

Cs-ECH-TMA: A novel and efficient bifunctional organocatalyst for green synthesis of polyhydroquinolines and acridinediones under mild conditions

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Abstract

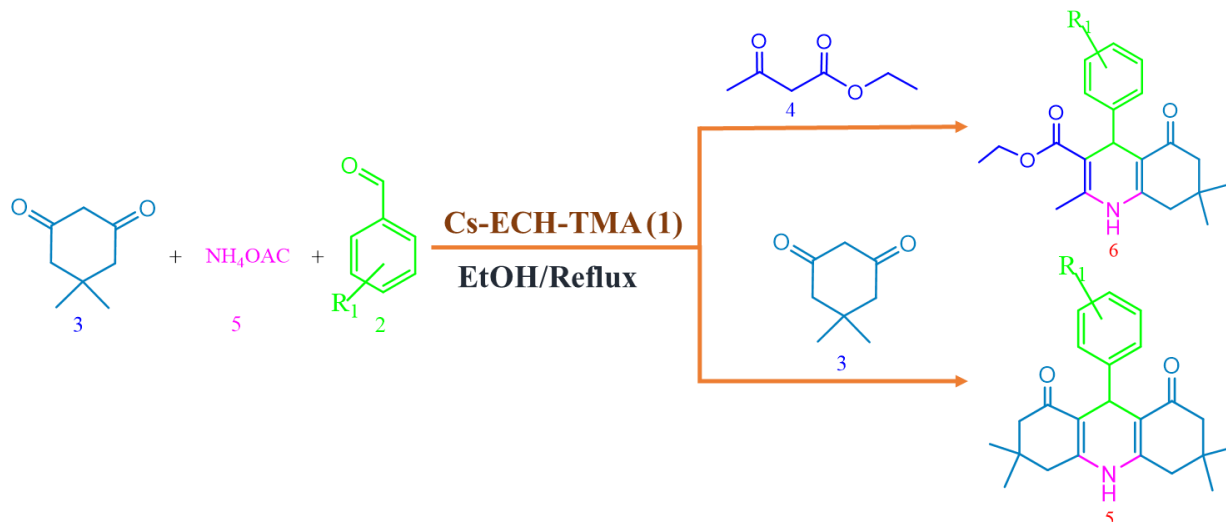
Here, an efficient and biodegradable catalytic system prepared through a simple procedure is presented by using chitosan (Cs), epichlorohydrin (ECH) and trimesic acid (TMA). The obtained bio-based Cs/ECH-TMA was characterized by using different spectroscopic and analytical methods. The Cs-ECH-TMA biopolymeric materials were used, as a bifunctional heterogeneous and green catalyst, for efficient synthesis of biologically-active scaffolds including polyhydroquinolines (PHQs) and acridinediones through Hantzsch reaction in a one-pot reaction. Both PHQs and acridinediones were synthesized in the presence of heterogeneous Cs/ECH-TMA catalyst from their corresponding substrates in EtOH under reflux conditions in high to quantitative yields. The Cs/ECH-TMA catalyst is recyclable and can be reused at least five times.

Keywords: Multicomponent reactions (MCRs); Polyhydroquinolines; Acridinediones; Chitosan; Heterogeneous catalyst.

Introduction

The development of new heterogeneous catalytic systems has become a major research area in recent years due to the minimization of contamination in the organic synthesis methodology. In addition, there are several positive aspects for using of heterogeneously-catalyzed process, including: simplification of the process, assistance to decreasing trend of the waste production, easy separation and recycling of the catalysts[1, 2]. Inorganic supports such as zeolites [3], alumina[4], metal organic frameworks (MOFs)[5] and diverse species synthetic organic polymers[6] are commonly used to stabilize catalytic agents on the surface and perform desired reactions. Recently, it seems that biopolymer substrates have become very attractive, because these biodegradable supports are simply extracted from an endless biological resource of a non-toxic nature [7]. Chitosan is one of the best biopolymer substrates that is easily obtained from natural sources and can be used for a variety of applications in numerous industrial areas. It is easily derived by the random *N*-deacetylation of chitin (a by-product of the fishing industry) under alkaline conditions. Also, it is a linear biopolymer with special feature such as, nitrogen richness, hydrophilicity, crystallinity, ionic conductivity and high viscosity that make it stand out from other biopolymers. In some cases, chitosan alone or with ligands has been used as a catalyst, and in other cases it has been used as a promotional agent along with nanomaterials to perform catalytic activity. The non-toxic structure of chitosan also makes it suitable as a drug delivery [8].

Literature survey shows that multi-component reactions are widely used to synthesize many drug nuclei including heterocycles [9]. One of the well-known methods for synthesis of PHQ and acridinedione derivatives, the use of a Hantzsch's reaction. Amlodipine, felodipine, nicardipine and nifedipine which are classified as economic drugs, obtained from this method. These drugs are used as ligands of L-type Ca^{2+} channels (LTCC) blockers and mainly applied for treatment of hypertension and angina [10]. Therefore, due to the applications and economics of these compounds, the utilization of Hantzsch's reaction is still considered. Herein, we wish to report trimesic acid-functionalized chitosan, as an efficient catalyst, for the synthesis of polyhydroquinoline and acridinedione derivatives [11].



Scheme 1. Synthesis of polyhydroquinoline and acridinedione derivatives catalyzed by Cs-ECH-TMA.

EXPERIMENTAL SECTION

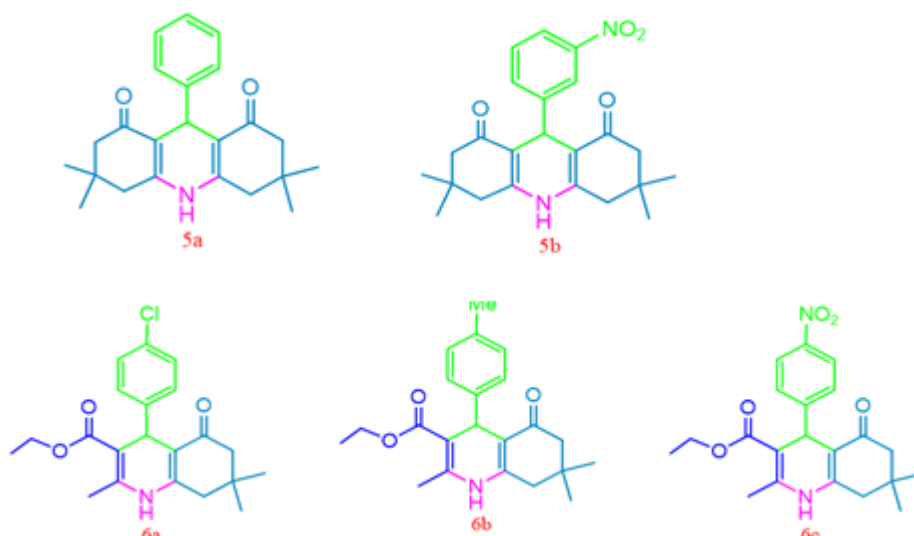
Reagents and apparatus

All chemicals and reagents were purchased from Merck and Aldrich and used without further purification, except for benzaldehyde, which was used as a freshly distilled sample. Chitosan (MW = 600,000 – 800,000 Dalton) was purchased from Acros Organics and used without any modification. Melting points were determined using a digital Electrothermal 9100 capillary apparatus. FT-IR spectra were recorded as KBr pellets on a Shimadzu FT-IR-8400S spectrometer. ¹HNMR (500 MHz) spectra were obtained using a Bruker DRX-500 Avance spectrometer. Analytical thin layer chromatography (TLC) was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates for monitoring of reactions.

General Procedure for the synthesis of polyhydroquinoline (6) and acridinedione derivatives catalyzed by Cs-ECH-TMA (1)

In a 10 mL round-bottom flask equipped with a magnetic stirring bar and reflux condenser, aldehyde (2, 1 mmol), dimedone (3, 2 mmol), NH₄OAc (4, 1.2 mmol), and Cs-ECH-TMA (1, 10 mg) were mixed in 96% EtOH (2 mL). The reaction mixture was stirred and heated under reflux conditions until the reaction was over. The progress of the reaction was monitored by TLC. After completion of the reaction, 96% EtOH (2 mL) was added to dissolve any solid product (5) and

remain the solid catalyst (**1**) insoluble. The mixture was separated by vacuum filtration and the filtrate was allowed to cool over time to give crystals of the desired acridinediones (**5a-b**). Crystals were collected by vacuum filtration, washed with 96% EtOH (2 mL) and dried at 50 °C for 1 h. In the case of PHQ derivatives (**6a-6c**), the same procedure was followed.



Scheme 2. Scope of synthesis of polyhydroquinoline (**6a-6c**) and acridinedione (**5a-5b**) derivatives in the presence of Cs-ECH-TMA.

Results and Discussion

Preparation of Cs-ECH-TMA was performed by grafting of the trimesic acid (TMA) to the chitosan backbone by using epichlorohydrin (ECH) as an applicable and inexpensive linker, under mild conditions. For this purpose (linkage of ECH to chitosan), several paths have been reported, and we chose the solvent Ethanol/H₂O (1:1), which was more appropriate and more efficient. Due to the greater reactivity of the epoxy ring, under the reported conditions, amino groups opens the ring instead of the chlorine substitution reaction. In the next step, we used aprotic and polar solvent DMSO in the presence of triethylamine organic base to activate the carboxylic acid group to complete the substitution reaction with chlorine atom and grafting the trimesic acid on the chitosan. It should be noted that due to the existence of several functional groups of trimesic acid, it is possible to form salts of carboxylic acid groups with triethylamine and prepare ammonium

carboxylate. Therefore, after preparing and washing the catalyst, we soaked it in dilute hydrochloric acid solution for several hours, to recover carboxylic acid.

Conclusion

In summary, trimesic acid-functionalized chitosan, as a reusable bifunctional organocatalyst, successfully catalyzing the multicomponent coupling reactions for synthesis of polyhydroquinolines (PHQs) and acridinediones; under mild and green conditions. Indeed, the use of low catalyst loading, metal-free, materials with commercially available, short reaction time and facility of separation Cs-ECH-TMA to the importance of using this new methodology. The use of nontoxic substances and metals in the synthesis of products is one of the advantages of this work.

Acknowledgements

We are grateful for the financial support from The Research Council of Iran University of Science and Technology (IUST), Tehran, Iran.

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