Catal Lett
DOI 10.1007/s10562-016-1822-6

Efficient Reduction of C–N Multiple Bonds Catalyzed by Magnetically Retrievable Magnetite Nanoparticles with Sodium Borohydride

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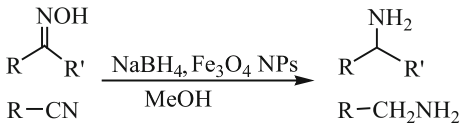
Received: 26 May 2016 / Accepted: 16 July 2016

Abstract A simple, rapid and efficient methodology has been developed for the reductive transformation of the compounds bearing C–N multiple bonds such as oximes and nitriles to the corresponding amines by sodium borohydride catalyzed by highly active solid Fe_3O_4 nanoparticles. The catalyst was easily recovered using external magnet and reused five times without losing its catalytic activity.

Graphical Abstract A simple, rapid, efficient and reusable heterogeneous catalytic system has been developed for the reductive transformation of oximes and nitriles into corresponding amines by sodium borohydride in presence of Fe_3O_4 nanoparticles.



Keywords Heterogeneous catalysis · Nanotechnology · Magnetic separation · Reduction · Nanoparticles · Recycling

1 Introduction

The reductive transformation of compounds bearing C–N multiple bonds to amines is one of the most versatile synthetic routes to synthesize various functionalized amines. Amine compounds represent a versatile class of biologically active molecules that includes various types of alkaloids, neurotransmitters, amino acids and pharmaceutical agents. Amines are crucial precursors for the biosynthesis of diverse biomolecules as well [1]. Various amino compounds have also been used to manufacture different types of dyes, antioxidants, photographic materials, agriculture chemicals and corrosion inhibitors. Recently, synthetic strategies for the reduction of oximes and nitriles into amines have received much attention in research and development programme at both academic and industrial level.

Sodium borohydride ($NaBH_4$) is one of the most widely used mild and selective hydride transferring agents in organic synthesis [2]. Sodium borohydride does not normally reduce groups like ester, nitro, amides and nitriles. The reduction capacities of sodium borohydride can be modified by some additives, in particular, transition metals. There are a few reports known for the reductive conversion of oximes and nitriles into amines using $NaBH_4$ in combination with some additives such as $NaBH_4/ZrCl_4$ [3], $NaBH_4/TiCl_4$ [4, 5] $NaBH_4/CuSO_4$ [6], $NaBH_4$ in acidic [7–9] or basic condition [10], $NaBH_4/NiCl_2$ [11], $NaBH_4/InCl_3$ [12] and $NaBH_4$/Nickel [13]. These methods suffer from some disadvantages such as harsh reaction conditions

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A part of the manuscript has been presented in "International Conference on Material Science & Technology" organized by Department of Chemistry, University of Delhi, New Delhi (March 1–4, 2016).

Electronic supplementary material The online version of this article (doi:10.1007/s10562-016-1822-6) contains supplementary material, which is available to authorized users.

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(strong acidic or basic reaction media), limitation to use acid or base sensitive functional groups, prolonged reaction time, high temperature, tedious isolation process, decomposition of the catalyst, formation of side products and low reducing capability which produces hydroxylamine. Therefore, there is an immense interest to develop an efficient, rapid, simple and reusable reductive system for the selective conversion of oximes and nitriles into corresponding amines.

Nanoparticles have been used as highly active, mild and selective catalysts in several organic transformations as they are exposed to more reactant molecules due to their large surface area [14]. Magnetic Fe_3O_4 (magnetite) nanoparticles have attracted a great attention as heterogeneous catalyst due to its simple handling, easy recovery with an external magnetic field, high stability and high catalytic activities in various organic transformations [15]. Recently, Magnetic Fe_3O_4 nanoparticles have been used as catalyst for efficient reduction of nitro compound [16] and organic azide compounds into corresponding amino compounds [17]. In continuation of our research pertaining to the use of sodium borohydride as a reducing agent for selective reductions of flavonoids [18], isoflavonoids [19] and atrazine [20], herein, we report reductive conversion of various oximes and nitriles to corresponding amines with sodium borohydride catalyzed by Fe_3O_4 nanoparticles under different reaction conditions.

2 Experimental

2.1 Methods and Materials

Powder X-ray diffraction data were carried out using a Bruker D8 Advance diffractometer using Ni-filtered CuKα radiation. Transmission electron microscopy (TEM) studies were carried out using a FEI Netherlands, Technai G^2T30, U-Twin TEM instrument operated at 200 kV. The dispersed sample of Fe_3O_4 nanoparticles prepared by treating nanoparticles in ethanol with ultrasound sonicator and then a few drops were put on a copper grid and dried in air. Scanning Electron Microscopy studies were carried out using JEOL, JSM 6610LV SEM instrument. ^{1}H NMR spectra were recorded using a Jeol, JNM-EXCP 400 NMR spectrometer at 400 MHz. FT-IR spectra were recorded using Perkin Elmer, Spectrum RXI—Mid IR. Thin layer chromatography (TLC) was done over silica gel 60 F254 aluminum sheet. All solvents and reagents were purchased from commercial sources with the best quality and they were used without further purification. All oximes were prepared by the reaction of corresponding aldehydes and ketones with hydroxylamine hydrochloride under different conditions [21].

2.2 Synthesis of Fe_3O_4 Nanoparticles

Nanoparticles of Fe_3O_4 were prepared by chemical coprecipitation method [22]. To a solution of $FeCl_3 \cdot 6H_2O$ (2.35 g) and $FeCl_2 \cdot 4H_2O$ (0.86 g) in distilled water (40 mL), aqueous ammonia solution (25 %, 40 mL) was added drop wise under nitrogen atmosphere with vigorous stirring over a period of 20 min. The solution was heated to 70 °C for 5 h, and Fe_3O_4 nanoparticles were separated from the resulting black dispersion by external magnet and washed three times with water and ethanol. The final product was dried under vacuum.

2.3 General Procedure for the Reduction of Oximes and Nitriles with Sodium Borohydride Catalyzed by Fe_3O_4 Nanoparticles

To the solution of substrate (10 mmol) in dry methanol (25 mL), Fe_3O_4 nanoparticles (50 mg) were added and the solution was sonicated for 10 min and then vigorously stirred at 40 °C. Sodium borohydride (30 mmol) was added in small lots cautiously while stirring the solution for 30 min and the progress of the reaction was monitored by thin layer chromatography (TLC). After the completion of reaction, the catalyst was separated by using external magnet and the reaction mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with brine solution and then separated and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography over silica gel (100–200 mesh) using ethyl acetate-hexane mixture (varying concentration) as the eluent. All products were analyzed by IR and NMR spectra which were in good agreement with the reported values [5, 10].

Benzylamine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.29–7.33 (m, 5H, ArH), 3.86 (s, 2H, CH_2), 1.49 (br s, 2H, NH_2); IR (film): 3367, 3296, 3062, 3027, 2919, 2850, 1586, 1495, 1453, 737, 698 cm^{-1}.

Cyclohexylamine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.59–2.54 (m, 1H, NCH), 1.78–1.74 (m, 2H, CH_2), 1.68–1.65 (m, 2H, CH_2), 1.57–1.53 (m, 1H, CH), 1.29 (br s, 2H, NH_2), 1.27–1.16 (m, 2H, CH_2), 1.11–1.03 (m, 1H, CH), 1.00–0.94 (m, 2H, CH_2); IR (film): 3349, 3249, 2927, 2853, 1586, 1449 cm^{-1}.

4-Methyl benzylamine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (d, J = 8.4 Hz, 2H, ArH), 7.17 (d, J = 8.4 Hz, 2H, ArH), 3.85 (s, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.51 (br s, 2H, NH_2); IR (film): 3381, 3309, 2919, 1481, 1329, 794 cm^{-1}.

4-Chloro benzylamine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.28 (m, 2H, ArH), 7.22 (m, 2H, ArH), 3.82 (s, 2H, CH_2), 1.48 (br s, 2H, NH_2); IR (film): 3369, 2861, 1595, 1491, 1091, 815 cm^{-1}.

4-Bromo benzylamine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.27 (m, 2H, ArH), 7.22 (m, 2H, ArH), 3.82 (s, 2H, CH_2), 1.49 (br s, 2H, NH_2).

1-Phenylethylamine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.32–7.21 (m, 5H, ArH), 4.10 (q, J = 7.2 Hz, 1H, NCH), 2.09 (br s, 2H, NH_2), 1.39 (d, J = 7.2 Hz, 3H, CH_3).

1-Propylamine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (t, *J* = 6.9, 2H, CH_2), 1.46–1.37 (m, 4H, NH_2 and CH_2), 0.87 (t, *J* = 7.3, 3H, CH_3); IR (film): 3418, 2923, 2851, 1560, 1466, 1053 cm^{-1}

1-Butyl amine ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.66 (t, *J* = 6.8 Hz, 2H, NCH_2), 1.42–1.27 (m, 6H, CH_2 and NH_2), 0.89 (t, *J* = 7.2 Hz, 3H, CH_3); IR (film): 3429, 2931, 1608, 1512, 1467 cm^{-1}.

3 Results and Discussion

3.1 Characterization of Magnetite (Fe_3O_4) Nanoparticles

Magnetite nanoparticles were prepared by chemical co-precipitation method under alkaline condition and were characterized by different techniques. The FT-IR spectrum of Fe_3O_4 MNPs (Supporting Information, Fig. S1) exhibits a prominent band as around 580 cm^{-1} which corresponds to stretching vibration of metal–oxygen bond ($Fe_{octahedral}$–O–$Fe_{tetrahedral}$ stretching vibrations) for the spinel structure of iron oxide [23]. A broad band at 3417 cm^{-1} indicates that presence of hydroxyl group on the surface of Fe_3O_4 nanoparticles. The phase and crystalline structures of Fe_3O_4 nanoparticles were determined by powder X-ray diffraction (P-XRD) (Fig. 1). It was found that the P-XRD pattern of Fe_3O_4 exhibits diffraction lines (hkl) corresponding to the crystal planes at (200) (311), (400), (422), (511) and (440). The position and relative intensity of diffraction peaks are in good agreement with the XRD standard for Fe_3O_4 nanoparticle (JCPDS no. 85-1436) [24]. The results indicate the spinel phase structure of magnetite nanoparticles and support a cubic crystal system. The morphology of the prepared magnetite nanoparticles was

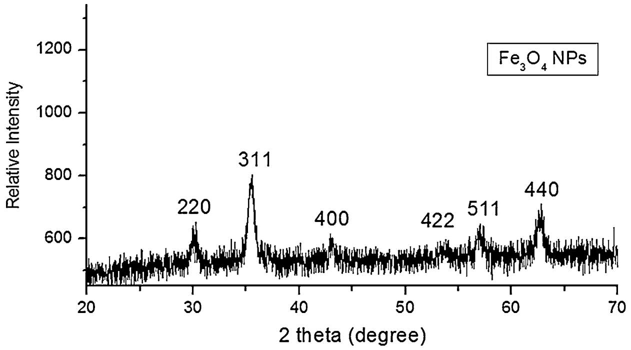


Fig. 1 Powder XRD data of Fe_3O_4 nanoparticles

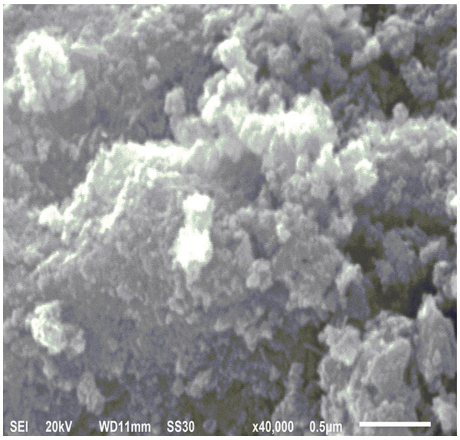


Fig. 2 SEM image of Fe_3O_4 nanoparticles

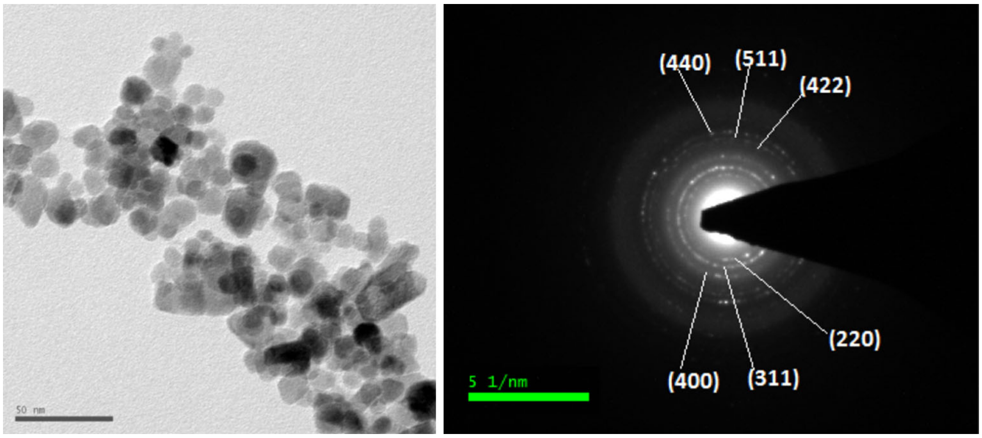


Fig. 3 TEM image of Fe_3O_4 nanoparticles (*left*), selected electron area diffraction pattern (SEAD) (*right*)

studied by scanning electron microscopy (SEM) technique (Fig. 2). The shape, size, and morphology of the Fe_3O_4 nanoparticles were also analyzed by using transmission electron microscopy (TEM) technique. It is observed from Fig. 3 that the magnetite nanoparticles are cubic in shape and their sizes are almost uniform. The SEAD pattern shows the reflections at (200), (311), (400), (422), (511) and (440) hkl positions (Fig. 3) which are also present in P-XRD pattern. The size distribution of nanoparticles is shown in Fig. 4. Energy-dispersive X-ray spectrometry data (EDX) (Supporting Information, Fig. S2) confirms the presence of iron and oxygen and thus the formation of Fe_3O_4 nanoparticles without any impurity peak. The presence of carbon and copper is due to the usage of carbon coated copper grid for sample preparation. The thermogravimetric analysis (TGA) (Supporting Information, Fig. S3) of Fe_3O_4 nanoparticles indicates decomposition at 100–290 °C which may be attributed to the removal of absorbed water molecules.

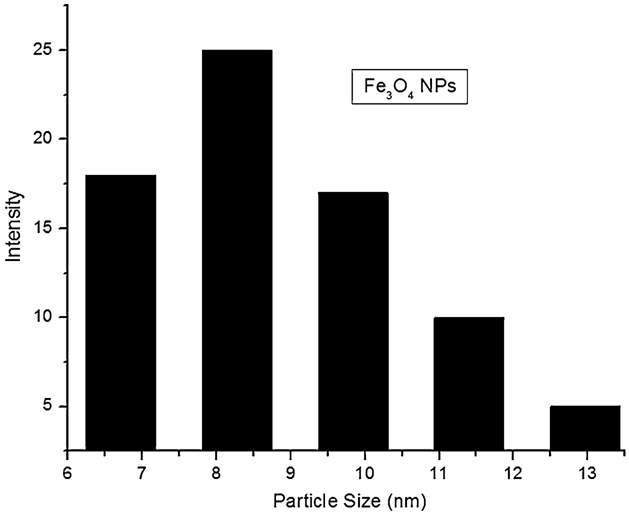
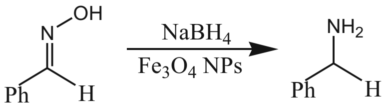


Fig. 4 Size distribution of Fe_3O_4 nanoparticles

3.2 Catalytic Activity of Fe_3O_4 Nanoparticles

The reductions of compounds containing C–N multiple bonds such as oximes and nitriles have been studied with sodium borohydride catalyzed by magnetite nanoparticles in methanol. To optimize the reaction conditions, benzaldehyde oxime was used as a model substrate (Table 1). The reduction of benzaldehyde oxime with sodium borohydride in absence of catalyst gives corresponding amine in poor yield. However, the presence of magnetite nanoparticles in this reduction reaction improves the yield of primary amine significantly (Table 1). It was observed that the yield increased considerably when the amount of sodium borohydride was increased from 1 mol equivalent to 3 mol equivalents with reference to the substrate. However, further increment in the amount of sodium borohydride to 6 mol equivalent was not much beneficial in terms of reductive transformation of oxime into amine. The yield was observed to be high at elevated temperature. Not much influence of the amount of magnetite nanoparticles was observed on the yield of amine product (Table 1, entry 4). The effect of solvent on the course of reduction was also studied and it was observed that the present reductive system works efficiently in methanol and ethanol. The results clearly indicate that the presence of a polar

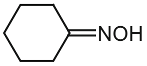
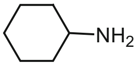
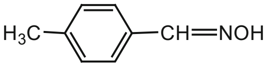
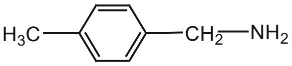
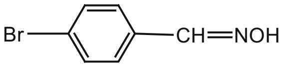
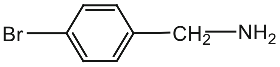
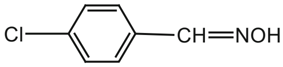
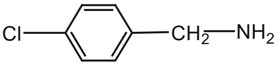
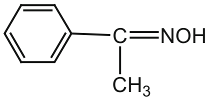
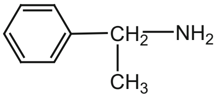
Table 1 Optimization of reaction conditions for benzaldehyde oxime (1 mmol), reaction time 30 min



Entry no.	$NaBH_4$ (mmol)	Catalyst (Fe_3O_4) (mg)	Solvent	Temp. (°C)	Yield[a] (%)
1	1.0	5.0	Methanol	rt	57
2	3.0	5.0	Methanol	rt	80
3	6.0	5.0	Methanol	rt	85
4	3.0	10.0	Methanol	rt	83
5	3.0	5.0	Methanol	40	88
6	3.0	5.0	Methanol	70	90
7	3.0	5.0	Ethanol	40	89
8	3.0	5.0	Propan-2-ol	40	75
9	3.0	5.0	Butanol	40	72
10	3.0	5.0	Tetrahydrofuran	40	53

[a] Isolated yields obtained following the general procedure

Table 2 Reduction of oximes with $NaBH_4$ catalyzed by Fe_3O_4 nanoparticles

Entry no.	Substrate	Product	Time (min)	Yield[a] (%)
1			30	64
2			30	78[b]
3			30	85
4			30	86
5			40	81

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[a] Isolated yields obtained following the general procedure

[b] The catalyst was recovered magnetically and reused, and the % yield of product is 78, 76, 73, 70 and 68 after 1st, 2nd, 3rd, 4th and 5th run respectively

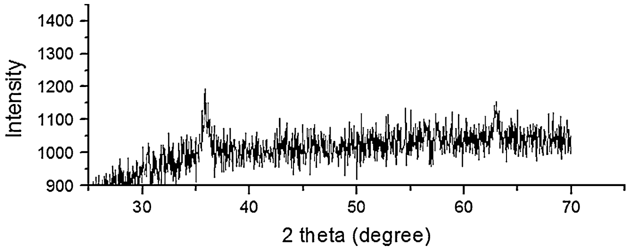


Fig. 5 Powder XRD of recovered Fe_3O_4 nanoparticles

protic solvent favours the reduction as the reaction was sluggish in tetrahydrofuran. Further, the efficiency of the present catalytic system could be correlated to the dielectric constants and thereby to the polarity of solvents (Dielectric Constants at 25 °C- methanol: 32.7, ethanol: 24.5,

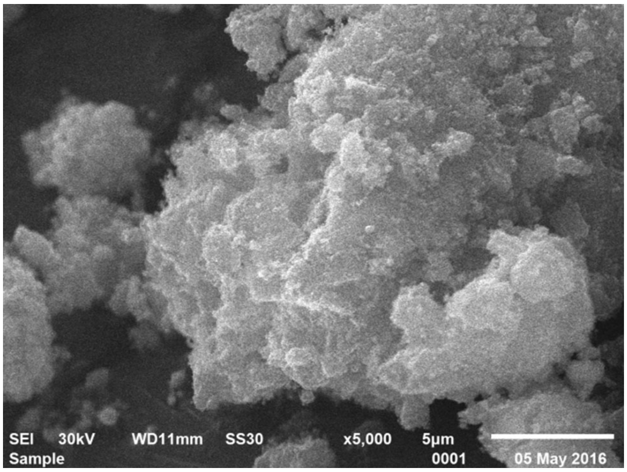
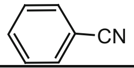
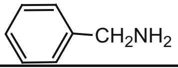
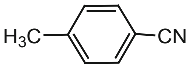
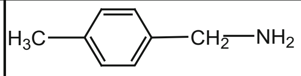
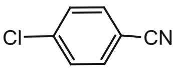
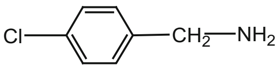


Fig. 6 SEM of recovered Fe_3O_4 nanoparticles

Table 3 Reduction of nitriles with $NaBH_4$ catalyzed by Fe_3O_4 nanoparticles

Entry no.	Substrate	Product	Time (min)	Yield[b] (%)
1	$CH_3{-}CH_2{-}CN$	$CH_3{-}CH_2{-}CH_2{-}NH_2$	30	72
2	$CH_3{-}CH_2{-}CH_2{-}CN$	$CH_3{-}CH_2{-}CH_2{-}CH_2{-}NH_2$	30	74
3			30	87
4			30	88
5			40	86

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[a] Isolated yields obtained following the general procedure

isopropyl alcohol: 19.9, butanol: 17.8, tetrahydrofuran: 7.6). Solvent with high polarity may contribute more towards the stabilization of reaction intermediates which are supposed to be more polarized/charged than the reactant molecules and thereby positive impact of solvent has been observed.

The scope and limitations of the present reductive system were studied by performing the reactions of different aldoximes and ketoximes with sodium borohydride catalyzed with Fe_3O_4 nanoparticles (Table 2). The present catalytic system worked well for different substituted oximes and corresponding amines were isolated and purified by column chromatography. The products were characterized by the NMR and IR spectroscopic data which were in good agreement with the reported data. The catalyst was separated by using external magnet and reused five times without any significant loss in its activity. The SEM and powder XRD pattern after fifth cycle of the reaction are shown in Figs. 5 and 6 which indicate that there is not much change in the morphology and phase of Fe_3O_4 nanoparticles. The TEM image of the recovered Fe_3O_4

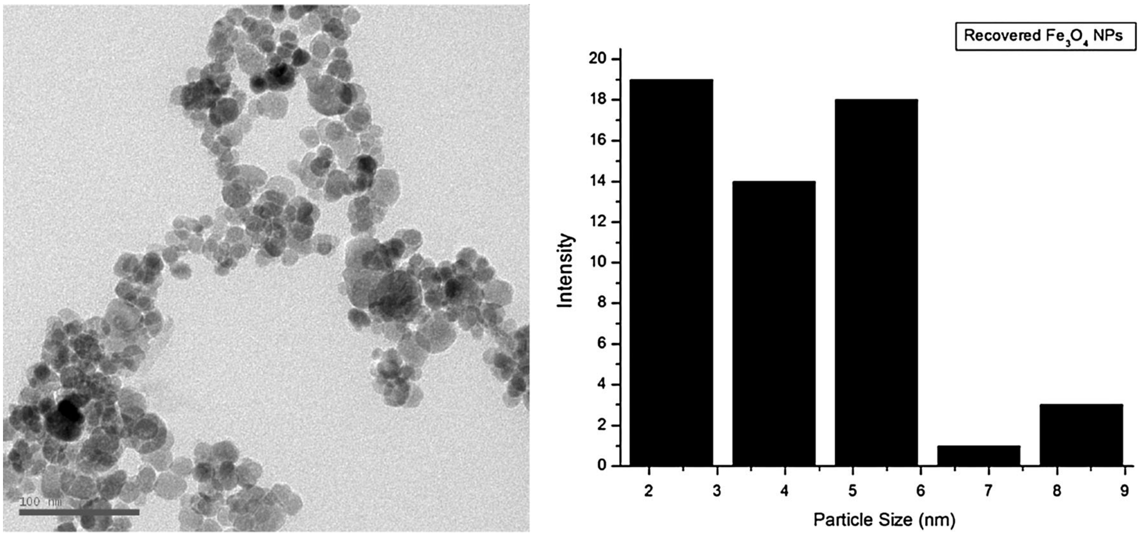
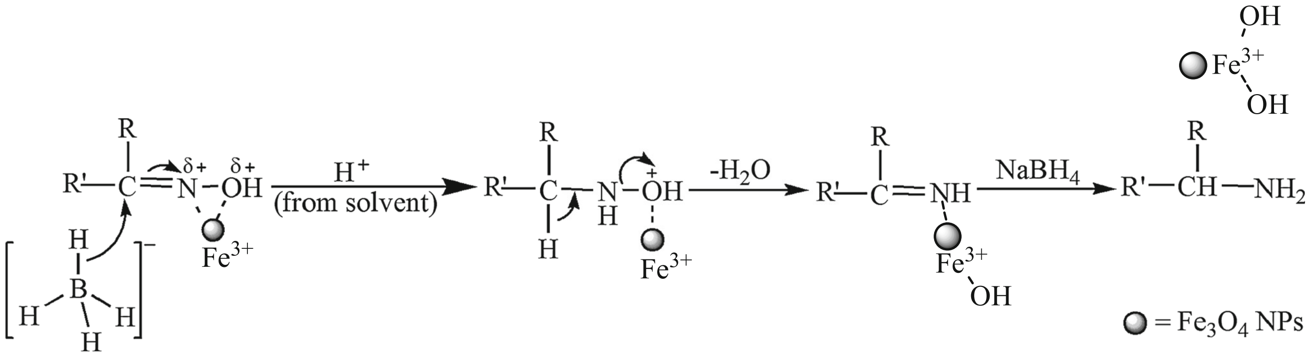


Fig. 7 TEM image (*left*), size distribution (*right*) of recovered Fe_3O_4 nanoparticles



Scheme 1 A plausible mechanism for Fe_3O_4 nanoparticles catalyzed reduction of oximes

nanoparticles also justifies that the shape of nanoparticles remains the same; however, the size distribution has changed (Fig. 7) which could be attributed to the interaction of magnetite with reactant in presence of $NaBH_4$. The SEAD pattern of recovered nano Fe_3O_4 also shows strong reflections at the same (hkl) positions verifying the pattern for Fe_3O_4 nanoparticles (Supporting Information, Fig. S17).

The reduction of different aliphatic and aromatic nitriles was also studied by sodium borohydride catalyzed by magnetite nanoparticles at 40 °C in methanol (Table 3). High yield of products were obtained under mild conditions.

The present catalytic system exhibited good activity and selectivity for the reduction of various oximes and nitriles. It is believed that Fe^{3+} of nano Fe_3O_4 coordinates to nitrogen and oxygen of oxime group or nitrogen of cyano group and thereby makes the carbon of >C=NOH bond or CN bond more electrophilic to facilitate the attack of hydride ion from sodium borohydride leading to the formation of imine intermediate (Scheme 1). Further, imine intermediate gets reduced to amine product by sodium borohydride in the presence of nano Fe_3O_4. The similar interaction of Fe^{n+} ion of Fe_3O_4 nanoparticles with electronegative atoms such as nitrogen and oxygen has also be explained in nano Fe_3O_4 catalyzed synthesis of various oximes and pyrimidine derivatives [25–27]. Various studies have been reported to explain the similar course of reductions assisted by transition metal—$NaBH_4$ system under different conditions whereby reactant such as nitrile binds to the solid surface of transition metal compound through nitrogen and thereby facilitating the attack of hydride ions from borohydride to electrophilic carbon of CN bond [28, 29].

4 Conclusion

Fe_3O_4 nanoparticles have been used as a promising catalyst for the reduction of oxime to amines using $NaBH_4$ under mild reaction conditions. The present catalytic system gives products with high yield and selectivity. The catalyst is magnetically separable which makes the work up of the reaction very easy. The catalyst is reusable for more than five reaction cycles for the conversion of oximes to the corresponding amine. This method offers some advantages in terms of clean reaction conditions, recyclability of castalyst, short reaction times, easy work-up procedure and suppression of side products.

Acknowledgments Authors acknowledge University of Delhi (Innovation Project DBC 306/2015-16) and Science and Engineering Research Board (SERB), New Delhi (Project File No. ECR/2015/000541) for financial support. Authors are also thankful to University Science Instrumentation Centre (USIC) & Department of Chemistry, University of Delhi, New Delhi for spectroscopic data and Deshbandhu College, Kalkaji, New Delhi for providing necessary facilities for the research work.

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