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Recent updates in the one-pot multicomponent synthesis of 3,4-disubstituted-isoxazole-5(4H)-ones and its activity: A review

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Original Research

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Abstract:

Isoxazole-5-(4H)-one derivatives have garnered considerable attention owing to their wide range of pharmacological activities, such as anti-inflammatory, analgesic, antimicrobial, and antitumor properties. The multicomponent synthesis of 3,4-disubstituted-isoxazole-5-(4H)-ones has attracted significant interest in recent years due to its effectiveness and capability to produce various molecular libraries. This review presents a thorough summary of the recent advancements in the synthetic methodologies utilized for the synthesis of these heterocyclic compounds. Emphasis is placed on the various catalytic systems, reaction conditions, reaction medium, and substrate scopes that have been explored to optimize yields and selectivity. Additionally, the review discusses the biological activities associated with 3,4-disubstituted-isoxazole-5-(4H)-ones, highlighting their potential as therapeutic agents. The integration of green chemistry principles and sustainable methodologies in these synthetic processes is also examined, reflecting the ongoing efforts to develop environmentally benign chemical processes. Through a critical analysis of recent literature, this review aims to provide a valuable resource for researchers in the field of heterocyclic chemistry and drug discovery, fostering further innovation and application of these versatile compounds.

Keywords: Anticancer; Green synthetic method; Isoxazol-5-ones; Multicomponent reactions

1. Introduction

Heterocyclic compounds serve as essential building blocks in medicinal chemistry and drug discovery due to their structural diversity and versatile biological activities [1]. Heterocyclic compounds containing nitrogen and oxygen atoms are a significant class in medicinal chemistry and organic synthesis due to their numerous biological activities [2, 3]. Among them, 3,4-disubstituted isoxazole-5 (4H)-ones is one of the most significant heterocyclic intermediates because it exhibits a variety of biological activities, including fungicidal [4], hypoglycaemic [5], immunosuppressive, anti-inflammatory, and antibacterial activities [6], as well as anticancer [7], anti-HIV [8], analgesic [9], and antiviral [10]. Furthermore, certain 3,4-disubstituted isoxazoline-5 (4H) ones are employed in the creation of nonlinear optical material [11, 12], filter dyes [13], optical storage devices [14], and light conversion in molecular devices [15]. Organic nonlinear optical (NLO) materials [16], photonic applications [17], and solar cells

[18] are likely to benefit from the isoxazol5(4H)-one motif as a potent electron acceptor. Several isoxazole-5 (4H)-one derivatives that are α,β-unsaturated exhibit potent biological activity. Recently, significant progress has been made in the advancement of convenient synthetic methods for these compounds, with one-pot multicomponent reactions emerging as a particularly useful approach. In modern organic synthesis, developing efficient and environmentally sustainable methods to construct heterocyclic compounds has become increasingly important [18]. One particularly exciting breakthrough in the field of heterocyclic chemistry is a multicomponent catalytic synthesis of isoxazole-5(4H)-ones. The integration of green chemistry principles into synthetic methodologies has received significant attention due to its potential to minimize environmental impact and enhance sustainability. Green protocols aim to reduce waste generation, energy consumption, and usage of hazardous solvents and catalysts [19]. This holds significant importance, especially in the formation of heterocyclic compounds such as 3,4-disubstituted isoxazole-5(4H)-ones, a class of compounds frequently encountered in biologically active substances and pharmaceutical agents.

One-pot multicomponent reactions are powerful tools for the rapid and streamlined assembly of complex molecular structures in a single step. It offers several advantages over traditional stepwise synthesis approaches. With the simultaneous incorporation of multiple functionalities into a single reaction vessel, MCR streamlines synthetic pathways, reduces synthetic steps, and increases overall efficiency. Additionally, the use of catalytic systems in MCRs further enhances their synthetic utility by promoting high yields, selectivity, and atom economy [20].

Different catalytic systems have been utilized for the one-pot multicomponent synthesis of 3,4-disubstituted isoxazole-5(4H)-ones, encompassing organocatalysts, nanocatalysts, supported nanocatalysts, and heterogeneous catalysts [21]. Each system offers unique advantages in terms of efficiency, selectivity, and sustainability, enabling the synthesis of complex isoxazole frameworks from readily available starting materials. The examination of the literature shows that a diverse array of homogeneous and heterogeneous catalysts have been utilized in the production of isoxazole derivatives. Homogenous catalytic systems such as organocatalyst succinic acid [16], starch solution [17], PPI [18], citric acid [19], L-valine [20], malic acid [21], salicylic acid [22], pyruvic acid [23], Itaconic acid [24], potassium 2,5-dioxoimidazolidin-1-ide [25] and GAA [26] has been employed for synthesis of 3,4-disubstituted-isoxazole-5-(4H)-ones. Recent advancements have focused on optimizing reaction conditions and developing novel catalytic systems. Heterogenous catalysts like NaCl [27], Nanocatalyst like ZnO@Fe_3O_4 [28], Nano SnII-Mont K10 [29], Nano-SiO_2-H_2SO_4 [30], 6-methylguanamine@$CoFe_2O_4$ [31], Sodium tetraborate [32], potassium bromide [33], boric acid [34], WEOFPA [35], phosphoric acid-based molten salt [36] Dowex1-x8OH [37], Cu@Met-β-CD [38]. Sulphonicacid [39] DOWEX®50WX4 [40] sodiummalonate [41], TBAP [42] azolium salt [43]. Each system offers unique advantages in terms of efficiency, selectivity, and sustainability, enabling the synthesis of complex isoxazole frameworks from readily available starting materials [10]. The researchers analyzed the biological activities exhibited by synthesized 3,4-disubstituted isoxazole-5(4H)-ones, elucidating their potential as therapeutic agents across various disease states. Figure 1 illustrates the bioactive compounds of isoxazole.

This review endeavors to furnish a thorough examination of the latest progressions in the one-pot multicomponent

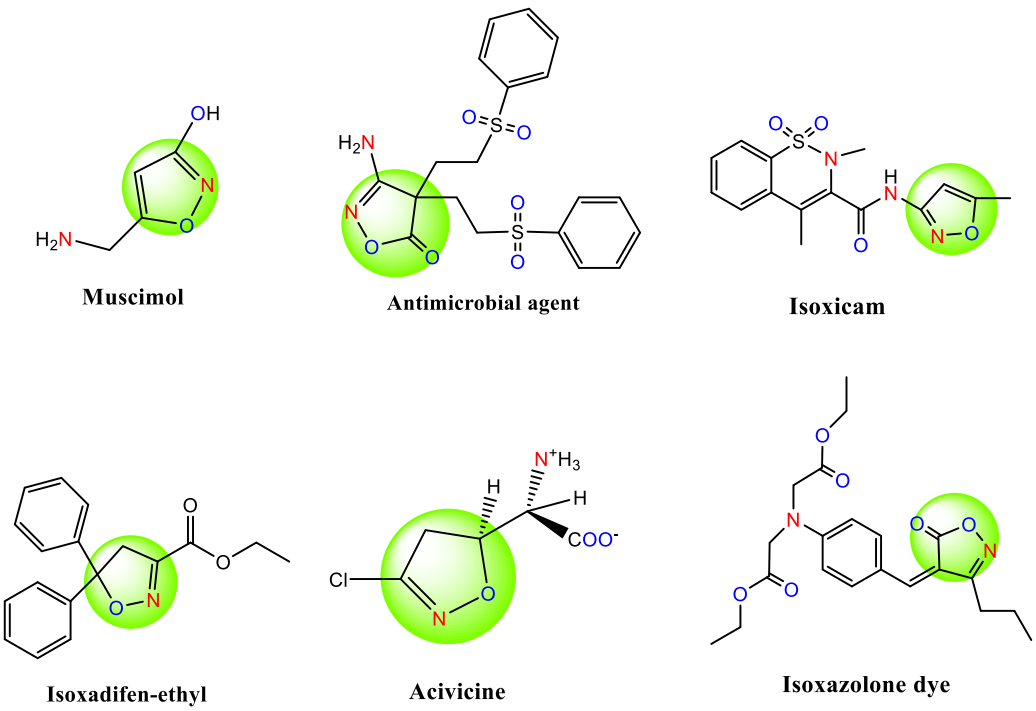


Figure 1. Illustrates instances of bioactive compounds and pharmaceutical agents that encompass the isoxazole moiety.

synthesis of 3,4-disubstituted-isoxazole-5-(4H)-ones. We will discuss various synthetic strategies, catalytic systems, and reaction conditions, along with their respective advantages and limitations. Additionally, the biological activities of these compounds will be examined, highlighting their potential as therapeutic agents. Through synthesizing recent literature, this review seeks to offer valuable insights for researchers in the fields of heterocyclic chemistry and drug discovery, promoting further innovation and application of these versatile compounds.

2. Homogenous catalysts for the preparation of 3,4-disubstituted isoxazole-5(4H)-ones

2.1 Organocatalysts

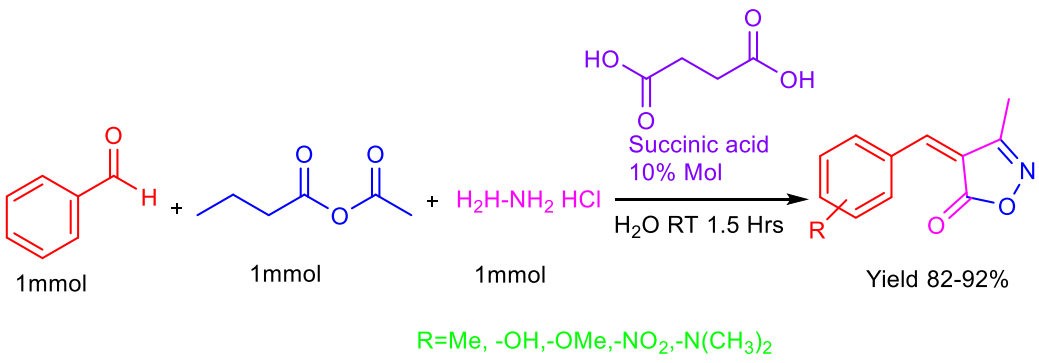
Ghogare et al. (2021) demonstrated a novel and straightforward multi-component process for the synthesis of 3,4-disubstituted isoxazole-5(4H)-ones derivatives using water as green media and succinic acid as a cheap and stable organocatalyst (Scheme 1). A mixture of substituted aromatic aldehyde (1 mmol), ethyl acetoacetate EAA (1 mmol), and hydroxylamine hydrochloride (1 mmol) was stirred in water (5 mL) with succinic acid (10 mol %) a catalyst at room temperature. Significant benefits of this approach include high conversion rates, outstanding yields, moderate reaction conditions, a green reaction medium, and the most affordable and stable catalyst. It was found that an aromatic aldehyde with an electron-donating group exhibits a high yield, whereas the intended product is not obtained by the electron-withdrawing group.

Vakeriya et al. (2017) described an effective approach for the one-pot, three-component synthesis of a range of 3,4-disubstituted isoxazole-5(4H)-one derivative, using a starch solution as the catalyst. (Scheme 2). The process involves stirring a mixture of ethyl acetoacetate (1 mmol), hydroxylamine hydrochloride (1 mmol), several substituted aromatic aldehydes (1 mmol), and 4 mL of starch solution at 90 °C for 60–80 minutes or irradiating it under microwave 300 W. This environmentally friendly reaction takes place in aqueous ethanol, using a biodegradable, reusable, and nontoxic catalytic system, providing excellent yields of the desired product. The advantages of this methodology include its gentle reaction conditions, good yields, great atom economy, simple work-up procedures, quick response times, and ease of usage.

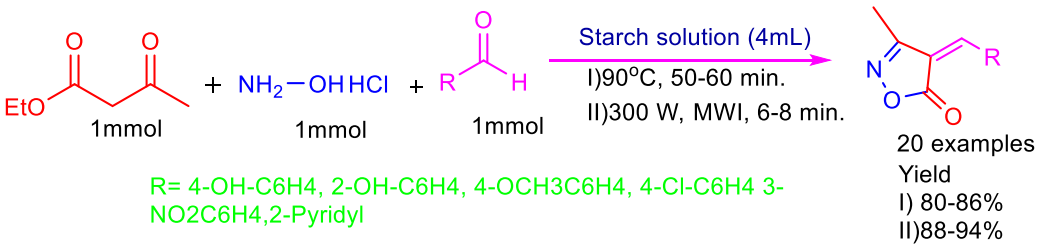
Kiyani et al. (2017) developed a one-pot method for producing 3,4-disubstituted isoxazole-5(4H)-one derivative. They used potassium phthalimide as a catalyst and water as a solvent, aiming for an environmentally friendly approach (Scheme 3). This method involved using potassium phthalimide (PPI) as a basic organocatalyst in a reaction with-hydroxylaminehydrochloride, β-oxoesters, and different aromatic aldehydes, which is a significant advancement in organic synthesis. The method has multiple benefits, including efficiency, simplicity, high yields, quick reaction times, and the use of a cost-effective and easily accessible catalyst.

Bashash et al. (2016) demonstrated a condensation reaction at room temperature. They combined aromatic aldehydes, EAA, and hydroxylamine hydrochloride to produce a variety of alkylidene isoxazol-5(4H)-ones with good yields (Scheme 4). They used citric acid in water as an active catalyst for preparing these compounds. The method resulted in high yields (70–90 %) and efficient reaction times (5–24 hours). This innovative protocol offers straightforward work-up and mild reaction conditions and uses H_2O as an environmentally friendly solvent, making it an attractive method for synthesizing these heterocycles.

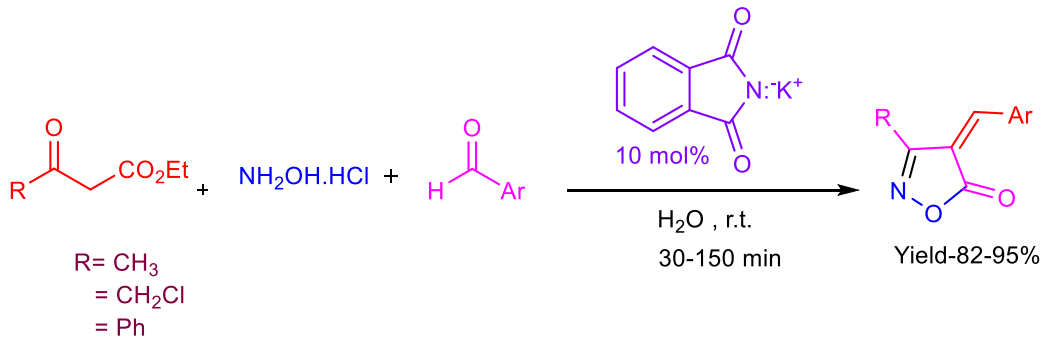
Sharma et al. (2020) devised a rapid domino multi-



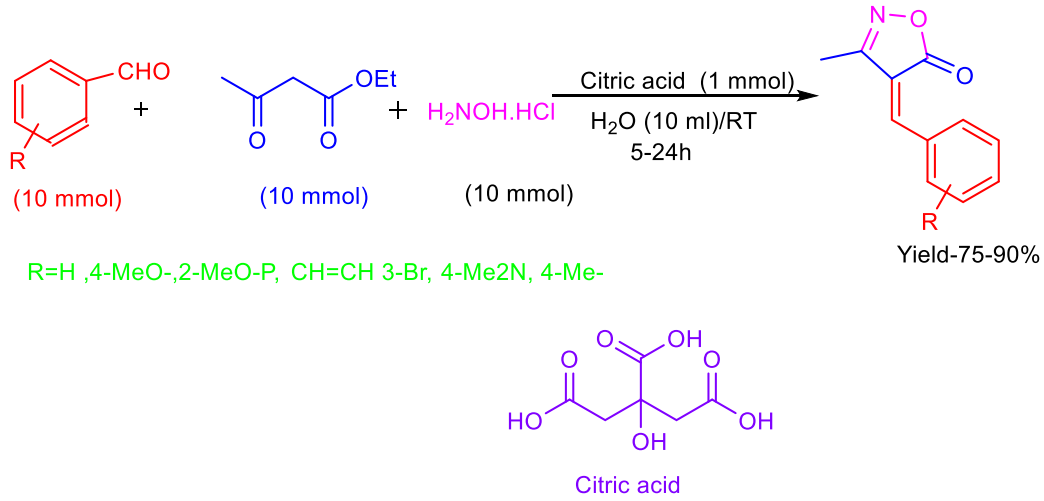
Scheme 1. The synthesis of 3,4-disubstituted isoxazole-5(4H)-ones derivatives using succinic acid in water.



Scheme 2. Multicomponent synthesis of various 3,4-disubstituted isoxazole-5 (4H)-one derivative catalyzed by starch solution.



Scheme 3. Synthesis of 3,4-disubstituted isoxazole-5 (4H)-one derivative using Potassium phthalimide as catalyst and water as a green medium.



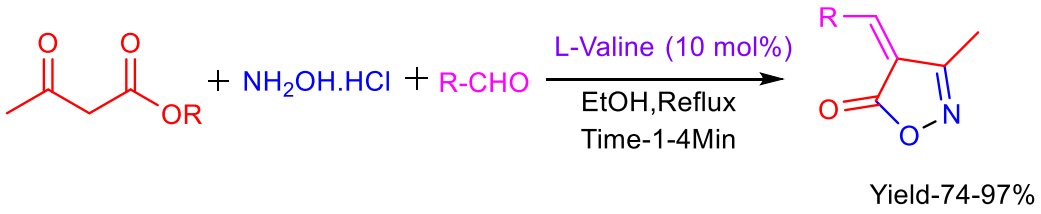
Scheme 4. Synthesis of various alkylidene isoxazol-5(4H)-ones using citric acid in water as a convenient catalyst.

component method for synthesizing substituted isoxazolone derivatives without the use of metals. Inthis methodology, alkylacetoacetates, hydroxylamine hydrochloride, and aldehydes undergo a three-component cyclo-condensation reaction in ethanol under reflux, which is accelerated by L-valine as catalyst (Scheme 5). The reaction displayed acceptable functional group tolerance, produced the required products in good to outstanding yields (74–97 %), and finished in less than 4 minutes for the majority of the substrates. Beneficial aspects of this approach include high yields, quick reaction times, noncorrosive organocatalysts, mild reaction conditions, clean reaction profiles, and the lack of laborious workup or purification.

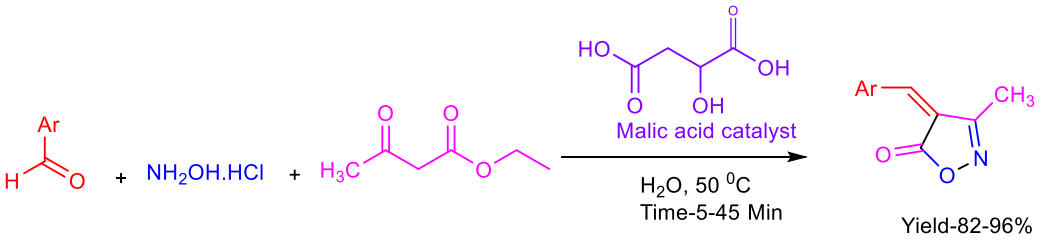
Tahmasabi et al. (2023) have developed a highly efficient, simple, and green method for the synthesis of 4-arylmethylene-3-methylisoxazol-5(4H)-one derivative. They used malic acid as a catalyst in a three-component heterocyclization reaction (Scheme 6). This process involved aryl/heteroaryl aldehydes, hydroxylamine hydrochloride, and either ethyl acetoacetate or ethyl benzoylacetate as reactants. They optimized the conditions and found that the ideal synthesis of the target heterocyclic compounds occurred with 10 mol % malic acid as the catalyst, water as the solvent, and a reaction temperature of 50 °C. Key aspects of this method encompass a straightforward experimental procedure, easy isolation of pure compounds, simple operation, elimination of harmful organic solvents, no need for chromatographic purification, clean reaction profiles, high yields, relatively short reaction times, and environmental friendliness.

Mosallanezhad et al. (2019) introduced an environment-friendly protocol for synthesizing isoxazol5(4H)-ones. 3-Substituted-4-arylmethylideneisoxazol5(4H)-ones synthesized from easily accessible aryl/heteroaryl aldehydes and β-keto esters through cyclo condensation reaction utilizing salicylic acid as an economical and environmentally friendly catalyst (Scheme 7). Notably, this process doesn't require extreme conditions such as thermal, microwave, or ultrasound treatment. Emphasizing its operational mildness and simplicity, the method yields the desired small heterocyclic compounds in good to high yields.

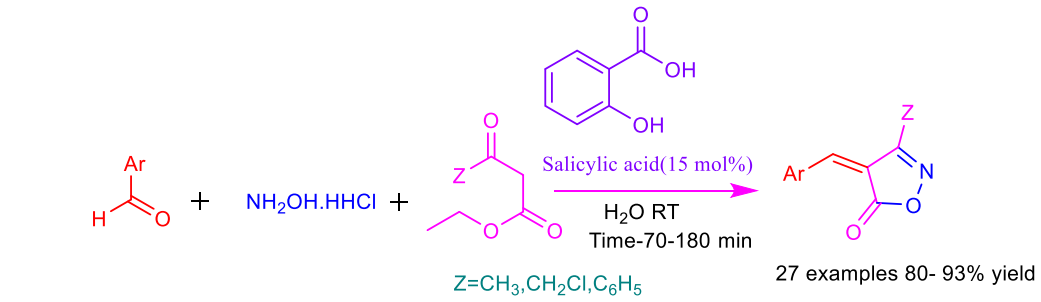
Deshmukh et al. (2022) have devised a novel approach for the production of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones. This technique entails a one-pot multicomponent reaction employing aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride alongside pyruvic acid serving as a catalyst (Scheme 8). The reaction mixture, comprising benzaldehyde (0.5 g, 4.71 mmol), hydroxylamine hydrochloride (0.327 g, 4.71 mmol), ethyl acetoacetate (0.613 g, 4.71 mmol), and a pyruvic acid catalyst (0.02 g, 0.023 mmol) in 10 mL of water, was subjected to reflux for a specified period. This method offers advantages such as straightforwardness, high yields, short reaction durations, utilization of a benign solvent, and an environmentally



Scheme 5. Multi-component synthesis of isoxazolone derivatives accelerated by L-valine as catalyst.

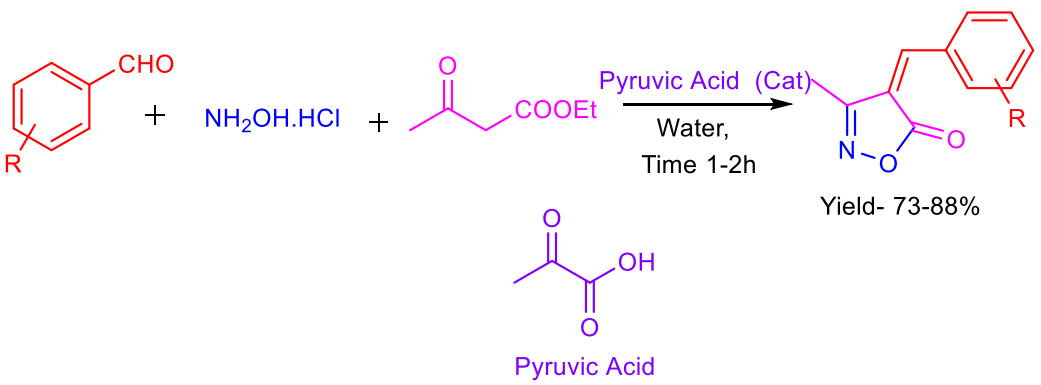


Scheme 6. Efficient synthesis of 4-arylmethylene-3-methylisoxazol-5(4H)-one derivative catalyzed by malic acid.



Ar=C6H54-, H3C-C6H4 ,4-HO-C6H4 ,3-HO-C6H4, 2-HO-C6H44-H3CO-C6H4 ,4-(H3C)2N-C6H4 ,4-HO-3-H3CO-C6H34H3CCONH-C6H42-HO-4-(CH3CH2)2N-C6H32-thienyl 3-thienyl

Scheme 7. Synthesis of isoxazol5(4H)-ones. 3-Substituted-4 arylmethylideneisoxazol5(4H)-ones using salicylic acid as a catalyst.



Scheme 8. Pyruvic acid-catalyzed synthesis of 3-methyl-4-arylmethylene isoxazole5(4H)-ones.

conscious approach. Such a procedure presents a convenient and effective substitute for conventional synthetic methodology.

Kasara et al. (2019) presented a sustainable method for the production of isoxazol-5(4H)-one derivatives utilizing itaconic acid as an environmentally friendly and harmless organocatalyst (Scheme 9). The utilization of water as a sustainable solvent, along with the application of ultrasonication as an eco-friendly energy input, were key aspects of the protocol. A reaction mixture comprising aromatic aldehyde (0.5 g, 1 mmol), hydroxylamine hydrochloride (0.20 g, 1 mmol), ethyl acetoacetate (0.20 g, 1 mmol), itaconic acid (5 mol %), and water (5 mL) was introduced into a 50 mL round-bottom flask and subjected to sonication at 50 °C. Upon completion of the reaction (validated by TLC), the mixture underwent extraction with ethyl acetate (3 × 5 mL), followed by drying of the organic layer with Na_2SO_4 and concentration under reduced pressure. The resulting crude material was further purified via column chromatography on silica gel utilizing ethyl acetate: hexane as the eluting agent. This procedure was conducted under standard conditions, with notable attributes such as a synthesis devoid of metals and mineral acids.

Kiyani et al. (2014) developed a highly effective method for synthesizing 4-arylidene-3-alkylisoxazole-5(4H)-ones. This was achieved through a three-component cyclocondensation process involving aryl(heteroaryl)aldehydes, hydroxylamine hydrochloride, and β-ketoesters (Scheme 10). The introduction of potassium 2,5-dioxoimidazolidin-1-ide as a novel organocatalyst facilitated the heterocyclization. The procedure involves using substituted benzaldehydes/heterocyclic aromatic aldehydes, hydroxylamine hydrochloride, and ethyl acetoacetate/propyl acetoacetate/butyryl acetoacetate as starting materials, yielding various substituted isoxazole-5(4H)-ones in significant yields. Ethylene glycol serves as the environmentally friendly reaction medium at 80 °C. The reduced catalyst loading further distinguishes this method from previously reported catalysts.

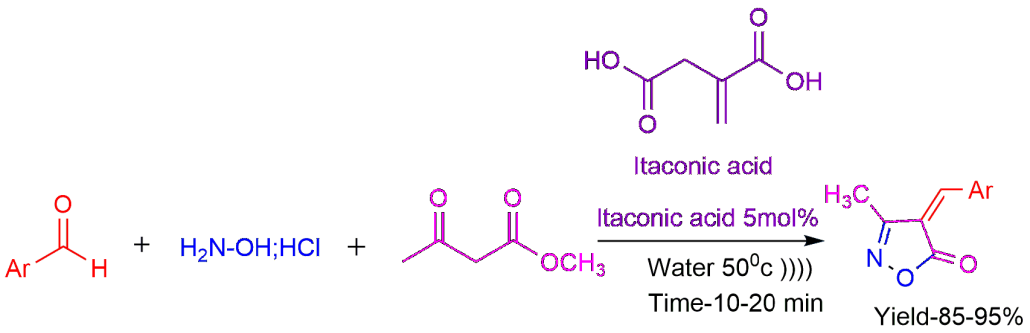
Shitre et al. (2023) introduced a simple, cost-effective, and innovative one-pot three-component method that reported for the green synthesis of 3,4-disubstituted isoxazole-5 (4H)-one derivative. The method involved using various aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride in an aqueous gluconic acid solution (Scheme 11). In this approach, the aqueous gluconic acid solution served as both the reaction medium and catalyst. It's important to note that the solution of gluconic acid can be recycled and reused up to seven times without losing its effectiveness. This method offers significant advantages, including being economical, non-toxic, having a shorter reaction time, operating under catalyst-free conditions, and utilizing a green reaction medium.

Haidary et al. (2024) have developed a method to efficiently synthesize various 4-arylideneisoxazol-5(4H)-one derivative using a one-pot process involving readily available starting materials (Scheme 12). This environmentally friendly method uses NaCl as a catalyst and eliminates the need for organic solvents. The resulting heterocyclic products can be easily separated and purified, making this approach a practical and attractive option for synthesizing these structures.

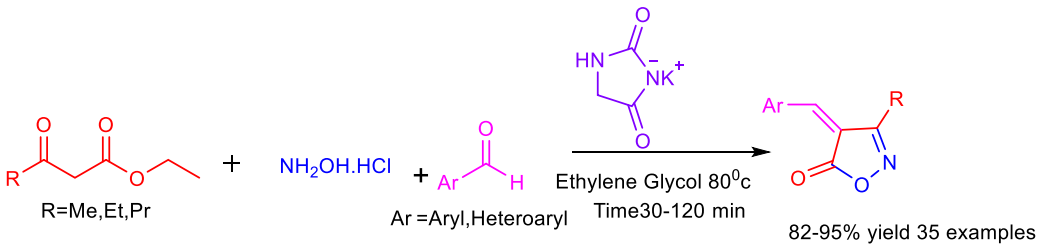
3. Heterogenous catalyst

3.1 Nanocatalysts

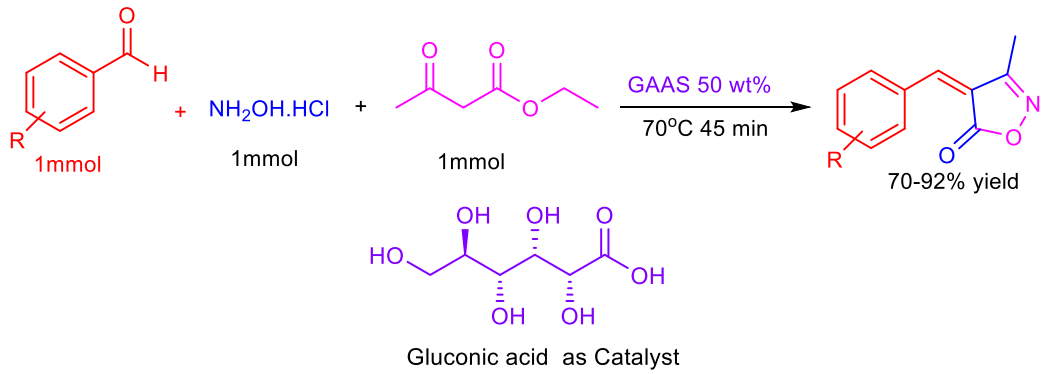
Shanshak et al. (2020) reported an effective and eco-friendly protocol for synthesizing isoxazole-5(4H)-one derivative utilizing a $ZnO@Fe_3O_4$ core-shell nanocatalyst (Scheme 13). This MCR method produces a satisfactory product by react-



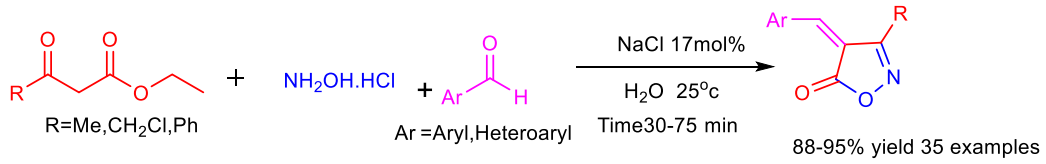
Scheme 9. Green methodology for synthesizing derivatives of isoxazol-5(4H)-ones using Itaconic acid as an organocatalyst.



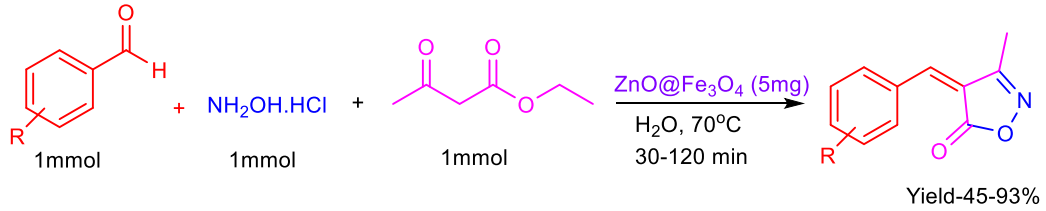
Scheme 10. Synthesis of 4-arylidene-3-alkylisoxazole-5(4H)-ones using potassium 2,5-dioxoimidazolidin-1-ide as a novel organocatalyst.



Scheme 11. A novel one-pot, three-component method using an aqueous gluconic acid solution as a catalyst for the green synthesis of 3,4-disubstituted isoxazol-5(4H)-one derivatives.



Scheme 12. A method for synthesizing various derivatives of 4-arylideneisoxazol-5(4H)-ones efficiently and cost-effectively through a multicomponent reaction using NaCl as an eco-friendly and inexpensive catalyst.



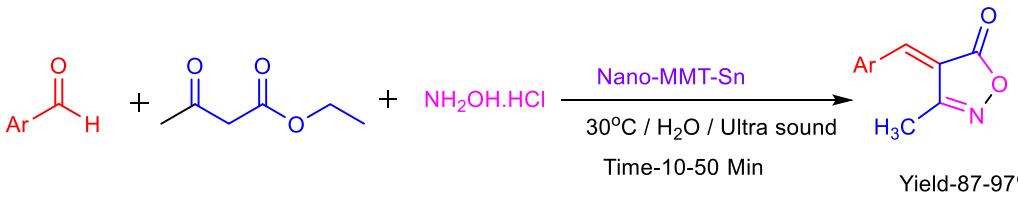
Scheme 13. Practical robust approach for the production of substituted isoxazole-5 (4H)-one derivative through utilization of a ZnO@Fe_3O_4 core-shell nanocatalytic system.

ing hydroxylamine hydrochloride, substituted aromatic or heterocyclic aldehyde, and ethyl acetoacetate in an aqueous solution at a slightly increased temperature. The process yields a range of isoxazole derivatives with characteristics that improve their friendliness with the environment. Benefits of the method include high functional group tolerance, low cost, moderate conditions, minimal waste, safety, atom efficiency, catalyst recyclability, quick workup, and the use of water as a solvent.

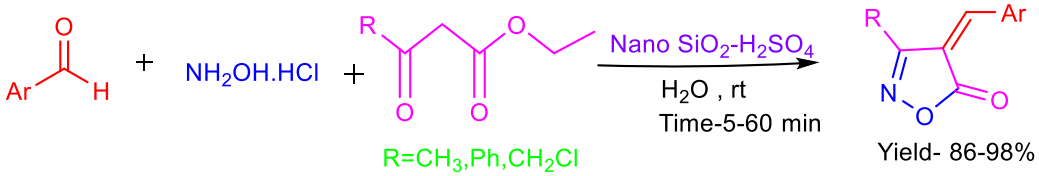
Ahmadzadeh et al. (2018) explored the utilization of Montmorillonite K10 exchanged with tin (SnII-Mont K10) via an ion exchange procedure involving $SnCl_2$ and montmorillonite K10. The analysis of SnII-Mont K10 was carried out utilizing X-ray diffraction, scanning electron microscopy, and energy-dispersive X-ray spectroscopy. The resulting catalyst was utilized for the effective synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones through a one-pot multicomponent cyclocondensation reaction involving hydroxylamine hydrochloride, ethyl acetoacetate, and benzaldehyde derivatives in water under ultrasound irradiation (Scheme 14). The yields of the products varied from 87 % to 96 %. This approach presents significant advantages, such as employing an economical and eco-friendly catalyst, attaining rapid reaction completion, eliminating the necessity for organic solvents, providing exceptional yields, and maintaining gentle reaction conditions.

Ghorbani et al. (2019) conducted a study on the nano-SiO_2-H_2SO_4 catalyzed three-component cyclo condensation involving aryl/heteroaryl aldehydes, hydroxylamine hydrochloride, and β-ketoesters for the production of α,β-unsaturated isoxazole-5 (4H)-ones in an environmentally friendly manner (Scheme 15). The reaction resulted in the formation of the respective heterocycles under ambient conditions within relatively short reaction durations. The mild reaction conditions facilitated the synthesis of numerous α,β-unsaturated isoxazole-5 (4H)-ones through this approach. Furthermore, the method enabled the generation and characterization of novel derivatives of isoxazolones. This technique proved to be effective, environmentally sound, uncomplicated, secure, and sustainable. Additionally, it was a cost-efficient process that eliminated the need for pre-treating the reactants. The three-component annulation was carried out without the utilization of external energy sources such as heat, ultrasound, or microwave radiation.

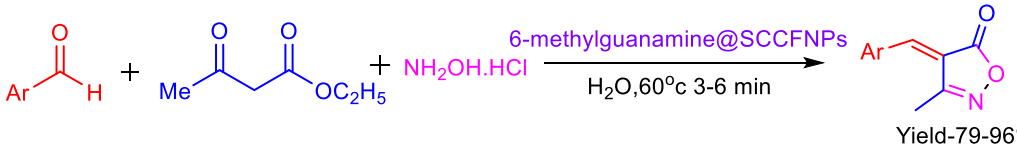
Saadati-Moshtaghin et al. (2020) have formulated a highly efficient and magnetically recoverable catalyst comprising 6-methylguanamine supported on $CoFe_2O_4$ nanoparticles for the synthesis of isoxazol-5(4H)-one derivatives (Scheme 16). The catalyst is used forsynthesis of isoxazol-



Scheme 14. An effective method for the synthesis of 3-methyl-4-arylmethylene isoxazole-5(4H)-ones utilizing SnII-Mont K10 as a catalyst in an aqueous solution with the assistance of ultrasound irradiation.



Scheme 15. Nano-SiO_2-H_2SO_4 catalysed synthesis of α,β-unsaturated isoxazole-5 (4H)-ones under green conditions.



Scheme 16. Synthesis of isoxazol-5(4H)-one derivative employing a highly efficient and magnetically retrievable catalyst composed of 6-methylguanamine immobilized on $CoFe_2O_4$ nanoparticles.

5(4H)-one derivativesThe characterization of this catalyst was carried out using a range of physicochemical methods, such as field emission scanning electron microscopy (FE-SEM), X-ray powder diffraction (XRD), and Fourier transform infrared spectroscopy (FT-IR). The catalyst's reusability was assessed through five successive reaction cycles. The methodology offers several advantages, including rapid workup, high product yields, short reaction durations, and the elimination of the necessity for organic solvents.

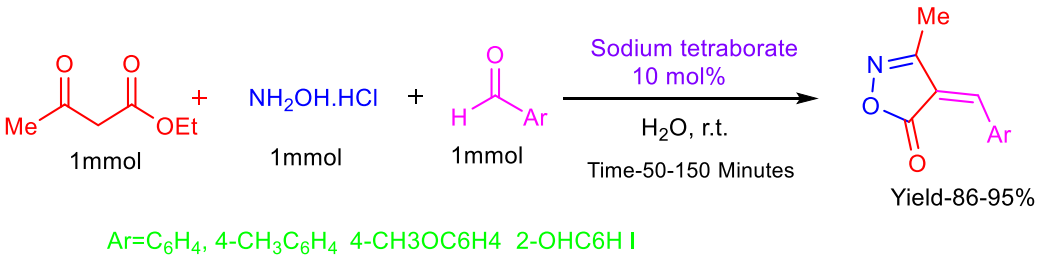
3.2 Inorganic heterogenous catalysts

Kiyani et al. (2013) introduced a methodology involving the utilization of sodium tetraborate as a catalyst in a one-pot, three-component condensation reaction aimed at the synthesis of aryl methylidene-isoxazole-5(4H)-ones through the employment of aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride under ambient conditions (Scheme 17). This particular reaction methodology presents various advantages, such as the provision of mild reaction conditions, facile work-up procedures, reduced reaction durations, enhanced safety measures, catalyst recyclability, and the utilization of water as a benign solvent. It has been ascertained that sodium tetraborate serves as an efficient and recyclable catalyst when operated under aqueous conditions at room temperature. The protocol's noteworthy merits encompass the exclusion of conventional organic solvents, heightened safety measures, adherence to principles of green chemistry, eco-friendliness, and straightforward product isolation techniques.

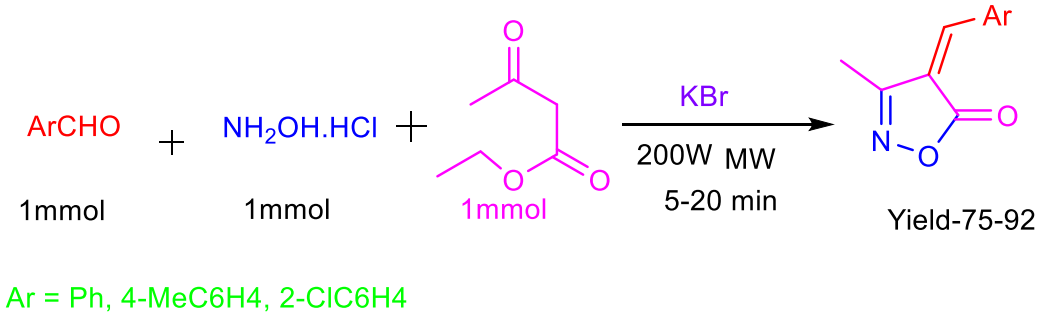
Kulkarni et al. (2021) devised a method for the one-pot three-component synthesis of 3-methyl-4-aryl methyl isoxazol-5 (4H)-ones utilizing microwave radiation in the absence of solvents, with potassium bromide acting as a catalyst (Scheme 18). This methodology resulted in the generation of compounds characterized by swift reaction kinetics, facile work-up procedures, and high yields. Due to its well-defined reaction mechanism and uncomplicated execution, this technique provides a straightforward and efficient approach for the production of this class of compounds. The process boasts various advantages, such as high yields, rapid reaction times, the elimination of hazardous chemicals and solvents, cost-effective and readily available catalysts, the utilization of non-traditional energy sources, and an environmentally friendly methodology.

Kiyani et al. (2013) reported a one-pot, three-component reaction involving aryl aldehydes, hydroxylamine hydrochloride, and either ethyl 3-oxobutanoate, ethyl 4-chloro-3-oxobutanoate, or ethyl 3-oxo-3-phenylpropanoate in the presence of boric acid (H_3BO_3) in water (Scheme 19). A mixture of equimolar quantities of hydroxylamine hydrochloride (0.07 g, 1 mmol) and a β-ketoester (0.130 g, 1 mmol) was stirred in 5 mL of water for 5 minutes. Then, aryl aldehyde (1 mmol) and 10 mol % boric acid were added, and the reaction mixture was stirred at room temperature for the specified time. This approach offers high yields, quick reaction times, ease of work-up, cleanliness, efficiency, and environmental friendliness.

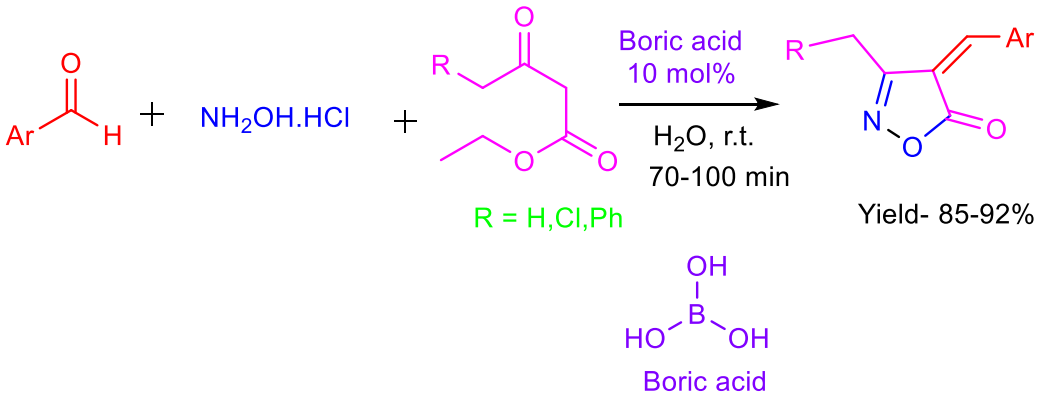
Badiger et al. (2022) presented a protocol detailing a multicomponent reaction aimed at synthesizing 3-methyl-4-(hetero) aryl methylene isoxazole-5(4H)-ones. This reaction involves the condensation of hydroxylamine hydrochloride, ethyl acetoacetate, and various substituted aromatic and heteroaromatic aldehydes, catalyzed by an agro-waste-based solvent medium within an oil bath set at 60 °C (Scheme 20). The resulting product exhibited notable anticancer properties and displayed interesting electrochemical behavior. No-



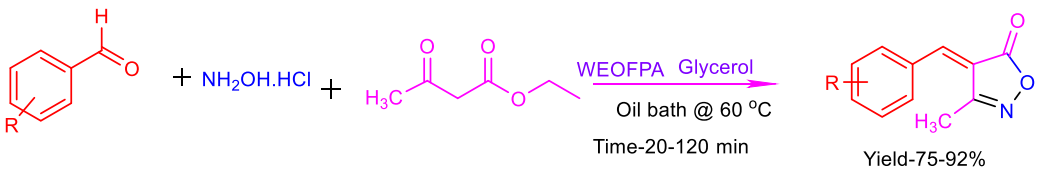
Scheme 17. A one-pot, three-component condensation reaction catalyzed by sodium tetraborate was employed for the production of aryl methylidene-isoxazole-5 (4H)-ones.



Scheme 18. One-pot three-component synthesis of 3-methyl-4-aryl methyl isoxazole-5(4H)-ones using microwave radiation under solvent-free conditions with potassium bromide as a catalyst.



Scheme 19. Synthesis of 4-arylmethylene-3-methylisoxazol-5(4H)-one derivative in the presence of boric acid, H_3BO_3, in water.



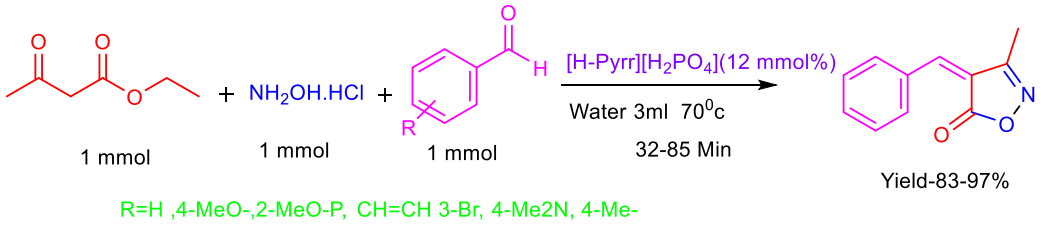
Scheme 20. Synthesis of 3-methyl-4-(hetero) aryl methylene isoxazole-5(4H)-ones Using WEOFPA as a catalyst.

tably, this methodology offers numerous advantages, including its benign and eco-friendly nature, efficiency, avoidance of hazardous solvents, cost-effectiveness, and the ability to yield isoxazole derivatives in the range of 86–92 %.

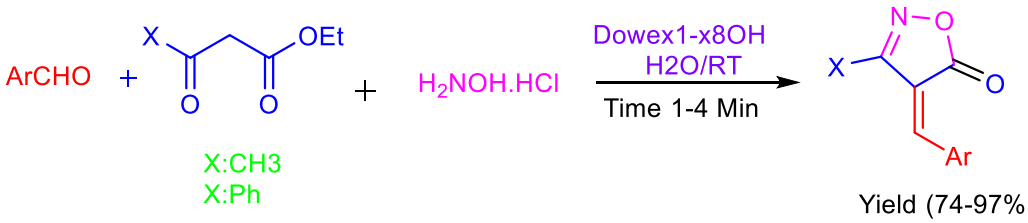
Asadi et al. (2021) presented a sustainable and environmentally friendly approach to produce 3-methyl-4-arylmethylene-isoxazole-5(4H)-one derivative under mild conditions using an innovative phosphoric acid-based molten salt as a catalyst (Scheme 21). The phosphoric acid-based molten salt, known as pyrrolidinium dihydrogen phosphate ([H-Pyrr][H_2PO_4]), was derived from cost-effective, readily available starting materials through a simple procedure and characterized using FT-IR and NMR techniques. This molten salt was utilized as a reusable and efficient catalyst in the synthesis of biologically active 3-methyl-4-arylmethylene-isoxazole-5(4H)-one derivative. The benefits of this approach include the utilization of environmentally friendly solvents and reagents, straightforward catalyst preparation, high yields of products, short reaction durations, catalyst recyclability, and cost efficiency.

Setamdideh et al. (2016) reported a one-pot, three-component synthesis of 3-methylisoxazol-5(4H)-ones using Dowex1-x8OH as a catalyst (Scheme 22). The reactions had appropriate durations (one to five hours) and achieved high yields (90–95 %). This method is user-friendly and environmentally friendly. The new protocol is appealing for synthesizing isoxazol-5(4H)-ones due to its high efficiency, shorter reaction times, simple work-up, mild conditions, catalyst reusability, and the use of water as a green solvent.

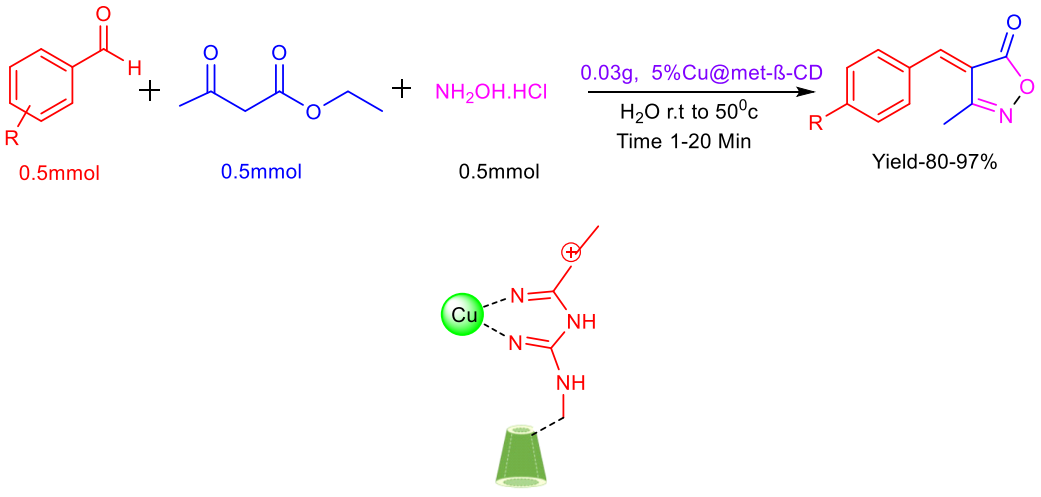
Tajbakhsh et al. (2022) introduced a novel and efficient method for the synthesis of 3-methyl-4-arylmethyleneisoxazol-5(4H)-ones via a three-component reaction involving aromatic aldehydes, ethyl acetoacetate, and hydroxylamine hydrochloride, catalyzed by Cu@Met-β-CD as a benign catalyst (Scheme 23). This catalyst, com-



Scheme 21. Eco-friendly and sustainable synthesis of 3-methyl-4-arylmethylene-isoxazole-5(4H)-one derivative under mild conditions using an innovative phosphoric acid-based molten salt as a catalyst.



Scheme 22. One pot three component synthesis of 3-methylisoxazol-5(4H)-ones using Dowex1-x8OH as catalyst.



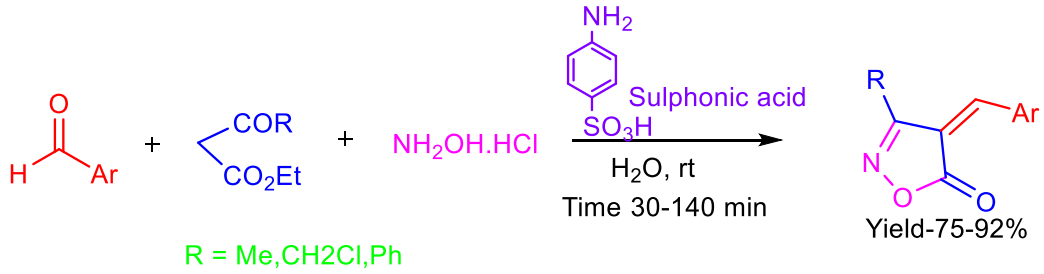
Scheme 23. Novel and efficient method for the synthesis of 3-methyl-arylmethyleneisoxazol-5(4H)-ones by Cu@Met-β-CD as a benign catalyst.

mercially available and affordable, possesses supramolecular properties, was biodegradable, and can be reused multiple times. The key benefits of this approach include its straightforward procedure, avoidance of column chromatography during workup, yielding products ranging from good to excellent, swift reaction times, and the use of environmentally safe solvents. Overall, it represents an eco-friendly synthetic process.

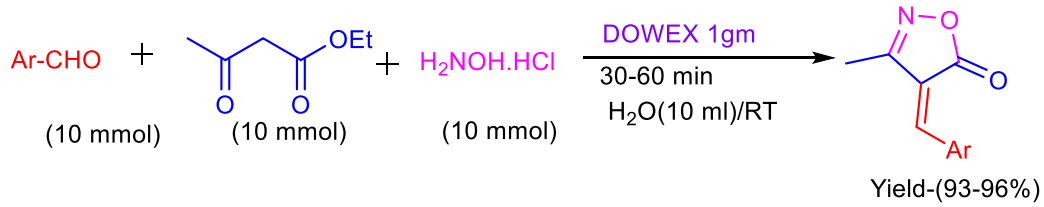
Kiyani et al. (2018) described a sulfonic acid-catalyzed multicomponent cyclocondensation reaction involving aromatic/hetero-aromatic aldehydes, hydroxylamine hydrochloride, and ethyl acetoacetate, ethyl 4-chloroacetoacetate, or ethyl benzoylacetate (Scheme 24). The reactions were conducted in water as an environmentally friendly solvent at room temperature. The resulting heterocyclic products were isolated through simple filtration and water washing. The solvent was subsequently evaporated from the filtrate to facilitate catalyst recycling. This method offers a straightforward, green, clean, and eco-friendly approach for synthesizing 4-arylidene-3-substituted isoxazole-5(4H)-ones and does not require heating, microwave, or ultrasound irradiation.

Setamdideh et al. (2015) developed a synthesis of 3-methyl-4-arylmethyleneisoxazol-5(4H)-ones using DOWEX®50WX4 as the catalyst. The products have quick reaction times (30–60 minutes) and good yields (93–96 %) (Scheme 25). This innovative protocol, which is distinguished by a clear reaction profile and simple operation, provides a simple and effective method for the synthesis of this family of molecules. This approach is interesting for the synthesis of these heterocycles because of its high efficiency, short reaction durations, ease of work-up, mild reaction conditions, reusable catalyst, and use of water as a green solvent.

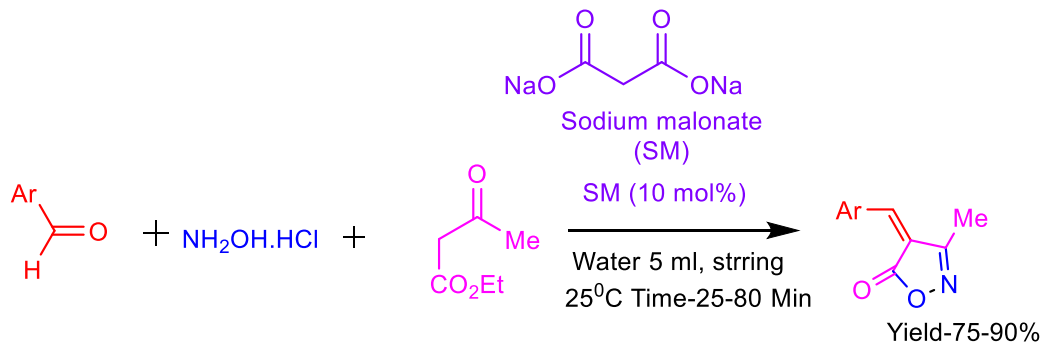
Gharehassanlou et al. (2022) developed a three-component cyclocondensation method for synthesizing isoxazol-5(4H)-ones from various aryl/heteroaryl aldehydes, hydroxylamine hydrochloride, and either ethyl acetoacetate or ethyl 4-chloro-3-oxobutanoate, using sodium malonate as an efficient catalyst (Scheme 26). This reaction was carried out in water as a sustainable reaction medium at 25 °C. Optimization of the reaction conditions revealed that the best results were obtained in an aqueous medium at room temperature with 10 mol % of the catalyst. This procedure offers several advantages, including reduced reaction times, easy isolation of pure products, avoidance of hazardous organic



Scheme 24. Sulphonic acid catalysed green synthesis 4-arylidene-3-substituted isoxazole5(4H)-ones.



Scheme 25. Multicomponent synthesis of 3-methyl-4-arylmethyleneisoxazol-5(4H)-ones using DOWEX®50WX4 as the catalyst.

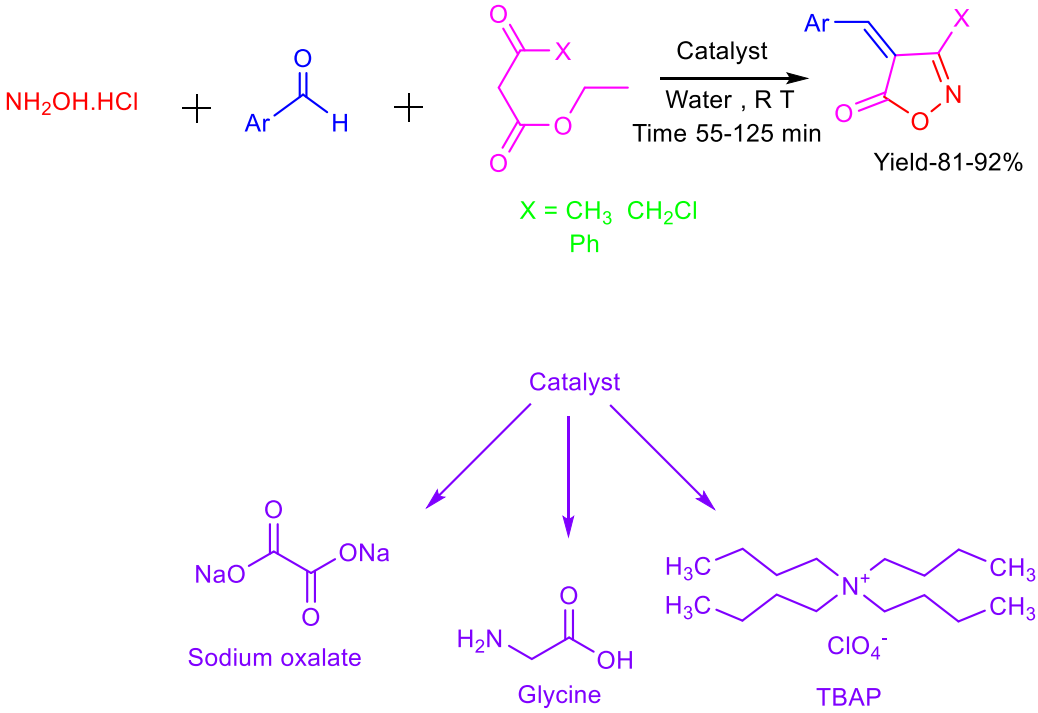


Scheme 26. Utilizing sodium malonate as a catalyst in a three-component cyclocondensation method for the synthesis of isoxazol-5(4H)-ones.

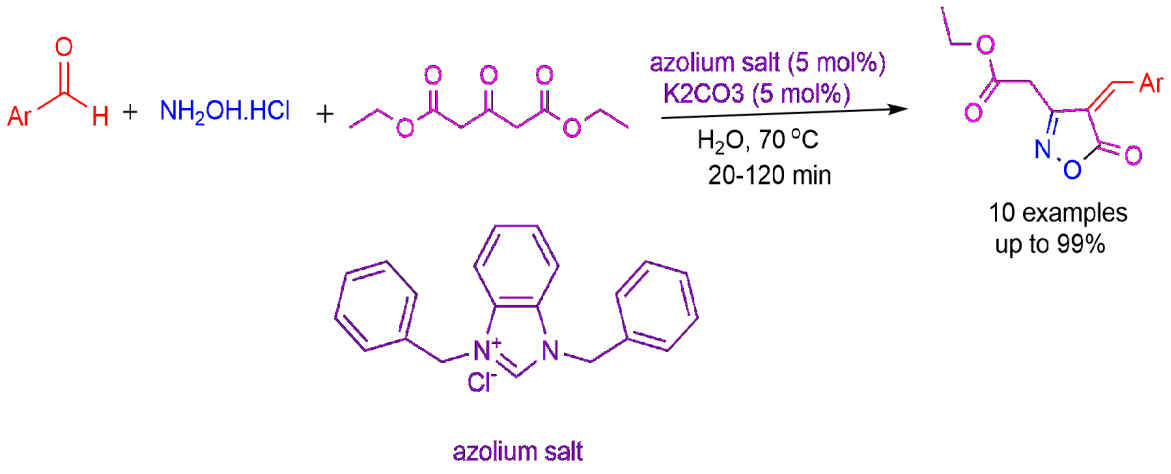
solvents, simplicity in experimental procedures, operational ease, and environmental friendliness.

Jabbari et al. (2014) reported a cyclocondensation procedure involving hydroxylamine hydrochloride, various aryl aldehydes, and β-oxoesters to synthesize multiple derivatives of 3,4-disubstituted isoxazol-5(4H)-ones (Scheme 27). This process was conducted at room temperature using water as the solvent and was catalyzed by glycine, sodium oxalate, and tetrabutylammonium perchlorate (TBAP). This method offers several advantages, including effectiveness, simplicity, environmental friendliness, easy setup, high yields, recyclability, avoidance of organic solvents, and relatively quick reaction times.

Delfani et al. (2022) demonstrated an efficient one-pot method for synthesizing 4-(arylmethylene)-5-oxo-4,5-dihydroisoxazol-3-yl)acetate derivatives. This innovative procedure involves a cyclocondensation reaction using diethyl 3-oxopentanedioate, aryl or heteroaryl aldehydes, and hydroxylamine hydrochloride, catalyzed by 1,3-dibenzyl-1H-benzo[d]imidazol-3-ium chloride in water (Scheme 28). The catalyst proved highly effective, yielding ethyl-2-(4-(arylmethylene)-5-oxo-4,5-dihydroisoxazol-3-yl) acetate derivatives from readily available materials without undesired by-products. Optimal conditions were found to be 5 mol% catalyst loading and a reaction temperature of 70 °C. Water was the most effective solvent, aligning with green chemistry principles. This method offers high yields and reasonable reaction times and eliminates the need for



Scheme 27. Synthesise of derivatives 3,4-disubstituted isoxazol-5(4H)-one using glycine, sodium oxalate, and tetrabutylammonium perchlorate (TBAP) as a catalyst.



Scheme 28. Synthesis of derivatives of 4-(arylmethylene)-5-oxo-4,5-dihydroisoxazol-3-yl)acetate catalysed by an azolium salt in an aqueous medium.

column chromatography, promoting atom and step economy with clean reaction profiles.

4. Conclusion

In conclusion, the one-pot multicomponent synthesis of 3,4-disubstituted-isoxazole-5-(4H)-ones represents a rapidly evolving area of research with significant implications for synthetic organic chemistry and drug discovery. Recent advancements in catalytic systems, reaction conditions, and substrate versatility have greatly enhanced the efficiency and selectivity of these synthetic processes, making them more attractive for generating structurally diverse and biologically active compounds. Moreover, the exploration of green chemistry principles and sustainable methodologies underscores the commitment to environmentally friendly practices in chemical synthesis. The diverse biological activities exhibited by these compounds further highlight their potential as therapeutic agents, opening new avenues for pharmaceutical development. This review has synthesized the latest findings, offering a valuable resource for researchers and encouraging continued innovation in this promising field.

Authors Contributions
All authors have contributed equally to prepare the paper.

Availability of Data and Materials
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interests
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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