Supporting information

Electrochemical TEMPO-Catalyzed Multicomponent C(sp^3)-H α-Carbamoylation of Free Cyclic Secondary Amines.

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1. General information

Unless otherwise stated, commercially available materials were used as received. Reactions were monitored by thin-layer chromatography (TLC) analysis using precoated silica gel aluminium foils (with fluorescent indicator 254 nm). Spots were visualized by UV irradiation or Kagi stain. Column chromatography was performed on silica gel (230-400 mesh, 40-63 µm).

^{1}H (300 MHz), ^{13}C (75 MHz) and ^{19}F (282 MHz) NMR spectra were recorded on a Bruker spectrometer. HRMS Spectra were recorded on a JEOL JMS-GC Mate II apparatus. Melting points were detected with a Wagner Munz Kofler hot bench.

Cyclic voltammetry (CV) was performed with a Metrohm Autolab PGSTAT101 potentiostat connected to a Nova software interface. CV was performed in a three-electrode cell connected to a Schlenk line under argon at 20 °C with a scan rate of 0.5 $V \cdot s^{-1}$. The working electrode was a glassy carbon disk (d = 1 mm), the counter electrode a platinum wire of *ca.* 0.2 cm^2 apparent area. The reference was a saturated calomel electrode (SCE) separated from the solution by a bridge filled with 3 mL of CH_3CN (containing $n Bu_4NBF_4$ 0.3 M).

Reversed-phase analytical HPLC was performed with Agilent Technologies 1200 series machine. Column: PROTO 200 C18 with 3 µm particles from Higgins analytical Inc., 100 mm length and 4.6 mm internal diameter. Method used was a custom method “default method” (Table 1), flow rate: 1 mL/min.

Time (min)	H_2O (%)	CH_3CN (%)
0	95	5
10	0	100
12	0	100
13	95	5

Table 1 Default method for analytical HPLC

Reversed-phase preparative HPLC was performed with Agilent Technologies 1260 series machine. Column: Nucleodur C18 Htec. with 5 µm particles from Macherey-Nagel, 250 mm length and 16 mm internal diameter. Method used was a custom method “default method” (Table 2), flow rate: 14 mL/min.

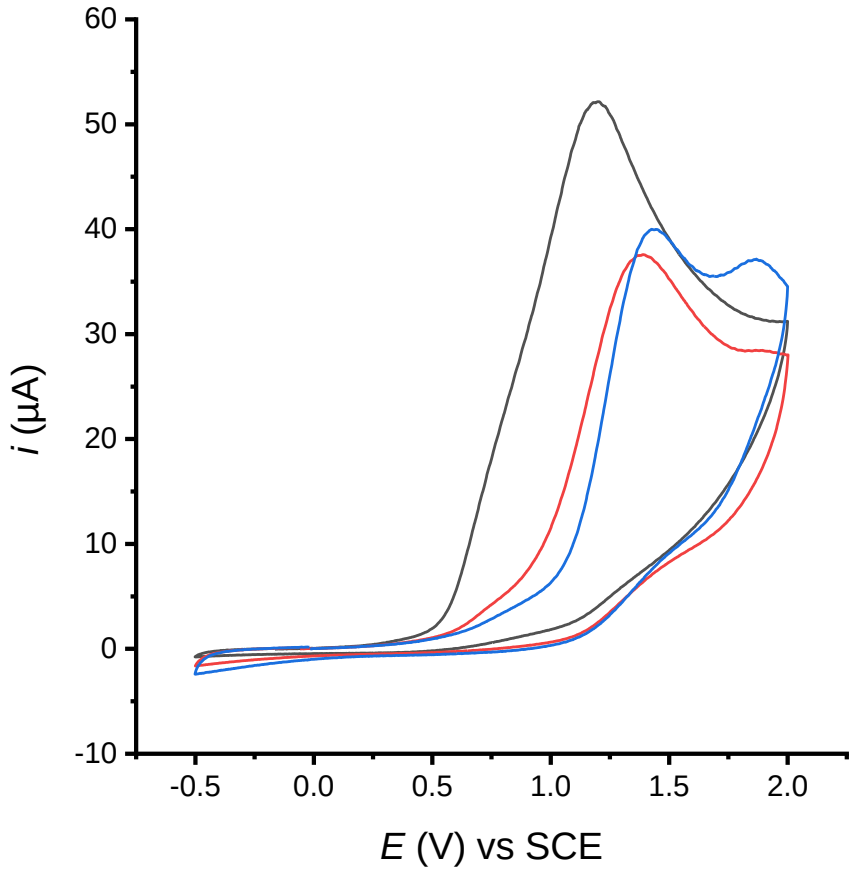
Time (min)	H_2O (%)	CH_3CN (%)
0	95	5
30	0	100
40	0	100
41	95	5

Table 2 Default method for preparative HPLC

Electrosynthesis was performed under constant current (12 mA or 6 mA) after the indicated reaction time with IKA ElectraSyn 2.0 in a 5 mL cell equipped with a graphite plate as anode and a nickel plate as cathode, or with a Metrohm Autolab PGSTAT101 potentiostat connected to a Nova software interface in a 5 mL cell equipped with a graphite plate as anode and a nickel plate as cathode and the distance of the 2 electrodes were kept the same as with IKA ElectraSyn 2.0.

2. Cyclic voltammetry

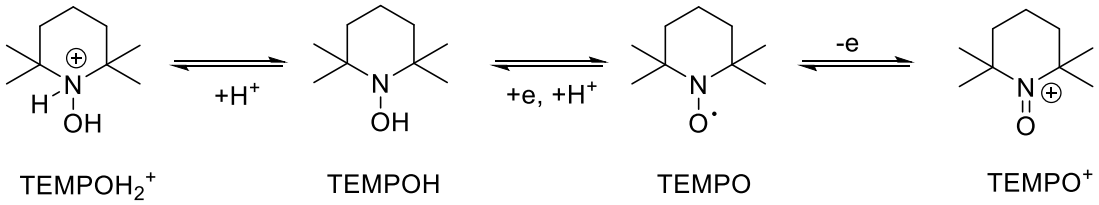
a) Shift of the oxidation potential of pyrrolidine under acidic conditions

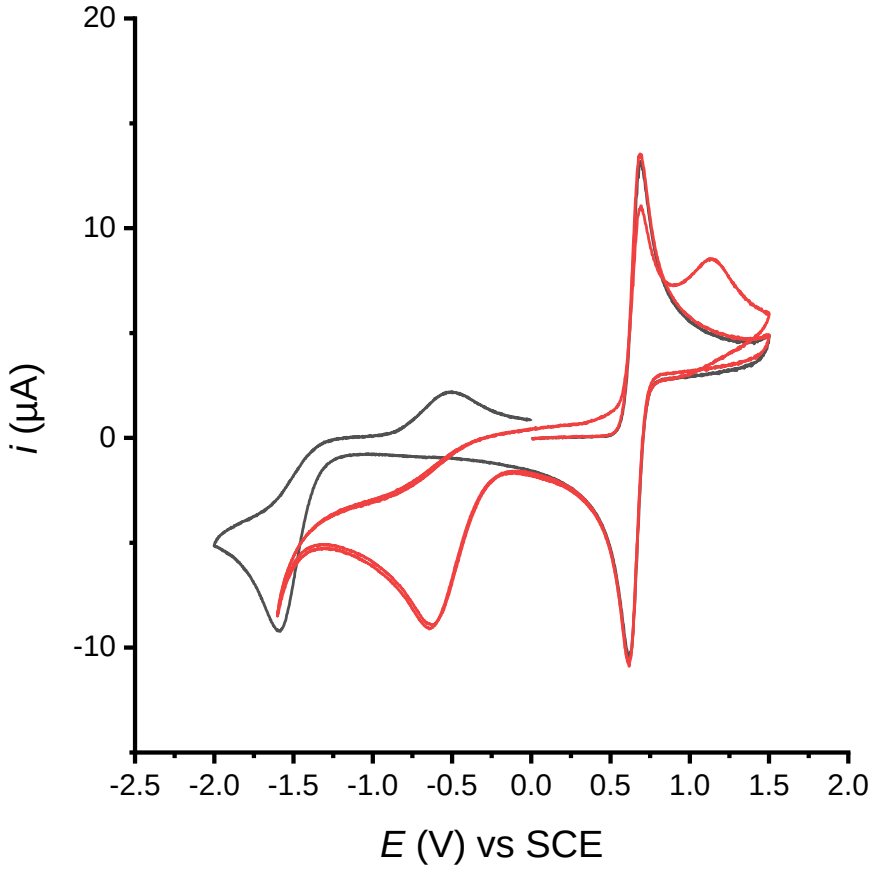


Cyclic Voltammetry towards oxidation potentials (0.3 M of $^{n}Bu_4NBF_4$ in MeCN, 20°C, 0.5 $V.s^{-1}$, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode) for 20 mM of pyrrolidine (black), with 1 equiv of AcOH (red) and with 2.5 equiv of AcOH (blue).

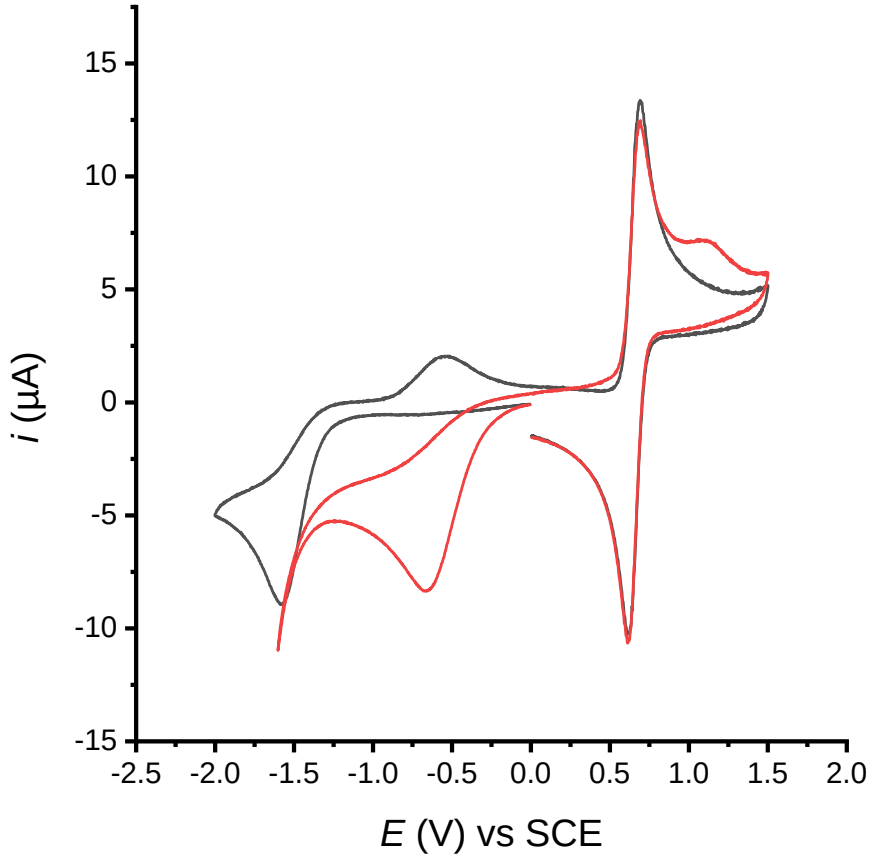
b) TEMPO oxidation in the presence of acetic acid

As already reported,[1],[2] CV for TEMPO is modified under acidic conditions. Indeed, the reduction of TEMPO is easier in the presence of 25 equiv of AcOH with a Ep_{red} at -1.0 V vs SCE (vs -1.75 V vs SCE in the absence of acid). On the reverse scan, there are two oxidation peaks: the first one (Ep_{ox} = +0.65 V) for TEMPO and the second one (Ep_{ox} = +1.14 V) standing for the oxidation of $TEMPOH_2^+$.





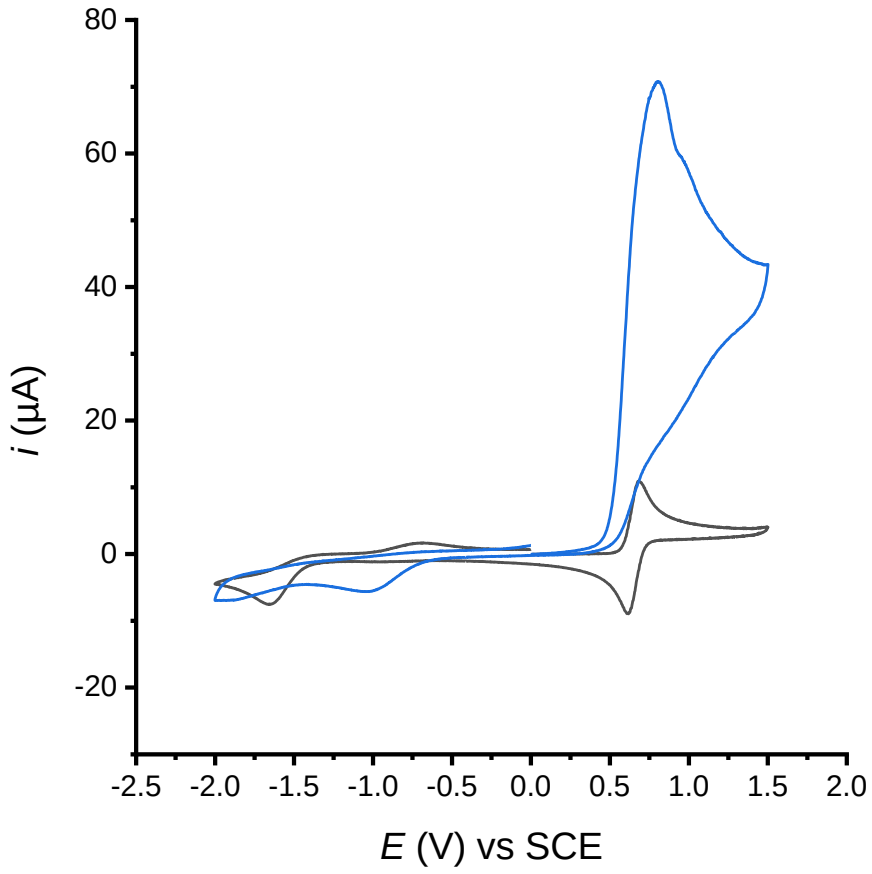
Cyclic Voltammetry towards oxidation potentials (0.3 M of $^{n}Bu_4NBF_4$ in MeCN, 20°C, 0.5 $V.s^{-1}$, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode) for 2 mM of TEMPO (black) and with 25 equiv of AcOH (red).



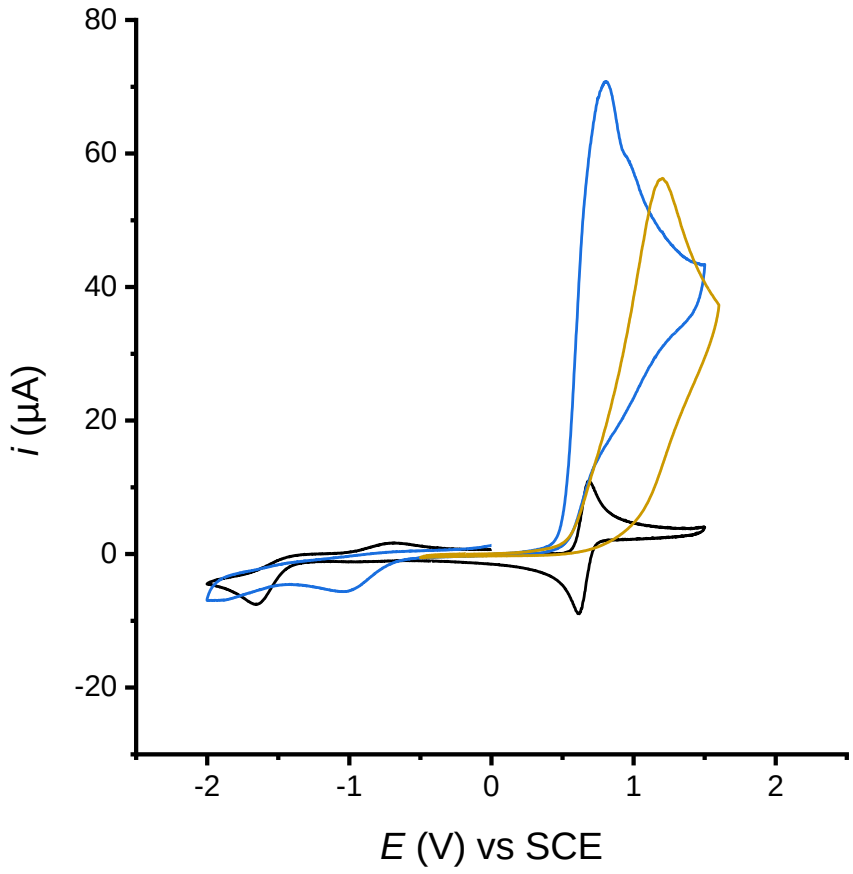
Cyclic Voltammetry towards reduction potentials (0.3 M of $^{n}Bu_4NBF_4$ in MeCN, 20°C, 0.5 $V.s^{-1}$, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode) for 2 mM of TEMPO (black) and with 25 equiv of AcOH (red).

c) TEMPO oxidation in the presence of pyrrolidine

After addition of 10 equiv of pyrrolidine to a solution of TEMPO, the oxidation peak for TEMPO dramatically increases with the loss of its reverse scan. Such evolution is consistent with an electrocatalytic effect: after oxidation of TEMPO to $TEMPO^+$, the latter reacts with pyrrolidine through a hydride transfer[3] to generate the corresponding iminium and TEMPOH. Due to the high potential applied, the latter is immediately oxidized to TEMPO regenerating the catalyst. This mechanism could explain the electrocatalytic effect observed for TEMPO in the presence of pyrrolidine.



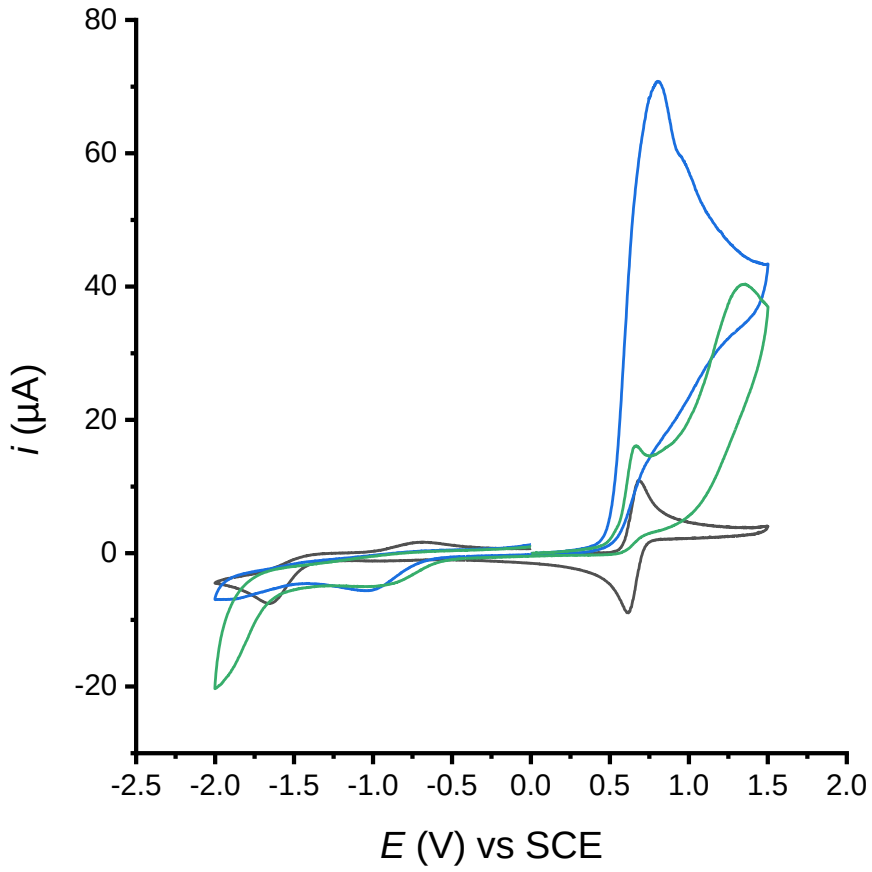
Cyclic Voltammetry towards oxidation potentials (0.3 M of $^{n}Bu_4NBF_4$ in MeCN, 20°C, 0.5 $V.s^{-1}$, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode) for 2 mM of TEMPO (black) and with 10 equiv of pyrrolidine (blue).



Cyclic Voltammetry towards oxidation potentials (0.3 M of $^{n}Bu_4NBF_4$ in MeCN, 20°C, 0.5 $V.s^{-1}$, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode) for 2 mM of TEMPO (black), 2 mM of TEMPO with 20 mM of pyrrolidine (blue) and 20 mM of pyrrolidine (brown).

d) TEMPO oxidation in the presence of pyrrolidine and acetic acid under relevant experimental conditions

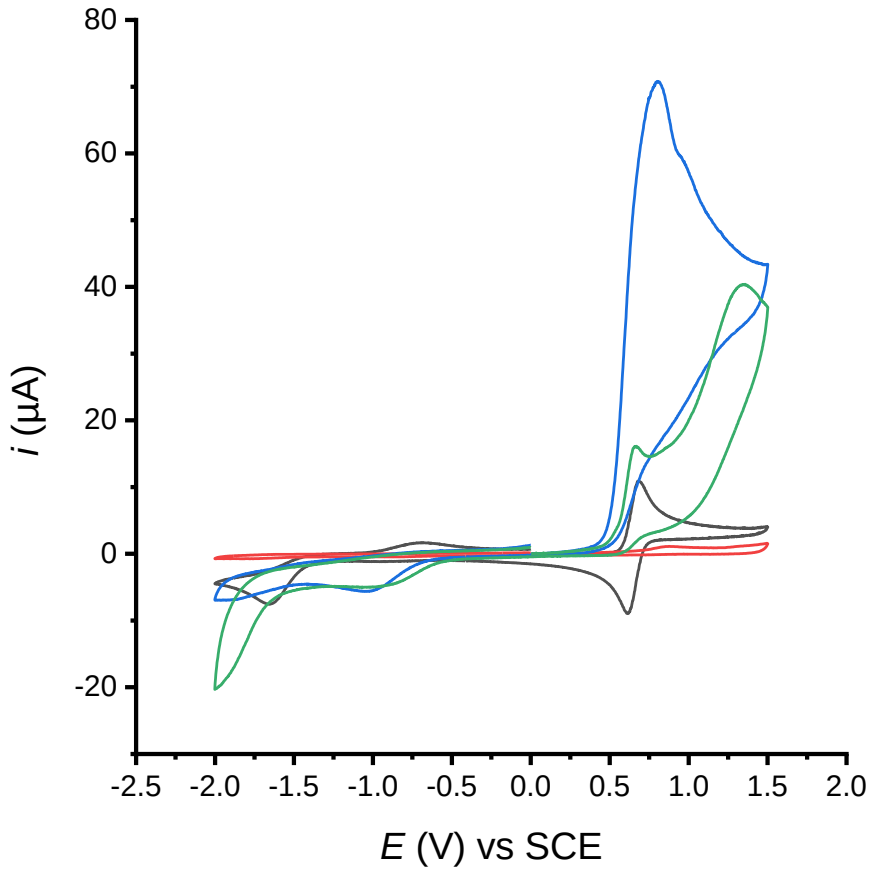
In the presence of both pyrrolidine (10 equiv) and AcOH (25 equiv), the electrocatalytic peak is still observed for TEMPO oxidation but at a lower extent due to the lower concentration of free pyrrolidine under such acidic conditions. Moreover, when the electrogenerated oxoammonium reacts with pyrrolidine, the formed TEMPOH is in equilibrium with $TEMPOH_2^+$ (pKa about 7), which is oxidized at +1.2 V vs SCE according to a two-electron process. The oxoammonium is thus regenerated and could react with free pyrrolidine.



Cyclic Voltammetry towards oxidation potentials (0.3 M of $^{n}Bu_4NBF_4$ in MeCN, 20°C, 0.5 $V.s^{-1}$, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode) for 2 mM of TEMPO (black), 2 mM of TEMPO with 20 mM of pyrrolidine (blue) and 2 mM of TEMPO with 20 mM of pyrrolidine and 50 mM of AcOH (green).

Therefore, we propose that the electrogenerated oxoammonium $TEMPO^+$ reacts with pyrrolidine to form the iminium and the TEMPOH, which is partly protonated under acidic conditions. $TEMPOH/TEMPOH_2^+$ are oxidized at the anode regenerating the oxoammonium.

In the scanned range of potentials, the isocyanide turned out to be non-electroactive as shown in the voltammogram below.



Cyclic Voltammetry towards oxidation potentials (0.3 M of $^{n}Bu_4NBF_4$ in MeCN, 20°C, 0.5 $V.s^{-1}$, glassy carbon as working electrode (d = 1 mm), Pt wire as counter electrode and SCE as reference electrode) for 20 mM of *t*-BuNC (red), 2 mM of TEMPO (black), 2 mM of TEMPO with 20 mM of pyrrolidine (blue) and 2 mM of TEMPO with 20 mM of pyrrolidine and 50 mM of AcOH (green).

3. Calibration of product 4 with standard on analytical HPLC

Standard: *N*-cyclohexylformamide

Six samples of mixture of standard and product **4** were prepared according to Table 3 and then dissolved in 2 mL H_2O/ACN (9:1).

No.	Mass of standard (mg)	Mass of product **4** (mg)
1	49.7	5.0
2	51.7	9.9
3	50.0	15.1
4	52.0	20.0
5	51.7	25.0
6	49.8	30.3

Table 3 Sample preparation

Each of the samples was injected 3 times into the analytical HPLC. The areas of both peaks were integrated and the ratios were calculated. Combined with the actual amount of standard and product **4** in the samples, the calibration curve (Figure 1) of product **4** with *N*-cyclohexylformamide was calculated.

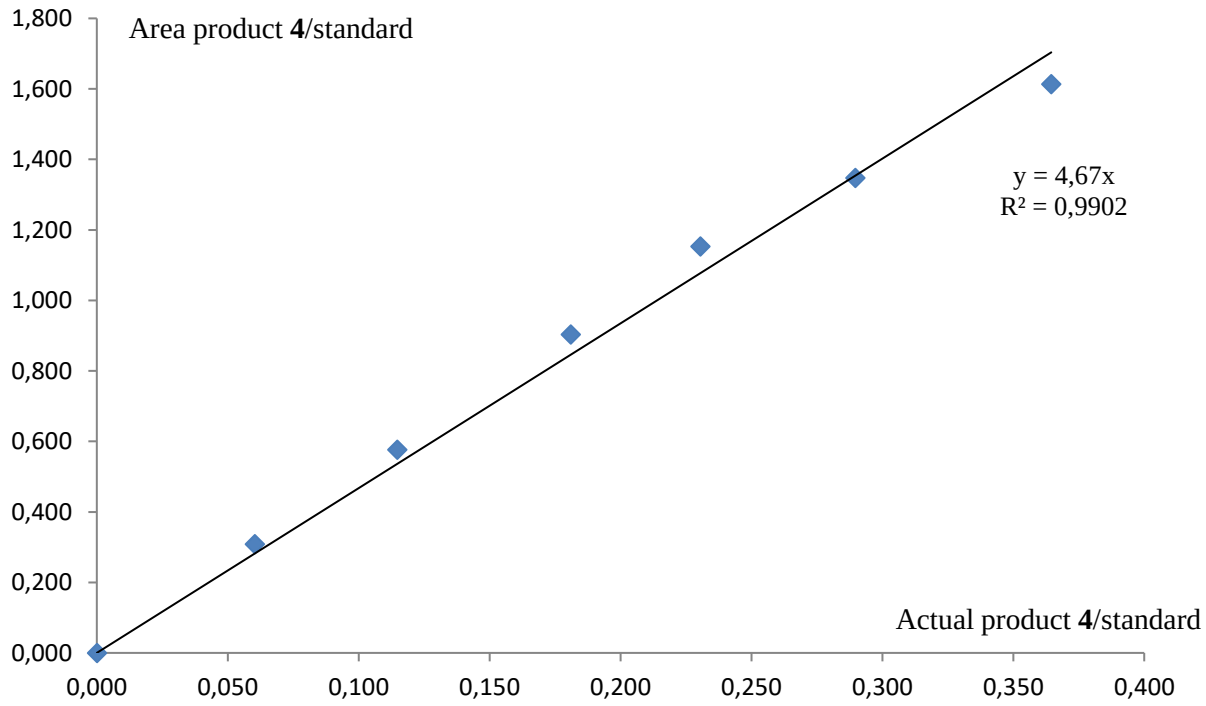
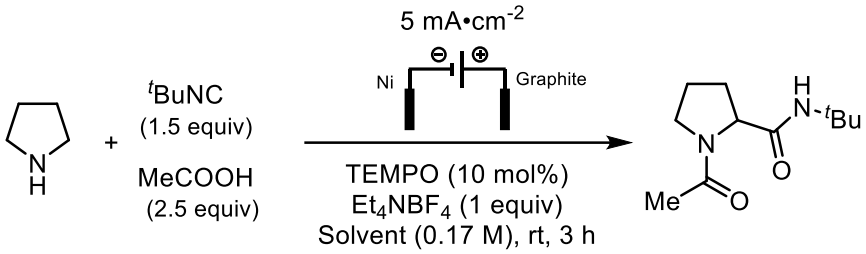


Figure 1 Calibration curve of product **4** with *N*-cyclohexylformamide as standard

4. Condition screening

All the reactions in condition screening were done with *N*-cyclohexylformamide as a standard inside the reaction mixtures before the reactions started. The HPLC yields were calculated with the calibration curve (Figure 1) above.

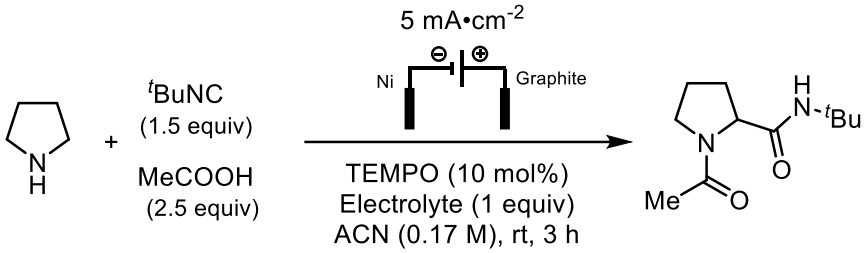
a) Solvent



Entry	Solvent	HPLC yield (%)
1	CH_3CN	54
2	DCM	46
3	DMF	3
4	HFiP	1
5	THF* (Bu_4NBF_4)	8
6	Isopropanol* (Bu_4NBF_4)	9

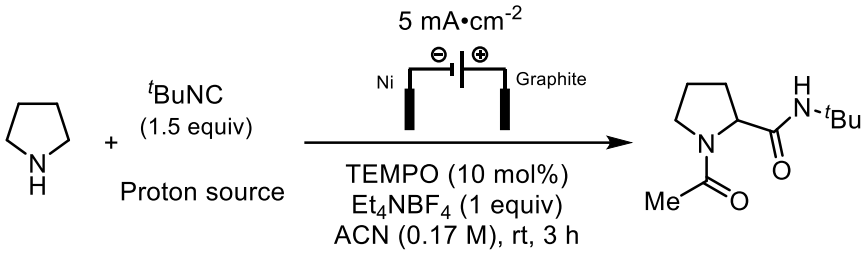
* Bu_4NBF_4 was used as electrolyte instead of Bu_4NBF_4 because of solubility issue.

b) Electrolyte



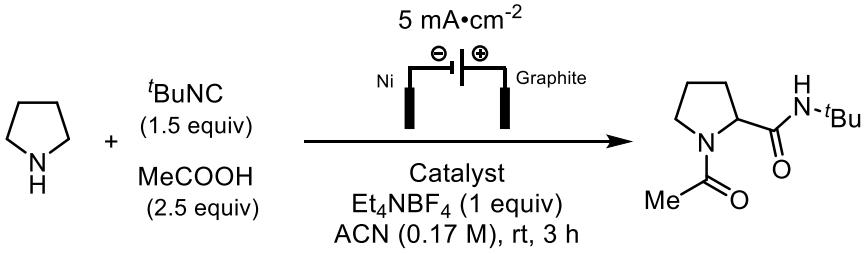
Entry	Electrolyte	HPLC yield (%)
1	Et_4NBF_4 (1 eq)	54
7	Et_4NPF_6 (1 eq)	48
8	Et_4NOTs (1 eq)	26
9	Bu_4NOAc (1 eq)	10
10	Bu_4NBF_4 (1 eq)	42
11	Bu_4NBF_4 (5 eq)	37
12	Bu_4NBF_4 (10 eq)	42
13	/	20

c) Proton source



Entry	Proton source	HPLC yield (%)
1	AcOH (2.5 eq)	54
14	AcOH (1 eq)	8
15	AcOH (1.5 eq)	32
16	AcOH (2 eq)	48
17	AcOH (4 eq)	44
18	AcOH (2.5 eq) + 0.5 eq CH_3OH (no TEMPO)	33
19	AcOH (2.5 eq) + 1 eq HFiP	35
20	AcOH (2.5 eq) + 1 eq H_2O	45
21	AcOH (2.5 eq) + 2 eq H_2O	36
22	AcOH (2.5 eq) + 4 eq H_2O	37

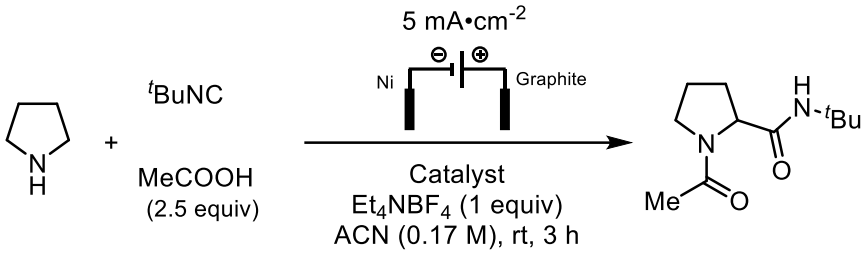
d) Catalyst



No.	Catalyst	HPLC yield (%)
1	TEMPO (0.1 eq)	54
23	TEMPO (0.3 eq)	40
24*	TEMPO (0.05 eq)	42
25	/	32
26	AcNH-TEMPO (0.1 eq)	50

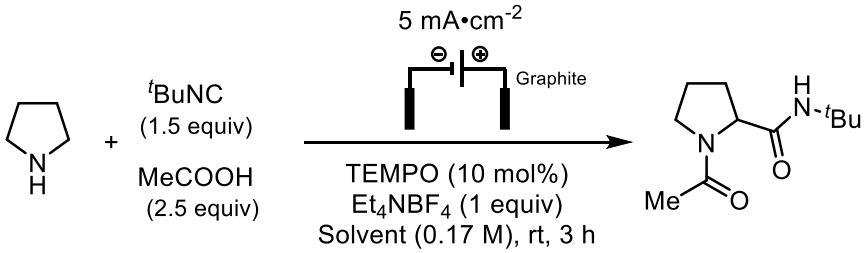
*2.5 $mA.cm^{-2}$, 6 h, 2.7F/mol.

e) tBuNC



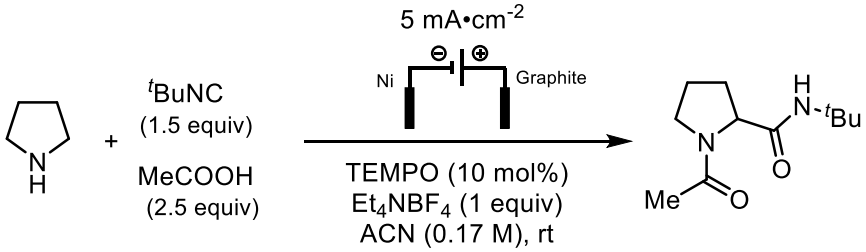
Entry	^{t}BuNC	HPLC yield (%)
1	1.5 eq	54
27	2.0 eq	51

f) Cathode



No.	Cathode	HPLC yield (%)
1	Ni	54
28	Pt	47
29	Ni foam	56
30	Stainless steel	39

g) Quantity of electricity

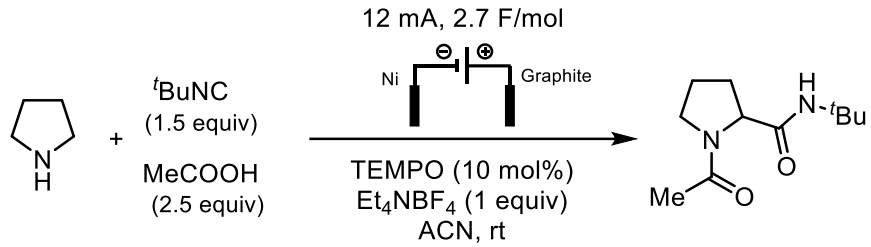


Entry	Time (h)	Q (F/mol)	HPLC yield (%)
1	3	2.69	54
35	4	3.58	57 (55)*

36	6	5.37	63
37	8	7.16	66 (58)*

*Isolated yield

h) Concentration



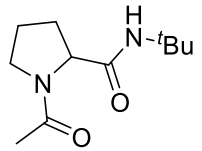
Entry	Concentration (mM)	Time (h)	HPLC yield (%)
1	0.17	3	54
38	0.50	9	64 (60)*

*Isolated yield

5. General procedure for electrosynthesis

Et_4NBF_4 (326 mg, 1.50 mmol, 1 equiv), TEMPO (23 mg, 0.15 mmol, 0.1 equiv), substrate (1.50 mmol, 1 equiv), acid (3.75 mmol, 2.5 equiv) and isocyanide (2.25 mmol, 1.5 equiv) were dissolved in 3 mL anhydrous CH_3CN in a 5 mL cell. The cell was then equipped with a graphite anode and a nickel cathode, and electrolysis was performed at a constant current of 12 mA (~ 5 mA/cm^2) for 9 hours. After the reaction time indicated, the reaction mixture was diluted with ethyl acetate (80 mL), washed with a saturated $NaHCO_3$ aqueous solution (10 mL), and then washed with a saturated NH_4Cl aqueous solution (7 mL *3). The organic phase was then dried over $MgSO_4$, filtered off, and concentrated *in vacuo*. The crude mixture was purified by preparative HPLC or column chromatography to give the desire product. In some cases, the product exists in the form of several rotamers, and changing the deuterated solvent induces a variation in relative proportions.

6. Experimental and characterization of electrochemical multicomponent α-carbamoylation products



Chemical Formula: $C_{11}H_{20}N_2O_2$
Molecular Weight: 212.2930

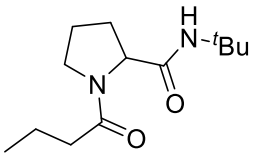
1-acetyl-*N*-(*tert*-butyl)pyrrolidine-2-carboxamide[4] (4)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and acetic acid (**3a**) (215 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **4** (191 mg, 60% yield) was obtained as a white solid after purification by preparative HPLC. In ^{1}H NMR timescale, two rotamers (15:1 ratio in C_6D_6, 6:1 ratio in $CDCl_3$ and 15:1 ratio in tol-d^8) were observed. **Melting point**: 122-124 °C. <u>*Major rotamer:*</u> **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.42 (br s, 1H), 4.29 (d, J = 7.0 Hz, 1H), 2.69 (td, J = 9.4, 2.6 Hz, 1H), 2.45-2.27 (m, 2H), 1.98-1.78 (m, 1H), 1.55 (s, 3H), 1.36 (s, 9H), 1.31-1.20 (m, 1H), 1.18-1.07 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 170.7, 169.9, 60.5, 50.9, 47.9, 28.8, 26.9, 25.1, 22.0 ppm. **HRMS (EI+)**: calcd for $C_{11}H_{20}N_2O_2$ $[M]^{+\bullet}$: 212.1519, found: 212.1523. <u>*Characteristic peaks for the minor rotamer:*</u> **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.32 (br s, 1H), 3.58 (dd, J = 8.4, 3.0 Hz, 1H), 3.38-3.26 (m, 2H), 1.73 (s, 3H), 1.14 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 203.9, 47.0, 30.1, 28.5 ppm.

<u>*Major rotamer:*</u> **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.98 (br s, 1H), 4.45 (dd, J = 8.1, 1.8 Hz, 1H), 3.62-3.49 (m, 1H), 3.40 (td, J = 9.6, 7.1 Hz, 1H), 2.45-2.34 (m, 1H), 2.21-2.11 (m, 1H), 2.10 (s, 3H), 2.01-1.91 (m, 1H), 1.83-1.69 (m, 1H), 1.31 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 171.0, 170.3, 60.4, 51.1, 48.5, 28.8, 27.3, 25.2, 22.7 ppm. <u>*Characteristic peaks for the minor rotamer:*</u> **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 5.17 (br s, 1H), 4.15 (dd, J = 8.4, 3.3 Hz, 1H), 2.03 (s, 3H),

1.34 (s, 9H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 63.1, 51.6, 46.9, 32.2, 23.1, 22.5 ppm.

Major rotamer: **^{1}H NMR** (300 MHz, tol-d^8): δ = 7.41 (br s, 1H), 4.25 (d, J = 8.0 Hz, 1H), 2.74 (td, J = 9.3, 2.4 Hz, 1H), 2.47 (td, J = 9.8, 7.0 Hz, 1H), 2.38-2.28 (m, 1H), 1.94-1.82 (m, 1H), 1.56 (s, 3H), 1.35-1.27 (m, 1H), 1.33 (s, 9H), 1.22-1.11 (m, 1H) ppm. **^{13}C NMR** (75 MHz, tol-d^8): δ = 170.6, 169.8, 60.4, 50.8, 47.9, 28.8, 26.9, 25.1, 21.8 ppm. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, tol-d^8): δ = 5.44 (br s, 1H), 3.60 (dd, J = 8.5, 2.7 Hz, 1H), 3.38-3.25 (m, 2H), 1.73 (s, 3H), 1.15 (s, 9H) ppm. **^{13}C NMR** (75 MHz, tol-d^8): δ = 28.4 ppm.

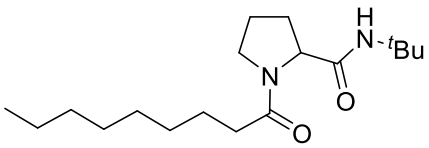


Chemical Formula: $C_{13}H_{24}N_2O_2$
Molecular Weight: 240.35

***N*-(*tert*-butyl)-1-butyrylpyrrolidine-2-carboxamide (5)**

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and butyric acid (**3b**) (342 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **5** (237 mg, 66% yield) was obtained as a white solid after purification by preparative HPLC. In ^{1}H NMR timescale, two rotamers (15:1 ratio in C_6D_6) were observed. **Melting point**: 103-105 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.70 (br s, 1H), 4.46 (d, J = 7.4 Hz, 1H), 2.80 (td, J = 9.3, 2.4 Hz, 1H), 2.60-2.42 (m, 2H), 2.05-1.86 (m, 1H), 1.86-1.78 (m, 2H), 1.78-1.54 (m, 2H), 1.38 (s, 9H), 1.35-1.26 (m, 1H), 1.23-1.05 (m, 1H), 0.89 (t, J = 7.3 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.8, 170.1, 60.3, 50.7, 47.1, 36.3, 28.9, 26.4, 25.2, 18.5, 14.0 ppm. **HRMS (EI+)**: calcd for $C_{13}H_{24}N_2O_2$ $[M]^{+\bullet}$: 240.1832, found: 240.1838. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.42

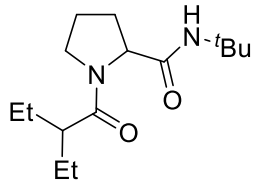
(br s, 1H), 3.81 (dd, *J* = 8.5, 2.4 Hz, 1H), 3.44 (dd, *J* = 8.5, 5.4 Hz, 2H), 1.17 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.5 ppm.



Chemical Formula: $C_{18}H_{34}N_2O_2$
Molecular Weight: 310.48

N-(*tert*-butyl)-1-nonanoylpyrrolidine-2-carboxamide (6)

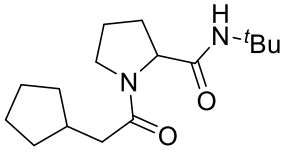
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and nonanoic acid (**3c**) (654 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **6** (312 mg, 67% yield) was obtained as a pale brown solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (10:1 ratio in C_6D_6) were observed. **Melting point**: 62-64 °C. <u>*Major rotamer:*</u> **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.70 (s, 1H), 4.48 (dd, *J* = 8.1, 1.5 Hz, 1H), 2.86 (td, *J* = 9.1, 2.5 Hz, 1H), 2.59 (td, *J* = 9.7, 7.1 Hz, 1H), 2.56-2.46 (m, 1H), 2.04-1.95 (m, 1H), 1.92 (t, *J* = 7.2 Hz, 2H), 1.70 (dq, *J* = 22.6, 6.6 Hz, 2H), 1.40 (s, 9H), 1.33-1.25 (m, 12H), 0.94- 0.89 (m, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.6, 170.4, 60.2, 50.9, 47.6, 34.7, 31.9, 29.5, 29.4, 29.2, 28.7, 26.9, 25.08, 25.05, 22.7, 14.1 ppm. <u>*Characteristic peaks for the minor rotamer:*</u> **^{1}H NMR** (300 MHz, C_6D_6): δ = 3.46 (m, 1H), 3.40 (t, *J* = 6.5 Hz, 1H), 2.99-2.92 (m, 1H), 2.72 (t, *J* = 6.5 Hz, 1H) ppm. **HRMS (EI+)**: calcd for $C_{18}H_{34}N_2O_2$ $[M]^{+\bullet}$: 310.2615, found: 310.2611.



Chemical Formula: $C_{15}H_{28}N_2O_2$
Molecular Weight: 268.40

N-(*tert*-butyl)-1-(2-ethylbutanoyl)pyrrolidine-2-carboxamide (7)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-ethylbutyric acid (**3d**) (472 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **7** (238 mg, 59% yield) was obtained as a yellow oil after purification by flash column chromatography. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.74 (s, 1H), 4.59 (dd, *J* = 8.0, 1.6 Hz, 1H), 3.00 (td, *J* = 9.1, 2.7 Hz, 1H), 2.81 (td, *J* = 9.7, 7.0 Hz, 1H), 2.51 (ddt, *J* = 11.5, 7.0, 2.0 Hz, 1H), 1.99 (dtd, *J* = 21.7, 9.3, 3.8 Hz, 2H), 1.76 (ddtd, *J* = 16.3, 12.7, 7.4, 3.4 Hz, 2H), 1.38 (s, 9H), 1.36-1.26 (m, 3H), 1.22-1.11 (m, 1H), 0.88 (t, *J* = 7.4 Hz, 3H), 0.78 (t, *J* = 7.4 Hz, 3H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 176.6, 170.2, 60.0, 50.8, 47.6, 47.0, 28.7, 26.5, 26.1, 25.4, 25.0, 12.1, 11.8 ppm. **HRMS (EI+)**: calcd for $C_{15}H_{27}N_2O_2$ $[M-H]^+$: 267.2067, found: 267.2061.

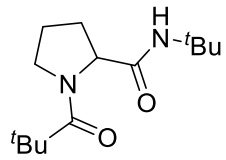


Chemical Formula: $C_{16}H_{28}N_2O_2$
Molecular Weight: 280.41

N-(*tert*-butyl)-1-(2-cyclopentylacetyl)pyrrolidine-2-carboxamide (8)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and cyclopentylacetic acid (**3e**) (472 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product

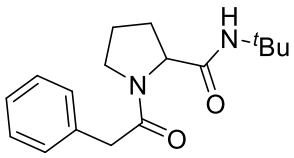
8 (259 mg, 62% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (21:1 ratio in C_6D_6) were observed. **Melting point**: 113-115 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.74 (br s, 1H), 4.50 (d, J = 7.2 Hz, 1H), 2.84 (td, J = 9.4, 2.4 Hz, 1H), 2.57 (td, J = 9.6, 6.8 Hz, 1H), 2.55-2.46 (m, 1H), 2.39 (ddd, J = 23.0, 15.6, 7.4 Hz, 1H), 1.96 (d, J = 6.9 Hz, 2H), 1.95-1.79 (m, 3H), 1.64-1.45 (m, 4H), 1.40 (s, 9H), 1.38-1.27 (m, 1H), 1.24-1.02 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.7, 170.0, 60.3, 50.7, 47.3, 40.7, 36.8, 32.94, 32.85, 28.9, 26.3, 25.40, 25.38, 25.3. **HRMS (EI+)**: calcd for $C_{11}H_{18}NO$ [M - *t*BuNHCO]$^+$: 180.1383, found: 180.1386. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.45 (br s, 1H), 3.90-3.83 (m, 1H), 3.51-3.40 (m, 2H), 1.19 (s, 9H). **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.5.



Chemical Formula: $C_{14}H_{26}N_2O_2$
Molecular Weight: 254.37

N-(*tert*-butyl)-1-pivaloylpyrrolidine-2-carboxamide (9)

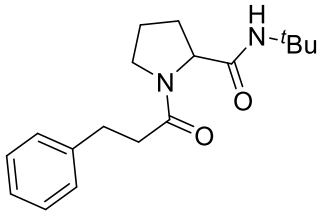
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and pivalic acid (**3f**) (383 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **9** (265 mg, 69% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 123-125 °C. **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.05 (br s, 1H), 4.59 (dd, J = 8.0, 2.8 Hz, 1H), 3.18-3.01 (m, 2H), 2.39-2.23 (m, 1H), 1.98-1.77 (m, 1H), 1.34 (s, 9H), 1.32-1.19 (m, 2H), 1.12 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 177.2, 170.7, 62.1, 50.6, 48.1, 39.2, 28.9, 27.7, 26.0, 25.9 ppm. **HRMS (EI+)**: calcd for $C_{14}H_{26}N_2O_2$ [M]$^{+\bullet}$: 254.1989, found: 254.1992.



Chemical Formula: $C_{17}H_{24}N_2O_2$
Molecular Weight: 288.39

_N_-(_tert_-butyl)-1-(2-phenylacetyl)pyrrolidine-2-carboxamide (10)

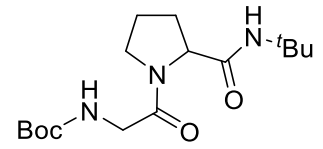
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and phenyl acetic acid (**3g**) (510 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **10** (234 mg, 54% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (26:1 ratio in C_6D_6) were observed. **Melting point**: 110-112 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.52 (br s, 1H), 7.24-7.11 (m, 4H), 7.09-7.01 (m, 1H), 4.47 (d, J = 7.1 Hz, 1H), 3.34 (d, J = 14.5 Hz, 1H), 3.26 (d, J = 14.5 Hz, 1H), 2.86 (td, J = 9.2, 2.4 Hz, 1H), 2.62 (td, J = 9.7, 7.0 Hz, 1H), 2.46-2.35 (m, 1H), 1.94-1.74 (m, 1H), 1.35 (s, 9H), 1.29-1.18 (m, 1H), 1.16-1.04 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 170.9, 169.8, 135.4, 129.1, 128.9, 127.1, 60.5, 50.7, 47.4, 42.1, 28.9, 26.4, 25.1ppm. **HRMS (EI+)**: calcd for $C_{12}H_{15}NO$ [M - *t*BuNCO]$^{+\bullet}$: 189.1148, found: 189.1156. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 3.99-3.92 (m, 1H), 1.12 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.5 ppm.



Chemical Formula: $C_{18}H_{26}N_2O_2$
Molecular Weight: 302.42

_N_-(_tert_-butyl)-1-(3-phenylpropanoyl)pyrrolidine-2-carboxamide (11)

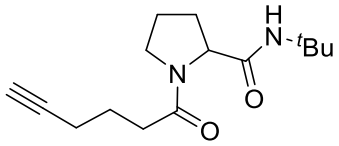
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3h**) (563 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **11** (308 mg, 68% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (18:1 ratio in C_6D_6) were observed. **Melting point**: 100-102 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.63 (br s, 1H), 7.23-7.01 (m, 5H), 4.41 (d, J = 7.9 Hz, 1H), 3.02 (dt, J = 14.7, 7.9 Hz, 1H), 2.92 (dt, J = 14.7, 7.4 Hz, 1H), 2.74-2.61 (m, 1H), 2.51-2.31 (m, 2H), 2.24-2.03 (m, 2H), 1.98-1.78 (m, 1H), 1.38 (s, 9H), 1.31-1.19 (m, 1H), 1.19-1.03 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.1, 169.9, 141.9, 128.8, 128.7, 126.4, 60.5, 50.7, 47.1, 36.5, 31.2, 28.9, 26.5, 25.1 ppm. **HRMS (EI+)**: calcd for $C_{18}H_{26}N_2O_2$ $[M]^{+\bullet}$: 302.1989, found: 302.1982. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.28 (br s, 1H), 3.67 (dd, J = 8.4, 3.0 Hz, 1H), 3.47-3.36 (m, 2H), 1.73 (s, 3H), 1.11 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.4 ppm.



Chemical Formula: $C_{16}H_{29}N_3O_4$
Molecular Weight: 327.42

Tert-butyl (2-(2-(*tert*-butylcarbamoyl)pyrrolidin-1-yl)-2-oxoethyl)carbamate (12)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and Boc-glycine (**3i**) (657 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **12** (210 mg, 43% yield) was obtained as a yellow solid after purification by flash column chromatography. **Melting point**: 137-139 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 5.46 (s, 1H), 4.20 (d, *J* = 8.0 Hz, 1H), 3.49 (dd, *J* = 9.7, 4.6 Hz, 2H), 2.48 (td, *J* = 9.1, 2.5 Hz, 1H), 2.36-2.26 (m, 1H), 2.19 (td, *J* = 9.7, 6.8 Hz, 1H), 1.77 (h, *J* = 10.2 Hz, 1H), 1.46 (s, 9H), 1.34 (s, 9H), 1.21-1.11 (m, 1H), 1.01 (tt, *J* = 11.9, 7.5 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.0, 168.6, 155.9, 79.7, 60.9, 51.1, 46.4, 43.1, 28.7, 28.4, 27.6, 24.9 ppm. **HRMS (EI+)**: calcd for $C_{16}H_{29}N_3O_4$ $[M]^{+\bullet}$: 327.2153, found: 327.2147.

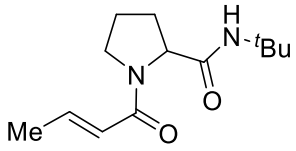


Chemical Formula: $C_{15}H_{24}N_2O_2$
Molecular Weight: 264.37

N-(*tert*-butyl)-1-(hex-5-ynoyl)pyrrolidine-2-carboxamide (13)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 5-hexynoic acid (**3j**) (413 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **13** (201 mg, 51% yield) was obtained as a yellow solid after purification by flash column chromatography. **Melting point**: 112-114 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.54 (s, 1H), 4.45-4.35 (m, 1H), 2.81 (td, *J* = 9.9, 2.4 Hz, 1H), 2.53 (td, J = 9.9, 7.0 Hz, 1H), 2.50 – 2.39 (m, 1H), 2.11 (td, *J* = 7.0, 2.7 Hz, 2H), 1.99-1.85 (m, 3H), 1.84-1.71 (m, 3H), 1.37 (s, 9H), 1.30 (ddt, *J* = 11.9, 7.0, 2.4 Hz, 1H), 1.13 (ddd, *J* = 11.8, 7.5, 4.3 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.3,

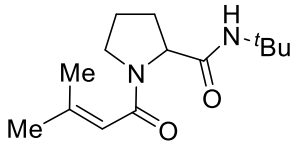
170.2, 83.5, 69.1, 60.2, 50.8, 47.4, 32.8, 28.6, 27.1, 24.9, 23.4, 17.7 ppm. **HRMS (EI+)**: calcd for $C_{15}H_{24}N_2O_2$ $[M]^{+\bullet}$: 264.1832, found: 264.1845.



Chemical Formula: $C_{13}H_{22}N_2O_2$
Molecular Weight: 238.33

(*E*)-1-(but-2-enoyl)-*N*-(*tert*-butyl)pyrrolidine-2-carboxamide (14)

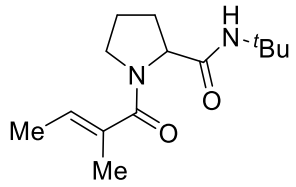
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and crotonic acid (**3k**) (323 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **14** (120 mg, 34% yield) was obtained as a yellow solid after purification by flash column chromatography. **Melting point**: 124-126 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.91 (s, 1H), 7.11 (dd, J = 14.9, 6.9 Hz, 1H), 5.78 (dd, J = 14.9, 1.7 Hz, 1H), 4.58 (dd, J = 8.0, 1.5 Hz, 1H), 2.94 (td, J = 9.0, 2.3 Hz, 1H), 2.69 (td, J = 9.8, 6.9 Hz, 1H), 2.59-2.45 (m, 1H), 2.06-1.86 (m, 1H), 1.48 (dd, J = 6.9, 1.7 Hz, 3H), 1.40 (s, 9H), 1.38-1.26 (m, 1H), 1.17-1.05 (m, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.2, 166.2, 142.3, 122.6, 60.4, 50.9, 47.4, 28.7, 26.9, 25.0, 18.2 ppm. **HRMS (EI+)**: calcd for $C_{13}H_{22}N_2O_2$ $[M]^{+\bullet}$: 238.1676, found: 238.1683.



Chemical Formula: $C_{14}H_{24}N_2O_2$
Molecular Weight: 252.36

***N*-(*tert*-butyl)-1-(3-methylbut-2-enoyl)pyrrolidine-2-carboxamide (15)**

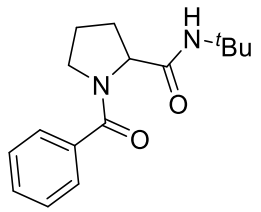
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 3,3-dimethylacrylic acid (**3l**) (375 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **15** (171 mg, 45% yield) was obtained as a white solid after purification by trituration in methyl-*tert*-butyl ether. **Melting point**: 94-96 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.88 (s, 1H), 5.57 (s, 1H), 4.57 (dd, *J* = 8.0, 1.7 Hz, 1H), 2.94 (td, *J* = 9.1, 2.6 Hz, 1H), 2.73 (dd, *J* = 9.8, 7.0 Hz, 1H), 2.55-2.49 (m, 1H), 2.16 (s, 3H), 2.04-1.85 (m, 1H), 1.54 (s, 3H), 1.40 (s, 9H), 1.32 (dtt, *J* = 12.1, 6.9, 2.5 Hz, 1H), 1.17-1.08 (m, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 170.3, 167.6, 149.8, 117.5, 59.8, 50.6, 47.7, 28.5, 26.8, 26.7, 24.9, 20.0 ppm. **HRMS (EI+)**: calcd for $C_{14}H_{24}N_2O_2$ $[M]^{+\bullet}$: 252.1832, found: 252.1830.



Chemical Formula: $C_{14}H_{24}N_2O_2$
Molecular Weight: 252.36

(*E*)-*N*-(*tert*-butyl)-1-(2-methylbut-2-enoyl)pyrrolidine-2-carboxamide (16)

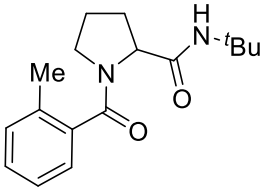
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and tiglic acid (**3m**) (375 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **15** (195 mg, 51% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 125-127 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.41 (s, 1H), 5.54 (q, *J* = 6.9 Hz, 1H), 4.56 (s, 1H), 2.98 (s, 2H), 2.52 (s, 1H), 1.73 (s, 3H), 1.72-1.61 (m, 1H), 1.36 (s, 9H), 1.34 (s, 3H), 1.27-1.12 (m, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.5, 170.3, 133.0, 127.6, 60.0, 5.1, 49.7, 28.8, 26.9, 25.3, 13.6, 13.5 ppm. **HRMS (EI+)**: calcd for $C_{14}H_{24}N_2O_2$ $[M]^{+\bullet}$: 252.1832, found: 252.1844.



Chemical Formula: $C_{16}H_{22}N_2O_2$
Molecular Weight: 274.36

1-benzoyl-*N*-(*tert*-butyl)pyrrolidine-2-carboxamide (17)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and benzoic acid (**3n**) (510 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **17** (288 mg, 70% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 165-167 °C. **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.49-7.30 (m, 3H), 7.10-6.97 (m, 3H), 4.66 (dd, J = 7.6, 5.1 Hz, 1H), 3.11-2.94 (m, 1H), 2.94-2.77 (m, 1H), 2.60-2.39 (m, 1H), 1.69-1.54 (m, 1H), 1.49-1.40 (m, 1H), 1.38 (s, 9H), 1.19-1.03 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 170.8, 169.8, 137.3, 130.1, 128.4, 127.7, 60.6, 50.9, 50.3, 28.9, 26.5, 25.6 ppm. **HRMS (EI+)**: calcd for $C_{16}H_{22}N_2O_2$ $[M]^{+\bullet}$: 274.1676, found: 274.1678.

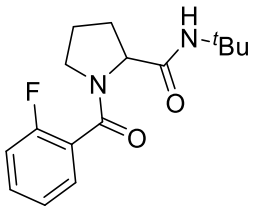


Chemical Formula: $C_{17}H_{24}N_2O_2$
Molecular Weight: 288.39

***N*-(*tert*-butyl)-1-(2-methylbenzoyl)pyrrolidine-2-carboxamide (18)**

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and *o*-toluic acid (**3o**) (510 mg, 3.75 mmol,

2.5 equiv), and following the aforementioned general procedure, product **18** (356 mg, 82% yield) was obtained as a white paste after purification by flash column chromatography. **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.57 (brs, 1H), 7.09-6.99 (m, 2H), 6.99-6.88 (m, 2H), 4.64 (dd, J = 8.1, 3.1 Hz, 1H), 2.82-2.73 (m, 1H), 2.69-2.61 (m, 1H), 2.57-2.48 (m, 1H), 2.23 (s, 3H), 1.79-1.67 (m, 1H), 1.40 (s, 9H), 1.39-1.29 (m, 1H), 1.24-1.13 (m, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.5, 169.8, 136.9, 133.9, 130.7, 129.3, 126.1, 125.4, 60.0, 51.2, 49.3, 28.9, 26.9, 25.1, 18.9 ppm. **HRMS (EI+)**: calcd for $C_{17}H_{24}N_2O_2$ $[M]^{+\bullet}$: 288.1832, found: 288.1838.

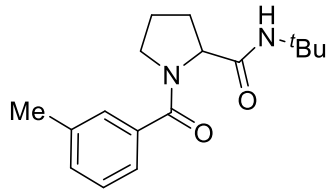


Chemical Formula: $C_{16}H_{21}FN_2O_2$
Molecular Weight: 292.35

N-(*tert*-butyl)-1-(2-fluorobenzoyl)pyrrolidine-2-carboxamide (19)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-fluorobenzoic acid (**3p**) (525 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **19** (224 mg, 51% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (15:1 ratio in C_6D_6) were observed. **Melting point**: 125-127 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.27-7.18 (m, 2H), 6.88-6.78 (m, 1H), 6.76-6.64 (m, 2H), 4.68 (dd, J = 8.2, 3.5 Hz, 1H), 3.00 (ddd, J = 10.3, 7.8, 5.3 Hz, 1H), 2.76 (dt, J = 10.3, 7.3 Hz, 1H), 2.48-2.33 (m, 1H), 1.76-1.59 (m, 1H), 1.50-1.35 (m, 1H), 1.40 (s, 9H), 1.23-1.10 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 169.6, 166.1, 158.8 (d, $J_{C\text{-}F}$ = 247.0 Hz), 131.3 (d, $J_{C\text{-}F}$ = 8.0 Hz), 129.0 (d, $J_{C\text{-}F}$ = 3.9 Hz), 126.1 (d, $J_{C\text{-}F}$

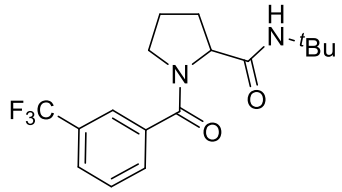
= 17.8 Hz), 124.6 (d, J_{C-F} = 3.4 Hz), 115.9 (d, J_{C-F} = 21.5 Hz), 60.6, 50.9, 48.5 (d, J_{C-F} = 3.1 Hz), 28.8, 27.2, 24.9 ppm. **^{19}F NMR** (282 MHz, C_6D_6): δ = -116.1 ppm. **HRMS (EI+)**: calcd for $C_{11}H_{11}FNO$ [M - *t*BuNHCO]$^+$: 192.0819, found: 192.0825. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.01 (br s, 1H), 3.88-3.81 (m, 1H), 3.77-3.67 (m, 2H), 1.07 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 47.1, 32.1, 28.4 ppm. **^{19}F NMR** (282 MHz, C_6D_6): δ = -115.1ppm.



Chemical Formula: $C_{17}H_{24}N_2O_2$
Molecular Weight: 288.39

N-(*tert*-butyl)-1-(3-methylbenzoyl)pyrrolidine-2-carboxamide (20)

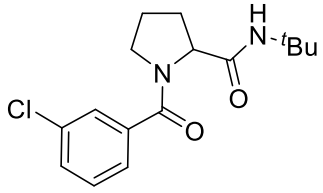
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and *m*-toluic acid (**3q**) (510 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **20** (284 mg, 66% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 166-168 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.43 (br s, 1H), 7.32 (s, 1H), 7.26 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J* = 7.6 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 4.78-4.66 (m, 1H), 3.13-3.00 (m, 1H), 2.99-2.87 (m, 1H), 2.64-2.40 (m, 1H), 2.02 (s, 3H), 1.64 (hept, *J* = 6.9 Hz, 1H), 1.52-1.42 (m, 1H), 1.39 (s, 9H), 1.20-1.06 (m, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 171.1, 170.0, 138.1, 136.3, 130.8, 128.1, 127.6, 124.0, 60.3, 51.0, 50.4, 28.6, 27.0, 25.3, 21.3 ppm. **HRMS (EI+)**: calcd for $C_{17}H_{24}N_2O_2$ [M]$^{+\bullet}$: 288.1832, found: 288.1825.



Chemical Formula: $C_{17}H_{21}F_3N_2O_2$
Molecular Weight: 342.36

_N_-(_tert_-butyl)-1-(3-(trifluoromethyl)benzoyl)pyrrolidine-2-carboxamide (21)

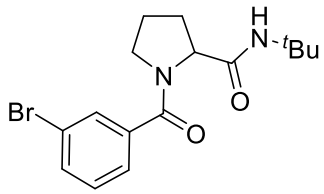
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-(trifluoromethyl)benzoic acid (**3r**) (713 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **21** (166 mg, 32% yield) was obtained as a white solid after purification by trituration in methyl-*tert*-butyl ether. **Melting point**: 190-192 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.90 (s, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 7.9 Hz, 1H), 7.14 (br s, 1H), 6.90 (t, J = 7.9 Hz, 1H), 4.62 (dd, J = 8.1, 4.9 Hz, 1H), 3.04-2.93 (m, 1H), 2.81-2.69 (m, 1H), 2.58-2.45 (m, 1H), 1.70 (hept, J = 6.8 Hz, 1H), 1.57-1.48 (m, 1H), 1.46 (s, 9H), 1.16 (dt, J = 13.0, 6.8 Hz, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 169.4, 137.2, 131.1 (q, $J_{C\text{-}F}$ = 32.8 Hz), 130.5, 129.1, 127.1 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.3 (q, $J_{C\text{-}F}$ = 3.7 Hz), 123.7 (q, $J_{C\text{-}F}$ = 273.0 Hz), 60.9, 51.4, 50.6, 28.8, 27.5, 25.6 ppm. **^{19}F NMR** (376 MHz, $CDCl_3$): δ = -62.8 ppm. **HRMS (EI+)**: calcd for $C_{12}H_{11}F_3NO$ [M - CONH^{t}Bu]$^+$: 242.0787, found: 242.0782.



Chemical Formula: $C_{16}H_{21}ClN_2O_2$
Molecular Weight: 308.81

_N_-(_tert_-butyl)-1-(3-chlorobenzoyl)pyrrolidine-2-carboxamide (22)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-chlorobenzoic acid (**3s**) (587 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **22** (173 mg, 37% yield) was obtained as a white solid after purification by trituration in methyl-*tert*-butyl ether. **Melting point**: 187-189 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.47 (s, 1H), 7.13 (d, J = 7.9 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.70 (t, J = 7.9 Hz, 1H), 4.53 (dd, J = 8.1, 4.8 Hz, 1H), 2.85 (dt, J = 10.4, 7.0 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.52 – 2.39 (m, 1H), 1.60 (tt, J = 13.7, 7.0 Hz, 1H), 1.45 – 1.35 (m, 1H), 1.36 (s, 9H), 1.07 (dq, J = 12.9, 6.8 Hz, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 169.4, 138.1, 134.5, 130.4, 129.9, 127.4, 125.2, 60.7, 51.2, 50.5, 28.8, 27.3, 25.5 ppm. **HRMS (EI+)**: calcd for $C_{16}H_{21}ClN_2O_2$ $[M]^{+\bullet}$: 308.1286, found: 308.1290.

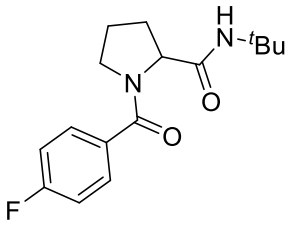


Chemical Formula: $C_{16}H_{21}BrN_2O_2$
Molecular Weight: 353.26

1-(3-bromobenzoyl)-*N*-(*tert*-butyl)pyrrolidine-2-carboxamide (23)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-bromobenzoic acid (**3t**) (754 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **23** (216 mg, 41% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 195-197 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.65 (s, 1H), 7.57 (d, J = 8.2 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 6.71 (s, 1H), 4.60 (dd, J = 7.6, 5.7 Hz, 1H), 3.59 – 3.51 (m, 1H), 3.48 – 3.37 (m, 1H), 2.49 – 2.39 (m, 1H), 2.11 – 1.99 (m, 2H), 1.88 – 1.77 (m, 1H), 1.36

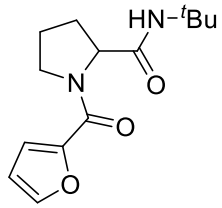
(s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 169.9, 169.3, 138.3, 133.4, 130.3, 130.1, 125.7, 122.6, 60.7, 51.3, 50.6, 28.8, 27.3, 25.5 ppm. **HRMS (EI+)**: calcd for $C_{16}H_{21}BrN_2O_2$ $[M]^{+\bullet}$: 352.0781, found: 352.0794.



Chemical Formula: $C_{16}H_{21}FN_2O_2$
Molecular Weight: 292.35

N-(*tert*-butyl)-1-(4-fluorobenzoyl)pyrrolidine-2-carboxamide (26)

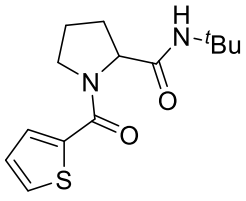
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-bromobenzoic acid (**3w**) (525 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **26** (307 mg, 70% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (21:1 ratio in C_6D_6) were observed. **Melting point**: 177-179 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.29-7.19 (m, 3H), 6.71-6.61 (m, 2H), 4.59 (t, J = 6.1 Hz, 1H), 3.05-2.87 (m, 1H), 2.85-2.68 (m, 1H), 2.58-2.35 (m, 1H), 1.71-1.55 (m, 1H), 1.50-1.40 (m, 1H), 1.37 (s, 9H), 1.17-1.01 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 169.8, 169.6, 163.9 (d, $J_{C\text{-}F}$ = 249.6 Hz), 133.2 (d, $J_{C\text{-}F}$ = 2.4 Hz), 130.1 (d, $J_{C\text{-}F}$ = 8.5 Hz), 115.3 (d, $J_{C\text{-}F}$ = 21.7 Hz), 60.8, 50.9, 50.3, 28.8, 26.7, 25.6 ppm. **^{19}F NMR** (282 MHz, C_6D_6): δ = -110.0 ppm. **HRMS (EI+)**: calcd for $C_{11}H_{11}FNO$ [M - CONH^{t}Bu]$^+$: 192.0819, found: 192.0820. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.36-7.31 (m, 2H), 6.75-6.71 (m, 2H), 3.56-3.43 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 115.1 (d, $J_{C\text{-}F}$ = 21.6 Hz) ppm. **^{19}F NMR** (282 MHz, C_6D_6): δ = -110.9 ppm.



Chemical Formula: $C_{14}H_{20}N_2O_3$
Molecular Weight: 264.32

N-(*tert*-butyl)-1-(furan-2-carbonyl)pyrrolidine-2-carboxamide (27)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-furoic acid (**3x**) (420 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **27** (190 mg, 48% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 142-144 °C. **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.52 (br s, 1H), 7.10-7.00 (m, 1H), 6.87-6.80 (m, 1H), 5.91 (dd, J = 3.3, 1.6 Hz, 1H), 4.64 (d, J = 7.1 Hz, 1H), 3.50 (t, J = 7.9 Hz, 1H), 3.20 (dd, J = 17.4, 9.2 Hz, 1H), 2.54-2.32 (m, 1H), 2.11-1.84 (m, 1H), 1.34 (s, 9H), 1.24-1.04 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 169.9, 159.2, 149.3, 144.2, 117.2, 111.6, 61.8, 50.8, 48.3, 28.8, 26.2, 25.7 ppm. **HRMS (EI+)**: calcd for $C_9H_{10}NO_2$ [M - CONH^{t}Bu]$^+$: 164.0706, found: 164.0706.

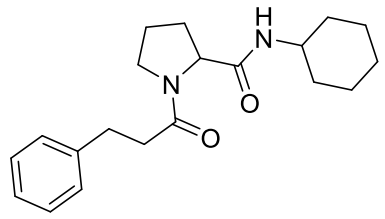


Chemical Formula: $C_{14}H_{20}N_2O_2S$
Molecular Weight: 280.39

N-(*tert*-butyl)-1-(thiophene-2-carbonyl)pyrrolidine-2-carboxamide (28)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and 2-thiophenecarboxylic acid (**3y**) (480 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure,

product **28** (144 mg, 34% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 138-140 °C. **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.45 (br s, 1H), 7.16 (1H), 6.86 (dd, *J* = 5.1, 1.1 Hz, 1H), 6.61 (dd, *J* = 5.1, 3.8 Hz, 1H), 4.80-4.46 (m, 1H), 3.35-3.16 (m, 1H), 3.14-2.95 (m, 1H), 2.54-2.27 (m, 1H), 2.04-1.75 (m, 1H), 1.34 (s, 9H), 1.30-1.21 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 169.8, 163.0, 139.9, 130.4, 130.3, 127.3, 62.1, 50.9, 49.3, 28.8, 26.4, 25.7 ppm. **HRMS (EI+)**: calcd for $C_9H_{11}NOS$ $[M]^{+\bullet}$: 181.0556, found: 181.0555.

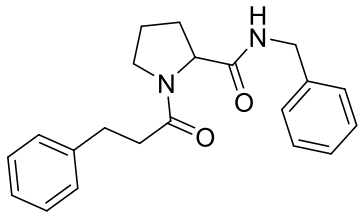


Chemical Formula: $C_{20}H_{28}N_2O_2$
Molecular Weight: 328.46

N-cyclohexyl-1-(3-phenylpropanoyl)pyrrolidine-2-carboxamide (29)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), cyclohexyl isocyanide (**2b**) (280 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (563 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **29** (308 mg, 62% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (9:1 ratio in C_6D_6) were observed. **Melting point**: 157-159 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.64 (d, *J* = 6.9 Hz, 1H), 7.23-7.11 (m, 4H), 7.11-7.03 (m, 1H), 4.48 (d, *J* = 7.7 Hz, 1H), 4.09-3.88 (m, 1H), 3.02 (td, *J* = 14.4, 7.4 Hz, 1H), 2.97 (td, *J* = 14.4, 7.4 Hz, 1H), 2.72-2.62 (m, 1H), 2.50 (dd, *J* = 11.9, 6.7 Hz, 1H), 2.40 (dt, *J* = 9.9, 6.9 Hz, 1H), 2.24-2.05 (m, 2H), 2.01-1.78 (m, 3H), 1.62-1.46 (m, 2H), 1.38-0.99 (m, 8H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.1, 169.8, 141.9, 128.9, 128.7, 126.4, 60.0, 48.3, 47.1, 36.5, 33.2, 33.1, 31.2, 26.6, 25.9,

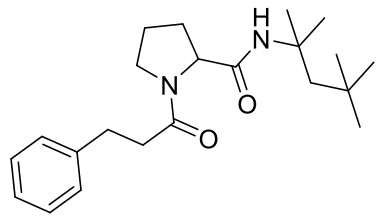
25.2, 24.9, 24.8 ppm. HRMS (EI+): calcd for $C_{20}H_{28}N_2O_2$ $[M]^{+\bullet}$: 328.2145, found: 328.2155. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.34 (d, J = 8.1 Hz, 1H), 3.83-3.75 (m, 2H), 3.51-3.40 (m, 2H) ppm.



Chemical Formula: $C_{21}H_{24}N_2O_2$
Molecular Weight: 336.44

_N_-benzyl-1-(3-phenylpropanoyl)pyrrolidine-2-carboxamide (30)

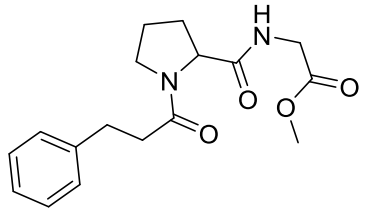
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), benzyl isocyanide (**2c**) (274 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (563 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **30** (224 mg, 42% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (15:1 ratio in C_6D_6) were observed. **Melting point**: 88-90 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.83 (br t, J = 6.0 Hz, 1H), 7.27-7.20 (m, 2H), 7.15-6.99 (m, 8H), 4.49-4.32 (m, 3H), 3.02-2.84 (m, 2H), 2.73-2.59 (m, 1H), 2.45-2.30 (m, 2H), 2.15-2.06 (m, 2H), 1.94-1.74 (m, 1H), 1.30-1.10 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.1, 170.9, 141.8, 139.7, 128.82, 128.76, 128.7, 127.9, 127.3, 126.4, 59.9, 47.0, 43.5, 36.5, 31.2, 27.1, 25.0 ppm. **HRMS (EI+)**: calcd for $C_{21}H_{24}N_2O_2$ $[M]^{+\bullet}$: 336.1832, found: 336.1826. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 6.10 (br t, J = 6.3 Hz, 1H), 4.21 (dd, J = 14.7, 6.4 Hz, 1H), 4.10 (dd, J = 14.7, 6.1 Hz, 1H), 3.82 (dd, J = 8.6, 2.4 Hz, 1H), 3.46-3.29 (m, 2H) ppm.



Chemical Formula: $C_{22}H_{34}N_2O_2$
Molecular Weight: 358.53

1-(3-phenylpropanoyl)-*N*-(2,4,4-trimethylpentan-2-yl)pyrrolidine-2-carboxamide (31)

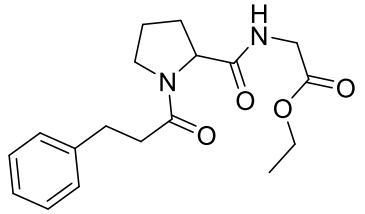
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), *tert*-Octyl isocyanide (**2d**) (394 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (563 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **31** (538 mg, 66% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (21:1 ratio in C_6D_6) were observed. **Melting point**: 95-97 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.64 (br s, 1H), 7.22-7.11 (m, 4H), 7.10-7.02 (m, 1H), 4.48 (d, *J* = 7.8 Hz, 1H), 3.08-2.88 (m, 2H), 2.77-2.64 (m, 1H), 2.57-2.35 (m, 2H), 2.27-2.07 (m, 2H), 2.01 (d, *J* = 14.8 Hz, 1H), 1.97-1.78 (m, 1H), 1.70 (d, *J* = 14.8 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.33-1.20 (m, 1H), 1.18-1.05 (m, 1H), 1.01 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.1, 169.2, 141.9, 128.9, 128.8, 126.5, 60.7, 54.6, 51.0, 47.1, 36.6, 31.7, 31.5, 31.2, 30.0, 29.4, 26.3, 25.1 ppm. **HRMS (EI+)**: calcd for $C_{22}H_{34}N_2O_2$ $[M]^{+\bullet}$: 358.2615, found: 358.2625. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.58 (br s, 1H), 3.71 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.49-3.38 (m, 2H), 0.85 (s, 9H) ppm.



Chemical Formula: $C_{17}H_{22}N_2O_4$
Molecular Weight: 318.37

Methyl (3-phenylpropanoyl)prolylglycinate (32)

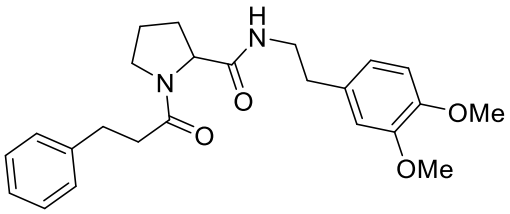
Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), methyl isocyanoacetate (**2e**) (137 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (563 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **32** (117 mg, 28% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (9:1 ratio in C_6D_6) were observed. **Melting point**: 85-87 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.93 (br t, J = 5.7 Hz, 1H), 7.27-7.09 (m, 4H), 7.09-6.99 (m, 1H), 4.54 (d, J = 7.5 Hz, 1H), 3.86 (dd, J = 17.8, 6.0 Hz, 1H), 3.74 (dd, J = 17.8, 5.7 Hz, 1H), 3.19 (s, 3H), 3.03 (t, J = 7.6 Hz, 2H), 2.74 (td, J = 9.3, 1.9 Hz, 1H), 2.47-2.32 (m, 2H), 2.30-2.09 (m, 2H), 1.93-1.72 (m, 1H), 1.31-1.11 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.2, 171.5, 170.2, 141.9, 128.9, 128.7, 126.4, 59.5, 51.4, 47.0, 41.2, 36.6, 31.3, 26.8, 24.9 ppm. **HRMS (EI+)**: calcd for $C_{17}H_{22}N_2O_4$ $[M]^{+\bullet}$: 318.1574, found: 318.1587. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 6.45 (br s, 1H), 3.40-3.31 (m, 1H), 2.03-1.96 (m, 2H), 1.63-1.50 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 61.4, 41.0, 32.0, 22.6 ppm.



Chemical Formula: $C_{18}H_{24}N_2O_4$
Molecular Weight: 332.40

Ethyl (3-phenylpropanoyl)prolylglycinate (33)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), ethyl isocyanoacetate (**2f**) (245 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (563 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **33** (156 mg, 31% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (10:1 ratio in C_6D_6) were observed. **Melting point**: 75-77 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.93 (br t, *J* = 6.1 Hz, 1H), 7.28-7.10 (m, 4H), 7.09-7.02 (m, 1H), 4.54 (d, *J* = 7.6 Hz, 1H), 3.90 (dd, *J* = 17.9, 6.1 Hz, 1H), 3.82 (q, *J* = 7.2 Hz, 2H), 3.74 (dd, *J* = 17.9, 5.5 Hz, 1H), 3.04 (t, *J* = 7.5 Hz, 2H), 2.71 (td, *J* = 9.2, 2.0 Hz, 1H), 2.45-2.33 (m, 2H), 2.29-2.09 (m, 2H), 1.92-1.73 (m, 1H), 1.30-1.04 (m, 2H), 0.83 (t, *J* = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.2, 171.4, 169.8, 141.9, 128.9, 128.7, 126.4, 60.8, 59.5, 47.0, 41.4, 36.6, 31.3, 26.7, 24.9, 14.0 ppm. **HRMS (EI+)**: calcd for $C_{18}H_{24}N_2O_4$ $[M]^{+\bullet}$: 332.1731, found: 332.1733. *Characteristic peaks for the minor rotamer:* ^{1}H NMR (300 MHz, C_6D_6): δ = 6.00 (br t, *J* = 5.8 Hz, 1H), 3.61 (dd, *J* = 6.1, 3.8 Hz, 2H), 3.57-3.48 (m, 1H), 3.45-3.33 (m, 1H), 3.10 (t, *J* = 7.5 Hz, 2H) ppm.

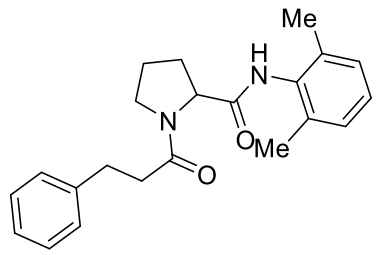


Chemical Formula: $C_{24}H_{30}N_2O_4$
Molecular Weight: 410.51

***N*-(3,4-dimethoxyphenethyl)-1-(3-phenylpropanoyl)pyrrolidine-2-carboxamide (34)**

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (**2g**) (245 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic

acid (**3g**) (430 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **34** (324 mg, 52% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (12:1 ratio in C_6D_6) were observed. **Melting point**: 98-100 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.45 (br t, J = 5.5 Hz, 1H), 7.21-7.00 (m, 5H), 6.74-6.65 (m, 2H), 6.65-6.59 (m, 1H), 4.41 (d, J = 7.6 Hz, 1H), 3.63-3.44 (m, 2H), 3.53 (s, 3H), 3.42 (s, 3H), 3.05-2.86 (m, 2H), 2.80-2.58 (m, 3H), 2.45-2.31 (m, 2H), 2.11 (t, J = 7.6 Hz, 2H), 1.94-1.73 (m, 1H), 1.33-1.04 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.0, 170.9, 150.3, 148.8, 132.3, 128.9, 128.8, 126.5, 121.1, 113.5, 112.7, 59.8, 55.8, 55.7, 47.0, 41.3, 36.5, 35.7, 31.2, 26.9, 25.0 ppm. **HRMS (EI+)**: calcd for $C_{24}H_{30}N_2O_4$ $[M]^{+\bullet}$: 410.2200, found:410.2190. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 6.59-6.51(m, 3H), 5.55 (br s, 1H), 3.81-3.74 (m, 1H) ppm.

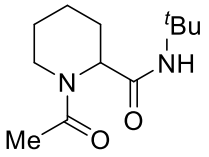


Chemical Formula: $C_{22}H_{26}N_2O_2$
Molecular Weight: 350.46

N-(2,6-dimethylphenyl)-1-(3-phenylpropanoyl)pyrrolidine-2-carboxamide (35)

Starting from pyrrolidine (**1a**) (107 mg, 1.5 mmol, 1 equiv), 2,6-dimethylpheynyl isocyanide (**2h**) (245 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (430 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **35** (178 mg, 34% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (15:1 ratio

in C_6D_6) were observed. **Melting point**: 141-143 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 8.64 (br s, 1H), 7.13-6.92 (m, 8H), 4.62 (d, J = 7.1 Hz, 1H), 3.04-2.87 (m, 2H), 2.79-2.69 (m, 1H), 2.52-2.35 (m, 2H), 2.23 (s, 6H), 2.22-2.14 (m, 2H), 1.90-1.72 (m, 1H), 1.34-1.14 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.3, 169.1, 141.7, 135.4, 135.3, 128.82, 128.76, 128.3, 126.8, 126.5, 60.1, 47.1, 36.5, 31.2, 27.0, 25.1, 18.7 ppm. **HRMS (EI+)**: calcd for $C_{22}H_{26}N_2O_2$ $[M]^{+\bullet}$: 3502.1989, found: 350.1994. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 6.53 (br s, 1H), 3.92-3.83 (m, 1H), 3.53-3.42 (m, 2H), 3.12-3.04 (m, 2H), 1.94 (s, 6H) ppm.

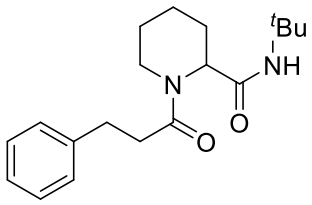


Chemical Formula: $C_{12}H_{22}N_2O_2$
Molecular Weight: 226.32

1-acetyl-*N*-(*tert*-butyl)piperidine-2-carboxamide (36)

Starting from piperidine (**1b**) (128 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and acetic acid (**3a**) (215 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **36** (127 mg, 37% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (8:1 ratio in C_6D_6) were observed. **Melting point**: 88-90 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 6.28 (br s, 1H), 5.17 (d, J = 5.4 Hz, 1H), 3.11-2.88 (m, 2H), 2.20-2.06 (m, 1H), 1.95 (qt, J = 13.0, 3.9 Hz, 1H), 1.69 (s, 3H), 1.39-1.31 (m, 1H), 1.28 (s, 9H), 1.21-1.10 (m, 2H), 1.06-0.89 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 170.5, 170.3, 52.3, 50.6, 44.1, 28.8, 25.7, 25.6, 21.4, 20.5 ppm. **HRMS (EI+)**: calcd for $C_{12}H_{22}N_2O_2$ $[M]^{+\bullet}$: 226.1676, found: 226.1676. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.70 (br s, 1H), 4.72 (d, J = 11.8

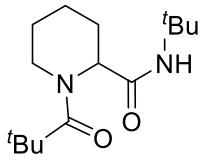
Hz, 1H), 3.94-3.77 (m, 1H), 2.54-2.31 (m, 2H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.6 ppm.



Chemical Formula: $C_{19}H_{28}N_2O_2$
Molecular Weight: 316.44

***N*-(*tert*-butyl)-1-(3-phenylpropanoyl)piperidine-2-carboxamide (37)**

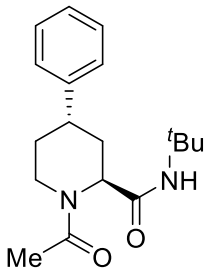
Starting from piperidine (**1b**) (128 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (430 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **37** (169 mg, 36% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (8:1 ratio in C_6D_6) were observed. **Melting point**: 138-140 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.15-7.09 (m, 2H), 7.09-7.02 (m, 3H), 6.20 (br s, 1H), 5.19 (d, *J* = 5.4 Hz, 1H), 3.15-3.02 (m, 1H), 2.97 (dd, *J* = 16.1, 7.8 Hz, 2H), 2.87 (td, *J* = 13.1, 3.0 Hz, 1H), 2.28 (t, *J* = 7.7 Hz, 2H), 2.17-2.07 (m, 1H), 1.96 (qt, *J* = 13.0, 3.9 Hz, 1H), 1.39-1.31 (m, 1H), 1.27 (s, 9H), 1.22-1.17 (m, 1H), 1.15-1.05 (m, 1H), 0.93 (tt, *J* = 12.9, 4.2 Hz, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.2, 170.4, 141.8, 128.8, 128.7, 126.4, 52.5, 50.6, 43.3, 35.4, 31.7, 28.8, 25.7, 25.6, 20.6 ppm. **HRMS (EI+)**: calcd for $C_{19}H_{28}N_2O_2$ $[M]^{+\bullet}$: 316.2145, found: 316.2153. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.41 (br s, 1H), 4.79 (d, *J* = 12.3 Hz, 1H), 3.97-3.86 (m, 1H), 2.47-2.34 (m, 2H), 1.16 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.6 ppm.



Chemical Formula: $C_{15}H_{28}N_2O_2$
Molecular Weight: 268.40

N-(*tert*-butyl)-1-pivaloylpiperidine-2-carboxamide (38)

Starting from piperidine (**1b**) (128 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and pivalic acid (**3e**) (383 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **38** (177 mg, 44% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 74-76 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 6.33 (s, 1H), 5.14 (d, *J* = 5.7 Hz, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 2.82 (dd, *J* = 13.0, 2.8 Hz, 1H), 2.25 (d, *J* = 13.0 Hz, 1H), 2.11-1.94 (m, 1H), 1.44-1.36 (m, 1H), 1.28 (s, 9H), 1.25-1.19 (m, 1H), 1.21-1.13 (m, 1H), 1.14 (s, 9H), 1.13-1.03 (m, 1H)ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 178.3, 170.3, 54.4, 50.9, 44.5, 38.9, 28.9, 28.3, 25.5, 25.2, 20.7 ppm. **HRMS (EI+)**: calcd for $C_{15}H_{28}N_2O_2$ $[M]^{+\bullet}$: 268.2145, found: 268.2154.

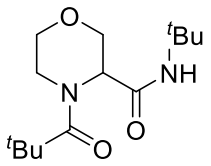


Chemical Formula: $C_{18}H_{26}N_2O_2$
Molecular Weight: 302.42

(2*R*,4*R*)-1-acetyl-*N*-(*tert*-butyl)-4-phenylpiperidine-2-carboxamide[5] (39)

Starting from 4-phenyl piperidine (**1c**) (242 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and acetic acid (**3a**) (215 µL, 3.75

mmol, 2.5 equiv), and following the aforementioned general procedure, product **36** (165 mg, 36% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (9:1 ratio in C_6D_6) were observed. **Melting point**: 152-154 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.21-7.14 (m, 2H), 7.14-7.01 (m, 3H), 6.38 (br s, 1H), 5.28 (dd, *J* = 5.8, 1.2 Hz, 1H), 3.44 (tt, *J* = 12.4, 3.5 Hz, 1H), 3.20-3.07 (m, 2H), 2.31 (ddt, *J* = 13.4, 3.6, 1.9 Hz, 1H), 1.72 (s, 3H), 1.52-1.42 (m, 1H), 1.40-1.32 (m, 1H), 1.31 (s, 9H), 1.26-1.17 (m, 1H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 170.5, 170.3, 146.1, 128.8, 127.2, 126.7, 52.5, 50.7, 44.2, 37.9, 33.6, 32.9, 28.8, 21.5 ppm. **HRMS (EI+)**: calcd for $C_{18}H_{26}N_2O_2$ $[M]^{+\bullet}$: 302.1989, found: 302.1985. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.79 (br s, 1H), 4.86 (d, *J* = 13.4 Hz, 1H), 3.95 (d, *J* = 5.3 Hz, 1H), 2.82-2.68 (m, 2H), 2.56 (td, *J* = 13.0, 3.3 Hz, 1H), 1.71 (s, 3H), 1.26 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 169.4, 168.4, 145.5, 58.7, 51.2, 39.8, 38.9, 34.4, 31.8, 28.7, 21.3 ppm.

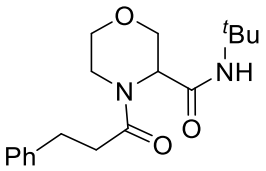


Chemical Formula: $C_{14}H_{26}N_2O_3$
Molecular Weight: 270.37

N-(*tert*-butyl)-4-pivaloylmorpholine-3-carboxamide (40)

Starting from morpholine (**1d**) (131 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and pivalic acid (**3e**) (383 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **40** (178 mg, 44% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 121-123 °C. **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.75 (br s, 1H), 4.71 (d, *J* = 2.7 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 3.55-3.36 (m, 2H), 3.28-3.17 (m, 1H), 3.15 (dd, *J* = 11.6, 3.8 Hz, 1H), 3.08-2.96 (m, 1H), 1.26

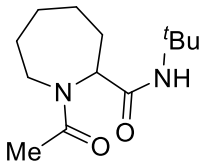
(s, 9H), 1.08 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 177.5, 168.2, 66.7, 66.1, 55.3, 50.9, 44.7, 38.7, 28.8, 28.1 ppm. **HRMS (EI+)**: calcd for $C_{14}H_{26}N_2O_3$ $[M]^{+\bullet}$: 270.1938, found: 270.1954.



Chemical Formula: $C_{18}H_{26}N_2O_3$
Molecular Weight: 318.42

N-(*tert*-butyl)-4-(3-phenylpropanoyl)morpholine-3-carboxamide (41)

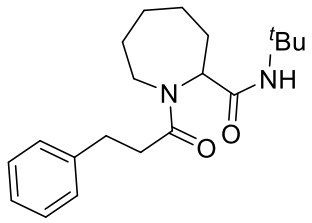
Starting from morpholine (**1d**) (131 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (430 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **41** (229 mg, 48% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (10:1 ratio in C_6D_6) were observed. **Melting point**: 127-129 °C. **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.16-7.10 (m, 3H), 7.04 (d, *J* = 7.6 Hz, 2H), 5.58 (s, 1H), 4.73 (d, *J* = 3.7 Hz, 1H), 4.25 (d, *J* = 11.9 Hz, 1H), 3.36 (dd, *J* = 11.4, 3.5 Hz, 1H), 3.32-3.21 (m, 1H), 2.96 (t, *J* = 7.6 Hz, 2H), 2.79 (td, *J* = 11.4, 2.9 Hz, 2H), 2.60 (d, *J* = 14.1 Hz, 1H), 2.19 (t, *J* = 7.6 Hz, 2H), 1.26 (s, 9H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 172.5, 168.2, 140.7, 128.6, 128.4, 126.4, 66.5, 66.0, 52.8, 51.3, 43.5, 34.8, 31.2, 28.7 ppm. **HRMS (EI+)**: calcd for $C_{18}H_{26}N_2O_3$ $[M]^{+\bullet}$: 318.1938, found: 318.1946.



Chemical Formula: $C_{13}H_{24}N_2O_2$
Molecular Weight: 240.35

1-acetyl-*N*-(*tert*-butyl)azepane-2-carboxamide (42)

Starting from azepane (**1e**) (170 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and acetic acid (**3a**) (215 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **42** (118 mg, 33% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (15:1 ratio in C_6D_6) were observed. **Melting point**: 153-155 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 6.75 (br s, 1H), 4.76 (dd, J = 12.2, 6.5 Hz, 1H), 3.15-2.90 (m, 2H), 2.15-1.98 (m, 1H), 1.86-1.76 (m, 1H), 1.73 (s, 3H), 1.57-1.38 (m, 2H), 1.34 (s, 9H), 1.19-1.10 (m, 1H), 0.98-0.76 (m, 3H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 171.1, 170.9, 57.5, 50.6, 44.5, 30.2, 29.4, 28.85, 28.78, 24.7, 21.4 ppm. **HRMS (EI+)**: calcd for $C_{13}H_{23}N_2O_2$ [M - H]$^+$: 239.1754, found: 239.1757. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.33 (br s, 1H), 4.46-4.31 (m, 1H), 3.70 (dd, J = 11.5, 6.1 Hz, 1H), 2.50-2.38 (m, 1H), 2.33-2.20 (m, 1H), 1.79 (s, 3H), 1.19 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 63.3, 42.3, 32.0, 29.2, 28.8, 28.6, 25.9 ppm.

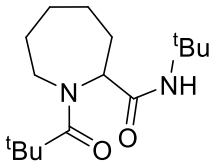


Chemical Formula: $C_{20}H_{30}N_2O_2$
Molecular Weight: 330.47

***N*-(*tert*-butyl)-1-(3-phenylpropanoyl)azepane-2-carboxamide (43)**

Starting from azepane (**1e**) (170 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (430 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **43** (215 mg, 43% yield) was obtained as a white solid after purification by flash column

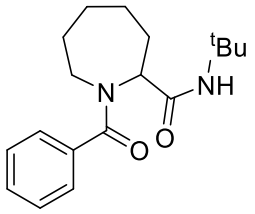
chromatography. In ^{1}H NMR timescale, two rotamers (18:1 ratio in C_6D_6) were observed. **Melting point**: 155-157 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.15-7.00 (m, 5H), 6.70 (br s, 1H), 4.76 (dd, J = 12.2, 6.5 Hz, 1H), 3.11-2.94 (m, 4H), 2.43-2.24 (m, 2H), 2.16-1.98 (m, 1H), 1.85-1.70 (m, 1H), 1.53-1.35 (m, 2H), 1.34 (s, 9H), 1.18-1.09 (m, 1H), 0.98-0.64 (m, 3H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 173.0, 170.8, 142.0, 128.9, 128.7, 126.4, 57.7, 50.6, 43.7, 35.1, 31.8, 30.2, 29.3, 28.9, 28.7, 24.6 ppm. **HRMS (EI+)**: calcd for $C_{15}H_{20}NO$ [M - CONH^{t}Bu]$^+$: 230.1539, found: 230.1534. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.21 (br s, 1H), 4.44-4.32 (m, 1H), 3.74 (dd, J = 11.5, 6.1 Hz, 1H), 1.16 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 172.0, 171.9, 62.3, 50.8, 42.4, 35.6, 31.4, 29.2, 28.6, 25.8 ppm.



Chemical Formula: $C_{16}H_{30}N_2O_2$
Molecular Weight: 282.43

N-(*tert*-butyl)-1-pivaloylazepane-2-carboxamide (44)

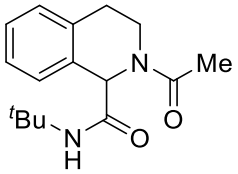
Starting from azepane (**1e**) (170 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and pivalic acid (**3e**) (383 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **44** (92 mg, 22% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 127-129 °C. **^{1}H NMR** (500 MHz, C_6D_6, T = 70 °C): δ = 6.02 (s, 1H), 4.84-4.54 (m, 1H), 3.79 (d, J = 15.2 Hz, 1H), 3.04 (t, J = 13.0 Hz, 1H), 2.05-1.88 (m, 2H), 1.65-1.54 (m, 1H), 1.51-1.42 (m, 2H), 1.39-1.33 (m, 1H), 1.29 (s, 9H), 1.21 (s, 9H), 1.14-1.03 (m, 2H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 178.4, 171.5, 60.6, 51.0, 44.6, 39.8, 29.7, 29.1 (2C), 28.8, 28.7, 25.0 ppm. **HRMS (EI+)**: calcd for $C_{16}H_{30}N_2O_2$ [M]$^{+\bullet}$: 282.2302, found: 282.2298.



Chemical Formula: $C_{18}H_{26}N_2O_2$
Molecular Weight: 302.42

1-benzoyl-*N*-(*tert*-butyl)azepane-2-carboxamide (45)

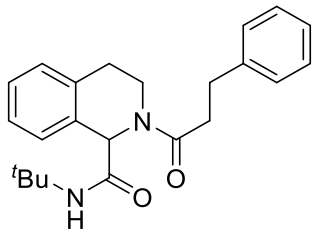
Starting from azepane (**1e**) (170 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and benzoic acid (**3n**) (510 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **45** (106 mg, 23% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (4:1 ratio in C_6D_6) were observed. **Melting point**: 127-129 °C. *Major rotamer:* **^{1}H NMR** (500 MHz, C_6D_6): δ = 7.31-7.24 (m, 2H), 7.04 (dd, J = 5.6, 1.8 Hz, 3H), 6.55 (s, 1H), 4.93 (dd, J = 12.1, 6.2 Hz, 1H), 3.35 (d, J = 15.6 Hz, 1H), 3.22-3.11 (m, 2H), 2.12 (q, J = 15.0, 11.6 Hz, 1H), 1.86 (dt, J = 15.0, 7.3 Hz, 1H), 1.61-1.53 (m, 1H), 1.44 (d, J = 13.2 Hz, 1H), 1.37 (s, 9H), 1.11-1.04 (m, 2H), 0.98-0.87 (m, 1H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$): δ = 173.3, 170.8, 137.0, 129.2, 128.6, 125.9, 58.3, 51.1, 45.8, 30.8, 29.0, 28.8, 28.7, 24.9 ppm. **HRMS (EI+)**: calcd for $C_{18}H_{26}N_2O_2$ $[M]^{+\bullet}$: 302.1989, found: 302.1998. *Characterisitic peaks for the minor rotamer:* **^{1}H NMR** (400 MHz, C_6D_6): δ = 7.42-7.35 (m, 2H), 4.74 (s, 1H), 4.61 (d, J = 13.8 Hz, 1H), 3.74 (t, J = 9.3 Hz, 1H), 2.91 (t, J = 12.6 Hz, 1H), 1.78-1.69 (m, 1H), 1.18 (s, 9H) ppm.



Chemical Formula: $C_{16}H_{22}N_2O_2$
Molecular Weight: 274.36

2-acetyl-*N*-(*tert*-butyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide[6] **(46)**

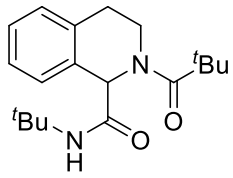
Starting from 1,2,3,4-tetrahydroisoquinoline (**1f**) (200 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and acetic acid (**3a**) (215 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure changing the current to 6 mA and reaction time to 36 hours, product **46** (225 mg, 55% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (18:1 ratio in C_6D_6) were observed. **Melting point**: 158-160 °C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.15-7.12 (m, 1H), 7.08-7.00 (m, 2H), 6.93-6.86 (m, 1H), 6.81 (br s, 1H), 5.98 (s, 1H), 3.49 (ddd, *J* = 12.7, 8.2, 4.1 Hz, 1H), 2.93-2.85 (m, 1H), 2.73-2.64 (m, 1H), 2.25 (ddd, *J* = 13.9, 8.9, 5.3 Hz, 1H), 1.66 (s, 3H), 1.31 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 170.0, 169.9, 135.6, 133.4, 128.2, 127.3, 126.6, 58.3, 51.1, 42.7, 29.0, 28.8, 21.6 ppm. **HRMS (EI+)**: calcd for $C_{12}H_{12}NO_2$ [M - NH^{t}Bu]$^+$: 202.0863, found: 202.0861. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.35 (br s, 1H), 4.89 (s, 1H), 4.42-4.21 (m, 1H), 1.97 (s, 3H), 1.08 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.4 ppm.



Chemical Formula: $C_{23}H_{28}N_2O_2$
Molecular Weight: 364.49

N-(*tert*-butyl)-2-(3-phenylpropanoyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (47)

Starting from 1,2,3,4-tetrahydroisoquinoline (**1f**) (200 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and hydrocinnamic acid (**3g**) (430 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure changing the current to 6 mA and reaction time to 36 hours, product **47** (282 mg, 52% yield) was obtained as a white solid after purification by flash column chromatography. In ^{1}H NMR timescale, two rotamers (18:1 ratio in C_6D_6) were observed. **Melting point**: 136-138°C. *Major rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.36 (d, J = 7.2 Hz, 1H), 7.20-7.01 (m, 8H), 6.89 (d, J = 7.1 Hz, 1H), 6.09 (s, 1H), 3.59 (ddd, J = 12.7, 8.5, 4.5 Hz, 1H), 3.13-2.97 (m, 2H), 2.97-2.89 (m, 1H), 2.73 (dt, J = 15.5, 5.3 Hz, 1H), 2.33 (ddd, J = 15.8, 9.3, 6.4 Hz, 1H), 2.28-2.15 (m, 2H), 1.36 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 171.9, 170.0, 141.9, 135.6, 133.5, 128.82, 128.79, 128.4, 128.1, 127.4, 126.6, 126.4, 58.5, 51.1, 42.0, 35.7, 31.6, 29.0, 28.8 ppm. **HRMS (EI+)**: calcd for $C_{18}H_{18}NO$ [M - NH^{t}Bu]$^+$: 264.1383, found: 264.1388. *Characteristic peaks for the minor rotamer:* **^{1}H NMR** (300 MHz, C_6D_6): δ = 5.34 (br s, 1H), 4.96 (s, 1H), 4.45-4.32 (m, 1H), 1.07 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 28.4 ppm.



Chemical Formula: $C_{19}H_{28}N_2O_2$
Molecular Weight: 316.44

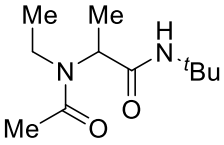
N-(*tert*-butyl)-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamide (48)

Starting from 1,2,3,4-tetrahydroisoquinoline (**1f**) (200 mg, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and pivalic acid (**3e**)

(383 mg, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure changing the current to 6 mA and reaction time to 36 hours, product **48** (316 mg, 67% yield) was obtained as a white solid after purification by flash column chromatography. **Melting point**: 138-140 °C. **^{1}H NMR** (300 MHz, C_6D_6): δ = 7.12-6.99 (m, 3H), 6.94-6.88 (m, 1H), 6.77 (br s, 1H), 6.03 (s, 1H), 3.78-3.66 (m, 1H), 3.66-3.53 (m, 1H), 2.54 (ddd, *J* = 16.5, 10.9, 5.1 Hz, 1H), 2.33 (dt, *J* = 16.1, 3.2 Hz, 1H), 1.31 (s, 9H), 1.14 (s, 9H) ppm. **^{13}C NMR** (75 MHz, C_6D_6): δ = 171.1, 169.9, 134.6, 132.9, 128.9, 128.7, 127.1, 126.4, 59.1, 50.9, 42.3, 38.7, 29.1, 28.8, 28.1 ppm. **HRMS (EI+)**: calcd for $C_{14}H_{18}NO$ [M - NH^{t}Bu]$^{+}$: 216.1383, found: 216.1383.

7. Preliminary experiments based on the use of acyclic secondary amines

To test the viability of our synthetic approach with regard to the use of acyclic secondary amines, diethylamine, the acyclic analog of pyrrolidine, was used as model substrate. In the previously optimized reaction conditions, we did witness the formation of the desired product (**49**), although accompanied with the generation of several unidentified byproducts. As a result, the multicomponent product **49**, could only be isolated in low yield (22%), which allowed to us to conclude that acyclic secondary amines are poor reaction partners. The major characterization of product **49** is as below, and the copies of ^{1}H and ^{13}C NMR spectra are available in section 9.



Chemical Formula: $C_{11}H_{22}N_2O_2$
Molecular Weight: 214.31

N-(*tert*-butyl)-2-(*N*-ethylacetamido)propanamide (49)

Starting from diethylamine (**1g**) (156 µL, 1.5 mmol, 1 equiv), *tert*-butyl isocyanide (**2a**) (254 µL, 2.25 mmol, 1.5 equiv) and acetic acid (**3a**) (215 µL, 3.75 mmol, 2.5 equiv), and following the aforementioned general procedure, product **49** (70 mg, 22% yield) was obtained as a yellowish solid after purification by flash column chromatography. **^{1}H NMR** (300 MHz, $CDCl_3$): δ = 6.30 (br s, 1H), 4.90 (q, J = 7.2 Hz, 1H), 3.29 (q, J = 7.2 Hz, 2H), 2.09 (s, 3H), 1.26-1.20 (m, 12H), 1.12 (t, J = 7.2 Hz, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ = 171.8, 171.2, 52.5, 51.0, 39.7, 28.7, 21.9, 15.5, 14.0 ppm.

8. References

[1] J. B. Gerken, Y. Q. Pang, M. B. Lauber, S. S. Stahl, *J. Org. Chem*. **2018**, *83*(14), 7323-7330.

[2] Y. Kato, Y. Shimizu, L. Yijing, K. Unoura, H. Utsumi, T. Ogata, *Elecrochimica Acta*, **1995**, *40*(17), 2799-2802.

[3] J. M. Bobbitt, A. L. Bartelson, W. F. Bailey, T. A. Hamlin, C. B. Kelly, *J. Org. Chem.* **2014**, *79*(3), 1055-1067.

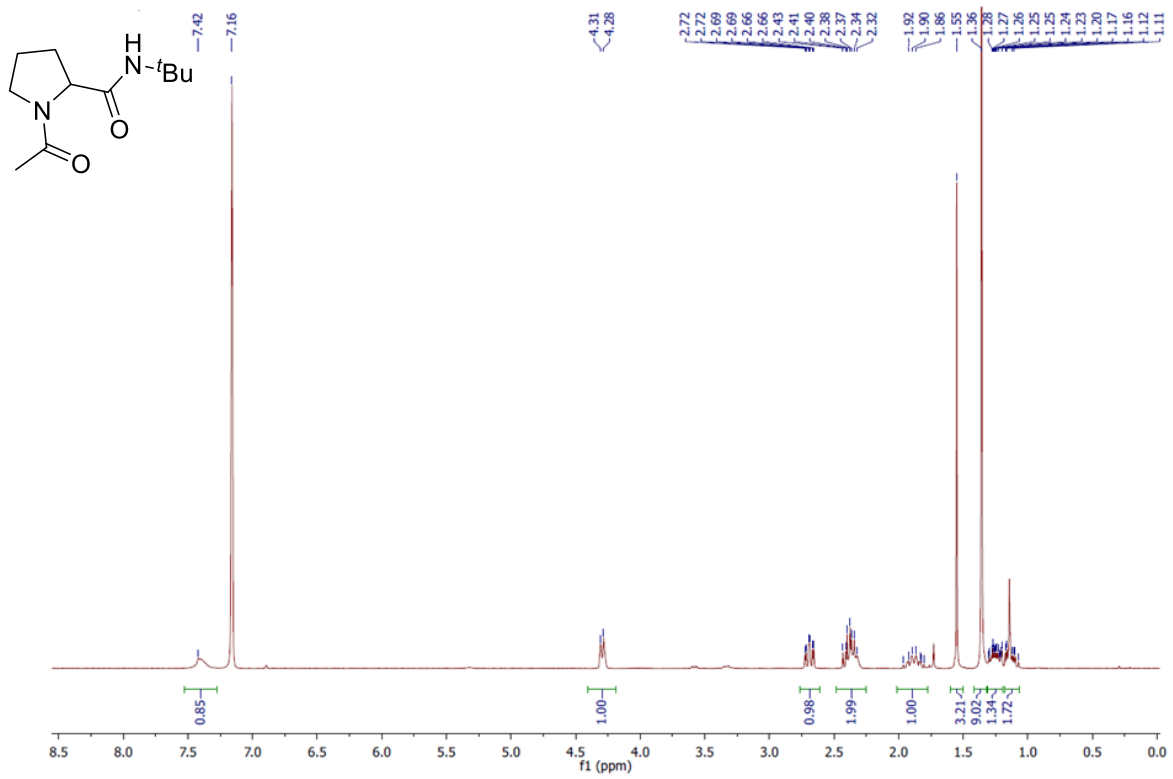
[4] For a previous synthesis, see: A. R. Ekkati, A. A. Campanali, A. I. Abouelatta, M. Shamoun, S. Kalapugama, M. Kelley, J. J. Kodanko, *Amino Acids*, **2010**, *38* (3), 747–751.

[5] For a previous synthesis, see: G. van der Heijden, T. B.van Schaik, V. Mouarrawis, M. J. M. de Wit, C. M. L. Vande Velde, E. Ruijter, R. V. A. Orru, *Eur. J. Org. Chem.* **2019**, Early view DOI: 10.1002/ejoc.201900399.

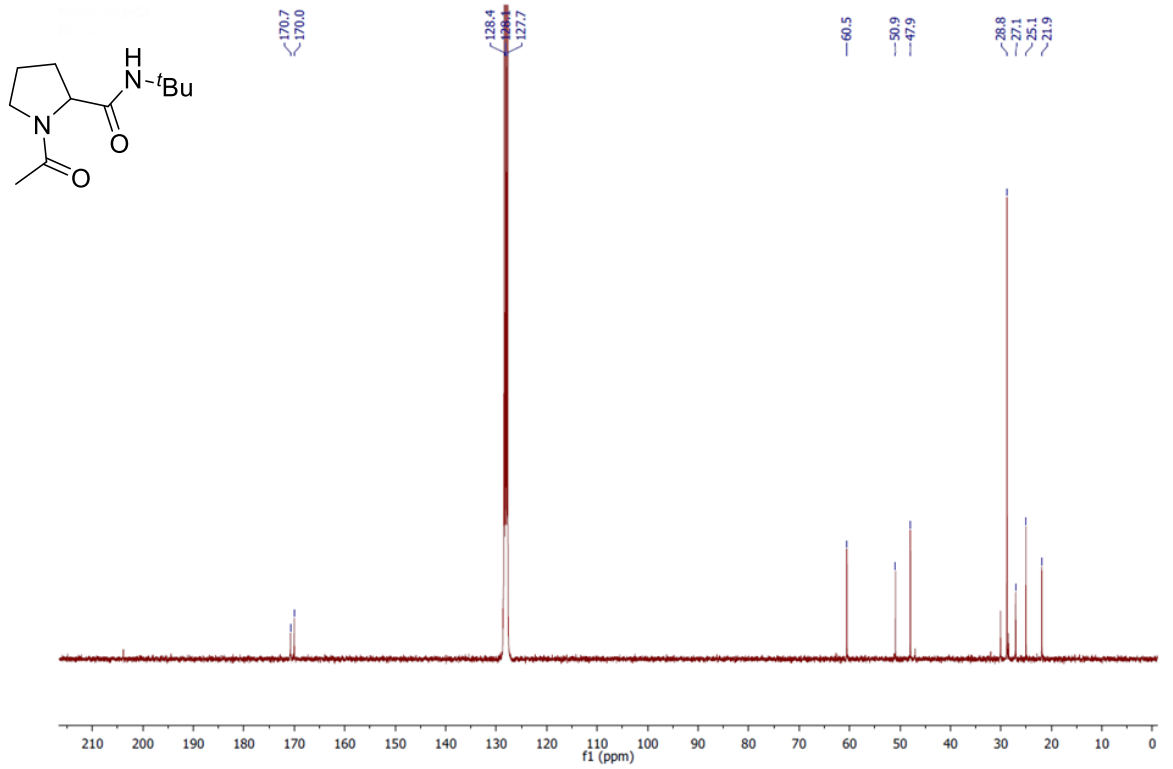
[6] For a previous synthesis, see: T. Ngouansavanh, J. Zhu, *Angew. Chem. Int. Ed*. **2007**, *46*(30), 5775-5778.

9. NMR spectra of electrochemical multicomponent α-carbamoylation products

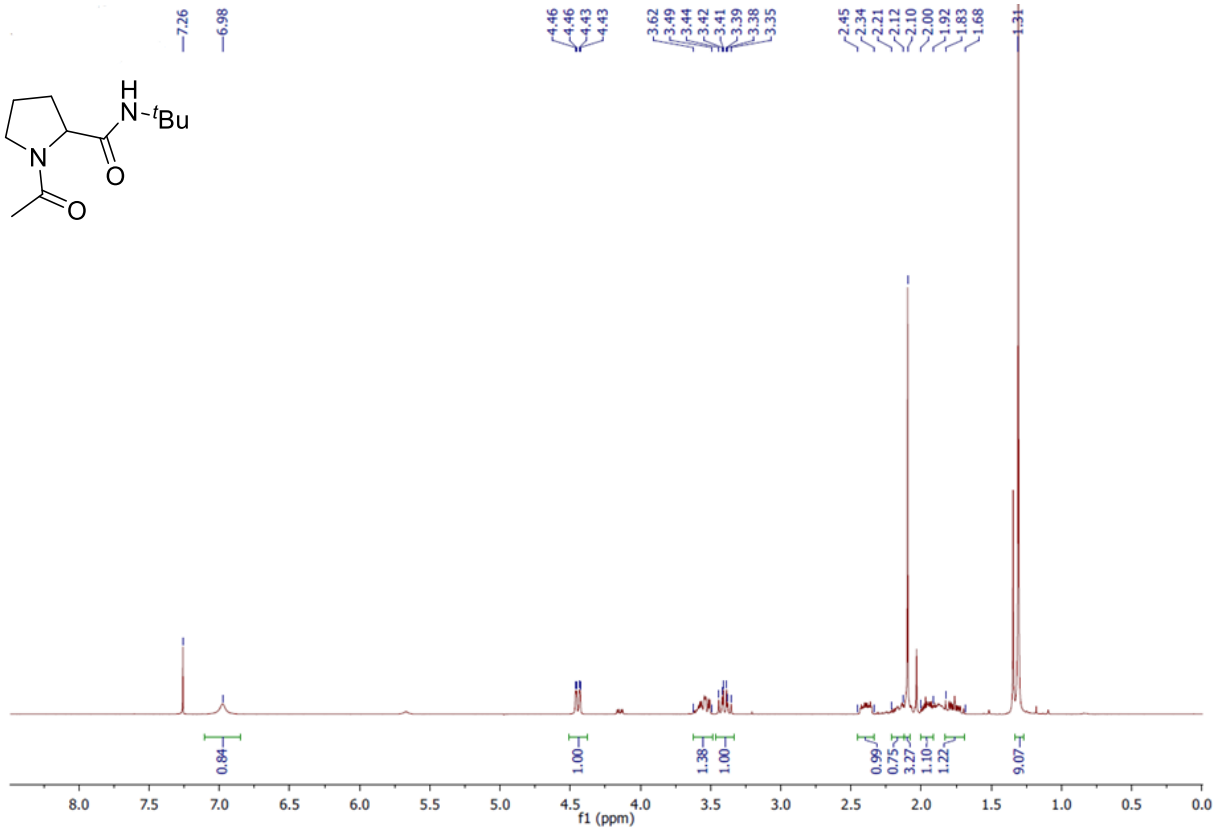
^{1}H NMR of **4** in C_6D_6



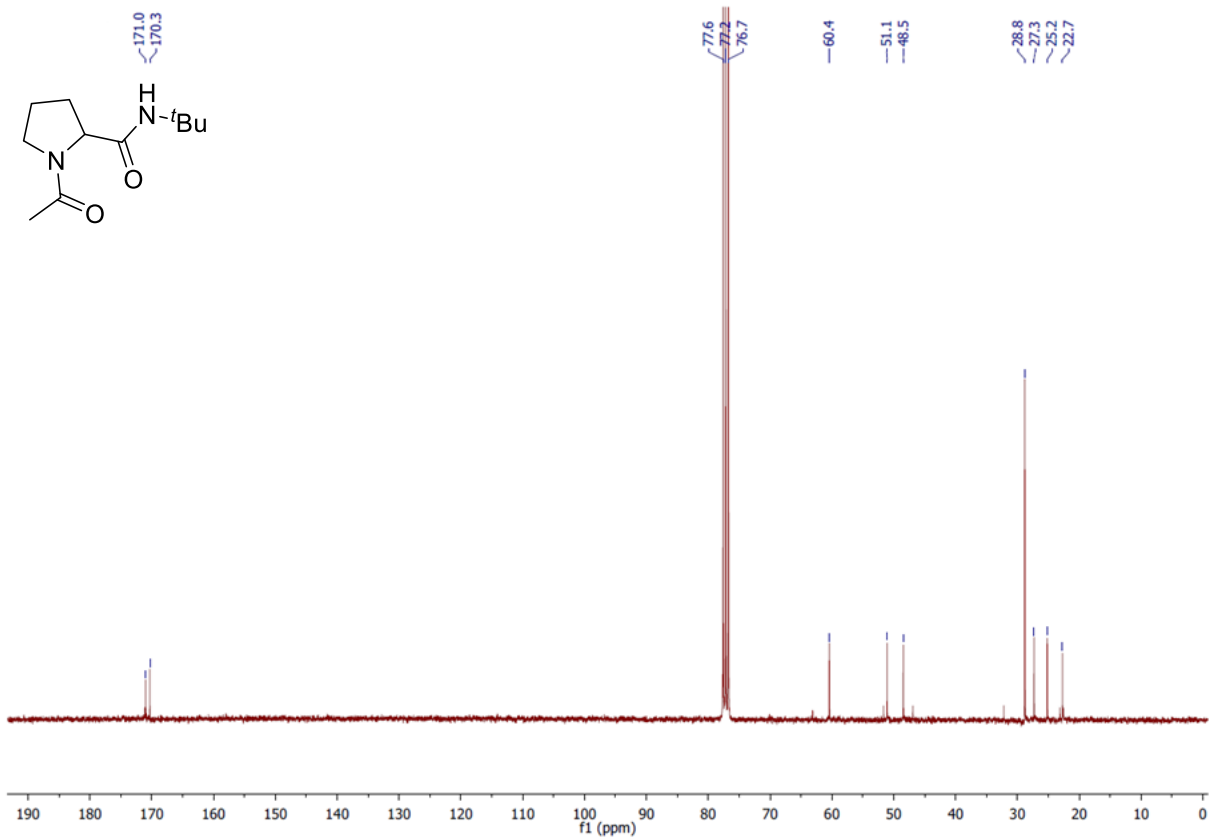
^{13}C NMR of **4** in C_6D_6



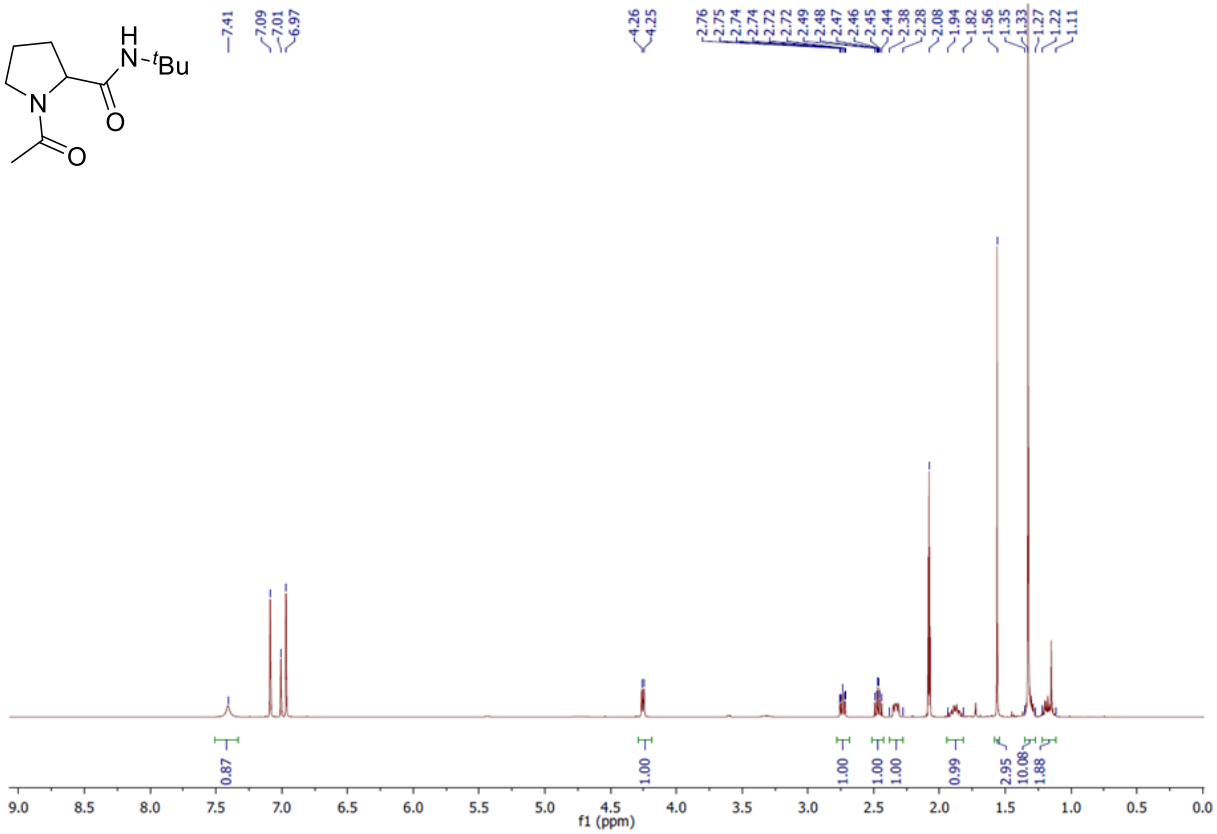
^{1}H NMR of **4** in $CDCl_3$



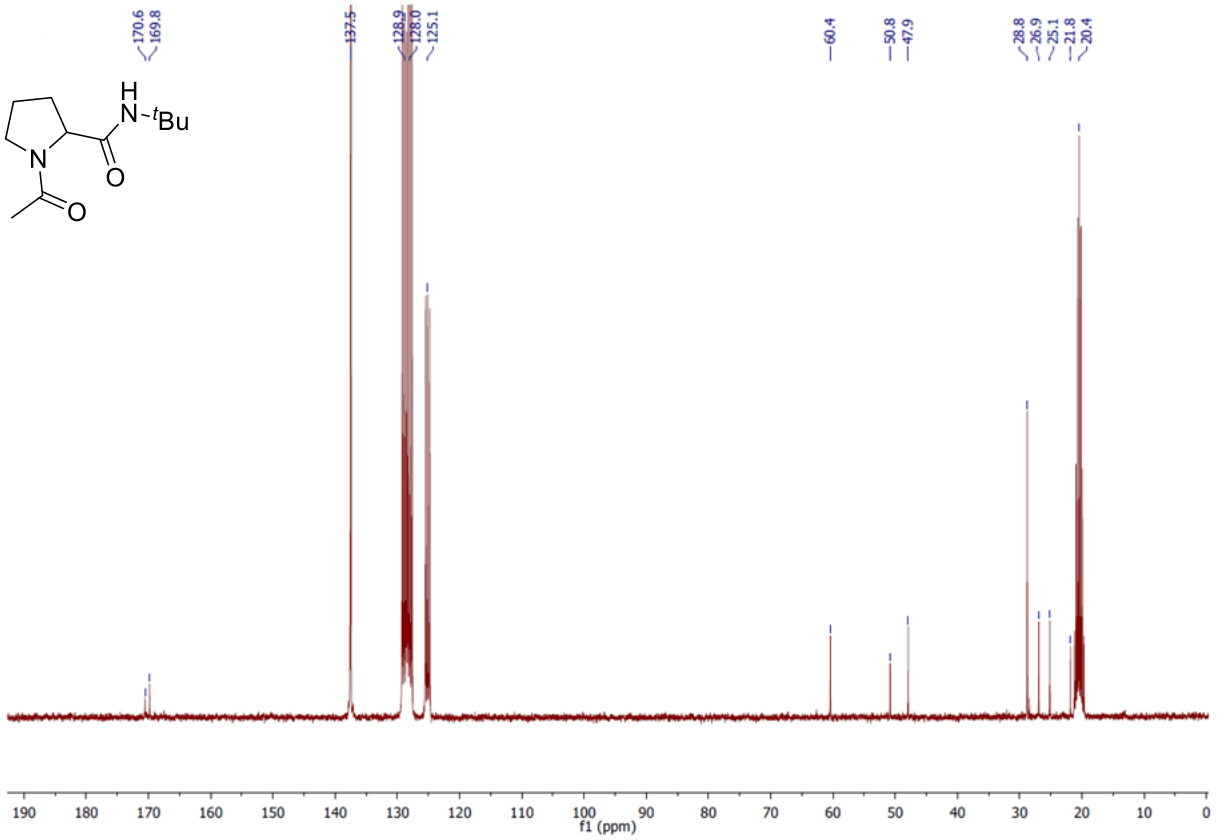
^{13}C NMR of **4** in $CDCl_3$



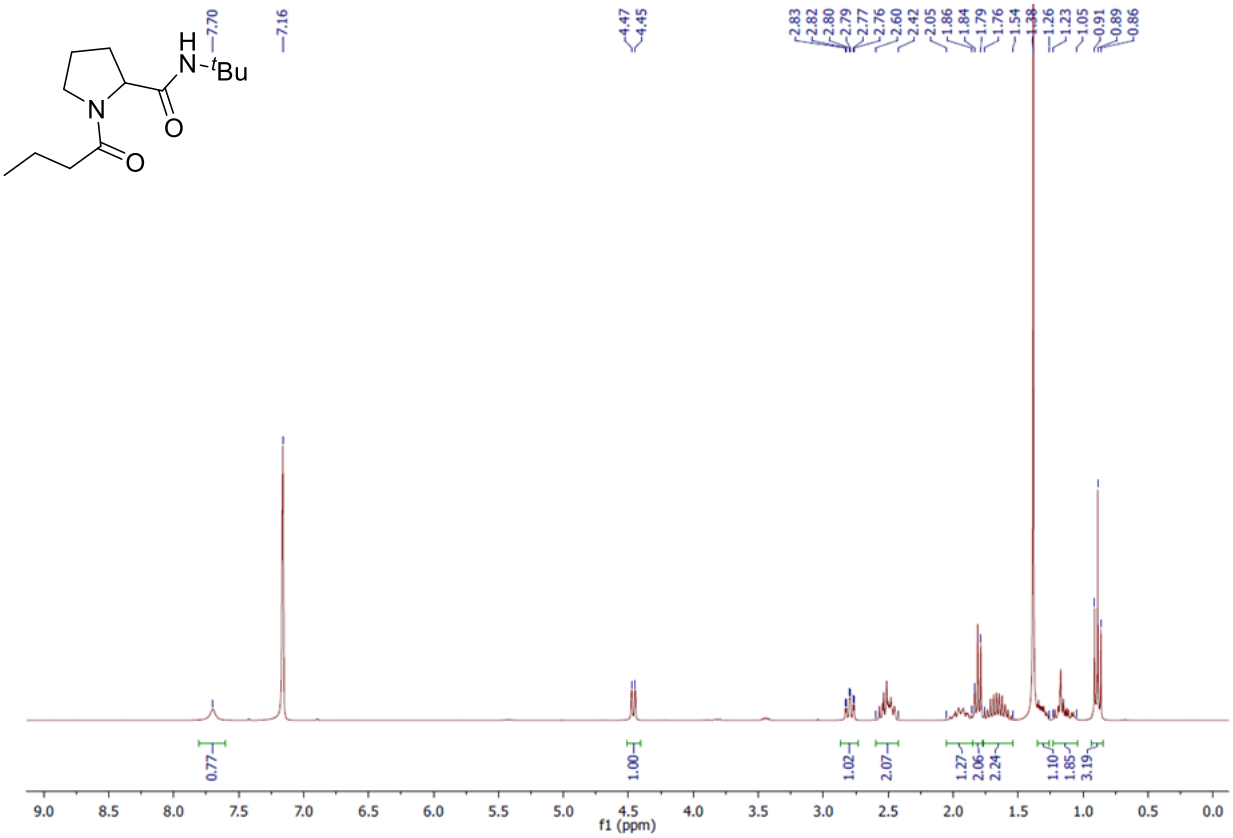
^{1}H NMR of **4** in tol-d^{8}



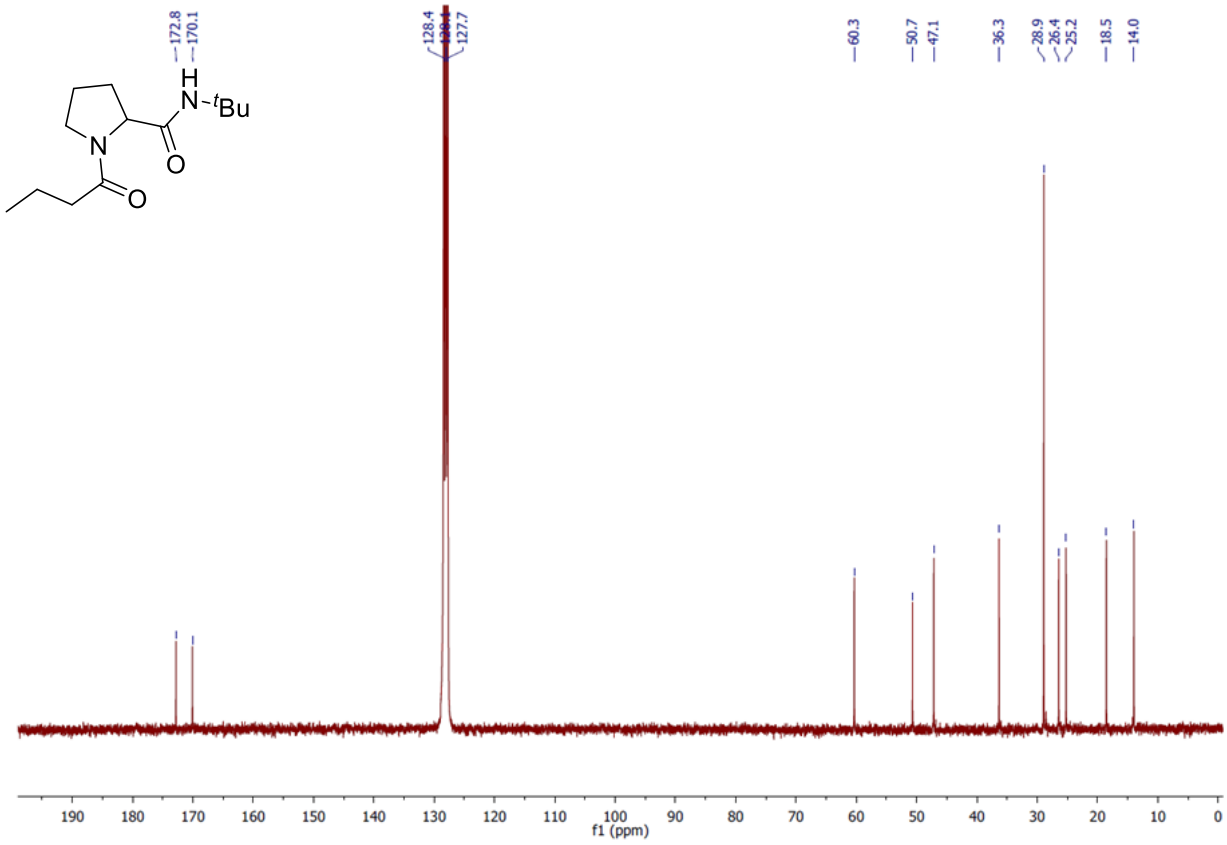
^{13}C NMR of **4** in tol-d^{8}



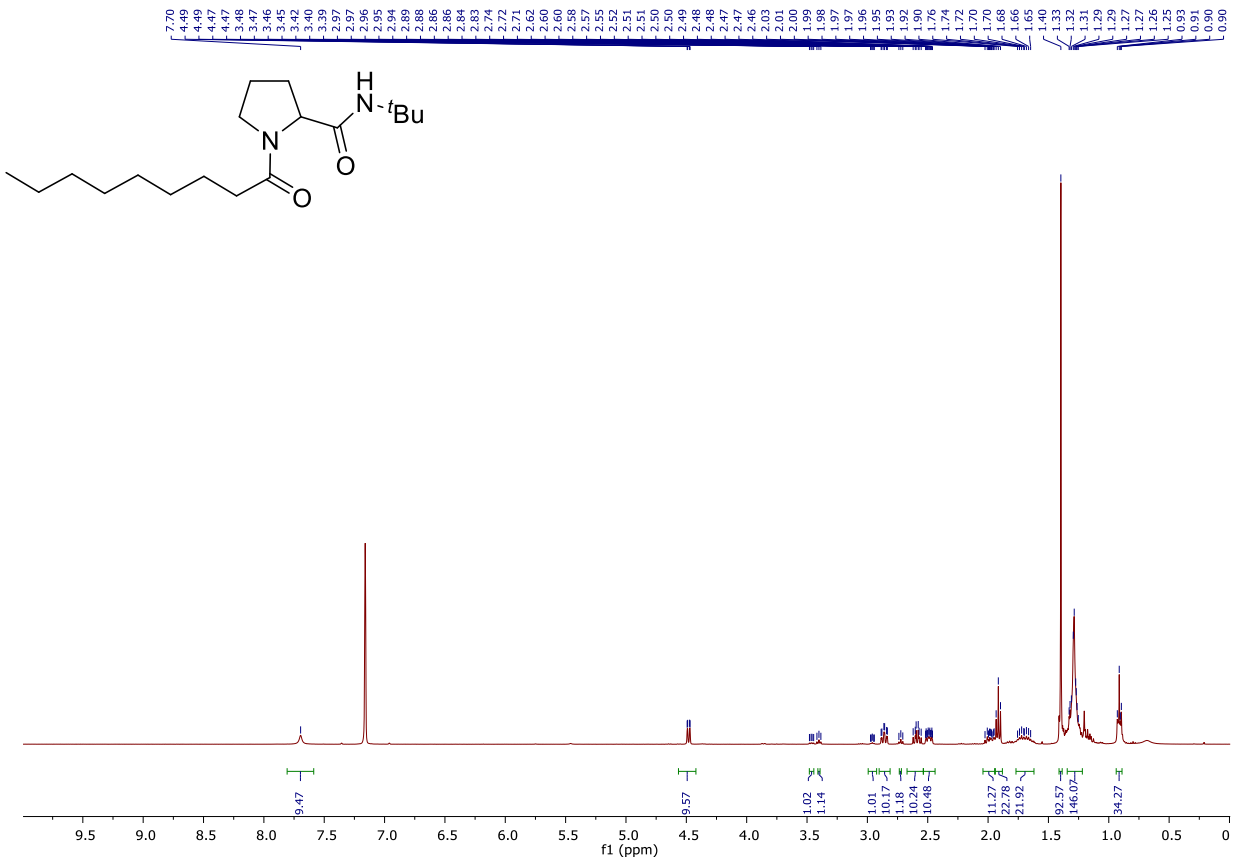
^{1}H NMR of **5** in C_6D_6



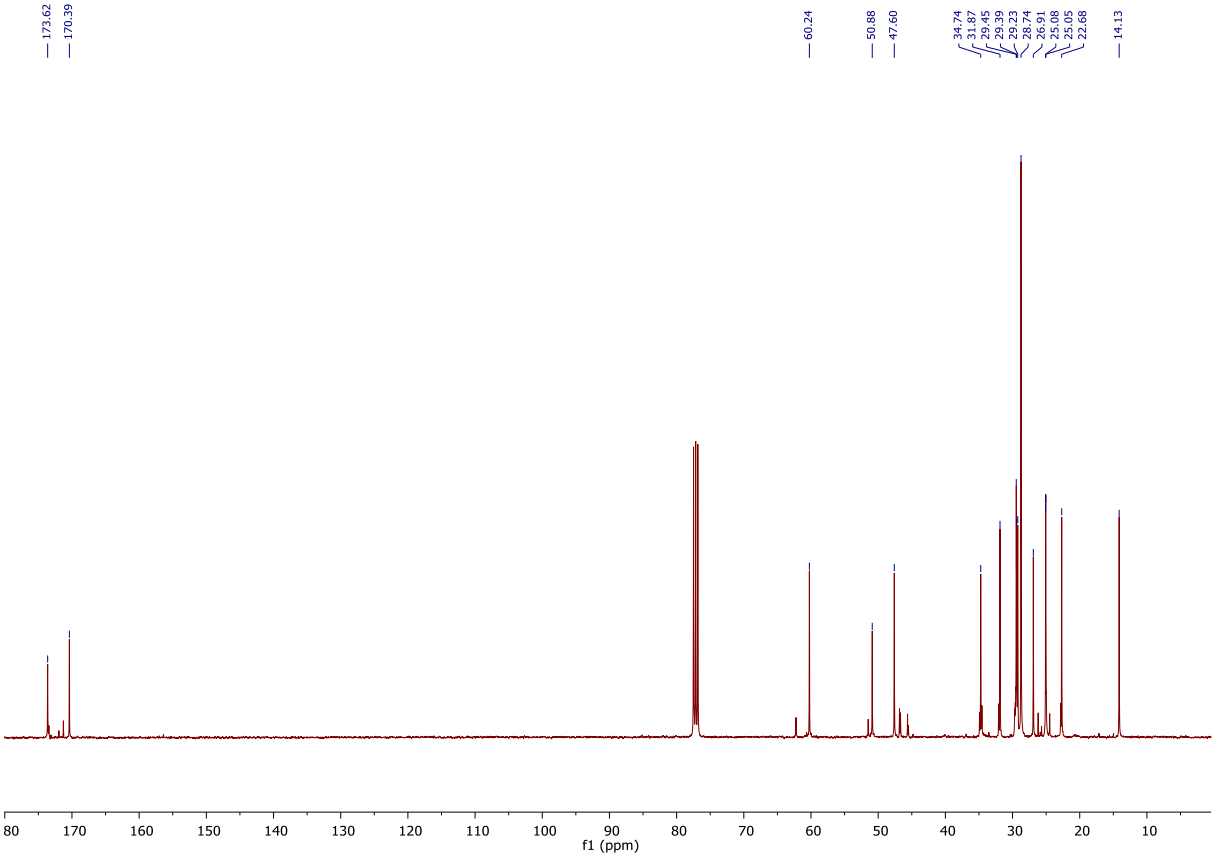
^{13}C NMR of **5** in C_6D_6



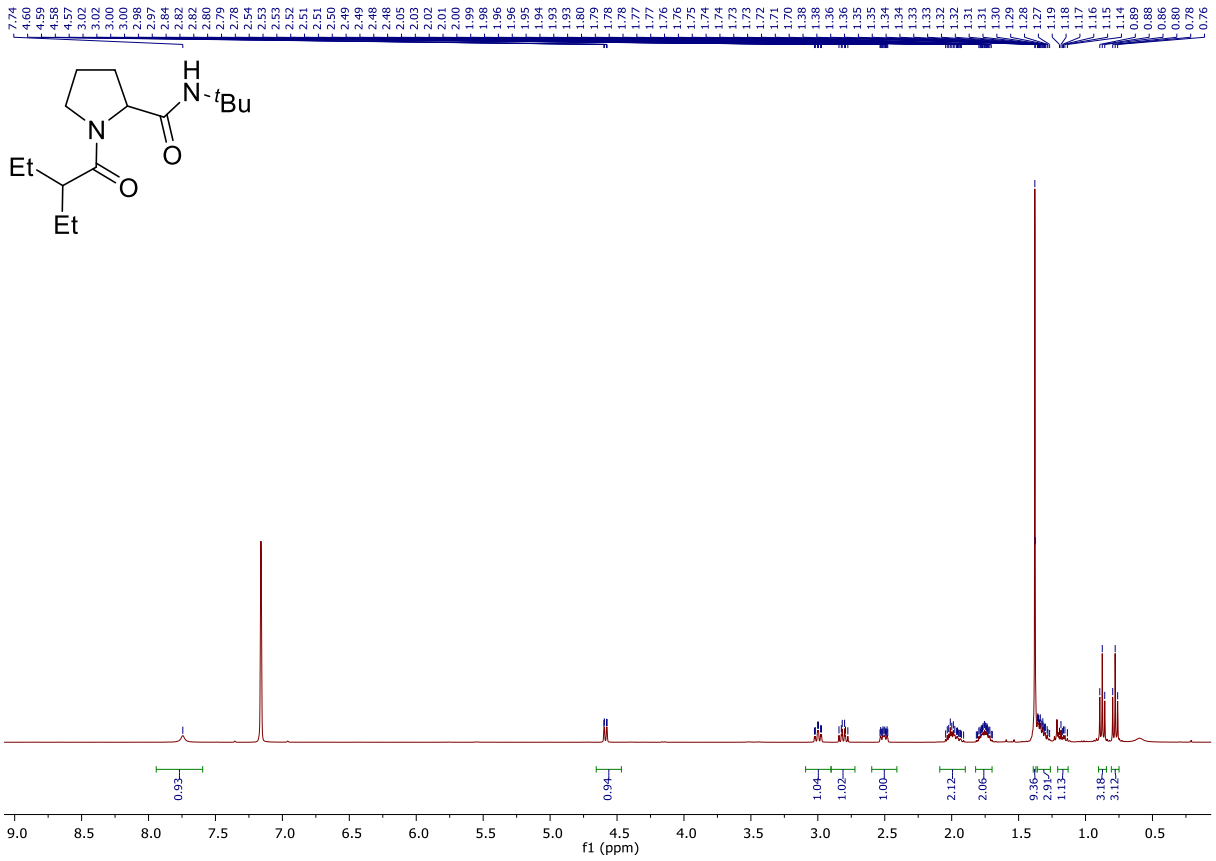
^{1}H NMR of **6** in C_6D_6



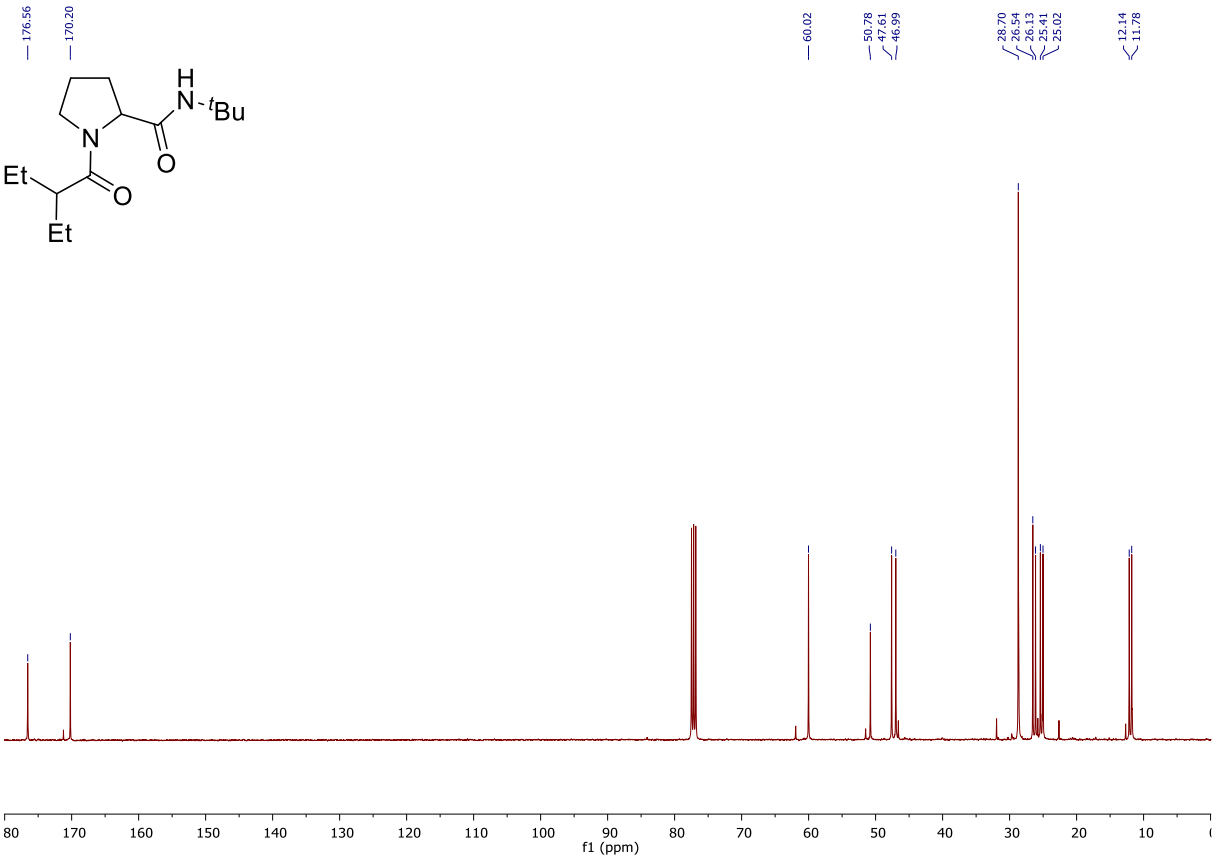
^{13}C NMR of **6** in $CDCl_3$



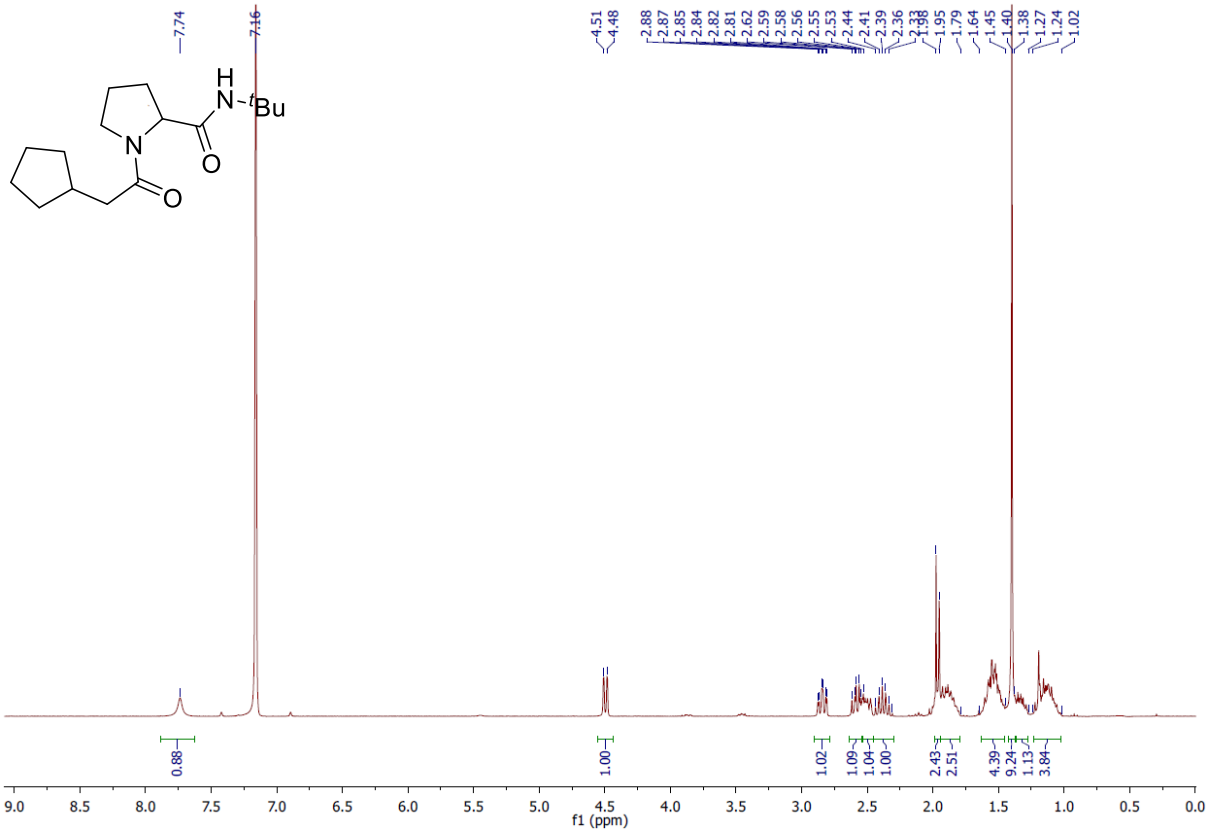
^{1}H NMR of **7** in C_6D_6



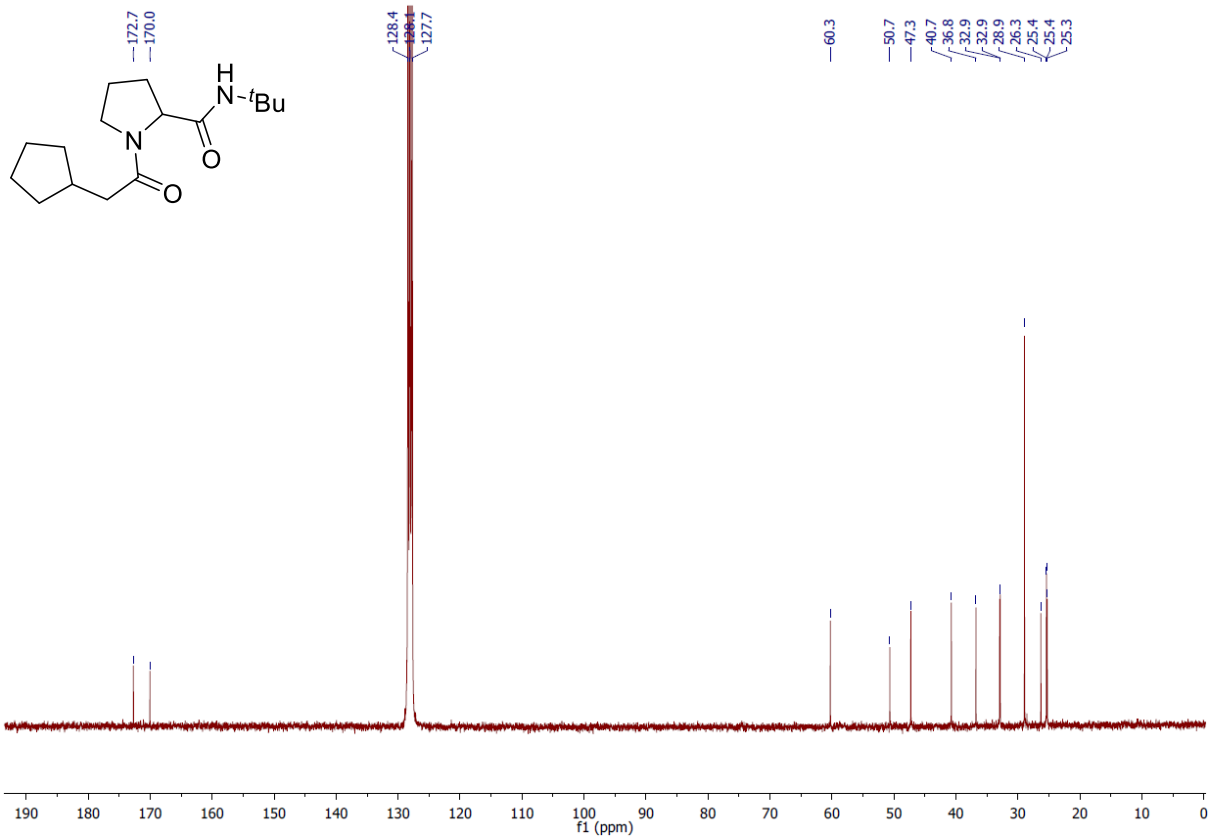
^{13}C NMR of **7** in $CDCl_3$



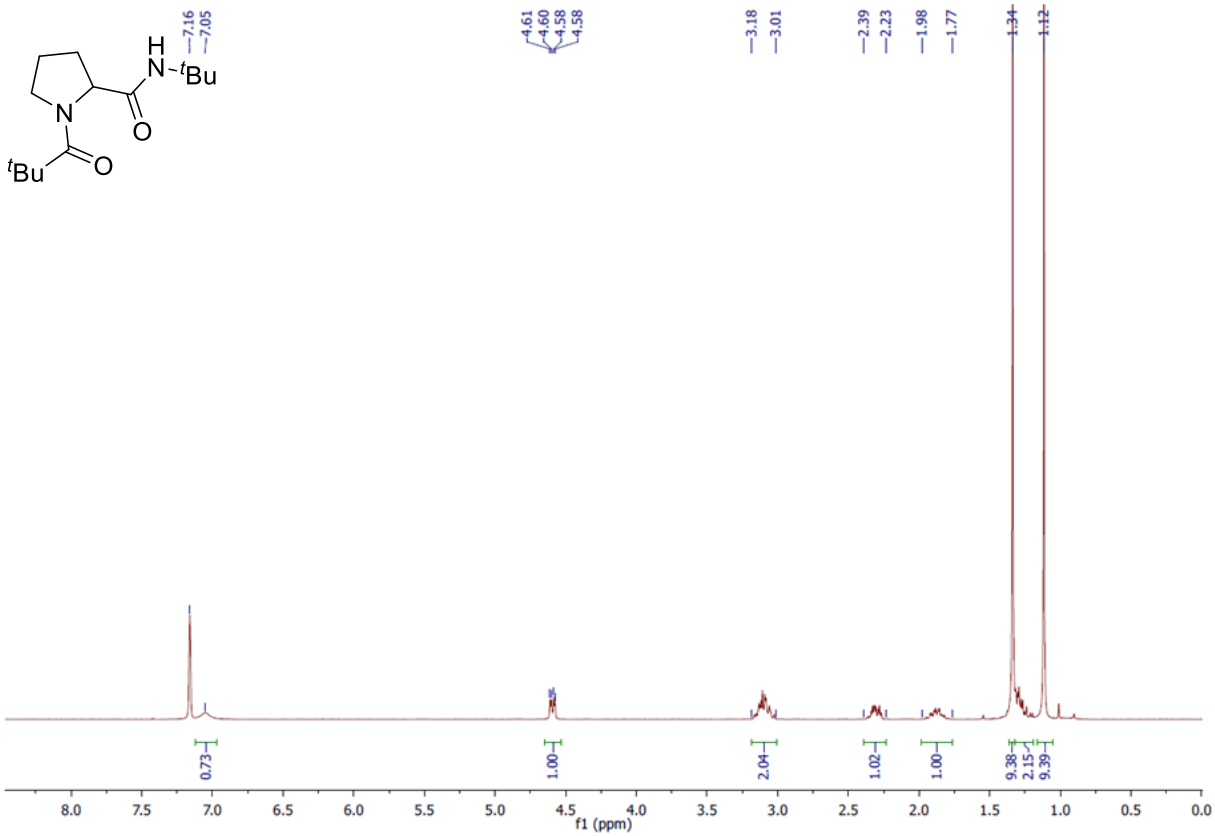
^{1}H NMR of **8** in C_6D_6



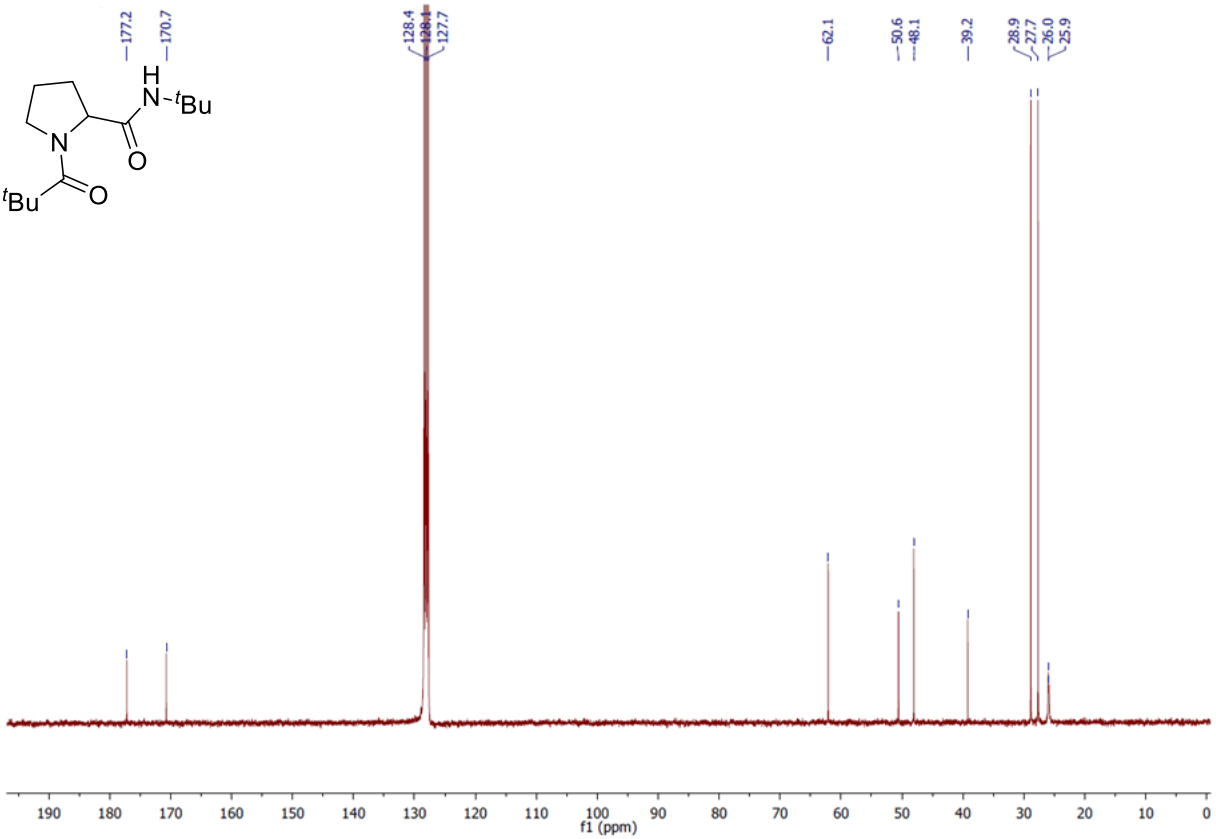
^{13}C NMR of **8** in C_6D_6



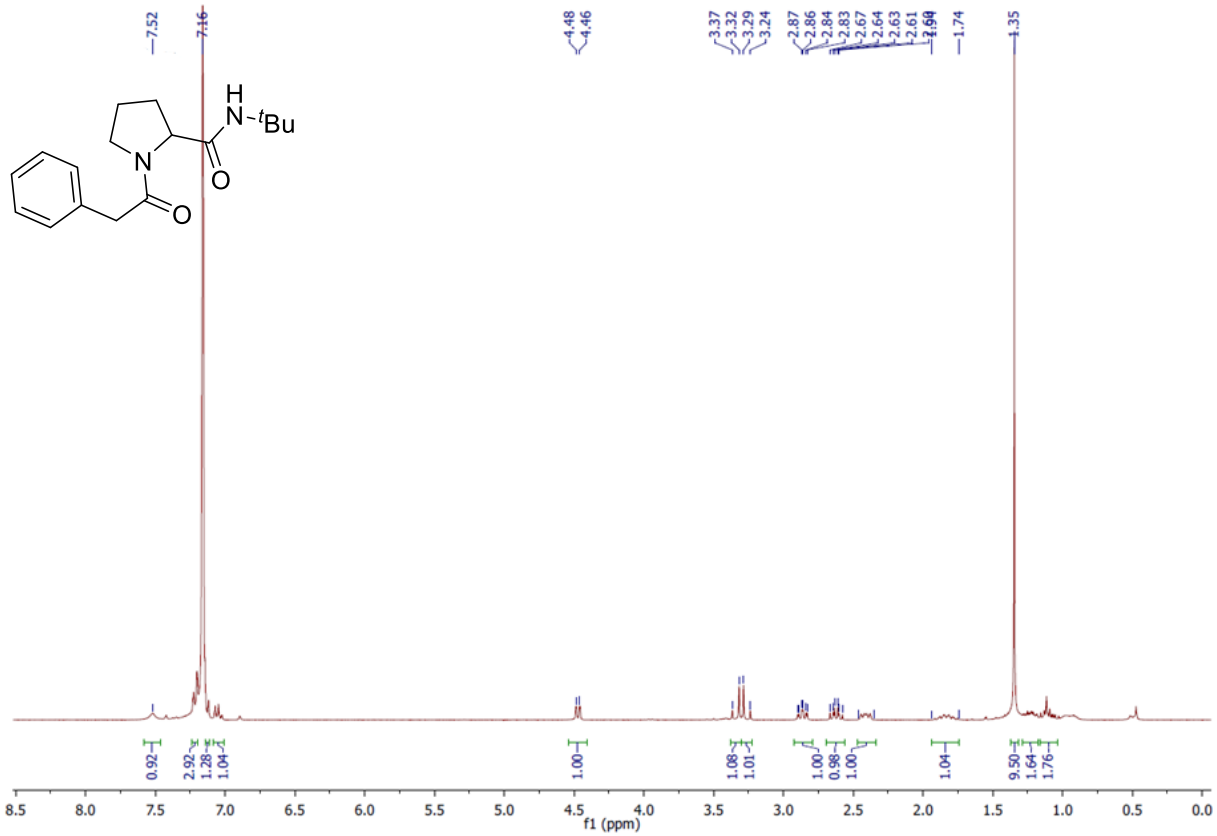
^{1}H NMR of **9** in C_6D_6



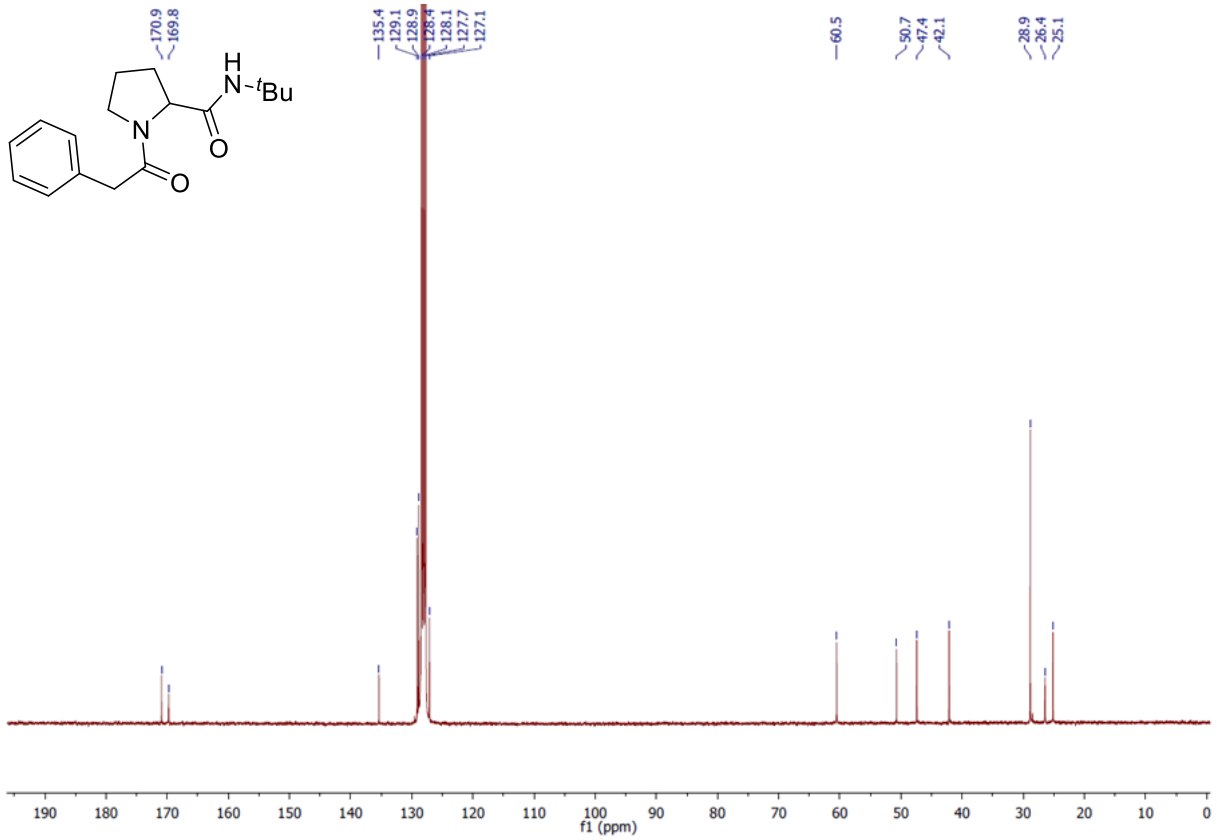
^{13}C NMR of **9** in C_6D_6



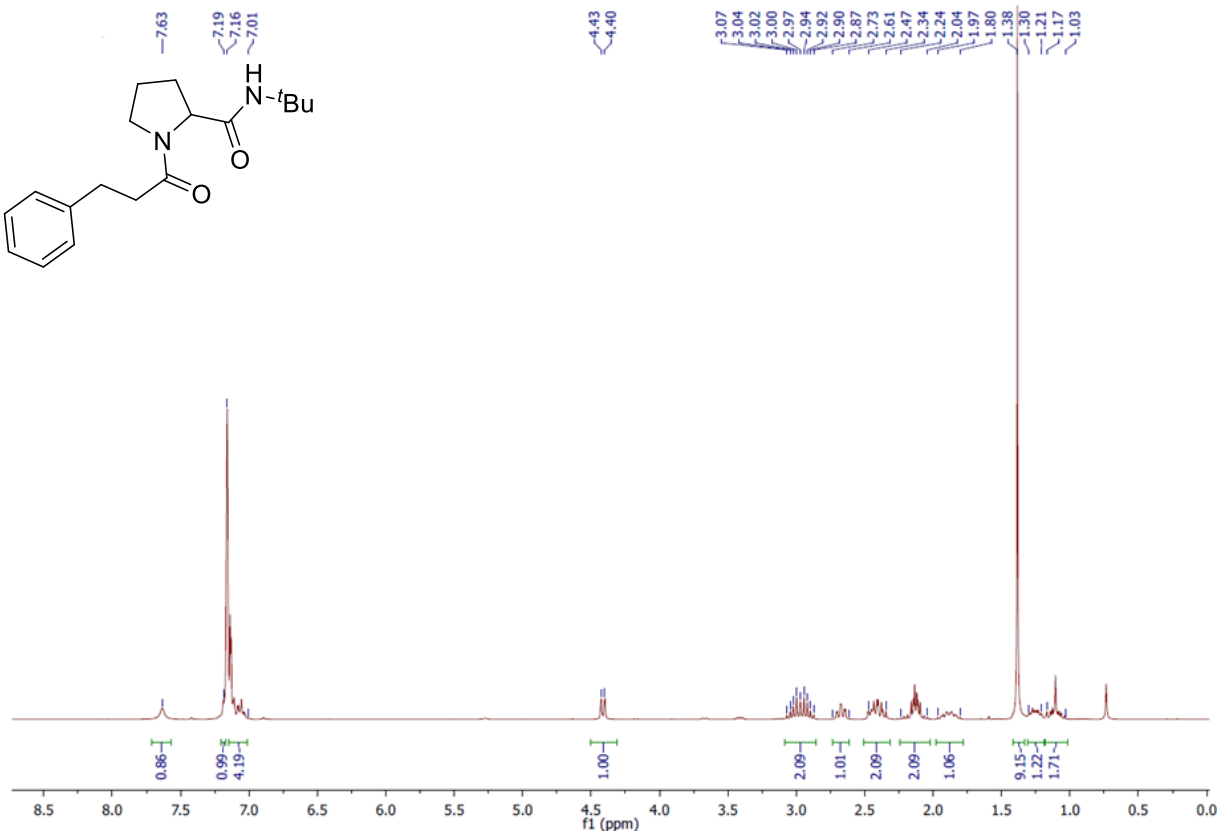
^{1}H NMR of **10** in C_6D_6



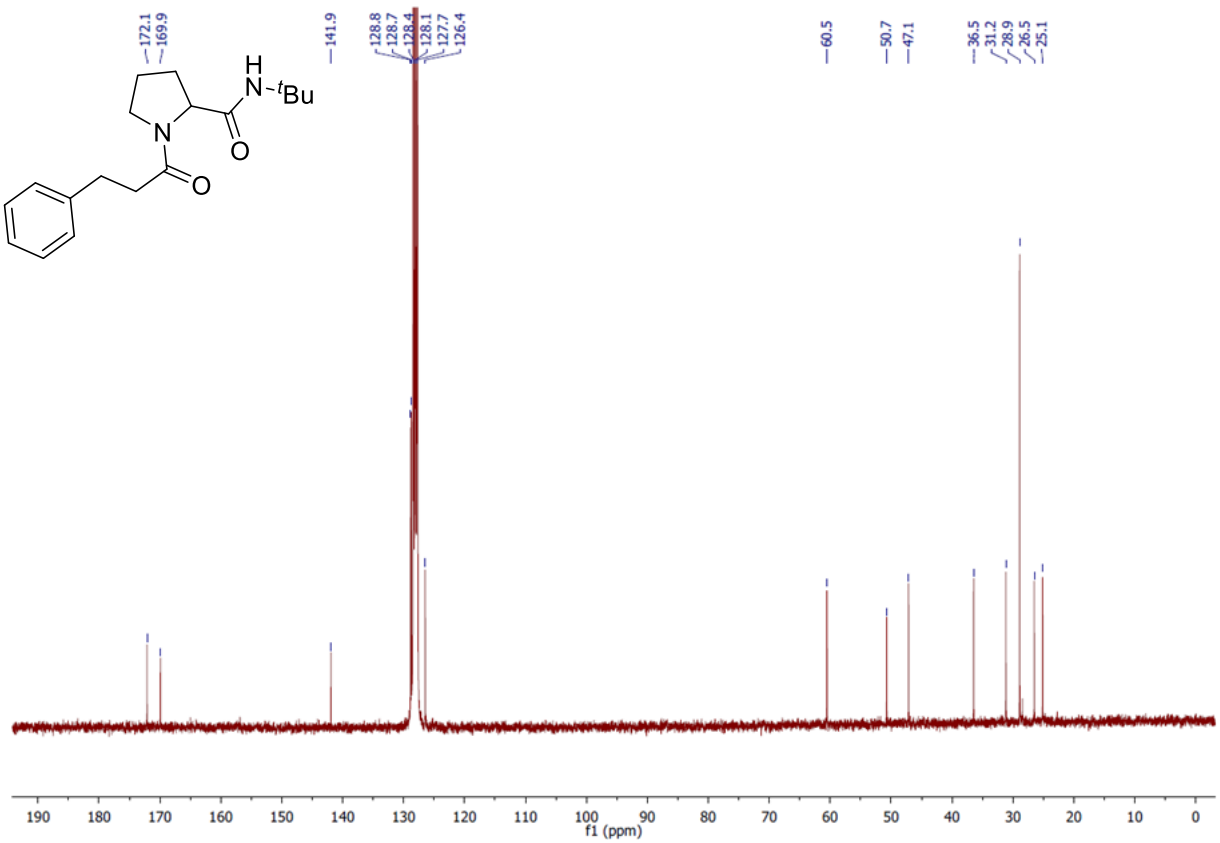
^{13}C NMR of **10** in C_6D_6



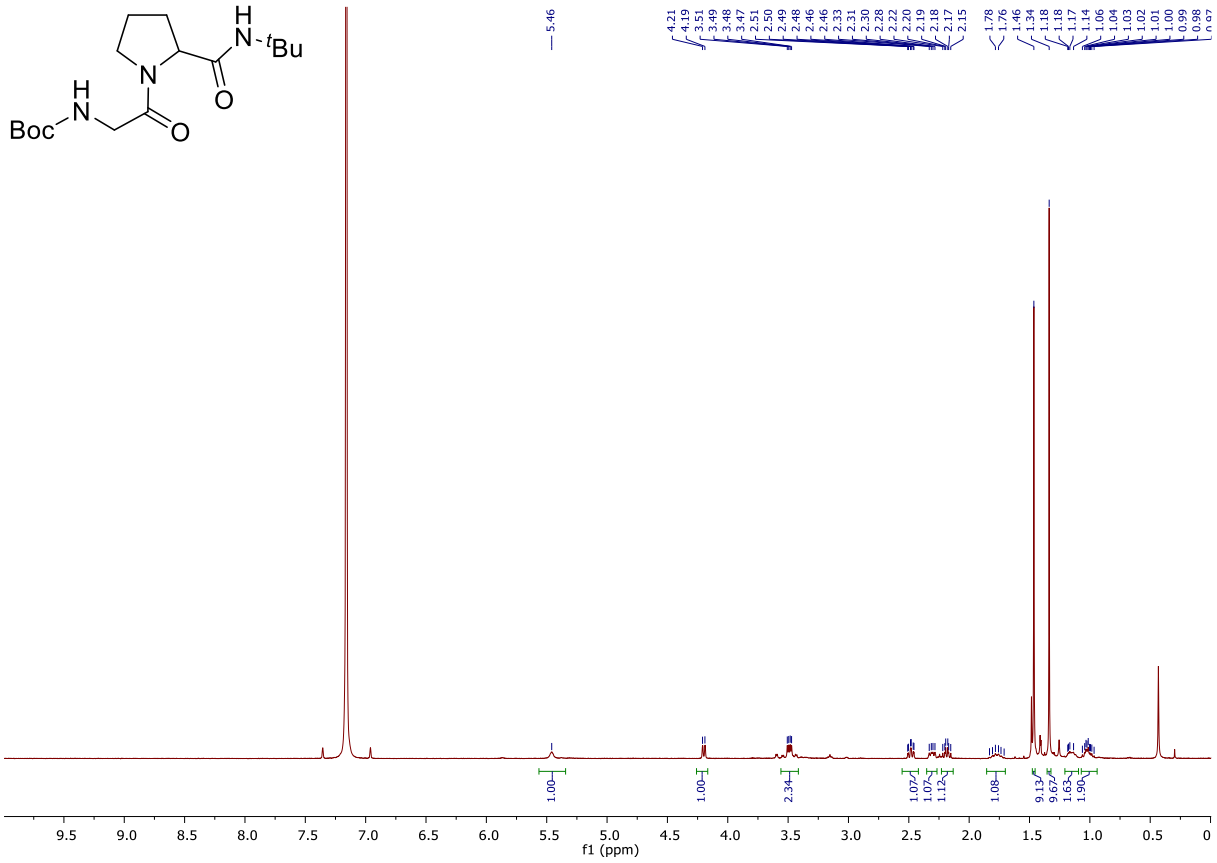
^{1}H NMR of **11** in C_6D_6



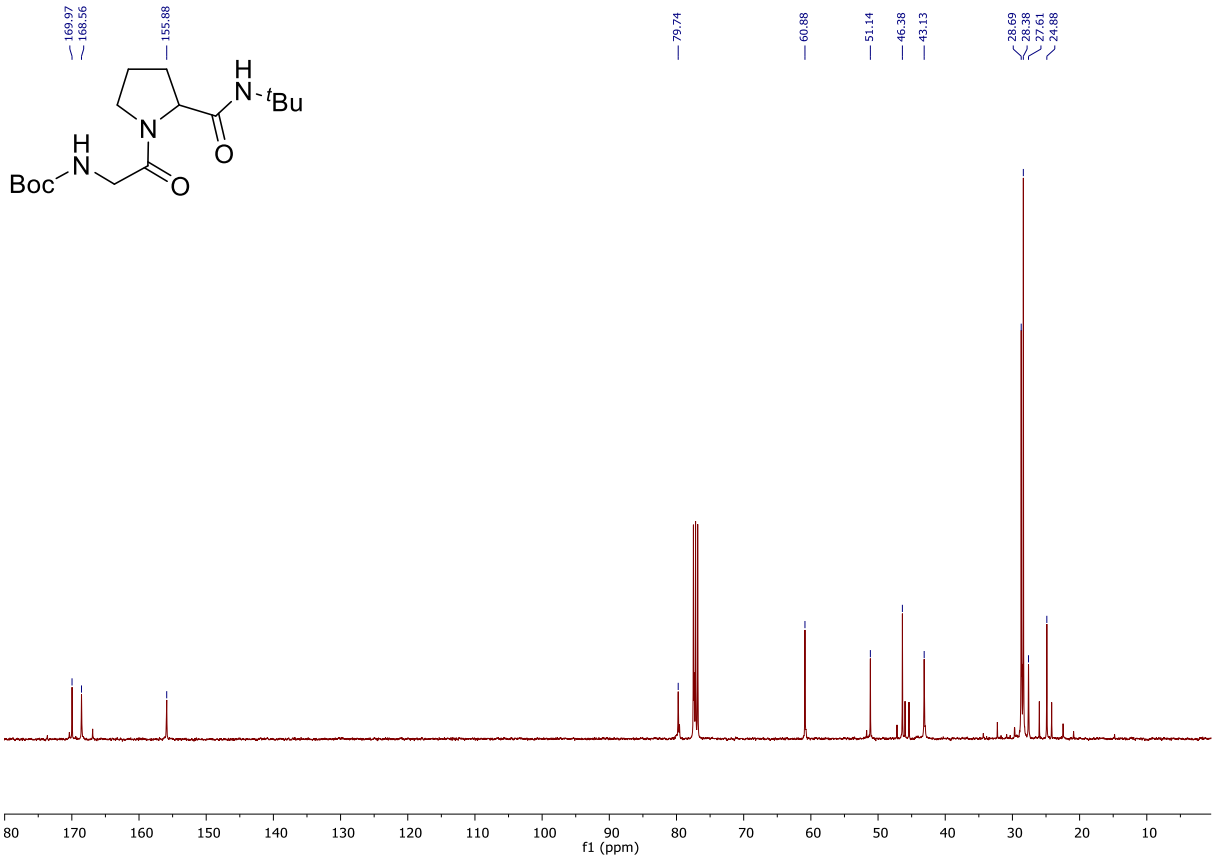
^{13}C NMR of **11** in C_6D_6



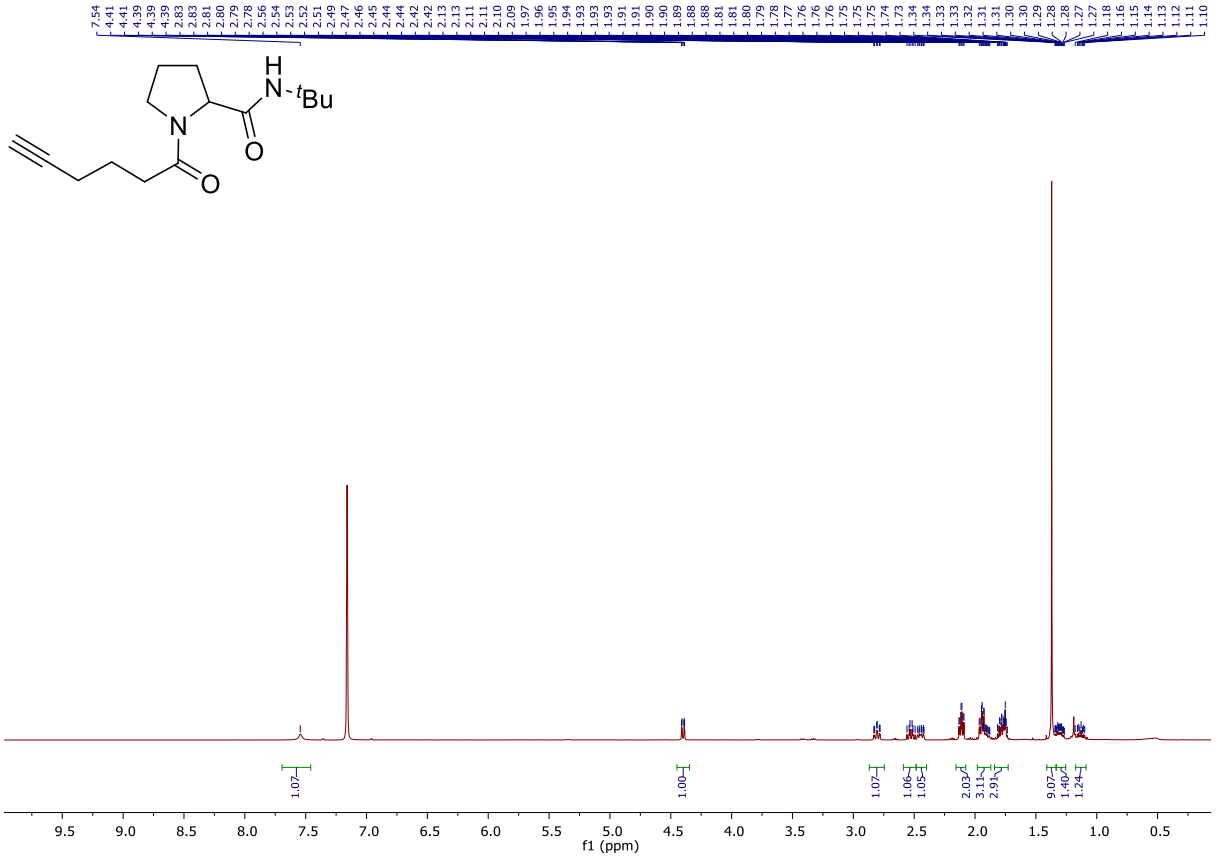
^{1}H NMR of **12** in C_6D_6



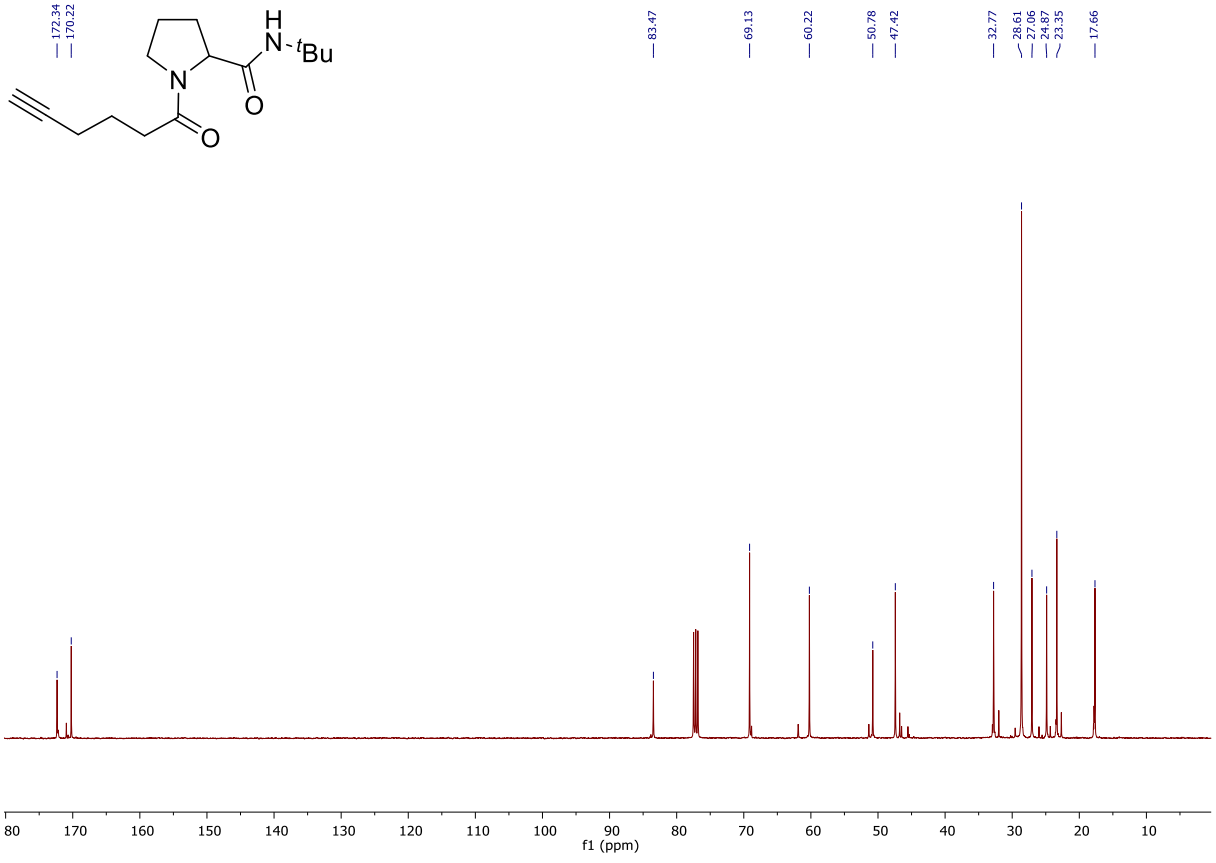
^{13}C NMR of **12** in $CDCl_3$



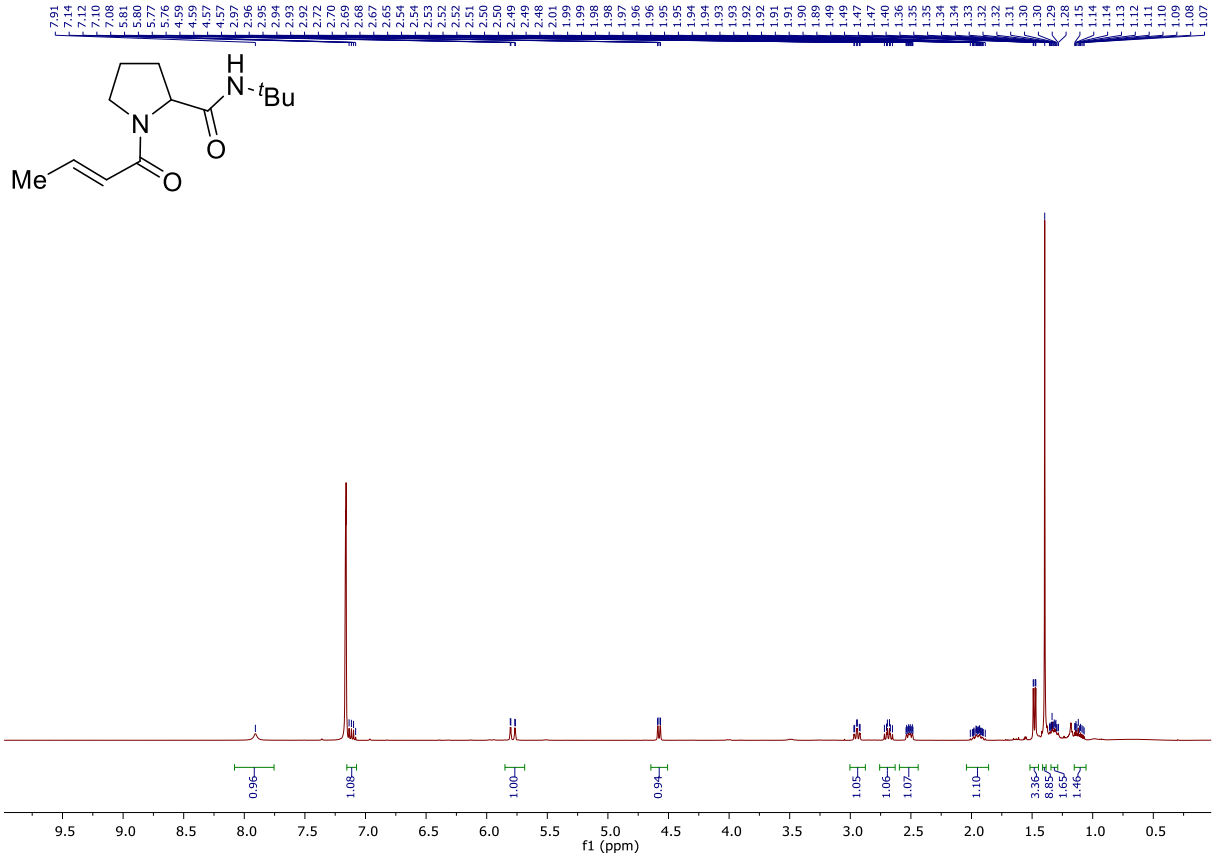
^{1}H NMR of **13** in C_6D_6



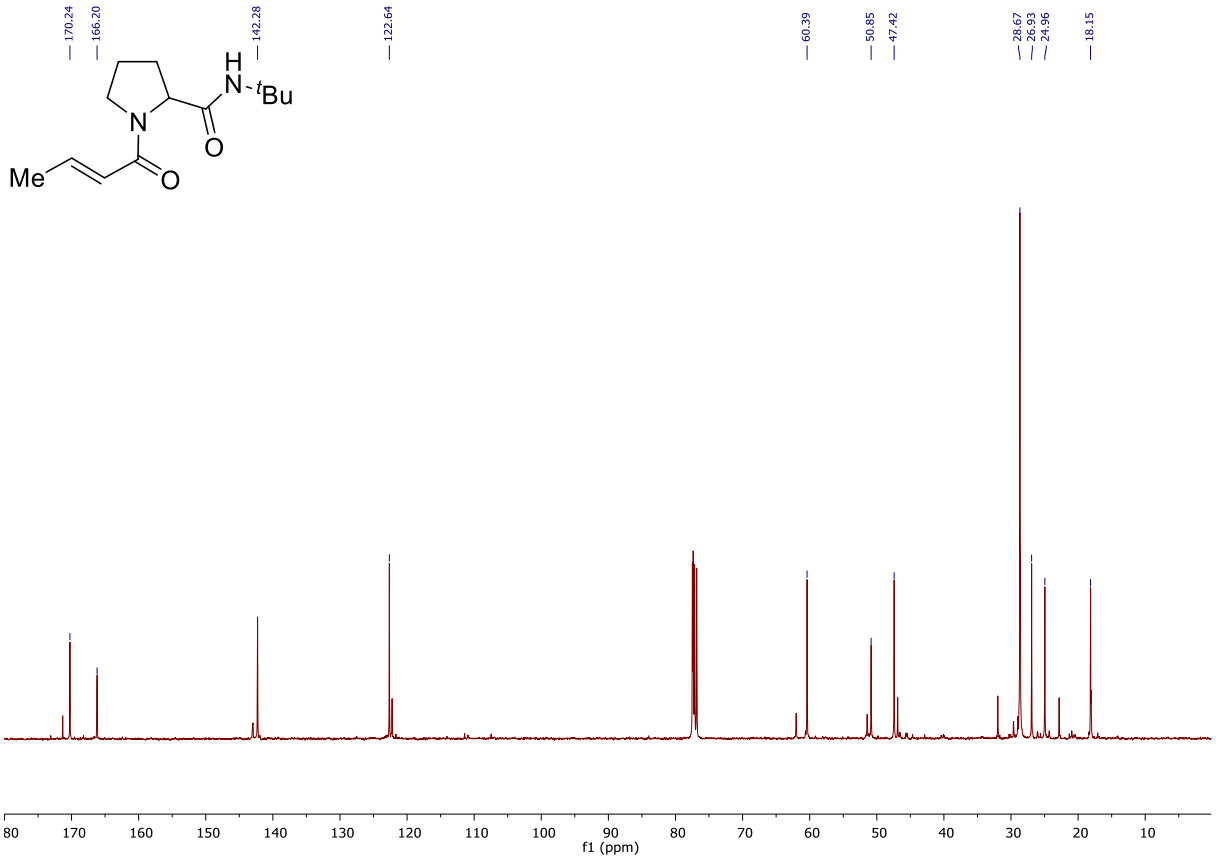
^{13}C NMR of **13** in $CDCl_3$



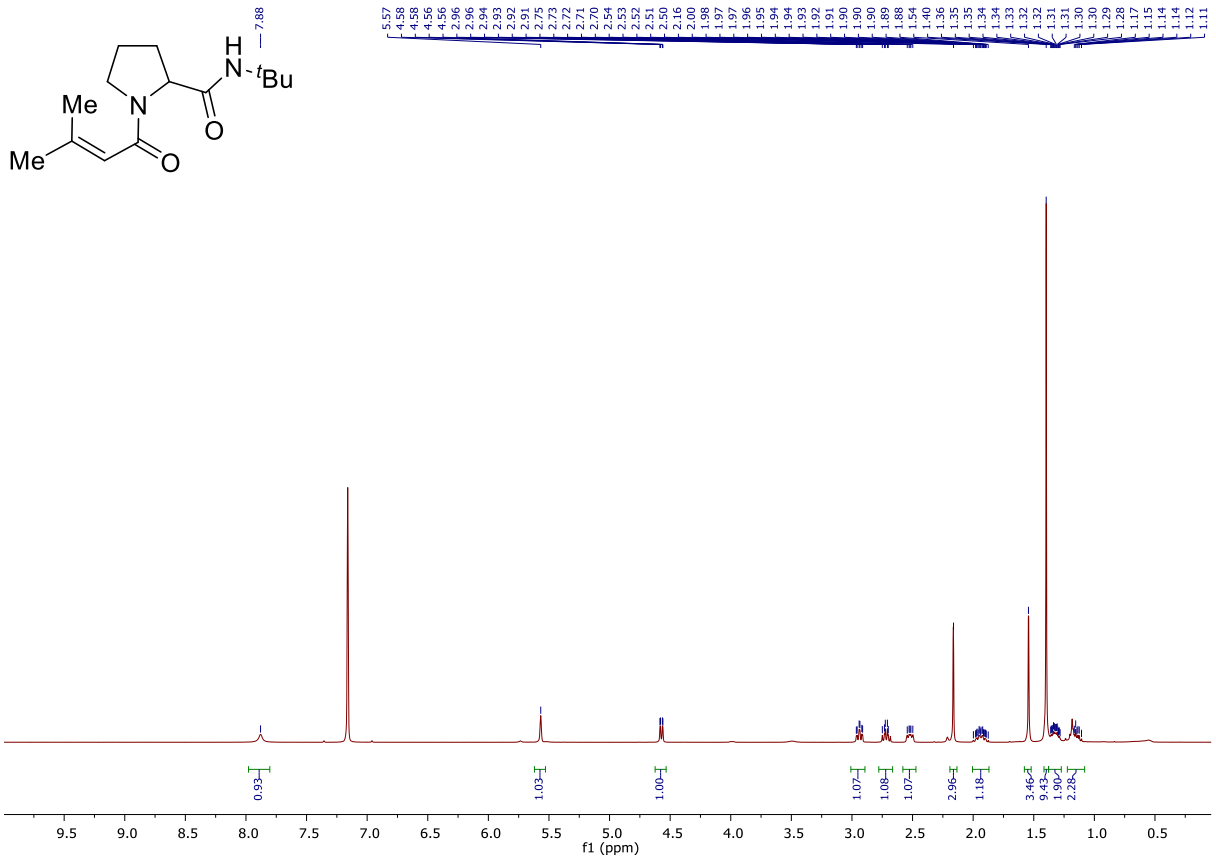
^{1}H NMR of **14** in C_6D_6



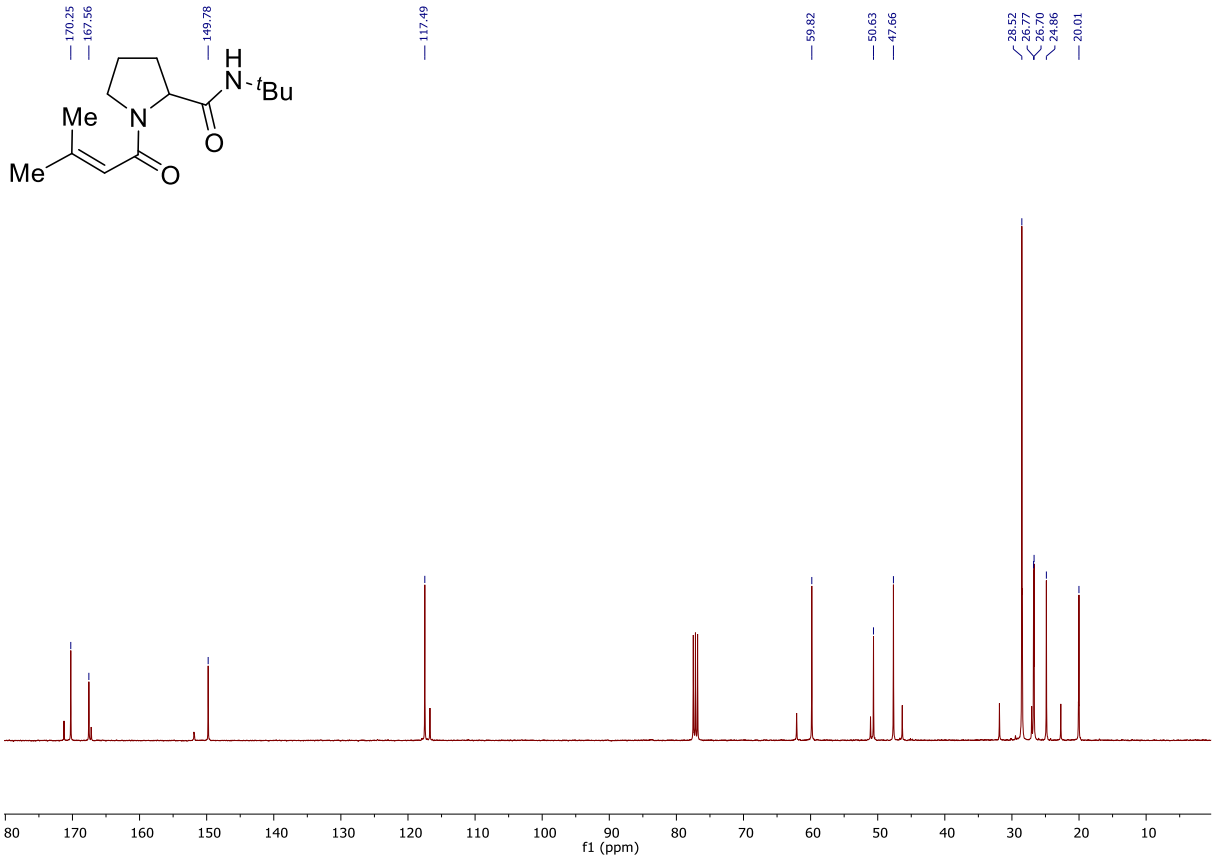
^{13}C NMR of **14** in $CDCl_3$



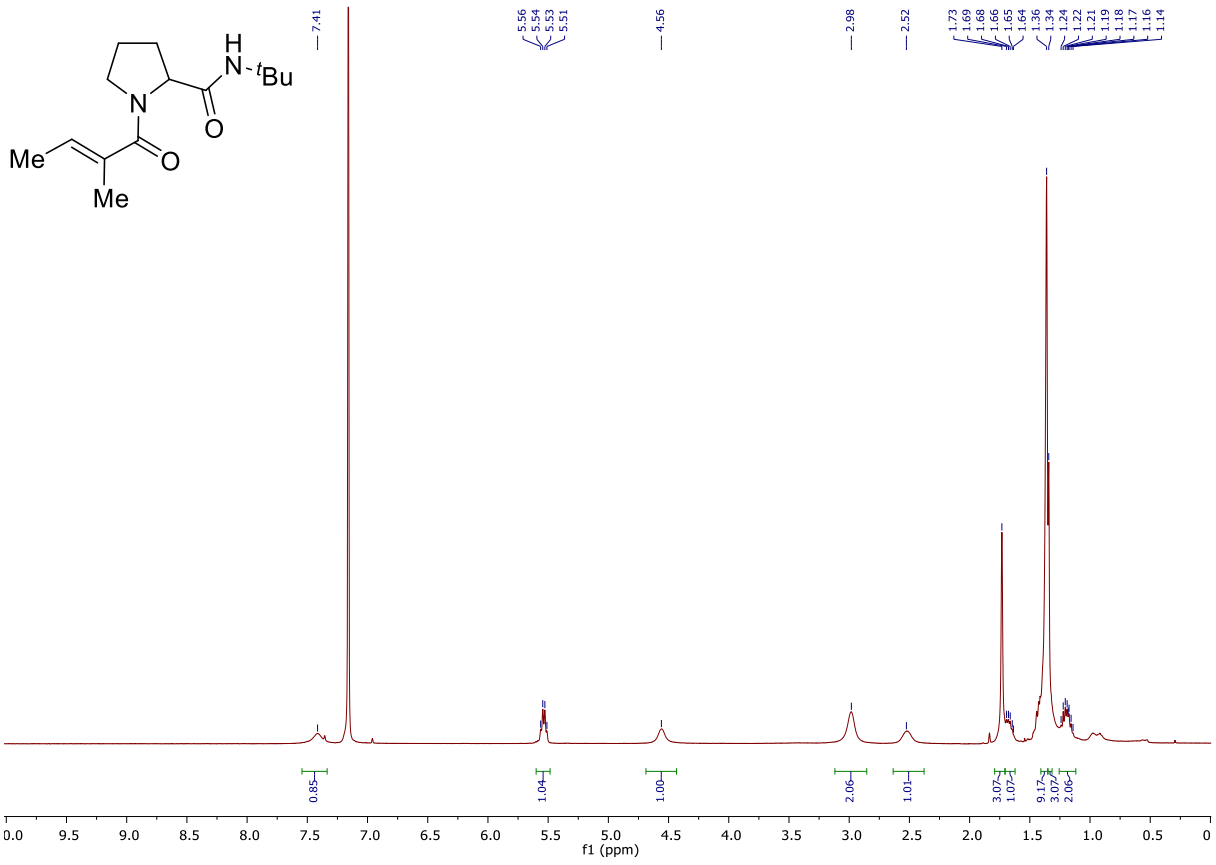
^{1}H NMR of **15** in C_6D_6



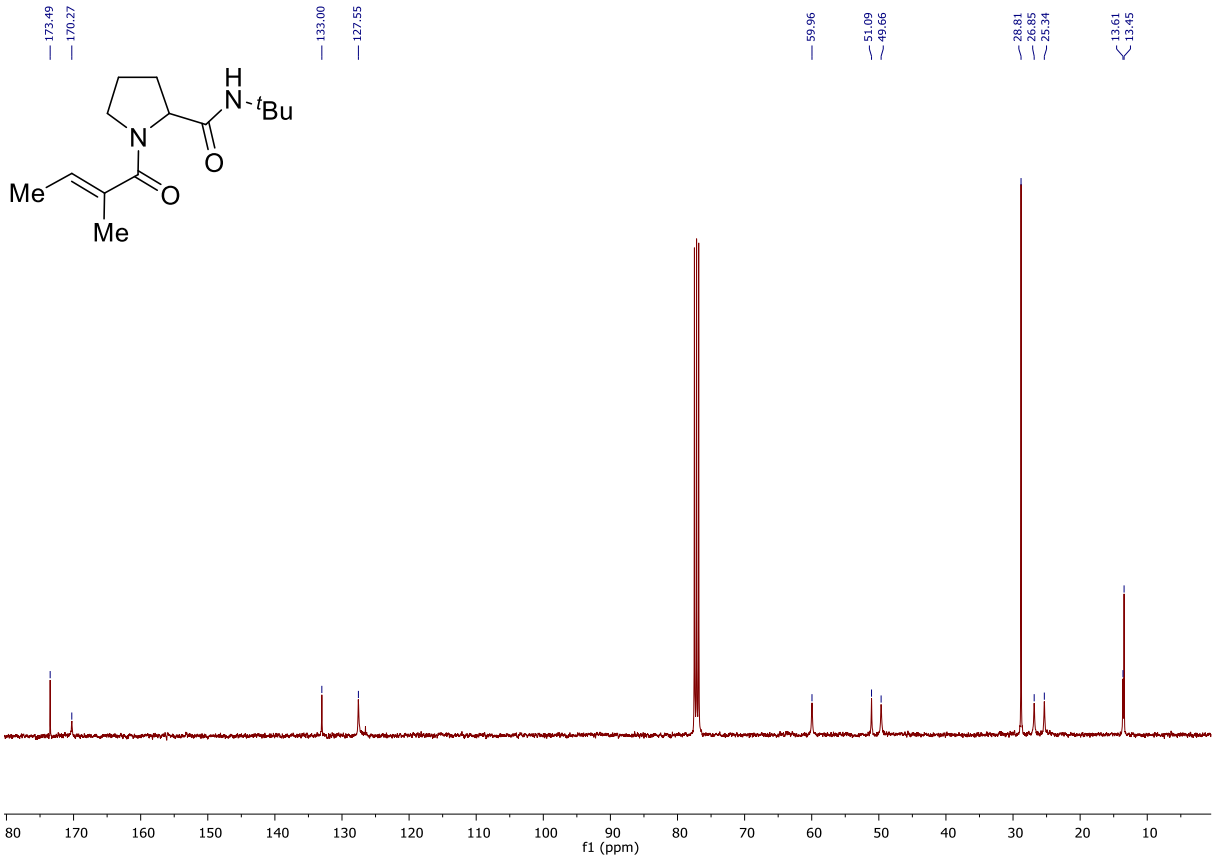
^{13}C NMR of **15** in $CDCl_3$



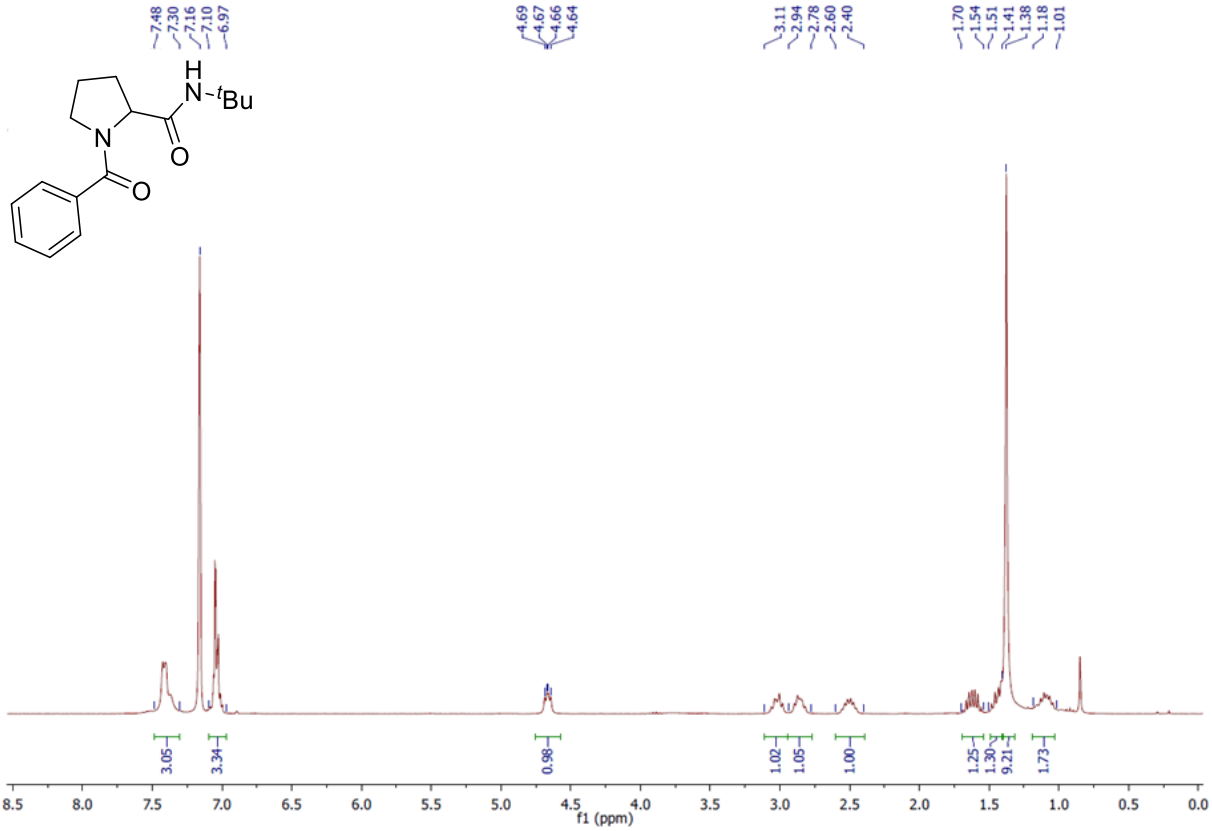
^{1}H NMR of **16**



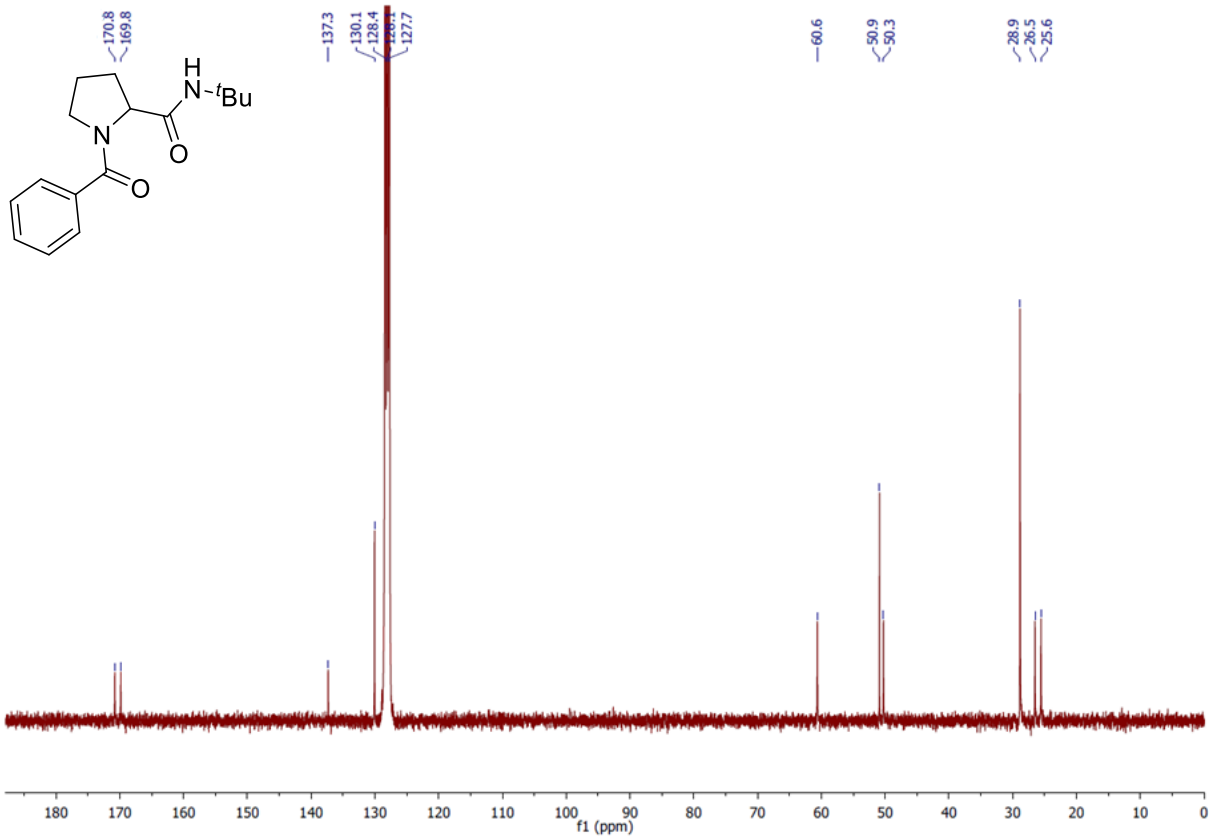
^{13}C NMR of **16** in $CDCl_3$



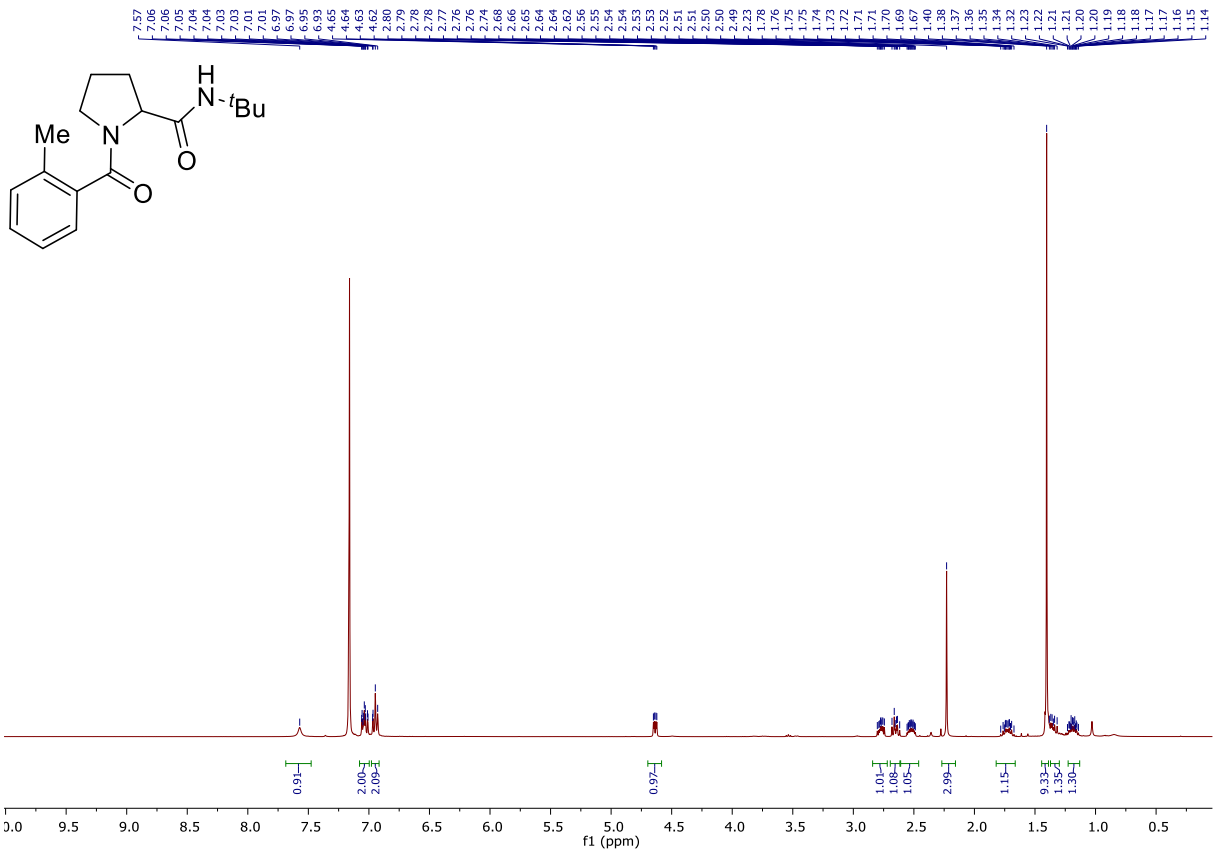
^{1}H NMR of **17** in C_6D_6



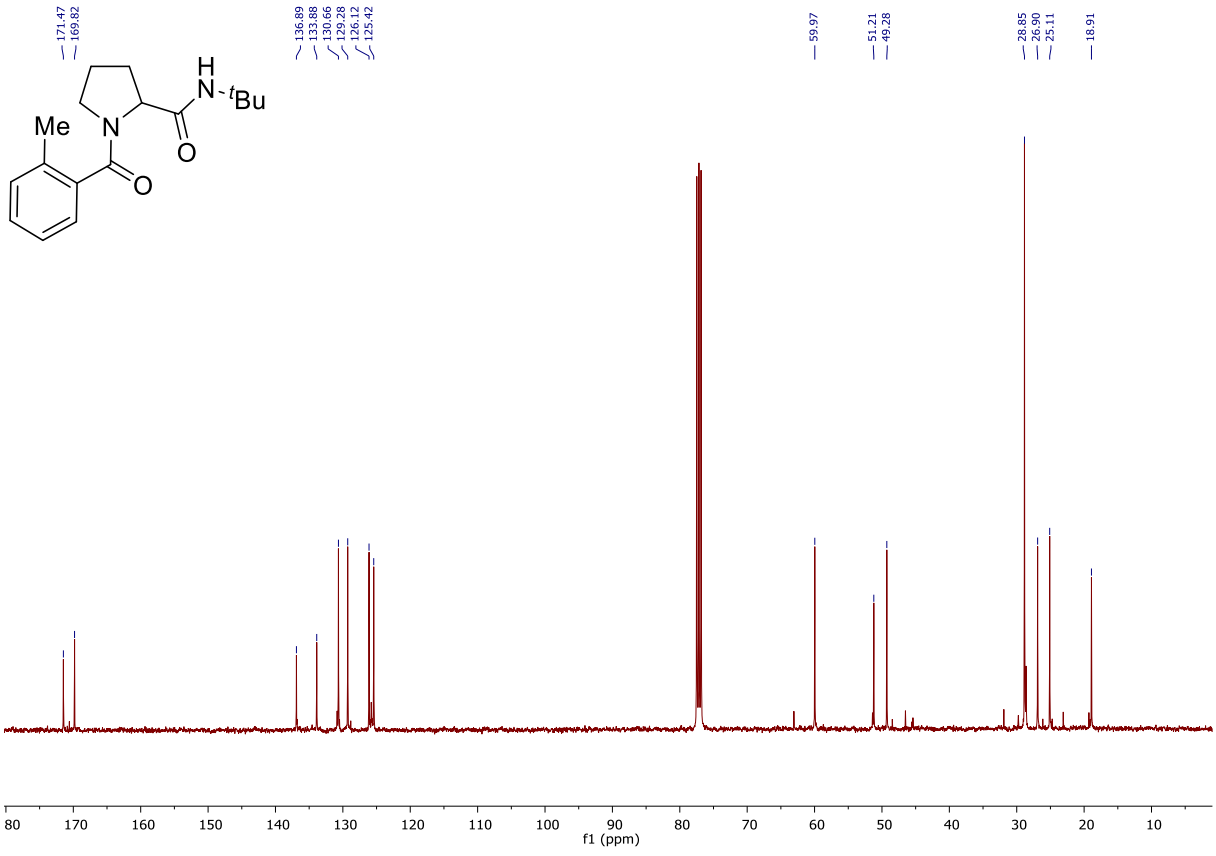
^{13}C NMR of **17** in C_6D_6



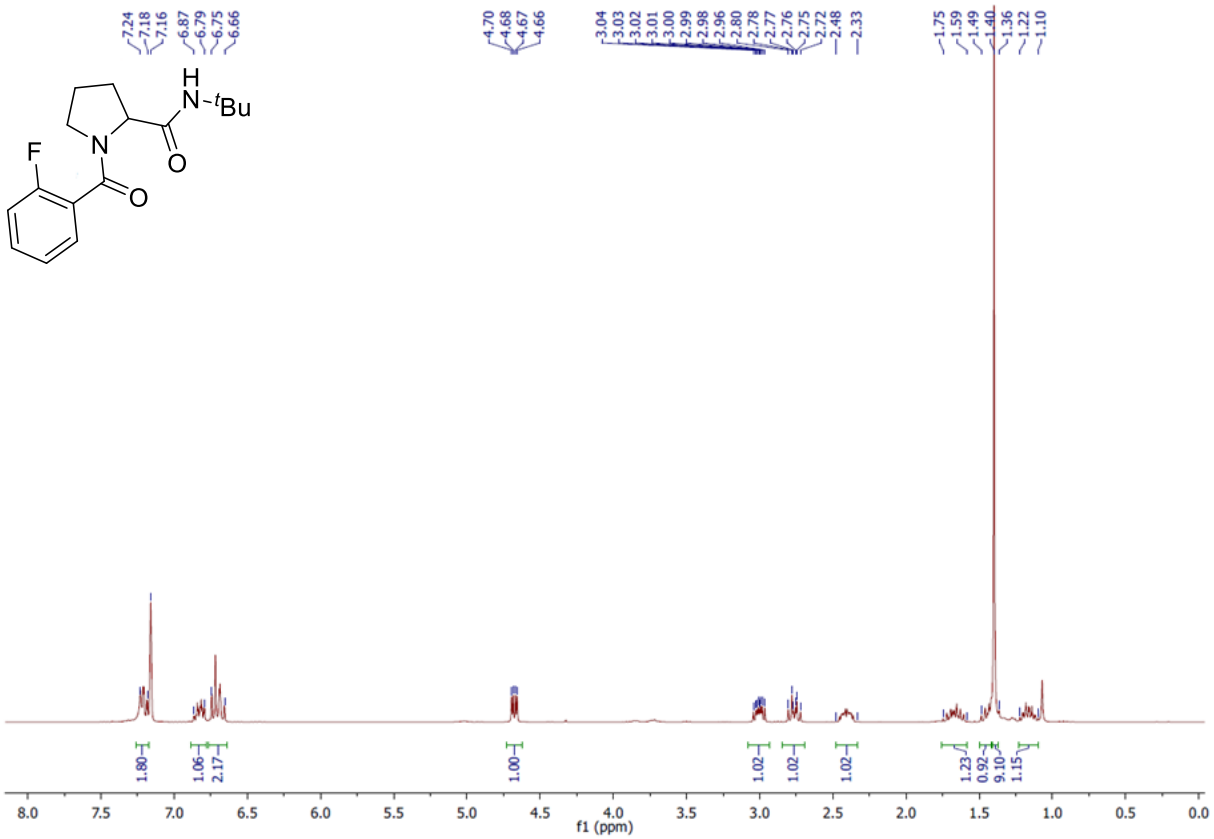
^{1}H NMR of **18** in C_6D_6



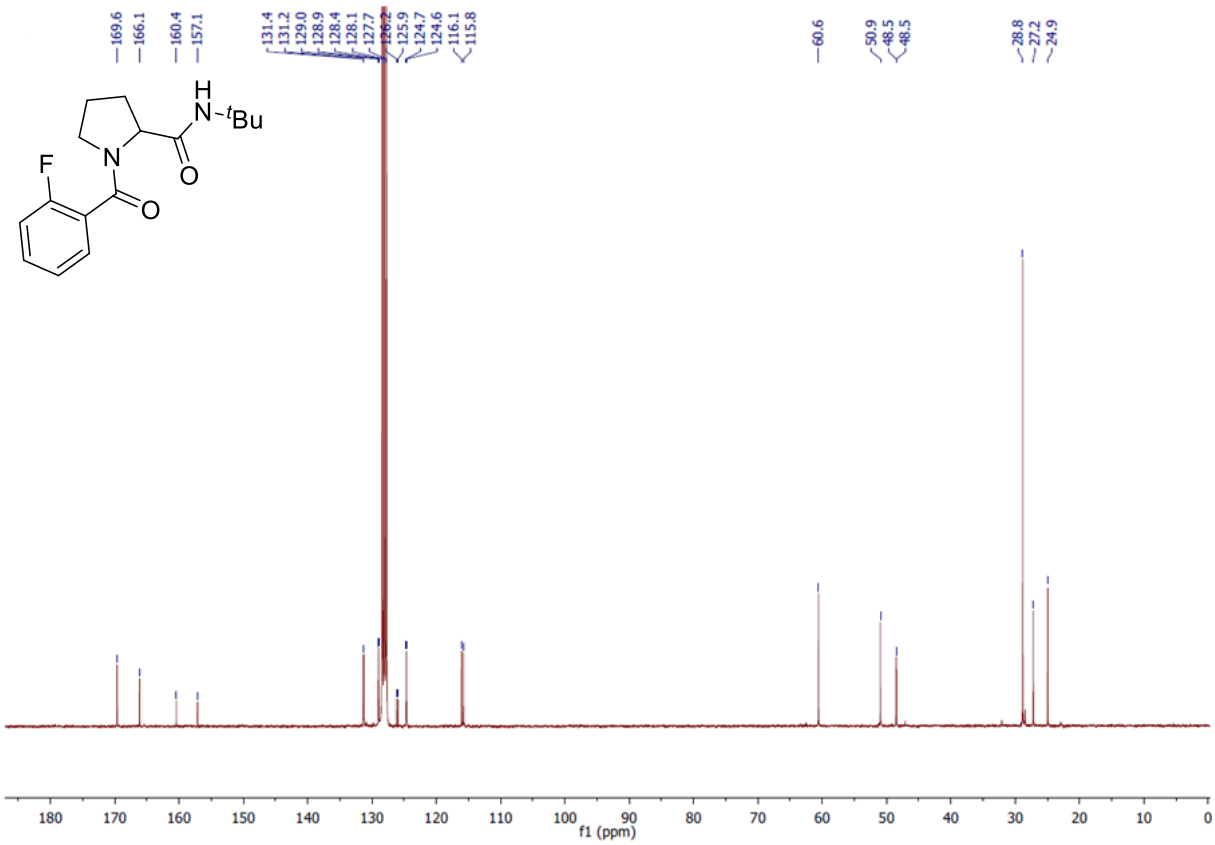
^{13}C NMR of **18** in $CDCl_3$



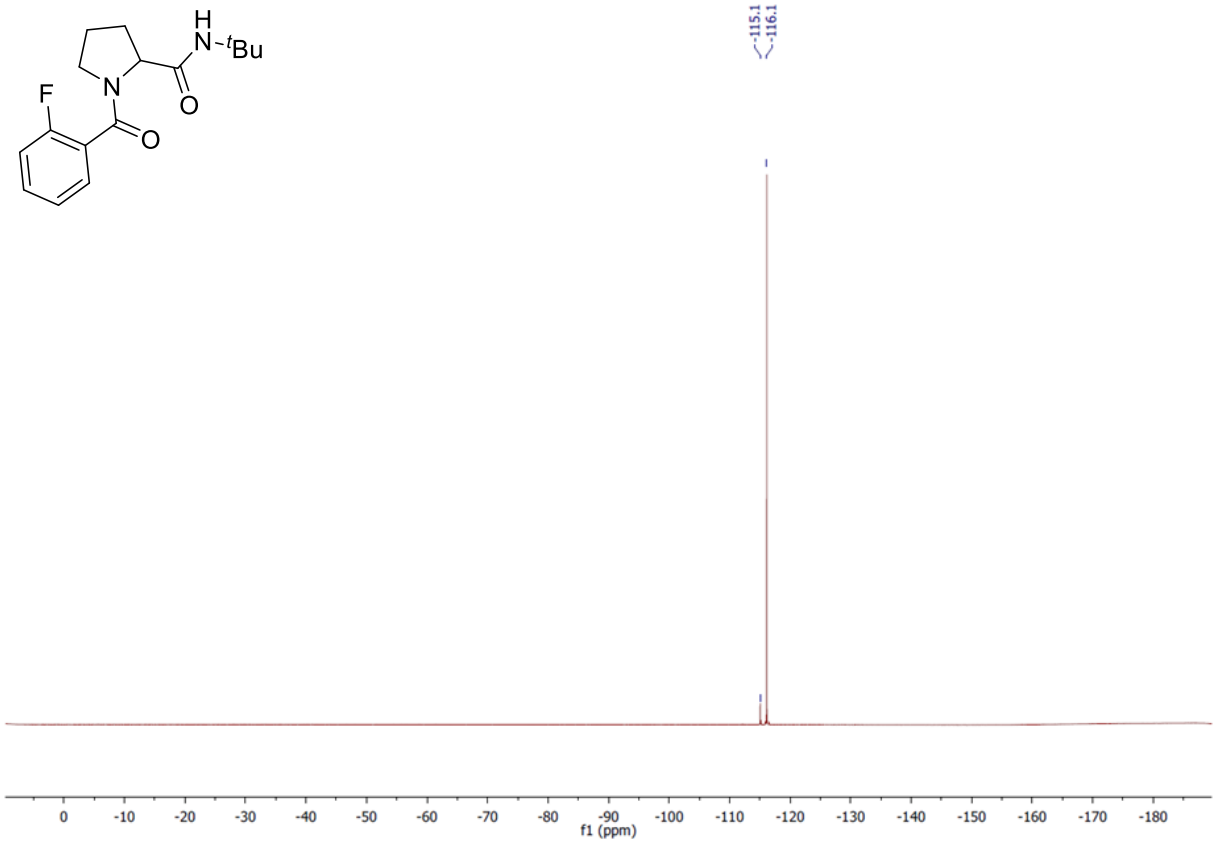
^{1}H NMR of **19** in C_6D_6



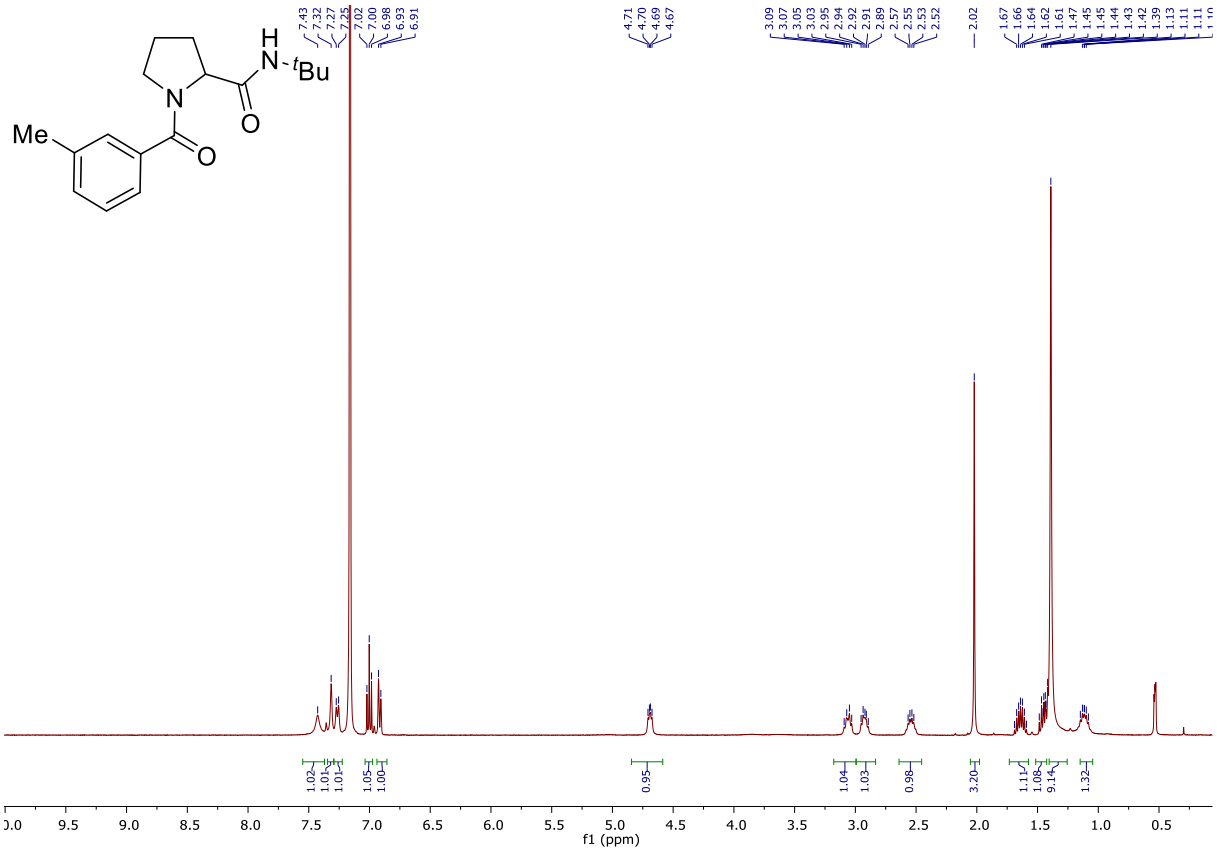
^{13}C NMR of **19** in C_6D_6



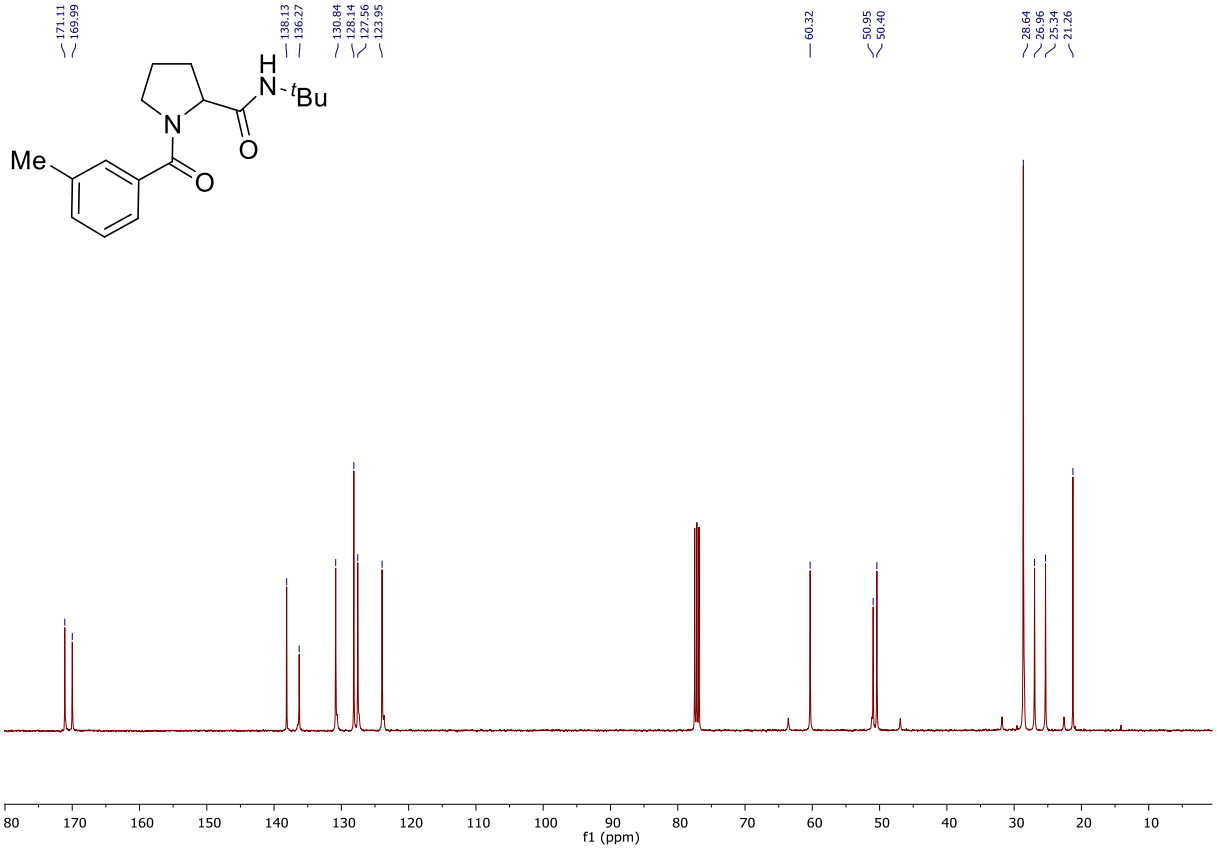
^{19}F NMR of **19** in C_6D_6



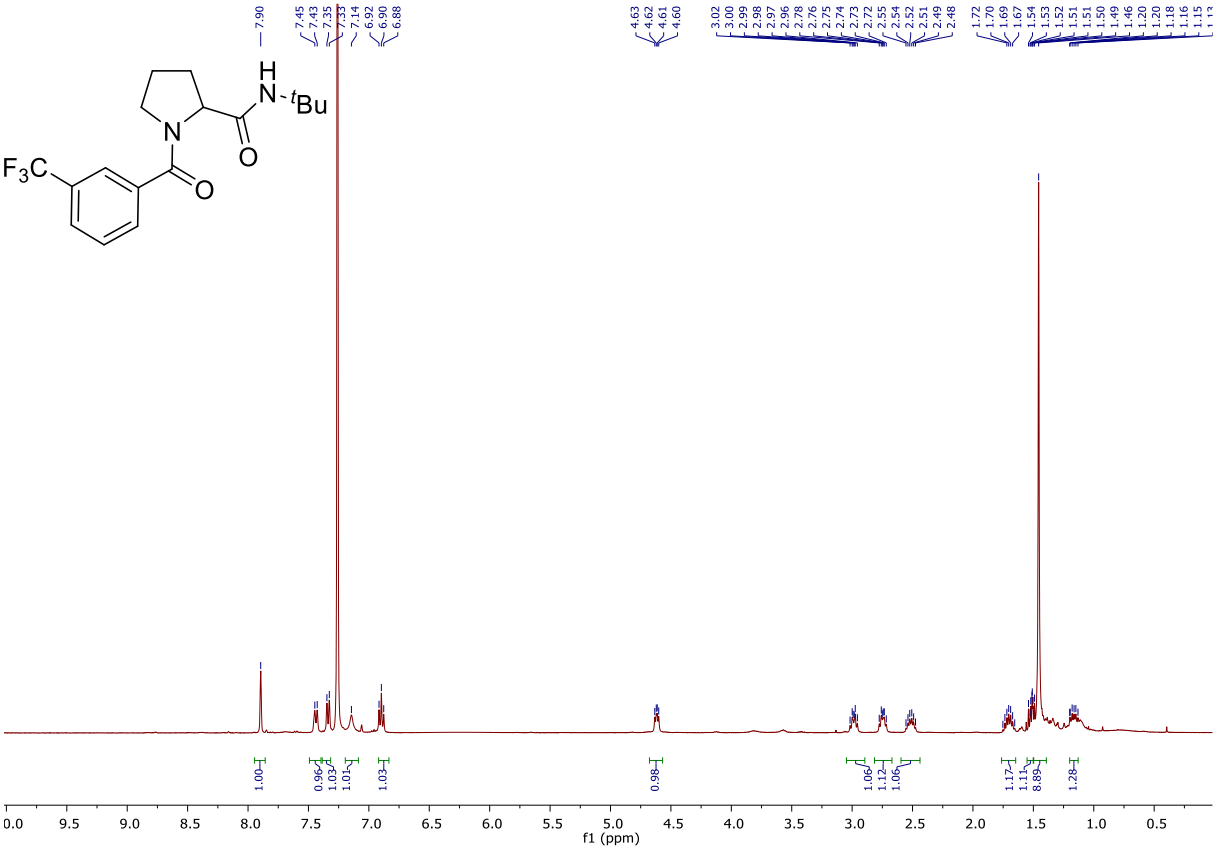
^{1}H NMR of **20** in C_6D_6



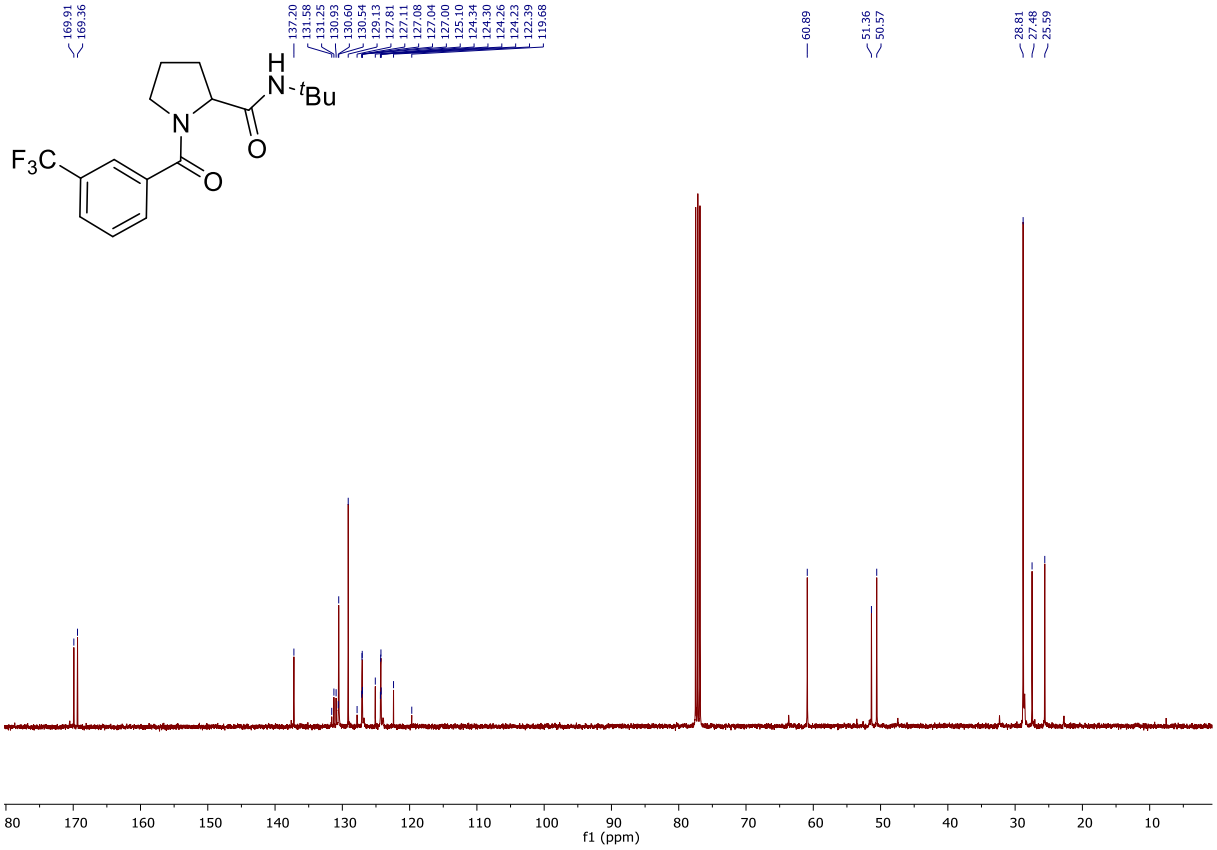
^{13}C NMR of **20** in $CDCl_3$



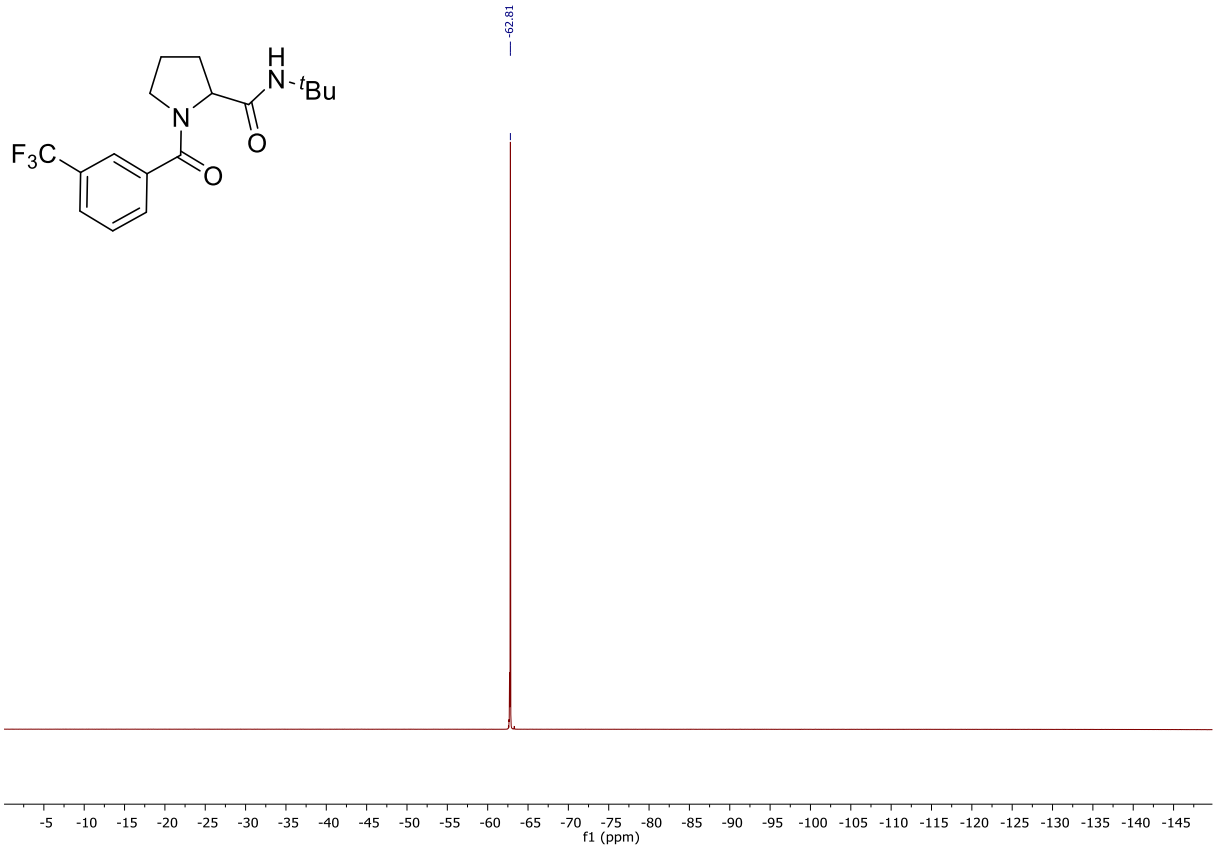
^{1}H NMR of **21** in C_6D_6



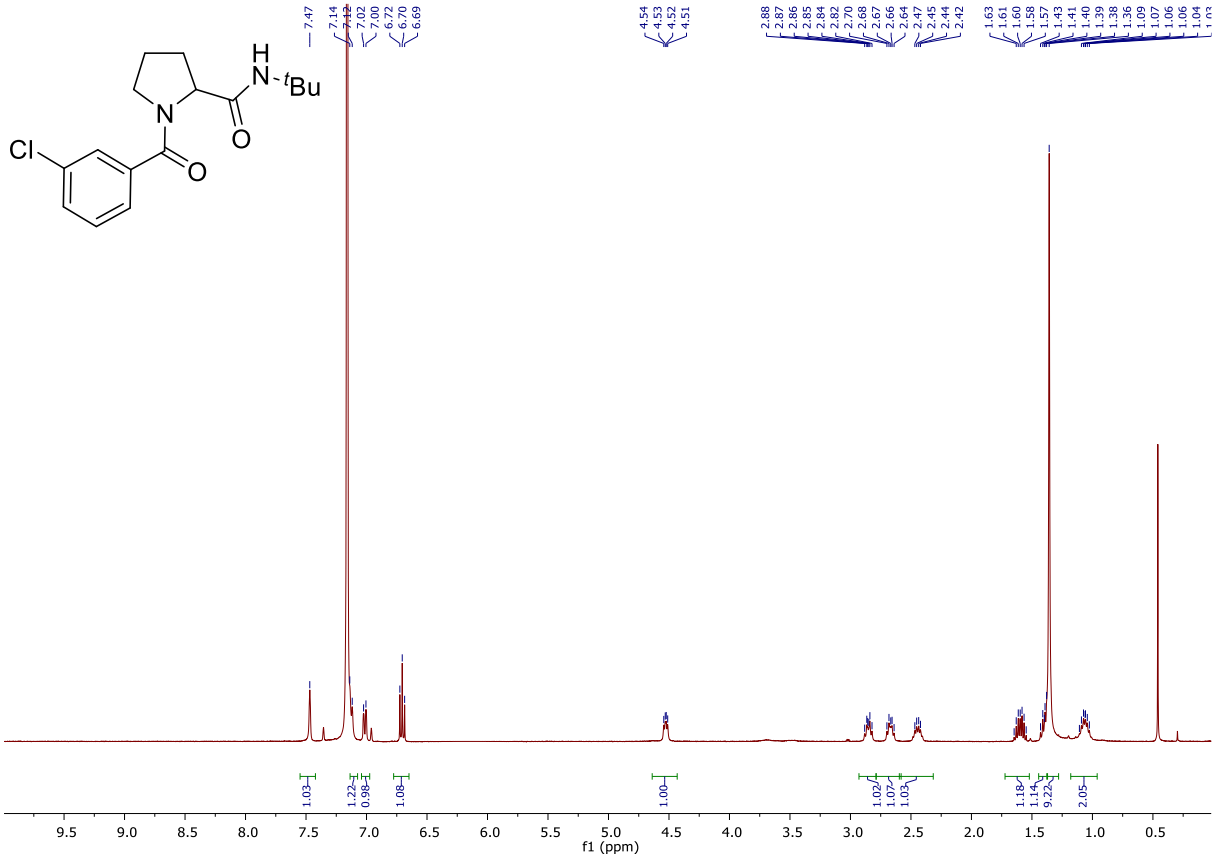
^{13}C NMR of **21** in $CDCl_3$



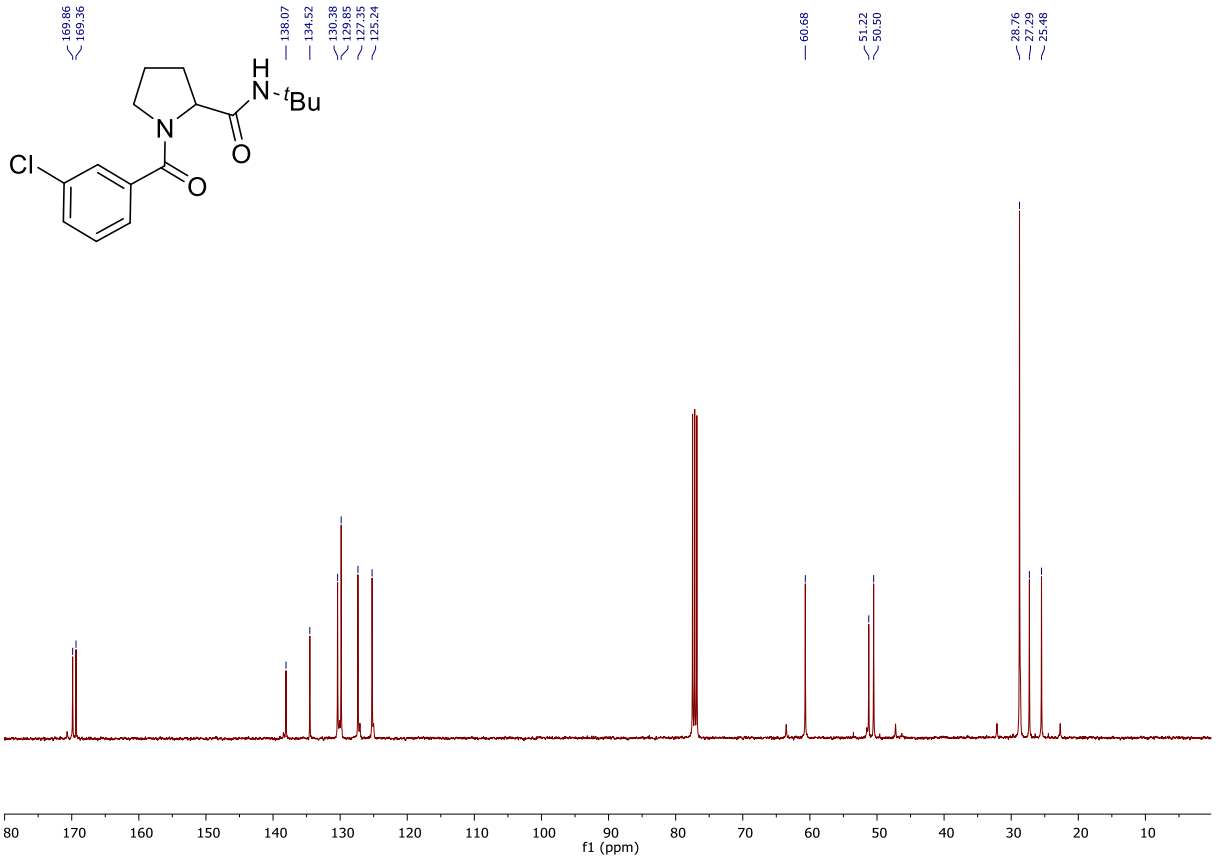
^{19}F NMR of **21** in $CDCl_3$



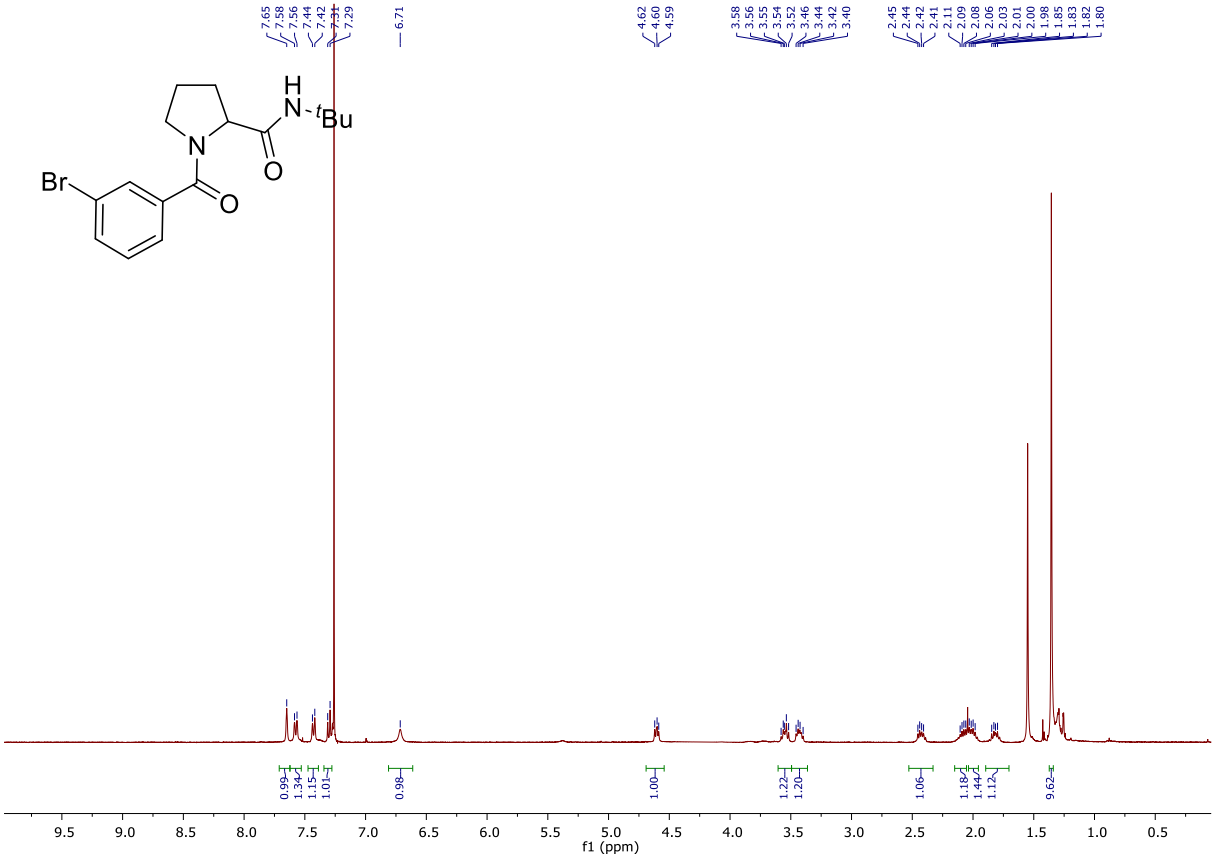
^{1}H NMR of **22** in C_6D_6



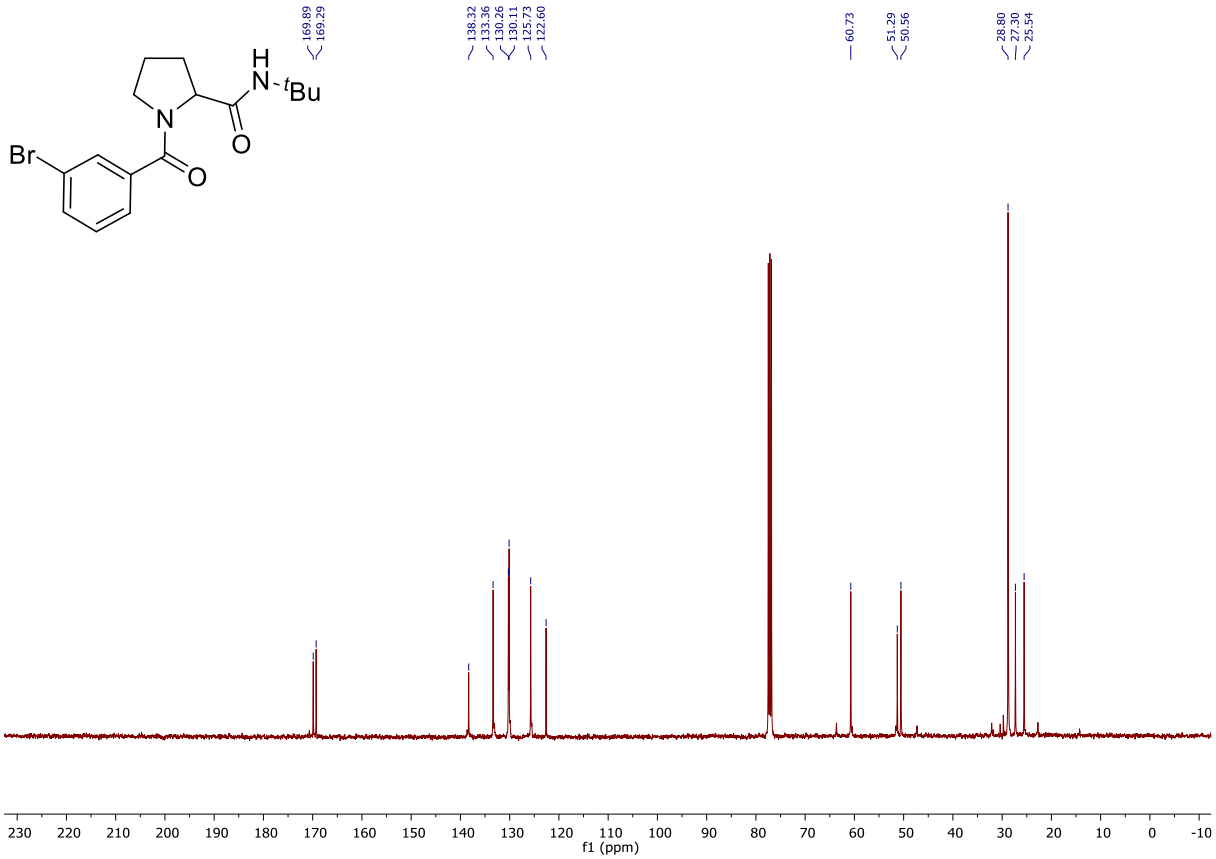
^{13}C NMR of **22** in $CDCl_3$



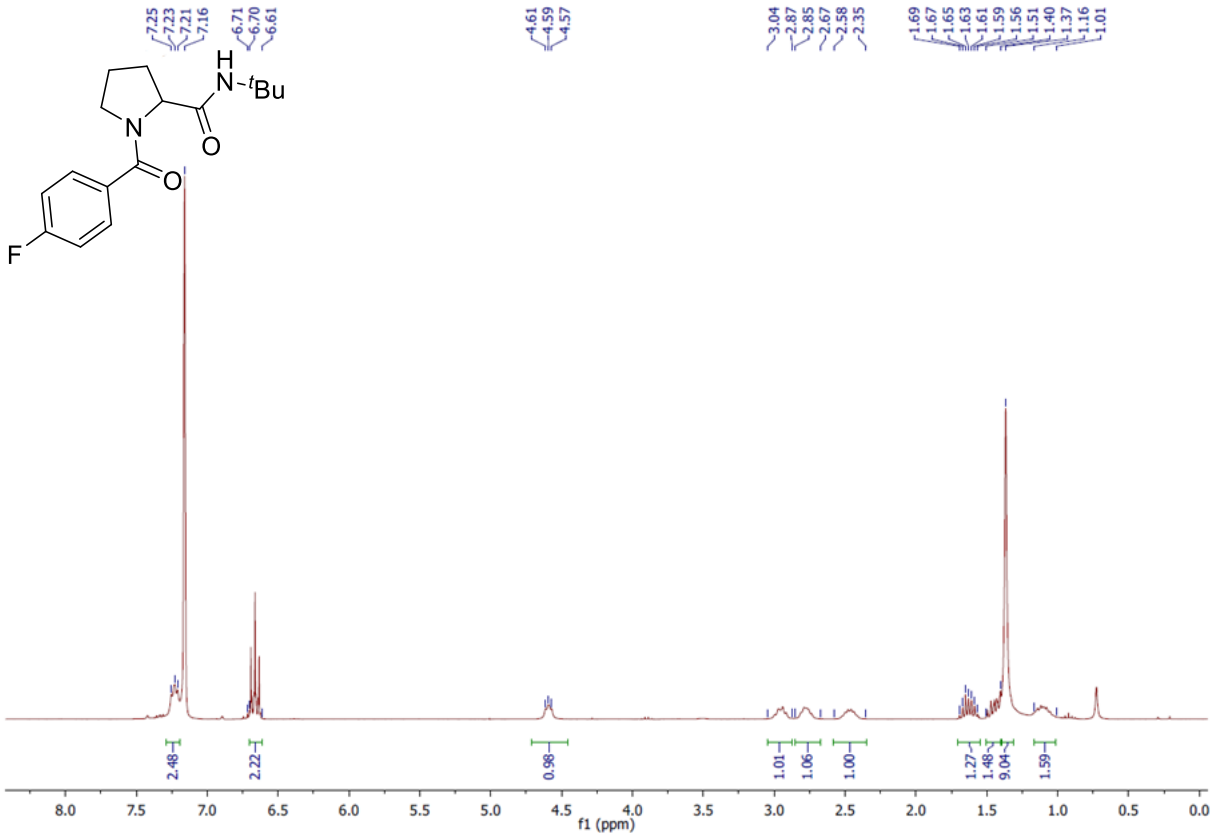
^{1}H NMR of **23** in C_6D_6



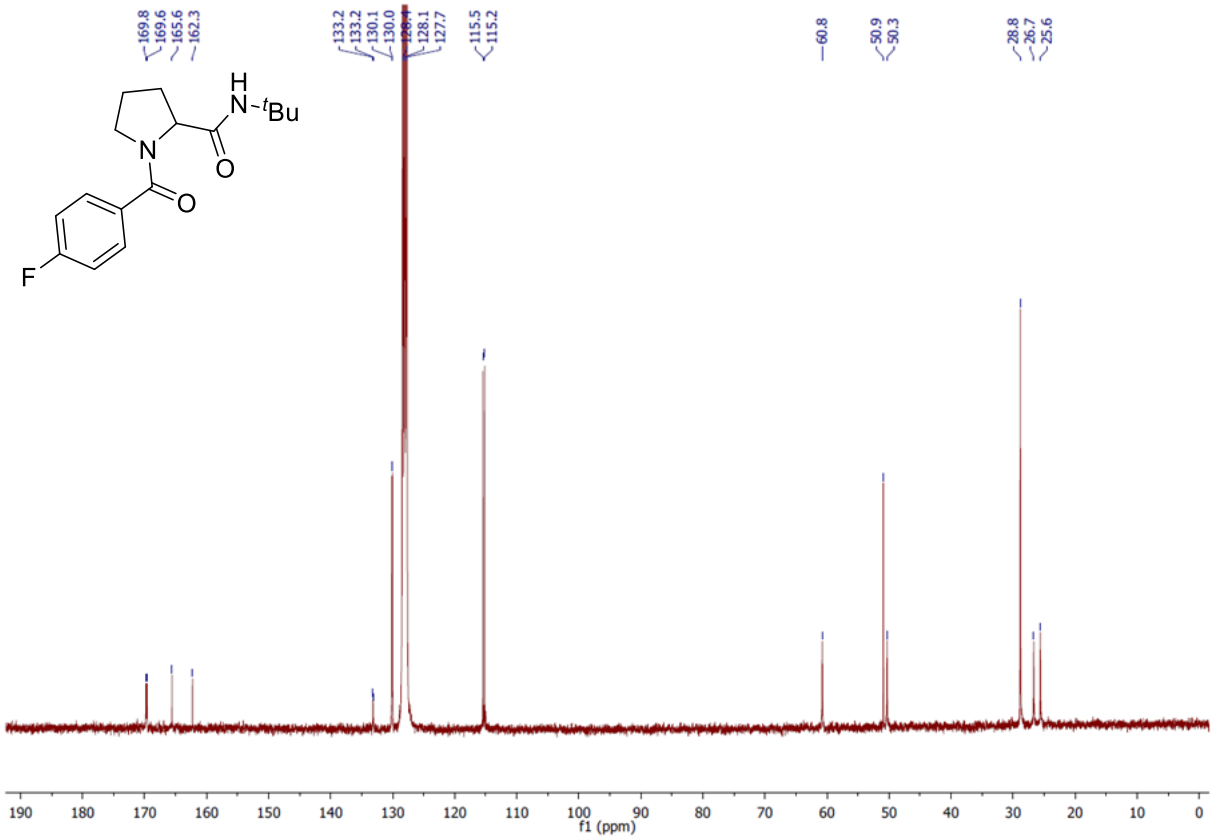
^{13}C NMR of **23** in $CDCl_3$



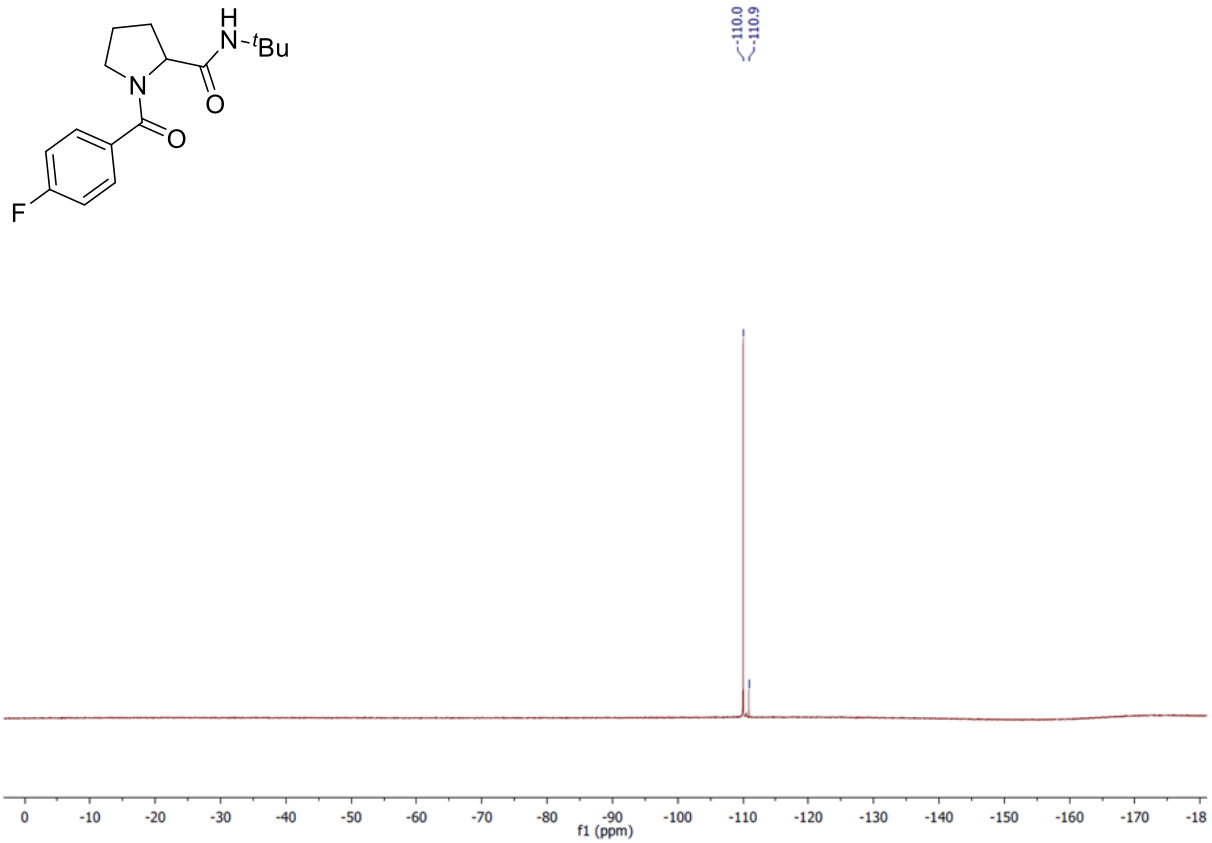
^{1}H NMR of **26** in C_6D_6



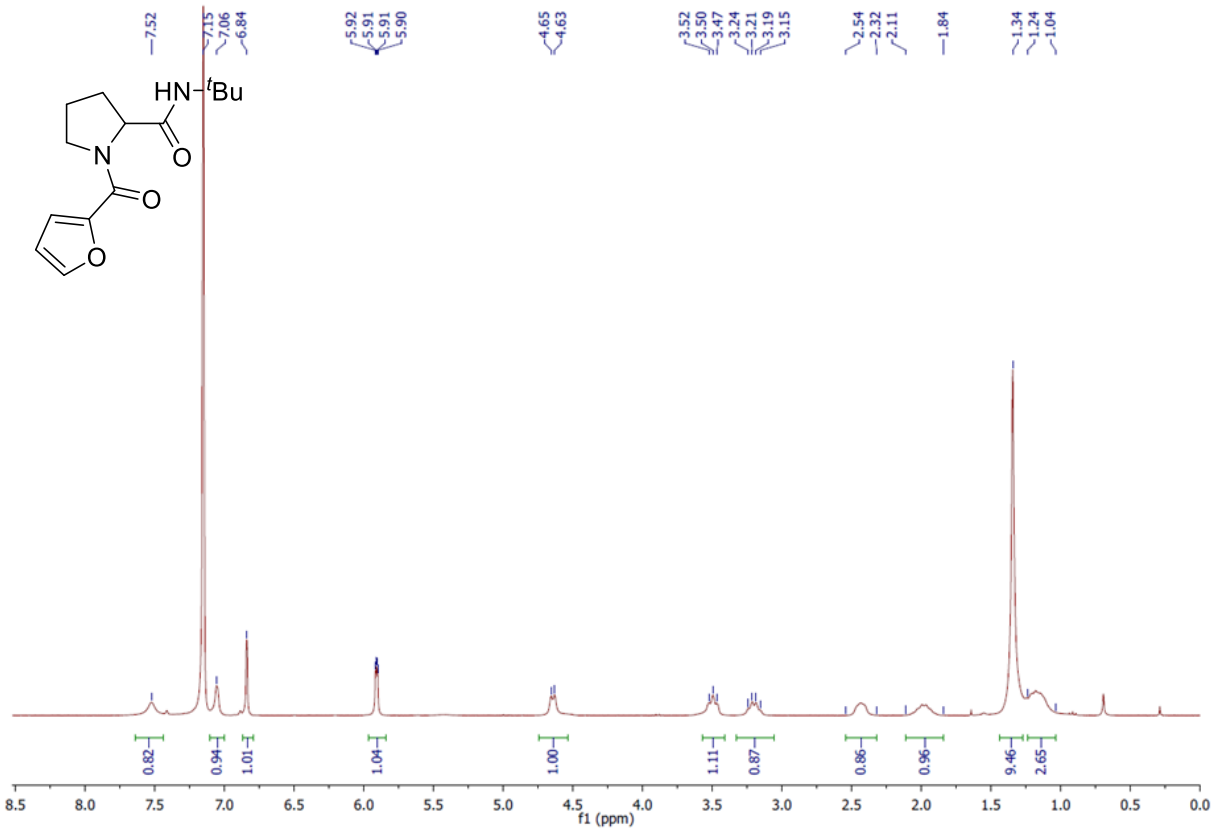
^{13}C NMR of **26** in C_6D_6



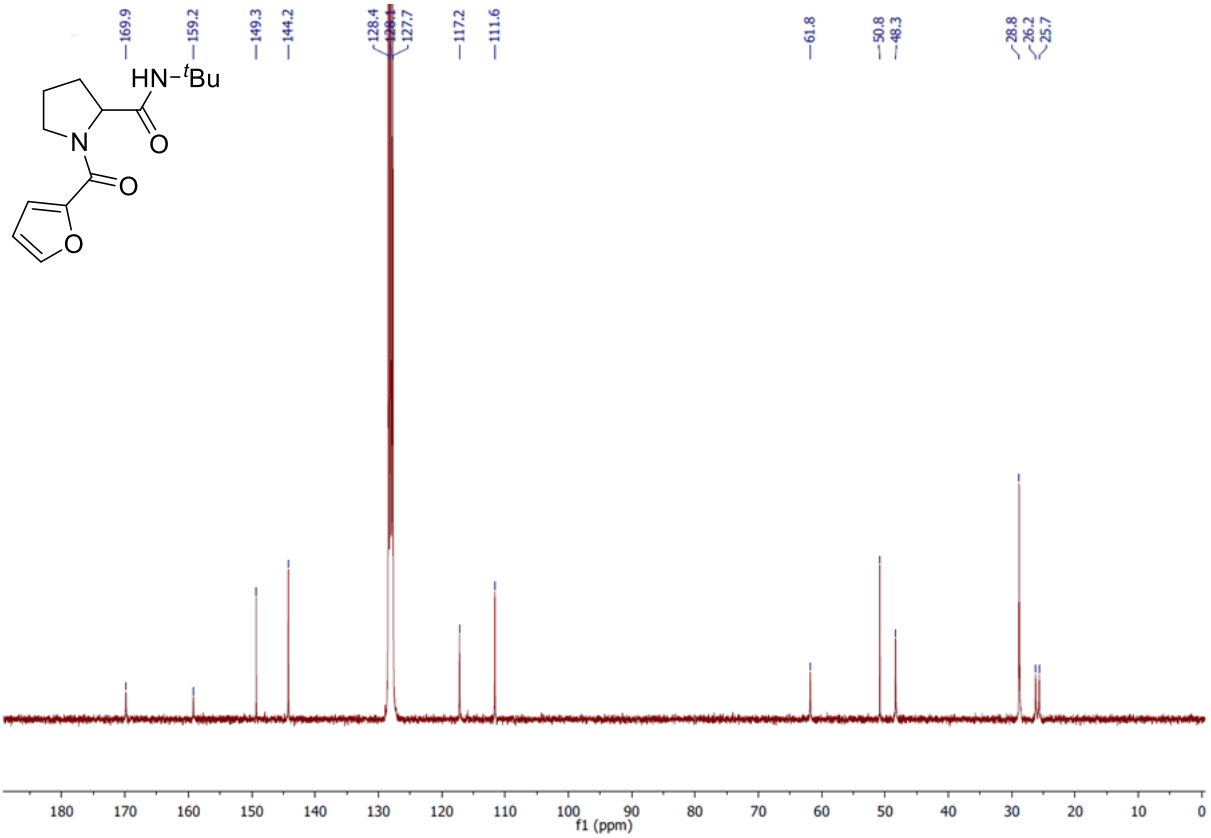
^{19}F NMR of **26** in C_6D_6



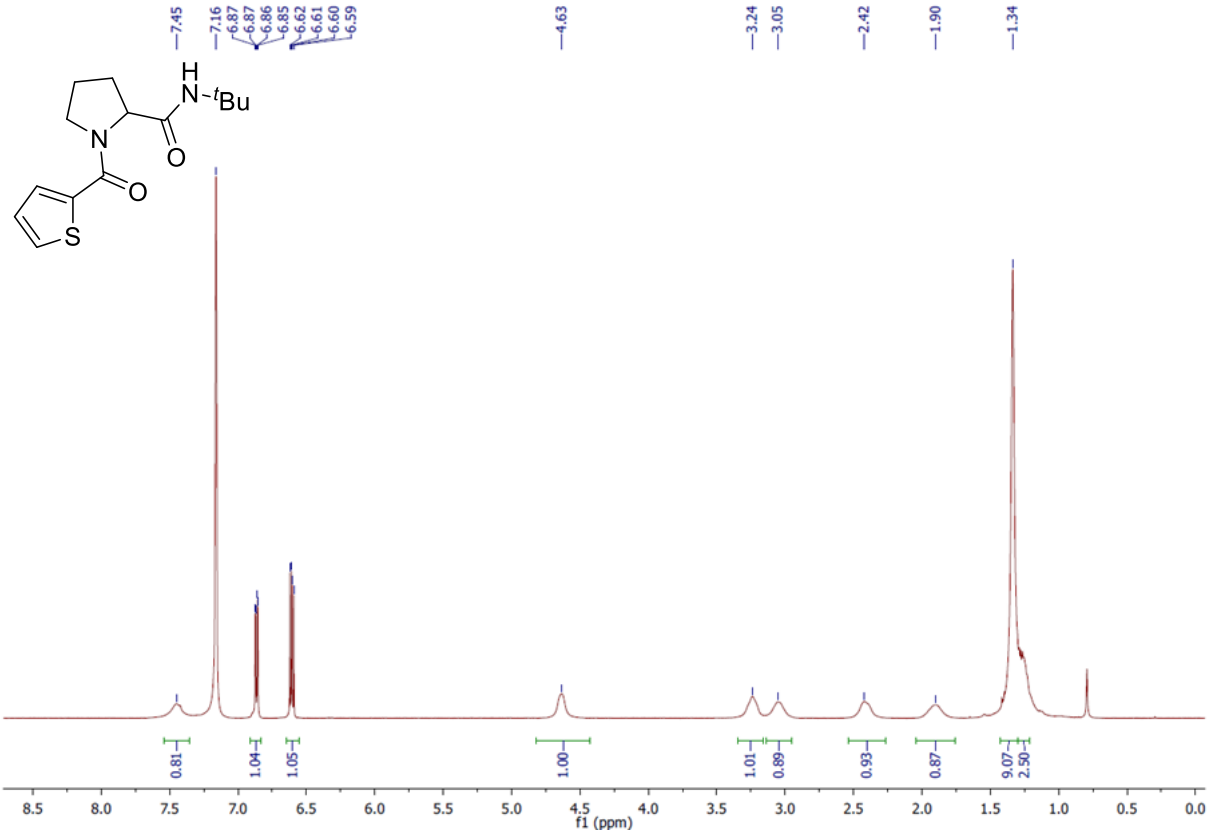
^{1}H NMR of **27** in C_6D_6



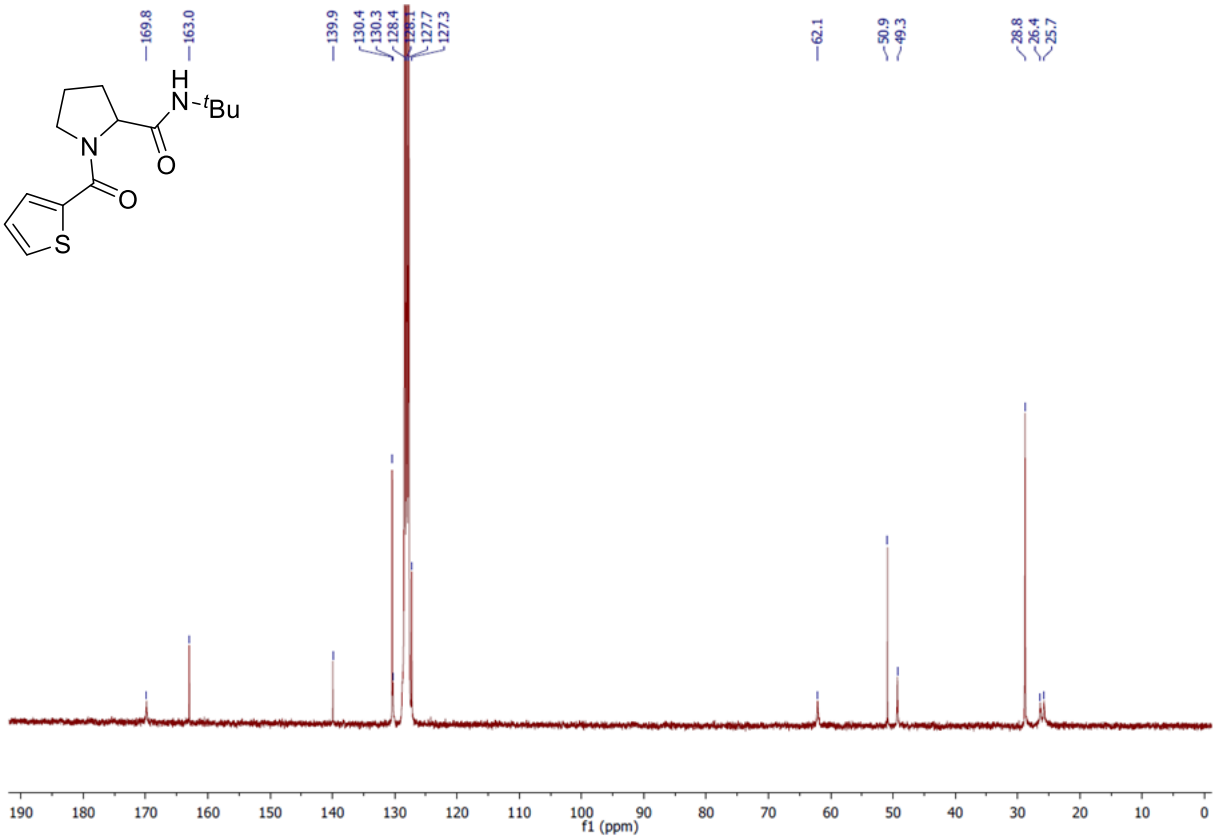
^{13}C NMR of **27** in C_6D_6



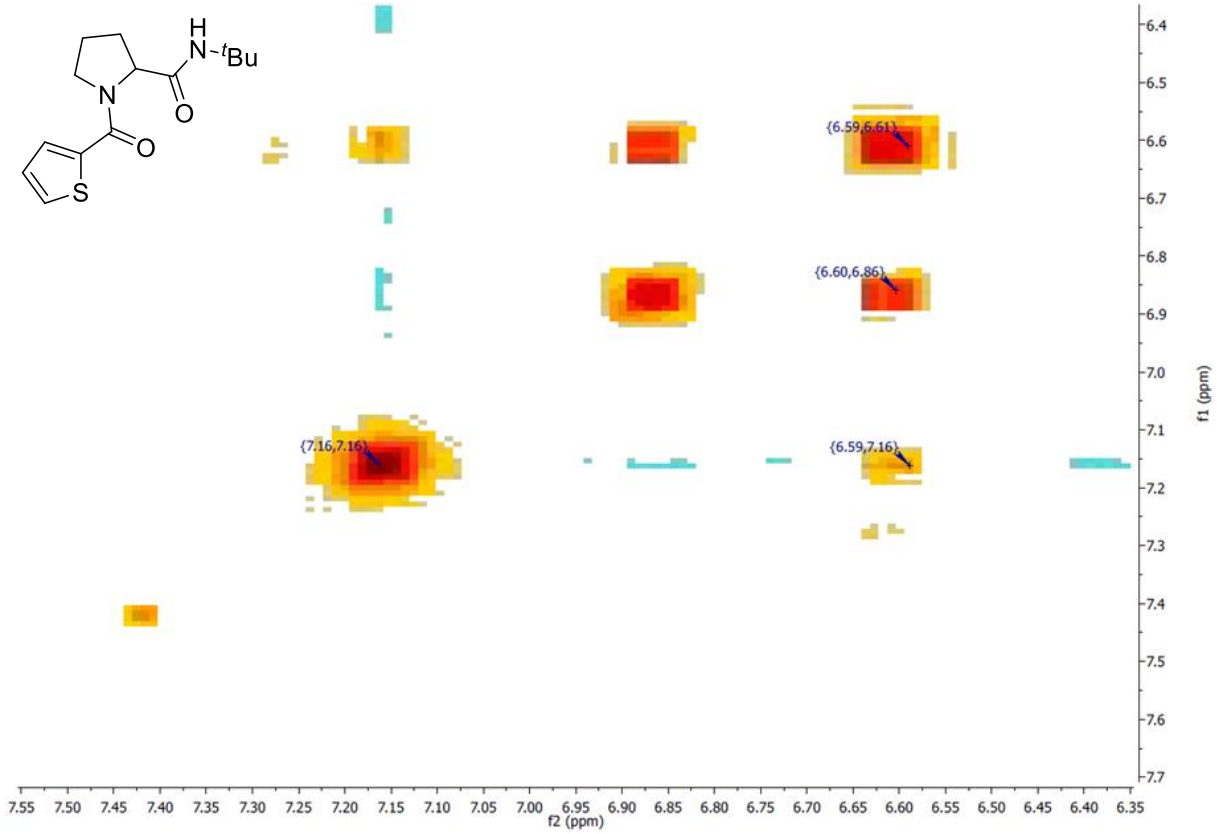
^{1}H NMR of **28** in C_6D_6



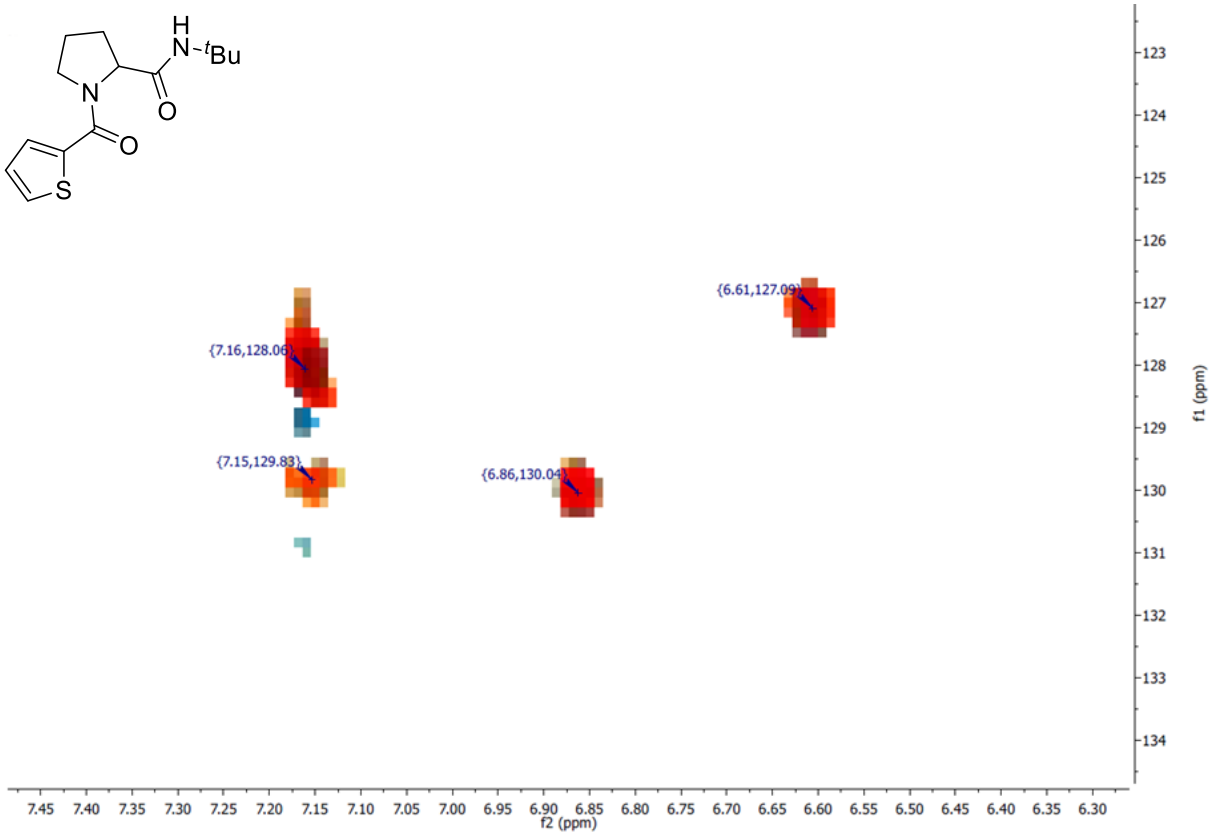
^{13}C NMR of **28** in C_6D_6



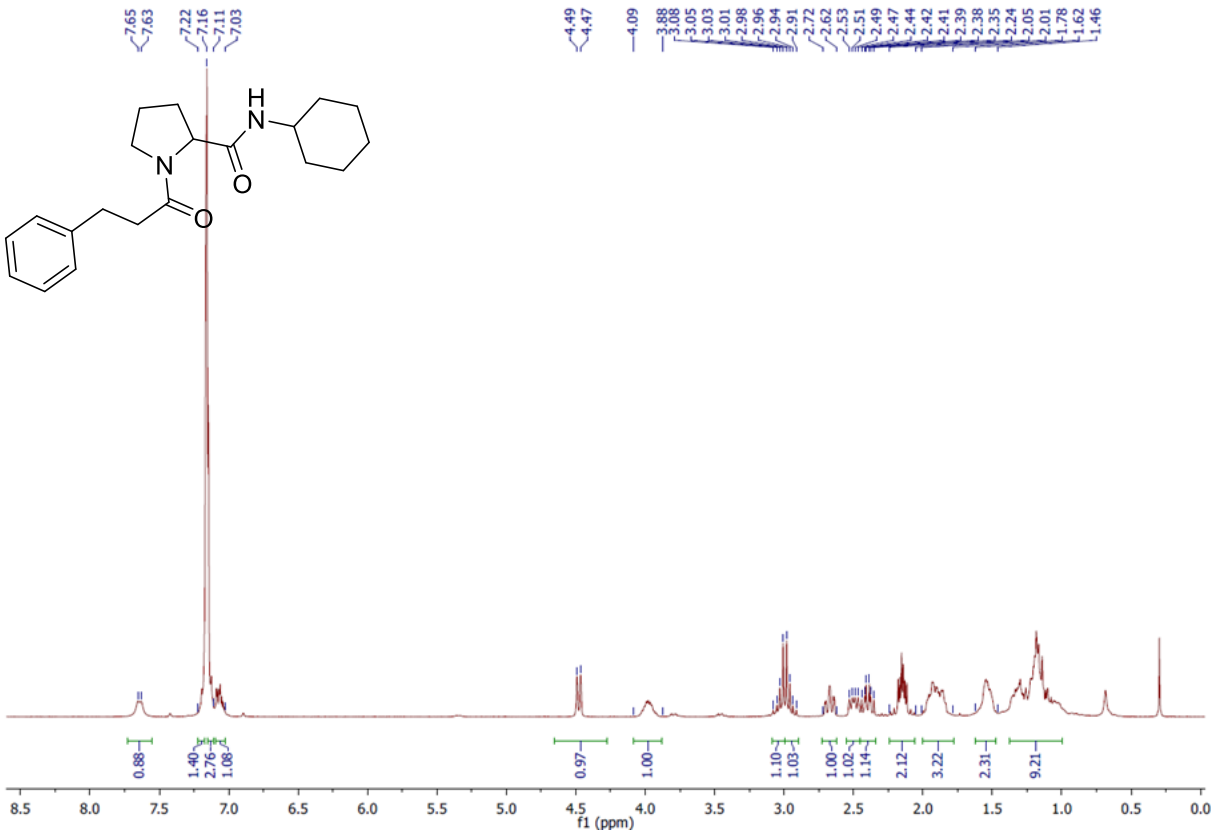
COSY of **28** in C_6D_6



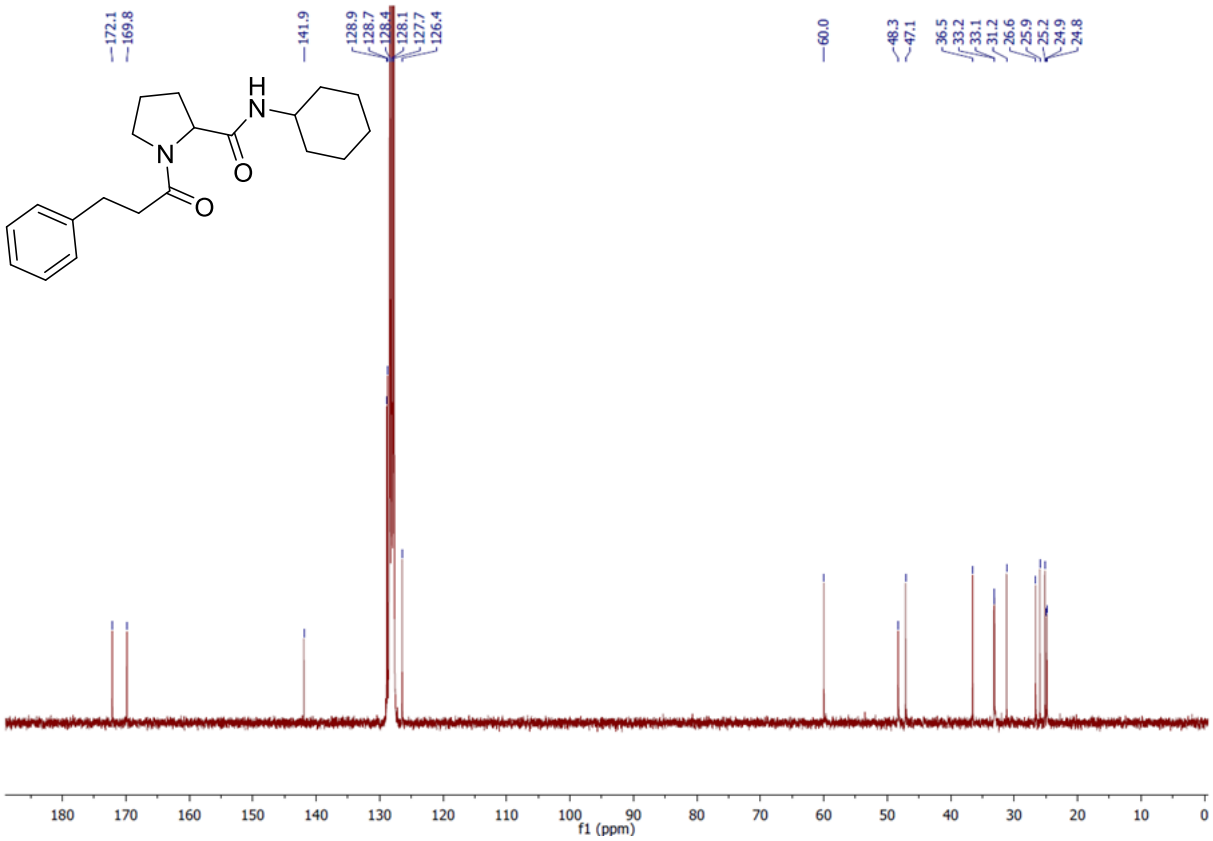
HSQC of **28** in C_6D_6



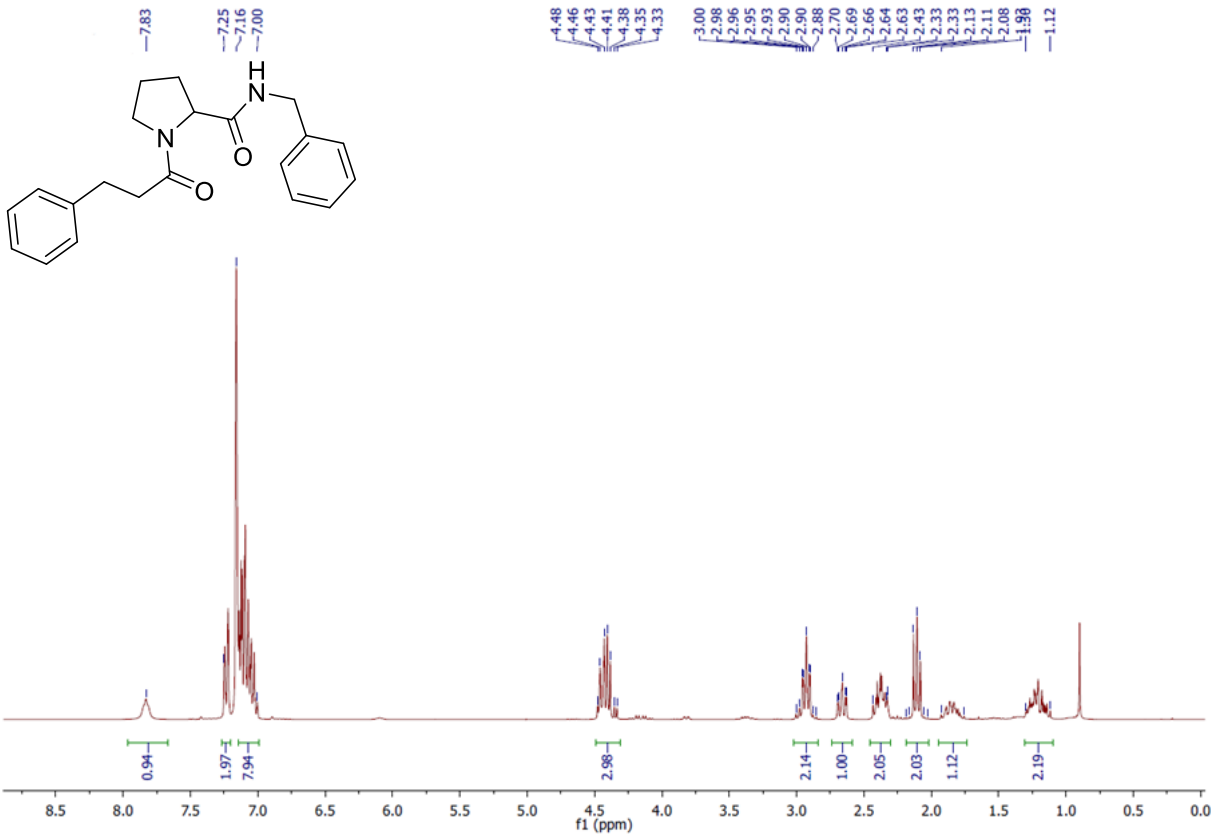
^{1}H NMR of **29** in C_6D_6



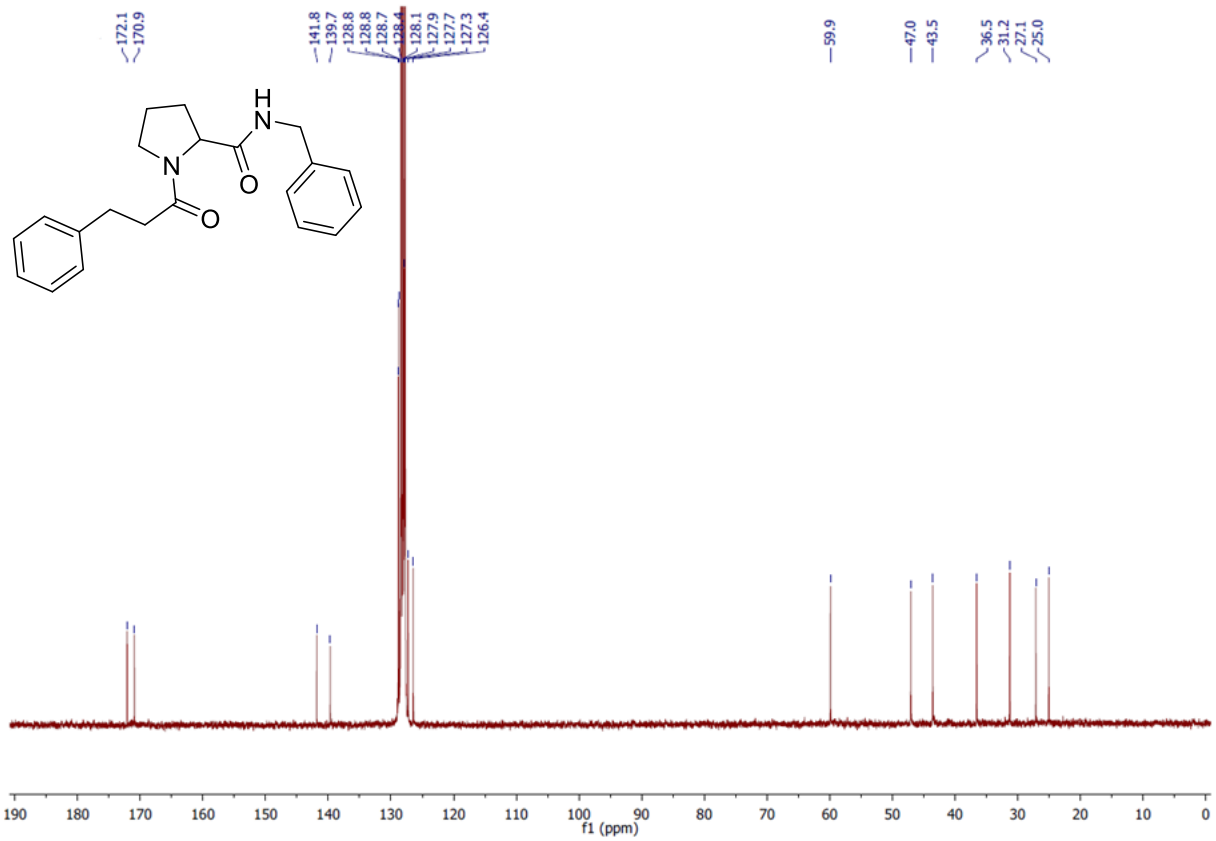
^{13}C NMR of **29** in C_6D_6



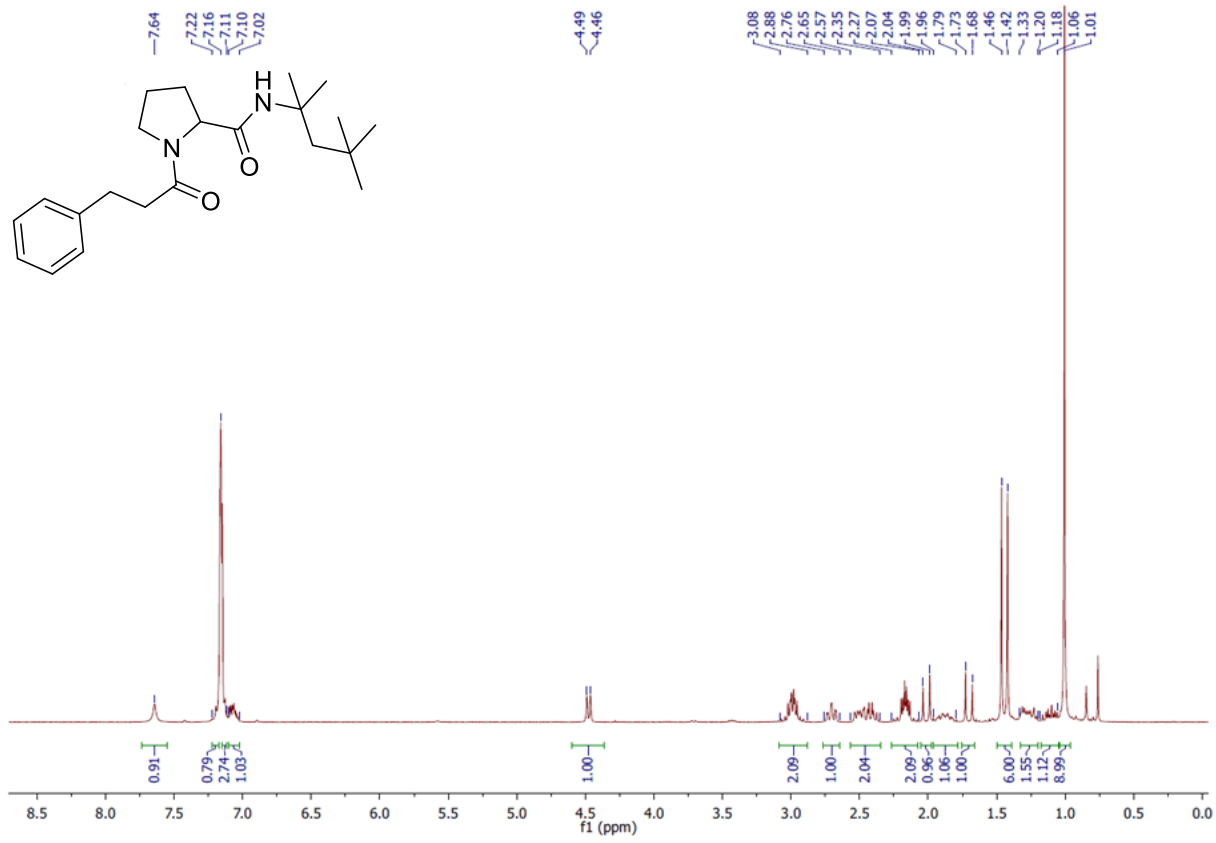
^{1}H NMR of **30** in C_6D_6



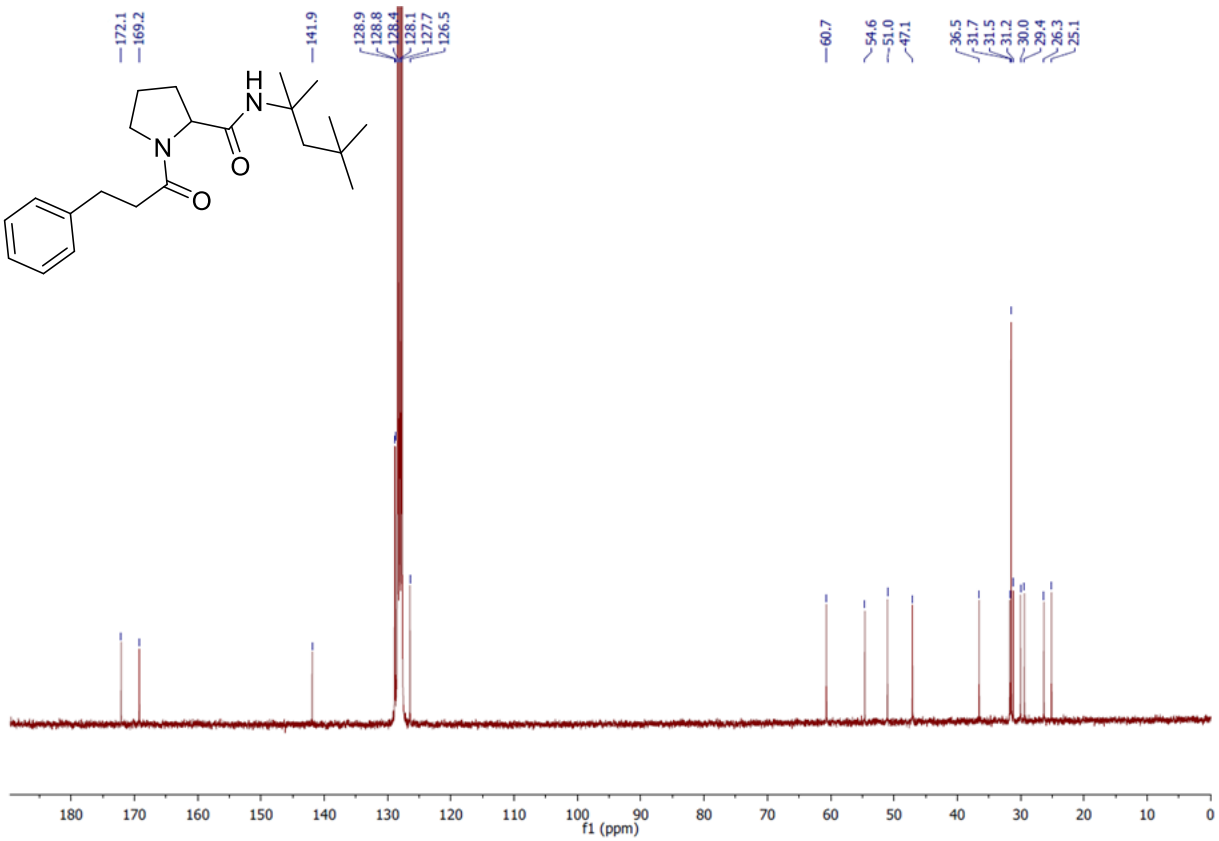
^{13}C NMR of **30** in C_6D_6



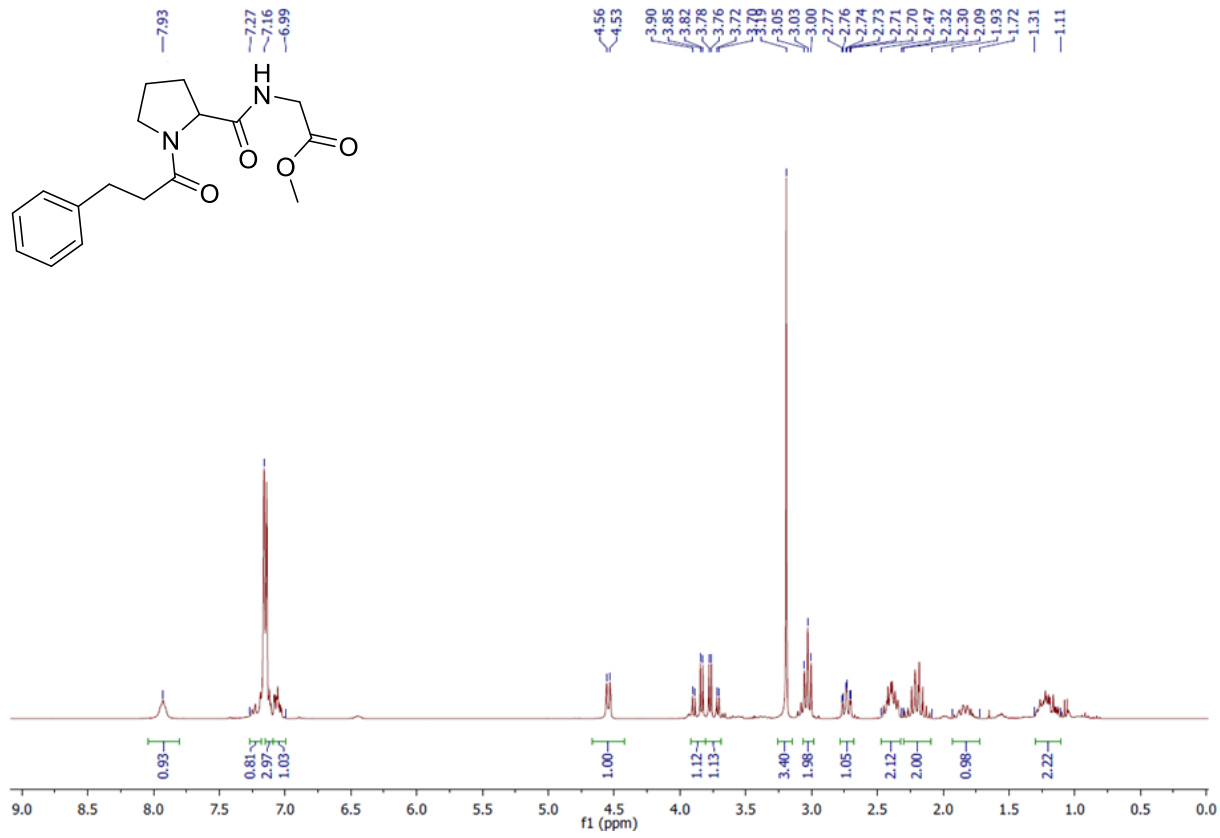
^{1}H NMR of **31** in C_6D_6



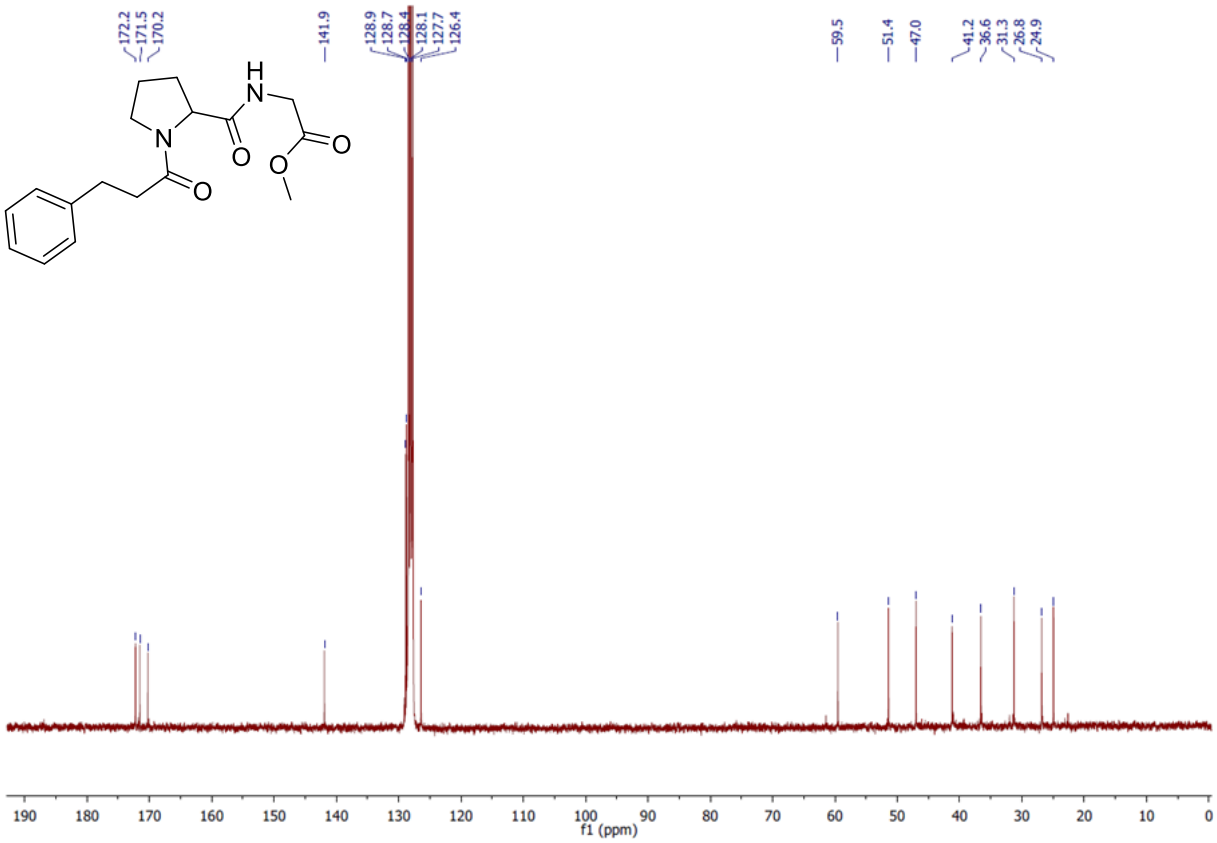
^{13}C NMR of **31** in C_6D_6



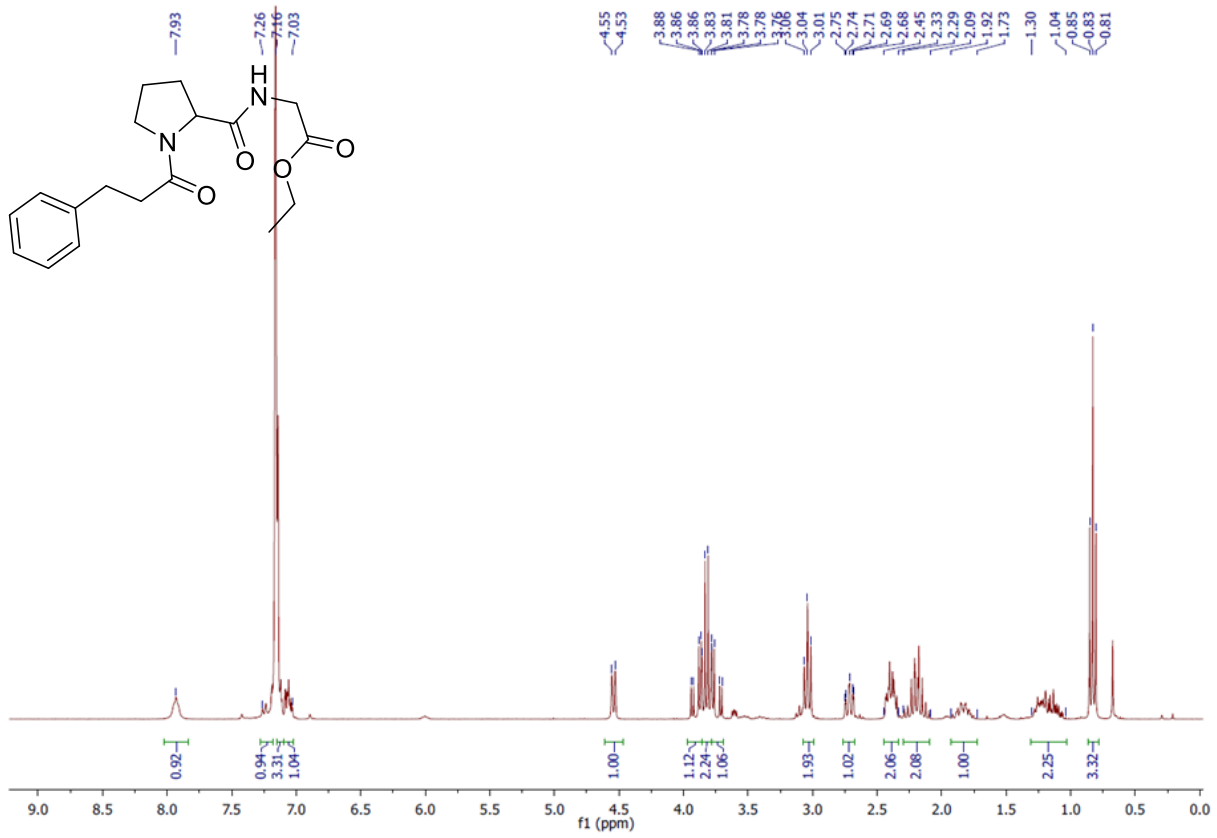
^{1}H NMR of **32** in C_6D_6



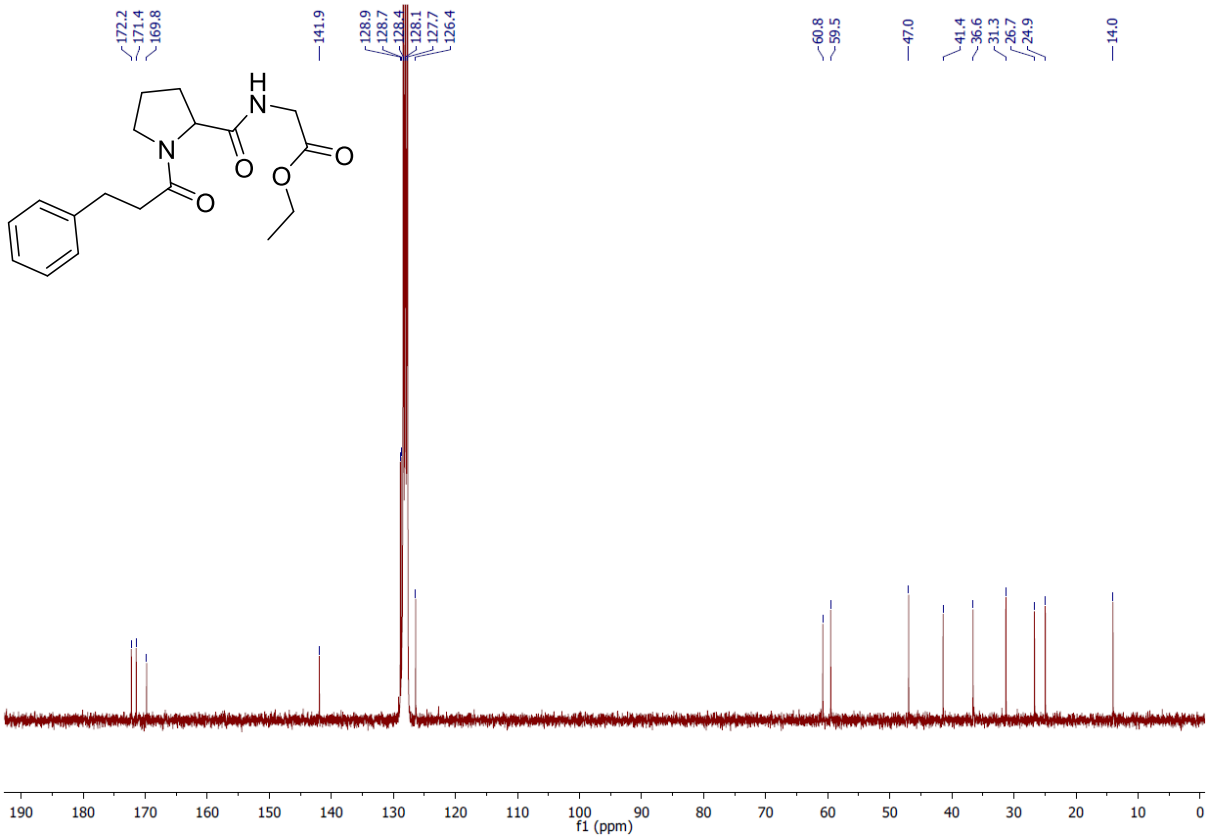
^{13}C NMR of **32** in C_6D_6



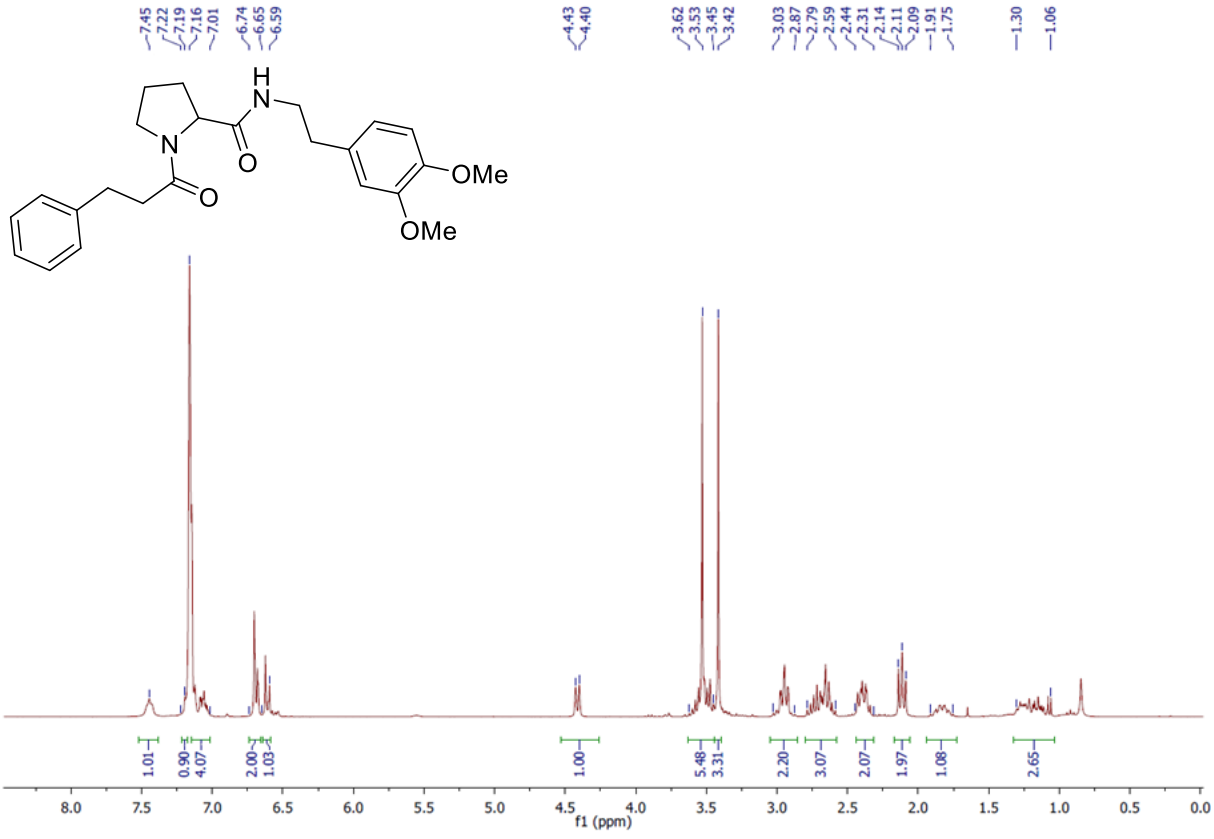
^{1}H NMR of **33** in C_6D_6



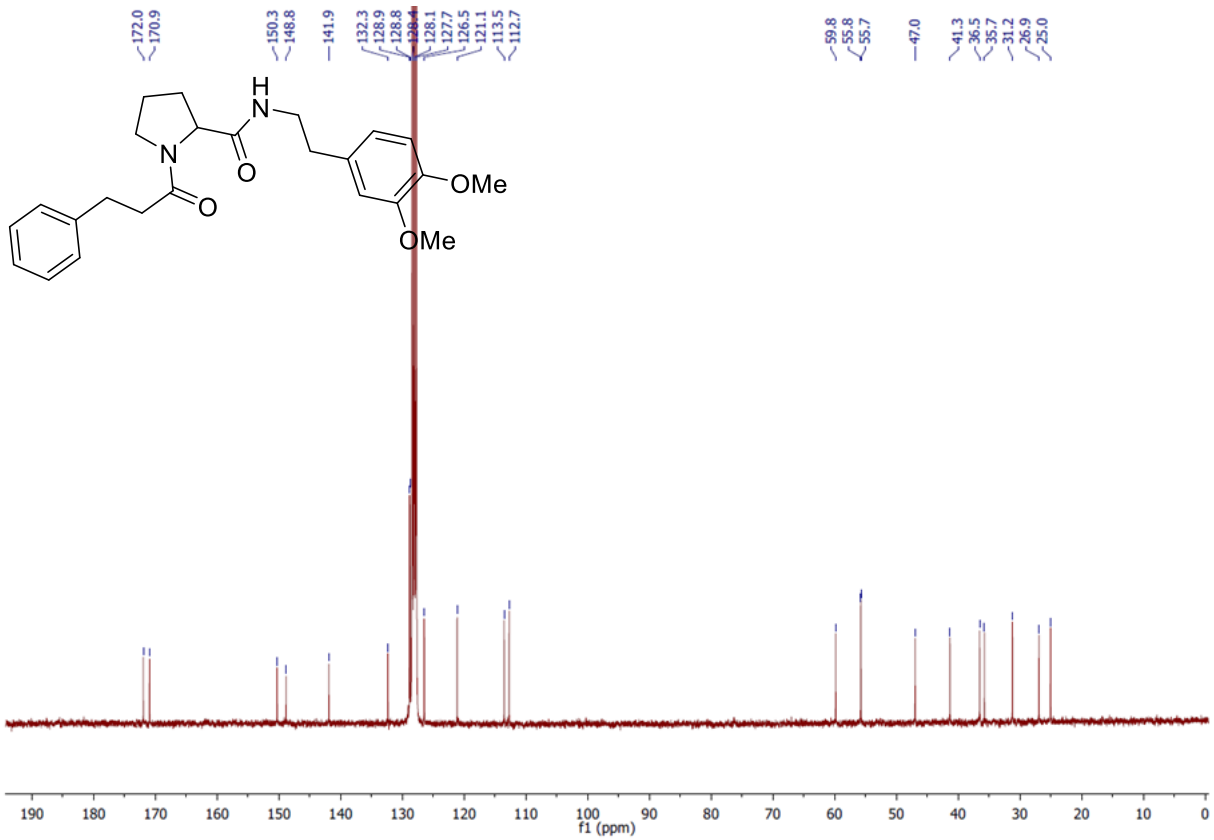
^{13}C NMR of **33** in C_6D_6



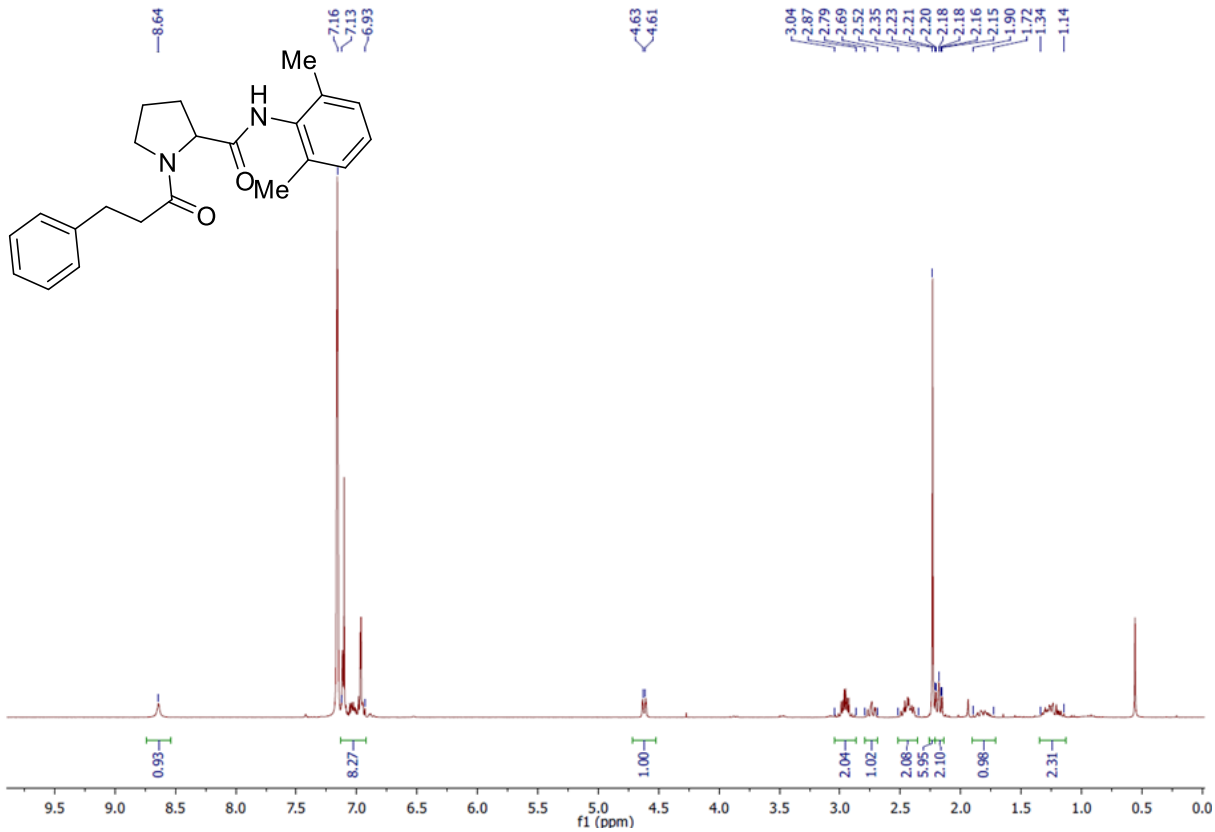
^{1}H NMR of **34** in C_6D_6



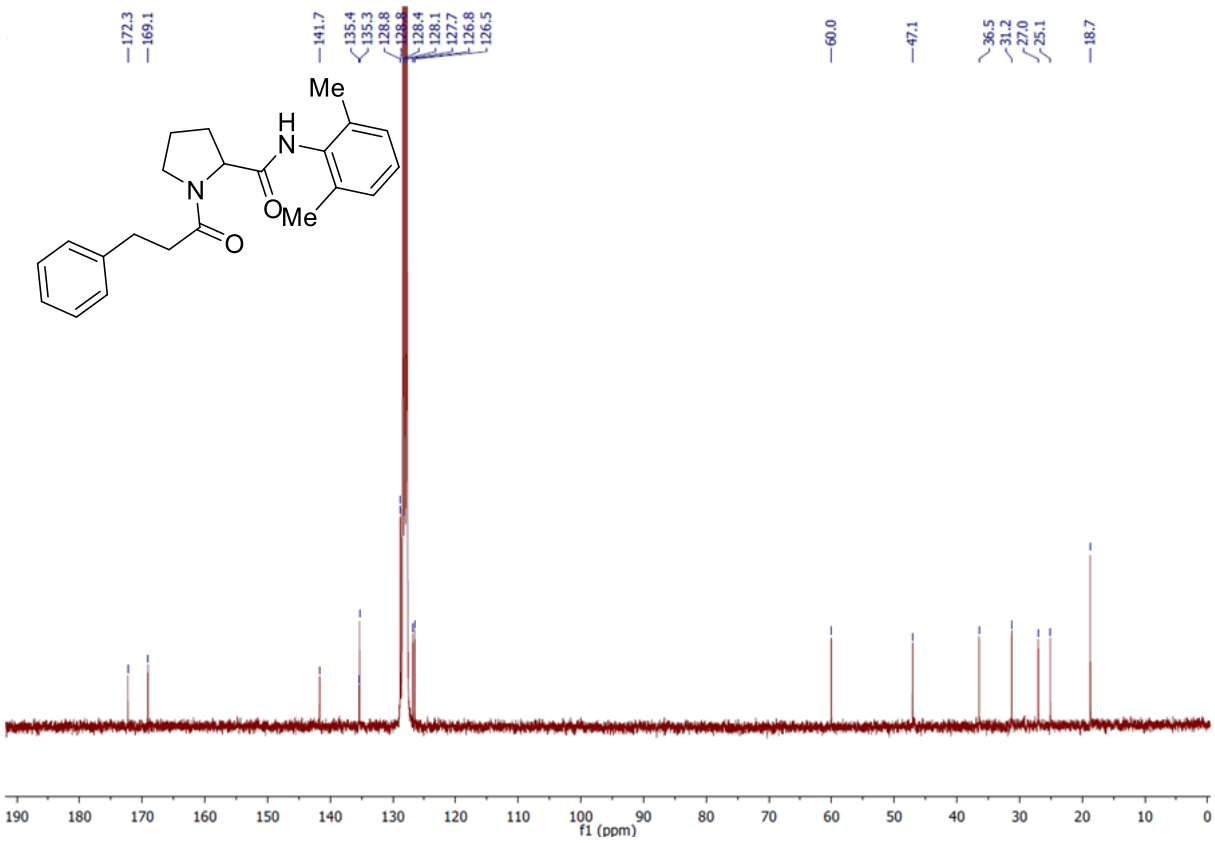
^{13}C NMR of **34** in C_6D_6



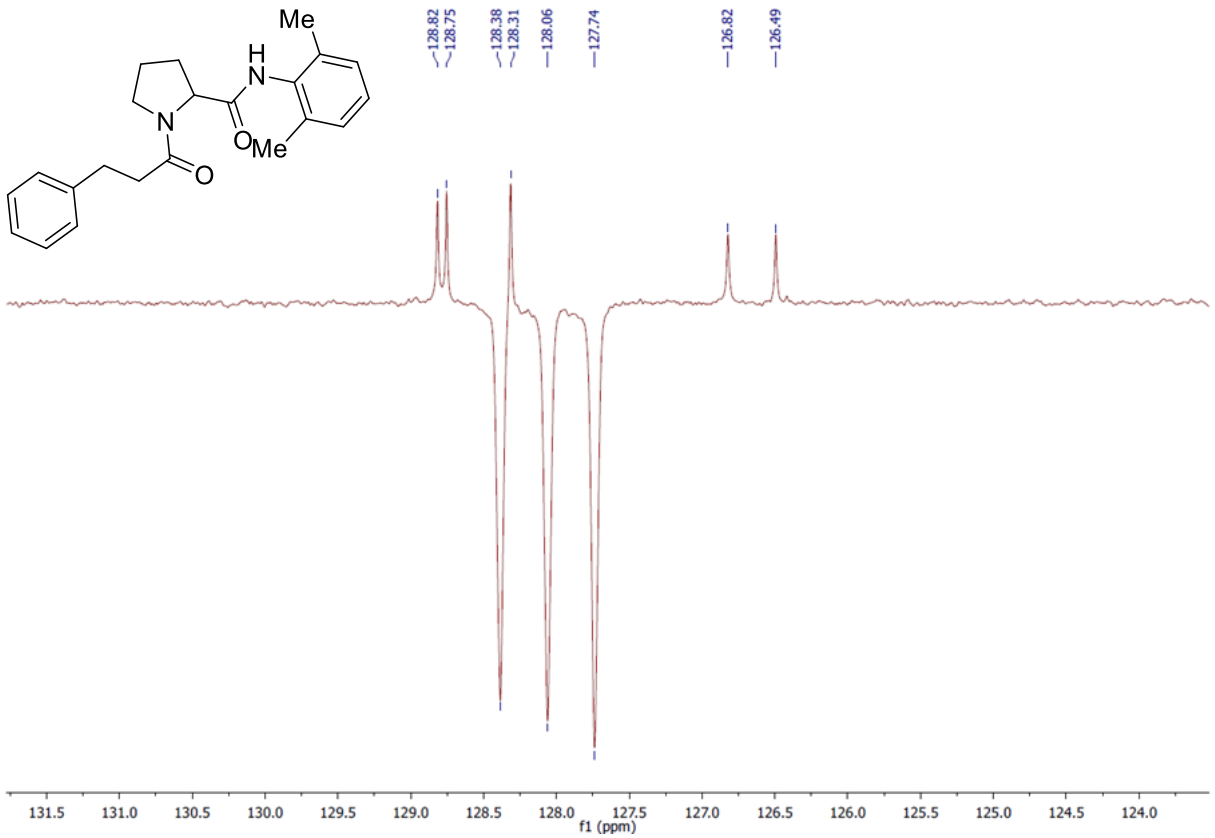
^{1}H NMR of **35** in C_6D_6



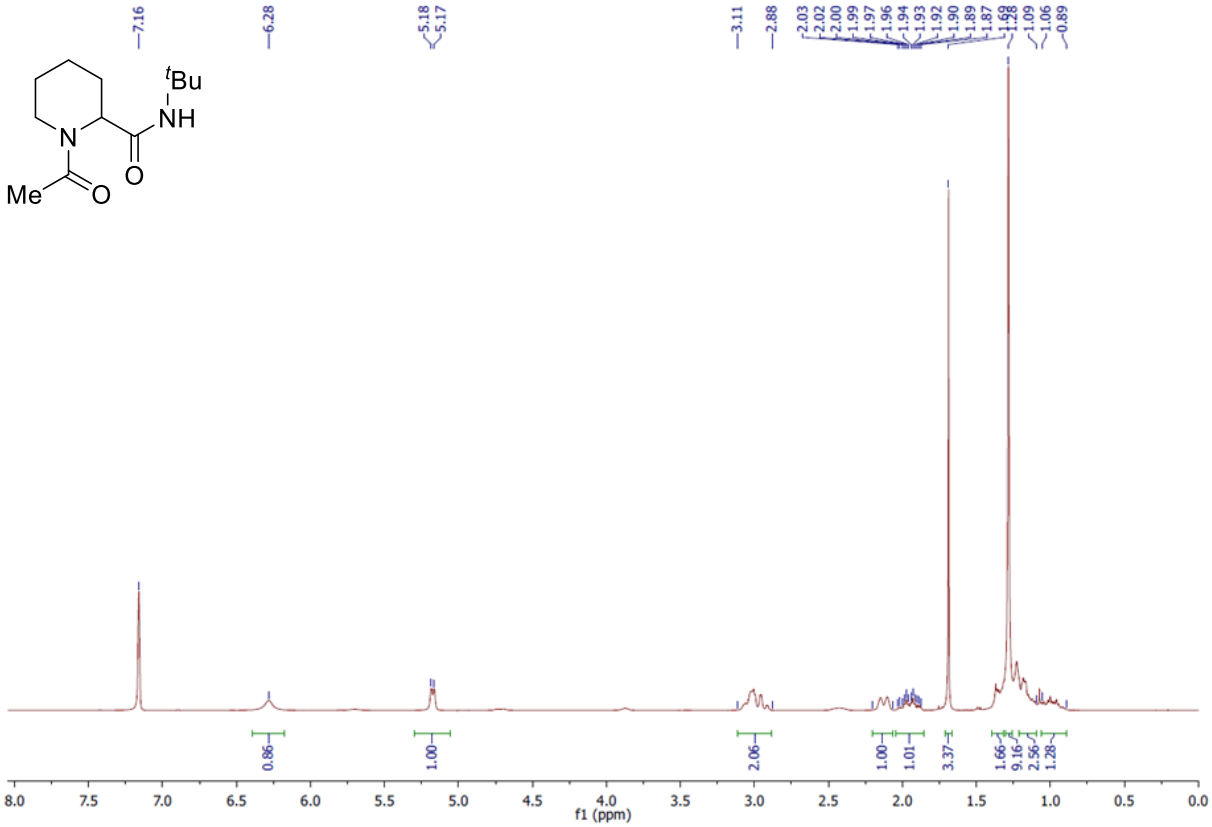
^{13}C NMR of **35** in C_6D_6



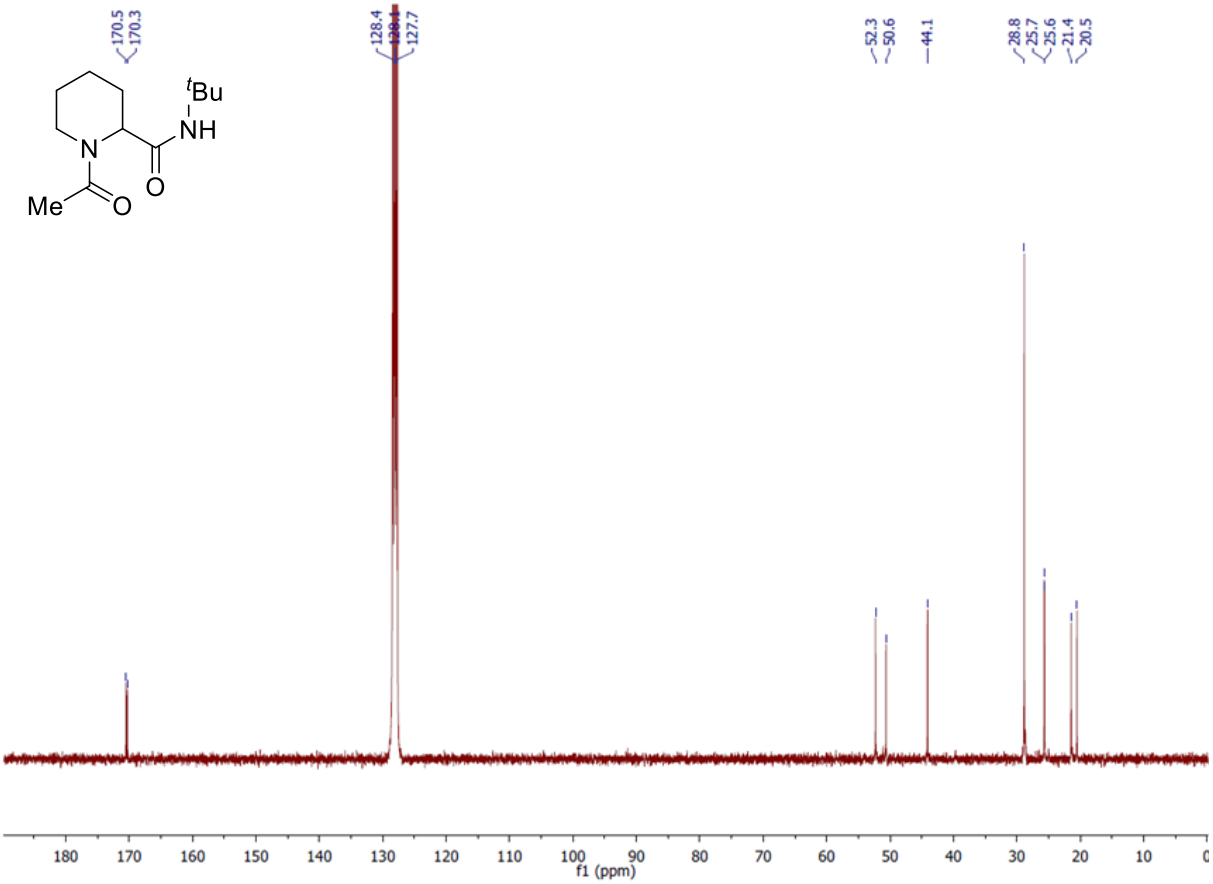
DEPT of **35** in C_6D_6



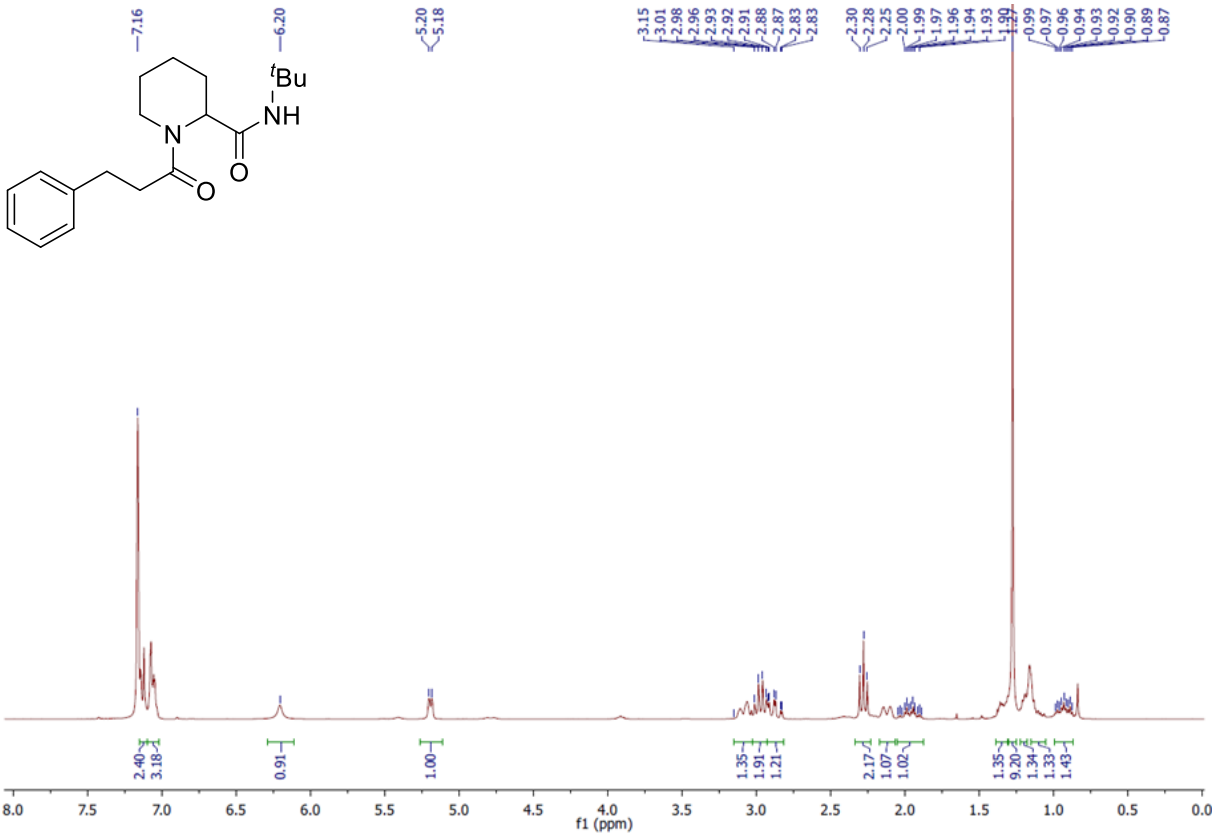
^{1}H NMR of **36** in C_6D_6



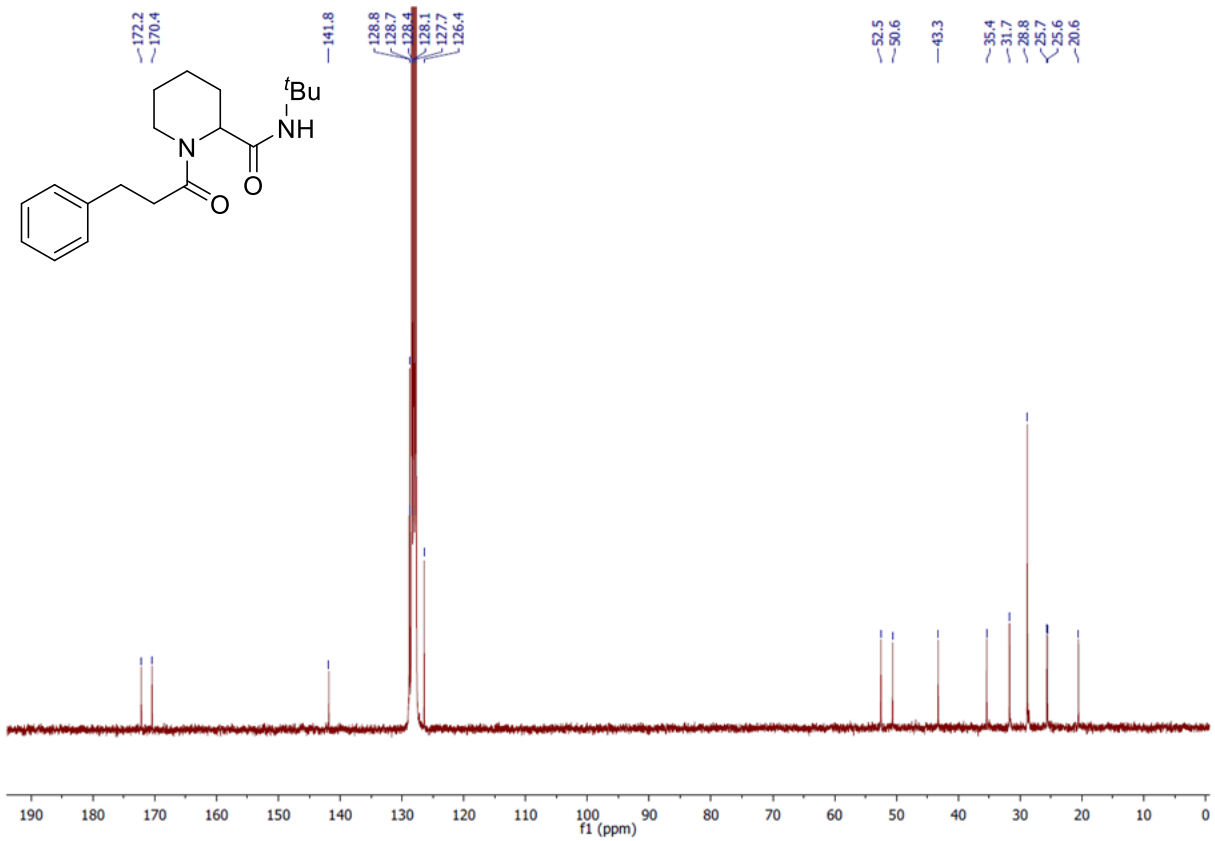
^{13}C NMR of **36** in C_6D_6



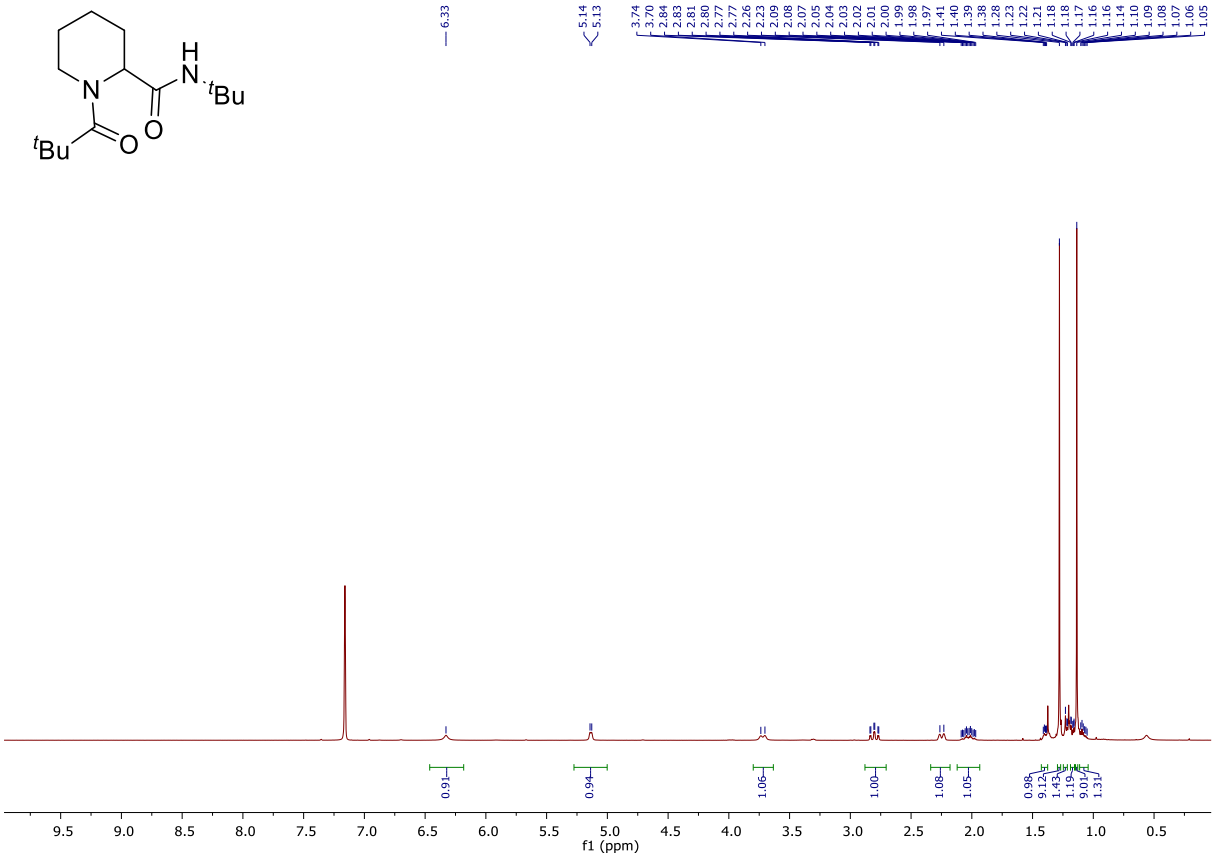
^{1}H NMR of **37** in C_6D_6



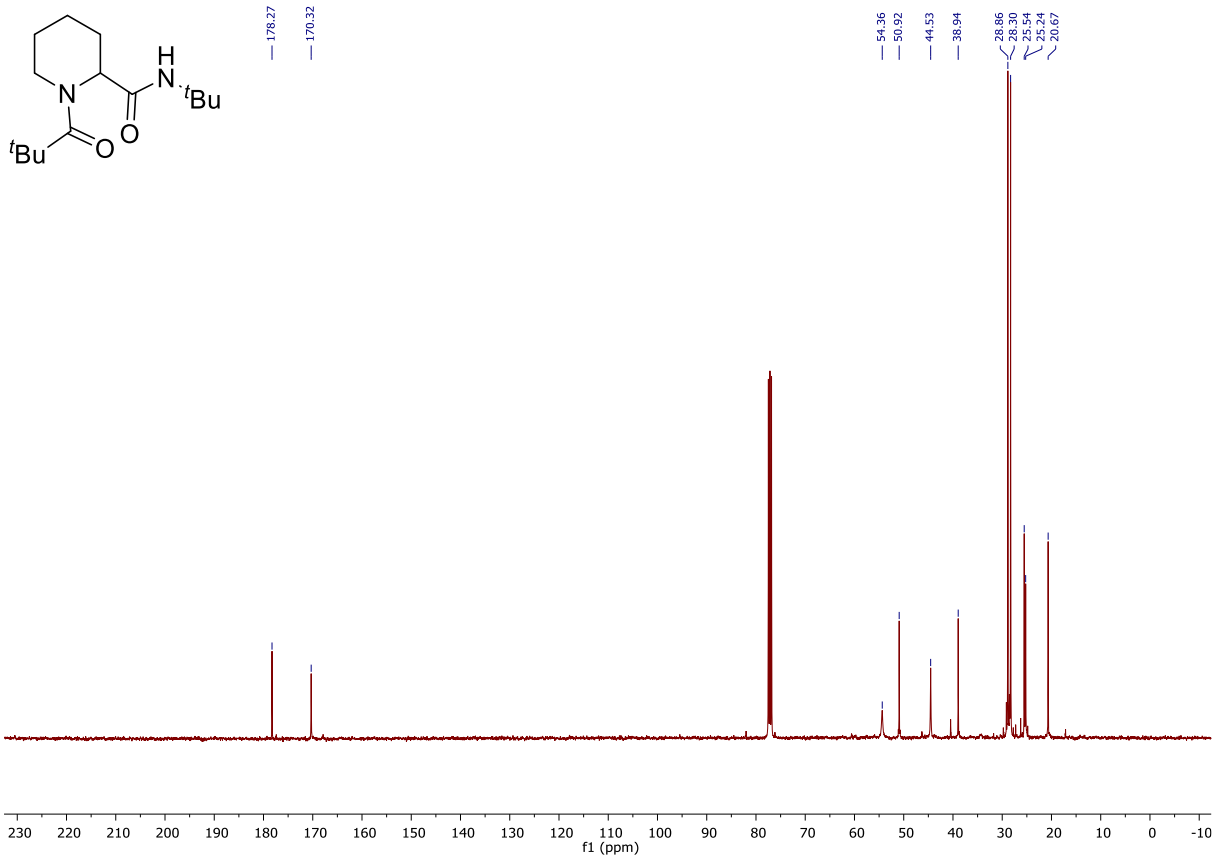
^{13}C NMR of **37** in C_6D_6



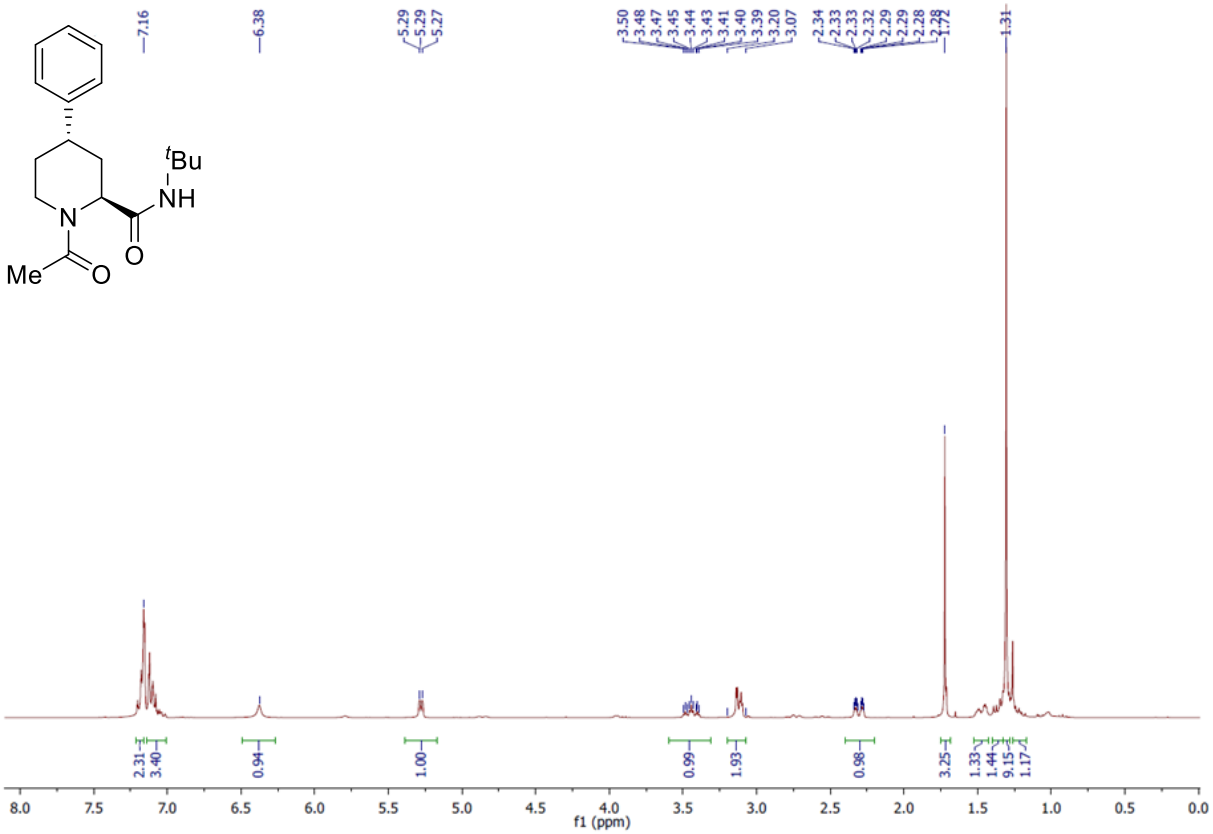
^{1}H NMR of **38** in C_6D_6



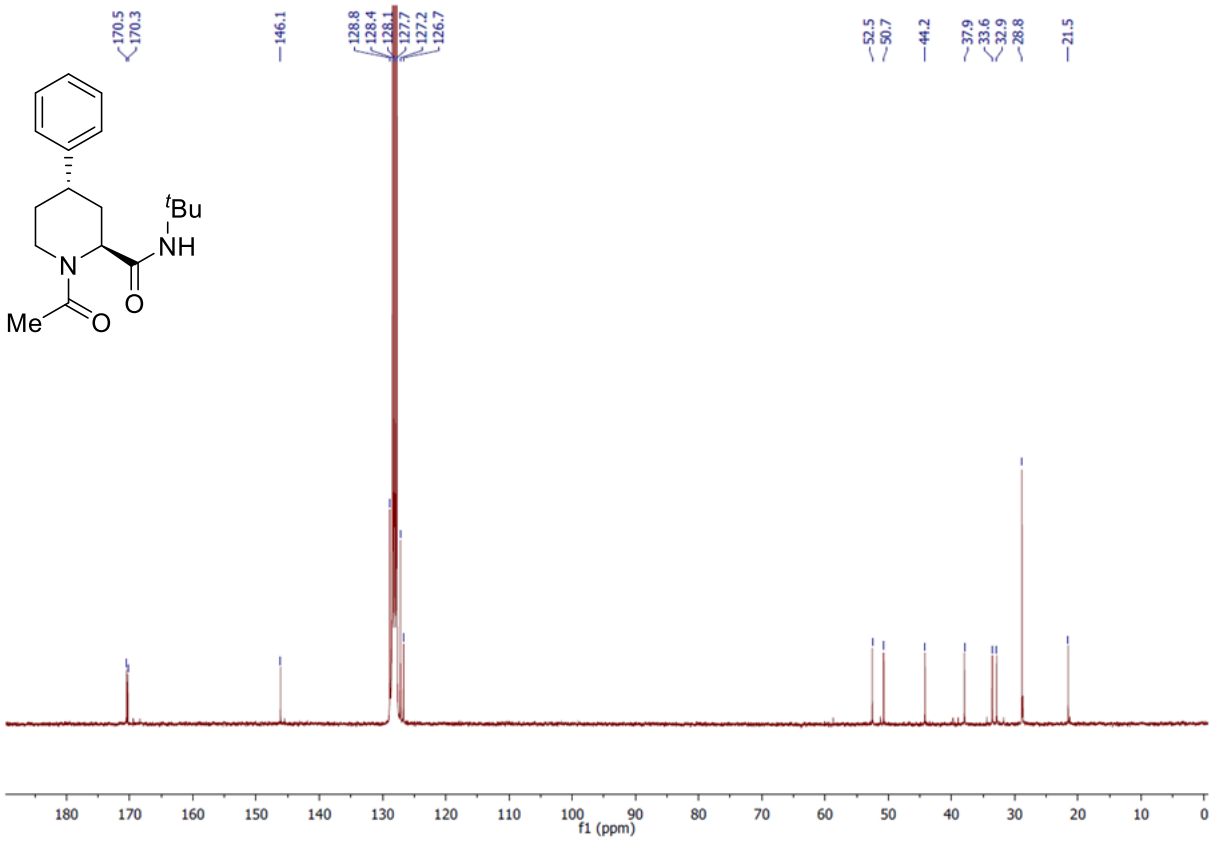
^{13}C NMR of **38** in $CDCl_3$



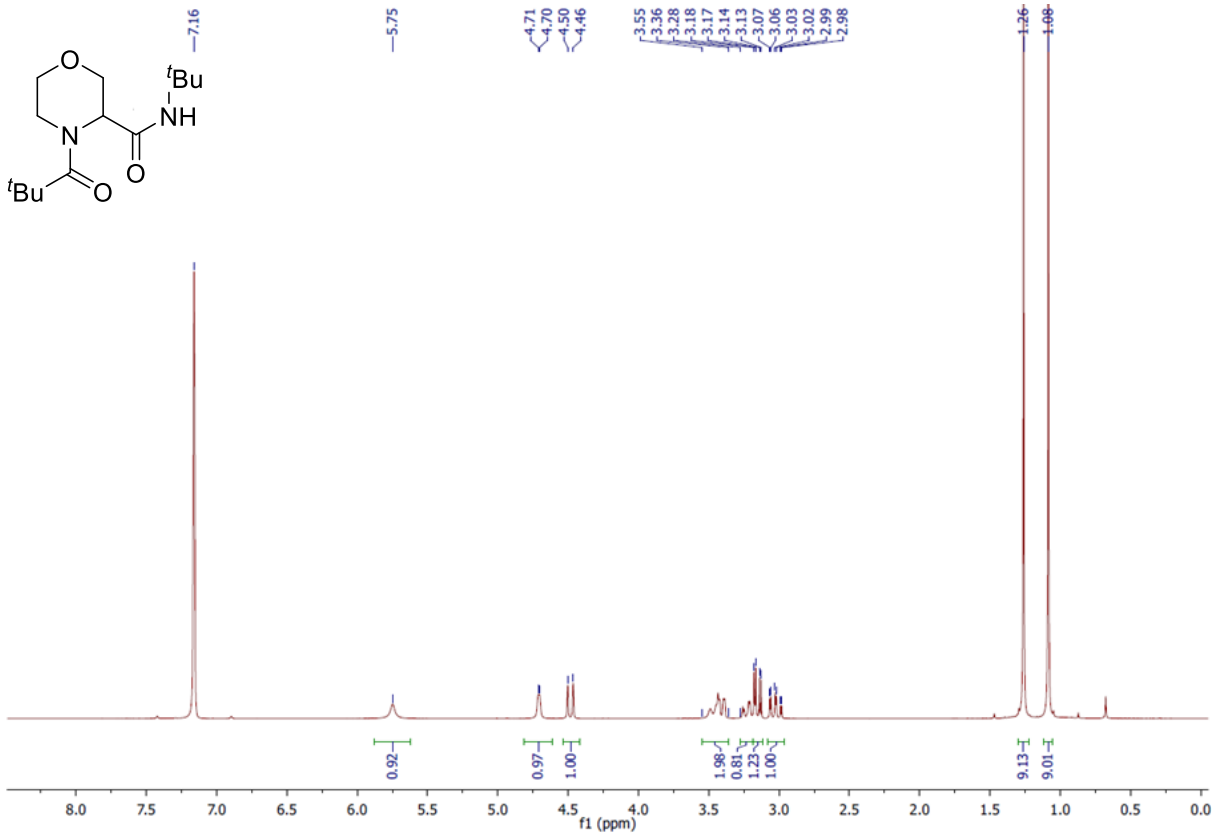
^{1}H NMR of **39** in C_6D_6



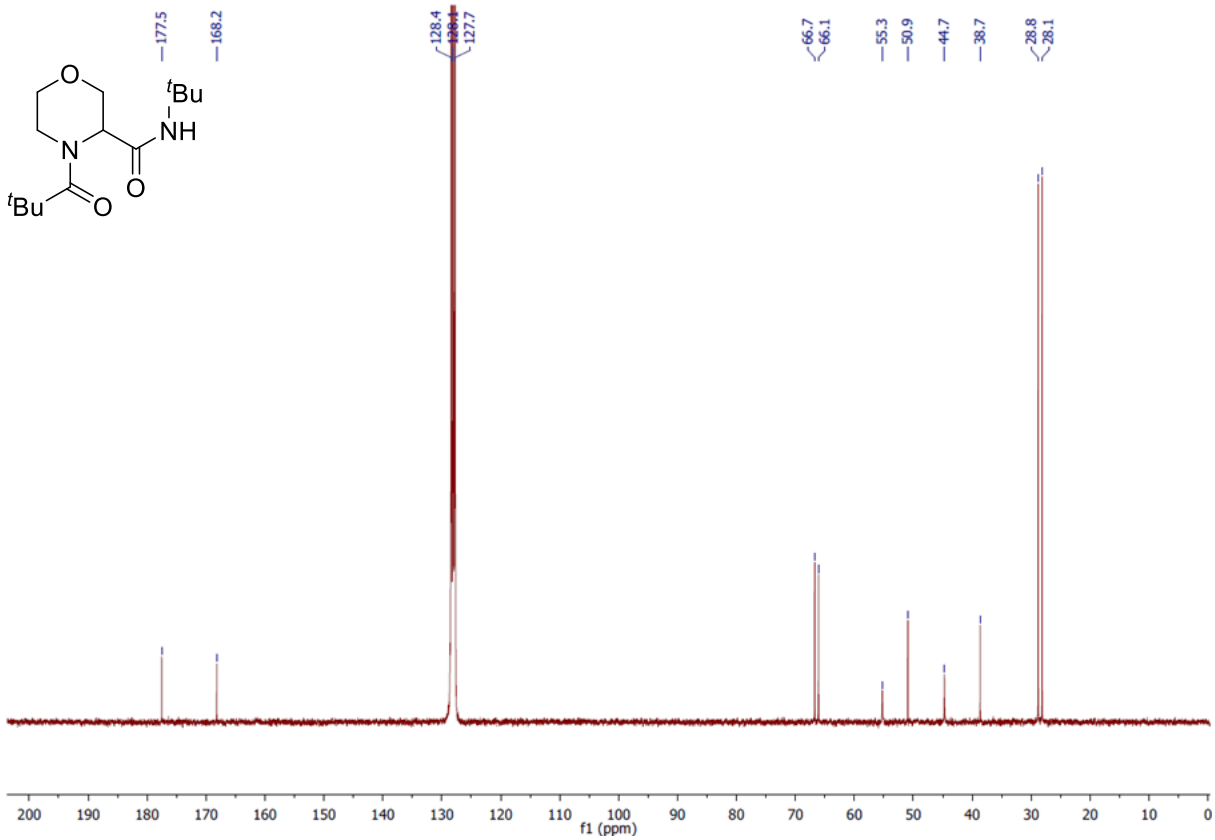
^{13}C NMR of **39** in C_6D_6



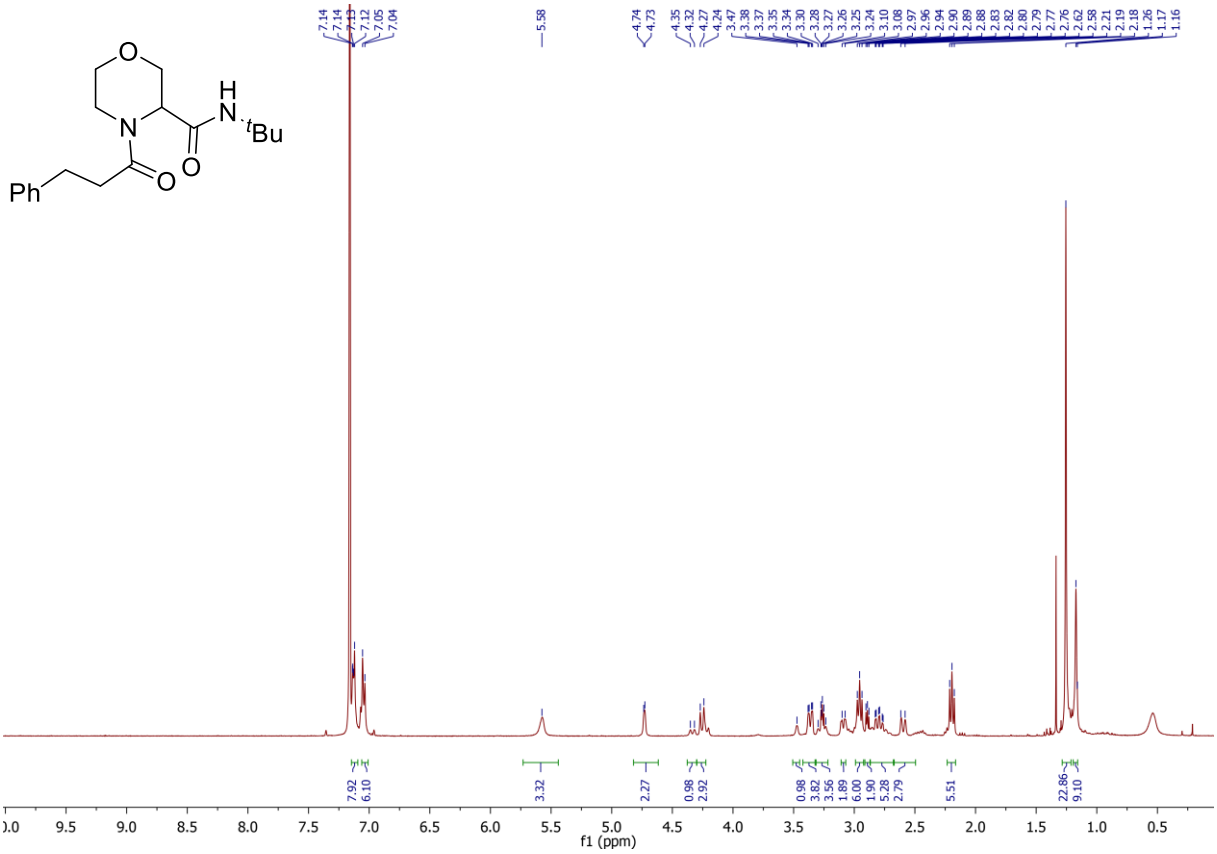
^{1}H NMR of **40** in C_6D_6



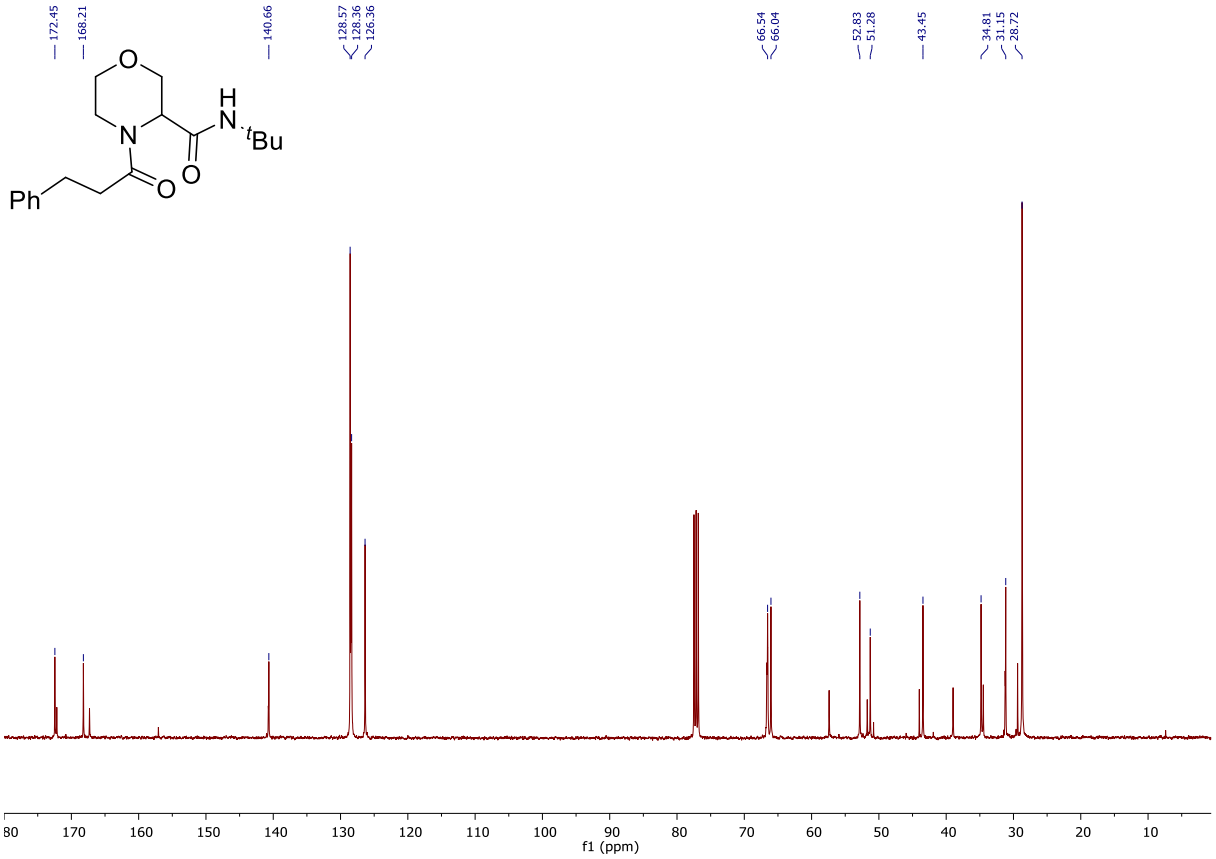
^{13}C NMR of **40** in C_6D_6



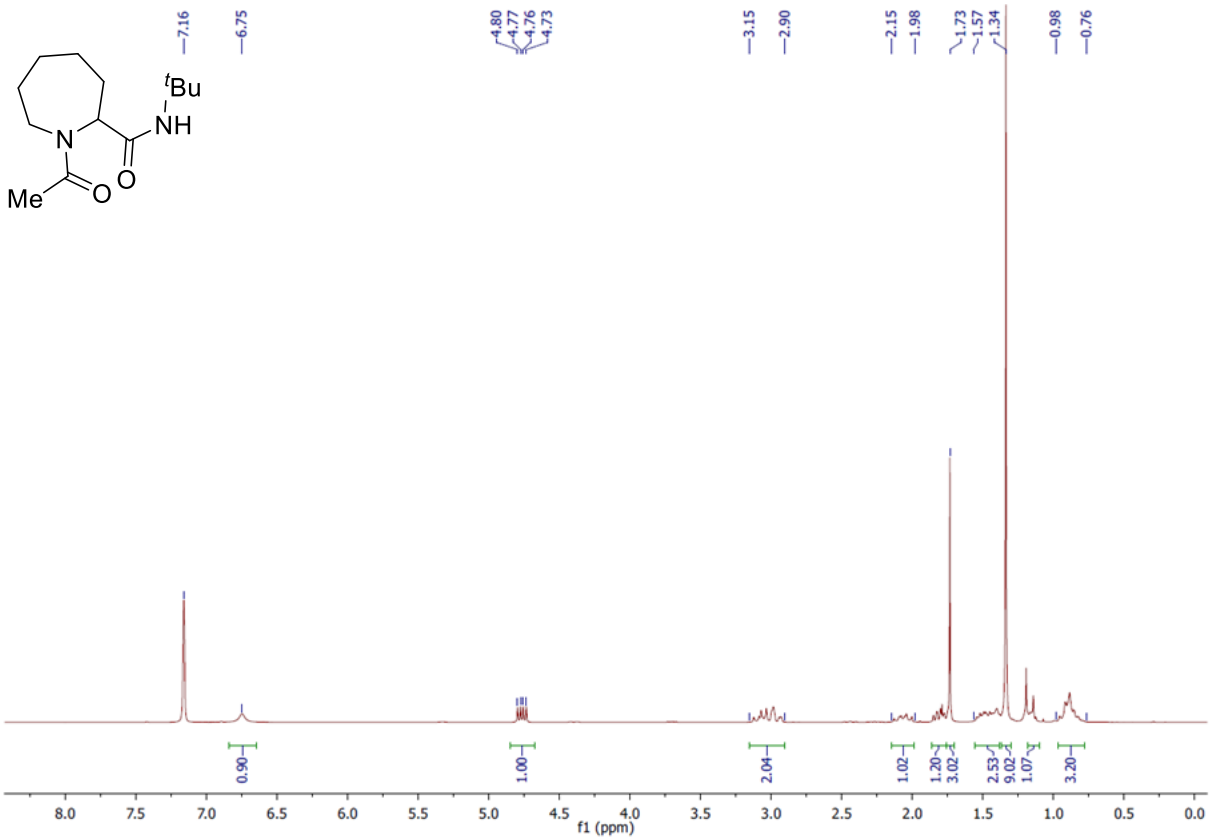
^{1}H NMR of **41** in C_6D_6



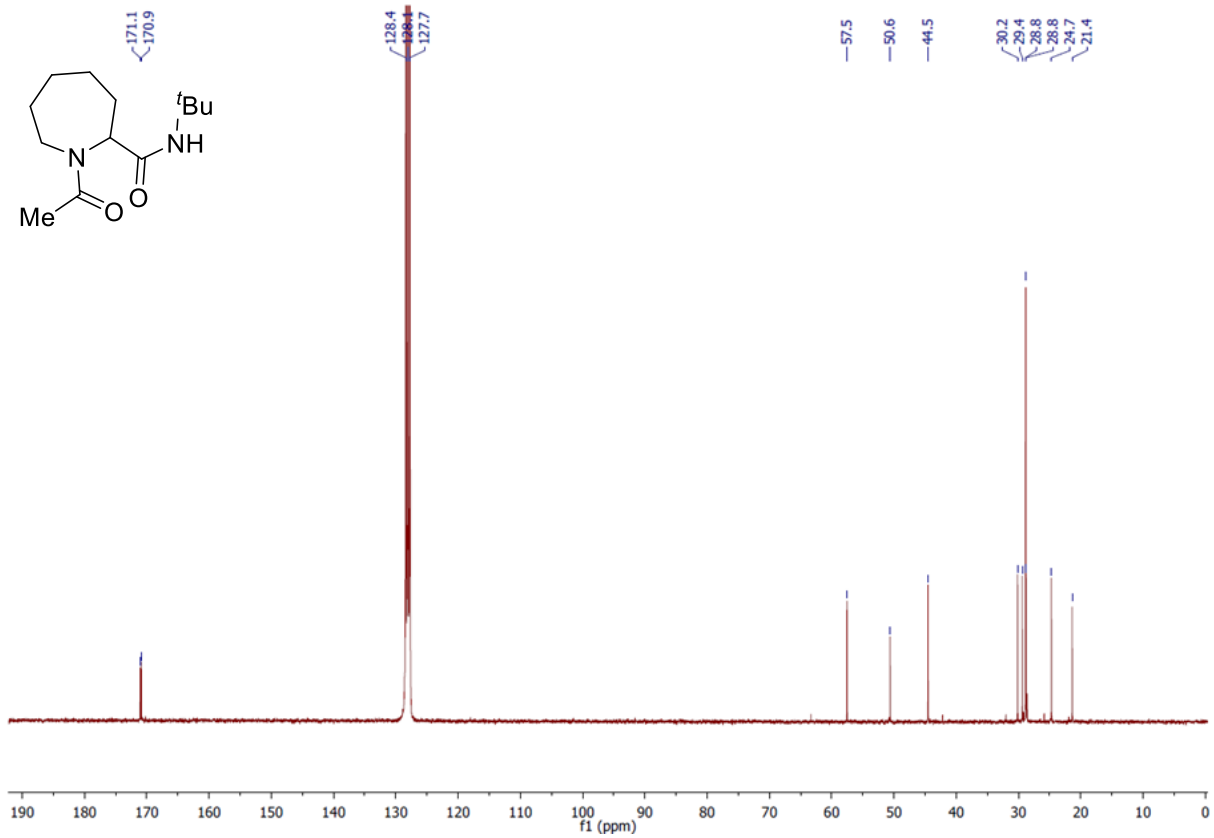
^{13}C NMR of **41** in $CDCl_3$



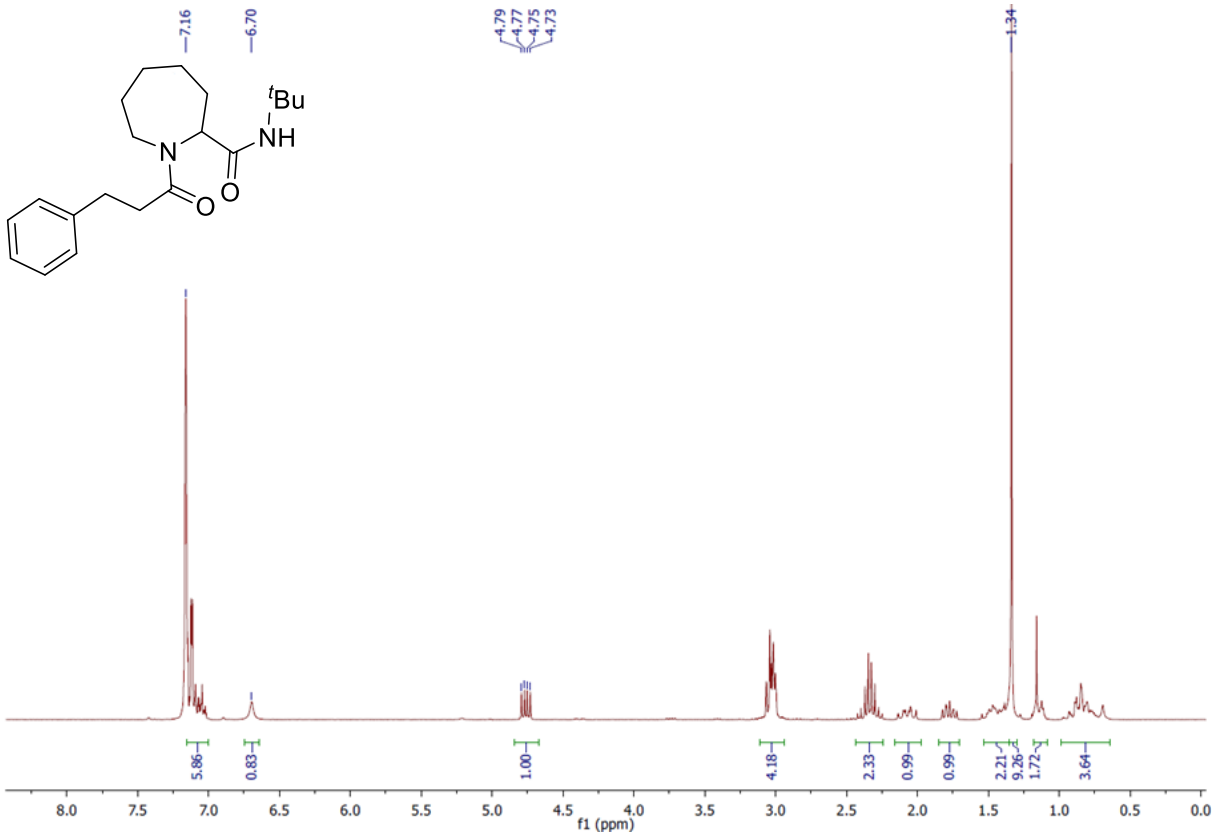
^{1}H NMR of **42** in C_6D_6



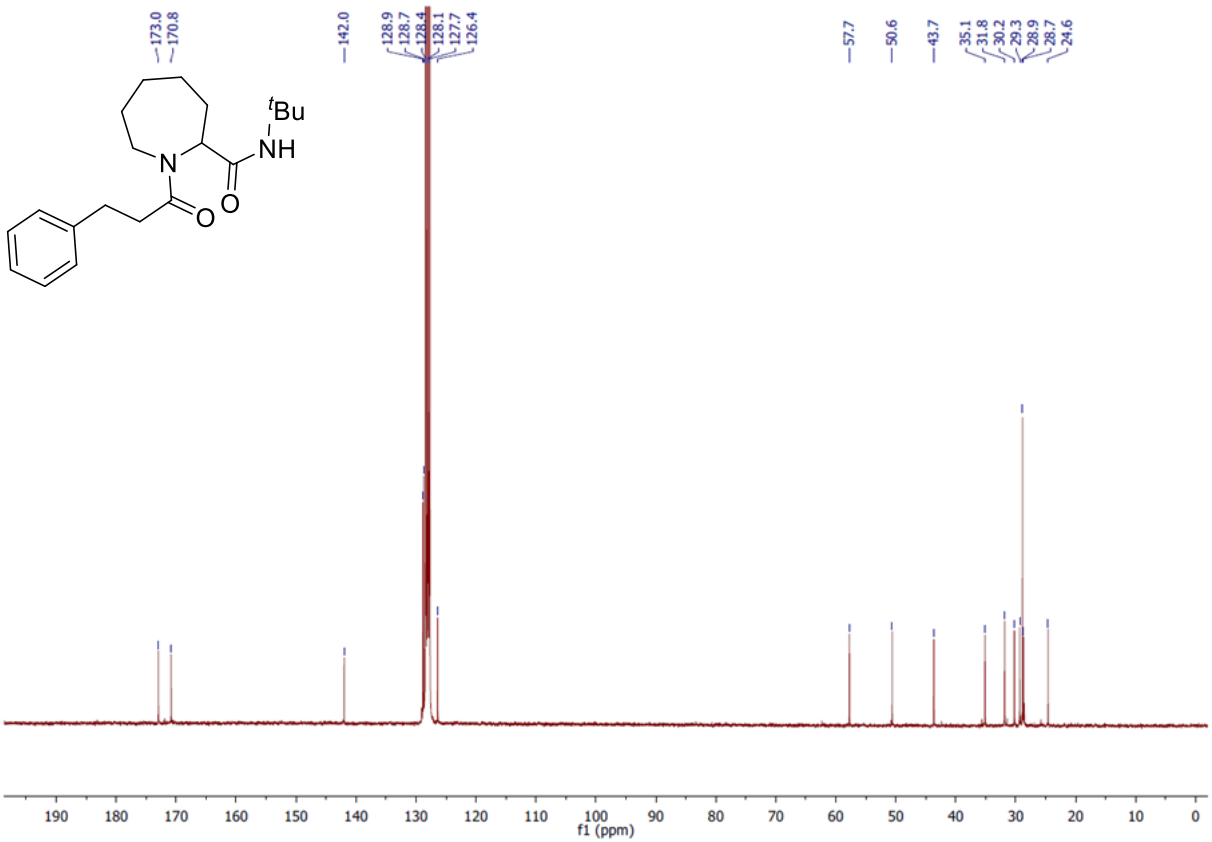
^{13}C NMR of **42** in C_6D_6



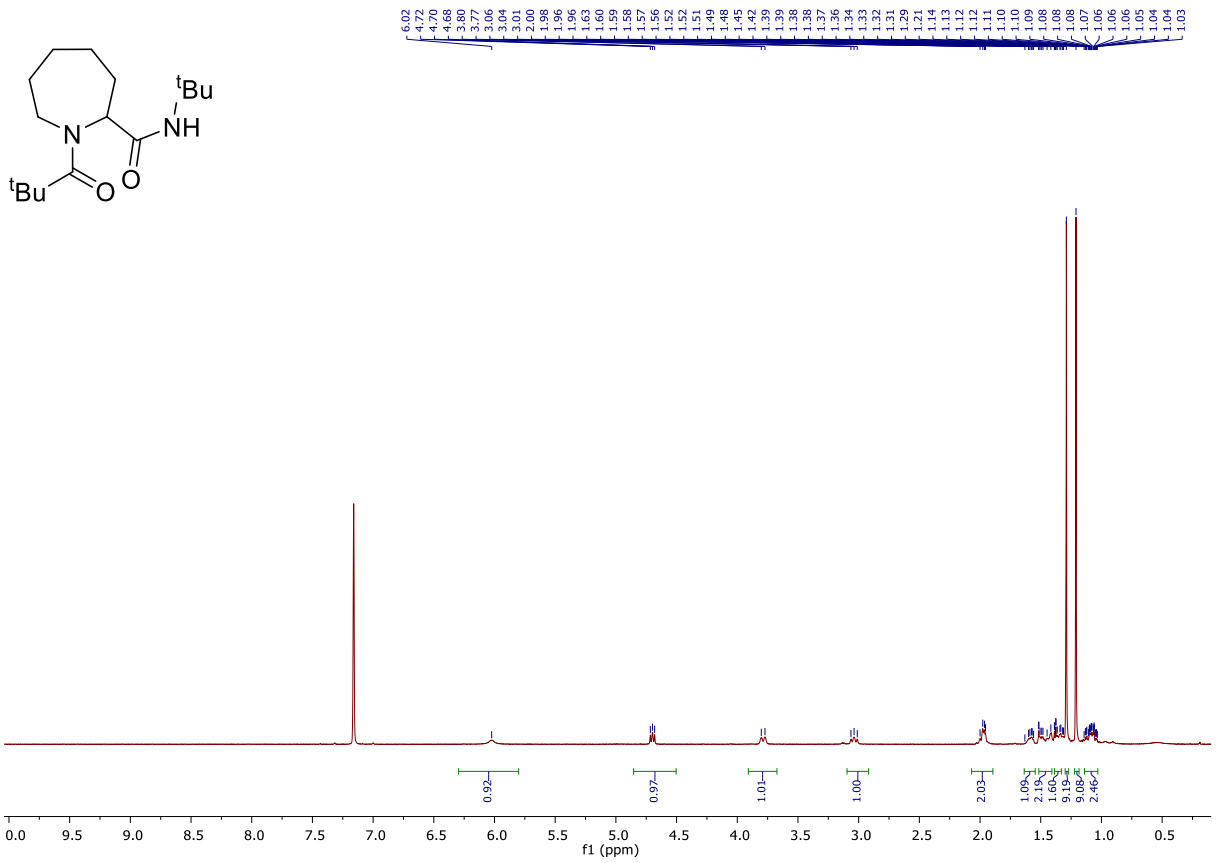
^{1}H NMR of **43** in C_6D_6



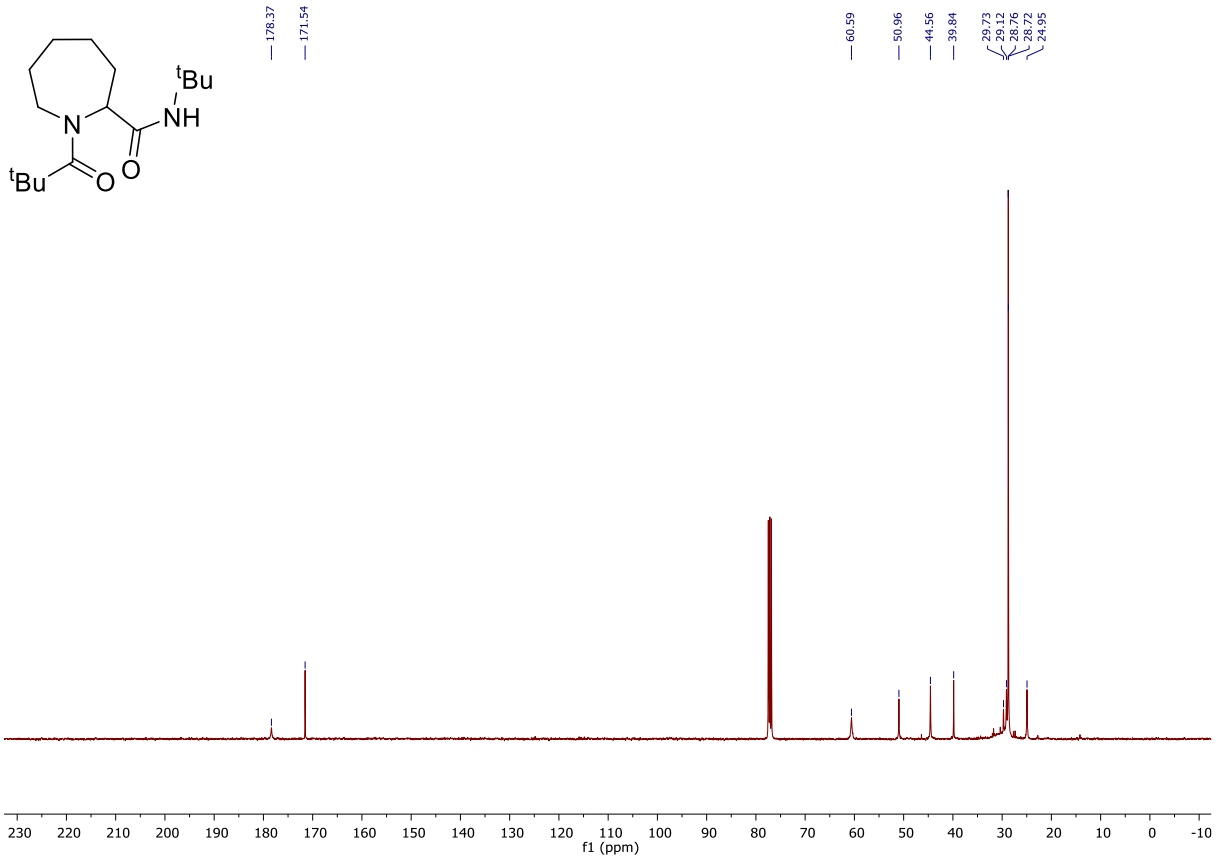
^{13}C NMR of **43** in C_6D_6



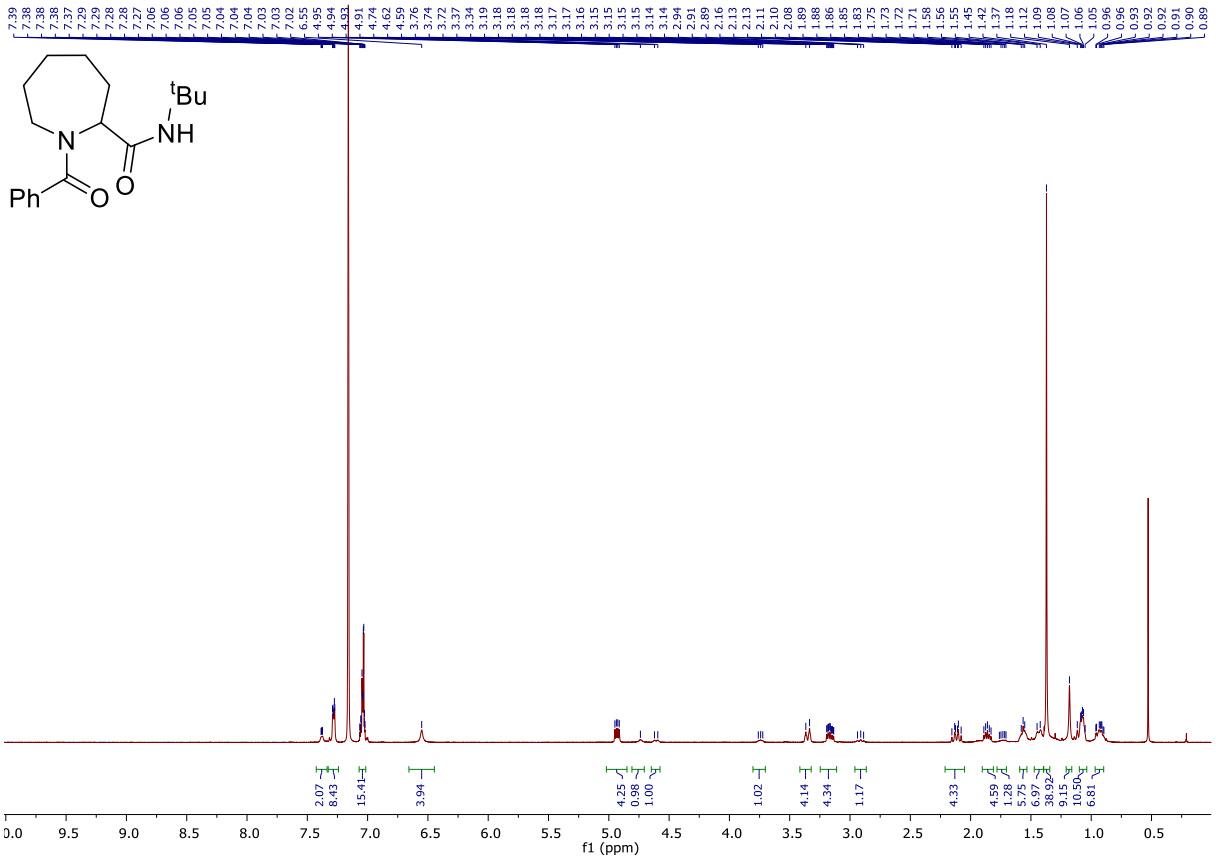
^{1}H NMR of **44** in C_6D_6



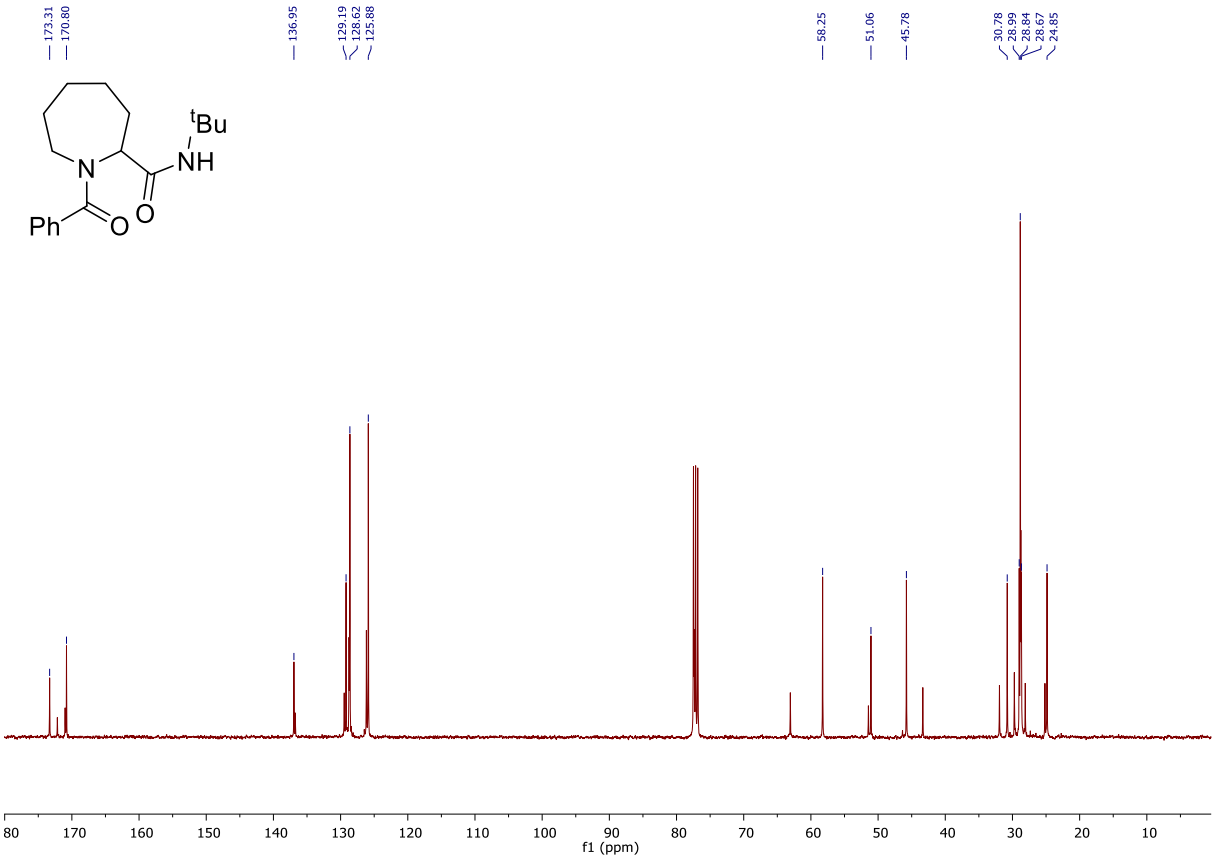
^{13}C NMR of **44** in $CDCl_3$



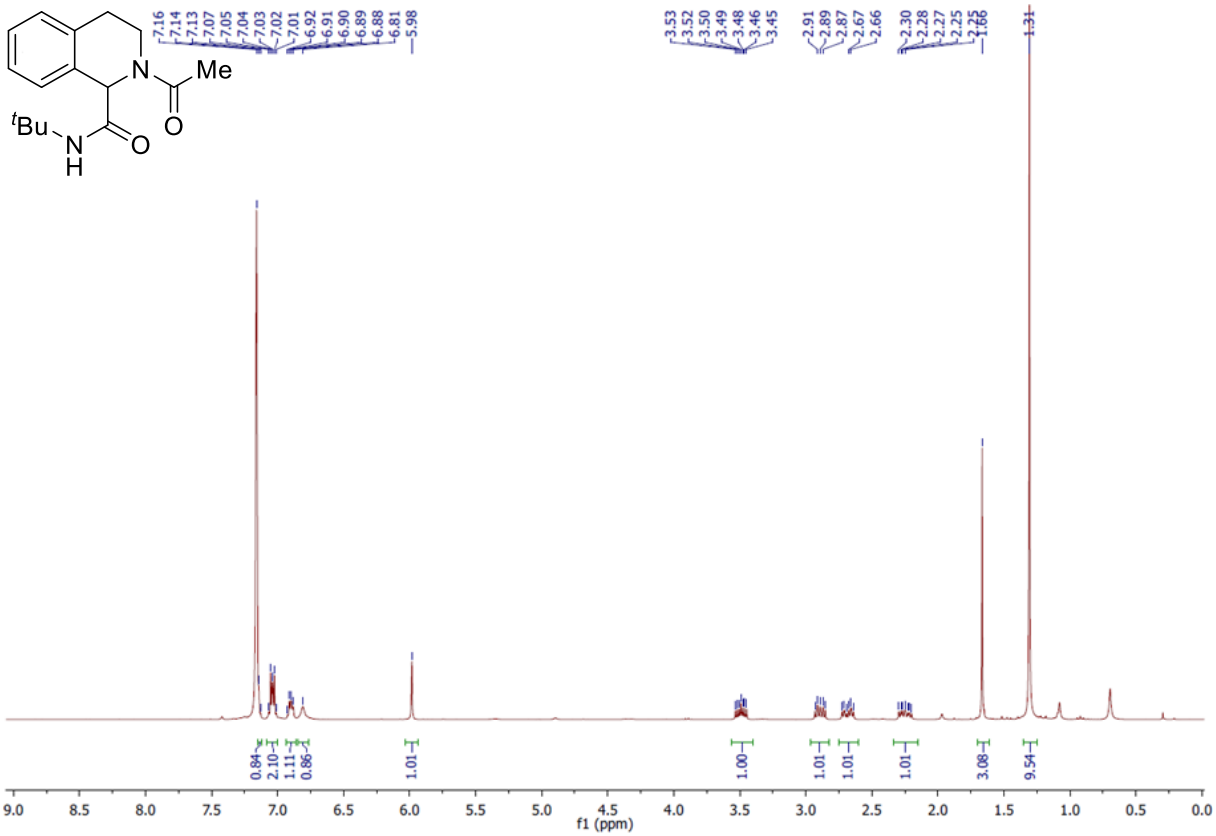
^{1}H NMR of **45** in C_6D_6



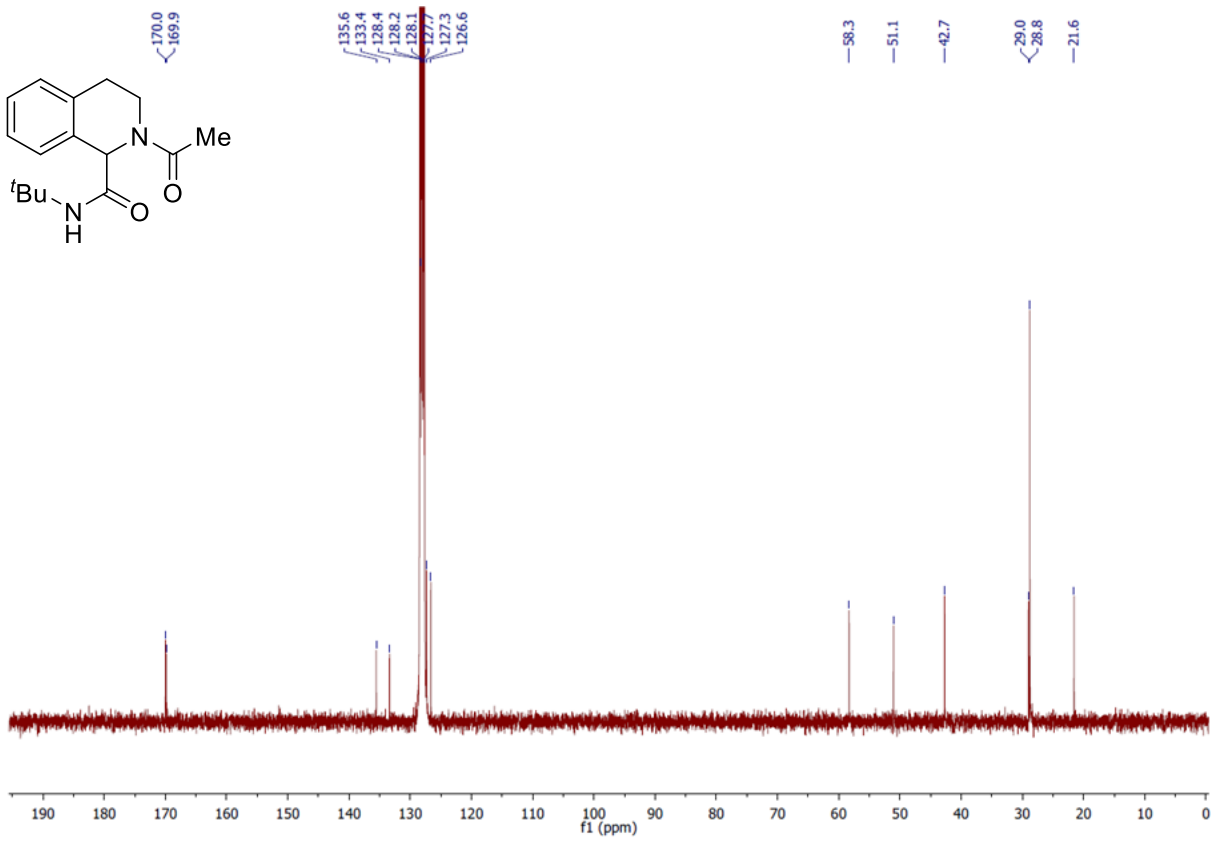
^{13}C NMR of **45** in $CDCl_3$



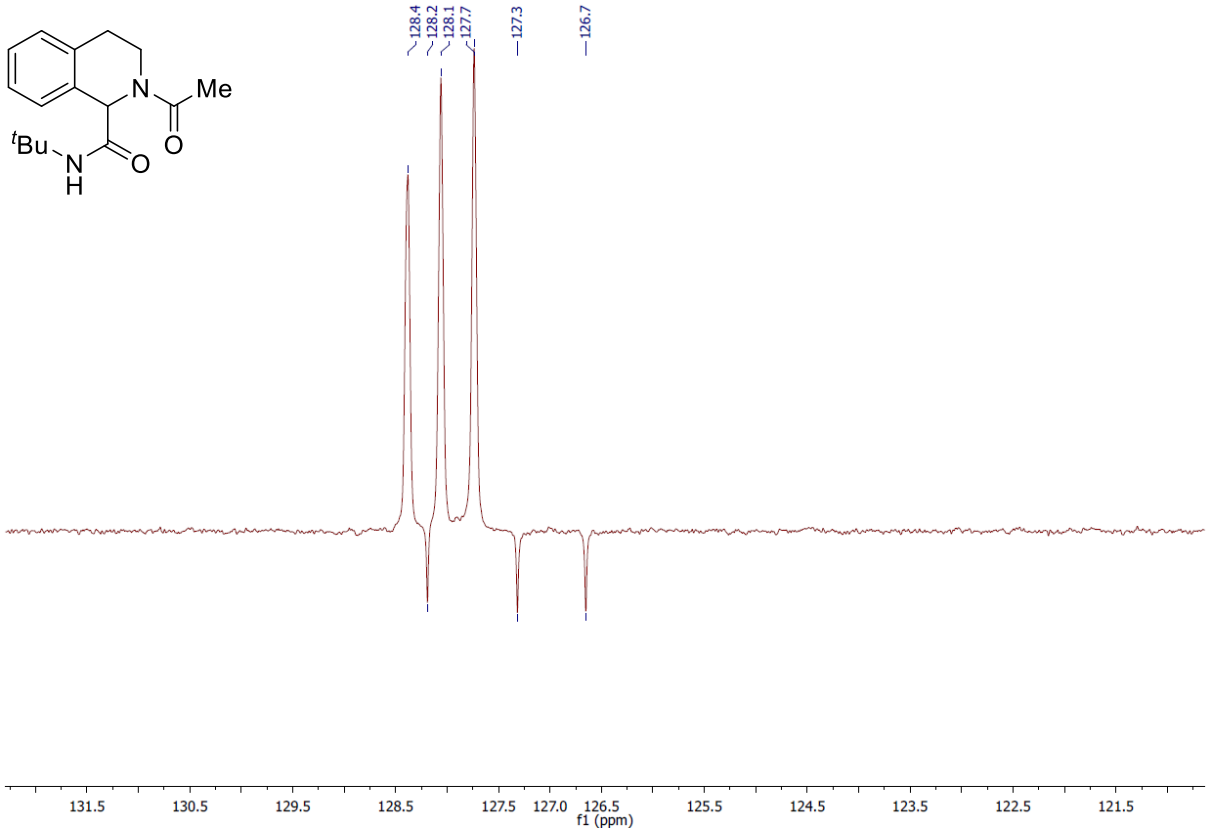
^{1}H NMR of **46** in C_6D_6



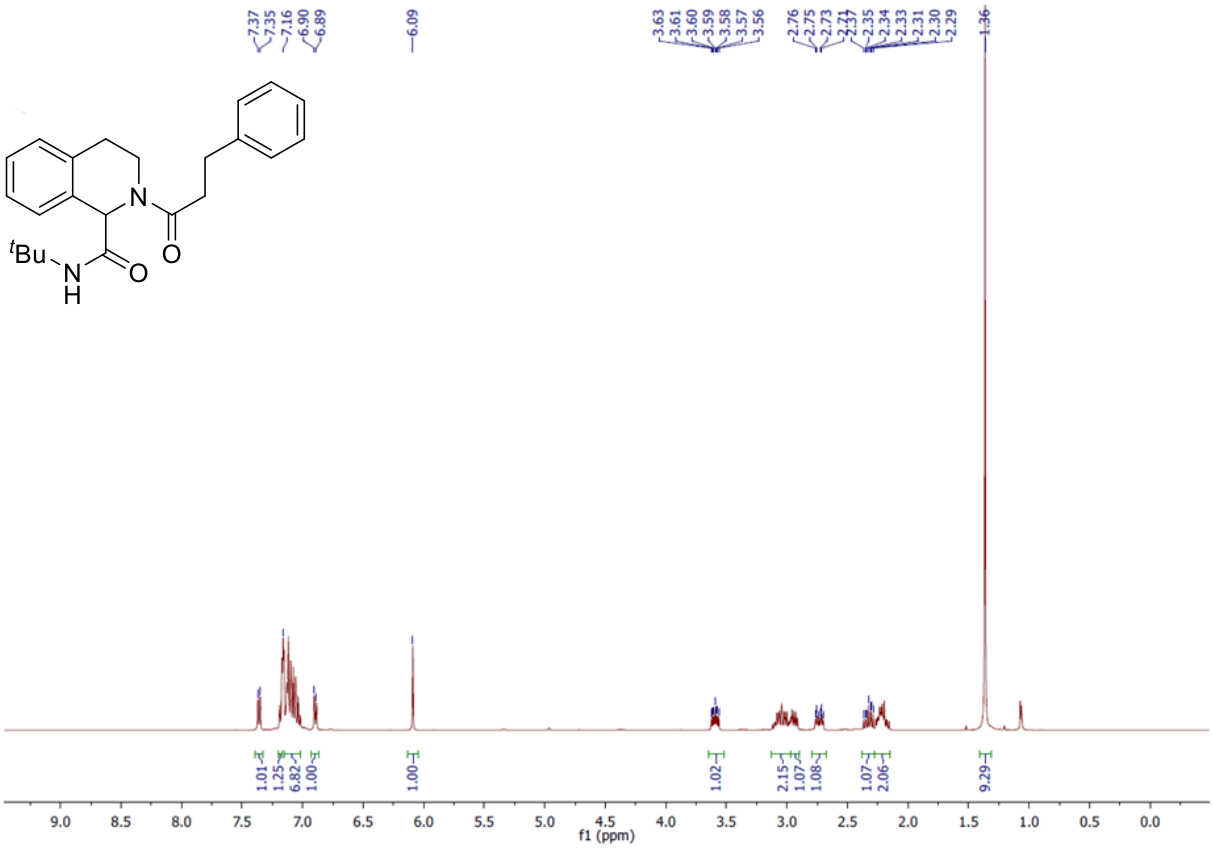
^{13}C NMR of **46** in C_6D_6



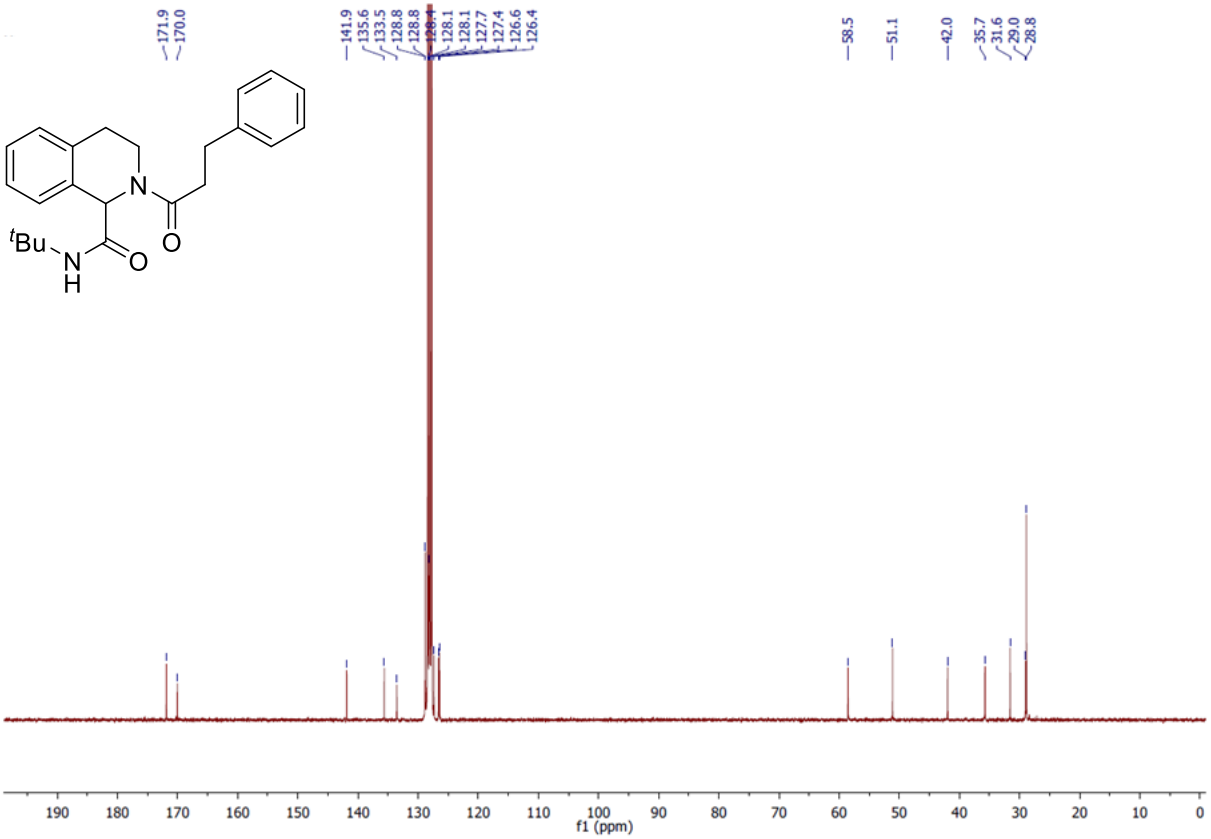
DEPT of **46** in C_6D_6



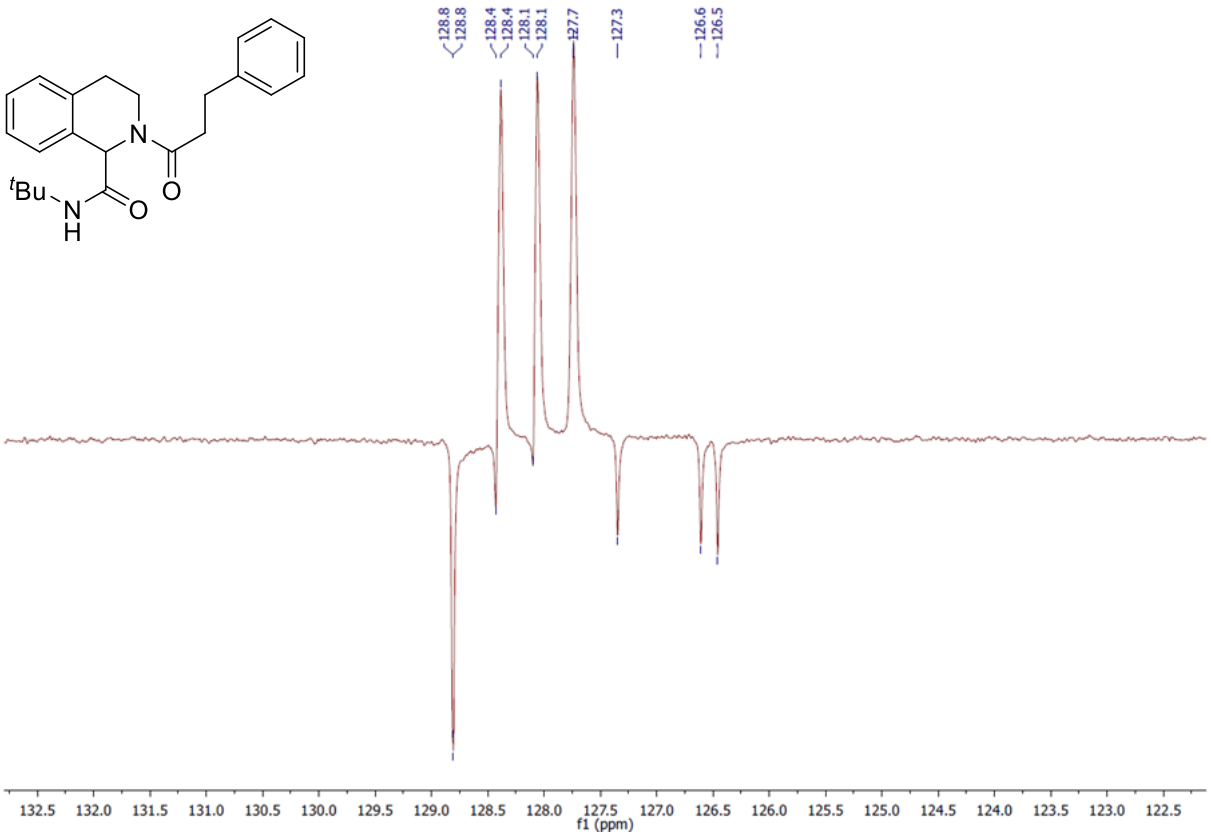
^{1}H NMR of **47** in C_6D_6



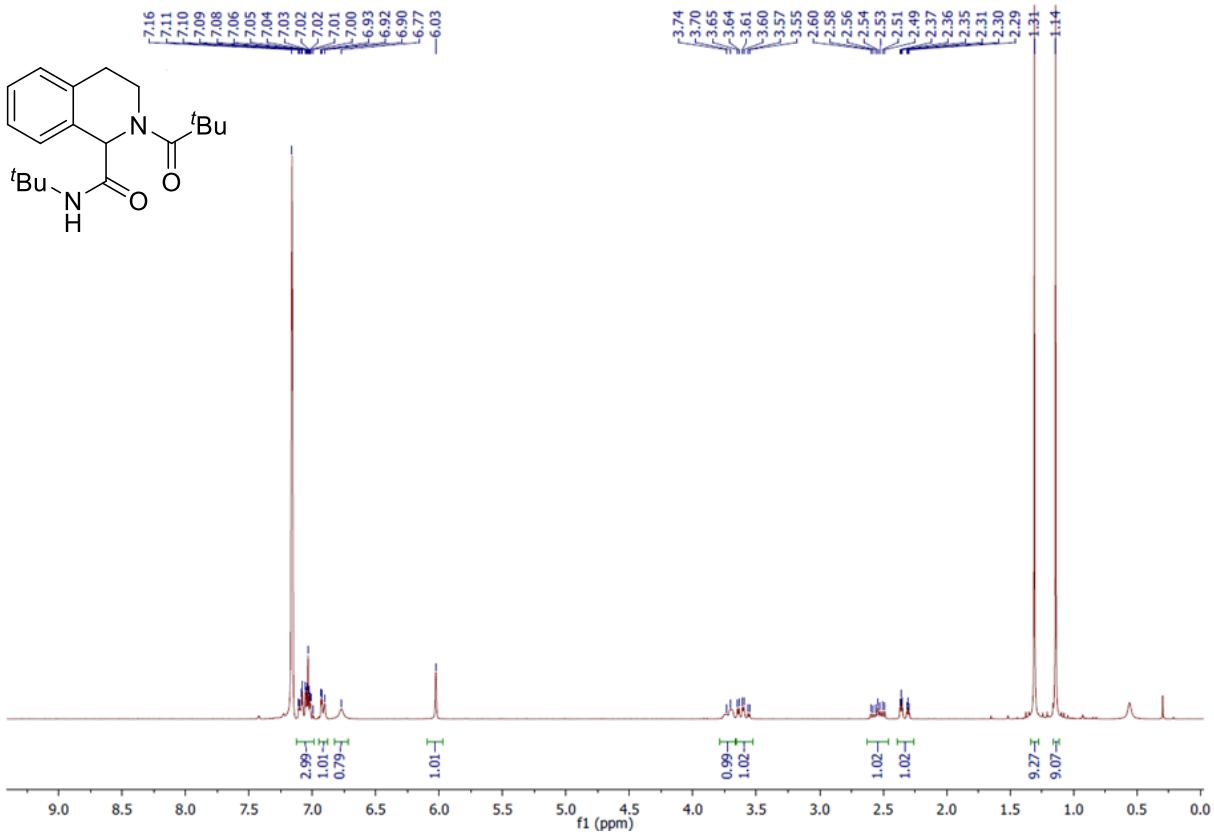
^{13}C NMR of **47** in C_6D_6



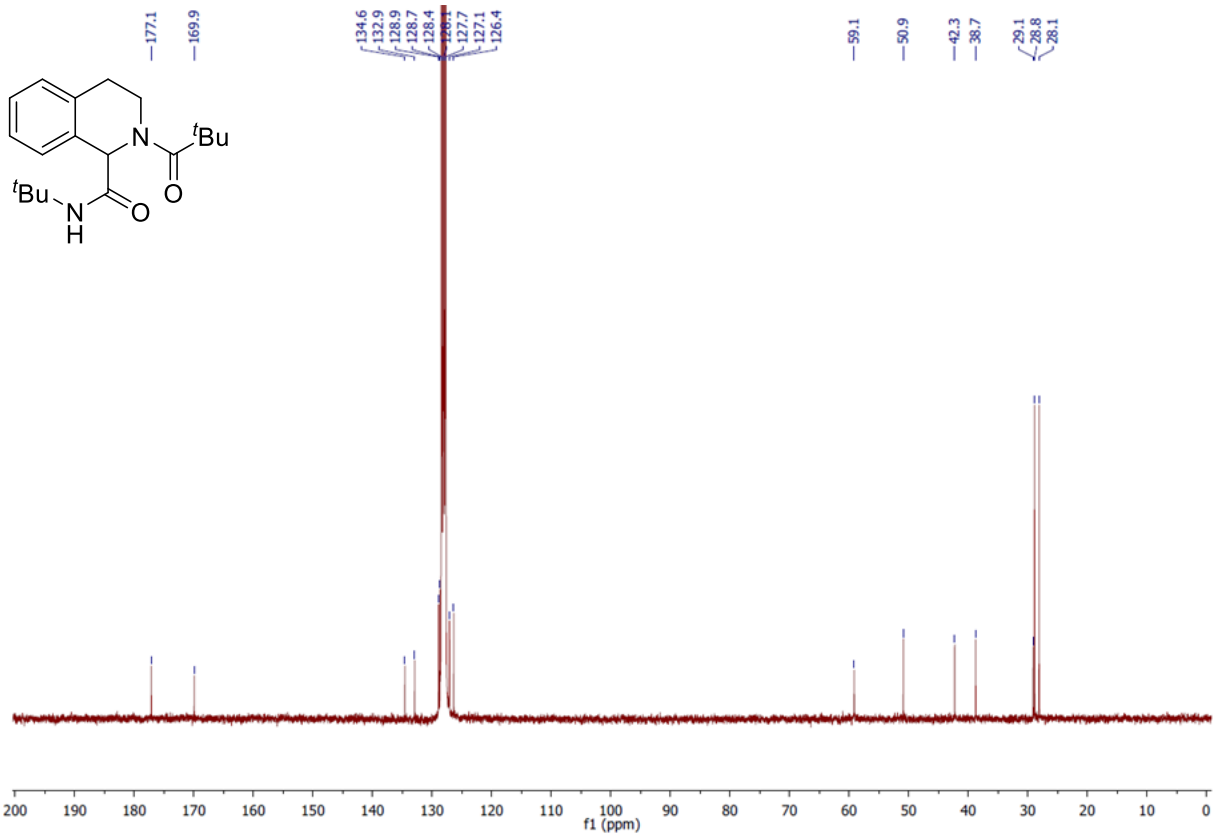
DEPT of **47** in C_6D_6



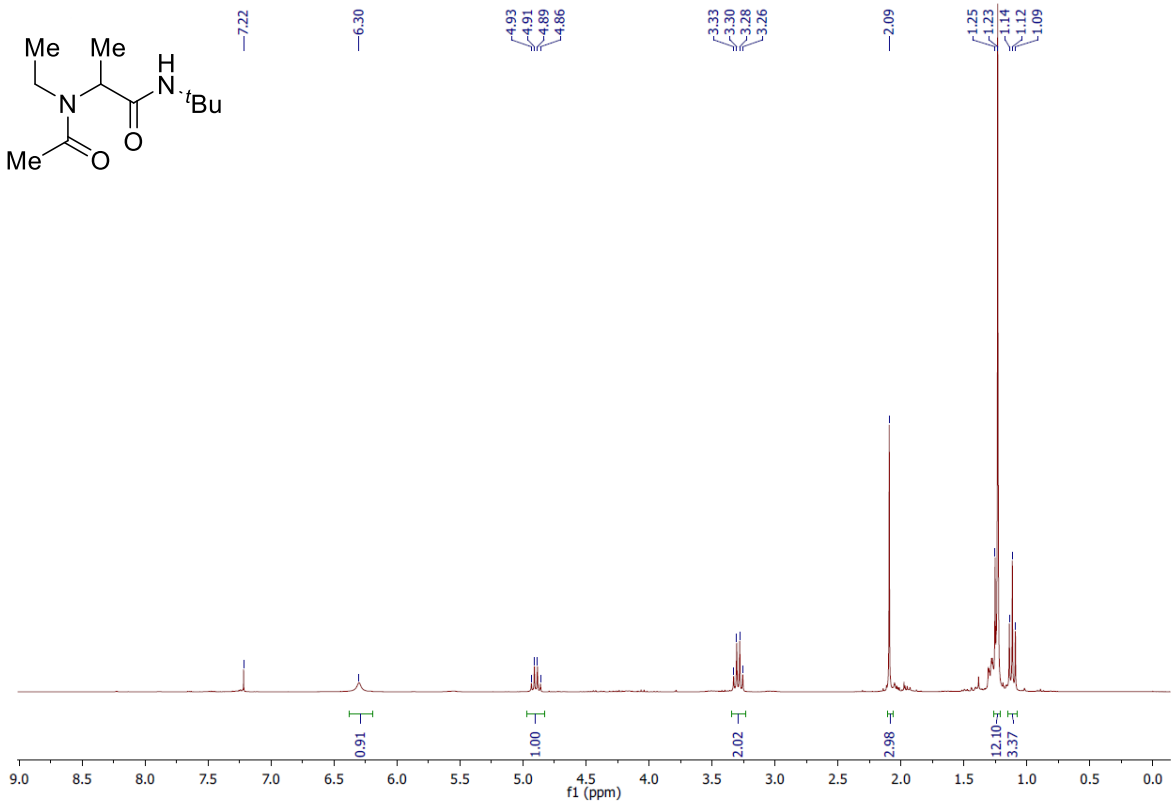
^{1}H NMR of **48** in C_6D_6



^{13}C NMR of **48** in C_6D_6



^{1}H NMR of **49** in $CDCl_3$



^{13}C NMR of **49** in $CDCl_3$