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Original article

Facile one-pot clean synthesis of benzimidazole motifs: Exploration on bismuth nitrate accelerated subtle catalysis

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ABSTRACT

In the present letter, an efficient, clean and one-pot synthesis of 2-substituted benzimidazole and 1,2-disubstituted benzimidazole derivatives has been explored by reacting *o*-phenylenediamine with aromatic aldehydes using bismuth nitrate as a catalyst in ethanol at ambient temperature. This methodology avails with faster reactions, excellent yield, mild reaction conditions, use of inexpensive and non-toxic catalyst compared to literature reported hitherto.

1. Introduction

At the beginning of this century, green chemistry has attracted a considerable importance in the development of environmentally benign routes to numerous materials. Green chemistry mainly emphasizes towards the pollution prevention through eco-friendly design of chemical products and processes [1]. The development of greener methodologies for syntheses of heterocyclic compounds is still a stimulating task in the field of organic synthesis. Among the heterocycles, benzimidazole derivatives are the important class of nitrogen containing heterocycles with a wide range of medicinal properties such as serotoninergic 5-HT3 and 5-HT4 receptors in the CNS [2], antihistamine [3], anticancer [4,5], antibacterial [6], antifungal [7], anti-inflammatory, antianalgesic [8], antioxidant [9], antidiabetic [10], selective neuropeptide YY1 receptor antagonists [11], antimalerial, antitubercular [12], antiulcer [13], *etc.* where moiety plays the role of 'Master Key' [14]. Therefore, it is an imperative anchor for development of new therapeutic drugs, as illustrated and supported by some commercial benzimidazole products in Fig. 1.

Generally, the synthesis of benzimidazole involves the reaction of *o*-phenylenediamine either with carboxylic acids, carboxaldehydes or their derivatives (chlorides, nitriles, and orthoesters) under strongly acidic conditions with high temperature [15], Furthermore, Cascade reactions of *o*-haloaniline with amidine hydrochlorides [16] and intramolecular palladium-catalyzed aryl amination are alternative ways for synthesis of benzimidazole [17,18]. A variety of catalysts are reported in the benzimidazole synthesis, such as $FeCl_3$-doped polyaniline nanoparticles [19], solvent free $SiO_2/ZnCl_2$ [20], cobalt (II) chloride hexahydrate [21], $[Sm(OTf)_3]$ [22], $[In(OTf)_3]$ [23], sodium metabisulfite [24], silphox$[POCl_{3-n}\ (SiO_2)_n]$ [25], potassium persulfate-$CuSO_4$ [26], indion 190 resin [27], ammonium acetate [28], thiamine hydrochloride [29], SDS micelles, DBSA, $Fe_3O_4@SiO_2@(NH_4)_6–Mo_7O_{24}$ magnetic core-shell nanocomposite, boron trifluoride etherate ($BF_3.OEt_2$), Cu-nanoparticles/SiO_2, LiBr [30], *etc.*

At present, bismuth (III) compounds have recently attracted much attention in organic transformations due to their high acidity, thermal stability, low toxicity, low cost, and good stability [31]. Furthermore, bismuth nitrate is reported as an eco-friendly nitrating agent for selective nitration of organic compounds [32,33]. Current literature reveals that bismuth nitrate has been utilized as an effective catalyst in the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones [34], guanidylation of *N*-benzoylthioureas [35], synthesis of coumarins [36], Paal–Knorr synthesis of pyrroles [37], chemoselective synthesis of acylals [38], *etc.*

Nevertheless, most of the aforesaid methods of benzimidazole synthesis have disadvantages like, use of expensive reagents and catalysts, harsh reaction conditions and long reaction time, *etc.* Moreover, several of these reactions have been reported at higher

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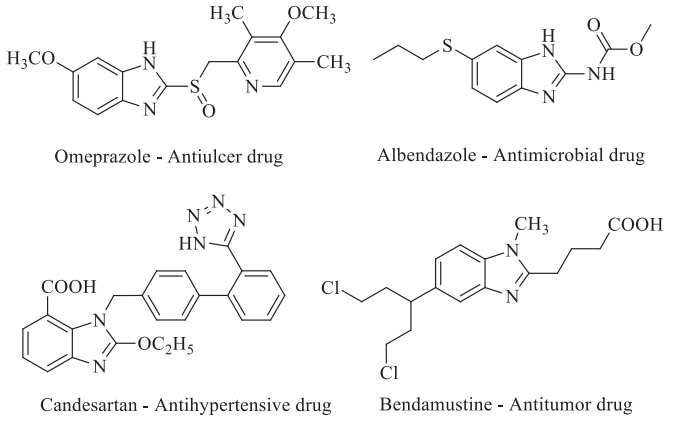


Fig. 1. Benzimidazole containing important commercial drugs.

temperatures which are not accepted as environmentally friendly. Therefore, the search continues for a better catalyst to synthesize benzimidazoles in term of operational simplicity. To address this problem, in our present research investigation, we wish to report bismuth nitrate as an efficient catalyst for synthesis of 2-substituted benzimidazoles and 1,2-disubstituted benzimidazoles. Very interestingly, herein, we revealed that a change of substituent, specifically a replacement of C_3 or C_4 hydrogen by either hydroxyl or methoxy group on the aldehyde unit, dramatically influences the course of the reaction.

2. Experimental

2.1. Chemicals and instruments

All chemicals and materials are procured from S. D. Fine Chemicals Ltd. and Spectrochem Chemicals Pvt. Ltd. and used without further purification. Melting points were determined with open capillary method and are uncorrected. IR spectra were recorded in KBr on Shimadzu IR Affinity-1 FT-IR spectrophotometer and ^{1}H NMR spectra were recorded on a Bruker Avance II 300 and 400 MHz NMR spectrophotometer in $CDCl_3$/DMSO using TMS as internal standard. Mass spectra were recorded on Waters, Q-Tof Micromass (LCMS) spectrometer and Varian Inc. 410 Prostar Binary LC with 500 Mass Spectrophotometer.

2.2. General procedure for the synthesis of 2-substituted benzimidazoles and 1, 2- disubstituted benzimidazoles

A mixture of *o*-phenylenediamine (1 mmol), ethanol (5 mL), and bismuth nitrate (10 mol%) was taken in a round-bottom flask. To this mixture, a solution of aldehyde 1.1 mmol for the synthesis of 2-substituted benzimidazoles and 2.1 mmol for the synthesis of 1,2 disubstituted benzimidazole in ethanol (5 mL) was added dropwise with stirring and stirring was continued until the completion of reaction at room temperature. After completion of the reaction (monitored by TLC, hexane: ethyl acetate), the reaction mixture was poured into crushed ice to give solid product, which was filtered, washed with water and dried. The crude product was recrystallized from ethanol to afford pure 2-substituted benzimidazoles or 1,2-disubstituted benzimidazoles in good to better yields. Spectroscopic data for all the synthesized compounds are depicted in supplementary data, which is in harmony with the structures.

Table 1
Effect of catalyst on synthesis of 2-(4-nitrophenyl) benzimidazole.[a]

Entry	Catalyst	Temp (°C)	Time (h)	Yield (%)[b]
1	None	r.t.	8	45
2	None	78–80	7	60
3	L-Proline	r.t.	8	52
4	$Bi(NO_3)_3{\cdot}5H_2O$	r.t.	1	96
5	$Bi(NO_3)_3{\cdot}5H_2O$[c]	r.t.	1	84
6	$Bi(NO_3)_3{\cdot}5H_2O$[d]	r.t.	1	91
7	$Bi(NO_3)_3{\cdot}5H_2O$[e]	r.t.	1	94
8	$ZrO(NO_3){\cdot}H_2O$	78–80	4	61
9	1,10-Phenanthroline	r.t.	4	56
10	1,10-Phenanthroline	78–80	5	70
11	$Cd(NO_3){\cdot}5H_2O$	r.t.	4	67
12	$Cd(NO_3){\cdot}5H_2O$	78–80	4	74
13	$Ba(NO_3)_2$	r.t.	5	65
14	$CsNO_3$	r.t.	8	58
15	$Pb(NO_3)_2$	r.t.	8	71
16	$Ca(NO_3)_2{\cdot}4H_2O$	r.t.	8	58

[a] Reaction condition: *o*-Phenylenediamine (1 mmol), 4-nitrobenzaldehyde (1.1 mmol), catalyst (10 mol%) and ethanol 10 mL.
[b] Isolated yield.
[c] Catalyst loading: 5 mol%.
[d] Catalyst loading: 15 mol%.
[e] Catalyst loading: 20 mol%.

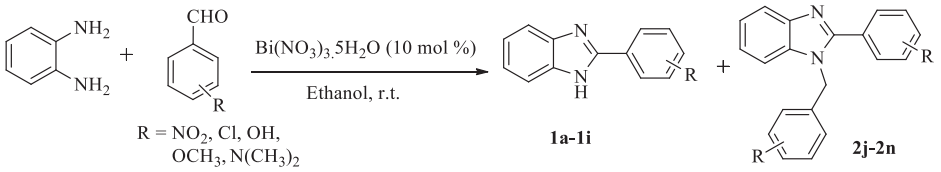
Table 2
Effect of solvent on synthesis of 2-(4-nitrophenyl)benzimidazole.[a]

Entry	Solvent	Temp	Time (h)	Yield (%)[b]
1	Solvent free	r.t.	1	49
2	THF	r.t.	4	21
3	Acetonitrile	r.t.	2	63
4	DMF	r.t.	2	65
5	Ethanol	r.t.	1	96
6	Methanol	r.t.	1	76
7	Dichloromethane	r.t.	5	58
8	Glycerol	r.t.	3	76
9	Glycerol	90 °C	4	78
10	Toluene	r.t.	6	40
11	PEG-400	r.t.	7	81
12	PEG-400	90 °C	3	82

[a] Reaction condition: *o*-Phenylenediamine (1 mmol), 4-nitrobenzaldehyde (1.1 mmol), and bismuth nitrate (10 mol %) as catalyst.
[b] Isolated yield.

3. Results and discussion

In this study, we examined the synthesis of 2-substituted benzimidazoles by the reaction of *o*-phenylenediamine with 4-nitrobenzaldehyde using bismuth nitrate as catalyst in ethanol at room temperature. The reaction was completed within 60 min to give the 2-(4-nitrophenyl)-1*H*-benzimidazole as a product with quantitative yield (Scheme 1). Encouraged by this result, we studied different parameters of reaction and the obtained results



Scheme 1. Bismuth nitrate mediated synthesis of 2-substituted benzimidazole derivatives.