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Bifunctional PEG/NH_2 silica-coated magnetic nanocomposite: An efficient and recoverable core–shell-structured catalyst for one pot multicomponent synthesis of 3-alkylated indoles via Yonemitsu-type condensation

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ABSTRACT

In the present work, a new, green and recyclable bifunctional PEG/NH_2 silica-coated Fe_3O_4 nanoparticle was prepared and successfully characterized by FT-IR spectroscopy, scanning electron microscopy (SEM), X-ray powder Diffraction (XRD), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), vibrating sample magnetometer (VSM) and Brunauer–Emmett–Teller (BET) analysis. The catalytic activity of this dual function silica-iron oxide hybrid nanocomposite, Fe_3O_4@SiO_2–PEG/NH_2, was successfully tested in the straightforward one-pot synthesis of groups of biologically active 3-alkylated indoles via three-component reaction between indole, aromatic aldehydes, and C–H activated acids. The results exhibited that a synergistic effect existed between the PEG and base groups. PEG units not only increase the reactivity of carbonyl groups by hydrogen bonding but also these hydrophilic groups accelerate the reaction by absorption of producing water as by-product. The significant features of the present protocol that enhance its effectiveness from an economic as well as environmental benefits are high yields, easy work-up procedure, short reaction times, high atom-economy, and recyclability of the catalyst.

1. Introduction

The core–shell-structured nanocomposite materials comprising of magnetic cores and nonmagnetic shells have newly developed as an interesting field of research mainly due to unique physicochemical properties and great potential applications in the greening of global chemical processes. [1–3] In this regard, the Fe_3O_4 nanoparticles coated with a SiO_2 shell is extensively investigated. The silica-shell not only improves the dispersibility of iron oxide nanoparticle, it can protect the magnetic cores from oxidation [4–6]. Moreover, interest in the preparation of this class of core–shell-structured nanomaterial is also increasing dramatically because the silica-shell can be easily functionalized by different organic functional groups and used as solid supports to construct magnetically separable nanocatalysts [7].

The design and preparation of multifunctional core–shell nanomaterial containing different types of active sites for many potential catalytic applications have become an important task in modern synthetic chemistry [8–12]. Therefore, some of the research teams have been following new and inventive approaches towards merging multiple functional groups into heterogeneous nanocatalysts thus that they may perform in a cooperative form to upgrade the reactivity of the catalyst [13].

Furthermore, one of the present challenges in organic synthesis is the production of molecular diversity and complexity conducting to the construction of biologically active heterocyclic molecules from simple and readily available substrates. Today one-pot multicomponent reactions (MCRs), is a good approach to the synthetic chemists generally for the creation of the structurally complex molecules due to its various benefits containing short reaction times, high atom-economy, low-priced, reducing waste production, and eluding the costly purification procedure, thus aggrandizing green and sustainable chemistry [14–16].

Due to the inherent biological activities, the indole nucleus is one of the most intensively studied structural patterns by synthetic as well as biological chemists [10,17]. Among the various structural

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motifs, 3-substituted indoles have attracted particular attention as medicinally potent lead molecules and a key synthon for the synthesis of miscellaneous therapeutic agents [18,19] The prevalence of this scaffold in pharmaceutical drugs and abundant potentially biologically active natural products continue to be a direction in the improvement of new method to discover beneficial compounds [20].

The successful one-pot three component condensation reaction of indole with Meldrum's acid and an aldehyde, first reported by Yonemitsu in thirty-eight years ago, [21] facilitates the synthesis of gem-diheteroarylmethanes involving indolyl moiety. Recently a few approaches have been utilized for the synthesis of β-functionalized indole derivatives by the replacement of the Meldrum's acid moiety by other source of active methylene compounds like acetoacetates, [22] nitroacetates, [23] 4-hydroxycoumarin, [24] 4-hydroxy-6-methyl-2H-pyran-2-one, [25] dimedone, [26] and N, N-dimethylbarbituric acid [14,20]. However, most of these approaches proffer obvious advantages, but due to the some limitations such as use of expensive or toxic metal-based catalysts, using a large quantity of volatile and toxic organic solvents, and harsh reaction conditions, the search for and development of a facile and good-yielding, eco-friendly method for the one-pot synthesis of such biologically active gem-(β-dicarbonyl) arylmethane motifs is a challenging task.

By having these facts in mind and in conjunction with ongoing work in our laboratory on the synthesis of bifunctional silica coated magnetic nanocomposites and exploration of their applications as recoverable nanocomposite in the one-pot catalytic synthesis of useful building blocks and/or biologically active heterocyclic compounds [27–32], very recently we successfully prepared a novel dual-function silica-iron oxide hybrid based nanocomposite, $Fe_3O_4@SiO_2$–PEG/NH_2, and investigated its application as an eco-catalyst for the solvent-free synthesis of polyhydroacridines and polyhydroquinolines [33]. Now we would like to test the catalytic activity of this nano magnetically-recoverable heterogeneous catalyst in the one-pot multicomponent Yonemitsu-type synthesis of 3-substituted indoles.

2. Experimental section

2.1. General

All chemical materials were purchased from Merck chemical company, used with no additional purification. The known products were recognized by comparison of their melting points and spectral data with their announced authentic samples in the articles. The ^{1}H NMR (400 or 300) and ^{13}C NMR (100 or 75 MHz) spectra were recorded on a Bruker AVANCE III instrument spectrometer using Tetramethylsilane as the internal standard. Reactions were routinely checked with thin-layer chromatography (TLC) using Merck silica gel 60 F_{254} plates. Melting points recorded in the Electrothermal IA9200 apparatus. Fourier transmission infrared (FT-IR) spectra of the powders (as pellets in KBr) were obtained using a Fourier transmission infrared spectrometer (Perkin Elmer BX-II) FT-IR spectrometer. X-ray diffraction (XRD) pattern of the sample was obtained on a Philips X-ray diffraction model PW 1840. The particle morphology was studied with SEM (Philips XL30 scanning electron microscope) and HR-TEM (FEI-Tecnai F 20–200 KV). Thermogravimetric analysis (TGA) of the catalyst was performed on a BAHR SPA 503 system under an N_2 atmosphere at a heating rate of 10 °C min^{-1}, over the temperature range of 25–750 °C. The magnetic property was determined on VSM (Meghnatis Daghigh Kavir Co Iran) vibrating sample magnetometer at room temperature. Nitrogen adsorption analysis was conducted at 77.4 K on a Micrometrics ASAP-2020 sorption-meter.

2.2. Preparation of the magnetic Fe_3O_4 nanoparticles

Nano-Fe_3O_4 was prepared using a co-precipitation method adapted from our previous reports [34]. To a solution of $FeCl_2 \cdot 4H_2O$ (3.1736 g, 16 mmol) in deionized water (320 ml), $FeCl_3 \cdot 6H_2O$ (7.57 g, 28 mmol) was added. After 1 h stirring the mixture under the nitrogen atmosphere at 80 °C, 40 ml ammonium hydroxide (25%) was rapidly added to the reaction mixture. The solution was stirred in the presence of nitrogen flux at 80 °C for 1 h and then cooled to room temperature. The precipitated particles were washed five times with hot water and collected with an external magnet. Lastly, the nano-Fe_3O_4 was dried under vacuum at 70 °C.

2.3. Preparation of silica-coated magnetic nanoparticles ($Fe_3O_4@SiO_2$)

Silica-coated magnetite nanoparticles were synthesized corresponding to our previous reports [35]. 2.0 g of the synthesized Fe_3O_4 nanoparticles were suspended in the mixture of solvent, water (120 ml) / ethanol (450 ml), and then ultrasonically dispersed at ambient temperature In the presence of nitrogen atmosphere for 25 min, and then 10 ml of ammonium hydroxide 25% solution was added to the suspension .Next, 2.0 ml TEOS was dropwise added to this suspension and stirred for 12 h, thus silica was coated the Fe_3O_4 nanoparticles. The silica-coated magnetic nanoparticles ($Fe_3O_4@SiO_2$) were finally isolated from the mixture using a magnet, and then washed several times with deionized water and dried at 60 °C under vacuum.

2.4. Synthesis of 3-chloropropyl-functionalized magnetic silica nanoparticles ($Fe_3O_4@SiO_2$–Cl)

2.0 g of $Fe_3O_4@SiO_2$ was ultrasonically dispersed in 100 ml of dry toluene for 30 min. Then, 1 ml of (3-chloropropyl) trimethoxysilane was added slowly into the mixture and ultrasonicated for 30 min. Finally, the mixture was refluxed at 110 °C under the nitrogen atmosphere for 24 h. The $Fe_3O_4@SiO_2$–Cl nanoparticles were isolated by a magnet and washed with toluene and ethanol and then dried in a vacuum.

2.5. Synthesis of PEG-functionalized magnetic silica nanoparticles ($Fe_3O_4@SiO_2$–PEG)

To a solution of PEG-300 (1.5 g, 5 mmol) in toluene (20 ml), a suspension of NaH (0.119 g, 5 mmol) in toluene (10 ml) was added at 0 °C under nitrogen atmosphere. Then, the system was stirred at 60 °C for 1 h to complete the terminal alkoxides formation of PEG. To the mixture, $Fe_3O_4@SiO_2$–Cl (1.5 g) suspended in 70 ml toluene, was added and stirred at 60 °C for 96 h. The $Fe_3O_4@SiO_2$–PEG nanoparticles were separated with a magnet and washed with ethanol and then deionized water and dried in a vacuum.

2.6. Synthesis of NH_2-functionalized PEG-modified magnetic silica nanoparticles ($Fe_3O_4@SiO_2$–PEG/NH_2)

1.0 g of $Fe_3O_4@SiO_2$–PEG was dispersed in toluene (100 ml) and ultrasonicated for 30 min. 2.0 ml of (3-aminopropyl) triethoxysilane was added slowly to the suspension and ultrasonicated for 30 min. Afterward; the mixture was stirred at 80 °C under the nitrogen atmosphere for 12 h. The $Fe_3O_4@SiO_2$–PEG/NH_2 nanoparticles were isolated by a magnet and washed with ethanol and then acetone and dried at 50 °C.

2.7. General procedure for synthesis of 3-alkylated indoles ($4a_1$–$4e_6$)

To the 1 mmol of C–H activated acid (dimedone, 4-hydroxycoumarin, 4-hydroxy- 6-methyl-2-pyrone, 1, 3-indandione,

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