SUPPORTING INFORMATION

In-water synthesis of isocyanides under micellar conditions

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Contents

General Methods and Materials

Solvents and Reagents. Commercially available reagents and solvents were used without further purification. p-TsCl was crystalized by using petroleum ether.

Chromatography. Flash column chromatography was performed using Biotage Isolera One on silica gel 60 (Merck Kieselgel 230-400 mesh ASTM) using the indicated eluents. Thin layer chromatography (TLC) was carried out on 5 x 20 cm plates with a layer thickness of 0.25 mm (Merck Silica gel 60 F254). TLC were developed using a 0.5% solution of 3,6-di-2-pyridyl-1,2,4,5-tetrazine in methanol.

Spectra. Infrared spectra were recorded on a FT-IR Bruker Alpha II spectrometer with absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). NMR spectra were recorded using a Bruker Avance Neo 400 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million referenced to the residual solvent peak. The multiplicity of each signal is designated using the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; sext, sextet; hept, heptet; m, multiplet; br s, broad singlet. Coupling constants (J) are reported in Hertz (Hz). High-resolution ESI-MS spectra were performed on a Thermo Fisher Q Exactive Plus Hybrid Quadrupole-Orbitrap mass spectrometer. Melting points were determined in open glass capillary with a Buchi melting point M-560.

Optical rotation. Optical rotations were measured on a JASCO P1010 polarimeter at 25°C (cell path length = 1 dm).

Synthesis of *N*-formamides

General synthesis of aliphatic *N*-formamides

The corresponding aliphatic amine (1 equiv.) was dissolved in methyl formate (0.8 M) and heated under reflux overnight. Afterwards, the reaction mixture was concentrated under reduced pressure and the crude product was used without further purification or analysis.

Adamantyl *N*-formamide and ***N*-(2-phenylpropan-2-yl)formamide** were synthesized according to literature procedure.[1]

N-(4-methoxyphenyl)formamide

4-methoxyaniline (1 equiv.) was dissolved in toluene (2.4 M) and formic acid (1.5 equiv.) was added. The mixture was heated under reflux overnight and then washed with HCl 2N. The organic phase was dried over sodium sulfate and concentrated under reduced pressure. The crude product was used without further purification or analysis.

Methyl formylphenylalaninate was synthesized according to literature procedure.[2]

Compounds characterization data

(2-isocyanoethyl)benzene 6
Eluent: Pet/EtOAc 9:1. Yellow oil, yield 64%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.49 – 7.23 (m, 5H), 3.64 (tt, *J*=7.1, 1.9 Hz, 2H), 3.02 (tt, *J*=7.1, 2.0 Hz, 2H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.6 (br t), 136.7, 128.8, 128.7, 127.3, 43.0 (t, *J*=6.7 Hz), 35.7 ppm.
IR (neat) ν 2147, 1496, 1454, 748, 699, 578 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_8H_9^+$ $[M+H-HCN]^+$: 105.06988, Found: 105.07001

1-Adamantyl isocyanide 7
Eluent: Pet/EtOAc 9:1. White solid, yield 89%, mp 185-189 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ = 2.15 – 2.06 (m, 3H), 2.03 (d, *J*=3.2 Hz, 6H), 1.75 – 1.62 (m, 6H) ppm.
^{13}C NMR (101 MHz, Acetone) δ = 153.6 (t, *J*=4.3 Hz), 54.0 (br t), 43.4, 35.2, 28.8 ppm.
IR (neat) ν 2122, 1693, 1453, 1307, 1075, 482 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{10}H_{15}^+$ $[M+H-HCN]^+$: 135.11683, Found: 135.11680

(3-isocyanopropyl)benzene 8
Eluent: Pet/EtOAc 9:1. Yellow oil, yield 68%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 – 7.32 (m, 2H), 7.30 – 7.20 (m, 3H), 3.39 (tt, *J*=6.6, 2.0 Hz, 2H), 2.82 (t, *J*=7.4 Hz, 2H), 2.08 – 1.97 (m, 2H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.4 (br t), 139.9, 128.7, 128.5, 126.5, 40.7 (t, *J*=6.5 Hz), 32.2, 30.6 ppm.
IR (neat) ν 2147, 1496, 1453, 744, 699, 489 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_9H_{11}^+$ $[M+H-HCN]^+$: 119.08553, Found: 119.08563

Isocyanocyclohexane 9
Eluent: Diethyl ether. Yellowish oil, yield 65%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.65 – 3.55 (m, 1H), 1.95 – 1.82 (m, 2H), 1.81 – 1.60 (m, 4H), 1.54 – 1.29 (m, 4H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 154.0 (t, *J*=5.3 Hz), 51.7 (t, *J*=5.6 Hz), 32.6, 25.0, 22.8 ppm.
IR (neat) ν 2136, 1450, 1366, 1041, 912, 893 cm^{-1}

(isocyanomethyl)benzene 10
Eluent: Pet/EtOAc 9:1. Colourless oil, yield 68%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.41 (m, 2H), 7.41 – 7.36 (m, 3H), 4.66 (t, *J*=2.3 Hz, 2H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.8 (t, *J*=5.3 Hz), 132.4, 129.0, 128.5, 126.7, 45.6 (t, *J*=7.2 Hz) ppm.
IR (neat) ν 2149, 1497, 1454, 734, 695, 602 cm^{-1}

(2-isocyanopropan-2-yl)benzene 11
Eluent: Pet/EtOAc 9:1. Yellowish oil, yield 60%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (dd, *J*=7.6, 1.9 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.39 – 7.33 (m, 1H), 1.82 (t, *J*=2.1 Hz, 6H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.4 (t, *J*=4.4 Hz), 142.3, 128.8, 127.8, 124.2, 60.7 (t, *J*=5.9 Hz), 32.0 ppm.
IR (neat) ν 22133, 1447, 1257, 1167, 763, 698 cm^{-1}

HRMS (ESI): *m/z*: calcd for $C_9H_{11}^+$ [M+H-HCN]$^+$: 119.08553, Found: 119.08554

1-(isocyanomethyl)-4-methoxybenzene 12
Eluent: Pet/EtOAc 85:15. Colourless oil, yield 55%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 – 7.26 (m, 2H), 6.97 – 6.91 (m, 2H), 4.59 (br t, 2H), 3.84 (s, 3H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.7, 157.1 (t, *J*=5.2 Hz), 128.2, 124.5, 114.4, 55.4, 45.1 (t, *J*=7.0 Hz) ppm.
IR (neat) ν 2147, 1513, 1250, 1178, 1032, 816 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_8H_9O^+$ [M+H-HCN]$^+$: 121.06479, Found: 121.06493

1-isocyano-4-methoxybenzene 13
Eluent: Pet/EtOAc 9:1. Yellow oil, yield 41%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.35 – 7.30 (m, 2H), 6.92 – 6.86 (m, 2H), 3.84 (s, 3H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 162.6 (br t), 159.9, 127.8, 114.6, 55.6 ppm.
IR (neat) ν 2122, 1504, 1252, 1193, 1028, 832 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_8H_8NO^+$ [M+H]$^+$: 134.06004, Found: 134.06028

1-isocyanododecane 14
Eluent: Pet/EtOAc 9:1. Colourless oil, yield 89%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.40 (tt, *J*=6.7, 1.9 Hz, 2H), 1.75 – 1.65 (m, 2H), 1.50 – 1.41 (m, 2H), 1.37 – 1.24 (m, 16H), 0.90 (br t, 3H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6 (t, *J*=5.8 Hz), 41.6 (t, *J*=6.4 Hz), 31.9, 29.6 (2C), 29.5, 29.4, 29.3, 29.1, 28.7, 26.3, 22.7, 14.1 ppm.
IR (neat) ν 2146, 1466, 1259, 1087, 1015, 797 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{13}H_{25}NNa^+$ [M+Na]$^+$: 218.18792, Found: 218.18799

3-(3-isocyanopropyl)-1*H*-indole 15
Eluent: Pet/EtOAc 85:15. Yellowish oil, yield 42%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.07 (br s, 1H), 7.67 – 7.61 (m, 1H), 7.45 – 7.37 (m, 1H), 7.28 – 7.22 (m, 1H), 7.21 – 7.14 (m, 1H), 7.06 (d, *J*=2.3 Hz, 1H), 3.41 (tt, *J*=6.6, 1.9 Hz, 2H), 2.99 (t, *J*=7.2 Hz, 2H), 2.16 – 2.04 (m, 2H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.9 (br t), 136.5, 127.2, 122.2, 122.0, 119.5, 118.7, 113.8, 111.3, 40.9 (t, *J*=6.4 Hz), 29.3, 21.7 ppm.
IR (neat) ν 3407, 2148, 1456, 1339, 1093, 743, 425 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{12}H_{13}N_2^+$ [M+H]$^+$: 185.10732, Found: 185.10761

1-chloro-4-(2-isocyanoethyl)benzene 16
Eluent: Pet/EtOAc 9:1. Colourless oil, yield 70%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.37 – 7.31 (m, 2H), 7.22 – 7.16 (m, 2H), 3.62 (tt, *J*=6.9, 1.8 Hz, 2H), 2.97 (tt, *J*=7.0, 2.2 Hz, 2H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.0 (t, *J*=5.4 Hz), 135.1, 133.2, 130.1, 129.0, 42.9 (t, *J*=6.7 Hz), 34.9 ppm.
IR (neat) ν 2147, 1492, 1089, 1015, 807, 550 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_8H_8Cl^+$ [M+H-HCN]$^+$: 139.03090, Found: 139.03108

1-(2-isocyanoethyl)-3-methoxybenzene 17
Eluent: Pet/EtOAc 9:1. Colourless oil, yield 73%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (t, *J*=7.9 Hz, 1H), 6.89 – 6.81 (m, 2H), 6.80 (t, *J*=2.1 Hz, 1H), 3.84 (s, 3H), 3.63 (tt, *J*=7.2, 1.9 Hz, 2H), 2.99 (tt, *J*=7.2, 2.0 Hz, 2H) ppm.

^{13}C NMR (101 MHz, $CDCl_3$) δ = 159.9, 156.7 (br t), 138.2, 129.8, 120.9, 114.5, 112.6, 55.2, 42.9 (t, *J*=6.6 Hz), 35.7 ppm.
IR (neat) ν 2147, 1260, 1154, 1054, 1042, 781 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{10}H_{12}NO^+$ $[M+H]^+$: 162.09134, Found: 162.09149

(2-isocyanoethane-1,1-diyl)dibenzene 18
Eluent: Pet/EtOAc 9:1. Whitish oil, yield 80%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 – 7.37 (m, 4H), 7.36 – 7.27 (m, 6H), 4.41 (t, *J*=7.6 Hz, 1H), 4.02 (d, *J*=7.6 Hz, 2H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 157.6 (t, *J*=5.1 Hz), 140.1, 128.9, 127.9, 127.5, 50.5, 46.2 (br t) ppm.
IR (neat) ν 2152, 1494, 1447, 752, 739, 700 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{14}H_{13}^+$ $[M+H-HCN]^+$: 181.10118, Found: 181.10131

(*S*)-(1-isocyanoethyl)benzene 19
Eluent: Pet/EtOAc 9:1. Yellowish oil, yield 63%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.47 – 7.34 (m, 5H), 4.85 (qt, *J*=6.9, 1.8, 1H), 1.71 (dt, *J*=6.9, 2.3 Hz, 3H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 156.4 (t, *J*=4.8 Hz), 138.6, 129.0, 128.3, 125.4, 53.8 (t, *J*=4.9 Hz), 25.2 ppm.
IR (neat) ν 2138, 1496, 1450, 1075, 758, 697 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_8H_9^+$ $[M+H-HCN]^+$: 105.06988, Found: 105.07002
$[\alpha]_D^{25}$ = -43.9° (c = 1.0, $CHCl_3$)

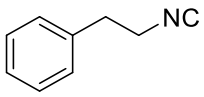
Methyl (*S*)-2-isocyano-3-phenylpropanoate 20
Eluent: Pet/EtOAc 9:1. Yellowish oil, yield 34%
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.32 (m, 3H), 7.30 – 7.26 (m, 2H), 4.49 (m, 1H), 3.83 (s, 3H), 3.29 (dd, *J*=13.9, 4.9 Hz, 1H), 3.17 (dd, *J*=13.9, 8.4 Hz, 1H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 166.6, 161.1 (br s), 134.4, 129.3, 128.8, 127.9, 58.0 (br s), 53.4, 38.9 ppm.
IR (neat) ν 2148, 1743, 1437, 1213, 1177, 1082, 700 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{11}H_{12}NO_2^+$ $[M+H]^+$: 190.08626, Found: 190.08632
$[\alpha]_D^{25}$ = -20.6° (c = 1.0, $CHCl_3$)

1-isocyanooctadecane 21
Eluent: Pet/EtOAc 9:1. Yellowish powder, yield 82%, mp 36.7 – 37.4 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.39 (tt, *J*=6.7, 1.9 Hz, 2H), 1.75 – 1.64 (m, 2H), 1.50 – 1.40 (m, 2H), 1.35 – 1.23 (m, 28H), 0.90 (t, *J*=6.7 Hz, 3H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 155.6 (br t), 41.6 (br t), 31.9, 29.7, 29.7, 29.7, 29.6, 29.5, 29.4, 29.1, 28.7, 26.3, 22.7, 14.1 ppm.
IR (neat) ν 2150, 1471, 1351, 853, 718, 549 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{19}H_{38}N^+$ $[M+H]^+$: 280.29988, Found: 280.30002

1-(dodecylamino)-3-methyl-1-oxobutan-2-yl 2-phenylacetate 24
Eluent: Pet/EtOAc 8:2. White powder, mp 41.2 – 42.1 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 – 7.26 (m, 5H), 5.51 (t, *J*=5.8 Hz, 1H), 5.10 (d, *J*=3.8 Hz, 1H), 3.72 (s, 2H), 3.11 (m, 1H), 2.97 (m, 1H),, 2.38 – 2.24 (m, 1H), 1.37 – 1.22 (m, 18H), 1.19 – 1.11 (m, 2H), 0.96 – 0.82 (m, 9H) ppm.
^{13}C NMR (101 MHz, $CDCl_3$) δ = 169.8, 169.0, 133.8, 129.2, 128.9, 127.5, 78.0, 41.8, 39.0, 31.9, 30.4, 29.7, 29.6, 29.6, 29.5, 29.4, 29.3, 29.2, 26.7, 22.7, 18.8, 16.5, 14.1 ppm.

IR (neat) ν 3289, 1736, 1656, 1566, 1243, 1131, 720, 694 cm^{-1}
HRMS (ESI): *m/z*: calcd for $C_{25}H_{42}NO_3^+$ $[M+H]^+$: 404.31592, Found: 404.31598

Copies of ^{1}H and ^{13}C spectra



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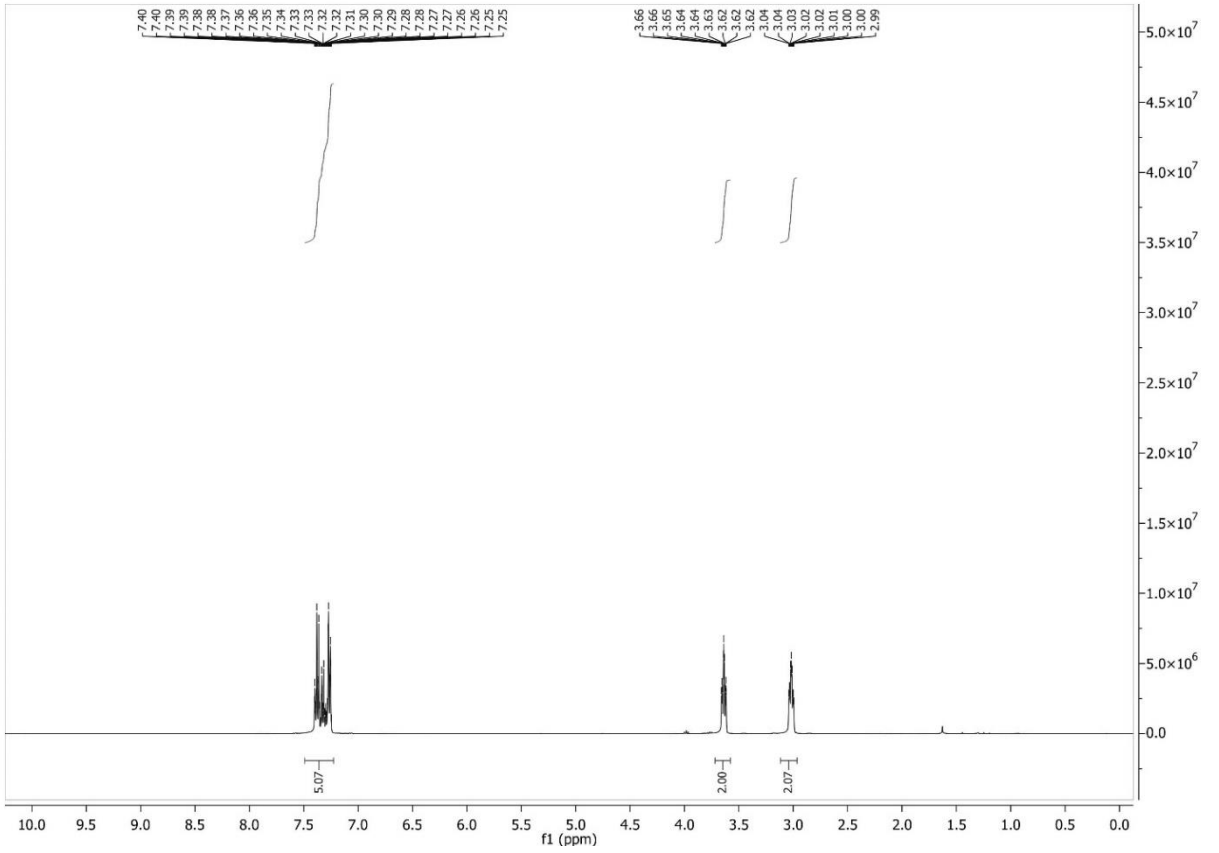

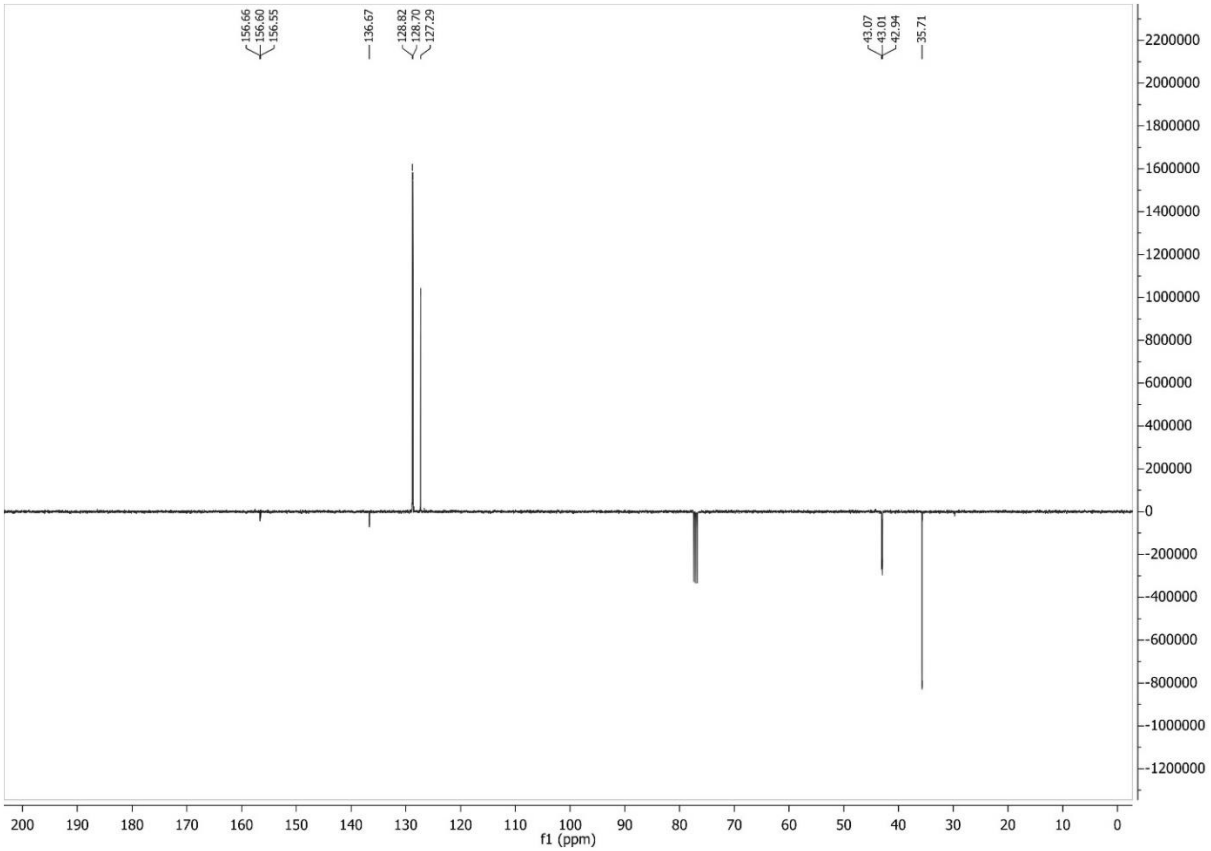

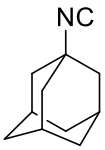
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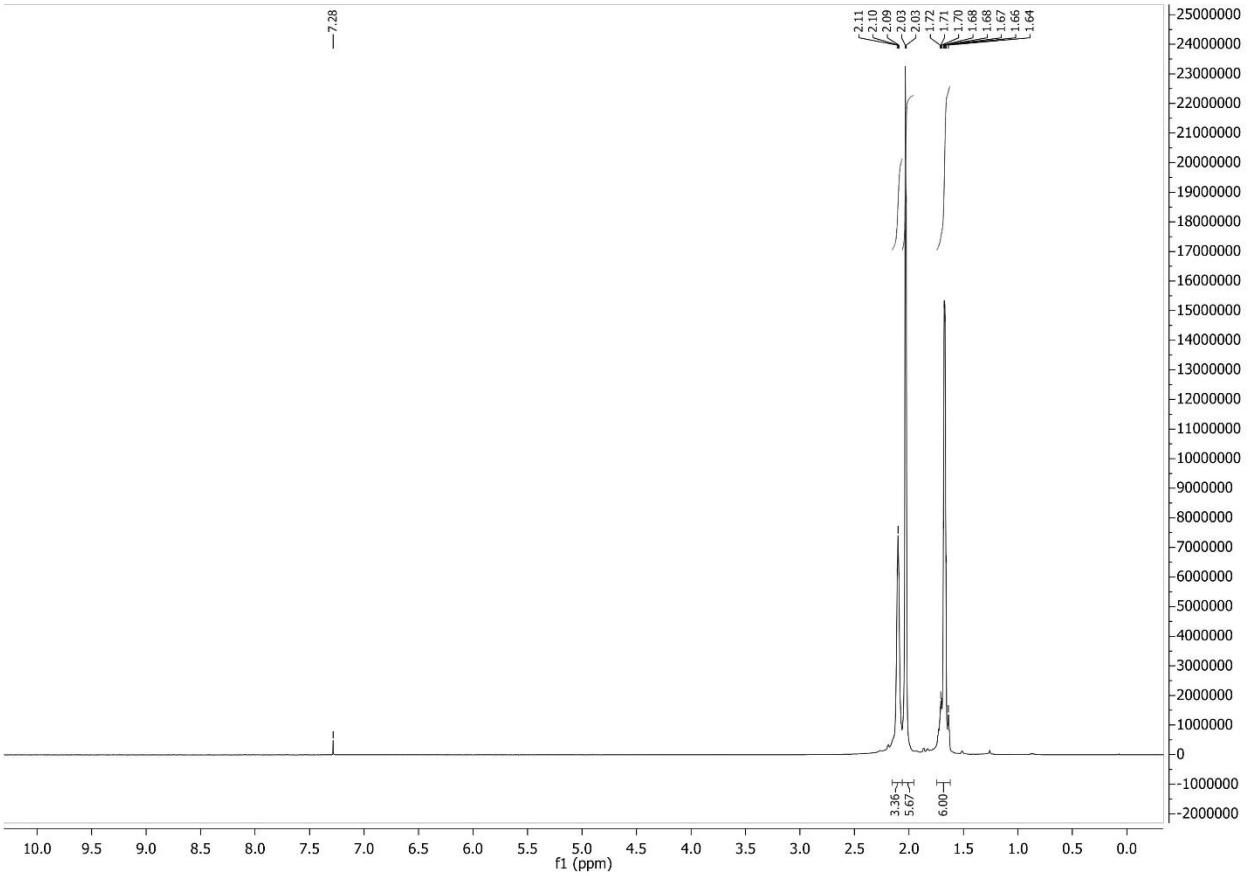
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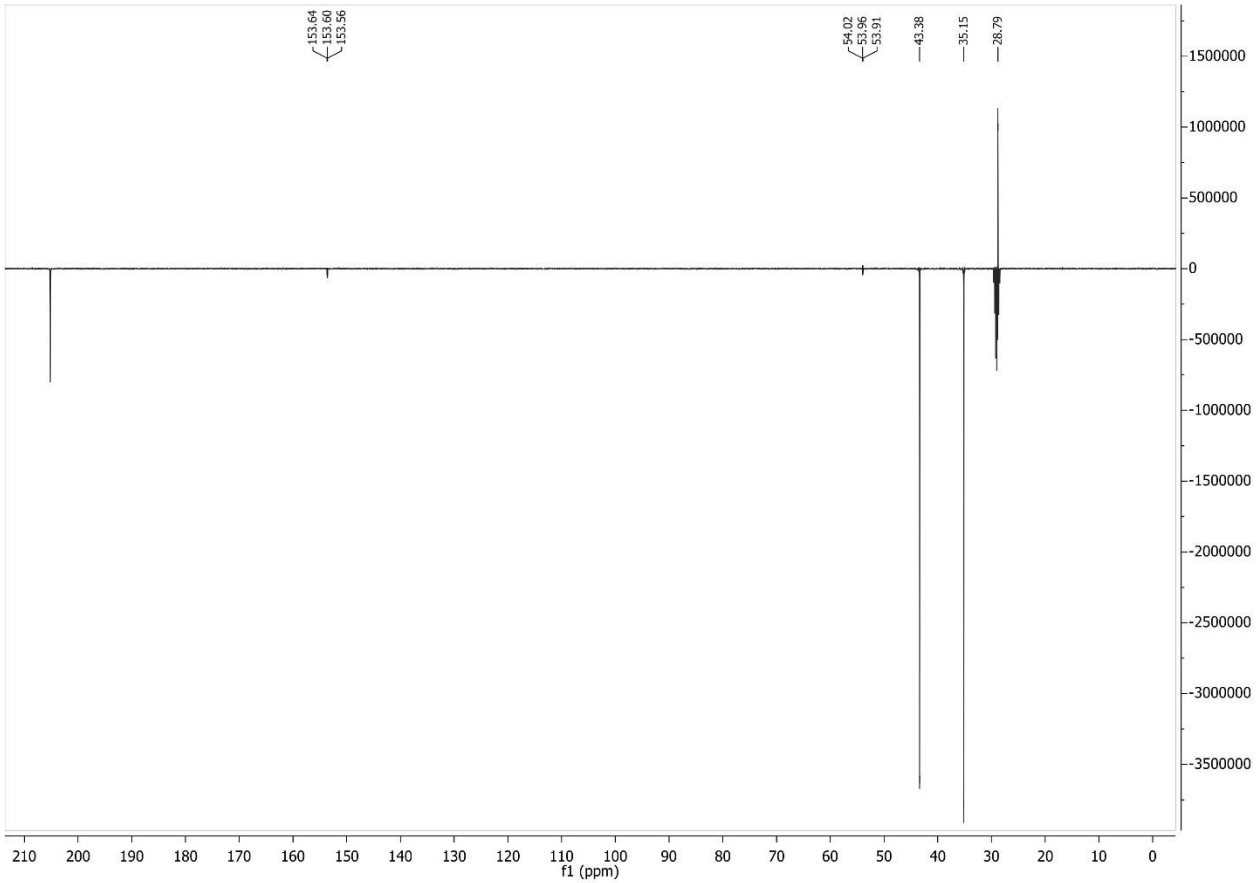
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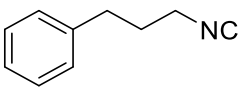
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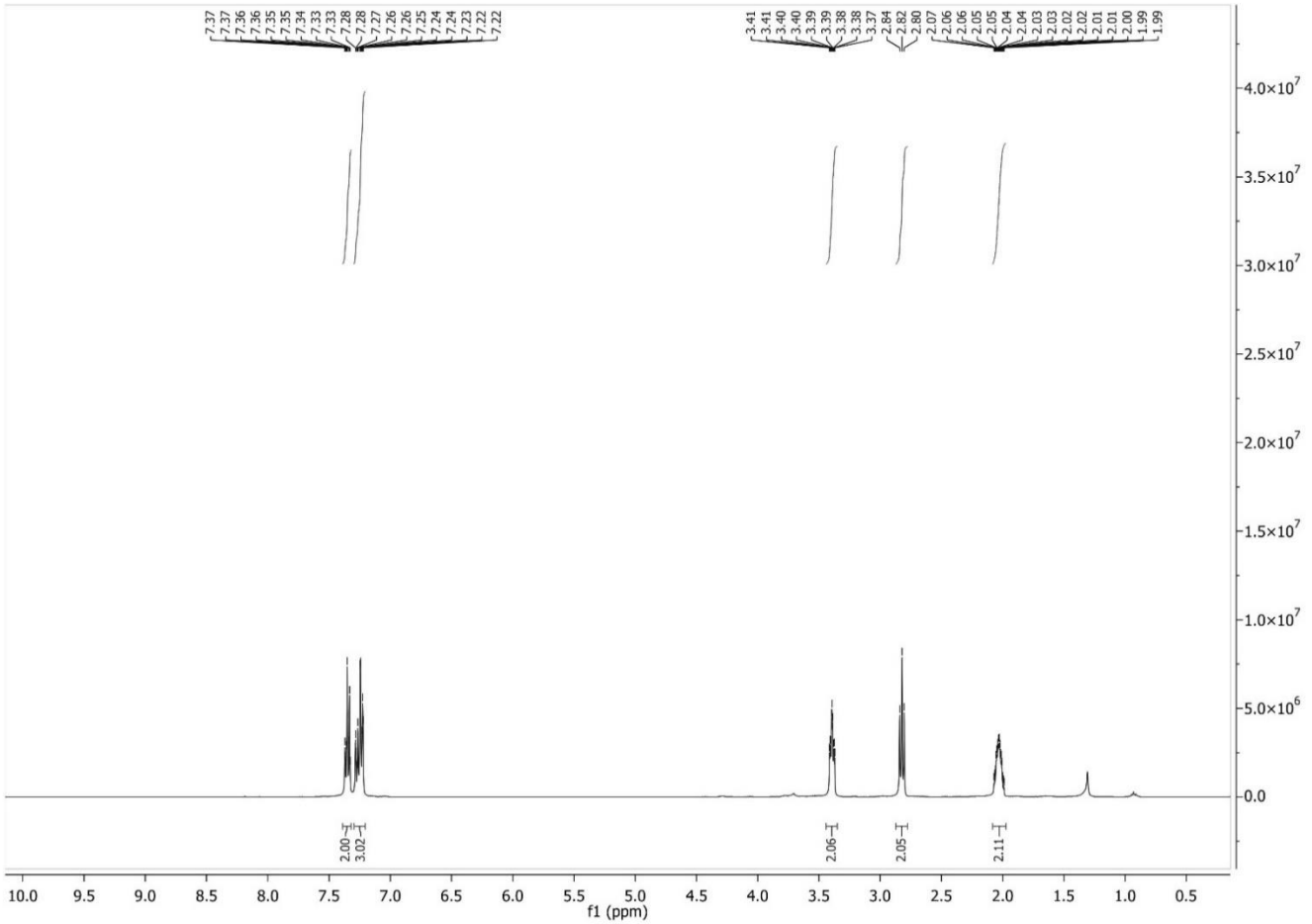
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2.06
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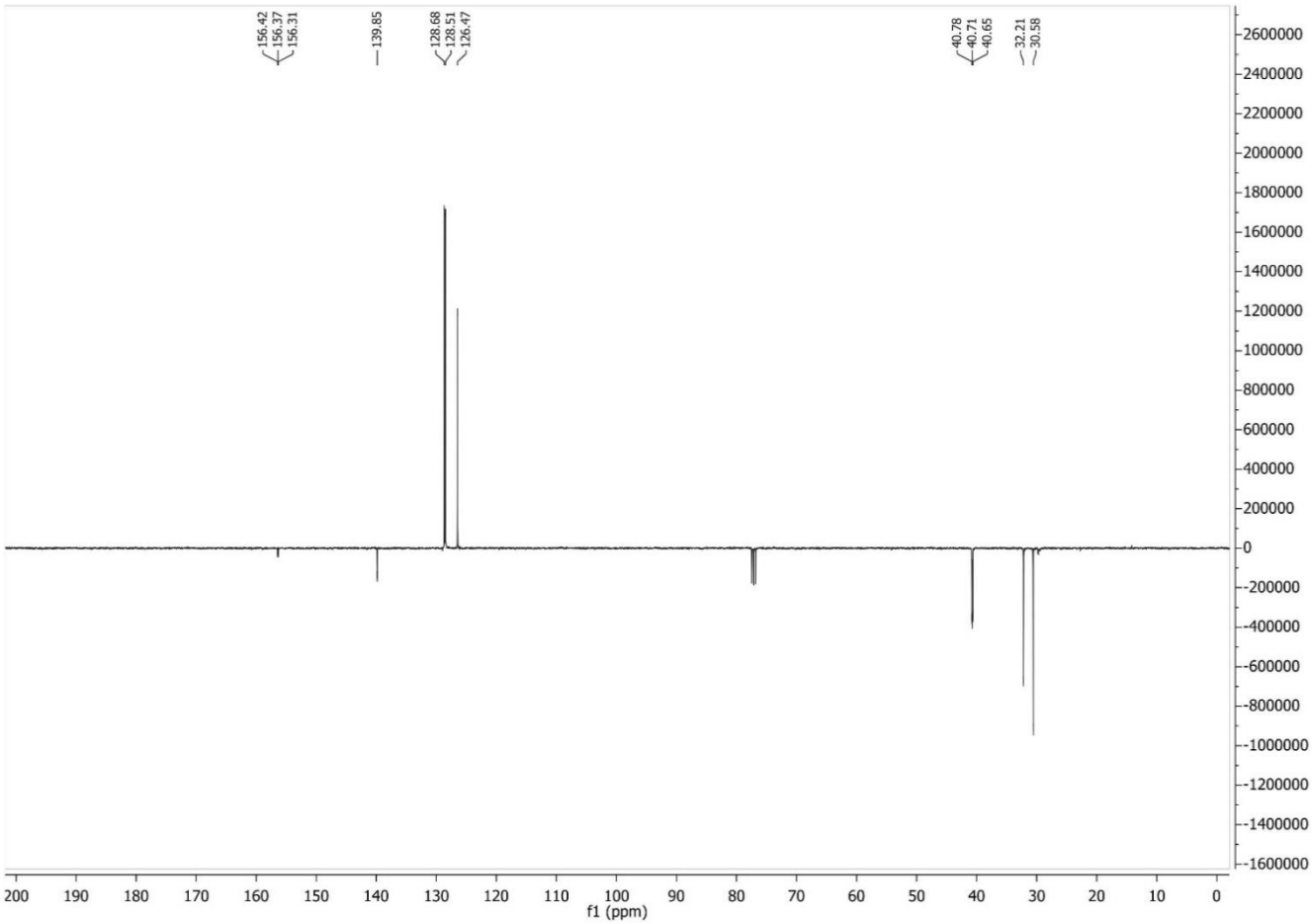
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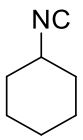
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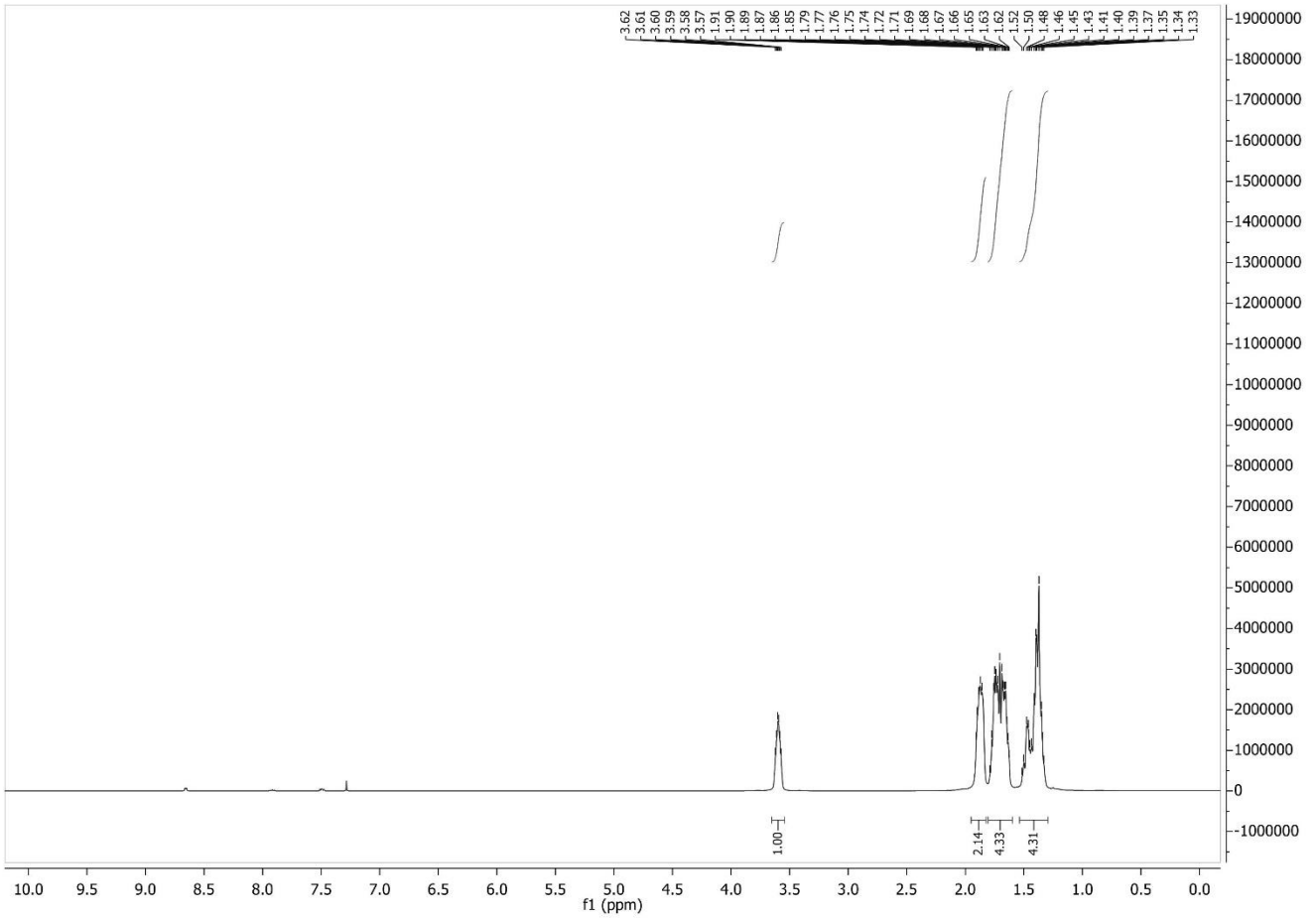
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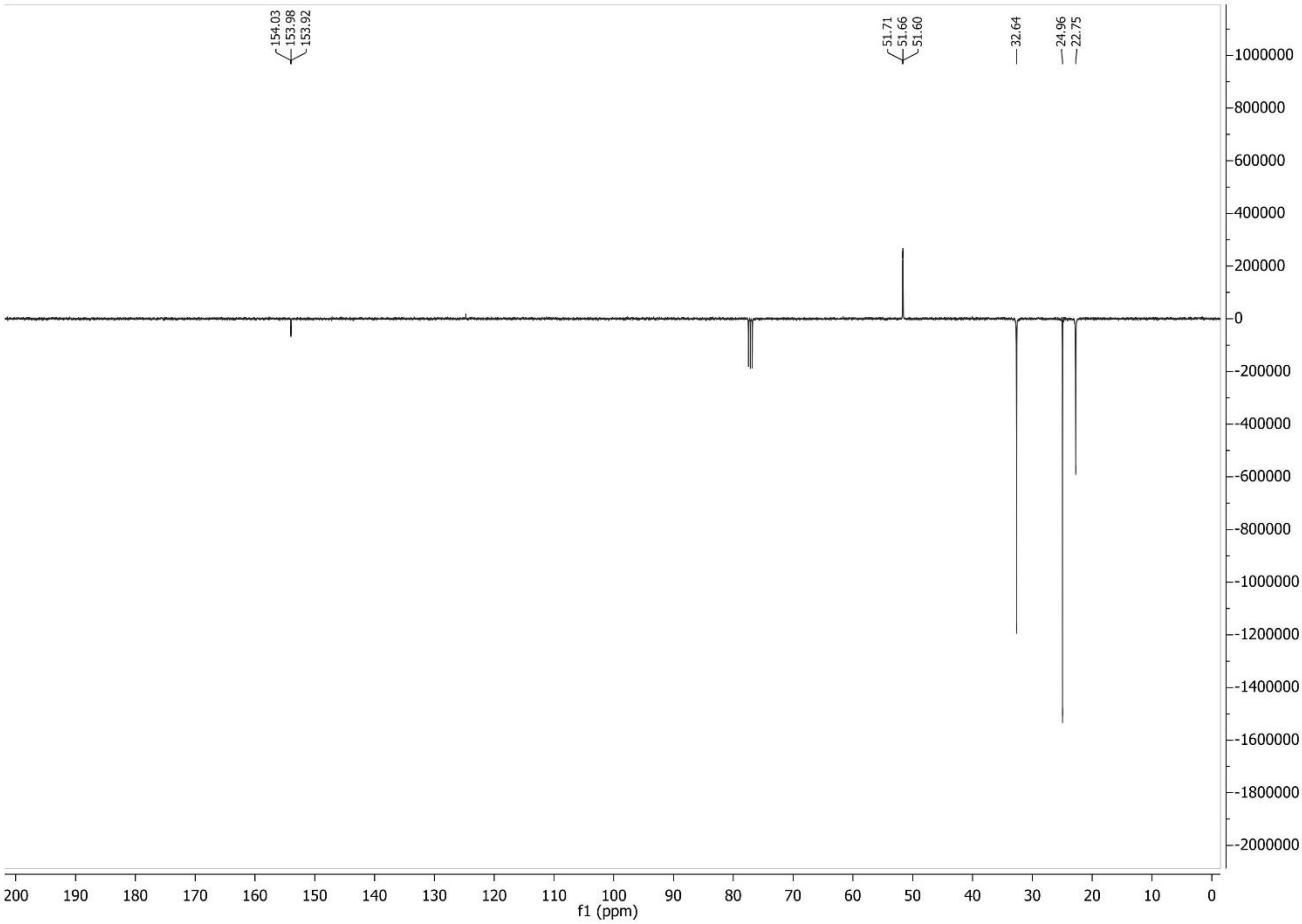
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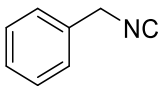
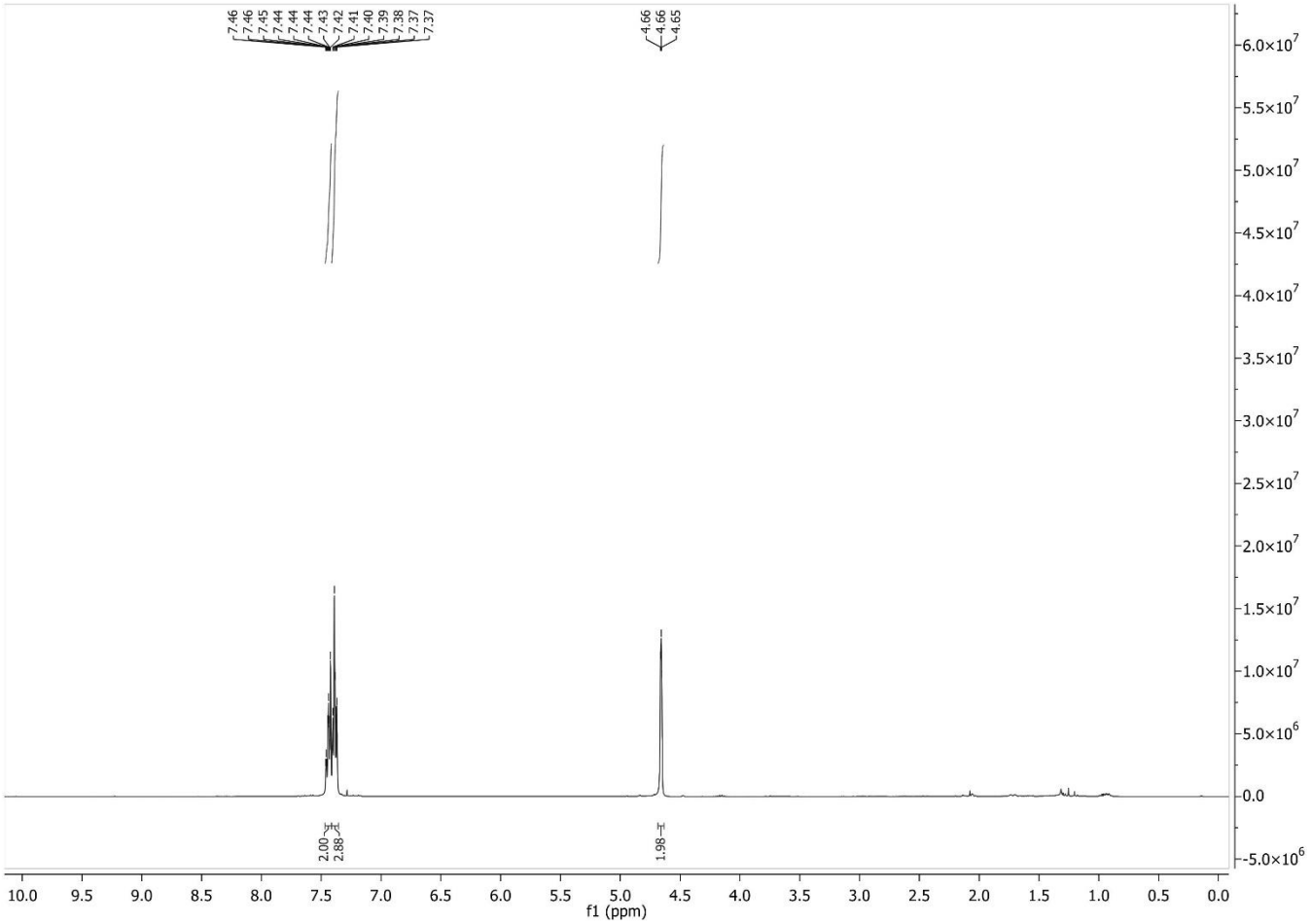
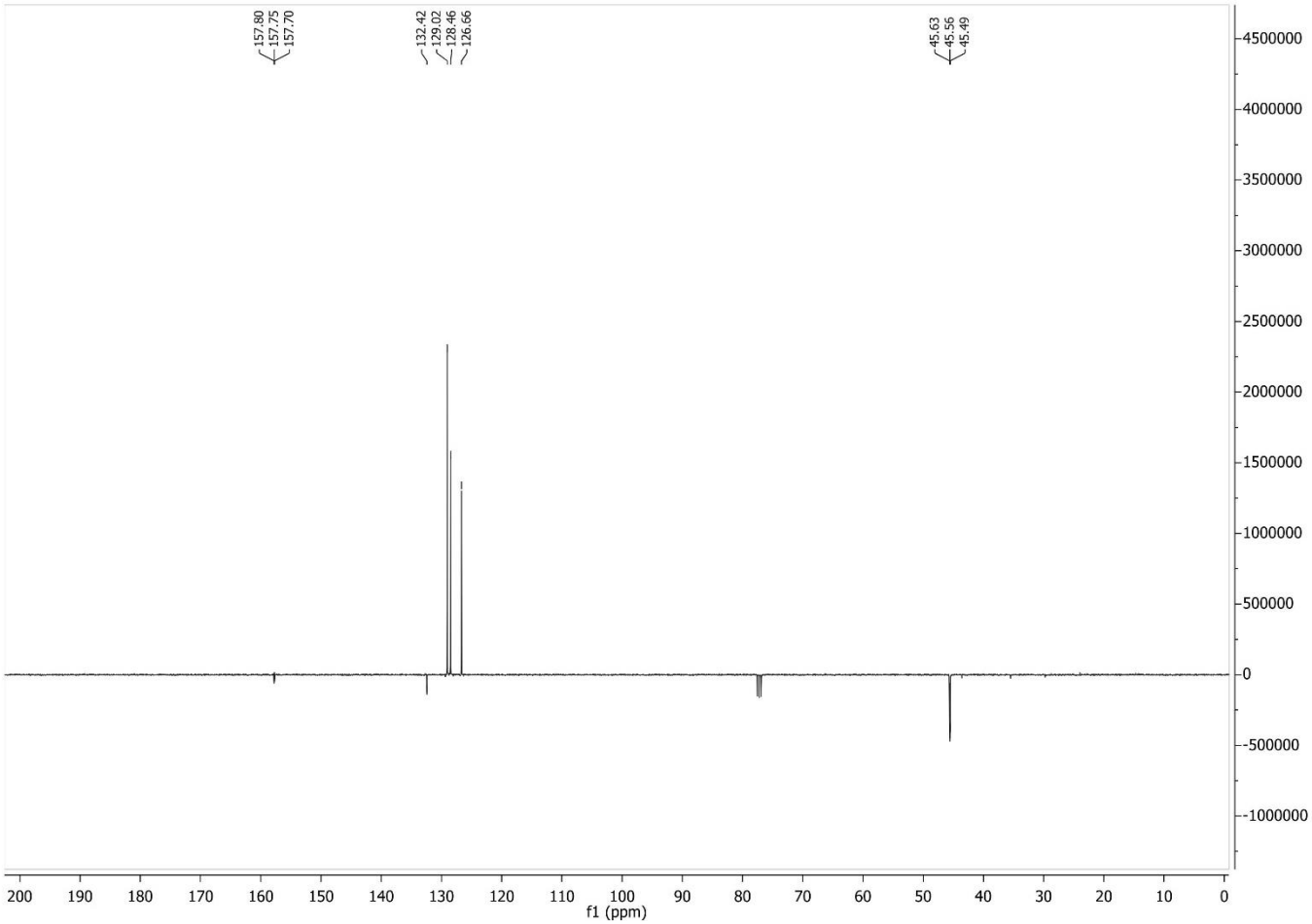
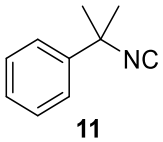
22.75
f1 (ppm)


NC

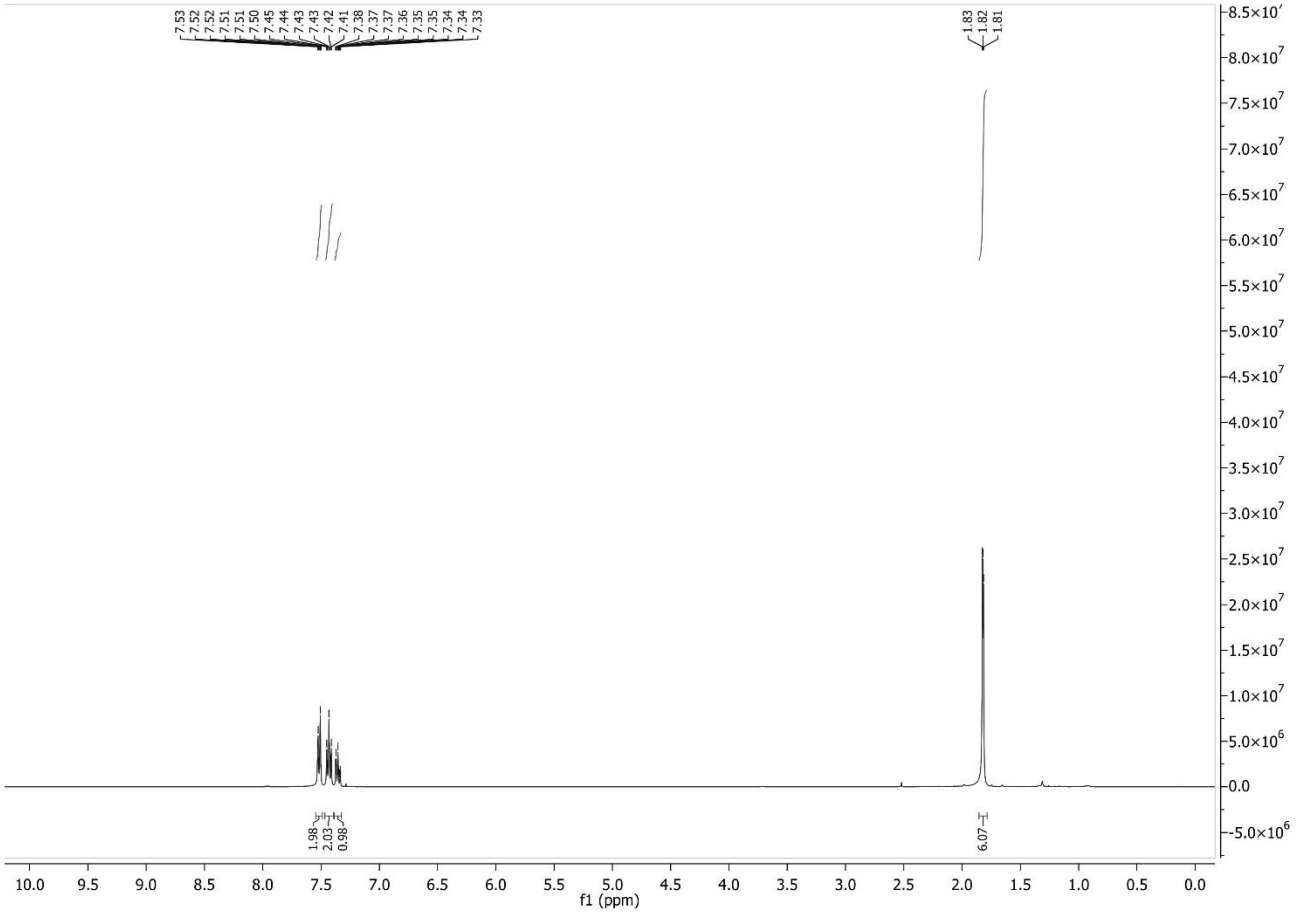
10

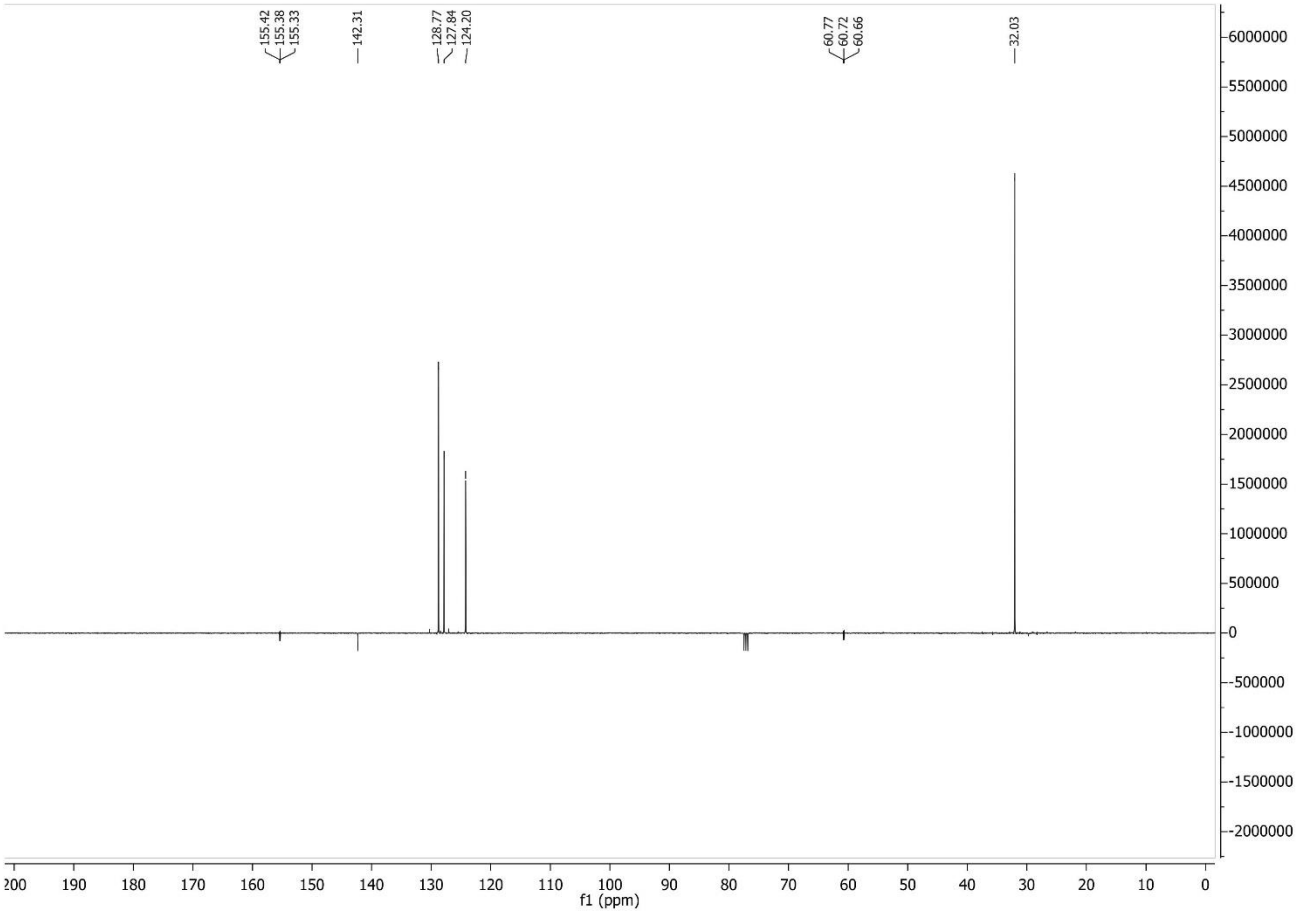

7.46
7.46
7.45
7.44
7.44
7.44
7.43
7.42
7.41
7.40
7.39
7.38
7.37
7.37
4.66
4.66
4.65
2.00
2.88
1.98
f1 (ppm)

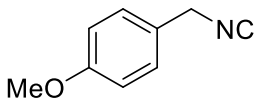

157.80
157.75
157.70
132.42
129.02
128.46
126.66
45.63
45.56
45.49
f1 (ppm)


NC

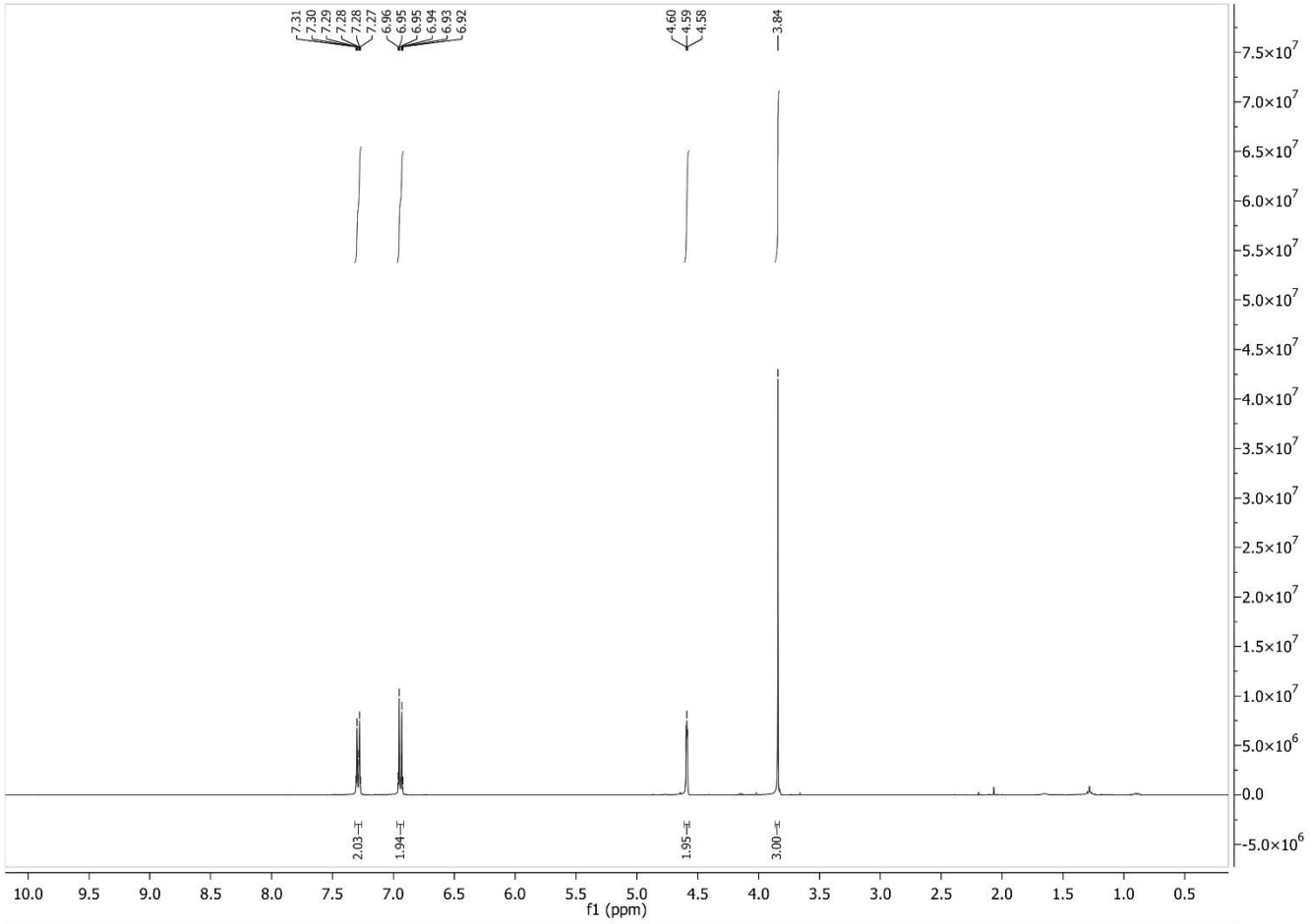
11

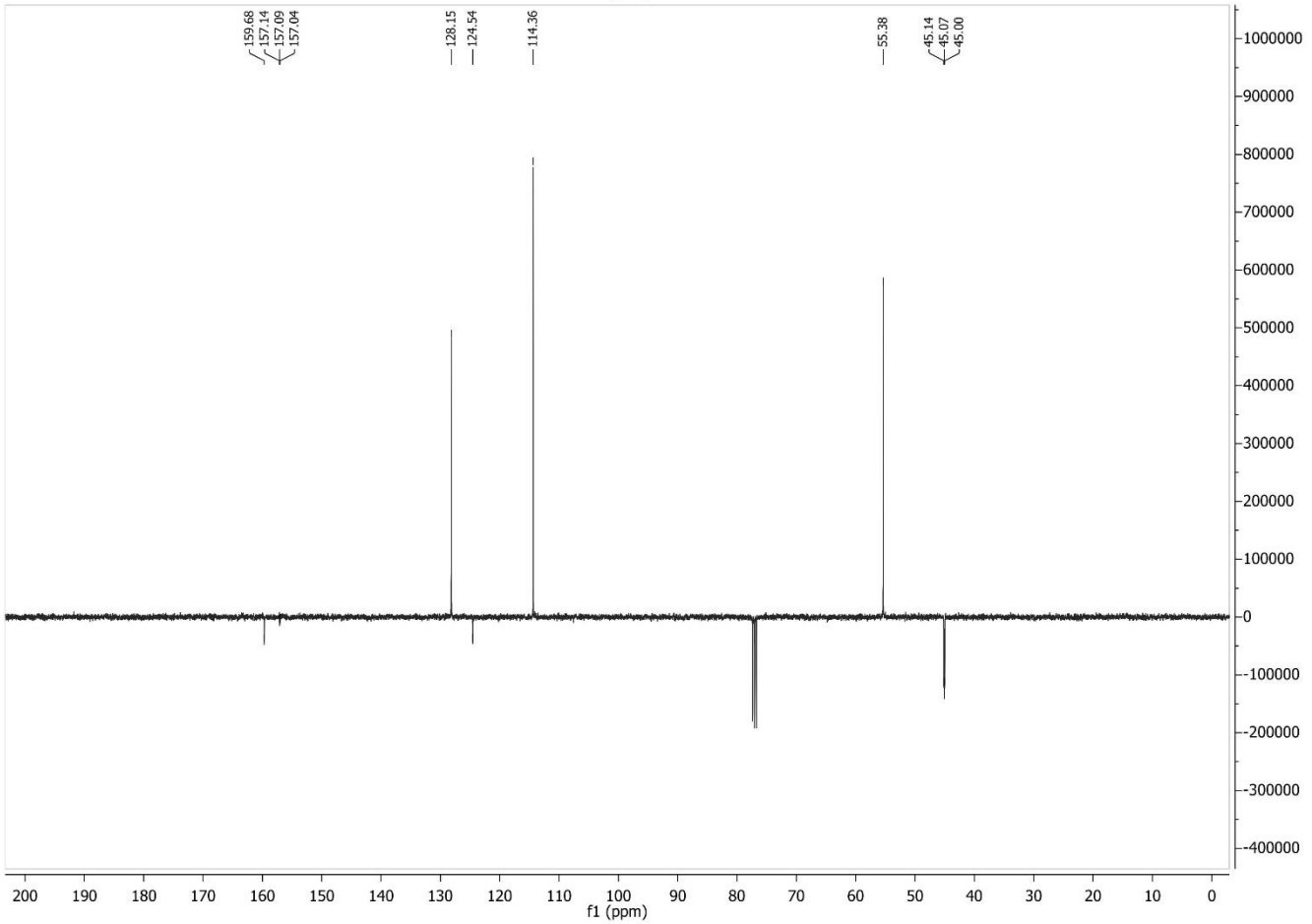

7.53
7.52
7.52
7.51
7.51
7.50
7.45
7.44
7.43
7.43
7.42
7.41
7.38
7.37
7.37
7.36
7.35
7.35
7.34
7.34
7.33
1.83
1.82
1.81
1.98
2.03
0.98
6.07
f1 (ppm)


155.42
155.38
155.33
142.31
128.77
127.84
124.20
60.77
60.72
60.66
32.03
f1 (ppm)


NC
MeO

12


7.31
7.30
7.29
7.28
7.28
7.27
6.96
6.95
6.95
6.94
6.93
6.92
4.60
4.59
4.58
3.84
2.03
1.94
1.95
3.00
f1 (ppm)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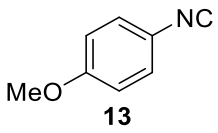
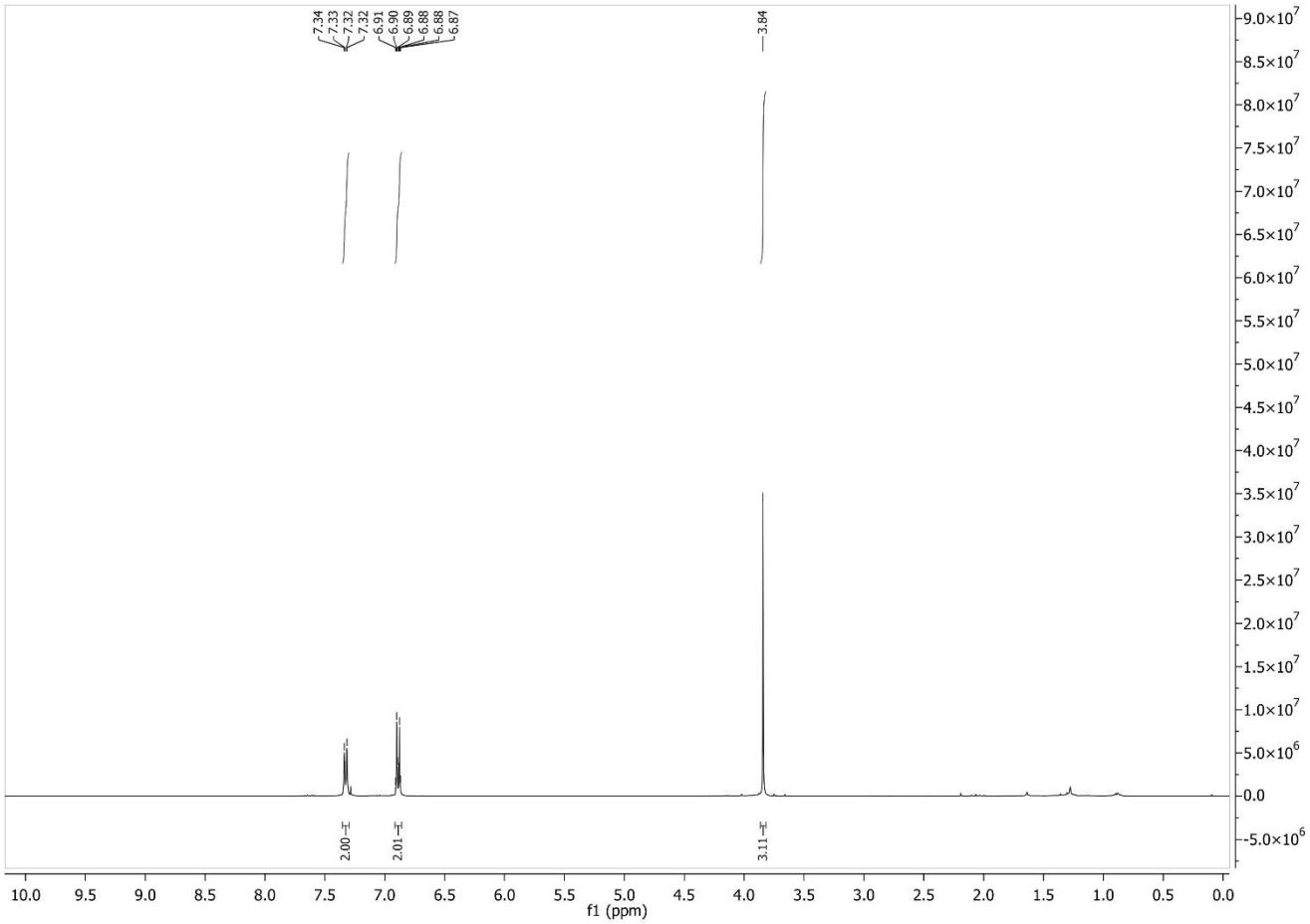
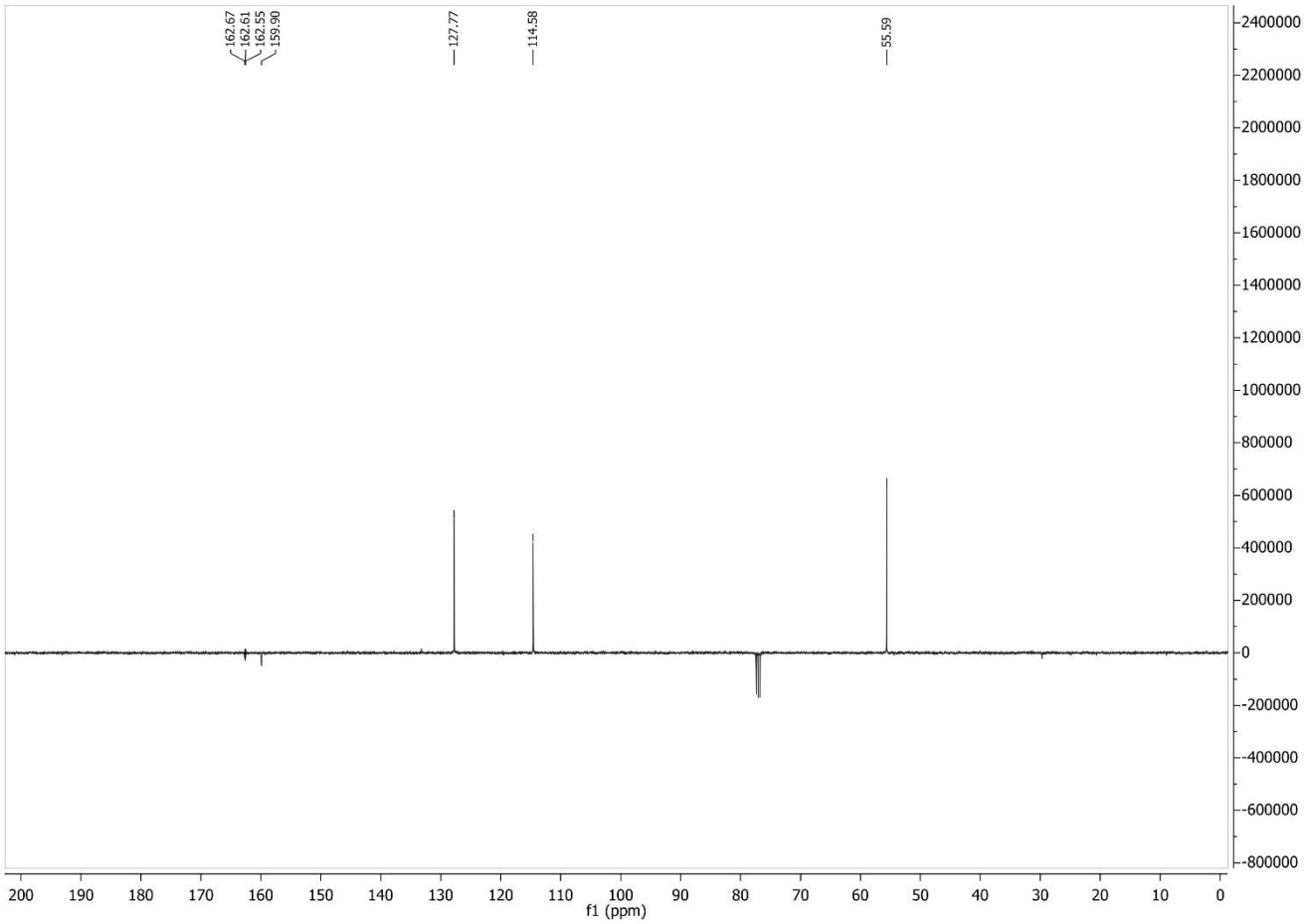
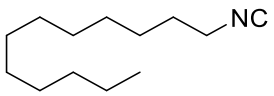
157.14
157.09
157.04
128.15
124.54
114.36
55.38
45.14
45.07
45.00
f1 (ppm)


NC
MeO

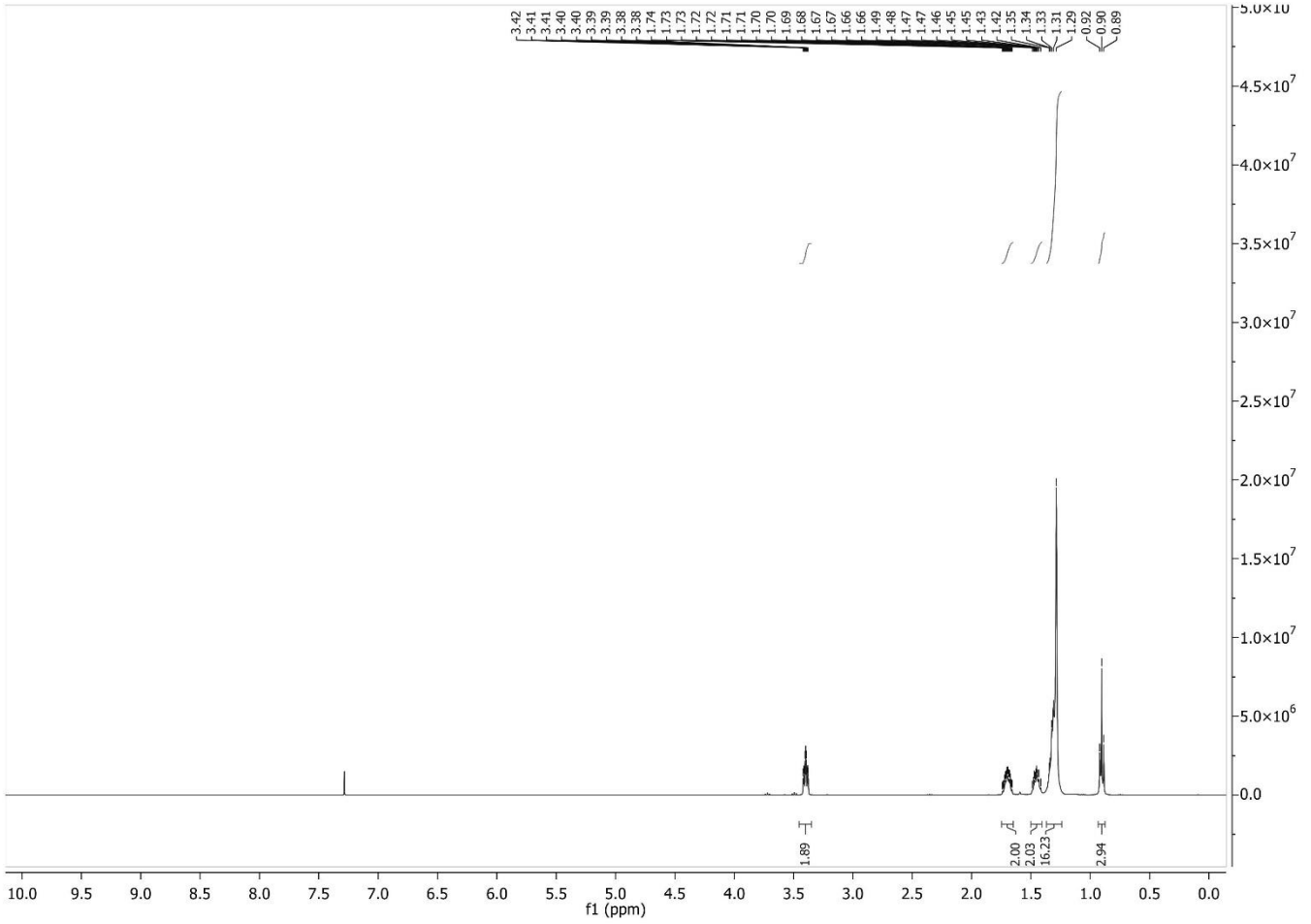
13


7.34
7.33
7.32
7.32
6.91
6.90
6.89
6.88
6.88
6.87
3.84
2.00
2.01
3.11
f1 (ppm)


162.67
162.61
162.55
159.90
127.77
114.58
55.59
f1 (ppm)


NC

14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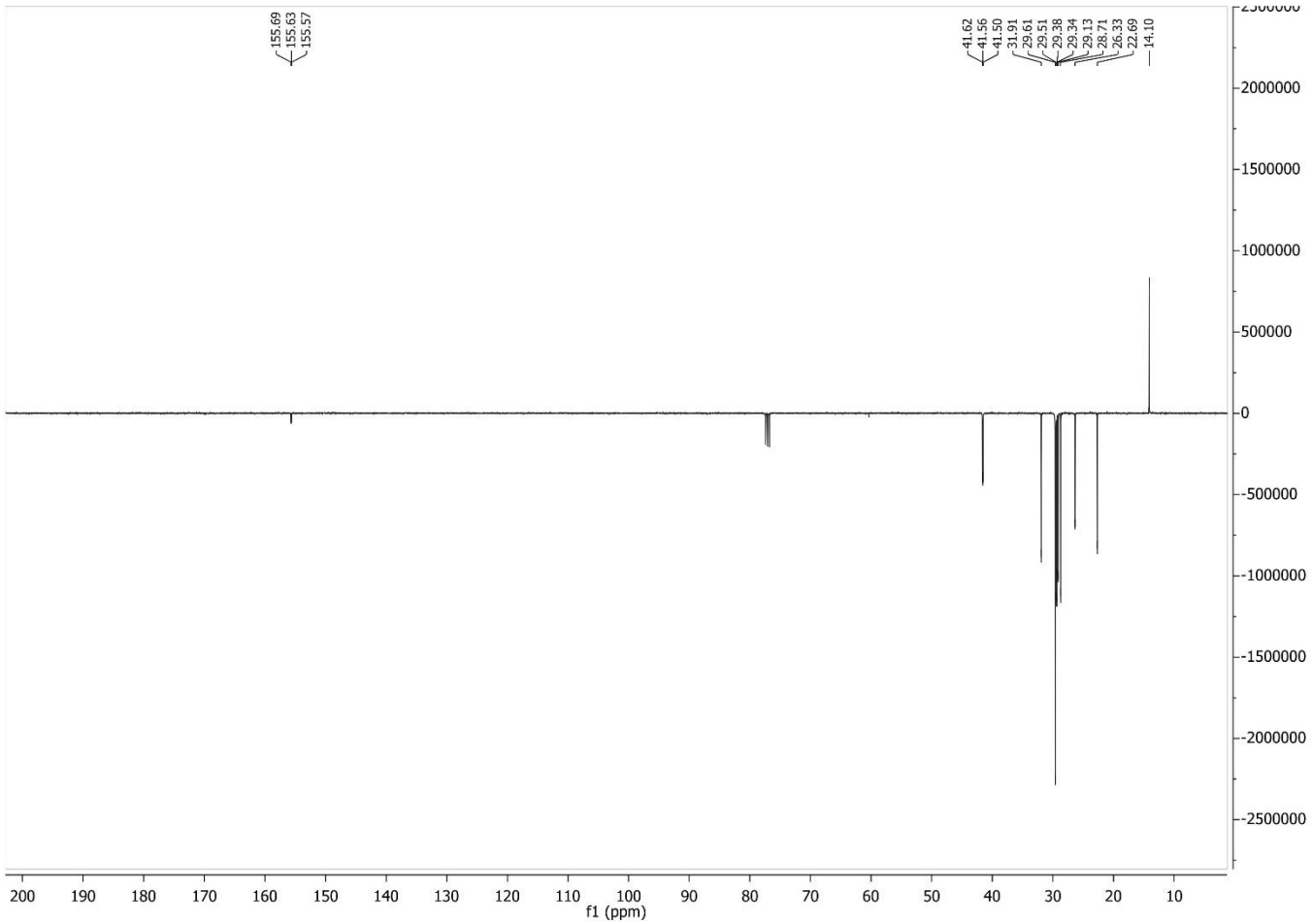
3.41
3.41
3.40
3.40
3.39
3.39
3.38
3.38
1.74
1.73
1.73
1.72
1.72
1.71
1.71
1.70
1.70
1.69
1.68
1.67
1.67
1.66
1.66
1.49
1.48
1.47
1.47
1.46
1.45
1.45
1.43
1.42
1.35
1.34
1.33
1.31
1.29
0.92
0.90
0.89
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
1.89
2.00
2.03
16.23
2.94
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)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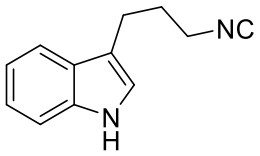
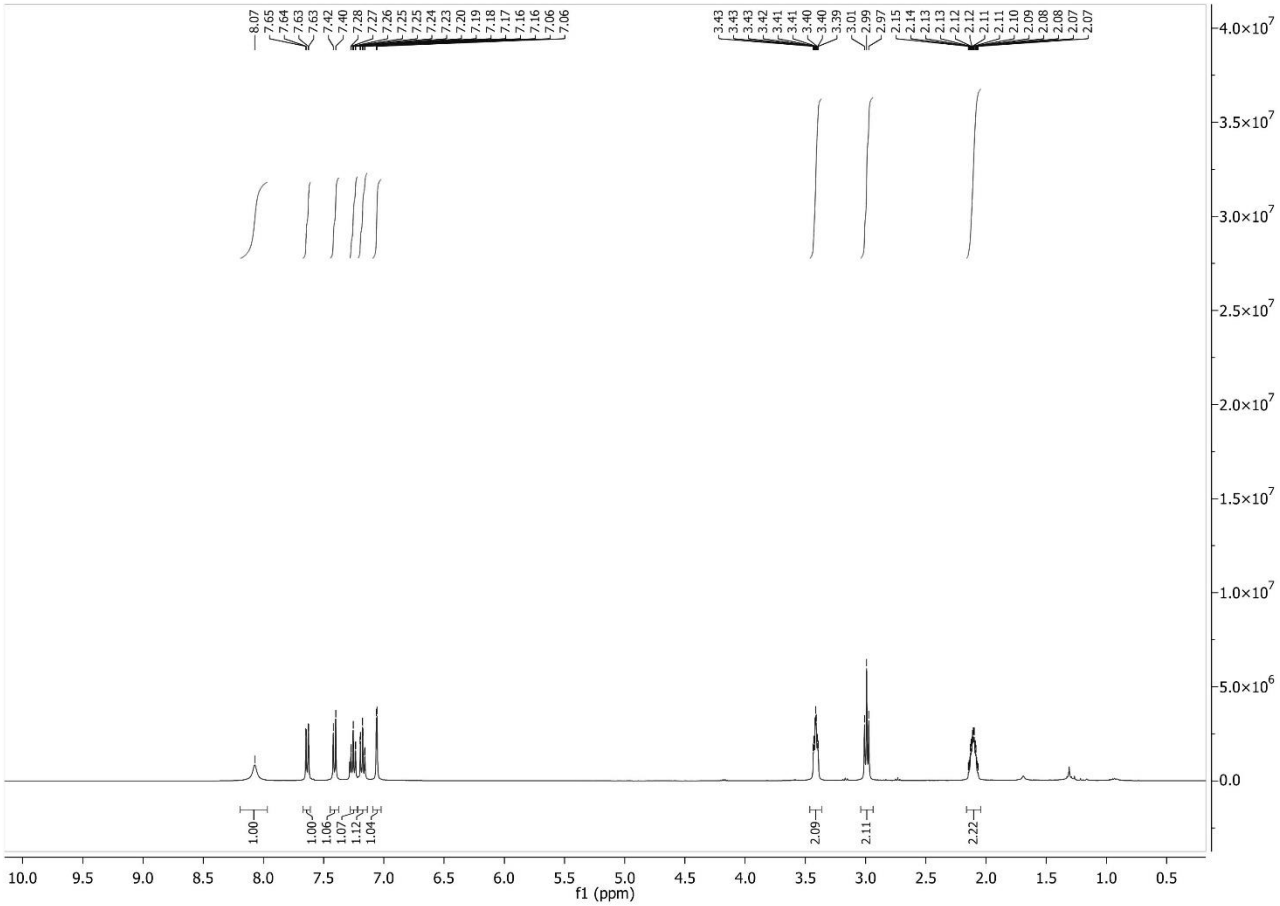
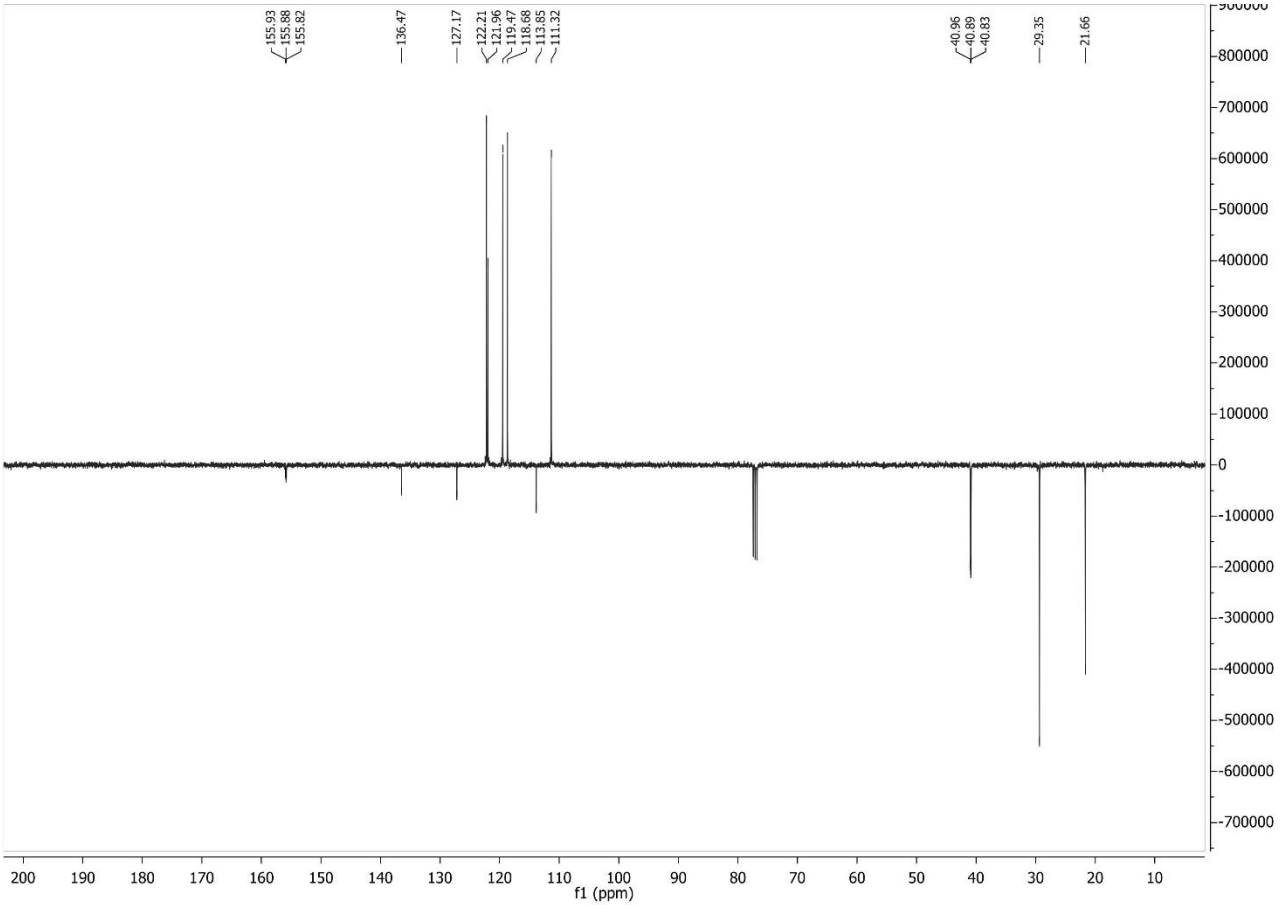
155.63
155.57
41.62
41.56
41.50
31.91
29.61
29.51
29.38
29.34
29.13
28.71
26.33
22.69
14.10
2000000
1500000
1000000
500000
0
-500000
-1000000
-1500000
-2000000
-2500000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


NC
N
H

15


8.07
7.65
7.64
7.63
7.63
7.42
7.40
7.28
7.27
7.26
7.25
7.25
7.24
7.23
7.20
7.19
7.18
7.17
7.16
7.16
7.06
7.06
3.43
3.43
3.43
3.42
3.41
3.41
3.40
3.40
3.39
3.01
2.99
2.97
2.15
2.14
2.13
2.13
2.12
2.12
2.11
2.11
2.10
2.09
2.08
2.08
2.07
2.07
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
1.00
1.00
1.06
1.07
1.12
1.04
2.09
2.11
2.22
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)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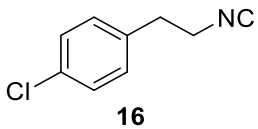
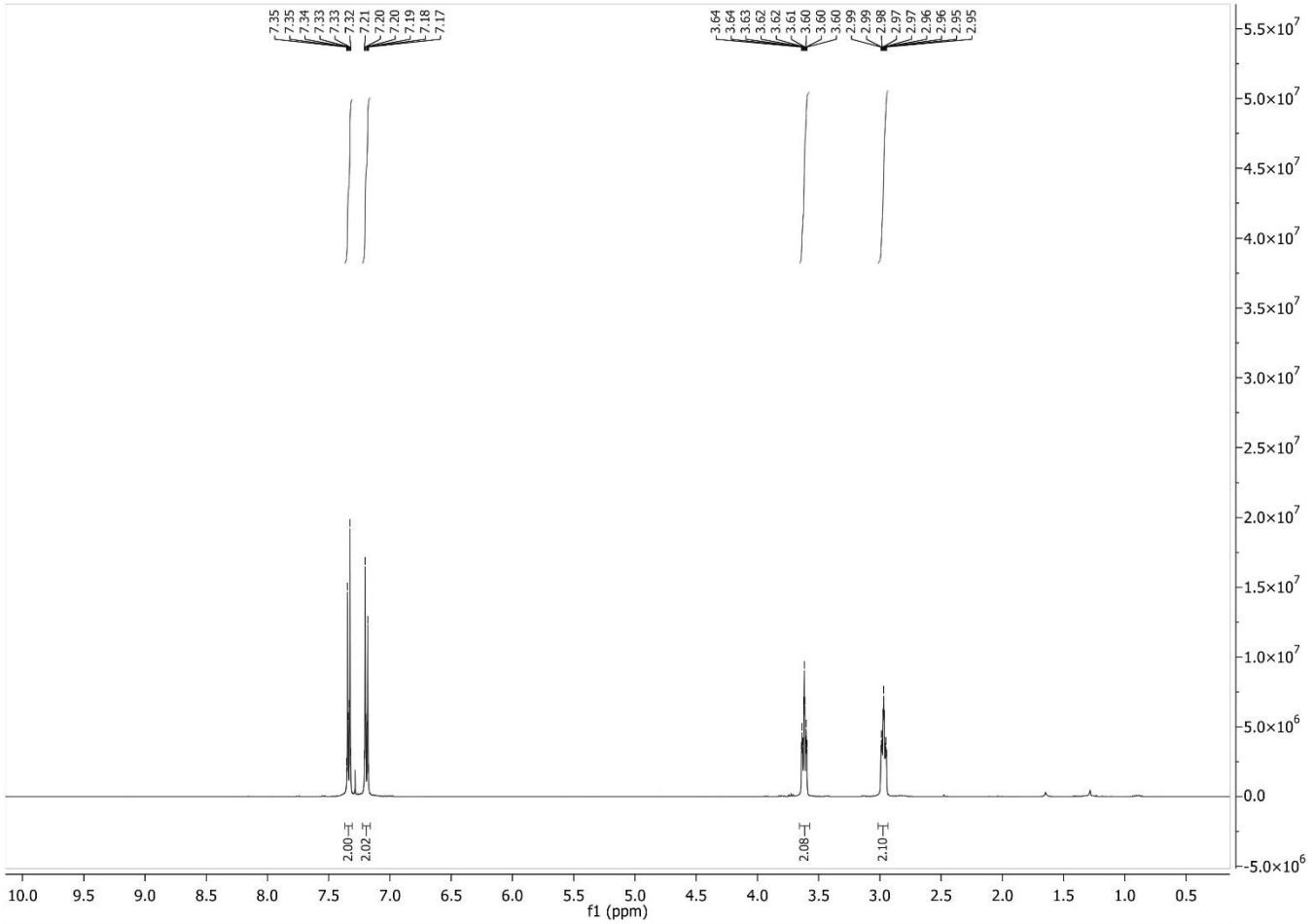
155.88
155.82
136.47
127.17
122.21
121.96
119.47
118.68
113.85
111.32
40.96
40.89
40.83
29.35
21.66
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
-200000
-300000
-400000
-500000
-600000
-700000
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


NC
Cl

16


7.35
7.35
7.34
7.33
7.33
7.32
7.21
7.20
7.20
7.19
7.18
7.17
3.64
3.64
3.63
3.62
3.62
3.61
3.60
3.60
2.99
2.99
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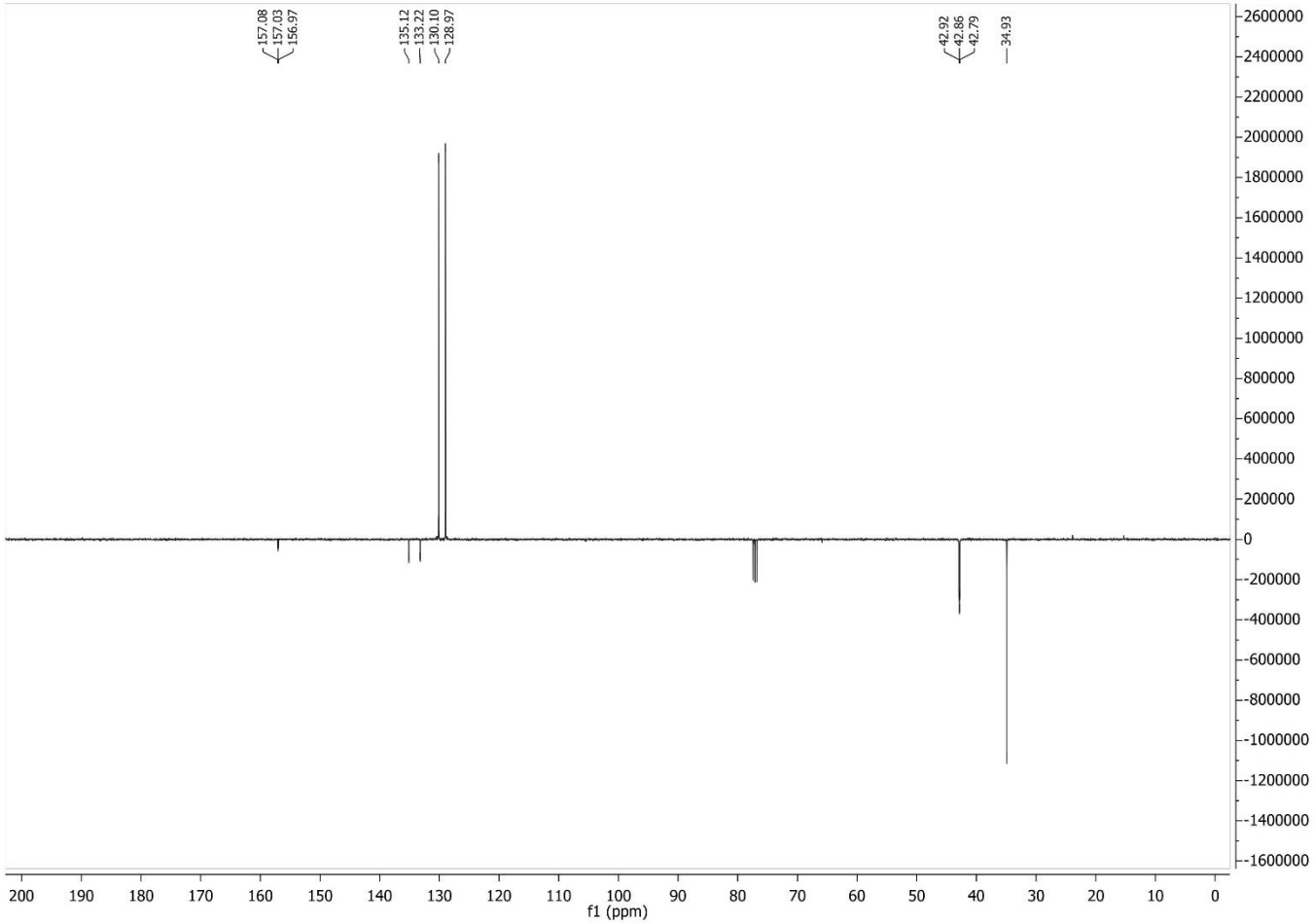
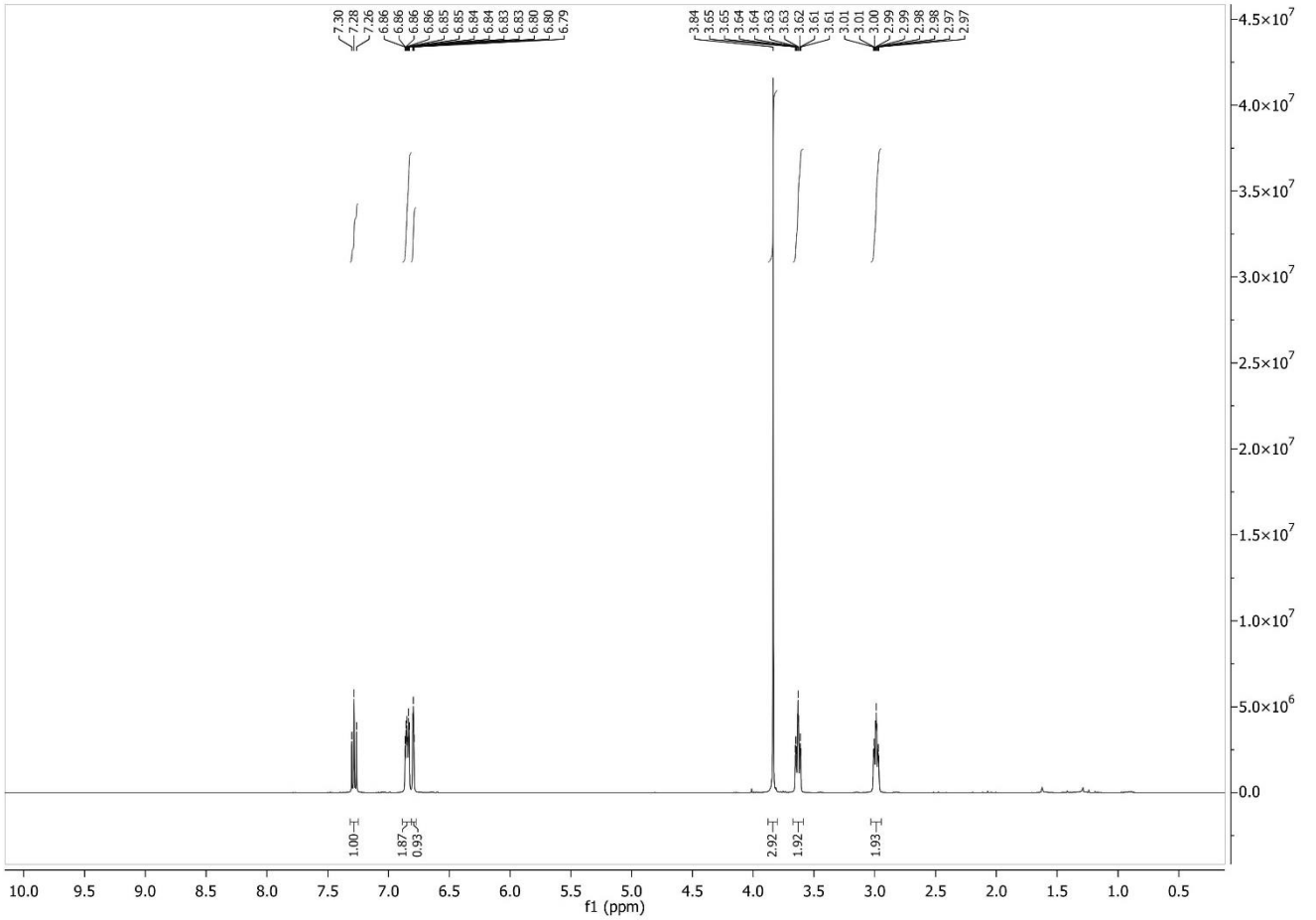
2.00
2.02
2.08
2.10
f1 (ppm)


157.08
157.03
156.97
135.12
133.22
130.10
128.97
42.92
42.86
42.79
34.93
f1 (ppm)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7.28
7.26
6.86
6.86
6.86
6.86
6.85
6.85
6.84
6.84
6.83
6.83
6.80
6.80
6.79
3.84
3.65
3.65
3.64
3.64
3.63
3.63
3.62
3.61
3.61
3.01
3.01
3.00
2.99
2.99
2.98
2.98
2.97
2.97
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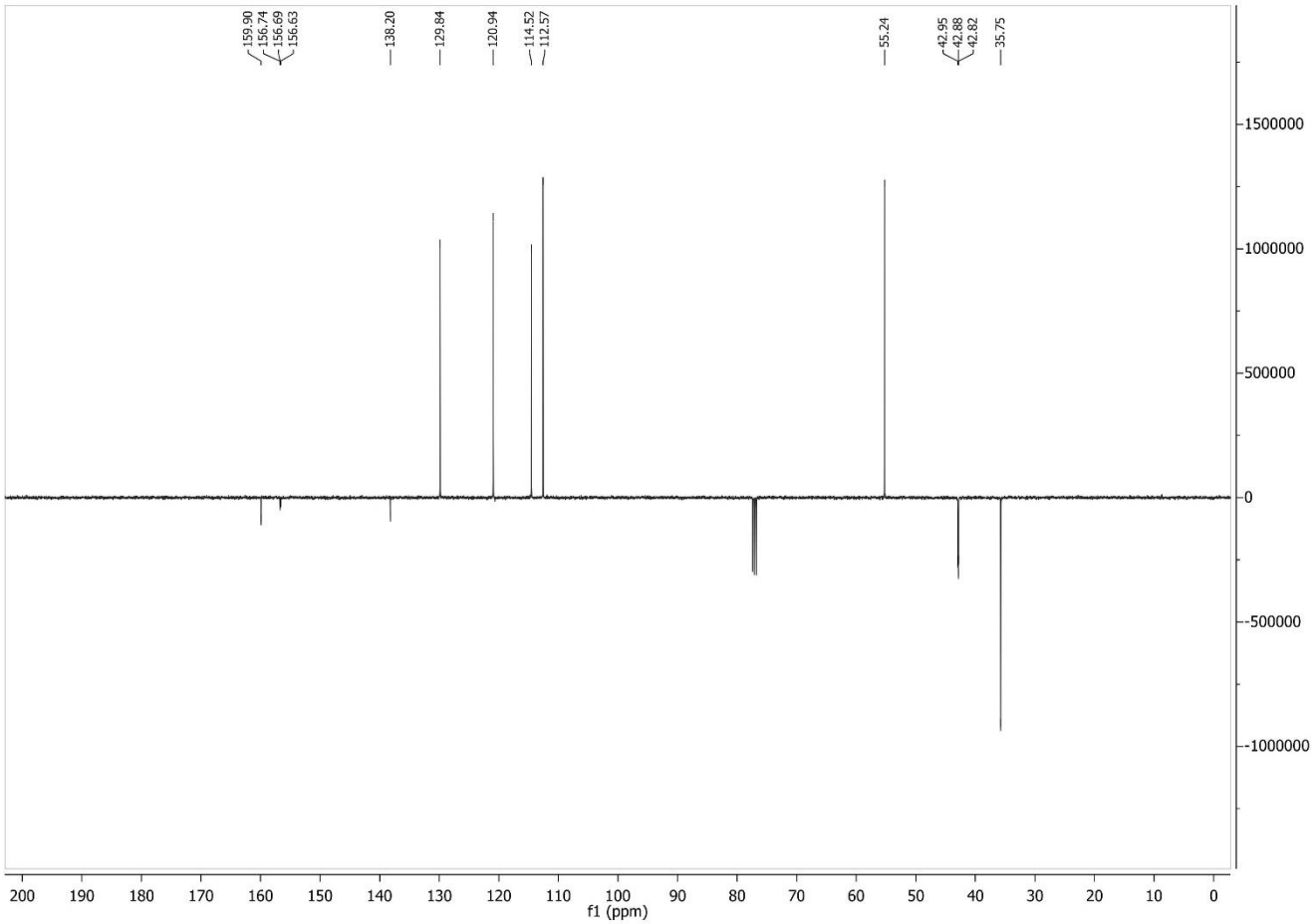
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
1.00
1.87
0.93
2.92
1.92
1.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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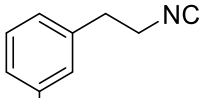
156.74
156.69
156.63
138.20
129.84
120.94
114.52
112.57
55.24
42.95
42.88
42.82
35.75
1500000
1000000
500000
0
-500000
-1000000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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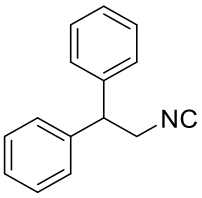
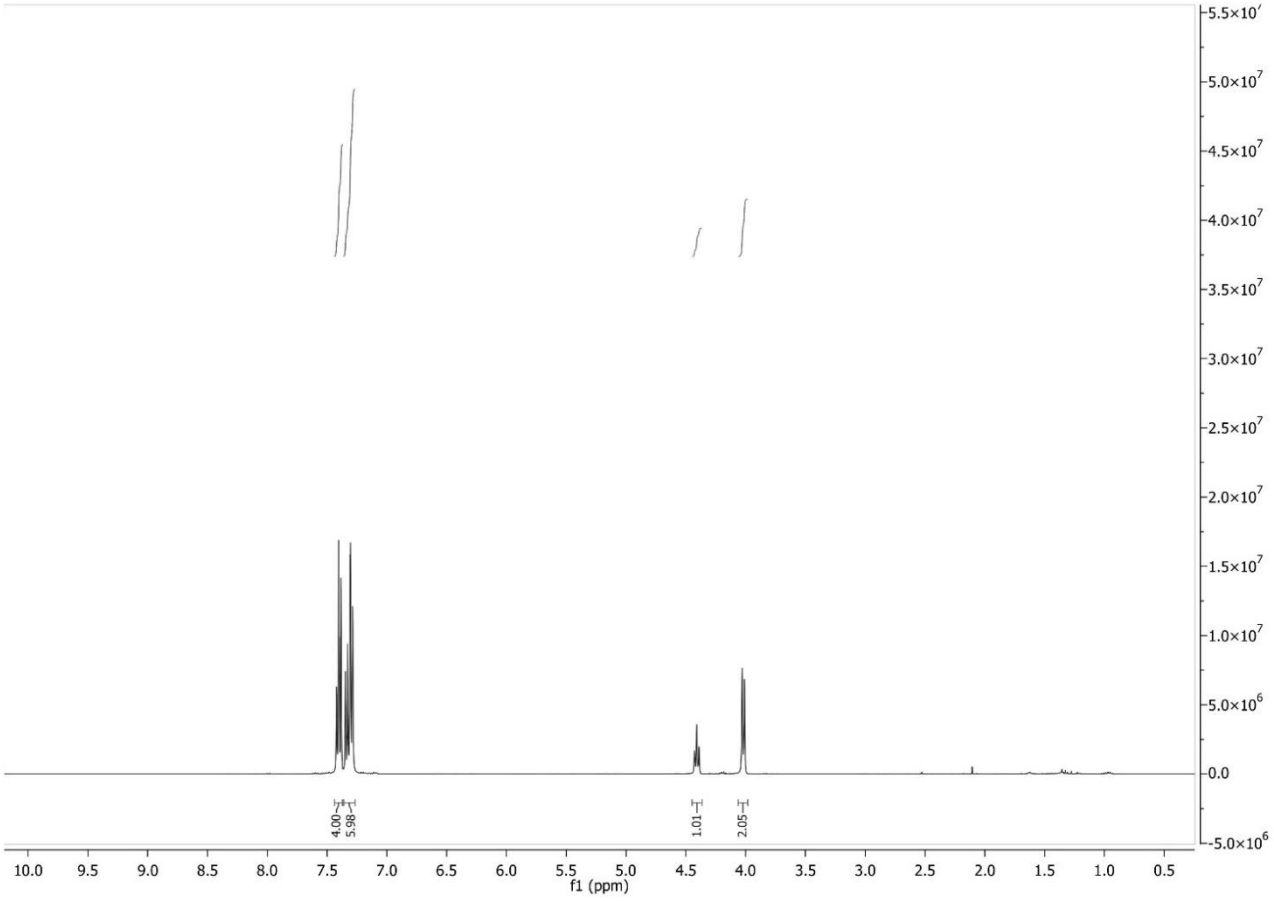
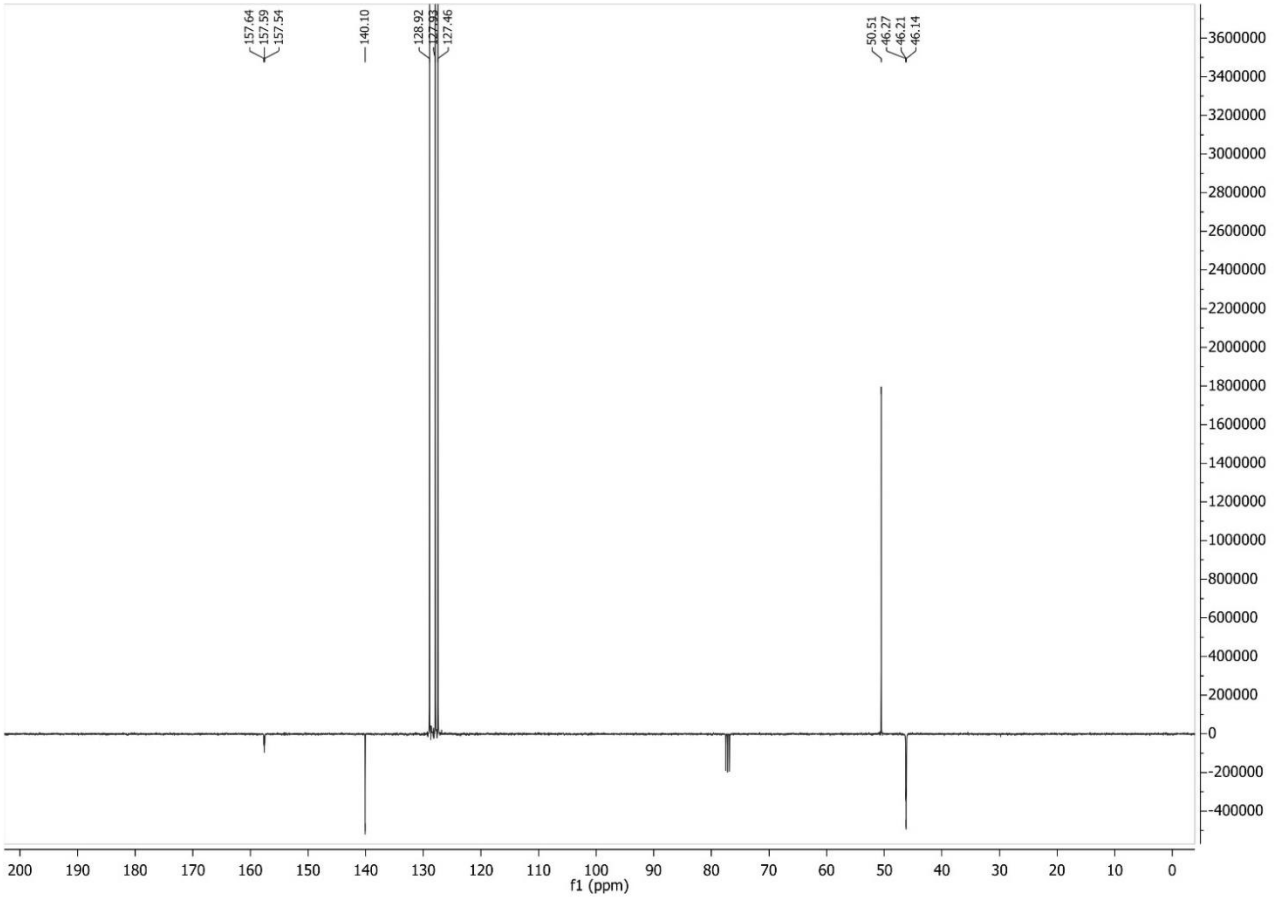

NC

18


4.00
5.98
1.01
2.05
f1 (ppm)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157.59
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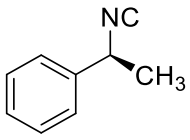
140.10
128.92
127.92
127.46
50.51
46.27
46.21
46.14
f1 (ppm)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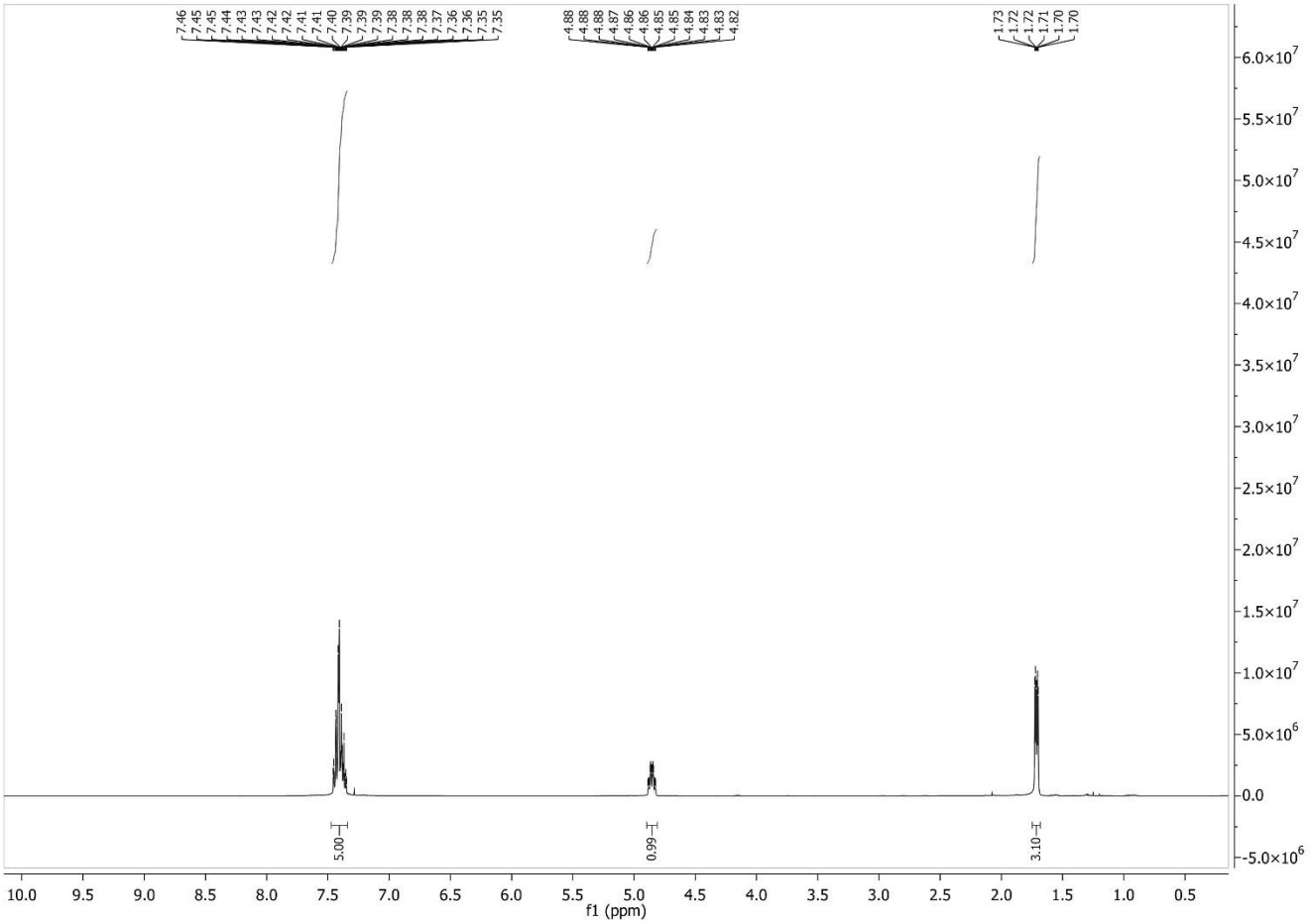
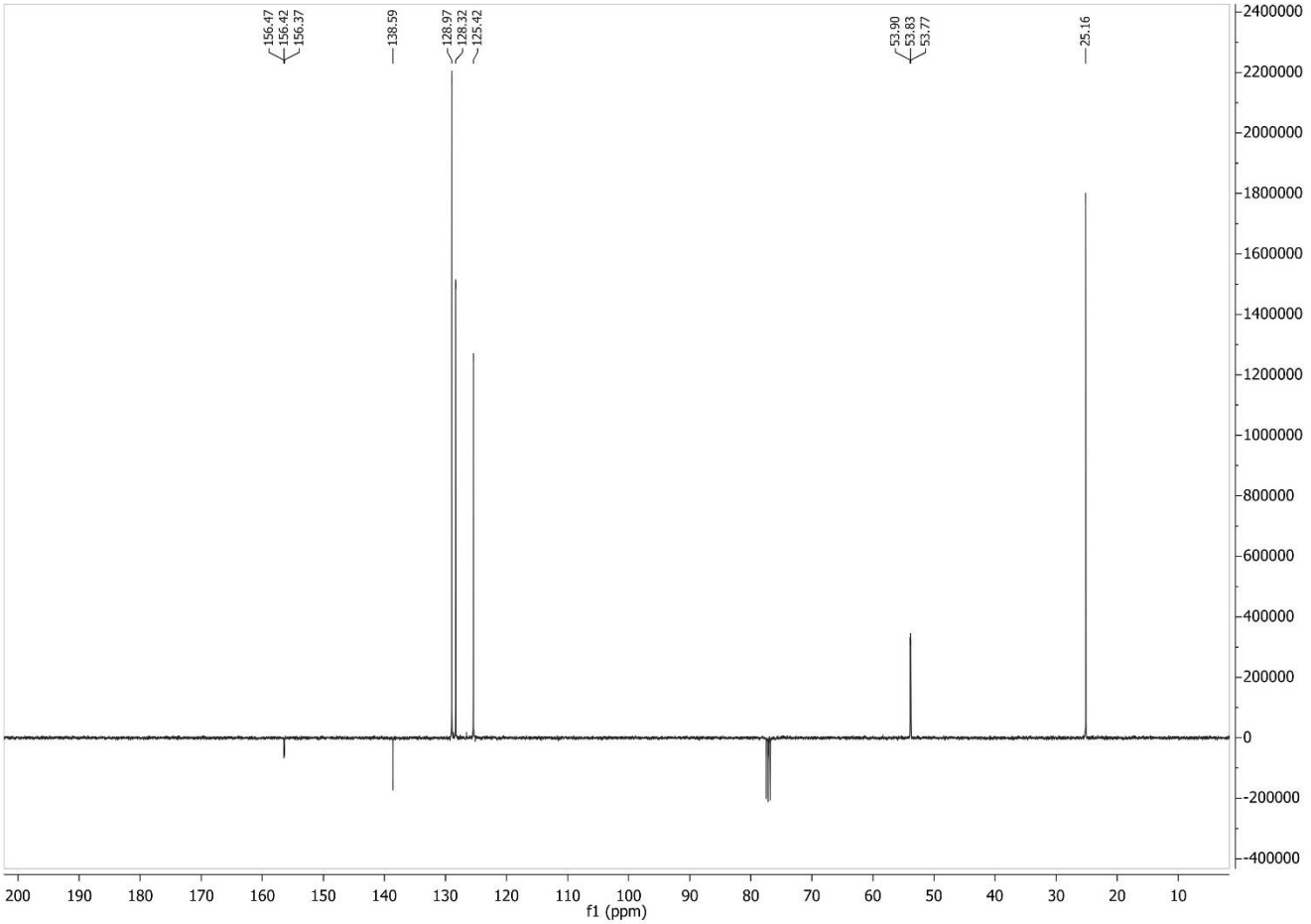
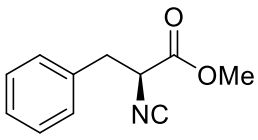
CH3

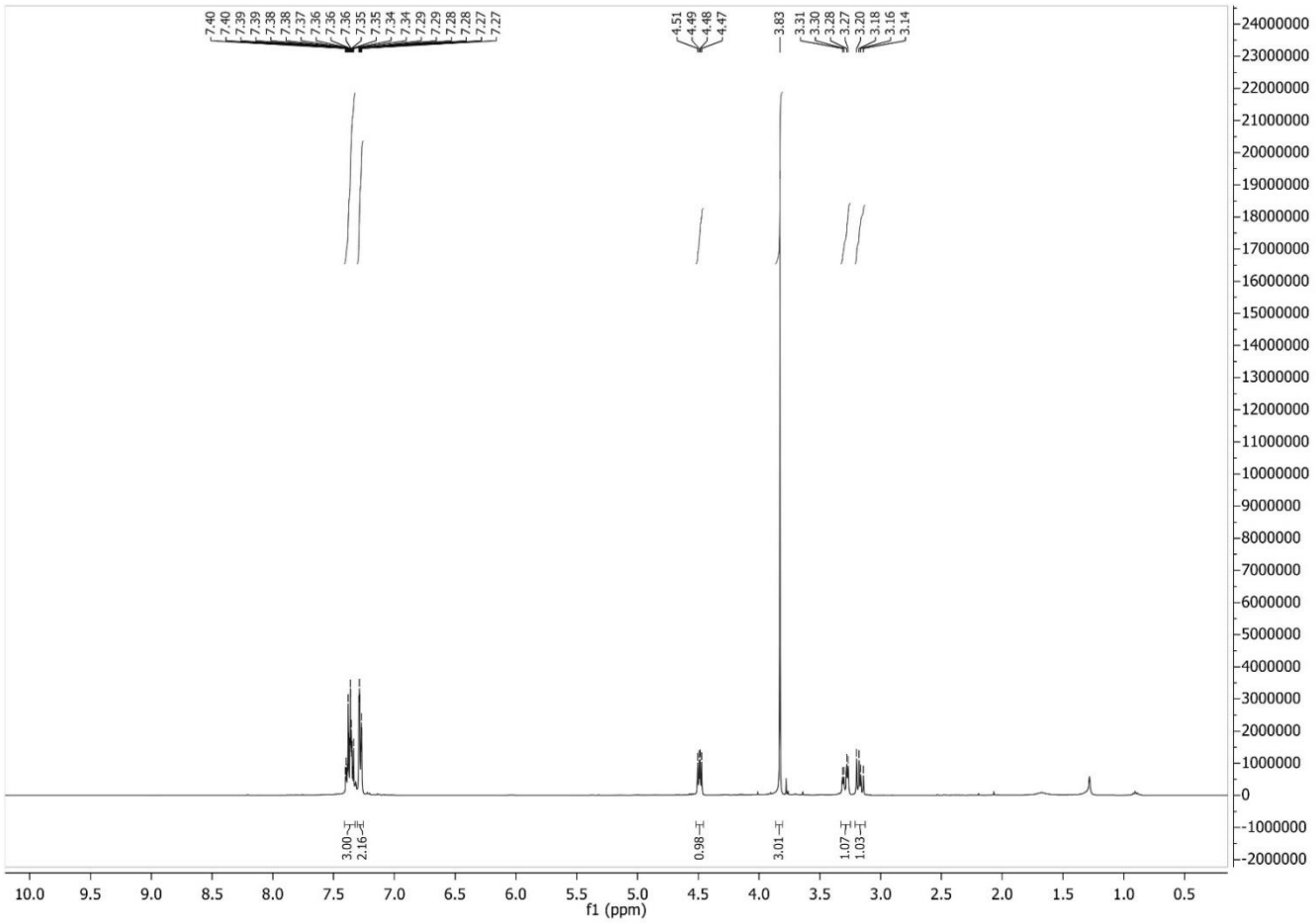
19

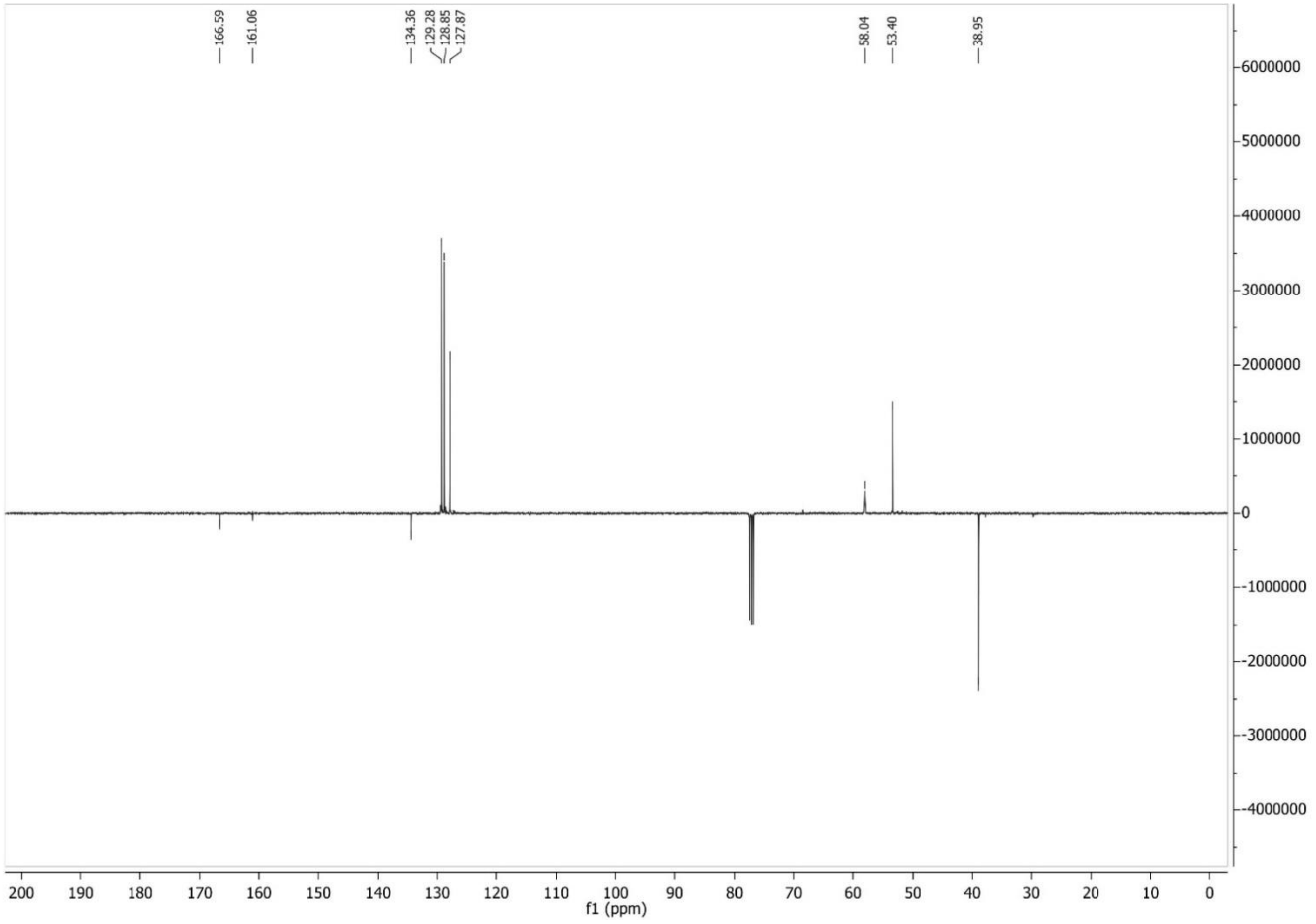

7.46 7.45 7.45 7.44 7.43 7.43 7.42 7.42 7.41 7.41 7.40 7.39 7.39 7.39 7.38 7.38 7.38 7.37 7.36 7.36 7.35 7.35
4.88 4.88 4.88 4.87 4.86 4.86 4.85 4.85 4.84 4.83 4.83 4.82
1.73 1.72 1.72 1.71 1.70 1.70
6.0×10^7
5.5×10^7
5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
-5.0×10^6
5.00
0.99
3.10
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)


156.47 156.42 156.37
138.59
128.97 128.32 125.42
53.90 53.83 53.77
25.16
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
-400000
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


O
OMe
NC

20


7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.36
7.36
7.36
7.35
7.35
7.34
7.34
7.29
7.29
7.28
7.28
7.27
7.27
4.51
4.49
4.48
4.47
3.83
3.31
3.30
3.28
3.27
3.20
3.18
3.16
3.14
3.00
2.16
0.98
3.01
1.07
1.03
f1 (ppm)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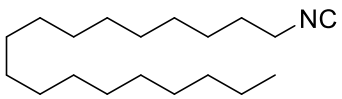
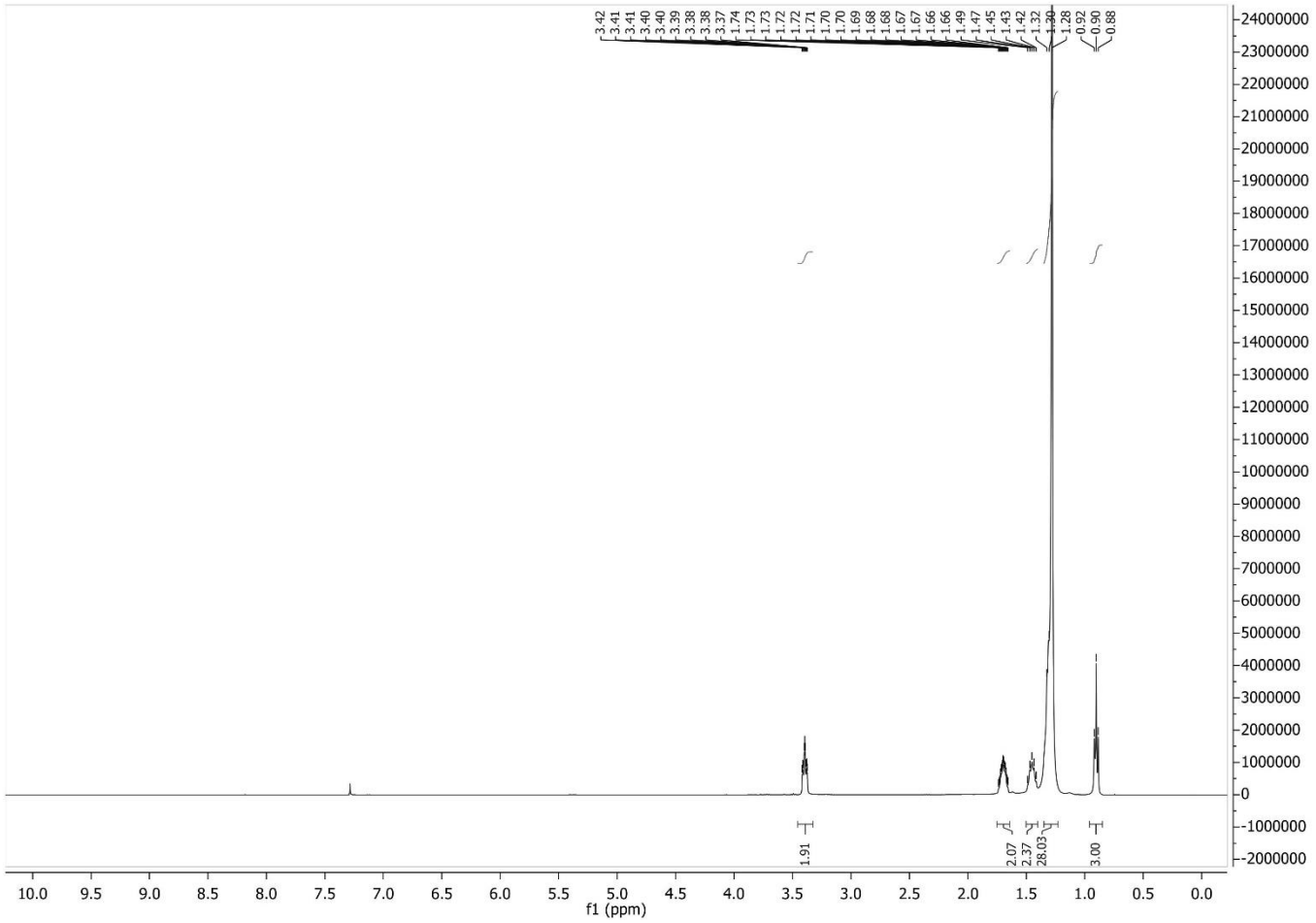
128.85
127.87
58.04
53.40
38.95
f1 (ppm)


NC

21


3.42
3.41
3.41
3.40
3.40
3.39
3.38
3.38
3.37
1.74
1.73
1.73
1.72
1.72
1.71
1.70
1.70
1.69
1.68
1.68
1.67
1.67
1.66
1.66
1.49
1.47
1.45
1.43
1.42
1.32
1.30
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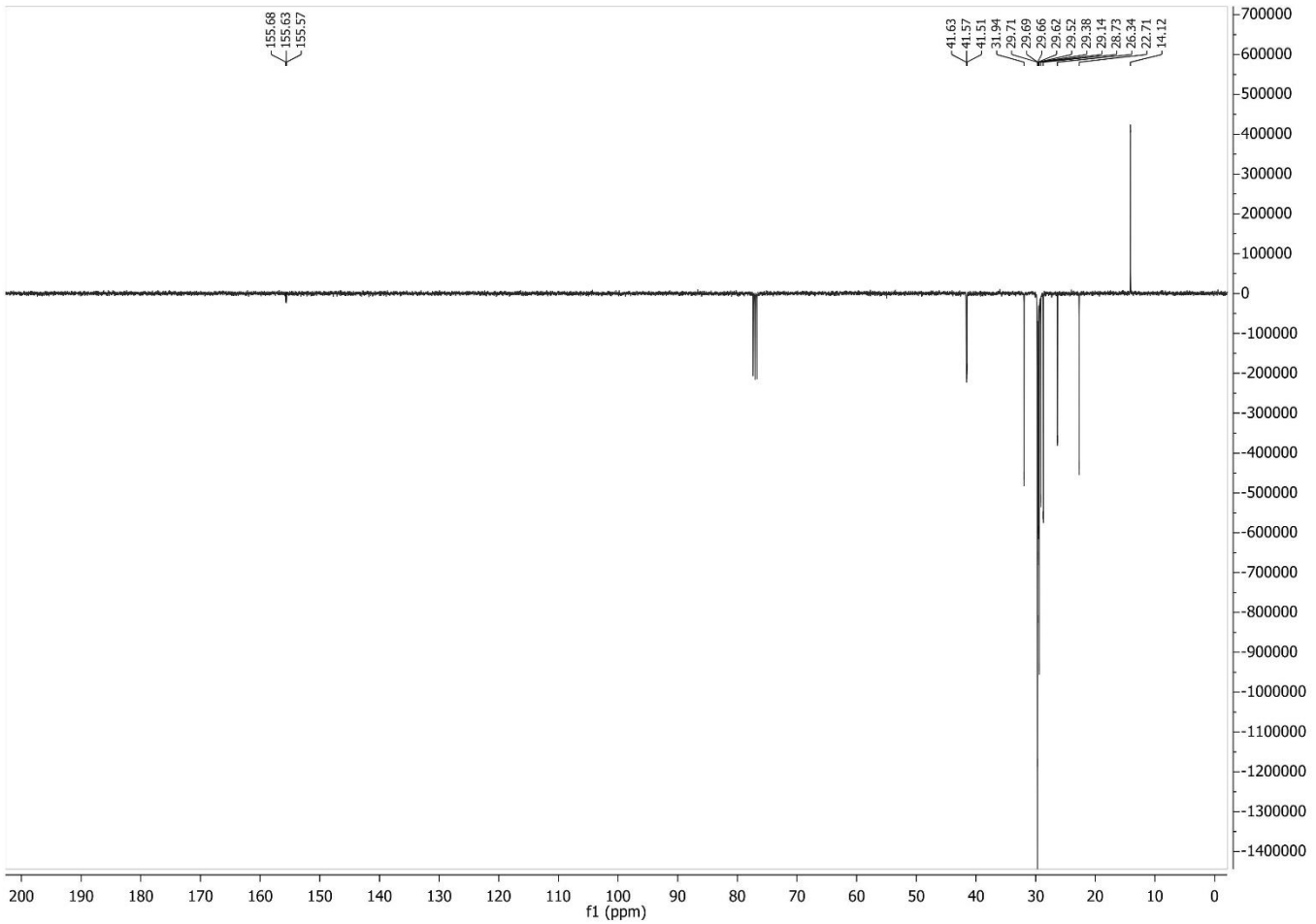
0.90
0.88
1.91
2.07
2.37
28.03
3.00
f1 (ppm)


155.68
155.63
155.57
41.63
41.57
41.51
31.94
29.71
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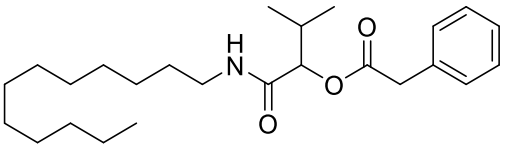
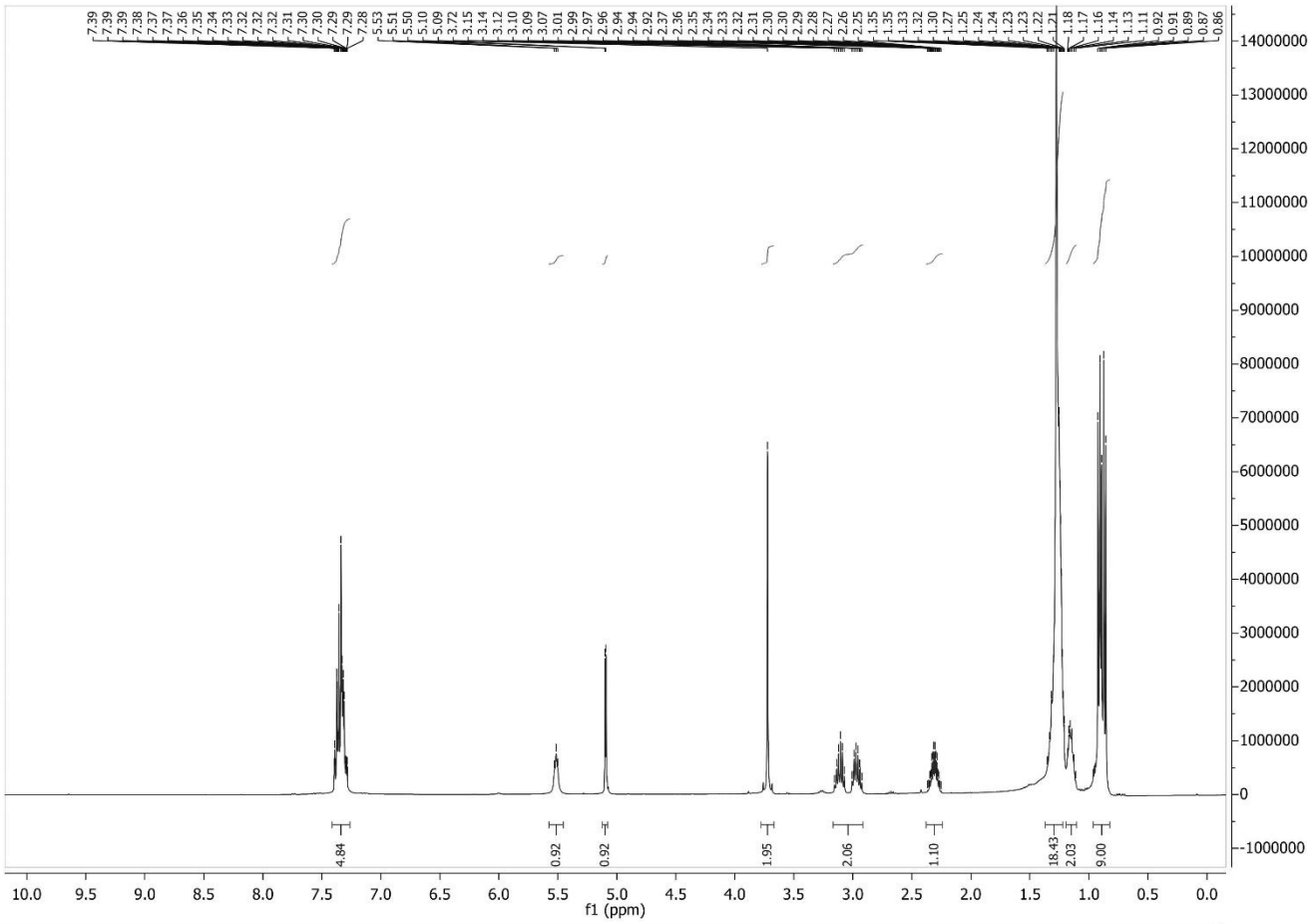
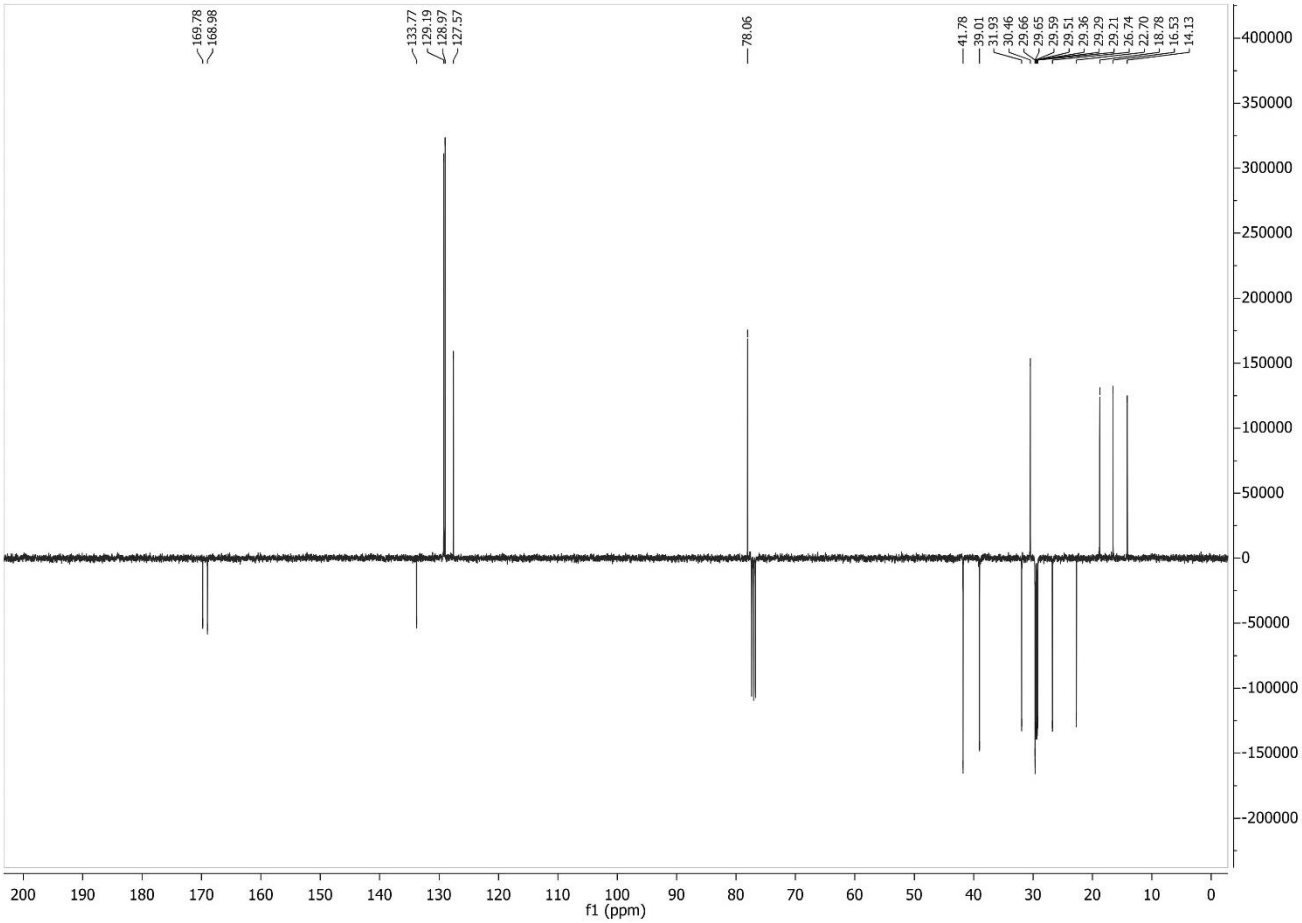
29.38
29.14
28.73
26.34
22.71
14.12
f1 (ppm)



24



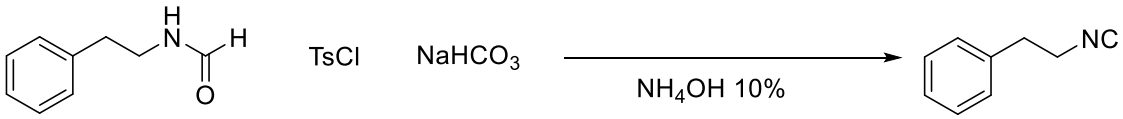


E-Factor calculation

E-factor = (Mass of Organic Waste) / (Mass of Product)

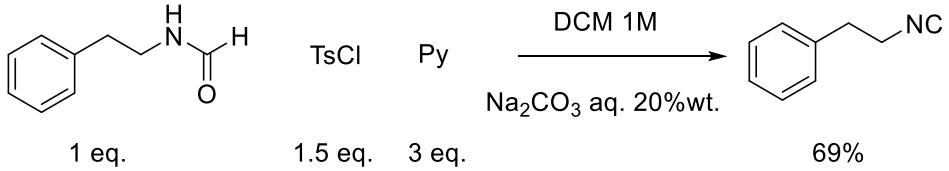
Compound 6

1. Our procedure



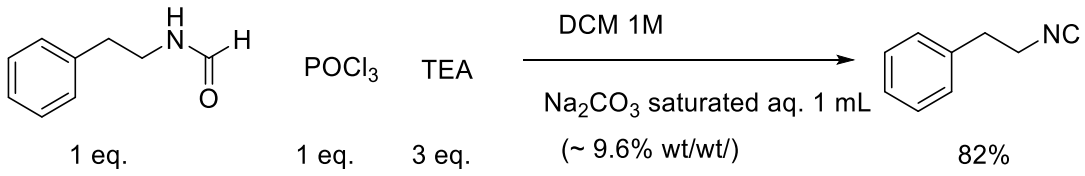
Amount of reactants:
Mass (*N*-(2-phenylethyl) formamide) = 100 mg
Mass (tosyl chloride) = 153.3 mg
Mass (sodium hydrogen carbonate) = 135.1 mg
Mass (NH_3): 67.0 mg
Mass (TPGS-750-M): 15.4 mg
Total mass of reactants = 470.8 mg
Total mass of organic waste = 470.8 - 56.3 = 414.5 mg
Amount of product = 56.3 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (414.5) / (56.3) = 7.4
E-Factor = 7.4

2. Synthesis of phenylethyl isocyanide following Meier's procedure:



Amount of reactants:
Mass (*N*-(2-phenylethyl) formamide) = 100 mg
Mass (tosyl chloride) = 191.7 mg
Mass (pyridine): 159.1 mg
Mass (sodium carbonate) = 134 mg
Mass (dichloromethane) = 0.67 mL x 1.33 g/mL = 891.1 mg
Total mass of reactants = 1475.9 mg
Total mass of organic waste = 1475.9 mg – 60.7 mg = 1415.2 mg
Amount of product = 60.7 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (1415.2) / (60.7) = 23.3
E-Factor = 23.3

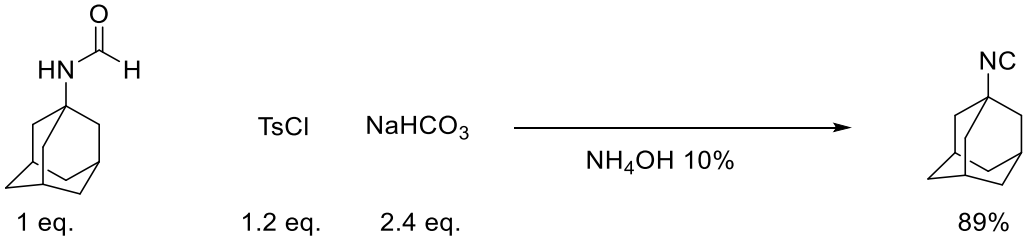
3. Synthesis of phenylethyl isocyanide following Ugi's procedure, using TEA:



Amount of reactants:
Mass (*N*-(2-phenylethyl) formamide) = 100 mg
Mass ($POCl_3$) = 102.8 mg
Mass (TEA): 339.1 mg
Mass (sodium carbonate) = 100 mg
Mass (dichloromethane) = 0.67 mL x 1.33 g/mL = 891.1 mg
Total mass of reactants = 1533 mg
Total mass of organic waste = 1533 mg – 72.1 mg = 1460.9 mg
Amount of product = 72.1 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (1460.9 mg) / (72.1) = 20.3

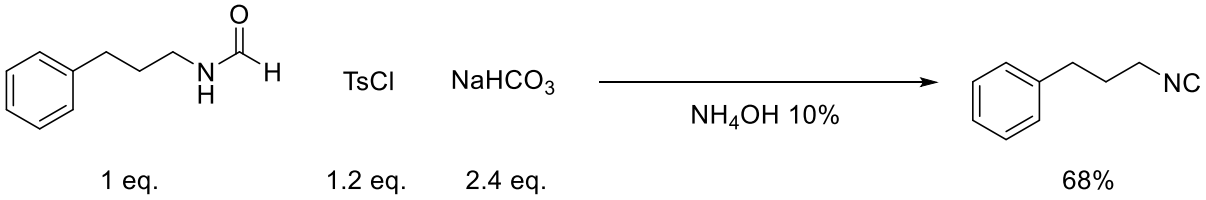
E-Factor = 20.3

Compound 7



Amount of reactants:
Mass (*N*-formamide) = 100 mg
Mass (tosyl chloride) = 159.5 mg
Mass (sodium hydrogen carbonate) = 140.6 mg
Mass (NH_3): 55.8 mg
Mass (TPGS-750-M): 13.6 mg
Total mass of reactants = 469.5 mg
Total mass of organic waste = 469.5 – 80.6 = 388.9 mg
Amount of product = 80.6 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (388.9) / (80.6) = 4.8
E-Factor = 4.8

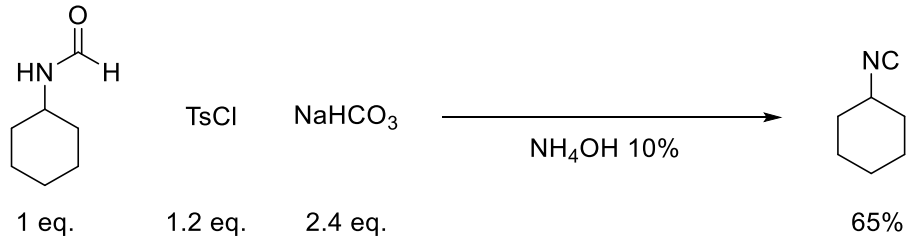
Compound 8



Amount of reactants:
Mass (*N*-formamide) = 100 mg
Mass (tosyl chloride) = 140.2 mg
Mass (sodium hydrogen carbonate) = 123.5 mg
Mass (NH_3): 61.3 mg
Mass (TPGS-750-M): 14.1 mg

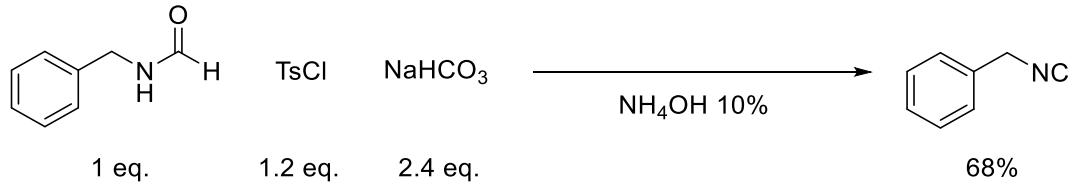
Total mass of reactants = 439.1 mg
Total mass of organic waste = 439.1 – 60.5 = 378.6 mg
Amount of product = 60.5 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (378.6) / (60.5) = 6.3
E-Factor = 6.3

Compound 9



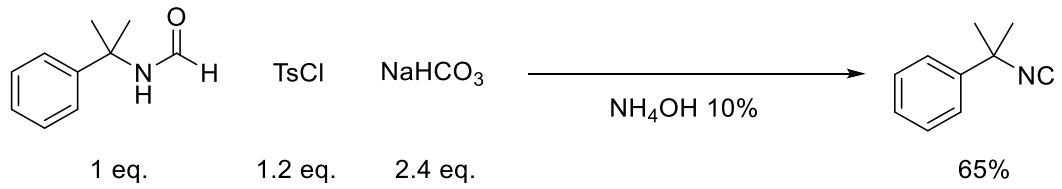
Amount of reactants:
Mass (*N*-formamide) = 150 mg
Mass (tosyl chloride) = 269.8 mg
Mass (sodium hydrogen carbonate) = 237.8 mg
Mass (NH_3): 118 mg
Mass (TPGS-750-M): 27.2 mg
Total mass of reactants = 802.8 mg
Total mass of organic waste =802.8 – 83.7 = 719.1 mg
Amount of product = 83.7 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (719.1) / (83.7) = 8.6
E-Factor = 8.6

Compound 10



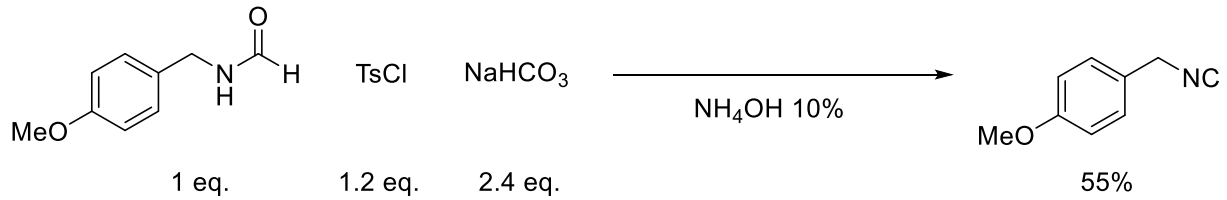
Amount of reactants:
Mass (*N*-formamide) = 150 mg
Mass (tosyl chloride) = 253.9 mg
Mass (sodium hydrogen carbonate) = 223.7 mg
Mass (NH_3): 110 mg
Mass (TPGS-750-M): 25.4 mg
Total mass of reactants = 763 mg
Total mass of organic waste = 763– 88.4 = 674.6 mg
Amount of product = 88.4 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (674.6) / (88.4) = 7.6
E-Factor = 7.6

Compound 11



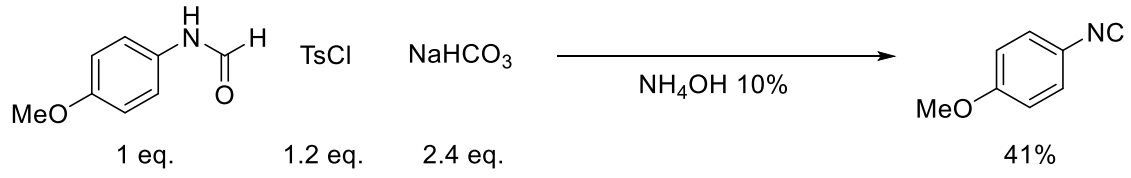
Amount of reactants:
Mass (*N*-formamide) = 150 mg
Mass (tosyl chloride) = 210.2 mg
Mass (sodium hydrogen carbonate) = 185.3 mg
Mass (NH_3): 100 mg
Mass (TPGS-750-M): 23.1 mg
Total mass of reactants = 668.6 mg
Total mass of organic waste = 668.6 – 86.7 = 581.9 mg
Amount of product = 86.7 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (581.9) / (86.4) = 6.7
E-Factor = 6.7

Compound 12



Amount of reactants:
Mass (*N*-formamide) = 100 mg
Mass (tosyl chloride) = 138.5 mg
Mass (sodium hydrogen carbonate) = 122.1 mg
Mass (NH_3): 60.5 mg
Mass (TPGS-750-M): 13.9 mg
Total mass of reactants = 466.2 mg
Total mass of organic waste = 466.2 – 49.1 = 417.1 mg
Amount of product = 49.1 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (417.1) / (49.1) = 7.9
E-Factor = 7.9

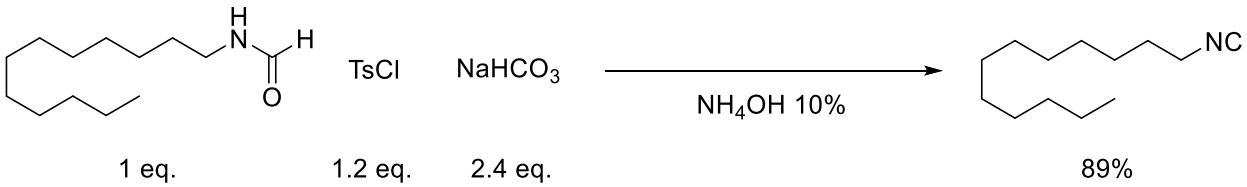
Compound 13



Amount of reactants:
Mass (*N*-formamide) = 100 mg
Mass (tosyl chloride) = 151.3 mg
Mass (sodium hydrogen carbonate) = 133.4 mg
Mass (NH_3): 66.2 mg
Mass (TPGS-750-M): 15.3 mg
Total mass of reactants = 466.2 mg
Total mass of organic waste = 466.2 – 36.4 = 429.8 mg

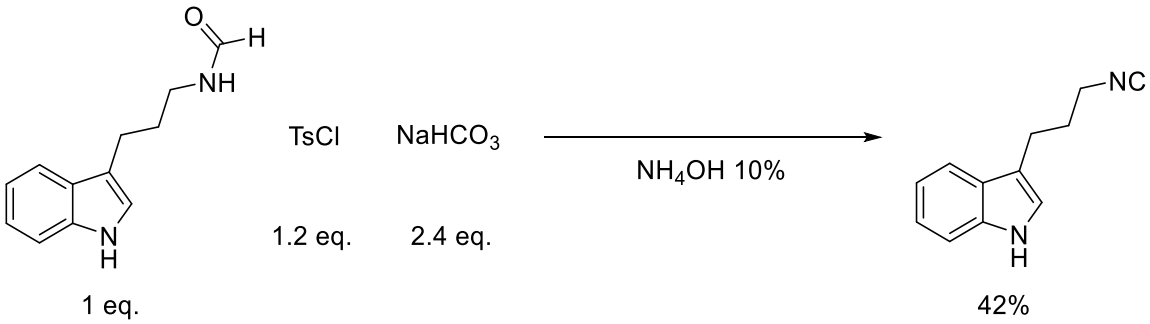
Amount of product = 36.4 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (429.8) / (36.4) = 11.8
E-Factor = 11.8

Compound 14



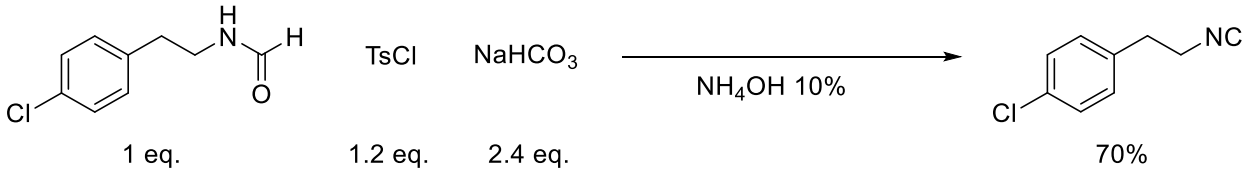
Amount of reactants:
Mass (*N*-formamide) = 100 mg
Mass (tosyl chloride) = 107.2 mg
Mass (sodium hydrogen carbonate) = 94.5 mg
Mass (NH_3): 46.9 mg
Mass (TPGS-750-M): 10.8 mg
Total mass of reactants = 359.4 mg
Total mass of organic waste = 359.4 – 81.7 = 277.2 mg
Amount of product = 81.7 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (277.2) / (81.7) = 3.4
E-Factor = 3.4

Compound 15



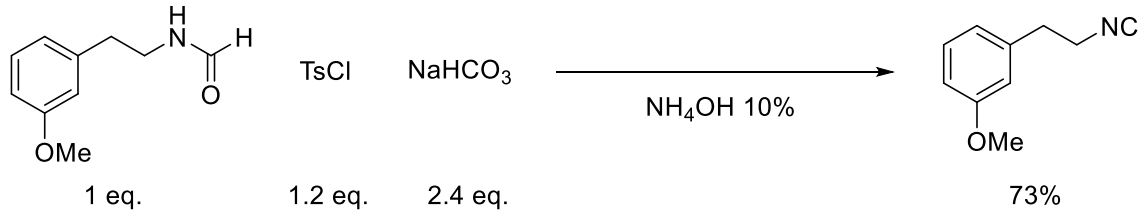
Amount of reactants:
Mass (*N*-formamide) = 103.5 mg
Mass (tosyl chloride) = 117.1 mg
Mass (sodium hydrogen carbonate) = 103.1 mg
Mass (NH_3): 51.2 mg
Mass (TPGS-750-M): 11.8 mg
Total mass of reactants = 386.7 mg
Total mass of organic waste = 386.7 – 39.0 = 347.7 mg
Amount of product = 39.0 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (347.7) / (39.0) = 8.9
E-Factor = 8.9

Compound 16



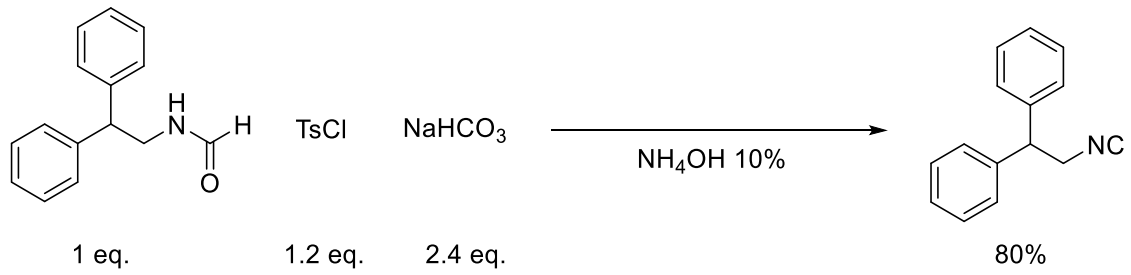
Amount of reactants:
Mass (*N*-formamide) = 101.0 mg
Mass (tosyl chloride) = 125.8 mg
Mass (sodium hydrogen carbonate) = 110.9 mg
Mass (NH_3): 55.0 mg
Mass (TPGS-750-M): 12.7 mg
Total mass of reactants = 405.4 mg
Total mass of organic waste = 405.4 – 63.8 = 341.6 mg
Amount of product = 63.8 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (341.6) / (63.8) = 5.4
E-Factor = 5.4

Compound 17



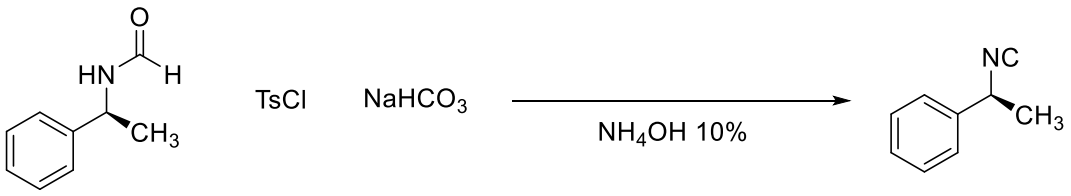
Amount of reactants:
Mass (*N*-formamide) = 53.8 mg
Mass (tosyl chloride) = 68.7 mg
Mass (sodium hydrogen carbonate) = 60.2 mg
Mass (NH_3): 29.9 mg
Mass (TPGS-750-M): 6.9 mg
Total mass of reactants = 219.5 mg
Total mass of organic waste = 219.5 – 35.1 = 184.4 mg
Amount of product = 35.1 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (184.4) / (35.1) = 5.3
E-Factor = 5.3

Compound 18



Amount of reactants:
Mass (*N*-formamide) = 120.0 mg
Mass (tosyl chloride) = 121.9 mg
Mass (sodium hydrogen carbonate) = 107.4 mg
Mass (NH_3): 53.3 mg
Mass (TPGS-750-M): 12.3 mg
Total mass of reactants = 414.9 mg
Total mass of organic waste = 414.9 – 88.5 = 326.4 mg
Amount of product = 88.5 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (326.4) / (88.5) = 3.7
E-Factor = 3.7

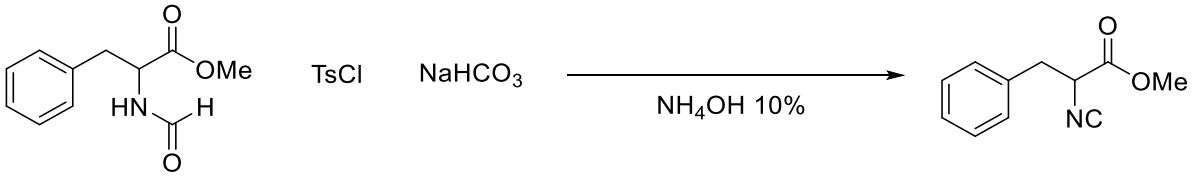
Compound 19



1 eq. 1.2 eq. 2.4 eq. 63%

Amount of reactants:
Mass (*N*-formamide) = 114.3 mg
Mass (tosyl chloride) = 160.7 mg
Mass (sodium hydrogen carbonate) = 154.5 mg
Mass (NH_3): 76.7 mg
Mass (TPGS-750-M): 17.7 mg
Total mass of reactants = 524 mg
Total mass of organic waste = 524 – 63.3 = 460.7 mg
Amount of product = 63.3 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (460.7) / (63.3) = 7.3
E-Factor = 7.3

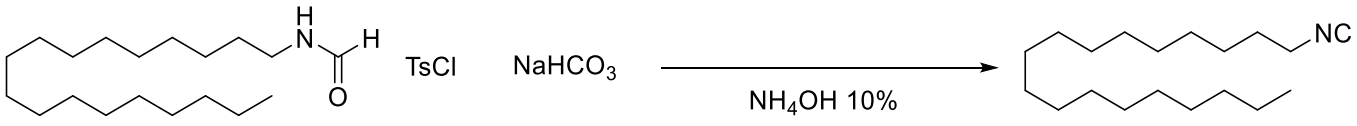
Compound 20



1 eq. 1.2 eq. 2.4 eq. 34%

Amount of reactants:
Mass (*N*-formamide) = 107.9 mg
Mass (tosyl chloride) = 119.1 mg
Mass (sodium hydrogen carbonate) = 105.0 mg
Mass (NH_3): 52.1 mg
Mass (TPGS-750-M): 12.0 mg
Total mass of reactants = 396.1 mg
Total mass of organic waste = 396.1 – 33.9 = 362.2 mg
Amount of product = 33.9 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (362.2) / (33.9) = 10.7
E-Factor = 10.7

Compound 21



1 eq. 1.2 eq. 2.4 eq. 82%

Amount of reactants:
Mass (*N*-formamide) = 100.0 mg
Mass (tosyl chloride) = 76.9 mg

Mass (sodium hydrogen carbonate) = 67.8 mg
Mass (NH_3): 33.6 mg
Mass (TPGS-750-M): 7.7 mg
Total mass of reactants = 286 mg
Total mass of organic waste = 286 – 77.0 = 209 mg
Amount of product = 77.0 mg
E-Factor = (Mass of Organic Waste) / (Mass of Product) = (209) / (77.0) = 2.7
E-Factor = 2.7

PMI values

PMI values were calculated using the "Process Mass Intensity Calculator Tool" developed by the ACS GCI Pharmaceutical Roundtable (https://www.acs.org/content/acs/en/greenchemistry/research-innovation/tools-for-green-chemistry.html)

In Table 1 are reported the PMI values calculated by taking into consideration all the reactants, water and solvents used for the reaction and during the quenching. The amount of reactants used for the reaction and the quenching are those reported in the section "E factor calculation". In these quantities is included the amount of TPGS-750-M which cannot be recycled, due to degradation during the reaction or because it is lost during extraction (46.1% in total). For our procedure, the amount of water used is the sum of those employed for the TPGS-750-M 5% wt solution (1M with respect to the formamide) and during the quenching (500 mg on a 0.5 mmol scale). For the Ugi procedure, the amount of water used is those employed during the quenching (1000 mg); the amount of solvent is those employed during the reaction (891.1 mg of DCM). For the Meier procedure, the amount of water used is those employed during the quenching (670 mg); the amount of solvent is those employed during the reaction (891.1 mg of DCM).

Table 1

Compound	6 Ugi procedure	6 Meier procedure	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
PMI Substrate, Reagents, Solvents, Water	35,1	35,4	29,1	19,3	25,7	29,7	26,7	25	31,4	44,7	16,3	35,9	22,8	29	16,4	28,3	41,8	14,6
PMI Substrate, Reagents, Solvents	21,3	24,3	8,4	5,8	7,3	9,6	8,6	7,7	8,9	12,8	4,4	9,9	6,4	6,3	4,7	8,3	11,7	3,7
PMI Substrates and Reagents	8,9	9,6	8,4	5,8	7,3	9,6	8,6	7,7	8,9	12,8	4,4	9,9	6,4	6,3	4,7	8,3	11,7	3,7
PMI Solvents	12,4	14,7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
PMI Water	13,9	11	20,8	13,5	18,4	20,1	18,1	17,3	22,5	31,9	11,9	25,9	16,5	22,8	11,7	20	30,1	10,9

In Table 2 we reported the PMI values calculated by taking into consideration the workup procedures too. To the quantities used for the calculation of the PMI values reported in Table 1, we have added the solvent used during the extraction (1 mL of EtOAc on a 0.5 mmol scale). This quantity is the same for Ugi and Meier procedures, with the difference that the solvent used is dichloromethane.

Table 2

Compound	6 Ugi procedure	6 Meier procedure	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
PMI Substrate, Reagents, Solvents, Water	53,6	57,3	45,2	30,5	40,6	40,4	36,9	35,4	49,7	69,5	27,3	59	36,9	54,7	26,6	42,5	68,4	26,3
PMI Substrate, Reagents, Solvents	39,7	46,2	24,4	17	22,2	20,4	18,8	18,1	27,2	37,6	15,4	33	20,5	32	14,9	22,5	38,3	15,4
PMI Substrates and Reagents	8,9	9,6	8,4	5,8	7,3	9,6	8,6	7,7	8,9	12,8	4,4	9,9	6,4	6,3	4,7	8,3	11,7	3,7
PMI Solvents	30,8	36,6	16	11,2	14,9	10,8	10,2	10,4	18,4	24,8	11	23,1	14,1	25,7	10,2	14,2	26,6	11,7
PMI Water	13,9	11	20,8	13,5	18,4	20,1	18,1	17,3	22,5	31,9	11,9	25,9	16,5	22,8	11,7	20	30,1	10,9

Although we demonstrated that with this procedure the isocyanide obtained could be either used in situ or without purification, in Table 3 we have reported the PMI values calculated by taking into consideration also the flash column chromatography procedures. The quantity of solvent used is the same for Ugi, Meier and our procedure. Having very similar Rf, all the isocyanides required approximately 45 mL of petroleum ether/EtOAc 8:2, which was then distilled and recovered (we assumed a recovery of 90%).

Table 3

Compound	6 Ugi procedure	6 Meier procedure	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
PMI Substrate, Reagents, Solvents, Water	99,8	112,2	104,3	71,9	95,6	80,2	74,6	73,8	117,6	161	68,1	144,4	89,2	149,6	64,2	95,2	166,7	69,6
PMI Substrate, Reagents, Solvents	85,9	101,1	83,6	58,4	77,2	60,2	56,5	56,5	95,1	129,1	56,2	118,5	72,7	126,9	52,5	75,2	136,6	58,7
PMI Substrates and Reagents	8,9	9,6	8,4	5,8	7,3	9,6	8,6	7,7	8,9	12,8	4,4	9,9	6,4	6,3	4,7	8,3	11,7	3,7
PMI Solvents	77	91,5	75,2	52,5	70	50,6	47,9	48,8	86,2	116,3	51,8	108,6	66,4	120,6	47,8	66,9	124,9	55
PMI Water	13,9	11	20,8	13,5	18,4	20,1	18,1	17,3	22,5	31,9	11,9	25,9	16,5	22,8	11,7	20	30,1	10,9

MI_R and MI_W values

In Table 3 are reported the calculated values of mass intensity for the reaction (MI_R) and for the workup (MI_W), the latter including also the quenching procedure. It's also reported the (MI_P) for the chromatography purification.

MI_R = (Total mass used for the reaction, including water) / (Mass of Product)

MI_W = (Total mass used for the workup, including water) / (Mass of Product)

MI_P = (Total mass used for the purification) / (Mass of Product)

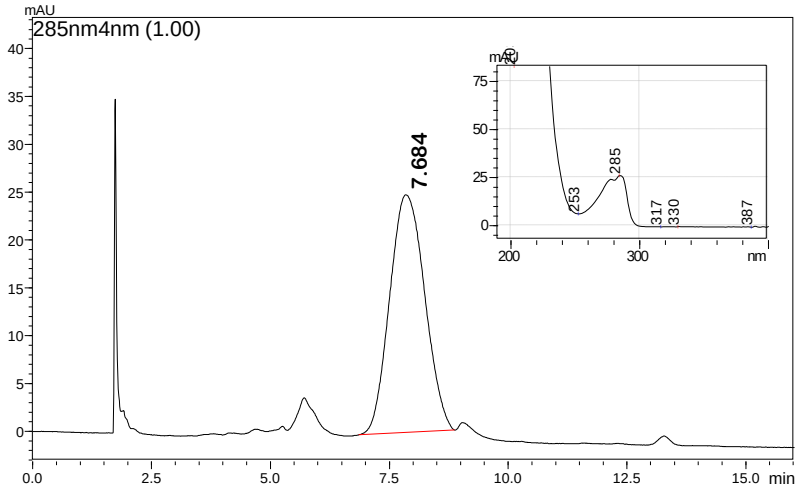
Table 4

Compound	6 Ugi procedure	6 Meier procedure	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
MI_R	19,9	22,1	18,8	12,3	16,4	21,9	19,5	17,8	19,7	28,8	9,4	21,4	13,9	12,9	10	18,9	25,2	7,5
MI_W	33,7	35,2	26,1	18,1	24,2	18,2	17,1	17,3	29,8	40,3	17,7	37,3	22,8	40,8	16,4	35,5	42,9	18,6
MI_P	46,2	54,9	59,2	41,3	55,1	39,8	37,7	38,4	67,9	91,5	40,8	85,4	52,2	94,9	37,6	52,6	98,3	43,3

Analysis of TPGS-750-M

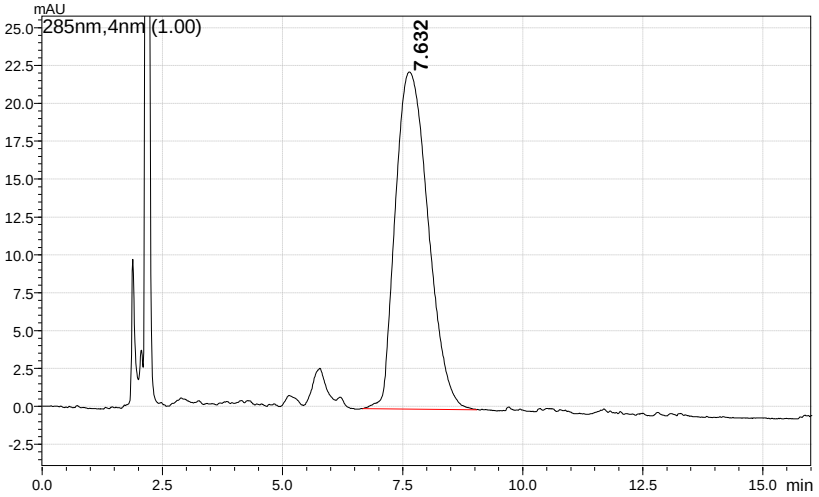
- Column: Supelco Ascentis® C8 15 cm × 4.6 mm *d.p.* 5 µ
- Eluant: acetonitrile
- Injection volume: 20 µL
- Detection: UV, λ=285 nm

TPGS-750-M standard solution 5 wt% diluted 1:50 with water-acetonitrile 1:1, (t_R=7.684 min, peak area= 1,276,169).



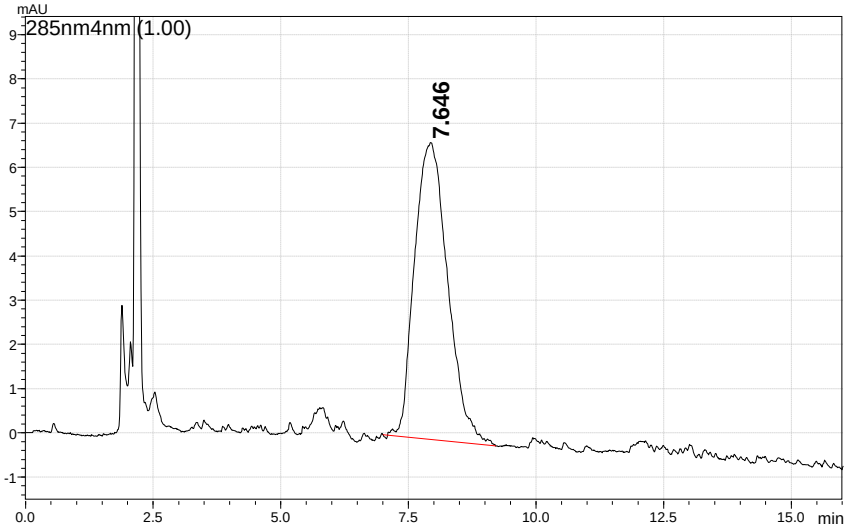
In order to evaluate the stability of TPGS-750-M upon the reaction conditions, we conducted the reaction as reported in the article and, after 16 hours, we determined the percentage of residual TPGS-750-M, which remained intact, as follows:

Reaction diluted 1:50 with water-acetonitrile 1:1, (t_R=7.632 min, peak area= 1,055,761; **82,7%** respect to TPGS standard).



For the determination of the amount of TPGS-750-M lost in the extraction process during the recycling experiments, we conducted the reaction as reported in the article and, after 16 hours, we extracted it with EtOAc (2.3 mL for a reaction of a 2.3 mmol scale). The organic phase was analyzed as follows, to determine the amount of TPGS extracted during the process:

Organic phase resuspended in the same volume of acetonitrile and diluted 1:50 with water-acetonitrile 1:1 (t_R=7.646 min, peak area= 303,822; **28.8%** respect to TPGS reaction solution).



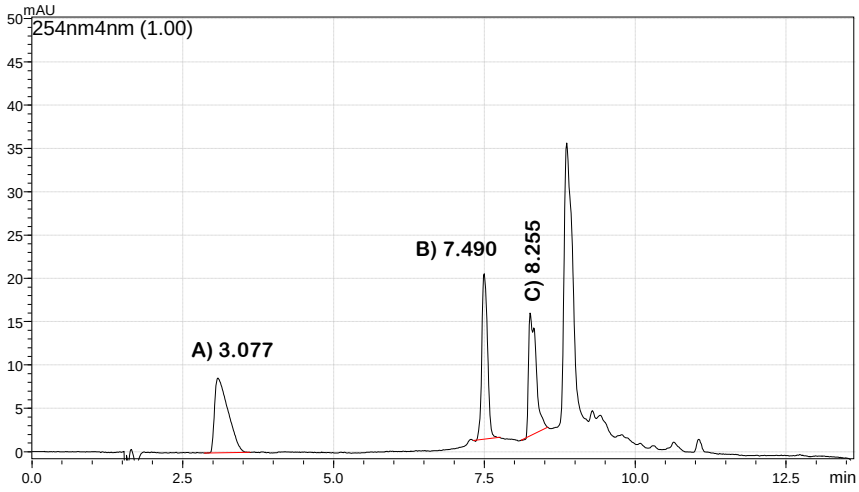
Evaluation of the hydrolytic stability of the reactants upon the reaction conditions

N-phenethylformamide and (2-isocyanoethyl)benzene **6** were analyzed as follows, after being individually stirred for 16 hours with TPGS-750-M (1M) and $NaHCO_3$.

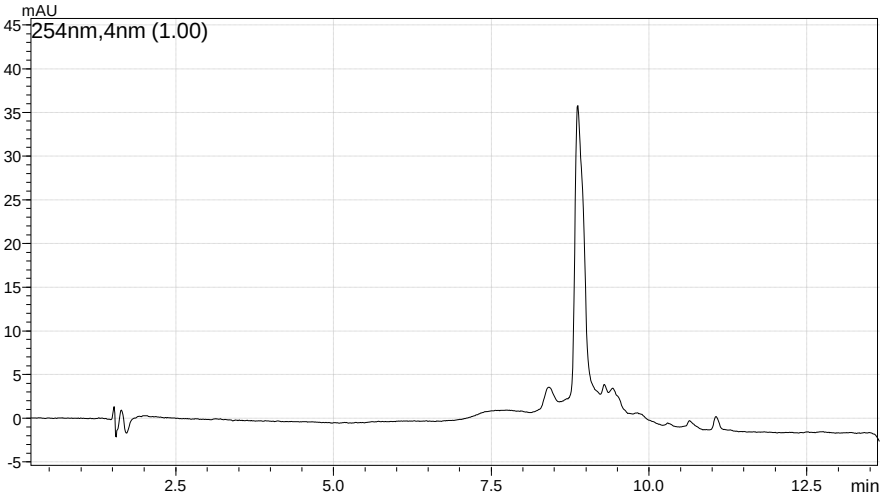
- Column: Phenomenex Kinetex C18 XB 15 cm × 4.6 mm *d.p.* 5 µ
- Eluant: A= 0.2% formic acid in water, B= methanol
- Injection volume: 20 µL
- Detection: UV, λ=254 nm
- Gradient program:

min	B%
0.00	20
5.00	90
9.50	90
10.00	20
15.00	20

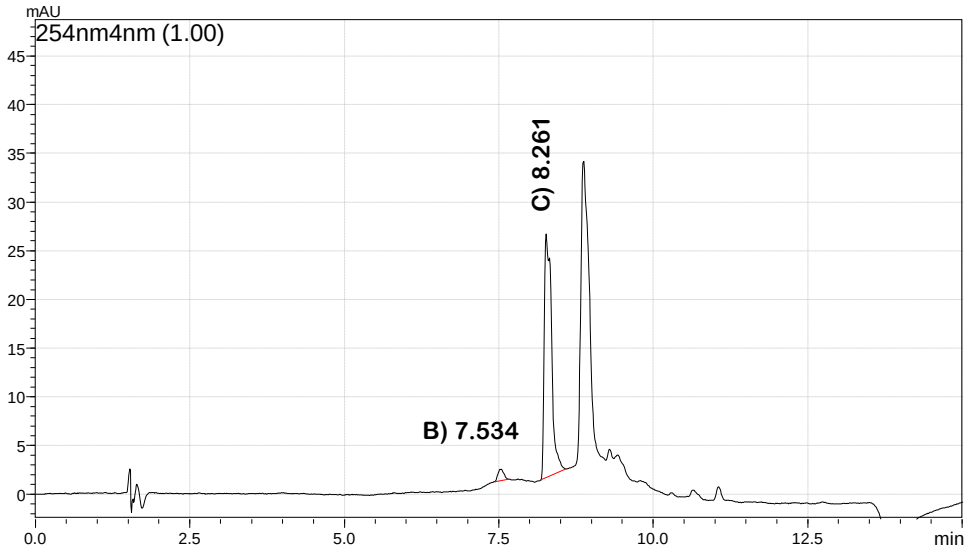
1) Standard solution of 2-phenylethan-1-amine (peak A, t_R=3.077 min), *N*-phenethylformamide (peak B, t_R=7.490 min), (2-isocyanoethyl)benzene **6** (peak C, t_R=8.255 min) 0.1 mg/mL in water-methanol 1:1.



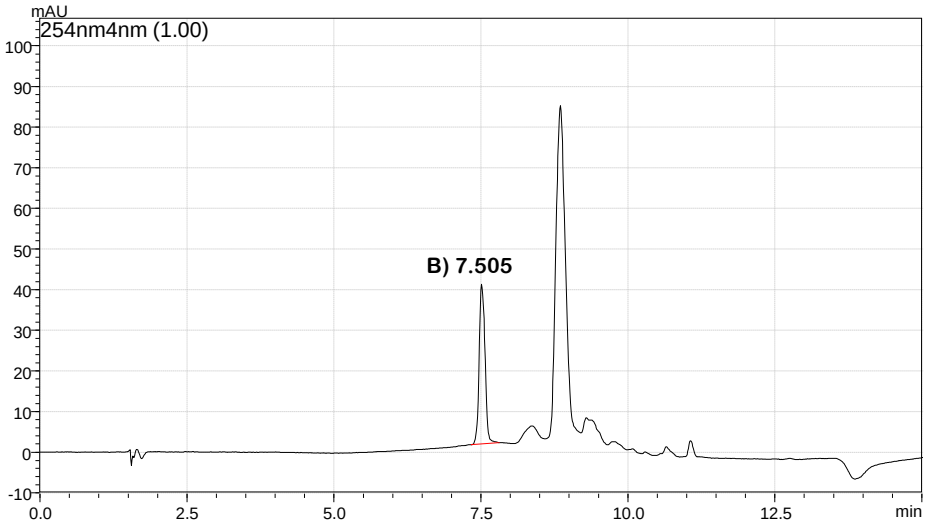
2) Blank solution: water-methanol 1:1.



3) Analysis of (2-isocyanoethyl)benzene **6** in water-methanol 1:1 (nominal concentration 0.2 mg/mL).



4) Analysis of *N*-phenethylformamide in water-methanol 1:1 (nominal concentration 0.2 mg/mL).



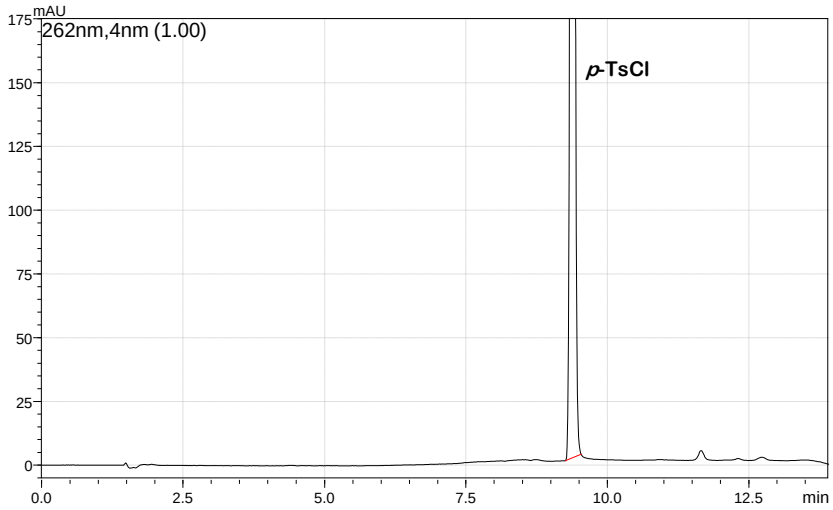
	Peak A	Peak B	Peak C
Standard solution	137.637	128.612	126.451
(2-isocyanoethyl)benzene **6** (normalized area)	Not detected	4.956 (<5% respect to standard)	125.832 **(>95% respect to standard)**
N-phenethylformamide (normalized area)	Not detected	130.380 **(>95% respect to standard**)	-

p-tosyl chloride was analyzed as follows, after being stirred for 16 hours with TPGS-750-M (1M) and $NaHCO_3$.

- Column: Phenomenex Kinetex C18 XB 15 cm × 4.6 mm *d.p.* 5 µ
- Eluant: A= 0.2% formic acid in water, B= 0.2% formic acid in acetonitrile
- Injection volume: 20 µL
- Detection: UV, λ=262 nm
- Gradient program:

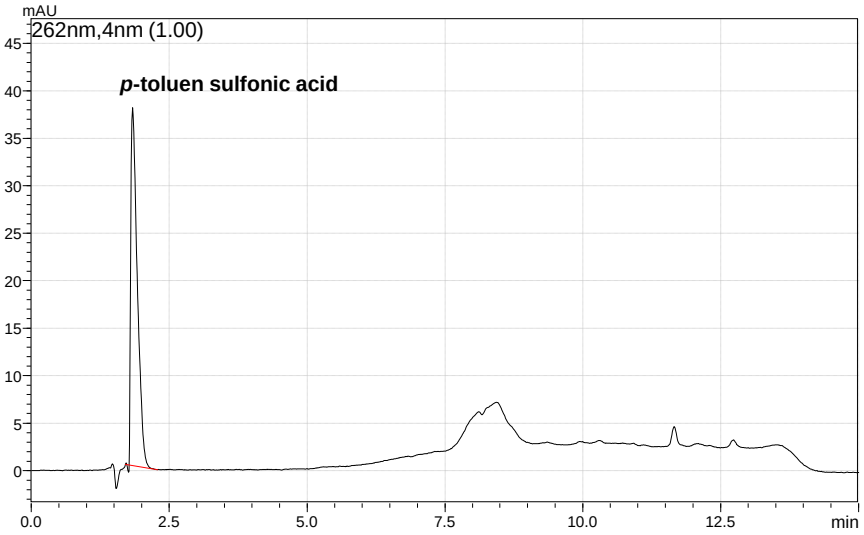
min	**B%**
0.00	30
6.00	80
9.50	80
10.00	30
15.00	30

1) *p*-TsCl standard solution (0.2 mg/mL) in acetonitrile. Peak t_R=9.348 min.

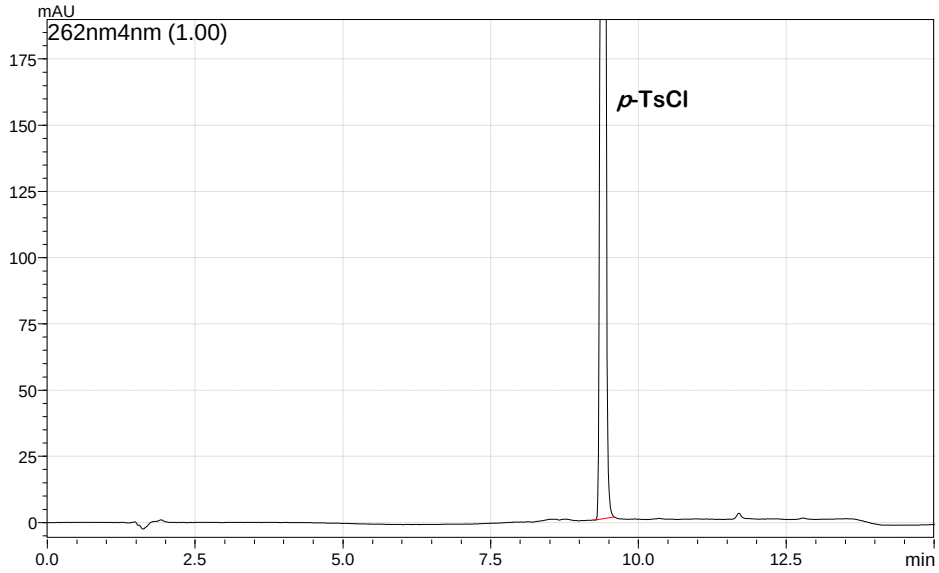


peak area *p*-TsCl = 4,857,054

2) *p*-toluen sulfonic acid monohydrate standard solution (0.2 mg/mL) in water-acetonitrile 1:1. Peak t_R=1.831 min.

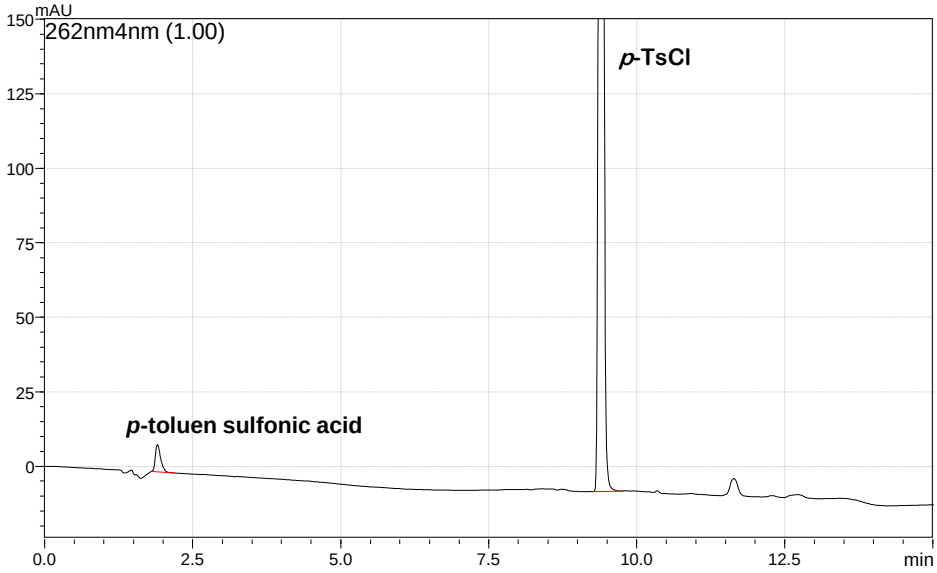


3) Reaction at t=0 diluted in acetonitrile: *p*-TsCl nominal concentration 0.21 mg/mL.



peak area *p*-TsCl = 5,176,543

4) Reaction at t=16 h diluted in acetonitrile: TsCl nominal concentration 0.21 mg/mL.



peak area *p*-TsCl = 4,553,003 (**88%** respect to t=0)

References

1. U. Galli, G. C. Tron, B. Purghè, G. Grosa, S. Aprile, *Chem. Res. Toxicol*. 2020, **33**, 955–966
2. Z.-P. Wang, Q. Wu, J. Jiang, X.-R. Li, X.-J. Peng, P.-L. Shao, Y. He *Organic Chemistry Frontiers* 2018, **5**, 36-40