



Sisal-DCT catalyzed rapid and clean synthesis of bis(indolyl)methanes under mild conditions

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ABSTRACT

Sisal supported 2, 4-dichloro-1, 3, 5-triazine (Sisal-DCT) was found to be an environmentally renewable, inexpensive solid acid catalyst for the electrophilic substitution reaction of indole with carbonyl compounds to the corresponding bis(indolyl)methanes in excellent yields. The important features of the procedure are cost effectiveness, faster reaction rates and cleaner conversions with simple work-up.

Keywords: Solid acid catalyst, Sisal-DCT, bis (indolyl)methanes.

INTRODUCTION

The chemistry of indole has long been known [1]. Indole and pyrroles are well known π - electron rich heterocyclic compounds, which shows Ehrlich Test with *p*-dimethyl aminobenzaldehyde [2]. Similarly indoles with aliphatic/aromatic aldehydes and ketone produce azfulvinium salts, These salts upon addition with second molecule of indole yields corresponding bis(indolyl)alkanes [3]. These derivatives of indole have many important applications in human life. They are known for their antibiotic properties [4]. It helps in promoting the proper estrogen metabolism [5]. Breast cancer prevention and control of cervical dysplasia as strong antiproliferative effect in human endometrial cancer cells [6], antibacterial agent etc [7].

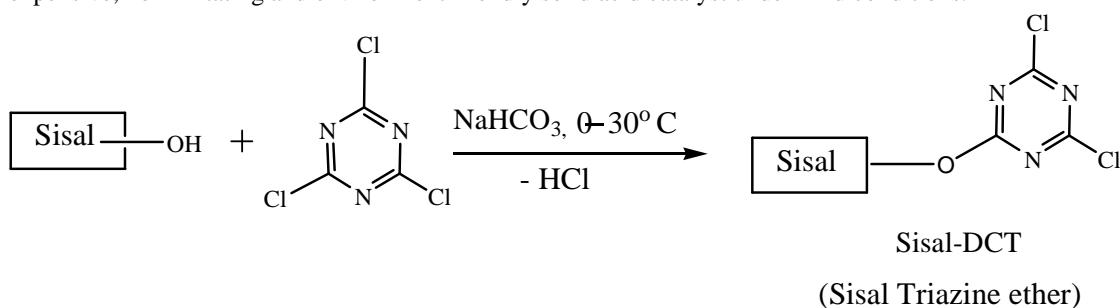
Because of immense important properties of bis (indolyl) alkanes in pharmaceutical industries [8], many researchers pay much more attention to develop the methods for the synthesis of title compound since many years.

Preparation of bis (indolyl) alkanes is carried out by electrophilic substitution reaction of indole with carbonyl compounds using various types of acids as catalyst[9,10]. Whereas many Lewis acids are prone to undergo decomposition in the presence of nitrogen containing reactants and this necessitates the use of excess and sometimes stoichiometric amount of Lewis acid [11]. Literature survey reveals several methods for the synthesis of Bis(indolyl)methanes using protic/Lewis acids[12,13]. Iodine [14], NBS [15], MontmorilloniteK-10[16], Rare earth Triflate[17], Ionic liquid[18], 2, 4, 6-trichloro-1, 3, 5-triazine (TCT) [19]. Recently we have reported phosphonitrilic chloride trimer [20] and phenyl phosphonic acid [21] for the rapid synthesis of Bis(indolyl)alkanes under mild conditions.

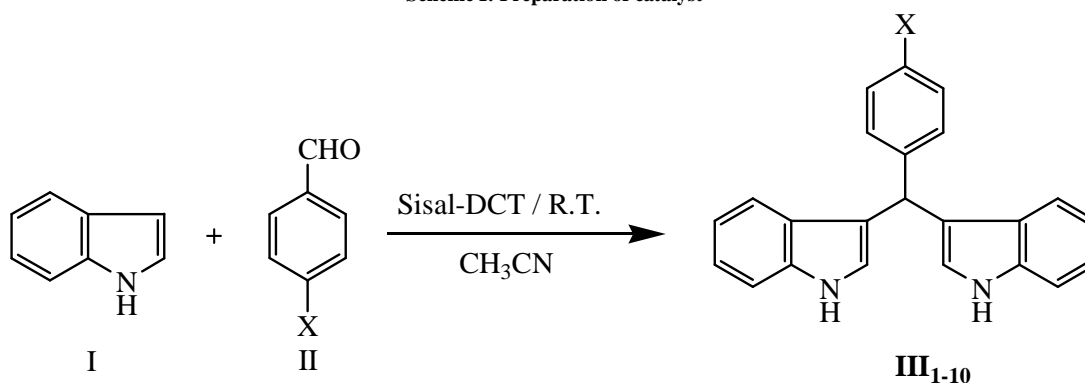
Now a day's heterogeneous solid acid catalysts are playing an important role for the synthesis of organic compounds due to its easy handling, no toxicity and importantly its recyclability [22]. Recently Chemical industries are forced to consider environmental aspects, therefore it becomes necessary to replace liquid acid with solid acid [23, 24], use of

naturally occurring polymers such as starch, cellulose, are attractive candidates to explore for supports for catalysts. Silica sulphuric acid [25], silica supported NaHSO_4 [26], cellulose sulphonic acid [27], starch sulphuric acids [28] are used as solid catalyst for various organic transformations. More recently 2, 4, 6-trichloro-1, 3, 5-triazine (TCT) was used for the synthesis of Bis(indolyl) alkanes. Although use of TCT facilitate the transformation cleanly however handling of TCT in laboratory becomes difficult because of its irritative nature. This prompted us to investigate the Sisal supported 2, 4-dichloro-1, 3, 5-triazine, Sisal-DCT (**Scheme I**) as an alternative catalyst for the synthesis of bis(indolyl)alkanes. Sisal-DCT is a colorless fibrous compound, which is prepared by the modification of Sisal by 2, 4, 6-trichloro-1, 3, 5-triazine [29]. Sisal-DCT containing two labile chloride atoms showed more reactivity towards nucleophiles. It has two labile chlorine atoms compared to 2, 4, 6-trichloro-1, 3, 5-triazine (TCT) having three labile chlorine atoms. Therefore, catalytic activity of Sisal-DCT is relatively less, but its non-irritating characteristics made it easy to handle. Sisal is easily available as renewable material in the nature and it could be easily modified to Sisal-DCT as a solid acid catalyst.

In continuation of our research work [38,39,40], we are reporting herein the synthesis of bis(indolyl)methanes (**Scheme II**) by electrophilic substitution reaction of indole with a variety of aromatic aldehydes using Sisal-DCT as an inexpensive, non-irritating and environment friendly solid acid catalyst under mild conditions.



Scheme I: Preparation of catalyst



Scheme II: Synthesis of Bis(indolyl)methanes using Sisal-DCT

EXPERIMENTAL SECTION

Chemicals and Materials

All chemicals were purchased from Merck, Fluka and Aldrich fine chemicals and used as received. Solvents were used after prior distillation.

Measurements

Melting points were observed in open capillary tubes in a circulating oil melting point apparatus. Products were characterized by comparison of their spectral and physical data with authentic samples. IR spectra were obtained using a Shimadzu FT-IR spectrophotometer. Mass spectra were determined on a Shimadzu GCMS-QP 1000 EX instrument. ^1H NMR spectra were recorded on a Bruker Avance Dpx-250.

General Procedure**A. Procedure for the preparation of catalyst:**

Sisal is extracted with methanol using soxhlet extraction assembly for 20 hours to remove soluble contaminants. Further it was dried and soaked in acetonitrile. A mixture of 2 mmol of sodium bicarbonate in 5 ml of distilled water and 2 mmol of 2, 4, 6- trichloro-1, 3, 5-triazine in 5 ml of acetonitrile was added to the soaked sisal at 0°C. It was constantly stirred and temperature was allowed to increase to 30°C within half an hour. Sisal-DCT formed was separated by decanting the liquor. The catalyst was finally washed with 10 mL of acetone dried and utilized for the above transformations. As the catalyst is a moisture sensitive, need to store in desiccator over P₂O₅.

B. Procedure for the preparation of Bis(indolyl)methanes:

Mixture of indole (0.234g, 2 mmol), aromatic aldehyde (1 mmol) and 10 Wt. % of Sisal-DCT was stirred magnetically in presence of acetonitrile as a solvent at room temperature. The progress of reaction was monitored by TLC. After completion of the reaction, it was filtered through Whatmann's filter paper to separate the catalyst from the product. Catalyst was washed by 5 ml of acetonitrile. Washing and filtrate was evaporated together under reduced pressure on the rotary evaporator to yield crude product. It was further purified by column chromatography over silica gel using pet ether and ethyl acetate [8:2] as an eluent. Separated solid support was washed with chloroform, dried in the oven at 70°C for two hours and reactivated again by reacting with TCT for further transformation.

RESULTS AND DISCUSSION

Sisal-DCT was found to be an efficient catalyst for the synthesis of bis (indolyl)methanes under mild conditions. Two equivalents of indole **I** was treated with one equivalent of aldehyde **II** in presence of Sisal-DCT (10Wt %) in acetonitrile at room temperature afforded excellent yields of corresponding bis(indolyl)methanes **III**₁₋₁₀ (**Scheme II**, **Table I**). The advantage of Sisal-DCT as catalyst is that firstly it is non-irrigating in nature and could be handled easily in the laboratory. 10 Wt. % amount with respect to the reactant was sufficient for the desired conversion. These results clearly indicate the generality and scope of this protocol showing the reactions of aromatic, and heteroaromatic aldehydes with indole to bis(indolyl)methane in excellent yields. The reactions of aromatic aldehydes having electron withdrawing groups (**entry 1, 2**) were relatively faster than that of electron donating groups (**entry 3, 4, 5, 6, and 10**). However both the kinds of substituent react to give good yield of the product. The heteroaromatic aldehydes also underwent reaction with indole furnishing the corresponding bis(indolyl)methanes (**Entry 9**).

Spectral Data of some Compounds:**1. III-1: 3, 3'-bis(indolyl)-4-nitrophenyl methane**

Blood red solid powder; yield 0.338mg (92%); M. P. = 218°C ; IR (KBr, cm⁻¹): 3419 (-N-H), 3390 (=C-H), 2925 (-C-H), 1595, 1507, 1341, 809, 743; ¹HNMR (CDCl₃, ppm): δ 5.99 (1H, s), 6.69 (2H,s), J= 7.2 Hz, 7.00-7.05(3H, m), 7.3(3H, d), 7.4(2H, d), 7.5(2H, d), 8.02(2H,br.s-NH), 8.15(2H,d); Ms(m/z, %): 366 (M⁺); Elemental analysis calc. for: M.F.: C₂₃H₁₇N₃O₂(367.40) C= 75.18%, H=4.66%, N= 11.43% and found: C=75.12%, H 4.58 %, N=11.39%.

2. III-2: 3, 3'-bis(indolyl)-4-chlorophenyl methane

Blood red solid powder; yield 0.339gm (95%); M. P. = 102°C ; IR (KBr, cm⁻¹): 3408 (-N-H), 3049 (=C-H), 2922 (-C-H), 2852, 1612, 1485, 1414, 1337; ¹HNMR (CDCl₃, ppm): δ 5.87 (1H, s), 6.64 (2H,d,J=1.4Hz), 7.00-7.38(12H,m,J=7.6Hz), 7.77-7.94(2H, br.-NH); Ms(m/z, %): 355.52 (M⁺); Elemental analysis calcd. for: M.F. - C₂₃H₁₇ClN₂ (356.8) (C= 77.41%, H=4.80%, N= 7.85% and found: C=77.38%, H 4.75 %, N=7.78%.

3. III-3: 3, 3'-bis(indolyl)-4-methoxyphenyl methane

Blood red solid powder; yield 0.334mg (95%); M. P. = 170°C ; IR (KBr, cm⁻¹): 3394 (-N-H), 3355 (=C-H), 2924 (-C-H), 1608, 1585, 1508, 1454, 1415, 1246; ¹HNMR (CDCl₃, ppm): δ 3.71(3H, s), 5.82(1H, s), 6.5-6.7(2H,d), 6.80(2H,d), 7.01(2H,t), J= 7.2 Hz 7.23-7.40(6H, m),7.92(2H,br.s-NH); Ms(m/z, %): 351.60 (M⁺); Elemental analysis calc. for M.F.: C₂₄H₂₀N₂O(352.43) C= 81.79%, H=5.72%, N= 7.94% and found: C=81.75%, H 5.69 %, N=7.89%.

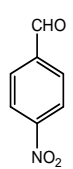
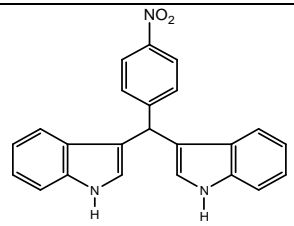
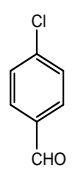
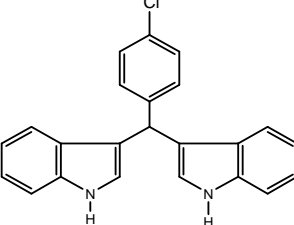
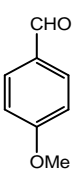
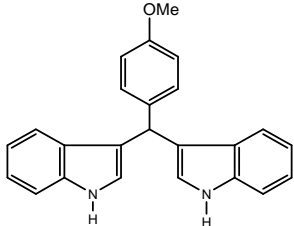
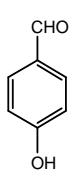
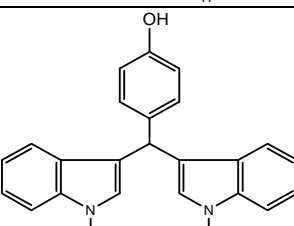
4. III-4: 3, 3'-bis(indolyl)-4-hydroxyphenylmethane

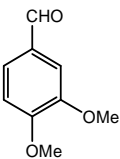
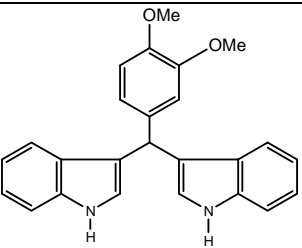
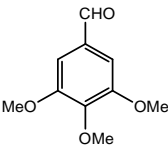
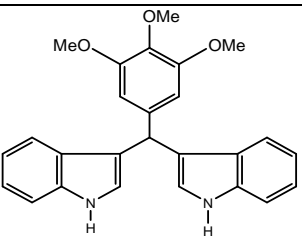
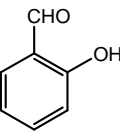
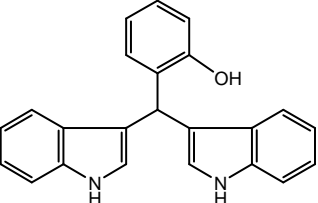
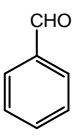
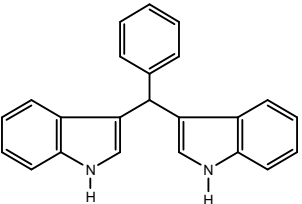
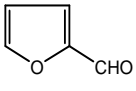
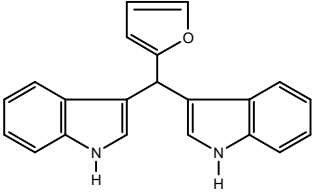
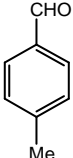
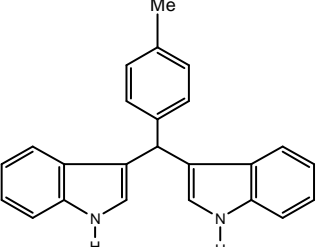
Blood red solid powder; yield 0.321 gm (95%); M. P. = 120°C ; IR (KBr, cm⁻¹): 3406 (-N-H), 3444(-OH),3051(=C-H), 2924 (-C-H), 2850, 1597, 1512, 1454, 1338; ¹HNMR (CDCl₃, ppm): δ 3.53(1H,s) 5.82 (1H, s), 6.66 (2H,s), 6.73-6.76(2H,d), 6.86-6.90(2H,t), J=7.2Hz,7.21-7.39(6H,m), 7.94(2H,br.s-NH); Ms(m/z, %): 337.58(M⁺); Elemental analysis calc. forM.F. - C₂₃H₁₈N₂O (338.40) C= 81.63%, H=5.36%, N= 8.27% and found: C=81.56%, H 5.34 %, N=8.22%.

5. III-6: 3, 3'-bis(indolyl)-3,4,5-trimethoxyphenylmethane

Reddish brown solid yield 0.379mg (93%); M. P. = 168°C ; IR (KBr, cm⁻¹): 3372(-N-H), 3040(=C-H), 2926 (-C-H), 2854, 1725, 1587, 1500, 1458, 1327, 1234, 1125; ¹HNMR (CDCl₃, ppm): δ1.25, 3.71(3H, s), 3.83, 3.93, 3.94, 5.82(1H, s), 6.59(2H,d), 6.70(2H,d), 6.99(2H,t), J= 7.2 Hz 7.12-7.40(6H, m),7.99(2H,br.s-NH), 9.87; Ms(m/z, %): 411.64 (M⁺); Elemental analysis calc. forM.F. :C₂₆H₂₄ N₂ O₃(412.43) C= 81.79%, H=5.72%, N= 7.94% and found: C=81.75%, H 5.69 %, N=7.89%.

Table 1: Synthesis of Bis(indolyl)methanes using various aldehydes

Entry	Aldehyde	Product ^a	Time (min.)	Yield ^b (%)	M.P. (°C) (Lit)
III-1			07	92	218 (220-223) ³²
III-2			05	95	102 (104-105) ³³
III-3			10	95	170 (179-181) ³³
III-4			10	95	122 (122-124) ³¹

III-5			15	92	195 (198-200) ³⁰
III-6			15	93	168
III-7			20	89	120 (122-123) ³⁶
III-8			20	85	120 (125-126) ³⁷
III-9			15	87	110 (113-115) ³⁴
III-10			15	87	92 (96-98) ³⁵

Reaction conditions:

Substituted benzaldehyde (1 mmol), indole (2mmole), Sisal-DCT (10 Wt. %), Temperature R.T.in presence of acetonitrile as a solvent;

^a product confirmed from physical and spectral analysis;

^b isolated yield of the product.

CONCLUSION

Sisal-DCT catalyst is non-irritating in nature and could be easily synthesized or reactivated simply by the reaction of a renewable Sisal biopolymer with TCT.

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