

Magnetically Recyclable CoFe₂O₄ Nanoparticles for Green Synthesis of 1,3,5-Trisubstituted-2-Pyrazolines

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Abstract:

A sustainable and operationally simple methodology has been developed for the synthesis of 1,3,5-trisubstituted-2-pyrazolines through the cyclocondensation of substituted chalcones with hydrazine hydrate in the presence of magnetically separable cobalt ferrite (CoFe₂O₄) nanoparticles as a heterogeneous catalyst. The transformation proceeds efficiently at room temperature in an ethanol–water (1:1) medium, delivering excellent product yields (87–93%) within relatively short reaction times. The structural features of the prepared CoFe₂O₄ nanoparticles were confirmed by X-ray diffraction (XRD) and Fourier transform infrared spectroscopy (FT-IR), verifying the formation of a crystalline inverse spinel phase with high purity. The catalyst was conveniently recovered using an external magnetic field and reused in five successive cycles without noticeable deterioration in catalytic performance. The developed protocol integrates environmental compatibility, catalyst recyclability, and procedural simplicity, providing a viable and eco-conscious alternative for the synthesis of pharmacologically relevant pyrazoline derivatives.

Keywords — Cobalt ferrite nanoparticles; Magnetic nanocatalyst; Green synthesis; Pyrazolines; Chalcones; Heterogeneous catalysis

I. Introduction

Nitrogen-containing heterocyclic frameworks constitute a fundamental component of numerous biologically active molecules and synthetic intermediates[1]. Among these, pyrazoline derivatives have received considerable attention due to their broad spectrum of pharmacological properties, including antimicrobial[2], antifungal[3], anti-inflammatory[4], anticancer[5], antidiabetic[6], and neuroprotective effects[7]. In particular, 1,3,5-trisubstituted-2-pyrazolines have emerged as valuable pharmacophores and selective COX-2 inhibitory agents[8].

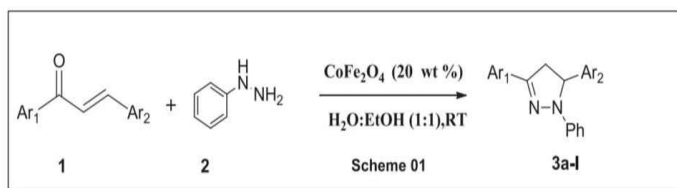
The conventional synthesis of pyrazolines generally involves the cyclization of α,β -unsaturated ketones (chalcones) with hydrazine derivatives under reflux or strongly acidic conditions. While effective, these approaches often require extended heating, generate

unwanted by-products, and involve labor-intensive purification steps⁸. In accordance with the guiding principles of green chemistry[9], there is increasing emphasis on developing catalytic systems that minimize environmental impact while enhancing efficiency and recyclability.

Magnetic nanomaterials have attracted significant interest in heterogeneous catalysis owing to their high surface-to-volume ratio and facile magnetic separation. Cobalt ferrite (CoFe₂O₄), an inverse spinel ferrite, exhibits notable thermal stability, moderate magnetization, and strong structural integrity[10]. These intrinsic characteristics render CoFe₂O₄ nanoparticles particularly suitable for reusable catalytic applications.

In this work, we present a green and efficient strategy for the synthesis of 1,3,5-trisubstituted-2-pyrazolines using magnetically recoverable CoFe₂O₄ nanoparticles under ambient reaction conditions.

II. EXPERIMENTAL SECTION

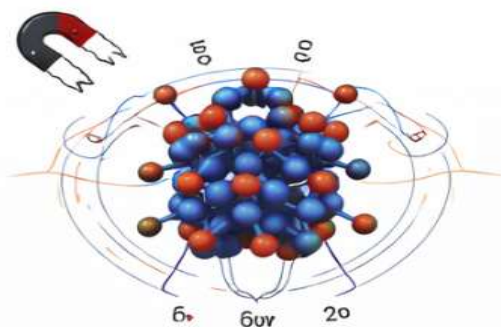


a) Materials and Method:

All chemicals were of analytical grade and used as received. Reaction monitoring was carried out by TLC using silica gel plates. Melting points were determined by open capillary method. FT-IR spectra were recorded using KBr pellets. ^1H NMR spectra were recorded at 400 MHz using TMS as internal standard.

b) Synthesis of CoFe_2O_4 Nanoparticles

Cobalt ferrite nanoparticles were prepared via a controlled co-precipitation approach based on a modified literature method[11]. Aqueous solutions of cobalt nitrate (0.1 M) and ferric nitrate (0.2 M) were mixed under continuous stirring. Ammonium hydroxide was gradually introduced until the pH reached 9, resulting in the formation of a dark precipitate. The mixture was maintained at 60 °C for 2 h to facilitate particle growth. The precipitate was subsequently filtered, thoroughly washed with distilled water, dried, and calcined at 500 °C for 3 h to yield crystalline CoFe_2O_4 nanoparticles.



c) General Procedure for Pyrazoline Synthesis

A reaction mixture comprising chalcone (2 mmol), hydrazine hydrate (4 mmol), and CoFe_2O_4 nanoparticles (20 wt%) was stirred in ethanol–water (1:1, 20 mL) at room temperature. The course of the reaction was followed by TLC analysis. After completion, the reaction mixture was poured into ice-cold water to induce precipitation of the product. The solid was isolated by filtration, washed, and

dried. The catalyst was retrieved magnetically, rinsed with acetone, dried at 100 °C, and reused in subsequent reactions. as per Scheme

Scheme : Synthesis of 1, 3, 5-trisubstituted 2-pyrazolines synthesis using CoFe_2O_4 MNP's

Table 1. Synthesis of 1,3,5-Trisubstituted-2-Pyrazolines

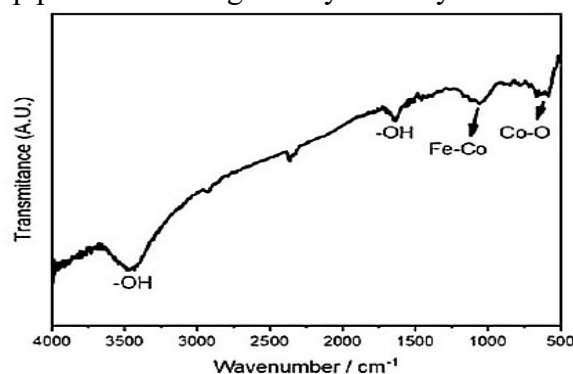
Compound No.	Ar ₁	Ar ₂	Time (h)	Yield (%)	MP (°C)
3a	C ₆ H ₅	C ₆ H ₅	2.8	93	133–135
3b	C ₆ H ₅	4-CH ₃ C ₆ H ₄	3.0	90	128–130
3c	C ₆ H ₅	4-OCH ₃ C ₆ H ₄	3.5	89	110–114
3d	C ₆ H ₅	4-ClC ₆ H ₄	4.0	91	133–137
3e	C ₆ H ₅	3-BrC ₆ H ₄	4.0	90	140–145

III. RESULTS AND DISCUSSION

a) Characterization of CoFe_2O_4 Nanoparticles

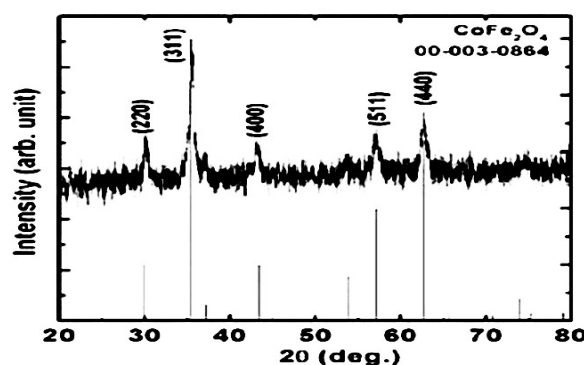
i) XRD pattern of CoFe_2O_4 nanoparticles:

The XRD pattern displayed diffraction peaks at 2θ values of 30.04°, 35.47°, 43.62°, 57.20°, and 62.64°, corresponding to (220), (311), (400), (511), and (440) planes. These peaks match well with JCPDS card No. 00-003-0864, confirming the formation of cubic inverse spinel CoFe_2O_4 structure [10]. The sharp peaks indicate good crystallinity



ii) FT-IR spectrum of CoFe_2O_4 nanoparticles:

The FT-IR spectrum showed a broad band at 3400 cm^{-1} and a band at 1620 cm^{-1} attributed to O–H vibrations. A strong absorption band near 598 cm^{-1} corresponds to Co–O stretching vibrations, while bands in the region 950–1200 cm^{-1} correspond to Fe–O vibrations in the spinel lattice [10–12]. These results confirm successful formation of spinel ferrite nanoparticles.



iii) Optimization of Reaction Conditions

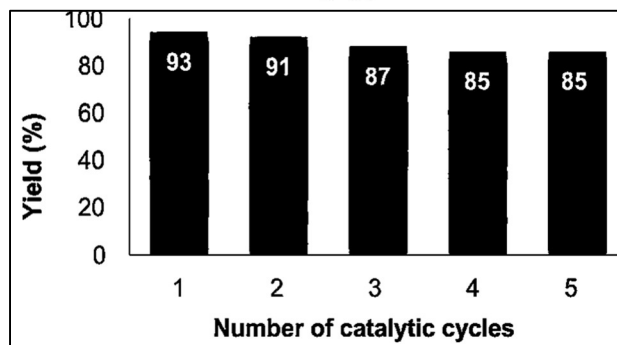
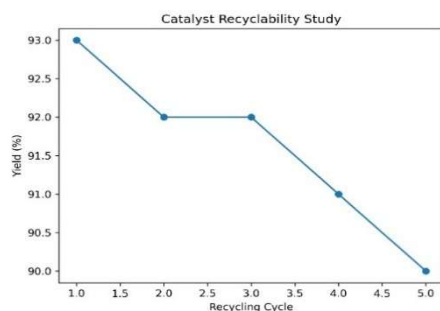
Solvent screening revealed that ethanol–water (1:1) gave the best yield (93%) within 2.8 h. (Table 2). Catalyst loading optimization showed that 20 wt% catalyst provided optimal results. Increasing catalyst amount beyond this did not significantly improve yield as per Table no. 3.

Table 2: Optimization of various solvents for synthesis

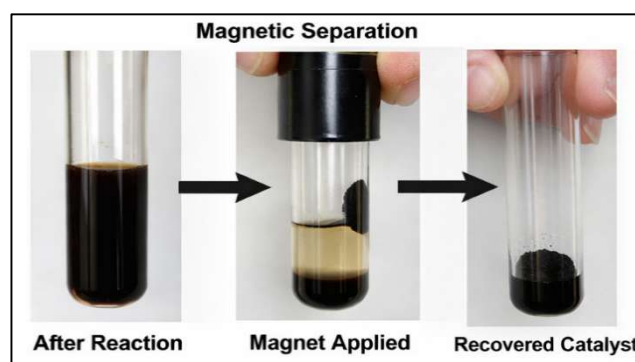
Solvent	Time (h)	Yield (%)
No solvent	5	48
Ethanol	3.0	89
Ethanol: Water (1:1)	2.8	93
Methanol	3.8	85
Water	5.5	68

Table 3: Catalyst Loading Optimization

Catalyst amount in wt. %	Time (h)	Yield (%)
05	5	77
10	5	81
15	4	88
20	3	93
25	3	93

**iv) Substrate Scope**

To explore the general applicability of the developed protocol, a variety of substituted chalcones bearing both electron-donating and electron-withdrawing groups were subjected to the optimized reaction conditions. Chalcones containing electron-donating substituents such as $-\text{CH}_3$ and $-\text{OCH}_3$ as well as electron-withdrawing substituents such as $-\text{Cl}$ and $-\text{Br}$ on the aromatic ring smoothly underwent cyclo-condensation with hydrazine hydrate to afford the corresponding 1,3,5-trisubstituted-2-pyrazolines in good to excellent yields (87–93%). The results clearly indicate that the electronic nature of substituents on the aromatic ring does not significantly affect the course of the reaction, demonstrating broad functional group tolerance of the catalytic system. Electron-donating groups slightly enhanced the reaction rate, possibly due to increased electron density on the chalcone double bond, facilitating nucleophilic attack by hydrazine. On the other hand, electron-withdrawing substituents also afforded high yields, suggesting that the catalytic activity of CoFe_2O_4 nanoparticles effectively activates the α,β -unsaturated carbonyl system irrespective of substituent effects. No significant side products were observed, and the products were obtained with good purity after simple filtration and recrystallization. These observations confirm the robustness and versatility of the developed methodology for synthesizing structurally diverse pyrazoline derivatives.

Catalyst Reusability

magnetic CoFe_2O_4 nanoparticles is their facile separation from the reaction mixture using an external magnet, eliminating the need for filtration or centrifugation. After completion of the reaction, the

catalyst was magnetically separated, washed thoroughly with acetone to remove any adsorbed organic species, dried at 100 °C, and reused for subsequent cycles under identical reaction conditions. The catalytic activity was evaluated over five consecutive cycles for the model reaction. The results revealed only a marginal decrease in yield after the fifth cycle, indicating negligible loss of catalytic efficiency. This minimal reduction may be attributed to slight mechanical loss of catalyst during handling rather than structural degradation. The sustained catalytic performance confirms the high stability, strong magnetic response, and structural robustness of CoFe₂O₄ nanoparticles under the reaction conditions. The excellent recyclability of the catalyst highlights the economic and environmental advantages of this protocol, making it highly suitable for sustainable and large-scale synthetic applications.

CONCLUSION

An efficient and environmentally benign protocol has been developed for the synthesis of 1,3,5-trisubstituted-2-pyrazolines using magnetically separable CoFe₂O₄ nanoparticles as a heterogeneous catalyst. The reaction proceeds under mild conditions in an ethanol–water (1:1) system, providing excellent yields within short reaction times. The catalyst exhibited good stability, easy magnetic recovery, and recyclability up to five cycles with negligible loss of activity. Overall, this green and sustainable methodology offers a practical and cost-effective approach for the synthesis of biologically important pyrazoline derivatives.

ACKNOWLEDGEMENTS

The authors acknowledge the Department of Chemistry, Rajarshi Chhatrapati Shahu College, Kolhapur for laboratory facilities and support.

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