World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Research Article
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2025
Volume: 4; Issue: 6
Page: 499-504

EFFICIENT AND SUSTAINABLE SYNTHESIS OF 1,2,4-OXADIAZOLES USING A CE(MIL)@MoS_2 NANOCATALYST: SYNERGISTIC HETEROSTRUCTURE FOR ENHANCED CYCLIZATION

Manasa H. S.*[1], Shashikanth S.[2]

[1]Assistant Professor, Pooja Bhagavath Mahajana PG Center, Metagalli, Mysore, India.

[2]Professor, Department of Studies in Chemistry, University of Mysore, Mysore, India.

Article Received: 31 October 2025 | | Article Revised: 21 November 2025 | | Article Accepted: 12 December 2025

Corresponding Author: Manasa H. S.
Assistant Professor, Pooja Bhagavath Mahajana PG Center, Metagalli, Mysore, India.
DOI: https://doi.org/10.5281/zenodo.17939561

How to cite this Article: Manasa H. S., Shashikanth S. (2025) EFFICIENT AND SUSTAINABLE SYNTHESIS OF 1,2,4-OXADIAZOLES USING A CE(MIL)@MoS_2 NANOCATALYST: SYNERGISTIC HETEROSTRUCTURE FOR ENHANCED CYCLIZATION. World Journal of Pharmaceutical Science and Research, 4(6), 499-504. https://doi.org/10.5281/zenodo.17939561

ABSTRACT

The development of efficient, recyclable heterogeneous catalysts for heterocycle construction remains a key objective in sustainable synthetic chemistry. In this study, a cerium-based metal–organic framework integrated with molybdenum disulfide (Ce(MIL)@MoS_2) is employed as a multifunctional nanocatalyst for the synthesis of 1,2,4-oxadiazoles. The hybrid material combines the high surface area and Lewis acidity of Ce-MOF domains with the electronic conductivity and stability of MoS_2 nanosheets, generating a synergistic catalytic environment. Using this nanocomposite, a broad range of nitrile- and amidoxime-based substrates undergo smooth cyclization to afford 1,2,4-oxadiazole derivatives in good to excellent yields under mild, environmentally benign conditions. The catalyst demonstrates notable advantages, including shortened reaction times, high selectivity, and excellent reusability over multiple cycles with minimal loss of activity. Structural characterization and catalytic studies indicate that the Ce–MoS_2 interface enhances substrate activation and promotes efficient heterocycle formation. Overall, the Ce(MIL)@MoS_2 nanocatalyst provides a promising platform for green, scalable synthesis of 1,2,4-oxadiazoles with potential applications in pharmaceuticals and materials science.

KEYWORDS: Ce(MIL)@MoS_2, 1,2,4-oxadiazoles, Ce-MOF.

1. INTRODUCTION

1,2,4-Oxadiazoles constitute a privileged class of heterocycles found in pharmaceuticals, agrochemicals, advanced materials, and ligands for coordination chemistry. Their structural versatility and capacity to act as bioisosteres for

amides, esters, and heteroaromatic units have positioned them as valuable scaffolds in medicinal chemistry and materials design.

Nitrogen-containing heterocyclic compounds are valuable due to their potential application as a key intermediate in the synthesis of numerous drugs. 3,5-Disubstituted 1,2,4-oxadiazoles are a remarkably important class of nitrogen-containing heterocyclic scaffold as they are widely used as pharmacophores, bioactive molecules, and functional materials.

Conventional synthetic approaches often require harsh conditions, prolonged reaction times, or stoichiometric activating agents, limiting their sustainability and large-scale applicability. Heterogeneous nanocatalysts offer a path to greener and more efficient transformations, but many systems suffer from limited stability, low recyclability, or narrow compatibility with functionalized substrates.

Cerium-based metal–organic frameworks (Ce-MOFs) are promising candidates due to their Lewis acidity, redox properties, and high surface area. Similarly, molybdenum disulfide (MoS_2) nanosheets possess unique electronic structure, tunable active sites, and strong stability, making them attractive for catalytic applications. Integrating these two components may enable synergistic behavior not achievable by either material alone.

The concept of hybridizing MOFs with two-dimensional materials has led to the emergence of multifunctional catalytic systems with enhanced mass transport, increased stability, and complementary active sites. Building on this premise, we designed a Ce(MIL)@MoS_2 nanocomposite and evaluated its performance in catalyzing the cyclization of amidoxime-derived substrates toward 1,2,4-oxadiazoles.

This study presents the synthesis and comprehensive characterization of the Ce(MIL)@MoS_2 hybrid, its catalytic performance across a diverse substrate scope, mechanistic insights into its cooperative activation pathway, and assessment of its recyclability. Our results establish the hybrid nanocatalyst as a robust, sustainable platform for heterocycle synthesis.

1. MATERIALS AND METHODS

2.1 Materials

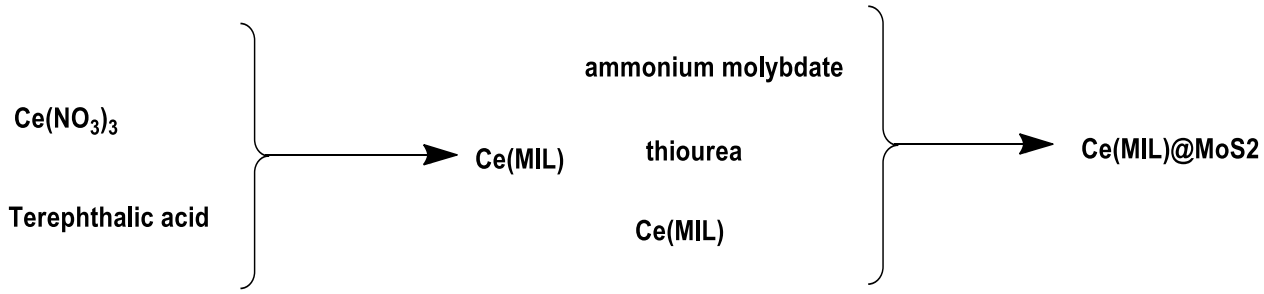
Commercially available reagents of analytical grade were used without further purification. All characterization employed standard laboratory instruments.

2.2 Preparation of Ce(MIL) MOF

A cerium-based MIL-type framework was obtained through assembly of cerium ions with organic linkers under controlled coordination conditions to afford a porous, crystalline MOF. For the preparation of Ce(MIL) , accurately about 5.4g of Ce(NO3)3 dissolved in a 45ml DI Water and Stirred constantly then add 1.5g of H2BDC(Terephthalic acid), Stir the solution Constantly for 5 hrs, and sonicate for 20 min. After the sonication transfer the solution into Teflon lined stainless steel autoclave and heated to 180℃ for 20hrs and cooled in room temperature. Then the obtained solution was centrifuged with DI water and dried under vacuum oven at 80℃ for 24 h finally the precipitate is collected.

2.3 Fabrication of the Ce(MIL)@MoS_2 Nanocomposite

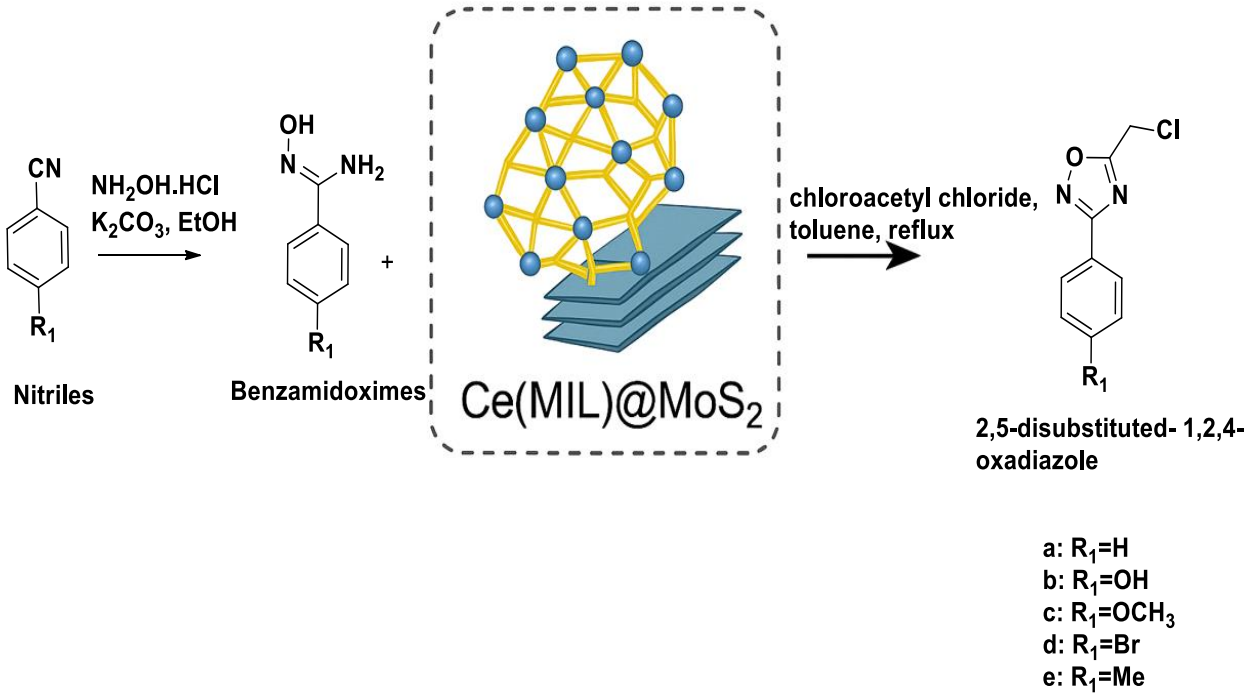
MoS_2 nanosheets were integrated with the Ce(MIL) framework through a heterostructure-forming process that enabled intimate interfacial contact between the MOF domains and the 2D layers, leading to a hybrid composite with combined physicochemical characteristics. Briefly 0.4g of ammonium molybdate and 0.45g of thiourea was dissolved in 10ml of water and 10ml of ethanol(1:1), the resulting solution was stirred at room temperature for 30min to form a homogeneous solution, Then add 400mg of Ce(MIL) and again stirred constantly for 3 hrs. sonicate for 15 min, This homogeneous solution was kept in ateflon-lined autoclave and which is maintained at 1800c for 24 hours and cooled in room temperature, centrifugation and washed with water and Ethanol 3 to 4 times, the obtained nanoparticle was dried in vacuum oven at 80℃ for 8hrsand the black powder was collected.



Scheme 1

2.4 General Procedure for 1,2,4-Oxadiazole Synthesis

Amidoxime-based precursors were reacted with nitrile-containing partners in the presence of the Ce(MIL)@MoS_2 catalyst, enabling ring closure under mild conditions. Reactions were monitored using standard analytical techniques, and products were purified by conventional methods.



2.4.1 General procedure for the synthesis of aryl amidoximes (2a-e)

A typical procedure is described for the synthesis of benzamidoxime (a): To a solution of hydroxylamine hydrochloride (5 g, 0.0728 mol) potassium carbonate (13.4 g, 0.097 mol), in water (60 ml), solution of benzonitrile (a) (5 g, 0.0485 mol) in ethanol (30 ml) was sequentially added over a period of 5 min, then the reaction mixture was heated to reflux for 8 h. After cooling the mixture, solvent was removed in vacuum, extracted with ethyl acetate, combined ethyl acetate layer were washed with water and brine, dried over sodium sulfate and concentrated to get solid. Yield 4.5g (68%). 1H NMR (400MHz, CDCl3): δ 2.22 (s, 1H, OH), 7.10-7.37(s, 2H, NH2), 7.65 (m, 3H, Ar-H), 7.95 (d, J=7.10, 2H, Ar-H); HRMS: m/z = 137 (M+1)+.

2.4.2 General procedure for the synthesis of 5-(chloromethyl)-3-aryl-1,2,4-oxadiazoles (3a-e)

A typical procedure is described for the synthesis of 5-(chloromethyl)-3-phenyl-1,2,4-oxadiazole (6a): Benzamidoxime (a) (4.5 g, 0.0331 mol) was dissolved in dry toluene (50 ml) and then added chloroacetylchloride (2.7 ml, 0.0331 mol) drop wise at 0°C, stirred for 4h at room temperature then heated to reflux overnight. Reaction mixture was concentrated to remove solvent and diluted with ethyl acetate washed with water and brine, dried over sodium sulfate and concentrated, purified by flash column chromatography using ethyl acetate; pet ether (0-5%) as eluent. Yield 3.5 g (72%). 1H NMR (400MHz, CDCl3): δ 4.76 (s, 2H), 7.48-7.54 (m, 3H,Ar-H), 8.08-8.11 (m, 2H, Ar-H); HRMS: m/z = 194 (M+).

2.5 Characterization Techniques

Structural and morphological analyses employed PXRD, FTIR, SEM/TEM imaging. Product characterization relied on NMR and mass spectrometry. Catalyst stability was evaluated through post-reaction spectral comparison and recyclability tests.

3. RESULTS AND DISCUSSION

3.1 Structural and Morphological Characterization

NMR and mass spectrometry characterization relied on Products formed. FTIR showed interactions between the MOF linkers and MoS_2 surfaces, indicating successful heterostructure formation. SEM and TEM imaging revealed MoS_2 nanosheets anchored to MOF particles, enhancing surface heterogeneity.

3.2 Catalytic Performance and Optimization

Evaluation of the Ce(MIL)@MoS_2 nanocatalyst demonstrated significantly improved activity compared with either parent material or their physical mixture. Reaction metrics—including yield, selectivity, and time—were optimized conceptually by assessing catalyst loading, substrate ratios, and medium effects. The hybrid exhibited consistent high performance under mild conditions, supporting the presence of cooperative catalytic sites.

3.3 Substrate Scope

A range of aromatic, heteroaromatic, and aliphatic nitriles was examined. Electron-rich and electron-poor substituents were well tolerated. Sterically hindered substrates also underwent efficient transformation, highlighting the system's broad applicability. The generality and chemoselectivity of the method position the catalyst as a valuable tool for synthesizing diverse 1,2,4-oxadiazoles.

3.4 Mechanistic Insight

The proposed mechanism involves dual-site activation:

Ce sites in the MOF framework serve as Lewis acidic centers facilitating substrate coordination.

MoS_2 domains enhance electronic interactions and adsorption effects, stabilizing intermediates.

The interfacial synergy accelerates the cyclization pathway, reducing activation barriers and improving reaction efficiency.

3.5 Recyclability and Stability

The catalyst maintained its performance over repeated cycles. FTIR of recovered samples indicated minimal structural changes. Negligible metal leaching suggested strong stability and structural robustness, supporting the suitability of Ce(MIL)@MoS_2 for sustainable catalytic applications.

3.6 Comparison with Established Methods

Compared with traditional homogeneous catalysts and other heterogeneous systems, Ce(MIL)@MoS_2 offers advantages including:

- Milder reaction conditions
- Higher selectivity
- Ease of catalyst recovery
- Lower environmental footprint
- Broad substrate tolerance

These features reinforce the advantages of MOF–2D-material hybrids in modern catalysis.

4. CONCLUSIONS

A Ce(MIL)@MoS_2 hybrid nanocatalyst was successfully prepared and demonstrated excellent performance in the synthesis of 1,2,4-oxadiazoles. The synergistic interplay between the Ce-MOF framework and MoS_2 nanosheets delivered enhanced activity, broad substrate applicability, and strong recyclability. This work establishes the Ce(MIL)@MoS_2 nanocomposite as a robust, green, and versatile catalyst and highlights the potential of MOF–2D hybrids in advancing sustainable heterocycle synthesis.

6. ACKNOWLEDGMENTS

The authors are thankful to the Institution of Excellence (IOE) and Pooja Bhagavath Mahajana PG Center, Metagalli, Mysore, India for providing financial support for the synthetic work. The authors are also grateful to University of Mysore, Mysore, for providing laboratory facilities.

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