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# 12-Tungstophosphoric Acid Immobilized on $\gamma$-$Fe_2O_3$@$SiO_2$ Core–Shell Nanoparticles: An Effective Solid Acid Catalyst for the Synthesis of Indole Derivatives in Water

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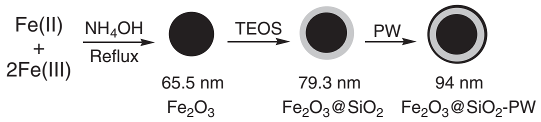
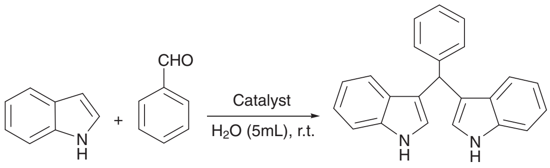
12-Tungstophosphoric acid immobilized on $\gamma$-$Fe_2O_3$@$SiO_2$ core–shell nanoparticles was used as novel solid acid catalyst for the synthesis of various bis(indolyl)methanes and $\beta$-functionalized indoles in water. The catalyst can be recovered simply using an external magnetic field and reused several times without appreciable loss of its catalytic activity.



**Scheme 1.** Design of the $\gamma$-$Fe_2O_3$@$SiO_2$–PW catalyst.[2]



**Scheme 2.** Model reaction.

Introducing of new, efficient, and strategically important processes, which are environmentally benign and lead to greater structural variation in a short period of time with high yields and simple workup procedure is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. Recent tendencies have been focused on the replacement of homogeneous catalysts with heterogeneous analogs, which can be easily recovered from the reaction mixture thereby eliminating the need for separation through distillation or extraction.

In the field of heterogeneous catalysis, solid-supported Keggin type heteropolyacids (HPAs), such as 12-tungstophosphoric acid, $H_3PW_{12}O_{40}$ (PW), arouse much attention for they not only have strong Brønsted acidity, but they can also be recovered from reaction media and reused. Among the supports that can be used to immobilize HPAs, acidic or natural substance like $SiO_2$, $TiO_2$, or active carbon is suitable and the Keggin structure of HPAs is retained upon adsorption onto their surfaces over a broad range of loading. However, although these solid-supported HPAs can be recovered by filtration or precipitation, lower activity or selectivity compared to homogeneous ones are commonly detected due to steric and diffusion factors. In addition, weak interaction between HPA and supports results in its leaching from the support surface in polar reaction media.[1]

In the attempt to resolve such problems, nanomagnetically recoverable HPA-based catalyst was first synthesized in our laboratory and used as novel special heterogeneous HPAs in Mannich type reactions in water.[2] A simple ferric oxide, $\gamma$-$Fe_2O_3$, was used as the magnetic material for its low price, simplicity, and nontoxicity. It was prepared through chemical coprecipitation, and subsequently was coated with silica shell by the Stöber process,[3] that is the hydrolysis of tetraethyl orthosilicate (TEOS) in an ethanol solution containing water and ammonia. After the surface coating by $SiO_2$, magnetic solid (designed as $\gamma$-$Fe_2O_3$@$SiO_2$) was used as support for immobilization of PW. The obtained catalyst (designed as $\gamma$-$Fe_2O_3$@$SiO_2$–PW) was collected by a permanent magnet and dried (Scheme 1).[2,4] Typically, a loading at ca. 31 wt% PW (1.1 mmol $g^{-1}$) was obtained. It was found that the $\gamma$-$Fe_2O_3$@$SiO_2$–PW catalyst exhibits several attractive features for the synthesis of fine chemicals. The magnetic properties make possible the complete recovery of the catalyst by means of an external magnetic field, which is an important advantage of the use of a magnetically separable catalyst.[5] Furthermore, nanoscale supports have high surface area resulting in high catalyst loading capacity, high dispersion, and outstanding stability. Also, they do not suffer from porosity and other problems associated with the transport of reactants and/or products to and from the catalytic sites. As a result, the immobilization of HPAs on the silica-coating magnetic core turned out to be beneficial, giving rise to an invariant high activity and improved numbers of recycle and reuse in comparison to immobilization on conventional solid supports. These findings encourage us to extend the catalytic application of $\gamma$-$Fe_2O_3$@$SiO_2$–PW for the synthesis of useful building blocks and/or biologically active compounds in water.

Among the different protocols for the synthesis of useful building blocks, we selected the synthesis of 3-substituted indoles, particularly 3-alkylindoles and bis(indolyl)methanes, because of their very high impact as synthons for the preparation of various bioactive compounds.[6,7]

Optimized experiments were carried out by using different amounts of $\gamma$-$Fe_2O_3$@$SiO_2$–PW catalyst in the model reaction (Scheme 2) and results were summarized in Table 1. Control experiment showed that the substrates hardly reacted together in the absence of catalyst (Table 1, Entry 1). $\gamma$-$Fe_2O_3$@$SiO_2$ showed poor effect on the yield of the product (Table 1, Entry 2). When using the $Fe_2O_3$@$SiO_2$–PW as catalyst, a significant improvement was observed (Table 1, Entry 3). As can be seen, by using of 0.05 g of $Fe_2O_3$@$SiO_2$–PW as catalyst, the product was obtained in excellent yield within short reaction time while more than 0.05 g of the catalyst had no effect on product yield (Table 1, Entries 3–7). Therefore, 0.05 g of catalyst was selected as the best catalyst loading in further

**Table 1.** Catalytic activity of $\gamma$-$Fe_2O_3$@$SiO_2$–PW in the reaction of benzaldehyde and indole as model substrates[a]

| Entry | Catalyst | Time /min | Yield /%[b] |
|---|---|---|---|
| 1 | — | 25 | 0 |
| 2 | $\gamma$-$Fe_2O_3$@$SiO_2$ (0.01 g) | 25 | 14 |
| 3 | $\gamma$-$Fe_2O_3$@$SiO_2$–PW (0.01 g) | 25 | 51 |
| 4 | $\gamma$-$Fe_2O_3$@$SiO_2$–PW (0.02 g) | 25 | 62 |
| 5 | $\gamma$-$Fe_2O_3$@$SiO_2$–PW (0.03 g) | 25 | 80 |
| 6 | $\gamma$-$Fe_2O_3$@$SiO_2$–PW (0.05 g) | 25 | 98 |
| 7 | $\gamma$-$Fe_2O_3$@$SiO_2$–PW (0.1 g) | 25 | 98 |
| 8 | $\gamma$-$Fe_2O_3$@$SiO_2$ (0.05 g) | 25 | 21 |
| 9 | PW (0.05 g) | 25 | 48 |

[a]Reaction conditions: indole (2 mmol), benzaldehyde (1 mmol), $H_2O$ (5 mL), room temperature. [b]Isolated yields.

investigations. The catalytic activity of 0.05 g of $Fe_2O_3$@$SiO_2$–PW catalyst was compared with $Fe_2O_3$@$SiO_2$ and unsupported PW on unit weight basis (Table 1, Entries 8 and 9). The results showed that $Fe_2O_3$@$SiO_2$ was not efficient in the reaction and the yield was much lower than that obtained using the $Fe_2O_3$@$SiO_2$–PW catalyst. However, when PW was used as the catalyst, a moderate yield of the product was obtained (Table 1, Entry 9). Nevertheless, the reaction proceeded in a homogeneous system, which makes catalyst recovery very difficult.

In order to exam the reusability of the catalyst, the model reaction was carried out by using 0.5 g of catalyst and the experiments were properly scaled up. At the end of reaction, bis(3-indolyl)phenylmethane was obtained as pinkish solid product. The reaction mixture was centrifuged and water was removed from the mixture to leave residue. The product was dissolved in acetonitrile and the catalyst easily separated from the product by attaching an external magnet onto the reaction vessel, followed by decantation of the product solution. The catalyst could be recovered and subsequently reused several times without significant loss of activity (Figure 1). To check the leaching of PW into the reaction mixture, the model reaction was carried out for 1 h under selected reaction conditions. Then, the reaction was stopped, catalyst and product were separated by centrifugation, and the filtrate was added to a mixture of indole and benzaldehyde as model substrates and stirred for 1 h. Only 15% of the corresponding product was obtained indicating negligible PW leaching into the reaction mixture. This observation confirmed that the reaction was catalyzed heterogeneously. In addition, the content of PW into filtrate was evaluated quantitatively by inductively coupled plasma atomic emission spectroscopy (ICP-AES), which showed 12.2% of the initial content was leached into reaction mixture. Nevertheless, the yield of product was not substantially modified (10% difference) after the fourth run.

To evaluate the scope and generality of this new protocol, various aldehydes and ketones, as well as amines and $\beta$-dicarbonyl compounds were tested as the substrates (Scheme 3). At first, we investigated the electrophilic substitution of indole with various aldehydes and ketones to probe their behavior under the current catalytic conditions (Scheme 4a).[8] The catalyst has been applied successfully for the condensation of hetero-aromatic aldehydes **2b** and **2c** to afford the corresponding bis(indolyl)methanes in excellent yields (Table 2, Entries 2 and 3). It is also worth mentioning that the reaction is general and is applicable to cyclic and aromatic ketones (Table 2, Entries 4 and 5) to afford the corresponding product in high yields, although longer reaction times were required for their conversion. 2-Methylindole (**1b**) reacted well with **2a** and **2d** to give the

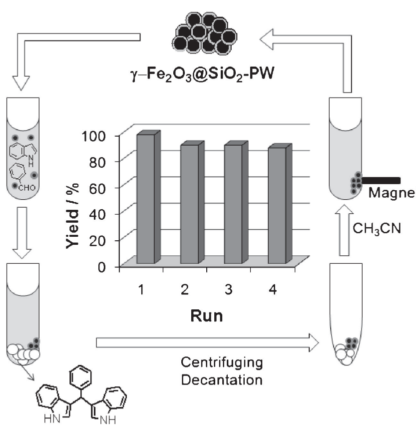
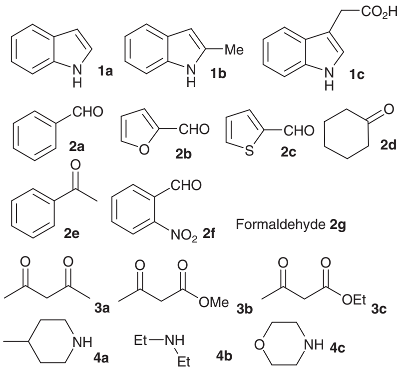
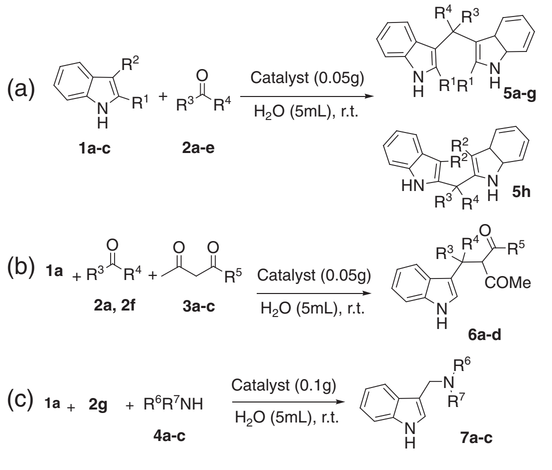


**Figure 1.** Reusability of $\gamma$-$Fe_2O_3$@$SiO_2$–PW (after 30 min).



**Scheme 3.** Various substrates.



**Scheme 4.** Various reactions for the synthesis of indole derivatives.

**Table 2.** Synthesis of various indole derivatives in the presence of $\gamma$-$Fe_2O_3$@$SiO_2$–PW

| Entry | Substrates | | | Product[a] | Time | Yield /%[b] |
|---|---|---|---|---|---|---|
| 1 | **1a** | **2a** | | **5a** | 30 min | 98 |
| 2 | **1a** | **2b** | | **5b** | 40 min | 94 |
| 3 | **1a** | **2c** | | **5c** | 45 min | 95 |
| 4 | **1a** | **2d** | | **5d** | 80 min | 86 |
| 5 | **1a** | **2e** | | **5e** | 330 min | 62 |
| 6 | **1b** | **2a** | | **5f** | 25 min | 98 |
| 7 | **1b** | **2d** | | **5g** | 75 min | 91 |
| 8 | **1c** | **2a** | | **5h** | 360 min | 80 |
| 9 | **1a** | **2a** | **3a** | **6a** | 45 min | 98 |
| 10 | **1a** | **2a** | **3b** | **6b** | 1 h | 95 |
| 11 | **1a** | **2a** | **3c** | **6c** | 1 h | 96 |
| 12 | **1a** | **2f** | **3b** | **6d** | 1 h | 76 |
| 13 | **1a** | **2g** | **4a** | **7a** | 3 h | 77 |
| 14[c] | **1a** | **2g** | **4a** | **7a** | 3 h | 94 |
| 15[d] | **1a** | **2g** | **4a** | **7a** | 3 h | 98 |
| 16[c] | **1a** | **2g** | **4b** | **7b** | 5 h | 86 |
| 17[c] | **1a** | **2g** | **4c** | **7c** | 5 h | 81 |

[a]All products were identified by comparing of their spectral data with those of the authentic samples.[9–14] [b]Isolated yields. [c]0.1 g of the catalyst was used in this reaction. [d]0.2 g of the catalyst was used in this reaction.

corresponding products **5f** and **5g** in excellent yields (Table 2, Entries 6 and 7). Under these reaction conditions, indole-3-acetic acid (**1c**) on reaction with **2a** gave **5h** in good yield (Table 2, Entry 8).

Considering the synthetic utility of $\beta$-diketones and $\beta$-ketoesters, their reactivity with indole and various aldehydes has also been investigated (Scheme 4b).[8] As expected, trimolecular condensation reaction of **1a** with **2a** and $\beta$-dicarbonyl compounds **3a**–**3c** afforded the corresponding products **6a**–**6c** in excellent yields (Table 2, Entries 9–11). These experimental conditions could successfully be extended to 2-nitrobenzaldehyde (**2f**) giving product **6d** with satisfactory yield (Table 2, Entry 12).

A Mannich-type reaction of secondary amine, formaldehyde, and indole was chosen as another way for the synthesis of $\beta$-functionalized indoles derivatives (Scheme 4c).[8] As the first case, the reaction of **1a**, 4-methylpiperidine (**4a**), and formaldehyde (**2g**) was performed under optimized conditions (Table 2, Entry 13). The corresponding product **7a** was obtained in good yield. Increasing the quantity of catalyst from 0.05 to 0.1 g improved the result to a greater extent while further addition of catalyst had no noticeable effect on the yield or reaction time (Table 2, Entries 13–15). Thus, 0.1 g of catalyst was used for the synthesis of compounds **7b** and **7c** in good yields (Table 2, Entries 16 and 17).

Based on these results, it is expected that the $\gamma$-$Fe_2O_3$@$SiO_2$–PW will be new promising catalysts in the synthesis of biologically active indole derivatives.

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8 General procedure for the synthesis of products **5a**–**5h**: A mixture of aldehyde (1 mmol), indole (2 mmol), catalyst (0.05 g), and $H_2O$ (5 mL) was stirred at room temperature. At the end of reaction, water was removed from the mixture by centrifugation. The product was dissolved in acetonitrile and the catalyst separated from the product by an external magnet. The solvent was evaporated in vacuum to give the product which was purified by column chromatography on silica gel. General procedure for the synthesis of products **6a**–**6d**: A mixture of indole (1 mmol), aldehyde (1 mmol), 1,3-dicarbonyl compound (1 mmol), and catalyst (0.05 g) in $H_2O$ (5 mL) was stirred at room temperature. Purification of products and recyclization of the catalyst are similar to above procedure. General procedure for the synthesis of products **7a**–**7c**: A mixture of indole (1 mmol), amine (1.2 mmol), formaldehyde (1.2 mmol), and catalyst (0.1 g) in $H_2O$ (5 mL) was stirred at room temperature. At the end of reaction, $CH_2Cl_2$ (2 × 5 mL) was added and the reaction mixture was stirred. The catalyst separated from the product by an external magnet onto the reaction vessel, followed by decantation of the reaction mixture. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography on silica gel to afford the pure product.

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