

# Bulk and Supported Tungstophosphoric Acid as Friendly, Efficient, Recyclable Catalysts for the Synthesis of Bis-indolylmethanes under Solvent-Free Conditions

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**ABSTRACT:** *The treatment of indole with structurally diverse aldehydes in the presence of catalytic amount of inorganic-supported polyoxometalates, heterogeneous, reusable and efficient catalysts at room temperature gave the corresponding bis-indolylmethanes in excellent yields and shorter reaction times under solvent-free conditions. The catalyst can be reused for several times, but it will be less active.* © 2009 Wiley Periodicals, Inc. Heteroatom Chem 20:325–331, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20554

## INTRODUCTION

Indole derivatives are found abundantly in a variety of natural plants, exhibit various physiological properties, and are potentially bioactive compounds [1–8]. Metabolites within this family elicit a myriad of biological responses that include cytotoxic and antitumor activities. The electrophilic substitution reactions of indoles with aromatic aldehydes afford the corresponding bis(indolyl)methanes [9].

Numerous methods describing the preparation of bis-indolylmethanes have been reported in the literature, employing protic acids [10,11] and Lewis acids such as LiClO<sub>4</sub> [12], InCl<sub>3</sub> [13], lanthanide triflates [14], *N*-bromosuccinimide, NBS [15], I<sub>2</sub> [16], KHSO<sub>4</sub> [17], montmorillonite K-10 [18], HY-zeolite [19], rare-earth perfluorooxanoates, [RE(PFO)<sub>3</sub>] [20], NaHSO<sub>4</sub>/amberlyst-15 [21], [bnmim][HSO<sub>4</sub>] [22], ZrOCl<sub>4</sub> [23], Ph<sub>3</sub>CCl [24], [hmim][HSO<sub>4</sub>] [25], and ZrCl<sub>4</sub> [26]. Most of the previously reported methods suffer from several setbacks such as requirement of a stoichiometric amount of the Lewis acid, expensive and highly toxic catalysts, and long reaction times.

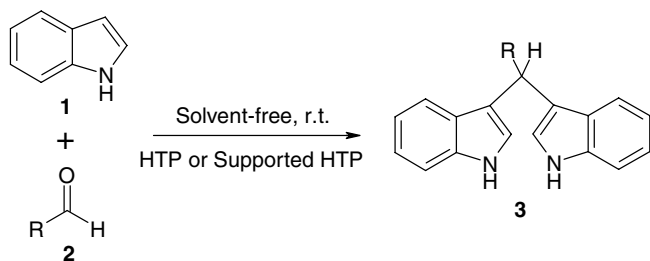
In recent decades, heteropolyacids (HPAs) as catalysts for fine organic synthetic processes have been used and are important for industries related to fine chemicals [27], including flavors, pharmaceuticals, and food industries [28]. It is important to increase the surface area or even better to increase the number of accessible acid sites of the HPA. This can be achieved by dispersing the HPA on solid support with high surface area [29–31]. An immobilization of HPAs on a number of porous supports such as silica, active carbon, montmorillonite K-10, zeolite, and so on was, therefore, extensively studied. But SiO<sub>2</sub>, which is relatively inert toward HPAs, is most often used [32–39]. In continuation of our work on the catalytic properties of HPAs [39], herein we introduce supported H<sub>3</sub>PW<sub>12</sub>O<sub>40</sub> (or supported HTP) as

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SCHEME 1

catalysts for synthesis of bis-indolylmethanes under solvent-free conditions (Scheme 1).

## RESULTS AND DISCUSSION

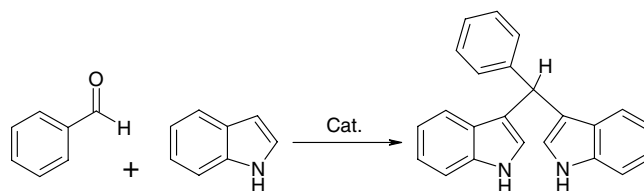
Following the above-mentioned reaction conditions, the catalytic effect of various supports used here ( $\text{SiO}_2$  (Cabosil) and  $\text{Al}_2\text{O}_3$ ) in the absence of catalyst was also studied. The experimental results showed that these supports were much less efficient for this purpose (Table 1, entries 2 and 3). The reaction did not proceed at all in the presence of  $\text{TiO}_2$ , and the starting materials were remained in tact after 10 h (Table 1, entry 4), but in the presence of supported HTP with different weight percentages of HTP this

conversion proceeded efficiently in few minutes under similar reaction conditions (Table 1, entries 12–16). With the increase in catalyst loading, the yield increased. The optimum loading can take as 40% HTP/ $\text{SiO}_2$  (Table 1, entries 12–14). Tungsten HPAs are preferred over molybdenum ones as acid catalysts because of their stronger acidity, higher thermal stability, and low reducibilities [29] (Table 1, entries 13 and 17).

Because of the current challenges in developing solvent-free and environment benign protocols, a wide range of bis-indolylmethanes were synthesized from a combination of an aromatic aldehyde, indole, bulk (1 mol%), or 40% HTP/support (3 mol%) under solvent-free conditions. The reactions were completed within 1–75 min (Table 2).

In the presence of these catalysts, both activated and deactivated aromatic aldehydes were converted to their corresponding bis-indolylmethanes in excellent yields (Table 2, entries I–VII). The reaction proceeded within 10–75 min in (87%–95%) yield in the absence of solvent.

More importantly, aromatic aldehydes carrying either electron-withdrawing (Table 2: **3I–III**) or electron-donating (Table 2: **3IV–VI**) substituents and aliphatic (Table 2: **3VIII** and **3IX**) underwent electrophilic substitution reaction with indol

TABLE 1 Effect of Catalysts on the Synthesis of Bis-Indolylmethanes<sup>a</sup>

Entry	Catalysts	Solvent	Temperature (°C)	Time (min and (h))	Yield (%) <sup>b</sup>
1	–	$\text{CH}_3\text{CN}$	80	(10)	–
2	$\text{SiO}_2$ (cabosil)	$\text{CH}_3\text{CN}$	80	(10)	15
3	$\text{Al}_2\text{O}_3$	$\text{CH}_3\text{CN}$	80	(10)	21
4	$\text{TiO}_2$	$\text{CH}_3\text{CN}$	80	(10)	–
5	HTP (1 mol%)	$\text{CH}_3\text{CN}$	80	20	68
6	HTP (2 mol%)	$\text{CH}_3\text{CN}$	80	5	89
7	HTP (3 mol%)	$\text{CH}_3\text{CN}$	80	5	89
8	HTP (2 mol%)	$\text{CH}_2\text{Cl}_2$	Reflux	45	70
9	HTP (2 mol%)	EtOAc	Reflux	60	55
10	HTP (1 mol%)	Solvent-free	RT	1	89
11	HTP (2 mol%)	Solvent-free	RT	1	92
12	25% HTP/ $\text{SiO}_2$ (3 mol%)	Solvent-free	RT	25	80
13	40% HTP/ $\text{SiO}_2$ (3 mol%)	Solvent-free	RT	15	84
14	60% HTP/ $\text{SiO}_2$ (3 mol%)	Solvent-free	RT	12	85
15	40% HTP/ $\text{SiO}_2$ (5 mol%)	Solvent-free	RT	12	85
16	40% HTP/ $\text{SiO}_2$ (3 mol%)	$\text{CH}_3\text{CN}$	80	65	75
17	40% $\text{H}_3\text{PMo}_{12}\text{O}_{40}$ / $\text{SiO}_2$ (3 mol%)	Solvent-free	RT	55	72

<sup>a</sup>1.0 mmol of benzaldehyde with indole (2.0 mmol) was used.

<sup>b</sup>Isolated yield.

**TABLE 2** Bulk and Supported HTP Catalyzed Synthesis of Bis(Indolyl)Methanes in Reaction of Indole (2.0 Mmol) and Aldehyde (1.0 mmol)<sup>a</sup>

Entry	2 Substrate (R)	Solvent-free 3 (Time (min): Yield (%))				Crystallization Solvent [26]	MP (°C)	
		HTP	SiO <sub>2</sub> /HTP	TiO <sub>2</sub> /HTP	Al <sub>2</sub> O <sub>3</sub> /HTP		Found	Reported [26]
I	3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	3:92	15:95	87:97	75:92	Et <sub>2</sub> O–EtOH	260–262	260–262
		3:92 <sup>b</sup>	3:90 <sup>b</sup>	3:68 <sup>b</sup>	3:56 <sup>b</sup>			
		3:92 <sup>c</sup>	3:65 <sup>c</sup>	3:58 <sup>c</sup>	3:46 <sup>c</sup>			
II	4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	2:92	14:95	45:85	70:90	hexane	222–224	222–228
III	4-ClC <sub>6</sub> H <sub>4</sub>	2:95	14:95	20:70	70:92	MeOH–H <sub>2</sub> O	103–105	103–106
IV	4-OHC <sub>6</sub> H <sub>4</sub>	1:95	18:95	45:95	75:90	EtOAc–hexane	122–126	120–122
V	4-OMeC <sub>6</sub> H <sub>4</sub>	1:92	10:89	10:85	68:90	MeOH–H <sub>2</sub> O	191–193	190–193
VI	4-MeC <sub>6</sub> H <sub>4</sub>	1:92	10:85	10:78	65:85	EtOAc–hexane	95–98	96–98
VII	ph	1:89	15:84	15:90	75:90	EtOAc–hexane	123–125	125–127
VIII	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>4</sub>	10:90	50:89	45:98	65:89	EtOAc–hexane	67–69	67–69
IX	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	60:90	75:89	55:92	75:87	EtOAc–hexane	65–67	68–70
X	2-furyl	3:90	20:98	15:98	75:90	Benzene–hexane	320–322	320–322
XI	Ph-CH = CH	2:78	60:75	75:75	75:85	EtOAc–hexane	96–99	96–98

Selected spectroscopic data:

3,3'-Bisindolyl-4-chlorophenylmethane (3III): Pink solid; mp 76–78°C; FT-IR (KBr):  $\nu = 744, 1012, 1089, 1418, 1455, 1487, 3054, 3410$  (NH)  $\text{cm}^{-1}$ . <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 5.86 (s, 1H, Ar-CH), 6.66 (s, 2H), 7.02 (d, 2H,  $J = 8.3$  Hz), 7.23–7.38 (m, 8H), 7.4 (d, 2H,  $J = 8.2$  Hz), 7.85 (br, s, 2H, NH).

3,3'-Bisindolylphenylmethane (3VII): Solid; mp: 125–127°C; FT-IR (KBr):  $\nu = 753, 1095, 1453, 1605, 1620, 3055, 3415$  (NH)  $\text{cm}^{-1}$ ; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>),  $\delta$  (ppm): 5.90 (s, 1H, Ar-CH), 6.62 (s, 2H), 7.00 (t, 2H,  $J = 7.0$  Hz), 7.20 (m, 3H), 7.33 (m, 2H), 7.35 (m, 6H), 7.90 (br, s, 2H, NH).

Yield refers to isolated pure products.

<sup>a</sup>Catalyst (bulk: 1 mol%, supported: 40% HTP/support (3mol%)).

<sup>b</sup>Only time was kept constant.

<sup>c</sup>Time and amount of active catalyst contents in bulk and supported forms were kept constant (bulk: 1 mol%, HTP/support (1 mol%)).

smoothly to afford a wide range of substituted bis(indolyl)methanes in good to excellent yields. Many of the pharmacologically relevant substitution patterns on the aromatic ring could be introduced with high efficiency by using this procedure. The heterocyclic aldehydes such as furfural also worked well without the formation of any side products (Table 2: 3X). Furthermore, unsaturated aldehydes, such as cinnamaldehyde, gave the corresponding bis(indolyl)methanes without polymerization under the above-mentioned reaction conditions (Table 2: 3XI).

In our method, in the same conditions (Table 2, entry 1, b and c), the activity of the catalysts follows the following order: HTP > HTP/SiO<sub>2</sub> > HTP/TiO<sub>2</sub> > HTP/Al<sub>2</sub>O<sub>3</sub>.

A reasonable pathway for the reaction of indole with aldehyde in the presence of supported-HTP is also presented in Scheme 2.

It should be emphasized that both catalyst preparation and solvent-free conditions are mild; thus it is reasonable that the Keggin unit should be intact under the solvent-free reaction conditions. We investigated the reusability and recycling of HTP/SiO<sub>2</sub>. When the reaction of 4-hydroxybenzaldehyde and indole with HTP/SiO<sub>2</sub> under solvent-free conditions was completed, the

catalyst was separated by simple filtration and recovered HTP/SiO<sub>2</sub> was reused in subsequent reactions without significant decrease in activity even after three runs (Table 3). For second and third runs, filtrates were used for determination of polyoxometalates (POM) leaching. No tungsten and molybdenum was detected in the filtrates by atomic absorption spectroscopy (also proved by XRD (Fig. 1) and FTIR (Fig. 2)). After third run, the POMs were leached from the supports (proved by NAA and atomic

**TABLE 3** Recycling of HTP/SiO<sub>2</sub> in the Reaction of 4-Hydroxybenzaldehyde and Indole<sup>a</sup>

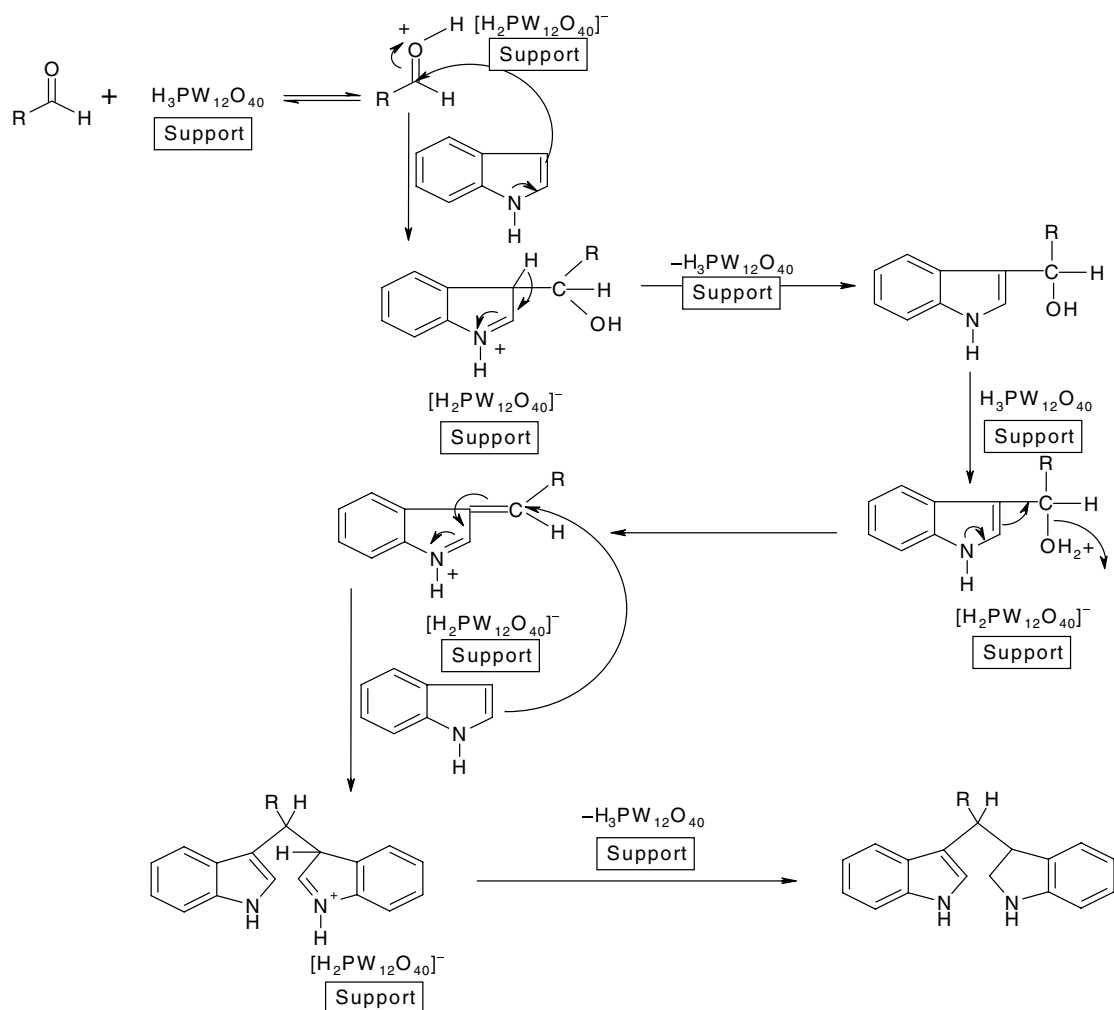
Run	Yield (%) <sup>b-d</sup>
	Solvent-free 40% HTP/SiO <sub>2</sub> (3 mol%)
1	95
2	92
3	92
4	43

<sup>a</sup>Reaction conditions: 4-hydroxybenzaldehyde (1.0 mmol), indole (2.0 mmol).

<sup>b</sup>Isolated yields after column chromatography.

<sup>c</sup>The <sup>1</sup>H NMR approved the reported yields.

<sup>d</sup>The recovered catalyst, washed with CH<sub>2</sub>Cl<sub>2</sub>, dried, and calcined at 250°C for 450 min [39].



SCHEME 2

absorption spectroscopy) and this led to the deactivation of heterogeneous catalysts. Since in the process of isolation, solvent was used and also because POM was weakly adsorbed on support (adsorption), the catalyst activities of the supported POM decrease the third time [39b]. But for the similar reaction in  $CH_3CN$ , the yields were gradually decreased in runs carried out using recycled catalyst. It is well known that in polar medium HPA dissolves and so in polar medium leaching of HPA from system HPA/support should be significant.

This protocol is superior to the literature data (Table 4) with respect to reaction time and eco-friendliness.

### Catalysts Characterization

The physico-chemical properties of supported HTP catalysts by XRD, FT-IR, and NAA demonstrated

that HTP was anchored on the surface of supports and HTP still remained with the Keggin structures [39].

### EXPERIMENTAL

The supported-HTP catalyst was prepared by impregnating support ( $SiO_2$  (cabosil 20),  $Al_2O_3$  (Merck, Darmstadt, Germany), or  $TiO_2$  (Degussa, Ridgefield, US)) with an aqueous solution of HTP (a method of incipient wetness). The mixture was stirred overnight at room temperature followed by drying using a rotary evaporator. The resulting pastes were dried for 4 h at  $110^\circ C$  and calcined for 4 h at  $250^\circ C$  [39]. All chemicals used were of analytical grade. FT-IR studies were carried out on Impact 400D FT-IR spectrophotometer in the range of  $400-4000\text{ cm}^{-1}$ . XRD patterns of supported POMs were recorded on

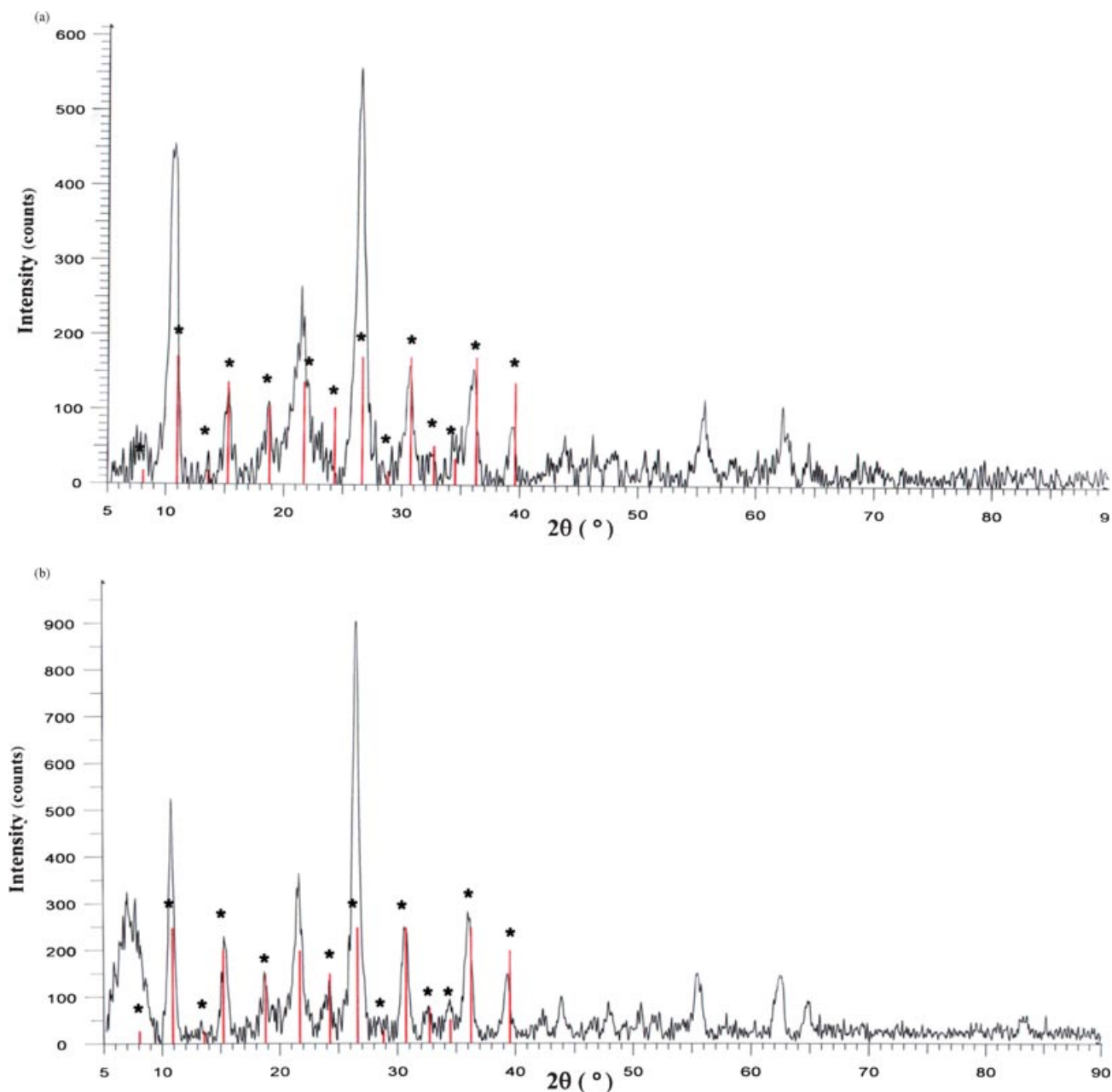


FIGURE 1 XRD patterns of the HTP-SiO<sub>2</sub> (a) before and (b) after the use.

TABLE 4 Comparison of HTP and HTP/SiO<sub>2</sub> with Several Catalysts for Synthesis of Bis-Indolylmethanes with Benzaldehyde

Entry	Catalyst	Time (min and [h])	Yield (%)	Reference
1	ZrCl <sub>4</sub>	30	96	[26]
2	HY-Zeolite	[2]	80	[19]
3	LiClO <sub>4</sub>	[5]	90	[12]
4	K10 clay	5	97	[18]
5	InCl <sub>3</sub>	25	71	[13]
6	ZrOCl <sub>4</sub>	35	89	[23]
7	Ph <sub>3</sub> CCl	20	90	[24]
8	[hmim][HSO <sub>4</sub> ]	60	97	[25]
9	HTP (solvent-free)	11	89	This work
10	40% HTP/SiO <sub>2</sub> (solvent-free)	15	84	This work

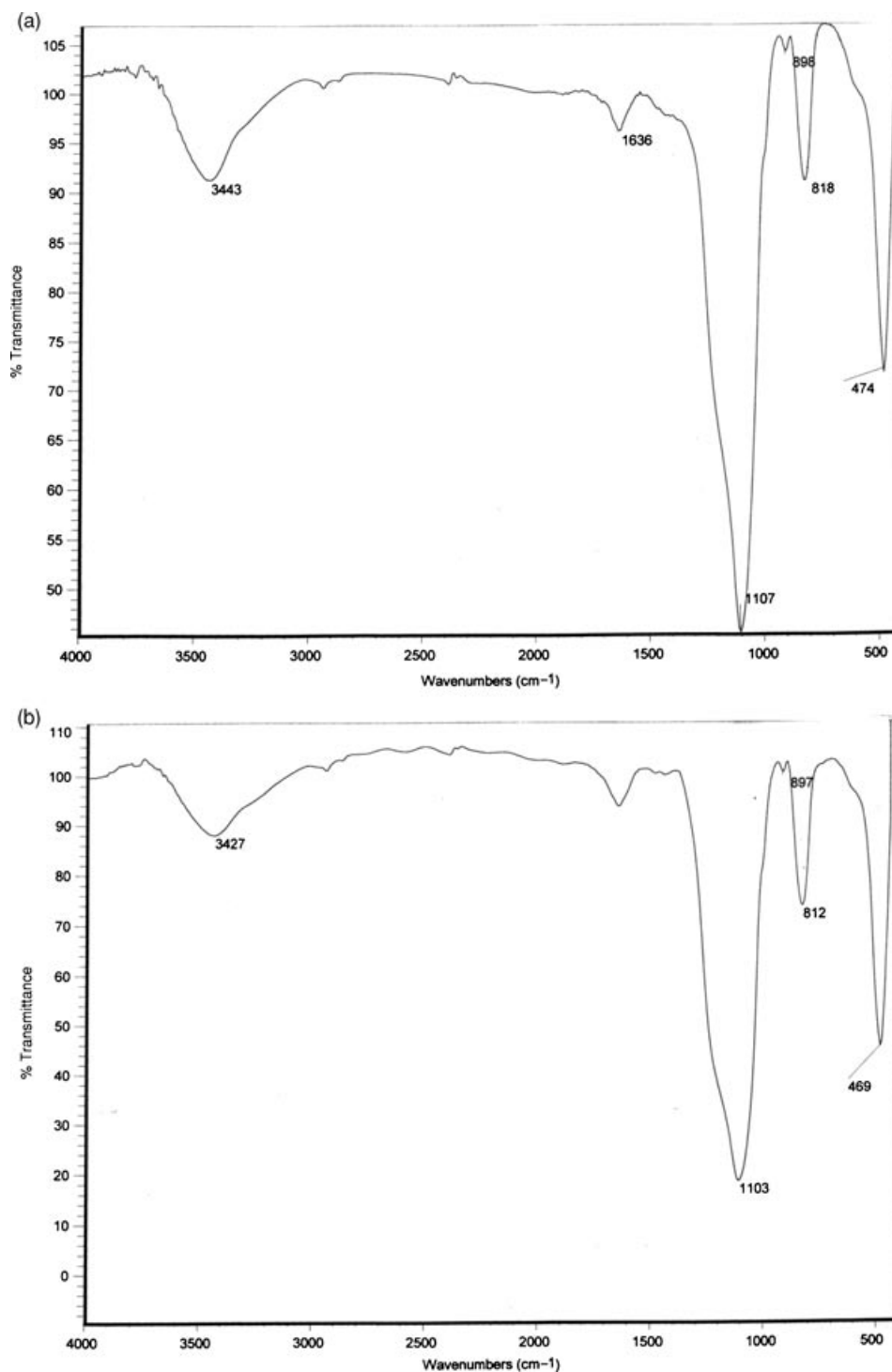


FIGURE 2 FT-IR spectra of the HTP-SiO<sub>2</sub> (a) before and (b) after the use.

a D8 Advance Bruker, using Cu K<sub>α</sub> radiation ( $2\theta = 5^{\circ}$ – $70^{\circ}$ ) [39]. Gas chromatography experiments (GC) were performed with Shimadzu GC-16A instrument using a 2-m column peaked with silicon DC-200 or Carbowax 20 m.

#### *Synthesis of Bis(indolyl)methanes under Solvent-Free Conditions: General Procedure*

A mixture of indole (2.0 mmol), aldehyde (1.0 mmol), and HTP (1 mol%) or supported HTP (0.2 g, 3 mol%)

was ground together in a mortar and pestle at room temperature a number of times as indicated in Table 2. In cases when the mixture stuck to the walls of the mortar, it was taken off from the walls with a spatula and grinding was done again. After completion of the reaction, as indicated by TLC, the reaction mixture was quenched with H<sub>2</sub>O (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layer was separated and dried (Na<sub>2</sub>SO<sub>4</sub>), concentrated in vacuo, and the product was purified by column chromatography on silica gel (EtOAc: *n*-hexane, 1:9) to give pure bis(indolyl)methanes.

### CONCLUSION

Preparation of bis(indolyl)methanes through the electrophilic substitution reactions of indoles with aldehydes by using HTP and supported HTP as non-toxic, inexpensive, and reusable catalyst was successfully performed in high yields under solvent-free conditions. This method is applicable to a wide range of aldehydes, including aromatic, aliphatic,  $\alpha,\beta$ -unsaturated, and heterocyclic substrates. The present procedure represents a clean, environment friendly, practical with high yields of the products, as well as simple experimental with easy work-up. All these characteristics make this protocol a useful and an attractive procedure for the synthesis of indole derivatives.

### REFERENCES

- [1] Kathleen, A.; Merrill, A. G. PCT. Int. Appl. WO 99; Chem. Abstr. 130, 276,765, 1999.
- [2] Bradeld, C. A.; Bjeldanes, L. F.; J. Toxicol Environ Health 1987, 21, 311.
- [3] Dashwood, R. H.; Uyetake, L.; Fong, A. T.; Hendricks, J. D.; Bailey, G. S. Food Chem Toxicol 1987, 27, 385.
- [4] Ge, X.; Fares, F. A.; Yannai, S. Chem. Abstr. 133 73, 462b, 2000.
- [5] Chang, Y.-C.; Riby, J.; Grace Chang, H. F.; Peng, G. F.; Bjeldanes, L. F. Bio Chem Pharmacol 1999, 58, 825.
- [6] Shilling, A. D.; Carlson, D. B.; Katchamart, S.; Williams, D. Toxicol Appl Pharmacol 2001, 170, 191.
- [7] Ge, X.; Yannai, S.; Rennert, G.; Gruener, N.; Fares, F. A. Biochem Biophys Res Commun 1996, 228, 153.
- [8] Ge, X.; Fares, F. A.; Yannai, S. Anticancer Res 1999, 19, 3199.
- [9] Remers, W. Chem Heterocycl Comp 1972, 1, 25.
- [10] Roomi, M.; MacDonald, S. Can J Chem 1970, 48, 139.
- [11] Gregorovich, B.; Liang, K.; Clugston, D.; MacDonald, S. Can J Chem 1968, 46, 3291.
- [12] Yadav, J. S.; Reddy, B. V. S.; Murthy Ch, V. S. R.; Mahesh, Kumar.; G, Madan Ch. Synthesis 2001, 5, 783.
- [13] Babu, G.; Sridhar, N.; Perumal, P. T. Synth Commun 2000, 30, 1609.
- [14] Chen, D.; Yu, L.; Wang, P. G. Tetrahedron Lett 1996, 37, 4467.
- [15] Koshima, H.; Matsuoka, W. J Heterocycl Chem 2002, 39, 1089.
- [16] Bandgar, B. P.; Shaikh, K. A. Tetrahedron Lett 2003, 44, 1959.
- [17] Nagrajan, R.; Perumal, P. T. Chem Lett 2004, 33, 288.
- [18] Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. Tetrahedron Lett 2002, 43, 4075.
- [19] Reddy, A. V.; Ravinder, K.; Reddy, V. L. N.; Goud, T. V.; Ravikant, V.; Venkateswarlu, Y. Synth Commun 2003, 33, 3687.
- [20] Wang, L.; Han, J.; Tian, H.; Sheng, J.; Fan, Z.; Tang, X. Synlett 2005, 2, 337.
- [21] Ramesh, C.; Banerjee, J.; Pal, R.; Das, B. Adv Synth Catal 2003, 345, 557.
- [22] Sadaphal, S. A.; Shelke, K. F.; Sonar, S. S.; Shingare, M. S. Cent Eur J Chem 2008, 6, 622.
- [23] Nagawade, R. R.; Shinde D. B. Acta Chim Slov 2006, 53, 210.
- [24] Khallafi-Nezhad A. Synthesis 2008, 617.
- [25] Gong, G. D.; Shun-Jun, Ji.; Zhao-Qin, J.; Min-Feng, Z.; Teck-Peng, L. Synlett 2005, 6, 959.
- [26] Zhang, Z.-H.; Yin, L.; Wang, Y.-M. Synthesis 2005, 12, 1949.
- [27] Kozhevnikov, I. V. In Catalysts for Fine Chemical Synthesis, Catalysis by Polyoxometalates 2; Derouane, E. (Ed.); Wiley: New York, 2002; p. 117.
- [28] Okuhara, T.; Mizuno, N.; Misono, M. Adv Catal 1996, 41, 221.
- [29] Khozhevnikov, I. V.; Kloestra, K. R.; Sinnema, A.; Zandbergen, H. W.; Van Bekkum, H. J Mol Catal A 1996, 114, 287.
- [30] Khozhevnikov, I. V.; Sinnema, A.; Jansen, R. J. J.; Pamin, K.; Van Bekkum, H. Catal Lett 1995, 30, 241.
- [31] Moffat, J. B. Metal-Oxygen Cluster: The Surface and Catalytic Properties of Heteropoly Oxometalates; Kluwer: New York, 2001.
- [32] Dias, J. A.; Caliman, E.; Dias, S. C. L.; Paulo, M. De.; Souza, A. T. C. P. Catal Today 2003, 85, 39.
- [33] Levevre, F.; Dupont, P.; Auroux, A. React Kinet Catal Lett 1995, 55, 3.
- [34] Kozhevnikova, E. F.; Kozhevnikov, I. V. J Catal 2004, 224, 164.
- [35] Kozhevnikova, E. F.; Rafiee, E.; Kozhevnikov, I. V. Appl Catal A Chem 2004, 260, 25.
- [36] Firouzabadi, H.; Iranpoor, H.; Jafari, A. A. J Mol Catal A Chem 2005, 247, 14.
- [37] Khozhevnikov, I. V. Catal Rev Sci Eng 1995, 37, 311.
- [38] (a) Firouzabadi, H.; Iranpoor, N.; Amani, K. Green Chem 2000, 3, 131; (b) Firouzabadi, H.; Jafari, A. A. J Iranian Chem Soc 2005, 2, 85.
- [39] (a) Fazaeli, R.; Tangestaninejad, S.; Aliyan, H.; Moghadam, M. Appl Catal A 2006, 309, 44; (b) Fazaeli, R.; Tangestaninejad, S.; Aliyan, H. Appl Catal A 2007, 318, 218; (c) Fazaeli, R.; Aliyan, H. Appl Catal A 2007, 331, 78; (d) Fazaeli, R.; Aliyan, H. Appl Catal A 2009, 353, 74; (e) Fazaeli, R.; Aliyan, H. Chin J Catal 2008, 29,10; (f) Fazaeli, R.; Tangestaninejad, S.; Aliyan, H. Can J Chem 2006, 84, 812. (g) Fazaeli, R.; Aliyan, H.; Tangestaninejad, S. Heterocycles 2007, 71, 805; (h) Fazaeli, R.; Tangestaninejad, S.; Aliyan, H. Catal Commun 2007, 8, 205.