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HIGHLY EFFICIENT ONE POT SYNTHESIS OF HETEROCYCLIC BENZIMIDAZOLES CATALYSED BY NANO CRYSTALLINE ZrO_2.

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ABSTRACT

The present study dealswith synthesis *of*2-phenyl benzimidazoles and its derivatives *using* Nano crystalline ZrO_2 as a Nano catalyst under mild condition. The present study also aimed comparative study of effectiveness of bulk ZrO_2 and Nano crystalline ZrO_2 over synthesis. The purity of synthetized heterocyclic compounds were estimated by TLC technique while their structures were established by the usual spectroscopic methods such as A UV, IR, MS and ^{1}H NMR. The purity of this product was established by its IR, NMR, spectra.

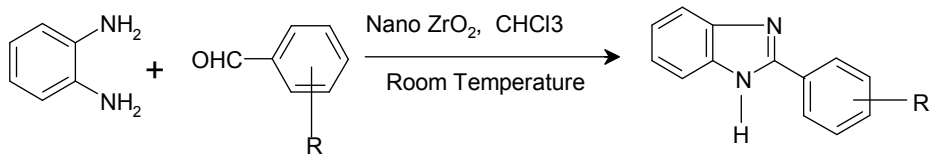
KEYWORDS: Synthesis, 2-phenyl benzimidazoles,cyclocondensation, Nanocrystalline ZrO_2.

I-INTRODUCTION

Benzimidazoles constitute an important class of heterocyclic organic compounds. Benzimidazoles are important pharmacophores for the synthesis of various medicinal products which are anti-helmintic,[1] anti-psychotic[2] and anti-fungal[3] in nature. Thus, Benzimidazoles are biologically active and hence commercially important organic compounds due to which several synthetic pathways have been developed to synthesize Benzimidazoles. It include cyclocondensation of o-phenylenediamine with aromatic aldehydes using Ammonium chloride,[4] Lithium bromide,[5] Copper (II) Hydroxide,[6]Zirconyl (IV) Nitrate,[7] Amberlite IR-120 under Ultra sound.[8] A novel Sodium iodide and Ammonium molybdate co-catalytic system is also used for synthesis of 2-benzimidazoles using Hydrogen peroxide under Ultrasound irradiation.[9] Polymer supported sulphanilic acid is used as heterogeneous catalyst for synthesis of benzimidazole derivatives.[10] Ionic liquids such as [Bmim]PF_6 under reflux[11] and 3-methyl-1-(3-sulfopropyl)-imidazoliumtrifluoro acetate under Ultra Sonication[12] were used in the synthesis of Benzimidazoles. There are many protocols which involves use of Nano catalysts for the synthesis of benzimidazoles. Some of these are Nano-Fe_3O_4/O_2,[13]SBA-15 Supported Cobalt Nanocatalysts,[14] Fe_3O_4@SiO_2/collagen,[15]$FeCl_3$ supported on Nano silica,[16]CuOnano-particles[17]andMesoporous mixed metal oxide Nanocrystals.[18]

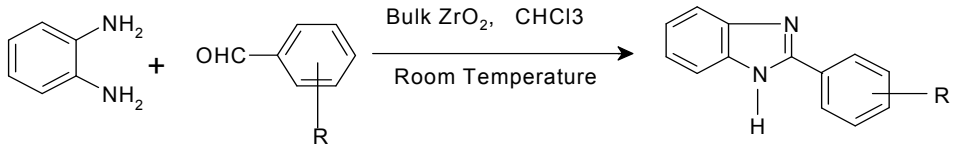
But all these protocols suffer from drawbacks such as requirement of vigorous reaction conditions, use of expensive, moisture sensitive reagents, difficult work up procedure and low yields.

In this regard, the present study reports a simple, efficient synthetic pathway involving use of NanocrystallineZrO_2 as a Nano-catalyst to synthesize 2-phenyl benzimidazoles (Scheme 1 and Scheme 2).



R = -Cl, -CH_3,-OH,-NO_2,-OCH_3

Scheme I



R = -Cl, -CH_3,-OH,-NO_2,-OCH_3

Scheme II

II-EXPERIMENTAL

II -1 Materials and Methods

All required chemicals were of analytical grade (AR) and used without further purification. ^{1}HNMR spectra of the synthesized Benzimidazoles were recorded using Varian Mercury plus 300 MHz NMR spectrometer. The values of all the chemical shifts were expressed in terms of δ with reference to Tetramethylsilane (TMS, δ=0) as an internal standard and expressed as ppm. All IR spectra were recorded on Perkin Elmer FT-IR spectrometer as KBr pellets. All the synthesized Benzimidazoles were known compounds and identified by comparing their melting point data with authentic information from Literature. The spectral data of selected Benzimidazoles was obtained.

II-2.1 General procedure for synthesis of 2-phenyl benzimidazoles

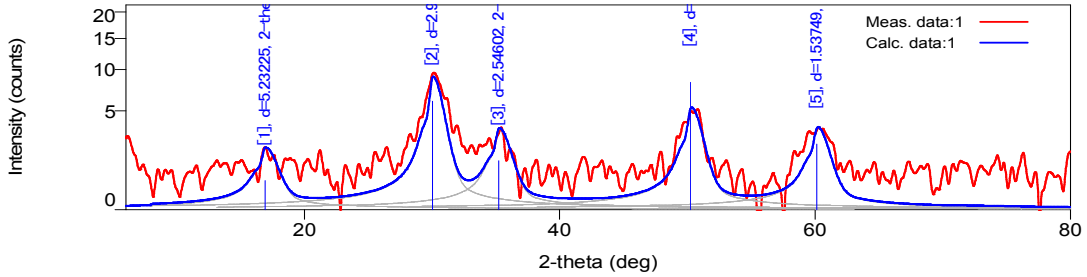
A reaction mixture was prepared by adding Nano ZrO_2 (0.029 g, 0.08 mmol) in a mixture of o-phenylenediamine (0.108 g., 1mmol) and aromatic aldehyde (1mmol) dissolved in C_2H_5OH (4 ml). The reaction mixture was magnetically stirred at room temperature and progress of reaction was studied by TLC. When reaction was completed (as indicated by TLC) it was diluted with $CHCl_3$ (3 x 5 ml) and filtered to separate catalyst. All extracts were dried over anhydrous Na_2SO_4 and further concentrated using reduced pressure method. The crude product was further purified by using Column chromatography (Silica gel-60 to120 mesh and mixture of Pet ether and Ethyl acetate in 10:2 as eluting system).The separated catalyst was repeatedly washed with $CHCl_3$ and dried. It could be used for more than 2 runs without loss of much activity. Similarly, other 2-phenyl benzimidazoles were prepared using same procedure (Table 3, 1)The same procedure was followed with bulk ZrO_2.

II-2.2 Synthesis and characterization of Nano crystalline ZrO_2.

Synthesis of Nano Zirconia done with the help of Zirconium Nitrate(1.65 gm.)as source of metal ion and calculated amount of glycine along with L-Ascorbic Acid has taken in minimum amount of de- ionized water .It is heated on hot plate at 80^{o}C in order to get homogenized and gel is formed after removal of excess of water transferent solution get

formed. After removal of water gel get swallowed and then release of brownish gases comes out for 2-3 seconds. At the end Cement colored powder get formed this powder further heated at 600^{o}C in the muffle furnace for 30 minutes in order to remove carbonaceous matter. Fine ZrO_2 nanoparticles get formed having particle in the range ofsize (78nm -118)nm. Characterization of nanomaterial done with XRD and SEM below.

Fig.II-2.2 a :XRD pattern of Nano ZrO_2.



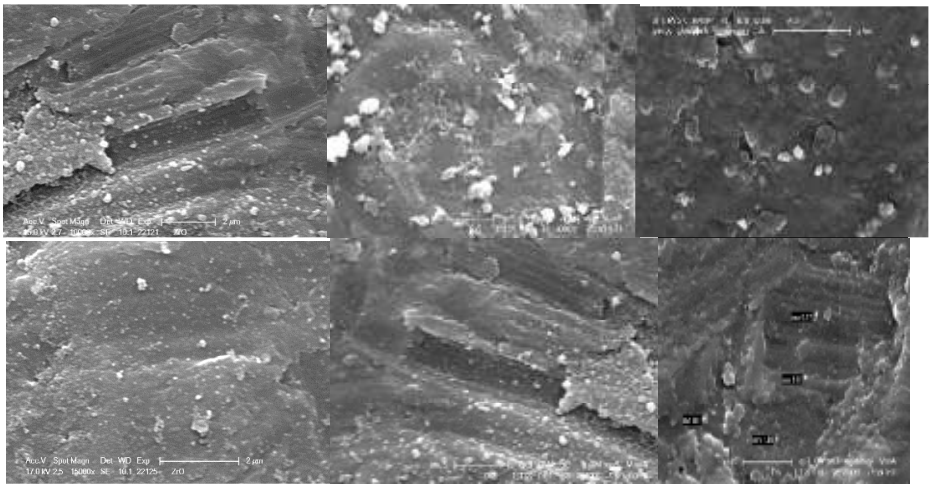


Fig.II-2.2 b: SEM Analysis of Nano ZrO_2.

III- RESULT AND DISCUSSION

III-1.The study of synthesis of 2-phenyl-1H-benzimidazoles

The appropriate reaction conditions were established by selecting cyclocondensation between o-phenylenediamine (0.108 gm, 1 mmol) and Benzaldehyde (0.101ml, 1 mmol) as model reaction for both bulk ZrO_2 and Nano ZrO_2.

III-1a: Selection of Solvent

An appropriate solvent was selected by screening range of solvents including non-polar and polar one for model reaction (Table 1, Entries 1 to 5). In non-polar solvents noticeable yield of product was obtained with both ZrO_2 and Nano ZrO_2but reaction time was long (Table 1, Entries 1 to 2). Among polar solvents, water failed to give any reaction (Table III-2a, Entry 5). A Significance increase in yields (82%and 96%, Table 1, Entry 4) at short reaction time was observed when the reaction was carried out in ethanol, a polar solvent. So, ethanol was selected as most appropriate solvent for the model reaction with both bulk ZrO_2 and Nano ZrO_2.

Table III-2a Investigation of solvent effects for the synthesis of 2-phenyl-1H-benzimidazole (1a)*

Entry	Solvent	Bulk ZrO_2		Nano ZrO_2	
		Time (min.)	Yield[c] (%)	Time (min.)	Yield[c'] (%)
1	CH_2Cl_2	85	62	45	70
2	$CHCl_3$	80	70	35	79
3	CH_3CN	72	79	25	82
4	C_2H_5OH	65	82	10	96
5	H_2O	No reaction	No reaction	No reaction	No reaction

*Reaction conditions: o-phenylenediamine (1 mmol), benzaldehyde (1 mmol), solvent (4 ml) and catalyst (bulk and Nano separately) at r.t.
[cc']Isolated Yield

III-1b: Selection of Catalytic loading amount

Similarly, catalytic activity of bulk ZrO_2 and Nano ZrO_2 was studied with respect to its loading amount in reaction mixture (Table **III-1b**).

Table **III-2b**: Investigation of catalytic effect of Nano ZrO_2 on synthesis of 2-phenyl-1H-benzimidazoles (1a) *

Entry	Amount of Catalyst, (mmol)	Bulk ZrO_2		Nano ZrO_2	
		Time (min.)	Yield[c](%)	Time (min.)	Yield[c'](%)
1	0.01	120	61	40	70
2	0.02	120	60	35	72
3	0.04	110	60	30	75
4	0.06	90	72	20	78
5	0.08	85	78	10	96
6	0.1	65	82	10	96
7	0.2	65	82	10	96

*Reaction conditions: o-phenylenediamine (1 mmol), benzaldehyde (1 mmol), solvent (4 ml) and catalyst (bulk and Nano separately) at r.t.
[cc']Isolated Yield

The effect of catalyst loading was studied by increasing its amount from 0.01mmol to 0.2 mmol. There was marginal increase in yield of product when amount of catalyst varied from 0.01 to 0.06 mmol (Table **III-2b**, Entries 1 to 4). An excellent yield (96%) was observed in short reaction time when 0.08 mmol of Nano ZrO_2 catalyst was used. In case of bulk ZrO_2, the corresponding yield was 78% and the trend of minor increase in yield with long reaction time was observed (Table **III-2b**, Entries 5, 6, 7).

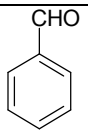
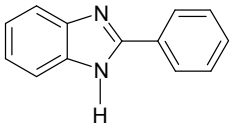
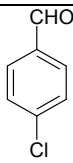
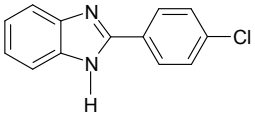
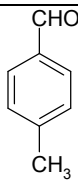
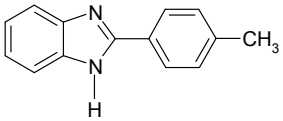
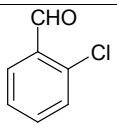
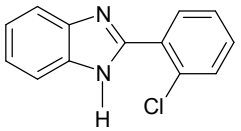
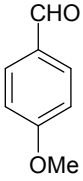
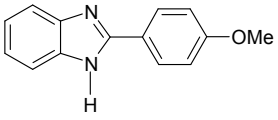
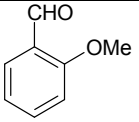
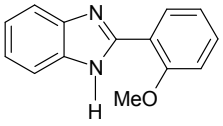
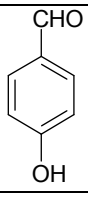
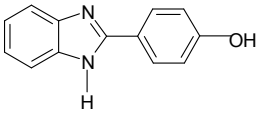
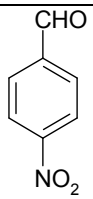
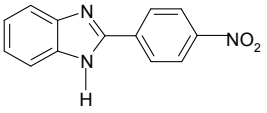
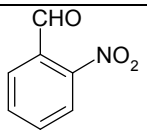
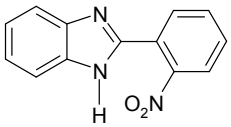
Thus, Nano ZrO_2 was found to be effective in small amount (0.08 mmol, 0.029 gm) to carry out conversions as compare to bulk ZrO_2 (0.1 mmol, 0.037 gm) (Table III-2b, Entries 6, 7). Even if the amount of catalyst was increased further, hardly any improvement in yield and reaction time was seen. Thus, use of Nano ZrO_2 (0.029 gm, 0.08 mmol) in C_2H_5OH was selected as most appropriate reaction condition for the synthesis of 2-phenyl benzimidazoles (Table**III-2b**).

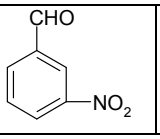
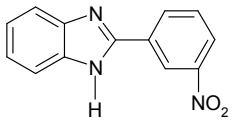
III-1c Study of Scope of reaction

The effectiveness and general applicability of Nano ZrO_2 as a catalyst was further established by preparing different 2-phenyl benzimidazoles in presence of both bulk ZrO_2 and Nano ZrO_2 and the results were compared (Table III-2c).To assess efficacy and generality of Nano ZrO_2, o-phenylenediamine wasreacted with various aromatic aldehydes under the optimized reaction conditions to furnish the corresponding products (Table III-2c). In this, the

effect of electron-releasing and electron-withdrawing substituents on the reactivity of aromatic ring of aldehydes was studied.

Table III-2c: Synthesis of 2-phenyl benzimidazoles using bulk ZrO_2 and Nano ZrO_2 catalysis*.

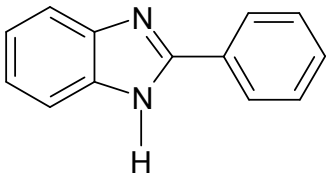
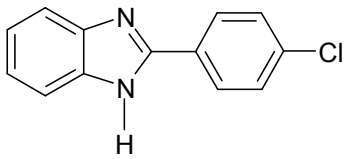
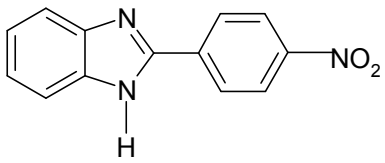
Entry	Aldehyde R[a]	Product 1(a-j)	ZrO_2(Bulk)		ZrO_2(Nano)		M.P.(^{0}C) (Lit. Value)
			Time (min.)	Yield[c] (%)	Time (min.)	Yield[c'] (%)	
1			65	82	10	96	290-291 (292)[22]
2			55	82	10	93	291-293 (292-294)[22]
3			70	80	20	92	267-268 (270)[22]
4			72	78	15	91	232-235 (234)[19]
5			75	79	20	91	223-225 (226)[19]
6			80	78	25	90	151-153 (153)[21]
7			60	83	10	93	255-256 (254-256)[23]
8			52	84	10	95	313-316 (316)[22]
9			65	81	15	93	255-258 (261-263)[20]

10			60	81	10	93	202-204 (204-205)[20]

*Reaction conditions; Aromatic aldehyde (1 mmol), o-phenylenediamine (1.0 mol), 0.08mmol of Nano ZrO2and 0.1mmol of bulk ZrO2 separately in C_2H_5OH (4 mmol) at r.t.
[cc] Isolated Yield.

Both bulk and Nano ZrO_2 were found to be effective in synthesis of Benzimidazoles (Table 3). The electron donating substituents in aromatic aldehydes were found to increase the reaction time to some extent (Table 3, Entries 3, 5, 6). Otherwise, all aromatic aldehydes bearing either electron donating or withdrawing substituents were found to be reacting smoothly under the established reaction condition in terms of yield and reaction time (Table 3, 1a-j).

SPECTRAL DATA OF THE PRODUCTS OF SCHEME 1(TABLE III-2d)

Entry	Products	Spectral Data
1		2-Phenylbenzimidazole M.P. 290-291^oC I.R.(KBr) cm^{-1}:736, 1274, 1400, 1448, 1597, 2877, 3051 H^1NMR(300MHz,$CDCl_3$): δ=7.20-7.45(m,5H,Ar-H,J=7.1Hz), 7.75(d,2H,Ar-H, J= 7.01Hz),7.80(m, 2H, Ar-H, J= 7.01Hz), 8.20 (s,NH)
2		2-(4-chlorophenyl)benzimidazole M.P. 291-293^oC I.R.(KBr) cm^{-1}:736,974,1274,1448, 1597,2877,3051 H^1NMR(300MHz,DMSO): δ=5.35(s,NH), 7.0-7.40(d,4H,Ar-H, J), 7.40-7.60(d,2H,Ar-H), 8.0-8.20(m,2H,Ar-H)
3		2-(4-nitrophenyl)benzimidazole M.P. 313-316^oC I.R.(KBr) cm^{-1}:740, 1105, 1338, 1438, 1516, 1598, 2783, 3045. H^1NMR(300MHz, DMSO): δ=5.75(s,1H,NH), 7.35(d,2H,Ar-H, J=7.01Hz), 7.60-7.75(m,2H,Ar-H, J= 7.01Hz), 8.20(d,2H,Ar-H,J=7.2Hz), 8.55(d,2H,Ar-H, J= 7.2Hz)

IV-Proposed Mechanism (Fig. IV)

The proposed mechanism which is consistent with literature[xxii] is shown in the fig.IV. It involves activation of aromatic aldehyde by Nano ZrO_2. Ortho-phenylenediamines attacks the carbon of carbonyl group of activated aldehyde and forms intermediate (I) which undergo elimination of water molecule to form Imine intermediate (III). The formed intermediate is activated by ZrO_2 of Nano catalyst to form new intermediate (III) which undergo air oxidation to form product (IV).

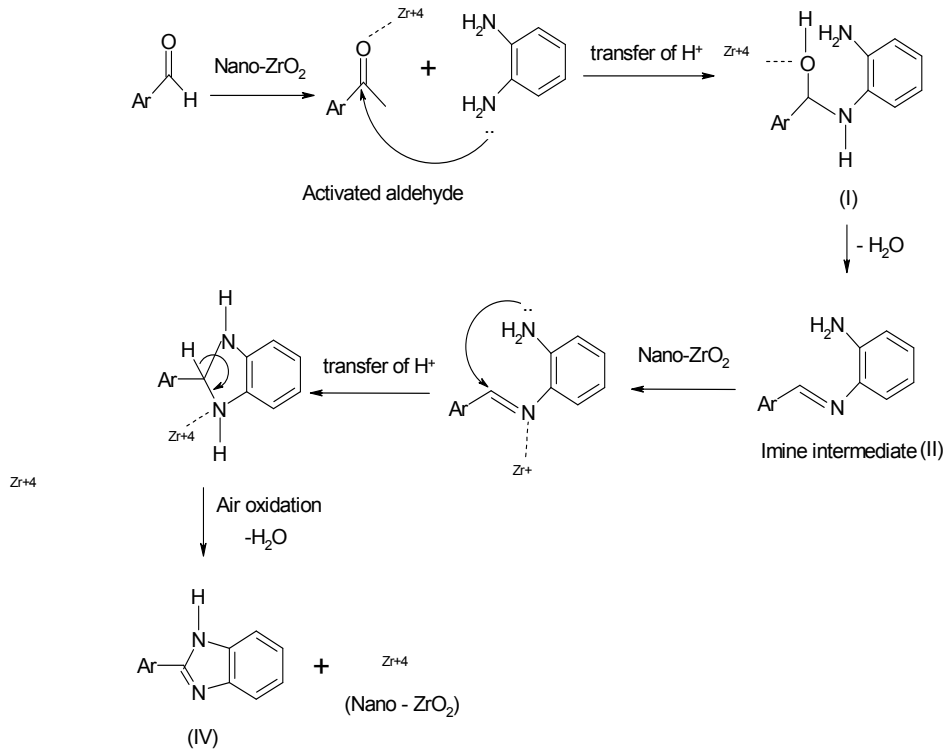


Fig. IV

III-1d: Study of reusability of Nano ZrO_2.

Nano ZrO_2 was found to be heterogeneous in reaction mixture during synthesis of 2-phenyl benzimidazoles. The easy recovery of catalyst encouraged to check its reusability in Scheme 1. It was observed that Nano ZrO_2 could afford corresponding products for at least three times without much loss in its catalytic activity as shown in Table III-2f.

Table III-2f : Study of reusability of Nano ZrO_2 in synthesis of 2-phenyl-1H-benzimidazole (1a)*

Run No.	1	2	3
Time (min.)	10	13	18
Yield[c] (%)	96	93	90

*Reaction conditions; Aromatic aldehyde (1 mmol), o-phenylenediamine (1.0 mol), 0.08mmol of Nano$ZrO_2$and 0.1mmol of bulk ZrO_2 separately in C_2H_5OH (4 mmol) at r.t.
[c]Isolated Yield

V- CONCLUSION:

Nano $ZrO_2$was found to be heterogeneous and reusable catalyst for synthesis of 2-phenyl benzimidazole.It is having more efficiency with respect to bulk ZrO_2 under given set of conditions.

VI-ACKNOWLEDGMENT

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