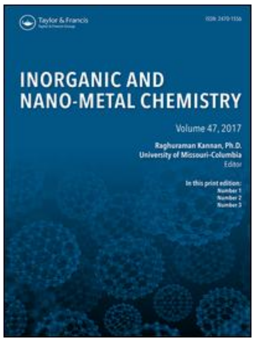

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Green synthesis of aminocarbonyl compounds using a nanostructured heterogeneous catalyst under mild reaction conditions

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ABSTRACT
The synthesis of aminocarbonyl derivatives as biologically active compounds by using polyethylene glycol (PEG-400)-SO_3H-coated Fe_2O_3 is reported. The heterogeneous nanocatalyst was prepared via *in-situ* co-precipitation method and its structure and morphology was characterized by Fourier-transform infrared spectroscopy, energy-dispersive X-ray analysis, X-ray diffraction pattern, field-emission scanning electron microscopy image, vibrating sample magnetometer curves, N_2 adsorption-desorption isotherm and inductively-coupled plasma analysis. Noteworthy, the green composite nanocatalyst was applied for the one-pot multicomponent synthesis of aminocarbonyl compounds at room temperature. This work had advantages such as significant nanocatalyst activity, recoverability, short process time, mild reaction conditions and high products yields.

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Heterogeneous nanocatalyst; nanocomposite; magnetic nanoparticles; polyethylene glycol (PEG-400); aminocarbonyls

Introduction

Multicomponent reactions (MCRs) as an efficient and powerful strategy in synthetic organic chemistry have received considerable attention by organic chemists. MCRs are reactions in which three or more starting materials react together in one-pot conditions at the same time to synthesize the products. Noteworthy, most of the reactive atoms were observed in the final products. They have several advantages in terms of environmentally benign due to reducing the number of synthetic steps, energy consumption and waste production.[1]

Much attention has been paid to aminocarbonyl compounds as an important class of *N*-containing heterocyclic compounds due to their interesting biological activities. Mannich reaction is the most known synthetic method for the synthesis of these compounds, in which three compounds under appropriate catalytic conditions brings together to form the desired products. Recently, an increasing interest has been focused on the synthesis of aminocarbonyl compounds due to their significant biological activity and several methods have been reported in the literature for the synthesis of these important nucleuses in the presence of various catalysts. These methods, however, have a few drawbacks such as toxic catalyst, longer reaction time and using of expensive metal salt as catalyst. Moreover, the main disadvantage of some of them is that the catalysts are destroyed and cannot be recovered and reused. Thus it is clearly evident that the design and development of inexpensive, general, and reusable catalysts in conjunction with multicomponent reactions strategy for the synthesis of aminocarbonyl compounds is of prime importance.[2]

According to green chemistry objective, the recovery and reusability of catalysts is an important factor in the organic synthetic reactions. Recently, magnetic nanoparticles (MNPs) have received considerable attention in the field of green sustainable catalysis due to easy preparation and functionalization, high surface area, high dispersion, high reactivity and easy separation due to their magnetic properties and nanoscale size. Moreover, the immobilization of biocompatible polymers onto the surface of (MNPs) such as Fe_2O_3 or Fe_3O_4 can provide a wide range of magnetic-functionalized catalyst with higher activity, improved colloidal stability in physiological media and low toxicity. Furthermore, these functionalized MNPs have emerged widely for organic synthesis.[3,4]

Poly(ethylene glycol) (PEG) as a biocompatible polyether is widely used for coating nanoparticle's surface.[5] Immobilization of PEG onto the surface of nanoparticles will enhance hydrophilicity and water-solubility of nanoparticle surfaces and minimizes agglomeration. In the recent years, several methods have been exploited for the modification of PEG-based MNPs. It is found that most of them suffer from some drawbacks such as complication and harsh reaction conditions.[6] In this regard, the introduction of new strategy for the synthesis of PEG-coated MNPs is required.

In following of our previous work on green magnetically recoverable nanocatalysts and our interest in one-pot MCRs,[7–13] herein, we wish to report a facile MCR for the synthesis of β-aminocarbonyl compounds **4a–l** via the condensation of aniline **1**, aldehyde **2** and ketone compound **3** in the presence of PEG-SO_3H-coated Fe_2O_3 as a superparamagnetic heterogeneous nanocatalyst at room temperature in high yields with rather short reaction times (Scheme 1).

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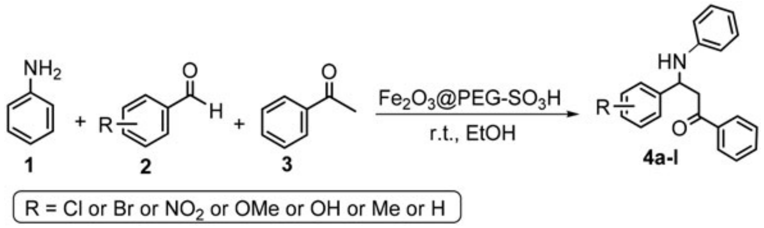


Scheme 1. Mannich-MCR for the synthesis of products **4a-l** catalyzed by Fe_2O_3@PEG-SO_3H.

Experimental

Preparation of Fe_2O_3@PEG nanoparticles

Fe_2O_3@PEG nanoparticles were prepared *via in-situ* co-precipitation method. Initially, 2.4 g of $FeCl_3$ and 3.0 g of $FeCl_2.5H_2O$ was solved in 80 mL of deionized water. After that, 30 mL of PEG-400 was mixed with 10 mL of $NH_3.H_2O$ at 30 °C in a three-necked flask. Then, the mixture of $FeCl_3$ and $FeCl_2.5H_2O$ was slowly added in NH_3-PEG solution during 130 min at 30 °C. The obtained Fe_2O_3/PEG precipitate was washed with deionized water until pH was reached to 7. Finally, it was dried at 80 °C in an oven.

Preparation of Fe_2O_3@PEG-SO_3H nanoparticles

At first, a 500-mL suction flask was equipped with a constant pressure dropping funnel. The gas outlet was connected to a vacuum system through an adsorbing solution of alkali trap. Fe_2O_3@PEG-400 (2.0 g) was added to the flask and dispersed by an ultrasonic bath for 10 min in chloroform (50 mL). Then, a solution of chlorosulfonic acid (1 mL) in chloroform (20 mL) was added dropwise over a period of 30 min at 0 °C. After completion of the addition, the mixture was shacked for 90 min, to remove residual HCl. After that, Fe_2O_3@PEG-SO_3H was separated from the reaction mixture by a magnetic bar and washed several times with dry chloroform. Finally, Fe_2O_3@PEG-SO_3H was dried under vacuum at 60 °C.

General procedure for the synthesis of aminocarbonyl compounds 4a–l

Initially, a mixture of 2.0 mmol of aromatic aldehyde and 2.0 mmol of amine and 0.010 g of Fe_2O_3@PEG-400-SO_3H was added to 5 mL of absolute EtOH as a green solvent. After that, the mixture was stirred at room temperature for 5-10 min until the starting materials had almost disappeared (monitored by thin layer chromatograph, TLC). Then, 3.0 mmol of ketone was added to the mixture and the mixture was stirred and the mixture was stirred for the appropriate time until the completion of the reaction as monitored by TLC. The catalyst was separated easily by an external magnet and reused as such for the next experiments. The products were isolated pure just by recrystallization from hot EtOH and no more purification was needed.

Results and discussion

Characterization of the prepared Fe_2O_3@PEG-SO_3H nanocatalyst

Fe_2O_3@PEG-400-SO_3H nanocatalyst was prepared by *in situ* co-precipitation method. As can be seen in Figure S1, the FT-IR spectrum of the Fe_2O_3@PEG-SO_3H magnetic nanocatalyst can verify the preparation of the expected product. It indicated that PEG was successfully composed onto the surfaces of Fe_2O_3 nanoparticles. The functionalization of SO_3H groups on Fe_2O_3@PEG-400 surface was also approved by the predicted almost all of the absorption bands.

Figure S2 shows the XRD measurements were performed with the dried powder samples of bare and PEG coated MNPs to identify the crystal phases present in the samples. The XRD pattern of a representative Fe_2O_3@PEG-SO_3H (curve a) along with bare Fe_2O_3 NPs (curve b). The pattern of the Fe_2O_3@PEG-SO_3H showed all the major peaks corresponding to Fe_2O_3. The diffraction angles (2θ) of can be assigned to appropriate planes, respectively; which are in accordance with Fe_2O_3 reference pattern. Additionally, one peak around $2\theta = 25°$ along with small peaks due to the PEG-SO_3H polymer are observed in the case of the Fe_2O_3@PEG-400-SO_3H. These results confirmed the surface modification of the Fe_2O_3 NPs with PEG-SO_3H.

The result of the EDX analysis of the Fe_2O_3@PEG-SO_3H magnetic nanoparticles was illustrated in Figure S3. It confirms the presence of carbon, oxygen and sulfur elements in the nanocatalyst. Furthermore, inductively coupled plasma (ICP) analyses of the catalysts revealed that the metal (Fe) content of the catalyst (±0.4%) were close to target metal content (12 wt%).

To clarify the morphology of the nanocatalyst, FE-SEM images of Fe_2O_3@PEG-SO_3H were provided (Figures S4 in supplementary materials). It can be seen that the nanocatalyst was uniformly prepared and the main structure of nanocatalyst was rod-like morphology along with the spherical iron oxide (II, III) nanoparticles. In addition, the nanosized structure and morphology of the catalyst was proved by FE-SEM images.

The magnetic properties of Fe_2O_3, Fe_2O_3@PEG and Fe_2O_3@PEG-SO_3H were measured by VSM curves at room temperature. As can be seen in Figure S5, the hysteresis loops of the superparamagnetic behavior can be clearly observed for all the nanoparticles. The saturation magnetization value of uncoated Fe_2O_3 MNPs, Fe_2O_3@PEG and Fe_2O_3@PEG-SO_3H confirmed the appropriate immobilization of PEG and SO_3H on the surface of the Fe_2O_3 NPs.

Table 1. One-pot synthesis of the compounds **4a–l** by using the magnetic nanocatalyst.

					Mp (°C)	
Entry	R	Product	Time (min)	Yield[a] (%)	Found	Reported [14]
1	4-OMe	**4a**	45	80	147–148	147–149
2	4-Br	**4b**	25	92	127–128	127–129
3	4-Me	**4c**	50	65	131–132	130–132
4	4-Cl	**4d**	25	95	116–117	116–119
5	H	**4e**	50	72	170–171	169–170
6	3-OH	**4f**	30	80	126–128	125–127
7	3-NO_2	**4g**	30	87	141–142	140–142
8	3-Br	**4h**	25	90	94–95	95–96
9	3-OMe	**4i**	30	78	106–107	106–107
10	2-NO_2	**4j**	40	80	160–161	158–162
11	2-Cl	**4k**	45	85	50–52	52–53
12	2-OMe	**4l**	50	65	121–123	122–124

[a]Isolated yield.

The specific surface area of the prepared nanomaterial was measured by using Brunauer–Emmett–Teller (BET) analysis with N_2 adsorption-desorption. BET surface area of Fe_2O_3@PEG-SO_3H was about 45 m^2 g^{-1}. The reduced amount of surface area in comparison with iron oxide (II, III) nanoparticles may be the consequence of immobilization of PEG-OSO_3H on Fe_2O_3 NPs.

Catalytic application of in the synthesis of aminocarbonyl compounds 4a-l

Initially, to optimize the reaction conditions for the synthesis of aminocarbonyl compounds, various parameters were studied on the reaction aniline (2 mmol), 4-chlorobenzaldehyde (2 mmol) and acetophenone (3 mmol), as a pilot test. First, the effect of the catalyst amount on the reaction yield was studied. It was found that using 0.01 g of the Fe_2O_3@PEG-SO_3H nanocatalyst is sufficient to complete the reaction and give **4d** after 25 min in 95% yield in 5 mL of EtOH as a green solvent at room temperature. The results summarized in Table S1. To compare the efficiency of ethanol, several solvents with different polarities were tested using the model reaction in the presence Fe_2O_3@PEG-SO_3H. As it is obvious from the results, ethanol was the superior solvent for this study than MeOH, H_2O, MeCN, DMF, *n*-hexane and ether in the presence of the nanocatalyst at room temperature.

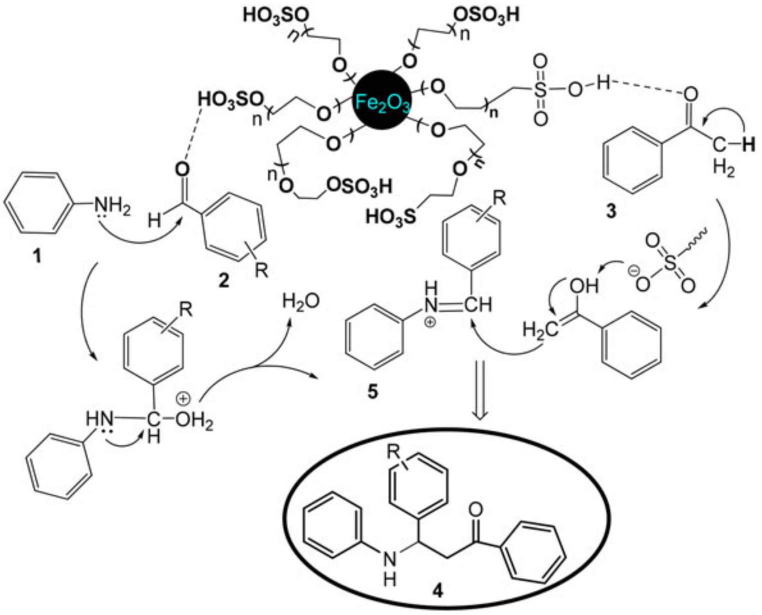
Finally, a comparison was done between the present work and others earlier reports for the synthesis of **4d**. The results summarized in Table S2 clearly demonstrate the superiority of the present work in saving energy, high yields of the products and the reusability of the nanocatalyst.

In order to investigate the scope and limitations of the present protocol and to show the application of Fe_2O_3@PEG-SO_3H in the synthesis of aminocarbonyl compounds, a variety of products were synthesized under the optimized conditions. The results summarized in Table 1 shows that all products were obtained in good-to-excellent yields after appropriate reaction times.

The suggested possible mechanism for the formation of aminocarbonyl compounds **4a-l** is shown in Scheme 2. On the basis of the literature and substrates chemistry, at first step the amine **1** attacks to the activated aldehyde **2** in the presence of Fe_2O_3@PEG-SO_3H, to form iminium **5**. Moreover, the enol form of ketone **3** was formed *via* tautomerisation in the presence of the nanocatalyst. Finally, the enol was added to **5** to yield the desired product **4.**[14]

Recyclability of the nanocatalyst

The recoverability of Fe_2O_3@PEG-400-SO_3H was studied in the pilot experiment. After completion of the reaction, it was separated by an external magnet and washed with CH_2Cl_2, dried and reused in subsequent reactions. As can be seen in Figure 1, the nanocatalyst can be reused at least five times without any significant decrease in the products yields. Additionally, after the nanocatalyst was reused five



Scheme 2. A proposed mechanism for the formation of aminocarbonyls using PEG-based magnetic nanocatalyst.

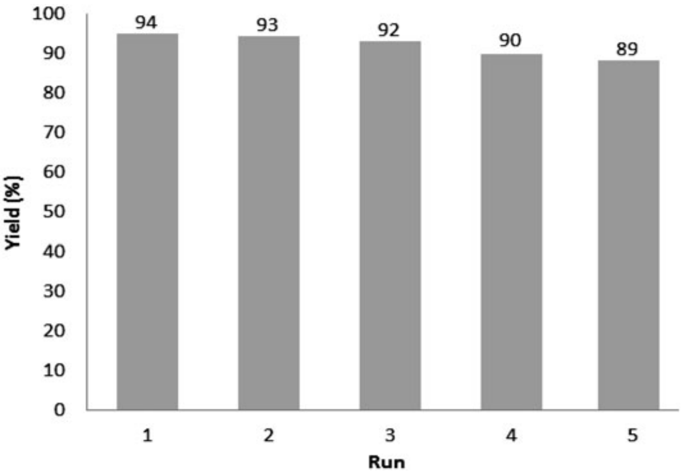


Figure 1. Recycling of the nanocatalyst in the synthesis of **4d.**

times in the model reaction, to study the structure and morphology of nanocatalyst, FT-IR spectroscopy (Figure S9 in supplementary material) and ICP analysis were taken again. According to those analyses can be concluded that structure of the nanocatalyst and the percentage of iron loading was not significantly changed or leached.

Conclusions

In summary, a green, cost-effective, magnetic heterogeneous nanocatalyst, Fe_2O_3@PEG-400-SO_3H, was prepared through a facile process and completely characterized by FT-IR, FE-SEM, XRD, EDX, VSM, BET and ICP instrumental analyses. Then, its catalytic performance was investigated in the synthesis of aminocarbonyl compounds via Mannich MCR. The products were obtained in high-to-excellent yields at room temperature under simple reaction conditions. The green nanocomposite catalyst was easily recovered by an external magnet and reused efficiently several times without significant decrease in its activity.

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