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Graphical Abstract

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

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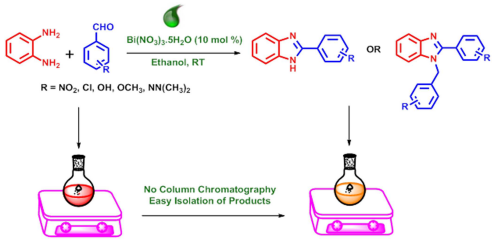

The present letter, one pot clean synthesis of 2-substituted benzimidazole and 1,2-disubstituted benzimidazole derivatives have been explored using bismuth nitrate as an efficient catalyst.

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 have 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.

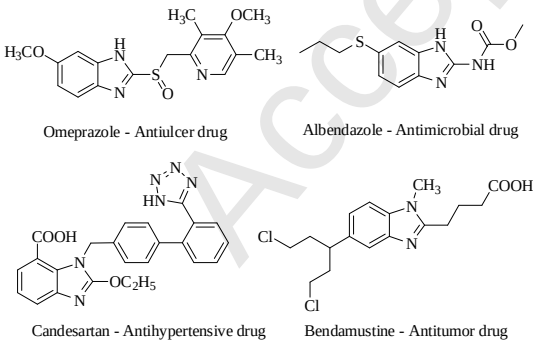

Fig. 1. Benzimidazole containing important commercial drugs.

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

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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 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

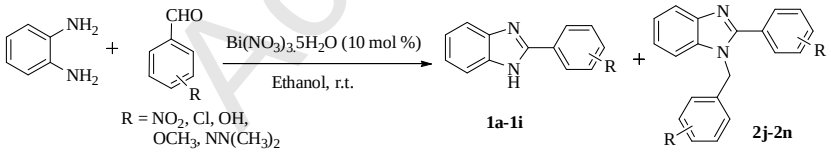
All chemicals and materials are procured from S. D. Fine Chemicals Ltd. and Spectrochem Chemicals Pvt. Ltd. and used without further purification. Melting points were determined with open capillary method and are uncorrected. IR spectra were recorded in KBr on Shimadzu IR Affinity-1 FT-IR spectrophotometer 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.

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 are summarized in Tables 1-3. In order to find out optimum reaction condition for the synthesis of 2-substituted benzimidazole, a separate study with different catalysts and solvents was performed. Bismuth nitrate was found to be an efficient catalyst for synthesis of 2-substituted benzimidazoles over the other catalyst studied.



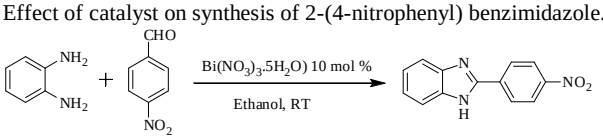
Scheme 1. Bismuth nitrate mediated synthesis of 2-substituted benzimidazole derivatives.

3.1. Effect of catalyst and solvent

In order to study the performance of catalyst, a controlled reaction was performed using *o*-phenylenediamine with 4-nitrobenzaldehyde in ethanol without catalyst. The percentages of products formed under controlled condition and with the different catalysts are summarized in Table 1. The results revealed that, under the controlled condition the percentage of products were less even after 8 h in most of the cases, whereas in the presence of bismuth nitrate the obtained yield was highest within a short reaction period of 1 h only. Amidst, in order to get more insides about the amount of catalyst required for the efficient conversion, we performed the experiments by using different percentage loading of catalyst in ethanol at room temperature (Table 1, entries 4-7). The experimentation revealed that 10 mol % loading of catalyst afforded the desired products with highest yield just within 1 h. Thus, it was

found that bismuth nitrate plays a benign role of accelerator promoting the time and cost effective formation of product. In order to study the effect of solvents over the oxidative coupling of 4-nitrobenzaldehyde with *o*-phenylenediamine, we carried out the reaction in different solvents. Less polar and aprotic solvents like dichloromethane, toluene and tetrahydrofuran were found to be unsuitable for the reactions, whereas, more polar and protic solvents like ethanol, glycerol, polyethylene glycol (PEG), *etc.*, were appropriate solvents to afford the higher yields (Table 2).

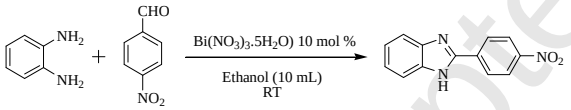
Table 1
Effect of catalyst on synthesis of 2-(4-nitrophenyl) benzimidazole.[a]



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	$Ca(NO_3)_2.4H_2O$	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.

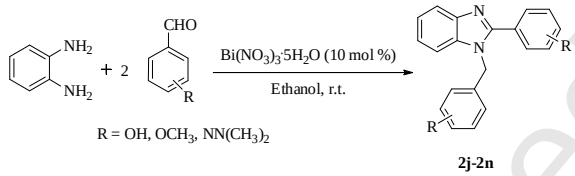
Under the optimized reaction conditions, we performed the reactions of aromatic and heteroaromatic aldehydes with *o*-phenylenediamine to give quantitative yields of products (Table 3). In some reactions, dialdimines were formed as byproducts (1%-5%) which were separated during recrystallization. Several functional groups such as Cl, Br, NO_2, OCH_3 and sensitive heterocyclic molecules like indole-3-carboxaldehyde and pyridyl-3-carboxaldehyde were compatible with the reaction conditions. All the synthesized compounds were isolated, purified and characterized by FT-IR, ^{1}H NMR, and LC-MS spectroscopic techniques. In ^{1}H NMR analysis (Supporting information), the compound (**2n**) shows the two sharp singlets for -NCH_3. This is due to conjugation of unpaired electrons on the nitrogen atom with aromatic π electrons and this conjugation makes a partial double bond between ipso carbon and nitrogen atom.

Table 3
Synthesis of benzimidazole derivatives from *o*-phenylenediamine and aldehydes.

Entry	R	Product	Time (min)	Yield (%)[b]	M.P. (°C)		Ref
					Found	Reported	
1	4-NO_2-C_6H_4	**1a**	60	96	314-316	317	[21]
2	3-NO_2-C_6H_4	**1b**	90	97	144-146	144	[21]
3	2-NO_2-C_6H_4	**1c**	60	95	264	260-263	[25]
4	2-Cl-C_6H_4	**1d**	55	76	234	234	[25]
5	4-Cl-C_6H_4	**1e**	60	84	290	292	[29]
6	3-Pyridinyl	**1f**	90	73	246	241-243	[26]
7	3-Indolyl	**1g**	60	85	222-224	225	[26]
8	2, 5-$(OCH_3)_2$-C_6H_3	**1h**	60	86	218-220	--	--
9	2-OH-C_6H_4	**1i**	90	85	242	242	[24]
10	3-OH-C_6H_4	**2j**	300	49	250-252	255-257	[39]
11	4-OH-C_6H_4	**2k**	300	50	210-212	222	[39]
12	4-OH,3-OCH_3-C_6H_3	**2l**	300	48	214-216	190-192	[39]
13	3,4 $(OCH_3)_2$-C_6H_3	**2m**	300	48	168-170	170-172	[39]
14	4-$(CH_3)_2N$-C_6H_4	**2n**	300	42	172-174	165-167	[40]

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

From the above data, it was observed that all the reactions would have offered the expected corresponding 2-substituted benzimidazoles, but surprisingly the reactions with aromatic aldehydes carrying either hydroxyl or methoxy groups at *meta* or *para* positions, resulted in the formation of 1,2-disubstituted benzimidazoles. As per the optimized conditions, we have used *o*-phenylenediamine: aldehydes (1:1.1 mmol), and found that, still after 5 h *o*-phenylenediamine was unreacted whereas other precursor *i.e.* aldehyde gets completely consumed. After isolation and purification of product it was observed that the obtained products was 1,2-disubstituted benzimidazoles and not expected 2-substituted benzimidazole. With this observation, we planned to set the reactions with two equivalents of aldehydes and one equivalent of *o*-phenylenediamine under the optimized conditions, where, 1,2-disubstituted benzimidazoles was obtained as major product with excellent yields (Table 4, Scheme 2).



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

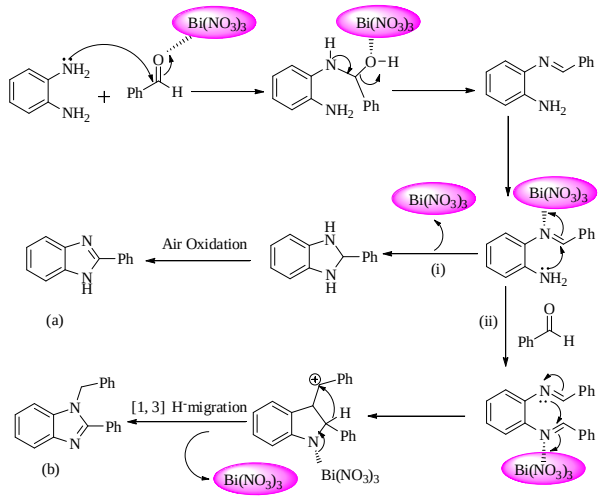
Table 4
Synthesis of 1, 2-disubstituted benzimidazole derivatives from *o*-phenylenediamine and aldehydes

Entry	Product	Time (min)	Yield (%)[b]
1	**2j**	60	90
2	**2k**	65	81
3	**2l**	75	91
4	**2m**	60	84
5	**2n**	60	85

[a] Reaction condition: *o*-Phenylenediamine (1 mmol), 4-nitrobenzaldehyde (2.1 mmol), and bismuth nitrate (10 mol%) as catalyst.
[b] Isolated yield.

3.2. Plausible mechanism

At the initial stage of synthesis of 2-substituted benzimidazoles, bismuth nitrate forms hydrogen bonding with aldehyde which leads to the activation of carbonyl carbon and subsequently facile attack of diamine over aldehyde forms 2-substituted benzimidazoles. Furthermore, In the synthesis of 1,2-disubstituted benzimidazoles, aldehyde initially reacted with diamine to form Schiff base as an intermediate in the presence of electrophilic catalyst, followed by intramolecular 1,3-hydride migration led to the formation of 1,2-disubstituted benzimidazoles (Scheme 3).



Scheme 3. Plausible mechanism for synthesis of (i) 2-substituted benzimidazoles (a) and (ii) 1,2-disubstituted benzimidazoles (b).

4. Conclusion

In summary, bismuth nitrate played a crucial role of mild and efficient green catalyst for the syntheses of 2-substituted and 1,2-disubstituted benzimidazoles in quantitative yields from *o*-phenylenediamine and a wide variety of aldehydes. This methodology followed column chromatography-free protocol availing the abolishment of large amount of organic solvents. A one pot synthesis with short reaction time; use of inexpensive, non-toxic, and easily available catalyst; easy isolation of products with higher yields are the key leads of the methodology executed herein. Thus, this work furthered a green, time as well as cost effective route to researcher's further dealing with these scaffolds in future.

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