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Silica Gel-Mediated Friedel–Crafts Alkylation of 3-Indolylmethanols with Indoles: Synthesis of Unsymmetrical 3,3′-Bis-indolylmethanes

Yongzhen Zou,[a] Cuili Chen,[a] Xianxiao Chen,[a] Xiaoxiang Zhang,*[a] and Weidong Rao*[a]

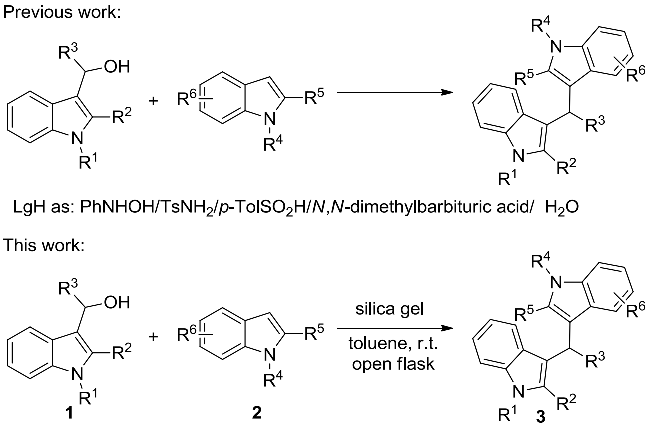
Abstract: An efficient and expedient approach for the synthesis of unsymmetrical 3,3′-Bis-indolylmethanes *via* silica gel-mediated Friedel–Crafts alkylation of 3-indolylmethanols with diverse indoles is described. The synthetic utility of this transformation was demonstrated by reusing silica gel up to 10 times without apparent loss of reactivity.

Introduction

The indole scaffold is an important and versatile structural motif that is frequently encountered in numerous biologically active natural products, pharmaceuticals as well as functional materials.[1-7] Among these indole derivatives, 3,3′-bis-indolylalkanes are important class of bioactive metabolite of terrestrial marine origin and ubiquitously found in many natural products.[2] Therefore, the development of efficient construction of 3,3′-bis-indolylalkanes has been actively pursued.[3-7, 12-13] As an example, a majority of studies show that symmetrical 3,3′-bis-indolylalkanes can readily be synthesized by condensation reactions of carbonyl compounds with indoles in the presence of Lewis or Brønsted acids.[3] Although significant effort has been made towards the synthesis of symmetrical 3,3′-bis-indolylalkanes, the synthesis of unsymmetrical 3,3′-bis-indolylalkanes is sparse and remains challenging. For this reason, the development of new and efficient methods for the preparation of unsymmetrical 3,3′-bis-indolylalkanes has and continues to receive significant synthetic interest.[4-7,13-14] In this respect, Vallee disclosed the first example of synthesizing unsymmetrical 3,3’-bisindolylmethanes with benzylhydroxylamine as the leaving group (Scheme 1).[4] Following this seminal work, there has only been a small handful of studies of demonstrating the preparation of unsymmetrical 3,3′-bis-indolylalkanes. Bhuyan and co-workers reported unsymmetrical 3,3’-bis-indolylmethanes could be synthesized under the catalyst-free conditions. However, under such conditions, *N*,*N*-dimethylbarbituric acid was inevitably formed as the by-product (Scheme 1, Lg = *N*,*N*-dimethylbarbituric acid).[5] Other similar examples were reported by You[6] and Petrini[7] that the preparation of unsymmetrical 3,3’-bis-indolylmethanes were achieved through the Friedel–Crafts alkylation of 3-indolylbenzylamines and 3-indolylarylsulfones with indoles in the presence of Brønsted acid. In these examples, tosylamide and *p*-toluenesulfinic acid were generated as the by-product, respectively (Scheme 1, Lg = NHTs, *p*-TolSO$_2$H).

Recently, Lewis and Brønsted acid-catalyzed reactions of alcohols as pro-electrophiles have emerged as efficient and expedient synthetic strategies for C-C and C-X bond formation.[8-13] Among them, Friedel–Crafts alkylation reactions that make use of alcohol pro-electrophiles with indoles continues to be actively pursued. [11-13] For example, Ji and co-workers[12] who reported an efficient synthetic protocol for the preparation of unsymmetrical 3,3’-bisindolylmethanes from 3-indolylmethanols with indoles using CAN as catalyst under ultrasonic irradiation(Scheme 1, Lg = OH). More recently, Xiao demonstrated that Ji’s reported transformation could be achieved in fluorinated alcohol[13b] or water[13a] under catalyst-free conditions. Although the advences of those reported methodologies, many of them were suffered from the formation of large amounts of by-product or harsh conditions. Hence, developing synthetic approaches to prepare this class of unsymmetrical 3,3’-bis-indolylmethanes that make use of readily available precursors, mild reaction conditions, simple operation and environmentally friendly catalysts are desirable. To the best of our knowledge, synthesis of unsymmetrical 3,3’-bis-indolylmethanes using a recyclable catalyst *via* Friedel–Crafts alkylation under mild conditions is not known.

Silica gel has proven versatile in mediating a wide variety of organic transformations to various synthetically valuable products[14-16]. The use of silica gel in mediating organic transformations is advantageous because silica gel is readily available, inexpensive, non-toxic and can be reused. The use of silica gel as a promoter features an environmentally benign, operational simplicity and highly desirable process. Herein, we disclose the details of silica gel-mediated Friedel–Crafts alkylation of 3-indolylmethanols with indoles, which leads to an efficient and environmentally benign manner for the preparation of unsymmetrical 3,3’-bis-indolylalkane derivatives (Scheme 1).



Scheme 1. General strategies for the synthesis of unsymmetrical 3,3’-bis-indolylalkanes

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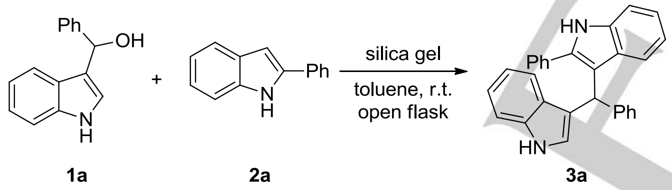
Results and Discussion

Initially, we chose to examine Friedel–Crafts alkylation of (1*H*-indol-3-yl)(phenyl)methanol **1a** with 2-phenyl-1*H*-indole **2a** as the model substrates to establish the reaction conditions (Table 1). This revealed that treating **1a** (0.2 mmol) with the **2a** (0.22 mmol) with silica gel (1 gram, source: Sigma-Aldrich, particle size: 230-400 Mesh) in toluene under ambient conditions at room temperature for 2 h gave **3a** in 99% yield (entry 1). Encouraged by this preliminary result, we next examined the silica gel with varying particle size from different suppliers. To our delight, the same yield of 99% was found on repeating the reaction with silica gel from different suppliers (source: Jiangyou silicone, particle size: 200-300 Mesh) (entry 2). In our hands, similar product yields of 94-97% along with increased reaction times were observed on changing the solvent from toluene to CH_2Cl_2, MeCN, EA-PE (v:v=1:20) (entries 3, 5-6). Longer reaction time of 9 hours and markedly lower product yield of 64% were observed when the reaction was repeated in ethanol (entry 7). However, switching the solvent to THF was found to result in no reaction observed on the basis of TLC and 1H NMR analysis (entry 4). On the contrary, further studies showed that excellent product yield of 99% was achieved even in the presence of reduced amount of silica gel (240 mg and 60 mg, entry 8, 9 respectively). Control experiment in the absence of silica gel was carried out for 24h and both starting materials were recovered in near quantitative yields, evidencing that acidic silica gel is the active species(entry 10).

Table 1. Optimization of the reaction conditions[a]

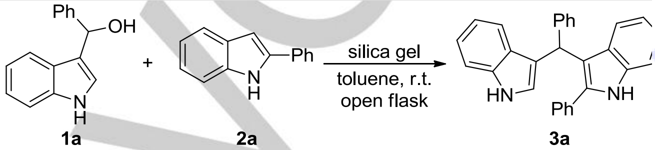


Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	silica gel I (1 g) [c]	Toluene	2	99
2	silica gel II (1g) [d]	Toluene	2	99
3	silica gel I (1 g)	CH_2Cl_2	6	97
4	silica gel I (1 g)	THF	24	N.R.
5	silica gel I (1 g)	EA-PE(1:20)	8	96
6	silica gel I (1 g)	CH_3CN	16	94
7	silica gel I (1 g)	EtOH	9	64
8	silica gel I (240 mg)	Toluene	2	99
9	silica gel I (60 mg)	**Toluene**	**2**	**99**
10	none	Toluene	24	N.R.

[a] Unless stated otherwise, all reactions were performed with 0.2 mmol of **1a** and 0.22 mmol **2a** in solvent (4 mL) at room temperature. [b] Isolated yield. [c] Supplied by Sigma-Aldrich (230-400 mesh). [d] Supplied by Jiangyou silicone Co., Ltd., Yantai, Shangdong province (200-300 mesh).

To examined the recyclability of silica gel in Friedel–Crafts alkylation of **1a** with **2a**, the reactions were carried out on 0.2 mmol scale with silica gel 1 gram as the promoter. The used silica gel was recovered by simple filtration, washed with ethyl acetate and dried under vacumm. To our delight, the silica gel could be reused at least nine times in the reactions. It is observed that all the reactions proceeded smoothly to afford **3a** in excellent yield under the same above-mentioned conditions without any apparent loss of reactivity (Table 2).

Table 2. Recyclable silica gel for Friedel–Crafts alkylation of **1a** with 2-phenylindole **2a**[a]



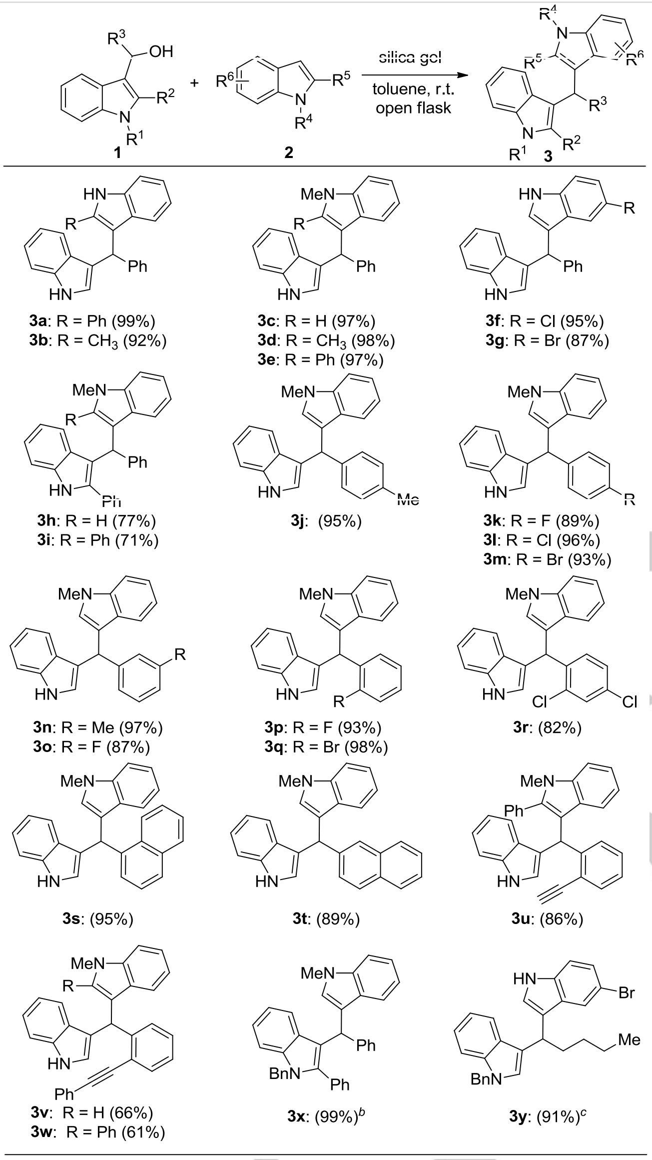
Run	1	2	3	4	5	6	7	8	9	10
Yield(%)[b]	99	97	94	96	96	98	95	92	95	93

[a] All reactions were performed with 0.2 mmol of **1a** and 0.22 mmol **2a** in toluene (4 mL) at room temperature with silica gel (1gram, source: Sigma-Aldrich, particle size: 230-400 Mesh). [b] Isolated yield.

To define the scope of the present procedure, we next sought to assess its generality for a series of sterically and electronically 3-indolylmethanols **1** with indoles **2** (Table 3). Overall, the reaction conditions were found to be general and a diverse set of unsymmetrical 3,3'-bisindolylmethanes **3a-y** containing a variety of substitution patterns were afforded in good to excellent yields (61–99%). Reactions of (1*H*-indol-3-yl)(phenyl)methanol **1a** with C-2 substituted indoles or C-2 substituted *N*-methyl indoles gave unsymmetrical 3,3'-bis-indolylmethanes **3a-e** in excellent yield of 92-99%. Having pendant of electron-withdrawing groups at C-5 position of indoles furnished the adduct **3f-g** in 87-95% yield. When 2-phenyl-3-indolylmethanol **1b** was used to react with both *N*-methylindole and 2-phenylindole under the optimized reaction conditions, the reactions were found to proceed efficiently to afford **3h-3i** in good yield (71-77%). The present procedure was also shown to proceed well for 3-indolylmethanols which containing a variety of substituents of different electronic properties on the aryl group with *N*-methylindole giving **3j-3r** in 82-98% yield. Similarly, the Friedel–Crafts alkylation of 3-indolylmethanol containing 1-naphthyl or 2-naphthyl group were also shown to be well-tolerated and furnished **3s** and **3t** in 95% and 89% yield, respectively. Notably, slightly lower yields of 3,3'-bis-indolylmethanes **3v-w** were obtained for the reactions of 3-indolylmethanols which contain phenylacetylene moiety on the aryl group. In contrast, the presence of acetylene instead of phenylacetylene as the substituent on the aryl group of 3-indolylmethanols furnished **3u** in good yield of 86%. The tolerance of an acetylene moiety under the reactions conditions provides potential for further functional groups transformations.

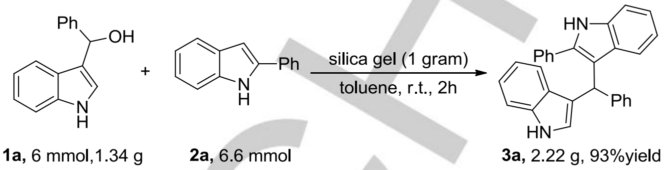
Interestingly, under the heating conditions, reaction of *N*-benzyl-3-indolylmethanol with *N*-methylindole was also found to be effective, giving **3x** in nearly quantitatively yield. Additionally, substrate with a alkyl moiety such as 1-(1-benzyl-1H-indol-3-yl)pentan-1-ol, was found to proceed well and provide **3y** in 91% yield.

Table 3. Friedel–Crafts alkylation of 3-indolylmethanols with diverse indoles mediated by silica gel[a]



[a] Unless stated otherwise, all reactions were performed with 0.2 mmol of **1** (0.2 mmol) and **2** (0.22 mmol) in toluene (4 mL) at room temperature with silica gel (60 mg, source: Sigma-Aldrich, particle size: 230-400 Mesh) for 2 h. Values in parenthesis denote isolated product yields [b] The reaction was carried out at 80 °C for 2h. [c] The reaction was carried out with 1-(1-benzyl-1H-indol-3-yl)pentan-1-ol (0.24 mmol) and 5-bromo-indole (0.2 mmol) in toluene (4 mL) at room temperature for 15 h.

Under the established conditions, we were pleased to find that this transformation could be readily scaled up. Reaction starting with (1*H*-indol-3-yl)(phenyl)methanol **1a** (6 mmol, 1.34g) and 2-phenyl-1*H*-indole **2a** (6.6 mmol) in toluene with reduced amount of silica gel (1 gram) under the conditions as described in Scheme 2 was successfully scaled, affording **3a** in excellent yield (93%).



Scheme 2. Gram-scale Friedel–Crafts alkylation of **1a** with 2-pehenylindole **2a** mediated by silica gel.

Conclusions

In summary, we have demonstrated an efficient and expedient approach for the synthesis of unsymmetrical 3,3'-bis-indolylmethanes *via* silica gel-mediated Friedel–Crafts alkylation of 3-indolylmethanols with indoles. The transformation exhibits good tolerance for structurally diverse set of 3-indolymethanols and indoles. Moreover, the operationally simplicity and mild reaction conditions of this protocol would provide potential for scale-up strategy for the preparation of unsymmetrical 3,3'-bis-indolylmethanes, which was demonstrated by gram-scale synthesis of one example in excellent yield. Added to this, the synthetic utility of this transformation was demonstrated by reusing silica gel for nine further consecutive transformations without any apparent decrease of reactivity. Further studies on the synthetic applications of the present methodology are currently underway in our laboratory.

Experimental Section

General Materials and Methods

Unless specified, all reagents and solvents were purchased from commercial sources and used as received. Analytical thin layer chromatography (TLC) was performed using Merck 60 F254 pre-coated silica gel plate. The products were purified by flash column chromatography on silica gel (200–300 mesh) eluted with a gradient of petroleum ether and ethyl acetate. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AVQ-400 spectrometer. Chemical shifts (ppm) were recorded in $CDCl_3$ with tetramethylsilane (TMS) as the internal reference standard. Multiplicities are given as: s (singlet), brs (broad singlet), d (doublet), t (triplet), dd (doublet of doublets), td (triplet of doublets), dt (doublet of triplet) or m (multiplets). The number of protons (*n*) for a given resonance is indicated by *n*H and coupling constants are reported as a *J* value in Hz. Infrared spectra were recorded on NICOLET 6700 FTIR Spectrometer. High resolution mass spectra (HRMS) were obtained using LTQ Orbitrap and reported in units of mass to charge (m/z).

General procedure for silica gel-mediated Friedel–Crafts alkylation of 3-Indolylmethanols with Indoles: To a solution of 3-indolylmethanols **1** (0.2 mmol), indoles **2** (0.22 mmol) in toluene (4 mL) was added silica gel (60 mg). The mixture was stirred at room temperature and monitored by TLC analysis. Upon completion, the reaction mixture was filtered and washed with ethyl acetate, the solvent was removed under reduced pressure and purified by flash chromatography on silica gel (eluent:

petroleum ether: ethyl acetate = 30:1 to 10:1) to give the desired product **3**.

3-((1H-indol-3-yl)(phenyl)methyl)-2-phenyl-1H-indole (3a)[13]: White solid (77 mg, 97% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.84 (s, 1H), 7.68 (s, 1H), 7.49-7.47 (m, 2H), 7.41-7.17 (m, 14H), 7.03 (td, J = 7.9, 0.9 Hz, 1H), 6.96 (td, J = 7.8, 1.1 Hz, 1H), 6.70 (dd, J = 2.3, 0.9 Hz, 1H), 6.07 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.0, 136.5, 136.3, 135.0, 133.0, 128.9, 128.8, 128.6, 128.0, 127.9, 127.4, 125.9, 124.2, 121.9, 121.5, 119.9, 119.5, 119.3, 119.0, 115.6, 111.1, 110.9, 39.3.

3-((1H-indol-3-yl)(phenyl)methyl)-2-methyl-1H-indole (3b)[6b]: White solid (62 mg, 92% yield); ^{1}H NMR (400 MHz, CDCl$_3$) δ = 7.88 (s, 1H), 7.73 (s, 1H), 7.38-7.18 (m, 10H), 7.09 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.68 (s, 1H), 5.95 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.0, 136.7, 135.2, 131.5, 128.8, 128.6, 128.1, 127.5, 125.9, 123.7, 121.9, 120.7, 119.9, 119.4, 119.3, 119.0, 114.0, 111.0, 110.0, 39.4, 12.3.

3-((1H-indol-3-yl)(phenyl)methyl)-1-methyl-1H-indole (3c) [6b,13]: White solid (65 mg, 97% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.85 (s, 1H), 7.46 (dd, J = 7.9, 2.8 Hz, 2H), 7.44-7.40 (m, 2H), 7.37-7.33 (m, 4H), 7.30-7.21 (m, 3H), 7.07 (tdd, J = 7.0, 2.3, 1.0 Hz, 2H), 6.67 (dd, J = 2.3, 0.8 Hz, 1H), 6.57 (d, J = 0.6 Hz, 1H), 5.96 (s, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.3, 137.5, 136.7, 128.8, 128.3, 128.3, 127.5, 127.1, 126.1, 123.7, 121.9, 121.5, 120.1, 120.0, 119.8, 119.2, 118.7, 118.2, 111.1, 109.2, 40.2, 32.7.

3-((1H-indol-3-yl)(phenyl)methyl)-1,2-dimethyl-1H-indole (3d)[13a]: White solid (69 mg, 98% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.86 (s, 1H), 7.40-7.13 (m, 11H), 7.03 (t, J = 7.6 Hz, 1H), 6.94 (t, J = 7.4 Hz, 1H), 6.69 (s, 1H), 6.00 (s, 1H), 3.70 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.3, 136.8, 136.7, 133.3, 128.8, 128.1, 127.6, 127.5, 125.8, 123.8, 121.9, 120.3, 119.9, 119.5, 119.3, 119.2, 118.6, 113.4, 111.0, 108.5, 39.7, 29.5, 10.7.

3-((1H-indol-3-yl)(phenyl)methyl)-1-methyl-2-phenyl-1H-indole (3e)[13a]: White solid (80 mg, 97% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.88 (s, 1H), 7.45-7.14 (m, 16H), 6.98-6.94 (m, 2H), 6.85 (s, 1H), 5.79 (s, 1H), 3.66 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.4, 138.1, 137.6, 136.5, 132.0, 130.8, 128.7, 128.4, 128.2, 128.0, 127.4, 127.2, 125.7, 123.9, 121.8, 121.3, 121.2, 120.0, 119.4, 119.1, 119.1, 115.5, 110.9, 109.3, 39.8, 31.0.

3-((1H-indol-3-yl)(phenyl)methyl)-5-chloro-1H-indole (3f): Colorless solid (68 mg, 95% yield); m.p. 139-141 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (s, 1H), 7.72 (s, 1H), 7.45-7.16 (m, 10H), 7.09-7.04 (m, 1H), 6.64-6.56 (m, 2H), 5.88 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 143.7, 136.8, 135.0, 128.7, 128.4, 128.2, 127.0, 126.4, 125.1, 125.0, 123.7, 122.3, 122.1, 119.9, 119.4, 119.3, 1193, 112.2, 111.3, 40.1; IR (KBr) v: 3423, 2930, 1631, 741 cm^{-1}; HRMS (ESI) calcd. for C$_{23}$H$_{18}$N$_2$Cl (M$^+$+H): 357.1159, found: 357.1164.

3-((1H-indol-3-yl)(phenyl)methyl)-5-bromo-1H-indole (3g)[6b]: White solid (70 mg, 87% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.78 (s, 1H), 7.75 (s, 1H), 7.60 (d, J = 1.4 Hz, 1H), 7.47-7.17 (m, 11H), 7.08 (t, J = 7.5 Hz, 1H), 6.59 (dd, J = 7.2, 1.9 Hz, 2H), 5.87 (s, 1H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 143.6, 136.8, 135.3, 128.8, 128.7, 128.4, 127.0, 126.4, 124.9, 124.9, 123.7, 122.3, 122.1, 119.9, 119.4, 119.4, 119.3, 112.7, 112.6, 111.2, 40.1.

1-methyl-3-(phenyl(2-phenyl-1H-indol-3-yl)methyl)-1H-indole (3h)[13]: White solid (64 mg, 77% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.08 (s, 1H), 7.56-7.54 (m, 2H), 7.46-7.33 (m, 8H), 7.28-7.17 (m, 6H), 7.04-7.00 (m, 1H), 6.98-6.93 (m, 1H), 6.77 (s, 1H), 6.11 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.2, 137.3, 136.3, 134.9, 133.0, 128.9, 128.8, 128.7, 128.5, 128.0, 127.9, 127.8, 125.8, 121.9, 121.5, 121.4, 120.0, 119.5, 118.8, 117.4, 115.8, 110.8, 109.1, 39.3, 32.7.

1-methyl-2-phenyl-3-(phenyl(2-phenyl-1H-indol-3-yl)methyl)-1H-indole (3i)[13]: White solid (69 mg, 71% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.90 (s, 1H), 7.42-7.21 (m, 12H), 7.17-7.12 (m, 6H), 7.00-6.94 (m, 4H), 6.89-6.85 (m, 1H), 6.04 (s, 1H), 3.52 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 145.0, 139.1, 137.2, 136.0, 135.2, 133.0, 132.0, 130.4, 129.3, 129.0, 128.3, 128.3, 128.2, 127.8, 127.7, 127.6, 127.4, 126.0, 121.9, 121.6, 121.4, 121.0, 119.4, 119.2, 115.7, 115.2, 110.6, 109.2, 40.2, 30.8.

3-((1H-indol-3-yl)(p-tolyl)methyl)-1-methyl-1H-indole (3j)[5,13]: White solid (67 mg, 71% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.79 (s, 1H), 7.48 (dd, J = 7.9, 3.7 Hz, 2H), 7.37-7.21 (m, 6H), 7.16 (d, J = 7.9 Hz, 2H), 7.10-7.05 (m, 2H), 6.68-6.67 (m, 1H), 6.58 (s, 1H), 5.93 (s, 1H), 3.70 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 141.3, 137.5, 136.7, 135.5, 129.0, 128.6, 128.3, 127.6, 127.2, 123.6, 121.9, 121.5, 120.1, 120.0, 119.2, 118.7, 118.4, 111.1, 109.2, 39.8, 32.7, 21.2.

3-((4-fluorophenyl)(1H-indol-3-yl)methyl)-1-methyl-1H-indole (3k): White solid (63 mg, 89% yield); m.p. 198-200 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.81 (s, 1H), 7.47 (dd, J = 7.9, 3.3 Hz, 2H), 7.40-7.36 (m, 4H) 7.32-7.25 (m, 2H), 7.16-7.02 (m, 4H), 6.65 (d, J = 1.6 Hz, 1H), 6.58 (s, 1H), 5.96 (s, 1H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 161.5(d, $J_{C\text{-}F}$ = 242.0 Hz, 1C), 140.0 (d, $J_{C\text{-}F}$ = 3.0 Hz, 1C), 137.5, 136.8, 130.2 (d, $J_{C\text{-}F}$ = 7.8 Hz, 1C), 128.3, 127.4, 127.0, 123.7, 122.1, 121.7, 120.1, 119.9 119.7, 119.4, 118.9, 118.1, 115.1(d, $J_{C\text{-}F}$ = 21.0 Hz, 1C), 111.2, 109.3, 39.5, 32.7; IR (KBr) v: 3379, 2933, 1603, 1217, 743 cm^{-1}; HRMS (ESI) calcd. for C$_{24}$H$_{20}$FN$_2$(M$^+$+H): 355.1611, found: 355.1623.

3-((4-chlorophenyl)(1H-indol-3-yl)methyl)-1-methyl-1H-indole (3l): White solid (71 mg, 96% yield); m.p. 214-216 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.83 (s, 1H), 7.44 (dd, J = 7.8, 3.7 Hz, 2H), 7.38-7.23 (m, 8H) 7.09 (td, J = 7.3, 3.4 Hz, 2H), 6.65 (s, 1H), 6.56 (s, 1H), 5.93 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 142.8, 137.5, 136.7, 131.8, 130.1, 128.4, 128.3, 127.3, 126.9, 123.7, 122.1, 121.7, 120.0, 119.9, 119.4, 119.3, 118.8, 117.6, 111.1, 109.3, 39.6, 32.7; IR (KBr) v: 3380, 2927, 1632, 743 cm^{-1}; HRMS (ESI) calcd. for C$_{24}$H$_{19}$N$_2$^{35}ClNa (M$^+$+Na): 393.1134, found: 393.1125.

3-((4-bromophenyl)(1H-indol-3-yl)methyl)-1-methyl-1H-indole (3m)[5] : White solid (77 mg, 93% yield); ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (s, 1H), 7.44-7.38 (m, 5H), 7.33 (d, J = 8.2 Hz, 1H), 7.29-7.20 (m, 4H), 7.07-7.02 (m, 2H), 6.68 (d, J = 1.6 Hz, 1H), 6.53 (s, 1H), 5.88 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 143.3, 137.5, 136.7, 131.3, 130.5, 128.3, 127.3, 126.9, 123.6, 122.1, 121.6, 119.9, 119.9, 119.9, 119.4, 119.3, 118.8, 117.5, 111.1, 109.2, 39.7, 32.7.

3-((1H-indol-3-yl)(m-tolyl)methyl)-1-methyl-1H-indole (3n): White solid (68 mg, 97% yield); m.p. 139-140 °C; ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.76 (s, 1H), 7.49 (dd, J = 7.9, 3.7 Hz, 2H), 7.37 (dd, J = 8.2, 3.6 Hz, 2H), 7.32-7.20 (m, 5H), 7.15-7.05 (m, 3H), 6.67 (dd, J = 2.2, 0.7 Hz, 1H), 6.59 (s, 1H), 5.94 (s, 1H), 3.70 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): δ = 144.3, 137.7, 137.5, 136.7, 129.5, 128.3, 128.2, 127.6, 127.2, 127.0, 125.8, 123.7, 121.9, 121.5, 120.1, 120.0, 119.9, 119.3, 118.7, 118.3, 111.1, 109.2, 40.2, 32.7, 21.6; IR (KBr) v: 3409, 2930, 1603, 741 cm^{-1}; HRMS (ESI) calcd. for C$_{25}$H$_{23}$N$_2$ (M$^+$+H): 351.1861, found: 351.1849.

3-((3-fluorophenyl)(1H-indol-3-yl)methyl)-1-methyl-1H-indole (3o): White solid (62 mg, 87% yield); m.p. 90-92 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (s, 1H), 7.45-7.43 (m, 2H), 7.37 (t, J = 8.2 Hz, 2H), 7.32-7.20 (m, 4H), 7.10-7.06 (m, 3H), 6.96 (t, J = 8.2 Hz, 1H), 6.69 (d, J = 1.0 Hz, 1H), 6.58 (s, 1H), 5.94 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0 (d, $J_{C\text{-}F}$ = 243.4 Hz, 1C), 147.1 (d, $J_{C\text{-}F}$ = 6.7 Hz, 1C), 137.5, 136.7, 129.7 (d, $J_{C\text{-}F}$ = 8.1 Hz, 1C), 128.3, 127.4, 127.0, 124.5 (d, $J_{C\text{-}F}$ = 2.4 Hz, 1C),, 123.6, 122.1, 121.6, 119.9, 119.8, 119.4, 119.2, 118.8, 117.5, 115.6 (d, $J_{C\text{-}F}$ = 21.4 Hz, 1C), 113.1 (d, $J_{C\text{-}F}$ = 21.1 Hz, 1C), 111.1, 109.2, 40.0, 32.7; IR (KBr) *v*: 3412, 2926, 1613, 742 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{20}N_2F$ $(M^+ +H)$: 355.1611, found: 355.1617.

3-((2-fluorophenyl)(1H-indol-3-yl)methyl)-1-methyl-1H-indole(3p): White solid (66 mg, 93% yield); m.p.187-189 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.89 (s, 1H), 7.45 (dd, J = 7.9, 4.4 Hz, 2H), 7.38 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.2 Hz, 1H), 7.28-7.20 (m, 4H), 7.14-7.02 (m, 4H), 6.73 (d, J = 1.6 Hz, 1H), 6.60 (s, 1H), 6.28 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7 (d, $J_{C\text{-}F}$ = 244.6 Hz, 1C), 137.5, 136.7, 131.1(d, $J_{C\text{-}F}$ = 14.0 Hz, 1C), 130.4 (d, $J_{C\text{-}F}$ = 4.1 Hz, 1C), 128.2, 127.8 (d, $J_{C\text{-}F}$ = 8.2 Hz, 1C), 127.3, 126.9, 123.9 (d, $J_{C\text{-}F}$ = 3.5 Hz, 1C), 123.6, 122.0, 121.6, 119.9, 119.8, 119.3, 118.8, 118.5, 116.7, 115.3 (d, $J_{C\text{-}F}$ = 22.1 Hz, 1C), 111.1, 109.2, 32.7, 32.5 (d, $J_{C\text{-}F}$ = 3.8 Hz, 1C); IR (KBr) *v*: 3417, 3052, 1483, 741 cm^{-1}; HRMS (ESI) calcd. for $C_{24}H_{20}N_2F$ $(M^+ +H)$: 355.1611, found: 355.1606.

3-((2-bromophenyl)(1H-indol-3-yl)methyl)-1-methyl-1H-indole (3q)[5,13]: White solid (81 mg, 98% yield); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90 (s, 1H), 7.65 (dd, J = 7.9, 1.2 Hz, 1H), 7.44 (t, J = 7.2 Hz, 2H), 7.38 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.28-7.16 (m, 4H), 7.12 (dd, J = 7.6, 1.7 Hz, 1H), 7.10-7.03 (m, 2H), 6.65 (d, J = 1.5 Hz, 1H), 6.51 (s, 1H), 6.35 (s, 1H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 136.5, 136.3, 135.1, 133.0, 128.9, 128.8, 128.6, 128.5, 128.1, 127.9, 127.4, 125.9, 124.3, 121.9, 121.5, 119.9, 119.4, 119.3, 118.9, 115.6, 111.2, 111.0, 39.3.

3-((2,4-dichlorophenyl)(1H-indol-3-yl)methyl)-1-methyl-1H-indole (3r)[13]: White solid (66 mg, 82% yield); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.46-7.34 (m, 4H), 729-7.20 (m, 4H), 7.21 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 8.4 Hz, 1H), 7.12-7.06 (m, 2H), 6.64 (dd, J = 2.3, 0.8 Hz, 1H), 6.53 (s, 1H), 6.33 (s, 1H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.3, 137.5, 136.7, 134.6, 132.4, 131.2, 129.3, 128.4, 127.3, 127.0, 126.9, 123.8, 122.2, 121.7, 119.9, 119.8, 119.5, 118.9, 118.0, 116.2, 111.2, 109.3, 36.3, 32.8.

3-((1H-indol-3-yl)(naphthalen-1-yl)methyl)-1-methyl-1H-indole (3s): White solid (73 mg, 95% yield); m.p. 227-229 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.34 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.90- 7.88 (m, 1H), 7.60-7.28 (m, 11H), 7.15 (t, J = 7.1 Hz, 2H), 6.83 (s, 1H), 6.53 (s, 1H), 6.51 (s, 1H), 3.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 137.5, 136.8, 134.0, 131.9, 129.0, 128.7, 127.5, 127.1, 127.0, 126.2, 125.9, 125.6, 125.3, 124.4, 124.4, 122.0, 121.5, 120.0, 119.9, 119.6, 119.3, 118.7, 117.7, 111.1, 109.2, 35.8, 32.7; IR (KBr) *v*: 3417, 3052, 1483, 741 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{23}N_2$ $(M^+ +H)$: 387.1861, found: 387.1874.

3-((1H-indol-3-yl)(naphthalen-2-yl)methyl)-1-methyl-1H-indole(3t): White solid (69 mg, 89% yield); m.p. 197-199 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.88 (m, 1H), 7.85-7.83 (m, 2H), 7.79-7.76 (m, 2H), 7.60 (dd, J = 8.5, 1.5 Hz, 1H), 7.52-7.47 (m, 4H), 7.37 (t, J = 7.3 Hz, 2H), 7.32-7.26 (m, 2H), 7.08 (t, J = 7.4 Hz, 2H), 6.66 (d, J = 1.6 Hz, 1H), 6.59 (s, 1H), 6.14 (s, 1H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.9, 137.5, 136.7, 133.7, 132.4, 128.5, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 126.8, 125.8, 125.4, 123.9, 122.0, 121.6, 120.2, 120.0, 119.6, 119.4, 118.8, 118.0, 111.1, 109.2, 40.4, 32.7; IR (KBr) *v*: 3406, 3052, 1459, 1332, 741 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{23}N_2$ $(M^+ +H)$: 387.1861, found: 387.1850.

3-((2-ethynylphenyl)(1H-indol-3-yl)methyl)-2-phenyl-1H-indole (3u): White solid (73 mg, 86% yield); m.p. 159-161 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 12.0 Hz, 1H), 7.73 (d, J = 14.4 Hz, 1H), 7.48-7.41 (m, 5H), 7.37-7.31 (m, 5H), 7.19-7.11 (m, 5H), 6.98-6.89 (m, 2H), 6.67-6.64 (m, 1H), 6.39 (s, 1H), 2.57 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =146.6, 136.8, 136.2, 135.6, 133.6, 133.1, 129.2, 128.8, 128.6, 128.4, 128.3, 127.7, 127.0, 126.0, 124.5, 122.2, 121.9, 121.7, 121.1, 120.0, 119.4, 119.2, 118.7, 114.1, 111.0, 110.9, 82.1, 81.6, 38.4; IR (KBr) *v*: 3412, 3055, 1456, 743 cm^{-1}; HRMS (ESI) calcd. for $C_{31}H_{22}N_2Na$ $(M^+ +Na)$: 445.1681, found: 445.1675.

3-((1H-indol-3-yl)(2-(phenylethynyl)phenyl)methyl)-1-methyl-1H-indole (3v): White solid (58 mg, 66% yield); m.p. 202-204 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H), 7.68-7.66 (m, 1H), 7.57-7.51 (m, 2H) 7.36-7.21 (m, 11H), 7.10-7.16 (m, 2H), 6.69-6.68 (m, 1H), 6.62-6.60 (m, 2H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.3, 137.5, 136.7, 132.3, 131.6, 128.7, 128.4, 128.4, 128.2, 128.1, 127.7, 127.3, 126.1, 123.7, 123.4, 122.8, 121.9, 121.5, 120.1, 120.0, 119.5, 119.3, 118.7, 117.6, 111.1, 109.1, 94.0, 88.4, 37.9, 32.7; IR (KBr) *v*: 3413, 3052, 1474, 738 cm^{-1}; HRMS (ESI) calcd. for $C_{32}H_{25}N_2$ $(M^+ + H)$: 437.2018, found: 437.2030.

3-((1H-indol-3-yl)(2-(phenylethynyl)phenyl)methyl)-1-methyl-2-phenyl-1H-indole (3w): White solid (65 mg, 63% yield); m.p. 189-191 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (s, 1H), 7.55 (dd, J = 7.5, 1.3 Hz 1H), 7.47 (t, J = 8.3 Hz, 2H), 7.37 (d, J = 8.2 Hz, 1H), 7.29-7.11 (m, 14H), 7.00-6.89 (m, 4H), 6.61 (s, 1H), 6.38 (s, 1H), 3.59 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 138.7, 137.4, 136.7, 132.4, 132.0, 131.5, 130.6, 129.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 125.9, 123.6, 123.5, 122.8, 121.7, 121.2, 120.6, 120.0, 119.7, 119.2, 119.1, 114.2, 110.8, 109.2, 93.6, 88.4, 38.6, 30.9; IR (KBr) *v*: 3410, 3054, 1463, 742 cm^{-1}; HRMS (ESI) calcd. for $C_{38}H_{29}N_2$ $(M^+ + H)$: 513.2331, found: 513.2338.

1-benzyl-3-((1-methyl-1H-indol-3-yl)(phenyl)methyl)-2-phenyl-1H-indole (3x): Pale-yellow solid (100 mg, 99% yield); m.p. 177-179 ^oC; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, J = 7.8 Hz, 1H), 7.38-7.10 (m, 18H), 6.99-6.95 (m, 4H), 6.72 (s, 1H), 5.82 (s, 1H), 5.29 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 138.7, 137.4, 136.7, 132.4, 132.0 131.5, 130.6, 129.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 125.9, 123.6, 123.5, 122.8, 121.7, 121.2, 120.6, 120.0, 119.7, 119.2, 119.1, 114.2, 110.8, 109.2, 93.6, 88.4, 38.6, 30.9; IR (KBr) *v*: 3409, 3052, 1463, 744 cm^{-1}; HRMS (ESI) calcd. for $C_{37}H_{31}N_2$ $(M^+ + H)$: 503.2482, found: 503.2488.

1-benzyl-3-(1-(5-bromo-1H-indol-3-yl)pentyl)-1H-indole (3y): Colorless oil (86 mg, 91% yield); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.91 (s, 1H), 7.73 (d, J = 1.6 Hz, 1H), 7.58 (d, J = 7.9 Hz, 1H), 7.36-7.01 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 137.0, 135.3, 128.9, 128.8, 127.7, 127.4, 126.5, 125.7, 124.6, 122.6, 122.3, 121.6, 120.3, 119.8, 119.1, 118.8, 112.5, 112.3, 109.7, 49.9, 35.3, 34.1, 30.5, 22.8, 14.1; IR (KBr) *v*: 3411, 3054, 1461 cm^{-1}; HRMS (ESI) calcd. for $C_{28}H_{28}{}^{79}BrN_2$ $(M^+ + H)$: 471.1430, found: 471.1441.

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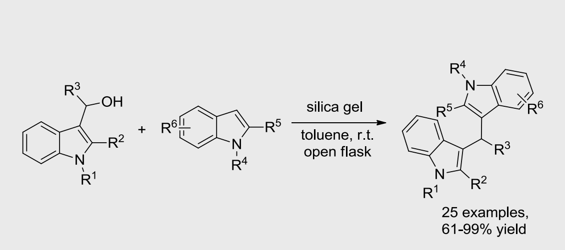

Bis-indolylmethanes **synthesis**

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Silica gel-mediated Friedel–Crafts alkylation of 3-indolylmethanols with indoles: synthesis of unsymmetrical 3,3′-bis-indolylmethanes

Unsymmetrical 3,3′-Bis-indolylmethanes can be synthesized from easily accessible 3-indolylmethanols and indoles mediated by silica gel under mild reaction conditions. The silica gel can be recovered and reused up to 10 times without apparent loss of its activity.