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RESEARCH

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

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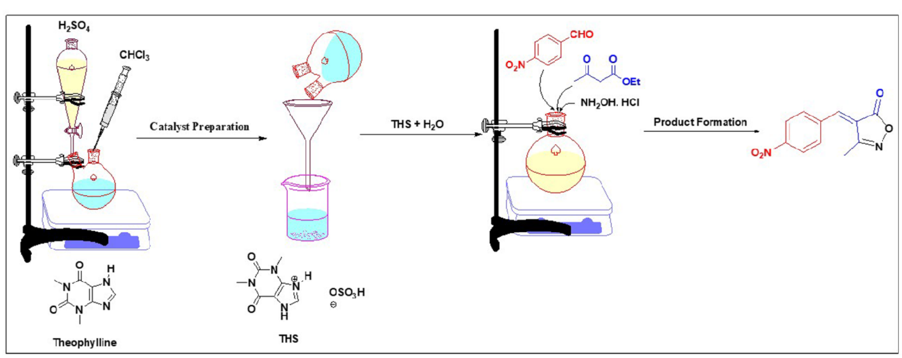
Abstract
A green and eco-friendly synthetic protocol has been established for the preparation of a series of isoxazole derivatives using Theophylline Hydrogen Sulfate (THS) as a highly efficient and reusable solid acid catalyst. In this method, aldehydes react smoothly with ethyl acetoacetate and hydroxylamine 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