Supplementary Materials: Iridium Catalyzed Synthesis of Tetrahydro-1*H*-Indoles by Dehydrogenative Condensation

Daniel Forberg, Fabian Kallmeier * and Rhett Kempe *

Contents

General Considerations

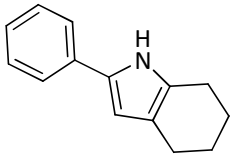
All reactions were carried out in a dry argon or nitrogen atmosphere using standard Schlenk or glove box techniques. Halogenated solvents were dried over P_4O10, and nonhalogenated solvents were dried over sodium (benzophenone as indicator). Deuterated solvents were ordered from Cambridge Isotope Laboratories, vented, stored over molecular sieves and distilled. All chemicals were purchased from commercial sources with purity over 95 % and used without further purification. NMR spectra were received using a Varian INOVA 300 MHz spectrometer at 298 K. Chemical shifts (δ) are reported in ppm relative to the deuterated solvent. Elemental analyses were carried out on an Elementar Vario EL *III*. GC analyses were carried out on an Agilent 6890N GC system equipped with a HP-5 column (30 m x 0.32 mm x 0.25 µm) using *n*-dodecane as internal standard. GC/MS analyses were carried out on an Agilent 7890A/MSD 5975C system equipped with a HP-5MS column (30 m x 0.32 mm x 0.25 µm). The PNP-Iridium[1] complex and the Pd@SiCN[2] catalyst were prepared according to literature.

General Procedures

General procedure for the synthesis of tetrahydro-1H-indoles: In a glove box 2.0 mL of a catalyst stock solution (0.02 mmol, 0.01 M in thf), secondary alcohol (15.22 mmol, 2 equivalents), 2-amino cyclohexanol (875 mg, 7.61 mmol, 1 equivalent), 10 mL thf and KOtBu (943 mg, 8.4 mmol, 1.1 equivalents) were added to a pressure tube and sealed with a semi-permeable membrane. The tube was heated at 105 °C (oil bath temperature) for 22 h. After cooling to room temperature, 3 mL water and dodecane as internal standard were added. The product was extracted with diethyl ether (2x) and purified by column chromatography or crystallization.

General procedure for the dehydrogenation reaction: In a 10 mL Schlenk tube, Pd@SiCN (50 mg, 0.18 mol% active metal), substrate (1.0 mmol) and 0.75 mL diglyme were evacuated and flushed with argon three times. A slight argon flow of 4-6 mL/min was adjusted and the mixture was stirred for 20 h at 180 °C (oil bath temperature). After cooling to room temperature, the catalyst was separated by centrifugation and washed with acetone twice. The organic phases were combined, and the solvent was removed under reduced pressure at 60 °C giving the pure product. If required, further purification was achieved by either column chromatography or crystallization.

Synthesis of 3a/4a:



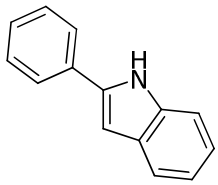
3a: 2-phenyl-4,5,6,7-tetrahydro-1*H*-indole

2.0 mL Catalyst **I** (0.02 mmol, 0.01 M in thf), 1-phenyl-1-ethanol (1826 µL, 15.22 mmol), 2-aminocyclohexanol (875 mg, 7.61 mmol), 10 mL thf, KO^{t}Bu (943 mg, 8.40 mmol), 22 h at 105 °C. Purification by column chromatography 40:1 → 5:1 → 1:1 pentane : diethyl ether. Yield: 1.14 g = 5.78 mmol = 76 % as light pink solid. M($C_{14}H_{15}N$) = 197.28 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.93 (s_br, 1H), 7.44-7.41 (m, 2H), 7.36-7.31 (m, 2H), 7.18-7.13 (m, 1H), 6.29-6.28 (m, 1H), 2.67-2.63 (m, 2H), 2.58-2.54 (m, 2H), 1.91-1.75 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 133.2, 130.2, 128.7, 128.5, 125.5, 123.3, 118.9, 105.2, 23.8, 23.4, 23.0, 22.9 ppm.

MS (EI, m/z): 197.0 (M^+).

elemental analysis (%) for $C_{14}H_{15}N$ calcd: C 85.24, H 7.66, N 7.10; found: C 84.96, H 7.55, N 6.51.



4a: 2-phenyl-1*H*-indole

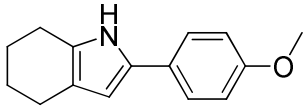
Yield: quantitative as colorless solid. M($C_{14}H_{11}N$) = 193.24 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 8.33 (s_br, 1H), 7.69-7.63 (m, 3H), 7.48-7.40 (m, 3H), 7.36-7.31 (m, 1H), 7.23-7.11 (m, 2H), 6.84-6.82 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 137.8, 136.8, 132.3, 129.2, 129.0, 127.7, 125.1, 122.3, 120.6, 120.2, 110.9, 99.9 ppm.

MS (EI, m/z): 193.0 (M^+).

elemental analysis (%) for $C_{14}H_{11}N$ calcd: C 87.01, H 5.74, N 7.25; found: C 86.90, H 5.88, N 6.88.

Synthesis of 3b/4b:



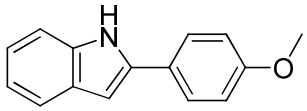
3b: 2-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1*H*-indole

2.0 mL Catalyst **I** (0.02 mmol, 0.01 M in thf), 1-(4-methoxyphenyl)ethanol (2148 µL, 15.22 mmol), 2-aminocyclohexanol (875 mg, 7.61 mmol), 10 mL thf, KO^{t}Bu (943 mg, 8.40 mmol), 22 h at 105 °C. Purification by crystallization from diethyl ether. Yield: 1.27 g = 5.60 mmol = 74 % as light yellow solid. M($C_{15}H_{17}NO$) = 227.30 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.89 (s_br, 1H), 7.36 (d, J = 8.7 Hz, 2H), 6.90 (d, J = 8.7 Hz, 2H), 6.19-6.18 (m, 1H), 3.83 (s, 3H), 2.66-2.62 (m, 2H), 2.58-2.54 (m, 2H), 1.91-1.76 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 157.8, 130.3, 127.7, 126.4, 124.8, 118.6, 114.2, 104.0, 55.2, 23.8, 23.4, 22.9, 22.8 ppm.

MS (EI, m/z): 227.2 (M^+).

elemental analysis (%) for $C_{15}H_{17}NO$ calcd: C 79.26, H 7.54, N 6.16; found: C 78.62, H 7.30, N 5.97.



4b: 2-(4-methoxyphenyl)-1*H*-indole

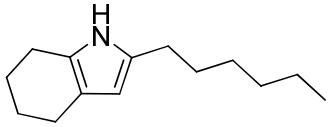
Yield: 97 % as colorless solid by recrystallization from diethyl ether. M($C_{15}H_{13}NO$) = 223.27 gmol^{-1}.

^{1}H NMR (300 MHz, THF-d_8, 298 K): δ = 10.39 (s_br, 1H), 7.68 (d, J = 8.4 Hz, 2H), 7.47-7.45 (m, 1H), 7.30-7.28 (m, 1H), 7.03-6.91 (m, 2H), 6.96 (d, J = 8.4 Hz, 2H), 6.66-6.65 (m, 1H), 3.80 (s, 3H) ppm. ^{13}C NMR (75 MHz, THF-d_8, 298 K): δ = 160.5, 139.3, 138.6, 130.8, 127.3, 126.9, 122.0, 120.8, 120.2, 115.2, 111.6, 98.8, 55.7 ppm.

MS (EI, m/z): 223.1 (M^+).

elemental analysis (%) for $C_{15}H_{13}NO$ calcd: C 80.69, H 5.87, N 6.27; found: C 80.28, H 5.69, N 6.19.

Synthesis of 3c/4c:



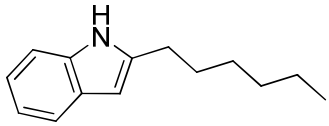
3c: 2-hexyl-4,5,6,7-tetrahydro-1*H*-indole

2.0 mL Catalyst **I** (0.02 mmol, 0.01 M in thf), 2-octanol (2418 µL, 15.22 mmol), 2-aminocyclohexanol (875 mg, 7.61 mmol), 10 mL thf, KO^{t}Bu (0.94 g, 8.37 mmol), 22 h at 105 °C. Purification by column chromatography 80:1 → 20:1 pentane : diethyl ether. Yield: 1.19 g = 5.80 mmol = 76 %. M($C_{14}H_{23}N$) = 205.18 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.41 (s_br, 1H), 5.68-5.67 (m, 1H), 2.58-2.48 (m, 6H), 1.84-1.72 (m, 4H), 1.67-1.57 (m, 2H), 1.44-1.31 (m, 6H), 0.92 (t, J = 6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 131.1, 125.1, 116.7, 103.9, 31.7, 29.8, 29.2, 27.9, 23.9, 23.5, 22.9, 22.7, 22.6, 14.1 ppm.

MS (EI, m/z): 205.2 (M^+).

elemental analysis (%) for $C_{14}H_{23}N$ calcd: C 81.89, H 11.29, N 6.82; found: C 81.15, H 11.06, N 6.65.



4c: 2-hexyl-1*H*-indole

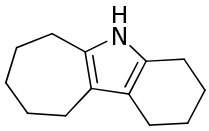
Yield: 99 % as brown oil. M($C_{14}H_{19}N$) = 201.15 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.84 (s_br, 1H), 7.56-7.53 (m, 1H), 7.31-7.26 (m, 1H), 7.15-7.05 (m, 2H), 6.25 (s, 1H), 2.76 (t, J = 7.5 Hz, 2H), 1.80-1.68 (m, 2H), 1.46-1.28 (m, 6H), 0.91 (t, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 140.0, 135.7, 128.8, 120.8, 119.6, 119.4, 110.3, 99.2, 31.6, 29.1, 29.0, 28.1, 22.6, 14.1 ppm.

MS (EI, m/z): 201.2 (M^+).

elemental analysis (%) for $C_{14}H_{19}N$ calcd: C 83.53, H 9.51, N 6.96; found: C 83.45, H 9.29, N 6.92.

Synthesis of 3d/4d:



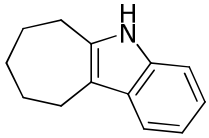
3d: 1,2,3,4,5,6,7,8,9,10-decahydrocyclohepta[*b*]indole

2.0 mL Catalyst **I** (0.02 mmol, 0.01 M in thf), cycloheptanol (1834 µL, 15.22 mmol), 2-aminocyclohexanol (875 mg, 7.61 mmol), 10 mL thf, KO*t*Bu (943 mg, 8.40 mmol), 22 h at 105 °C. Purification by column chromatography 40:1 → 10:1 pentane : diethyl ether. Yield: 1.38 g = 7.29 mmol = 96 % as light yellow oil. M($C_{13}H_{19}N$) = 189.30 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.23 (s_br, 1H), 2.67-2.64 (m, 2H), 2.56-2.40 (m, 6H), 1.82-1.71 (m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 128.2, 122.9, 118.9, 116.7, 31.9, 29.2, 29.1, 28.0, 25.3, 23.6, 23.3, 22.5, 21.3 ppm.

MS (EI, m/z): 189.2 (M^+).

elemental analysis (%) for $C_{13}H_{19}N$ calcd: C 82.48, H 10.12, N 7.40; found: C 82.17, H 9.91, N 6.97.



4d: 5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole

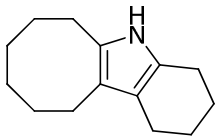
Yield: quantitative as colorless solid. M($C_{13}H_{15}N$) = 185.26 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.67 (s_br, 1H), 7.52-7.47 (m, 1H), 7.30-7.24 (m, 1H), 7.14-7.06 (m, 2H), 2.86-2.83 (m, 4H), 1.96-1.89 (m, 2H), 1.81-1.76 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 137.4, 134.2, 129.2, 120.6, 119.0, 117.6, 113.7, 110.1, 31.8, 29.6, 28.7, 27.5, 24.6 ppm.

MS (EI, m/z): 185.2 (M^+).

elemental analysis (%) for $C_{13}H_{15}N$ calcd: C 84.28, H 8.16, N 7.56; found: C 84.09, H 8.10, N 7.34.

Synthesis of 3e/4e:



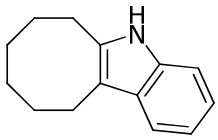
3e: 2,3,4,5,6,7,8,9,10,11-decahydro-1*H*-cycloocta[*b*]indole

2.0 mL Catalyst **I** (0.02 mmol, 0.01 M in thf), cyclooctanol (2004 µL, 15.22 mmol), 2-aminocyclohexanol (875 mg, 7.61 mmol), 10 mL thf, KO*t*Bu (943 mg, 8.40 mmol), 22 h at 105 °C. Purification by column chromatography 80:1 → 20:1 pentane : diethyl ether. Yield: 1.38 g = 6.79 mmol = 95 % as light yellow oil. M($C_{14}H_{21}N$) = 203.17 gmol^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.20 (s_br, 1H), 2.28-2.62 (m, 2H), 2.55-2.48 (m, 4H), 2.40-2.37 (m, 2H), 1.83-1.72 (m, 4H), 1.64-1.56 (m, 4H), 1.54-1.42 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 126.2, 123.5, 116.6, 116.2, 29.6, 29.3, 25.9, 25.8, 25.7, 23.7, 23.5, 22.7, 22.5, 21.2 ppm.

MS (EI, m/z): 203.0 (M^+).

elemental analysis (%) for $C_{14}H_{21}N$ calcd: C 82.70, H 10.41, N 6.89; found: C 82.56, H 10.42, N 6.75.



4e: 6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indole

Yield: 97 % as colorless solid. M($C_{14}H_{17}N$) = 199.29 gmol^{-1}.

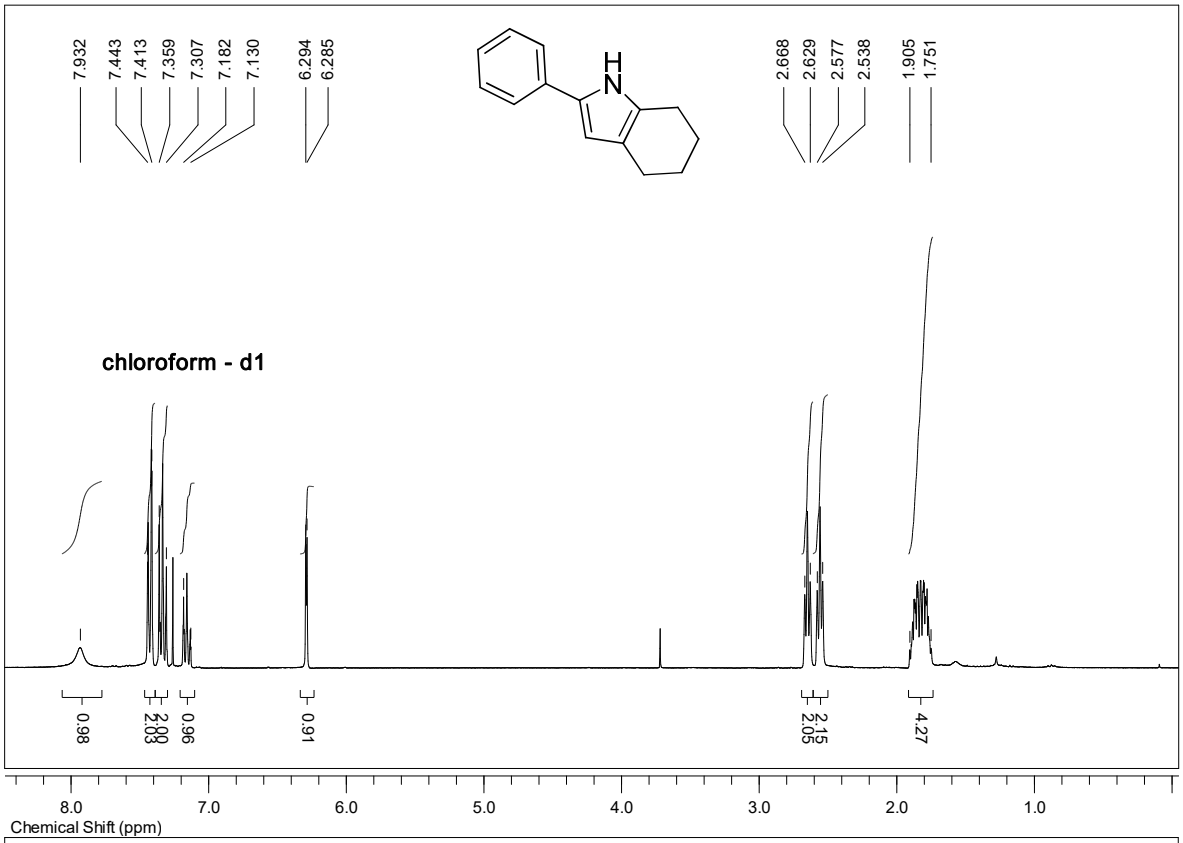
^{1}H NMR (300 MHz, $CDCl_3$, 298 K): δ = 7.70 (s_br, 1H), 7.51-7.47 (m, 1H), 7.30-7.27 (m, 1H), 7.13-7.05 (m, 2H), 2.89-2.83 (m, 4H), 1.81-1.70 (m, 4H), 1.52-1.39 (m, 4H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 298 K): δ = 135.6, 135.0, 128.6, 120.6, 118.9, 117.6, 111.7, 110.2, 29.6, 29.5, 26.0, 25.9, 22.1, 22.1 ppm.

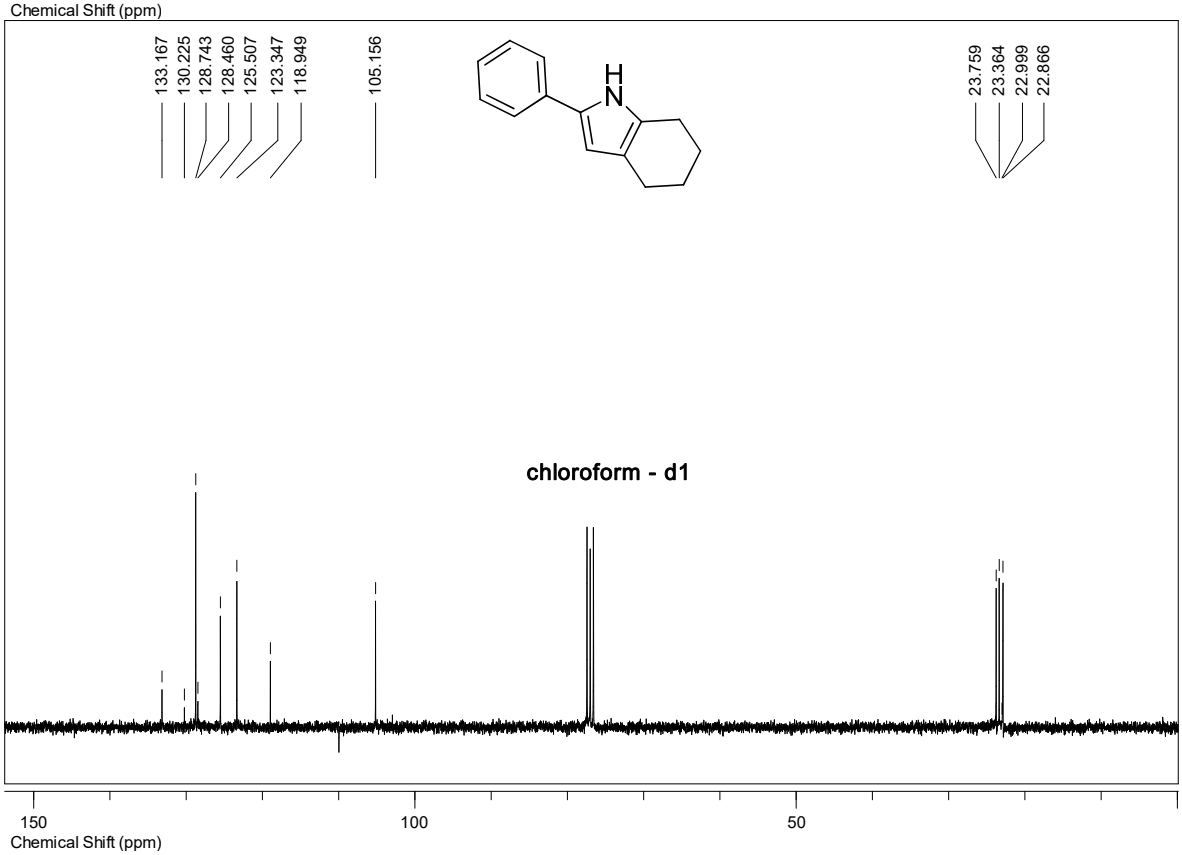
MS (EI, m/z): 199.2 (M^+).

elemental analysis (%) for $C_{14}H_{17}N$ calcd: C 84.37, H 8.60, N 7.03; found: C 83.64, H 8.54, N 6.80.

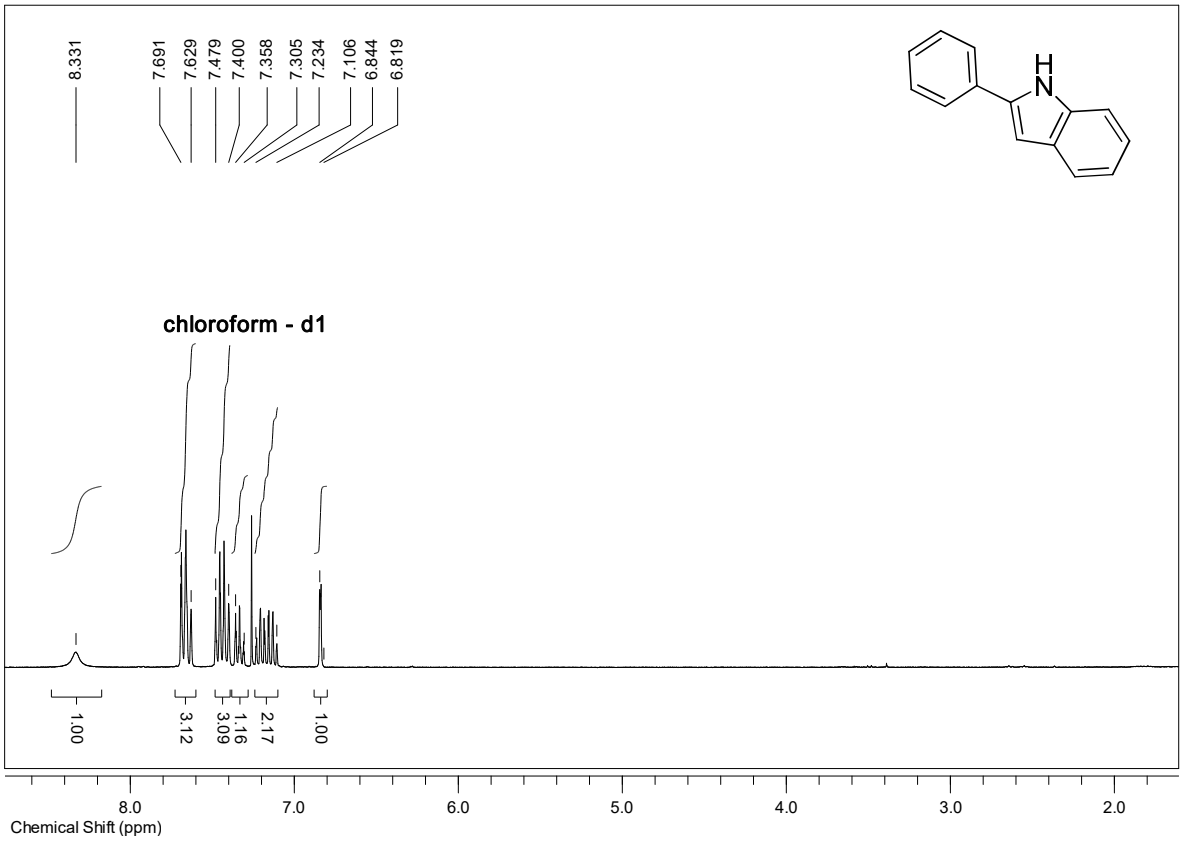
NMR Spectra

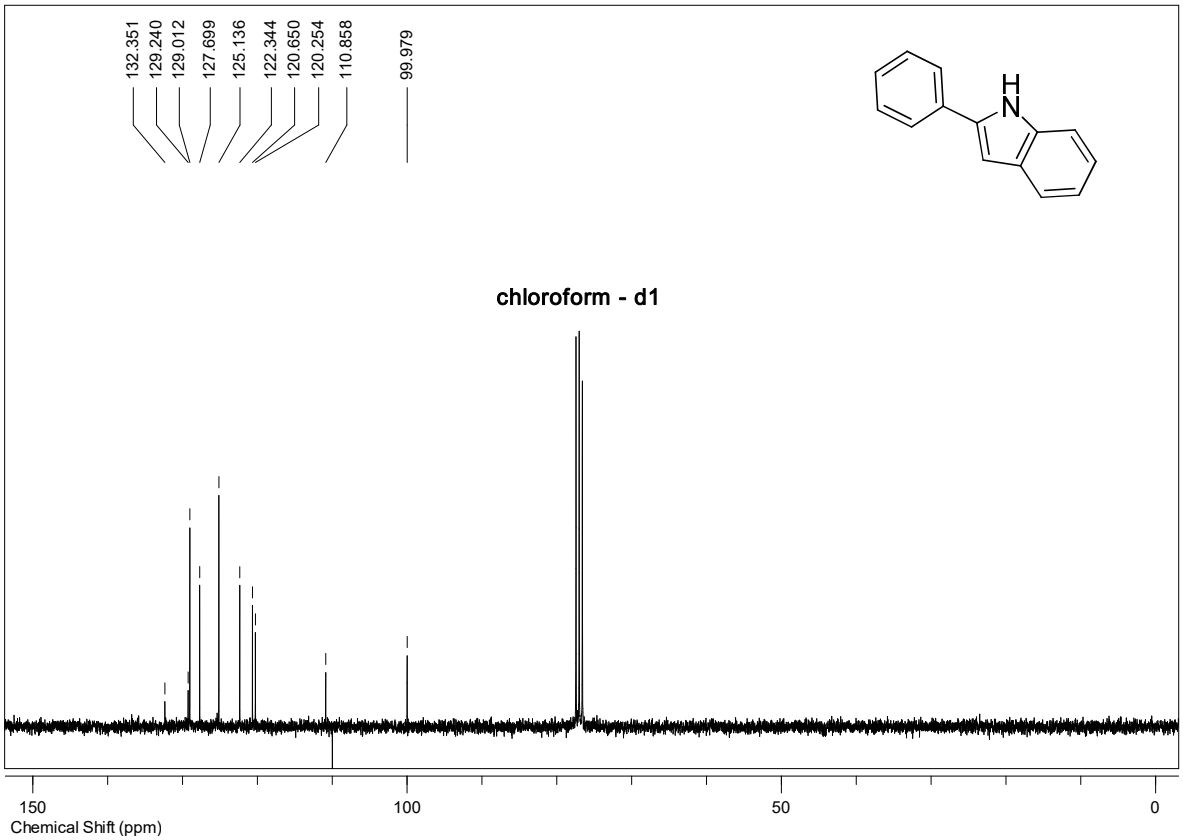
3a:



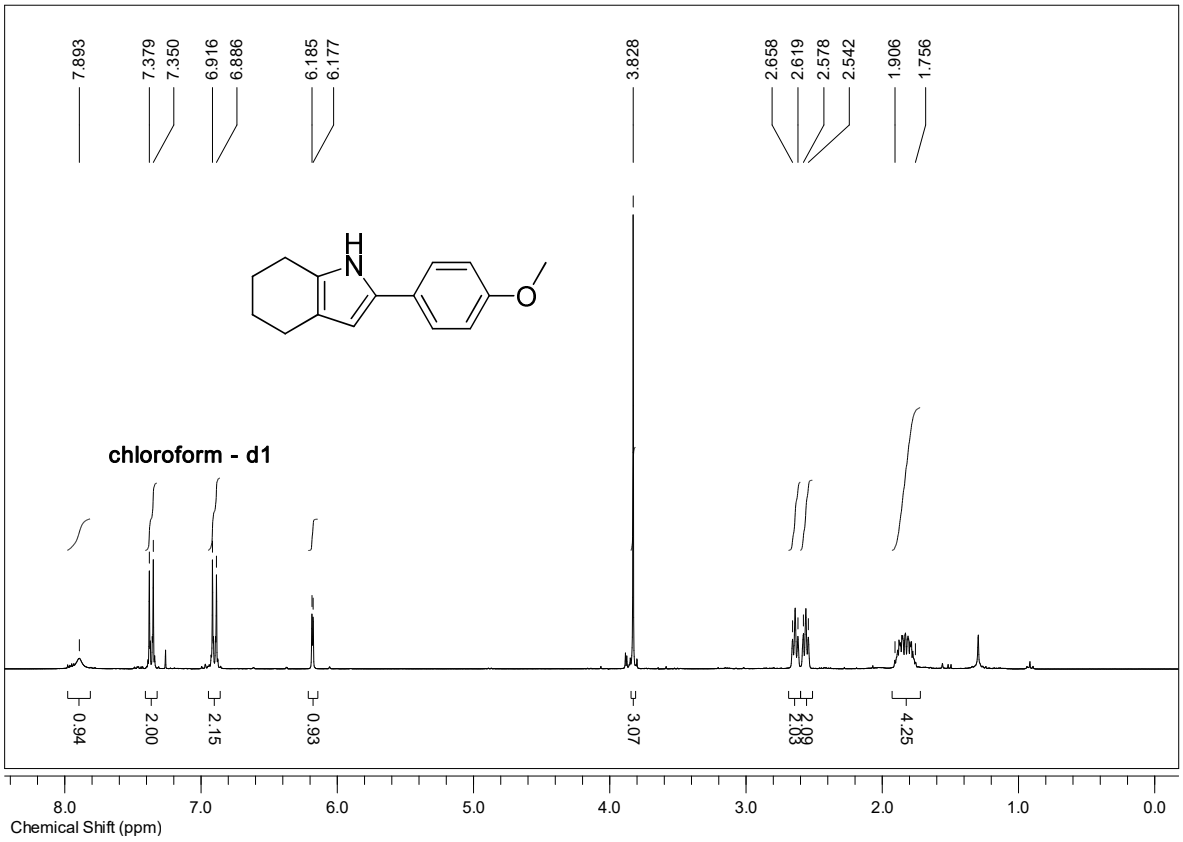


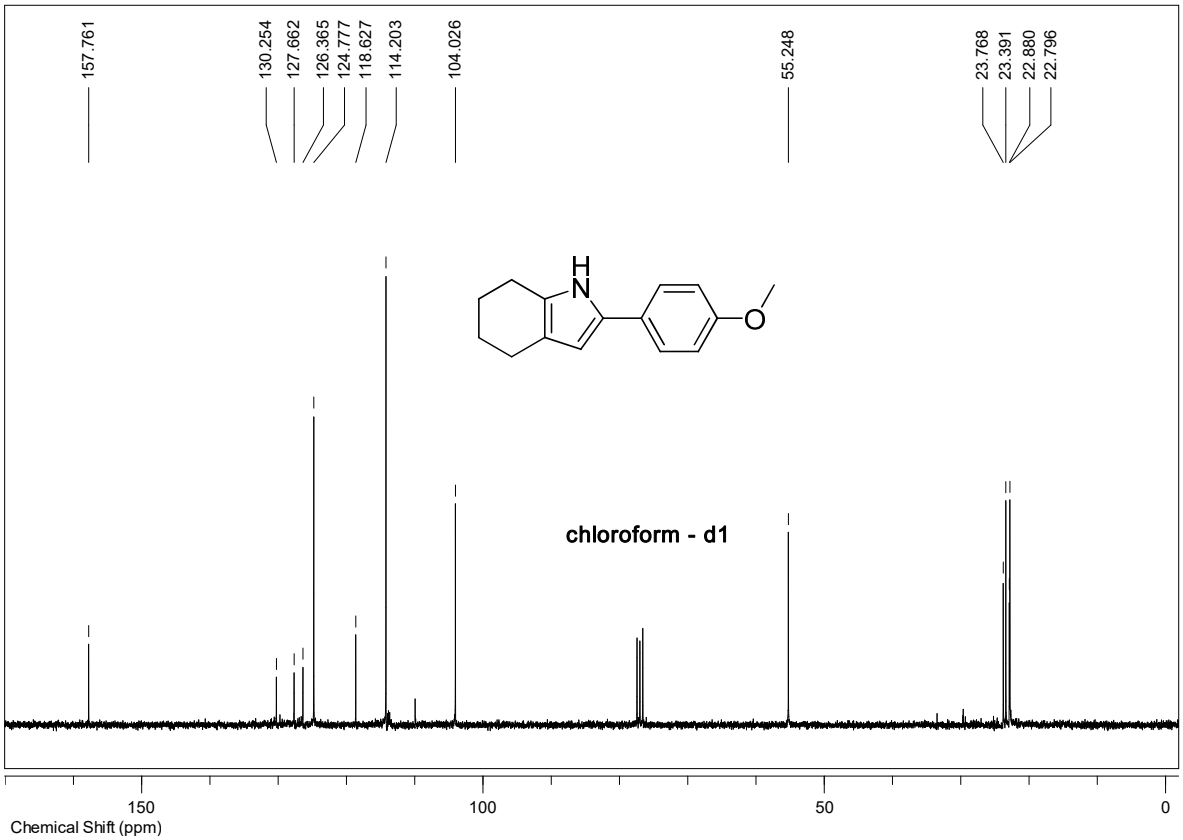
4a:


8.331
7.691
7.629
7.479
7.400
7.358
7.305
7.234
7.106
6.844
6.819
chloroform - d1
1.00
3.12
3.09
1.16
2.17
1.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
Chemical Shift (ppm)

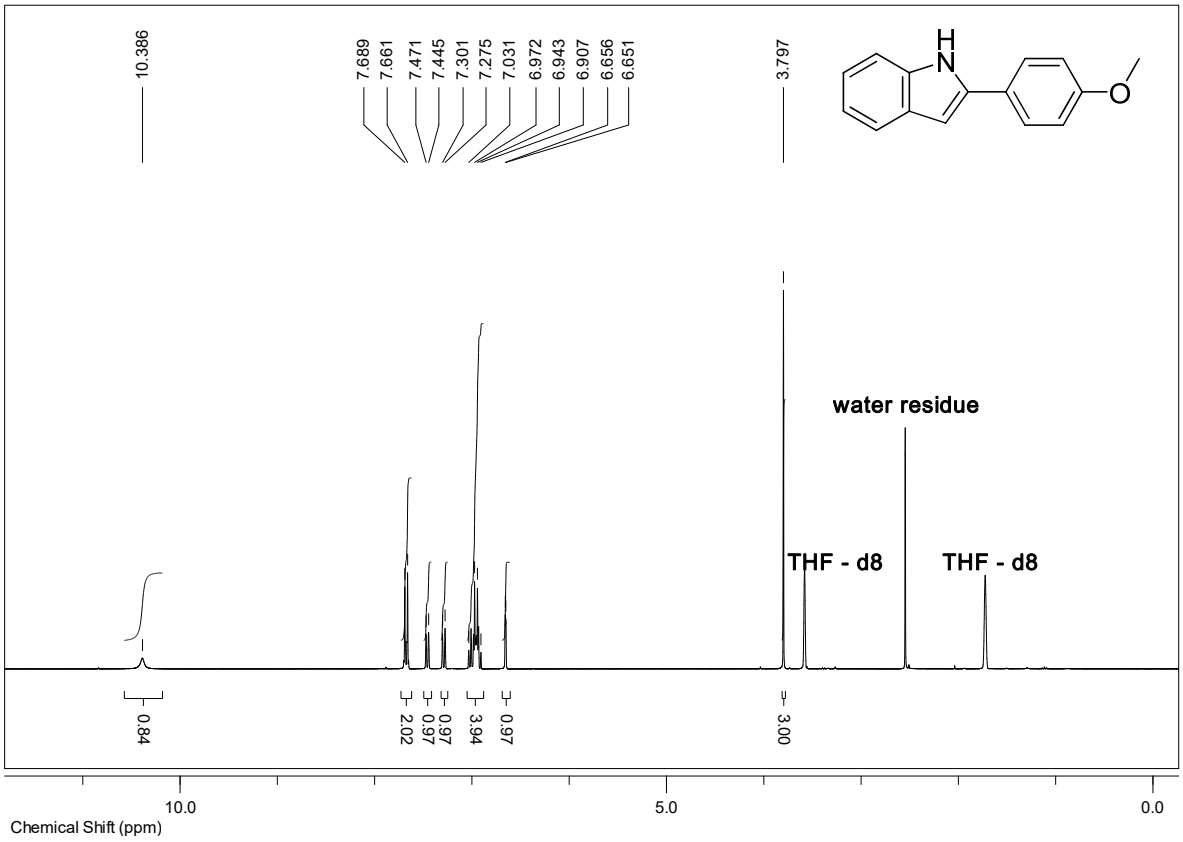

132.351
129.240
129.012
127.699
125.136
122.344
120.650
120.254
110.858
99.979
chloroform - d1
150
100
50
0
Chemical Shift (ppm)

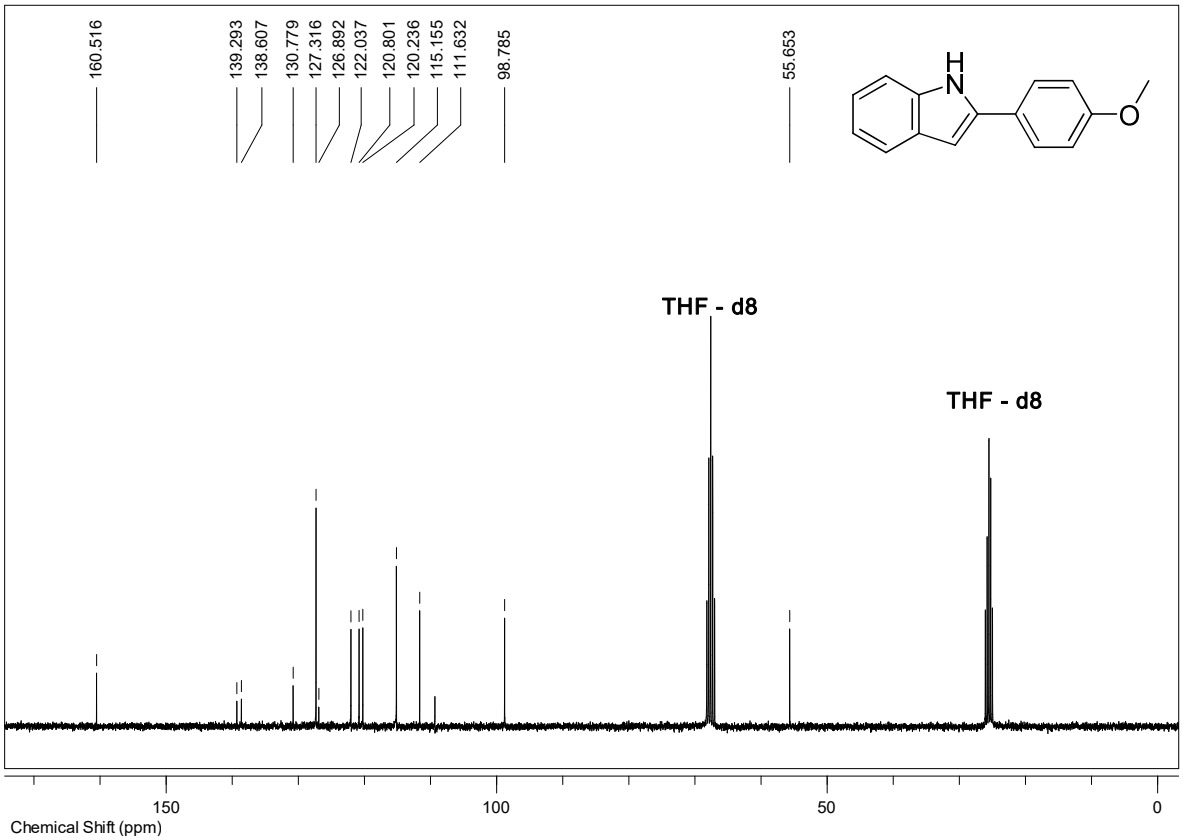
3b:


7.893
7.379
7.350
6.916
6.886
6.185
6.177
3.828
2.658
2.619
2.578
2.542
1.906
1.756
chloroform - d1
0.94
2.00
2.15
0.93
3.07
2.09
2.03
4.25
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Chemical Shift (ppm)

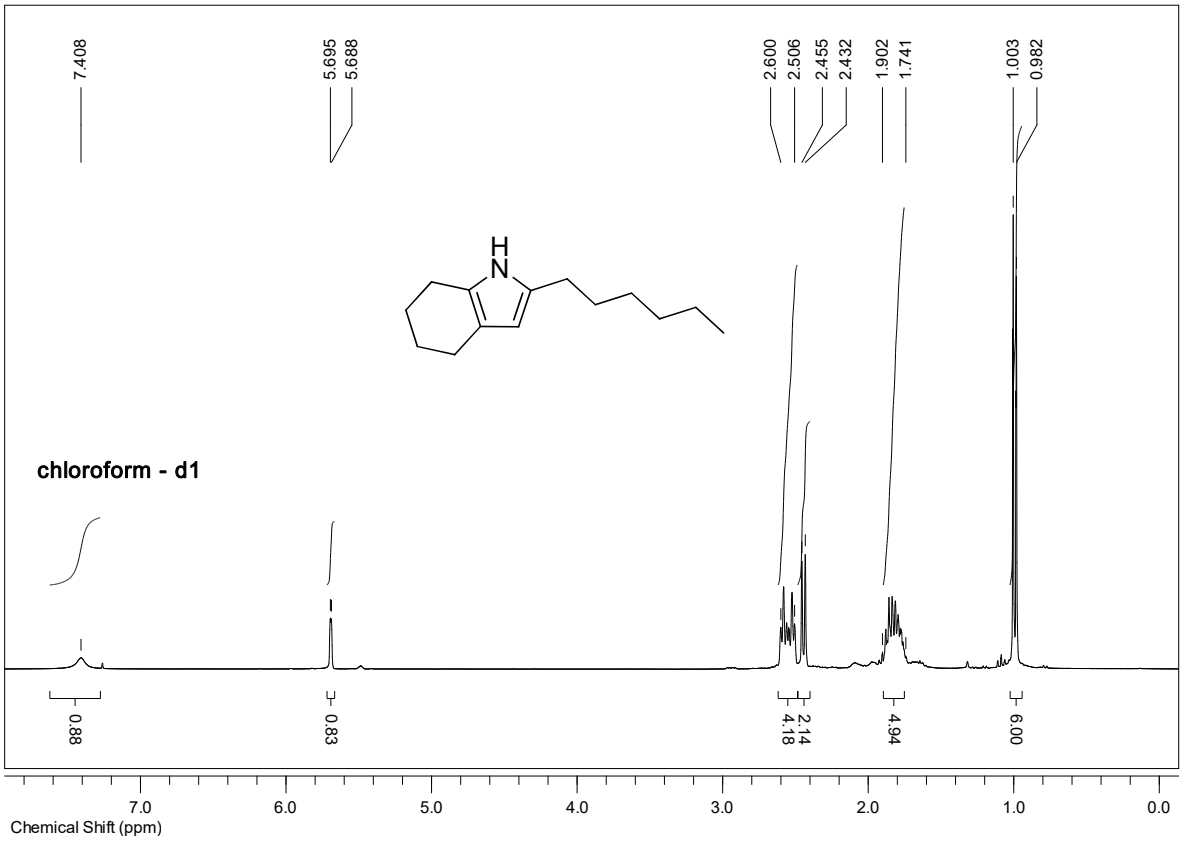

157.761
130.254
127.662
126.365
124.777
118.627
114.203
104.026
55.248
23.768
23.391
22.880
22.796
chloroform - d1
150
100
50
0
Chemical Shift (ppm)

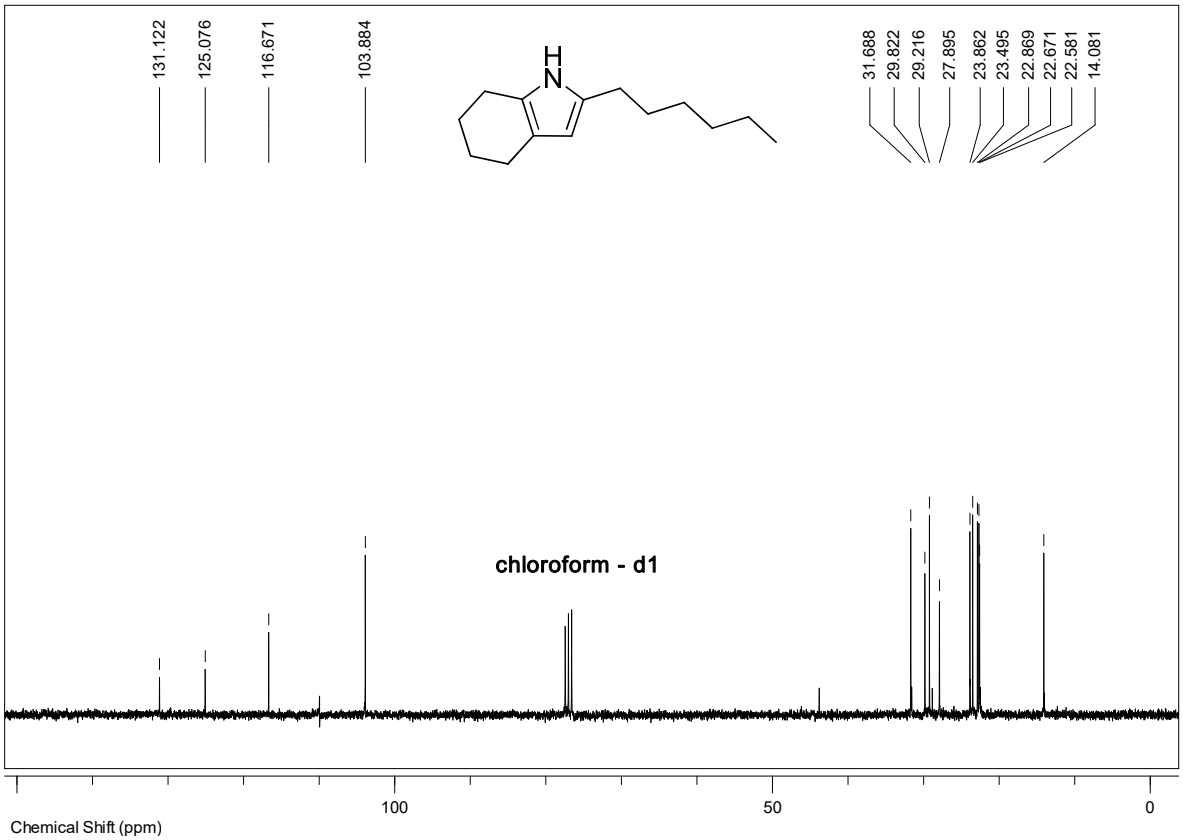
4b:


10.386
7.689
7.661
7.471
7.445
7.301
7.275
7.031
6.972
6.943
6.907
6.656
6.651
3.797
water residue
THF - d8
THF - d8
0.84
2.02
0.97
0.97
3.94
0.97
3.00
10.0
5.0
0.0
Chemical Shift (ppm)

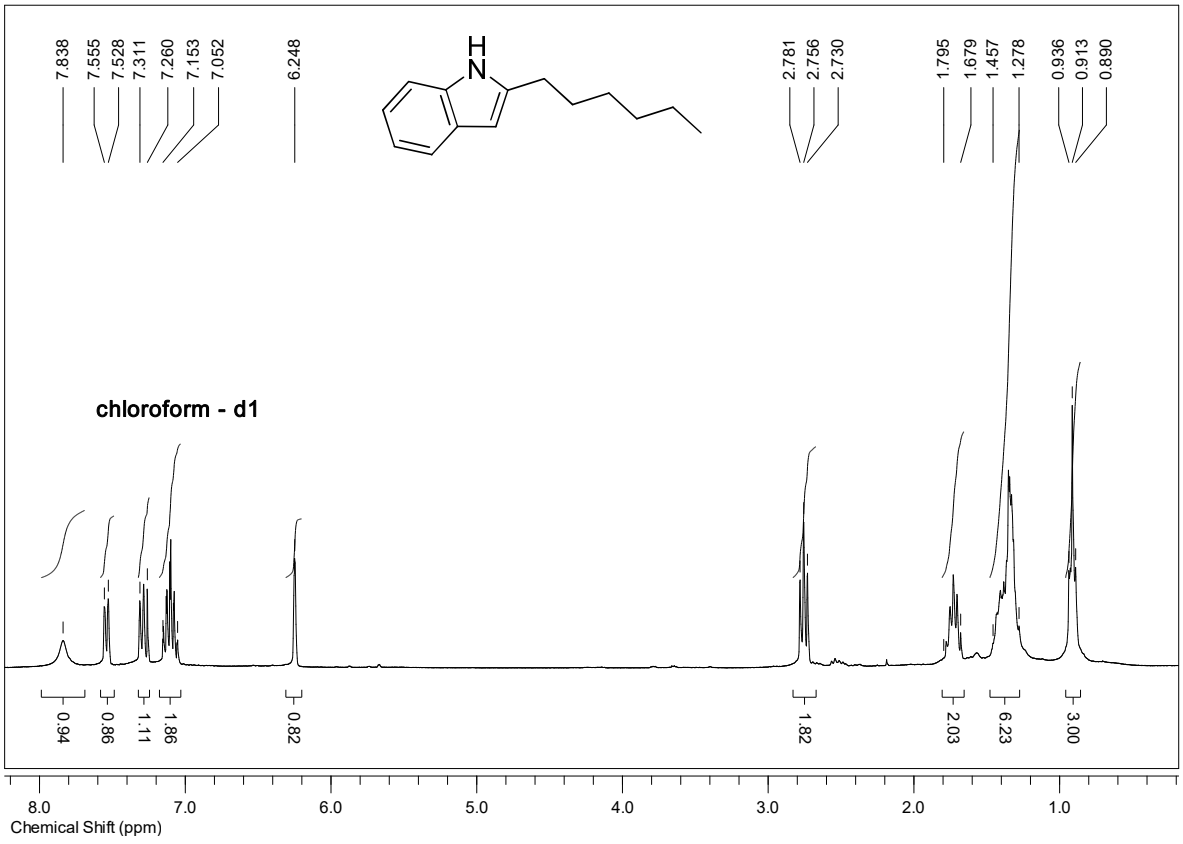

160.516
139.293
138.607
130.779
127.316
126.892
122.037
120.801
120.236
115.155
111.632
98.785
55.653
THF - d8
THF - d8
150
100
50
0
Chemical Shift (ppm)

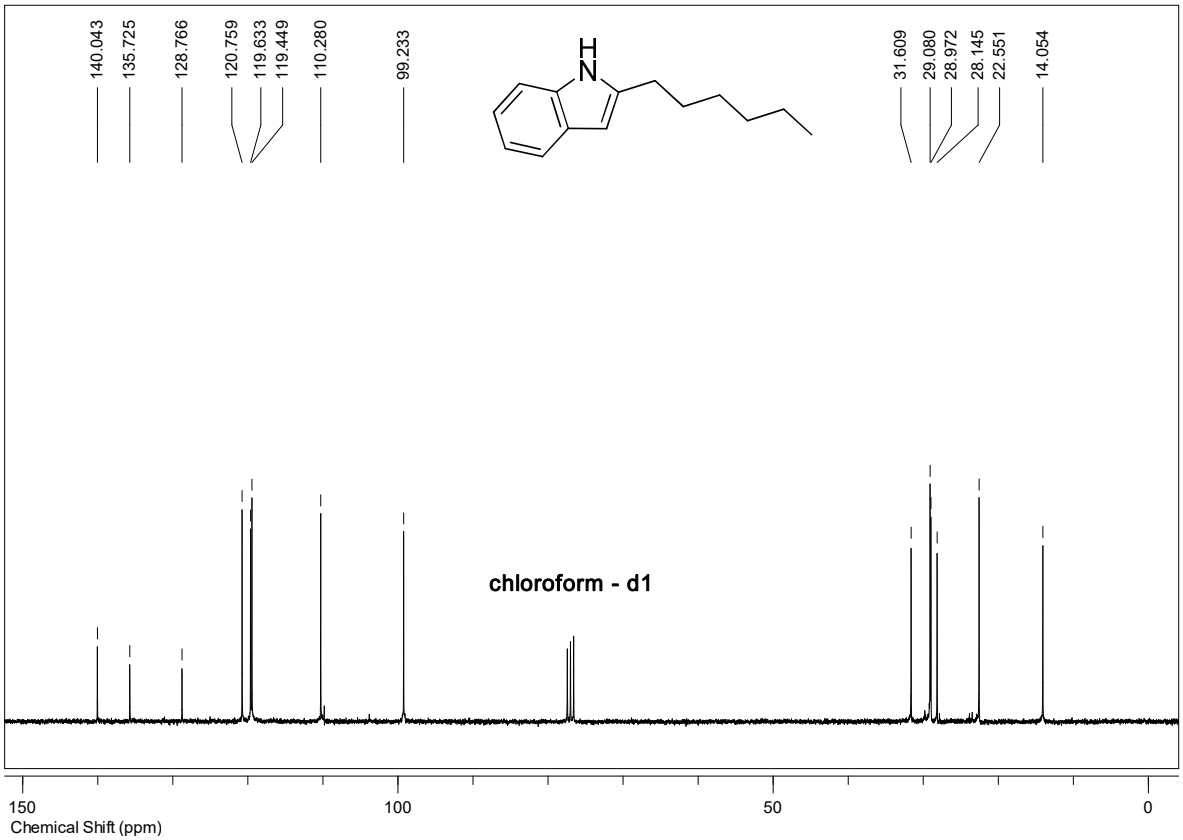
3c:


7.408
5.695
5.688
2.600
2.506
2.455
2.432
1.902
1.741
1.003
0.982
chloroform - d1
0.88
0.83
4.18
2.14
4.94
6.00
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Chemical Shift (ppm)

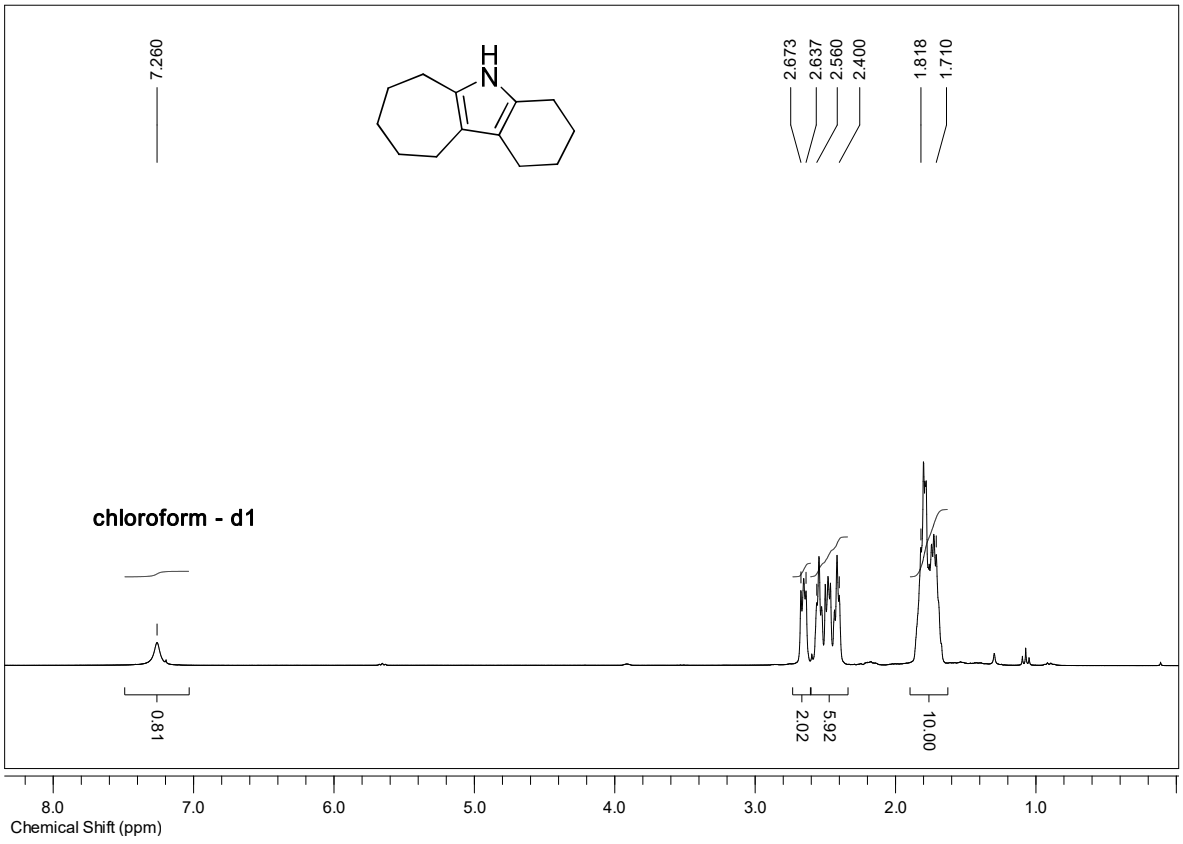

131.122
125.076
116.671
103.884
31.688
29.822
29.216
27.895
23.862
23.495
22.869
22.671
22.581
14.081
chloroform - d1
100
50
0
Chemical Shift (ppm)

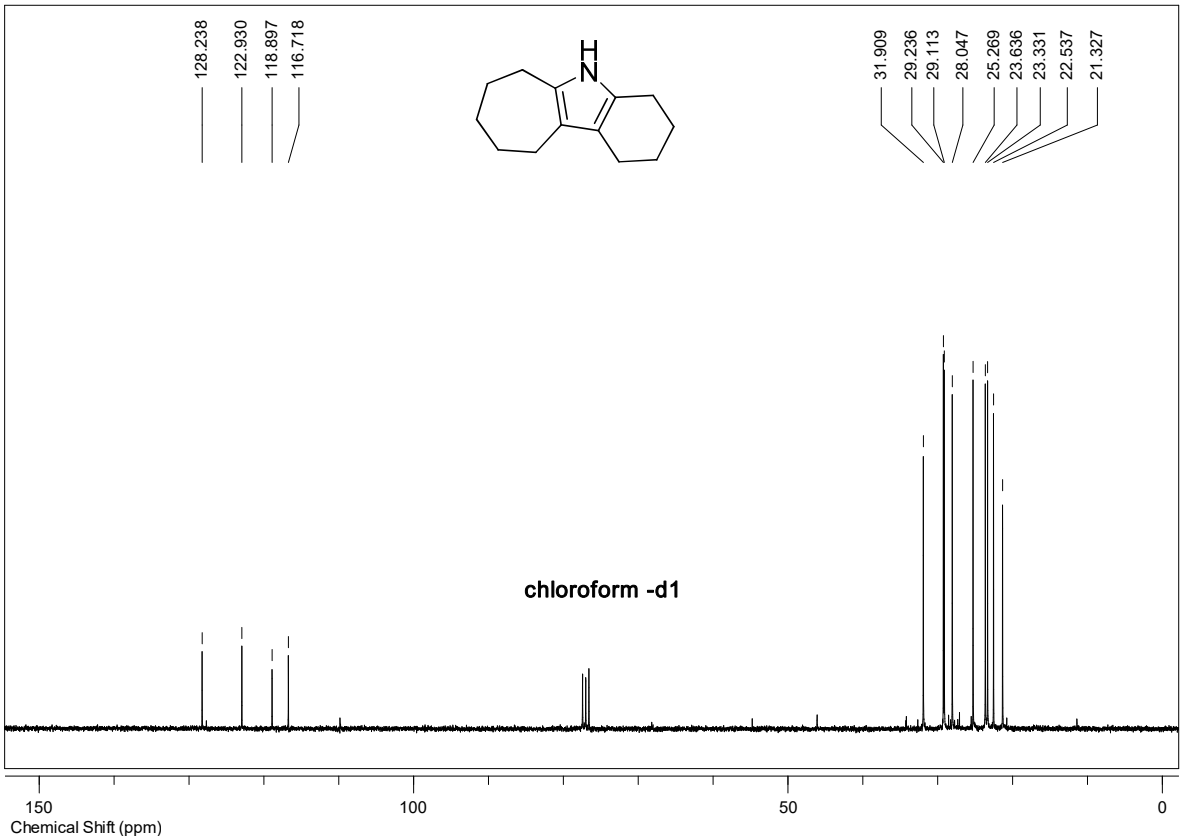
4c:


7.838
7.555
7.528
7.311
7.260
7.153
7.052
6.248
2.781
2.756
2.730
1.795
1.679
1.457
1.278
0.936
0.913
0.890
chloroform - d1
0.94
0.86
1.11
1.86
0.82
1.82
2.03
6.23
3.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Chemical Shift (ppm)

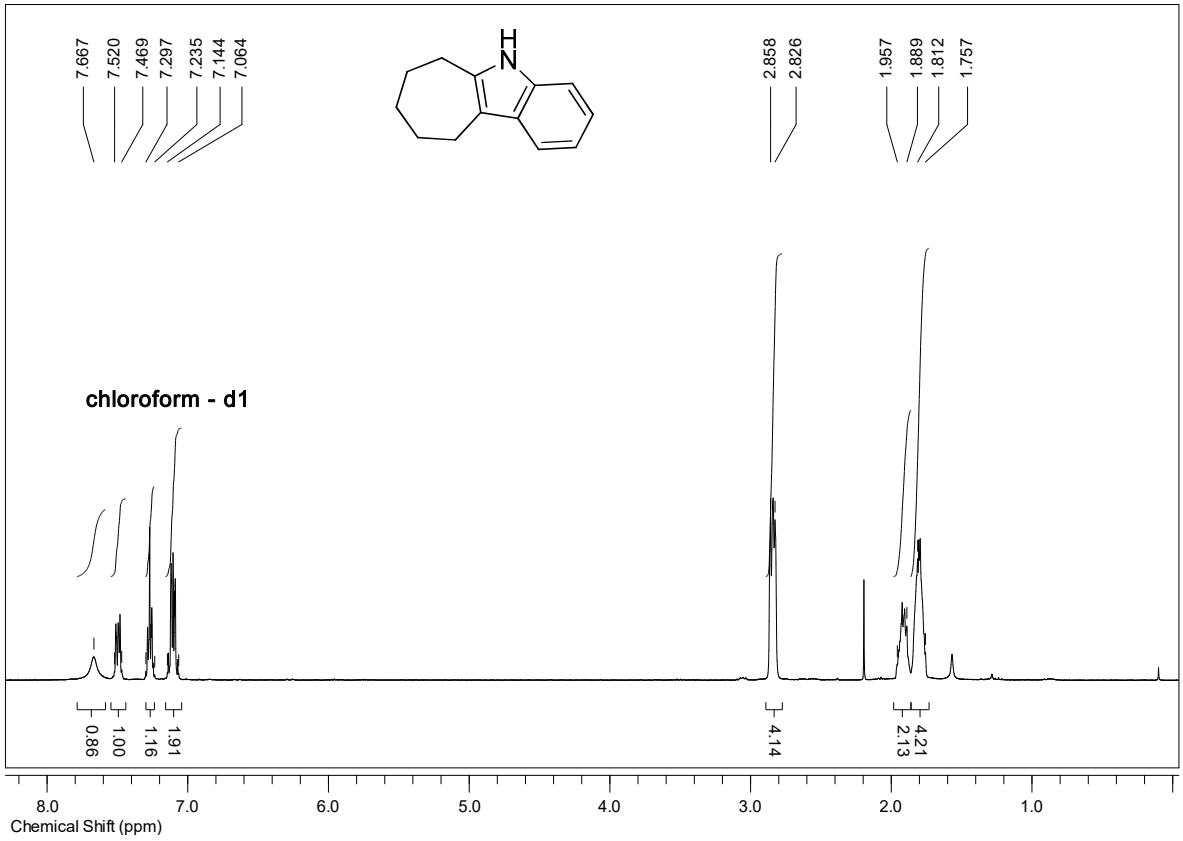

140.043
135.725
128.766
120.759
119.633
119.449
110.280
99.233
31.609
29.080
28.972
28.145
22.551
14.054
chloroform - d1
150
100
50
0
Chemical Shift (ppm)

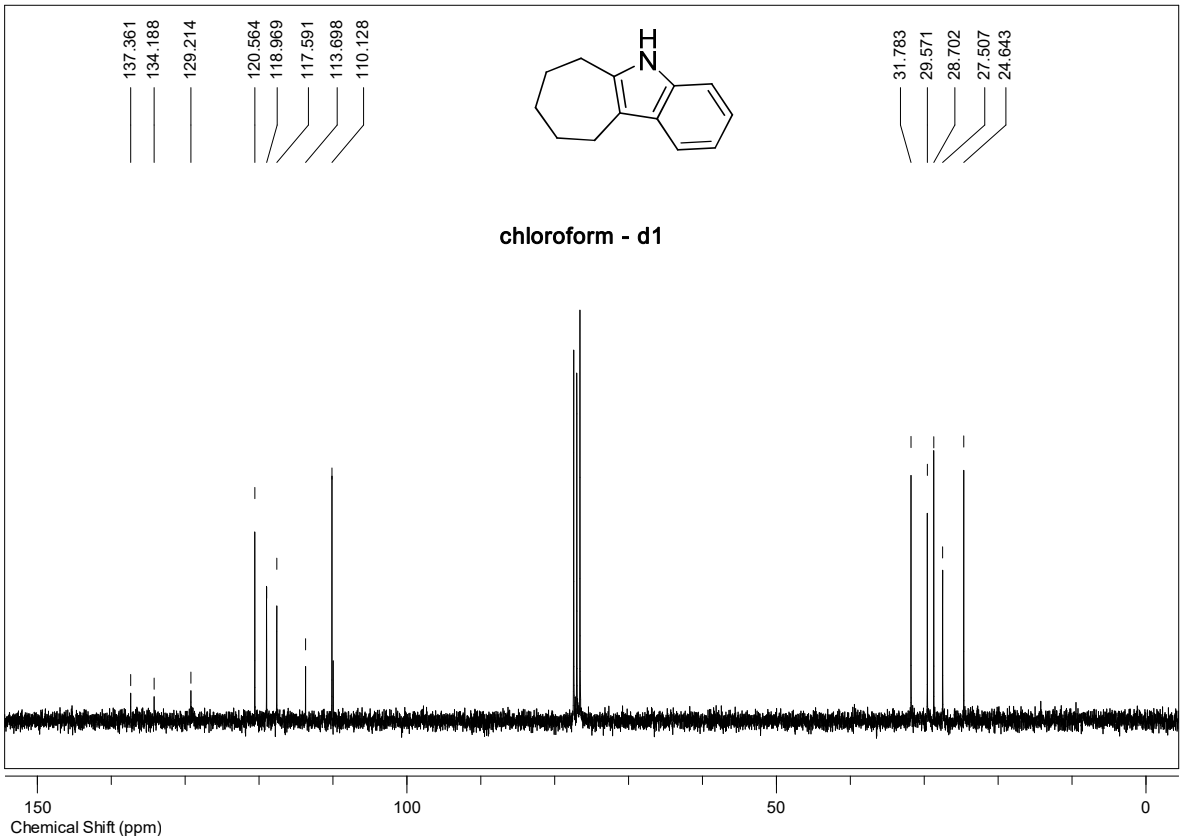
3d:


7.260
H
N
2.673
2.637
2.560
2.400
1.818
1.710
chloroform - d1
0.81
2.02
5.92
10.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Chemical Shift (ppm)

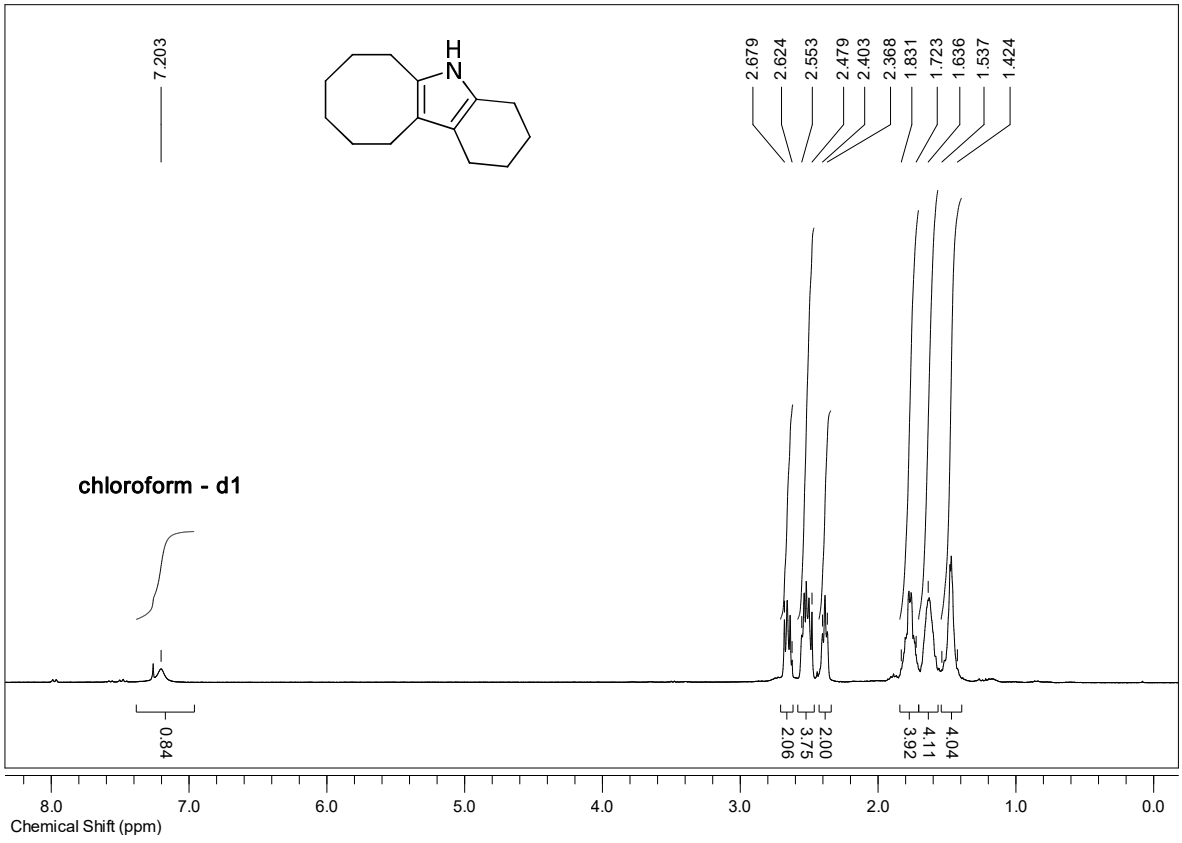

128.238
122.930
118.897
116.718
H
N
31.909
29.236
29.113
28.047
25.269
23.636
23.331
22.537
21.327
chloroform -d1
150
100
50
0
Chemical Shift (ppm)

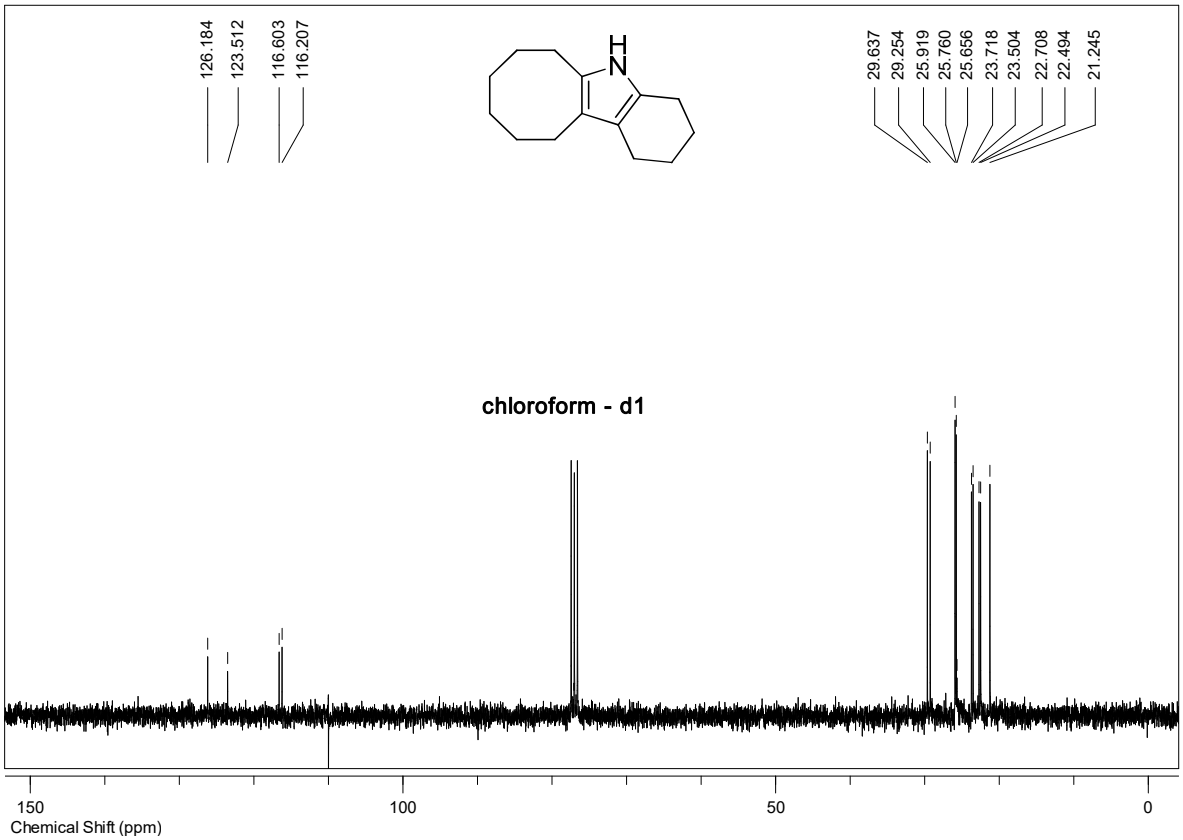
4d:


7.667
7.520
7.469
7.297
7.235
7.144
7.064
2.858
2.826
1.957
1.889
1.812
1.757
chloroform - d1
0.86
1.00
1.16
1.91
4.14
2.13
4.21
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Chemical Shift (ppm)

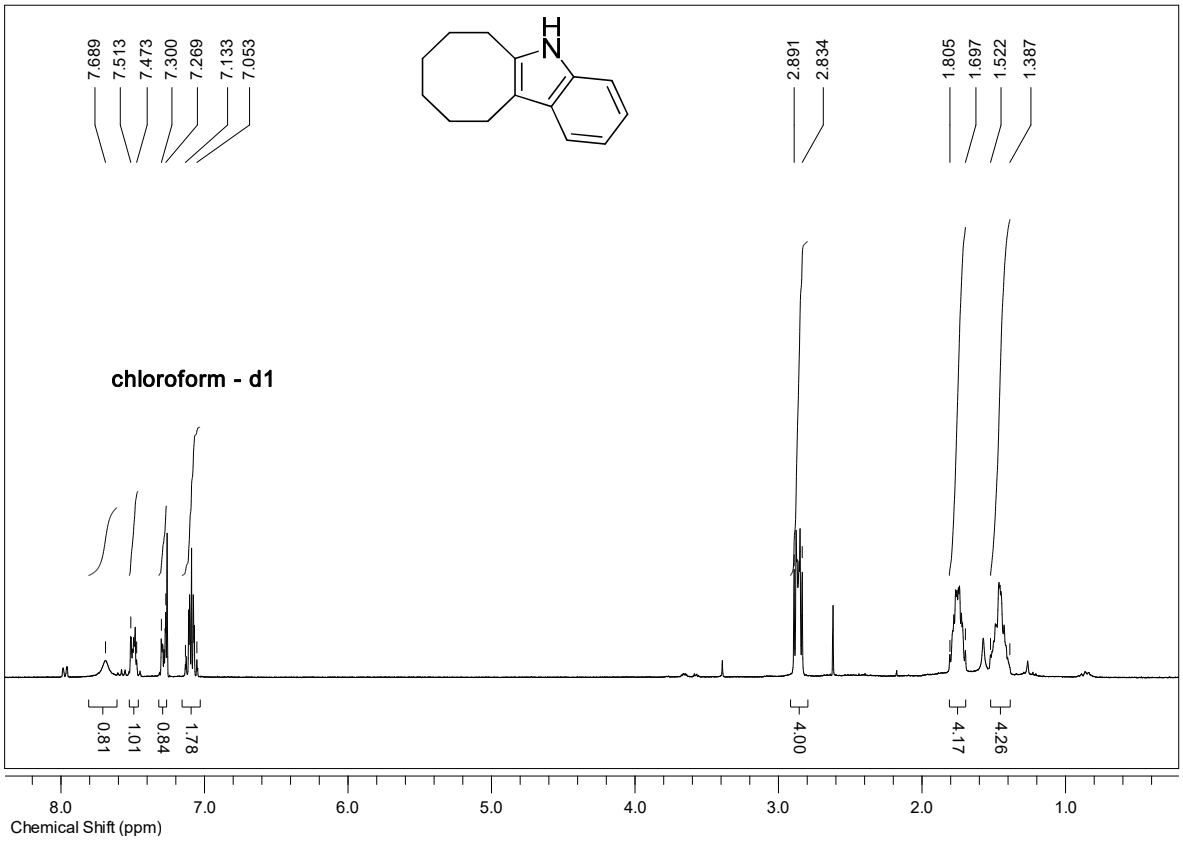

137.361
134.188
129.214
120.564
118.969
117.591
113.698
110.128
31.783
29.571
28.702
27.507
24.643
chloroform - d1
150
100
50
0
Chemical Shift (ppm)

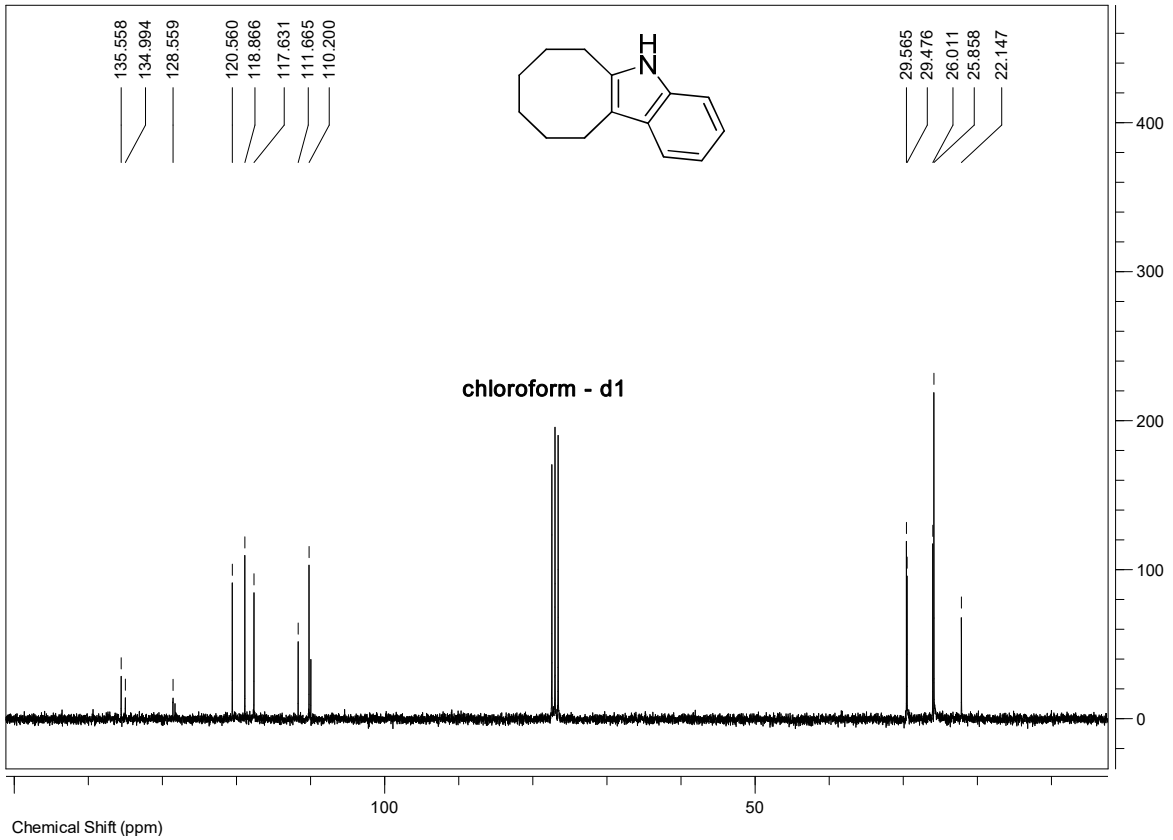
3e:


7.203
2.679
2.624
2.553
2.479
2.403
2.368
1.831
1.723
1.636
1.537
1.424
chloroform - d1
0.84
2.06
3.75
2.00
3.92
4.11
4.04
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Chemical Shift (ppm)


126.184
123.512
116.603
116.207
29.637
29.254
25.919
25.760
25.656
23.718
23.504
22.708
22.494
21.245
chloroform - d1
150
100
50
0
Chemical Shift (ppm)

4e:


7.689
7.513
7.473
7.300
7.269
7.133
7.053
2.891
2.834
1.805
1.697
1.522
1.387
chloroform - d1
0.81
1.01
0.84
1.78
4.00
4.17
4.29
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
Chemical Shift (ppm)


135.558
134.994
128.559
120.560
118.866
117.631
111.665
110.200
29.565
29.476
26.011
25.858
22.147
chloroform - d1
400
300
200
100
0
100
50
Chemical Shift (ppm)

References

(1) Michlik, S.; Kempe, R. A Sustainable Catalytic Pyrrole Synthesis. *Nat. Chem.* **2013**, *5* (2), 140–144.

(2) Forberg, D.; Schwob, T.; Kempe, R. Catalytic Condensation for the Formation of Polycyclic Heteroaromatic Compounds. *Nat. Commun.* **2018**, *9* (1), 1751.