IOSR Journal of Multidisciplinary Research (IOSR -JMR)
ISSN: 3048-7439 (January 2026) PP 17-23
www.iosrjournals.org

Significant Review of Synthesis of Substituted Imidazole Derivatives Using Diffrent Catalysis

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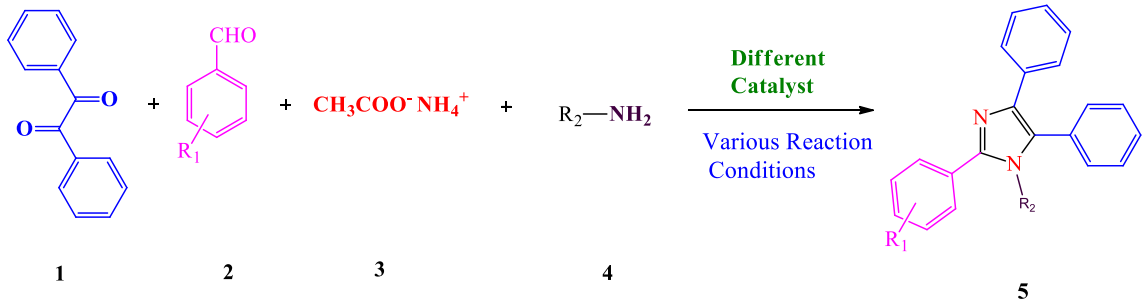
Abstract
Imidazole and its derivatives are vital heterocyclic compounds found in numerous natural products and pharmaceutical drugs. Molecules containing the imidazole core exhibit a wide range of important pharmacological and biological activities. Compounds containing an imidazole ring system exhibit a wide range of pharmacological properties and play a vital role in various biochemical processes. The advanced approach known as green chemistry or sustainable technology shifts the focus from traditional process efficiency, which mainly emphasizes product yield, to more environmentally responsible practices. This review highlights the recently developed methods for the synthesis of tri and tetrasubstituted imidazole derivatives.

Graphical abstract



Keywords
Multicomponent Reactions, N-containing heterocycles, trisubstituted/tetra-substituted imidazoles, organocatalyst

I. Introduction

Heterocyclic compounds are a crucial class of organic molecules widely found in natural products, pharmaceuticals, agrochemicals, and dyes. In view of broad biological and industrial relevance, developing efficient synthetic methods to access these structures remains a central objective in organic chemistry. [1] Conventional methods for heterocyclic synthesis often rely on toxic solvents, harsh reaction conditions, and non-recyclable catalysts, leading to significant environmental and economic concerns. [2] Heterocyclic frameworks are prevalent in commercially available drug molecules and serve as key structural motifs in many naturally occurring compounds. Numerous synthetic heterocyclic scaffolds have demonstrated a broad spectrum of biological activities in the synthesis of diverse heterocyclic compounds, selecting an appropriate catalyst is crucial. Currently, researchers favour metal-free organocatalyst to prevent metal contamination in the final products. [3]

Heterocyclic compounds not only form the backbone of many biologically active natural products used in traditional medicine and approved prescription drugs, but several of their synthetic derivatives varying in ring size also exhibit significant pharmacological potential. Heterocyclic compounds have long been attractive targets in synthetic organic chemistry. Heterocyclic compounds have consistently created significant interest in the field of synthetic organic chemistry. [4]

Microwave (MW) technology is also transforming synthetic chemistry, supporting the shift toward greener practices. It can significantly reduce reaction times—from hours to minutes—while improving yields, minimizing side reactions, and enhancing reproducibility compared to conventional heating. Traditional methods of chemical synthesis are proving to be unsustainable from both environmental and economic

perspectives. As a result, there's a growing need for more efficient and eco-friendly alternatives. Multicomponent coupling reactions offer a promising solution because they are more cost-effective, efficient, and generate less waste than traditional approaches.[5].

Microwave (MW) irradiation has emerged as an effective tool in this regard. It can significantly shorten reaction times—from hours to minutes—while also minimizing side reactions, improving yields, and enhancing reproducibility compared to traditional heating methods. Studies have shown notable improvements in both reaction rate and yield when performed under microwave irradiation. Some newly reported methods still face limitations, including low product yields, complex isolation processes, the use of costly catalysts, and environmental pollution. As environmental awareness continues to grow in both research and industry, there is an urgent need for cleaner, more sustainable chemical processes that avoid harmful organic solvents. [6]. Microwave-assisted organic synthesis (MAOS) is an emerging and rapidly growing field in synthetic organic chemistry, where microwave irradiation significantly accelerates reactions and often improves yields compared to conventional heating. [7].

One-pot, multi-component reactions are of great interest because they produce a single product in high yield. These reactions offer a convenient and efficient approach for synthesizing biologically and pharmaceutically active organic compounds. [8] Multi-component reactions have been developed as an efficient and powerful tool in modern synthetic organic chemistry, enabling the straightforward formation of multiple new bonds in a single one-pot process. [9]

Imidazole is a nitrogen-rich heterocyclic compound, and its derivatives have wide-ranging applications across various fields, including sensors, catalysis, electro catalysis, drug discovery, fuel cell development, and conducting polymers. Given the significance of imidazole-based compounds, developing an optimized and efficient synthetic methodology is crucial. [10] Imidazole-containing derivatives have shown potential as anti-tubercular agents, and their structure-activity relationships have been studied. This valuable information can help guide the future design of more effective imidazole-based anti-tubercular drugs. [11]

Imidazole and its derivatives are vital heterocyclic compounds found in numerous natural products and pharmaceutical drugs. Molecules containing the imidazole core exhibit a wide range of important pharmacological and biological activities. [12] In green chemistry, imidazole derivatives used as ionic liquids serve as electrolytes or environmentally friendly solvents due to their low vapour pressure and high chemical stability. [13]

Imidazole are well-known heterocyclic compounds that are widely available and possess valuable properties, including antiseptic [9], antifungal [10],antiviral [15] antidepressant [18], anti-HIV [19], ,antitumor [20], antiallergic [21]. Additionally, many heterocycles play important roles in materials science, being used in dyes, fluorescent sensors, brightening agents, plastics, and analytical reagents. Imidazole derivatives play a crucial role across various scientific domains due to their unique structural and physicochemical properties

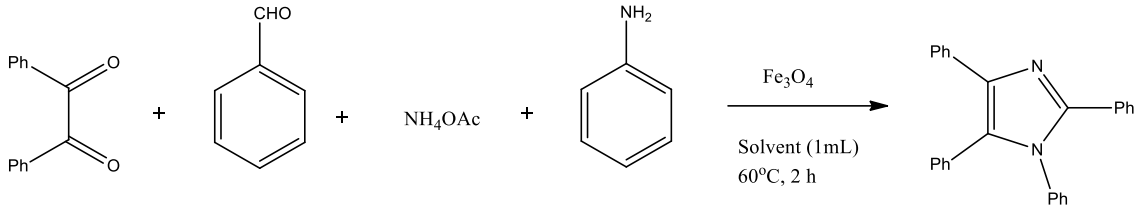
The imidazole ring, characterized by aromaticity and the presence of two nitrogen atoms, allows for strong hydrogen bonding, coordination with metal ions, and interaction with biological targets. These features make imidazole a highly valuable scaffold in medicinal chemistry, drug development, and material science Medicinal Chemistry and Drug Development, Drug Design and Targeting, Material Science and Industrial Applications. Organic synthesis has emerged as a powerful tool in the field of chemistry, significantly enhancing reaction rates, improving yields, and reducing reaction time. [14]

The tetrasubstituted Imidazole are an important class of imidazole which are prepared via the one-pot multi-component condensation of benzil with aldehyde, primary amine and ammonium acetate using a green catalyst. The main part of imidazole in production is used in production of biologically active compounds. [14]

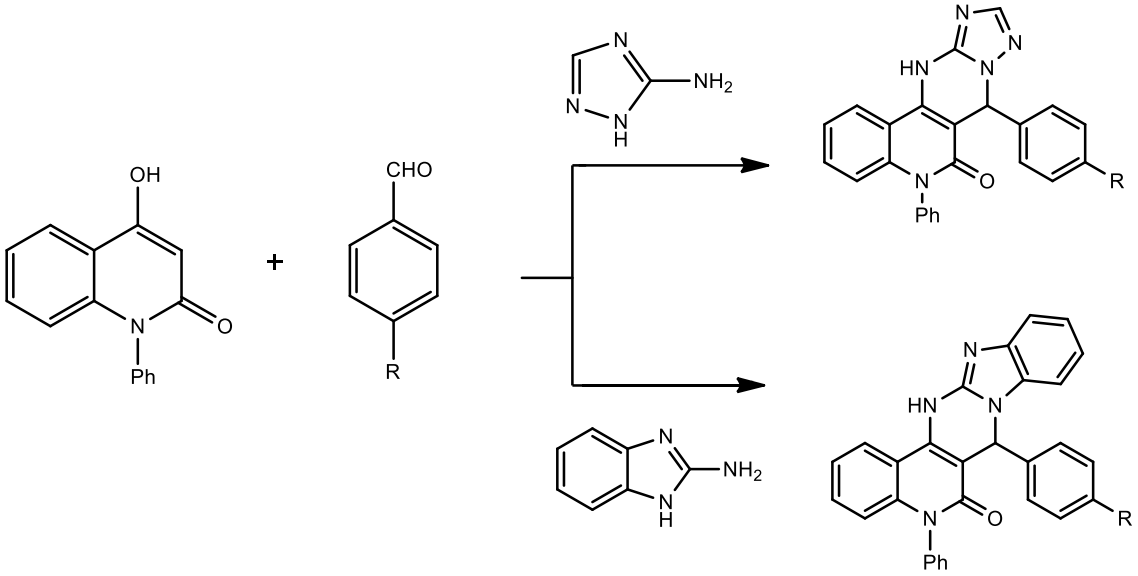
The demand for more environmentally friendly methods is growing in chemical synthesis, pharmaceutical industries, and heterocyclic compound production. These organic compounds are characterized by unique properties such as high thermal and chemical stability, low volatility, and non-flammability. [15]

II. Synthesis of Imidazole Derivatives

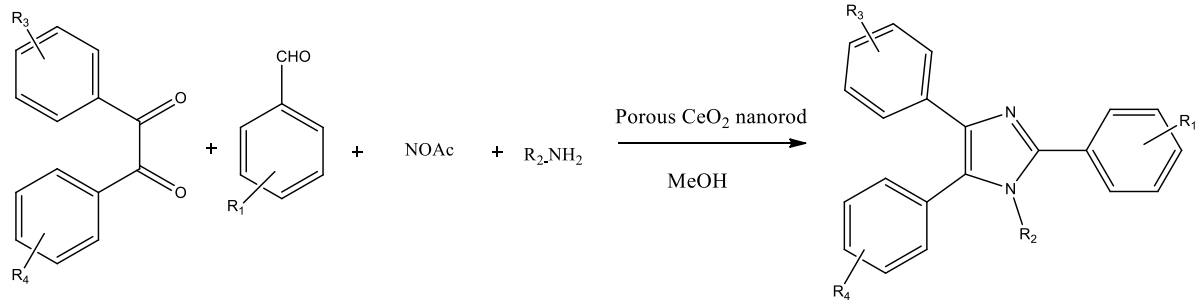
Najmoddin Aziizi et. al. [22] **(2014)** have developed a one-pot, four-component approach towards the synthesis of tetra substituted imidazoles using aldehydes, amines, ammonium acetate, and 1,2-diphenylethane-1,2-dione using iron oxide nanoparticles as a catalyst. The advantages of these reactions are high yield of product, short reaction time and easy work up procedure. (Scheme 2.1)



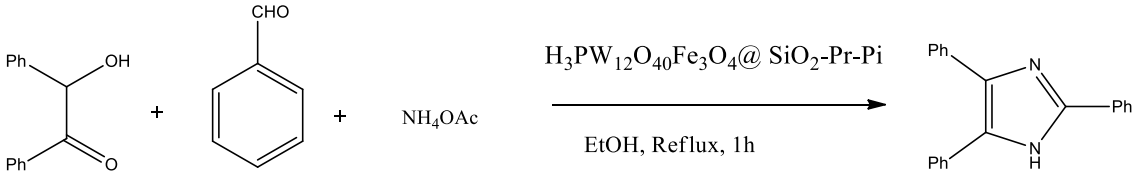
Aboul-Fetouh E. Mourad et. al. [23] **(2014)** has explained Biginelli condensation reactions under microwave irradiation synthesized pyrimido[5,4-c]quinolin-5-one derivatives and 2H-pyrano[3,2-c] quinolines in high yields from 4-hydroxy-1-phenylquinolin-2(1H)-one, aryl aldehydes, and urea/thiourea or other amines.



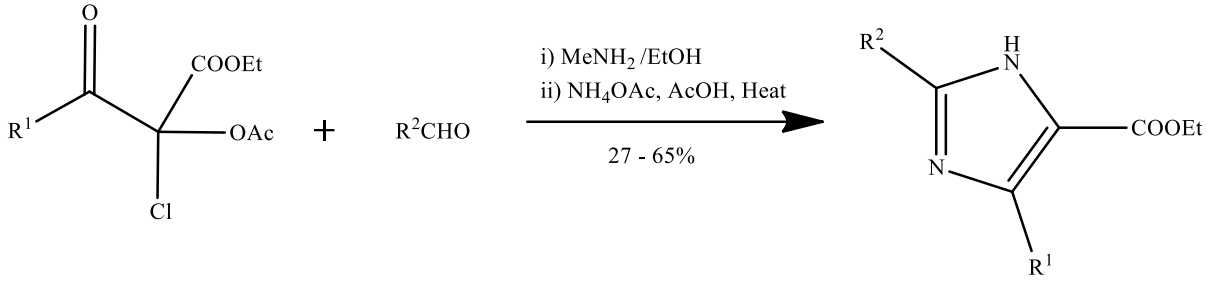
Yue Fang et al. [24] **(2017)** Tetrasubstituted imidazoles were synthesized via a four component reaction using aromatic aldehydes, amines, substituted benzils and ammonium acetate catalysed by porous CeO_2 nanorods



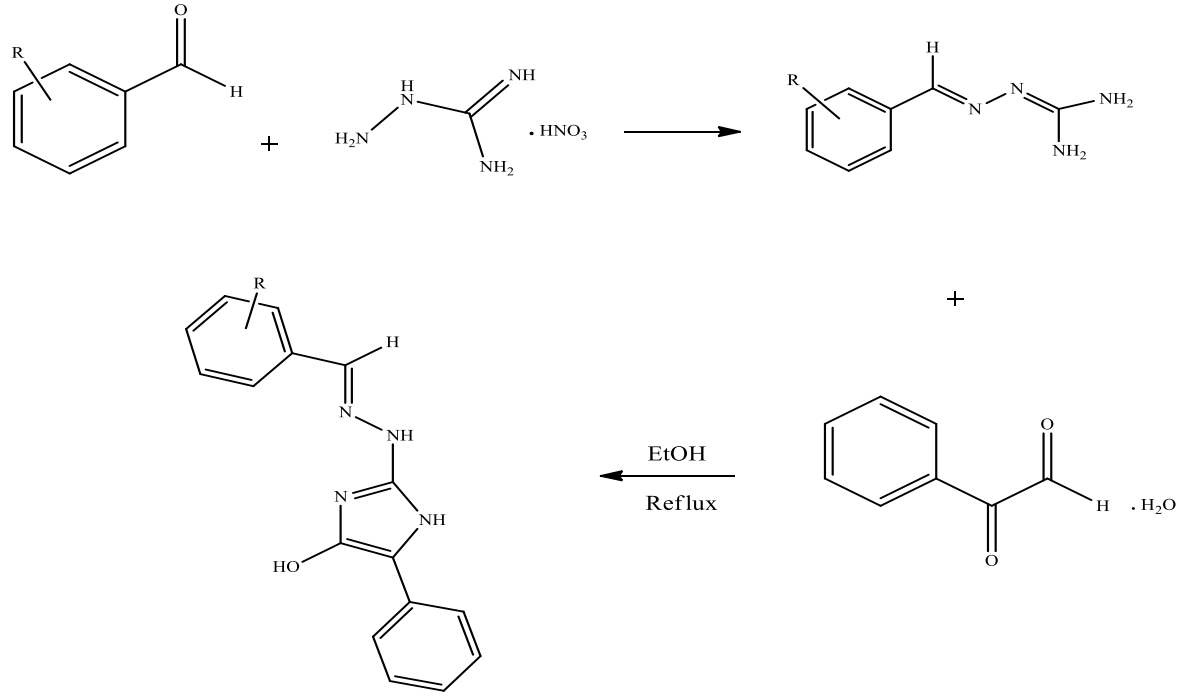
Ramin Ghorbani-Vaghei, Vida Izadkhah, Jafar Mahmoodi et. al. [25] **(2018)** have developed Tri- and tetra-substituted imidazole derivatives were synthesized using a catalyst (H2PW12O40¯ loaded on magnetic nanoparticle-supported ionic liquid). The method offers easy catalyst separation using a magnet. The compounds showed antioxidant and antifungal activities with varying biological effects. A mixture of benzoin, aldehyde and ammonium acetate was reacted in EtOH with a magnetic catalyst under reflux conditions.



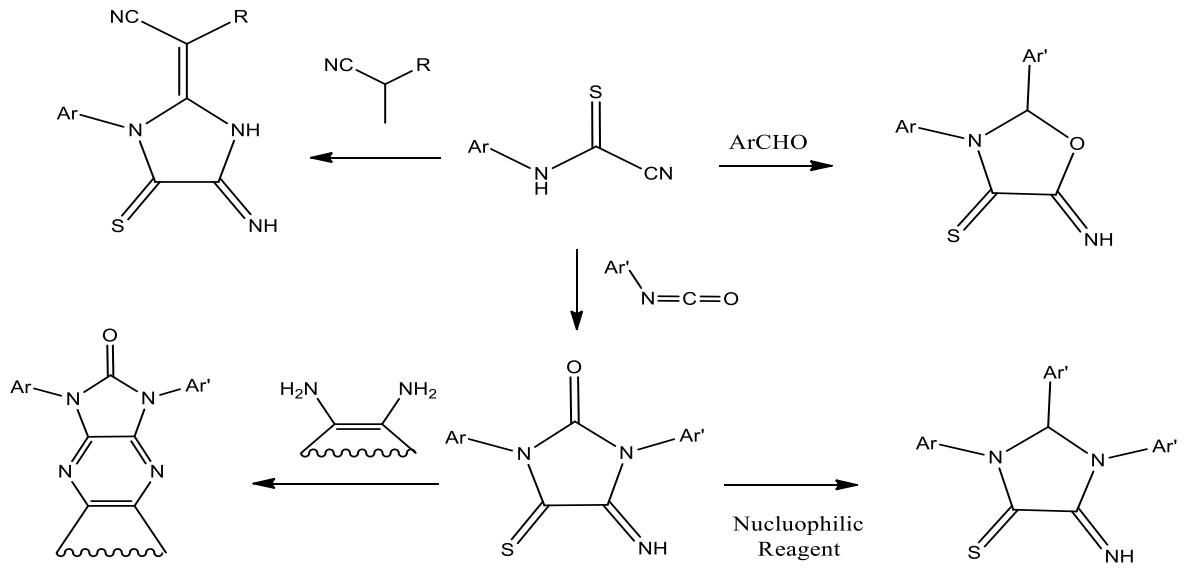
Wong, L. C. et.al. [26] **(2012)** have developed a one-pot method for synthesizing trisubstituted imidazole derivatives using α-acetoxy-α-chloro-β-keto-esters, aldehydes, and ammonium acetate as starting materials. Advantages of this methodology is to avoids the production of triphenylphospine oxide as a by-product



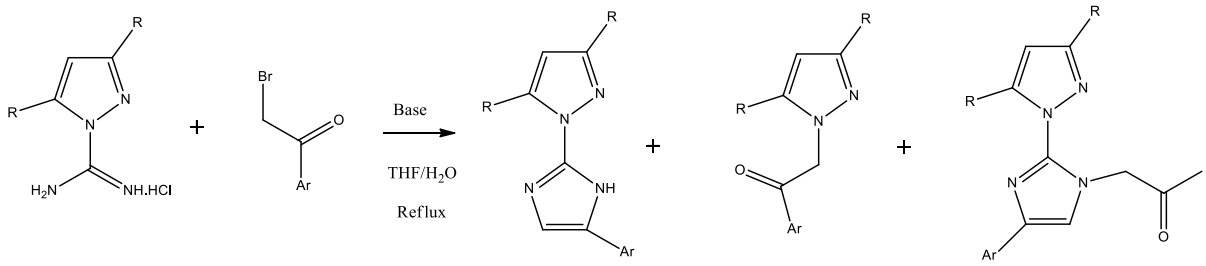
Yavuz, S. C. et al. [27] **(2019)** have synthesized a series of imidazole derivatives via a two-component condensation reaction between phenylglyoxal monohydrate and guanylhydrazone. The structures of the synthesized compounds were confirmed by spectroscopic and analytical techniques. They have been detected that changes in the imidazole nucleus show promising anticancer activities.



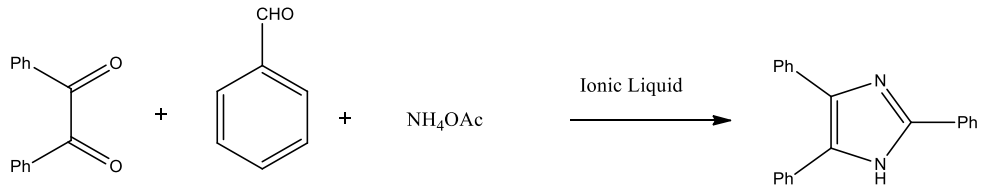
Abbas, S. Y. et.al. [28] **(2020)** reported that cyanothioformamide derivatives react with electrophiles to yield various heterocycles, including imidazole, oxazole, thiazole, 2,5-thiadiazole, bis-imidazole, and bis-oxazole derivatives. In contrast, their reactions with nucleophiles lead to the formation of benzoxazole, quinolinone, triazole, bis-triazole, benzoxazinethione, and 1,3,4-thiadiazole derivatives. These compounds show applications as medicinal and pharmacological agents.



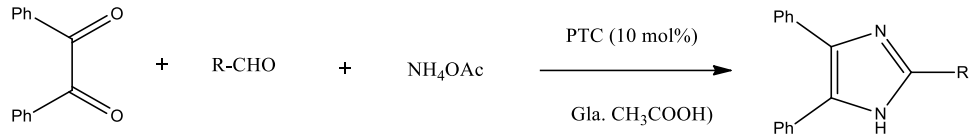
Punia, S. et al. [29] **(2020)** stated a regioselective synthesis of highly substituted 1,2,4-trisubstituted imidazoles via a base-mediated domino reaction of an amidine framework with phenacyl bromide, followed by in situ N-alkylation. The reaction was optimized to assist neutralization, condensation, and N-alkylation in a one-pot process.



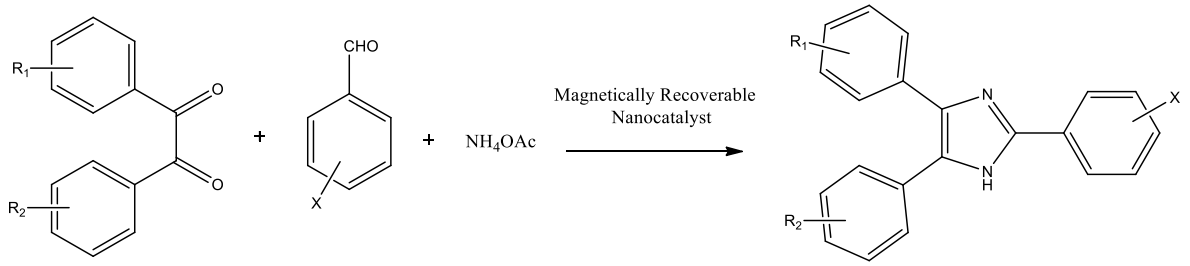
Vaishali S. Sharma's et.al. [30] **(2025)** evaluation highlights the growing importance of eco-friendly methods in organic synthesis, focusing on ionic liquids (ILs) as green catalysts and solvents. Owing to their unique properties, ILs have been efficiently employed in the sustainable synthesis of various heterocycles, particularly imidazoles—valuable compounds with potential therapeutic applications. The article provides a comprehensive overview of recent advancements in using environmentally benign ILs for the efficient synthesis of diverse imidazole derivatives.



T. DuraiAnanda Kumar et al. [31] **(2014)** developed a high-yielding and versatile phase-transfer-catalyzed synthesis of 2,4,5-triaryl-1H-imidazoles using response surface methodology (RSM). The study evaluated the effects of catalyst type, catalyst loading, and solvent volume, identifying PEG400 and glacial acetic acid as the optimal components. Under optimized conditions—PEG400 (10.61 mol%) and glacial acetic acid (10.71 mL) for 5 hours—the reaction yielded 4,5-diphenyl-2-nitrophenyl-1H-imidazole with 97% efficiency, closely aligning with the predicted yield of 97.5%.



Mostafa Kazemi [32] **(2020)** highlights the importance of imidazole-containing molecules in pharmaceutical and medicinal chemistry due to their significant biological activities and roles in natural product synthesis. Numerous methods for synthesizing imidazole derivatives have been reported. Recently, nanomagnetic catalysts have attracted considerable attention for their high catalytic activity and ease of separation. Application of nanomagnetic catalysts in the synthesis of imidazole derivatives, aiming to promote further advancements in this field.



III. Conclusion

Given today's synthetic demands, environmentally friendly multicomponent reactions using green methods are especially valuable. Green catalyst is one of the key of green chemistry protocol have been demonstrated to be efficient techniques for various organic transformation without using harmful organic solvent.

Acknowledgements

This research was financially supported by Diamond Jubilee Research Initiation Scheme of Shivaji University, Kolhapur [File No. SU/C & U.D.S/2022-2023/9/396 dated: 11th Oct. 2023].

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