

One-pot reductive Amination of Carbonyl compounds using NaBH_4 and Fe_3O_4 magnetic nanoparticles

Mehdi Forouzani^a, Navabeh Nami^{b*}, Hassan Ghasemnejad-Bosra^c, Omid Khalilpour Tylami^b

^a Department of Chemistry, Payame noor University, Sari Center, 19395-4697, Tehran, Iran

^b Department of Chemistry, Qaemshahr Branch, Islamic Azad University, Mazandaran, Iran

^c Department of Chemistry, Babol Branch, Islamic Azad University, P.O. BOX 755, Mazandaran, Iran

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Abstract

One-pot reaction of aldehydes or ketons with aniline derivatives was performed using NaBH_4 and Fe_3O_4 magnetic nanoparticles (MNPs). The optimum amount of Fe_3O_4 MNPs was 5 mol% under solvent free condition. The corresponding products were obtained in good to excellent yields. The magnetically recoverable iron oxide nanoparticles are found to be efficient for synthesis of amine derivatives. These nanoparticles are effective in green chemistry and could be successfully reuse. In addition to having the general advantages attributed to the inherent magnetic property of nanocatalyst, Fe_3O_4 MNPs exhibited exceptionally high catalytic activity, compared to other catalysts, to yield the desired products in short reaction time and mild reaction conditions.

Keywords: Fe_3O_4 (MNP_S); aniline derivative; aldehyde; ketone; amine; NaBH_4 .

Introduction

Amines and their derivatives are important functionalities as organic intermediates in the

fields of medicinal, bioorganic, industrial and synthetic organic chemistry, for the synthesis of drugs, herbicides, bactericides, corrosion

*Corresponding author: Navabeh Nami

Tel: +98 (911) 1133578, Fax: +98 (123) 2145040

E-mail: Navabehnami@yahoo.com

Fe₃O₄ MNPs were prepared by a simple, low cost and convenient method from the reaction of FeCl₂.4H₂O and FeCl₃.6H₂O in ammonia solution [20].

The IR spectra of prepared Fe₃O₄ nanoparticles are shown in Figure 1. The

results in this spectra show that the data are the same as reported in literature [21]. A strong peak at around 590 cm⁻¹ is related to Fe-O stretching frequency. The broad band at around 3500–3000 cm⁻¹ is attributed to adsorbed water.

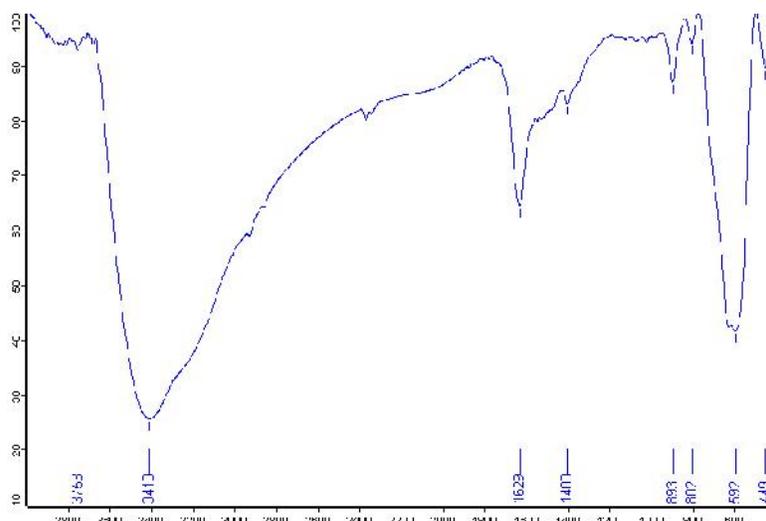
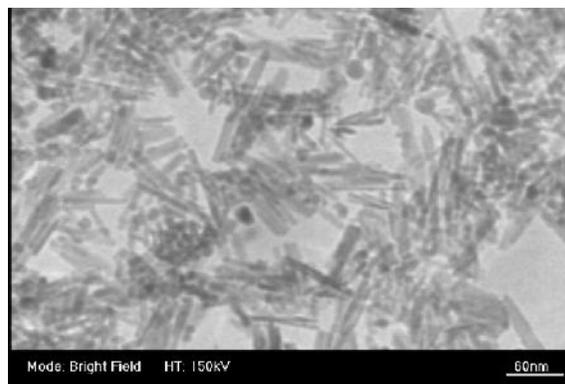
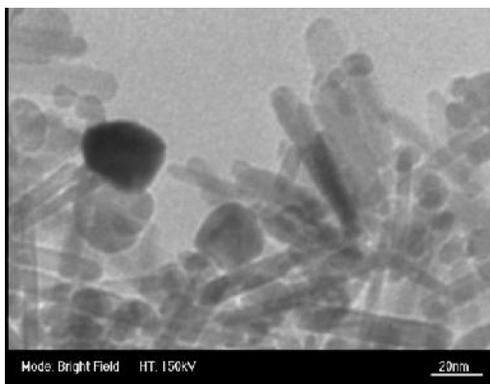


Figure 1. FT-IR spectra of Fe₃O₄ magnetic nanoparticles

The morphology and particle size distribution of Fe₃O₄ MNPs were studied using Transmission Electron Microscopy

(TEM) as shown in Figure 2, which an average particle size is about 20-60 nm.



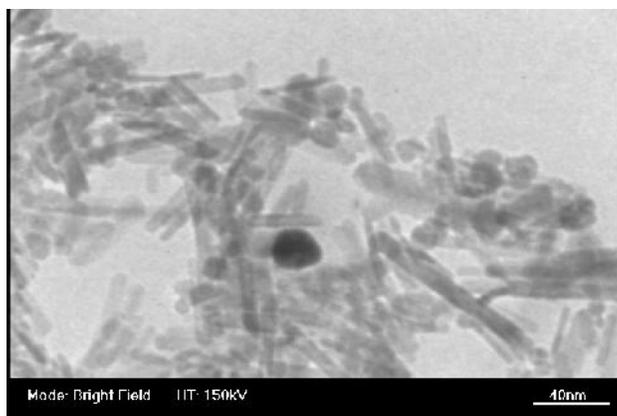


Figure 2. TEM image of Fe₃O₄ MNPs

In the preliminary stage of investigation, the model reaction of benzaldehyde and aniline was carried out by using various amounts of Fe₃O₄ nanoparticles in the presence of NaBH₄ in various solvents and solvent-free conditions. The optimum amount of nano-Fe₃O₄ was 5 mol% as shown in Table 1. Increasing the amount of catalyst does not improve the yield of the product any further, whereas decreasing the amount of catalyst leads to decrease in the product (Table 1, Entry 5).

It was found that in the absence of Fe₃O₄ magnetic nanoparticles, only trace of

the desired product was observed on TLC plate even after 2 h of reaction (Table 1, Entry 21). When the reaction was performed in the presence of Fe₃O₄ magnetic nanoparticles, it proceeded to give the desired product. The best results were obtained with 5 mol% of Fe₃O₄ magnetic nanoparticles under solvent-free conditions (Table 1, Entry 24). Increasing the amount of catalyst does not improve the yield of the product any further, whereas decreasing the amount of catalyst leads to decrease in the product (Table 1, Entry 21-25).

Table 1. Reaction of benzaldehyde (1mmol), aniline (1 mmol) and NaBH₄ (1 mmol) under different conditions at R.T.

Entry	Solvent	Catalyst	Catalyst (mol%)	Time	Yield ^a (%)
1	THF	-	-	2h	trace
2	THF	Fe ₃ O ₄ MNPs	3	1h	60
3	THF	Fe ₃ O ₄ MNPs	4	50min	76

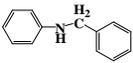
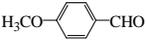
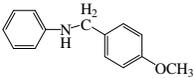
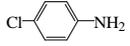
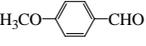
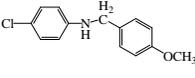
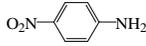
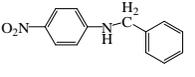
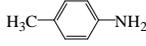
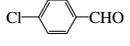
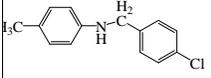
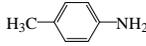
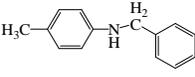
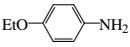
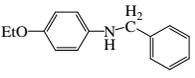
4	THF	Fe ₃ O ₄ MNPs	5	40min	93
5	THF	Fe ₃ O ₄ MNPs	10	40min	92
6	CH ₃ CN	-	-	2h	trace
7	CH ₃ CN	Fe ₃ O ₄ MNPs	3	1h	35
8	CH ₃ CN	Fe ₃ O ₄ MNPs	4	1h	62
9	CH ₃ CN	Fe ₃ O ₄ MNPs	5	1h	79
10	CH ₃ CN	Fe ₃ O ₄ MNPs	10	1h	79
11	<i>n</i> -Hexane	-	-	2h	trace
12	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	3	2h	25
13	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	4	2h	43
14	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	5	2h	65
15	<i>n</i> -Hexane	Fe ₃ O ₄ MNPs	10	2h	64
16	EtOEt	-	-	2h	trace
17	EtOEt	Fe ₃ O ₄ MNPs	3	1h	61
18	EtOEt	Fe ₃ O ₄ MNPs	4	1h	72
19	EtOEt	Fe ₃ O ₄ MNPs	5	1h	83
20	EtOEt	Fe ₃ O ₄ MNPs	10	1h	84
21	Solvent-free	-	-	2h	trace
22	Solvent-free	Fe ₃ O ₄ MNPs	3	1h	75
23	Solvent-free	Fe ₃ O ₄ MNPs	4	50 min	85
24	Solvent-free	Fe ₃ O ₄ MNPs	5	30 min	97
25	Solvent-free	Fe ₃ O ₄ MNPs	10	30 min	97

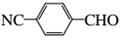
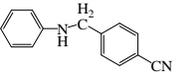
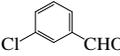
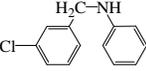
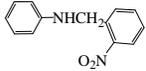
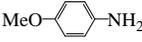
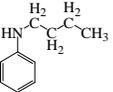
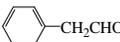
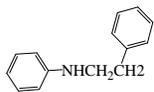
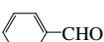
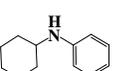
^a Isolate Yield

To evaluate the scope and limitations of this methodology, we extended our studies to include a variety of structurally different carbonyl compounds or amines carrying both electron-donating and electron-withdrawing substituent produced the corresponding amines. The results are summarized in Table

2 (Table 2, Entry 1–14). In almost all cases, the reactions proceeded smoothly within 15–30 min, providing the corresponding products in good isolated yields without the formation of any side products.

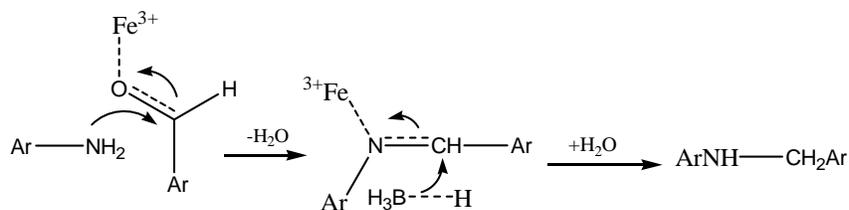
Table 2. Reductive amination of carbonyl compounds catalyzed by Fe₃O₄ MNPs

Entry	Amine	Carbonyl Compound	Reductive Amination Production	Method 1	Method 1	Method 2	Method 2	Ref.
				Reaction time (min) in THF	Yield (%) In THF	Reaction time (min) Solvent-free	Yield (%) Solvent-free	
1				40	93	30	97	[22-25]
2				60	84	52	90	[22-25]
3				60	80	30	93	[23]
4				90	72	30	91	[24]
5				40	83	90	15	[25]
6				50	90	15	94	[22]
7				50	92	15	89	[26]

8				60	83	20	94	[27]
9				60	82	20	93	[28]
10				60	75	15	91	[28]
11		$\text{CH}_3\text{CH}_2\text{CH}_2\text{CHO}$		50	86	25	95	[22]
12				60	78	15	88	[29]
13	$\text{CH}_3\text{-CH}_2\text{-NH}_2$			60	82	15	90	[29]
14				60	89	15	96	[30]

A plausible mechanism for the reaction is envisaged in scheme 2. Carbonyl group is first activated by MNPs (Fe^{3+}), then the amine nitrogen attacks to positive center to

afford imine intermediate. Imine bond is activated by MNPs to provide more positive center for reductive amination and absorption of hydride group.



Scheme 2. Plausible mechanism for reductive amination of carbonyl compounds using NaBH_4 and Fe_3O_4 MNPs

The catalyst was simply recovered by external magnetic field, washed with ethanol, and dried at $60\text{ }^\circ\text{C}$ for 1 h. The recovered catalyst was then added to a fresh reaction mixture under the same conditions and

reused 7 times without significant loss of activity (Table 3). Further recycling of the nanocatalyst led to gradual loss of the catalyst during the recovering and washing stages.

Table 3. Recycling of the Fe_3O_4 MNPs catalyst

Number of cycle	Yield ^a (%)
1	93
2	93
3	92
4	90
5	89
6	88
7	88

^a Isolated yield after chromatography

A comparison of the efficacy of Fe_3O_4 MNPs catalyst with some of those reported in the literature is presented in Table 3. The model reaction of aniline and benzaldehyde was considered as a representative example (Table 4). In addition to having the general advantages attributed to

the inherent magnetic property of nanocatalyst, Fe_3O_4 MNPs exhibited exceptionally high catalytic activity compared to other catalysts to yield the desired products in short reaction time and mild reaction conditions.

Table 4. Comparison of the efficacy of Fe₃O₄ MNPs with some of those reported in the literature

Entry	Catalyst	Time	Yield	Ref.
1	Cu(PPh ₃) ₂ BH ₄	1.5h	94	[31]
2	Fe ²⁺ /EDTA-Na ₂	12h	88	[32]
3	[Ir(cod) ₂]BF ₄ /[Bmim]BF ₄	24h	91	[27]
4	(HMIm)BF ₄ /NaBH ₄	4h	94	[33]
5	Fe ₃ O ₄ MNPs	30min	94	This work

Experimental

All solvents were purified and dried using established procedures. FT-IR measurements were recorded on a Shimadzu 8400s spectrometer with KBr plates. The NMR spectra were recorded on Bruker XL 500 (500 MHz) instruments, melting points were determined on an Electrothermal 9100 without further corrections. The sizes of MNPs were evaluated using a transmission electron microscope (TEM, 150 kV, and Philips-CM 10).

Preparation of Fe₃O₄ MNPs

The MNPs were prepared according to a previously reported procedure [20-21]. Typically, FeCl₃·6H₂O (0.02 mol) and FeCl₂·4H₂O (0.01 mol) were dissolved in distilled water (100 mL) in a three-necked round-bottom flask (250 mL). The resulting transparent solution was heated at 90 °C with rapid mechanical stirring under N₂ atmosphere for 1 h. A solution of concentrated aqueous ammonia (10 mL, 25 wt %) was then added to the solution in a dropwise manner over a 30 min period using

a dropping funnel. The reaction mixture was then cooled to room temperature and the resulting magnetic particles collected with an external magnet and rinsed thoroughly with distilled water.

General procedure for the reductive amination of carbonyl compounds in solvent (Method 1)

Carbonyl compound (1mmol) and amine (1mmol) were mixed in THF (5 mL), and then Fe₃O₄ magnetic nanoparticles (5 mol%) was added. The mixture was vigorously stirred at room temperature, after 20 min NaBH₄ (1mmol) was added. The mixture was stirred again and the progress of the reaction was monitored by TLC (*n*-hexane: EtOAc / 4:1). At the end of the reaction, the catalyst was recovered by an external magnet, washed with EtOH, dried at 60 °C for 1 h and reused seven times for the same reaction. The residue of the reaction mixture was evaporated, and the crude product was purified by short-column chromatography on silica gel (eluent: *n*-hexane: EtOAc / 4:1). All products were identified by comparison of

their ^1H NMR, FT-IR spectra and physical data with those of authentic samples.

General procedure for the reductive amination of carbonyl compounds under solvent-free conditions (Method 2)

Carbonyl compound (1mmol) and amine (1mmol) were mixed, and then Fe_3O_4 magnetic nanoparticles (5 mol %) were added, the mixture was vigorously stirred at room temperature for 10 min, and then NaBH_4 (1mmol) was added under solvent-free condition at room temperature. After completion of the reaction as monitored by TLC (*n*-hexane: EtOAc/ 4:1), Et_2O (20 mL) was added to the mixture of the reaction. The catalyst was recovered by an external magnet, washed with EtOH, dried at 60 °C for 1 h and reused seven times for the same reaction. The residue of Et_2O solution was evaporated, and the crude product was purified by short-column chromatography on silica gel (eluent: *n*-hexane : EtOAc 4:1). All products were identified by comparison of their ^1H NMR and FT-IR spectra and physical data with those of authentic samples.

selected spectral data:

***o*-Nitrophenylbenzylamine**

FT-IR (KBr, max cm^{-1}): 3420(N-H), 3020(CH_{Ar}), 2940(CH_2), 1630(C=C), 1350-1550(NO_2).

^1H -NMR (400 MHz, CDCl_3 ppm): 7.71 (1H, d, $J=10$, CH_{Ar}), 7.59 (1H, m, CH_{Ar}), 7.45 (1H, m, CH_{Ar}), 7.22 (2H, m, CH_{Ar}), 6.79 (1H, m, CH_{Ar}), 6.62 (2H, dd, $J=9$, 1, CH_{Ar}), 4.76 (2H, s, CH_2), 4.41 (1H, br, NH).

N-phenylbenzylamine

FT-IR (KBr, max cm^{-1}): 3300(N-H), 2900(CH_2), 1610(C=C).

^1H -NMR (400 MHz, CDCl_3 ppm): 7.34 (2H, m, CH_{Ar}), 7.20 (2H, m, CH_{Ar}), 7.02 (1H, s, CH_{Ar}), 6.74 (1H, t, $J=7$, CH_{Ar}), 6.66 (2H, dd, $J=8$, 1, CH_{Ar}), 4.35 (2H, d, $J=5$, CH_2), 4.06 (1H, br, NH).

N-Phenyl(*p*-methyl benzyl) amine

^1H -NMR (400 MHz, CDCl_3 ppm): 7.33-7.49 (4H, m, CH_{Ar}), 7.08 (2H, d, $J=10.6$, CH_{Ar}), 6.64 (2H, d, $J=11.0$, CH_{Ar}), 4.38 (2H, s, CH_2), 3.91 (1H, br, NH), 2.34 (3H, s, CH_3).

N-(*m*-Chlorophenyl)benzylamine

^1H -NMR (400 MHz, CDCl_3 ppm): 7.46 (1H, s, CH_{Ar}), 7.27-7.36 (5H, m, CH_{Ar}), 6.84 (1H, m, CH_{Ar}), 6.71 (2H, m, CH_{Ar}), 4.37 (2H, s, CH_2), 4.01 (1H, br, NH).

Conclusion

In summary, an efficient protocol for the one-pot reductive amination was described. The reactions were carried out at room temperature and the corresponding products were obtained in good to excellent yields. The advantages of this method are short

reaction time, high conversion, easier and less expensive than the other methods. The magnetic Fe₃O₄ nanoparticles are effective in green chemistry and increases reaction speed without air pollution, this nanoparticles could be successfully recovered and reuse.

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