CHAPTER-II

A highly efficient, eco-friendly, room temperature synthesis of bis(indolyl)methanes using the mesoporous titanosilicate Ti-TUD-1

And

Stannic chloride - glycerol, an unique and efficient composite for the fast and efficient synthesis of bis(indolyl)methanes
INTRODUCTION

In this section an efficient, eco-friendly and room temperature syntheses of the highly biologically active bis(indolyl)methane has been discussed. The syntheses have been carried out in two different ways. One is heterogeneous catalyzed while the other being homogenous catalyzed. Section A involves the study of the heterogeneous catalyzed synthesis over the high surface area mesoporous titanosilicate catalyst Ti-TUD-1 while section B deals with the homogeneous stannic chloride catalyzed synthesis in glycerol.

General structure of Bis(indolyl)methanes

Importance of Bis(indolyl)methanes

Indole derivatives have assumed tremendous importance in organic chemistry owing to their promising utility in the field of pharmaceuticals, material science, drugs, neurohormones and agrochemicals. Particularly, the substrates containing the bis(indolyl)methane (BIM) nucleus are of significant importance because of their potential antitumor activities. Bis(indolyl)methane is an effective anticancer component of Brassica vegetables and its use as a supplement in human diet increases the 2-hydroxylation of estrogen urinary metabolites. BIMs efficiently inhibit the growth of human prostate cancer and mammary tumor cells. They are also similarly active against a variety of viral and antibiotic resistant bacterial infections including HIV, HPV, hepatitis and influenza. Apart from their medicinal properties, these 3,3'-disubstituted indole derivatives are also important precursors of a wide range of indole compounds which have other important applications. Due to their profound
biological and chemical importance, the low cost, energy saving routes towards the synthesis of bis(indolyl)methanes has come into prominence.

A brief review on the synthesis of Bis(indolyl)methanes

The indole nucleus shows strong affinity towards electrophilic substitution reactions. The reactivity of indole and its derivatives can be rationalized by calculating the frontier electron density by employing CNDO treatment (molecular orbital calculations with the complete neglect of differential overlap). This method was used to calculate the energy of HOMO (Highest Occupied Molecular Orbital) of various indoles and hence their order of reactivity. As the energy of the HOMO was taken as a measure of the ability to donate electrons skatole (3-methyl indole) was the best donor in the series. This molecule has the most unstable HOMO. Indole has the most stable HOMO and therefore has the lowest donor ability. The stability of the HOMO of the members of the indole family could be rationalized as:

Indole > N-Methyl indole > 2 methyl indole > 6-methoxy indole > 3-Methylindole.

The donor ability would follow the reverse order.

The C-3 centre in all the molecules has the highest frontier (HOMO) electron density. Therefore C-3 will act as a powerful carbanion centre and hence would be the site for electrophilic substitution. In 3-substituted indoles C-3 has been found to undergo disubstitution to give the 3,3-disubstituted indoleninium cation followed by migration of one of the groups to C-2. This Wagner-Meerwein rearrangement of the 1,2-type is known as Plancher Rearrangement. The migration of R/R' would depend upon the greater migratory aptitude of the particular group (Scheme 1).
This property enables indoles to undergo many novel and unusual reactions. Voluminous literature on these indole reactions has been published. Since this part of the dissertation is mainly concerned with the synthesis of bis(indolyl)methanes it was thought pertinent to present a brief review on bis(indolyl)methanes.

P. Wang et al reported lanthanide catalyzed reactions of indoles with aldehydes and ketones in aqueous ethanol solution. They investigated the reaction of indoles with different type of aromatic and aliphatic aldehydes which gave exclusively the bis(indolyl)methane adduct (Scheme 2). Different lanthanide triflates were examined in the model reaction of indole with benzaldehyde. Dysprosium triflate gave the best result.

Bandgar et al reported a rapid and highly efficient route for the synthesis of bis(indolyl)methanes from the reaction of indoles with various aldehydes and ketones using an inexpensive and easily available catalyst iodine in acetonitrile. The reactions proceeded smoothly at room temperature and in very short time, usually <1 min (Scheme 3). The
reaction occurred with aliphatic aldehydes, α,β-unsaturated aldehydes, a variety of substituted aromatic aldehydes as well as aliphatic, alicyclic and aromatic ketones with indoles to give the corresponding bis(indolyl)methanes in excellent yields.

![Scheme 3](image)

Efficient reactions of indoles with various aromatic aldehydes were carried out by S. -J. Ji using a catalytic amount of iodine under solvent free conditions to afford the corresponding bis(indolyl)methanes in good yields (Scheme 4).8

![Scheme 4](image)

T. P. Loh and co-workers synthesized BIMs in ionic liquids applying different Lewis acids as catalysts at ambient temperature.9 Among the different tested liquids viz. [bmim][BF₄], [bmin][PF₆], [hmim][Cl], [omim][PF₆], [hmim][PF₆], [dmim][PF₆] the [omim][PF₆] was found to be most efficient. Similarly using other different catalysts In(OTf)₃ afforded the best results in shortest time with excellent yields (Scheme 5).
In 2005, S. -J. Ji et al extended this protocol of using ionic liquids in the synthesis of bis(indolyl)methanes formed by the reactions of indoles with various aldehydes. As these types of reactions are acid catalysed, acidic ionic liquids were used instead of Lewis acids in ionic liquids because of their good solvating capability, wide liquid range and acidity. In ethanol the reaction was found to proceed best at room temperature (Scheme 6).

An efficient method involving the electrophilic substitution reactions of indoles with various aldehydes proceeded smoothly in acetonitrile using silicotungstic acid as a heteropoly acid (H$_4$[Si(W$_3$O$_{10}$)$_3$]) to afford di(indolyl)pyrazolyl methanes at room temperature. A wide variety of indoles and pyrazoline aldehydes were employed in the reaction and in all the cases the reaction time was short producing high yields (Scheme 7).
Application of another heteropoly acid, the tungstophosphoric acid was demonstrated by Saidi and his group when they coupled variety of aldehydes and ketones with indole and its derivatives in aqueous medium. The product was developed in excellent yield within short reaction time (Scheme 8).

![Scheme 8](image)

Synthesis of bis(indolyl)methanes was carried out over a solid acid catalyst HY zeolite at room temperature in dichloromethane medium by Y. Genkateswarlu et al (scheme 9). Different types of carbonyl compounds were used to afford the products in high yields. After the reaction the catalyst was recovered.

![Scheme 9](image)

Application of microwave irradiation in the synthesis of BIMs was exploited by M. Xia et al. Bis(indolyl)methane derivatives were rapidly and smoothly prepared under solvent-free microwave irradiation, through Lewis acid catalyzed electrophilic substitution of indoles with a variety of ketones (Scheme 10).

![Scheme 10](image)
M. A. Zolfigol et al studied the electrophilic substitution reaction of indoles to carbonyl compounds in presence of various metal dodecyl sulfates as catalysts utilizing surfactant phenomenon (scheme 11). The reactions were carried out in water involving micellization technique. A wide variety of indoles and carbonyl compounds were used to provide the product in high yield within short time.

\[ \text{Scheme 11} \]

R. V. Jayaram and his group\textsuperscript{16} employed 12-tungstophosphoric acid (TPA) supported on zirconia as an efficient and heterogeneous solid acid catalyst for the liquid phase electrophilic substitution reaction of indoles with aldehydes (Scheme 12). The catalyst was highly effective and afforded bis(indolyl)methanes in excellent yields and could be recycled for new runs.

\[ \text{Scheme 12} \]

Very recently, a different approach was proposed by Perumal et al\textsuperscript{17} for this synthesis without the involvement of any aldehydes. Alkylation of indoles has been achieved via Pd-catalyzed aliphatic C–H bond activation of tertiary amine coupling with indole followed by C–N bond cleavage and subsequent addition of a second molecule of indole. This method involves the migration of the alkane chain from tertiary amine to indole (Scheme 13).
By means of immobilizing the acidic homopolymer, poly(4-styrenesulfonyl(perfluorobutylsulfonyl)imide) (PSFSI), onto mesoporous SBA-15 silica, a new type of strongly acidic composite catalyst was developed and its catalytic activity was employed in the efficient synthesis of bis(indolyl)methanes by Nie and his group. The solid acid catalyst was highly effective and could be recycled at least five times without loss of activity (Scheme 14).

Scheme 13

Scheme 14
SECTION A: “A highly efficient, eco-friendly, room temperature synthesis of bis(indol-3-yl)methanes using the mesoporous titanosilicate Ti-TUD-1”.

➤ RESULTS AND DISCUSSION

In this section of the dissertation the exclusive synthesis of bis(indolyl)methane nucleus has been demonstrated by coupling of indole and 2-methyl indole with different aromatic aldehydes using the mesoporous titanosilicate catalyst Ti-TUD-1 at ambient conditions.

Advantages of the methodology

Due to profound biological importance of bis(indolyl)methanes, developing low cost, energy saving and eco-friendly routes towards their synthesis has become important. Lewis acid or protic acid catalyzed condensations of indoles or indolyl Grignard reagents with aldehydes (or acetals), ketones, ketoacids, imines and nitrones have provided useful synthetic routes to BIMs. However, many of them involve drastic conditions, hazardous chemicals and exposure to excess and harmful solvents. In the context of green approach, the versatile use of solid Lewis acids prompted extensive research to design and develop new catalysts as potential candidates to contribute to the synthesis of BIMs. A number of catalysts have been utilized. Again, deactivation of the catalyst and its reusability remains a problem. In this section Ti-TUD-1, a mesoporous titanosilicate catalyst, was used for the synthesis of BIMs from the reaction of indoles with different aldehydes at room temperature for the first time. The operational simplicity, ambient reaction condition, high efficiency, fast reaction and reusability of catalyst are the significant features of this method, developed by the candidate.
Physical Characterization of Mesoporous titanosilicate Ti-TUD-1

Mesoporous Ti-TUD-1 with different Ti loading (Ti/Si mole ratio = 0.01, 0.03, 0.05, named as catalysts x, y, z respectively) was prepared by non-hydrothermal sol-gel technique. It was then characterized by SEM, TEM, X-Ray diffraction, FT-IR, UV Fluorescence emission spectroscopy and BET surface area analysis.

SEM images (Fig. 2.1A and 2.1B) depict the surface morphology of the material. Apparently the surface is spongy in nature. The particles are of uneven shape and size. TEM images of the catalyst (Fig. 2.2A and 2.2B) clearly show that the surface to be highly porous in nature with a wormhole-like arrangement. There are mixtures of small and large pores well distributed over the whole surface. The pore sizes range between 5-15 nm. The porous channels formed are also visible in the TEM image (Fig. 2.2A). Ti metal is equally symmetrically distributed over the Si matrix. The main reason behind its high activity is probably the strong interaction between the Ti atoms and the silanols. However, the identification of Ti atoms could not be detected from TEM images.

The mesoporosity was also confirmed from X-ray powder diffraction (XRD) studies. Both the low angle and wide angle diffraction patterns were studied (Fig. 2.3). A sharp peak was observed in the 2θ range 0.5-1.0° which is a clear indication of the sample being mesoporous in nature (inset).20 A broad diffraction band around 2θ = 25° confirmed the amorphous silica matrix. However, the XRD spectra did not show the characteristic diffraction lines for anatase or rutile titania phase which indicates that there was no free titanium dioxide formed in the catalyst.

Due to the high porosity the surface area was also found to be high. The high surface area ensured greater accessibility of the substrates towards the active sites of the catalyst. BET surface area of the catalysts was found to range between 380–450 m²/g. However, since the catalysts were prepared by a non-hydrothermal method, the development of pores might be less effective than hydrothermal method. Again, due to loading the surface area was found to be somewhat lower than that prepared hydrothermally.
IR analysis of the Ti-TUD-1 (3 mol %) catalyst has been shown in Fig. 2.4. A strong band at 1099 cm$^{-1}$ indicated the Si-O-Si asymmetric stretching vibration which is an evidence of a silicate material. In the IR spectrum the weak but characteristic band at 960 cm$^{-1}$ showed the presence of Si-O-Ti bond formed in the catalyst surface which proved the presence of some active Ti species in tetrahedral state. The band at 3438 cm$^{-1}$ was due to free Si-OH bond where hydroxyl groups were directly linked to Si atoms on the surface. Those bands somewhat depicted the nature of the catalyst surface where the basic structure was a Si linkage rather than silica-oxygen chains where silanols were being formed mostly and some of the Si became attached to Ti atoms (symmetrical distribution) with oxygen replacing the Si-OH hydrogens.

From the fluorescence emission spectrum of Ti-5-TUD-1 catalyst (Fig. 2.5), the well defined characteristic bands of Ti were discernible. A sharp maxima at 425 nm appeared due to Ti$^{4+}$ emission.
Fig. 2.1. SEM images of the surface morphology (A and B).

Fig. 2.2. TEM images of the Ti-TUD-1; lamellar and porous morphology (A and B).
Fig. 2.3. a) Wide angle X-ray diffraction pattern and b) small angle pattern (inset) of the catalyst.

Fig. 2.4. FT-IR study of the catalyst
Optimization of reaction conditions

In order to study the generality of this methodology, optimization of reaction conditions appeared important. A comparison study was carried out with a variety of catalysts along with the Ti-TUD-1 with different Ti loadings and the results have been summarized in Table 1. Primarily, indole was treated with benzaldehyde as a model reaction in the presence of the catalyst in dry dichloromethane under N₂ atmosphere. The reaction did not proceed in the absence of any catalyst. Also with TUD-1 and bulk TiO₂ as catalysts, no product was obtained. Other titanosilicates like Ti-MCM-48 and TS-1 did not prove to be highly efficient in this reaction. Ti-TUD-1 catalysts with different Ti/Si content were studied and it was observed that with Ti/Si mol ratio 0.03 (catalyst y, entry 6, table 1) provided the best result.
Table 1. Study of catalyst variation in the synthesis of bis(indolyl)methanes*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>TUD-1</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>3</td>
<td>TiO₂</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td>Ti-MCM-48</td>
<td>24</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>Ti-TUD-1 (x)</td>
<td>6</td>
<td>85</td>
</tr>
<tr>
<td>6</td>
<td>Ti-TUD-1 (y)</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>7</td>
<td>Ti-TUD-1 (z)</td>
<td>6</td>
<td>78</td>
</tr>
<tr>
<td>8</td>
<td>TS-1</td>
<td>12</td>
<td>48</td>
</tr>
</tbody>
</table>

*Reaction condition: 2 mmol benzaldehyde, 4 mmol indole, 10 mg catalyst, room temperature; isolated yield after purification.

Table 2. Use of Ti-TUD-1 catalyst in different solvents*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>24</td>
<td>—</td>
</tr>
<tr>
<td>2</td>
<td>Dichloromethane</td>
<td>6</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>Chloroform</td>
<td>12</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Acetonitrile</td>
<td>12</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>Tetrahydrofuran</td>
<td>12</td>
<td>32</td>
</tr>
</tbody>
</table>

*Reaction condition: 2 mmol benzaldehyde, 4 mmol indole, 10 mg catalyst, room temperature; isolated yield after purification.

The optimization of the conditions was continued using the best catalyst (3 mol% Ti-TUD-1) with different solvent variations. Several solvents of variable polarity were used in the reaction and the observations are shown in Table 2. It is interesting to note that in dry
dichloromethane the reaction proceeded smoothly with the best yield (89%) (entry 2, Table 2). Other solvents like toluene, chloroform, acetonitrile and tetrahydrofuran resulted in low to moderate yields (entry 3-6). In the absence of solvent no product was obtained.

After standardization of conditions, a series of reactions were carried out to study the scope and generality of Ti-TUD-1 (γ) catalyst using various aromatic aldehydes and indoles. The results have been summarized in Table 3. The bis(indolyl)methanes 3a-o were synthesized by utilizing indole 1a and 2-substituted indole 1b with a variety of aromatic aldehydes 2a-l under optimum condition. In all the cases BIMs were obtained as the sole product following excellent chemoselectivity. Most of the aldehyde including the heteroaromatic furfural (entry 15) reacted with indoles to produce the bis(indolyl)methanes in high yield. The effect on the yields based on the electron withdrawing and electron donating substituents on the aldehydes have been shown in Table 3 (entries 2 and 7). It was observed that the reaction proceeded faster and in better yields with 2-methyl indole 1b than indole 1a. This is possibly due to higher electron density at C-3. With indole the reaction time was between 6-8 hours while with 2-methyl indole the reaction was complete within 45-120 minutes depending upon the electrophiles used. However, the catalyst did not show any activity towards ketones, viz. acetone 2m, acetophenone 2n and cyclohexanone 2o. After prolonged reaction time at room temperature as well as on heating up to 60 °C both starting materials remained unchanged. This may be attributed to the lower electrophilicity of ketones compared to aldehydes.
Table 3. Synthesis of bis(indolyl)methanes over mesoporous titanosilicate Ti-TUD-1*.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Product 3</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H (1a)</td>
<td>C₆H₅ (2a)</td>
<td>3a</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>H (1a)</td>
<td>(4-NO₂) C₆H₄ (2b)</td>
<td>3b</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>H (1a)</td>
<td>(4-Me) C₆H₄ (2c)</td>
<td>3c</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>H (1a)</td>
<td>(4-Cl) C₆H₄ (2d)</td>
<td>3d</td>
<td>84</td>
</tr>
<tr>
<td>5</td>
<td>H (1a)</td>
<td>(3-NO₂) C₆H₄ (2e)</td>
<td>3e</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>H (1a)</td>
<td>(4-OH) C₆H₄ (2f)</td>
<td>3f</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>H (1a)</td>
<td>(4-NMe₂) C₆H₄ (2g)</td>
<td>3g</td>
<td>64</td>
</tr>
<tr>
<td>8</td>
<td>H (1a)</td>
<td>(4-OMe) C₆H₄ (2h)</td>
<td>3h</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>H (1a)</td>
<td>(4-OH) (3-OMe) C₆H₃ (2i)</td>
<td>3i</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>H (1a)</td>
<td>(3, 4-di OMe) C₆H₃ (2j)</td>
<td>3j</td>
<td>75</td>
</tr>
<tr>
<td>11</td>
<td>H (1a)</td>
<td>(3, 4, 5-tri OMe) C₆H₂ (2k)</td>
<td>3k</td>
<td>78</td>
</tr>
<tr>
<td>12</td>
<td>Me (1b)</td>
<td>C₆H₅ (2a)</td>
<td>3l</td>
<td>91</td>
</tr>
<tr>
<td>13</td>
<td>Me (1b)</td>
<td>(4-NO₂) C₆H₄ (2b)</td>
<td>3m</td>
<td>96</td>
</tr>
<tr>
<td>14</td>
<td>Me (1b)</td>
<td>(4-Cl) C₆H₄ (2d)</td>
<td>3n</td>
<td>86</td>
</tr>
<tr>
<td>15</td>
<td>Me (1b)</td>
<td>2-furyl (2l)</td>
<td>3o</td>
<td>88</td>
</tr>
<tr>
<td>16</td>
<td>H (1a)</td>
<td>acetone (2m)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>17</td>
<td>H (1a)</td>
<td>cyclohexanone (2n)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>18</td>
<td>H (1a)</td>
<td>acetophenone (2o)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Reaction condition: 2 mmol carbonyl compound, 4 mmol indole, 10 mg catalyst, room temperature; isolated yield after purification.
> **Reusability of the catalyst and study of mechanism of the reaction**

Ti-TUD-1 is a very stable catalyst and can be recycled. After the reaction the reaction mixture was filtered off and the residue was washed exhaustive with acetone and dried at 60 °C. It was reused for 5 consecutive operations after being dried. No appreciable loss in its catalytic activity was observed as was evident from the yields (Fig. 2.6).

The high catalytic activity of Ti-TUD-1 is probably due to the high accessibility of the substrate molecules to the catalytic sites of the mesoporous system where Ti⁴⁺ is in tetrahedral coordination and symmetrically dispersed over the three dimensional surface. Regarding the mechanism it can be presumed that Ti-O-Si linkages (which makes the Ti⁴⁺ ion strongly Lewis acidic in nature) of the surface bind with the aldehyde oxygen and increase the carbonyl activity. Indole attacks the activated carbonyl to generate an indolenium cation. This intermediate, being unstable, is attacked by a second indole molecule with subsequent loss of water resulting in the formation of bis(indolyl)methane.

![Graph](image)

**Fig. 2.6.** Recycling of the catalyst with the reaction condition: 2 mmol benzaldehyde, 4 mmol indole, 10 mg catalyst, room temperature; isolated yield.
EXPERIMENTAL

• General

All the chemicals were of analytical grade and used as such without further purification. The solvents were purified by distillation before use. All IR spectra were recorded on Perkin Elmer RX-1 FTIR spectrophotometer. $^1$H NMR and $^{13}$C NMR were studied in a Bruker-Avance Digital 300 MHz Spectrometer. TMS was used as internal standard. A JEOL JMS 600 mass spectrometer was used to record the HRMS. TEM images were obtained from a Hitachi H-9000 NAR Transmission Electron Microscope at an operating voltage of 100 kV. The sample was prepared by placing one drop of the dispersed solution of the catalyst in acetone solvent on a carbon coated copper grid followed by drying over air. SEM was performed in a Hitachi-S 3400 N microscope at an operating voltage of 15 kV. The sample was coated with gold for effective imaging before being charged. X-Ray powder diffraction study was carried out on a Philips PW-1830 X-Ray diffractometer at a voltage of 35 kV and a current of 25 mA using CuKα radiation (λ=154 nm) at the scanning rate of 1°/minute in the 2θ range 0-5° and 10-70°. The emission fluorescence spectrum was recorded on a Perkin-Elmer spectrophotometer. Melting points (uncorrected) were determined on a Köfler Block apparatus. Analytical TLC was performed using E. Merck aluminium-backed silica gel plates coated with silica gel G and monitored under UV light (254 and 360 nm) and also by exposing to iodine chamber. Indole, aldehydes and ketones were purchased from Merck and synthetic grade chemicals from Acros and E-Merck were used for the preparation of the catalyst.

• Representative procedure for the synthesis of bis(indoly)methanes

A mixture of benzaldehyde (98 mg, 2 mmol) and indole (200 mg, 4 mmol) were taken in a 50 mL round-bottom flask containing 5 mL dry dichloromethane. Ti-TUD-1 catalyst (20 mg) was then added to the reaction mixture and stirred continuously at room temperature under nitrogen atmosphere till the full consumption of starting materials was observed (by TLC.
technique). After the completion of reaction the catalyst was filtered carefully. The residue obtained was washed with ethyl acetate, dried at 100 °C and reused as catalyst. The filtrate was dried under reduced pressure to get the crude product and was purified by column chromatography using neutral alumina as support and appropriate ethyl acetate/petroleum ether mixture as eluent. The products were characterized by melting point measurement, IR, $^1$H NMR, $^{13}$C NMR and HRMS spectral analysis and elemental analysis (C, H, N) and were compared with authentic data for the known compounds.

- **Typical procedure for the synthesis of mesoporous Ti-TUD-1 catalyst**

The mesoporous titanosilicate Ti-TUD-1 was prepared following a simple and modified synthetic procedure. Modifications were done in terms of tuning of porosity development mechanism where a non-hydrothermal sol-gel technique was used with a higher content of structure directing template. Tetraethyl orthosilicate (TEOS) and titanium (IV) butoxide were used as the precursor for silica and titanium respectively. In the typical procedure titanium butoxide was added slowly to the TEOS solution. A mixture of triethanolamine (TEA) and water was added to a stirring solution and then triethyl ammonium hydroxide (TEAOH) (20% aqueous solution) was added dropwise to pH 10. The final molar ratio of the reagents was $1.0\text{SiO}_2: m\text{TiO}_2 (m = 0.01, 0.03, 0.05): 3.0\text{TEA}: 0.3 \text{TEAOH}: 15\text{H}_2\text{O}$. The clear solution was aged for 24 hours at room temperature. It was then dried at 115 °C for 16 hours and finally calcined at 700 °C for 12 hours at the rate of 2 °C/minute under the flow of air. The nature of the synthesized calcined product was a glassy crystalline entity.

The material was characterized by SEM, TEM, X-ray diffraction study, FT-IR and Fluorescence Emission spectral analysis.
CONCLUSION

Thus a new environmentally benign methodology for the synthesis of biologically active bis(indolyl)methanes catalyzed over the mesoporous titanosilicate catalyst Ti-TUD-1 has been developed. The high surface area due to high porosity, large number of active sites per unit area resulting in high reactivity and reusability are the best features of the catalyst which have been utilized in the process. The reaction procedure involved simple operational techniques, did not produce any hazardous wastes as byproducts and good yield were obtained.

PUBLICATION

“A highly efficient, eco-friendly, room temperature synthesis of bis(indol-3-yl)methanes using the mesoporous titanosilicate Ti-TUD-1: electrophilic substitution reactions of indoles - Part-XXIII”

Bikash Karmakar, Anupam Nayak, Biswajit Chowdhury, and Julie Banerji*

SECTION B: “Stannic chloride - glycerol, an unique and efficient composite for the fast and efficient synthesis of bis(indolyl)methanes”

> RESULTS AND DISCUSSION

Tin (IV) chloride/glycerol composite has been found to be an efficient Lewis acid-base pair for the chemoselective synthesis of bis(indolyl)methanes at room temperature. Variety of indoles and carbonyl compounds have been coupled together to afford the bis(indolyl)methane as the sole product.

SnCl₄, Glycerol

<table>
<thead>
<tr>
<th>R</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

> Importance of the methodology

SnCl₄ itself, being a strong Lewis acid catalyst, would have the tendency to polarize the indole system easily resulting in the dimerisation of the indole nucleus as has been observed earlier with hydrochloric acid. Glycerol has been used in the reaction as a suppressant to lower the high reactivity of SnCl₄. This is due to the fact that although the valence shells of Sn (IV) in stannic chloride are filled with eight electrons, it has two empty d orbitals which can readily accept an electron pair, specially due to electron-withdrawing of chlorine. This therefore results in the high electrophilicity of SnCl₄. In recent times glycerol has evolved as a versatile, cheap and green solvent. Glycerol, in addition to its role as a solvent, also functions as a Lewis base in the reaction medium. Therefore a Lewis acid-base complex is being generated in situ. This chelation would help to diminish the reactivity of SnCl₄ and the chelate would be the active catalyst in the reaction (scheme 15). Earlier reports has shown the use of glycerol in the synthesis of bis(indolyl)methanes which took a longer time for
completion and also required heating condition. Addition of catalytic amount of SnCl$_4$ changes the scenario. The reaction was complete within very short time and that too under ambient conditions. Moreover, this type of combo catalyst (involving chelation) has not been reported earlier.

> Optimization of reaction conditions

Initially, stabilization of the reaction conditions appeared important for the controlled synthesis of bis(indolyl)methanes. A survey was performed on the variation of reaction conditions for this synthesis and the results have been summarized in Table 1. Using SnCl$_4$ different solvents like dichloromethane, tetrahydrofuran and glycerol have been used. The best result was obtained with glycerol at room temperature in short time (entry 4). The other solvents did not have the ability to control the high reactivity of SnCl$_4$ which though efficient, thus generated other byproducts in considerable yields. Apart from SnCl$_4$, other Lewis acids like AlCl$_3$, TiO$_2$, FeCl$_3$, CoCl$_2$ and NiI$_2$ were also tried using glycerol under different conditions. Moderate yields were obtained with TiO$_2$, CoCl$_2$ and NiI$_2$ (entry 6, 8, 9). Although FeCl$_3$ and AlCl$_3$ furnished high yields, the reactions took longer periods for completion (entry 5, 7). 0.1 Mol% of the catalyst was found to be optimum. The higher the catalyst content the more the byproducts obtained. To protect the catalyst from hydrolysis, the reaction was done in absolutely anhydrous conditions under dry nitrogen atmosphere.

![Scheme 15. Generation of active catalyst in situ](image-url)
Table 1. Survey on the variation of conditions for the synthesis of bis(indolyl)methanes*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SnCl₄</td>
<td>0 °C</td>
<td>CH₂Cl₂</td>
<td>25 min</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>SnCl₄</td>
<td>room temp</td>
<td>CH₂Cl₂</td>
<td>15 min</td>
<td>58</td>
</tr>
<tr>
<td>3</td>
<td>SnCl₄</td>
<td>65 °C</td>
<td>THF</td>
<td>4 h</td>
<td>&lt;10</td>
</tr>
<tr>
<td>4</td>
<td>SnCl₄</td>
<td>room temp</td>
<td>glycerol</td>
<td>15 min</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>AlCl₃</td>
<td>room temp</td>
<td>glycerol</td>
<td>12 h</td>
<td>88</td>
</tr>
<tr>
<td>6</td>
<td>TiO₂</td>
<td>80 °C</td>
<td>glycerol</td>
<td>12 h</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>FeCl₃</td>
<td>room temp.</td>
<td>glycerol</td>
<td>2 h</td>
<td>85</td>
</tr>
<tr>
<td>8</td>
<td>CoCl₂</td>
<td>60 °C.</td>
<td>glycerol</td>
<td>6 h</td>
<td>62</td>
</tr>
<tr>
<td>9</td>
<td>Ni₂</td>
<td>room temp.</td>
<td>glycerol</td>
<td>8 h</td>
<td>68</td>
</tr>
</tbody>
</table>

*Reaction condition: 0.5 mmol benzaldehyde, 1 mmol indole, 0.1 mol % catalyst, nitrogen atmosphere; isolated yield after purification.

On determining the optimum condition, a series of BIMs were synthesized with indole (1 mmol) and variety of aromatic aldehydes (0.5 mmol) in the presence of 0.1 mol% SnCl₄ in order to justify the generality. As shown in Table 2 all aldehydes reacted with indole effectively to afford the corresponding BIMs within very short time with yields ranging between 71-94%. Reactions with nitro aldehydes (entries 2 and 3, Table 2) were remarkably fast and proceeded in high yields (94% and 88%) possibly due to the activated aldehyde carbonyl. Even electron rich systems like 4-methyl, 4-hydroxy benzaldehydes (entries 4 and 6, Table 2) and methoxyl containing aldehydes (entries 7-10, Table 2) afforded good yields of the products. The catalytic system also worked well with the acid sensitive heterocyclic aldehyde like furfural (entry 11, Table 2) and the α, β-unsaturated aldehyde (entry 12, Table 2). No side products were obtained.
Table 2. Stannic Chloride catalyzed reaction between indole 1 and aromatic aldehydes 2 for the synthesis of Bis(indolyl)methanes*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product 3</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenyl</td>
<td>3a</td>
<td>15 min</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-nitrophenyl</td>
<td>3b</td>
<td>10 min</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>3-nitrophenyl</td>
<td>3c</td>
<td>10 min</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>4-methylphenyl</td>
<td>3d</td>
<td>35 min</td>
<td>82</td>
</tr>
<tr>
<td>5</td>
<td>4-chlorophenyl</td>
<td>3e</td>
<td>20 min</td>
<td>83</td>
</tr>
<tr>
<td>6</td>
<td>4-hydroxyphenyl</td>
<td>3f</td>
<td>25 min</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>4-methoxyphenyl</td>
<td>3g</td>
<td>35 min</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>4-hydroxy-3-methoxyphenyl</td>
<td>3h</td>
<td>35 min</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>3,4-dimethoxyphenyl</td>
<td>3i</td>
<td>25 min</td>
<td>80</td>
</tr>
<tr>
<td>10</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>3j</td>
<td>25 min</td>
<td>83</td>
</tr>
<tr>
<td>11</td>
<td>2-furyl</td>
<td>3k</td>
<td>20 min</td>
<td>82</td>
</tr>
<tr>
<td>12</td>
<td>cinnamyl</td>
<td>3l</td>
<td>90 min</td>
<td>71</td>
</tr>
</tbody>
</table>

*Reaction condition: 0.5 mmol aldehyde, 1 mmol indole, 0.03 mol % catalyst, N\textsubscript{2} atmosphere, room temperature; isolated yield after purification.

The reaction was extended to the more electron rich 2-methyl indole using different aromatic aldehydes under similar reaction conditions. The results summarized in Table 3 reveal that all the aldehydes underwent efficient coupling with 2-methyl indole to afford the corresponding...
product in excellent yields (78-96%). The reactions were faster with 2-methyl indole possibly due to higher reactivity provided by the α-methyl group.

Table 3. Stannic Chloride catalyzed reactions between 2-methyl indole 4 and aromatic aldehydes for the synthesis of bis(indolyl)methanes*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Product 5</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>phenyl</td>
<td>5a</td>
<td>10 min</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>4-nitrophenyl</td>
<td>5b</td>
<td>5 min</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>4-chlorophenyl</td>
<td>5c</td>
<td>15 min</td>
<td>87</td>
</tr>
<tr>
<td>4</td>
<td>4-methylphenyl</td>
<td>5d</td>
<td>15 min</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>4-hydroxyphenyl</td>
<td>5e</td>
<td>15 min</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>3,4-dimethoxyphenyl</td>
<td>5f</td>
<td>20 min</td>
<td>78</td>
</tr>
<tr>
<td>7</td>
<td>3,4,5-trimethoxyphenyl</td>
<td>5g</td>
<td>20 min</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>2-furyl</td>
<td>5h</td>
<td>10 min</td>
<td>83</td>
</tr>
<tr>
<td>9</td>
<td>2-nitrophenyl</td>
<td>5i</td>
<td>5 min</td>
<td>91</td>
</tr>
</tbody>
</table>

♦Reaction condition: 0.5 mmol carbonyl compound, 1 mmol indole, 0.03 mol % catalyst, N2 atmosphere, room temperature; isolated yield after purification
Probable mechanism of the reaction

Regarding the mechanism, it appears to be plausible that the active catalyst formed between SnCl₄ and glycerol activates the carbonyl compounds to form a carbocationic chelate after ring opening of the cyclic active catalyst. This then reacts with indole at the electron rich C-3 site thus generating the indole-3-carbinol which releases a molecule of water and generate the indolenium cation. This on reaction with another indole moiety produces the bis(indolyl)methanes exclusively (Scheme 16).

![Scheme 16. Probable mechanism for the formation of bis(indolyl)methane](image)

EXPERIMENTAL

• General

In the synthetic procedure the reagents (A.R. grade) used were from Qualigens and Merck. Indoles were bought from Lancaster. SnCl₄ was used as 1(M) solution in dichloromethane (Spectrochem). For TLC, silica precoated aluminium plates (E-Merck) were used. Column chromatography was carried out over activated anhydrous neutral alumina (Merck) and all the solvents used for chromatography were distilled and dried over activated anhydrous sodium sulphate. In all the reactions, dry solvents were used. For the preparation of dry glycerol commercial grade solvent was distilled and then dried over pre-activated molecular
sieves (4Å). The $^1$H NMR (300 MHz) and $^{13}$C NMR (75.5 MHz) spectra were done on a Bruker Avance 300 Digital MHz NMR spectrometer using TMS as internal standard. IR spectra were obtained using a Perkin Elmer RX-1 spectrophotometer. Melting points were determined (uncorrected) on a Köfler Block apparatus.

- **Representative procedure for the synthesis of bis(indolyl)methanes**

In a 50 mL round bottom flask, indole (1.0 mmol) and aldehyde (0.55 mmol) was taken in 5 mL dry glycerol as solvent. The reaction mixture was stirred at room temperature prior to addition of the catalyst. 0.03 Mol% of catalyst was added and stirred under the same condition. The entire reaction flask was flushed with nitrogen balloons. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was added to ice water, extracted with dichloromethane (3 x 10 mL). The combined organic layer was washed with saturated NaHCO$_3$ solution and further washed with brine solution. It was finally dried over sodium sulphate and concentrated. The concentrated mass was purified by column chromatography on activated neutral alumina and ethyl acetate/hexane mixture as eluents. The structure of the products were confirmed by $^1$H- and $^{13}$C-NMR, FT-IR, elemental analysis, melting point determination and also by comparison with authentic samples obtained commercially or prepared by reported methods.

➢ **CONCLUSION**

In conclusion, a new methodology has been developed for the chemoselective synthesis of bis(indolyl)methanes under mild and efficient conditions in the presence of catalytic amount of SnCl$_4$ in glycerol generating a combo Lewis acid-base catalyst in situ. This worked well with various types of aldehydes at room temperature. The simplicity, efficiency of the reaction procedure and excellent yields within a short period of time ensures our method to be one of choice for the synthesis of biologically active bis(indolyl)methanes.
SPECTROSCOPIC DATA OF SOME CHARACTERISTIC COMPOUNDS

3-[(1H-Indol-3-yl) (phenyl) methyl]-1H-indole
Red crystalline solid; mp 124-126 °C; $R_f = 0.62$ (20% EtOAc–PE); IR (KBr): 3397.1, 3049.9, 1600.5, 1453.3, 1338.4, 1218.0, 1089.0, 1008.0, 745.7 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta = 5.78$ (s, 1H), 6.47 (s, 2H), 6.90 (t, $J = 7.1$ Hz, 2H), 7.04–7.3 (m, 11H), 7.56 (br s, 2H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 40.2$, 111.0, 119.2, 119.6, 119.9, 121.9, 123.6, 126.1, 127.1, 128.2, 128.7, 136.6, 144.0. HRMS: m/z = 321.2728 [M–H]$^+$. Anal. Calcd. for C$_{23}$H$_{18}$N$_2$: C, 85.71; H, 6.0; N, 8.7%. Found: C, 85.67; H, 5.98; N, 8.73%.

3-[(1H-Indol-3-yl) (4-nitrophenyl) methyl]-1H-indole
Orange crystalline solid; mp 220-224 °C; $R_f = 0.58$ (20% EtOAc–PE); IR (KBr): 3392.9, 3053.4, 1593.9, 1503.3, 1337.2, 1227.7, 1091.1, 741.8 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-d$_6$): $\delta = 6.12$ (s, 1H), 6.93 (t, $J = 8.0$ Hz, 2H), 7.1 (t, $J = 8.1$ Hz, 2H), 7.36 (d, $J = 7.7$ Hz, 2H), 7.4 (s, 2H), 7.43 (d, $J = 8.1$ Hz, 2H), 7.67 (d, $J = 8.5$ Hz, 2H), 8.2 (d, $J = 8.8$ Hz, 2H), 10.16 (br s, 2H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta = 40.9$, 112.3, 118.4, 119.6, 120.0, 122.3, 124.1, 124.8, 127.8, 130.5, 138.1, 145.3, 153.9. HRMS: m/z = 365.2552 [M–2H]$^+$. Anal. Calcd. for C$_{23}$H$_{17}$N$_3$O$_2$: C, 75.20; H, 4.63; N, 11.44%. Found: C, 75.24; H, 4.69; N, 11.41%.

3-[(1H-Indol-3-yl) (4-methylphenyl) methyl]-1H-indole
Pink red crystalline solid; mp 95-98 °C; $R_f = 0.69$ (20% EtOAc–PE); IR (KBr): 3408.2, 3045.5, 1610.9, 1509.7, 1453.5, 1417.0, 1340.1, 1214.3, 1091.6, 742.5 cm$^{-1}$; $^1$H NMR
(300 MHz, acetone-d$_6$): $\delta$ = 2.27 (s, 3H), 5.89 (s, 1H), 6.81 (m, 2H), 6.88-6.95 (m, 2H), 6.91 (m, 2H), 7.04-7.09 (m, 2H), 7.06 (m, 2H), 7.29 (d, $J$ = 8.0 Hz, 2H), 7.38 (m, 2H), 9.94 (br s, 2H, NH). $^{13}$C NMR (75.5 MHz, acetone-d$_6$): $\delta$ = 21.0, 40.7, 112.1, 119.2, 120.0, 120.3, 122.0, 124.5, 128.1, 129.3, 129.4, 135.8, 138.1, 142.8. HRMS: m/z = 335.1220 [M-H$^+$], 336.1254 [M]$^+$. Anal. Calcd. for C$_{24}$H$_{20}$N$_2$: C, 85.71; H, 5.95; N, 8.33%. Found: C, 85.76; H, 5.92; N, 8.37%.

$\triangleright$ 3-[[1H-Indol-3-yl] (4-chlorophenyl) methyl]-1H-indole

Red crystalline solid; mp 78-80 °C; $R_f$ = 0.65 (20% EtOAc–PE); IR (KBr): 3407.9, 1610.3, 1485.5, 1416.5, 1340.6, 1215.6, 1090.2, 1011.1, 744.6 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 5.86 (s, 1H), 6.64 (d, $J$ = 1.5 Hz, 2H), 7.02 (t, $J$ = 8.0 Hz, 2H), 7.18 (t, $J$ = 8.1 Hz, 2H), 7.22-7.30 (m, 4H), 7.36 (d, $J$ = 8.2 Hz, 4H), 7.95 (s, 2H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 39.6, 111.1, 119.3, 119.8, 122.1, 123.6, 126.9, 128.5, 130.1, 131.8, 136.7, 142.6. HRMS: m/z = 355.2770 [M-H$^+$]. Anal. Calcd. for C$_{24}$H$_{17}$N$_2$Cl: C, 77.42; H, 4.77; N, 7.85%. Found: C, 77.36; H, 4.81; N, 7.88%.

$\triangleright$ 3-[[1H-Indol-3-yl] (3-nitrophenyl) methyl]-1H-indole

Orange yellow crystalline solid; mp 145 °C; $R_f$ = 0.56 (20% EtOAc–PE); IR (KBr): 3410.8, 3054.9, 1696.6, 1524.1, 1345.9, 1220.5, 1090.9, 742.4 cm$^{-1}$; $^1$H NMR (300 MHz, acetone-d$_6$): $\delta$ = 6.13 (s, 1H), 6.92 (m, 2H), 7.1 (m, 2H), 7.39 (m, 2H), 7.39 (m, 2H), 8.26 (s, 1H), 7.56 (t, $J$ = 7.9 Hz, 1H), 7.85 (d, $J$ = 7.7 Hz, 1H), 8.1 (d, $J$ = 8.2 Hz, 1H), 10.16 (br s, 2H, NH). $^{13}$C NMR (75.5 MHz, acetone-d$_6$): $\delta$ = 39.8, 112.3, 118.6, 119.6, 120.0, 121.8, 122.3, 123.9, 124.8, 127.8, 130.1, 135.9, 138.1, 148.5, 149.3. HRMS: m/z = 390.1217 [M+Na]$^+$. 
> **3-[(1H-Indol-3-yl) (4-hydroxyphenyl) methyl]-1H-indole**

Pale pink crystalline solid; mp 128 °C; \( R_f = 0.62 \) (20% EtOAc–PE); IR (KBr): 3412.8, 3049.6, 1607.1, 1509.1, 1438.1, 1340.1, 1179.5, 1085.5, 745.7 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): \( \delta = 5.67 \) (s, 1H), 6.62 (d, \( J = 8.4 \) Hz, 2H), 6.74 (s, 2H), 6.81 (t, \( J = 7.4 \) Hz, 2H), 6.98 (t, \( J = 7.5 \) Hz, 2H), 7.1 (d, \( J = 5.4 \) Hz, 2H), 7.22 (t, \( J = 7.8 \) Hz, 2H), 7.29 (d, \( J = 5.7 \) Hz, 2H), 9.01 (s, 1H, OH), 10.7 (br s, 2H, NH). \(^13\)C NMR (75.5 MHz, DMSO-d\(_6\)): \( \delta = 39.3, 111.8, 115.2, 118.5, 118.7, 119.6, 121.2, 123.8, 126.7, 129.6, 135.3, 136.7, 155.3 \). HRMS: m/z = 338.1236 [M]+. Anal. Calcd. for C\(_{23}\)H\(_{19}\)N\(_2\)O: C, 81.66; H, 5.32; N, 8.28%. Found: C, 81.71; H, 5.33; N, 8.32%.

> **3-[(1H-Indol-3-yl) (4-methoxyphenyl) methyl]-1H-indole**

Orange red crystalline solid; mp 187 °C; \( R_f = 0.62 \) (20% EtOAc–PE); IR (KBr): 3352, 1689.2, 1505.7, 1427.6, 1242.2, 1095.9, 1029.8, 741.7 cm\(^{-1}\). \(^1\)H NMR (300 MHz, acetone-d\(_6\)): \( \delta = 3.72 \) (s, 3H), 5.86 (s, 1H), 7.39-6.78 (m, 12H), 9.95 (br s, 2H, NH). \(^13\)C NMR (75.5 MHz, acetone-d\(_6\)): \( \delta = 40.3, 55.4, 112.1, 114.2, 119.3, 120.2, 120.3, 122.0, 124.5, 128.1, 130.4, 137.9, 139.1, 158.9 \). MS: m/z = 353 [M+H]+. Anal. Calcd. for C\(_{24}\)H\(_{20}\)N\(_2\)O: C, 81.82; H, 5.68; N, 7.95%. Found: C, 81.84; H, 5.72; N, 7.97%.

> **3-[(1H-Indol-3-yl) (4-hydroxy-3-methoxyphenyl) methyl]-1H-indole**

Pink powdered solid; mp 112 °C; \( R_f = 0.48 \) (20% EtOAc–PE); IR (KBr): 3426.4, 3045.2, 1606.9, 1506.5, 1452.0, 1210.6, 1086.6, 737.8 cm\(^{-1}\). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 3.76 \) (s,
$\delta$ = 3.85 (s, 3H), 3.81 (s, 3H), 5.84 (s, 1H), 6.65 (d, $J = 2.3$ Hz, 2H), 6.93 (s, 1H), 7.03 (t, $J = 8.0$ Hz, 2H), 7.2 (t, $J = 8.1$ Hz, 2H), 7.34-7.45 (m, 6H), 7.92 (br s, 2H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 39.77, 55.82, 55.84, 110.0, 110.9, 112.2, 120.0, 120.6, 121.9, 123.5, 127.0, 135.5, 136.7, 147.3, 148.7. HRMS: m/z = 405.1506 [M+Na]$^+$. Anal. Calcd. for C$_{25}$H$_{22}$N$_2$O$_2$: C, 78.53; H, 5.76; N, 7.33%. Found: C, 78.57; H, 5.73; N, 7.28%.

$\triangleright$ 3-[(1H-Indol-3-yl) (3,4,5-trimethoxyphenyl) methyl]-1H-indole

Light pink powdered solid; mp 201 °C; $R_f = 0.60$ (20% EtOAc–PE); IR (KBr): 3381.8, 1594.0, 1502.8, 1454.2, 1329.6, 1223.3, 1124.1, 741.6 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ = 3.50 (s, 3H), 3.71 (s, 3H), 3.83 (s, 3H), 5.81 (s, 1H), 6.60 (s, 2H), 6.69 (s, 2H), 7.01 (t, $J = 8.0$ Hz, 2H), 7.17 (t, $J = 7.0$ Hz, 2H), 7.39 (q, $J = 7.8$ Hz, 4H), 8.0 (br s, 2H, NH). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 40.6, 50.9,
3-[(2-methyl-1H-Indol-3-yl) (phenyl) methyl]-2-methyl-1H-indole

Reddish brown crystalline solid, mp 162-164 °C; $R_f = 0.68$ (20% EtOAc-PE); IR (KBr): 3395.6, 3046.5, 1459.4, 1219.7, 1015.3, 746.0 cm$^{-1}$; $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta = 2.0$ (s, 6H), 5.87 (s, 1H), 6.62 (t, $J = 7.5$ Hz, 2H), 6.75 (d, $J = 7.9$ Hz, 4H), 6.84 (t, $J = 7.5$ Hz, 2H), 7.13–7.23 (m, 5H), 10.7 (br s, 2H, NH). $^{13}$C NMR (75.5 MHz, DMSO-d$_6$): $\delta =$ 12.0, 38.8, 110.4, 112.3, 118.0, 118.9, 119.6, 125.8, 128.4, 128.8, 132.1, 135.2, 144.4. MS: m/z = 350 [M$^+$]. Anal. Calcd. for C$_{26}$H$_{24}$N$_2$O$_3$: C, 75.73; H, 5.82; N, 6.80%. Found: C, 75.76; H, 5.78; N, 6.73%.

3-[(2-methyl-1H-Indol-3-yl) (4-nitrophenyl) methyl]-2-methyl-1H-indole

Light yellow crystalline solid; mp 225 °C d; $R_f = 0.60$ (20% EtOAc-PE); IR (KBr): 3391.4, 2371.9, 1627.2, 1515.5, 1341.6, 1011.4, 747.3 cm$^{-1}$. $^1$H-NMR (300 MHz, acetone-d$_6$): $\delta = 2.04$ (s, 3H), 6.07 (s, 1H), 6.63 (t, $J = 7.5$ Hz, 2H), 6.84 (t, $J = 8.2$ Hz, 2H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.19 (d, $J = 7.9$ Hz, 2H), 7.38 (d, $J = 8.3$ Hz, 2H), 8.02 (d, $J = 8.8$ Hz, 1H), 9.92 (br s, 2H, NH). $^{13}$C-NMR (75.5 MHz, acetone-d$_6$): $\delta = 12.3, 40.2, 112.3, 113.3, 119.4, 119.5, 121.0, 123.8, 129.3, 130.8, 133.4, 136.5, 147.1, 153.9. MS: m/z = 397 [M+H$^+$]. Anal. Calcd. for C$_{25}$H$_{23}$N$_2$O$_2$: C, 75.95; H, 5.32; N, 8.10%. Found: C, 75.92; H, 5.39; N, 8.13%.
3-[(2-methyl-1H-Indol-3-yl) (4-chlorophenyl) methyl]- 2-methyl-1H-indole

Reddish crystalline solid; mp 220 °C d; \( R_f = 0.62 \) (20% EtOAc–PE); IR (KBr): 3395.9, 3048.3, 1691.8, 1458.9, 1011.6, 746.3 cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): \( \delta = 2.02 \) (s, 3H), 5.88 (s, 1H), 6.62 (m, 2H), 6.76 (d, \( J = 8.1 \) Hz, 2H), 6.84 (t, \( J = 7.5 \) Hz, 2H), 7.45 (t, \( J = 7.5 \) Hz, 2H), 7.57 (m, 2H), 7.91 (d, \( J = 6.9 \) Hz, 2H), 10.7 (br s, 2H, NH). \(^13\)C NMR (75.5 MHz, DMSO-d\(_6\)): \( \delta = 12.0, 39.1, 110.4, 112.3, 118.6, 119.6, 125.8, 128.8, 132.2, 132.9, 135.1, 144.3, 167.4, MS: 385.5 [M+H\(^+\)]. Anal. Calcd. for C\(_{25}\)H\(_{20}\)N\(_2\)Cl: C, 78.02; H, 5.46; N, 7.28%. Found: C, 78.07; H, 5.39; N, 7.31%.

3-[(2-methyl-1H-Indol-3-yl) (2-furyl) methyl]- 2-methyl-1H-indole

Dark Grey solid; mp >300 °C; \( R_f = 0.45 \) (20% EtOAc–PE); IR (KBr): 3401.7, 3053.1, 1620.2, 1586.0, 1461.8, 1218.6, 1094.1, 750.2 cm\(^{-1}\); \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): \( \delta = 2.1 \) (s, 3H), 5.77 (s, 2H), 6.33 (s, 1H), 6.68 (t, \( J = 7.4 \) Hz, 2H), 6.86 (t, \( J = 7.8 \) Hz, 4H), 7.16 (s, 1H), 7.54 (s, 1H), 10.7 (bs, 2H, NH); \(^13\)C NMR (75.5 MHz, DMSO-d\(_6\)): \( \delta = 11.6, 32.7, 106.9, 110.3, 110.4, 110.8, 118.1, 118.2, 119.7, 127.8, 131.8, 135.0, 141.3, 151.4, Anal. Calcd. for C\(_{23}\)H\(_{20}\)N\(_2\): C, 81.18%; H, 5.88; N, 8.23. Found: C, 81.09; H, 5.86; N, 8.30%.

3-[(2-methyl-1H-Indol-3-yl) (4-methylphenyl) methyl]- 2-methyl-1H-indole

Pale pink solid, \( R_f = 0.65 \) (20% EtOAc–PE); IR (KBr): 3384.7, 2915.0, 1895.4, 1507.9, 1442.9, 1023.0, 746.6 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.95 \) (s, 6H), 2.25 (s, 3H), 5.87 (s, 1H), 6.77 (t, \( J = 7.5 \) Hz, 2H), 6.90-6.98 (m, 6H), 7.07
(d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.57 (bs, 2H, NH); $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ = 12.4, 21.04, 38.8, 109.9, 113.6, 119.03, 119.41, 120.55, 128.8, 128.9, 131.7, 135.02, 135.3, 140.6; Anal. Calcd. for C$_{26}$H$_{24}$N$_2$: C, 85.71; H, 6.59; N, 7.69%. Found: C, 85.63; H, 6.65; N, 7.63%.

> 3-[2-methyl-1H-Indol-3-yl] (4-hydroxyphenyl) methyl]-2-methyl-1H-indole

Deep red solid, $R_f$ = 0.4 (20% EtOAc–PE); IR (KBr): 3482.6, 3385.3, 3053.6, 1607.1, 1509.6, 1456.7, 1302.0, 1239.8, 1172.8, 744.9 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ = 2.01 (s, 6H), 5.76 (s, 1H), 6.58-6.65 (m, 4H), 6.75-6.86 (m, 4H), 7.05 (d, $J$ = 8.4 Hz, 2H), 7.15 (d, $J$ = 8.0 Hz, 2H), 9.12 (bs, 1H, OH), 10.64 (bs, 2H, NH); $^{13}$C NMR (75.5 MHz, DMSO-d$_6$): $\delta$ = 12.0, 37.9, 110.27, 112.8, 114.8, 117.9, 118.6, 119.47, 128.4, 129.54, 131.9, 134.4, 135.1, 155.3; Anal. Calcd. for C$_{25}$H$_{22}$N$_2$O: C, 81.97; H, 6.01; N, 7.65%. Found: C, 81.93; H, 6.06; N, 7.59%.

> 3-[2-methyl-1H-Indol-3-yl] (2-nitrophenyl) methyl]-2-methyl-1H-indole

Yellow solid, $R_f$ = 0.52 (20% EtOAc–PE); IR (KBr): 3391.7, 3058.0, 1529.7, 1022.3, 748.0 cm$^{-1}$. $^1$H NMR (300 MHz, DMSO-d$_6$): $\delta$ = 1.99 (s, 6H), 6.54 (s, 1H), 6.66 (q, J = 7.6 Hz, 4H), 6.87 (t, J = 7.2 Hz, 2H), 7.2 (m, 3H), 7.45-7.78 (m, 2H), 7.80 (d, $J$ = 7.8 Hz, 1H), 10.8 (bs, 2H, NH); $^{13}$C NMR (75.5 MHz, DMSO-d$_6$): $\delta$ = 11.7, 34.0, 109.9, 110.62, 117.8, 118.4, 119.9, 124.56, 127.8, 128.2, 130.6, 132.43, 132.73, 135.12, 137.9, 150.2; Anal. Calcd. for C$_{25}$H$_{2}$N$_3$O$_2$: C, 75.95; H, 5.32; N, 10.63%. Found: C, 75.99; H, 5.26; N, 10.53%.
3-[(2-methyl-1H-Indol-3-yl) (3,4-dimethoxyphenyl) methyl]- 2-methyl-1H-indole

Pale pink solid, \( R_f = 0.48 \) (20% EtOAc–PE); IR (KBr): 3396, 3369, 2918, 1510, 1458, 1243, 1128, 1020, 745 cm\(^{-1}\); \( ^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 1.61 \) (s, 6H), 3.25 (s, 3H), 3.42 (s, 3H), 5.51 (s, 1H), 6.3 (s, 2H), 6.47 (s, 1H), 6.43 (t, \( J = 7.5 \) Hz, 2H), 6.61 (t, \( J = 7.2 \) Hz, 4H), 6.79 (t, \( J = 7.7 \) Hz, 2H), 7.26 (bs, 2H, NH); \( ^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \( \delta = 12.4, 38.8, 55.8, 55.8, 109.9, 110.7, 112.7, 113.6, 119.0, 119.3, 120.6, 120.8, 128.9, 131.6, 133.9, 135.0, 136.3, 147.3, 148.8; Anal. Calcd. for C\(_{27}\)H\(_{27}\)N\(_2\)O\(_2\): C, 78.83; H, 6.57; N, 6.81%. Found: C, 78.89; H, 6.50; N, 6.77%.

3-[(2-methyl-1H-Indol-3-yl) (3,4,5-trimethoxyphenyl) methyl]- 2-methyl-1H-indole

Pale orange solid, \( R_f = 0.48 \) (20% EtOAc–PE); IR (KBr): 3396, 3338, 2937, 1593, 1505, 1458, 1321, 1242, 1124, 1008, 754 cm\(^{-1}\); \( ^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta = 2.07 \) (s, 6H), 3.64 (s, 6H), 3.85 (s, 3H), 5.94 (s, 1H), 6.56 (s, 2H), 6.87 (t, \( J = 7.5 \) Hz, 2H), 7.03 (t, \( J = 8.0 \) Hz, 4H), 7.22 (t, \( J = 7.0 \) Hz, 2H), 7.75 (bs, 2H, NH); \( ^{13}\)C NMR (75.5 MHz, CDCl\(_3\)): \( \delta = 12.4, 56.1, 60.9, 106.5, 109.9, 113.4, 119.1, 119.2, 120.6, 128.9, 131.6, 135.0, 136.4, 139.4, 153.0; Anal. Calcd. for C\(_{28}\)H\(_{30}\)N\(_2\)O\(_3\): C, 77.06; H, 6.88; N, 6.42%. Found: C, 77.01; H, 6.95; N, 6.38%.
Fig. 2.7.1. $^1$H NMR (A) and $^{13}$C NMR (B) (CDCl$_3$) spectra of 3-[(1H-Indol-3-yl) (phenyl) methyl]-1H-indole
Fig. 2.7.2. $^1$H NMR (A) and $^{13}$C NMR (B) (d6-acetone) spectra of 3-[(1H-Indol-3-yl) (4-nitrophenyl) methyl]-1H-indole
Fig. 2.7.3. $^1$H NMR (A) and $^{13}$C NMR (B) (d6-acetone) spectra of 3-[(1H-Indol-3-yl) (4-methylphenyl) methyl]-1H-indole
Fig. 2.7.4. $^1$H NMR (A) (d6-acetone) and IR (B) (KBr) spectra of 3-[(1H-Indol-3-yl) (3-nitrophenyl) methyl]-1H-indole
Fig. 2.7.5. $^1$H NMR (A) and $^{13}$C NMR (B) (d6-DMSO) spectra of 3-[(1H-indol-3-yl) (4-hydroxyphenyl) methyl] -1H-indole
Fig. 2.7.6. $^1$H NMR (A) and $^{13}$C NMR (B) (d6-acetone) spectra of 3-[(l-tf-Indol-3-yl) (4-methoxyphenyl) methyl]-1H-indole
Fig. 2.7.7. $^1$H NMR (with expansion) (A) (CDCl$_3$) and HRMS (B) spectra of 3-[(1-$H$-Indol-3-yl) (3,4-dimethoxyphenyl) methyl]-1-$H$-indole
Fig. 2.7.8. $^1$H NMR (A) (CDCl$_3$) and HRMS (B) spectra of 3-[[1H-Indol-3-yl] (3,4,5-trimethoxyphenyl) methyl]-1H-indole
Fig. 2.7.9. $^1$H NMR (A) and IR (B) (KBr) spectra of 3-[(2-methyl-1H-Indol-3-yl) (phenyl) methyl]-2-methyl-1H-indole
Fig. 2.7.10. $^1$H NMR (A) and $^{13}$C NMR (B) (d6-acetone) spectra of 3-[(2-methyl-1H-Indol-3-yl) (4-nitrophenyl) methyl]-2-methyl-1H-indole
Fig. 2.7.11. $^1$H NMR (A) and $^{13}$C NMR (B) (d6-DMSO) spectra of 3-[(2-methyl-1H-Indol-3-yl) (4-chlorophenyl) methyl]-2-methyl-1H-indole
Fig. 2.7.12. $^1$H NMR (A) (d6-DMSO) and IR (B) (KBr) spectra of 3-[(2-methyl-1H-Indol-3-yl) (2-furyl) methyl]-2-methyl-1H-indole
Fig. 2.7.13. $^1$H NMR (A) and $^{13}$C NMR (B) (CDCl$_3$) spectra of 3-[(2-methyl-1H-Indol-3-yl) (4-methylphenyl) methyl]-2-methyl-1H-indole
Fig. 2.7.14. $^1$H NMR (A) and $^{13}$C NMR (B) (CDCl$_3$) spectra of 3-[\{(2-methyl-1H-Indol-3-yl) (3,4-dimethoxyphenyl) methyl\}-2-methyl-1H-indole

(A)

(B)

Fig. 2.7.14. $^1$H NMR (A) and $^{13}$C NMR (B) (CDCl$_3$) spectra of 3-[(2-methyl-1H-Indol-3-yl) (3,4-dimethoxyphenyl) methyl]-2-methyl-1H-indole
Fig. 2.7.15. $^1$H NMR (A) (CDCl$_3$) and IR (B) (KBr) spectra of 3-[(2-methyl-1H-Indol-3-yl) (3,4,5-trimethoxyphenyl) methyl]-2-methyl-1H-indole
References


