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Efficient Room Temperature Synthesis of 2-Aryl benzimidazoles Using ZnO Nanoparticles as Reusable Catalyst

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Abstract

A facile and green protocol has been developed for the synthesis of 2-aryl-1,3-benzimidazole derivatives using ZnO nanoparticles as reusable catalyst. The reactions are very fast, high yielding and the nano-catalyst was recycled for ten times. In this paper we have reported the synthesis of 2-aryl-1,3-benzimidazole derivatives from aromatic aldehydes (containing electron donating group like, -OMe, -Me etc. and electron withdrawing group like, $-NO_2$ etc.) and 1,2-phenyl-diamine.We have synthesized a series of 2-aryl-1,3-benzimidazoles with various 5- and 6-position substituent (-H, $-OCH_3$, $-CH_3$, -OH, -Cl, -Br, $-NO_2$,) derivatives.

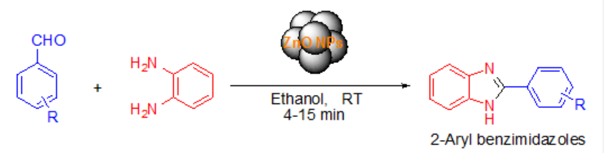
Keywords: Nano-catalysis; ZnO nanoparticles; 2-Aryl-1,3-benzimidazoles; Reusable catalyst; Green synthesis

Introduction

Synthesis of biologically potent 2-substituted benzimidazole derivatives is important because of their wide applications in medicinal chemistry and reported to act as antiviral [1], antiulcer [2] antihypertension [3] and anticancer agent [4]. Thus, development of environmentally benign synthetic methodology for the construction of 2-substituted benzimidazole derivatives is appreciated in the context of green chemistry. Generally, benzimidazole derivatives have been synthesized by the condensation of 1,2-phenylenediamine with aldehydes using various catalysts. Many of the methods utilized homogeneous catalysts such as $FeCl_3$,6H2O [5a] $I_2/KI/K_2CO_3/H_2O$ [5b], sodium metabisulfite [5c] $Na2S_2O_5$ [5d] iodobenzenediacetate(IBD) [5e], CAN/H_2O_2 [5f] HCl/H_2O_2 [5g], $Co(OH)_2/CoO(II)$ [5h], $Pd(OAc)_2/O_2$ [5i], $TiCl_3OTf$ [5j], $B(C6F5)_3$ [5k] $VOSO_4$ [5l], Ru(byp)$3Cl_2$ [5m] $Na_2S_2O_4$ or $Na2S_2O_5$ [5n], Pd(dppf)Cl_2 [5o] and few protocols used solid supported catalysts such as SiO_2/sulphuric acid [6a], AlKIT-5 [6b], FeCl3/Montmorillonite K-10 [6c], polymer-supported hypervalent iodine [6d] and KHSO4/SiO_2 [6e].

However, most of the methods involves use of toxic catalysts, acid reaction conditions, salts of heavy metal and expensive Pd-catalyst, poor catalytic efficiency due to the low surface area supporting materials and finally these catalysts were not environment-friendly in nature. Thus, introduction of an efficient heterogeneous catalyst for the synthesis of 2-substituted benzimidazole derivatives is important.

Recently, catalysis by nanoparticles (NPs) has become attractive area of research due to their large and reactive surface areas, chemo-selectivity and ability to perform the reaction under mild reaction conditions. In addition, NPs have considered as bridge between homogeneous and heterogeneous catalysis and advantages of both disciplines can be achieved by using a nano-catalyst. Among them, oxide NPs were snatched attractive attention because these NPs are relatively more stable compare to metal NPs due to presence of oxide (O-) and hydroxyl (-OH) groups in the surface. Moreover, surface of oxide NPs has exhibit redox and Lewis acid-Lewis basic properties [7]. Recently, few NPs (NPs (CuO NPs [8a]. nano-ZSM-5 [8b], CeO_2NPs) [8c], have also been applied as catalyst for the synthesis of 2-substituted benzimidazole derivatives. However, these NPs were toxic in nature. As a part of our research interest in catalysis by oxide NPs [9], here we have demonstrated synthesis of 2-aryl benzimidazole derivatives using environment-friendly free-ZnO NPs as reusable catalyst at room temperature (Scheme 1).



Scheme 1: Synthesis of 2-aryl benzimidazole derivatives using ZnO NPs as catalyst.

Materials and Methods

Initially, ZnO NPs have been synthesized following our previously reported method [8], simply by condensing Zn(OAc)2. 2H2O in a basic medium 70oC temperature by sol-gel method and stored this nano-catalyst in ethanol medium. The detail experimental procedure for the synthesis of ZnO NPs has been given in reference section. The formation of ZnO NPs was confirmed by transmission electron microscopy (TEM) study. The TEM image indicates the formation of nearly spherical shaped particles with average size of 50 nm (Figure 1). The formation of crystalline ZnO NPs was evident from powder X-ray diffraction (XRD) study (Figure 1). The average particle size of ZnO NPs was determined to be 30 nm from the XRD study from the full-width at half wave full maxima (FWHM) via Scherrer formula.

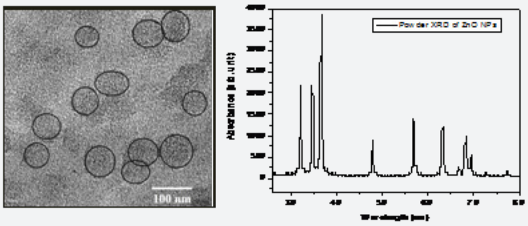


Figure 1: TEM image (left) and powder XRD (right) of ZnO NPs.

Results and Discussion

Table 1: Optimization of reaction conditions for the synthesis of 2-phenyl benzimidazole.

Entry	Catalyst	Solvent	Time (min.)	Yield(%)a
1	ZnO NPs	EtOH	10	95
2	ZnO NPs	Neat	5	98
3	ZnO NPs	THF	60	65
4	ZnO NPs	CH_2Cl_2	60	67
5	ZnO NPs^b	EtOH	10	99
6	ZnO NPs^b	Neat	5	98
7	ZnSO4	Neat	20	85
8	$Zn(OAc)_2$	Neat	17	90
9	$ZnCl_2$	Neat	25	88
10	ZnO powder	Neat	30	88
11	$Zn(NO_3)_2$	Neat	40	83
12	Fe_2O_3 NPs	EtOH	30	83
13	Fe2O$_3$ NPs	Neat	30	80
14	CuO NPs	EtOH	40	78
15	CuO NPs	Neat	40	70
16	No Catalyst	EtOH	60	0

Reaction conditions: 1,2-phenyl-diamine(1 mmol), benzaldehyde (1 mmol), catalyst (5 mg), room temparature, continuous stirring. aIsolated yield. bCatalyst (10 mg).

Initially by the freshly prepared ZnO NPs has tested for the synthesis of 2-phenyl-1,3-benzimidazole *via* the condensation of 1,2-phenyl-diamine with benzaldehyde in ethanol medium. When a mixture 1,2-phenyl-diamine (1 mmol), benzaldehyde (1 mmol) and ZnO NPs (5 mg) was stirred at room temperature in ethanol (2 ml) an excellent yield of product (95%) was obtained after 10 minutes. Next, we have optimized the experimental conditions by changing the reaction parameters such as solvent, reaction time and also the amount of catalyst etc. The results were summarized in Table 1. The high yield of product was obtained by using ZnO NPs (5 mg) as catalyst Entry 2, (Table 1) and the reaction was not initiated in absence of ZnO NPs even after 1 hour Entry 16, (Table 1).

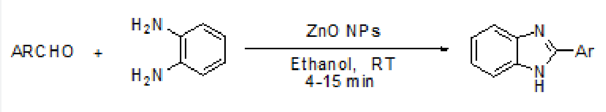


Figure 2: Aryl aldehydes bearing both electron withdrawing (e.g. $–NO_2$) and electron donating (e.g. –OMe, –Cl, –OH, –Br) group.

Screening of different solvents revealed that ZnO NPs were more efficient ethanol compared to non-polar solvent like tetrahydrofuran (THF), dichloromethane (CH2Cl2) etc. However, a best result was obtained in the basis of time and yield under solvent free reaction condition. In the solvent free condition 5 mg of ZnO NPs is sufficient to produced excellent yield of product (98%; Table 1, Entry 2). ZnO NPs showed superior catalytic activity compared to other Zn-catalyst, Fe3O4 NPs and CuO NPs as listed in (Table 1) (Entry 12-15). No such changes have been observed in increasing the amount of the catalyst 5 mg to 10 mg (99 %; Table 1, Entry 5). We have also performed the reaction under solvent free condition using 10 mg of the catalyst for five minutes but no such changes have been observed in the formation of yield with respect to the time 10 minutes. To investigate the scope of this protocol, next using the optimized reaction conditions i.e., taking ZnO NPs (5 mg) catalyst and solvent-free condition (solid aldehyde required solvent; EtOH) we have tried to synthesize series of 2-aryl benzimidazole derivatives (Figures 2 & 3), 1a-i using variety of aryl aldehydes.

In a general experimental procedure, the ZnO NPs were very efficiently catalyzed the condensation of 1,2-diaminobenzene with several aromatic aldehydes at room temperature. Aryl aldehydes bearing both electron withdrawing (e.g. –NO2) and electron donating (e.g. –OMe, –Cl, –OH, –Br) group underwent condensation smoothly within very short time period (4-15 minutes).

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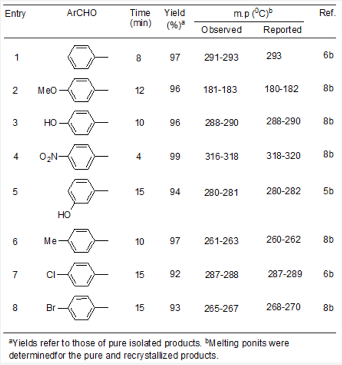
All the reactions tested here are fast and high yielding (92-99%). The completions of reactions were checked by monitoring TLC. After the reaction the products were separated from catalyst simply by filtration and purified by recrystallization from hot ethanol. The formation of products was initially confirmed by checking their melting points. All the 2-aryl benzimidazole derivatives prepared here are known to literature (Figure 3) and the observed melting points of each benzimidazole derivative were in well accordance to the literature values. The corresponding references are given in Figure 3. Then the products were further characterized by spectroscopic data. The ZnO NPs were recycled and reused for at least 10 times without significant loss of catalytic activity (Figure 4).



Entry	ArCHO	Time (min)	Yield (%)[a]	m.p (^{0}C)[b]		Ref.
				Observed	Reported	
1		8	97	291-293	293	6b
2	MeO	12	96	181-183	180-182	8b
3	HO	10	96	288-290	288-290	8b
4	O_2N	4	99	316-318	318-320	8b
5	HO	15	94	280-281	280-282	5b
6	Me	10	97	261-263	260-262	8b
7	Cl	15	92	287-288	287-289	6b
8	Br	15	93	265-267	268-270	8b

[a]Yields refer to those of pure isolated products. [b]Melting ponits were determinedfor the pure and recrystallized products.

Figure 3: ZnO NPs catalyzed synthesis of 2-aryl benzothiazoles derivatives.

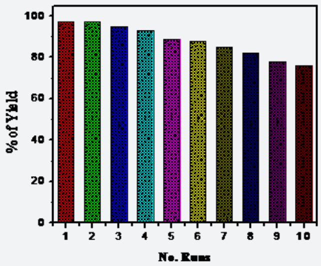


Figure 4: Represents the reusability of nano-ZnO for the synthesis of 2-phenyl-1H-benzo[d]imidazole (Figure 3, entry 1).

Conclusion

In conclusion, an efficient protocol has been developed for the synthesis of 2-aryl benzimidazole derivatives at room temperature using uncapped ZnO NPs as catalyst. All the reactions tested here were very fast (4-15 minutes) and high yielding (92-99%). The protocol is very mild (room temperature) and neutral in nature, the products were purified by recrystallization and thus use of volatile and hazardous solvents has been avoided here. Finally, this present ZnO NPs catalyzed synthesis of biologically important 2-aryl-benzoimidazole derivatives fulfills the criteria for green synthesis.

Representative method

A mixture of 1,2-diphenyl amine (1 mmol; 108 mg) benzaldehyde (1 mmol; 106 mg) and ZnO NPs (10 mg) in ethanol (1 ml)was stirred at room temperature for 8 minutes (TLC monitored). After that solid product was dissolved in hot ethanol and separated the ZnO NP by simple filtration (Whatman 41 filter paper) and recrystallized from ethanol. Pure 2-phenyl benzimidazole (Figure 3), entry 1; 97%, 188.10 mg) was obtained from the filtrate.

The formation of the product was confirmed by melting point and spectroscopic (1H NMR and 13C NMR) studies. (Figure 3), entry 1): Melting point- 291-293OC; 1H NMR (400 MHz, CDCl3): d = 8.18 (d, J = 7.3 Hz, 2H), 7.65-7.58 (m, 1H), 7.51-7.39 (m, 4H), 7.21-7.12 (m, 2H); 13C-NMR (100 MHz, CDCl3): d = 151.4, 143.5, 135.1, 130.0, 129.7, 129.3, 126.9, 122.5, 121.6, 118.4, 111.5. The same protocol was used for the synthesis of all compounds listed in Figure 3. The ZnO NPs were dried and recycled for subsequent reactions.

Preparation of ZnO NPs 2M solution of NaOH in ethanol (100 mL) was slowly added drop by drop to 50 ml of 1M stirred solution of $Zn(CH_3COO)_2{\bullet}2H_2O$ in ethanol at 70°C and the pH was maintained at 11. The final solution was stirred at 70°C for 2 h. After 2 h the solution were cooled to room temperature and settled down the solution. After that the solids were separated by centrifugation and washed from de-ionized water (3x15 ml) and ethanol (2x5 ml), and finally dried in air. To allow formation of ZnO nanoparticles and prevent precipitation of hydroxides, it is critical to maintain the temperature above 60°C. The formation of nanoparticles was confirmed from TEM studies (Figure 1b in main text) and powder XRD studies (Figure 1b in main text). The average particle sizes of the NPs were found to ~ 30 nm.

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