

# **Microwave-Assisted Synthesis of Novel Acylhydrazoneoximes: A Comparative Evaluation with the Conventional Method**

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**Abstract:** The present work reports an efficient microwave-assisted synthesis of novel acylhydrazoneoxime ligands derived from para-substituted isonitrosoacetophenones and terephthalohydrazide. The synthesized compounds were characterized using elemental analysis, UV-Visible, FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and mass spectrometry techniques. A comparative assessment between the conventional reflux method and microwave irradiation clearly demonstrates the superiority of the microwave-assisted approach in terms of reaction time, yield, energy efficiency, and operational simplicity. Microwave synthesis resulted in higher yields within significantly shorter reaction times, highlighting its advantages as a green and sustainable alternative to conventional heating methods.

**Keywords:** Microwave-assisted synthesis, Conventional method, Acylhydrazoneoximes, Isonitrosoacetophenones, Terephthalohydrazide

## **I. INTRODUCTION**

Hydrazones and oxime derivatives constitute an important class of Schiff base compounds that have attracted sustained scientific interest owing to their structural versatility, rich coordination chemistry, and wide spectrum of applications in analytical, medicinal, and materials chemistry<sup>1</sup>. Among these, acylhydrazoneoximes represent a unique subclass in which both hydrazone and oxime functionalities coexist within the same molecular framework. The presence of multiple donor atoms, such as azomethine nitrogen, oxime nitrogen, carbonyl oxygen, and amide nitrogen, enables these molecules to act as effective polydentate ligands toward transition metal ions.<sup>2</sup> As a result, acylhydrazoneoximes have been extensively explored for their coordination behavior, biological activity, and catalytic potential.

Hydrazones and oximes are widely used in analytical chemistry for the selective detection, separation, and quantitative estimation of carbonyl compounds and metal ions.<sup>3</sup> In coordination chemistry, these ligands form stable complexes with a variety of metal ions, often exhibiting enhanced physicochemical and biological properties compared to the free ligands. Several reports have highlighted their pharmacological relevance, including antibacterial, antifungal, anticancer, antitubercular, and anti-inflammatory activities.<sup>4,5</sup> The biological activity of these compounds is strongly influenced by the nature of substituents, ligand flexibility, and metal-binding ability, making the synthesis of structurally diverse acylhydrazoneoximes an area of continuous research interest.

Conventionally, the synthesis of hydrazone and oxime derivatives involves condensation reactions between carbonyl compounds and hydrazine or hydroxylamine derivatives under reflux conditions in polar solvents such as ethanol, methanol, or dimethyl sulfoxide. Although this classical method is straightforward and widely adopted, it suffers from several inherent limitations.<sup>6,7</sup> Conventional reflux synthesis typically requires prolonged reaction times ranging from several hours to even days, leading to increased energy consumption and operational costs. Additionally, extended heating may cause thermal degradation of sensitive functional groups, formation of side products, and reduced product



selectivity. The requirement of large volumes of organic solvents further raises environmental and safety concerns, particularly in the context of sustainable chemical synthesis.<sup>8</sup>

In recent years, the principles of green chemistry have driven significant efforts toward the development of alternative synthetic methodologies that minimize environmental impact while maintaining or improving reaction efficiency. In this regard, microwave-assisted organic synthesis (MAOS) has emerged as a powerful and sustainable technique.<sup>9</sup> Microwave irradiation offers rapid and uniform heating by directly coupling electromagnetic energy with polar molecules and solvents, resulting in efficient internal heating. Unlike conventional heating, which relies on slow heat transfer from the vessel walls to the reaction medium, microwave heating ensures instantaneous energy delivery, thereby accelerating reaction rates and improving product yields.<sup>10</sup>

Microwave-assisted synthesis has been successfully applied to a wide range of organic transformations, including condensations, cyclizations, oxidations, and polymerizations. Numerous studies have demonstrated that reactions conducted under microwave irradiation often proceed with shorter reaction times, higher yields, improved purity, and reduced solvent usage. Additionally, microwave synthesis aligns well with green chemistry principles by lowering energy consumption, minimizing waste generation, and enhancing reaction safety. These advantages make MAOS particularly attractive for the synthesis of complex organic molecules and functional ligands.<sup>11,12</sup>

Despite the extensive application of microwave-assisted techniques in organic synthesis, systematic comparative studies focusing on the synthesis of acylhydrazoneoxime ligands remain limited. In particular, there is a need to critically evaluate the effectiveness of microwave irradiation relative to conventional reflux methods in terms of reaction efficiency, yield, structural integrity, and environmental impact. Such comparative studies are essential to establish microwave-assisted synthesis as a reliable and scalable alternative for ligand preparation.

Terephthalohydrazide is an important bifunctional precursor that offers two reactive hydrazide groups capable of undergoing condensation with carbonyl or oxime-containing compounds, leading to the formation of symmetrical or extended ligand systems. Para-substituted isonitrosoacetophenones, on the other hand, introduce electronic and steric variations that can significantly influence the coordination behavior and physicochemical properties of the resulting ligands.<sup>14,15</sup> The combination of terephthalohydrazide with para-substituted isonitrosoacetophenones provides an effective strategy for designing novel acylhydrazoneoxime ligands with tunable structural and electronic characteristics. The present work focuses on the synthesis of novel acylhydrazoneoxime ligands via the condensation of terephthalohydrazide with para-substituted isonitrosoacetophenones using both conventional reflux and microwave-assisted methods. A detailed comparison between these two synthetic approaches is presented, emphasizing reaction time, yield, energy efficiency, and environmental considerations. The synthesized ligands were thoroughly characterized using elemental analysis, UV–Visible spectroscopy, Fourier transform infrared (FTIR) spectroscopy, proton and carbon nuclear magnetic resonance (<sup>1</sup>H and <sup>13</sup>C NMR) spectroscopy, and mass spectrometry to confirm their structural integrity.

By integrating green chemistry concepts with modern synthetic techniques, this study aims to demonstrate the advantages of microwave-assisted synthesis for the efficient preparation of acylhydrazoneoxime ligands. The findings of this work are expected to contribute to the development of sustainable synthetic protocols and provide a foundation for future studies on the coordination chemistry, biological activity, and functional applications of acylhydrazoneoxime-based systems.

## II. LITERATURE REVIEW

Hydrazones and oxime derivatives have been widely studied for their biological activities, including antibacterial, antifungal, anticancer, and antitubercular properties. Several researchers have reported metal complexes of hydrazone ligands exhibiting enhanced biological and catalytic activities.<sup>16–18</sup> Oxime-based ligands are also extensively employed in analytical chemistry for metal ion detection and separation.

Conventional synthesis of hydrazones typically involves refluxing carbonyl compounds with hydrazine derivatives in alcoholic solvents for several hours. Although effective, this method is energy-intensive and time-consuming.<sup>19</sup> Recent reports indicate that microwave-assisted synthesis significantly reduces reaction time while improving yields and selectivity.<sup>20</sup>



Pingale and Shukla demonstrated the advantages of microwave heating in polymer chemistry, while Gup and Gizioglu extensively studied hydrazone ligands synthesized under conventional conditions. However, systematic comparative studies highlighting the benefits of microwave synthesis for acylhydrazoneoximes remain limited, justifying the need for the present investigation.

### **III. MATERIALS AND METHODS**

All chemicals used in the present study were of analytical reagent (AR) grade and used without further purification. Substituted acetophenones were procured from Loba Chemicals, while dimethyl terephthalate, hydrazine hydrate, dimethyl sulfoxide (DMSO), and glacial acetic acid were obtained from Sigma-Aldrich. Para-substituted isonitrosoacetophenones were synthesized by reported literature methods. Terephthalohydrazide was prepared by the reaction of dimethyl terephthalate with hydrazine hydrate. Conventional synthesis was carried out under reflux conditions using DMSO as solvent. Microwave-assisted reactions were performed in Raga's open-vessel microwave system with controlled power and temperature. Reaction progress was monitored by thin-layer chromatography. The products were isolated by filtration, washed with distilled water, and dried under vacuum. Melting points were determined using a digital melting point apparatus. The synthesized compounds were characterized by elemental analysis, UV-Visible, FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and mass spectrometry.

#### **3.1 Synthesis of Terephthalohydrazide**

##### **Conventional Method**

In the conventional method, dimethyl terephthalate was allowed to react with hydrazine hydrate under reflux conditions using dimethyl sulfoxide (DMSO) as the solvent. The reaction mixture was heated continuously at reflux temperature for a period of 4–6 hours with constant stirring to ensure homogeneity.<sup>21</sup> Conventional thermal heating was supplied through an external heating mantle, requiring gradual heat transfer from the vessel walls to the reaction medium. The progress of the reaction was monitored periodically using thin-layer chromatography. Prolonged heating was necessary to achieve complete conversion of the ester to the corresponding hydrazide. Careful control of temperature was required to avoid thermal decomposition or side reactions. After completion of the reaction, the mixture was allowed to cool slowly to room temperature. The cooled reaction mixture was then poured into excess distilled water to precipitate the product.

The resulting solid was filtered under vacuum and washed repeatedly with water to remove unreacted reagents and solvent residues. Further purification was carried out by washing with chloroform to eliminate unreacted ester. The isolated product was dried in a vacuum desiccator to constant weight. Although the method is straightforward, it is time-consuming and energy-intensive. The conventional approach also involves higher solvent consumption and longer processing time compared to microwave-assisted synthesis.

##### **Microwave-Assisted Method**

In the microwave-assisted method, dimethyl terephthalate and hydrazine hydrate were reacted using dimethyl sulfoxide (DMSO) as the solvent. The reaction mixture was placed in Raga's open-vessel microwave synthesis system. Microwave irradiation was applied at a power of 700 W for a duration of 20 minutes with intermittent stirring. Uniform and rapid heating of the reaction medium was achieved through direct interaction of microwave energy with polar molecules. The progress of the reaction was monitored by thin-layer chromatography. After completion, the reaction mixture was allowed to cool to room temperature naturally. The mixture was then transferred to a separating funnel and extracted with chloroform to remove unreacted ester. Addition of excess distilled water resulted in the precipitation of terephthalohydrazide.<sup>22</sup> The solid product was collected by filtration, washed thoroughly with water, and dried under vacuum. The microwave-assisted method afforded the product in good yield (~80%) with high purity and significantly reduced energy consumption compared to the conventional reflux method.

#### **3.2 Synthesis of Acylhydrazoneoxime Ligands**

##### **Conventional Method**

In the conventional method, terephthalohydrazide was condensed with para-substituted isonitrosoacetophenones using dimethyl sulfoxide (DMSO) as a polar solvent. The reaction mixture was taken in a round-bottom flask and heated



under reflux conditions. Continuous heating was maintained for a period of 6–8 hours to ensure completion of the condensation reaction. Constant stirring was required to maintain uniformity throughout the reaction. The progress of the reaction was periodically monitored using thin-layer chromatography.<sup>23</sup> Prolonged heating was necessary due to inefficient heat transfer associated with conventional heating methods. After completion, the reaction mixture was cooled to room temperature and poured into excess water. The resulting precipitate was filtered and washed to remove unreacted reagents. Additional purification steps such as solvent washing were often required. The conventional method generally resulted in moderate yields and involved higher energy consumption and longer reaction time.

#### **Microwave-Assisted Method**

Under microwave irradiation, the condensation reaction between terephthalohydrazide and para-substituted isonitrosoacetophenones was carried out efficiently using dimethyl sulfoxide as the solvent. The reaction mixture was subjected to microwave heating at a power of 560 W and a controlled temperature of 160 °C. The total reaction time was reduced to approximately 30 minutes, representing a significant improvement over the conventional reflux method. Rapid and uniform heating promoted effective molecular interactions between the reactants. The progress of the reaction was monitored by thin-layer chromatography. Upon completion, the reaction mixture was allowed to cool naturally to room temperature. The product was isolated by dilution with water, leading to the formation of intensely colored yellow precipitates. The solids were filtered, washed thoroughly, and dried under vacuum. The microwave-assisted method afforded improved yields in the range of 70–78%. Additionally, this approach minimized solvent consumption and suppressed side reactions, resulting in cleaner products with enhanced purity and efficiency.<sup>24</sup>

## **IV. RESULTS AND DISCUSSION**

### **4.1 Comparative Synthesis Efficiency**

A clear comparison between the two methods reveals that microwave-assisted synthesis is significantly superior to the conventional method. Reaction times were reduced from several hours to minutes, while yields were enhanced or maintained. Additionally, microwave synthesis required less solvent and energy, aligning well with green chemistry principles.

**Table: 4.1 Comparative Evaluation of Conventional and Microwave-Assisted Methods for Acylhydrazoneoxime Synthesis**

Parameter	Conventional Reflux Method	Microwave-Assisted Method
Reaction time	6–8 hours	20–30 minutes
Heating mechanism	External conductive heating	Direct microwave volumetric heating
Reaction efficiency	Moderate	High
Product yield	Moderate (60–70%)	Higher (70–78%)
Energy consumption	High due to prolonged heating	Low due to short reaction time
Solvent requirement	Large volume	Reduced volume
Temperature control	Slow and non-uniform	Rapid and uniform
Side reactions	More likely	Significantly minimized
Product purity	Moderate, requires extensive purification	Higher with minimal purification
Environmental impact	Higher carbon footprint	Environmentally benign
Alignment with green chemistry	Limited	Strong compliance

### **4.2 Spectroscopic Characterization**

The structural confirmation of the synthesized acylhydrazoneoxime ligands was achieved through comprehensive spectroscopic analysis, including UV-Visible, FTIR, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and mass spectrometry techniques. These



complementary techniques collectively validated the successful formation of the desired ligands and provided insight into their electronic and structural features.

#### 4.2.1 UV-Visible Spectral Analysis

The UV-Visible spectra of the ligands exhibited characteristic absorption bands in the range of 296–381 nm, which are attributed to  $\pi\rightarrow\pi^*$  transitions associated with the aromatic rings and azomethine groups, as well as  $n\rightarrow\pi^*$  transitions arising from non-bonding electrons on nitrogen and oxygen atoms. The presence of these transitions confirms the formation of extended conjugated systems within the acylhydrazoneoxime framework. Substituent effects were observed as slight shifts in absorption maxima, indicating the influence of electron-donating or electron-withdrawing groups on the electronic environment of the ligands.<sup>25</sup>

#### 4.2.2 Infrared Spectral Analysis

FTIR spectroscopy further supported ligand formation by revealing distinct vibrational bands corresponding to key functional groups. The appearance of strong bands in the region 1676–1720  $\text{cm}^{-1}$  confirmed the presence of amide carbonyl ( $\text{vC=O}$ ) groups, while bands around 1600–1635  $\text{cm}^{-1}$  were assigned to azomethine ( $\text{vC=N}$ ) stretching vibrations. Additional bands in the region 1560–1575  $\text{cm}^{-1}$  were attributed to oxime ( $\text{vC=N}$ ) groups. The broad absorption observed between 3300 and 2600  $\text{cm}^{-1}$  corresponds to  $\text{v(O-H)}$  stretching of the oxime group, often broadened due to intramolecular hydrogen bonding. The presence of  $\text{v(N-H)}$  stretching vibrations further confirms the hydrazide moiety within the ligands.<sup>26</sup>

#### 4.2.3 NMR Spectral Analysis

##### The $^1\text{H-NMR}$ spectra

The  $^1\text{H-NMR}$  spectra of the synthesized ligands provided definitive evidence for the proposed structures. Characteristic singlets observed in the  $\delta$  8.0–8.3 ppm region were assigned to azomethine ( $-\text{CH}=\text{N}-$ ) protons, while singlets in the  $\delta$  10.5–11.0 ppm region correspond to amide NH protons. The oxime OH protons appeared as downfield singlets in the  $\delta$  12.2–13.2 ppm range, indicative of strong intramolecular hydrogen bonding. Multiplets in the aromatic region ( $\delta$  7.0–8.0 ppm) further supported the presence of substituted phenyl rings.<sup>27</sup>

##### The $^{13}\text{C-NMR}$ spectra

The  $^{13}\text{C-NMR}$  spectra showed characteristic signals corresponding to azomethine carbon atoms, aromatic carbons, and amide carbonyl carbons, typically appearing in the  $\delta$  160–190 ppm region. These signals confirm the successful condensation between terephthalohydrazide and substituted isonitrosoacetophenones, leading to the formation of the acylhydrazoneoxime backbone.<sup>27</sup>

#### 4.2.4 Mass Spectral Analysis

Mass spectrometric analysis revealed prominent molecular ion peaks corresponding to the calculated molecular weights of the synthesized ligands, along with characteristic fragmentation patterns. The observed fragments were consistent with cleavage at hydrazone and amide linkages, further supporting the proposed molecular structures.

Importantly, a comparative evaluation of the spectroscopic data for ligands synthesized via conventional reflux and microwave-assisted methods showed no significant differences in spectral features. This observation confirms that microwave irradiation does not affect the molecular structure or integrity of the synthesized acylhydrazoneoxime ligands. Instead, microwave-assisted synthesis offers improved efficiency while maintaining the same structural and spectroscopic characteristics as the conventional method.<sup>28</sup>

## V. GREEN CHEMISTRY ASSESSMENT

Microwave-assisted synthesis strongly aligns with the principles of green chemistry by significantly reducing reaction time and overall energy consumption. The rapid and uniform heating achieved under microwave irradiation minimizes energy losses associated with prolonged conventional heating. Reduced solvent usage further contributes to lowering environmental and safety concerns. The method limits the formation of side products, thereby decreasing chemical waste generation. Shorter reaction times enhance operational safety and efficiency in laboratory practice. The open-vessel microwave system avoids excessive pressure buildup, making the process safer to handle. Overall, microwave-assisted synthesis represents an environmentally benign, sustainable, and efficient alternative to conventional synthetic methodologies.<sup>29-31</sup>



## VI. APPLICATIONS AND FUTURE SCOPE

The synthesized acylhydrazoneoxime ligands exhibit strong coordination ability due to the presence of multiple donor atoms, making them suitable for the formation of stable transition metal complexes. Such metal complexes can be explored for their enhanced physicochemical and magnetic properties. The ligands and their complexes hold significant potential in biological studies, including antibacterial, antifungal, and anticancer activity evaluations. Their chelating nature may improve bioavailability and therapeutic effectiveness upon metal coordination. Additionally, these ligands can serve as efficient catalysts or catalyst supports in organic transformations. The extended conjugation and functional groups present in the ligands make them promising candidates for sensing applications. They may be utilized in the development of metal ion sensors and chemosensors. Future work may focus on structure–activity relationship studies. Further exploration of electrochemical and photophysical properties can broaden their application scope in materials science.

## VII. CONCLUSION

The microwave-assisted synthesis of acylhydrazoneoxime ligands represents a rapid, efficient, and environmentally friendly alternative to the conventional reflux method. Compared to traditional synthesis, the microwave approach offers shorter reaction times, higher yields, reduced solvent consumption, and lower energy requirements without compromising product purity or structural integrity. This study clearly demonstrates the advantages of microwave-assisted synthesis and supports its application in the preparation of functional ligands for coordination chemistry and related fields.

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