

Supporting Information

A green process for the Fischer indole synthesis catalyzed by novel SO₃H-functionalized ionic liquids in water

Dan-Qian Xu, Jian Wu, Shu-Ping Luo, Ji-Xu Zhang, Jia-Yi Wu, Xiao-Hua Du,
Zhen-Yuan Xu

State Key Laboratory Breeding Base of Green Chemistry-Synthesis Technology,
Zhejiang University of Technology, Hangzhou 310032, P. R. China

General remarks

NMR data were obtained on Bruker AVANCE III 500MHz for ¹H at 500 MHz and for ¹³C at 125 MHz with TMS as the internal standard. MS (EI) data were determined on an Agilent 6890N GC system with a 5973N mass selective detector. HRMS data were measured on an Agilent 6120 LC/TOF-MS with ESI source or Waters Premier GC/ TOF-MS with EI source.

UV-VIS acidity evaluation

Tested ethanol solutions were prepared from dried ethanol, 3-nitroaniline and ionic liquids, or 98% H₂SO₄, 85% H₃PO₄ and 37% HCl. All the spectra were recorded on a SHIMADZU UV-2550 spectrophotometer at room temperature. The results are shown Figure 1-3.

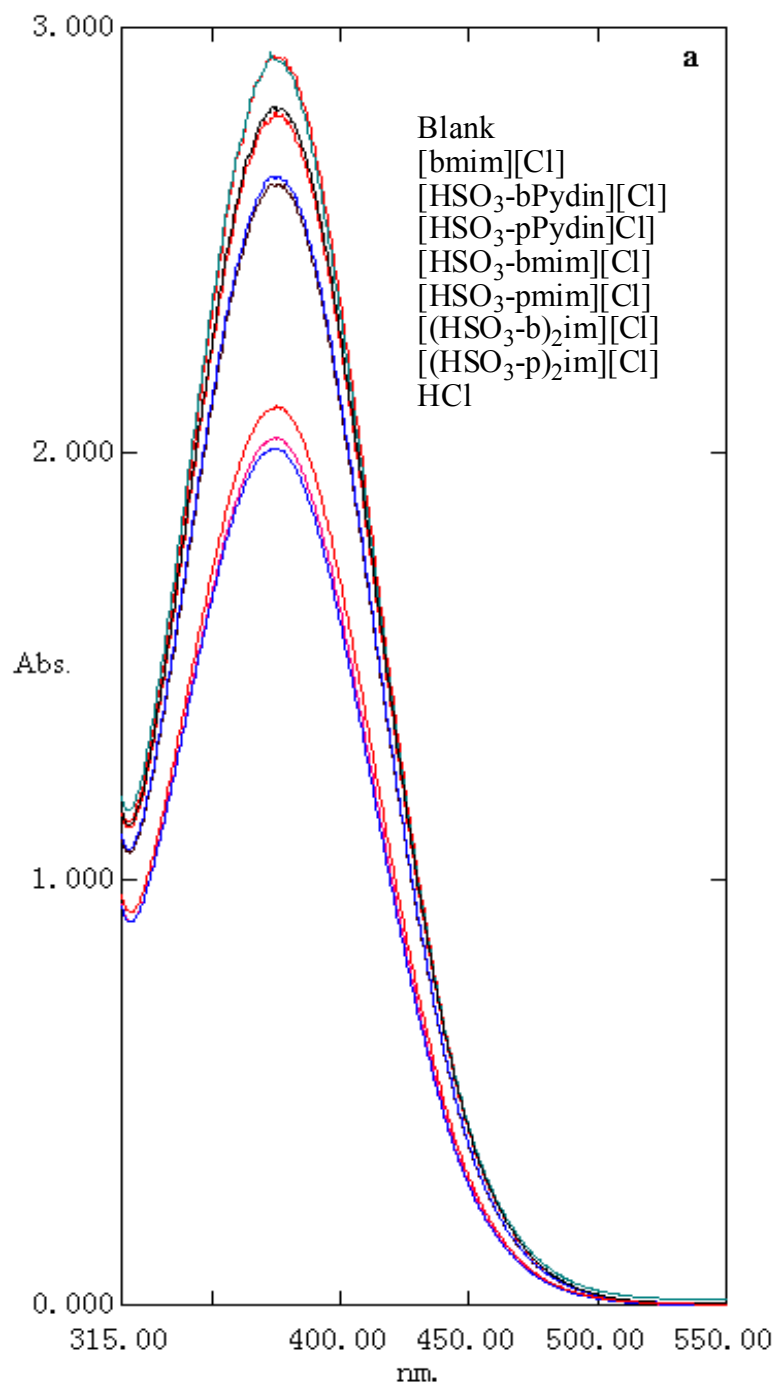


Fig. 1 Absorption spectra of 3-nitroaniline for [Cl]-type acids in ethanol

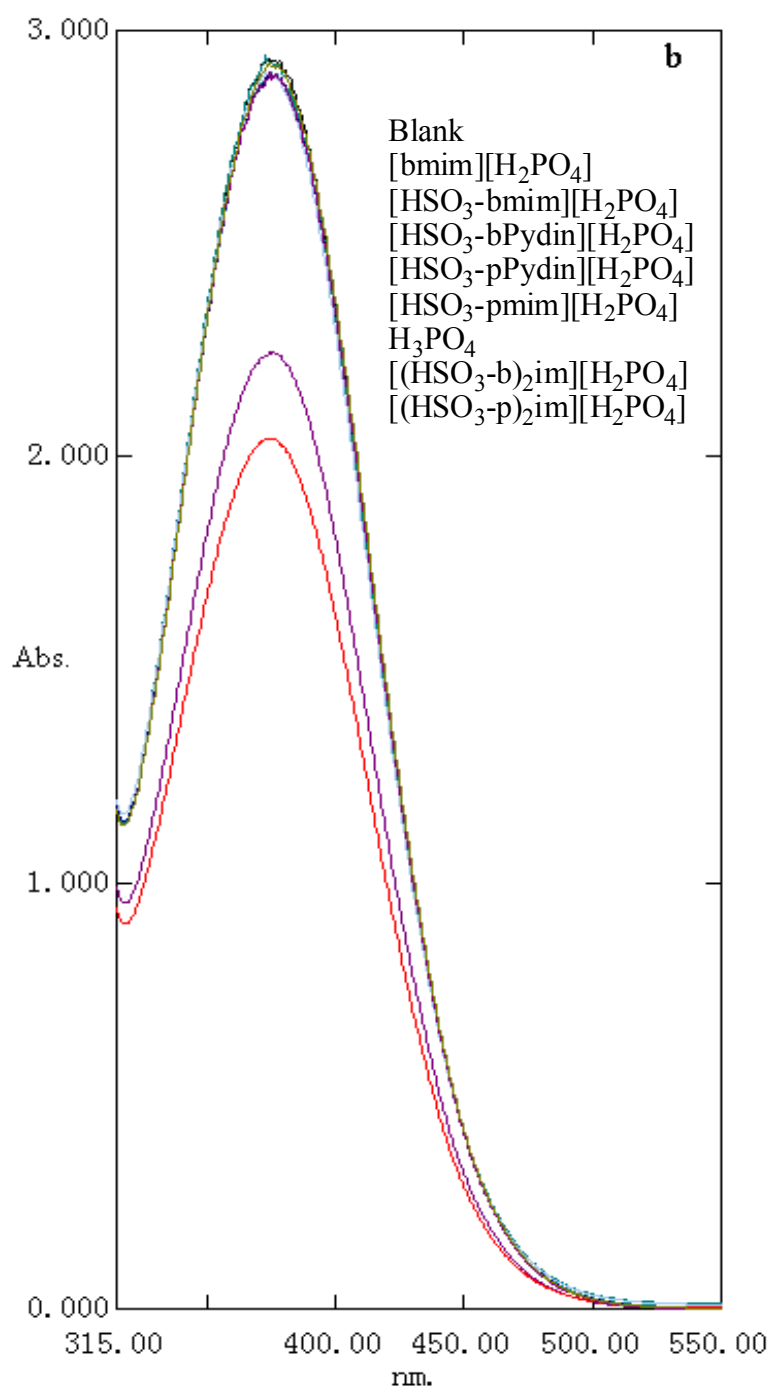


Fig. 2 Absorption spectra of 3-nitroaniline for [H₂PO₄]-type acids in ethanol

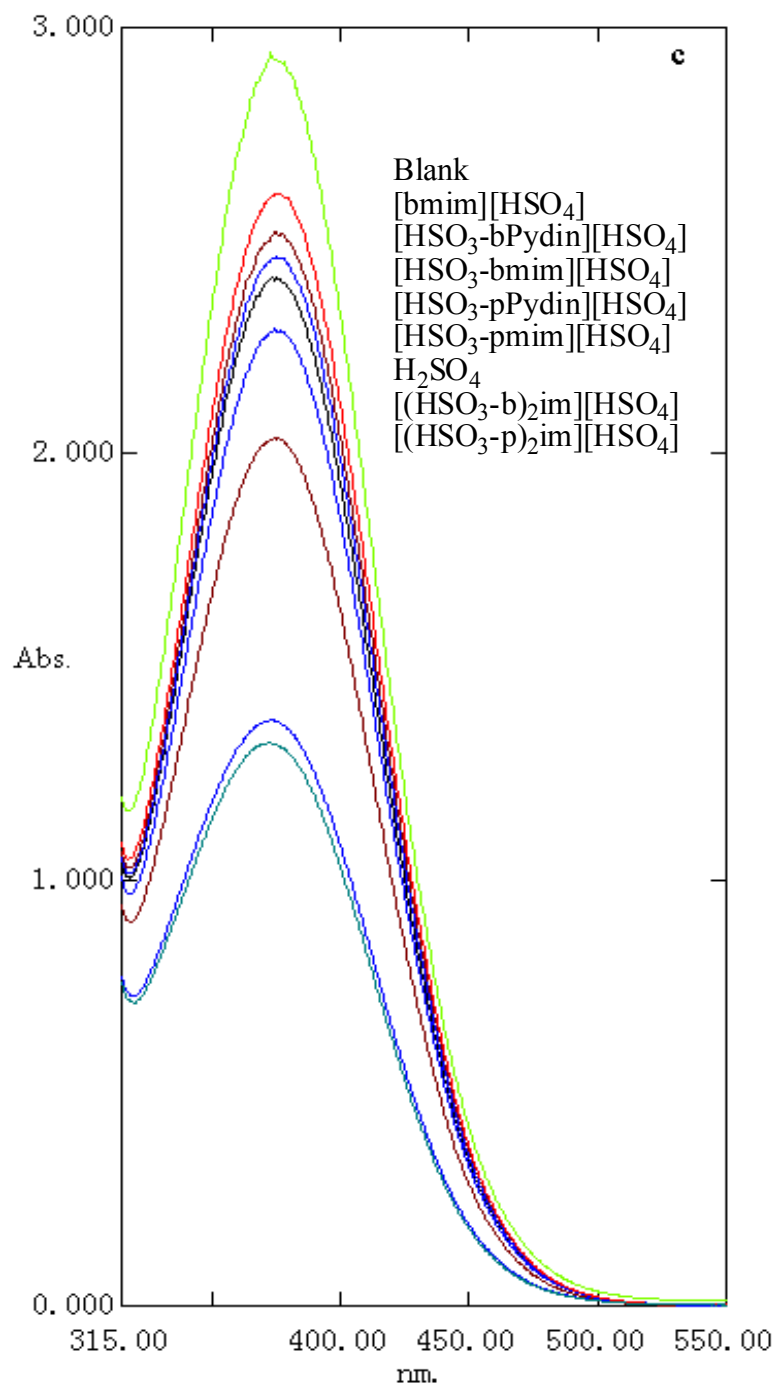


Fig. 3 Absorption spectra of 3-nitroaniline for [HSO₄]-type acids in ethanol

General procedure for the one-pot Fischer indole synthesis

Cyclohexanone (0.49 g, 5.0 mmol) was mixed with the catalyst in water (15 mL), and phenylhydrazine (0.54 g, 5.0 mmol) was added. The mixture was then stirred at 80 °C for about 0.5 h. Reaction progress was monitored by GC-MS. After completion, the reaction mixture was cooled to room temperature, and 1,2,3,4-tetrahydrocarbazole

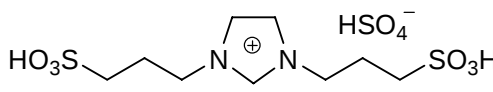
was obtained by filtration and drying without further purification.

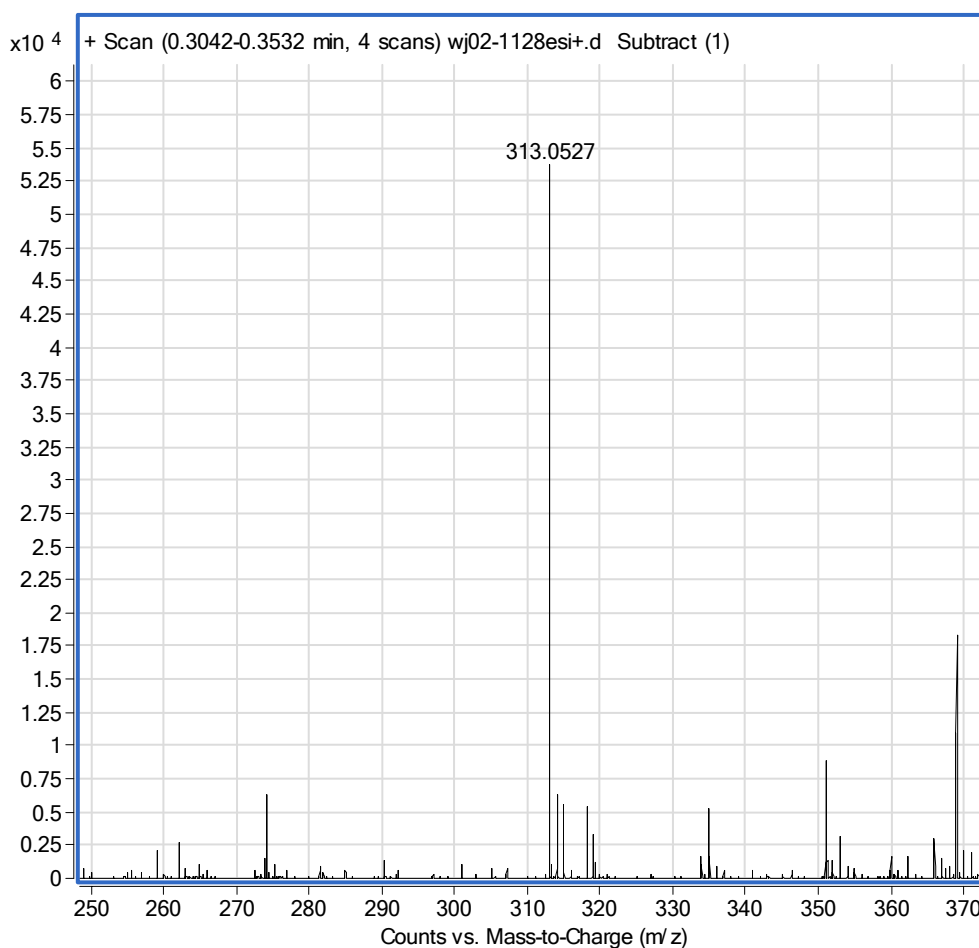
Table 1 The Fischer indole synthesis of cyclohexanone with phenylhydrazine in water ^a

Entry	Acidic catalyst	Time / h	Conversion (%)	Isolated yield (%)
1	Dowex-50 acid resin	10	32	--
2	p-TsOH	2	90	80
3 ^b	p-TsOH	3	60	38
4 ^b	HCl	3	92	77
5	H ₃ PO ₄	3	83	70
6 ^b	H ₃ PO ₄	8	55	34
7 ^b	H ₂ SO ₄	1	98	84
8 ^c	H ₂ SO ₄	10	65	42
9	[bmim][Cl]	10	30	--
10	[bmim][H ₂ PO ₄]	8	68	40
11	[bmim][HSO ₄]	5	80	68
12	[HSO ₃ -pmim][Cl]	10	60	30
13	[HSO ₃ -pmim][H ₂ PO ₄]	8	80	60
14	[HSO ₃ -pmim][HSO ₄]	3	89	77
15	[HSO ₃ -bmim][Cl]	8	55	30
16	[HSO ₃ -bmim][H ₂ PO ₄]	8	75	50
17	[HSO ₃ -bmim][HSO ₄]	3	86	74
18	[HSO ₃ -pPydin][Cl]	8	59	30
19	[HSO ₃ -pPydin][H ₂ PO ₄]	8	75	50
20	[HSO ₃ -pPydin][HSO ₄]	3	85	73
21	[HSO ₃ -bPydin][Cl]	8	54	30
22	[HSO ₃ -bPydin][H ₂ PO ₄]	8	72	53
23	[HSO ₃ -bPydin][HSO ₄]	3	83	71
24 ^b	[(HSO ₃ -p) ₂ im][Cl]	7	86	75
25 ^b	[(HSO ₃ -p) ₂ im][H ₂ PO ₄]	4	97	86
26 ^b	[(HSO₃-p)₂im][HSO₄]	0.5	>99	93
27 ^b	[(HSO ₃ -b) ₂ im][Cl]	7	84	72
28 ^b	[(HSO ₃ -b) ₂ im][H ₂ PO ₄]	4	98	83
29 ^b	[(HSO ₃ -b) ₂ im][HSO ₄]	0.5	>99	90
30 ^c	[(HSO ₃ -p) ₂ im][HSO ₄]	0.5	>99	90
31 ^d	[(HSO ₃ -p) ₂ im][HSO ₄]	6	55	30
32 ^e	[(HSO ₃ -p) ₂ im][HSO ₄]	12	>99	89
33 ^{b,f}	[(HSO ₃ -p) ₂ im][HSO ₄]	3	96	84

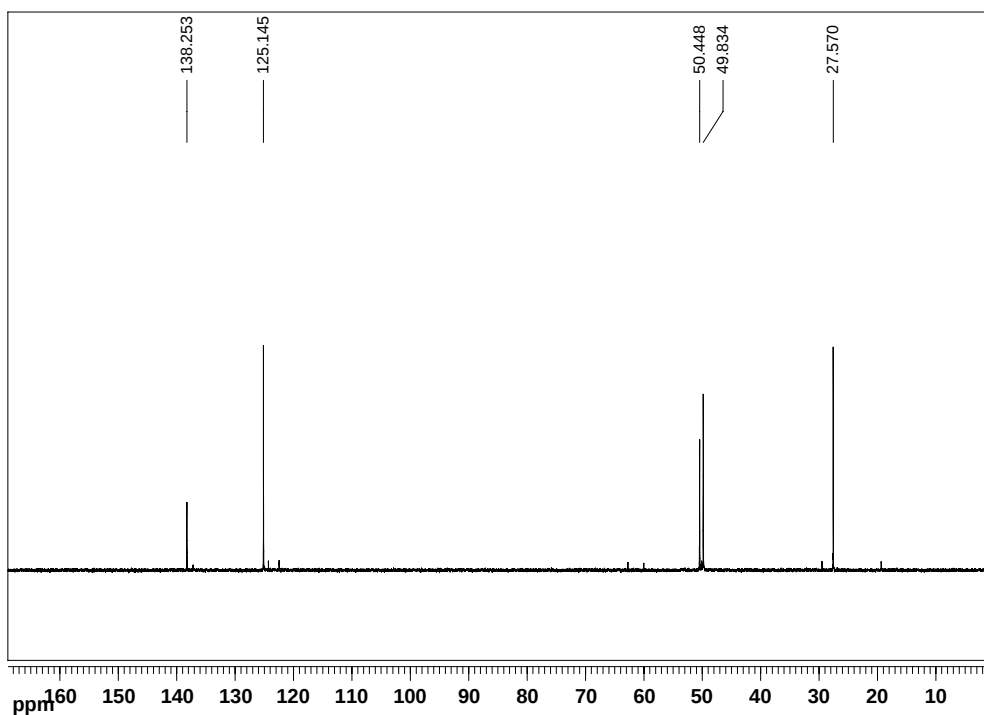
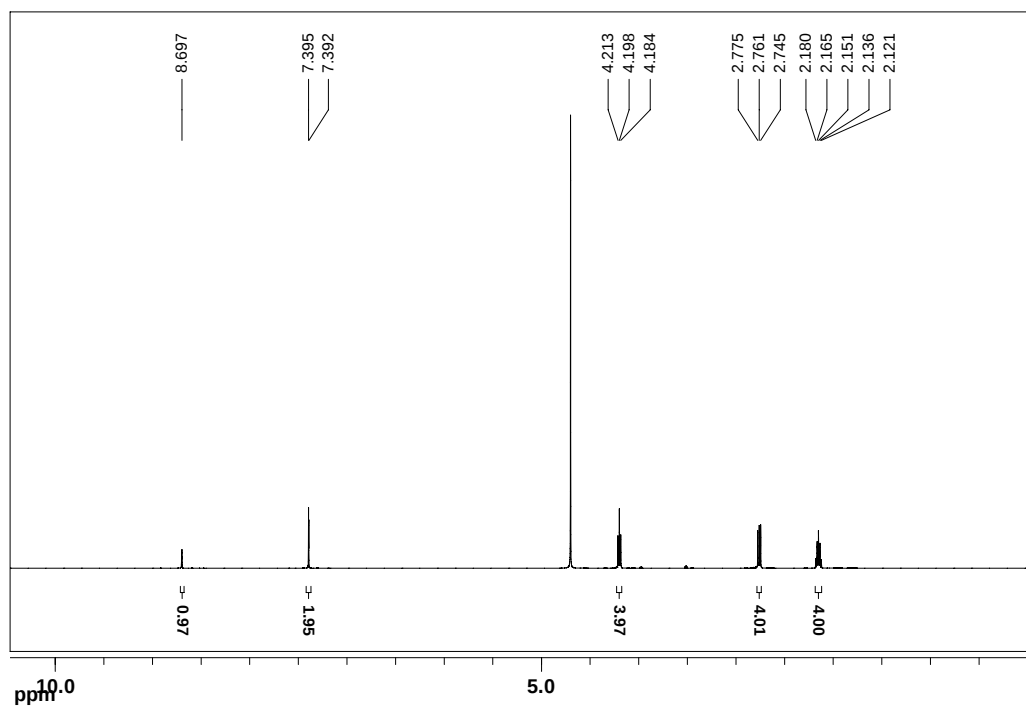
^a Reaction conditions: cyclohexanone (5 mmol), phenylhydrazine (5 mmol), acidic catalyst (5 mmol), water (15 mL). ^b The amount of catalyst: 2.5 mmol. ^c The amount of catalyst: 1.5 mmol. ^d The amount of catalyst: 1 mmol. ^e The reaction was carried out at room temperature. ^f 2.5 mmol NH₄OH was previously added into the reaction system.

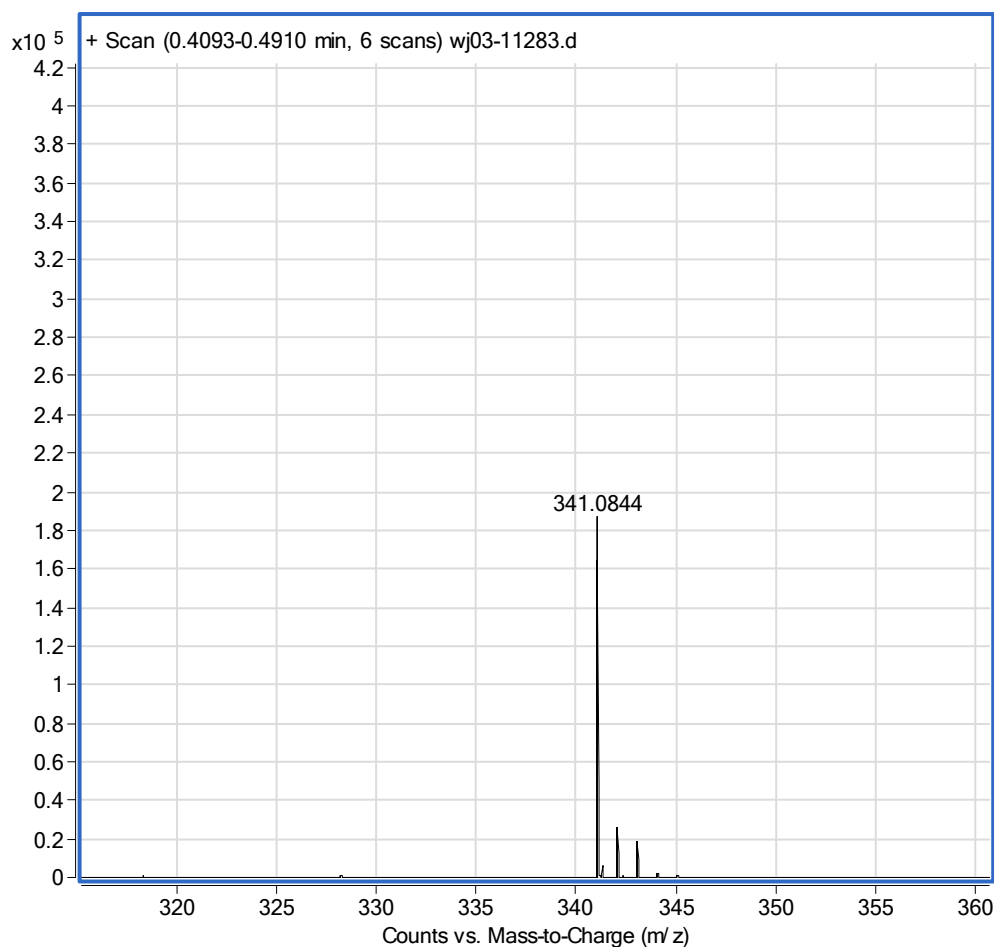
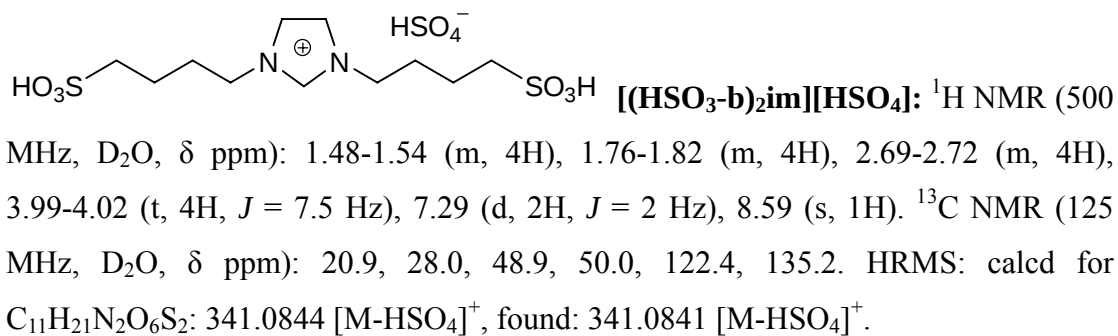
Spectra and data of typical SO₃H-functionalized ionic liquids


[(HSO₃-p)₂im][HSO₄]⁻: ¹H NMR (500 MHz, D₂O, δ ppm): δ 2.12-2.18 (m, 4H), 2.75-2.78 (t, 4H, *J* = 7.5 Hz), 4.18-4.21 (t, 4H, *J* = 7.5 Hz), 7.39-7.40 (d, 2H, *J* = 1.5 Hz), 8.70 (s, 1H). ¹³C NMR (125 MHz, D₂O, δ ppm): 27.6, 49.8, 50.4, 125.1, 138.3. HRMS: calcd for C₉H₁₇N₂O₆S₂: 313.0527 [M-HSO₄]⁺, found: 313.0528 [M-HSO₄]⁺.

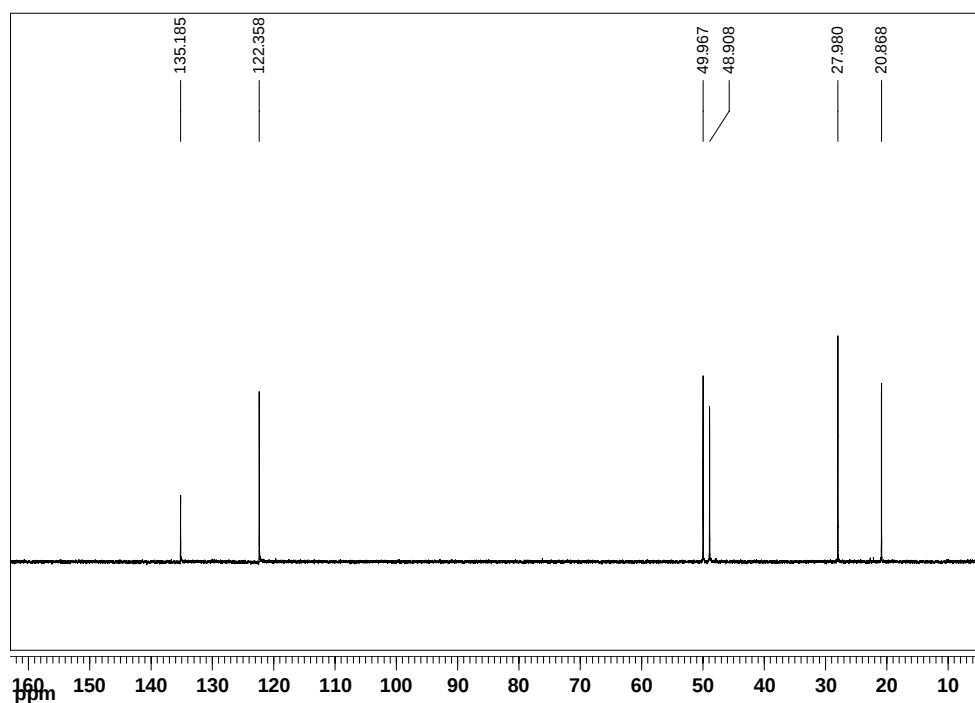
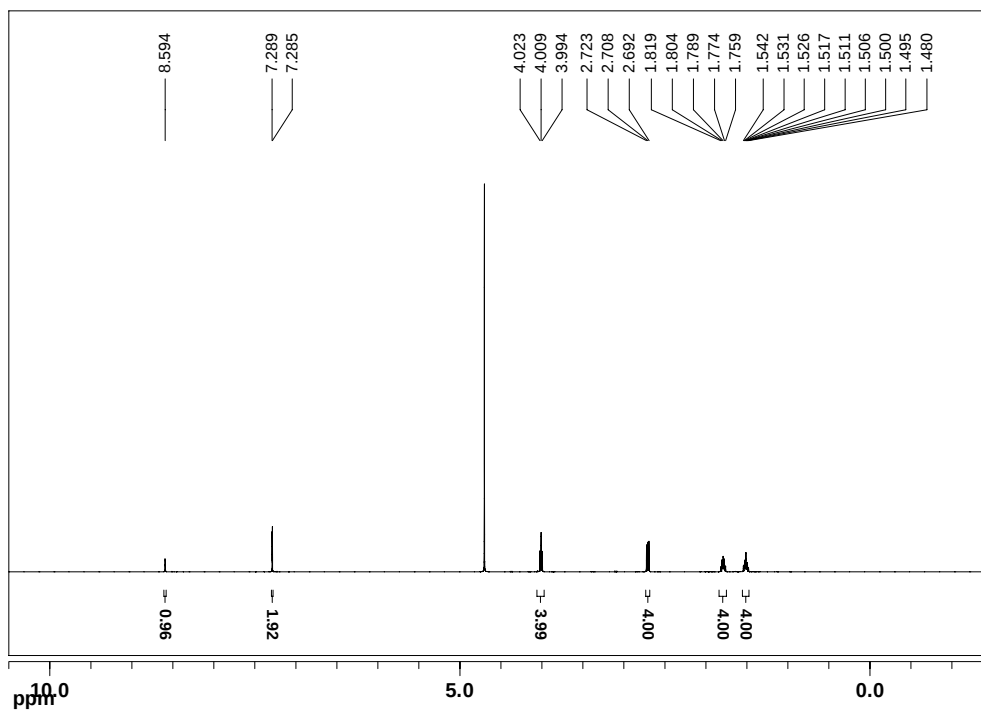


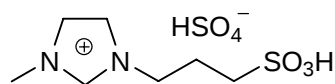
Formula (M)	Score	Mass	Calc Mass	Difference (ppm)	DBE
C ₉ H ₁₇ N ₂ O ₆ S ₂	100	313.0527	313.0528	0.33	2.5



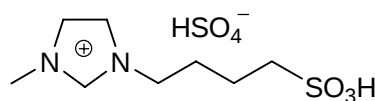
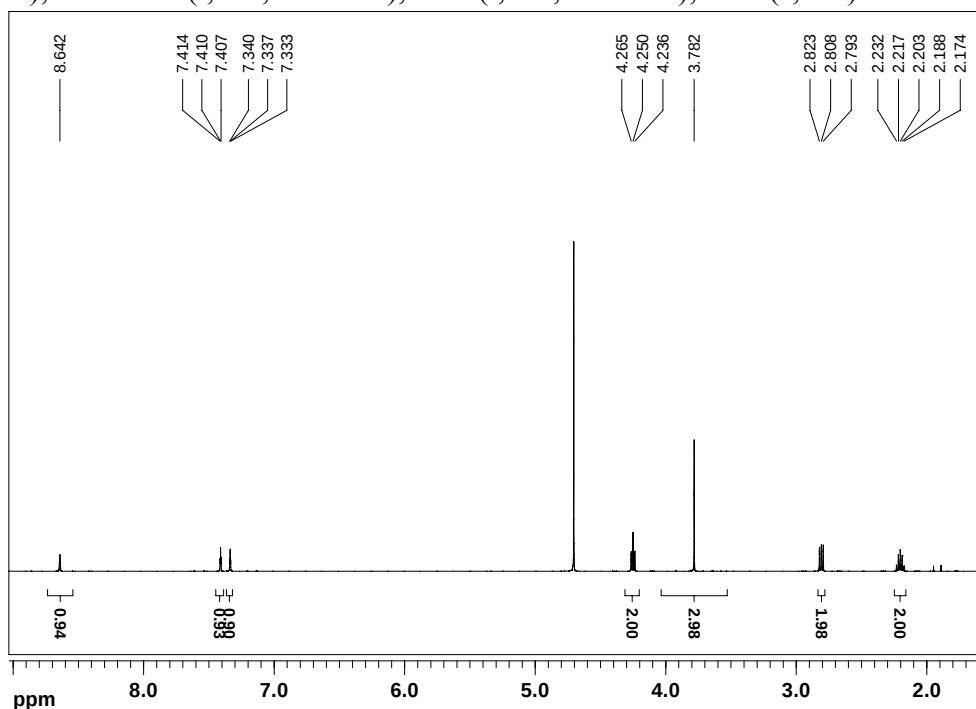


Formula (M)	Score	Mass	Calc Mass	Difference (ppm)	DBE
C ₁₁ H ₂₁ N ₂ O ₆ S ₂	100	341.0844	341.0841	-0.87	2.5

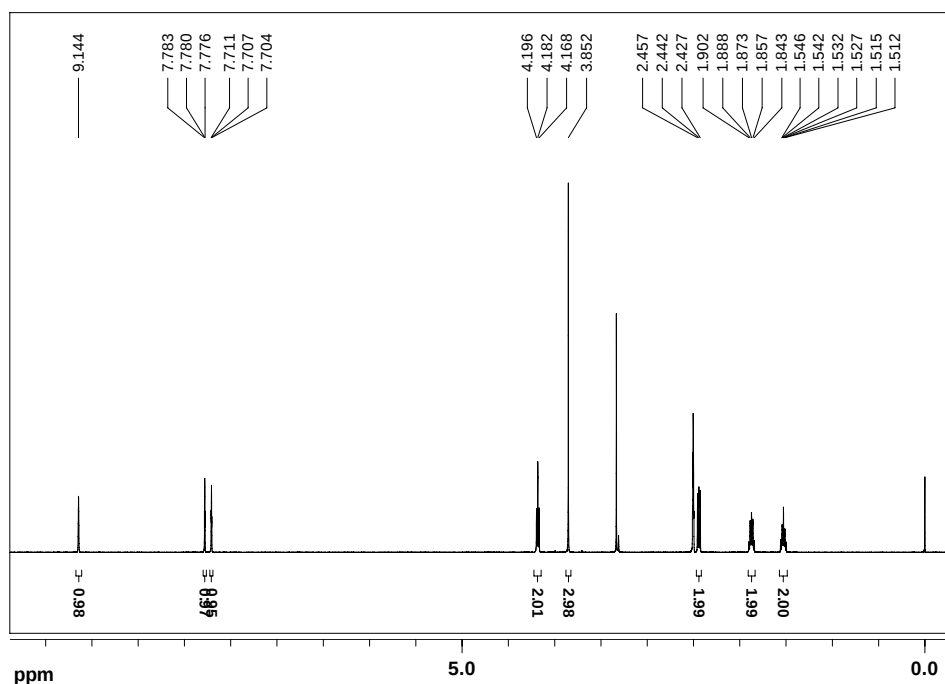




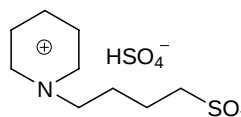
[HSO₃-pmim][HSO₄]: ¹H NMR (500 MHz, D₂O, δ ppm): 2.17-2.23 (m, 2H), 2.79-2.82 (t, 2H, *J* = 7.5 Hz), 3.78 (s, 3H), 4.24-4.27 (t, 2H, *J* = 7.5 Hz), 7.33-7.34 (t, 1H, *J* = 2 Hz), 7.41 (t, 1H, *J* = 2 Hz), 8.64 (s, 1H).



[HSO₃-bmim][HSO₄]: ¹H NMR (500 MHz, DMSO, δ ppm): 1.51-1.55 (m, 2H), 1.84-1.90 (m, 2H), 2.43-2.46 (t, 2H, *J* = 7.5 Hz), 3.85 (s, 3H), 4.17-4.20 (t, 2H, *J* = 7 Hz), 7.70-7.71 (t, 1H, *J* = 2 Hz), 7.78 (t, 1H, *J* = 2 Hz), 9.14 (s, 1H).



¹H NMR spectrum of compound 10a in CDCl₃. The x-axis represents chemical shift in ppm, ranging from 9.0 to 2.0. The spectrum shows several peaks: a multiplet at 8.797 ppm (1H), a multiplet at 8.480 ppm (1H), a multiplet at 8.003 ppm (1H), a sharp singlet at 4.696 ppm (2H), a multiplet at 2.902 ppm (2H), and a multiplet at 2.384 ppm (2H). Integration values are provided below the peaks: 1.91, 0.89, 1.83, 2.11, 2.01, and 2.00. Solvent peaks for CDCl₃ are visible at 7.26, 7.26, and 7.26 ppm.

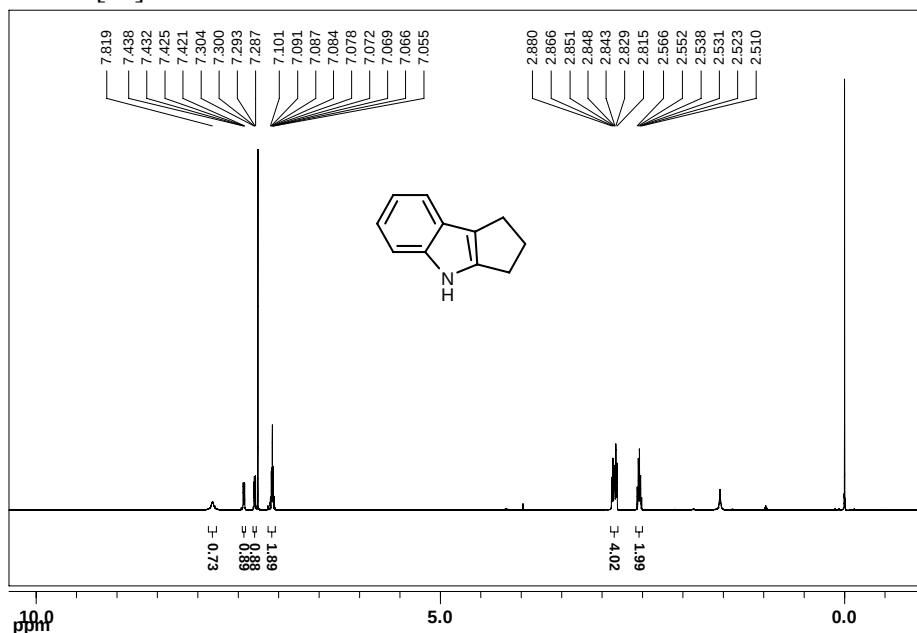


¹H NMR spectrum (CDCl₃) of compound 1. The x-axis represents chemical shift in ppm, ranging from 0 to 9.0. The spectrum shows several peaks with corresponding integration values below the baseline:

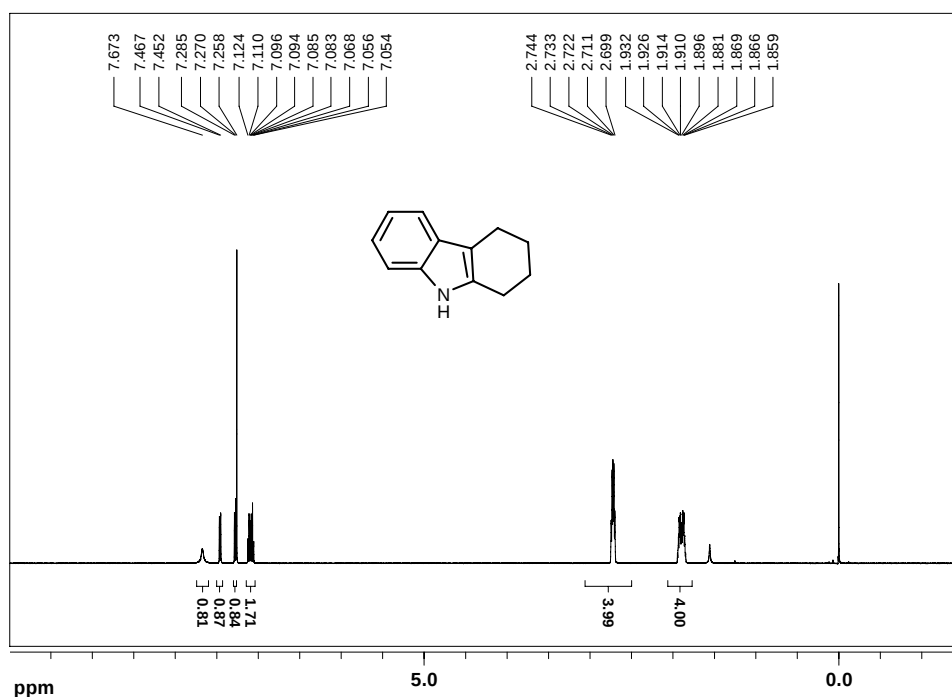
- 8.717, 8.706, 8.414, 8.398, 8.382 (1.89H)
- 7.937, 7.924, 7.910 (1.85H)
- 4.523, 4.508, 4.494 (2.12H)
- 2.826, 2.811, 2.796, 2.767, 2.754, 2.039, 2.023, 2.008 (1.98H)
- 1.993, 1.680, 1.664, 1.649, 1.633, 1.618 (2.12H)
- 2.00 (2.00H)

Spectra and data of indole products^[1-5]

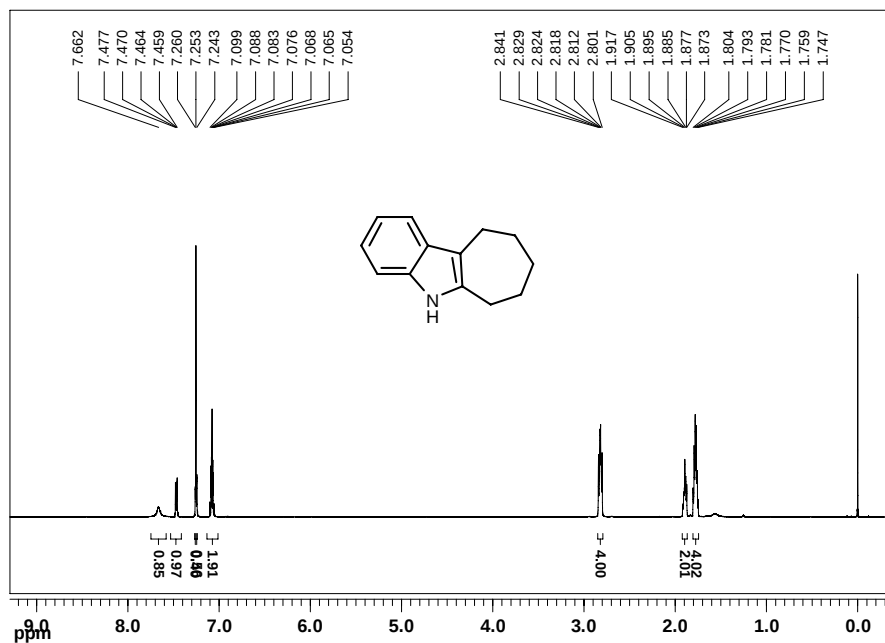
1,2,3,4-Tetrahydrocyclopenta[b]indole: mp 101-103°C (lit^[7] 102-104°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 2.51-2.57 (m, 2H), 2.82-2.88 (m, 4H), 7.06-7.10 (m, 2H), 7.29-7.30 (dd, 1H, *J* = 2.5 Hz), 7.42-7.44 (dd, 1H, *J* = 2.5 Hz), 7.82 (s, 1H). MS (EI): *m/z* 157 [M]⁺.



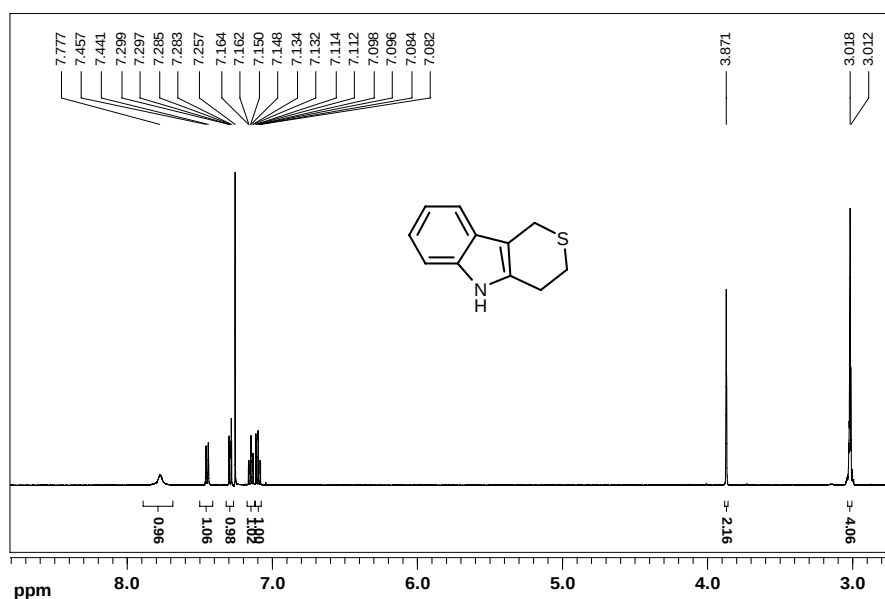
2,3,4,9-Tetrahydro-1H-carbazole: mp 116-118 °C (lit^[8] 118-119°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 1.86-1.93 (m, 4H), 2.70-2.74 (m, 4H), 7.05-7.12 (m, 2H), 7.27-7.29 (d, 1H, *J* = 7.5 Hz), 7.45-7.47 (d, 1H, *J* = 7.5 Hz), 7.67 (s, 1H). MS (EI): *m/z* 171 [M]⁺.



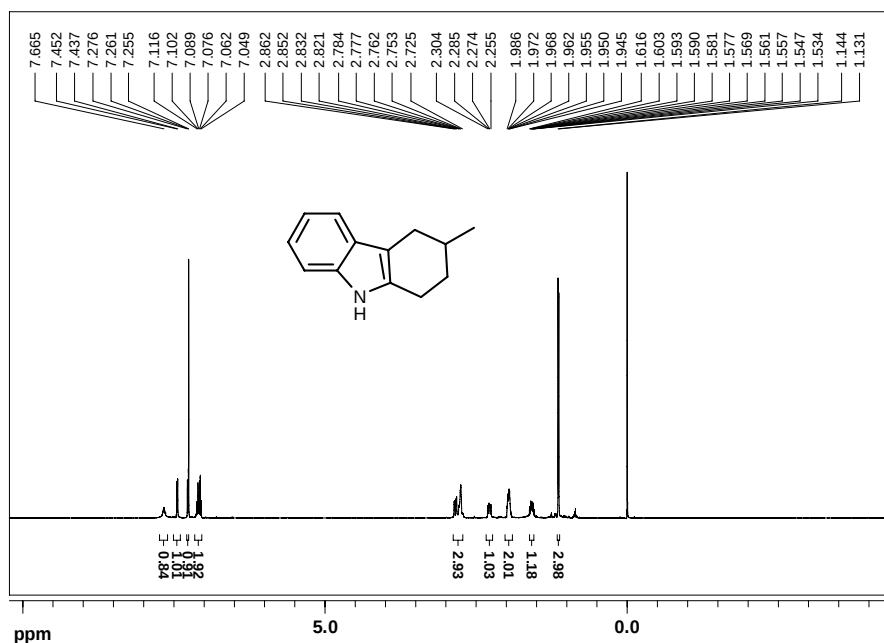
5,6,7,8,9,10-Hexahydrocyclohepta[b]indole: mp 143-144°C. (lit^[2] 138-142°C) ¹H NMR (500MHz, CDCl₃, δ ppm): 1.75-1.80 (m, 4H), 1.87-1.92 (m, 2H), 2.80-2.84 (m, 4H), 7.05-7.10 (m, 2H), 7.24-7.26 (d, 1H, *J* = 8.5 Hz), 7.46-7.48 (dd, 1H, *J* = 2.5 Hz, 3.5 Hz), 7.66 (s, 1H). MS (EI): *m/z* 185 [M]⁺.



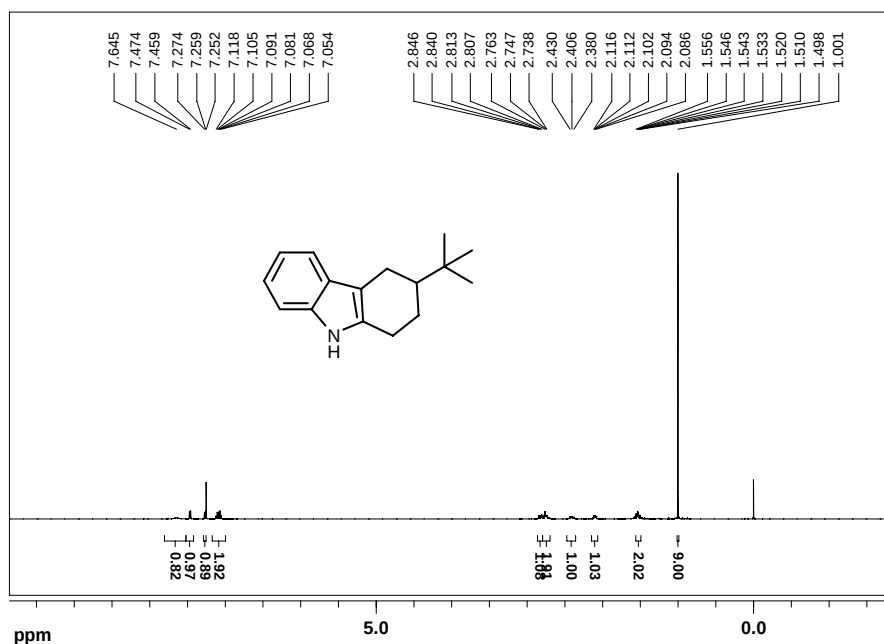
1,3,4,5-Tetrahydrothiopyrano[4,3-b]indole: mp 157-159 °C (lit^[9] 158-160°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 3.01-3.02 (d, 4H, *J* = 3 Hz), 3.87 (s, 2H), 7.08-7.11 (m, 1H), 7.13-7.16 (m, 1H), 7.28-7.30 (dd, 1H, *J* = 1 Hz, 7 Hz), 7.44-7.46 (d, 1H, *J* = 8 Hz), 7.78 (s, 1H). MS (EI): *m/z* 189 [M]⁺.



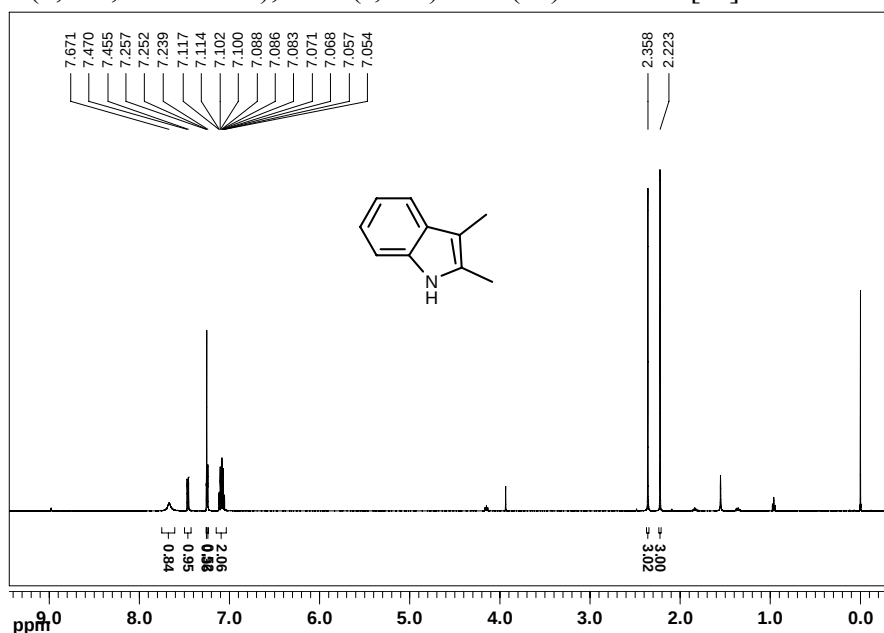
3-Methyl-2,3,4,9-tetrahydro-1H-carbazole: mp 109-110 °C (lit^[10] 108-111 °C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 1.13-1.14 (d, 3H, *J* = 6.5 Hz), 1.53-1.62 (m, 1H), 1.95-1.99 (m, 2H), 2.26-2.30 (dd, 1H, *J* = 9.5 Hz, 15 Hz), 2.73-2.78 (m, 2H), 2.82-2.86 (dd, 1H, *J* = 5 Hz, 15 Hz), 7.05-7.12 (m, 2H), 7.26-7.28 (d, 1H, *J* = 7.5 Hz), 7.44-7.45 (d, 1H, *J* = 7.5 Hz), 7.67 (s, 1H). MS (EI): *m/z* 185 [M]⁺.



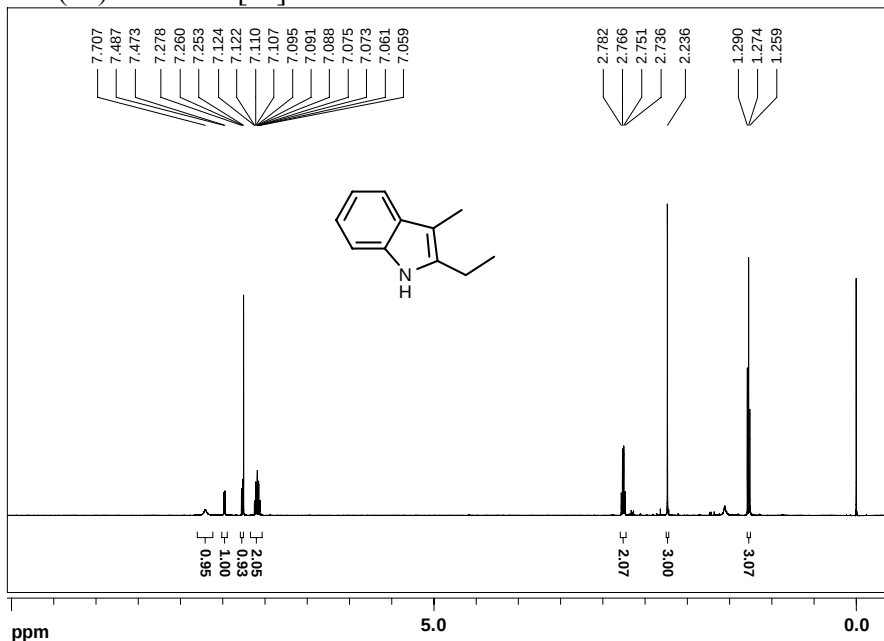
3-*tert*-Butyl-2,3,4,9-tetrahydro-1H-carbazole: mp 126-127 °C (lit^[11] 126-127 °C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 1.00 (s, 9H), 1.50-1.56 (m, 2H), 2.09-2.12 (m, 1H), 2.38-2.43 (t, 1H, *J* = 12.5 Hz), 2.74-2.85 (m, 3H), 7.05-7.12 (m, 2H), 7.26-7.27 (d, 1H, *J* = 7.5 Hz), 7.46-7.47 (d, 1H, *J* = 7.5 Hz), 7.65 (s, 1H). MS (EI): *m/z* 228 [M+1]⁺.



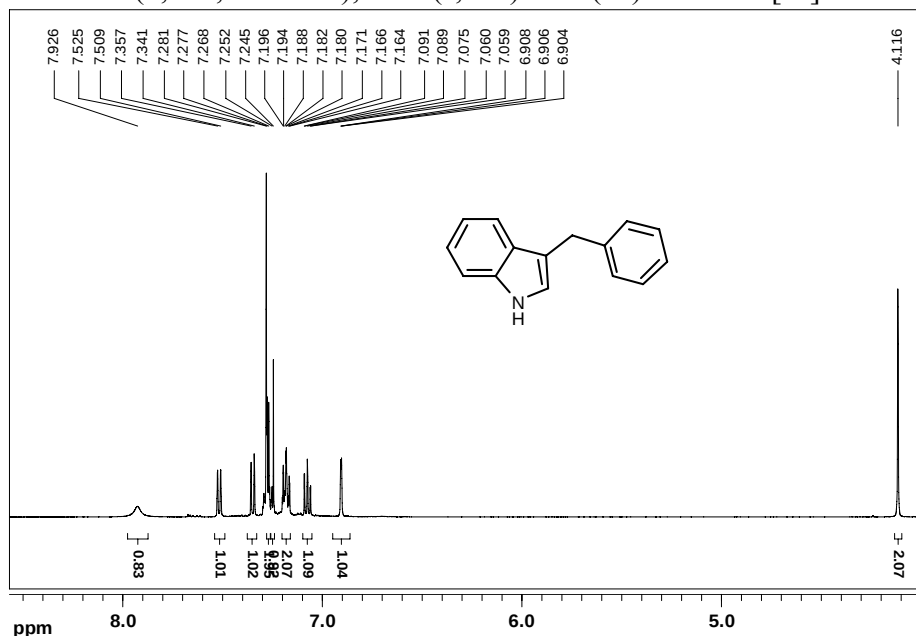
2,3-Dimethyl-1H-indole: mp 106-107 °C (lit^[7]107°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 2.22 (s, 3H), 2.36 (s, 3H), 7.05-7.12 (m, 2H), 7.24-7.26 (d, 1H, *J* = 9 Hz), 7.46-7.47 (d, 1H, *J* = 7.5 Hz), 7.67 (s, 1H). MS (EI): *m/z* 145 [M]⁺.



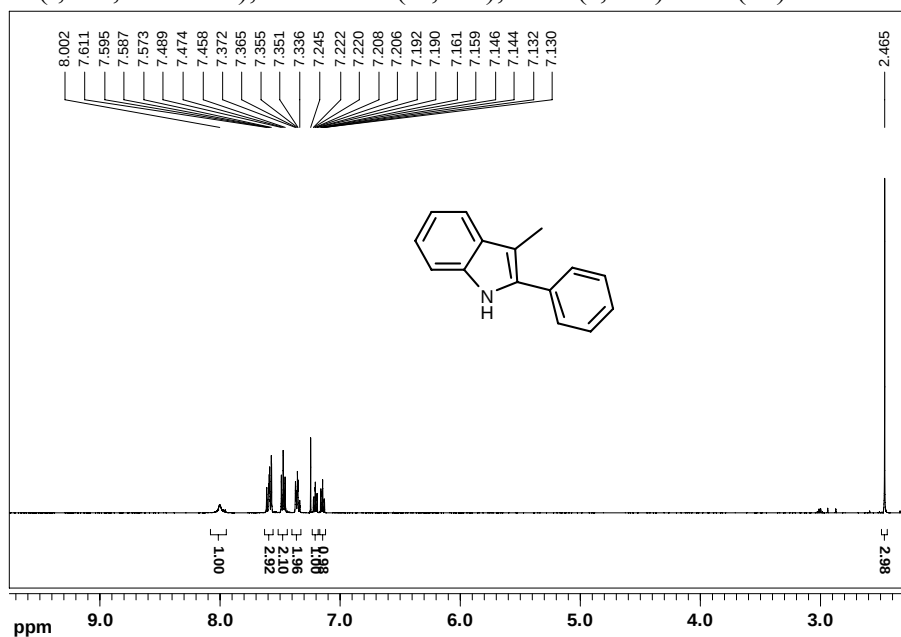
2-Ethyl-3-methyl-1H-indole: mp 64-65 °C (lit^[11]64-65°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 1.26-1.29 (t, 3H *J* = 7.5 Hz), 2.24 (s, 3H), 2.74-2.78 (t, 2H, *J* = 7.5 Hz), 7.06-7.12 (m, 2H), 7.26-7.28 (d, 1H, *J* = 9 Hz), 7.47-7.49 (t, 1H, *J* = 7 Hz), 7.71 (s, 1H). MS (EI): *m/z* 159 [M]⁺.



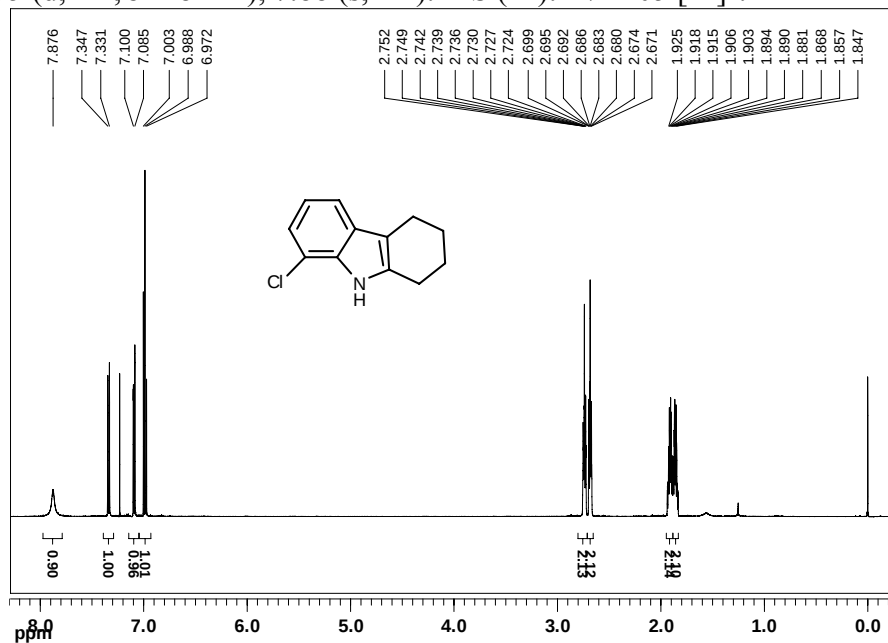
3-Benzyl-1H-indole: mp 103-105 °C (lit^[12] 102-105°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 4.12 (s, 2H), 6.90-6.91 (t, 1H, *J* = 1 Hz), 7.06-7.10 (m, 1H), 7.16-7.20 (m, 2H), 7.25 (d, 1H, *J* = 3.5 Hz), 7.27-7.28 (d, 2H, *J* = 4.5 Hz), 7.34-7.36 (d, 1H, *J* = 8 Hz), 7.51-7.53 (d, 1H, *J* = 8 Hz), 7.93 (s, 1H). MS (EI): *m/z* 207 [M]⁺.



3-Methyl-2-phenyl-1H-indole: mp 92-93 °C (lit^[3] 93-94°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 2.47 (s, 3H), 7.13-7.16 (m, 1H), 7.19-7.22 (m, 1H), 7.34-7.37 (m, 2H), 7.46-7.49 (t, 2H, *J* = 8 Hz), 7.57-7.61 (m, 3H), 8.00 (s, 1H). MS (EI): *m/z* 207 [M]⁺.



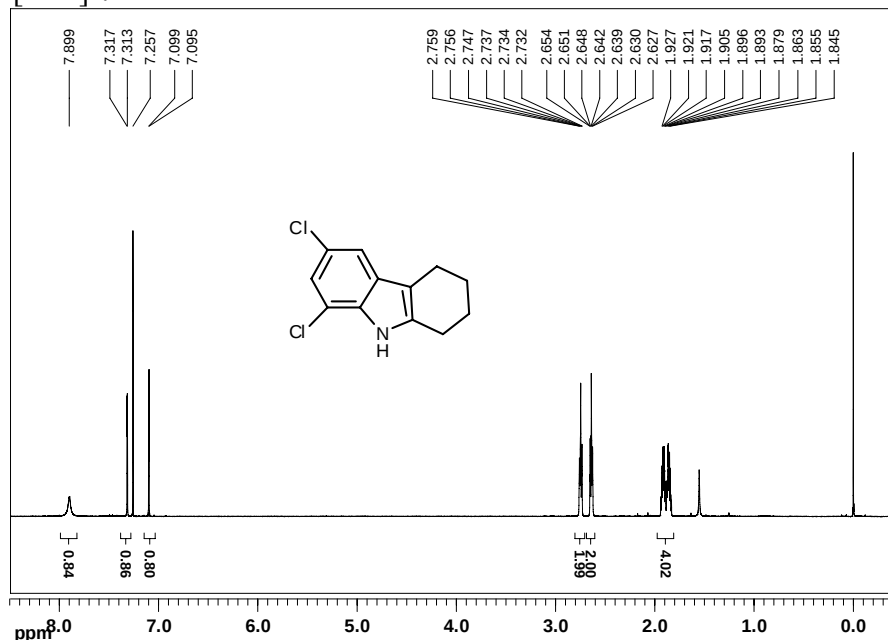
8-Chloro-2,3,4,9-tetrahydro-1H-carbazole: mp 178-180 °C (lit^[1] 178-180°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 1.85-1.88 (m, 2H), 1.89-1.93 (m, 2H), 2.67-2.70 (m, 2H), 2.72-2.75 (m, 2H), 6.97-7.00 (t, 1H, *J* = 8 Hz), 7.09-7.10 (d, 1H, *J* = 7.5 Hz), 7.33-7.35 (d, 1H, *J* = 8 Hz), 7.88 (s, 1H). MS (EI): *m/z* 205 [M]⁺.



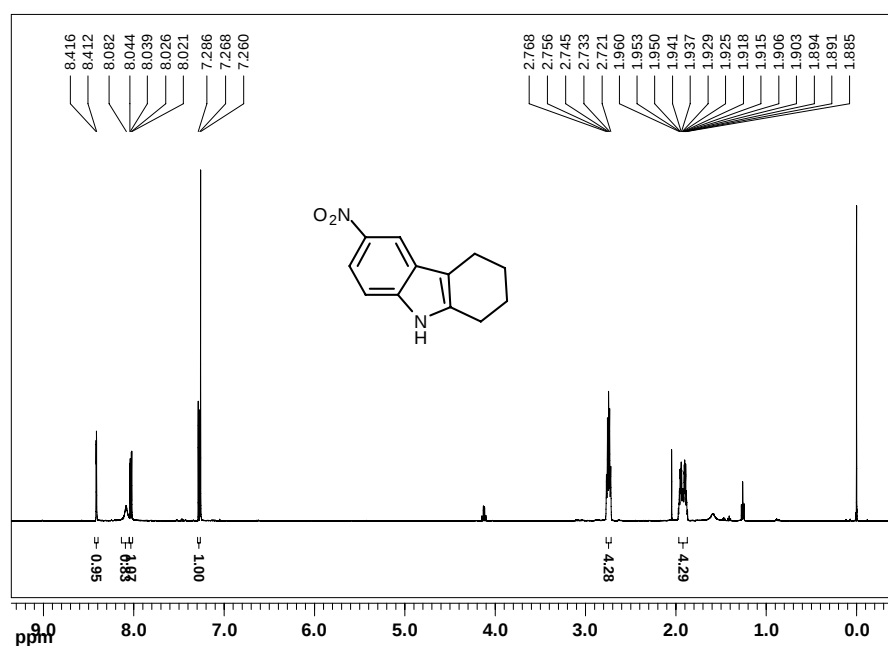
6-Chloro-2,3,4,9-tetrahydro-1H-carbazole: mp 141-143°C (lit^[1] 142-144°C). ¹H NMR (500 MHz, CDCl₃, δ ppm): 1.85-1.89 (m, 2H), 1.89-1.92 (m, 2H), 2.64-2.67 (m, 2H), 2.71-2.73 (m, 2H), 7.04-7.06 (dd, 1H, *J* = 2 Hz, 8.5 Hz), 7.17-7.18 (d, 1H, *J* = 8.5 Hz), 7.41 (d, 1H, *J* = 2 Hz), 7.70 (s, 1H). MS (EI): *m/z*: 205 [M]⁺.



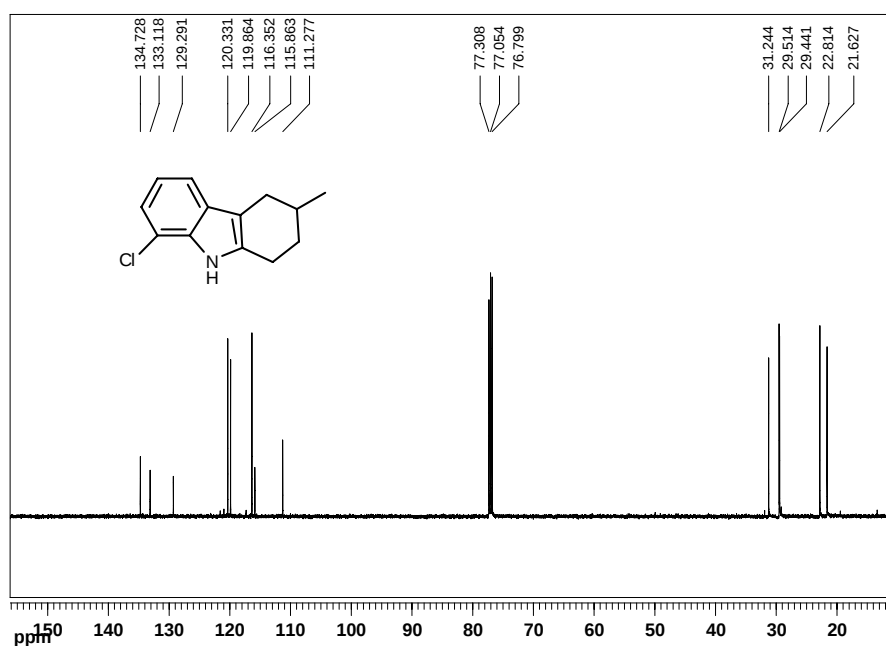
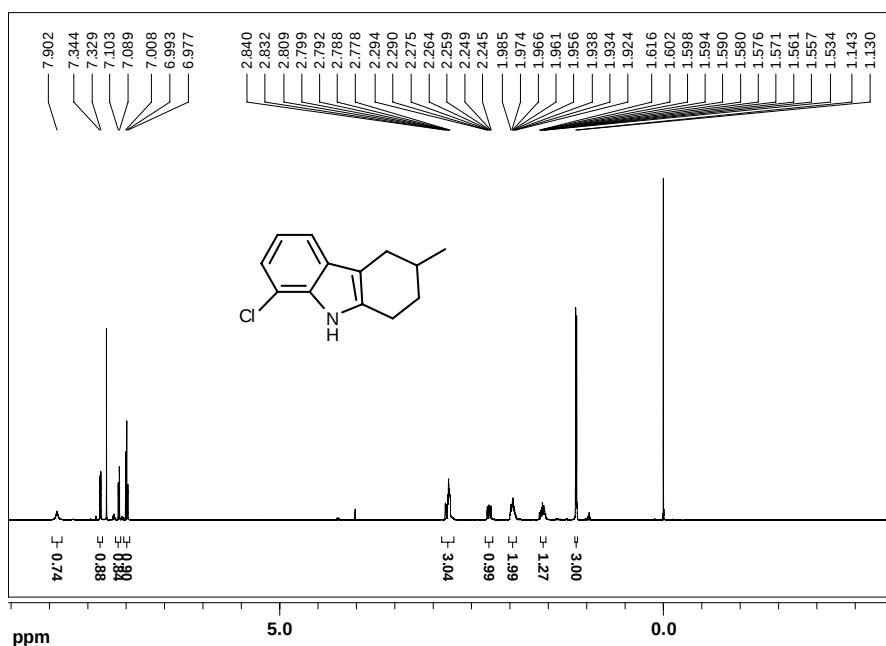
6,8-Dichloro-2,3,4,9-tetrahydro-1H-carbazole: mp 64-66°C. ^1H NMR (500 MHz, CDCl_3 , δ ppm): 1.85-1.88 (m, 2H), 1.89-1.93 (m, 2H), 2.63-2.65 (m, 2H), 2.73-2.76 (m, 2H) 7.10 (d, 1H, $J = 2$ Hz), 7.31-7.32 (d, 1H, $J = 2$ Hz), 7.90 (s, 1H). MS (EI): m/z 239 $[\text{M}-1]^+$.



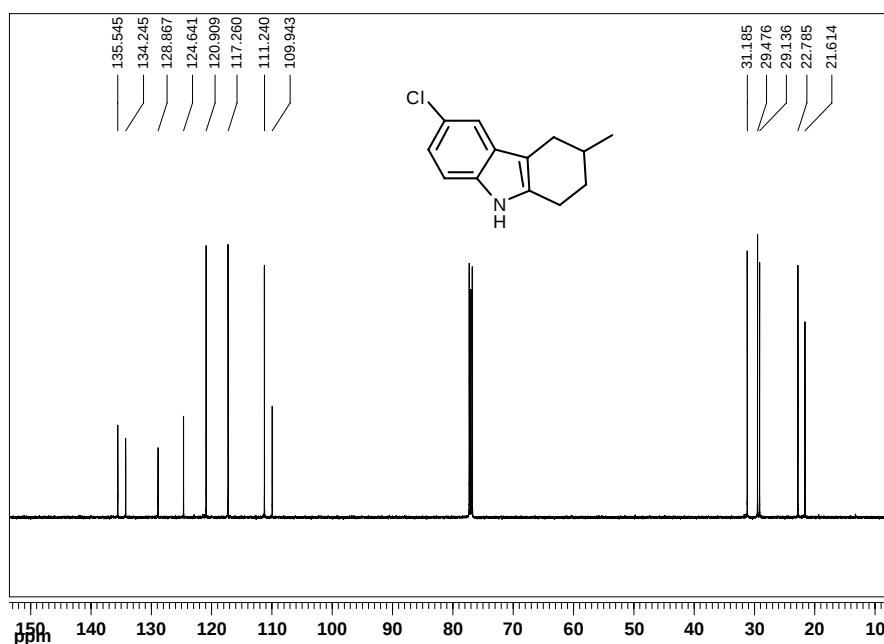
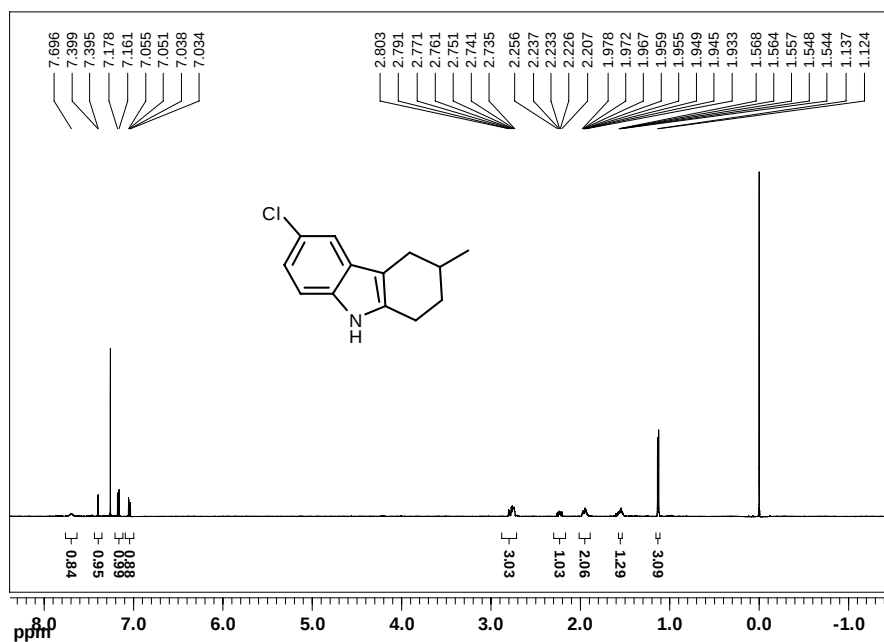
6-Nitro-2,3,4,9-tetrahydro-1H-carbazole: mp 165-166 °C. ^1H NMR (500 MHz, CDCl_3 , δ ppm): 1.89-1.96 (m, 4H), 2.72-2.77 (m, 4H), 7.27-7.29 (d, 1H, $J = 9$ Hz), 8.02-8.04 (dd, 1H, $J = 2.5$ Hz), 8.08 (s, 1H), 8.41-8.42 (d, 1H, $J = 2$ Hz). MS (EI): m/z 216 $[\text{M}]^+$.



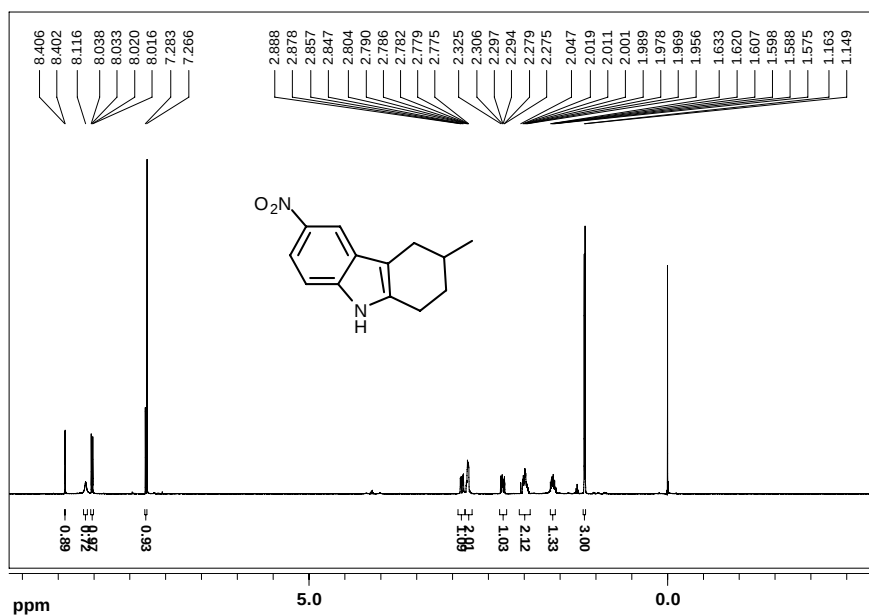
8-Chloro-3-methyl-2,3,4,9-tetrahydro-1H-carbazole: mp 98-100 °C. ^1H NMR (500 MHz, CDCl_3 , δ ppm): 1.13-1.14 (d, 3H, $J = 6.5$ Hz), 1.53-1.62 (m, 1H), 1.92-1.99 (m, 2H), 2.25-2.29 (m, 1H), 2.78-2.84 (m, 3H), 6.98-7.01 (t, 1H, $J = 8$ Hz), 7.09-7.10 (d, 1H, $J = 7$ Hz), 7.33-7.34 (d, 1H, $J = 7.5$ Hz), 7.90 (s, 1H). ^{13}C NMR (125 MHz, CDCl_3 , δ ppm): 21.6, 22.8, 29.4, 29.5, 31.2, 111.3, 115.9, 116.4, 119.9, 120.3, 129.3, 133.1, 134.7. HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{NCl}$: 219.0816 $[\text{M}]^+$, found: 219.0815 $[\text{M}]^+$.



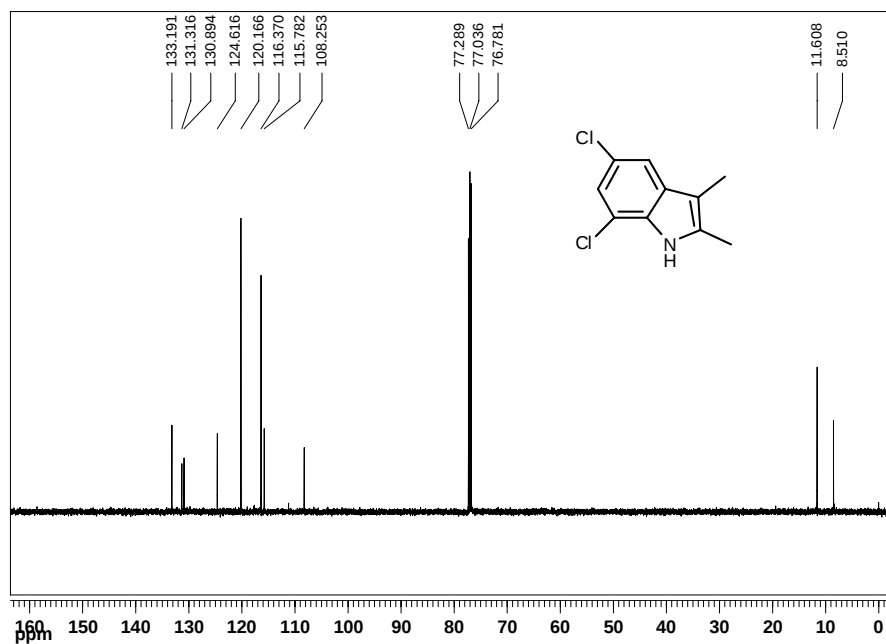
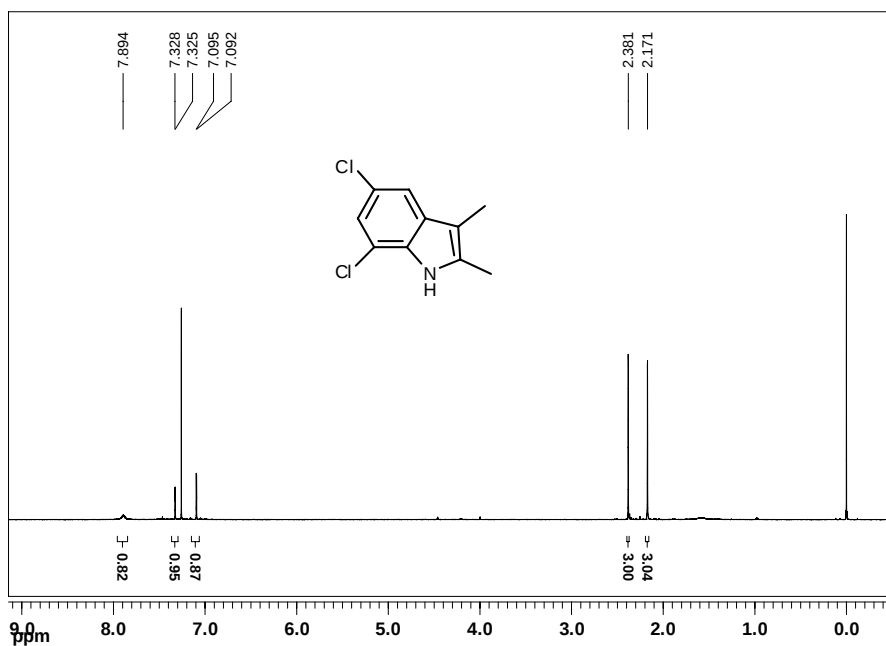
6-Chloro-3-methyl-2,3,4,9-tetrahydro-1H-carbazole: mp 106-108 °C. ^1H NMR (500 MHz, CDCl_3 , δ ppm): 1.12-1.14 (d, 3H, $J = 6.5$ Hz), 1.54-1.57 (m, 1H), 1.93-1.98 (m, 2H), 2.21-2.26 (m, 1H), 2.74-2.80 (m, 3H), 7.03-7.06 (dd, 1H, $J = 2$ Hz, 8.5Hz), 7.16-7.18 (d, 1H, $J = 8.5$ Hz), 7.40 (d, 1H, $J = 2$ Hz), 7.70 (s, 1H). ^{13}C NMR (125 MHz, CDCl_3 , δ ppm): 21.6, 22.8, 29.1, 29.5, 31.2, 109.9, 111.2, 117.3, 120.9, 124.6, 128.9, 134.2, 135.5. HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{NCl}$: 219.0822 $[\text{M}]^+$, found: 219.0815 $[\text{M}]^+$.



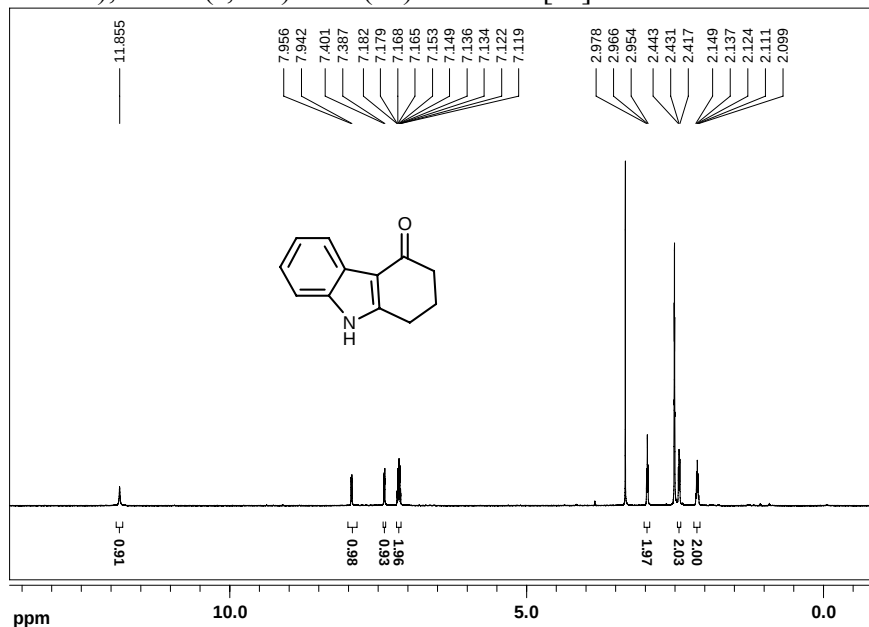
3-Methyl-6-nitro-2,3,4,9-tetrahydro-1H-carbazole: mp 149-151 °C. ^1H NMR (500 MHz, CDCl_3 , δ ppm): 1.15-1.16 (d, 3H, $J = 7$ Hz), 1.58-1.63 (m, 1H), 1.96-2.05 (m, 2H), 2.28-2.33 (m, 1H), 2.78-2.80 (m, 2H), 2.85-2.89 (dd, 1H, $J = 5$ Hz, 15.5 Hz), 7.27-7.28 (d, 1H, $J = 8.5$ Hz), 8.02-8.04 (dd, 1H, $J = 2$ Hz, 8.5 Hz), 8.12 (s, 1H), 8.40-8.41 (d, 1H, $J = 2$ Hz). MS (EI): m/z 230 $[\text{M}]^+$.



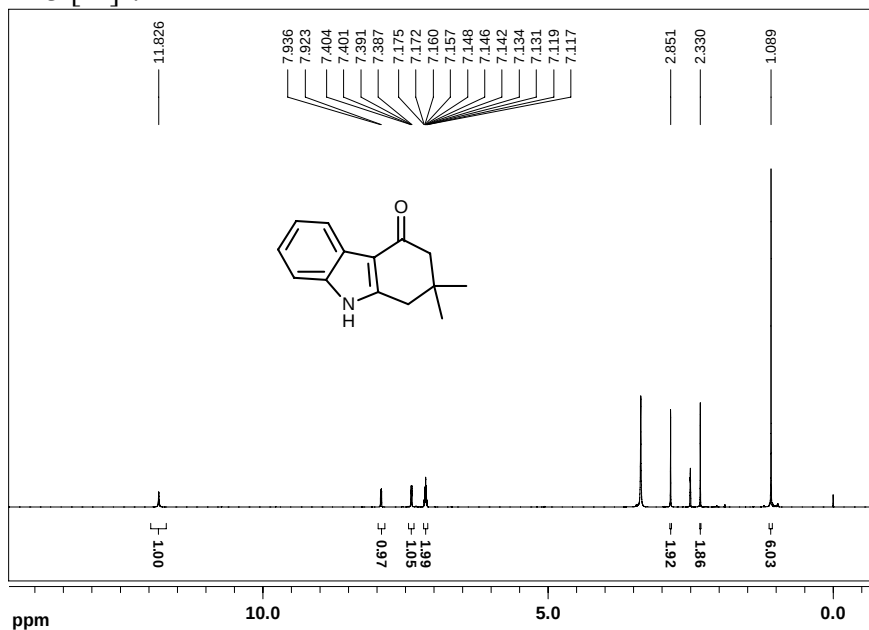
2,3-Dimethyl-5,7-dichloro-1H-indole: mp 93-94°C. ^1H NMR (500MHz, CDCl_3 , δ ppm): 2.17 (s, 3H), 2.38 (s, 3H), 7.09-7.10 (d, 1H, $J = 1.5$ Hz), 7.33 (d, 1H, $J = 1.5$ Hz), 7.89 (s, 1H). ^{13}C NMR (125MHz, CDCl_3 , δ ppm): 8.5, 11.6, 108.3, 115.8, 116.4, 120.2, 124.6, 130.9, 131.3, 133.2. HRMS calcd for $\text{C}_{13}\text{H}_{14}\text{NCl}$: 213.0116 $[\text{M}]^+$, found: 213.0112 $[\text{M}]^+$.



2,3-Dihydro-1H-carbazol-4(9H)-one: mp 224-225 °C (lit^[13] 223-224 °C). ¹H NMR (500 MHz, DMSO, δ ppm): 2.10-2.15 (m, 2H), 2.42-2.44 (t, 2H, *J* = 6.5 Hz), 2.95-2.98 (t, 2H, *J* = 6 Hz), 7.12-7.18 (m, 2H), 7.39-7.40 (d, 1H, *J* = 2 Hz), 7.94-7.96 (d, 1H, *J* = 7 Hz), 11.86 (s, 1H). MS (EI): *m/z* 185 [M]⁺.



2,2-Dimethyl-2,3-dihydro-1H-carbazol-4(9H)-one: mp 195-196°C. ¹H NMR (500 MHz, DMSO, δ ppm): 1.09 (s, 6H), 2.33 (s, 2H), 2.85 (s, 2H), 7.12-7.18 (m, 2H), 7.39-7.40 (dd, 1H, *J* = 2 Hz, 7 Hz), 7.92-7.94 (d, 1H, *J* = 6.5 Hz), 11.83 (s, 1H). MS (EI): *m/z* 213 [M]⁺.



References

1. J. Chen and Y. Hu, *Synth. Commun.*, 2006, **36**, 1485-1494.
2. M. J. van Eis, M. Lutz, A. L. Spek, W. H. de Wolf and F. Bickelhaupt, *Tetrahedron*, 2007, **60**, 1689-1694.
3. K. K. Kapoor, B. A. Ganai, S. Kumar and C. S. Andotra, *Synth. Commun.*, 2006, **36**, 2727-2735.
4. R. C. Morales, V. Tambyrajah, P. R. Jenkins, D. L. Davies and A. P. Abbott, *Chem commun.*, 2004, 158-159.
5. S. Whitney, R. Grigg, A. Derrick and A. Keep, *Org. Lett.*, 2007, **9**, 3299-3302.
6. C. P. Jones, K. W. Anderson and S. L. Buchwald, *J. Org. Chem.*, 2007, **72**, 7968-7973.
7. P. A. Wender and A. W. White, *Tetrahedron*, 1983, **39**, 3767-3776.
8. P. G. Gassman, T. J. van Bergen, D. P. Gilbert and B. W. Cue, *J. Am. Chem. Soc.*, 1974, **96**, 5495-5508.
9. T. E. Young, C. J. Ohnmacht and C. R. Hamel, *J. Org. Chem.*, 1967, **32**, 3622-3626.
10. C. U. Rogers and B. B. Corson, *J. Am. Chem. Soc.*, 1947, **69**, 2910-2911.
11. S. Raucher and G. A. Koolpe, *J. Org. Chem.*, 1983, **48**, 2066-2069.
12. P. Stuetz and P. A. Stadler, *Org. Synth.*, 1977, **56**, 8.
13. X. N. Li and R. Vince, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 3517-3521.