Research Article

Cobalt ferrite Nanoparticle-Catalyzed Green Synthesis of Benzothiazole Derivatives

Akash B. Thombre,[1] Pooja M. Chavan,[1] Sonali A. Korde,[2] Suresh C. Jadhavar[1,*]

Article DOI:
10.55434/CBI.2025.10103

Author's Affiliations

[1]Department of Chemistry, Yogeshwari Mahavidyalaya, Ambajogai, 431517, Maharashtra, India

[2]Department of Chemistry, Sunderrao Solanke Mahavidyalaya, Majalgaon, Maharashtra, 431131, India

Corresponding Author

Sangita Sanjay Makone.

Emails:
sujadhavar1978@gmail.com

Received- 17th September 2025,
Accepted- 15th December 2025

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ISSN 0799-3757

http://caribjscitech.com/

Abstract

Using recyclable cobalt ferrite ($CoFe_2O_4$) nanoparticles as a heterogeneous photocatalyst under visible light-assisted conditions, an effective and ecologically safe method for the production of benzothiazole derivatives has been established. The process provides good benzothiazole compounds by cyclocondensing substituted 2-aminobenzenethiols with different aromatic and aliphatic aldehydes. While retaining excellent efficiency and atom economy, the use of visible irradiation drastically shortens the reaction time to 2–3.5 h. The approach is both economically and environmentally appealing because the cobalt ferrite nano catalyst can be readily recovered and reused for six cycles. Nine different benzothiazole compounds were produced, with isolated yields ranging from 85% to 95%. The technique is a sustainable method for the synthesis of pharmaceutically significant benzothiazole scaffolds because it has several benefits, such as easy operation, quick reaction times, high product yields, catalyst recyclability, and little waste production.

Keywords:

Aldehydes; dimedone, urea;$Zn(OAc)_2$•$2H_2O$;Biginelli-type; quinazolinones; Lewis acid; multi-component reactions

1. Introduction

Heterocyclic compounds are of great interest in organic chemistry due to their various biological activity and medicinal uses.[1-4] Because of their wide range of biological and pharmacological actions, benzothiazoles-a significant class of fused heterocyclic compounds containing sulphur and nitrogen- have garnered a lot of interest (**Figure 1**).[5–16]

Benzothiazole-containing compounds have found use in materials science, agrochemicals, fluorescence probes, dyes, corrosion inhibitors, and pharmaceuticals.[17] The condensation reaction of carbonyl or cyano with 2-aminobenzenethiols is typically used to report the synthesis of benzothiazoles.[18–20] Even though a number of synthetic protocols have been documented, many of them have drawbacks such difficult reaction conditions, long reaction durations, costly catalysts, time-consuming work-up processes, and the production of waste that is dangerous to the environment.

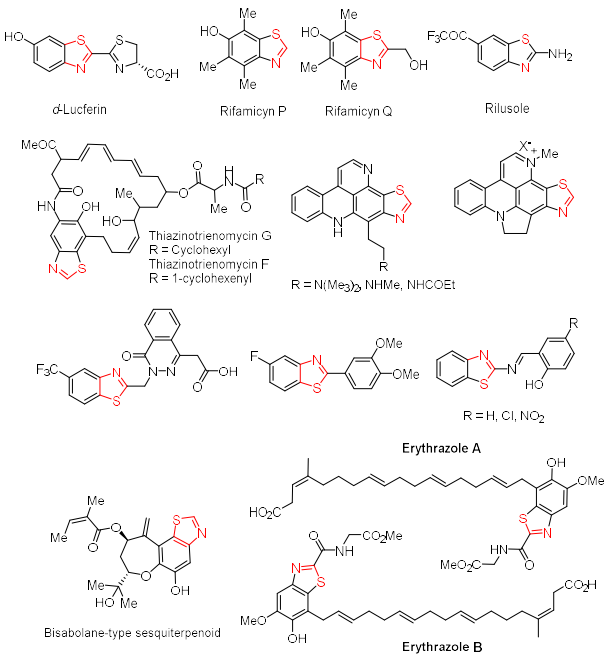


Figure 1. Biologically relevant FDA-approved benzothiazole-containing marketed drugs[21-30]

As a result, the development of effective and environmentally friendly synthetic processes for the synthesis of benzothiazole derivatives continues to be an important field of study.[21–44]

A potent method for increasing reaction efficiency while reducing environmental impact is nanocatalysis.[45] Because of their low-lying unoccupied orbitals for bonding and their potential to significantly increase the coordination sphere, transition metal nanoparticles are attractive in catalytic applications.[46–48]

Multi-metallic nanoparticles (MMNPs) have recently garnered significant interest due to their inclusion of different metal atoms within a single nanostructure.[49] Cobalt ferrite ($CoFe_2O_4$) nanoparticles have attracted a lot of attention among other MMNPs because of their strong catalytic activity, huge surface area, superior thermal stability, and magnetic characteristics.[50-51] Anchored or impregnated cobalt ferrite nanoparticles are attractive heterogeneous catalysts for eco-friendly organic transformations due to their special physicochemical characteristics.[52–69]

Herein, we describe an effective synthesis of benzothiazole derivatives employing recyclable cobalt ferrite nanoparticles as a heterogeneous catalyst, motivated by the advantages of bimetallic nanocatalysts. Using easily accessible aminobenzenethiols and substituted aromatic and aliphatic aldehydes as starting materials, the process produces the required benzothiazole products in high yields with quick reaction times. The developed procedure includes extensive research on conventional, sonochemical, microwave, mechanochemical, and visible light-mediated methods.

2. Experimental

2.1. Materials and Methods

Nanocatalyst cobalt ferrite (773352-5G) was purchased from Sigma-Aldrich. All reactions were conducted in a microwave. Analytical thin-layer chromatography performed using TLC pre-coated silica gel 60 F_{254} MERCK (20x20 cm). Visualization was achieved by exposure to UV light (254 nm). Organic solutions were concentrated by rotary evaporation on BUCHI-Switzerland R-120 rotary evaporator and vacuum pump V-710. Column chromatography was performed on Merck silica gel 230-400 mesh size. Melting points were uncorrected.

IR spectra were recorded with a Thermo Nicolet Nexus 670. ^1H and ^{13}C NMR/DEPT spectra were recorded with BRUKER 400 MHz NMR instruments. Chemical data for protons were reported in parts per million (ppm, scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.26). Carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$: δ 77.0 or other solvents as mentioned). Mass spectra were recorded with an Agilent LC-MS instrument. Photocatalytic reactions were conducted in a borosilicate RB flask positioned 5 cm from a commercial LED bulb (Philips India). Light intensity at the reaction vessel was measured using a Thorlabs PM100D optical power meter.

2.2 General procedure for synthesis of $CoFe_2O_4$ nanoparticles-catalyzed benzothiazole

A mixture of 2-aminothiophenol (1 mmol), aromatic aldehyde (1 mmol) and $CoFe_2O_4$ nanoparticles (~36 mg) in ethanol was stirred utilizing a 12 W white LED at 25 °C for the time specified in **Figure 2**, to obtain a crude product (**3a-i**). The progress of the reaction was monitored by thin layer chromatography (TLC). After completion of the reaction, the crude product was dissolved by adding ethanol and the $CoFe_2O_4$ nanoparticles were separated by centrifugation, followed by decantation. $CoFe_2O_4$ nanoparticles were dried in vacuum desiccators and the crude product was recrystallised in ethanol. All synthesized compounds were obtained in good to excellent yields (85–95%).

The structures of the products were established by FT-IR, ^{1}H NMR, ^{13}C NMR, and mass spectrometric analyses. All synthesized compounds are known, and compared the spectral data with the precedent literature.[36-39] The LED was positioned 4.5 cm from the reactor, and homogeneity was consistently maintained throughout the catalytic reactions. The emission of the white LED spans the visible range (~420–700 nm).

2.3 Spectral data for selected compounds

2.3.1 2-phenylbenzo[*d*]thiazole (3a): TLC (EtOAc: hexane 1:5) R_f = 0.25; **IR (NaCl):** 3069, 3038, 1605, 1588, 1491, 1452, 1334, 1305, 1268, 1223, 1174, 1114, 1081, 1020, 962, 897, 851, 803, 756, 732, 694cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$δ ppm):** 8.08–8.02 (m, 2H), 7.92–7.88 (m, 1H), 7.68–7.58 (m, 3H), 7.50–7.38 (m, 3H).**^{13}CNMR (100 MHz, CDCl$_3$ δ ppm):** 168.0, 151.2, 140.4, 136.9, 130.3, 128.7, 128.0, 126.3, 125.5, 123.9, 122.2, 121.6. **LCMS:** Exact Mass; 211.05, observed Mass: M+1=212.01.

2.3.2 2-(4-bromophenyl) benzo[*d*]thiazole (3b): TLC (EtOAc: hexane 1:5) R_f = 0.27; **IR (NaCl):** 3054, 2357, 1918, 1555, 1473, 1430, 1393, 1286, 1224, 1156, 1102, 1065, 1020, 967, 825, 752, 681, 565cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$δ ppm):** 8.12–8.04 (m, 2H), 7.96–7.88 (m, 1H), 7.80 (d, J = 8.4 Hz, 2H), 7.68–7.58 (m, 1H), 7.56 (d, J = 8.4 Hz, 2H).**^{13}C NMR (100 MHz, CDCl$_3$ δ ppm):** δ 166.6, 154.0, 135.0, 132.5, 132.2, 129.0, 126.5, 125.4, 123.2, 121.6. **LCMS:** Exact Mass: 288.96, observed Mass: M+1=290.01.

2.3.3 2-(benzo[*d*]thiazol-2-yl)phenol (3c): TLC (EtOAc: hexane 1:5) R_f = 0.25; **IR (NaCl):** 3067, 2356, 1585, 1477, 1313, 1269, 1249 1214, 969, 858, 815, 756, 722, cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$δ ppm):** 12.51 (s,1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.70–7.68 (m, 1H), 7.52-7.48 (m, 1H), 7.42-7.36 (m, 1H), 7.11-7.09 (m, 1H), 6.97-6.93 (m, 1H), **^{13}C NMR (100 MHz, CDCl$_3$ δ ppm):**δ 157.9, 151.8, 132.7, 132.5, 128.3, 128.4, 126.6, 125.5, 122.1, 121.4, 119.4, 119.4, 117.8, 116.75. **LCMS:** Exact Mass: 227.04; observed Mass: M+1=228.4.

2.3.4 ethyl benzo[*d*]thiazole-2-carboxylate (3h): TLC (EtOAc: hexane 1:5) R_f = 0.21; **IR (NaCl):** 3061, 3030, 3001, 2972, 2940, 2913, 2872, 2355, 1791, 1745, 1551, 1496, 1483, 1456, 1425, 1386, 1359, 1313, 1287, 1252, 1157, 1126, 1046, 1009, 936, 889, 851, 803, 752, 689, 577cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$) δ:** 8.27 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.60–7.52 (m, 2H), 4.45 (q, *J*=6.8, 2H), 1.51 (t, *J*=7.2, 3H) **^{13}C NMR (100 MHz, CDCl$_3$ δ ppm):** 160.50, 158.39, 153.03, 136.60, 127.38, 126.93, 125.34, 121.92, 63.0, 16.3.**LCMS:** Exact Mass; 207.04; observed Mass: M-1=206.1.

2.3.5 2-(chloromethyl)benzo[*d*]thiazole (3i): TLC (EtOAc: hexane 1:5) R_f = 0.23; **IR (NaCl):** 3064, 3010, 2958, 1790, 1700, 1595, 1557, 1512, 1456, 1432, 1313, 1279, 1261, 1245, 1204, 1158, 1113, 1063.97 1013, 975, 930, 861, 758, 709, 673, 622, 596 cm^{-1}. **^{1}H NMR (400 MHz, CDCl$_3$δ ppm):** 8.03 (d, *J* = 8.4 Hz, 1H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.53–7.51 (m, 1H), 7.45–7.40 (m, 1H), 4.45–4.90 (s, 2H)· **^{13}C NMR (100 MHz, CDCl$_3$ δ ppm):** 166.75, 152.74, 135.77, 126.42, 125.71, 123.40, 121.74, 42.01. **LCMS:** Exact Mass: 182.99, observed Mass: M+1=184.04.

3. Results & Discussion

3.1. Optimization of Reaction Conditions

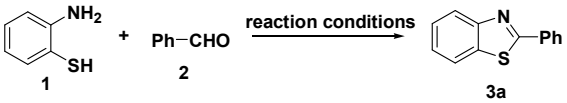
The reaction between 2-aminobenzenethiol (**1**) and benzaldehyde (**2a**) was chosen as a model reaction to determine the ideal reaction conditions for the production of benzothiazole derivatives. We have tried the model reaction using different iron and cobalt salts eg., Fe_2Cl_3, $FeCl_3.6H_2O$, $CoCl_2.6H_2O$, $Co(NO_3)_2{\cdot}6H_2O$ and $Fe(NO_3)_3{\cdot}9H_2O$, but they did not yield the corresponding product in the given conditions.

Using $CoFe_2O_4$ nanoparticles as the catalyst under standard circumstances, the effects of catalyst

loading and solvent were methodically examined (**Table 1**). Using pure ethanol as the solvent under ambient conditions, the ideal catalyst dose was determined to be 36 mg (15 mol%), as **Table 1** illustrates. Without a catalyst, the reaction could not proceed, and the presence of $CoFe_2O_4$ nanoparticles greatly increased the rate of reaction. With only 36 mg of catalyst, a discernible increase in yield was seen; additional increases in catalyst dose did not offer any more improvement. Further optimization research showed that at catalyst loadings of 48 and 60 mg, the yield slightly decreased and the reaction time increased.

Aggregation of the catalyst and/or the formation of less-active catalytic species at higher catalyst concentrations may be the cause of the yield decline and reaction time increase seen at greater catalyst loading. Additionally, too much catalyst might encourage competing side reactions or catalyst deactivation, which lowers the active catalytic species' effective concentration. These findings imply that in order to attain optimal catalytic efficiency, an ideal catalyst loading is necessary.

Table 1. Effect of $CoFe_2O_4$-NPs catalyst dose on the synthesis of **3a**



Entry[a]	Catalyst dose (mg)	Time (h)	Yield (%)[b]
1	None	8 h	NR
2	12	4 h	7
3	24	4 h	38
4	**36**	**2**	**94**
5	48	2.5	90
6	60	2.5	88

[a]2-aminobenzenethiol (1 mmol) and benzaldehyde (1 mmol) in ethanol at 25 °C; [b]Isolated yields

Different solvents were also tested and among the tested, ethanol was found to be the best using 15 mol% of $CoFe_2O_4$ nanoparticles at ambient temperature (**Table 2**).

Table 2. Effect of solvent on the synthesis of **3a**

Entry[a]	Catalyst dose (mg)	Time (h)	Yield (%)[b]
1	Neat	8	NR
2	CH_3CN	6.5	58
3	$CHCl_3$	6.5	37
4	THF	2	94
5	Dioxane	2.5	90
6	**EtOH**	**2.0**	**94**
7	EtOAc	6	Trace
8	DMF	6	25
9	DMSO	6	31

[a]2-aminobenzenethiol (1 mmol), benzaldehyde (1 mmol) and 15 mol% $CoFe_2O_4$ nanoparticles at 25 °C; [b]Isolated yields

Inspired by the results, we have evaluated different reaction media parameters for the synthesis of **3a,** such as mechanochemical, ultrasonication, microwave and visible light media, and the results are disclosed in **Table 3.**

Table 3. Study of different reaction media parameters

Entry[a]	Reaction conditions	Time (min/h)	Yield (%)[b]
1	Conventional: Ethanol, 25 °C	4 h	94
2	Microwave: 400 W, 120 °C	3 min	95
3	Sonication: Ethanol, RT	40 min	91
4	Grinding: neat, RT	15 min	90
5	**Visible light:12 W white LED at RT, Ethanol**	**2 h**	**94**

[a]2-aminobenzenethiol (1 mmol), benzaldehyde (1 mmol) and 15 mol% $CoFe_2O_4$ nanoparticles; [b]Isolated yields

Under visible light-assisted conditions, the same reaction afforded 94% isolated yield within 2 h. Taken together, these experiments support a beneficial combined effect of $CoFe_2O_4$ nanoparticles and visible light on the overall benzothiazole transformation. TON of catalyst for benzothiazole (**3a**) formation is 6.27 and TOF = 3.135 h^{-1}.

Control experiments were performed using the model reaction to evaluate the contributions of $CoFe_2O_4$ nanoparticles, and visible irradiation to the

observed reaction efficiency (**Table 4**). In the absence of $CoFe_2O_4$ nanoparticles the reaction did not afford the desired indole even after stirring for 12 h, demonstrating the catalyst alone is capable of promoting benzothiazole transformation under the investigated conditions. Whereas, only visible light irradiation is not sufficient to carry forward the reaction. When the model reaction was performed in the dark, the reaction yielded low yield of the desired product (5.5 h, 38%).

Table 4. Control Experiment to verify the role of $CoFe_2O_4$ nanoparticles and light

Entry	Reaction Conditions	Time	Yield (%)
1	Visible irradiation	12 h	NR
2	No $CoFe_2O_4$ nanoparticles	12 h	NR
2	$CoFe_2O_4$ nanoparticles + dark	5.5 h	38
3	$CoFe_2O_4$ nanoparticles+ visible light	2 h	91
4	$CoFe_2O_4$ nanoparticles + ethanol, UV-assisted	2 h	94

We have utilized the visible light mediated strategy, which is sustainable green as defined by the United Nations SDGs (Sustainable Development Goals) 7 and 9, based on **Table 3** and **4**'s control experiments conducted utilizing several possible approaches. Pure, limitless, and controllable is visible light. One of organic chemistry's fastest-growing fields since 2008 is visible-light-induced catalysis, which has evolved into a powerful technique for promoting controlled radical reactions. Effective methods for creating organic frameworks that are challenging to achieve by thermal procedures are provided by photo-induced reactions.[70] Light-driven catalysis has proven to be a widely applicable chemical transformation technique that has a major impact on human health, energy, environmental sustainability, and pharmaceutical development.[71] Few publications utilizing graphitic carbon nitride (g-C_3N_4), fluorescein, eosin Y and other catalysts were found throughout the literature review.[72-73]

3.2. Substrate Scope

Using a variety of aromatic and aliphatic aldehydes, the protocol's universality was investigated after the reaction conditions were improved (**Figure 2**).

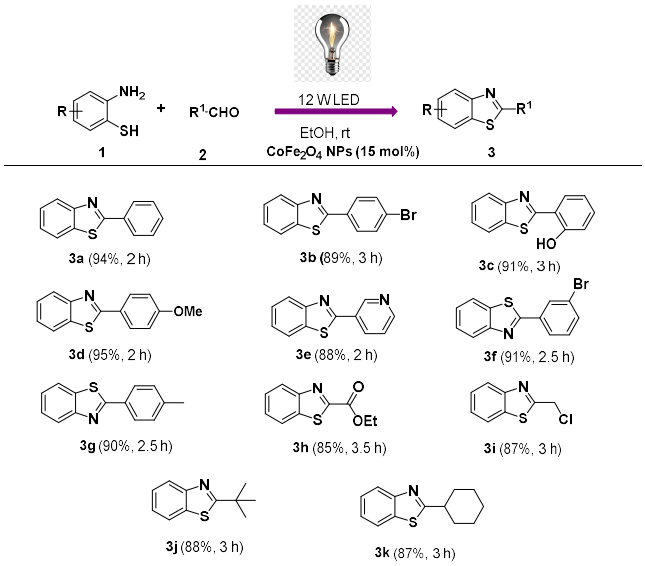


Figure 2. Substrate scope for the synthesis of benzothiazole: Visible light mediated $CoFe_2O_4$ as nano photocatalyst.

The related benzothiazole compounds were produced in great yields, demonstrating the methodology's high efficiency and wide applicability. Excellent yields of the corresponding product were obtained by tolerating electron-donating substituents on the aromatic aldehyde, such as hydroxy, methoxy, and methyl groups (entry **3c**, **3d**, and **3**g). Similarly, high yields of the required benzothiazoles were obtained from aldehydes containing electron-withdrawing substituents, such as bromine (**3b**, **3f**). Using this procedure, heteroaromatic aldehyde also contributed as well (**3e**). The ester-functionalized benzothiazole derivative was produced in 85% yield (**3h**) using ethyl glyoxylate as a suitable substrate. Additionally, the equivalent chloromethyl-substituted benzothiazole was produced in an 87% yield by smooth cyclization of chloroacetaldehyde (**3i**).

In a similar fashion, other aliphatic aldehydes responded well and the corresponding products were (entries **3j** and **3k)** obtained in good yields. All things considered, the new approach demonstrated outstanding tolerance to functional groups in both

electron-rich and electron-deficient aldehydes. The required benzothiazole products were produced in exceptional yields ranging from 85% to 95% as the reactions progressed cleanly in 2–3.5 h.

3.3. Catalyst Recyclability

Additionally, the magnetic $CoFe_2O_4$ nanocatalyst exhibited excellent recyclability and operational stability under the optimized reaction conditions. Owing to its magnetic nature, the catalyst could be readily separated from the reaction mixture using an external magnet, eliminating the need for conventional filtration or centrifugation procedures. The recovered catalyst was subsequently washed, dried, and reused in successive catalytic cycles. Notably, the $CoFe_2O_4$ nanocatalyst retained a high level of catalytic activity even after six consecutive cycles, with only a negligible decrease in product yield. This remarkable recyclability demonstrates that the catalyst possesses good structural and catalytic stability during repeated use (probably no leaching occurred as the reaction was carried out at ambient temperature).

The recyclability of the $CoFe_2O_4$ nanocatalyst was evaluated over six consecutive catalytic cycles. As shown in **Figure 3**, the catalyst afforded product yields of 94%, 94%, 91%, 90%, 90%, and 89% in the first through sixth cycles, respectively. Although a gradual decrease in catalytic efficiency was observed upon repeated use, the catalyst retained 89% yield even after the sixth cycle, corresponding to only a 5 percentage-point decrease from the initial cycle. These results clearly demonstrate the excellent stability, recyclability, and practical potential of the magnetic $CoFe_2O_4$ nanocatalyst. These features highlight the potential of magnetic $CoFe_2O_4$ nanoparticles as a cost-effective, sustainable, and practically attractive heterogeneous nanocatalyst for the synthesis of the target compounds.

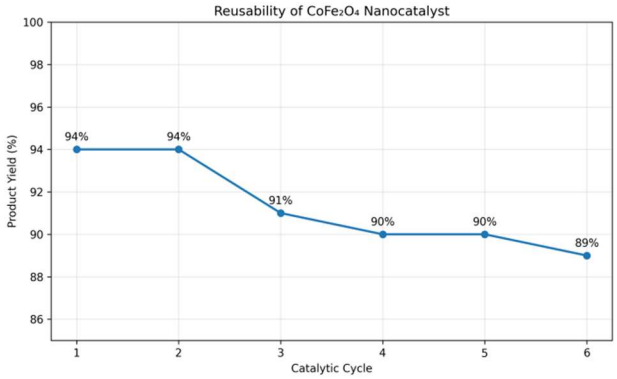


Figure 3. Recycling studies

3.4. Plausible Reaction Mechanism

The surface of $CoFe_2O_4$ contains coordinatively unsaturated Co^{2+}/Co^{3+} and Fe^{2+}/Fe^{3+} centers**.** These act as Lewis-acidic sites and coordinate with the carbonyl oxygen of the aldehyde (**Figure 4**). An imine intermediate is produced by subsequent condensation with the amino/thiol functionality of the substrate, and the benzothiazoline intermediate is formed by intramolecular cyclization. Ultimately, the appropriate benzothiazole derivative is formed through oxidative aromatization. The vast surface area and synergistic redox characteristics of $CoFe_2O_4$ nanoparticles, which allow both cyclization and oxidation stages, may be responsible for their high catalytic activity.

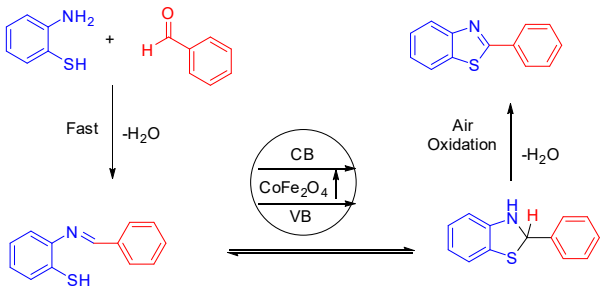


Figure 4. Plausible mechanism for the$CoFe_2O_4$ nanoparticles catalyzed synthesis of benzothiazoles

The redox-active Co^{2+}/Co^{3+} and Fe^{2+}/Fe^{3+} couples can facilitate electron-transfer processes, while surface oxygen species or molecular oxygen can participate in reoxidation, depending on the reaction conditions. The most important feature of $CoFe_2O_4$ is therefore the cooperative action of Co and Fe sites.

In **Table 5**, we compared our findings to prior reports, and the results showed that $CoFe_2O_4$NPs had good catalytic performance for the synthesis of benzothiazole. Because of the mild working conditions, shorter reaction times, and solvent-free environment, the approach was more appealing from the standpoint of green chemistry.

Table 5. Comparison of the efficiency of Cobalt Ferrite Nanoparticles with that previously reported for the literature for the synthesis of 2-phenylbenzothiazole

Entry	Catalyst	Reaction conditions	Time	Yield (%)	Ref
1	$Zn(OAc)_2.2H_2O$	5 mol%, 80 °C, Neat	30 min	94%	36
2	Imidazolium chlorozincate (II) ionic liquid supported into Fe_3O_4 nanoparticles	4 mg, Sonication, 70 °C	30 min	90%	37
3	Cetyltrimethyl ammonium bromide (CTAB)	5 mol%, 100°C, H_2O	1.5 h	98%	38
4	Bi_2O_3 nanoparticles	10 mol%, 60 °C, ethanol	1 h	95%	39
5	NH_4Cl	70 mol%, RT, MeOH : H_2O	40 min	80%	40
6	4-Methoxy TEMPO	120 °C, xylene	9 h	80%	41
7	H_2O_2/HCl	10 mol% of 30% H_2O_2 and 37% H_2O	RT, 45 min	90%	42
8	**$CoFe_2O_4$ nanoparticles**	**Visible light, EtOH, RT**	**2 h**	**94 %**	This work
9	Laccase (Suberase)	MeOH :H_2O CH_3CN and acetate buffer, RT	24 h	85%	43
10	Poly[4-diacetoxyiodo] styrene (PDAIS)	RT, DCM	10 min	92%	44

4. Conclusions

In conclusion, recyclable cobalt ferrite ($CoFe_2O_4$) nanoparticles have been designed as a heterogeneous catalyst in an effective, sustainable, and visible light-assisted approach for the production of benzothiazole derivatives. The process uses easily accessible substituted 2-aminobenzenethiols or 2-nitrobenzenethiols along with aromatic/aliphatic aldehydes to produce the required benzothiazole compounds in high yields (85–95%) in a brief reaction time. Ethanol is an efficient and environmentally safe reaction medium that produces higher yields under ideal circumstances, according to optimization studies. Excellent functional group tolerance to both electron-donating and electron-withdrawing substituents was demonstrated by the protocol's wide substrate scope.

This process is an appealing and eco-friendly way to synthesize physiologically significant benzothiazole scaffolds because it combines visible irradiation, excellent atom economy, catalyst recyclability, and green reaction conditions.

Acknowledgements

One of the Authers, Mr. Akash B. Thombre, is gratefully thankful to Chhatrapati Shahu Maharaj Research, Training and Human Development Institute

(SARTHI), Pune for Junior Research Fellowship and Principal of Yogeshwari Mahavidyalaya, Ambajogai, 431517 for providing infrastructural facilities and constant encouragement.

Author Contributions

Akash B. Thombre: Execution of work, methodology, investigation, and writing - original draft; Suresh C. Jadhavar: Supervision and editing; Pooja M. Chavan and Sonali A. Korde: investigation.

Availability of Data and Materials

The authors declare that the data supporting the findings of this study are available within the paper and its Supplementary Information files. Should any raw data files be needed in another format they are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they do not have any conflict of interest.

ORCID

Akash B. Thombre: 0009-0004-8095-3529
Pooja M. Chavan: 0009-0004-5179-6413
Sonali A. Korde:0000-0002-4859-7796
Suresh C. Jadhavar: 0009-0002-4077-3051

Funding

Not applicable

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