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Cadmium chloride (CdCl_2): a mild and efficient catalyst for the synthesis of benzimidazoles

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Abstract

One-pot synthesis of benzimidazoles has been carried out using ortho-phenylenediamine and aldehydes. The condensation reaction smoothly took place in the presence of a mild Lewis acid cadmium chloride. All the reactions were carried out in acetonitrile at 80°C to 85°C.

Keywords: Benzimidazoles, Aldehydes, Ortho-phenylenediamine, Cadmium chloride

Background

Molecules having benzimidazole as a basic structural unit are known to exhibit a wide range of biological properties [1-3]. The potency and wide applicability of imidazole pharmacophore can be attributed to its hydrogen bond donor/acceptor capability as well as its high affinity for metals, which are present in many protein active sites [4-6]. The benzimidazole molecular skeleton is found in a number of clinical therapeutic agents such as anticancer, antiulcerative, antihypersensitive, antiviral, antifungal, anti-tumor and antihistaminic [7-9] (Figure 1). The synthesis of benzimidazoles and its derivatives occupies pivotal position in the field of organic synthesis. In this contest, several efforts have been developed for the synthesis of benzimidazole derivatives. One of the most common methods for the preparation of benzimidazole derivatives involves the condensation of arylenediamines and carbonyl compounds such as aldehydes and acid derivatives [10-12]. The condensation of phenylene diamine and carboxylic acid (derivatives) often requires strong acidic conditions and/or high temperature [13-18]. The other way involves the oxidative cyclodehydrogenation of Schiff bases, which is generated from phenylene diamine and aldehyde in the presence of various oxidative and catalytic reagents. This is the most popular approach in general for the synthesis of benzimidazole derivatives. The reagents are CAN, K_3PO_4 , oxone, sulfamic acid, DDQ, $\text{PhI}(\text{OAc})_2$, iodine and KHSO_4 [19-24]. In addition, several catalysts such as metal halides and metaloxychlorides [25-30], metal oxides, PTSA, metal

triflate, ionic liquid, heteropoly acid, BDSB [31-36], proline, solid-supported catalysts, polymer-supported catalysts and microwave-promoted [37-41] reactions have been reported in the literature.

Unfortunately, many of these methods suffer from drawbacks such as drastic reaction conditions [14], low yields [16], tedious workup procedures [22] and co-occurrence of several side reactions [20]. As a consequence, the introduction of an efficient and mild method is still needed to overcome these limitations.

Methods

Results and discussion

Herein, we report a simple and efficient protocol for the synthesis of benzimidazoles using the catalyst cadmium chloride. In a preliminary study, we have examined the reaction of 1,2-phenylenediamine or ortho-phenylenediamine (OPD) (1 in Scheme 1) and benzaldehyde (2 in Scheme 1) in the presence of cadmium chloride to optimize the reaction conditions. The optimal conditions were found to involve the use of OPD and aldehydes in 1:1 molar ratios, with the catalyst loading of 10 mol% in acetonitrile at 80°C to 85°C. As per the optimized conditions, the OPD and benzaldehyde reaction was completed within 3 h to give the corresponding product of 2-phenylbenzimidazole (3a) in excellent yield, as shown in Scheme 1.

Encouraged by the result obtained with benzaldehyde and OPD, the method was applied to various aldehydes to establish the generality of the protocol. As shown in the Table 1, aromatic, heteroaromatic, α - and β -unsaturated aldehyde and aliphatic aldehydes reacted very well

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to afford the corresponding products of benzimidazole derivatives in very good to excellent yields. In general, the aromatic aldehydes having electron-donating groups and heteroaromatic compounds reacted faster when compared with other aldehydes. Also, the aliphatic aldehydes and aromatic aldehydes containing electron-withdrawing groups reacted comparatively slower in terms of reaction rate and yields. Among several organic solvents tested for this condensation reaction, such as dichloromethane, DMF, methanol, dioxane, THF and acetonitrile, the better conversion and easy isolation of products were found to be with acetonitrile. To test the solvent's role in the reaction, one experiment was carried out with benzaldehyde and OPD in the presence of the catalyst cadmium chloride, but in the absence of solvent. This reaction did not go to completion (80%) even after stirring for a period of 10 h. In a similar manner, one blank experiment was carried out without the use of catalyst, and no product was formed after 10 h of stirring. Finally, it was decided that the suitable conditions for this condensation is in a solvent and in the presence of an activator or promoter. In general, under the optimized condition, all the reactions went to completion within 3 to 5 h, with the desired product in the range of 80% to 90%. All of the products were characterized by their proton nuclear magnetic resonance (^1H NMR), infrared (IR) and mass spectroscopy data.

Experimental

General methods

Melting points were recorded on a Buchi R-535 apparatus (BUCHI India Private Ltd., Mumbai, India) and were uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer (PerkinElmer, Inc., Waltham, MA, USA) using a KBr disk. ^1H NMR spectra were recorded on a Gemini-200 spectrometer (HORIBA India Private Ltd., New Delhi, India) in CDCl_3 using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer (THERMO Scientific, Waltham, MA, USA) operating at 70 eV.

General procedure

A mixture of ortho-phenylenediamine (216 mg, 2 mmol) and benzaldehyde (212 mg, 2 mmol) in the presence of

cadmium chloride (18.3 mg, 10 mol%) was stirred in acetonitrile (5 mL) at 80°C to 85°C . The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude products were purified by column chromatography using ethyl acetate-hexane mixture in 3:7 ratio. All the products were identified by their ^1H NMR, IR and mass spectroscopy data and compared with literature reports.

Spectral data for selected compounds

2-Phenylbenzimidazole (3a)

Melting range, 291°C to 293°C . IR (KBr): ν 3,296, 3,084, 2,957, 2,839, 1,651, 1,579, 1,523, 1,438, 1,396, 1,267, 1,159, 1,083, 967, 842 and 739 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 6.91 to 6.98 (m, 2 H), 7.18 to 7.28 (m, 4 H), 7.42 to 7.52 (m, 1 H), 7.90 to 7.96 (m, 1 H) and 11.85 (brs, 1 H, NH). EIMS m/z (%): 194 (m^+100), 192 (12), 179 (10), 167 (20), 117 (15), 103 (35), 77 (25), 76 (30) and 51 (40).

2-(4-Chlorophenyl) benzimidazole (3e)

Melting range, 292°C to 293°C . IR (KBr): ν 3,256, 3,061, 2,979, 2,847, 1,626, 1,548, 1,425, 1,372, 1,253, 1,139, 1,081, 1,015, 978, 835 and 743 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 7.02 to 7.15 (m, 2 H), 7.25 to 7.35 (m, 3 H), 7.50 to 7.60 (m, 1 H), 8.01 to 8.16 (m, 1 H) and 12.50 (brs, 1 H, NH). EIMS m/z (%): 230 (m^+10), 228 (15), 215 (15), 193 (30), 139 (52), 117 (100), 113 (12), 91 (15), 76 (70) and 51 (18).

2-(Naphthalen-2-yl) benzimidazole (3f)

IR (KBr): ν 3,312, 3,054, 2,969, 2,831, 1,623, 1,560, 1,431, 1,356, 1,249, 1,122, 1,132, 1,073, 1,006, 984, 827 and 749 cm^{-1} . ^1H NMR ($\text{DMSO}-d_6$): δ 7.20 to 7.30 (m, 2 H), 7.55 to 7.70 (m, 4 H), 7.90 to 8.10 (m, 3 H), 8.35 to 8.45 (m, 1 H), 8.75 (brs, 1 H) and 11.85 (brs, 1 H, NH). EIMS m/z (%): 244 (m^+100), 229 (10), 153 (40), 127 (65), 102 (18), 97 (21), 77 (20), 76 (22) and 51 (30).

2-Propylbenzimidazole (3k)

Melting range, 154°C to 155°C . IR (KBr): ν 3,291, 3,079, 2,963, 2,845, 1,561, 1,433, 1,342, 1,263, 1,156, 1,108, 1,093, 1,021, 971, 834 and 751 cm^{-1} . ^1H NMR

Table 1 Cadmium chloride-catalyzed synthesis of benzimidazoles

Serial number	Aldehyde	Product (3a to 3o)	Reaction time (h)	Yield (%)
a			3.0	88
b			4.5	85
c			3.0	90
d			5.0	81
e			4.0	85
f			4.5	83
g			3.5	81
h			3.0	90
i			3.0	90
j			4.0	85
k			4.5	80
l			5.0	85
m			5.0	82
n			3.5	80
o			4.0	81

(DMSO- d_6): δ 0.98 (t, 3 H, $J=7.5$ Hz), 1.80 to 1.90 (m, 2 H), 3.05 (t, 2 H, $J=7.5$ Hz), 7.20 to 7.30 (m, 2 H), 7.50 to 7.60 (m, 2 H) and 12.5 (brs, 1 H, NH). EIMS m/z (%): 160 (m^+ 30), 131 (12), 116 (10), 90 (15), 76 (100) and 51 (25).

Conclusions

In conclusion, the catalyst cadmium chloride has been demonstrated as a novel and efficient promoter for the synthesis of benzimidazoles in high yields, from ortho-phenylenediamine and a wide variety of aldehydes. All the reactions were carried out at 80°C to 85°C, while using the catalyst cadmium chloride in 10 mol%. The reaction conditions were very mild, and the isolation of products was also very easy.

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