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CuI-catalyzed one-pot synthesis of benzothiazolones from 2-iodoanilines-derived carbamates and sodium sulfide

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ABSTRACT

A copper-catalyzed procedure was developed for assembling benzothiazolones from ethyl 2-iodophenylcarbamates and sodium sulfide. A number of functional groups, such as methoxy, acyl, amide, carboxylate, trifluoromethyl, fluoro, and chloro, were tolerated under these conditions, providing benzothiazolones in good yields.

The skeleton of benzothiazolones has been frequently found in medicines, pesticides, and dyestuffs. For example, tiaramide (**1**) (Fig. 1) is a well-known antiinflammatory and analgesic drug;[1] SN-56 (**2**) is a highly potent and selective sigma-1 receptor ligand;[2] benazolin (**3a**) and chlobenthiazone (**3b**) are widely used in agriculture as herbicides and fungicides;[3] compound **4** has shown atypical antipsychotic property;[4] sibenadet (**5**) is a promising drug that is developed by AstraZeneca for the treatment of asthma,[5] while compound **6** has been used in combination with steroidal[3,2-C]pyrazole for the treatment of respiratory diseases.[6]

Traditionally, benzothiazolones were prepared by reacting 2-aminothiophenols with phosgene.[7] To avoid the use of toxic phosgene, several alternative reagents such as $ClCO_2Et$,[8] 1,1′-carbonyldimidazole (CDI),[9] disuccinimido carbonate (DSC),[10] and urea[11] were examined and they generally gave benzothiazolones with satisfactory yields. Additionally, $Pd(OAc)_2$-catalyzed cyclocarbonylation of 2-aminothiophenols could also be employed for this transformation.[12] However, for diverse synthesis, these approaches suffer from the limitation of commercially available substituted 2-aminothiophenols. To overcome this drawback, Hirashima and coworkers attempted to use 2-halonitrobenzenes as starting materials.[13] They found that heating a mixture of 2-halonitrobenzenes, carbon monoxide, and sulfur under high pressure could directly provide benzothiazolones. This transformation was believed to involve three consecutive reactions, namely, nucleophilic displacement, reduction, and carbonylation. Herein, we wish to report another alternative protocol for preparing benzothiazolones, in which 2-haloanilines derived carbamates are used as the starting materials.

Recently, we discovered that sodium sulfide could be used as a partner for copper-catalyzed coupling reaction with aryl halides.[14] In case of 2-haloanilides as substrates, coupling products

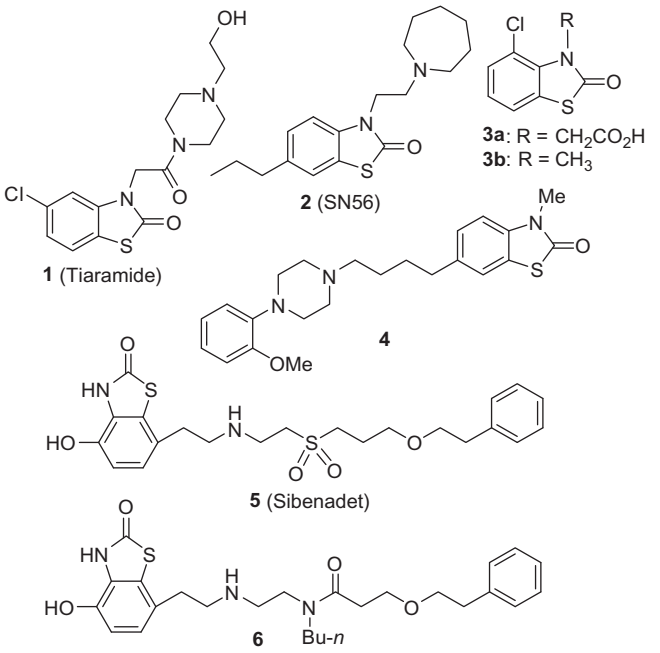

Figure 1. Structures of bioactive benzothiazolones.

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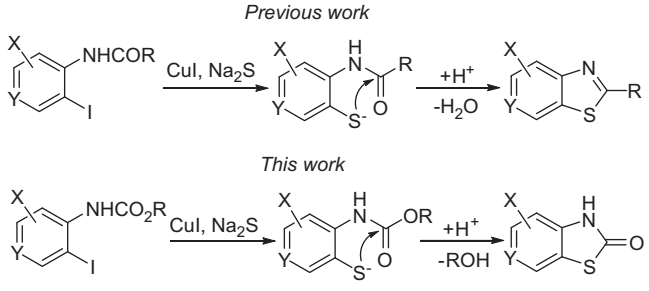
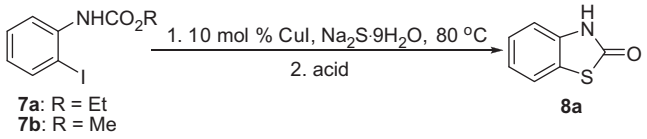


Scheme 1.

Table 1
Reaction conditions screening for the synthesis of benzothiazolone from 2-iodophenylcarbamates **7** and metal sulfide[a]



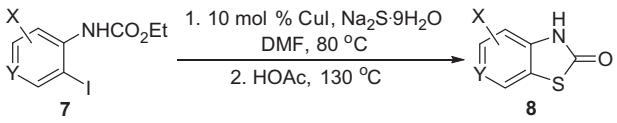
Entry	Aryl iodide	Solvent	Acid	Temp (°C)	Yield[b] (%)
1	**7a**	DMF	HCl	80	20
2	**7a**	DMF	HCl	120	73
3	**7a**	DMF	15% H_2SO_4	120	62
4	**7a**	DMF	TFA	120	62
5	**7a**	DMF	HOAc	120	80
6	**7a**	DMF	HOAc	130	89
7	**7b**	DMF	HOAc	130	19
8	**7a**	DMSO	HOAc	130	7
9	**7a**	DMA	HOAc	130	20

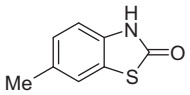
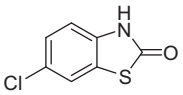
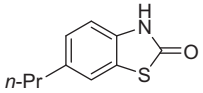
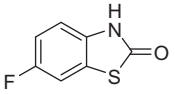
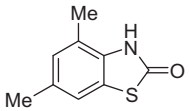
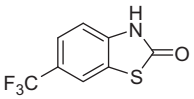
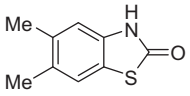
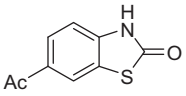
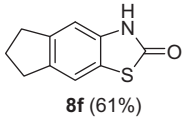
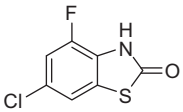
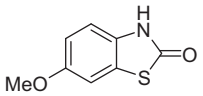
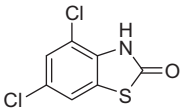
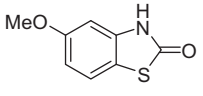
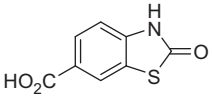
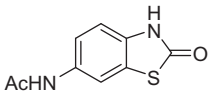
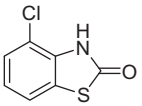
[a] Reaction conditions: Step 1: 2-iodophenylcarbamates (1 mmol), $Na_2S·9H_2O$ (3 mmol), CuI (0.1 mmol), solvent (2 mL), 80 °C, 12 h. Step 2: Acid was added and the reaction mixture was stirred at the indicated temperature.
[b] Isolated yield.

underwent intramolecular condensation to afford substituted benzothiazoles (Scheme 1). We envisioned that if 2-iodoanilines-derived carbamates were used for coupling with sodium sulfide, their products might go through another intramolecular condensation under suitable conditions, providing benzothiazolones after elimination of the alkoxy group.

With this idea in mind, we conducted a coupling reaction of ethyl 2-iodophenylcarbamate **7a** with $Na_2S·9H_2O$. It was found that in the catalysis of CuI this reaction completed at 80 °C after 12 h. Upon treatment with HCl at the same temperature, **8a** was isolated with 20% yield (Table 1, entry 1). Since the coupling reaction proceeded well, we assumed that low yield might result from poor conversion or side-reactions in the cyclization step, and therefore tried to improve this transformation. After some experimentation, we were pleased to find that increasing the reaction temperature to 120 °C could increase the yield to 73% (entry 2). At this temperature, changing the acid from HCl to 15% H_2SO_4 or TFA decreased the reaction yields (entries 3 and 4). However, a better yield was obtained when acetic acid was used (entry 5). Further attempts revealed that the best result could be observed when cyclization reaction was carried out at 130 °C (entry 6). Interestingly, under the same conditions, methyl 2-iodophenylcarbamate **7b** only gave a 19% yield (entry 7), presumably because its carbonyl group could be attacked more easily than that of **7a** in a coupling step. Additionally, solvent also played an important role for this transformation, as evidenced by that poor yields were obtained in the case of DMSO or DMA as the solvent (entries 8 and 9).

Table 2
CuI-catalyzed synthesis of benzothiazolones from 2-iodophenylcarbamates **7**[a]



Entry	Product[b] (yield)	Entry	Product[b] (yield)
1	 **8b** (72%)	9	 **8j** (70%)
2	 **8c** (69%)	10	 **8k** (65%)
3[c]	 **8d** (80%)	11	 **8l** (66%)
4	 **8e** (77%)	12	 **8m** (64%)
5	 **8f** (61%)	13	 **8n** (68%)
6	 **8g** (76%)	14	 **8o** (72%)
7	 **8h** (67%)	15	 **8p** (84%)
8	 **8i** (69%)	16	 **8q** (61%)

[a] Reaction conditions: ethyl 2-iodophenylcarbamates **7** (1 mmol), $Na_2S·9H_2O$ (3 mmol), CuI (0.1 mmol), DMF (2 mL), 8 °C, 10–16 h; then HOAc was added and the reaction was stirred at 130 °C for 36 h.
[b] Isolated yield.
[c] The product was directly isolated at the coupling reaction step.

We next investigated the scope of this one-pot procedure by varying 2-iodophenylcarbamates and the results were summarized in Table 2. To our delight, the generality of this process is satisfactory, as evident from the following characters: (1) both electron-rich and electron-deficient 2-iodophenylcarbamates proceeded smoothly under these conditions, providing the corresponding benzothiazolones in 61–84% yields (entries 1–15); (2) a number of functional groups, such as methoxy, acyl, amide, carboxylate, trifluoromethyl, fluoro, and chloro, were tolerated under our conditions; (3) besides 4,5- or 6-monosubstituted 2-iodophenylcarbamates, some 4,6- and 5,6-disubstituted 2-iodophenylcarbamates

also worked well, delivering benzothiazolones **8e**, **f**, **n**, and **o** with good yields. Benzothiazolones **8c**, **q** could be applied in the synthesis of bioactive compound SN-56,[2] benazolin **3a** and chlobenthiazone **3b**,[3] respectively. Interestingly, when ethyl 4,6-dimethyl-2-iodophenylcarbamate was employed, **8d** could be obtained directly after coupling reaction (entry 3), indicating that the substituents and their orientations could alter the cyclization process dramatically.

As a conclusion, we have developed a concise procedure for assembling substituted benzothiazolones, which relied on a copper-catalyzed coupling reaction between ethyl 2-iodophenylcarbamates and sodium sulfide.[15] By using conveniently available 2-iodoanilines as starting materials, a series of substituents could be introduced into the benzene ring of benzothiazolones at different orientations. This advantage will make the present method applicable in the synthesis of pharmaceutically important compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.006.

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