Journal of Organometallic Chemistry 859 (2018) 18–23

Contents lists available at ScienceDirect

Journal of Organometallic Chemistry

journal homepage: www.elsevier.com/locate/jorganchem

# One-pot reaction for the synthesis of *N*-substituted 2-aminobenzoxazoles using triphenylbismuth dichloride as cyclodesulfurization reagent

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ARTICLE INFO

*Article history:*
Received 4 December 2017
Received in revised form
18 January 2018
Accepted 23 January 2018

*Keywords:*
One-pot reaction
Benzoxazole
Triphenylbismuth dichloride
Thioureas
Cyclodesulfurization

ABSTRACT

The treatment of various 2-aminophenols with isothiocyanates afforded thioureas, which were reacted *in situ* with triphenylbismuth dichloride in the presence of triethylamine to give the expected *N*-substituted benzoxazol-2-amines in good to excellent yields. Triphenylbismuth dichloride promoted the successful cyclodesulfurization of thioureas with short reaction times under mild reaction conditions. This reaction is the first example of the synthesis of heterocyclic rings using a pentavalent organobismuth reagent.



## 1. Introduction

Benzoxazoles are important heterocycles, serving as key functional groups in many bioactive molecules and organic materials [1–5]. Among these, *N*-substituted benzo[*d*]oxazol-2-amines (2-aminobenzoxazoles) have attracted significant interest because of their potential as biological and pharmaceutical therapeutic agents. For instance, suvorexant **I** [6,7] has been recently approved as a therapeutic drug for insomnia, compound **II** [8] is a potent inhibitor of 5-lipoxygenase, compound **III** [9] behaves as a potent inhibitor of p90 Ribosomal S6 kinases, and compound **IV** [10] displays potent inhibitory activity against α-glucosidase (Fig. 1). Consequently, many methods have been developed for the synthesis of 2-aminobenzoxazoles. Among these methods, an efficient approach involves the treatment of 2-aminophenols with isothiocyanates to generate the corresponding thioureas, which subsequently undergo cyclodesulfurization with the assistance of diverse desulfurizing agents. Known desulfurization reagents include transition metal reagents such as NiO [11], HgO [12], $FeCl_3$ [13,14], and $CuCl_2$ [15], Brønsted acids such as $CF_3CO_2H$ [16] and TfOH [17], and other reagents such as TsCl/NaOH [18], $LiOH/H_2O_2$ [19], polymer-supported carbodiimides [20], hypervalent iodine (III) [21], and 1,1′-(ethane-1,2-diyl)dipyridinium bistribromide (EDPBT) [22]. Phakhodee et al. recently reported a rapid ultrasound-assisted synthesis of 2-aminobenzoxazoles using a $Ph_3P–I_2$ system [23]. However, these reagents have some disadvantages such as their toxicity and the long reaction times or harsh conditions required: moreover, the substrate scope and scalability for the synthesis of 2-aminobenzoxazoles are a problem that also remain unsolved.

Organobismuth compounds are generally nontoxic, environmentally benign, and useful synthetic reagents [24–28]. Among them, the utility of triarylbismuth dichlorides ($Ar_3BiCl_2$) has attracted much attention in recent years. These reagents are used as arylating agents in the *C*– and *O*–arylation of phenol derivatives [29–31], the *N*–arylation of pyridin-2-ones [32,33], and the α–arylation of α,β–unsaturated carbonyls [34] in the presence of a base. They are also used in the Pd-catalyzed C(Ar)–C(Ar, $sp^2$) bond formation reaction with hypervalent iodium salts, organostananes, and vinyl epoxides [35–37]. Furthermore, they can also be used for the oxidation of alcohols and in the phosphine-catalyzed α–arylation of enones [38,39]. However, to be the best of our

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https://doi.org/10.1016/j.jorganchem.2018.01.041
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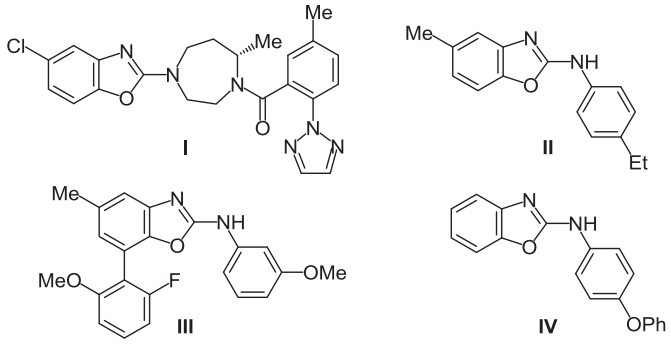


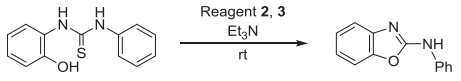

**Fig. 1.** Biologically active 2-aminobenzoxazoles.

knowledge, there are no reports of triarylbismuth dichloride-promoted ring closure reactions for the synthesis of heterocycles. Herein, we report a versatile synthesis of 2-aminobenzoxazoles *via* the triphenylbismuth dichloride-assisted cyclodesulfurization of thioureas generated from 2-aminophenols and isothiocyanates.

## 2. Results and discussions

We initially focused our attention on determining suitable experimental conditions for the cyclodesulfurization of 1-(2-hydroxyphenyl)-3-phenylthiourea **1a**. Standard reaction conditions used bismuth and antimony reagents **2** and **3** in the presence of triethylamine as base at room temperature under aerobic conditions. The screening results of active reagents and suitable solvents for the reaction are summarized in Table 1. Initially, the reaction of **1a** and bismuth reagents **2a-d** was performed in DMF at room temperature in order to compare their reactivity (entries 1–4). Pentavalent organobismuth compounds **2a**, **b** and trichlorobismuth **2d** gave the expected 2-aminobenzoxazole **4a** in excellent yield. In terms of yield and reaction time, triphenylbismuth dichloride ($Ph_3BiCl_2$) **2a** was found to be the best reagent for this cyclization, producing 90% of expected product **4a**, and side product triphenylbismuthane **2c** in 91% yield (entry 1). Triphenylbismuthane **2c** was converted back to $Ph_3BiCl_2$ **2a** by oxidative chlorination with $SO_2Cl_2$ for reuse. When antimony reagents **3a-d** were employed instead of bismuth reagents, pentavalent organoantimony compounds **3a** and **b** were found to be effective for this reaction (entries 5–8). However, the recovery of renewable triphenylstibane **3c** was low. A solvent screen showed that the reaction took place effectively in DMF, DMSO, THF, $CH_3CN$, and $CH_3OH$, among which DMF gave the highest yield of product **4a** (Table 1, entries 9–12). However, the reaction in $CH_2Cl_2$ did not produce the desired product (Table 1, entry 13). This reaction was found to be stoichiometric as decreasing the loading of $Ph_3BiCl_2$ **2a** to either 0.5 or 0.3 equivalents significantly reduced the yield of **4a**, which was obtained in accordance to the amount of $Ph_3BiCl_2$ used (entries 14, 15). When the reaction was carried out without triethylamine, the yield of **4a** remarkably decreased (entry 16). The best result was obtained when **1a** was treated with one equivalent amount of $Ph_3BiCl_2$ **2a** in DMF at room temperature in the presence of base. This cyclization could also be scaled up to 10 mmol and desired product **4a** was obtained in excellent yields of up to 75%, generating up to 1.58 g of the product.

**Table 1**
Cyclodesulfurization of thiourea **1a** using Bi and Sb reagents. [a]




| Entry | Reagent (eq) | Solvent | Time | Yield (%)[b] | |
|---|---|---|---|---|---|
| | | | | **4a** | **2c** or **3c** |
| 1 | **2a**: $Ph_3BiCl_2$ (1) | DMF | 10 min | 90 | **2c**: 91 |
| 2 | **2b**: $Ph_3Bi(OAc)_2$ (1) | DMF | 22 h | 83 | **2c**: 46 |
| 3 | **2c**: $Ph_3Bi$ (1) | DMF | 24 h | 0 | **2c**: 93 |
| 4 | **2d**: $BiCl_3$ (1) | DMF | 4 h | 84 | – |
| 5 | **3a**: $Ph_3SbCl_2$ (1) | DMF | 10 min | 85 | **3c**: 56 |
| 6 | **3b**: $Ph_3Sb(OAc)_2$ (1) | DMF | 10 min | 86 | **3c**: 84 |
| 7 | **3c**: $Ph_3Sb$ (1) | DMF | 24 h | 0 | **3c**: 95 |
| 8 | **3d**: $SbCl_3$ (1) | DMF | 24 h | 0 | – |
| 9 | **2a**: $Ph_3BiCl_2$ (1) | DMSO | 4 h | 83 | **2c**: 91 |
| 10 | **2a**: $Ph_3BiCl_2$ (1) | THF | 5 h | 79 | **2c**: 69 |
| 11 | **2a**: $Ph_3BiCl_2$ (1) | $CH_3CN$ | 5 h | 75 | **2c**: 37 |
| 12 | **2a**: $Ph_3BiCl_2$ (1) | $CH_3OH$ | 5 h | 73 | **2c**: 58 |
| 13 | **2a**: $Ph_3BiCl_2$ (1) | $CH_2Cl_2$ | 24 h | 0 | **2c**: 94 |
| 14 | **2a**: $Ph_3BiCl_2$ (0.5) | DMF | 6 h | 44 | **2c**: 89 |
| 15 | **2a**: $Ph_3BiCl_2$ (0.3) | DMF | 6 h | 27 | **2c**: 91 |
| 16[c] | **2a**: $Ph_3BiCl_2$ (1) | DMF | 24 h | 38 | **2c**: 45 |

[a] Reaction conditions: **1a** (0.5 mmol), **2** or **3** (0.15–0.5 mmol), $Et_3N$ (1.0 mmol).
[b] Isolated yield.
[c] Without $Et_3N$.

To investigate the scope of the reaction, we carried out the one-pot synthesis of 2-aminobenzoxazoles **4** from various 2-aminophenols **5** (0.5 mmol) and isothiocyanates **6** (0.5 mmol) using $Ph_3BiCl_2$ (0.5 mmol) and triethylamine. The key intermediates **1** were prepared *in situ* from **5** and **6** at room temperature by a reported method [40] and the formation of **1** was confirmed by thin layer chromatography. DMF, which gave excellent results in the cyclodesulfurization reaction, was selected as the solvent (Table 1, entry 1). The results are summarized in Table 2. The reaction of 2-aminophenol **5a** with aryl isothiocyanates **6** containing electron-donating or electron-withdrawing groups on the phenyl ring afforded the corresponding products **4b-f** in good to excellent yields. The reaction of sterically hindered *ortho*-substituted isothiocyanates with **5a** gave the corresponding oxazoles **4g** and **4h** without any difficulty. Moreover, the reaction of benzyl isothiocyanate and **5a** afforded the corresponding product **4i**. Next, we treated various 2-aminophenol derivatives **5** with phenyl isothiocyanate **6a** under the same reaction conditions. Substrates bearing either electron-donating or electron-withdrawing groups at the 4-position on the phenyl ring afforded the corresponding benzoxazoles **4j-n** in good to excellent yields. 2-Aminophenols with methyl groups at the 3-, 5-, and 6-position gave products **4o**, **4p**, and **4q**, respectively, in satisfactory yields. The reaction of 3-amino-2-naphthol with **6a** gave tricyclic compound **4r**. On the other hand, the reaction with 3-amino-2-anthracenol generated a low yield of tetracyclic compound **4s** due to the low solubility of the thiourea. This one-pot reaction could also be applied to the synthesis of 6- and 7-membered heterocyclic rings **8** and **9** (Scheme 1).

At present, the mechanism of the cyclodesulfurization reaction is unclear. We consider that the mechanism would be similar to that of the reaction using a hypervalent iodine such as diacetoxyiodobenzene proposed by Patel et al. [21]. Moreover, the reaction of aniline (0.5 mmol) with phenyl isothiocyanate (0.5 mmol) in the presence of $Ph_3BiCl_2$ (0.5 mmol) afforded *N*,*N*-diphenylcarbodiimide and triphenylbismuthane in 72% and 71% yields, respectively. A possible mechanism for the present cyclodesulfurization reaction is shown in Scheme 2. The initial step would be the generation of intermediate **A** from the reaction of thiourea **1** and $Ph_3BiCl_2$ through the attack of the sulfur atom of **1** to the thiophilic bismuth center [41,42]. The reductive elimination of **A** leads to the formation of carbodiimide **B**, triphenylbismuthane, sulfur, and triethylamine hydrochloride ($Et_3N{\cdot}HCl$) and finally **B** undergoes intramolecular cyclization to give benzoxazole **4** (path A). Another potential route