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Zirconium Chloride ($ZrCl_4$): An efficient Catalyst for the Synthesis of Benzimidazole Derivatives

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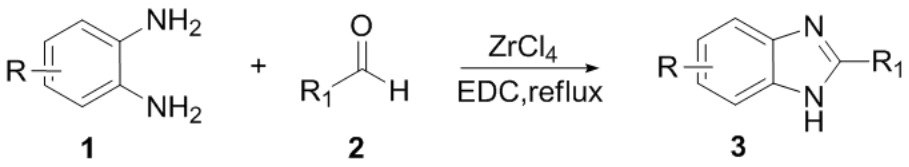
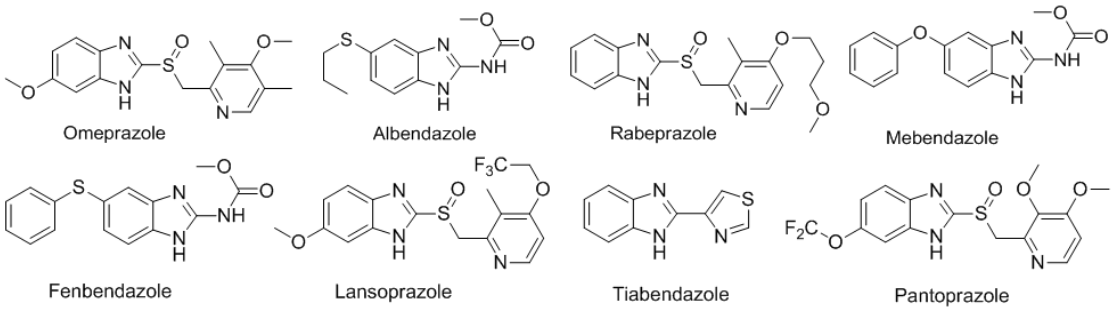
Graphical abstract



***Abstract**: One pot synthesis of benzimidazole derivatives from ortho-phenylenediamine and aldehydes at reflux in ethylenedichloride. All the reactions were carried out in presence of zirconium tetrachloride.*
***Keywords:** Benzimidazoles, aldehydes, ortho-phenylenediamine, $ZrCl_4$.*

I. 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. Imidazole and substituted imidazole moiety is structurally related to purine bases and found in a variety of naturally occurring compounds. The benzimidazole derivatives are exhibiting antitumor, antimicrobial, antihypertensive, antiulcer, antifungal and antihistamine activity.[1-3] The biological applications of the benzimidazole compounds has prompted extensive studies for their synthesis. In this contest, several numerous 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 an *ortho*-phenylenediamines and aldehydes, which is the most popular approaches in general for the synthesis of benzimi dazole derivatives using various catalysts.[4-10] In addition, several catalysts such as metal halides and metaloxychlorides,[11-16] metal oxides, *p*TSA, metal triflates,[17-21] ionic liquid, heteropoly acid, BDSB,[22-25] proline, supported catalysts[26-29] and microwave promoted[30-32] reactions have been reported in the literature.

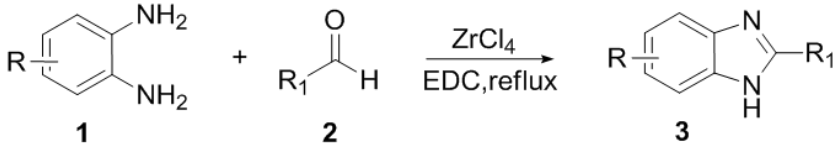


Many of the methods suffer from drawbacks such as drastic reaction conditions, low yields and tedious workup procedures. As a result, the introduction of an efficient and mild method is still needed to overcome these limitations. Zirconium tetrachloride is known as a mild and efficient catalyst for various organic transformations in the literature.[33,34]

II. Results and Discussion:

As part of our on going program in developing new synthetic methodologies herein, we report a simple and efficient protocol for the synthesis of benzimidazoles. 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 zirconium tetrachloride 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 used was ethylene dichloride (EDC) at reflux conditions. As per the above ideal reaction conditions, the OPD and benzaldehyde reaction was completed within 5 h to give the corresponding product, 2-phenylbenzimidazole (**3a**) in excellent yield, as shown in the scheme 1.



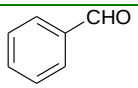
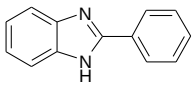
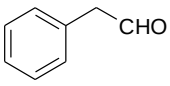
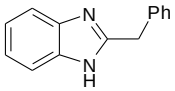
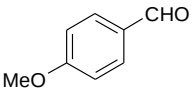
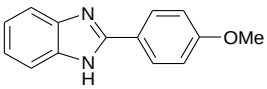
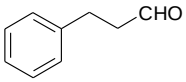
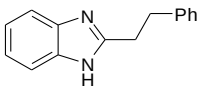
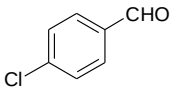
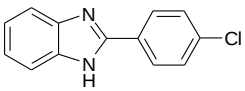
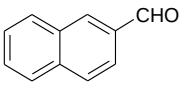
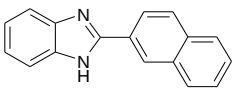
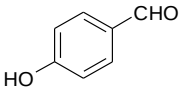
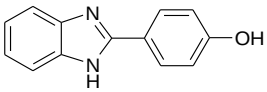
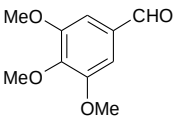
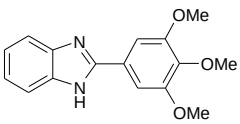
Scheme-1

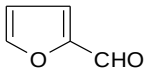
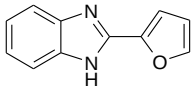
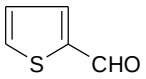
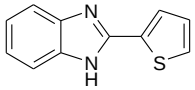
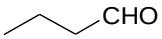
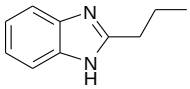
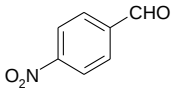
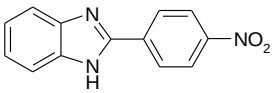
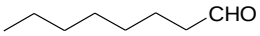
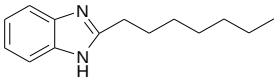
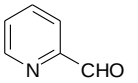
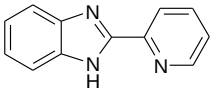
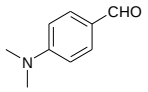
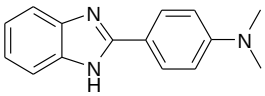
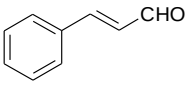
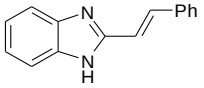
Encouraged by the result obtained with benzaldehyde and OPD, the method was applied for various aldehydes to establish the generality of the protocol. As shown in the table 1, aromatic, heteroaromatic, α, β-unsaturated aldehyde and aliphatic aldehydes were reacted very well to afford the corresponding 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. In general, all the reactions were completed within 5.0 to 7.0 hours of reaction time and the obtained yields are 75 to 90%. All the products were characterized by their ^{1}H NMR, IR and mass spectroscopy data.

III. Conclusion:

In conclusion, the zirconium tetrachloride has been employed as a novel and efficient catalyst for the synthesis of benzimidazoles in high yields from *ortho*-phenylenediamine and a wide variety of aldehydes. All the reactions were carried out at reflux, while using the catalyst $ZrCl_4$ in 10 mol%. The reaction conditions were very mild and the isolation of products also very easy.

Table 1: Zirconium tetrachloride catalyzed synthesis of benzimidazoles.

S.No	Aldehyde	Product (3a-3o)	Reaction Time (h)	Yield (%)
A			5.0	83
B			6.0	80
C			5.0	88
D			7.0	80
E			6.0	85
F			6.0	81
G			6.0	80
H			5.0	90

I			5.0	88
J			6.0	82
K			7.0	75
L			7.0	83
M			7.0	78
N			5.0	80
O			6.0	81
P			6.0	79

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 zirconium tetrachloride (20 mol%) was stirred in ethylene dichloride (10 mL) at reflux. 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.

Spectral data for selected compounds:

2-Phenylbenzimidazole (**3a**): 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). IR (KBr). υ 3256, 3061, 29 79, 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**). 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**): 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).

Acknowledgements:

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