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Bismuth (III) Triflate Catalyzed Multicomponent Synthesis of 2,4,5-Trisubstituted Imidazoles

Sophie C. Thorp, Sebastian T. Chisari, Rem Quintin V. David, Abby Gjata, Abby L. Good, Erick Lopez, Ram S. Mohan*

Laboratory for Environmentally Friendly Organic Synthesis, Department of Chemistry & Biochemistry, Illinois Wesleyan University, Bloomington, IL, USA
Email: *rmohan@iwu.edu

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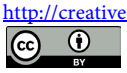


Abstract

Substituted imidazoles are of interest because of their useful biological activities. While several methods have been developed for the synthesis of such compounds, some of the reported methods utilize corrosive or toxic catalysts. We report a bismuth (III) triflate catalyzed multicomponent synthesis of 2,4,5-trisubstituted imidazoles. Bismuth (III) compounds are attractive from a green chemistry perspective because they are remarkably non-toxic and non-corrosive. Multicomponent syntheses save time and generate less waste.

Keywords

Imidazoles, Heterocycles, Bismuth Compounds, Green Chemistry, Multicomponent Reactions

1. Introduction

Heterocyclic compounds are of particular interest in medicinal chemistry due to the range of biological properties they exhibit [1] [2]. Among the various heterocycles, the imidazole ring has attracted a lot of attention due to the wide range of biological activities exhibited by substituted imidazoles [3] [4]. The imidazole ring is found in many common drugs such as eprosartan **1** (hypertension) [5], ketoconazole **2** (antimycotic) [6], losartan **3** (hypertension) [7], and olmesartan **4** (hypertension) (**Figure 1**) [8].

2,4,5-trisubstituted imidazoles exhibit many biological activities and hence have attracted attention. 2-substituted-4,5-diphenylimidazoles have been shown to exhibit antinociceptive and anti-inflammatory properties [9]. Owing to their useful biological properties, several methods have been developed for the syn-

thesis of 2,4,5-trisubstituted imidazoles. The first synthesis, which remains one of the most viable routes, involved a multicomponent reaction between an aldehyde **5**, benzil **6** and ammonium acetate **7** to generate a 2,4,5-trisubstituted imidazole **8** (Scheme 1) [10].

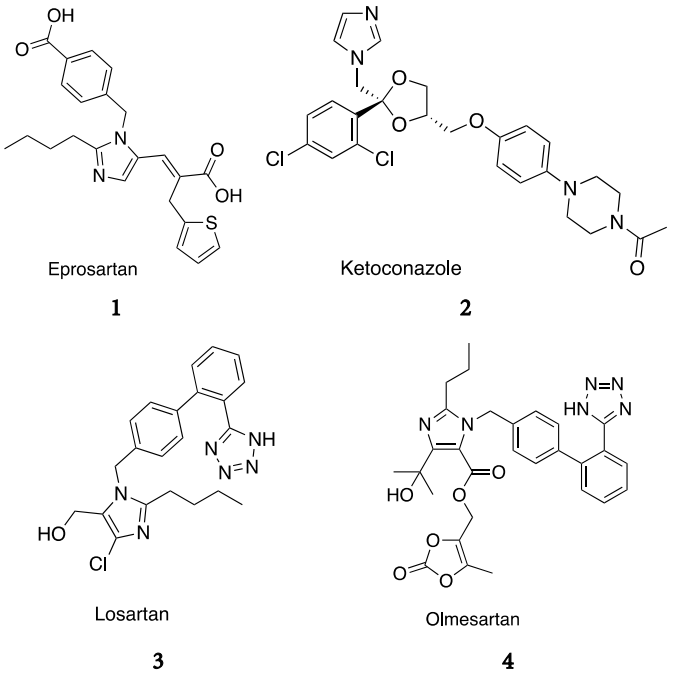
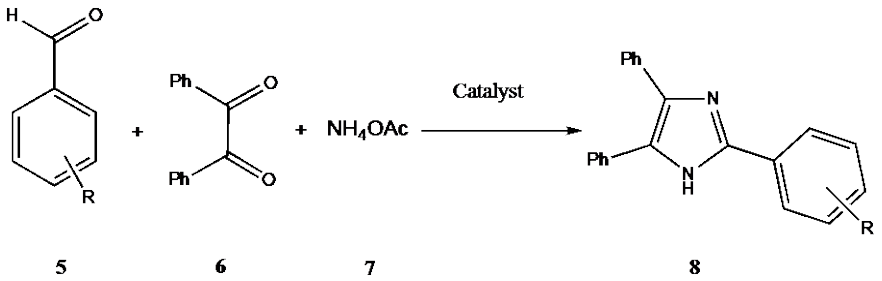


Figure 1. Some drugs containing the imidazole nucleus.

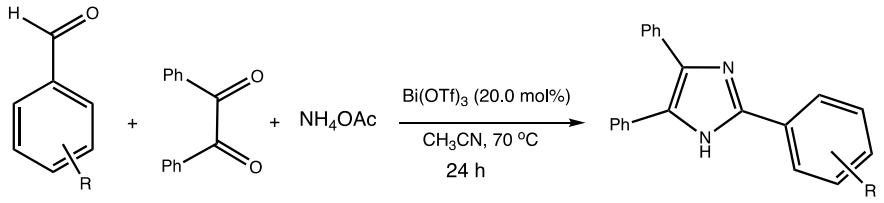


Scheme 1. Multicomponent synthesis of 2,4,5-trisubstituted imidazoles.

Since the early method suffered from harsh reaction conditions, considerable efforts have been directed towards improving the reaction to provide high yields under milder conditions. Methods for the synthesis of polysubstituted imidazoles have been reviewed [11] [12]. Several catalysts have been used for the synthesis of 2,4,5-trisubstituted imidazoles. A few representative examples are cited here and include $Yb(OTf)_3$ [13], silica sulfuric acid [14], $NiCl_2{\cdot}6H_2O$ [15], microwave irradiation [16], sodium bisulfite [17], tetrabutylammonium bromide [18], MoO_3/SiO_2 [19], lipase [20], mesoporous silica [21], silica coated magnetite nanoparticles [22], benzethonium chloride [23], lactic acid [24], magnetic nanoparticles [25], CH_3SO_3H [26], and mandelic acid [27]. While some of these catalysts are corrosive, a few others require preparation which detracts from their

synthetic utility. In view of our continued interest in bismuth (III) salts, we investigated their use as catalysts for the synthesis of 2,4,5-trisubstituted imidazoles. Herein, we report a multicomponent synthesis of 2,4,5-trisubstituted imidazoles catalyzed by bismuth triflate, $Bi(OTf)_3 \cdot xH_2O$ ($1 < x < 4$) (**Table 1**). Bismuth compounds are of interest because they are remarkably nontoxic and readily available [28]. Several reviews have summarized the applications of bismuth compounds in organic synthesis [29] [30] [31] [32]. The results of this study are summarized in **Table 1**.

Table 1. Bismuth(III) triflate catalyzed multicomponent synthesis of 2,4,5-trisubstituted imidazoles.[a]



entry	aldehyde	yield (%)[b,c,d]
1	PhCHO	82 [22]
2	*p*-OHC_6H_4CHO	70 [22][e]
3	*p*-$CH_3C_6H_4CHO$	87 [22]
4	*p*-$CH_3OC_6H_4CHO$	72 [22]
5	*p*-BrC_6H_4CHO	81 [13]
6	*p*-ClC_6H_4CHO	91 [22]
7	*p*-FC_6H_4CHO	67 [16]
8	2,4-$Cl_2C_6H_3CHO$	88 [22]
9	*m*-ClC_6H_4CHO	80 [18]
10	*m*-$CH_3OC_6H_4CHO$	87 [22]
11	*m*-$CH_3C_6H_4CHO$	81 [22]
12	*p*-$NO_2C_6H_4CHO$	64 [13][f]

[a]*Representative procedure* (entry 4): A mixture of *p*-anisaldehyde (0.208 g, 1.528 mmol, 1.1 equiv), benzil (0.292 g, 1.389 mmol, 1.0 equiv), and ammonium acetate (0.428 g, 5.552 mmol, 4.0 equiv) in CH_3CN (4.0 mL) was stirred as $Bi(OTf)_3$ (0.182 g, 0.277 mmol, 20.0 mol%) was added. The reaction mixture was heated at 70˚C using a temperature controlled hot plate. Reaction progress was followed by TLC (CH_3OH/CH_2Cl_2, 3/97, v/v). After 24 h (disappearance of aldehyde), the mixture was concentrated on a rotary evaporator. Hot methanol (5.0 mL) was added to the residue and the mixture was stirred and cooled in ice. The resulting crystals were collected by suction filtration to yield 0.324 g (72%) of a white solid that was analyzed by ^1H, ^{13}C NMR spectroscopy and TLC. [b]Refers to yield of isolated product that was deemed to be at least 98% pure by ^1H NMR spectroscopy. All products were characterized by ^1H and ^{13}C NMR spectroscopy, TLC and by comparison to literature data. [c]All products have been previously reported. Spectral data were compared to those reported in the literature. [d]Superscript against yield refers to literature reference for spectral data of product. [e]Workup was modified as follows: The reaction mixture was concentrated by rotary evaporation and the residue was loaded onto 30 g of silica gel. Product was isolated by elution with CH_2Cl_2/CH_3OH (10/90, v/v). [f]Reaction was run for 45 h using 40.0 mol% catalyst.

We investigated the utility of a few different Lewis acids as catalysts for the multicomponent synthesis of 2,4,5-trisubstituted imidazoles. These included $BiO(NO_3)$, $BiBr_3$, $Bi(OTf)_3$, $FeCl_3$, $Fe(OTf)_3$ in several solvents: CH_3OH, CH_3CH_2OH, CH_3COOH and CH_3CN. We also investigated the use of $Fe(OTs)_3$ as a catalyst for this reaction [33]. The best results were obtained with bismuth(III) triflate, $Bi(OTf)_3$, as a catalyst, in CH_3CN as the solvent. With all other catalysts significant amounts of starting material remained even after 24 h at 70˚C. Similar results were obtained in the absence of a catalyst. The multicomponent nature of this reaction allowed for the facile synthesis of the product in good to moderate yields in a single step that also eliminated the generation of an aqueous waste stream [34]. As can be seen from **Table 1**, good to moderate yields were obtained with a variety of aldehydes.

2. Conclusion

We have developed a bismuth (III) triflate catalyzed multicomponent synthesis of 2,4,5-trisubstituted imidazoles from a variety of substituted aldehydes, benzil, and ammonium acetate in CH_3CN as the solvent. The nontoxic nature of bismuth compounds, along with the multicomponent nature of this method, makes this an attractive route for the synthesis of 2,4,5-trisubstituted imidazoles.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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