Article

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Synthesis of Pharmacologically Active Bis(indolyl) and Tris(indolyl) Derivatives Using Chlorotrimethylsilane

Nongthombam G. Singh, Chingrishon Kathing, Jims W. S. Rani and Rishan L. Nongkhlaw*
Department of Chemistry, North Eastern Hill University, Shillong, Meghalaya-793022, India

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Chlorotrimethylsilane is found to be a comparatively fast and efficient catalyst for carrying out electrophilic substitution reactions of indoles with various aldehydes/ketones/triethylorthoformate, yielding excellent amount of bis(indolyl)methanes/tris(indolyl)methanes. The merits of this protocol are avoidance of any external energy source, minimal reaction time, simple and easy procedure and high yield under solvent free room temperature condition. The versatility of this method has been tested with various aldehydes/ketones and received satisfactory results.

Keywords: Indole; Chlorotrimethylsilane [TMSCl]; Bis(indolyl)methane [BIMS]; Tris(indolyl)methane [TIMS]; Solvent free.

INTRODUCTION

The compounds bearing indole moiety has generated immense interest nowadays due to its broad spectrum of biological activity.[1] Indole plays an important role in the field of drug design as well as synthesis and it has been exploited to various ends in medicinal chemistry.[2] Bis(indolyl)methanes constitute an important class of indole derivative which serve the purpose of antibiotics[3] and also play a vital role in cancer chemotherapy due to its apoptosis, growth inhibition and antiangiogenic activities in various cancer cell lines and tumors.

The process of carrying out energy efficient chemical transformations involving coupling of two or more components in a single catalytic step avoiding large amount of solvents, and complex purification methods is the main target of every synthetic chemist. Many methods have been reported for the synthesis of BIMS using various Lewis acids[4,6]/protic acids[5] such as $InCl_3$,[6] $Ln(OTf)_3$,[7] acetic acid,[8] $FeCl_3$,[9] $Dy(OTf)_3$,[10] $In(OTf)_3$,[11] zeolites,[12] $LiClO_4$,[13] $KHSO_4$,[14] NBS,[15] $NaHSO_4.SiO_2$,[16] clay,[17] $PPh_3.HClO_4$ (TPP),[18] InF_3,[19] I_2,[20] etc and some have even reported with ionic liquids like 1-butyl-3-methylimidazolium tetrafluoroborate or 1-butyl-3-methylimidazolium hexafluorophosphate ionic liquids.[21] However, these methods suffer from various drawbacks such as longer reaction times,[6,10,13,21] use of expensive reagents,[7,8,11] use of large amount of solvents,[7,11,12,13] use of either conventional heating (reflux) or microwave,[12] low yields[11] involvement of complicated purification processes, etc.

Another derivative of indole i.e. tris(indolyl)methanes have recently gained importance for preparation of cage compounds, photochemical transformations,[22-26] physicochemical studies, and as dyes. Various research groups have reported the preparation of TIMS using different catalysts.[27-30]

Hence, due to their broad spectrum of biological and synthetic applications, the preparation of bis(indolyl)methanes and tris(indolyl)methanes has instigated researchers to develop improved protocols for milder and high-yielding methods.

RESULTS AND DISCUSSION

Our present study gives emphasis on the synthesis of bis(indolyl)methanes and tris(indolyl)methanes using TMSCl as a catalyst under solvent free condition. The reactions were carried out by simple mixing of indole and aldehyde/ketone/triethtylorthoformate at room temperature and extraction was done with ethyl acetate. Our method (Scheme I) minimizes the reaction time and avoids usage of additional energy source. The yield is found to vary from good to excellent yield depending on the aldehyde/ketone used.

The versatility of our method was tested using different aromatic and aliphatic aldehydes/ketones. Effect of the substituents on the aromatic ring did not have profound effect on the yield; however electron withdrawing groups on the aromatic ring gave slightly better yield. The reaction seems to proceed *via* formation of azafulvenium salt (7) which reacts with another molecule of indole to give the 3-alkylated bis(indolyl) derivative (3) as the predominant

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* Corresponding author. E-mail: rlnongkhlaw@nehu.ac.in

Scheme I Synthesis of various derivatives of indole

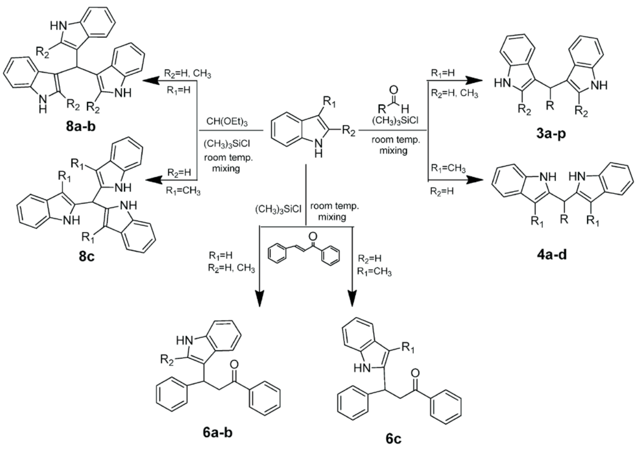


Table 1. Screening for the optimum amount of TMSCl required under different solvent conditions for the synthesis of **3c**

TMSCl (Eq. mol)	Indole (Eq. mol)	Conditions	Solvent	Reaction time (min)	Yield (%)
0.2	2	rt mixing	-	*	47
0.3	2	rt mixing	-	*	65
0.5	2	rt mixing	-	*	96
1	2	rt mixing	-	*	96
2	2	rt mixing	-	*	90
0.5	2	rt stirring	CH_2Cl_2	15	95
0.5	2	rt stirring	H_2O	15	30
0.5	2	rt stirring	CH_3CN	15	89
0.5	2	rt stirring	EtOH	15	94
0.5	2	Reflux (80 °C)	EtOH	2	95

*Product formed immediately on addition of catalyst.

product without formation of any N-alkylated product. The most plausible pathway or mechanism is depicted in the figure (Figure 1) below.

The reaction of indole with α,β-unsaturated aldehyde such as cinnamaldehyde produced the normal bis(indolyl) 1,2-addition product, however the reaction with α,β-unsaturated ketone such as chalcone did not form the expected 1,2-addition product but instead gave the 1,4-addition product as shown in Scheme I.

Optimization of the quantity of TMSCl for preparation of **3c** was done as shown in Table 1 and it was found that 0.5 mole equivalent of TMSCl per 2 mole equivalent of indole was the ideal amount for excellent yield. On further increasing the quantity of the catalyst, the yield was found to decrease. This may be due to over saturation of the desired product by the catalyst.

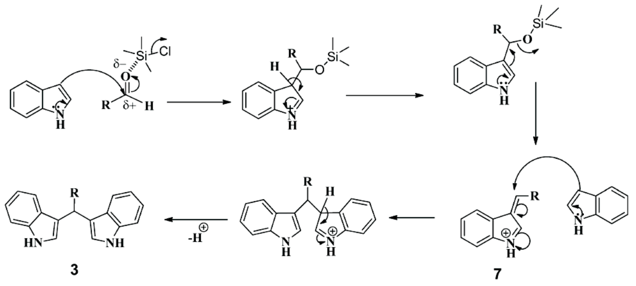


Fig. 1. Proposed mechanism for the formation of bis-(indolyl) alkane via azafulvene. In case of 3-substituted indole, alkylation occurs at C-2 and the mechanism proceeds by rearrangement pathway (Figure 2).

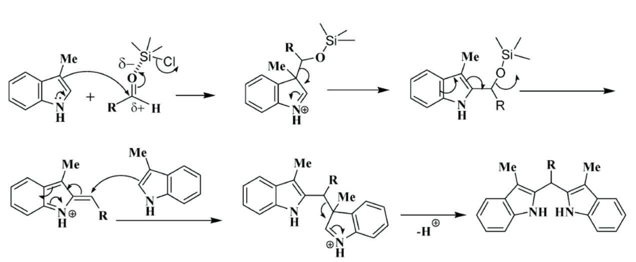


Fig. 2. Rearrangement of substituent from position C3 to C2.

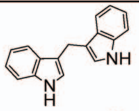
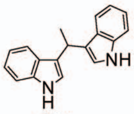
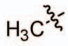
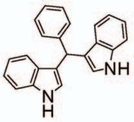
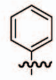
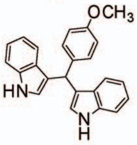
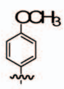
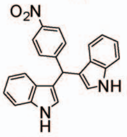
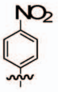
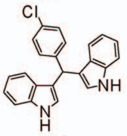
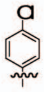
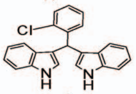
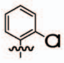
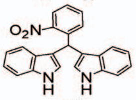
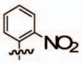
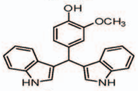
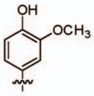
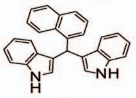
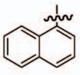
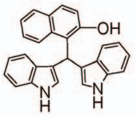
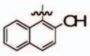
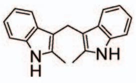
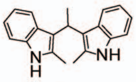
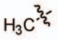
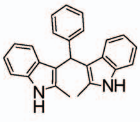
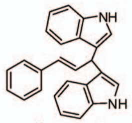
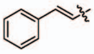
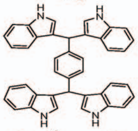
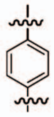
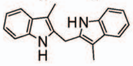
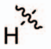
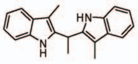
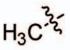
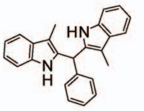
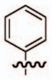
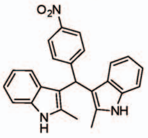
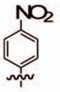
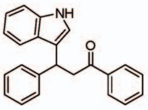
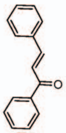
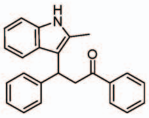
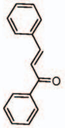
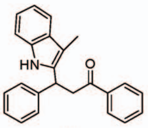
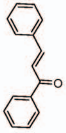
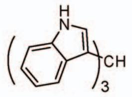
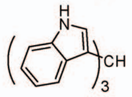
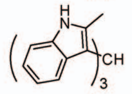
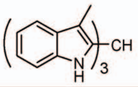
Tris(indolyl)methanes were also prepared under solvent-free room temperature condition using 1:3 TMSCl-Indole ratio. Here we replaced the aldehyde/ketone by triethylorthoformate. The schematic representation is given in Scheme I.

EXPERIMENTAL

All the concerned chemicals were purchased from Merck and S.D.-Fine and were used without any further purification. Products were confirmed by IR, ^{1}H NMR, ^{13}C NMR, Mass spectra, elemental analysis and melting point data. Melting points were determined in open capillary tubes and are uncorrected. Infrared spectra were recorded on a BOMEM DA-8 FTIR instrument and the frequencies are expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II-400 and DRX-300 MHz Bruker spectrometer. Mass spectral data were obtained with a JEOL D-300 (EI) mass spectrometer. Elemental analyses were carried out on a Heraeus CHN-O-Rapid analyzer. All reactions were monitored by thin layer chromatography (TLC) using precoated aluminum sheets (silica gel 60 F 254 0.2 mm thickness) and developed in an iodine chamber. Column chromatographic separations were carried out using ACME silica gel (60–120 mesh).

General procedure for preparation of 3a-p, 4a-d, 6a-c, 8a-c: To a mixture of Indole and aldehyde/ketone, TMSCl was added and thorough mixing was done. The formation of the prod-

Table 2. Indole derivatives 3a-p, 4a-d, 6a-c and 8a-c produced via Scheme I

Entry	Product	R_1	R_2	R	Melting Point (°C)	Yield (%)
3a		H	H		163-165[8]	90
3b		H	H		157-158[8]	93
3c		H	H		124–125[35]	96
3d		H	H		192–195[37]	95
3e		H	H		220-222[35]	98
3f		H	H		78–80[35]	96
3g		H	H		70–73	94
3h		H	H		210-213[37]	96
3i		H	H		100–101[8]	92
3j		H	CH_3		248-250[8]	93
3k		H	H		203-205	94
3l		H	CH_3		103-107	88
3m		H	CH_3		145-148	85
3n		H	H		120-123	93
3o		H	H		98-100[8]	90
3p		H	H		197-200	93
4a		CH_3	H		132-134	87
4b		CH_3	H		87-89	85
4c		CH_3	H		123–125	88
4d		H	CH_3		130-134	92
6a		H	H		130-133[36]	95
6b		H	CH_3		113-115[36]	95
6c		CH_3	H		141-143	92
8a		H	H	$CH(OEt)_3$	241-243[29]	95
8a		H	H	$CH(OMe)_3$	241-243[29]	93
8b		H	CH_3	$CH(OEt)_3$	334-335[29]	89
8c		CH_3	H	$CH(OEt)_3$	319–320[29]	85

uct was noticed by the appearance of a coloured solid and was further confirmed by TLC. Extraction of the compound was done using ethyl acetate and then washed with water (3 × 15 mL) and brine solution (1 × 15 mL). Finally the product was triturated with hexane as a precautionary measure in order to remove any indole or aldehyde remnants. The products obtained were further puri-

Table 3. Comparative study of preparation of **3c** under different catalyst condition. Yields are approximately the same

Catalyst	Conditions	Solvent	Reaction time (min)	References
$Cu(BF_4)_2.SiO_2$	reflux 80 °C	CH_2Cl_2	30	[31]
ZnO	Heat 80 °C	---	45	[32]
Polyindole salt	rt stirring	EtOH	180	[33]
$FeCl_3.6H_2O$	rt stirring	[omim]PF_6	90	[34]
$Dy(OTf)_3$	rt stirring	[BMIM]BF_4	60	[10]
Ln $(OTf)_3$	rt stirring	EtOH/H_2O	720	[7]
$InF_3.H_2O$	rt stirring	Aqueous	600-900	[19]
TMSCl	rt mixing	---	*	-

*Product formed immediately on addition of catalyst.

fied by column chromatography using Ethyl acetate-Hexane as eluent.

For products **3a-o, 3p, 4a-d, 6a-c and 8a-c** the same procedure is followed with the variations in mole percentage as shown below:

For 3a-o, 4a-d: Indole (2 mmol) and aldehyde/ketone (1 mmol), TMSCl (0.5 mmol). **For 3p:** *I*ndole (4 mmol), terephthaldehyde (1 mmol), TMSCl (1 mmol). **For 6a-c:** Indole (1 mmol), chalcone (1 mmol), TMSCl (0.5 mmol). **For 8a-c:** Indole (3 mmol), triethylorthoformate/trimethylortho-formate (1 mmol), TMSCl (1 mmol).

Spectral data of selected compounds are given below: **di(1*H*-indol-3-yl)methane (3a):** Red Solid, Yield 90%, mp 163-165 °C; IR (KBr): ν 1342, 1613, 3107, 3387 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.18 (s, 2H), 6.88 (s, 2H), 7.02 (t, *J* = 7.6 Hz 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 8 Hz, 2H), 7.54 (d, *J* = 8 Hz, 2H), 7.8 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7, 111.0, 115.6, 119.1, 119.2, 121.8, 122.2, 127.5, 136.4; MS: *m/z* 247 [M+1]; Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90; H, 5.73; N, 11.37%; Found: C, 82.76; H, 5.88; N, 11.17%. **2,2′-(phenylmethylene)-bis(3-methyl-1*H*-indole) (4c):** Yellow solid, yield 88%, mp 123–125 °C; IR (KBr): ν 1325, 1453, 2919, 3320 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 6H), 5.92 (s, 1H), 7.03-7.49 (m, 13H), 7.52 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.5, 39.8, 107.6, 109.8, 117.4, 118.4, 120.6, 126.3, 127.4, 128.0, 128.4, 132.3, 134.2, 139.0; MS: *m/z* 351 [M+1]; Anal. Calcd. for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99%; Found: C, 85.80; H, 6.23; N, 7.88%. **3-(1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (6a):** Pink solid, Yield 95%, mp 130-133 °C: IR (KBr): ν 1354, 1593, 1672, 3350 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.62 (dd, *J* = 7.6 Hz, 1H), 3.72 (dd, *J* = 6.8 Hz, 1H), 4.99 (t, *J* = 7.2 Hz, 1H), 6.93 (s, 1H), 7.08 (m, 2H), 7.27 (m, 3H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.46 (m, 4H), 7.85 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.2, 45.2, 111.1, 119.3, 119.4, 119.5, 121.4, 122.1, 126.2, 127.8, 128.1, 128.4, 128.5, 133.8, 136.6, 137.1, 144.2, 198.5; MS: *m/z* 326 [M+1]; Anal. Calcd. for $C_{23}H_{19}NO$: C, 84.89; H, 5.89; N, 4.30%; Found: C, 84.76; H, 5.70; N, 4.50%. **tris(1*H*-indol-3-yl)methane (8a)**: Red solid, Yield: 95%, mp: 241-243 °C, IR (KBr): 3395, 3045, 1484, 1454, 1418,1348, 1228, 1029, 804, 744 cm^{-1}; ^{1}H NMR (300 MHz, Acetone-d6): δ 6.19 (s, 1H), 6.86 (m, 6H), 7.04 (t, *J* = 7.5 Hz, 3H), 7.36 (d, *J* = 8.1 Hz, 3H) ArC-H), 7.47 (d, *J* = 8.1 Hz, 3H), 9.92 (s, 3H); ^{13}C NMR (75 MHz, Acetone-d6): δ 32.2, 112.1, 119.1, 120.0, 120.5, 121.9, 124.3, 128.2, 138.1; ESI-MS (positive mode): 360 [M-1].

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