

KHSO₄-SiO₂ catalyzed facile synthesis of bis(indolyl)methanes

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Abstract: This work presents a highly efficient and simple method for the synthesis of bis(indolyl)methanes, catalyzed by KHSO₄-SiO₂ with excellent yields. Various substituted aldehydes with indole under this reaction condition is elucidated. This method is an environmentally benign, efficient reaction, requires shorter reaction time and simple experimental and workup procedures.

Keywords: KHSO₄-SiO₂; aldehydes; indole; bisindolylmethanes; solvent-free reaction.

1. Introduction

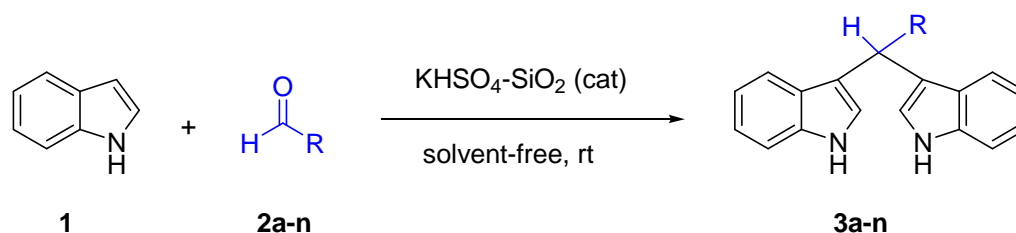
The indole ring system is present in many natural products, pharmaceuticals, agrochemicals, and other compounds of importance¹. They are known to exhibit various biological activities including antibacterial, cytotoxic, antioxidative and insecticidal activities². The feasibility of electrophilic substitution at the 3-position of indole is such that it is widely used in organic synthesis³. Bis(indolyl)methanes have been obtained by reactions of indoles with various aldehydes via azafulvenium salt as intermediate form in the presence of several Bronsted⁴ and Lewis acid catalyst such as LiClO₄⁵, In(OTf)₃⁶, Dy(OTf)₃⁷, Sc(OTf)₃^{8,9}, CAN¹⁰, ZrOCl₂¹¹, InCl₃¹², AlPW₁₂O₄₀¹³, ionic liquids¹⁴, trichloro-1,3,5 triazine¹⁵, PFPAT¹⁶, HFIP¹⁷ and KHSO₄¹⁸.

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Many of the methods used have such disadvantages as long reaction times¹⁹, the use of expensive reagents or preformed reagents^{20,21} and poor yields of bis(indolyl)methanes. Although some of these reactions are performed under mild conditions, most of them require a long period for completion, tedious work-up, the formation of side products and only modest yields of the products. Therefore, a convenient, rapid and efficient method for preparation of bis(indolyl)methane is still sought. When compared with $\text{NaHSO}_4 \cdot 2\text{H}_2\text{O}$ ²², $\text{NaHSO}_4 \cdot \text{SiO}_2$ ²³ and KHSO_4 ¹⁸, the $\text{KHSO}_4 \cdot \text{SiO}_2$ is an efficient catalyst for the synthesis of bis(indolyl)methanes due to the time factor and solvent system. The previous reports were mentioned long reaction time and also used different solvents, in our study all the reactions were done in very short timings (in mins) and solvent free system and it is an added advantage. In this report we wish to introduce $\text{KHSO}_4 \cdot \text{SiO}_2$ as an efficient catalyst for the synthesis of bis(indolyl)methanes in high yields for the first time. The method is highly efficient and free from aforesaid drawbacks.

2. Results and discussion

In continuation of our research and interest in the development of novel synthetic methodologies^{24,25} herein, we would like to report that $\text{KHSO}_4 \cdot \text{SiO}_2$ is an efficient catalyst for the formation of bis(indolyl)methanes by one-pot two component reaction of an aldehyde and indole under solvent-free conditions (Scheme 1).



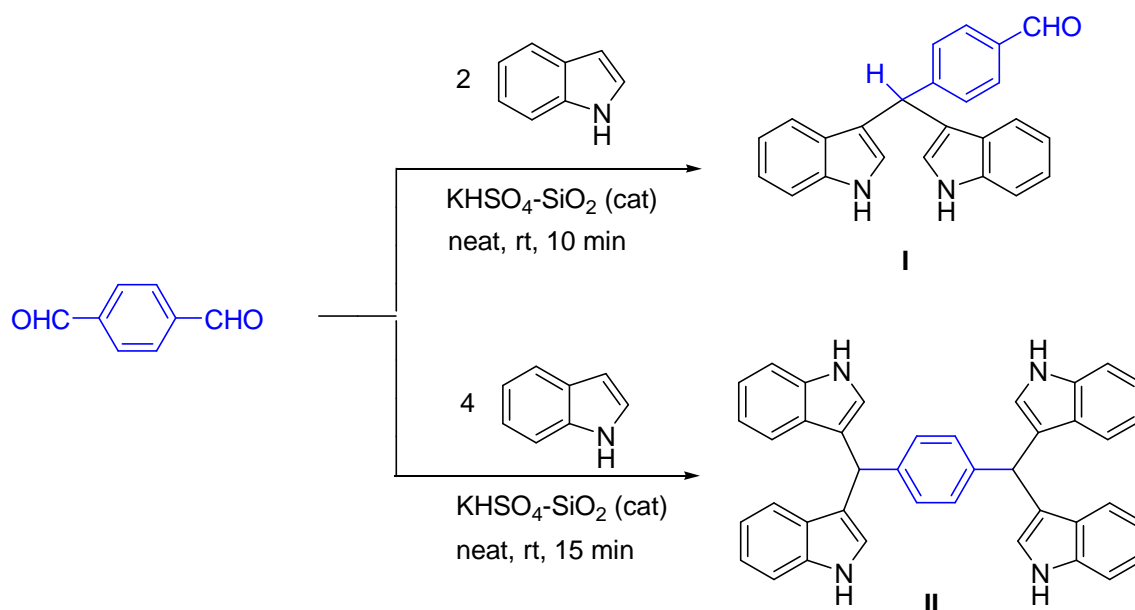
Scheme 1. Synthesis of Bis(indolyl)methanes

To evaluate the effect of solvent, various solvents such as THF, toluene, acetonitrile and ethanol were used for the model reaction. The desired product was obtained in 40, 48, 58, 75% yields respectively, after the prolonged reaction time 5-6 h. Whereas the neat condition afforded the product in excellent 97% yield within very short time 2 min. It shows that the use of solvent retards the rate of reaction which leads to decrease in yield of product.

To determine the appropriate concentration of the catalyst $\text{KHSO}_4 \cdot \text{SiO}_2$, we investigate the model reaction at different concentrations of catalyst like 1, 3, 5 and 7 mol%. The product formed in 72, 86, 97 and 97% yield respectively. This indicates that 5 mol% of $\text{KHSO}_4 \cdot \text{SiO}_2$ is sufficient for the best result by considering the reaction time and yield of product.

Interestingly, the catalyst was effectively used for the synthesis of di-bis(indolyl)methanes from indole and terephthalaldehyde (Scheme 2). The reaction of 2 equivalents of indole with 1 equivalent of terephthalaldehyde proceeded successfully to give bis(indolyl)methane benzaldehyde [26] (**I**) in excellent yield. On the other hand, using 4 equivalents of indole di(bis-indolylmethane)benzene [26] (**II**) was obtained in high yield (Scheme 2) within 10-15 min under similar reaction conditions.

Synthesis of bis(indolyl)methanes



Scheme 2. Synthesis of di(bisindolyl)methanes

The synthetic route for the bis(indolyl)methanes in good yields (84–97%) involved reaction of various substituted aldehydes (**2a–n**) with indole (**1**) in presence of $\text{KHSO}_4\text{-SiO}_2$ at room temperature. The chemical structures of (**3a–n**) were confirmed by ^1H , ^{13}C and mass spectral data. The $-\text{NH}$ protons gave singlet in the region of (δ 10.78–8.01) and the methyleneoxy protons resonated as multiplets at (δ 4.06–4.01)²⁵. The alkene protons gave singlet in the region of δ 6.73–6.31. Similarly the Ar-CH- protons also gave singlet in the region of δ 8.89–5.14.

The scope of application of the presented method is demonstrated by using the various substituted aromatic and heterocyclic aldehydes to react with indole. The results are summarized in (Table 1). The electronic nature of the substituents in the aromatic ring did not show any noticeable effect on this conversion. In addition, the present methodology is found to be highly efficient for the preparation of bisindolylmethanes.

Table 1. Preparation of bis-indolylmethane derivatives catalyzed by $\text{KHSO}_4\text{-SiO}_2$ at room temperature from indoles.

Entry	R	Yield [%]	Time (min)
2a	5-OEt,2-OH.C ₆ H ₃	90	5
2b	4-Cl,2-OH.C ₆ H ₃	85	6
2c	5Br,2OH.C ₆ H ₃	91	8
2d	3-NO ₂ .C ₆ H ₄	97	2
2e	2-NO ₂ .C ₆ H ₄	86	3
2f	4-NO ₂ .C ₆ H ₄	95	2
2g	3-Cl,4-NO ₂ .C ₆ H ₃	91	2
2h	4-Cl.C ₆ H ₄	95	4
2i	4-CN.C ₆ H ₄	93	5
2j	4-OCH ₂ C ₆ H ₅ .C ₆ H ₄	93	10
2k	2-NO ₂ .C ₆ H ₄ CH=CH	84	12
2l	2-S.C ₄ H ₃	89	9
2m	3-N.C ₅ H ₄	95	10
2n	4N.C ₃ H ₄	90	8

3. Conclusion

The condensation of indole with carbonyl compounds was successfully carried out in the presence of a $\text{KHSO}_4\text{-SiO}_2$ at room temperature under solvent-free condition. This procedure accomplished short reaction time, high yields, economically viable and environment friendly protocol.

4. Experimental

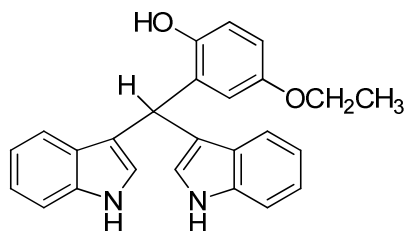
Indole, carbonyl compounds, KHSO_4 and silica gel were purchased from Fluka Chemical Companies. The progress of the reactions was monitored by thin layer chromatography (TLC) using silica gel 60 F₂₅₄ (pre-coated aluminium sheets) from Merck. ¹H NMR and ¹³C NMR spectra were obtained in CDCl₃ on a Varian 400 MHz NMR spectrometer by using TMS as an internal standard. Infrared Spectra (ν_{max} in cm⁻¹) were recorded as KBr pellets on a Perkin-Elmer, FT-IR 100 spectrophotometer. E.S.I Mass spectra were recorded on API-3000 mass spectrometer.

4.1. General procedure for condensation of indole with benzaldehyde by $\text{KHSO}_4\text{-SiO}_2$

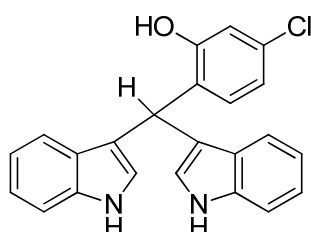
To a mixture of indole (0.002 mole) and 2-benzyloxy benzaldehyde (0.001 mole), $\text{KHSO}_4\text{-SiO}_2$ (5 mol%) was added. The resulting mixture was stirred at room temperature for the appropriate time. When the reaction was complete, water (10 mL) was added to quench the reaction and extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were dried using anhydrous Na₂SO₄, filtered and the solvent evaporated. The crude products were purified by column chromatography and eluted with ethyl acetate and petroleum ether mixture to afford the products. The products were isolated and identified by comparison of their physical and spectral data with authentic samples prepared according to previous methods.

Synthesis of bis(indolyl)methanes

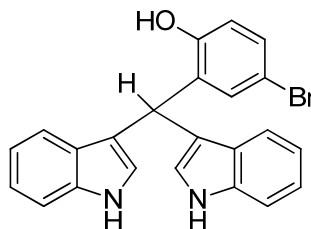
4.2. Spectroscopic data for title compounds



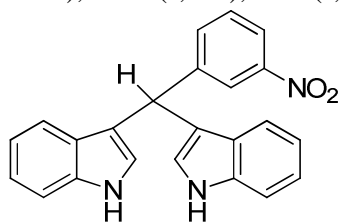
3,3'-((5-ethoxy-2-hydroxyphenyl)methylene)bis(1H-indole) (3a): Reddish brown Solid; mp. 112-113 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.82 (s, 1H, OH), 8.69 (brs, 2H, NH), 7.39-6.75 (m, 11H, Ar-H), 6.73 (s, 2H), 5.74 (s, 1H, Ar-CH), 4.12-3.91 (m, 2H, OCH_2), 1.29 (t, 3H, $J = 7.0$ Hz); EIMS: m/z : 381 ($\text{M}-1$) $^+$.



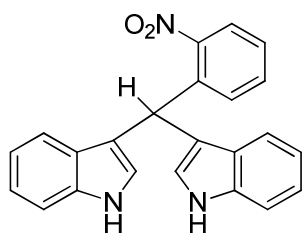
3,3'-((4-chloro-2-hydroxyphenyl)methylene)bis(1H-indole) (3b): Reddish brown Solid; mp. 218-220 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.80 (s, 1H, OH), 9.63 (brs, 2H, NH), 7.52-6.75 (m, 11H, Ar-H), 6.25 (s, 2H), 5.14 (s, 1H, Ar-CH); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 157.2, 139.4, 134.2, 131.5, 129.5, 127.5, 126.6, 125.3, 124.6, 120.2, 119.8, 118.2, 112.7, 111.8, 43.4; Anal. Calc. for $\text{C}_{23}\text{H}_{17}\text{ClN}_2\text{O}$: C, 74.09; H, 4.60; N, 7.51; Found: C, 73.96; H, 4.56; N, 7.45.



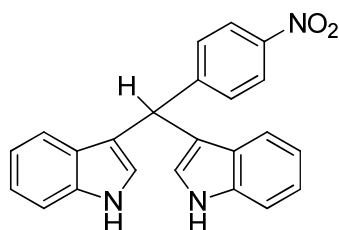
3,3'-((5-bromo-2-hydroxyphenyl)methylene)bis(1H-indole) (3c): Solid; mp. 136-138 °C; Lit²⁷. mp. 138-140 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 10.81 (s, 1H, OH), 9.80 (brs, 2H, NH), 7.35-6.76 (m, 11H, Ar-H), 6.13 (s, 2H), 5.72 (s, 1H, Ar-CH).



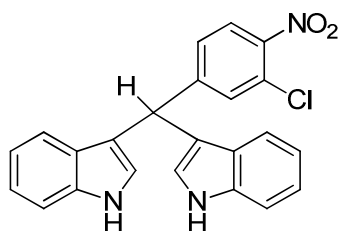
3,3'-((3-nitrophenyl)methylene)bis(1H-indole) (3d): Reddish brown Solid; mp. 220-222 °C Lit²⁸. mp 218-220 °C; IR (KBr): 3420 (NH), 3050, 1595, 1510, 1455, 1340 cm^{-1} ; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.05 (brs, 2H, NH), 7.50 -7.00 (m, 12H, Ar-H), 6.70 (s, 2H), 5.92 (s, 1H, Ar-CH); EIMS: m/z : 369 ($\text{M}+1$) $^+$; Anal. Calc. for $\text{C}_{23}\text{H}_{17}\text{N}_3\text{O}_2$: C, 75.2; H, 4.7; N, 11.4 %; Found: C, 75.3; H, 4.5; N, 11.6 %.



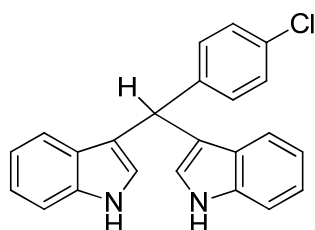
3,3'-((2-nitrophenyl)methylene)bis(1H-indole) (3e): Reddish brown Solid; mp. 221-223 °C; Lit²⁹. mp. 220-222°C; ¹H NMR (400 MHz, CDCl₃): δ 8.15 (brs, 2H, NH), 7.96 -7.35 (m, 12H, Ar-H), 6.70 (s, 2H), 5.98 (s, 1H, Ar-CH).



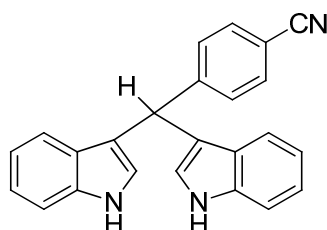
3,3'-((4-nitrophenyl)methylene)bis(1H-indole) (3f): Reddish brown Solid; mp. 263-265 °C; Lit²⁹. mp. 265-266°C; IR (KBr): 3426 (NH), 3052, 1598, 1514, 1450, 1348 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 8.19 (brs, 2H, NH), 8.05 (d, 2H, *J* = 8.8), 7.50 (d, 2H, *J* = 8.8), 7.40 -7.12 (m, 8H, Ar-H), 6.70 (s, 2H), 5.91 (s, 1H, Ar-CH); EIMS: *m/z*: 369 (M+1)⁺; Anal. Calc. for C₂₃H₁₇N₃O₂: C, 75.2; H, 4.7; N, 11.4 %; Found: C, 75.1; H, 4.3; N, 11.3 %.



3,3'-((4-nitro-3-chlorophenyl)methylene)bis(1H-indole) (3g): Reddish brown Solid; mp. 118-120 °C; IR (KBr): 3415 (NH), 3055, 1490, 1450, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.95 (brs, 2H, NH), 7.78-7.05 (m, 11H, Ar-H), 6.65 (s, 2H), 5.80 (s, 1H, Ar-CH).

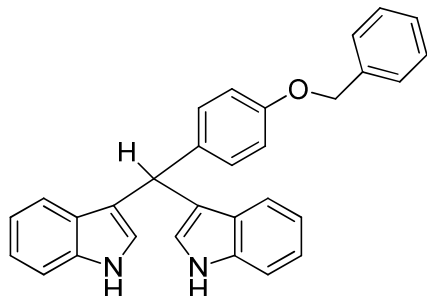


3,3'-((4-chlorophenyl)methylene)bis(1H-indole) (3h): Reddish brown Solid; mp. 104-106 °C; Lit²⁹. mp.104-106°C; IR (KBr): 3415, 3055, 1490, 1450, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 7.95 (brs, 2H, NH), 7.35-7.25 (m, 8H, Ar-H), 7.15 (d, 2H, *J* = 7.9), 7.05 (d, 2H, *J* = 8.3), 6.65 (s, 2H), 5.80 (s, 1H, Ar-CH).

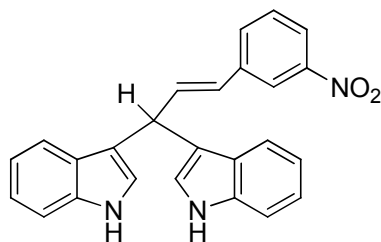


Synthesis of bis(indolyl)methanes

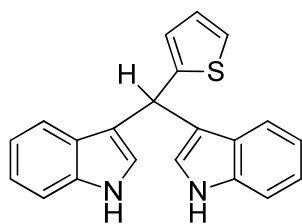
4-(Di(1*H*-indol-3-yl)methyl)benzonitrile (3i): White Solid; mp. 212–214 °C Lit³⁰. mp.210-212°C; IR (KBr): 3406, 2225, 1736, 1651, 1363, 1215, 1091, 740 cm⁻¹. ¹H NMR (400MHz, CDCl₃): δ 8.05 (brs, 2H), 7.54 (d, *J* = or 8.4 Hz, 2H), 7.43 (d, *J* = 8.2Hz, 2H), 7.34-7.01 (m, 8H), 6.63 (s, 2H), 5.93 (s, 1H). ¹³C NMR (100MHz, CDCl₃): δ 149.8, 136.7, 132.1, 129.3, 126.8, 123.7, 122.3, 119.2, 119.5, 119.2, 118.1, 111.3, 109.9, 40.3.



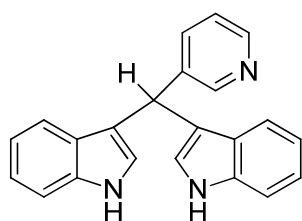
3,3'-((4-benzyloxy)phenyl)methylene)bis(1*H*-indole) (3j): Reddish brown Solid; mp. 264-266 °C; Lit²⁹. mp.264-266 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 10.78 (brs, 2H, NH), 7.37-6.77 (m, 17H, Ar-H), 6.31 (s, 2H, Ar-H), 5.14 (s, 1H, Ar-CH) 4.06-4.01 (m, 2H, O-CH₂); ¹³C NMR (100 MHz, DMSO*d*₆): δ 155.7, 137.8, 137.0, 133.7, 129.5, 128.6, 127.9, 127.5, 127.4, 121.2, 120.7, 119.3, 118.5, 118.2, 112.8, 111.8, 69.7, 47.8; EIMS: *m/z*: 428 [M]⁺.



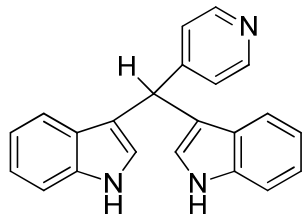
3,3'-((3-(2-nitrophenyl)prop-2-ene-1,1-diyl)bis(1*H*-indole) (3k): Greenish Solid; mp. 150-152 °C; ¹H NMR (400 MHz, DMSO-*d*₆): δ 8.02 (brs, 2H, NH), 7.91 (dd, 1H, *J* = 8 & 1.5 Hz.), 7.66-7.00 (m, 14H, Ar-H & one =CH), 6.77 (dd, *J* = 15.5 & 7.5 Hz, 1H, =CH-C), 5.48 (d, 1H, *J* = 7.5 Hz, Ar-CH); ¹³C NMR (100 MHz, DMSO-*d*₆): δ 147.7, 137.7, 136.7, 133.7, 132.9, 129.0, 127.5, 126.8, 125.8, 124.4, 122.7, 122.0, 119.8, 119.3, 117.6, 111.1, 37.7; EIMS: *m/z*: 394 [M]⁺; Anal. Calcd. for C₁₅H₂₀NO₇P: C, 50.42; H, 5.60; N, 3.92 %. Found: C, 50.38; H, 5.67; N, 3.99%;



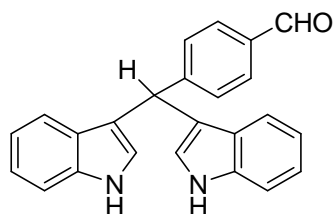
3,3'-((Thiophen-2-yl)methylene)bis(1*H*-indole)(3l): Reddish brown Solid; mp. 150–152 °C; Lit³⁰. mp. 152-154°C; IR (KBr): 3412(NH), 1739, 1651, 1366, 1215, 1091, 740 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ8.84 (brs, 2H), 7.41-7.06 (m, 11H, Ar-H), 6.69 (s, 2H, Ar-H), 5.89 (s, 1H, Ar-CH); ¹³C NMR (100 MHz, CDCl₃): δ148.7, 136.5, 126.7, 126.5, 125.1, 123.6, 123.2, 122.0, 119.7, 119.6, 119.3, 111.2, 35.3; EIMS: *m/z*: 328[M]⁺.



3,3' -((3-pyridyl)methylene)bis(1H-indole) (3m): Reddish brown Solid, mp. 136-138 °C; Lit³¹. mp. 138-140 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.43 (d, 1H, *J* = 7.6Hz, Pyridine-CH), 8.18 (brs, 2H, NH), 7.40-7.03 (m, 11H, Ar-H), 6.69 (s, 2H, Ar-H), 5.89 (s, 1H, Ar-CH).

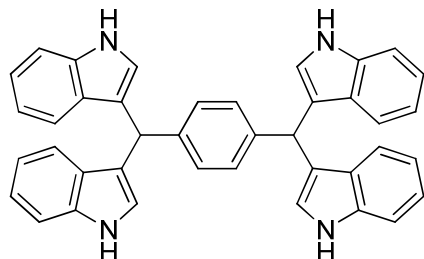


3,3' -((4-pyridyl)methylene)bis(1H-indole) (3n): Reddish brown Solid, mp. 160-162 °C; Lit³². mp. 161-163 °C; ¹H NMR (400 MHz, CDCl₃): δ 8.50 (d, 2H, *J* = 8Hz, Pyridine-CH), 8.18 (brs, 2H, NH), 7.40-7.03 (m, 10H, Ar-H), 6.69 (s, 2H, Ar-H), 5.89 (s, 1H, Ar-CH); ¹³C NMR (100 MHz, CDCl₃): δ 155.7, 137.8, 137.0, 133.7, 129.5, 128.6, 127.9, 124.1, 121.2, 119.3, 118.5, 112.8, 32.3; EIMS: *m/z* (%) 322 (100) [M]⁺,



Analytical data for compound I

Solid; mp. Reddish brown 253-255°C; Lit³³. mp.257 °C; ¹H NMR(400 MHz, DMSO-*d*₆), δ 9.12 (s, -CHO), 8.31 (brs, 2H, NH), 7.50–7.10 (m, 12H, Ar-H), 6.29 (s, 2H), 5.75 (s, 1 H, Ar-CH).



Analytical data for compound II

Reddish brown Solid; mp. 194 -196 °C; Lit³³. Mp.194 °C; IR (KBr): 3405, 3049, 1620, 1451,1213 cm⁻¹. ¹H NMR (400 MHz, DMSO-*d*₆), δ 8.31 (brs, 4H, NH), 7.78–7.06 (m, 20H, Ar-H), 6.29 (s, 4H), 5.75 (s, 2 H, Ar-CH); ¹³C NMR (100 MHz DMSO-*d*₆), δ 142.5, 136.764, 128.1, 126.8, 123.6, 120.9, 119.2, 118.4, 118.3, 111.5, 29. 1; EIMS: *m/z* 566.2.

Acknowledgment

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Synthesis of bis(indolyl)methanes

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