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Magnetic nanoparticle γ -Fe₂O₃-immobilized 1,5,7-triazabicyclo[4.4.0]dec-5-ene as a highly recyclable and efficient nanocatalyst for the synthesis of α' -oxindole- α hydroxyphosphonates

Xiao Juan Yang*

Magnetic nanoparticle γ -Fe₂O₃-immobilized 1,5,7-triazabicyclo[4.4.0]dec-5-ene as a novel magnetic nanocatalyst was synthesized and characterized. The nanoparticle reagent catalyzed efficiently the synthesis of α '-oxindole- α -hydroxyphosphonates from isatins and dimethyl phosphate under solvent-free conditions at 60 °C. More importantly, the catalyst could be easily recovered by an external magnet and reused six times without significant loss of activity. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords: nanomagnetic iron oxide; a'-oxindole-a-hydroxyphosphonates; heterogeneous catalysis; nanoparticles; solvent-free

Introduction

Oxindole motifs bearing a C₃ quaternary structure are considered important and useful synthetic building blocks, and are present in a variety of natural products^[1] and biologically active molecules.^[2] On the other hand, α -hydroxyphosphonates are an important class of bioactive molecules and display a wide range of biological activities such as antimicrobial,^[3] antioxidant^[4] and anti-HIV activities.^[5] They are also used as versatile intermediates in the synthesis of other phosphorus compounds.^[6] Thus it is suspected that quaternary α' -oxindole- α -hydroxyphosphonates, in which the PO(OR)₂ and oxindolylmoieties are located at a tetra-substituted carbon atom, potentially have some unique bioactivities. The increased importance of unnatural hydroxyl acids in the modification of natural and unnatural products to improve bioactivity and stability makes the synthesis of hydroxyl phosphonates a significant subject.

The most frequently used methods for the synthesis of α' oxindole- α -hydroxyphosphonates involve the reaction of isatins with dialkyl phosphites in the presence of Amberlyst-15,^[7] PEG-400^[8] and β -cyclodextrin.^[9] In view of the importance of the α' -oxindole- α -hydroxyphosphonates, there still remains the necessity to develop a new methodology.

In recent years, nanoparticles as heterogeneous catalysts have attracted a great deal of attention because of their interesting structures and high catalytic activities.^[10] Furthermore, nanometer-sized particles are easily dispersible in solution by forming stable suspensions.^[11] In spite of these advantages, the tedious recovery procedure via expensive ultracentrifugation and the inevitable loss of solid catalysts in the separation process have limited their application. To further address the issues of recyclability and reusability, magnetic nanoparticles (MNPs) have emerged as excellent supports amenable to simple magnetic separation.^[12]

Moreover, MNPs can be functionalized easily through appropriate surface modifications, which are able to load various functionalities.^[13]

Driven by the unique properties of magnetic nanoparticles, herein we report a novel MNP γ -Fe₂O₃-immobilized 1,5,7-triazabicyclo[4.4.0]dec-5-ene (MNP-TBD) and its application as a highly efficient and magnetically recoverable catalyst for the synthesis of α' -oxindole- α -hydroxyphosphonates (Scheme 1).

Experimental

Materials and Instrumentation

X-ray powder diffraction (XRD) patterns were recorded using a Cu- K_{α} radiation source on a Bruker D8 Avance powder diffractometer. Scanning electron microscopy (SEM) studies were conducted on an Inspect F50 scanning electron microscope. Transmission electron microscopy (TEM) studies were performed using a FEI Tecnai G2 20 transmission electron microscope with an accelerating voltage of 150 kV. Elemental compositions were determined with a Hitachi S-4800 scanning electron microscope equipped with an EDAX energy-dispersive spectrometer (SEM-EDS). Magnetic measurements of particles were made using a vibrating sample magnetometer (MPMS-XL-7). N₂ adsorption–desorption isotherm was measured using a NOVOE 4000/TriStar II 3020 at liquid nitrogen temperature (77 K). The specific surface

College of Chemistry and Chemical Engineering, Xinxiang University, Xinxiang, Henan, 453003, China

^{*} Correspondence to: Xiao Juan Yang, College of Chemistry and Chemical Engineering, Xinxiang University, Xinxiang, Henan 453003, China. E-mail: yangxiaojuan2005@126.com



Scheme 1. MNP-TBD catalyzed the synthesis of α' -oxindole- α -hydroxyphosphonates.



Scheme 2. Preparation of MNP-TBD.

area was calculated using the BET (Brunauer, Emmett and Teller) equation. TGA was carried out under nitrogen using a DT-40 thermoanalyzer. IR spectra were determined on an FTS-40 infrared spectrometer. All solvents used were strictly dried according to standard operations and stored over 4 Å molecular sieves. All other chemicals (AR grade) were obtained from commercial resources and used without further purification.

Preparation of Large-Scale Magnetic γ-Fe₂O₃ Nanoparticles

 $FeCI_2 . 4H_2O$ (9.25 mmol) and $FeCI_3.6H_2O$ (15.8 mmol) were dissolved in deionized water (150 ml) under Ar atmosphere at room temperature. An NH₄OH solution (25%, 50 ml) was then





added dropwise to the stirring mixture at room temperature to change the reaction pH to 11. The resulting black dispersion was continuously stirred for 1 h at room temperature and then heated to reflux for 1 h to yield a brown dispersion. The MNPs were then purified by a repeated centrifugation, decantation and redispersion cycle three times. The as-synthesized sample was heated at $2 \,^{\circ}\mathrm{C\,min^{-1}}$ up to 200 °C and then kept in the furnace for 3 h to give a reddish-brown powder.

Preparation of MNP-TBD

A mixture of γ -Fe₂O₃ (5.0 g) and (3-chloropropyl) triethoxysilane (5.0 ml, 42.5 mmol) in 50 ml toluene was stirred at room temperature for 15 min and then refluxed for 24 h. After cooling to room temperature, the products were sedimented on a magnet and washed successively with dry toluene (50 ml) and dried under reduced pressure at 100 °C for 8 h. An amount of this material containing chlorine groups (5 g) is was then dispersed in 50 ml dry toluene by sonication for 1 h, and a solution of 0.5 g 1,5,7-triazabicyclo [4.4.0]dec-5-ene in 20 ml toluene was added. The reaction mixture was refluxed under nitrogen gas for 1 day. After this time, solids were collected using a permanent magnet, followed by washing with toluene $(3 \times 20 \text{ ml})$ and dichloromethane $(3 \times 20 \text{ ml})$ and drying at room temperature for 24 h.

General Procedure for the Preparation of α' -Oxindole- α -Hydroxyphosphonates

A mixture of substituted isatin (1 mmol), dialkylphosphite (1 mmol) and MNP-TBD (40 mg) was heated at 60 °C for the appropriate time (Table 2). The progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was dissolved in dichloromethane and the catalyst was separated by an external magnet. The filtrate was evaporated and dried over anhydrous Na₂SO₄. The resulting product was further purified by column chromatography using ethyl acetate and hexane (5:5, v/v) as eluent to afford pure α' -oxindole- α -hydroxyphosphonates.







Figure 3. XRD of MNP-TBD.



Figure 4. TG analysis of MNP-TBD.



Figure 5. SEM of MNP-TBD.

All products were characterized by comparison of their spectral and physical data with those previously reported.^[7-9]

Dimethyl 5,7-dichloro-3-hydroxy-2-oxoindolin-3-yl-3-phosphonate (3f)

Semisolid. IR (KBr, cm⁻¹): 3353 (NH), 3229 (OH), 1258 (P—O). ¹H NMR (400 MHz, CDCl₃) δ 8.42 (s, 1H, NH), 7.36–7.31 (m, 2H, CH of indoline), 3.73 (d, J=10.0 Hz, 3H, P—OCH₃), 3. 64 (d, J=10.0 Hz, 3H, P—OCH₃), 3.50 (s, 1H, OH). ¹³ C NMR (100 MHz, CDCl₃) δ 166.2 (C1), 134.3 (C8), 133.6 (C7), 130.4 (C5), 128.8 (C3), 113.2 (C6), 111.6 (C4), 71.1 (C2), 58.5 (P—OCH₃). ³¹ P NMR (161.3 MHz, CDCl₃) δ 23.0. Anal. Calcd for C₁₀H₁₀C₁₂NO₅P: C, 36.83; H, 3.09; N, 4.30. Found: C, 36.76; H, 3.13; N, 4.22.





Figure 6. TEM of MNP-TBD.

Results and Discussion

MNP-TBD was prepared by covalent attachment of TBD on to the surface of γ -Fe₂O₃. In the initial step (3-chloropropyl) triethoxysilane was treated with γ -Fe₂O₃, where binding between the groups occurs through covalent bonds, giving 3-chloropropyl γ -Fe₂O₃. After this, nucleophilic addition of chlorine with TBD gave MNP-TBD (Scheme 2). The MNP-TBD was characterized by FT-IR spectroscopy, energy-dispersive spectroscopy (EDS), SEM, TEM, XRD, vibrating sample magnetometer (VSM), TGA and elemental analysis. The specific surface area of the powders was determined by use of the BET method. Unfortunately, owing to the magnetic properties of MNP-TBD, it is actually impossible to further characterize this material using solid-state NMR spectroscopy.

To be able to warrant the successful functionalization γ -Fe₂O₃, we employed IR to give detailed investigations of the obtained MNP-TBD (Fig. 1). Compared with the unfunctionalized γ -Fe₂O₃, the significant features observed for MNP-TBD were the appearances of the peaks 2918 and 2846 cm⁻¹ (C—H stretching vibration), 1126 and 1001 cm⁻¹ (Si—O stretching vibrations), 1628 and 1320 cm⁻¹ (C—N and C—N vibrations of the TBD ring, respectively). This analysis, in combination with microanalysis data (Fig. 2), indicated the successful anchoring of the TBD groups on the surface of γ -Fe₂O₃.

XRD measurements of MNP-TBD exhibit diffraction peaks at around 30.62, 35.92, 43.48, 54.00, 57.62 and 63.36, corresponding to the (220), (311), (400), (422), (511) and (440) faces. The observed diffraction peaks agree well with the tetragonal structure of maghemite (Fig. 3). It was clear that no other phases except maghemite were detectable. The average crystallite size was calculated to be 14.2 nm using the Scherrer equation.

The stability of the MNP-TBD was determined by TGA (Fig. 4). The TG curve indicates initial weight loss of 5.3% up to 78 °C due to surface γ -Fe₂O₃ and the adsorbed water in γ -Fe₂O₃. Complete loss of all the covalently attached organic structure was seen in the temperature range of 250–760 °C. Therefore, the MNP-TBD is stable around or below 220 °C. The shouldering observed from 289 °C onwards may be due to the decomposition of alkyl-TBD groups. The amount of organic moiety was found to be about 24.6% against total solid catalyst.

The shape and surface morphology of the samples were examined on a scanning electron microscope (Inspect F50). TEM images were obtained from a FEI Tecnai G2 20 transmission electron microscope with an accelerating voltage of 150 kV. The samples for TEM observation were dispersed in anhydrous ethanol under ultrasonication, and a drop of solution was deposited on a carbon-coated copper grid before evaporating naturally. As shown in Fig. 5, the low-magnification SEM images show small nano-sized grains having spherical and guasi-spherical morphology with a narrow size distribution, which indicates the nanocrystalline nature of γ -Fe₂O₃ nanoparticles. The presence of some larger particles is attributed to aggregating or overlapping smaller particles. The sizes of MNP-TBD were further analyzed by TEM and the results (Fig. 6) showed the nanoparticles to have a nano dimension ranging from 10 to 20 nm. In TEM images, the shapes are relatively rather rectangular, which is attributed to the presence of TBD covalently attached to the γ -Fe₂O₃ surfaces.

The magnetic properties of the MNP-TBD were investigated at room temperature (Fig. 7). The figure shows the room-temperature magnetization curve of MNP-TBD. The magnetization of samples exhibited typical superparamagnetic behavior, showing no observed hysteresis. The saturation magnetization value was 48.91 emu g⁻¹. The value was slightly smaller than that of γ -Fe₂O₃ (61.2 emu g⁻¹), which is probably due to the increasing amount of non-magnetic material (organic ligands) on the parti-



Figure 7. Magnetic curves of MNP-TBD.



Figure 8. (a) N₂ adsorption–desorption isotherm of γ -Fe₂O₃. (b) N₂ adsorption–desorption isotherm of MNP-TBD.

cle surface, making a larger percentage of the particle mass nonmagnetic. However, this value is sufficiently high for magnetic separation. The strong magnetization of the nanoparticle was also revealed by simple attraction with an external magnet.

The N₂ adsorption–desorption isotherm provided a valuable tool for studying textural and structure properties. The specific surface area of the powders was determined by use of the BET method. BET results showed that the average surface area of γ -Fe₂O₃ was 73.79 m²g⁻¹ and that of MNP-TBD was 29.87 m²g⁻¹

Table 1. Optimization of reaction conditions for synthesis of dimethyl 3-hydroxy-2- oxoindolin-3-ylphosphonate ^a										
Entry	Solvent	T (°C)	Cat.	Time (h)	Yield (%) ^b					
1	H ₂ O	60	MNP-TBD, 40 mg	24	Trace					
2	EtOH	60	MNP-TBD, 40 mg	24	Trace					
3	DMF	60	MNP-TBD, 40 mg	10	68					
4	CH₃CN	60	MNP-TBD, 40 mg	24	18					
5	CHCl₃	60	MNP-TBD, 40 mg	24	Trace					
6	Solvent-free	r.t.	MNP-TBD, 40 mg	10	52					
7	Solvent-free	60	MNP-TBD, 40 mg	6	90					
8	Solvent-free	80	MNP-TBD, 40 mg	6	89					
9	Solvent-free	60	MNP-TBD, 0 mg	24	27					
10	Solvent-free	60	MNP-TBD, 30 mg	6	73					
11	Solvent-free	60	MNP-TBD, 50 mg	6	90					
12	Solvent-free	60	γ -Fe ₂ O ₃ , 40 mg	24	2					
13	Solvent-free	60	TBD _, 40 mg	6	79					
^a Reaction conditions: isatin (1 mmol), dimethyl phosphate (1 mmol). ^b lsolated vield.										

(Fig. 8). It was noted that γ -Fe₂O₃ had a much higher surface area than MNP-TBD. This seems logical due to the successful anchoring TBD on the surface of γ -Fe₂O₃, decreasing the surface area.

To begin with, the investigation of the reaction conditions for the model hydrophosphonylation reaction between dimethyl phosphate (1 mmol) and isatin (1 mmol) in terms of the catalyst amount, reaction time and product yield demonstrated that 40 mg mmol⁻¹ of the catalyst under solvent-free conditions at 60 °C was optimal for the desired reaction (Table 1, entry 7). It was found that only 2% of the target compound **3a** was obtained in the presence of nano γ -Fe₂O₃. When this reaction was carried out with TBD, the yield of the expected product was 79%.

With a set of optimized reaction conditions at hand, we explored the scope of the reaction by using various different substituted istins and dialkyl phosphite. The results are summarized in Table 2. It was found that all the reactions proceeded smoothly and afforded the desired adducts under the optimized reaction conditions. A wide range of istin derivatives bearing electron-withdrawing and electron-donating groups could be employed in the reaction with dialkyl phosphate and were nicely converted into corresponding products (**3a–3n**) in moderate to good yields ranging from 79% to 93%.

The recovery and reuse of a catalyst is highly preferable for a greener process Thus the recyclability of MNP-TBD was investigated using dimethyl phosphate and isatin as model substrates. The catalyst was easily separated by attaching an external magnet after the reaction, then washed with ethyl acetate, dried under vacuum and reused in a subsequent reaction (Fig. 9). an almost quantitative amount of catalyst (up to 98%) could be recovered from each run. In a test of six cycles, the catalyst could be reused without any significant loss of catalytic activity (Fig. 10).

Table 2.	Preparation of α' -oxinc	lole-α-hydroxyphos	ohonates ^a				
	R·		0 MN " Solv R₃0´ H`OR₃ —	Ps-TBD ent-free, 60 °C	$\begin{array}{c} \begin{array}{c} 4 \\ 5 \\ R_1 \\ \hline 1 \\ \hline 0 \\ 6 \\ 7 \\ \end{array} \begin{array}{c} HO \\ P(OR) \\ \hline 1 \\ O \\ R_2 \end{array}$	3)2	
		1	2		3		
Entry	R ¹	R ²	R ³	Time (h)	Product	Yield (%) ^b	Ref.
1	Н	Н	Me	6	3a	90	9
2	5-Me	Н	Me	5	3b	91	9
3	5-Br	Н	Me	7	3c	88	8
4	5-F	Н	Me	7	3d	85	8
5	5-NO ₂	Н	Me	7	3e	84	7
6	5,7-(Cl) ₂	Н	Me	8	3f	80	7
7	Н	Н	Et	5	3 g	92	9
8	5-Me	Н	Et	6	3 h	91	9
9	5-MeO	Н	Et	6	3i	93	7
10	5-Br	Н	Et	7	3ј	83	9
11	5-NO ₂	Н	Et	7	3 k	86	9
12	5,7-(Cl) ₂	Н	Et	8	31	82	7
13	Н	Ph	Et	6	3 m	85	9
14	Н	PhCH ₂	Et	7	3n	79	9

^aReaction conditions: isatins (1 mmol), dialkyl phosphate (1 mmol); MNP-TBD (40 mg); 60 °C; neat. ^bIsolated yield.



Figure 9. Reaction mixture containing MNP-TBD (left) and MNP-TBD collected using an external magnet after the reaction (right).



Figure 10. Recycling experiments for the synthesis of dimethyl 3-hydroxy-2-oxoindolin-3-yl phosphonate.

Conclusion

We have demonstrated an efficient and mild method for the synthesis of α -oxindole- α -hydroxyphosphonates using MNP-TBD as catalyst. This method offers several advantages, including high yield, short reaction time, simple work-up procedure, ease of separation and recyclability of the magnetic catalyst, as well as the ability to tolerate a wide variety of substitutions in the reagents.

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References

- a) J. Kohno, Y. Koguchi, M. Nishio, K. Nakao, M. Juroda, R. Shimizu, T. Ohnuki, S. Komatsubara, *J. Org. Chem.* **2000**, *65*, 990; b) Y. Q. Tang, I. Sattler, R. Thiericke, S. Grabley, X. Z. Feng, *Eur. J. Org. Chem.* **2001**, 261; c) C.-Y. Gan, T. Kam, *Tetrahedron Lett.* **2009**, *50*, 1059.
- [2] a) R. R. Goehring, Y. P. Sachdeva, J. S. Pisipati, M. C. Sleevi, J. F. Wolfe, J. Am. Chem. Soc. **1985**, 107, 435; b) Y. Koguchi, J. Kohno, M. Nishio, K. Takahashi, T. Okuda, T. Ohnuki, S. Komatsubara, J. Antibiot. **2000**, 53, 105; c) T. Tokunaga, W. E. Hume, T. Umezome, K. Okazaki, Y. Ueki, K. Kumagai, S. Hourai, J. Nagamine, H. Seki, M. Taiji, H. Noguchi, R. Nagata, J. Med. Chem. **2001**, 44, 4641; d) P. Hewawasam, M. Erway, S. L. Moon, J. Knipe, H. Weiner, C. G. Boissard, D. J. Post-Munson, Q. Gao, S. Huang, V. K. Gribkoff, N. A. Meanwell, J. Med. Chem. **2002**, 45, 14879; e) T. Tokunaga, W. E. Hume, J. Nagamine, T. Kawamura, M. Taiji, R. Nagata, Bioorg. Med. Chem. Lett. **2005**, 15, 1789.
- [3] G. S. Reddy, C. S. Sundar, S. S. Prasad, E. Dadapeer, C. N. Raju, C. S. Reddy, *Der Pharma Chemica* 2012, 4, 2208.
- [4] K. U. M. Rao, C. S. Sundar, S. S. Prasad, C. Rani, C. S. Reddy, Bull. Korean Chem. Soc. 2011, 32, 3343.
- [5] B. Stowasser, K. H. Budt, D. Ruppert, Tetrahedron Lett. 1992, 33, 6625.
- [6] a) T. Yokomatsu, S. Shibuya, *Tetrahedron: Asymmetry* **1992**, *3*, 377; b)
 L. Maier, *Phosphorus Sulfur* **1993**, *76*, 119; c) T. Yamagishi, T. Kusano,
 B. Kaboudin, T. Yokomatsu, C. Sakuma, S. Shibuya, *Tetrahedron* **2003**, *59*, 767.
- [7] K. U. M. Rao, G. D. Reddy, C.-M. Chung, Phosphorus Sulfur 2013, 188, 1104.
- [8] L. Nagarapu, R. Mallepalli, U. N. Kumar, P. Venkateswarlu, R. Bantu, L. Yeramanchi, *Tetrahedron Lett.* **2012**, *53*, 1699.
- [9] J. Shankar, K. Karnakar, B. Srinivas, Y. V. D. Nageswar, *Tetrahedron Lett.* 2010, 51, 3938.
- [10] N. Yan, C. X. Xiao, Y. Kou, Coord. Chem. Rev. 2010, 254, 1179.
- [11] V. Polshettiwar, R. S. Varma, Green Chem. 2010, 12, 743.
- [12] a) S. Shylesh, V. Schunemann, W. R. Thiel, *Angew. Chem. Int. Ed.* 2010, 49, 3428; b) V. Polshettiwar, R. Luque, A. Fihri, H. B. Zhu, M. Bouhrara, J. M. Bassett, *Chem. Rev.* 2011, 111, 3036.
- [13] a) S. Shylesh, L. Wang, W. R. Thiel, *Adv. Synth. Catal.* 2010, *352*, 425; b) K. Mori, N. Yoshioka, Y. Kondo, T. Takeuchi, H. Yamashita, *Green Chem.* 2009, *11*, 1337; c) M. M. Ye, Q. Zhang, Y. X. Hu, J. P. Ge, Z. D. Lu, L. He, Z. L. Chen, Y. D. Yin, *Chem. Eur. J.* 2010, *16*, 6243; d) R. Cano, M. Yus, D. J. Ramon, *Tetrahedron* 2011, *67*, 5432.