Facile Synthesis of Benzothiazoles via Cascade Reactions of 2-Iodoanilines, Acid Chlorides and Lawesson's Reagent

Qiuping Ding,[†] Xi-Gen Huang,[§] and Jie Wu*[,†,‡]

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China, State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China, and Department of Chemistry, Jiangxi Agricultural University, Nanchang 330045, China

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In the presence of Lawesson's reagent, metal-free one-pot cascade reactions of 2-iodoanilines with acid chlorides proceeded smoothly leading to 2-substituted benzothiazoles in good to excellent yields under mild conditions. Three steps were involved in the reaction process: (1) 2-iodoanilines reacted with acid chlorides to afford benzamides, (2) benzamides transferred to benzothioamides in the presence of Lawesson's reagent, and (3) intramolecular cyclization of benzothioamides generated the expected benzothiazoles.

Introduction

As a privileged scaffold, the benzothiazole core structures can be found in many pharmaceuticals that exhibit remarkable biological activities (Figure 1).[1] For example, zopolrestat has been used in the clinic for the treatment of diabetes.[1a] 5F203 was discovered to have antitumor properties.[1d] (*R*)-CVT-3501 shows excellent activity as a fatty acid oxidation inhibitor.[1f] Moreover, benzothiazole-based compounds have been applied in other fields,[2] for example as ratiometric fluorescent pH indicators.[2a] Thus, continuous efforts have been made to develop new methods for their construction. Usually, methods for generation of the benzothiazole scaffold rely on the condensation of 2-aminothiophenols with carboxylic acids or aldehydes,[3] although the starting material 2-aminothiophenols are not easily accessible. Alternative approaches employing 2-haloanilides have been reported previously. For instance, Itoh and Mase reported an efficient synthesis of benzothiazoles via palladium-catalyzed C−S cross-coupling reactions of 2-haloanilides.[4e] Very recently, Ma and co-workers described CuI-catalyzed coupling reactions of aryl halides with metal sulfides for the synthesis of substituted benzothiazoles.[5] Although there are several routes to benzothiazoles, development of efficient methodologies for the synthesis of functionalized benzothiazoles under mild conditions is still of high interest.

It is well-recognized that the development of cascade reactions for the efficient construction of small molecules is an important pursuit in combinatorial chemistry from the viewpoints of operational simplicity and assembly efficiency.[6−8] In our continuous efforts toward accessing privileged scaffolds,[9] we became interested in exploring novel cascade reactions to facilitate the generation of benzothiazoles. We noticed that benzamide could be easily transformed to benzothioamide in the presence of Lawesson's reagent.[10] Meanwhile, the elaboration of heterocycles through copper-catalyzed coupling reactions is well-developed.[11,12] Prompted by the ease of accessing benzothioamide from benzamide and the advancement of copper-catalyzed cross-coupling reactions, we set out to investigate the cascade one-pot reaction starting from 2-haloaniline **1**. We envisioned that 2-haloaniline **1** would react with acid chloride **2** leading to the corresponding *N*-(2-iodophenyl)benzamide **A**, which would then convert to the *N*-(2-iodophenyl)-benzothioamide **B** in the presence of Lawesson's reagent. The benzothiazole **3** would be obtained subsequently via copper(I)-catalyzed intramolecular C−S coupling of *N*-(2-iodophenyl)-benzothioamide **B** (Scheme 1).

Results and Discussion

At the outset of the studies, 2-iodoaniline **1a** and benzoyl chloride **2a** in the presence of Lawesson's reagent were selected as model substrates for reaction development (Scheme 2, also see Supporting Information). The reaction was initially studied in the presence of CuI (5 mol %), 1,10-phenanthroline (10 mol %), and DABCO (2.0 equiv) in toluene. Under this condition, the formation of desired product **3a** with 65% isolated yield was observed. A control experiment indicated that the presence

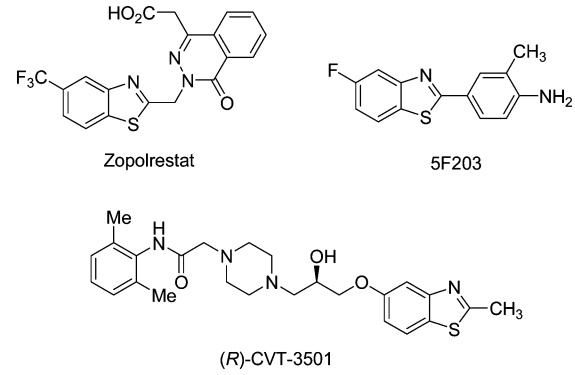

Figure 1

* To whom correspondence should be addressed. E-mail: jie_wu@fudan.edu.cn.
[†] Fudan University.
[§] Jiangxi Agricultural University.
[‡] Shanghai Institute of Organic Chemistry.

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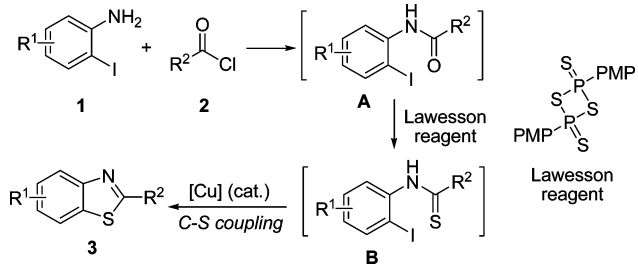
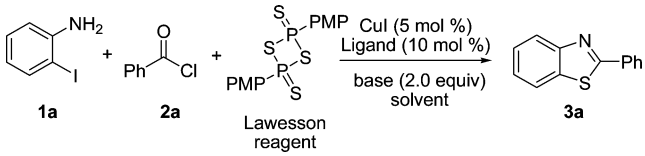
Scheme 1



Scheme 2. Condition Screening for the Cascade One-Pot Reactions of 2-Iodoanilines **1** with Acid Chlorides **2** in the Presence of Lawesson'S Reagent



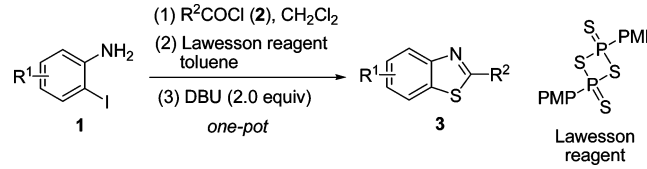
of ligand was not essential to the reaction. The yield increased to 92% when dichloromethane was added as a cosolvent. Further screening of bases revealed that DABCO or DBU was the best choice in the reaction. Similar results were obtained when the catalytic amount of CuI was reduced to 1 mol %. Furthermore, conducting the reaction in the absence of CuI produced a satisfactory yield of **3a**, which confirmed the mechanism of the ring closure was not metal mediated. It was rationalized that a S_NAr2 nucleophilic substitution might be involved in the reaction process on the basis of the following factors: (1) after deprotonation, the imine is an electron-withdrawing group, (2) the sulfur anion is a very strong nucleophile, and (3) the intramolecular ring closure to a 5-membered ring is highly favored.

With this preliminary optimized reaction condition in hand [DABCO (2.0 equiv), CH_2Cl_2/toluene], the scope of this cascade one-pot reaction was investigated, and the results are summarized in Table 1. Since many 2-iodoanilines and acid chlorides are commercially available or synthetically accessible, this reaction sequence can be employed to generate a small library of benzothiazoles. Indeed, the desired products **3** were obtained in good to excellent yield with a range of 2-iodoanilines **1** and acid chlorides **2** (Table 1). In addition to benzoyl chloride, reaction of 2-iodoaniline **2a** with furan-2-carbonyl chloride **2f** or acetyl chloride **2g** also worked well to give rise to the corresponding products in good yields (Table 1, entries 6 and 7). All reactions studied proceeded smoothly to afford the desired benzothiazoles in good yields.

Conclusion

In conclusion, we have described a simple, general, and efficient synthesis of benzothiazoles via metal-free one-pot cascade of 2-iodoanilines with acid chlorides in the presence of Lawesson's reagent. Three steps were involved in the reaction process: (1) 2-iodoanilines reacted with acid chlorides to afford benzamides, (2) benzamides transferred to benzothioamides in the presence of Lawesson's reagent, and (3) intramolecular cyclization of benzothioamides generated the expected benzothiazoles. High efficiency and good substrate generality are displayed in this transformation under mild reaction conditions. We believe that this method provides an excellent complement to existing benzothiazole synthesis methodology due to easy accessibility of starting materials and suitability to combinatorial format.

Table 1. Cascade One-Pot Reactions of 2-Iodoanilines **1** with Acid Chlorides **2** in the Presence of Lawesson's Reagent



entry	R^1	R^2	product **3**	yield (%)[a]
1	H (**1a**)	C_6H_5 (**2a**)	**3a**	87
2	H (**1a**)	4-$MeOC_6H_4$ (**2b**)	**3b**	80
3	H (**1a**)	3-MeC_6H_4 (**2c**)	**3c**	87
4	H (**1a**)	2-$MeOC_6H_4$ (**2d**)	**3d**	82
5	H (**1a**)	3,5-$(CF_3)_2C_6H_3$ (**2e**)	**3e**	75
6	H (**1a**)	2-furyl (**2f**)	**3f**	81
7	H (**1a**)	Me (**2g**)	**3g**	66
8	4-CH_3 (**1b**)	C_6H_5 (**2a**)	**3h**	93
9	4-CH_3 (**1b**)	4-$MeOC_6H_4$ (**2b**)	**3i**	83
10	4-CH_3 (**1b**)	3-MeC_6H_4 (**2c**)	**3j**	91
11	4-CH_3 (**1b**)	3,5-$(CF_3)_2C_6H_3$ (**2e**)	**3k**	90
12	4-CH_3 (**1b**)	2-furyl (**2f**)	**3l**	90
13	4-F (**1c**)	C_6H_5 (**2a**)	**3m**	92
14	4-F (**1c**)	4-$MeOC_6H_4$ (**2b**)	**3n**	95
15	4-F (**1c**)	3-MeC_6H_4 (**2c**)	**3o**	91
16	4-F (**1c**)	3,5-$(CF_3)_2C_6H_3$ (**2e**)	**3p**	75
17	4-F (**1c**)	2-furyl (**2f**)	**3q**	84
18	4-CF_3 (**1d**)	C_6H_5 (**2a**)	**3r**	87
19	4-CF_3 (**1d**)	4-$MeOC_6H_4$ (**2b**)	**3s**	93
20	4-CF_3 (**1d**)	3,5-$(CF_3)_2C_6H_3$ (**2e**)	**3t**	77

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

Experimental Section

Preparation of 2-Phenylbenzo[*d*]thiazole (3a). General Procedure for the Preparation of Benzothiazoles. A solution of 2-iodoaniline **1a** (65.7 mg, 0.3 mmol) and acid chloride **2a** (46.2 mg, 0.33 mmol) in CH_2Cl_2 (3.0 mL) was stirred at room temperature for 10 min under N_2. Subsequently, Lawesson's reagent (72.7 mg, 0.18 mmol) and toluene (3.0 mL) were added. The mixture was stirred at 100 °C for 3 h. After cooling to room temperature, DBU (151 mg, 0.6 mmol) was added and the solution was stirred for an additional 1 h at room temperature. After completion of reaction as indicated by TLC, the solvent was concentrated and then quenched with water (10 mL), extracted with EtOAc (2 × 10 mL), and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel (EtOAc/hexane, 1:5 v/v) provided 55 mg (87% yield) of the title compound **3a**[13] as an amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (dt, J = 1.2, 8.2 Hz, 1H), 7.45−7.50 (m, 4H), 7.87 (d, J = 7.8 Hz, 1H), 8.05−8.09 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.5, 123.1, 125.1, 126.2, 127.5, 128.9, 130.9, 133.5, 134.9, 154.1, 167.9.

Compounds **3b**−**3t** were prepared in the same manner.

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Supporting Information Available. Experimental procedures, characterization data, and ^{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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