Electronic Supplementary Material (ESI) for Chemical Communications

Supporting Information

for

Addition of Lithium Carbenoids to Isocyanates: a Direct Access to Synthetically Useful *N*-substituted 2-Haloacetamides

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Materials and methods.

All ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance spectrometers operating at 200, 300, 400 or 500 MHz and at 50, 75, 100, or 125 MHz, respectively, from $CDCl_3$ solutions. The (residual) solvent signal was used as an internal standard which was related to TMS with δ 7.26 ppm (^{1}H) and δ 77.0 ppm (^{13}C). The ^{15}N and ^{19}F NMR experiments were conducted on a Bruker Avance 400 spectrometer (40 MHz and 377 MHz, respectively). The ^{15}N NMR spectra were referenced against external nitromethane, for the ^{19}F NMR spectra absolute referencing via the Ξ ratio was used. Spin-spin coupling constants (*J*) are given in Hz. Full and unambiguous assignment of ^{1}H, ^{13}C, ^{15}N and ^{19}F-NMR resonances was achieved by combining standard NMR techniques, such as fully ^{1}H-coupled ^{13}C-NMR spectra, APT, DEPT, HSQC, HMBC and NOESY experiments.

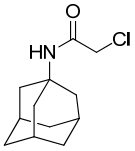
All melting points are uncorrected. Column chromatography purifications were conducted on silica gel 60 (40-63 μm). TLC was carried out on aluminum sheets precoated with silica gel 60F254; the spots were visualized under UV light (λ = 254 nm) and/or $KMnO_4$ (aq.) was used as revealing system.

Elementary microanalyses were carried out using a Leco® CHNS 932 equipment. IR absorption spectra were recorded on a Perkin-Elmer System 2000 FT-IR spectrophotometer.

General Procedure for the Chemoselective Addition of Li Carbenoids to Isocyanates.

To a cooled (- 78 °C) solution of the isocyanate (1.0 equiv.) in dry diethyl ether (1 M concentration) was added the dihalomethane derivative (1.5 equiv.) and, after 2 min, an ethereal solution of MeLi-LiBr (1.5 M, 1.2 equiv.) was added dropwise during 5 min. The resulting solution was stirred for the appropriate time (see Tables 1 and 2) at that temperature, before a saturated aqueous solution of NH_4Cl was added (2 mL / mmol substrate). After removal of the cooling bath, the mixture was stirred till it reached rt and then, extracted with additional diethyl ether and washed with water and brine. The organic phase was dried over anhydrous sodium sulfate, filtered and, after removal of the solvent under reduced pressure pure samples of haloacetamides were obtained.

_N_-Chloroacetyl-1-aminoadamantane (2a)[1]



By following the general procedure, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **2a** was obtained in 97% yield (839 mg) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.22 (bs, 1H), 3.90 (s, 2H), 2.12-2.03 (m, 3H), 2.03-1.95 (m, 6H), 1.66 (t, J = 2.8 Hz, 6H).

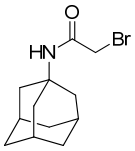
^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.5, 52.3, 42.8, 41.1, 36.1, 29.3.

IR (NaCl, ν_{max}, cm^{-1}): 3239, 3080, 2108, 1662, 1569, 1234.

Mp: 119 °C (lit.[1] 119-120 °C)

Elemental Analysis (%) for $C_{12}H_{18}ClNO$. Calcd: C, 63.29; H, 7.97; N, 6.15. Found: C, 63.42; H, 8.09; N, 6.27.

_N_-Bromoacetyl-1-aminoadamantane (2b)[2]



By following the general procedure, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), ICH_2Br (1.26 g, 0.43 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-bromoacetamide **2b** was obtained in 93% yield (962 mg) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.12 (bs, 1H), 3.77 (s, 2H), 2.10 (s, 3H), 2.01 (d, J = 3.0 Hz, 6H), 1.69 (t, J = 6.3 Hz, 6H).

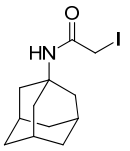
^{13}C NMR (50 MHz, $CDCl_3$) δ: 164.1, 52.5, 41.1, 36.2, 29.9, 29.3.

IR (NaCl, ν_{max}, cm^{-1}): 3243, 2105, 1661, 1572, 1232.

Mp: 124 °C (lit.[2] 123-125 °C).

Elemental Analysis (%) for $C_{12}H_{18}BrNO$. Calcd: C, 52.95; H, 6.67; N, 5.15. Found: C, 53.09; H, 6.82; N, 5.30.

_N_-Iodoacetyl-1-aminoadamantane (2c)



By following the general procedure, starting from 1-adamantyl isocyanate (0.67 g, 3.8 mmol), I_2CH_2 (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-iodoacetamide **2c** was obtained in 94% yield (1140 mg) as a yellow solid.

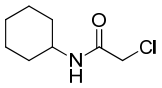
^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.17 (s, 1H), 3.60 (s, 2H), 2.22 – 1.81 (m, 9H), 1.77 – 1.57 (m, 6H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.86, 52.70, 41.18, 36.39, 29.44, 1.60.

IR (NaCl, ν_{max}, cm^{-1}): 3250, 1664, 1570, 1230, 996.

Elemental Analysis (%) for $C_{12}H_{18}INO$. Calcd: C, 45.16; H, 5.68; N, 4.39. Found: C, 45.31; H, 5.75; N, 4.52.

2-Chloro-*N*-cyclohexylacetamide (4a)[3]



By following the general procedure, starting from cyclohexyl isocyanate (0.47 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4a** was obtained in 97% yield (647 mg) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.40 (bs, 1H), 3.96 (s, 2H), 3.73-3.69 (m, 1H), 1.87-1.84 (m, 2H), 1.65-1.63 (m, 2H), 1.5-1.53 (m, 1H), 1.33-1.29 (m, 2H), 1.16-1.13 (m, 3H).

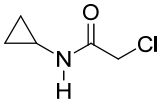
^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.8, 48.6, 42.7, 32.8, 25.4, 24.7.

IR (NaCl, ν_{max}, cm^{-1}): 3241, 1651, 1567, 1223.

Mp: 113 °C (lit.[3] 113-115 °C).

Elemental Analysis (%) for $C_8H_{14}ClNO$. Calcd: C, 54.70; H, 8.03; N, 7.97. Found: C, 54.83; H, 8.14; N, 8.12.

2-Chloro-*N*-cyclopropylacetamide (4b)



By following the general procedure, starting from isocyanatocyclopropane (0.32 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4b** was obtained in 95% yield (480 mg) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.64 (bs, 1H, NH), 4.01 (s, 2H, CH_2Cl), 2.74 (m, 1H, NCH), 0.82 (m, 2H. $CHCH_2CH_2$), 0.57 (m, 2H, $CHCH_2CH_2$).

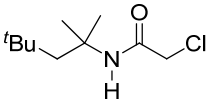
^{13}C NMR (100 MHz, $CDCl_3$) δ: 167.2 (C=O), 42.5 (CH_2Cl), 22.8 (NCH), 6.4 ($CHCH_2$), 6.4 ($CHCH_2$).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -262.5 (amide)

IR (NaCl, ν_{max}, cm^{-1}): 3246, 1648, 1230, 990.

Elemental Analysis (%) for C_5H_8ClNO. Calcd: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.15 ; H, 6.23; N, 10.24.

2-chloro-*N*-(2,4,4-trimethylpentan-2-yl)acetamide (4c)



By following the general procedure, starting from 2-isocyanato-2,4,4-trimethylpentane (0.59 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4c** was obtained in 95% yield (740 mg) as a white solid.

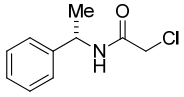
^{1}H NMR (200 MHz, $CDCl_3$) δ: 6.43 (s, 1H), 3.90 (s, 2H), 1.50 – 1.29 (m, 7H), 1.06 – 0.92 (m, 10H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 164.6, 55.8, 51.9, 43.1, 32.9, 31.8, 31.5, 31.2, 29.4, 28.8.

IR (NaCl, ν_{max}, cm^{-1}): 3251, 1656, 1236, 907.

Elemental Analysis (%) for $C_{10}H_{20}ClNO$. Calcd: C, 58.38; H, 9.80; N, 6.81. Found: C, 58.19; H, 9.95; N, 6.68

(*S*)-2-Chloro-*N*-(1-phenylethyl)acetamide (4d)



By following the general procedure, starting from (*S*)-methylbenzyl isocyanate (96 % *ee* purity) (0.56 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4d** was obtained in 96% yield (721 mg) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30-7.18 (m, 5H), 6.74 (s, 1H), 5.05 (quint., J = 7.0 Hz, 1H), 3.98 (m, 2H), 1.46 (d, J = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 165.0, 144.2, 128.8, 127.3, 125.8, 49.3, 42.7, 21.7.

IR (NaCl, ν_{max}, cm^{-1}): 3260, 2974, 1652, 1542, 1230, 907.

Mp: 100 °C (lit.[1] 101-102 °C).

Elemental Analysis (%) for $C_{10}H_{12}ClNO$. Calcd: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.89; H, 6.29; N, 7.24.

HPLC analysis: Column Chiralpak IA; eluent: hexane – *i*-propanol 95:5; 1 mL/min, 28 °C.

t_r^{min} = 8.713 s (*R*)-enantiomer, t_r^{maj} = 11.194 s. (*S*)-enantiomer. 96% *ee* purity.

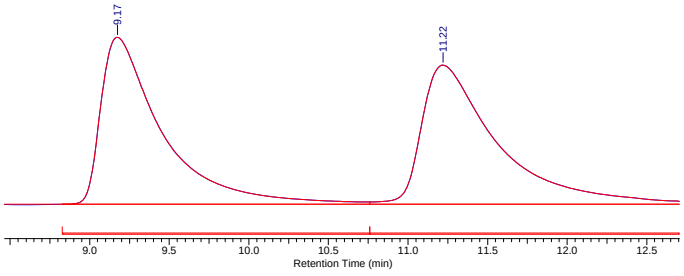
Racemic sample: t_r = 9.173 s (*R*)-enantiomer, t_r^{maj} = 11.219 s. (*S*)-enantiomer

Analytical data for ***rac*-(4d)** match perfectly with those ones reported for the enantiopure compound.

Racemic

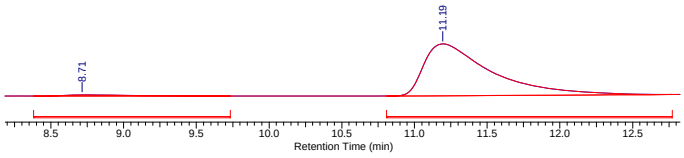
DAD1A.ch

Retention time (min)	Area [mAU*s]	Area [%]
9.173	15940133.000	49.585
11.220	16207125.000	50.415

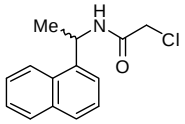


Enantiopure

Retention time (min)	Area [mAU*s]	Area [%]
8.713	615411.563	2.110
DAD1A,ch 11.193	23051788.000	97.890



(*R*)-2-Chloro-*N*-(1-(naphthalen-1-yl)ethyl)acetamide (4e)[4]



By following the general procedure, starting from (*R*)-(−)-1-(1-naphthyl)ethyl isocyanate (> 99 % *ee* purity) (0.75 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4e** was obtained in 97% yield (913 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H,), 7.86 (d, *J* = 7.6 Hz, 1H), 7.56 (m, 4H), 6.81 (s, 1H), 4.15 (s, 2H), 1.74 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.4, 137.0, 133.5, 130.5, 128.5, 128.2, 126.2, 125.5, 124.8, 122.6, 122.1, 44.8, 42.2, 20.4.

IR (NaCl, ν_{max}, cm^{-1}): 3284, 1649, 1537, 1231.

Mp: 140 °C (lit.[4] 140 °C).

Elemental Analysis (%) for $C_{14}H_{14}ClNO$. Calcd: C, 67.88; H, 5.70; N, 5.65. Found: C, 67.99; H, 5.87; N, 5.82.

HPLC analysis: Column Chiralcel OD-H; eluent: hexane – *i*-propanol 80:20; 1 mL/min, 28 °C.

t_r^{maj} = 6.393 s (*R*)-enantiomer, t_r^{min} = 11.586 s; (*R*)-enantiomer. > 99% *ee* purity.

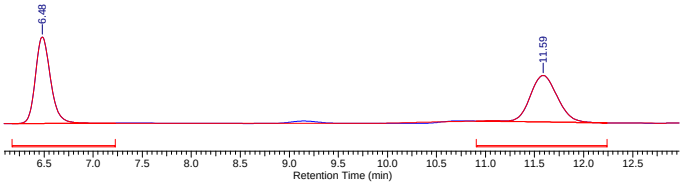
Racemic sample: t_r = 6.481 s (*R*)-enantiomer; t_r = 11.586 s, (*S*)-enantiomer

Analytical data for ***rac*-(4e)** match perfectly with those ones reported for the enantiopure compound.

Racemic

DAD1A,Ch1

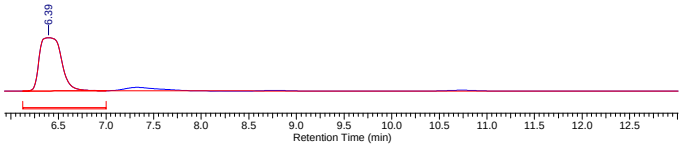
Retention time (min)	Area [mAU*s]	Area [%]
6.480	11765876.000	48.663
11.587	12412223	51.337



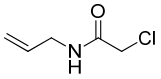
Enantiopure

DAD1A.ch

Retention time (min)	Area [mAU*s]	Area [%]
6.393	39227660.000	> 99
11.587	-	< 1



_N_-Allyl-2-chloroacetamide (4f)[5]



By following the general procedure, starting from allyl isocyanate (0.32 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4f** was obtained in 98% yield (508 mg) as a light orange oil.

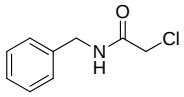
^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.69 (bs, 1H), 5.82-5.74 (m, 1H), 5.18-5.10 (m, 2H), 4.00 (s, 2H), 3.88-3.86 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 164.8, 133.2, 115.7, 42.0, 41.1.

IR (NaCl, ν_{max}, cm^{-1}): 3294, 1662, 1542, 1419, 1261, 992.

Elemental Analysis (%) for C_5H_8ClNO. Calcd: C, 44.96; H, 6.04; N, 10.49. Found: C, 45.11; H, 6.21; N, 10.68.

_N_-Benzyl-2-chloroacetamide (4g)[6]



By following the general procedure, starting from benzyl isocyanate (0.50 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4g** was obtained in 95% yield (663 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31-7.16 (m, 5H), 6.81 (bs, 1H), 4.42 (d, J = 6.1 Hz, 2H), 4.02 (s, 2H).

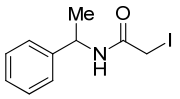
^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.9, 137.3, 128.8, 127.9, 127.8, 43.9, 42.6.

IR (NaCl, ν_{max}, cm^{-1}): 3286, 1658, 1535, 994.

Mp: 95 °C (lit.[6] 95-96 °C)

Elemental Analysis (%) for $C_9H_{10}ClNO$. Calcd: C, 58.86; H, 5.49; N, 7.63. Found: C, 59.11; H, 5.65; N, 7.84.

2-iodo-_N_-(1-phenylethyl)acetamide (4h)



By following the general procedure, starting from methylbenzyl isocyanate (0.56 g, 3.8 mmol), I_2CH_2 (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-iodoacetamide **4h** was obtained in 98% yield (1099 mg) as a light yellow solid.

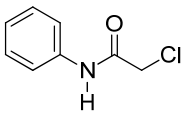
^{1}H NMR (300 MHz, acetone-d_6) δ: 7.93 (bs, 1H), 7.33-7.13 (m, 5H), 4.99-4.93 (m, 1H), 3.71 (m, 2H), 1.37 (m, 3H).

^{13}C NMR (75 MHz, acetone-d_6) δ: 167.0, 144.6, 128.8, 127.3, 126.6, 49.5, 22.0, 0.0.

IR (NaCl, ν_{max}, cm^{-1}): 3298, 1655, 1551, 994.

Elemental Analysis (%) for $C_{10}H_{12}INO$. Calcd: C, 41.54; H, 4.18; N, 4.84. Found: C, 41.63; H, 4.32; N, 5.01.

2-Chloro-_N_-phenylacetamide (4i)[7]



By following the general procedure, starting from isocyanatobenzene (0.45 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4i** was obtained in 98% yield (632 mg) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.27 (bs, 1H), 7.63 – 7.49 (m, 2H), 7.47 – 7.30 (m, 2H), 7.24 – 7.02 (m, 1H), 4.18 (s, 2H).

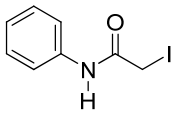
^{13}C NMR (50 MHz, $CDCl_3$) δ: 164.0, 136.8, 129.2, 125.4, 120.3, 43.0.

IR (NaCl, ν_{max}, cm^{-1}): 3262, 1651, 1546, 1235, 990, 907.

Mp: 134 °C (lit.[7] 134-135 °C).

Elemental Analysis (%) for C_8H_8ClNO. Calcd: C, 56.65; H, 4.75; N, 8.26. Found: C, 56.81; H, 4.93; N, 8.12.

2-Iodo-*N*-phenylacetamide (4j)[8]



By following the general procedure, starting from isocyanatobenzene (0.45 g, 3.8 mmol), I_2CH_2 (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-iodoacetamide **4j** was obtained in 96% yield (952 mg) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.86 (bs, 1H), 7.62 – 7.43 (m, 2H), 7.43 – 7.28 (m, 2H), 7.21 – 7.05 (m, 1H), 3.86 (s, 2H).

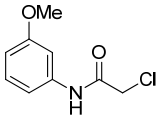
^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.3, 129.2, 125.2, 120.1, 0.1.

IR (NaCl, ν_{max}, cm^{-1}): 3271, 1647, 1241, 992.

Mp: 145 °C (lit.[8] 143-146 °C).

Elemental Analysis (%) for C_8H_8INO. Calcd: C, 36.81; H, 3.09; N, 5.37. Found: C, 36.81; H, 3.09; N, 5.37.

2-Chloro-*N*-(3-methoxyphenyl)acetamide (4k)[9]



By following the general procedure, starting from 3-methoxyphenyl isocyanate (0.57 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4k** was obtained in 94% yield (713 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 (bs, 1H), 7.21-7.15 (m, 2H), 6.94 (m, 1H), 6.67-6.64 (m, 1H), 4.11 (s, 2H), 3.74 (s, 3H).

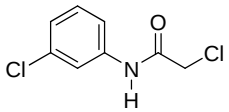
^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.7, 160.3, 137.8, 129.9, 112.2, 111.0, 105.9, 55.4, 42.9.

IR (NaCl, ν_{max}, cm^{-1}): 3291, 1661, 1543, 1376, 1254

Mp: 93 °C (lit.[9] 92-94 °C).

Elemental Analysis (%) for $C_9H_{10}ClNO_2$. Calcd: C, 54.15; H, 5.05; N, 7.02. Found: C, 54.33; H, 5.23; N, 7.27.

2-chloro-*N*-(3-chlorophenyl)acetamide (4l)[7]



By following the general procedure, starting from 1-chloro-3-isocyanatobenzene (0.58 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4l** was obtained in 96% yield (744 mg) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 8.29 (bs, 1H), 7.69 (t, *J* = 2.0 Hz, 1H), 7.51 – 7.28 (m, 2H), 7.25 – 7.10 (m, 1H), 4.21 (s, 2H).

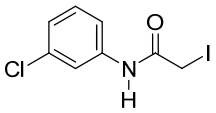
^{13}C NMR (50 MHz, $CDCl_3$) δ: 164.34, 138.19, 135.25, 130.55, 125.75, 120.63, 118.48, 43.24.

IR (NaCl, ν_{max}, cm^{-1}): 3278, 1661, 1267, 990.

Mp: 100 °C (lit.[7] 98-100 °C).

Elemental Analysis (%) for $C_8H_7Cl_2NO$. Calcd: C, 47.09; H, 3.46; Cl, 34.75; N, 6.86; O, 7.84

***N*-(3-Chlorophenyl)-2-iodoacetamide (4m)**



By following the general procedure, starting from 1-chloro-3-isocyanatobenzene (0.58 g, 3.8 mmol), I_2CH_2 (1.53 g, 0.46 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-iodooacetamide **4m** was obtained in 93% yield (1.044 g) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.99 (bs, 1H), 7.66 (t, *J* = 1.9 Hz, 1H), 7.46 – 7.28 (m, 2H), 7.16 (dt, *J* = 7.8, 1.6 Hz, 1H), 3.90 (s, 2H).

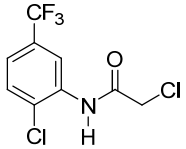
^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.89, 138.81, 135.18, 130.50, 125.52, 120.51, 118.38, -0.00.

IR (NaCl, ν_{max}, cm^{-1}): 3289, 1659, 909.

Mp: 84-85°C.

Elemental Analysis (%) for C_8H_7ClINO. Calcd: C, 32.52; H, 2.39; N, 4.74. Found: C, 32.39; H, 2.21; N, 4.88.

2-Chloro-*N*-(2-chloro-5-(trifluoromethyl)phenyl)acetamide (4n)



By following the general procedure, starting from 1-chloro-2-isocyanato-4-(trifluoromethyl)benzene (0.80 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4n** was obtained in 98% yield (1.013 g) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ:9.01 (bs, 1H, NH), 8.73 (d, *J* = 2.0Hz, 1H, Ph H-6), 7.51 (m, 1H, Ph H-3), 7.34 (m, 1H, Ph H-4), 4.25 (s, 2H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.1 (C=O), 134.2 (Ph C-1), 130.3 (q, *J* = 33.2 Hz, Ph C-5), 129.6 (Ph C-3), 123.4 (q, *J* = 272.6 Hz, CF_3), 121.9 (q, *J* = 3.8Hz, Ph C-4), 117.9 (q, *J* = 4.0 Hz, Ph C-6), 44.0 (CH_2Cl).

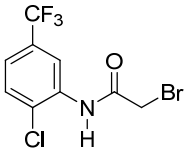
^{15}N NMR (40 MHz, $CDCl_3$) δ: -259.3 (amide)

^{19}F NMR (235 MHz, $CDCl_3$) δ: -62.4 (q, *J* = 0.7 Hz, CF_3)

IR (NaCl, ν_{max}, cm^{-1}): 3293, 1664, 1242, 990.

Elemental Analysis (%) for $C_9H_6Cl_2F_3NO$. Calcd: C, 39.73; H, 2.22; N, 5.15. Found: C, 39.56; H, 2.07; N, 5.29.

***N*-(2-chloro-5-(trifluoromethyl)phenyl)-2-iodoacetamide (4o)**



By following the general procedure, starting from 1-chloro-2-isocyanato-4-(trifluoromethyl)benzene (0.80 g, 3.8 mmol), ICH_2Br (1.26 g, 0.43 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-bromoacetamide **4o** was obtained in 88% yield (1.21 g) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ:8.89 (bs, 1H, NH), 8.71 (d, *J* = 1.8 Hz, 1H, Ph H-6), 7.52 (d, *J* = 8.4 Hz, 1H, Ph H-3), 7.35 (dd, *J* = 8.4, 2.0 Hz, 1H, Ph H-4), 4.09 (s, 2H, CH_2Cl).

^{13}C NMR (100 MHz, $CDCl_3$) δ: 163.6 (C=O), 134.5 (Ph C-1), 130.3 (q, *J* = 33.2 Hz, Ph C-5), 129.6 (Ph C-3), 123.4 (q, *J* = 272.5 Hz, CF_3), 121.9 (q, *J* = 3.8 Hz, Ph C-4), 117.9 (q, *J* = 4.0 Hz, Ph C-6), 29.4 (CH_2Br).

^{15}N NMR (40 MHz, $CDCl_3$) δ: -257.3 (amide)

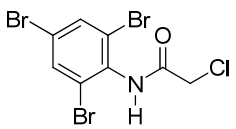
^{19}F NMR (235 MHz, $CDCl_3$) δ: -62.7 (s, CF_3)

IR (NaCl, ν_{max}, cm^{-1}): 3288, 1662, 1246, 996, 910.

Mp: 87-88 °C.

Elemental Analysis (%) for $C_9H_6ClIF_3NO$. Calcd: C, 29.74; H, 1.66; N, 3.85. Found: C, 29.56; H, 1.50; N, 3.69.

2-Chloro-*N*-(2,4,6-tribromophenyl)acetamide (4p)



By following the general procedure, starting from 1,3,5-tribromo-2-isocyanatobenzene (1.46 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4p** was obtained in 82% yield (1.27 g) as a white solid.

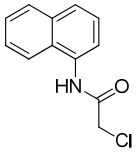
^{1}H NMR (200 MHz, $CDCl_3$) δ:7.50 (s, 2H), 4.57 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$) δ: 141.46, 133.93, 108.94 43.6.

IR (NaCl, ν_{max}, cm^{-1}): 3287, 1660, 998.

Elemental Analysis (%) for $C_9H_6ClIF_3NO$. Calcd: C, 23.65; H, 1.24; N, 3.45. Found: C, 23.79; H, 1.36; N, 3.62.

2-chloro-*N*-(naphthalen-1-yl)acetamide (4q)[10]



By following the general procedure, starting from 1-naphthyl isocyanate (0.64 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4q** was obtained in 92% yield (768 mg) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.78 (bs, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.88 (m, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.58-7.51 (m, 3H), 4.36 (s, 2H).

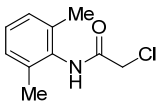
^{13}C NMR (125 MHz, $CDCl_3$) δ: 164.3, 134.1, 131.2, 128.9, 127.0, 126.9, 126.7, 126.5, 126.2, 125.7, 120.6, 120.2, 43.3.

IR (NaCl, ν_{max}, cm^{-1}): 3273, 2963, 1663, 1552, 1509, 1399, 1270, 1251.

Mp: 154 °C (lit.[11] 153-159 °C).

Elemental Analysis (%) for $C_{12}H_{10}ClNO$. Calcd: C, 65.61; H, 4.59; N, 6.38. Found: C, 65.80; H, 4.77; N, 6.59.

2-Chloro-*N*-(2,6-dimethylphenyl)acetamide (4r)[12]



By following the general procedure, starting from 2,6-dimethylphenyl isocyanate (0.56 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4r** was obtained in 97% yield (729 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (bs, 1H), 7.15-7.10 (m, 3H), 4.26 (s, 2H), 2.25 (s, 6H).

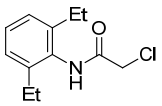
^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.3, 135.4, 132.7, 128.4, 127.9, 42.8, 18.3.

IR (NaCl, ν_{max}, cm^{-1}): 3266, 2975, 1655, 1588, 1331, 1251, 997.

Mp: 140 °C (lit.[13] 138-140 °C).

Elemental Analysis (%) for $C_{10}H_{12}ClNO$. Calcd: C, 60.76; H, 6.12; N, 7.09. Found: C, 60.91; H, 6.31; N, 7.22.

2-chloro-*N*-(2,6-diethylphenyl)acetamide (4s)[14]



By following the general procedure, starting from 2,6-diethylphenyl isocyanate (0.66 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4s** was obtained in 95% yield (815 mg) as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.82 (bs, 1H), 7.19-7.04 (m, 3H), 4.13 (s, 2H), 2.49 (q, J = 6.4 Hz, 4H), 1.11 (t, J = 6.4 Hz, 6H).

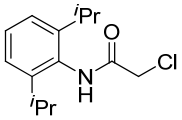
^{13}C NMR (75 MHz, $CDCl_3$) δ: 165.0, 141.4, 131.6, 128.5, 126.5, 42.8, 24.8, 14.4.

IR (NaCl, ν_{max}, cm^{-1}): 3259, 2970, 2873, 1657, 1592, 1470, 1330, 1247.

Mp: 201 °C (lit.[14] 199-204 °C).

Elemental Analysis (%) for $C_{12}H_{16}ClNO$. Calcd: C, 63.85; H, 7.14; N, 6.21. Found: C, 64.00; H, 7.22; N, 6.35.

2-chloro-*N*-(2,6-diisopropylphenyl)acetamide (4t)[1]



By following the general procedure, starting from 2-isocyanato-1,3-diisopropylbenzene (0.77 g, 3.8 mmol), ICH_2Cl (1.0 g, 0.41 ml, 5.7 mmol) and MeLi-LiBr (3.04 ml, 4.56 mmol) in Et_2O, α-chloroacetamide **4t** was obtained in 97% yield (935 mg) as a white solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.87 (s, 1H), 7.46 – 7.20 (m, 3H), 4.30 (s, 2H), 3.07 (p, J = 6.9 Hz, 2H), 1.26 (d, J = 6.9 Hz, 12H).

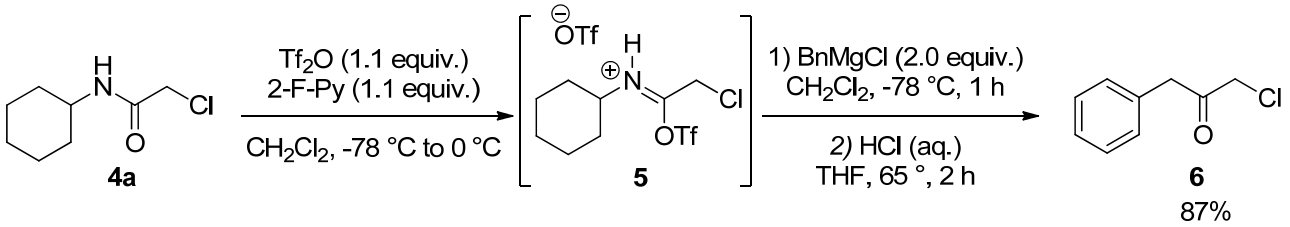
^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.5, 146.1, 130.1, 129.0, 123.8, 42.9, 28.9, 23.7.

IR (NaCl, ν_{max}, cm^{-1}): 3248, 1678, 1660, 1533, 998.

Mp: 149 °C (lit.[1] 148-149 °C).

Elemental Analysis (%) for $C_{14}H_{20}ClNO$. Calcd: C, 66.26; H, 7.94; N, 5.52. Found: C, 66.09; H, 8.10; N, 5.69.

Preparation of 1-chloro-3-phenylacetone (6) *via* Charette's chemistry.[15]



To a solution of chloroacetamide **4a** (200 mg, 1.04 mmol, 1.0 equiv.) in dry dichloromethane (26 mL, concentration 0.044 M), was added 2-fluoropyridine (62 mg, 1.26 mmol, 0.11 mL, 1.1 equiv.) and the resulting solution was cooled at -78 °C and stirred for 2 min. Triflic anhydride (354 mg, 1.26 mmol, 0.21 mL, 1.1 equiv.) was added dropwise at that temperature and the mixture was then stirred for 10 min. The solution was warmed at 0 °C and the reaction was stirred for 20 min. The reaction was then cooled at -78 °C and a solution of benzyl magnesium chloride 2.0 M in THF (2.08 mmol, 1.04 mL, 2.0 equiv.) was added dropwise during 10 min and stirred for further 50 min. The reaction was quenched with 8 mL of HCl 0.5 M and 8 mL of THF. The biphasic system was warmed at 65 °C leaving the flask open for 2 h. After extraction of the organic phase with additional DCM (10 mL), drying it over sodium sulphate, filtering and removal of the solvent under reduced pressure crude **6** was obtained. After chromatography on silica gel (eluent: petroleum ether ethyl acetate 9.5:0.5 v/v), pure chloroketone **6** (152 mg, 87% yield) was obtained as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.38 – 7.23 (m, 5H), 4.13 (s, 2H), 3.91 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ: 199.1, 132.8, 129.4, 128.9, 127.5, 47.7, 46.8.

IR (NaCl, ν_{max}, cm^{-1}): 3082, 1737, 992, 897.

Elemental Analysis (%) for C_9H_9ClO. Calcd: C, 64.11; H, 5.38. Found: C, 64.29; H, 5.53.

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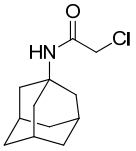
COPIES OF ^{1}H and ^{13}C-NMR SPECTRA FOR ALL THE COMPOUNDS



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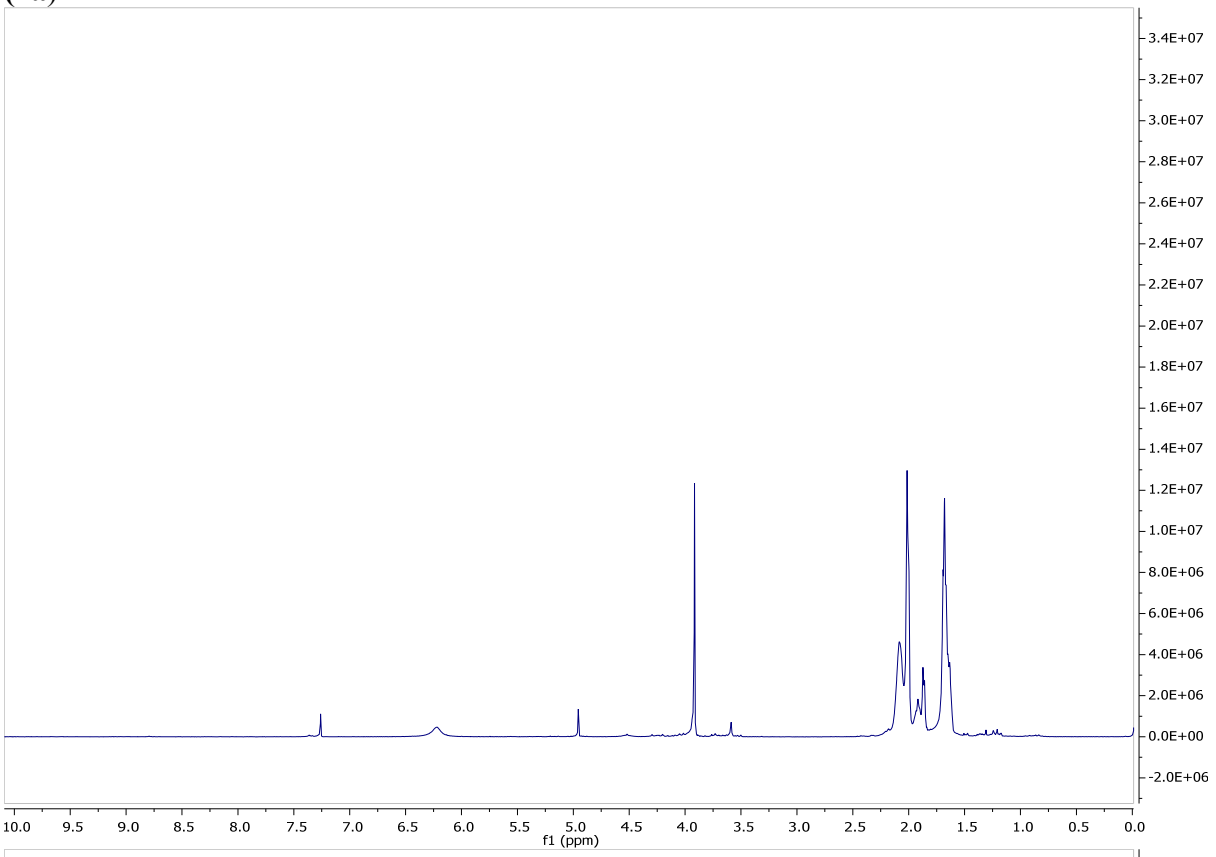

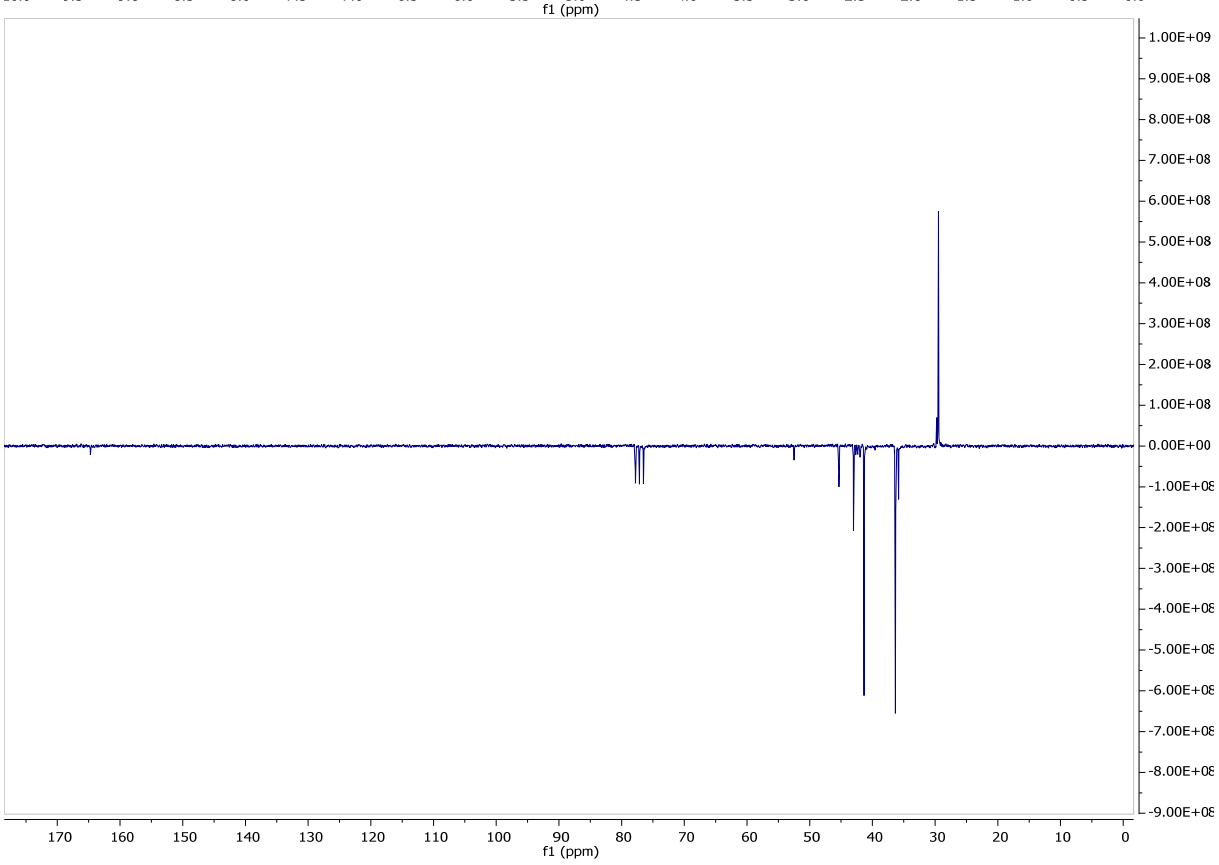

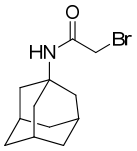

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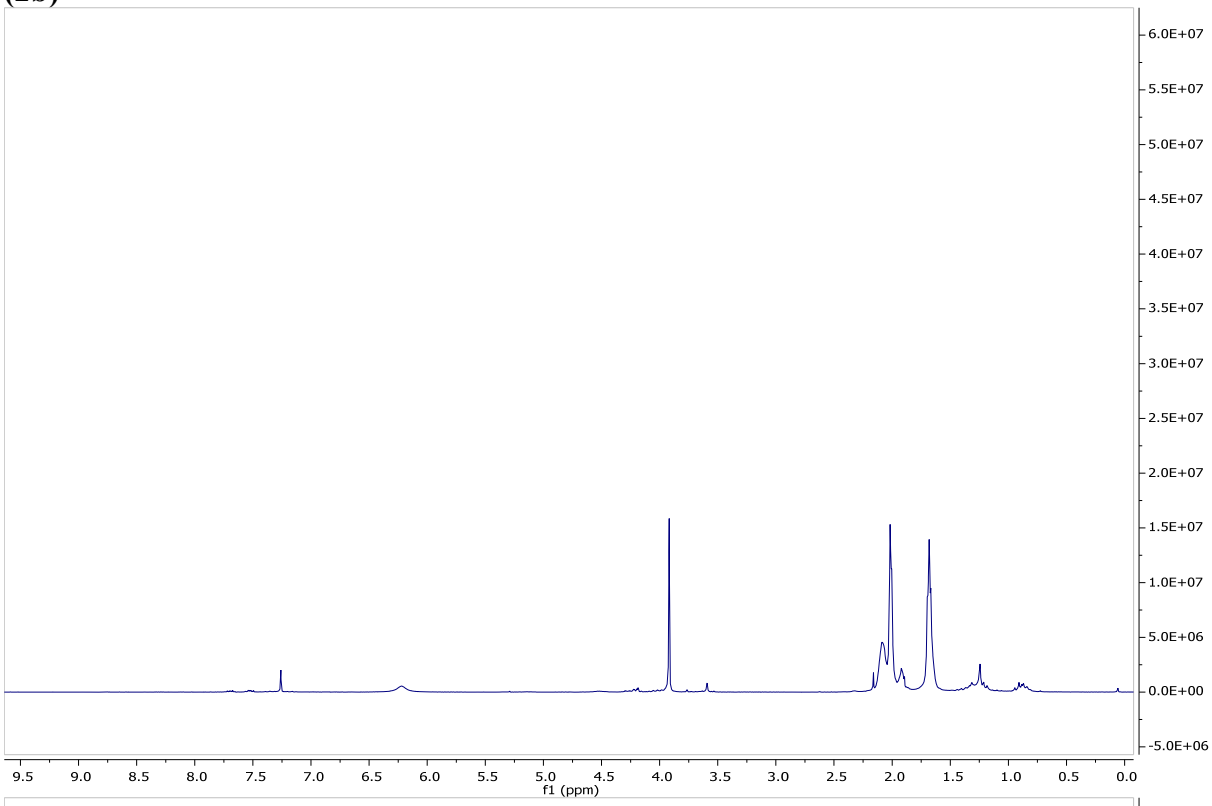

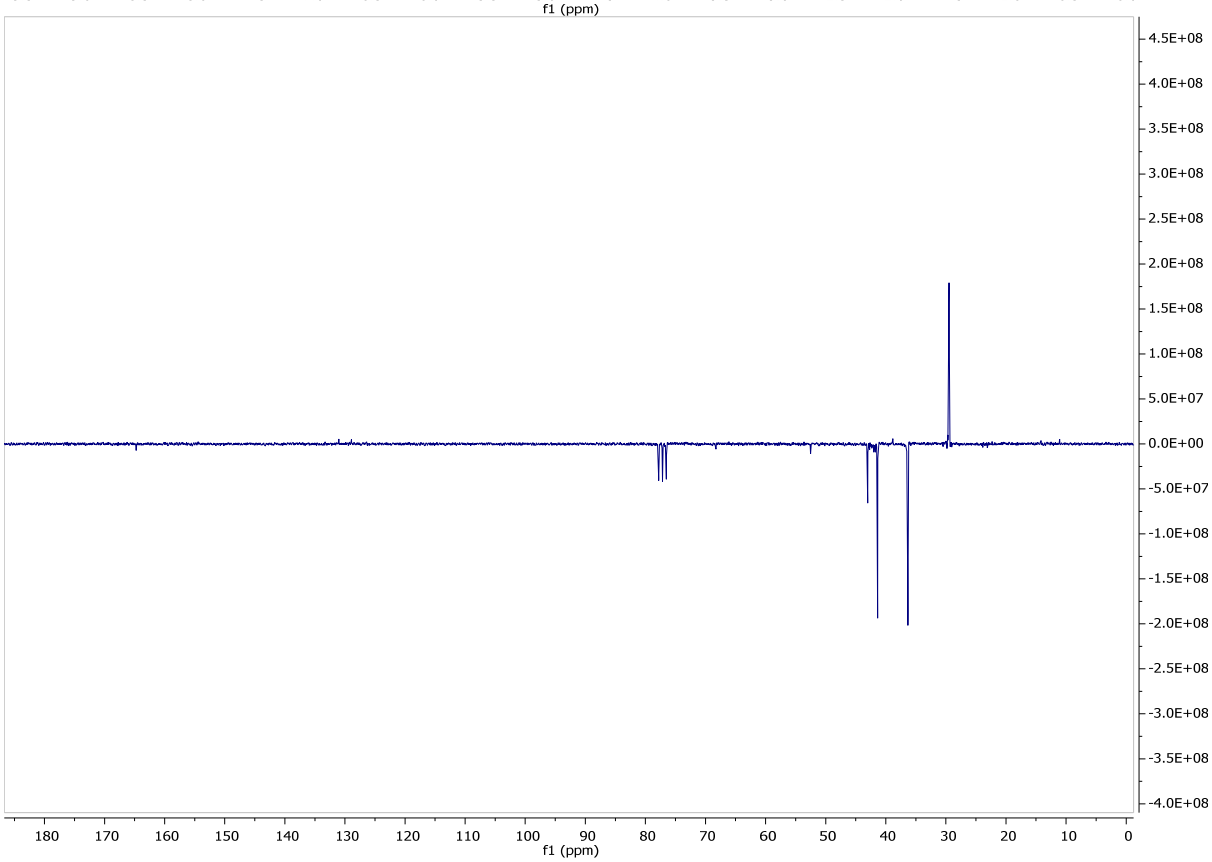

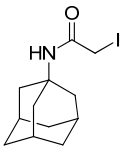

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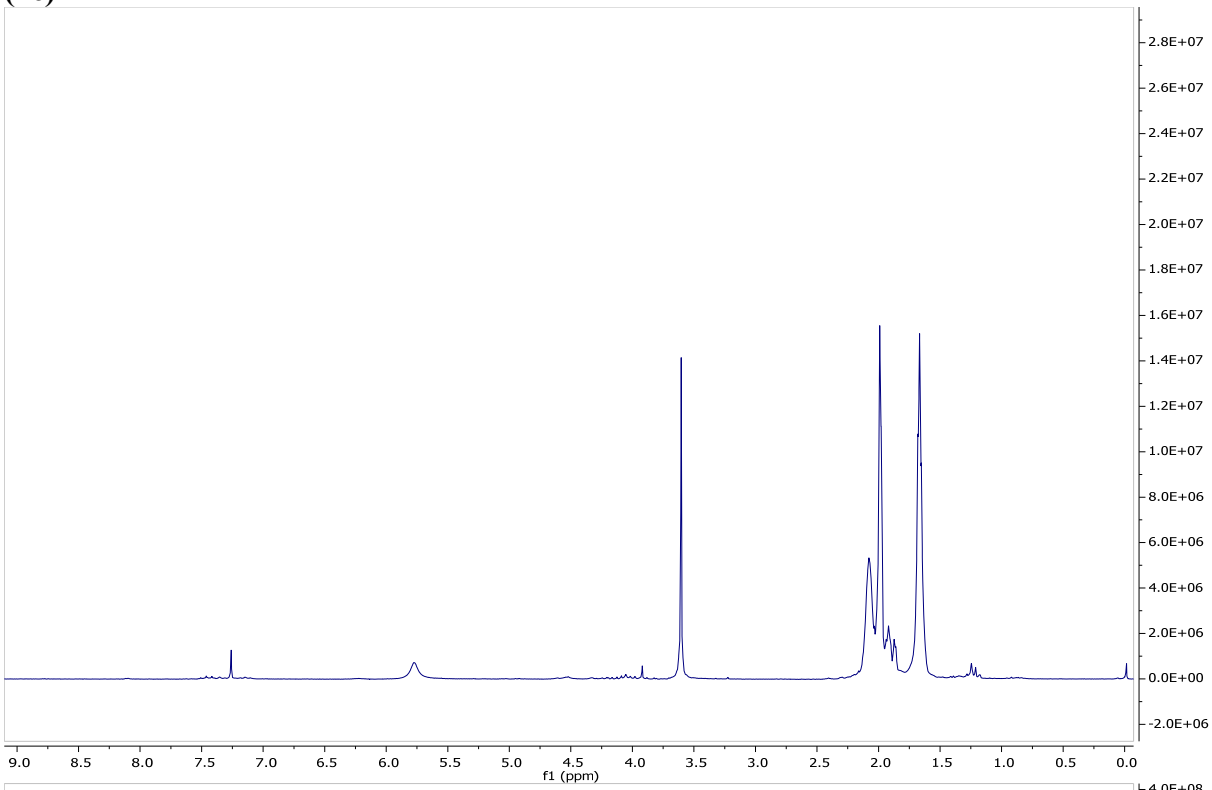
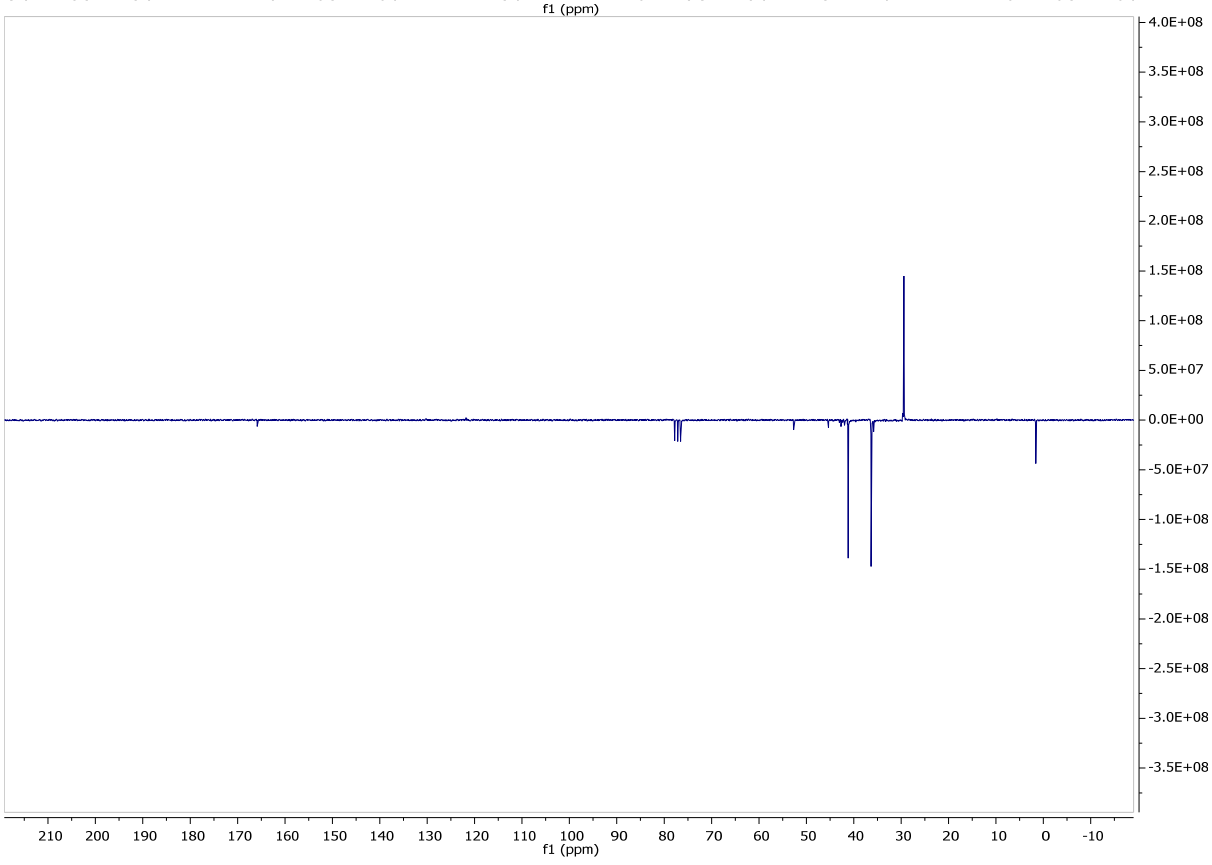
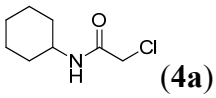
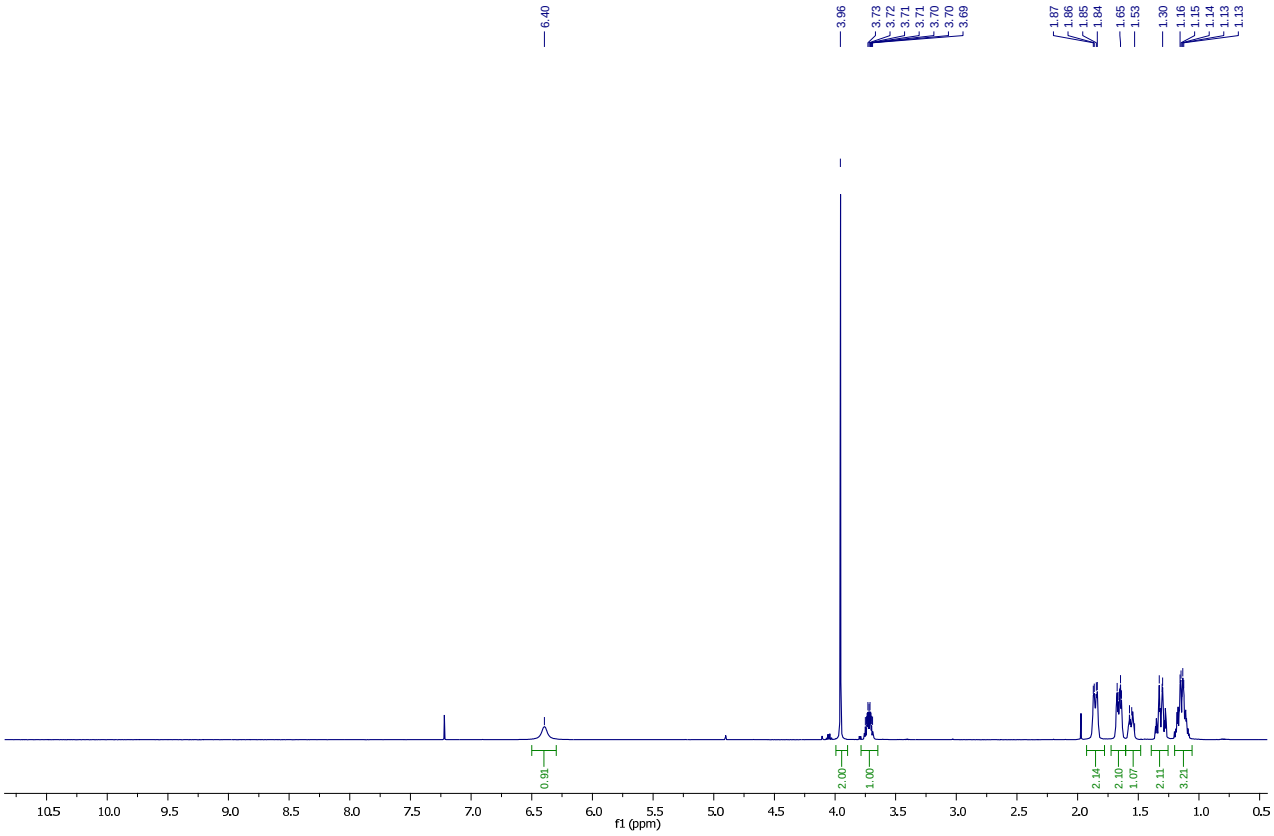
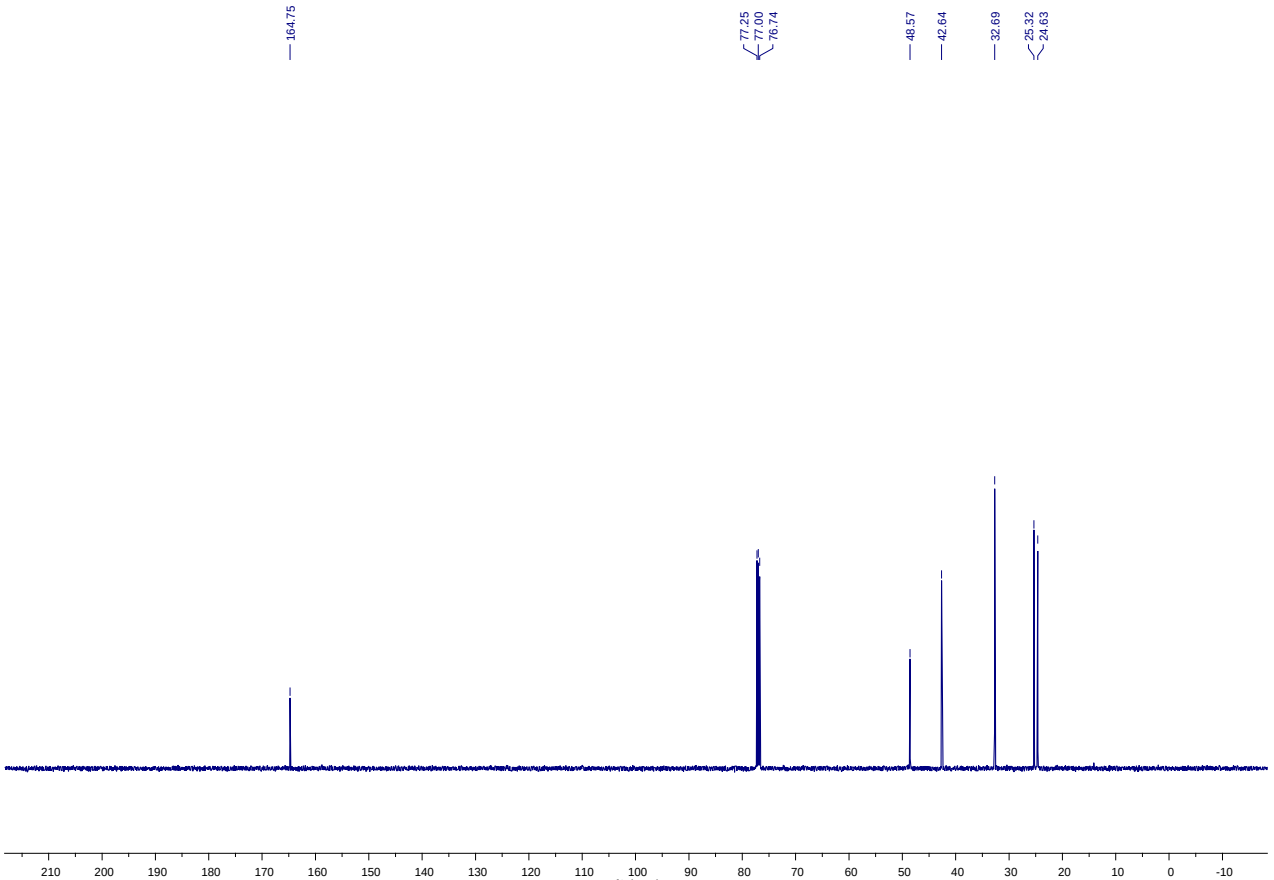


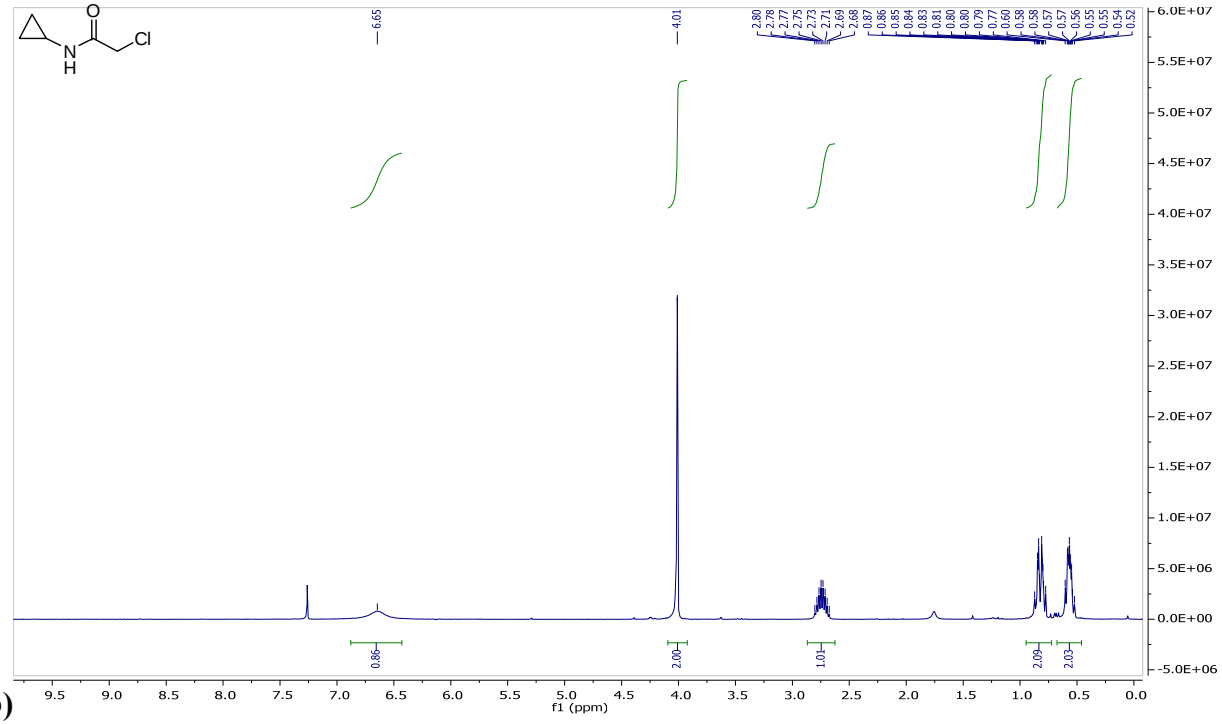



O
N
H
Cl

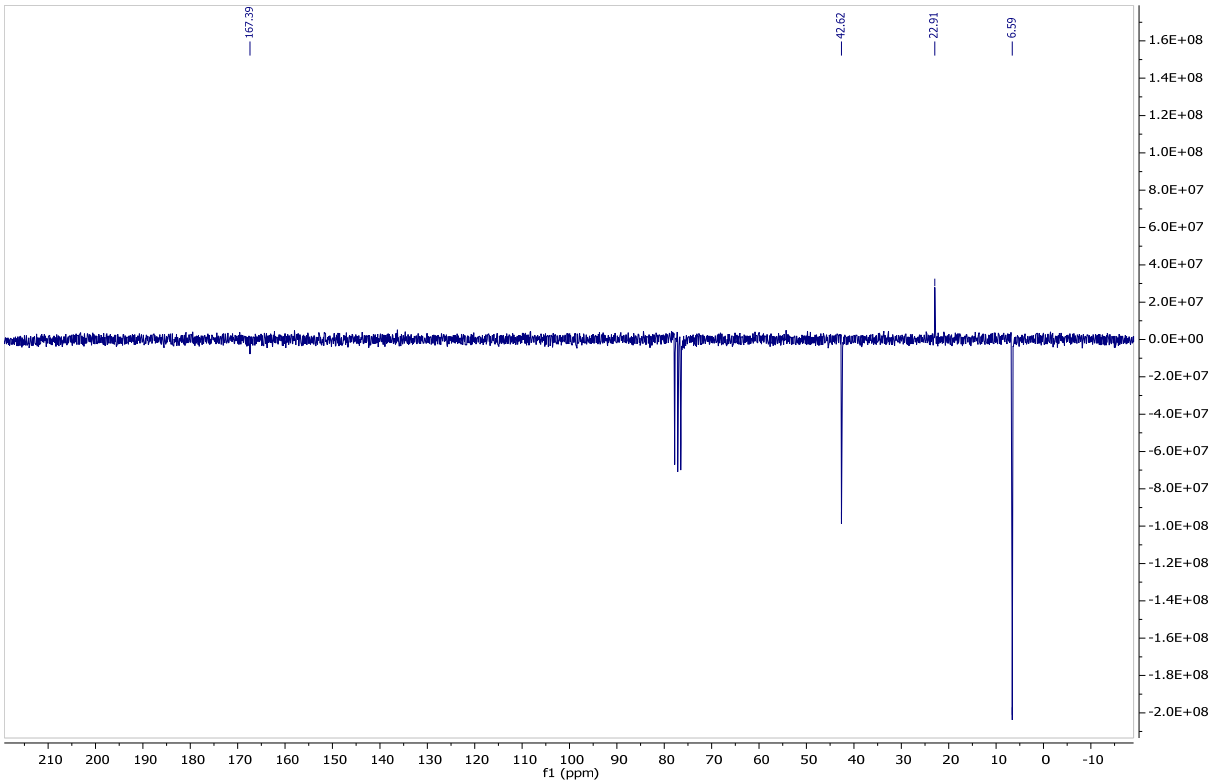
(4a)

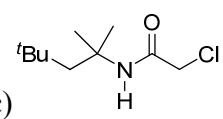

6.40
3.96
3.73
3.72
3.71
3.71
3.70
3.70
3.69
1.87
1.86
1.85
1.84
1.65
1.53
1.30
1.16
1.15
1.14
1.13
1.13
0.91
2.00
1.00
2.14
2.10
1.07
2.11
3.21
f1 (ppm)


164.75
77.25
77.00
76.74
48.57
42.64
32.69
25.32
24.63
f1 (ppm)

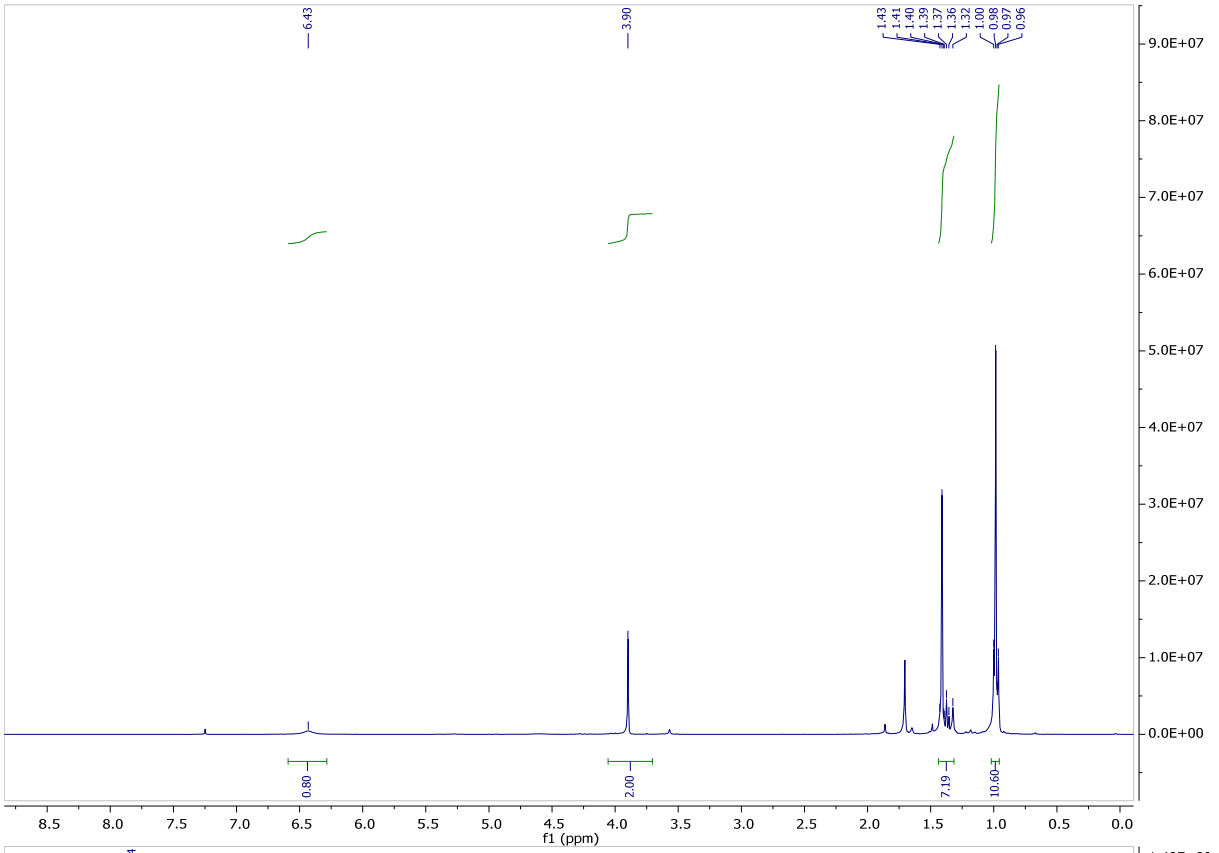

O
N
H
Cl
6.65
4.01
2.80
2.78
2.77
2.75
2.73
2.71
2.69
2.68
0.87
0.86
0.85
0.84
0.83
0.81
0.80
0.80
0.80
0.79
0.77
0.60
0.58
0.58
0.57
0.57
0.56
0.55
0.55
0.54
0.52
0.86
2.00
1.01
2.09
2.03
f1 (ppm)

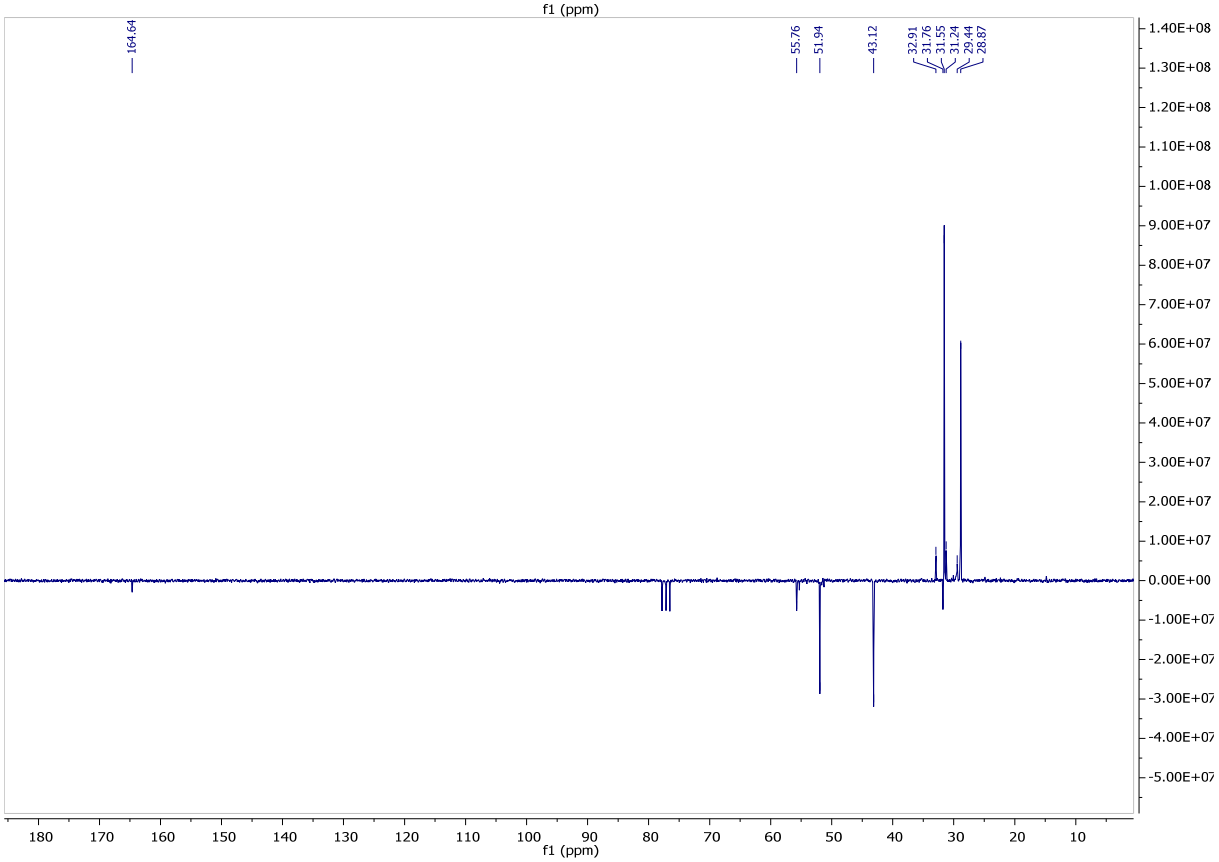
(4b)


167.39
42.62
22.91
6.59
f1 (ppm)

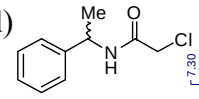

tBu
O
N
H
Cl

(4c)

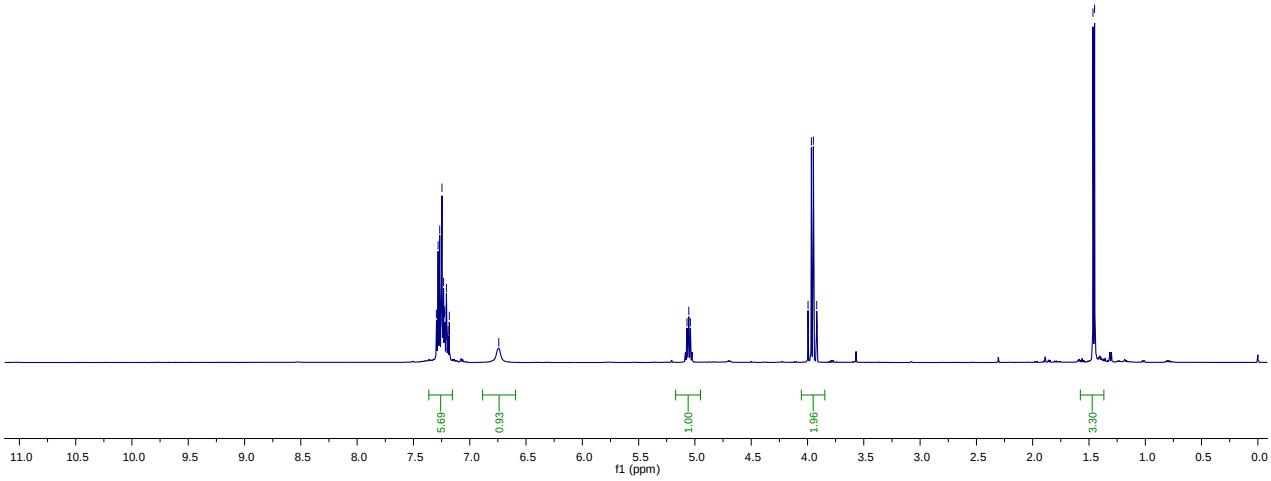




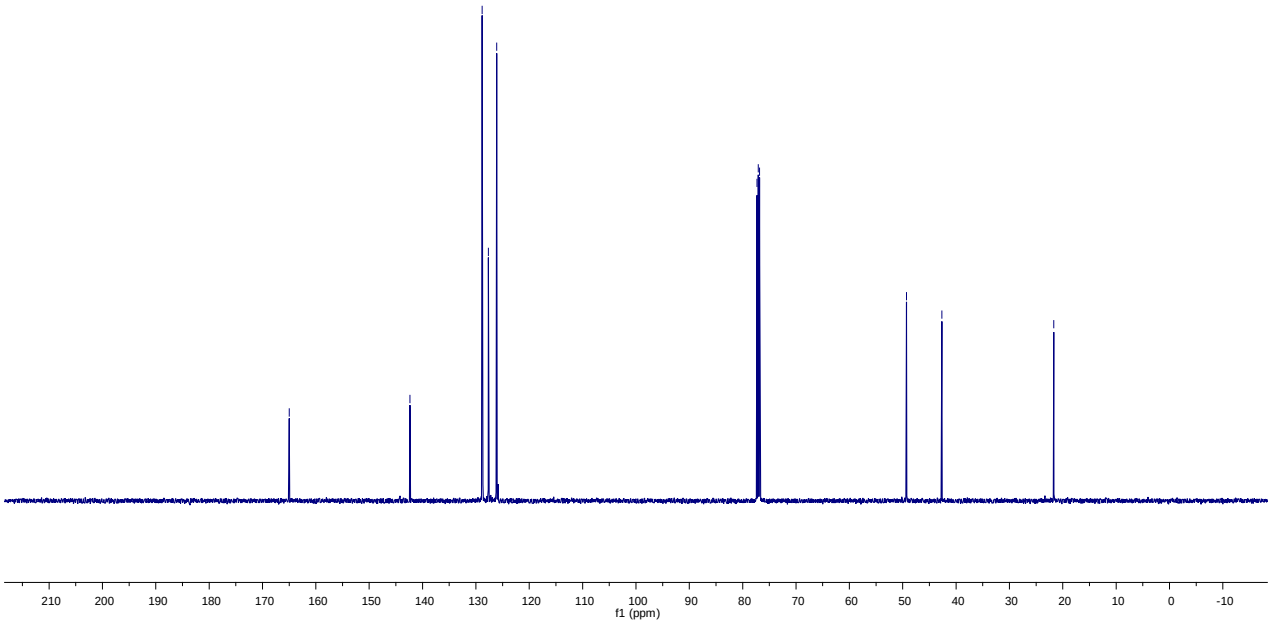
(4d)


Me
O
Cl
N
H

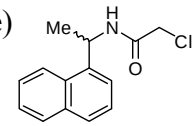

7.30
7.29
7.28
7.27
7.27
7.25
7.25
7.24
7.23
7.22
7.22
7.22
7.21
7.21
7.20
7.20
7.19
7.18
6.74
5.07
5.05
5.04
4.00
3.97
3.95
3.92
1.46
1.45


5.69
0.93
1.00
1.96
3.30
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

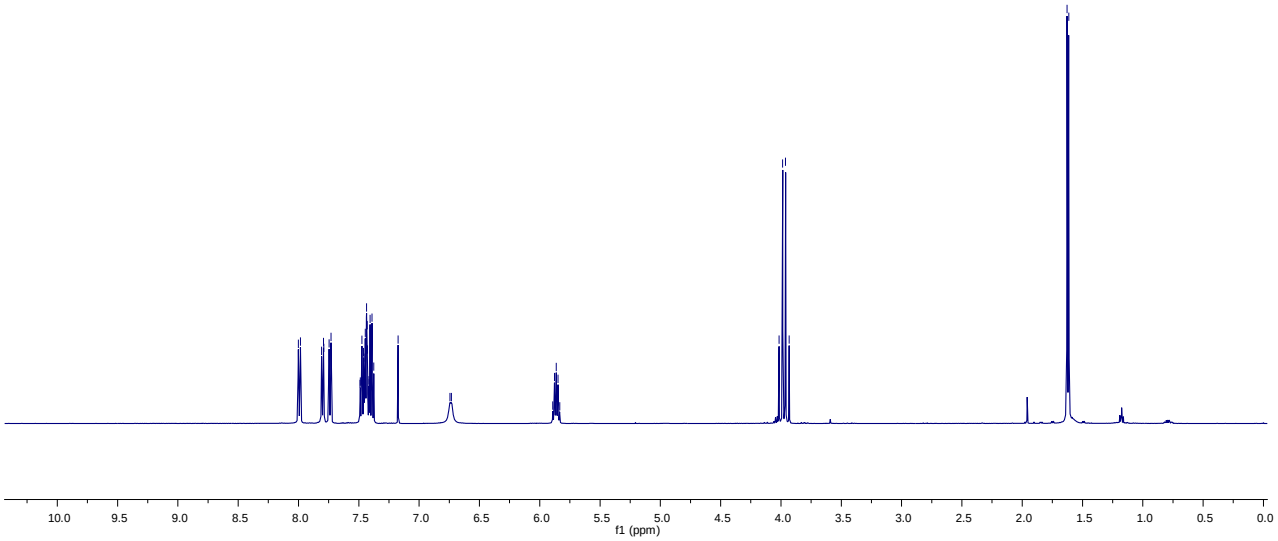

165.00
142.35
128.82
127.67
126.11
77.33
77.08
76.82
49.28
42.66
21.70


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

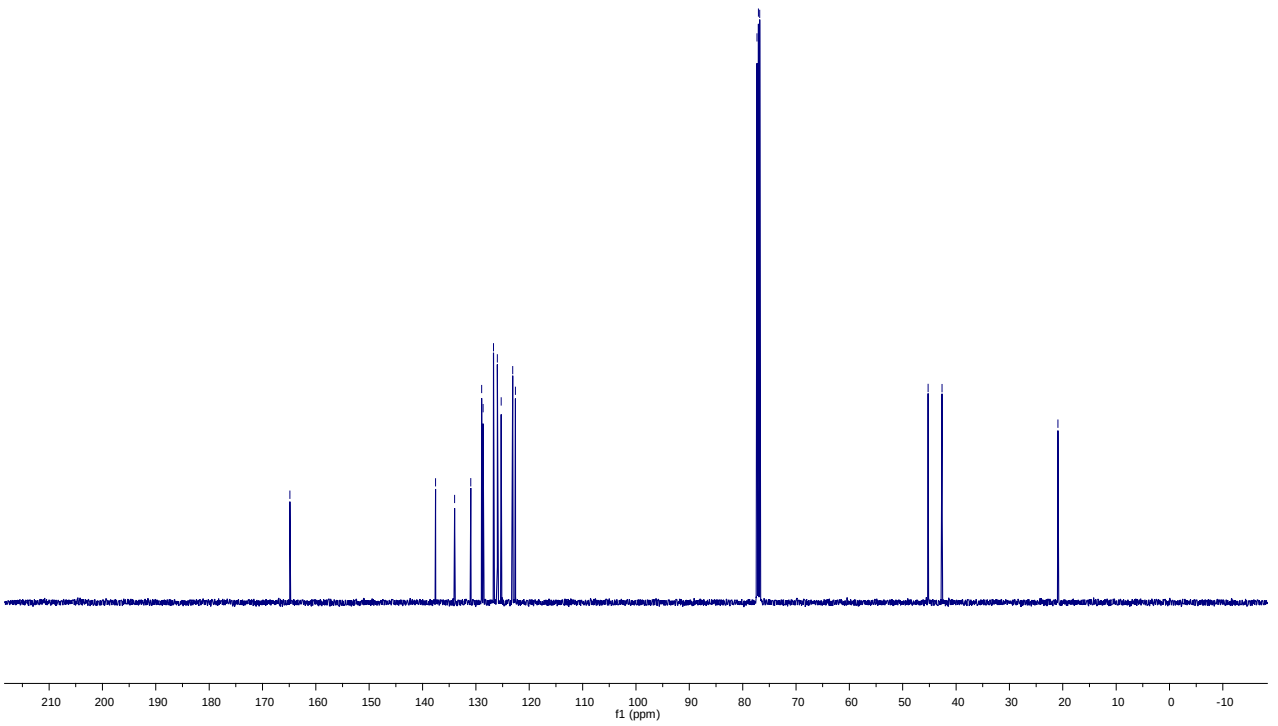
(4e)

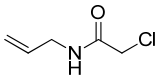


8.00
7.98
7.73
7.39
7.17
6.74
6.73
5.89
5.88
5.86
5.85
5.83
4.02
3.99
3.96
3.93
1.63
1.61

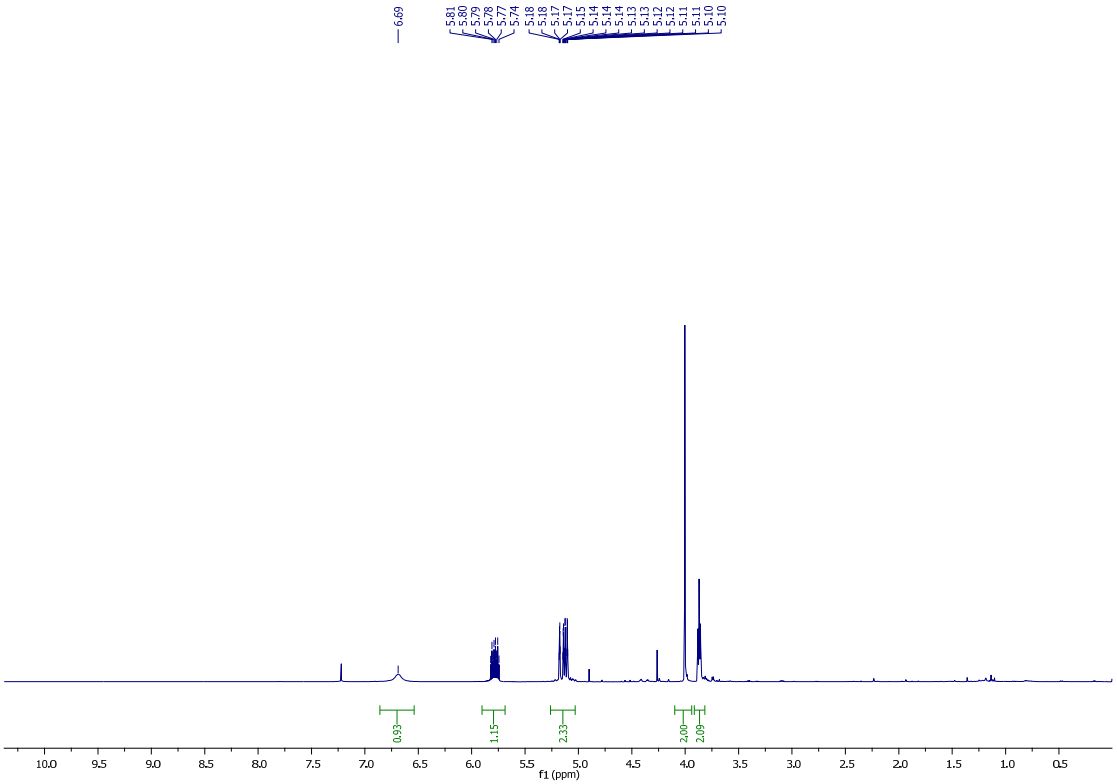


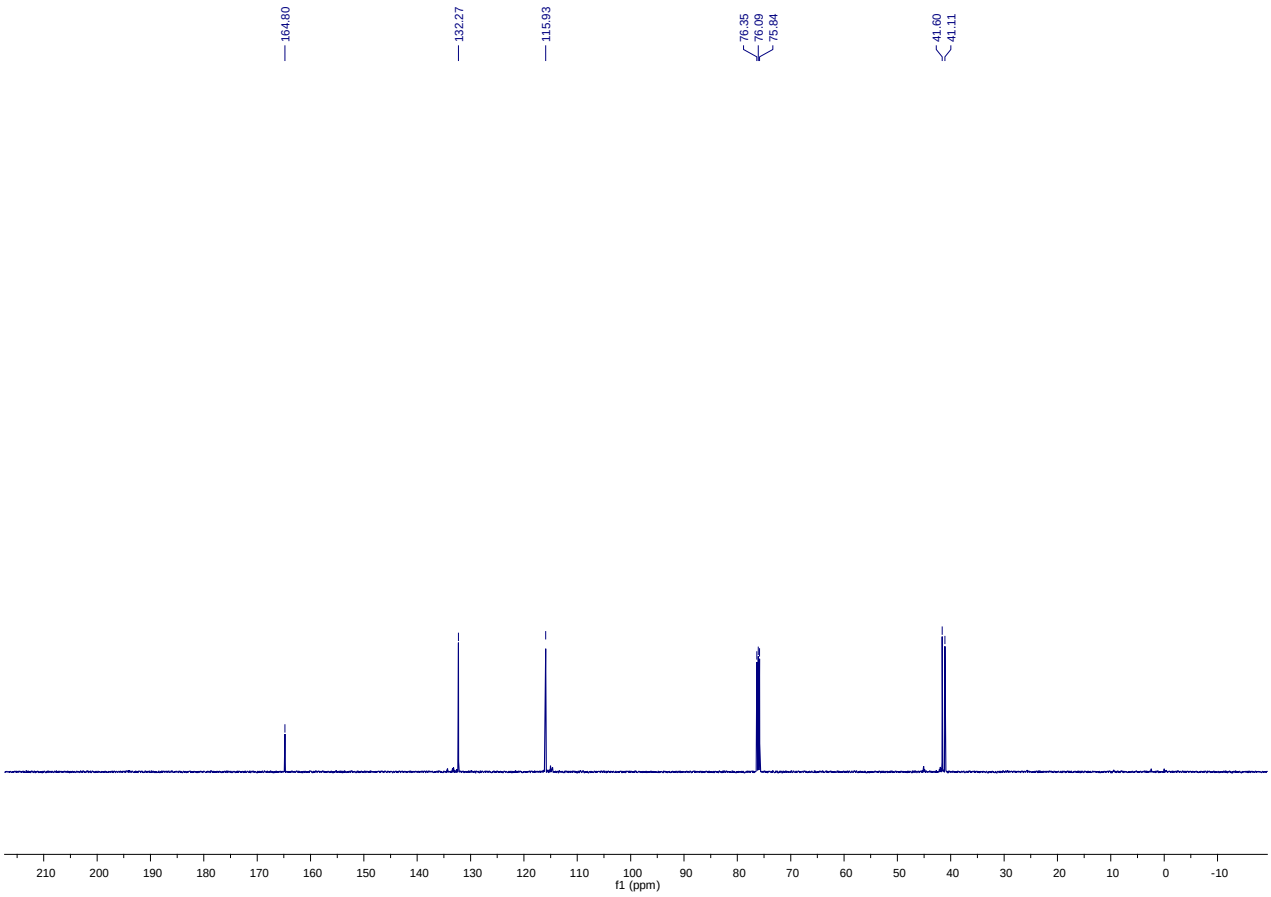
164.86
137.57
133.99
130.95
128.93
128.64
126.71
125.97
125.27
123.11
122.60
77.31
77.06
76.80
45.25
42.62
20.91

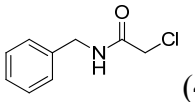




(4f)

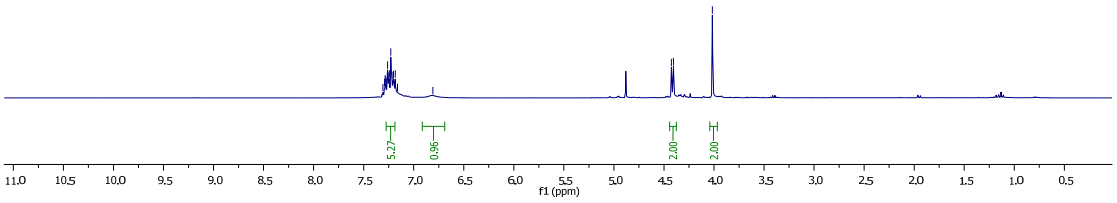

6.69
5.81
5.80
5.79
5.78
5.77
5.74
5.18
5.18
5.17
5.17
5.15
5.14
5.14
5.14
5.13
5.13
5.12
5.12
5.11
5.11
5.10
5.10
0.93
1.15
2.33
2.00
2.09
f1 (ppm)


164.80
132.27
115.93
76.35
76.09
75.84
41.60
41.11
f1 (ppm)

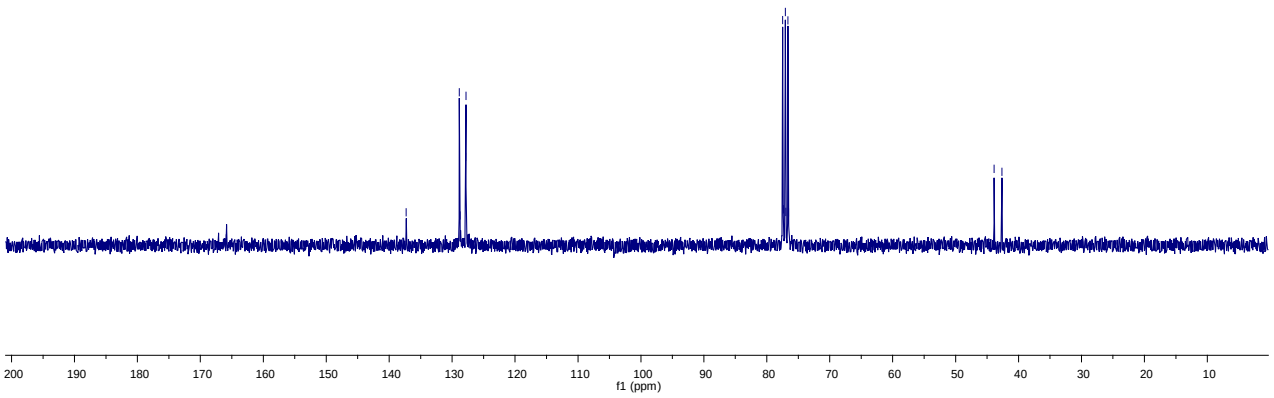


(4g)

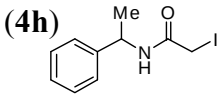

7.31
7.29
7.28
7.28
7.27
7.26
7.25
7.24
7.23
7.21
7.20
7.18
7.16
6.81
4.43
4.41
4.02

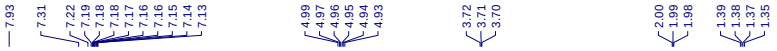

5.27
0.96
2.00
2.00
f1 (ppm)

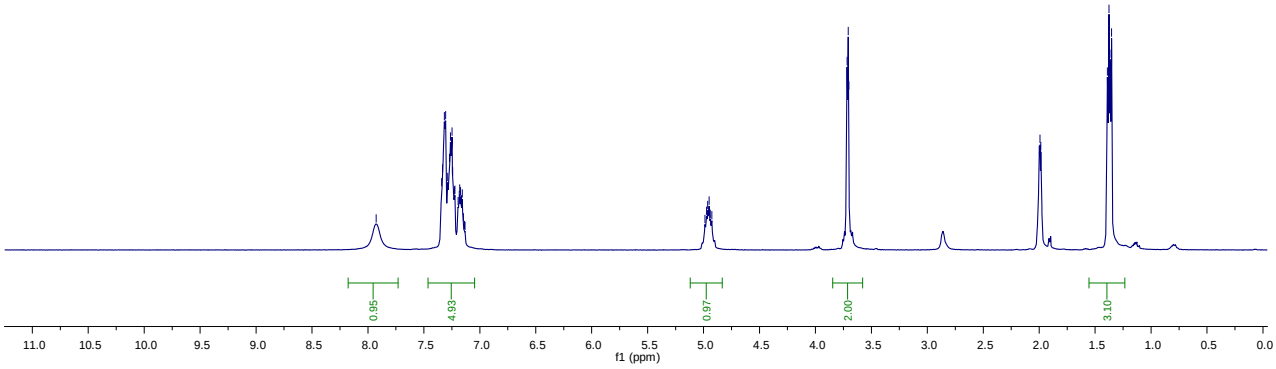

165.88
137.29
128.86
128.74
127.83
127.80
77.48
77.38
77.06
76.96
76.63
76.54
43.87
42.63

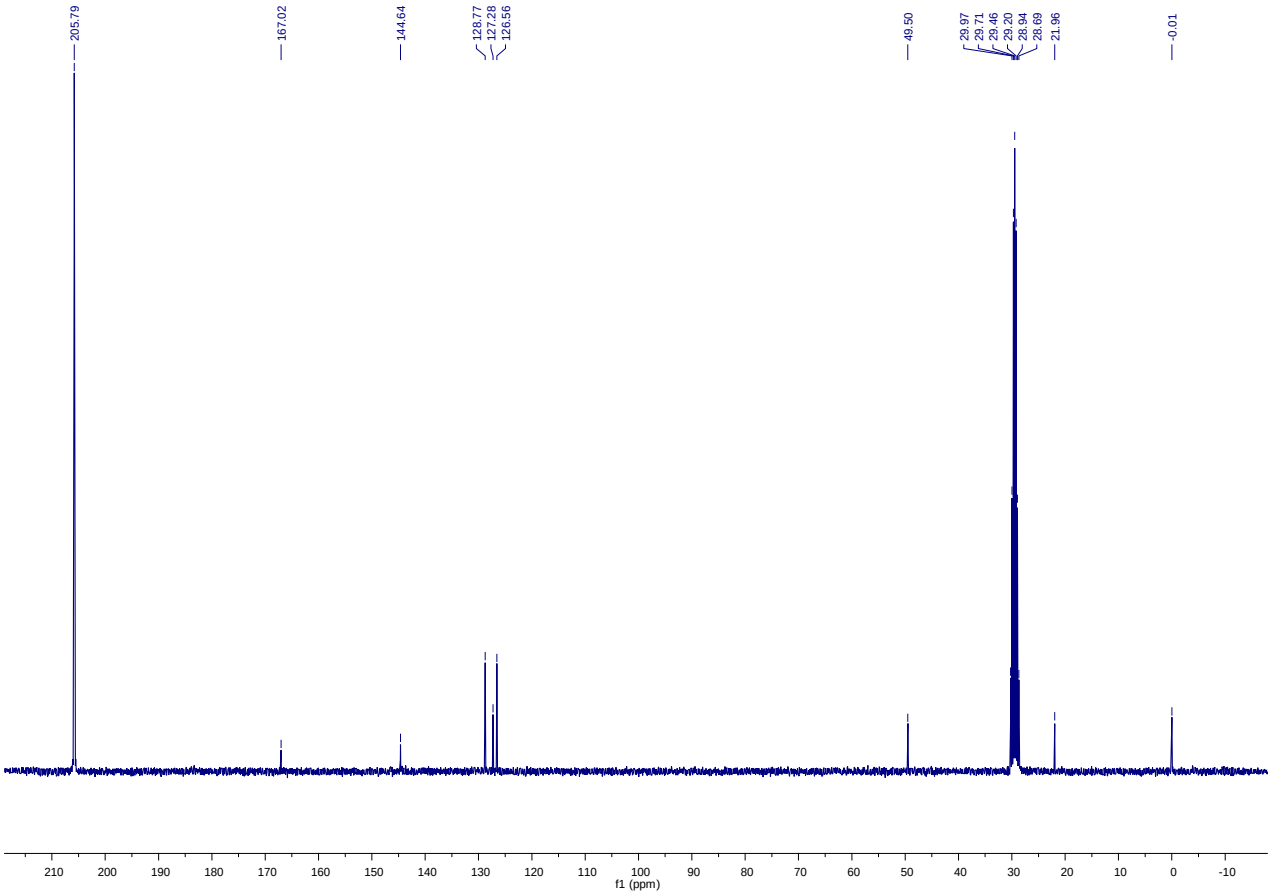

f1 (ppm)

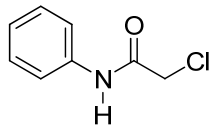
(4h)



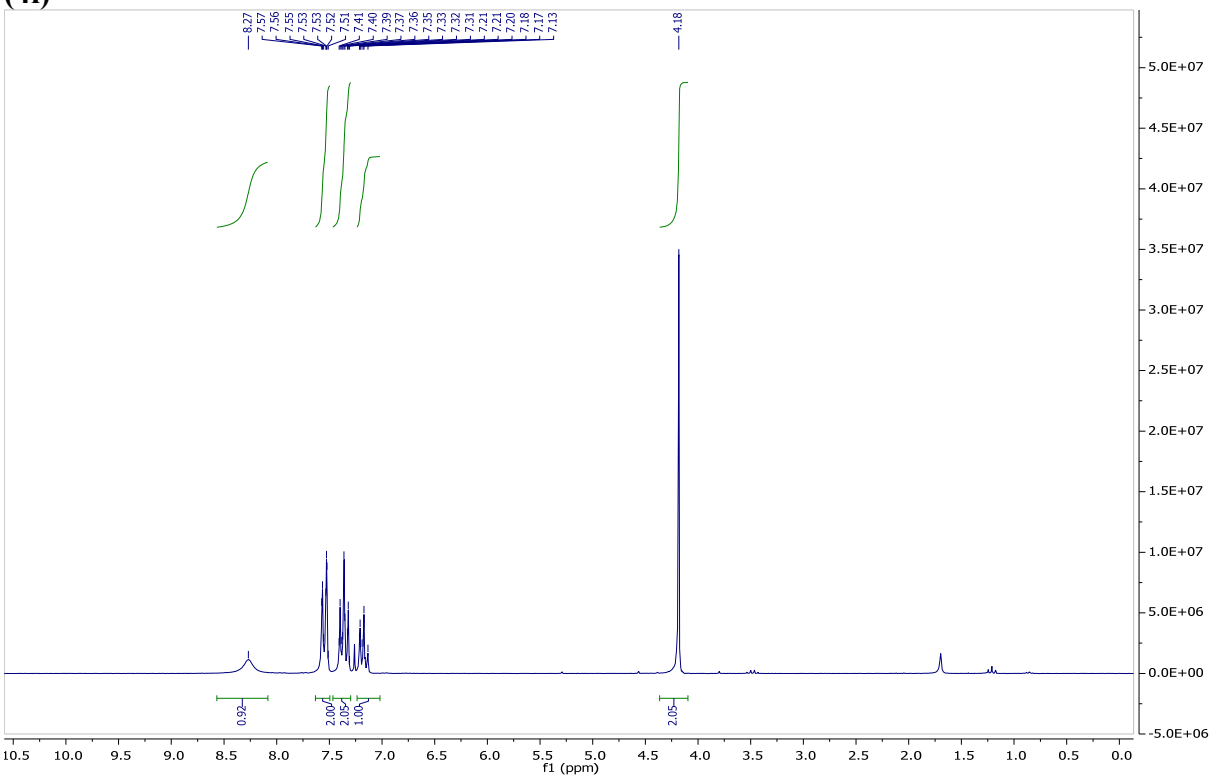


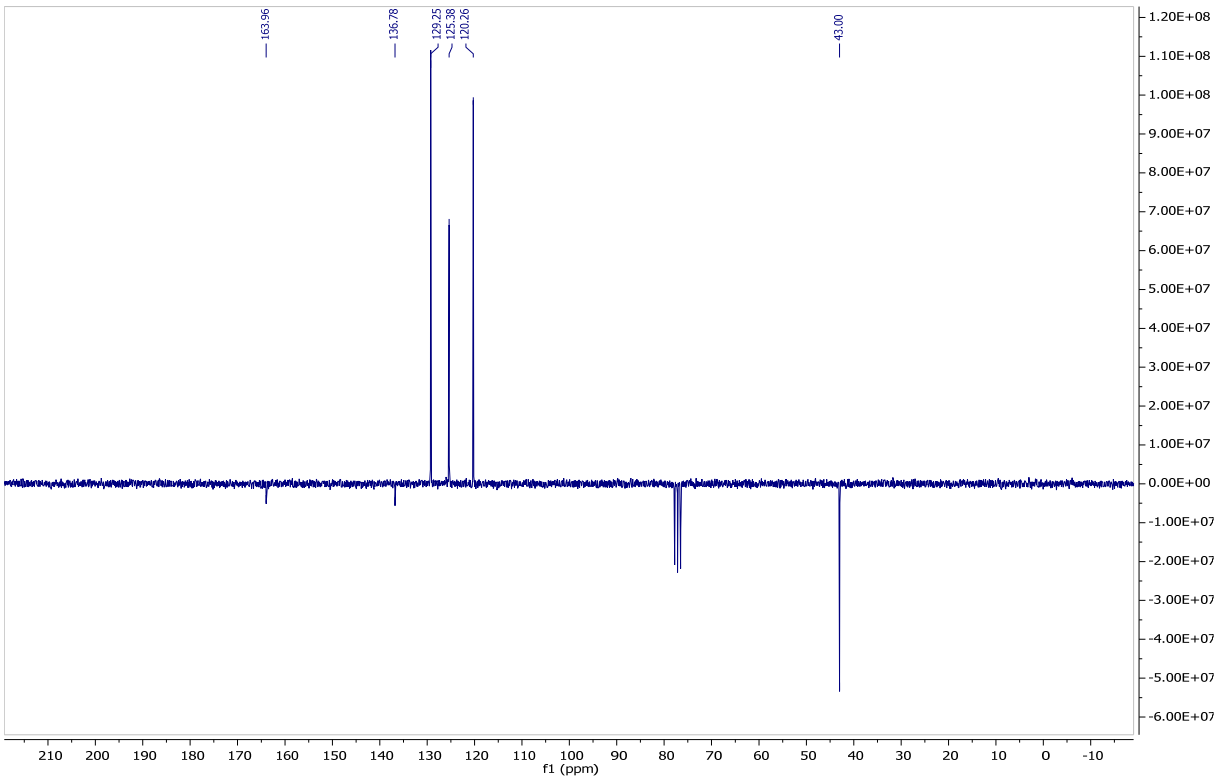


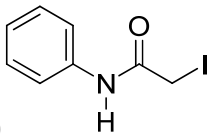



O
Cl
N
H

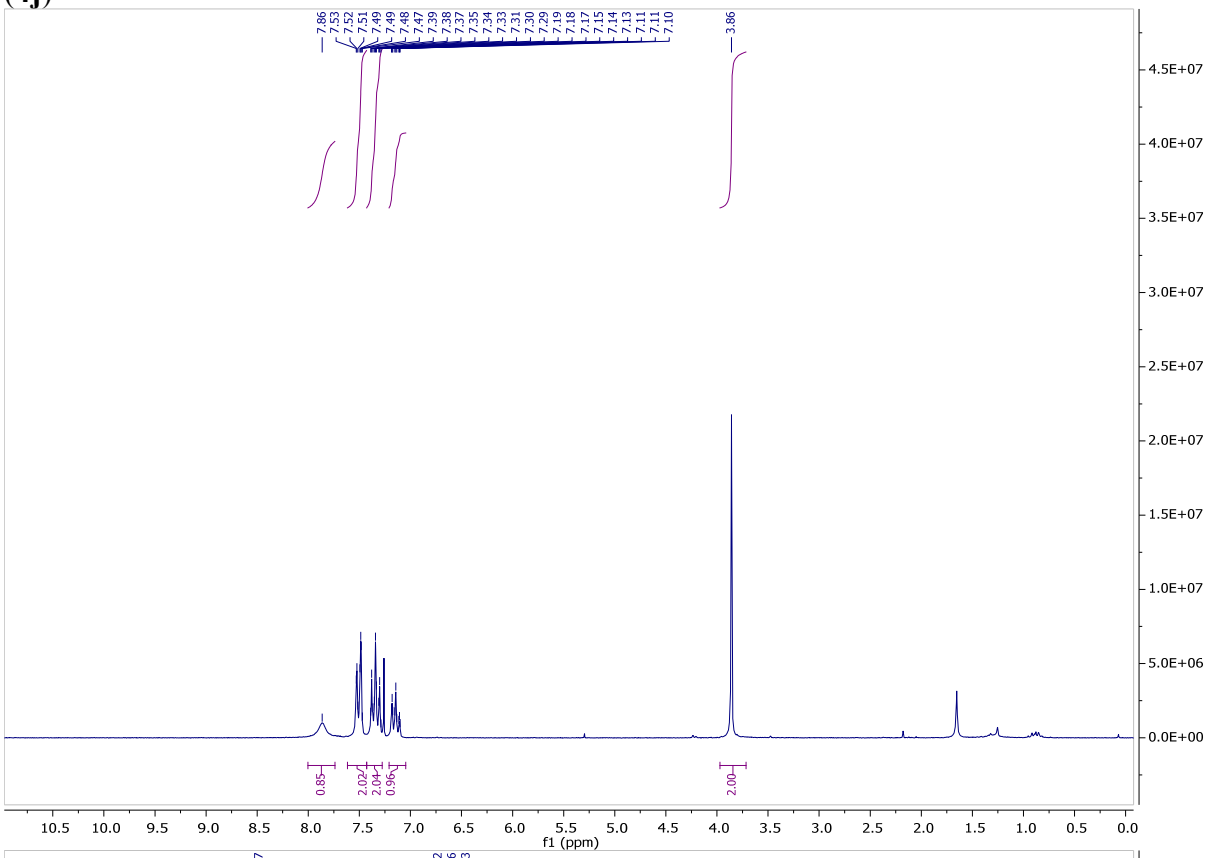
(4i)

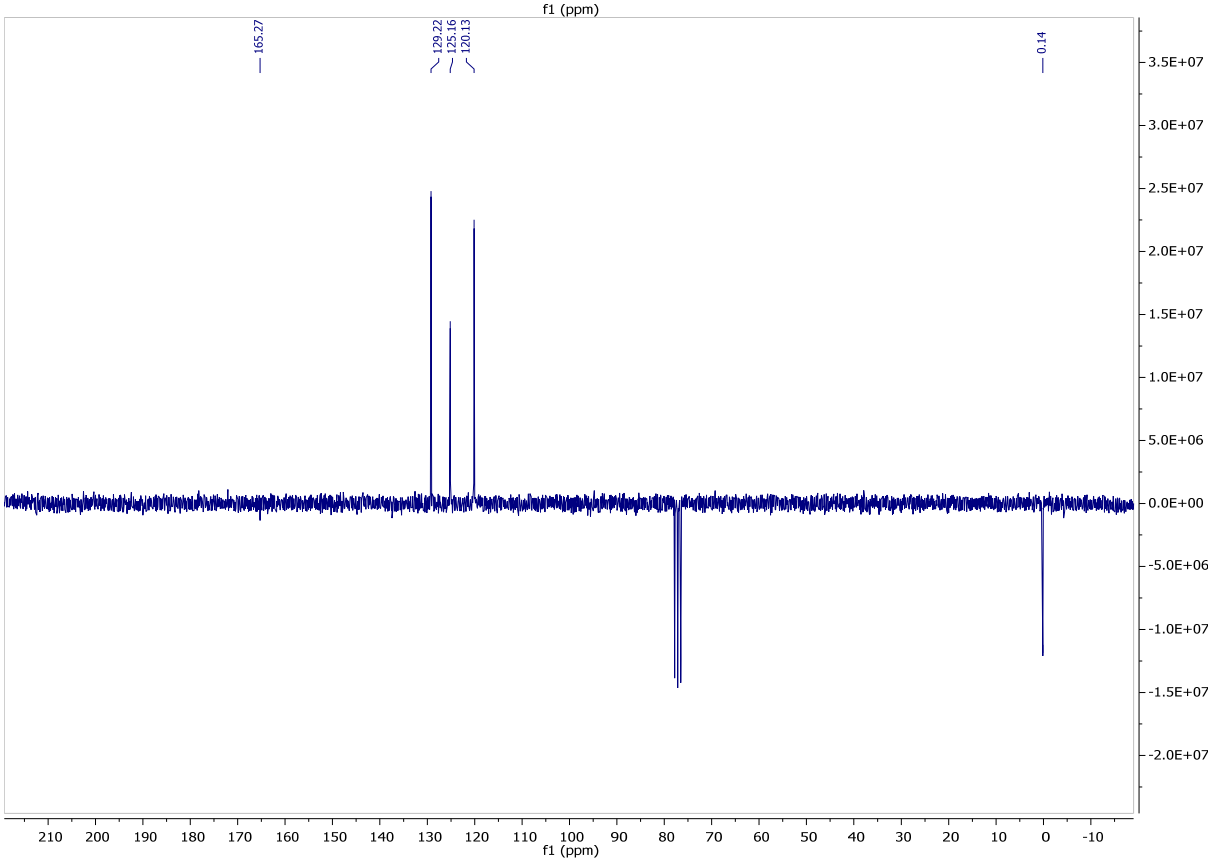

8.27
7.57
7.56
7.55
7.53
7.53
7.52
7.51
7.41
7.40
7.39
7.37
7.36
7.35
7.33
7.32
7.31
7.21
7.21
7.20
7.18
7.17
7.13
4.18
0.92
2.00
2.05
1.00
2.05
f1 (ppm)


163.96
136.78
129.25
125.38
120.26
43.00
f1 (ppm)

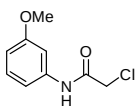


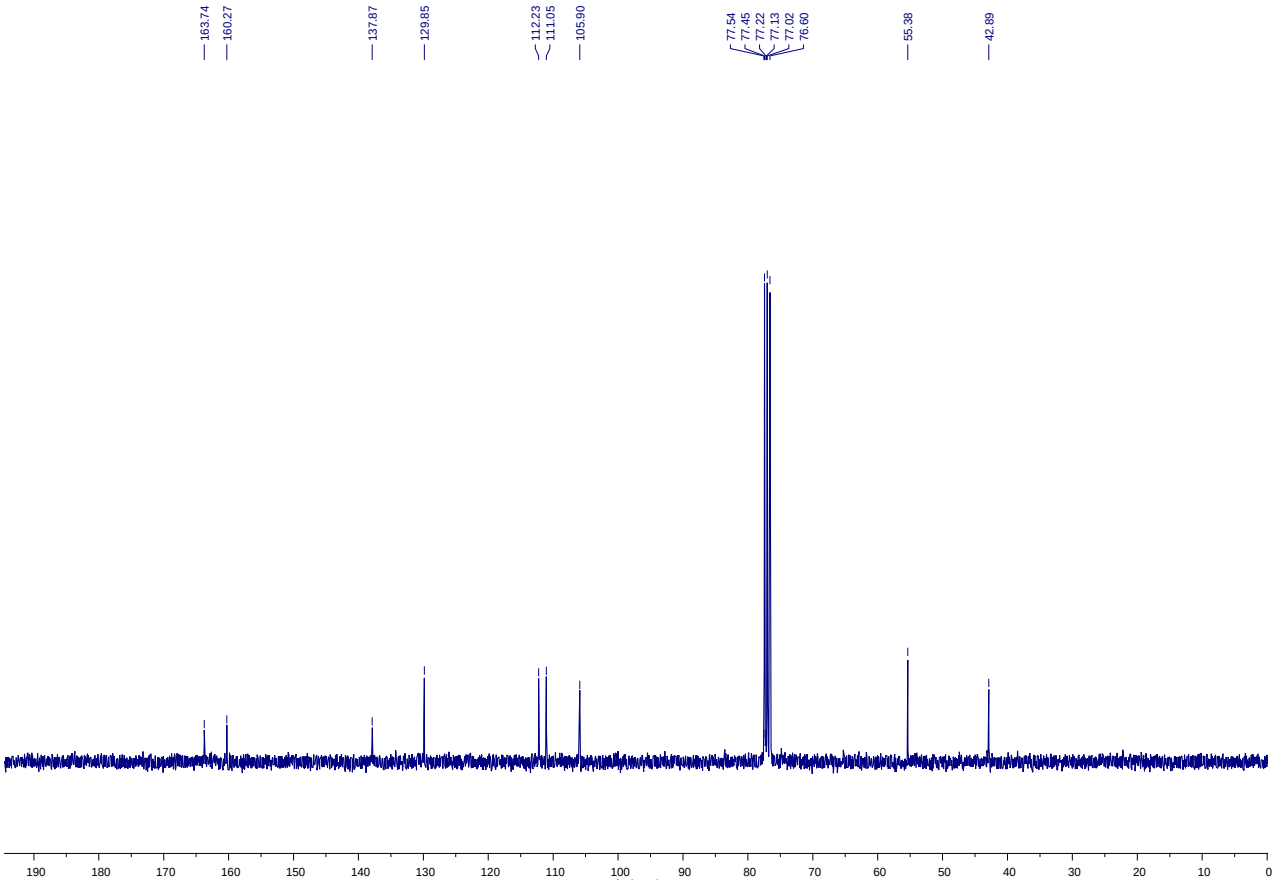
(4j)

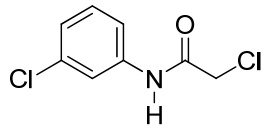




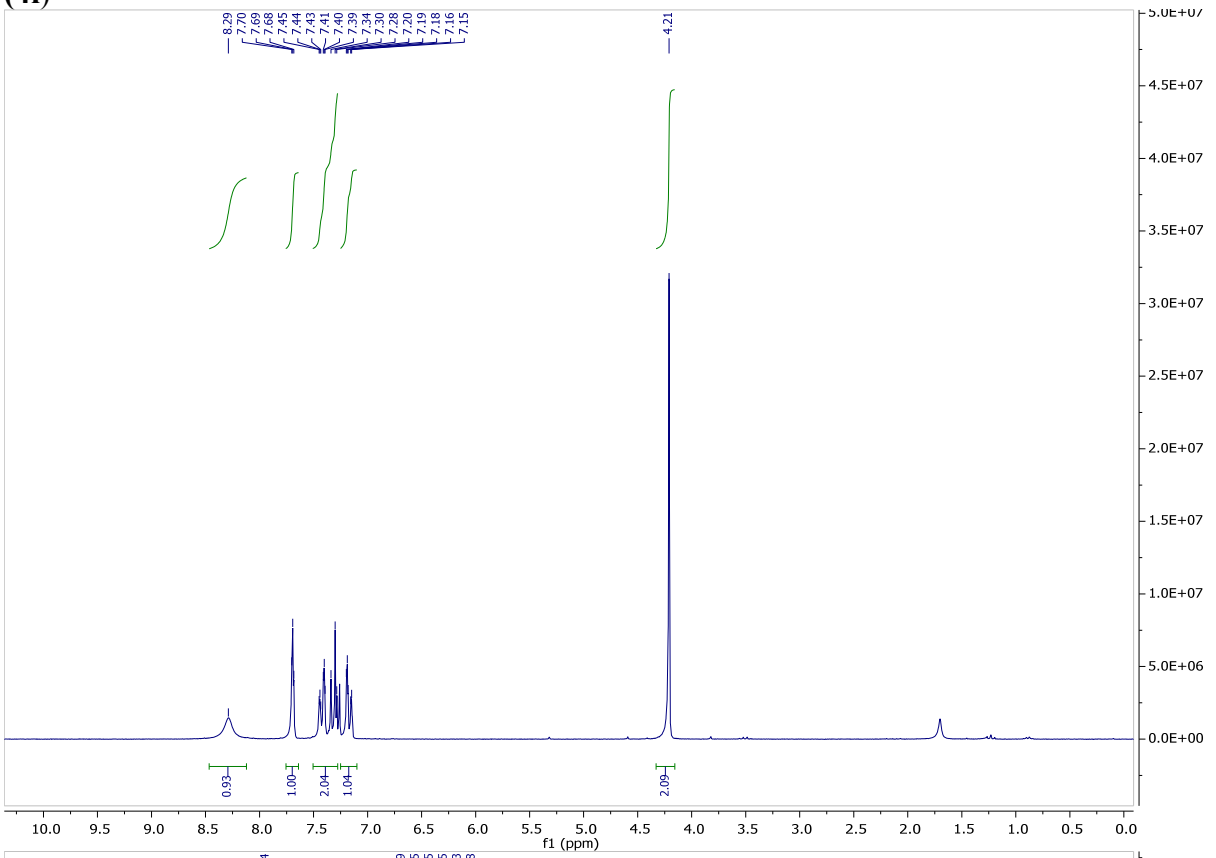
(4k)

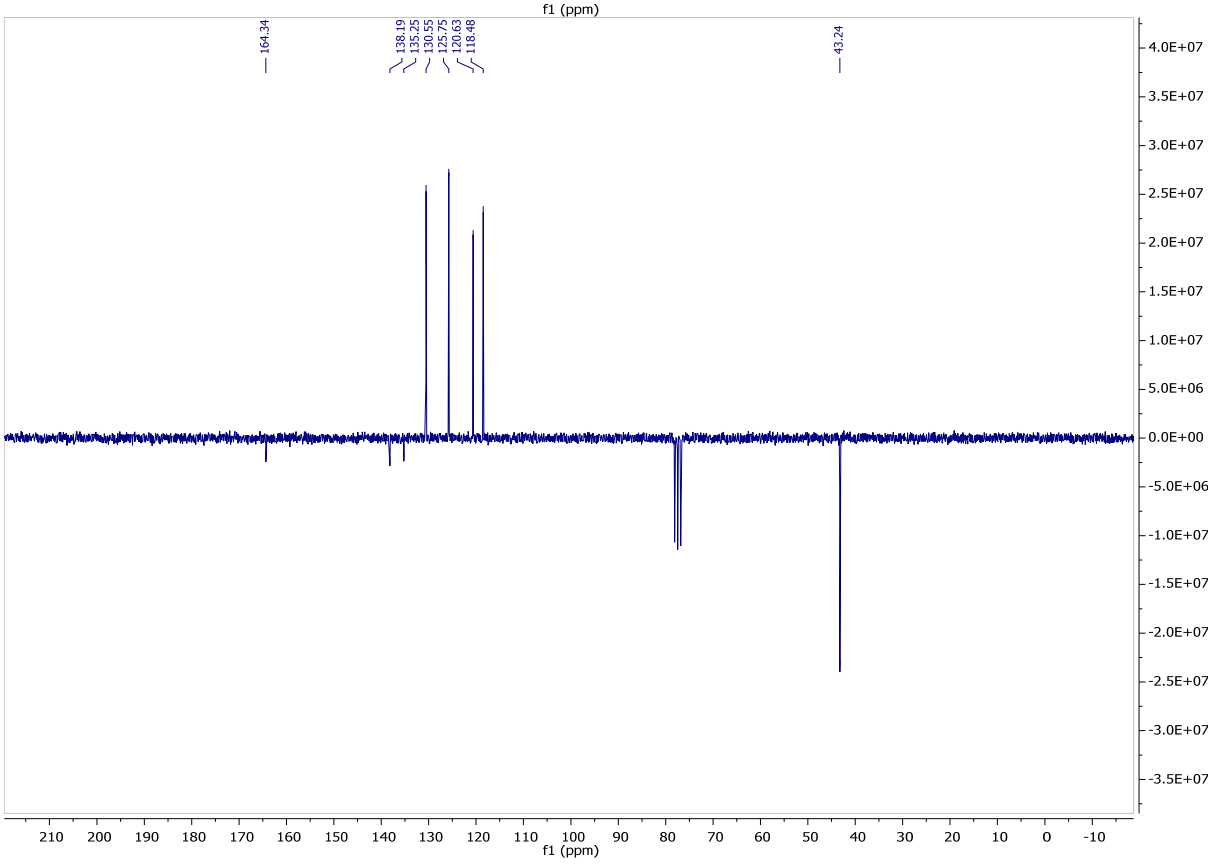


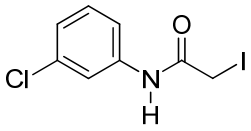



O
Cl
Cl
N
H

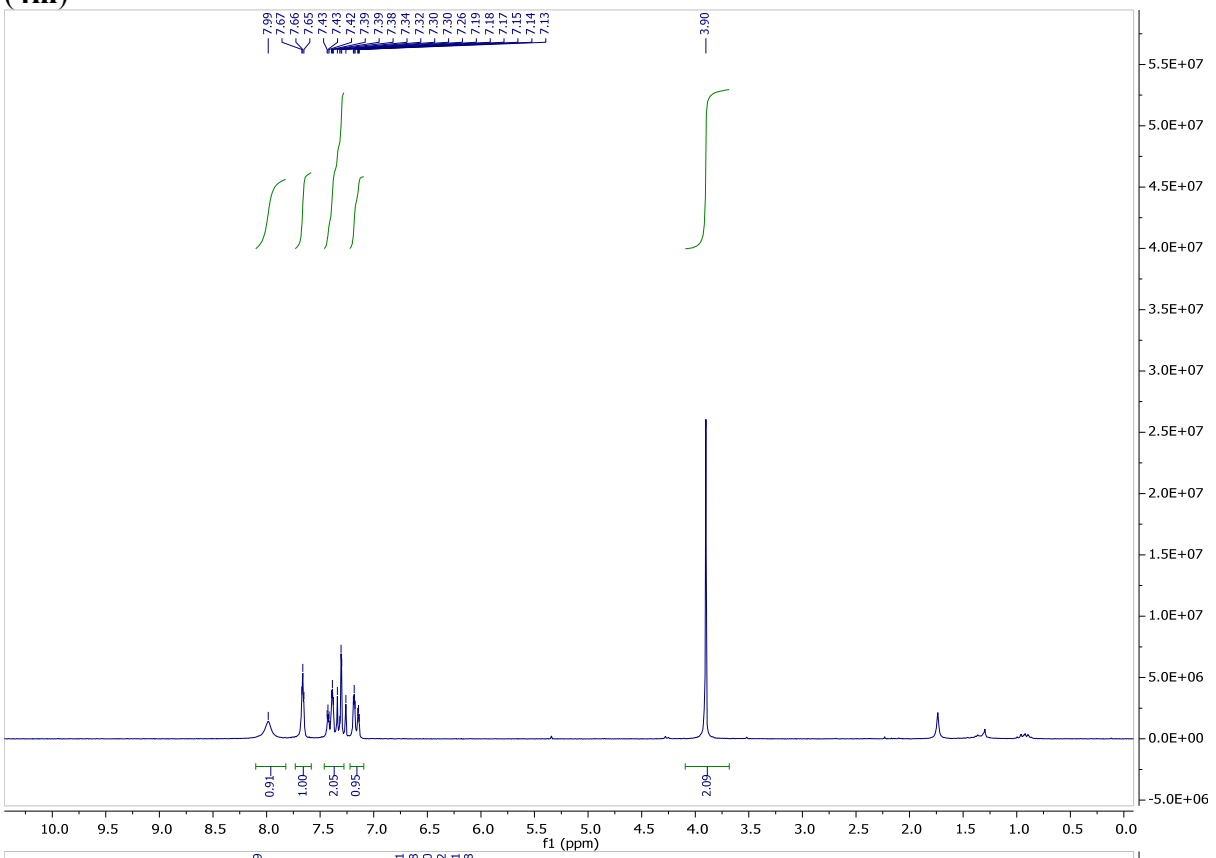
(4l)

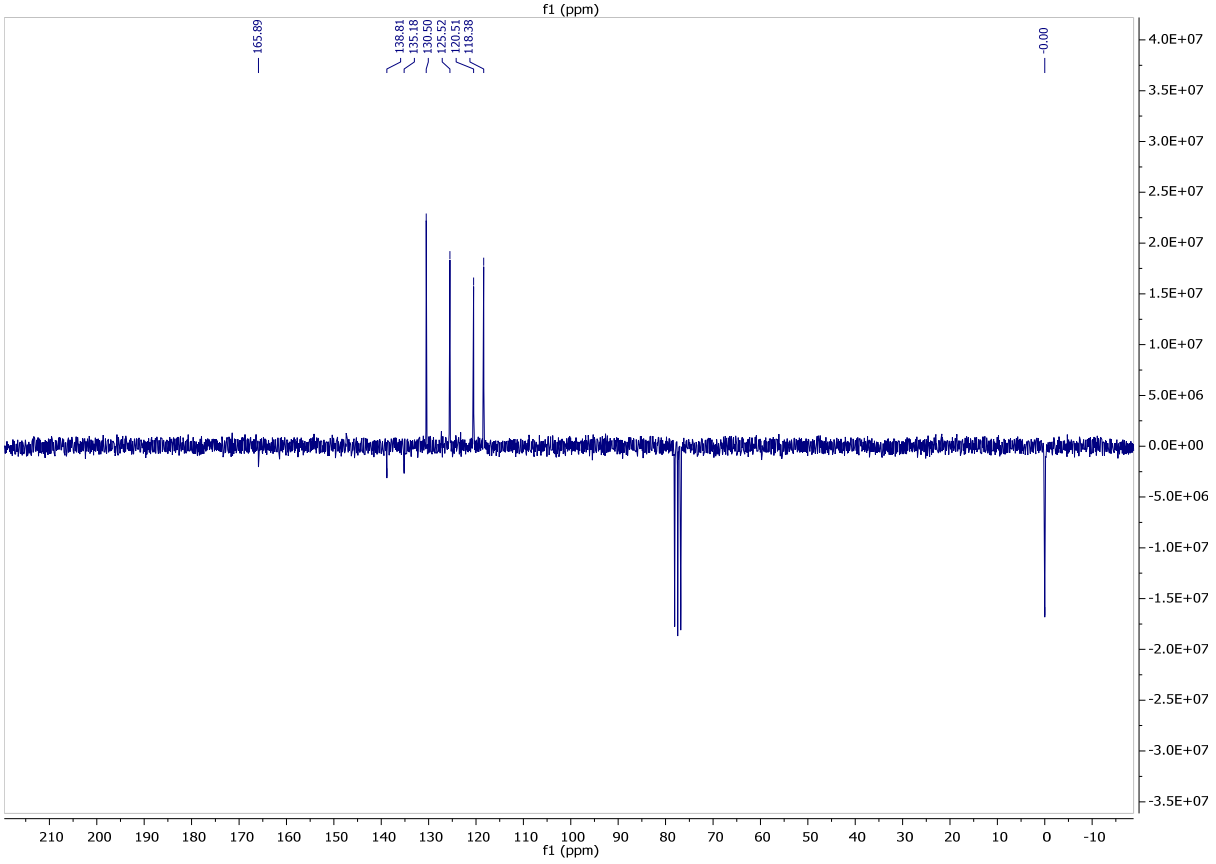

8.29
7.70
7.69
7.68
7.45
7.44
7.43
7.41
7.40
7.39
7.34
7.30
7.28
7.20
7.19
7.18
7.16
7.15
4.21
0.93
1.00
2.04
1.04
2.09
f1 (ppm)

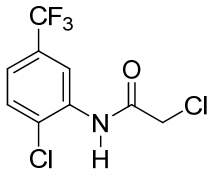

164.34
138.19
135.25
130.55
125.75
120.63
118.48
43.24
f1 (ppm)



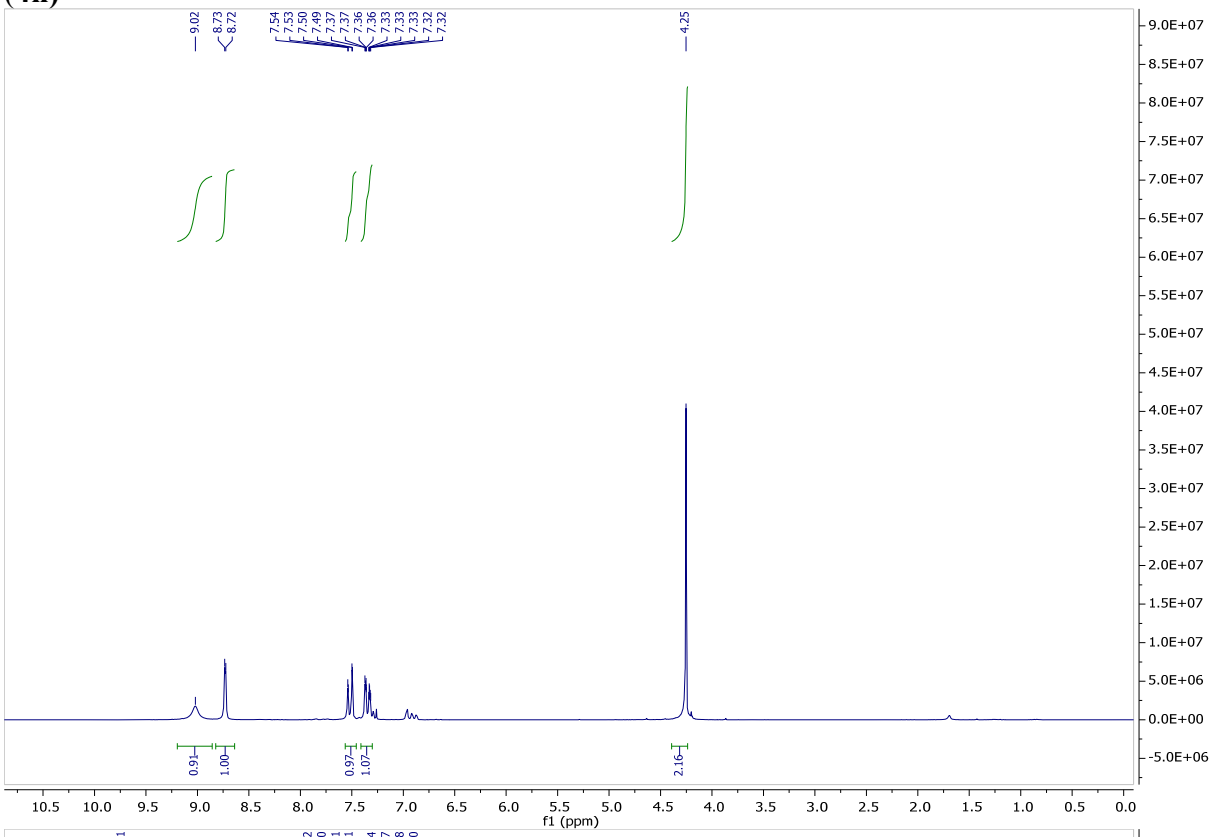
(4m)

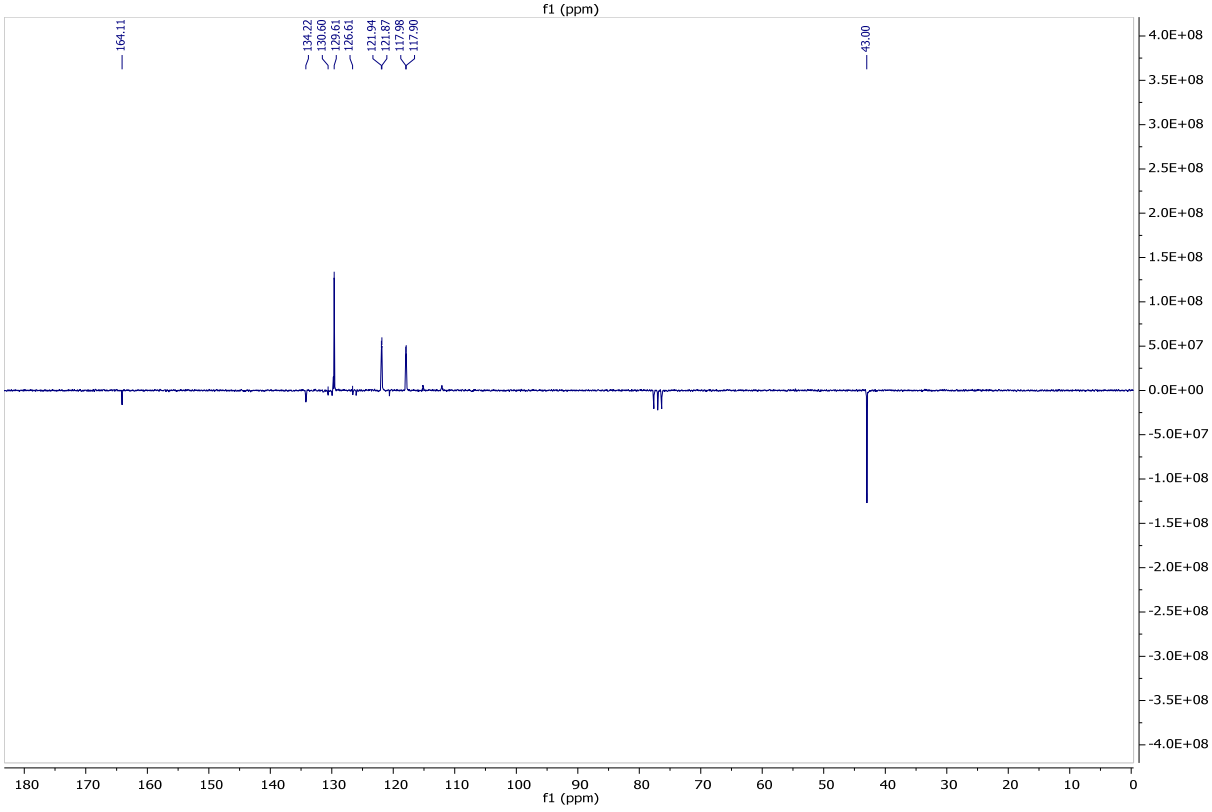


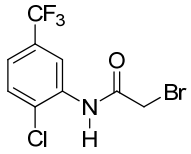




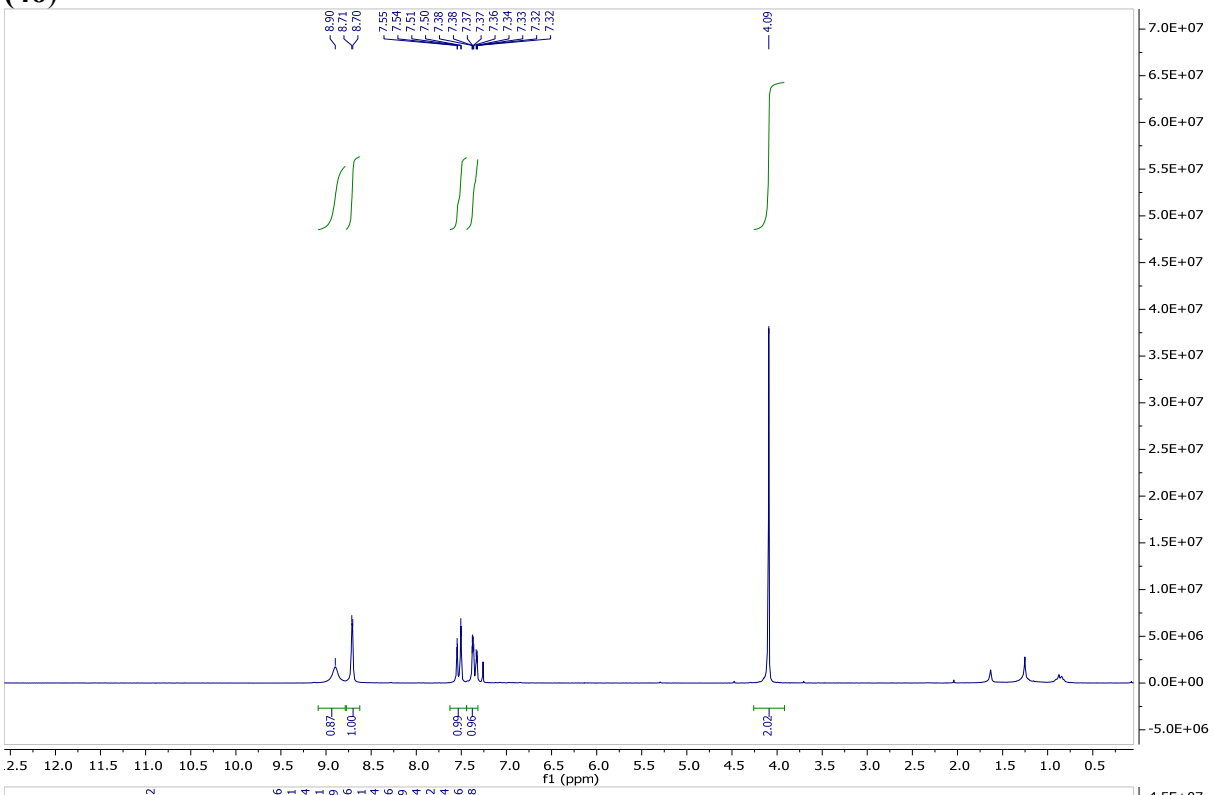
(4n)

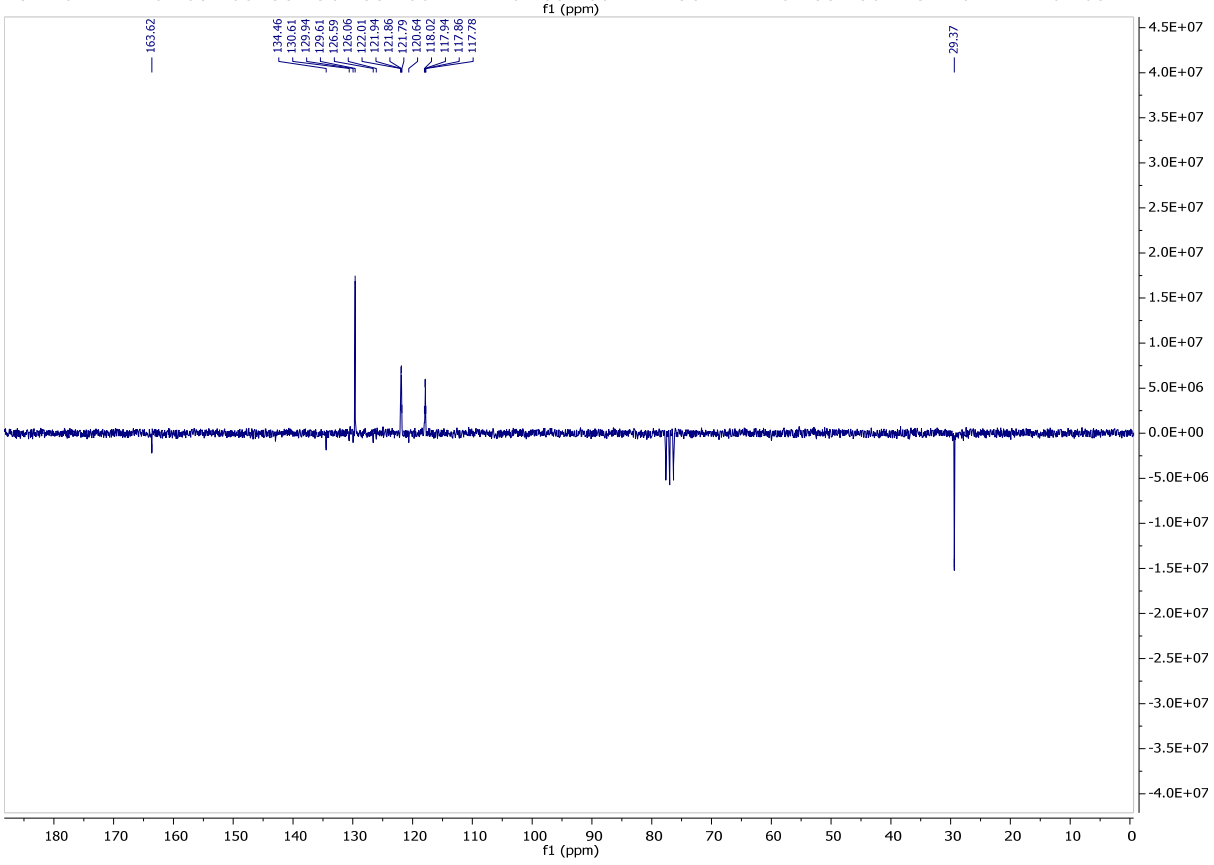


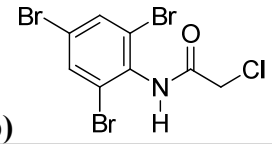



CF3
O
N
H
Br
Cl

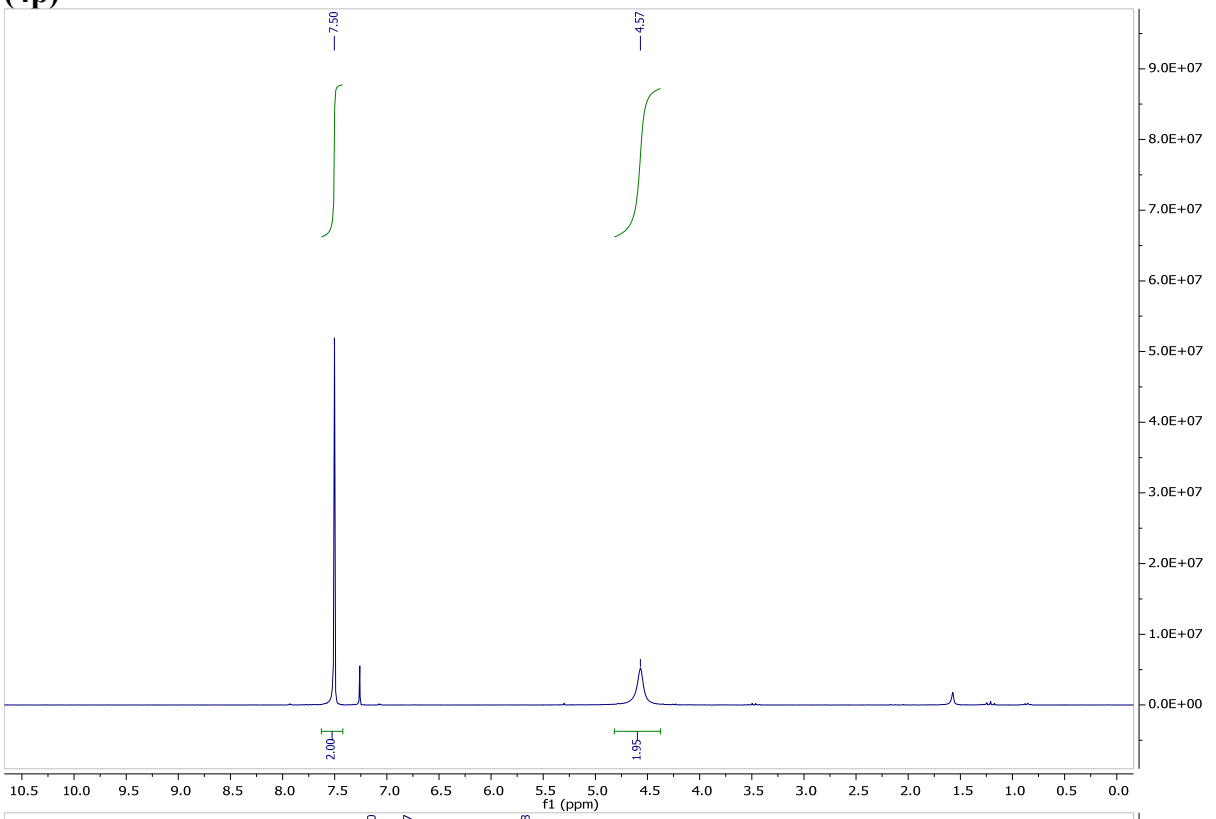
(4o)

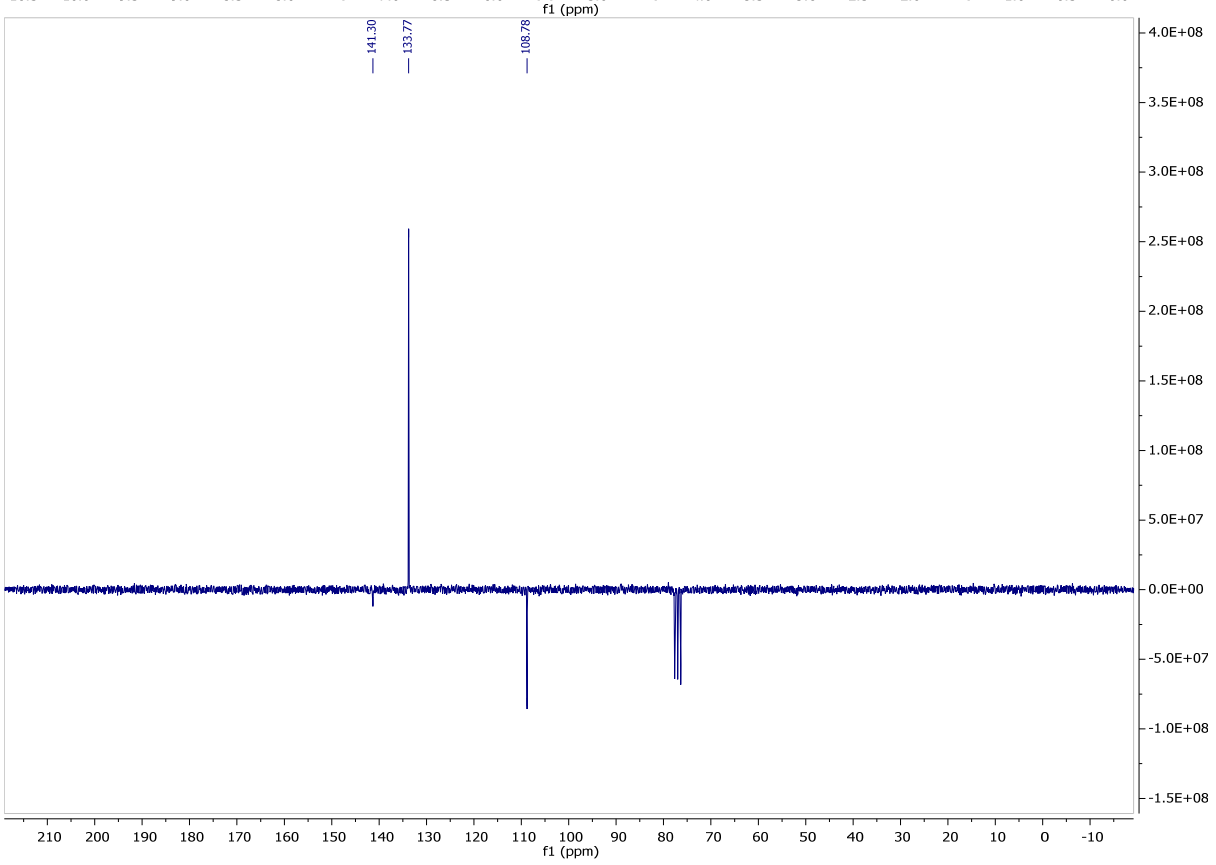

8.90
8.71
8.70
7.55
7.54
7.51
7.50
7.38
7.37
7.37
7.36
7.34
7.33
7.32
7.32
4.09
0.87
1.00
0.99
0.96
2.02
f1 (ppm)


163.62
134.46
130.61
129.94
129.61
126.59
126.06
122.01
121.94
121.86
121.79
120.64
118.02
117.94
117.86
117.78
29.37
f1 (ppm)

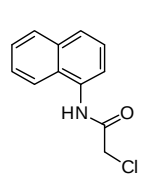

Br
Br
O
Cl
N
H
Br

(4p)

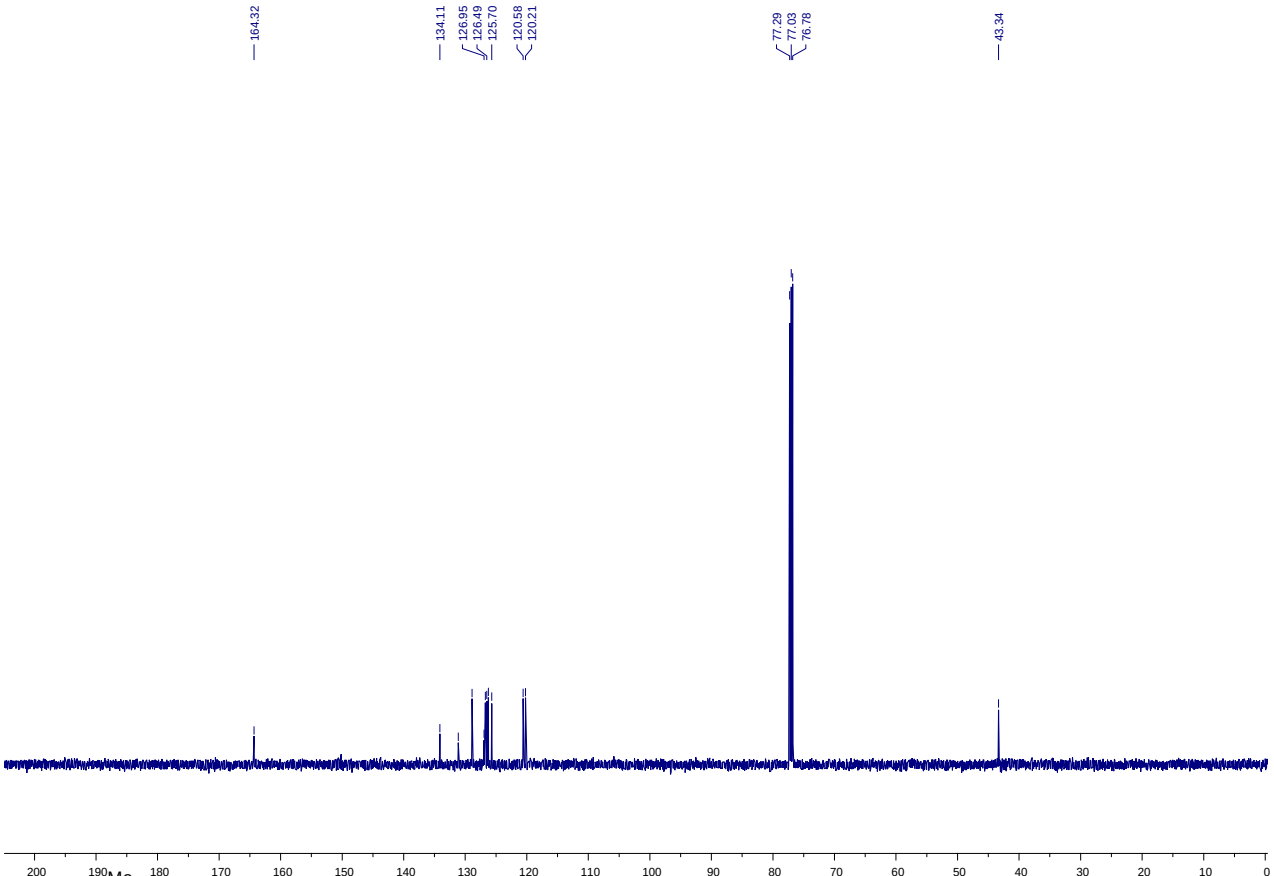

7.50
4.57
2.00
1.95
9.0E+07
8.0E+07
7.0E+07
6.0E+07
5.0E+07
4.0E+07
3.0E+07
2.0E+07
1.0E+07
0.0E+00
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


141.30
133.77
108.78
4.0E+08
3.5E+08
3.0E+08
2.5E+08
2.0E+08
1.5E+08
1.0E+08
5.0E+07
0.0E+00
-5.0E+07
-1.0E+08
-1.5E+08
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

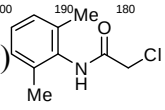
(4q)

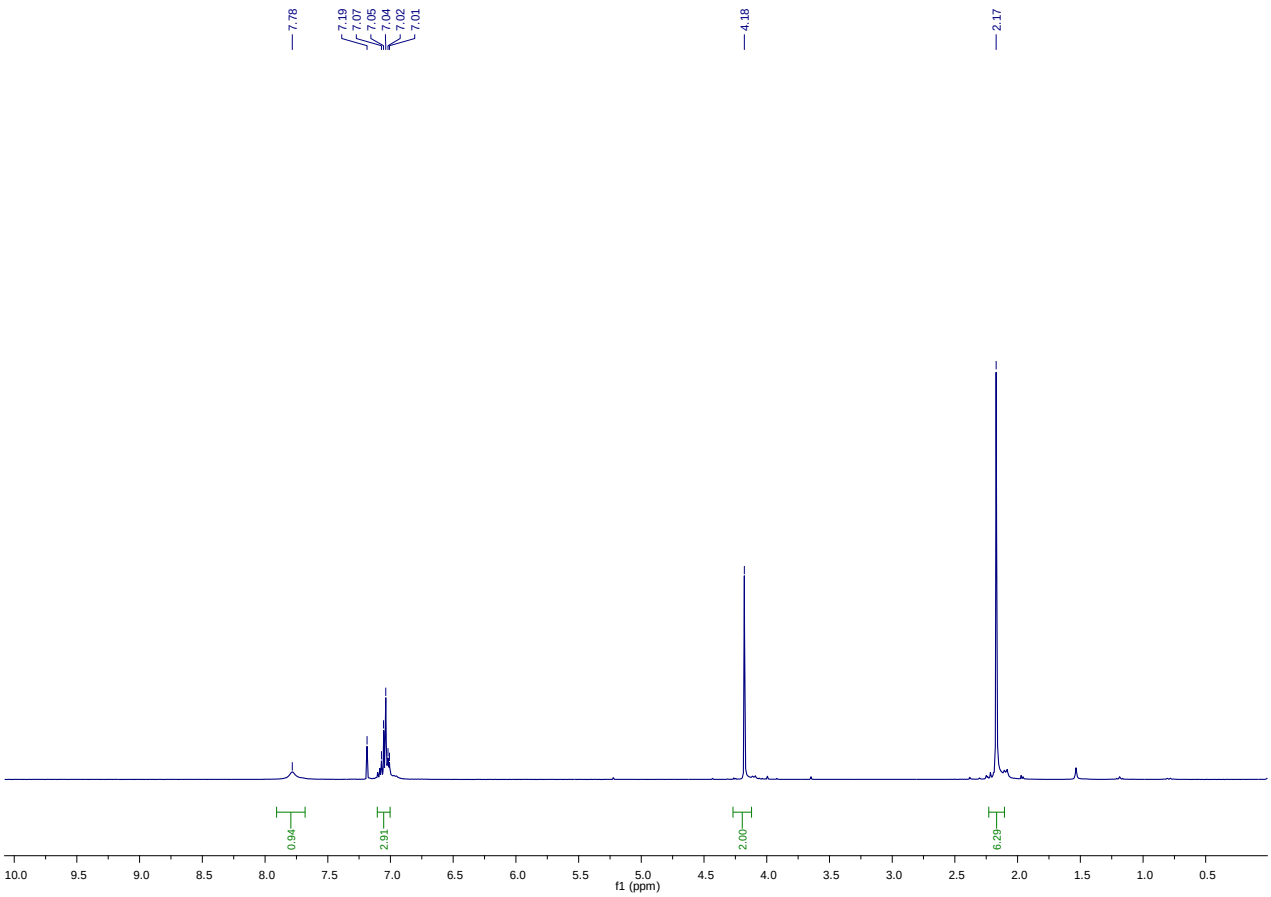

HN
O
Cl

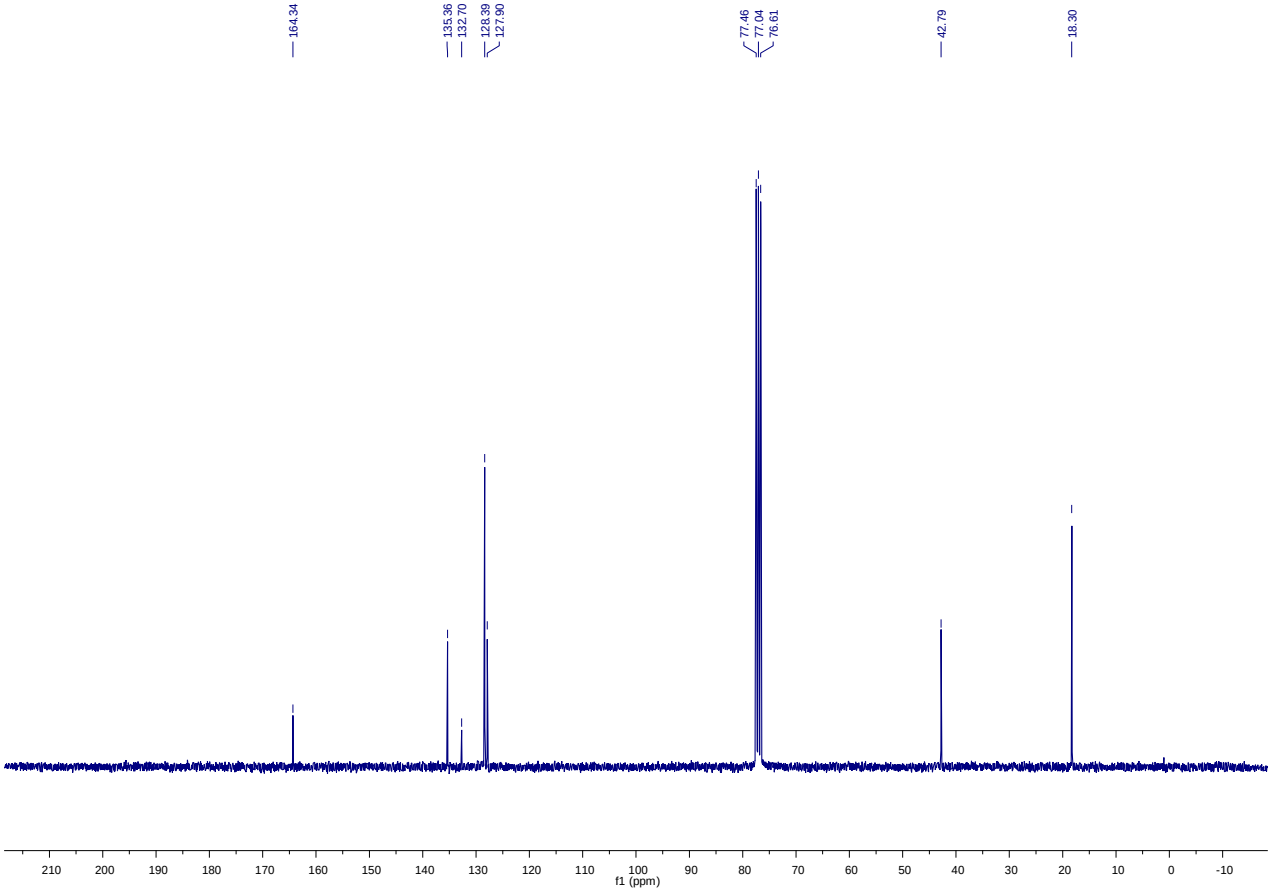
8.78
7.99
7.90
7.89
7.87
7.77
7.76
7.51
7.27
4.36
f1 (ppm)


164.32
134.11
126.95
126.49
125.70
120.58
120.21
77.29
77.03
76.78
43.34
f1 (ppm)

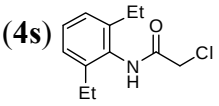
(4r)

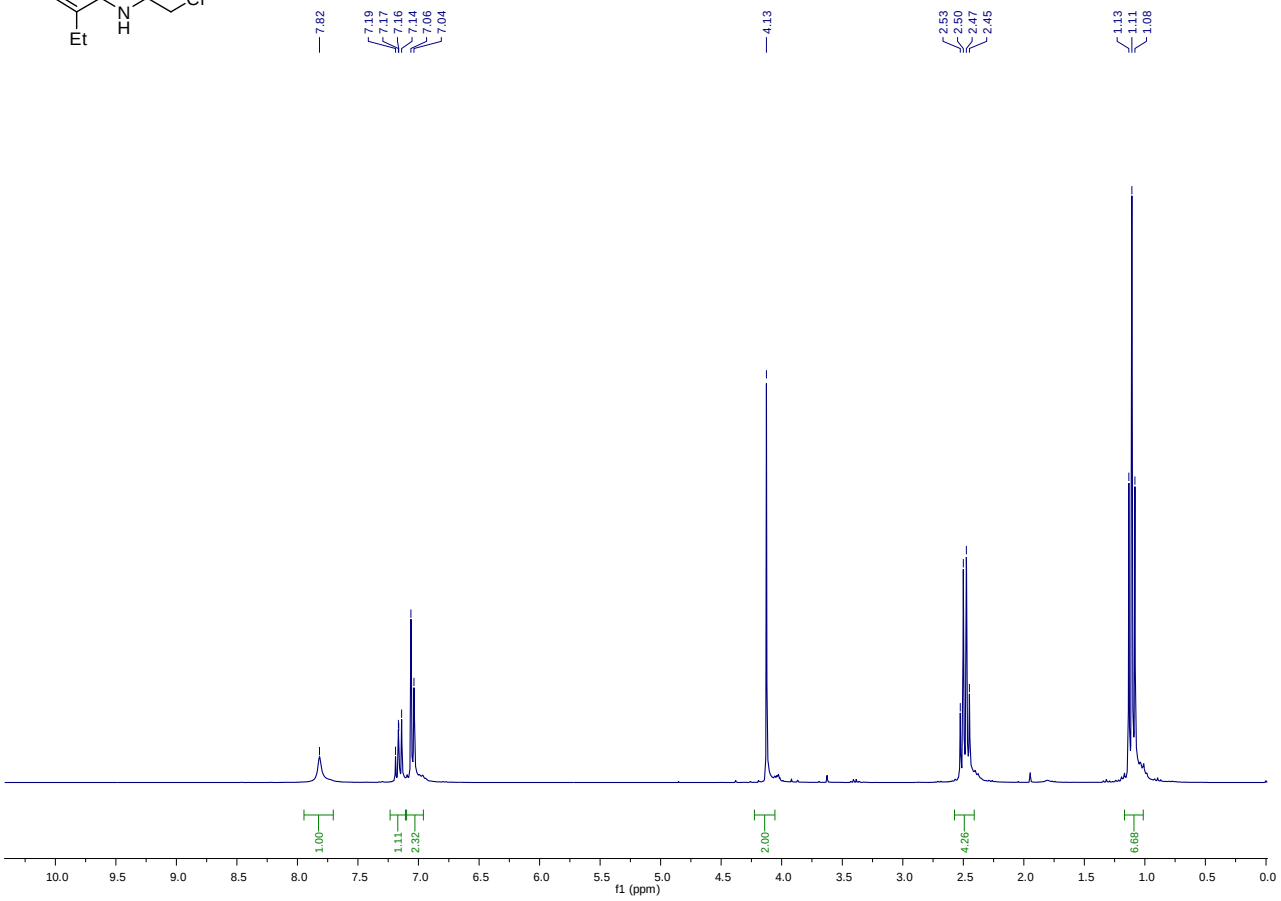

Me
O
N
H
Cl
Me

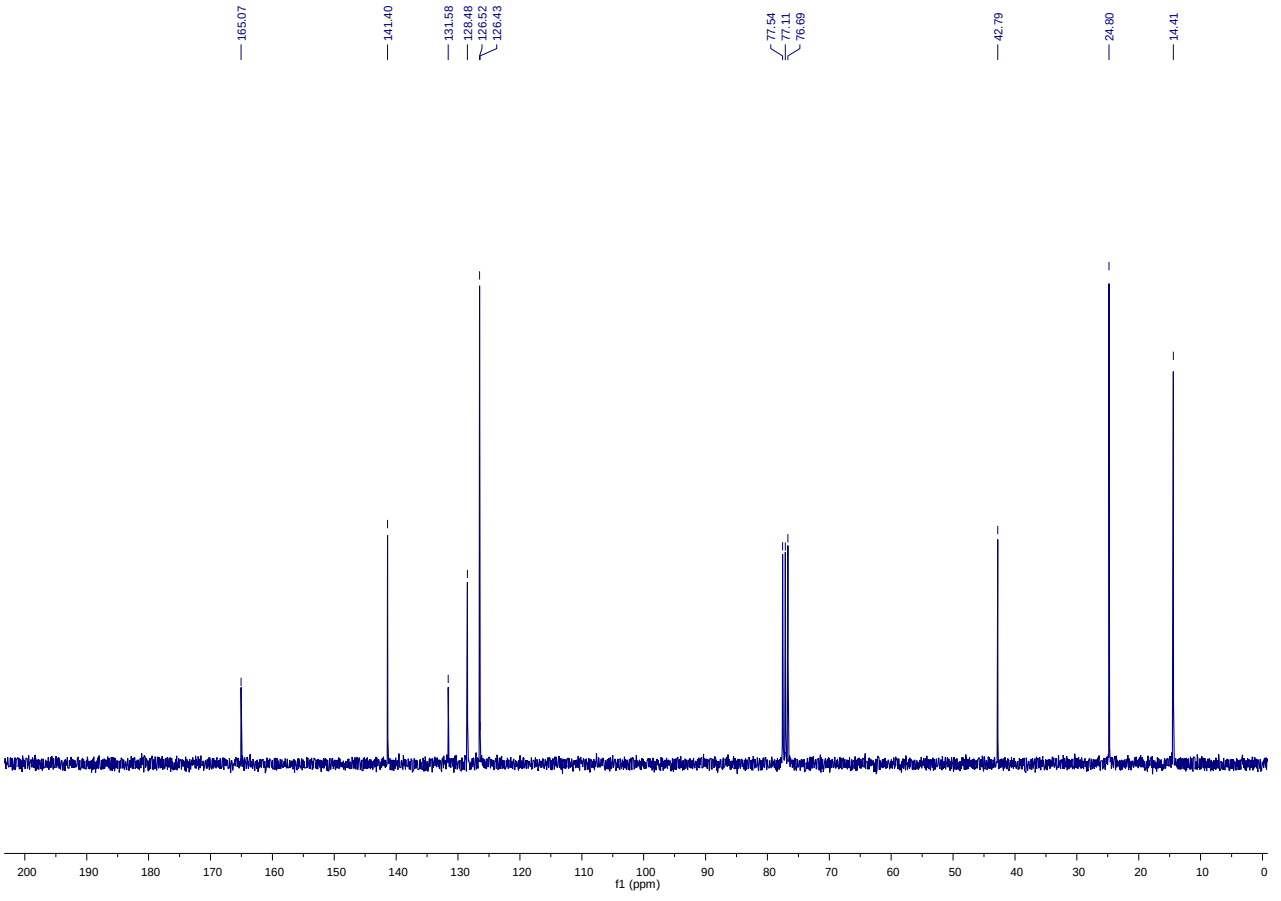


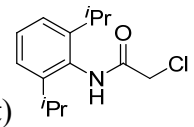


(4s)

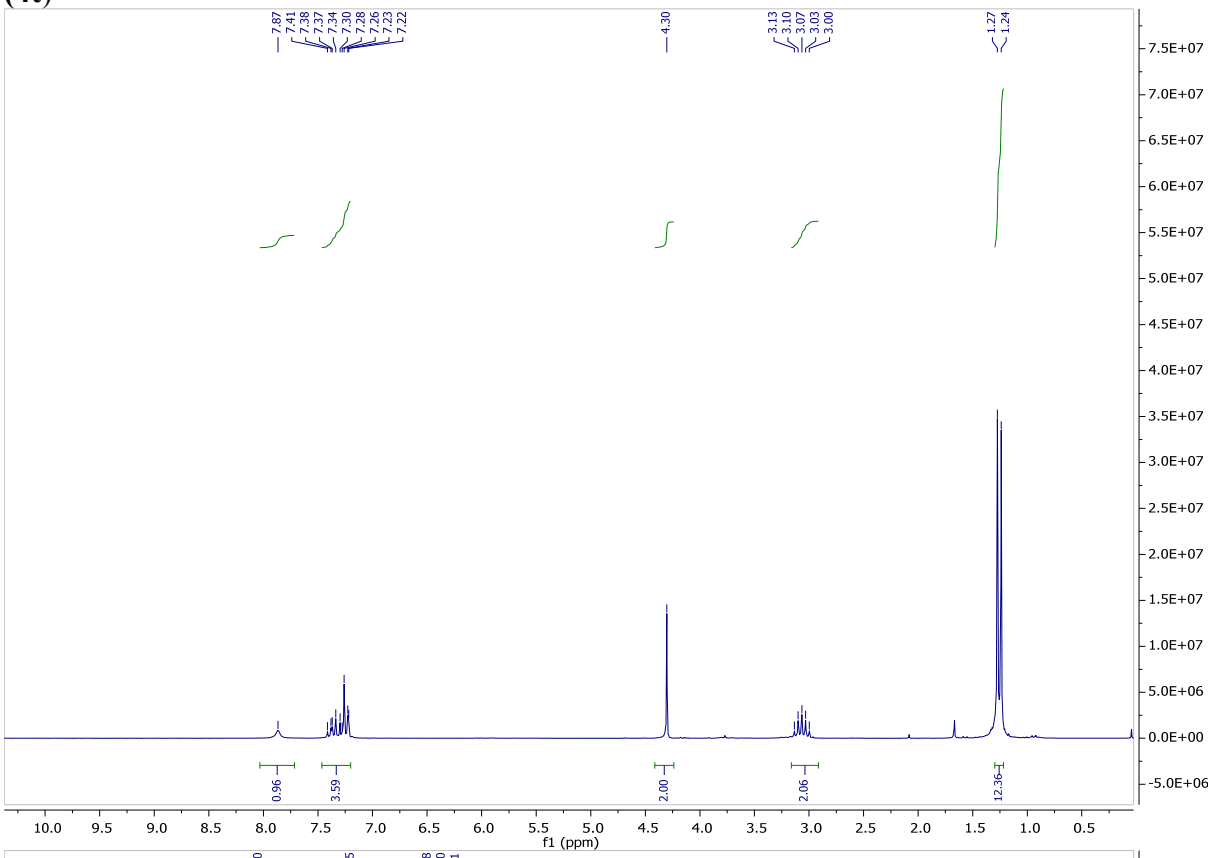


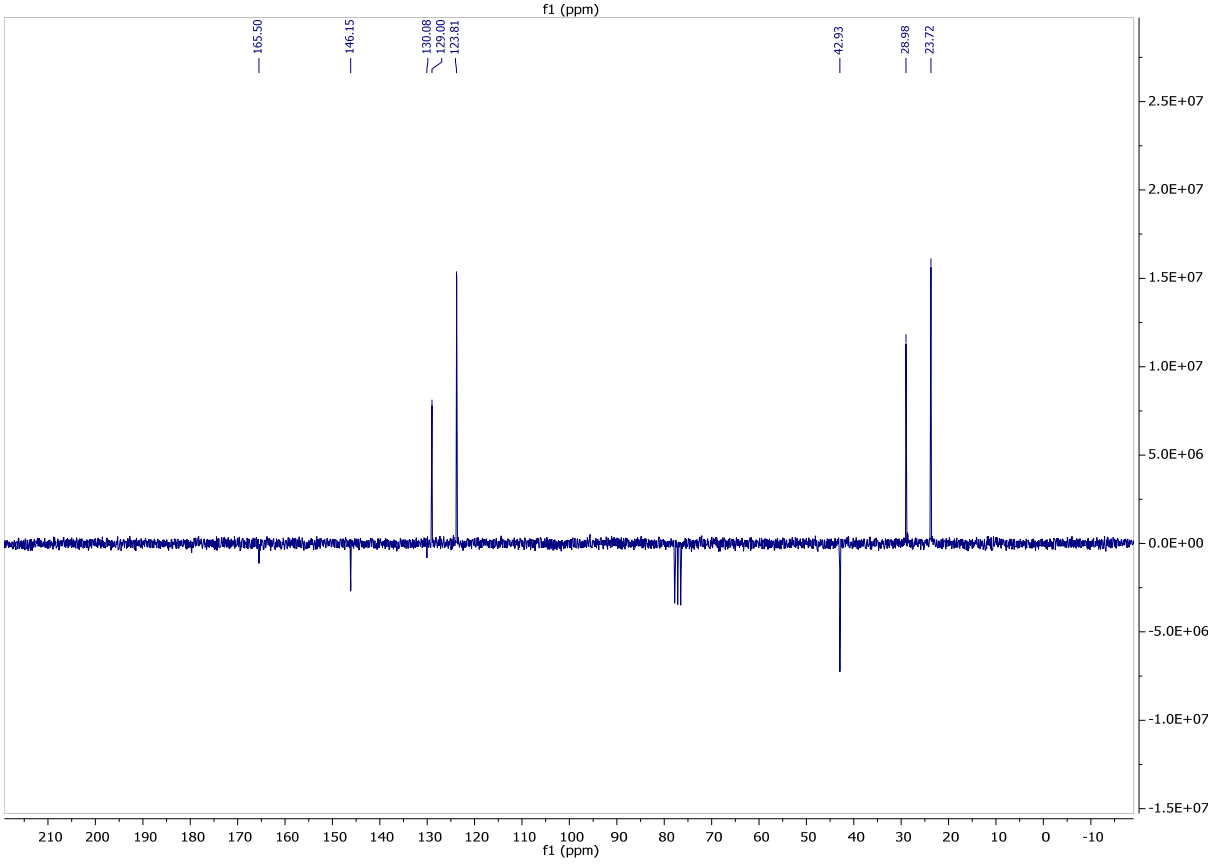




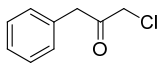

iPr
O
Cl
N
H
iPr

(4t)


7.87
7.41
7.38
7.37
7.34
7.30
7.28
7.26
7.23
7.22
4.30
3.13
3.10
3.07
3.03
3.00
1.27
1.24
0.96
3.59
2.00
2.06
12.36
f1 (ppm)

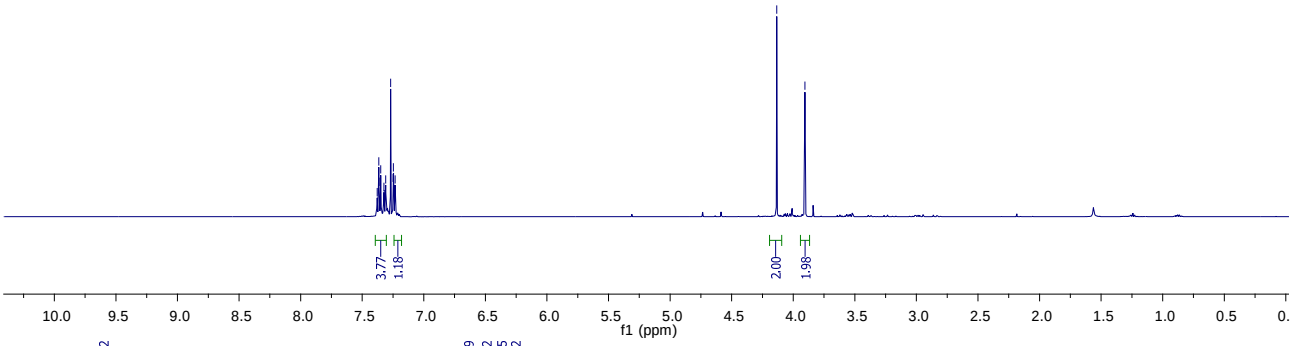

165.50
146.15
130.08
129.00
123.81
42.93
28.98
23.72
f1 (ppm)

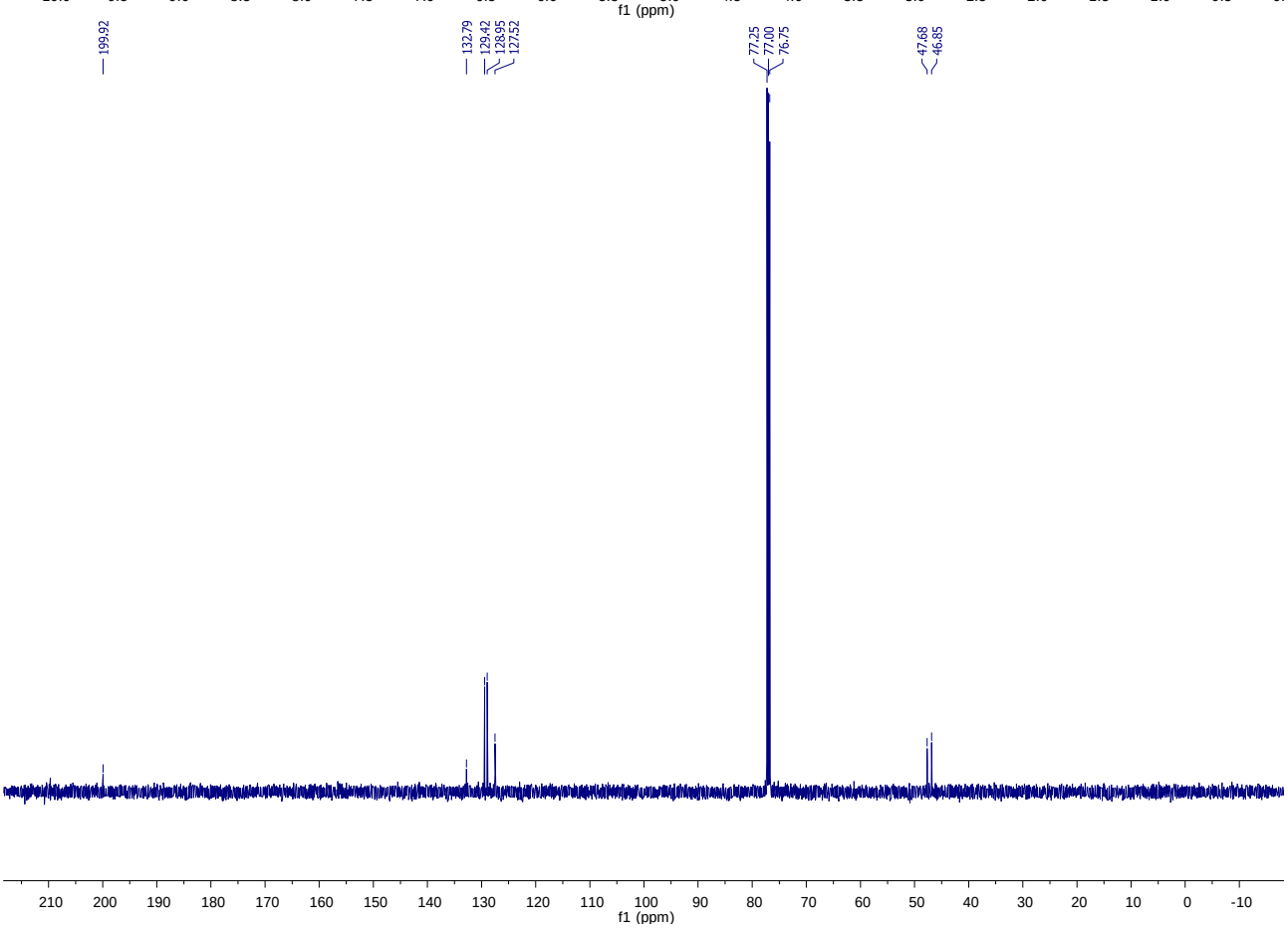
(6)


Cl
O


7.38
7.36
7.36
7.35
7.35
7.32
7.32
7.31
7.27
7.25
7.25
7.23


4.13
3.91


3.77
1.18
2.00
1.98
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


199.92
132.79
129.42
128.95
127.52
77.25
77.00
76.75
47.68
46.85
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)