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A convenient one-pot synthesis of 2-substituted benzimidazoles

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Abstract

2-Substituted benzimidazoles have been synthesized in excellent yields in a single pot under solvent-free conditions from *o*-phenylenediamine and aldehydes in the presence of a catalytic amount of $In(OTf)_3$ at room temperature.

Keywords: Benzimidazole; *o*-Phenylenediamine; Aldehydes; Indium(III) triflate

1. Introduction

The benzimidazole ring is an important pharmacophore in modern drug discovery [1]. Benzimidazole derivatives exhibit significant activity against several viruses such as HIV [2], herpes (HSV-1) [3], RNA [4], influenza [5], and human cytomegalovirus (HCMV) [2a]. Benzimidazole and its derivatives have been used to act as topoisomerase inhibitors [6], selective neuropeptide Y Y 1 receptor antagonists [7], angiotensin II inhibitors [8], inhibitors of HCMV replication [2a], 5-HT_3 antagonists in isolated guinea pig ileum [9], potential antitumor agents [10], antimicrobial agents [11], smooth muscle cell proliferation inhibitors [12], a treatment for interstitial cystitis [13], as factor Xa inhibitors [14], and in diverse areas of chemistry [15]. In addition, benzimidazoles are very important intermediates in organic reactions [16]. Therefore, the preparation of benzimidazoles has gained considerable attention in recent years [17–19].

Despite their importance from pharmacological, industrial, and synthetic point of views, comparatively few methods for the preparation of benzimidazoles have been reported. These include the condensation of *o*-aryldiamines and aldehyde in refluxing nitrobenzene [20], the condensation of *o*-aryldiamines with carboxylic acids or their derivatives in the presence of strong acids such as polyphosphoric acid [21] or mineral acids [22], and thermal or acid promoted cyclization of *N*-(*N*-arylbenzimidoyl)-1,4-benzoquinoneimines [23]. The direct condensation of *o*-aryldiamines and aldehydes at room temperature is less far developed [24–28]. However, many of these methods have some drawbacks such as low yields, long reaction times, drastic reaction conditions, tedious work-up procedures, and co-occurrence of several side reactions. In some cases more than one step is involved in the synthesis of these compounds. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the work-up procedure and cannot be recovered or reused. Therefore, the search continues for a better catalyst for the synthesis of benzimidazoles in terms of operational simplicity, reusability, economic viability, and greater selectivity.

2. Results and discussion

In recent years, indium triflate has received considerable attention as a mild Lewis acid for an array of organic transformations [29] because the catalyst is quite stable in water and is reusable. The catalyst indium triflate [$In(OTf)_3$] is commercially available and can be used for the preparation of benzimidazoles from *o*-phenylenediamines and aldehydes. In continuation of our work to develop new synthetic methodologies, [30] we report herein a facile method for the synthesis of 2-substituted benzimidazoles by the condensation of *o*-phenylenediamine with aldehydes in the presence of a catalytic amount of $In(OTf)_3$ under solvent-free conditions.

The reactions were carried out in neat at room temperature for 30 min by taking a 1:1.1 mol ratio mixture of

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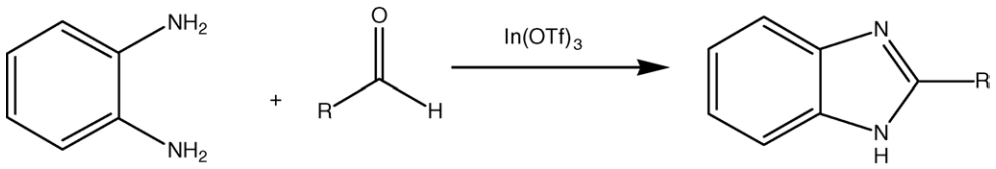
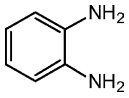
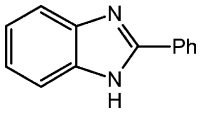
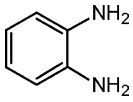
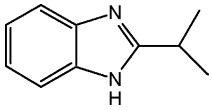
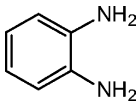
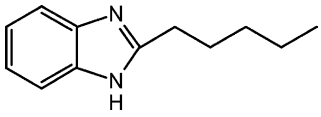
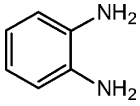
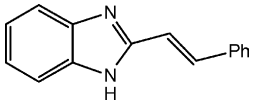
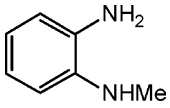
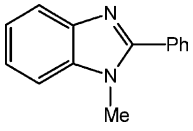
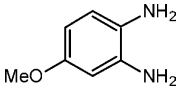
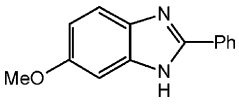
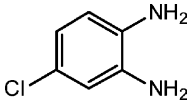
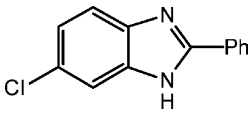
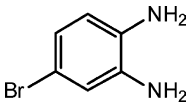
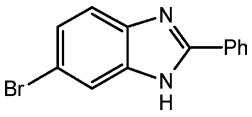
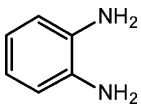
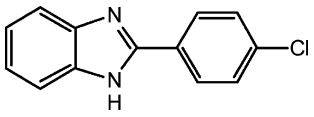
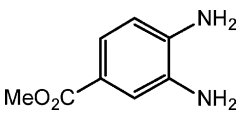
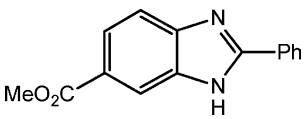
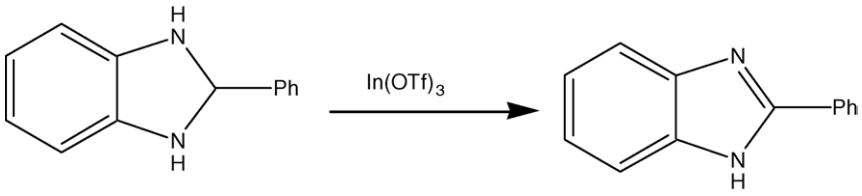


Scheme 1.

Table 1
$In(OTf)_3$-catalyzed formation of benzoimidazoles

Entry	Amine	Aldehyde	Product	Yield[a] (%)
1		Benzaldehyde		95
2		Isobutyraldehyde		89
3		Hexanal		86
4		*trans*-Cinnamaldehyde		91
5		Benzaldehyde		78
6		Benzaldehyde		87
7		Benzaldehyde		83
8		Benzaldehyde		82
9		4-Chlorobenzaldehyde		85
10		Benzaldehyde		74

[a] Yields refer to isolated pure products and were characterized by NMR and mass spectra, and also all products are commercially available (Aldrich).



Scheme 2.

o-phenylenediamine and the aldehydes in the presence of 5 mol% $In(OTf)_3$ to give the desired products in excellent yield (Scheme 1). As shown in Table 1, aromatic, aliphatic, and unsaturated aldehydes react without any significant difference in rates to give the corresponding 2-substituted benzimidazoles in good yield. The method has the ability to tolerate other functional groups such as methoxy, ester, halides, and olefins. We also observed that without catalyst oxidation is very slow; we isolated 2-phenyldydrobenzimidazole. This fact suggests that catalyst promotes the air-oxidation of the intermediate towards the formation of benzimidazole derivatives (Scheme 2). Among the various metal triflates such as $Cu(OTf)_2$, $La(OTf)_3$, $Lu(OTf)_3$, $Nd(OTf)_3$, and $Ce(OTf)_3$ studied for this reaction, $In(OTf)_3$ was found to be the most effective catalyst in terms of conversion and reaction rates. The scope and generality of this process is illustrated with respect to various aliphatic, aromatic, and unsaturated aldehydes and the results are summarized in Table 1.

3. Experimental

Melting points are uncorrected. NMR spectra were recorded on a Bruker ARX 300 (300 MHz) instrument. Low resolution mass spectra (CI, EI) were recorded on a Finnigan 4000 mass spectrometer. High resolution mass spectra (HRMS, EI, CI, ESI) were recorded on Finnigan MAT XL95 mass spectrometer. The reactions were monitored by TLC, and visualized with UV light followed by development using 15% phosphomolybdic acid in ethanol. All solvents and reagents were purchased from Aldrich with high-grade quality, and used without any purification. All products are known and were identified by comparison with those reported in the literature.

3.1. Typical procedure

A mixture of *o*-phenylenedianmine (540 mg, 5 mmol) and benzaldehyde (583 mg, 5.5 mmol) was stirred in the presence of commercially available anhydrous (Aldrich) $In(OTf)_3$ (141 mg, 5 mol%) at room temperature. After completion of the reaction (TLC), the reaction mixture was diluted with ethyl acetate (50 mL), washed with water (20 mL), dried ($MgSO_4$), and concentrated. The crude residue was purified by silica gel column chromatography (20% ethyl acetate in hexane) to afford a pure product (921 mg, 95%). All reactions were completed within 30 min. The aqueous layer containing the catalyst could be evaporated under reduced pressure (50 mm, Hg pressure at 80 °C) to give a white solid. The IR spectrum of the recovered catalyst was identical to that of the commercially available catalyst (Aldrich), which could be reused for the next reaction with only a modest loss in activity. The catalyst has been recovered and reused for four times (reaction yields 90, 84, 73, 61%). The recovered catalyst was dried (under high pressure at 80 °C for 3 h) prior to use in the next reaction.

3.2. Product characterization data

2-Phenylbenzimidazole (Compound **1**, entry 1): Mp 293–294 °C, Ref. [31] 295 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.22 (m, 2 H), 7.48 (m, 5 H), 7.58 (s, 1 H), 8.04 (dd, J = 8, 1.6 Hz, 2 H); Compound **2**: mp 235–236 °C, Ref. [32] 236 °C; Compound **3**: mp 164–165 °C, Ref. [33] 165 °C; Compound **4**: mp 201–203 °C, Ref. [34] 202 °C; Compound **5**: mp 90–91 °C, Ref. [35] 92 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.88 (s, 3 H), 7.28 (m, 2 H), 7.56 (m, 3 H), 7.62 (d, J = 7.8 Hz, 1 H), 7.69 (d, J = 8 Hz, 1 H), 7.86 (dd, J = 8, 1.6 Hz, 2 H); Compound **6**: mp 144-145 °C, Ref. [36] 145 °C; Compound **7**: mp 214–215 °C, Ref. [33] 215 °C; Compound **8**: mp 201–202 °C, Ref. [33] 203 °C; Compound **9**: mp 301–303 °C, Ref. [33] 301 °C.

4. Conclusion

In conclusion, we describe a mild and efficient method for the synthesis of benzimidazoles. The easy work-up procedure, recyclable catalyst, short reaction times, and very good yields make this method a valid contribution to the existing methodologies.

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