An Easy and Efficient Synthesis of Bisindolylmethanes and Tetraindolylmethane Tröger's Base Catatlyzed by $AgBF_4$

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This work presents a highly efficient and simple method for the synthesis of bisindolylmethanes, catalyzed by $AgBF_4$, with excellent yields. Various substituted aldehydes and ketones with indole under this reaction condition is elucidated. This reaction occurs efficiently under mild reaction conditions, such as are applied with methoxy or furfural, which commonly undergoes cleavage under strongly acidic reaction conditions. The presented approach was suitable for the synthesis of complex systems, such as tetraindolylmethane Tröger's Base.

Keywords: $AgBF_4$; Condensation; Indole; Carbonyl compounds; Tröger's base; Bisindole.

1. INTRODUCTION

The first isolation of hallucinogenic bisindolylalkanes from a fungus in 1977[1] and the subsequent isolation of other bisindolylalkanes, including some bioactive members, from natural sources[2] have attracted considerable scientific attention. Some indole derivatives, such as 3-substituted indoles derivatives, are of pharmaceutical interest in several therapeutic areas.[3] They are known to exhibit various biological activities including antibacterial, cytotoxic, antioxidative and insecticidal activites.[4] The feasibility of electrophilic substitution at the 3-position of indole is such that it is widely used in organic synthesis.[5]

Bisindolylmethanes have been obtained by reactions of indoles with various aldehydes or ketones in the presence of either protic[6] or Lewis acids.[7] With the rapid development in the field of catalytic and synthetic chemistry, researchers have started to pay more attention to the development of eco-friendly and reusable catalysts to eliminate or minimize problems of environmental pollution. In particularly, indoles and carbonyl compounds have been successfully condensed using catalysts such as amberlyst (sulfonic acid form),[8] $AuCl_3$,[9] diammonium hydrogen phosphate,[10] $FeCl_3$,[11] I_2,[12] montmorillonite K10,[13] sulfamic acid,[14] TCT,[15] zeolite,[16] CAN,[17] triflates,[18] ferric dodecyl sulfonate,[19] ion exchange resins,[20] aminocatalysis by benzoic hydrazide derived catalyst,[21] ionic liquids,[22] antimony sulfate,[23] $CuBr_2$,[24] HMTAB,[25] nitrates,[26] PPh_3-$HClO_4$,[27] silica supported sodium hydrogen sulfate and amberlyst-15,[28] tetrabutylammonium triborimide,[29] Yb-amberlist,[30] ZnO,[31] NBS,[32] $KHSO_4$,[33] InF_3,[34] $ZrCl_4$,[35] 1-butyl-3-methylimidazolium tetrafluoroborate,[36] $MoO_2(acac)_2$,[37] $MgSO_4$,[38] *p*-TsOH,[39] triphenylmethyl chloride,[40] lanthanum perfluorooctanoate,[41] H_3PO_4-SiO_2,[42] ruthenium(III) chloride hydrate,[43] carbohydrate-based tolylsulfonyl hydrazines,[44] sodium dodecylsulfate,[45] $SbCl_3$,[46] 3-(*n*-hexyl)-1-methylimidazolium hydrogensulfate,[47] heteropoly acids,[48] iron(III) fluoride,[49] 1-dodecanesulfonic acid,[50] $CeCl_3.7H_2O$,[51] $SmI_2(THF)_2$,[52] and sodium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.[53] Many of the methods used have such disadvantages as long reaction periods,[54] the use of expensive reagents[7f] or preformed reagents,[55–56] and poor yields of bisindolylmethanes (around 2%).[2a] Although some of these reactions are performed under mild conditions, most of them require a long period for completion, tedious work-up, the formation of side products and only modest yields of the products (Table 1). Therefore, a convenient, rapid and efficient method for preparation of bisindolemethane is still sought. Because of the wide range of biological interest in these compounds, this study pursues a mild, efficient and expedient protocol for synthesizing bisindolylmethanes.

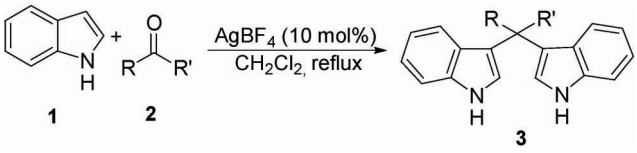
Silver tetrafluoroborate is a fluorodesulfurization reagent;[57] is used in the synthesis of 1,6-diketones from siloxycyclopropanes;[58] is a potent promoter of chemical glycosylation;[59] causes the silver ion-induced rearrangement of *N*-chloramines;[60] causes the silver-induced allylation of β-bromo ethers with allylsilanes,[61] and has other im-

Table 1. Various Lewis acids catatlyzed synthesis of bisindolylmethanes using aldehydes and ketones with indole

Entry	Lewis Acid	Temp (°C)	Solvent	Time (h)	Yield (%)	Reference
1	$Ln(OTf)_3$	rt	$EtOH/H_2O$	12-36	47-99	7f
2	$AuCl_3$	rt	CH_3CN	12	64-93	9
3	$FeCl_3$	20	Various	1.25	96	11
4	$FeCl_3{\cdot}6H_2O$	rt	$[omim]PF_6$	0.25-10	78-98	11
5	CAN	rt	$DMSO/H_2O$	0.08-1	99	17
6	$Sc(OTf)_3$	40	CH_3CN	1	71-88	18b
7	$Dy(OTf)_3$	rt	ionic liquids	1-24	84-99	18c
8	$Zr(OTf)_3$	rt	$EtOH/H_2O$	24-72	4-99	18e
9	$Fe(DS)_3$	rt	H_2O	2-12	80-97	19
10	$Sb_2(SO_4)_3$	rt	MeOH	1.1-9	75-96	23
11	$CuBr_2$	rt	CH_3CN	0.25-8	38-95	24
12	$Sb(SO_3)_4$	rt	MeOH	1.1-9	75-95	25b
13	ZnO	80	free	0.33-2	63-99	31
14	InF_3	20	H_2O	13	99	34
15	$ZrCl_4$	20	CH_3CN	6	87	35
16	$MoO_2(acac)_2$	20	H_2O	20	90	37
17	$MgSO_4$	50	free	20	94	38
18	$La(PFO)_3$	20	EtOH	0.5	95	41
19	$RhCl_3.H_2O$	reflux	MeOH	3	77	43
20	$SbCl_3$	20	CH_3CN	1	96	46
21	$CeCl_3.7H_2O$	75	glycerol	2	96	51
22	$SmI_2(THF)_2$	rt	CH_2Cl_2	0.5-18	79-91	52
23	$AgBF_4$-$C_{17}H_{18}Br_2N_4Pd$	25	AcOH	24	20	62

portant uses. Biffis et al. reported the $AgBF_4$-NHC carbene complexes induced the reaction between indoles and ethyl phenylpropiolate to produce diaddition product.[62] A new and efficient method for the synthesis of bisindolylmethanes, presented herein, represents a further use for silver tetrafluoroborate (Scheme I).

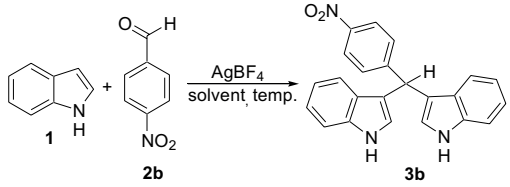
Scheme I $AgBF_4$ catalyzed synthesis of bisindolylmethanes



2. RESULTS AND DISCUSSION

The optimal conditions for synthesizing bisindolylmethane using *p*-nitrobenzaldehyde (**3b**) and indole in the presence of $AgBF_4$ (10%) in acetonitrile resulted in a poor yield (45%), but synthesis in methylene chloride gave a 98% yield at room temperature. (Table 2, entry 1-2). The optimal amount of catalyst for the reaction is 10 mol%, which is associated with clean and efficient conversion to bisindolylmenthane within 10 h (Table 2, entry 2-4). Temperature is a critical factor in the efficiency of the reaction, and at reflux temperature, the reaction proceed to completion within a short time (3 h) (Table 2, entry 4-5).

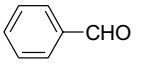
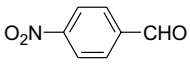
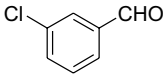
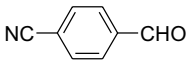
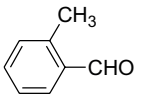
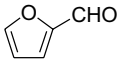
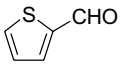
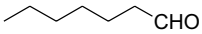
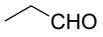
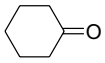
Table 2. Optimal conditions in the synthesis of **3b**



Entry	Solvent	Time (h)	Catalyst (mol%)	Temp (°C)	Yield (%)
1	CH_3CN	8	20	rt	45
2	CH_2Cl_2	8	20	rt	98
3	CH_2Cl_2	10	10	rt	96
4	CH_2Cl_2	20	5	rt	73
5	CH_2Cl_2	3	10	reflux	96

The scope of application of the presented method is demonstrated by using the various substituted aromatic, heteroaromatic and aliphatic carbonyl compounds to react with indole. The results that are summarized in Table 3

Table 3. $AgBF_4$ catatlyzed synthesis of bisindolylmethanes using various substituted aldehydes and ketones with indole

Entry	Substrate		Product	Time (h)	Yield (%)
1		**2a**	**3a**	1.5	94
2		**2b**	**3b**	2	96
3		**2c**	**3c**	1.5	97
4		**2d**	**3d**	3	95
5		**2e**	**3e**	2	94
6		**2f**	**3f**	4	92
7		**2g**	**3g**	4	84
8		**2h**	**3h**	4.5	93
9		**2i**	**3i**	4	96
10		**2j**	**3j**	5	83

clearly reveal the scope of the reaction using various substituted aldehydes and ketones to react with indole in the presence of $AgBF_4$ at room temperature. Heterocyclic aldehydes, such as furfural and 2-thiophenecarboxaldehyde, performed well in this reaction without the formation of any side products. The reaction conditions were mild enough to prevent damage to the methoxy or acid-sensitive moieties, such as furfural, which commonly undergoes cleavage under strongly acidic reaction conditions. The reaction of cyclohexanone with indole is more sluggish than that with aldehydes.

The following mechanism of to the silver tetrafluoroborate-catalyzed synthesis of bisindolylmenthane is proposed. First, an aldehyde or ketone was activated by the silver tetrafluoroborate and underwent an elecotrophilic substitution reaction at the 3-position of the indole. After dehydration, intermediate **5** was formed and was further activated by silver tetrafluoroborate to become an electrophile, which was attacked by a second molecule of indole, to form bisindolylmenthane **3**.

The possible use of this reaction in synthesizing more complex systems was studied. For example, tetraindolyl compounds are formed by the condensation of Tröger's base **8** with four equivalents of indole under similar conditions in good yield. Initially, compound **7** was synthesized by the condensation of 4-bromoaniline with paraformaldehyde using TFA as solvent.[63] Lithium-halogen exchange of **7**, followed by quenching by *N*-formyl piperidine, furnished dialdehyde **8**. Further reaction of compound **8** with four equivalents of indole and 20 mol% of silver tetrafluoroborate under the aforementaioned conditions afforded **9** in good yield.

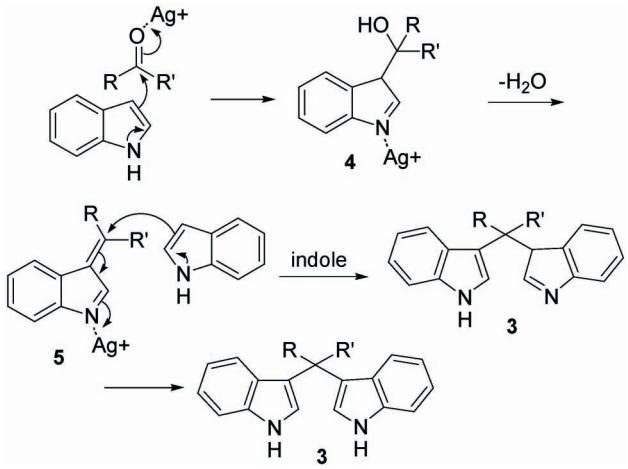
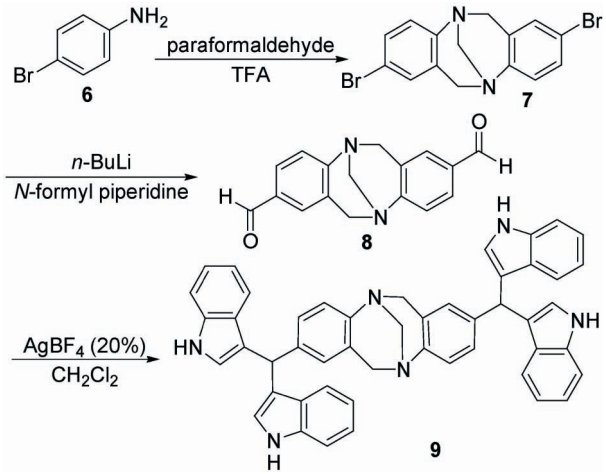


Fig. 1. Proposed mechanism for $AgBF_4$ catalyzed synthesis of bisindolylmethanes.

Scheme II $AgBF_4$ catalyzed synthesis of tetraindolylmethane Tröger's Base



3. CONCLUSIONS

In summary, the electrophilic substitution reactions of indole with aromatic, heteroaromatic and aliphatic carbonyl compounds were successfully carried out in the pres-

ence of a catalytic amount of $AgBF_4$ in dichloromethane at reflux temperature. This method offers several significant advantages over common methods, such as high conversion rates, ease of handling, and clean reaction profiles, which make it attractive for the rapid synthesis of substituted bisindolylmethanes. The presented approach was proved to be suitable for the synthesis of complex systems, such as tetraindolylmethane Tröger's Base.

4. EXPERIMENTAL

4.1. General Chemical Procedures

All reactions were carried out in anhydrous solvents. Tetrhydrofuran and diethyl ether were distilled from sodium-benzophenone under argon. Toluene, acetonitrile, dichloromethane, and hexane were distilled from calcium hydride. ^{1}H NMR spectra were acquired at 400 (indicated in each case), and ^{13}C NMR were acquired at 100.6 MHz on a Bruker NMR spectrometer. Chemical shifts (δ) are reported in ppm relative to $CDCl_3$ (7.26 and 77.0 ppm). Mass spectra (MS) were determined on a Micromass Platform II mass spectrometer at a 70 eV. High resolution mass spectra (HRMS) were determined on a Finnigan/Thermo Quest MAT 95XL mass spectrometer. Infrared spectra were recorded on a JASCO FT/IR 410 spectrometer. Flash column chromatography was performed using MN silica gel 60 (70-230 mesh) purchased from Macherey-Nagel.

4.2. General Procedure

To a solution of aldehyde (1 eq.) in dichloromethane (5 mL), indole (2 eq.) and then catalytic $AgBF_4$ (10 mol%) were added at room temperature. After the reaction mixture was refluxed for the specified time (Table 1), it was diluted with water and the aqueous solution was extracted with ethyl acetate. The combined organic layers were washed with water (10 mL) and brine (10 mL), and then dried over anhydrous $MgSO_4$, before been evaporated *in vacuo* to give a crude product, which was purified by column chromatography (silica gel, 5-20% EtOAc in hexane).

3,3′-(Phenylmethylene)bis(1*H*-indole) (3[a])

M.p. 88–90 °C ; IR (KBr): 3412, 1739, 1454, 1363, 1215, 1091 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (bs, 2H), 7.23 (m, 11H), 7.03 (m, 2H), 6.58 (m, 2H), 5.91 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 144.0, 136.6, 128.7, 128.5, 128.2, 127.1, 126.1, 123.7, 121.9, 119.9, 119.6, 119.2, 111.1, 40.2. MS-EI (*m/z*): 322 (M^+, 100), 245 (51), 243 (15), 204 (27). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{23}H_{18}N_2$, 322.1470; found 322.1475.

3.3′-((4-Nitrophenyl)methylene)bis(1*H*-indoel) (3b)

M.p. 220–222 °C; IR (KBr): $\bar{\nu}$ = 3417, 1739, 1654, 1454, 1366, 1215, 1111 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (m, 2H), 8.01 (bs, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.20 (m, 2H), 7.03 (m, 2H), 6.68 (t, *J* = 1.6 Hz, 2H), 5.99 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 151.8, 146.5, 136.6, 129.5, 126.6, 123.6, 122.3, 119.6, 119.5, 118.1, 111.2, 40.2. MS-EI (*m/z*): 367 (M^+, 86), 245 (59), 204 (60), 176 (24), 117 (100), 89 (82). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{23}H_{17}N_3O_2$, 367.1321; found 367.1310.

3,3′-((3-Chlorophenyl)methylene)bis(1*H*-indole) (3c)

M.p. 151–153 °C; IR (KBr): 3406, 1739, 1654, 1454, 1366, 1215, 1091, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (bs, 2H), 7.41 (d, *J* = 7.9 Hz, 2H), 7.34 (t, *J* = 9.6 Hz, 3H), 7.22 (m, 5H), 7.06 (t, *J* = 7.4 Hz, 3H), 6.56 (d, *J* = 1.4 Hz, 2H), 5.88 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 146.2, 136.6, 134.0, 129.5, 128.8, 127.0, 126.9, 123.7, 122.1, 119.8, 119.4, 118.8, 111.2, 39.9. MS-EI (*m/z*): 356 (M^+, 100), 245 (76), 240 (13), 243 (18), 204 (16), 122 (12). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{23}H_{17}ClN_2$, 356.1080; found 356.1076.

4-(Di(1*H*-indol-3-yl)methyl)benzonitrile (3d)

M.p. 212–214 °C; IR (KBr): 3406, 2225, 1736, 1651, 1363, 1215, 1091, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05 (bs, 2H), 7.54 (d, *J* = 6.4 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 7.34 (m, 4H), 7,20 (m, 2H), 7.02 (m, 2H), 6.63 (t, *J* = 1.6 Hz, 2H), 5.93 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 149.8, 136.7, 132.1, 129.5, 126.7, 123.7, 122.2, 119.5, 119.5, 119.2, 118.1, 111.3, 109.9, 40.3. MS-EI (*m/z*): 347 (M^+, 100), 245 (63), 229 (24), 122 (12). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{24}H_{17}N_3$, 347.1422; found 347.1414.

3,3′-(*o*-Tolylmethylene)bis(1*H*-indole) (3e)

IR (KBr): 3412, 1739, 1454, 1352, 1215, 1091, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (bs, 2H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.23 (m, 4H), 7.14 (d, *J* = 6.5 Hz, 1H), 7.08 (m, 3H), 6.46 (d, *J* = 2.1 Hz, 2H), 6.08 (s, 1H), 2.44 (s, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 142.2, 136.7, 136.1, 130.3, 128.4, 127.2, 126.2, 125.9, 124.0, 121.9, 119.8, 119.2, 119.0, 111.2, 36.2, 19.6. MS-EI (*m/z*): 336 (M^+, 100), 245 (41), 243 (14), 218 (56), 217 (21). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{24}H_{20}N_2$, 336.1626; found 336.1632.

3,3′-(Furan-2-ylmethylene)bis(1*H*-indole) (3f)

M.p. 325–326 °C; IR (KBr): 3406, 1736, 1454, 1363, 1215, 1006, 781, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ

= 7.77 (bs, 2H), 7.52 (d, *J* = 7.9 Hz, 2H), 7.37 (s, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 7.20 (t, *J* = 7.0 Hz, 2H), 7.08 (t, *J* = 7.2 Hz, 2H), 6.74 (d, *J* = 0.8 Hz, 2H), 6.33 (s, 1H), 6.08 (d, *J* = 2.5 Hz, 1H), 5.96 (s, 1H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 157.1, 141.3, 136.5, 126.7, 123.2, 121.9, 119.7, 119.3, 117.0, 111.2, 110.2, 106.7, 34.1. MS-EI (*m/z*): 312 (M^+, 28), 167 (32), 141 (22), 117 (100), 89 (77), 63 (36). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{21}H_{16}N_2O$, 312.1263; found 312.1256.

3,3′-(Thiophen-2-ylmethylene)bis(1*H*-indole) (3g)

M.p. 185–187 °C; IR (KBr): 3412, 1739, 1651, 1366, 1215, 1091, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (bs, 2H), 7.48 (d, *J* = 7.9 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 148.7, 136.5, 126.7, 126.5, 125.1, 123.6, 123.2, 122.0, 119.7, 119.6, 119.3, 111.2, 35.3. MS-EI (*m/z*): 328 (M^+, 74), 243 (35), 210 (84), 184 (25), 139 (22), 89 (100). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{21}H_{16}N_2S$, 328.1034; found 328.1025.

3,3′-(Heptane-1,1-diyl)bis(1*H*-indole) (3h)

M.p. 65–66 °C; IR (KBr): 3406, 2923, 2351, 1739, 1651, 1456, 1366, 1215, 1091, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (bs, 1H), 7.65 (d, *J* = 7.9 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 7.19 (m, 2H), 7.09 (m, 2H), 6.93 (d, *J* = 2.2 Hz, 2H), 4.50 (t, *J* = 7.4 Hz, 1H), 2.25 (m, 2H), 1.43 (m, 4H), 1.30 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 136.5, 127.2, 121.7, 121.5, 120.5, 119.7, 119.0, 111.1, 35.9, 34.0, 31.9, 29.5, 28.3, 22.8, 14.2. MS-EI (*m/z*): 330 (M^+, 10), 245 (100), 217 (12), 130 (21). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{23}H_{26}N_2$, 330.2096; found 330.2086.

3,3′-(Propane-1,1-diyl)bis(1*H*-indole) (3i)

M.p. 128–129 °C; IR (KBr): 3406, 2923, 1739, 1651, 1454, 1366, 1215, 1091, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86 (bs, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.16 (m, 2H), 7.05 (m, 2H), 6.96 (d, *J* = 2.2 Hz, 2H), 4.39 (t, *J* = 7.4 Hz, 1H), 2.26 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 136.5, 127.2, 121.7, 121.5, 120.3, 119.7, 118.9, 111.1, 35.9, 28.7, 13.1. MS-EI (*m/z*): 274 (M^+, 20), 245 (100), 144 (15), 89 (11), 57 (20). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{19}H_{18}N_2$, 274.1470; found 274.1466.

3,3′-(Cyclohexane-1,1-diyl)bis(1*H*-indole) (3j)

M.p. 119–120 °C; IR (KBr): 3406, 2928, 1739, 1454, 1363, 1212, 1102, 738 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (bs, 2H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.10 (t, *J* = 7.4 Hz, 2H), 7.04 (d, *J* = 2.2 Hz, 2H), 6.95 (t, *J* = 7.5 Hz, 2H), 2.58 (t, *J* = 4.6 Hz, 4H), 1.66 (m, 6H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 137.0, 126.3, 123.6, 122.1, 121.5, 121.2, 118.5, 111.1, 39.6, 36.8, 26.8, 23.0. MS-EI (*m/z*): 314 (M^+, 93), 271 (100), 257 (17), 243 (10), 130 (31). HRMS-EI (*m/z*): $[M]^+$ calcd. for $C_{22}H_{22}N_2$, 314.1783; found 314.1775.

4.3. Synthesis of Tröger base (9)

2,8-Dibromo-6*H*,12*H*-5,11-methano-dibenzo[*b*,*f*][1,5]-diazocine (7)

p-Bromoaniline (0.50 g, 2.90 mmol) and then para-formaldehyde (0.17 g) were added in portions to CF_3COOH (30 mL) under vigorous stirring at –15 °C. The resulting mixture was allowed to reach r.t. and stirred for 18 h. Then, 2 M NaOH was added to the reaction mixture untill it became basic. Extraction with dichloromethane, drying of the organic layer over anhydrous Na_2SO_4, and removal of the solvent in vacuo gave a crude product, which was purified using a silica gel column with 25% ethyl acetate in hexane to give product **7** (0.14 g, 0.37 mmol, 26%). IR (KBr): 3434, 2895, 1646, 1473, 1322, 1207, 1078, 825 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (m, 2H), 7.04 (d, *J* = 2.2 Hz, 2H), 7.00 (d, *J* = 8.6 Hz, 2H), 4.63 (d, *J* = 16.8 Hz, 2H), 4.24 (s, 2H), 4.09 (d, *J* = 16.8 Hz, 2H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 146.8, 130.6, 129.7, 129.6, 126.7, 116.7, 66.6, 58.3.

6*H*,12*H*-5,11-Mehano-dibenzo[*b*,*f*][1,5]diazocine-2,8-dicarbaldehyde (8)

A solution of **7** (1.00 g, 2.63 mmol) in dry THF (35 mL) was cooled to –78 ºC and n-BuLi (6.57 mL, 6.57 mmol, 2.5 eq., 1 M in hexane) was added to under inert atmosphere. Stirring was continued for 15 min, and then N-formyl piperidine (0.73 mL, 6.57 mmol, 2.5 eq.) was added at the same temperature. This reaction mixture was stirred for 2 h then temperature was brought to r.t. and stirred for additional 4 h. Reaction was quenched by adding water (30 mL) to it, extracted by ethyl acetate, dried over anhydrous $MgSO_4$ and concentrated. Further purification was subjected to a silica gel column chromatography using 20% ethyl acetate in hexane as mobile phase to give product **8** (0.21 g, 0.78 mmol, 30%). IR (KBr): 3434, 1684, 1602, 1563, 1327, 1204, 963, 836 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.83 (s, 2H), 7.68 (m, 2H), 7.47 (d, *J* = 1.3 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 4.80 (d, *J* = 16.9 Hz, 2H), 4.30 (d, *J* = 16.0 Hz, 4H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 191.0, 153.9, 132.5, 129.1, 129.0, 128.1, 125.6, 66.5, 58.6.

2,8-Bis-[bis-(1*H*-indol-3-yl)-methyl]-6*H*,12*H*-5,11-methano-dibenzo[*b*,*f*][1,5]diazocine (9)

To a solution of aldehyde **8** (0.069 g. 0.24 mmol) and indole (0.12 mmol, 0.99 mmol) in dichloromethane (5 mL) was added $AgBF_4$ (0.0096 g, 20 mol %) at room temperature. After refluxing the reaction mixture for 8 h, the reaction solution was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with water (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a crude product which was purified by column chromatography (silica gel, 5-20% EtOAc in hexane) to furnish the product **9** (0.13 g, 0.19 mmol, 75%). IR (KBr): 3406, 2923, 1648, 1412, 1094, 743 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.74 (bs, 4H), 7.31 (m, 8H), 7.00 (m, 10H), 6.79 (m, 8H), 5.67 (s, 2H), 4.48 (d, J = 16.8 Hz, 2H), 4.12 (s, 2H), 3.99 (d, J = 16.7 Hz, 2H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 146.3, 140.4, 136.9, 127.8, 127.2, 127.0, 127.0, 126.6, 124.9, 123.9, 123.8, 121.2, 119.4, 118.7. 118.5, 118.5, 111.8, 67.4, 66.6, 58.3, 56.5, 25.5, 19.0. MS-FAB (*m/z*): 710 (M^+, 1.4), 360 (1.4), 307 (23), 289 (18), 154 (100), 136 (88); HRMS-FAB (*m/z*): $[M]^+$ calcd. for $C_{49}H_{38}N_6$, 710.3158; found 710.3144.

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