YTTRIUM (III) CHLORIDE: A MILD AND EFFICIENT CATALYST FOR THE SYNTHESIS OF BENZIMIDAZOLES

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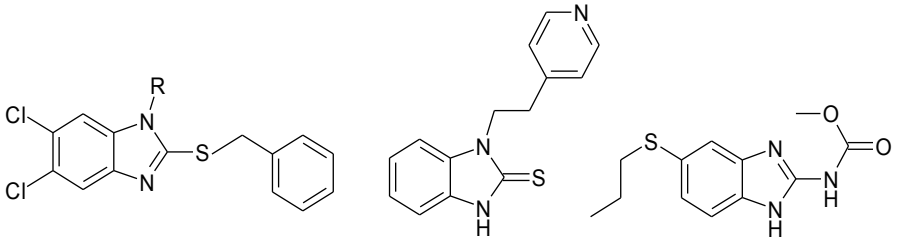
ABSTRACT: A simple and efficient synthesis of benzimidazole derivatives from *ortho*-phenylene diamine and aldehydes by using a Lewis acid catalyst yttrium (III) chloride has been described. Compared with classical benzimidazole synthesis, this method has advantage of excellent yields and short reaction times. All the reactions were carried out using the catalyst in 10 mol %, in acetonitrile at room temperature.

Keywords: Benzimidazoles, aldehydes, orthophenylenediamine, yttrium (III) chloride.

INTRODUCTION

Nitrogen containing heterocyclic compounds possesses immense pharmaceutical importance and the development of novel strategy for their synthesis occupies high priority in the field of organic synthesis. Combinatorial synthesis of heterocyclic provides enormous structural diversity, which has greatly helped in the design and choice of lead structures in the drug discovery process.[1] The imidazole and substituted imidazole moiety are structurally related to purine bases and found in a variety of naturally occurring compounds, such as nonpeptide luteinizing hormone-releasing hormone antagonist, lymphocyte specific kinase inhibitor, *N*-methyl-D-aspartate antagonist, neuropeptide YY1 receptor antagonist, nonpeptide thrombin inhibitor, 5-lipoxygenase inhibitor, hepatitis C virus NS5B polymerase inhibitor and GABA-receptor.[2] The benzi midazole derivatives are also exhibiting antitumor, antimicrobial, antihypertensive, antiulcer, antifungal and antihistamine activity.[3] The high profile of biological applications of the benzimidazole compounds has prompted extensive studies for their synthesis. In this context, numerous efforts have been made for the synthesis of benzimidazole derivatives. One of the most common methods for the preparation of benzimidazole derivatives involves the condensation of an arylenediamines and carbonyl compounds such as aldehydes and acid derivatives.

The condensation of phenylene diamine and carboxylic acid (derivatives) requires strong acidic conditions and some times combines at very high temperature.[4] The other method involves the oxidative cyclo-dehydrogenation of Schiff bases, which is generated from phenylenediamine and aldehyde in presence of various oxidative and catalytic reagents. This is one of the most popular approaches in general for the synthesis of benzimidazole derivatives.



The reagents are CAN, K_3PO_4, oxone, sulfamic acid, DDQ, $PhI(OAc)_2$, Iodine and $KHSO_4$.[5] In addition, several catalysts such as metal halides and metaloxychlorides,[6] metal oxides, PTSA, metal triflates, ionic liquid, heteropoly acid, BDSB,[7] proline, solid supported catalysts, polymer supported catalysts and microwave promoted[8] reactions have been reported in the literature.

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

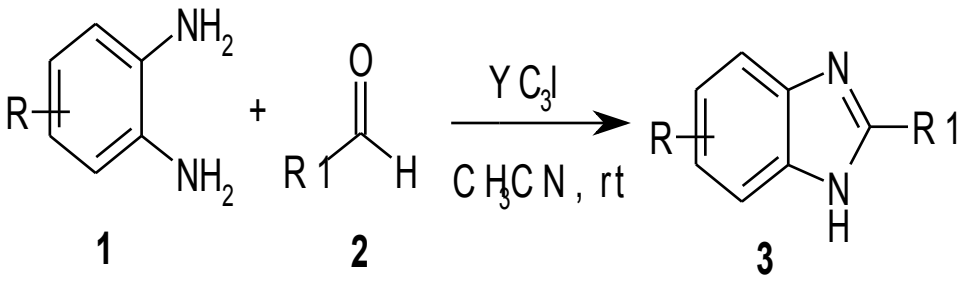
Experimental section:

General methods: Melting points were recorded on Buchi R-535 apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT-IR 240-c spectrophotometer using KBr disk. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

General procedure: A mixture of *ortho*-phenylenediamine (2 mmol) and aldehyde (2.2 mmol) in presence of ytterbium trichloride (29 mmol) was stirred in acetonitrile (5ml) at room temperature. The progress of the reaction was monitored by thin layer chromato graphy (TLC). After completion of the reaction as indicated by TLC, the solvent was removed under reduced pressure. The residue was dissolved in ethylacetate 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. All the products were identified by their ^{1}HNMR, IR and mass spectroscopy data and compared with literature reports.

RESULTS AND DISCUSSION

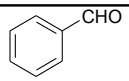
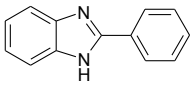
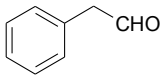
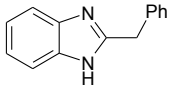
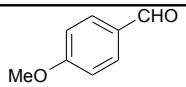
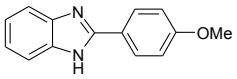
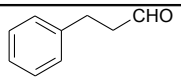
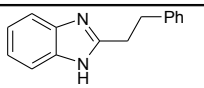
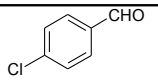
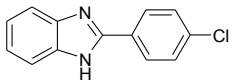
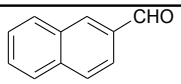
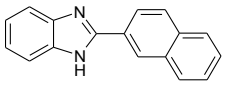
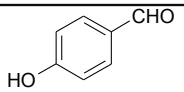
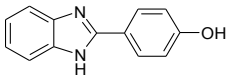
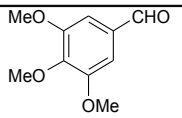
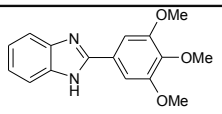
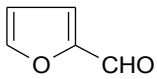
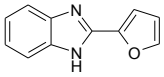
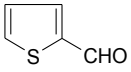
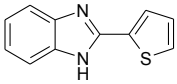
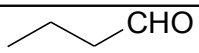
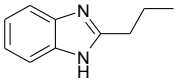
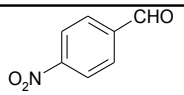
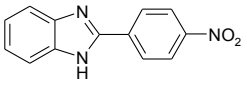
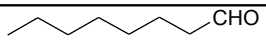
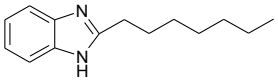
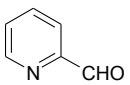
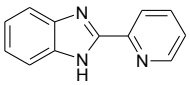
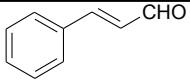
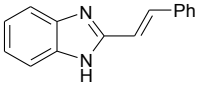
Herein, we report a simple and efficient protocol for the synthesis of benzimidazoles using the catalyst yttrium (III) chloride. In a preliminary study, we have examined the reaction of 1, 2-phenylenediamine or *ortho*-phenylenediamine (OPD) **1** and benzaldehyde **2** in the presence of yttrium (III) chloride to optimize the reaction conditions. The ideal reaction condition can be claimed as the use of OPD and aldehydes in 1:1.1 molar ratios, the catalyst is in 10 mol% and the solvent acetonitrile at room temperature. As per the above ideal reaction conditions, the OPD and benzaldehyde reaction was completed within 3.0h to gave the corresponding product of 2-phenylbenzimidazole **3a** in excellent yield, as shown in the scheme 1.



Scheme-1

Encouraged by the result obtained with benzaldehyde and OPD, the method was applied for various aldehydes to establish the generality of the protocol. As shown in the table 1, aromatic, heteroaromatic, α, β-unsaturated aldehyde and aliphatic aldehydes were reacted very well 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 are reacting little faster when compared with other aldehydes. In a similar manner, the aliphatic aldehydes and aromatic aldehydes containing electron withdrawing groups are reacting comparatively little slower in terms of conversion as well as 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 role in the reaction, one experiment was carried out with benzaldehyde and OPD in presence of the catalyst yttrium (III) chloride, in absence of solvent. But the reaction was not going completion (80%) even after stirring for a period of 10 hours. In a similar manner, a blank experiment was carried out without the use of catalyst and the reaction progress was not found even after 10 hours stirring. Finally, it was decided that the suitable condition for this condensation is in a solvent medium and in presence of an activator or promoter. In general, all the reactions were completed with in 3.0 to 5.0 hours of reaction period and the obtained yields also 80 to 90%. All the products were characterized by their ^{1}H NMR, IR and mass spectroscopy data.

Table 1: Yttrium (III) chloride catalyzed synthesis of benzimidazoles.

S.No	Aldehyde	Product (3a-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

CONCLUSION

In conclusion, the catalyst yttrium (III) 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 room temperature, while using the catalyst yttrium (III) chloride in 10 mol%. The reaction conditions were very mild and the isolation of products also very easy.

Spectral data for selected compounds:

2-Phenylbenzimidazole (3a).MP, 291-293^{0}C. IR (KBr). υ 3296, 3084, 2957, 2839, 1651, 1579, 1523, 1438, 1396, 1267, 1159, 1083, 967, 842, 739 cm^{-1}; ^{1}H NMR (DMSO-d_6). δ 6.91-6.98 (m, 2H), 7.18-7.28 (m, 4H), 7.42-7.52 (m, 1H), 7.90-7.96 (m, 1H), 11.85 (brs, 1H, NH).; EIMS *m/z* (%). 194 (m^{+}100), 192 (12), 179 (10), 167 (20), 117 (15), 103 (35), 77 (25), 76 (30), 51 (40).

2-(4-Chlorophenyl) Benzimidazole (3e). MP, 292-293^{0}C. IR (KBr). υ 3256, 3061, 2979, 2847, 1626, 1548, 1425, 1372, 1253, 1139, 1081, 1015, 978, 835, 743 cm^{-1}; ^{1}H NMR (DMSO-d_6). δ 7.02-7.15 (m, 2H), 7.25-7.35 (m, 3H), 7.50-7.60 (m, 1H), 8.01-8.16 (m, 1H), 12.50 (brs, 1H, NH).; EIMS *m/z* (%). 230 (m^{+}10), 228 (15), 215 (15), 193 (30), 139 (52), 117 (100), 113 (12), 91 (15), 76 (70), 51 (18).

2-(Naphthalen-2-yl) Benzimidazole (3f). MP. 292-293^{0}C. IR (KBr). υ 3312, 3054, 2969, 2831, 1623, 1560, 1431, 1356, 1249, 1122, 1132, 1073, 1006, 984, 827, 749 cm^{-1}; ^{1}H NMR (DMSO-d_6). δ 7.20-7.30 (m, 2H), 7.55-7.70 (m, 4H), 7.90-8.10 (m, 3H), 8.35-8.45 (m, 1H), 8.75 (brs, 1H), 11.85 (brs, 1H, NH). EIMS *m/z* (%). 244 (m^{+}100), 229 (10), 153 (40), 127 (65), 102 (18), 97 (21), 77 (20), 76 (22), 51 (30).

2-Propylbenzimidazole (3k). MP, 154-155^{0}C. IR (KBr). υ 3291, 3079, 2963, 2845, 1561, 1433, 1342, 1263, 1156, 1108, 1093, 1021, 971, 834, 751 cm^{-1}; ^{1}H NMR (DMSO-d_6). δ 0.98 (t, 3H, J = 7.5 Hz), 1.80-1.90 (m, 2H), 3.05 (t, 2H, J = 7.5 Hz), 7.20-7.30 (m, 2H), 7.50-7.60 (m, 2H), 12.5 (brs, 1H, NH). EIMS *m/z* (%). 160 (m^{+} 30), 131 (12), 116 (10), 90 (15), 76 (100), 51 (25).

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