Electronic Supplementary Material (ESI) for RSC Advances

Acceleration of the Eschenmoser Coupling Reaction by Sonication: Efficient Synthesis of Enaminones

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Supporting Information

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Experimental

Experimental

Materials: ^{1}H and ^{13}C NMR spectra were obtained using a Varian 400/54 (400 MHZ) spectrometer. The residual solvent signals were used as references ($CDCl_3$: δH = 7.26 ppm, δC = 77.16 ppm). Multiplicities of signals are reported as broad (br), singlet (s), doublet (d), double doublet (dd), four doublets (dddd), triplet (t), three triplets (tt), quartet (q), septet (sep) and multiplet (m). Infrared spectra were recorded on an Avatar 360 FT–IR. Thin layer chromatography (TLC) was performed on 250 µm glass or aluminum-backed silica gel plates. Visualization was accomplished using a short wave UV light (254 nm), with an iodine chamber, or basic aqueous KMnO4 solution. Flash column chromatography was performed using Sorbent silica gel 60 Å (40–63 µm). Petroleum ether refers to those fractions that distill at 30–60 °C. Anhydrous Na_2CO_3 was purchased from Fisher (LOT AD-9195-27). Unless specified, all chemical reagents and solvents were obtained from commercial sources. Aldrich's Zerostat® 3 gun was used to neutralize static electricity during the Na_2CO_3 weighing and transfer. THF was dried using LC technology's SPBT-1 bench top solvent purification system.

High resolution mass spectra and liquid chromatography were performed on a Thermo Scientific Exactive LC-MS instrument. The instrument was operated in a positive ion electrospray mode by Dr. K. P. Roberts and J. Holland at the Department of Chemistry and Biochemistry, The University of Tulsa. Chromatographic separation was performed on this instrument with a Thermo Scientific Hypersil Gold HPLC Column (50 x 2.1mm I.D.; particle size 1.9 µm) coupled to a UV detector. A wave length of 254 nm was used for detection. The following mixture was used as a mobile phase with a flow rate of 1 mL/min.

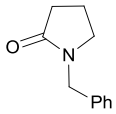
Time (Min)	Pump A, Water with 0.1 % formic acid (%)	Pump B, Acetonitrile with 0.1 % formic acid (%)
0	90	10
2	90	10
10	10	90
16	0	100
18	90	10

Sonication was conducted either by an ultrasonic bath (VWR, model no. 97043-968) or probe sonicator (Sonics, Vibra cell, model no. VC X 130) equipped with a standard probe (tip dia. 6mm, length 113 mm). The pulse settings were 7 sec. on and then 1 sec. off with a100% amplitude.

Particle size distribution of the sonicated (water bath and probe sonicator) sodium carbonate was measured by Microtrac particle size analyzer (model number: NPA 15231A-0000-000-10M), using '**Zetatrac**' mode.

Probe sonication set-up

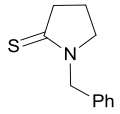
Benzylpyrrolidin-2-one [1]



NaH (60% dispersion in paraffin liquid, 516 mg, 12.9 mmol) was washed with petroleum ether in a round bottom flask. A magnetic stirrer was added and the flask was purged with argon. Dried THF (20 mL) was added, and the suspension was cooled to 0 °C. 2-pyrrolidone (1.01 g, 11.8 mmol) and benzyl bromide (1.60 mL, 12.9 mmol) were added drop wise to the stirred suspension. After 1 h, the reaction mixture was heated to 60 ^{o}C for 21 hours. The reaction was quenched with ether at 0 °C and partitioned between ether and water. The organic layer was

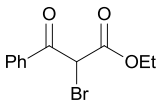
dried with $MgSO_4$ and evaporated. Column chromatography (40%, then 70%, then 100% EtOAc in hexanes) gave pure **1-benzylpyrrolidin-2-one** as a transparent viscous liquid (1.89 g, 10.8 mmol, 92% yield). R_f = 0.41 (EtOAc). IR (neat) ν_{max}/cm^{-1}: 1685, 1486, 1420, 1414, 1409, 1280, 1255; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.30 (m, 2H), 7.28–7.24 (m, 3H), 4.45 (s, 2H), 3.24 (t, J = 7.2 Hz, 2H), 2.41 (t, J = 8.2 Hz, 2H), 2.00–1.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.3, 136.1, 128.1, 127.5, 127.0, 46.0, 45.9, 30.4, 17.2; HRMS (ESI$^+$): Calcd. for $C_{11}H_{13}NO$ (M+H$^+$): 176.1070, found 176.1056; *m/z* (ESI$^+$) 176 (M + H$^+$); HPLC, t_R = 6.12 min.

Benzylpyrrolidine-2-thione (1f) [2, 3]



Dichloromethane (2.30 mL) was added to a reaction flask containing Lawesson's reagent (238 mg, 0.57 mmol). Benzylpyrrolidin-2-one (200 mg, 1.14 mmol) was dissolved in CH_2Cl_2 (2.30 mL) and added to the reaction flask. The reaction was stirred for 2 h at RT, concentrated, and purified by column chromatography (20 % petroleum ether in dichloromethane) to provide pure **1f** as a white crystalline solid (219 mg, 1.14 mmol, 100% yield). R_f = 0.22 (petroleum ether: CH_2Cl_2 1:4). m.p.: 42–44 $^\circ$C. IR (neat) ν_{max}/cm^{-1}: 2916, 1508, 1452, 1466, 1424, 1409, 1308; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.27 (m, 5H), 4.98 (s, 2H), 3.58 (t, J = 7.6 Hz, 2H), 3.09 (t, J = 8.0 Hz, 2H), 2.02 (tt, J = 8.0, 7.6 Hz, 2H); ^{13}C NMR (100 MHz, CDCl3) δ: 201.9, 135.2, 128.9, 128.4, 128.1, 54.1, 51.7, 45.0, 19.5; HRMS (ESI$^+$): Calcd. for $C_{11}H_{13}NS$ (M+H$^+$): 192.0841, found 192.0827; *m/z* (ESI$^+$) 192 (M + H$^+$); HPLC, t_R = 6.82 min.

Ethyl 2-bromo-3-oxo-3-phenylpropanoate (2c) [4]



This reaction was conducted in the dark. Ethyl benzoylacetate (300 mg, 1.50 mmol) was dissolved in toluene (5 mL) and added to a flask containing KBr (893 mg, 7.50 mmol). The vial, which originally contained ethyl benzoylacetate, was washed twice with toluene (2.5 mL). The washings were added to the reaction flask. A 1.0 M solution of HCl (7.5 mL, 7.5 mmol) and 35% H_2O_2 (3.4 mL, 30 mmol) were added and the reaction was stirred vigorously for 1.5 h (the color of reaction kept changing from yellow to orange and back in the initial 30 min). Ethyl acetate (10

mL) was added and the organic layer was separated. It was washed with water (10 mL), sat. aq. $Na_2S_2O_3$ (10 mL), water (10 mL) and dried over anhydrous $MgSO_4$. Column chromatography (30%, the 40% then 50% CH_2Cl_2 in petroleum ether) provided **2c** (329 mg, 1.21 mmol, 81% yield). R_f = 0.36 (Petroleum ether/EtOAc = 9/1). IR (neat) ν_{max}/cm^{-1}: 2984, 1761, 1683, 1597, 1581, 1449, 1368, 1186, 1025, 1001, 938, 858, 805; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00–7.97 (m, 2H), 7.64–7.60 (m, 1H), 7.51–7.47 (m, 2H), 5.65 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.2, 165.2, 134.3, 133.5, 129.3, 129.1, 63.4, 46.5, 13.9; HRMS (ESI$^+$): Calcd. for $C_{11}H_{11}BrO_3$ (M+H$^+$): 270.9964, found 270.9955; *m/z* (ESI$^+$) 273 (M + H$^+$ + 2, 97%), 271 (M + H$^+$, 100%) 193 (17%); HPLC, t_R = 8.52 min.

Preparation of Na_2CO_3 sonicated with ultrasonic bath

Dichloromethane (0.8 mL) was added to a test tube containing Na_2CO_3 (39.0 mg) and sonicated for 2.5 h. The solvent was evaporated and the base was used for the next reaction.

Synthesis of 3c [2, 5] using Na_2CO_3 sonicated with ultrasonic bath

A solution of **1b** (11.5 mg, 114 μmol) in 0.40 mL of CH_2Cl_2 was added to a test tube containing the above prepared Na_2CO_3 (3.2 eq). Bromide **2a** (2 eq) was dissolved in 0.20 mL CH_2Cl_2 and added to the reaction vessel. Each vial, which originally contained **1b** and **2a,** was washed twice with 0.50 mL CH_2Cl_2, and the contents were transferred to the reaction mixture. The test tube was capped and stirred at room temperature for 2.5 h. TLC analysis suggested complete conversion of thioamide **1b** into the enaminone **3c**.

Preparation of Probe Na_2CO_3 sonicated with ultrasonic probe system

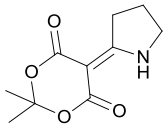
Dichloromethane (1.30 mL) was added to a test tube containing Na_2CO_3 (59.0 mg) and sonicated for 8.5 h. Solvent was evaporated and the base was used for the next reaction.

Synthesis of 3i [2, 6] using Na_2CO_3 sonicated with ultrasonic probe system

A solution of **1e** [2] (20.0 mg, 174 μmol) in 0.50 mL of CH_2Cl_2 was added to a test tube containing the above prepared Na_2CO_3 (3.2 eq). Bromide **2a** (2 eq) was dissolved in 0.40 mL CH_2Cl_2 and added to the reaction vessel. Each vial, which originally contained **1e** and **2a,** was washed twice with 0.10 mL CH_2Cl_2, and the contents were transferred to the reaction mixture. The test tube

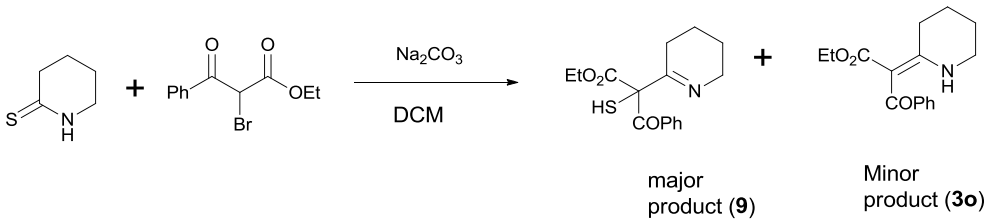
was capped and stirred at room temperature for 2.5 h. TLC analysis suggested < 50% conversion of thioamide **1e** into the enaminone **3i**.

2,2-Dimethyl-5-(pyrrolidin-2-ylidene)-1,3-dioxane-4,6-dione (3n) [2, 7]



A solution of **1b** [2] (20 mg, 198 µmol) in CH_2Cl_2 (0.50 mL) was added to a flame dried round bottom flask under an argon atmosphere. The vial, which originally contained **1b** was washed with CH_2Cl_2 (0.50 mL) and the contents were transferred to the round bottom flask. A solution of **2d** (71.5 mg, 237 µmol) was dissolved in CH_2Cl_2 (0.50 mL) and transferred to the reaction vessel. Additional CH_2Cl_2 (0.50 mL) was used to wash the vial in which **2d** was weighed and the contents were transferred to the reaction vessel. Tritely amine (1.2 eq., 237 µmol) was added and the reaction was stirred at RT for 1 hour. Column chromatography (40% ethyl acetate in petroleum ether) gave pure **14** as a yellow oil (27.0 mg, 128 µmol, 65% yield). R_f = 0.31 (petroleum ether: EtOAc 2:3). IR (neat) ν_{max}/cm^{-1}: 3313, 2922, 2839, 1716, 1663, 1599, 1448, 1406, 1374, 1359, 1263, 916, 828, 807; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.12 (s, br, 1H), 3.73 (t, J = 7.6 Hz, 2H), 3.39 (t, J = 8.0 Hz, 2H), 2.15 (tt, J = 7.6, 8.0 Hz, 2H), 1.66 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.0, 166.5, 163.2, 103.1, 81.8, 48.5, 34.9, 26.8, 20.9 ; HRMS (ESI$^+$): Calcd. for $C_{10}H_{13}NO_4$ $(M+H)^+$: 212.0917, found 212.0904; *m/z* (ESI$^+$) 212 (M + H$^+$); HPLC, t_R = 4.68 min.

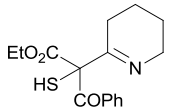
Synthesis of 3o and 9



The reaction was performed according to the general procedure A. It was sonicated for 2.5 h to convert **1c**[2] (20.0 mg, 174 µmol) into a crude mixture of **9** and **3o**. Column chromatography

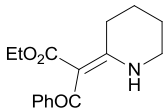
(20%, then 40% ethyl acetate in petroleum ether) provided pure **9** (46.6 mg, 153 μmol, 70%) and **3o** (13.5 mg, 49.4 μmol, 28% yield) as a single diastereomer.

Ethyl 2-mercapto-3-oxo-3-phenyl-2-(3,4,5,6-tetrahydropyridin-2-yl)propanoate (9)



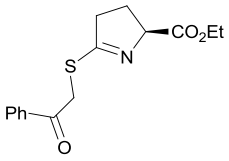
R_f = 0.43 (petroleum ether: EtOAc 7:3). IR (neat) ν_{max}/cm^{-1}: 3232, 3134, 2950, 2863, 1665, 1629, 1583, 1271, 1230, 1199; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.67 (s, br, 1H), 8.04–8.02 (m, 2H), 7.57–7.53 (m, 1H), 7.46–7.42 (m, 2H), 4.11 (q, J = 7.2 Hz, 2H), 3.40 (s, br, 2H), 2.75–2.71 (m, 1H), 2.47–2.42 (m, 1H), 1.78–1.67 (m, 4H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 192.7, 170.4, 168.8, 137.2, 133.1, 128.6, 127.5, 75.1, 59.8, 41.9, 27.8, 21.7, 19.7, 14.6; HRMS (ESI$^+$): Calcd. for $C_{16}H_{19}NO_3S$ (M + H$^+$): 306.1158, found 306.1133; *m/z* (ESI$^+$) 306 (M + H$^+$, 100%), 221(59%), 162(24%); HPLC, t_R = 9.11 min.

Ethyl (2*E*)-3-oxo-3-phenyl-2-(piperidin-2-ylidene)propanoate (3o) [5]



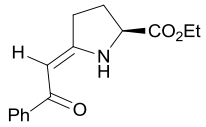
R_f = 0.27 (petroleum ether: EtOAc 7:3). IR (neat) ν_{max}/cm^{-1}: 3058, 3022, 2925, 2868, 1685, 1593, 1562, 1332, 1312, 1276; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 12.06 (s, br, 1H), 7.49 (s, br, 2H), 7.35–7.33 (m, 3H), 3.75(s, br, 2H), 3.47 (s, br, 2H), 2.85 (t, J = 5.6 Hz, 2H), 1.86–1.70 (m, 4H), 0.68 (s, br, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.1, 170.3, 169.1, 143.4, 129.8, 128.0, 127.0, 99.9, 59.7, 41.9, 27.5, 21.4, 19.1, 13.5; HRMS (ESI$^+$): Calcd. for $C_{16}H_{19}NO_3$ (M + H$^+$): 274.1438, found 274.1416; *m/z* (ESI$^+$) 274 (M + H$^+$, 100%), 245(66%), 173(24%); HPLC, t_R = 7.58 min.

(*S*)-Ethyl 5-((2-oxo-2-phenylethyl)thio)-3,4-dihydro-2*H*-pyrrole-2-carboxylate (10)



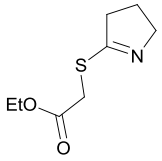
The reaction was performed according to the general procedure A. It was sonicated for 10 min. to convert **1d** [8] (20.0 mg, 115 μmol) into crude **10**. Column chromatography (20% ethyl acetate in petroleum ether) provided pure **10** (31.8 mg, 109 μmol, 95%). R_f = 0.32 (petroleum ether /EtOAc = 4/1). IR (neat) ν_{max}/cm^{-1}: 2922, 2848, 1735, 1682, 1581, 1448, 1277, 1192, 1706, 1030, 748; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.05–8.03 (m, 2H), 7.60–7.56 (m, 1H), 7.46 (t, J = 8 Hz, 2H), 4.70 (s, 2H), 4.68–4.65 (m, 1H), 4.18 (q, J = 7.2 Hz, 2H), 2.87–2.67 (m, 2H), 2.37–2.17 (m, 2H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 194.0, 173.2, 172.7, 135.8, 133.7, 128.8, 128.8, 73.4, 61.2, 38.6, 29.8, 28.0, 14.3 ; HRMS (ESI$^+$): Calcd. for $C_{15}H_{17}NO_3S$ (M + H$^+$): 292.1001, found 292.0985; *m/z* (ESI$^+$) 292 (M + H$^+$); HPLC, t_R = 7.21 min.

Ethyl (2*S*,5*Z*)-5-(2-oxo-2-phenylethylidene)pyrrolidine-2-carboxylic Acid Ethyl Ester (3p) [9]



The reaction was set up according to the general procedure B. Instead of CH_2Cl_2 , xylenes were used as a solvent. The reaction was sonicated for 10 min. to convert **1d** [8] (20.0 mg, 115 μmol) into crude **10**. Triphenylphosphine (130 mg, 496 μmol) was added to the reaction vessel and the reaction was sonicated for 11 h. Column chromatography (30 % ethyl acetate in petroleum ether) provided pure **3p** (23.9 mg, 91.9 μmol, 80% yield) as a single diastereomer. R_f = 0.29 (petroleum ether: EtOAc 4:1). IR (neat) ν_{max}/cm^{-1}: 3324, 2922, 2848, 1739, 1616, 1580, 1532, 1189, 1051, 1020; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 10.33 (s, br, 1H), 7.89–7.87 (m, 2H), 7.44–7.37 (m, 3H), 5.86 (s, 1H), 4.50 (dd, J = 8.4, 5.2 Hz, 1H), 4.26–4.19 (m, 2H), 2.91–2.72 (m, 2H), 2.41–2.32 (m, 1H), 2.27–2. 16 (m, 1H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 188.9, 171.5, 167.8, 140.1, 130.9, 128.3, 127.3, 87.7, 61.8, 61.4, 32.0, 25.7, 14.2; HRMS (ESI$^+$): Calcd. for $C_{15}H_{17}NO_3$, (M + H$^+$): 260.1281, found 260.1261; *m/z* (ESI$^+$) 260 (M + H$^+$); HPLC, t_R = 7.96 min.

Ethyl 2-((3,4-dihydro-2*H*-pyrrol-5-yl)thio)acetate (11) [10]



The reaction was performed according to the general procedure A. It was sonicated for 1.5 h to convert **1b** [2] (20.0 mg, 198 μmol) into crude **11**. Column chromatography (20% ethyl acetate in petroleum ether) provided pure **11** (35.4 mg, 189 μmol, 96% yield). R_f = 0.26 (petroleum ether: EtOAc 4:1). IR (neat) ν_{max}/cm^{-1} : 2927, 2866, 1740, 1596, 1297, 1155, 1082, 1029, 972; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.18 (dq, J = 1.2, 7.2 Hz, 2H), 3.86 (d, J = 1.2, 2H), 3.83–3.79 (m, 2H), 2.64–2.59 (m, 2H), 2.02–1.80 (m, 2H), 1.26 (dt, J = 1.2, 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.7, 169.2, 61.8, 60.7, 38.2, 33.2, 23.9, 14.2 ; HRMS (ESI$^+$): Calcd. for $C_8H_{13}NO_2S$ (M + H$^+$): 188.0740, found 188.0734; *m/z* (ESI$^+$) 188 (M + H$^+$, 100%), 142 (10%); HPLC, t_R = 0.94 min.

References:

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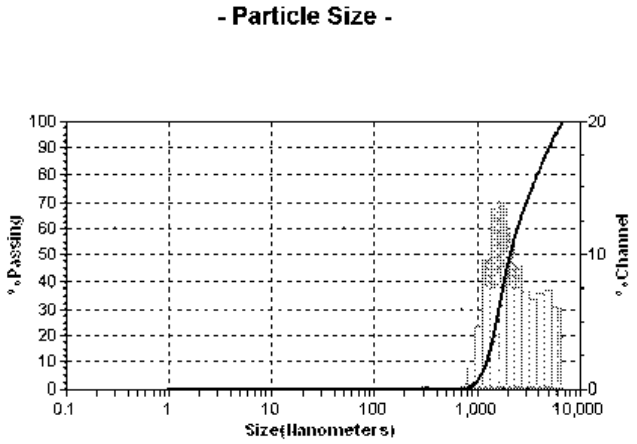
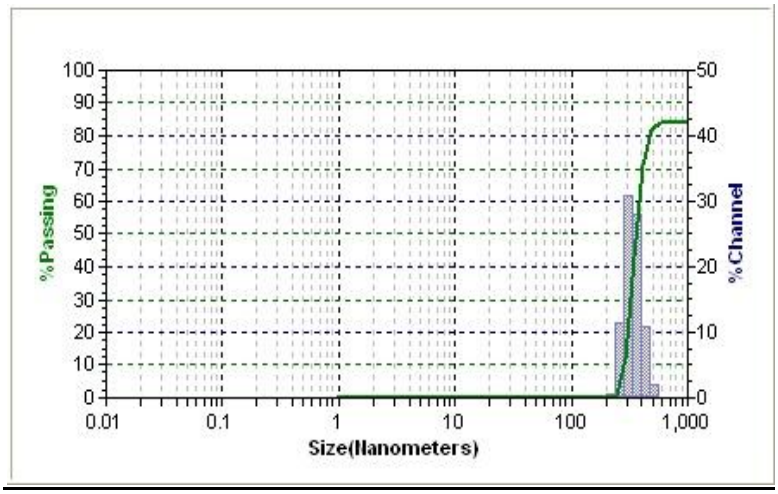
Particle distribution of commercially avilable sodium carbonate (Fisher Lot AD-9195-27):



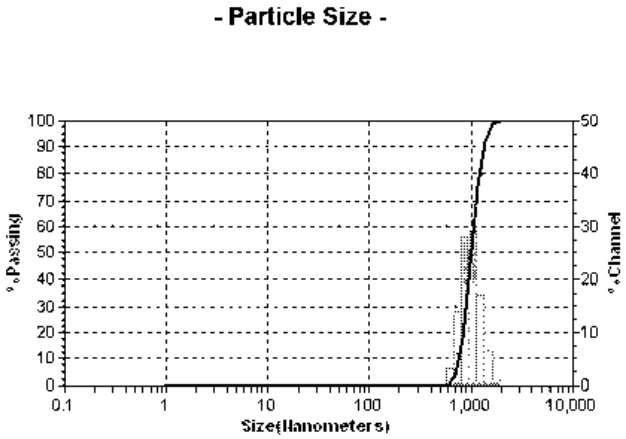
S.no	Data	Values
1.	MV(nm)	2,630
2.	MN(nm)	1,097
3.	MA(nm)	2,003

Particle distribution of probe sonicated sodium carbonate (prepared according to the procedure described on page S5 but sonicated for 2.5 h:



S.no	Data	Values
1.	MV(nm)	646
2.	MN(nm)	324
3.	MA(nm)	394

Particle distribution of water bath sonicated sodium carbonate:



S.no	Data	Values
1.	MV(nm)	1025
2.	MN(nm)	898
3.	MA(nm)	979

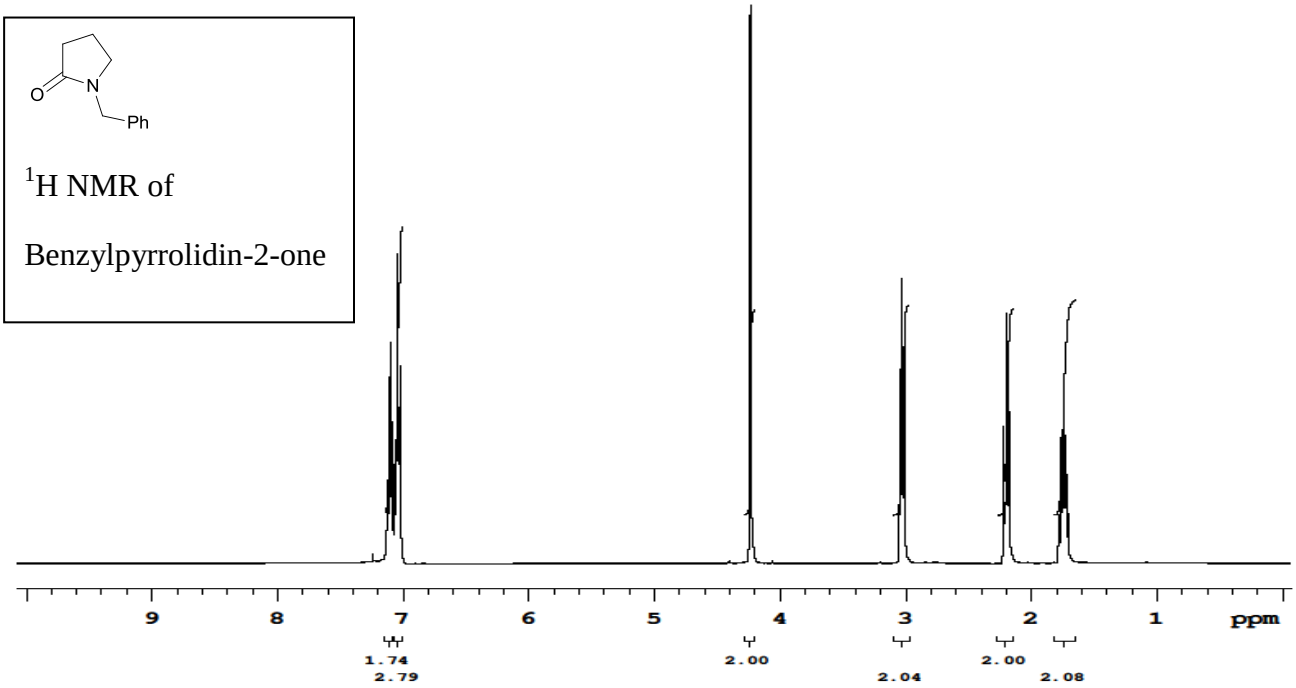
MV- Mean Volume diameter. It "represents the center of gravity of the distribution. Implementation of the equation used to calculate MV will show it to be weighted (strongly influenced) by coarse particles. It is a type of "average particle size.""[1]

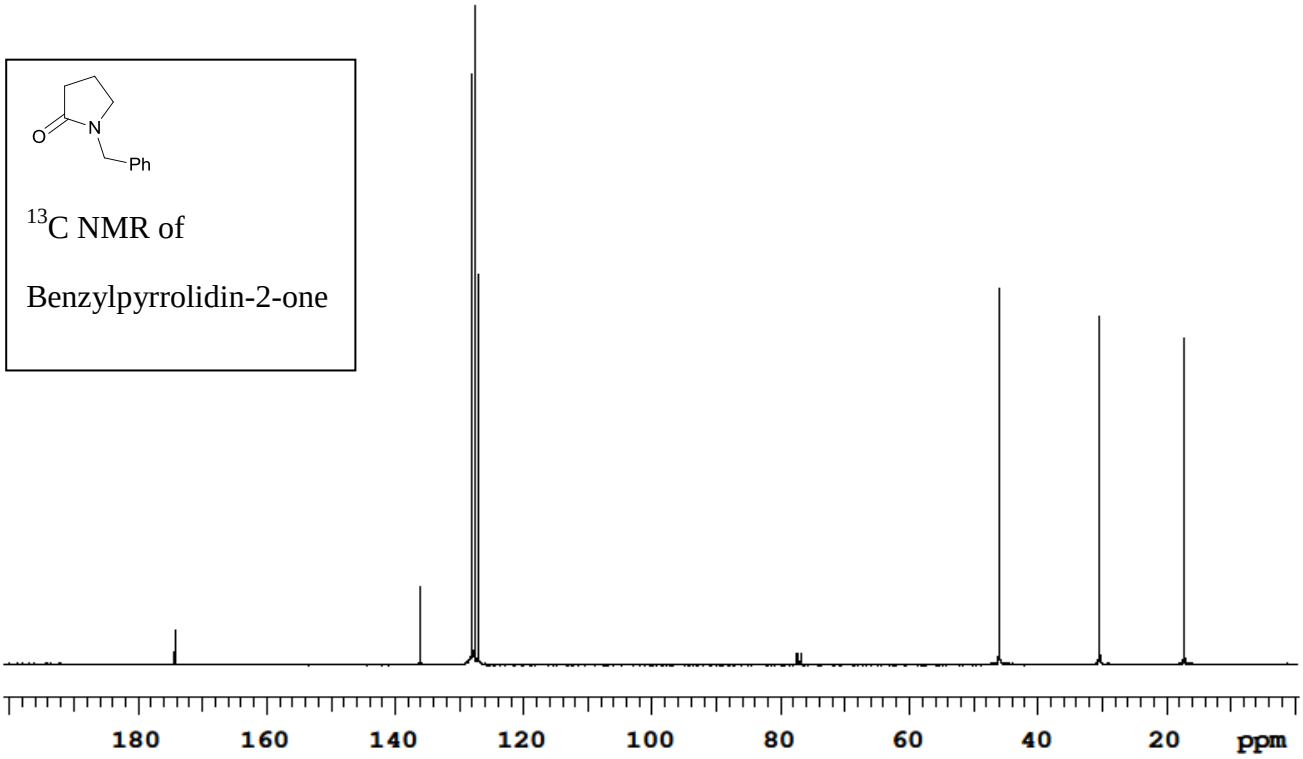
MN- Mean Number diameter. It "is calculated using the volume distribution data and is weighted to the small particles. This type of "average particle size" is related to population."[1]

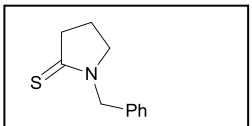
MA- Mean Area Diameter. It "is calculated from the volume distribution. The area mean is a type of "average" that is less weighted than MV by the presence of coarse particles, and therefore shows smaller particle size. Mean diameter represents a particle surface measurement."[1]

Reference: 1. Microtrac FLEX Software Operations Manual, P/N: SW 0003, 2008, p 33.

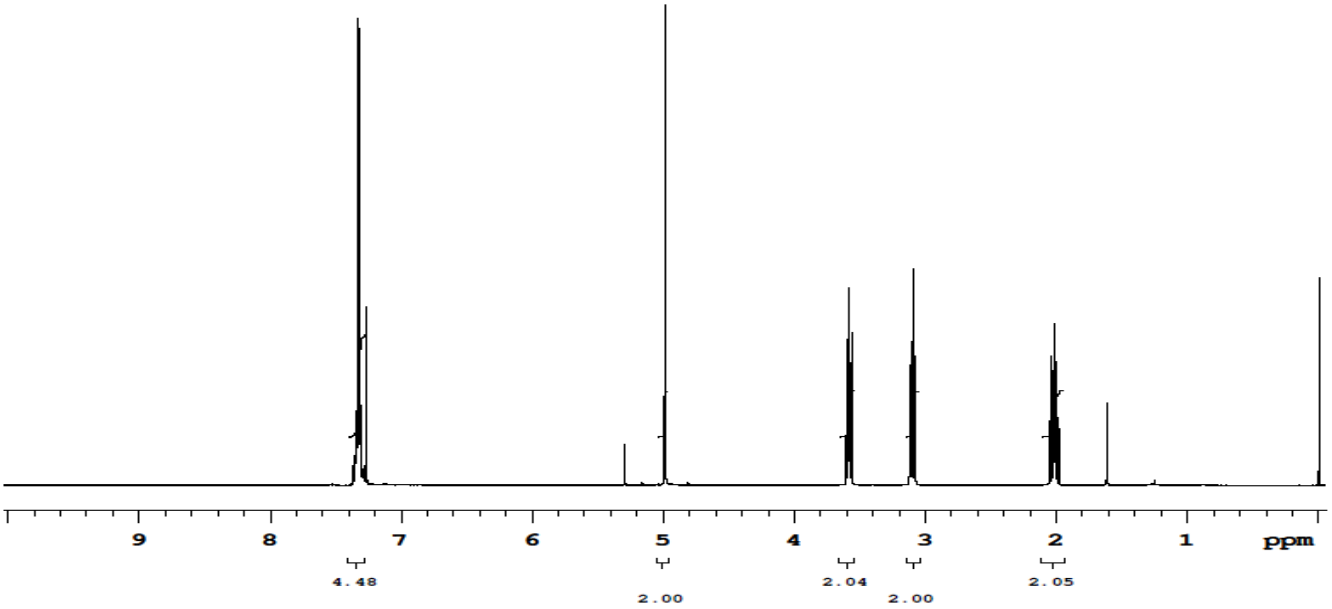
^{1}H NMR and ^{13}C NMR spectra of isolated compounds

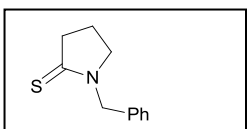




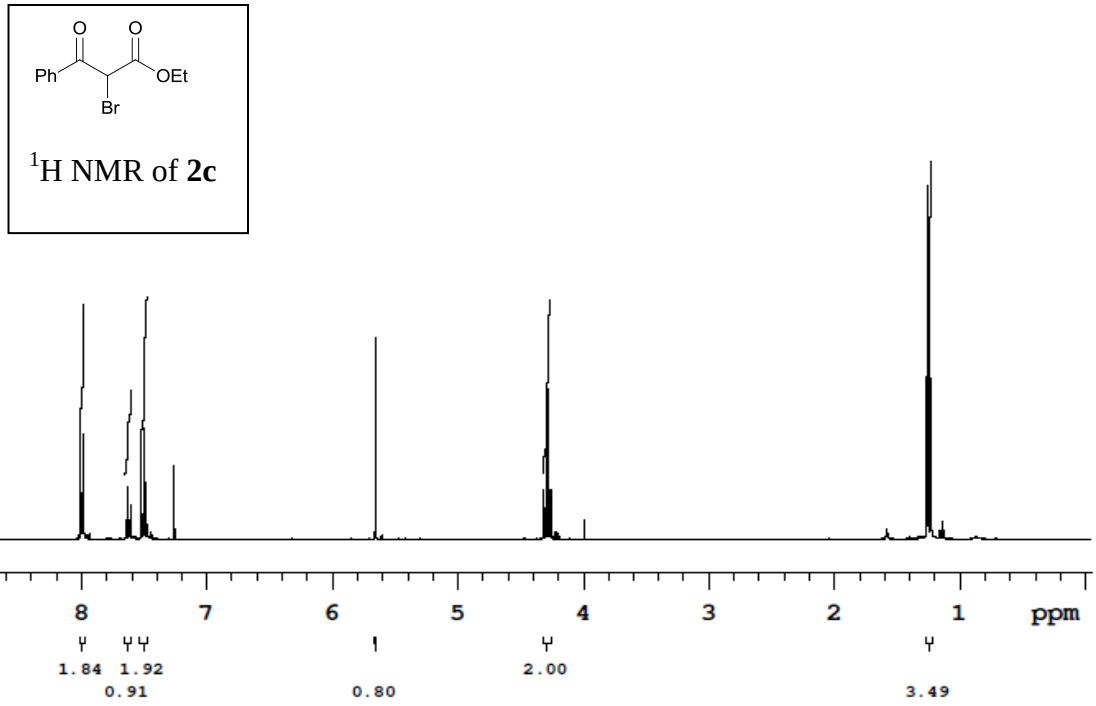


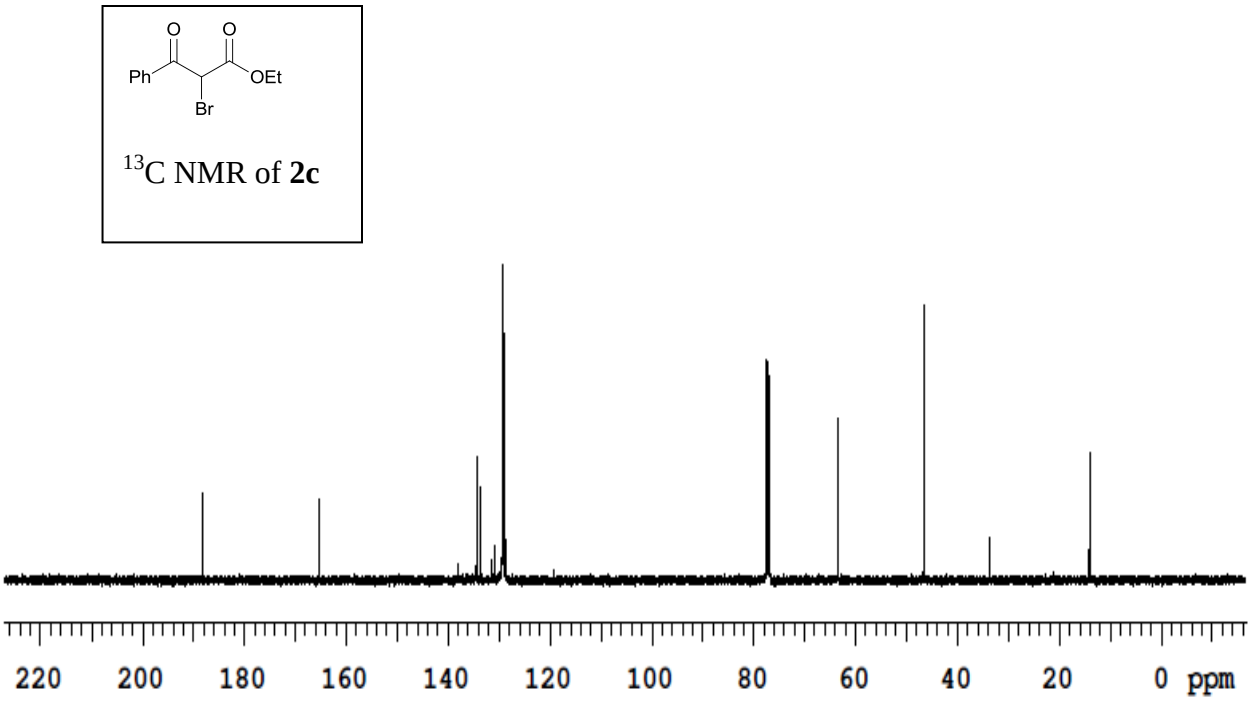
^{1}H NMR of **1f**

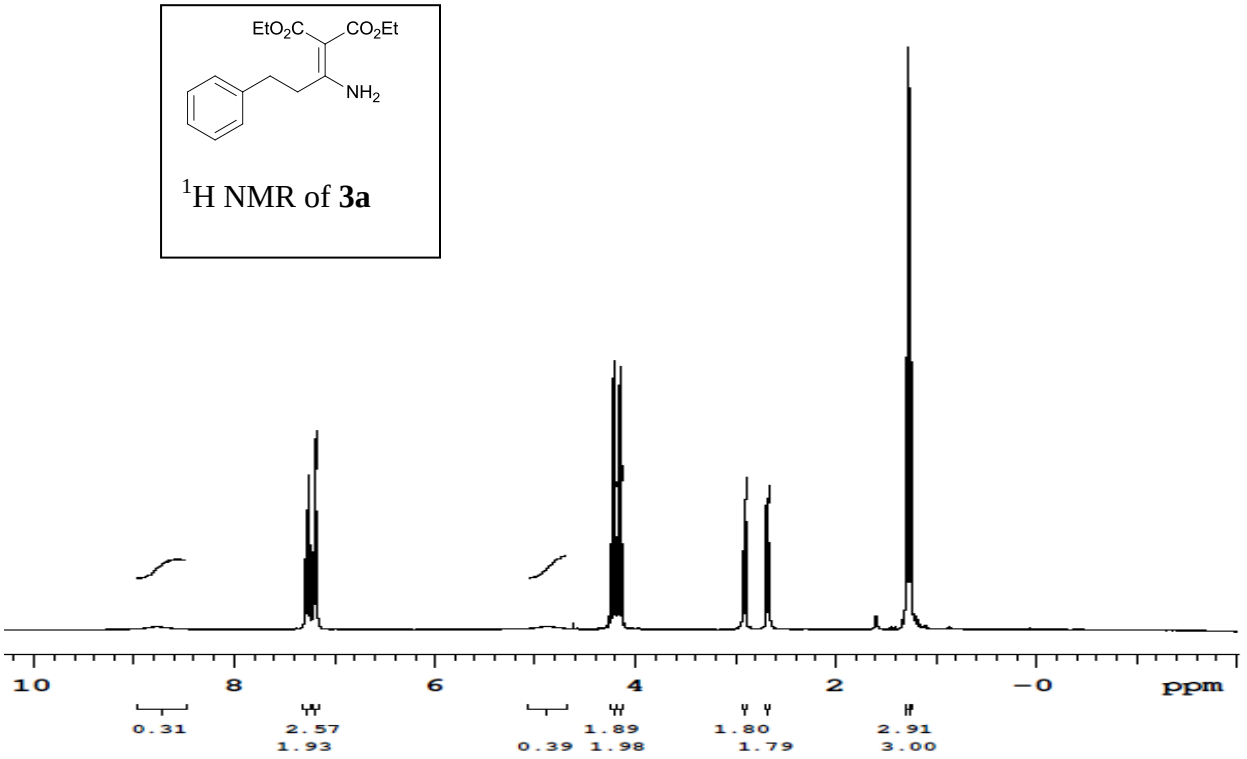


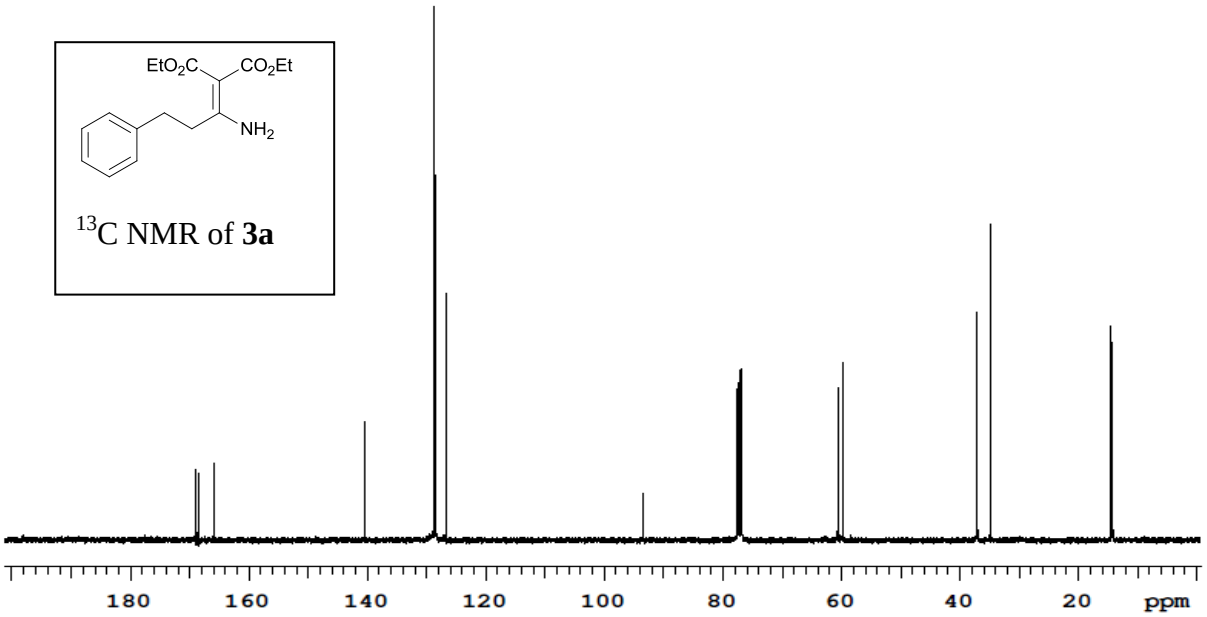


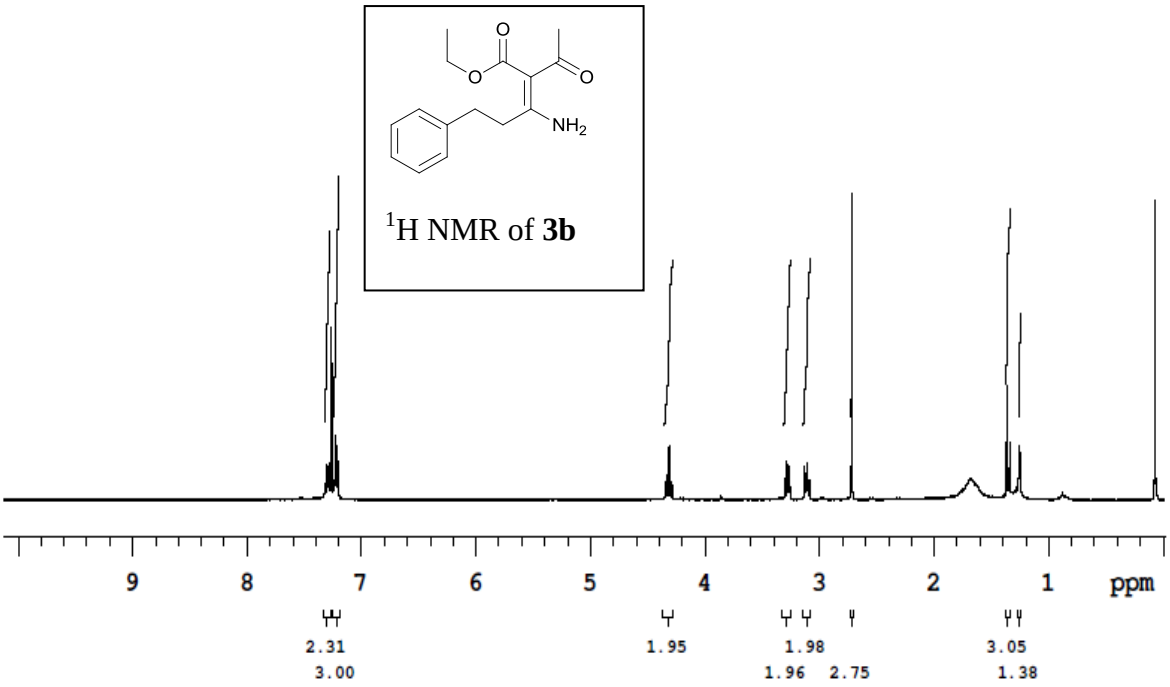
^{13}C NMR of **1f**



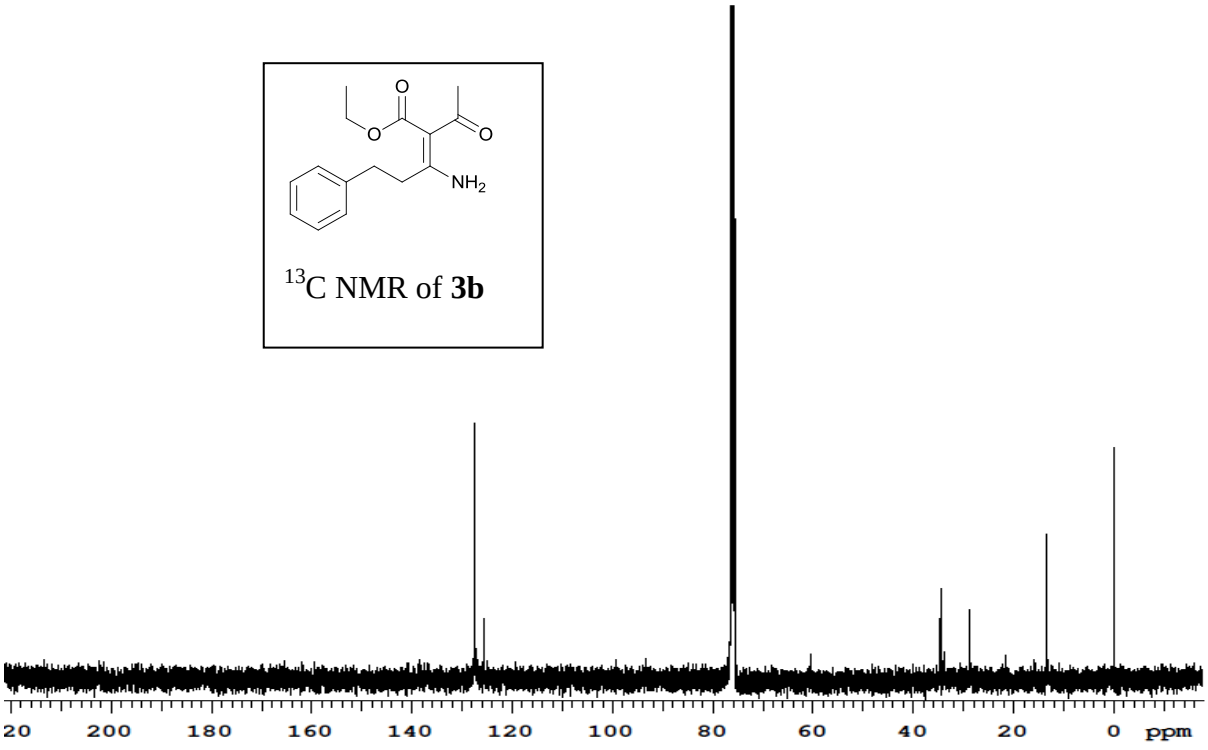




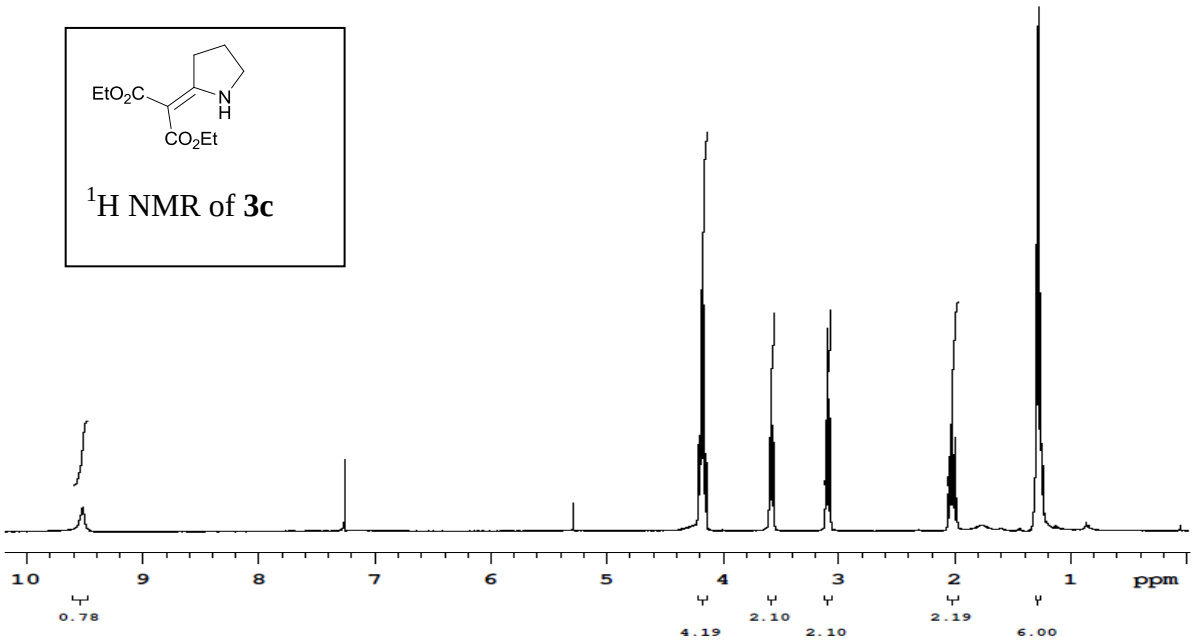




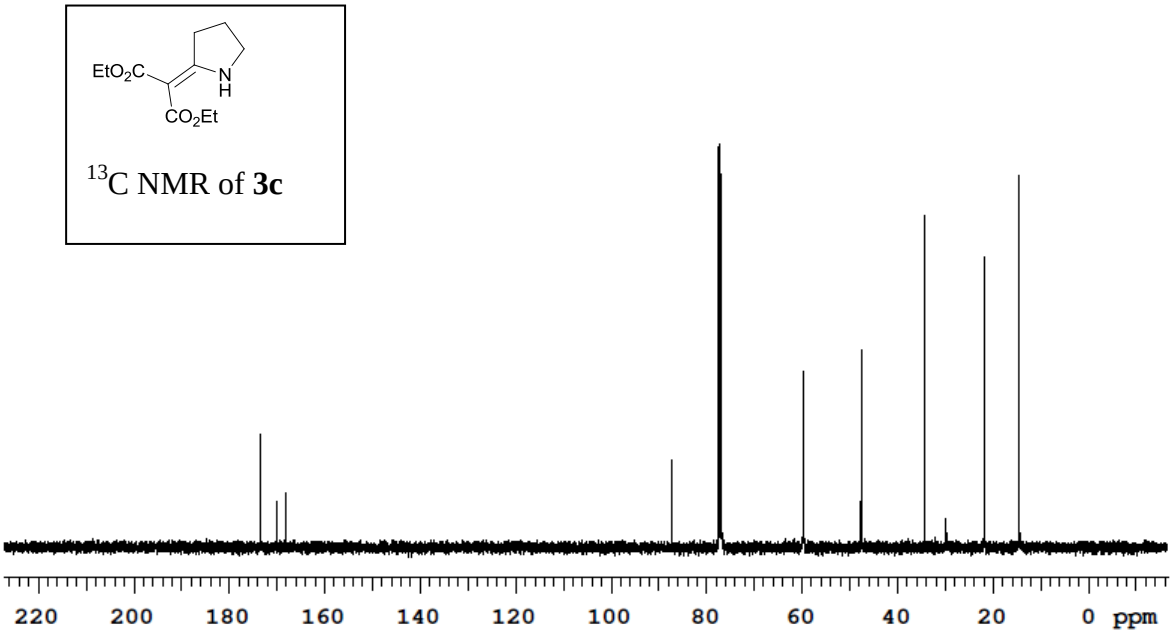
^{1}H NMR of **3b**



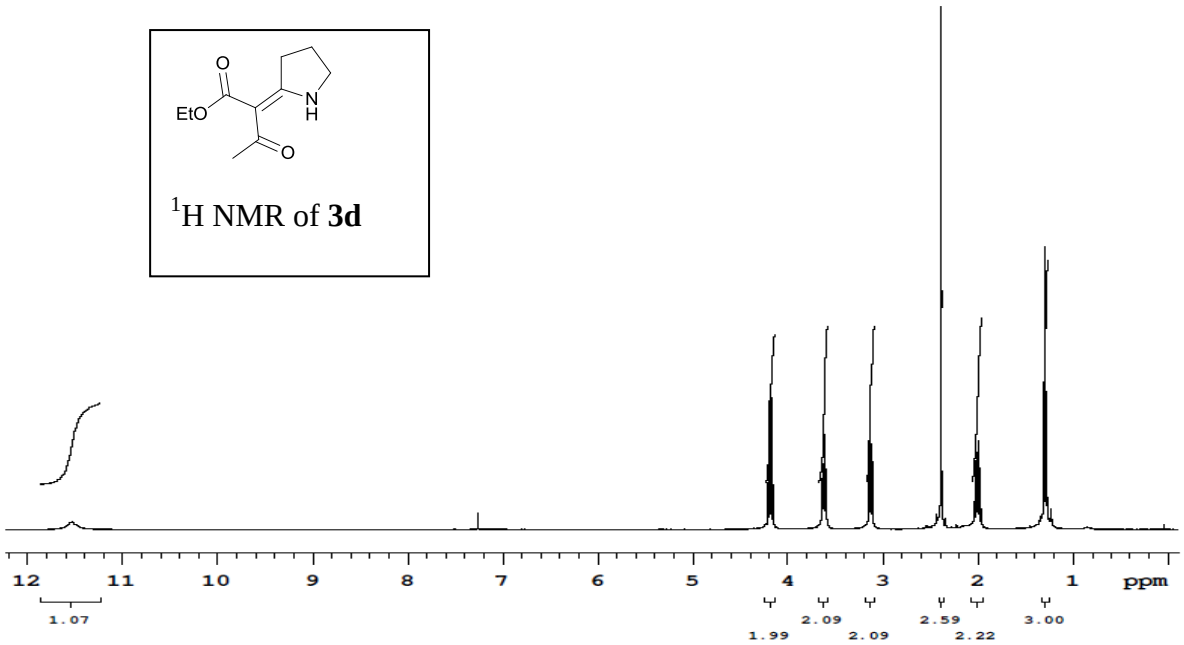
^{13}C NMR of **3b**



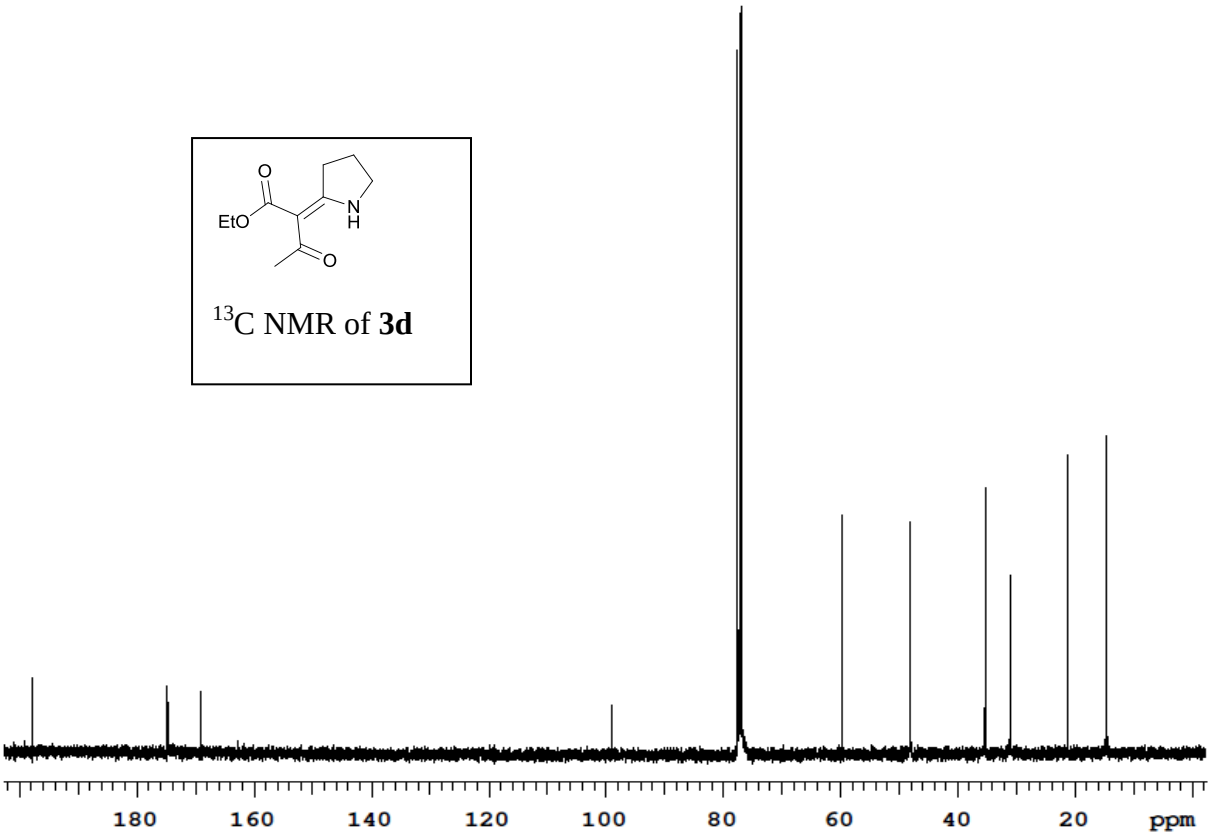
^{1}H NMR of **3c**



^{13}C NMR of **3c**



^{1}H NMR of **3d**



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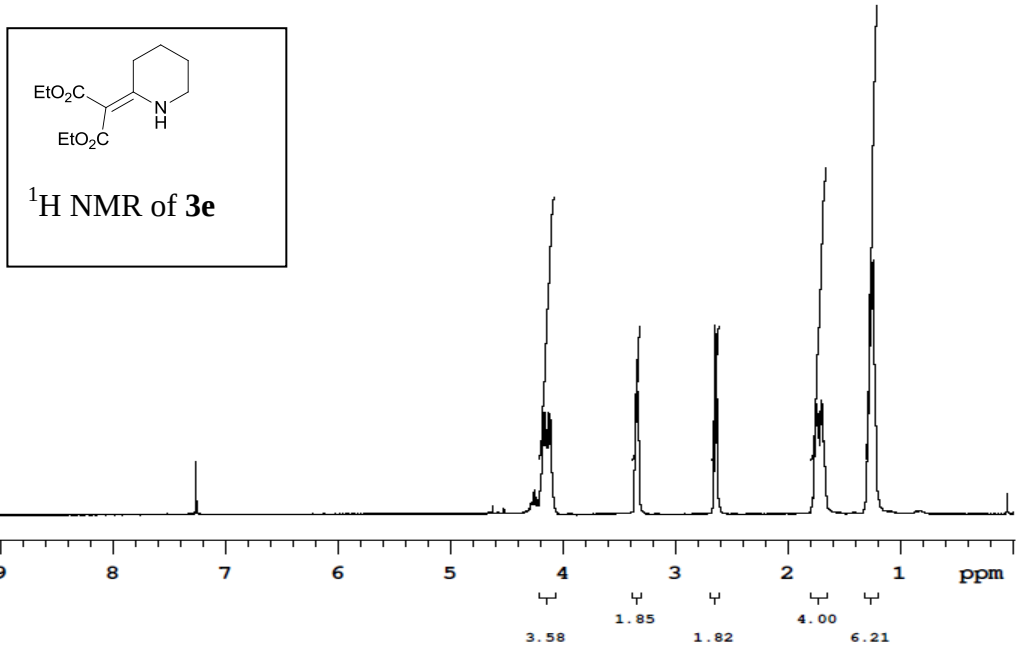
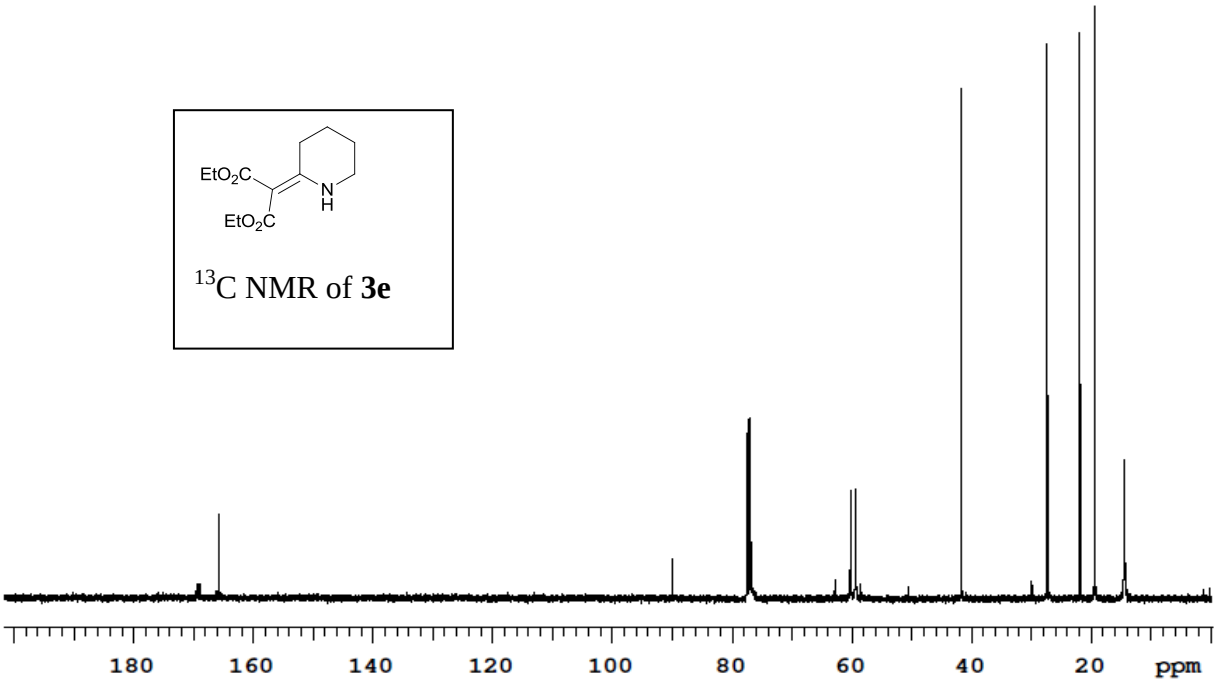
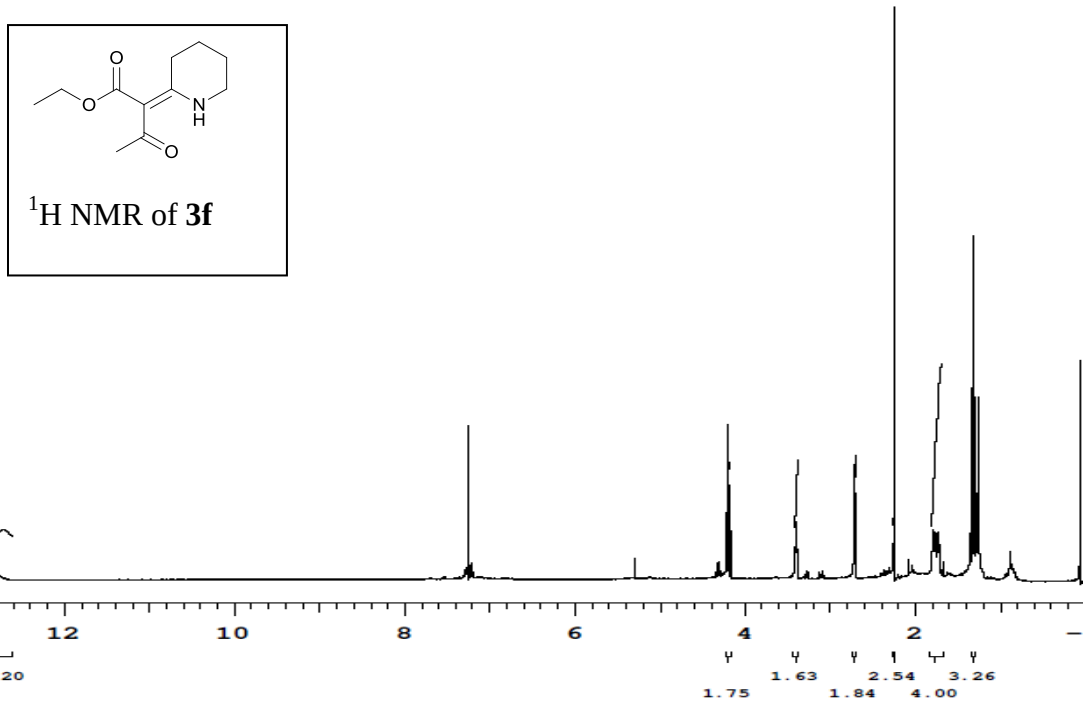


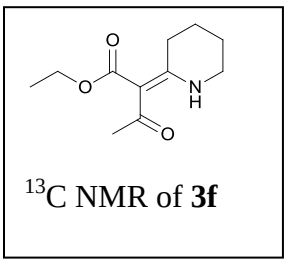
^{1}H NMR of **3e**



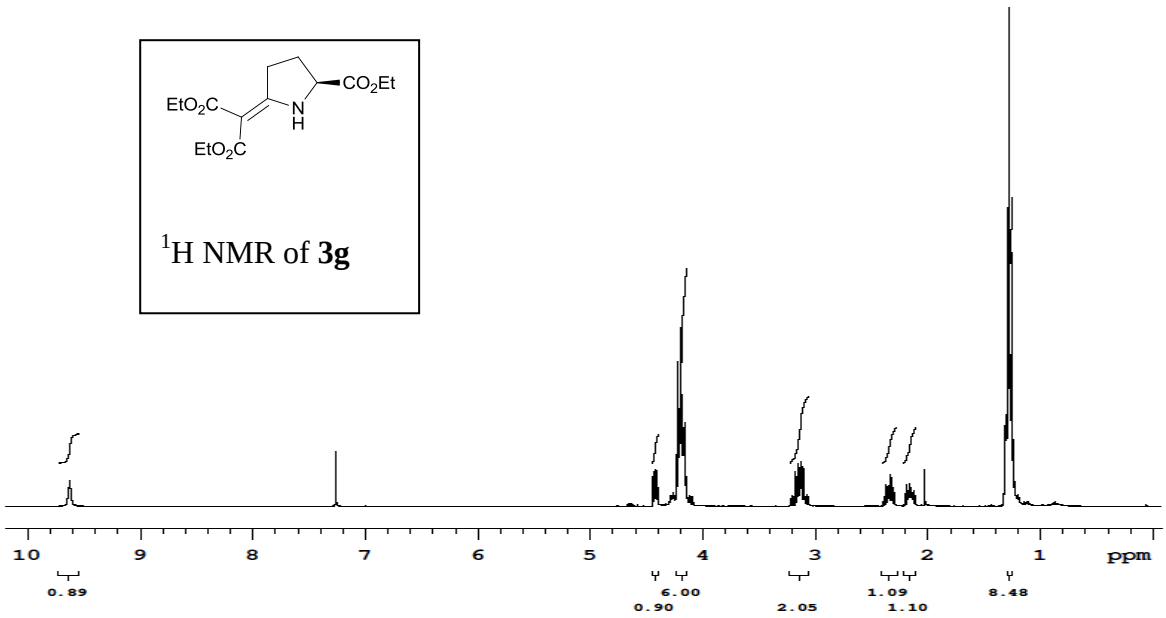
^{13}C NMR of **3e**

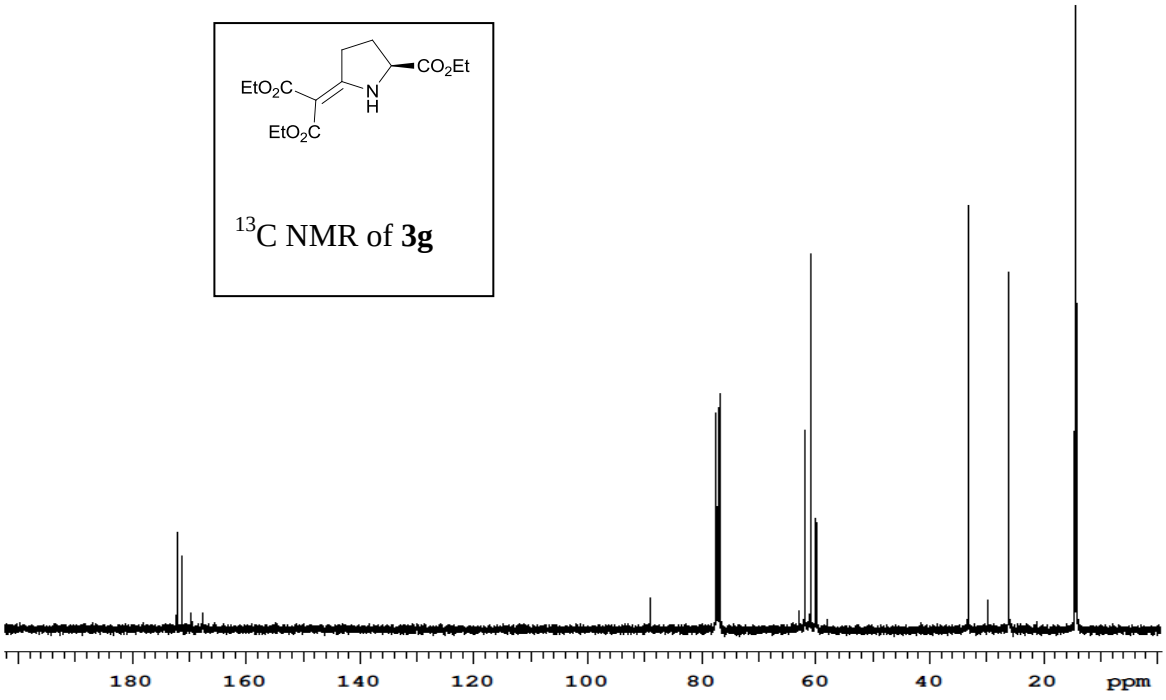


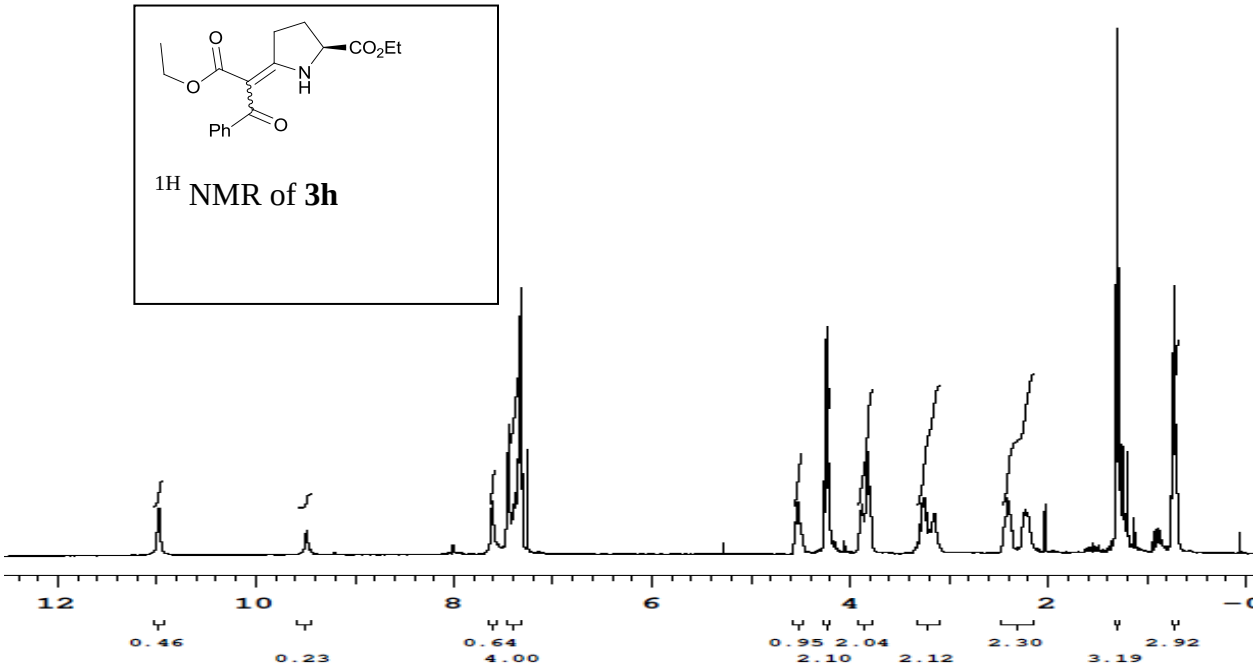
^{1}H NMR of **3f**

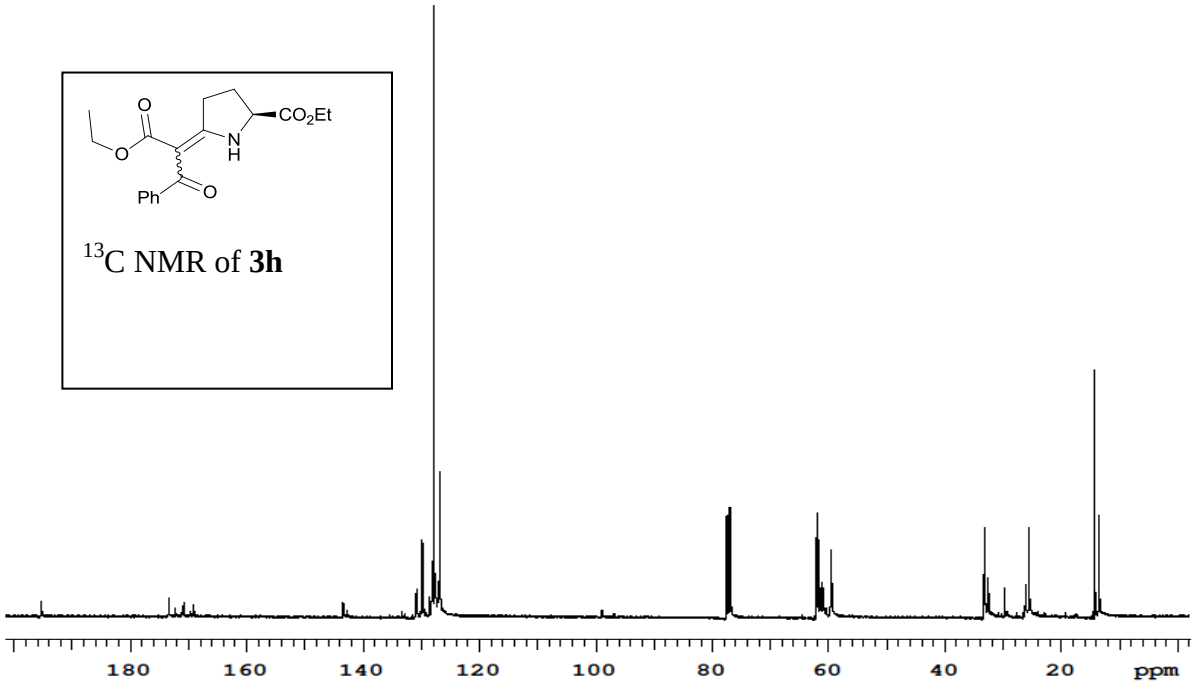


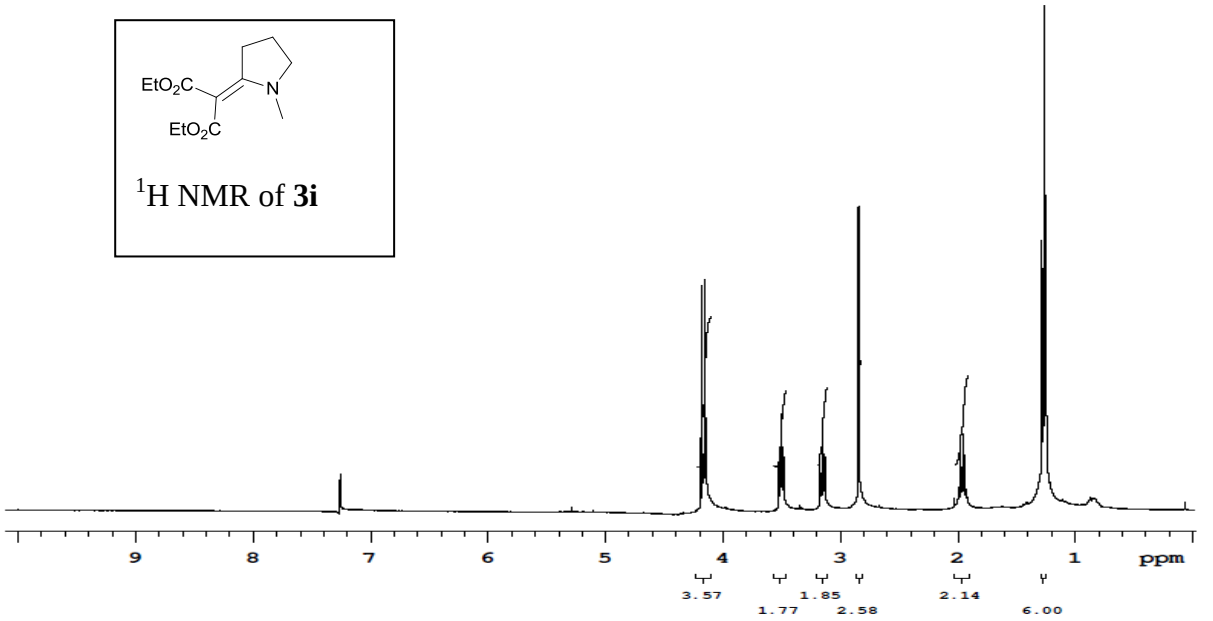
^{13}C NMR of **3f**

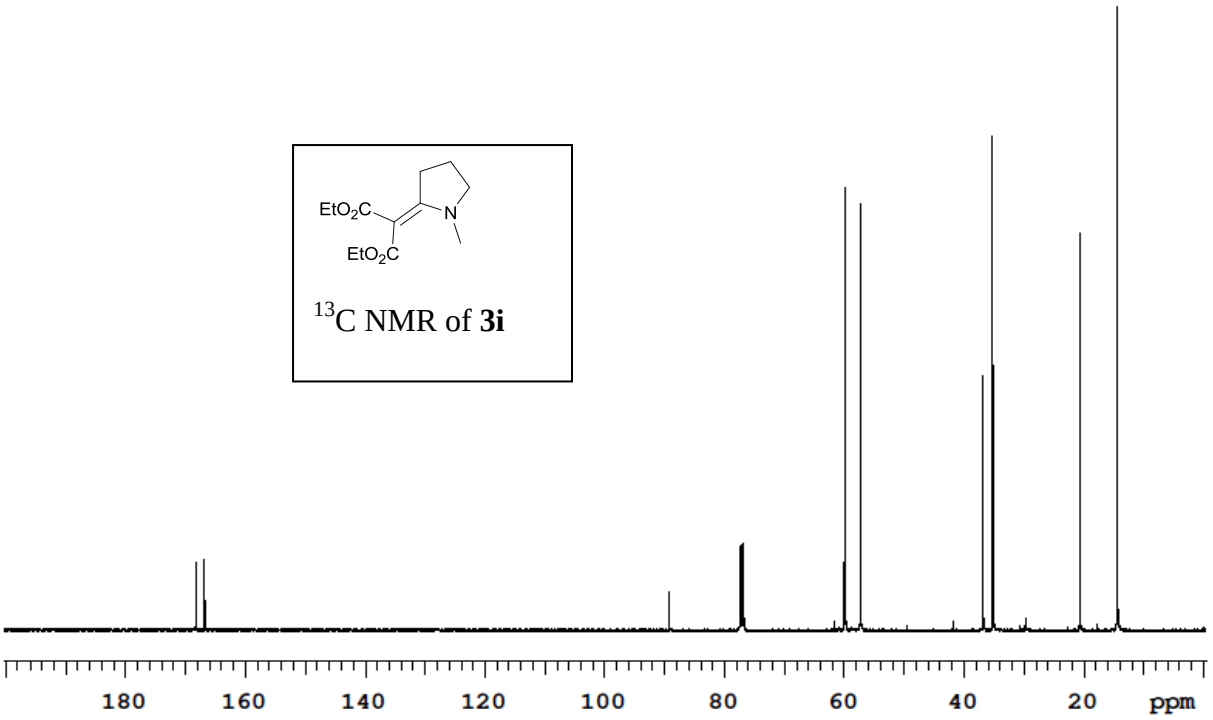


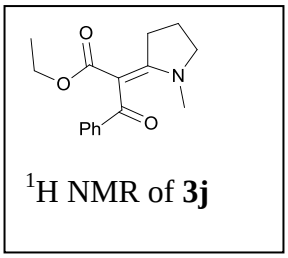




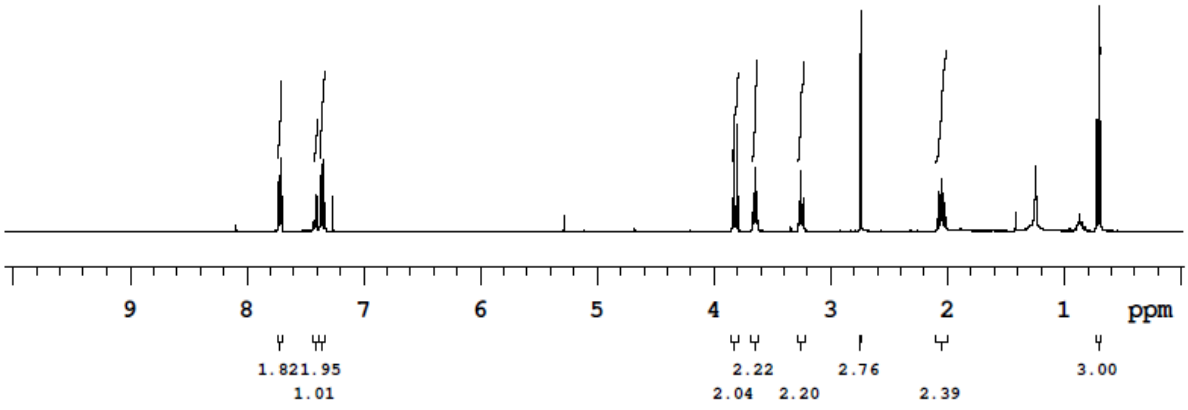


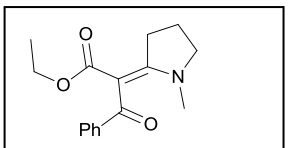




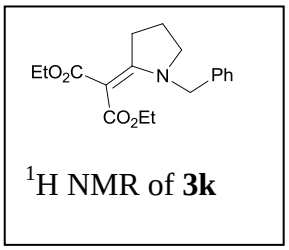


^{1}H NMR of **3j**





^{13}C NMR of **3j**



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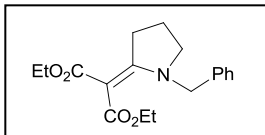

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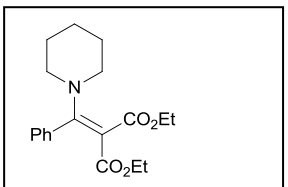
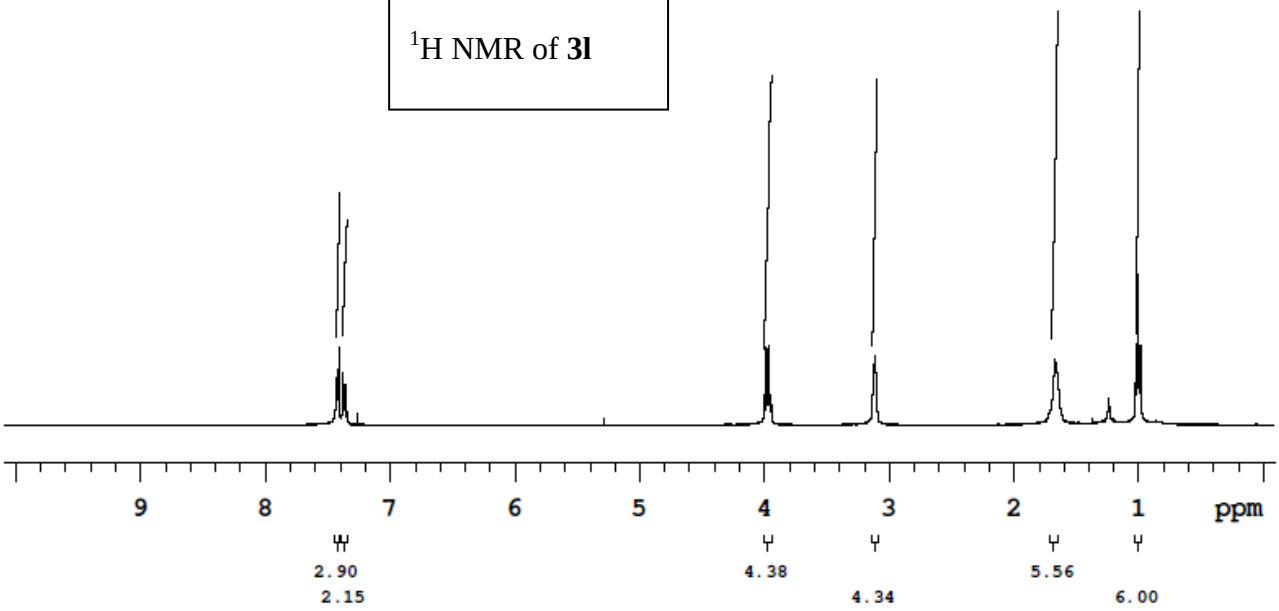
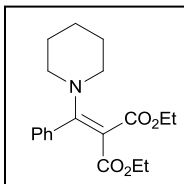
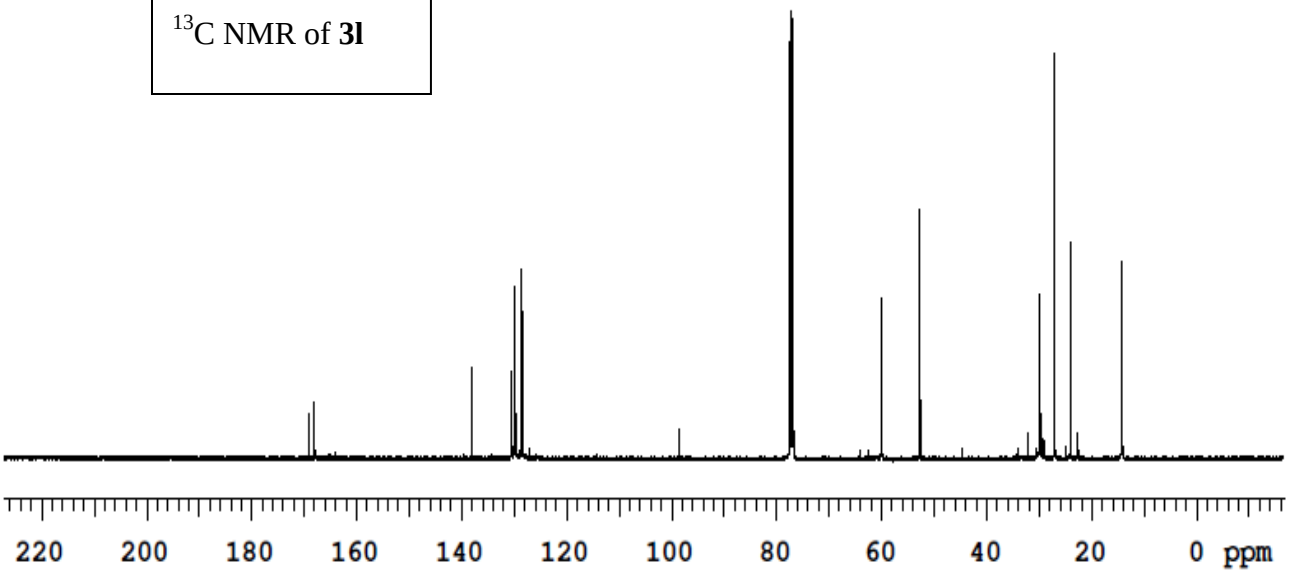


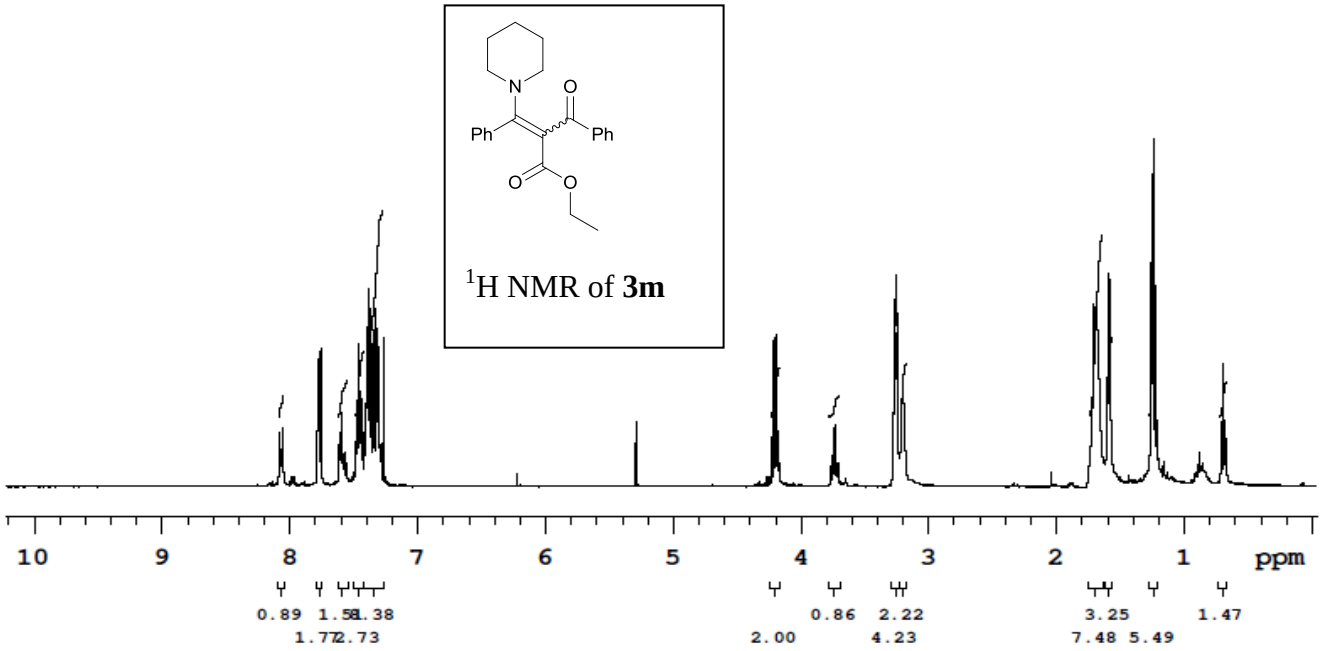
^{1}H NMR of **3l**



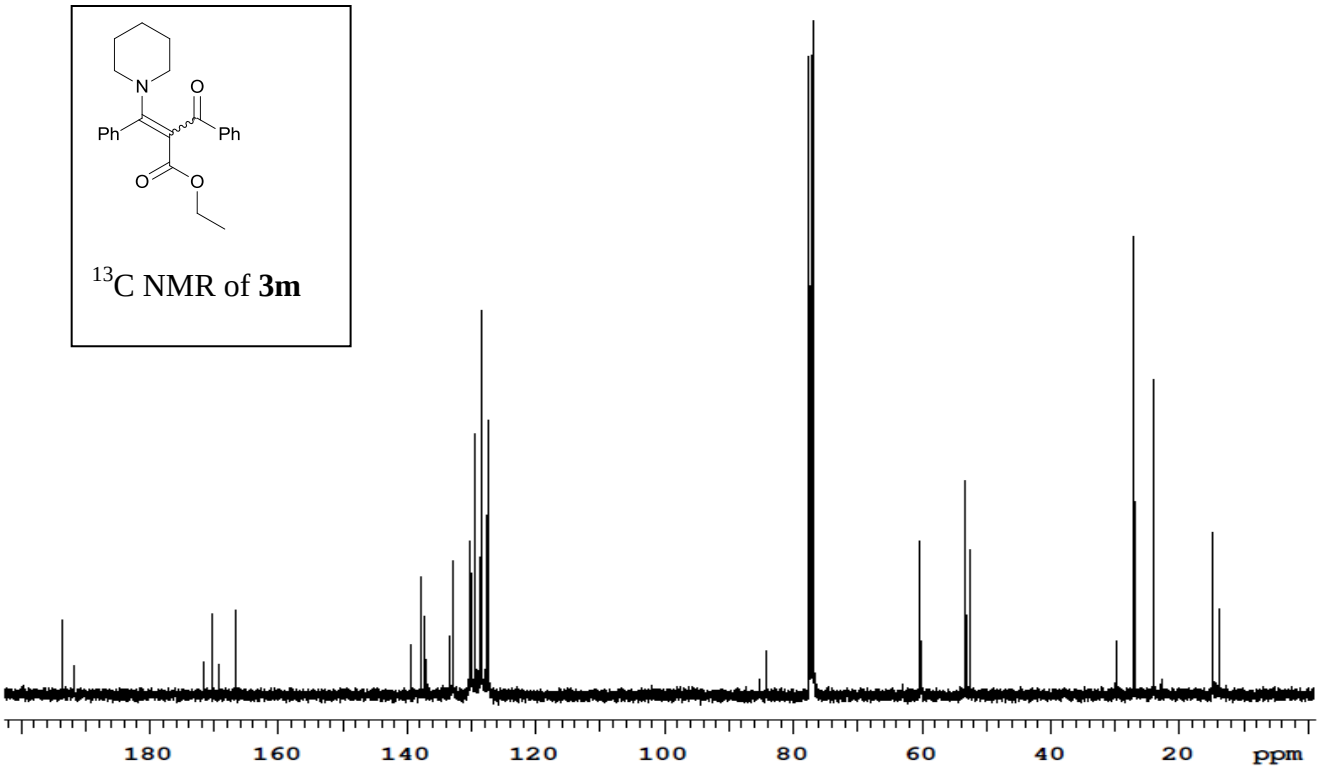


^{13}C NMR of **3l**

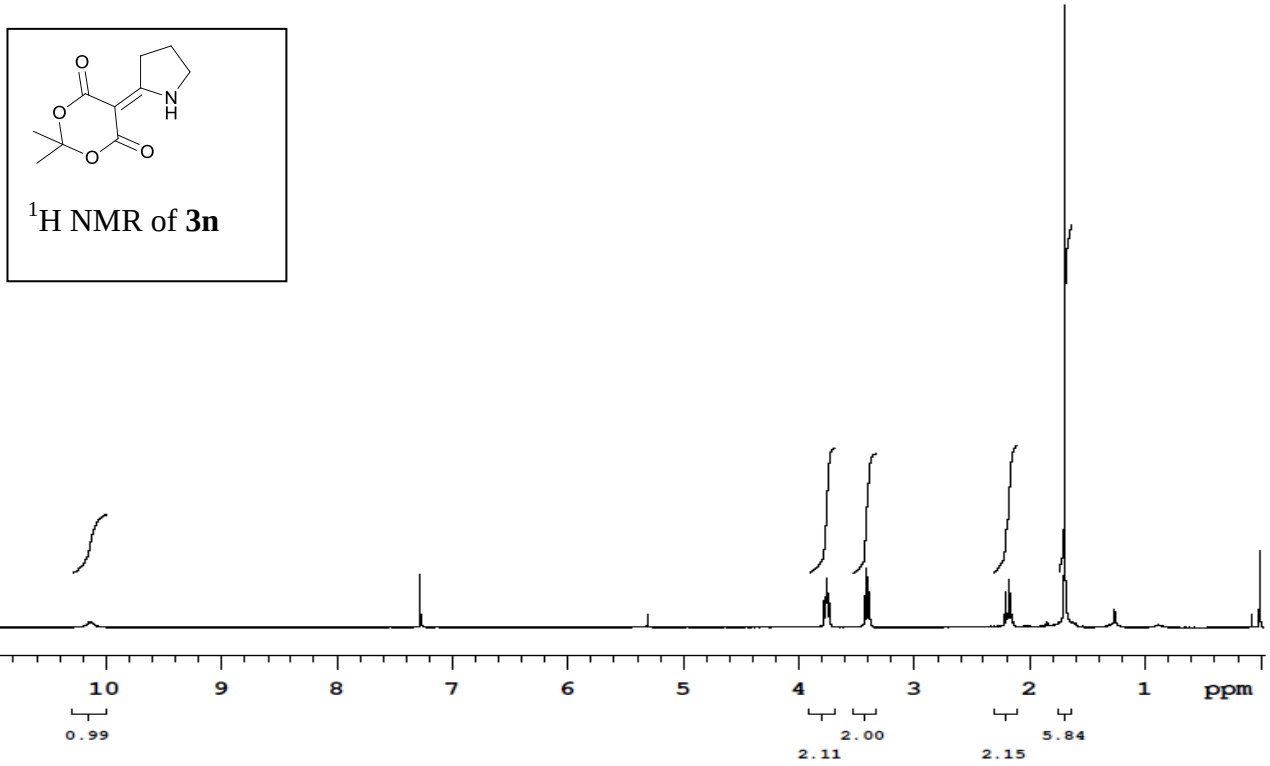




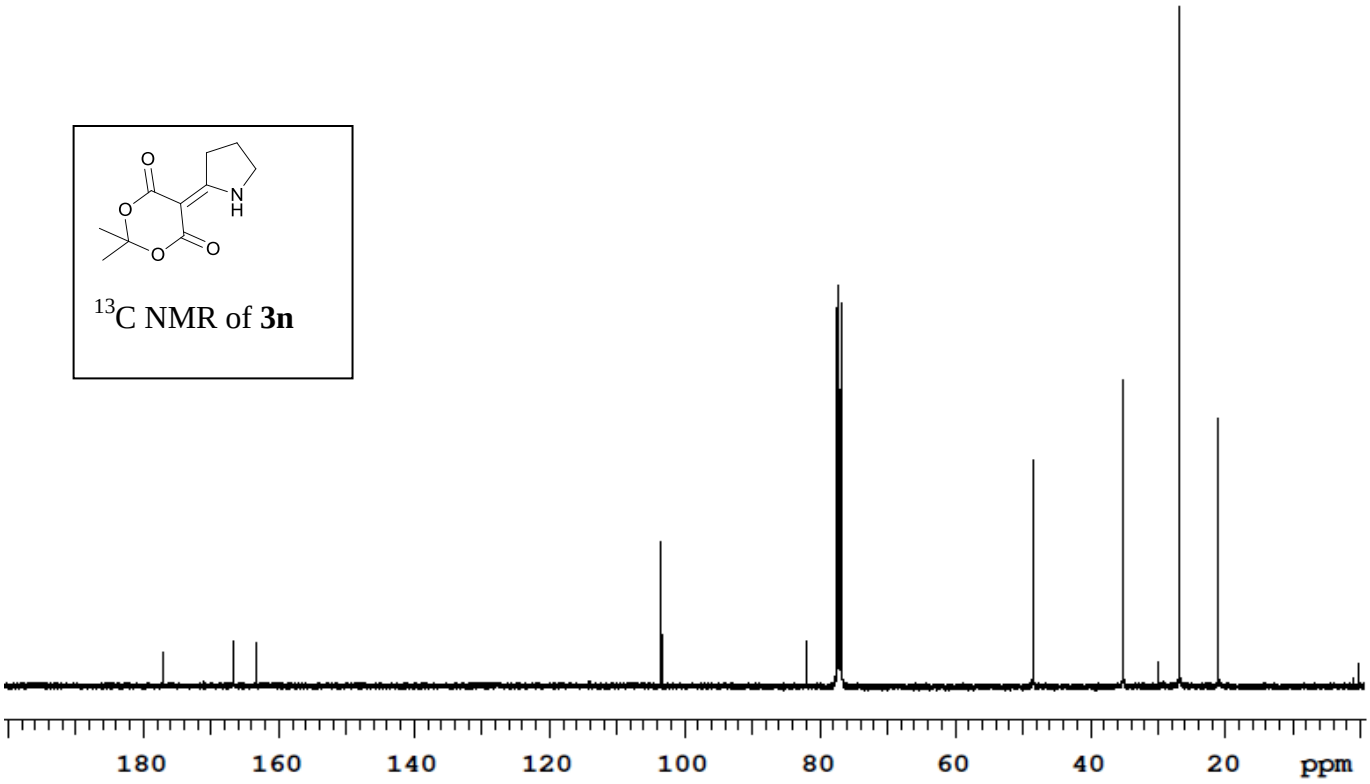
^{1}H NMR of **3m**



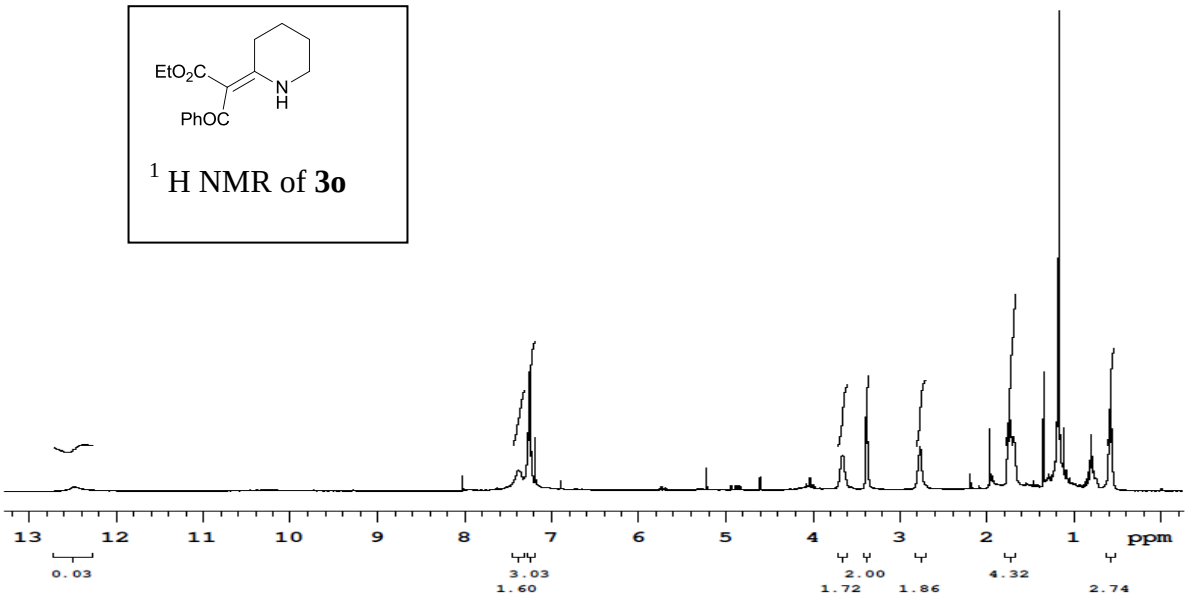
^{13}C NMR of **3m**



^{1}H NMR of **3n**



^{13}C NMR of **3n**



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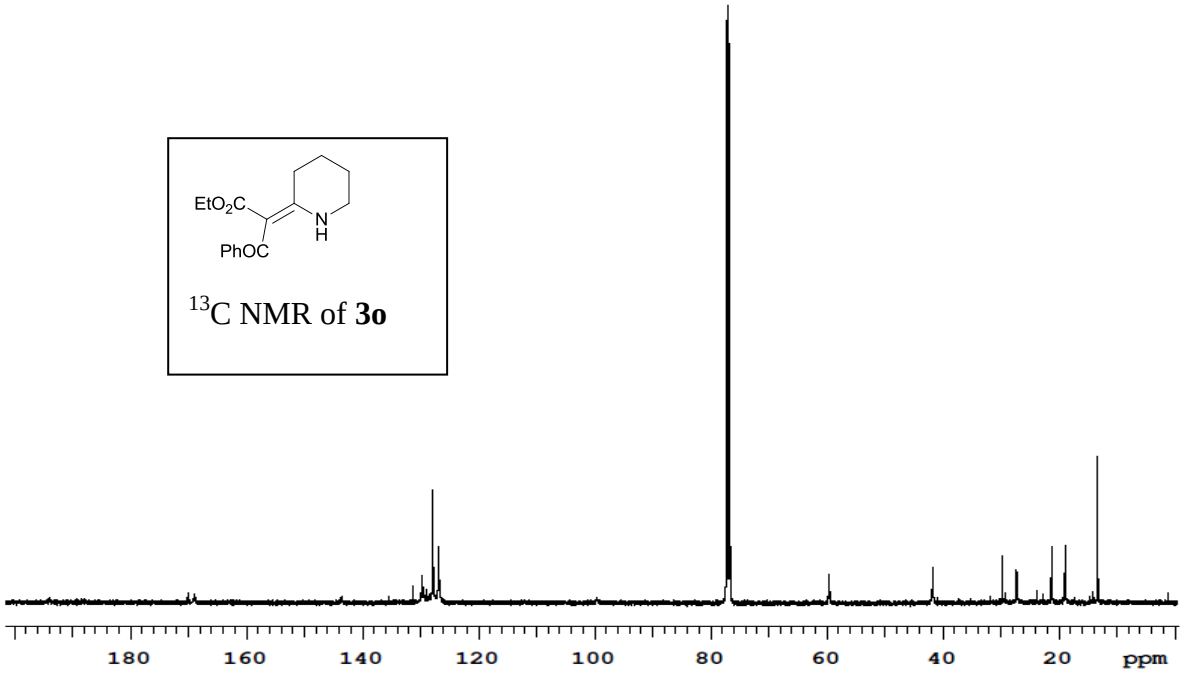
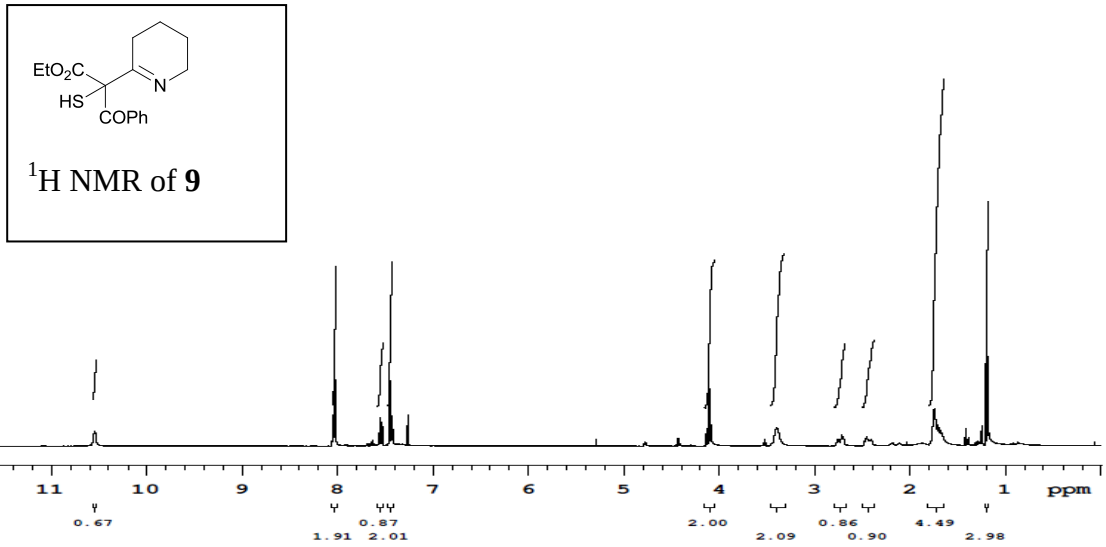
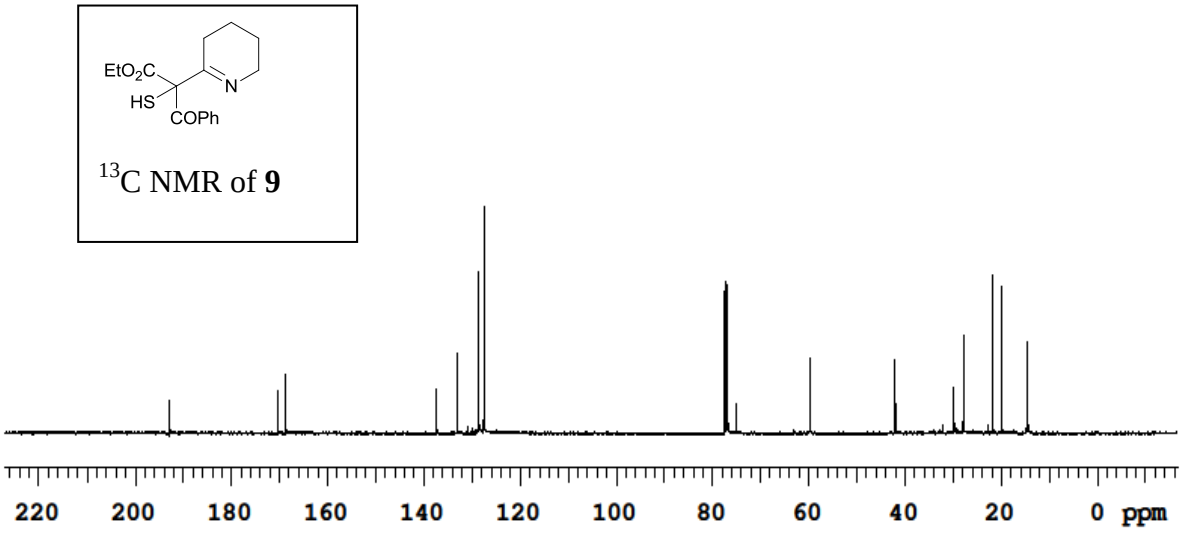
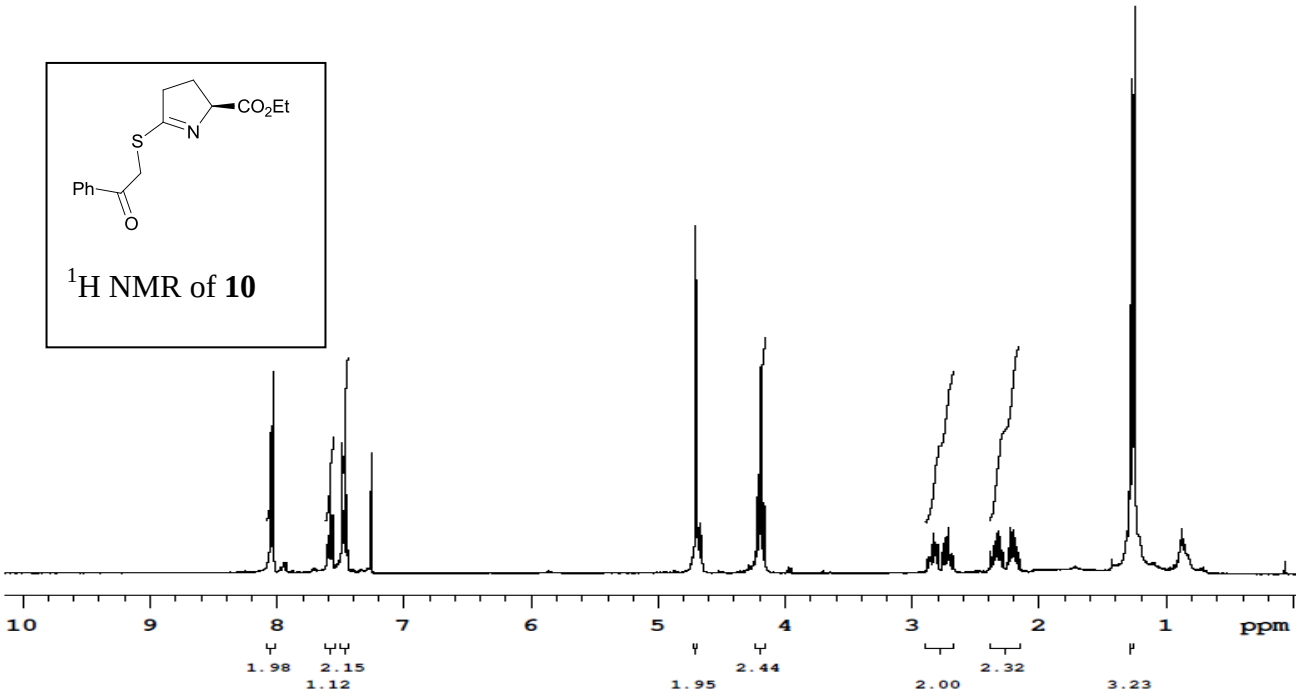


^{13}C NMR of **3o**



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S
Ph
O
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10
9
8
7
6
5
4
3
2
1
ppm
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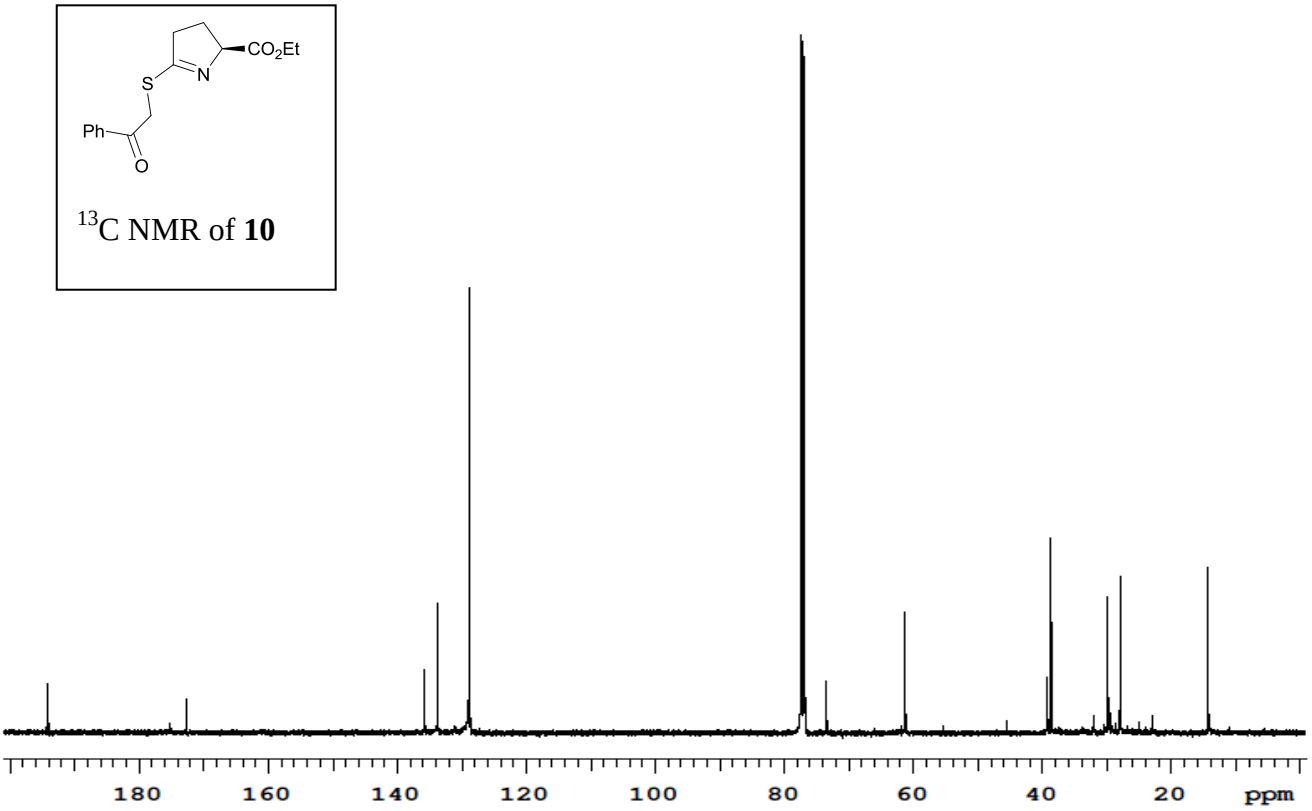
1.12
1.95
2.44
2.00
2.32
3.23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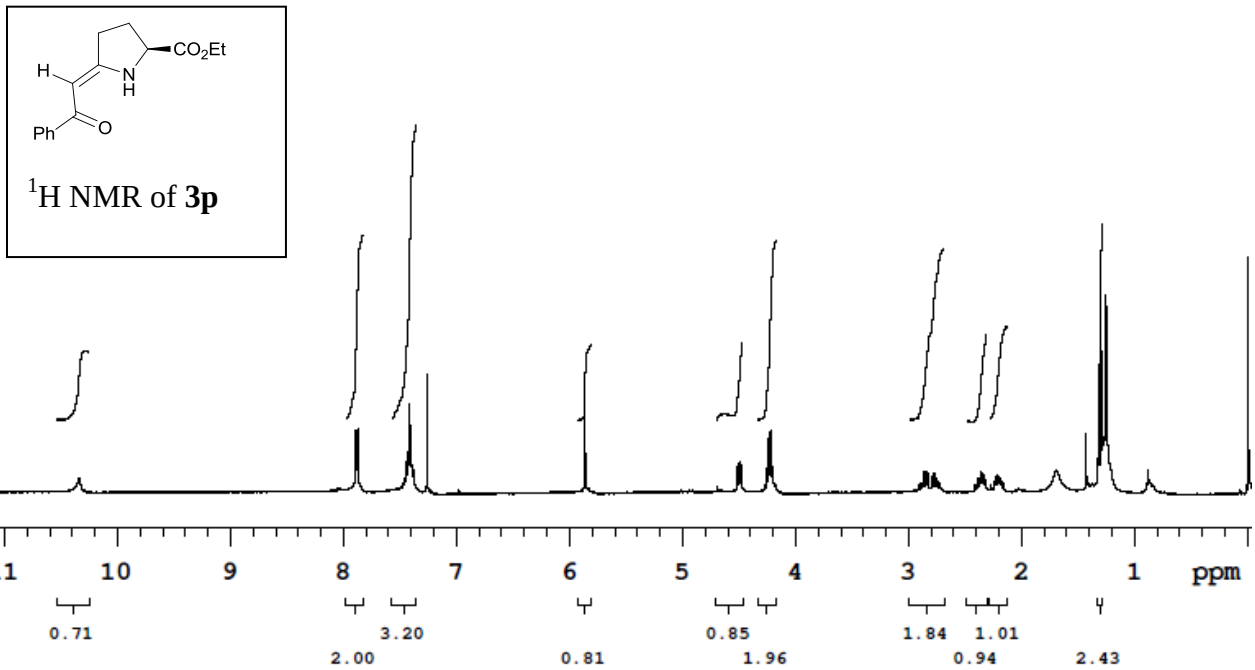
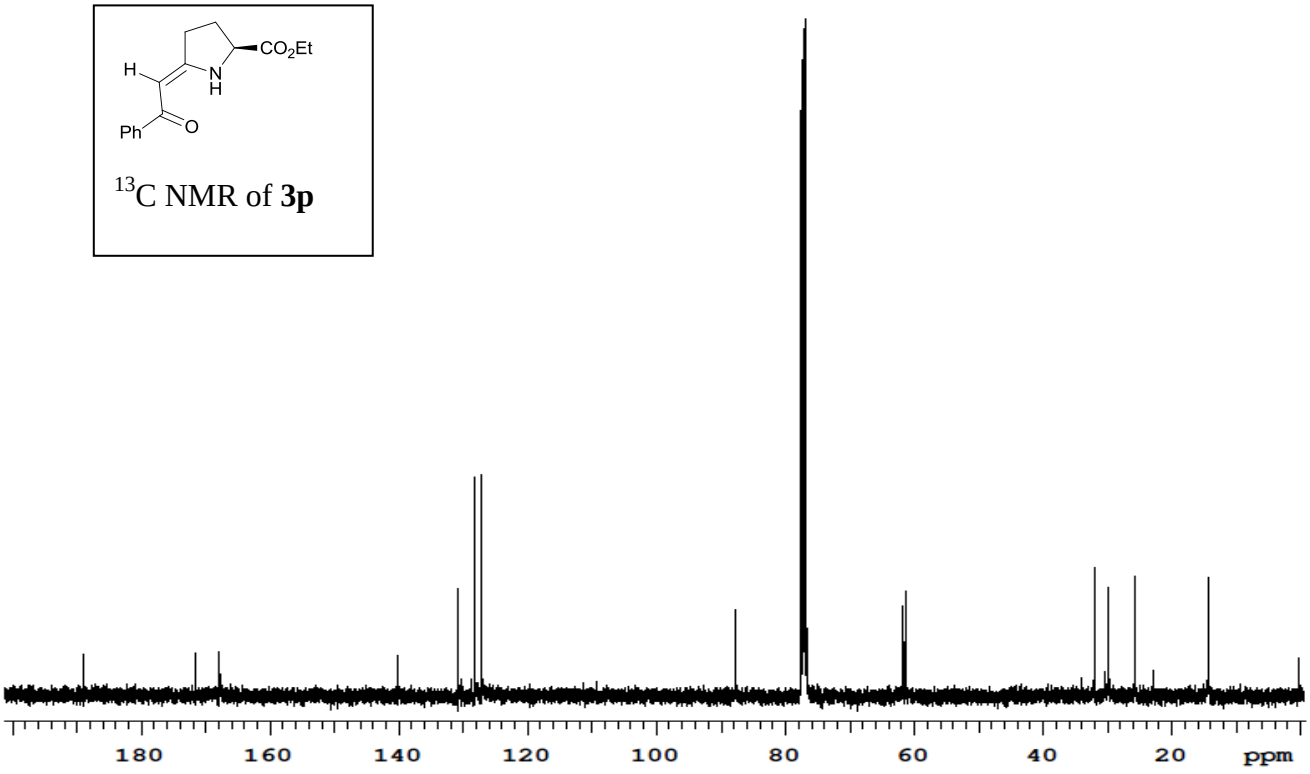
N
S
Ph
O
13C NMR of 10
180
160
140
120
100
80
60
40
20
ppm



^{1}H NMR of **3p**



^{13}C NMR of **3p**