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SUPPORTING INFORMATION

Title: Iron–Palladium Association in the Preparation of Indoles and One-Pot Synthesis of Bis(indolyl)methanes
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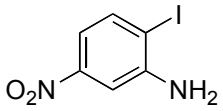
Ref. No.: O200700831

General Remarks: Reactions were carried out in round bottom flasks equiped with a magnetic stirring bar and capped with a septum. DCE and dioxane was distilled over CaH_2 and Na respectively. TLC analyses were performed on Merck silica gel 60 F_{254} TLC plates. FT-IR spectra were recorded with a Perkin Elmer Spectrum BX spectrometer and 1H and 13C spectra were recorded with Bruker 200, Avance-300 and 500 spectrometers and referenced to $CDCl_3$ unless otherwise noted. Mass spectra were obtained from the mass spectrometry facilities operated by the Institut de Chimie des Substances Naturelles. 5-Chloro-2-iodoaniline,[1] 2-iodo-4-methylaniline,[2] 4-methyl-2-(phenylethynyl)aniline,[3] 5-methoxy-2-(phenylethynyl)aniline,[3] 2-ethynylaniline,[4] 2-((4-nitrophenyl)ethynyl)aniline,[5] 2-((4-methoxyphenyl)ethynyl)aniline[6] and (2-thienylthynyl)aniline[8] have been prepared according to previously reported literature.

Preparation of 2-iodo-5-nitroaniline

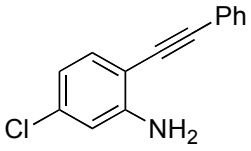


ICl (6.5 g, 40 mmol) in solution in acetic acid (20 mL) was added dropwise to a suspension of 3-nitroaniline (5 g, 36 mmol) in acetic acid (30 mL). The reaction mixture was heated at 80°C overnight. After cooling to 0°C, the reaction mixture was basified using 1M aqueous solution of sodium hydroxide and then extracted with EtOAc (3 times). The combined organic extracts were washed with brine, dried over $MgSO_4$. The resulting yellow solution was concentrated in vacuo and the residue purified by flash chromatography (silica gel, EtOAc/heptane 2/8) to provide 2-iodo-5-nitroaniline 5 (4.0 g, 42%) as a yellow solid: R_f 0.68 (CH_2Cl_2); mp 156°C (Lit.[7] 160°C); ^{1}H NMR ($CDCl_3$, 500 MHz) δ (*ppm*) : 4.46 (br s, 2H), 7.30 (dd, *J* = 2.5, 8.6 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*ppm*) : 91.2, 108.1, 113.8, 139.8, 147.8, 149.4; IR (neat) ν (cm^{-1}) 3426, 3309, 2359, 1739, 1615, 1504, 1469, 1330; MS (EI) *m/z* 264 ($[M]^+$, 24%), 91 (100%), 90 (49%).

General procedure for the Sonogashira couplings:[8]

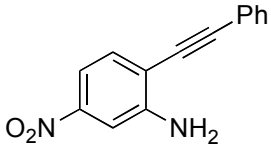
The aryl iodide (1 equiv.), CuI (5%) and $PdCl_2(PPh_3)_2$ (5%) were suspended in THF (5 mL/1 mmol of iodide) under argon. Et_3N (3 equiv.) and alkyne (1.3 equiv.) were successively added and the reaction mixture was stirred at rt for 2h. The reaction mixture was diluted with Et_2O, filtered through Celite and washed sequentially with water, NH_4Cl and NaCl. After evaporation of the solvents, the crude product was purified by column chromatography on silica gel.

5-chloro-2-(phenylethynyl)aniline



The reaction was carried out according to general procedure for Sonogashira coupling with 5-chloro-2-iodoaniline (254 mg, 1 mmol), phenylactylene (143 µL, 1.3 mmol), CuI (7 mg, 0.05 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), Et_3N (420 µL, 3 mmol) in THF (5 mL). Purification by flash column chromatography (silica gel, EtOAc/heptane 1/9) provided 5-chloro-2-(phenylethynyl)aniline (233 mg, 95%) as a light brown solid. mp 104-105°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (*ppm*) : 4.37 (br s, 2H), 6.72 (m, 2H), 7.31 (d, J = 7.9 Hz, 1H), 7.35-7.41 (m, 3H), 7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*ppm*) : 84.8, 95.3, 106.4, 114.0, 118.1, 122.9, 128.4 (3C), 131.4 (2C), 133.0, 135.2, 148.6; IR (neat) ν (cm^{-1}) 3489, 3388, 1606, 1424, 1308, 1254; HRMS (ESI) calcd. for $C_{14}H_9ClN$ $[M-H]^-$ 226.0424, found 226.0419.

5-nitro-2-(phenylethynyl)aniline



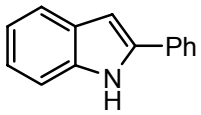
The reaction was carried out according to general procedure for Sonogashira coupling with 2-iodo-5-nitroaniline (264 mg, 1 mmol), phenylactylene (143 µL, 1.3 mmol), CuI (7 mg, 0.05 mmol), $PdCl_2(PPh_3)_2$ (35 mg, 0.05 mmol), Et_3N (420µL, 3 mmol) in THF (5 mL). Purification by flash column chromatography (silica gel, EtOAc/heptane 1/9) yielded 5-nitro-2-(phenylethynyl)aniline (230 mg, 93%) as a red solid. mp 125-126°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ (*ppm*) : 4.64 (br s, 2H), 7.37-7.60 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*ppm*) :

84.1, 98.9, 108.3, 112.4, 113.9, 122.1, 128.5 (2C), 129.1, 131.6 (2C), 132.5, 148.1 (2C); IR (neat) ν (cm^{-1}) 3467, 3374, 1618, 1598, 1495, 1332; HRMS (ESI) calcd. for $C_{14}H_9N_2O_2$ $[M-H]^-$ 237.664, found 237.0663.

General procedure for the indole synthesis:

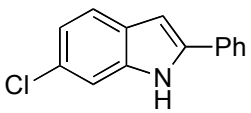
A solution of ethynylaniline, $FeCl_3.6H_2O$ (2%) and $PdCl_2$ (1%) was heated in DCE (1mL/0.15mmol) at 80°C for 4h. After cooling to room temperature, the reaction mixture was diluted with water. The aqueous layers were extracted with DCM, and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography.

2-phenyl-1*H*-indole



The reaction was carried out according to above mentioned general procedure for indole synthesis. Purification by flash column chromatography (silica gel, EtOAc/hexane 1/9) yielded 2-phenyl-1*H*-indole as a yellow solid. mp 89-90°C (Lit.[8] 89-90°C). 1H NMR (CDCl3, 300 MHz) δ (*ppm*) : 7.58–7.51 (m, 2H), 7.42–7.32 (m, 4H), 7.18–7.11 (m, 1H), 6.77–6.69 (m, 2H), 4.22 (s, br, 2H). 13C NMR (CDCl3, 75 MHz) δ (*ppm*) : 147.8, 132.1, 131.4, 129.7, 128.4, 128.2, 123.3, 118.0, 114.3, 107.9, 94.7, 85.9.
Data are in accordance with previously reported data.[8]

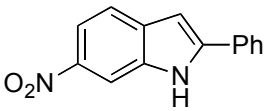
6-chloro-2-phenyl-1*H*-indole



The reaction was carried out according to above mentioned general procedure for indole synthesis. Purification by flash column chromatography (silica gel, EtOAc/heptane 2/8) yielded 6-chloro-2-phenyl-1*H*-indole (85 mg, 83%) as a white solid. mp 186-187°C (Lit.[9] 180-181°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (*ppm*) : 6.81 (dd, J = 0.8, 2.2 Hz, 1H), 7.11 (dd, J = 1.9, 8.5 Hz, 1H), 7.32-7.50 (m, 4H), 7.54 (d, J = 8.4 Hz, 1H), 7.64-7.69 (m, 2H), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*ppm*) : 99.9, 110.8, 121.0, 121.4, 125.1 (2C), 127.8, 128.0 129.1 (3C), 131.9, 137.1, 138.6

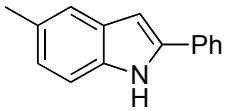
Data are in accordance with previously reported data.[9]

6-nitro-2-phenyl-1*H*-indole



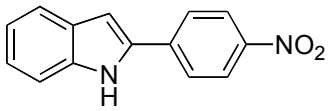
The reaction was carried out according to above mentioned general procedure for indole synthesis. Purification by flash column chromatography (silica gel, EtOAc/heptane 2/8) yielded 6-nitro-2-phenyl-1*H*-indole (88 mg, 82%) as a yellow solid. mp 213-214°C (Lit.[10] 215-216°C); ^{1}H NMR (d_6-DMSO, 300 MHz) δ (*ppm*) : 7.13 (d, *J* = 1.1 Hz, 1H), 7.42 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.69 (d, *J* = 8.8 Hz, 1H), 7.87-7.96 (m, 3H), 8.29 (d, *J* = 1.5 Hz, 1H), 12.31 (br s, 1H); ^{13}C NMR (d_6-DMSO, 75 MHz) δ (*ppm*) : 99.8, 107.8, 114.8, 120.1, 125.7 (2C), 128.9, 129.1 (2C), 130.8, 133.7, 135.4, 141.9, 144.1
Data are in accordance with previously reported data.[10]

5-methyl-2-phenyl-1*H*-indole



The reaction was carried out according to above mentioned general procedure for indole synthesis. Purification by flash column chromatography (silica gel, EtOAc/heptane 2/8) yielded 5-methyl-2-phenyl-1*H*-indole (74 mg, 80%) as a white solid. mp 218-219°C (Lit.[3] 218-219°C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (*ppm*) : 2.48 (s, 3H), 6.78 (d, *J* = 1.6 Hz, 1H), 7.05 (dd, *J* = 1.1, 8.3 Hz, 1H), 7.26-7.37 (m, 2H), 7.41-7.49 (m, 3H), 7.64-7.69 (m, 2H), 8.22 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*ppm*) : 21.5, 100.0, 110.5, 120.3, 124.0, 125.0 (2C), 127.6, 129.0 (2C), 129.5, 129.5, 132.5, 135.2, 137.9
Data are in accordance with previously reported data.[3]

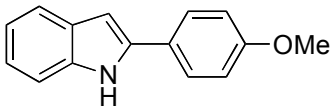
2-(4-nitrophenyl)-1H-indole



The reaction was carried out according to above mentioned general procedure for indole synthesis. Purification by flash column chromatography (silica gel, EtOAc/heptane 2/8) yielded 2-(4-nitrophenyl)-1H-indole (29 mg, 40%) as a yellow solid. mp 250-251°C (Lit.[11] 250-251°C); ^{1}H NMR (d_6-DMSO, 300 MHz) δ (*ppm*) : 7.05 (t, *J* = 7.4 Hz, 1H), 7.19 (m, 2H), 7.45 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 8.12 (d, *J* = 8.9 Hz, 2H), 8.31 (d, *J* = 8.9 Hz, 2H), 11.83 (br s, 1H); ^{13}C NMR (d_6-DMSO, 75 MHz) δ (*ppm*) : 102.4 , 111.7 , 119.9 , 120.8 , 123.1 , 124.2 (2C), 125.4 (2C), 128.4 , 135.2 , 137.9 , 138.5 , 145.8

Data are in accordance with previously reported data.[11]

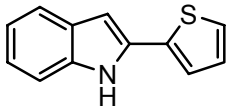
2-(4-methoxyphenyl)-1H-indole



The reaction was carried out according to general procedure for indole synthesis with 2-((4-methoxyphenyl)ethynyl)aniline (67 mg, 0.30 mmol) and $FeCl_3.6H_2O$ (1.6 mg, 2%) in DCE (2 mL). Purification by flash column chromatography (silica gel, EtOAc/heptane 2/8) yielded 2-(4-methoxyphenyl)-1H-indole (51 mg, 76%) as a white solid. mp 230-231°C (Lit.[12] 224-227°C); ^{1}H NMR (d_6-DMSO, 300 MHz) δ (*ppm*) : 3.80 (s, 3H), 6.75 (s, 1H), 6.96-7.10 (m, 4H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 11.41 (br s, 1H) ; ^{13}C NMR (d_6-DMSO, 75 MHz) δ (*ppm*) : 55.1 , 97.3 , 111.0 , 114.3 (2C), 119.2 , 119.7 , 121.0 , 124.9 , 126.3 (2C), 128.8 , 136.9 , 137.8 , 158.8

Data are in accordance with previously reported data.[12]

2-thienyl-1*H*-indole



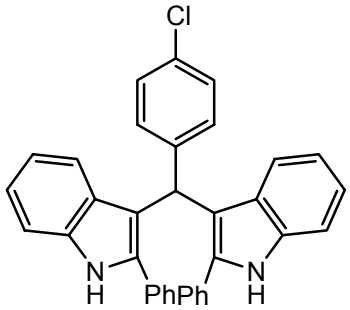
The reaction was carried out according to above mentioned general procedure for indole synthesis. Purification by flash column chromatography (silica gel, cyclohexane/diethylether 9/1) yielded 2-thienyl-1H-indole (50%) as yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (*ppm*) : 6.63 (d, *J* = 1.2 Hz, 1H), 7.23–6.96 (m, 6H), 7.50 (d, *J* = 7.5 Hz, 1H), 8.07 (s, br, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (*ppm*) : 136.9, 136.0, 132.8, 129.5, 128.3, 125.0, 124.4, 123.0, 121.0, 120.9, 111.2, 100.9.

Data are in accordance with previously reported data.[8]

General procedure for the bis(indolyl)methane synthesis:

A solution of ethynylaniline, aldehyde derivative (0.5 eq.), $FeCl_3.6H_2O$ (2%) and $PdCl_2$ (1%) was heated in DCE (1mL/0.15mmol) at 80°C for 4h. After cooling to room temperature, the reaction mixture was diluted with water. The aqueous layers were extracted with DCM, and the combined organic phases were dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography.

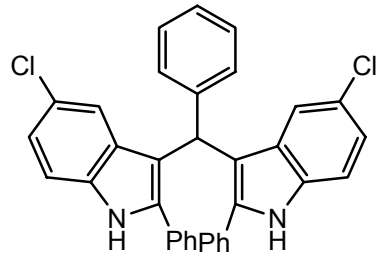
Bis(indolyl)methane 10



The reaction was carried out according to above mentioned general procedure for bisindolylmethane synthesis. Purification by flash column chromatography (silica gel, DCM) yielded bis(indolyl)methane **10** (59%) as purple solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (*ppm*) : 6.07 (s, 1H); 6.87 (m, 2H); 7.09 (m, 2H); 7.19 (m, 16H); 7.34 (d, 2H, *J* = 8.0Hz); 8.07 (s, 2H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (*ppm*) : 143.0; 136.0; 135.7; 132.9; 130.6; 128.6; 128.5; 128.3; 128.2; 127.6; 121.8; 121.6; 119.1; 115.0; 110.7; 39.5.

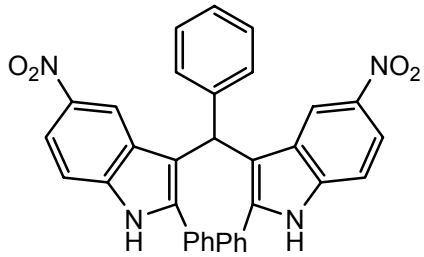
Data are in accordance with previously reported data.

Bis(indolyl)methane 11



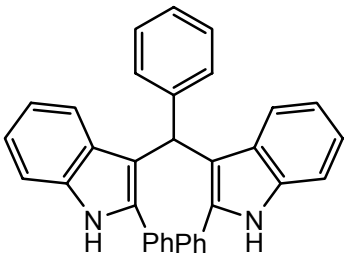
The reaction was carried out according to above mentioned general procedure for bisindolylmethane synthesis. Purification by flash column chromatography (silica gel, DCM) yielded bis(indolyl)methane **11** (42%) as yellow solid. mp. 190-193°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (*ppm*) : 5.98 (s, 1H); 6.72 (m, 4H); 7.10 (m, 10H); 7.19 (m, 6H); 7.23 (m, 2H, *J* = 1.5Hz); 7.96 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (*ppm*) : 144.7; 136.2; 132.4; 129.11; 128.4; 128.1; 127.8; 127.6; 127.2; 126.4; 122.2; 120.4; 115.3; 110.5; 39.7.

Bis(indolyl)methane 12



The reaction was carried out according to above mentioned general procedure for bisindolylmethane synthesis. Purification by flash column chromatography (silica gel, DCM) yielded bis(indolyl)methane **12** (40%) as yellow solid. mp. 250-253°C; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (*ppm*) : 6.14 (s, 1H); 6.79 (d, 2H, *J* = 8.9Hz);7.13 (m, 4H, *J* = 1.7Hz, J=8.6Hz); 7.20 (m, 4H); 7.30 (m, 7H); 7.74 (dd, 2H, *J* = 2.1Hz, *J* = 9.0Hz); 8.28 (d, 2H, *J* = 2.0Hz); 8.49 (s, 1H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (*ppm*) : 142.8; 141.7; 134.1; 133.09; 131.3; 129.0; 128.8; 128.6; 128.2; 127.1; 120.7; 115.9; 115.4; 107.6; 39.7.

Bis(indolyl)methane 13

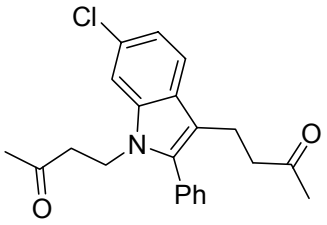


The reaction was carried out according to above mentioned general procedure for bisindolylmethane synthesis. Purification by flash column chromatography (silica gel, DCM) yielded bis(indolyl)methane **13** (51%) as yellow solid. mp. 263-265°C (Lit.[14] 262-263°C); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (*ppm*) : 6.12 (s, 1H); 6.83 (ddd, 2H, *J* = 0.9Hz, *J* = 7.1Hz, *J* = 8.1Hz); 7.00 (d, 2H, *J* = 8.0Hz); 7.10 (m, 3H); 7.17 (m, 6H); 7.22 (m, 6H); 7.33 (m, 4H); 8.05 (s, 2H)

^{13}C-NMR ($CDCl_3$, 100 MHz) δ (*ppm*) : 144.8; 135.7; 135.5; 133.0; 129.2; 128.8; 128.3; 128.2; 128.2; 127.4; 126.0; 121.8; 121.7; 119.5; 115.6; 110.6; 40.03.

Data are in accordance with previously reported data.[14]

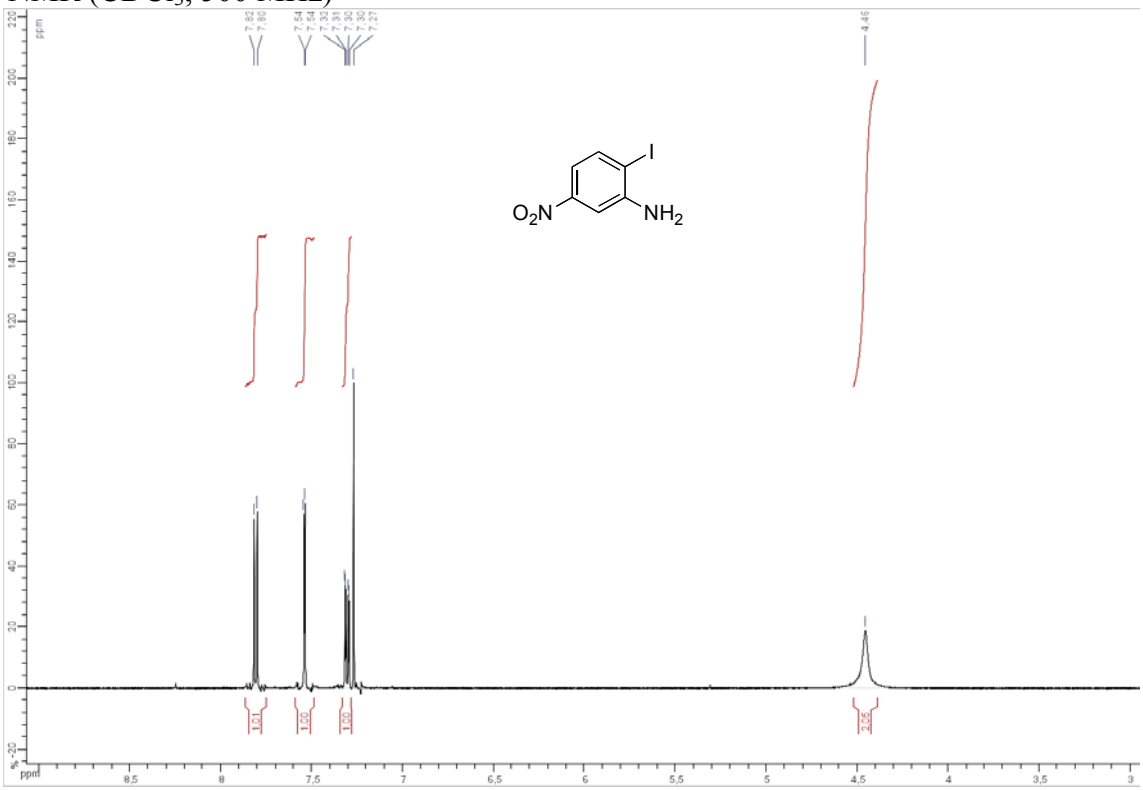
Trisubstituted indole 14



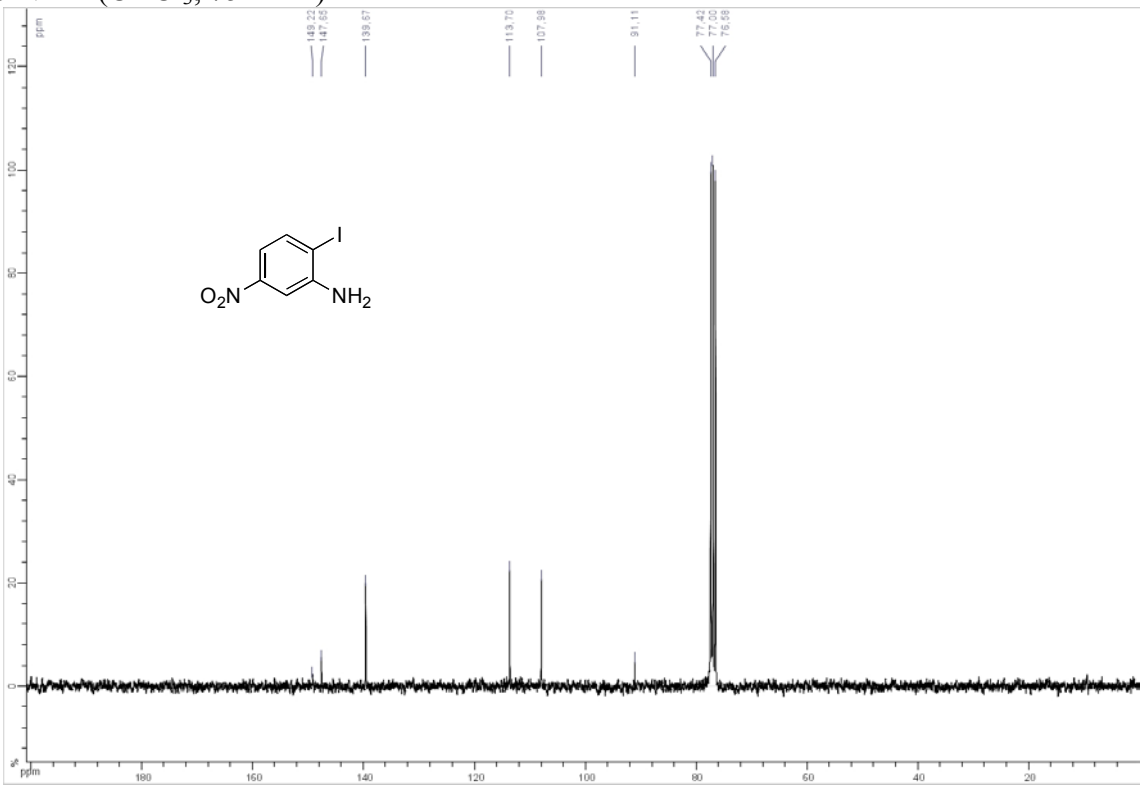
Purification by flash column chromatography (silica gel, DCM) yielded Trisubstituted indole **14** (80%); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ (*ppm*) : 1.94 (s, 3H); 1.95 (s, 3H); 2.55 (dt, 4H, *J* = 3.9Hz, *J* = 7.5Hz); 2.83 (m, 2H); 4.16 (m, 2H); 7.04 (dd, 1H, *J* = 1.7Hz, *J* = 8.4Hz); 7.26 (m, 3H); 7.41 (m, 4H). ^{13}C-NMR ($CDCl_3$, 100 MHz) δ (*ppm*) : 208.3; 206.0; 138.1; 136.4; 131.2; 130.3; 128.8; 128.7; 127.9; 126.2; 120.2; 119.8; 112.8; 109.6; 44.6; 43.1; 38.4; 30.1; 29.9; 18.7.

2-iodo-5-nitroaniline

^{1}H NMR ($CDCl_3$, 500 MHz)

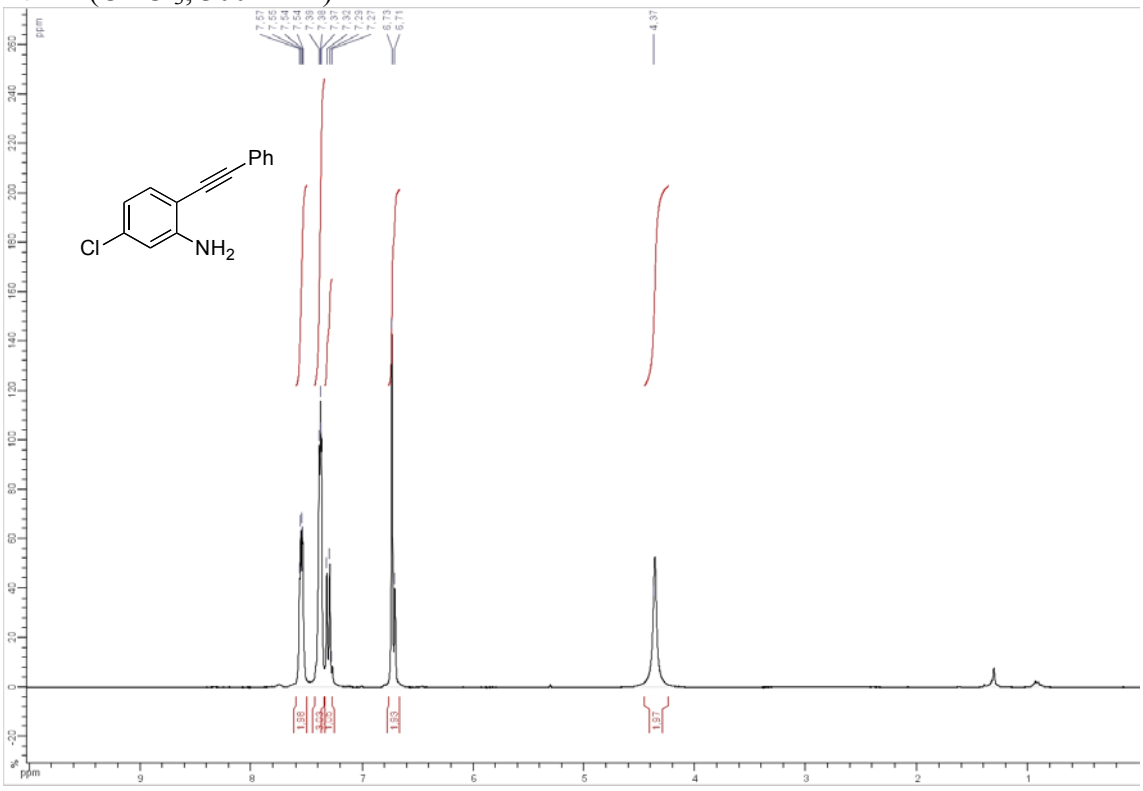


^{13}C NMR ($CDCl_3$, 75 MHz)

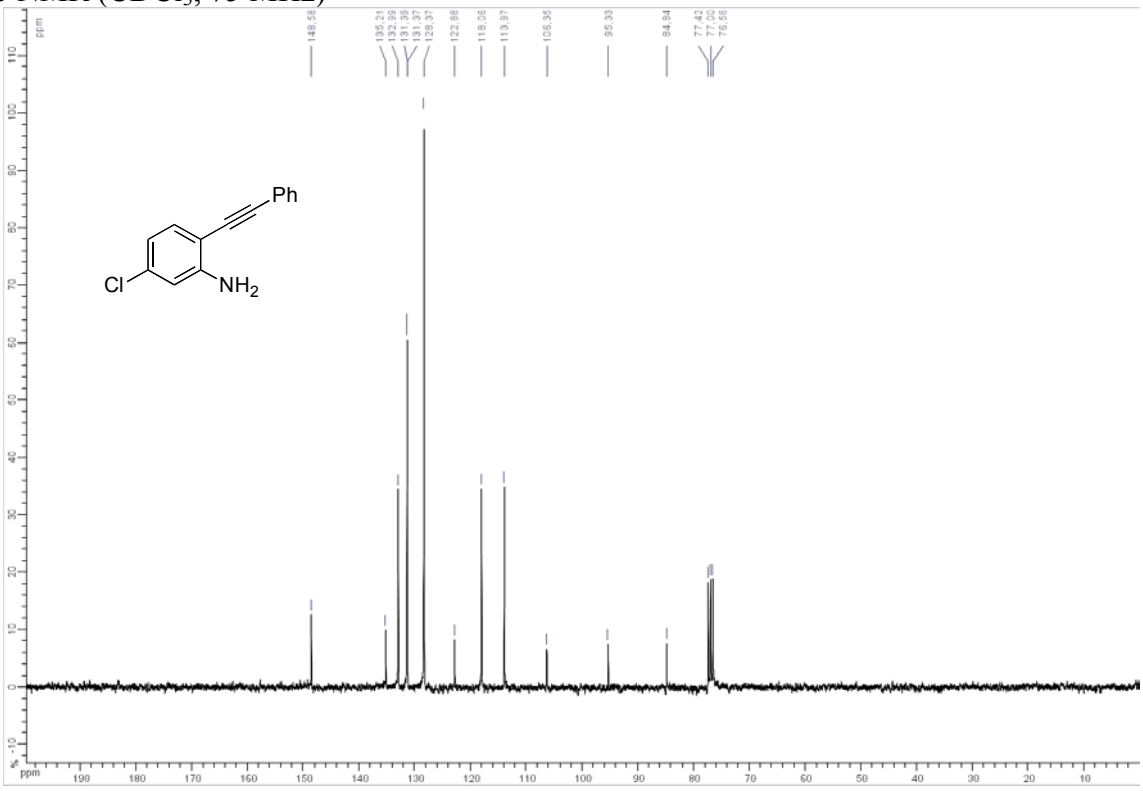


5-chloro-2-(phenylethynyl)aniline

^{1}H NMR ($CDCl_3$, 300 MHz)

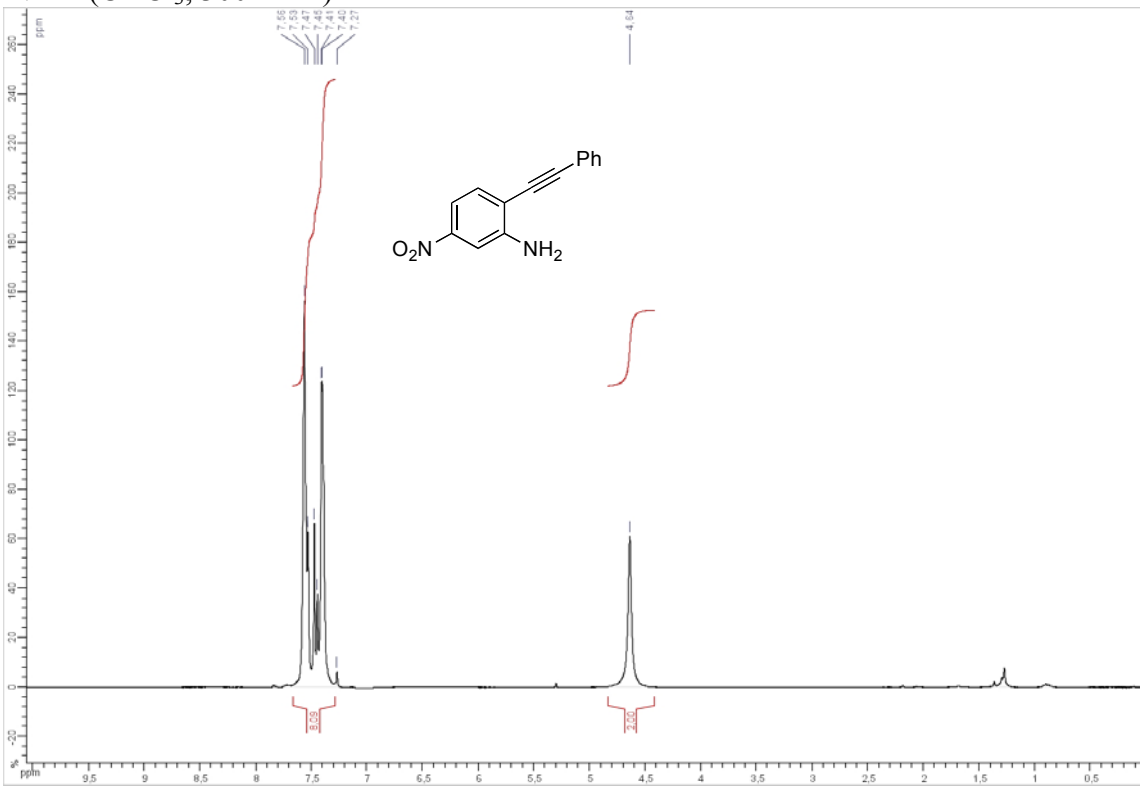


^{13}C NMR ($CDCl_3$, 75 MHz)

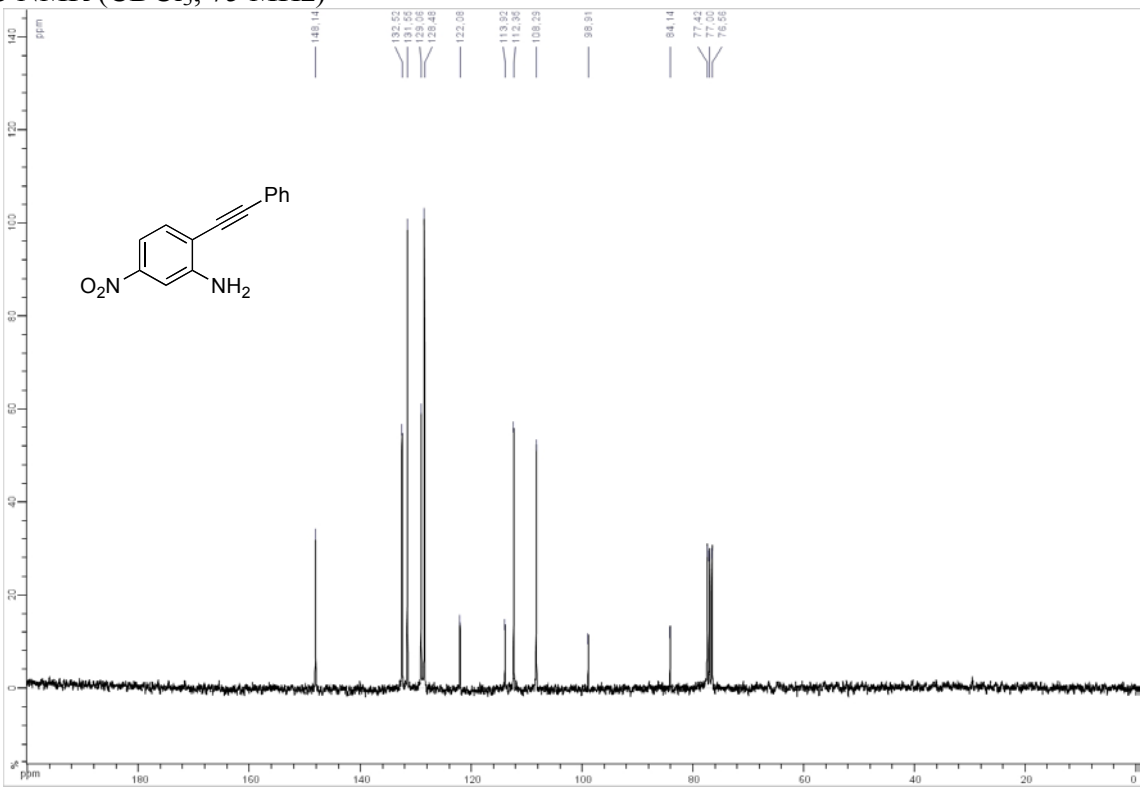


5-nitro-2-(phenylethynyl)aniline

^{1}H NMR ($CDCl_3$, 300 MHz)

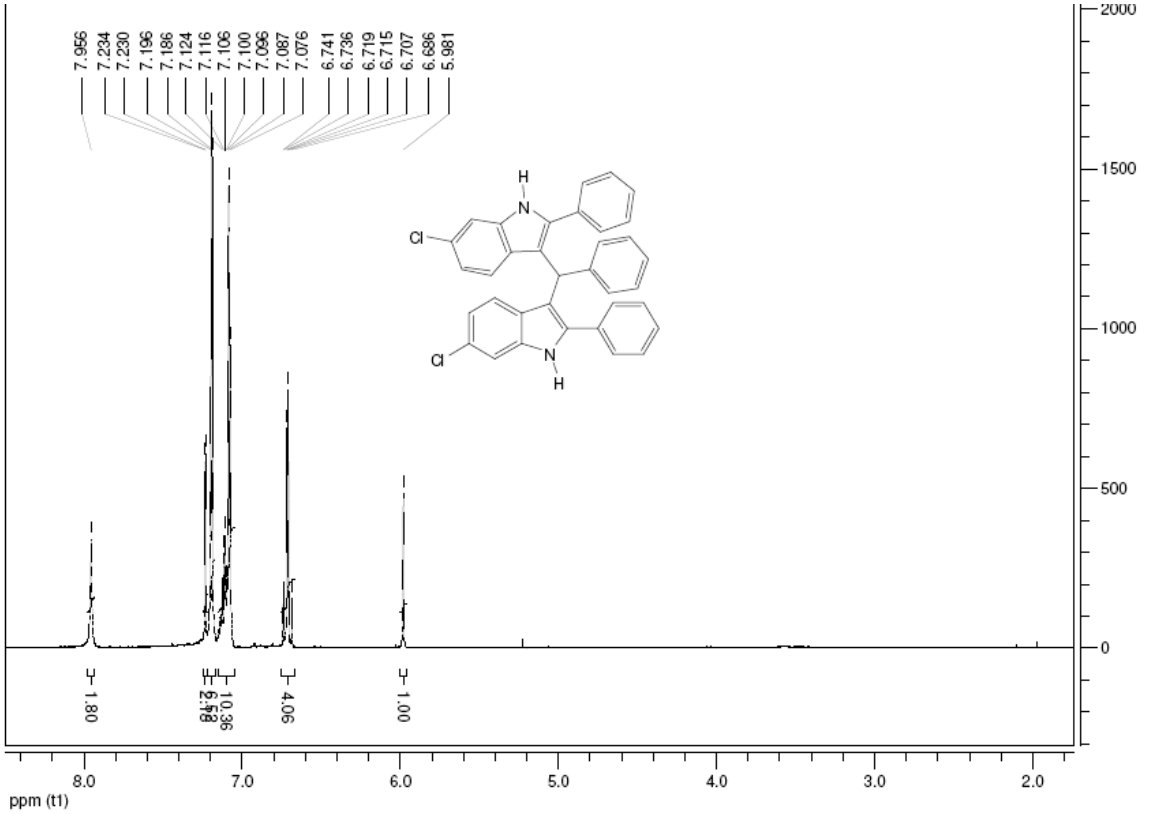


^{13}C NMR ($CDCl_3$, 75 MHz)

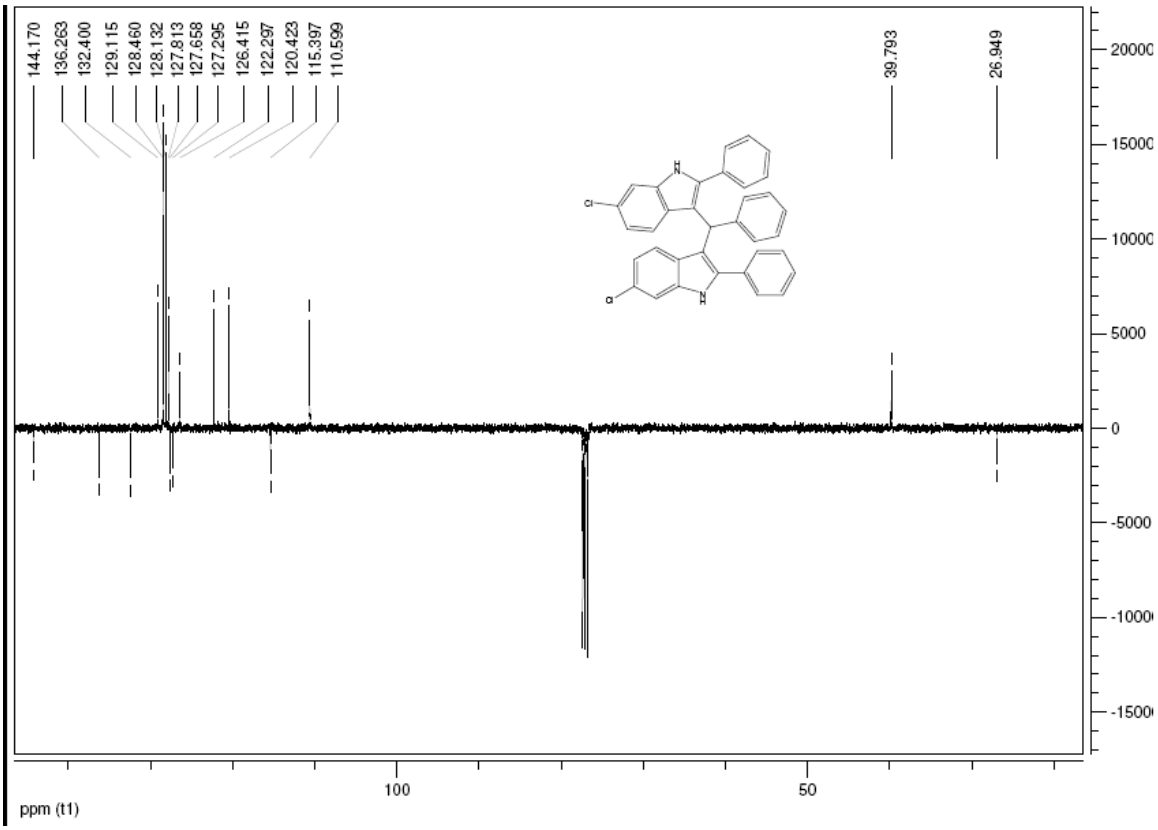


Bisindolylmethane 11

^{1}H NMR ($CDCl_3$, 400 MHz)

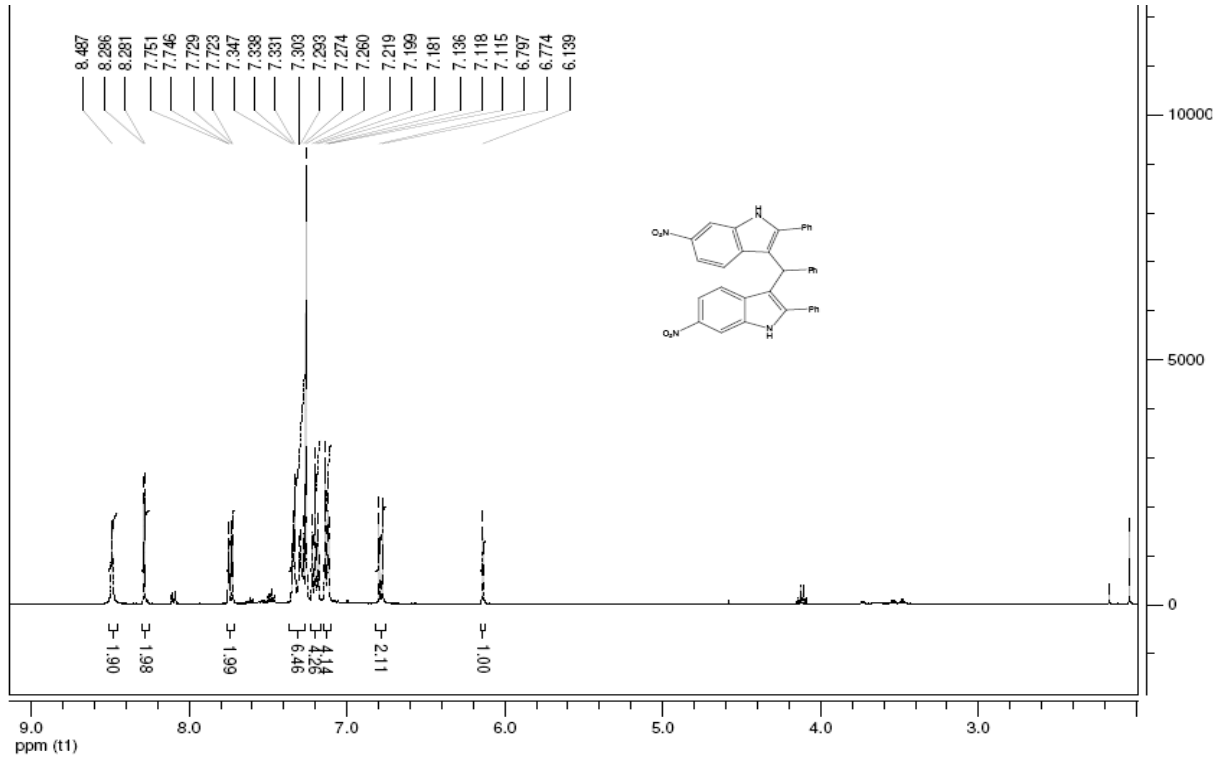


^{13}C NMR ($CDCl_3$, 100 MHz)

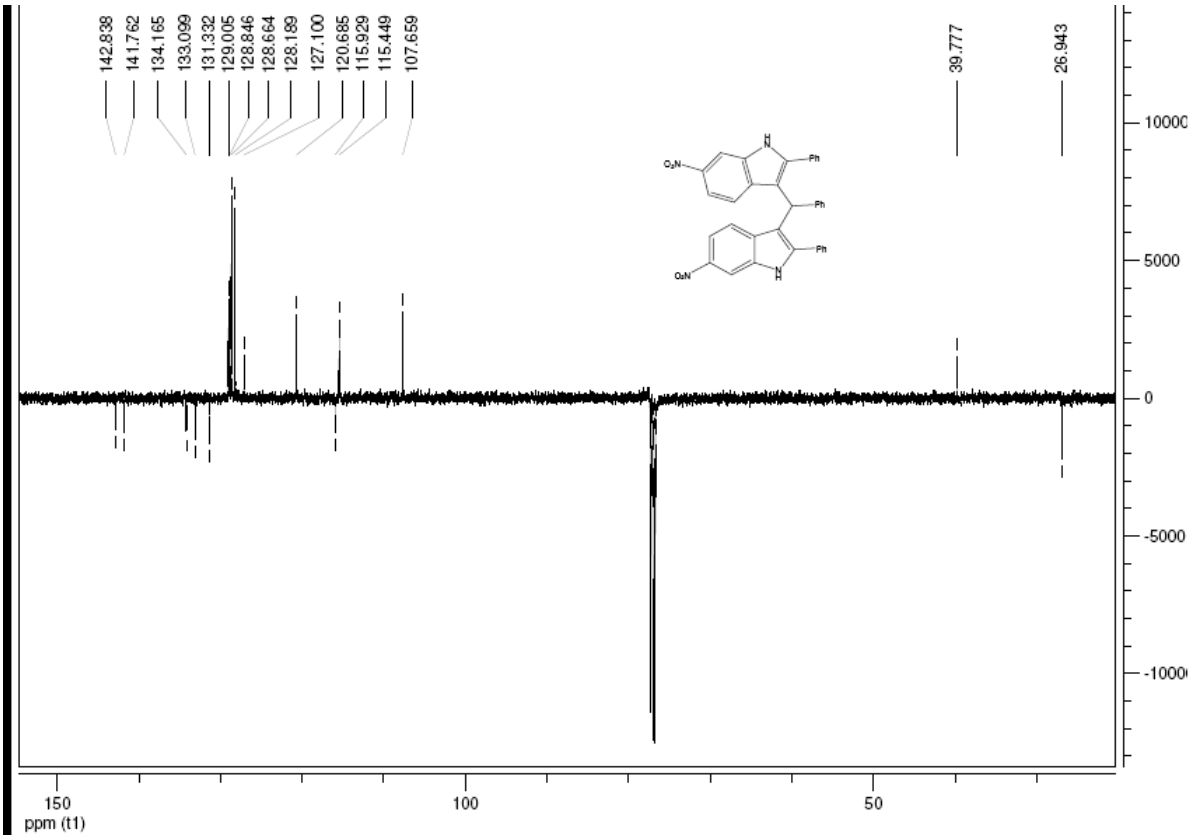


Bisindolylmethane 12

^{1}H NMR ($CDCl_3$, 400 MHz)

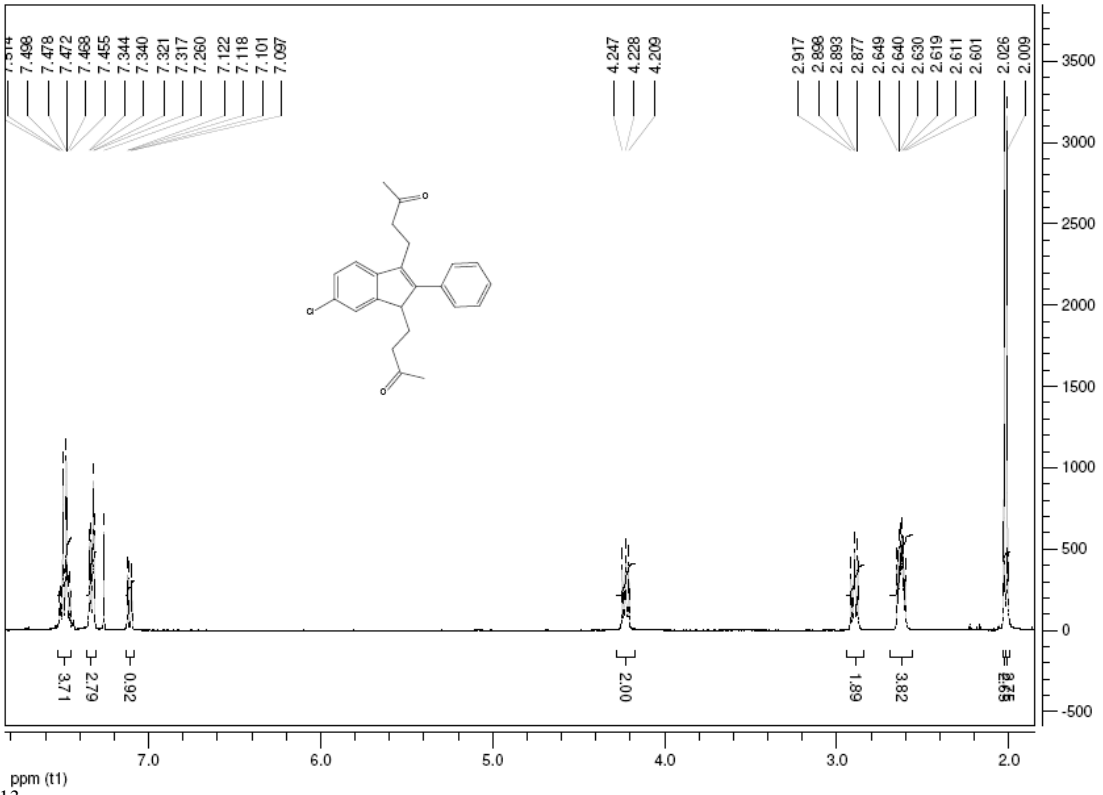


^{13}C NMR ($CDCl_3$, 100 MHz)

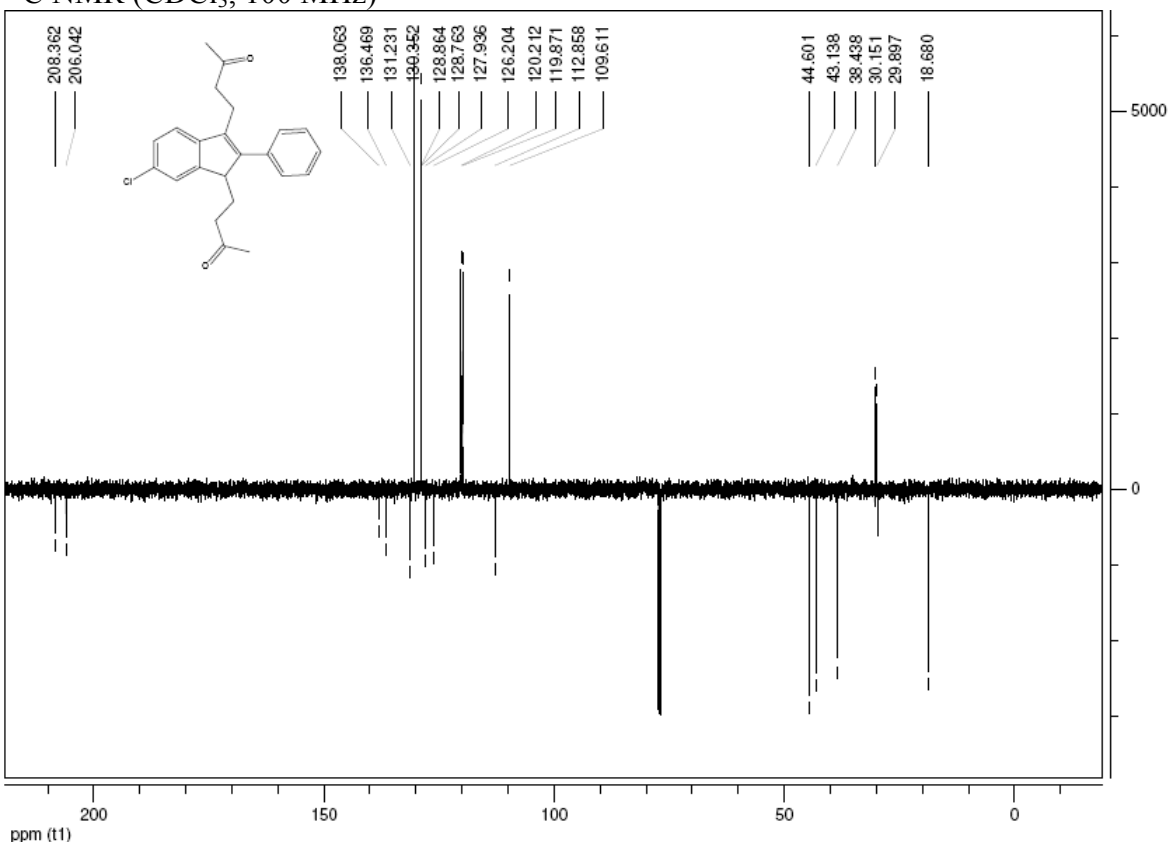


trisubstituted indole 14

^{1}H NMR ($CDCl_3$, 400 MHz)



^{13}C NMR ($CDCl_3$, 100 MHz)



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