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## Review Paper

# Recent Advances in Hantzsch Synthesis: Green, Heterogeneous And Medicinal Perspectives

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### ABSTRACT

The Hantzsch synthesis is a key multicomponent reaction that is commonly employed to create 1,4-dihydropyridine derivatives, known for their considerable biological and pharmaceutical properties. Recent years have seen numerous improvements aimed at enhancing the efficiency, selectivity and ecological sustainability of this reaction. This review emphasizes the latest progress in Hantzsch synthesis from 2011 to 2024, particularly emphasizing green synthesis techniques, the use of heterogeneous catalysts and the medicinal applications of dihydropyridine derivatives. This study offers a brief overview of contemporary strategies that improve reaction conditions and encourage eco-friendly practices in organic synthesis.

### INTRODUCTION

The Hantzsch synthesis is a well-established multicomponent reaction that provides access to 1,4-dihydropyridine (DHPs) polyhydroquinolines, and related heterocyclic derivatives. These compounds have attracted wide attention due to their diverse biological and pharmacological properties, including anti-oxidant, antimicrobial, and anti-inflammatory activities. Over the years the scope of this reaction has expanded significantly, not only in terms of the variety of heterocycles accessible but also in the diversity of

catalytic systems and reaction condition that can employed between 2011 and 2024, researchers have introduced a range of innovative methods to improve the Hantzsch reaction. A notable trend is the shift toward green and sustainable chemistry, where scientists have employed catalysts such as humic acid (a bio-organic material) and eggshell composites as eco-friendly alternatives to traditional catalysts. In addition, heterogeneous catalysts like modified metal-organic framework (MOFs), nanomaterials, and coordination polymers have been developed, offering enhanced

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catalytic efficiency, reusability, and reduced environmental impact.

Another major direction is the exploration of catalyst-free and microwave-assisted methods. For example, studies in 2022 and 2017 demonstrated efficient synthesis of dihydropyridines using microwave irradiation and solvent-free conditions, achieving high yields with minimal energy consumption. Furthermore, recent reviews highlight the growing role of visible light-driven synthesis and organocatalysis, which align with the principles of sustainability and green chemistry.

The importance of these advances goes beyond methodology. Many of the newly synthesized compounds exhibit promising applications in medicinal chemistry, particularly as calcium channel blockers, Nrf2 activators, cathepsin S inhibitors, and antioxidant agents. Thus, modern research on the Hantzsch reaction demonstrates a dual focus: improving the

environmental profile of synthetic methods while simultaneously expanding the biological potential of the resulting heterocycles. This paper will provide an overview of recent developments (2011-2024) in Hantzsch synthesis, with emphasis on green catalysis, heterogeneous and

nanocatalytic methods, catalyst-free strategies, and pharmaceutical applications.

### Advancements in Green Catalysis:

One of the most prominent directions in the recent development of the Hantzsch synthesis is the application of green catalysts. Green catalysis emphasizes sustainability, reduced toxicity, and environmental safety, while maintaining or improving efficiency and product yield. Several approaches documented between 2017 and 2024 highlight how natural, bio-based, and recyclable catalytic systems can effectively promote Hantzsch condensation reactions.

In 2024, Debolina Mukherjee and co-workers [1] reported the use of a highly scalable ribbon-like coordination polymer as a robust green catalyst for the Hantzsch reaction. Their work demonstrated that this polymer was not only efficient in synthesizing dihydropyridines (DHPs) but also applicable in producing bioactive drug molecules. The research emphasized the scalability, robustness, and reusability of the material, underscoring its potential in environmentally friendly pharmaceutical synthesis.

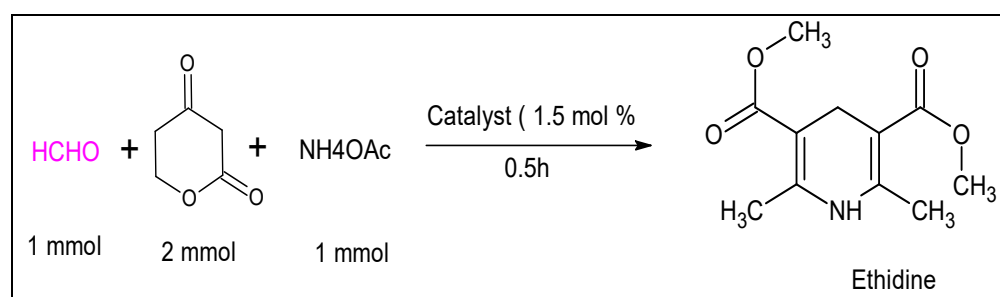


Fig.1

Similarly, Swadhin Swaraj Acharya and Bibhuti Bhusan Parida (2024)[2] explored humic acid, a natural bioorganic material, as a promising green catalyst. Their findings showed that humic acid could serve as an eco-friendly alternative to

conventional catalysts in organic synthesis. By providing high catalytic activity under mild conditions, humic acid further supports the integration of renewable and biodegradable resources into synthetic organic chemistry.

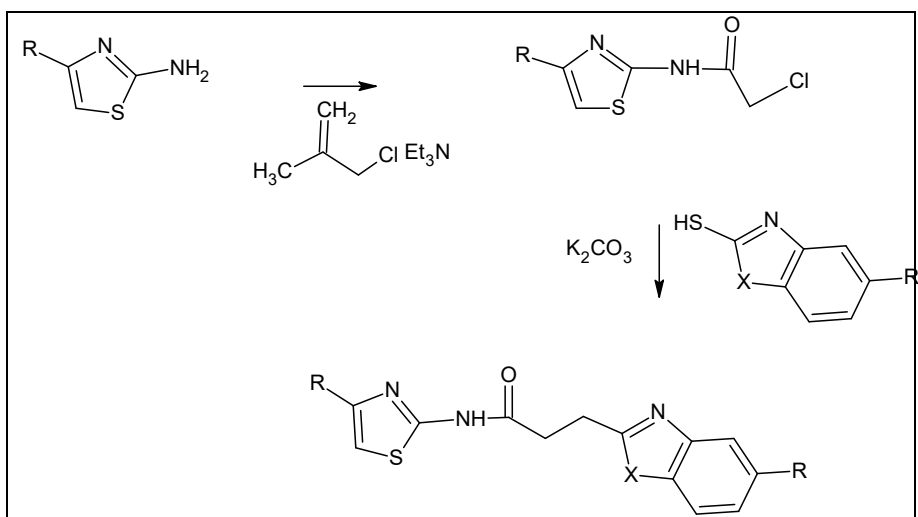


Fig.2

Another example of eco-friendly catalysis was presented by Harshita N. Anchan and colleagues in 2023[3], who utilized gluconic acid in aqueous solution as a green organocatalyst. Their study focused on the synthesis of both Biginelli and

Hantzsch products derived from bio renewable furfurals. The aqueous medium and renewable feedstocks made this method particularly attractive, offering a sustainable route to valuable heterocycles.

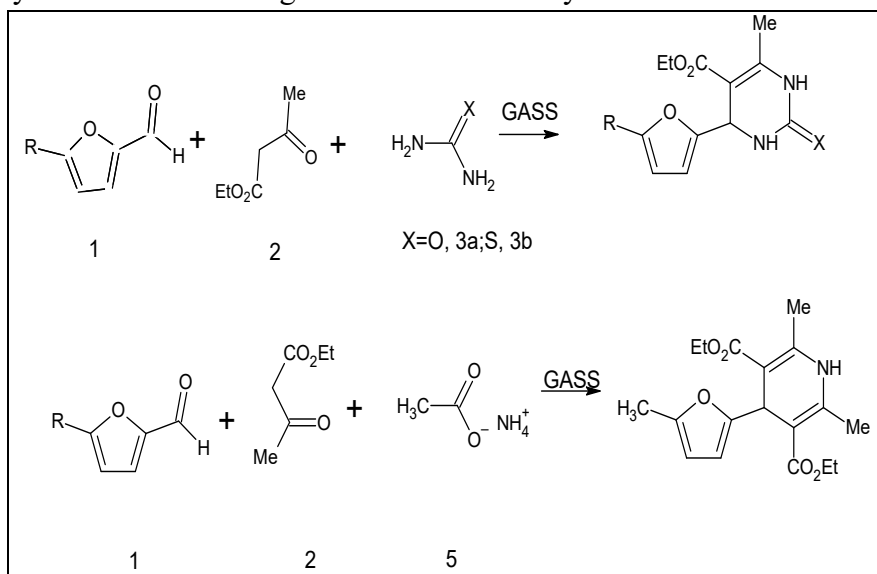


Fig.3

Green catalysis has also benefited from biowaste-derived catalysts. In 2019[4], A.H.Cahyaa and co-workers employed an Fe<sub>3</sub>O<sub>4</sub>/eggshell composite as a catalyst for Hantzsch condensation in acridine synthesis. This approach combined magnetic

nanoparticles with a biogenic material, creating a low-cost and recyclable catalytic system. Their study highlighted the effectiveness of waste-derived materials in promoting green synthesis.

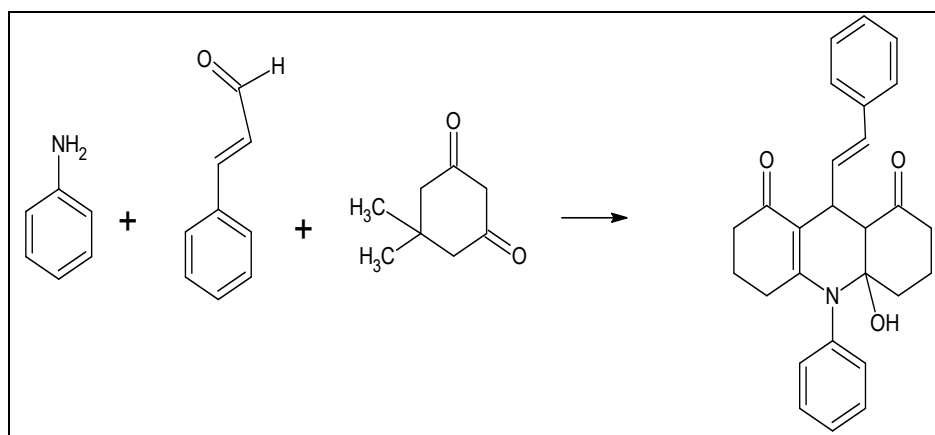


Fig.4

Earlier, in 2017[5], Imene Sheout and colleagues developed a solvent-free Hantzsch reaction catalyzed by a natural organic acid. This method enabled the synthesis of polyhydroquinolines and 1,8-dioxodecahydroacridines, representing another step towards absence of solvents and use of a natural acids as catalyst made this approach both efficient and sustainable.

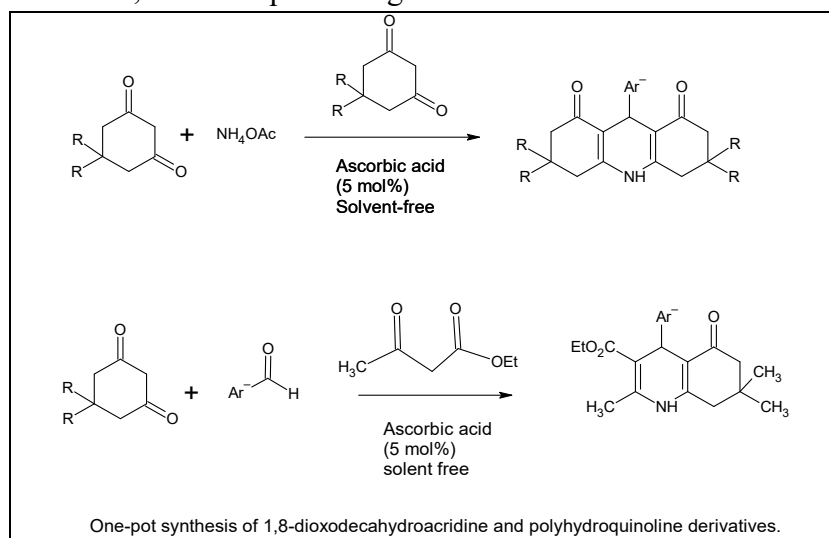


Fig.5

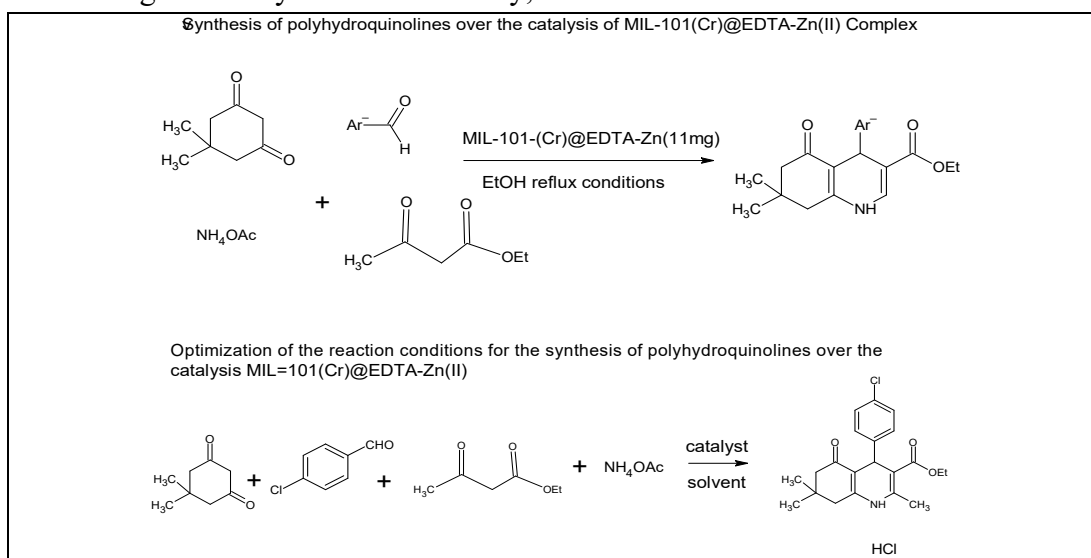
Collectively, these studies illustrate how green catalysis in Hantzsch synthesis has evolved from the use of natural acids to complex coordination polymers and bio-waste composites. This eco-friendly systems not only minimize hazardous by products and environmental burden but also demonstrated scalability and reusability, making them practical for industrial and pharmaceutical applications.

### Heterogeneous and Nanocatalytic Approaches:

Along side green catalysis, the use of heterogeneous and nanocatalytic systems has significantly expanded the scope of Hantzsch reaction. These catalysts are valued for their high efficiency, ease of separation, reusability, and alignment with green chemistry principles. Research from 2011 to 2024 demonstrated continuous innovation in this area, ranging from modified metal-organic frameworks (MOFs) to silica-based nanomaterials and recyclable thin films.

In 2024[6], Ahmad Nikseresht, Fatemeh Ghoochi, and Masoud Mohammadi reported the postsynthetic modification of MIL-101(Cr) with EDTA-Zn(II) complex, resulting in an efficient heterogeneous catalyst for the synthesis of polyhydroquinolines. The modified framework exhibited high catalytic performance, excellent reusability, and stability, underscoring its potential for sustainable large-scale synthesis. Similarly,

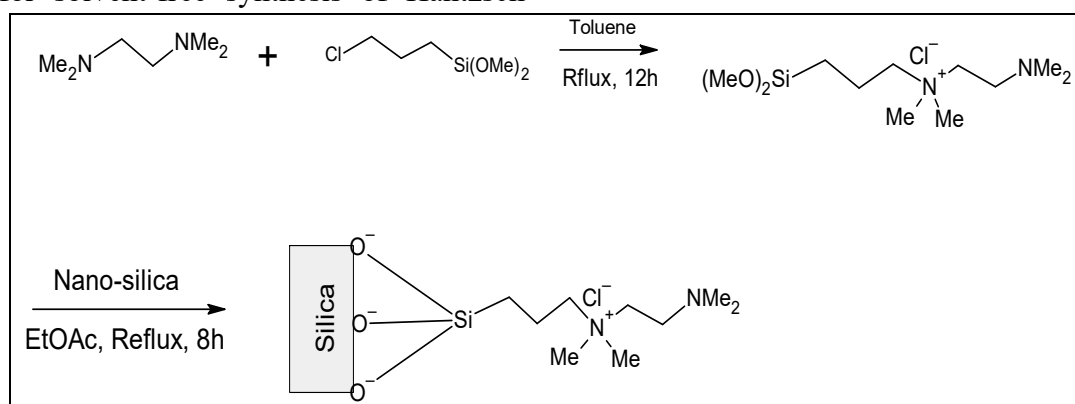
Reza Taghavi and Sadega Rostamina (2022) employed Cu-IRMOF-3 as a heterogeneous catalyst in a four-component unsymmetrical Hantzsch reaction. Their systems provided efficient synthesis of polyhydroquinolines with strong reusability, highlighting the promise of MOF-based catalysts.



**Fig.6**

Nanomaterial have also played a critical role in advancing Hantzsch synthesis. For example, Abeer Anazi and co-workers (2022)[8] developed a mesoporous basic silica-based nanomaterial as a catalyst for solvent-free synthesis of Hantzsch

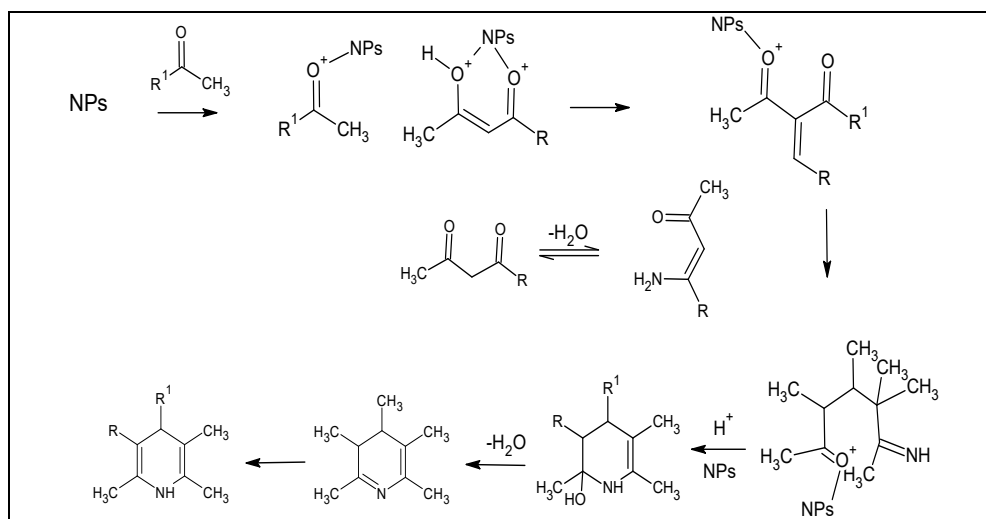
derivatives. This approach proved both effective and rapid, enabling high yields while eliminating the need for solvents, thereby reducing environmental burden.



**Fig.7**

Additionally, Gnanamani Lavnya and colleagues (2024)[9] review the application of catalytic nanomaterial in the synthesis of dihydropyridines and their fused systems. Their work emphasized

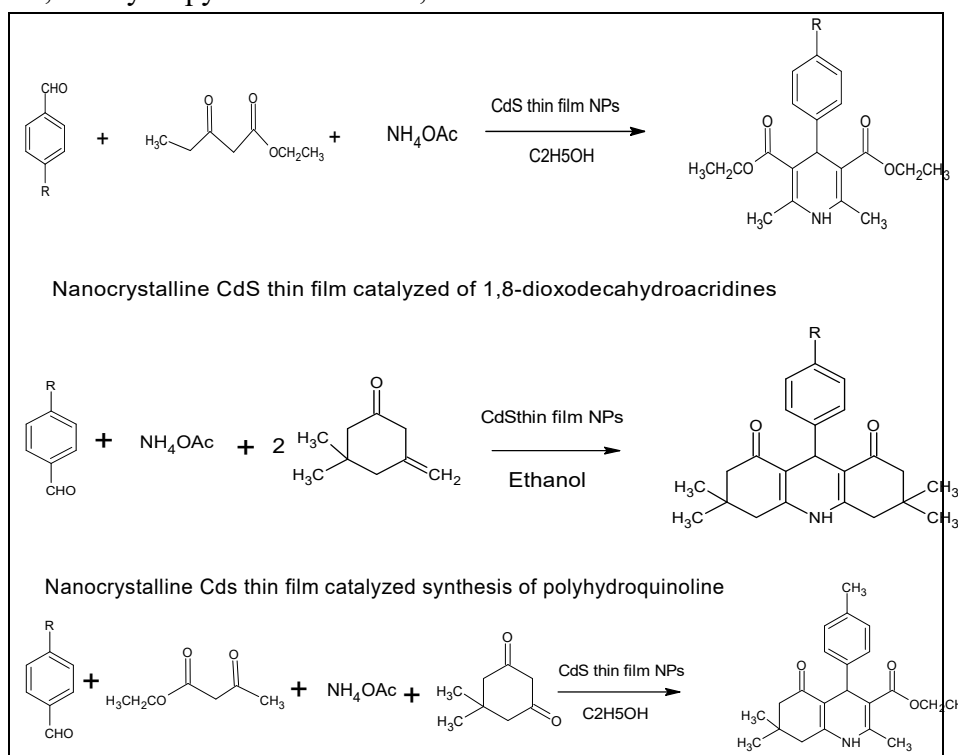
how nanocatalyst improve practices, pointing to their growing relevance in sustainable synthesis.



**Fig.8**

Earlier studies also contributed valuable insights In 2019[10] G. Lavnya and collaborators introduced a recyclable naocrystalline CdS thin film catalyst for the eco-friendly synthesis of Hantzsch 1,4-Dihydropyridines 1,8-

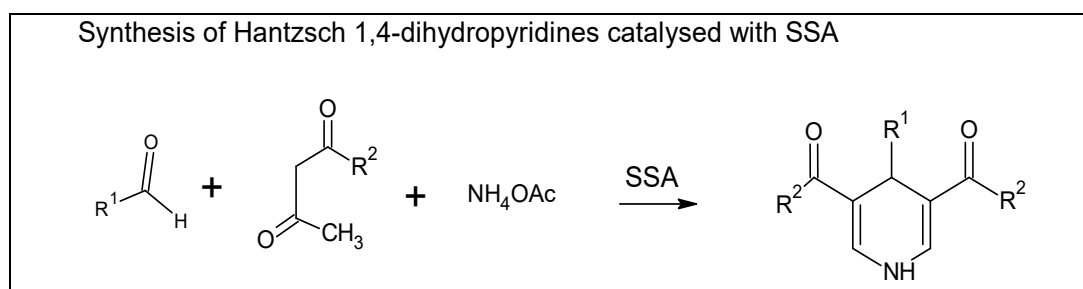
Dioxodecahydroacridine and polyhydroquinolines. This work highlighted the importance of recyclable nanocatalyst in achieving both environmental and practical advantages.



**Fig.9**

Furthermore, Eskandar Kolavari et.al. (2011)[11] Demonstrated the efficiency of silica sulfuric acid as heterogeneous reusable catalyst under solvent-free conditions for synthesizing 1,4-

Dihydropyridines. This simple and practical method illustrated the potential of solid-supported catalyst in green synthesis.



**Fig.10**

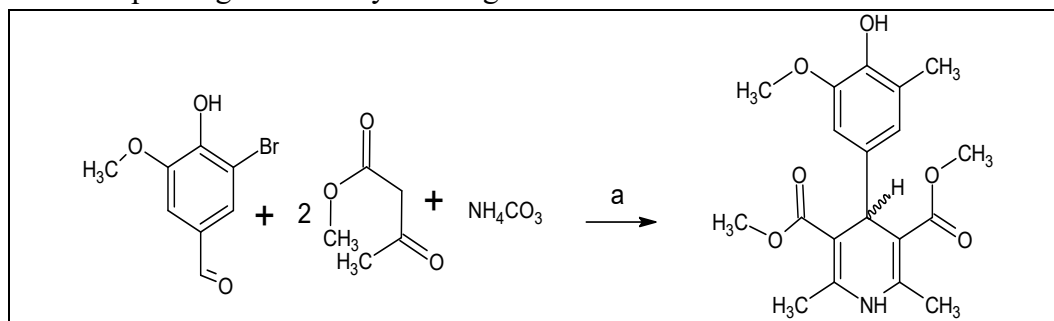
Taken together, these studies show that heterogeneous and nanocatalytic approaches not only enhance reaction efficiently and selectively but also provide practical benefits such as recyclability and ease of catalyst recovery. By integrating nanostructured materials, MOFs, and solid-supported catalysts, researchers have significantly advanced the sustainability and scalability of the Hantzsch synthesis.

### Catalyst-free and Microwave-Assisted synthesis:

In parallel with green and heterogeneous catalysis, another important line of progress in the Hantzsch reaction has been the development of catalyst-free and microwave-assisted methods. These approaches seek to minimize the use of external catalyst while improving efficiency through

alternative energies inputs, such as microwave irradiation and visible light. By eliminating and reducing catalysts, researchers achieve simpler reaction setups, lower costs, and environmentally friendly processes.

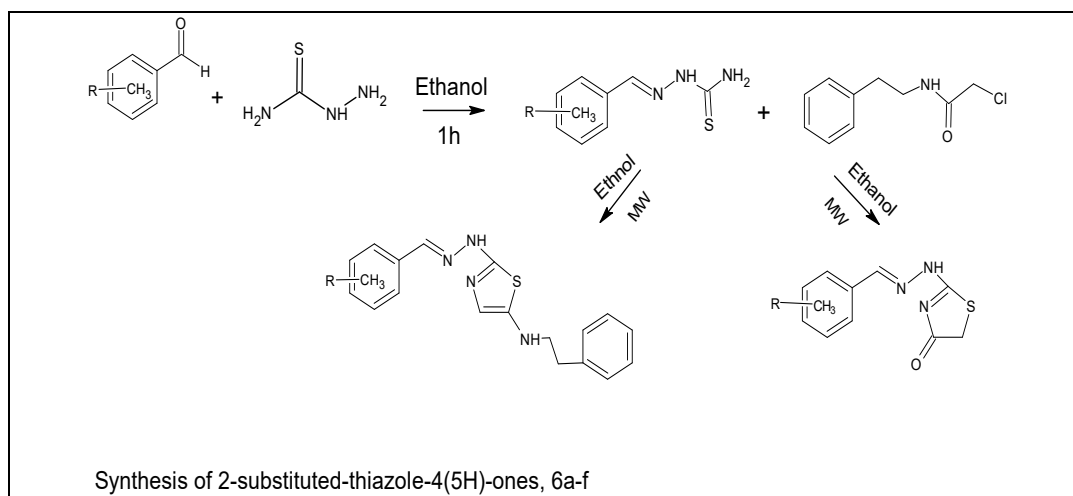
In 2022[12], Minaxi S. Maru, Dongwon Kim, Jagriti Behal, and Ok-sang Jung reported a microwave-irradiation, catalyst-free solid-phase method for the synthesis of Hantzsch 1,4-dihydropyridines. Their study not only described the synthetic procedure but also provide spectral characterization, fluorescence studies, and crystal structure analyses of the resulting compounds. This work demonstrated that microwave-irradiation can effectively replace traditional heating, leading to faster reactions and higher yields without requiring external catalysts.



**Fig.11**

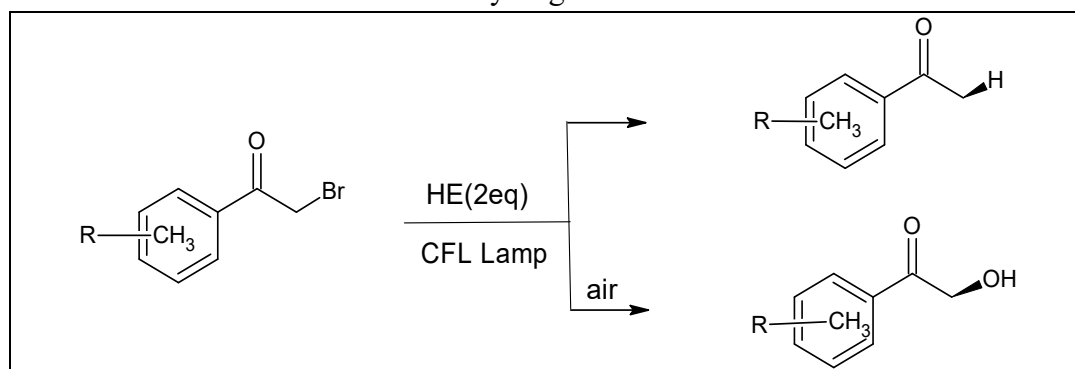
Microwave-assisted strategies were also highlighted in a 2022[13] studied by Swaranagowari Nayak and Santosh L. Gaonkar, who developed a microwave-assisted synthesis of 2-substituted thiazole derivatives via Hantzsch condensation. This method offer significant

improvements in reaction rates and yields compared to conventional approaches, reinforcing the role of microwaves as an energy efficient alternative to heterocyclic synthesis.

**Fig.12**

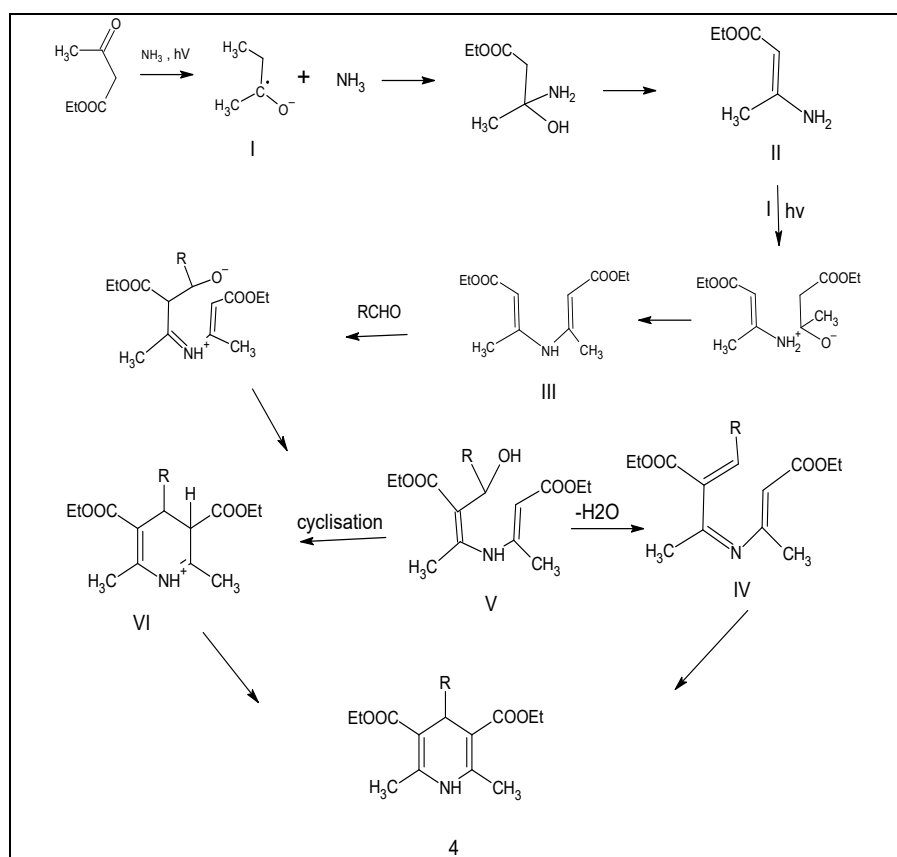
Another promising direction involves visible-light-driven processes. In 2022[14], Grish Yedase and co-workers published a review emphasizing catalyst-free Hantzsch ester-mediated organic transformations under visible-light. Their work showed that Hantzsch esters can act as hydrogen

donors and redox mediators, enabling organic transformations without the need for additional catalysts. This approach aligns with sustainable chemistry principles by using light as a clean energy source.

**Fig.13**

Earlier contributions also paved the way for these developments. For examples, Arun Kumar Pramanik and colleagues (2012)[15] reported a method for synthesizing 1,4-dihydropyridines in aqueous ethanol using visible lights. Their advantages of employing light energy in promoting efficient, eco-friendly reactions. Likewise, Ryan M. Bain and collaborators (2014)

introduced an innovative approach using electrospray synthesis to accelerate the Hantzsch reaction, providing temporal control over intermediates. This mechanistic insight demonstrated how novel energy sources and conditions can refine the efficiency and selectivity of multicomponent reactions.

**Fig.14**

Collectively, these advancements illustrated how microwave-irradiation, visible-light, and catalyst-free protocols provide simple, rapid, and environmentally responsible alternative to traditional Hantzsch synthesis. By minimizing reliance on conventional catalysts, these methods reduce costs and waste, while opening new opportunities for sustainable heterocyclic chemistry.

### Medicinal and Biological Significance:

Beyond methodological advances, the Hantzsch synthesis has played an increasingly important role in medicinal and biological chemistry. Many of the dihydropyridines (DHPs), polyhydroquinolines,

and fused heterocycles obtained through this reaction have demonstrated significant pharmacological properties, reinforcing the relevance of this chemistry to drug discovery and therapeutic applications.

In 2024[17], Paul J. Bernard, Alexey Simakov, and Irene Pachon-Angona designed and synthesized multifunctional ligands through the Hantzsch reaction. These ligands were found to activate the Nrf2 pathway, inhibit Ca<sup>2+</sup> channels, and block cathepsin S, in addition to possessing strong antioxidant properties. Such multifunctional activity makes them promising candidates for treating diseases linked to oxidative stress and inflammation.

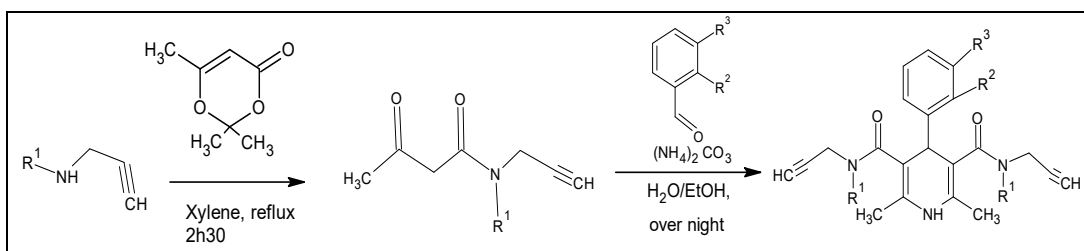


Fig.15

The important of antioxidant activity was also observed earlier. In 2011[18], A.M.Vijesh and co-workers synthesized new 1,4-dihydropyridine derivatives using the Hantzsch reaction and evaluated them as antimicrobial and antioxidant

agents. Their study demonstrated that structural modification of DHPs could enhance biological activity, broadening the potential of these compounds in therapeutic contexts.

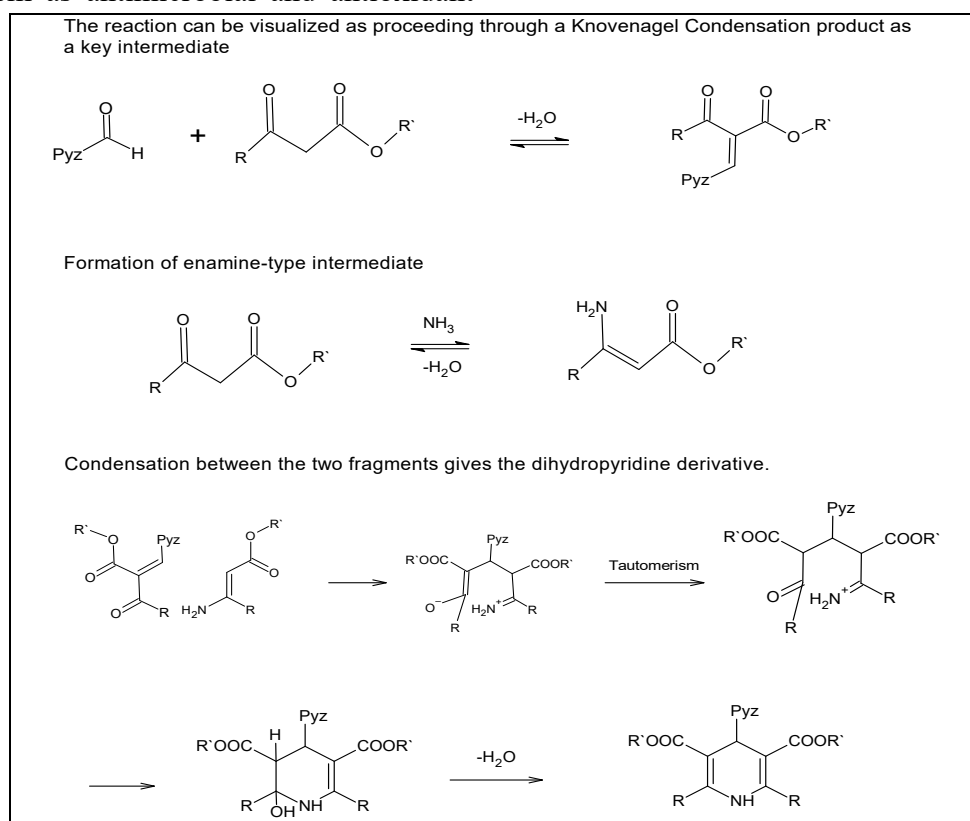


Fig.16

Several studies have also connected Hantzsch-derived compounds with drug developments applications. For instance, the 2024[19] study by Debolina Mukherjee and colleagues emphasized that their ribbon-like coordination polymer

catalyst could be applied to the synthesis of bioactive drug molecules, suggesting direct pharmaceutical relevance for the methods.

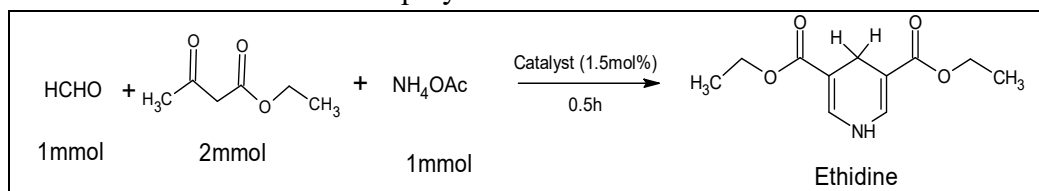
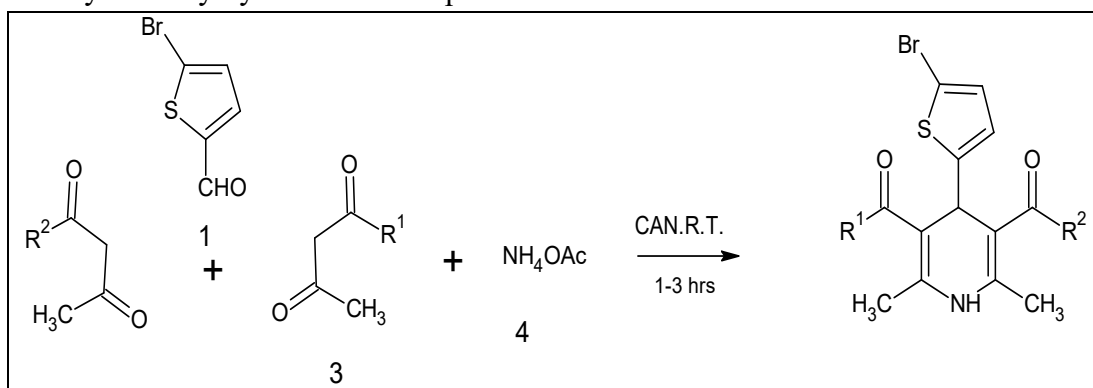


Fig.17

Similarly, the 2017[21] work of M.G.Sharma, D.P.Rajani, and H.M.Patel described an environmentally friendly synthesis of thiophene-

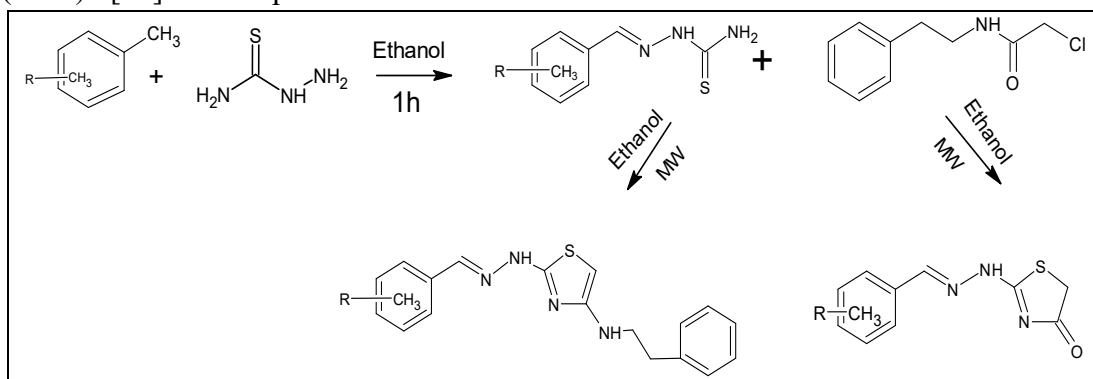
based Hantzsch 1,4-dihydropyridines with potential pharmaceutical importance, noting their high yields and short reaction times.



**Fig.18**

Additionally, the synthesis of thiazole derivatives via Hantzsch condensation has been linked to medicinal chemistry. For example, Swaranagowari Nayak and Santosh L. Gaonkar(2022) [20] developed a microwave-

assisted Hantzsch condensation method to obtain 2-substituted thiazole, compounds with significant pharmaceutical potential.



**Fig.19**

Earlier, in 2018[21], Weiam Hussein and Gilhan Turanzitouni reviewed the synthesis of thiazole derivatives and highlighted their therapeutic

importance, further underscoring the role of heterocycles derived from Hantzsch chemistry in drug discovery.

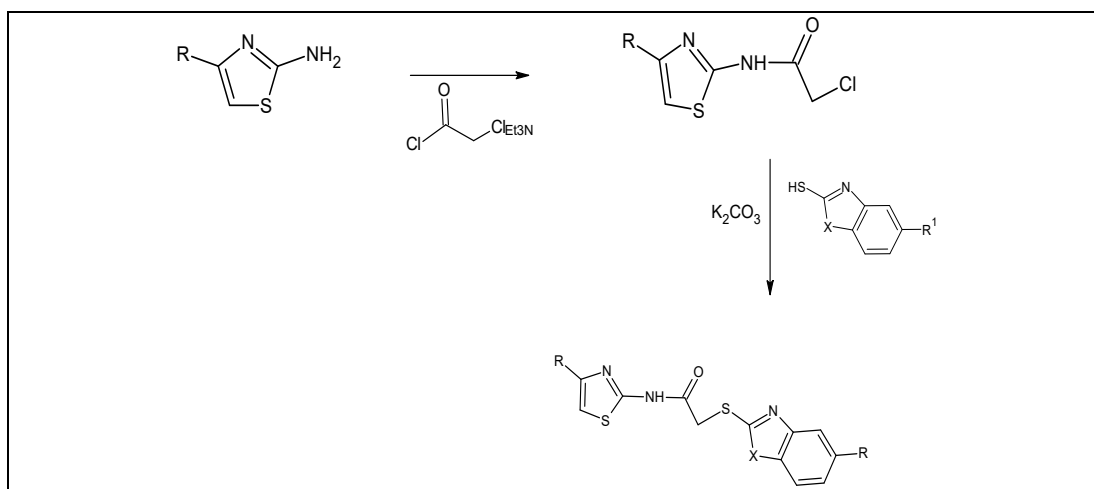


Fig.20

Overall, these studies reveal that Hantzsch-derived heterocycles are not only synthetically versatile but also biologically impactful. From antioxidant and antimicrobial activity to enzyme inhibition and drug development, the reaction has proven to be a key contributor at the intersection of organic synthesis and medicinal chemistry. The ability to couple environmentally friendly methods with the production of biologically active compounds further enhances the attractiveness of the Hantzsch synthesis in modern pharmaceutical research.

## CONCLUSION

The Hantzsch synthesis continues to stand out as one of the most important multicomponent reactions in organic chemistry, offering straightforward access to dihydropyridines, polyhydroquinolines, and fused heterocyclic systems. Between 2011 and 2024, the reaction has undergone remarkable transformations, driven by the dual goals of sustainability and pharmaceutical relevance. Looking forward, the trajectory of research suggests that the Hantzsch synthesis will continue to evolve through the integration of renewable resources, recyclable nanocatalysts, and energy-efficient reaction conditions. These advances not only reinforce its central role in sustainable organic synthesis but also ensure its

continued impact in the design of bioactive molecules and pharmaceutical agents.

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