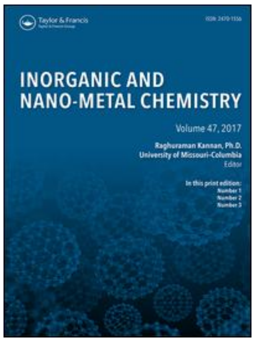

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Preparation of 2-Arylbenzimidazole Derivatives using CuO Nanoparticles /H_2O_2 system

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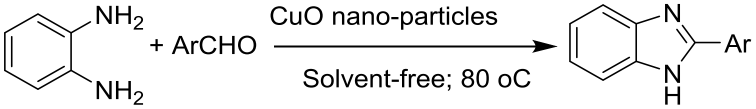
Abstract

CuO nanoparticles were prepared in watery lemon juice media and were characterized by XRD, FE-SEM, DLS, TGA and BET analysis. The as-prepared catalyst was efficient and recyclable for a high yielding, and practical method for the synthesis of 2-arylbenzimidazoles *via* cyclo-condensation reaction of 1,2-benzenediamine and aldehydes using copper oxide (CuO) nanoparticles is reported. Solvents and solvent-free effects on the reaction were investigated. Solvent plays a significant role in the reaction, and best results were achieved in solvent-free condition at 80°C. All reactions were completed in short reaction times (20-120 min) with 76-97% yields.

Graphical Abstract



Keywords

2-arylbenzimidazole; CuO nanoparticles; lemon water; heterogeneous catalyst; cyclo-condensation

Introduction

Among the heterocyclic compounds, which can overcome the viruses and bacteria disease, benzimidazole derivatives have attracted more attention for many chemistries and pharmacy professionals, because of their significant activities against several viruses such as HIV, herpes (HSV-1), antimicrobial, anti-inflammatory, RNA, human cytomegalovirus (HCMV), influenza and potential antitumour. [1,2] Moreover, these structures have interesting possibilities due to their potent anti-ulcer, antihypertensive, antiviral, anti-fungal, anti-cancer and anti-histaminic activity. [1,2] On the other hands, benzimidazole derivatives are commonly used as intermediates in synthetic courses as well as a ligand in asymmetric catalysis. [3] Due to the widespread use of benzimidazoles, easy and cost-effective development of new methods based on the synthesis of these compounds is in demands.

In the past, varieties of oxidative or reductive coupling, bond cleavage, and C-N bond formation methods for the synthesis of benzimidazoles have been developed. [4-8] The synthesis of benzimidazoles is reported by Palladium-catalyzed oxidative C--H amination of *N*,*N′*-bis(aryl)amidines.[9] Majumdar, et-al. reported the synthesis of benzimidazoles *via* condensation of 1,2-diamino benzene and β-ketoester/amide followed by C-C bond cleavage using a catalytic amount of SiO_2--$FeCl_3$.[10] Recently, an efficient method for the preparation of multi-substituted benzimidazoles was developed by Ugi 4CC/aza-Wittig sequence.[11]

The condensation of 1,2-benzenediamine with aldehydes or carboxylic acids derivatives is the reaction which, has been more attention due to its simplicity. This method is achieved in the presence of various catalysts under thermal and microwave conditions. Some of catalysts used are Ytterbium perfluorooctane sulfonates, [12] H_2O_2/HCl, [13] $H_2O_2/Fe(NO_3)_3$, [14] Ceric ammonium nitrate (CAN), [15] oxone®, [16] PEG-400, [17] SiO_2-$FeCl_3$, [18] and $BF_3.OEt_2$. [19] However, there are several reports of the use of copper salts such as $Cu(OAc)_2$, CuBr, and CuI as catalysts for the synthesis of benzimidazoles,[20-24] the use of green prepared CuO nanoparticles for the synthesis of 2-arylbenzimidazoles by the reaction of 1,2-benzenediamine and aldehydes is hereto-unknown.

In continue of our works on the synthesis of heterocyclic compounds,[25-29] herein, we report the synthesis of benzimidazoles from the cyclo-condensation reaction of 1,2-benzenediamine and aldehydes using CuO nanoparticles as an efficient catalyst and H_2O_2 as an oxidant (Scheme 1).

Result and Discussions

The crystal phase of the CuO nanoparticles was examined by powder X-ray diffraction (XRD) analysis (Figure 1). The representative XRD peaks appear in 32.5, 35.4, 35.5, 38.7, 38.9, 48.7, 58.3, 61.5, 65.8, 66.2 and 68.1 [2Theta degree] could be indexed to the monoclinic crystal system of CuO [Reference Code: 00-005-0661, Space group: C2/c]. The average crystal size of the CuO nanoparticles was estimated using Scherrer's formula as 50 nm.

Figure 2 shows the FE-SEM image of CuO nanoparticles prepared in a solution of lemon water. High-resolution FE-SEM micrograph reveals the nano-diameter and uniform shape of CuO particles. The particle size was confirmed to be less than 100 nm.

DLS measurement technique investigated the particle size distribution analysis of CuO nanoparticles. A Zetasizer Nano ZS (Malvern) was used for measuring the size distribution of nanoparticles in ethanol as solvent. The sample was dispersed in ethanol ($1 gL^{-1}$) and sonicated in for 2h. The results of DLS analysis is shown in Figure 3. According to DLS-measurement, the size distribution of the nanoparticles is almost in less than 100 nm with an average of 53 nm.

Figure 4 shows the thermogravimetric analysis (TGA) of CuO nanoparticles after and before calcination at 500°C. In both samples, the endothermic peaks are related to the removal of water and organic contaminants. The calcined CuO nanoparticles show a maximum of 6% weight losses which can be attributed to the elimination of surface adsorbed water of CuO nanoparticles (Figure 4a). The weight losses of the crude sample, however, is about 66% which can be considered as belonging to the removal of adsorbed water and organic contaminants present in lemon water (Figure 4b). These organic contaminants may be adsorbed on the surface of CuO or bonded to the Cu ions.

The nitrogen adsorption-desorption isotherm shows the inner porous nature of CuO nanoparticles (Figure 5). As shown in Figure 4, the IV type isotherm of nanoparticles indicates the mesoporous characteristic of the sample. Barrett--Joyner--Halenda (BJH) method was used for the pore size distribution of CuO nanoparticles, and the isotherm is shown in Figure 6. Figure 6 illustrated that the samples have mesopore structure with the pore radius between 4 and 8 nm. The specific surface area of CuO nanoparticles was measured by BET (Brunauer--Emmett-- Teller) method and was found to be 96 m^2g^{-1}.

Catalytic preparation of 2-arylbenzimidazole derivatives

When benzene-1,2-diamine reacted with benzaldehyde, an equilibrium will be created between starting materials and (E)-2-(benzylideneamino)aniline **(A)** as an intermediate (Scheme 2). The formed Schiff base (intermediate **A**) subsequently equilibrated with 2-phenyl-2,3-dihydro-1H-benzo[d]imidazole (intermediate **B**), as reported by Kumar et-al.. [30]

As the aim of this procedure is to prepare a variety of 2-aryl benzimidazoles, thus the presence of an oxidant is needed. Given chemical durability and environmentally friendly, H_2O_2 is a good candidate to be an oxidant in the above reaction. Due to the high activation barrier of hydrogen peroxide, it should be activated by a catalyst [31-32]. CuO nanoparticles could be a suitable activator for H_2O_2 oxidant. The mechanism involves the formation of an intermediate complex of H_2O_2 and CuO [31] which finally decomposed by the formation of H_2O *via* oxidative dehydrogenation of adduct **B** affords the desired 2-arylbenzimidazoles (Scheme 2).

Initially, the cyclo-condensation of benzaldehyde (1.0 mmol), and benzene-1,2-diamine (1 mmol) was performed in different solvents and catalyst dosages (Table 1). In a solvent with a boiling point less than 70°C e.g. Et_2O, cyclohexane, CH_2Cl_2, and hexane no product was formed. In other solvents including CH_3CN, THF, DMF, MeOH, EtOH, and EtOAc a complex mixture was formed due to the reaction of solvents with starting materials and oxidant. Thus solvent-free was chosen as the suitable media for this transformation. Further, to optimize the catalyst dosages, various amount of catalyst including 0.5, 0.25, 0.1 and 0.05 mmol were investigated. The results show that under the solvent-free condition the 0.25 mmol of CuO nanoparticles provides the desired products in higher yield.

Next, by applying the optimal reaction conditions, the effect of substitution of electron-withdrawing and electron-donating groups on the aromatic ring of aldehydes, on the reaction rate and efficiency of the reaction was investigated. In general, electron-withdrawing groups have experienced higher reaction rate than those of electron-donating groups. The substitution in the *ortho* position will be reduced the rate of productivity of the reaction. Despite the reaction times, the yields of all the reactions are excellent (Table 2). 2-Pyridinecarbadehyde also contributed to the reaction and gave the product in 76% yield.

The recyclability of the catalyst was checked using the following condition: benzaldehyde (1.0 mmol), and benzene-1,2-diamine (1 mmol) and CuO nanoparticles (0.25 mmol). During the purification of the products, the catalyst was separated by simple filtration, dried and reused for the similar reaction. The results of catalyst recovery are shown in Figure 7. As shown, the recovered CuO nanoparticles could reuse without significant loss in its catalytic activity.

In summary, we have utilized a novel, inexpensive and environmentally friendly method for the synthesis of copper oxide nanoparticles in a watery lemon juice media. The as-prepared copper oxide nanoparticles were used in the synthesis of 2-arylbenzimidazoles *via* cyclo-condensation reaction of 1,2-benzenediamine and aldehydes which were shown a high efficiency on the productivity in a short reaction time. This method is feasible, is environmentally friendly from the view of organic material removal in the preparation copper oxide nanoparticles and is advantageous for the high-efficiency production of 2-arylbenzimidazoles.

Experimental

The chemicals used were purchased from Merck and Aldrich companies. For the measurement of powder X-Ray diffraction patterns a D_8-Advance Bruker axs, diffractometer (CuKα radiation, $\lambda = 1.54178$ Å) was used. A HITACHI Microscope (Model S-4160) was applied for creation of Field Emission Scanning Electron Microscopy (FE-SEM) images. N_2 adsorption, specific surface area, and total pore volume measurements were carried out using Quantachrome instrument (Model Nova 2000, USA). A Malvern Zetasizer Nano ZS (ZEN 3600) device was used for the

Dynamic light scattering (DLS) measurement. The ^1H-and ^{13}C-NMR spectra were measured in DMSO-d_6 by a Bruker Avance DPX 400 MHz instrument. Melting points were determined in open capillaries with a BUCHI 510 melting point apparatus.

Preparation of CuO nanoparticles:

20 mmol of copper acetate was dissolved in 50 mL of distillate water and subsequently mixed with 100 mL of lemon water. The solution was refluxed for 30 min with vigorous stirring. Afterward, the pH value was increased to basic area by the addition of sodium hydroxide solid into the above boiling solution. The mixture was cooled, centrifuged and the precipitate was washed with distilled water dried and calcinated in 500°C for 2h.

Typical Procedure:

1,2-benzenediamine (1 mmol), aryl aldehydes (1 mmol) and H_2O_2 (aq. 30%; 0.5 mL) were charged into a test tube and combined with CuO nanoparticles (0.25 mmol). The mixture was heated up to 80°C until completion of the reaction (Table 2). After completion (TLC monitoring), the contents was cooled to 25°C, dissolved in CH_2Cl_2 and filtrate to remove the catalyst. Finally, the crude product was purified by recrystallization from ethanol after removal of CH_2Cl_2.

Acknowledgments

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Table 1: Optimization of the reaction conditions (Scheme 1)

Entry	Catalyst amount (mmol)	Solvent (5 mL)	Temperature (°C)	Time (h)/ Yield (%)[a]
1	0.25	Hexane	Reflux	2/0
2	0.25	Cyclohexane	Reflux	2/0
3	0.25	Et_2O	Reflux	2/0
4	0.25	CH_2Cl_2	Reflux	2/0
5	0.25	THF	80	2/36
6	0.25	DMF	80	2/48
7	0.25	EtOAc	Reflux	2/56*
8	0.25	EtOH	Reflux	2/75*
9	0.25	CH_3CN	Reflux	2/71*
10	0.25	MeOH	Reflux	2/69*
11	0.25	-	80	30min/93
12	0.5	-	80	30min/89
13	0.1	-	80	30min/68
14	0.05	-	80	30min/31

[a] Isolated yield

[*] complex mixture

Table 2: Synthesis of 2-arylbenzimidazole derivatives using CuO nanoparticles (0.25 mmol) as catalyst

Entry	Aldehyde	Time (min)	Yield (%)[a]	m.p. [lit. m.p.°C][ref]
1	Benzaldehyde	30	93	287-289 [288-290][15]
2	3,4,5-Trimethoxybenzaldehyde	120	85	287-289 [288-290][15]
3	3,4-Dimethoxybenzaldehyde	90	79	233-235 [232-234][16]
4	2-Hydroxybenzaldehyde	80	77	241-243 [240-242][9]
5	4-Methoxybenzaldehyde	56	94	225-227 [225-226][9]
6	4-Methylbenzaldehyde	50	90	269-271 [268-270][9]
7	4-Chlorobenzaldehyde	30	89	293-295 [292-293][15]
8	4-Nitrobenzaldehyde	20	97	314-316 [312-314][9]
9	3-Nitrobenzaldehyde	20	97	308-310 [310-311][15]
10	2-Nitrobenzaldehyde	55	86	210-212 [209-210][9]
11	2-Chlorobenzaldehyde	45	96	233-235 [232-234][11]
12	4-Flourobenzaldehyde	40	90	251-253 [250-252][16]

13	2-Pyridinecarbadehyde	60	76	215-217 [217-219][8]

[a] Isolated yields.

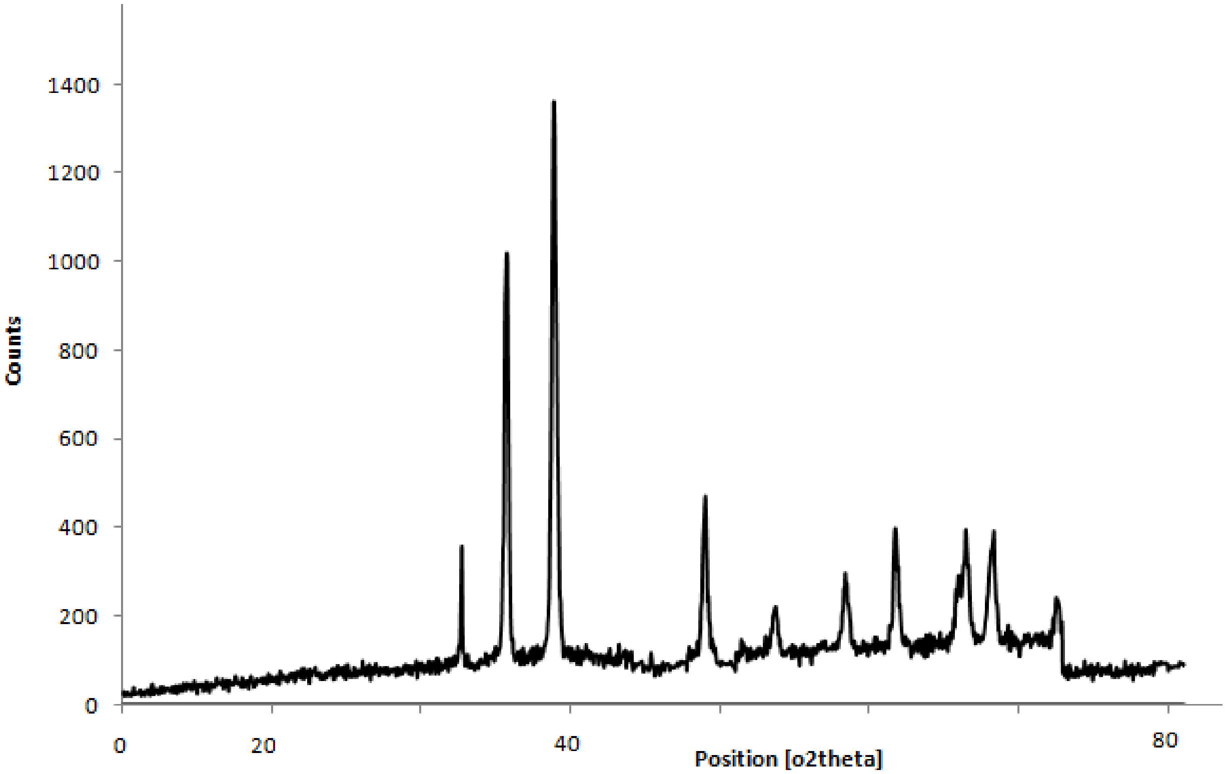


Figure 1: X-ray diffraction (XRD) spectra of CuO particles

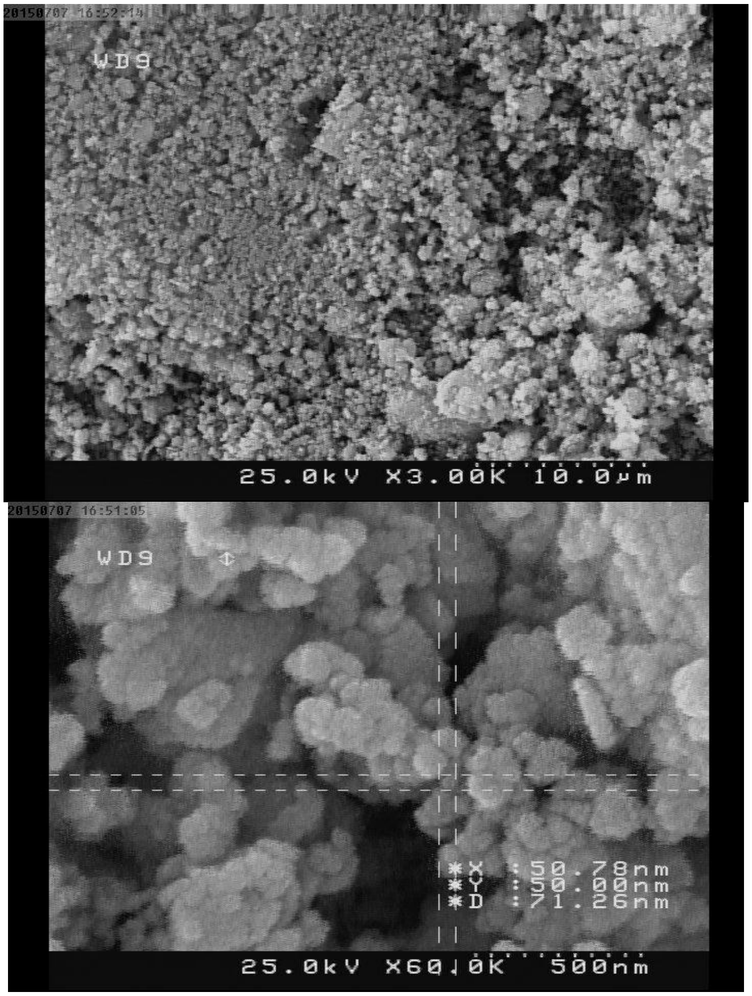


Figure 2: FE-SEM image of CuO nanoparticles

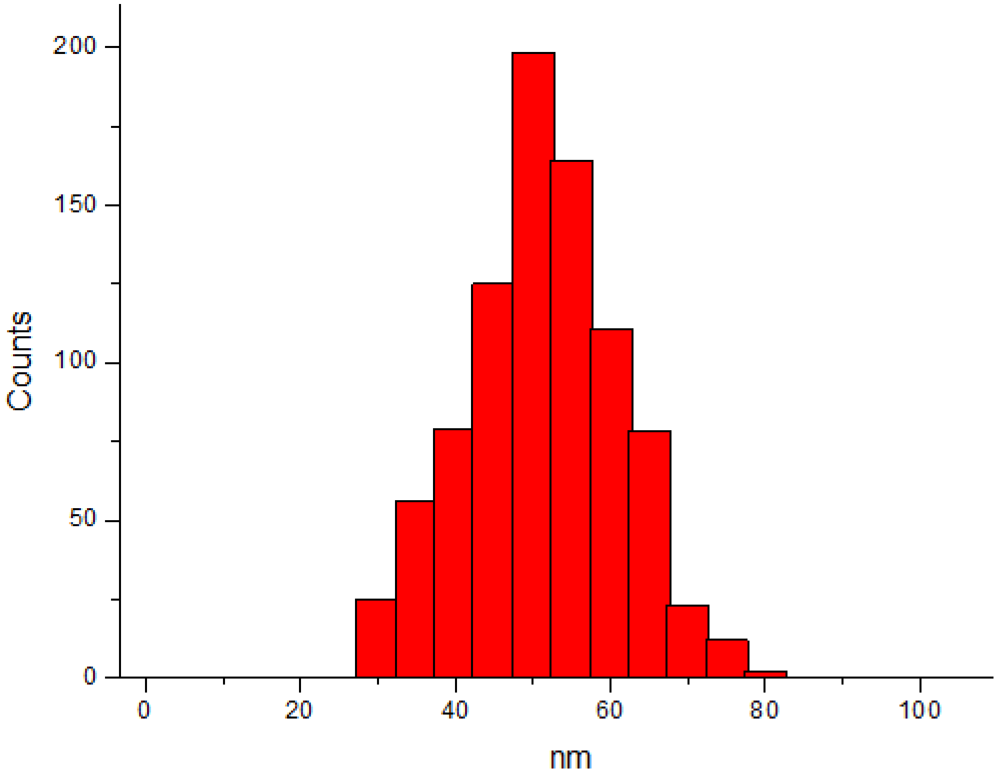


Figure 3: particle size distribution analysis of CuO nanoparticles

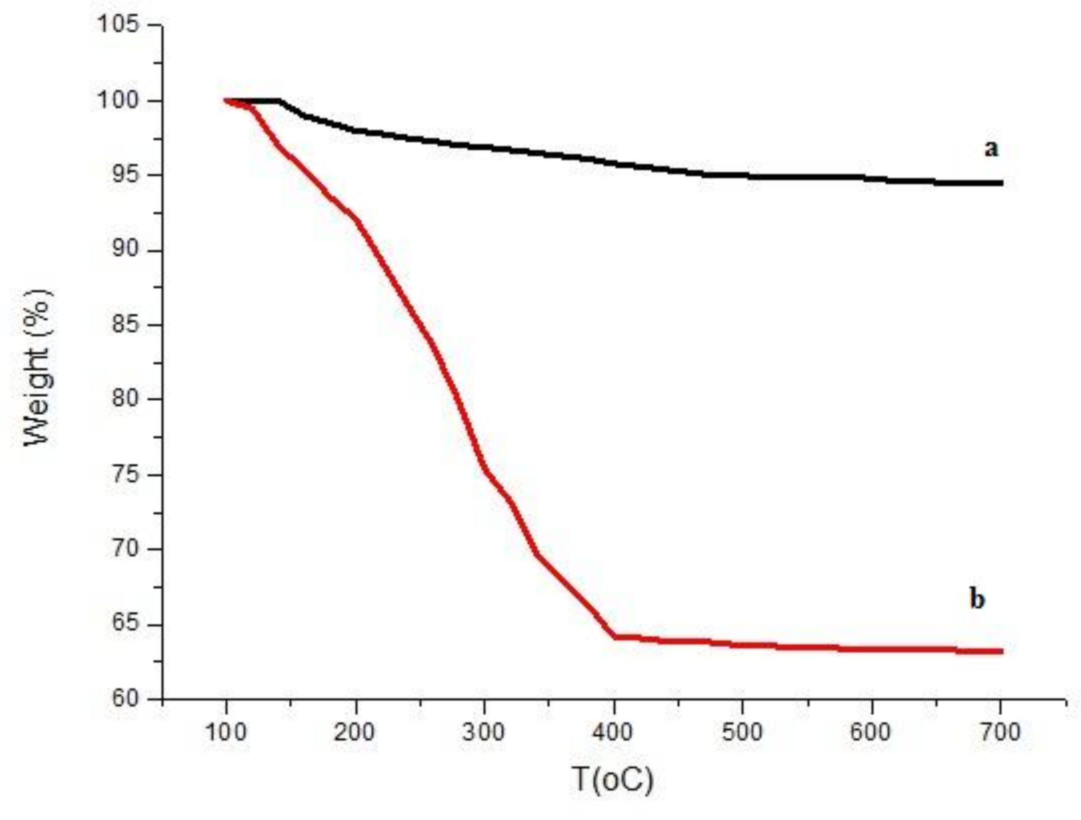


Figure 4: Thermo gravimetric analyses of CuO nanoparticles after calcinations at 500 °C (a) and before calcinations (b)

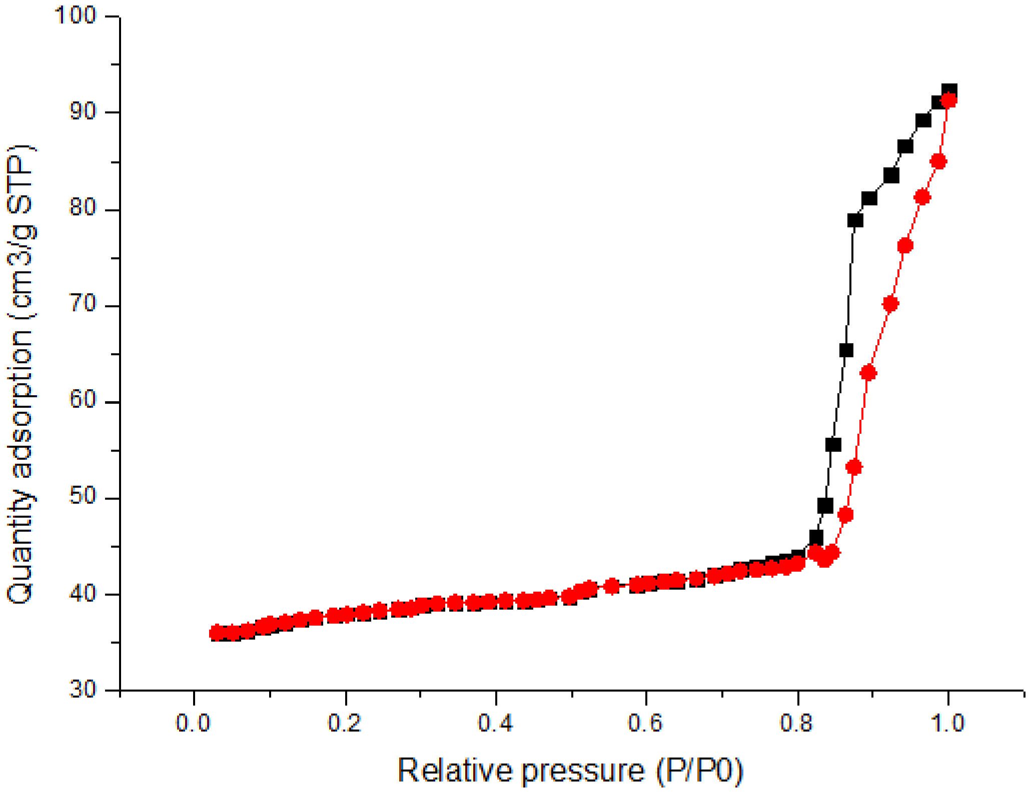


Figure 5: The nitrogen adsorption-desorption isotherm of CuO nanoparticles.

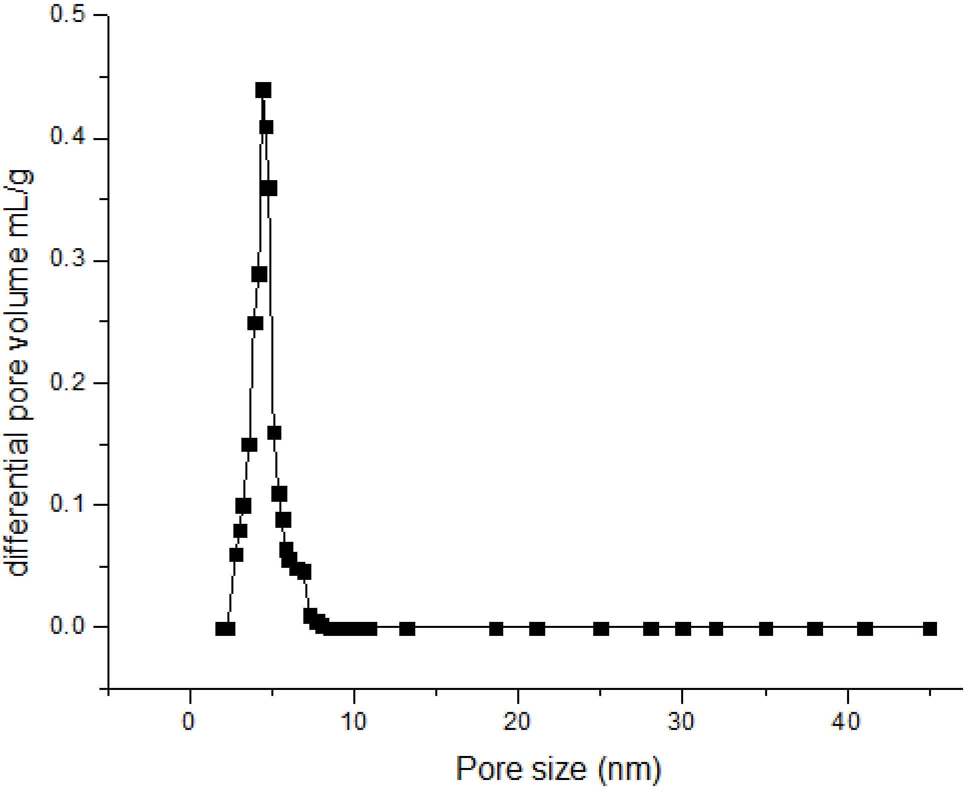


Figure 6: the pore size distribution of CuO nanoparticles

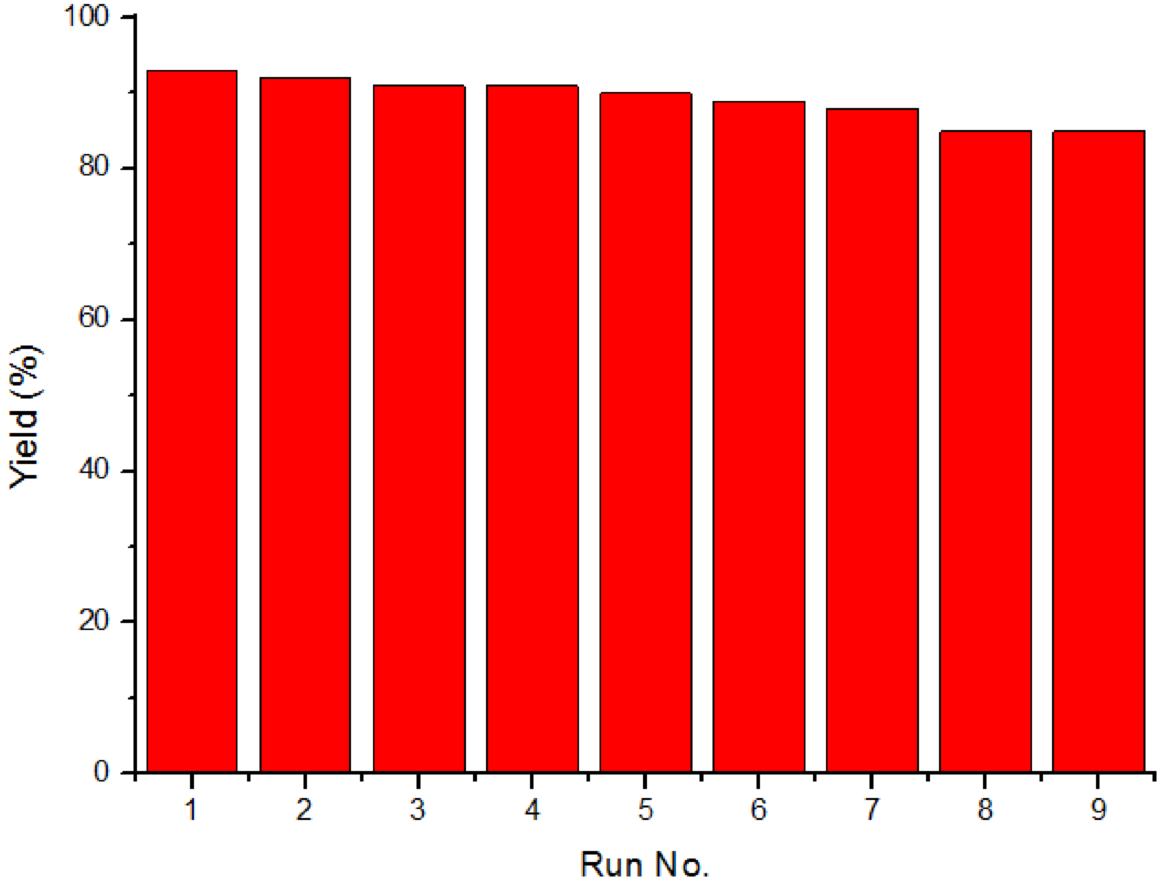
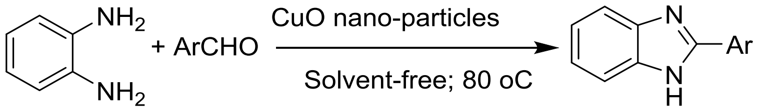
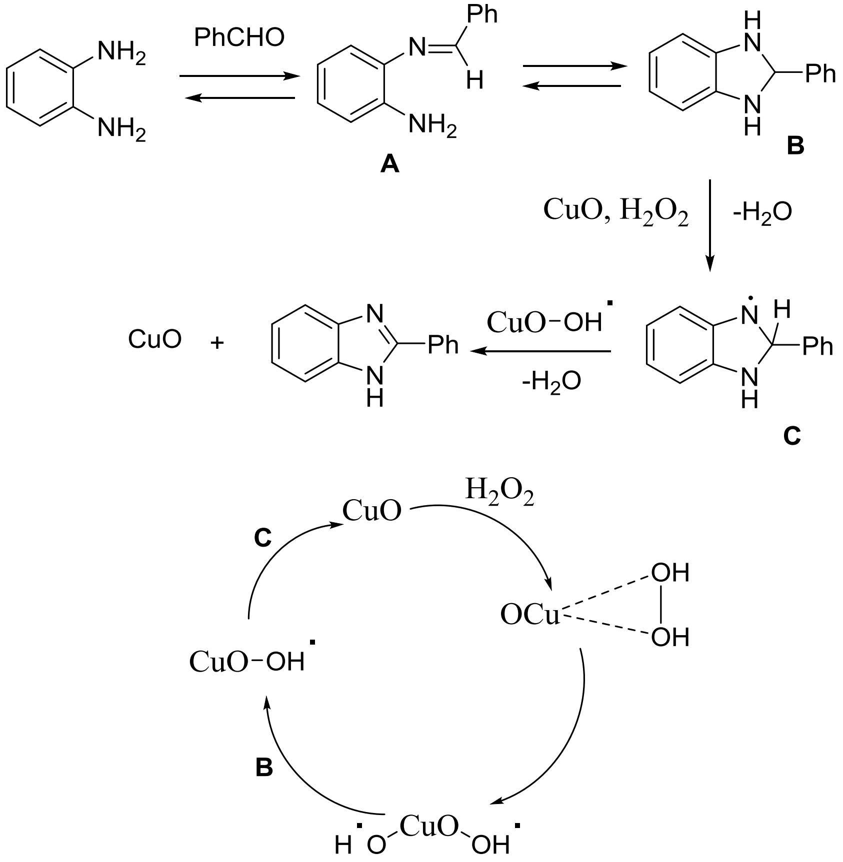


Figure 7: Reusability of CuO nanoparticles



Scheme 1: Preparation of 2-aryl benzimidazoles



Scheme 2: Proposed mechanism for the preparation of 2-arylbenzimidazoles