synthesis of 2-aminobenzothiazoles from isocyanide, amine, and metal sulfide. Herein, we wish to detail our results.



Scheme 1 Synthesis of 2-aminobenzothiazoes

Our initial investigation began with 2-iodophenyl isocyanide (**1a**) and piperidine (**2a**) in the presence of K_2S, CuCl and tetramethylethylenediamine (TMEDA) in DMF. To our delight, the desired product of 2-aminobenzothiazole (**3a**) was obtained in 88% yield (Table 1, entry 1). Encouraged by this result, a series of other copper catalysts, including CuBr, CuI, $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$) were tested (entries 2–6), and the results showed that they are favourable to the three-components reaction. To further improve the efficiency, the effects of ligands were examined when we selected the CuCl as the catalyst. The ligands 1,10-phen, and bipy showed the equal efficiency as TMEDA and the ligand L-proline gave the inferior result (entries 7–10). Furthermore, the yield of 2-aminobenzothiazole was lightly decreased when no ligand involved into the reaction. In the examination of the solvent, it was found that DMF gave the higher yields comparing with DMSO, NMP, and CH_3CN (entries 11–13). Subsequently, the other sulfur source such as Li_2S and Na_2S were screened, and the yield of 2-aminobenzothiazole (**3a**) was decreased obviously (entries 14-15). Finally, we investigated the effects of the reaction temperature. When the reaction temperature decreased to 60 °C (entry 16), the desired product was afforded in 94% by extending reaction time. When the reaction was carried out in 100 °C (entry 17), it only took 2 h to give a 95% yield of **3a**.

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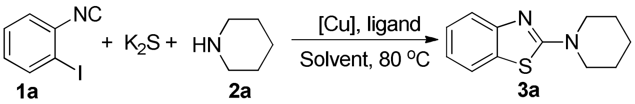
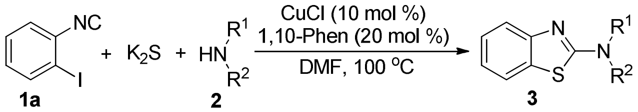
Table 1 Optimization of reaction conditions[a]

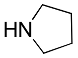
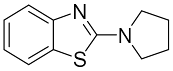
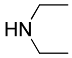
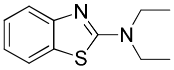
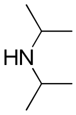
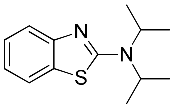
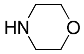
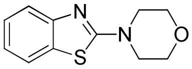
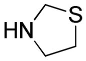
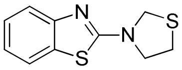
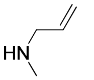
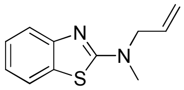
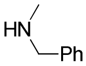
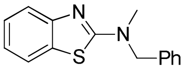
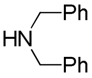
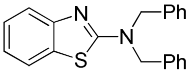
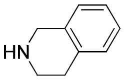
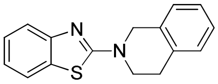
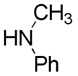
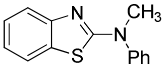
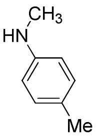
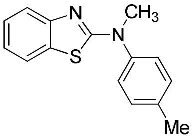
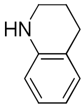
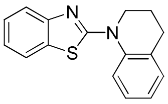


Entry	Catalyst	Ligand	Solvent	yield/**3a**[b]
1	CuCl	TMEDA	DMF	88
2	CuBr	TMEDA	DMF	85
3	CuI	TMEDA	DMF	87
4	CuBr$_2$	TMEDA	DMF	89
5	Cu(OAc)$_2$	TMEDA	DMF	87
6	Cu(OTf)$_2$	TMEDA	DMF	84
7	CuCl	-	DMF	84
8	CuCl	1,10-phen	DMF	89
9	CuCl	L-proline	DMF	73
10	CuCl	bipy	DMF	89
11	CuCl	1,10-phen	DMSO	75
12	CuCl	1,10-phen	NMP	80
13	CuCl	1,10-phen	CH_3CN	72
14[c]	CuCl	1,10-phen	DMF	52
15[d]	CuCl	1,10-phen	DMF	64
16[e]	CuCl	1,10-phen	DMF	94
17[f]	CuCl	1,10-phen	DMF	95

[a] Conditions: **1a** (0.30 mmol), K$_2$S (0.90 mmol), **2a** (0.30 mmol), Cu catalyst (10 mol %), ligand (20 mol %), solvent (2 mL), air, at 80 °C for 2 h. [b] Isolated yield. [c] Li$_2$S instead of K$_2$S. [d] Na$_2$S instead of K$_2$S. [e] 60 °C, 12 h. [f] 100 °C, 2 h.

Table 2 Synthesis of *N*-substituted 2-aminobenzothiazoles [a]



Entry	Substrate	Product	Yield (%)[b]
1	 **2b**	 **3b**	98
2	 **2c**	 **3c**	94
3[c]	 **2d**	 **3d**	68
4	 **2e**	 **3e**	94
5	 **2f**	 **3f**	82
6	 **2g**	 **3g**	95
7	 **2h**	 **3h**	97
8	 **2i**	 **3i**	85
9	 **2j**	 **3j**	98
10	 **2k**	 **3k**	56
11	 **2l**	 **3l**	68
12	 **2m**	 **3m**	68

[a] Conditions: **1a** (0.30 mmol), K$_2$S (0.90 mmol), **2** (0.30 mmol), CuCl (10 mol %), 1,10-Phen (20 mol %), DMF (2 mL), air, 100 °C, 2 h. [b] Isolated yield. [c] 100 °C, 8 h.

With the optimal reaction conditions in hand, we explored the substrate scope of amines. Various secondary amines were successfully applied to the reactions of 2-iodophenyl isocyanide with K$_2$S under the optimized conditions and the results are summarized in table 2. The corresponding 2-aminobenzothiazoles were obtained in good to perfect yields. First, the aliphatic secondary amines, including circular pyrrolidine, linear diethylamine, were found that they provided the corresponding product in 98% and 94% yield respectively. However, the N,N-diisopropylbenzo[d]thiazol-2-amine is only given 68% yield. The result attributed to the steric hindrance effect of diisopropylamine. Happily, heteroatom-containing amines such as morpholine and thiazolidine could smoothly react with 2-iodophenyl isocyanide with K$_2$S, and afforded **3e** and **3f** in 94% and 82% yield, respectively. Then, the allyl and benzyl substituted secondary amines such as N-methylallylamine, N-methylbenzylamine, dibenzylamine, and 1,2,3,4-tetrahydroisoquinoline were screened, and their desired products all afforded in perfect yields. Finally, the aryl substituted secondary amines including N-methylaniline, N,4-dimethylaniline and 1,2,3,4-tetrahydroquinoline were examined, and the results showed that the corresponding products were achieved in moderate yields. The most likely reason is that the weaker nucleophilicity of the aromatic amines. The reactivity of primary amines such as benzyl amine and aniline were investigated. However, the reaction became very messy, and the

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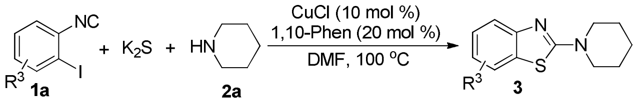
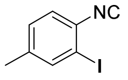
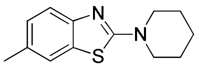
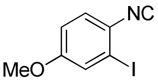
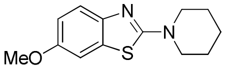
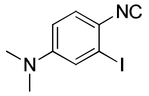
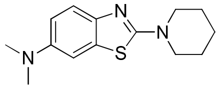
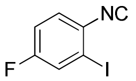
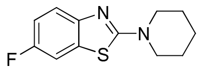
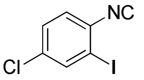
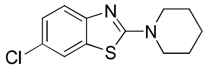
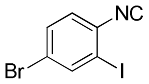
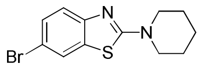
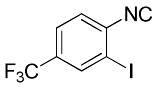
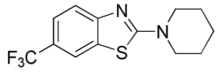
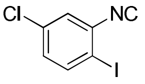
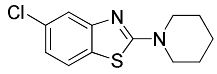
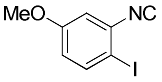
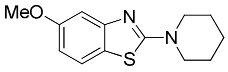
expected product was not isolated. Finally, we investigated the reactivity of 2-bromophenyl isocyanide, affording the corresponding product in 17% yield.

To expand the scope of this methodology, a series of substituted 2-iodophenyl isocyanides were examined, and the results were summarized in table 3. Under the standard reaction conditions, the both electron-rich and electron-deficient groups substituted 2-iodophenyl isocyanides could be smoothly transformed into the desired products. For example, the electron-donating groups such as methyl, methyoxyl and dimethylamino or the electron-withdrawing groups such as fluoro, chloro and bromo substituted 2-(piperidin-1-yl)benzo[d]thiazole were obtained in good yields. It is noteworthy that halo-substituted 2-aminobenzothiazole could be used for further modification. Unfortunately, the 2-(piperidin-1-yl)-6-(trifluoromethyl)benzo[d]thiazole and 5-chloro-2-(piperidin-1-yl)benzo[d]thiazole were obtained in 47% and 60% yield, respectively.

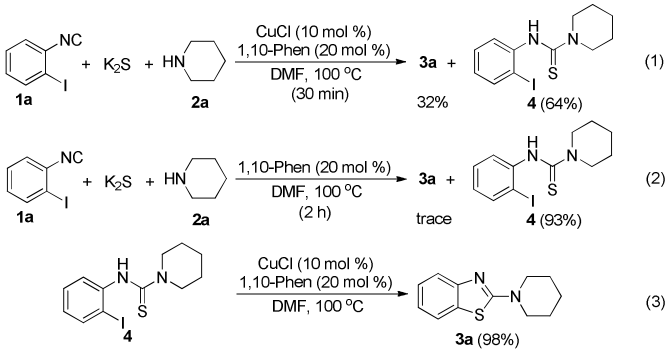
Table 3 Synthesis of 2-aminobenzothiazolones from substituted *o*-iodophenyl isocyanides [a]



Entry	Substrate	Product	Yield (%)[b]
1	 **1n**	 **3n**	80
2	 **1o**	 **3o**	89
3	 **1p**	 **3p**	87
4	 **1q**	 **3q**	81
5	 **1r**	 **3r**	83
6	 **1s**	 **3s**	85
7	 **1t**	 **3t**	47
8	 **1u**	 **3u**	60
9	 **1v**	 **3v**	78

[a] Conditions: **1a** (0.30 mmol), K_2S (0.90 mmol), **2** (0.30 mmol), CuCl (10 mol%), 1,10-Phen (20 mol%), DMF (2 mL), air, 100 °C, 2 h. [b] Isolated yield.

To shed light on the mechanism of this reaction, several control experiments were performed, as shown in scheme 2. At first, **1a** was allowed to react with piperidine and K_2S for 30 minutes under the standard conditions. **3a** was formed in 32% yield along with 64% yield of thiourea **4**. Then, we conducted the same reaction in DMF at 100 °C for 2 h without the helping of CuCl catalyst, and found that the thiourea **4** was obtained in 93% yield. Finally, when the thiourea **4** was performed under the standard conditions, **3a** was obtained in 98% yield. This result indicated that thiourea **4** is an important precursor of the formation of 2-aminobenzothiazole, and CuCl could catalyze the cyclization of thiourea **4** to form **3a**.



Scheme 2 Control experiments

In summary, we have established a simple and practical approach for the synthesis of 2-aminobenzothiazoles *via* a copper-promoted cascade reaction involving isocyanides, potassium sulfide and amines. The tandem reactions successfully afford the corresponding 2-aminobenzothiazoles in moderate to excellent yields. Work to probe the detailed mechanism and apply the reaction in organic synthesis is currently ongoing.

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