

# Microwave-Assisted Piloty-Robinson Synthesis of 3,4-Disubstituted Pyrroles

## Supporting Information

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**General Information**

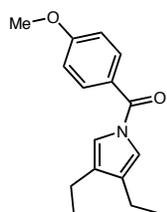
Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain followed by heating. Infrared spectra were recorded on an FT-IR spectrometer.  $^1\text{H-NMR}$  spectra are reported in ppm using solvent as an internal standard ( $\text{CDCl}_3$  at 7.26 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled  $^{13}\text{C-NMR}$  spectra are reported in ppm using solvent as an internal standard ( $\text{CDCl}_3$  at 77.0 ppm).

**Representative procedure for the synthesis of azine compounds**

To a round bottom flask equipped with a magnetic stir bar was added diethyl ether (90 mL) and butyraldehyde (64.3 mL, 713 mmol). The solution was cooled to 0 °C and hydrazine hydrate (17.3 mL, 357 mmol) was added dropwise over 30 min. The reaction was warmed to 23 °C and stirred for 30 minutes. The water produced in the reaction was then removed by pipette and anhydrous potassium carbonate was added to dry the reaction further. The mixture was filtered and the resulting solution was concentrated carefully under reduced pressure (400 mbar) to afford azines that are used directly in the subsequent Piloty-Robinson reactions.

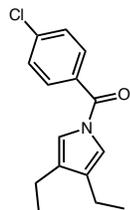
### Representative procedure for the synthesis of pyrrole compounds

To a dry 20 mL microwave vial equipped with a magnetic stir bar was added unpurified azine (1 equiv) and pyridine (3.7 equiv). Aroyl chloride (2.1 equiv) was then added slowly and the vial capped with a rubber septum. The vial was shaken vigorously and then heated in the microwave at 180 °C for 30-60 min. After heating, the vessel was cooled, diluted with ethyl acetate (50x volume of azine) and filtered through a coarse frit funnel. The solution was concentrated under reduced pressure and the remaining material was purified by silica gel flash column chromatography.



**(3,4-diethyl-1H-pyrrol-1-yl)(4-methoxyphenyl)methanone (6):** Purified with 5% ethyl acetate/ 15% toluene/ 80% hexanes, yielding 0.27 g (27%) of a tan oil.

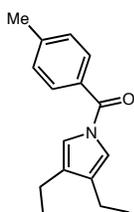
$R_f = 0.23$  (5:15:80 ethyl acetate/toluene/hexanes); IR (film) 2964, 2933, 1681, 1606, 1510, 1375, 1307, 1251, 1173, 1136, 1030, 888, 843, 807, 763, 615  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 8.8$  Hz, 2H), 7.02 (s, 2H), 6.98 (d  $J = 8.8$ , 2H), 3.86 (s, 3H), 2.42 (q,  $J = 7.3$ , 4H), 1.20 (t,  $J = 7.3$ , 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  166.5, 162.4, 131.5, 130.1, 125.7, 117.3, 113.5, 55.3, 18.3, 13.4; LRMS (ESI): Mass calculated for  $\text{C}_{16}\text{H}_{19}\text{NO}_2$   $[\text{M}]^+$ , 257.3. Found  $[\text{M}+\text{H}]^+$ , 258.5.



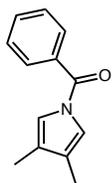
**(3,4-diethyl-1H-pyrrol-1-yl)(4-chlorophenyl)methanone (7):** Purified with 2% ethyl acetate/ 10% toluene/ 88% hexanes, yielding 0.55 g (55%) of a white solid.  $R_f$

$= 0.34$  (2:10:88 ethyl acetate/toluene/hexanes); IR (film) 2965, 2932, 1688, 1592, 1528, 1488, 1462, 1402, 1379, 1314, 1273, 1247, 1136, 1091, 1016, 886, 842, 806, 754  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.68(d,  $J = 8.1$  Hz, 2H), 7.49 (d,  $J = 8.8$ , 2H), 7.00 (s, 2H), 2.42 (q,  $J$

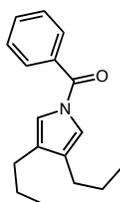
= 6.6, 4H), 1.20 (t,  $J = 7.3$ , 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ 166.0, 138.1, 132.1, 131.1, 130.6, 128.7, 117.2, 18.5, 13.4; LRMS (ESI): Mass calculated for  $\text{C}_{15}\text{H}_{16}\text{NCIO}$   $[\text{M}]^+$ , 283.2. Found  $[\text{M}+\text{H}]^+$ , 284.4,  $[\text{M}+\text{Na}]^+$ , 306.6.



**(3,4-diethyl-1H-pyrrol-1-yl)(p-tolyl)methanone (8):** Purified with 1% ethyl acetate/ 30% toluene/ 69% hexanes, yielding 0.42 g (42%) of a white solid.  $R_f = 0.22$  (1:30:65 ethyl acetate/toluene/hexanes); IR (film) 2965, 2931, 1687, 1611, 1527, 1461, 1376, 1311, 1274, 1247, 1182, 1134, 888, 807, 750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.64 (d,  $J = 7.3$  Hz, 2H), 7.31 (d,  $J = 7.3$  Hz, 2H), 7.03 (s, 2H), 2.42 (q,  $J = 6.6$ , 4H), 1.20 (t,  $J = 7.3$ , 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ 167.1, 142.3, 130.8, 130.4, 129.4, 129.0, 117.4, 21.5, 18.4, 13.4; LRMS (ESI): Mass calculated for  $\text{C}_{16}\text{H}_{19}\text{NO}$   $[\text{M}]^+$ , 241.2. Found  $[\text{M}+\text{H}]^+$ , 242.5.

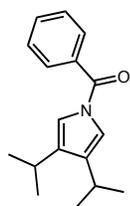


**(3,4-dimethyl-1H-pyrrol-1-yl)(phenyl)methanone (9):** Purified with 3% ethyl acetate/10% toluene/hexanes, yielding 0.65 g (65%) of a brown oil.  $R_f = 0.27$  (3:10:87 ethyl acetate/toluene/hexanes); IR (film) 3060, 2925, 1688, 1602, 1532, 1492, 1446, 1396, 1341, 1249, 1136, 1029, 999, 881, 791, 719, 667  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 7.0$  Hz, 2H), 7.58 (dd,  $J = 7.7$  Hz, 1H), 7.50 (dd,  $J = 7.7$  Hz, 2H), 7.01 (s, 2H), 2.02 (s, 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$ 167.0, 133.7, 131.7, 129.1, 128.3, 124.4, 118.3, 10.2; LRMS (ESI): Mass calculated for  $\text{C}_{13}\text{H}_{13}\text{NO}$   $[\text{M}]^+$ , 199.3. Found  $[\text{M}+\text{H}]^+$ , 200.9.

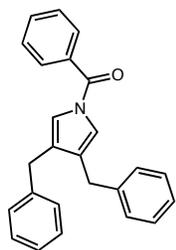


**(3,4-propyl-1H-pyrrol-1-yl)(phenyl)methanone (10):** Purified with 5% isopropyl alcohol/ 10% toluene/ 85% hexanes, yielding 0.52 g (52%) of a tan oil.  $R_f = 0.34$

(5:10:85 isopropyl alcohol/toluene/hexanes); IR (film) 2958, 2930, 2870, 1690, 1601, 1526, 1448, 1396, 1324, 1276, 1247, 1135, 887, 792, 719, 698  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 7.7$  Hz, 2H), 7.58 (dd,  $J = 7.3$  Hz, 1H), 7.50 (dd,  $J = 7.7$  Hz, 2H), 7.01 (s, 2H), 2.37 (t,  $J = 7.7$ , 4H), 1.60 (tq,  $J = 7.3$ , 4H) 0.99 (t,  $J = 7.3$ , 6H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  167.33, 135.1, 132.1, 130.1, 129.4, 129.0, 118.9, 28.3, 23.6, 14.8; LRMS (ESI): Mass calculated for  $\text{C}_{17}\text{H}_{21}\text{NO}$   $[\text{M}]^+$ , 255.4. Found  $[\text{M}+\text{Na}]^+$ , 288.8.



**(3,4-diisopropyl-1H-pyrrol-1-yl)(phenyl)methanone (11):** Purified with 2% isopropyl alcohol/hexanes, yielding 0.34 g (34%) of a tan crystal.  $R_f = 0.27$  (2:98 isopropyl alcohol/hexanes); mp = 63  $^\circ\text{C}$ ; IR (film) 2959, 2926, 2868, 1696, 1388, 1370, 1270, 1157, 1130, 879, 803, 719, 699, 664  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.74 (d,  $J = 7.7$  Hz, 2H), 7.60 (dd,  $J = 7.0$  Hz, 1H), 7.52 (dd,  $J = 7.3$  Hz, 2H), 7.02 (s, 2H), 2.85 (qq,  $J = 7.0$ , 2H), 1.24 (d  $J = 7.0$ , 12H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  167.2, 135.6, 133.7, 131.7, 129.2, 128.3, 116.3, 24.9, 23.8; LRMS (ESI): Mass calculated for  $\text{C}_{17}\text{H}_{21}\text{NO}$   $[\text{M}]^+$ , 255.2. Found  $[\text{M}+\text{H}]^+$ , 256.4.

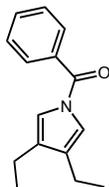


**(3,4-dibenzyl-1H-pyrrol-1-yl)(phenyl)methanone (12):** Purified with 3% ethyl acetate/ 10% toluene/ 87% hexanes, yielding 0.40 g (40%) of a tan oil.  $R_f = 0.24$  (3:10:87 ethyl acetate/toluene/hexanes); IR (film) 3083, 3061, 3027, 2905, 2841, 1696, 1602, 1526, 1494, 1448, 1363, 1246, 1131, 1029, 880, 792, 697  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.75 (d,  $J = 7.3$  Hz, 2H), 7.60 (dd,  $J = 7.3$  Hz, 1H), 7.51 (dd,  $J = 7.7$  Hz, 2H), 7.32 (dd,  $J = 7.7$  4H), 7.24 (dd,  $J = 7.7$ , 2H), 7.19 (d,  $J = 7.3$ , 4H) 7.03 (s, 2H), 3.68 (s,

4H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$ 167.3, 141.0, 134.6, 132.3, 130.1, 129.5, 129.2, 129.0, 128.2, 127.0, 120.8, 32.6; LRMS (ESI): Mass calculated for  $\text{C}_{24}\text{H}_{21}\text{NO}$   $[\text{M}]^+$ , 351.4. Found  $[\text{M}+\text{Na}]^+$ , 374.0.

### Representative procedure for the large scale synthesis of *N*-benzoyl-3,4-diethylpyrrole

To a dry 20 mL microwave vial equipped with a magnetic stir bar was added butyraldehyde azine (3.76 g, 27 mmol) and pyridine (8.11 mL, 100 mmol). Benzoyl chloride (6.66 mL, 57 mmol) was then added slowly and the vial capped with a rubber septum. The vial was then shaken vigorously and allowed to stir in the microwave at 170 °C for 1.25 hours. This procedure was repeated another four times and the unpurified material from all four runs was combined and filter through a coarse fritted funnel using ethyl acetate as the eluant. After filtration, the solvent was removed under reduced pressure and the remaining material was passed through a pad of silica gel (400 mL) using using chloroform. A liter of eluant was collected and the solvent was removed under reduced pressure. The oil remaining purified by distillation (122-125 °C @ 60 mT) to afford 15.9 g of *N*-benzoyl-3,4-diethylpyrrole as a tan oil that crystallized upon standing (52%.)



**(3,4-diethyl-1H-pyrrol-1-yl)(phenyl)methanone (5):** Purified by filtering through silica and vacuum distillation, yielding 15.9 g (52%) of a tan oil.  $R_f = 0.71$  (20:80 ethyl acetate/hexanes); mp = 43 °C; IR (film) 2965, 1688, 1377, 1317, 1274, 1246, 1136, 884, 807, 717, 668  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.72 (d,  $J = 7.3$  Hz, 2H), 7.57 (dd,  $J = 7.3$  Hz, 1H), 7.50 (dd,  $J = 7.3$  Hz, 2H), 7.00 (s, 2H), 2.43 (q,  $J = 7.3$ , 4H), 1.21 (t,  $J = 7.3$ , 6H);

$^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  164.7, 133.8, 131.7, 130.8 129.2 128.3 117.4 18.4 13.4; LRMS (ESI): Mass calculated for  $\text{C}_{15}\text{H}_{17}\text{NO}$   $[\text{M}]^+$ , 227.3. Found  $[\text{M}+\text{H}]^+$ , 228.5.

**Procedure for the synthesis of 2,3,7,8,12,13,17,18-octaethylporphyrin from *N*-benzoyl-3,4-diethylpyrrole**

A 100 mL round-bottomed flask is charged with *N*-benzoyl-3,4-diethylpyrrole (3.30 g, 14.5 mmol), EtOH (20 mL),  $\text{H}_2\text{O}$  (10 mL) and KOH (2.45 g, 43.6 mmol). The tan solution is stirred for 15-20 min at room temperature and monitored by thin layer chromatography. After consumption of the starting material, the reaction is then diluted with water (50 mL) and extracted with hexanes (150 mL). The organic layer is washed with saturated aqueous  $\text{NaHCO}_3$ , saturated aqueous brine, and water, then dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure to yield 3,4-diethylpyrrole (1.79 g) as a tan oil judged to be >95% pure by  $^1\text{H}$  NMR spectroscopy and used directly in the next reaction.  $R_f$  = 0.62 (20% EtOAc, 80% hexanes);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  6.55 (d,  $J$  = 2.2, 1H), 2.49 (q,  $J$  = 7.3, 4H), 1.22 (t,  $J$  = 7.3, 6H).

A 1 L three-neck round-bottomed flask wrapped with aluminum foil is equipped with a magnetic stir bar, a Dean-Stark trap, a reflux condenser, and nitrogen inlet. The flask is charged with unpurified 3,4-diethylpyrrole (1.79 g, 14.5 mmol), benzene (536 mL), and a 37% solution of aqueous formaldehyde (1.3 mL, 16.0 mmol). The solution is stirred for 10 min at 100-105 °C before *p*-toluenesulfonic acid (0.6 g, 2.9 mmol) is added to the flask. After 7 hr at refluxing temperature, the solution is cooled, and the Dean-Stark trap and condenser are replaced with a glass aerator. Oxygen is bubbled through the dark purple mixture while it is stirred for an additional 24 hr. Following the reaction, benzene is removed from the flask under reduced

pressure, and the brown residue is dissolved in chloroform (100 mL). The organic solution is washed once with 1 M NaOH and twice with water. The chloroform was removed under reduced pressure and the crude material was run through a pad of silica gel (50 mL) with methylene chloride. One liter of eluent was collected and the solvent was removed under reduced pressure. The resultant purple solid was then recrystallized from 2 mL chloroform/ 10 mL methanol to yield pure 2,3,7,8,12,13,17,18-octaethylporphyrin (**14**, 0.99 g, 1.85 mmol, 51% from *N*-benzoyl-3,4-diethylpyrrole) as a purple powder.  $R_f = 0.44$  (methylene chloride);  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  10.13 (s, 4H), 4.13 (q,  $J = 7.7$ , 16H), 1.95 (t,  $J = 7.7$ , 24H), -3.71 (s, 2H).

## Calorimetry Data

### DSC

The Mettler DSC 821 was used in the study. The samples were first sealed in glass ampoules and ramped in the DSC furnace from 0°C to 300°C at 10°C/minute.

### ARC

The TIAX Accelerating Rate Calorimeter was used in the study. The samples were first loaded into glass or titanium pressure bombs and then attached to the calorimeter with a pressure transducer. The sample is heated in heat-wait-search steps of 10°C. When self-heating is detected, the calorimeter maintains the airspace around the bomb at the same temperature as the sample and tracks the exotherm until reaching a preset pressure or temperature limit, after which the test is concluded.

Two series of two tests were run for this study, one in glass test cells and one in titanium test cells. For the first test in each series, the benzoyl chloride was added to the crude azine and pyridine, attached to the ARC, and the search for exothermic activity was started immediately at room temperature. For the second test of each series, the test cell was heated to the reaction temperature (170°C) before searching for exothermic activity. In both tests, using titanium test cells, exotherms were immediately detected and continued throughout the test.

Table 1: Benzoyl Addition ARC Charges: Test in Glass Test Cell Starting at Room Temperature

Material	Source/Lot	Amount
Crude Azine	88021-019-D	0.925g
Pyridine	Aldrich/03847DD	1.960g
Benzoyl Chloride	Aldrich/05521DD	2.110g

Table 2: Benzoyl Addition ARC Charges: Test in Glass Test Cell Starting at 170°C

Material	Source/Lot	Amount
Crude Azine	88021-019-D	0.846g
Pyridine	Aldrich/03847DD	1.884g
Benzoyl Chloride	Aldrich/05521DD	2.040g

Table 3: Benzoyl Addition ARC Charges: Test in Titanium Test Cell Starting at Room

Material	Source/Lot	Amount
Crude Azine	88021-019-D	0.9962g
Pyridine	Aldrich/03847DD	2.0640g
Benzoyl Chloride	Aldrich/05521DD	2.1162g

Table 4: Benzoyl Addition ARC Charges: Test in Titanium Test Cell Starting at 170°C

Material	Source/Lot	Amount
Crude Azine	88021-019-D	0.9235g
Pyridine	Aldrich/03847DD	1.9797g
Benzoyl Chloride	Aldrich/05521DD	2.1097g

### Omnical SuperCRC

The Omnical SuperCRC (Chemical Reactivity Calorimeter) calorimeter was used to evaluate the benzoyl chloride addition. The experiment was performed in a glass vial with a septum and a magnetic stir bar at 22°C. The calorimeter charges are summarized in Table 5. The vial was loaded with crude azine and pyridine. Once thermal equilibrium was reached, benzoyl chloride was injected to the vial via syringe. When the heat flow returned to baseline, the test was concluded.

Table 5: Benzoyl Addition SuperCRC Charges

Material	Source/Lot	Amount
Crude Azine	88021-019-D	0.9790g
Pyridine	Aldrich/03847DD	2.074g
Benzoyl Chloride	Aldrich/05521DD	2.11g

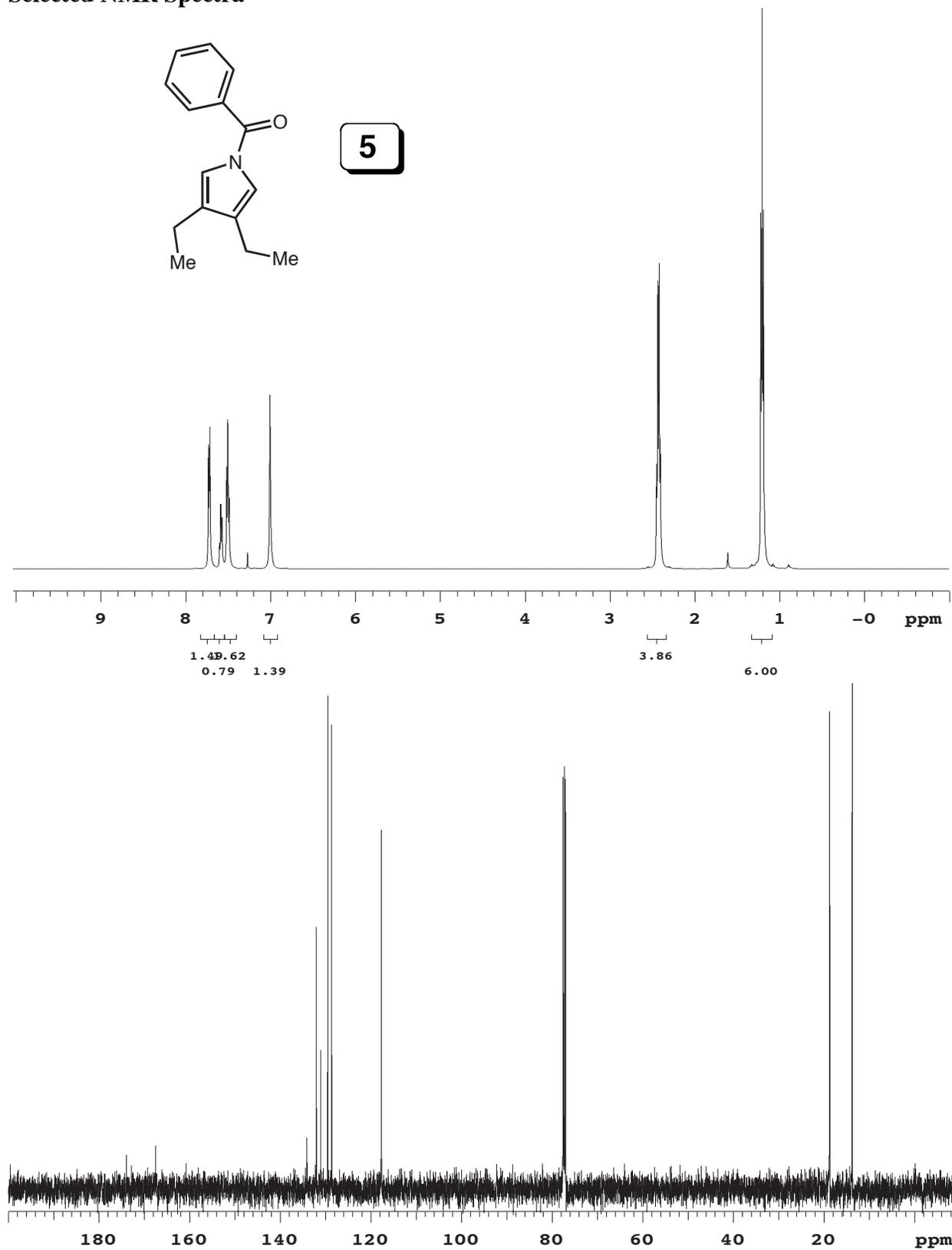
**RC1**

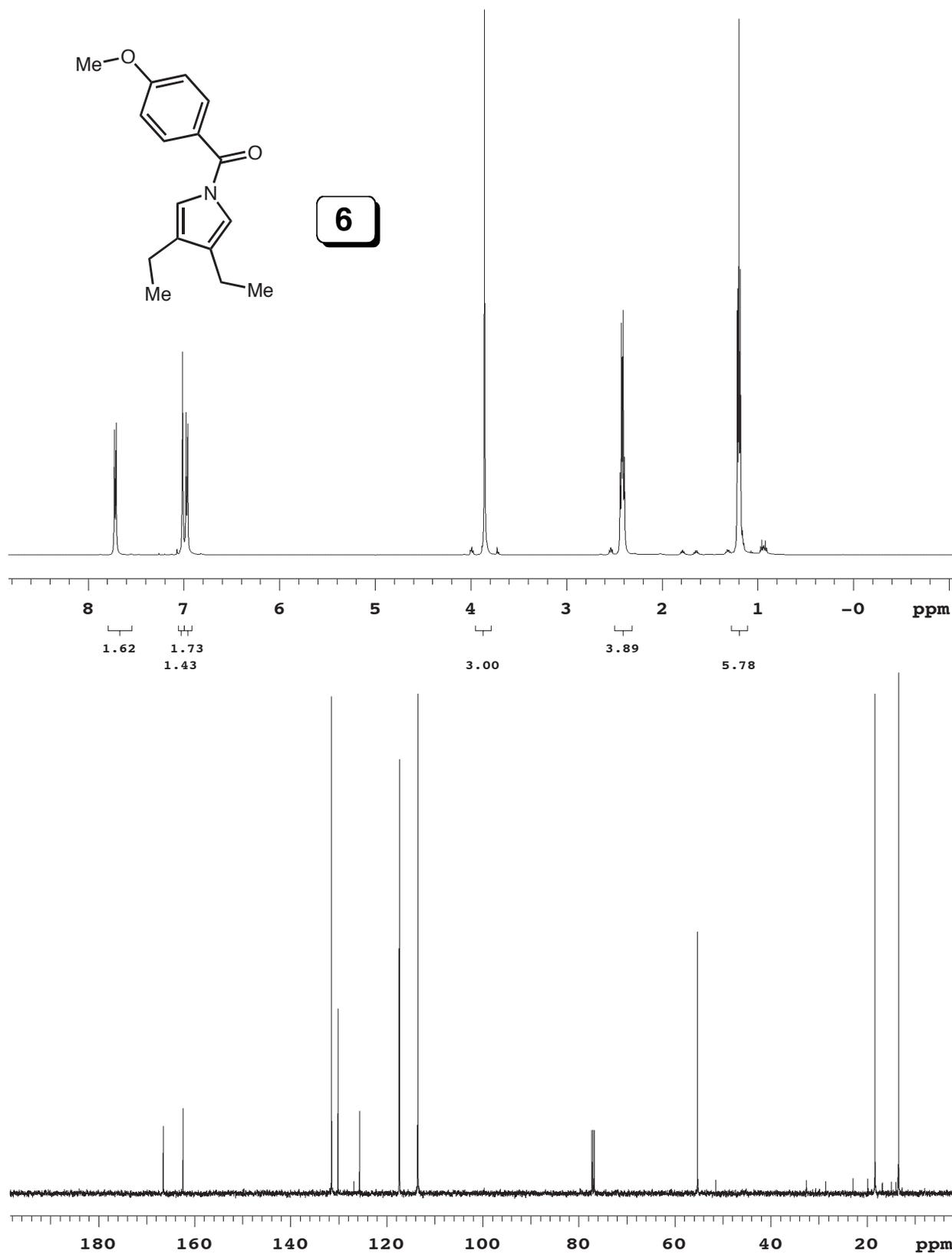
Table 6: Azine Formation RC1 Charges

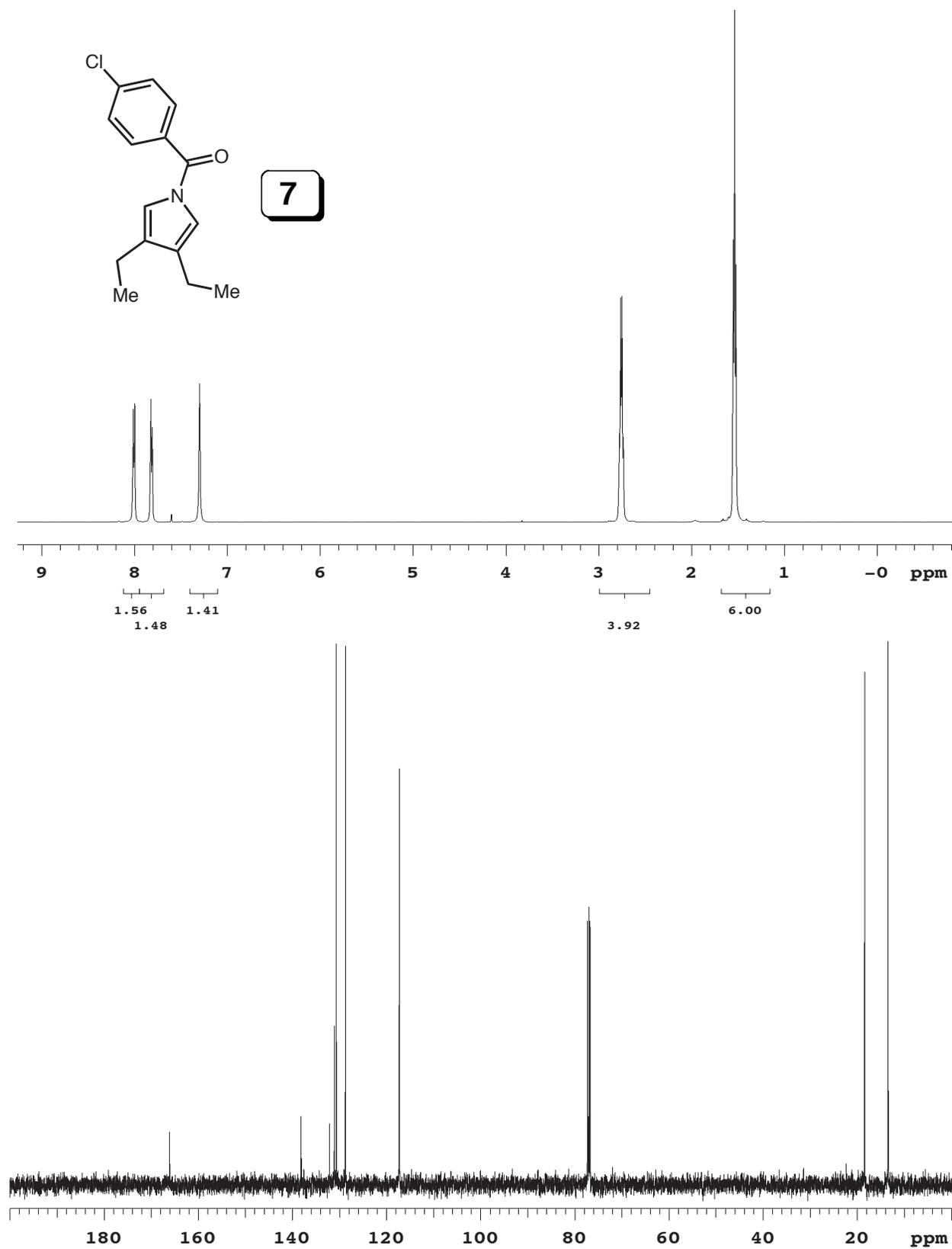
<b>Material</b>	<b>Source / Lot</b>	<b>Amount</b>	<b>Unit</b>	<b>MW</b>	<b>mmole</b>	<b>Eq</b>
Butyraldehyde	Aldrich/09924EE	15.0	g	72.11	208	1.0
Ethyl Ether	Aldrich/11090AE	18.67	g	74.12	252	1.2
Hydrazine Hydrate	Aldrich/03308TD	5.22	g	50.06	104	0.5

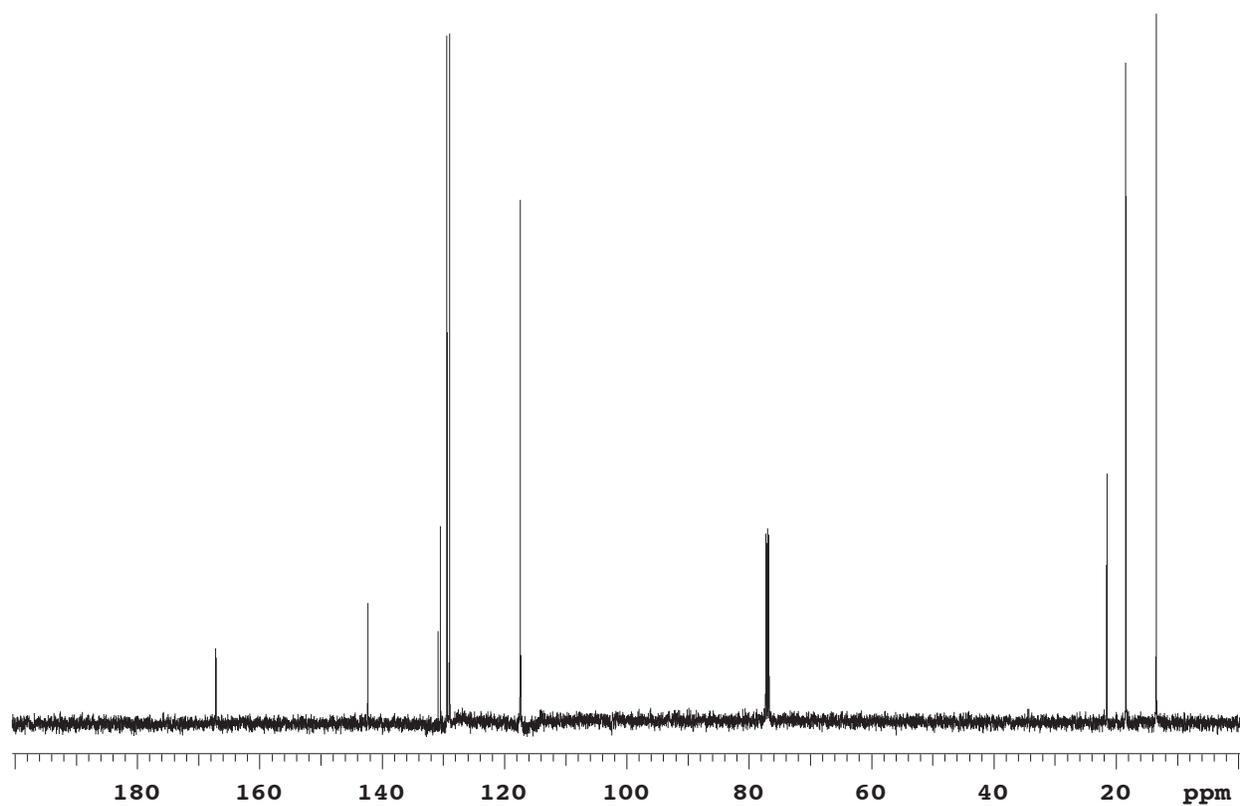
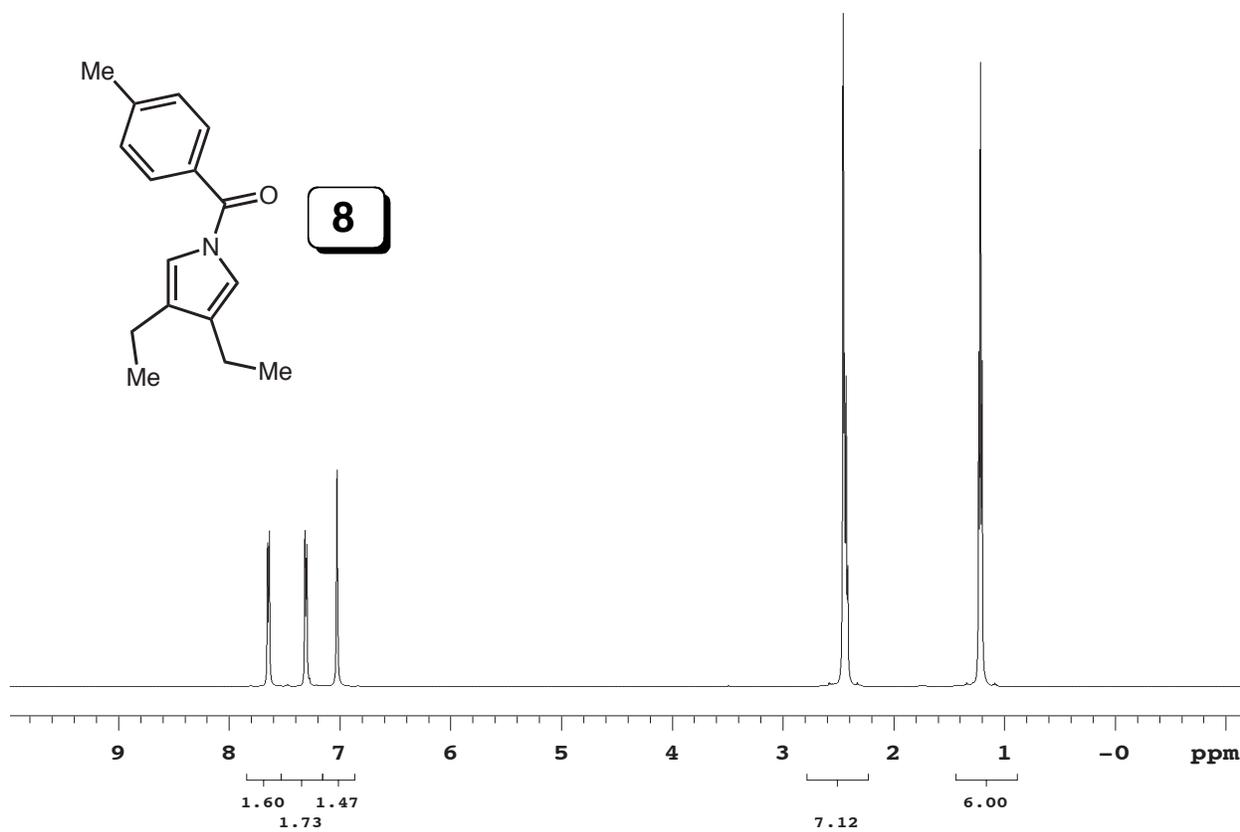
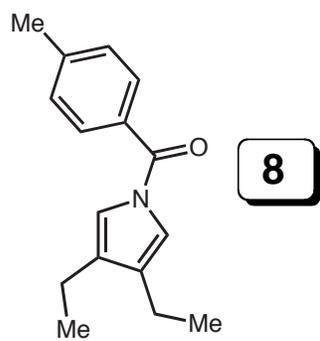
Butyraldehyde and ether were charged into the 80 mL RC1 reactor equipped with a turbine agitator. The reactor contents were ramped to 25°C and after calibration, hydrazine hydrate was added over 30 minutes via pressure transfer. The reaction was held at 25°C for 45 minutes and after calibration, the aqueous layer was removed via pipette. Samples of the aqueous and organic layers were taken for thermal stability testing and the organic layer was dried using anhydrous potassium carbonate. The Reactor contents were then removed and filtered, after which remaining ethyl ether was removed under reduced pressure to produce 13.18 g of a slightly yellow liquid.

## Selected NMR Spectra

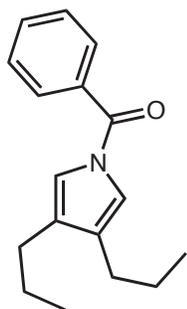




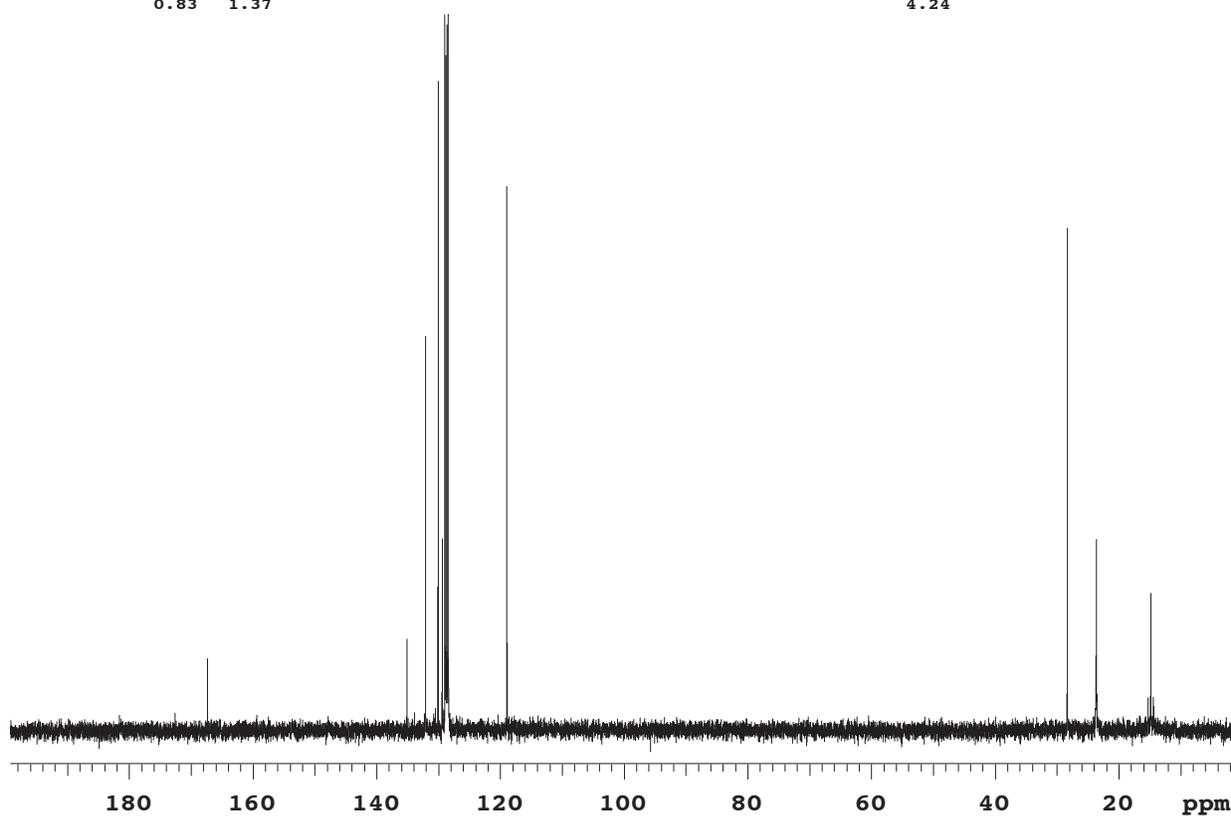
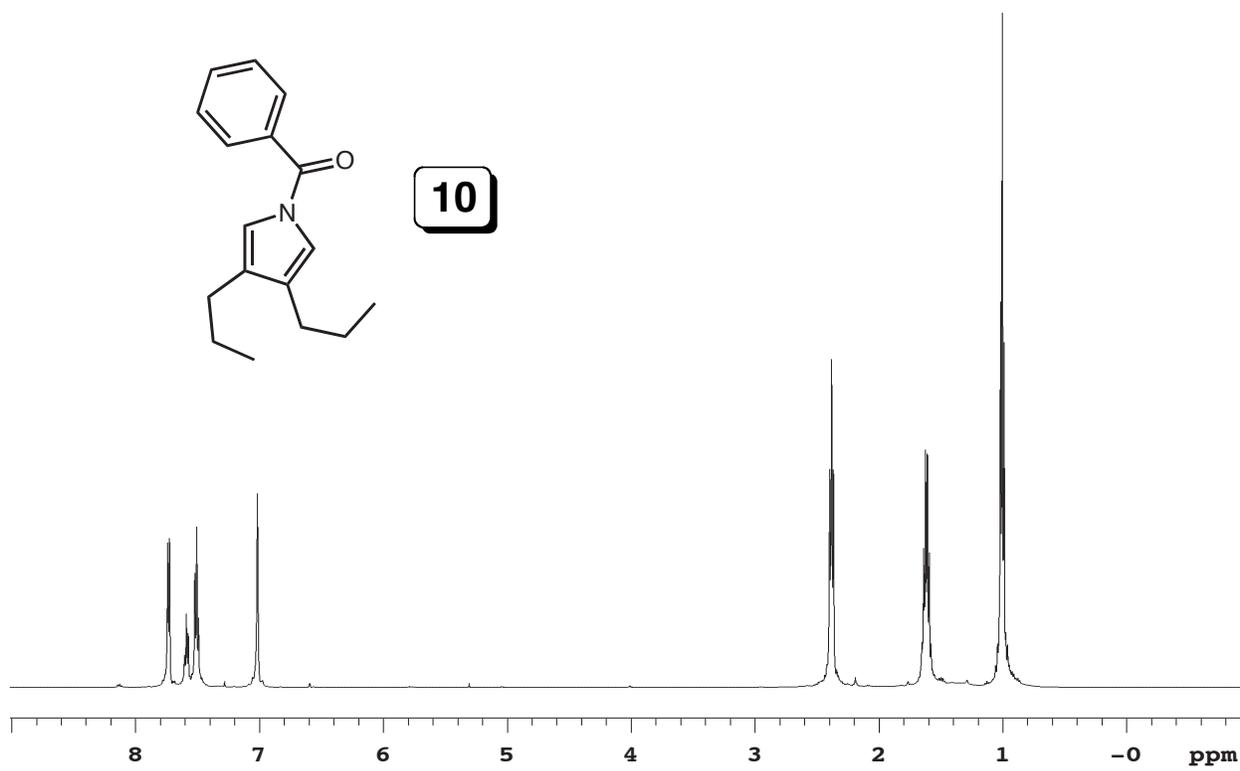


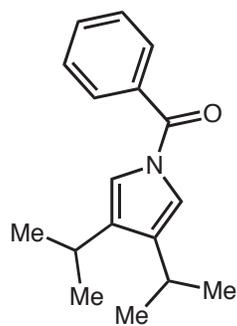




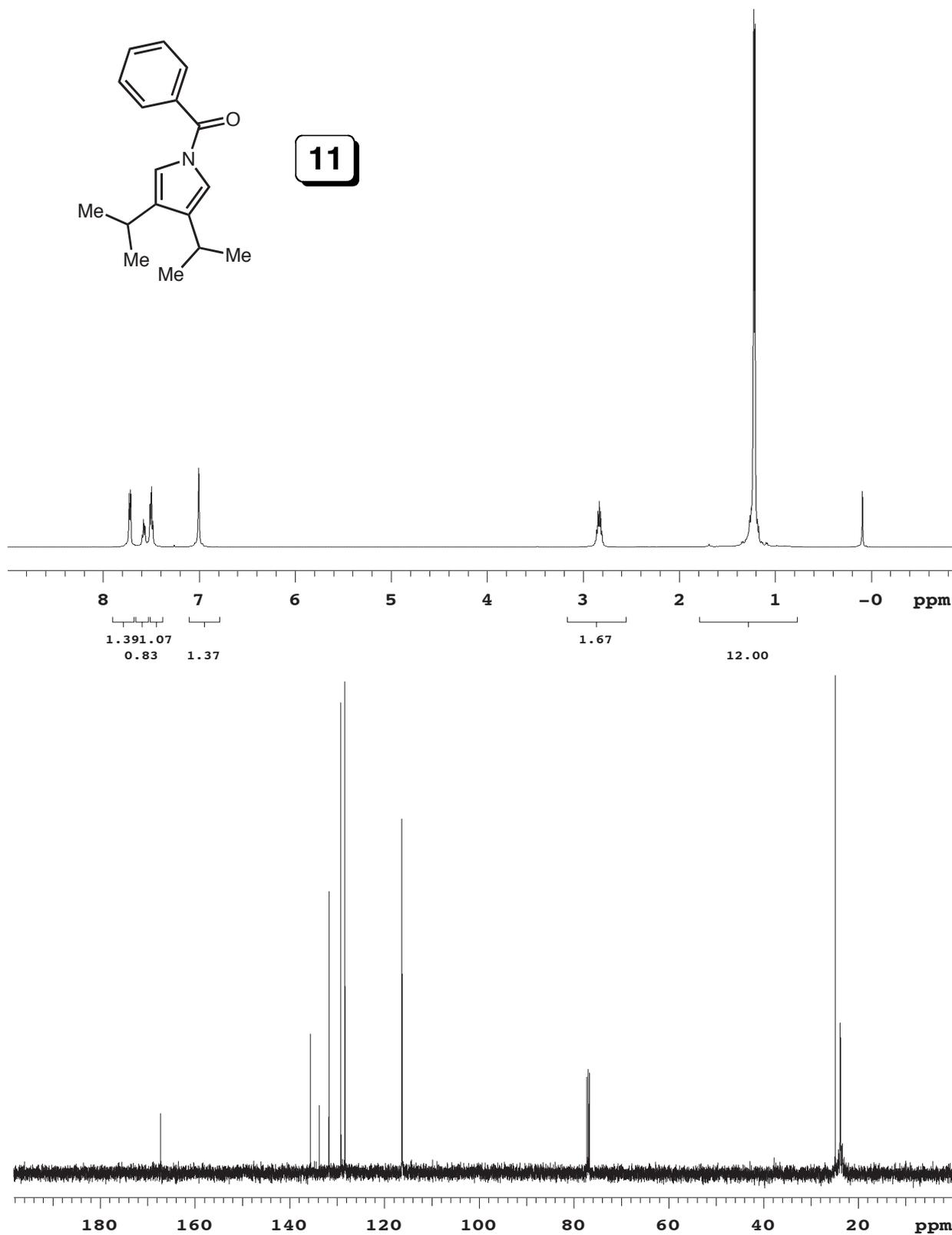


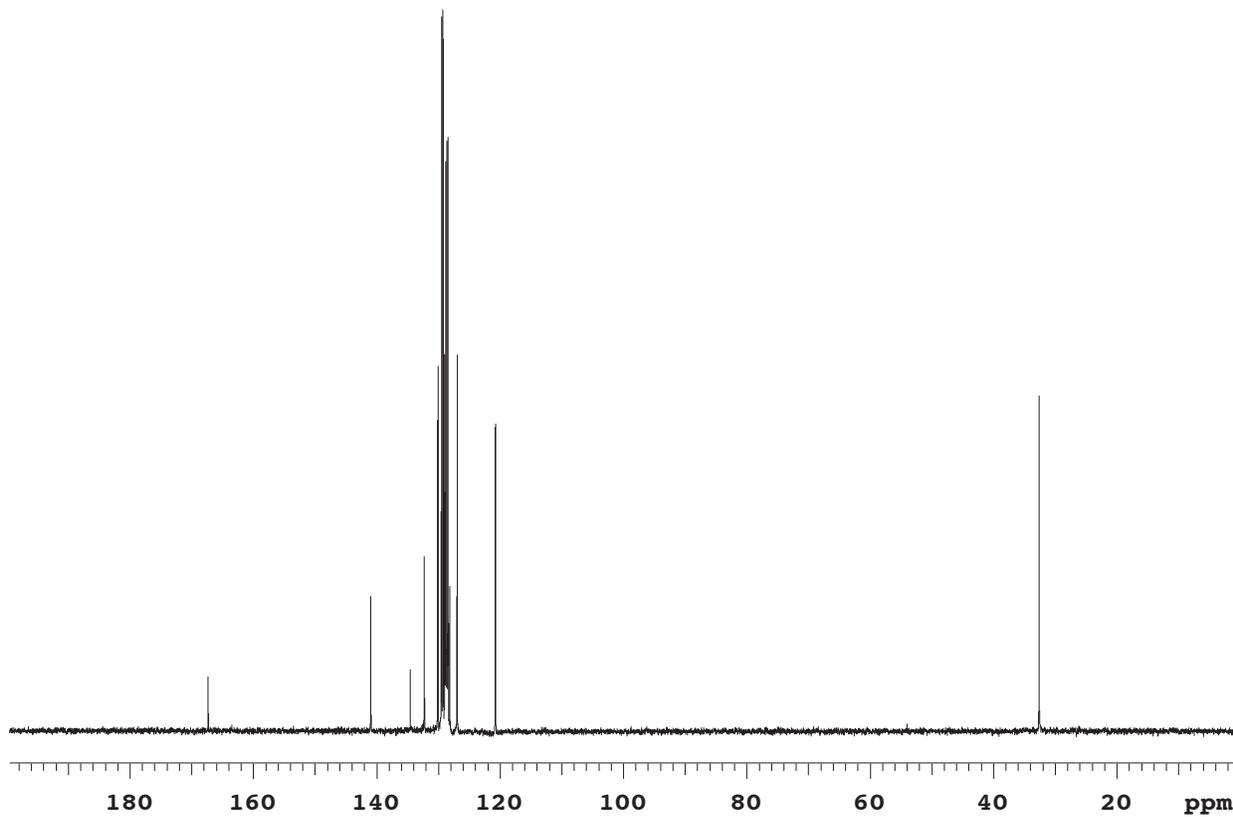
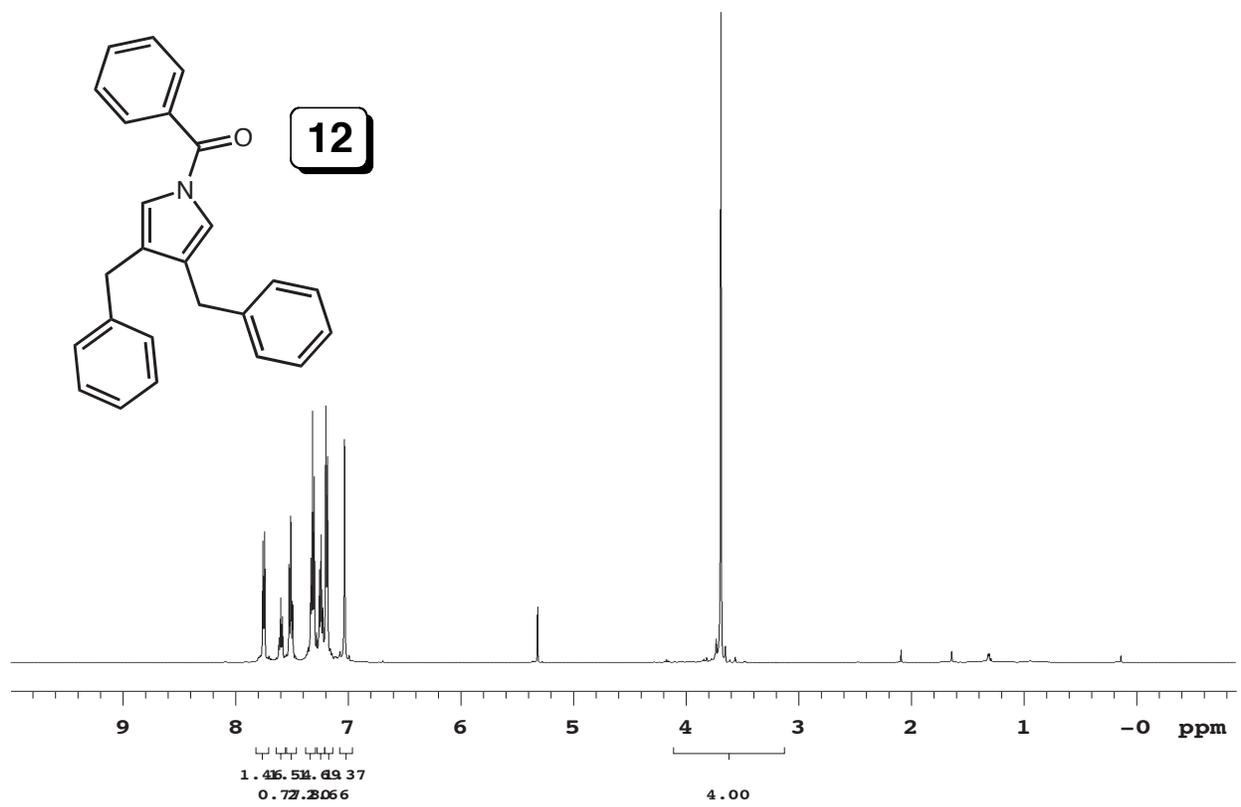
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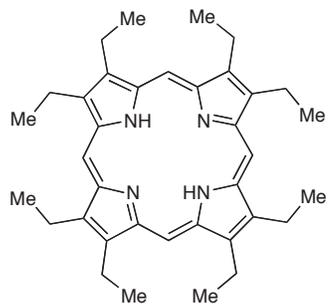




**11**







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