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Preparation and Characterization of 5-Sulfosalicylic Acid Grafted to Chitosan-Based Support for the Synthesis of Quinazoline Derivatives under Green Chemistry Conditions †

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Abstract: In this research, the three-component synthesis of quinazoline derivatives with various substitutions has been investigated using a new chitosan-based catalyst grafted by 5-sulfosalicylic acid under green chemistry conditions. FT-IR, NMR, XRD, EDX, VSM, and FESEM spectroscopic, microscopic, or analytical methods were used for characterization of the new catalyst as well as identification of quinazoline derivatives. The obtained results showed the significant catalytic activity of the supramolecular nanocatalyst for the expeditious and efficient synthesis of 2,3-dihydroquinazoline-4(1*H*)-one derivatives, as an important pharmaceutical scaffold, via a three-component one-pot condensation of isotonic anhydride and aromatic aldehydes with amine sources.

Keywords: multicomponent reactions (MCRs); green and sustainable chemistry; modified chitosan nanomaterials; quinazoline derivatives; solid acid catalyst

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1. Introduction

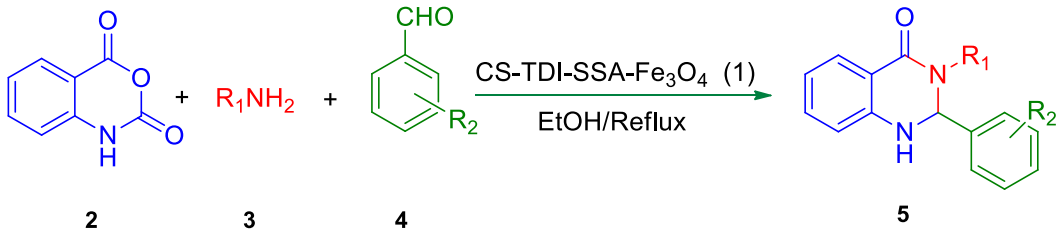
One of the main and important research areas has been the development of new heterogeneous catalytic systems in recent years. The reason for that is the special attention to minimize pollution in the organic synthetic methods. In addition, easy separation, simplification of the processes, helping to reduce waste production and recycling of the catalysts can be mentioned as the positive aspects of using the heterogeneous catalytic systems [1,2].

Chitosan is one of the best biopolymer substrates that can be obtained from natural resources without much effort and can be used in many industrial processes. The distinguishing feature of this linear biopolymer from others is its special characteristics such as hydrophilicity, nitrogen richness, ionic conductivity, crystallinity and high viscosity. In most cases, chitosan is used as a multifunctional agent together with nanomaterials to perform a catalytic reaction, and in some cases, it is used alone or together with ligands as a catalyst. Chitosan can also be useful for drug delivery because its structure is non-toxic [3].

A review of the literature shows that multicomponent reactions (MCRs) are widely used for the synthesis of many pharmaceuticals. MCRs have emerged as an interesting tool that allows the simple synthesis of complex molecules in one pot, without separating, and purifying intermediates, thus leading to a reduction in cost, time, and energy [4,5].

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of heterocyclic compounds that have received much attention. The synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones derivatives was previously carried out in several steps. In multi-component reactions, not only the production of these derivatives was done in one step, but also by simply changing

the reactant components, a lot of variety is created. In addition, the development of efficient, fast, simple, low-cost, easy-to-use, and environmentally friendly with energy saving synthetic protocols using recyclable catalysts and green solvents under mild reaction conditions for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones would be desirable [6]. Quinazolines and their derivatives are one of the most prominent compounds that have a wide range. of medicinal activities such as analgesic, antioxidant, anti-inflammatory, anti-blood pressure, anti-tuberculosis, antibacterial, antiviral, and anti-cancer activities [7,8]. In continuation of our ongoing efforts to design heterogeneous catalysts for various MCRs and organic transformations [1–3,9–16], we would like herein to report the preparation and characterization of new chitosan-based catalyst grafted by 5-sulfosalicylic acid (CS-TDI-SSA-Fe_3O_4,**1**). In addition, its catalytic activity was investigated in the three-component synthesis of isatoic anhydride (**2**), ammonium acetate (**3**), and aldehydes (**4**) (Scheme 1).



Scheme 1. Synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives catalyzed by CS-TDI-SSA-Fe_3O_4 (**1**).

2. Experimental Section

2.1. Reagents and Instruments

All the materials of this research as well as the reagents were purchased from Merck and Aldrich and were used in the processes without further purification, only benzaldehyde was used as a freshly distilled sample in the processes. FT-IR spectra were recorded as KBr pellets on a Shimadzu FT-IR-8400S spectrometer. ^{1}H NMR spectra (500 MHz) was obtained using Bruker DRX-500 Avance spectrometer. To monitor the reactions, analytical thin layer chromatography (TLC) was performed using Merck 60 F-254 Al 0.2 mm silica gel plates.

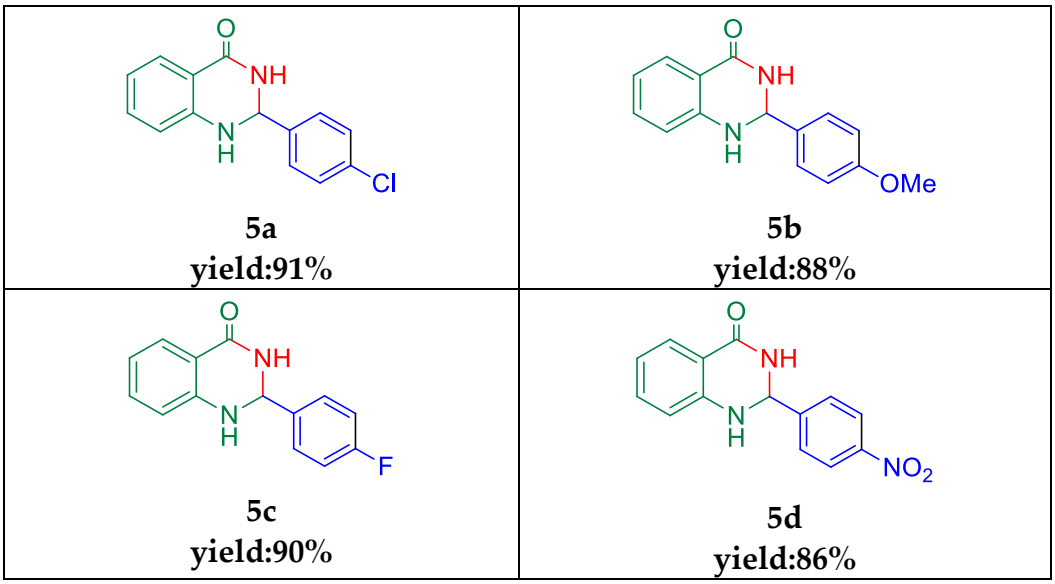
2.2. General Procedure for the Synthesis of 2,3-Dihydroquinazoline-4(1H)-One Derivatives Catalyzed by Cs-TDI-SSA-Fe_3O_4

In a 10 mL flask, 0.5 mmol of aldehyde (**4**), 1.5 mmol of ammonium acetate (**3**), and 0.5 mmol of isotonic anhydride (**2**) along with 0.02 g of CS-TDI-SSA-Fe_3O_4 (**1**) were added. Then, 2.5 mL ethanol was added as a solvent and the mixture was placed on a magnetic stirrer under reflux conditions. The progress of the reaction was monitored by thin layer chromatography (TLC) with ethyl acetate and n-hexane solvents in a ratio of 3:1. After the completion of the reaction, 2.5 mL of ethanol was added to the reaction mixture and it was filtered off to separate the CS-TDI-SSA-Fe_3O_4 (**1**). The filtrate was allowed to give pure product by the recrystallization method using the water-ethanol system. The crystals were collected by vacuum filtration, washed with EtOH and dried at 70 °C for 1 h.

3. Results and Discussion

The catalytic activity of CS-TDI-SSA-Fe_3O_4 (**1**) was evaluated in the green synthesis of 2,3-dihydroquinazolin-4(1*H*)-one derivatives by condensing amine, isatoic anhydride, and diverse aldehyde derivatives in ethanol under reflux conditions. According to Scheme 2, using 0.02 g of CS-TDI-SSA-Fe_3O_4 (**1**), as a nanocatalyst, the desired products were synthesized within a short time and high yield. This nanocatalyst can be recycled

and separated with minimal effort, and this process can be done at least five times, which is one of its advantages.



Scheme 2. Scope of 2,3-dihydroquinazolin-4(1*H*)-one derivatives (**5a–d**) synthesis catalyzed by CS-TDI-SSA-Fe_3O_4 (**1**).

4. Conclusions

In summary, we have employed an effective and practical procedure for the synthesis of 2,3-dihydro quinazoline-4(1*H*)-ones via the one-pot three-component condensation of isotonic anhydride, aromatic aldehyde, and amine using a new catalytic system. The advantages of this method include easy separation and reusability of the catalyst, high to excellent yield of products, use of green solvent, and mild reaction conditions. Moreover, this organic catalyst was recovered and reused at least five times without a significant decrease in its activity.

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