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## COMMUNICATION

## Copper-Catalyzed Synthesis of 2-Aminobenzothiazoles from Carbodiimide and Sodium Hydrosulfide

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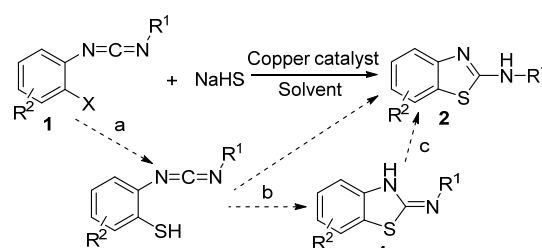
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An efficient copper-catalyzed method for the synthesis of a variety of 2-aminobenzothiazoles has been developed. The reaction proceeded from carbodiimide and sodium hydrosulfide *via* a tandem reaction in the presence of copper(II) trifluoromethanesulfonate to afford the corresponding 2-aminobenzothiazole derivatives in good to perfect yields.

2-Aminobenzothiazoles,<sup>1-5</sup> categorized as significant derivatives of benzothiazoles, are broadly found in bioorganic and medicinal chemistry with applications in drug discovery and development for the treatment of various diseases, such as aids,<sup>2</sup> diabetes,<sup>3</sup> epilepsy,<sup>4</sup> and tuberculosis.<sup>5</sup> Consequently, many efficient methods were developed for the synthesis of 2-aminobenzothiazoles. Among them, the common method was based on metal-catalyzed intermolecular cross-coupling reaction between 2-halobenzothiazoles and amines,<sup>6</sup> 2-aminobenzothiazoles and aryl halides,<sup>7</sup> or simple benzothiazoles and amines.<sup>8</sup> The other two methods of direct construction of 2-aminobenzothiazole have attracted more attention from the viewpoints of operational simplicity: (1) intramolecular cyclization of *o*-haloarylthioureas or arylthioureas,<sup>9</sup> and (2) intermolecular cyclization of 2-halophenylamines or 2-aminobenzenethiols with isothiocyanates.<sup>10</sup> However, these methods usually require several steps and harsh reaction conditions for the preparation of sulfur-containing substrates such as benzothiazoles, arylthioureas, isothiocyanates, which limit their application in synthesis. Recently, Ma and co-worker developed a simple method for the synthesis of 2-aminobenzothiazoles used the carbon disulfide as sulfur source.<sup>11</sup> Nevertheless, the toxicity and unpleasant odor of carbon disulfide impedes its application. Therefore, used simple, nontoxic, readily

available sulfur sources for the synthesis of 2-aminobenzothiazoles are of great value.

Recently, the nontoxic, odorless, and readily available sulfur sources such as metal sulfides have received considerable attention to synthesize the sulfur-containing heterocyclic compounds *via* a double thiolation reaction.<sup>12</sup> We are also interested in this synthetic strategy, and have successfully synthesized benzo[*b*]thiophene,<sup>13</sup> benzo[*d*]thiazole<sup>14</sup> and benzo[*d*]thiazol-2(3H)-one<sup>15</sup> used potassium sulfide as sulfur source. In the present research, we found that *o*-haloarylcarbodiimide<sup>16</sup> and metal sulfides could undergo a cascade process to afford 2-aminobenzothiazoles. As shown in scheme 1, the proposed reaction might proceed through a cross-coupling of *o*-haloarylcarbodiimide **1** and NaHS under copper-catalyzed conditions (step a, the plausible intermediate **3** would be formed, and copper catalyst was regenerated),<sup>12-15,17</sup> followed by the formation of 2-aminobenzothiazoles **2** or the intermediate of benzo[*d*]thiazol-2(3H)-imine **4** *via* an intramolecular nucleophile addition (step b, the process might be analogous to those reported nucleophile addition to a certain extent).<sup>16,18</sup> Rearrangement and isomerization of the intermediate **4** also give rise to the product **2** (step c). Here in, we wish to detail our results.



**Scheme 1** Proposed one-pot synthesis of 2-aminobenzothiazoles via a copper-catalyzed coupling/addition process

In this work, *N*-phenylbenzo[*d*]thiazol-2-amine was obtained in good yields from *N*-(2-iodophenyl)-*N*-phenylmethanediimine **1a** and NaHS in one pot, *via* a copper-catalyzed double thiolation. The results of the screening for optimal reaction conditions are shown in Table 1. Our investigation started by an attempted thiolation of substrate **1a** with K<sub>2</sub>S in DMF at 120 °C in the presence of CuBr<sub>2</sub> as the catalyst, and the desired product **2a** was isolated in 48% yield (entry 1). This result encouraged us to develop an efficient system to synthesize 2-aminobenzothiazole using *N*-(2-iodophenyl)-carbodiimine as a starting substrate. A

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variety of sulfur sources, such as  $K_2S$ ,  $Na_2S$ ,  $NaHS$ ,  $S$ ,  $Na_2S_2O_3$ , were screened (entries 1-5). The results indicated that  $NaHS$  was the best one for this reaction. Subsequently, the effects of copper catalysts (including  $CuBr$ ,  $CuI$ ,  $CuCl$ ,  $CuCN$ ,  $CuOTf$ ,  $Cu(OAc)_2$ ,  $Cu(OTf)_2$ ) are examined (entries 6-12).  $Cu(OTf)_2$  achieved the best result, and the product **2a** was obtained in 74% yield. It is noteworthy that copper II has much better catalysis activity than copper I. The possible reason attributes copper II could promote the nucleophile addition of carboniimide.<sup>18</sup> Without the copper catalyst, the desired product decreased to 11% yield (entry 13). Then, the effects of ligands (include 2,2'-Bipyridine, 1,10-Phen, L(-)-Proline, TMEDA) were checked also (entries-14-17). However, the ligands did not show better results. Solvents such as DMSO and NMP were evaluated, and 60% and 67% yield of the product **2a** were isolated respectively (entries 18-19). Finally, the amount of catalyst and the reaction temperature were evaluated, and relatively low yields were found with any reduction in the reaction temperature or the amount catalyst (entries 20-21). Thus, the optimized reaction condition were as follow: **1a** (0.3 mmol),  $NaHS$  (0.9 mmol),  $Cu(OTf)_2$  (20 mol%), in DMF (2 mL) under a  $N_2$  atmosphere at 120 °C.

**Table 1** Optimization of reaction conditions<sup>a</sup>

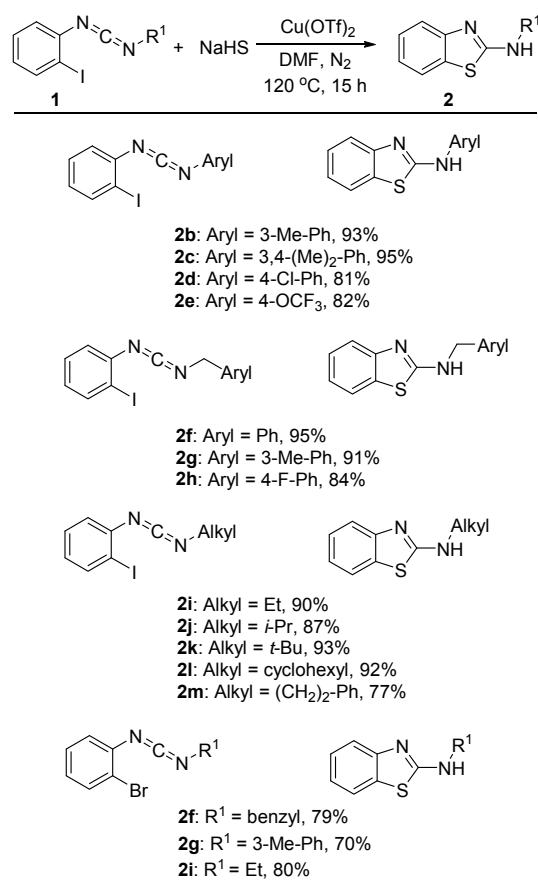
Entry	Sulfur source	Catalyst	Ligand	Solvent	yield/ <b>2a</b> <sup>b</sup>
1	$K_2S$	$CuBr_2$	-	DMF	48
2	$NaHS$	$CuBr_2$	-	DMF	66
3	$Na_2S$	$CuBr_2$	-	DMF	53
4	$Na_2S_2O_3$	$CuBr_2$	-	DMF	58
5 <sup>c</sup>	$S$	$CuBr_2$	-	DMF	36
6	$NaHS$	$CuI$	-	DMF	46
7	$NaHS$	$CuBr$	-	DMF	53
8	$NaHS$	$CuCl$	-	DMF	41
9	$NaHS$	$CuCN$	-	DMF	45
10	$NaHS$	$CuOTf$	-	DMF	48
11	$NaHS$	$Cu(OAc)_2$	-	DMF	60
12	$NaHS$	$Cu(OTf)_2$	-	DMF	74
13	$NaHS$	-	-	DMF	11
14	$NaHS$	$Cu(OTf)_2$	1,10-phen	DMF	71
15	$NaHS$	$Cu(OTf)_2$	2,2-py	DMF	62
16	$NaHS$	$Cu(OTf)_2$	TMEDA	DMF	68
17	$NaHS$	$Cu(OTf)_2$	L(-)-Proline	DMF	73
18	$NaHS$	$Cu(OTf)_2$	-	DMSO	60
19	$NaHS$	$Cu(OTf)_2$	-	NMP	67
20 <sup>d</sup>	$NaHS$	$Cu(OTf)_2$	-	DMF	70
21 <sup>e</sup>	$NaHS$	$Cu(OTf)_2$	-	DMF	64

<sup>a</sup> Conditions: **1a** (0.30 mmol), sulfur source (0.90 mmol), Cu catalyst (20

mol%), ligand (20 mol%), Solvent (2 mL),  $N_2$ , 120 °C, 15 h. <sup>b</sup> Isolated yield. <sup>c</sup>  $Cs_2CO_3$  (0.90 mmol), <sup>d</sup> 100 °C, <sup>e</sup>  $Cu(OTf)_2$  (10 mol%).

Under the optimized conditions, the substituent of the nitrogen moiety of *o*-iodobenzylcarboniimide was screened, and the results were summarized in table 2. Various *N*-substituted 2-aminobenzothiazoles were obtained from good to perfect yields. Initially, the substituents of aryl were screened. The results showed that increasing the electron density on the nonhalogenated ring might favor the intramolecular addition process. For instance, the presence of a weak electron-donating group (*m*-Me) and a weak electron-withdrawing group (*p*-Cl) on the aromatic ring of **1** provided 93% and 81% yield of corresponding products. Similarly, *N*-benzyl substituted 2-aminobenzothiazoles could be obtained in good to high isolated yields. For example, *N*-benzylbenzo[*d*]thiazol-2-amine was obtained in 95% yield under the optimized condition. For the *N*-alkyl substituted benzo[*d*]thiazol-2-amine, they with linear-chain, branched-chain, and cycloalkyl groups could all be afforded in perfect yields. This result showed that the alkyl substituent did not remarkably affect the reaction. Finally, we investigated the reactivity of *o*-bromobenzylcarboniimides. Importantly, the *o*-bromobenzylcarboniimides could efficiently reacted with  $NaHS$  and good yields of the products were given.

**Table 2** Synthesis of *N*-substituted 2-aminobenzothiazoles



To expand the scope of this methodology, we also examined a

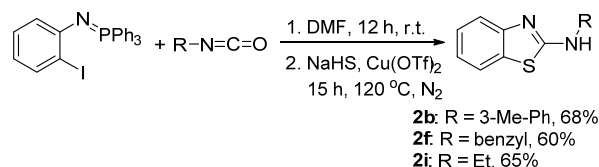
series of substituted *N*-benzyl-*N*-(2-iodophenyl)methanediimine and *N*-(4-chlorophenyl)-*N*-(2-iodophenyl)methanediimine. As summarized in table 3, for *N*-benzyl-*N*-(2-iodophenyl)methanediimine with either electron-withdrawing groups such as chloro (4-Cl, 5-Cl) and trifluoromethyl or electron-donating group such as methyl (4-methyl, 4,6-dimethyl) on iodobenzene ring, all well-tolerated under the reaction conditions and proceed with almost equal efficiency. These results indicated that electronic effect on benzene ring did not play a significant role in regulating the reaction, and revealed the inherent high reactivity of *o*-iodobenzylcarbonylimide. Unfortunately, bromo-substituted 2-aminobenzothiazole only afforded in 66% yield. However, bromo-substituted 2-aminobenzothiazole could offer an opportunity for further cross-coupling, and facilitating the expedient synthesis of complex compounds.

**Table 3** Synthesis of 2-aminobenzothiazolones from substituted *o*-iodobenzylcarbonylimide<sup>a</sup>

Entry	Substrate	Product	Yield (%) <sup>b</sup>
1			85
2 <sup>c</sup>			96
3			87
4			89
5			90
6			92
7 <sup>c</sup>			66

<sup>a</sup> Conditions: **1** (0.30 mmol), NaHS (0.90 mmol), Cu(OTf)<sub>2</sub> (20 mol%), DMF (2 mL), N<sub>2</sub>, 120 °C, 15 h. <sup>b</sup> Isolated yield. <sup>c</sup> R<sup>2</sup> = 4-Cl-Ph.

To our delight, this synthetic method to synthesize 2-aminobenzithiazoles could be further extend from the initial starting material in one step. For example, *N*-(2-iodophenyl)triphenyliminophosphane reacted with isocyanate in DMF for 12 h, then NaHS and Cu(OTf)<sub>2</sub> were added, and the reaction was further stirred for 15 h at 120 °C, and the corresponding 2-aminobenzithiazoles were obtained in good yields (scheme 2).



**Scheme 2** One-pot synthesis of 2-aminobenzothiazoles

In summary, we have developed an efficient coupling/addition tandem reaction from *o*-haloarylcarbonylimide and NaHS for the synthesis of 2-aminobenzothiazoles. In this copper-catalyzed system, the tolerance of diverse functional groups in *o*-haloarylcarbonylimide makes this present system attractive in the synthesis of various 2-aminobenzothiazoles. To our best knowledge, this is the first example of the use of NaHS as the sulfur source in the synthesis of 2-aminobenzothiazole derivatives.

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Copper-catalyzed a coupling/addition tandem reaction for the synthesis of 2-aminobenzothiazoles from *o*-haloarylcarbonimide and NaHS.

