

Trimesic Acid-Functionalized Chitosan: A Novel And Efficient Multifunctional Organocatalyst For Green Synthesis of Polyhydroquinolines And Acridinediones Under Mild Conditions

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Research Article

Keywords: Modified biopolymers, Heterogeneous organocatalysis, Biodegradable catalyst, Multicomponent reactions (MCRs), Heterocycles, Green and sustainable chemistry.

Posted Date: November 12th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-1054554/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Heliyon on June 1st, 2023. See the published version at <https://doi.org/10.1016/j.heliyon.2023.e16315>.

Abstract

Trimesic acid-functionalized chitosan (Cs/ECH-TMA) material was prepared through a simple procedure by using chitosan (Cs), epichlorohydrin (ECH) and trimesic acid (TMA). The obtained bio-based Cs/ECH-TMA material was characterized using energy-dispersive X-ray (EDX) and Fourier-transform infrared spectroscopy (FTIR) spectroscopy, field emission scanning electron microscopy (FESEM) and X-ray diffraction (XRD) analysis. The Cs/ECH-TMA material was successfully used, as a multifunctional heterogeneous and sustainable catalyst, for efficient and expeditious synthesis of medicinally important polyhydroquinoline (PHQ) and polyhydroacridinedione (PHA) scaffolds through the Hantzsch condensation in a one-pot reaction. Indeed, the heterogeneous Cs/ECH-TMA material can be considered as a synergistic multifunctional organocatalyst due to the presence of a large number of acidic active sites in its structure as well as hydrophilicity. Both PHQs and PHAs were synthesized in the presence of biodegradable heterogeneous Cs/ECH-TMA catalytic system from their corresponding substrates in EtOH under reflux conditions and high to quantitative yields. The Cs/ECH-TMA catalyst is recyclable and can be reused at least four times without significant loss of its catalytic activity.

Introduction

The use of agricultural, fishery and industrial biopolymeric byproducts have become very attractive in designing of new heterogeneous catalytic systems mainly as appropriate supports in the recent years. Indeed, these biodegradable supports are simply extracted from endless biological resources of a non-toxic nature as well as demonstrate proper synergistic catalytic activity with the active catalytic centers and biodegradability¹⁻⁹. The development of new heterogeneous catalytic systems has become a major research area in recent decades due to the minimization of contamination in the organic synthesis methodology. In addition, there are several positive aspects for using of heterogeneously-catalyzed processes including simplification of procedures, assistance to decreasing trend of the waste production, easy separation and recycling of the catalysts¹⁰⁻¹³. Interestingly, these biomaterials are environmentally-friendly alternative supports for other materials such as diverse synthetic organic polymers¹⁴⁻¹⁷, metal organic frameworks (MOFs)¹⁸, graphene-oxide or its reduced form¹⁹⁻²², diverse synthetic organic polymers¹⁴⁻¹⁷, alumina²³, and silica and zeolites or their magnetic composites^{17,24-28} to stabilize active catalytic agents on the surface of supports to tune desired catalytic activities.

Chitosan is one of the best biopolymeric substrates which is easily obtained from natural sources and can be used for a variety of applications in numerous industrial areas²⁹⁻³¹. It is easily derived by the random *N*-deacetylation of chitin, a byproduct of the fishing industry, under alkaline conditions. Also, chitosan is a linear biopolymer with special features including hydrophilicity, crystallinity, ionic conductivity, high viscosity and nitrogen richness that make it stand out from other biopolymeric materials^{32,33}. Due to the presence of both amino and hydroxyl groups with proper geometry on the chitosan backbone, it has a great ability to form coordination interactions and covalent bonds with a variety of metals and organic compounds, respectively. Hence, chitosan has been widely studied as an

appropriate precursor or ingredient in various research areas³¹. Interestingly, chitosan has been used as a heterogeneous catalyst alone in some organic transformations³⁴. In other cases, chitosan after post-modification with proper ligands or metallic species has also been used along with nanomaterials to proceed different catalytic reactions^{6,7,19,35-43}. Furthermore, the non-toxic structure, presence of proper functional groups and hydrophilicity of chitosan or its derivatives make them an appropriate choice for drug delivery, anti-bacterial wound dressing materials, bioelectronics, sensors, adsorbents, hydrogels, etc^{22,44-56}. Hence, designing, preparation, and exploring the applications of new chitosan-derived materials in various research fields is in high demand.

Furthermore, trimesic acid (TMA) is an organic compound with a complementary functional groups which can easily be used for various applications such as the synthesis of self-assembled dendrimers or architectures^{57,58}, coordination polymers and metal-organic framework⁵⁹⁻⁶¹, nonporous materials⁶², polyamides⁶³, and absorbance of toxic substances and metals^{64,65}. TMA can act as a hydrogen donor or receptor by creating a variety of resonance structures⁶⁶. Due to the structural symmetry and multiplicity of the acidic agent groups of TMA, we were interested to use it by grafting to the chitosan backbone to prepare a cost-effective catalytic agent with proper catalytic efficiency.

On the other hand, literature survey shows that multi-component reactions (MCRs) are widely used to synthesize many pharmaceutical nuclei, new surfaces with proper functionalities, laser dyes or chemosensors as well as biomimetic asymmetric transfer hydrogenation and electron donors and proton sources in photoredox catalyzed processes including Hantzsch esters^{17,25,67-75}. One of the well-known methods for synthesis of polyhydroquinolines (PHQs) and polyhydroacridinediones (PHAs), as two scaffolds containing 1,4-dihydropyridines (1,4-DHP) moiety, is the Hantzsch condensation. For example, amlodipine, felodipine, nicardipine and nifedipine which are classified as economic drugs, obtained from this method. These pharmaceuticals are considered as L-type Ca^{2+} channels (LTCC) blockers and mainly applied for the treatment of hypertension and angina⁷⁶. Therefore, due to significant and wide applications of 1,4-DHPs in different areas as well as efficiency and low cost of Hantzsch method for the synthesis of these compounds, the multicomponent reaction of 1,3-dicarbonyl compounds, aldehydes and an amine source is still considered as the first choice. Hence, different homogeneous or heterogeneous acidic and basic catalytic systems have been introduced to proceed Hantzsch condensation more efficiently. Some recent catalytic systems for promoting of PHQs and PHAs synthesis are sulfonic acid supported $\gamma\text{-Fe}_2\text{O}_3$ ⁷⁷, $\text{Zn}[(\text{L})\text{proline}]_2$ ⁷⁸, 3,4,5-trifluorobenzeneboronic acid in ionic liquid⁷⁹ $\text{Co}_3\text{O}_4\text{-CNT}$ nanocomposites, platinum nanoparticles supported with reduced graphene oxide⁸⁰, nickel containing ionic liquid based ordered nanoporous organosilica, 1,3,5-tris(2-hydroxyethyl) isocyanurate covalently functionalized MCM-41, urease enzyme⁸¹, layered double hydroxides and PPh_3 ⁸². It is obvious that each of these catalytic systems has simultaneously their own advantages and disadvantages for catalyzing of Hantzsch's reaction. Hence, there is still much room for designing and exploring of new and more efficient catalytic systems with tailored functional groups, which address green and sustainable chemistry principles. In continuation of our interest to develop natural biopolymers

or their modified products, as efficient catalytic systems for different organic transformation, we wish herein to report trimesic acid-functionalized chitosan (Cs/ECH-TMA) materials for efficient synthesis of PHQs and PHAs in EtOH/H₂O under reflux conditions (Scheme 1). Indeed, avoiding the use of toxic substances and metals in the synthesis of Cs/ECH-TMA catalyst is one of the advantages of this work. This was achieved by the use of commercially available and biodegradable chitosan polysaccharide and epichlorohydrin.

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 and are uncorrected. Fourier-transform infrared spectroscopy (FTIR) spectra were recorded, as KBr pellets, on a Shimadzu FT-IR-8400S spectrometer. ¹H NMR spectra (500 MHz) were obtained using a Bruker DRX-500 Avance spectrometer. All ¹H NMR spectra were run in CDCl₃ solution, relative to TMS (0.00 ppm), at ambient temperature. Analytical thin layer chromatography (TLC) was performed using Merck 0.2 mm silica gel 60 F-254 Al-plates for monitoring of reactions. All products were characterized by spectroscopic methods (IR and ¹H NMR spectra) and melting points.

General procedure for the preparation of heterogeneous Cs/ECH-TMA organocatalyst (1)

In a 100 mL round bottom flask, chitosan (MW = 600,000–800,000 Dalton, Acros Organics, 1 g) was suspended in 50 mL of EtOH/H₂O (1:1). Then, epichlorohydrin (d = 1.183 g.ml⁻¹, 1 ml, 12.8 mmol) was added to the obtained mixture, stirred and heated under reflux conditions for 3 h. After that, the obtained solid was filtered off and suspended in EtOH (3 x 2 ml) for 10 min and then filtered by vacuum filtration. The solid was dried in an oven at 60 °C for 8 h to afford the epichlorohydrine-grafted chitosan (Cs-ECH). In the next step, Cs-ECH (0.5 g) and triethylamine (TEA, 2 ml) were suspended in DMSO (30 ml) and stirred for 30 min. at room temperature. Then, trimesic acid (TMA, 2.4 mmol, 0.5 g) was added to the obtained mixture and stirred at 100 °C for 4 h. The obtained solid was filtered and washed with acetone (3 x 2 ml) and soaked in HCl solution (1 M) for 3 h. Then, the obtained deep cream powder was washed with deionized water (3 x 5 ml) and dried in oven to afford catalyst 1.

General procedure for the synthesis of PHQ (6a-n) and PHA (7a-l) derivatives catalyzed by Cs/ECH-TMA (1)

In a 10 mL round-bottom flask equipped with a magnetic stirring bar and reflux condenser, aldehyde (**2a-l**, 1 mmol), dimedone (**3**, 1 mmol) and ethyl acetoacetate (**5**, 1 mmol), NH_4OAc (**5**, 1.2 mmol), and Cs/ECH-TMA (**1**, 10 mg) were mixed in EtOH (96%, 2 mL). The reaction mixture was stirred and heated under reflux conditions for the reaction times indicated in Table 3. The progress of the reaction was monitored by TLC. After completion of the reaction, EtOH (96%, 2 mL) was added to dissolve any solid crude product **6** and remain the solid catalyst **1** insoluble. The mixture was separated by vacuum filtration, allowing the filtrate solution to cool over time to obtain the desired polyhydroquinolines (PHQs, **6**) crystals. The products were finally collected by vacuum filtration, washed with EtOH (96%, 2 mL) and dried at 50 °C for 1 h. In the case of polyhydroacridinediones (PHAs, **7**), aldehyde (**2**, 1 mmol), dimedone (**3**, 2 mmol), NH_4OAc (**4**, 1.2 mmol) and Cs/ECH-TMA (**1**, 10 mg) were mixed in EtOH (96%, 2 mL) by following the same described procedure.

Results And Discussion

Preparation of the Cs/ECH-TMA organocatalyst (**1**)

The trimesic acid-functionalized chitosan (Cs/ECH-TMA) materials were simply prepared by grafting of the trimesic acid (TMA) to the chitosan (Cs) backbone using epichlorohydrin (ECH), as an applicable and inexpensive linker, under mild conditions (**Scheme 1**). For this purpose, several paths have been reported. However, the EtOH/ H_2O (1:1) solvent was chosen, which demonstrated to be more efficient than chloride group other solvents⁸³. Due to the higher reactivity of the epoxy ring of ECH, under the reported conditions, the amine group opens the ring instead of the chlorine substitution reaction. In the next step, the aprotic and polar DMSO solvent was used in the presence of trimethylamine (TEA) organic base to activate the carboxylic acid group of TMA and completion of the chloride group substitution reaction. It should be noted that due to the existence of three acidic functional groups of trimesic acid, different ammonium carboxylate salts with triethylamine can be formed. Hence, after preparing and washing the catalyst **1**, it was soaked in dilute HCl solution for several hours to recover the remaining carboxylic acid functional groups of TMA moiety.

Characterization of the Cs/ECH-TMA organocatalyst (**1**)

In order to investigate the surface functionalization of Cs with TMA moieties, several appropriate techniques such as Fourier transform infrared (FTIR) spectroscopy, field emission scanning electron microscopy (FESEM), thermal gravimetric analysis (TGA), energy dispersive X-ray (EDX) spectroscopy and X-ray powder diffraction (XRD) were used. **Fig. 1** shows the FTIR spectra of chitosan (a), Cs/ECH (b) and Cs/ECH-TMA (c), respectively. As can be seen, the signal related to the asymmetric and symmetric stretching vibration of N–H bond at ~3500 is observed in the all spectra (a-c). Of course, the broad adsorption band at 3450-3150 cm^{-1} can be attributed to the stretching vibration of the hydroxyls group of both Cs and ECH linker. Furthermore, the strong absorption band at 1725 cm^{-1} is assigned to the stretching vibration of carbonyl group (C=O) and confirms the presence of trimesic acid in the structure of

Cs/ECH-TMA (**1**, spectrum c). On the other hand, two absorption bands near 1240 and 1370 cm^{-1} are related to the in-plane bending vibration of hydroxyl groups, respectively ⁸⁴.

The presence of chlorine element in the EDX analysis of Cs/ECH (a) confirms that the first step in the preparation of the catalyst **1** was successfully performed. Subsequent elimination of the chlorine element in the EDX analysis of Cs/ECH-TMA (b) is a clear indication of its substitution with the carboxylic acid functional groups of TMA by a covalent binding to the chitosan backbone (**Fig. 2**).

Field emission scanning electron microscopy (FESEM) images (**Fig. 3**) show the morphology of Cs/ECH-TMA material (c-d) compared to the commercial chitosan (a-b). The surface of the commercial chitosan is almost smooth (**3a-b**) and free of cross-linked groups including ECH and TMA. However, additional particles have spread across the surface of the Cs support and demonstrating its uniform functionalization by the TMA units grafted by the ECH linker (**3c-d**). The bulk of these particles is probably related to hydrogen bondings and the self-assembly of TMA moieties.

The XRD spectra of the commercial chitosan and Cs/ECH-TMA material was also studied (**Fig. 4**). The characteristic peaks at about $2\theta = 10^\circ$ and 20° are related to the structure of pristine chitosan (**4a**). After grafting of TMA on the chitosan backbone, its crystalline structure changes and new signals appear at 21.2° , 23.0° , 28.3° , 30.7° and 41.8° (**4b**). Furthermore, observation of wide peaks in the spectrum (**4b**) indicates lower crystallinity of the catalyst **1** than the pristine chitosan which can be attributed to the linkage of TMA on the surface of chitosan.

Investigation of the catalytic activity of Cs/ECH-TMA for synthesis of PHQ and PHA derivatives

In order to evaluate the catalytic activity of Cs/ECH-TMA and achieve the desired conditions for the synthesis of polyhydroquinolines (PHQs) and polyhydroacridinediones (PHAs), different factors including solvent, temperature and time in the presence of the variable amount of Cs/ECH-TMA catalyst **1** were examined (Table 1). For this purpose, the four component condensation of ethyl acetoacetate (**3**, 1.0 mmol), dimedone (**4**, 1.0 mmol), 4-chlorobenzaldehyde (**2a**, 1.0 mmol) and ammonium acetate (**5**, 1.2 mmol), was investigated as the model reaction. The results have been summarized in **Tables 1** and **2**.

Initially, the reaction was performed without any catalyst, and the reaction efficiency for the synthesis of desired product, 4-(4-chlorophenyl)-2,7,7-trimethyl-5-oxo-5,6,7,8-tetrahydroquinoline-3-carboxylate (**6a**), was below 30% after three hours (entry 1). Then, commercial chitosan was used, as a catalyst, in the model reaction which did not afford high yield of the desired product **6a** (entry 2). To determine the optimized conditions, different amounts of catalyst loading were used (entries 3-6). The best conditions are given in entry 5 of **Table 1**. The results clearly confirm the high impact of Cs/ECH-TMA to proceed the model reaction. Investigation of the solvent effect showed that polar protic solvents (entries 5, 10 and 18) demonstrate higher efficiency than polar aprotic solvents (entries 13-16). On the other hand, solvent-free conditions afforded moderate yields of the desired products at both 60 and 110 $^\circ\text{C}$ (entries 11 and 17).

To show the general scope of the reaction, different aromatic aldehydes bearing electron-withdrawing or electron-donating substituents **2a-n** were investigated under optimized conditions (10 mg Cs/ECH-TMA loading in EtOH under reflux conditions). The results have been summarized in Table 2. Indeed, the catalyst **1** demonstrated a high activity for the synthesis of corresponding PHQa and the desired products were obtained in high to excellent yields and short reaction time. As shown in the **Table 2**, aldehydes with electron-withdrawing groups on the aromatic ring (entries 1-2, 6, 8 and 12) produced higher yields of the desired products in shorter reaction times compared to those ones bearing electron-donating groups. This can be attributed to higher susceptibility of the carbonyl group in aldehydes with electron-withdrawing groups toward nucleophilic addition of the enolic components of Hantzsch reaction in order to form the corresponding Knoevenagel intermediates. However, aldehydes bearing nitro groups (entries 3 and 5) afforded lower yields of their corresponding PHQ derivatives compared to other electron-withdrawing groups. This behavior is relevant to simultaneous formation of the corresponding imines of nitro derivatives by reaction with NH₃ demonstrating lower activity as well as redox disproportionation of their PHQs ⁶. In general, other aldehydes have been well activated by the catalyst **1** and yields of desired products under optimized conditions were shown to be high to excellent.

In addition, the catalyst activity under optimized conditions was investigated for the production of 3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-2*H*,5*H*-1,8-acridinedione derivatives (PHAs, **7a-l**) from pseudo-four-component condensation of dimedone (**4**), aromatic aldehydes **2a-l** and ammonium acetate (**5**). As shown in **Table 3**, it takes less time to produce PHA derivatives **7** than PHQs ones **6** under the same conditions. Aldehydes with electron-withdrawing groups on the aromatic ring, except nitro groups (entries 1-2, 6, 8 and 12), are more reactive than aldehydes bearing electron-releasing groups in the same way.

According to the obtained results, the mechanism presented in **Scheme 2** can be proposed for the synthesis of PHQs (**6a-n**) and (**5a-l**) catalyzed by Cs/ECH-TMA (**1**). In the first step, acidic protons of the trimesic acid moiety of catalyst **1** cause activation of the carbonyl functional group of aldehydes **2** to react with the enolic form of dimedone (**3'**) and affording the corresponding Knoevenagel intermediates (**II**). This α,β -unsaturated dicarbonyl is then activated by Cs/ECH-TMA (**1**) and react with the enol form of β -dicarbonyls (**3'** or **4'**) to form the Michael adduct intermediate (**IV**). In the next step, the intermediate (**IV**) react on its ketone functional group with the ammonia source (**5**) and forms imine intermediate (**V**). After tautomerization of the imine intermediate (**V**) and its conversion to the corresponding enamine intermediate (**VI**), the intramolecular reaction between enamine (**VI**) and remaining ketone functional group leads to ring closure. Eventually, by elimination of the third H₂O molecule, PHQ (**6**) or PHA (**7**) derivatives are produced. Furthermore, due to the presence of a large numbers of hydroxyl groups in the chitosan backbone and the ECH linker of the Cs/ECH-TMA catalyst **1**, water molecules can be adsorbed on its surface to promote the Hantzsch condensations smoothly. Moreover, this hydroxyl groups contribute to more activation of carbonyl groups by development hydrogen bonding. Hence, the heterogeneous Cs/ECH-TMA materials can be considered as a synergistic multifunctional organocatalyst due to the presence of a large number of acidic active sites in its structure as well as hydrophilicity.

Due to the importance of heterogeneous catalyst recycling for industrial applications, we investigated this important aspect of the Cs/ECH-TMA catalyst properties. Therefore, after completion the reaction, the Cs/ECH-TMA material was separated from the reaction medium and washed three times with acetone solvent. Then, the separated catalyst was dried in an oven at 60 °C for 6 h to be used for the next run. As shown in **Fig. 5**, the activity of catalyst for synthesis of desired products was still significant after five uses.

Finally, in order to further clarify the high efficiency of Cs/ECH-TMA organocatalyst (**1**) and the merits of the present protocol for the synthesis of polyhydroquinolines and acridinediones, several previously reported methods are listed in **Table 4** for comparison. As can be seen, the present work is indeed preferable to several of the others in terms of the use of biodegradable catalyst, isolated yields, short reaction time, elimination of toxic transition metals and solvents, and use of low catalyst loading to accelerate synthesis of PHQs and PHAs.

Conclusions

In summary, novel trimesic acid-functionalized chitosan (Cs/ECH-TMA) materials were prepared through a simple procedure and properly characterized. The Cs/ECH-TMA material was used, as a reusable, and multifunctional organocatalyst, for the multicomponent reactions for synthesis of polyhydroquinolines (PHQs) and polyhydroacridinediones (PHAs) under mild and sustainable conditions. The heterogeneous Cs/ECH-TMA material was demonstrated to act as synergistic multifunctional organocatalyst due to the presence of a large number of acidic active sites in its structure as well as hydrophilicity. Indeed, the use of a metal-free and low loading catalyst with facile separation from the reaction mixture and its reusability as well as commercially available biomaterial precursor and short reaction time in a green solvent are important advantages of this new methodology.

Declarations

Acknowledgements

We are grateful for the financial support from The Research Council of Iran University of Science and Technology (IUST), Tehran, Iran (Grant No: 160/19810). The partial financial support of The Iran Nanotechnology Initiative Council (INIC) is also gratefully acknowledged.

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Scheme

Schemes 1 and 2 are available in the Supplemental Files section

Tables

Due to technical limitations, tables 1 to 4 are only available as a download in the Supplemental Files section.

Figures

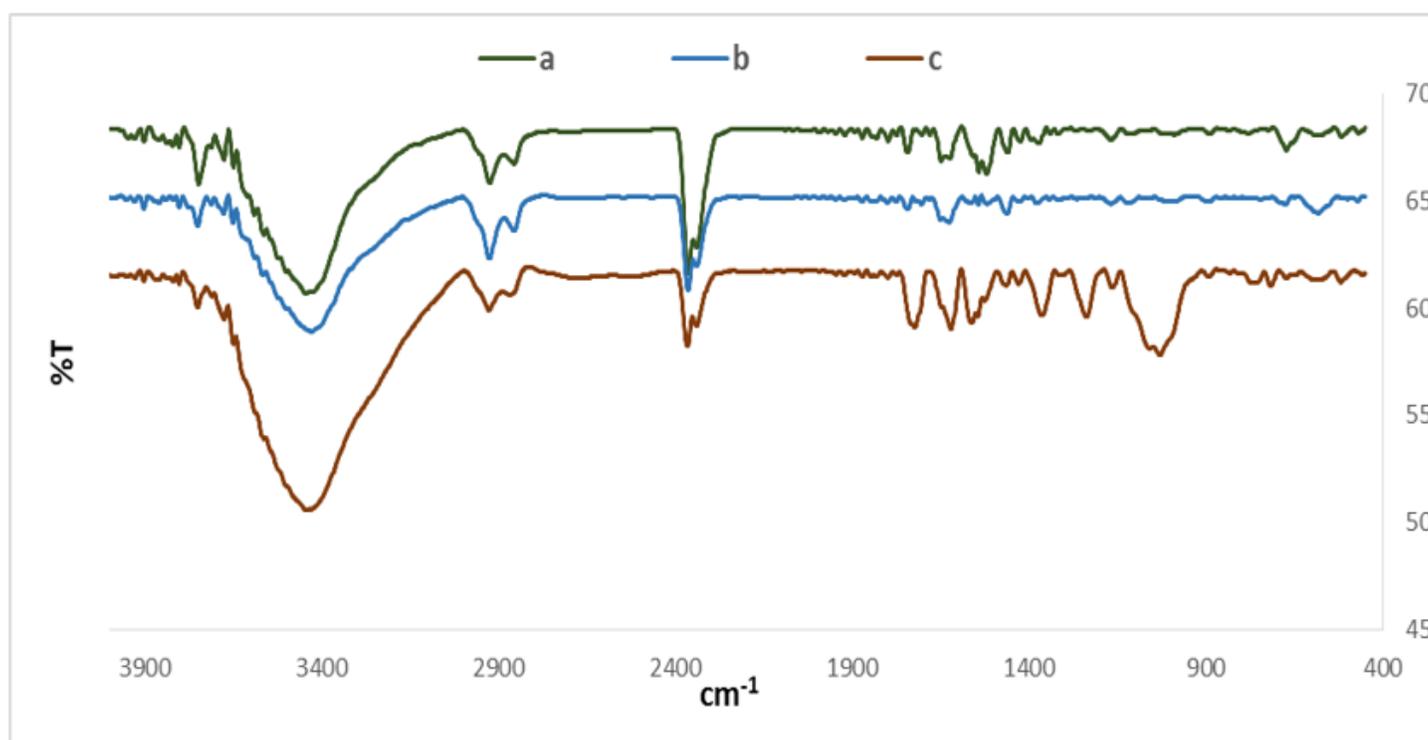


Figure 1

FTIR spectra of the commercial chitosan (a), chitosan containing epichlorohidrin linker (Cs/ECH, b) and the Cs/ECH-TMA material (1, c).

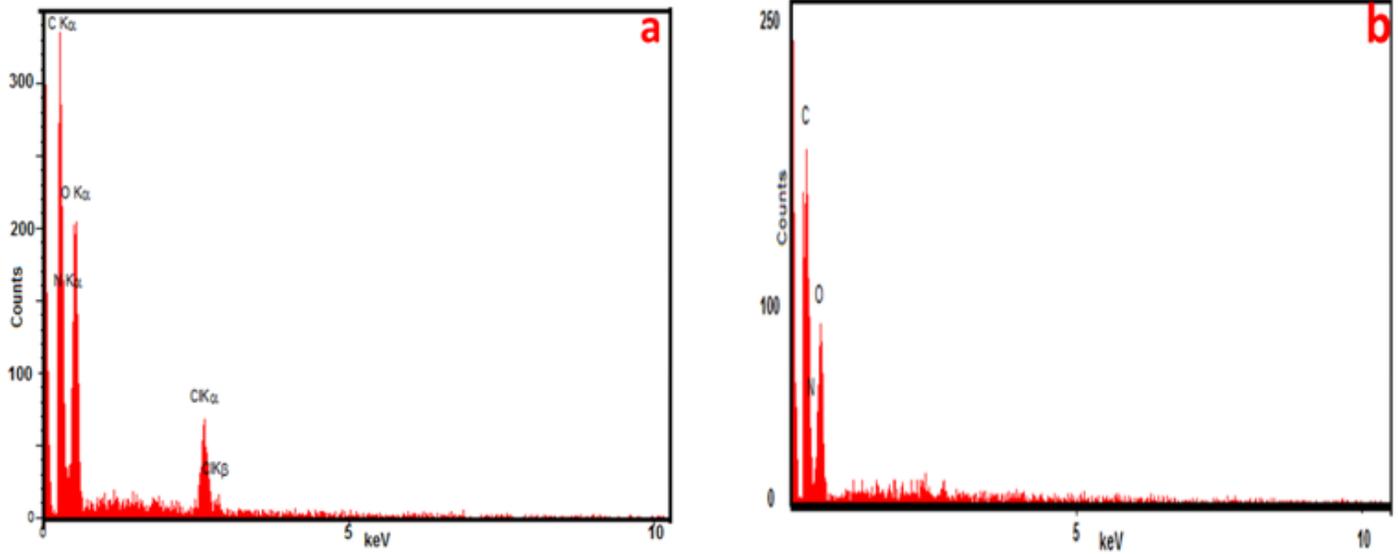


Figure 2

Energy dispersive spectroscopy (EDX) analysis of the Cs/ECH (a) and the Cs/ECH-TMA material (1, b).

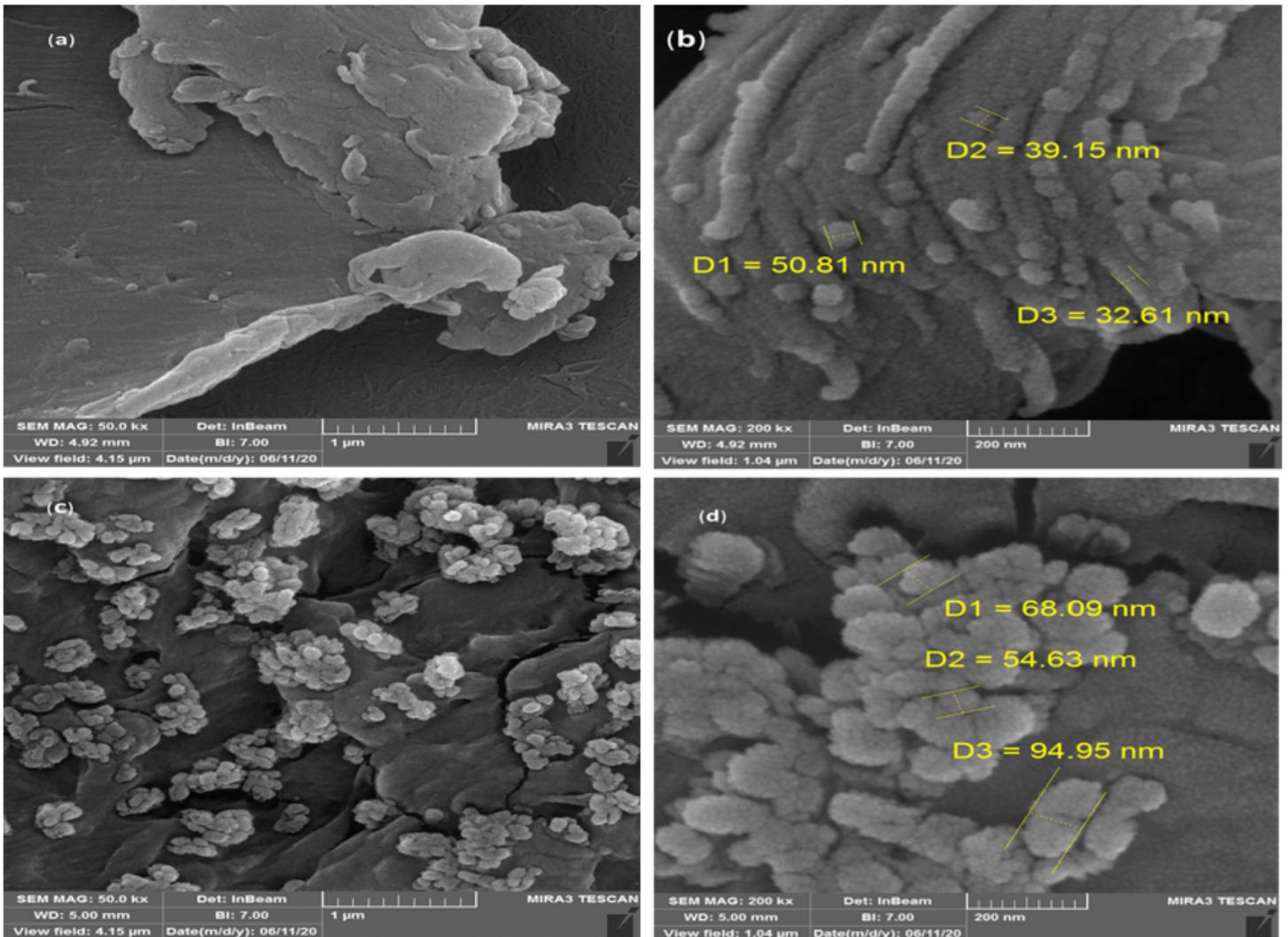


Figure 3

FESEM images of the commercial chitosan (a-b) and the Cs/ECH-TMA (1) material (c-d).

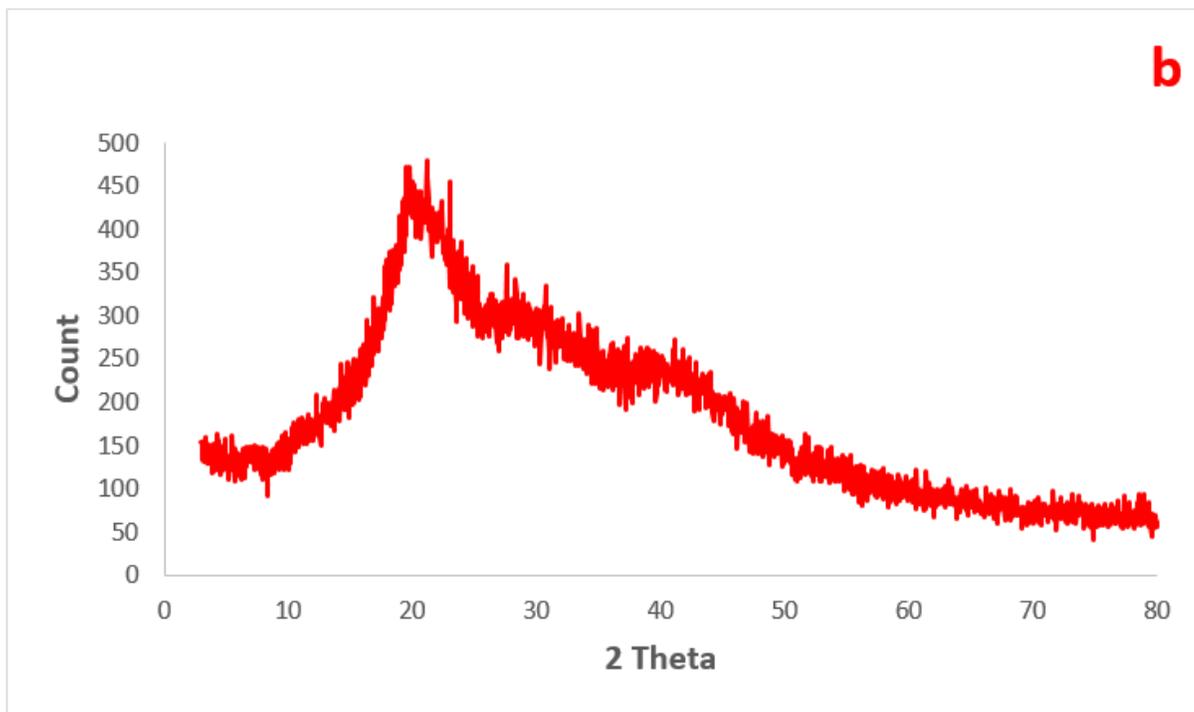
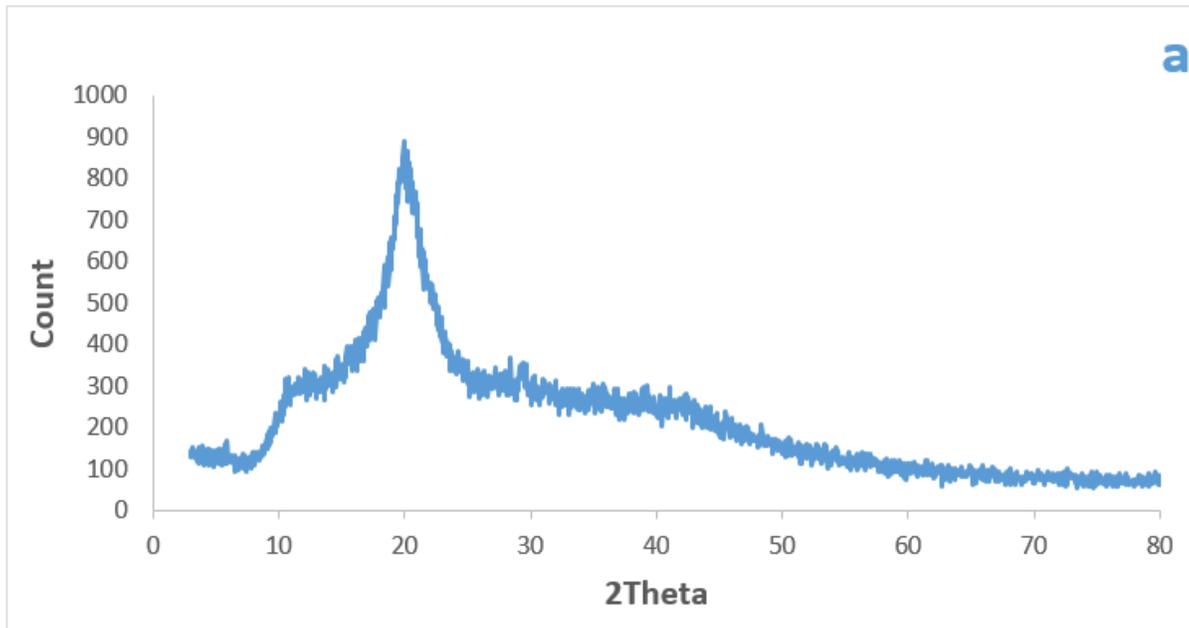


Figure 4

XRD pattern of the commercial chitosan (a) and the Cs/ECH-TMA material (1, b).

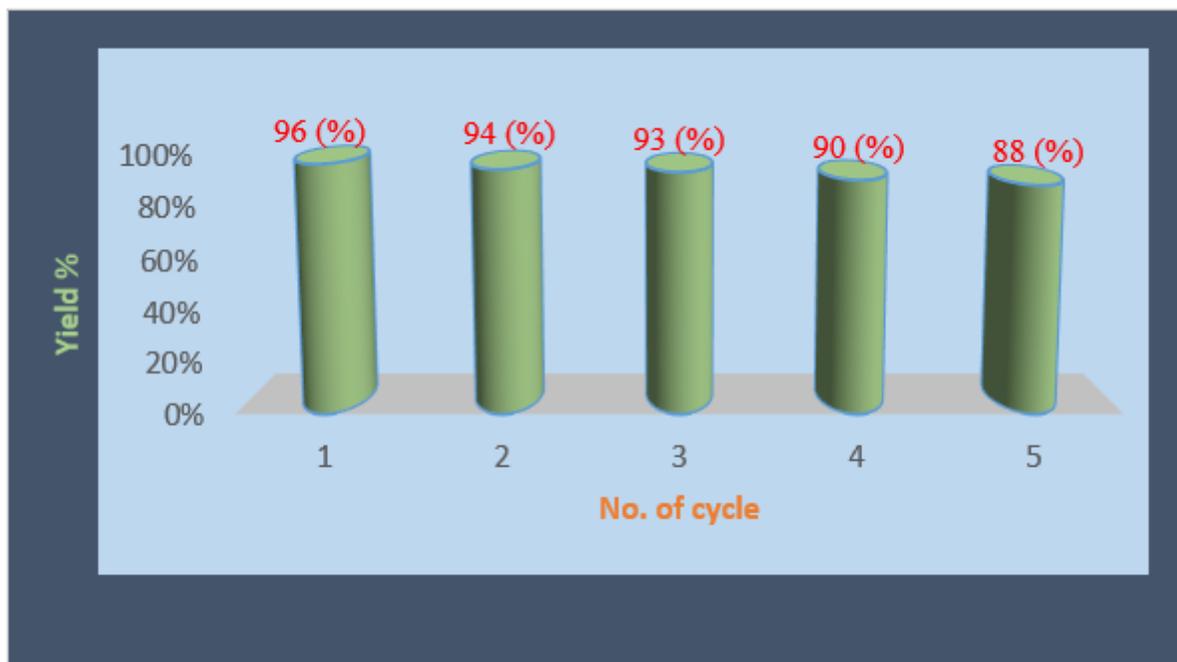


Figure 5

Reusability of the Cs/ECH-TMA catalyst (1) for synthesis of PHQ derivative 6a from 4-chlorobenzaldehyde (2a), dimedone (3), ethyl acetoacetate (4) and NH₄OAc (5).

Supplementary Files

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