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$ZnCl_2$-SiO_2 Catalyzed solvent free synthesis of Benzimidazole derivatives under Microwave irradiation.

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ABSTRACT

An expeditious synthesis of Synthesis of Various benzimidazole derivatives under micro-wave irradiation from simple and substituted ortho phenylenediamines (OPDA) with various arylaldehydes using zncl$_2$/ sio$_2$ as catalyst is described and proceeds efficiently in the absence of organic solvent under thermal condition and microwave irradiation with high yields. The structure of synthesized compounds have been established on the basis of spectral and analytical data.

Keywords: Benzimidazole , OPD, $ZnCl_2$, Silicon Dioxide, Solvent Free.

INTRODUCTION

Benzimidazole is a heterocyclic aromatic organic compound having imidazole ring fused with benzene. The most prominent benzimidazole compound in nature is N-ribosyl-dimethyl benzimidazole, which serves as an axial ligand for cobalt in vitamin B12. Extensive biochemical and pharmacological studies have confirmed that benzimidazole molecules are effective against various strains of microorganisms[1,2]. Benzimidazoles are regarded as a promising class of bioactive heterocyclic compounds that exhibit a range of biological activities. Specifically, its derivatives possessed various biological activities such as antioxidant, antiparasitic, antihelmintics, antiproliferative, anti-HIV, anticonvulsant, anti-inflammatory, antihypertensive, antineoplastic, analgesic, and antitrichinellosis activities. Owing to the immense importance and varied bioactivities exhibited by benzimidazoles, efforts have been made from time to time to generate libraries of these compounds and screened them for potential biological activities[3].

These methods for the synthesis of benzimidazole derivatives include the coupling of o-phenylenediamine with aldehydes or β-keto ester or carboxylic acid in presence of various catalysts like CAN[4], p-TsOH[5], $NaHSO_4{\cdot}SiO_2$[6], $Fecl_3/Al_2O_3$[7], PS-PyCl-$XAlCl_3$[8], T-(o-Cl)PPFe^{III} Cl^b , $FeCl_3{\cdot}SiO_2$[9]: $Co(NO_3)_2/H_2O_2$, $Ni(NO_3)_2/H_2O_2$[10]; Fe/MgO, sulfamic acid[11]; $Yb(OTf)_3$, $Sc(OTf)_3$, $KHSO_4$, $HfCl_4$, $H_2O_2{\cdot}HCl$, $FeBr_3$[12]; oxalic acid, L-preline, glyoxalic acid, SDS[13], *N*- halosuccinamide (X = Cl, Br, I)[13]; 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 boric acid[14], Bf_3OEt_2[15], SABA[16], PSSA[13],DBH[17], ammonium salts[18], glycerol[19], sulfonic acid functionalized silica (SiO_2-Pr-SO_3H)[20], P_2O_5-SiO_2[21], K_4[Fe(CN)6][22], TsOH-SiO_2[8], $Zn(OAc)_2$[23], $FePO_4$[24], TBAF[25] have been used for solvent free methods.

In recent years, solvent-free synthesis of Benzimidazole under microwave irradiation using $Yb(OTf)_3$, KSF clay, PPA, Na_2SO_4, K-10 clay[16], metal halide supported alumina[15], $H_2SO_4SiO_2$[26], AMA[27] $NaHSo_3$[28], Amberlite IR-120[8] and have been reported. The application of MW irradiation as a non-conventional energy source for the activation of reactions has now become a very popular and useful technology in organic chemistry. Moreover, the combination of MW activation and solvent-free conditions leads to enhanced conversion rates, higher yields, and easier work-up and in general cleaner reactions confirming therefore the real advantages of this approach in the framework of green chemistry[29]. In the present work, Benzimidazole derivatives were prepared by microwave irradiation technique using $ZnCl_2$-SiO_2 as catalyst.

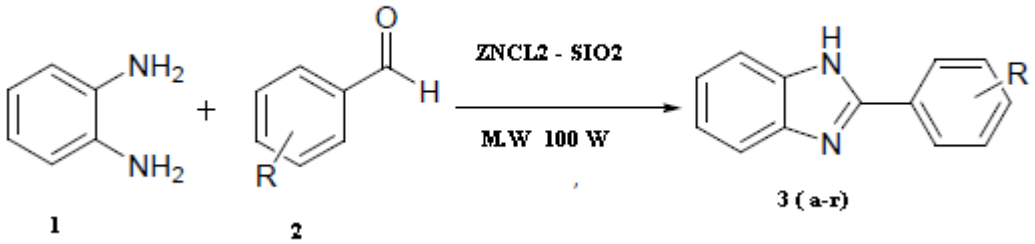
MATERIALS AND METHODS

All the reactions were carried out using a conventional (unmodified) microwave oven (LG, 230 V, ~50 Hz). Melting points are recorded and were obtained in Polmon MP 96. TLC checking was done on using aluminium plates coated with silica gel (Merck) using 20% ethylacetate,80% petroleum ether as an eluent. supplied by Merck & Co., and spotting was done using iodine or UV lamp .The synthesized compounds were analyzed by NMR, Mass, and IR spectroscopy. H NMR spectra were recorded on a Varian Gemini 200- and 400-MHz instrument in CDCl and DMSO-d6 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.

Preparation of $ZnCl_2$ - SiO_2: $ZnCl_2$(12.5 m.mol) was added to the suspension of silica gel (23.5 g, 230-400 mesh) in diethyl ether. The mixture was concentrated and the residue heated at 100 °C for 72 hours under vacuum to afford $ZnCl_2$ -SiO_2 as a free flowing powder.

General procedure for the Synthesis of simple and substituted benzimidazole derivatives : Ortho phenylene diamine (1.0mmol) and various different types of aldehydes was adsorbed on $ZnCl_2$-SiO_2 (2.00mmol) and transferred in to a microwave vial. The vial was sealed and placed in microwave. The reaction was run at 80 °C for 5 min. For the entire experiment, the power setting was held at 100 W. After the completion of reaction, the reaction mixture was cooled to room temperature and purified by SiO_2 gel column chromatography with hexane: EtOAc (90:10%) to get the substituted benzimidazoles.

Scheme-1



1 2 3 (a-r)

SPECTRAL DATA

1. 2-phenyl-1H-benzo[*d*]imidazole: Solid; Molecular formula: $C_{13}H_{10}N_2$, Y ield-94%, m.p-296 °c; 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(-NH), 3042(Ar-CH), 1742, 1631(-C = N) cm ;Mass (LCMS): *m/z* 195 (M + H)

2. 4-hydroxyphenyl-1H-benzimidazole : Solid; Molecular formula:$C_{13}H_{10}N_2O$, Yield - 78%, m.p-271 °c; 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(-OH), 3078(-Ar-CH), 1461(C = N) cm-1; Mass (LCMS):*m/z 2*11 (M + H).

3. 2-thiophene-2yl-1H-benzoimidazole : solid, molecular formula $C_{11}H_8N_2S$, Yield - 90%, m.p. 328 °C (Lit.30 330 °C); IR (KBr, cm-1): 1624 (C=N), 3445 (NH); 1H-NMR (300 MHz, DMSO-*d6*, *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), Mass (LCMS):*m/z 197* (M + H).

4. 2-Furan-2-yl-1H-benzoimidazole**:** solid, molecular formula $C_{11}H_8N_2F$, Yield - 95%, m.p. 290 °C (Lit.36 287–288 °C); IR (KBr, cm-1): 1625 (C=N), 3425 (NH); 1H-NMR (300 MHz, DMSO-*d6*, *δ* / ppm): 6.78 (2H, *s*, aromatic), 7.50 (1H, *s*, aromatic), 7.60–7.70 (4H, *m*, aromatic), 12.89 (1H, *bs*, NH) Mass (LCMS):*m/z 213* (M + H).

5. 2-(3-nitrophenyl)-1H-benzimidazole Solid; Molecular formula:$C_{13}H_9N_3O_2$, Yield -95%, m.p-285 °c;1H-NMR (300 MHz, DMSO-*d6*, *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 (-OCH), 1588(-C=N) cm-1; Mass (LCMS): *m/z* 225 (M +H).

6. 2-(3-methoxyphenyl)-1H-benzo[*d*]imidazole :- Solid; Molecular formula:$C_{14}H_{12}N_2O$, Y ield -94%, m.p-256 °c 1H NMR (DMSO-d6): δ13.5 (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); (LC-MS) m*/z:* 225.07 [M+H]..

7. 2-(3-chlorophenyl)-1H-benzo[*d*]imidazole Y ield -85%, m.p-251 °c 1H NMR (400 MHz, DMSO-d6, *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), cm-1; Mass (LCMS): *m/z*: 229.0 (M+1), 231 (M+3);*Anal. Calcd* for $C_{13}H_9N_2Cl$: C, 68.28; H, 3.97; N, 12.25.Found: C, 68.40; H, 3.89; N, 12.48%

8. 2-benzyl-1H-benzo[*d*]imidazole $C_{14}H_{12}N_2$ 2 Y ield -93% m.p. 186 °C ; IR (KBr, cm-1): 1623 (C=N), 3427 (NH); 1H-NMR (300 MHz, DMSO-*d6*, *δ* / ppm): 4.20 (2H, *s*, - CH2-), 7.17–7.20 (2H, *d*, aromatic, *J* = 7.3 Hz), 7.25–7.27 (1H, *m*, aromatic), 7.36–7.41 (4H, *m*, aromatic), 7.45–7.47 (1H, *d*, aromatic, *J* = 6.4 Hz), 7.55–7.57 (1H, *d*, aromatic, *J* = 8.9 Hz), 12.27 (1H, *bs*, NH). (LC-MS) m*/z:* 209.10 [M+H]+

9. 2-(2-flurophenyl)-1H-benzo[*d*]imidazole :- Y ield -96% m.p. 260°C 1H NMR (400 MHz, DMSO-d6, *δ* ppm): 12.98 (s, 1H, -NH), 8.05 (d, *J* = 8.50 Hz, 2H), 7.29(m, 4H), 7.17 (m, 1H); Mass (LCMS): *m/z* = 213 (M+); IR (KBr,cm-1): 3447 (NH), 1624 (C=N); *Anal. Calcd* $C_{13}H_9FN_2$: C,73.57; H, 4.27; N, 13.20. Found: C, 73.92; H, 4.48; N,13.19%.

10. ***2-(2-Naphthyl)-1H-benzimidazole)*** Yield -94% m.p. 265 °C 1H NMR (400 MHz, DMSO-d6, *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); Mass (LCMS): *m/z* = 245 (M+1); IR (KBr, cm-1): 3055, 2925, 1654(C=N), *Anal. Calcd* for $C_{13}H_9FN_2$: C, 83.61; H, 4.92; N,11.47; Found: C, 83.87; H, 4.88; N, 11.01%.

11. 2-Pyridin-3-yl-1H-benzimidazole :- Molecular formula :$C_{12}H_9N_3$ Yield -95% mp 247oC; IR (KBr) : 3068, 1449, 1402,1280, 746 cm-1; Mass (LCMS): *m/z* 194 (M-H, 100 %); 1H-NMR spectrum (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); 13C-NMR (50 MHz, CD3OD, δ ppm): 112.1, 119.2, 121.3, 121.7,123.1, 124.5, 134.9, 137.3, 143.8, 148.5, 149.2, 150.7.

12. ***[2-(4'-Methylphenyl)benzimidazole*** Molecular formula $C_{14}H_{12}N_2$ Isolated as light yellow crystal. Yield -96% mp 234oC; 1H NMR _: 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) ; Mass (LCMS) *m/z*: 209[M+H]+. IR (KBr): 3294(-NH), 3103(Ar-CH), 1184 (-OCH), 1588(-C=N) cm-1.

13. ***2-Butyl-1H-benzimidazole*** *:* Molecular formula $C_{11}H_{14}N_2$ Yield -96% m.p. 151 °C (Lit.50 148–149 °C); IR (KBr, cm-1): 1630 (C=N), 3438 (NH); 1H-NMR (300 MHz, DMSO-*d6*, δ / ppm): 1.01–1.03 (3H, *t*, CH3, *J* = 7.3 Hz), 1.44–1.46 (2H, *m*, -CH2-, *J* = 7.0 Hz), 1.89–1.91 (2H, *m*, -CH2-, *J* = 7.0 Hz), 2.95–2.98 (2H, *t*, -CH2-, *J* = 7.0 Hz), 7.29–7.36 (4H, *m*, aromatic), 9.44 (1H, *bs*, NH). Mass (LCMS) *m/z*: 189[M+H]+.

14. ***2-(4-Bromophenyl)-1H-benzimidazole****:* Molecular formula $C_{13}H_9BrN_2$ Yield -94% mp: 289 °C; IR (KBr, cm-1): 1624 (C=N), 3415 (NH); 1H-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). Mass (LCMS) *m/z*: 249[M+H]+.

15. ***2-(2-Hydroxyphenyl)-1H-benzimidazole*** *:* Molecular formula $C_{13}H_{10}N_2O$ Yield -92% mp:243 °C ; IR (KBr, cm-1):1622 (C=N), 3245, 3350, 3410 (NH, OH); 1H-NMR (300 MHz, DMSO-*d6*, *δ* / ppm): 7.67–7.77 (4H, *m*, aromatic), 7.79–7.86 (3H, *m*, aromatic), 7.88 (1H, *s*, aromatic), 12.98 (2H, *bs*, NH, OH). Mass (LCMS) *m/z*: 208[M+H]+

RESULTS AND DISCUSSION

In our preliminarily investigation on the model reaction of *o*-phenylenediamine and benzaldehyde, it was found that the reaction could be finished under very simple reaction conditions in the presence of catalytic amount $ZnCl_2$ / SiO_2 in reflux of ethanol solvent, which gives the desired 2-phenyl benzimidazole product moderate yield in 8hr. When the same reaction was carried out under micro-wave irradiation in the presence of solid support $ZnCl_2$ / SiO_2 under solvent free condition for 5 to 8min, **3 (a-r)** obtained in high yields. This method seems to be the best choice among all conventional synthetic methodologies. We carried out the same reaction with various substituted aldehydes **(Table-I)**.

In brief, micro-wave assisted synthesis of benzimidazole derivatives in the presence of solid support has been studied. The best results are obtained under micro-wave irradiation technique.

Table1: Synthesis of substituted benzimidazoles under microwave irradiation

ENTRY	PRODUCT	R	TIME/%YIELDS	M.P
1	3a	H	(5min/94)	296 ^oC
2	3b	4-OH	(7min/78)	271^oC
4	3c	2-thiophenealdehyde	(8min/90)	328^oC
3	3d	Furfural	(6min/95)	290^oC
6	3e	3-NO2	(6min/95)	285^oC
7	3f	3-OME	(7min/94)	256^oC
8	3g	3-CL	(6min/85)	251^oC
9	3h	2-Benzene	(8min/93)	186^oC
10	3i	2-F	(6min/96)	260^oC
11	3j	2-Naphtalene	(5min/94)	265^oC
12	3k	2-Pyridine	(5min/95)	247^oC
13	3l	4-methylphenol	(7min/96)	234^oC
14	3m	2-Butanol	(5min/96)	151^oC
15	3n	4-Br	(6min/94)	289^oC
16	3o	2-hydroxyphenol	(7min/92)	243^oC
17	3p	2-OME	(5min/89)	274^oC
18	3q	4-OME	(7min/91)	285^oC
19	3r	2-CL	(8min/85)	270^oC

APPLICATION

The benzimidazole derivatives is Prepared under solvent-free conditions using inexpensive reagents, short reaction times and easy workup procedure.

CONCLUSION

We have developed a simple and efficient method for the synthesis of benzimidazole derivatives using $ZnCl_2$ / SiO_2 as catalyst under solvent-free conditions. The notable advantages of this method are the experimental simplicity, inexpensive reagents, short reaction times and easy workup procedure.

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