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An efficient and green synthetic protocol for the preparation of bis(indolyl)methanes catalyzed by H₆P₂W₁₈O₆₂·24H₂O, with emphasis on the catalytic proficiency of Wells-Dawson versus Keggin heteropolyacids

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ABSTRACT

A simple, atom economy, and a highly well-organized green protocol has been developed for the synthesis of bis(indolyl)methanes. Wells-Dawson diphosphooctadecatungsticacid ($H_6P_2W_{18}O_{62}\cdot24H_2O$) was employed as a proficient, a highly water tolerant, and green heteropolyacid catalyst for the electrophilic substitution reactions of indole with various aldehydes and ketones to afford the corresponding bis(indolyl)methane derivatives under solvent-free condition. Presumably, discrepancies observed in the reactivity patterns of various heteropolyacids would be explained concerning differences in the acidity, structural diversity, and dissimilarities in the approach of the substrates to the bulk of the heteropolyacid catalysts. It is confirmed that the identity of the catalyst was retained almost completely during the catalytic reaction.

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1. Introduction

There has been a lot of interest to the development of highly efficient transformations for the preparation of organic compounds, as well as, biologically active materials, with potential application in pharmaceutical or agrochemical industries. There is also a need for synthetic chemists to find new, efficient, and strategically acceptable protocols, which are environmentally benign and lead to the greater structural variations with high yields and simple work-up procedures. For these reasons, enormous advances have been made to chemical processes to achieve the ultimate goal of waste-free and energy-efficient synthesis over the last few decades [1].

The reactions of indole have received much interest due to their vast applications in material sciences, occurrence of a number of their derivatives in nature and many applications in the field of pharmaceuticals and agrochemicals [2–4]. Particularly, the substrates including bis(indolyl)methane moieties such as secondary metabolites [5], and marine sponge alkaloids [6], are of remarkable significance. The third position of indole is the preferred site for electrophilic substitution reaction and three-substituted indoles are versatile intermediates for the synthesis of a wide range of

indole compounds [7]. One of the simplest and direct methods for the synthesis of three-substituted indoles is through the reaction of two equivalents of indole with one equivalent of the carbonyl group in the presence of either protic [8] or Lewis acids [9] in excess and under drastic conditions.

To abate the environmental impacts of the pollutions resulting from harmful acids used for the condensation of indole with carbonyl compounds and to improve the efficacy of the protocol, a number of catalytic systems such as NaHSO₄/SiO₂ [10], Zeolites [11], ionic liquids [12], and LiClO₄ [13] have been successfully utilized. Also, rare earth catalysts such as La(OTf)₃ [14], and InCl₃ [15] have been employed for the promotion of this reaction. Nonetheless, it has been reported that many Lewis acids are deactivated or sometimes decomposed by nitrogen atom of indoles [16] and, therefore, may be consumed in more than stoichiometric amount. Moreover, the acids commonly applied are generally toxic catalysts, difficult to handle, and require tedious work-up, along with the use of environmentally harmful organic solvents. Therefore, cheaper Lewis acid catalysts that secure catalytic activity, low toxicity, high stability towards humidity, and air tolerance have been considered to prepare bis(indolyl)alkane derivatives under green solvent-free conditions.

Generally, stronger acidity and greater stability of many Keggin type polyoxoanions in comparison with other structural types of polyoxometalates guarantees their wide applications as

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R= alkyl, halogen, hydroxyl, nitro, methoxy R'= H, methyl

Scheme 1.

homogeneous and heterogeneous catalysts in many organic transformations [17,18]. However, because of the distinct features of the Wells-Dawson heteropolyacids, such as greater selectivity and higher reactivity in some acid catalyzed reactions [19], these compounds had been the target of several research groups during the past decade [20–23].

Solvent-free condensation of indole with carbonyl compounds is scarce in the literature [24]. Due to our interest to explore new catalytic activities for structurally different heteropolyacids [25–34], an efficient carbon–carbon bond formation between indole and carbonyl compounds to achieve various bis-(indolyl)methanes catalyzed by Wells-Dawson diphosphooctadecatungstic acid $H_6P_2W_{18}O_{62}\cdot 24H_2O$ under solvent free condition is introduced (Scheme 1). To the best of our knowledge, this announcement is the first systematic study on the application of Well-Dawson heteropolyacid, $H_6P_2W_{18}O_{62}\cdot 24H_2O$, as a powerful catalyst for this transformation.

 $H_6P_2W_{18}O_{62}.24H_2O$ is prepared as per standard procedure from commercially available cheap starting materials. This compound is stable and tolerant towards humidity and air, having low toxicity and is not corrosive. Handling of $H_6P_2W_{18}O_{62}.24H_2O$ is easy and does not need special precautions.

2. Experimental

Reagents and starting materials were purchased from commercial resources and were used as received. All products were characterized by comparison of their spectral and physical data with those previously reported. Silica gel 60 (70–230 mesh) was performed for column chromatography. Progress of the reactions were monitored by TLC. Infrared spectra were recorded (KBr pellets) on a 8700 Shimadzu Fourier Transform spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Bruker AVANCE 300-MHz instrument using TMS as an internal reference. The catalysts were prepared and characterized according to literature procedures [35–42].

2.1. Preparation of $K_6P_2W_{18}O_{62}$ ·10H₂O and its acidic form $H_6P_2W_{18}O_{62}$ ·24H₂O

Na₂WO₄·2H₂O (100 g) was added to 350 ml of water and the solution was heated to boiling. Then, 150 ml of 85% H₃PO₄ was added and the resulting yellow-green solution was refluxed for 13 h. The solution was cooled, and the product was precipitated by addition of 100 g of solid KCl. The light green precipitate was collected and re-dissolved in a minimum amount of hot water and allowed to crystallize at 5 °C overnight. The typical yield was 70 g after drying at 80 °C under vacuum for several hours. The K₆P₂W₁₈O₆₂ prepared by this way is always a mixture of α and β isomers. The acid H₆P₂W₁₈O₆₂·24H₂O was prepared from an aqueous solution of α/β K₆P₂W₁₈O₆₂ salt by passing of it from a cationic

resin. Characterization of this product with ³¹P- and ¹⁸³W NMR, confirmed that 90–95% of the solid product is in the α -form. ³¹P NMR: α = -12.7 ppm, β = -11 and -11.6 ppm, ¹⁸³W NMR: α = -125 and -170 ppm, β = -112, -131, -171 and -191 ppm.

2.2. General procedure for the preparation of bis-(indolyl)methanes using $H_6P_2W_{18}O_{62}$ ·24 H_2O

A mixture of carbonyl compound (1 mmol), indole (0.234 g, 2 mmol) and the catalyst (2–7 mol%) was stirred at the elevated temperature (120 °C) for the appropriate reaction time. After completion of the reaction, as indicated by TLC, chloroform (3 ml) was added to the reaction mixture and the catalyst was filtered off. Then, silica gel (~1 g) was added to the filtrate, and after evaporation of the solvent, a dark pinkish solid mixture was obtained. Purification of the product was performed by a short column chromatography eluted with ethylacetate/petroleum ether (1/9) to give a pinkish solid product in high yields. Products were known compounds and were identified by means of IR and ¹H NMR spectroscopy and/or comparison of their melting points with those reported in the literature.

3. Results and discussion

In order to optimize the reaction conditions, 2 mol% of $H_6P_2W_{18}O_{62}\cdot 24H_2O$ was employed as catalyst in the condensation of benzaldehyde (1 mmol) and indole (2.1 mmol) in the absence of solvent at 120 °C. A highly sticky orange mixture including the desired bis(3-indolyl)phenylmethane was obtained in a maximum yield of 78% after 15 min. Conducting the same reaction, but without catalyst, led to only a trace amount of the desired product (<5%) after 4 h. Expanding the reaction time to 24 h did not improve the yield of the desired product.

3.1. Effect of heteropolyacid nature, role of structure and acidity on the catalytic activity

To compare the reactivity of $H_6P_2W_{18}O_{62}.24H_2O$ with other indicative familiar heteropolyoxomatalates for the catalytic preparation of bis(indolyl)methane, different heteropolyacids and their salts were inspected in the model reaction (Table 1 and Fig. 1). Almost, all of the introduced acids were strong and have been applied as active catalysts both for acidic and oxidative reactions in different catalytic organic transformations. Heteropolyacid catalysts introduced in Table 1 could be structurally divided into two important subclasses, Keggin and Wells-Dawson. Both structures are formed from close-packed frameworks of MO_6 octahedra. These octahedra are joined by common edges and form the M_3O_{13} subunits. These subunits joined by common vertices and could form T_d (Keggin) or D_3h (Wells-Dawson) symmetry structures. The heteropoly atom in Keggin anion occupied a tetrahedral position and

Synthesis of bis(3-indolyl)phenylmethane in the presence of some Keggin and Wells-Dawson heteropolyoxometalates.

Entry	Catalyst	Time (h)	Yield (%)
1	$H_5PW_{10}V_2O_{40}\cdot xH_2O$	15 min	80
2	$H_3PW_{12}O_{40} \cdot xH_2O$	15 min	83
3	$H_6P_2W_{18}O_{62} \cdot 24H_2O$	15 min	78
4	$H_7SiW_9V_3O_{40}\cdot xH_2O$	20 min	58
5	H ₅ SiW ₉ Mo ₂ VO ₄₀ ·xH ₂ O	45 min	65
6	H ₅ PMo ₁₀ V ₂ O ₄₀ · <i>x</i> H ₂ O	45 min	40
7	$H_3PMo_{12}O_{40} \cdot xH_2O$	2	58
8	$H_3PMo_{12}O_{40} \cdot xH_2O$	4	40 ^b
9	$2Na_2OP_2O_5 \cdot 12WO_3$	2	50
10	$2Na_2OP_2O_5 \cdot 12WO_3$	3	30 ^b
11	K ₆ P ₂ W ₁₈ O ₆₂ ·10H ₂ O	3	15
12	$K_6P_2W_{18}O_{62} \cdot 10H_2O$	4	7 ^b
13	H ₁₄ NaP ₅ W ₃₀ O ₁₁₀ · <i>x</i> H ₂ O	4	15

A mixture of carbonyl compound (1 mmol), indole (2 mmol) and catalyst (2 mol%) was stirred under solvent free condition at 120 °C. At the end of the reaction, the catalyst was separated and the crude product was purified by column chromatography as is explained in Section 2.

^b At room temperature.

is coordinated by μ_3O atoms belonging to four different M_3O_{13} subunits; whereas, in the Wells-Dawson structure, the heteropoly atom is coordinated only to three O_a atoms. As shown in Fig. 1, there are four different positions for oxygen in both structures: O_a atom in the P–O bonds, O_b atoms joining [M_3O_{13}] subunits, O_c atoms in M_3O_{13} subunits and O_d terminal atoms in M=O double bond [43].

Generally, polyoxometalate anions having charge densities considerably lower than those observed in non-coordinative inorganic anions possess low charge density, such as ClO_4^- and NO_3^- . Accordingly, the extensive application of heteropolyacids in acid catalysis organic transformations originates from their very high acidity. The simplest explanation for this abnormally high acid strength is based on the fact that the negative charge of the anion is smeared over the numerous (36 in Keggin and 56 in Wells-Dawson structure) external oxygen atoms and the attraction of protons is very much weaker than, for example, in the case of sulphuric acid. It has been demonstrated that, the MO₆ octahedra, which bearing one terminal oxygen O_d, are strongly distorted. Hence, the partial negative charges residing on the outermost terminal oxide ligands, M=O_d double bond, are generally lower than those on the bridging oxide anions embedded within the clusters. Therefore, the cation is shifted towards the exterior of the anion. This shift results in the formation of a layer of oxygen atoms, strongly polarized (due to $d\pi$ - $p\pi$ interactions) towards the inside of the polyanion. Such



Fig. 1. Keggin (a) and Wells-Dawson (b) structures [43].

polarized oxygen atoms are weakly basic and weakly attract protons [43–46].

After a concise review on the acidic characteristics of heteropolyacids, it is the time to discuss the relevance of heteropolyacid strength to the efficiency of the catalytic condensation of indole with carbonyl group to afford the corresponding three-substituted indole. $H_6P_2W_{18}O_{62}\cdot24H_2O$, as a strong acid ($pK_1 = 4.39$), behaved as the most familiar heteropolyacid, $H_3PW_{12}O_{40}$ ($pK_1 = 4.7$), and was capable of converting indole to bis(indolyl)methane with 78% yield after 15 min. A little less efficiency of $H_6P_2W_{18}O_{62}\cdot24H_2O$ compared to $H_3PW_{12}O_{40}$ could not be explained regarding more acidity of $H_6P_2W_{18}O_{62}\cdot24H_2O$ [47]. Furthermore, despite a little difference between the acidity of $H_3PW_{12}O_{40}$ and $H_3PM_{012}O_{40}$ ($pK_1 = 4.68$), both with Keggin structure, the molybdenum analogue was distinctly less efficient than $H_3PW_{12}O_{40}$ and produced 58% of conversion after long time 2 h.

Another indicator which confirmed the present protocol is not totally acid catalyzed, is based on the high catalytic activity of vanadium substituted mixed metal heteropolyacids. Vanadium substituted mixed metal heteropolyacids were comparatively effective and furnished 40-65% of products in 20-45 min. Findings have shown that the acidity of heteropolyacids diminishes with replacement of Mo^{VI} or W^{VI} atoms by V^{V} [46,48,49]. Although, $H_5PW_{10}V_2O_{40}$ is considerably a weaker acid than $H_3PW_{12}O_{40}$, this compound behaved as efficient as H₃PW₁₂O₄₀ and furnished 80% of conversion after 15 min. Albeit H₅PMo₁₀V₂O₄₀ is only slightly less acidic than $H_5PW_{10}V_2O_{40}$ [45], the former was completely ineffectual and furnished 40% of conversion after 45 min. Surprisingly, substitution of two vanadium atoms in $H_3PMo_{12}O_{40}$ to obtain less acidic H₅PMo₁₀V₂O₄₀, did not change the Keggin structure, whereas, an enhancement (>three times) was observed in the catalytic activity of the later. H₅PMo₁₀V₂O₄₀ led to 40% conversion after 45 min; whereas, in the case of H₃PMo₁₂O₄₀ the corresponding conversion was reached to 58% after 120 min.

Substitution of P^V with Si^{IV} in the vanadium substituted H₅PW₁₀V₂O₄₀, afforded the less acidic H₇SiW₉V₃O₄₀ heteropolyacid [44]. Anyhow, H₇SiW₉V₃O₄₀ showed comparatively good catalytic activity and produced 58% of product after 20 min. H₅SiW₉Mo₂VO₄₀ as a mixed metal Si-substituted Keggin type heteropolyacid, showed good catalytic activity and produced 65% of bis(indolyl)methane after 45 min. Sodium phosphotungstate dibasic hydrate, $2Na_2OP_2O_5 \cdot 12WO_3$, potassium salt K₆P₂W₁₈O₆₂, and preyssler H₁₄NaP₅W₃₀O₁₁₀ were unproductive in this catalytic system and provided only (15–50%) of the desired product after long time (2–4 h).

Several studies have shown that the acidity of heteropolyacids slightly is affected by their structural composition. Many heteropolyacids, in particular those possessing the Keggin structure, are close to the spherical shape. According to the electrostatic laws of Marcus, this structural geometry affects the acid strength of heteropolyacids [48,49]. Hence, it is expected that heteropolyacids with Keggin structure should be intrinsically stronger acids than Wells-Dawson and Preyssler types. Higher efficiency of the Keggin heteropolyacids than Preyssler types in the synthesis of bis(indolyl)methanes would be explained considering Marcus postulation.

As mentioned above, $H_6P_2W_{18}O_{62}.24H_2O$ showed higher activity than the other structurally different heteropolyacids in this catalytic system (Fig. 2). This behavior could be demonstrated regarding the approach of substrate absorption into the bulk of the heteropolyacid. This trend differs from the activity series obtained for many catalytic systems using heteropolyacid as catalyst under liquid-phase conditions. It seems that polar reactant molecules penetrate into the bulk of the heteropolyacid crystallites, then, after chemical transformation, the products release to the outside of the solid bulk. So, the diffusion and the reaction in the bulk of



Fig. 2. Comparing the catalytic activity of different Keggin and Wells-Dawson heteropolyoxometalates in the preparation of bis(indolyl)phenylmethane. $H_6P_2W_{18}O_{62}$ bearing $24H_2O$ and other catalysts have xH_2O molecules.



Scheme 2. Pseudo-liquid catalysis on the bulk of the heteropolyacid crystallites.

the heteropolyacid are faster than the reaction occurring on the external surface of the catalyst and occurrence of the catalytic reaction in the pseudo liquid phase would be a crucial step [43]. In this case, solid heteropolyacid behaves in some respects like liquid. According to the polarity and size of the reactants in the preparation of the desired products by the mediation of Keggin and Wells-Dawson heteropolyacids under solvent free condition, the bulk type I reactions (or pseudo-liquid catalysis) proposed by Misono would be followed (Scheme 2) [50].



Fig. 3. Effect of $H_6P_2W_{18}O_{62}\cdot 24H_2O$ (mol%) on the preparation of bis(indolyl)phenylmethane.

3.2. Effect of catalyst mol%

Expectedly, the catalytic system should be influenced by various reaction parameters, such as the kind and amount of the employed catalyst, solvent system, and temperature. To establish the optimal reaction conditions, a set of experiments varying the amount of $H_6P_2W_{18}O_{62}$ ·24 H_2O , changing quantities of indole with respect to aromatic aldehyde, and effect of temperature were taken into account.

At first, different mol% of $H_6P_2W_{18}O_{62}\cdot 24H_2O$ were examined as described in Fig. 3. As mentioned before, the synthetic route is drastically dependent on the presence of the catalyst and very low conversion was attained in the absence of $H_6P_2W_{18}O_{62}\cdot 24H_2O$. The optimum catalyst mol% was found to be 2. More or fewer amount of catalyst resulted in a pronounced decrease in conversion. $H_6P_2W_{18}O_{62}\cdot 24H_2O$ supplied 53 and 40% of conversion, respectively, after 60 min (for 1 mol%) and 40 min (for 10 mol%).

3.3. Comparing the catalytic activity of heteropolyacids with other catalysts

The superiority of the present method over reported methodologies can be seen by comparing our results with those reported previously (Table 2). The reaction of benzaldehyde with indole for the synthesis of bis(3-indolyl)methane was selected as a model reaction and the comparison was in terms of mol% of the catalysts, temperature, reaction time, and percentage yields. Although, other introduced additives catalyzed the reaction, even though at room temperature, they required longer reaction times and higher mol% of catalyst. The present methodology utilized a low amount (2 mol%) of Keggin and/or Wells-Dawson heteropolyacid under solvent free condition and distinctly required shorter reaction time.

Table 2

Comparison of the catalytic efficiency of H₆P₂W₁₈O₆₂·24H₂O and H₅PW₁₀V₂O₄₀ with some different catalysts reported for the reaction of indole with benzaldehyde.

Entry	Catalyst	Catalyst (mol%)	Time (min)	Yield (%)	Condition	Ref.
20	$H_6P_2W_{18}O_{62} \cdot 24H_2O$	2	15	>80	Solvent free/120 °C	This work
	$H_5PW_{10}V_2O_{40}\cdot xH_2O$					
21	ZrOCl ₂ ·8H ₂ O	5	40	84	Solvent free/50 °C	[24]
22	TiO ₂ (nano)	10	12 h	64	$CH_2Cl_2/r.t$	[51]
23	LiClO ₄	10	5 h	90	CH₃CN/r.t	[52]
24	La(PFO) ₃	5	30	90	CH ₃ CN/r.t	[53]
25	Ln(OTF) ₃	5	25	71	CH ₃ CN/r.t	[54]

Effect of different solvents on the synthesis of bis(indolyl)methane in the presence of $H_6P_2W_{18}O_{62}$ ·24 H_2O (2 mol%) at 60 °C.

Entry	Solvent	Boiling point	Time (h)	Yield (%)
26	H ₂ O	100	3	19
27	CH ₃ CN	81	1	64
28	CH ₃ OH	65	0.7	51
29	C_2H_5OH	78	1.5	56
30	CHCl ₃	61	1	50
31	-	-	0.7	68

Reaction condition is described in Table 1 legend.

Table 4

Effect of temperature on the synthesis of bis(indolyl)methane in the presence of $H_6P_2W_{18}O_{62}\cdot24H_2O$ (2 mol%) under solvent free condition.

Entry	Time (min)	Yield (%)	Temperature (°C)
32	60	50	25
33	45	65	50
34	15	78	120
35	10	82	140

Reaction condition is described below Table 1 legend.

3.4. Effect of solvent

Despite the fact that, this methodology is under solvent free conditions even though the effect of different solvents such as water, ethanol, methanol, and chloroform were studied on the model reaction and the obtained results were compared with solvent free case (Table 3). This study was carried out at a fixed temperature, 60 °C, in all cases. Obviously, the solvent free approach was found to be more effective than the solvent system. Almost all reactions in the introduced solvents were less efficient than the solvent free case, considering the reaction time and the obtained yield.

3.5. Effect of temperature

The effect of temperature on the synthesis of bis(indolyl)methane in the presence of H₆P₂W₁₈O₆₂·24H₂O (2 mol%) under solvent free condition was also studied (Table 4). Results revealed that yield% was enhanced by increasing reaction temperature from 25 to 140 °C. Even though, the product yield at 140 °C was slightly higher than 120 °C, considering technical limitations, the lower temperature was selected as the best temperature for all the reactions. Additionally, it should be mentioned that besides the type of the catalyst, the catalytic solvent free system is generally more effective at 120 °C than in room temperature. The reactivity pattern obtained for K₆P₂W₁₈O₆₂, 2Na₂OP₂O₅·12WO₃, and $H_3PMo_{12}O_{40}$ illustrated that the conversion% was diminished to ~half amount in room temperature in comparison with the elevated temperature.

3.6. Condensation of different carbonyl compounds with indole

This methodology is effective for a series of structurally diverse aldehydes bearing electron withdrawing or donating substituents on phenyl ring and provides substituted bis(indolyl)methanes in good to excellent yields (Table 5). A series of aromatic and aliphatic aldehydes, along with some simple ketones, underwent electrophilic substitution reaction with indole smoothly to afford a wide range of products. This method is equally effective for aldehydes bearing electron withdrawing or donating substituents in the aromatic rings. Furthermore, acid sensitive aldehydes, such as salysilaldehyde, worked well without any decomposition or polymerization under the reported reaction conditions. Aliphatic aldehydes also achieved their corresponding bis(indolyl)methanes satisfactorily under these conditions, but needed longer times. Moreover, simple ketones like cyclohexanone, cyclohepentanone, and 2-butanone reacted in the same manner albeit with longer reaction time. The reaction of indole with acetophenone in the presence of $H_6P_2W_{18}O_{62}$ ·24 H_2O was not successful and most of the starting materials remained intact after a prolonged reaction time.

3.7. The excellence of $H_6P_2W_{18}O_{62}$ ·24 H_2O over some well-known metal/non-metal oxides

Table 6 tabulates the excellence of H₆P₂W₁₈O₆₂·24H₂O in comparison with other catalysts used in the similar reaction. Evidently, the required mole ratio for most of the introduced catalysts was >2% and the reaction times were much longer (1-12h). Silicon dioxide family behaved as effective catalysts in the synthesis of bis(indolyl)methane. 0.1 g, ~20 mol%, of MCM-41 and MCM-48, with hexagonal and cubic structures, respectively, disclosed very good activity and produced 60-70% of conversion under solvent free conditions after 25 min. While, the same amount of bulk SiO₂ (silica gel 60, 70-230 mesh) provided only 35% of product under the same condition after 35 min. Higher amounts of the bulk silicon dioxide (50 mol%) was needed to obtain high conversion (85%) after 25 min. It is noteworthy that this catalyst was effective in room temperature and 50 mol% of SiO₂ provided 84% of conversion in acetonitrile at room temperature after 40 min. It seems that crystalline structure, pore size, and surface area of silicon dioxide strongly affected its catalytic activity. Proficiency of titanium dioxide was also investigated in comparison with other catalysts introduced in Table 6. 50 mol% of TiO₂ led to 45% of conversion under solvent free condition after 40 min. Zirconium dioxide, potassium dihydrogenphosphate, zinc oxide, and copper oxide showed low activity in this catalytic system and did not give an appreciable amount of product even after long times.

3.8. Chemoselectivity of the protocol

This methodology is also highly chemoselective for aldehydes. For example, when a 1:1 mixture of benzaldehyde and acetophenone was allowed to react with indole in the presence of $H_6P_2W_{18}O_{62}$ ·24 H_2O , it was found that only phenyl-3,3bis(indolyl)methane was obtained, while acetophenone was intact under the reported reaction condition (Scheme 3). This reaction was clean and the corresponding product was obtained in high yield without formation of any side reactions such as N-alkylation.

The catalytic system is capable of selective condensation of 1,4-dicarboxaldehydebenzene, as a di-aldehyde, to the corresponding bis-(indolyl)methane via controlling the molar ratio of indole (Scheme 4). The results showed that (1) would be achieved in the presence of 2 equivalents of indole; whereas, treatment of 4 equivalents of indole with terephthaldialdehyde led selectively to appearance of the corresponding di [bis-(indolyl)methane] (2).

3.9. Reaction pathway

A reasonable pathway for the reaction of indole with carbonyl compounds in the presence of $H_6P_2W_{18}O_{62}\cdot 24H_2O$ is presented by Scheme 5. The reaction between aldehyde and indole most probably takes place via the formation of indolyl carbinol which further converts to azafulvenium salt. The produced azafulvenium salt, as an electrophile, can undergo further addition with the second indole molecule giving the corresponding bis(indolyl)methane derivative [64,65]. It may be assumed that polar benzaldehyde molecule could penetrate the bulk of $H_6P_2W_{18}O_{62}\cdot 24H_2O$ crystallites and catalytic reaction occurs in the pseudoliquid phase.

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Synthesis of different bis(indolyl)methanes in the presence of H₆P₂W₁₈O₆₂·24H₂O (2 mol%) under solvent free condition.

Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P.	Ref.
1			15	78	149–150	[55]
2	-C OMe	MeO H MeO H H MeO H C	20	87	139–141	[56]
3	MeO H	HO HO C	20	91	195 (Dec.)	[57]
4		HO H	35	71	122-123	[58]
5			10	91	98 (clear melt.)	[57]
6	H NO ₂	D ₂ N H	15	93	139-141	[59]
7	$O_2N - \begin{pmatrix} & H \\ & & \\ & & \end{pmatrix} - C \begin{pmatrix} H \\ & & \\ & & \\ & & 0 \end{pmatrix}$	VC NH H	15	86	218-220	[57]

Table 5 (Continued)

Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P.	Ref.
		O ₂ N C N				
8	NO_2 O	N H Br	15	93	220–222	[60]
9	$ \begin{array}{c} $	CH ₃	15	90	189–191	This work
10	H_3C C	Me CH ₃	360	10	189–190	[45]
11	H ₃ C		300	20	195–197	[59]
12			35	70	76-77	[61]
13		CI NH H H H H	20	75	108–109	[59]
14			45	67	95–97	[59]

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Table 5 (Con	ntinued)					
Entry	Aldehyde	Product	Time (min)	Yield (%)	M.P.	Ref.
15			120	60	118-120	[62]
16		E _t E _t	180	50	116-119	This work
17	O II E t E t E t	N N H ⁿ Pr	160	40	129-130	This work
18	CH ₃ CH ₂ CH ₂ CH ₂ C	H H H ₃ C-H ₂ C	60	70	118-119	This work
19	CH ₃ CH ₂ CH ₃	CH ₃ H	120	50	198-200	This work
20	// СН ₃ С Н		85	55	92-93	[63]

Reaction condition is described below Table 1 legend. Products were identified by means of IR and ¹H NMR spectroscopy and/or comparison of their melting points with those reported in the literature.





Scheme 4.

3.10. Characterization and reusability of $H_6P_2W_{18}O_{62}$ ·24 H_2O

FTIR spectroscopy was employed for the confirmation of the stabilization of Wells-Dawson catalyst (Fig. 4). $H_6P_2W_{18}O_{62}\cdot 24H_2O$ exhibited four major bands at 1093, 965, 912 and 776 cm⁻¹

which are assigned to stretching absorption modes of oxygen atom bonded to tungsten and phosphorous (W···O), (P–O) and (W–O–W). The band at 1093 cm⁻¹ assigned to the stretching frequency of the PO₄ tetrahedron and, by comparison with the Keggin structure, the band at 965 cm⁻¹ corresponded to the W···O



Scheme 5. Proposed reaction pathway for the condensation of indole with aldehyde by the mediation of $H_6P_2W_{18}O_{62}$ ·24H₂O.

Entry	Catalyst	mol%	Conditio	Condition		Yield
			CH₃CN RT	Solvent free 120°C	(min)	(%)
56	-	-		*	240	<5
57	$H_6P_2W_{18}O_{62}$. 24 H_2O	2		*	15	78
58	ZrO ₂	50	*		240	<5
59	ZrO ₂	50		*	180	7
60	SiO ₂	60	*		40	84
61	SiO ₂	20		*	35	35
62	SiO ₂	60		*	25	85
63	MCM-41	20		*	25	70
64	MCM-48	20		*	25	60
65	ZnO	50	*		120	7
66	ZnO	50		*	90	20
67	TiO ₂	50	*		90	25
68	TiO ₂	50		*	40	45
69	KH ₂ PO ₄	50	*		360	<5
70	KH ₂ PO ₄	50		*	180	30
71	CuO (nano)	4 mg		*	120	<5

Reaction condition is described below Table 1 legend.

(terminal bonds). The vibration bands at 912 and 776 cm⁻¹ were assigned to the 'inter' and 'intra' W–O–W bridges, respectively [66].

In order to prove the reusability of $H_6P_2W_{18}O_{62}$ ·24 H_2O , it was separated from the reaction mixture and washed with chloroform. The catalyst was dried in vacuum and reused for fresh lot of benzaldehyde (2 mmol) with indole (4 mmol). The catalyst was found to be reusable for five cycles without significant loss in activity. Reusability studies showed that the activity of the exhausted catalyst was almost similar to the new one, demonstrating the efficiency of the catalyst (Fig. 5).

The FTIR spectrum of the recovered $H_6P_2W_{18}O_{62}.24H_2O$ after the 5th run confirmed any significant change in the Wells-Dawson structure of the catalyst (Fig. 4, bottom). Therefore, the identity of the catalyst was retained almost completely during the catalytic reaction. Reusability studies showed that the activity of the spent catalyst was almost the same as the new one, clearly demonstrating the efficiency of the catalyst.

3.11. Spectral data for selected bis(indolyl)methanes [67,68]

Bis(indolyl)phenylmethane. ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 5.91 (s, 1H, CH), 6.68 (s, 2H), 7.10 (t, *J* = 7.3 Hz, 2H, arom), 7.22 (t, *J* = 7.3 Hz, 2H, arom), 7.23 (t, *J* = 7.2 Hz, 1H, arom), 7.30–7.40 (m, 2H, arom), 7.35–7.45 (m, 4H, arom), 7.41 (d, *J* = 7.9 Hz, 2H, arom), 7.90 (s, br, 2H, NH). ¹³C NMR, δ(ppm): 40.6, 111.4, 119.7, 120.2, 120.4, 122.4, 124.1, 126.6, 127.5, 128.6, 129.2, 137.1, and 144.4. IR (KBr, cm⁻¹) υ_{max} : 760, 820, 890, 960, 1080, 1200, 1410, 1640, 2380, 2880, 2900, 3340.

Bis(indolyl)-4-nitrophenylmethane. ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 5.92 (s, 1H, CH), 6.63 (s, 2H), 6.91 (t, *J* = 7.3 Hz, 2H, arom), 7.08 (t, *J* = 7.3 Hz, 2H, arom), 7.25 (d, *J* = 7.9 Hz, 2H, arom), 7.32 (d, *J* = 8.1 Hz, 2H, arom), 7.44 (d, *J* = 8.6 Hz, 2H, arom), 8.04 (d, *J* = 8.6 Hz, 2H, arom), 9.31 (s, br, 2H, NH). ¹³C NMR, δ(ppm): 40.5, 111.8, 117.8, 119.4, 119.7, 122.1, 123.8, 124.4, 127.0, 129.9, 137.3, 146.7, 152.8; IR (KBr, cm⁻¹) υ_{max} : 736, 1086, 1343, 1416, 1457, 1506, 1636, 3447.

Bis(indolyl)-4-*chlorophenylmethane*. ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 5.82 (s, 1H), 6.54 (brs, 2H), 7.0 (t, 2H), 7.15 (t, 2H), 7.25–7.35 (m, 8H), 7.81 (brs, 2H, NH); ¹³C NMR, δ(ppm): 39.4, 111.2, 129.2, 129.4, 129.8, 122.0, 123.2, 126.4, 128.0, 130.0, 131.4, 136.2, 142.5; IR (KBr, cm⁻¹) υ_{max} : 667, 761, 856, 1012, 1040, 1091, 1124, 1216, 1338, 1416, 1455, 1486, 1518, 1616, 1726, 2853, 2925, 3011, 3056, 3413.





Fig. 4. FTIR spectrum of the new (up) and the recovered (bottom) Wells-Dawson heteropolyacid $H_6P_2W_{18}O_{62}$ ·24 H_2O .



Fig. 5. Studying reusability of $H_6P_2W_{18}O_{62}\cdot 24H_2O$ in the reaction of benzaldehyde with indole.

Bis(indolyl)-2,6-dichlorophenylmethane. ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 6.58 (s, 1 H), 6.68 (s, 2 H), 6.86-7.03 (m, 7 H), 7.09 (d, 2 H, *I*=7.8 Hz), 7.41 (d, 2 H, *I*=7.8 Hz), 7.71 (brs, NH); ¹³C NMR, δ(ppm): 37.2, 110.7, 114.4, 119.3, 119.6, 121.4, 121.8, 124.7, 127.2, 128.2, 128.6, 136.3, 138.7.

Bis(indolyl)-2-nitrophenylmethane. ¹H NMR (CDCl₃, 300 MHz), δ(ppm): 6.12 (s, 1 H), 6.91 (s, 2 H), 7.08–7.17 (m, 4 H), 7.29 (d, 2 H, *J* = 7.8 Hz), 7.47 (d, 2 H, *J* = 7.9 Hz), 7.57–7.66 (m, 2H), 7.79–7.90 (m, 2H), 8.21 (d, 2H, *J* = 8.6 Hz).

Bis(indolyl)-(1-Methyl)methanediyl. ¹H NMR (CDCl₃, 300 MHz), δ (ppm): δ 1.91 (d, 3H, *J* = 6.8 Hz), 4.50 (m, 1H), 6.85 (t, 2H, *J* = 6.8 Hz), 7.03 (m, 2H), 7.07 (t, 2H, J=8 Hz), 7.25 (d, 2H, J=8 Hz), 7.40 (d, 2H, I = 8 Hz), 7.84 (brs, 2H); IR (KBr, cm⁻¹) v_{max} : 3399, 3389, 2958.

Bis(indolyl)-Cyclohexanediyl. ¹H NMR (CDCl₃, 300 MHz), δ (ppm): δ 1.61 (m, 6H), 2.54 (m, 4H), 3.25 (m, 1H), 4.60 (s, 1H), 6.89 (t, 2H, I = 7.2 Hz, 7.07 (m, 4H), 7.29 (d, 2H, I = 8.1 Hz), 7.55 (d, 2H, I = 8.1 Hz), 7.92 (brs, 2H); IR (KBr, cm⁻¹) v_{max} : 3450, 3030, 2929, 1658, 1550, 1461,740.

Bis(indolyl)-3,4-dimethoxyphenylmethane. ¹H NMR (CDCl₃, 300 MHz), δ(ppm): δ 3.76 (s, 3H), 3.85 (s, 3H), 5.83 (s, 1H), 6.65 (d, 2H), 6.78 (d, 2H), 7.0 (t, 3H), 7.17 (t, 2H), 7.29-7.43 (m, 4H), 7.91 (bs, NH, 2H); IR (KBr, cm⁻¹) v_{max} : 3480, 3020, 1604, 1512, 1456, 1418, 1336, 1216, 1091, 1033, 759.

 ^{1}H *Bis(indolyl)-2-hydroxyphenylmethane.* NMR (CDCl₃. 300 MHz), δ(ppm): δ 3.79 (s, 1H), 5.83 (s, 1H), 6.67 (d, 2H), 6.81 (d, 2H), 7.01 (t, J=7.2 Hz, 2H), 7.28-7.46 (m, 6H), 7.92 (br, s, NH, 2H); (KBr, cm⁻¹) v_{max} : 3485, 3021, 2848, 1616, 1517, 1465, 1411, 1326, 1221, 1094.

¹H NMR (CDCl₃, Bis(indolyl)-2-methoxylphenylmethane. 90 MHz), δ(ppm): 3.82 (s, 3H), 6.32 (s, 1H), 6.61 (s, 2H), 6.81–7.40 (m, ArH, 12H), 7.80 (br s, NH, 2H); (KBr, cm^{-1}) v_{max} : 3408, 3056, 2932, 1597, 1486, 1450, 1335, 1102, 745.

Bis(indolyl)-3-nitrophenylmethane. ¹H NMR (CDCl₃, 90 MHz), δ (ppm): 8.46 (br s, 2H), 7.02-7.87 (m, 12H), 6.61 (s, 2H), 5.34 (s, 1H).

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