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Green synthesis of Isoxazole-5(4 H)-one derivatives using Theophylline Hydrogen Sulfate as a catalyst

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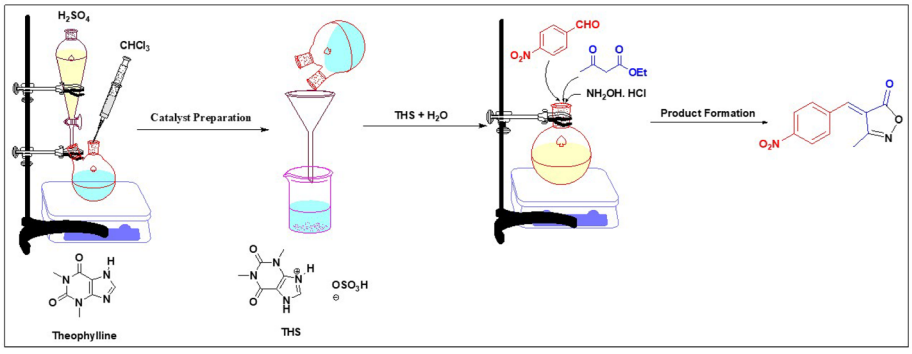
Abstract

A green and eco-friendly synthetic protocol has been established for the preparation of a series of isoxazole derivatives using Theophylline Hydrogen Sulfate (THS) as a highly efficient and reusable solid acid catalyst. In this method, aldehydes react smoothly with ethyl acetoacetate and hydroxylamine hydrochloride in aqueous medium under ambient conditions with continuous stirring. The use of water as a solvent, along with THS, not only promotes the reaction efficiently but also eliminates the need for hazardous organic solvents or harsh conditions. The protocol provides multiple advantages such as short reaction times, high to excellent product yields, operational simplicity, and easy catalyst recovery and reuse. Owing to its environmentally benign nature, low cost, and sustainability, this method represents a practical approach for the green synthesis of isoxazole derivatives and can be a promising alternative for large-scale and industrial applications.

Keywords Isoxazole-5(4*H*)-one derivatives, THS, Green catalysis, Aqueous medium, Heterocyclic synthesis

Graphical abstract



1 Introduction

The fields of chemical industries and processes have seen tremendous improvements in recent decades. These industries, however, have had a negative impact on human health, the environment, and animals. As a result, there is an increasing trend in chemical research to eliminate or reduce hazardous chemical processes. Because of this, green chemistry has become more and more well-known among chemists. Green chemistry is a collection of 12 principles that, when followed, result in ecologically beneficial and healthy processes and reactions. This method eliminates the hazards connected with harmful compounds while also lowering energy usage and increasing efficiency [1–3].

Multi-component reactions (MCRs) provide a highly efficient way of creating desired chemicals in a remarkably short duration [4–6]. They have various advantages, including shorter reaction times, higher yields, lower costs, and less waste generation. Notably, nearly all of the reactants in MCRs are actively involved in product creation, removing the need to segregate intermediates. This is consistent with green substituted chemistry principles, reduces energy usage, and maximizes efficiency [7–9].

Nitrogen-containing heterocyclic compounds are basic building blocks of many synthetic and natural biologically active substances [10–12]. A recent investigation found that at least one heterocyclic component containing nitrogen is present in over 60% of small-molecule medications authorized by the US Food and Drug Administration. Isoxazoles possess a broad range of biological activity and distinctive physicochemical characteristics, making them valuable in medicine, agriculture, and technology, as well as in organic synthesis [13]. Their stability as aromatic heterocycles, primarily due to a weak oxygen-nitrogen bond, allows for modification without opening the five-membered heterocyclic ring. While maintaining their cyclic structure, isoxazoles can sometimes be transformed into functionalized acyclic compounds, further enhancing their versatility in various applications. Some natural sources like Amanita muscaria and legume seeds also contain the isoxazole ring [14]. Isoxazole and its derivatives are a noteworthy class of compounds because they have a heterocyclic structure that includes both nitrogen and oxygen. Synthesis of Isoxazole derivatives using methods such as cycloaddition, cyclomerization, condensation, and functionalization. Numerous fields, including organic synthesis, medicinal chemistry, the pharmaceutical industry, optoelectronic device development, and light-conversion molecular systems, find wide uses for them [15] and some finding application in agrochemical compounds. To illustrate, the isoxazole structure is present in merocyanine dyes used in optical recording, nonlinear optical research, and certain liquid crystalline materials [16–18] Additionally, isoxazole compounds possess diverse biological properties, including anti-obesity [19], anti-inflammatory [20], Antifungal [21], anticancer [22], antitumor [23], antibacterial [24], anticonvulsant [25], and anti-HIV [26] activities (Fig. 1).

Breast cancer ranks as the second leading cause of death among women. While several FDA-approved drugs exist for its treatment, they often encounter challenges such as drug resistance, toxicity, and selectivity issues. Additionally, alternative therapies like hormonal therapy, surgery, radiotherapy, and immune therapy, although utilized, often come with side effects including bioavailability concerns, lack of selectivity, and pharmacokinetic-pharmacodynamic complications. Consequently, there's a pressing demand for the development of new compounds that are both non-toxic and more efficient in cancer treatment. In recent years, isoxazole derivatives have garnered attention due

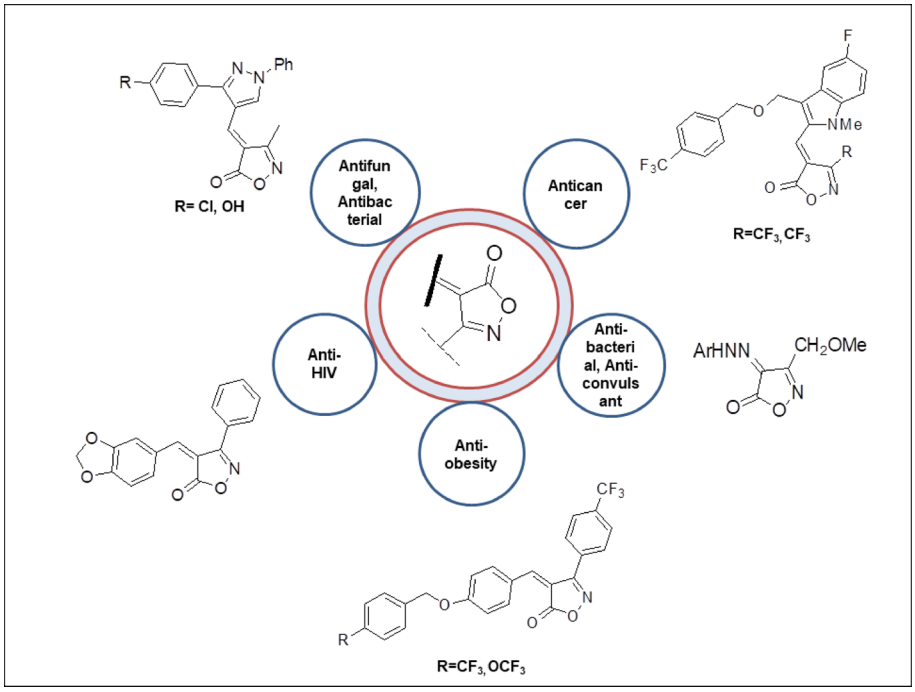


Fig. 1 Biological scaffolds of Isoxazole-5(4 H)-ones

to their promising anticancer properties with minimal side effects. These derivatives exhibit anticancer activity through various mechanisms, including apoptosis induction, aromatase inhibition, disruption of tubulin assembly, topoisomerase inhibition, HDAC inhibition, and ERa inhibition [27].

The arrangement of oxygen and nitrogen atoms in the isoxazole moiety, with a low bond dissociation energy, renders it weakly basic and susceptible to breaking, particularly under conditions like photolysis or thermolysis due to the fragility of the nitrogen-oxygen bond. Chemically, the isoxazole moiety can undergo electrophilic aromatic substitution at the 4-position and nucleophilic aromatic substitution at the 3 and 5 positions of the isoxazole ring. Additionally, deprotonation of the isoxazole moiety may initiate ring-opening reactions, leading to further substitution, which can enhance therapeutic activity. Isoxazole derivatives, forming a distinctive and unified class of compounds, showcase antibiotic, antiproliferative, and antiviral properties, and also serve as modulators of nicotinic receptors. Using 3,5-diarylsubstituted isoxazoles to create novel drug-like compounds and assessing their biological effects against various cancer cell lines, as well as an immortalized normal prostate epithelial cell [28].

Several catalysts were employed to synthesize Isoxazole molecule such as Ag, Ce@SNC/A1SCA [29], Triphenylphosphine [30], Natural deep eutectic solvents (NaDESs) [31], Eucalyptol [32], Natural sunlight [33], GO@Fe$(ClO_4)_3$ [34], WEOFPA/glycerol [35], Lipase [36], Citrazinic acid [37], Vitamin B1 [38], Nano-MgO [39], Boric acid [40], Imidazole [41], Fe_3O_4@C-SO_3H [42], Phthalimide-N-oxyl salts [43], Cu/TCH-pr@SBA-15 [44], Ag/SiO2 [45], Sodium malonate [46]. Although the mentioned protocols have produced positive results in many cases, they have a number of drawbacks. These include the use of costly catalysts or reagents, lengthy reaction periods, complex workup processes, severe reaction conditions, the reliance on metal catalysts, the requirement for large amounts of catalyst or specialized equipment, and the use of poisonous organic

solvents. Therefore, a highly effective, eco-friendly, simplified, applicable, and high-yielding method for synthesizing different isoxazole-5(4*H*)-ones scaffolds needs to be investigated.

As a result, the use of solid acid catalysts is a feasible alternative to traditional and severe liquid acids such as nitric acid, hydrochloric acid, and sulfuric acid, which cannot be used in stoichiometric amounts [47]. The ease of separating the catalyst from the product is a vital consideration for chemists, and solid acid catalysts facilitate this separation, making them much applicable in diverse reactions. Notable benefits of solid acid catalysts include low toxicity, readily available precursors, high stability and good selectivity, use in low-energy synthesis processes for a variety of organic transformations, and economic and commercial viability [48]. Isoxazole derivatives exhibit a broad range of therapeutic effects, including anti-cancer, antiviral, antimicrobial, and anti-inflammatory properties. Within the isoxazole structure, oxygen and nitrogen atoms are arranged in a 1:2 ratio, with relatively low bond dissociation energies: nitrogen-nitrogen (N-N) bond energy is 945.4 kJ/mol ^{1}, nitrogen-oxygen (N-O) bond energy is 630.7 kJ/mol ^{1}, and carbon-oxygen (C-O) bond energy is 1076.4 kJ/mol 1 [49].

Theophylline Hydrogen Sulfate (THS) is a solid acid catalyst derived from the naturally occurring xanthine alkaloid, theophylline. It is highly efficient, reusable, and environmentally friendly, making it an attractive catalyst for green organic synthesis. THS promotes various organic transformations under mild reaction conditions, often in aqueous media, minimizing the need for toxic solvents. Its solid nature facilitates easy recovery and reuse, contributing to sustainable chemistry practices. These properties, along with its high catalytic activity, make THS an ideal choice for the synthesis of heterocyclic compounds, including isoxazole derivatives.

We have introduced a successful and appropriate procedure for producing Isoxazole-5(4*H*)-ones derivatives by considering the previously mentioned details on synthetic techniques and catalysts, and our purpose to creating environmentally friendly synthetic approaches,. This involves the reaction of different aldehydes, ethyl aceto-acetate and hydroxyl amine hydrochloride using THS as a sustainable solid acid catalyst. (Fig. 2)

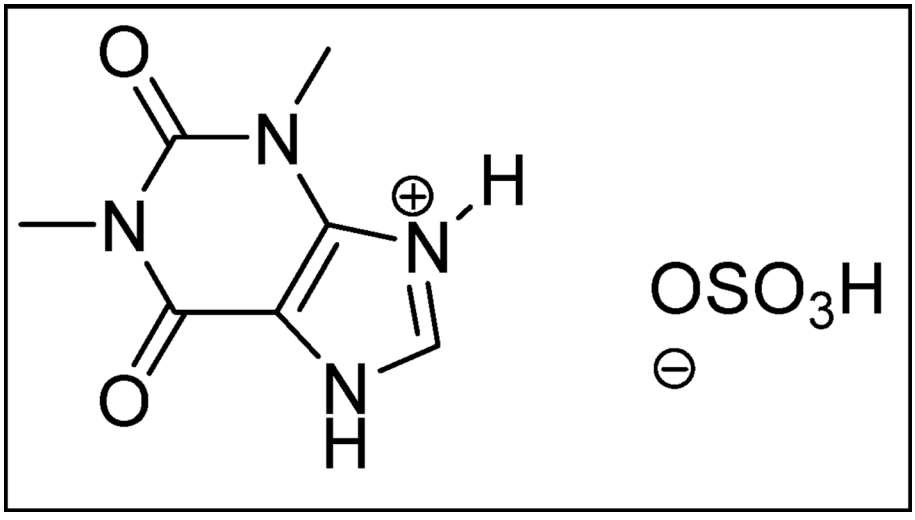


Fig. 2 Theophylline Hydrogen Sulphate (THS) catalyst's structure

2 Experimental

2.1 General

The chemical firms Loba and Sigma-Aldrich provided all of the compounds, which were utilised without further purification. Water that had been double-distilled was used as the aqueous medium. Using melting/boiling point equipment (Eq. 730 A-EQUIPTRONICS), melting points were determined to be incorrect. The ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, using a Bruker or JEOL spectrometer. Electrospray ionization (ESI) was used using a Waters Synapt G2 to record high-resolution mass spectra.

2.2 General procedure for the synthesis of THS

A mixture of 50 ml of chloroform and 10 mmol of theophylline was stirred at R.T. for fifteen minutes in a clean, and dry round-bottom flask. The mixture was then gradually mixed with 10 mmol of sulfuric acid. For two more hours, the reaction stirred continuously. After filtering, the resultant precipitate underwent several acetone leaching procedures to eliminate any remaining sulfuric acid [50, 51]. Ultimately, the white powder that was produced was dried for two hours in an oven. The spectrum data for the synthesized catalyst are included in the supplemental section.

2.3 General procedure for the synthesis of Isoxazole-5(4 H)-ones

A mixture containing aldehyde (1 mmol), ethyl aceto-acetate (1 mmol), hydroxyl amine hydrochloride (1 mmol), and 10 mol% THS in 5 ml double-distilled water was subjected to stirring using a magnetic stirrer at R.T. Within 25 min, the crude product was obtained. The progress of the reaction was monitored by Thin Layer Chromatography (TLC) in n-hexane: ethyl acetate (7:3). The solid product was isolated through simple filtration with water washings. The separated solid product underwent recrystallization using ethanol and was subsequently characterized through Nuclear Magnetic Resonance (NMR), and High-Resolution Mass Spectrometry (HRMS).

2.4 Spectral data of THS catalyst

THS: White Solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.46 (s, 3 H), 3.65 (s, 3 H), 7.52 (s, 1H), 7.78 (broad, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 28.60, 30.14, 105.76, 139.69, 149.32, 152.83, 153.68.

2.5 Spectroscopic data for some target compounds are as follows

1. *3-methyl-4-(4-methoxybenzylidene)isoxazol-5(4H)-one (Table 1, entry 12)*
   Yellow Solid, m.p. 176 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.28 (s, 3 H), 3.92 (s, 3 H), 7.00-7.02 (d, 2 H), 7.34 (s, 1H), 8.43–8.45 (d, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.67, 55.73, 114.67, 116.37, 125.84, 136.98, 149.35, 161.30, 164.63, 168.79; HRMS: 218.0817 (M + 1).
2. *3-methyl-4-(4-(dimethylaminobenzylidene)isoxazol-5(4H)-one (Table 1, entry 3)*
   Red Solid, m.p. 206 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.24 (s, 3 H), 3.16 (s, 6 H), 6.70–6.73 (d, 2 H), 7.21 (s, 1H), 8.39–8.41 (d, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.73, 40.12, 111.25, 111.53, 121.55, 137.62, 149.24, 154.25, 161.57, 170.12; HRMS: 231.1133 (M + 1).

3. *3-methyl-4-(4-nitrobenzylidene)isoxazol-5(4H)-one (Table 1, entry 2)*
   Yellow Solid, m.p. 142 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.36 (s, 3 H), 7.48–7.51 (d, 4 H), 10.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 123.71, 124.08, 124.35, 127.68, 130.53, 131.63, 133.99, 138.19, 148.37.
4. *3-methyl-4-(3,4,5-trimethoxybenzylidene)isoxazol-5(4H)-one (Table 1, entry 6)*
   Yellow solid, m.p. 128 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.30 (s, 3 H), 3.96 (s, 6 H), 4.00 (s, 3 H), 6.82 (s, 1H), 7.27 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.69, 56.42, 61.22, 1.4.09, 111.80, 118.00, 127.73, 143.87, 149.82, 152.92, 153.50, 161.19, 168.58.
5. *3-methyl-4-(4-chlorobenzylidene)isoxazol-5(4H)-one (Table 1, entry 5)*
   Bright yellow solid, m.p. 134 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.498 (s, 3 H), 6.915–6.921 (d, 2 H), 7.548 (s, 1H), 8.199–8.202 (d, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.76, 115.98, 116.87, 119.66, 120.01, 125.23, 132.46, 137.38, 145.60, 160.12, 163.01.
6. *3-methyl-4-(2-hydroxybenzylidene)isoxazol-5(4H)-one (Table 1, entry 7)*
   Light yellow, m.p. 196 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.216 (s, 3 H), 6.901–6.913 (m, 2 H), 7.541–7.563 (m, 1H), 7.991 (s, 1H), 8.734–8.749 (d, 1H), 9.983 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.72, 116.73, 116.98, 119.63, 119.99, 133.78, 138.20, 144.53, 160.21, 163.53, 168.51.
7. *3-methyl-4-benzylideneisoxazol-5(4H)-one (Table 1, entry 1)*
   Yellow Solid, m.p. 196 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.25 (s, 3 H), 7.52–7.55 (t, 2 H), 7.60–7.64 (t, 1H), 7.98 (s, 1H), 8.34–8.39 (d, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.70, 118.30, 128.98, 132.98, 133.95, 134.25, 151.99, 152.53, 168.21.
8. *3-methyl-4-(4-fluorobenzylidene)isoxazol-5(4H)-one (Table 1, entry 4)*
   Pale yallow Solid, m.p. 137 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.09 (s, 3 H), 7.64 (d, 2 H), 7.92 (s, 1H), 8.41 (d, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11, 128,134, 133, 164.6, 168.3.
9. *3-methyl-4-(2-nitrobenzylidene)isoxazol-5(4H)-one (Table 1, entry 8)*
   Yellow Solid, m.p. 137 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.209 (s, 3 H), 6.899–6.904 (m, 2 H), 7.540–7.561 (m, 1H), 7.956 (s, 1H), 8.726–8.732 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.68, 116.70, 116.90, 119.59, 119.98, 133.68, 138.25, 144.56, 160.25, 163.65, 168.58.
10. *3-methyl-4-(3-methoxy, 4-hydroxybenzylidene)isoxazol-5(4H)-one (Table 1, entry 9)*
    Orange Solid, m.p. 212 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.231 (s, 3 H), 3.836 (s, 3 H), 6.951 (s, 1H), 7.565–7.861 (m, 2 H), 8.499 (s, 1H), 10.432 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.69, 55.99, 114.15, 116.30, 117.15, 125.59, 132.48, 147.68, 152.25, 154.26, 162.75, 169.45.
11. *3-methyl-4-(3, 4-dihydroxybenzylidene)isoxazol-5(4H)-one (Table 1, entry 10)*
    Yellow solid, m.p. 210 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.41 (s, 3 H), 6.85 (d, 1H), 7.46 (d, 1H), 7.66 (s, 1H), 7.70 (s, 1H), 8.16 (s, 1H), 8.70 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.6, 114.8, 115.8, 126.4, 127.3, 128.7, 136.9, 145.8, 146.3, 158.2, 168.7.
12. *3-methyl-4-(2-hydroxynaphthalene-1-ylbenzylidene)isoxazol-5(4H)-one (Table 1, entry 11)*
    Yellow solid, m.p. 196 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3 H), 7.54–7.67 (m, 3 H), 8.05 (d, 1H), 8.17 (d, 1H), 8.27 (d, 1H), 8.44 (d, 1H), 8.66 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 11.5, 121.4, 124.8, 124.40, 126.8, 127.9, 128.15, 130.80, 131.44, 132.89, 149.1, 159.8, 161.8, 167.9, 169.1.

Table 1 Derivatives of Isoxazole-5(*4H*)-ones in THS

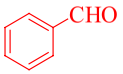
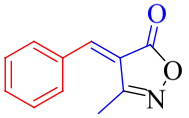
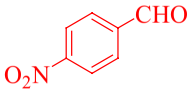
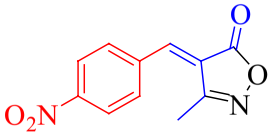
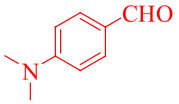
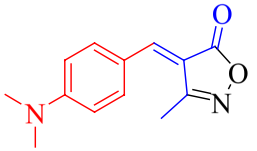
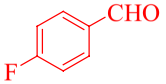
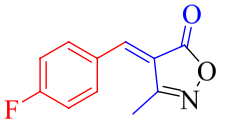
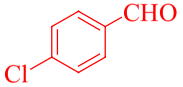
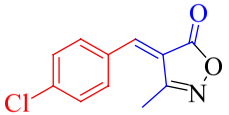
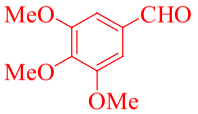
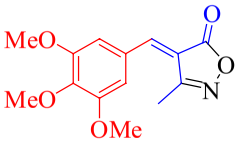
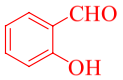
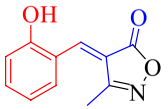
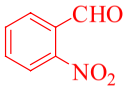
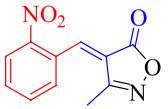
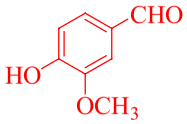
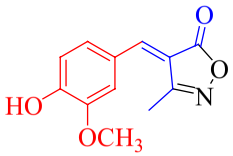
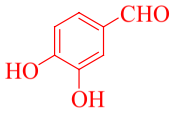
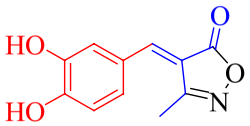
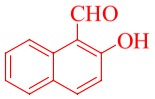
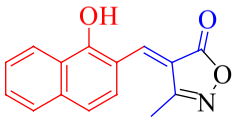
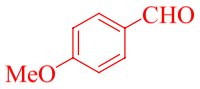
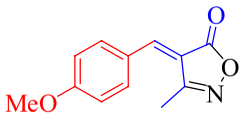
Entry	Aldehyde (1 mmol)	Product	M.*P* (Obs.)^{0}C	M.*P* (Theo.)^{0}C	Yield %
1			96 145–146	141–143 [52]	92
2			140–142	142–144 [53]	
3			204–206	206–209 [54]	90
4			136–137	139 [55]	86
5			132–134	135–136 [56]	88
6			126–128	128–130 [26]	82

Table 1 (continued)

Entry	Aldehyde (1 mmol)	Product	M.*P* (Obs.)^{0}C	M.*P* (Theo.)^{0}C	Yield %
7			194–196	196–198 [57]	84
8			136–137	138–140 [22]	85
9			210–212	212–214 [58]	83
10			209–210	211–212 [59]	91
11			195–196	198–200 [21]	88
12			175–176	178–179 [61]	94

Reaction Condition: Aldehyde (1mmol), Ethyl aceto acetate (1mmol), Hydroxylamine hydrochloride (1mmol), H_2O (5 ml), THS (10 mol%), R.T.

3 Result and discussion

THS is a solid acid catalyst exhibiting high solubility in water and insolubility in organic solvents, reflecting its ionic nature [50]. Its aqueous solubility makes it particularly suitable for the synthesis of Isoxazole-5(4 H)-one derivatives, which are obtained in high yields under these conditions. THS was chosen due to the well-established advantages of solid acid catalysts in one-pot multicomponent reactions. The synthesized derivatives were characterized by standard spectroscopic techniques.

To synthesize Isoxazole-5(4 H)-one derivatives, substituted aldehydes, ethyl acetoacetate, hydroxylamine hydrochloride, and THS were reacted in aqueous medium. Under optimized conditions (10 mol% THS, R.T., 25 min), the products were obtained in high to excellent yields (Scheme 1).

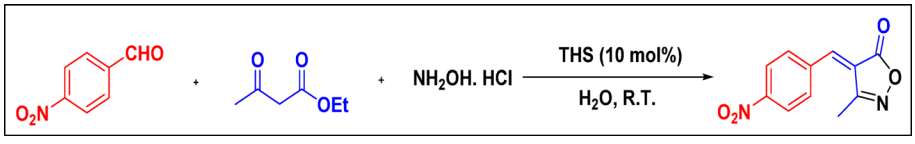
After that, we used the optimized conditions to perform the condensation reaction of aromatic aldehydes containing both electron-donating and electron-withdrawing groups for the synthesis of isoxazole-5(4 H)-ones, using 10 mol% THS in an aqueous medium at R.T. (Table 1).

The proposed mechanism for the synthesis of Isoxazole-5(4 H)-ones is presented in Fig. 3 The reaction begins with the activation of the carbonyl group of ethyl acetoacetate (A) by the Theophylline Hydrogen Sulfate (THS) catalyst, enhancing its electrophilicity (B). This activated species reacts with hydroxylamine to form intermediate (C), which further undergoes condensation with the activated aldehyde via a Knoevenagel reaction to give intermediate (H). Subsequent intramolecular cyclization followed by elimination of ethanol affords the target isoxazole-5(4 H)-one derivative (K). The THS catalyst thus plays a dual role, both in facilitating carbonyl activation and in promoting condensation and cyclization, leading to efficient product formation.

The primary objective of this investigation was to explore the catalytic efficiency for generating Isoxazole-5(4 H)-ones. The model reaction selected involved the interaction of aldehyde with ethyl aceto-acetate and hydroxyl amine hydrochloride (refer to Table 2). After 5 h. of reflux and R.T. stirring of the reaction mixture in water, a trace quantity of product had been generated (Table 2, Entries 1, 2). However, employing 5 mol% THS at R.T. in water and also in Ethanol: Water resulted in a 76–80% yield of the desired product (Table 2, Entries 3, 4).

To optimize reaction conditions, several experiments were conducted, exploring different solvents, temperatures, and catalyst. Various solvents such as water, methanol, ethanol, ethanol: water, were examined (Table 2, Entries 5–7). Notably, the use of water as the solvent system yielded a significantly high product yield (Table 2, Entry 8). In contrast, other solvents, including ethanol: water, ethanol, methanol, provided lesser yields than Water (Table 2, Entries 1–7, and 9).

The suitability of the aqueous medium for this transformation was confirmed. Subsequently, catalyst loading at different temperatures, including R.T., and reflux, was examined. The results revealed that a 10% loading of THS was optimal for this reaction.



Scheme 1 THS mediated synthesis of Isoxazole-5(4 H)-ones

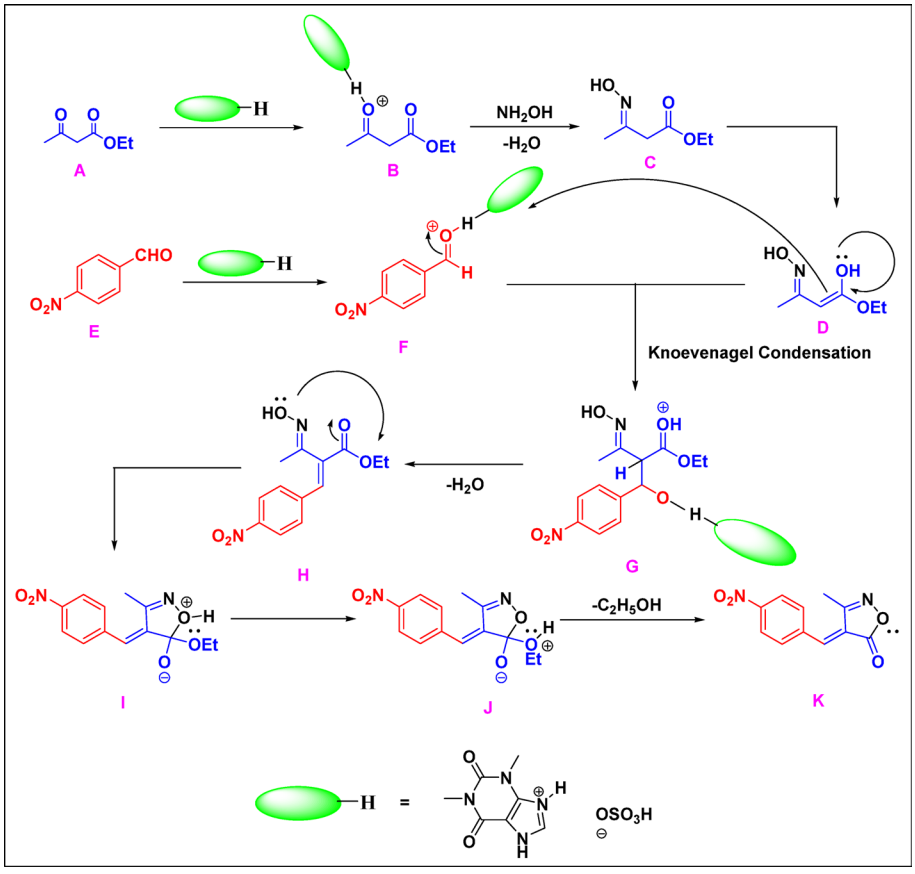
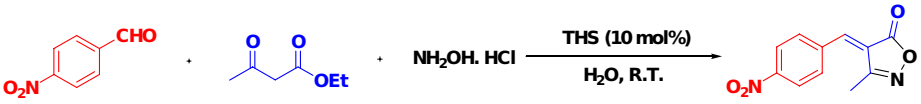


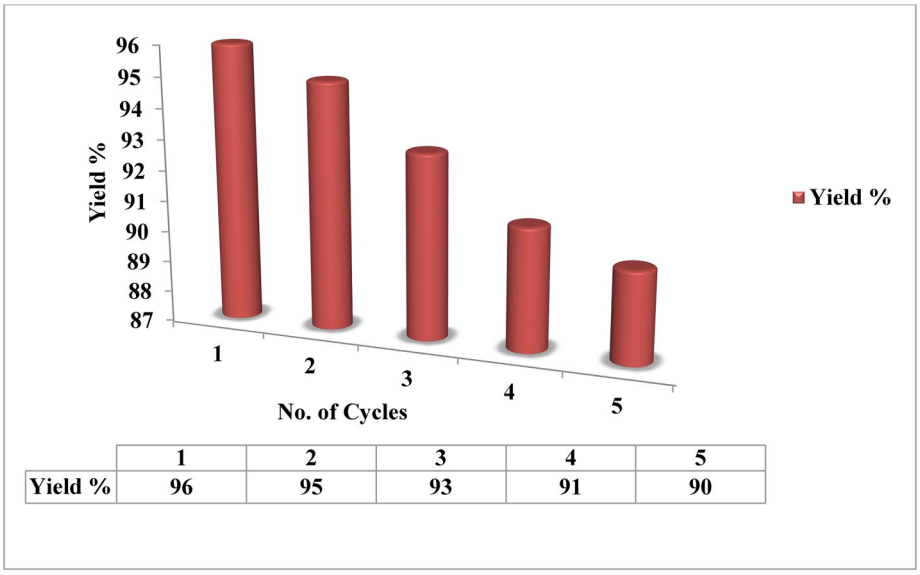
Fig. 3 A plausible reaction mechanism for the synthesis of Isoxazole-5(4 H)-ones catalyzed by Theophylline Hydrogen Sulfate (THS) in aqueous medium

Table 2 Screening of parameters for the synthesis of Isoxazole-5(4 H)-ones



Entry	THS (mol %)	Solvent/conditions	Time	Isolated yields (%)
1.	Catalyst free	Water, r. t	5 h	Trace
2.	Catalyst free	Water, reflux	5 h	Trace
3.	5 mol %	Ethanol: Water, r. t	2.8 h	76
4.	5 mol %	Water, r. t	2 h	80
5.	10 mol %	Ethanol: Water, r. t	35 min	90
6.	10 mol %	Ethanol	40 min	86
7.	10 mol %	Methanol	1 h	84
8.	**10 mol %**	**Water, r. t**	**25 min**	**96**
9.	15 mol %	Water, r. t	28 min	92

Reaction Condition: Aldehyde (1mmol), Ethyl aceto acetate (1mmol), Hydroxylamine hydrochloride (1mmol), H_2O (5 ml), THS (10 mol%),. r. t (Room temperature)



	1	2	3	4	5
Yield %	96	95	93	91	90

Fig. 4 Recyclability of Theophylline Hydrogen Sulfate (THS)

Table 3 A comparative study with reported reaction conditions

Sr. no.	Catalyst	Solvent/condition	Time (min)	Yield %	Reference
1.	Lemon Juice	H_2O: EtOH (9:1), 90 °C	50–60	90–98	[61]
2.	NH_2-MMT	H_2O, 30 °C	10–50	80–97	[62]
3.	Nano-MMT-Sn	H_2O, 30 °C	20	96	[63]
4.	Visible light	sodium acetate in aqueous ethanol, hv	5–10	56–89	[64]
5.	Antimony trichloride	H_2O, r. t	120	90	[65]
6.	PDAN-Ni@Fe_3O_4	H_2O, 50 °C	25	95	[66]
7.	Sulfated polyborate	Solvent free, 80 °C	15	90	[67]
8.	$NaHSO_4/SiO_2$	Toluene	50	94	[68]
8.	THS	H_2O, r. t	25	96	Present work

Reducing to 5 mol% or increasing to 15 mol% did not significantly enhance the product yield (Table 2, Entries 4 and 9).

3.1 Recyclability of catalyst

The recyclability of the THS catalyst was evaluated under the optimized reaction conditions. After each cycle, the catalyst was separated from the reaction mixture by simple filtration. To remove any adsorbed organic impurities, the filtrate was extracted with ethyl acetate, and the aqueous layer containing THS was concentrated for reuse [50]. As shown in Fig. 4, the catalyst could be reused for five consecutive cycles with only a slight decrease in yield (from 96% in the first cycle to 90% in the fifth cycle). This demonstrates the high stability, cost-effectiveness, and environmental friendliness of THS for isoxazole synthesis.

In this study, we have comparatively studied the impact of THS as a catalyst with previously documented catalysts in the synthesis of Isoxazole-5(4*H*)-ones derivatives, with the outcomes presented in Table 3. Moreover, Solid acid catalyst in aqueous medium, this procedure presents environmentally friendly advantages compared to methods conducted in organic solvents. This heterocycle formation reaction is favored for several reasons, including relatively shorter reaction times, higher yield, increased efficiency,

and straightforward workup procedures, strongly indicate that THS serves as a competent and sustainable acid catalyst for this methodology.

4 Conclusion

In conclusion, we have successfully developed an efficient and environmentally sustainable method for the synthesis of Isoxazole-5(4 H)-one derivatives using THS as a reusable solid acid catalyst. The catalyst not only demonstrated excellent activity and high product yields but also offered operational simplicity, as it can be easily recovered by simple filtration without the need for column chromatography. Additionally, the use of water as a reaction medium, mild conditions, and the recyclability of THS make this protocol a cost-effective and eco-friendly alternative compared to conventional methods. Therefore, this green approach has strong potential for wider application in sustainable organic synthesis and could serve as a viable strategy for large-scale industrial processes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s44371-025-00438-y.

Supplementary material 1.

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Author contributions
Nilam S. Dhane: Conceptualization and collection of information and writing the manuscript.Rohit G. Patil: Collection of information, interpretation of the result.Nilesh T. Pandit: helped to interpret the data. Surekha N. Jadhav: Collection of Information, Interpretation of the resultSamadhan P. Pawar: helped to interpret the data.Pravina B. Piste: Supervision of the research.Santosh B. Kamble: Supervision, Design and implementation of the research. Kishor V. Gaikwad: Supervision, design and implementation of the research.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent for participate
This study did not involve any experiments on humans or animals. Therefore, ethical approval was not required. Not applicable, as the study does not involve human participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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