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Phospho Sulfonic Acid: A Highly Efficient and Novel Catalyst for Formation of Bis(Indolyl)Alkanes from Aldehydes and Indole under Aqueous Conditions

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Abstract—Bis(indolyl)alkanes are a class of alkaloids that possess significant biological activities. Every year, the varieties of bis(indolyl)alkanes isolated from natural sources are increasing. Nevertheless, the deficiency of natural products from natural sources led to a decrease in the exploration of natural products for biological investigations. Corresponding to this fact, there is a demand to develop efficient protocols for the construction of bis(indolyl)alkanes. In this regards, we have prepared phospho sulfonic acid (PSA), which is a non-corrosive, highly reactive, inexpensive and low toxic catalyst, and have applied to construct bis(indolyl)alkanes. The catalyst was prepared by reaction of diammonium hydrogen phosphate with chloro sulfuric acid and was fully characterized by FTIR spectrometry. PSA has been used as a solid acid catalyst to promote the electrophilic substitution reaction of indole with aldehydes under water to furnish a library of bis(indolyl)alkanes in excellent yields over short reaction times. The present method eliminates use of toxic catalyst and solvent, and tolerates a series of functional groups. The catalyst can be reused several times without any important activity loss. The methodology has several advantages, for example, simple experimental procedure, cost efficiency (use of inexpensive catalyst), ease of preparation and handling of the catalyst and no side reactions.

Keywords: bis(indolyl)methanes, bis(indolyl)alkanes, phospho sulfonic acid, catalyst, synthesis

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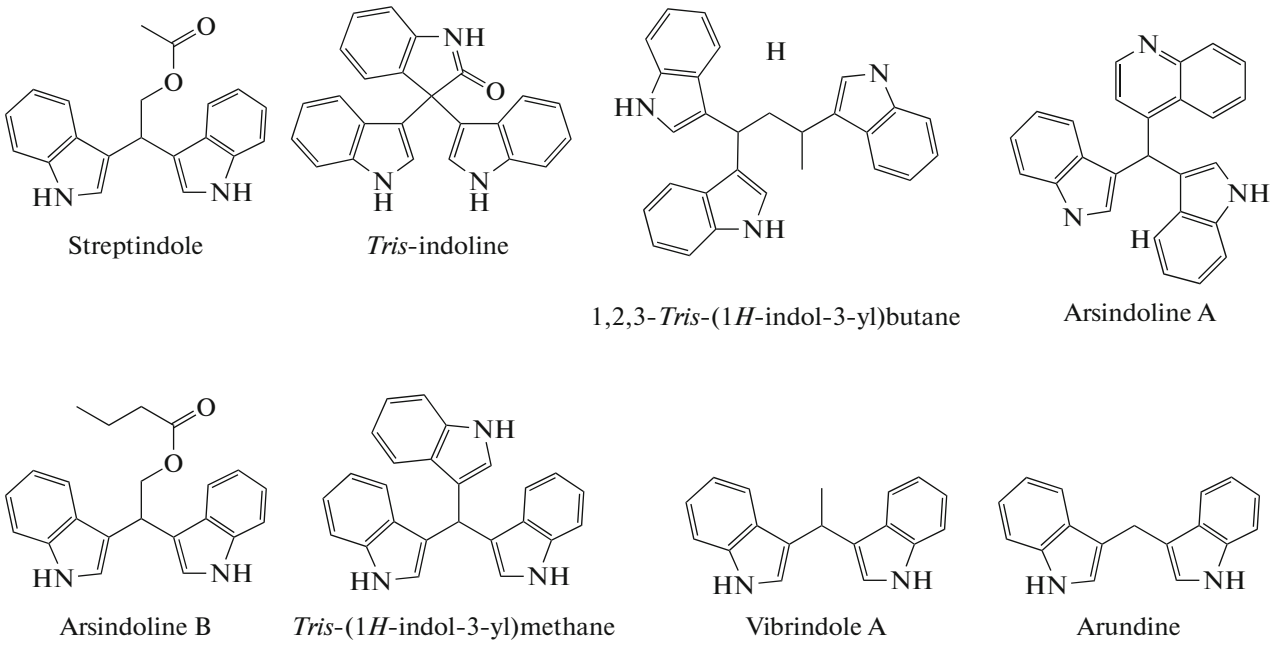
INTRODUCTION

Indole analogs are richly found in a diversity of natural plants and exhibit various physiological properties and are potentially bioactive compounds [1]. Bis(indolyl)alkanes (also called bis(indolyl)methanes or bis(indolyl)methane) are important derivatives of indole. A large number of bis(indolyl)methanes have been separated from marine and terrestrial natural sources, for instance, sponges, tunicates and parasitic bacteria, and some of these possess important pharmaceutical biological profiles.

Bis(indolyl)alkanes are observed to assist estrogen metabolism in both men and women and is probable to have an application in inhibition of breast cancer [2]. Recently, cancer chemotherapy with bis(indolyl)alkanes were reviewed [3]. 3,3'-Diindolylmethane and its analogous are also employed as dietary supplements for humans [4]. Bis(indolyl)alkanes serve as cytodifferentiating agents [5], have inhibitory activities on phenobarbital-induced hepatic CYP gene expression [6], exhibit antibiotic activity and antibacterial activity [7], exhibit antimicrobial and antifungal activities [8], use as inhibitors of the platelet-derived growth factor receptor kinase [9], serve as topoisomerase IIR catalytic inhibitors [10], have anti-tumorigenic activity [11], have growth inhibitory potency on prostate cancer cell lines [12], prevent the process of proliferation in breast tumor cells [13], bring apoptosis in prostate cancer [14], prevent mammary tumor growth [15], are active against colon cancer [16], have development inhibitory potency on lung cancer cells [17], prevent renal cell carcinoma growth and bladder cancer growth [18], have analgesic and anti-inflammatory activities [19], have growth promoting activity [2], have radical scavenging activity [1] and are also employed as glass-forming high-triplet energy materials and tranquilizers [20]. Vibrindole A was demonstrated for the first time to exhibit anti-bacterial potency against *Bacillus subtilis*, *Scaphirhynchus albus*, and *Staphylococcus aureus* [21]. Thus, indole and its derivatives have been a topic of research interest. In light of their potential therapeutic applications, the development of new strategies and procedures for the construction of these entities continues to attract important levels of attention from synthetic organic chemists.



Structures of bis(indolyl)alkanes separated from natural products.

Attributed to the symmetric skeleton of the bis(indolyl)alkane entity, they are easy to prepare from two units of indole and acetone/aldehyde using reagents and catalysts. In the past decades, several reagents and catalysts have been disclosed for the formation of bis(indolyl)alkanes from carbonyl compounds and indoles such as trityl chloride [22], P_2O_5/SiO_2 [23], silica chloride [24], $MgSO_4$ [25], NBS [26], I_2 [27] and ionic liquids [28]. Other catalysts such as $Re(PFO)_3$, $Ln(OTf)_3$, $Dy(OTf)_3$, $LnCl_3$, $In(OTf)_3$, $InCl_3$, $ZrOCl_2$, $LiClO_4$, $PEG-O-C_6H_4-SO_3H$, $SnCl_2 \cdot 2H_2O$, $Bi(OTf)_3$, $NbCl_5$, $SbCl_3$, VCl_3, $NaBF_4$, $H_4SiMo_{12}O_{40}$, $H_3PMo_{12}O_{40}$, silica sulfuric acid [29–32], $SiO_2/AlCl_3$ [33], pyridinium tribromide [34], zirconyl dodecyl sulfate [35], Al_2O_3 [36], $FeCl_3 \cdot 6H_2O$ [37], ZnO [38] and $GaCl_3$ [39] have also been reported for this transformation. Further, protic acids such as oxalic acid [40], cellulose sulfuric acid [41], NH_4Cl [42], oxone [43], and montmorillonite clay [44] were also utilized to promote these transformations.

However, many of these catalysts are expensive, and are sometimes decomposed or deactivated by nitrogen containing reactants. Even when the required reactions progress, more than stoichiometric amounts of catalysts are desired [45]. Moreover, in most of the reported methods chlorinated solvents such as chloroform are used as a reaction medium and/or for the separation of catalyst which is not in accord with green chemistry protocols. Some of the documented procedures suffered from the cumbersome work-up procedures, low product yields, prolonged reaction times (e.g., 4–10 h) and application of an additional ultrasound or microwave irradiation [1, 2]. Hence, the construction environmentally friendly, convenient, reusable, efficient, new and simple method for the formation of these medicinally significant entities is still demanding. As part of our continued passion in construction of highly beneficial approaches for the development of heterocyclic entities of pharmaceutical importance [46–48], herein, we wish to describe phospho sulfonic acid (PSA), which is observed to be highly efficient, clean and economically valuable catalyst in reaction of aromatic aldehydes with indole under water as solvent to furnish bis(indolyl)alkanes. PSA as a heterogeneous and solid acid catalyst was simply synthesized by the stirring of diammonium hydrogen phosphate (DAP) and chlorosulfuric acid in dichloromethane (DCM) at room temperature. A possible mechanism for construction of bis(indolyl)alkane core is proposed to interpret the observed reactivity. The present approach is also compared with previous reported approaches.

EXPERIMENTAL

Materials and General Methods

All reagents were of high-grade quality and obtained from Merck, Fluka and Aldrich. ^1H NMR, C^{13} NMR and P^{31} NMR spectra were measured on a Bruker Avance 300 MHz spectrometer using tetramethylsilane as an internal standard (in DMSO-d_6) at room temperature. FT-IR measurements were performed using KBr disc on JASCO IR-A-302 spectrometer. Melting points were taken in a Riechert Thermover instrument and are uncorrected.

Catalyst Preparation

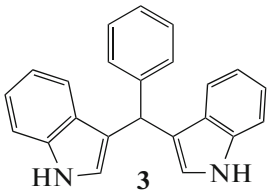
A 50 mL vacuum flask was fitted with a constant pressure dropping funnel. A vacuum system was coupled with gas outlet through an alkali trap and adsorbing solution (water). The vacuum flask was charged with diammonium hydrogen phosphate (2 g, 15 mmol). Then, over a time period of 40–50 min at room temperature, solution of chlorosulfuric acid (5.24 g, 45 mmol) in CH_2Cl_2 (5 mL) was poured drop wise into the flask. Thereafter, the resulting mixture was stirred for about 2 h, while the residual hydrochloric acid and ammonia gases was removed *via* suction system. After that, to isolate the unreacted chlorosulfuric acid, washing of resulting mixture was carried out by using CH_2Cl_2 (3 × 10 mL). Lastly, phospho sulfonic acid was obtained as a solid white powder (8.50 g, 83%); free-flowing precipitate could be stored at r. t. for almost 160 days. The melting point was found to be 127–130°C.

General Procedure for the Preparation of Bis(Indolyl)Alkanes

In 100-mL round bottom flask, a mixture of aldehyde (1 mmol) and indole (2 mmol) was charged to a stirring solution of phospho sulfonic acid (0.06 g) in H_2O (40 mL), and the resulting reaction contents was vigorously stirred at 100°C for appropriate period of time (2–3 h). After completion of the reaction, as observed by thin-layer chromatography (EtOAc : PET ether = 1 : 2), the reaction content was filtered and washed with distilled water to separate the catalyst. The residue contains crude bis(indolyl)alkane products and filtrate contains phospho sulfonic acid (recovered catalyst). The resulting residue was decontaminated via silica gel-mediated chromatographic purification technique using EtOAc in PET ether solution (2 : 8) as eluent to furnish the required products. After washing filtrate with EtOAc and then drying, the obtained phospho sulfonic acid was reused for subsequent reactions. All the products were identified by comparing the analytical data (melting point, IR, ^{1}H NMR) with those reported data.

Representative Spectral Data

Bis(indolyl)methane 3.

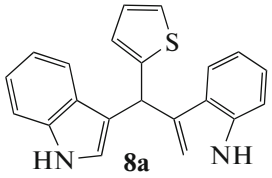


3

3,3'-(Phenylmethylene)bis(1*H*-indole)

Appearance: yellowish solid; R_f = 0.49 (*n*-hexane : EtOAc = 5 : 5); m.p. 140–142°C; IR, cm^{-1}: 669, 757, 1017, 1093, 1215, 1419, 1456, 1522, 1601, 3019, 3478; ^{1}H NMR, δ_H, ppm: 7.93 (s), 7.35–7.42 (m, 6H), 7.28–7.31 (m, 2H), 7.14–7.22 (m, 3H), 7.11 (t, J = 6.9 Hz, 2H), 6.66 (s, 2H), 5.86 (s, 1H); ^{13}C NMR, δ, ppm: 145.2, 137.0, 128.6, 128.5, 127.1, 126.3, 124.0, 121.2, 119.5, 118.4, 111.9, 110.9, 31.6. Anal. calcd. for $C_{23}H_{18}N_2$: N, 8.69; H, 5.63; C, 85.68. Found: N, 8.64; H, 5.63; C, 85.63. The spectral data are in good agreement with the literature values [49].

Bis(indolyl)methane 8a.

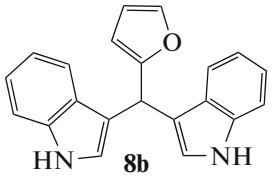


8a

3,3'-(Thiopen-2-ylmethylene)bis(1*H*-indole)

Appearance: yellowish solid; R_f = 0.87 (*n*-hexane : EtOAc = 5 : 5); m. p. 146–147°C; ^{1}H NMR, δ_H, ppm: 7.94 (s), 6.97–7.45 (m, 11H), 6.86 (s, 2H), 6.08 (s, 1H); ^{13}C NMR, δ, ppm: 145.5, 136.7, 128.9, 126.3, 125.3, 123.5, 122.6, 121.8, 120.0, 119.3, 111.5, 110.3, 35.9. Anal. calcd. for $C_{21}H_{16}N_2S$: S, 9.76; N, 8.53; H, 4.91; C, 76.80. Found: S, 9.73; N, 8.53; H, 4.93; C, 76.81. The spectral data are in good agreement with the literature values [49].

Bis(indolyl)methane 8b.

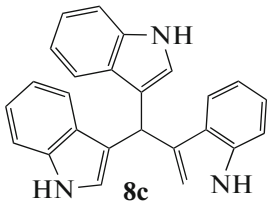


8b

3,3'-(Furan-2-ylmethylene)bis(1*H*-indole)

Appearance: brownish solid; R_f = 0.56 (*n*-hexane : EtOAc (1 : 9)); m. p. 315–317°C; IR, cm^{-1}: 670, 757, 1021, 1093, 1216, 1419, 1456, 1600, 2399, 3019, 3477; ^{1}H NMR, δ_H, ppm: 8.00 (s), 7.08–7.43 (m, 11H), 6.90 (s, 2H), 5.97 (s, 1H); ^{13}C NMR, δ, ppm: 142.0, 135.9, 126.3, 124.3, 121.7, 119.7, 119.3, 118.0, 112.2, 111.3, 110.2, 106.5, 34.8. Anal. calcd. for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97; O, 5.12. Found: C, 80.73; H, 5.14; N, 8.94; O, 5.13. The spectral data are in good agreement with the literature values [50].

Bis(indolyl)methane 8c.

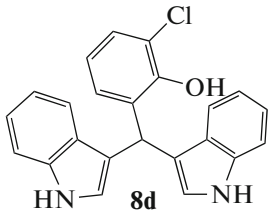


8c

Tri(1*H*-indol-3-yl)methane

Appearance: yellowish solid; $R_f = 0.34$ (*n*-hexane : EtOAc (4:6)); m. p. 161–164°C; ^{1}H NMR, δ_H, ppm: 10.59 (s, 3H), 7.52 (d, $J = 7.9$ Hz, 3H), 7.35 (d, $J = 7.9$ Hz, 3H), 7.05 (m, 3H), 6.86–6.91 (m, 6H), 6.11 (s, 1 H); ^{13}C NMR, δ, ppm: 136.4, 126.6, 123.0, 120.5, 119.1, 118.1, 117.8, 111.2, 30.8. Anal. calcd. for $C_{25}H_{19}N_3$: C, 83.08; H, 5.30; N, 11.63. Found: C, 83.03; H, 5.34; N, 11.63. The spectral data are in good agreement with the literature values [51].

Bis(indolyl)methane 8d.

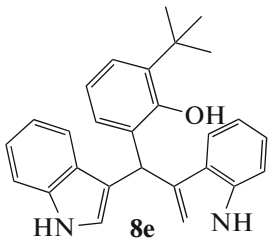


8d

2-Chloro-6-[di(1*H*-indol-3-yl)methyl]phenol

Appearance: brown solid; $R_f = 0.78$ (*n*-hexane : EtOAc (5 : 5)); m.p. 201–203°C; IR, cm^{-1}: 805, 1139, 1245, 1469, 1552, 3286, 3325, 3395; ^{1}H NMR, δ_H, ppm: 5.77 (s, 1H), 6.23 (s, 1H), 6.70 (s, 2H), 6.74 (d, $J = 10.0$ Hz, 1H), 7.06–6.95 (m, 3H), 7.18 (q, $J = 8.6$ Hz, 3H), 7.34 (d, $J = 8.4$ Hz, 2H), 7.40 (d, $J = 7.6$ Hz, 2H), 7.90 (s, 2H); ^{13}C NMR, δ, ppm: 34.0, 111.0, 118.0, 119.3, 119.8, 120.1, 120.6, 122.0, 123.5, 126.8, 127.0, 128.5, 131.4, 136.7, 149.1. Anal. calcd. for $C_{23}H_{17}ClN_2O$: C, 74.09; H, 4.60; Cl, 9.51; N, 7.51; O, 4.29. Found: C, 74.19; H, 4.62; Cl, 9.56; N, 7.56; O, 4.25. The spectral data are in good agreement with the literature values [52].

Bis(indolyl)methane 8e.

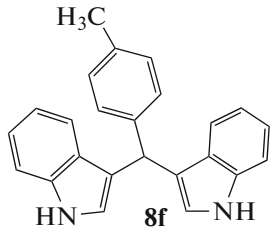


8e

2-(*tert*-Butyl)-6-[di(1*H*-indol-3-yl)methyl]phenol

Appearance: pale yellowish solid; $R_f = 0.43$ (*n*-hexane : EtOAc (5 : 5)); m.p. 189–191°C; IR, cm^{-1}: 729, 1132, 1261, 1394, 1549, 3278, 3336, 3386; ^{1}H NMR, δ_H, ppm: 1.34 (s, 9H), 5.56 (s, 1H), 5.94 (s, 1H), 6.77 (s, 2H), 7.03–6.97 (m, 4H), 7.18 (t, $J = 7.2$ Hz, 4H), 7.37 (t, $J = 7.6$ Hz, 4H), 8.00 (s, 2H); ^{13}C NMR, δ, ppm: 29.7, 34.6, 36.2, 111.1, 116.9, 118.8, 119.5, 119.9, 121.4, 122.3, 123.7, 125.3, 126.8, 127.6, 129.4, 136.8, 153.4. Anal. calcd. for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10; O, 4.06. Found: C, 82.20; H, 6.65; N, 7.6; O, 4.05. The spectral data are in good agreement with the literature values [52].

Bis(indolyl)methane 8f.

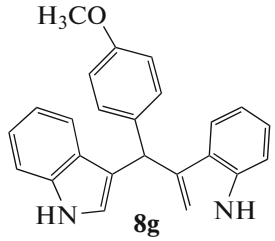


8f

3,3'-(*p*-Tolylmethylene)bis(1*H*-indole)

Appearance: brown solid; $R_f = 0.34$ (*n*-hexane : EtOAc (5 : 5)); m.p. 98–99°C; IR, cm^{-1}: 669, 759, 1021, 1091, 1215, 1417, 1456, 1512, 1602, 3020, 3480; ^{1}H NMR, δ_H, ppm: 7.94 (bs, 2H), 6.85–7.40 (m, 12H), 6.64 (s, 2H), 5.84(s, 1H), 2.31 (s, 3H); ^{13}C NMR, δ, ppm: 39.8, 55.9, 119.2, 119.9, 121.9, 123.5, 127.1, 128.9, 136.7. Anal. calcd. for $C_{24}H_{20}N_2$: C, 85.68; H, 5.99; N, 8.33. Found: C, 85.69; H, 5.93; N, 8.34. The spectral data are in good agreement with the literature values [53].

Bis(indolyl)methane 8g.

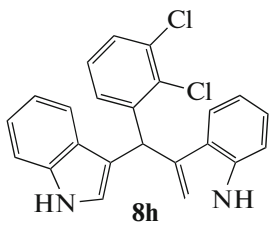


8g

3,3'-[(4-Methoxyphenyl)methylene]bis(1*H*-indole)

Appearance: brown solid; $R_f = 0.78$ (*n*-hexane : EtOAc (1 : 9)); m.p. 179–182°C; IR, cm^{-1}: 759, 1033, 1091, 1216, 1336, 1417, 1456, 1455, 1509, 1610, 2838, 3019, 3480; ^{1}H NMR, δ_H, ppm: 7.89 (bs, 2H), 7.26–7.40 (m, 6H), 7.2 (t, 2H), 7.03 (t, 2H), 6.83 (d, 2H), 6.64 (d, 2H), 5.84 (s, 1H), 3.77 (s,3H); ^{13}C NMR, δ, ppm: 38.6, 55.2, 110.9, 113.6, 119.2, 119.4, 119.9, 120, 121.9, 123.5, 127.1, 136.2, 136.7. Anal. calcd. for $C_{24}H_{20}N_2O$: C, 81.79; H, 5.72; N, 7.95; O, 4.54. Found: C, 81.73; H, 5.73; N, 7.93; O, 4.54. The spectral data are in good agreement with the literature values [54].

Bis(indolyl)methane 8h.



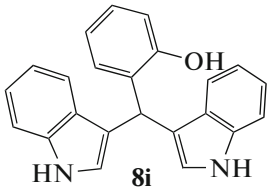
8h

3,3'-[(2,3-Dichlorophenyl)methylene]bis(1*H*-indole)

Appearance: yellowish solid; $R_f = 0.34$ (*n*-hexane : EtOAc (5 : 5)); m.p. 96–98°C; IR, cm^{-1}: 740, 1090,

1328, 1471, 1515, 1623, 2853, 2925, 3400; ^{1}H NMR, δ_H, ppm: 6.30 (s, 1H), 6.60 (d, J = 1.2 Hz, 2H), 7.05 (dd, J = 7.6, J = 7.2 Hz, 2H), 7.20–7.12 (m, 4H), 7.40–7.34 (m, 5H), 7.88 (br s, 2H); ^{13}C NMR, δ, ppm: 36.7, 111.2, 117.7, 119.50, 119.6, 122.2, 123.8, 126.8, 127.7, 130.2, 130.6, 132.3, 132.6, 136.7, 143.3. Anal. calcd. for $C_{23}H_{16}Cl_2N_2$: C, 70.60; H, 4.12; Cl, 18.12; N, 7.16. Found: C, 70.60; H, 4.14; Cl, 18.13; N, 7.15. The spectral data are in good agreement with the literature values [55].

Bis(indolyl)methane 8i.

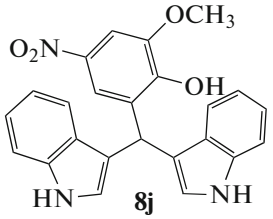


8i

2-[Di(1*H*-indol-3-yl)methyl]phenol

Appearance: golden oil; R_f = 0.67 (*n*-hexane : EtOAc (5 : 5)); ^{1}H NMR, δ_H, ppm: 5.82 (s, 1H), 6.50 (br s, 1H), 6.59 (s, 2H), 6.89 (t, 2H, J = 6.5 Hz), 7.03–7.09 (m, 2H), 7.11–7.23 (m, 6H), 7.45 (d, 2H, J = 7.8 Hz), 7.64 (s, 2H); ^{13}C NMR, δ, ppm: 154.4, 137.2, 136.8, 130.1, 129.5, 127.9, 126.8, 124.5, 122.3, 120.8, 120.0, 119.5, 117.6, 111.3, 29.8. Anal. calcd. for $C_{23}H_{18}N_2O$: C, 81.63; H, 5.36; N, 8.28; O, 4.73. Found: C, 81.64; H, 5.34; N, 8.24; O, 4.74. The spectral data are in good agreement with the literature values [56].

Bis(indolyl)methane 8j.

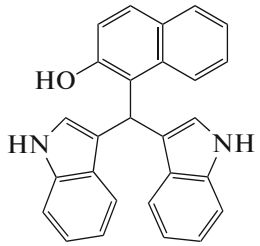


8j

2-[Di(1*H*-indol-3-yl)methyl]-6-methoxy-4-nitrophenol

Appearance: yellowish solid; R_f = 0.65 (*n*-hexane : EtOAc (1 : 9)); m. p. 229–230°C; IR, cm^{-1}: 824, 1249, 1438, 1562, 3294, 3371, 3401; ^{1}H NMR, δ_H, ppm: 3.91 (s, 3H), 6.23 (s, 1H), 6.79 (s, 2H), 6.86 (t, J = 7.2 Hz, 2H), 7.02 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 8.0 Hz, 2H), 7.63 (s, 2H), 10.34 (s, 1H), 10.81 (s, 2H); ^{13}C NMR, δ, ppm: 32.2, 56.7, 105.0, 112.0, 117.0, 118.1, 118.7, 119.0, 121.4, 124.1, 126.9, 132.1, 137.0, 139.4, 147.5, 150.9. Anal. calcd. for $C_{24}H_{19}N_3O_4$: C, 69.72; H, 4.63; N, 10.16; O, 15.48. Found: C, 69.75; H, 4.65; N, 10.14; O, 15.44. The spectral data are in good agreement with the literature values [52].

Bis(indolyl)methane 8k.

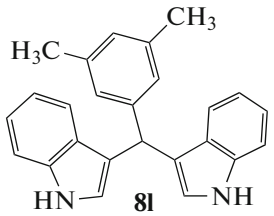


8k

2-[Di(1*H*-indol-3-yl)methyl]naphthalene-2-ol

Appearance: yellowish solid; R_f = 0.78 (*n*-hexane:EtOAc (5:5)); m.p. 246–248°C; IR, cm^{-1}: 755, 1132, 1312, 1513, 1605, 3283, 3327, 3409; ^{1}H NMR, δ_H, ppm: 6.48 (s, 1H), 6.74 (s, 1H), 6.78 (s, 2H), 6.98 (q, J = 5.0 Hz, 3H), 7.19 (t, J = 7.4 Hz, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.0 Hz, 1H), 7.98 (s, 2H), 8.13 (d, J = 8.4 Hz, 1H); ^{13}C NMR, δ, ppm: 32.2, 109.9, 111.3, 116.4, 119.4, 119.7, 122.4, 122.6, 123.0, 123.8, 126.7, 128.7, 129.0, 129.4, 132.8, 137.0, 153.9. Anal. calcd. for $C_{27}H_{20}N_2O$: C, 83.48; H, 5.19; N, 7.21; O, 4.12. Found: C, 83.45; H, 5.15; N, 7.24; O, 4.14. The spectral data are in good agreement with the literature values [52].

Bis(indolyl)methane 8l.

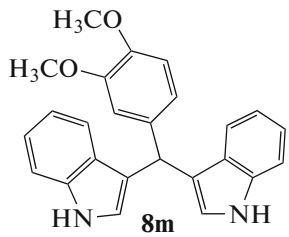


8l

3,3'-[(3,5-Dimethylphenyl)methylene]bis(1*H*-indole)

Appearance: white soild; R_f = 0.45 (*n*-hexane : EtOAc (1 : 9)); m.p. 94–97°C; IR, cm^{-1}: 795, 1145, 1285, 1482, 1572, 3316, 3349; ^{1}H NMR, δ_H, ppm: 2.23 (s, 6H), 5.79 (s, 1H), 6.65 (s, 2H), 6.83 (s, 1H), 7.01–6.95 (m, 4H), 7.16–7.12 (m, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.86 (s, 2H); ^{13}C NMR, δ, ppm: 21.3, 40.0, 110.8, 119.1, 119.9, 121.7, 123.5, 126.4, 127.1, 127.7, 136.6, 137.4, 143.8. Anal. calcd for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.65; H, 6.34; N, 8.00. The spectral data are in good agreement with the literature values [52].

Bis(indolyl)methane 8m.

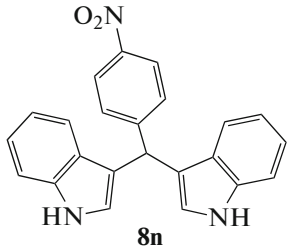


8m

3,3'-[(3,4-Dimethoxyphenyl)methylene]bis(1*H*-indole)

Appearance: yellowish solid; $R_f = 0.34$ (*n*-hexane : EtOAc (5 : 5)); m.p. 196–197°C; IR, cm^{-1}: 759, 1033, 1091, 1216, 1336, 1418, 1456, 1512, 1604, 3020, 3480; ^1H NMR, δ_H, ppm: 7.91 (bs, 2H, NH), 7.29–7.43 (m, 4H), 7.17 (t, 2H), 7.0 (t, 3H), 6.78 (d, 2H), 6.65 (d, 2H), 5.83 (s, 1H), 3.85 (s, 3H), 3.76 (s, 3H); ^{13}C NMR, δ, ppm: 39.8, 55.8, 111, 112.3, 119.2, 119.8, 121.9, 123.5, 127.1, 136.7, 147.4. Anal. calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32; O, 8.37. Found: C, 78.54; H, 5.81; N, 7.36; O, 8.35. The spectral data are in good agreement with the literature values [57].

Bis(indolyl)methane 8n.

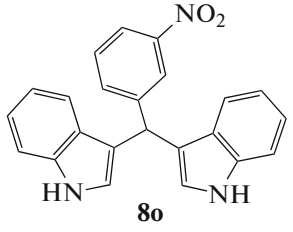


8n

3,3'-[(4-Nitrophenyl)methylene]bis(1*H*-indole)

Appearance: yellowish solid; $R_f = 0.45$ (*n*-hexane : EtOAc (1 : 9)); m.p. 221–222°C; IR, cm^{-1}: 775, 1150, 1296, 1490, 1586, 3329, 3356; ^1H NMR, δ_H, ppm: 6.11 (s, 1H), 6.94–6.90 (m, 4H), 7.11–7.07 (m, 2H), 7.36 (d, $J = 8.0$ Hz, 2H), 7.43 (d, $J = 8.4$ Hz, 2H), 7.67 (t, $J = 8.8$ Hz, 2H), 8.19 (d, $J = 8.8$ Hz, 2H); ^{13}C NMR, δ, ppm: 41.0, 112.3, 118.3, 119.6, 120.0, 122.3, 124.1, 124.7, 127.8, 130.6, 137.9, 147.3, 154.1. Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44; O, 8.71. Found: C, 75.12; H, 4.65; N, 11.46; O, 8.72. The spectral data are in good agreement with the literature values [58].

Bis(indolyl)methane 8o.

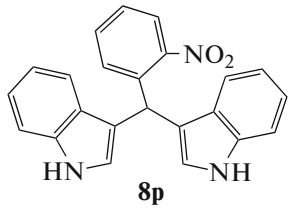


8o

3,3'-[(3-Nitrophenyl)methylene]bis(1*H*-indole)

Appearance: reddish solid; $R_f = 0.78$ (*n*-hexane : EtOAc (1 : 9)); m. p. 260–262°C; ^1H NMR, δ_H, ppm: 5.98 (s, 1H), 6.64 (s, 2H), 7.03 (dd, $J = 5.6$, $J = 7.6$ Hz, 2H), 7.19 (t, $J = 7.6$ Hz, 2H), 7.44–7.33 (m, 5H), 7.69 (d, $J = 7.6$ Hz, 1H), 7.99 (br s, 2H), 8.08 (d, $J = 8.0$ Hz, 1H), 8.20 (s, 1H); ^{13}C NMR, δ, ppm: 39.9, 111.3, 118.2, 119.4, 119.5, 121.5, 122.3, 123.6, 123.7, 126.6, 129.1, 134.9, 136.7, 146.4, 148.4. Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44; O, 8.71. Found: C, 75.16; H, 4.64; N, 11.43; O, 8.72. The spectral data are in good agreement with the literature values [58].

Bis(indolyl)methane 8p.

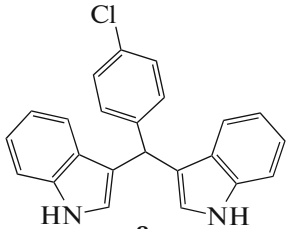


8p

3,3'-[(2-Nitrophenyl)methylene]bis(1*H*-indole)

Appearance: black-red solid; $R_f = 0.45$ (*n*-hexane : EtOAc (1 : 9)); m. p. 138–140°C; IR, cm^{-1}: 727, 1239, 1326, 1426, 1521, 1649, 3022, 3345; ^1H NMR, δ_H, ppm: 6.42 (d, $J = 1.6$ Hz, 2H), 6.61 (s, 1H), 6.94 (t, $J = 7.6$ Hz, 2H), 7.10 (t, $J = 7.2$ Hz, 2H), 7.20–7.18 (m, 2H), 7.25–7.22 (m, 2H), 7.34–7.29 (m, 3H), 7.77–7.73 (m, 3H); ^{13}C NMR, δ, ppm: 34.8, 111.4, 117.5, 119.5, 119.7, 122.2, 124.0, 124.4, 126.8, 127.3, 131.1, 132.5, 136.7, 138.1, 149.8. Anal. calcd. for $C_{23}H_{17}N_3O_2$: C, 75.19; H, 4.66; N, 11.44; O, 8.71. Found: C, 75.11; H, 4.68; N, 11.47; O, 8.72. The spectral data are in good agreement with the literature values [58].

Bis(indolyl)methane 8q.

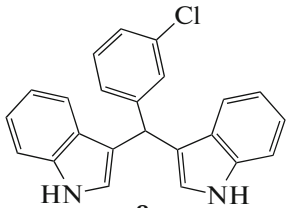


8q

3,3'-[(4-Chlorophenyl)methylene]bis(1*H*-indole)

Appearance: whitish solid; $R_f = 0.56$ (*n*-hexane : EtOAc (1 : 9)); m.p. 74–75°C; IR, cm^{-1}: 670, 759, 1015, 1091, 1216, 1417, 1456, 1523, 1600, 2927, 3020, 3478; ^1H NMR, δ_H, ppm: 5.86 (s, 1H), 6.63 (d, $J = 1.6$ Hz, 2H), 7.01 (t, $J = 7.6$ Hz, 2H), 7.18 (dd, $J = 8.4$, $J = 7.6$ Hz, 2H), 7.28–7.24 (m, 4H), 7.36 (d, $J = 8.4$ Hz, 4H), 7.93 (br s, 2H); ^{13}C NMR, δ, ppm: 39.6, 111.1, 119.2, 119.4, 119.8, 122.1, 123.6, 126.9, 128.4, 130.1, 131.8, 136.7, 142.6. Anal. calcd. for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; Cl, 9.94; N, 7.85. Found: C, 77.44; H, 4.79; Cl, 9.91; N, 7.82. The spectral data are in good agreement with the literature values [59].

Bis(indolyl)methane 8r.

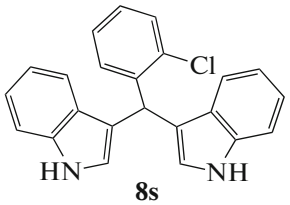


8r

3,3'-[(3-Chlorophenyl)methylene]bis(1*H*-indole)

Appearance: whitish solid; R_f = 0.45 (*n*-hexane : EtOAc (1 : 9)); m.p. 91–94°C; ^{1}H NMR, δ_H, ppm: 5.84 (s, 1H), 6.61 (d, *J* = 1.6 Hz, 2H), 7.03 (dd, *J* = 8.8, *J* = 8.0 Hz, 2H), 7.24–7.15 (m, 5H), 7.38–7.33 (m, 5H), 7.87 (br s, 2H); ^{13}C NMR, δ, ppm: 40.0, 111.1, 119.0, 119.4, 119.8, 122.1, 123.6, 126.4, 126.8, 126.9, 128.8, 129.5, 134.1, 136.7, 146.2. Anal. calcd. for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; Cl, 9.94; N, 7.85. Found: C, 77.42; H, 4.82; Cl, 9.93; N, 7.83. The spectral data are in good agreement with the literature values [59].

Bis(indolyl)methane 8s.



8s

3,3'-[(2-Chlorophenyl)methylene]bis(1*H*-indole)

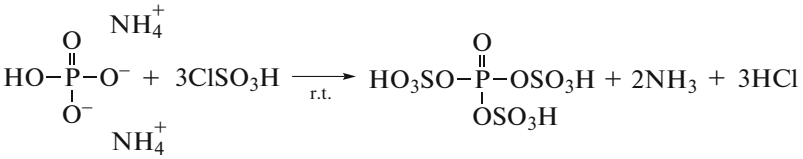
Appearance: reddish solid; R_f = 0.45 (*n*-hexane : EtOAc (1 : 9)); m.p. 73–74°C; IR, cm^{-1}: 730, 1208, 1305, 1424, 1517, 1615, 3016, 3425; ^{1}H NMR, δ_H, ppm: 6.31 (s, 1H), 6.49 (d, *J* = 1.7 Hz, 2H), 7.06–6.97 (m, 2H), 7.20–7.09 (m, 5H), 7.28 (d, *J* = 8.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 3H), 7.70 (br s, 2H); ^{13}C NMR, δ, ppm: 36.7, 111.2, 118.3, 119.3, 119.9, 122.1, 123.9, 126.7, 127.0, 127.6, 129.5, 130.4, 133.9, 136.7, 141.4. Anal. calcd. for $C_{23}H_{17}ClN_2$: C, 77.41; H, 4.80; Cl, 9.94; N, 7.85. Found: C, 77.42; H, 4.81; Cl, 9.84; N, 7.83. The spectral data are in good agreement with the literature values [59].

RESULTS AND DISCUSSION

Phospho Sulfonic Acid Preparation and Properties

Over the past few years, the application of recyclable solid acid catalysts has received significant attention in organic synthesis as a result of their profitable and environmental benefits. These types of reagents not only make simpler purification processes but also help in reducing the liberation of toxic reaction residues into the environment [60–62]. The solid acid catalysts are simply removed from the reaction mixture by filtration or centrifugation without the need for neutralization, thereby enabling more eco-friendly processes. Phospho sulfonic acid (PSA) as a new solid acid catalyst was reported by Kiasat et al. in 2013. It has been employed as a promising solid acid catalyst in various organic functionalizations [60, 63].

PSA as a heterogeneous and solid acid catalyst was simply synthesized by the stirring of DAP and chlorosulfuric acid in DCM at room temperature (Scheme 1). The yield was 83% and the melting point was observed to be 127–130°C. It is observed that this reaction is clean and easy because the by-products of the reaction are NH_3 and HCl gases, which are evolved immediately from there action flask. It is also noticed that PSA is a non-volatile, non-corrosive, recyclable, and eco-friendly solid acid catalyst. Moreover, it also offers numerous advantages such as cleaner reactions, long catalytic life, excellent solubility in water, safe and inexpensive in comparison to classical catalysts. Moreover, it displayed high thermal stability, reactivity and catalytic activities, and can easily be handled and removed from the reaction content [63–65].



Scheme 1. Synthesis of phospho sulfonic acid.

Characterization of Phospho Sulfonic Acid

One of the useful methods for an examination of catalyst development is infrared spectroscopy. Accordingly, the formation of the phospho sulfonic acid was determined by spectrum of infrared spectrometer *via* the potassium bromide disc approach (Fig. 1). As illustrated in Fig. 1, the sharp peaks in the range of 3422–3336 cm^{-1} and range of 3172–3085 cm^{-1} are related to the O–H stretch of the SO_3H group [61, 62]. The signal at 1237 cm^{-1} is owing to the S=O asymmetric stretching and signal at 1147 cm^{-1} is attributed to the S=O symmetric stretching vibrations. The signal at 730 cm^{-1} is due to S–O stretching vibrations. The O=S=O symmetric and asymmetric stretching signals, and stretching S–O signal precisely confirmed the presence of the SO_3 group linkage [63–65]. Appearance of signals at 1048 and 998 cm^{-1} are owing to stretching vibration of P=O and P–O bonds, respectively. The sulfonic acid loading of PSA was calculated based on titration of the proton-exchanged brine solution and shown the loading of 11.0 $mmol_{SO_3H}$/g of acidic catalyst [66].

In order to investigate the structure and purity of synthesized PSA, ^{31}P NMR of PSA was carried out

(Fig. 2). Orthophosphate is a salt or ester of orthophosphoric acid, or any compound containing the trivalent group $-PO_4$. Hence, a peak at −4 ppm indicating the presence of $O{=}P(OX)_3$ in the structure of PSA. Further, a single peak of phosphorous of PSA in spectrum demonstrates the absence of starting material in catalyst material, revealing that the synthesized PSA is highly pure.

In order to study the thermal stability of the PSA, thermal gravimetric analysis (TGA) was performed in the range of temperature from 20 to 280°C (Fig. 3). In the TGA curve, two-stage decomposition is noticed corresponding to different weight lose ranges. The first stage is from 20 to 241°C, accompanied by a weight loss of around 8.03% and corresponding to desorption of trapped water and organic solvents, which were used in synthesis the catalyst. The second decomposition stage occurred from 241 to 416°C, accompanied by a large weight loss of approximately 83% and corresponding to the thermal decomposition of catalyst and/or breaking of bonds. From the TGA, it can be deduced that PSA could be employed safety in organic reactions due to large thermal stability up to around 210°C.

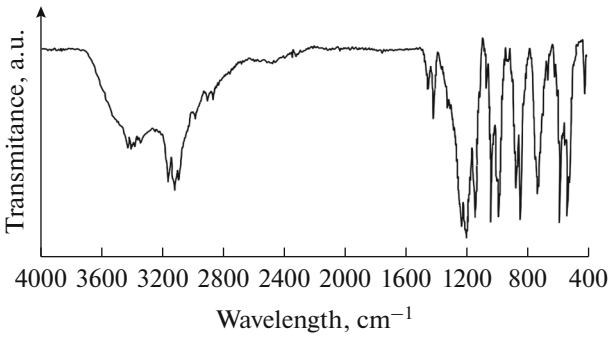


Fig. 1. FT-IR spectrum of the phospho sulfonic acid.

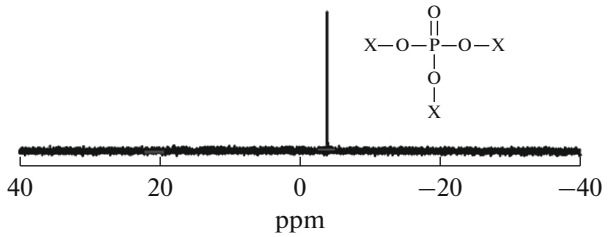


Fig. 2. ^{31}P NMR spectrum of PSA.

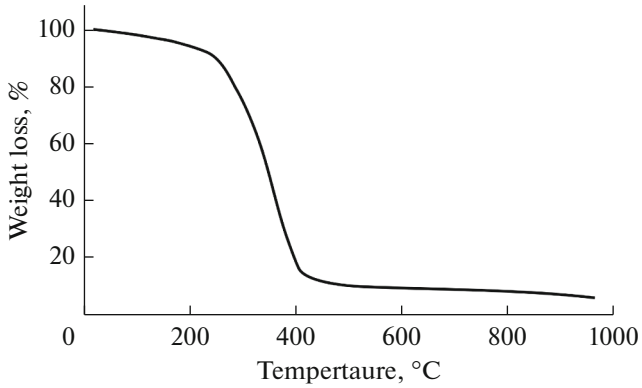


Fig. 3. The TGA curve of PSA.

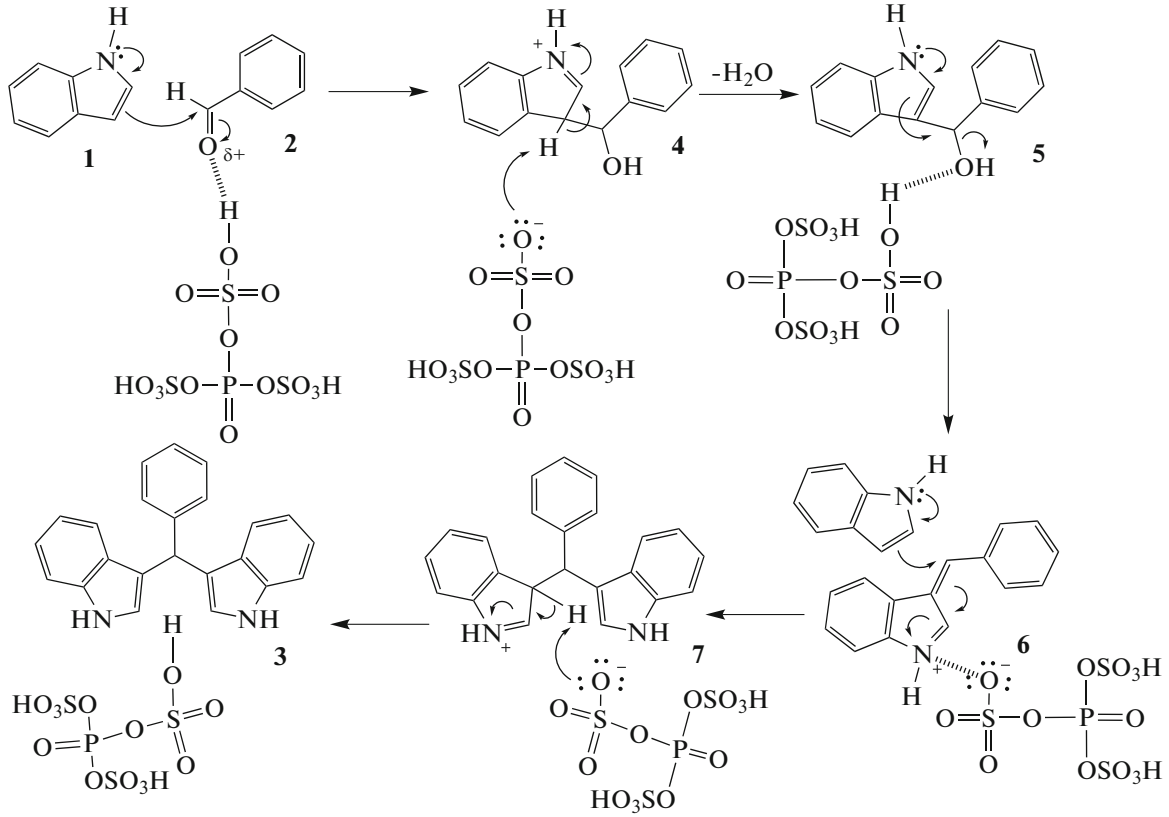
Catalytic Activity of Phospho Sulfonic Acid and Reaction Conditions Optimization

Initially, we decided to investigate the efficiency of PSA as a catalyst in the synthesis of bis(indolyl)alkanes. To optimize the reaction conditions, benzaldehyde **2** was selected as a model for the electrophilic substitution reaction with indole **1**. Benzaldehyde **2** (1 mmol) was reacted with indole **1** (2 mmol) in the presence of phospho sulfonic acid as a catalyst under various conditions (Table 1). Several different solvents were screened against the model reaction, including water, chloroform, acetonitrile, ethanol, methanol and tetrahydrofuran (THF), which gave the best results in terms of the reaction time and yield. Following a period of screening, the optimal reaction conditions for the model reaction were determined to be 1 mmol aldehyde, 2 mmol benzaldehyde, and 0.06 g of the phospho sulfonic acid catalyst in 30 mL of H_2O at refluxing, as shown in Table 1. It is interesting to note that further increases in the amount of catalyst or temperature did not lead to any improvements in the reaction time or yield. In the solvent free conditions, even in the presence of 0.06 g of the catalyst at 100°C, the yields are low. The yields of **3** were measured by ^1H NMR spectroscopy using 1,3,5-trimethylbenzene as an internal standard. Noteworthy, the beauty of this methodology is that the reaction takes place in water to afford the product in acceptable yield. Recently, organic reactions conducted in aqueous media have received much attention, because water is nontoxic, cheap, abundantly available and benign to the environment [67, 68]. Water not only increases the rate and yield of reactions, but also enhances enantioselectivity in chiral synthesis. In addition, reactions in aqueous media illustrate unique selectivity and reactivity that are not frequently noticed in organic environment [69].

Plausible Mechanistic Pathway of the Synthesis of Bis(Indolyl)Alkanes

In the initial step, proton on phospho sulfonic acid activate the carbonyl unit of the aromatic aldehyde, resulting in formation of complex **4** via attack by indole on carbonyl group of aldehyde and removal of

proton of phospho sulfonic acid (Scheme 2). Next, abstraction of proton by nucleophilic attack of phospho sulfonic acid on proton of indole and subsequent phospho sulfonic acid-assisted elimination of water via rearrangement afforded intermediate **6**. Then, another indole molecule is coupled with intermediate **6** via an aza-Michael addition reaction to deliver intermediate **7**. Finally, through the significant collaboration between nitrogen and phospho sulfonic acid in **7**, abstraction of proton by nucleophilic attack is enhanced, and complex **7** is converted into **3**, and the catalyst phospho sulfonic acid then enters another catalytic cycle (Scheme 2). The study of mechanism reveals that water also plays important role during reaction. All the steps of reactions were also accelerated by water attributed to enforced hydrophobic interactions during the activation process and enhanced hydrogen bonding.



Scheme 2. Proposed reaction for construction of bis(indolyl)alkane framework.

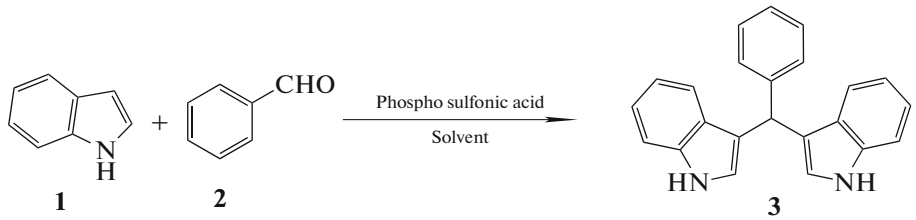
Reusability of Phospho Sulfonic Acid Catalyst

The recyclability of the phospho sulfonic acid catalyst was also studied in the same model reaction under optimized conditions (Fig. 4). Upon reaction completion, the recovered catalyst by filtration was washed with thoroughly with water and then EtOAc. After drying, it was reused for subsequent reactions. The procedure was repeated and the results indicated that the catalyst could be recycled for almost four times with only a small loss of activity. Briefly, the fresh catalyst afforded **3** in 92% yield in reaction time of 120 min. In first cycle, the catalyst provides **3** in 86% yield in the same period of reaction time. In second cycle, the catalyst delivers **3** in 81% yield in reaction time of 130 min. In third run, the catalytic efficiency decreases significantly, i.e., yield of **3** becomes 72% in reaction time of 130 min. In fourth run, the catalyst gives 70% yield in reaction time of 140 min. This indicated that the phospho sulfonic acid was an operative and recyclable catalyst for the preparation of bis(indolyl)alkanes. The decrease in product yield with number of reuses is might be owing to handling loss during work-up. For this, we have also performed the recovery wt % of catalyst after each cycle and decrease in wt % from 100 to 91% was noticed (Fig. 4).

Synthesis of Library of Bis(Indolyl)Alkanes

To demonstrate the generality of the procedure, the reaction protocol was then extended towards a library of aromatic aldehydes **7** with indole **1** and the consequences are illustrated in Table 2. Pleasingly, current

Table 1. Yield of bis(indolyl)alkane at different reaction conditions*



1 **2** **3**

Entry	Solvent	Phospho sulfonic acid, g	*t*, min	*T*, °C**	^{1}H NMR yield, %***
1	H_2O	0.04	120	100	87
2	$CHCl_3$	0.04	160	60	83
3	CH_3CN	0.04	140	82	82
4	EtOH	0.04	120	80	86
5	CH_3OH	0.04	120	65	82
6	THF	0.04	140	65	81
7	**H_2O**	**0.06**	**120**	**100**	**92**
8	H_2O	0.08	120	100	91
9	H_2O	0.06	160	100	92
10	$CHCl_3$	0.06	160	60	86
11	CH_3CN	0.06	140	82	87
12	EtOH	0.06	120	80	89
13	CH_3OH	0.06	120	65	85
14	THF	0.06	140	65	85
15	No solvent	0.06	120	100	81

* Reaction conditions: benzaldehyde (1 mmol), indole (2 equiv), phospho sulfonic acid in refluxing solvent.
** Oil bath temperature.
*** ^{1}H NMR yields, using 1,3,5-trimethylbenzene as an internal standard.

technique tolerates a series of functional groups, for example, halo, methoxy and hydroxyl, and a broad spectrum of aromatic aldehydes containing an electron-donating (i.e., CH_3, OCH_3 and OH; Table 2, entries 5–7, 9–12) or electron-withdrawing/deactivating (i.e., Cl and NO_2; Table 2, entries 4, 8, 14–19) group at the *para*-, *meta*- or *ortho*-position of their benzene ring were readily converted to the corresponding 3,3'-(arylmethylene)bis(4-hydroxycoumarins) in excellent isolated yields over short reaction times under the optimized conditions. Both deactivating (Table 2, entries 4, 8, 14–19) and electron-donating/electron-releasing (Table 2, entries 5–7, 9–12) substituents had no significant effect on the reaction yields. However, in-depth analysis reveals interesting finding that substrates having electron-donating groups (Table 2, entries 6, 7 and 13) *para* to the position of the electrophilic substitution afforded excellent yields in the somewhat smaller time. Most probably, it is because an electron releasing unit increases the density of electron at the *p*-position to it, resulting that position more vulnerable to electrophilic attack. On the reaction results, the presence of halo substituent on the ring of aldehydes had an insignificant effect (Table 2, entries 8, 17–19). Heteroaromatic aldehydes also afforded the respective bis(indolyl)alkanes in high yields (Table 2, entries 1–3). Additionally, the conditions of reaction were mild enough to bring any damage to the acid-sensitive moieties (Table 2, entries 4, 5, 9–11). Hence, the experimental technique is very convenient, effective and simple, and has the capability to tolerate a diversity of functional groups.

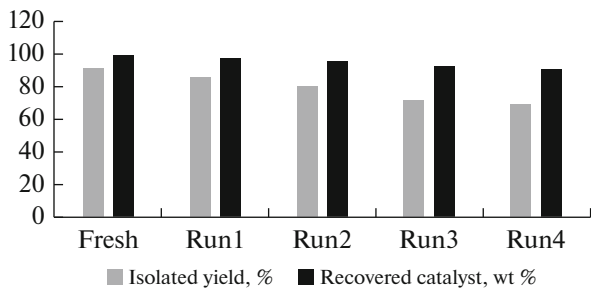
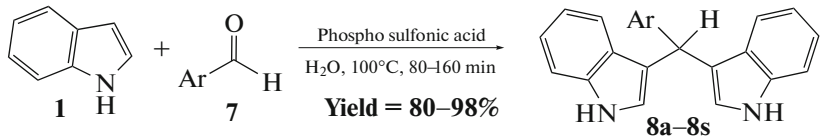


Fig. 4. Reusability of phospho sulfonic acid catalyst in the synthesis of **3**.

Table 2. Synthesis of library of bis(indolyl)alkanes



Entry	R_1	Product	Yield, %*	Time, min	Melting point, °C	
					experimented	reported [ref.]
1	2-Thienyl	**8a**	81	120	146–147	150–153 [49]
2	2-Furyl	**8b**	82	130	315–317	316–318 [50]
3	3-Indolyl	**8c**	86	120	161–164	160–161 [51]
4**	2-OH-3-ClC_6H_3	**8d**	89	140	201–203	202–204 [52]
5	2-OH-3-^{t}BuC_6H_3	**8e**	82	160	189–191	188–190 [52]
6	4-$CH_3C_6H_4$	**8f**	97	80	98–99	95–97 [53]
7	4-$OCH_3C_6H_4$	**8g**	98	90	179–182	179–181 [54]
8	2,3-Di-ClC_6H_3	**8h**	83	120	96–98	96–97 [55]
9	2-OHC_6H_4	**8i**	80	120	Liquid	Liquid [56]
10	2-OH-3-OCH_3-5-$NO_2C_6H_2$	**8j**	84	160	229–230	228–230 [52]
11***	2-OHNp	**8k**	85	160	246–248	245–248 [52]
12	3,5-$CH_3C_6H_3$	**8l**	91	140	94–97	94–96 [52]
13	4,5-Di-$OCH_3C_6H_3$	**8m**	97	80	196–197	198–200 [57]
14	4-$NO_2C_6H_4$	**8n**	83	130	221–222	220–222 [58]
15	3-$NO_2C_6H_4$	**8o**	87	120	260–262	260–261 [58]
16	2-$NO_2C_6H_4$	**8p**	89	140	138–140	140–141 [58]
17	4-ClC_6H_4	**8q**	81	140	74–75	74–75 [59]
18	3-ClC_6H_4	**8r**	84	130	91–94	91–92 [59]
19	2-ClC_6H_4	**8s**	83	120	73–74	72–73 [59]

* Isolated yield.
** 0.7 g of phospho sulfonic acid catalyst is used.
*** 0.8 g of phospho sulfonic acid catalyst is used.

Table 3. Comparison of phospho sulfonic acid catalytic performance with other reported catalysts

Entry	Reagent and conditions	Time, min	Yield, %*	Ref.
1	$H_6P_2W_{18}O_{62}$, solvent-free, 110°C	40	96	[71]
2	Silica sulfuric acid, solvent-free, r. t.	40	95	[72]
3	Zeolite, CH_2Cl_2, r. t.	120	88	[73]
4	$AlPW_{12}O_{40}$, CH_3CN, r. t.	15	92	[74]
5	$La(PFO)_3$, EtOH	30	90	[75]
6	Zeokarb-225, CH_3CN	450	95	[76]
7	$PPh_3 \cdot HClO_4$, CH_3CN	30	61	[77]
8	$Zn(HSO_4)_2$	180	91	[78]
9	$In(OTf)_3$, CH_3CN	25	71	[79]
10	$Ln(OTf)_3$, $EtOH{\cdot}H_2O$	720	95	[80]
11	$ZrOCl_2 \cdot 8H_2O$, solvent-free, 50°C	40	84	[81]
12	[Bmim]Br, microwave (400 W), 150°C	8	95	[82]
13	Trityl chloride, solvent-free, r. t.	20	90	[83]
14	P_2O_5/SiO_2, solvent-free, r. t.	30	94	[84]
15	$MgSO_4$, solvent-free, 50°C	25	92	[85]
16	PEG-SO_3H, H_2O, r. t.	20	92	[70]
17	Phospho sulfonic acid, H_2O, 100°C	120	92	This work

* Isolated yield.

Characterization of Bis(Indolyl)Alkanes

All synthesized bis(indolyl)alkanes were verified through FTIR, ^{1}H and ^{13}C NMR spectroscopic techniques. Along with peaks of substituent, heteroaromatic or/and aromatic proton in proton of bis(indolyl)alkanes, the spectra showed peaks at $\delta = 3.72–3.78$ (t, =CH–R, R = *n*-alkyl) or 5.71–4.86 (s, =CH–R, R = hetaryl, aryl) and at $\delta = 8.81–8.06$ (br s, NH), respectively [52]. The remaining peaks of protons in spectra were noticed in the expected ranges. In the ^{13}C NMR spectra of the bis(indolyl)alkanes, the peaks in the range of 54.2–32.3 ppm were noticed. The peaks are owing to carbon of Ar–CH, evidencing the construction of bis(indolyl)alkane moieties. The FTIR spectra of the bis(indolyl)alkanes displayed the characteristic signals at 1580–1613 (C=C–N), 1660–1676 (aromatic C=C), 2850–2860 (aliphatic C–H), 3037–3062 (aromatic C–H) and 3170–3747 (N–H) cm^{-1} [59].

Comparison of Phospho Sulfonic Acid Catalytic Performance with Other Catalysts

The efficiency of phospho sulfonic acid (PSA) for the preparation of the bis(indolyl)alkanes was compared with that of other catalysts reported in the literature [70]. From Table 3, it is clear that the present method is more effective when all terms including catalyst, conditions, reaction times and yields are taken into account. Contrary to some of the previously reported methods; this work does not require any ionic liquids, hazardous solvents such as chloroform or special devices such as ultrasound and microwave. Hence, it is the most promising choice for preparation of bis(indolyl)alkanes.

CONCLUSIONS

To sum up, an approach for using phospho sulfonic acid (PSA) as an effective catalyst for reactions of indole with aldehydes has been disclosed as anticipated, which provides structurally diverse bis(indolyl)alkanes within 80–160 min in 80–98% yields. In this approach, reactions take place in water and hence, environmentally unfavorable volatile organic solvents have been completely avoided by adopting this strategy. To understand the observed reactivity, a possible mechanism of construction of bis(indolyl)alkane skeleton is proposed. The notable characteristics of this new technique are no side reactions, ease of product separation, work-up procedures, simple experimental, cleaner reaction profiles, high conversions and shorter reaction times. The recyclability of catalyst makes the process more environment-friendly and economically viable for the preparation of various biologically and industrially important chemicals. Hopefully, it will encourage present and future synthetic chemists to employ this approach and enlarge the area of bis(indolyl)alkane preparation.

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