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Ni-doped Zinc Oxide as an Effectual Catalyst for the Synthesis of Substituted Benzimidazoles from o-Phenylene Diamine and Aldehydes at Room Temperature and their Biological Activity

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Abstract: *Ni-doped Zinc oxide has been used as a reusable green catalyst in the search for a more environmentally friendly way to synthesize substituted Benzimidazoles. At normal temperature, a reaction between 1, 2-diamine and a suitable aldehyde yielded several substituted benzimidazole moieties. The reaction is carried out in an agate pestle mortar under solvent-free, moderate conditions, yielding a high yield (90-99 percent) in a much shorter time (3-8 min.). The formation of the chosen product was verified by spectral data and physical constants. Antimicrobial activity of synthesized benzimidazoles was also tested, and they were shown to be considerably active against a variety of gram positive and gram negative bacteria, as well as certain fungi.*

Keywords: Solvent free, Ni-doped ZnO Catalyst, Short reaction time, Benzimidazole, o-phenylene diamine, Aromatic aldehydes, green synthesis, antimicrobial activity.

I. INTRODUCTION

Structures comprising substituted benzimidazole derivatives are quite important in veterinary medicine and offer a variety of biological features such as antihypertensive, anticancer, antifungal, and so on [1]. The benzimidazole nucleus is found in the majority of natural products as well as pharmacologically active chemicals [2]. It has a wide range of biological and pharmacological effects [3-14]. The synthesis of substituted benzimidazoles has received a lot of attention due to their intriguing pharmacological characteristics. Several synthetic approaches have been described in the literature [15-20].

Zinc oxide (ZnO) is an inorganic compound with a white powder that is insoluble in water. It is made synthetically. According to several research, zinc oxide is an effective catalyst in organic synthesis. It demonstrates exceptional activity, particularly in the synthesis of heterocycles. Cu-doped zinc oxide has shown increased catalytic activity. D-block doping ions are the most frequent.

To achieve accessible chemical space that is not currently accessible by current techniques, the synthesis of new methodologies will be critical to the chemistry world. As a result, extensive research into diverse methods of synthesizing substituted benzimidazoles would be critical. Work proposed in several fields of research, primarily synthetic organic chemistry, catalysis, solid state chemistry and physics, microbiology & Nanochemistry.

II. MATERIALS AND METHODS

2.1 Chemicals and Instruments

The chemicals and solvents were acquired from commercial vendors such as Spectrochem and Avara, as well as Sigma-Aldrich, and were utilised without previous purification. The substances' IR absorption spectra were obtained using ATR on a Shimadzu IR-Afinity FTIR. The ^{1}H NMR spectra were obtained in Dimethyl sulfoxide using a Bruker AQS 300 Advance instrument at 300 MHz (DMSO-d6). TLC was used to monitor the reaction's development. GCMS spectra were collected using a Shimadzu GCMS-QP 1000 EX Gas Chromatography-MS system (GCMS-QP 1000 EX). X-ray diffraction methods were used to characterize the catalyst.

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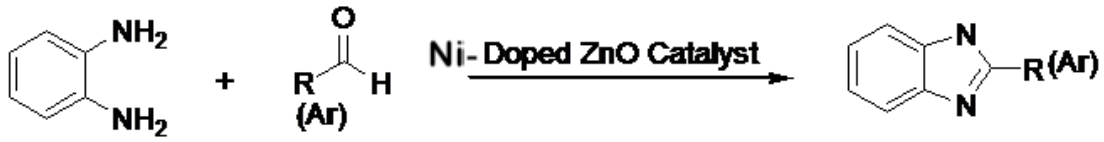
2.2 Synthesis of Catalyst

Different Cu- doped Zinc oxide catalysts with doping levels ranging from 2 to 5% were manufactured by dissolving a determined quantity of Zinc Acetate and Nickel Acetate in distilled water and sonicating for 15 minutes to create a homogeneous solution. The mixture was then hydrolyzed with liquid Ammonia. The resulting homogenous precipitate of zinc hydroxide and nickel hydroxide is filtered, dried, and calcined in a muffle furnace at 950 ºC. The synthesized catalyst was tested for catalytic activity.

2.3 Synthesis of Substituted Benzimidazoles:

Scheme



The reaction was carried out in a natural agate pestle mortar. A blend of substitutes 1,2–diamine (1mmole), catalyst (0.200gm) aldehyde (1mmole) crushed solvent free. After the reaction was completed, TLC (Ethyl acetate: Hexane (3:7) was used to monitor the development of the reaction. This response takes 10 minutes. The catalyst was recovered from the reaction mixture and may be utilized four to six times more for the subsequent reaction.

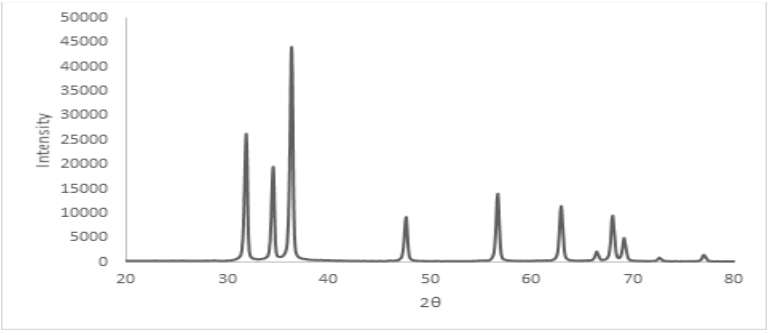
2.4 Microbial Study

The synthesized benzimidazoles derivatives were evaluated against two strains of Gram +ve bacteria (Bacillus subtils, Staphylococcus aureus), two strains of Gram –ve bacteria (Pseudomonas aeruginosa, Escherichia coli), Yeast (Candida albicans) and Fungi (Aspergillus Niger) [23]

III. Result and Discussion

3.1 Synthesis and Characterization of Catalyst

An XRD pattern was used to analyse a Ni-doped zinc oxide catalyst that was synthesized. The resulting XRD pattern fits the normal JCPDS card really well. The catalyst's composition was validated by qualitative and quantitative examination of Zn and nickel doping. The XRD shown is of 5% Ni doped ZnO.



3.2 Synthesis and Characterization of Substituted Benzimidazoles

Using a Ni-doped zinc oxide catalyst, a novel approach for the easy and quick synthesis of a range of biologically significant substituted benzimidazoles in high yields has been disclosed. Without a catalyst, the reaction yields less. This approach has been expanded to a range of aromatic aldehydes and 1,2-diamines mentioned in Table 1. Because it boosts the electrophilic nature of aromatic aldehydes towards the 1,2-diamine, the reaction is especially rapid for aldehydes containing electron withdrawing groups. The appearance of frequency in the product FTIR spectrum that corresponds to the C=N and N-H functional groups verifies the production of benzimidazoles.

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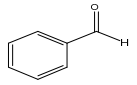
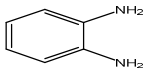
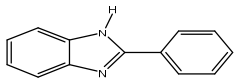
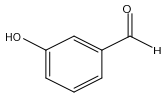
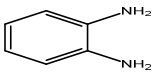
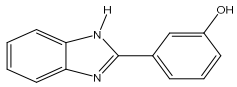
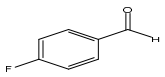
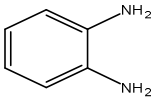
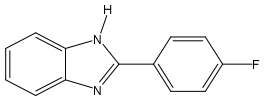
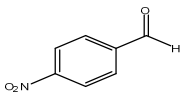
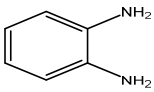
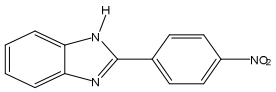
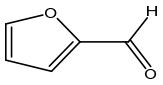
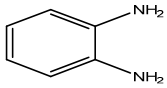
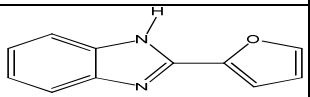
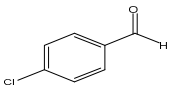
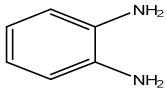
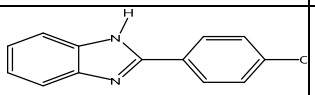
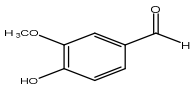
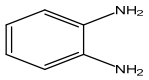
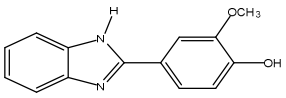
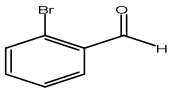
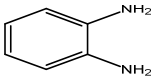
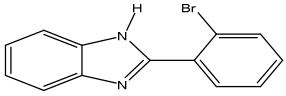
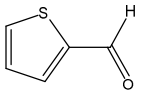
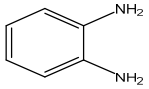
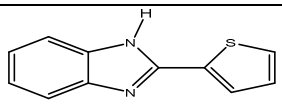
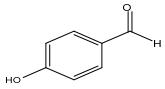
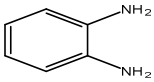
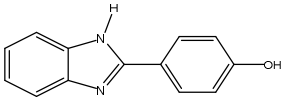
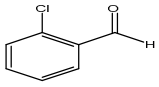
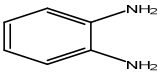
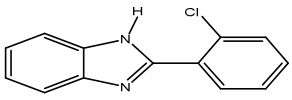
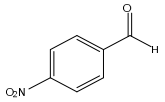
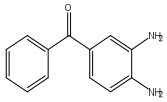
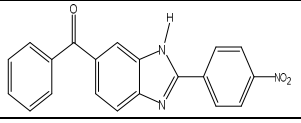
Table 1: Synthesis of 2-Substituted Benzimidazole derivatives

Sr. No.	Aldehyde	Diamine	Product	Average reaction time (min)	Yield (%)
P1				6 Minute	96%
P2				7 Minute	92%
P3				5 Minute	94%
P5				3 Minute	98%
P6				8 Minute	90%
P7				5 Minute	97%
P8				5 Minute	90%
P9				6 Minute	96%
P10				8 Minute	92%
P11				6 Minute	96%
P12				5 Minute	91%
P13				5 Minute	98%

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3.3 Antimicrobial activity of substituted Benzimidazoles

The inhibitory zones on the microorganism generated by the different manufactured substances were investigated. Table 2 shows the results of the screening biological tests. Compounds P3, P4, P5, P7, P9, P11, P12, and P13 were evaluated for antifungal and antibacterial activities. Compound P9 was shown to be significantly active against Bacillus subtillis and Escherichia coli, but only somewhat active against Aspergillus niger and nearly negligibly active against Pseudomonas aerginosa, according to the data below. P3 was discovered to be very effective against Staphylococcus aureus and Candida albicans. Except for P11, all of the investigated drugs were found to be inert against Pseudomonas aerginosa. Compound P5 was also shown to be inert against Pseudomonas aeruginosa, Escherichia coli, and Candida albicans. Comp P5 was discovered to be ineffective against Escherichia coli.

Table 2: Antifungal activity and Antibacterial activity of synthesized compounds

Sr. No.	Test Organism	Strain No	Inhibition Zone Diameter * (mm)							
			Sample Code							
			P3	P4	P5	P7	P9	P11	P12	P13
1	Bacillus subtilis G+	NCIM 2549	21.3	20	15	15	23.5	18	21	16.6
2	Staphylococcus aureus G+	ATCC 25923	20.3	19.6	18.6	13.3	16.3	19.3	17.6	14
3	Escheriachia Coli G-	ATCC 25922	20	18	0	17.5	21	19	20.5	0
4	Pseudomonas aeruginosa G-	ATCC 27853	0	0	0	0	0	10.3	0	0
5	Aspergillus niger (Fungi)	ATCC 6275	14	10.3	13.3	12.3	10.6	10.3	11	10.6
6	Candida albicans (yeast)	ATCC 10231	26	11.3	10.6	14.6	13	11.5	15	12.5

*Inhibition zone diameters are average of triplicate readings

3.4 Spectral Data

1) 2-Phenyl-1H-benzimidazole [P1]: Solid Yellow; m.p: 287˚C - 289˚C; Rf:-. 0.42 (Ethyl acetate : Hexane =3/7)1H NMR (300 MHz ,DMSO-d6) : δ 7.16 - 7.27 (2H, m, aromatic) , 7.51 - 7.65 (5H, m, aromatic), 8.30-8.33 (2H, d, J=7.1Hz, aromatic) ,12.92 (1H, bs, NH) ; (GC-MS) m/*z:* 194.08 (Cacd m/z 194.08)[M + H]+; IR (KBr, cm-1): 1670,1593(C=N), 2920,2964(CH) , 3161(NH).

2) 2-(3-Hydroxyphenyl)-1H-benzo[*d*]imidazole (P2) Solid yellow; m.p: 181˚C - 183˚C; Rf :- 0.43 (Ethyl acetate : Hexane =3/7).1H NMR (300 MHz ,DMSO-d6): δ 7.57-7.67 (4H, m, aromatic), 7.69 - 7.76 (3H, m, aromatic), 7.79 (1H,s,aromatic) , 9.85 (1H,bs, OH), 12.66 (1H,bs,NH); (GC-MS) m/*z:* 212.00 [M + H]+ (Cacd m/z 212.07) , IR (KBr, cm-1): 1591(C=N), 3281,3356,3418(NH,OH).

3) 2-(4-Fluorophenyl)-1H-benzo[d]diazole : Solid yellow; m.p: 246˚C - 248˚C; Rf :- 0.40 (Ethyl acetate : Hexane =3/7). 1H NMR (300 MHz ,DMSO-d6): δ 7.15-7.20 (2H, m, aromatic), 7.20 - 7.40 (2H, m, aromatic), 7.45-7.52 (2H,m,aromatic) , 7.60-7.70(m,2H,aromatic),8.00 (1H,bs, NH) ; (GC-MS) m/*z:* 213.00 [M + H]+ (Cacd m/z 212) , IR (KBr, cm-1): 1597,1633(C=N),3475(NH).

4) 2-(4-nitrophenyl)-1H-benzo[*d*]imidazole (P5) : Ornage Red solid; m.p: 309˚C - 311˚C; ; Rf:-. 0.52 (Ethyl acetate : Hexane =3/7) 1H NMR (300MHz, DMSO-d6): δ 7.32-7.44 (4H ,m, aromatic), 8.02-8.15 (4H, m, aromatic), 12.87(1H, bs,NH); (GC-MS) m/*z*: 241.00 [M + H]+ (Cacd m/z 239,240); IR (KBr, cm-1): 1342, 1514 (NO_2), 1602(C=N), 3466(NH).

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5) 2-(2-Furyl)-1H-benzo[*d*]imidazole (P6) : Solid; m.p: 286˚C - 288˚C; ; Rf:-. 0.52 (Ethyl acetate : Hexane =3/7) 1H NMR (300 MHz , DMSO-d6): δ 6.78(2H, s, aromatic), 7.50 (1H, s, aromatic), 7.60-7.70 (4H ,m, aromatic); 12.89 (1H,bs,NH). (LC-MS) m/*z*: 184.06 [M + H]**+;** IR (KBr, cm-1): 1625(C=N), 3425(NH).

6) 2-(4-Chlorophenyl)-1H-benzo[*d*]imidazole (P7) : Solid Pale Yellow ; ,m.p: 285˚C - 287˚C; Rf:-. 0.65(Ethyl acetate : Hexane =3/7), 1H NMR (300 MHz DMSO-d6): δ 7.21-7.29 (2H ,m, aromatic), 7.55-7.64 (4H, m, aromatic), 8.22 (2H, d, J = 8.5Hz, aromatic), 12.96 (1H, bs, NH). (GC-MS) m/*z:* 230.00 [M + H]+ (Cacd m/z 228,230) ,IR (KBr, cm-1): 2877,1599(C=N), 3477(NH)

7) 4-(1H-Benzo[d]imidazol-2-yl)-2-methoxyphenol (P8). : Red Solid ;mp: 218–220∘C; Rf:-. 0.45(Ethyl acetate : Hexane =3/7; 1H NMR (300MHz, DMSO- *d* 6): *δ* 12.65 (s, 1H), 9.31 (s, 1H), 7.52–7.63 (m, 4H), 7.13–7.19 (m, 2H), 7.05 (d, *J* = 8.2Hz, 1H), 3.85 (s, 3H); (LC-MS) m/*z:* 240.09(Cacd m/z 240.09) [M + H]+ (cm−1, KBr): 3290(NH), 2910, 1500(C=N), 1450, 1265(CH), 1033, 910, 736;

8) 2-(2-Bromophenyl)-1H-benzo[*d*]imidazole (P9) : Solid Grey ; m.p: 293˚C - 295˚C; Rf:-. 0.56 (Ethyl acetate : Hexane = 3/7) 1H NMR (300MHz ,DMSO-d6) : δ 7.25-7.30 (2H ,m, aromatic), 7.51-7.61 (5H, m, aromatic), 7.89-7.93 (1H, m, aromatic), 13(1H, bs, NH). (GC-MS) m/*z:* 276.00 [M + H]+ (Cacd m/z 274,275) , IR (KBr, cm-1): 1593 (C=N), 3473 (NH)1494,1367(CH),1272,967,690.

9) 2-(2-Thienyl)-1H-benzo[*d*]imidazole (P10) : Yello solid; m.p: 328˚C - 330˚C; Rf:-. 0.46 (Ethyl acetate : Hexane = 3/7) 1H NMR (300 MHz ,DMSO-d6) : δ 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). (GC-MS) m/*z*: 200.00 [M + H]+ (Cacd m/z 200,201),; IR (KBr, cm-1): 1595(C=N), 3454(NH).

10) 2-(4-Hydroxyphenyl)-1H-benzo[*d*]imidazole (P11) : Solid pale yellow; m.p : 253˚C - 255˚C; Rf:-. 0.44(Ethyl acetate : Hexane =3/7) 1H NMR (300 MHz ,DMSO-d6) : δ 7.61-7.71 (4H,m,aromatic), 7.73-7.79 (2H, m, aromatic), 7.81- 7.86 (2H ,m, aromatic) , 9.89 (1H, bs, OH), 12.71 (1H, bs,NH) ; (GC-MS) m/*z:* 212.00 [M + H]+ (Cacd m/z 212.07) , IR (KBr, cm-1) : 1602(C=N), 3188,3313,3396(NH,OH).

11) 2-(2-chlorophenyl)-1H-benzo[*d*]imidazole (P12) : Solid saddle brown; m.p: 230˚C - 232˚C ; Rf:-. 0.44 (Ethyl acetate : Hexane =3/7); 1H NMR (300MHz ,DMSO-d6) : δ 7.25-7.30 (2H ,m, aromatic), 7.51-7.61 (5H, m, aromatic), 7.89-7.93 (1H, m, aromatic), 12.64 (1H, bs, NH). (GC-MS) m/*z:* 228.00 [M + H]+ (Cacd m/z 228.05), IR (KBr, cm-1): 1604 (C=N), 3473,3375 (NH).

12) [2-(4-nitrophenyl)-1H-benzimidazol-5-yl](phenyl)methanone (P13): Solid Orange; m.p: 240˚C - 242˚C ; Rf:-. 0.42 (Ethyl acetate : Hexane =3/7); 1H NMR1H NMR (300MHz ,DMSO-d6) : δ 8.27-8.13 (3H ,m, aromatic), 7.81-7.72 (6H, m, aromatic), 7.45-7.38 (3H, m, aromatic), 4.70 (1H, bs, NH). (LC-MS) m/*z:* 343.33 [M + H]**+** , IR (KBr, cm-1): 1647 (C=N), 3191 (NH), 3970,2912(CH), 1714(C=O).

IV. CONCLUSION

The catalytic activity of all manufactured catalysts was higher than that of pure zinc oxide catalyst. By combining aryl aldehyde with o-phenylenediamine in the presence of Ni-Doped zinc oxide catalyst under solvent-free conditions, the current work is a one-pot, easy work up and highly efficient, economical, and environmentally friendly synthesis of 2-arylsubstituted benzimidazoles. The key benefit of this study is the separation and isolation of the catalyst, as well as the ability to reuse the catalyst at least four to six times without losing its catalytic activity. The effectiveness of the synthesized catalyst is explained by the high yields of the products and the short reaction time. Antimicrobial activity of synthesized Benzimidazoles was shown against a variety of model microorganisms, including bacteria and fungi. This research should be continued in order to find more effective catalysts and more complicated bioactive compounds.

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