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A Mild and Efficient Synthesis of Benzimidazole by Using Zinc Chloride under Solvent Free Condition

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ABSTRACT

A straightforward, efficient and more sustainable solvent-free method has been developed for the synthesis of benzimidazole derivatives to achieve yields that were comparable to or better than, those in conventional media. It is noteworthy that the reaction was exclusively carried out in Zinc chloride catalysis system, rendering the methodology highly valuable from both environment and economic points of view. The various benzimidazoles were synthesized by the reaction of o-phenylenediamine with different types of aldehydes and characterized by their Physical constant, FT-IR Spectra, ^{1}H NMR Spectra and LCMS. The excellent chemo selectivity, mild reaction condition, short reaction times and excellent yield made the best method then other methods.

KEYWORDS

Benzimidazoles, Zinc Chloride, Solvent Free.

INTRODUCTION

Benzimidazole nucleus is an important heterocyclic ring because of its synthetic utility and broad range of pharmacological activities. The syntheses of some new biologically active benzimidazoles have been reported. Resistance to number of anti-microbial agents (β-lactam antibiotics, macrolides, quinolones and vancomycin) among a variety of clinically significant species of bacteria is becoming increasingly important global problem. In particular, increasing drug resistance among Gram-positive a bacterium such as staphylococci, enterococci and streptococci is a significant health matter. Benzimidazole ring displays an important heterocyclic pharmacophor in drug discovery.

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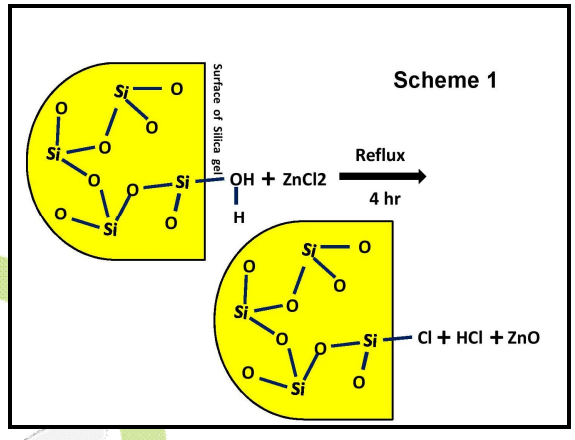
These compounds carrying different substituent's in the benzimidazole structure are associated with a wide range of biological activities including antimicrobial & antibacterial effects[1], antiallergic activity[2], HIV Inhibtors[3], antiviral effect[3], antiparasitic effect[4], anti hypertensive agents[5], cardiotonic activity[6], antiulcer activity[7], antiproliferative activity[8], anti-inflammatory activity[9], analgesic activity[10], antioxidant activity[11], antiprotozoal activity[12], antidiabetic activity[13], diuretic activity[14], androgen receptor antagonist[15], anticonvulsant agents[16].

A number of methods have been reported for the synthesis of benzimidazoles such as the condensation of o-aryldiamines and aldehyde[17]. In recent years, solvent-free synthesis of Benzimidazole under microwave irradiation using $Yb(OTf)_3$[18], KSF clay[18], PPA[18], Na_2SO_4[18], K-10 clay[18], metal halide supported alumina[19],

$H_2So_4SiO_2$[20], AMA[21] $NaHSo_3$[22], Amberlite IR-120[23] and have been reported. Various oxidative and catalytic reagents such as CAN[24], p-TsOH[25], $NaHSO_4 \cdot SiO_2$[26], $FeCl_3/Al_2O_3$[27], PS-PyCl-$XAlCl_3$[23], H_2O_2/HCl[28], NaY zeolite[29], $FeCl_3 \cdot SiO_2$[30], $Co(NO_3)_2/H_2O_2$[31], $Ni(NO_3)_2/H_2O_2$[31], Fe/MgO[32], sulfamic acid[33], $Yb(OTf)_3$[33], $Sc(OTf)_3$[33], $KHSO_4$[33], $HfCl_4$[33], $H_2O_2 \cdot HCl$[33], $FeBr_3$[33], Oxalic acid[34], L-preline[34], Glyoxalic acid[34], SDS[34], *N*- halosuccinamide (X = Cl, Br, I) [34] using solvents like ethanol, methanol, DMSO, THF, DMF, PEG, $CHCl_3$, HCl, Polyphosphoric acid, CH_2Cl_2 , DCM, CH_3CN, H_2O_2 , Acetic Acid.However, in above some reported methods suffer from one or more drawbacks such as prolonged reaction times, use of environmentally unfavorable solvents and frequently low yields. Thus, the development of a new method for the synthesis of Benzimidazole derivatives would be highly desirable. The solvent-free organic synthesis have offered more advantages as compared to their homogeneous counterparts due to the growing concern for the influence of organic solvent on the environment as well as on human body, economical demands and simplicity in the processes. various catalysts like as PSSA[34], Boric acid[35], Bf_3OEt_2[36], SABA[18], DBH[37], ammonium salts[38], Glycerol[39], Sulfonic acid functionlized silica (SiO_2-Pr-SO_3H)[40], P_2O_5-SiO_2[41], $Ku[Fe(CN)_6]$[42], TsOH-SiO_2[8], $Zn(OAc)_2$[43], $FePo_4$[44], TBAF[45] have been used for solvent free methods.

Recent research is mainly focused on the use of environmental benign catalysts under solvent free conditions. Clays function as efficient catalysts for various organic transformations due to their Bronsted and Lewis acidities in their natural and ion-exchanged forms. Commercially available SiO_2 clay is one such material that can fulfill these requirements. SiO_2 is an environmentally benign and economically feasible solid catalyst that offers several advantages, such as ease of handling, non-corrosiveness, low cost, and regeneration. Its high surface area ($250m^2/g$) makes it as a useful and active catalyst. Such Solid supports have found wide applications in organic reactions. It should be noted that the silica gel is used extensively as a support in organic chemistry[30,41]. In this work, as can be seen in Scheme 1, we prepared silica chloride from the reaction of readily available materials such as silica gel and the zinc chloride. Considering the wide use of catalyst in chemistry, we tried to report a new application of silica chloride (SiO_2-Cl) on synthesizing the substituted benzimidazoles.

Scheme 1: Synthesis of silica chloride.



MATERIALS AND METHODS

All chemicals were purchased from sigma-Aldrich and Lancaster and were used without further purification. All reactions and purity of benzimidazole derivatives were monitored by thin layer chromatography (TLC) using aluminium plates coated with silica gel (Merck) using pertroleum ether:ethylacetate(8:2) as an eluent. The isolated products were further purified by column-chromatography using silica gel (100–200 mesh) purchased from Sisco Research Laboratories Pvt. Ltd. Mumbai, India and purified products were recrystallized by hexane. ^1H NMR spectra were recorded on a Varian Gemini 200- and 400-MHz instrument in $CDCl_3$ and DMSO-d_6 using Tetramethylsilane (TMS) as an internal standard. The mass spectra were measured on a Liquid Chromatography / Mass Spectrometry (LCMS) Agilent mass spectrometer. The IR spectra were recorded on a Nicolet 740 Fourier transform infrared (FTIR) spectrometer. The temperature of the reaction mixture was measured through a non-contact

infrared thermometer (AZ, Mini Gun Type, Model 8868).

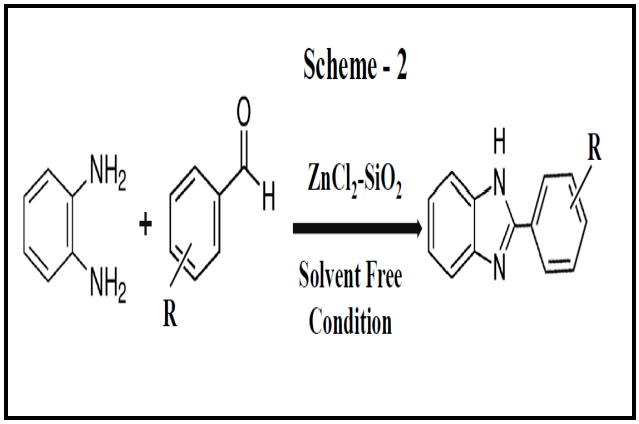
General Procedure

Mixtures of *o*-phenylenediamine (2 mmol: 216 mg) add various aldehyde (2 mmol) and Zinc chloride (5mmol) was stirred magnetically at room temperature and the progress of the reaction was monitored by thin-layer chromatography (TLC). The reaction mixture was filtered and extracted with ethyl acetates (3x30ml). The combined ethyl acetates extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure to give pure in excellent yields. In all the cases, the product obtained after the usual work up gave satisfactory spectral data.

RESULTS AND DISCUSSION

In connection with our studies on synthesis of organic compounds, we have now found that silica chloride can be used as an efficient, safe and very cheap catalyst for the condensation of *o*-phenylenediamine and various aldehydes under solvent-free conditions to afford benzimidazole derivatives in good to excellent yields (Scheme 2). Silica chloride is a strong solid acid so that it can decrease the energy of transition state of the nucleophilic attack step. The two possible tautomeric forms of benzimidazole (and of those of its derivatives possessing a plane of symmetry) are identical and a definite assignment of structure is possible.

Scheme 2: Synthesis of Benzimidazoles using silica chloride.



A solvent-free reaction obviously reduces pollution, and brings down handling costs due to simplification of experimental procedure, work up technique and saving in labor. These would be especially important during industrial production. Interest in the environmental control of chemical processes has increased remarkably during three decades ago (Over the past three decades) as a response to public concern about the use of hazardous chemicals. Therefore, to improve the effectiveness of this method in preventing chemical waste, it is important to investigate its optimal conditions. For establishing the simple and suitable conditions to prepare benzimidazole derivatives using SiO_2-Cl as a solid acid catalyst, the treatment *o*-phenylenediamine and various aldehyde under solvent-free conditions was chosen as a model reaction. At first, we found that in the absence of the catalyst, the reaction did not proceed even at a high temperature. After examining the various amounts of SiO_2-Cl according to Table 1, it was found that the condensation reaction can be efficiently carried out by adding 4 mmol% of the catalyst at 45°C under solvent-free conditions in a short time span of 8 min. The use of excessive amounts of the catalyst does not increase the yield and reaction rate.

Table 1: Synthesis of 1*H*-benzimidazole catalyzed with various amounts of SiO_2-Cl under solvent-free conditions at 45°C.

ENTRY	CATALYST (mmol)	TIME (Min.)	≠YIELD (%)
1	-	80	10.00 ± 1.0
2	1	40	70.33 ± 1.53
3	2	20	81.00 ± 1.73
4	3	10	90.33 ± 1.53
5	4	8	94.33 ± 0.56
6	5	8	94.00 ± 1.00
7	6	8	95.33 ± 0.57

≠Each Value is mean of three.

To optimize the reaction condition, the reaction of benzaldehyde and *o*-phenyldiamine was selected as model to investigate the effects of the catalyst at different temperature on the yield. The best result was obtained by carrying out the reaction at 45 under solvent-free condition and under this condition was obtained in 94.17% yield after 8 min (Table 2, compound A).

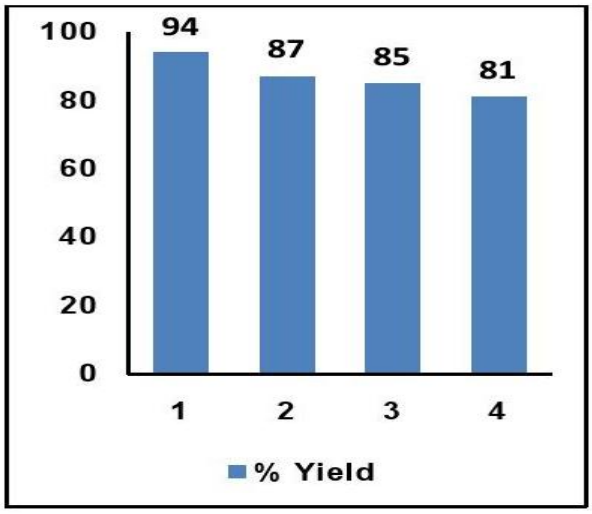
Table 2: Synthesis of 1*H*-benzimidazole catalyzed with SiO_2-Cl (4 mmol %) at several temperatures under solvent-free conditions.

ENTRY	TEMP (°C)	TIME (Min.)	≠YIELD (%)
1	25	300	11.50 ± 1.50
2	30	232	24.00 ± 1.32
3	35	150	54.00 ± 1.00
4	40	50	73.67 ± 1.53
5	45	8	94.17 ± 1.04
6	55	5	94.83 ± 1.26

≠Each Value is mean of three.

In order to prove the versatility of this method, after optimizing the reaction conditions, we have treated different types of aldehydes with *o*-phenylenediamine under solvent-free and thermal conditions. The results are summarized in Table 3 and Spectral data analysis. Not only the ecological profile (through helping to decrease hazardous industrial waste), but also the economic profile (through the elimination of expensive organic solvent) is further improved if the catalyst is recyclable and reaction conditions are solvent-free. In this process, as indicated in Figure 1, the recycled catalyst was used for four cycles during which a little appreciable loss was observed in the catalytic activities. A plausible mechanism for the reaction is supposed, The Si—Cl bond is liable and can give rise to Lewis acid centers on silica. The Cl is easily displaced selectively by aldehyde by a nucleophilic substitution reaction generating a cationic center on the oxygen which makes a living group on aldehyde and cationic center that subsequently is easily attacked by the nitrogen of *o*-phenylenediamine which cyclizes intramolecularly in the presence of silica chloride to form benzimidazole.

Figure 1: Recyclability of SiO_2-Cl as catalyst for the synthesis of under solvent-free conditions at 45°C. Reaction time: 8 min.



SPECTRAL DATA:

A. 2-phenyl-1*H*-benzoimidazole: Solid; Molecular formula:$C_{13}H_{10}N_2$; Yield-94%; M.P.-295 °C; ^{1}H NMR: δ6.06(bs, 1H, NH), 6.82(d, 2H, aromatic), 6.98(d,2H, aromatic), 7.06(t,1H, aromatic), 7.28(m, 2H,aromatic), 7.52(m, 2H, aromatic); IR (KBr): 3426(N-H), 3042(Ar-CH), 1631(C = N) cm^{-1}; Mass (LCMS) *m/z* 195 (M + H).

B. 2-(4-chlorophenyl)-1*H*-benzimidazole: Solid; Molecular formula:$C_{13}H_9N_2Cl$; Yield-83%; M.P.-251°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ /ppm): 12.55 (br s, -NH), 8.14 (d, 2H), 7.61 (m, 1H), 7.23-7.28 (m, 3H), 7.12-7.04 (m 2H); IR (KBr): 3053 (NH),1682 (C=N), 755(C-Cl) cm^{-1}; Mass (LCMS) *m/z*: 229.0 (M+1).

C. 2-(2-Flurophenyl)-1*H*-benzimidazole: Solid; Molecular formula:$C_{13}H_9N_2F$; Yield-90%; M.P.-260°C; ^{1}H NMR (400 MHz, DMSO-d_6, δ /ppm): 12.98 (s, 1H, -NH), 8.05 (d, J = 8.50 Hz, 2H), 7.29(m, 4H), 7.17 (m, 1H); IR (KBr): 3447 (N-H), 1624 (C=N), 1096(C-F) cm^{-1}; Mass (LCMS) *m/z:* 213 (M+).

D. 2-(4-Bromophenyl)-1*H*-benzimidazole: Solid, Molecular formula:$C_{13}H_9N_2Br$; Yield-89%; M.P.-289°C; ^{1}H-NMR (300 MHz, DMSO-*d6*, *δ*/ppm): 7.22–7.29 (2H, *m*, aromatic), 7.33–7.44 (6H, *m*, aromatic), 12.89 (1H, *bs*, NH); IR (KBr): 1624 (C=N), 3415 (N-H), 589(C-Br) cm^{-1}; Mass (LCMS) *m/z*: 249[M+H]+.

E. 2-(4-nitrophenyl)-1*H*-benzimidazole: Solid; Molecular formula:$C_{13}H_9N_3O_2$; Yield-91%; M.P.-285°C; ^{1}H NMR(300 MHz, DMSO-d_6, *δ* /ppm): 7.25–7.40 (4H, *m*, aromatic), 7.67–7.80 (4H, *m*, aromatic), 12.89 (1H, *bs*, NH); IR (KBr): 3294(-NH), 3103(Ar-CH), 1184 (O-C), 1588(C=N) cm^{-1}; Mass (LCMS) *m/z:* 225 (M +H).

F. 2-(4-hydroxyphenyl)-1*H*-benzimidazole: Solid; Molecular formula:$C_{13}H_{10}N_2O$; Yield- 82%, M.P.-271°C; ^{1}HNMR: δ 6.06(bs, 1H, NH), 6.82(d, 2H, aromatic), 6.98(d,2H, aromatic), 7.21(d,2H, aromatic), 7.52(d,2H, aromatic); IR (KBr): 3379(-NH), 3211(O-H), 3078(Ar-CH), 1461(C = N) cm^{-1}; Mass (LCMS) *m/z: 2*11 (M + H).

G. 2-(4-Methylphenyl)-1*H*-benzimidazole: Light Yellow Crystal; Molecular formula:$C_{14}H_{12}N_2$; Yield-93%; M.P.-234°C; ^{1}H NMR (400 MHz, DMSO-d_6, *δ* /ppm): 12.83 (s, 1H), 8.07 (d, 2H, *J* = 8.1 Hz), 7.64(s, 1H), 7.52 (s, 1H), 7.36 (d, 2H, *J* = 7.9 Hz), 7.20 (s, 2H), 2.38 (s, 3H) ; IR (KBr): 3294(N-H), 3103(Ar-CH), 1184 (O-C), 1588(C=N) cm^{-1}; Mass (LCMS) *m/z*: 209[M+H]+.

H. 2-(4-methoxyphenyl)-1*H*-benzimidazole: Solid; Molecular formula:$C_{14}H_{12}N_2O$; Yield-92%; M.P.-256°C; ^{1}H NMR (DMSO-d_6, *δ* /ppm): 13.5 (br s, 1H), 8.29 (d, J= 7.2 Hz, 1H), 7.76-7.74 (m, 2H), 7.63-7.59 (m, 1H), 7.39-7.32 (m,3H), 7.22-7.18 (m, 1H), 4.06 (s, 3H); Mass (LCMS) m*/z:* 225.07 [M+H].

I. 2-(2-Furyl)-1*H*-benzimidazole: Solid; Molecular formula:$C_{11}H_8N_2O$; Yield-92%; M.P.-290 °C; ^{1}H NMR (300 MHz, DMSO-d_6, *δ* /ppm): 6.78 (2H, *s*, aromatic), 7.50 (1H, *s*, aromatic), 7.60–7.70 (4H, *m*, aromatic), 12.89 (1H, *bs*, NH); IR (KBr): 1625 (C=N), 3425 (NH) cm^{-1}; Mass (LCMS) *m/z:* 213 (M + H).

J. 2-(Thiophene-2yl)-1*H*-benzimidazole: Solid; Molecular formula: $C_{11}H_8N_2S$; Yield-90%; M.P.-328°C; ^{1}H NMR (300 MHz, DMSO-d_6, *δ* /ppm): 7.15–7.22(3H, *m*, aromatic), 7.52–7.61(2H, *m*, aromatic), 7.79–7.86(2H, *m*, aromatic), 12.97 (1H, *bs*, NH); IR (KBr, cm-1): 1624 (C=N), 3445 (NH) cm^{-1}; Mass (LCMS) *m/z:* 197 (M + H).

K. 2-(Pyridin-3-yl)-1*H*-benzimidazole: Solid; Molecular formula: $C_{12}H_{10}N_3$; Yield-91%, M.P.-247°C; ^{1}H NMR (200 MHz, DMSO, δ ppm): 13.05 (s, 1H, NH), 9.35 (d, 1H, *J*=8.2 Hz, C2′-H), 8.75 (d,1H, *J*=1.8 Hz, C6′-H), 8.60 (m, 1H, C4′-H), 7.70 (m, 3H, C4-H, C7-H, C5′-H), 7.40 (m,2H, C5-H, C6-H); IR(KBr):3068, 1449, 1402,1280, 746 cm^{-1}; Mass (LCMS) *m/z:* 194 (M+H).

L. 2-(2-Naphthyl)-1*H*-benzimidazole: Solid; Molecular formula:$C_{17}H_{15}N_2$; Yield-93%, M.P.-265°C, ^{1}H NMR(400 MHz, DMSO-d_6, *δ* /ppm): 11.86 (s, 1H, -NH), 8.75 (brs, 1H), 8.39 (dd, 1H, *J* =8.0 & 2.2 Hz), 8.02-790 (m, 3H), 7.26 (m, 2H, Ar-H); IR (KBr,): 1659□(C=N) 3426(N-H), 3052(Ar-CH), cm^{-1}; Mass (LCMS) *m/z:* 245 (M+1).

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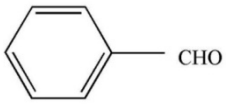
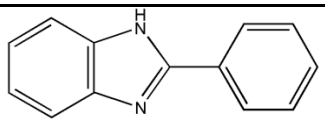
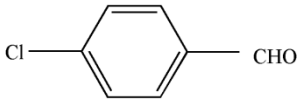
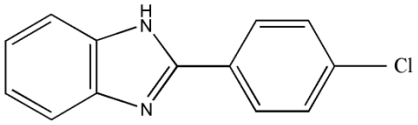
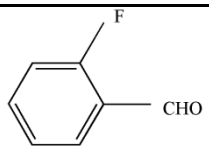
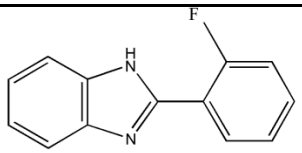
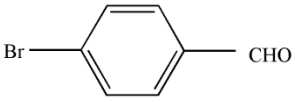
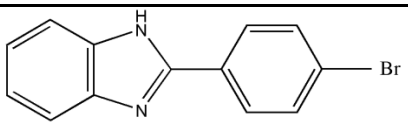
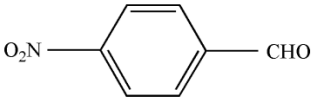
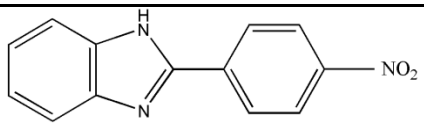
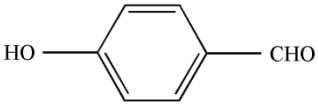
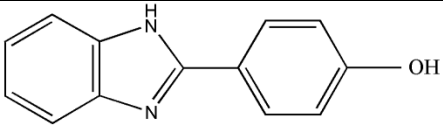
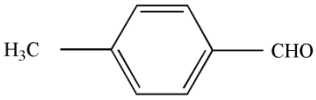
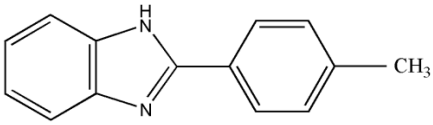
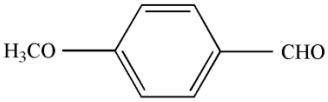
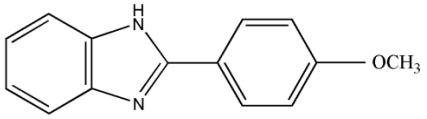
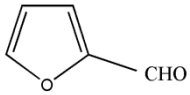
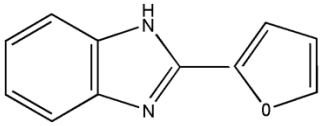
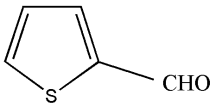
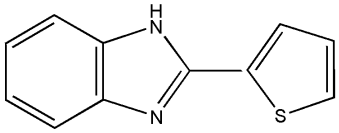
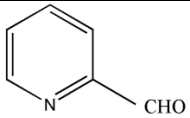
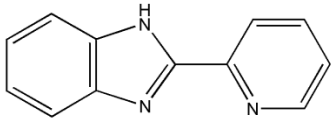
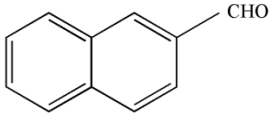
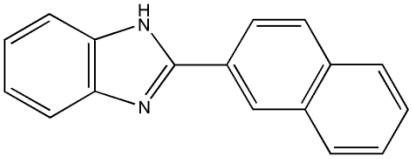
CONCLUSION

In conclusion, this work describes a method in which Zinc chloride is a highly efficient catalyst for the synthesis of benzimidazole derivatives. The advantages include low cost, ease of catalyst handling, mild reaction conditions and reactions carried out at room temperature with excellent yields.

ENTRY	ALDEHYDE	PRODUCT	YIELD (%)
1			94
2			83
3			90
4			89
5			91
6			82
7			93
8			92
9			92
10			90
11			91
12			93

REFERENCES

1. Rathee PS, Dhankar R, Bhardwaj S, Gupta M, Rakesh Kumar, "Synthesis and antimicrobial studies of substituted 2-phenylbenzimidazole derivatives". J. Appl. Pharm. Sci., 2011, 1(10), 140-142.
2. Nakano H, Inoue T, Kawasaki N, Miyataka H, Matsumoto H, Taguchi T, Inagaki N, Nagai H, Satoh T, "Synthesis of benzimidazole derivatives as antiallergic agents with 5-lipoxygenase inhibiting action". Chem Pharm Bull, 1999, 47(11), 1573-1578.
3. Fonseca T, Gigante B, Marques MM, Gilchrist TL, Clercq ED, "Sythesis and antiviral evaluation of benzimidazoles, quinoxalines and indoles from dehydroabietc acid", Bioorg. Med. Chem., 2004, 12, 103-112.
4. Vazquez GN, Yepez L, Campos AH, Tapia A, Luis FH, Cedillo R, Gonzalez J, Fernandez AM, Grueiro MM, Castillo R, "Synthesis and Antiparasitic Activity of Albendazole and Mebendazole Analogues", Bioorg. Med. Chem., 2003, 1, 4615–4622.
5. Serafin B, Borkowska G, Główczyk J, Kowalska I, Rump S, "Potential antihypertensive benzimidazole derivatives". Pol J Pharmacol Pharm, 1989, 41(1), 89-96.
6. Bethke T, Brunkhorst D, von der Leyen H, Meyer W, Nigbur R, Scholz H, "Mechanism of action and cardiotonic activity of a new phosphodiesterase inhibitor, the benzimidazole derivative adibendan (BM 14.478), in guinea-pig hearts", Arch Pharmacol, 1988, 337(5), 576-582.
7. Khan FR, Asnani AJ, "Synthesis and Antiulcer, Anti-secretory Activity of Some New substituted 2-(Pyrimidinylsulfinyl) Benzamidazoles Derivatives", Int. J. Res. Pharm. Biomed. Sci., 2011, 2(2), 695-700.
8. Al-Douh MH, Sahib HB, Osman H, Hamid SA, Salhimi SM, "Anti-Proliferation Effects of Benzimidazole Derivatives on HCT-116 Colon Cancer and MCF-7 Breast Cancer Cell Lines", Asian Pacific J Cancer Prev, 2012, 13, 4075-4079.
9. Lazer ES, Matteo MR, Possanza GJ, "Benzimidazole derivatives with atypical antiinflammatory activity", J Med Chem, 1987, 30(4), 726-729.
10. Aydin S, Beis R, Can OD, "Analgesic and antispasmodic activities of 2-(2-nitro-phenyl)-1H-benzimidazole 5-carboxylic acid: evidence for the importance of the 2-(o-substituted phenyl) group", Pharmazie, 2003, 58(6), 405-408.
11. Ateş-Alagöz Z, Kuş C, Coban T, "Synthesis and antioxidant properties of novel benzimidazoles containing substituted indole or 1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene fragments", J Enzyme Inhib Med Che., 2005, 20(4), 325-331.
12. Kazimierczuk Z, Upcroft JA, Upcroft P, Górska A, Starościak B, Laudy A, "Synthesis, antiprotozoal and antibacterial activity of nitro- and halogeno-substituted benzimidazole derivatives". Acta Biochim Pol, 2002, 49(1), 185-195.
13. Vinodkumar R, Vaidya SD, SivaKumar BV, Bhise UN, Bhirud SB, Mashelkarb UC, "Synthesis, anti-bacterial, anti-asthmatic and anti-diabetic activities of novel N-substituted 2-(4-styrylphenyl)-1H-benzimidazole and N-substituted-3[4-(1H-benzimidazole-2-yl)-phenyl]-acrylic acid tert-butyl ester". ARKIVOC, 2008, xi(v), 37-49.
14. Pashinski VG, Romanova TV, Mukhina NA, Shkrabova LV, Tetenchuk KP, "Diuretic activity of benzimidazole urea derivatives", Farmakol Toksikol, 1978, 41(2), 196-199.
15. Ng RA, Guan J, Alford VC, Lanter JC, Allan GF, Sbriscia T, Linton O, Lundeen SG, Sui Z, "Synthesis and SAR of potent and selective androgen receptor antagonists: 5,6-Dichloro-benzimidazole derivatives", Bioorg Med Chem Lett, 2007, 17(3), 784-788.
16. Bhrigu B, Siddiqui N, Pathak D, Alam MS, Ali R, Azad B, "Anticonvulsant Evaluation of Some Newer Benzimidazole Derivatives:

Design And Synthesis, Acta Pol. Pharm., 2012, 69(1), 53-62.

17. Yadagiri B, Lown JW, "Convenient Routes to Substituted Benzimidazoles and Imidazolo[4,5-b]pyridines Using Nitrobenzene as Oxidant", Synth. Commun., 1990, 20(7), 955-963.
18. Sajjadifar S, Mirshokraie SA, Javaherneshan N, Louie O, "SBSA as a New and Efficient Catalyst for the One-Pot Green Synthesis of Benzimidazole Derivatives at Room Temperature", American Journal of Organic Chemistry, 2012, 2(2), 1-6.
19. Nagawade RR, Shinde DB, "$BF_3.OEt_2$ Promoted Solvent-free Synthesis of Benzimidazole Derivatives". Chin. Chem. Lett., 2006, 17(4), 453-456.
20. Guruswamy B, Arul RA, "Micro-wave assisted synthesis of Benzimidazole derivatives using solid support", Der Pharma Chemica, 2011, 3(6), 483-486.
21. Monajjemi M, Sheikhi M, Hashemi MM, Molaamin F, Zhiani R, "NMR and NBO calculation of benzimidazoles and pyrimidines: Nano physical parameters investigation", Int. J. Phys. Sci., 2010, 7(13), 2010-2031.
22. López SE, Restrepo J, Pérez B, Ortiz S, Salazar J, "One Pot Microwave Promoted Synthesis of 2-Aryl-1H-Benzimidazoles Using Sodium Hydrogen Sulfite", Bull. Korean Chem. Soc., 2009, 30(7), 1628-1630.
23. Boroujeni KP, Zhianinasab A, Jafarinasab M, "Polystyrene-supported pyridinium chloroaluminate ionic liquid as a new heterogeneous Lewis acid catalyst for selective synthesis of benzimidazoles". J. Serb. Chem. Soc., 2012, 77, 1-17.
24. Rajeshkumar, Joshi YC, "Mild and Efficient One Pot Synthesis of Imidazolines and Benzimidazoles from Aldehydes", E-J. Chem., 2007, 4(4), 606-610.
25. Xiangming H, Huiqiang M, Yulu W, "p-TsOH Catalyzed synthesis of 2-arylsubstituted benzimidazoles". ARKIVOK, 2007, xiii, 150-154.
26. RaviKumar K, Satyanarayan PVV, Reddy BS, "$NaHSO_4$-SiO_2 promoted synthesis of Benzimidazole derivatives", Arch. Appl. Sci. Res., 2012, 4(3), 1517-1521.
27. Chen GF, Dong XY, "Facile and Selective Synthesis of 2-Substituted Benzimidazoles Catalyzed by $FeCl_3/Al_2O_3$". E-J. Chem., 2012, 9(1), 289-293.
28. Kiumars B, Mohammad MK, Iman K, "H_2O_2/HCl as a new and efficient system for synthesis of 2-substituted benzimidazoles", J. Chem. Res., 2006, 12(2), 783-784.
29. Akbar M, Naser F, Mojgan Z, Mahsa J, "Conversion of Aldehydes to Benzimidazoles using NaY Zeolite. Synth. React. Inorg., Met.-Org., Nano-Met. Chem. 2008, 38(4), 390-393.
30. Fazlinia A, Mosslemin MH, Sadoughi H, "An Efficient Procedure for the Synthesis of Benzimidazoles Using H_2O_2/SiO_2-$FeCl_3$ System", J. Korean Chem. Soc., 2010, 54(5), 579-581.
31. Chandrachood PS, Garud DR, et al. "A Cobalt Nitrate/Hydrogen Peroxide System as an Efficient Reagent for the Synthesis of 2-Aryl Benzimidazoles and Benzothiazoles", Acta Chim. Slov., 2011, 58, 367-371.
32. Borhade AV Tope, DR, Patil DR. An efficient synthesis of Benzimidazole by cyclization–oxidation processes using Fe/MgO as a heterogeneous recyclable catalyst. J. Chem. Pharm. Res. 2012, 4(5), 2501-2506.
33. Kidwai M, Jahan A, Bhatnagar D, "Polyethylene glycol: A recyclable solvent system for the synthesis of benzimidazole derivatives using CAN as catalyst", J. Chem. Sci., 2010, 122(4), 607-612.
34. Patila PP, Deshmukh MB, et al. "An Efficient, Greener synthesis of 2-Aryl-1-Arylmethyl-1HBenzimidazoles using Polystyrene Sulfonic acid as a Catalyst", Der Pharma Chemica, 2011, 3(6), 599-605.

35. Shelke KF, Sapkal SB, Kakade GK, Shinde PV, Shingate BB, Shingare MS, "Boric acid as an efficient catalyst for the synthesis of 1,1-diacetate under solvent-free condition", Chin. Chem. Lett., 2009, 20, 1453-1456.

36. Nagawade RR, Shinde DB, "$BF_3.OEt_2$ Promoted Solvent-free Synthesis of Benzimidazole Derivatives" Chin. Chem. Lett., 2006, 17(4), 453-456.

37. Forouzani M, Bosra HG, "1,3-Dibromo 5,5-dimethylhydantoin (DBH)-Catalyzed Solvent-Free Synthesis of 2-arylbenzimidazoles under Microwave Irradiation" E-J. Chem., 2012, 9(3), 1064-1069.

38. Nannapaneni DT, Gupta AV, SSS, Reddy MI, Sarva RC, "Synthesis, Characterization, and Biological Evaluation of Benzimidazole Derivatives as Potential Anxiolytics" J Young Pharm, 2010, 2(3), 273-279.

