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# Mild and Efficient Synthesis of Benzoxazoles, Benzothiazoles, Benzimidazoles, and Oxazolo[4,5-*b*]pyridines Catalyzed by Bi(III) Salts Under Solvent-Free Conditions

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**Summary.** A series of benzoxazoles, benzothiazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines was efficiently synthesized from the reactions of *o*-aminophenols, *o*-aminothiophenol, *o*-phenylenediamines, and 2-amino-3-hydroxypyridine with orthoesters in the presence of catalytic amounts of Bi(III) salts, such as $Bi(TFA)_3$, $Bi(OTf)_3$, and $BiOClO_4 \cdot xH_2O$ under solvent-free conditions. The remarkable features of this new protocol are high conversion, very short reaction times, cleaner reaction profiles under solvent-free conditions, straightforward procedure, and use of relatively non-toxic catalysts.

**Keywords.** Benzoxazoles; Benzothiazoles; Benzimidazoles; Oxazolo[4,5-*b*]pyridines; Bi(III) salts.

## Introduction

Benzoxazole, benzothiazole, benzimidazole, and oxazolo[4,5-*b*]pyridine moieties have attracted a great deal of interest in diverse fields of chemistry [1]. Some of these nuclei are found in various naturally occurring compounds [2]. These heterocycles have achieved significance in pharmacology as antibacterial [3], antiviral [4], antifungal [5], anticancer [6], antibiotic [7], anticonsulvant [8], and immunosuppressant [9] agents. They have also been used as ligands in asymmetric syntheses [10].

Several methods have been developed for the preparation of these heterocycles including the condensation of carboxylic acids [11], acid chlorides [12], nitriles [13], orthoesters [14], amides [15], esters [16], and aldehydes [17] with *o*-aminophenols, *o*-aminothiophenols, and *o*-phenylenediamines, dehydration of *o*-acylaminophenols [18], the reaction of *o*-quinones with amines [19], *Beckmann* rearrangement of *o*-acylphenol oximes [20], and photocyclization of phenolic *Schiff* bases [21]. However, all of these procedures suffer from one or more of the following disadvantages such as long reaction times, low yields of the products, harsh reaction conditions, the use of excess amounts of reagents, tedious workup procedures, and co-occurrence of several side reactions. In addition, some of the catalysts and reagents are expensive, toxic, and air sensitive. Therefore, there is still a need to search for better catalysts that could be superior to the existing ones with regards to toxicity, handling, and operational simplicity.

## Results and Discussion

Recently there has been growing interest in the use of Bi(III) salts as catalysts in various organic reactions due to their low toxicity, ease of handling, and relative insensitivity to air and moisture [22]. Bismuth has been heralded as a green element, and the low toxicity of many bismuth compounds is evident from their $LD_{50}$ (rat, oral $LD_{50} = 2–22\,g/kg$ [23]). In continuation of our research on the use of Bi(III)

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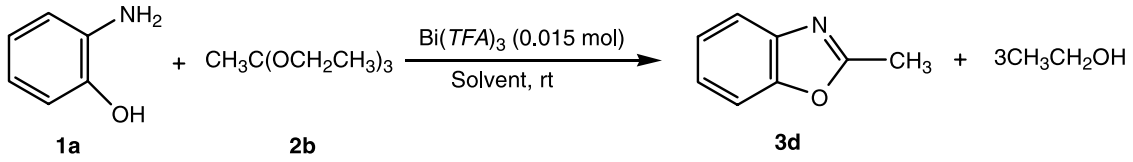



1a 2b 3d

**Scheme 1**

salts in organic transformations [24], we now report a simple and environmentally benign methodology for the synthesis of benzoxazole, benzothiazole, benzimidazole, and oxazolo[4,5-*b*]pyridine derivatives from orthoesters under solvent-free conditions using Bi(III) salts as catalysts.

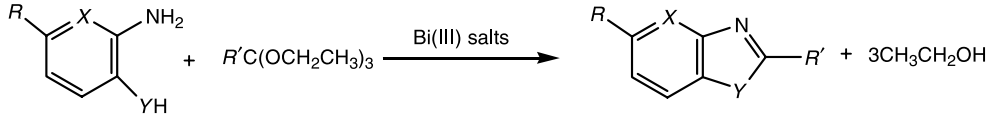
At first, the solvent effect was examined by the reaction of 1 equiv. *o*-aminophenol (**1a**) with 1.1 equiv. triethyl orthoacetate (**2b**) in the presence of 0.015 equiv. Bi(*TFA*)$_3$ (Scheme 1) in different solvents, such as $ClCH_2CH_2Cl$, $CHCl_3$, $CH_3OH$, $CH_3CN$, and also under solvent-free conditions at room temperature (Table 1). The best result was obtained under solvent-free conditions, which is also economically and environmentally favourable (Table 1, entry 5). On the other hand, further examination illustrated that Bi(*TFA*)$_3$ is essential for this transformation whereas in the absence of the catalyst, only 5% of the product was obtained from the reaction mixture (Table 1, entry 6).

**Table 1.** Investigation of solvent and catalyst effects on the synthesis of 2-methylbenzoxazole (**3d**)

| Entry | Catalyst | Solvent | Time/min | Yield/% |
|---|---|---|---|---|
| 1 | Bi(*TFA*)$_3$ | $ClCH_2CH_2Cl$ | 15 | 83 |
| 2 | Bi(*TFA*)$_3$ | $CHCl_3$ | 10 | 87 |
| 3 | Bi(*TFA*)$_3$ | $CH_3OH$ | 20 | 50 |
| 4 | Bi(*TFA*)$_3$ | $CH_3CN$ | 10 | 85 |
| 5 | Bi(*TFA*)$_3$ | – | 2 | 96 |
| 6 | – | – | 20 | 5 |

The applicability of this method was then examined for the preparation of benzoxazole, benzothiazole, benzimidazole, and oxazolo[4,5-*b*]pyridine derivatives from various orthoesters under solvent-free conditions. To this aim, different orthoesters were reacted with 2-substituted anilines and 2-amino-3-hydroxypyridine in the presence of catalytic amounts of Bi(*TFA*)$_3$, Bi(O*Tf*)$_3$, or $BiOClO_4 \cdot xH_2O$ (Scheme 2) and the corresponding products were obtained in high to excellent yields (Table 2).

The results showed that 2-substituted benzoxazoles were efficiently and rapidly formed under mild reaction conditions at room temperature in the presence of the above mentioned catalysts in excellent yields (Table 2, entries 1–6), whereas synthesis of benzoxazoles unsubstituted at 2-position needs heating at 85°C (Table 2, entries 7–9). 2-Aminothiophe-




| | X | Y | R | | R′ |
|---|---|---|---|---|---|
| **1a** | C | O | H | **2a** | $CH_3CH_2$ |
| **1b** | C | O | Cl | **2b** | $CH_3$ |
| **1c** | C | O | $CH_3$ | **2c** | H |
| **1d** | C | S | H | | |
| **1e** | C | NH | H | | |
| **1f** | C | NH | $CH_3$ | | |
| **1g** | N | O | H | | |

| | X | Y | R | R′ |
|---|---|---|---|---|
| **3a** | C | O | H | $CH_3CH_2$ |
| **3b** | C | O | Cl | $CH_3CH_2$ |
| **3c** | C | O | $CH_3$ | $CH_3CH_2$ |
| **3d** | C | O | H | $CH_3$ |
| **3e** | C | O | Cl | $CH_3$ |
| **3f** | C | O | $CH_3$ | $CH_3$ |
| **3g** | C | O | H | H |
| **3h** | C | O | Cl | H |
| **3i** | C | O | $CH_3$ | H |
| **3j** | C | S | H | $CH_3CH_2$ |
| **3k** | C | S | H | $CH_3$ |

| | X | Y | R | R′ |
|---|---|---|---|---|
| **3l** | C | S | H | H |
| **3m** | C | NH | H | $CH_3CH_2$ |
| **3n** | C | NH | $CH_3$ | $CH_3CH_2$ |
| **3o** | C | NH | H | $CH_3$ |
| **3p** | C | NH | $CH_3$ | $CH_3$ |
| **3q** | C | NH | H | H |
| **3r** | C | NH | $CH_3$ | H |
| **3s** | N | O | H | $CH_3CH_2$ |
| **3t** | N | O | H | $CH_3$ |
| **3u** | N | O | H | H |

**Scheme 2**

**Table 2.** Synthesis of benzoxazoles, benzothiazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines catalyzed by Bi(III) salts under solvent-free conditions

| Entry | 1 | 2 | 3 | Catalyst (eq.) | Time/min (Yield/%[a,b]) | | | M.P. °C | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | $Bi(TFA)_3$ | $Bi(OTf)_3$ | $BiOClO_4 \cdot xH_2O$ | | |
| 1 | **1a** | **2a** | **3a** | 0.01 | 4 (97) | 5 (93) | 10 (92) | Oil | [14c] |
| 2 | **1b** | **2a** | **3b** | 0.005 | 0.5 (98) | 1 (95) | 2 (95) | 59–61 | [20] |
| 3 | **1c** | **2a** | **3c** | 0.01 | 2.5 (95) | 4 (93) | 10 (90) | 29–31 | [20] |
| 4 | **1a** | **2b** | **3d** | 0.015 | 2 (96) | 3 (93) | 10 (85) | Oil | [14c] |
| 5 | **1b** | **2b** | **3e** | 0.01 | 0.5 (95) | 1 (90) | 5 (90) | 53–55 | [20] |
| 6 | **1c** | **2b** | **3f** | 0.02 | 5 (95) | 10 (90) | 15 (85) | Oil | [20] |
| 7[c] | **1a** | **2c** | **3g** | 0.005 | 12 (88) | 10 (93) | 10 (90) | Oil | [14c] |
| 8[c] | **1b** | **2c** | **3h** | 0.005 | 8 (88) | 7 (92) | 8 (90) | 36–38 | [25a] |
| 9[c] | **1c** | **2c** | **3i** | 0.005 | 15 (87) | 10 (90) | 15 (88) | 42–44 | [25b] |
| 10 | **1d** | **2a** | **3j** | 0.01 | 2 (86) | 4 (81) | 4 (80) | Oil | [14c] |
| 11 | **1d** | **2b** | **3k** | 0.01 | 3 (81) | 5 (80) | 5 (80) | Oil | [14a] |
| 12 | **1d** | **2c** | **3l** | 0.01 | 5 (83) | 5 (81) | 7 (83) | Oil | [14a] |
| 13[c] | **1e** | **2a** | **3m** | 0.03 | 11 (87) | 9 (93) | 8 (88) | 163–165 | [25c] |
| 14[c] | **1f** | **2a** | **3n** | 0.04 | 5 (84) | 6 (91) | 5 (88) | 160–163 | [25d] |
| 15[c] | **1e** | **2b** | **3o** | 0.03 | 5 (82) | 4 (90) | 4 (82) | 172–174 | [25e] |
| 16[c] | **1f** | **2b** | **3p** | 0.04 | 5 (90) | 4 (85) | 4 (85) | 198–200 | [25d] |
| 17[c] | **1e** | **2c** | **3q** | 0.015 | 9 (92) | 7 (85) | 6 (80) | 170–172 | [14a] |
| 18[c] | **1f** | **2c** | **3r** | 0.04 | 8 (85) | 8 (83) | 10 (80) | 112–114 | [25f] |
| 19[c] | **1g** | **2a** | **3s** | 0.01 | 10 (83) | 6 (85) | 8 (83) | 51–53 | [14b] |
| 20[c] | **1g** | **2b** | **3t** | 0.01 | 12 (82) | 8 (85) | 10 (83) | 70–72 | [25g] |
| 21[c] | **1g** | **2c** | **3u** | 0.03 | 12 (52) | 10 (55) | 12 (53) | 69–72 | [14b] |

[a] Products were identified by comparison of their physical and spectral data with those of authentic samples. [b] Isolated yields. [c] The reaction was performed at 85°C

nol was also rapidly reacted with orthoesters at room temperature to afford the corresponding benzothiazoles in high yields (Table 2, entries 10–12). The reactions of *o*-phenylenediamines with orthoesters were also investigated. We found that *o*-phenylenediamines reacted rapidly with orthoesters in the presence of Bi(III) salts at 85°C and the corresponding benzimidazoles were isolated in high yields (Table 2, entries 13–18). 2-Amino-3-hydroxypyridine was also reacted with orthoesters at 85°C and the corresponding oxazolo[4,5-*b*]pyridines were isolated in good to high yields (Table 2, entries 19–21).

In conclusion, a very simple and convenient protocol for the synthesis of 2-substituted benzoxazoles, benzothiazoles, benzimidazoles, and oxazolo[4,5-*b*]pyridines using catalytic amounts of Bi(III) salts under solvent-free conditions was demonstrated. Furthermore, availability, stability, and non-toxicity of the catalysts are other noteworthy advantages which make this method eco-friendly and environmentally benign. In addition, mild reaction conditions, absence of solvent, very short reaction times, high yields of the products, and easy workup make this methodology a valid contribution to the existing processes in the field of these heterocycle syntheses.

## Experimental

Chemicals were purchased from Merck or Aldrich chemical companies. Melting points were determined using a Stuart scientific apparatus, the accuracy of which was checked using standard compounds of known melting points. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer. $^1H$ NMR spectra were recorded in $CDCl_3$ solvent on a Bruker 500 MHz.

*General Procedure for the Synthesis of Benzoxazoles, Benzothiazoles, Benzimidazoles and Oxazolo[4,5-b]-pyridines Under Solvent-Free Conditions*

To a mixture of orthoester (1.1 mmol) and *o*-aminophenol, *o*-aminothiophenol, *o*-phenylenediamine, or 2-amino-3-hydroxypyridine (1 mmol) was added the catalyst (0.005–0.04 mmol $Bi(TFA)_3$, $Bi(OTf)_3$, or $BiOClO_4 \cdot xH_2O$). The mixture was stirred at room temperature or at 85°C for the appropriate time according to Table 2. The progress of the reaction was monitored by TLC (*n*-hexane:*EtOAc*, 2:1). After completion of the reaction, the crude product was purified by col-

umn chromatography or recrystallization to afford the pure product (Table 2).

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