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An Efficient Citric Acid Catalyzed Synthesis Of 3-(5-Phenylisoxazol-3-Yl) Pyridine From Chalcone And Hydroxylamine.

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Abstract

An efficient and environmentally benign method for the synthesis of 3-(5-phenylisoxazol-3-yl) pyridine has been developed using citric acid as a green and inexpensive catalyst. In the present study, the target heterocyclic compound was synthesized through the cyclization of 3-(3-pyridyl)-1-phenyl-2-propen-1-one (chalcone) with hydroxylamine hydrochloride under mild reaction conditions. The reaction was carried out in ethanol in the presence of a catalytic amount of citric acid, providing a simple and eco-friendly approach for the formation of the isoxazole ring. The proposed method offers several advantages such as the use of a biodegradable catalyst, mild reaction conditions, shorter reaction time, and good product yield. The synthesized compound was purified by recrystallization and characterized using standard spectroscopic techniques such as IR, ^{1}H NMR, and Mass spectrometry.

Keywords: 2-acetylpyridine, benzaldehyde, citric acid, reflux, green chemistry.

Introduction

Isoxazole derivatives constitute an important class of five-membered heterocyclic compounds containing nitrogen and oxygen atoms, which have attracted considerable attention due to their wide range of biological and pharmaceutical activities. Compounds containing the isoxazole ring system have been reported to exhibit antimicrobial, anti-inflammatory, anticancer, antiviral, and antioxidant properties, making them valuable scaffolds in medicinal chemistry[1-3]. In addition to pharmaceutical importance, isoxazole derivatives are also widely used as synthetic intermediates, agrochemicals, and functional materials[4].Several synthetic methods have been developed for the preparation of isoxazole derivatives. Among them, the cyclization of α,β-unsaturated ketones (chalcones) with hydroxylamine are one of the most convenient and widely employed strategies for the synthesis of substituted isoxazoles[5]. In this method, chalcones react with hydroxylamine to form an oxime intermediate, which subsequently undergoes intramolecular cyclization to generate the isoxazole ring. Various catalysts such as acidic reagents, metal salts, and bases have been reported to facilitate this transformation[6]. However, many of these methods suffer from certain limitations including harsh reaction conditions, toxic catalysts, long reaction times, and environmentally hazardous reagents. In recent years, increasing attention has been directed toward the development of green and sustainable synthetic methodologies that minimize environmental impact. Green chemistry emphasizes the use of environmentally benign catalysts, safer solvents, and energy-efficient processes[7]. Organic acids have emerged as attractive alternatives to conventional catalysts because of their low toxicity, biodegradability, and ease of handling. Among these, citric acid, a naturally occurring tricarboxylic acid, has gained significant importance as a green catalyst in organic synthesis due to its affordability, eco-friendliness, and catalytic efficiency in promoting various condensation and cyclization reactions[8-9]. Furthermore, the incorporation of pyridine moieties into heterocyclic systems has been shown to enhance biological and pharmacological properties of organic molecules. Pyridine-containing heterocycles are widely found in numerous biologically active compounds and pharmaceutical agents[10]. Therefore, the development of efficient synthetic strategies for pyridine-substituted isoxazole derivatives is of significant interest in heterocyclic chemistry. In view of the growing demand for environmentally friendly synthetic methods, we report herein an eco-friendly and efficient synthesis of 3-(5-phenylisoxazol-3-yl)pyridine via the cyclization of 3-(3-pyridyl)-1-phenyl-2-propen-1-one (chalcone) with hydroxylamine in the presence of citric acid as a green catalyst. The developed method provides a simple, mild, and environmentally benign approach for the construction of the isoxazole ring with good yield and operational simplicity.

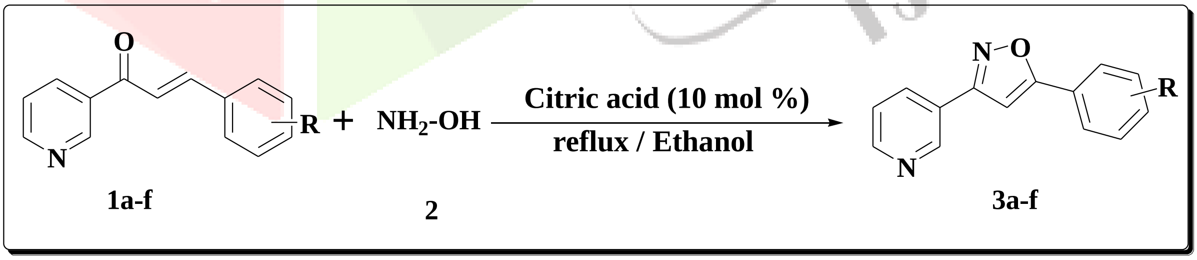
Methods and Materials

General

All of the synthetic grade reagents and chemicals were purchased from Sigma Aldrich India. They weren't further purified before being used. A Buchi melting-point B-540 device was used to record melting points in open capillaries. A Bruker instrument (400 MHz) was used to obtain ^{1}H NMR spectra, and chemical shifts are reported in δppm. High-resolution LC–MS.

General procedure for the synthesis of Isoxazole (3a-f)

In a round bottom flask **1** 3-(3-pyridyl)-1-phenyl-2-propen-1-one (1 mmol), **2** Hydroxylamine Hydrochloride (1.2 mmol) in the presence of catalytic amount of Citric acid (10 mol%) in ethanol. The reaction was refluxed at 70 to 80 °C for completion of reaction to produce 3-(5-Phenylisoxazol-3-yl) Pyridine i.e. Isoxazole (3a-f) scheme-1. The reaction mixture was monitored by TLC (ethyl acetate-hexane, 2:8). After the completion of the reaction, the reaction mixture was poured on crushed ice and filtered it. The crude product was collected and recrystallized in ethanol and dried. The entire product was characterized by physical constant and spectroscopic techniques and compared with the standard method Scheme-1.



Scheme-1

Results and Discussion

The target compound 3-(5-phenylisoxazol-3-yl)pyridine was synthesized through the cyclization reaction of 3-(3-pyridyl)-1-phenyl-2-propen-1-one (chalcone) with hydroxylamine hydrochloride in the presence of citric acid as a catalyst**.** The reaction was carried out in ethanol under reflux conditions, and the progress of the reaction was monitored by thin layer chromatography (TLC). The reaction proceeded smoothly and afforded the desired isoxazole derivative in good yield after purification by recrystallization.

Table: 1 Synthesis of Isoxazole Derivatives Using Citric Acid Catalyst

Entry	R	Reaction Time (h)	Yield (%)	Melting Point (°C)
3a	H (Phenyl)	4	85	168–170
3b	4-CH_3	4	83	172–174
3c	4-OCH_3	3.5	90	176–178
3d	4-Cl	4.5	80	182–184
3e	4-NO_2	5	82	188–190
3f	3-Br	4	75	186–188

Reaction conditions: Chalcone (1 mmol), Hydroxylamine HCl (1.2 mmol), Citric acid (10 mol%), Ethanol, Reflux**.**

Initially, the reaction was performed without a catalyst; however, only a trace amount of product was observed even after prolonged heating. The use of citric acid as a catalyst significantly enhanced the reaction rate and yield**.** Different catalyst loadings were examined to optimize the reaction conditions. It was found that 10 mol % citric acid provided the best results in terms of reaction time and product yield. Increasing the catalyst amount beyond this level did not produce a significant improvement in the yield. Using the optimized reaction conditions, several chalcone derivatives bearing different substituents on the aromatic ring were subjected to reaction with hydroxylamine hydrochloride in the presence of citric acid. The results are summarized in Table **1**. The reaction tolerated both electron-donating and electron-withdrawing substituents on the aromatic ring, giving the corresponding pyridine-substituted isoxazole derivatives in moderate to good yields. The effect of solvent was also studied using various solvents such as methanol, ethanol, and water. Among these, ethanol was found to be the most suitable solvent, giving better solubility of reactants and higher product yield. The optimized reaction conditions involved heating the reaction mixture in ethanol at 70–80 °C for approximately 3- 4 hrs, which resulted in the formation of the desired product in good yield (75 to 90% yield) Show in table no. 1. The formation of 3-(5-phenylisoxazol-3-yl) pyridine can be explained through a cyclization mechanism involving an oxime intermediate. In the first step, the carbonyl group of the chalcone reacts with hydroxylamine to form the corresponding oxime intermediate**.** The presence of citric acid protonates the carbonyl oxygen**,** thereby increasing the electrophilicity of the carbonyl carbon and facilitating nucleophilic attack by hydroxylamine. Subsequently, the oxime intermediate undergoes intramolecular cyclization across the activated double bond of the chalcone, leading to the formation of the five-membered isoxazole ring. Finally, dehydration and rearrangement result in the formation of the aromatic 3-(5-phenylisoxazol-3-yl) pyridine structure.

Characterization of the Synthesized Compound

The structure of the synthesized compound was confirmed by spectroscopic analysis.

3a. 3-(5-phenylisoxazol-3-yl)pyridine

Molecular formula: $C_{14}H_{10}N_2O$

IR (KBr, υ = cm−1) 3050, 1600, 1250, 1000, 750-850 cm−1; 1 H NMR (500 MHz, DMSO-d6): δ = 6.5 (s, 1H,), 7.2–7.6 (m, 5H), 8.5-8.9 (d, J = 6 Hz, 2H), 7.7–7.2 (d, 7.5, 1.5 Hz, 2H), 7.3–7.8 (dd, 1H), 6.44 (s, 1H). Mass spectrum (m/z) = 222 $(M)^+$

3b. 3-(5-p-tolylisoxazol-3-yl) pyridine

Molecular formula: $C_{15}H_{12}N_2O$

IR (KBr, υ = cm−1) 3050, 2890, 1610, 1470, 1375, 1010, 1100, 750. 1H NMR (500 MHz, DMSO-d6): 8.8-8.6 (d,1H), 8.8-8.4 (d, 1H),7.2-8.2(t, 1H),7.4-7.8 (t, 1H),6.5-7.0 (s, 1H),7.1-7.3(d, 2H),7.0-7.2(d, 2H),2.25-2.40 (s, 3H). Mass spectrum (m/z) = 236 $(M)^+$

3c. 3-(5-(4-methoxyphenyl)isoxazol-3-yl)pyridine

Molecular formula: $C_{15}H_{12}N_2O_2$

IR (KBr, υ = cm−1) 3055, 2893, 1611, 1475, 1365, 1020, 1100, 755. 1H NMR (500 MHz, DMSO-d6): 8.7-8.6(d,1H), 8.7-8.4 (d, 1H),7.3-8.4(t, 1H),7.5-7.9 (t, 1H),6.5-7.2 (s, 1H),7.1-7.4(d, 2H),7.0-7.4(d, 2H), 3.70-3.90 (s, 3H). Mass spectrum (m/z) = 252$(M)^+$

Conclusion

An efficient and environmentally benign method has been developed for the synthesis of 3-(5-phenylisoxazol-3-yl)pyridine through the cyclization of 3-(3-pyridyl)-1-phenyl-2-propen-1-one (chalcone) with hydroxylamine hydrochloride in the presence of citric acid as a green catalyst. The proposed protocol provides a simple and effective route for the construction of the isoxazole ring under mild reaction conditions using an inexpensive, biodegradable, and non-toxic catalyst. The reaction proceeds smoothly in ethanol, giving the desired product in good yield with a straightforward work-up procedure. Overall, the developed method represents a green and practical synthetic approach for the preparation of pyridine-substituted isoxazole derivatives**,** which are important scaffolds in heterocyclic and medicinal chemistry. This methodology may also be extended to the synthesis of other biologically significant isoxazole derivatives**,** highlighting the potential application of citric acid as an efficient catalyst in sustainable organic synthesis**.**

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