

REGULAR ARTICLE

# Green and efficient synthesis of aryl/alkylbis(indolyl)methanes using Expanded Perlite-PPA as a heterogeneous solid acid catalyst in aqueous media

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**Abstract.** Expanded Perlite-Polyphosphoric acid (EP-PPA) as a novel, efficient, recyclable and eco-benign heterogeneous catalyst has been applied for the green and rapid synthesis of aryl/alkylbis(indolyl)methanes, in water, in good to excellent yields. The catalyst was characterized by XRF, FT-IR, TGA/DTG, ICP-OES, SEM-EDX and pH analysis. Importantly, the newly synthesized heterogeneous solid acid catalyst can be recovered and reused six times without any significant loss in its catalytic potential. The remarkable features of the present methodology are high conversions, shorter reaction times, cleaner reaction profiles and simple work-up procedures.

**Keywords.** Expanded Perlite-PPA; aryl/alkylbis(indolyl)methanes; carbonyl compounds; heterogeneous catalyst.

## 1. Introduction

Indole and its natural and synthetic derivatives are important heterocyclic compounds due to their wide-ranging biological and pharmaceutical activities.<sup>1–3</sup> Among the different indole derivatives, aryl/alkylbis(indolyl)methanes are well-known as an old but privileged class of bioactive metabolites,<sup>4–6</sup> due to their representation in natural products<sup>7</sup> and extensive applications in pharmaceuticals.<sup>8</sup> Over the past few years, a variety of bis(indolyl)methanes have been isolated from earthly and marine natural sources such as parasitic bacteria, tunicates, and sponges,<sup>3,9</sup> and these have exhibited antibacterial activity against *Staphylococcus aureus*, *S. albus* and *Bacillus subtilis*,<sup>10</sup> in addition to anti-inflammatory and antibacterial activity.<sup>11</sup>

Bis(indolyl)methanes are the most active cruciferous substances for promoting beneficial estrogen metabolism.<sup>12</sup> These can be effective in the prevention of cancer and moreover may normalize the abnormal cell growth associated with cervical dysplasia.<sup>13</sup> Therefore, the synthesis of this class of compounds is of considerable interest for synthetic organic chemists (towards the development of new protocols) and biologists. To seek efficient and convenient synthetic routes of bis(indolyl)methanes, great efforts have been made.

Traditionally, bis(indolyl)methanes have been synthesized by electrophilic substitution reaction of indoles

with carbonyl compounds, catalyzed by either protic or Lewis acids<sup>14,15</sup> such as montmorillonite clay,<sup>16,17</sup> oxone,<sup>18</sup>  $\text{NH}_4\text{Cl}$ ,<sup>19</sup> cellulose sulfuric acid,<sup>20</sup> ionic liquid,<sup>21</sup> oxalic acid,<sup>22</sup>  $\text{La}(\text{OTf})_3$ ,<sup>23</sup>  $\text{In}(\text{OTf})_3$ ,<sup>24</sup> zirconium tetrakis(dodecyl sulfate),<sup>25</sup>  $\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}$ ,<sup>26</sup> phosphated zirconia,<sup>27</sup> 12-tungstophosphoric acid supported on zirconia,<sup>28</sup>  $\text{GaCl}_3$ ,<sup>29</sup>  $\text{ZnO}$ ,<sup>30</sup>  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ ,<sup>31</sup>  $\text{Al}_2\text{O}_3$ ,<sup>32</sup> zirconyldodecylsulfate,<sup>33</sup>  $\text{I}_2$ ,<sup>34</sup> silica gel,<sup>35</sup> pyridinium tribromide,<sup>36</sup>  $\text{SiO}_2/\text{AlCl}_3$ ,<sup>37</sup> Iron(III) dodecyl sulfate,<sup>38</sup> PPA- $\text{SiO}_2$ ,<sup>39,40</sup> ammonium niobium oxalate and tetrabutylammonium hydrogen sulfate.<sup>41</sup> The reported methods indicate that the catalysts commonly used for such a transformation, are generally associated with one or more of the following disadvantages such as high toxicity, high cost, difficulty of handling, low thermal stability and un-recyclability. In addition to these drawbacks, tedious methods required for the separation of the products, along with using the environmentally harmful organic solvents in some of these approaches, are definitely far from the concept of “Green Chemistry”. Also, because of either the strong adsorption or polymerization of indole by Lewis acid sites, these methods consume more reactants than the required amounts, according to the stoichiometries of the reactions.<sup>42</sup> Likewise, many Lewis acids are deactivated or sometimes decomposed by nitrogen-containing reactants, which would lead to use of more than stoichiometric amounts of Lewis acids, besides the generation of harmful wastes, which would pose environmental problems.<sup>42</sup> Furthermore, although solid acid catalysts promote the synthesis

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of bis(indolyl)methane, some of them require very high temperature for reactivation.<sup>43</sup>

Keeping in view the increasing importance of bis(indolyl)methane derivatives in pharmaceutical and industrial chemistry, there is still much demand to develop a better catalytic process, that would abate the environmental impact of the pollution resulting from the above mentioned methods reported for the synthesis of such significant scaffolds.

Polyphosphoric acid (PPA) has been employed as an efficient protic acid catalyst for numerous organic reactions.<sup>44</sup> Nevertheless, the difficulty of PPA handling, due to its viscous nature, has limited its application. To surmount this problem and in continuation of our ongoing research in synthetic organic chemistry, for the development of efficient and environmentally benign heterogeneous catalysts,<sup>45</sup> herein, we report Expanded Perlite-PPA (EP-PPA), as a novel, green and efficient heterogeneous catalyst (Scheme 1). The catalytic activity of EP-PPA was verified by the synthesis of aryl/alkylbis(indolyl)methanes through the one-pot reaction of indole and carbonyl compounds, in water. Importantly, this distinguished catalyst is easy to prepare and handle and could be separated simply by filtration and also recycled for six times without significant loss of its catalytic activity.

## 2. Experimental

### 2.1 Materials

All chemical reagents and solvents were purchased from Merck and Sigma-Aldrich and were used as received without further purification. Expanded Perlite was obtained from Iran: Birjand resources.

### 2.2 Instrumentation analysis

The purity determination of the products and the progress of the reactions were monitored by 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. The FT-IR spectra were recorded on an Avatar 370 FT-IR Thermo Nicolet spectrometer. The NMR spectra were

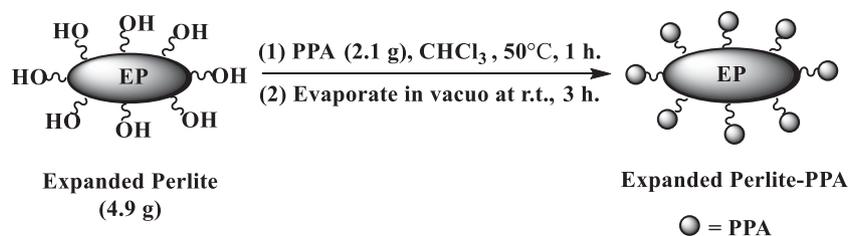
recorded on Bruker Avance 300 and 500 MHz instruments in  $\text{CDCl}_3$  and  $\text{DMSO}-d_6$ . Mass spectra were recorded with a Shimadzu GC-MS-QP5050 and CH7A Varianmat Bremen instrument at 70 eV, in  $m/z$  (rel %). Thermogravimetric analyses (TGA and DTG) were carried out using a Shimadzu Thermogravimetric Analyzer (TG-50) in the temperature range of 25–900°C at a heating rate of 10°C  $\text{min}^{-1}$ , under air atmosphere. Inductively coupled plasma optical emission spectroscopy (ICP-OES) was carried out on a 76004555 SPECTRO ARCOS ICP-OES analyzer. SEM images were recorded using a Leo1450 VP scanning electron microscope equipped with an SC7620 energy-dispersive X-ray spectrometer (EDX), presenting a 133 eV resolution at 20 kV. The chemical compositions of the expanded perlite were specified with X-ray fluorescence spectroscopy (XRF), using BRUKER axs-S4 EXPLORER spectrometer. All of the obtained products are known compounds and their physical (color, melting points) and spectral (mass spectrometry) data were found to be identical with those of authentic compounds. The selected compounds were further identified by FT-IR,  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy which compared with literature data.

### 2.3 Preparation of EP-PPA

A mixture of polyphosphoric acid (2.1 g) in  $\text{CHCl}_3$  (100 mL) was stirred at 50°C for 1 h. Expanded Perlite (4.9 g) was added to the resulting solution and the mixture was stirred vigorously. After 1 h,  $\text{CHCl}_3$  was removed under reduced pressure and the resulting solid was dried *in vacuo* at room temperature for 3 h.

### 2.4 Typical procedure for the synthesis of 3,3'-(phenylmethylene)bis(1H-indole) in the presence of EP-PPA

To a mixture of indole (2 mmol, 0.234 g) and benzaldehyde (1 mmol, 0.106 g) in  $\text{H}_2\text{O}$  (3 mL), EP-PPA (0.04 g) was added. The mixture was allowed to stir at 60°C. Upon completion of the reaction (monitored by TLC analysis), the catalyst was separated by filtration. After the filtration,  $\text{H}_2\text{O}$  (10 mL) was added and the product was extracted into ethyl acetate ( $3 \times 15$  mL). The combined organic layer was dried over anhydrous  $\text{Na}_2\text{SO}_4$  and then evaporated under vacuum to afford the crude product, which was further purified by thin layer chromatography (preparative TLC was carried out using a Merck GF 254 silica gel on a glass support)



**Scheme 1.** Preparation of Expanded Perlite-PPA.

using *n*-hexane:ethyl acetate (3:1) as eluent. The pure 3,3'-(phenylmethylene)bis(1*H*-indole) was obtained in 98% yield (0.315 g).

### 3. Results and Discussion

Expanded Perlite is a green and inexpensive mixture of mineral oxides, which mainly consists of silica and alumina<sup>46</sup> (Table 1). The exclusive features of Expanded Perlite include high porosity besides strong adsorbability, thermal and chemical stability, low toxicity, low cost, non-corrosiveness and ease of handling.<sup>47</sup> These distinctive properties make the Expanded Perlite an excellent support for the preparation of heterogeneous catalysts.<sup>48</sup> EP-PPA was prepared by the concise route outlined in Scheme 1. The current method has many advantages such as simplification of the catalyst system and its synthesis, as well as using an inexpensive and available precursor. The as-synthesized white heterogeneous, non-hygroscopic catalyst is very stable under the reaction conditions. This new catalyst was characterized by different techniques such as fourier transform infrared spectroscopy (FT-IR),

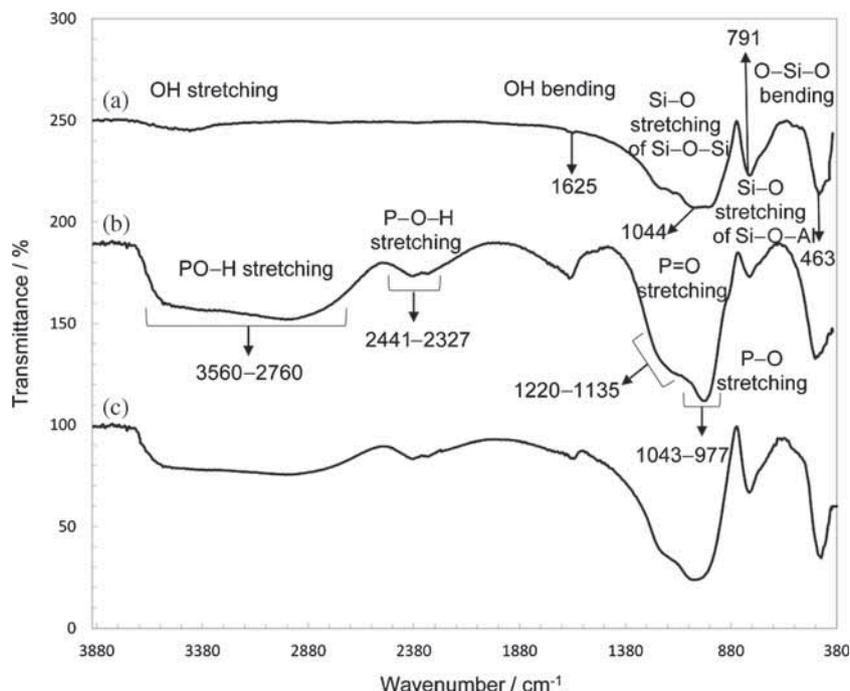
thermogravimetric/differential thermogravimetric analysis (TG/DTG), scanning electron microscopy (SEM), energy-dispersive X-ray spectroscopy (EDX), Inductively coupled plasma optical emission spectroscopy (ICP-OES) and pH analysis. The obtained results from these techniques confirmed the successful preparation of the new catalyst.

#### 3.1 Characterization of the catalyst

**3.1a FT-IR spectroscopy of the catalyst:** FT-IR spectra of Expanded Perlite and EP-PPA are shown in Figure 1. As it is obvious in Figure 1a, there are five significant absorption bands in the infrared spectrum of Expanded Perlite.<sup>49</sup> The indicative bands corresponding to the stretching and bending modes of hydroxyl groups on the surface of Expanded Perlite (mainly Si-OH groups) and the adsorbed water molecules are depicted at 3439 cm<sup>-1</sup> and 1625 cm<sup>-1</sup>, respectively.<sup>48b</sup> The peaks at 1044 cm<sup>-1</sup> and 791 cm<sup>-1</sup> are assigned to Si-O stretching vibrations of Si-O-Si and Si-O-Al, respectively.<sup>50</sup> Moreover, O-Si-O bending vibrations are evident at about 463 cm<sup>-1</sup>.<sup>49</sup> In the spectrum of

**Table 1.** The chemical composition of Expanded Perlite based on XRF analysis.

| Constituent | SiO <sub>2</sub> | Al <sub>2</sub> O <sub>3</sub> | K <sub>2</sub> O | Fe <sub>2</sub> O <sub>3</sub> | Na <sub>2</sub> O | CaO  | MgO  |
|-------------|------------------|--------------------------------|------------------|--------------------------------|-------------------|------|------|
| Percentage  | 75.22            | 12.77                          | 5.18             | 0.74                           | 2.52              | 0.60 | 0.22 |
| Constituent | BaO              | SO <sub>3</sub>                | ZrO <sub>2</sub> | TiO <sub>2</sub>               | Rb <sub>2</sub> O | SrO  | MnO  |
| Percentage  | 0.08             | 0.06                           | 0.01             | 0.11                           | 0.01              | 0.01 | 0.06 |



**Figure 1.** FT-IR spectrum of, (a) Expanded Perlite; (b) EP-PPA and (c) 6th recovered EP-PPA.

EP-PPA, absorption band at about  $1043\text{--}977\text{ cm}^{-1}$  is ascribed to P–O stretching vibration of PPA.<sup>51</sup> Another band at around  $1220\text{--}1135\text{ cm}^{-1}$  is related to stretching vibration of P=O bond.<sup>51</sup> In addition, the P–O–H stretching modes are observed as broad peaks at about  $2441\text{--}2327\text{ cm}^{-1}$ .<sup>51</sup> It is worth to note that the intensity of O–H stretching vibration from  $3300\text{ to }3450\text{ cm}^{-1}$  in the case of EP-PPA is more than that of Expanded Perlite, which clearly indicates the incorporation of PPA on the Expanded Perlite surface.

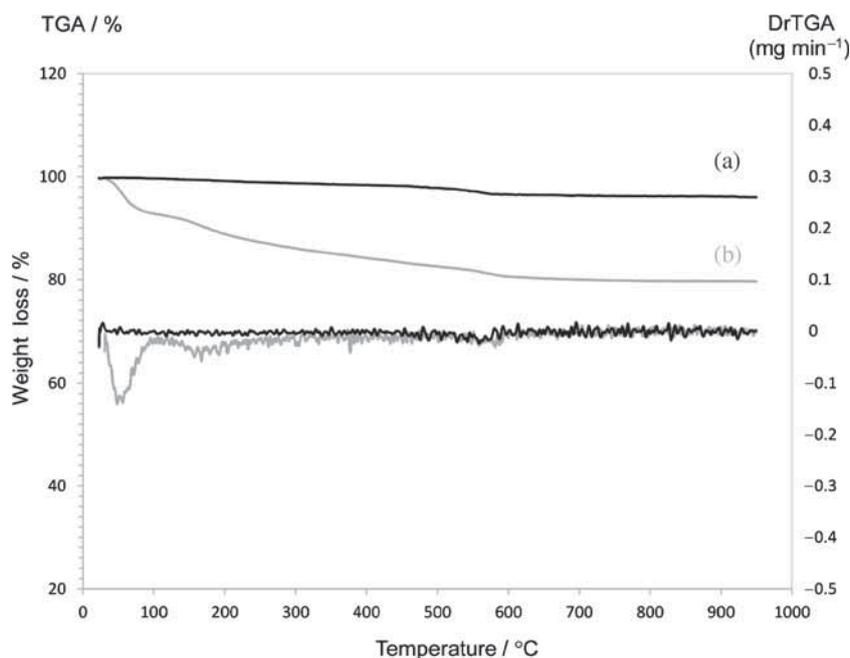
**3.1b TGA of the catalyst:** Thermogravimetric (TG) and differential thermogravimetric (DTG) analysis were used to investigate the thermal stability of the acidic catalyst. TGA thermograms of EP-PPA and bare Expanded Perlite are shown in Figure 2. The results demonstrate that the Expanded Perlite (Figure 2a) showed an initial weight loss, occurring below  $120^\circ\text{C}$  (about 0.5%) which is attributed to the loss of the physically adsorbed water molecules. After that, Expanded Perlite had a steady weight loss at temperature lower than  $600^\circ\text{C}$  (about 3%), which presumably corresponds to the dehydroxylation of Expanded Perlite.<sup>52</sup>

TGA thermogram of EP-PPA (Figure 2b) shows initial weight loss below  $200^\circ\text{C}$ , which is due to the absorbed water molecules on the Expanded Perlite surface. The second step involves the decomposition of PPA, which started after  $200^\circ\text{C}$  and continued up to  $600^\circ\text{C}$ . According to the TGA, the amount of polyphosphoric acid supported on the Expanded Perlite is estimated to be 14%.

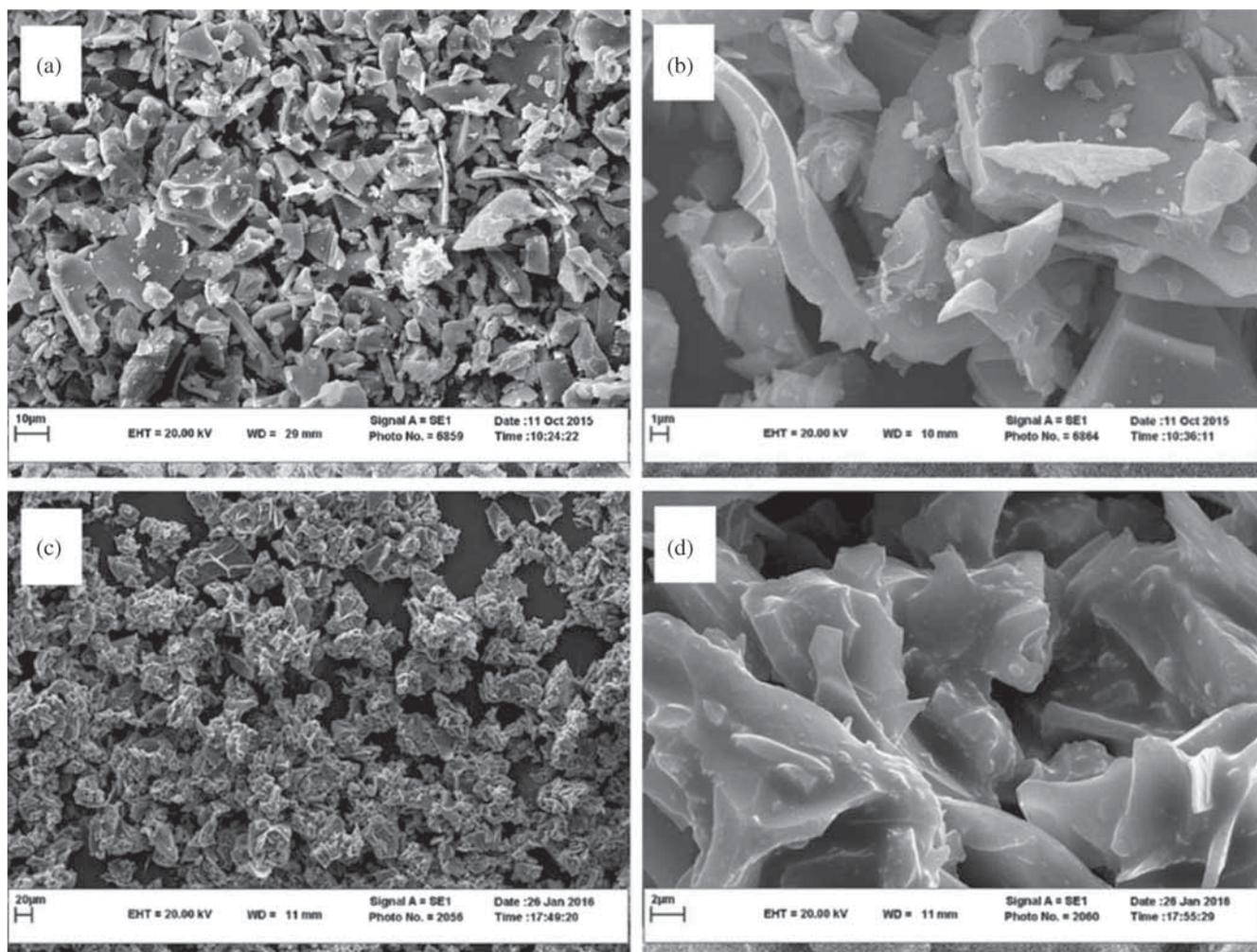
**3.1c pH analysis of the catalyst:** The amount of acidic sites in EP-PPA was determined by back-titration analysis of the catalyst, wherein 100 mg of the catalyst was stirred with sodium hydroxide solution (0.1 N, 15 ml) at room temperature, for 12 h. Afterwards, the suspension was filtered and the filtrate was neutralized using a standard solution of HCl (0.1 M). The required volume of HCl to reach the equivalence point of titration was 7.3 ml. Accordingly, the number of acidic sites for EP-PPA was found to be  $4.7\text{ mmol g}^{-1}$ . Furthermore, on the basis of ICP-OES analysis, the total amount of grafted P was calculated to be  $2.48\text{ mmol g}^{-1}$ , which matched well with the results evaluated by TGA and pH analysis.

**3.1d SEM analysis of the catalyst:** Selected SEM images for the Expanded Perlite and EP-PPA, were used to study the structure and morphology of the catalyst (Figure 3). It is clear that the morphology of Expanded Perlite is a layered porous structure, which remains constant after the immobilization of PPA on its surface.

**3.1e EDX analysis of the catalyst:** Figure 4 depicts the elemental components of Expanded Perlite and EP-PPA by the energy-dispersive X-ray spectroscopy (EDX). As can be seen in Figure 4, the presence of C, O, Na, Al, Si, and K elements are evident in the EDX analysis of both Expanded Perlite and Expanded Perlite-PPA. The existence of P element in the EDX analysis of EP-PPA, confirms the successful immobilization of PPA on the Expanded Perlite.



**Scheme 2.** TG/DTG thermograms of (a) Expanded Perlite and (b) EP-PPA.



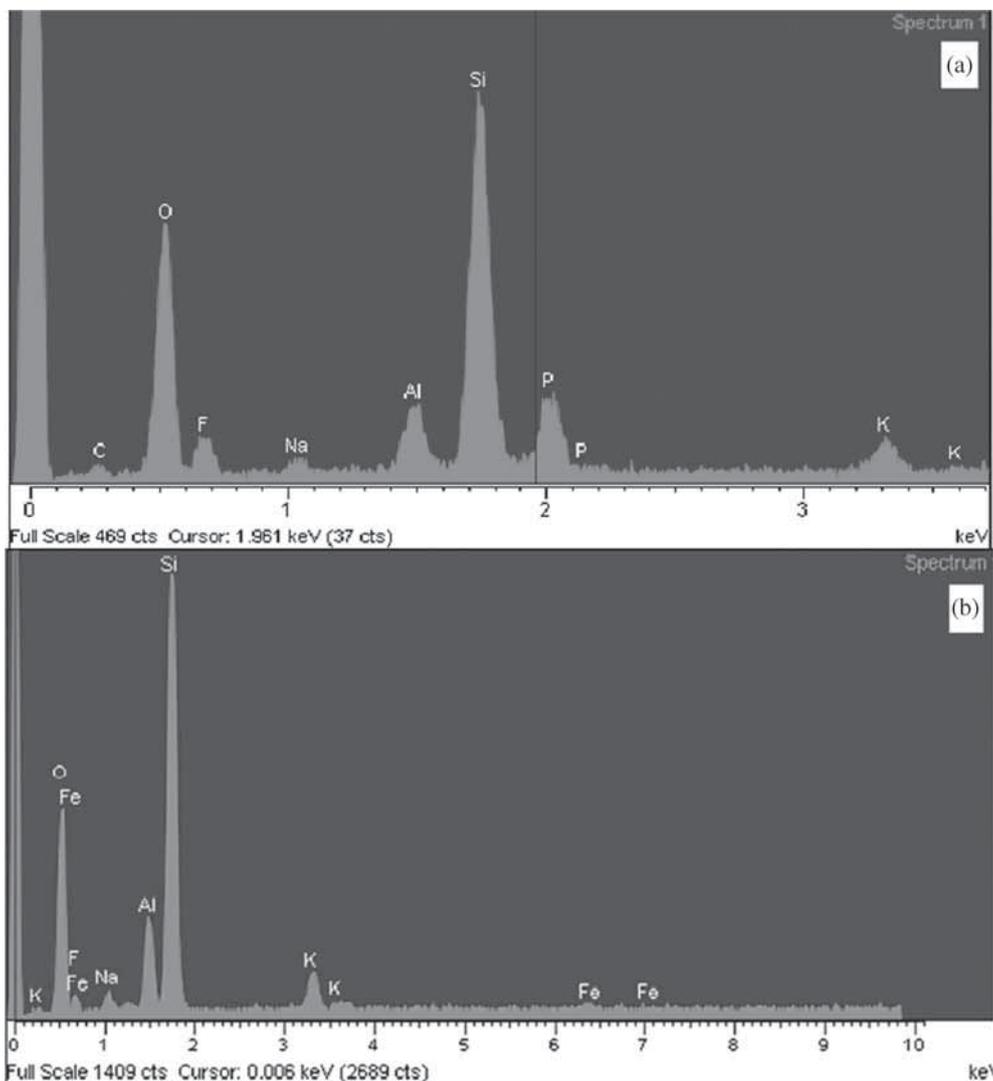
**Scheme 3.** SEM images of Expanded Perlite (a, b) and EP-PPA (c, d).

### 3.2 Catalytic synthesis of aryl/alkylbis(indolyl)methane derivatives

In the present study, a series of bis(indolyl)methanes were prepared by the condensation of indole (**1**), with different carbonyl compounds (**2**) in the presence of EP-PPA, as heterogeneous green catalyst (Scheme 2). The reactions proceeded efficiently to afford the desired bis(indolyl)methanes (**3a–x**) in good to excellent yields.

At the outset, the reaction between benzaldehyde (1 mmol) and indole (2 mmol) was studied as a model reaction from the viewpoint of temperature, solvent, and the amounts of catalyst (Table 2). It is well-known that indole is not active enough in the Friedel-Crafts alkylations, without using any catalyst (Table 2, entry 1). So, choosing a suitable catalyst is crucial for the highly efficient alkylation of indole with benzaldehyde. Therefore, PPA, Expanded Perlite, and EP-PPA were examined on the model reaction at 80°C, under solvent-free condition (Table 2, entries 2–4). It is clear that PPA by itself was not effective for this transformation,

which is certainly related to the sticky state of PPA in the solvent free condition at 80°C, that has disrupted the magnetic stirring during the reaction. However, in the presence of Expanded Perlite and EP-PPA, the corresponding bis(indolyl)methane was obtained in 40% and 70% yields, respectively. As can be seen, EP-PPA afforded an excellent yield of product in a short reaction time, in H<sub>2</sub>O (Table 2, entry 5). To improve the bis(indolyl)methane formation, at the same reaction conditions, the effect of temperature and catalyst amount was studied and we found that the best result was acquired at 60°C by applying 0.04 g of EP-PPA (Table 2, entries 6–9). In an effort to develop still better reaction conditions, the reaction was examined in H<sub>2</sub>O/C<sub>2</sub>H<sub>5</sub>OH (1:1, v:v) and C<sub>2</sub>H<sub>5</sub>OH as solvent (Table 2, entries 10–11). In the presence of these solvents, the reaction was sluggish. As shown in Table 2, H<sub>2</sub>O was found to be the solvent of choice for the preparation of 3,3'-(phenylmethylene)bis(1*H*-indole), in the presence of EP-PPA. Performing the organic reactions in aqueous media has attracted much attention owing to

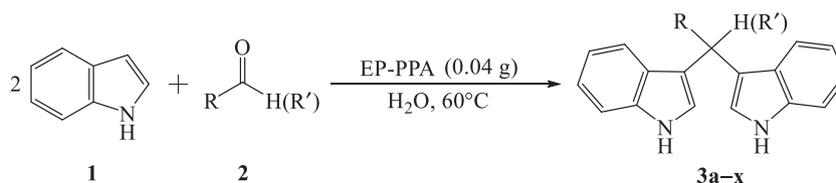


**Scheme 4.** EDX analysis of (a) Expanded Perlite and (b) EP-PPA.

the wonderful properties of water. Considering the significantly safe, cheap, non-toxic and environmentally friendly nature of water compared to organic solvents, it would be one of the best and greenest reaction media in organic synthesis.<sup>53</sup>

In order to emphasize the efficiency of EP-PPA in comparison with PPA and Expanded Perlite in aqueous media, the reaction was performed in the absence of the catalyst and in the presence of PPA and Expanded Perlite (in H<sub>2</sub>O at 60°C) (Table 2, entries 12–14). In all cases, the product yield was not convincing.

With these impressive results in hand, to investigate the scope of this new methodology, the reaction was extended through the condensation of indole with various carbonyl compounds and the results are summarized in Table 3. It can be seen that a wide range of aromatic aldehydes can effectively react with indole to give the corresponding products. However, the nature of substitution on the aromatic ring showed some effect on the reaction progress. Aromatic aldehydes bearing electron-withdrawing groups, provided the desired products in excellent yields within shorter reaction times,



**Scheme 2.** Synthesis of aryl/alkylbis(indolyl)methane derivatives in the presence of EP-PPA.

**Table 2.** Synthesis of 3,3'-(phenylmethylene)bis(1*H*-indole) under different reaction conditions.

| Entry           | Catalyst/g | Solvent   | Temperature/°C | Time/min | Isolated yield/% |
|-----------------|------------|---|----------------|----------|------------------|
| 1               | 0          | —   | 80             | 10/24 h  | 0/0              |
| 2 <sup>a</sup>  | 0.05       | —   | 80             | 30       | 0                |
| 3 <sup>b</sup>  | 0.05       | —   | 80             | 60       | 40               |
| 4               | 0.05       | —   | 80             | 15       | 70               |
| 5               | 0.05       | H <sub>2</sub> O                                  | 80             | 10       | 98               |
| 6               | 0.04       | H <sub>2</sub> O                                  | 80             | 10       | 98               |
| 7               | 0.04       | H <sub>2</sub> O                                  | 70             | 10       | 98               |
| 8               | 0.04       | H <sub>2</sub> O                                  | 60             | 10       | 98               |
| 9               | 0.03       | H <sub>2</sub> O                                  | 60             | 20       | 60               |
| 10              | 0.04       | H <sub>2</sub> O/C <sub>2</sub> H <sub>5</sub> OH | 60             | 15       | 75               |
| 11              | 0.04       | C <sub>2</sub> H <sub>5</sub> OH                  | 60             | 15       | 50               |
| 12              | 0          | H <sub>2</sub> O                                  | 60             | 15       | 0                |
| 13 <sup>c</sup> | 0.05       | H <sub>2</sub> O                                  | 60             | 15       | 40               |
| 14 <sup>d</sup> | 0.05       | H <sub>2</sub> O                                  | 60             | 15       | 35               |

<sup>a</sup>The reaction was performed in the presence of PPA under the solvent-free condition.

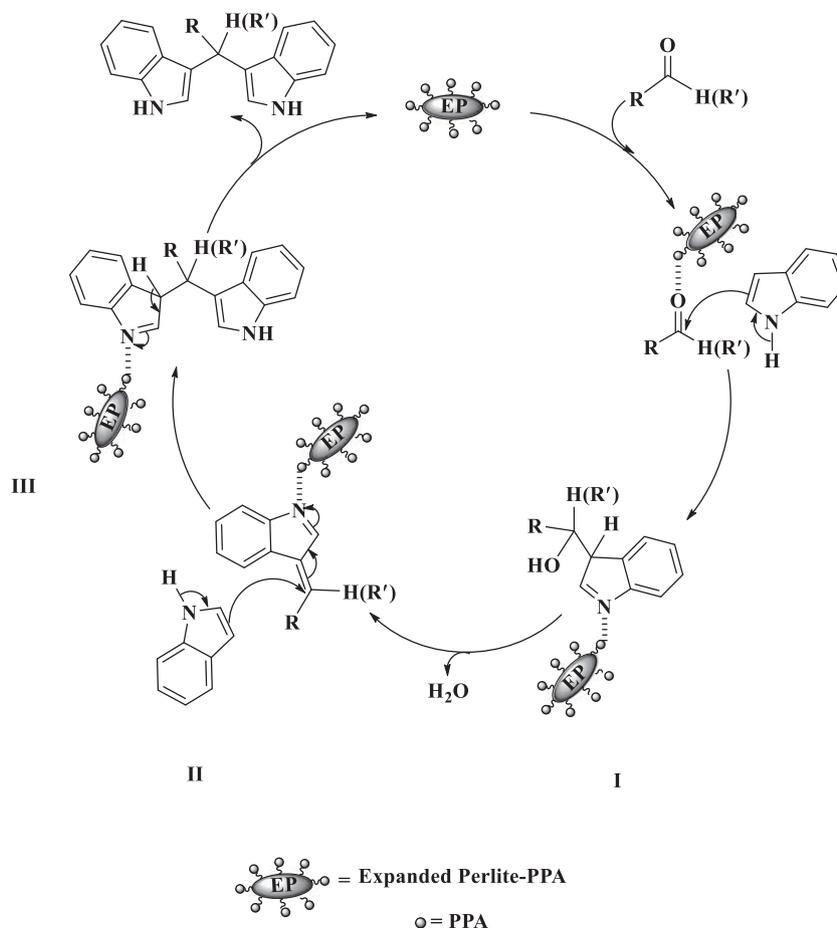
<sup>b</sup>The reaction was performed in the presence of Expanded Perlite under the solvent-free condition.

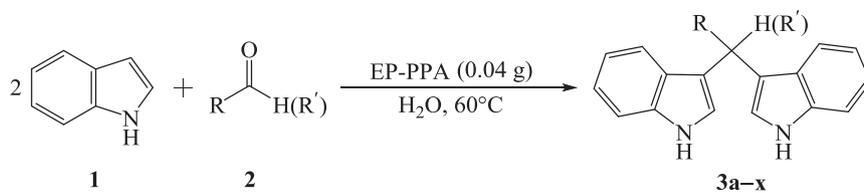
<sup>c</sup>The reaction was performed in the presence of PPA in H<sub>2</sub>O.

<sup>d</sup>The reaction was performed in the presence of Expanded Perlite in H<sub>2</sub>O.

whereas the condensation reaction with aldehydes having electron-donating groups took a longer time, albeit good yield of the products were obtained (Table 3,

entries 1–10 vs. 11–16). Heteroaromatic aldehydes such as thiophene-2-carbaldehyde and pyridine-3-carboxaldehyde were also suitable substrates in this protocol,

**Scheme 3.** Proposed mechanism for the preparation of aryl/alkylbis(indolyl)methanes in the presence of EP-PPA.

**Table 3.** Synthesis of structurally different aryl/alkylbis(indolyl)methanes in the presence of EP-PPA.

| Entry | Carbonyl compound | Product | Time/min | Isolated yield/% |
|-------|-------------------|---------|----------|------------------|
| 1     |                   |         | 10       | 98               |
| 2     |                   |         | 7        | 94               |
| 3     |                   |         | 5        | 96               |
| 4     |                   |         | 7        | 95               |
| 5     |                   |         | 3        | 95               |

Table 3. (Continued)

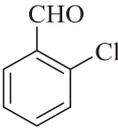
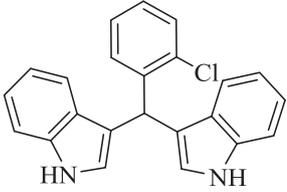
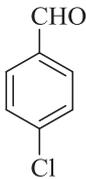
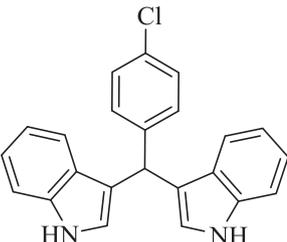
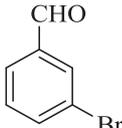
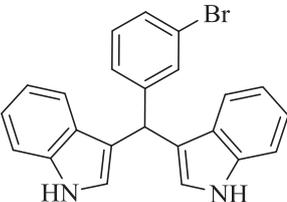
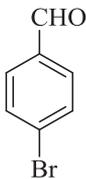
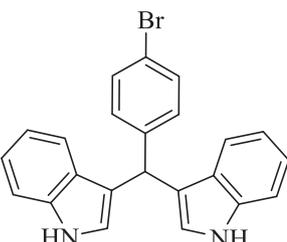
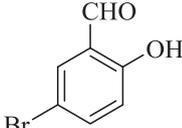
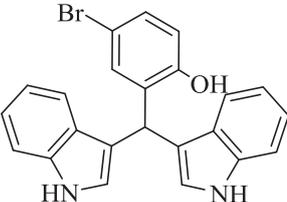
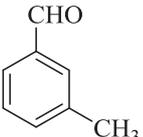
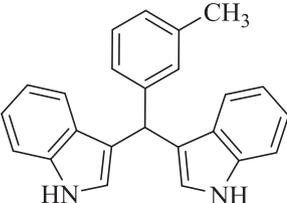
|    |   |   |    |    |
|----|---|---|----|----|
| 6  |    | <br><b>3f</b>   | 5  | 97 |
| 7  |    | <br><b>3g</b>   | 8  | 96 |
| 8  |   | <br><b>3h</b>  | 15 | 87 |
| 9  |  | <br><b>3i</b> | 10 | 90 |
| 10 |  | <br><b>3j</b> | 30 | 90 |
| 11 |  | <br><b>3k</b> | 30 | 82 |

Table 3. (Continued)

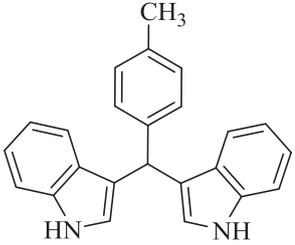
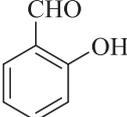
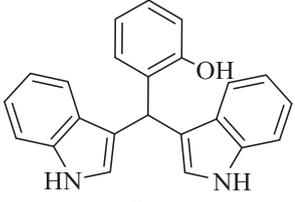
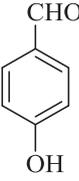
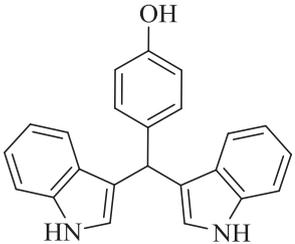
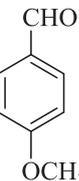
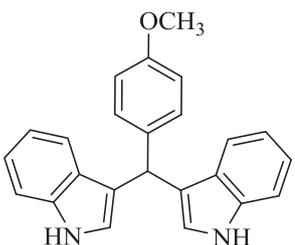
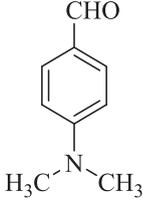
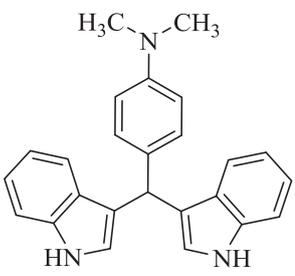
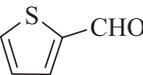
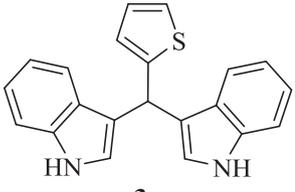
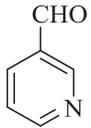
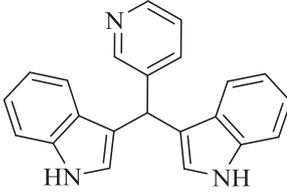
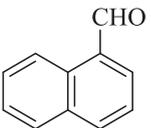
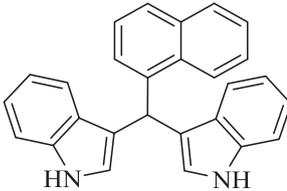
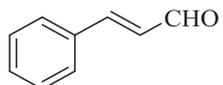
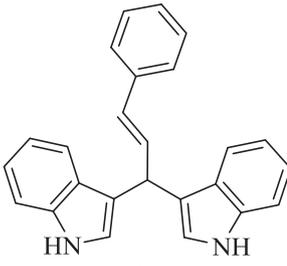
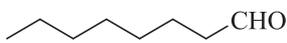
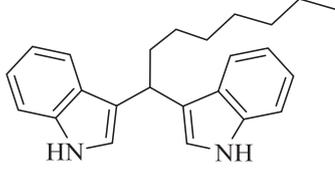
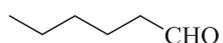
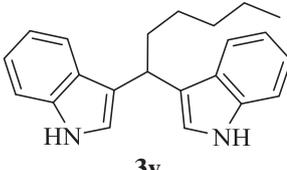
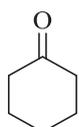
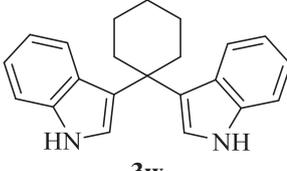
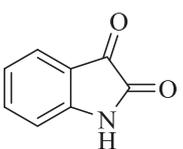
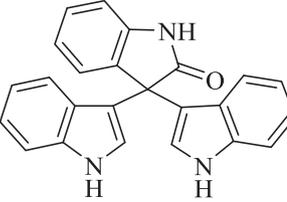
|    |   |   |    |    |
|----|---|---|----|----|
| 12 |    |    | 30 | 87 |
| 13 |    |    | 35 | 86 |
| 14 |   |   | 30 | 88 |
| 15 |  |  | 20 | 89 |
| 16 |  |  | 25 | 91 |
| 17 |  |  | 25 | 78 |

Table 3. (Continued)

|    |   |  |            |       |
|----|---|--|------------|-------|
| 18 |    |     | 15 min/2 h | 50/80 |
| 19 |    |     | 20 min/3 h | 48/72 |
| 20 |   |     | 25         | 75    |
| 21 |  |  | 15         | 70    |
| 22 |  |   | 25         | 70    |
| 23 |  |   | 55         | 60    |
| 24 |  |   | 40         | 65    |

although the corresponding reaction rates were diminished to some extent (Table 3, entries 17 and 18). Likewise, structurally hindered aldehydes (such as 1-naphthaldehyde), cinnamaldehyde and aliphatic aldehydes (such as octanal and hexanal) reacted smoothly with indole to give the corresponding products in moderate yields (Table 3, entries 19–22). Further, we also examined the reaction of some ketones with indole, but the results were far from satisfactory. In the case of cyclohexanone and isatin, the reactions were not completed even after a prolonged reaction time and the best obtained yields of the products were low: 60 and 65%, respectively (Table 3, entries 23, 24). Moreover, the electrophilic substitution reactions of ethyl methyl ketone, 2-heptanone, methyl vinyl ketone, isobutyl methyl ketone, and cyclopentanone with indole were also examined under the optimized condition, but the best obtained range of the products yields were only 10–20%, even after a long period of time (data are not given in Table 3). However, no product was obtained when aryl ketones such as acetophenone and propiophenone were used in this reaction under the same conditions (data are not given in Table 3). It can be concluded that the progress of this transformation was not convincing with ketones, which is most probably due to their lower reactivity as compared to the aldehydes.

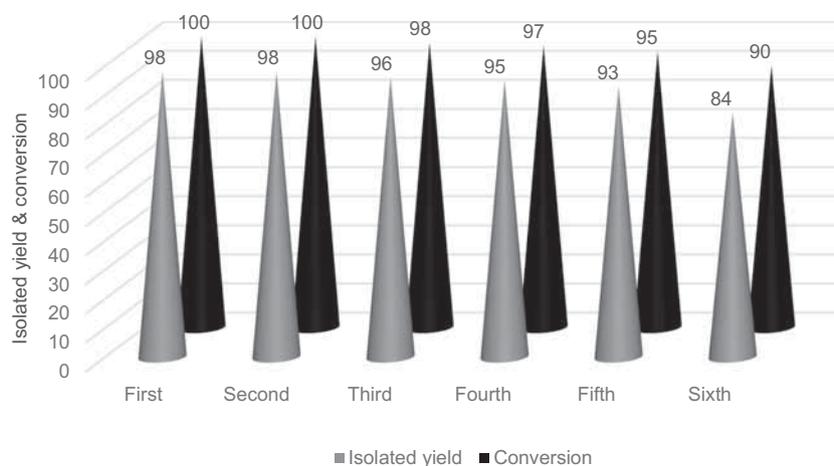
Melting points of the obtained aryl/alkylbis(indolyl) methanes were closely matching with those reported in the literature. The FT-IR spectra of aryl/alkylbis(indolyl) methanes reveal the characteristic absorption bands at 3408–3367 (N–H), 2925–2922 (aliphatic C–H), 1617–1602 and 1455–1454  $\text{cm}^{-1}$  (aromatic C=C). Moreover,  $^1\text{H}$  NMR spectra confirmed the condensation reactions by the appearance of the characteristic signals at  $\delta$  7.9–7.73 (br s, NH), 5.9–5.74 (s, aliphatic C–H) and 7.03–6.54 (s, pyrrole C–H).

A plausible mechanism for the EP-PPA catalyzed synthesis of aryl/alkylbis(indolyl) methanes is shown in Scheme 3. In the initial step, EP-PPA activates the carbonyl group of the carbonyl compound, making it susceptible to attack by indole. Nucleophilic attack of indole to activated carbonyl compound leads to the formation of intermediate **I**, which generates **II** by losing water. Further addition of the second molecule of indole affords intermediate **III**, which then suffers a hydride shift to furnish aryl/alkylbis(indolyl) methanes formation. In the entire mechanism, EP-PPA was regenerated and reused for the consecutive runs.

Recyclability of the EP-PPA catalyst was checked for the model reaction of indole and benzaldehyde. After completion of the reaction, the catalyst was separated by filtration and then washed with deionized water and ethanol 3 times. The separated catalyst was dried at 50°C and utilized for subsequent preparation of 3,3'-(phenylmethylene)bis(1*H*-indole). The procedure was repeated six times without any significant loss of efficiency, as the catalyst remained active even after the sixth run and led to 84% yield of the product (Figure 5).

Furthermore, the FT-IR spectrum for the reused catalyst after 6 runs indicates that all of the characteristic peaks have been well preserved in terms of shape, position, and relative intensity. These results reveal that no significant changes have occurred in the chemical structure of functional groups and the hydrogen bonding network of the catalyst, during the reaction progress and multiple recovery operations.

The superior catalytic activity of EP-PPA compared with some other acidic catalysts for the synthesis of 3,3'-(phenylmethylene)bis(1*H*-indole) was investigated and results are shown in Table 4. Among these catalysts, EP-PPA presents the best performance in this transformation, with respect to shorter reaction time,



**Figure 5.** Synthesis of 3,3'-(phenylmethylene)bis(1*H*-indole) in the presence of reused EP-PPA.

**Table 4.** Comparison between the efficiency of EP-PPA and some other catalysts for the synthesis of 3,3'-(phenylmethylene)bis(1*H*-indole).

| Entry | Catalyst  | Solvent                         | Time/min | Yield/% | Ref.          |
|-------|---|---------------------------------|----------|---------|---------------|
| 1     | Oxalic acid   | H <sub>2</sub> O                | 45       | 96      | 22            |
| 2     | H <sub>6</sub> P <sub>2</sub> W <sub>18</sub> O <sub>62</sub> | –                               | 40       | 96      | 26            |
| 3     | Squaric acid  | H <sub>2</sub> O                | 3/h      | 90      | 54            |
| 4     | HMTAB <sup>a</sup>  | H <sub>2</sub> O                | 2.5/h    | 86      | 55            |
| 5     | Cu <sub>1.5</sub> PMo <sub>12</sub> O <sub>40</sub>           | Ionic liquid                    | 10       | 95      | 56            |
| 6     | Cu(BF <sub>4</sub> ) <sub>2</sub> .SiO <sub>2</sub>           | CH <sub>2</sub> Cl <sub>2</sub> | 30       | 96      | 57            |
| 7     | Cu/MWCNT-GAA@Fe <sub>3</sub> O <sub>4</sub> <sup>b</sup>      | H <sub>2</sub> O                | 40       | 88      | 58            |
| 8     | Br <sub>2</sub>   | H <sub>2</sub> O                | 6/h      | 93      | 59            |
| 9     | EP-PPA  | H <sub>2</sub> O                | 10       | 98      | Present study |

<sup>a</sup>Hexamethylenetetramine-bromine.

<sup>b</sup>Copper nanocatalyst based on magnetic guanidine acetic acid (GAA) functionalized multi-wall carbon nanotube (MWCNT).

lower temperature, and higher yield. In addition, several of the previously reported procedures involved using toxic, non-recyclable, expensive chemicals or difficult and time-consuming synthesis-based catalysts, whereas the current catalyst shows unique advantages including simplification of the catalytic system and its synthesis, besides the application of inexpensive, natural, nontoxic, and availability of precursor to prepare the catalyst. Moreover, the presented green, recyclable and highly efficient heterogeneous catalyst is accompanied with ease of handling and a clean and mild reaction conditions, which are notable features that support this approach in a movement toward the green chemistry.

#### 4. Conclusions

In conclusion, EP-PPA (an inexpensive and eco-friendly catalyst) was found to be an efficient catalyst for the electrophilic substitution reaction of indole with various carbonyl compounds to afford aryl/alkylbis(indolyl) methane derivatives in good to excellent yields. This method is applicable to a wide range of aldehydes and ketones. The merit of this methodology is that it is simple, mild, and efficient with excellent yields of products, shorter reaction times, simple operational procedure for purification of products, and recovery and reuse of the catalyst six times without considerable loss of efficiency. Another important feature of this methodology is using environmentally benign conditions such as applying stoichiometric amounts of reactants and avoidance of hazardous organic solvents. Therefore, we believe that the present methodology will find applications in organic synthesis and green chemistry.

#### Supplementary Information (SI)

Supplementary Information is available at [www.ias.ac.in/chemsci](http://www.ias.ac.in/chemsci).

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