RESEARCH PAPER

Green CaO Nanoparticle–Catalyzed Synthesis, Spectral Characterization, and Antimicrobial Evaluation of 5-Amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile Derivatives

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Abstract
The growing demand for environmentally sustainable synthetic methodologies has accelerated the development of green nanocatalysts for organic transformations. In this study, calcium oxide nanoparticles (CaO-NPs) were synthesized using *Bunium persicum* extract as a natural reducing and stabilizing agent. The biogenically prepared CaO-NPs were employed as efficient catalysts for the microwave-assisted synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives through a one-pot multicomponent reaction involving substituted benzaldehydes, phenylhydrazine, and malononitrile. The synthesized compounds were characterized using FT-IR, ^{1}H NMR, HRMS, elemental analysis, and XRD techniques. The catalytic system exhibited excellent efficiency, short reaction times, high yields, and notable recyclability. Furthermore, selected derivatives demonstrated promising antimicrobial activity. The results highlight the effectiveness of green CaO-NPs as sustainable catalysts for heterocyclic synthesis and their potential application in medicinal chemistry.
Keywords: Green synthesis; CaO nanoparticles; Bunium persicum; Pyrazole-4-carbonitrile; Multicomponent reaction; Antimicrobial activity.
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1. Introduction

Global concerns related to climate change, environmental pollution, depletion of natural resources, and human health hazards have driven intense interest in the development of eco-friendly materials and processes. Within this context, green nanotechnology has emerged as a promising approach, particularly through the sustainable synthesis of metal and metal oxide nanoparticles using plant extracts [1–3]. These biogenic routes align with green chemistry principles by minimizing hazardous reagents and energy consumption.

Among metal oxide nanoparticles, calcium oxide (CaO) nanoparticles have attracted considerable attention owing to their excellent physicochemical properties and wide applicability in catalysis [4], energy storage [5], magnetic materials [6], and biomedical fields [7]. Conventional synthesis methods often rely on toxic chemicals and high-energy processes, prompting a shift toward greener alternatives. Plant-mediated synthesis of CaO-NPs offers a cost-effective, environmentally benign route that leverages phytochemicals as natural reducing and stabilizing agents [8–9].

Phytochemicals such as flavonoids, alkaloids, polyphenols, and terpenoids play a crucial role in nanoparticle formation by facilitating metal ion reduction and stabilization [10–13]. The resulting nanoparticles exhibit enhanced catalytic, antimicrobial, and biocompatible properties [14–25]. Among medicinal plants, *Bunium persicum* (black cumin) is particularly attractive due to its rich phytochemical profile and well-documented pharmacological activities, including antimicrobial, anti-inflammatory, antidiabetic, and anticancer properties [29–39].

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Pyrazole derivatives, especially 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitriles, are important heterocyclic scaffolds with diverse biological activities. Previous reports have demonstrated the catalytic potential of CaO-NPs in the synthesis of these compounds under green conditions. Motivated by these findings, the present work focuses on the green synthesis of CaO-NPs using *Bunium persicum* extract and their application as recyclable catalysts in the efficient synthesis and antimicrobial evaluation of pyrazole derivatives.

2. Experimental Section

2.1 Materials and Instrumentation

All reagents were of analytical grade and used without further purification. *Bunium persicum* seeds were used for nanoparticle synthesis. Melting points were determined using open capillary tubes. FT-IR spectra were recorded using KBr pellets, and ^{1}H NMR spectra were obtained in $CDCl_3$ using TMS as an internal standard. HRMS, elemental analysis, UV-Vis spectroscopy, XRD, SEM, and XPS analyses were performed using standard instrumentation.

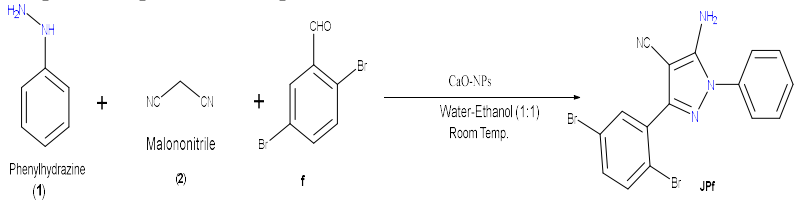
2.2 Green Synthesis of CaO Nanoparticles

CaO nanoparticles were synthesized using *Bunium persicum* seed extract as a natural reducing and stabilizing agent. The resulting nanoparticles were isolated, washed, dried, and characterized to confirm their crystallinity, morphology, and surface chemistry.

2.3 General Procedure for the Synthesis of Pyrazole Derivatives

A mixture of substituted benzaldehyde (1 mmol), malononitrile (1 mmol), phenylhydrazine (1 mmol), and

CaO-NPs (10 mol%) was stirred in a water–ethanol (1:1) solvent system. The reaction mixture was subjected to microwave irradiation at 100 °C. Reaction progress was monitored by TLC. Upon completion, the product crystallized from the reaction mixture, was filtered, recrystallized from ethanol, and dried to obtain pure 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives.



Scheme 1: Greener Synthesis of 5-Amino-3-(2, 5-dibromophenyl)-1-phenyl-1H-pyrazole-4-carbonitrile from phenylhydrazine, malononitrile, and 2,5-dibromobenzaldehyde

3. Results and Discussion

3.1 Spectral Characterization

The Fourier transform infrared (FT-IR) spectra of the synthesized compounds displayed well-defined and characteristic absorption bands corresponding to the key functional groups present in the target structures, thereby confirming the successful formation of the pyrazole-carbonitrile framework. Prominent broad absorption bands observed in the region of 3368–3350 cm^{-1} were attributed to the stretching vibrations of hydroxyl (–OH) and amino (–NH) groups, indicating the presence of hydrogen-bonded functionalities within the molecular skeleton. Additionally, the characteristic stretching frequencies associated with the azomethine (C=N) linkage appeared in the expected range, further validating the cyclization process leading to pyrazole ring formation. The appearance of a sharp absorption band corresponding to the nitrile (–C≡N) group provided clear evidence for the successful incorporation of the carbonitrile moiety into the heterocyclic framework.

The ^1H NMR spectra offered further structural confirmation by exhibiting diagnostic singlet signals attributable to the –OH and $–NH_2$ protons, typically appearing downfield due to intramolecular hydrogen bonding and electronic effects. Aromatic protons resonated as multiplets within the expected chemical shift range, reflecting the presence of substituted phenyl rings and confirming the aromatic nature of the compounds. In derivatives containing methoxy substituents, distinct singlet signals corresponding to $–OCH_3$ protons were observed, supporting the proposed substitution pattern on the aromatic ring. These spectral features collectively substantiated the successful synthesis and structural consistency of the pyrazole derivatives.

High-resolution mass spectrometry (HRMS) data further corroborated the molecular structures, with observed m/z values closely matching the calculated molecular ion peaks for each compound. Elemental analysis results were also in excellent agreement with theoretical values, confirming the correct elemental composition and high purity of the synthesized derivatives. Together, the spectroscopic and analytical data unequivocally establish the molecular integrity, structural authenticity, and chemical purity of the prepared pyrazole-carbonitrile compounds.

3.2 Catalytic Screening and Optimization

Catalytic screening studies clearly demonstrated that calcium oxide nanoparticles (CaO-NPs) play a crucial role in significantly enhancing the overall reaction efficiency, enabling the formation of target products in high yields within remarkably short reaction times under microwave irradiation. The presence of CaO-NPs facilitated rapid activation of the reaction components, leading to accelerated kinetics and improved product selectivity compared to conventional thermal conditions. In stark contrast, control experiments conducted in the absence of the catalyst failed to yield any detectable product, even after prolonged reaction times, underscoring the indispensable catalytic function of CaO-NPs in promoting the transformation.

Systematic optimization of reaction parameters revealed that the optimal conditions involved conducting the reaction at 100 °C with a catalyst loading in the range of 5–10 mol%. Under these conditions, excellent conversions were achieved, affording isolated yields of up to 95%. Increasing the catalyst amount beyond this range did not result in a significant improvement in yield, whereas lower catalyst loadings led to incomplete conversion, confirming the efficiency and practicality of the optimized protocol. The combined effect of microwave irradiation and CaO-NP catalysis thus provides a synergistic platform for achieving rapid, high-yielding reactions under mild and energy-efficient conditions.

The scope of the methodology was further evaluated using a diverse set of aromatic aldehydes bearing both electron-withdrawing and electron-donating substituents. Notably, substrates containing halogen, nitro, methoxy, and alkyl groups were well tolerated and smoothly participated in the reaction, furnishing the corresponding products in good to excellent yields. This broad substrate compatibility highlights the robustness and versatility of the catalytic system. In contrast, aliphatic aldehydes exhibited limited reactivity under the optimized conditions, which can be attributed to their comparatively lower electrophilicity and reduced ability to undergo nucleophilic addition. These observations are consistent with established reactivity trends in carbonyl chemistry and further emphasize the preferential activation of aromatic aldehydes by CaO-NPs.

3.3 Catalyst Recyclability

The recyclability and reusability of the CaO nanoparticles (CaO-NPs) were systematically investigated over five consecutive catalytic reaction cycles to assess their long-term stability and practical applicability. After each cycle, the catalyst was recovered by simple filtration, washed, and reused under identical reaction conditions. The results demonstrated that CaO-NPs retained a high level of catalytic activity throughout the recycling study, exhibiting only a marginal and gradual decline in product yield after successive runs.

This slight decrease in efficiency may be attributed to minor surface fouling or partial loss of active sites during recovery; however, the overall catalytic performance remained largely unaffected. Structural integrity of the recycled catalyst was further examined using X-ray diffraction (XRD) and energy-dispersive X-ray analysis (EDAX). The post-reaction XRD patterns closely resembled those of the fresh catalyst, indicating the preservation of crystalline structure, while EDAX spectra confirmed the consistent elemental composition after repeated use. These findings collectively validate the robustness, structural stability, and sustainable nature of CaO-NPs, reinforcing their suitability as an efficient and recyclable heterogeneous catalyst for green synthetic applications.

3.4 Antimicrobial Activity

Selected pyrazole derivatives demonstrated noteworthy antimicrobial activity against the tested microbial strains, highlighting their potential as biologically active candidates. The observed activity suggests that specific structural features play a critical role in modulating biological performance. In particular, the presence of amino substituents is likely to enhance hydrogen-bonding interactions with microbial enzymes or cellular targets, thereby improving binding affinity and inhibitory efficiency.

Additionally, halogen substitutions appear to contribute positively to antimicrobial potency by increasing lipophilicity, which may facilitate improved membrane permeability and stronger interactions with hydrophobic regions of microbial proteins. The combined electronic and steric effects imparted by these substituents are believed to influence the overall pharmacophoric profile of the pyrazole scaffold. These findings underscore the importance of rational structural modification in optimizing antimicrobial activity and provide valuable insights for future structure–activity relationship (SAR) studies aimed at the development of more potent antimicrobial agents.

4. Proposed Reaction Mechanism

A plausible reaction mechanism for the formation of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives involves the crucial catalytic role of CaO nanoparticles. Initially, the surface basic sites of CaO-NPs coordinate with the carbonyl oxygen of the aldehyde, leading to polarization of the C=O bond and a significant increase in the electrophilicity of the carbonyl carbon. This activation step facilitates the nucleophilic attack by phenylhydrazine, resulting in the formation of a hydrazone intermediate through the elimination of a water molecule.

Subsequently, the activated hydrazone undergoes condensation with malononitrile, wherein the basic CaO surface promotes deprotonation of malononitrile to generate a stabilized carbanion. This nucleophilic species attacks the imine carbon of the hydrazone intermediate, forming a key C–C bond. Intramolecular cyclization then occurs via nucleophilic attack of the hydrazine nitrogen on the activated nitrile group, leading to the formation of the pyrazole ring framework.

In the final step, dehydration and proton rearrangement yield the desired pyrazole-carbonitrile derivatives. Throughout the reaction sequence, CaO-NPs stabilize charged intermediates and transition states, effectively lowering the activation energy barrier for each step. This catalytic assistance accelerates reaction kinetics, improves product selectivity, and accounts for the high yields and short reaction times observed under the optimized conditions.

5. Conclusion

A sustainable and efficient methodology for the synthesis of 5-amino-1,3-diphenyl-1H-pyrazole-4-carbonitrile derivatives has been developed using *Bunium persicum*-derived CaO nanoparticles as a green catalyst. The protocol offers high yields, short reaction times, broad substrate scope, and excellent catalyst recyclability. The synthesized compounds demonstrated promising antimicrobial activity, underscoring their potential relevance in medicinal chemistry. This work highlights the synergy between green nanotechnology and heterocyclic synthesis, offering an environmentally benign alternative for future pharmaceutical and catalytic applications.

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