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Synthesis of pyrrole derivatives through multicomponent reaction strategy in the presence of new heterogeneous catalyst based on chitosan

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Abstract: The aim of this study is to synthesis of pyrrole derivatives by using phenacyl bromide and amine, which is promoted by a green and heterogeneous chitosan-based catalyst under optimal laboratory conditions through the multi-component reaction strategy namely Hantzsch pyrrole synthesis. This bio-based CS-EDTA-THEIC network contains appropriate basic and acidic active sites to act as a multifunctional catalyst. Indeed, the CS-EDTA-THEIC nanomaterial used in the multicomponent reaction for synthesis of pyrrole derivatives showed excellent yields in short reaction times. Furthermore, the CS-EDTA-THEIC network, as a heterogeneous catalyst, illustrated magnificent reusability and can be used at least six times without significant loss of its activity.

Keywords: Pyrrole derivatives; Chitosan-Based catalyst; Multicomponent reaction (MCR) strategy; multifunctional heterogeneous catalyst; Green chemistry

1. Introduction

Pyrrole is one of the most important five-organ single-ring aromatic compounds, found in natural products such as heme and chlorophyll and in abnormal products. Some known pyrroles have features such as anti-malaria and mycobacterial activity. Pyrrole compounds are also commonly used as hydrogen absorbers. There are some drugs that include pyrrole rings, and today in pharmacies, Atorvastatin, Tolmetin and Sunitinib are lowering blood cholesterol and for preventing cardiovascular diseases, analgesic, and anticancer drugs, respectively [1-2]. Recently, academic chemists have rehabilitated their interest into MCRs. In part, the pharmaceutical industry has been driven into this renaissance because of the growing need to assemble libraries of structurally complex substances for evaluation as lead compounds in drug discovery and development programs [2-3]. The application of MCRs to these increasingly important objective remains limited by the relatively small number of such reactions that can be broadly applied to prepare biologically relevant or natural-product-like molecular frameworks [7].

Recently, there has been special attention given to the development of MCRs using catalysts that are metal-free and cost-effective to prevent environmental pollution. Until now, the focus of catalyst research has been on increasing catalyst efficiency and the ability for efficient recovery [4,5,8]. The aim of this study is to synthesis pyrrole derivatives by using phenacyl bromide, ethyl acetoacetate and amine, which are promoted by a green-based chitosan catalyst under optimal laboratory conditions through a MCR strategy namely Hantzsch synthesis. [2-7].

Chitosan is easily accessible and possesses antimicrobial properties, making it a subject of significant interest in medicinal chemistry and biotechnology. Since this popular biopolymer contains many amine and hydroxyl functions on its surface, it can be used alone or in chemically modified forms, as a heterogeneous catalyst, in a variety of organic reactions [4—6, 8-11]. In this work, chitosan was grafted by using ethylenediaminetetraacetic acid (EDTA) and 1,3,5-tris(2-hydroxyethyl) isocyanurate (THEIC) to afford CS-EDTA-THEIC nanomaterial.

2. Materials and Methods

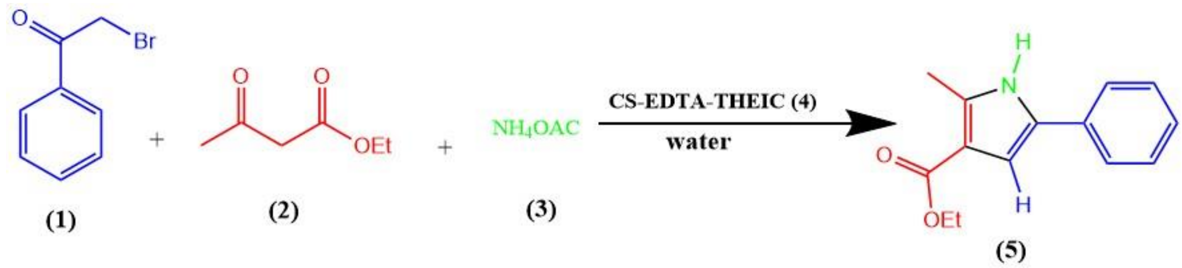
2.1. Materials

All chemical reagent were purchased from Merck. To determine the completion of the reaction, analytical thin-layer chromatography (TLC) was performed on pre-coated silica-gel plates (Merk Silica Gel F254). Product stains were detected eighter under UV light or by placing in an iodine chamber. Also, melting points were determined in open capillaries using an Electrothermal 9100 apparatus. Chitosan (Medium molecular weight, provided by Sigma-Aldrich) was used.

2.2. Methods

2.2.1. General procedure for the synthesis of pyrrole derivatives

In a 10 ml round-bottom flask, phenacyl bromide **(1,** 1 mmol), ammonium acetate (**2,** 1 mmol), ethyl acetoacetate (**3,** 1 mmol) and catalyst (**4**, 15 mg) were added in a 5 mmol of H_2O. Then, the obtained mixture was refluxed for 10 h and after that the mixture was cold at the room temperature. The reaction progress was monitored by using thin layer chromatography and after completion of the reaction, the crude product was purified by crystallization in EtOH. Also, the separated catalyst **4** was used for the next reactions.



Scheme 1. Synthesis of pyrrole via one-pot three component condensation of phenacyl bromide (**1**), ethyl acetoacetate (**2**) and ammonium acetate (**3**) in the presence of CS-EDTA-THEIC (**4**) catalyst.

3. Results and Discussion

The general scheme for the multicomponent synthesis of pyrrole derivatives has been shown in **Scheme 1**. The reaction of phenacyl bromide (**1**), ethyl acetoacetate (**2**) and ammonium acetate (**3**) was used as the model reaction. The effect of different factors on the reaction rate was studied. According to the obtained results, it was concluded that using of the CS-EDTA-THEIC catalyst (**4**), which is a green catalyst can afford pyrrole derivatives through the multicomponent Hantzsch reactions in a shorter reaction time compared to previous protocols. The corresponding products **5a** was obtained in high to excellentv yeilds. By using spectroscopic analyses such as FTIR and ^{1}H NMR spectroscopy, the structure of products was identified and confirmed.

4. Conclusion

Briefly, the inexpensive and eco-friendly CS-EDTA-THEIC catalyst, which is easily prepared, has advantages such as low catalyst loading, high efficiency, good recyclability, and reusability, at least for five runs, for the synthesis of pyrrole derivatives through the multicomponent reaction strategy.

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