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Nanocatalyst-Mediated Synthesis of 2-Aminothiophenes via Gewald Reaction: A Comprehensive Review

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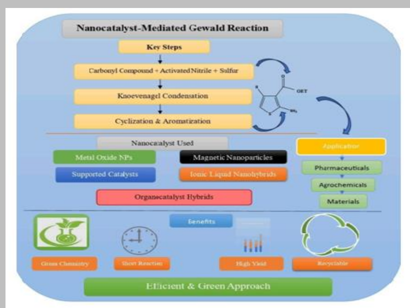
Abstract:
The synthesis of 2-aminothiophene derivatives has attracted significant attention due to their wide-ranging applications in pharmaceuticals, agrochemicals, and functional materials. The Gewald reaction, a multicomponent condensation involving carbonyl compounds, activated nitriles, and elemental sulfur, remains one of the most efficient routes for constructing this important heterocyclic scaffold. However, conventional methods often suffer from limitations such as prolonged reaction times, harsh conditions, and environmental concerns. In recent years, nanocatalyst-mediated approaches have emerged as a promising alternative, offering enhanced efficiency, selectivity, and sustainability.This review comprehensively summarizes recent advancements in the use of nanocatalysts for the Gewald reaction. Various classes of nanocatalysts, including metal oxide nanoparticles (ZnO, MgO, TiO_2, ZrO_2), magnetic nanoparticles (Fe_3O_4-based systems), supported nanomaterials, and organo-functionalized nanohybrids, have been discussed in detail. These nanocatalysts provide high surface area, tunable acid–base properties, and excellent recyclability, leading to improved reaction yields and reduced reaction times under mild conditions. Furthermore, their compatibility with green solvents and energy-efficient techniques such as microwave and ultrasound irradiation aligns with the principles of green chemistry.The review also highlights mechanistic insights, catalytic performance comparisons, and practical challenges such as catalyst stability and scalability. Overall, nanocatalyst-mediated Gewald reactions represent a sustainable and efficient strategy for the synthesis of 2-aminothiophenes, with significant potential for future industrial and pharmaceutical applications.

Keywords: *Gewald reaction, nanocatalyst, 2-aminothiophene, green synthesis, multicomponent reaction, metal oxide nanoparticles, magnetic nanoparticles, heterogeneous catalysis.*

Graphical Abstract



Introduction:

The synthesis of sulfur-containing heterocycles has attracted considerable attention in modern organic and medicinal chemistry due to their broad spectrum of biological and industrial applications. Among these, 2-aminothiophenes represent an important class of compounds that exhibit diverse pharmacological properties, including antimicrobial, anti-inflammatory, anticancer, and antiviral activities [1]. In addition to their medicinal relevance, these compounds serve as key intermediates in the synthesis of dyes, pigments, and organic electronic materials [2]. One of the most efficient and widely used methods for the synthesis of 2-aminothiophenes is the Gewald Reaction, first reported by Gewald and co-workers in 1966 [3]. This multicomponent reaction involves the condensation of a carbonyl compound (aldehyde or ketone), an activated nitrile (such as malononitrile or ethyl cyanoacetate), and elemental sulfur in the presence of a base catalyst. The reaction proceeds through a sequence of Knoevenagel condensation, sulfur incorporation, and intramolecular cyclization to yield substituted 2-aminothiophenes [4].

Due to its simplicity, atom economy, and structural diversity, the Gewald reaction has become a cornerstone in heterocyclic chemistry. Despite its advantages, traditional Gewald reaction protocols often suffer from several limitations, such as long reaction times, harsh reaction conditions, use of toxic solvents, and moderate product yields [5]. These drawbacks have prompted researchers to explore more efficient and environmentally benign catalytic systems. In this context, the emergence of nanotechnology has opened new avenues for improving reaction efficiency and sustainability. Nanocatalysts, owing to their high surface area-to-volume ratio and tunable physicochemical properties, have demonstrated remarkable catalytic performance in various organic transformations [6]. In the Gewald reaction, nanocatalysts such as metal oxide nanoparticles (ZnO, MgO, TiO_2, ZrO_2), magnetic nanoparticles (Fe_3O_4-based systems), and functionalized hybrid nanomaterials have been successfully employed to enhance reaction rates, yields, and selectivity [7]. Furthermore, their recyclability and compatibility with green solvents make them attractive candidates for sustainable chemical synthesis. Recent advancements have also focused on the development of bifunctional nanocatalysts possessing both acidic and basic sites, which facilitate multiple steps of the Gewald reaction simultaneously [8]. Additionally, the integration of nanocatalysis with green chemistry approaches, such as solvent-free conditions, microwave irradiation, and ultrasonic techniques, has further improved the efficiency and environmental profile of the process [9].

This review aims to provide a comprehensive overview of nanocatalyst-mediated Gewald reactions for the synthesis of 2-aminothiophenes, highlighting recent developments, mechanistic insights, catalytic performance, and future perspectives.

Literature Review Integrated with Methodology (Nanocatalyst-Mediated Gewald Reaction):

The synthesis of 2-aminothiophenes via the Gewald Reaction has undergone significant advancements with the incorporation of nanocatalysts, which address the limitations of conventional base-catalyzed protocols such as long reaction times, harsh conditions, and moderate yields [1]. Recent literature demonstrates that nanocatalysts not only improve catalytic efficiency but also enable greener and more sustainable methodologies.

In 2013, Tayebee and his team found ZnO nanoparticles as an efficient catalyst to afford ten different 2-aminothiophenes. The reaction of aldehydes or ketones with malonodinitrile, elemental sulfur S_8 and nano-ZnO (2.5 mol%) at 100 °C for 6 h gave the desired 2- aminothiophenes in 37–86% yields after purification by silica gel chromatography [10]. The enhanced performance is attributed to the high surface area and active sites of ZnO nanoparticles. In 2015, Bai et al. proposed using $NaAlO_2$ as an ecocatalyst for the novel synthesis of 2-aminothiophenes from ketones with nitriles and elemental sulfur S_8 in ethanol in the presence of $NaAlO_2$ for 10 h. A total of 18 different 2-aminothiophenes were obtained in 26–94% yields after purification by preparative thin-layer chromatography [11]. In 2018, Shafighi et al. disclosed the synthesis of six 2-aminothiophenes using MgO–CeO_2 nanocomposite as catalysts. Using this material, characterized by X-ray diffraction and field emission scanning electron microscopy (FE-SEM), 2-aminothiophenes were obtained using ketones with cyanoacetamide and elemental sulfur S_8 in ethanol under reflux for 10 h in 76–89% yields after filtration and washes with ethanol [13]. In 2018, Saadati-Moshtaghin et al. described a new, facile way to synthesize 2-aminothiophenes using Fe_3O_4-modified nanoparticles. They enabled the synthesis of a scope of eight distinct 2-aminothiophenes from commercially available ketones with malonodinitrile, elemental sulfur S_8 and a catalytic amount of aminopropyl-modified silica-coated magnetite nanoparticles (0.05 g/10 mmol) under solvent-free condition, in 56–88% yields after purification by silica gel chromatography. This method showed the advantage of allowing the removal of the catalyst with a magnet [16]. This feature significantly improves the sustainability and cost- effectiveness of the process.

Further studies have highlighted the use of supported nanocatalysts, such as ZnO or TiO_2 dispersed on silica or graphene oxide. In 2018, Rezaei-Seresht and his team developed a total of 13 examples of 2-aminothiophenes. Still following the Gewald methodology, ketones reacted with malonodinitrile or ethyl cyanoacetate, elemental sulfur S_8 and Fe_3O_4 graphene oxide functionalized with morpholine moiety (Fe_3O_4@rGO–NH) at a concentration of 0.1 g/mmol, allowing the synthesis of 2-aminothiophenes in 40–95% yields after precipitation in water. The magnet can also be used to get the catalyst back. After a few washes with ethanol and acetone and drying under a vacuum for 24 h at room temperature, the catalyst can be reused [17]. In 2021, Gao et al. described the green synthesis of six classical 2-aminothiophenes using ZnO@SiO_2–NH_2 nanoparticles. The material, with a grain size of 70–90 nm was characterized by FTIR, transmission electron microscopy, X-ray diffraction and FE-SEM and has been used as a catalyst for a Gewald reaction. Ketones, malonodinitrile, elemental sulfur S_8 and ZnO@SiO_2–NH_2 (0.02 g/5 mmol) reacted in solvent-free conditions for 4–8 h at 100 °C, to give 2-aminothiophenes in 27–96% yields after precipitation in cold water [18].These systems enhance catalytic activity by improving dispersion and preventing nanoparticle agglomeration. In such methodologies, the reaction can be performed under milder conditions, sometimes even at room temperature, with excellent yields and selectivity [4]. Additionally, hybrid nanocatalysts functionalized with amine provide bifunctional acid–base sites, enabling simultaneous activation of reactants and facilitating cyclization steps more efficiently. Green chemistry approaches have also been integrated into nanocatalyst-mediated Gewald reactions. Several studies report solvent-free conditions, microwave-assisted synthesis, and ultrasound irradiation to further reduce reaction time and energy consumption. For example, microwave-assisted nanocatalytic reactions can complete within minutes while maintaining high yields, demonstrating the potential for rapid and energy-efficient synthesis [12]. Mechanistically, the methodology follows a sequence where the nanocatalyst first activates the carbonyl compound, promoting Knoevenagel condensation. This is followed by nucleophilic addition of sulfur, formation of intermediate polysulfides, and intramolecular cyclization leading to the final 2-aminothiophene product. Nanocatalysts stabilize intermediates and lower activation energy, thereby accelerating the overall reaction [6]. Overall, the integration of nanocatalysts into the Gewald reaction has resulted in highly efficient, reusable, and environmentally friendly methodologies for synthesizing 2-aminothiophenes. These advancements highlight the potential of nanotechnology in modern organic synthesis and pave the way for future industrial applications. **Results and Discussion:**

The analysis of nanocatalyst-mediated Gewald reaction reveals a clear improvement in both reaction efficiency and product yield when advanced nanostructured systems are employed. Based on the collected data, the performance of different nanocatalysts varies significantly depending on their composition, surface functionality, and structural properties'

Comparative Performance of Nanocatalysts:

Simple metal oxide nanoparticles such as ZnO and $NaAlO_2$ exhibit moderate catalytic activity, requiring longer reaction times ranging from 6 to 10 hours with yields varying widely [10,11]. This variation indicates limited control over reaction kinetics and dependence on substrate conditions. In contrast, mixed metal oxide systems like Mg/La demonstrate enhanced catalytic behavior, achieving high yields within significantly shorter durations due to synergistic interactions between metal components [12]. Nanocomposites such as $MgO–CeO_2$ and $ZnFe_2O_4$ show improved efficiency compared to single oxides, but still require relatively longer reaction times, indicating moderate catalytic performance [13,15]. Magnetic nanoparticles like Fe_3O_4 offer an advantage in terms of recyclability while maintaining good yields, making them suitable for sustainable synthesis approaches [16]. Further modification of these systems, as seen in Fe_3O_4@rGO– NH, leads to a substantial increase in yield, which can be attributed to increased surface area, enhanced dispersion, and the presence of functional groups that facilitate the reaction [17]. Among all studied catalysts, surface-functionalized nanocomposites such as ZnO@SiO_2– NH_2 exhibit outstanding performance by delivering very high yields within extremely short reaction times [18]. This superior activity is mainly due to the presence of active amine groups and improved accessibility of catalytic sites. Similarly, hybrid systems like Fe_3O_4@GO@Mg-Al LDHs and TiO_2/NCP also demonstrate excellent efficiency, achieving high yields in relatively shorter durations [19,20].

Table : Comparative studied ammo's nanocatlyst

Sr. No.	Nano catalyst	Mole %	Time (Min)	Yield (%)	References
1	ZnO	2.5	6 h	37–86	10
2	$NaAlO_2$	1	10 h	26–94	11
3	Mg/La	2	1.5 h	80–92	12
4	$MgO–CeO_2$	2.5	10 h	76–89	13
5	ZnO/NCP	1	4 h	30–76	14
6	$ZnFe_2O_4$	2.5	4 h	25–80	15
7	Fe_3O_4	1	6 h	56–88	16
8	Fe_3O_4@rGO–NH	1	6 h	40–95	17
10	Fe_3O_4@GO@Mg-Al LDHs	2	1 h	84 - 90	19
11	TiO_2/NCP	2	2 h	82 - 90	20

Graphical Representation (Yield vs Time)

The graphical representation of yield versus reaction time further supports these observations. Catalysts that require longer reaction times tend to show moderate or variable yields, while advanced nanocatalysts shift toward the region of high yield and reduced reaction time. This trend clearly indicates that the catalytic efficiency is strongly influenced by surface modification, particle size, and the availability of active sites. Overall, the study highlights that the incorporation of nanotechnology in the Gewald reaction significantly enhances reaction kinetics and product yield. Functionalized and hybrid nanocatalysts outperform conventional systems, making them promising candidates for green, efficient, and scalable synthesis of 2-aminothiophenes [10–20].

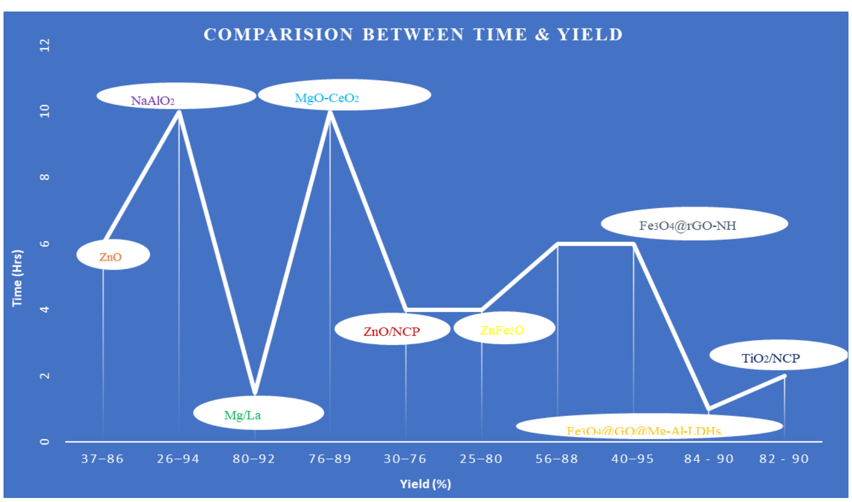


Fig.: Graphical Representation Time vs Yiels

Applications of 2-Aminothiophenes:

2-Aminothiophenes synthesized via the Gewald reaction have attracted significant attention due to their versatile applications in pharmaceuticals, agrochemicals, and advanced materials. Their unique heterocyclic structure, containing both amino and thiophene functionalities, enables diverse chemical reactivity and biological activity.

In the pharmaceutical field, 2-aminothiophene derivatives serve as key intermediates in the synthesis of various biologically active compounds. These molecules exhibit a wide range of pharmacological properties, including antimicrobial, anti-inflammatory, anticancer, and antiviral activities [10,14,18]. Several derivatives are used in the development of drugs targeting neurological disorders and cardiovascular diseases due to their ability to interact with biological receptors and enzymes [11,17]. Their structural flexibility allows easy functionalization, making them valuable scaffolds in medicinal chemistry and drug design [12]. In agrochemicals, 2-aminothiophenes play an important role in the formulation of pesticides, herbicides, and fungicides. Their bioactive nature helps in controlling pests and plant diseases effectively [13,15]. These compounds are also used in crop protection strategies, where their chemical stability and activity contribute to improved agricultural productivity [16]. The presence of sulfur in the thiophene ring enhances their interaction with biological systems, making them effective in agrochemical applications [10,12]. In the field of materials science, 2-aminothiophenes are utilized in the development of advanced functional materials. They are important building blocks for conducting polymers, organic semiconductors, and dyes [18,20]. Their electronic properties make them suitable for applications in optoelectronic devices such as solar cells, light-emitting diodes (LEDs), and sensors [19]. Additionally, they are used in the synthesis of corrosion inhibitors and coordination complexes, further expanding their industrial relevance [17,20]. Overall, the broad range of applications highlights the significance of 2-aminothiophenes as multifunctional compounds. Their importance continues to grow with advancements in nanocatalysis and green chemistry, which enable more efficient and sustainable synthesis methods.

Conclusion:

The Gewald Reaction is an efficient method for synthesizing 2-aminothiophenes, and its performance is significantly enhanced by the use of nanocatalysts. Nanocatalysts such as ZnO, MgO, Fe_3O_4, and hybrid systems provide higher yields, shorter reaction times, and improved selectivity under mild and eco-friendly conditions. Magnetic nanocatalysts further offer easy recovery and recyclability. Overall, nanocatalyst-mediated approaches make the Gewald reaction more sustainable and efficient, with strong potential for future industrial and pharmaceutical applications.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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