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NiO HETEROGENEOUS NANO-CATALYST MEDIATED SIMPLE, RAPID AND EFFICIENT SYNTHESIS OF 2-ARYL SUBSTITUTED BENZOTHIAZOLES

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ABSTRACT

A variety of benzothiazole derivatives have been prepared via the reaction of aryl aldehydes and substituted *o*-amino thiophenol using nickel oxide as a nanocatalyst with an aqueous medium. By fabricating the recoverable heterogeneous nanocatalyst, the obtained nanocatalyst has been analyzed using various techniques such as powder XRD and SEM. There are some advantages of this protocol like the eco-friendly nature of the catalyst, loading of the low percentage of catalyst, good yield of products, reusability of the nanocatalyst, lesser reaction duration, high selectivity, and effortless workup. The corresponding product structures have been analyzed by the use of spectral techniques (IR, ^{1}H NMR, and ^{13}C NMR) and elemental analysis.

Keywords: Benzothiazoles, *O*-Aminothiophenols, One-Pot Synthesis, Green Reaction Conditions, NiO NPs.

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INTRODUCTION

The heterocyclic scaffold provides a vast perspective on the invention of novel therapeutics in medicine recognition of natural biomolecules and clinically they were used as drugs. Benzothiazole is a fused heterocycle having nitrogen and sulfur atoms which is found in numerous marine, earthly biologically active natural products and a vital framework in organic chemistry.[1] In the modern era, it has been recognized as a potential pharmacophore containing dissimilar therapeutic activities like anti-cancer, anthelmintic, anti-viral, anti-inflammatory, anti-bacterial, and inhibition of enzymes.[2-7] In addition, benzothiazole rings are enclosed in numerous natural substances, e.g. vitamin $B_{12,}$ and too in organic useful substances like fluorescent pigments.[8-9] (Fig.-1) Numerous techniques have been reported for the formation of derivatives of benzothiazole, for instance, preparation of 2-aryl (alkyl)benzothiazoles in air/DMSO oxidant system via the reaction between *o*-aminothiophenol and aldehydes, by virtue of iron phthalocyanine as a catalyst and condensation of 2-aminothiophenols with various cyclization agents.[10-13] However, these methods bear limitations or ruthless reaction environments like the use of toxic reagents, elevated temperature, strong acid catalysts, air-sensitive less product yield, etc. These aspects encourage chemists to look for and design a more effectual and environmentally benign route. The globular economy is steadily substituting linear economies, thus making sure that utilized resources and chemical rudiments are used capably in the upcoming time. By means of this concept, we intend to conserve the desires of upcoming generations in terms of energy expenditure, secure resources, and viable access to raw and feasible feedstock.[14] In organic synthesis, nanoparticles as catalysts amplified significantly for the reason of their high competence under a green reaction environment.[15] The main objective of the beneficiary of chemistry is to create catalysts that can be isolated and recuperate from the reaction with elevated selectivity, activity, and good product yield.[16] At room temperature, nanoparticles are crucial in the mineralization of organic substances causing a risk. In addition, it is really effective and proficient in cleansing water zones.[17] Some of the significance comprises recyclability, simple continuance, safety, and environmental friendliness.[18] In the earlier period, the utilization of heterogeneous catalysts as a recyclable, profitable, and eco-friendly

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catalyst has fascinated a lot of courtesy in scholastic and industrialized purposes. In prolongation of our interest, herein we designed a superficial route for the synthesis of 2-aryl substituted benzothiazole derivatives in good to excellent yield of the product via the reaction between substituted *o*-amino thiophenol and diverse aryl aldehydes in the catalytic existence of heterogeneous NiO as an extremely proficient and retrievable nanocatalyst under gentle reaction conditions by using eco-friendly solvent (water) under reflux condition.

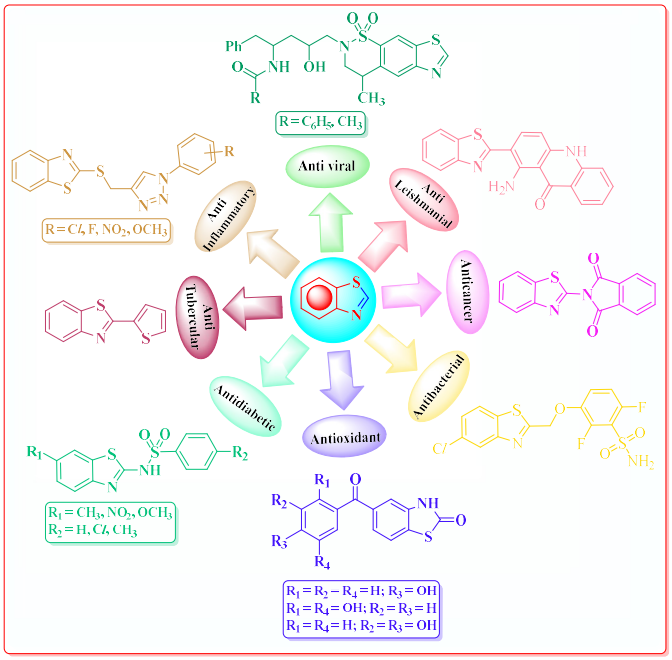


Fig.-1: Demonstrates a Number of Compounds with Biological Activity Enclosing Benzothiazole Scaffolds

EXPERIMENTAL

Materials and Apparatus

The *o*-amino thiophenol derivatives and benzaldehyde derivatives used in this research task were bought from the Merck and Sigma-Aldrich chemical companies and used directly without employing any refinement process. JEOL RESONANCE NMR spectrometer was used to measure the spectra of proton (^{1}H) NMR (400 MHz) and, carbon (^{13}C) NMR (100 MHz) using $CDCl_3$ as the solvent, an NMR spectrometer was used to measure the chemical shift values of the synthesized compounds and the obtained values are reported in δ ppm with respect to TMS, which is an internal standard. The morphological and crystalline characterization of synthesized nanoparticles was performed Utilizing XRD and SEM, from an X-ray diffractometer (D8 Advance, Bruker, Germany; CuKα λ = 1.5418Å; 40 kV and 40 mA) and SNE-4500M SEM respectively. A melting point apparatus was used to determine the uncorrected melting points of the prepared benzothiazole derivatives in an open capillary.

Synthesis of Catalyst NiO NPs

We have synthesized NiO NPs by following literature[19] with some minor modifications. After the preparation of NiO NPs, the prepared nanoparticles were characterized by IR and XRD techniques. The produced NiO NPs morphology was examined with the help of SEM technique.

Typical Approach for the Formation of 2-Aryl Substituted Benzothiazole Derivatives

o-aminothiophenol derivatives (1.0 mmol), aryl aldehydes (1.0 mmol), and NiO NPs (10 mg) in green and environmental benign water solvent (2.0 mL) were combined and magnetically stirred at reflux for the suitable moment (Table-1) in a 50 mL round-bottom flask. For the appropriate amount of time, the reaction mixture was refluxed while being continuously stirred. After the finishing of the process, it was monitored by TLC (hexane: ethyl acetate, 90:10) and ethyl acetate in the crude solid product. After removing the nanocatalyst from the reaction mixture by filtering it, the product was concentrated under low pressure.

Finally, pure 2-aryl substituted benzothiazole derivatives were obtained by employing silica gel column chromatography to purify the crude product.

Characterization Data of 2-Phenyl Benzothiazole Compound (3a)

Color (%Yield) = Light Yellowish Solid (94%); **M.P. =** 109-111°C; **^{1}H-NMR (400 MHz, CDC*l*$_3$):** δ_H (ppm) = 7.43 (t, 1H); 7.52-7.55 (m, 4H); 7.91-7.93 (d, 1H); 8.15-8.19 (m, 3H); **^{13}C-NMR (100 MHz, CDC*l*$_3$):** δ_C (ppm) = 121.87, 122.78, 126.06, 127.20, 128.13, 129.44, 132.10, 133.91, 151.74, 169.19.

RESULTS AND DISCUSSION

Characterization of the NiO Nanoparticles

The morphological and crystalline characterization of synthesized nanoparticles was performed utilizing XRD and SEM techniques, from an X-ray diffractometer (CuKα λ = 1.5418 Å; 2θ range = 5-80°; scan rate = 1° min^{-1}; scan size = 0.02° and SNE-4500M SEM respectively. In Fig.-2, the NiO nanoparticle SEM images are displayed. It can be clearly seen from the SEM image that the NiO nanoparticles are randomly distributed and form aggregates instead of individual particles. It indicates the self-aggregating nature of the NiO nanoparticles.

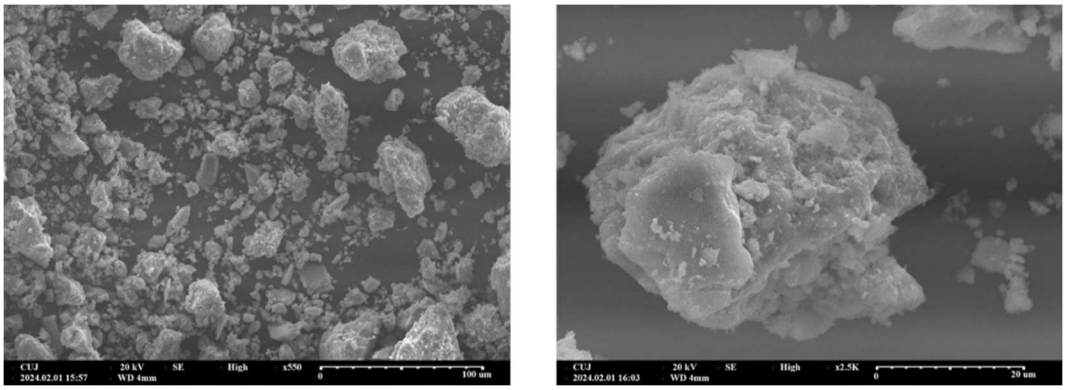


Fig.-2: SEM Images of NiO Particles

The XRD technique was utilized to verify the crystalline structure of the synthesized NiO nanoparticles. An X-ray diffractometer was used to record the XRD pattern (D8 Advanced, Bruker, Germany, Kα = 1.54 Å in the range of angle 2θ between 5° and 80° and the obtained spectra are shown in Fig.-3. The highest intensity peak (111) was observed at 33.4° and other characteristic peaks were observed at 38.6° (200), and 59.1° (220). These patterns show the face-centered cubic (FCC) structured NiO.

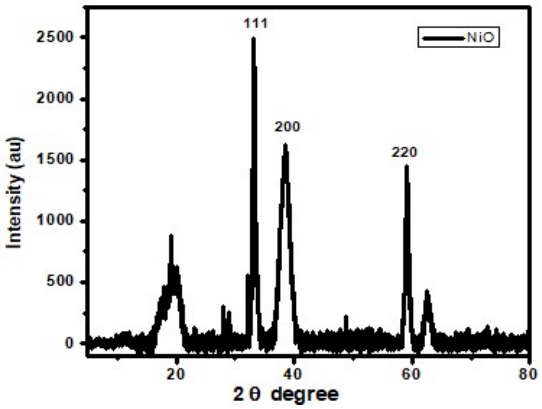
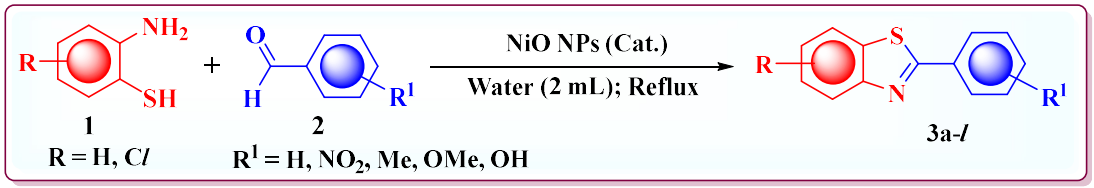


Fig.-3: XRD Patterns of NiO Particles

Catalytic Efficiency of NiO NPs for the Synthesis of Benzothiazole Derivatives

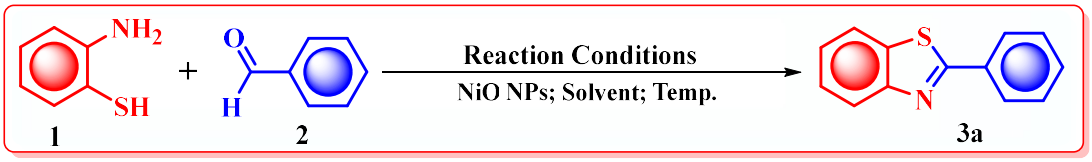
To explore the catalytic efficiency, the prepared NiO nanocatalyst was employed for the formation of benzothiazole derivatives by the condensation of a 1:1 molar ratio of substituted *o*-aminothiophenols and benzaldehyde derivatives (Scheme-1).



Scheme-1: Common Protocol for the Preparation of Benzothiazole Derivatives

Reaction Conditions

Aryl aldehydes (1.0 mmol), *o*-aminothiophenol derivatives (1.0 mmol), NiO nanocatalyst (10 mg), water (solvent), reflux conditions. We examined the catalytic activity of NiO NPs as an untried and green heterogeneous nanocatalyst for the formation of 2-aryl substituted benzothiazoles after characterizing the structure of the nanocatalyst. Using the reaction between *o*-aminothiophenol (1) and benzaldehyde (2) as a model reaction, we can adjust several parameters such as the amount of catalyst, reaction temperature, and solvent (Scheme-2).



Scheme-2: Model Reaction for the Preparation of Benzothiazole

The most notable result was achieved in the existence of 10 mg of nanocatalyst (Table-1, entry 3), whereas control studies demonstrated that trace amounts of product were formed in the lack of NiO NPs (Table-1, entry 1). Table-1 shows that after testing a number of solvents, including EtOH, EtOAc, DCM, and CH_3CN, it was discovered that H_2O is more efficient for this reaction (Table-1, entry 3). Investigations into the impact of heat on the said reaction revealed that reflux settings produce the optimum reaction outcomes (Table-1, entry 3). The optimal reaction conditions for the production of 2-aryl benzothiazoles were discovered to be 10 mg of NiO NPs in water at reflux.

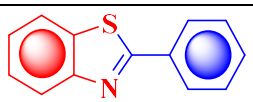
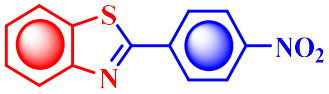
Table-1: Optimization for the Reaction Condition

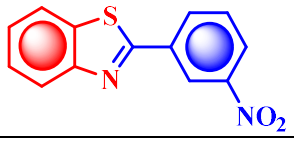
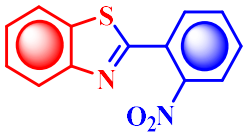
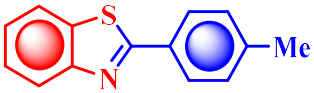
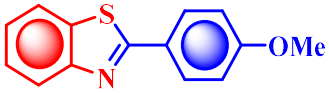
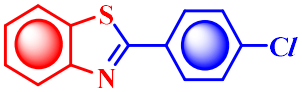
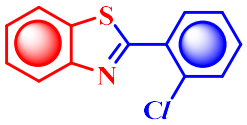
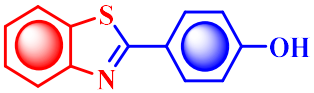
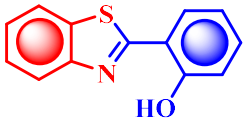
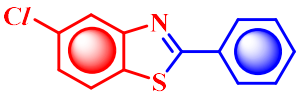
Entry	Catalyst (mg)	Solvent	Temp. (°C)	Time	Yield (%)[a]
1	0	H_2O	RT	4 hrs	Trace
2	5	H_2O	70	5 hrs	45
3	10	H_2O	Reflux	45 min.	94
4	5	EtOH	50	4 hrs	42
5	10	EtOH	Reflux	5 hrs	65
6	10	EtOAc	Reflux	6 hrs	60
7	10	DCM	Reflux	4.5 hrs	52
8	10	CH_3CN	Reflux	6 hrs	48

[a]Isolated yield of the product.

Considering these results, the catalytic activity of NiO NPs was furthermore inspected for the reaction between various substituted benzaldehydes and substituted *o*-aminothiophenols. The results are provided in Table-2 to study the usefulness and generality of this approach.

Table-2: Preparation of 2-Aryl Substituted Benzothiazole Derivatives Catalysed by NiO Nanoparticles in Water at Reflux Condition

Entry	R	R^1	Product	Time (min.)	Yield (%)[a]	M.P. (°C)	
						Observed	Reported
3a	H	H		70	94	109-111	111-113
3b	H	4-NO_2		85	92	220-224	219-221

3c	H	3-NO_2		92	90	180-182	181-183
3d	H	2-NO_2		84	91	135-138	136-138
3e	H	4-Me		110	92	81-83	84-88
3f	H	4-OMe		75	90	120-121	120-124
3g	H	4-C*l*		95	91	112-114	112-113
3h	H	2-C*l*		112	89	80-83	81-83
3i	H	4-Br		105	89	128-130	129-132
3j	H	4-OH		110	92	223-225	223-227
3k	H	2-OH		120	90	132-133	131-133
3*l*	C*l*	H		122	89	129-131	130-131

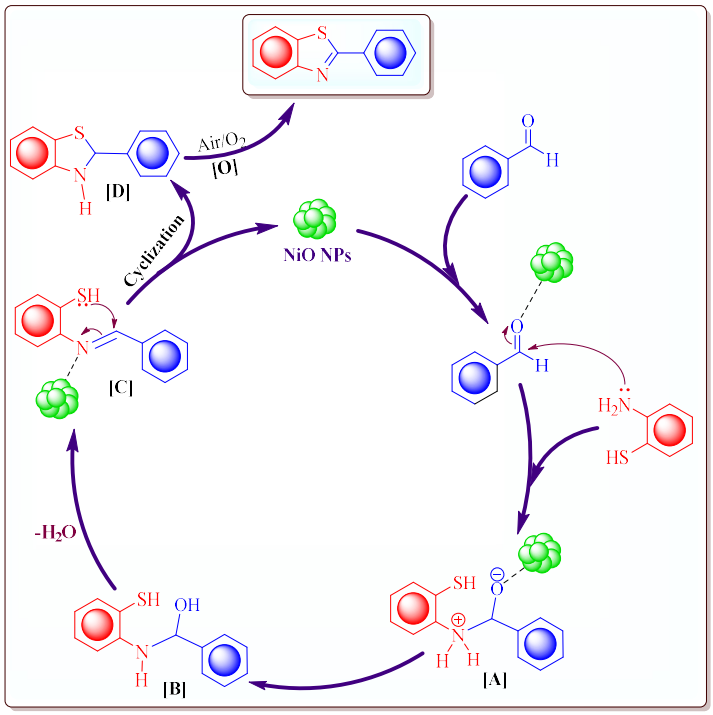
Reaction conditions: Benzaldehyde derivatives (1.0 mmol); substituted *o*-aminothiophenols (1.0 mmol); catalyst (10 mg)
[a]Isolated yield of the product.

Plausible Mechanism of the Reaction

o-aminothiophenols (1) and benzaldehyde derivatives (2) react through condensation and cyclization reactions. Regarding the rate and yields, the catalyst is essential to the reaction's progress. Our results are listed in Table-2. In Scheme-3, a potential pathway for the synthesis of benzothiazoles is illustrated. Firstly, the NH_2 group is added nucleophilically to the benzaldehydic sp^2 carbon to produce the intermediate (A), which readily tautomerizes to intermediate (B). Intermediate (B) quickly changed into the imine intermediate (C) during the condensation reaction. The latter is subsequently cyclized by the nucleophilic attack of the -SH group on the imine carbon center, resulting in intermediate (D). Finally, air oxidation provides the desired product. A proposed mechanism is shown in Scheme-3.

It was fascinating to note that the product yield is unaffected by the type of substitute on the aromatic ring. This procedure was also successful in achieving a satisfactory reaction for aromatic aldehydes with e-donating or e-withdrawing groups. The results of the synthesis of 2-arylbenzothiazole in the existence of several stated nanocatalysts in relation to product timing and yield are presented in **(Table-3),** so that the benefits of our work can be investigated, along with other reported procedures. These results suggest that

our catalyst, NiO NPs, is unfaltering in air, non-toxic, and produces a good product yield in aqueous solvent in a shorter span of time.



Scheme-3: Probable Mechanistic Pathway for the Preparation of 2-arylbenzothiazoles

Table-3: Comparative Description of the NiO Nanocatalyst with Other Different Nanocatalysts Stated in Scholarly Works

Entry	Catalyst	Reaction Conditions (Solvent & Temp.)	Time	Yield (%)	Literature
1	Cu NPs/SiO_2 (10 mol%)	MeOH, R.T.	4-8 hrs	72-86	20
2	CeO_2 NPs (10 mol%)	H_2O, R.T.	20-40 min	58-97	21
3	Fe(III)–Schiff base/SBA-15 nanocatalyst	H_2O, Reflux	3 hrs	79-92	22
4	Fe_3O_4@SiO_2/collagen	EtOH (4 mL), Reflux	90-100 min	70-73	23
5	Nano ZnO	EtOH, Reflux	80-100 min	70-86	24
6	Fe_3O_4@SiO_2-phenanthroline-Pd	PEG (3 mL), 80°C	6 hrs	89-98	25
7	NiO NPs	H_2O (2 mL), Reflux	70-122 min	89-94	This work

Reusability of Heterogeneous Nanocatalyst

Under optimal conditions, the nanocatalyst's potential for reuse was examined during the synthesis of benzothiazole (Fig.-4). In order to create benzothiazole, 3a for this investigation, we employed benzaldehyde in a reaction with *o*-aminothiophenol. After each run was finished, the centrifugation technique made it simple to isolate the NiO NPs. The solid-state catalyst was washed thoroughly with ethanol and EtOAc to eliminate any remaining product. It was then desiccated in an oven at 70°C temperature before being utilized without altering the reaction conditions in the following run. (Table-4).

Table-4: Recyclability of NiO NPs in the Production of 2-aryl-1,3-benzothiazole Derivatives

Entry	Number of Recycle	Yield (%)
1	Fresh	98
2	1	98
3	2	95
4	3	93
5	4	90

Fig. -4: Recyclability of the NiO nanocatalyst

CONCLUSION

It is evident that using a NiO nanocatalyst to prepare several derivatives of 2-aryl substituted benzothiazole is a common and viable alternative to the existing protocol. This approach uses an inexpensive, recyclable, extremely effective catalyst that is also environmentally friendly. This protocol's experimental process is incredibly easy to follow, safe for the environment, and doesn't require the use of expensive or risky organic solvents. The above characteristic makes this method an appealing addition to existing methodologies.

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CONFLICT OF INTERESTS

The authors declare that none of their known personal or financial conflicts could have an impact on the work described in this paper.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to the preparation of this manuscript, participated in reviewing and editing it, and gave their approval for publishing the manuscript in its final form. The authors' research profile can be validated using their ORCID IDs, which are listed below:

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