



Tin (IV) chloride catalysed synthesis of di(indolyl)methanes during electrophilic substitution of indoles and 2-methyl indoles

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An efficient methodology has been developed for the synthesis of di(indolyl)methanes in moderate to good yields during the study of the reactions of indole and 2-methyl indole using a series of aliphatic ketones in the presence of stannic chloride. It appears worth mentioning that with 2-methyl indole and acetone and ethyl methyl ketone the highly “elusive” indolylcarbinols, the postulated intermediates in the synthesis of di(indolyl)methanes, have been isolated.

Keywords: Tin (IV) catalyst, ketones, indole, 2-methyl indole

A large variety of biologically active natural products contain the indole system as a central element of their structure¹. Over the last few years' preparation of indole derivatives has been the focus of applied research due to their promising use in the field of pharmaceuticals, material science, drugs, neurohormones and agrochemicals¹. Particularly, the substrate containing the di(indolyl)methane (DIM) nucleus are of importance for their biological activities and hence the continuing interest in their synthesis.

Di(indolyl)methane (DIM) is a major digestive product of indole-3-methanol, a potential anticancer component of cruciferous vegetables². It is a potent activator of the immune response system *in vivo*³. It activates and potentiates Interferon-Gamma signaling in human cells⁴ and its use as a supplement in human diet increases the 2-hydroxylation of estrogen metabolites⁵. DIM reduces the growth of breast cancer cells by 95%⁶. It also exhibits potent antiproliferative and antiandrogenic properties in androgen-dependent human prostate cancer cells⁷.

Stannic chloride has been reported to be an efficient Lewis acid catalyst for the synthesis of various organic compounds⁸. However there are no reports on its use in the synthesis of the important DIMs. We would like to report for the first time, the use of SnCl₄ for developing an efficient synthesis of

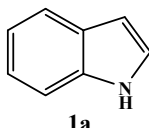
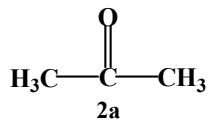
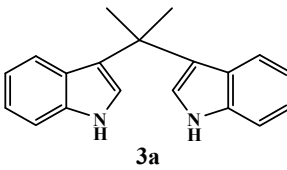
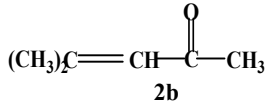
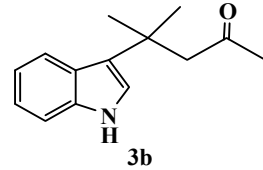
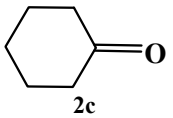
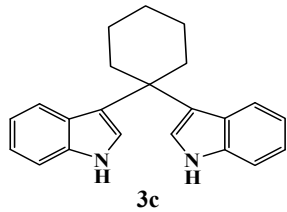
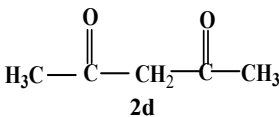
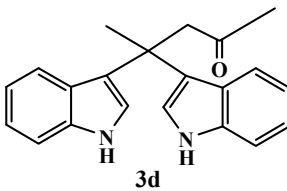
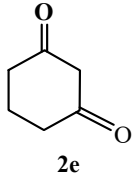
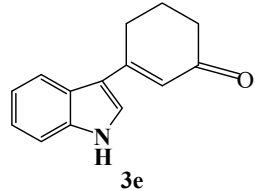
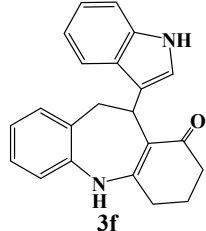
these compounds under mild conditions, *viz.* at ice-salt temperature. All the products were characterized by UV-Vis, FT-IR, NMR and mass spectrometry and melting point measurements. The results have been summarized in Table I and Table II.

Result and Discussion

A survey of the literature on indole chemistry has revealed that considerable amount of work with indole and 2-methyl indoles have been carried out with aldehydes⁹⁻²⁰. However, some reports have appeared with ketones^{15,18,19-22}. In the present study, SnCl₄ was used as it is inexpensive and has two advantages, *i.e.* strong acidity and involves mild reaction conditions. This catalyst was not chosen at random but with a definite objective because of the ability of tin(IV) in stannic chloride to expand its valence shell. Although the valence shell of tin(IV) in SnCl₄ is filled with eight electrons, it has two empty d-orbitals which can each accept an electron pair. Thus a co-ordinate covalent bond can be formed. This would generate highly reactive species which could then undergo various reactions and rearrangements.

In the earlier studies²¹⁻²⁵ it was found that the simple electrophile acetone was a fascinating system due to its ability of generating C₃-, C₆- and C₉- units *in situ* resulting in the synthesis of novel heterocyclic systems through interesting reaction pathways. For

Table I — SnCl₄ – catalysed substitution of indole **1a** with ketones **2**^a

Entry	Indole	Ketone	Product	Time (h)	Yield (%) ^b
1				6	80 ^[21,22,23,24]
2	1a			8	85 ^[26]
3	1a			7.5	82 ^[26]
4	1a			7	78 ^[26]
5	1a			9	80 ^[28]
				9	78 ^[28]

^a Reaction conditions: Indole **1a** (8.5 mmol), Ketone **2** (8.5 mmol), SnCl₄ (0.85 mmol), dichloromethane (20 mL), N₂ atmosphere, 0°C; ^b yield refers to pure product characterized from spectral data

our study seven aliphatic ketones were selected (acyclic aliphatic ketone: acetone, ethyl methyl ketone; an α,β -unsaturated ketone: mesityl oxide; the diketones: 2,4-pentadione and cyclohexa 1,3-dione; the cyclic ketones: cyclohexanone and cycloheptanone). However, in most cases with SnCl₄ the reaction stopped at the di(indolyl)methane stage akin to Montmorillonite clay K-10 (Ref. 26) but this method was more efficient. Another interesting feature of this study was the isolation of the

intermediate indolyl carbinols (**4a**) and (**4c**) during the reaction of 2-methyl indole with acetone and ethyl methyl ketone. Also there are three new di(indolyl)methanes (**4e**, **4f**, **4h**; Table II) have been isolated when the reaction occurs in between 2-methyl indole and acetyl acetone, cyclohexanone and cycloheptanone respectively. So there will be total five new compounds in the reaction scheme.

With the exception of mesityl oxide and cyclohexane 1,3-dione all the reactions afforded the

Table II — SnCl₄ catalysed substitution of 2-methyl indole **1b** with ketones **2**^a

Entry	2-Methylindole	Ketone	Product	Time (h)	Yield (%) ^b
1				10	72
				10	21 ^[21]
2	1b			9	68
3	1b			7	80 ^[22a]
4	1b			7	68
5	1b			7	82
6	1b			6	78 ^[20c]
7	1b			6	70

^a Reaction conditions: 2-Methylindole **1b** (8.5 mmol), Ketone **2** (8.5 mmol), SnCl₄ (0.85 mmol), dichloromethane (20 mL), N₂ atmosphere, 0°C; ^b yield refers to pure product characterized from spectral data

di(indolyl)methanes. SnCl_4 showed its catalytic behavior similar to Montmorillonite clay K-10 (Ref. 26) but the former catalyst was more efficient and the conditions involved were milder which would not affect vulnerable groups.

Another interesting feature of this study was the isolation of the “elusive” indolyl carbinols in high yields in the reaction of 2-methyl indole with acetone and ethyl methyl ketone. This therefore provided circumstantial evidence to the formation of these systems in the generation of the highly reactive indolenium cation (Scheme I). However, with cyclohexane 1,3-dione and indole the desired di(indolyl)methane could not be isolated (Table I).

This was the only reaction where SnCl_4 showed similar catalytic activity as $\text{BF}_3 \cdot \text{Et}_2\text{O}^{23}$. The indolenium cation appeared to be the more powerful electrophile compared to cyclohexane 1,3-dione. It was only after the formation of the indole dimer earlier obtained by G.F. Smith²⁷ using mineral acid that subsequent protonation of the aniline nitrogen occurred with ring opening of the indoline system followed by reaction with cyclohexane 1,3-dione²⁸. The C₃-substituted product was also obtained as was the case with 2-methyl indole (Table I and Table II). Both indole and 2-methyl indole with mesityl oxide afforded the 1:1 addition products similar to Montmorillonite clay K-10 (Ref. 26).

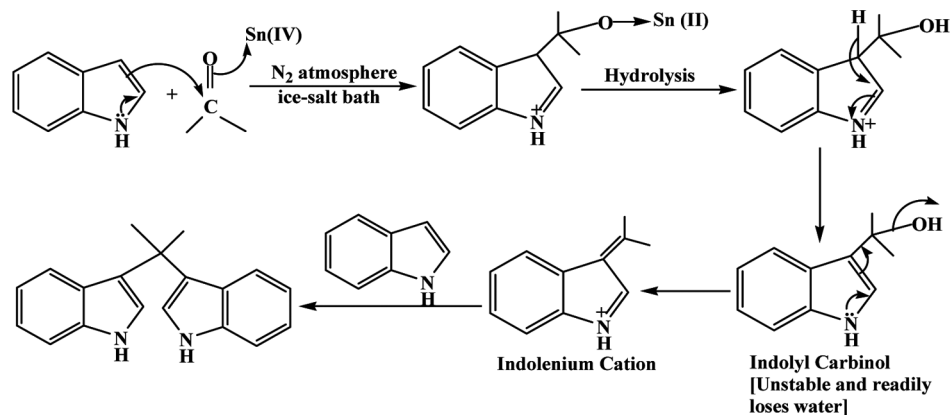
The plausible mechanism of formation of di(indolyl)methane has been shown in Scheme I.

To study the solvent effect the reactions were carried out using indole and 2-methyl indole with acetone varying the solvents under similar reaction conditions. The results obtained have been given in Table III. It is interesting to note that in dry dichloromethane as solvent the reaction proceeded smoothly with the best yield (80%) and minimum reaction time. Other solvents like chloroform, acetonitrile, tetrahydrofuran and toluene resulted in moderate to low yields.

Experimental Section

The melting points were recorded in an electrically heated bath and are uncorrected. The UV-Vis absorption spectra were measured in a Hitachi U-2000 spectrophotometer in 95% aldehyde free ethanol, the infrared spectra using KBr pellet in a Perkin-Elmer 782 spectrophotometer, the ¹H and ¹³C NMR spectra using Bruker AM-300L and Varian XL-400 spectrometers. The NMR spectral solvents used were CDCl_3 , acetone-*d*₆ and methanol-*d*₄ (as indicated). The mass spectra were recorded on a JEOLJMS 600 mass spectrometer.

Column and thin layer chromatographic analysis were carried out using neutral alumina standardized according to Merck and silica gel G [Merck,



Scheme I — Mechanism of formation of di(indolyl)methane

Table III — Use of SnCl_4 catalyst in different solvents^a

Entry	Solvent	Time (hrs)	Yield ^b (%)
1	Dichloromethane	6	80
2	Chloroform	14	30
3	Acetonitrile	15	45
4	Tetrahydrofuran	13	35
5	Toluene	40	10

^a Reaction condition: 8.5 mmol acetone, 8.5 mmol indole, 0.15 mL catalyst, ice-salt bath; ^b isolated yield after purification.

Spectrochem 60-120 mesh] respectively. The spots were detected in an iodine chamber. The analytical samples were dried *in vacuo* over P₂O₅ for 24 h. Anhydrous sodium sulphate and molecular sieves (4 Å) were used to dry the organic solvents. Petrol refers to petroleum ether (b.p. 60-80°C) and hexane refers to *n*-hexane.

Representative experimental procedure

To a solution of indole (1g, 8.5 mmol) at 0°C in dry methylene chloride (20 mL) and acetone (0.493 g, 8.5 mmol) distilled at 22.5°C/8 mm over dry magnesium, was added followed by dropwise addition of stannic chloride (0.15 mL, 0.85 mmol) with constant stirring. The reaction mixture was stirred for 6 hours at 0°C under a nitrogen blanket. The reaction mixture was extracted with methylene chloride, washed with 2% sodium bicarbonate and finally with water. It was dried over anhydrous sodium sulphate and concentrated. Column chromatography of the concentrate was carried out over neutral alumina, the column being eluted with solvents of increasing polarity. Petrol-benzene (1:1) eluate afforded compound **3a** (80%) as a white solid, m.p. 150°C; R_f = 0.56 (benzene).

2-(2-Methyl-1H-indol-3-yl)-propan-2-ol, 4a: White solid (72%). m.p.177-78°C. IR (KBr): 3422, 3231, 2969, 1461, 1328, 734 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 9.95 (1H, br,s.), 7.50 (1H, t, *J* = 7.6 Hz), 7.22 (1H, d, *J* = 8.0 Hz), 6.95 (1H, t, *J* = 7.3 Hz), 6.83 (1H, d, *J* = 7.2 Hz), 2.85 (1H, s), 2.05 (3H, s), 1.84 (6H, s); ¹³C NMR (75.5 MHz, acetone-*d*₆): δ 136.2, 133.6, 128.6, 121.1, 120.8, 119.4, 112.9, 111.2, 67.6, 25.2, 14.4; HRMS: *m/z* 189.135 [M⁺]. Anal. Calcd for C₁₂H₁₅NO: C, 85.73; H, 5.93; N, 8.34. Found: C, 85.79; H, 5.97; N, 8.39%.

2-(2-Methyl-1H-indol-3-yl)-butane-2-ol, 4c: Light yellow solid (68%). m.p.200-202°C. IR (KBr): 3422, 3226, 2970, 1462, 1328, 736 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 9.95 (1H, br,s.), 7.49 (1H, d, *J* = 7.4 Hz), 7.20 (1H, d, *J* = 8.1 Hz), 6.92 (1H, t, *J* = 7.8 Hz), 6.82 – 6.73 (1H, m), 2.89 (3H, s), 2.52 – 2.44 (5H, m), 2.70 (1H, s), 1.82 (3H, s); ¹³C NMR (75.5 MHz, acetone-*d*₆): δ 136.2, 133.6, 128.7, 121.1, 120.8, 119.4, 111.2, 110.3, 67.6, 31.2, 25.2, 15.2, 14.4; HRMS: *m/z* 226.112 [M⁺ + Na]. Anal. Calcd for C₁₃H₁₇NO: C, 81.65; H, 5.35; N, 8.27. Found: C, 81.73; H, 5.31; N, 8.31%.

4,4-Bis-(2-methyl-1H-indol-3-yl)-pentane-2-one, 4e: Light yellow solid (68%). m.p.210-11°C. IR (KBr):

3241, 2916, 1654, 1549, 1424, 1326, 736 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 10.41 (2H, s), 7.64 (2H, d, *J* = 8.4 Hz), 7.34 (2H, d, *J* = 8.4 Hz), 7.12 – 7.02 (4H, m), 2.99 (2H, s), 2.62 (6H, s), 2.54 (3H, s), 1.72 (3H, s); ¹³C NMR (75.5 MHz, acetone-*d*₆): δ 198.7, 136.7, 135.4, 128.0, 124.8, 122.0, 120.7, 120.0, 116.7, 111.7, 32.1, 28.7, 21.0, 13.6; HRMS: *m/z* 344.113 [M⁺]. Anal. Calcd for C₂₃H₂₄N₂O: C, 82.67; H, 6.25; N, 8.37. Found: C, 82.73; H, 6.19; N, 8.47%.

2,2'-Dimethyl 3,3'-bis(indolyl)cyclohexaylmethane, 4f: Light brown solid (82%). m.p.81-82°C. IR (KBr): 3420, 3227, 2923, 1666, 1612, 1460, 1325, 734 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 10.0 (2H, s), 7.51 (2H, d, *J* = 7.4 Hz), 7.23 (2H, d, *J* = 7.8 Hz), 6.98 – 6.93 (2H, m), 6.84 – 6.75 (2H, m), 2.47 (6H, s), 2.06 – 2.03 (4H, m), 1.85 – 1.83 (6H, m); ¹³C NMR (75.5 MHz, acetone-*d*₆): δ 136.2, 133.6, 128.6, 121.1, 120.8, 118.9, 111.2, 110.2, 30.5, 30.3, 29.0, 25.2, 14.4; HRMS: *m/z* 342.122 [M⁺]. Anal. Calcd for C₂₄H₂₆N₂: C, 83.45; H, 6.55; N, 8.47. Found: C, 83.51; H, 6.47; N, 8.39%.

2,2'-Dimethyl 3,3'-bis(indolyl)cycloheptylmethane, 4h: Yellow solid (70%). m.p.213-15°C. IR (KBr): 3419, 3224, 2966, 1666, 1611, 1459, 1324, 733 cm⁻¹; ¹H NMR (300 MHz, acetone-*d*₆): δ 10.22 (2H, br,s.), 7.73 (2H, d, *J* = 7.8 Hz), 7.45 (2H, d, *J* = 7.8 Hz), 7.16 (2H, t, *J* = 7.2 Hz), 7.02 (2H, m), 3.15-2.68 (12H, m), 2.06 (6H, s); ¹³C NMR (75.5 MHz, acetone-*d*₆): δ 136.4, 133.8, 128.8, 121.3, 119.7, 118.6, 113.1, 111.4, 30.8, 25.4, 14.6; HRMS: *m/z* 356.253 [M⁺]. Anal. Calcd for C₂₅H₂₈N₂: C, 85.75; H, 6.03; N, 8.71. Found: C, 85.69; H, 5.97; N, 8.77%.

Conclusion

A highly efficient protocol has thus been developed for the synthesis of di(indolyl)methanes and the isolation of the intermediate indolyl carbinols during the reaction of 2-methyl indole with acetone and ethyl methyl ketone under mild conditions.

Supplementary Information

Supplementary information is available in the website <http://nopr.niscair.res.in/handle/123456789/58776>.

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