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Fe_3O_4@Sucrose: A Green Catalyst for Syntheses of Polyhydroquinolines

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Abstract

By aid of environmental-friendly, moderated conditions and a novel hydrogen-bond-rich Nano catalyst, we ran a simple synthesis of penta-substituted Polyhydroquinolines (PHQs). Expected products have been made from two different sorts of 1,3-dicarbonyls, conjugated aldehydes and ammonium acetate. New core-shell type, magnetic nanoparticles (MNPs) after formation based on table sugar as an inexpensive carbohydrate are precisely characterized using common analyses such as FT-IR, XRD, VSM, TGA, SEM and EDX. Besides its economical or semi-industrial purposes, reusability of magnetic catalyst developed its great interest in replacement of conventional homogeneous promoters. This property has led to total yield for more than 78% of starting performance (after 7th run) is considerable.

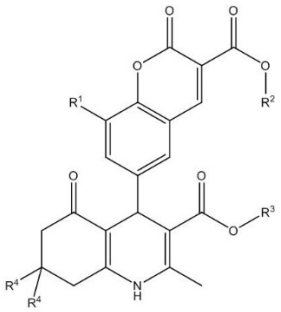
Keywords: Hantzsch reaction; Sugar-based catalyst; Sucrose; Hydrogen bonding catalyst; Magnetic nanoparticles

Introduction

Since early of 1900s, the era of Mannich, multicomponent reactions (MCRs) played an important role in the vast world of organic synthetic chemistry specially concerned for pharmaceutical-active molecules [1]. The Hantzsch reaction is one of earliest and the most well-known four-component class could be considered so useful for some intriguing biological application e.g., anti-tumorous, antidiabetic and anticonvulsant properties [1,2]. Among a wide variety of Hantzsch processes, the formation of a bicyclic polyhydroquinolines (PHQs) similar to their monocyclic analogues, 1,4-dihydropyridines (DHPs), has strongly attracted the scientists' tendency to itself for a long time [3-6].

During last twenty years many endeavors could be engaged with synthesis of more different kinds of polyhydroquinolines skeletons either by change of aldehyde part or nitrogen source as the lonely heteroatom [2]. Although widely facilitated protocols are employed into the traditional way of production of PHQs or DHPs [2-13] that are driven under metal-based or non-metallic catalyzed manuals or even by free-catalyst conditions, but recently reported Nano-scaled catalysts have proven more potential activity; among them could be mentioned e.g., Fe_3O_4@B-MCM-41 [7], Nano-sized CuO [8], GSA-MNPs [9], ([NS-C_4(DABCO-SO_3H)$_2$].4Cl) [10], {[TPPSP]OTf} [11], Fe_3O_4 NPs [12] and Fe_3O_4-SA-PPCA [13].

At a small glance the literatures show almost clearly the absence of activated but coated magnetic nanoparticles containing green methods for Hantzsch's synthesis. However, some pure magnetic oxides such as Fe_3O_4 NPs [12] or even grafted carbonaceous scaffold e.g., Co_3O_4-CNT NPs [14] are applied, self-aggregation of bare nanoparticles is a vital problem which remained unsolved. Hence, it was necessary to use a green, omnipresent, inexpensive and Hydrogen-bond rich matter that we found Sucrose/Table Sugar (the most available simple carbohydrate around the world) as the best option. Biodegradable innate of sucrose implies on being environmental-friend compound. Among essential building blocks contain PHQs, Coumarin-Dihydropyridine [15] (Scheme 1) is one of important product which had been synthesized through Hantzsch 4-components pathway.

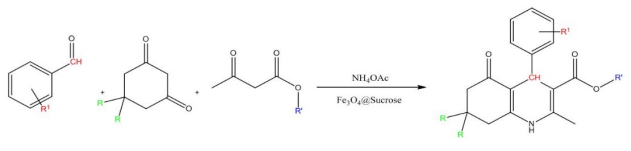


Scheme 1: Coumarin-Dihydropyridine contains PHQ in molecular skeleton.

Protected aldehyde motif of sucrose because of two natural hemi-acetalized sites in glucose- and frutose-division made it as an exclusive non-reducing disaccharide. This fact would be useful for our obtained PHQs than other world-wide famous sugars e.g., D-(+)-glucose, D-(-)-fructose or etc. [16].

It is highly desirable to utilize new, environment-friendly organ catalyst system for the synthesis of Polyhydroquinolines (PHQs). Herein, we firstly report an efficient, environmental-directed and Nano-magnetic catalyzed protocol for the synthesis of hexahydro quinolines in ethanol medium (Scheme 2). One of major problem about previous acidic catalysts is related for formation of product with starting aldehydes contains amino-groups (3a) since formation of partial ammonium salt in nitrogen-site would cease catalyst activity. Hence, sucrose immobilized on the surface of magnetic-recoverable support of magnetite (Fe_3O_4@Sucrose). It should be noted, applying simple carbohydrate was recently reported by our team as a green approach to synthesize Pyrazole derivatives [17]. In continuation, we decided to run green and environment-friendly following four-

component one-pot condensation by a green and approximately catalyst. Besides, different derivatives could help enrich literature database in view point of variety of products.



Scheme 2: General synthesis of PHQs via Fe_3O_4 Sucrose.

Materials and Methods

All the experiments were performed in an oven-dried glass apparatus. Each one of the commercially available reagents were purchased from Merck or Sigma-Aldrich which were used without further purification. All reagents were transferred to the reaction vessel (Pyrex tube with a screw cap). FT-IR spectra were collected with a Nicolet IR 100 FT-IR in the wave number range of 400-4000 (cm^{-1}) using spectroscopic grade KBr. The melting points of products tested by Barnstead Electronics 9100. Additionally, the ^{1}H-NMR (500 MHz) spectra were recorded on a Bruker Advance DPX-500 NMR spectrometer instrument that were recorded in $CDCl_3$ as solvent. The morphology of the catalyst was studied using scanning electron microscopy (SEM; Philips XL 30 and S4160) with coated gold equipped with dispersive Xray spectroscopy capability. Powder Xray diffraction (XRD) spectra were recorded at room temperature with a Philips XPert 1710 diffractometer using Co Kα radiation (λ=1.78897 Å) at a voltage of 40 kV and current of 40 mA to define the crystalline structure of the catalyst nanoparticles. Data were collected from 10° to 90° (2θ) with a scan speed of 0.02° s^{-1}. The magnetic properties were measured with a vibrating magnetometer/alternating gradient force magnetometer (MDCo., Iran, www.mdkmagnetic.com). Thermogravimetric analysis (TGA) was performed using a thermal analyzer with a heating rate of 20°C min^{-1} over the temperature range 25°C-900°C under flowing compressed nitrogen (as inert gas).

Preparation of Fe_3O_4@Sucrose

Magnetic nanoparticles of Fe_3O_4 were prepared as reported previously [18]. Technically, two source of iron cations, $FeCl_24H_2O$ (0.994 g, 5 mmol) and $FeCl_36H_2O$ (2.703 g, 10 mmol) were dissolved in 40 ml of deionized water in a 500-ml flask. The solution was stirred vigorously (800 rpm) at 80°C for 1 h. Then, 15 ml of solution of 25% (w/w) ammonia was rapidly added into the mixture. The reaction system turned black quickly. The mixture of magnetite nanoparticles (Fe_3O_4 NPs) and sucrose solution (optimized at 3 mmol sucrose per 1 g Fe_3O_4 NPs) was exposed to ultrasonic waves for 20 min. The resulting superparamagnetic nanoparticles (Fe_3O_4@Sucrose NPs) were first separated from aqueous medium then washed several times with deionized water then ethanol and dried at 60°C overnight.

General procedure for catalytic synthesis of polyhydroquinolines

Through a one-pot pathway, benzaldehyde (1 mmol), dimedone (1 mmol), Ethyl acetoacetate (1 mmol) and ammonium acetate (1.5 mmol) were conducted to a reflux tube containing 30 mg of catalyst and 2 ml solvent (EtOH). The current mixture was heated during stirring for 30 min at 60°C. After completion of reaction, the resulting solid residue of product was treated by hot ethanol then its magnetic catalyst separated by an external magnet. To purify final product, this final solution was heated to gain solid mixture which main product isolated by flash chromatography using EtOAc/n-Hexane as eluent.

Results and Discussion

Analysis of catalyst

The corresponding FT-IR spectra of Fe_3O_4@Sucrose is presented in Figure 1 the successful immobilization of sucrose on surface of magnetite has been confirmed by appearance of 1085, 1365, 1412, 1695, 2860 and 2922 cm^{-1} which are corresponded with attachment of sucrose vibration modes to primary free magnetite (574 cm^{-1}, Fe-O stretching mode).

In order for presentation of the more specific characterization, wide angle XRD pattern (Figure 2) thoroughly have shown pure magnetite (Fe_3O_4) core in nanoparticles (corresponded to JCPDS 75-0033 reference) [19]. The magnetic saturation value of nanoparticles before and after of sucrose-Fe_3O_4 core-shell was determined by vibrating sample magnetometer (VSM). The superparamagnetic behavior of magnetite and its sucrose-coated homologue are represented in Figure 3, showing no observed hysteresis (Figure 3). There is only a 17 emu/g decreasing corresponded to immobilized sucrose on the surface of magnetite (from 49 emu/g to 32 emu/g along immobilization of sucrose).

The diagram related to thermogravimetric analysis (TGA) of Fe_3O_4@Sucrose are depicted in Figure 4. According to the thermogravimetric (TG) and differential thermogravimetric (DTG) diagrams, weight loss of the catalyst occurred in one step, after 280°C to around of 630°C belongs to sugar part decomposition (around 40% w/w thermal decomposition occurred).

The surface morphology of catalyst surveyed via SEM-EDX technique. The energy-dispersive X-ray spectroscopy (EDX) of the Nano catalyst (Figure 5) proved the presence of the expected elements (H, C and O from Sucrose; O and Fe for Fe_3O_4) in such structure. The scanning electron microscope (SEM) micrographs of the catalyst has been shown in Figure 6 in which is a good agreement with calculated average size through Debye-Scherrer's equation (via XRD pattern of Figure 2).

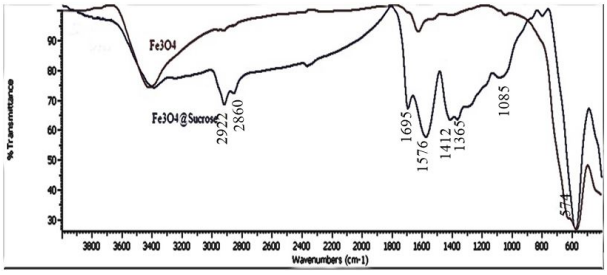


Figure 1: FT-IR spectrum of pure (upper) and sucrose-coated (lower) magnetite (Fe_3O_4).

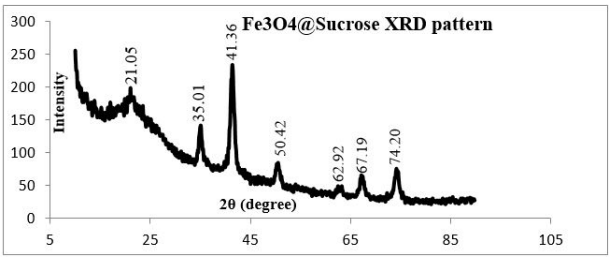


Figure 2: XRD pattern of Fe_3O_4@Sucrose.

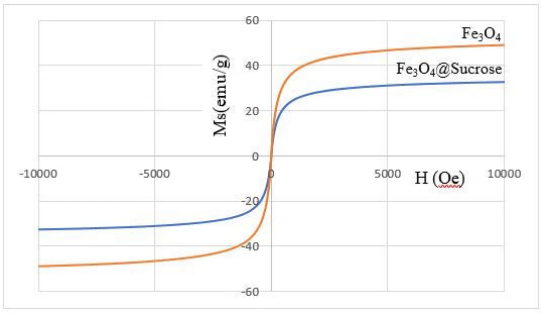


Figure 3: VSM curves corresponded to pure Fe_3O_4 and Fe_3O_4@Sucrose.

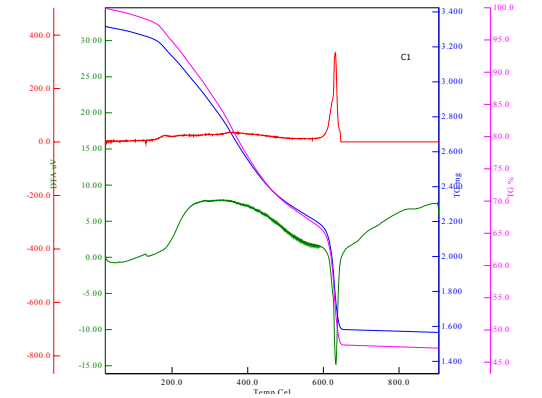


Figure 4: TGA diagram of Fe_3O_4@Sucrose nanoparticles.

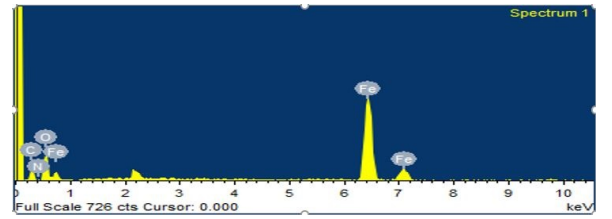


Figure 5: Abundance of each element on the surface Fe_3O_4@Sucrose NPs (EDX analysis).

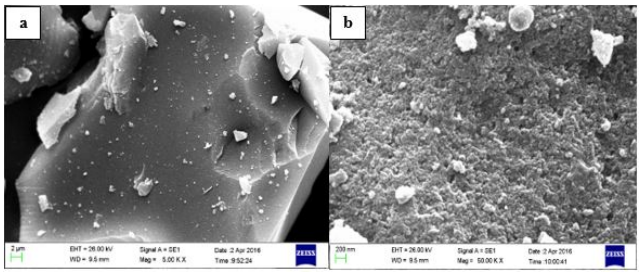


Figure 6: SEM images of Fe_3O_4@Sucrose NPs taken in two different scale: a) 2 μm and b) 200 nm.

Optimization steps

In the first step, eight different media tested for assigning of best solvent. The favorable result belongs to ethanol (EtOH) for both states of either in presence of 20 mg catalyst or without it (Figure 7). Here we could see first coordinating result with previous works [9,20]. As well as current strategy of earlier attempts, amount of catalyst (Figure 8) per one equivalent of reagents (Scheme 2) and reaction time (Figure 9) were optimized at 30 mg of catalyst and perceiving no further gradual increase after 30 min (when reaction improvement got steadily.) in yields of desired product, respectively. Final optimized chart depicted in Figure 10 is correlated to catalyst reusability. The most optimistic turn-over of catalyst after end of each step has determined five times (85%). Noticeable recession in yields percentages were considered for releasing sugar from primary catalyst during reaction test and its following work-ups.

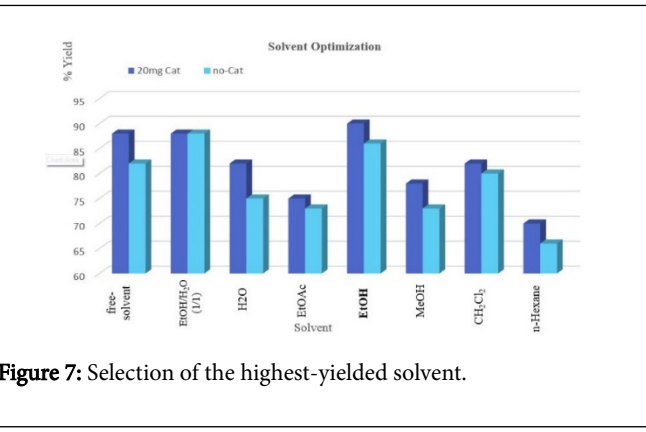


Figure 7: Selection of the highest-yielded solvent.

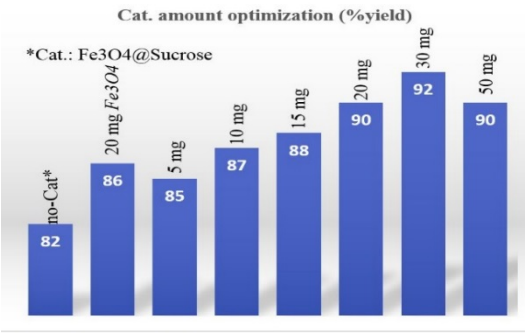


Figure 8: Amount of catalyst optimization.

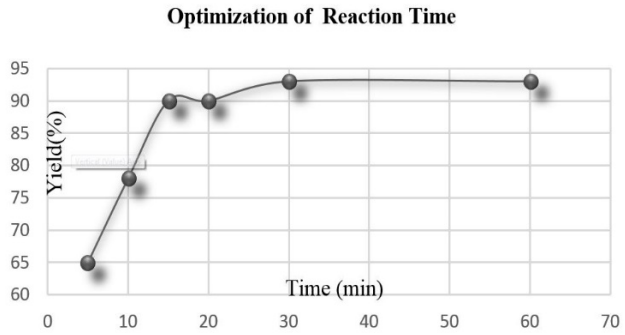


Figure 9: Optimization of passed time.

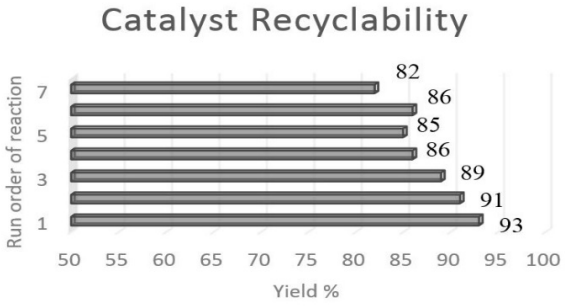
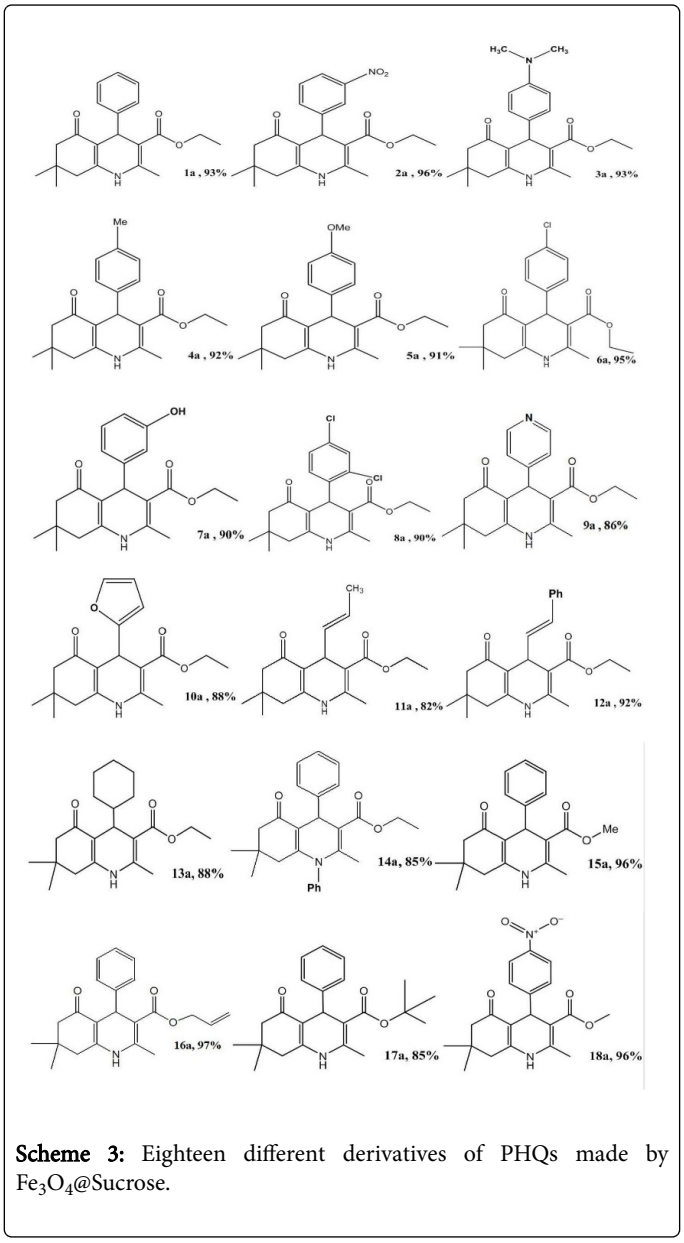


Figure 10: Usage justifiability of worked-up catalyst after seven runs.

Various derivatives

In order to survey on different structures, except dimedone and ammonium acetate (except only entry 14 situated with aniline), two other components altered. The total eighteen structures have efficiently been synthesized by mentioned NPs are demonstrated in subsequent division (Scheme 3). Discussion on the role of electron-donating or -withdrawing groups about aldehyde motifs have not been conclusive for trend of yield percentages and furtherly are out of capacity of this article. This conclusion could be solely related to irregular and fluctuating numbers of final yields of PHQs in an overall view. In addition, no obvious vision and rationalization has been comprehended along study of yields done on the ester-headed component of variable 1,3-dicarbonyls. All of related spectral and physical data of products is afforded in Supplementary Information file.



Scheme 3: Eighteen different derivatives of PHQs made by Fe_3O_4@Sucrose.

Conclusion

Whatever should be noted about this catalyst and its strength are afforded throughout in latter sections. In brief, the novel catalyst carried out 4-components one-pot Hantzsch reaction through nature of hydrogen-bond-donating catalyst to produce 18 various PHQs. We are willing to expand such simple tactics for running a wide reaction by applying various structures like carbohydrate that are represented here. Having no acidic catalyst is other point of benefits which could bring any formation of amine salt with amine motif of reaction. Such dominance let reaction go forward without interruption.

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