

Copper immobilized on aminated ferrite nanoparticles by 2-aminoethyl dihydrogen phosphate ($\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$) catalyses the conversion of aldoximes to nitriles

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Cu^{II} immobilized on aminated ferrite nanoparticles by 2-aminoethyl dihydrogen phosphate ($\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$) was prepared and characterized using FT-IR, TGA, TEM, EDX, VSM, XRD, CHN and ICP techniques. The easily prepared heterogeneous nanocatalyst demonstrated a significant catalytic performance for the transformation of aldoximes to nitriles that is far superior to previously reported methods. The reaction allows for the conversion of a wide variety of aldoximes including aromatic, aliphatic and heterocyclic aldoximes in good to excellent yields (50–98%). High efficiency, mild reaction conditions, easy work-up, operational simplicity, simple purification of products and safe handling of the catalyst are important advantages of this method. In addition, the environmentally benign heterogeneous nanocatalyst can be easily recovered from reaction mixtures using an external magnet and reused several times without any loss of activity. Copyright © 2015 John Wiley & Sons, Ltd.

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Introduction

Nitriles are an important class of compounds in chemistry as well as biology.^[1] They serve as a versatile precursor for various functional group transformations^[2] and heterocyclic synthesis.^[3] Moreover, nitriles as key components of numerous natural products are industrially important for the production of agrochemicals, pharmaceuticals, polymers, dyes and pigments.^[4–9] There are a variety of synthetic routes to nitriles from diverse chemical precursors reported in the literature, including Sandmeyer reaction,^[10] ammoxidation of aldehydes,^[11] metal-catalysed cyanation of aryl halides, nucleophilic substitution of alkyl halides with cyanides, oxidation of amines,^[12] hydrocyanation of alkenes,^[13] Kolbe nitrile synthesis,^[14] Rosenmund–von Braun reaction^[15] and dehydration of amides and aldoximes.^[16] Among these, the dehydration of aldoximes into nitriles is one of the most suitable candidate reactions for clean nitrile synthesis, because of the availability of starting materials and the avoidance of very toxic cyanide ion. At first, the aldoxime–nitrile transformation was investigated by Gabriel and Meyer.^[17] In the recent past, a number of efficient reagents and conditions have been described for the dehydration of aldoximes, such as NCS/PPh₃,^[18] (NCS/Py),^[19] Ph₃P/I₂,^[20] Ph₃PO/(COCl)₂,^[21] thionyl chloride-benzotriazole,^[22] *N*-(*p*-toluenesulfonyl)imidazole,^[23] Vilsmeier reagent,^[24] Burgess reagent,^[25] cyanuric chloride,^[26] *S,S*-dimethyl dithiocarbonate,^[27] sulfonyl chlorides,^[28] triflyl imidazole,^[29] bromodimethylsulfonium bromide,^[30] 8-bromocaffeine,^[31] tetrachloropyridine,^[32] PEG-SO₃H,^[33] silica gel,^[34] phthalic anhydride,^[35] clay,^[36] ethyl 2-cyano-2-(hydroxyimino)acetate^[37] and Ac₂O/K₂CO₃/dimethylsulfoxide.^[38] In recent decades several metal catalysts such as [RuCl₂(*p*-cymene)]₂/molecular sieves,^[39] rhenium(VII)oxo complexes,^[40] InCl₃,^[41] TiCl₃(OTf),^[42] Cu salts,^[43]

PtCl₄(EtCN)₂,^[44] Ga(OTf)₃,^[45] Bi(OTf)₃,^[46] W–Sn hydroxide,^[47] SnCl₄,^[48] Pd(OAc)₂ in the presence of PPh₃,^[49] Pd(en)(NO₃)₂,^[50] molecular sieve modified with copper(II),^[51] CoCl₂/NaF,^[52] Raney nickel,^[53] cetyltrimethylammonium dichromate,^[54] AlCl₃·6H₂O/KI/H₂O/CH₃CN,^[55] (La³⁺, Ce³⁺, Re³⁺, Sm³⁺) Na–Y zeolites,^[56] In(NO₃)₃,^[57] and Zn(OTf)₂,^[58] have been used to carry out the same transformation. The reported methods have paid much attention to the activation of the hydroxyl group in aldoxime as leaving group for the subsequent 1,2- elimination to give nitrile.^[59] Despite the development of dehydration methods for conversion of aldoximes to nitriles, it is still an interesting topic to current organic chemists. Also, the reported methods may have limitations in some respects such as harsh reaction conditions, low yields, lack of generality and use of high-cost or less readily available reagents, high microwave power and high temperature. Therefore, to overcome the mentioned limitations, we decided to apply a new reaction medium for the conversion of aldoximes to nitriles.

Our aim was to prepare an amino-functionalized Fe_3O_4 nanoparticle (NP) carrier, using 2-aminoethyl dihydrogen phosphate (AEPH₂) as a bifunctional short-chained organic molecule that has both a phosphate group and an amino group. Because there is a relatively high affinity between phosphate ions and hydrated oxide particles, in particular iron(III) oxides,^[60,61] the phosphate group of AEPH₂ is useful for binding with Fe_3O_4 NPs. As the amino group

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can also work as an anchoring point for bonding of several metal ions,^[62] immobilization of Cu^{II} on aminated Fe₃O₄ NPs (Fe₃O₄@AEPH₂-Cu^{II}) was investigated. The catalytic activity of Fe₃O₄@AEPH₂-Cu^{II}, as a new magnetically recoverable heterogeneous catalyst, was studied in the conversion of aldoximes to nitriles.

Experimental

General procedure

The purity determinations of the products were accomplished using TLC on silica gel polygram STL G/UV 254 plates. The melting points of products were determined with an Electrothermal type 9100 melting point apparatus. Fourier transform infrared (FT-IR) spectra were recorded with a Nicolet Avatar 370 FT-IR Thermo spectrometer. NMR spectra were obtained with Bruker AMX 100 and 400 MHz instruments in CDCl₃. Elemental analyses were performed using a Thermo Finnegan Flash EA 1112 series instrument. Mass spectra were recorded with Agilent Technologies (HP) 5973 Network Mass Selective Detector and Shimadzu GC-MS-QP 5050 instruments at 70 eV. Thermogravimetric analysis (TGA) was performed with a Shimadzu thermogravimetric analyser (TG-50) under air atmosphere at a heating rate of 10°C min⁻¹. Transmission electron microscopy (TEM) was performed with a Leo 912 AB (120 kV) microscope (Zeiss, Germany). Inductively coupled plasma (ICP) analysis was carried out with a Varian VISTA-PRO, CCD (Australia). Elemental compositions were determined with energy-dispersive X-ray analysis (EDX; model 7353, Oxford Instruments, UK), with 133 eV resolution.

The crystal structure of the catalyst was analysed using X-ray diffraction (XRD) with a Bruker D8 ADVANCE diffractometer using a Cu target ($\lambda = 1.54 \text{ \AA}$). The magnetic property of the catalyst was measured using vibrating sample magnetometry (VSM; model 7400, Lake Shore). All of the products were known compounds and characterized using FT-IR spectroscopy, mass spectrometry and comparison of their melting points with known compounds. The structure of selected products was further confirmed using ¹H NMR spectroscopy.

Preparation of Fe₃O₄ NPs

In a 500 ml three-necked round-bottom flask, a mixture of FeCl₃·6H₂O (46 mmol, 12.4 g) and FeSO₄·7H₂O (23 mmol, 6.3 g) was dissolved in 150 ml of deionized water. Argon was imported for 3 min to exclude air. Then 20 ml of ammonium hydroxide (25%) was added quickly into the iron solution under vigorous stirring. After 30 min, 3 ml of oleic acid was added into the reaction mixture. The mixture was heated at 75°C under argon atmosphere. After 1 h, the reaction mixture was cooled to room temperature. The Fe₃O₄ NPs were collected through magnetic separation and washed with deionized water and ethanol three times each. The Fe₃O₄ NPs were then dried under vacuum conditions.^[63]

Preparation of aminated Fe₃O₄ NPs (Fe₃O₄@AEPH₂)

To a suspension of Fe₃O₄ NPs (1.15 g, 5 mmol) in deionized water (20 ml), AEPH₂ (0.7 g, 5 mmol) was added portion by portion at room temperature. The flask was swept with argon for 3 min to exclude air and then closed. The closed flask was then shaken for 48 h. The resulting Fe₃O₄@AEPH₂ product was isolated using an external magnet, washed with distilled water and dried *in vacuo* at 50°C for 6 h.

Preparation of Fe₃O₄@AEPH₂-Cu^{II}

Cu(OAc)₂·H₂O (0.2 g, 1 mmol) was added to a suspension of Fe₃O₄@AEPH₂ (1 g) in ethanol (50 ml). The mixture was refluxed with vigorous stirring. After 24 h, the resulting Fe₃O₄@AEPH₂-Cu^{II} product was collected using an external magnet and washed repeatedly with ethanol and then dried at room temperature *in vacuo* for 6 h.

Typical procedure for preparation of nitriles

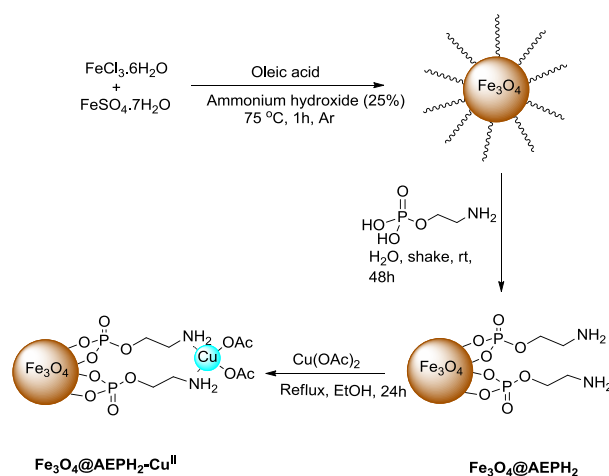
To a solution of 4-nitrobenzaldehyde (0.08 g, 1.00 mmol) in dry acetonitrile (2 ml), Fe₃O₄@AEPH₂-Cu^{II} (0.088 g, 8 mol%) was added with stirring. The reaction mixture was refluxed for 1 h. The progress of reaction was monitored using TLC. After completion of the reaction and separation of the catalyst using a magnetic field, the residue was purified using flash column chromatography on silica gel with *n*-hexane–ethyl acetate (4:1) as eluent to afford 4-nitrobenzonitrile (0.144 g, 98%).

Results and discussion

Synthesis and characterization of Fe₃O₄@AEPH₂-Cu^{II}

Recently, heterogeneous and magnetically recoverable catalysts with reagents immobilized on solid supports have been widely used in organic reactions, because of their advantages over conventional solution-phase reactions, such as good dispersion of active reagent sites, better selectivity and easier work-up. Also, recyclability of these solid-supported reagents renders these processes truly eco-friendly green protocols. In continuation of our study to design efficient heterogeneous catalysts,^[64] we have prepared Fe₃O₄@AEPH₂-Cu^{II} as an efficient, heterogeneous and magnetically recoverable catalyst which has been characterized using FT-IR spectroscopy, TGA, TEM, EDX, VSM, XRD, elemental analysis and ICP techniques. Initially, Fe₃O₄ NPs were prepared and purified using the method described in the literature^[63] (Scheme 1).

To confirm the existence of the bonded species, the catalyst structure was defined using FT-IR spectroscopy. Figure 1 illustrates the FT-IR spectra of Fe₃O₄ NPs, Fe₃O₄@AEPH₂ and Fe₃O₄@AEPH₂-Cu^{II}. The principal bands for Fe₃O₄ NPs (Fig. 1(a)) are observed at 3250–3400 cm⁻¹ (as a broad absorption band attributed to stretching frequencies of hydroxyl groups and bound water on the



Scheme 1. Preparation of Cu^{II} immobilized on aminated Fe₃O₄ NPs (Fe₃O₄@AEPH₂-Cu^{II}).

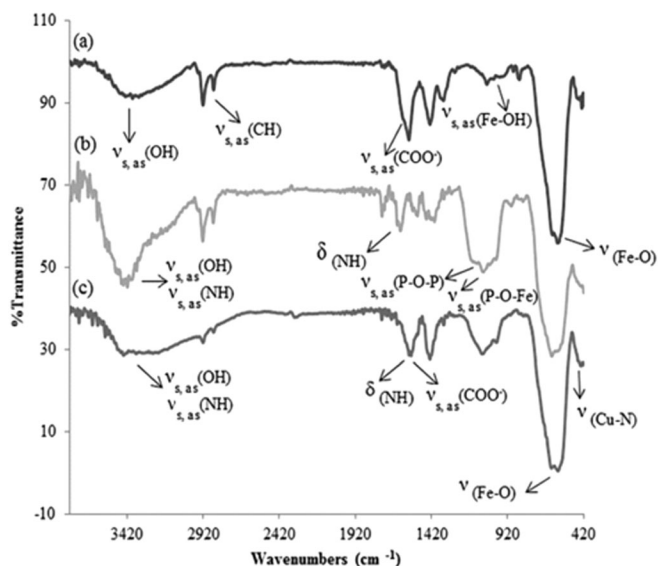


Figure 1. FT-IR spectra of (a) Fe_3O_4 NPs, (b) $\text{Fe}_3\text{O}_4\text{@AEPH}_2$ and (c) $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.

surface of Fe_3O_4 NPs), 2927, 2856, 1573 and 1436 cm^{-1} (asymmetric and symmetric vibrational frequencies of CH_2 and carboxylate group of the adsorbed oleate anion), 1060 and 847 cm^{-1} (asymmetric and symmetric stretching vibrations characteristic of Fe-O-H bond) and $580\text{--}620\text{ cm}^{-1}$ (attributed to vibrational frequency of Fe-O bond).

Upon the reaction of Fe_3O_4 NPs with AEPH₂, all the oleate anions are replaced by phosphonate groups. Thus in the FT-IR spectrum of $\text{Fe}_3\text{O}_4\text{@AEPH}_2$, absorption bands at 1573 and 1436 cm^{-1} (asymmetric and symmetric vibrational frequencies of carboxylate group of the adsorbed oleate anion) are removed completely (Fig. 1(b)).

The characteristic band of $\text{Fe}_3\text{O}_4\text{@AEPH}_2$ appears at 1153 cm^{-1} due to stretching vibration of P=O . The presence of P-O-Fe bond is confirmed by two absorption bands at 1012 and 987 cm^{-1} (asymmetric and symmetric stretching vibrations). Also, absorption bands at 1099, 981 and $570\text{--}604\text{ cm}^{-1}$ correspond to the asymmetric and symmetric stretching and bending vibrations of O-P-O bond, respectively. The latter absorption band is covered by the broad characteristic band of Fe-O at around $580\text{--}620\text{ cm}^{-1}$. Two absorption bands at 3457 and 3415 cm^{-1} are attributed to -NH_2 stretching frequencies and, furthermore, two other absorption bands at 1619 and 1238 cm^{-1} are assigned to -NH bending vibration and -CN stretching vibration, respectively (Fig. 1(b)).

In the FT-IR spectrum of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$, coordination of Cu^{II} on aminated Fe_3O_4 NPs is confirmed by the presence of an absorption band at 428 cm^{-1} . This absorption due to Cu-N vibration is covered by structural vibrations of Fe_3O_4 NPs (Fig. 1(c)). The intensities of -NH_2 stretching bands (3457 and 3415 cm^{-1}) are decreased significantly upon coordination of Cu^{II} on aminated Fe_3O_4 NPs. Also, coordination of Cu^{II} moves the -NH bending absorption band to lower frequency (1619 to 1590 cm^{-1}). A broad absorption band with rather low intensity at around $1455\text{--}1580\text{ cm}^{-1}$ is attributed to the asymmetric and symmetric stretching vibrations of acetate ions (OAc) which confirms that the acetate ions are still connected to Cu^{II} .

The TGA thermogram of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ (Fig. 2) shows two main weight losses. The first one (2.4%, $27\text{--}200^\circ\text{C}$) is accounted for by physically and hydrogen bonded water in the structure of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$. The second one which occurs at $200\text{--}500^\circ\text{C}$ (6.2%) is related to the decomposition of organic segment anchored to the Fe_3O_4 NP surface. This part of the thermogram

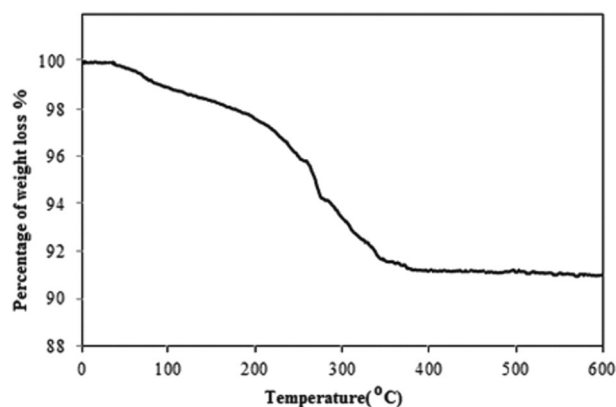


Figure 2. TGA thermogram of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.

reveals the amount of AEPH₂ combined on Fe_3O_4 NPs to be 6.2% (w/w). So, the elevated temperature for pending organic group removal indicates the high thermal stability of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$. This high thermal stability of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ confirms the covalent bonding of AEPH₂ on the surface of Fe_3O_4 NPs.

In addition to the structural confirmation of the catalyst using FT-IR spectroscopy and TGA, quantitative determination of covalently bonded AEPH₂ on the surface of Fe_3O_4 NPs was performed using elemental analysis. The elemental analysis of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ shows the carbon and nitrogen contents to be 1.71 and 0.948%, respectively. The results of elemental analysis of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ are in good agreement with those of TGA. The elemental analysis data for the catalyst reveal that 0.75 mmol of AEPH₂ is incorporated into 1.000 g of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.

The copper content of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ is found, using ICP analysis, to be 58 320 ppm, 0.057 g or 0.91 mmol of Cu per 1.000 g of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.

TEM micrographs and size distributions (25 nm) of Fe_3O_4 NPs and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ are shown in Fig. 3. TEM images indicate that most of the prepared Fe_3O_4 NPs (Figs 3(a) and (b)) and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ (Figs 3(c) and (d)) are spherical in shape and have sizes of 10–20 nm. The TEM results reveal that incorporation of AEPH₂ on the surface of Fe_3O_4 NPs and immobilization of Cu^{II} on $\text{Fe}_3\text{O}_4\text{@AEPH}_2$ do not change the particle size of Fe_3O_4 NPs.

XRD was used to identify the crystalline structure of Fe_3O_4 NPs and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$. As shown in Fig. 4, all the diffraction peaks can be indexed to (2, 2, 0), (3, 1, 1), (4, 0, 0), (4, 2, 2), (5, 1, 1) and (4, 4, 0) reflections, matching well with the characteristic peaks of

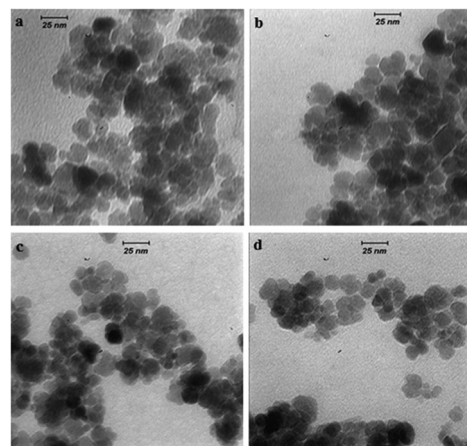


Figure 3. TEM images of (a, b) Fe_3O_4 NPs and (c, d) $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.

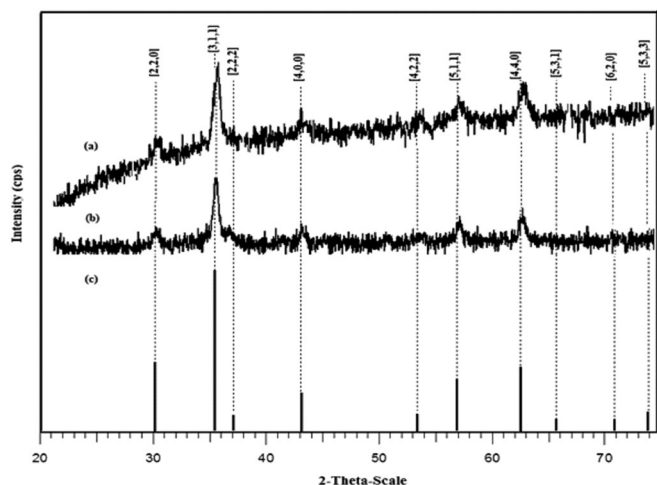


Figure 4. XRD patterns of (a) $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$, (b) Fe_3O_4 NPs and (c) standard reference (JCPDS 19-0629).

cubic structure (JCPDS 19-0629). The average crystallite sizes, d , of Fe_3O_4 NPs and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ calculated using the Debye-Scherrer equation $d = K \lambda / \beta \cos \theta$ are about 16.5 and 13 nm, respectively. As the peak positions of Fe_3O_4 NPs (Fig. 4(b)) are unchanged during the production of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ (Fig. 4(a)), we can conclude that the crystalline structure of Fe_3O_4 NPs is conserved after the surface modification with AEPH₂ and Cu^{II}.

EDX indicates the presence of C, O, P, Fe and Cu elements (Fig. 5). This analysis confirms that Cu^{II} is supported on aminated Fe_3O_4 NPs.

The $M-H$ hysteresis curves of Fe_3O_4 NPs and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ are shown in Fig. 6. The magnetization curves measured at room temperature show that Fe_3O_4 NPs and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ are superparamagnetic. This is because the diameters of Fe_3O_4 NPs and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ are smaller than 25 nm. It can be seen that the saturation magnetizations of Fe_3O_4 NPs and $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ are 54.6 and 45.0 emu g^{-1} , respectively. The decrease in the saturation magnetization of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ indicates the presence of surface-bound AEPH₂-Cu^{II}.

Catalytic conversion of aldoximes to nitriles

In continuation of our recent studies of the application of Cu^{II} in organic reactions,^[64-67] after preparation and characterization of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$, its catalytic activity as a new magnetic nanocatalyst was investigated in the preparation of a library of nitriles through dehydration of aldoximes by acetonitrile (Scheme 2).

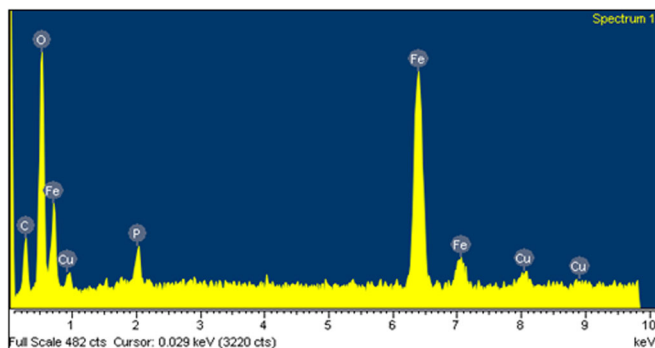


Figure 5. EDX trace of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.

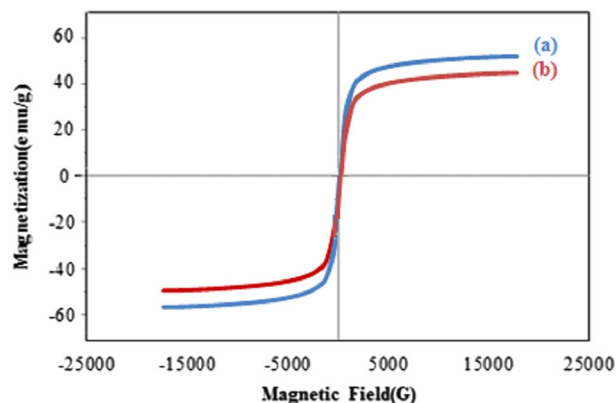
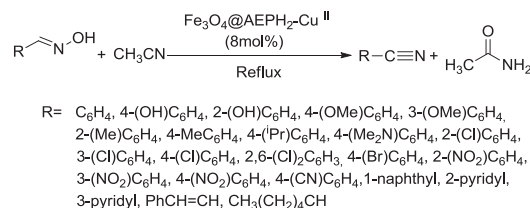


Figure 6. Magnetization curves of (a) Fe_3O_4 NPs and (b) $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.



Scheme 2. Synthesis of a variety of nitriles in the presence of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$.

In order to achieve the maximum yield and efficiency for the synthesis of various nitrile compounds, the experimental conditions must be carefully optimized. Conversion of 4-nitrobenzaloxime to 4-nitrobenzonitrile as a model reaction was studied in the presence of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ and acetonitrile as dehydrating agent and subjected to a series of reaction conditions (applying various amounts of catalyst at various temperatures). The obtained results are summarized in Table 1. The best results are obtained using 8 mol% (0.0880 g) of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ (containing 0.08 mmol of Cu) in refluxing acetonitrile (Table 1, entry 2). When the reaction is carried out at lower temperatures, the rate of reaction is reduced considerably with the formation of 4-nitrobenzamide as by-product (Table 1, entry 1). Higher catalyst loading (16 mol%, 0.1760 g containing 0.16 mmol of Cu) has no significant influence on the reaction rate, while a lower amount of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ decreases the reaction rate (Table 1, entries 4 and 5). To improve the reaction conditions, conversion of 4-nitrobenzaloxime to 4-nitrobenzonitrile was performed with stoichiometric amount of acetonitrile (1:1 molar ratio of 4-nitrobenzaloxime to CH₃CN) in the presence of 8 mol% (0.0880 g) of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ (Table 1, entry 3). As can be seen, stoichiometric amount of acetonitrile reduces the catalytic activity of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ efficiently, and 4-nitrobenzamide is produced as by-product.

The major role of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$ as a catalyst in the conversion of aldoximes to nitriles was established by performing the model reaction in the absence of $\text{Fe}_3\text{O}_4\text{@AEPH}_2\text{-Cu}^{\text{II}}$. After a long reaction time (24 h), the reaction proceeds to only 10% conversion (trace amount of 4-nitrobenzonitrile and 8% yield of 4-nitrobenzamide) and no additional conversion is obtained even after a longer reaction time (Table 1, entry 6). Similarly, performing the model reaction in the presence of $\text{Fe}_3\text{O}_4\text{@AEPH}_2$ and Fe_3O_4 NPs gives the same results (Table 1, entries 7 and 8).

In the presence of the optimized amount of Cu^{II} (0.0051 g, 0.08 mmol), using 0.0159 g (7 mol%) of Cu(OAc)₂·H₂O, the

Table 1. Conversion of 4-nitrobenzaloxime to 4-nitrobenzonitrile in the presence of various amounts of Fe₃O₄@AEPH₂-Cu^{II} and 2 ml of acetonitrile, and at various temperatures

Entry	Catalyst (mol%)	Temp. (°C)	Time (h)	Conversion (%)	4-Nitrobenzonitrile (%)	4-Nitrobenzamide (%)
1	8 (0.0880 g)	60	2	50	40	10
2	8 (0.0880 g)	Reflux	1	100	100	0
3 ^a	8 (0.0880 g)	Reflux	1	30	10	20
4	16 (0.1760 g)	Reflux	0.83	100	100	0
5	4 (0.0440 g)	Reflux	3	90	85	5
6	None	Reflux	24	10	Trace	8
7 ^b	8 (0.0168 g)	Reflux	24	10	Trace	8
8 ^c	8 (0.0180 g)	Reflux	24	10	Trace	8
9 ^d	7 (0.0159 g)	Reflux	1	90	60	30

^a1:1 molar ratio of 4-nitrobenzaloxime to acetonitrile.^bIn the presence of Fe₃O₄@AEPH₂.^cIn the presence of Fe₃O₄NPs.^dIn the presence of Cu(OAc)₂·H₂O.**Table 2.** Dehydration of various aldoximes in the presence of Fe₃O₄@AEPH₂-Cu^{II} and acetonitrile

$\text{R}-\text{C}(\text{OH})=\text{N} + \text{CH}_3\text{CN} \xrightarrow[\text{Reflux}]{\text{Fe}_3\text{O}_4@\text{AEPH}_2\text{-Cu}^{\text{II}} (8\text{mol}\%)} \text{R}-\text{C}\equiv\text{N}$				
Entry	R	Time (h)	Isolated yield (%)	M.p. (°C)
1	C ₆ H ₅	2	90	Oil ^[68]
2	4-OHC ₆ H ₄	1	98	108–110 ^[46]
3 ^a	2-OHC ₆ H ₄	4	50	92–94 ^[33]
4	4-OMeC ₆ H ₄	1	95	56–58 ^[48]
5	3-OMeC ₆ H ₄	2	95	Oil ^[49]
6	2-MeC ₆ H ₄	4	85	Oil ^[69]
7	4-MeC ₆ H ₄	2	95	26–27 ^[70]
8	4-iso-PrC ₆ H ₄	2	90	Oil ^[46]
9	4-(Me ₂ N)C ₆ H ₄	2	85	70–72 ^[71]
10	2-ClC ₆ H ₄	4	90	40–41 ^[48]
11	3-ClC ₆ H ₄	1.5	95	92–93 ^[72]
12	4-ClC ₆ H ₄	1	96	89–90 ^[48]
13	2,6-(Cl) ₂ C ₆ H ₃	4	85	140–143 ^[32]
14	4-BrC ₆ H ₄	1	98	112–113 ^[70]
15	2-NO ₂ C ₆ H ₄	4	75	106–108 ^[48]
16	3-NO ₂ C ₆ H ₄	2	90	114–115 ^[73]
17	4-NO ₂ C ₆ H ₄	1	98	146–148 ^[73]
18	4-CNC ₆ H ₄	1	95	218–220 ^[72]
19	1-Naphthyl	2	95	32–34 ^[74]
20	1-Pyridyl	3	75	Oil ^[68]
21	3-Pyridyl	3	90	46–50 ^[75]
22	C ₆ H ₄ CH=CH ₂	1.5	98	Oil ^[21]
23	C ₆ H ₁₂	1	95	Oil ^[76]

^aIn the presence of equimolar amount of triethylamine.

dehydration reaction of 4-nitrobenzaloxime is completed after 1 h with the formation of 60% of 4-nitrobenzonitrile and 30% of 4-nitrobenzamide (Table 1, entry 9). Therefore, we may conclude that immobilization of Cu^{II} on the surface of Fe₃O₄@AEPH₂ not only increases the catalytic activity but also improves the selective formation of 4-nitrobenzonitrile (compare entries 2 and 9).

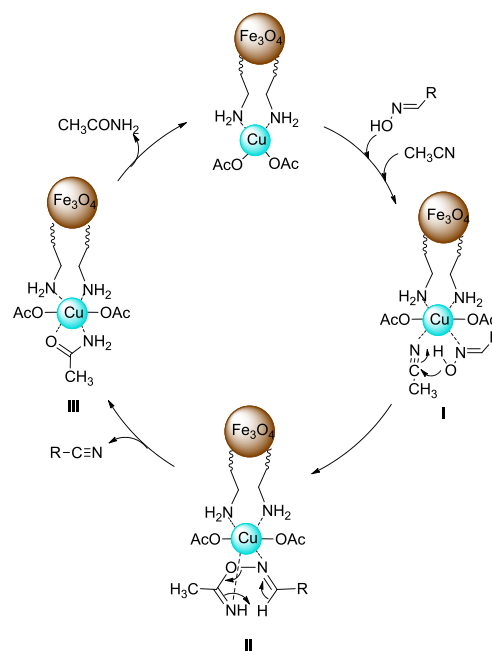
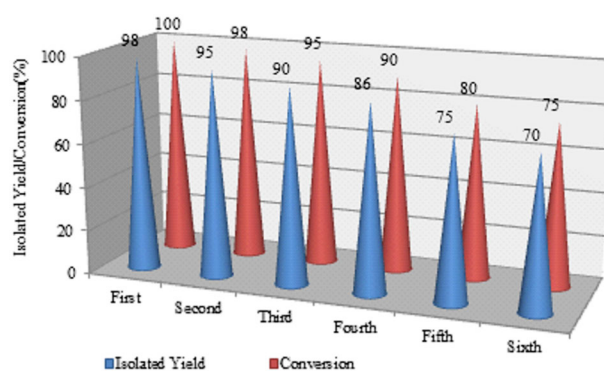
**Scheme 3.** Proposed mechanism of conversion of aldoximes to nitriles in the presence of Fe₃O₄@AEPH₂-Cu^{II}.**Figure 7.** Dehydration of 4-nitrobenzaloxime in the presence of reused Fe₃O₄@AEPH₂-Cu^{II}.

Table 3. Comparison of various catalysts in conversion of aldoximes to nitriles

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Yield (%)	Ref.
1	SnCl ₄	—	90	0.5	92	48
2	<i>S,S</i> -Dimethyl dithiocarbonate	Dioxane	90	8	70	27
3	Ga(OTf) ₃	Acetonitrile	120	16	82	45
4	PEG-SO ₃ H	Acetonitrile	Reflux	5	90	33
5	Pd(OAc) ₂ /PPH ₃	Acetonitrile	Reflux	3	90	49
6	Bi(OTf) ₃	Acetonitrile	Reflux	16	95	46
7	Cu(II)/MS 4 Å	Acetonitrile	Reflux	8	96	51
8	Cu(OAc) ₂	Acetonitrile	Reflux	1	88	43
9	Fe ₃ O ₄ @AEPH ₂ -Cu ^{II}	Acetonitrile	Reflux	1	98	This study

Based on the optimized reaction conditions, 0.0880 g of the catalyst (containing 0.08 mmol of Cu) in refluxing acetonitrile, to extend the scope and versatility of the present findings, different aldoximes possessing a wide range of functional groups (Scheme 2) were dehydrated and the corresponding nitriles are produced within 1–4 h with good to excellent yields. The results are summarized in Table 2. Aromatic aldoximes containing both electron-withdrawing and electron-donating groups undergo conversion smoothly. This means that aldoximes appear to be insensitive to substitution. The difference in dehydration rate of *ortho*-substituted aldoximes and the other aromatic aldoximes can be rationalized by the steric effect (compare entries 3, 6, 10, 13, 15 with the other aromatic aldoximes in Table 2). Under the same reaction conditions, salicylaldoxime cannot be dehydrated. It is well known that strong intramolecular hydrogen bonding between the aldoxime nitrogen and the *o*-hydroxyl group in salicylaldoxime can hinder the complex formation of the oxime with Cu^{II} and leads to weak reactivity of salicylaldoxime (Table 2, entry 3). To improve the dehydration tendency of salicylaldoxime, triethylamine should be added to the reaction mixture to disrupt this hydrogen bonding. Conversion of 50% is obtained with equimolar amount of triethylamine. Additional amount of triethylamine does not lead to complete conversion of salicylaldoxime to *o*-hydroxybenzoxime after a long reaction time because of steric hindrance. 1-Naphthaldehydeoxime, and also 2-pyridinealdoxime and 3-pyridinealdoxime as heteroaromatic oximes are dehydrated the same as the other oximes (Table 2, entries 19–21). The present method was further examined for dehydration of aliphatic aldoximes. Comparatively, aliphatic aldoximes undergo this reaction with equal efficiency as aromatic aldoximes (Table 2, entries 22 and 23).

In our experiments, the completion of the reaction is confirmed by the disappearance of the aldoximes using TLC followed by the disappearance of OH and C=N stretching frequencies at 3570–3600 and 1480–1690 cm⁻¹ in the FT-IR spectra. Also, the appearance of absorption bands at 2200–2260 cm⁻¹ due to CN group of nitriles in the FT-IR spectra confirms the formation of nitriles. All of the products are known compounds and characterized using FT-IR spectroscopy, mass spectrometry and comparison of their melting points with known compounds. See the supporting information for details.

According to these observations and by analogy with previous reports,^[64] we propose the mechanism shown in Scheme 3. In the absence of Fe₃O₄@AEPH₂-Cu^{II} a trace amount of product is observed in dehydration of 4-nitrobenzaloxime after a long reaction time (Table 1, entry 6). Although the role of Fe₃O₄@AEPH₂-Cu^{II} in dehydration of aldoximes is not clear definitively, it is speculated that the Lewis acidity of the Cu^{II} complex plays an essential role in dehydration reaction of aldoximes. Initially, interaction of nitrogen atom of aldoxime and acetonitrile with Cu^{II} forms **I** which facilitates

the nucleophilic addition of oxygen atom of aldoxime to activated acetonitrile. Then, hydrogen shift leads to the formation of intermediate **II**. Cleavage of **II** leads to fast extrusion of nitrile and acetamide. The catalyst re-enters the catalytic cycle by making the active sites for further turnovers. Further investigation of the elucidation of the mechanism and scope of this reaction is currently underway in our laboratory.

Catalyst reusability was assessed in the dehydration of 4-nitrobenzaloxime. The reaction was stopped after 1 h (i.e. at 100% conversion) and the catalyst retrieved from the reaction mixture using an external magnet and washed with ethyl acetate several times to remove the products, followed by drying at room temperature under vacuum for 6 h. Figure 7 shows the results obtained after six reuse cycles. As can be seen, no significant loss of activity of the catalyst is observed. ICP analysis shows that freshly prepared Fe₃O₄@AEPH₂-Cu^{II} contains 58 320 ppm, 0.057 g or 0.91 mmol of Cu per 1.000 g of Fe₃O₄@AEPH₂-Cu^{II}, while Fe₃O₄@AEPH₂-Cu^{II} after six cycles contains 29 850 ppm, 0.0295 g or 0.4680 mmol of Cu per 1.000 g of Fe₃O₄@AEPH₂-Cu^{II}. In other words, during the recovery process of the catalyst the catalytic activity is maintained effectively after six reuses of Fe₃O₄@AEPH₂-Cu^{II}. No significant loss of activity of the catalyst is observed, in spite of some leaching of Cu^{II} during the recovery process of the catalyst.

To obtain a better idea about the efficiency of the present catalyst in the dehydration of aldoximes to nitriles, the model reaction was compared with previously reported methods in the literature (Table 3). As is evident from Table 3, some of the reported methods, in addition to using expensive, hazardous or corrosive reagents and tedious work-up procedures, require longer reaction times to achieve reasonable yields. In comparison, Fe₃O₄@AEPH₂-Cu^{II}, as a new and environmentally benign heterogeneous nanocatalyst, is an efficient catalyst for the conversion of aldoximes to nitriles under mild reaction conditions. More importantly, this catalyst can be easily removed from the reaction mixture using an external magnet.

Conclusions

In summary, we presented here a simple and effective method for the synthesis of nitriles from aldoximes using Fe₃O₄@AEPH₂-Cu^{II} as a new, heterogeneous and magnetically reusable catalyst. Fe₃O₄@AEPH₂-Cu^{II} is easily prepared and stable to air. Selective dehydration of various aldoximes to nitriles can be performed in the presence of the magnetic and nano-sized heterogeneous catalyst with excellent catalytic performance. Simple separation of the magnetic nanocatalyst from the reaction mixture offers easy

work-up and high yields. Also, the other significant feature of this efficient and environmentally benign catalyst is its reusability after six consecutive cycles.

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References

- a) S. Arseniyadis, K. S. Kyler, D. S. Watt, *Organic Reactions*, Wiley, New York, **1984**; b) A. Kleemann, J. Engel, B. Kutscher, D. Reichert, *Pharmaceutical Substances: Synthesis, Patents, Applications*, 4th edn, Georg Thieme, Stuttgart, **2001**; c) J. S. Miller, J. L. Manson, *Acc. Chem. Res.* **2001**, *34*, 563; d) M. B. Smith, J. March, *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th edn, Wiley, Hoboken, NJ, **2007**.
- a) J. M. Muñoz, J. Alcázar, A. Hoz, A. Díaz Ortiz, *Tetrahedron Lett.* **2011**, *52*, 6058; b) S. Caddick, A. K. K. Haynes, D. B. Judd, M. R. V. Williams, *Tetrahedron Lett.* **2000**, *41*, 3513.
- a) B. Heller, B. Sundermann, H. Buschmann, H. J. Drexler, J. You, U. Holzgrabe, E. Heller, G. Oehme, *J. Org. Chem.* **2002**, *67*, 4414; b) L. Bosch, J. Vilarrasa, *Angew. Chem. Int. Ed.* **2007**, *46*, 3926; c) V. Aureggi, G. Sedelmeier, *Angew. Chem. Int. Ed.* **2007**, *46*, 8440; d) M. Aldhoun, A. Massi, A. J. Dondoni, *Org. Chem.* **2008**, *73*, 9565; e) N. A. Bokach, M. L. Kuznetsov, M. Haukka, V. I. Ovcharenko, E. V. Tretyakov, V. Y. Kukushkin, *Organometallics* **2009**, *28*, 1406.
- K. Friedrich, K. Wallenfels, *The Chemistry of the Cyano Group*, Wiley-Interscience, New York, **1970**.
- A. J. Fatiadi, S. Patai, *Preparation and Synthetic Applications of Cyano Compounds*, Wiley, New York, **1983**.
- M. Sundermeier, A. Zapf, M. Beller, S. Sans, *Tetrahedron Lett.* **2001**, *42*, 6707.
- S. Fustero, E. Salavert, J. F. Sanz Cervera, J. Piera, A. Asensio, *Chem. Commun.* **2003**, 844.
- S. Ozaki, *Med. Res. Rev.* **1996**, *16*, 51.
- a) R. C. Larock, *Comprehensive Organic Transformations*, Wiley-VCH, New York, **1989**; b) C. Grundmann, H. Weyl, *Methoden Der Organischen Chemie*, 4th edn, Georg Thieme Verlag, Stuttgart, **1985**.
- a) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 1946; b) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1885**, *18*, 1492; c) T. Sandmeyer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2650.
- a) G. P. Ellis, T. M. Romney Alexander, *Chem. Rev.* **1987**, *87*, 779; b) R. Raja, R. D. Adams, D. A. Blom, W. C. Pearl, E. Gianotti, J. M. Thomas, *Langmuir* **2009**, *25*, 7200.
- D. T. Mowry, *Chem. Rev.* **1948**, *42*, 189.
- L. Bini, C. Muller, J. Wiltling, L. Chrzanowski, A. L. Spek, D. Vogt, *J. Am. Chem. Soc.* **2007**, *129*, 12622.
- L. Friedman, H. Shechter, *J. Org. Chem.* **1960**, *25*, 877.
- a) K. W. Rosenmund, E. Struck, *Ber. Dtsch. Chem. Ges.* **1919**, *2*, 1749; b) J. Lindley, *Tetrahedron* **1984**, *40*, 1433.
- a) J. K. Augustine, R. Kumar, A. Bombrun, A. B. Mandal, *Tetrahedron Lett.* **2011**, *52*, 1074; b) A. V. Narsaiah, K. Nagaiah, *Adv. Synth. Catal.* **2004**, *346*, 1271; c) K. Ishihara, Y. Furuya, H. Yamamoto, *Angew. Chem.* **2002**, *114*, 3109.
- S. Gabriel, R. Meyer, *Chem. Ber.* **1881**, *14*, 2332.
- N. Iranpoor, H. Firouzabadi, G. Aghapour, *Synth. Commun.* **2002**, *32*, 2535.
- M. Guzman, W. M. Golebiewski, *Synthesis* **2008**, 1997.
- A. V. Narsaiah, D. Sreenu, K. Nagaiah, *Synth. Commun.* **2006**, *36*, 137.
- R. M. Denton, J. An, P. Lindovska, W. Lewis, *Tetrahedron* **2012**, *68*, 2899.
- S. S. Chaudhari, K. G. Akamanchi, *Synth. Commun.* **1999**, *29*, 1741.
- M. N. Soltani Rad, A. Khalafi Nezhad, Z. Amini, M. Behrouz, *Synth. Commun.* **2010**, *40*, 2429.
- J. P. Dulcere, *Tetrahedron Lett.* **1981**, *22*, 1599.
- C. P. Miller, D. H. Kaufman, *Synlett* **2000**, 1169.
- a) J. K. Chakrabarti, T. M. Hotten, *J. Chem. Soc. Chem. Commun.* **1972**, 1226; b) V. Rammooorthy, B. Fischer, *J. Org. Chem.* **2002**, *67*, 711.
- A. T. Khan, S. Peruncheralathan, H. Ila, H. Junjappa, *Synlett* **2004**, 2019.
- H. Sharghi, M. H. Sarvari, *Tetrahedron* **2002**, *58*, 10323.
- R. G. Kalkhambkar, S. D. Bunje, K. L. Laali, *Tetrahedron Lett.* **2011**, *52*, 5184.
- L. D. S. Yadav, V. P. Srivastava, R. Patel, *Tetrahedron Lett.* **2009**, *50*, 5532.
- M. N. S. Rad, S. Behrouz, A. Nekoei, *Synlett* **2012**, 1191.
- N. Lingaiah, R. Narender, *Synth. Commun.* **2002**, *32*, 2391.
- X. C. Wang, L. Li, Z. J. Quan, H. P. Gong, H. L. Ye, X. F. Cao, *Chin. Chem. Lett.* **2009**, *20*, 651.
- S. Dewan, R. Singh, *Synth. Commun.* **2003**, *33*, 3085.
- E. Wang, K. Huang, H. Chen, C. Wu, G. Lin, *J. Chin. Chem. Soc.* **2004**, *51*, 619.
- a) H. M. Meshram, *Synthesis* **1992**, 943; b) B. P. Bandgar, V. S. Sadavarte, K. R. Sabu, *Synth. Commun.* **1999**, *29*, 3409.
- D. Dev, N. B. Palakurthy, N. Kumar, B. Mandal, *Tetrahedron Lett.* **2013**, *54*, 4397.
- Y. Song, D. Shen, Q. Zhang, B. Chen, G. Xu, *Tetrahedron Lett.* **2014**, *55*, 639.
- S. H. Yang, S. Chang, *Org. Lett.* **2001**, *3*, 4209.
- K. Ishihara, Y. Furuya, H. Yamamoto, *Angew. Chem. Int. Ed.* **2002**, *41*, 2983.
- D. C. Barman, A. Thakur, J. D. Prajapati, J. S. Sandhu, *Chem. Lett.* **2000**, *29*, 1196.
- N. Iranpoor, B. Zeynizadeh, *Synth. Commun.* **1999**, *29*, 2747.
- O. Attanasi, P. Palma, F. Serra Nanetti, *Synthesis* **1983**, 741.
- A. V. Makarycheva Mikhailova, N. A. Bokach, M. Haukka, V. Y. Kukushkin, *Inorg. Chim. Acta* **2003**, *356*, 382.
- P. Yan, P. Batamack, G. K. S. Prakash, G. A. Olah, *Catal. Lett.* **2005**, *101*, 141.
- M. Sridhar, M. K. K. Reddy, V. V. Sairam, J. Raveendra, K. R. Godala, C. Narsaiah, B. C. Ramanaiah, C. S. Reddy, *Tetrahedron Lett.* **2012**, *53*, 3421.
- K. Yamaguchi, H. Fujiwara, Y. Ogasawara, M. Kotani, N. A. Mizuno, *Angew. Chem. Int. Ed.* **2007**, *46*, 3922.
- U. Patil, A. Kuwar, A. Nikum, K. Desale, P. Mahulikar, *Int. J. Chem. Tech. Res.* **2013**, *5*, 24.
- H. S. Kim, S. H. Kim, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 1717.
- K. Tambaraa, G. Panto, *Org. Biomol. Chem.* **2013**, *11*, 2466.
- A. Kiss, Z. Hell, *Synth. Commun.* **2013**, *43*, 1778.
- P. Tamilselvan, Y. B. Basavaraju, E. Sampathkumar, R. Murugesan, *Catal. Commun.* **2009**, *10*, 716.
- D. R. Zuidema, A. L. Dennison, E. Y. Park, R. C. Mebane, *Synth. Commun.* **2008**, *38*, 3810.
- S. Sahu, S. Patel, B. K. Mishra, *Synth. Commun.* **2005**, *35*, 3123.
- M. Boruah, D. Konwar, *J. Org. Chem.* **2002**, *67*, 7138.
- B. Thomas, S. Sugunan, *J. Porous Mater.* **2007**, *14*, 471.
- C. L. Allen, C. Burel, J. M. J. Williams, *Tetrahedron Lett.* **2010**, *51*, 2724.
- S. Enthaler, M. Weidauer, F. Schröder, *Tetrahedron Lett.* **2012**, *53*, 882.
- B. R. Cho, N. S. Cho, S. K. Lee, *J. Org. Chem.* **1997**, *62*, 2230.
- P. Persson, N. Nilsson, S. Sjöberg, *J. Colloid Interface Sci.* **1996**, *177*, 263.
- M. I. Tejedor-Tejedor, M. A. Anderson, *Langmuir* **1990**, *6*, 602.
- J. Jover, R. Bosque, J. Sales, *Dalton Trans.* **2008**, 6441.
- J. Qu, G. Liu, Y. Wang, R. Hong, *Adv. Powder Technol.* **2010**, *21*, 461.
- N. Razavi, B. Akhlaghinia, *RSC Adv.* **2015**, *5*, 12372.
- B. Akhlaghinia, S. Rezazadeh, *J. Braz. Chem. Soc.* **2012**, *23*, 2197.
- B. Akhlaghinia, S. Tavakoli, *Synthesis* **2005**, 1775.
- S. S. E. Ghodsinia, B. Akhlaghinia, E. Safaei, H. Eshghi, *J. Braz. Chem. Soc.* **2013**, *24*, 895.
- N. Coskun, *Synth. Commun.* **2004**, *34*, 1625.
- N. Jiang, A. J. Ragauskas, *Tetrahedron Lett.* **2010**, *51*, 4479.
- A. Ghorbani Choghamarani, M. A. Zolfigol, M. Hajjami, S. Sardari, *Synth. Commun.* **2013**, *43*, 52.
- N. D. Kokare, D. B. Shinde, *Monatsh. Chem.* **2009**, *140*, 185.
- M. B. Madhusudana Reddy, M. A. Pasha, *Chin. Chem. Lett.* **2010**, *21*, 1025.
- A. R. Sardarian, Z. Shahsavari Fard, H. R. Shahsavari, Z. Ebrahimi, *Tetrahedron Lett.* **2007**, *48*, 2639.
- H. Sharghi, M. Hosseini Sarvari, *Synthesis* **2003**, 243.
- M. Heravi, S. Sadjadi, R. Hekmatshoar, H. Oskooie, F. Bamoharram, *Chin. J. Chem.* **2009**, *27*, 607.
- J. A. Campbell, G. McDougald, H. McNab, L. V. C. Rees, R. G. Tyas, *Synthesis* **2007**, 3179.

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