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Original Research Article

A facile synthesis of benzimidazole derivatives over zinc sulfide nanoparticles as heterogeneous catalyst

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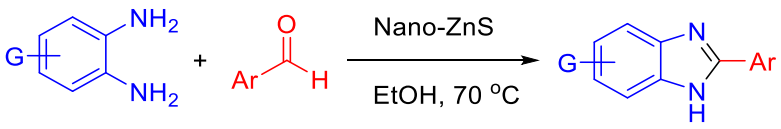
ABSTRACT

An efficient and eco-friendly method for the synthesis of benzimidazole derivatives through the one-pot cyclocondensation of the substituted aldehydes with *o*-phenylenediamines over zinc sulfide nanoparticles (nano-ZnS) in ethanol as solvent at 70 °C has been described. The present method has several advantages such as high yields, easy purification, mild reaction conditions, easy work-up and short reaction times. The nanoparticles are easily synthesized, cheap, air and moisture stable, and also heterogenic and green catalysts.

Graphical Abstract



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Introduction

Benzimidazoles moieties are a very important class of heterocyclic compounds that have great applications in drug discovery [1]. Recently, researchers have done a wide varieties of researches on benzimidazole derivatives due to the fact that these derivatives have shown various spectrum of pharmacological activities; including, vitamin B_{12} [2], anti-ulcer, anti-tumour and anti-viral [3], anti-microbial [4], anti-cancer [5], anti-helminthic [6], anti-hypertensive [7], anti-oxidant [8], anti-tubercular [9], anti-inflammatory [10], anti-malarial [11], selective inhibition of the platelet-derived growth factor receptor [12], *etc*. The most prominent benzimidazole in nature which is *N*-ribosyl-dimethyl benzimidazole serves as an axial ligand for cobalt in vitamin B_{12} [13], a proton pump inhibitor [14], and omeprazole, pantoprazole and lansoprazole [15]. In recent years, several methods have been reported for the synthesis of benzimidazoles using various catalysts such as rose bengal [16], *p*-toluenesulfonic acid/graphite and *N,N*-dimethyl aniline/graphite [17], NH_4Cl [18] and ytterbium perfluorooctane sulfonates ($Yb(OPf)_3$) [19]. Generally, the condensation of *o*-phenylenediamines with aldehydes in the presence of acid [20], base or metal catalyst [21] produces benzimidazoles. Other methods include condensation of *o*-phenylenediamines with carboxylic acids, nitriles and ortho-esters under dehydrating conditions [22], the dehydration of *N*-acylated, *o*-phenylenediamines using acetic acid [23], *p*-TSA [24] or amberlyst-15 which also produces benzimidazoles. These procedures, however, suffer from some drawbacks such as the use of toxic, highly acidic and expensive catalysts and require prolonged reaction times. Moreover, the yields of the corresponding benzimidazoles are not always satisfactory. Recently, a flow chemistry protocol has been developed to synthesize benzimidazoles by the condensation of *o*-phenylenediamines with aldehydes [25].

Nowadays, ZnS is an important member of this family as it has been extensively investigated [26]. ZnS nanoparticles have attracted a tremendous amount of attention because of their remarkable properties such as low cost, easy synthesis, high stability, small size *etc*. [27].

Because of the importance of benzimidazoles and the catalytic ability of ZnS nanoparticles in the organic reactions, we wish to report a facile and efficient method for the synthesis of benzimidazole derivatives in the presence of catalytic amounts of ZnS nanoparticles in ethanol as solvent at 70 °C.

Experimental

Materials and methods

All materials were purchased from Fluka, Aldrich and Merck and used without further purification. The products were characterized by comparing their physical properties and

spectroscopic data with those reported in the literature. Infrared (IR) spectra were recorded on KBr Pellets on a Shimadzu IR Presting-21 spectrophotometer in the range of 4000–400 cm^{-1}. NMR spectra were recorded in DMSO-d_6 on a Bruker Advanced DPX 400 MHz spectrometer using TMS as an internal reference. Melting points were obtained in open capillary tubes and were measured on a Buchi melting point B-540 B.V.CHI apparatus.

Synthesis of ZnS nanoparticles

First, carboxymethyl cellulose (CMC) (0.25 g) was dissolved in water and, then 50 mL solution of $ZnCl_2$ (0.05 M) was added to the CMC solution under stirring at room temperature in 30 min. Afterward, a white precipitate was appeared. The precipitate was filtered off, washed with water and, then, calcinated at 500 °C for 2 hr.

General procedure for the synthesis of benzimidazoles

A mixture of aldehydes (1 mmol), *o*-phenylenediamines (1 mmol), and nano-ZnS (0.003 g) was heated in EtOH at 70 °C for an appropriate time. The progress of the reaction was monitored by TLC (*n*-hexane/ethyl acetate, 1:2). After completion of the reaction, the mixture was washed with cold ethanol and the crude product was recrystallized by ethanol to obtain the pure benzimidazole derivatives in 80-98% yields.

2-(4-nitrophenyl)-1H-benzo[d]imidazol

Mp 99-102, IR (KBr, υ_{max}/cm^{-1}): 3347, 1635, 1540, 1448, 1367, and 1225. ^{1}H NMR (400 MHz, DMSO-d_6): δ 5.00 (brs, 1H, NH), 7.26-8.25 (m, 8H, aromatic). ^{13}C NMR (100 MHz, DMSO-d_6): δ 115.1, 117.1, 121.6, 123.2, 128.7, 136.3, 139.3, 148.0, 152.2, 158.1, 164.3, 164.2, 168. (Table 5, entry 3).

4-(1H-benzo[d]imidazole-2-yl)-N-methylbenzenamic

Mp 193-195 °C, IR (KBr, υ_{max}/cm^{-1}): 3371, 3325, 1749, 1542, 1500, and 1150. ^{1}H NMR (400 MHz, DMSO): δ 2.780 (s, 3H, CH_3), 4.0 (brs, 1H, NH), 5.0 (brs, 1H, NH), 6.49-7.70 (m, 9H, aromatic). ^{13}C NMR (100 MHz, DMSO): δ 29.5 (CH_3), 113.2, 114.7, 118.8, 119.1, 122.2, 123.3, 126.4, 128.1, 137.8, 147.6, 148.3, 151.8, 157.2 (Table 5, entry 4).

2-(1H-benzo[d]imidazole-2-yl)-6-methoxyphenol

Mp 95-97 °C, IR (KBr, υ_{max}/cm^{-1}) 3357, 3300, 1679, and 1538. ^{1}HNMR (400 MHz, DMSO): δ 3.71 (s, 3H, OCH_3), 5.0 (brs, NH), 5.0 (brs, 1H, OH), 6.56-7.70 (m, H, aromatic). ^{13}C NMR (100 MHz, DMSO), δ: 56.2 (OCH_3), 113.7, 114.9, 117.5, 121.3, 122.4, 123.5, 128.2, 128.5, 138.1, 153.4, 152 3, 162.3, 171.0 (Table 5, entry 5).

4-(1H-benzo[d]imidazole-2-yl)phenol

Mp 180-182 °C, IR (KBr, υ_{max}/cm^{-1}) 3334, 3320, 1720, 1672, and 1621. ^{1}HNMR (100 MHz, DMSO): δ 5.2 (brs, 1H, OH), 5.2 (brs, 1H, NH), 6.79-7.85 (m, H, aramotic). ^{13}C NMR (100 MHz, DMSO): δ 115.4, 116.8, 116.9, 123.1, 127.3, 128.5, 136.4, 136.3, 138.2, 151.2, 153.4, 163.5, 168.7 (Table 5, entry 7).

2-(3,4-dimethoxyphenyl)-1H-benzo[d]imidazole

Mp 136-138 °C, IR (KBr, υ_{max}/cm^{-1}) 3334, 1620, 1692, and 1633. ^{1}H NMR (400 MHz, DMSO): δ 3.2 (d, 6H OCH_3), 5.0 (brs, 1H, NH), 6.72-7.80 (m, H, aramotic). ^{13}C NMR (100 MHz, DMSO): δ 56.4 (OCH_3), 56.1(OCH_3), 113.7, 114.9, 116.8, 123.2, 138.2, 149.1, 149.2, 150.5, 153.4, 163.5, 168.7, 170.1, 172.3 (Table 5, entry 8).

Results and Discussion

The zinc sulfide nanoparticles were characterized by UV-visible spectrophotometer and SEM image. The UV-visible spectrum showed the surface plasmon peaks in the range between 4520-460 nm (Figure 1). The SEM image showed that the particle size of ZnS nanoparticles is about 120 nm (Figure 2).

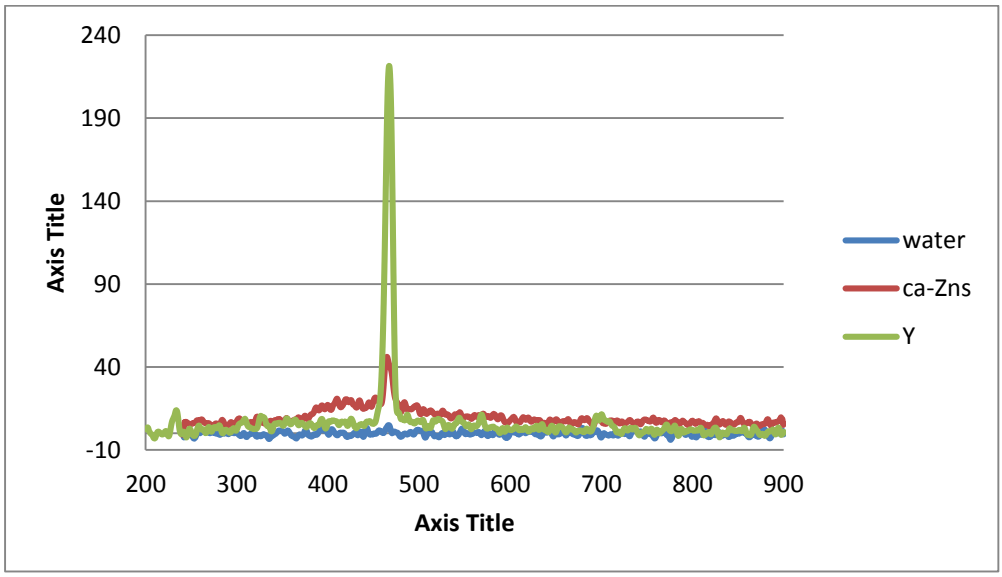


Figure 1. UV–visible spectrum for ZnS nanoparticles dissolved in toluene

After characterization of the catalyst, and in order to evaluate the catalytic activity of ZnS nanoparticles, they are used in the synthesis of benzimidazoles. To find the best reaction conditions, the reaction of benzaldehyde (1 mmol) and phenylenediamine (1 mmol) was performed under various conditions and different quantities of nano-ZnS (Scheme 1).

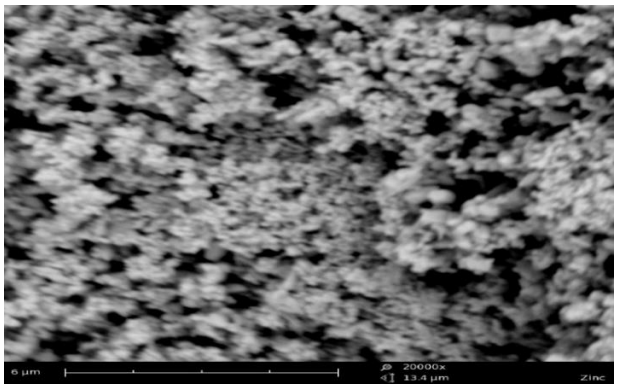
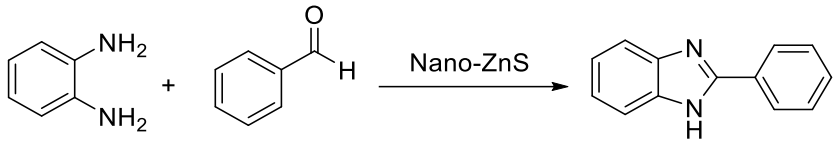


Figure 2. The SEM image of ZnS nanoparticles



Scheme 1. Synthesis of benzimidazole with Nano-ZnS

In order to establish the better catalytic activity of nano-ZnS, the reaction in the preaence of other catalysts in ethanol at 70 °C was investigated (Table 1). The results showed that the nano-ZnS, as compared to other catalysts, gave the better yield of the desired product (Table 1, entry 9).

To determine the optimum quantity of nano-ZnS, the reaction of bezaldehyde and *o*-phenylenediamine was carried out in EtOH at 70 °C using different quantities of nano-ZnS (Table 2). The results showed that 0.003 g of the catalyst gave the excellent yield of the product (Table 2, entry 3).

Table 1. Evaluation of the activity of different catalysts for the synthesis of 2-phenyl-1*H*-benzimidazole

Entry	Catalyst	Time (min)	Yield (%)
1	–	60	20
2	$Yb(OPf)_3$	60	50
3	Rose Bengal	60	60
4	$Al_5Y_3O_{12}$	60	65
5	N,N-Dimethyl aniline/graphite	60	70
6	Nd_2O_3	60	75
7	*p*-TSA/graphite	60	78
8	NH_4Cl	60	80
9	Nano ZnS	60	98

Table 2. Optimization amount of nano-ZnS for the synthesis of 2-phenyl-1*H*-benzimidazole

Entry	Catalyst (g)	Time (min)	Yield (%)
1	-	60	0
2	0.001	60	65
3	0.003	60	98
4	0.009	60	85
5	0.020	60	86

The above reaction was also examined in various solvents (Table 3). The results indicated that different solvents affected the efficiency of the reaction. Most of these solvents required a longer time and gave moderate yields, and the best results were obtained in ethanol (Table 3, entry 5).

Investigating the reaction in EtOH at different temperatures showed that the best temperature for obtaining the desired product is 70 °C (Table 4, entry 4).

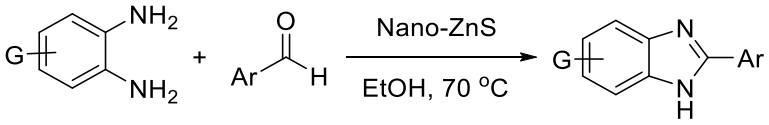
Table 3. Effect of the solvent in the synthesis of 2-phenyl-1*H*-benzimidazole using nano-ZnS

Entry	Solvent	Time (min)	Yield (%)
1	H_2O	60	0
2	EtOAc	60	55
3	$CHCl_3$	60	60
4	CH_2Cl_2	60	65
5	EtOH	60	96

Table 4. Optimization of the reaction temperature in the synthesis of 2-phenyl-1*H*-benzimidazole using nano-ZnS

Entry	Temperature (°C)	Time (min)	Yield (%)
1	25	60	15
2	40	60	70
3	60	60	80
4	70	60	96

After the optimisation of the reaction conditions, the synthesis of 2-arylsubstituded benzimidazoles was carried out by the reaction of different diamines with various aldehydes (Scheme 2 and Tables 5, 6, 7).



Scheme 2. Synthesis of benzimidazole derivatives using ZnS nanoparticles

Table 5. Reaction between *o*-phenylendiamine and different aldehydes catalyzed by nano-ZnS (0.003 g) in EtOH at 70 °C

Entry	Ar	Time (min)	Yield (%)	M.p. (°C)
1	2-$NO_2C_6H_4$	60	95	99-102
2	3-$NO_2C_6H_4$	60	95	115-117
3	4-$NO_2C_6H_4$	60	96	149-151
4	4-$NHCH_3C_6H_4$	60	91	193-195
5	2-OH-3$CH_3OC_6H_4$	60	85	95-97
6	4-ClC_6H_4	60	87	Oil
7	4-OHC_6H_4	60	98	180-182
8	3,4$(CH_3O)_2C_6H_3$	60	89	136-138

Table 6. Reaction between 4-nitro-1,2-phenylenediamine and different aldehydes catalysed by nano-ZnS (0.003 g) in EtOH at 70 °C

Entry	Ar	Time (min)	Yield (%)	M.p. (°C)
]	2-$NO_2C_6H_4$	60	92	133-136
2	3-$NO_2C_6H_4$	60	94	170-172
3	4-$NO_2C_6H_4$	60	96	220-222
4	4-$NHCH_3C_6H_4$	60	95	Oil
5	2-OH-3$CH_3OC_6H_4$	60	88	Oil
6	4-OHC_6H_4	60	98	145-147

Conclusions

In conclusion, the present study described the synthesis of 2-arylsubstituted benzimidazoles using zinc sulfide nanoparticles as an efficient heterogeneous catalyst. This catalytic procedure offers several advantages such as mild reaction condition, easy work-up, high yield, green aspects–such as avoiding hazardous organic solvents, toxic catalysts and waste–ease of recovery and reuse of the catalyst.

Table 7. Reaction between 4-methyl-1,2-phenylenediamine and different aldehydes catalysed by nano-ZnS (0.003 g) in EtOH at 70 °C

Entry	Ar	Time (min)	Yield (%)	M.p. (°C)
1	$2\text{-}NO_2C_6H_4$	60	86	188-190
2	$3\text{-}NO_2C_6H_4$	60	89	108-110
3	$4\text{-}NO_2C_6H_4$	60	90	103-106
4	$4\text{-}NHCH_3C_6H_4$	60	87	137-139
5	$2\text{-}OH\text{-}3CH_3OC_6H_4$	60	85	112-115
6	$4\text{-}ClC_6H_4$	60	80	Oil
7	$4\text{-}OHC_6H_4$	60	98	143-145
8	$3,4(CH_3O)_2C_6H_3$	60	97	Oil

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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