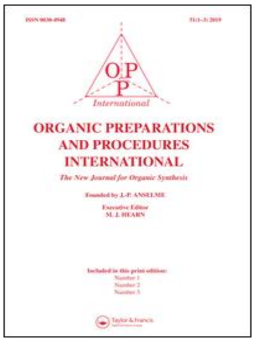

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EXPERIMENTAL PAPER

One-pot Synthesis of Pyranoquinoline Derivatives Using a New Nanomagnetic Catalyst Supported on Functionalized 4-Aminopyridine (AP) Silica

Amir Shabanloo, Ramin Ghorbani-Vaghei, and Sedigheh Alavinia

Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Iran

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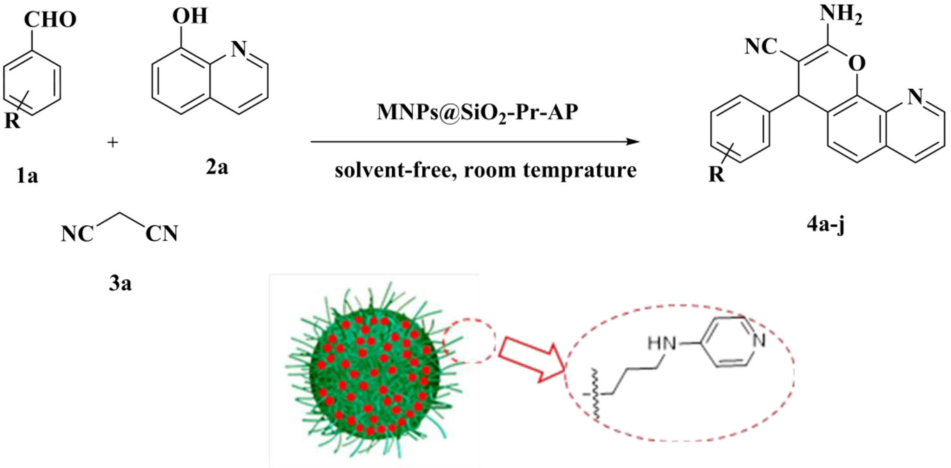
Multi-component reactions (MCRs) are important tools in combinatorial chemistry because of their capability to prepare target compounds in high yields with superior atom economy.[1] Heterogeneous catalysts have attracted renewed attention over homogeneous catalysts, because of their simplicity in recovery and regeneration.[2–3] In some ways, nano catalysts act as a bridge between heterogeneous and homogeneous catalysts.[4] Moreover, magnetic nanoparticles (MNPs) offer such benefits as high stability, facile separation by an external magnetic field, easy preparation and functionalization, and environmental benignity; they have high surface area and high loading capacity.[5–6] In continuation of our investigations on the application of metal nanoparticles as heterogeneous catalysts in organic reactions,[7–10] we now describe in this study an efficient method for the one-pot synthesis of pyranoquinoline derivatives from aryl aldehydes, malononitrile, and 8-hydroxyquinoline. We used MNPs@SiO_2-Pr-AP[11] for our work.

We sought to enrich the diversity of pyranoquinoline chemistry while still maintaining those aspects of structure that lead to useful activities.[12–13] One of the best known pyranoquinoline scaffolds is 2-amino-4*H*-pyranoquinoline. Biological properties of its derivatives include anti-microbial,[14] cardiotonic,[15] anti-inflammatory,[16] and anti-tumor properties.[17] A number of methods deal with the synthesis of 2-amino-4*H*-pyranoquinolines using such catalysts as pyridine,[18] piperidine,[19] KF/Al_2O_3,[20] DABCO,[21] and MgO.[22] These methods are useful, but some of them have their own drawbacks, including the need for lessening their environmental impact using the principles of green chemistry.[23–24] In this context, we now introduce MNPs@SiO_2-Pr-AP as a highly efficient, reusable and heterogeneous catalyst for the preparation of 2-amino-4*H*-pyranoquinolines at room temperature under solvent-free conditions (Scheme 1).

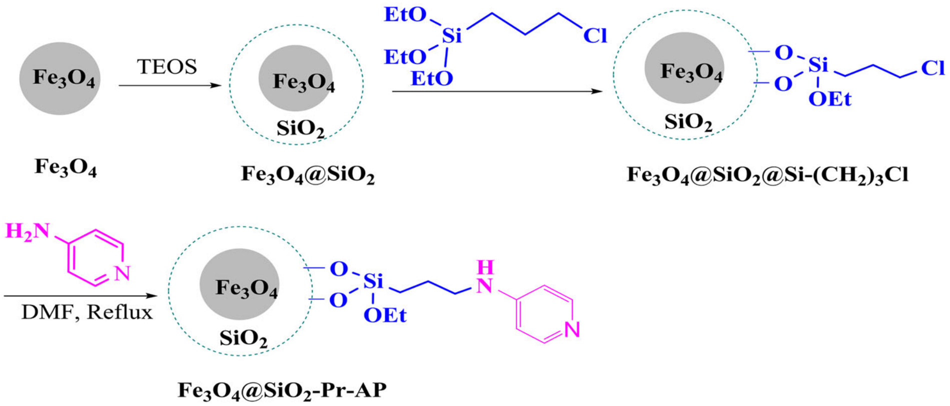
The Fe_3O_4 MNPs and their chloro-functionalized silica coated magnetic nanoparticles (Fe_3O_4@SiO_2-$(CH_2)_3$-Cl) were prepared following a known method (see Scheme 2 and Experimental section).[11] The MNPs@SiO_2-Pr-AP nanoparticles were characterized by FT-IR, SEM, TGA, XRD, and EDX. The latter data are available from the corresponding author upon request. In this report, we focus on the catalytic activity of the nanoparticles. Fig. 1 shows that these nanoparticles are nearly spherical with nano-dimension.

CONTACT Ramin Ghorbani-Vaghei ✉ rgvaghei@yahoo.com Department of Organic Chemistry, Faculty of Chemistry, Bu-Ali Sina University, Hamedan, Iran

Supplemental data for this article can be accessed here.



Scheme 1. Three-component one-pot reaction for the the synthesis of pyranoquinoline.



Scheme 2. The preparation of the nanocatalyst.

The peaks of iron, oxygen, nitrogen, carbon, and silica can be detected that confirmed the presence of these elements in the structure of the catalyst (Fig. 2).

We studied the effectiveness of our catayst on the reaction of Scheme 1. The effects of different parameters including catalyst loading, solvent and temperature were studied on a model reaction as summarized in Table 1. In the model, we ran the reaction of benzaldehyde (1 mmol), malononitrile (1 mmol), and 8-hydroxyquinoline (1.2 mmol) in the presence or absence of MNPs@SiO$_2$-Pr-AP. It was observed that the reaction could not proceed without the catalyst even after a prolonged reaction time (Table 1, entry 1). Various amounts of the catalyst were examined (Table 1, entries 2-7). The best result was obtained in the presence of 70 mg of catalyst under solvent-free conditions (Table 1, entry 6). No improvements were observed by reducing the amount of catalyst to 60 mg (Table 1, entry 5). The effects of several solvent systems on the reaction times and yields of the product were tested (Table 1, entries 8-10). The superior effectiveness of MNPs@SiO$_2$-Pr-AP over Fe$_3$O$_4$@SiO$_2$ (20 mg) was clearly observed (Table 1, entry 11).

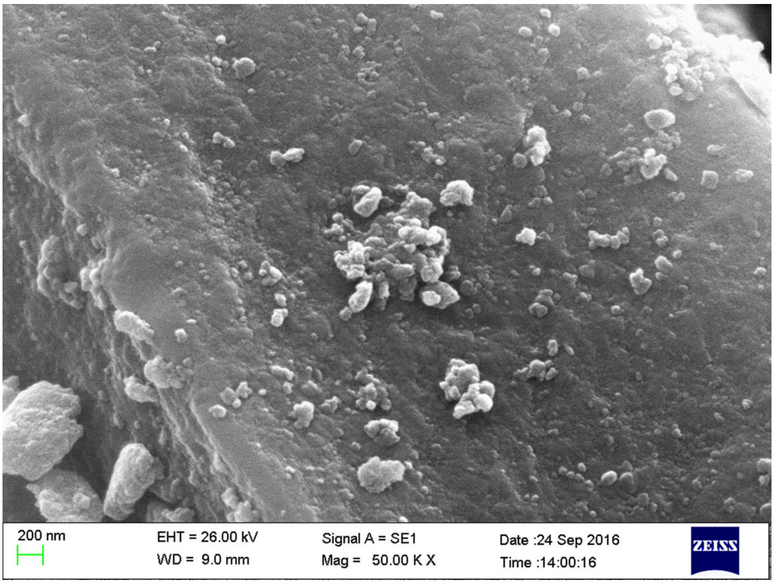


Figure 1. SEM image of MNPs@SiO$_2$-Pr-APbefore reaction.

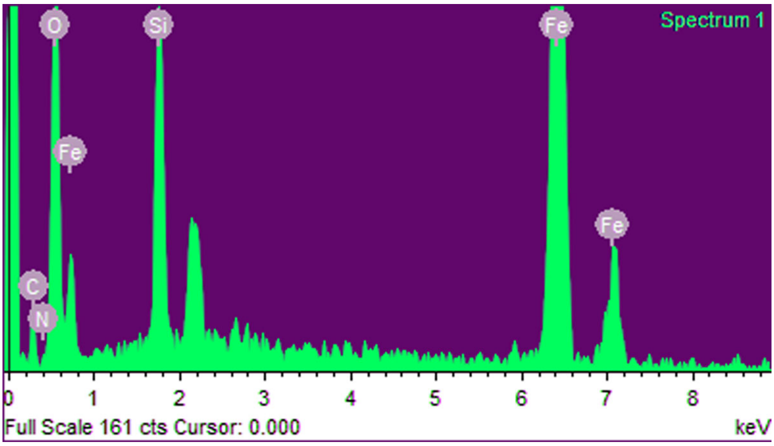


Figure 2. The EDX analysis of the synthesized catalyst.

After finding suitable conditions, several substituted aldehydes were examined in the procedure and the results are shown in Table 2. Yields were not particularly sensitive to the effect of substitution or to electron-rich or electron-poor aldehydes. All of the reactions were complete within 10-45 min. This suggests that the one-pot reaction may be quite general and has a good substrate scope.

The recyclability of the catalyst was studied in the model reaction. The reusability of MNPs@SiO$_2$-Pr-AP was tested through seven cycles, with percentage yields of 98, 97, 96, 96, 95, 94 and 91 respectively for the synthesis of 2-amino-4*H*-pyrano[3,2-*h*] quinoline under the optimized reaction conditions (Fig. 3). Furthermore, Fig. 4 displays the SEM image of the catalyst after five consecutive reactions. We see the catalyst ranging from 41 to 82 nm in size; the image suggests that the morphology of spherical nanoparticles was saved without change during the organic reactions.

Table 1. Optimizing the reaction conditions.

Entry	Catalyst (mg)	Conditions	Time (min)	Yield[a] (%)
1	——————	Solvent-free, r.t.	12 h	32
2	MNPs@SiO_2-Pr-AP (30)[b]	Solvent-free, r.t.	60	34
3	MNPs@SiO_2-Pr-AP (40)[b]	Solvent-free, r.t.	30	45
4	MNPs@SiO_2-Pr-AP (50)[b]	Solvent-free, r.t.	45	68
5	MNPs@SiO_2-Pr-AP (60)[b]	Solvent-free, r.t.	40	79
6	**MNPs@SiO_2-Pr-AP (70)[b]**	**Solvent-free, r.t.**	**30**	**96**
7	MNPs@SiO_2-Pr-AP (80)[b]	Solvent-free, r.t.	30	96
8	MNPs@SiO_2-Pr-AP (70)	EtOH, reflux	40	75
9	MNPs@SiO_2-Pr-AP (70)	H_2O/EtOH (1:1), reflux	50	85
10	MNPs@SiO_2-Pr-AP (70)	CH_3CN, reflux	50	73
11	Fe_3O_4@SiO_2 (20)[b]	Solvent-free, rt	37	65

[a] Isolated yield.

[b] Reaction conditions: benzaldehyde (1 mmol), malononitrile (1 mmol), and 8-quinolinol (1.25 mmol), solvent-free.

To show the utility of this method, the obtained results for the synthesis of **4a** were compared with other methods which have been reported for the synthesis of the same products previously (Table 3). As can be seen, the selected compound was synthesized in short times with high yields in the presence of the title catalyst.

In summary, we have introduced MNPs@SiO_2-Pr-AP as a reusable, stable and heterogeneous catalyst for the one-pot multi-component reaction of aldehydes, malononitrile, and 8-hydroxyquinoline to prepare pyranoquinoline derivatives. The promising merits of the present method are its generality, high product yields, short reaction times, simple workup procedures and reusability of the catalyst.

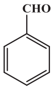
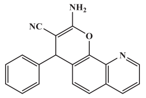
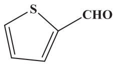
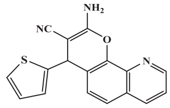
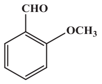
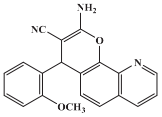
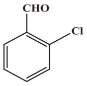
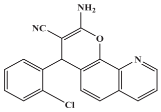
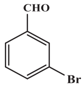
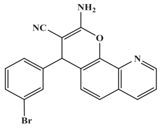
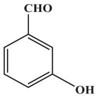
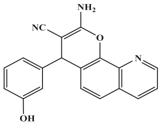
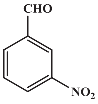
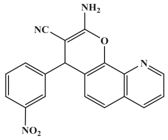
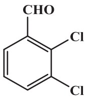
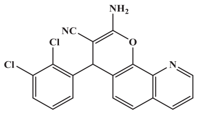
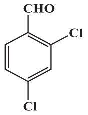
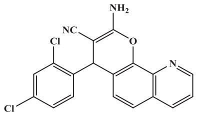
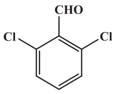
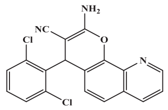
Experimental section

All commercially available chemicals were purchased from Merck and Fluka companies. Nuclear magnetic resonance (NMR) spectra were recorded in DMSO-d_6 on Bruker Avance spectrometers (400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR) using TMS as an internal standard; chemical shifts were expressed in parts per million (ppm). Infrared (IR) spectra were recorded on a Perkin Elmer GX FT-IR spectrometer. Mass spectra were recorded on a Shimadzu QP 1100 BX Mass Spectrometer. Melting points were determined on a Stuart Scientific SMP3 apparatus. The chemical structure of the synthesized catalyst and prepared compounds were investigated with a Shimadzu Fourier transform infrared spectrophotometer (FT-IR-470, Japan). Size and morphology of the prepared nanoparticles were examined under a Philips XL 30 scanning electron microscope (SEM, Netherlands).The qualitative analysis of MNPs@SiO_2-Pr-AP was performed by using energy-dispersive X-ray spectroscopy (EDX). Energy dispersive X-ray analysis of the prepared catalyst was performed on a FESEM-SIGM instrument. Thermo-gravimetric analysis (TGA) was performed on a PYRIS DIAMOND instrument. Ultrasonication was done in a 2200 ETH-SONICA ultrasound cleaner with a frequency of 45 kHz.

Synthesis of MNPs@SiO_2-Pr-AP[11]

The Fe_3O_4 MNPs and their chloro-functionalized silica coated magnetic nanoparticles (Fe_3O_4@SiO_2-$(CH_2)_3$-Cl) were prepared following a known method.[25] Firstly, Fe_3O_4 MNPs were prepared by co-precipitation of Fe^{3+} and Fe^{2+} ions with the $[Fe^{3+}]/[Fe^{2+}]$

Table 2. Synthesis of 2-amino-4*H*-pyranoquinolines.

Comp	Aldehyde	Product	Time (min)	Yield (%)	m.p (°C) (lit. mp^{ref})
4a			30	96	211-213 (224-226[11])
4b			35	88	237-239 (237-239[11])
4c			30	97	197-200 (197-200[11])
4d			40	97	285-288 (285-289[11])
4e			45	94	218-221 (216-220[11])
4f			30	93	299-301 (300-302[11])
4g			35	94	210-204 (198-200[11])
4h			10	96	290-293 (292-296[11])
4i			25	96	299-301(295-298[11])
4j			25	93	274-276 (261-263[11])

molar ratio of 2:1. In brief, FeCl$_3$·6H$_2$O (5.83 g) and FeCl$_2$·4H$_2$O (2.147 g) were dissolved in deionized (DI) water (100 mL) at 80 °C under a N$_2$ atmosphere with vigorous stirring. Then, 10 mL of 25% NH$_4$OH was added dropwise to the reaction mixture at a constant drop rate of 1 mLmin^{-1} in order to gain small and uniform Fe$_3$O$_4$ MNPs.

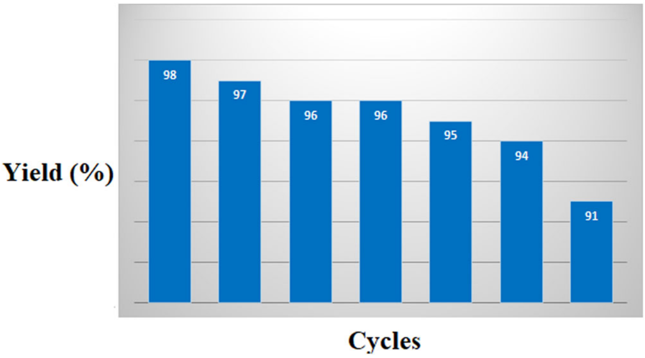


Figure 3. Recyclability of theMNPs@SiO_2-Pr-AP.

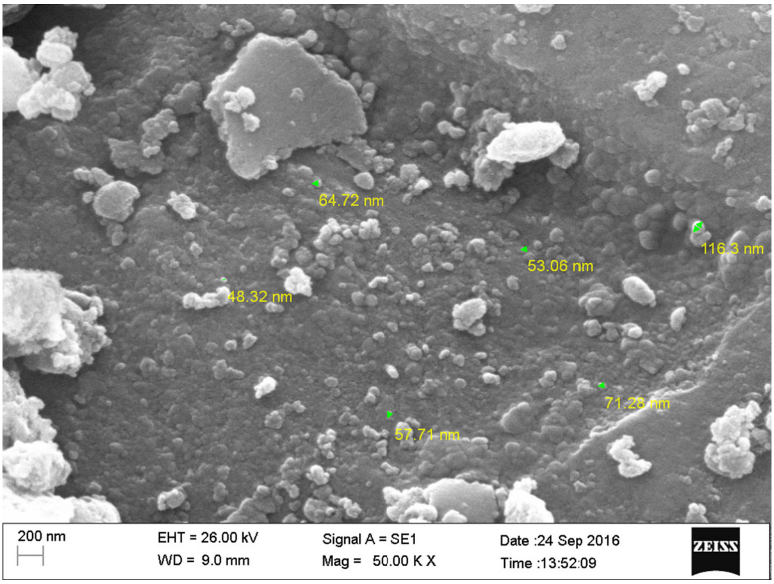


Figure 4. SEM images of MNPs@SiO_2-Pr-AP after five consecutive reactions.

After 30 min of stirring the reaction mixture, the reaction was completed and the mixture was cooled to room temperature. The precipitated black particles of Fe_3O_4 were washed twice with DI water (250 mL) and a 0.02 M solution of NaCl (100 mL). The particles were decanted each time using an external magnet. Due to instability of Fe_3O_4 MNPs under acidic conditions, a silica layer was coated on the surface of the synthesized particles. The synthesized MNPs (1.0 g) was homogeneously dispersed in 500 mL of ethanolic ammonia (25 mL, 25 wt %), under stirring at 80 °C followed by dropwise addition of an ethanolic solution of TEOS (10.8% v/v). After stirring at 80 °C for 2 h, the Fe_3O_4@SiO_2 nanoparticles were obtained and washed several times with a mixture of water–ethanol (1:1). Then, the synthesized nanoparticles were dried at 100 °C for 5 h. The color of the synthesized Fe_3O_4@SiO_2 nanoparticles was dark brown. The chloro-functionalized silica coated Fe_3O_4 nanoparticles (Fe_3O_4@SiO_2-$(CH_2)_3$-Cl) were synthesized by treating the Fe_3O_4 nanoparticles with 3-chloropropyltrimethoxysilane (CPTMS) in 50 mL of toluene under sonication for 30 min. Then, the reaction mixture was stirred

Table 3. Comparison of the activity of MNPs@SiO_2-Pr-AP with other catalysts used to make **4a**.

Entry	Conditions	Yield(%)(Ref)
1	Ce-Zr/SiO_2, ethanol, 70 °C, 2 h	94[25]
2	Piperidine, ethanol, 100 °C, 2h	95[19]
3	DABCO, H_2O:EtOH; 80 °C, 1 h	95[21]
5	KF-Al_2O_3,ethanol, 100 °C, 5 h	78[20]
6	MNPs@SiO_2-Pr-AP, solvent-free, room temperature, 30 min	96 This work

under a nitrogen atmosphere at 80 °C for 24 h to obtain the chloro-functionalized Fe_3O_4@SiO_2 nanoparticles. The resulting Fe_3O_4@SiO_2-$(CH_2)_3$-Cl MNPs were decanted by using an external magnet, repeatedly washed with ethanol, and dried at room temperature. Finally, the Fe_3O_4@SiO_2@Cl–NPs were reacted with 4-aminopyridine to achieve MNPs@SiO_2-Pr-AP. Synthesis of MNPs@SiO_2-Pr-AP was carried out by the post-synthesis grafting method. At first, 1.0 g of synthesized MNPs was dispersed in 50 mL of DMF by stirring for 0.5 h at 50 °C. After that, 0.94 g of 4-aminopyridine was added to the mixture. The mixture was heated up to 90 °C and stirred for 48 h. After 48 h, the solid product was filtered and washed with DMF several times and was dried at 60 °C.The MNPs@SiO_2-Pr-AP nanoparticles were characterized by FT-IR, SEM, TGA, XRD, and EDX. Characterization data were submitted for review and are available from the corresponding author upon request.

General procedure for the synthesis of pyranoquinolines using MNPs@SiO_2-Pr-AP

A mixture of aryl aldehyde (1 mmol), malononitrile (1 mmol, 66 mg) and 8-quinoline (1.25 mmol, 174 mg) in the presence of MNPs@SiO_2-Pr-AP (70 mg) was stirred at room temperature for the appropriate time as mentioned in Table 2, monitored by thin layer chromatography (silica gel, *n*-hexane/ethylacetate, 11/3). After completion of the reaction, an external super magnet was used to separate the nano catalyst. Then, ethanol (95%, 5 mL) was added and the product was recrystallized. All of the products are known and were identified on the basis of comparison of their melting points with literature values. In addition, IR, H-NMR, ^{13}C-NMR and LRMS spectra were submitted for each compound for review. For the sake of completeness, spectroscopic data are shown for compound **4a** below.

2-Amino-4-phenyl-4H-pyrano[3,2-h] quinoline-3-carbonitrile (4a)

Yield: 63 mg, 96%. FT-IR (KBr): 3466, 3324, 3189, 3019, 2191, 1653, 1626, 1596, 1467, 1245, 1048, 744 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 400 MHz): δ_H (ppm) 4.95 (s, 1H, CH), 7.20–7.34 (m, 7H, NH_2& Ph), 7.59-7.65 (m, 3H, Ph), 8.34 (dd, $J = 1.2$, 1H, Ph), 8.95 (dd, $J = 1.6$ Hz, 1H, Ph). ^{13}C-NMR (DMSO-d_6, 100 MHz): δ_C (ppm) 160.28, 150.22, 145.62, 142.96, 137.45, 136.00, 128.98, 128.73, 128.52, 127.66, 126.99, 126.93, 123.57, 122.14, 121.94, 120.44, 55.92, 41.07; Mass (m/z): 299, 255, 222, 195, 167, 140, 116, 77.

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