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The Effect Study of Various Parameters on the Synthesis of Benzoxazole Derivatives Utilizing Cadmium Oxide Nanoparticles

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Abstract: Due to its straightforward approach, the co-precipitation technique for producing nanomaterials has gained popularity over time. In this study, we employed cadmium nitrate to synthesize cadmium oxide nanomaterials (CdO NPs). The morphology and size of the synthesized CdO NPs were determined using Scanning Electron Microscopy (SEM) and Atomic Force Microscopy (AFM) respectively. To find the functional groups that are present in the nanoparticles and are involved in their decrease and stabilization, a Fourier Transform Infrared Spectroscopy (FTIR) study was carried out. Additionally, X-ray diffraction analysis (XRD) was employed to confirm the crystalline nature of the NPs. By utilizing the synthesized catalyst CdO NPs, we successfully synthesized benzoxazole derivatives with improved yields by reacting o-amino phenol with various aldehydes, achieving yields of 90-93%. The structures of the synthesized molecules were characterized using NMR and FTIR spectroscopy. Noteworthy advantages of this method include its short reaction time, high product yields, and the catalyst's recyclability.

Keywords: Benzoxazole, Cadmium oxide NPs, Nanoparticles, co-precipitation

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1. INTRODUCTION

Nanomaterials have become very promising compounds in the field of nanochemistry in recent years. They are more catalytically active than bulk materials because of their smaller size and higher surface area (1). Due to its outstanding catalytic activity and several biological uses, such as antioxidant, anticancer, and antibacterial capacity, cadmium oxide nanoparticles (CdO-NPs) in particular have attracted substantial attention in the field of nanotechnology (2-6). In the synthesis of new organic compounds and biologically active molecules, heteroaromatic compounds have received a lot of attention (7-10). Due to their importance in biology and pharmacology, heterocyclic molecules containing oxygen and nitrogen have attracted the most attention. We have chosen to focus on benzoxazoles in our ongoing search for effective strategies to synthesize physiologically relevant heterocyclic chemicals. The "isosteres of natural nucleotides" known as oxazole derivatives have drawn the attention of various researchers who want to develop synthetic analogs with effective chemotherapeutic properties (11-16). Many naturally occurring and synthesized bioactive chemicals, which show a variety of biological functions, have the benzoxazole scaffold. Inhibition of the eukaryotic topoisomerase II enzyme (17-19), effectiveness against multidrug-resistant cancer cells (20-25), antimalarial and antileishmanial effects (26), antiviral properties (27,28), antibacterial activity (29), are a few of these activities. The literature contains numerous attempts to synthesize the benzoxazole scaffold. Ortho-aminophenol is often condensed with a carboxylic acid (COOH) or

acyl chloride (COCl) in the presence of a strong acid at a high temperature in order to produce the O1-C2 and N3-C2 linkages (30). The oxidative cyclization of phenolic Schiff bases derived from aldehydes is another frequently used approach. This method makes use of a various of oxidizing agents, including $Mn(OAc)_3$ (31), DDQ (32), $ThClO_4$ (33), NiO_2 (34), $ZrOCl_2{\cdot}8H_2O$ (35), PCC-supported silica gel (36), DessMartin reagent (37), $BaMnO_4$ (38), and $Pb(OAc)_4$ (39). The development of heterogeneous catalysts has received significant attention in modern synthetic chemistry. With homogeneous catalysts, it has proven to be extremely difficult to separate the catalysts from the reaction mixture while under catalytic conditions. Researchers have looked into using suitable supports, in particular nanoscale materials, as homogeneous catalysts to solve this problem. High atomic efficiency, simplified product purification, and the possibility of reusing the catalysts are only a few benefits of this method (40). The fabrication of cadmium oxide nanoparticles and their use in the synthesis of benzoxazole derivatives are the goals of this study. The study also intends to evaluate the effects of several conditions on the reaction process, such as reaction time, catalyst type and quantity, and solvent type.

2. Experimental

2.1. Materials and methods

The necessary materials utilized in the experiment were obtained from Sigma-Aldrich or BDH and were not purified. To track the progress of the reaction, Thin Layer Chromatography (TLC) was employed, utilizing Silica Gel 60 TLC plates and UV light at 254 nm. The melting points of the synthesized compounds were evaluated using a Stuart melting point apparatus, SMP30. The products obtained were analyzed using FTIR spectra, obtained from a Bruker alpha 2 instrument (Germany), and H-NMR spectra, obtained from a Bruker Bio Spin GmbH Spectrometer (400 MHz), with DMSO as the solvent.

2.2. Co-precipitation procedure for the fabrication of CdO NPs-Ther

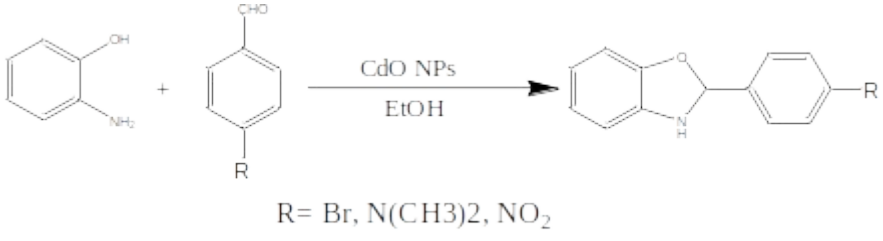
To form CdO NPs-Ther, a method known as co-precipitation was utilized (40). In a round bottom flask equipped with a magnetic stirrer, a solution of 15 mmoles of Cd $(NO_3)_2.4H_2O$ was prepared in a mixture of (60 mL) of water and ethanol (1:1). While continuously stirring, a solution containing 4 mmoles of threonine in 1 mL of deionized (DI) water was added. The pH value of the mixture was adjusted to 10 using a 2 M aqueous solution of NaOH. The finding combination was stirred for 12 hours at room temperature. Subsequently, the solution was centrifuged at (5000 rpm) for 25 minutes. The producing precipitate pellet was then subjected to another round of centrifugation and washed with a solution of DI water and ethanol (ratio: 1:1). As well as, the precipitate was dried in an oven at 80 °C for 20 hours to obtain the desired product, CdO NPs-Ther. Additionally, CdO NPs and $CdNiO_2$ NPs without threonine surface modification were synthesized utilizing the same procedure, but threonine was not added.

2.3. Characterization of nano cadmium oxide NPs

The morphology and surface of the fabricated nano cadmium oxide NPs were analyzed for characterization purposes. The NPs compounds were characterized using X-ray diffraction (XRD) with a Rigaku model. XRD measurements of the samples were conducted at ambient temperature in the 2θ range of 0^0-80^0, utilizing Copper (Cu) with a wavelength (λ) of 1.54056 Å. Scanning Electron Microscope (SEM) images of the samples were captured utilizing a Zeiss SEM analyzer, operating at a voltage of (20 KV). Additionally, Atomic Force Microscopy (AFM) images were obtained using a DME dualscope c21 instrument from Denmark.

2.4. Synthesis of 2-aryl benzoxazole derivatives using CdO NPs

A solution containing 0.001 mol of various aldehydes and 0.001 mol of o-amino phenol in 3 mL of ethanol was prepared, to which 10 mg of cadmium oxide NPs were added. The reaction solution was stirred at laboratory temperature for 3 hours. The progress of the reaction was monitored utilizing Thin Layer Chromatography with ethyl acetate-n-hexane (2:1) as the eluent. Once the reaction was complete, the solution was filtered to remove the catalyst. The solvent was then evaporated, and the residue was purified through recrystallization using ethanol. The structures of the synthesized compounds were characterized utilizing FTIR and HNMR spectra, with most of the compounds being well-known.



Scheme 1: CdO NPs- catalyzed synthesis of benzoxazole derivatives.

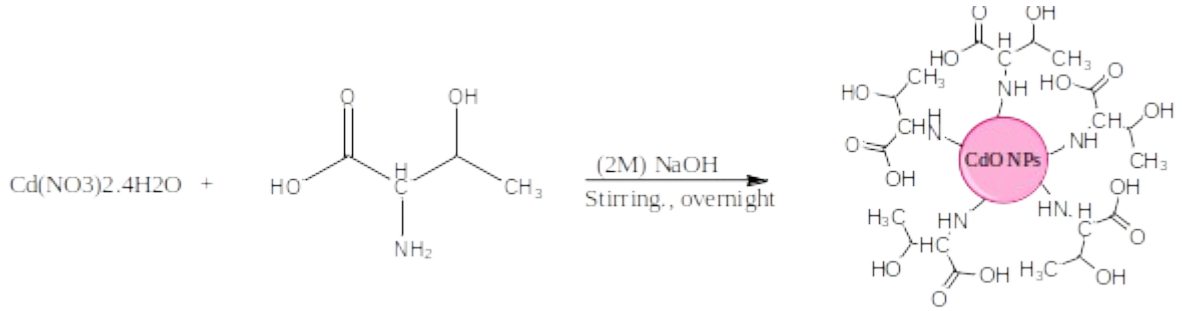
2-(4-nitrophenyl)benzoxazole. Solid compound; m.p:272-275 ^{0}C (lit.(41) 275-277 ^{0}C); FTIR: 3358 cm^{-1}(NH), 1624 cm-^{1} (C=N), 3082 cm^{-1} (C-H or.), 1586 cm^{-1} (C=C), 1479 cm^{-1} (NO_2); H-NMR (DMSO-d6, 400 MHz): δ9.240 (s,1H, NH), 8.900 (s,1H, H-oxazole), 6.844-8.368(m,8H, aromatic proton).

2-(4-N, N-dimethyl phenyl)benzoxazole. Solid compound; m.p:286-288 ^{0}C (lit.(42) 285-288); FTIR: 3323 cm^{-1} (NH), 1611 cm-^{1} (C=N), 3068 cm^{-1} (C-H or.), 1583 cm^{-1} (C=C), 2903 cm^{-1} (CH_{al}.); H-NMR (DMSO-d6, 400 MHz): δ8.682 (s,1H, NH), 8.511(s,1H, H-oxazole), 6.794-7.856(m,8H, aromatic proton), 3.011(s,6H,N(CH_3)$_2$).

2-(4-bromophenyl)benzoxazole. Solid compound; m.p:163-165-275 °C (lit.(43) 166-169 °C); FTIR: 332 cm^{-1} (NH), 1624 cm^{-1} (C=N), 3066 cm^{-1}(C-H or.), 1586 cm^{-1} (C=C), 757 cm^{-1} (C-Br); H-NMR (DMSO-d6, 400 MHz): δ9.049 (s,1H, NH), 8.710 (s,1H, H-oxazole), 6.814-8.002 (m,8H, aromatic proton).

3. RESULTS AND DISCUSSION

The fabrication of cadmium oxide nanoparticles (NPs), cadmium oxide NPS-Threonine, and $NiCdO_2$ NPs was achieved using a co-precipitation method. $Cd(NO_3)_2.4H_2O$ and $Ni(NO_3)_2.6H_2O$ were utilized as the sources of cadmium and nickel, respectively, while sodium hydroxide served as the precipitation agent. To form the solution, $Cd(NO_3)_2$ was mixed with an amino acid solution (threonine) in a dropwise manner. The pH was adjusted to 10 by adding sodium hydroxide solution. The suggested reaction mechanism is illustrated in Scheme 2.



Scheme. 2. Synthesis of CdO NPs derivatives.

3.1. Surface Functional Group Analysis.

FTIR spectroscopy was utilized to evaluate the groups present on the surface of CdO nanoparticles. In Figure 1, the FTIR spectrum of the synthesized CdO nanoparticles clearly appears at a peak at 3555 cm^{-1}, which corresponds to the stretching vibration of (OH groups) on the CdO surface (2). Additionally, the band at 1390 cm^{-1} is characteristic of CdO (44). The FTIR spectrum of CdO nanoparticles with Threonine exhibits prominent peaks at 3451 and 3619 cm^{-1}, indicating (N-H) symmetric stretching and the presence of (OH groups) (45). The peaks at 1630 cm^{-1} can be attributed to the C=O vibration modes of the carbonyl group in threonine (45). The presence of the Cd-O bond is indicated by the peak at 633 cm^{-1} (47). Furthermore, the spectra of $CdNiO_2$ nanoparticles reveal that the peaks between 690 cm^{-1} and 1451 cm^{-1} are assigned to CdO (3). The peak at 1362 cm^{-1} corresponds to the stretching of the Cd-O-Ni bond, which is formed by tetrahedral building units in the structure (48).

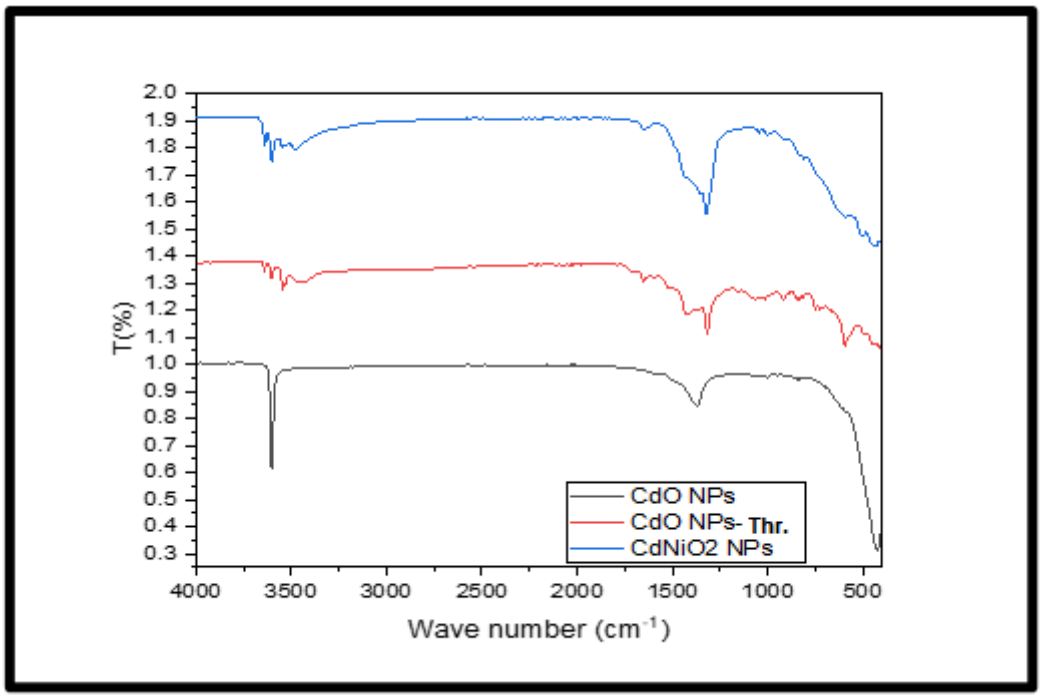


Figure 1: FTIR spectra of synthesized CdO Nanoparticles.

3.2. Xray diffraction analysis (XRD)

In order to evaluate the size of the CdO nano-particles (NPs) formed through the co-precipitation procedure with the inclusion of an amino acid like threonine or NiO, we can employ the Scherrer equation. This equation establishes a relationship between the broadening of peaks observed in X-ray diffraction (XRD) patterns and the size of the crystallites.

$$D = K\lambda/\beta\cos\theta \quad \text{(Eq. 1)}$$

The Scherrer equation defines the variables as follows: D represents the crystallite size, K is the Scherrer constant (approximately 0.9), λ denotes the wavelength of the X-ray source (typically Cu Kα, 1.5406 Å), β represents the full width at half maximum (FWHM) of the XRD peak, and θ corresponds to the Bragg angle. Depending on the Scherrer equation, the crystallite size of the samples is presented in the following table.

3.3. Morphological study

An SEM analysis was conducted on CdO nanoparticles (NPs) synthesized utilizing the co-precipitation procedure. The SEM image revealed a mixture of spherical and needle-shaped CdO NPs, with agglomerated clusters. Furthermore, the SEM image indicated the absence of impurities in the sample, suggesting that all reactants were thoroughly eliminated during the synthesis process. The J image software was employed to evaluate the size distribution of the CdO NPs, with the average size of the spherical particles measuring 258 nm.

Similarly, when CdO NPs were synthesized via the co-precipitation method with the addition of an amino acid like threonine, an SEM image provided valuable insights into the morphology, size, and distribution of the particles. The SEM image demonstrated the presence of spherical CdO + amino acid (threonine) NPs, which were uniformly dispersed. Additionally, no impurities were observed in the sample, indicating the complete removal of all reactants during synthesis. The average size of these particles was measured to be 108.07 nm.

In the case of CdNiO2 NPs, the SEM image revealed irregularly shaped particles. The image also exhibited that the CdNiO2 NPs were agglomerated in clusters, appearing as white foreign particles, suggesting the presence of residual precursors or reactants that were not entirely eliminated during synthesis. The average size of these particles was determined to be 367.4 nm.

Table.1: Crystalline size of synthesized nanoparticles.

Sample	crystallite size (nm)
CdO NPs	33.9 nm
CdO + amino acid(threonine)	28.3 nm
$CdNiO_2$ NPS	27.9 nm

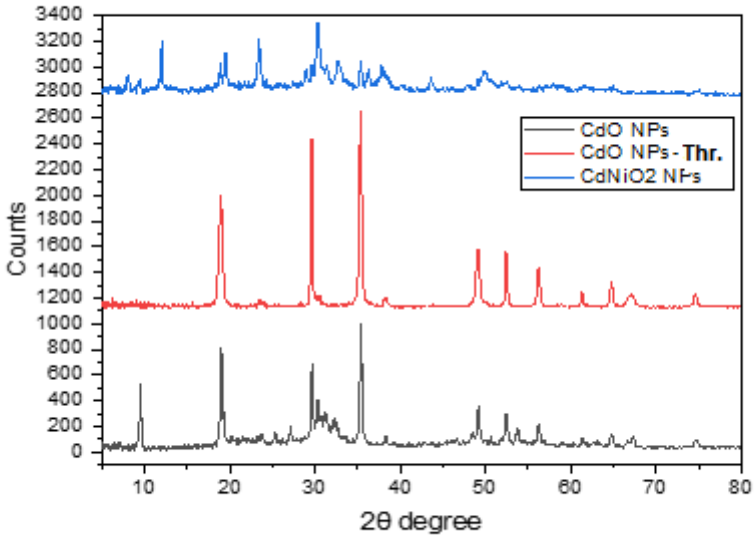


Figure 2: XRD diagram of synthesized CdO Nps.

3.4. Optimization for benzoxazole derivatives synthesis method

We conducted a study on synthesizing benzoxazole derivatives through the cyclocondensation of o-amino phenol and various substituted aromatic aldehydes. In this study, we utilized cadmium oxide nanoparticles as catalysts and investigated the influence of different factors such as catalyst type and amount, solvent type, and reaction time. Among the catalysts tested, namely $Cd(NO_3)_2$, CdO NPs, CdO NPs-Thr, and $CdNiO_2$ NPs, CdO NPs demonstrated favorable yields of 88%, 80%, and 87% for 2(4-NO_2PY)OX, 2(4-N(Me)$_2$PY)OX, and 2(4-BrPY)OX, respectively. However, despite having a smaller particle size compared to CdO NPs and $CdNiO_2$ NPs, CdO NPs-Ther. yielded lower amounts of synthesized benzimidazole derivatives. This can be attributed to the coating of CdO NPs with the amino acid (threonine), resulting in high roughness and heterogeneity, as depicted in Figure 5.

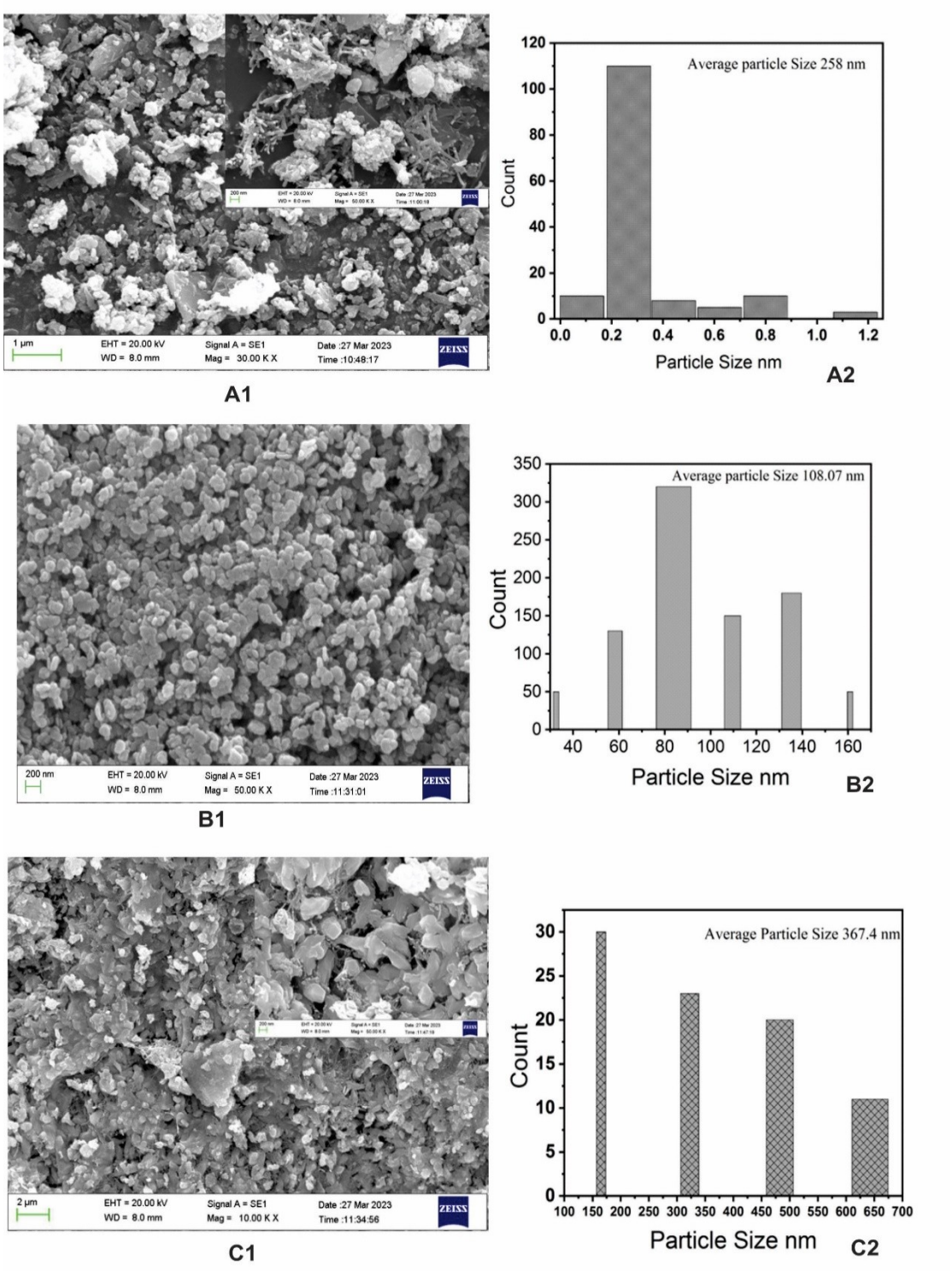


Figure 3: SEM and histogram of CdO NPs (A1&A2), CdO NPs-Thr (B1&B2) and $CdNiO_2$ NPs(C1&C2).

Figure 4 illustrates the surface characteristics of compound CdO NPs-Thr, demonstrating its high roughness and heterogeneity compared to CdO NPs and $CdNiO_2$ NPs.

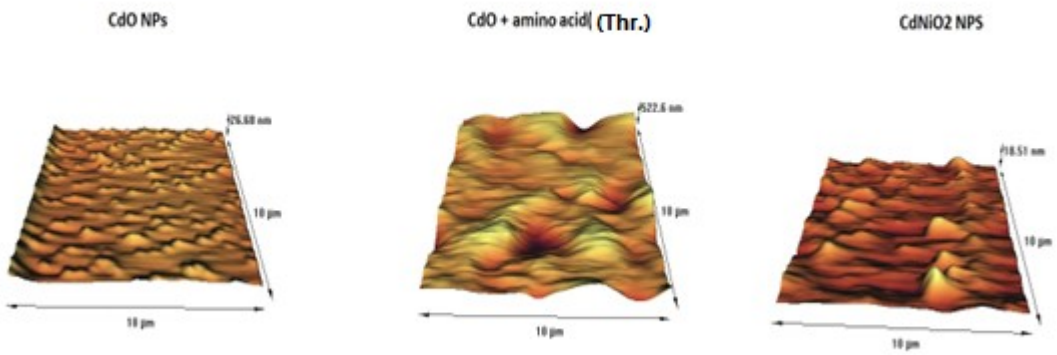


Figure 4: 3D AFM picture and distribution map of granularity accumulation of CdO nanostructure.

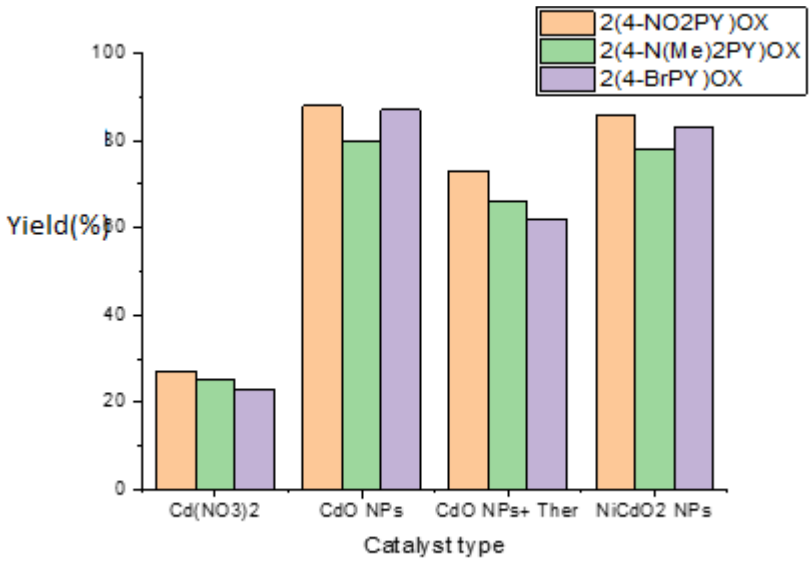


Figure 5: Effect of catalyst type on the yield of product.
*2-(4-nitrophenyl)benzoxazole [2(NO_2PY)OX]; 2(4-($N(Me)_2$phenyl)benzoxazole [2(4-$(Me)_2$PY)OX]; 2(4-bromophenyl)benzoxazole [2(4-BrPY)OX]

Certainly, the catalyst amounts play a crucial role in determining the yields of the different compounds in the chemical reaction. A catalyst is a substance that facilitates a chemical reaction without being consumed in the process. It speeds up the reaction rate by providing an alternative reaction pathway with lower activation energy. Various quantities of catalyst (Cdo NPs) ranging from 0.005 to 0.02 g were investigated. According to Figure .6, the perfect yields for 2(4-NO_2PY) OX, 2(4-$N(Me)_2$PY) OX, and 2(4-BrPY)OX were obtained with catalyst amounts of 0.005 g, 0.02 g, and 0.015 g, respectively. For 2(4-NO_2PY)OX, the highest yield was obtained with a catalyst amount of 0.005 g. This suggests that a smaller quantity of catalyst was sufficient to promote the reaction and achieve a desirable yield for this particular compound. On the other hand, 2(4-N(Me)2PY)OX demonstrated the highest yield when the catalyst amount was 0.02 g. This indicates that a larger quantity of catalyst was required to optimize the reaction and maximize the yield of this compound. Similarly, 2(4-BrPY)OX exhibited the highest yield with a catalyst amount of 0.015 g. This suggests that an intermediate catalyst quantity was most effective in promoting the reaction and obtaining a favorable yield for this compound. Overall, the findings highlight the importance of carefully selecting the appropriate catalyst amount to achieve optimal yields for different compounds. The specific amounts can vary depending on the nature of the compounds, the reaction conditions, and the catalytic properties of the catalyst itself.

The polarity of solvents plays a significant role in chemical reactions, particularly in terms of solubility and reaction rates. The polarity of a solvent refers to the separation of electric charge within the molecule, resulting in regions of partial positive and partial negative charges. Various solvents including ethanol, acetonitrile, dichloromethane, THF, and toluene were utilized, and their outcomes are illustrated in figure.7. As a result of ethanol's higher polarity in comparison to the other solvents, it

yielded favorable results of 88%, 85%, and 89% for 2(4-NO_2PY)OX, 2(4-$(Me)_2$PY)OX, and 2(4-BrPY)OX, respectively. In the case of the mentioned compounds, their favorable yields with ethanol can be attributed to the high polarity of ethanol. The polar nature of ethanol facilitates the dissolution of the reactants and products involved in the reaction, resulting in efficient molecular interactions and a higher likelihood of successful reactions. In contrast, solvents with lower polarity, such as acetonitrile, dichloromethane, THF, and toluene, may have exhibited lower yields due to reduced solubility or less favorable molecular interactions with the reactants. Overall, the choice of solvent with the appropriate polarity is crucial in optimizing reaction conditions and achieving desired yields. The polarity of solvents influences the solubility of reactants, the stability of reaction intermediates, and the overall reaction kinetics.

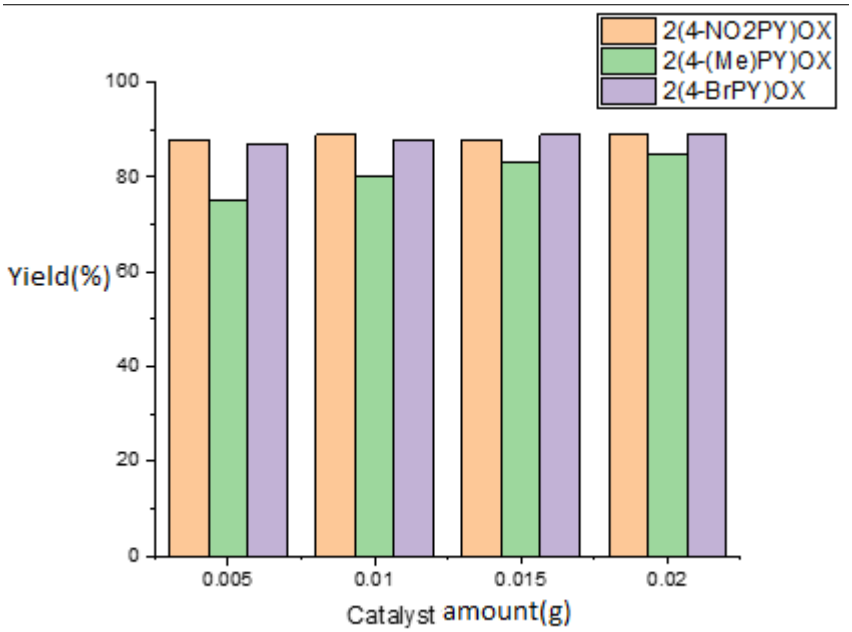


Figure 6: Effect of catalyst amount on the yield of product.

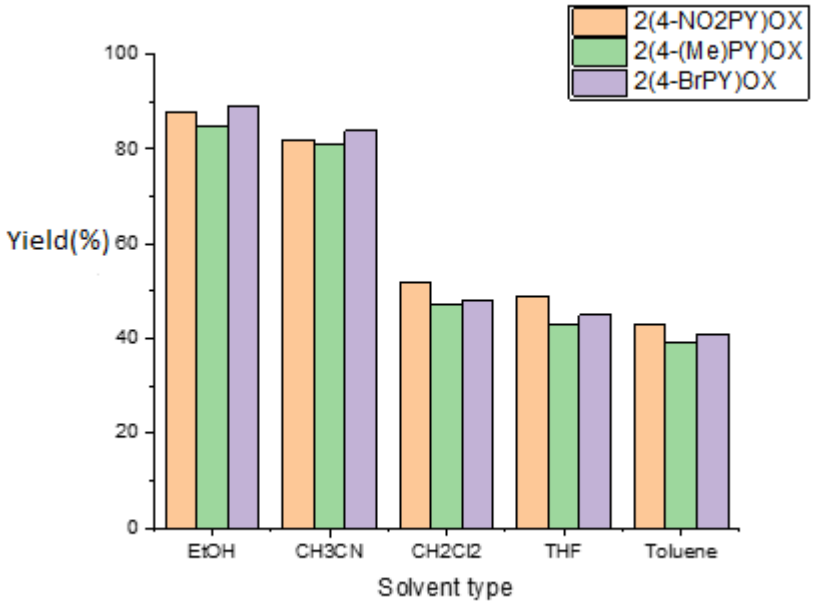


Figure 7: Effect of solvent type on the yield of product.

Figure 8 presents the investigation of different time intervals ranging from 2.0 to 6.0 hours. The results indicate that time intervals of 2.0 and 5.0 hours yielded high percentage yields for 2(4-NO_2PY)OX, 2(4-N(Me)$_2$PY)OX, and 2(4-BrPY)OX, respectively.

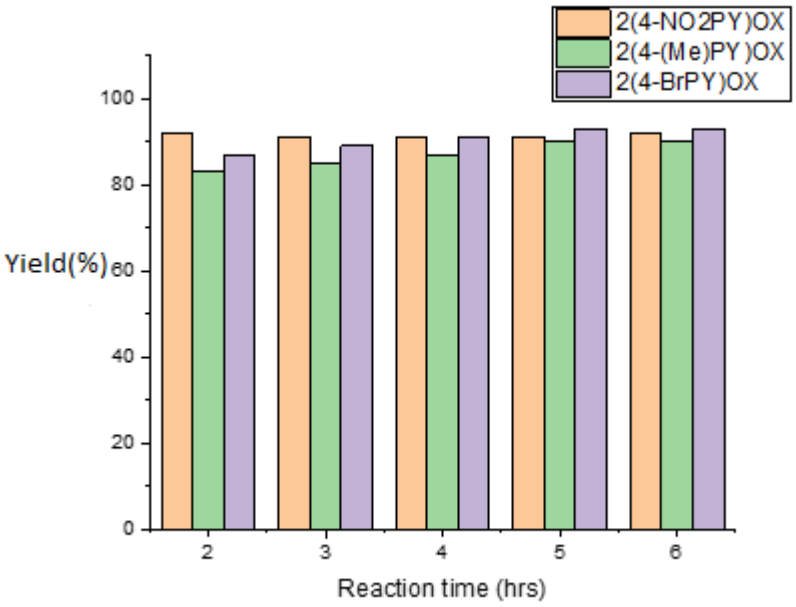


Figure 8: Effect of reaction time on the yield of product.

Table 2 presents the optimal conditions for benzoxazole synthesis and explores the impact of substituted groups on the benzene ring. Interestingly, it was observed that the addition of the catalyst nullified the influence of the substituted group on the percentage of the product.

Table 2: Optimum conditions and effect of substituted group.

Substituted group(R)	Type of catalyst	Solvent type	Amount of catalyst (g)	Time (hrs)	m.p ^{0}C	Yield (%)
NO_2	CdO NPs	EtOH	0.005	2	272-274	92
N(Me)$_2$			0.02	5	286-288	90
Br			0.015	5	165-167	93

4. CONCLUSION

Cadmium oxide nanoparticles were successfully synthesized using the co-precipitation method, and various characterization techniques were employed to determine the size, crystallinity, and stability of the nanoparticles. The size of the CdO NPs, CdO NPs-Thr, and $CdNiO_2$ NPs crystallites was calculated to be approximately 33.9 nm, 28.3 nm, and 27.9 nm, respectively, using the Scherrer equation based on XRD data. The SEM images confirmed that the particles exhibited spherical and needle, spherical, and irregular shapes for CdO NPs, CdO NPs-Thr, and $CdNiO_2$ NPs, respectively. This method is the sole approach known for producing benzoxazole derivatives with high yields using CdO NPs. The current methodology offers a simple workup process, shorter reaction time, and reduced costs.

5. ACKNOWLEDGMENTS

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