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Synthesis of Pyrano[2,3-c]pyrazole Derivatives via a Multi-Component One-Pot Strategy Using a Cellulose–EDTA–Sodium Alginate-Based Catalyst Under Green Conditions †

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Abstract

In this study, a novel bio-based heterogeneous catalyst composed of cellulose, EDTA, and sodium alginate was designed and synthesized through a straightforward protocol. In this regards, the catalyst benefits from an interconnected, synergistic network in which cellulose acts as a renewable matrix, EDTA serves as a chelating agent to improve active site accessibility, and sodium alginate contributes biodegradability and structural stability. The resulting composite shows excellent thermal endurance, catalytic recyclability, and green compatibility. Furtheremore, this catalyst was employed in a one-pot multicomponent condensation reaction for the synthesis of pyrano[2,3-c]pyrazole derivatives. The reaction involved aromatic aldehydes, a pyrazole-based amine compound, and either malononitrile or ethyl acetoacetate as the active methylene sources, conducted in ethanol under mild reflux conditions. The protocol demonstrated high efficiency, delivering the desired products in excellent yields with short reaction times and minimal environmental impact. Moreover, the recyclability of the catalyst was confirmed over multiple cycles with negligible loss of activity. Importantly, pyrano[2,3-c]pyrazoles are known for their wide range of pharmacological properties, including antimicrobial, anticancer, anti-inflammatory, and antioxidant effects. This study introduces a sustainable synthetic route that not only advances heterocyclic design but also aligns with green chemistry principles, offering potential for further applications in medicinal and pharmaceutical research.

Keywords: cellulose-based catalyst; green chemistry; pyrano[2,3-c]pyrazole; multicomponent reaction; one-pot synthesis; pharmaceutical relevance

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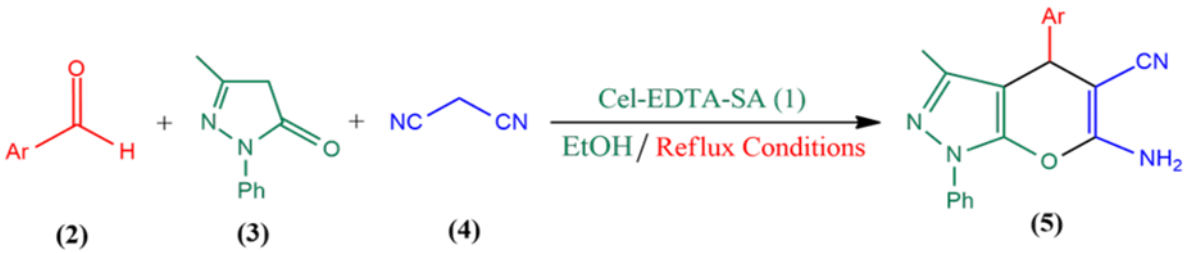
1. Introduction

Heterocyclic compounds play a central role in modern organic and medicinal chemistry due to their wide range of biological and pharmacological activities. Accordingly, the development of sustainable strategies for the synthesis of such compounds has received increasing attention in the past two decades. Multicomponent reactions (MCRs)

have emerged as powerful tools in this field, as they reduce the number of synthesis steps, save time and energy, and improve the selectivity and efficiency of synthesis [1,2]. At the same time, the principles of green chemistry have been increasingly applied to minimize the environmental footprint of chemical processes [3,4].

Biopolymer-based catalysts such as alginate, chitosan, and cellulose derivatives are very attractive for sustainable catalysis due to their natural abundance, biodegradability, and cost-effectiveness [5,6]. For example, cellulose modified with chelating agents such as EDTA has been reported to increase active site accessibility and improve adsorption or catalytic efficiency [7]. Similarly, hybrid biopolymer networks combining chitosan and cellulose with EDTA have shown good stability and recyclability in catalytic applications [8]. Among nitrogen-containing heterocyclic frameworks, pyrano[2,3-c]pyrazoles have attracted considerable attention due to their broad pharmacological properties, including antimicrobial, anticancer, anti-inflammatory, and antioxidant activities [9]. Recent reviews on the synthesis of these derivatives emphasize advancements in green chemistry, illustrating the use of various catalysts, including homogeneous, heterogeneous, and nanoparticle systems [10]. The synthesis of these compounds via multicomponent reactions is particularly well-suited for green chemistry, combining high atom economy with minimal separation steps [11].

In line with these considerations, we designed a novel bio-heterogeneous catalyst composed of cellulose, EDTA, and sodium alginate. This synergistic combination provides a renewable structural framework, enhanced chelation and activation of reaction sites, and improved stability and biodegradability. This catalyst was then employed in a three-component one-pot condensation reaction involving aromatic aldehydes, pyrazole-based amines, and malononitrile as the active methylene source, carried out in ethanol under reflux. Based on the substrates proposed in the abstract, a malononitrile-based synthetic route was selected and its structural investigations were presented.



Scheme 1. Synthesis of pyrano[2,3-c]pyrazole derivatives catalyzed by cellulose–EDTA–sodium alginate (1).

2. Experimental Section

2.1. General

All chemicals and reagents were of analytical grade and used without further purification unless otherwise specified. Microcrystalline cellulose (≥99%, Merck), ethylenediaminetetraacetic acid (EDTA, ≥99%, Sigma-Aldrich), and sodium alginate (viscosity 200–400 mPa·s, Sigma-Aldrich) were used as base materials for catalyst preparation. Aromatic aldehydes bearing electron-donating and electron-withdrawing substituents and malononitrile (≥99%, Sigma-Aldrich) were used as starting materials for the synthesis of pyrano[2,3-c]pyrazole derivatives. All solvents, including absolute ethanol (≥99.8%, HPLC grade, Merck), were used as the starting material. Deionized water was used in all aqueous preparations.

The reactions were carried out in standard borosilicate glassware equipped with a condenser for reflux operation. The progress of the reaction was monitored by thin-layer

chromatography (TLC) on silica gel plates (Merck 60 F254) using n-hexane/ethyl acetate as eluent. The melting points of the synthesized compounds were determined using an electrothermal melting point apparatus and are uncorrected.

2.2. Synthesis of Cellulose–EDTA–Sodium Alginate (Cell–EDTA–SA) Catalyst

Microcrystalline cellulose (1.0 g) was dispersed in aqueous NaOH (1 M, 8.0 mL) in a 50 mL round-bottom flask under an argon atmosphere and heated to 80 °C for 3 h to activate the hydroxyl groups. Subsequently, sodium alginate (1.0 g) was added to the alkaline cellulose suspension, and the mixture was stirred for an additional 1 h at 80 °C until a homogeneous viscous dispersion was obtained. Ethylenediaminetetraacetic acid dianhydride (EDTAD, 0.8 g) was then introduced gradually as a bifunctional crosslinker, and the reaction mixture was maintained at 80 °C for 12 h under continuous stirring.

After completion, the reaction mixture was cooled to room temperature, and the pH was adjusted to approximately 7.0 by the dropwise addition of 1 M HCl. The resulting white solid was collected by vacuum filtration, washed thoroughly with distilled water, ethanol, and diethyl ether to remove any unreacted reagents or by-products, and dried in an oven at 50 °C for 4 h. The obtained composite was designated as Cell–EDTA–SA.

In this biopolymer-based heterogeneous catalyst, the EDTA dianhydride forms covalent ester and amide linkages with hydroxyl groups on cellulose and carboxylate sites on alginate, generating abundant chelating, acidic, and basic active centers. The incorporation of sodium alginate enhances the structural integrity, hydrophilicity, and reusability of the catalyst, making it an efficient and environmentally benign support for green organic transformations.

2.3. General Procedure for the Synthesis of Pyrano[2,3-c]pyrazole Derivatives Catalyzed by Cellulose–EDTA–Sodium Alginate

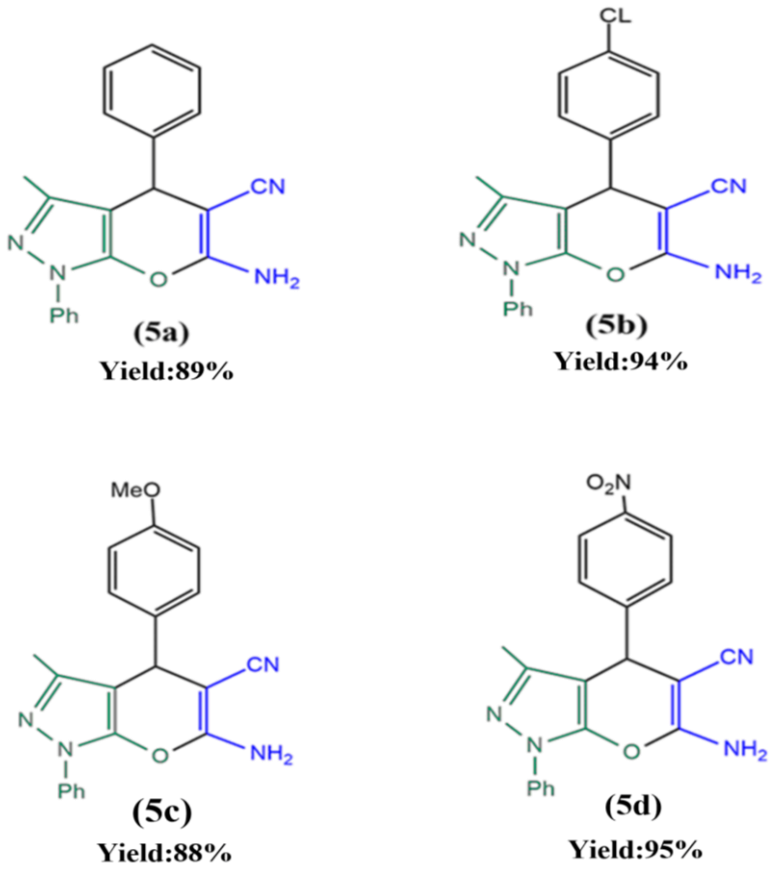
In a typical experiment, an aromatic aldehyde (1.0 mmol), a pyrazole-based amine (1.0 mmol), and malononitrile (1.0 mmol) were combined in a 25 mL round-bottom flask containing absolute ethanol (5 mL). Then, the cellulose-EDTA-sodium alginate catalyst (about 10 mg) was added, and the reaction mixture was stirred under reflux (78 °C) for 0.5–2 h. The progress of the reaction was monitored by thin layer chromatography (TLC) on silica gel using appropriate solvent systems (usually hexane/ethyl acetate).

After completion, the reaction mixture was cooled to room temperature and the heterogeneous catalyst was recovered by filtration, washed with ethanol and dried for reuse. The filtered solution was concentrated under reduced pressure and the crude product was purified by recrystallization from ethanol or ethanol-water mixtures. In cases where recrystallization was not possible, column chromatography was used.

Pyrano[2,3-c]pyrazole derivatives were obtained in high yields as crystalline solids and the catalyst could be efficiently recycled with negligible loss of activity.

3. Results and Discussion

The catalytic efficiency of cellulose-EDTA-sodium alginate composite in the green synthesis of pyrano[2,3-c]pyrazole derivatives via one-pot condensation of aromatic aldehydes, pyrazole-based amines and malononitrile under ethanolic conditions was investigated. As shown in Scheme 2, the reactions proceeded smoothly with only a small amount of catalyst (≈10 mg) and afforded the desired heterocycles in excellent yields in short reaction times.



Scheme 2. Scope of pyrano[2,3-c]pyrazole derivatives (5a–d) synthesis catalyzed by cellulose–EDTA–sodium alginate (1).

A notable advantage of this catalytic system is its direct recovery from the reaction mixture by simple filtration. The catalyst was reused for at least five consecutive cycles without significant loss of activity, emphasizing its recyclability and potential for sustainable synthesis.

These results confirm that the cellulose-EDTA-sodium alginate network acts as an efficient, reusable, and environmentally friendly catalyst and offers a practical route to pyrano[2,3-c]pyrazole derivatives with pharmaceutical relevance.

4. Conclusions

In summary, a bio-based heterogeneous catalyst comprising cellulose, EDTA, and sodium alginate was developed and successfully applied to the one-pot multicomponent synthesis of pyrano[2,3-c]pyrazole derivatives. Under mild reflux in ethanol, the protocol delivered the target scaffolds efficiently with short reaction times and straightforward work-up, in good agreement with green-chemistry principles. The composite catalyst was readily separated by simple filtration and retained its catalytic activity over multiple reuse cycles (≥5) with negligible loss of performance, demonstrating operational stability and practicality. Collectively, these results establish a sustainable and scalable route to pharmaceutically relevant pyrano[2,3-c]pyrazoles. Future work will target mechanistic elucidation, expansion of the substrate scope (including more challenging and functionalized substrates), systematic green-metric assessment, and comprehensive physicochemical characterization of the catalyst to further optimize and validate its preparative potential.

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Conflicts of Interest:

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