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ISSN: 0474-9030

Vol-68-Issue-1-January-2020

"Facile and Efficient One Pot Synthesis of Substituted Benzimidazoles under Ultrasonic Irradiation Using Novel Active 3% Cu-Doped Zinc Oxide Catalyst and Their Antimicrobial Activity "

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Abstract :

Herein, we report for the first time, the synthesis of substituted benzimidazoles through the coupling of Aromatic aldehydes with o-phenylenediamine by using recyclable, highly efficient and new 3% Cu-doped Zinc oxide catalyst in Ethanol under ultrasound irradiation and afforded high yields (92-99 %) in a short period of time(10-20 min). Spectral data and Physical constant confirmed the formation of favored product. Antimicrobial activity of synthesized benzimidazoles compounds were checked and found extensively active against various gram positive , gram negative bacteria, yeast and some fungus. Simple methodology, short reaction times ,environmentally benign, mild reaction conditions with easy work-up procedure, inorganic low cost recyclable catalyst are the prominent features of this method. Great achievement of this work is to used catalyst atleast five to six times without losing its catalytic activity.

Key words :

Ultrasonic Irradiation , Active 3% Cu-doped Zinc oxide Catalyst, Benzimidazole, o-phenylene diamine, Aromatic aldehyde, Ethanol , Antimicrobial activity.

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1. Introduction :

Benzimidazole ring is an important pharmacophore present in most of the drugs and agrochemicals that's why its derivatives are more useful in the field of medicinal chemistry. Benzimidazole derivatives show biological properties such as antiviral , antihypertensive, antitumor, antifungal etc., in veterinary medicine [1]. Most of natural products as well as pharmacologically active compounds contain benzimidazole nucleus [2]. It shows a broad spectrum of biological and pharmacological properties [3-11]. Due to their pharmacological importance, great attention has been given to the synthesis of substituted benzimidazoles by chemists. Various synthetic routes have been developed for synthesis of substituted benzimidazoles *via* the microwave irradiation, condensation, ultrasound irradiation of *o*-aryldiamine with aldehydes using different catalyst which is reported in literature[12-20] but all these methods have some limitations such as costly reagents, low yields, deadly work up procedures and co-occurrence of side reactions. Due to all these drawbacks , it is very important to develop more efficient inorganic recyclable, low cost catalysts for the preparation of these compounds.

In the last two decades, ultrasound- promoted synthetic route has been broadly developed in organic synthesis[21]. Ultrasound-promoted organic synthesis have received more attention due to minimum energy requirements, avoidance of poisonous reagents, reduction of waste and increasing reaction efficiency[22,23].

Powder form of ZnO is white in color and insoluble in water. It is prepared synthetically. Zinc oxide is an efficient catalyst in synthesis of heterocycles has been reported in most of the paper. Activity of ZnO catalyst has been increased by doping of Cu.

2. Materials and Methods

2.1 Chemicals and Instruments :

All these commercially available chemicals and solvents were purchased from Spectrochem, Sigma -Aldrich and were used without further purification. IR absorption spectra of the synthesized compounds were recorded on Shimadzu IR-Affinity FTIR using ATR. The ^{1}H NMR spectra were acquired on Bruker AQS 300 Advance instrument at 300 MHz in Dimethyl

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sulfoxide (DMSO-d6). The improvement of the reaction was monitored by TLC. GCMS-QP 1000 EX Shimadzu Gas Chromatography-MS apparatus was used for GCMS spectra . Sonochemical synthesis was performed with the help of an ultrasonic instrument (Bio-Technics India ISO 9001 : 2008) . The catalyst was characterized by Xray diffraction techniques.

2.2 Synthesis of catalyst :

The different calculated amount of Zinc Acetate and Copper Acetate were dissolved in distilled water and sonicated for 20 minutes for making homogenous solution . Then treated with liquor ammonia. The homogeneous hydroxide precipitate is filtered on funnel, dried & calcined in muffle furnace at 900-950 ^{o}C. Then different amount of (1-5%) Cu- doped Zinc oxide catalyst were prepared and screened for their catalytic activity. Out of above catalyst , 3% Cu-doped ZnO catalyst is found to be highly active.

2.3 Synthesis of Substituted Benzimidazoles :

Reaction Scheme :

Aromatic aldehyde (1mmole, 1) and 1,2–diamine (1mmole, 2) were dissolved in Ethanol (2 ml) in a 25 ml round bottom flask. Catalyst (0.200gm) was then added to it and the mixture was irradiated in the water bath of an ultrasonic cleaner at 25-35^{o}C (bath temperature, the temperature inside the reactor was also 30-40^{o}C) for a period time as indicated in Table **1.** The completion of the reaction was checked by TLC (Ethyl acetate: Hexane (3:7). 10 to 20 minutes time required for this reaction. Very simple way to recovered catalyst from the reaction mixture and used five to six times for the further reaction without losing its catalytic activity.

2.4 Microbial Study :

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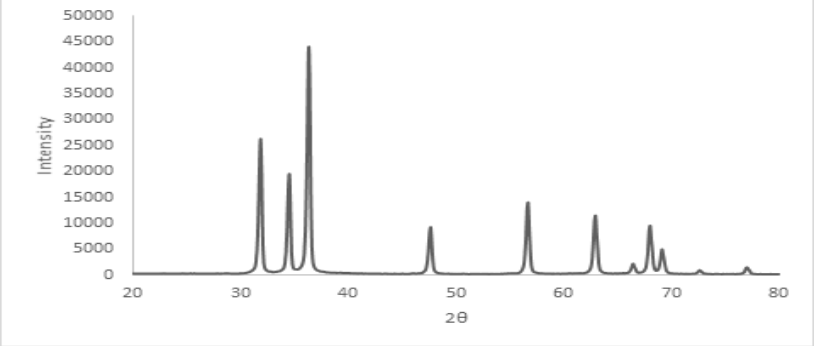
Two strains of Gram +ve bacteria (Bacillus subtils, Staphylococcus aureus), two strains of Gram –ve bacteria (Pseudomonas aeruginosa, Escherichia coli) , Yeast (Candida albicans) and Fungi (Aspergillus niger) were used for the biological activity of synthesized benzimidazole compounds [24].

3. Result and Discussion

3.1 Synthesis and Characterization of catalyst :

Various amount of Cu-doped zinc oxide catalyst was synthesized and characterized by XRD pattern. The observed XRD pattern was compared with the standard JCPDS card. Composition of catalyst was confirmed by qualitative and quantitative analysis of Zn and doping Copper. Different percentage of Cu-doped ZnO catalyst were prepared .Out of this 3% Cu-doped ZnO catalyst were found to be good. Presented XRD is of 3% Cu doped ZnO.



3.2 Synthesis and Characterization of Substituted benzimidazoles :

A novel synthetic route for facile and efficient one pot synthesis of a variety of biologically significantly substituted benzimidazoles in high yields using Cu- doped zinc oxide catalyst is reported. This method is extended to a variety of aromatic aldehydes and 1,2-diamines listed in **table no 1.** Aldehyde having electron withdrawing group gives fast reaction than electron donating group because it increases the electrophilic character of aromatic aldehydes towards the 1,2-diamine. Appearance of frequency corresponds to C=N and N-H functional group in product FTIR spectrum confirms formation of benzimidazoles.

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Table-1 Synthesis of 2-Substituted Benzimidazole derivatives

Sr. No.	Aldehyde	Diamine	Product	Reaction time (min)	Yield (%)
1			P_1	15 Minute	98%
2			P_2/P_4	20 Minute	96%
3			P_3	12 Minute	96%
4			P_5	10 Minute	99%
5			P_6	20 Minute	92%
6			P_7	13 Minute	98%

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3.3 Antimicrobial activity of substituted Benzimidazoles

The antimicrobial activity of synthesized benzimidazole compounds were tested on different microorganism by inhibition zone method . The screening biological activity test result are reported in **Table No 2**. The antifungal activity and antibacterial activity of compounds P3, P4, P5, P7 were tested. From the below data, it is clear that compound P3 was found to be extremely active against Candida albicans and highly active against Bacillus subtilis, Staphylococcus aureus and slightly active against Aspergillus niger . Compound P3, P4, P5 was found to be active against Staphylococcus aureus. But all the tested compounds were found to be inactive against Pseudomonas aerginosa. Similarly, compound P5 were found to inactive against Escherichia coli and Candida albicans.

Table No – 2 Antifungal activity and Antibacterial activity of Synthesized compounds

Sr. No.	Test Organism	Strain No	Inhibition Zone Diameter * (mm)			
			Sample Code			
			P2(P4)	P3	P5	P7
1	Bacillus subtilis G+	NCIM 2549	22	21.5	16	16
2	Staphylococcus aureus G+	ATCC 25923	19.8	20.6	18.4	13.5
3	Escheriachia Coli G-	ATCC 25922	16	21	0	17.6
4	Pseudomonas aeruginosa G-	ATCC 27853	0	0	0	0
5	Aspergillus niger (Fungi)	ATCC 6275	10.6	16	13.5	12.5
6	Candida albicans (yeast)	ATCC 10231	11.5	27	10.8	14.8

*Inhibition zone diameters are average of triplicate readings

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3.4 Spectral Data :

1) 2-Phenyl-1H-benzimidazole (P1) :

Solid Yellow ; m.p : 286˚C - 288˚C ; Rf :-. 0.50 (Ethyl acetate : Hexane =3/7) ^{1}H NMR (300 MHz ,DMSO-d6) : δ 7.15 - 7.29 (2H, m, aromatic) , 7.52 - 7.68 (5H, m, aromatic), 8.32-8.35 (2H, d, J=7.1Hz, aromatic) ,12.91 (1H, bs, NH) ; (GC-MS) m*/z:* 194.06 (Cacd m/z 194.08)[M $^{+}$ H^{+}]; IR (KBr, cm^{-1}): 1675,1595(C=N), 2925,2968(CH) , 3163(NH).

2) 2-(3-Hydroxyphenyl)-1H-benzo[*d*]imidazole (P2/P4) :

Solid yellow; m.p: 182˚C - 184˚C; Rf :- 0.46 (Ethyl acetate : Hexane =3/7).^{1}H NMR (300 MHz ,DMSO-d6): δ 7.55-7.69 (4H, m, aromatic), 7.67 - 7.74 (3H, m, aromatic), 7.79 (1H,s,aromatic) , 9.82 (1H,bs, OH), 12.64 (1H,bs,NH); (GC-MS) m*/z:* 212.02 [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 (P3) :

Solid yellow; m.p: 245˚C - 247˚C; Rf :- 0.48 (Ethyl acetate : Hexane =3/7). ^{1}H NMR (300 MHz ,DMSO-d6): δ 7.13-7.18 (2H, m, aromatic), 7.21 - 7.38 (2H, m, aromatic), 7.42-7.50 (2H,m,aromatic) , 7.62-7.68(m,2H,aromatic),8.00 (1H,bs, NH) ; (GC-MS) m*/z:* 212.08 [M $^{+}$ H^{+}] (Cacd m/z 212) , IR (KBr, cm^{-1}): 1595,1632(C=N),3473(NH).

4) 2-(4-nitrophenyl)-1H-benzo[*d*]imidazole (P5) :

Orange Red solid; m.p: 308˚C - 312˚C; ; Rf:-. 0.56 (Ethyl acetate : Hexane =3/7) ^{1}H NMR (300MHz, DMSO-d6): δ 7.30-7.42 (4H ,m, aromatic), 8.04-8.13 (4H, m, aromatic), 12.86(1H, bs,NH); (GC-MS) m*/z*: 240.00 [M $^{+}$ H^{+}] (Cacd m/z 239,240); IR (KBr, cm^{-1}): 1344, 1516 (NO_2), 1604(C=N), 3468(NH).

5) 2-(2-Furyl)-1H-benzo[*d*]imidazole (P6) :

Yellow Solid; m.p: 284˚C - 286˚C; ; Rf:-. 0.58 (Ethyl acetate : Hexane =3/7) ^{1}H NMR (300 MHz , DMSO-d6): δ 6.76(2H, s, aromatic), 7.52 (1H, s, aromatic), 7.62-7.72 (4H ,m, aromatic); 12.87 (1H,bs,NH). (LC-MS) m*/z*: 184.20 [M $^{+}$ H^{+}**]** **(**Calcd m/z 184,186**);** IR (KBr, cm^{-1}): 1628(C=N), 3428(NH).

6) 2-(4-Chlorophenyl)-1H-benzo[*d*]imidazole (P7) :

Solid Pale Yellow ; ,m.p: 284˚C - 288˚C; Rf:-. 0.68(Ethyl acetate : Hexane =3/7), ^{1}H NMR (300 MHz DMSO-d6): δ 7.20-7.28 (2H ,m, aromatic), 7.53-7.66 (4H, m, aromatic), 8.24 (2H,

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d, J = 8.5Hz, aromatic), 12.98 (1H, bs, NH). (GC-MS) m*/z:* 230.04 [M^+ H^+] (Cacd m/z 228,230) ,IR (KBr, cm-1): 2878,1602(C=N), 3475(NH)

4. Conclusion :

In summary, we have developed an alternative, facile and efficient pathway for the formation of substituted benzimidazoles catalyzed by 3% Cu- doped ZnO under ultrasound irradiation . Important features of this procedure is milder conditions, easy recovery and reusability of the catalyst five to six times without losing its catalytic activity. The main advantage of this paper is high yields of the products and reduced reaction time itself explains efficiency of synthesized catalyst. Synthesized Benzimidazoles shown excellent antimicrobial activities against various model microbes such as bacteria and fungus..

5. Acknowledgement :

Authors are thankful to Principal, Dr. B. N. Purandare Arts, Smt. S. G. Gupta Commerce and Smt. S .A. Mitaiwala Science College, Science College for providing the Laboratory facilities, B.C.U.D. , SPPU, Pune. (Funding Agency), CIF and Dept. of Chemistry, SPPU, Pune(Characterization Facility). The authors are also thankful to Editor-in-Chief of the journal for his kind support and encouragement.

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