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Magnetic mesoporous poly-melamine–formaldehyde: an efficient and recyclable catalyst for straightforward one-pot synthesis of imidazo[1,2-a]pyridines

Mohammad Heydari¹ · Najmedin Azizi² · Zohreh Mirjafari¹ · Mohammad Mahmoudi Hashemi¹

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Abstract

Magnetically separable mesoporous poly-melamine–formaldehyde nanocomposite ($Fe_3O_4@mPMF$) has been synthesized and characterized by FTIR spectroscopy, SEM, XRD spectroscopy and EDS. The magnetically separable $Fe_3O_4@mPMF$ catalyst had excellent efficiency for the synthesis a wide diversity of imidazo[1,2-a]pyridines by a three-component reaction of a 2-aminopyridine, aldehyde and isocyanide in good-to-excellent yields within a short reaction time, through an environmental friendliness and straightforward procedure. The nanocomposite that is easily recoverable and also found to be reusable can be recovered and reused when the reaction is completed for several times without distinct deterioration in catalytic activity.

Graphic abstract



Keywords $Fe_3O_4@mPMF \cdot Groebke reaction \cdot Imidazo[1,2-a]pyridines \cdot Green chemistry \cdot Isocyanide reaction$

Introduction

The development of simple and low-cost protocols to improve the preparation of important heterocyclic compounds while combining economic and environmental

Najmedin Azizi azizi@ccerci.ac.ir

aspects has been an active topic in the field of modern organic chemistry [1, 2]. One approach to address this challenge involves the development of any operationally simple, green and practical multicomponent reactions (MCRs) [3–11]. Among the known MCRs, those based upon the reactivity of isocyanides play a pivotal role in organic synthesis for their capacity to provide complex products from simple reactants [12–23]. Due to the high biological activity of therapeutically relevant fused imidazoles bridgehead nitrogen heterocyclic in a number of biologically or pharmacologically important compounds, various methods have been reported for their synthesis via multicomponent reactions [24–27]. Among the reported methods,

¹ Department of Chemistry, Science and Research Branch, Islamic Azad University, Tehran, Iran

² Chemistry and Chemical Engineering Research Center of Iran, P.O. Box 14335-186, Tehran, Iran

three-component isocyanide-based reactions starting from 2-aminoazine, aldehydes and isocyanides catalyzed by Lewis or Bronsted acids as well as ionic liquid are common strategies [28–36].

Traditional homogenous catalysts consumed in large amounts for a range of products in chemistry, pharmacy, food, flavor and coatings sectors were the main sources of pollution [37, 38]. On the other hand, magnetically separable nanostructured catalysts showing the enhanced and sustainable properties is receiving increasing attention as an alternative reaction media that circumvent the problems associated with many of the traditional catalysts [39, 40].

Porous organic polymers have recently attracted huge research interest due to the regular pore structure and high surface area, thereby proving potential applications in areas of energy and environmental research, catalyst and supports supercapacitors [41, 42]. Mesoporous poly-melamine-formaldehyde (mPMF) polymer is an interesting catalyst in the context of green chemistry due to their unique properties, such as a high surface area, good porosity and high density of amine and triazine groups [43, 44]. In addition, by incorporating a functional group to the mPMF, it was possible to make functional polymer, that provides more active reaction sites, which was favorable for the catalytic applications [45-49]. However, pure mPMF has usually some shortcomings including a light density, low specific surface area, and difficult to separate from the reaction mixture leading to a fair obstacle in its applications. Therefore, it is necessary to solve the above-mentioned issues, and coupling with magnetic Fe₃O₄ nanoparticle is a feasible route and may offer a convenient solution to catalytic recycling problem [49].

Experimental

General

All chemicals such as aldehydes, isocyanide, amine, Fe_3O_4 , melamine and paraformaldehydes were commercially available. Melting points were determined on Buchi 535 melting point apparatus. ¹H NMR spectra were recorded on 500 MHz NMR spectrometer using DMSO-d₆ as solvent. Solvents were distilled before use. FTIR spectra were determined on a Bruker Vector-22 infrared spectrometer using KBr disks.

Preparation of magnetic mesoporous poly-melamine-formaldehyde

The magnetic Fe_3O_4 nanoparticle was synthesized using a modified method reported in the literature [43]. Melamine (0.378 g, 3 mmol), paraformaldehyde (1.8 eq. 0.162 g, 5.4 mmol) and Fe_3O_4 (0.2 g) were mixed with 3.36 mL of

dimethyl sulfoxide (DMSO) in a 25 mL Teflon container secured in a steel reactor. The reaction mixture was heated to 120 °C in an oven for 2 h. The reactor was then carefully removed from the oven for stirring on a magnetic stirrer plate to obtain a homogeneous solution. It was then heated to 170 °C in the oven for 72 h. The reaction was allowed to cool to room temperature, and the obtained solid was crushed, filtered and washed with acetone, ethyl acetate and CH_2Cl_2 . The resulting solid was dried under vacuum at 80 °C for 24 h (Scheme 1).

General procedure

A test tube, equipped with a magnetic stir bar, 2-aminopyridine (0.2 mmol), benzaldehyde (0.2 mmol), cyclohexyl isocyanide (0.2 mmol) and magnetic mPMF(10 mg), was added in EtOH (1 mL), respectively, and the resulting mixture was stirred at 60 °C until the reaction was complete. After completion of the reaction controlled by TLC, the crude product was concentrated under reduced pressure, and the solid residue was crystallized from ethyl acetate. All synthesized compounds are known and were characterized by melting points found to be identical with the ones described in literature. white powder, mp = $176-178 \degree C$, ¹H NMR (500 MHz, CDCl₃): $\delta = 1.22$ (s, 3H, CH), 1.34 (d, *J*=10 Hz, 2H, CH), 1.63 (s, 3H, CH), 1.69 (m, 2H, CH), 1.74 (d, J=Hz, 2H, CH), 2.98-3.01 (m, 1H, CH), 4.18-4.21 (br s, 1H, CH), 7.17 (m, 1H, H), 7.39-7.42 (m, 1H, CH), 7.46-7.50 (m, 3H, Ar-H), 8.17 (d, 2H, Ar-H) 8.21 (m, 1H, Ar–H), 8.44 (d, *J*=5 Hz, 1H, Ar–H).

Results and discussion

This project is a part of our ongoing effort to develop green chemistry toward several multicomponent reactions for the synthesis of fused heterocycle compounds [50–53]. In continuation of this project, we now report a one-pot synthesis of 3-aminoimidazo-fused heterocycles by a three-component reaction of 2-aminopyridine, aldehyde and isocyanide in the presence of magnetic mPMF as a promising recycle catalyst. Magnetic mPMF was synthesized from the melamine precursors according to previous literatures [40]. Hydrothermal reaction of the melamine and paraformaldehydes in the presence of Fe₃O₄ produces the requisite magnetic mPMF in a simpler manner (Scheme 1).

The morphology and structure of the $Fe_3O_4@mPMF$ were investigated by SEM, FTIR spectroscopy, XRD spectroscopy and EDX spectroscopy. The FTIR spectra exhibit the patterns of a high density of triazine and aminal (-NH-CH2-NH-) functional groups present in $Fe_3O_4@mPMF$ that are shown in Fig. 1. FTIR spectrum of shows broad peaks associated with -NH-stretching and



Scheme 1 Synthesis of magnetic mPMF



Fig. 1 FTIR spectra of Fe₃O₄@mPMF

physisorbed water molecules at 3429 cm⁻¹ together with the band at 2998 cm⁻¹ (CH₂ stretching). Other characteristic peaks around 1337 cm⁻¹ indicate that the triazine units are efficiently incorporated in PMF sample. The characteristic broad peak of Fe–O at 580–660 cm⁻¹ is attributed to the existence of Fe₃O₄ MNPs.

The chemical composition and percentage of $Fe_3O_4@$ mPMF were confirmed using energy-dispersive spectroscopic (EDS) analysis which clearly showed the presence of C, N, Fe and O and confirmed that the Fe_3O_4 nanoparticles were successfully introduced onto the surface of PMF (Fig. 2). Scanning electron microscopy (SEM) revealed that PMF formed a foam-like structure with interconnected mesoporous networks (Fig. 3). After Fe_3O_4 nanoparticles were introduced and grafted onto the surface of PMF, the morphological properties of PMF keep intact.

The crystal structure of the of $Fe_3O_4@mPMF$ was measured by XRD, and the results are shown in Fig. 4. The XRD pattern of $Fe_3O_4@mPMF$ shows characteristic peaks and relative intensity, which match well with the standard Fe_3O_4 sample. The broad peak at 2θ of 27° and 45° are consistent with an amorphous mPMF in the nanocomposite.

To explore the feasibility of $Fe_3O_4@mPMF$ as recyclable catalyst in the isocyanide-based multicomponent reaction,



Fig. 3 FE-SEM images of Fe₃O₄@mPMF



Fig. 4 X-ray diffraction pattern of Fe₃O₄@mPMF

 Table 1 Optimization of reaction conditions



Entry	Fe ₃ O ₄ @mPMF (mg)	Solvent	Yields (%) ^a
1	5	Ethanol	62
2	10	Ethanol	74
3	15	Ethanol	81
4	20	Ethanol	94
5 ^b	20	Ethanol	48
6 ^c	20	Ethanol	90
7 ^d	20	Ethanol	25
8	40	Ethanol	94
9	20	Water	68
10	20	Ethylacetate	70
11	20	CH ₃ CN	74
12	20	THF	46
13	20	CH ₂ Cl ₂	75
14	20	Methanol	94

 $^a\mathrm{Isolated}$ yields, $^b\mathrm{room}$ temperature, $^c\mathrm{PMF}$ as catalyst, $^d\mathrm{Fe}_3\mathrm{O}_4$ as catalyst

the reaction of benzaldehyde (1a), 2-aminopyridine (2) and cyclohexyl isocyanide (3) was selected as a model to find out the optimal reaction conditions and the results are mentioned in Table 1. In our initial experiments, we evaluated various trial reactions in the model reaction. The experimental process could be easily achieved with simple operation under mild reaction conditions. Our studies revealed that imidazo[1,2-a]pyridin 4a was formed in excellent yields (94%) in the presence of Fe₃O₄@mPMF, and the reaction was complete within 120 min furnishing **4a** in 94% yield (Table 1, entry 8). The optimal amount of the Fe₃O₄@mPMF was 20 mg, beyond which further increase in the amount of the catalyst did not increase the yield appreciably. The influence of reaction temperature on yield was investigated. The results show that 60 °C is sufficient to carry out reaction in the optimum yield and increase in temperature further does not enhance the yield. Additionally, the influence of various commercial aprotic and protic solvents like THF, CH₃CN, ethyl acetate, methanol and water on the reaction yield was investigated and the results are given in Table 1 (entries 9–14). Control experiments performed using PMF (Table 1, entry 6) and Fe₃O₄ (Table 1, entry 7) did not offer more than 94% of desired product.

With the optimized reaction conditions, we extended our studies to one-pot multicomponent reaction of various substituted aldehydes, 2-aminopyridine and cyclohexyl isocyanide in the presence of 20 mg of Fe_3O_4 @mPMF using ethanol as solvent to evaluate the scope of this methodology, and the results are presented in Table 2. As shown in Table 2, this procedure represents an efficient and general access to imidazo[1,2-a]pyridines derivatives with any kind of different functional group, and all the corresponding products were obtained in good-to-excellent yields. The electronic nature of the aldehydes had an influence on the reaction efficiency and benzaldehydes with an electron-withdrawing group on the aryl ring like nitro, bromo and chloro which afforded the corresponding imidazo-[1,2-a]pyridines in excellent yields and with shorter reaction times. For benzaldehydes bearing an electron-donating group such as methyl and methoxy, the product was obtained in moderate yield with longer reaction times. Interestingly, some heteroaryl aldehydes also underwent the multicomponent reaction in good yields.

In addition, our green procedure was expanded from the laboratory scale to the gram scale that is eco-friendly manner for industrial preparation. The model reaction was carried out in a 10 mL ethanol using 10 mmol of reactants in the presence of 50 mg of Fe₃O₄@mPMF. After 200 min., **4a** was obtained in 90% yield.

An attractive feature of $Fe_3O_4@mPMF$ as catalyst is being facile, and rapid separation by using a magnet is highlighted in Fig. 5. Further investigation involved the reusability of the $Fe_3O_4@mPMF$ for model reaction in the production of **4a** under optimized conditions for 5 mmol scale (Table 2, entry 1). Upon the completion of the reaction, $Fe_3O_4@$ mPMF was easily separated by using an external magnet. The recovered $Fe_3O_4@mPMF$ was washed with ethyl acetate and dried under vacuum. The resultant residues were used directly without further treatment for the next run after being charged with fresh starting materials. Using this procedure, $Fe_3O_4@mPMF$ could be reused up to five times without any significant loss of the initial catalytic activity (Fig. 5). The







atomic absorption spectrometer (FAAS) analysis. After compilation of reaction, Fe_3O_4 @mPMF was magnetically separated and the supernatant was analyzed in order to establish the leached quantity of total iron. The leaching of iron was obtained below the detectable level.

Conclusion

Fig. 5 Recycling results of the $Fe_3O_4@mPMF$

FTIR spectrum of recovered Fe₃O₄@mPMF suggested no significant change in functionality. Furthermore, recycled sample was prepared for the Fe₃O₄ leaching study by flame

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In summary, novel $Fe_3O_4@mPMF$ were synthesized and investigated as a non-toxic and reusable catalyst in the synthesis of fused imidazoles bridgehead nitrogen heterocyclic compounds from the Ugi-type isocyanide-based multicomponent reaction in a clean and efficient manner. The mild reaction conditions, good-to-excellent yields, short reaction times and recyclability of the Fe_3O_4 @mPMF are the outstanding features of the current work [54–57].

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