Research Article

A Sustainable and Greener Approach for the Synthesis of Trisubstituted Imidazole Mediated by Soft Ferrite as a Catalysis

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ABSTRACT

This study presents a microwave assisted with a rapid and environmentally benign protocol for synthesizing imidazole derivatives using a one-pot condensation strategy. The reaction involves the condensation of benzil, various aromatic aldehydes, and ammonium acetate, catalyzed by $CuFe_2O_4$ a recyclable catalyst. Microwave irradiation was employed as an alternative energy source to enhance reaction efficiency and reduce processing time, enabling the transformation under mild reaction conditions with notable acceleration. The copper ferrite catalyst was thoroughly characterized by SEM, XRD, and FTIR Analysis. The catalytic system proved to be highly efficient, with the microwave-assisted reaction significantly. The copper ferrite catalyst could be easily recovered by filtration and reused for at least three successive reaction cycles without a notable loss in catalytic performance, emphasizing its stability and reusability. The synthesized products were purified and characterized using melting point determination, FT-IR, ^1H NMR spectroscopy, and mass spectrometry, confirming their structural integrity and high purity. This approach offers a green, cost-effective, and operationally simple alternative to conventional protocols for the development of sustainable synthetic methodologies targeting pharmaceutically relevant heterocyclic compounds.

Keywords: Trisubstituted imidazole, Catalyst, Multicomponent synthesis, Microwave.

INTRODUCTION

In organic chemistry a powerful synthetic strategy involving three or more starting materials react in a single operation to yield desired products. These reactions are monitored and characterized by their simplicity, good atom economy, structural and functional diversity, convergent pathways, and the ability to rapidly construct molecular complexity. Multicomponent reactions offer a practical and environmentally friendly alternative to traditional stepwise syntheses, as they minimize the need for purification of intermediates, reduce solvent usage, and decrease overall reaction times and waste production. Because of these advantages, Multicomponent reactions have attracted considerable attention in drug discovery, combinatorial chemistry, natural product synthesis, and materials science.[1, 2] Their ability to generate diverse chemical libraries in a single synthetic step makes them invaluable tools for modern organic synthesis and sustainable chemical methodologies. Imidazole and their derivatives possess a broad range of biological activities and serve as essential structural scaffolds in medicinal chemistry. These nitrogen-containing heterocyclic are widely recognized for their versatility as synthetic intermediates in the construction of natural products and bioactive compounds. Owing to their distinctive electronic characteristics and strong hydrogen-bonding potential, imidazole-based molecules have been extensively investigated as therapeutic agents for the treatment of various conditions, including inflammation, fungal infections, cancer, and hypertension.[3, 4]

Imidazoles occupy a privileged position in both synthetic and medicinal chemistry owing to their unique electronic structure, broad biological profile and versatility as building blocks.[5] Imidazole based compounds exhibiting antibacterial, anti-inflammatory, antidiabetic, antiparasitic, antituberculosis, antifungal, antioxidant, antitumor, antimalarial, anticancer, and antidepressant activities, among others, constitute a versatile and invaluable scaffold in medicinal chemistry, and numerous new bioactive derivatives have been reported in diverse studies. Nanocomposites serve as a vital bridge between nanoscale phenomena and macroscopic performance, catalyzing innovation from fundamental physical chemistry to state-of-the-art biomedical devices and finding wide-ranging applications in chemistry, physico-chemistry, medicine, biology, materials science, and the development of robust structural materials.[6]

In the past decade, metal nanoparticles have emerged as powerful catalysts, prized for their exceptional activity selectivity profiles and for the straightforward separation, recovery, and reuse they offer. Copper nanoparticles are especially prominent, driving a range of sustainable organic transformations. However, the preparation and application of ferrite based nanocatalysts still poses challenges achieving uniform particle size and dispersion, lowering the high reaction temperatures and lengthy reaction times often required, and eliminating hazardous reagents and solvents.[7-11]

Imidazole is a nitrogen rich heteroaromatic scaffold whose derivatives are widely employed in chemical and biosensor devices, [12] homogeneous and heterogeneous catalysis, [13-15] and drug discovery and development.[16-18] Because the creation of environmentally benign synthetic methodologies remains a priority in modern organic chemistry, [19-20] we have engineered a high-surface area ferrite nanocatalyst that exhibits redox properties and efficiently promotes the solvent-free, microwave-assisted synthesis of substituted imidazoles. This catalyst enables condensation cyclization reactions, furnishing the desired products in excellent yields within short reaction times. Moreover, its heterogeneous nature allows separation and reusability of catalyst over multiple cycles with negligible loss of activity, aligning the protocol with the principles of green chemistry. [21] Therefore, according to the significance of imidazole compounds, herein we used a new ferrite catalyst for the preparation of substituted imidazole compounds.

MATERIALS AND METHODS

All chemicals employed in the present study were of analytical grade and all solvents were carefully distilled to ensure the removal of impurities. The progress of the reactions and the purity of the synthesized products were monitored by thin-layer chromatography. All melting points of the final compounds were determined on digital melting point apparatus. Structural elucidation and confirmation of the synthesized compounds were performed through spectroscopic and analytical techniques. The ^{1}H NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. The FT-IR spectra were obtained using a Perkin Elmer spectrophotometer in the range of 4000–400 cm^{-1}. The XRD was carried out using a Bruker AXS-D8 Advance diffractometer. SEM features were investigated using a JEOL JSM-6390LV scanning electron microscope. The TG/DTA analysis were performed using a Perkin Elmer STA 6000 simultaneous thermal analyzer. Microwave-assisted reactions were conducted under precisely controlled conditions using a scientific microwave synthesizer system developed by Ragatech Electronics.

Procedure for the Preparation of Spinel Ferrite Nanoparticles

The spinel ferrite nanoparticles were synthesized using modified citrate complexation method. Stoichiometric amounts of $Cu(NO_3)_2{\cdot}3H_2O$ and $Fe(NO_3)_3{\cdot}9H_2O$ were dissolved separately in deionized water to obtain 0.1 M solutions. These metal nitrate solutions were then combined, followed by the gradual addition of an aqueous solution of $C_6H_8O_7$. The pH of the mixed solution was carefully adjusted to 7.0 using a dilute solution of NH_4OH under constant stirring. The solution was then refluxed and after reflux, the viscous gel-like precursor was subjected to thermal decomposition in a muffle furnace at 500 °C for four hours in air to yield $CuFe_2O_4$ nanoparticles. The obtained spinel ferrite powders were ground and stored in airtight containers for further characterization.

Synthesis Procedure for preparation of imidazole derivatives

In one-pot procedure, a stoichiometric mixture comprising ammonium acetate (1 mmol), substituted aromatic aldehydes (1 mmol), benzil (1 mmol), and a catalytic amount of ferrite nanocatalyst was placed into a round-bottom flask. The mixture was subjected to microwave irradiation under solvent-free conditions. The progress of the reaction was monitored periodically by TLC using silica gel plates. Upon completion, the reaction mixture was diluted with hot ethanol to dissolve the organic products. The ferrite catalyst was separated by simple filtration, washed thoroughly with ethanol and dried in a hot air oven for reuse for consequent reaction cycles. The structure, identity, and purity of the synthesized imidazole derivatives were confirmed by spectroscopic analysis, including ^{1}H NMR and Fourier Transform Infrared spectroscopy. The observed spectral data were in good agreement with the expected structures of the synthesized compounds.

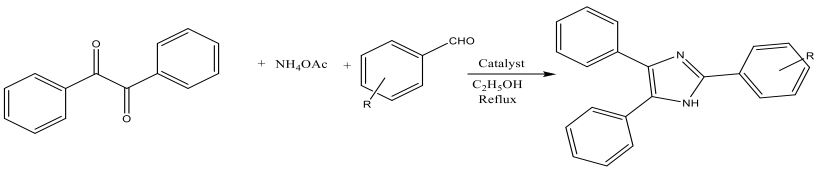
Respective spectral data

2-(3,4-dihydroxyphenyl)-4,5-diphenyl-1H-imidazole:

FT-IR (cm^{-1}): 3049, 1490, 1393, 1252, 692,578; ^{1}H-NMR (400 MHz, DMSO-*d6*): δ 6.7 (d, 2H), 7.2 to 7.3(m, 6H), 7.4 (d, 5H), 9.0(s, 1H), 9.2(s, 1H), 9.6 (s, 1H); MS: M/Z 328.12 (M). MP 260-262°C

RESULTS AND DISCUSSION

In order to investigate on a model multicomponent reaction, a system involving ammonium acetate, various benzaldehydes, and benzil was designed to evaluate the synthetic route under varied reaction conditions (Scheme-1). This preliminary study aimed to optimize the formation of imidazole derivatives using an environmentally benign and efficient approach. A systematic evaluation was conducted to assess the influence of critical reaction parameters, including solvent choice, catalyst concentration, microwave irradiation power, reaction temperature, and the molar ratios of the reactants. Each parameter was independently varied while maintaining the others constant to determine its individual contribution toward reaction efficiency, product yield, and purity. The outcome of this optimization provided the most suitable conditions that facilitated a rapid, high-yielding, and reproducible synthesis under microwave-assisted conditions, highlighting the importance of precise control over these parameters in developing an efficient green protocol.

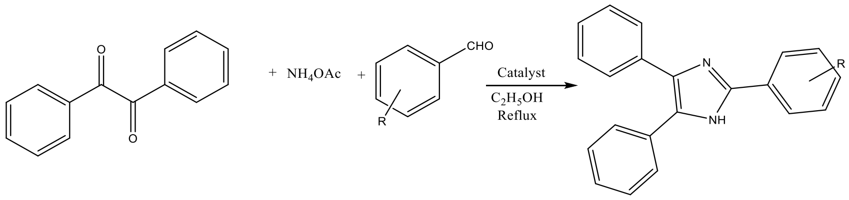


Scheme-1: Synthesis of imidazole using catalyst

Table 1: Optimization of reaction conditions for imidazole synthesis and the effect of solvents on product formation

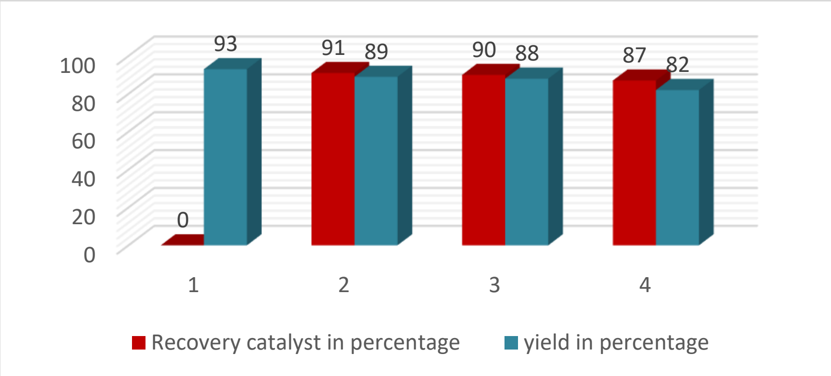
Sr. No	Catalyst (wt %)	Condition/ Solvents	Time (min.)/ Yield [b] (%)
1	Without catalyst	Microwave/solvent free	28/16
2	10	Microwave/solvent free	09/93
3	10	Reflux/water	120/58
4	10	Reflux/ethanol	120/70

Table 2: Synthesis of imidazole derivatives with catalyst



Entry	Product	Substrate R	Substrate (x)	Reaction Time (min.)	Yield[b] (%)	M.P. °C
1	4a	Ph	NH_4OAc	13	91	271-272
2	4b	$4\text{-}OCH_3C_6H_4$	NH_4OAc	12	90	226-228
3	4c	$2\text{-}OHC_6H_4$	NH_4OAc	15	87	206-210
4	4d	$3\text{-}NO_2C_6H_4$	NH_4OAc	12	91	265-267
5	4e	$3,4\text{-}OH\text{-}C_6H_3$	NH_4OAc	10	93	268-270
6	4f	$3,4(OCH_3)_2C_6H_3$	NH_4OAc	13	88	258-260

[a]Reaction conditions: aromatic aldehyde (1 mmol); benzil (2 mmol); ammonium acetate (1 mmol); catalyst (10 wt.%). [b]Isolated yields.



[a] catalyst recovered by filtration and washing with alcohol, [b] yields of the product

Figure 1: Reusability of catalyst

In order to assess the efficiency of our microwave-assisted protocol for imidazole synthesis, a series of reactions was performed using various aromatic aldehydes reacted efficiently with benzyl and ammonium acetate under identical conditions in good to excellent yields as it can be summarized in Table-1. Experiment was carried out in a series of aromatic aldehyde bearing either electron donating groups on the ring. In presence and absence of catalyst results shows that in presence of catalyst forms product in very less time and good yield was obtained. The catalyst was recovered from reaction mixture by adding volatile solvent and then filtered for reusability of catalyst for further runs. The recovered catalyst was reused for three times under same reaction conditions for synthesis without loss in activity of catalyst.

The outcomes of this present investigation demonstrate that our microwave-assisted, ferrite-catalyzed protocol for imidazole synthesis combines operational simplicity, rapid reaction times, and high product yields with a significantly reduced environmental impact.

CONCLUSION

In the present study, we prepared ferrite catalyst and catalyst was then evaluated in the one-pot synthesis of imidazoles under solvent-free microwave irradiation. A typical reaction involved mixing of benzil, an aromatic aldehydes, and ammonium acetate with ferrite catalyst in a microwave reactor. Under these optimized conditions, a broad range of aldehydes bearing electron-donating and electron-withdrawing substituents afforded the corresponding imidazole derivatives in excellent isolated yields. After completion of reaction monitored by TLC, the catalyst was simply recovered by filtration, washed with ethanol, and air-dried and shows excellent recyclability. The key advantages of this protocol includes green and sustainable conditions, mild reaction profile, high efficiency and recyclability. Together, these features establish ferrite as an eco-friendly catalyst for the rapid synthesis of pharmaceutically relevant imidazole scaffolds.

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