

GREEN AND SUSTAINABLE STRATEGIES IN KNOEVENAGEL CONDENSATION REACTIONS**Madavi Sanjay Kanase¹, Dr. Leena Sarkar² and Dr. Shweta Rathore³**¹Department of Chemistry, J. V. M.'s Mehta Degree College²Professor and Head Department of Chemistry, J. V. M.'s Mehta Degree College³Assistant Professor, Department of Chemistry, J. V. M.'s Mehta Degree College**ABSTRACT**

The Knoevenagel condensation is a classical and versatile carbon-carbon bond-forming reaction that plays a crucial role in the synthesis of α , β -unsaturated compounds, which are key intermediates in pharmaceuticals, dyes, agrochemicals, and fine chemicals. Despite its synthetic importance, traditional Knoevenagel methodologies commonly rely on synthetic bases and volatile organic solvents that are toxic, expensive, and environmentally hazardous. The increasing global emphasis on sustainable development and environmental protection has therefore encouraged the development of greener and more eco-friendly alternatives for this reaction. In recent years, green chemistry-based approaches to Knoevenagel condensation have attracted significant attention. The use of green solvents, renewable resources, plant derived materials, and bio-based catalysts has emerged as an effective strategy to minimize environmental impact while maintaining high catalytic efficiency. Plant extracts and agro waste-derived materials are particularly promising, as they are rich in naturally occurring basic compounds, enzymes, and functional biomolecules capable of promoting Knoevenagel reactions under mild and benign conditions. These systems often function as both solvent and catalyst, thereby eliminating the need for additional hazardous reagents. Recent literature demonstrates that agro-waste-mediated Knoevenagel condensations offer notable advantages, including shorter reaction times, improved yields, operational simplicity, and excellent atom economy. Moreover, the valorization of agricultural waste aligns strongly with the core principles of green chemistry, such as waste prevention, use of renewable feedstocks, and reduction of toxic substances. This review critically summarizes recent advancements in sustainable Knoevenagel condensation methodologies, highlighting their efficiency, environmental benefits, and potential for broader application in green and sustainable organic synthesis.

Keywords: Green Chemistry, Knoevenagel condensation, atom economy, renewable resources, Sustainable.

INTRODUCTION:

The Knoevenagel condensation is one of the most established and widely applied carbon-carbon (C-C) bond-forming reactions in synthetic organic chemistry. Since its first report by Emil Knoevenagel in 1896, this reaction has remained an essential tool for constructing structurally diverse α,β -unsaturated compounds. The reaction involves the condensation of an active methylene compound—such as malononitrile or ethyl cyanoacetate—with carbonyl compounds including aldehydes or ketones^{1,2}. Mechanistically, it proceeds through a nucleophilic addition step resembling an aldol reaction, followed by dehydration to afford the conjugated product.

Conventionally, the Knoevenagel condensation is carried out in the presence of weak organic bases or Lewis acids and often employs volatile organic solvents. Although these methods are effective, they raise concerns related to environmental impact, toxicity, and sustainability. In response to these challenges, recent research has increasingly focused on aligning this classic reaction with the principles of green chemistry. Considerable attention has been given to the development of environmentally benign catalysts derived from renewable resources and agro-waste materials, such as banana peel extracts, orange peel ash, and other plant-based catalysts. In addition, alternative activation techniques, including solvent-free and grindstone methods, have emerged as efficient and sustainable approaches.

Owing to its simplicity, high efficiency, and broad substrate scope, the Knoevenagel condensation plays a vital role in the synthesis of pharmaceuticals, fine chemicals, dyes, and biologically active molecules³. As a result, continued innovation in greener reaction conditions and catalyst design has reinforced the relevance of this transformation in modern organic synthesis.

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CONCEPT OF ACTIVE METHYLENE COMPOUND:

The Knoevenagel condensation fundamentally relies on the unique reactivity of active methylene compounds toward carbonyl substrates such as aldehydes and ketones. An active methylene compound contains a methylene ($-\text{CH}_2-$) unit flanked by two strong electron-withdrawing groups, including cyano ($-\text{CN}$), ester ($-\text{COOR}$), or carboxyl ($-\text{COOH}$) functionalities. The presence of these substituents significantly increases the acidity of the methylene hydrogen atoms, making them readily removable under mild catalytic conditions.

During the reaction, a base or suitable catalyst abstracts a proton from the active methylene group, generating a resonance-stabilized carbanion. This nucleophilic species subsequently attacks the electrophilic carbon atom of the carbonyl group, leading to the formation of a β -hydroxy intermediate analogous to an aldol addition product. The reaction is completed by a dehydration step, in which a molecule of water is eliminated, yielding a conjugated α,β -unsaturated compound as the final product.

Recent advancements in synthetic methodology have adapted this classical concept to align with green chemistry principles. Environmentally benign catalysts, bio-derived bases, and solvent-free or mechanochemical approaches such as the grindstone technique have been successfully employed to enhance reaction efficiency while minimizing waste generation and energy consumption, thereby improving the overall sustainability and atom economy of the Knoevenagel condensation process⁴⁻⁸.

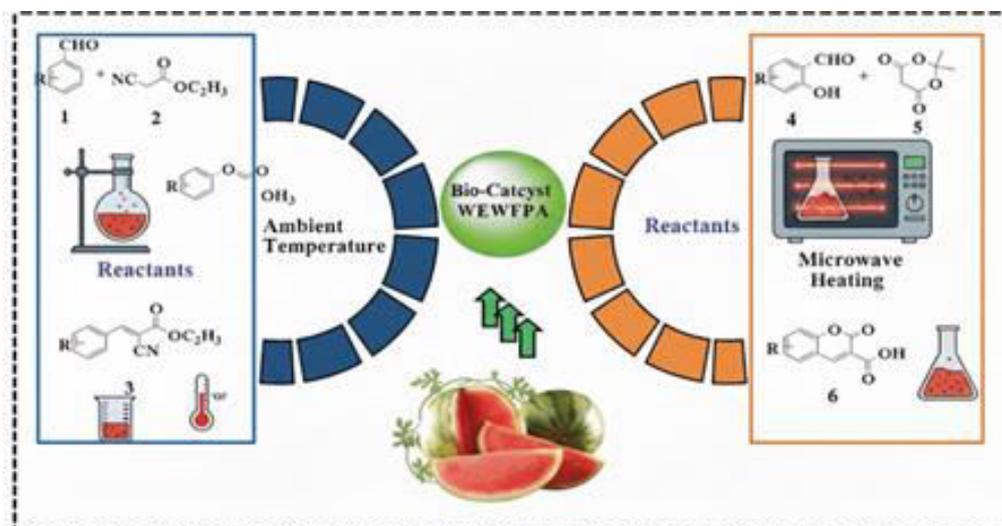
Applications of the Knoevenagel condensation reaction:

The Knoevenagel condensation is a fundamental and versatile carbon-carbon bond-forming reaction in organic chemistry with extensive applications across various scientific fields. In the pharmaceutical industry, it serves as a critical step in synthesizing intermediates for several life-saving and top-selling drugs, including Atorvastatin (used for cholesterol), Pioglitazone (for diabetes), and Pregabalin. The reaction is also essential for creating biologically active molecules such as arylidenes and 2-amino-4H-chromenes, which exhibit therapeutic properties ranging from antifungal to anti-cancer activities. Beyond medicine, the Knoevenagel reaction is widely employed in the production of fine chemicals, including perfumes, cosmetics, and sunscreens, as well as in agriculture for the synthesis of herbicides and insecticides⁹⁻¹¹.

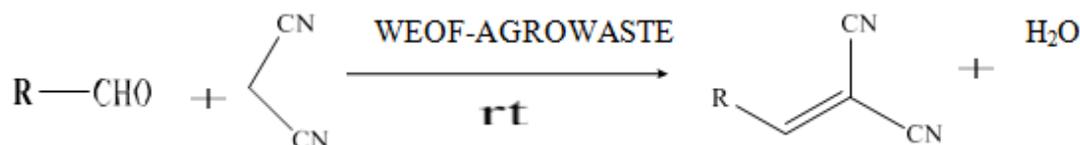
In the realm of advanced materials science, this reaction is used to develop functional polymers, pigments, and dyes. Its significance in modern technology was highlighted by its role in creating "molecular machines" and "molecular rotors," contributing to the research that earned the 2016 Nobel Prize in Chemistry. Furthermore, recent research focuses on "Green Chemistry" applications, utilizing eco-friendly catalysts like Water Extract of Banana (WEB), L-Tyrosine, Quinine, and Trizma. These methods allow the reaction to proceed under solvent-free or mild conditions, such as the grindstone method or microwave irradiation, reducing environmental toxicity and energy consumption. Thus, the Knoevenagel reaction remains a cornerstone of synthetic chemistry, bridging the gap between basic laboratory research and large-scale industrial manufacturing¹²⁻¹⁴.

LITERATURE REVIEW:

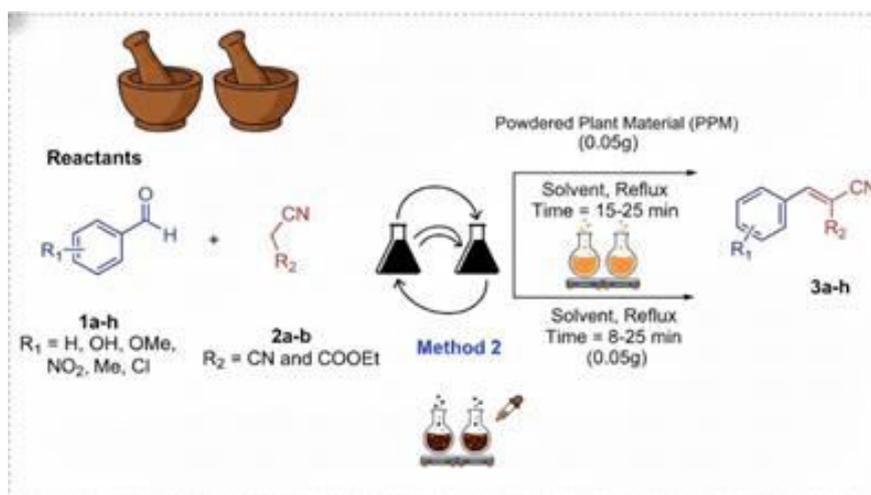
- ❖ Krishnappa B. Badiger, Santosh Y. Khatavi, Prashant B. Hiremath, and Kantharaju Kamanna (2022)¹⁵ reported an environmentally friendly strategy for synthesizing value-added organic derivatives using the Knoevenagel condensation reaction. In their work, aromatic aldehydes were condensed with ethyl cyanoacetate to obtain ethyl benzylidene cyanoacetate. Furthermore, the authors successfully prepared 2-oxo-2H-1-benzopyran derivatives via the reaction of salicylaldehyde with Meldrum's acid, highlighting the versatility of this green synthetic approach.



- ❖ In a related study, Kantharaju Kamanna (2022)¹⁶ developed an efficient and solvent-free Knoevenagel condensation protocol employing catalysts derived from agricultural waste. This sustainable methodology offers a cost-effective and eco-friendly alternative to conventional base-catalyzed systems and was shown to deliver excellent yields across a wide range of aromatic and heterocyclic substrates.

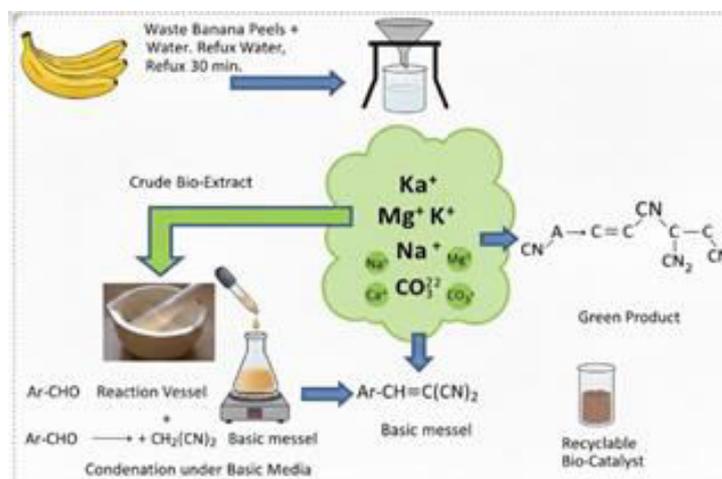


- ❖ Chavan, Suryawanshi, and Kumbhar (2023)¹⁷ reported a sustainable approach for converting discarded pomegranate peels into an efficient solid acid catalyst. Instead of treating this agricultural waste as refuse, the authors chemically tailored the biomass to impart catalytic activity, enabling it to promote key organic transformations such as the Knoevenagel condensation. The synthesized catalyst was subsequently examined using advanced characterization tools, including high-resolution microscopic techniques, to verify its morphology, composition, and structural stability.

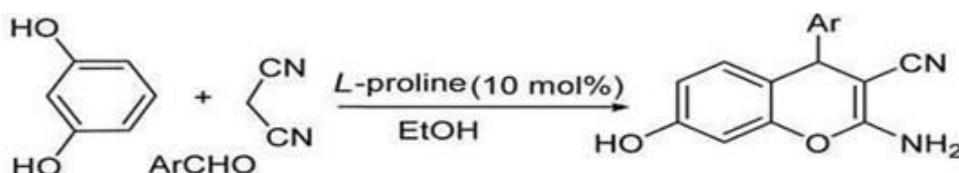


- ❖ K. Kantharaju, Prashant B. Hiremath, and S. Y. Khatavi (2019)¹⁸ demonstrated that water extract of banana (WEB) can serve as an effective and environmentally benign biocatalyst for organic reactions. In their noteworthy work, they developed a sustainable and highly efficient methodology for the Knoevenagel condensation involving substituted aromatic and heteroaromatic aldehydes with malononitrile. This green protocol avoids the drawbacks of conventional methods—such as extended reflux conditions, elevated

temperatures, and the use of toxic organic solvents—by employing a simple and innovative grindstone technique carried out at room temperature.

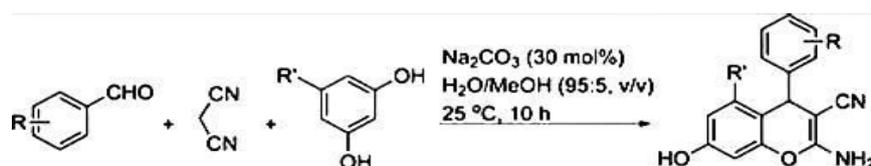


- ❖ Behbahani, Farahnaz K. and Mehraban, Sima (2015)¹⁹ used L-proline as a biocatalyst for synthesizing 2-Amino-3-cyano-7-hydroxy-4H-chromenes by reacting Benzaldehyde and malonitrile with resorcinol



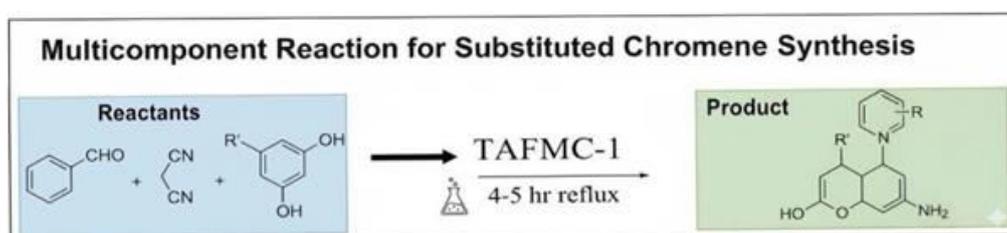
Reaction of Benzaldehyde & malonitrile with resorcinol

- ❖ Masesane, Ishmael B., and Mihigo, Shetonde O. (2014)²⁰ reported an environmentally benign approach for the synthesis of 2-amino-4H-chromenes by employing sodium carbonate as a mild catalyst. In their study, malononitrile and benzaldehyde derivatives were reacted with phloroglucinol or resorcinol in an aqueous medium, leading to efficient formation of the desired chromene derivatives.



Synthesis of 2-Amino-3-Cyano-4H-Chromene

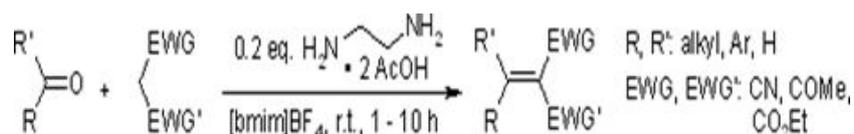
- ❖ Kundu and Sudipta K. (2013)²¹ reported the development of a tungstate-modified, amino-functionalized magnetic catalyst (TAFMC-1) for use in a multicomponent synthetic protocol. The study demonstrated that this magnetically recoverable catalyst efficiently promotes the formation of structurally complex heterocyclic compounds, particularly 2-Amino-4H-chromenes. The ability to easily separate and reuse the catalyst, combined with reduced reaction steps and waste generation, highlights this methodology as a representative and practical application of green chemistry principles.



Synthesis of 2-Amino-4H-Chromenes

- ❖ Ce Su, Zhen-Chu Chen*, and Qin-Guo Zheng (2003)²² reported an efficient catalytic strategy in which an ionic liquid was combined with ethylenediammonium diacetate (EDDA). This integrated system acted as a highly effective catalyst, significantly promoting the formation of carbon-carbon double bonds.

Reaction of Aldehyde & active methylene compound



- ❖ Kantharaju and Hiremath (2018)²³ demonstrated that WENBA, derived from agricultural waste, can serve as an effective and environmentally benign catalyst for the Knoevenagel condensation. The approach avoids the use of hazardous bases and organic solvents while delivering products in high yield and purity. Owing to its simplicity, low cost, and green nature, this method represents a sustainable alternative to traditional protocols, particularly for the synthesis of biologically important compounds such as 3-carboxy coumarins.



METHODOLOGY

In the Conventional Methodology²⁴, the reaction is typically carried out by refluxing the reactants in organic solvents such as Ethanol or Benzene, using a secondary amine like Piperidine as a catalyst. For example, the synthesis of Benzylidenemalononitrile from Benzaldehyde and Malononitrile requires several hours of heating. While effective, this traditional approach faces criticism due to long reaction times and the environmental impact of hazardous solvent waste.

Grindstone Technology has emerged as a sustainable alternative¹⁸. This solvent-free method involves physically grinding the reactants, such as 4-Nitrobenzaldehyde and Malononitrile, with a catalyst like agro waste using a mortar and pestle. The mechanical energy generated during grinding facilitates the reaction within 15–20 minutes at room temperature, making it an eco-friendly "Green Chemistry" practice.

Microwave-Assisted Organic Synthesis²⁵ has revolutionized the efficiency of this reaction. By applying microwave irradiation to a mixture of Vanillin and Ethyl Cyanoacetate, the reaction reaches completion in just 1–2 minutes. This method provides high thermal efficiency and superior yields compared to conventional heating. In conclusion, while the conventional method remains a standard laboratory technique, the transition toward Grindstone and Microwave methodologies offers significant advantages in terms of speed, energy conservation, and environmental safety.

CONCLUSION:

This review highlights the diverse synthetic strategies employed for reactions involving active methylene compounds, with emphasis on the Knoevenagel condensation as a versatile carbon-carbon bond-forming methodology. Active methylene substrates play a pivotal role in organic synthesis due to their ability to generate

structurally complex frameworks, especially heterocyclic systems that form the core of many contemporary pharmaceutical agents. Advances in reaction conditions, catalysts, and greener protocols have significantly improved the efficiency, selectivity, and sustainability of these transformations. Collectively, these developments have enabled faster and more practical routes to value-added organic molecules, reinforcing the continuing relevance of the Knoevenagel condensation in modern synthetic and medicinal chemistry. Ongoing innovation in this area is expected to further broaden its applications in drug discovery and functional material synthesis.

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