Synthesis of 2-Aminobenzothiazole via Copper(I)-Catalyzed Tandem Reaction of 2-Iodobenzenamine with Isothiocyanate

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Copper(I)-catalyzed tandem reaction of 2-iodobenzenamine with isothiocyanate under mild conditions is described, which provides an efficient and practical route for the synthesis of 2-aminobenzothiazole.

Introduction

Tandem C−C bond formations are powerful methods for the synthesis of structurally complex molecules from relatively simple starting materials in a convergent way.[1,2] In particular, the development of tandem reactions for the efficient construction of small molecules is an important goal in combinatorial chemistry from the viewpoints of operational simplicity and assembly efficiency. Recently, we have described a novel and efficient method for the synthesis of 2,4-dihydro-1*H*-benzo[*d*][1,3]thiazine derivatives via AgOTf-catalyzed tandem addition−cyclization reactions of 2-alkynylbenzenamines with isothiocyanates (Scheme 1, eq 1).[3] In this reaction process, the thiourea sulfur atom attacked the Ag(I)-coordinated carbon−carbon unsaturated bond, giving rise to the corresponding products. Prompted by this result, we envisioned that 2-iodobenzenamine could be utilized as starting material for similar transformation (Scheme 1, eq 2). After generation of intermediate **B** via addition of amine **1** to isothiocyanate **2**, the transition metal catalyzed intramolecular C−S coupling might occur under suitable conditions to form 2-aminobenzothiazoles **3**.

As a privileged fragment, the 2-aminobenzothiazole core is found in many pharmaceuticals and agrochemicals that exhibit remarkable biological activities[4] although the benzothiazole nucleus is bioactivatible.[5] Many efforts continue to be given to the development of new 2-aminobenzothiazole structures and new methods for their constructions.[6] Usually, 2-aminobenzothiazole was synthesized via palladium- or copper-catalyzed cyclization of *ortho*-bromobenzothioureas.[6] However, an additional step for generation of *ortho*-bromobenzothioureas was necessary, starting from reactions of amines with 2-bromophenyl isothiocyanates or reactions of 2-haloanilines with isothiocyanates. Moreover, high temperature had to be employed for completion of reactions. Recently, we have developed efficient tandem reactions for the expeditious synthesis of biologically relevant heterocyclic compounds.[7,8] In light of our interest in natural productlike compound construction, we required an efficient method to generate a 2-aminobenzothiazole based scaffold, with a hope of finding more active hits or leads for our particular biological assays. Thus, we started to investigate the possibility to develop novel methods to build up the 2-aminobenzothiazole structures via the tandem addition/C−S coupling reactions as shown in Scheme 1. The transition metal catalyzed cross-coupling reactions of thiols with aryl halides to achieve aryl C−S bond formation are well-developed.[9−11] Usually, palladium or copper is employed as the catalyst in such reactions. Recently, copper-catalyzed cross-couplings of aryl halides with thiols have attracted much attention. There are several advantages over Pd-catalyzed methods, including the low cost of the catalysts and the avoidance of problems associated with the removal of palladium residues from polar reaction products, especially during the late stages of pharmaceutical compound synthesis. In addition, convenient methods for the synthesis of various heterocyclic compounds based on the copper-catalyzed C−X bond formation have been developed.[12−15] Herein, we would like to disclose our recent efforts toward the synthesis of various 2-aminobenzothiazoles via copper(I)-catalyzed tandem reactions of 2-iodoanilines with isothiocyanates. The transformation proceeded smoothly under mild conditions and the corresponding products were generated in good yield.

Result and Discussion

Our studies commenced with the reaction of 2-iodoaniline **1a** and phenyl isothiocyanate **2a**. The reaction was catalyzed by copper(I) iodide (10 mol %) in the presence of ligand and base at 50 °C. To our delight, the desired 2-aminobenzothiazole **3a** was generated with 43% yield when ligand 1,10-phenanthroline was employed in the reaction, in the presence of K_3PO_4 as a base in toluene (Table 1, entry 1). The structure of compound **3a** was also verified by X-ray crystallography (Figure 1, also see the Supporting Information). The yield increased to 63% when the base was changed to K_2CO_3 (Table 1, entry 2). Further screening of bases revealed that DABCO was the best choice for this kind of transformation (88% yield, Table 1, entry 7). Inferior results were observed when other

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Scheme 1

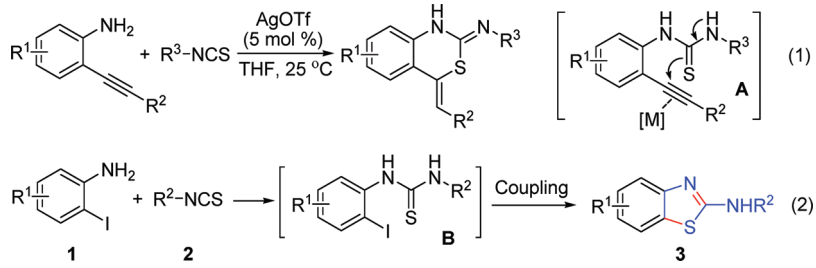
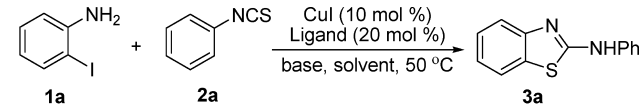


Table 1. Condition Screening for Copper-Catalyzed Tandem Reaction of 2-Iodoaniline **1a** with Phenyl Isothiocyanate **2a**[a]



entry	ligand	base	solvent	yield (%)[b]
1	1,10-phenanthroline	K_3PO_4	toluene	43
2	1,10-phenanthroline	K_2CO_3	toluene	63
3	1,10-phenanthroline	Na_2CO_3	toluene	40
4	1,10-phenanthroline	Cs_2CO_3	toluene	31
5	1,10-phenanthroline	NaOAc	toluene	51
6	1,10-phenanthroline	DBU	toluene	71
7	1,10-phenanthroline	DABCO	toluene	88
8	1,10-phenanthroline	DABCO	THF	80
9	1,10-phenanthroline	DABCO	DME	78
10	1,10-phenanthroline	DABCO	DCE	52
11	1,10-phenanthroline	DABCO	dioxane	72
12	1,10-phenanthroline	DABCO	MeCN	74
13	glycine	DABCO	toluene	51
14	proline	DABCO	toluene	54
15		DABCO	toluene	50
16[c]	1,10-phenanthroline	DABCO	toluene	57
17[d]	1,10-phenanthroline	DABCO	toluene	56

[a] Reaction conditions: 2-iodoaniline **1a** (0.3 mmol), phenyl isothiocyanate **2a** (1.2 equiv), CuI (10 mol %), ligand (20 mol %), base (2.0 equiv), solvent (3 mL), 50 °C. [b] Isolated yield based on 2-iodoaniline **1a**. [c] In the presence of CuI (5 mol %) and 1,10-phenanthroline (10 mol %). [d] CuBr was used as a replacement of CuI.

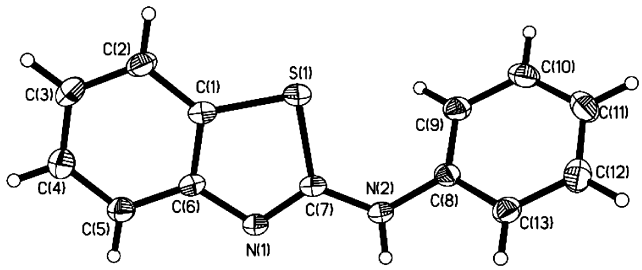
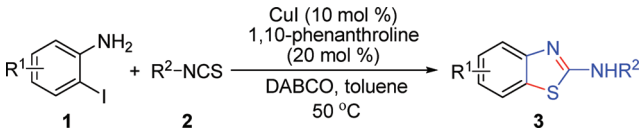


Figure 1. ORTEP crystallography of 2-aminobenzothiazole **3a** (30% probability ellipsoids).

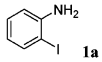
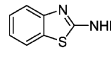
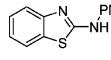
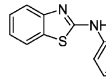
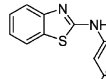
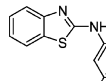
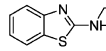
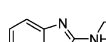
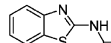
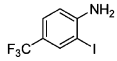
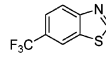
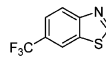
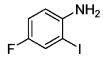
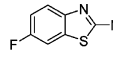
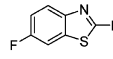
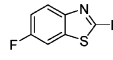
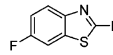
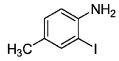
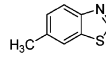
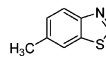
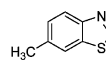
solvents were utilized (Table 1, entries 8−12). We also tested other ligands such as glycine and proline in the reaction. These ligands usually showed highly efficiency in copper-catalyzed cross-coupling reactions.[11,12] However, the yield could not be improved (Table 1, entries 13−14). Blank experiment showed that ligand 1,10-phenanthroline was necessary in the reaction in order to obtain the respectable yield (Table 1, entry 15). However, the use of a ligand could not speed up the reaction. Lower yield was observed when the amount of catalyst was decreased to 5 mol % (Table 1, entry 16). Employing CuBr as catalyst in the reaction as a replacement of CuI diminished the yield of product **3a** (Table 1, entry 17).

With this promising result in hand, the scope of this reaction was then investigated under the optimized conditions [CuI (10 mol %), 1,10-phenanthroline (20 mol %), DABCO (2.0 equiv), toluene, 50 °C], and the results are summarized in Table 2. Since many 2-iodoanilines and isothiocyanates are commercially available or synthetically accessible,[16] this design might be applicable to generate a small size library of 2-aminobenzothiazole based molecules. For most cases, the reaction proceeded smoothly to afford the corresponding product **3** in good yields. With respect to the aryl or alkyl isothiocyanates, the expected 2-aminobenzothiazoles resulting from reactions of 2-iodoaniline **1a** were obtained and isolated in moderate to good yields (Table 2, entries 1−7). We found that the conditions have proven to be useful for various isothiocyanates. As expected, both electron-rich and electron-poor aryl isothiocyanates are suitable partners in this process due to the high electrophilicity of isothiocyanate. For instance, 2-iodoaniline **1a** reacted with 4-methoxyphenyl isothiocyanate **2b** leading to the desired product **3b** in 98% yield (Table 2, entry 2), while 99% yield of product **3c** was afforded when 4-nitrophenyl isothiocyanate **2c** was employed in the reaction (Table 2, entry 3). Again, lower yields were observed without the addition of ligand 1,10-phenanthroline. Similar results were observed when 3-trifluoromethylphenyl isothiocyanate **2d** or 3,5-ditrifluoromethylphenyl isothiocyanate **2e** was employed in the reaction of 2-iodoaniline **1a** (Table 2, entries 4 and 5). Since aryl isothiocyanates with electron-withdrawing groups attached on the aromatic ring are more reactive in the nucleophilic addition step, thus the reactions involving these substrates usually finished in 2 h. Besides aryl isothiocyanates, reactions of alkyl isothiocyanates such as ethyl isothiocyanate **2f** also proceeded smoothly to give rise to the corresponding products **3f** in 67% yield (Table 2, entry 6). Moderate yield (45%) was obtained when *n*-propyl isothiocyanate **2g** was utilized as substrate in the reaction of 2-iodoaniline **1a** (Table 2, entry 7). However, the reactions required 48 h for completion due to the lower electrophilicity of alkyl isothiocyanates. In a second set of experiments, the scope of the process with respect to 2-iodobenzenamine **1** substituted with electron-rich and -poor substituents was investigated. All the expected products were generated under our standard

Table 2. Copper(I)-Catalyzed Tandem Reaction of 2-Iodobenzenamine **1** with Isothiocyanate **2**



1 2 3

Entry	2-Iodoaniline **1**	Isothiocyanate **2**	Product **3**	Yield (%)[a] / Time
1	 **1a**	 **2a**	 **3a**	88 (8 h)
2	**1a**	 **2b**	 **3b**	98 (20 h)
3	**1a**	 **2c**	 **3c**	99 (2 h)
4	**1a**	 **2d**	 **3d**	97 (2 h)
5	**1a**	 **2e**	 **3e**	91 (2 h)
6	**1a**	 **2f**	 **3f**	67 (48 h)
7	**1a**	 **2g**	 **3g**	45 (48 h)
8	**1a**	 **2h**	 **3h**	41 (48 h)
9	 **1b**	 **2a**	 **3i**	82 (30 h)
10	**1b**	 **2c**	 **3j**	99 (30 h)
11	 **1c**	 **2a**	 **3k**	51 (30 h)
12		 **2b**	 **3l**	40 (30 h)
13	**1c**	 **2c**	 **3m**	98 (20 h)
14	**1c**	 **2h**	 **3n**	60 (24 h)
15	 **1d**	 **2a**	 **3o**	93 (10 h)
16	**1d**	 **2b**	 **3p**	97 (16 h)
17	**1d**	 **2c**	 **3q**	99 (2 h)
18	**1d**	 **2f**	**3r**	83 (48 h)

[a] Isolated yield based on 2-iodoaniline **1**.

experimental conditions, whatever the nature of the substituents. For example, reaction of 2-iodo-4-trifluoromethylbenzenamine **1b** with phenyl isothiocyanate **2a** afforded the desired product **3i** in 82% yield (Table 2, entry 9). Almost quantitative yield of 2-aminobenzothiazole **3j** was generated when 4-nitrophenyl isothiocyanate **2c** was used as a replacement (Table 2, entry 10). A similar result was obtained for the reaction of 2-iodo-4-fluorobenzenamine **1c** with 4-nitrophenyl isothiocyanate **2c** (98% yield, Table 2, entry 13). When cyclohexyl isothiocyanate **2h** was used as substrate instead of aryl isothiocyanate, the reaction also occurred smoothly to generate the corresponding product **3n** in 60% yields (Table 2, entry 14). 2-Iodo-4-methylbenzenamine **1d** was also a good partner in the reactions of isothiocyanates under these conditions. For instance, excellent yield was isolated in the reaction of aryl isothiocyanate (Table 2, entries 15−17). Reaction of ethyl isothiocyanate **2f** also proceeded well, leading to the desired 2-aminobenzothiazole **3r** in 83% yield (Table 2, entry 18).

Conclusion

In conclusion, the copper(I)-catalyzed tandem reactions of 2-iodobenzenamines with isothiocyanates disclosed herein represent a simple, general, efficient, and practical synthesis of 2-aminobenzothiazoles. Depending on the different electrophilicity of isothiocyanates, the reactions usually finish in 2−48 h. The advantages of this method include high efficiency, good substrate generality, mild reaction conditions, and experimental ease.

Experimental Section

All reactions were performed in test tubes under a nitrogen atmosphere. Flash column chromatography was performed using silica gel (60-Å pore size, 32−63 μm, standard grade). Analytical thin-layer chromatography was performed using glass plates precoated with 0.25 mm 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography (TLC) plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25−35 °C. Commercial reagents and solvents were used as received.

General Procedure for Copper(I)-Catalyzed Tandem Reaction of 2-Iodoaniline 1 with Isothiocyanate 2. A solution of isothiocyanate **2** (0.33 mmol, 1.1 equiv) in toluene (1.0 mL) was added to a mixture of 2-iodoaniline **1** (0.3 mmol), DABCO (0.6 mmol, 2 equiv), CuI (0.03 mmol, 10 mol %), and 1,10-phenanthroline (0.06 mmol, 20 mol %) in toluene (1 mL) at room temperature. The mixture was then allowed to stir at 50 °C for 2−48 h. After completion of the reaction as indicated by TLC, the mixture was cooled to room temperature. The solvent was evaporated, and the residue was diluted with EtOAc (20 mL), washed with H_2O (20 mL) and brine (20 mL), and dried by anhydrous $MgSO_4$. Evaporation of the solvent followed by purification on silica gel provided the corresponding product **3**. Data of the selected example: *N*-phenyl-1,3-benzothiazol-2-amine **3a**.[17] Yield: 88%. ^{1}H

NMR (400 MHz, DMSO-d_6) δ 7.02 (t, J = 7.3 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.30−7.41 (m, 3H), 7.61 (d, J = 7.8 Hz, 1H), 7.78−7.85 (m, 3H), 10.48 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 118.3, 119.7, 121.5, 122.5, 122.8, 126.4, 129.5, 130.5, 141.2, 152.7, 162.1. (For details, please see the Supporting Information).

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Supporting Information Available. Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of compound **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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