Electronic Supplementary Material (ESI) for Chemical Communications

Synthesis of Sterically Hindered Enamides via a Ti-Mediated Condensation of Amides with Aldehydes and Ketones

Julien Genovino, Bharat Lagu, Yaping Wang, and B. Barry Touré*

Novartis Institutes for Biomedical Research (NIBR) - 250 Massachusetts Avenue, Cambridge 02139, MA, USA

barry.toure@novartis.com

Supporting information

Table of contents

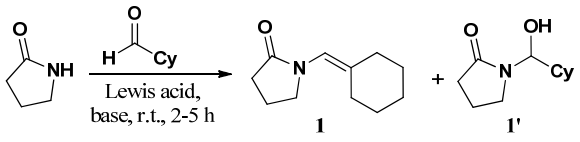
1. General methods

All reactions were carried out in oven-dried glasswares under a nitrogen atmosphere using 8cc vials fitted with Teflon caps. Chromatographic purification of products was accomplished using neutral alumina gel (Sigma, Activity grade I, type WN-3: neutral). Nuclear magnetic resonance (NMR) spectra were acquired on a Bruker Avance 400 spectrometer (400 MHz). All ^{1}H NMR spectra are reported in parts per million (ppm) and were measured relative to the signals at 7.26 ppm ($CHCl_3$) or at 5.32 ppm (CH_2Cl_2). All ^{13}C NMR spectra were also reported in parts per million (ppm) and measured relative to the signals at 77.16 ppm ($CHCl_3$) or at 53.8 ppm (CH_2Cl_2). Data for ^{1}H NMR are described as follow: chemical shift (δ in ppm), multiplicity (s: singlet; d: doublet; t: triplet; q: quartet; quint: quintuplet; m: multiplet; br: broad signal), integration, coupling constant *J* (Hz). Data for ^{13}C NMR spectra are described in terms of chemical shift (δ in ppm). All tested compounds were 95 % purity (unless stated otherwise) as determined by LC/ESI-MS Data recorded using an Agilent 6220 mass spectrometer with electrospray ionization source and Agilent 1200 liquid chromatograph. The mass accuracy of the system has been found to be < 5 ppm. When determined, crude ^{1}H NMR yields were obtained using dimethyl terephthalate (Aldrich, 99+ %) as an external standard. In practice, a known amount of dimethyl terephthalate in chloroform (100 mg / mL) was added to the reaction mixture following the quench with water.

2. Condition optimization

Our preliminary screening to optimize the reaction conditions was carried out using 2-pyrrolidone and cyclohexanecarboxaldehyde.

Table 1 Lewis acid and base screening for the condensation of amides and aldehydes.[a]



entry	Lewis acid	base	**1**: yield (%)[a, d]
1	BF_3•OEt_2	NEt_3	trace
2	$Zn(OTf)_2$	NEt_3	0
3	$AlCl_3$	NEt_3	**1**: 0 ; **1'**: 30[c]
4	$MgCl_2$	NEt_3	**1**: 0 ; **1'**: 100[c]
5	$Ti(O\textit{i}\text{-}Pr)_4$	NEt_3	**1**: 0 ; **1'**: 73[c]
6	$TiCl_4$	—	0
7	$TiCl_4$	NEt_3 (1 equiv.)	7[b]
8	$TiCl_4$	NEt_3 (2.5 equiv.)	15[b]
9	**$TiCl_4$**	**NEt_3 (5 equiv.)**	**73**[b]
10	$TiCl_4$	NEt_3 (10 equiv.)	46[b]
11	$TiCl_4$	DIPEA	53[b]
12	$TiCl_4$	DBU	15[b]
13	$TiCl_4$	DABCO	trace
14	$TiCl_4$	*t*-BuONa	trace
15	$TiCl_4$	Cs_2CO_3	11[b]
16	$TiCl_4$	NaOH	trace

[a] Standard conditions: amide (1 equiv.), aldehyde (1.1 equiv.), Lewis acid (1.2 equiv.), base (5 equiv.), 0 °C to r.t., DCM. 2-5 h; [b] Isolated yield; [c] NMR yield; [d] *N*-acyl amine intermediate **1'** was observed in trace amount in all cases except for entries 3, 4, and 5.

Notes:

- The concentration did not appear to be influencial on the yields.
- Pre-mixing $TiCl_4$ with NEt_3 provides a characteristic brown color identical to the one obtained after addition of the base in the standard procedure possibly indicating an adduct formation. The excess of NEt_3 in the medium may be influential for Lewis acid-base activation.
- Rigorous screening of bases that have different steric hindrance, nucleophilicity, and basicity is under investigation but proved so far unconclusive to corroborate or rule out a mechanism based on the activation of a Lewis acid by a Lewis base.
- To test a possible Ti-NEt_3 adduct formation $TiCl_4$ (1 equiv.) was mixed with NEt_3 (5 equiv.) in DCM in the absence of any starting amide and carbonyl compounds. ^{1}H NMR of the resulting dark brown solution showed broadening of the triethylamine signals with a downfield chemical shift (i.e. 0.2 ppm) compared to NEt_3 alone. At this stage, an interpretation on the nature of the active species is still not possible.

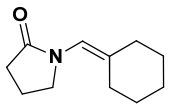
2. Representative procedure

A nitrogen-flooded sealed vial containing cyclohexanecarboxaldehyde (151.0 mg, 1.3 mmol, 1.1 equiv.) in dry dichloromethane (5 mL) was cooled down to 0 °C before titanium tetrachloride (1M solution in dichloromethane or neat, 1.2 equiv.) was added dropwise. The resulting light yellow / orange solution was stirred at this temperature for 5 min and 2-pyrrolidinone (104.2 mg, 1.2 mmol, 1 equiv.) pre-dissolved in dichloromethane (5 mL) was added slowly followed by dropwise addition of triethylamine (6.1 mmol, 5 equiv.). The color of the reaction mixture turned black upon addition of the base, a color change that did not occur when using most other bases. The reaction mixture was allowed to warm up to r.t. and was stirred over 3 h with regular monitoring using thin layer chromatography plates (eluent: ethyl acetate 1:2 heptane). The crude mixture was cooled to 0 °C and water (10 mL) was added dropwise before diluting with dichloromethane (10 mL). The layers were separated and the organic phase was extracted with dichloromethane (3 × 50 mL). The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was then purified by flash chromatography on neutral alumina gel (ethyl acetate / heptane, gradient from 1:20 to 1:2) to provide clean enamide **1** (159.0 mg, 0.9 mmol, 73 %) as a light yellow oil.

Notes:

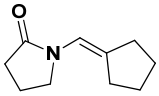
- The procedure that used 1,8-diazabicyclo[5,4,0]undec-7-ene (2.5 equiv.) in place of triethylamine is identical.
- The yields reported for the compounds therein correspond to the conditions described above unless mentioned otherwise.
- In several instances, the reaction mixtures were left under stirring for 16 h to make sure a high conversion was reached, it did not seem to improve conversion however compare to a 5-7 h reaction time.

3. Products characterization



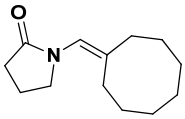
1

Deviation from representative procedure: none; reaction time: 2 h; yield: 73% (isolated) when using NEt_3, 15% (isolated) when using DBU; light yellow oil, R_f = 0.16 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 1.58 (m, 6H), 2.08 (m, 2H), 2.15 (m, 4H), 2.43 (t, 2H, *J* = 8.1 Hz), 3.60 (t, 2H, *J* = 7.7 Hz), 5.93 (s, 1H); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 18.8, 26.4, 27.3, 28.1, 28.9, 30.8, 34.0, 49.8, 116.3, 135.7, 174.9; HRMS: ($M+H^+$) calcd. 180.1388; found 180.1384.



2

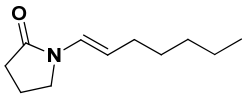
Deviation from representative procedure: none; reaction time: 16 h; yield: 49% (NMR yield), 33% (isolated), 0% when using DBU; light yellow oil, R_f = 0.14 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 1.49 (tt, 2H, *J* = 7.3 Hz, 6.0 Hz), 1.61 (tt, 2H, *J* = 7.2, 6.5 Hz), 1.98 (dt, 2H, *J* = 8.0, 7.3 Hz), 2.23 (td, 2H, *J* = 8.5 Hz, 1.5 Hz), 2.28 (td, 2H, *J* = 8.5 Hz, 1.5 Hz), 2.30 (t, 2H, *J* = 8.0 Hz), 3.63 (t, 2H, *J* = 7.3 Hz), 6.32 (t, 1H, *J* = 2.2 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 18.4, 26.0, 26.8, 29.1, 30.5, 33.0, 48.0, 115.5, 131.5, 173.7; HRMS: ($M+H^+$) calcd. 166.1227; found 166.1228.



3

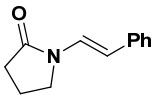
Deviation from representative procedure: none; reaction time: 16 h; yield: 62% (isolated), 0% when using DBU; colorless oil, R_f = 0.10 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 1.54 (m, 5H), 1.58 (m, 5H), 2.01 (tt, 2H, *J* = 8.1 Hz, 7.1 Hz), 2.16 (m, 4H), 2.33 (t, 2H,

J = 8.1 Hz), 3.53 (t, 2H, *J* = 7.1 Hz), 5.91 (s, 1H); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 18.7, 25.8, 25.9, 26.6, 27.0, 27.7, 29.0, 30.6, 34.2, 48.9, 119.7, 137.3, 174.4; HRMS: ($M+H^+$) calcd. 208.1696; found 208.1697.



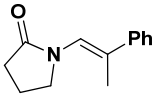
4

Deviation from representative procedure: DBU (2.5 equiv.) in place of NEt_3; reaction time: 16 h; yield: 53% (isolated); colorless oil, R_f = 0.10 (EtOAc / heptane = 1:3); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 0.83 (t, 3H, *J* = 7.4 Hz), 1.32 (m, 4H), 1.40 (m, 2H), 2.09 (m, 4H), 2.50 (t, 2H, *J* = 7.8 Hz), 3.52 (t, 2H, *J* = 7.2 Hz), 4.96 (dt, 1H, *J* = 14.4 Hz, 7.2 Hz), 6.86 (d, 1H, *J* = 14.4 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 14.1, 17.4, 22.5, 29.8, 30.0, 31.2, 31.3, 45.3, 112.6, 123.5, 172.8; HRMS: ($M+H^+$) calcd. 182.1545; found 182.1547.



5

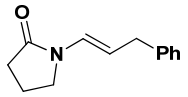
Deviation from representative procedure: NEt_3 (2.5 equiv.); reaction time: 16 h; yield: 46% (isolated), 15% (isolated) when using DBU; colorless oil; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 2.05 (tt, 2H, *J* = 7.5 Hz, 7.9 Hz), 2.40 (t, 2H, *J* = 7.9 Hz), 3.55 (t, 2H, *J* = 7.5 Hz), 5.82 (d, 1H, *J* = 14.8 Hz), 7.08 (t, 1H, *J* = 7.5 Hz), 7.20 (dd, 2H, *J* = 7.9 Hz, 7.5 Hz), 7.28 (d, 2H, *J* = 7.9 Hz), 7.52 (d, 1H, *J* = 14.8 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 17.9, 31.6, 45.6, 111.6, 124.0, 125.9, 126.8, 129.0, 137.0, 173.6; HRMS: ($M+H^+$) calcd. 188.1075; found 188.1084.



6

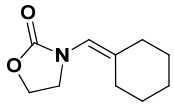
Deviation from representative procedure: NEt_3 (2.5 equiv.); reaction time: 16 h; yield: 43% (isolated as a mixture of *cis* / *trans* isomers, 1:1.3), 30% when using DBU (isolated as a mixture of *cis* and *trans* isomers in the same ratio as above); Both isomers were isolated for

characterization purposes; *Trans* isomer: colorless oil; ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 1.70 (tt, 2H, *J* = 15.6, 7.5 Hz), 1.97 (d, 3H, *J* = 1.0 Hz), 2.19 (t, 2H, *J* = 8.0 Hz), 2.83 (t, 2H, J = 7.0 Hz), 6.55 (s, 1H), 7.16 (t, 1H, *J* = 7.2 Hz), 7.24 (dd, 2H, *J* = 7.9, 7.2), 7.32 (d, 2H, *J* = 7.9 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 17.9, 23.0, 29.6, 47.3, 119.8, 122.3, 126.2, 127.1, 127.6, 140.0, 174.0; HRMS: ($M+H^+$) calcd. 202.1232; found 202.1234.



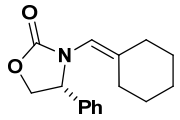
7

Deviation from representative procedure: none; reaction time: 16 h; Yield: 35% (NMR yield), 35% (isolated), 0% when using DBU; light brown oil, R_f = 0.16 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 1.98 (tt, 2H, *J* = 7.5 Hz), 2.38 (t, 2H, *J* = 8.5 Hz), 3.31 (d, 2H, *J* = 7.3 Hz), 3.39 (t, 2H, *J* = 7.5 Hz), 4.99 (dt, 1H, *J* = 14.3 Hz, 7.5 Hz), 6.92 (d, 1H, *J* = 14.3 Hz), 7.12 (m, 3H), 7.20 (dd, 2H, *J* = 8.3 Hz, 7.5 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 17.5, 31.3, 36.6, 45.3, 111.1, 124.6, 126.2, 128.4, 128.5, 140.7, 173.1; HRMS: ($M+H^+$) calcd. 202.1227; found 202.1234.



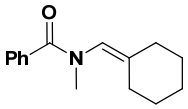
8

Deviation from representative procedure: NEt_3 (2.5 equiv.); reaction time: 16 h; yield: 54% (isolated), 14% (isolated) when using DBU; colorless oil, R_f = 0.21 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, CD_2Cl_2) = 1.49 (m, 6H), 2.07 (m, 4H), 3.65 (t, 2H, *J* = 8.0 Hz), 4.24 (t, 2H, *J* = 8.0 Hz), 5.71 (s, 1H); ^{13}C NMR: δ_C (100 MHz, CD_2Cl_2) = 25.0, 25.9, 26.8, 27.0, 32.3, 45.5, 60.8, 114.5, 134.3, 156.0; HRMS: (M+H+) calcd. 182.1181; found 182.1174.



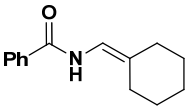
9

Deviation from representative procedure: NEt_3 (2.5 equiv.), $TiCl_4$ (2 equiv.); reaction time: 16 h; yield: 54% isolated; colorless oil; ^1H NMR: δ_H (400 MHz, CD_2Cl_2) = 1.40 (m, 2H), 1.53 (m, 4H), 2.05 (t, 2H, J = 5.5 Hz), 2.13 (m, 1H), 2.21 (m, 1H), 4.15 (dd, 1H, J = 8.5 Hz, 7.0 Hz), 4.68 (t, 1H, J = 8.5 Hz), 4.15 (dd, 1H, J = 8.5 Hz, 7.0 Hz), 5.41 (t, 1H, J = 1.0 Hz), 7.31 (dd, 2H, J = 8.5 Hz, 2.0 Hz), 7.41 (m, 3H); 13C NMR: δ_C (100 MHz, CD_2Cl_2) = 26.6, 27.3, 28.5, 29.3, 33.6, 62.5, 70.2, 114.3, 127.3, 129.1, 129.4, 138.8, 141.5, 157.0; HRMS: (M+H+) calcd. 258.1494; found 258.1504.



10

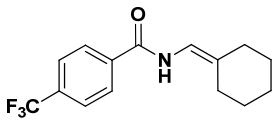
Deviation from representative procedure: dichloroethane was used in place of dichloromethane in order to heat the reaction at 60 °C; reaction time: 16 h; yield: 75% (NMR yield), 63% (isolated), 0% when using DBU; White solid, R_f = 0.38 (EtOAc / heptane = 1:2); ^1H NMR: δ_H (400 MHz, $CDCl_3$) = 1.19 (m, 2H), 1.44 (m, 4H), 1.91 (m, 4H), 3.16 (s, 3H), 5.88 (s, 1H), 7.35 (m, 3H), 7.53 (dd, 2H, J = 7.7 Hz, 1.5 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 26.0, 26.1, 24.7, 27.7, 32.8, 36.2, 123.4, 127.5, 128.5, 129.8, 136.3, 139.2, 171.1; HRMS: ($M+H^+$) calcd. 230.1545; found 230.1538.



11

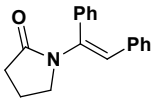
Deviation from representative procedure: NEt_3 (3 equiv.), $TiCl_4$ (1 equiv.); reaction time: 16 h; yield: 20% isolated; colorless oil, ^1H NMR: δ (400 MHz, $CDCl_3$) = 1.60 (m, 6H), 2.18 (m, 4H), 6.75 (d, 1H, J = 10.5 Hz), 7.47 (dd, 2H, J = 7.5 Hz, 7.0 Hz), 7.54 (td, 1H, J = 7.5 Hz, 1.5 Hz),

7.81 (dd, 2H, J = 7.0 Hz, 1.5 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 26.7, 27.0, 27.7, 28.1, 33.6; 114.2, 124.4, 126.9, 128.7, 131.7, 134.3, 164.3.



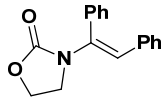
12

Deviation from representative procedure: none; reaction time: 16 h; yield: 17% (NMR yield), 11% (isolated); white solid, R_f = 0.34 (EtOAc / heptane = 1:4); ^{1}H NMR: δ_H (400 MHz, CD_2Cl_2) = 1.50 (m, 6H), 2.09 (m, 4H), 6.59 (dt, 1H, *J* = 10.3 Hz, 1.1 Hz), 7.52 (bd, 1H, *J* = 10.3 Hz), 7.63 (d, 2H, *J* = 8.1 Hz), 7.81 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR: δ_C (100 MHz, CD_2Cl_2) = 26.9, 27.4, 28.1, 28.6, 33.9, 114.2, 124.3 (q, *J* = 272 Hz), 126.0 (q, *J* = 2.8 Hz), 127.8, 133.5 (q, *J* = 32 Hz), 138.2, 163.1; HRMS: ($M+H^+$) calcd. 284.1262; found 284.1234.



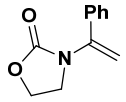
14

Deviation from representative procedure: none; reaction time: 6 h; yield: 51% (NMR yield), 40% (isolated) when using DBU; white solid; R_f = 0.21 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 1.93 (tt, 2H, *J* = 7.9, 7.2 Hz), 2.39 (t, 2H, *J* = 7.9 Hz), 3.33 (t, 2H, *J* = 7.2 Hz), 6.64 (s, 1H), 6.89 (dd, 2H, *J* = 7.9 Hz, 1.9 Hz), 6.99 (m, 3H), 7.15 (dd, 2H, *J* = 7.5 Hz, 1.9 Hz), 7.22 (m, 3H); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 18.8, 32.6, 49.6, 123.6, 126.9, 128.3,128.7, 128.9, 129.5, 129.5, 129.8, 135.8, 136.3, 137.3, 174.7; HRMS: ($M+H^+$) calcd. 264.1388; found 264.1396. The double bond geometry was assigned by nOe correlation between the olefinic proton and the CH_2 alpha to the nitrogen.



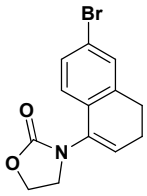
15

Deviation from representative procedure: none; reaction time: 7 h; yield: 50% (NMR yield), 45% (isolated); white solid; R_f = 0.29 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 3.55 (dd, 2H, J = 7.8 Hz, 6.9 Hz), 4.28 (dd, 2H, 7.8 Hz, 6.9 Hz), 6.75 (s, 1H), 6.89 (m, 2H), 7.01 (m, 3H), 7.22 (m, 2H), 7.26 (m, 3H); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 45.9, 61.6, 122.8, 126.8, 127.9, 128.8, 128.9, 129.2, 129.5, 134.3, 135.4, 135.5, 156.1; HRMS: ($M+H^+$) calcd. 266.1181; found 266.1178. The double bond geometry was assigned by analogy to enamide **17**, which geometry was confirmed by nOe correlation (see above).



16

Deviation from representative procedure: none; reaction time: 3 h; yield: 52% (NMR yield); 50% (isolated); light brown solid; R_f = 0.21 (EtOAc / heptane = 1:4); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 3.75 (dd, 2H, *J* = 8.1 Hz, 6.9 Hz), 4.40 (dd, 2H, *J* = 8.1 Hz, 6.9 Hz), 5.22 (s, 1H), 5.25 (s, 1H), 7.36 (m, 5H; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 46.4, 61.8, 106.8, 126.7, 128.5, 128.8, 135.8, 143.0, 155.9; HRMS: ($M+H^+$) calcd. 190.0868; found. 190.0870.



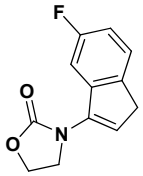
17

Deviation from representative procedure: none; reaction time: 7 h; yield: 54% (NMR yield), 43% (isolated); light-yellow orange solid; R_f = 0.33 (EtOAc / heptane = 1:1); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 2.36 (td, 2H, *J* = 7.1 Hz, 4.8 Hz), 2.68 (t, 2H, *J* = 8.1 Hz), 3.76 (dd, 2H, *J* = 8.1 Hz, 7.9 Hz), 4.44 (dd, 2H, *J* = 8.1 Hz, 7.8 Hz), 6.10 (t, 1H, *J* = 4.8 Hz), 6.97 (d, 1H, *J* = 8.0 Hz),

7.14 (d, 1H, *J* = 2.1 Hz), 7.23 (dd, 1H, 8.0 Hz, 2.1 Hz),; ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 22.4, 26.8, 47.2, 62.2, 120.3, 124.9, 126.9, 129.5, 130.7, 132.5, 133.4, 135.3, 157.0; HRMS: ($M+H^+$) calcd. 294.0130; found. 294.0135.

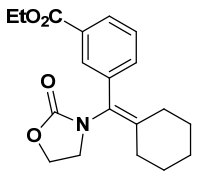
18

Deviation from representative procedure: none; reaction time: 6 h; yield: 54% (NMR yield), 49% (isolated); white solid; R_f = 0.13 (EtOAc / heptane = 1:4); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 3.78 (dd, 2H, *J* = 8.9 Hz, 6.7 Hz), 4.45 (dd, 2H, *J* = 8.9 Hz, 6.7 Hz), 4.93 (d, 2H, *J* = 4.0 Hz), 5.88 (t, 1H, *J* = 4.0 Hz), 6.78 (dd, 1H, *J* = 8.0 Hz, 7.8 Hz), 7.00 (dd, 1H, *J* = 7.8 Hz, 1.5 Hz), 7.36 (dd, 1H, *J* = 8.0 Hz, 1.5 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 47.0, 62.4, 65.8, 110.5, 118.3, 121.0, 122.1, 122.3, 131.8, 133.6, 151.8, 156.7; HRMS: ($M+H^+$) calcd. 294.9844; found. 294.9844.



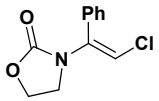
19

Deviation from representative procedure: none; reaction time: 7 h; yield: 46% (NMR yield), 38% (isolated); light-yellow orange solid; R_f = 0.9 (EtOAc / heptane = 1:4); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 3.32 (d, 2H, *J* = 2.2 Hz), 3.99 (dd, 2H, *J* = 8.0 Hz, 6.9 Hz), 4.46 (dd, 2H, *J* = 8.0 Hz, 6.9 Hz), 6.24 (t, 1H, *J* = 2.2 Hz), 6.87 (td, 1H, *J* = 8.7 Hz, 2.2 Hz), 7.27 (m, 2H); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 35.5, 46.8, 62.5, 108.6 (d, *J* = 24,7 Hz), 112.5 (d, *J* = 23.8 Hz), 122.0, 124.6 (d, *J* = 9.4 Hz), 138.6 (d, *J* = 2.2 Hz), 139.0 (d, *J* = 3.2 Hz) 141.1 (d, *J* = 9.4 Hz), 155.6, 162.0 (d, *J* = 242 Hz); HRMS: ($M+H^+$) calcd. 220.0774; found. 220.0780.



20

Deviation from representative procedure: none; reaction time: 16 h; yield: 32% (NMR yield), 19% (isolated); white solid; R_f = 0.20 (EtOAc / heptane = 1:2); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 1.41 (t, 3H, *J* = 7.1 Hz), 1.61 (m, 4H), 1.73 (m, 2H), 2.20 (t, 2H, *J* = 6.0 Hz), 2.32 (t, 1H, *J* = 6.1 Hz), 3.49 (t, 2H, *J* = 7.7 Hz), 4.37 (t, 2H, *J* = 7.7 Hz), 4.40 (q, 2H, 7.1 Hz), 7.45 (t, 1H, *J* = 7.5 Hz), 7.49 (dt, 1H, *J* = 7.5 Hz, 1.6 Hz), 7.92 (t, 1H, *J* = 1.6 Hz), 8.00 (dt, 1H, *J* = 7.5 Hz, 1.6 Hz); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 14.3, 26.4, 27.5, 27.8, 30.6, 31.1, 45.6, 61.2, 61.9, 124.9, 128.6, 128.9, 130.4, 130.6, 133.7, 136.5, 142.2, 156.7, 166.4; HRMS: ($M+H^+$) calcd. 330.1705; found. 330.1707.

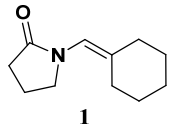


21

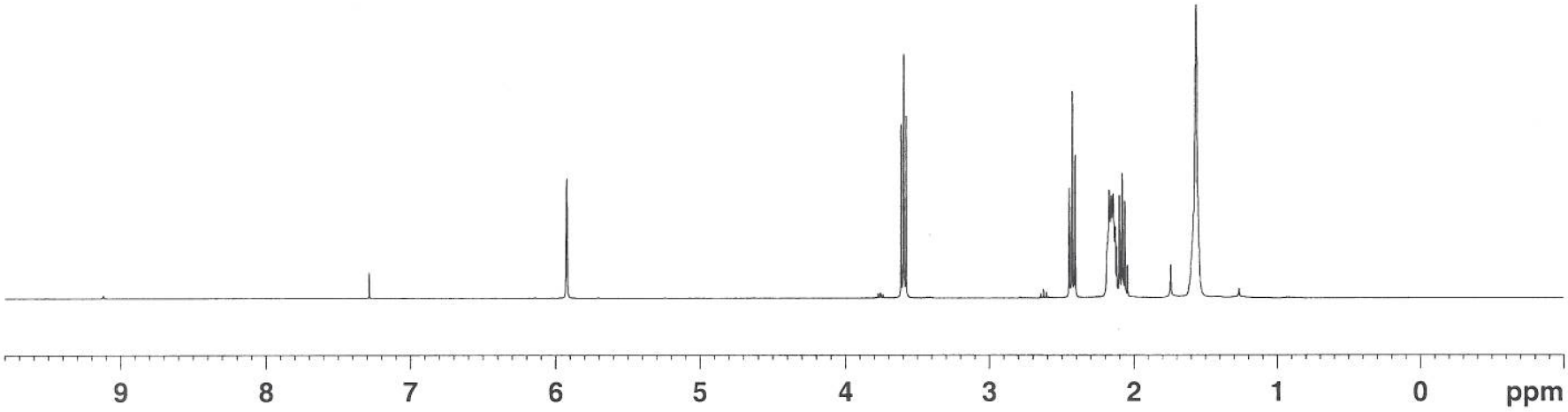
Deviation from representative procedure: none; reaction time: 16 h; yield: 18% (NMR yield); 11% (isolated); light yellow oil; R_f = 0.97 (EtOAc / heptane = 1:4); ^{1}H NMR: δ_H (400 MHz, $CDCl_3$) = 3.56 (dd, 2H, *J* = 7.8 Hz, 6.8 Hz), 4.38 (dd, 2H, *J* = 7.8 Hz, 6.8 Hz), 6.55 (s, 1H), 7.45 (m, 5H); ^{13}C NMR: δ_C (100 MHz, $CDCl_3$) = 46.0, 61.8, 113.9, 129.0, 129.3, 129.5, 132.1, 136.6, 156.0; HRMS: ($M+H^+$) calcd. 224.0478; found. 224.0479. The double bond geometry was assigned by analogy to enamide **17**, which geometry was confirmed by nOe correlation (see above); While the (*E*)-olefin was the only isomer after work up, the product seemed to be prone to minor isomerization during purification.

4. NMR spectra

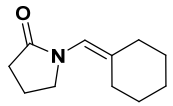
^{1}H NMR / 400 MHz / $CDCl_3$



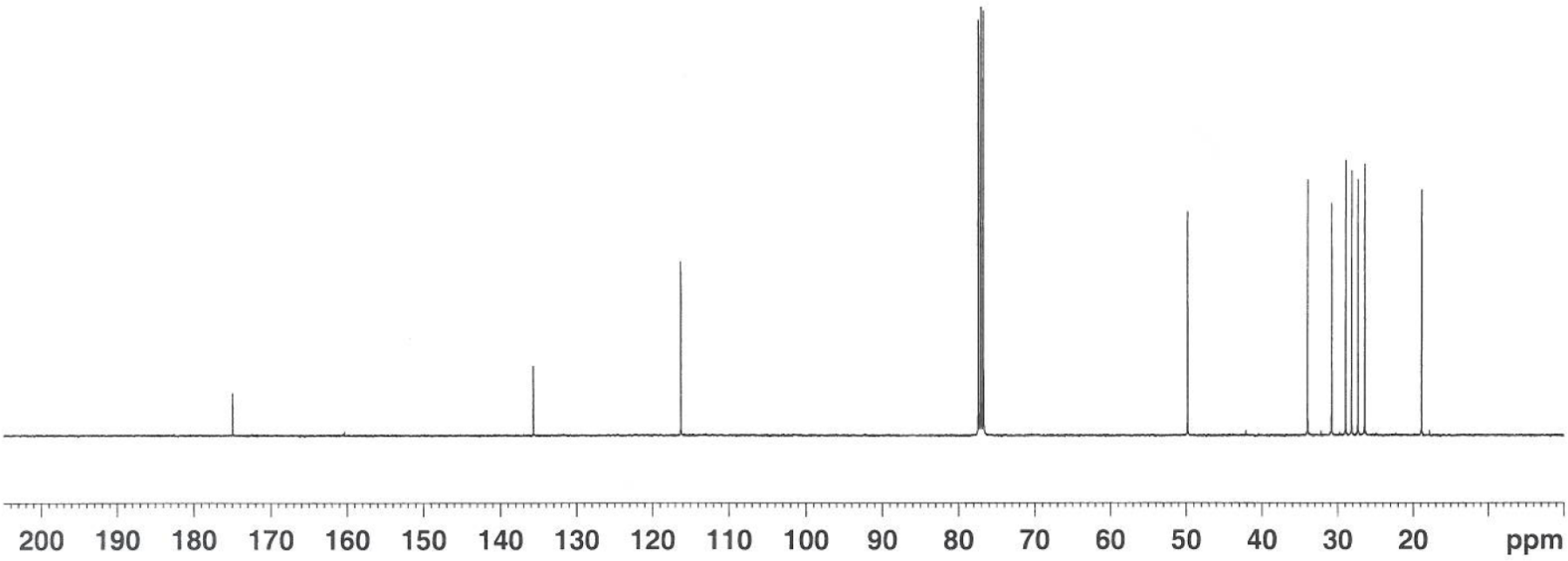
1



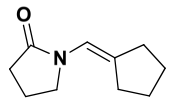
^{13}C NMR / 100 MHz / $CDCl_3$



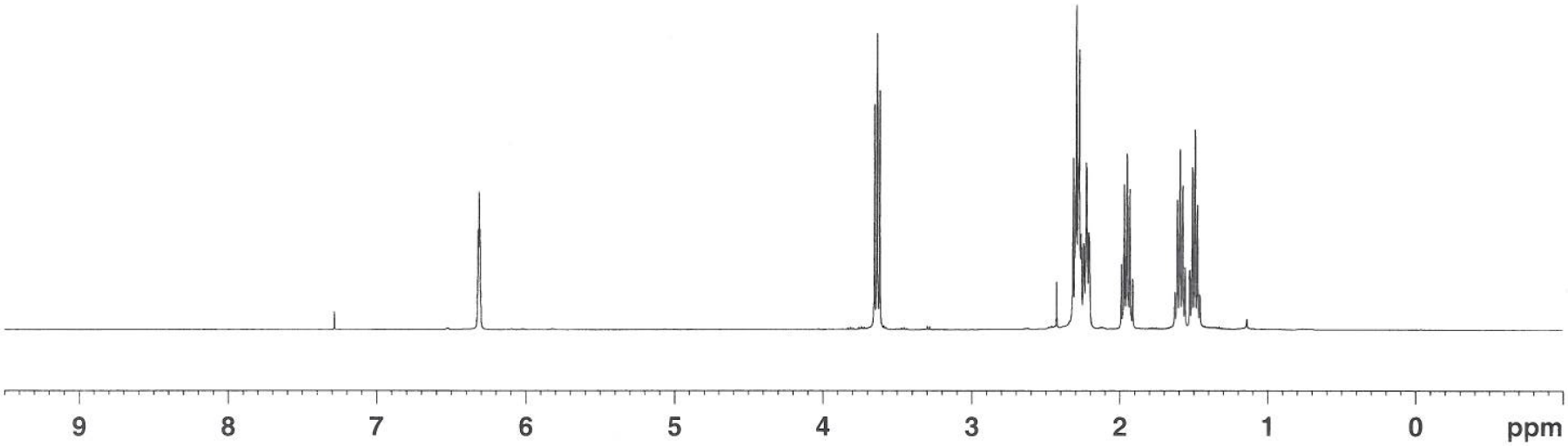
1



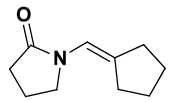
^{1}H NMR / 400 MHz / $CDCl_3$



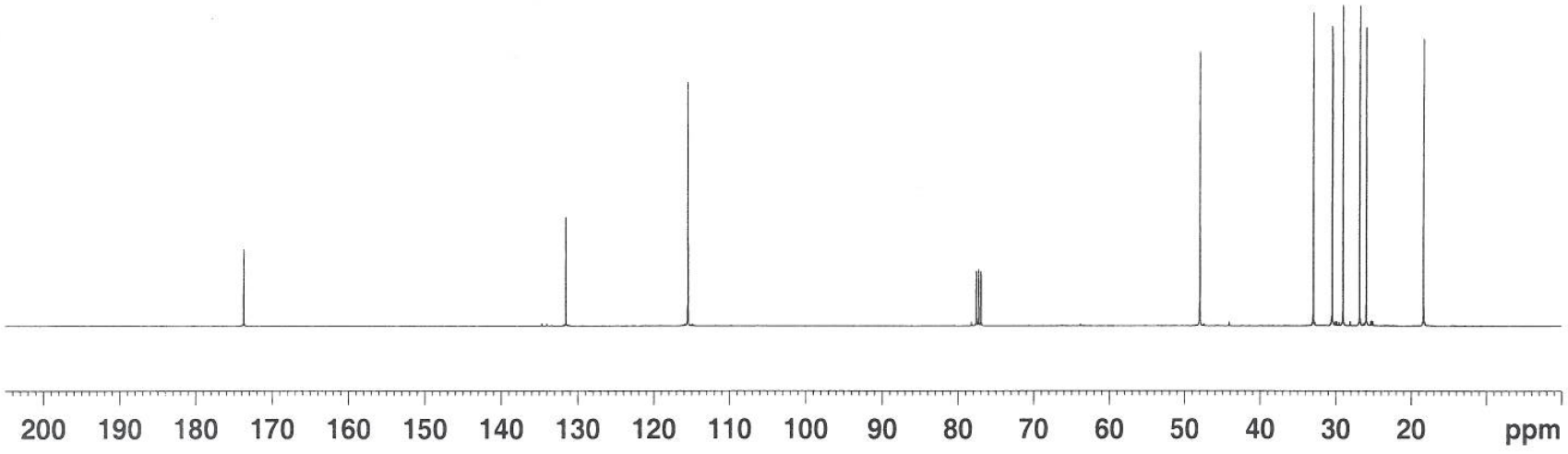
2



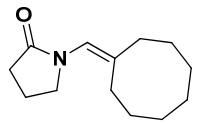
^{13}C NMR / 100 MHz / $CDCl_3$



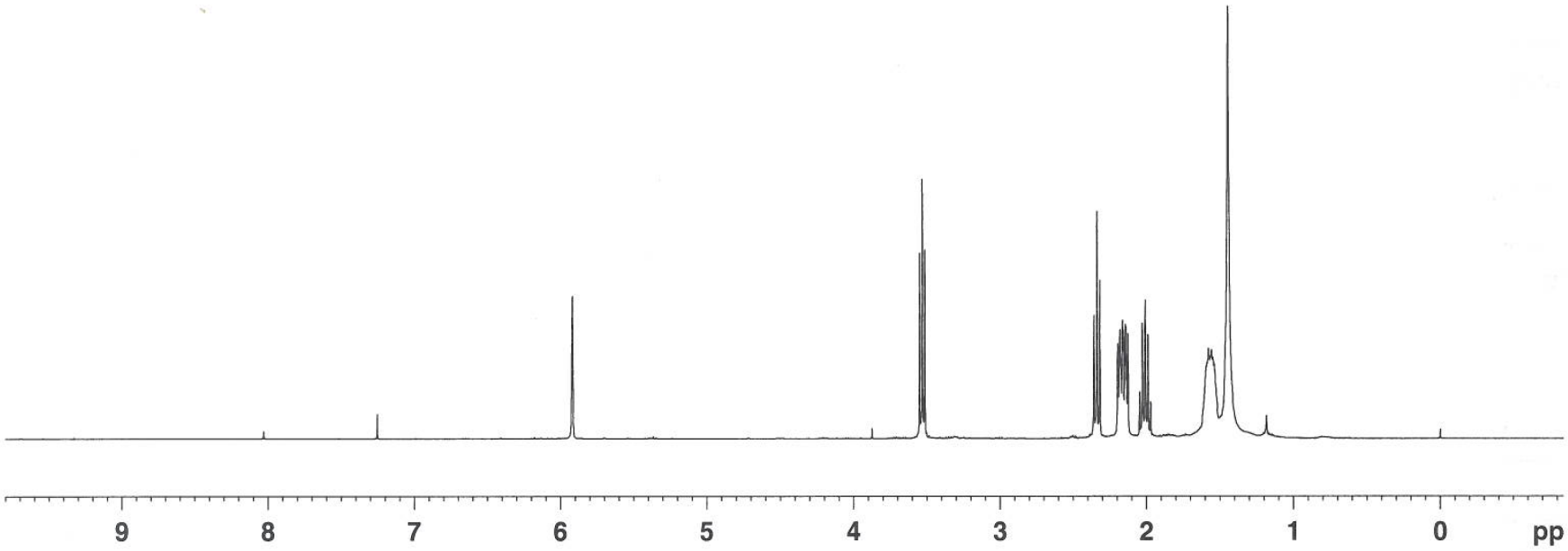
2



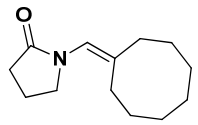
^{1}H NMR / 400 MHz / $CDCl_3$



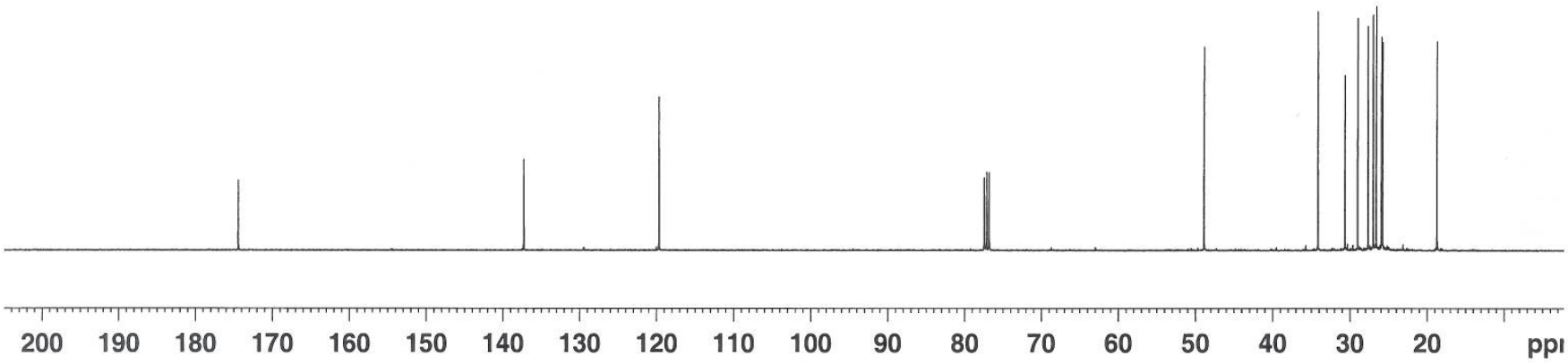
3



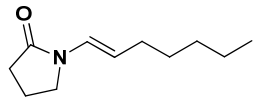
^{13}C NMR / 100 MHz / $CDCl_3$



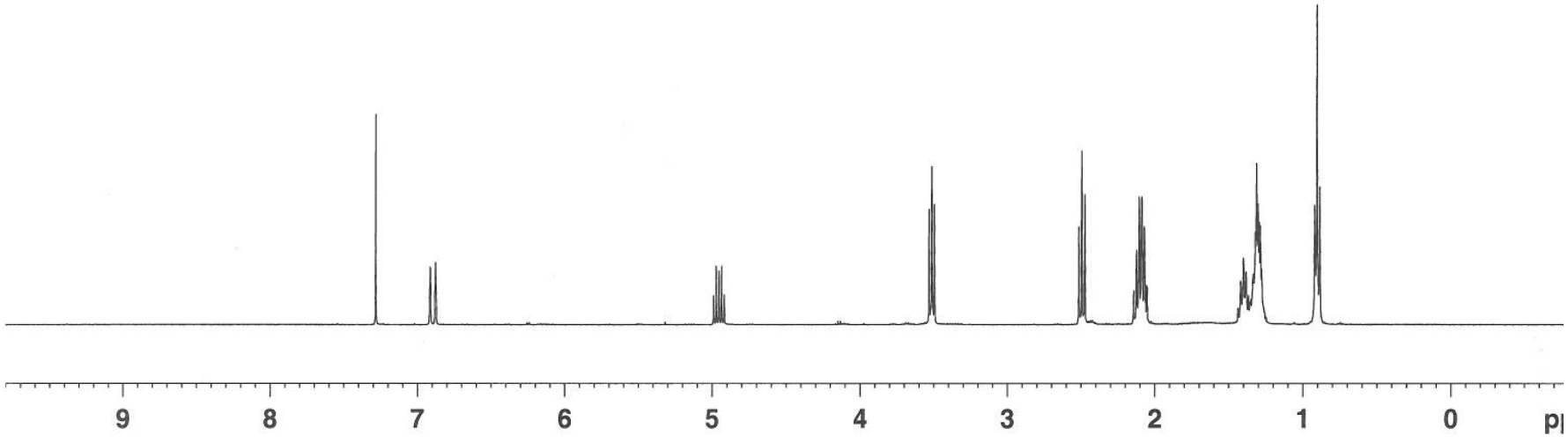
3



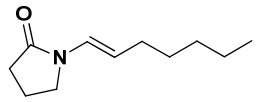
^{1}H NMR / 400 MHz / $CDCl_3$



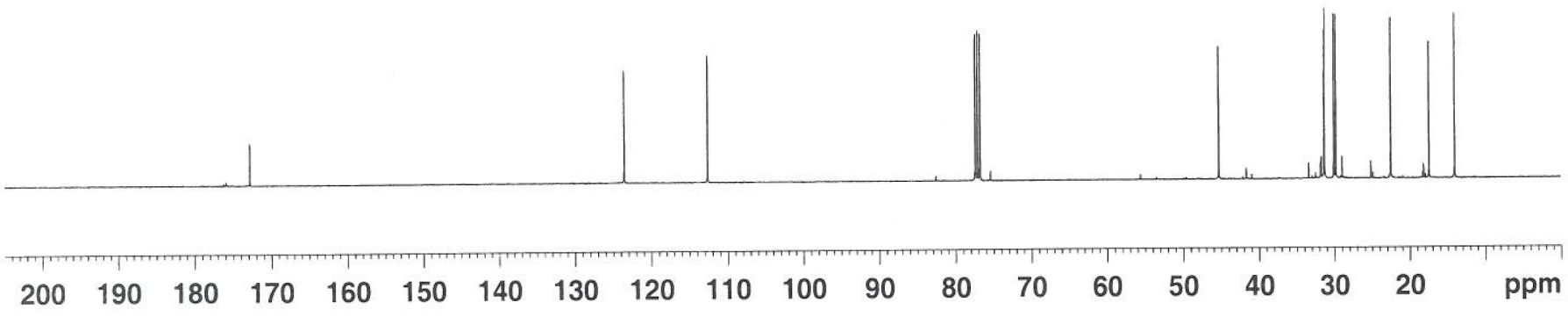
4



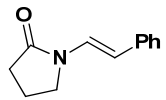
^{13}C NMR / 100 MHz / $CDCl_3$



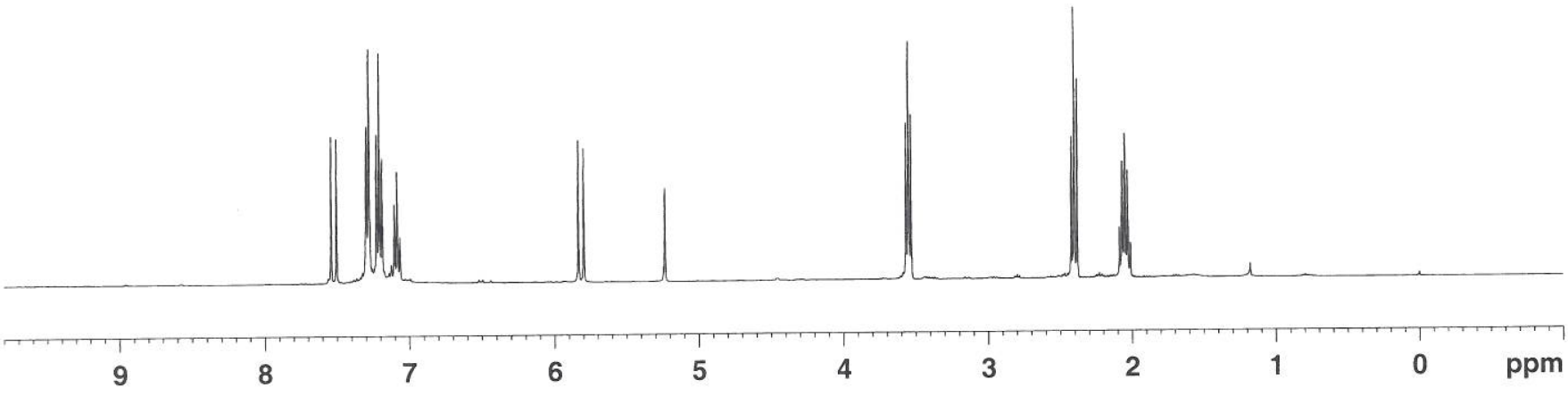
4



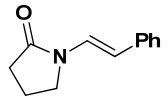
^{1}H NMR / 400 MHz / $CDCl_3$



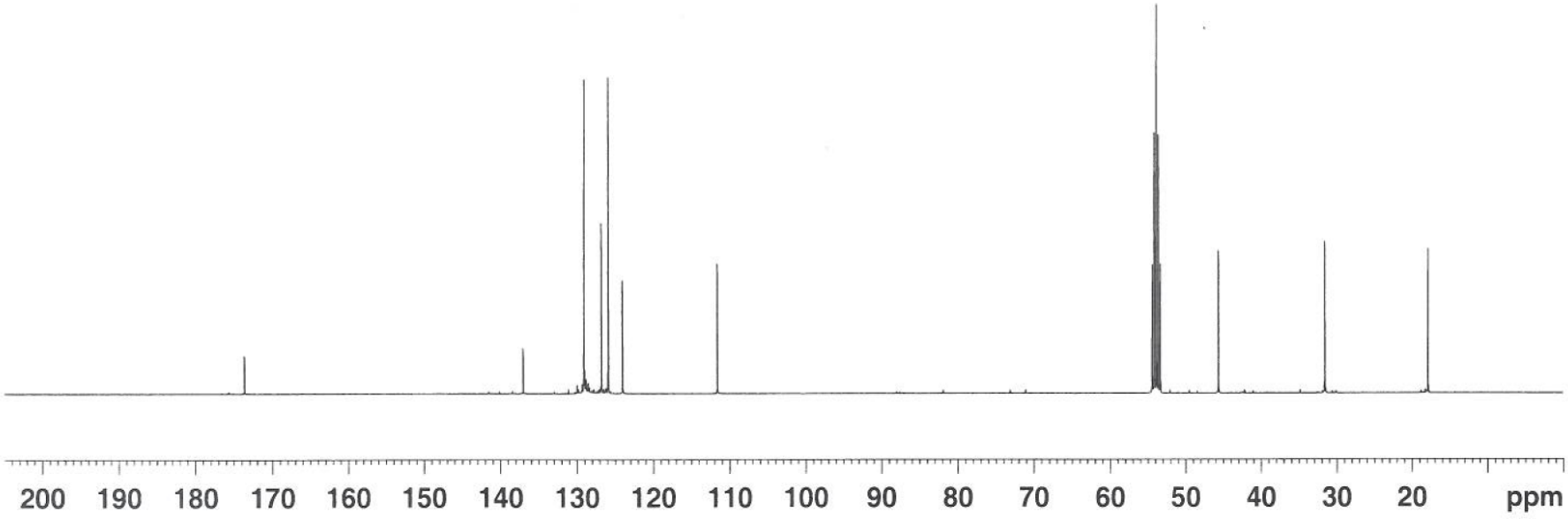
5



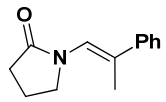
^{13}C NMR / 100 MHz / CD_2Cl_2



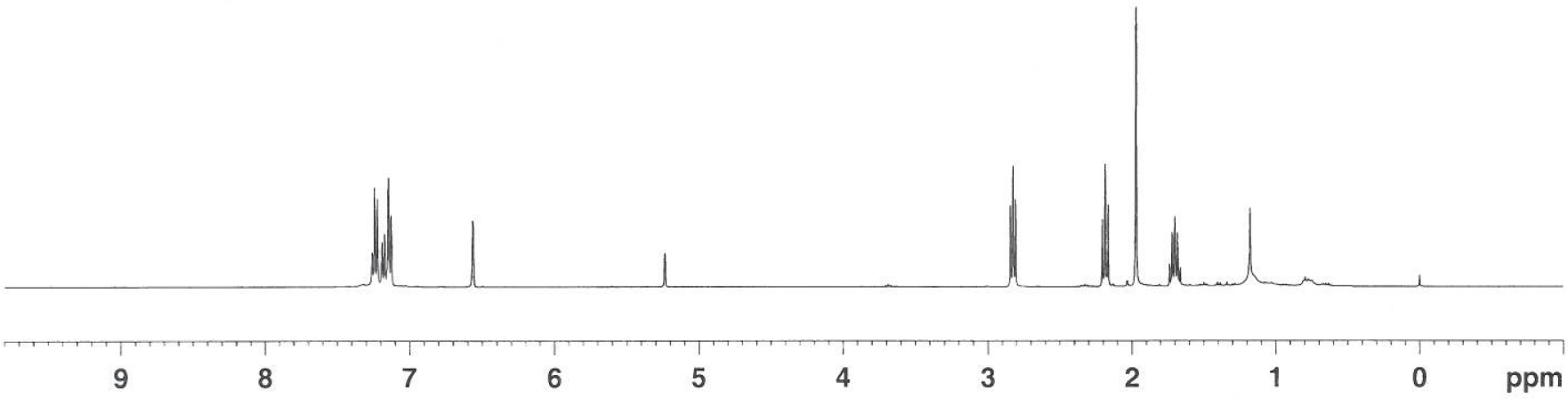
5



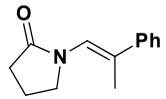
^{1}H NMR / 400 MHz / CD_2Cl_2



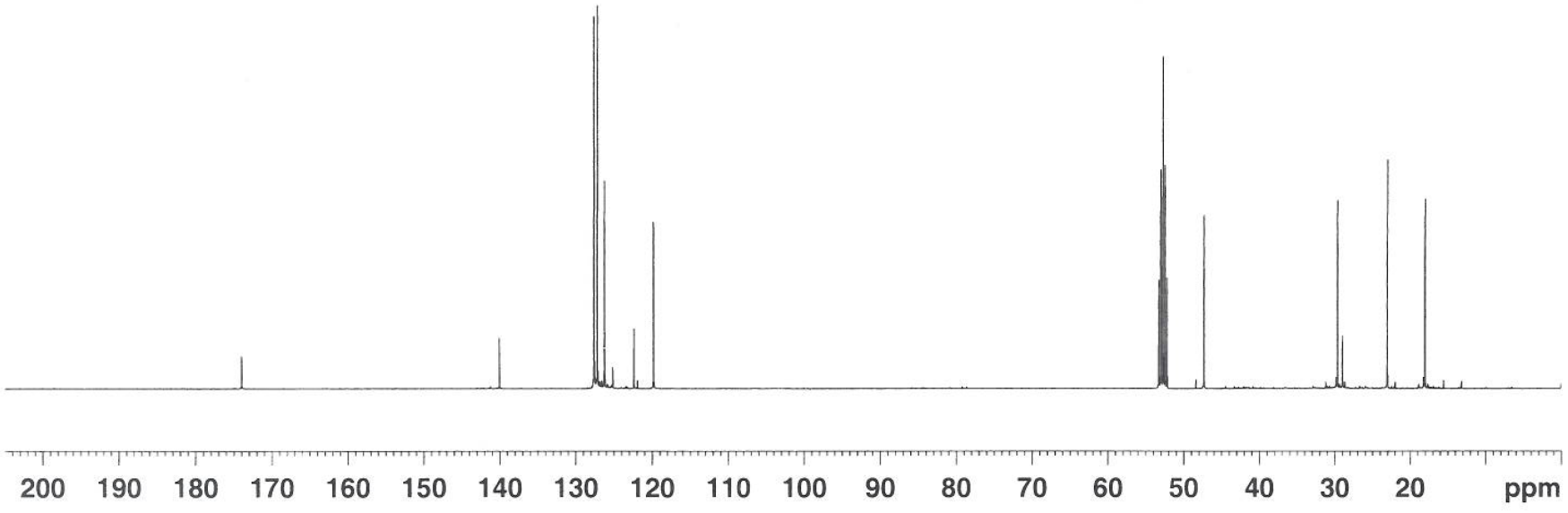
6



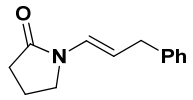
^{13}C NMR / 100 MHz / CD_2Cl_2



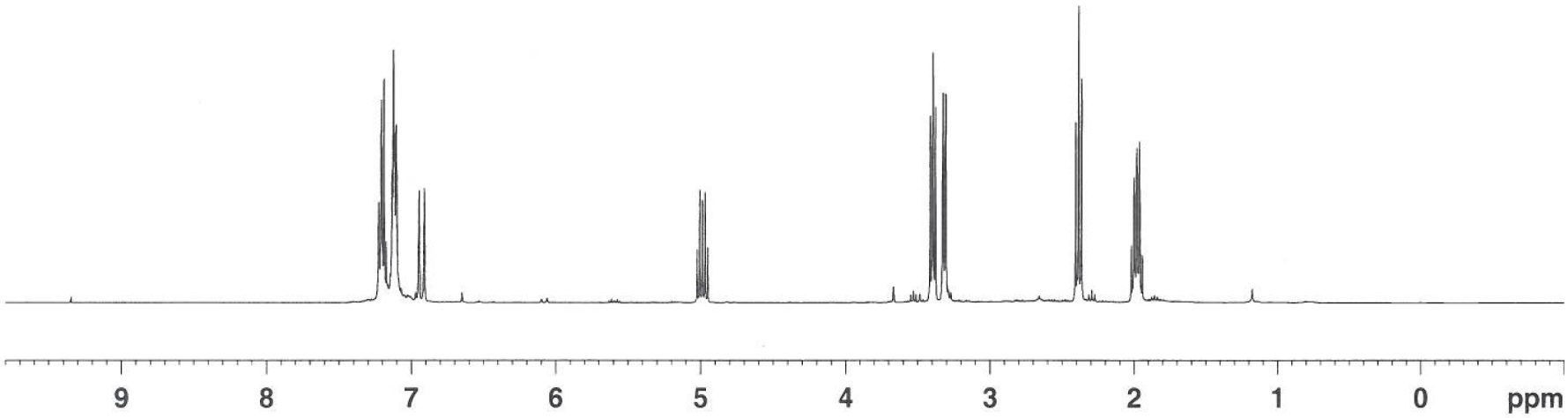
6



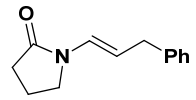
^{1}H NMR / 400 MHz / $CDCl_3$



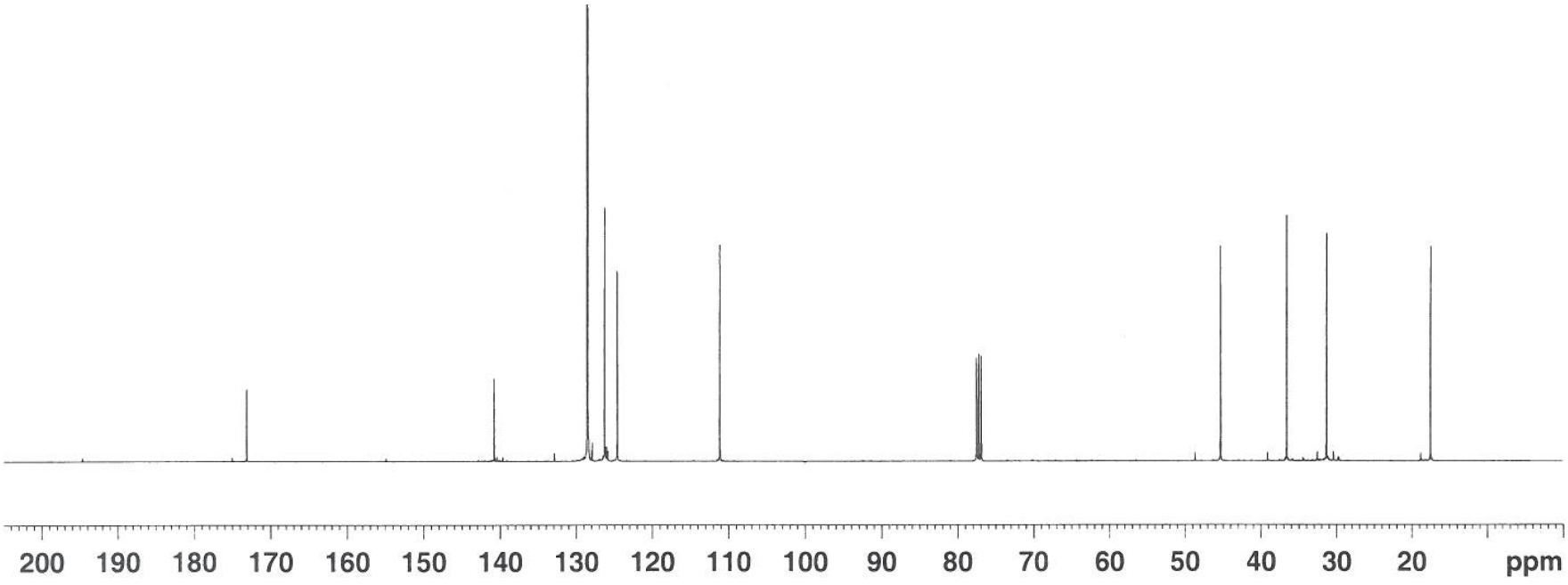
7



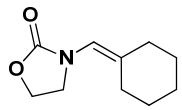
^{13}C NMR / 100 MHz / $CDCl_3$



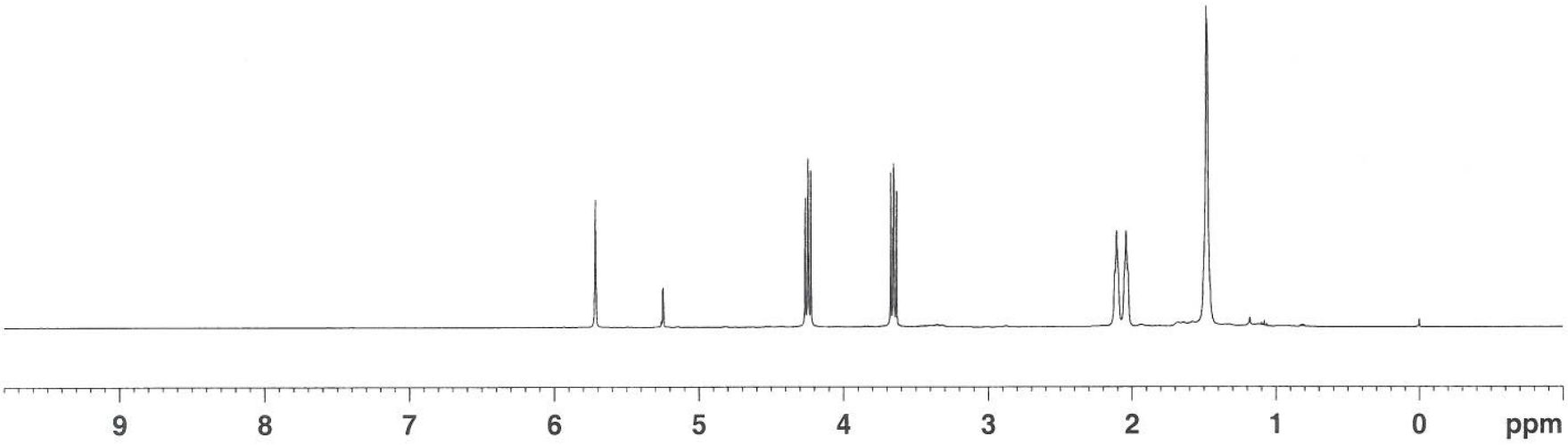
7



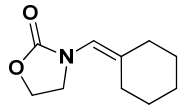
^{1}H NMR / 400 MHz / CD_2Cl_2



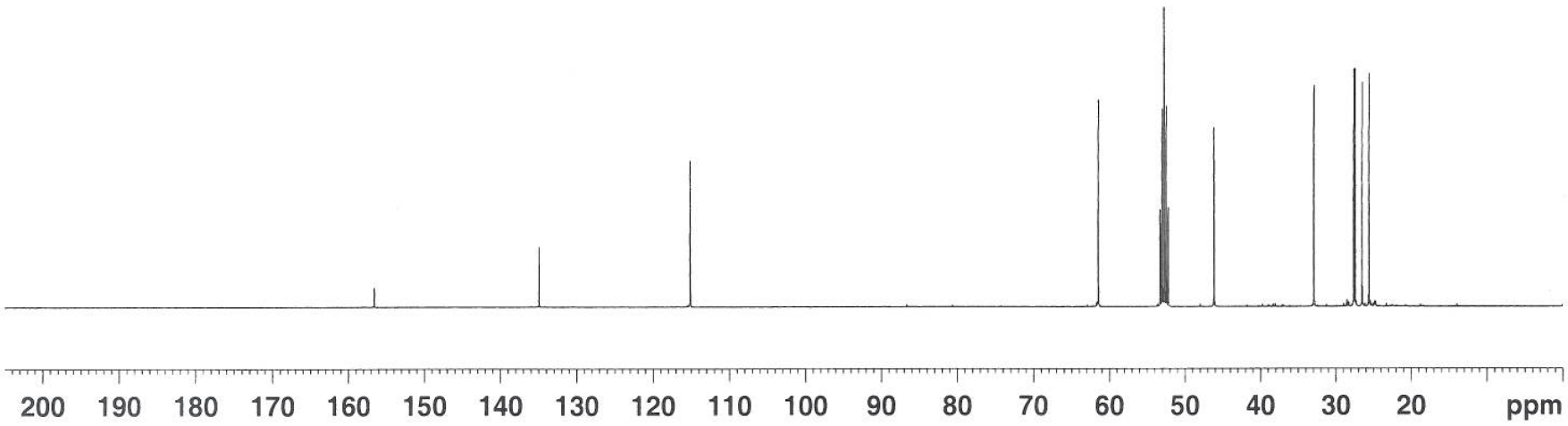
8



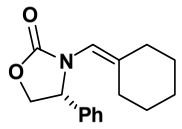
^{13}C NMR / 100 MHz / CD_2Cl_2



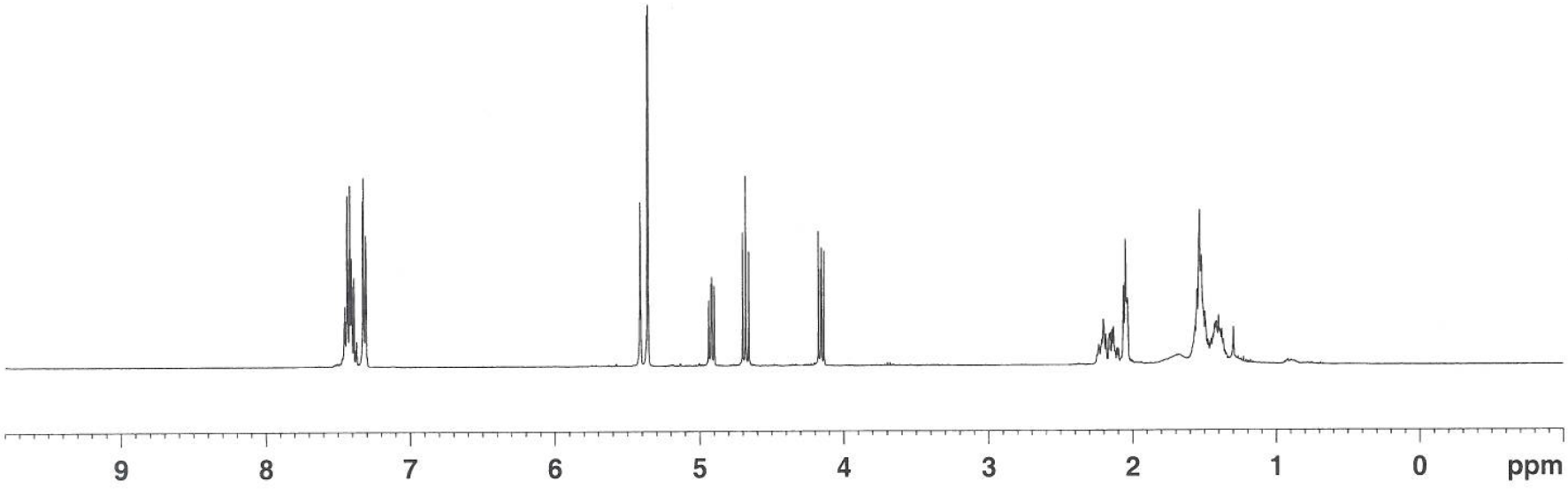
8



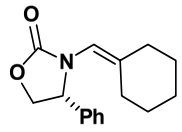
^{1}H NMR / 400 MHz / CD_2Cl_2



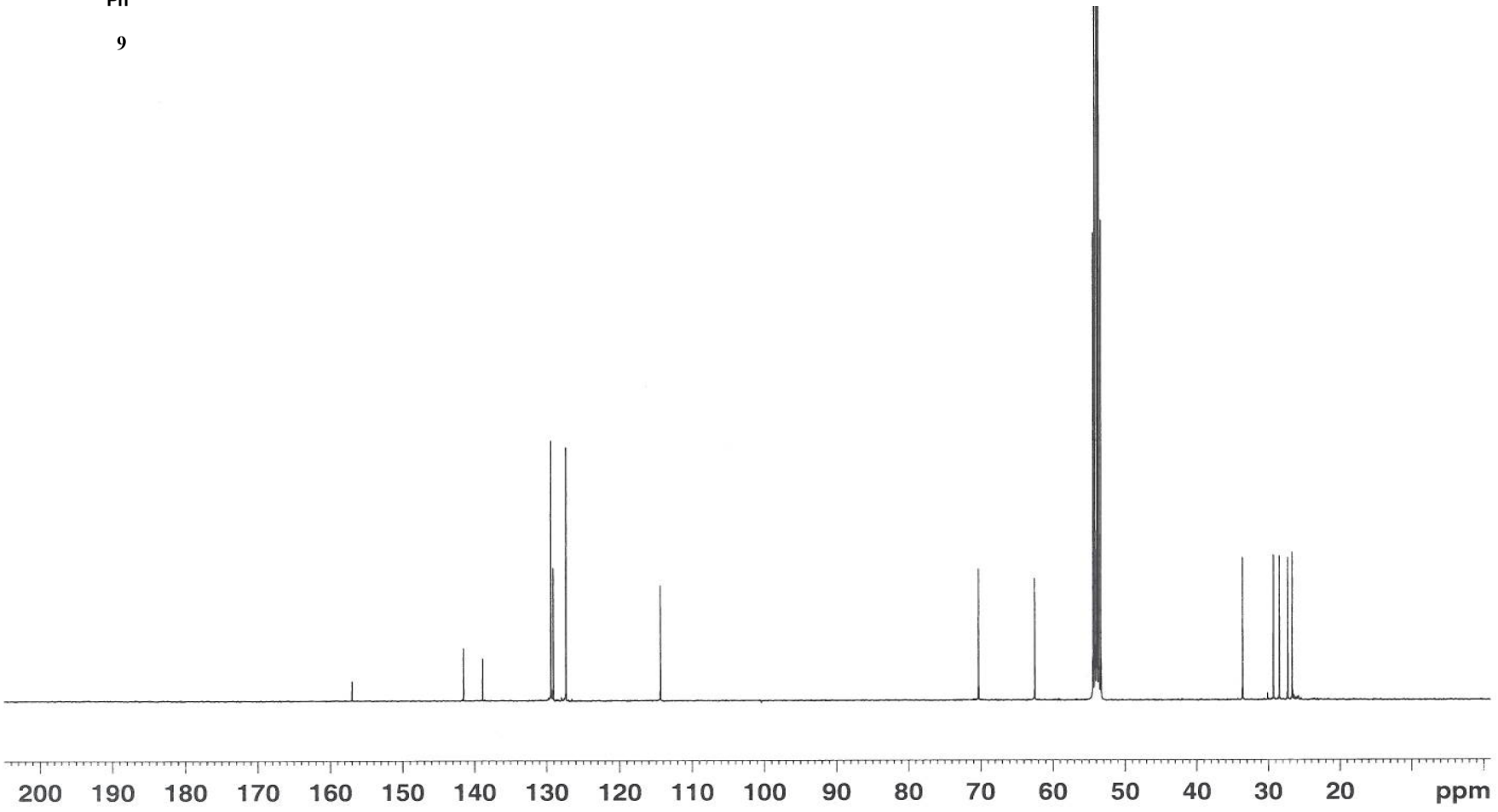
9



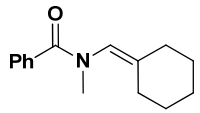
^{13}C NMR / 100 MHz / CD_2Cl_2



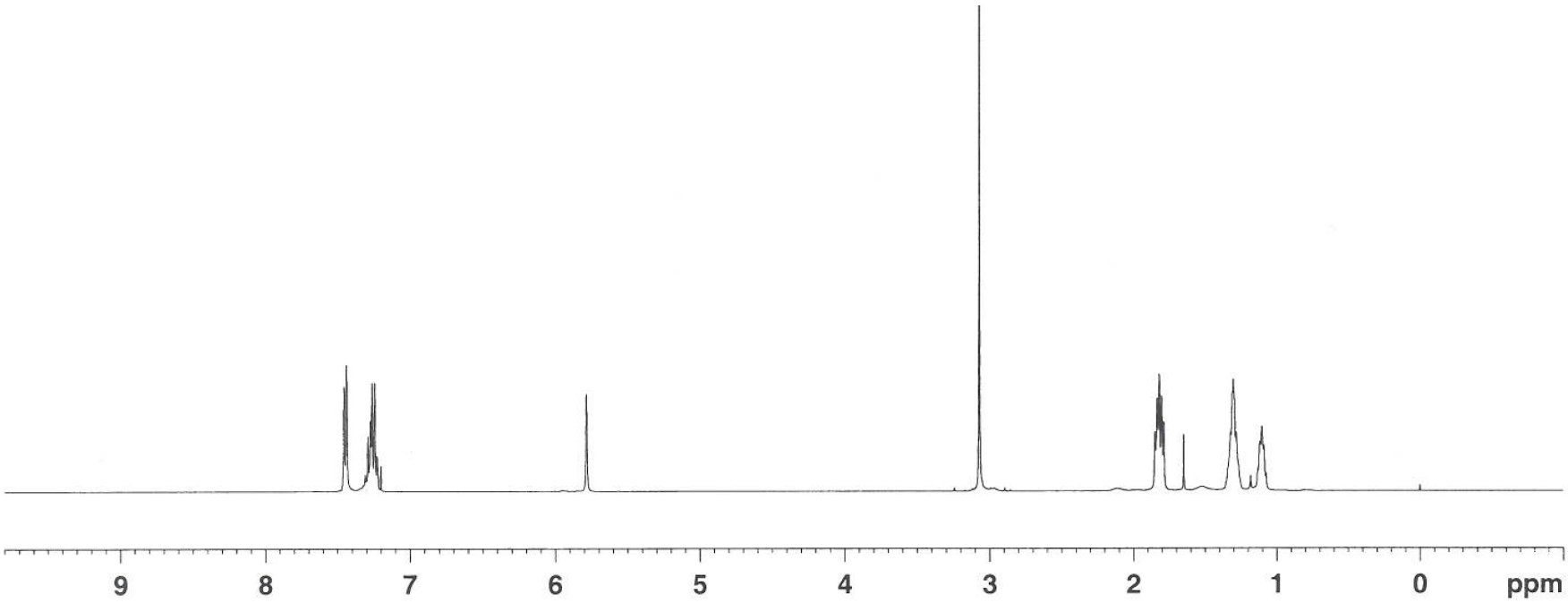
9



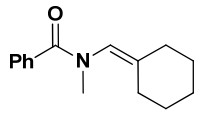
^{1}H NMR / 400 MHz / $CDCl_3$



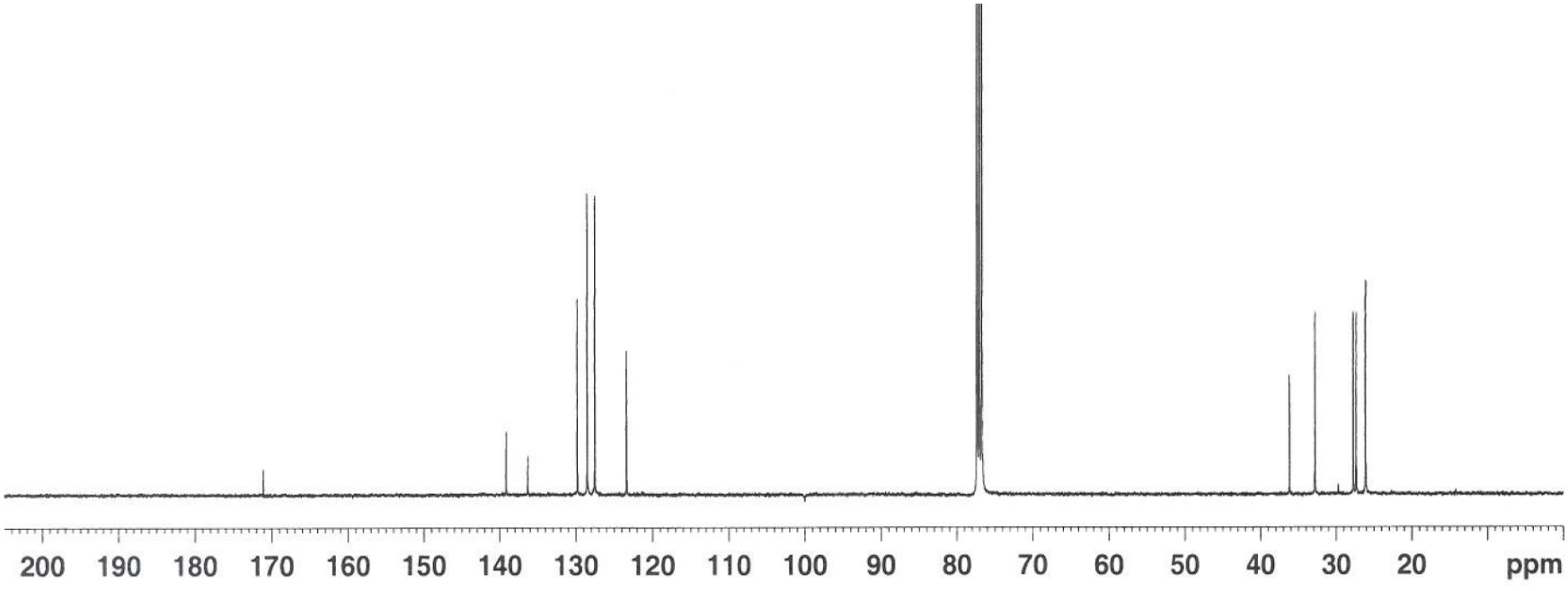
10



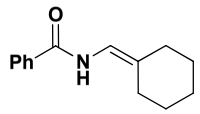
^{13}C NMR / 100 MHz / $CDCl_3$



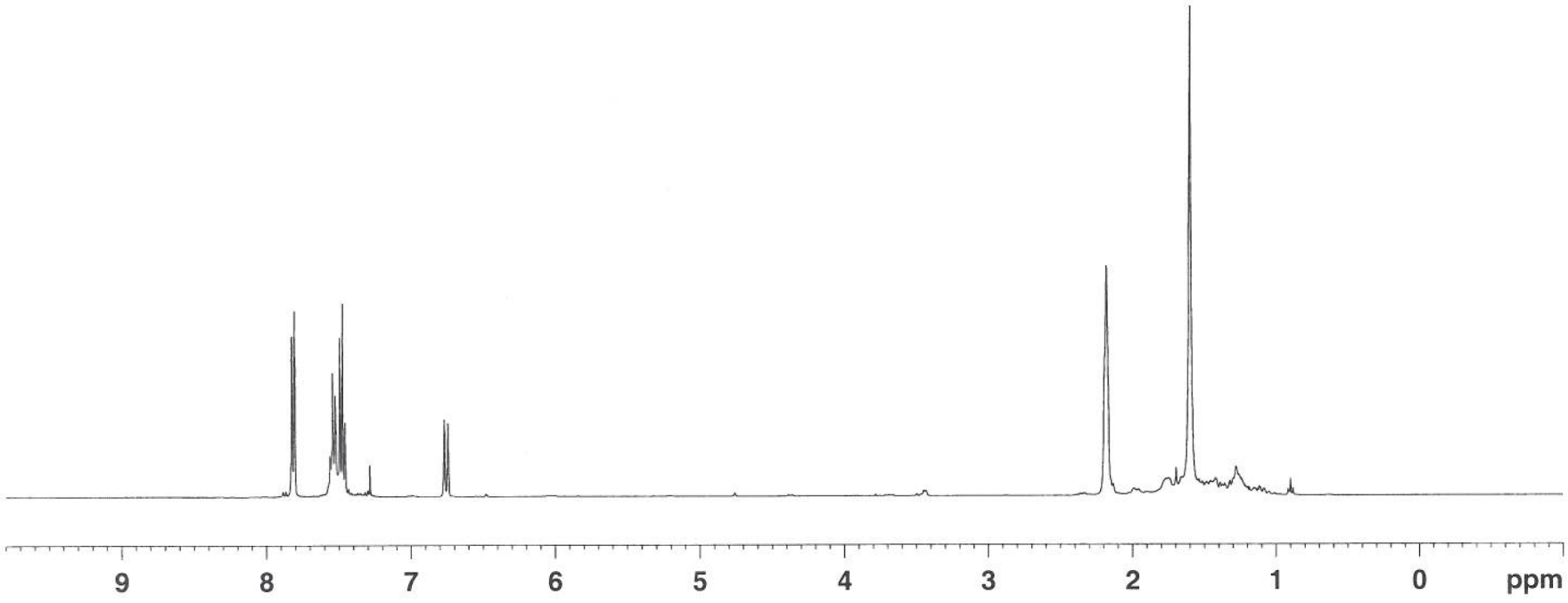
10



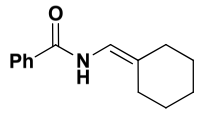
^{1}H NMR / 400 MHz / $CDCl_3$



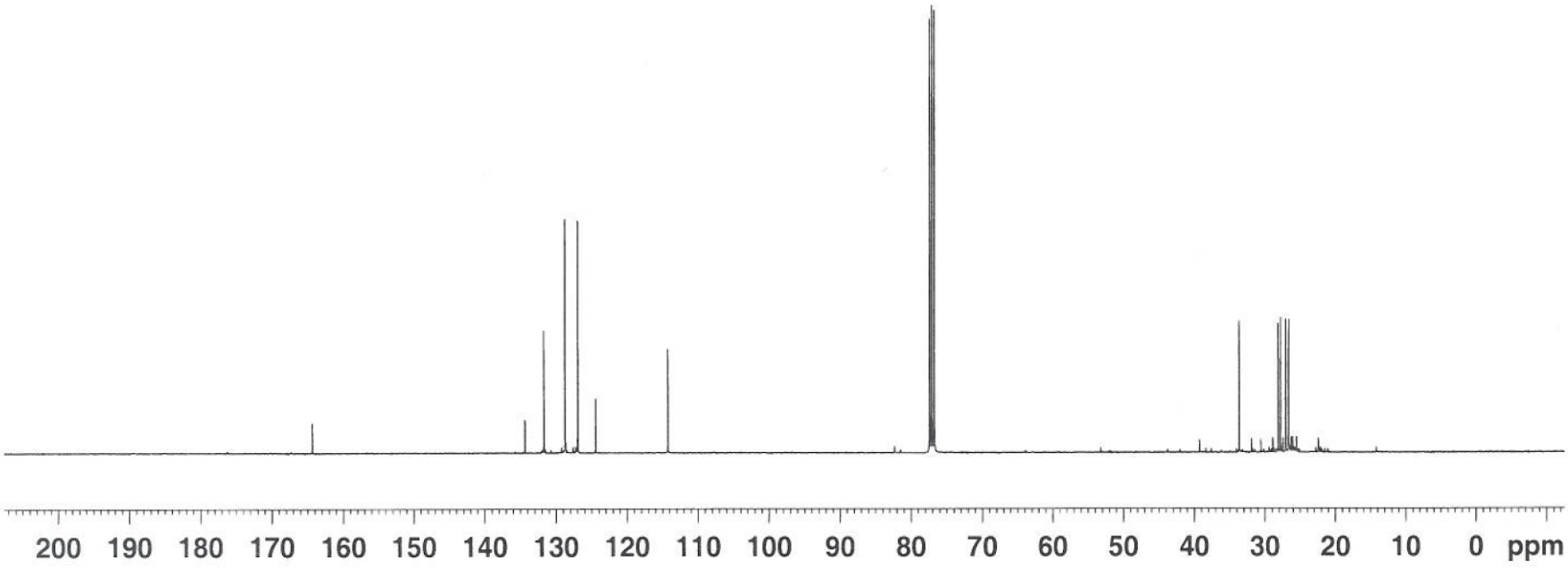
11



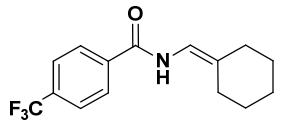
^{13}C NMR / 100 MHz / $CDCl_3$



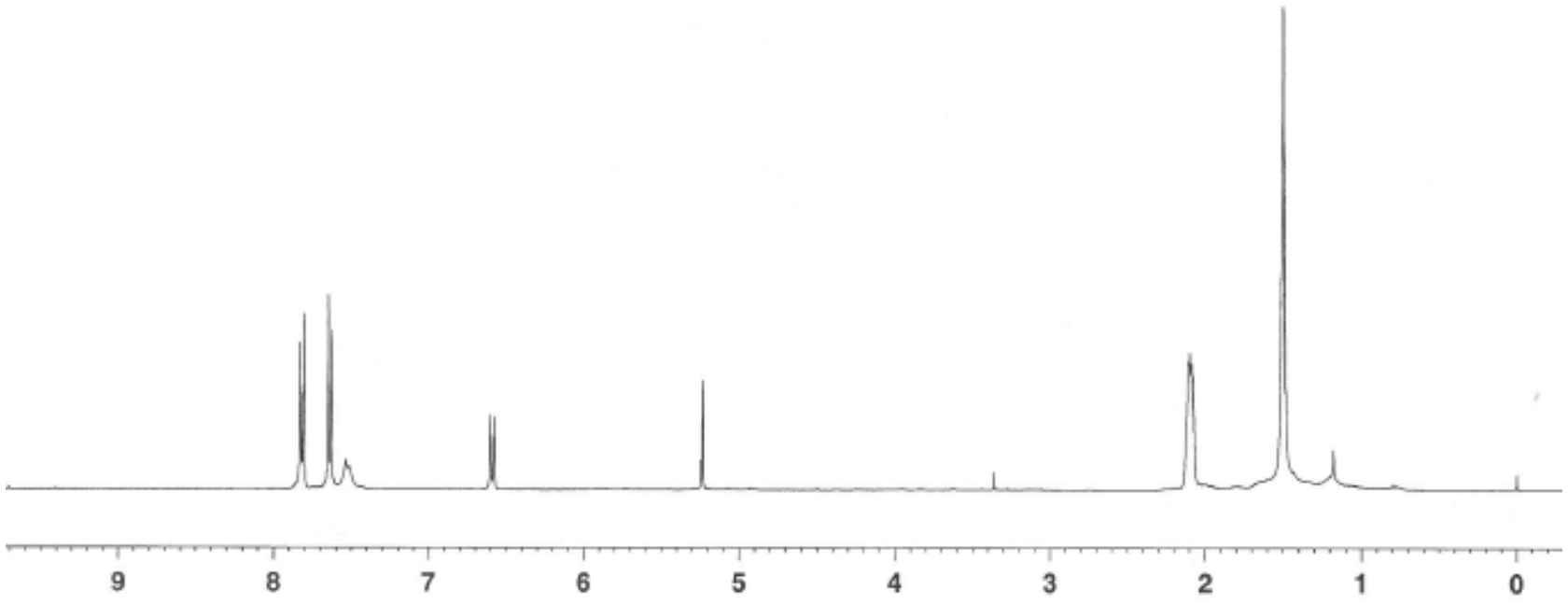
11



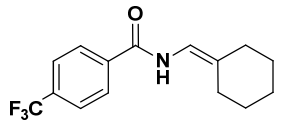
^{1}H NMR / 400 MHz / CD_2Cl_2



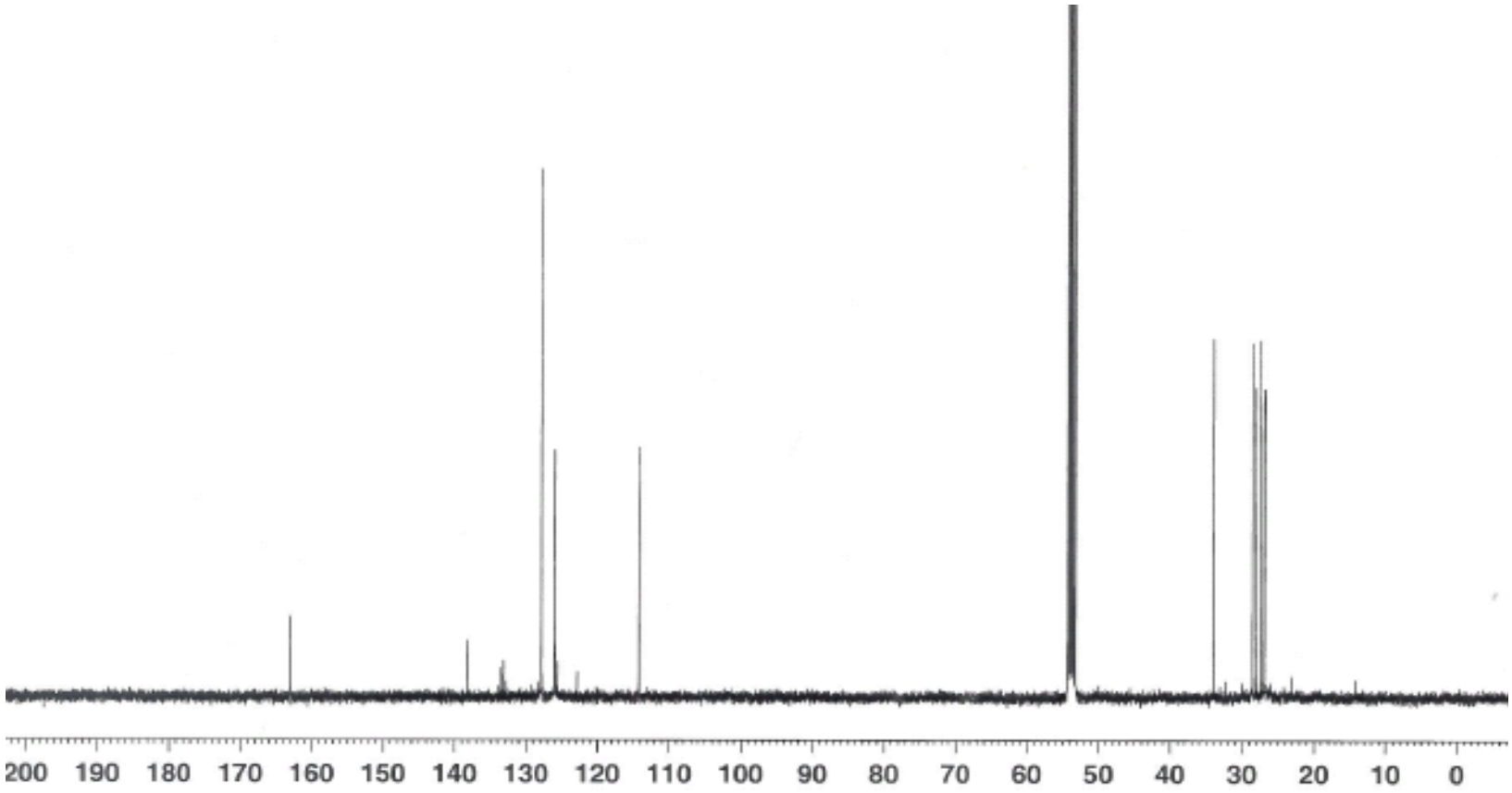
12



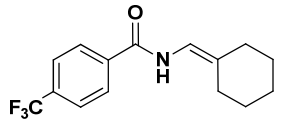
^{13}C NMR / 100 MHz / CD_2Cl_2



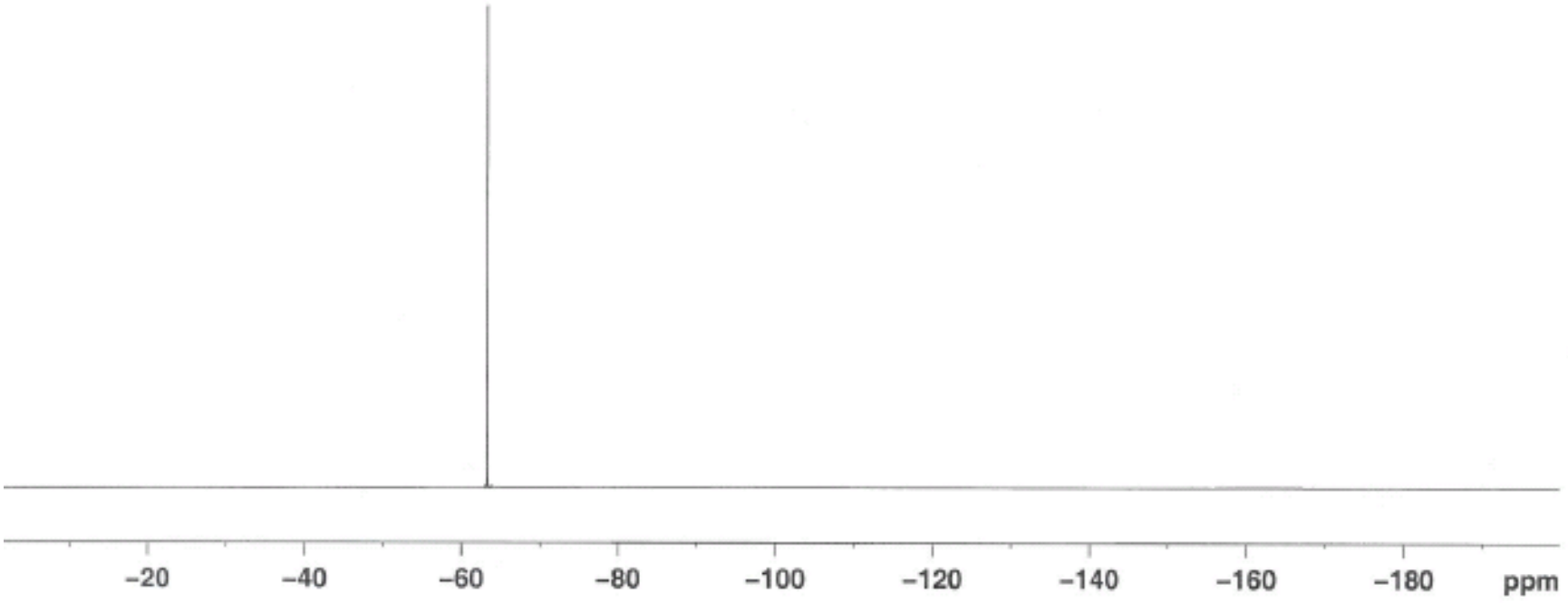
12



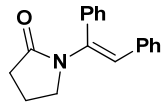
^{19}F NMR / 400 MHz / CD_2Cl_2



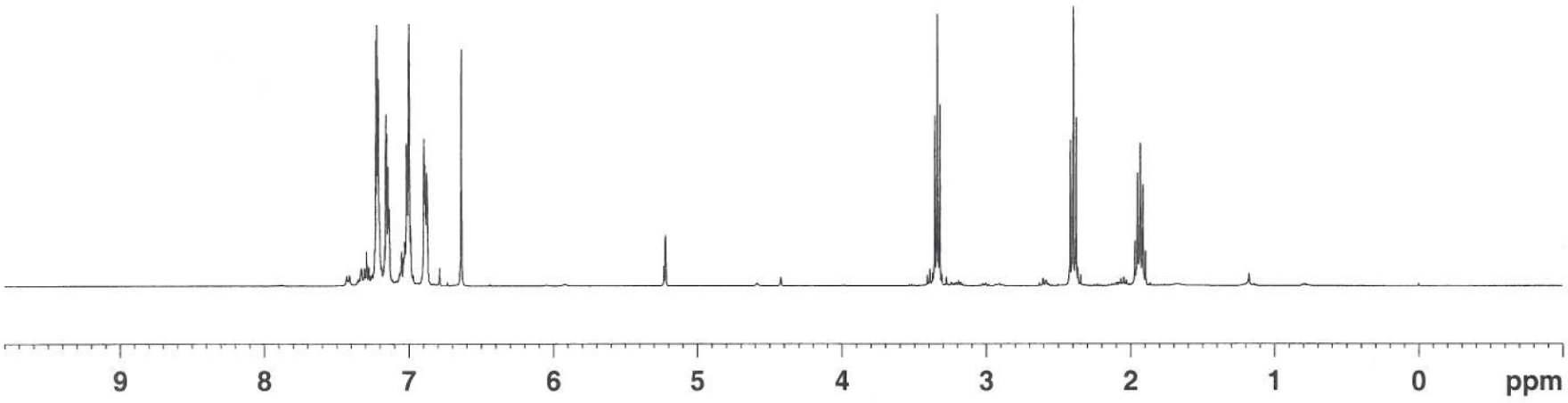
12



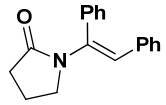
^{1}H NMR / 400 MHz / CD_2Cl_2



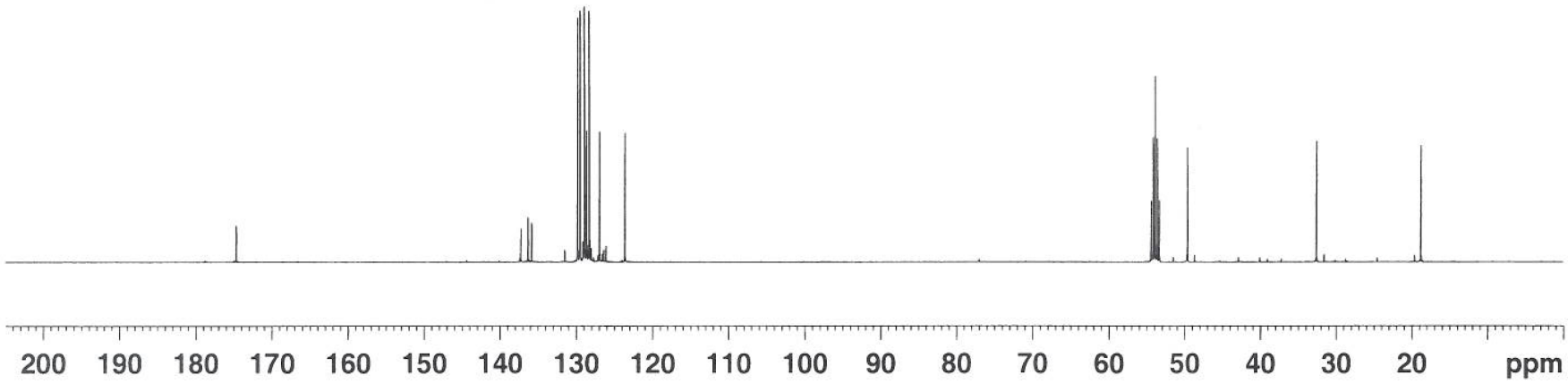
14



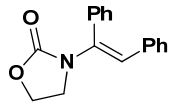
^{13}C NMR / 100 MHz / CD_2Cl_2



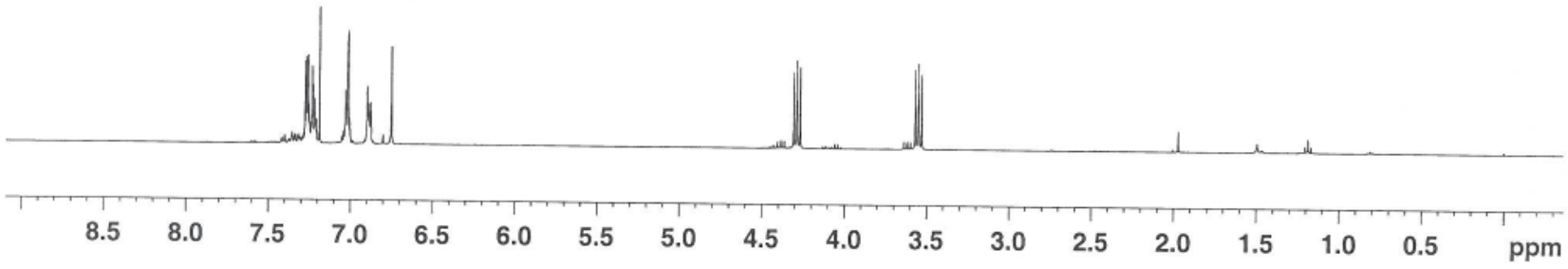
14



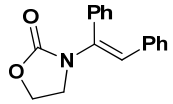
^{1}H NMR / 400 MHz / $CDCl_3$



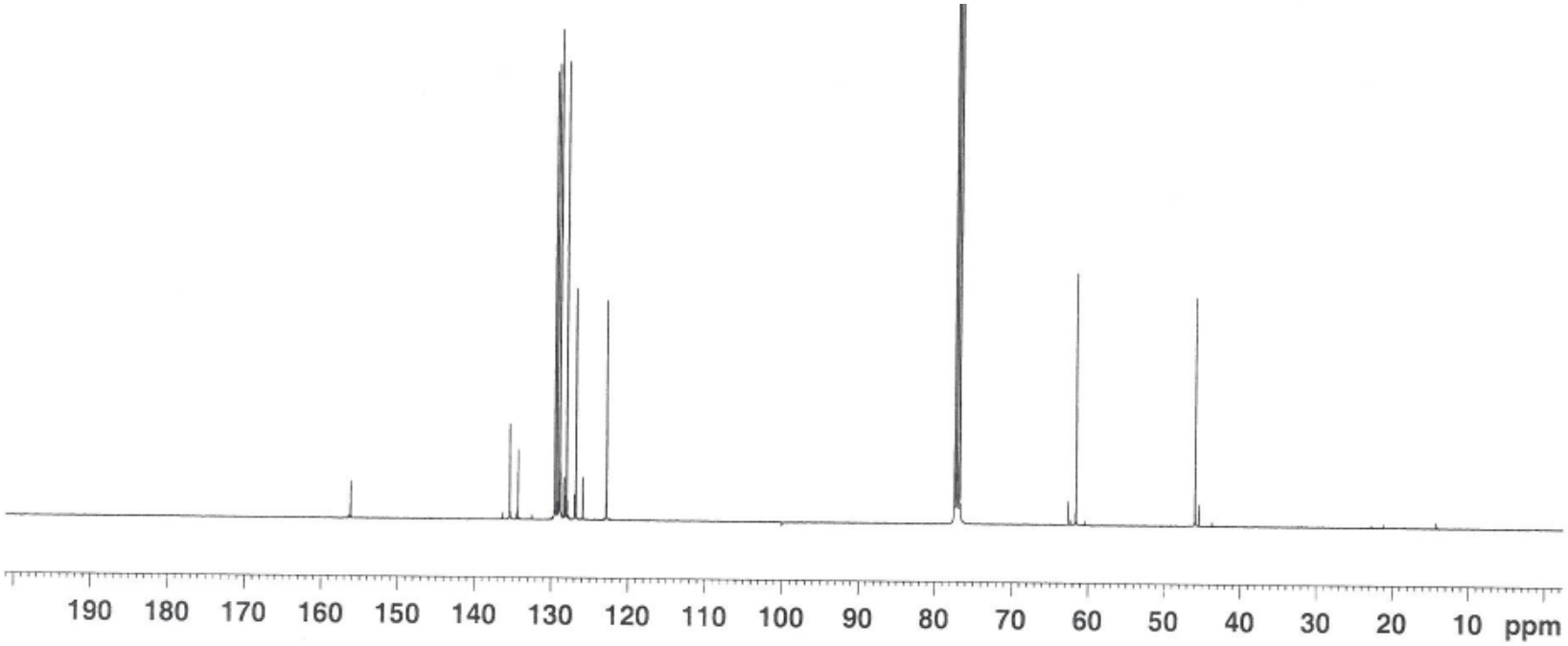
15



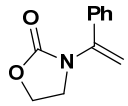
^{13}C NMR / 100 MHz / $CDCl_3$



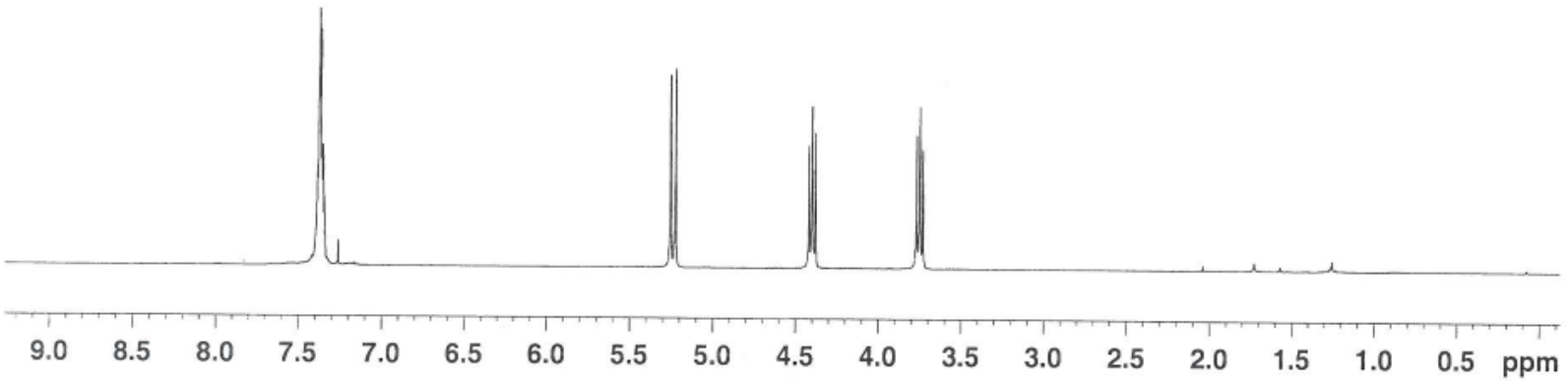
15



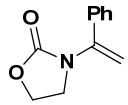
^{1}H NMR / 400 MHz / $CDCl_3$



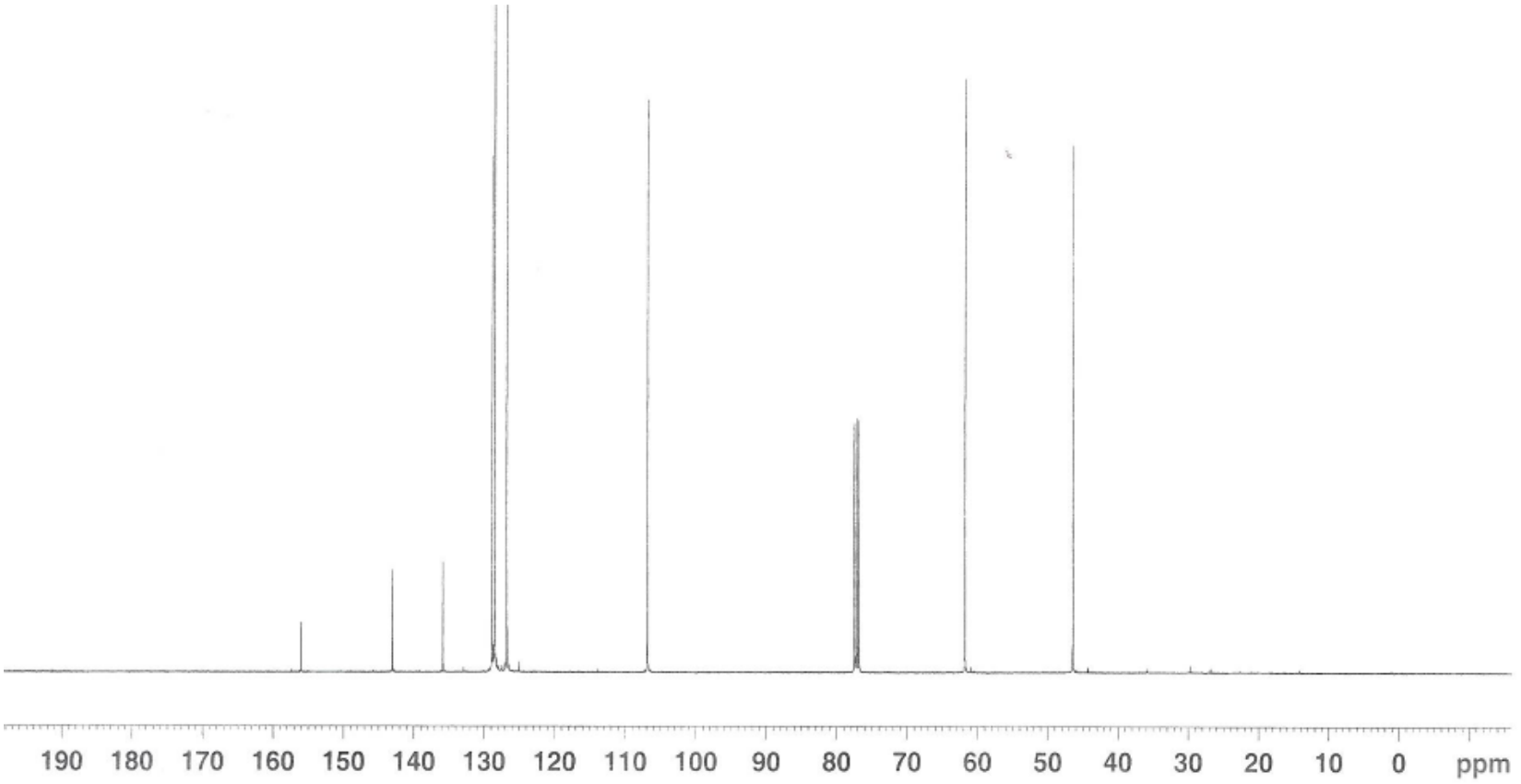
16



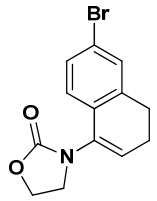
^{13}C NMR / 100 MHz / $CDCl_3$



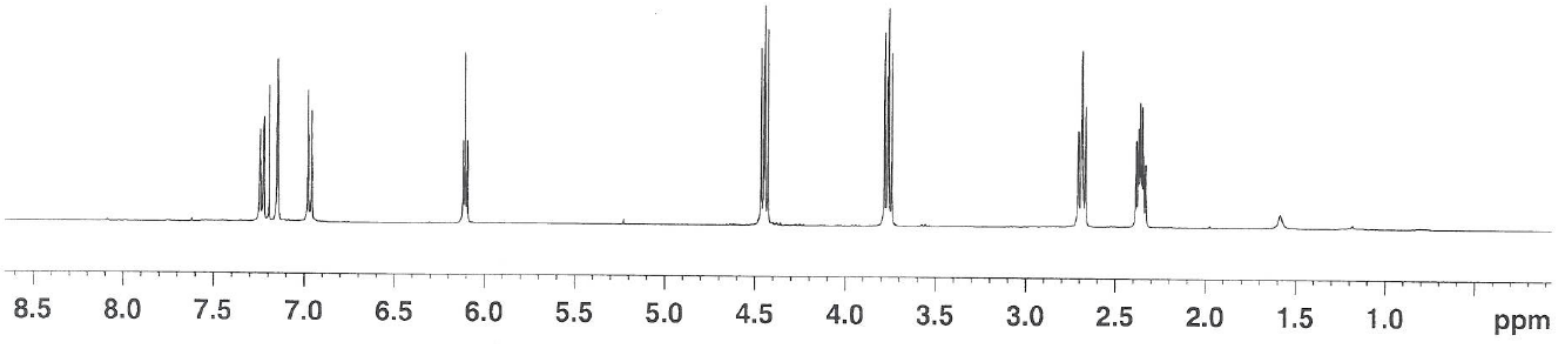
16



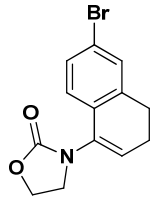
^{1}H NMR / 400 MHz / $CDCl_3$



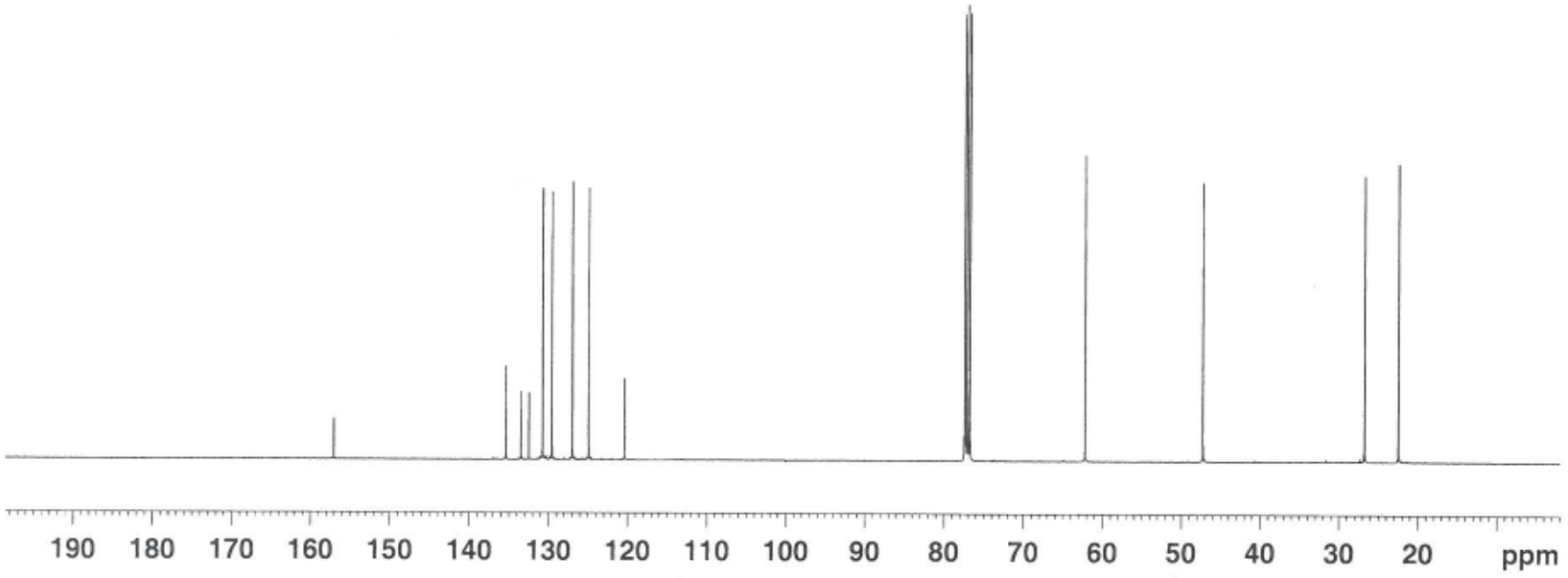
17



^{13}C NMR / 100 MHz / $CDCl_3$

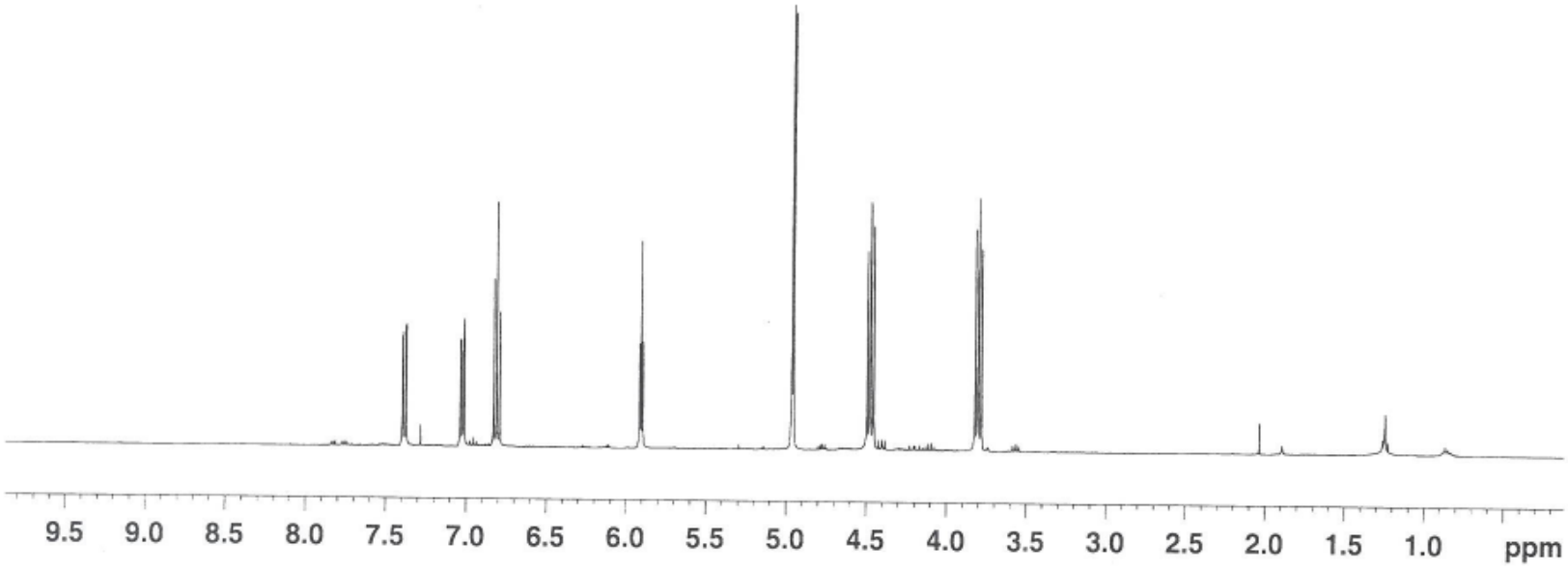


17



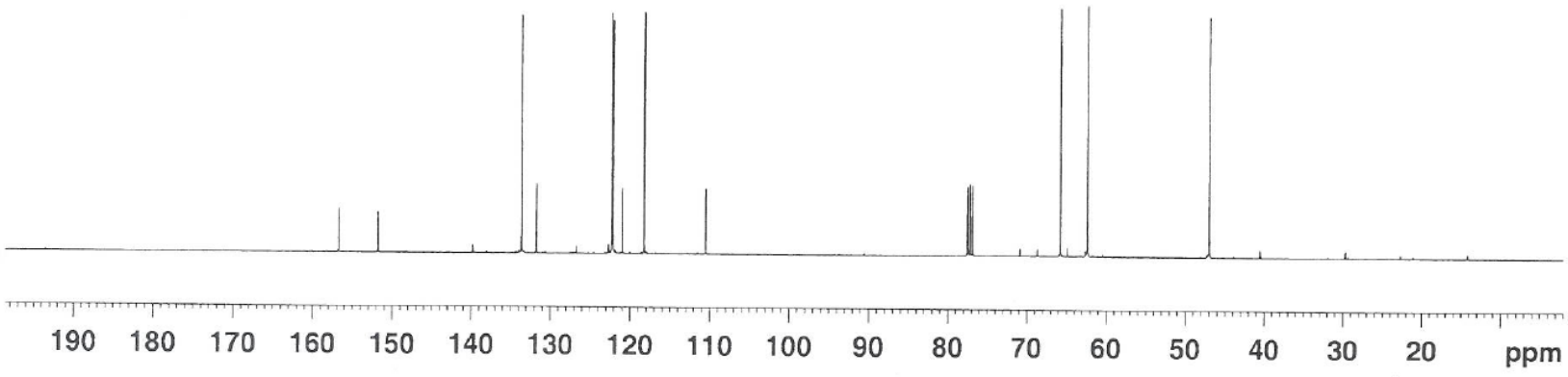
^{1}H NMR / 400 MHz / $CDCl_3$

18

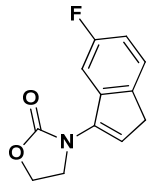


^{13}C NMR / 100 MHz / $CDCl_3$

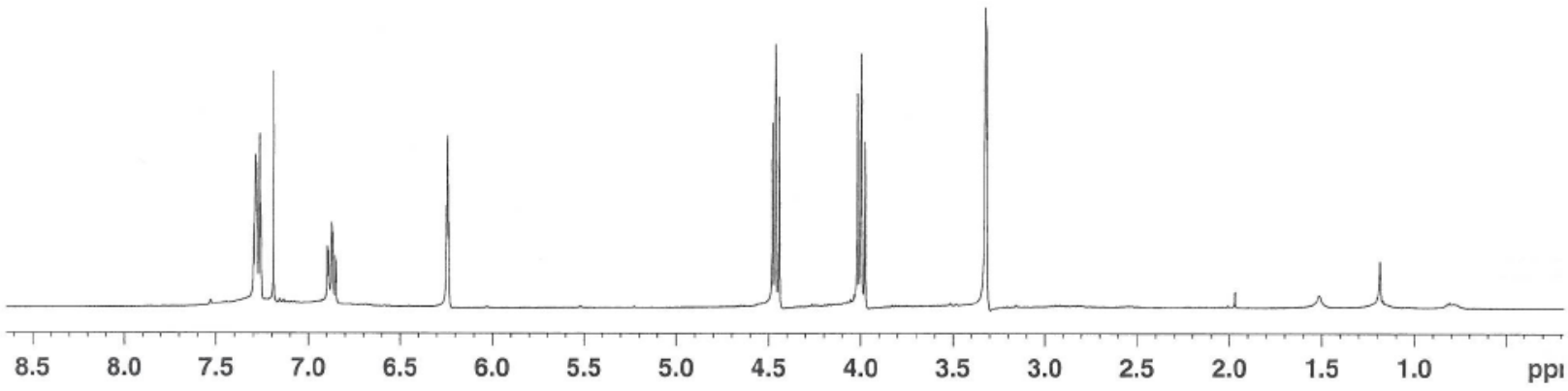
18



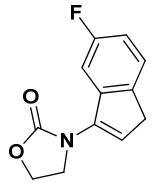
^{1}H NMR / 400 MHz / $CDCl_3$



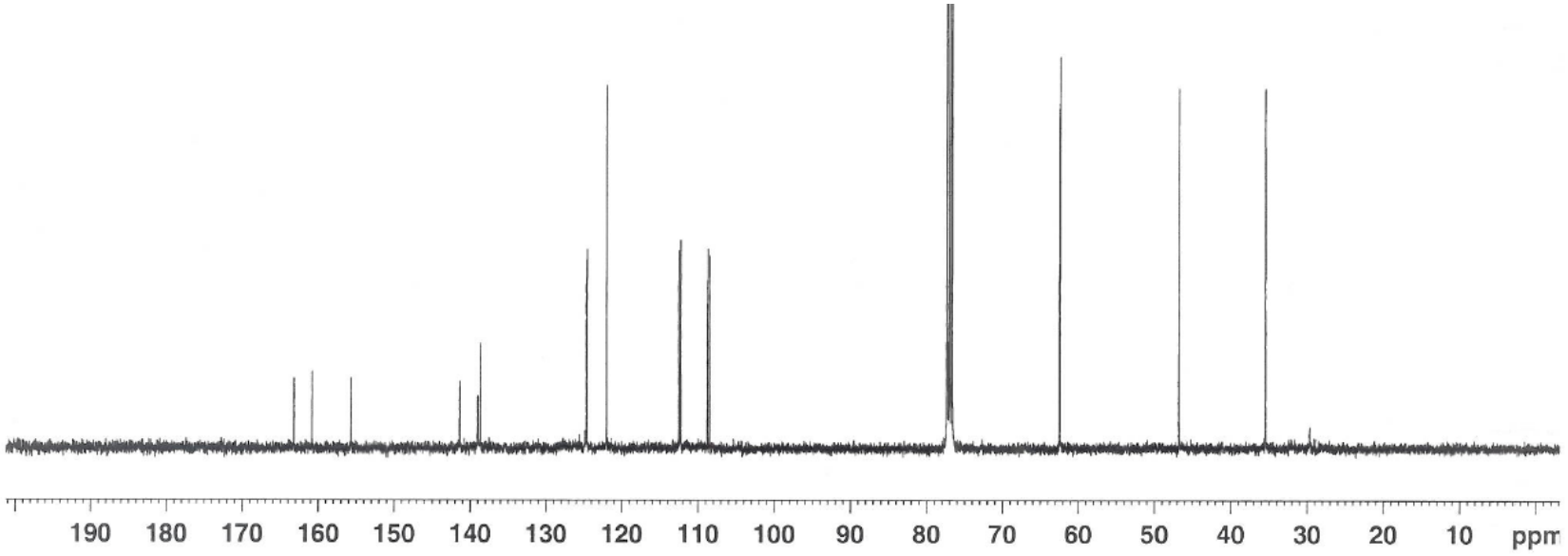
19



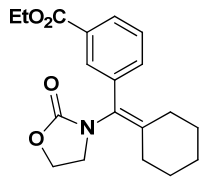
^{13}C NMR / 100 MHz / $CDCl_3$



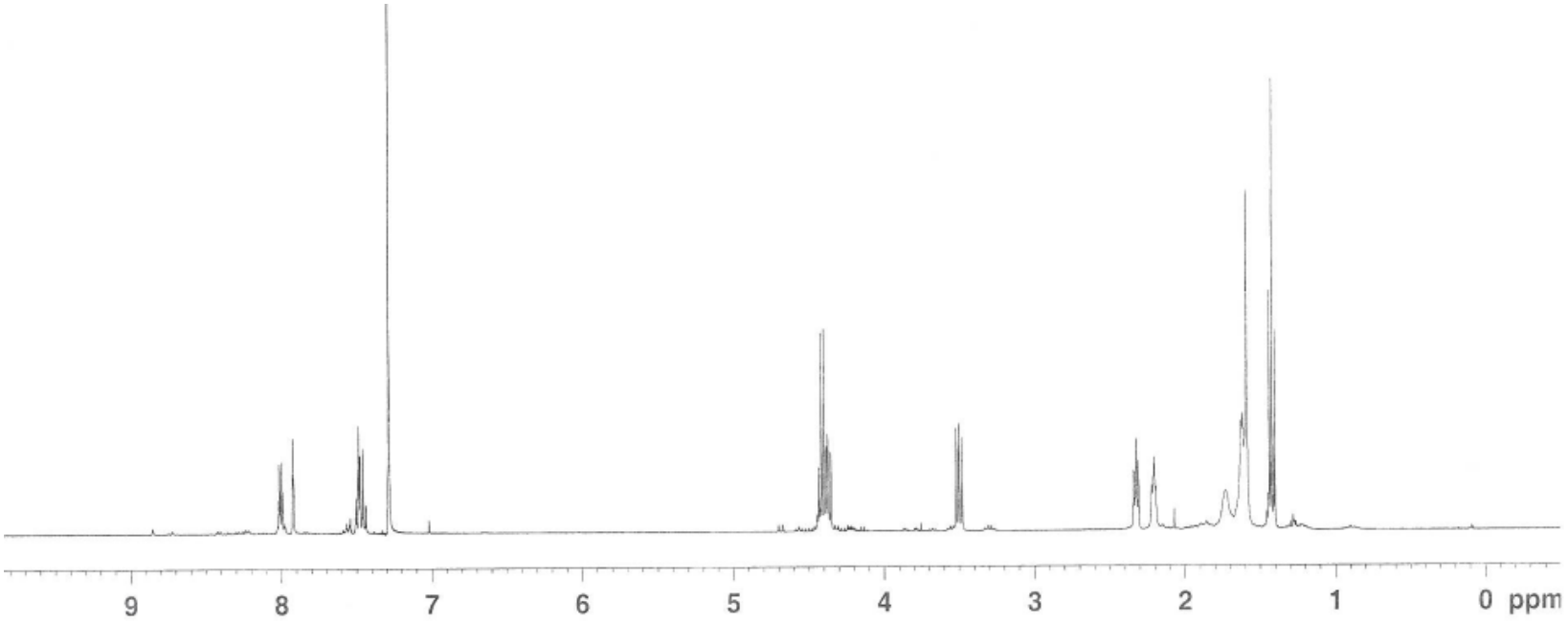
19



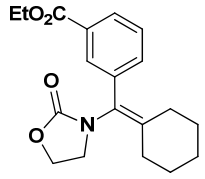
^{1}H NMR / 400 MHz / $CDCl_3$



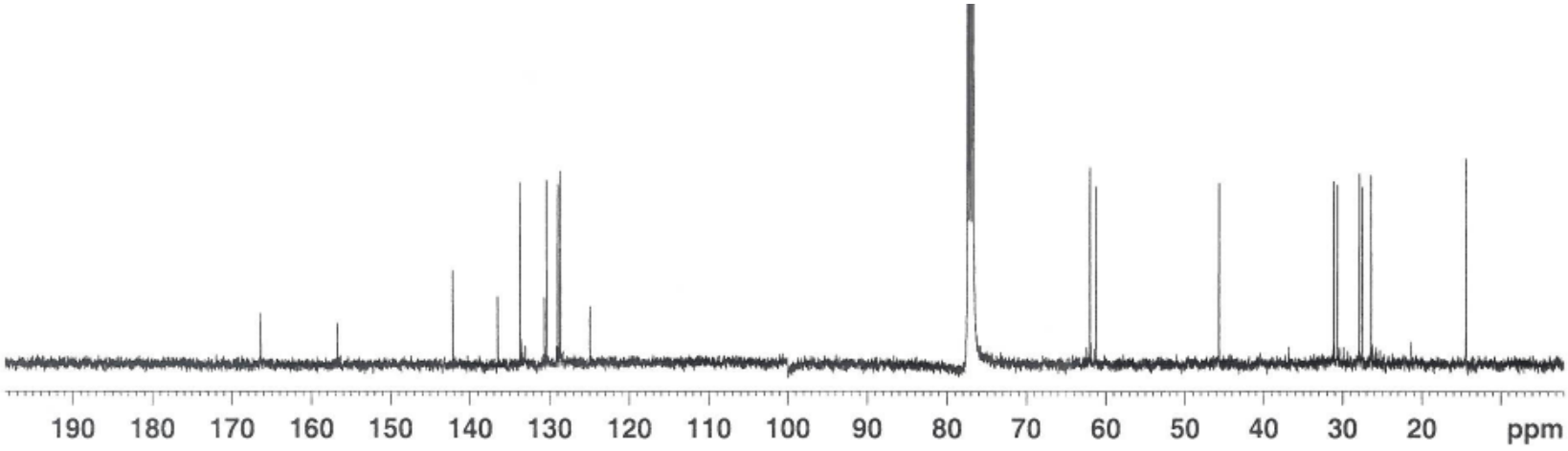
20



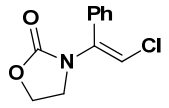
^{13}C NMR / 100 MHz / $CDCl_3$



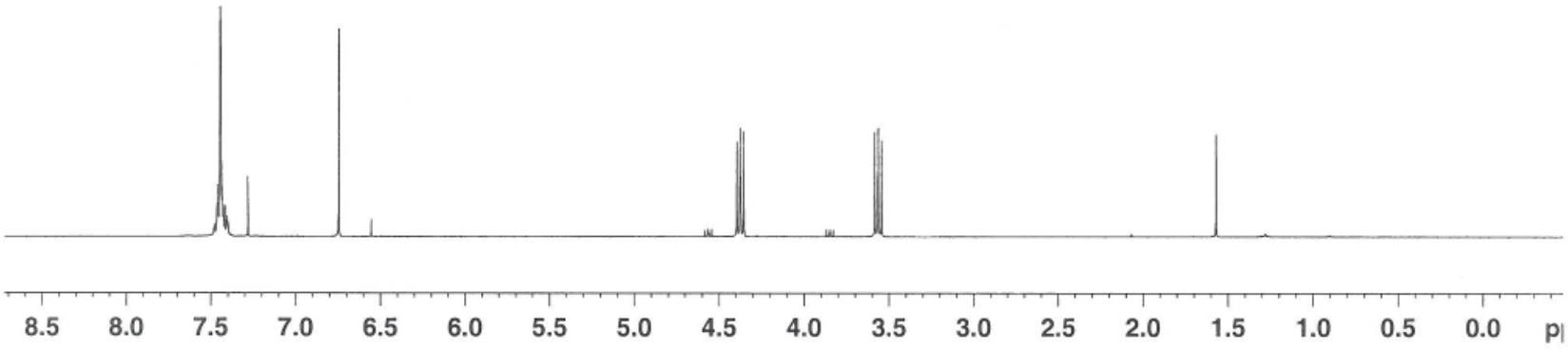
20



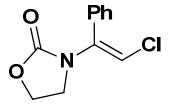
^{1}H NMR / 400 MHz / $CDCl_3$



21



^{13}C NMR / 100 MHz / $CDCl_3$



21