

One-Pot Synthesis of β -Acetamido Ketones Using Eco-Friendly Catalysts

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Abstract: *The one-pot synthesis of β -acetamido ketones has attracted considerable attention due to their significant biological and pharmaceutical importance. In recent years, a wide range of eco-friendly and sustainable catalytic systems have been developed to improve the efficiency, selectivity, and environmental compatibility of this multicomponent reaction. This review summarizes recent advancements in the synthesis of β -acetamido ketones using green catalysts, including solid acid catalysts, organocatalysts, metal oxides, nanocatalysts, ionic liquids, and biogenic materials.*

Various catalytic systems such as boric acid, iodine, silica sulfuric acid, sulfamic acid, and heteropoly acids have demonstrated excellent activity under mild and solvent-free conditions. Organocatalysts like L-proline provide an environmentally benign alternative with good reusability and selectivity. Nanocatalysts, particularly zinc oxide (ZnO) and magnetic nanoparticles, have shown enhanced catalytic efficiency due to their high surface area and ease of recovery. Additionally, the use of green techniques such as microwave irradiation and ultrasound-assisted synthesis has significantly reduced reaction time and improved product yields.

Most reported methodologies involve a four-component condensation reaction between aldehydes, ketones, acetonitrile, and acetylating agents, leading to β -acetamido ketones in high yields with minimal by-products. These approaches align with the principles of green chemistry by minimizing hazardous reagents, reducing waste generation, and improving energy efficiency.

Overall, the development of eco-friendly catalytic systems for the one-pot synthesis of β -acetamido ketones represents a significant advancement in sustainable organic synthesis. Future research should focus on the design of more efficient, reusable, and scalable catalysts for industrial applications..

Keywords: One-Pot Synthesis of β -Acetamido Ketones Using Eco-Friendly Catalysts

I. INTRODUCTION

β -Acetamido ketones constitute an important class of organic intermediates due to their extensive applications in medicinal chemistry, natural product synthesis, and the pharmaceutical industry. These compounds serve as key precursors for the synthesis of biologically active molecules such as β -amino alcohols, 1,3-amino alcohols, and various nitrogen-containing heterocycles, which exhibit significant pharmacological properties including antimicrobial, anti-inflammatory, antiviral, and anticancer activities. Owing to their wide applicability, the development of efficient and sustainable synthetic routes for β -acetamido ketones has gained considerable attention in recent years.

Conventional methods for the synthesis of β -acetamido ketones typically involve multi-step procedures that require harsh reaction conditions, elevated temperatures, prolonged reaction times, and the use of toxic reagents. These methods often suffer from drawbacks such as low atom economy, generation of hazardous by-products, and the need for tedious purification steps, which limit their practical and industrial applicability. Furthermore, increasing environmental concerns and regulatory pressures have necessitated the development of greener and more sustainable synthetic methodologies.



In this context, one-pot multicomponent reactions (MCRs) have emerged as powerful and efficient tools in modern organic synthesis. MCRs involve the simultaneous reaction of three or more reactants in a single reaction vessel, leading to the formation of structurally complex products with high atom economy and reduced waste generation. The one-pot synthesis of β -acetamido ketones generally involves a four-component condensation reaction between an aldehyde, a ketone, acetonitrile, and an acetylating agent such as acetyl chloride or acetic anhydride. This approach offers several advantages, including operational simplicity, shorter reaction times, and improved overall efficiency.

The success of MCR-based synthesis largely depends on the choice of catalyst, which plays a crucial role in activating the reactants and facilitating the formation of intermediates. Over the years, a variety of catalytic systems have been explored, including Lewis acids, Brønsted acids, solid-supported catalysts, organocatalysts, and nanocatalysts. Among these, environmentally benign and reusable catalysts such as boric acid, iodine, sulfamic acid, silica sulfuric acid, and L-proline have gained prominence due to their low toxicity and high efficiency under mild reaction conditions.

In addition to catalyst development, the use of alternative energy sources such as microwave irradiation and ultrasonic waves has significantly improved the efficiency of these reactions. Microwave-assisted synthesis enables rapid and uniform heating, thereby reducing reaction times and enhancing product yields. Similarly, ultrasound-assisted synthesis enhances reaction rates through acoustic cavitation, improving mass transfer and catalytic activity.

More recently, nanotechnology has provided new opportunities for the development of highly efficient catalytic systems. Nanocatalysts, particularly metal oxide nanoparticles such as ZnO and TiO₂, exhibit superior catalytic performance due to their high surface area and unique physicochemical properties. Moreover, green synthesis approaches utilizing plant extracts and biodegradable materials have been developed for the preparation of such nanocatalysts, aligning with the principles of sustainable chemistry.

Despite these advancements, several challenges remain, including the need for cost-effective catalyst systems, improved recyclability, and scalability for industrial applications. Therefore, ongoing research efforts are focused on the development of novel, efficient, and environmentally friendly catalytic protocols for the synthesis of β -acetamido ketones.

In this context, the present study aims to explore the development of an efficient and green synthetic methodology for the one-pot synthesis of β -acetamido ketones using eco-friendly catalytic systems. The approach integrates the principles of green chemistry, multicomponent reactions, and advanced catalytic techniques to achieve a sustainable and practical synthetic process.

II. LITERATURE REVIEW

One-Pot Synthesis of β -Acetamido Ketones Using Eco-Friendly Catalysts

Development of Catalytic Systems

Conventional Catalysts

Early methodologies for the synthesis of β -acetamido ketones relied on strong mineral acids and homogeneous catalysts. However, these methods suffered from drawbacks such as corrosion, difficulty in catalyst recovery, and environmental hazards. The need for greener alternatives led to the exploration of eco-friendly catalytic systems.

Halogen and Lewis Acid Catalysts

The use of iodine as a mild and efficient catalyst marked a significant advancement in this field. Studies demonstrated that iodine could effectively catalyze the multicomponent reaction under mild conditions, providing high yields within shorter reaction times. Similarly, Lewis acids such as indium chloride and iron(III) chloride were found to be effective catalysts, offering improved reaction rates and selectivity. However, concerns regarding toxicity and recyclability limited their widespread application.



Solid Acid Catalysts

To overcome the limitations of homogeneous catalysts, researchers introduced heterogeneous solid acid catalysts such as silica sulfuric acid, sulfamic acid, and montmorillonite clay. These catalysts are environmentally benign, reusable, and easy to separate from the reaction mixture. Studies have shown that these catalysts can efficiently promote the synthesis of β -acetamido ketones under solvent-free conditions, aligning with green chemistry principles.

Organocatalysts

Organocatalysis has emerged as an attractive approach due to its metal-free nature and environmental compatibility. Catalysts such as L-proline have been successfully employed for the synthesis of β -acetamido ketones, providing high yields with excellent selectivity. These catalysts are biodegradable, non-toxic, and often operate under mild conditions, making them suitable for sustainable synthesis.

Nanocatalysts and Metal Oxides

The application of nanotechnology has significantly enhanced the efficiency of catalytic systems. Metal oxide nanoparticles, particularly zinc oxide (ZnO), have shown remarkable catalytic activity due to their high surface area and unique electronic properties. Studies have demonstrated that ZnO nanoparticles can effectively catalyze the one-pot synthesis of β -acetamido ketones with high yields and shorter reaction times. Additionally, magnetic nanoparticles have been developed to facilitate easy recovery and reuse of catalysts, improving the overall sustainability of the process.

Ionic Liquids and Green Solvents

Ionic liquids have gained attention as alternative green solvents and catalysts due to their negligible vapor pressure and high thermal stability. These systems provide a dual role as both solvent and catalyst, enhancing reaction efficiency while minimizing environmental impact. However, issues related to cost and biodegradability remain challenges for large-scale applications.

III. GREEN CHEMISTRY APPROACHES

Solvent-Free Synthesis

Solvent-free conditions have been widely adopted to reduce environmental pollution and improve reaction efficiency. Many studies have reported successful synthesis of β -acetamido ketones using solid catalysts under solvent-free conditions, resulting in higher yields and reduced reaction times.

Microwave-Assisted Synthesis

Microwave irradiation has been utilized to accelerate reaction rates and enhance product yields. This technique reduces energy consumption and reaction time, making it an attractive approach for green synthesis.

Ultrasound-Assisted Synthesis

Ultrasound irradiation enhances reaction efficiency through acoustic cavitation, which improves mass transfer and increases reaction rates. This method has been successfully applied in the synthesis of β -acetamido ketones, providing higher yields under milder conditions.

Reaction Mechanism

The synthesis of β -acetamido ketones generally follows a multicomponent reaction mechanism involving:

1. Activation of the carbonyl group of the aldehyde by the catalyst.
2. Formation of an iminium ion intermediate with acetonitrile.
3. Nucleophilic addition of the ketone.
4. Acetylation to form the final β -acetamido ketone product.



Catalysts play a crucial role in stabilizing intermediates and facilitating bond formation, thereby enhancing reaction efficiency.

Comparative Analysis of Catalysts

Catalyst Type	Advantages	Limitations
Halogen (I ₂)	Simple, effective	Limited recyclability
Solid acids	Reusable, eco-friendly	Moderate activity
Organocatalysts	Non-toxic, biodegradable	Slower reactions
Nanocatalysts	High efficiency, reusable	Cost of synthesis
Ionic liquids	Dual role (solvent + catalyst)	Expensive

IV. RECENT ADVANCES (2020–2025) IN β -ACETAMIDO KETONE SYNTHESIS

Recent years have witnessed significant progress in the development of sustainable and efficient catalytic systems for the one-pot synthesis of β -acetamido ketones. These studies emphasize green chemistry principles, including the use of recyclable catalysts, solvent-free conditions, and energy-efficient techniques.

1. Copper-Catalyzed Multicomponent Synthesis (2024)

A study reported the synthesis of propargylated β -acetamido ketones using a CuSO₄-catalyzed one-pot multicomponent reaction, eliminating the need for chromatographic purification. This method demonstrated improved atom economy and operational simplicity.

2. Phenylboronic Acid Catalyzed Green Synthesis (2020–2021)

Recent work explored phenylboronic acid as a low-toxicity catalyst, achieving high yields (65–98%) under mild conditions. The method demonstrated biological relevance, including enzyme inhibition potential.

3. Trifluoroacetic Acid Catalyzed Dakin–West Reaction (2020)

A green multicomponent approach using trifluoroacetic acid showed efficient synthesis of β -acetamido ketones under mild conditions with low catalyst loading, highlighting improved sustainability.

4. ZnO Nanoparticle-Based Catalysis (2020–2024)

Nanocatalysis continues to dominate recent research. ZnO nanoparticles have been widely reported as efficient, reusable catalysts for multicomponent synthesis, offering high yields and room-temperature reactions with easy recovery.

5. Ultrasound-Assisted Green Synthesis (2020–2022)

Ultrasound-assisted synthesis has gained importance due to reduced reaction time and enhanced yields. Cavitation effects improve mass transfer and catalytic activity, making the process more efficient and environmentally friendly.

6. Recent Advances in Ritter-Type Reactions (2025)

Modern developments in Ritter-type amide synthesis highlight improved catalytic systems for sustainable amide formation, which are directly relevant to β -acetamido ketone synthesis pathways.

7. Magnetic Nanocatalyst Systems (2020–2023)

Recent studies have focused on Fe₃O₄-supported catalysts, which allow easy magnetic separation and recyclability. These systems significantly reduce catalyst loss and improve industrial applicability.



8. Ionic Liquid-Based Catalysis (2020–2022)

Eco-friendly ionic liquids have been utilized as both solvent and catalyst, improving reaction efficiency while minimizing volatile organic compound (VOC) emissions.

9. Deep Eutectic Solvent (DES) Systems (2021–2024)

DES-based systems have emerged as green alternatives to conventional solvents, offering biodegradability, low toxicity, and high catalytic performance.

10. Biogenic Nanocatalysts (Plant-Mediated) (2021–2025)

Recent work has explored plant-extract-mediated nanoparticle synthesis (e.g., ZnO, Fe $\square$ O $\square$), aligning with sustainable chemistry and waste valorization approaches.

11. Microwave-Assisted Green Synthesis (2020–2023)

Microwave irradiation significantly reduces reaction time from hours to minutes while maintaining high yields and selectivity.

12. Heteropoly Acid Catalysts (2020–2022)

Advanced heteropoly acid catalysts have been used under solvent-free conditions, providing excellent yields with high catalytic efficiency and recyclability.

13. Metal–Organic Framework (MOF)-Based Catalysts (2022–2025)

MOFs have emerged as highly efficient catalysts due to their tunable porosity and high surface area, improving selectivity and reaction rates.

14. Graphene-Supported Catalysts (2021–2024)

Graphene-based hybrid catalysts have shown enhanced catalytic activity due to improved electron transfer and stability.

15. Visible-Light Photocatalysis (2022–2025)

Photocatalytic approaches using visible light have been explored for sustainable synthesis, reducing energy consumption and avoiding harsh reaction conditions.

Critical Analysis of Recent Trends

From the above studies, the following trends are clearly observed:

- 1. Shift Toward Nanotechnology :** ZnO, magnetic nanoparticles, and MOFs dominate recent research High surface area → better catalytic efficiency
- 2. Energy-Efficient Techniques :** Microwave and ultrasound-assisted methods reduce reaction time. Visible-light catalysis promotes sustainability
- 3. Green Solvent Systems :** DES and ionic liquids replace toxic solvents Solvent-free reactions gaining popularity
- 4. Catalyst Reusability :** Magnetic and heterogeneous catalysts enable easy recovery Important for industrial scalability



V. DISCUSSION

The present review clearly demonstrates that the synthesis of β -acetamido ketones has undergone a significant transformation from conventional multi-step procedures to highly efficient one-pot multicomponent reactions (MCRs). This evolution is primarily driven by the growing demand for sustainable, cost-effective, and environmentally benign synthetic methodologies in line with green chemistry principles. One of the most notable observations from the literature is the **critical role of catalysts** in determining reaction efficiency, selectivity, and sustainability. Traditional homogeneous catalysts, although effective, present limitations such as difficulty in recovery, environmental hazards, and lack of reusability. In contrast, **heterogeneous catalysts**, particularly solid acids such as silica sulfuric acid and sulfamic acid, have demonstrated improved performance due to their recyclability, ease of separation, and reduced environmental impact. The emergence of **organocatalysts**, such as L-proline, has further strengthened the green chemistry approach by eliminating the need for metal-based catalysts. These systems offer advantages such as biodegradability, low toxicity, and operational simplicity, although they may exhibit relatively slower reaction rates compared to metal-based systems. A major advancement highlighted in recent studies (2020–2025) is the increasing application of **nanotechnology in catalysis**. Nanocatalysts, especially metal oxides like ZnO and magnetic nanoparticles, have shown exceptional catalytic activity due to their high surface area and enhanced active sites. The incorporation of magnetic properties enables easy catalyst recovery, addressing one of the key challenges in catalytic processes. Additionally, the development of **biogenic nanocatalysts using plant extracts** aligns well with sustainable and eco-friendly synthesis strategies. Another important trend is the integration of **alternative energy sources**, such as microwave and ultrasound irradiation, into synthetic protocols. These techniques significantly reduce reaction time, improve yields, and enhance reaction kinetics. Ultrasound-assisted synthesis, in particular, utilizes acoustic cavitation to improve mass transfer and catalyst dispersion, leading to higher efficiency. Similarly, microwave-assisted synthesis provides rapid and uniform heating, making the process more energy-efficient. The adoption of **green solvents and solvent-free conditions** is also a key advancement. Deep eutectic solvents (DES) and ionic liquids have emerged as promising alternatives to conventional organic solvents due to their low volatility and environmental compatibility. However, issues related to cost and large-scale applicability still need to be addressed. From a mechanistic perspective, the multicomponent reaction pathway involving carbonyl activation, iminium ion formation, nucleophilic addition, and acetylation is well-established. Catalysts play a vital role in stabilizing intermediates and lowering activation energy, thereby enhancing reaction efficiency. Despite these advancements, several challenges remain. The **scalability of these green methodologies** is still limited, particularly for industrial applications. Additionally, the **cost of nanocatalyst synthesis**, potential aggregation issues, and lack of long-term stability studies pose limitations. Furthermore, most studies are conducted under controlled laboratory conditions, and there is a need for **real-world wastewater or industrial applicability validation**. Overall, the discussion highlights that while significant progress has been made in developing sustainable catalytic systems, further research is required to bridge the gap between laboratory-scale success and industrial implementation.

VI. CONCLUSION

The one-pot synthesis of β -acetamido ketones using eco-friendly catalysts represents a significant advancement in the field of sustainable organic chemistry. The transition from traditional multi-step synthetic methods to multicomponent reaction strategies has greatly improved efficiency, reduced waste generation, and enhanced atom economy. A wide range of catalytic systems, including solid acids, organocatalysts, nanocatalysts, and ionic liquids, have been successfully employed to achieve high yields under mild and environmentally benign conditions. Among these, nanocatalysts and green-synthesized materials have shown exceptional promise due to their high catalytic activity, reusability, and compatibility with green chemistry principles. The incorporation of modern techniques such as microwave and ultrasound-assisted synthesis has further improved reaction efficiency and reduced energy consumption. Additionally, the use of alternative solvent systems, including solvent-free conditions and deep eutectic solvents, has contributed to minimizing environmental impact. Recent developments (2020–2025) indicate a clear shift



toward **sustainable, recyclable, and energy-efficient catalytic systems**, with increasing emphasis on nanotechnology and green synthesis approaches. However, challenges related to cost, scalability, and industrial applicability remain to be addressed. In conclusion, the continued development of efficient, reusable, and environmentally friendly catalytic systems is essential for advancing the synthesis of β -acetamido ketones. Future research should focus on the design of cost-effective catalysts, large-scale process optimization, and real-world application studies to fully realize the potential of these green synthetic methodologies in industrial and pharmaceutical sectors.

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