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Magnetic Fe₃O₄ Nanoparticle-Supported Phosphotungstic Acid as a Recyclable Catalyst for the Kabachnik–Fields Reaction of Isatins, Imines, and Aldehydes under Solvent-Free Conditions

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Magnetic-nanoparticle-supported phosphotungstic acid has been used to efficiently catalyze the hydrophosphonylation reaction of isatins, imines, and aldehydes using dimethyl and diethyl phosphite as a nucleophile to give the corresponding α hydroxy and α -amino phosphonates in excellent yields for a wide range of substrates. The reaction conditions were simple, green, and efficient. The catalyst was recycled up to five times with retention of its activity. Based on the NMR spectroscopy studies, a probable catalytic cycle was proposed.

Introduction

The addition of a phosphorus-hydrogen bond to electrophilic centers like C=O or C=N is considered to be one of the most interesting topics in synthetic organic chemistry owing to its widespread application and intriguing biological activities. Among organophosphorus compounds, α -hydroxy and α amino phosphonic acids have received considerable interest in the pharmaceutical industry, as biophosphate mimics, as antibiotics, as antivirals, and as antitumor agents.^[1] Various attempts have been made to develop efficient catalytic systems for this versatile reaction like $ZrCI_{4\prime}^{[2]} TiO_{2\prime}^{[3]} LiCIO_{4\prime}^{[4]}$ ionic liquids,^[5] montmorillonite KSF,^[6] lanthanide triflate,^[7] samarium diiodide,^[8] indium chloride,^[9] TaCl₅-SiO₂,^[10] (bromodimethyl)sulfonium bromide,^[11] alumina-supported reagents,^[12] oxalic acid,^[13] Amberlite IR120,^[14] and KHSO₄.^[15] Ghosh et al. studied the one-pot synthesis of α -amino phosphonates using In(OTf)₃ as a catalyst (10 mol%) and achieved good conversion ranging from 16 to 99%.^[16] Wu et al. used N-bromosuccinimide (NBS) or CBr₄ (5 mol%) as a catalyst for the three-component synthesis of α -amino phosphonates and found that both catalysts showed good catalytic activity under solvent-free conditions.^[17] Heydari et al. reported the hydrophosphonylation of aldehydes using guanidine hydrochloride as a catalyst with water as a solvent and achieved good conversion (60-95%).[18] Chakraborti et al. studied the catalytic activity of Mg(ClO₄)₂ for the three-

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component reaction of aldehydes and ketones using different phosphites with solvent-free conditions and found that it is efficient and resulted in excellent conversion for a wide range of substrates.^[19] Rezaei et al. used FeCl₃ as a catalyst for the synthesis of simple and $bis(\alpha$ -amino phosphonates) with good conversion (80-95%) using tetrahydrofuran (THF) as a solvent and also studied its cytotoxic activity.^[20] Petrini et al. studied the hydrophosphonylation of unsaturated systems using CaO and found that the system worked well under solvent-free conditions with good conversions (49-91%) at room temperature.^[21] Wang et al. reported Yb(PFO)₃ as a catalyst for the hydrophosphonylation of aldimines at room temperature.^[22] Jeong et al. used BF₃·SiO₂ as a catalyst in an ionic-liquid medium for the one-pot hydrophosphonylation of aldimines and achieved good conversions (80–97%) of α -amino phosphonates.^[23] Although it is gratifying to acknowledge the pioneering advances in the hydrophosphonylation reaction,[24-27] most of the catalytic protocols need hazardous organic solvents, expensive and moisture-sensitive catalysts, suffer from high catalyst loading, longer reaction time, and limited substrate scope. Heydari et al.^[28] used H₃PW₁₂O₄₀ as a catalyst for the hydrophosphonylation of aldimines using dichloromethane as a solvent. But most of the reported catalysts are not recyclable making the process industrially nonviable. As part of our ongoing development of recyclable and solvent-free catalytic systems for organic transformations,^[29] herein we report a supported heteropoly acid (phosphotungstic acid) as a recyclable catalyst for the hydrophosphonylation reaction. The heteropoly acid type of catalyst is well known for its catalytic activity in diverse organic transformations like C-C bond-formation reactions. As a result of being impressed by its catalytic performance, we wished to further explore the catalytic activity of phosphotungstic acid and also to demonstrate its extensive application in the one-pot hydrophosphonylation reaction of

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a variety of substrates like aldehydes and aldimines, and less reactive substrates likes isatins and its derivatives under solvent-free conditions. Furthermore, the catalyst was recycled with retention of its activity and its mechanism was also investigated by using NMR spectroscopy.

Results and Discussion

Initially, to optimize the conditions, benzaldehyde (1) and dimethyl phosphite (DMP, **2**) as a source of nucleophile were considered as model substrates. It is well known in the literature^[30] that Lewis acid and/or Brønsted acid based catalysts are efficient for the phosphonylation reaction of diverse electrophiles like carbonyl compounds, imines, and activated olefins in the presence of a base to activate the nucleophile. With this backdrop, we screened various acidic catalysts for the hydrophosphonylation reaction under solvent-free conditions (Figure 1). Among the various catalysts, like molybdenum trichloride (MoCl₃), molybdenum tetrachloride (MoCl₄), tetrabutyl ammonium hexafluorophosphate (TBAHFP), silico tungstic acid, H β -zeolite, and phosphotungstic acid (PTA), it was found



Figure 1. Screening of catalysts for the hydrophosphonylation reaction.

that heteropoly acid PTA was the most effective catalyst and gave good yields of the desired product within a short period of time under solvent-free conditions (Figure 1). Though the other catalysts were also found to catalyze the reaction, they had a lower yield and a longer reaction time under solventfree conditions (Figure 1).

With these results in hand, we proceeded to evaluate the reaction conditions using PTA as a catalyst. We increased the reaction temperature to see whether the yield of the desired product would also increase, and indeed there was a slight increase (Table 1, entry 1). Furthermore, to assess the effect of the solvent, various solvents like dichloromethane, tetrahydrofuran, methanol, toluene, acetonitrile, and chloroform were used and it was found that the best results were obtained under solvent-free conditions (Figure 1). Although PTA was found to be effective, tedious catalyst-recovery procedures like centrifugation and/or filtration and the unavoidable loss of solid catalyst makes the separation process difficult and limits its application. Among the many solid supports, the recently



reported magnetic nanoparticles (MNPs) are fascinating in view of their high surface area, which results in a high catalyst-loading capacity, high dispersion, outstanding stability, and convenient catalyst recycling.^[31-39] Furthermore, the MNPs are easy to prepare and the separation renders the recovery of catalysts from liquid-phase reactions much easier than by cross-flow filtration and centrifugation.^[31-39]

Recently, Zhang et al. reported phosphotungstic acid supported on silica-coated magnetic nanoparticles as an efficient catalyst for the synthesis of 5ethoxymethylfurfural.^[31] With this understanding and the results obtained with Keggin-type phosophotungstic acid, we were encouraged to synthesize silica-coated magnetic-nanoparticle-supported PTA (Fe₃O_{4@}SiO₂-PTA) to check its catalytic activity on the

hydrophosphonylation reaction. This catalyst (Scheme 1) was well characterized and the data were found to be in agree-



Scheme 1. Synthesis of catalyst Fe₃O₄@SiO₂-PTA.

ment with the reported procedure.^[31] The X-ray diffraction (XRD) patterns are shown in Figure 2 and the diffraction peaks (220, 311, 400, 511, 440) were found to be similar to the reported values (JCPDS 00-001-1111).^[31] The average particle size calculated using the Scherrer equation showed that the synthesized particles are nanometer sized. Furthermore, the TEM image (Figure 3) also supports the particle size calculated from the XRD. This MNP-supported PTA, used as a catalyst for the

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Figure 2. XRD patterns of catalysts Fe₃O₄@SiO₂-PTA and Fe₃O₄@SiO₂.



Figure 3. TEM image of Fe₃O₄@SiO₂. Scale bar: 5 nm.

hydrophosphonylation reaction of 1 and 2, resulted in a good yield (98%) at room temperature in six hours under solventfree conditions (Table 1, entry 10). To check the influence of simple MNPs, a reaction was carried out under the same conditions and it was found that there is no marginal effect and gave the desired product in very low yield (12%) (Table 1, entry 8). This clearly confirms that the MNP-supported PTA showed better catalytic activity in terms of yield and reaction time. On decreasing the amount of catalyst (from 50 to 25 mg), there was no effect on the yield but the reaction took a little longer for completion (Table 1, entry 10). Furthermore, a decrease in the amount of catalyst results in a lower yield (Table 1, entry 11). Having identified the choice of catalyst and the optimized reaction conditions, we turned our attention to the scope of different substrates for the hydrophosphonylation reaction.

Hydrophosphonylation of aldehydes and aldimines

The efficacy of catalyst $Fe_3O_4@SiO_2-PTA$ was tested by using different substituents on the aromatic ring and it was found that the catalyst was efficient and gave the desired α -hydroxy phosphonate products with good to excellent yield (Table 2). Moreover, the catalyst also worked well with diethyl phosphite (DEP) as a nucleophile. Substituents with electron-donating or -withdrawing nature in *ortho, meta*, and *para* positions showed only a marginal effect in the yield of the desired product (Table 2).

After the successful utilization of the catalyst for the synthesis of α -hydroxy phosphonates, we attempted to check the catalytic activity of Fe₃O₄@SiO₂-PTA in the one-pot synthesis of α -amino phosphonates using various aldehydes, amines, and phosphites. To our delight, the catalyst showed excellent activi-

Table 2. $Fe_3O_4@SiO_2$ -PTA-catalyzed hydrophosphonylation reaction of different aldehydes and phosphites under solvent-free conditions. ^[a]					
R	^{©O} + ^{R'} O Ph	$\begin{array}{c} O \\ H \\ - \\ H \\ - \\ - \\ - \\ - \\ - \\ - \\ -$	at R	OH O O R'	
Entry	R	Phosphite	<i>t</i> [h]	Yield [%] ^[b]	
1	Н	DMP	6	96	
2	Н	DEP	6	96	
3	4-OMe	DMP	6	95	
4	4-OMe	DEP	6	88	
5	4-Me	DMP	6	91	
6	4-Me	DEP	6	86	
7	4-Cl	DMP	4	96	
8	4-Cl	DEP	4	94	
9	4-NO ₂	DMP	4	97	
10	4-NO ₂	DEP	4	91	
11	2-Me	DMP	8	80	
12	2-Me	DEP	8	72	
13	2-CF ₃	DMP	6	88	
14	$2-CF_3$	DEP	6	80	
15	2-OMe	DMP	6	96	
16	2-OMe	DEP	6	89	
17	3-Cl	DMP	4	95	
18	3-Cl	DEP	4	93	
19	2-NO ₂	DMP	4	94	
20	2-NO ₂	DEP	4	91	
21	3-OMe	DMP	6	89	
22	3-OMe	DEP	6	81	
23	2-Br	DMP	6	90	
24	4-Br	DMP	6	91	
25	4-CN	DMP	5	92	
26	3-Me	DMP	8	89	
[a] Reaction conducted on a 5 mmol scale. [b] Yield of isolated product.					

ty and resulted in the desired product in good to excellent yield under solvent-free conditions.

The electronic effect or the position of substituents on the aldehyde moiety of the phenyl ring does not affect the yield of the desired product (Table 3). We also varied the primary amines like aniline and benzylamine (Table 3) and secondary amines like morpholine (Table 4) by using **2** as the nucleophile. The catalyst was found to be efficient for a wide range of substrates for the one-pot synthesis of α -amino phosphonates under solvent-free conditions.

Hydrophosphonylation of isatins and isatin-derived imines

The results obtained with a wide range of substrates derived from aldehydes and aldimines using $Fe_3O_4@SiO_2$ -PTA as a catalyst encouraged us to explore this catalytic protocol towards less-active compounds like isatins and its derivatives. Initially we used the optimized reaction conditions for isatin-based substrates and found that the yield of the desired product was moderate (68%) at room temperature in six hours (Table 5, entry 1).

To increase the yield of the product, the reaction was carried out at higher temperatures (Table 5, entries 2 and 3) using $Fe_3O_4@SiO_2$ -PTA as a catalyst under solvent-free conditions. It was observed that the yield increased significantly when the

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hydes catalyzed by $Fe_3O_4@SiO_2$ -PTA under solvent-free conditions. ^[a]						
	R ¹ _{NH}					
		0	Fe ₃ O ₄ @SiO ₂ -	PTA		
	$^{10} + R^{1} - N$	H ₂ + ^{R'} ~о́ ¦~о́ ^Р	('	→[]	J of the second	
R	Amin	e Phosphite	, RI	\checkmark	R'	
		1 Hoopinto				
Entry	R	Amines	Phosphite	t [h]	Yield [%] ^[b]	
1	Н	aniline	DMP	3	97	
2	Н	aniline	DEP	6	91	
3	Н	benzylamine	DEP	4	94	
4	4-OMe	aniline	DMP	4	92	
5	4-OMe	aniline	DEP	6	87	
6	4-OMe	benzylamine	DEP	4	93	
7	4-Cl	aniline	DMP	3	91	
8	4-Cl	aniline	DEP	6	87	
9	4-Cl	benzylamine	DEP	4	94	
10	4-NO ₂	aniline	DMP	3	96	
11	4-NO ₂	aniline	DEP	4	92	
12	4-NO ₂	benzylamine	DEP	6	94	
13	2-Me	aniline	DMP	3	80	
14	2-Me	aniline	DEP	4	72	
15	2-CF ₃	aniline	DMP	3	88	
16	2-CF ₃	aniline	DEP	4	80	
17	2-OMe	aniline	DMP	4	96	
18	2-OMe	aniline	DEP	6	88	
19	2-OMe	benzylamine	DEP	6	91	
20	2-Cl	aniline	DMP	3	94	
21	2-Cl	aniline	DEP	4	93	
22	2-Cl	benzylamine	DEP	6	92	
23	2-NO ₂	aniline	DMP	3	95	
24	2-NO ₂	aniline	DEP	4	92	
25	2-NO ₂	benzylamine	DEP	6	92	
[a] Reaction conducted on a 5 mmol scale. [b] Yield of isolated product.						

Table 3. One-pot synthesis of α -amino phosphonates from various alde-

 Table 4. One-pot three-component hydrophosphonylation reaction of aldehydes using secondary amine and DMP/DEP as nucleophile catalyzed by $Fe_3O_4@SiO_2-PTA.^{(a)}$

 O

 N

R	+ + +	$ \begin{array}{ccc} R' & & & Pe_3O_4(\\ O' & H & O' \\ Phosphite \end{array} $	@SiO₂-PTA ►	P'O'R'	
Entry	R	Phosphite	<i>t</i> [h]	Yield [%] ^[b]	
1	Н	DMP	6	90	
2	4-OMe	DMP	6	93	
3	4-CN	DMP	4	97	
4	4-NO ₂	DMP	3	96	
5	4-Br	DMP	3	87	
6	2-OMe	DMP	6	92	
7	2-Br	DMP	3	93	
8	2-NO ₂	DMP	3	95	
[a] Reaction conducted on a 5 mmol scale. [b] Yield of isolated product.					

reaction was carried out at 80 °C. Under these optimized conditions, various substituted isatins also resulted in good to excellent yields (Table 5).

After obtaining an excellent yield using isatin-based substrates, we tried to explore the catalytic activity of $Fe_3O_4@SiO_2$ -PTA for isatin-derived imines using DMP and DEP under sol-

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vent-free conditions. It was found that the catalyst was effective and resulted in the desired product with moderate to excellent yield at $80\,^{\circ}$ C (Table 6).

Mechanism

To develop a basic understanding of the precise role of the catalyst in the hydrophosphonylation reaction we performed time-dependent studies using benzaldehyde and dimethyl phosphite as model substrates. In the kinetic runs, the plots of the formation of the desired product with time were found to



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Figure 4. Time-dependent plot of the formation of the product.

be linear in the beginning of the reaction and attained saturation near its completion (Figure 4). On the basis of this observation, the initial rate constants, k_{obs} , were determined by directly estimating the amount of product formed up to the completion of the reaction.

Moreover, to understand the interaction of the substrate with the catalyst, we conducted a series of NMR spectroscopy experiments (Figure 5). For the sake of clarity, we have used simple PTA as a catalyst in the NMR spectroscopy studies. As an active catalytic species it is necessary to study its role and possible mode of interaction with the substrate and nucleophile. All the NMR spectroscopy experiments were performed on samples in CD₃OD.

Initially, the PTA active species interacted with benzaldehyde and it was found that the proton corresponding to benzaldehyde shifted downfield, which indicated an interaction through the carbonyl oxygen (see the Supporting Information and Figure 5a). This also has

been confirmed by the downfield shift of the catalyst (Figure 5b). Furthermore, after the addition of **2** to the PTA active species, generation of a new peak in the ³¹P and ¹³C NMR spectra clearly confirmed the generation of the phosphite form (Figure 5c, d). Thus the generated phosphite attacks the electrophilic carbonyl carbon to form the C–P bond and thereby leads to the desired product while leaving behind the catalyst for the catalytic cycle (Scheme 2).



Figure 5. (a) Study of the interaction of the catalyst with substrate and nucleophile using ¹H NMR spectra, of samples recorded in CD₃OD: (1) catalyst (PTA), (2) catalyst + DMP, (3) catalyst + benzaldehyde. (b) Study of the interaction of catalyst with substrate and nucleophile using ³¹P NMR spectra: (4) catalyst (PTA), (5) catalyst + DMP, (6) catalyst + benzaldehyde, recorded for samples in CD₃OD. (c) Study of the interaction of catalyst with nucleophile using ³¹P NMR spectra: (7) DMP, (8) catalyst + DMP, recorded for samples in CD₃OD. (d) Study of the interaction of catalyst with nucleophile using ¹³C NMR spectra: (9) DMP and (10) catalyst + DMP, recorded for samples in CD₃OD. Scale: δ /ppm.

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Recycling studies

After the successful utilization of MNP-supported PTA as a catalyst for the hydrophosphonylation reaction of various substrates and nucleophiles we decided to check the recyclability of catalyst $Fe_3O_4@SiO_2$ -PTA. After the first catalytic run, the product was dissolved in ethyl acetate and the catalyst was separated by using a magnet (Figure 6). The recovered catalyst



Figure 6. (a) Reaction mixture and (b) recovery of catalyst from the reaction mixture using an external magnet.



Recyclability of catalyst

Figure 7. Recyclability of the catalyst.

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was washed, dried, and activated for two hours before its reuse in subsequent catalytic runs. The result reveals that the catalyst worked well for five cycles without any significant loss in its activity (Figure 7).

Conclusion

In conclusion, we have developed a simple, efficient, and solvent-free protocol for the synthesis of α -hydroxy and α -amino phosphonates using Fe₃O₄@SiO₂-PTA as a catalyst. The advantage of this catalyst is that it can be easily recyclable up to five times with retention of its activity and resulted in good to excellent yields for a wide range of substrates in solvent-free conditions. We have also extended the catalytic protocol for the less reactive isatin and its imines. A probable catalytic cycle was proposed based on NMR spectroscopy studies.

Experimental Section

The different aldehydes, amines, and reagents were used as received. All the isatin derivatives were purchased from Sigma Aldrich. NMR spectra were obtained with a Bruker F113V spectrometer (200 and 500 MHz) and were referenced internally with tetramethylsilane (TMS). For the product purification flash chromatography was performed using silica gel (100–200 mesh).

Preparation of catalyst

Synthesis of Fe₃O₄

Fe₃O₄ was synthesized according to a reported procedure.^[31] FeSO₄•7H₂O (5 mmol) and FeCl₃·6H₂O (10 mmol) were dissolved in deionized water (50 mL) and stirred mechanically at 80 °C for 15 min under a nitrogen atmosphere. This was followed by dropwise addition (about 10 min) of NH₃·H₂O (8 mL) to the reaction mixture. Subsequently, 1 m citric acid (1 mL) was added and the mixture was stirred for 2 h. Then the precipitate was collected by a strong permanent magnet and washed with deionized water to pH 7. The collected brown precipitate was washed twice with ethanol and dried under vacuum at 70 °C overnight to obtain the Fe₃O₄ nanoparticles.

Synthesis of silica-coated Fe₃O₄^[31]

The synthesized Fe₃O₄ nanoparticles (2 g) were dispersed in a mixture of ethanol (70 mL) and H₂O (10 mL) by sonication for 15 min. To the dispersed solution, aqueous ammonia (5 mL) and tetraethyl orthosilicate (5 mL) were added and the mixture was stirred vigorously for 24 h. Then the silicacoated Fe₃O₄ was collected by a permanent magnet, was washed repeatedly with deionized water until it became neutral, and was rinsed with ethanol three times. The collected precipitate was dried under vacuum to obtain the silica-coated Fe₃O₄.

Synthesis of Fe₃O₄@SiO₂-PTA^[31]

The synthesized silica-coated Fe_3O_4 (2 g) was firstly dispersed in deionized water (30 mL) by sonication for 30 min. This was followed by the addition of an aqueous

solution of phosphotungstic acid (0.8 g in 5 mL of water) and the reaction mixture was stirred for 24 h. The precipitate was collected by a permanent magnet and was washed with deionized water. Finally, the precipitate was dried at 100 °C for 12 h to obtain the active catalyst.

General procedure for the hydrophosphonylation of aldehydes using $Fe_3O_4@SiO_2$ -PTA as catalyst

In an oven-dried reaction vial, the catalyst (25 mg) and aldehydes (0.3 mmol) were mixed and stirred for 15 min at RT. Then the phosphite source (0.3 mmol) was added slowly over a period of 10 min. The reaction was monitored by TLC using hexane/ethyl acetate (90:10) as eluent. After the reaction was over the product was separated from the catalyst by using a permanent magnet and purified by flash column chromatography on silica gel (eluted with hexane/ethyl acetate 90:10). The purified α -hydroxy phosphonate products were characterized by ¹H NMR spectroscopy, which was in agreement with the reported values.^[19]

General procedure for the one-pot hydrophosphonylation using $Fe_3O_4@SiO_2-PTA$ as catalyst

In an oven-dried reaction vial, catalyst (25 mg), aldehydes (0.3 mmol), and amine (0.3 mmol) were mixed and stirred for 15 min at RT. Then the phosphite source (0.3 mmol) was added slowly over a period of 10 min. The reaction was monitored by TLC using hexane/ethyl acetate (90:10) as eluent. After the reaction was complete, the product was separated from the catalyst by using a permanent magnet and purified by flash-column chromatography on silica gel (eluted with hexane/ethyl acetate 90:10). The purified α -amino phosphonate products were characterized by ¹H NMR spectroscopy, which was in agreement with the reported values.^[40]

General procedure for the hydrophosphonylation of isatins and its imines using Fe₃O₄@SiO₂-PTA as catalyst

In an oven-dried reaction vial, the catalyst (25 mg) and isatins/ isatin-derived imines (0.3 mmol) were mixed and stirred for 15 min at RT. Then the phosphite source (0.3 mmol) was added slowly over a period of 10 min. The reaction mixture was stirred at 80 °C and monitored by TLC using hexane/ethyl acetate (90:10) as eluent. After the reaction was complete, the product was separated from the catalyst by using a permanent magnet and purified by flash-column chromatography on silica gel (eluted with hexane/ ethyl acetate 90:10). The purified products were characterized by ¹H NMR spectroscopy, which was in agreement with the reported values.^[41]

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A neat idea: The present study describes the catalytic efficiency of a magnetic-particle-supported heteropoly acid for the C–P bond-formation reaction. The catalyst worked very well under solvent-free conditions for a wide range of substrates and resulted in good to excellent yields of desired products like α -hydroxy and α -amino phosphonates (see figure). This catalytic protocol is simple, green, efficient, and recyclable.

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Magnetic Fe₃O₄ Nanoparticle-Supported Phosphotungstic Acid as a Recyclable Catalyst for the Kabachnik–Fields Reaction of Isatins, Imines, and Aldehydes under Solvent-Free Conditions