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Sustainable One-Pot Synthesis of Pyrazoline Derivatives Using Recyclable ZnO Nanoparticles in Aqueous Medium

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Abstract: *An efficient approach was devised for the synthesis of pyrazoline derivatives involving benzaldehyde, aromatic ketones, and phenyl hydrazine in aqueous media, employing ZnO nanoparticles as a catalyst at 40°C. This one-pot addition-cyclocondensation strategy afforded pyrazoline derivatives in good to excellent yields. The ZnO nanoparticles exhibited high reusability with negligible loss of catalytic performance. The structural elucidation of the obtained compounds was carried out using advanced analytical techniques.*

Keywords: ZnO nanoparticle, aromatic aldehyde, cyclcondensation, acetophenone etc

I. INTRODUCTION

The field of synthetic heterocyclic chemistry utilizing green methodologies has garnered considerable interest in recent years due to its straightforward operation, eco-friendly nature, and cost-effective processes. Such approaches have opened new avenues for synthesizing complex molecules with minimal environmental impact, aligning perfectly with the principles of green chemistry. Among these strategies, one-pot multi-component reactions (MCRs) have become increasingly popular as a highly efficient synthetic tool for assembling target compounds (1). MCRs significantly enhance the efficiency of chemical synthesis by enabling the simultaneous formation of multiple bonds in a single reaction vessel. This strategy not only minimizes reaction times but also improves overall chemical yields compared to traditional multi-step syntheses. The latter typically involves multiple reaction and purification steps, resulting in synthetic inefficiency, increased labor, and the generation of large quantities of waste.

Pyrazoles, an important class of nitrogen-containing heterocycles, have attracted considerable attention due to their wide-ranging applications in medicinal chemistry and pharmaceutical research. These compounds are key structural motifs in numerous therapeutic agents and biologically active natural products. Pyrazole derivatives have been shown to exhibit a diverse range of biological activities, including antifungal (2), antioxidant (3), anticancer (4), antimalarial (5), and anti-inflammatory (6) properties, underscoring their importance in drug discovery. The broad utility of pyrazoles in medicinal chemistry has driven significant efforts to develop efficient and sustainable synthetic routes for their production.

Over the years, various methods for synthesizing substituted pyrazoles have been developed, employing different catalysts to enhance reaction efficiency and selectivity. These include urea (7), trisodium citrate dihydrate (8–10), $ZnCl_2$, dodecylbenzenesulfonic acid (11), L-proline (12), molecular iodine (13), ZrO_2 nanoparticles (14), cesium fluoride (15), ionic liquids (16), maltose (17), and $AlCl_3$ (18). While these methods have contributed significantly to the field, many suffer from limitations such as prolonged reaction times, moderate product yields, and challenges with catalyst recovery and reuse. The environmental concerns associated with some of these methods, particularly the use of non-recyclable catalysts and hazardous solvents, have also motivated researchers to explore more sustainable alternatives.

By addressing key challenges associated with conventional synthetic strategies, our work highlights the importance of integrating green chemistry principles into modern organic synthesis. The combination of operational simplicity, high efficiency, and environmental sustainability makes this approach well-suited for broader applications in pharmaceutical

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and industrial chemistry. Furthermore, the methodology's potential scalability and adaptability to other heterocyclic systems pave the way for its use in diverse areas of synthetic and medicinal chemistry.

In our research, we addressed these limitations by developing an eco-friendly, one-pot synthetic methodology for producing pyrazoline derivatives. The reaction employed ZnO nanoparticles as a catalyst and was conducted in an aqueous solvent system at a relatively low temperature of 40°C. This innovative method demonstrated several advantages over conventional approaches, including excellent product yields, significantly reduced reaction times, and the ability to reuse the ZnO catalyst multiple times without a substantial loss in activity. These features not only improve the overall efficiency of the process but also align with the principles of green chemistry by reducing waste and avoiding the use of toxic solvents.

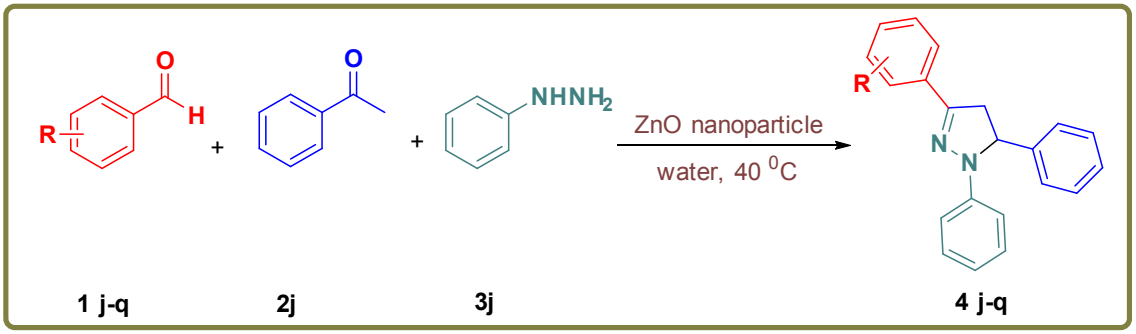
The use of water as a reaction medium further enhances the environmental sustainability of this approach, as water is non-toxic, readily available, and biodegradable. Additionally, the recyclability of the ZnO catalyst minimizes resource consumption and reduces the overall cost of the process, making it highly attractive for large-scale applications. This methodology represents a significant advancement in sustainable heterocyclic synthesis, offering a practical and environmentally responsible alternative to traditional methods.

II. EXPERIMENTAL

The chemicals utilized in this study were procured from Sigma-Aldrich and used as received, without further purification. The melting points of the synthesized compounds were measured using the uncorrected open capillary method. Product purity and identity were confirmed through thin-layer chromatography (TLC). Infrared (IR) spectra were recorded using a Bruker spectrophotometer with KBr pellets, while proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in DMSO-d6 on an Advance 300 MHz spectrometer, with tetramethylsilane (TMS) serving as the internal reference.

III. GENERAL PROCEDURE FOR THE SYNTHESIS OF PYRAZOLINE:

A reaction mixture was composed of aromatic acetophenone (2.0 mmol), aromatic benzaldehyde (2.0 mmol), potassium hydroxide solution (18%, 3 mL), and phenyl hydrazine (6.0 mmol), using water (15 mL) as the solvent. ZnO nanoparticles were utilized as the catalyst, and the reaction was conducted at 40°C in a round-bottom flask. The progress of the reaction was periodically assessed through thin-layer chromatography (TLC). Upon completion, the reaction mixture was cooled by pouring it onto crushed ice, resulting in the precipitation of the product as a solid. The precipitate was collected by filtration, thoroughly washed, and purified via recrystallization in methanol to obtain the pyrazoline derivatives.



IV. RESULT AND DISCUSSION

The synthesis of 1,3,5-triaryl pyrazoline was carried out through a cyclocondensation reaction involving an aromatic aldehyde, an aromatic ketone, and phenyl hydrazine under optimized conditions. The selection of a suitable solvent was crucial for improving reaction efficiency, and several solvents were systematically evaluated (Table 1).

Carbon tetrachloride, a non-polar solvent, produced a 52% yield of the target compound over a prolonged reaction time of 9 hours, which was deemed unsatisfactory. Trials with polar solvents such as acetonitrile, dichloromethane (DCM),

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and water resulted in moderate yields of 61%, 59%, and 67%, respectively, with reaction times of 6.5, 7, and 5 hours. However, these conditions were still suboptimal in terms of both yield and reaction time.

The use of water as the reaction medium during the final optimization significantly enhanced both yield and reaction kinetics, achieving a superior yield of 78% within a reduced reaction time of 4 hours. This improvement is likely due to water's ability to enhance reactant solubility and facilitate efficient interactions with the catalyst. Consequently, water emerged as the most effective solvent among those tested, demonstrating its potential as a sustainable and efficient medium for this synthetic protocol.

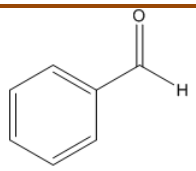
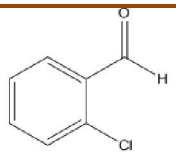
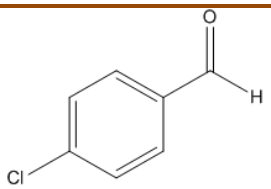
Table 1: Solvent Selection for Enhanced Reaction Efficiency in Pyrazoline Synthesis

Sr. number	Solvent	Time in (hrs.)	Yield in (%)
1	Carbon tetrachloride	9	52
2	Acetonitrile	6.5	61
3	DCM	7	59
4	DMSO	5	67
5	**Water**	**4**	**78**

The reaction was systematically evaluated using aromatic aldehydes bearing various electron-withdrawing and electron-donating substituents to assess the impact of electronic effects on product yield. As shown in Table 2, aldehydes with electron-withdrawing groups significantly improved reaction efficiency, yielding higher amounts of pyrazoline derivatives. Notably, entry 4 in Table 3 recorded an exceptional 91% yield within a short reaction time of 3 hours, highlighting the ability of electron-withdrawing substituents to stabilize reaction intermediates and promote the cyclocondensation process.

In contrast, substrates with electron-donating substituents produced moderate yields, likely due to decreased electrophilicity of the aromatic aldehydes, which reduced their reactivity under the optimized conditions. Despite this variation, the results demonstrate the broad applicability of the protocol, achieving good to excellent yields across diverse substituents. This optimized methodology, characterized by high efficiency and broad substrate compatibility, underscores its practicality and scalability for the synthesis of bioactive heterocyclic compounds, offering significant potential for applications in medicinal and synthetic organic chemistry.

Table 2: Influence of Substituted Aromatic Aldehydes on Pyrazoline Synthesis Optimization.

Sr. number	Benzaldehyde	Pyrazoline derivative	Time Hrs.	Yield[x]
1		**4j**	4	78
2		**4k**	3.5	81
3		**4l**	4	84

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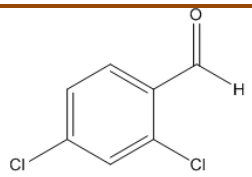
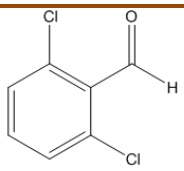
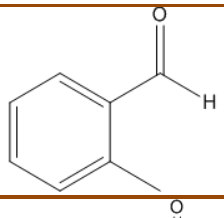
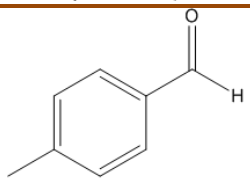
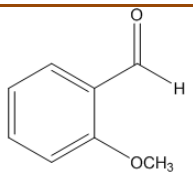
4		**4m**	3	91
5		**4n**	4	80
6		**4o**	5.5	69
7		**4p**	5	73
8		**4q**	6.5	63
x represent isolated product				

V. CONCLUSION

The synthesis of pyrazoline derivatives was efficiently accomplished using benzaldehyde, ketones, and phenyl hydrazine under heating at 40°C with ZnO nanoparticles as a catalyst in water as the solvent. This method afforded yields ranging from good to excellent. Key advantages of the protocol include shorter reaction times, high product yields, and straightforward catalyst recovery. The reaction proceeded smoothly, with the ZnO nanoparticle catalyst demonstrating excellent reusability, retaining its catalytic activity over four successive cycles without significant loss in performance. This reusability not only enhances the sustainability of the process but also reduces costs, making the method viable for large-scale applications. The simplicity, efficiency, and economic viability of this approach position it as a valuable method for the synthesis of pyrazoline derivatives, particularly in the fields of pharmaceutical and medicinal chemistry.

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