

Fe₃O₄/SiO₂/(CH₂)₃N⁺Me₃Br₃⁻ core-shell nanoparticles: An efficient catalyst for the synthesis of functionalized 5-oxo-hexahydroquinolines

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ABSTRACT

The four-component Hantzsch condensation reaction of dimedone, ethyl acetoacetate, ammonium acetate, and various aromatic and aliphatic aldehydes in the presence of catalytic amount of a magnetic nanoparticle-supported tribromide, as a green catalyst, under solvent-free conditions at 80 °C affords functionalized 5-oxo-hexahydroquinolines in good to excellent yields. The magnetic Fe₃O₄-SiO₂-(CH₂)₃N⁺Me₃Br₃⁻, was characterized by infrared spectroscopy (FT-IR), X-ray diffraction (XRD) spectroscopy, transmission electron microscope (TEM) and vibrating sample magnetometer (VSM). The method offers several advantages including high yields, short reaction time, simple work-up procedure and catalyst reusability for several runs. The catalyst could be readily separated by using a magnetic force and reused six times without any significant loss of catalytic activity.

Keywords: Magnetically retrievable, Heterogeneous catalysis, Nanohybrid, Hantzsch condensation, 5-Oxo-hexahydroquinolines, Solvent-free.

1. Introduction

Synthesis of magnetic nanoparticles (MNPs) has been of scientific and technological interest due to their potential applications in biosensors [1], drug delivery [2], bioseparation [3], and catalysis [4-6]. Pure magnetic nanoparticles are likely to form a large aggregate, easily oxidized or dissolved in an acid medium and have fewer activating groups [7]. Silica covered on the surface of magnetic nanocomposites prevents the aggregation induced by the magnetic dipolar attraction between MNPs. In addition, it can prevent oxidation of the Fe₃O₄ core by the outer atmosphere [8]. When MNPs are used as supports, the size of material is reduced to the nanometer scale, and most of the catalytic sites on the external surface of the particles can be accessible to the substrates [9]. The MNPs supported catalysts are readily recovered by simple magnetic decantation and can be recycled several times with no significant loss of catalytic activity.

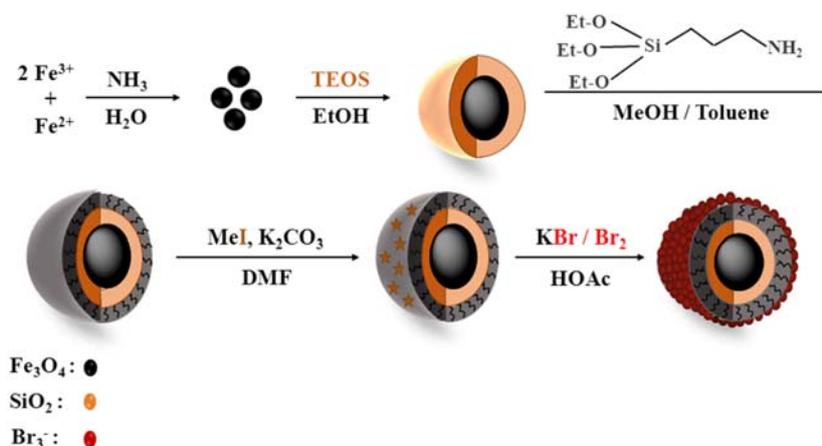
Tribromide has been widely used in organic synthesis and catalytic reactions because of their strong acidity and favorable redox properties. The main disadvantage of reagents based on bromine is their separation from the products which usually needs filtration or centrifugation. This drawback can be overcome by immobilizing these reagents or catalysts on MNPs, which can be easily removed from the reaction mixture by magnetic separation.

Recently, we reported the synthesis of tribromide functionalized Fe₃O₄-SiO₂-(CH₂)₃NH₂ (Scheme 1) as a heterogeneous catalyst for the syntheses of imidazole, benzothiazole, and perimidine derivatives, under solvent-free conditions [10]. Herein, we show catalytic use of Fe₃O₄-SiO₂-(CH₂)₃N⁺Me₃Br₃⁻ magnetic catalyst in the preparation of functionalized 5-oxo-hexahydroquinolines at 80 °C under solvent-free conditions.

2. Experimental

All chemicals and solvents were obtained from Merck and used without further purification.

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Scheme 1. Preparation of $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-(CH}_2\text{)}_3\text{N}^+\text{Me}_3\text{Br}_3^-$ magnetic catalyst.

Melting points were determined using an Electrothermal-9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu IR-460 spectrometer. ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-300 Avance instrument at 300 and 75 MHz, respectively.

2.1 General procedure for the synthesis of 5-Oxo-hexahydroquinolines

A mixture of aldehyde (1 mmol), 1,3-diketone (1 mmol), β -ketoester (1 mmol), ammonium acetate (0.156 g, 1.5 mmol), and tribromide-modified silica-coated magnetic nanoparticles (MNP-supported tribromide; 0.007 g) was heated at 80 °C. After completion of the reaction [TLC (AcOEt/hexane 1:3) monitoring], EtOH (10 mL) was added. The catalyst was recovered by an external magnet, and the reaction mixture was poured into ice-water (30 mL). The solid product was filtered, washed with ice-water, and dried.

Selected spectral data

Ethyl 4-(2-chlorophenyl)-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4f):

^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ = 0.86 (s, 3 H, Me), 1.01 (s, 3 H, Me), 1.08 (t, J = 6.8 Hz, 3 H, Me), 1.90–2.44 (m, 7 H), 3.94 (q, J = 6.8 Hz, 2 H, CH_2), 5.18 (s, 1H, CH), 7.06–7.29 (m, 4 H, ArH), 9.08 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ = 14.0, 18.1, 26.4, 29.1, 31.9, 34.8, 50.2, 51.31, 58.9, 103.2, 109.5, 126.6, 127.2, 128.9, 131.8, 144.9, 145.1, 149.7, 166.8, 193.8 ppm.

Ethyl 4-propyl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4j):

^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ = 0.88 (s, 3 H, Me), 1.00 (s, 3 H, Me), 1.14 (t, J = 6 Hz, 3 H, Me), 2.00 (d, J = 12 Hz, 2 H), 2.15 (d, J = 12 Hz, 2 H), 2.35

(d, J = 12 Hz, 2 H), 2.27 (s, 3H, Me), 2.29 (s, 3 H, Me), 4 (q, J = 6 Hz, 2 H, CH_2), 4.79 (s, 1 H, CH), 7.17 (t, J = 6 Hz, 1H, Ar H), 7.39 (t, J = 9 Hz, 1 H, Ar H), 7.70 (d, J = 6 Hz, 1 H, ArH), 9.91 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ = 12.0, 14.2, 18.3, 26.2, 26.8, 28.8, 32.1, 50.2, 59.0, 103.1, 109.6, 117.2, 125.0, 126.0, 128.9, 129.3, 139.6, 144.4, 147.8, 148.8, 166.9, 194.2 ppm.

Ethyl 2-methyl-5-oxo-4-tolyl-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4s):

^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ = 1.12 (t, 3 H, J = 6.8 Hz), 1.75–1.76 (m, 2 H), 1.89–1.92 (m, 10 H), 3.98 (q, 2 H, J = 6.8 Hz), 4.88 (s, 1 H), 7.15 (d, 2 H, J = 8 Hz), 7.24 (d, 2 H, J = 8 Hz), 9.11 (s, 1H) ppm. ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ = 14.1, 18.2, 20.7, 26.0, 26.3, 35.3, 36.6, 59.1, 103.0, 110.7, 128.4, 129.3, 130.2, 145.3, 146.7, 151.5, 166.7, 194.6 ppm.

Ethyl 2-methyl-4-(4-chlorophenyl)-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4u):

^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ = 1.13 (t, 3 H, J = 7.2 Hz), 1.70–1.93 (m, 2 H), 2.16–2.49 (m, 7 H), 3.98 (q, 2 H, J = 7.2 Hz), 4.85 (s, 1 H), 6.97 (d, 2 H, J = 8 Hz), 7.02 (d, 2 H, J = 8 Hz), 9.09 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ = 14.1, 18.2, 20.7, 26.1, 35.1, 36.7, 58.9, 103.6, 111.2, 127.2, 128.3, 134.5, 144.7, 144.9, 151.2, 166.9, 194.6 ppm.

Ethyl 2-methyl-5-oxo-4-(furan-2-yl)-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (4x):

^1H NMR (400 MHz, $\text{DMSO-}d_6$): δ = 1.18 (t, 3 H), 1.82–1.92 (m, 5 H), 2.26–2.51 (m, 4 H), 4.07 (m, 2 H), 5.06 (s, 1 H), 5.82 (m, 1 H), 6.23 (m, 1 H), 7.37 (m, 1H), 9.21 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $\text{DMSO-}d_6$): δ = 14.2, 18.1, 20.8, 26.1, 29.5, 36.6, 59.1, 100.6, 104.0, 107.6, 110.1, 140.9, 145.7, 152.3, 158.4, 166.70, 194.4 ppm.

3. Results and Discussion

To find the optimized amount of MNP-supported tribromide as shown in (Fig. 1), the reaction was carried out with varying the amount of the catalyst on the synthesis of 5-oxo-hexahydroquinolines **4**. It is observed that 7 mg of the MNP-supported tribromide catalyst is needed for carrying out condensation of aldehyde, dimedone, ethyl acetoacetate and ammonium acetate. Further increase in the catalyst amount does not have any marked impact on the yield of the product (Fig. 1a).

The reaction has been studied at various temperatures from 50 to 100 °C (Fig. 1b). The yield of the product increased up to 80 °C. After 80 °C, increasing temperature in the mentioned reaction did not have any significant effect on product yield.

The scope and efficiency of this approach were explored for the synthesis of a wide variety of 5-oxo-hexahydroquinolines by treating aldehydes possessing electron-donating and electron-withdrawing groups, with dimedone, ethyl acetoacetate, ammonium acetate and results are summarized in Table 1. As Table 1 shows, the yields are good to excellent in most cases.

The comparison of the efficiency of catalytic activity of the MNP-supported tribromide with several previous methods is presented in Table 2. The results show that this method is superior to some of the earlier methods in terms of yield and reaction time.

The reusability of the catalysts is an important benefit and makes them useful for commercial applications. Thus, the recovery and reusability of $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-(CH}_2\text{)}_3\text{N}^+\text{Me}_3\text{Br}_3^-$ were investigated. The recyclability of the catalyst in the reaction of *p*-chlorobenzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), dimedone (1 mmol) and ammonium acetate (1.5 mmol) in the presence of $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-(CH}_2\text{)}_3\text{N}^+\text{Me}_3\text{Br}_3^-$ (0.007 g) was checked. The catalyst was readily recovered by simple

magnetic decantation, washed with EtOH and dried at 60 °C for 2 h. The recycled catalyst was used in the mentioned reaction for six times, with little loss of activity (The yields were 95, 95, 95, 90, 90 and 90%, respectively).

The EDX analysis results, shown in Fig. 2 confirmed the elemental composition of the recovered nanoparticles and the existence of Br in the catalyst attached to the surface of core-shell structure.

4. Conclusions

In conclusion, we have reported an efficient and eco-friendly method for one pot synthesis of functionalized 5-oxo-hexahydroquinolines using nano $\text{Fe}_3\text{O}_4\text{-SiO}_2\text{-(CH}_2\text{)}_3\text{N}^+\text{Me}_3\text{Br}_3^-$ as the catalyst under solvent-free conditions. The catalyst could be readily separated by using a magnetic force and reused six times without any significant loss of catalytic activity.

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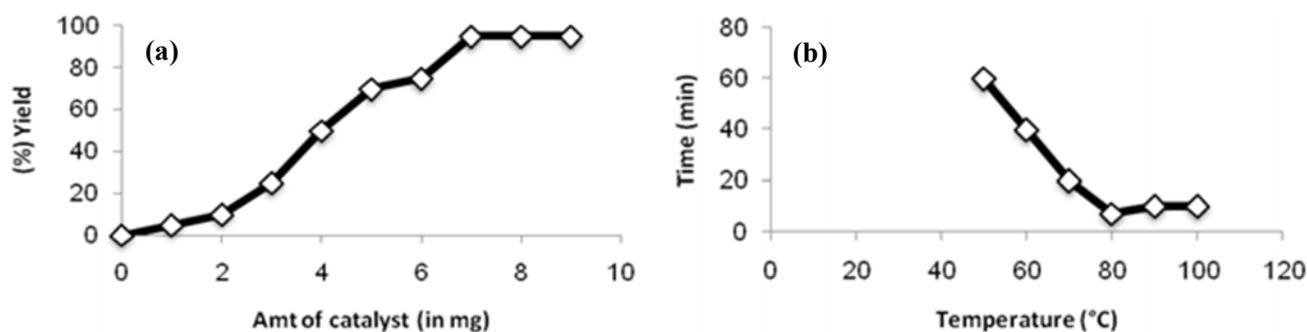
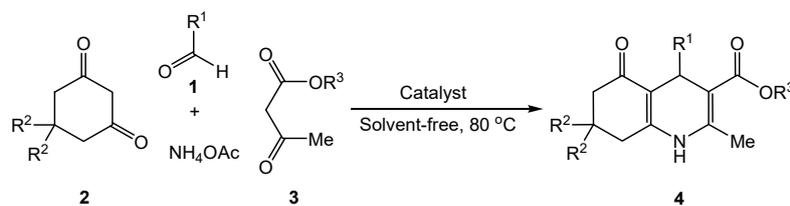


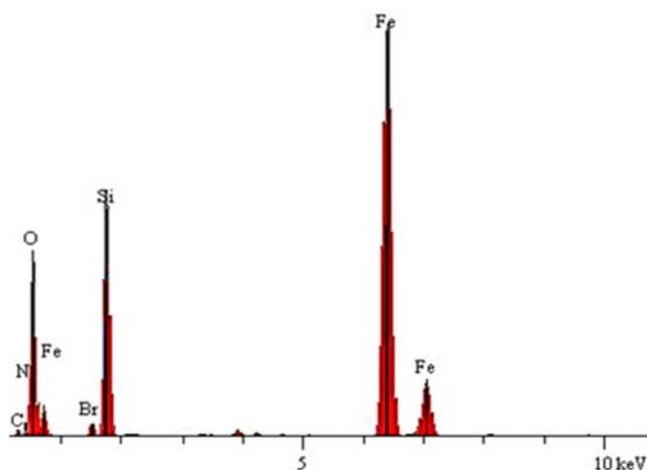
Fig. 1. Effect of catalyst weight (a) and temperature (b) on the synthesis of 5-oxo-hexahydroquinolines **4**.

Table 1. Application of MNP-supported tribromide for the synthesis of compounds **4**.

Entry	R ¹	R ²	R ³	Product	Time (min)	Yield (%)	m.p. (°C)		Ref.
							Observed	Reported	
1	Ph	Me	Et	4a	7	92	141-142	140-142	[11]
2	4-MeOC ₆ H ₄	Me	Et	4b	7	95	254-256	257-259	[11]
3	4-MeC ₆ H ₄	Me	Et	4c	7	95	256-257	260-261	[11]
4	4-HOC ₆ H ₄	Me	Et	4d	7	92	233-234	232-234	[11]
5	4-ClC ₆ H ₄	Me	Et	4e	7	95	232-234	232-234	[12]
6	2-ClC ₆ H ₄	Me	Et	4f	12	90	206-208	207-209	[13]
7	3-O ₂ NC ₆ H ₄	Me	Et	4g	12	90	177-178	176-177	[14]
8	4-O ₂ NC ₆ H ₄	Me	Et	4h	10	90	242-243	242-244	[14]
9	2-Furyl	Me	Et	4i	10	92	245-247	246-248	[11]
10	<i>n</i> -Pr	Me	Et	4j	15	85	147-148	147-148	[11]
11	Et	Me	Et	4k	15	85	140-142	142-144	[11]
12	Ph	Me	Me	4l	7	92	258-260	258-260	[16]
13	4-MeOC ₆ H ₄	Me	Me	4m	7	95	254-256	256-257	[17]
14	4-MeC ₆ H ₄	Me	Me	4n	7	95	280-283	283-285	[15]
15	4-ClC ₆ H ₄	Me	Me	4o	7	95	220-221	221-222	[15]
16	4-O ₂ NC ₆ H ₄	Me	Me	4p	10	90	248-250	250-252	[14]
17	Ph	H	Et	4q	10	90	239-241	240-241	[12]
18	4-MeOC ₆ H ₄	H	Et	4r	9	92	200-202	193-195	[12]
19	4-MeC ₆ H ₄	H	Et	4s	9	92	242-244	241-242	[12]
20	4-HOC ₆ H ₄	H	Et	4t	9	90	220-222	220-222	[12]
21	4-ClC ₆ H ₄	H	Et	4u	9	92	235-237	234-235	[12]
22	4-O ₂ NC ₆ H ₄	H	Et	4v	15	90	203-205	204-205	[12]
23	3-O ₂ NC ₆ H ₄	H	Et	4w	15	90	198-200	198-200	[12]
24	2-Furyl	H	Et	4x	10	92	209-211	210-212	[18]

Table 2. Comparison of catalytic activity of MNP-supported tribromide with several known catalysts.

Entry	Catalyst/Catalyst loading	Solvent/temp (°C)	Time (min)	Yield (%)	Ref.
1	Fe ₃ O ₄ -SiO ₂ -(CH ₂) ₃ N ⁺ Me ₃ Br ₃ ⁻ /1 mol%	Solvent-free/80	7	95	This work
2	MCM-41/1 mol%	Solvent-free/90	15	89	[19]
3	[HMIM]BF ₄ /12 mol%	Solvent-free/90	10	95	[20]
4	L-Proline/10 mol%	EtOH/Reflux	360	92	[21]
5	Palladium(0) NP	THF/Reflux	240	87	[22]
6	ZnO/10 mol%	EtOH/80	60	92	[23]
7	K ₇ [PW ₁₂ CoO ₄₀]/1 mol%	MeCN/Reflux	35	80	[24]
8	Silica gel/NaHSO ₄ /5 mol%	r.t.	360	85	[25]
9	HClO ₄ -SiO ₂ /0.05 g	Solvent-free/80	20	95	[26]
10	PSA/4.5 mol%	Solvent-free/80	15	98	[27]
11	Nano SnO ₂ /1 mol%	EtOH/r.t.	9	94	[28]
12	Nano ZnO/10 mol%	Solvent-free/r.t.	20	98	[29]

**Fig. 2.** EDX analysis of the recovered catalyst.

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