ISSN: 2249-894X IMPACT FACTOR : 3.8014 (UIF) VOLUME - 6 | ISSUE - 8 | MAY - 2017

REVIEW OF RESEARCH

ECO-BENIGN AND EFFICIENT SYNTHESIS OF BIS(INDOLYL)ALKANES USING SODIUM HYDROGEN SULFATE SUPPORTED ON SILICA GEL

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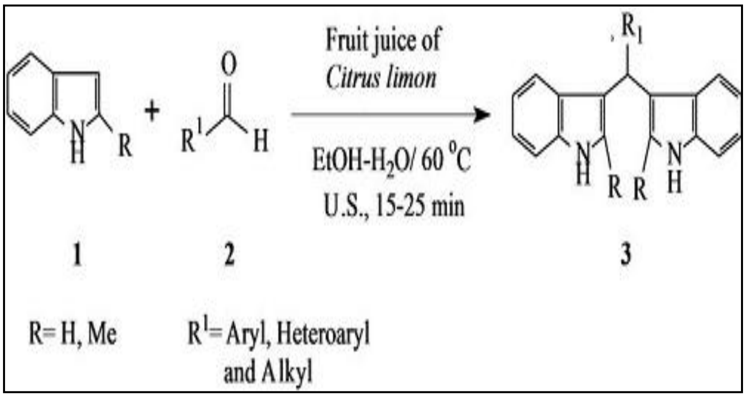
ABSTRACT:

Reacting indole and substituted indole with structurally diverse aldehydes in the presence of Sodium hydrogen sulfate supported on silica gel as an efficient, mild, and inexpensive catalyst under solvent free condition at room temperature afforded biologically important bis(indolyl)methane in excellent yields .

KEYWORDS: *Indole, bis(indolyl) methanes, aldehydes, Sodium hydrogen sulfate supported on silica gel.*

INTRODUCTION:

Indoles and their derivatives are one of the most prominent class of the compounds which have been widely identified as pharmacophores, with representation in more than 3000 naturally isolated compounds and are known to possess broad spectrum of biological and pharmaceutical activities.[1,2] Among various indole derivatives, di(1-H-indolyl-3-yl)methanes (DIM) and 1,4-bis[di(1H-indol-3-yl)methyl]benzenes display diverse pharmacological activities and are useful in the treatment of fibromyalgia, chronic fatigue and irritable bowel syndrome.[3] The 3-subsituted indole derivatives, bis(indolyl)alkanes can be considered as an important class of organic compounds because of their wide occurrence in various natural products possessing biological activity [4] and usefulness for drug design.[5] Several bis(indolyl)alkanes and their derivatives have been isolated from terrestrial and marine natural sources, viz. parasitic bacteria, tunicates, sponges and some of these possess significant biological activities.[6] Thus, the development of high-throughput methods for the synthesis of bis(indolyl) methanes remains a topic of paramount importance in view of their versatile biological and pharmacological activities. Consequently, numerous methods have been reported for the synthesis of these compounds.[7] Of these methods, the acid-catalyzed electrophilic substitution reaction of indoles with aldehydes is one of the most simple and straightforward approaches. A variety of reagents such as acetic acid,[8] $InCl_3$,[9] $In(OTf)_3$,[10] InF_3,[11] $Dy(OTf)_3$,[12] $Ln(OTf)_3$,[13] $LiClO_4$,[14] glycerin , $CeCl_3$,[15] I_2,[16] $KHSO_4$,[17] silica bonded S-sulfonic acid,[18] Ph_3CCl,[19] CAN,[20] Zeolites,[21] T3P,[22] $H_6P_2W_{18}O_{62}$,[23] and $[La(PFO)_3]$[24] have been employed to accomplish this transformation.

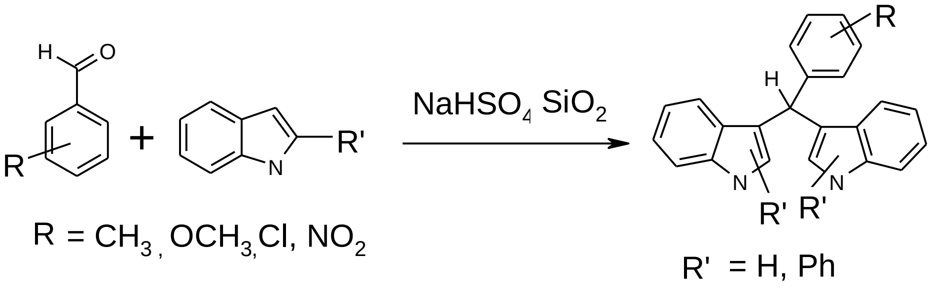


Sodium hydrogen sulfate supported on silica gel has been proved to be a heterogeneous catalyst of choice of many researchers, due to its ease of preparation, using readily available reagents as well as its high catalytic efficiency.[25] It has been used earlier in α-bromination of ketones,[26] in the cleavage of MOM-ethers and prenylesters,[27a,b] in the synthesis of dihydropyridines[28a] as well as homo-allylic amines[28b], Our earlier experiences with the use of heterogeneous solid acid catalyst[29] as well as the recent surge in the development of solvent-free and environmentally benign protocols prompted us to test the feasibility of using sodium hydrogen sulfate supported on silica gel for the synthesis of bis(indolyl)methanes.

RESULTS AND DISCUSSION

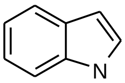
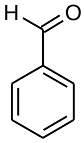
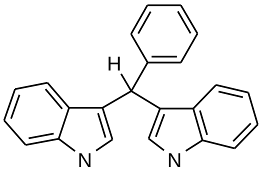
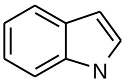
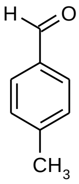
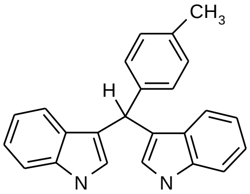
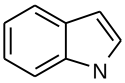
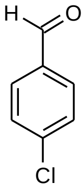
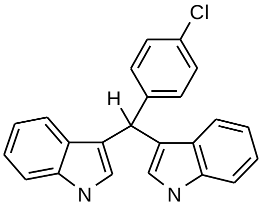
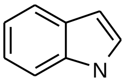
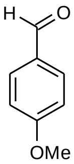
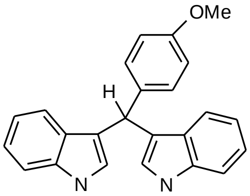
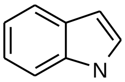
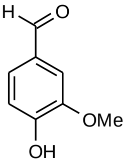
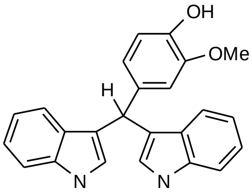
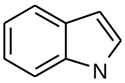
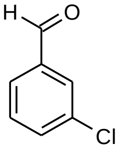
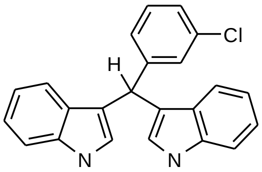
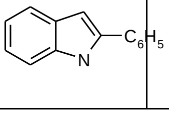
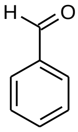
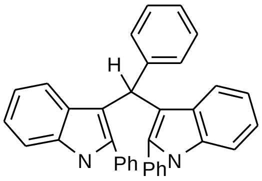
In the present article, a facile route using sodium hydrogen sulfate supported on silica gel as a mild and highly efficient catalyst for a comparative synthesis of di(1 H-indol-3-yl)methanes is described.

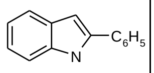
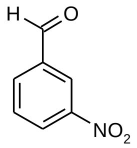
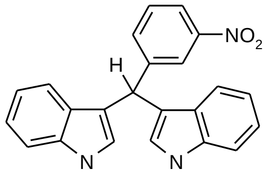
In conclusion, we have developed a highly efficient, cost-effective and environmentally benign protocol for the synthesis of bis(indolyl)methanes. using $NaHSO_4.SiO_2$ a heterogeneous and reusable catalyst. This operationally simple procedure can be used as a useful alternative to the existing protocols for the synthesis of bis(indolyl)methanes. (Scheme-1) As the reaction is carried out under solvent free and desired product can be separated from catalyst by filtration this protocol is operationally simple. The catalyst can be reused after drying, at least three cycles without any loss in its catalytic activity.



Scheme-1

Table -1 :Synthesis of di(1 H-indol-3-yl)methanes using catalytic amount of sodium hydrogen sulfate supported on silica gel ($NaHSO_4.SiO_2$) .

Entry No.	Indole a	Aldehyde b	Product c	Time (Min)	Yield (%)
1				20	97
2				25	95
3				30	89
4				25	96
5				40	83
6				30	88
7				50	82

8				50	84

Attempts to synthesize some known di(1 H-indol-3-yl)methane derivatives using catalysts such as I_2,[16] silica sulfuric acid,[17] $HClO_4$ -SiO_2[18] under thermal conditions, revealed that the reactions took very long time for completion, required a huge amount of catalyst, afforded low to moderate yields, and in some cases many by-products were formed.

In comparison with the reported methods, $NaHSO_4.SiO_2$ a heterogeneous and reusable catalyst afforded the products in excellent yields. Thus, a mixture of lindole or its derivative 1a–8a and aldehyde 2b–8b (2:1 mmol) were reacted under solvent free conditions in presence of catalytic amount of $NaHSO_4.SiO_2$ a heterogeneous catalyst. The resulting di(1 H-indol-3-yl)methanes 3 were obtained in excellent yields especially with aromatic and heteroaromatic aldehydes, but in the case of aliphatic aldehydes the yields low (Table 1).

The work-up of these reactions is easy because after completion of reaction the reaction is diluted with dichlorometnane and filtered the solid acid catalyst remains on filter paper and product is dissolved in dichlorometnane. Pure product is obtained by evaporation of solvent.

Table -1 Synthesis of di(1 H-indol-3-yl)methanes using catalytic amount of sodium hydrogen sulfate supported on silica gel ($NaHSO_4.SiO_2$) .

All products 3 were characterized by spectroscopic and elemental analyses. The IR spectra of di(1 H-indol-3-yl)methanes show characteristic IR absorptions at 3747–3170 (N–H), 3062–3037 (aromatic C–H), 2860–2850 (aliphatic C–H), 1676–1660 (aromatic C=C), and 1613–1580 (C=C–N) cm–1.

Melting points of di(1 H-indol-3-yl)methanes c1 to c8 closely match those reported in the literature.

EXPERIMENTAL SECTION

Indole (E Merck, Lancaster and SD Fine chemicals), aldehydes (SD Fine and SRL chemicals) were used as received. IR spectra were recorded on Perkin-Elmer FT-IR-783 spectrometer. NMR spectra were recorded on Bruker AC-200 or MSL-300 (200 MHz or 300 MHz for 1H NMR and 50 MHz or 75 MHz for 13C NMR) spectrometer in $DMSOD_6$ using TMS as an internal standard and δ values are expressed in ppm. Melting points recorded are uncorrected.

GENERAL PROCEDURES.

A mixture of indole (2 mmol), aldehyde (2.1 mmol) and $NaHSO_4.SiO_2$ (200 mg,) was stirred until completion of reaction (TLC). Upon cooling to room temperature, the reaction mixture was diluted with dichloromentane, the catalyst was filtered and washed with dichloromentane. From the combined filtrate solvent was removed under vacuum and the residue was filtered through a short column of silica gel to afford pure Product. All the resultant di(1 H-indol-3-yl)methanes were characterized by various spectral methods and the spectral data of the compounds is summarized below.

Spectral Data

3,3'-(Phenylmethylene)bis(1H-indole) (Entry 1 Table 1): Red colour solid; mp- found, 152 ºC; Reported: 150−152 °C. IR (KBr, ν cm-1): 742, 1088, 398, 1603, 1621, 3098, 25.1H NMR (400 MHz, CDCl3): δ 5.85 (s, 1H), 6.72 (s, 2H), 7.02 (t, 2H, J=6.7 Hz), 7.12−7.20 (m, 3H), 7.25−7.30 (m, 2H), 7.34−7.40 (m, 6H), 7.90 (br, 2H).13C MR (DMSO): δ 25.2, 27.4, 28.8, 43.4, 111.0, 112.1, 119.6, 120.5, 121.7, 22.8,130.2, 131.5, 131.6. MS: m/z = 322 (M+).

3,3'-(p-Tolylmethylene)bis(1H-indole) (Entry 2, Table 1): Dark pink colour solid; mp-found, 94−95 ºC; Reported: 94−96 °C IR (KBr, ν cm-1): 772, 1062, 1216, 1520, 1613, 2948, 3421.1H NMR (400 MHz, CDCl3): δ 2.38 (s, 3H), 5.82 (s, 1H), 6.65 (s, 2H), 6.97 (t, 2H, J=7.5Hz), 7.2 (d, 2H, J=7.3 Hz), 7.19−7.26 (m, 6H), 7.2 (d, 2H, J=7.3 Hz), 7.91 (br, 2H).13C NMR (DMSO) δ 20.9, 44.6, 111.3, 112.2, 119.7, 120.6, 121.7, 122.9, 127.2, 129.0,129.3, 131.8, 134.5, 136.7. MS: m/z = 336 (M+).

3,3'-(4-Chlorophenyl)methylen)bis(1H-indole) (Entry 3, Table 1): Red colour solid; mp-found, 77 ºC; Reported: 76−77 °C. IR (KBr, ν cm-1): 1092, 1474, 502, 3052, 3430. 1H NMR (400 MHz, CDCl3): δ 6.02 (s, 1H), 6.67 (s, 2H), 7.12 (t, 3H, J=8.5 Hz), 7.20 (t, 2H, J=7.9 Hz), 7.27−7.40 (m, 8H), 7.97 (br, 2H). 13C NMR(DMSO) δ 44.6, 111.5, 112.4, 119.9, 120.5, 121.7, 122.9, 127.3, 129.8, 130.2, 131.4, 134.5, 136.4. MS: m/z = 356 (M+).

3,3'-(4-Methoxyphenyl)methylene)bis(1H-indole) (Entry 4, Table 1): Red colour solid; mp-found, 187−188 ºC; Reported: 187−189 °C. IR (KBr, ν cm-1): 223, 1230, 1462, 1520, 1613, 2942, 3418.1H NMR (400 MHz, CDCl3): δ 3.75 (s, 3H), 5.78 (s, 1H), 6.62 (s, 2H), 6.80 (d, 2H, J=8.2 Hz), 7.16 (t, 2H, J=7.2 Hz), 7.16 (t, 2H, J=7.3 Hz), 7.21 (s, 2H), 7.26−7.40 (m,4H), 7.87 (br, 2H).13C NMR (DMSO) δ 44.5, 56.0, 111.2, 112.3, 114.1, 119.7, 120.9, 121.2, 121.8 122.8, 127.2, 130.3, 131.6, 159.5. MS: m/z = 380 (M+).

4-(Di(1H-indole-3-yl)methyl)-2-methoxyphenol (Entry 5, Table 1): Red colour solid; mp-found, 110 ºC; Reported: 110−112 °C. IR (KBr, ν cm-1): 752, 1397, 652, 3422, 3498.1H NMR (400 MHz, CDCl3): δ 3.72 (s, 3H), 5.78 (s, 1H), 6.66 (s, 2H), 7.35−6.92 (m, 11H), 7.90 (s, 1H), 9.92 (br, 2H).13C NMR (DMSO) δ 4.8, 56.3, 116.6, 111.6, 112.1, 119.6, 120.5, 121.7, 122.8, 127.4, 131.3, 136.5, 39.9, 149.1. MS: m/z = 368 (M+).

,3'-(Phenylmethylene)bis(2-phenyl-1 H -indole) (Entry 7, Table 1). Colorless crystals; mp 272–274 °C (methanol) (lit.24 280 °C; lit.26 261 °C). IR (KBr): 3420, 3055, 2860, 1676, 1597 cm–1, 1H NMR (300 MHz, DMSO- d6): δ 11.31 (br s, 2H, NH), .39–6.65 (m, 23H, ArH), 5.99 (s, 1H, CH). MS: m/z (%) 474 (100) [M+].

3,3'-(3-Nitrophenylmethylene)bis(2-phenyl-1H -indole) (Entry 8, Table 1). Yellow crystals; mp 269–271 °C (methanol). IR (KBr): 3444, 3056, 2860, 1660, 1605 cm–11H NMR (300 MHz, DMSO-d6): δ 11.43 (br s, 2H, NH), 8.10–6.69 (m, 22H, ArH), 6.12 (s, 1H, CH). MS: m/z (%) 519 (100) [M+]. Anal. calcd. for $C_{35}H_{25}N_3O_2$: C, 80.91; H, 4.85; N, 8.09. Found: C, 80.34; H, 5.11; N, 7.98.

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