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REGULAR ARTICLE

SO_3H-functionalized magnetic Fe_3O_4 nanoparticles as an efficient and reusable catalyst for one-pot synthesis of α-amino phosphonates

HOSEIN HAMADI* and MEYSAM NOROUZI
Chemistry Department, Faculty of Science, Shahid Chamran University of Ahvaz, Ahvaz, Iran
E-mail: H.Hammadi@scu.ac.ir

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Abstract. Nanomagnetic Fe_3O_4@SiO_2-SO_3H (SO_3H-MNPs) was prepared *via* grafting sulfonic acid on the silica-coated Fe_3O_4 magnetite nanoparticles (MNPs). The catalytic activity of the prepared SO_3H-MNPs was probed through the one-pot synthesis of N-hydroxy-α-amino phosphonates and α-amino phosphonates via three-component couplings of phenylhydroxylamine or amines with aldehydes and trialkyl phosphites at room temperature. The synthesized SO_3H-MNPs were characterized by XRD, FT-IR, and SEM. The recoverability of the catalyst was achieved by a simple magnetic decantation and reused at least five times without significant degradation in catalytic activity.

Keywords. Magnetic nanoparticle; N-hydroxy-α-amino phosphonate; catalysis; one-pot synthesis; multicomponent reaction.

1. Introduction

The amino phosphonates compounds and their derivatives are known as biologically active compounds with broad range applications in different fields. These compounds are structural analogues of natural amino acids and their biologically effects as anti-cancer agents,[1] enzyme inhibitors,[2] antibiotics,[3] anti-thrombotic agents,[4] peptidases, proteases,[5] HIV protease,[6] fungicides,[7] herbicides, insecticides and plant growth regulators,[8] indicate the importance of scientific research to develop their synthetic procedures.[9–11]

Although a number of synthetic methods have been developed for the synthesis of α-amino phosphonates, there are only a few methodologies for the synthesis of N-hydroxy-α-amino phosphonates. The basic method for the preparation of α-amino phosphonates, involves the condensation of a primary or secondary amine, a carbonyl compound (aldehyde or ketone) and dialkyl or trialkyl phosphite,[12–17] which have been promoted by Lewis or Brønsted acids such as $Yb(OTf)_3$,[18] ytterbium perfluorooctanoate [$Yb(PFO)_3$],[19] $Cu(OTf)_2$,[20] $InCl_3$,[21] SmI_2,[22] $ZnCl_2$,[23] $SnCl_4$,[24] $TaCl_5$–SiO_2,[25] SiO_2-$ZnBr_2$,[26] alumina supported reagents,[27] $MgClO_4$,[28] $LiClO_4$,[29] $Sn(OTf)_2$,[30] CF_3CO_2H,[31] Scandium tris(dodecyl sulphate) $Sc(DS)_3$,[32] BF_3-Et_2O,[33] aq. HCOOH,[34] $(COOH)_2$,[35] $Cd(ClO_4)_2 \cdot xH_2O$,[36] PEG-SO_3H,[37] KH_2PO_4,[38] Magnetic nanoparticle,[39] Aluminium pillared interlayered clay (Al-PILC),[40] Pentafluorophenylammonium triflate (PFPAT),[41] and Cellulose-SO_3H.[42]

On the other hand, N-hydroxy-amino phosphonic acids which are fascinating biologically active compounds, are phosphorus analogue of N-hydroxy-α-amino acid, which have an important role in many metabolic and biological processes.[43] N-hydroxy-α-amino phosphonates were also announced as suitable synthons for pseudo peptides and illustrate herbicidal and growth-regulating activity.[44] They are also used for the preparation of α-amino phosphonates and phosphorylated nitrones.[45]

The efficient oriented synthesis of N-hydroxy-α-amino phosphonates has been reported using different reagents and catalysts. However, these methods have various drawbacks like their difficulties in the preparation of catalysts such as LPDE (lithium perchlorate-diethyl ether) and reagents such as dimethyl (trimethylsilyl) phosphate.[45,46] Palladium hydrogenation of

*For correspondence

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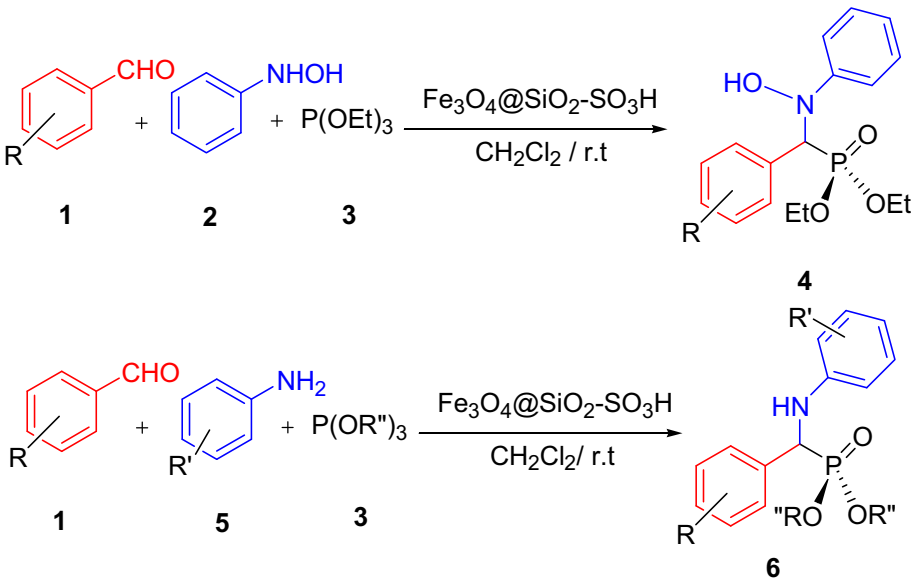


Scheme 1. Synthesis of α-amino phosphonate derivatives catalyzed by Fe_3O_4@SiO_2-SO_3H.

N-hydroxy-α-imino phosphonates using Brønsted acid as activator also reported to produce the N-hydroxy-α-amino phosphonates.[43] As an alternative, the use of ionic liquid [bmim][BF_4] as a catalyst has been reported to catalyze the combination of hydroxylamine derivatives with carbonyl groups.[47]

Among various catalyst separations in organic reaction, a simple magnetic isolation process eliminates the requirement of catalyst filtration and centrifugation. Magnetic nanoparticles (MNPs) have gained considerable attention as a solid support for immobilization of homogeneous catalysts.[48,49] Nanoparticles can be well dispersed in the reaction medium providing a large surface for ready access of catalytic sites. After completing the reactions, the MNPs supported catalysts can be isolated efficiently from the solution through a simple magnetic separation.[50,51] Furthermore; there are no reports on the use of the nanomagnetic catalysts as promoters for three-component coupling reaction of aldehydes, hydroxylamines and trialkyl phosphites to produce N-hydroxy-α-amino phosphonates.

As part of an ongoing development of efficient protocols for the preparation of phosphonate compounds and in continuation of our recently reported work on MCR,[39] herein, we report SO_3H-functionalized silica-coated magnetic nanoparticles [Fe_3O_4@SiO_2-SO_3H] as an efficient and recoverable catalyst for the synthesis of N-hydroxy-α-amino phosphonates and α-amino phosphonates at room temperature (25 °C), through three-component reaction of aromatic aldehydes, trialkyl phosphite and phenylhydroxylamine or amines (Scheme 1). The reaction occurred via *in situ* formations of nitrone, a highly reactive intermediate, or imine. All the products are well known and compared with the reported literature.

2. Experimental

2.1 *General*

Iron (II) chloride tetrahydrate (99%), iron (III) chloride hexahydrate (98%), aromatic aldehydes and other chemicals were purchased from Fluka and Merck companies and used without further purification. Products were characterized by comparison of their physical data, IR and ^{1}H NMR and ^{13}C NMR spectra with known samples. NMR spectra were recorded on a Bruker Advance DPX 400 MHz instrument spectrometer using TMS as an internal standard. The infrared spectra were recorded on a Perkin Elmer spectrum two FT-IR spectrometers. The purity determination of the products and reaction monitoring was accomplished by TLC on TLC-Cards Silica gel-G/UV 254 nm. X-ray diffraction (XRD) patterns of samples were taken on a Philips X-ray diffractometer (Model PW 1840) in the range 2θ range 50–70. SEM images were also recorded using Philips XL30 scanning electron microscope.

2.2 *Preparation of the Fe_3O_4@SiO_2*

Fe_3O_4 MNPs and Silica-coated Fe_3O_4 nanoparticles (Si-MNPs) were prepared according to the procedure reported by Kiasat and Ghasemzadeh.[52–54] Briefly, a solution of $FeCl_3 \cdot 6H_2O$ (55.98 mmol, 15.13 g) and $FeCl_2 \cdot 4H_2O$ (31.9 mmol, 6.34 g) in 640 mL of deionized water was stirred at 80 °C and then 80 mL of concentrated ammonia (25%) was added until the pH reached 11–12. The mixture was stirred vigorously at 80 °C until precipitation. Afterwards, the

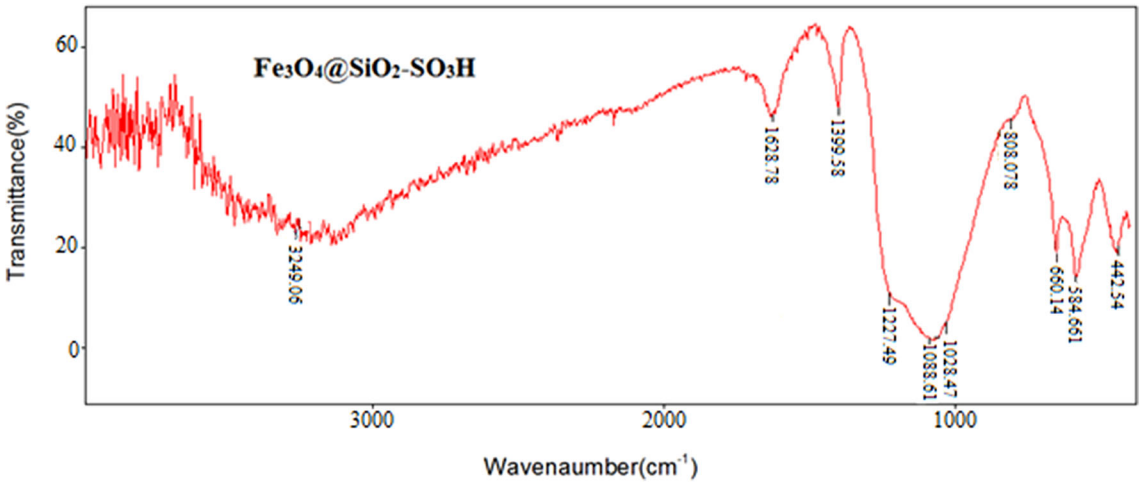


Figure 1. FT-IR spectra of Fe_3O_4@SiO_2-SO_3H.

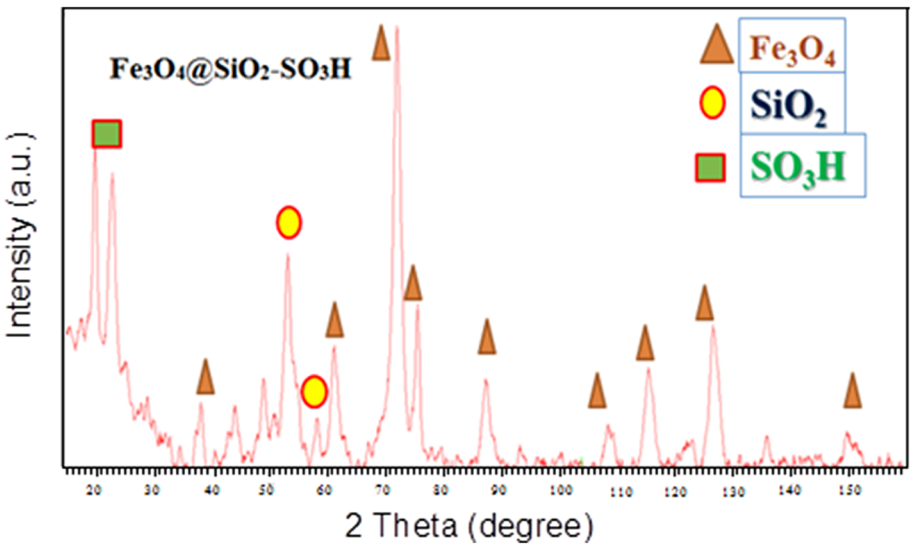


Figure 2. X-ray diffraction for Fe_3O_4@SiO_2-SO_3H.

prepared magnetic NPs were separated magnetically, washed with deionized water and then dried at 70 °C for 8 h.

In order to prepare the Silica-coating Fe_3O_4 nanoparticles, 2 g of the prepared Fe_3O_4 NPs were sonicated in a mixture of ethanol (450 mL), deionized water (120 mL) and concentrated ammonia aqueous solution (10 mL, 25 wt%), followed by the addition of TEOS (2 mL). After stirring at room temperature for 15 h, the Fe_3O_4@SiO_2 was separated using an external magnet and washed several times with deionized water and dried under vacuum at 60 °C overnight.

2.3 *Preparation of the Fe_3O_4@SiO_2-SO_3H*

According to the literature[56] the as-synthesized Fe_3O_4@SiO_2 (2.5 g) was added to dry CH_2Cl_2 (75 mL) in a 500 mL suction flask bearing constant pressure dropping funnel

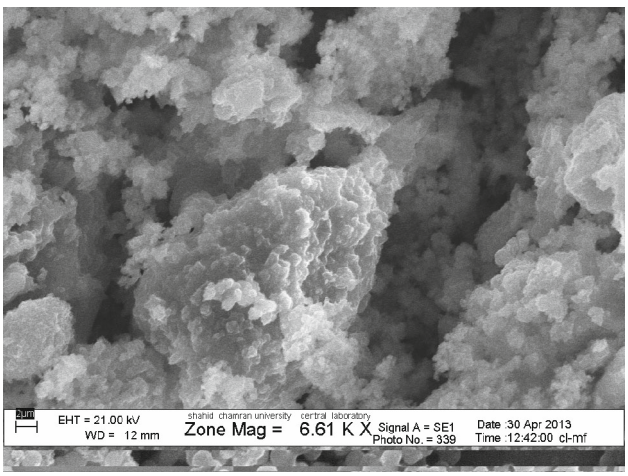
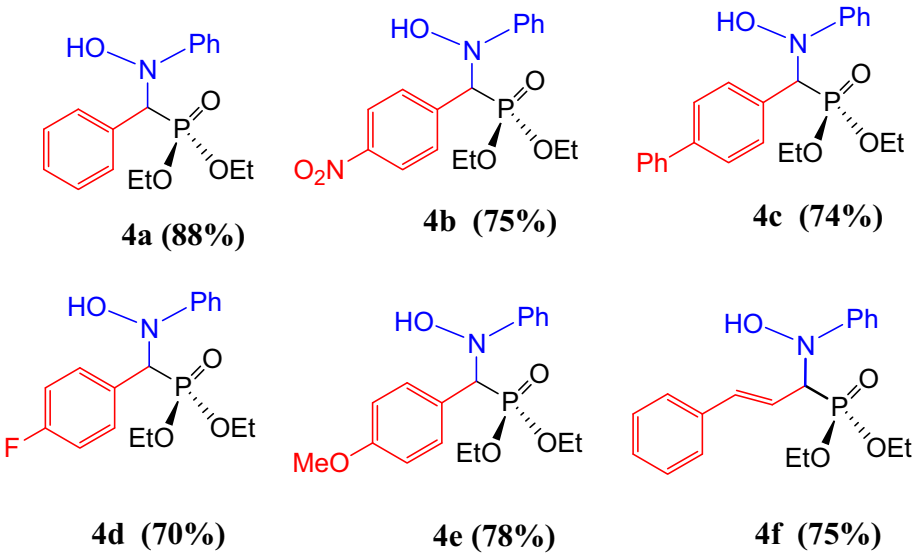


Figure 3. SEM image of Fe_3O_4@SiO_2-SO_3H.

Table 1. Optimization of the reaction conditions[a].

Entry	Catalyst (g)	Solvent	Temp. (°C)	Time (h)	Yield (%)
1	No catalyst	Neat	25	4	Trace
2	No catalyst	Neat	100	4	Trace
3	0.05	CH_2Cl_2	25	3	66
4	0.05	CH_3CN	25	4	45
5	0.05	EtOH	25	4	20
6	0.05	$CHCl_3$	25	3	62
7	0.07	CH_2Cl_2	25	3	78
8	**0.1**	**CH_2Cl_2**	**25**	**2**	**88**
9	0.1	CH_2Cl_2	40	2	89
10	0.15	CH_2Cl_2	25	2	88

[a]Benzaldehyde (1.0 mmol), phenylhydroxylamine (1.2 mmol), triethyl phosphite (1.2 mmol), Fe_3O_4@SiO_2-SO_3H.



Scheme 2. Synthesis of N-hydroxy-α-amino phosphonates **4**.

linked to the gas outlet. The mixture was homogenized by ultrasonic for 10 min. Then chlorosulfonic acid (1.75 g, ca. 1 mL, 15 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise over a period of 30 min at room temperature. After completion of the addition, the mixture was shaken for 90 min, while the residual HCl was eliminated by suction. Then, the Fe_3O_4@SiO_2-SO_3H was separated by an external magnet from the mixture and washed several times with dried CH_2Cl_2. Finally, Fe_3O_4@SiO_2-SO_3H was dried under vacuum at 60 °C. The identities of the catalyst were confirmed according to the reference by XRD, SEM and FT-IR.

2.4 *General procedure*

0.1 g the catalyst (Fe_3O_4@SiO_2-SO_3H) was added to the solution of Aldehyde (2 mmol), phenylhydroxylamine (2 mmol, 22 mg), and diethyl phosphite (2 mmol, 28 mg) in 2 mL CH_2Cl_2 and stirred at room temperature (25 °C) for the appropriate time (Table 2). The progress of the reaction was monitored by TLC. In the end, CH_3Cl was added to dilute the reaction mixture and the organic layer was simply decanted by means of an external magnet. The isolated solution was purified on a silica-gel plate to obtain the pure product. The

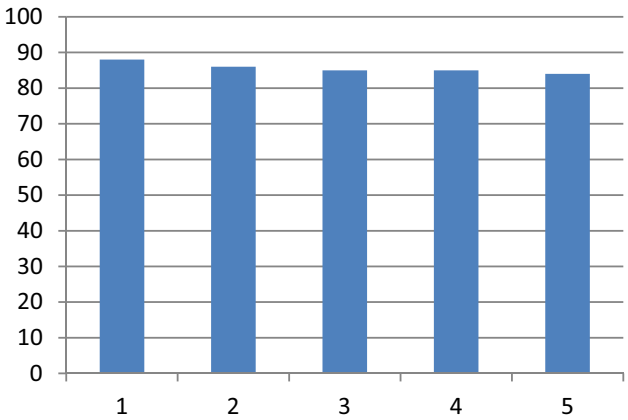
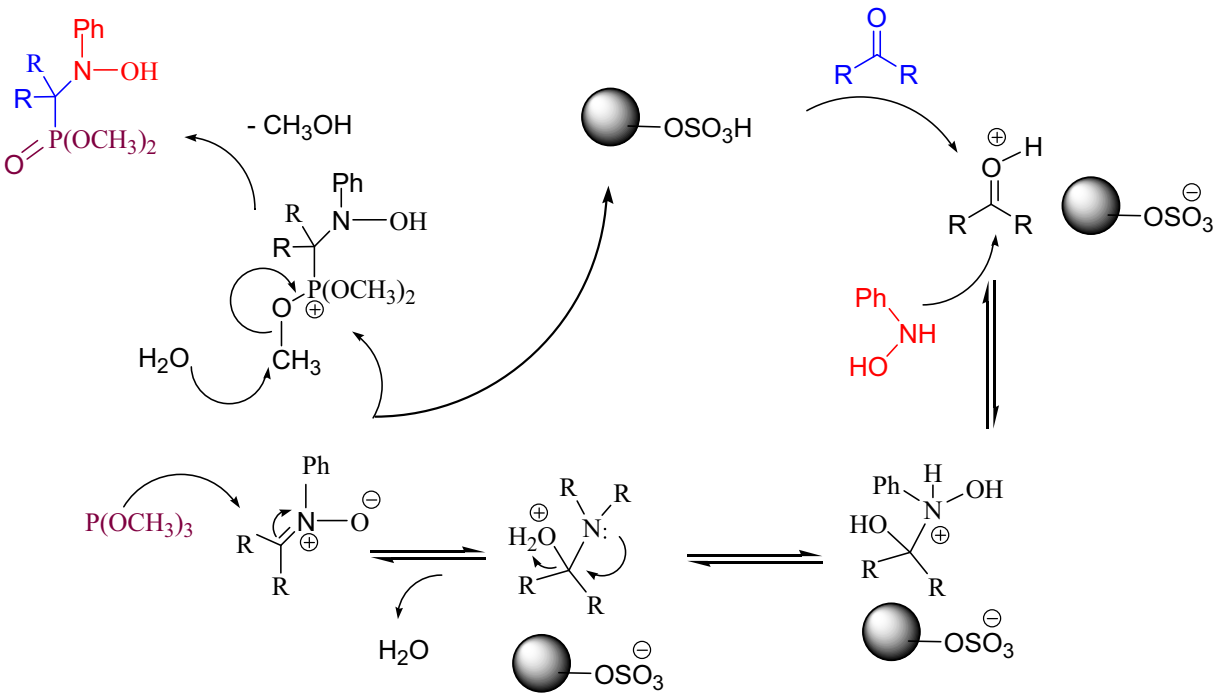


Figure 4. Recyclability of the catalyst.



Scheme 3. The proposed mechanism for the synthesis of N-hydroxy-α-amino phosphonates.

identities of the products were confirmed by FT-IR and ^{1}H NMR spectral data related to reference.[47–49,51,55,56]

2.5 *Representative spectroscopic data*

4a: Viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1 (t, J = 6.8 Hz, CH_3), 1.26 (t, J = 6.8 Hz, CH_3), 3.51–3.56 (m, 1H), 3.79–3.85 (m, 1H), 4.11–4.18 (m, 2H), 4.98 (brs, OH), 5.24–5.31 (d, 1H, J_{P-H} = 22 Hz), 6.51–6.59 (d, J = 8.1 Hz, 2H), 6.61–6.63 (t, J = 7.6 Hz, 1H), 7.01–7.06 (m, 3H), 7.17–7.21 (m, 1H), 7.48–7.50 (m, 2H) ppm. IR (KBr, υ_{max} cm^{-1}): 3375, 2970, 1602, 1499, 1227, 1022, 967, 748, 670.

6g: Yellow solid, M.p.: 123–125 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 1.18–1.22 (t, J = 7.1 Hz, CH_3), 1.26–1.34 (t, J = 7.1 Hz, CH_3), 3.88–3.90 (m, 1H), 4.03–4.09 (m, 1H), 4.13–4.19 (m, 2H), 4.85–4.91 (d, J_{P-H} = 24.8 Hz, 1H), 6.55-6.57 (d, J = 8 Hz, 2H), 6.74–6.78 (t, J = 6.8 Hz, 1H), 7.12–7.15 (t, J = 7.6 Hz, 2H), 7.67–7.70 (m, 2H), 8.20–8.23 (d, J = 8.8 Hz, 2H) ppm.

6i: Viscous liquid; ^{1}H NMR (400.13 MHz, $CDCl_3$): 1.05–1.10 (t, J = 7.2 Hz, CH_3), 1.32–1.36 (t, J = 7.2 Hz, CH_3), 3.61–3.64 (m, 1H), 3.89–3.93 (m, 1H), 4.21–4.28 (m, 2H), 4.08–4.19 (m, 2H), 5.35–5.41 (d, J_{P-H} = 24.4 Hz, 1H), 6.62–6.64 (d, J = 8.4 Hz, 2H), 6.70–6.73 (t, J = 7.2, 1H), 7.11–7.15 (t, J = 8.4 Hz, 3H), 7.27–7.30 (t, J = 7.6, 1H), 7.57–7.62 (t, J = 8.4, 2H) ppm.

6j: Yellow solid, M.p.: 62–65 °C; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ 1.02–1.05 (t, J = 7.2 Hz, CH_3), 1.19–1.23 (t, J = 7.2 Hz, CH_3), 3.54–3.65 (m, 1H), 3.84–3.87 (m, 1H), 4.01–4.07 (m, 2H), 4.66–4.72 (d, J_{P-H} = 24.4 Hz, 1H), 6.51–6.53 (d, J = 7.6 Hz, 2H), 6.6–6.64 (t, J = 7.6 Hz, 1H), 7.01–7.05 (m, 2H), 7.18–7.21 (m, 1H), 7.24–7.27 (m, 2H), 7.39–7.40 (m, 1H) ppm. IR (KBr, υ_{max} cm^{-1}): 3298, 2988, 1607, 1494, 1241, 1047, 986, 799, 747.

6n: Viscous colorless liquid; ^{1}H NMR (400.13 MHz, $CDCl_3$): 1.10–1.14 (t, J = 7.2 Hz, CH_3), 1.23–1.26 (t, J = 7.2 Hz, CH_3 Hz), 3.73–3.77 (m, 1H), 3.96–3.99 (m, 1H), 4.06–4.14 (m, 2H), 5.48–4.56 (dd, 1H), 5.8 (brs, NH), 6.45–6.47 (d, J = 8.4 Hz, 1H), 6.56–6.60 (t, J = 1.2 Hz, 1H), 7.25–7.36 (m, 4H), 7.52–7.54 (t, J = 1.2 Hz, 2H), 8.05–8.07 (t, 1H) ppm.

3. Results and Discussion

The catalyst was synthesized according to the report[52] and characterized by X-ray powder diffraction (XRD), Scanning electron microscope (SEM) and Fourier transform infrared (FT-IR). The Fe_3O_4 magnetic nanoparticles as the catalyst core were prepared by a simple method using the co-precipitation of $FeCl_2$ and $FeCl_3$ in ammonia solution. The synthesis of sulphuric acid immobilized on Si-MNPs was achieved by using the reported method.[52]

The FT-IR spectrum of Fe_3O_4@SiO_2-SO_3H shows the peaks at 1090, 806 and 462 cm^{-1} assigned to the Si-O-Si. The presence of sulphonyl group is confirmed by 1217 and 1124 cm^{-1} bands that were covered by a stronger absorption of the Si-O bond at 1092 cm^{-1}. In addition, the characteristic peaks of Fe-O at 580 cm^{-1} and Si-OH at 956 cm^{-1} were also observed (Figure 1).

Table 2. Synthesis of α-amino phosphonates (**6**) in the presence of Fe_3O_4@SiO_2-SO_3H via Scheme 1[a].

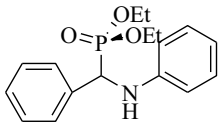
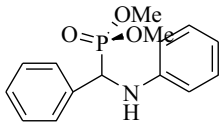
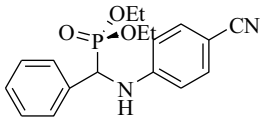
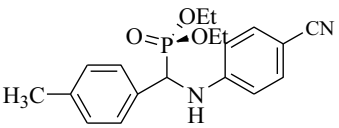
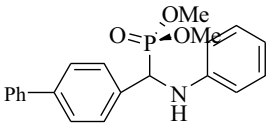
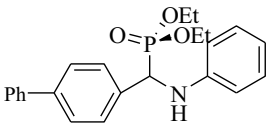
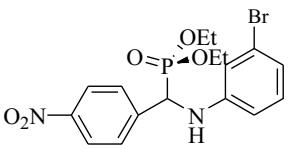
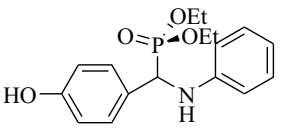
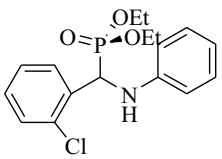
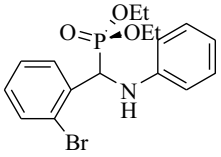
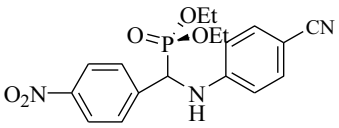
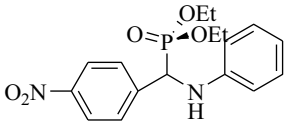
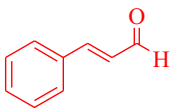
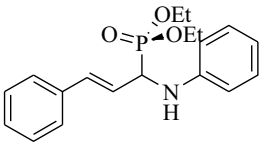
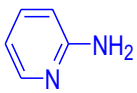
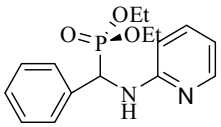
Entry	Aldehyde	Amine	$P(OR)_3$		Time (min)	Yield (%)[b]
a	C_6H_5CHO	$C_6H_5NH_2$	$P(OEt)_3$		45	92
b	C_6H_5CHO	$C_6H_5NH_2$	$P(OMe)_3$		50	96
c	C_6H_5CHO	4-$CNC_6H_4NH_2$	$P(OEt)_3$		60	92
d	4-MeC_6H_4CHO	4-$CNC_6H_5NH_2$	$P(OEt)_3$		40	90
e	4-PhC_6H_4CHO	$C_6H_5NH_2$	$P(OMe)_3$		55	92
f	4-PhC_6H_4CHO	$C_6H_5NH_2$	$P(OEt)_3$		55	85
g	4-$NO_2C_6H_4CHO$	3-$BrC_6H_5NH_2$	$P(OEt)_3$		60	88
h	4-HOC_6H_4CHO	$C_6H_5NH_2$	$P(OEt)_3$		60	82
i	2-ClC_6H_4CHO	$C_6H_5NH_2$	$P(OEt)_3$		70	88

Table 2. continued

Entry	Aldehyde	Amine	P(OR)$_3$		Time (min)	Yield (%)[b]
j	2-BrC$_6$H$_4$CHO	C$_6$H$_5$NH$_2$	P(OEt)$_3$		70	85
k	4-NO$_2$C$_6$H$_4$CHO	4-CNC$_6$H$_5$NH$_2$	P(OEt)$_3$		65	82
l	4-NO$_2$C$_6$H$_4$CHO	C$_6$H$_5$NH$_2$	P(OEt)$_3$		55	84
m		C$_6$H$_5$NH$_2$	P(OEt)$_3$		70	84
n	C$_6$H$_5$CHO		P(OEt)$_3$		90	65

[a]All reactions were carried out at room temperature, 1 mmol aldehyde, 1 mmol amine, 1 mmol trialkyl phosphite and 0.15 g catalyst.
[b]Isolated yields.

The X-ray diffraction patterns of Fe_3O_4@SiO_2-SO_3H are shown in Figure 2. XRD diagram of the bare MNPs displayed patterns consistent with the patterns of spinel ferrites described in the previous report.[52] The average MNPs core diameter Fe_3O_4@SiO_2-SO_3H was calculated to be 8.2 and 9.6 nm, respectively from the XRD results by Scherrer's equation. The average size of the crystallites can be calculated using the Scherrer equation ($D = K\lambda/\beta \cos\theta$), wherein this equation D is the mean crystalline size, K is a grain shape dependent constant (0.9), λ is the incident beam wavelength (0.154), θ is the Bragg reflection angle and β is the full width at half maximum (FWHM) of the main diffraction peak.[57–59]

The SEM image of Fe_3O_4@SiO_2-SO_3H is presented in Figure 3, shows a spherical shape with nano dimension ranging from 117 to 220 nm.

The loading capacity of the Fe_3O_4@SiO_2-SO_3H was determined by titration and found to be 2.58 mmol/g.

A test reaction using phenylhydroxylamine, benzaldehyde, and triethyl phosphite at room temperature and 100 °C in the absence of Fe_3O_4@SiO_2-SO_3H was performed in order to establish the real effectiveness of the catalyst (Table 1, entry 1, 2). It was found that no conversion to product was obtained even after 4 hours of heating (Monitoring by TLC). To optimize the catalyst loading, a model reaction using phenylhydroxylamine, benzaldehyde, and triethyl phosphite was carried out under different amount of catalyst in different solvents (Table 1). It was observed that 0.1 g loading of the catalyst in CH_2Cl_2 provides the maximum yield in minimum time (Table 1, entry 8). Higher percentage loading of the catalyst neither increased the yield nor lowered the reaction time.

By using the optimized reaction conditions, the efficiency of this protocol was studied for the synthesis of various N-hydroxy-α-amino phosphonates, and the results are summarized in Scheme 2. In most cases, the reaction proceeded with high efficiency and broad functional-group tolerance on aldehyde which displayed high reactivity under the optimized reaction

Table 3. Comparison of various catalysts in Synthesis of N-hydroxy-α-amino phosphonates and α-amino phosphonates.

Reaction	Catalyst	Solvent	Temp. (°C)	Time	Yield (%)	Ref.
Synthesis of N-hydroxy-α-aminophosphonates	$[Bmim]BF_4$	–	r.t	2.5 h	92	[47]
	$[Bmim]PF_6$	–	r.t	3.5 h	89	[47]
	LPDE	–	r.t	15 min	90	[45,46]
	Fe_3O_4@SiO_2-SO_3H	**CH_2Cl_2**	**r.t**	**2 h**	**88**	**This work**
Synthesis of α-aminophosphonates	$SbCl_3/Al_2O_3$	CH_3CN	r.t	3 h	91	[27]
	PEG-SO_3H	–	50	3.5h	98	[37]
	Nano Fe_3O_4	–	50	48 min	94	[39]
	$Cd(ClO_4)_2 \cdot xH_2O$	–	r.t	40 min	92	[36]
	In/HCl	H_2O	r.t	1.5 h	88	[21]
	Fe_3O_4@SiO_2-SO_3H	**CH_2Cl_2**	**r.t**	**45 min**	**92**	**This work**

conditions and generated the desired products in high yields. However, unfortunately, when some aliphatic aldehydes such as isobutyraldehyde and cyclohexane carboxaldehyde were used in this protocol under the above-optimized conditions, the desired products could not be obtained.

Since the catalyst was separated by simple magnetic decantation, it was washed with ether and reused in the subsequent reaction. Yields of the product decreased only slightly after four time's reuse of catalyst. For example, the reaction of benzaldehyde, phenylhydroxylamine and triethyl phosphite afforded the corresponding N-hydroxy-α-amino phosphonates in 88%, 86%, 85%, 85% and 84% yields over five cycles (Figure 4).

A possible mechanism for the synthesis of N-hydroxy-α-amino phosphonates catalyzed by Fe_3O_4@SiO_2-SO_3H has been proposed (Scheme 3). The reaction proceeds *via* the nitrone intermediate, which was formed by the nucleophilic addition of phenylhydroxylamine to an aldehyde. Fe_3O_4@SiO_2-SO_3H as Brønsted acid plays a role in increasing the electrophilic character of the starting aldehyde. Subsequent nucleophilic addition of the triethyl phosphite provides the adduct intermediate that on subsequent reaction followed by elimination of MeOH afforded the product.

According to the mechanism of these reactions, the planar nitrone and iminium intermediate are formed followed by nucleophilic attack of the trialkyl phosphite. It can be concluded that racemic mixture of the product is obtained.

Bearing in mind the important properties of α-amino phosphonates, we decided to explore this magnetically effective catalyst for the preparation of α-amino phosphonates using the optimized condition (Scheme 1). The results are summarized in Table 2.

We investigated various aromatic and heteroaromatic aldehyde containing electron withdrawing or electron donating functional groups as well as an amine with trialkyl phosphonate $P(OR)_3$ (R: Me, Et) at r.t. (25 °C) (Table 2). The given results in Table 2 show that this one pot, three component condensations completed within 45–95 min, with good isolated yields. The 2-aminopyridine gave less yield and required more time, probably due to the low reactivity of amino group. The reaction was compatible with various functional groups such as Cl, Br, CN, OMe, NO_2, and OH not interfering with the competitive complex formation with the catalyst.

The activity of Fe_3O_4@SiO_2-SO_3H by considering the yield for the model reaction is compared with various heterogeneous catalysts in Table 3. In addition to easily magnetic decantation of Fe_3O_4@SiO_2-SO_3H, it showed efficient catalytic activity in relatively short reaction time, with excellent yields.

4. Conclusion

In summary, this paper describes the three-component reaction of aromatic aldehydes, trialkyl phosphite and phenylhydroxylamine or amines to produce N-hydroxy-α-amino phosphonates and α-amino phosphonates using SO_3H-functionalized silica-coated magnetic nanoparticles [Fe_3O_4@SiO_2-SO_3H] as a novel promoter. The simple operation combined with easy recovery and reuse of this novel catalyst, make this a more convenient, economical and user-friendly process for the synthesis of N-hydroxy-α-amino phosphonates and α-amino phosphonates of biological and medicinal importance. Our results here did not detect leaching of acidic site spices and the Fe_3O_4@SiO_2-SO_3H can be easily

removed by an external magnet and used 5 cycles in the reaction without significant loss in activity.

Supplementary Information (SI)

Supplementary Information is available at www.iac.ac.in/chemsci.

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