

## A Weinreb Approach to the Synthesis of Trifluoromethylketones

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#### Key to Abbreviated Terms:

SOCl<sub>2</sub>- Thionyl Chloride  
CDCl<sub>3</sub>-Deuterated Chloroform  
CDI- 1,1 Carbonyl Diimidazole  
DCM-Dichloromethane  
Et<sub>2</sub>O- Diethyl Ether  
EtOAc- Ethyl  
Hex: Hexanes  
TBAF-Tetrabutylammonium Fluoride  
TFMK- Trifluoromethyl Ketone  
THF – Tetrahydrofuran  
TLC- Thin Layer Chromatography  
TMS, Me<sub>3</sub>Si- Trimethylsilyl  
TMS-CF<sub>3</sub>- Trifluoromethyl(trimethyl)silane

## General Considerations:

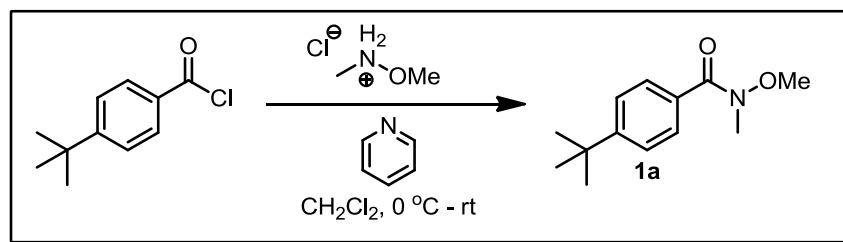
### General:

All chemical transformations requiring inert atmospheric conditions or vacuum distillation utilized Schlenk line techniques with a 3- or 4-port dual-bank manifold. Nitrogen was used to provide such an atmosphere. NMR Spectra ( $^1\text{H}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$ ) were performed at 298 K on either a Brüker Avance Ultra Shield 300 MHz NMR, Brüker DRX-400 400 MHz NMR, or Brüker Avance 500 MHz NMR.  $^1\text{H}$ -NMR Spectra obtained in  $\text{CDCl}_3$  were referenced to residual non-deuterated chloroform (7.26 ppm) in the deuterated solvent or in deuterated methanol referenced to TMS (0.00 ppm).  $^{13}\text{C}$ -NMR Spectra obtained in  $\text{CDCl}_3$  were referenced to chloroform (77.3 ppm) or to deuterated acetone (29.84 ppm).  $^{19}\text{F}$ -NMR spectra were referenced to hexafluorobenzene ( $-164.9$  ppm)<sup>1</sup>. Reactions were monitored by an Agilent Technologies 7820A Gas Chromatograph attached to a 5975 Mass Spectrometer,  $^1\text{H}$ -NMR, and/or by TLC on silica gel plates (60Å porosity, 250  $\mu\text{m}$  thickness). High-resolution mass spectra were obtained using a JEOL AccuTOF-DART SVP 100 in positive direct analysis in real time (DART) ionization method, using PEG as the internal standard. TLC analysis was performed using hexanes/ethyl acetate as the eluent and visualized using permanganate stain, *p*-anisaldehyde stain, Seebach's Stain, and/or UV light. Flash chromatography and silica plugs utilized Dynamic Adsorbants Inc. Flash Silica Gel (60Å porosity, 32-63  $\mu\text{m}$ ).

### Chemicals:

Deuterated NMR solvents ( $\text{CDCl}_3$ , Acetone- $d_6$ ) were purchased from Cambridge Isotope Laboratories.  $\text{CDCl}_3$  was stored over 4Å molecular sieves and  $\text{K}_2\text{CO}_3$ . Sodium sulfate, sodium carbonate, THF (reagent grade),  $\text{CH}_2\text{Cl}_2$ ,  $\text{SOCl}_2$ , diethyl ether (ACS Grade and reagent grade), TBAF (1M in THF), were purchased from Sigma-Aldrich. Commercially available acid chlorides were purchased from Sigma-Aldrich or prepared by the procedure of Womack & McWhirter<sup>2</sup> from commercially carboxylic acids and used without further purification. Hexafluorobenzene was purchased from ACROS. Trifluoromethyltrimethylsilane, Carbonyl Diimidazole, and N,O-dimethylhydroxyamine hydrochloride were purchased from Synquest Laboratories.

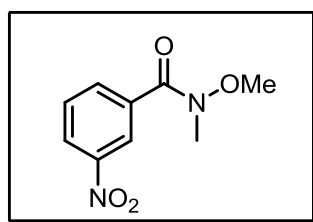
## Synthesis of Weinreb Amide Substrates



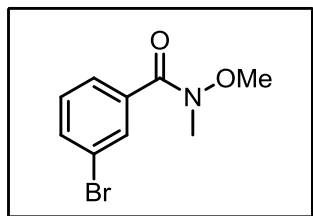
### General Procedure A: Weinreb Amides From Acid Chlorides<sup>3</sup>

#### 4-(*tert*-butyl)-*N*-methoxy-*N*-methylbenzamide<sup>4</sup> (1a)

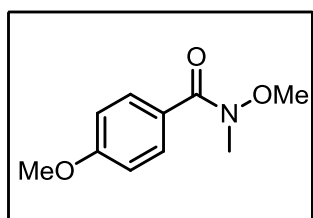
To a 250 mL round bottom flask equipped with stirbar was added 4-*t*-butylbenzoyl chloride (7.867 g, 40 mmol, 1.0 equiv), DCM (80 mL, 0.5 M in the acid chloride), followed by *N*-*O*-dimethylhydroxylamine hydrochloride (4.098 g, 42 mmol, 1.05 equiv). The flask was cooled to 0 °C in an ice bath for 10 minutes. Pyridine (6.638 g, 84 mmol, 2.1 equiv) was added drop-wise to the flask over a period of 10 minutes. The reaction flask was taken out of the ice bath and upon warming, a white precipitate formed. The reaction was allowed to stir overnight. The reaction mixture was then diluted with DCM (200 mL) and was transferred into a separatory funnel. The organic layer was washed with 2 x 120 mL of 1 M HCl, 2 x 140 mL of a saturated sodium bicarbonate solution, and 1 x 120 mL of brine. The resulting organic solution was dried over Na<sub>2</sub>SO<sub>4</sub>, decanted, and the solvent was removed *in vacuo* by rotary evaporation to yield the pure Weinreb amide (7.91 g, 89%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ ppm 1.30 (s, 9 H) 3.32 (s, 3 H) 3.54 (s, 3 H) 7.38 (d, *J*=8.83 Hz, 2 H) 7.60 (d, *J*=8.20 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 31.32 (CH<sub>3</sub>) 34.06 (CH<sub>3</sub>) 34.97 (C) 61.13 (CH<sub>3</sub>) 125.07 (CH) 128.25 (CH) 131.24 (C) 154.06 (C) 170.10 (C) GC-MS (EI) 221 ([M]<sup>+</sup>, .01%), 161 (100%), 146 (14%), 118 (14%), 115 (8%), 91 (10%), 77 (6%).



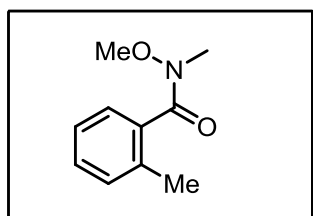
*N*-methoxy-*N*-methyl-3-nitrobenzamide<sup>5</sup> (1b) (5.83 g, 69%) was prepared according to the representative procedure from 3-nitrobenzoyl chloride (7.423 g, 40 mmol) giving the pure Weinreb amide as an off-white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 3.41 (s, 3 H) 3.56 (s, 3 H) 7.61 (t, *J*=7.95 Hz, 1 H) 8.04 (d, *J*=7.58 Hz, 1 H) 8.33 (d, *J*=9.29 Hz, 1 H) 8.58 (s, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 33.48 (CH<sub>3</sub>) 61.60 (CH<sub>3</sub>) 123.75 (CH) 125.48 (CH) 129.46 (CH) 134.58 (CH) 135.75 (C) 148.00 (C) 167.39 (C) GC-MS (EI) 210 ([M]<sup>+</sup>, 2%), 150 (100%), 104 (39%), 92 (4%), 76 (33%), 75 (9%), 50 (11%), 43 (6%).



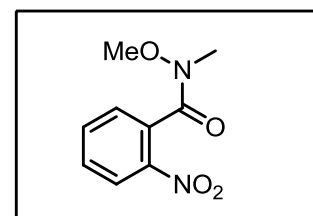
**3-bromo-N-methoxy-N-methylbenzamide<sup>6</sup> (1c)** (3.26 g, 67%) was prepared according to the representative procedure from 3-bromobenzoyl chloride (4.389 g, 20 mmol) giving the pure Weinreb amide as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ ppm 3.35 (s, 3 H) 3.55 (s, 3 H) 7.28 (t, *J*=7.88 Hz, 1 H) 7.59 (m apparent overlapping doublets, 2 H) 7.82 (s, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 33.71 (CH<sub>3</sub>) 61.37 (CH<sub>3</sub>) 122.17 (C) 126.97 (CH) 129.81 (CH) 131.38 (CH) 133.72 (CH) 136.14 (C) 168.33 (C) **GC-MS** (EI) 245 ([M]<sup>+</sup>, 4%), 243 ([M]<sup>+</sup>, 4%), 185 (97%), 183 (100%), 157 (38%), 155 (39%) 76 (27%), 75 (22%), 74 (9%), 50 (14%).



**N,4-dimethoxy-N-methylbenzamide<sup>5</sup> (1d)** (7.05 g, 90%) was prepared according to the representative procedure from 4-methoxybenzoyl chloride (6.824 g, 40 mmol) giving the pure Weinreb amide as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 3.34 (s, 3 H) 3.55 (s, 3 H) 3.83 (s, 3 H) 6.89 (d, *J*=9.05 Hz, 2 H) 7.72 (d, *J*=9.05 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 34.14 (CH<sub>3</sub>) 55.56 (CH<sub>3</sub>) 61.13 (CH<sub>3</sub>) 113.49 (CH) 126.27 (C) 130.79 (CH) 161.77 (C) 169.63 (C) **GC-MS** (EI) 195 ([M]<sup>+</sup>, 1%), 135 (100%), 107 (8%), 92 (12%), 77 (15%), 64 (6%).



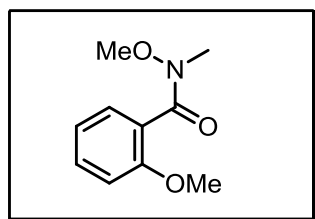
**N-methoxy-N,2-dimethylbenzamide<sup>7</sup> (1e)** (4.42g, 75%) was prepared according to the representative procedure from 2-nitrobenzoyl chloride (10.0 g, 60 mmol) giving the pure Weinreb amide as a clear colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ ppm 2.27 (s, 3 H) 3.23 (br. s., 3 H) 3.43 (br. s., 3 H) 7.09 - 7.16 (m, 2 H) 7.16 - 7.25 (m, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 19.04 (CH<sub>3</sub>) 33.19 (broad, CH<sub>3</sub>) 61.00 (CH<sub>3</sub>) 125.38 (CH) 126.15 (CH) 129.16 (CH) 130.11 (CH) 134.75 (C) 135.25 (C) 170.81 (C) **GC-MS** (EI) 179 ([M]<sup>+</sup>, 1%), 119 (100%), 91 (60%), 65 (19%) 51 (3%)



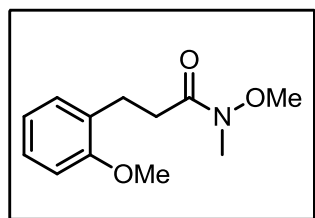
**N-methoxy-N-methyl-2-nitrobenzamide<sup>8</sup> (1f)** (3.41 g, 85%) was prepared according to the representative procedure from 2-nitrobenzoyl chloride (3.45 g, 22.17 mmol) giving the pure Weinreb amide as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ ppm 3.26 (br. s., 3 H) 3.27 (br. s., 3 H) 7.46 (d, *J*=7.57 Hz, 1 H) 7.53 (t, *J*=8.20 Hz, 1 H) 7.66 (t, *J*=7.60 Hz, 1 H) 8.06 (d, *J*=8.20 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 33.41 (CH<sub>3</sub>) 61.39 (CH<sub>3</sub>) 123.93 (C) 128.50 (CH) 130.19 (CH) 131.56 (CH) 134.14 (CH) 145.84 (C) 168.85 (C) **GC-MS** (EI) 210 ([M]<sup>+</sup>, 0.1%), 163



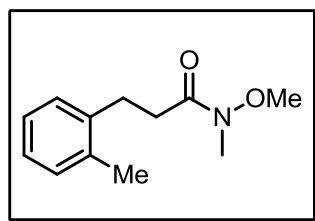
(1%), 150 (100%), 121 (17%), 104 (25%), 92 (10%), 78 (18%), 77(14%), 76 (70%), 75 (15%), 74 (15%), 63 (10%), 51(53%)



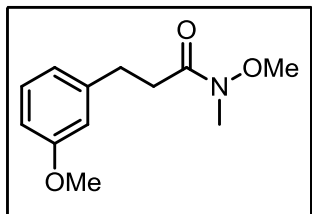
**N,2-dimethoxy-N-methylbenzamide<sup>5</sup> (1g)** (6.27 g, 80%) was prepared according to the representative procedure from 2-methoxybenzoyl chloride (6.82 g, 40 mmol) giving the pure Weinreb amide as a off- yellow solid. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz) δ ppm 3.26 (br. s., 3 H) 3.36 - 3.71 (m, 3 H) 3.79 (s, 3 H) 6.88 (d, *J*=8.20 Hz, 1 H) 6.92 (t, *J*=7.88 Hz, 1 H) 7.22 (d, *J*=6.94 Hz, 1 H) 7.30 (td, *J*=7.88, 1.70 Hz, 1 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) δ ppm 32.59 (CH<sub>3</sub>) 55.82 (CH<sub>3</sub>) 61.10 (CH<sub>3</sub>) 111.24 (CH) 120.54 (CH) 125.37 (C) 127.74 (CH) 130.71 (CH) 155.89 (C) 169.66 (C) **GC-MS** (EI) 195 ([M]<sup>+</sup>, 1%), 135 (100%), 120 (4%), 92 (18%), 77 (26%), 51 (4%),



**N-methoxy-3-(2-methoxyphenyl)-N-methylpropanamide (1h)** (7.78 g, 87%) was prepared according to the representative procedure from 3-(2-methoxyphenyl)propanoyl chloride (7.946 g, 40 mmol) giving the pure Weinreb amide as a colorless oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.71 (t, *J*=7.25 Hz, 2 H) 2.95 (t, *J*=8.20 Hz, 2 H) 3.17 (s, 3 H) 3.61 (s, 3 H) 3.82 (s, 3 H) 6.84 (d, *J*=7.57 Hz, 1 H) 6.88 (t, *J*=7.88 Hz, 1 H) 7.14 - 7.23 (m, 2 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) δ ppm 26.00 (CH<sub>2</sub>) 32.18 (CH<sub>2</sub>) 32.20 (CH<sub>3</sub>) 55.30 (CH<sub>3</sub>) 61.25 (CH<sub>3</sub>) 110.33 (CH) 120.58 (CH) 127.57 (CH) 129.69 (C) 130.22 (CH) 157.65 (C) 174.41 (C) **GC-MS** (EI) 223 ([M]<sup>+</sup>, 11%), 163 (27%), 135 (17%), 121 (100%), 105 (7%), 91 (40%), 77 (11%), 65 (7%), 44 (7%). **HRMS** (ESI+), calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>3</sub> [M+H]<sup>+</sup> 224.1287, found: 224.1278



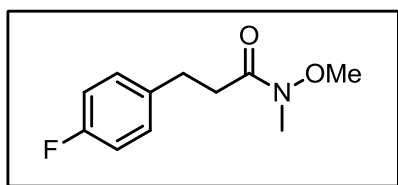
**N-methoxy-N-methyl-3-(o-tolyl)propanamide (1i)** (2.31 g, 68%) was prepared according to the representative procedure from 3-(o-tolyl)propanoyl chloride (3.00 g, 16.43 mmol) giving the pure Weinreb amide as a colorless oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.35 (s, 3 H) 2.70 (apparent triplet, *J*=8.10 Hz, 2 H) 2.96 (apparent triplet, *J*=8.00 Hz, 2 H) 3.20 (s, 3 H) 3.62 (s, 3 H) 7.06 - 7.22 (m, 4 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) δ ppm 19.44 (CH<sub>3</sub>) 28.32 (CH<sub>2</sub>) 32.39 (CH<sub>3</sub>) 32.73 (CH<sub>2</sub>) 61.39 (CH<sub>3</sub>) 126.30 (CH) 126.48 (CH) 128.96 (CH) 130.45 (CH) 136.20 (C) 139.62 (C) 173.98 (C) **GC-MS** (EI) 207 ([M]<sup>+</sup>, 0.1%), 147 (6%), 119 (41%), 105 (100%), 91 (17%), 77 (14%), 61 (32%), 39 (3%). **HRMS** (ESI+), calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 208.1338, found: 208.1313



***N*-methoxy-3-(3-methoxyphenyl)-*N*-methylpropanamide<sup>9</sup> (1j)**

(3.11 g, 60%) was prepared according to the representative procedure from 3-(3-methoxyphenyl)propanoyl chloride (4.86 g, 23.31 mmol) giving the pure Weinreb amide as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.73 (*apparent triplet*, *J*=7.60 Hz, 2 H) 2.93 (*apparent triplet*, *J*=8.30 Hz, 2 H) 3.17 (s, 3 H) 3.60 (s, 3 H)

3.78 (s, 3 H) 6.74 (d, *J*=8.07 Hz, 1 H) 6.77 (s, 1 H) 6.81 (d, *J*=7.58 Hz, 1 H) 7.19 (t, *J*=7.82 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 30.89 (CH<sub>2</sub>) 32.36 (CH<sub>3</sub>) 33.85 (CH<sub>2</sub>) 55.30 (CH<sub>3</sub>) 61.38 (CH<sub>3</sub>) 111.57 (CH) 114.36 (CH) 120.94 (CH) 129.61 (CH) 143.14 (C) 159.86 (C) 173.84 (C) GC-MS (EI) 223 ([M]<sup>+</sup>, 25%), 163 (44%), 135 (61%), 121 (100%), 105 (14%), 91 (32%), 77 (16%), 65 (10%).



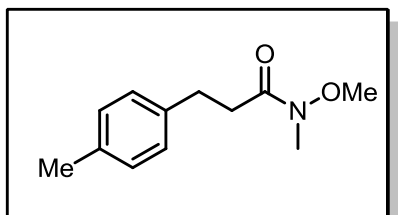
**3-(4-fluorophenyl)-*N*-methoxy-*N*-methylpropanamide (1k)**

(2.46 g, 66%) was prepared according to the representative procedure from 3-(4-fluorophenyl)propanoyl chloride (3.50 g, 18.75 mmol) giving the pure Weinreb amide as a colorless oil.

<sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.70 (*apparent triplet*,

*J*=7.30 Hz, 2 H) 2.92 (*apparent triplet*, *J*=8.60 Hz, 2 H) 3.16 (s, 3 H) 3.59 (s, 3 H) 6.95 (t, *J*=8.68 Hz, 2 H) 7.17 (dd, *J*=8.31, 5.62 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 30.02 (CH<sub>2</sub>) 32.39 (CH<sub>3</sub>) 33.98 (CH<sub>2</sub>) 61.41 (CH<sub>3</sub>) 115.36 (d, *J*<sub>C-C-F</sub>=20.54 Hz, CH) 130.06 (d, *J*<sub>C-C-F</sub>=8.07 Hz, CH) 137.18 (d, *J*<sub>C-C-C-F</sub>=3.67 Hz, C) 161.60 (d, *J*<sub>C-F</sub>=243.55 Hz, C-F) 173.66 (C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -119.41 - -119.31 (m, 160 F) -82.35 (s, 202 F)

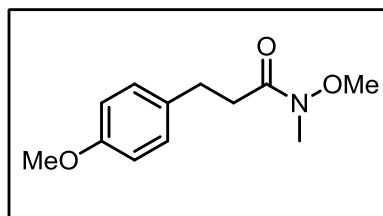
GC-MS (EI) 211 ([M]<sup>+</sup>, 14%), 151 (8%), 123 (36%), 109 (100%), 103 (14%), 83 (9%), 75 (6%), 61 (18%), 57 (3%). HRMS (ESI+), calcd for C<sub>11</sub>H<sub>14</sub>FNO<sub>2</sub> [M+H]<sup>+</sup> 212.1087 found: 212.1099



***N*-methoxy-3-(*p*-tolyl)-*N*-methylpropanamide (1l)**

(3.94 g, 62%) was prepared according to the representative procedure from 3-(*p*-tolyl)propanoyl chloride (5.60 g, 30.7 mmol) giving the pure Weinreb amide as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.32 (s, 3 H) 2.73 (*apparent triplet*, *J*=7.60 Hz, 2 H) 2.93 (*apparent triplet*, *J*=8.10 Hz, 2 H) 3.18 (s, 3 H)

3.61 (s, 3 H) 6.97 - 7.21 (m, 4 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 21.26 (CH<sub>3</sub>) 30.51 (CH<sub>2</sub>) 32.44 (CH<sub>3</sub>) 34.20 (CH<sub>2</sub>) 61.46 (CH<sub>3</sub>) 128.56 (CH) 129.39 (CH) 135.82 (C) 138.51 (C) 174.08 (C) GC-MS (EI) 207 ([M]<sup>+</sup>, 15%), 147 (11%), 119 (29%), 105 (100%), 91 (16%), 77 (12%), 65 (6%), 61 (9%), 39 (3%). HRMS (ESI+), calcd for C<sub>12</sub>H<sub>17</sub>NO<sub>2</sub> [M+H]<sup>+</sup> 208.1338, found: 208.1343



***N*-methoxy-3-(4-methoxyphenyl)-*N*-methylpropanamide<sup>10</sup>**

**(1m)** (5.11 g, 61%) was prepared according to the representative procedure from 3-(4-methoxyphenyl)propanoyl chloride (7.45 g, 37.5 mmol) giving the pure Weinreb amide as a colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.70

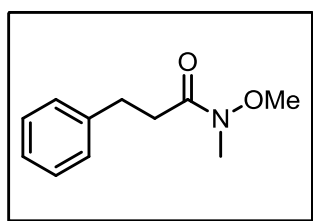
(apparent triplet, *J*=7.80 Hz, 2 H) 2.89 (apparent triplet, *J*=8.10

Hz, 2 H) 3.16 (s, 3 H) 3.59 (s, 3 H) 3.77 (s, 3 H) 6.82 (d, *J*=8.07 Hz, 2 H) 7.14 (d, *J*=8.31 Hz, 2

H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 30.01 (CH<sub>2</sub>) 32.38 (CH<sub>3</sub>) 34.22 (CH<sub>2</sub>) 55.45 (CH<sub>3</sub>)

61.41 (CH<sub>3</sub>) 114.06 (CH) 129.57 (CH) 133.60 (C) 158.16 (C) 174.01 (C) **GC-MS** (EI) 223

([M]<sup>+</sup>, 8%), 192(4%), 163 (4%), 135 (7%), 121 (100%), 105 (3%), 91 (11%), 77 (8%), 65 (4%).



***N*-methoxy-*N*-methyl-3-phenylpropanamide<sup>10</sup>** (**1n**) (10.74 g, 93%)

was prepared according to the representative procedure from 3-phenylpropanoyl chloride (10.1172 g, 60 mmol) giving the pure Weinreb amide as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm

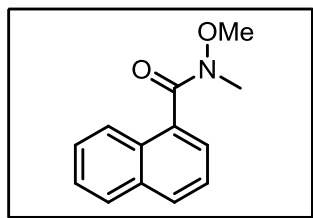
2.77 (t, *J*=7.60 Hz, 12 H) 2.99 (t, *J*=8.30 Hz, 2 H) 3.20 (s, 3 H) 3.61

(s, 3 H) 7.04 - 7.47 (m, 5 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm

30.50 (CH<sub>2</sub>) 31.92 (CH<sub>3</sub>) 33.56 (CH<sub>2</sub>) 60.93 (CH<sub>3</sub>) 125.91 (CH) 128.25 (2 x CH) 141.17 (C)

173.35 (C) **GC-MS** (EI) 193 ([M]<sup>+</sup>, 24%), 133 (20%), 105 (100%), 103 (16%), 91 (95%), 77

(24%), 65 (12%), 61 (18%), 51 (11%), 39 (5%).



***N*-methoxy-*N*-methylnaphthalene-1-carboxamide<sup>5</sup>** (**1p**) (8.17 g,

95%) was prepared according to the representative procedure from naphthalene-1-carbonyl chloride (7.625 g, 40 mmol) giving the pure Weinreb amide as a white solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ

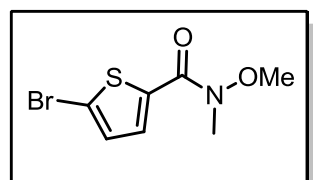
ppm 2.81 - 3.78 (overlapping s br, 6 H) 7.44 - 7.57 (m, 4 H) 7.82 -

7.95 (m, 3 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 33.06 (CH<sub>3</sub>)

61.06 (CH<sub>3</sub>) 124.13 (CH) 124.64 (CH) 124.74 (CH) 126.11 (CH) 126.71 (CH) 128.17 (CH)

129.39 (CH) 129.55 (C) 133.05 (C) 133.15 (C) 169.70 (C) **GC-MS** (EI) 215 ([M]<sup>+</sup>, 3%), 155

(100%), 127 (84%), 101 (5%), 77 (9%), 44 (8%).



**5-bromo-*N*-methoxy-*N*-methylthiophene-2-carboxamide** (**1q**)

(4.77 g, 38% over two steps<sup>a</sup>) was prepared according to the

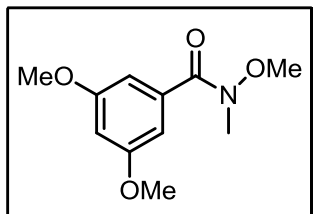
representative procedure from 5-bromothiophene-2-carboxylic acid (50 mmol) giving the pure Weinreb amide as a yellow oil. <sup>1</sup>H NMR

(CDCl<sub>3</sub>, 500 MHz) δ ppm 3.25 (s, 3 H) 3.68 (s, 3 H) 6.99 (d, *J*=4.21

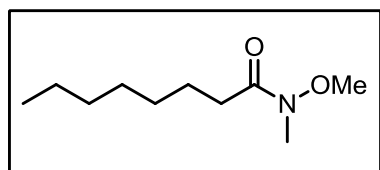
Hz, 1 H) 7.63 (d, *J*=4.21 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ

<sup>a</sup> Note that in the case of this substrate the acid chloride was prepared *in situ* in the reaction flask just prior to use.

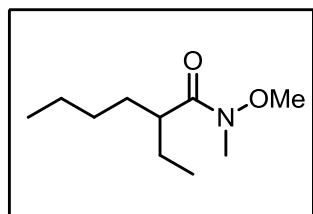
ppm 32.86 (CH<sub>3</sub>) 61.69 (CH<sub>3</sub>) 120.55 (C) 129.73 (CH) 133.53 (C) 134.64 (CH) 160.98 (C) **GC-MS** (EI) 251 ([M]<sup>+1</sup>, 9%), 250 ([M]<sup>+</sup>, 1%), 191 (100%), 189 (98%), 119 (7%), 117 (7%), 82 (28%), 44 (5%). **HRMS** (ESI+), calcd for C<sub>7</sub>H<sub>8</sub>BrNO<sub>2</sub>S [M + H]<sup>+</sup> 249.9537, found: 249.9528



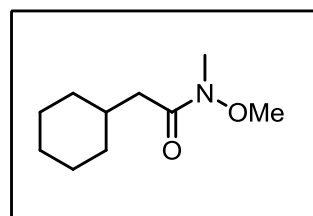
**N,3,5-trimethoxy-N-methylbenzamide**<sup>11</sup> (**1s**) (3.84 g, 69%) was prepared according to the representative procedure from 3,5-dimethoxybenzoyl chloride (5.016 g, 25 mmol) giving the pure Weinreb amide as a yellow oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz) δ ppm 3.28 (s, 1 H) 3.54 (s, 3 H) 3.75 (s, 3 H) 6.49 (s, 1 H) 6.74 (s, 2 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz) δ ppm 34.14 (CH<sub>3</sub>) 55.60 (CH<sub>3</sub>) 61.26 (CH<sub>3</sub>) 102.87 (CH) 106.04 (CH) 136.16 (C) 160.52 (C) 169.73 (C) **GC-MS** (EI) 225 ([M]<sup>+</sup>, 9%), 165 (100%), 137 (27%), 122 (24%), 107 (11%), 79 (6%), 77 (8%).



**N-methoxy-N-methyloctanamide**<sup>12</sup> (**1t**) (7.22 g, 96%) was prepared according to the representative procedure from octanoyl chloride (6.506 g, 40 mmol) giving the pure Weinreb amide as a colorless oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz) δ ppm 0.81 (t, *J*=6.90 Hz, 3 H) 1.16 - 1.32 (m, 8 H) 1.56 (quin, *J*=7.25 Hz, 2 H) 2.35 (t, *J*=7.25 Hz, 2 H) 3.11 (s, 3 H) 3.62 (s, 3 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) δ ppm 14.07 (CH<sub>3</sub>) 22.63 (CH<sub>2</sub>) 24.67 (CH<sub>2</sub>) 29.11 (CH<sub>2</sub>) 29.42 (CH<sub>2</sub>) 31.74 (CH<sub>2</sub>) 31.90 (CH<sub>2</sub>) 32.12 (CH<sub>2</sub>) 61.16 (CH<sub>3</sub>) 174.76 (C) **GC-MS** (EI) 187 ([M]<sup>+</sup>, 1%), 127 (60%), 109 (7%), 103 (11%), 61 (53%), 57 (100%), 55 (18%), 43 (25%), 41 (21%).

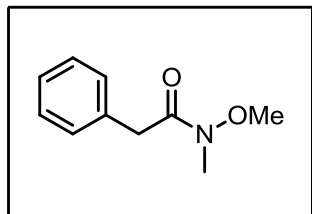


**2-ethyl-N-methoxy-N-methylhexanamide**<sup>13</sup> (**1u**) (7.14 g, 95%) was prepared according to the representative procedure from 2-ethylhexanoyl chloride (6.51 g, 40 mmol) giving the pure Weinreb amide as a colorless oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz) δ ppm 0.83 (t, *J*=7.80 Hz, 6 H) 1.13 - 1.33 (m, 4 H) 1.33 - 1.51 (m, 2 H) 1.53 - 1.66 (m, 2 H) 2.62 - 2.82 (broad s, 1 H) 3.16 (s, 3 H) 3.64 (s, 3 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 125 MHz) δ ppm 12.29 (CH<sub>3</sub>) 14.15 (CH<sub>3</sub>) 23.05 (CH<sub>2</sub>) 25.88 (CH<sub>2</sub>) 30.09 (CH<sub>2</sub>) 32.37 (CH<sub>2</sub>) 42.58 (CH<sub>3</sub>) 47.23 (CH) 61.55 (CH<sub>3</sub>) 178.20 (C) **GC-MS** (EI) 187 ([M]<sup>+</sup>, .01%), 127 (21%), 99 (12%), 57 (100%), 55 (15%), 43 (15%), 40 (54%).



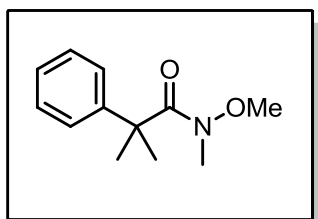
**2-cyclohexyl-N-methoxy-N-methylacetamide**<sup>14</sup> (**1v**) (6.40 g, 86%) was prepared according to the representative procedure from 2-cyclohexylethanoyl chloride (6.426 g, 40 mmol) giving the Weinreb amide as a colorless oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 500 MHz) δ ppm 0.87 (qd, *J*=12.19, 3.15 Hz, 2 H) 1.05 (apparent q, 1 H) 1.19 (apparent q, 2 H) 1.53 - 1.69 (m, 5 H) 1.69 - 1.81 (m, 1 H) 2.20 (d, *J*=6.94 Hz, 2

H) 3.08 (s, 3 H) 3.58 (s, 3 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 26.18 ( $\text{CH}_2$ ) 26.32 ( $\text{CH}_2$ ) 32.05 ( $\text{CH}_3$ ) 33.39 ( $\text{CH}_2$ ) 34.52 ( $\text{CH}_2$ ) 39.36 (CH) 61.18 ( $\text{CH}_3$ ) 174.04 (C) **GC-MS** (EI) 185 ( $[\text{M}]^+$ , 2%), 125 (76%), 103 (22%), 97 (98%), 83 (22%), 73 (13%), 61 (35%), 55 (100%), 41 (24%), 39 (12%).



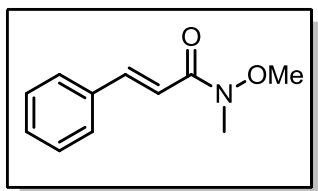
**N-methoxy-N-methyl-2-phenylacetamide**<sup>15</sup> (**1x**) (6.25 g, 87%) was prepared according to the representative procedure from 2-phenylacetyl chloride (6.184 g, 40 mmol) giving the pure Weinreb amide as a yellow oil.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  ppm 3.14 (s, 3 H) 3.55 (s, 3 H) 3.73 (s, 2 H) 7.17 - 7.22 (m, 1 H) 7.24 - 7.31 (m, 4 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  ppm 32.30 ( $\text{CH}_3$ ) 39.46 ( $\text{CH}_2$ )

61.34 ( $\text{CH}_3$ ) 126.84 (CH) 128.56 (CH) 129.38 (CH) 135.05 (C) 172.53 (C) **GC-MS** (EI) 179 ( $[\text{M}]^+$ , 3%), 119 (4%), 118 (32%), 91 (100%), 65 (14%), 61 (10%), 40 (28%).



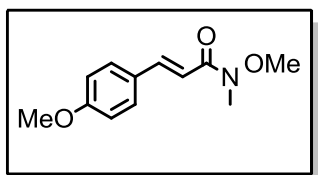
**N-methoxy-N,2-dimethyl-2-phenylpropanamide** (**1y**) (7.03 g, 88%) was prepared according to the representative procedure from 2-methyl-2-phenylpropanoyl chloride (7.08 g, 39 mmol) giving the pure Weinreb amide as a yellow oil.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  ppm 1.54 (s, 6 H) 2.64 (s, 3 H) 3.09 (s, 3 H) 7.19 (*apparent tt*,  $J=7.20$ , 1.30 Hz, 1 H) 7.25 - 7.28 (m, 2 H) 7.29 - 7.34 (m, 2 H)  $^{13}\text{C NMR}$

( $\text{CDCl}_3$ , 125 MHz)  $\delta$  ppm 26.81 ( $\text{CH}_3$ ) 33.60 ( $\text{CH}_2$ ) 47.01 (C) 59.08 ( $\text{CH}_3$ ) 125.72 (CH) 126.26 (CH) 128.46 (C) 146.28 (C) 177.91 (C) **GC-MS** (EI) 207 ( $[\text{M}]^+$ , 3%), 147 (8%), 119 (100%), 103 (8%), 91 (43%), 77 (10%), 40 (12%). **HRMS** (ESI+), calcd for  $\text{C}_{12}\text{H}_{17}\text{NO}_2$   $[\text{M}+\text{H}]^+$  208.1338, found: 208.1334



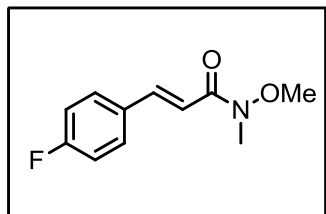
**N-methoxy-N-methylcinnamide**<sup>16</sup> (**1aa**) (3.46 g, 91%) was prepared according to the representative procedure from *trans*-cinnamoyl chloride (3.332 g, 20 mmol) giving the pure Weinreb amide as a white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm 3.31 (s, 3 H) 3.77 (s, 3 H) 7.04 (d,  $J=15.89$  Hz, 1 H) 7.35 - 7.40 (m, 3 H) 7.57 (*apparent d*,  $J=7.58$  Hz, 2 H) 7.74 (d,  $J=15.89$  Hz, 1 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 32.79 ( $\text{CH}_3$ )

62.16 ( $\text{CH}_3$ ) 116.06 (CH) 128.32 (CH) 129.07 (CH) 130.11 (CH) 135.45 (C) 143.73 (CH) 167.24 (C) **GC-MS** (EI) 191 ( $[\text{M}]^+$ , 5%), 131 (100%), 103 (47%), 77 (27%), 51 (10%), 44 (42%), 40 (4%).



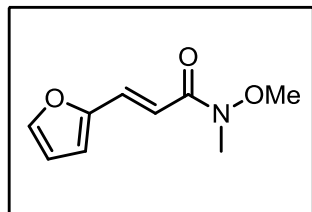
**(E)-N-methoxy-3-(4-methoxyphenyl)-N-methylacrylamide**<sup>17</sup> (**1bb**) (1.90 g, 86%) was prepared according to the representative procedure from 4-methoxycinnamoyl chloride (1.966 g, 10 mmol) giving the Weinreb amide as a colorless oil.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$

ppm 3.24 (s, 3 H) 3.69 (s, 3 H) 3.75 (s, 3 H) 6.80 - 6.89 (m, 3 H) 7.46 (d,  $J=8.80$  Hz, 2 H) 7.64 (d,  $J=15.65$  Hz, 1 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 32.55 ( $\text{CH}_3$ ) 55.37 ( $\text{CH}_3$ ) 61.85 ( $\text{CH}_3$ ) 113.40 (CH) 114.28 (CH) 127.91 (C) 129.69 (CH) 143.09 (CH) 161.10 (C) 167.37 (C) **GC-MS** (EI) 221 ( $[\text{M}]^+$ , 3%), 161 (100%), 133 (20%), 118 (8%), 103 (4%), 89 (8%), 77 (6%).



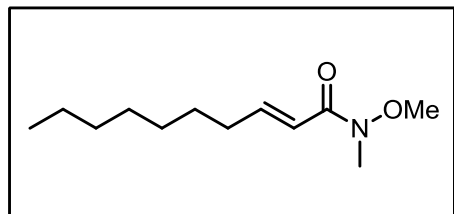
**(E)-3-(4-fluorophenyl)-N-methoxy-N-methylacrylamide<sup>18</sup> (1cc)** (4.06 g, 65%) was prepared according to the representative procedure from 4-fluorocinnamoyl chloride (5.538 g, 30 mmol) giving the pure Weinreb amide as a white solid.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  ppm 3.27 (s, 3 H) 3.73 (s, 3 H) 6.93 (d,  $J=15.76$  Hz, 1 H) 7.03 (t,  $J=8.51$  Hz, 2 H) 7.47 - 7.56 (m, 2 H) 7.66 (d,  $J=15.76$

Hz, 1 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  ppm 32.66 ( $\text{CH}_3$ ) 62.05 ( $\text{CH}_3$ ) 115.73 (CH) 116.04 (d,  $J_{\text{C-C-F}} = 21.08$  Hz, CH) 130.03 (d,  $J_{\text{C-C-C-F}} = 8.20$  Hz, CH) 131.58 (d,  $J_{\text{C-C-C-C-F}} = 3.70$  Hz, C) 142.29 (CH) 163.79 (d,  $J_{\text{C-F}} = 250.20$  Hz, C-F) 166.96 (C)  $^{19}\text{F NMR}$  ( $\text{CDCl}_3$ , 377 MHz) - 113.64 **GC-MS** (EI) 209 ( $[\text{M}]^+$ , 2%), 207 (9%), 149 (100%), 121 (35%), 101 (30%), 95 (5%), 75 (10%), 44 (23%).



**(E)-3-(furan-2-yl)-N-methoxy-N-methylprop-2-enamide<sup>19</sup> (1dd)** (1.15 g, 80%) was prepared according to the representative procedure from (E)-3-(furan-2-yl)prop-2-enoyl chloride (1.266 g, 8 mmol) giving the pure Weinreb amide as a brown oil.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm 3.22 (s, 3 H) 3.69 (s, 3 H) 6.46 (apparent doublet,  $J=54.30$  Hz, 2 H) 6.86 (apparent d,  $J=15.41$  Hz, 1 H) 7.35 - 7.50 (m, 2 H)  $^{13}\text{C}$

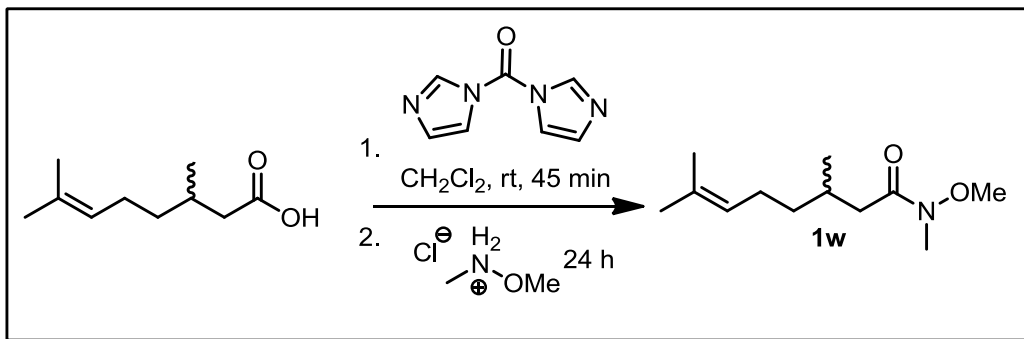
**NMR** ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 32.61 ( $\text{CH}_3$ ) 61.98 ( $\text{CH}_3$ ) 112.32 (CH) 113.72 (CH) 114.39 (CH) 129.96 (CH) 144.26 (CH) 151.76 (C) 167.05 (C) **GC-MS** (EI) 181 ( $[\text{M}]^+$ , 7%), 121 (100%), 93 (4%), 65 (24%), 63 (4%), 39 (9%).



**(E)-N-methoxy-N-methyldec-2-enamide<sup>20</sup> (1ee)** (6.94 g, 82%) was prepared according to the representative procedure from (E)-dec-2-enoyl chloride (7.54 g, 40 mmol) giving the pure Weinreb amide as a yellow oil.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 500 MHz)  $\delta$  ppm 0.87 (t,  $J=6.94$  Hz, 3 H) 1.21 - 1.32 (m, 8 H) 1.46 (quin,  $J=6.90$  Hz, 2 H) 2.22

(q,  $J=7.15$  Hz, 2 H) 3.23 (s, 3 H) 3.69 (s, 3 H) 6.38 (d,  $J=15.13$  Hz, 1 H) 6.97 (dt,  $J=15.76$ , 6.90 Hz, 1 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 125 MHz)  $\delta$  ppm 14.24 ( $\text{CH}_3$ ) 22.81 ( $\text{CH}_2$ ) 28.50 ( $\text{CH}_2$ ) 29.25 ( $\text{CH}_2$ ) 29.33 ( $\text{CH}_2$ ) 31.95 ( $\text{CH}_2$ ) 32.56 ( $\text{CH}_3$ ) 32.69 ( $\text{CH}_2$ ) 61.81 ( $\text{CH}_3$ ) 118.78 (CH) 148.27 (CH) 167.34 (C) **GC-MS** (EI) 213 ( $[\text{M}]^+$ , 3%), 153 (100%), 83 (24%), 81 (15%), 69 (47%), 55 (82%), 43 (16%), 41 (23%).

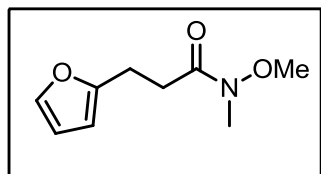




## General Procedure B: Weinreb Amides from Carboxylic Acid *via* CDI Activation<sup>21</sup>

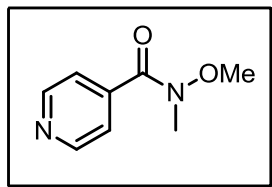
### *N*-methoxy-*N*,3,7-trimethyloct-6-enamide<sup>21</sup> (**1w**)

To a 250 mL round bottom flask equipped with stir bar was added (±)-citronellic acid (4.01 g, 23.5 mmol, 1 equiv) and DCM (80 mL  $\approx$  0.3M). To this stirred solution was added 1,1'-carbonyl diimidazole (4.19 g, 25.8 mmol, 1.1 equiv.) in one portion, turning the solution yellow and resulting in the evolution of CO<sub>2</sub> gas. The now yellow solution was allowed to stir for 45 minutes. At this time, *N*-*O*-dimethylhydroxylamine hydrochloride (2.52 g, 25.8 mmol, 1.1 equiv) was added all at once and the reaction mixture was stirred overnight. The reaction mixture was then quenched with 30 mL of 1 M HCl and stirred vigorously for 10 minutes. After this time, the solution was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with DCM (2 X 100 mL). The combine organic layers were washed with 1 M HCl (50 mL), deionized water (50 mL) and a 1:1 mixture of brine and a saturated sodium bicarbonate solution (100 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo* by rotary evaporation to afford the pure amide (3.98 g, 79.4%). **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm 0.90 (d,  $J=6.60$  Hz, 3 H) 1.09 - 1.23 (m, 1 H) 1.29 - 1.40 (m, 1 H) 1.55 (s, 3 H) 1.63 (s, 3 H) 1.86 - 2.05 (m, 3 H) 2.15 - 2.29 (m, 1 H) 2.29 - 2.44 (m, 1 H) 3.14 (s, 3 H) 3.63 (s, 3 H) 5.06 (t,  $J=6.97$  Hz, 1 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 17.81 (CH<sub>3</sub>) 19.99 (CH<sub>2</sub>) 25.73 (CH<sub>2</sub>) 25.88 (CH<sub>3</sub>) 29.73 (CH) 32.27 (CH<sub>3</sub>) 37.30 (CH<sub>2</sub>) 39.29 (CH<sub>2</sub>) 61.33 (CH<sub>3</sub>) 124.70 (CH) 131.44 (C) 174.51 (C) **GC-MS** (EI) 213 ([M]<sup>+</sup>, 1%), 153 (35%), 135 (6%), 130 (6%), 109 (62%), 83 (16%), 81 (18%), 73 (10%), 69 (100%), 67 (17%), 61 (62%), 55 (24%), 43 (14%), 41 (43%).



**3-(furan-2-yl)-*N*-methoxy-*N*-methylpropanamide (**1o**)** (3.40 g, 79%) was prepared according to the representative procedure from 3-(furan-2-yl)propanoic acid<sup>22</sup> (3.29g, 23.5 mmol) giving the pure Weinreb amide as a clear light brown oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm 2.77 (t,  $J=7.60$  Hz, 2 H) 2.98 (t,  $J=8.30$  Hz, 2 H) 3.18 (s, 3 H) 3.65 (s, 3 H) 6.03 (*apparent* dd,  $J=2.20, 1.00$  Hz, 1 H) 6.27 (dd,  $J=3.18, 1.96$  Hz, 1 H)

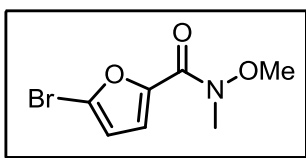
7.30 (dd,  $J=1.83, 0.86$  Hz, 1 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 23.21 ( $\text{CH}_2$ ) 30.55 ( $\text{CH}_2$ ) 32.35 ( $\text{CH}_3$ ) 61.38 ( $\text{CH}_3$ ) 105.38 (CH) 110.36 (CH) 141.18 (CH) 155.03 (C) 173.35 (C) **GC-MS** (EI) 183 ( $[\text{M}]^+$ , 20%), 123 (13%), 94 (12%), 81 (100%), 67 (10%), 61 (19%), 53 (10%). **HRMS** (ESI+), calcd for  $\text{C}_9\text{H}_{13}\text{NO}_3$   $[\text{M} + \text{H}]^+$  184.0973, found: 184.0975.



**N-methoxy-N-methylisonicotinamide**<sup>23</sup> (**1r**) (5.23 g, 78%) was prepared according to the representative procedure from isonicotinic acid (4.924 g, 40 mmol) with the following modifications<sup>24</sup>:

a) The reaction was stirred for 150 min; b) After the reaction was complete, the reaction was quenched with 225 mL of a  $\approx 1$  M NaOH solution. The aqueous layer was extracted with DCM (2 X 200 mL)

washed with brine (1 X 100 mL), dried with  $\text{Na}_2\text{SO}_4$  and the solvent was removed *in vacuo* via rotary evaporation to give the pure Weinreb amide as a yellow oil.  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm 3.13 (s, 3 H) 3.32 (s, 3 H) 7.30 (d,  $J=4.65$  Hz, 2 H) 8.48 (d,  $J=4.65$  Hz, 2 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 32.83 ( $\text{CH}_3$ ) 61.11 ( $\text{CH}_3$ ) 121.69 (CH) 141.48 (C) 149.63 (CH) 167.24 (C) **GC-MS** (EI) 166 ( $[\text{M}]^+$ , 5%), 135 (12%), 106 (100%), 78 (71%), 51 (31%), 50 (11%).

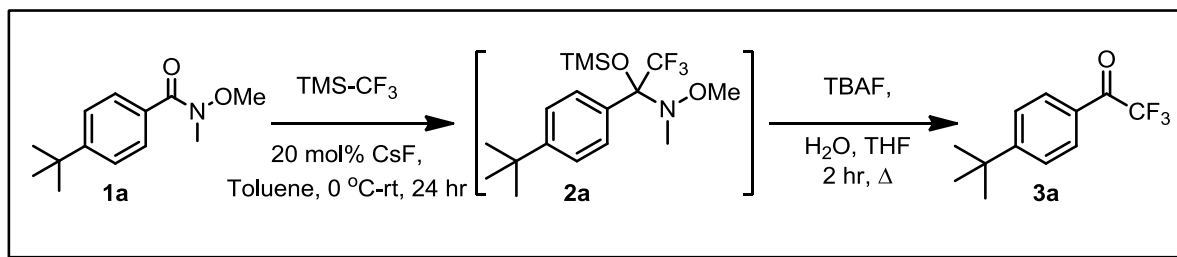


**5-bromo-N-methoxy-N-methylfuran-2-carboxamide**<sup>25</sup> (**1z**) (5.70 g, 70%) was prepared according to the representative procedure from 5-bromo-2-furanoic acid (6.69 g, 35 mmol) with the following modifications: a) The reaction was worked up six hours after addition of the *N-O*-dimethylhydroxylamine hydrochloride. The pure Weinreb

amide was obtained as a clear yellow oil  $^1\text{H NMR}$  ( $\text{CDCl}_3$ , 400 MHz)  $\delta$  ppm 3.17 (s, 3 H) 3.62 (s, 3 H) 6.32 (d,  $J=3.42$  Hz, 1 H) 6.94 (d,  $J=3.67$  Hz, 1 H)  $^{13}\text{C NMR}$  ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  ppm 32.98 ( $\text{CH}_3$ ) 61.34 ( $\text{CH}_3$ ) 113.54 (CH) 119.64 (CH) 126.31 (C) 147.57 (C) 157.75 (C) **GC-MS** (EI) 235 ( $[\text{M}]^+$ ,  $^{81}\text{Br}$  7%), 233 ( $[\text{M}]^+$ ,  $^{79}\text{Br}$  7%), 175 ( $^{81}\text{Br}$  98%), 173 ( $^{79}\text{Br}$  100%), 119 ( $^{81}\text{Br}$  24%), 117 ( $^{79}\text{Br}$  24%) 66 (16%) 38 (19%).



## General Procedure for Trifluoromethylketone Synthesis



### General Procedure A: Small Scale Synthesis of TFMKs:

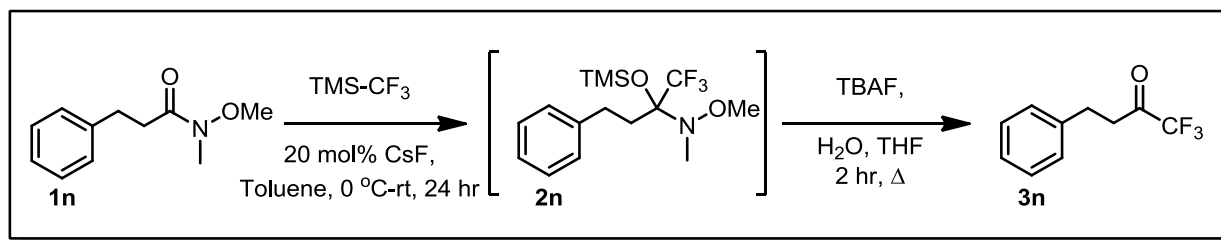
#### 1-(4-(*t*-butyl)phenyl)-2,2,2-trifluoroethanone<sup>26</sup> (3a)

To a 50 mL round bottom flask equipped with a stir bar was added CsF (0.1512 g, 1.0 mmol, 0.2 equiv). Toluene (2.5 mL) was added to the flask, followed by 4-(tert-butyl)-N-methoxy-N-methylbenzamide (1.11 g, 5.0 mmol, 1 equiv). The flask was sealed with a septum equipped with an inlet needle as an exit valve. The flask was cooled to 0 °C for 10 minutes. Once cooled, TMS-CF<sub>3</sub> (1.42 g, 10.0 mmol, 2 equiv) was added to the reaction mixture dropwise over a period of ≈ 10 minutes. After completion of addition, the reaction mixture was allowed to stir at 0 °C for 10 minutes. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature. **CAUTION: Upon reaching room temperature, the reaction occurs and is mildly exothermic and gas is evolved.** After completion of addition, the reaction mixture was allowed to stir at room temperature overnight. Reaction progress was monitored by <sup>1</sup>H NMR<sup>b</sup>. Note: Over this time period the solution became dark yellow to dark brown in color.

Once complete conversion to the silylated intermediate was confirmed, water (5 mL) followed by TBAF (5 mL, 1 M in THF, 1 equiv) were added to the reaction flask. The flask was equipped with a reflux condenser, open to air. The contents were then heated to 50 °C by either conventional or microwave methods, and allowed to stir at that temperature for 2 hours. Once cooled to room temperature, the reaction mixture were diluted with Et<sub>2</sub>O (≈ 30 mL), and transferred to a separatory funnel. The organic layer was washed with deionized water (3 X 30 mL), followed with a brine solution (1 X 30 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo* by rotary evaporation to yield crude trifluoromethylketone. Further purification was accomplished by flash chromatography (8:2 Hex:EtOAc) produced the pure CF<sub>3</sub> ketone as an orange solid (0.935 g, 81%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 1.36 (s, 9 H) 7.56 (d, *J*=8.80 Hz, 2 H) 8.02 (d, *J*=8.07 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 31.15 (CH<sub>3</sub>) 35.73 (C) 117.10 (q, *J*<sub>C-C-F</sub> = 289.80 Hz, CF<sub>3</sub>) 126.42 (CH) 127.64 (C) 130.45 (q, *J*<sub>C-C-C-F</sub> = 2.20 Hz, CH) 160.13 (C) 180.37 (q, *J*<sub>C-C-F</sub> = 34.50 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz)

<sup>b</sup> Most, if not all, substrates converted near quantitatively after stirring for 24 h.

$\delta$  ppm -74.73. **GC-MS** (EI) 230 ( $[M]^+$ , 15%), 215 (100%), 187 (32%), 161 (56%), 159 (11%), 146 (10%), 118 (24%), 115 (14%), 91 (12%), 77 (8%), 69 (3%), 57 (3%).



### Synthesis of TFMK Procedure B (Large Scale):

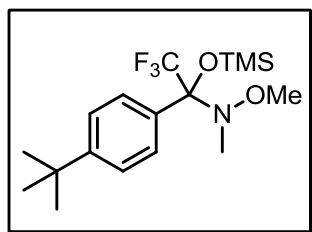
#### 1,1,1-trifluoro-4-phenylbutan-2-one<sup>27</sup> (3n)

To a 250 mL round bottom flask equipped with a stir bar was added CsF (0.820 g, 5.4 mmol, 0.2 equiv). Toluene (54 mL, 0.5 M in the Weinreb amide) was added to the flask, followed by *N*-methoxy-*N*-methyl-3-phenylpropanamide (5.30 g, 27 mmol, 1 equiv). The flask was sealed with a septum equipped with an inlet needle as an exit valve. The flask was cooled to 0 °C for 10 minutes. TMS-CF<sub>3</sub> (7.82 g, 55 mmol, 2 equiv) was added to the reaction mixture dropwise over a period of  $\approx$  10 minutes. After completion of addition, the reaction mixture was allowed to stir for 10 minutes. The cooling bath was removed and the reaction mixture was allowed to stir at room temperature. **CAUTION: Upon reaching room temperature, the reaction occurs and is mildly exothermic and gas is evolved.** After completion of addition, the reaction mixture was allowed to stir at room temperature overnight. Reaction progress was monitored by <sup>1</sup>H NMR<sup>c</sup>. *Note:* Over this time period the solution became dark yellow to dark brown in color.

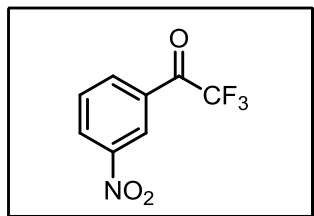
Once complete conversion to the silylated intermediate was confirmed, the toluene was removed *in vacuo* by rotary evaporation. Hexanes (20 mL), followed by Water (27 mL) followed by 1M solution of TBAF in THF (27 mL, 27 mmol, 1 equiv) were added to the reaction flask. The flask was equipped with a reflux condenser, open to air. The reaction mixture was then heated to 50 °C in an oil bath and allowed to stir 2 hours. Once cooled to room temperature, the reaction mixture were diluted with Et<sub>2</sub>O ( $\approx$  120 mL), and transferred to a separatory funnel. The organic layer was washed with deionized water (3 X 120 mL), followed with a brine solution (1 X 120 mL). The organic layer was dried with Na<sub>2</sub>SO<sub>4</sub> and the solvent was removed *in vacuo* by rotary evaporation to yield crude trifluoromethylketone. Further purification was accomplished Vacuum distillation (b.p. 77-80 °C @ 6 mmHg) afforded the pure CF<sub>3</sub> ketone as a clear colorless oil (4.16 g, 76%). <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz)  $\delta$  ppm 2.99 - 3.23 (m, 4 H) 7.28 - 7.38 (m, 3 H) 7.38 - 7.48 (m, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz)  $\delta$  ppm 28.49 (CH<sub>2</sub>) 38.24 (CH<sub>2</sub>) 115.83 (q, J<sub>C-F</sub> = 292.00 Hz, CF<sub>3</sub>) 126.89 (CH) 128.50 (CH) 128.94 (CH) 139.55 (C) 190.87 (q, J<sub>C-C-F</sub> = 35.20

<sup>c</sup> Most, if not all, substrates converted near quantitatively after stirring for 24 h.

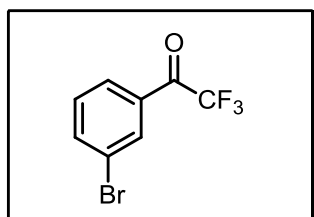
Hz, C) **<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.01 **GC-MS** (EI) 202 ([M]<sup>+</sup>, 38%), 133 (42%), 105 (37%), 103 (11%), 91 (100%), 77 (17%), 69 (6%), 65 (12%), 51 (11%), 39 (5%).



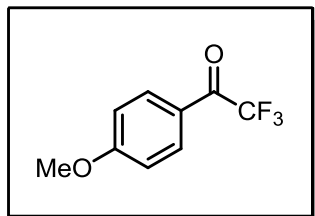
**N-(1-(4-(tert-butyl)phenyl)-2,2,2-trifluoro-1-((trimethylsilyloxy)ethyl)-N,O-dimethylhydroxylamine (2a)** (1.56 g, 86%) was prepared according to the representative procedure **A** from 4-(tert-butyl)-N-methoxy-N-methylbenzamide (1.11 g, 5 mmol) **with the following modifications:** prior to the cleavage step the contents were filtered and the toluene removed *in vacuo* to produce the intermediate as a brown oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 300 MHz) δ ppm 0.30 (s, 9 H) 1.34 (s, 9 H) 2.32 (s, 3 H) 3.60 (s, 3 H) 7.37 (d, *J*=8.48 Hz, 2 H) 7.55 (d, *J*=8.48 Hz, 2 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) δ ppm 2.27 (CH<sub>3</sub>) 31.61 (CH<sub>3</sub>) 34.82 (C) 36.94 (q, *J*<sub>C-N-C-C-F</sub> = 1.50 Hz, CH<sub>3</sub>) 59.66 (CH<sub>3</sub>) 93.49 (q, *J*<sub>C-C-F</sub> = 29.30 Hz, C) 123.99 (q, *J*<sub>C-F</sub> = 291.20 Hz, CF<sub>3</sub>) 125.11 (CH) 127.54 (CH) 134.86 (C) 152.09 (C) **<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 377 MHz) δ ppm -76.60 **GC-MS** (EI) 303 ([M]<sup>-60</sup>, 39%), 174 (5%), 161 (100%), 73 (23%). **HRMS** (ESI<sup>+</sup>), calcd for C<sub>17</sub>H<sub>28</sub>F<sub>3</sub>NO<sub>2</sub>Si [M- C<sub>2</sub>H<sub>6</sub>NO]<sup>+</sup> 303.1392, found: 303.1409.



**2,2,2-trifluoro-1-(3-nitrophenyl)ethanone<sup>28</sup> (3b)** (0.865 g, 78%) was prepared according to the representative procedure **A** from *N*-methoxy-*N*-methyl-3-nitrobenzamide (1.05 g, 5 mmol) (**4a**). Flash chromatography on deactivated silica (8:2 hexanes/EtOAc, 10% NEt<sub>3</sub>) afforded the pure CF<sub>3</sub> ketone as a yellow solid. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz) δ ppm 7.82 (t, *J*=8.07 Hz, 1 H) 8.40 (d, *J*=7.82 Hz, 1 H) 8.57 (dd, *J*=8.19, 0.86 Hz, 1 H) 8.88 (s, 1 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) δ ppm 116.47 (q, *J*<sub>C-F</sub> = 287.60 Hz, 6 CF<sub>3</sub>) 125.11 (m, CH) 129.86 (CH) 130.90 (CH) 131.33 (C) 135.54 (CH) 148.85 (C) 179.09 (q, *J*<sub>C-C-F</sub> = 35.90 Hz, C) **<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 377 MHz) δ ppm -74.89 **GC-MS** (EI) 150 (100%), 123 (10%), 104 (36%), 95 (10%), 76 (31%), 69 (5%), 50 (12%).

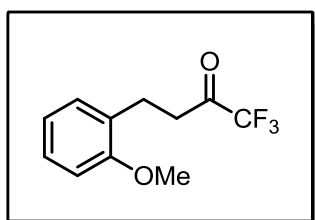


**1-(3-bromophenyl)-2,2,2-trifluoroethanone<sup>29</sup> (3c)** (0.908 g, 72%) was prepared according to the representative procedure **A** from 3-bromo-*N*-methoxy-*N*-methylbenzamide (1.220 g, 5 mmol) (**4a**). Flash chromatography (8:2 Hex/EtOAc) afforded the pure CF<sub>3</sub> ketone as a yellow oil. **<sup>1</sup>H NMR** (CDCl<sub>3</sub>, 400 MHz) δ ppm 7.45 (t, *J*=7.95 Hz, 1 H) 7.85 (d, *J*=9.05 Hz, 1 H) 8.01 (s, 1 H) 8.20 (s, 1 H) **<sup>13</sup>C NMR** (CDCl<sub>3</sub>, 100 MHz) δ ppm 116.65 (q, *J*<sub>C-F</sub> = 291.20 Hz, CF<sub>3</sub>) 123.64 (C) 128.79 (CH) 130.88 (CH) 131.81 (C) 133.08 (CH) 138.66 (CH) 179.60 (q, *J*<sub>C-C-F</sub> 35.90 Hz, C) **<sup>19</sup>F NMR** (CDCl<sub>3</sub>, 377 MHz) δ ppm -74.59 **GC-MS** (EI) 254 ([M]<sup>+2</sup>, 24%), 252 ([M]<sup>+</sup>, 25%), 185 (97%), 183 (100%), 157 (61%), 155 (63%), 76 (37%), 75 (34%), 74 (20%), 69 (9%), 50 (26%).



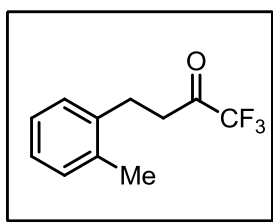
**2,2,2-trifluoro-1-(4-methoxyphenyl)ethanone<sup>30</sup> (3d)** (0.90 g, 88%) was prepared according to the representative procedure **A** from *N*,4-dimethoxy-*N*-methylbenzamide (0.976 g, 5 mmol) (**4a**). Flash chromatography (8:2 Hex/ EtOAc) afforded the pure CF<sub>3</sub> ketone as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 3.89 (s, 3 H) 6.98 (dd, *J*=9.05, 2.45 Hz, 2 H) 8.02 (d, *J*=8.07 Hz, 2 H) <sup>13</sup>C NMR

(CDCl<sub>3</sub>, 100 MHz) δ ppm 55.84 (CH<sub>3</sub>) 114.68 (CH) 117.21 (q, *J*<sub>C-C-F</sub> = 291.20 Hz, CF<sub>3</sub>) 122.98 (C) 132.95 (CH) 165.73 (C) 179.13 (q, *J*<sub>C-C-F</sub> = 34.50 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -73.82 **GC-MS** (EI) 204 ([M]<sup>+</sup>, 21%), 135 (100%), 107 (13%), 92 (24%), 77 (29%), 69 (4%), 64 (11%).



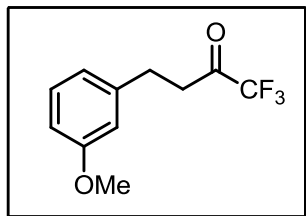
**1,1,1-trifluoro-4-(2-methoxyphenyl)butan-2-one (3h)** (3.46 g, 75%) was prepared according to the representative procedure **B** from *N*-methoxy-3-(2-methoxyphenyl)-*N*-methylpropanamide (4.425 g, 20 mmol) (**4a**). Vacuum distillation (b.p. 56-57 °C @ 0.3 mmHg) afforded the pure CF<sub>3</sub> ketone as a clear colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.74 - 3.22 (m, 4 H) 3.83 (s, 3 H) 6.85-

6.91 (m, 2H) 7.15 (d, *J*=7.34 Hz, 1 H) 7.23 (t, *J*=7.30 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 24.27 (CH<sub>2</sub>) 36.75 (CH<sub>2</sub>) 55.29 (CH<sub>3</sub>) 110.53 (CH) 115.88 (q, *J*<sub>C-F</sub> = 292.00 Hz, CF<sub>3</sub>) 120.82 (CH) 127.79 (C) 128.33 (CH) 130.37 (CH) 157.68 (C) 191.42 (q, *J*<sub>C-C-F</sub> = 35.20 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.11 **GC-MS** (EI) 232 ([M]<sup>+</sup>, 51%), 163 (9%), 121 (100%), 108 (12%), 91 (100%), 77 (13%), 69 (4%), 65 (13%), 51 (7%). **HRMS** (ESI+), calcd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup> 233.0789, found: 233.0777

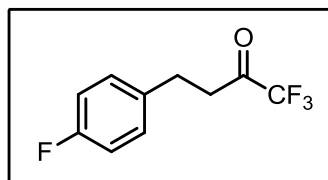


**1,1,1-trifluoro-4-(*o*-tolyl)butan-2-one (3i)** (1.51 g, 66%) was prepared according to the representative procedure **B** from *N*-methoxy-3-(*o*-tolyl)-*N*-methylpropanamide (2.2 g, 10.62 mmol) giving the pure Weinreb amide as a colorless oil. Vacuum distillation (b.p. 74-76 °C @ 2.5 mmHg) afforded the pure CF<sub>3</sub> ketone as a clear colorless oil. <sup>1</sup>H

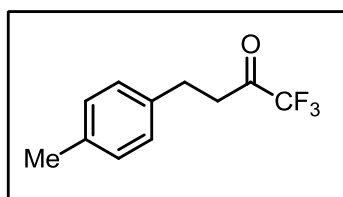
**NMR** (CDCl<sub>3</sub>, 500 MHz) δ ppm 2.36 (s, 3 H) 2.83 - 3.14 (m, 4 H) 7.14 - 7.23 (m, 4 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 19.45 (CH<sub>3</sub>) 25.97 (CH<sub>2</sub>) 37.06 (CH<sub>2</sub>) 115.85 (q, *J*<sub>C-F</sub> = 292.30 Hz, CF<sub>3</sub>) 126.62 (CH) 127.12 (CH) 128.76 (CH) 130.80 (CH) 136.15 (C) 137.62 (C) 191.02 (q, *J*<sub>C-C-F</sub> = 34.80 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.24 **GC-MS** (EI) 216 ([M]<sup>+</sup>, 30%), 147 (19%), 129 (17%), 119 (13%), 105 (100%), 91 (21%), 77 (17%), 69 (8%), 65 (8%). **HRMS** (ESI+), calcd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>O [M + H - H<sub>2</sub>O]<sup>+</sup> 199.0735, found: 199.0730



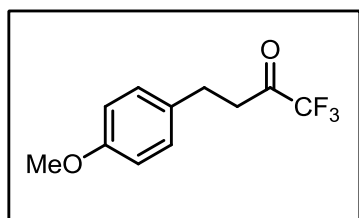
**1,1,1-trifluoro-4-(3-methoxyphenyl)butan-2-one (3j)** (6.07 g, 81%) was prepared according to the representative procedure **B** from *N*-methoxy-3-(3-methoxyphenyl)-*N*-methylpropanamide (7.20 g, 32.24 mmol). Vacuum distillation (b.p. 56-59 °C @ 0.1 mmHg) afforded the pure CF<sub>3</sub> ketone as a clear colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) 3.00 (*apparent triplet*, *J*=6.50 Hz, 2 H) 3.08 (*apparent triplet*, *J*=6.50 Hz, 2 H) 3.83 (s, 3 H) 6.76 - 6.84 (m, 3 H) 7.23 - 7.30 (m, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 28.59 (CH<sub>2</sub>) 38.26 (CH<sub>2</sub>) 55.44 (CH<sub>3</sub>) 112.18 (CH) 115.82 (q, *J*<sub>C-F</sub> = 289.90 Hz, CF<sub>3</sub>) 114.43 (CH) 120.80 (CH) 130.02 (CH) 141.12 (C) 160.15 (C) 190.89 (q, *J*<sub>C-C-F</sub> = 33.90 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.33 **GC-MS** (EI) 232 ([M]<sup>+</sup>, 78 %), 163 (14%), 135 (88%), 121 (100%), 105 (15%), 91 (56%), 77 (21%), 69 (10%). **HRMS** (ESI+), calcd for C<sub>11</sub>H<sub>11</sub>F<sub>3</sub>O<sub>2</sub> [M + H]<sup>+</sup> 233.0789, found: 233.0798



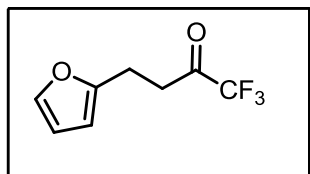
**1,1,1-trifluoro-4-(4-fluorophenyl)butan-2-one (3k)** (1.46 g, 61%) was prepared according to the representative procedure **B** from *N*-methoxy-3-(4-fluorophenyl)-*N*-methylpropanamide (2.30 g, 10.89 mmol) giving the pure Weinreb amide as a colorless oil. Vacuum distillation (b.p. 68-70 °C @ 3.0 mmHg) afforded the pure CF<sub>3</sub> ketone as a clear colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 2.97 (t, *J*=6.40 Hz, 2 H) 3.03 (t, *J*=6.10 Hz, 2 H) 6.99 (t, *J*=8.56 Hz, 2 H) 7.17 (dd, *J*=8.19, 5.50 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 27.78 (CH<sub>2</sub>) 38.37 (CH<sub>2</sub>) 115.77 (q, *J*<sub>C-F</sub> = 291.20 Hz, CF<sub>3</sub>) 115.78 (d, *J*<sub>C-C-F</sub> = 21.27 Hz, CH) 130.05 (d, *J*<sub>C-C-C-F</sub> = 7.34 Hz, CH) 135.18 (d, *J*<sub>C-C-C-C-F</sub> = 2.93 Hz, C) 161.96 (d, *J*<sub>C-F</sub> = 245.02 Hz, C-F) 190.78 (*J*<sub>C-C-F</sub>, *J* = 35.90 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -119.41 - -119.31 (m, 1 F) -82.35 (s, 3 F) **GC-MS** (EI) 220 ([M]<sup>+</sup>, 23%), 151 (28%), 123 (10%), 109 (100%), 96 (9%), 83 (10%), 69 (8%), 63 (3%). **HRMS** (ESI+), calcd for C<sub>10</sub>H<sub>8</sub>F<sub>4</sub>O [M + H - H<sub>2</sub>O]<sup>+</sup> 203.0484, found: 203.0489



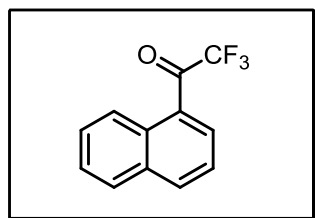
**1,1,1-trifluoro-4-(*p*-tolyl)butan-2-one<sup>31</sup> (3l)** (3.97 g, 78%) was prepared according to the representative procedure **B** from *N*-methoxy-3-(*p*-tolyl)-*N*-methylpropanamide (6.70 g, 47.1 mmol) giving the pure Weinreb amide as a colorless oil. Vacuum distillation (b.p. 68-71 °C @ 1.2 mmHg) afforded the pure CF<sub>3</sub> ketone as a clear colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 22.34 (s, 3 H) 2.97 (*apparent triplet*, *J*=6.80 Hz, 2 H) 3.04 (*apparent triplet*, *J*=6.60 Hz, 2H) 7.08 - 7.16 (m, 4 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 21.18 (CH<sub>3</sub>) 28.13 (CH<sub>2</sub>) 38.44 (CH<sub>2</sub>) 115.83 (q, *J*<sub>C-F</sub> = 292.00 Hz, CF<sub>3</sub>) 128.40 (CH) 129.64 (CH) 136.46 (C) 136.50 (C) 190.97 (q, *J*<sub>C-C-F</sub> = 35.20 Hz, CF<sub>3</sub>) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.24 **GC-MS** (EI) 216 ([M]<sup>+</sup>, 35%), 147 (22%), 119 (9%), 105 (100%), 91 (16%), 77 (14%), 69 (7%), 65 (6%).



**1,1,1-trifluoro-4-(4-methoxyphenyl)butan-2-one**<sup>31</sup> (**3m**) (9.28 g, 73%) was prepared according to the representative procedure **B** from *N*-methoxy-3-(4-methoxyphenyl)-*N*-methylpropanamide (12.27 g, 54.96 mmol). Vacuum distillation (b.p. 68-71 °C @ 0.2 mmHg) afforded the pure CF<sub>3</sub> ketone as a clear colorless oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ ppm 2.94 (*apparent triplet*, *J*=6.80 Hz, 2 H) 3.02 (*apparent triplet*, *J*=6.60 Hz, 2 H) 3.79 (s, 3 H) 6.85 (d, *J*=8.56 Hz, 2 H) 7.12 (d, *J*=8.56 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 27.73 (CH<sub>2</sub>) 38.61 (CH<sub>2</sub>) 55.49 (CH<sub>3</sub>) 115.77 (q, *J*<sub>C-F</sub>=292.00 Hz, CF<sub>3</sub>) 114.36 (CH) 129.51 (CH) 131.53 (C) 158.62 (C) 191.00 (q, *J*<sub>C-F</sub>=35.90 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.34 δ ppm **GC-MS** (EI) 232 ([M]<sup>+</sup>, 19%), 121(100%), 91 (13%), 77 (10%), 69 (4%), 65 (5%).

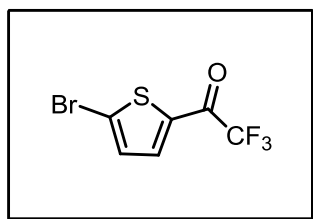


**1,1,1-trifluoro-4-(furan-2-yl)butan-2-one** (**3o**) (1.01 g, 52%) was prepared according to the representative procedure **B** from 3-(furan-2-yl)-*N*-methoxy-*N*-methylpropanamide (1.86 g, 0.01015) with the following modification: Flash chromatography (*Gradient Hex* to 8:2 Hex:EtOAc) afforded the pure CF<sub>3</sub> ketone as a clear light brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ ppm 3.03 (*apparent t*, *J*=6.90 Hz, 2 H) 3.09 (*apparent t*, *J*=6.30 Hz, 2 H) 6.05 (d, *J*=2.52 Hz, 11 H) 6.29 (t, *J*=2.50 Hz, 12 H) 7.31 (d, *J*=1.26 Hz, 11 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ ppm 21.17 (CH<sub>2</sub>) 35.11 (CH<sub>2</sub>) 106.17 (CH) 110.58 (CH) 115.81 (q, *J*<sub>C-F</sub>=290.50 Hz, CF<sub>3</sub>) 141.83 (CH) 152.90 (C) 190.50 (q, *J*<sub>C-C-F</sub>=35.90 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.21 **GC-MS** (EI) 192 ([M]<sup>+</sup>, 29%), 123 (24%), 95 (8%), 81 (100%), 69 (10%), 53 (21%), 39 (10%). **HRMS** (ESI+), calcd for C<sub>8</sub>H<sub>7</sub>F<sub>3</sub>O<sub>2</sub> [M+H]<sup>+</sup>193.0476, found: 193.0486

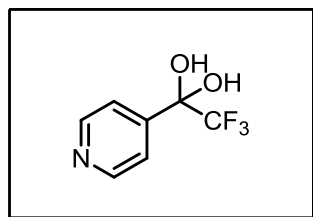


**2,2,2-trifluoro-1-(naphthalen-1-yl)ethanone**<sup>32</sup> (**3p**) (0.941 g, 84%) was prepared according to the representative procedure **A** from *N*-methoxy-*N*-methylnaphthalene-1-carboxamide (1.076 g, 5 mmol). Flash chromatography (8:2 hexanes/ CH<sub>2</sub>Cl<sub>2</sub>) produced the pure CF<sub>3</sub> ketone as a brown solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 7.55 (t, *J*=7.83 Hz, 1 H) 7.60 (t, *J*=7.60 Hz, 1 H) 7.70 (t, *J*=8.30 Hz, 1 H) 7.91 (d, *J*=8.31 Hz, 1 H) 8.13 (d, *J*=8.07 Hz, 1 H) 8.21 (d, *J*=7.58 Hz, 1 H) 8.87 (s, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 116.94 (q, *J*<sub>C-F</sub>= 293.40 Hz, CF<sub>3</sub>) 124.38 (CH) 125.44 (CH) 126.54 (C) 127.38 (CH) 129.25 (CH) 129.74 (CH) 131.44 (C) 131.95 (q, *J*<sub>C-C-C-F</sub>= 3.67 Hz,) 134.21 (C) 136.45 (CH) 182.54 (q, *J*<sub>C-C-F</sub>= 34.50 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -73.01 **GC-MS** (EI) 224 ([M]<sup>+</sup>, 31%), 155 (87%), 127 (100%), 101 (7%), 77 (11%), 69 (3%), 63 (10%).

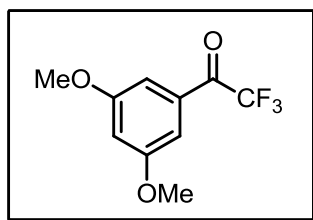




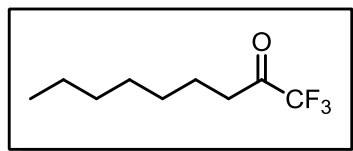
**1-(5-bromothiophen-2-yl)-2,2,2-trifluoroethanone<sup>33</sup> (3q)** (0.785 g, 63%) was prepared according to the representative procedure **A** from 5-bromo-*N*-methoxy-*N*-methylthiophene-2-carboxamide (1.251 g, 5 mmol) (**4a**). Flash chromatography (100 % Hex) afforded the pure CF<sub>3</sub> ketone as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 7.21 (d, *J*=4.16 Hz, 1 H) 7.69 (m, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 116.42 (q, *J*<sub>C-F</sub> = 292.00 Hz, CF<sub>3</sub>) 128.21 (C) 132.69 (CH) 137.10 (q, *J*<sub>C-C-C-F</sub> = 2.90 Hz, CH) 138.00 (C) 172.76 (q, *J*<sub>C-F</sub> = 36.70 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -75.33 **GC-MS** (EI) 260 ([M]<sup>+</sup>, 31%), 258 ([M]<sup>-</sup>, 30%), 191 (100%), 189 (99%), 163 (11%), 161 (11%), 119 (11%), 117 (11%), 82 (47%), 69 (14%), 57 (10%).



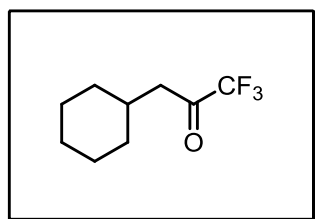
**2,2,2-trifluoro-1-(pyridin-4-yl)ethane-1,1-diol<sup>34</sup> (3r)** (0.865 g, 80%) was prepared according to the representative procedure **A** from *N*-methoxy-*N*-methylisonicotinamide (0.831 g, 5 mmol) *with the following modifications to the cleavage step*: Prior to the addition of TBAF/H<sub>2</sub>O, the reaction mixture was cooled to 0 °C. At this time 5 mL of deionized H<sub>2</sub>O was added to the flask followed by dropwise addition of 20 mL of a **0.25M** solution of TBAF **CAUTION: The first few drops induce a violent reaction and evolved gas therefore slow addition over 10 minutes is recommended.** The remained of the cleavage and subsequent workup was carried out as detailed in Procedure A. This afforded the pure CF<sub>3</sub> ketone in its hydrated form as a tan solid. <sup>1</sup>H NMR (Acetone-*d*<sub>6</sub>, 400 MHz) δ ppm 7.09 (br. s., 2 H) 7.66 (d, *J*=4.65 Hz, 2 H) 8.64 (d, *J*=4.65 Hz, 2 H) <sup>13</sup>C NMR (Acetone-*d*<sub>6</sub>, 100 MHz) δ ppm 93.34 (q, *J*<sub>C-C-F</sub> = 32.30 Hz, C) 124.11 (q, *J*<sub>C-F</sub> = 287.60 Hz, CF<sub>3</sub>) 123.00 (CH) 147.66 (C) 150.40 (CH) <sup>19</sup>F NMR (Acetone-*d*<sub>6</sub>, 377 MHz) δ ppm - 84.13 **GC-MS** (EI) 175 ([M]<sup>+</sup>, 38%), 106 (95%), 78 (100%), 69 (12%), 59 (12%), 51 (52%), 50 (20%), 44 (28%).



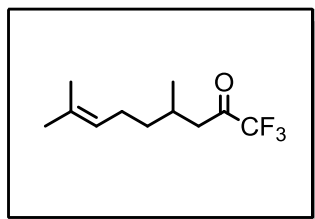
**1-(3,5-dimethoxyphenyl)-2,2,2-trifluoroethanone (3s)** (1.16 g, 99%) was prepared according to the representative procedure **A** from *N*,3,5-trimethoxy-*N*-methylbenzamide (1.113 g, 5 mmol) giving the pure CF<sub>3</sub> ketone as a light brown oil. No further purification was required. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 3.82 (s, 6 H) 6.75 (s, 1 H) 7.15 (s, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 55.83 (CH<sub>3</sub>) 107.91 (CH) 108.16 (CH) 116.86 (q, *J*<sub>C-F</sub> 291.20 Hz, CF<sub>3</sub>) 131.66 (C) 161.31 (C) 180.46 (q, *J*<sub>C-F</sub> = 35.20 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -73.91 **GC-MS** (EI) 234 ([M]<sup>+</sup>, 69%), 165 (100%), 137 (35%), 122 (49%), 107 (20%), 79 (11%), 77 (16%), 69 (11%), 63 (16%). **HRMS** (ESI+), calcd for C<sub>10</sub>H<sub>9</sub>F<sub>3</sub>O<sub>3</sub> [M+ H]<sup>+</sup> 235.0582, found: 235.0582



**1,1,1-trifluorononan-2-one<sup>35</sup> (3t)** (1.84 g, 59%) was prepared according to the representative procedure **B** from *N*-methoxy-*N*-methyloctanamide (3.00 g, 16 mmol) (**4a**). Vacuum distillation (b.p. 67-70 °C @ 12 mmHg) afforded the pure CF<sub>3</sub> ketone as a pale yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 0.87 (t, *J*=6.60 Hz, 3 H) 1.22 - 1.33 (m, 8 H) 1.66 (quin, *J*=6.97 Hz, 2 H) 2.69 (t, *J*=7.21 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 14.22 (CH<sub>3</sub>) 22.68 (CH<sub>2</sub>) 22.83 (CH<sub>2</sub>) 29.00 (CH<sub>2</sub>) 29.15 (CH<sub>2</sub>) 31.85 (CH<sub>2</sub>) 36.62 (CH<sub>2</sub>) 115.92 (q, *J*<sub>C-F</sub> = 292.00 Hz, CF<sub>3</sub>) 191.88 (q, *J*<sub>C-C-F</sub> = 33.70 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.51 GC-MS (EI) 127 (92%), 109 (7%), 84 (17%), 69 (41%), 57 (100%), 55 (43%), 43 (49%), 41 (50%), 39 (15%).

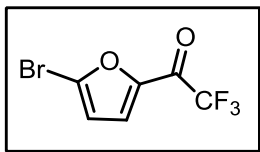


**3-cyclohexyl-1,1,1-trifluoropropan-2-one<sup>35</sup> (3v)** (1.82 g, 61%) was prepared according to the representative procedure **B** from 2-cyclohexyl-*N*-methoxy-*N*-methylacetamide (3.000 g, 16 mmol) (**4a**). Vacuum distillation (b.p. 55-57 °C @ 7 mmHg) afforded the pure CF<sub>3</sub> ketone as a pale yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 0.98 (apparent q, *J*=10.80 Hz, 2 H) 1.15 (apparent q, *J*=12.00 Hz, 1 H) 1.29 (apparent q, *J*=12.00 Hz, 2 H) 1.61 - 1.76 (m, 5 H) 1.86-1.99 (m, 1 H) 2.56 (d, *J*=6.85 Hz, 2 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 26.16 (CH<sub>2</sub>) 26.26 (CH<sub>2</sub>) 33.13 (CH<sub>2</sub>) 33.16 (CH) 44.04 (CH<sub>2</sub>) 115.82 (q, *J*<sub>C-C-F</sub> = 292.70 Hz, CF<sub>3</sub>) 191.32 (q, *J*<sub>C-F</sub> = 34.50 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.51 GC-MS (EI) 194 ([M]<sup>+</sup>, .01%), 125 (73%), 97 (72%), 82 (87%), 69 (24%), 67 (51%), 55 (100%), 41 (37%), 39 (20%).

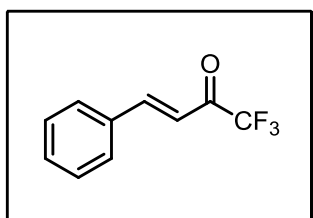


**1,1,1-trifluoro-4,8-dimethylnon-7-en-2-one<sup>36</sup> (3w)** (0.538 g, 48%) was prepared according to the representative procedure **A** from *N*-methoxy-*N*,3,7-trimethyloct-6-enamide (1.067 g, 5 mmol) (<sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ ppm 0.96 (d, *J*=6.94 Hz, 3 H) 1.22 - 1.42 (m, 2 H) 1.60 (s, 3 H) 1.69 (d, *J*=1.26 Hz, 3 H) 1.91 - 2.07 (m, 2 H) 2.12 (sxt, *J*=6.30 Hz, 1 H) 2.48 - 2.58 (m, 1 H) 2.70 (dd, *J*=17.97, 5.36 Hz, 1 H) 5.07 (t, *J*=7.40 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 17.81 (CH<sub>3</sub>) 19.68 (CH<sub>3</sub>) 25.61 (CH<sub>2</sub>) 25.88 (CH<sub>3</sub>) 28.29 (CH) 36.86 (CH<sub>2</sub>) 43.72 (CH<sub>2</sub>) 115.83 (q, *J*<sub>C-F</sub> = 291.00 Hz, CF<sub>3</sub>) 124.06 (CH) 132.24 (C) 191.43 (q, *J*<sub>C-C-F</sub> = 34.50 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -82.59 GC-MS (EI) 222 ([M]<sup>+</sup>, 20%), 153 (7%), 109 (26%), 95 (26%), 83 (12%), 69 (100%), 67 (12%), 55 (35%), 43 (7%), 41 (53%), 39 (10%).

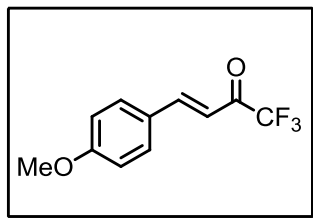




**1-(5-bromofuran-2-yl)-2,2,2-trifluoroethanone<sup>37</sup> (3z)** (2.75 g, 66%) was prepared according to the representative procedure **B** from 5-bromo-*N*-methoxy-*N*-methylfuran-2-carboxamide (4.00 g, 17.09 mmol) (**4a**). Vacuum distillation (b.p. 73-75 °C @ 8 mmHg) afforded the pure CF<sub>3</sub> ketone as a bright yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 500 MHz) δ ppm 6.64 (d, *J*=3.78 Hz, 1 H) 7.41 - 7.45 (m, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 116.28 (q, *J*<sub>C-F</sub> = 289.10 Hz, 3 C) 115.75 (CH) 126.29 (CH) 134.26 (C) 148.86 (C) 167.47 ((q, *J*<sub>C-C-F</sub> = 38.10 Hz, 4 C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -76.54 GC-MS (EI) 245 ([M]<sup>+</sup>, <sup>81</sup>Br 7%), 243([M]<sup>+</sup>, <sup>79</sup>Br 7%), 175 (<sup>81</sup>Br 97%), 173 (<sup>79</sup>Br 100%), 147 (<sup>81</sup>Br 6%), 147 (<sup>79</sup>Br 6%) 119 (<sup>81</sup>Br 35%), 117 (<sup>79</sup>Br 36%) 94 (8%) 69 (33%) 66 (19%) 38 (30%).

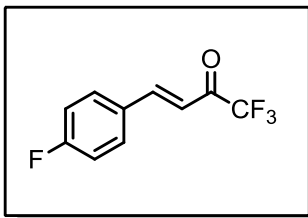


**(E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one<sup>38</sup> (3aa)** (.221 g, 22%) was prepared according to the representative procedure **A** from *N*-methoxy-*N*-methylcinnamide (0.956 g, 5 mmol) with the following modification: The cleavage was conducted at room temperature<sup>d</sup> rather than heating at 50 °C. Flash chromatography (8:2 Hex/EtOAc) afforded the pure CF<sub>3</sub> ketone as a yellow oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 7.03 (d, *J*=15.89 Hz, 1 H) 7.42 - 7.54 (m, 3 H) 7.65 (d, *J*=7.58 Hz, 2 H) 7.98 (d, *J*=15.89 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 116.69 (q, *J*<sub>C-F</sub> = 291.20 Hz, CF<sub>3</sub>) 116.89 (CH) 129.51 (2 X CH) 132.60 (CH) 133.59 (C) 150.44 (CH) 180.28 (q, *J*<sub>C-C-F</sub> = 35.20 Hz, C) <sup>19</sup>F NMR δ ppm (CDCl<sub>3</sub>, 377 MHz) -80.73 GC-MS (EI) 200 ([M]<sup>+</sup>, 50%), 131 (100%), 103 (85%), 77 (34%), 69 (6%), 51 (24%).



**(E)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one<sup>39</sup> (3bb)** (0.535 g, 46%) was prepared according to the representative procedure **A** from (*E*)-*N*-methoxy-3-(4-methoxyphenyl)-*N*-methylacrylamide (1.106 g, 5 mmol) with the following modification: The cleavage was conducted at room temperature<sup>d</sup> rather than heating at 50 °C. Flash chromatography (8:2 Hex/EtOAc) afforded pure CF<sub>3</sub> ketone as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 3.87 (s, 3 H) 6.88 (d, *J*=15.89 Hz, 1 H) 6.95 (d, *J*=8.80 Hz, 2 H) 7.60 (d, *J*=8.07 Hz, 2 H) 7.93 (d, *J*=15.89 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 55.77 (CH<sub>3</sub>) 114.28 (CH) 115.02 (CH) 116.84 (q, *J*<sub>C-F</sub> = 291.02 Hz, CF<sub>3</sub>) 126.43 (C) 131.66 (CH) 150.23 (CH) 163.48 (C) 180.15 (q, *J*<sub>C-C-F</sub> = 32.30 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -80.58 GC-MS (EI) 230 ([M]<sup>+</sup>, 37%), 161 (100%), 133 (34%), 118 (16%), 89 (16%), 69 (4%), 63 (10%).

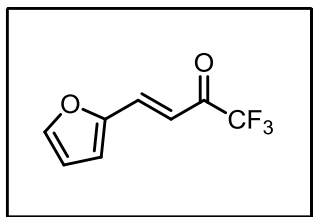
<sup>d</sup> Heating leads to decreased yield of the desired α,β-unsaturated CF<sub>3</sub> ketone and an increase in the undesired 1,4-addition product



**(E)-1,1,1-trifluoro-4-(4-fluorophenyl)but-3-en-2-one<sup>40</sup> (3cc)**

(0.450 g, 41%) was prepared according to the representative procedure **A** from (*E*)-3-(4-fluorophenyl)-*N*-methoxy-*N*-methylacrylamide (1.046 g, 5 mmol) with the following modification: The cleavage was conducted at room temperature rather than heating at 50 °C. Flash chromatography (9:1

Hex/EtOAc) afforded the pure CF<sub>3</sub> ketone as a yellow solid. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 6.95 (d, *J*=15.89 Hz, 1 H) 7.15 (t, *J*=8.44 Hz, 2 H) 7.66 (dd, *J*=8.56, 5.62 Hz, 2 H) 7.93 (d, *J*=15.89 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 125 MHz) δ ppm 116.65 (q, *J*<sub>C-F</sub>=289.80 Hz, CF<sub>3</sub>) 116.62 (CH) 116.84 (d, *J*<sub>C-C-F</sub>=22.01 Hz, CH) 129.96 (d, *J*<sub>C-C-C-F</sub>=2.94 Hz, C) 131.68 (d, *J*<sub>C-C-C-F</sub>=8.80 Hz, CH) 148.99 (CH) 165.40 (d, *J*=255.29 Hz, C-F) 180.14 (q, *J*<sub>C-C-F</sub>=35.20 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -80.70 (s, 3 F) -108.71 - -108.59 (m, 1 F) GC-MS (EI) 218 ([M]<sup>+</sup>, 30%), 149 (100%), 121 (51%), 101 (55%), 95 (10%), 75 (18%), 69 (8%).

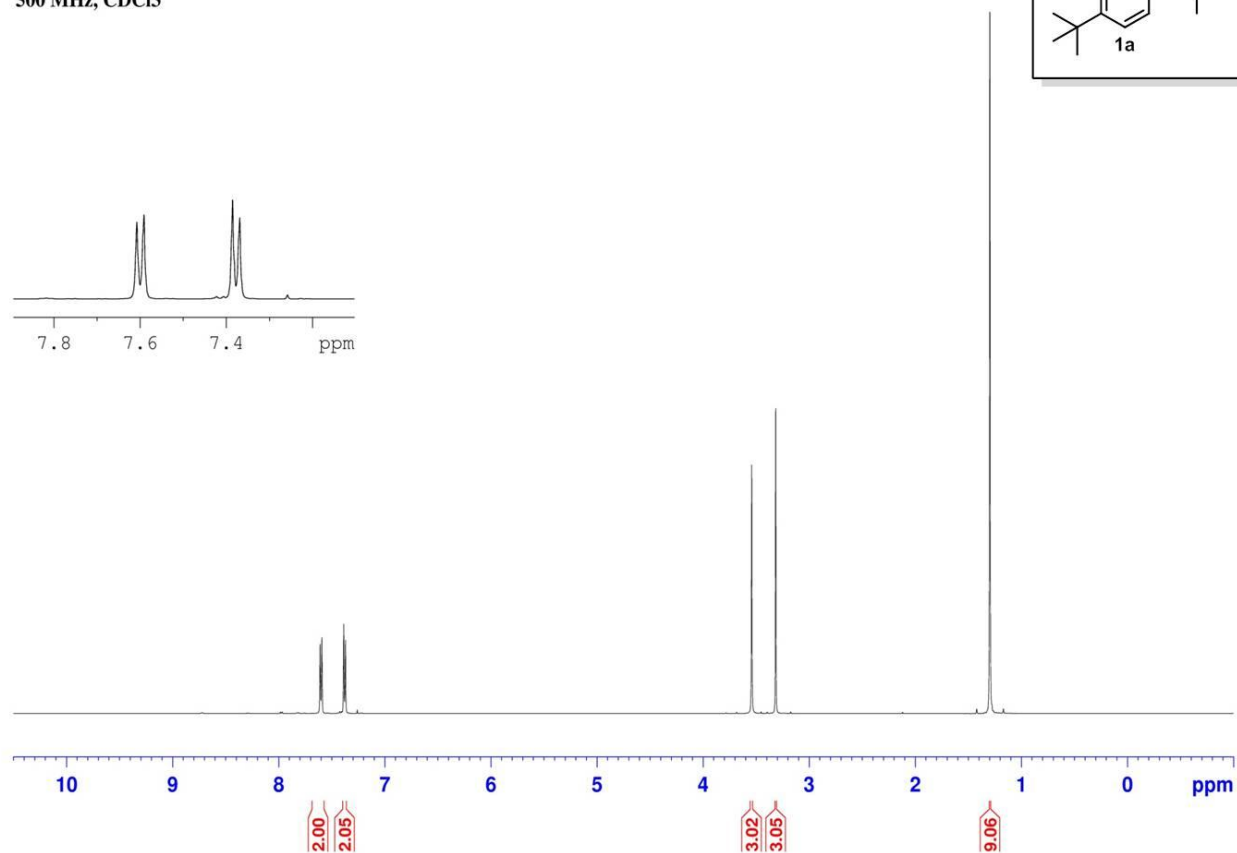
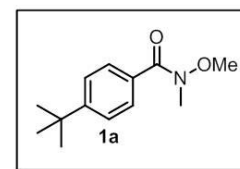


**(E)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one<sup>40</sup> (3dd)** (0.482 g, 51%) was prepared according to the representative procedure **A** from (*E*)-3-(furan-2-yl)-*N*-methoxy-*N*-methylprop-2-enamide (0.906 g, 5 mmol) with the following modification: The cleavage was conducted at room temperature<sup>d</sup> rather than heating at 50 °C. Flash

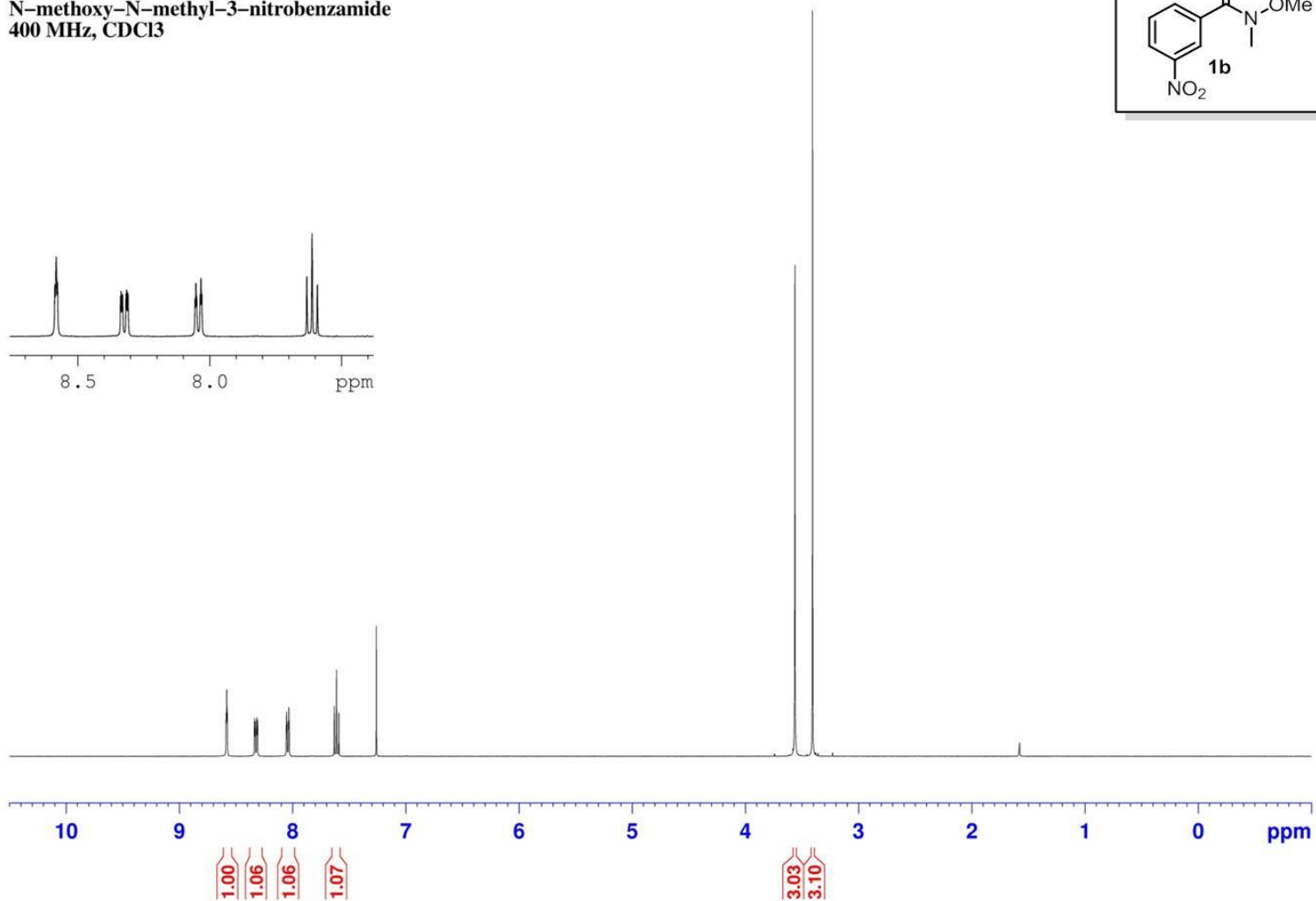
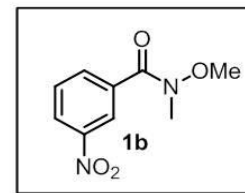
chromatography (*Gradient* 9:1 to 8:2 Hex:EtOAc) afforded the pure CF<sub>3</sub> ketone as a brown oil. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400 MHz) δ ppm 6.57 (dd, *J*=3.42, 1.71 Hz, 1 H) 6.85 - 6.93 (m, 2 H) 7.60 (d, *J*=0.49 Hz, 1 H) 7.68 (d, *J*=15.65 Hz, 1 H) <sup>13</sup>C NMR (CDCl<sub>3</sub>, 100 MHz) δ ppm 116.72 (q, *J*<sub>C-F</sub>=290.50 Hz, CF<sub>3</sub>) 113.71 (CH) 114.15 (CH) 120.21 (CH) 135.02 (CH) 147.26 (CH) 150.84 (C) 180.13 (*J*<sub>C-C-F</sub>=35.20 Hz, C) <sup>19</sup>F NMR (CDCl<sub>3</sub>, 377 MHz) δ ppm -80.69 GC-MS (EI) 190 ([M]<sup>+</sup>, 36%), 121 (100%), 93 (7%), 69 (9%), 65 (56%), 63 (12%), 39 (20%).

## <sup>1</sup>H-NMR Spectra of Synthesized Compounds

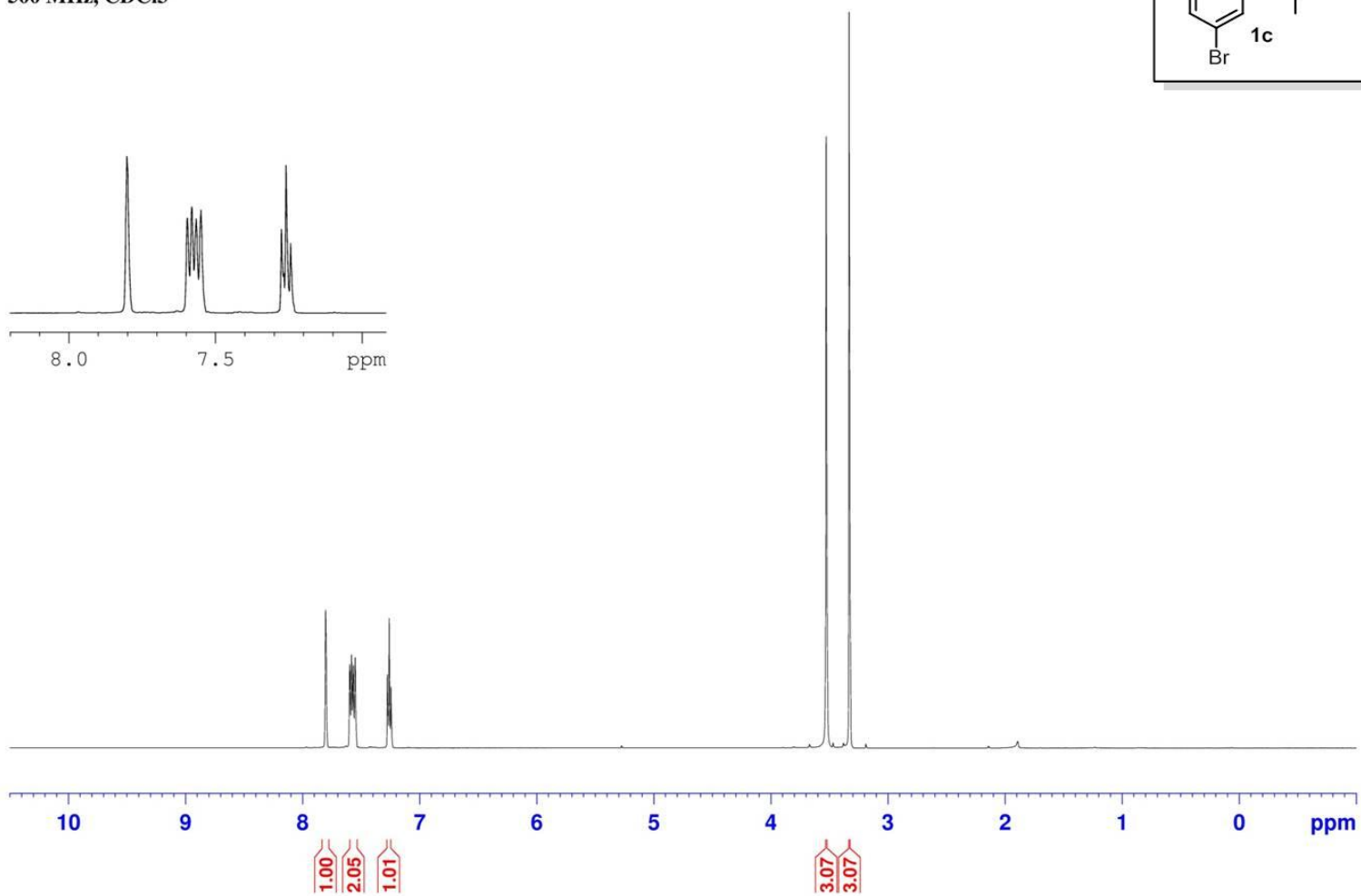
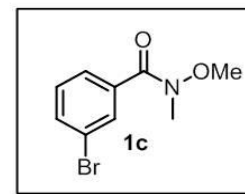
4-tert-butyl-N-methoxy-N-methylbenzamide  
500 MHz, CDCl<sub>3</sub>



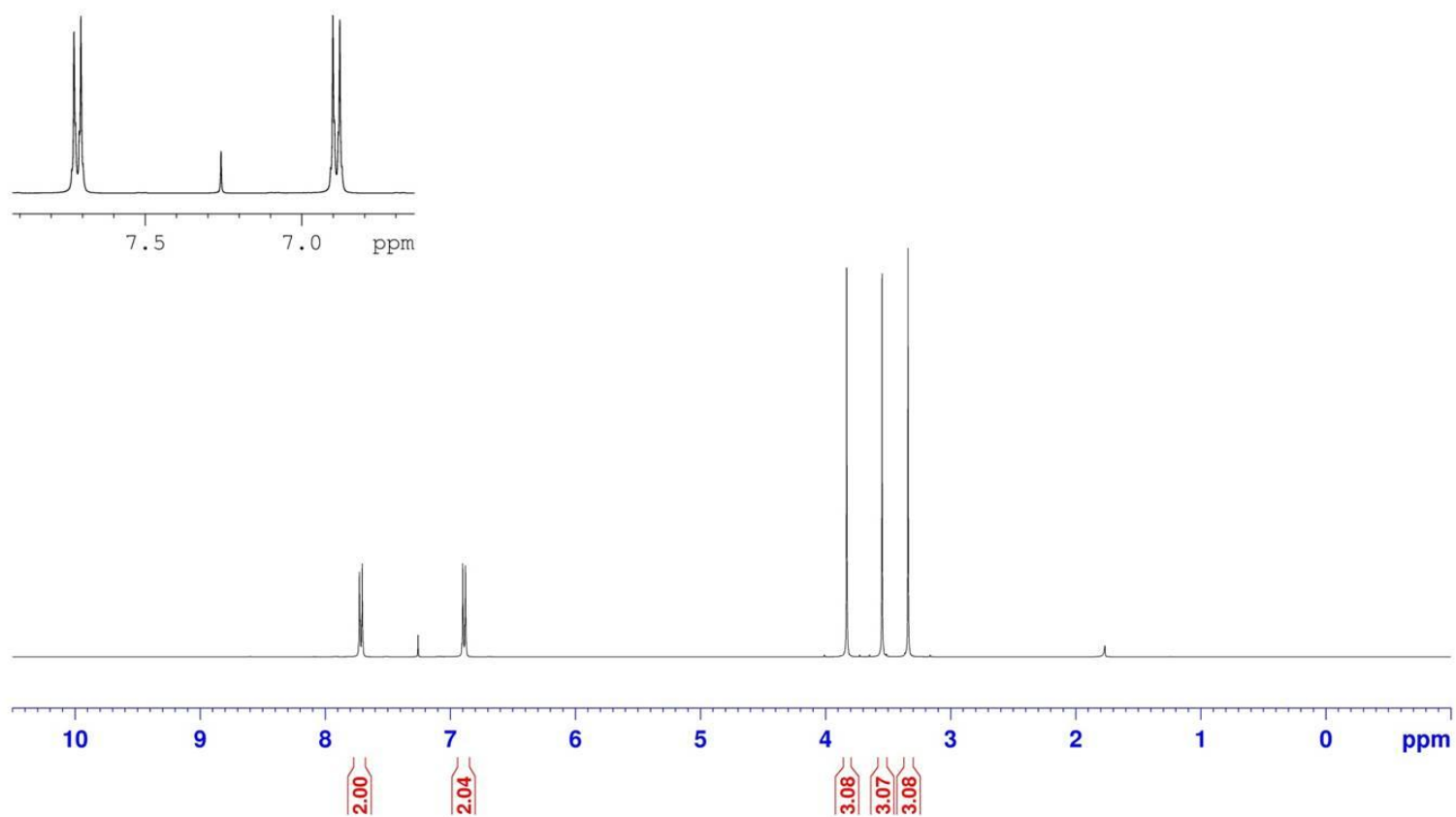
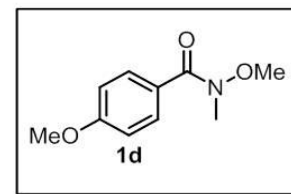
**N-methoxy-N-methyl-3-nitrobenzamide**  
400 MHz, CDCl<sub>3</sub>



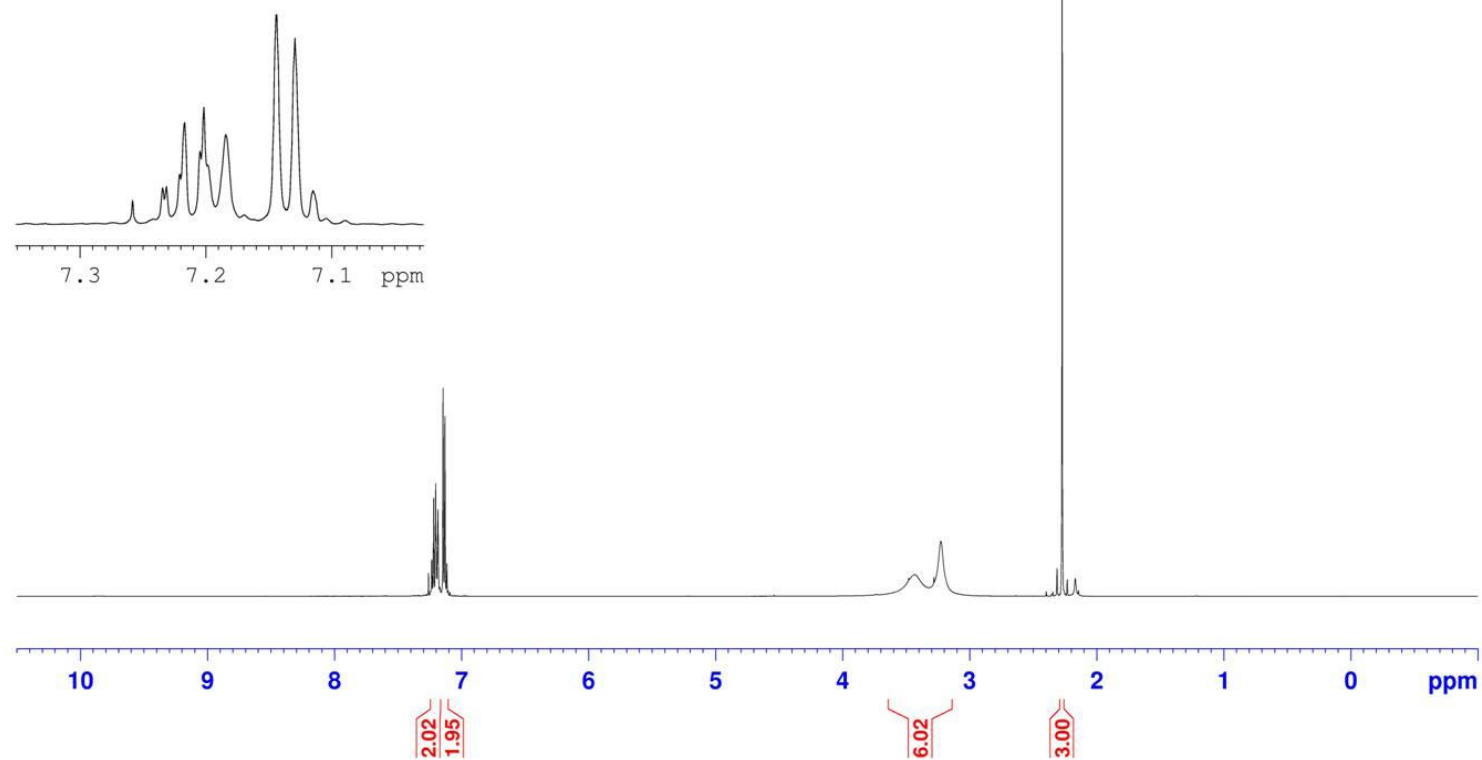
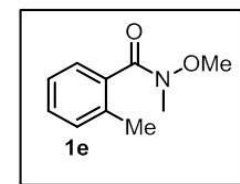
**3-bromo-N-methoxy-N-methylbenzamide**  
500 MHz, CDCl<sub>3</sub>



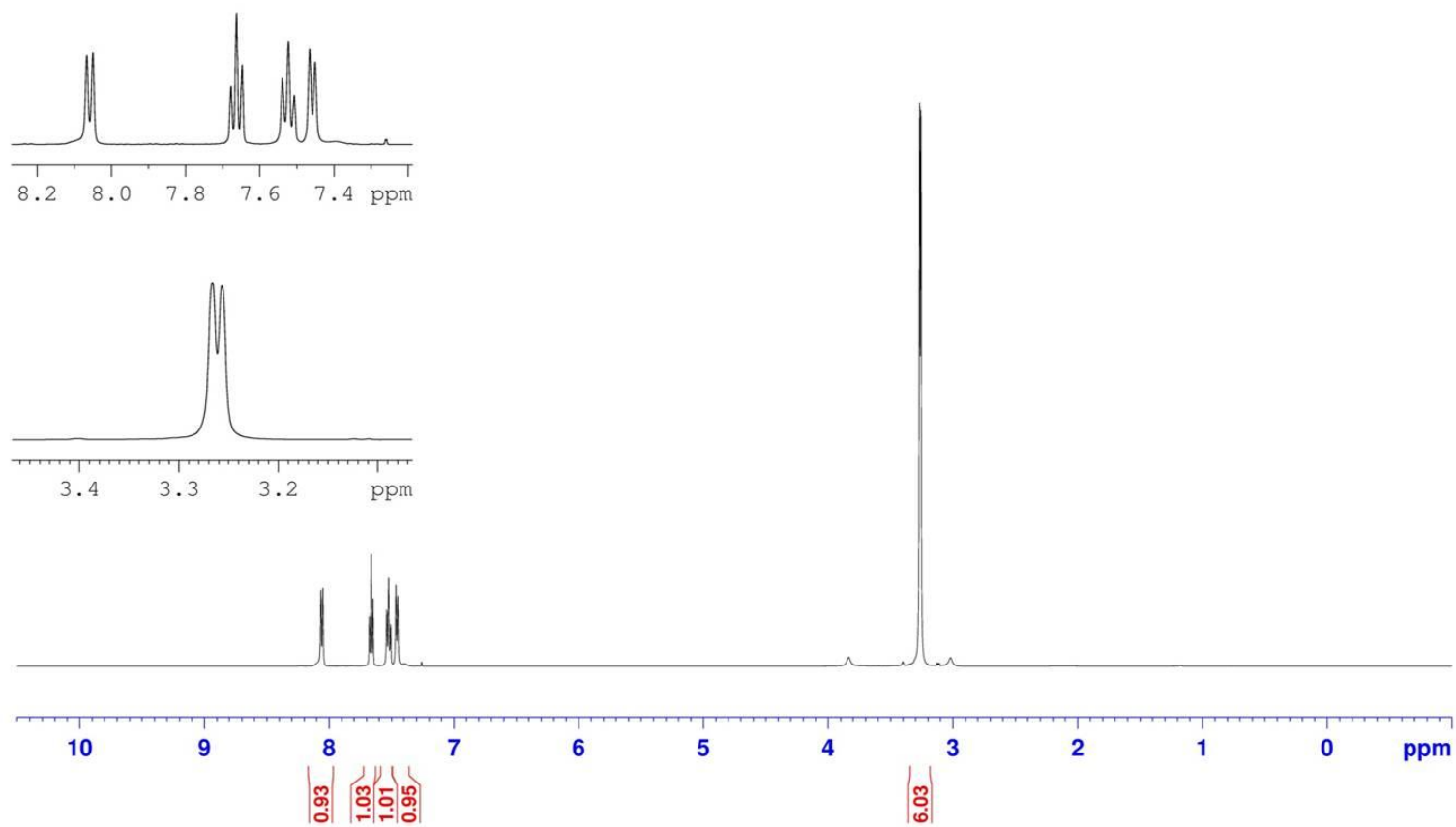
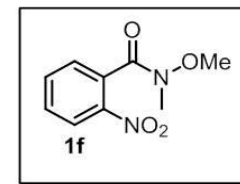
**N,4-dimethoxy-N-methylbenzamide**  
400 MHz, CDCl<sub>3</sub>



**N-methoxy-N,2-dimethylbenzamide**  
500 MHz, CDCl<sub>3</sub>

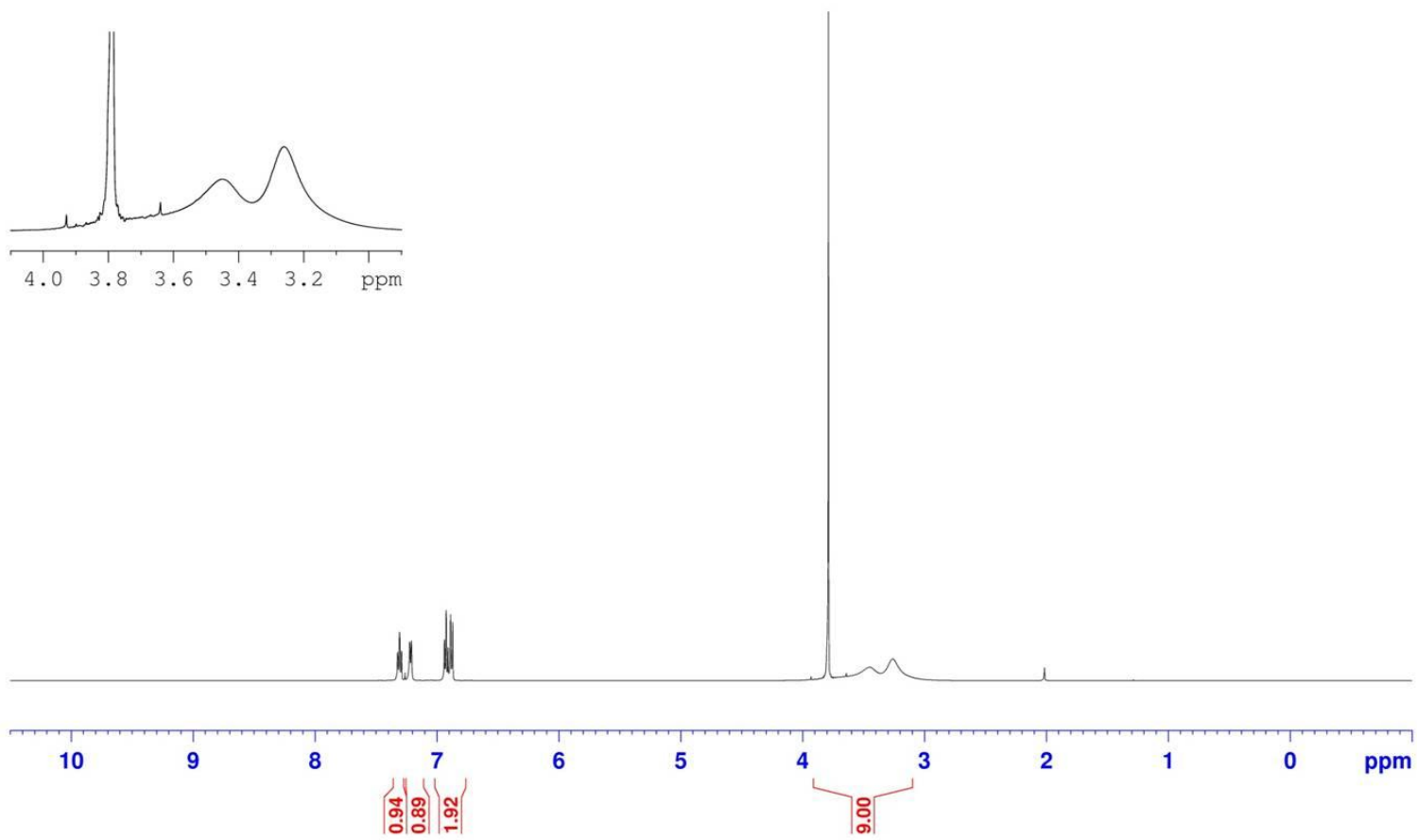
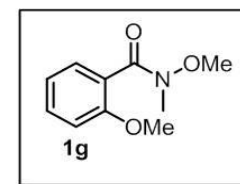


**N-methoxy-N-methyl-2-nitrobenzamide**  
500 MHz, CDCl<sub>3</sub>

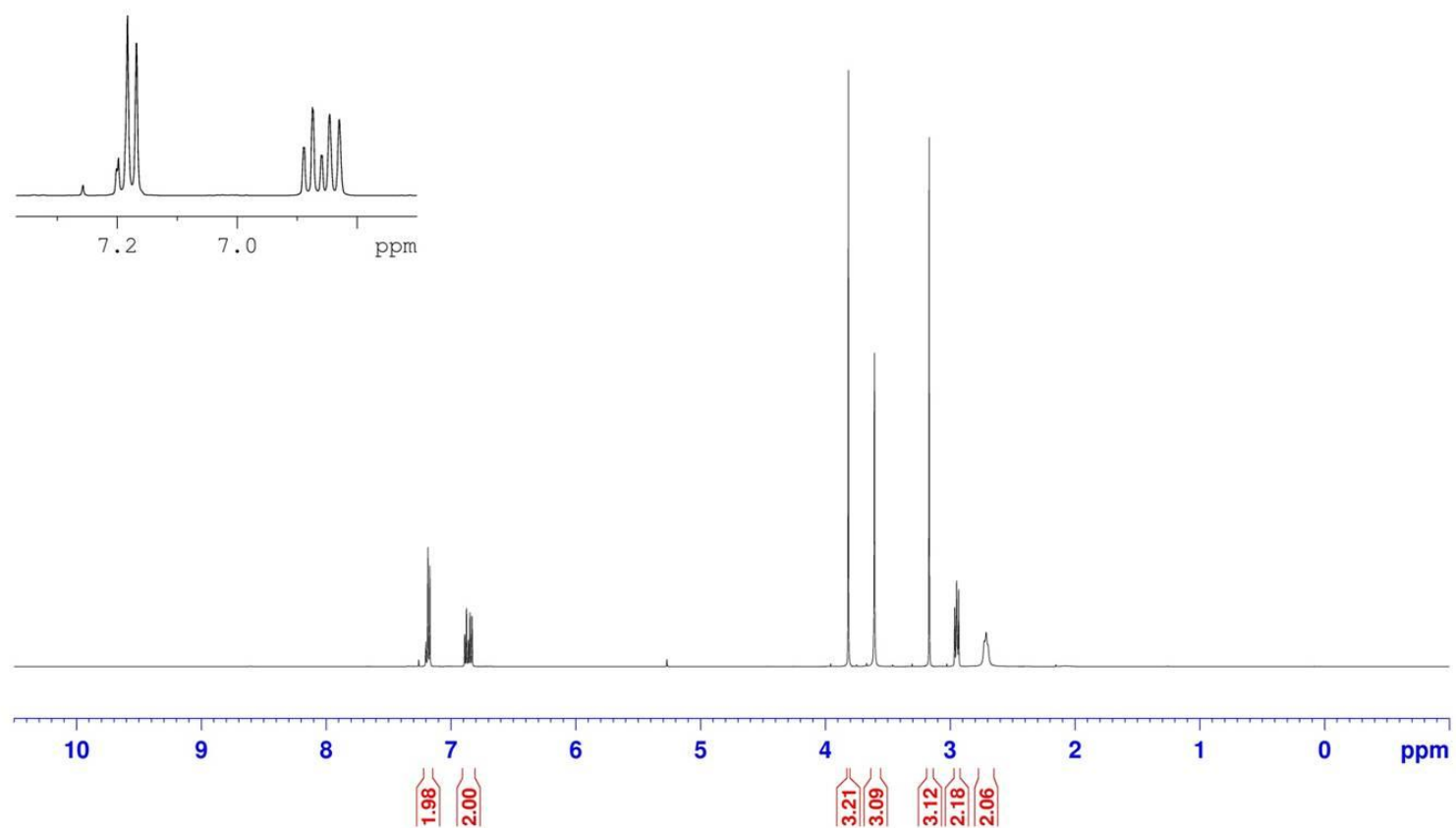
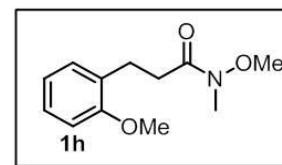




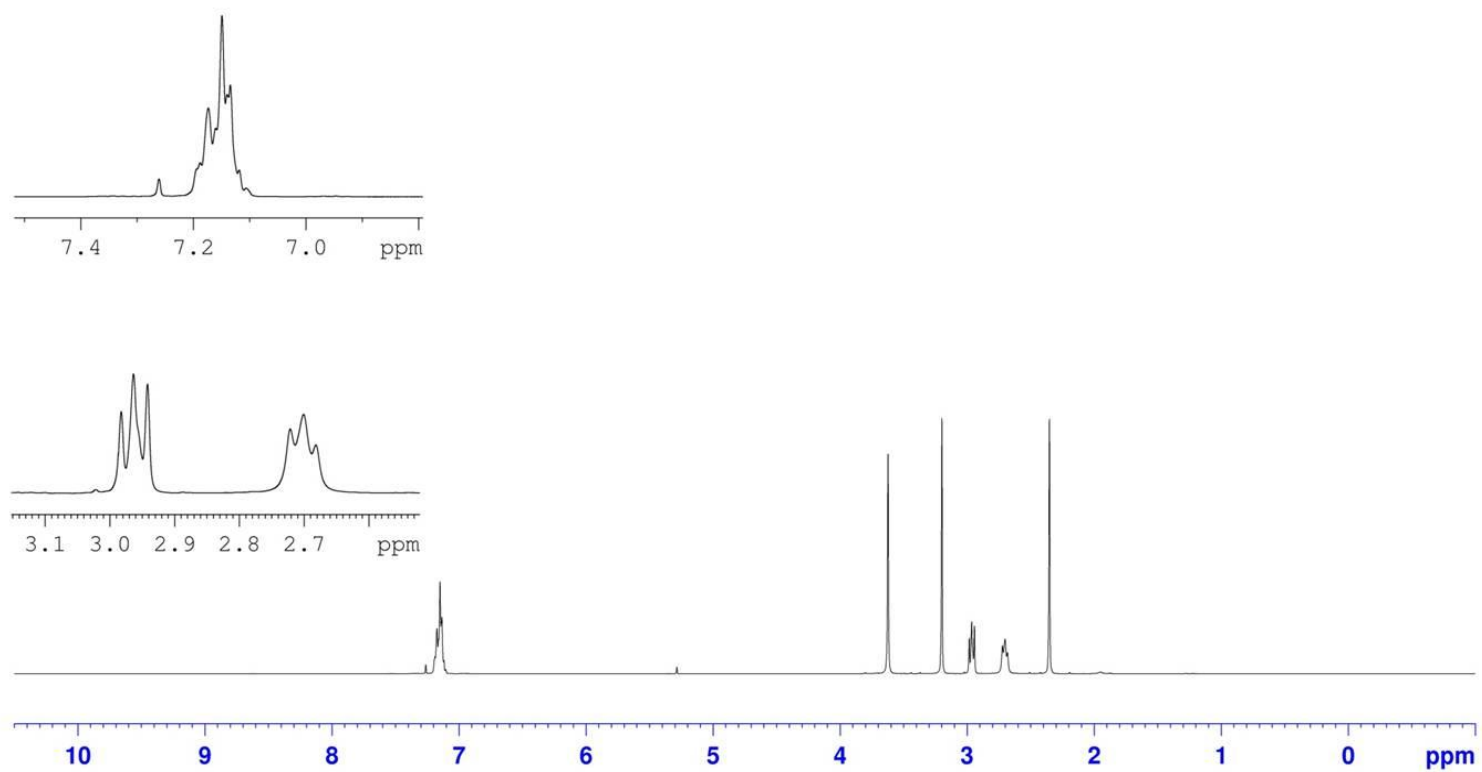
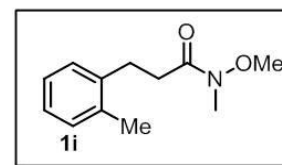
**N,2-dimethoxy-N-methylbenzamide**  
500 MHz, CDCl<sub>3</sub>



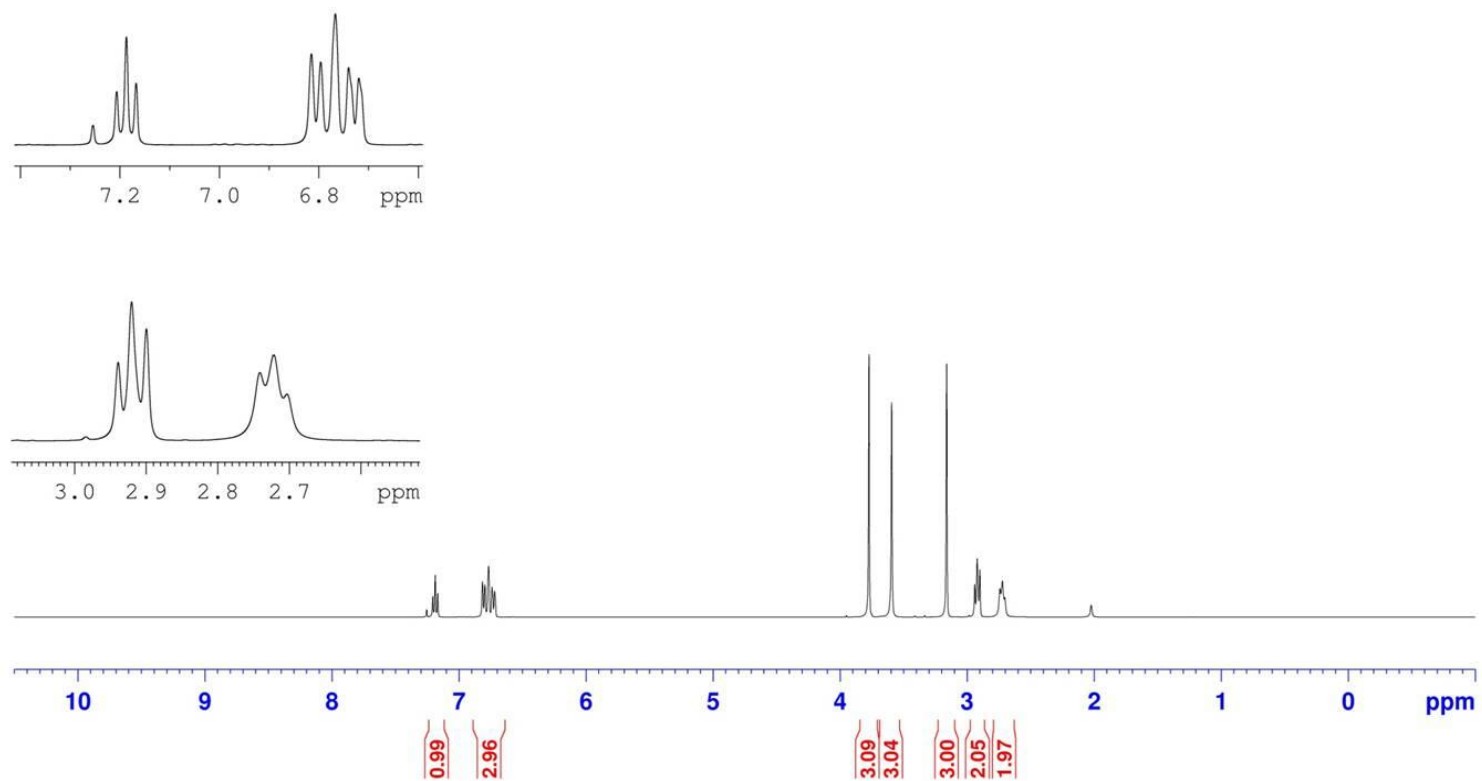
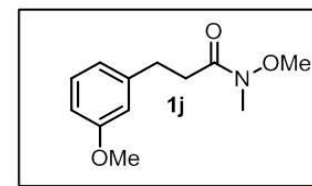
**N-methoxy-3-(2-methoxyphenyl)-N-methylpropanamide**  
500 MHz, CDCl<sub>3</sub>



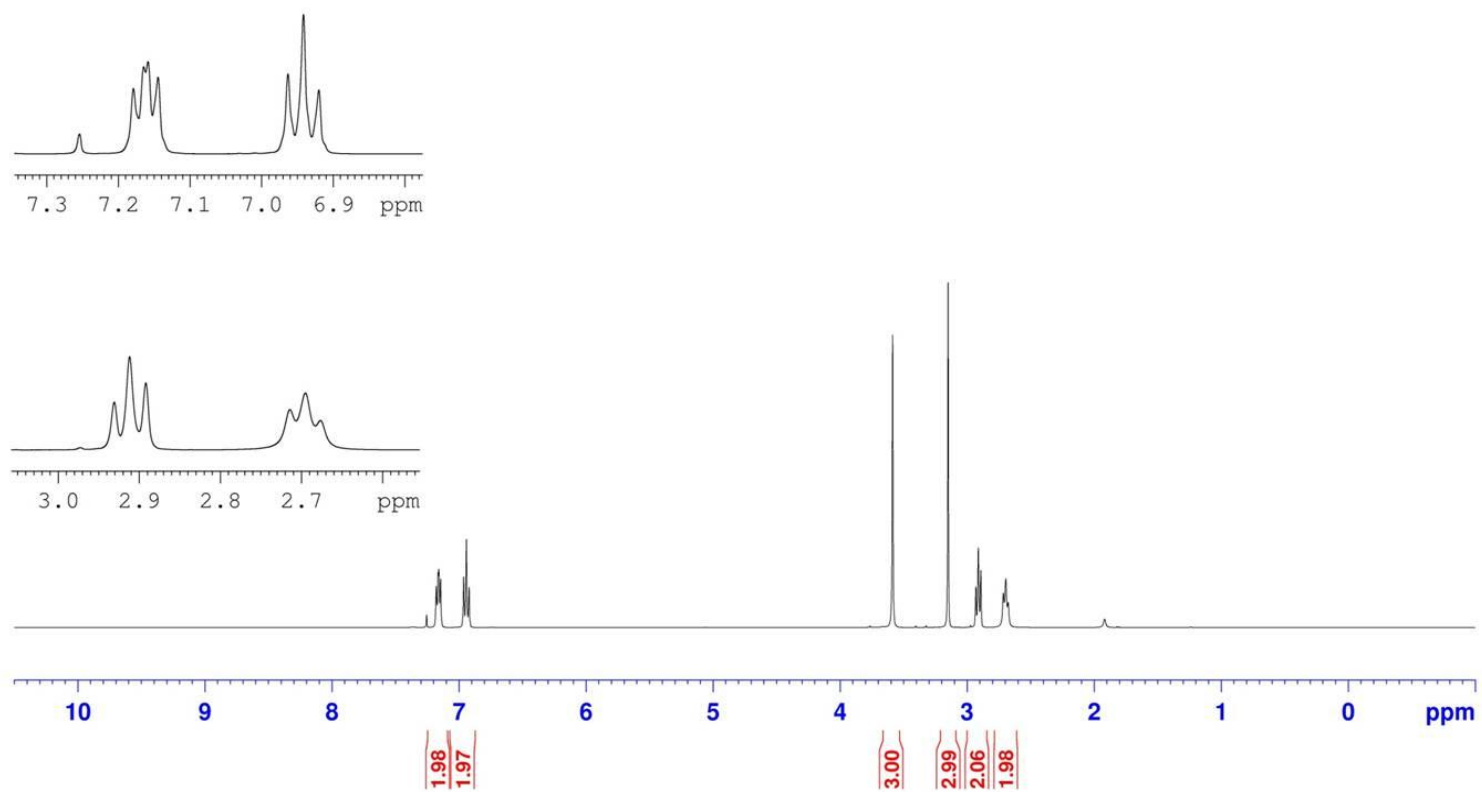
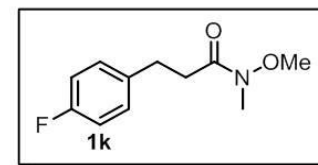
**N-methoxy-N-methyl-3-o-tolylpropanamide**  
400 MHz, CDCl<sub>3</sub>



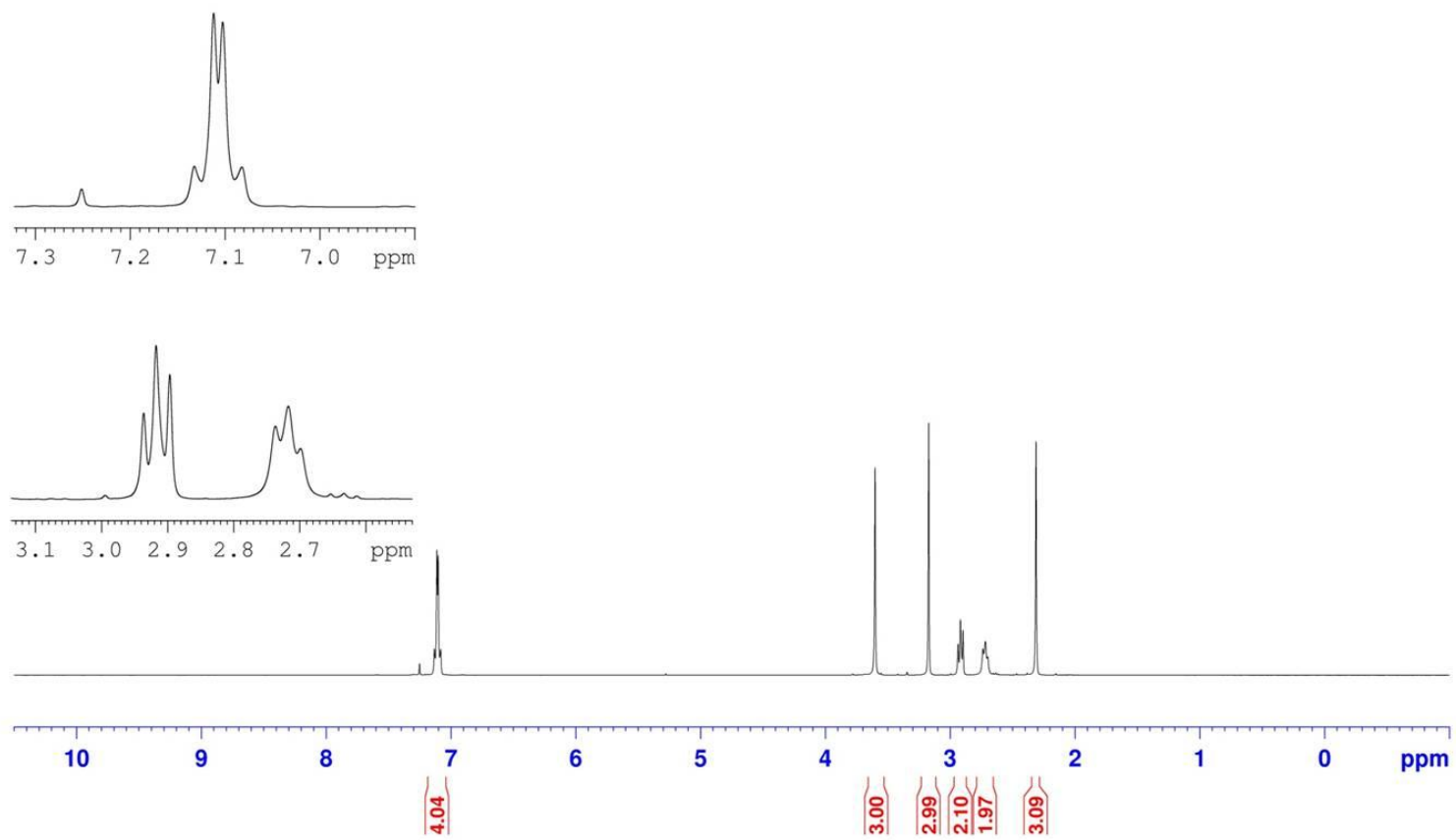
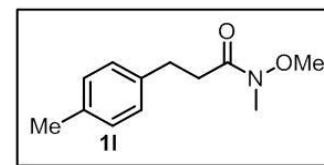
**N-methoxy-3-(3-methoxyphenyl)-N-methylpropanamide**  
400 MHz, CDCl<sub>3</sub>



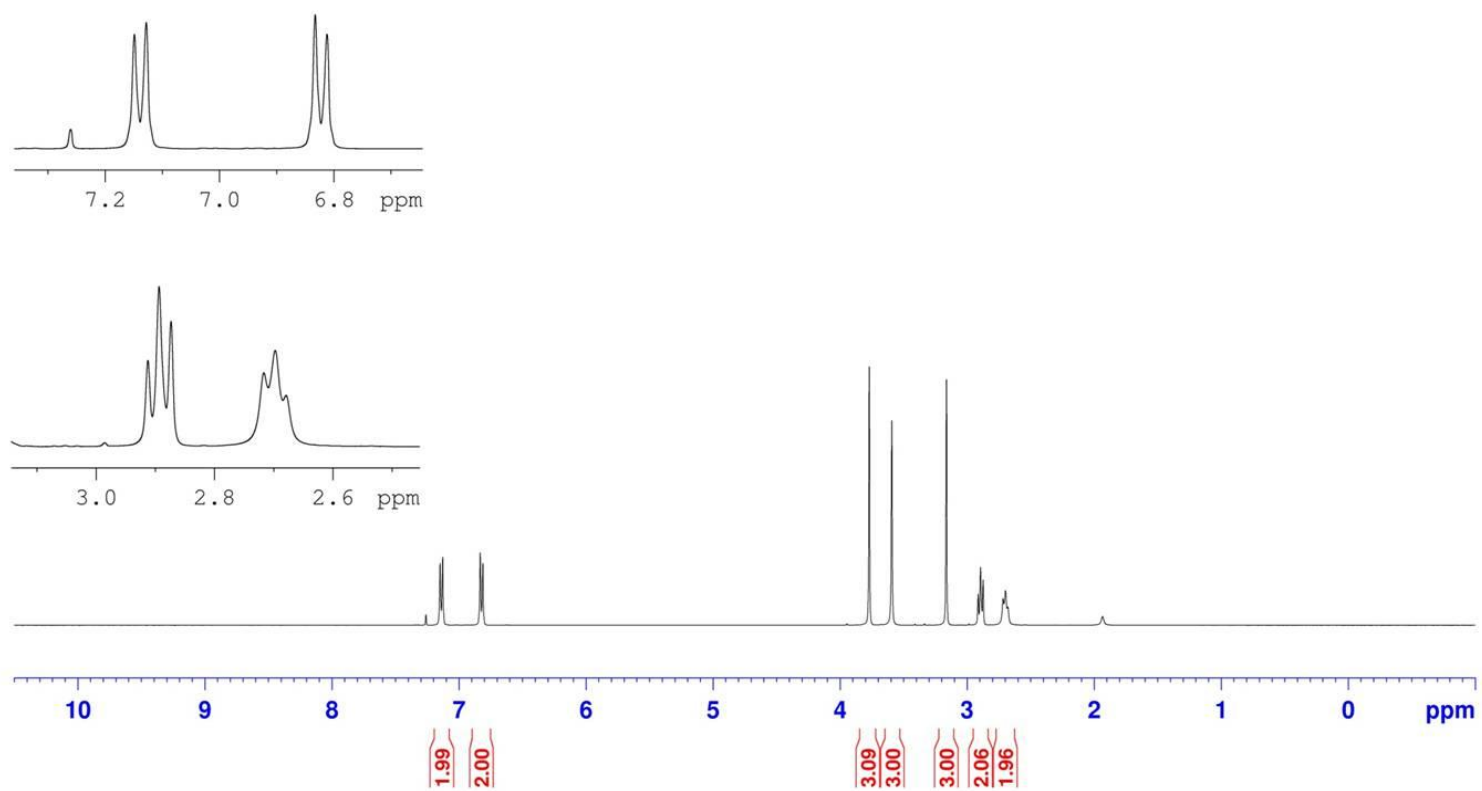
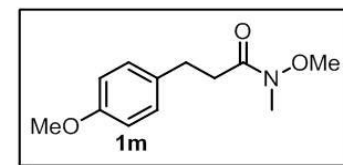
**3-(4-fluorophenyl)-N-methoxy-N-methylpropanamide**  
400 MHz, CDCl<sub>3</sub>



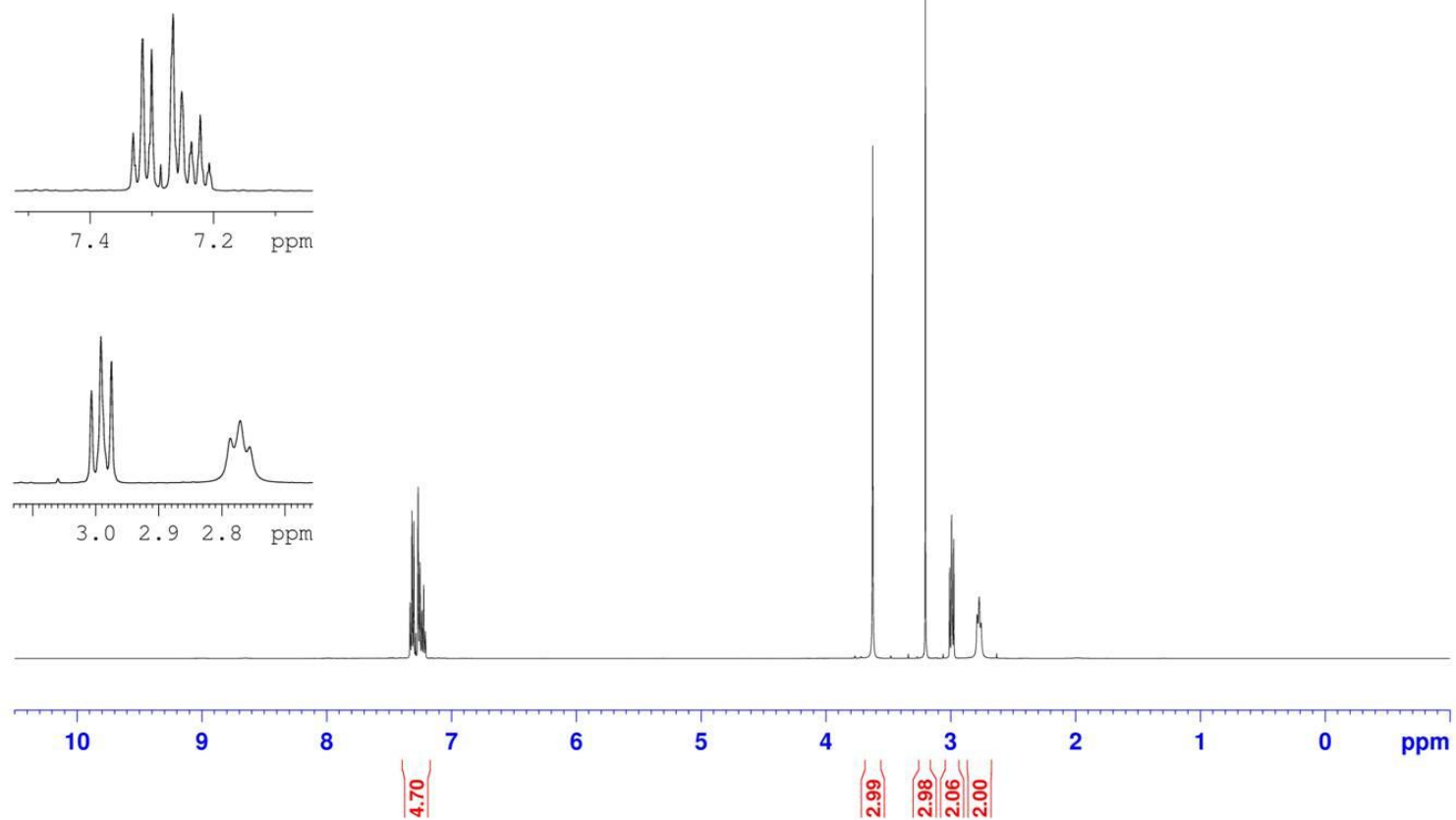
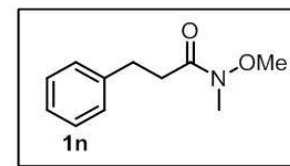
**N-methoxy-N-methyl-3-p-tolylpropanamide**  
400 MHz, CDCl<sub>3</sub>



**N-methoxy-3-(4-methoxyphenyl)-N-methylpropanamide**  
400 MHz, CDCl<sub>3</sub>

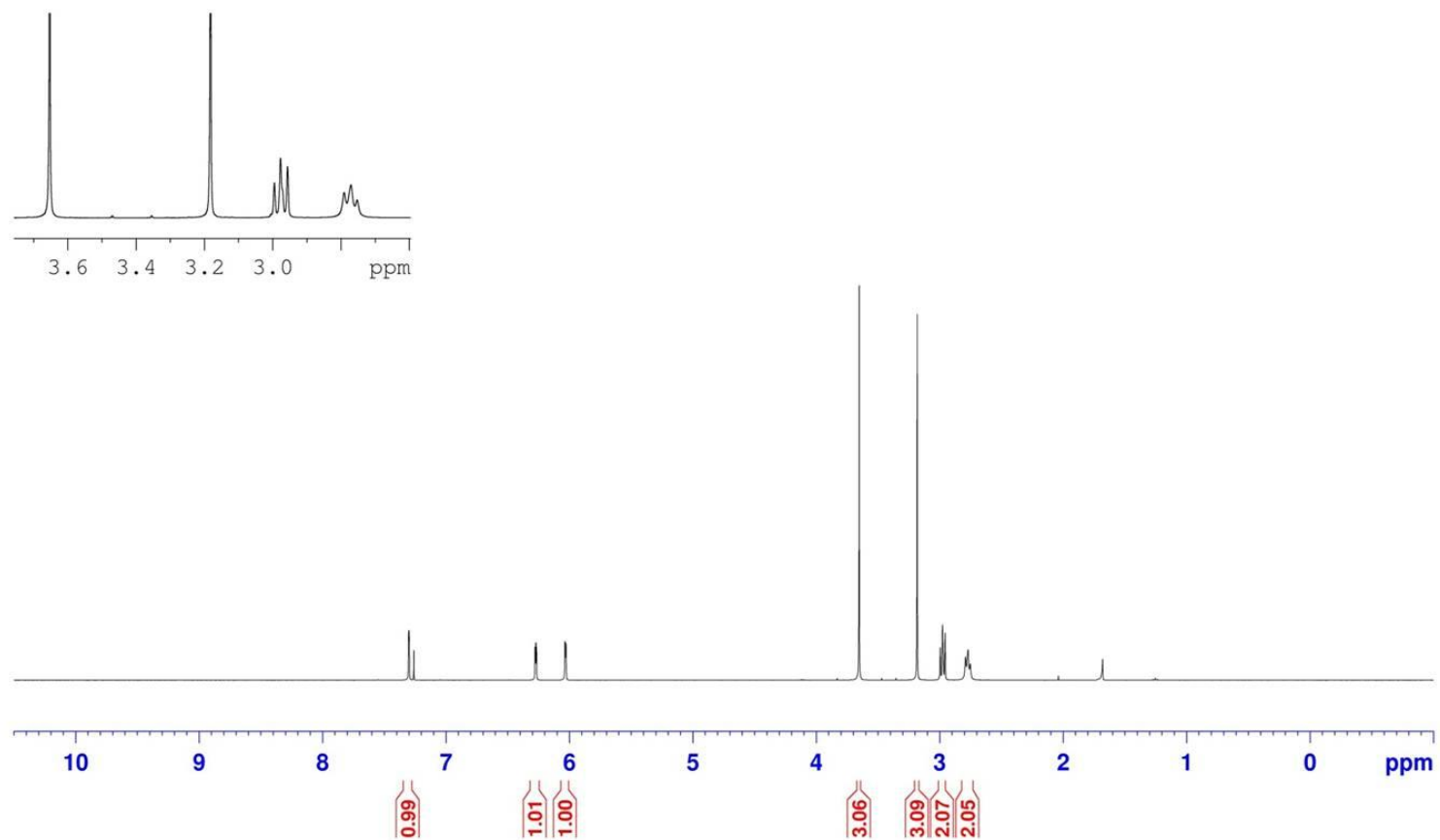
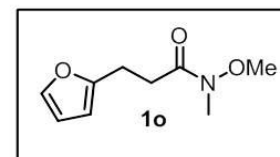


**N-methoxy-N-methyl-3-phenylpropanamide**  
500 MHz, CDCl<sub>3</sub>

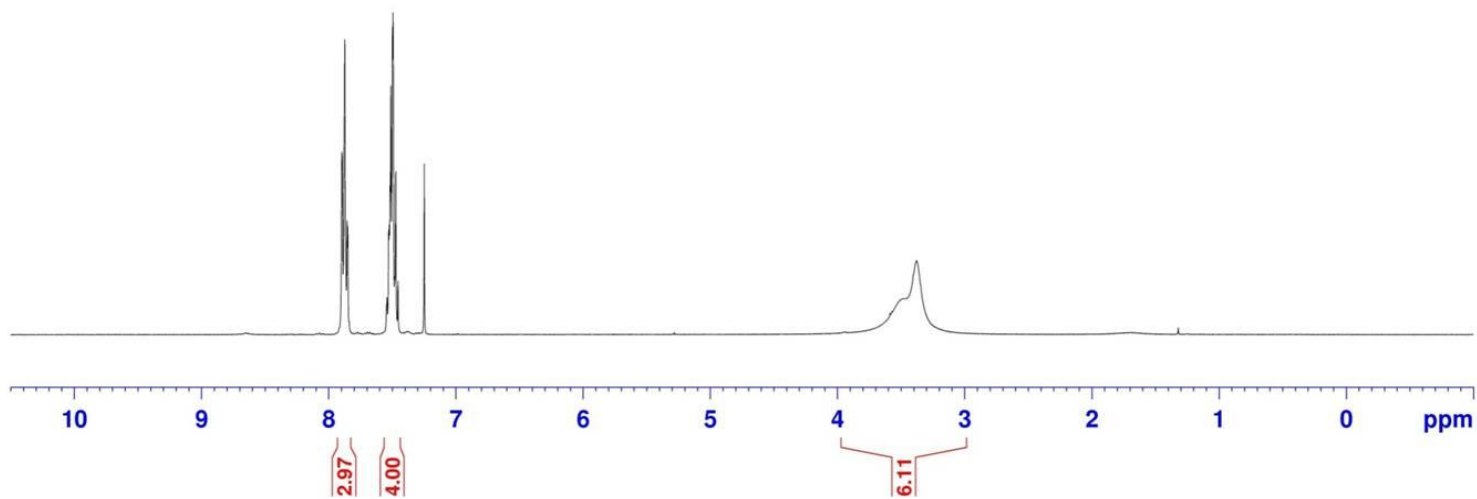
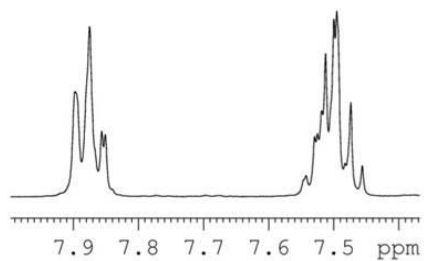
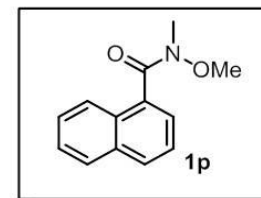




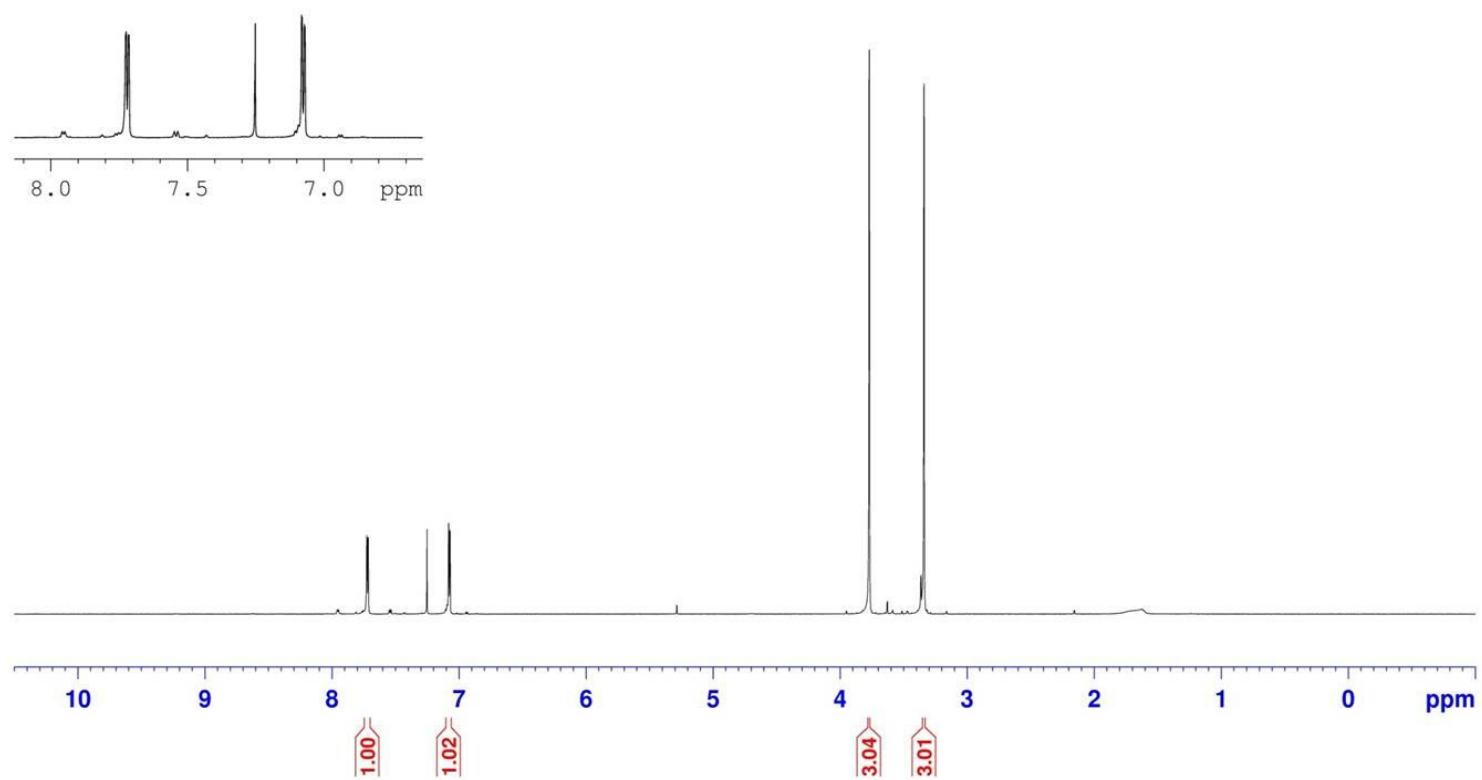
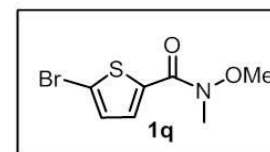
3-(furan-2-yl)-N-methoxy-N-methylpropanamide  
400 MHz, CDCl<sub>3</sub>



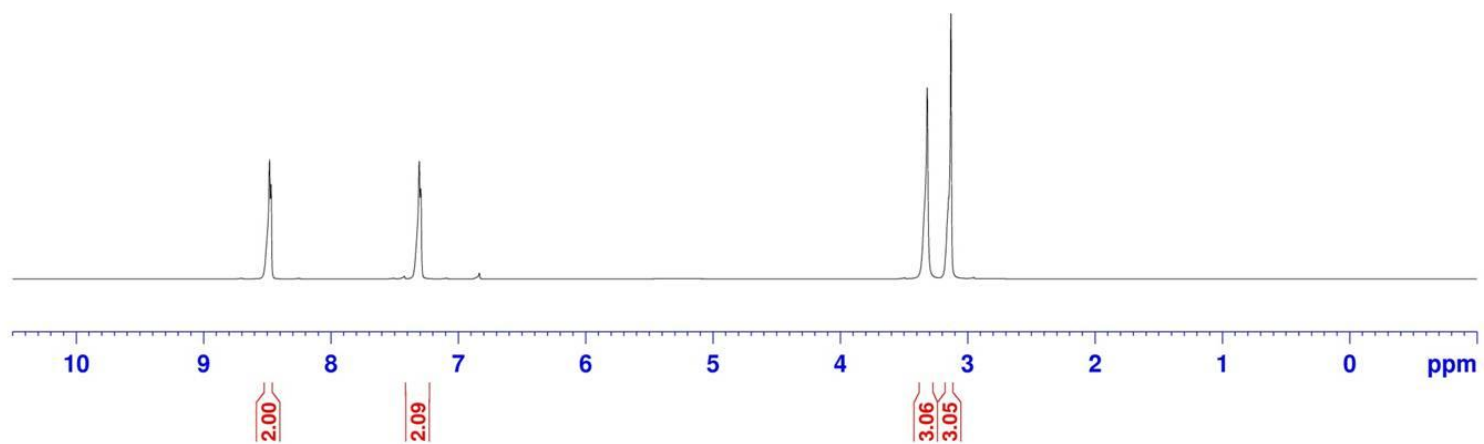
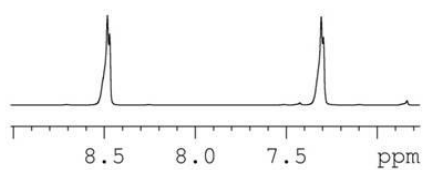
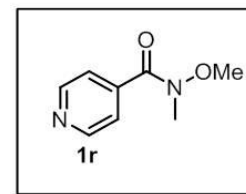
**N-methoxy-N-methyl-1-naphthamide**  
400 MHz, CDCl<sub>3</sub>



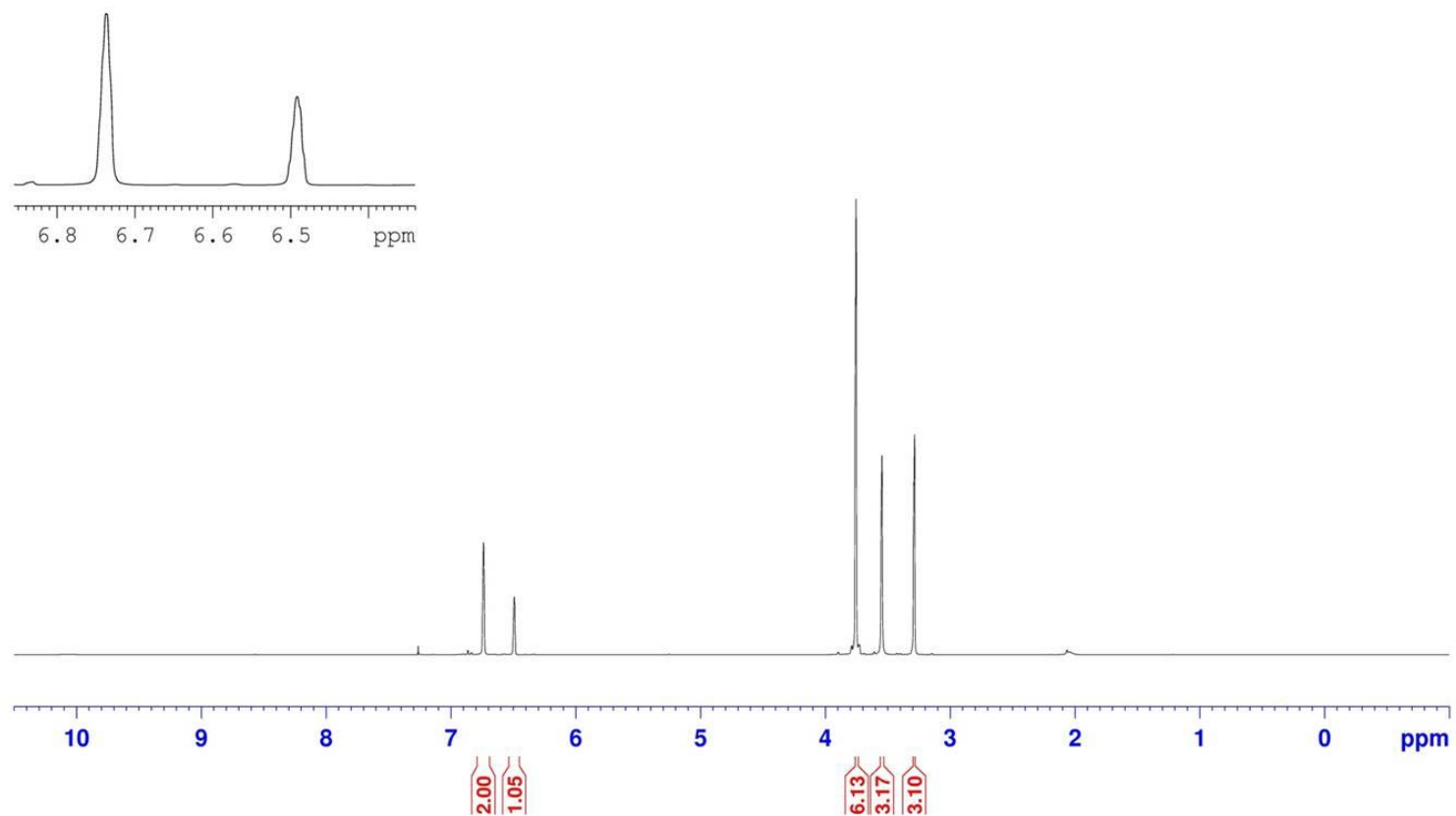
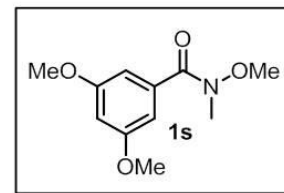
**5-bromo-N-methoxy-N-methylthiophene-2-carboxamide**  
400 MHz, CDCl<sub>3</sub>



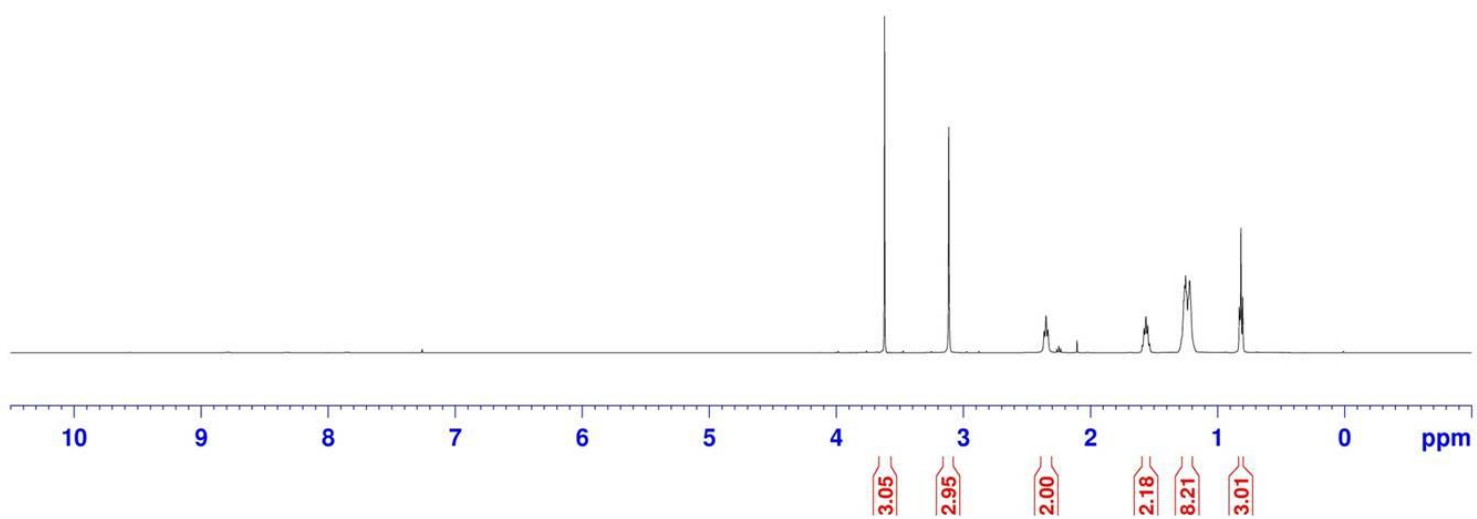
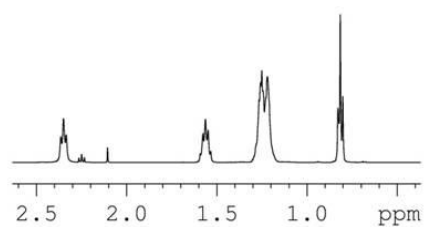
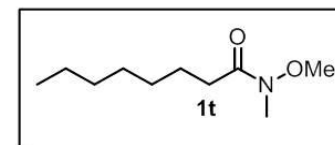
**N-methoxy-N-methylisonicotinamide**  
400 MHz, CDCl<sub>3</sub>



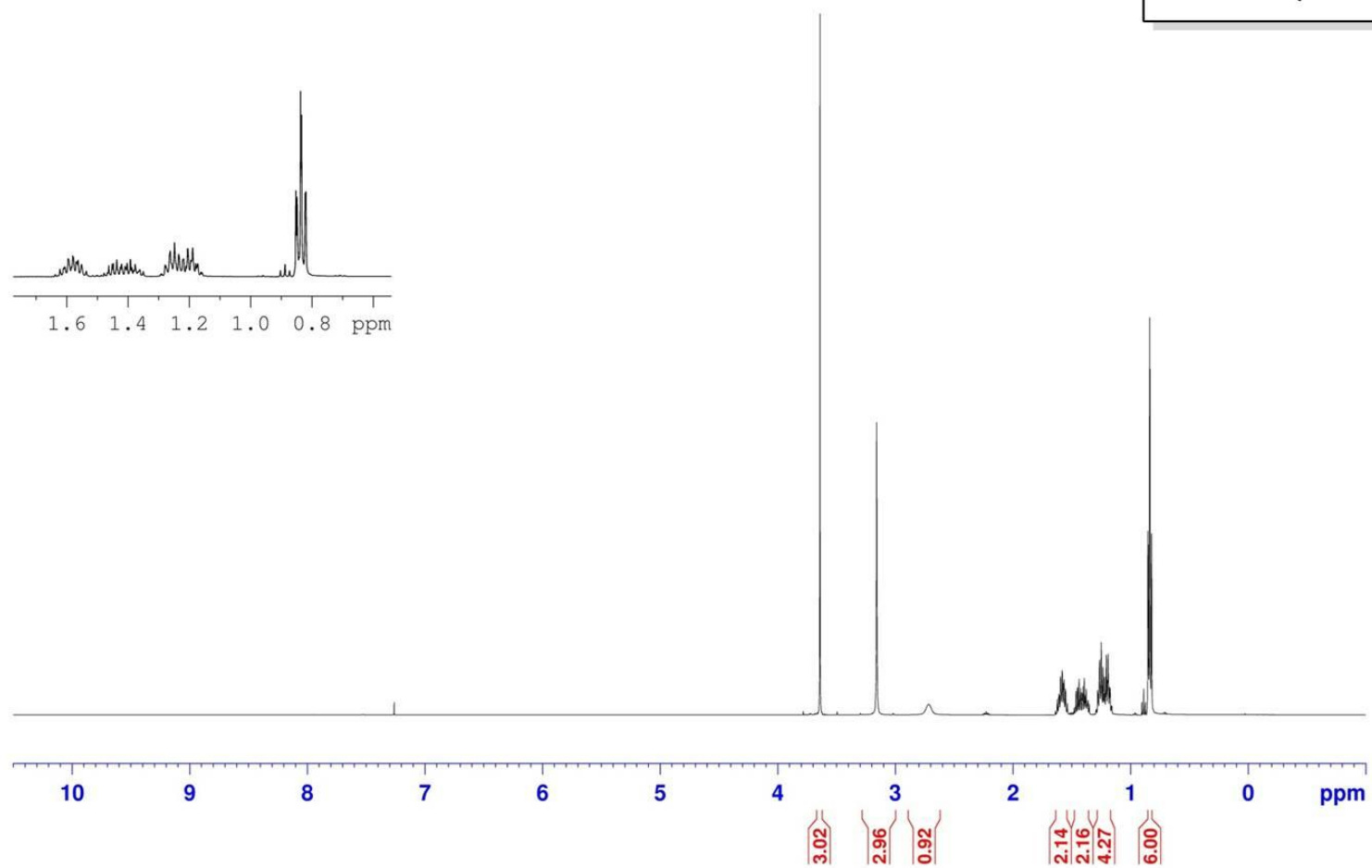
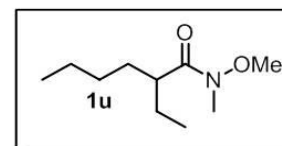
**N,3,5-trimethoxy-N-methylbenzamide**  
500 MHz, CDCl<sub>3</sub>



**N-methoxy-N-methyloctanamide**  
500 MHz, CDCl<sub>3</sub>

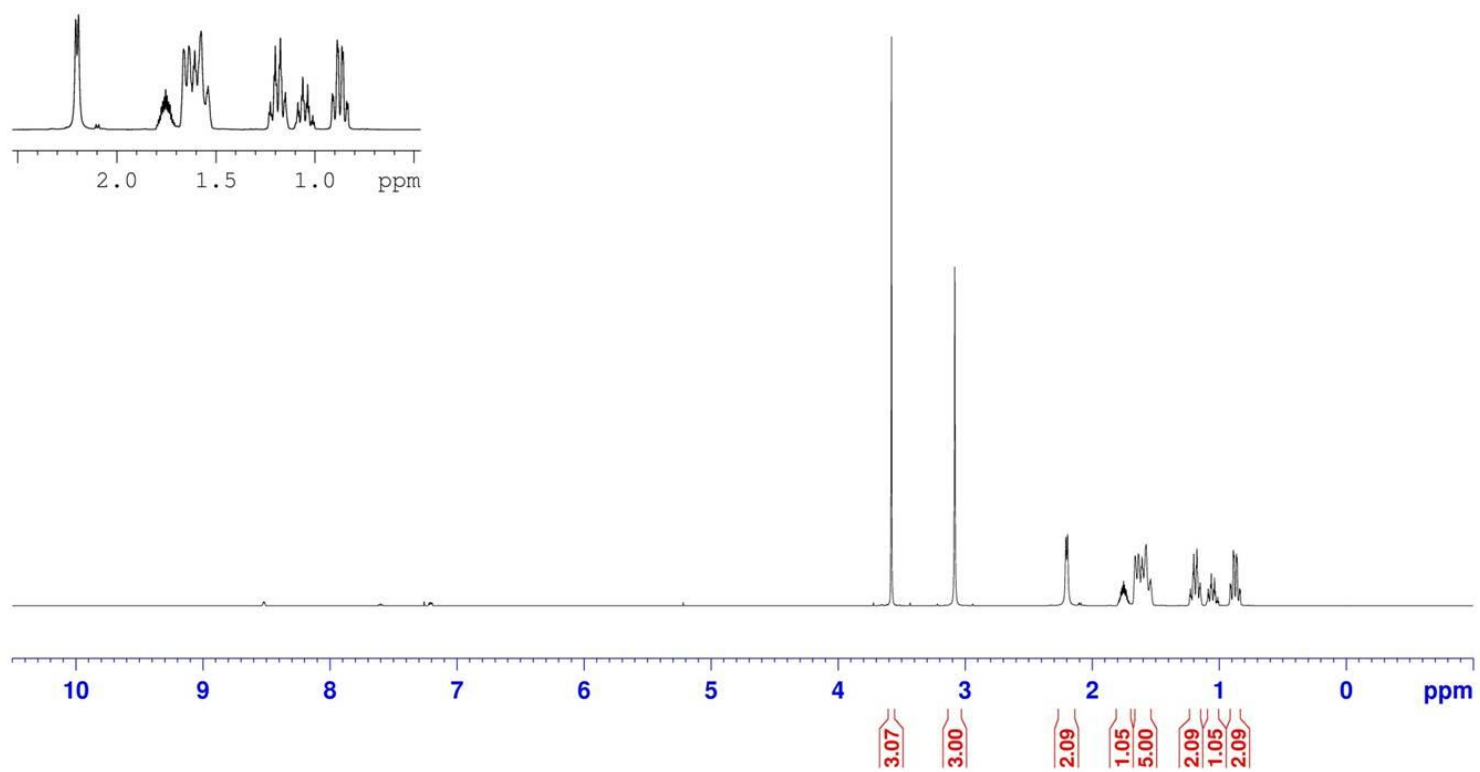
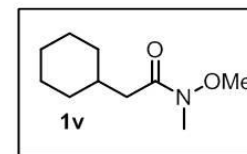


**3-ethyl-N-methoxy-N-methylhexanamide**  
500 MHz, CDCl<sub>3</sub>

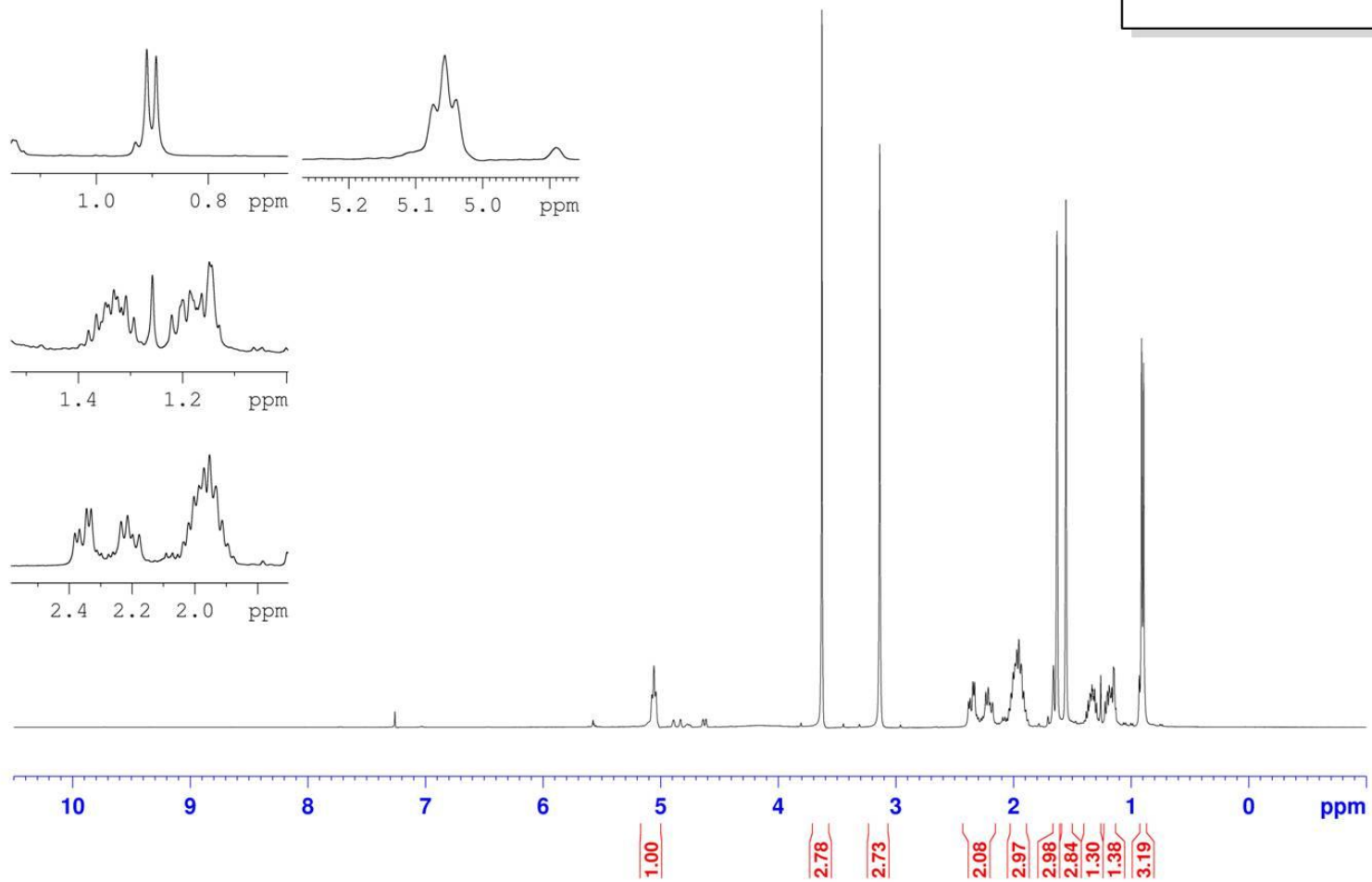
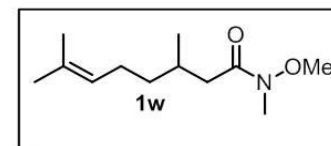




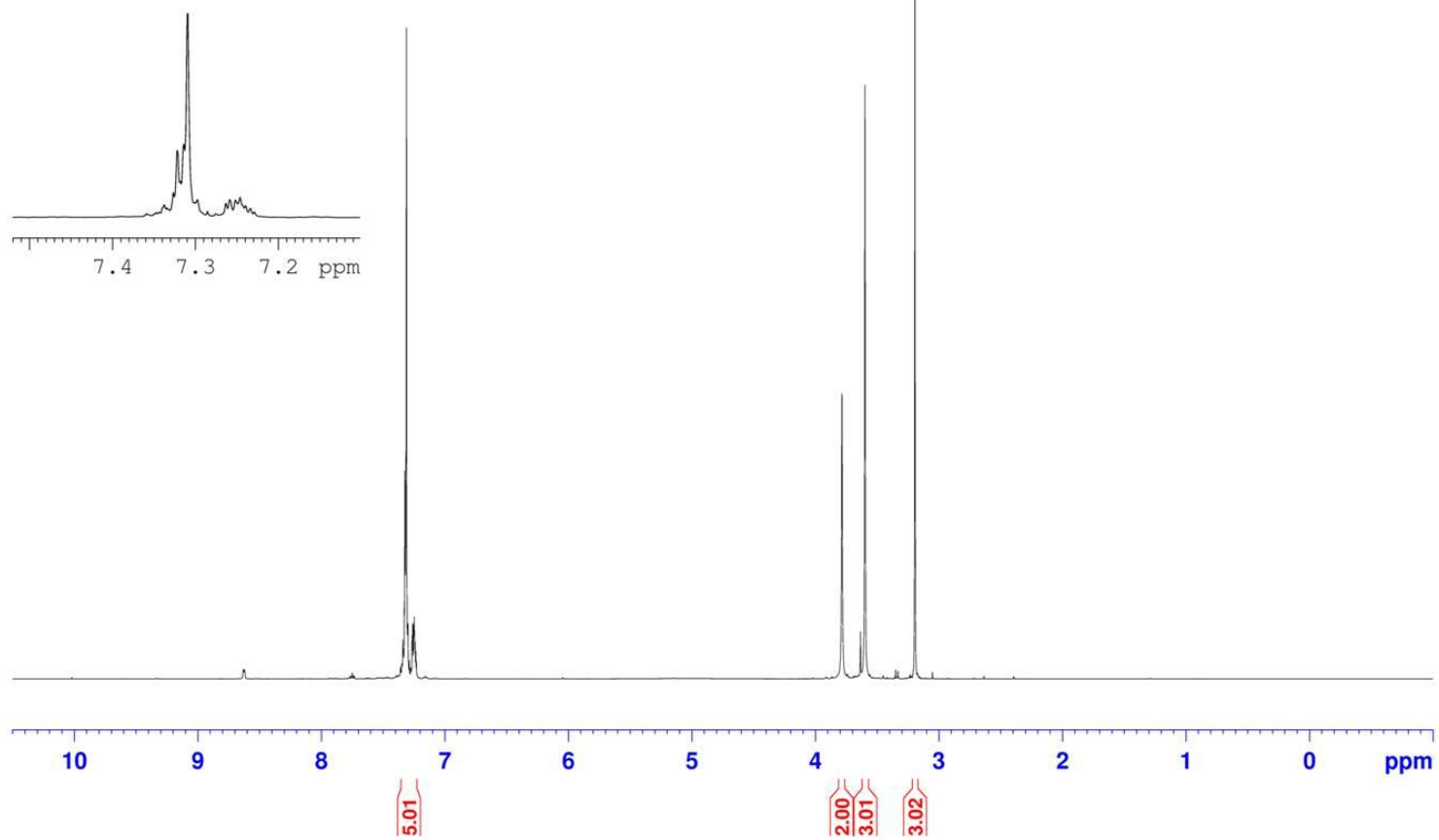
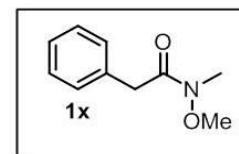
2-cyclohexyl-N-methoxy-N-methylacetamide  
500 MHz, CDCl<sub>3</sub>



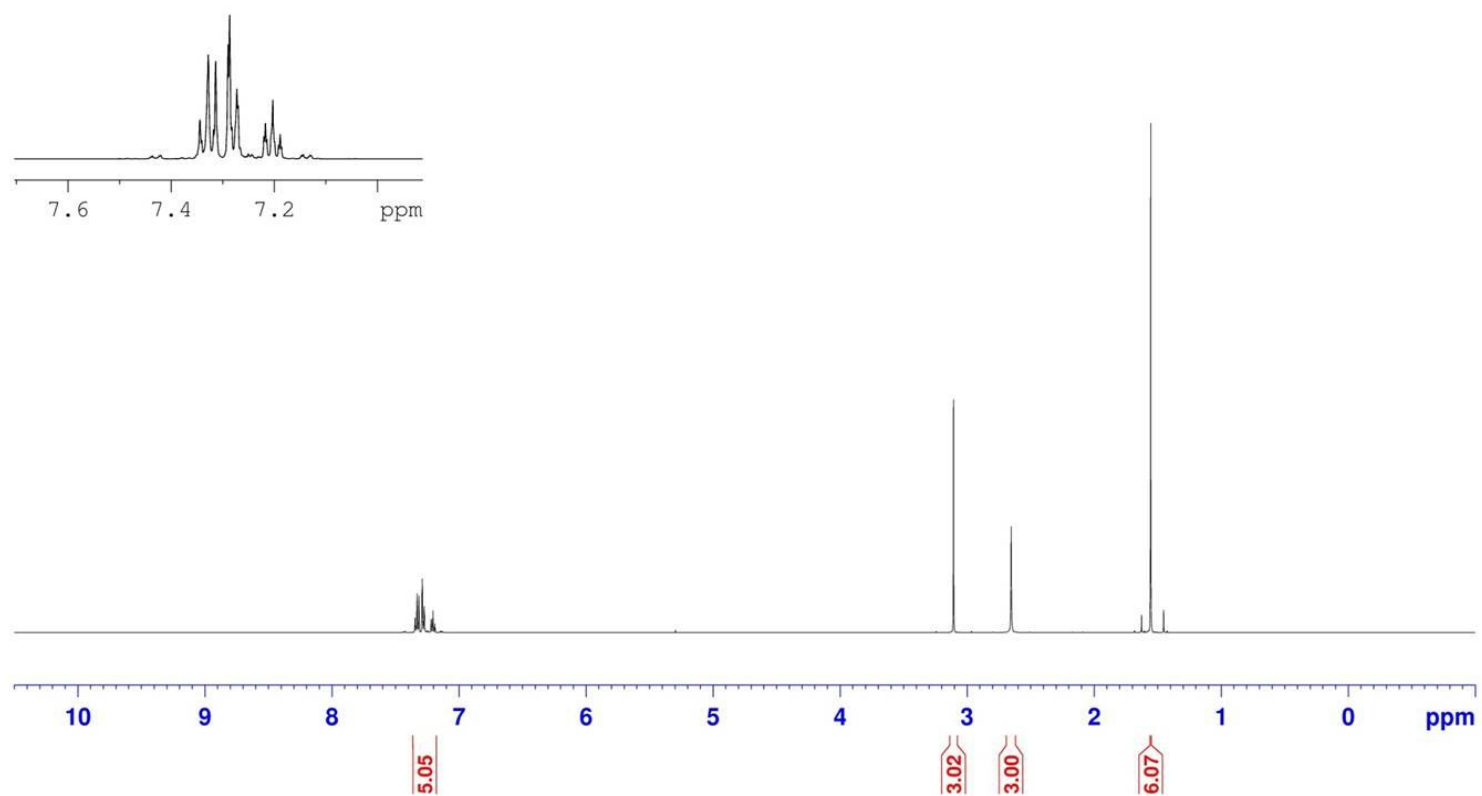
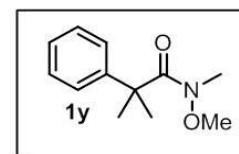
**N-methoxy-N,3,7-trimethyloct-6-enamide**  
400 MHz, CDCl<sub>3</sub>



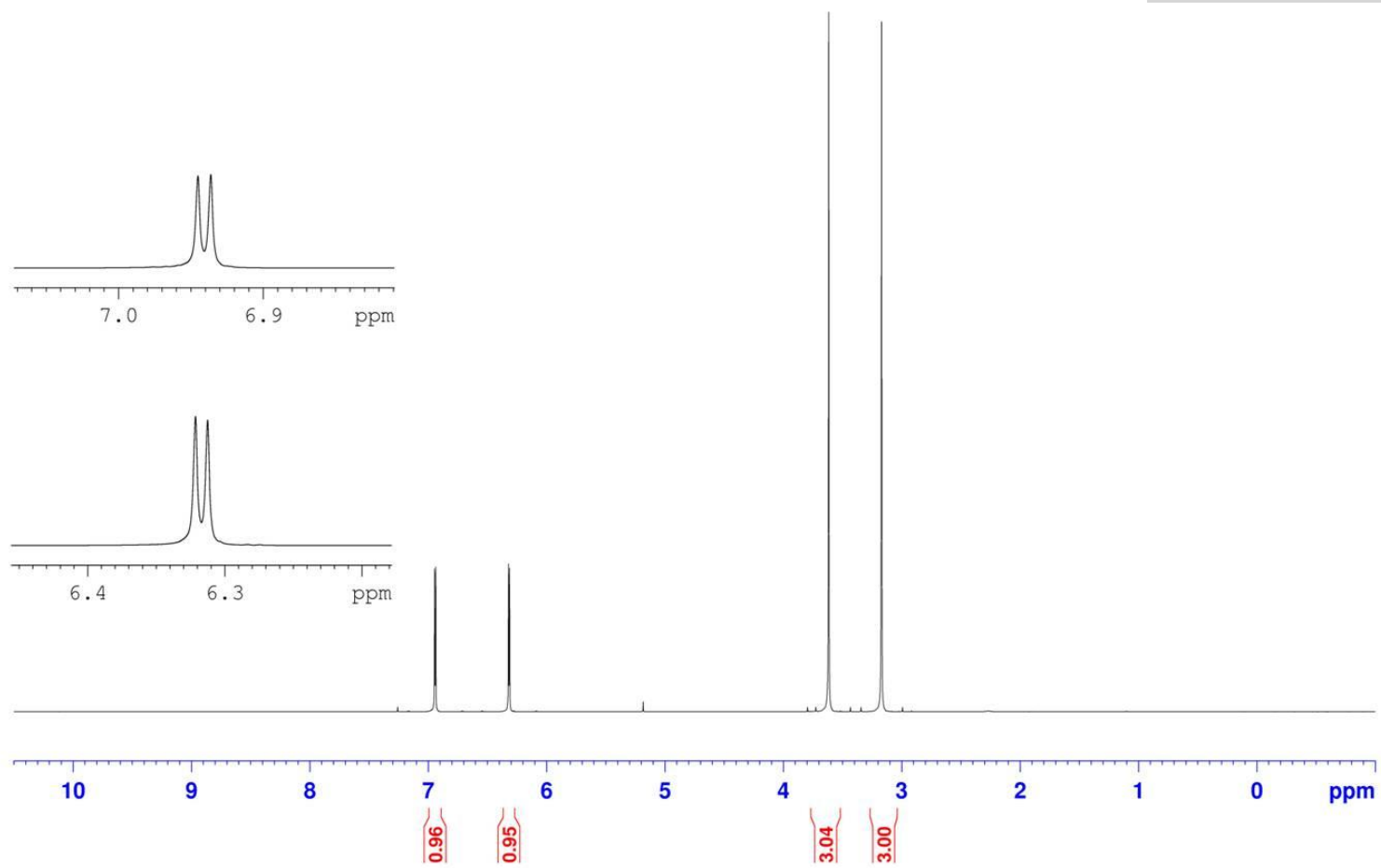
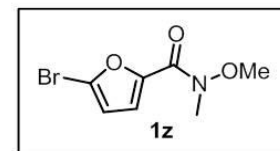
**N-methoxy-N-methyl-2-phenylacetamide**  
500 MHz, CDCl<sub>3</sub>



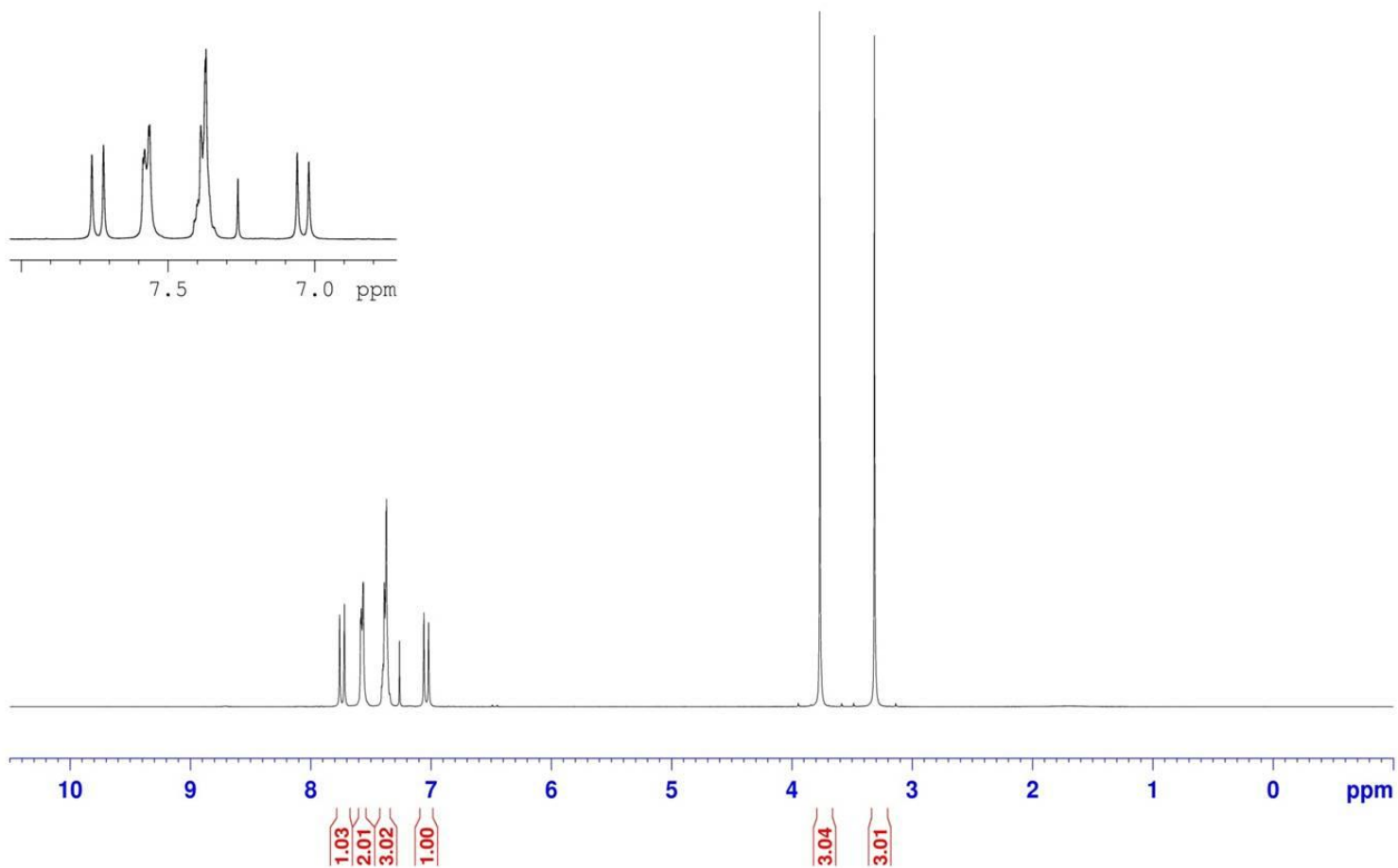
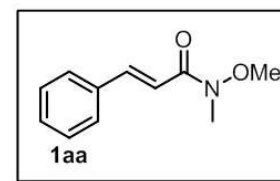
**N-methoxy-N,2-dimethyl-2-phenylpropanamide**  
500 MHz, CDCl<sub>3</sub>



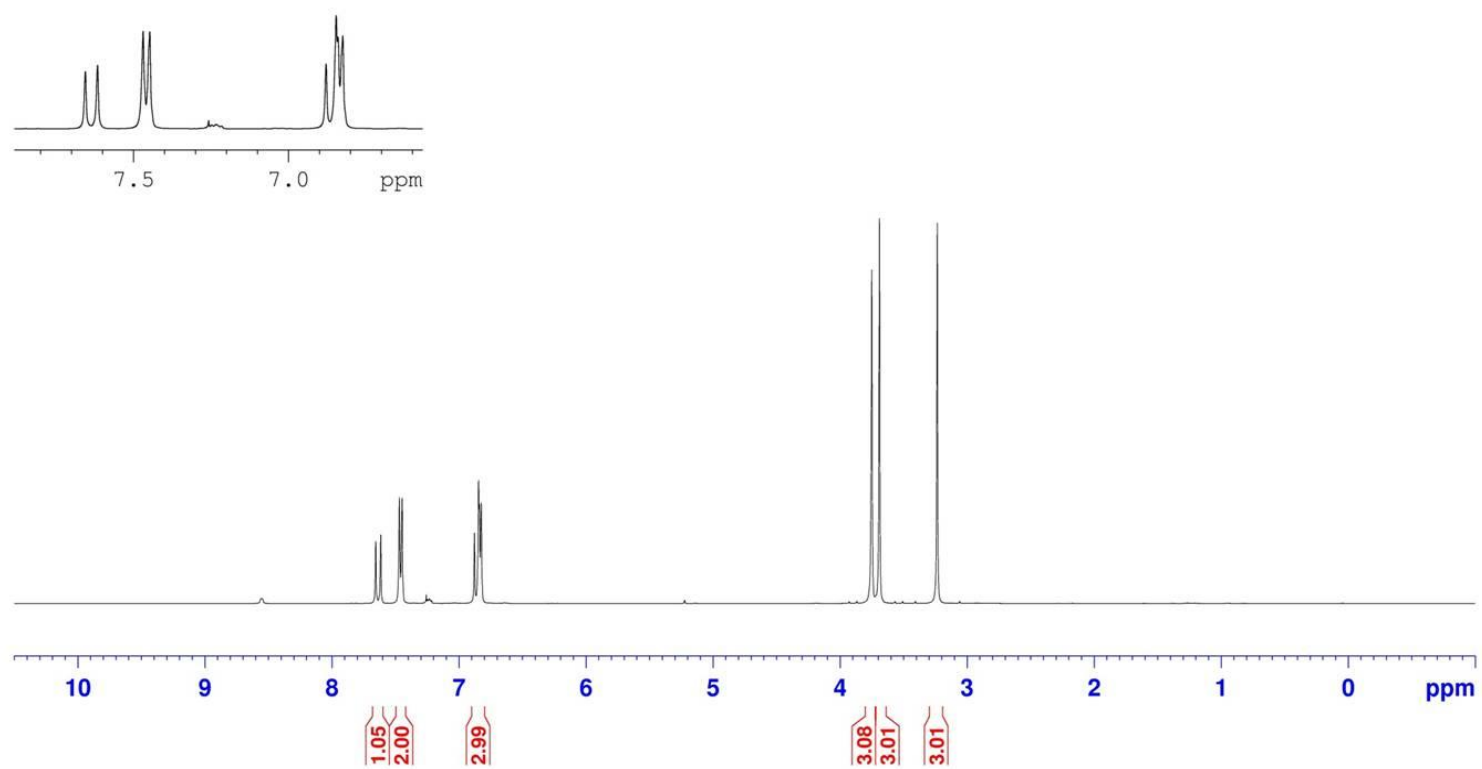
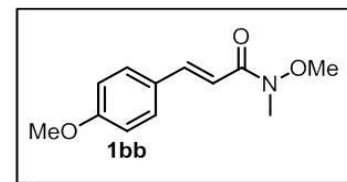
**5-bromo-N-methoxy-N-methylfuran-2-carboxamide**  
400 MHz, CDCl<sub>3</sub>



**N-methoxy-N-methylcinnamamide**  
400 MHz, CDCl<sub>3</sub>

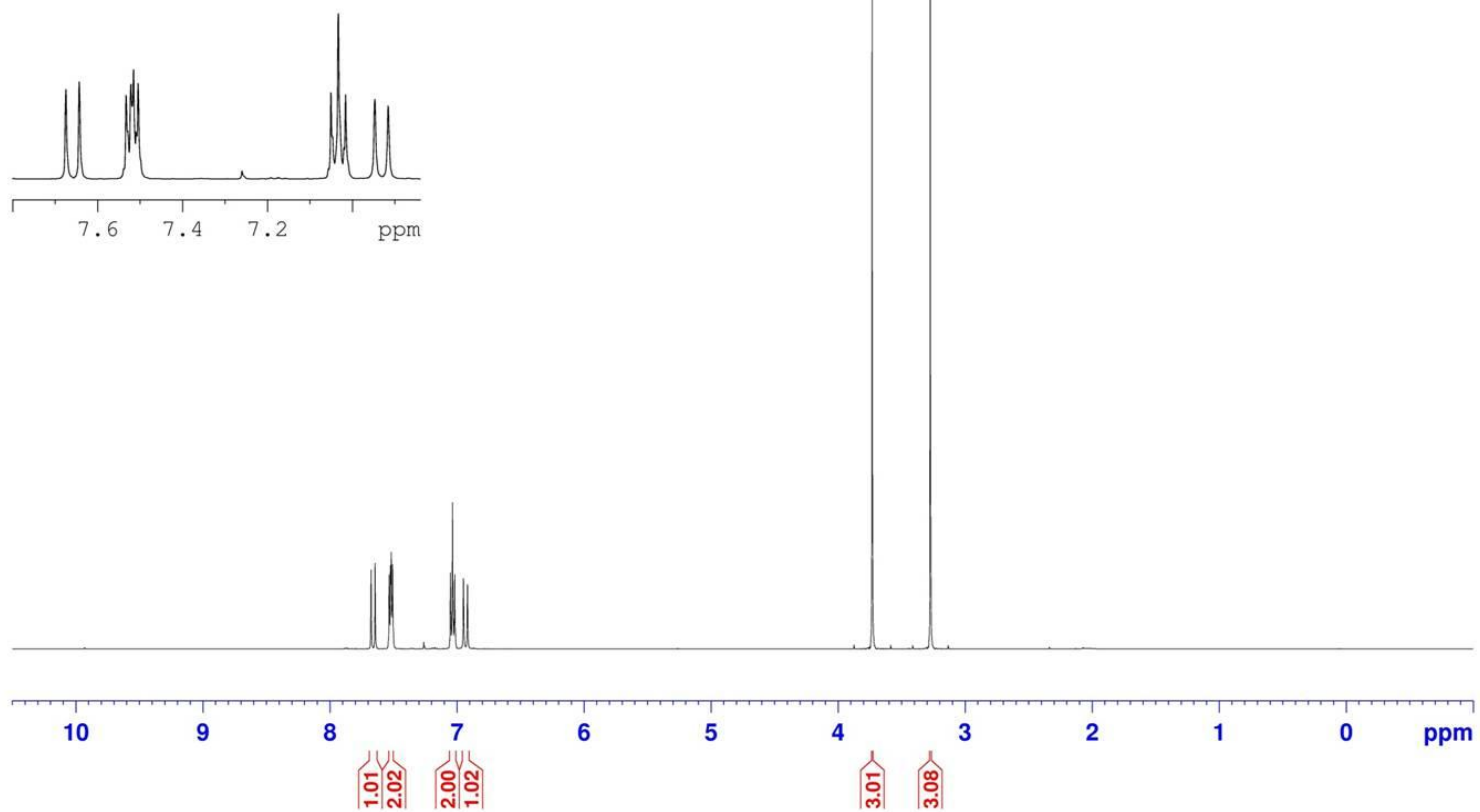
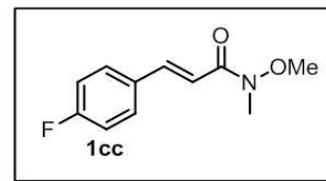


(E)-N-methoxy-3-(4-methoxyphenyl)-N-methylacrylamide  
400 MHz, CDCl<sub>3</sub>

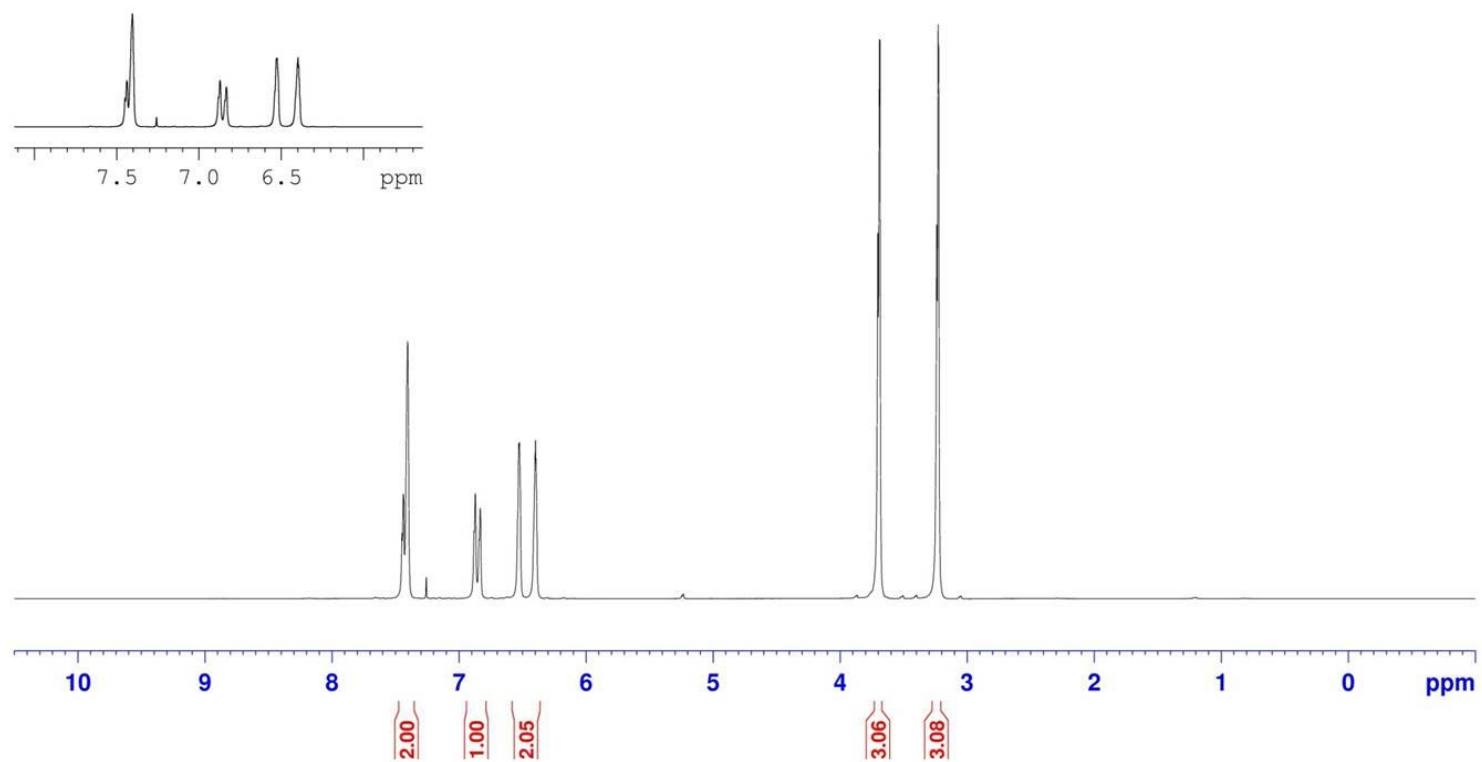
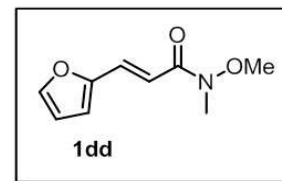




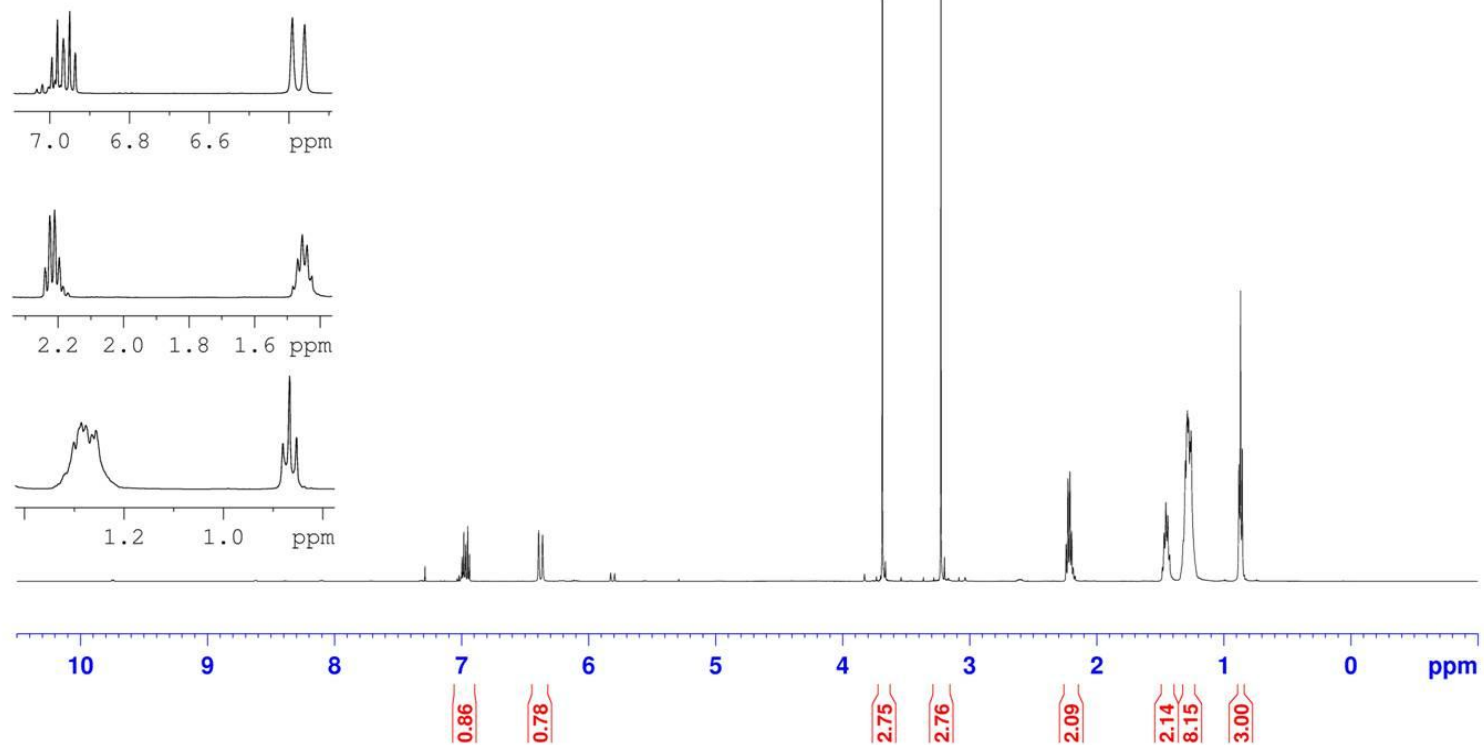
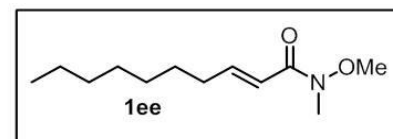
(E)-3-(4-fluorophenyl)-N-methoxy-N-methylacrylamide  
500 MHz, CDCl<sub>3</sub>



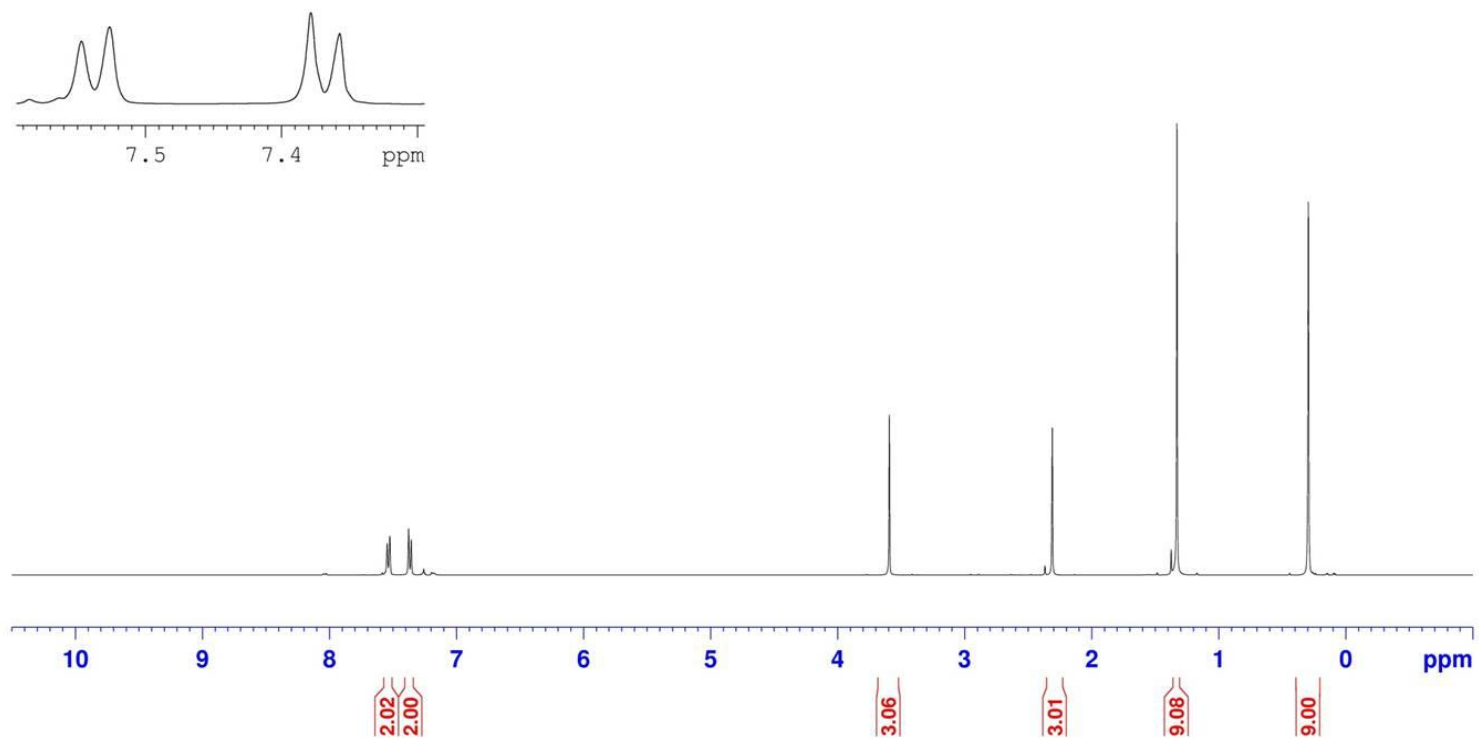
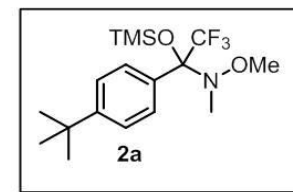
(E)-3-(furan-2-yl)-N-methoxy-N-methylacrylamide  
400 MHz, CDCl<sub>3</sub>



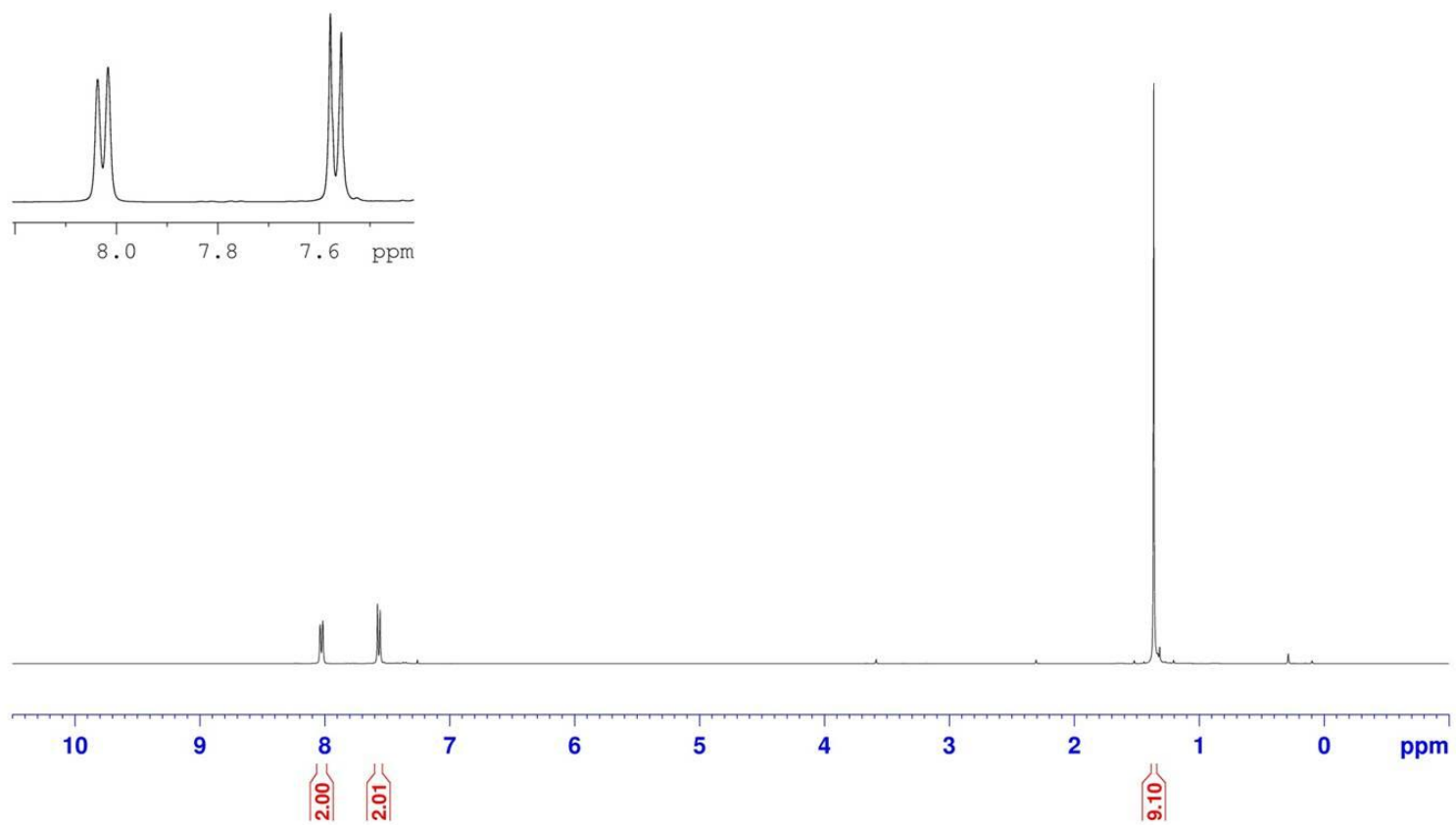
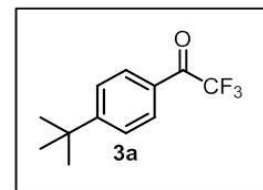
(E)-N-methoxy-N-methyldec-2-enamide  
500 MHz, CDCl<sub>3</sub>



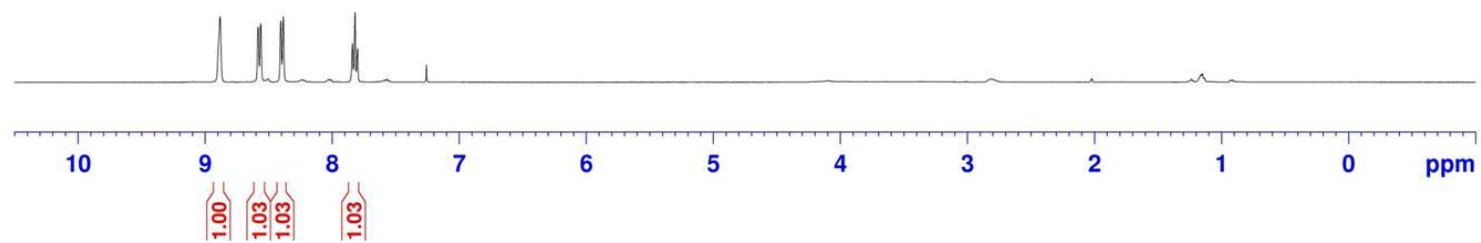
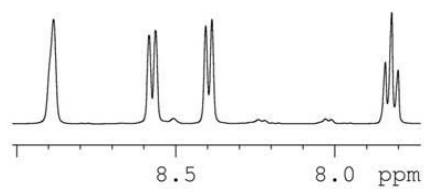
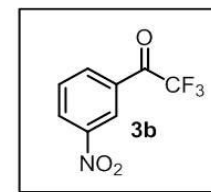
**N-(1-(4-(tert-butyl)phenyl)-2,2,2-trifluoro-1-((trimethylsilyloxy)ethyl)-N,O-dimethylhydroxylamine**  
400 MHz, CDCl<sub>3</sub>



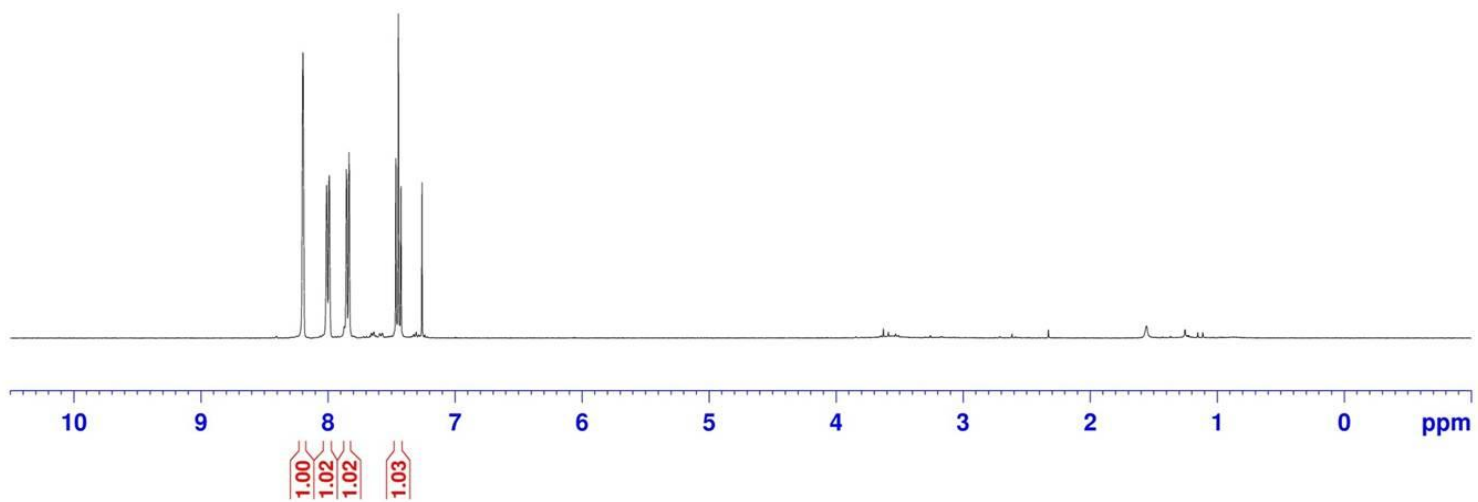
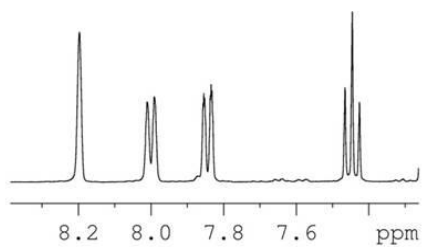
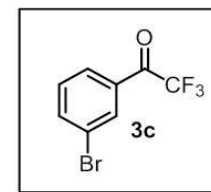
**1-(4-(tert-butyl)phenyl)-2,2,2-trifluoroethanone**  
400 MHz, CDCl<sub>3</sub>



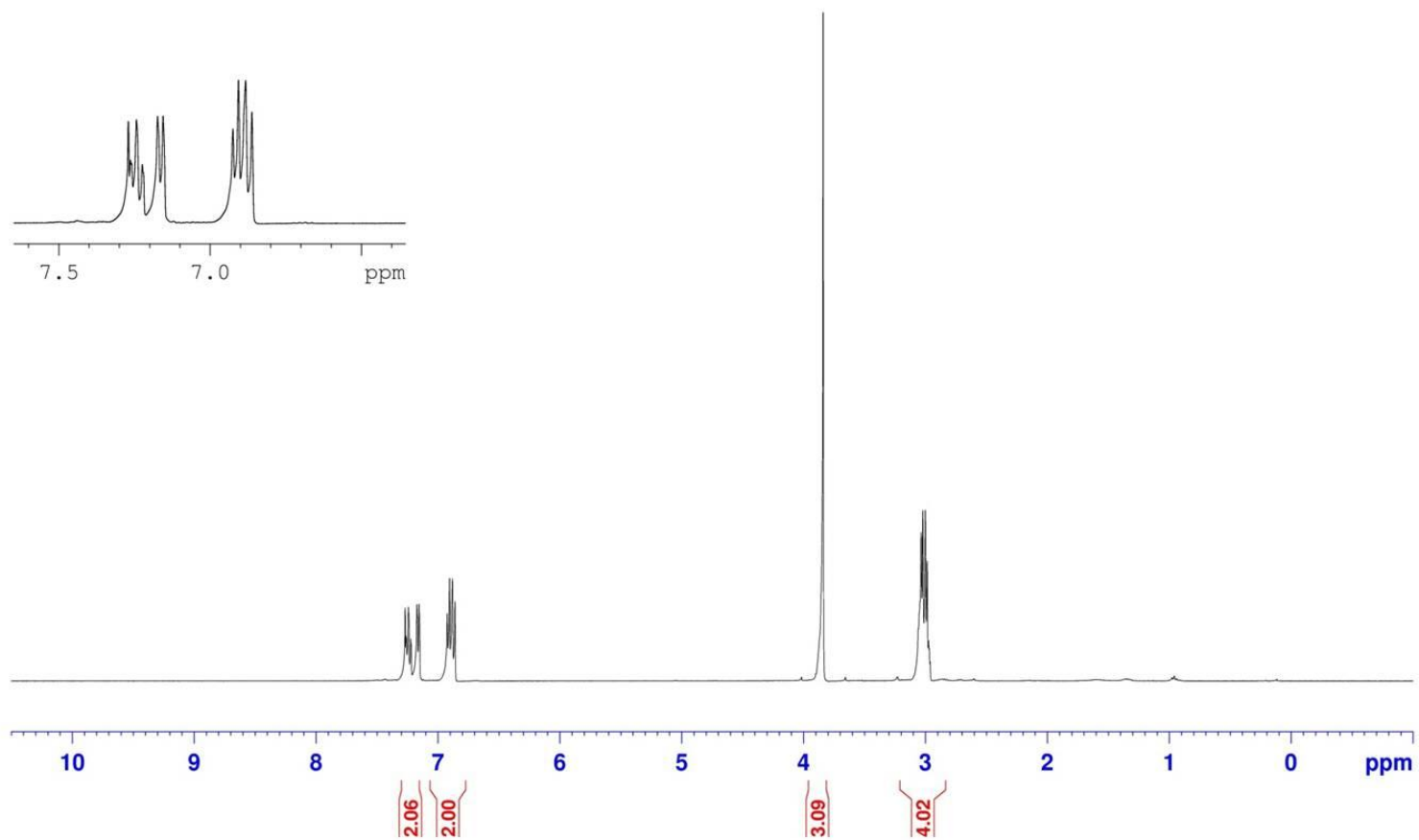
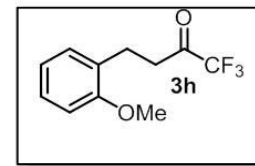
2,2,2-trifluoro-1-(3-nitrophenyl)ethanone  
400 MHz, CDCl<sub>3</sub>



**3-bromo-N-methoxy-N-methylbenzamide**  
400 MHz, CDCl<sub>3</sub>

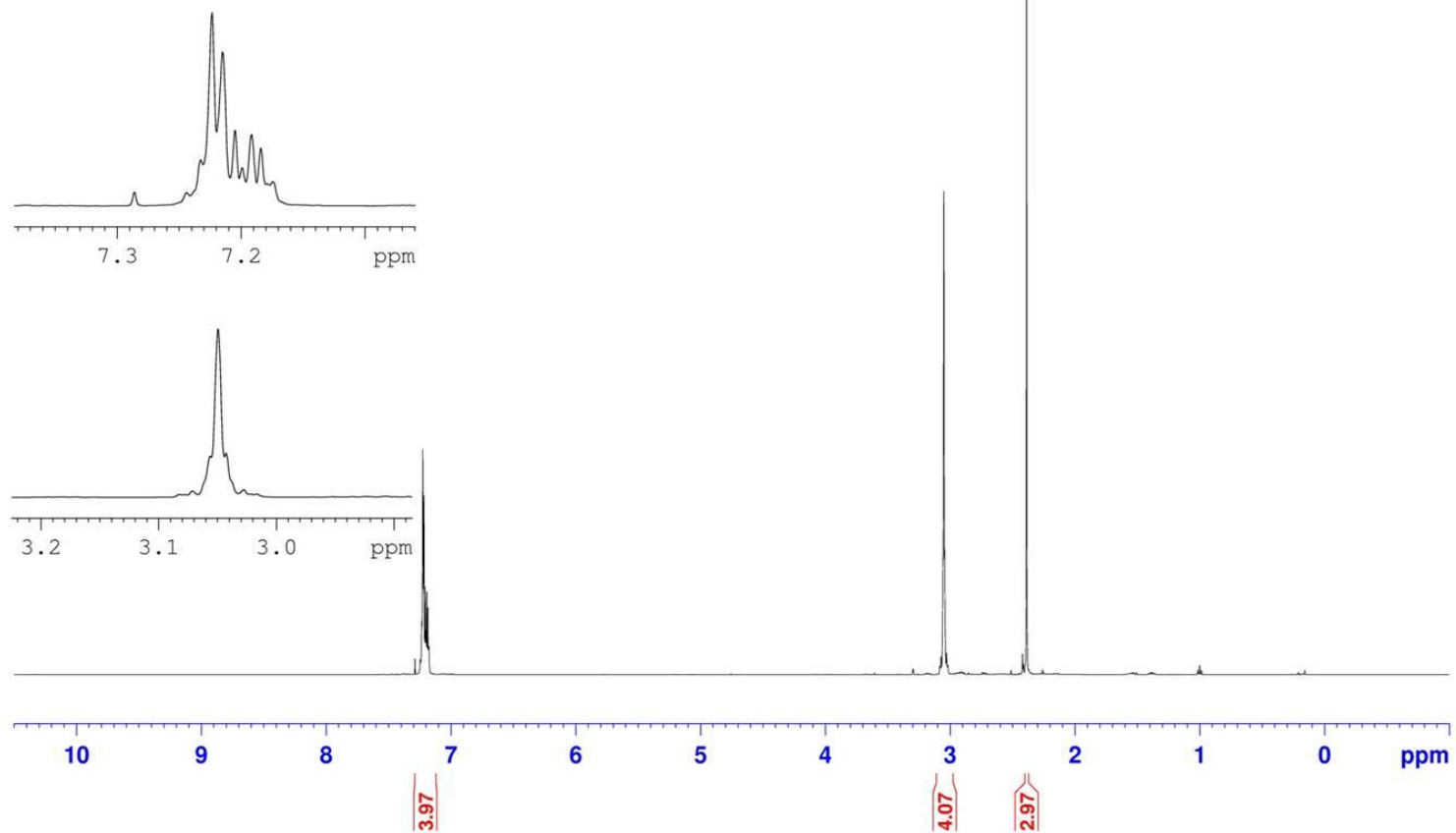
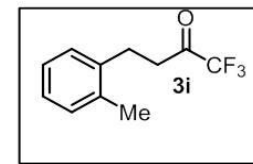


**1,1,1-trifluoro-4-(2-methoxyphenyl)butan-2-one**  
400 MHz, CDCl<sub>3</sub>

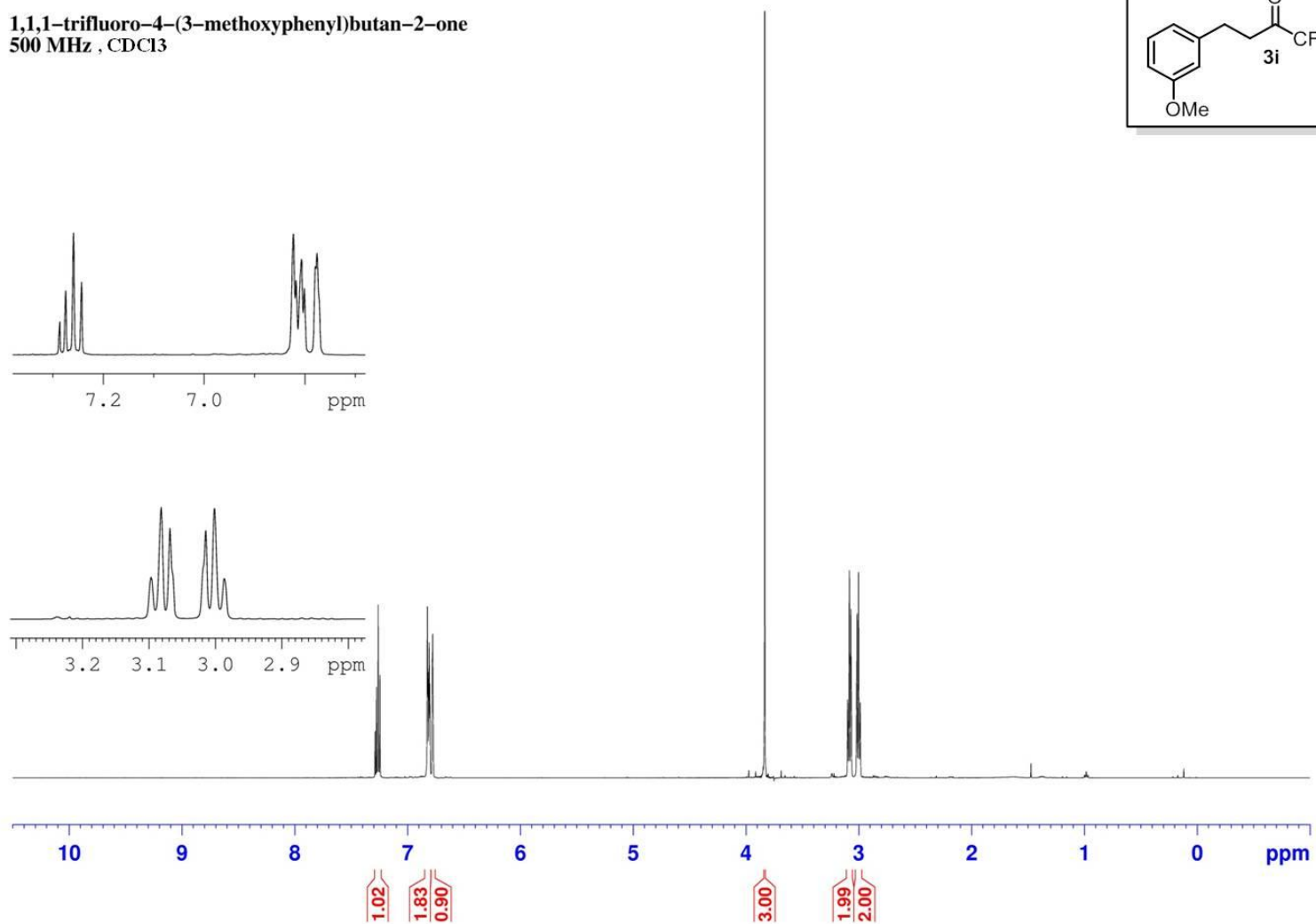
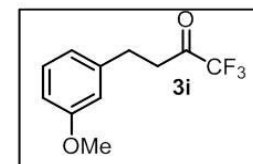




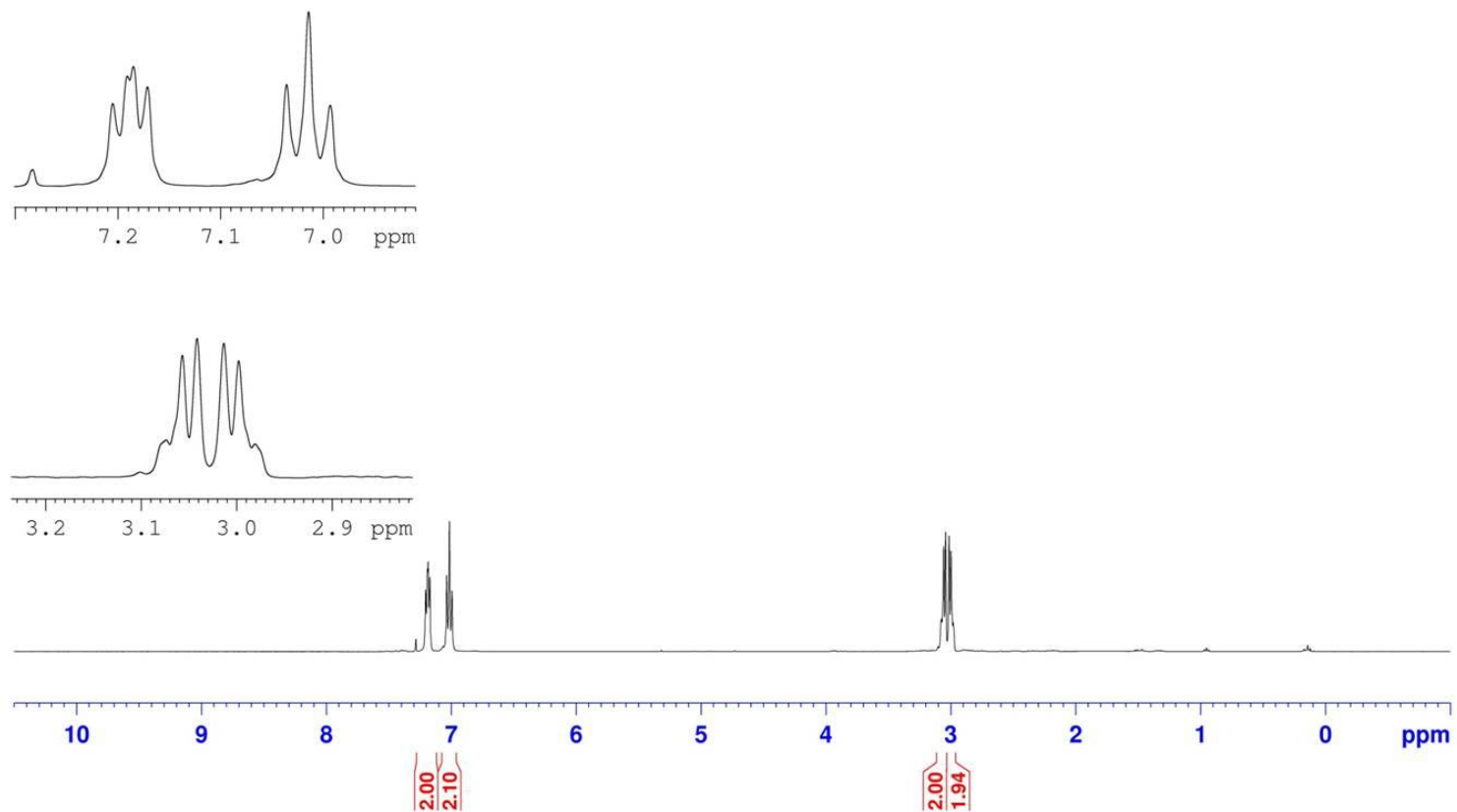
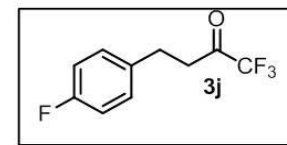
**1,1,1-trifluoro-4-(o-tolyl)butan-2-one**  
500 MHz, CDCl<sub>3</sub>



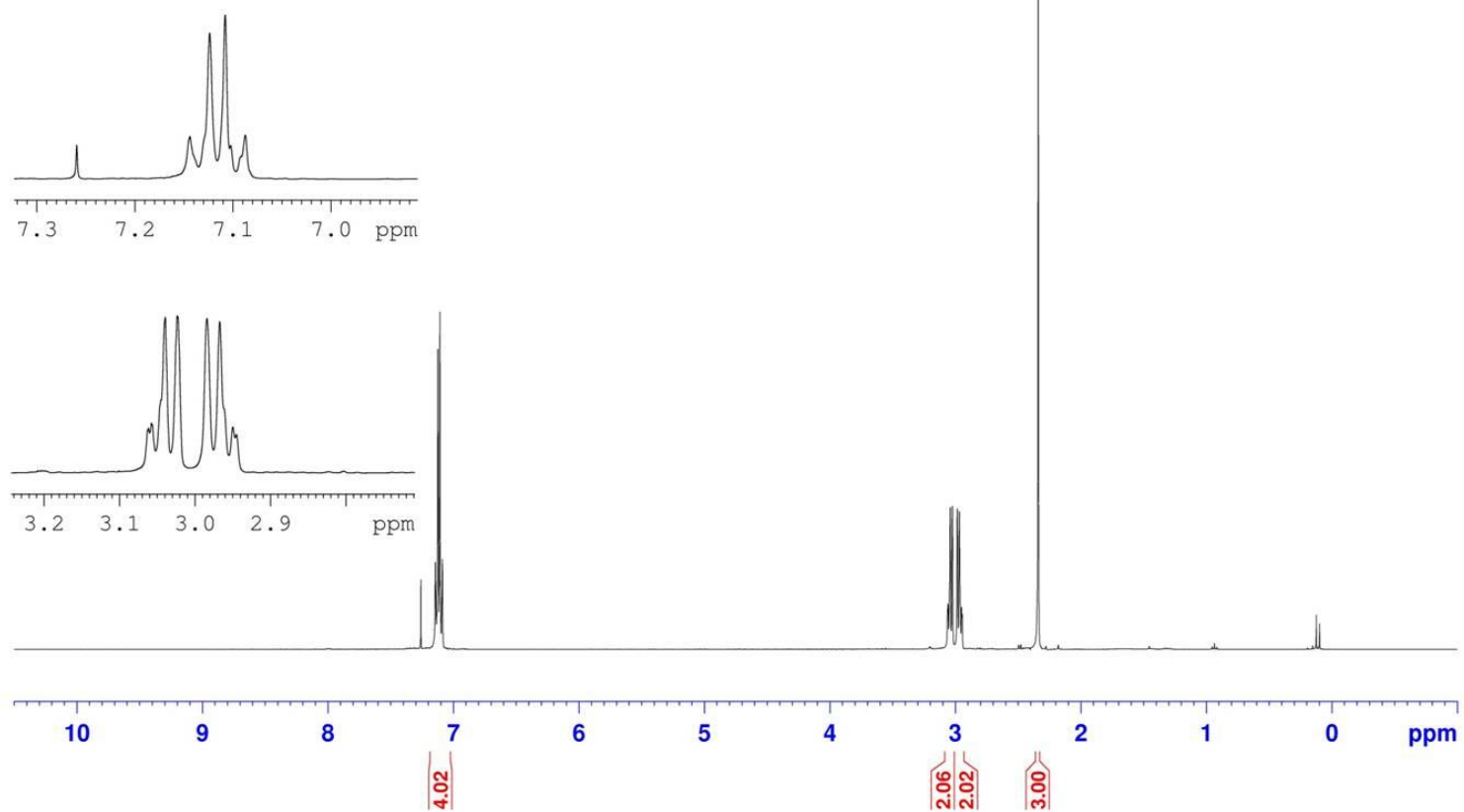
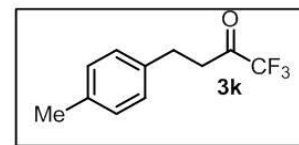
**1,1,1-trifluoro-4-(3-methoxyphenyl)butan-2-one**  
500 MHz, CDCl<sub>3</sub>



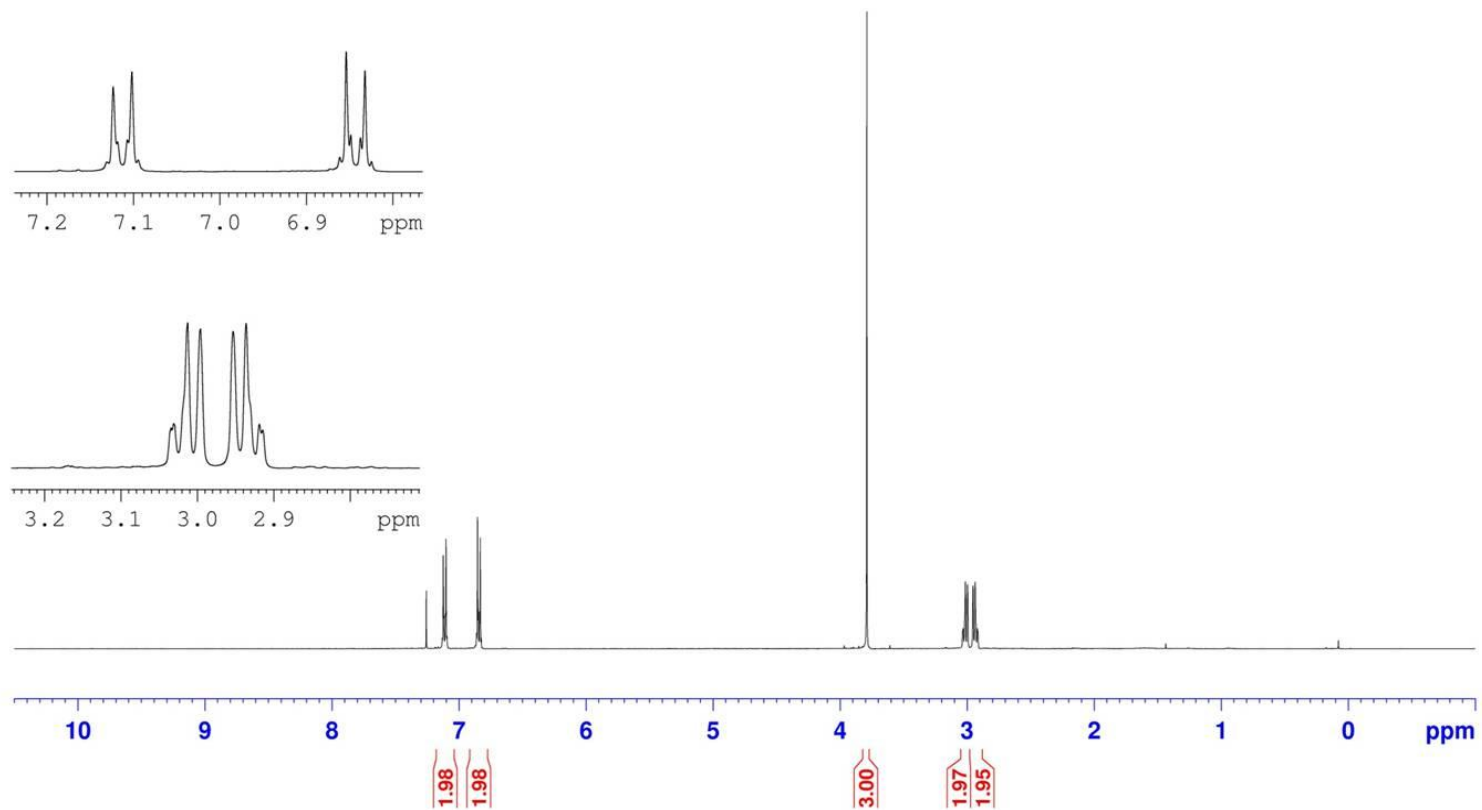
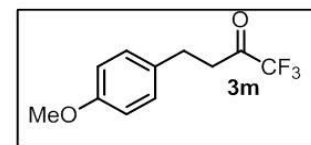
**1,1,1-trifluoro-4-(4-fluorophenyl)butan-2-one**  
400 MHz, CDCl<sub>3</sub>



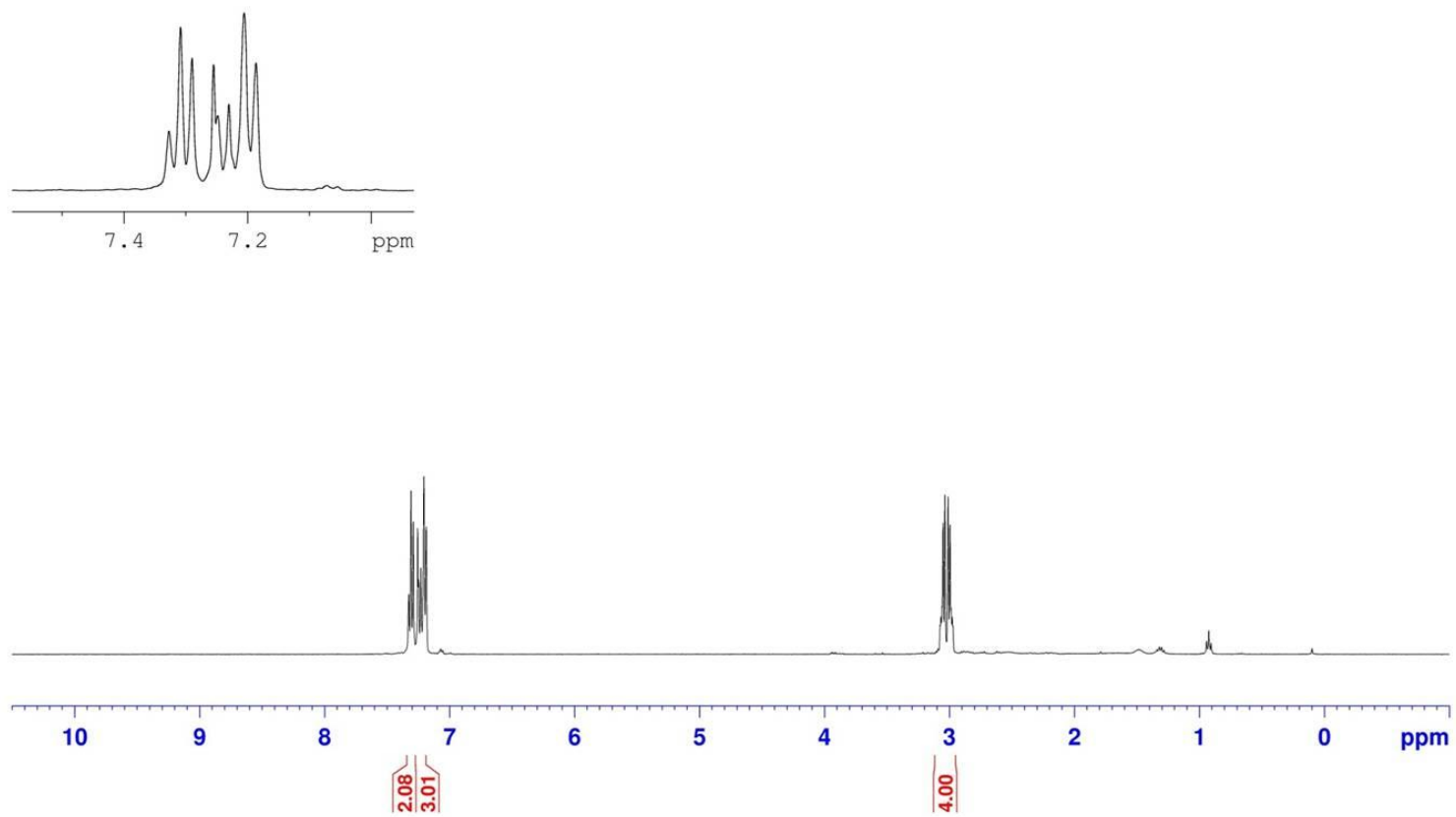
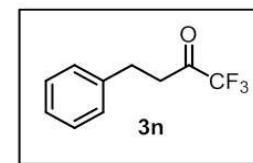
**1,1,1-trifluoro-4-p-tolylbutan-2-one**  
400 MHz, CDCl<sub>3</sub>



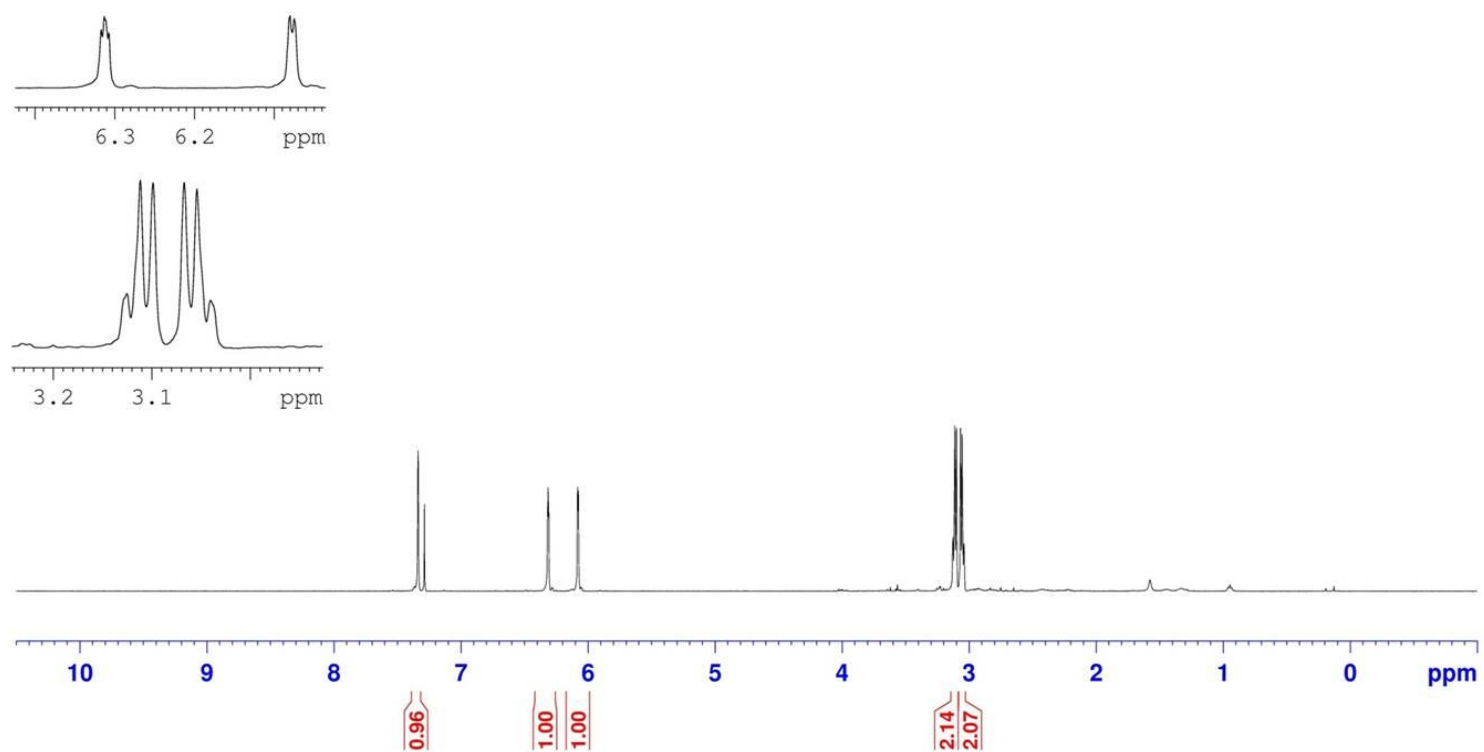
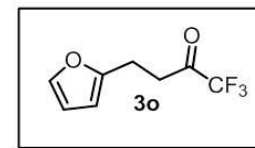
**1,1,1-trifluoro-4-(4-methoxyphenyl)butan-2-one**  
400 MHz, CDCl<sub>3</sub>



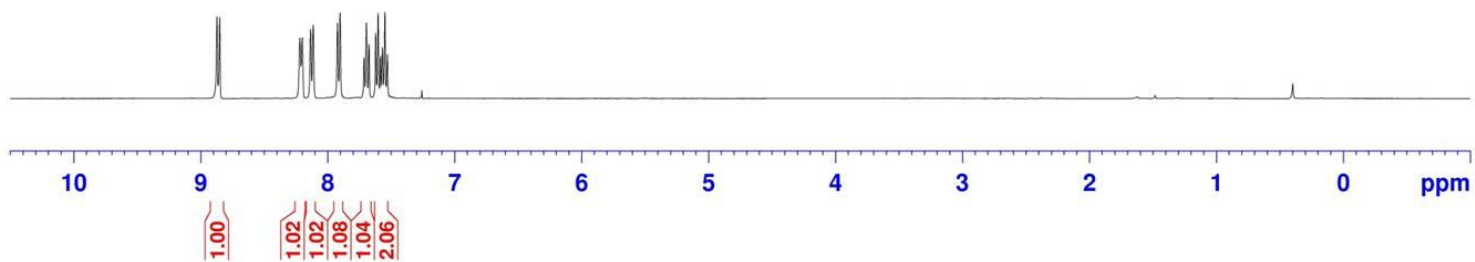
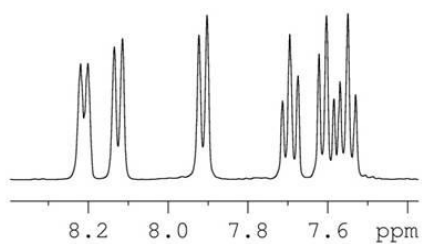
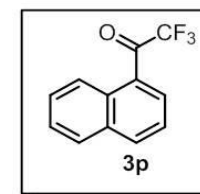
**1,1,1-trifluoro-4-phenylbutan-2-one**  
400 MHz, CDCl<sub>3</sub>



**1,1,1-trifluoro-4-(furan-2-yl)butan-2-one**  
500 MHz, CDCl<sub>3</sub>

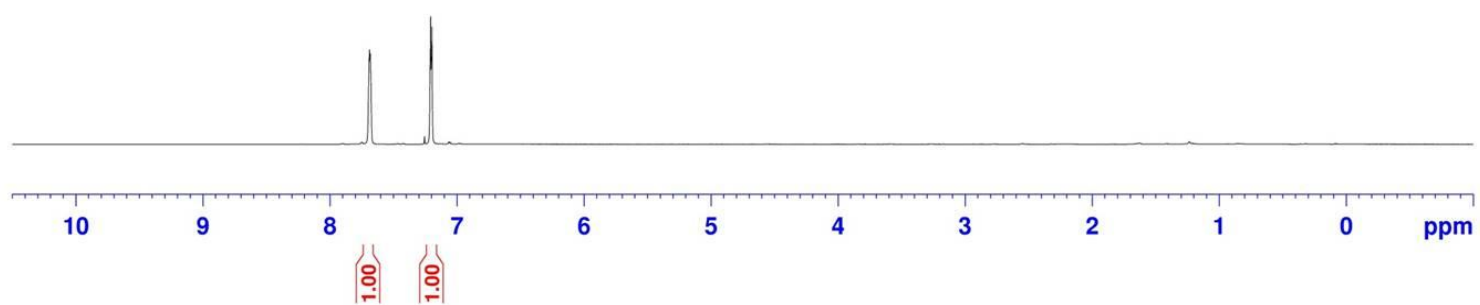
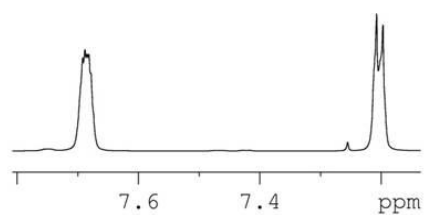
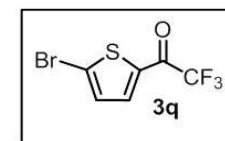


**2,2,2-trifluoro-1-(naphthalen-1-yl)ethanone**  
400 MHz, CDCl<sub>3</sub>

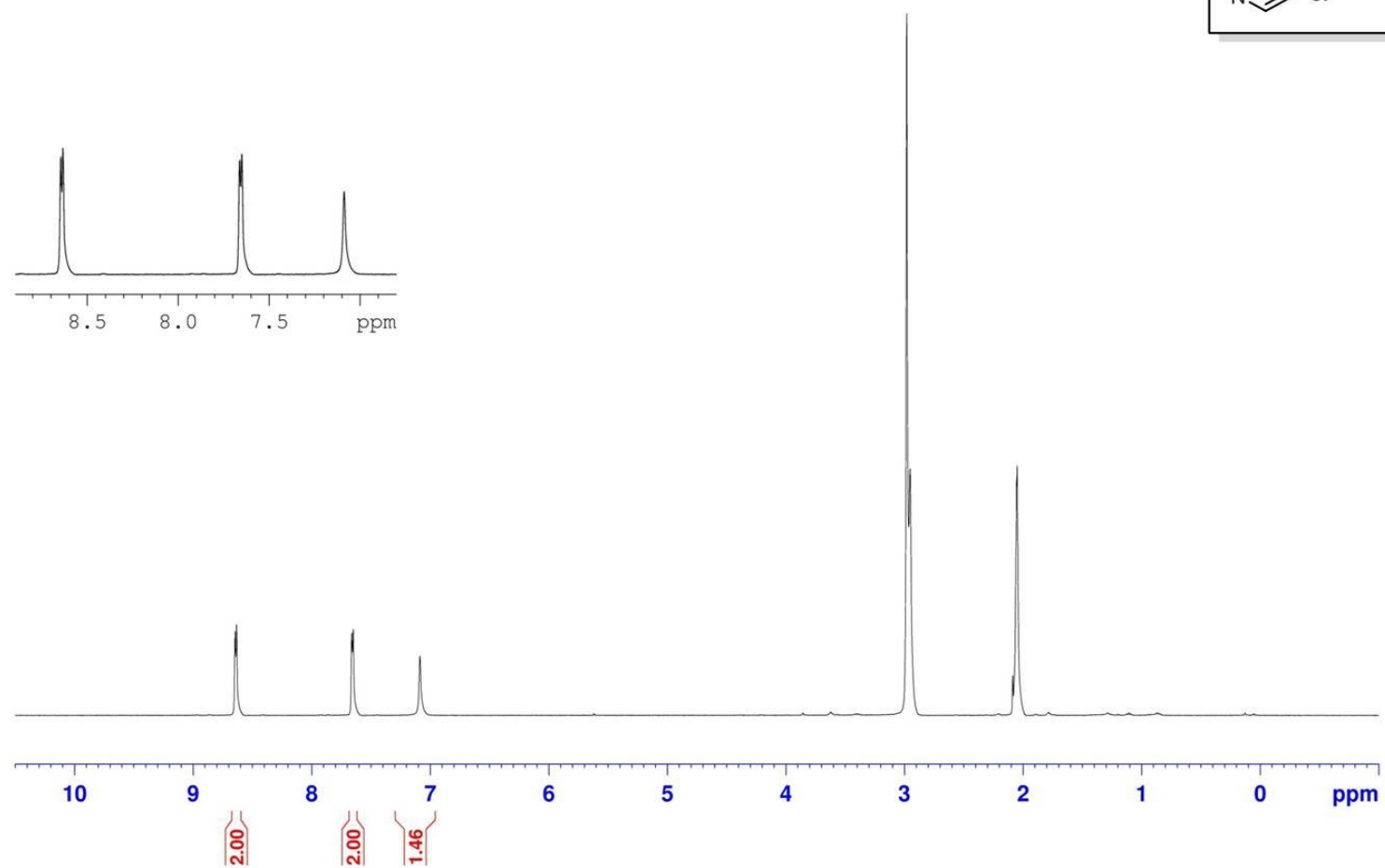
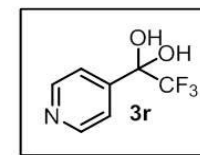




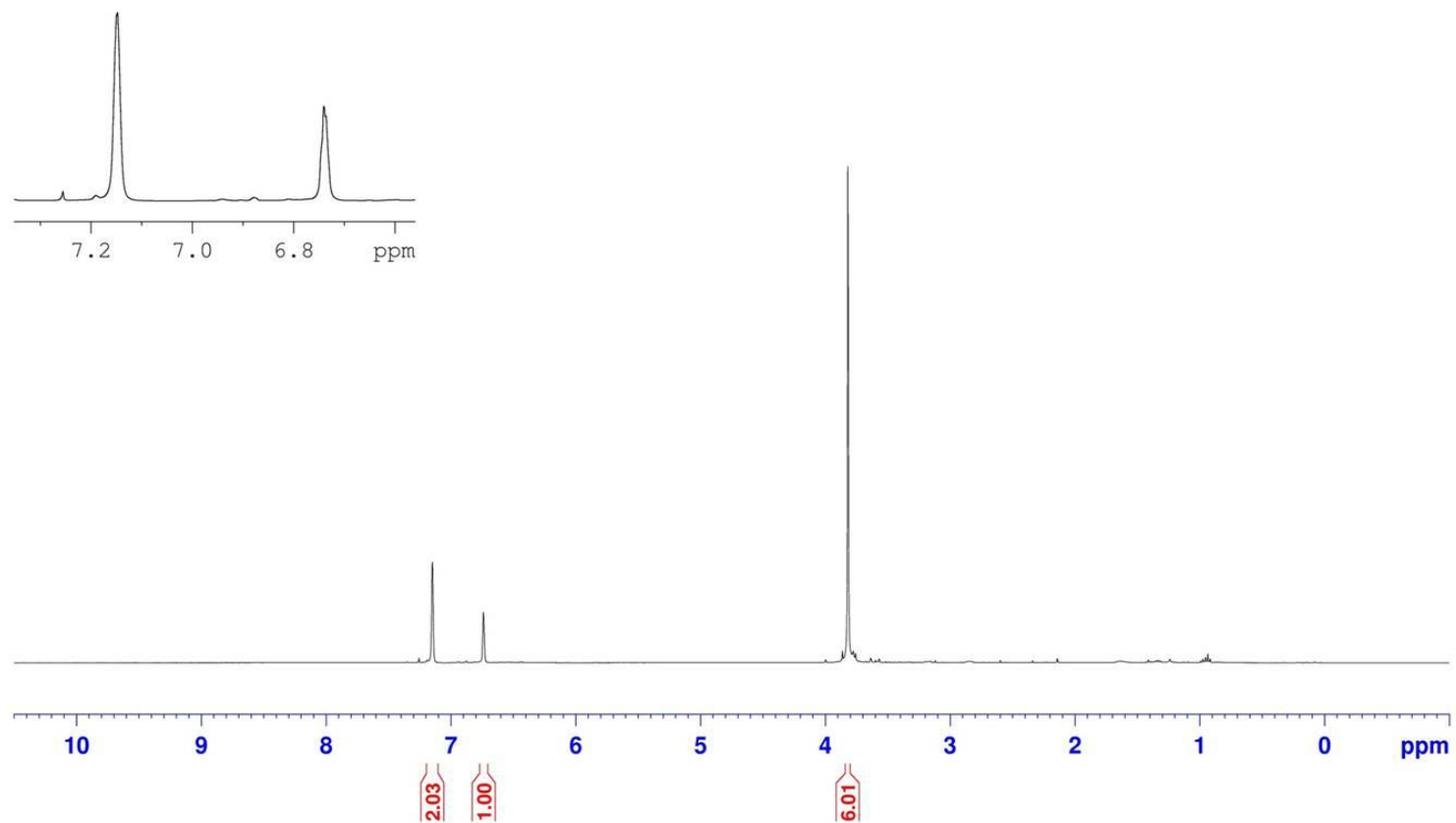
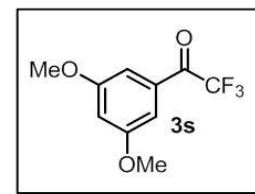
1-(5-bromothiophen-2-yl)-2,2,2-trifluoroethanone  
400 MHz, CDCl<sub>3</sub>



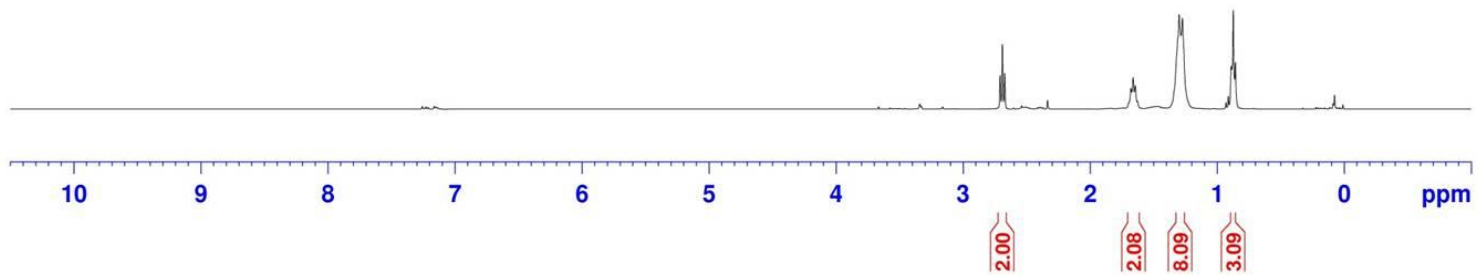
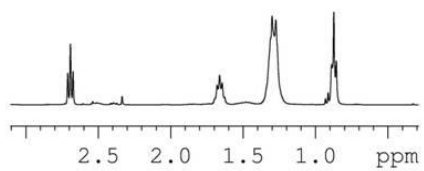
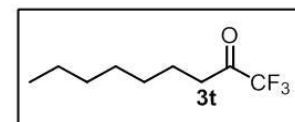
2,2,2-trifluoro-1-(pyridin-4-yl)ethane-1,1-diol  
400 MHz, Acetone-*d*<sub>6</sub>



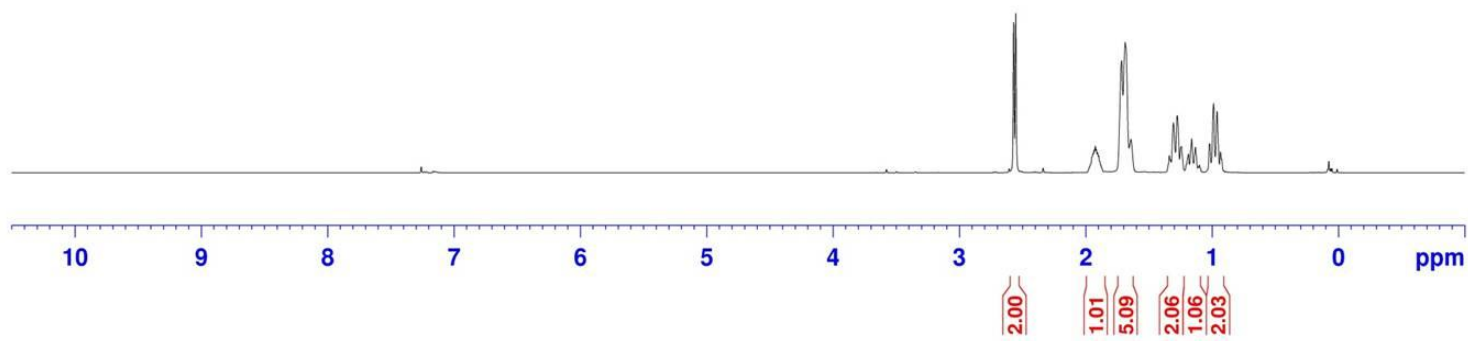
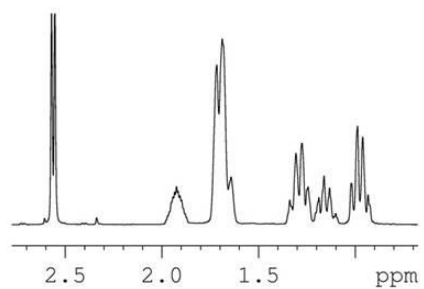
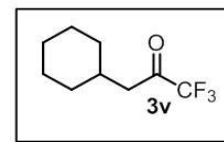
**1-(3,5-dimethoxyphenyl)-2,2,2-trifluoroethanone**  
400 MHz, CDCl<sub>3</sub>



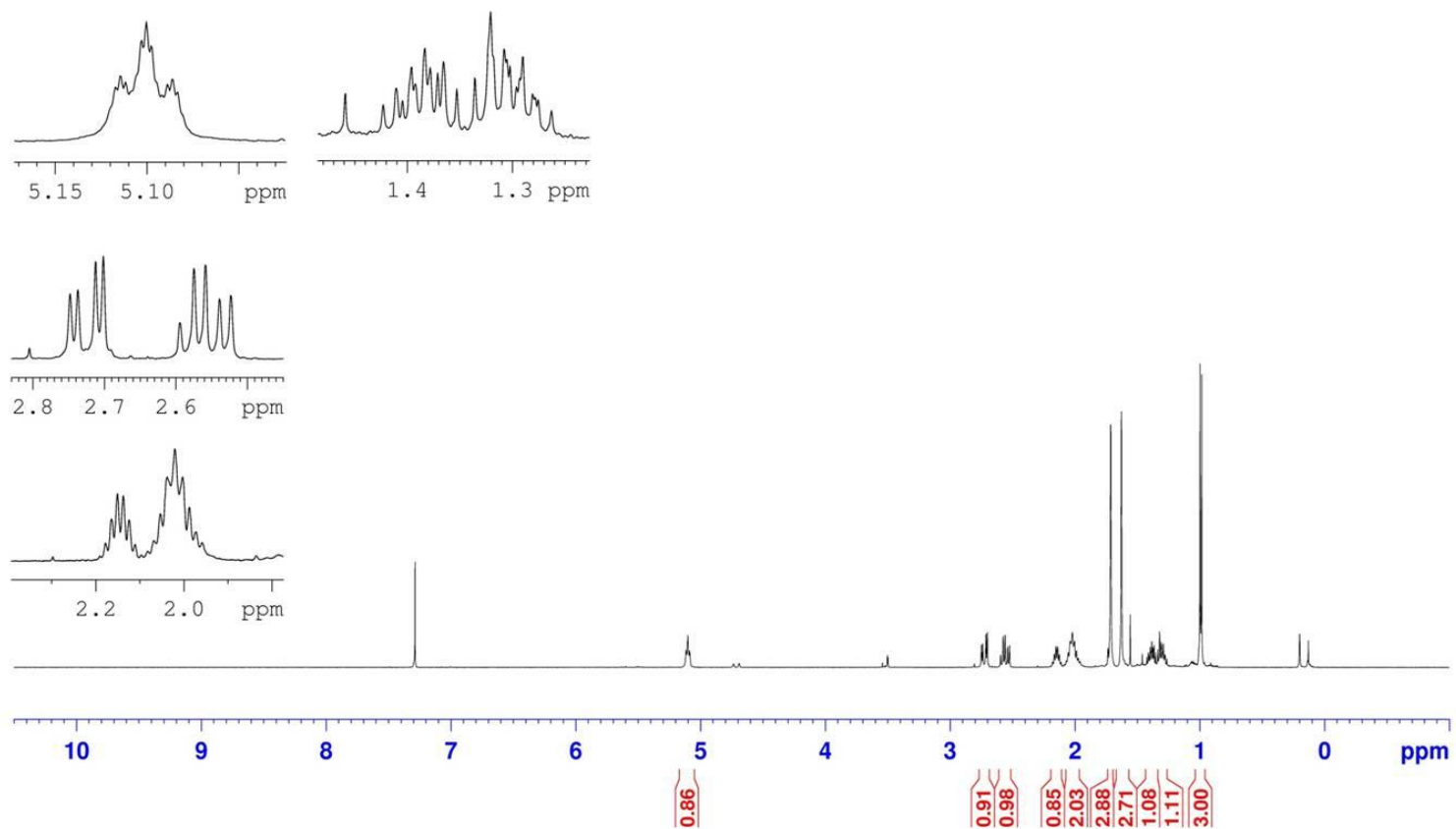
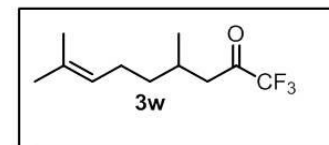
**1,1,1-trifluorononan-2-one**  
400 MHz, CDCl<sub>3</sub>



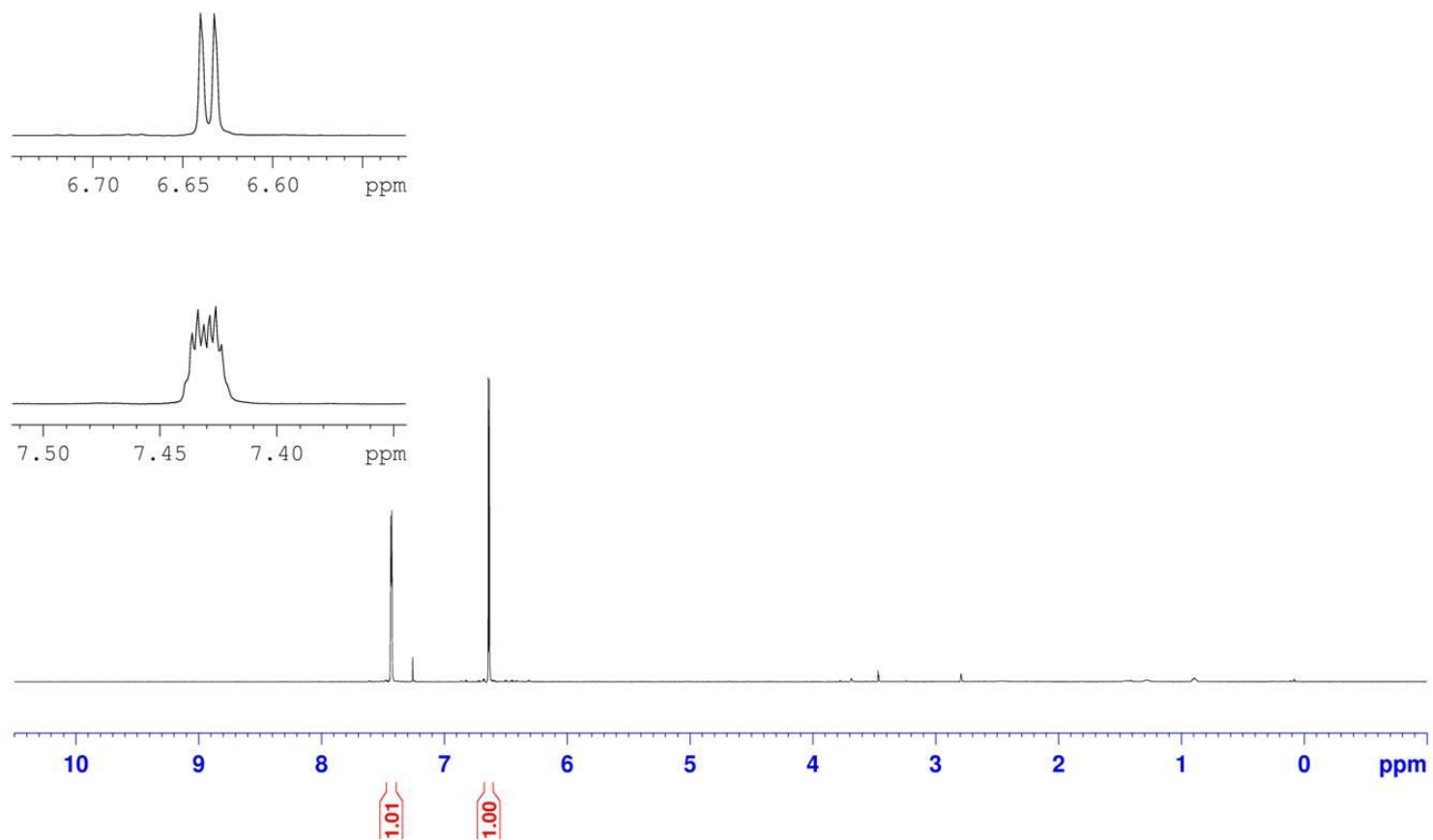
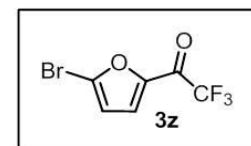
3-cyclohexyl-1,1,1-trifluoropropan-2-one  
400 MHz, CDCl<sub>3</sub>



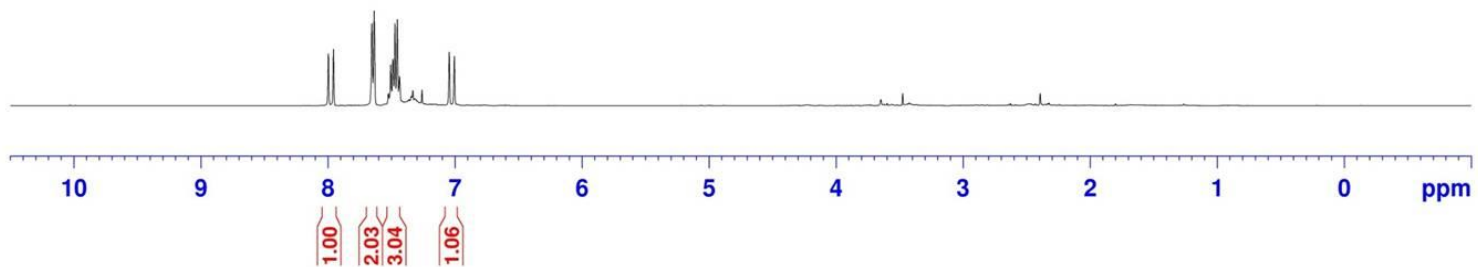
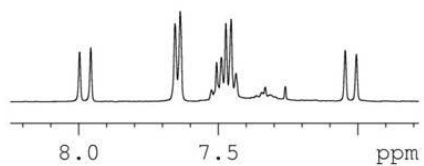
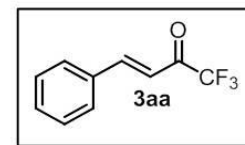
**N-methoxy-N,3,7-trimethyloct-6-enamide**  
500 MHz, CDCl<sub>3</sub>



**1-(5-bromofuran-2-yl)-2,2,2-trifluoroethanone**  
500 MHz, CDCl<sub>3</sub>

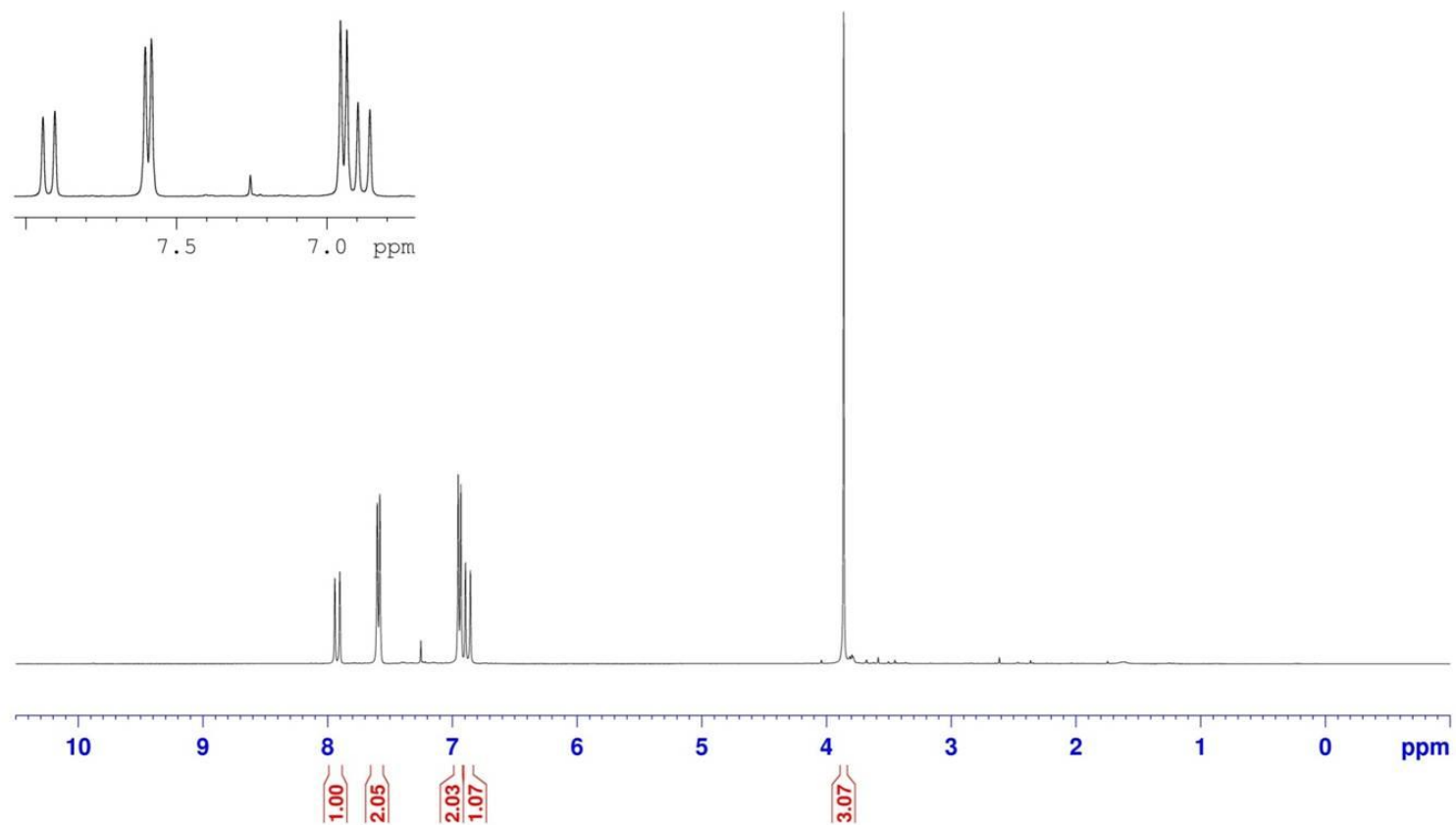
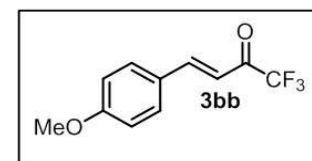


(E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one  
400 MHz, CDCl<sub>3</sub>

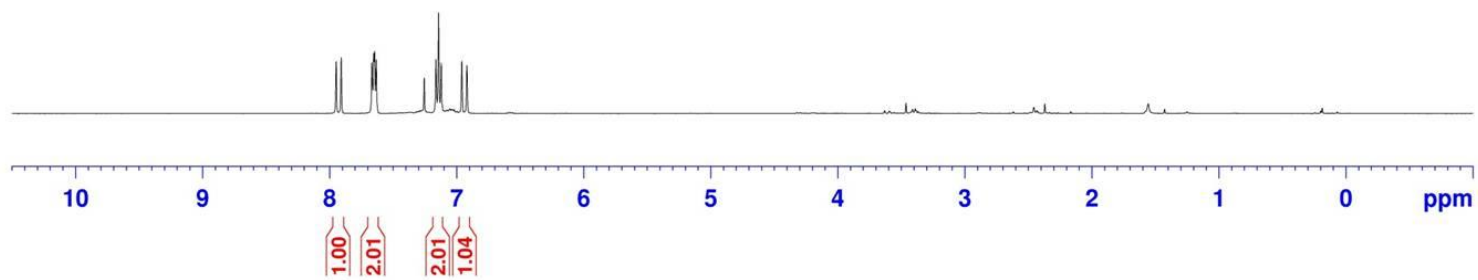
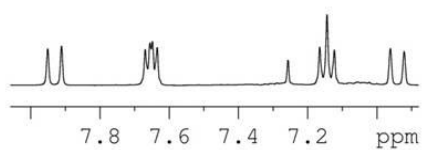
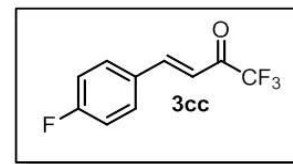




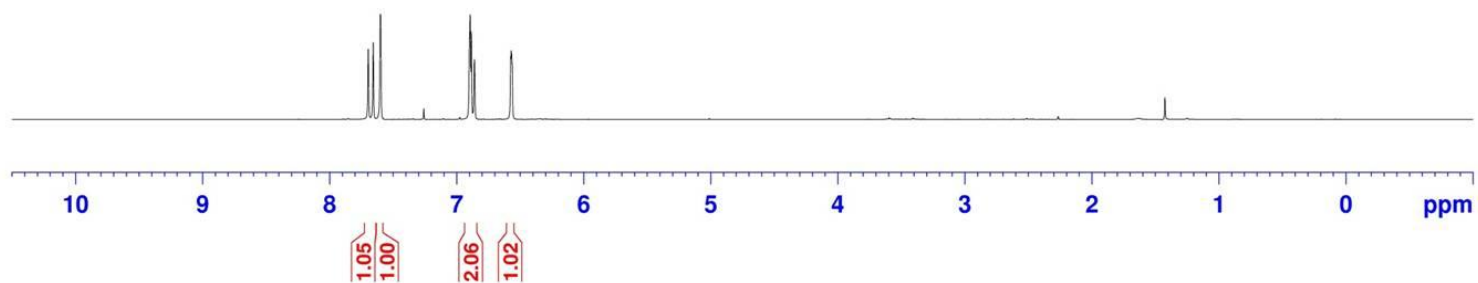
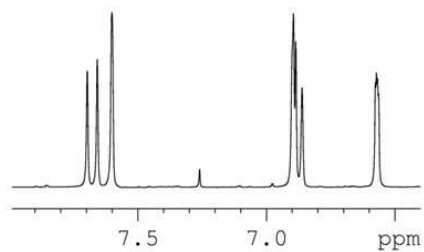
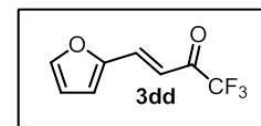
(E)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one  
400 MHz, CDCl<sub>3</sub>



(E)-1,1,1-trifluoro-4-(4-fluorophenyl)but-3-en-2-one  
400 MHz, CDCl<sub>3</sub>

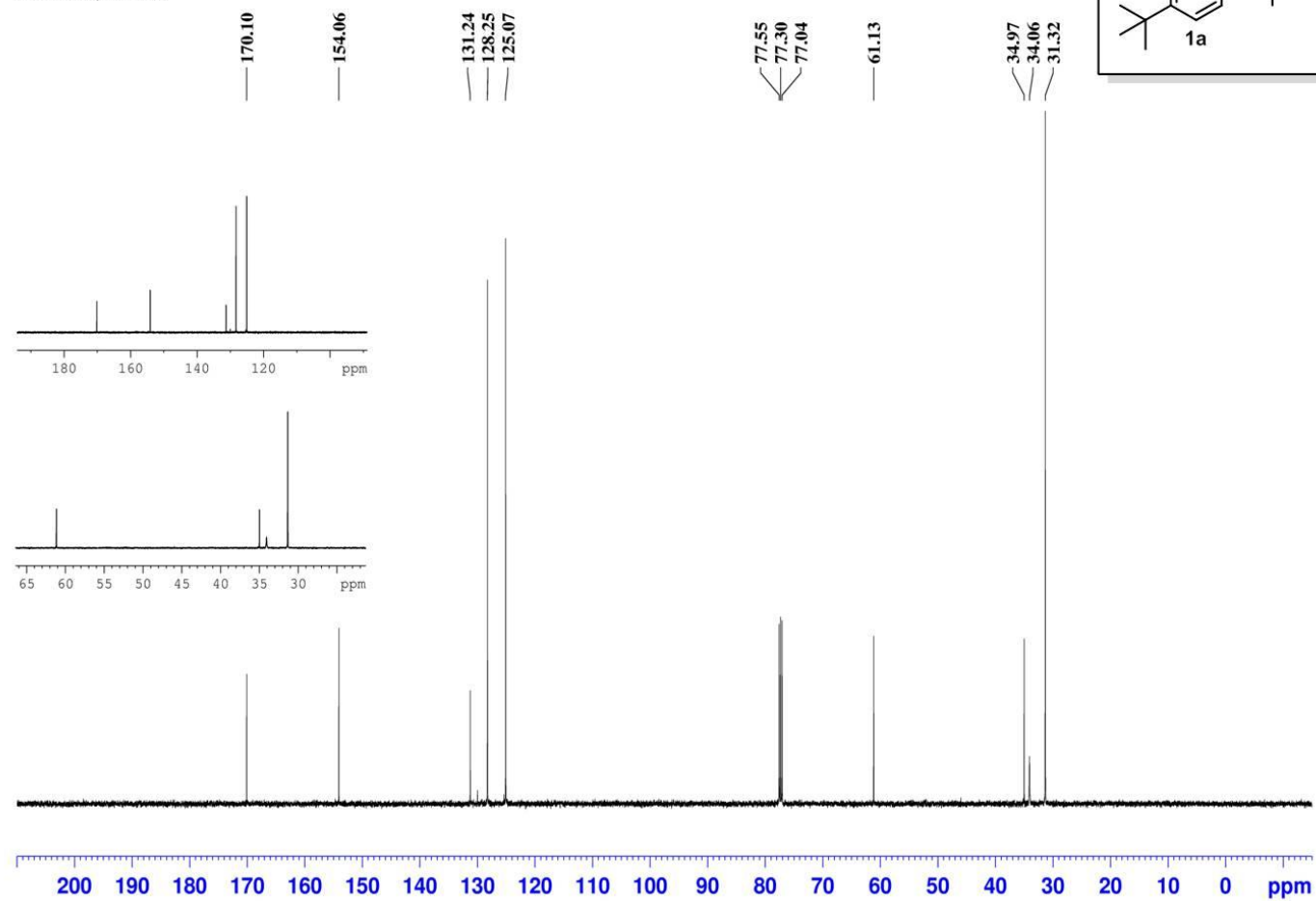


(E)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one  
400 MHz, CDCl<sub>3</sub>

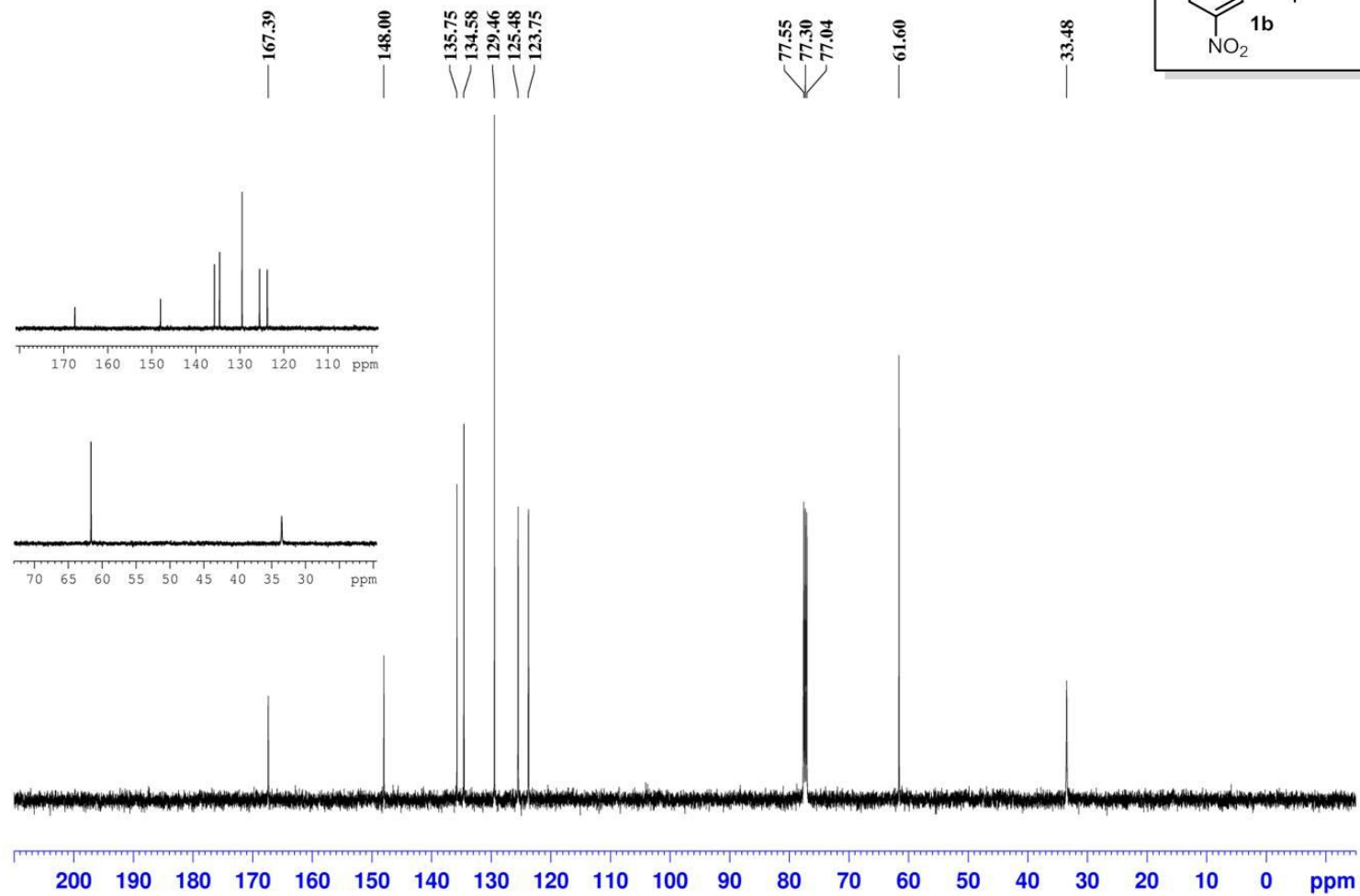


### <sup>13</sup>C-NMR Spectra of Synthesized Compounds

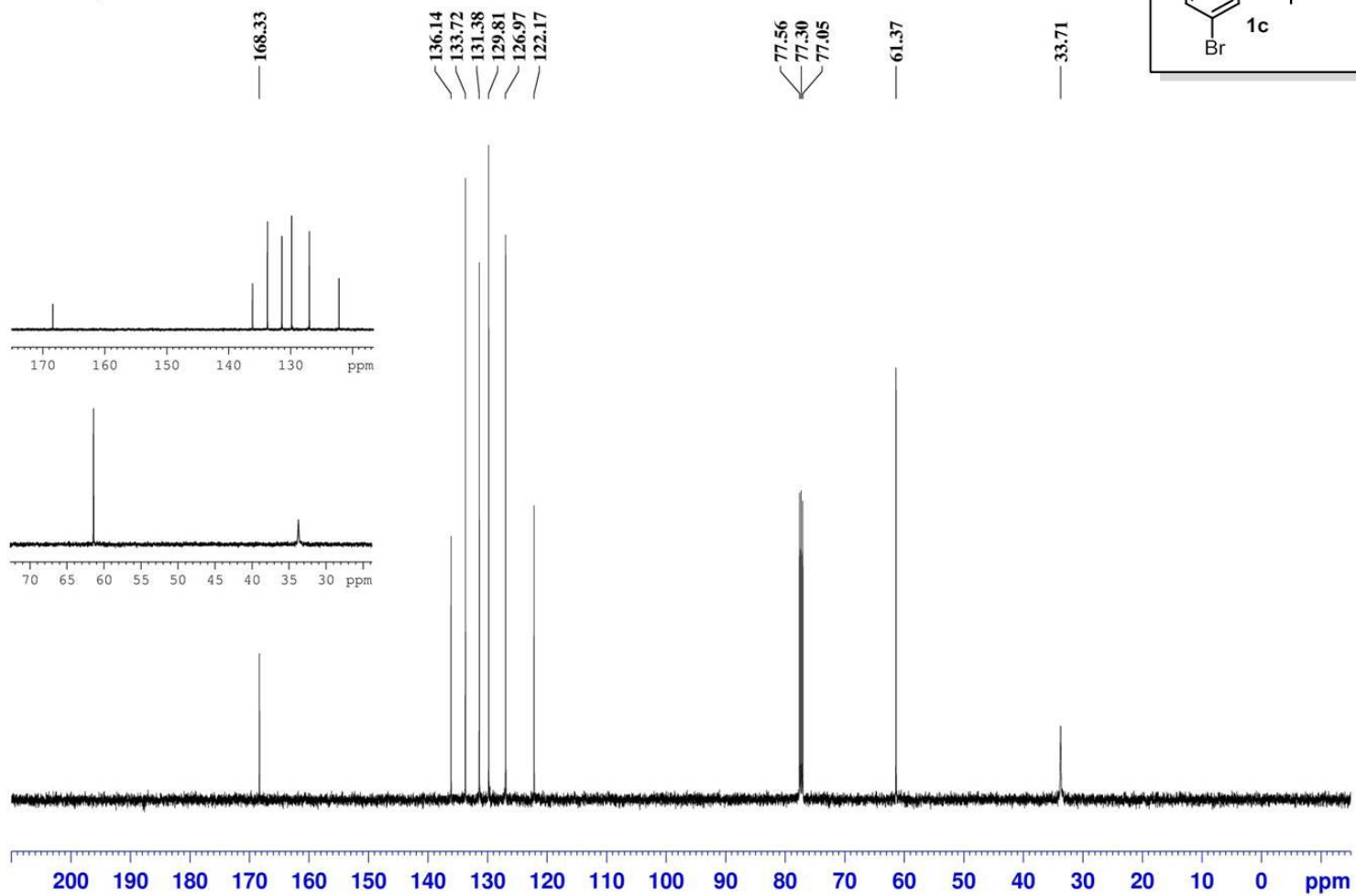
4-tert-butyl-N-methoxy-N-methylbenzamide  
125 MHz, CDCl<sub>3</sub>



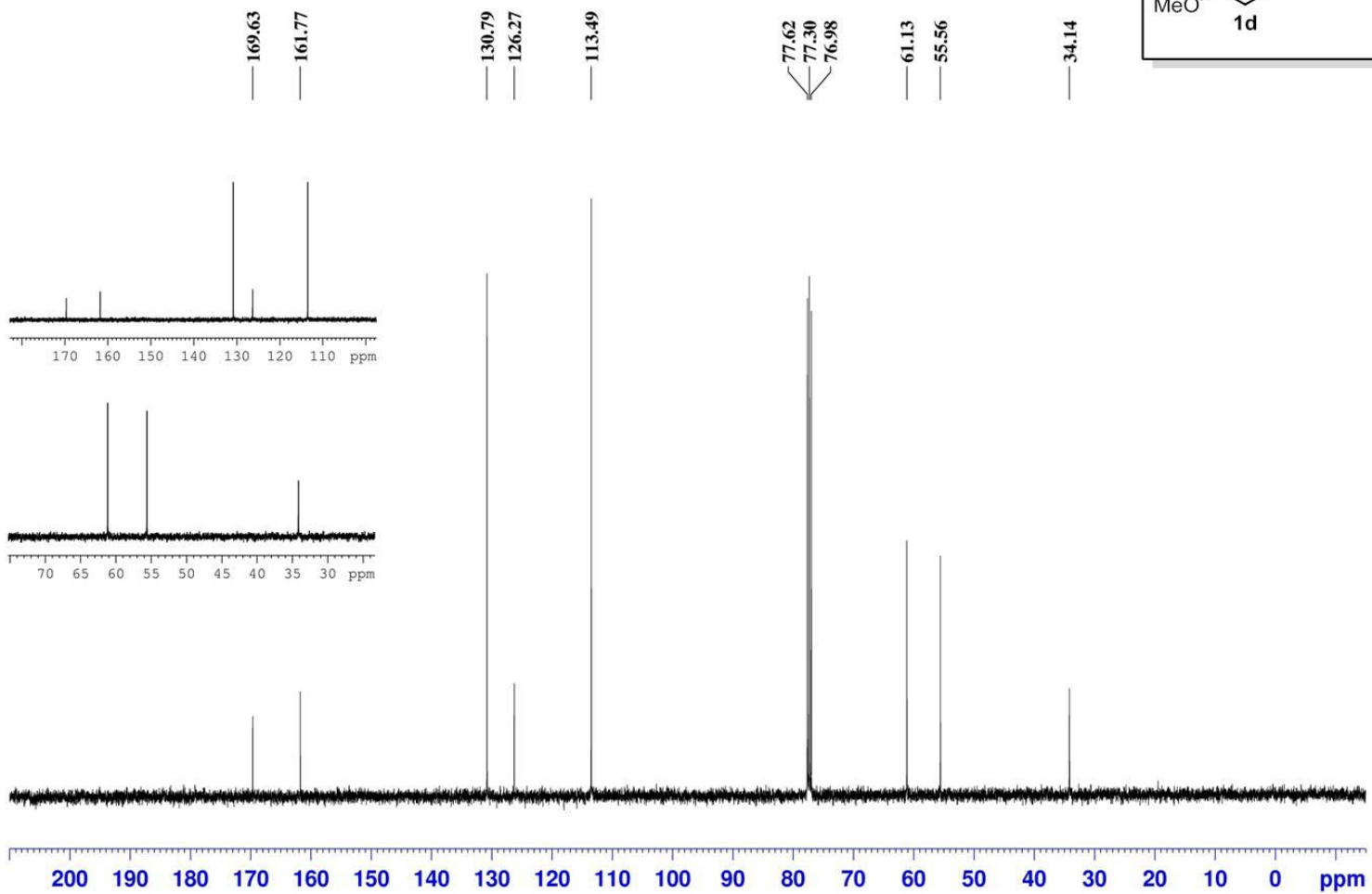
**N-methoxy-N-methyl-3-nitrobenzamide**  
125 MHz, CDCl<sub>3</sub>

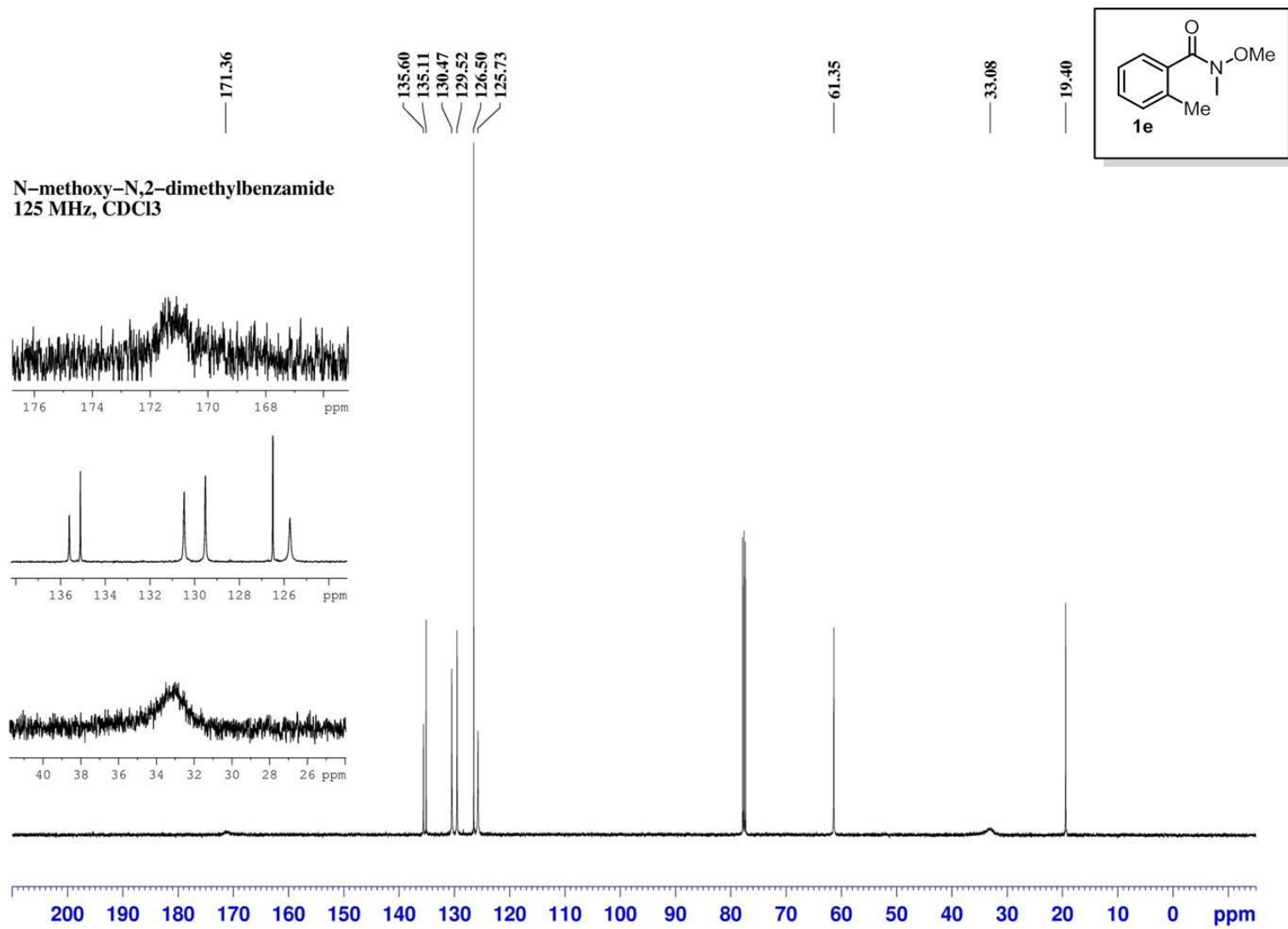


**3-bromo-N-methoxy-N-methylbenzamide**  
125 MHz, CDCl<sub>3</sub>

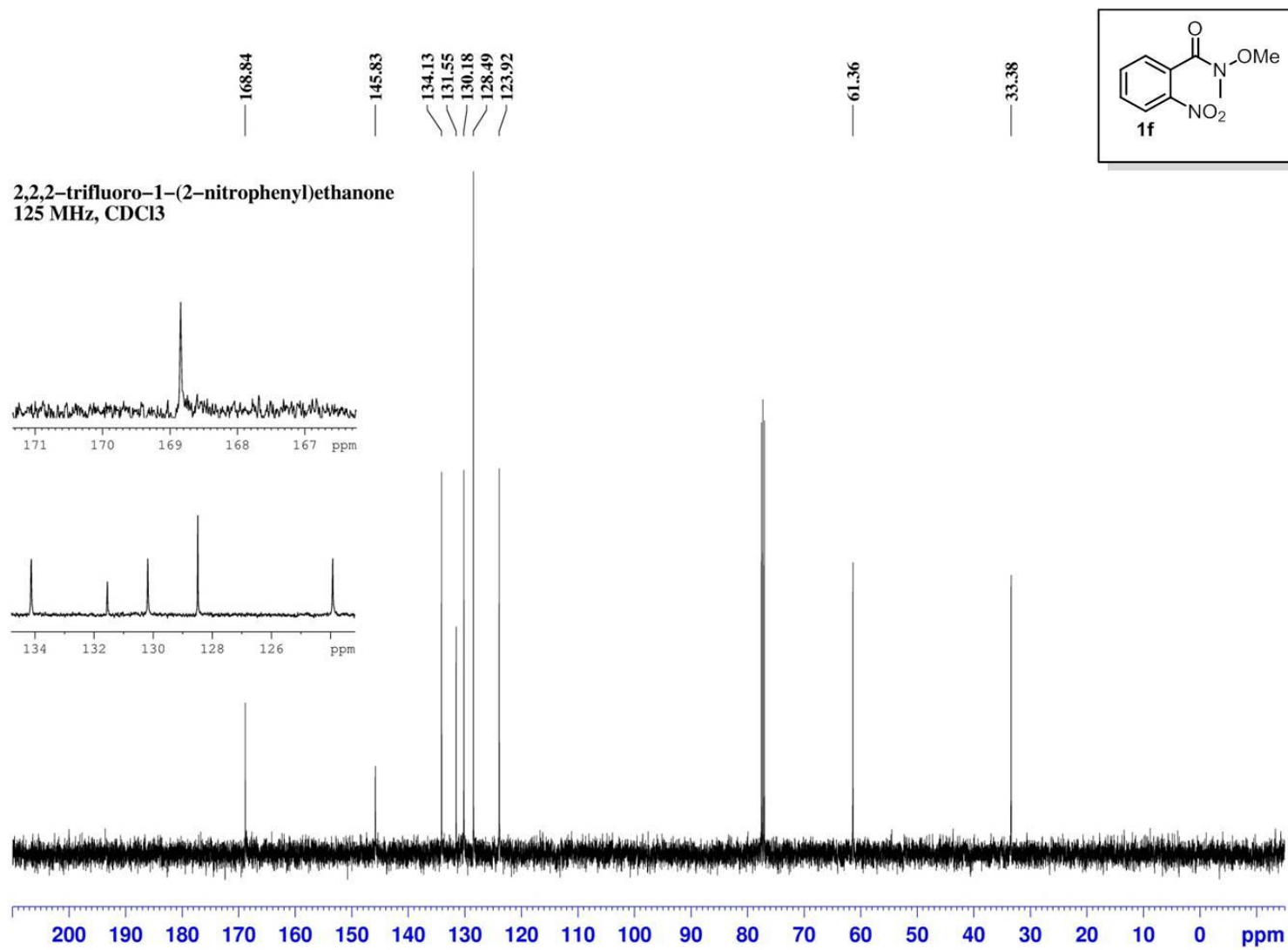


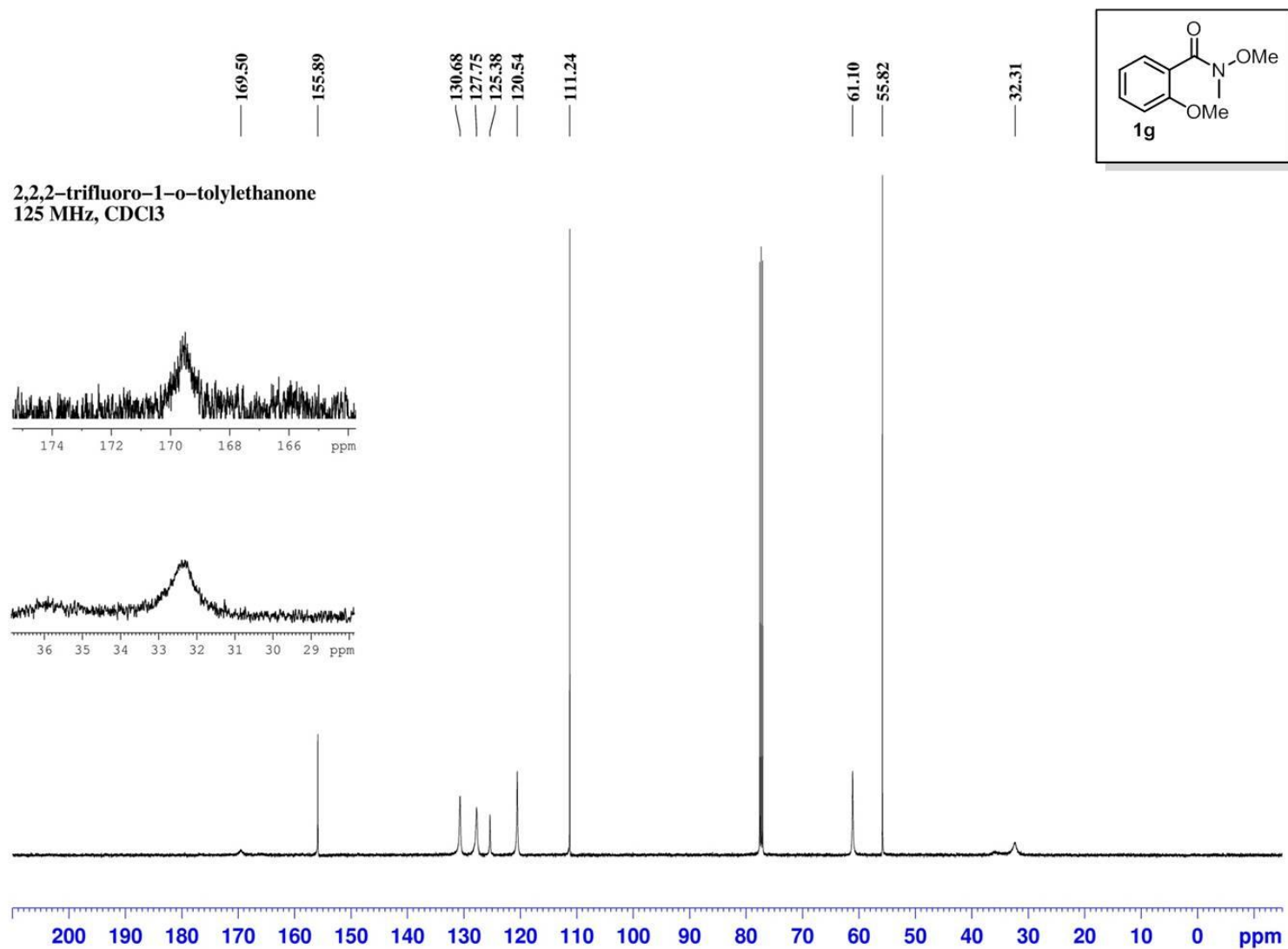
**N,4-dimethoxy-N-methylbenzamide**  
100 MHz, CDCl<sub>3</sub>



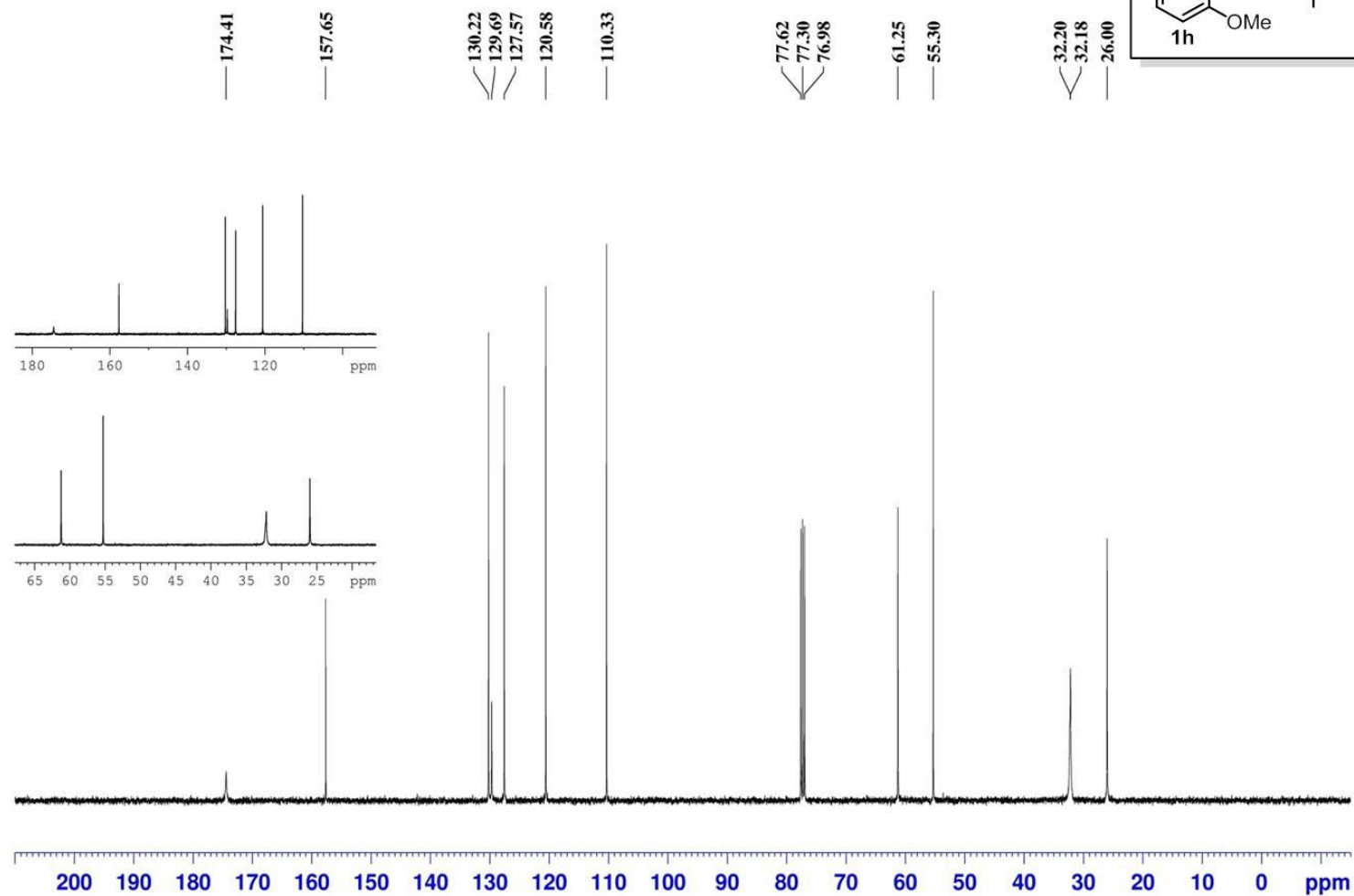


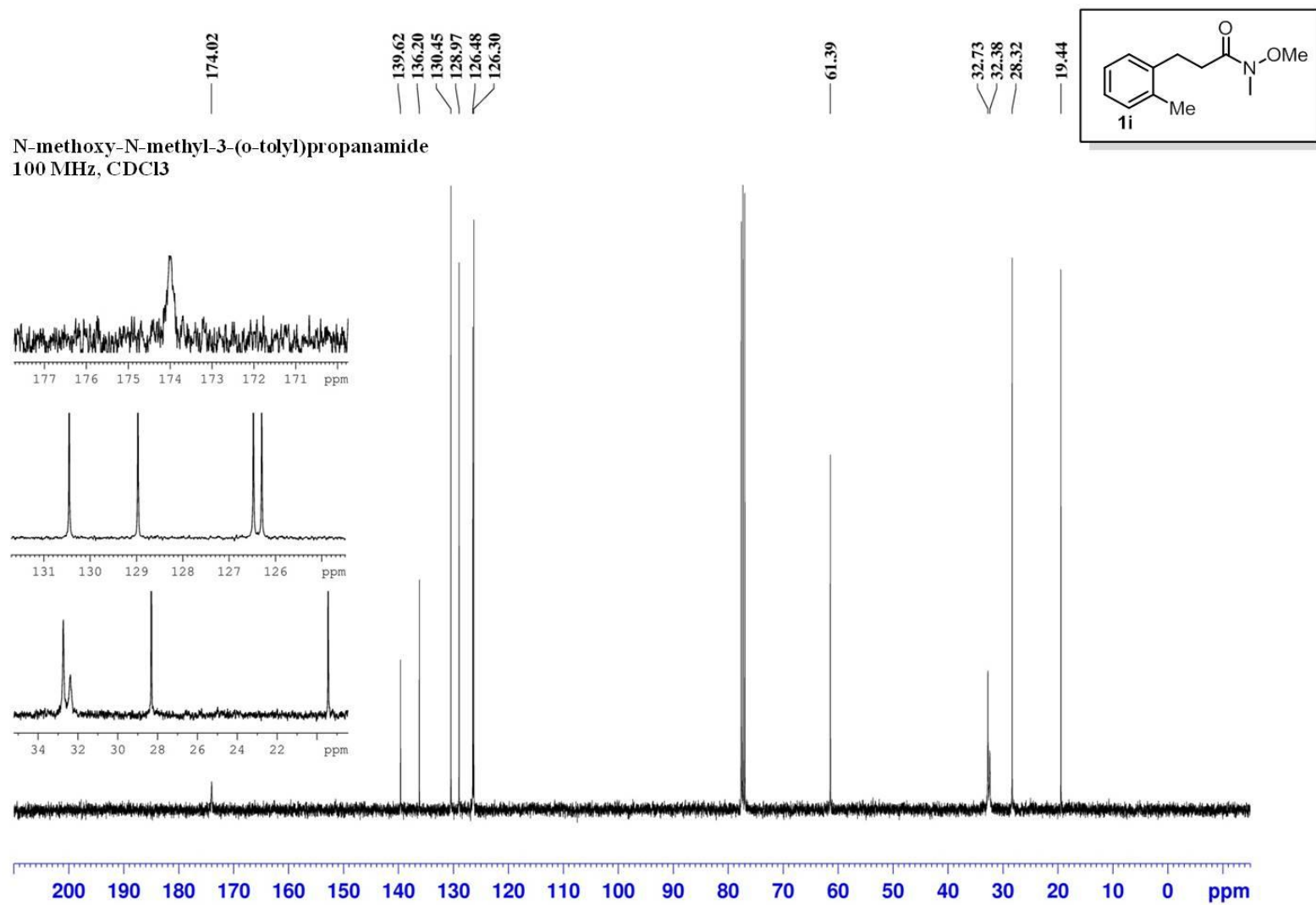


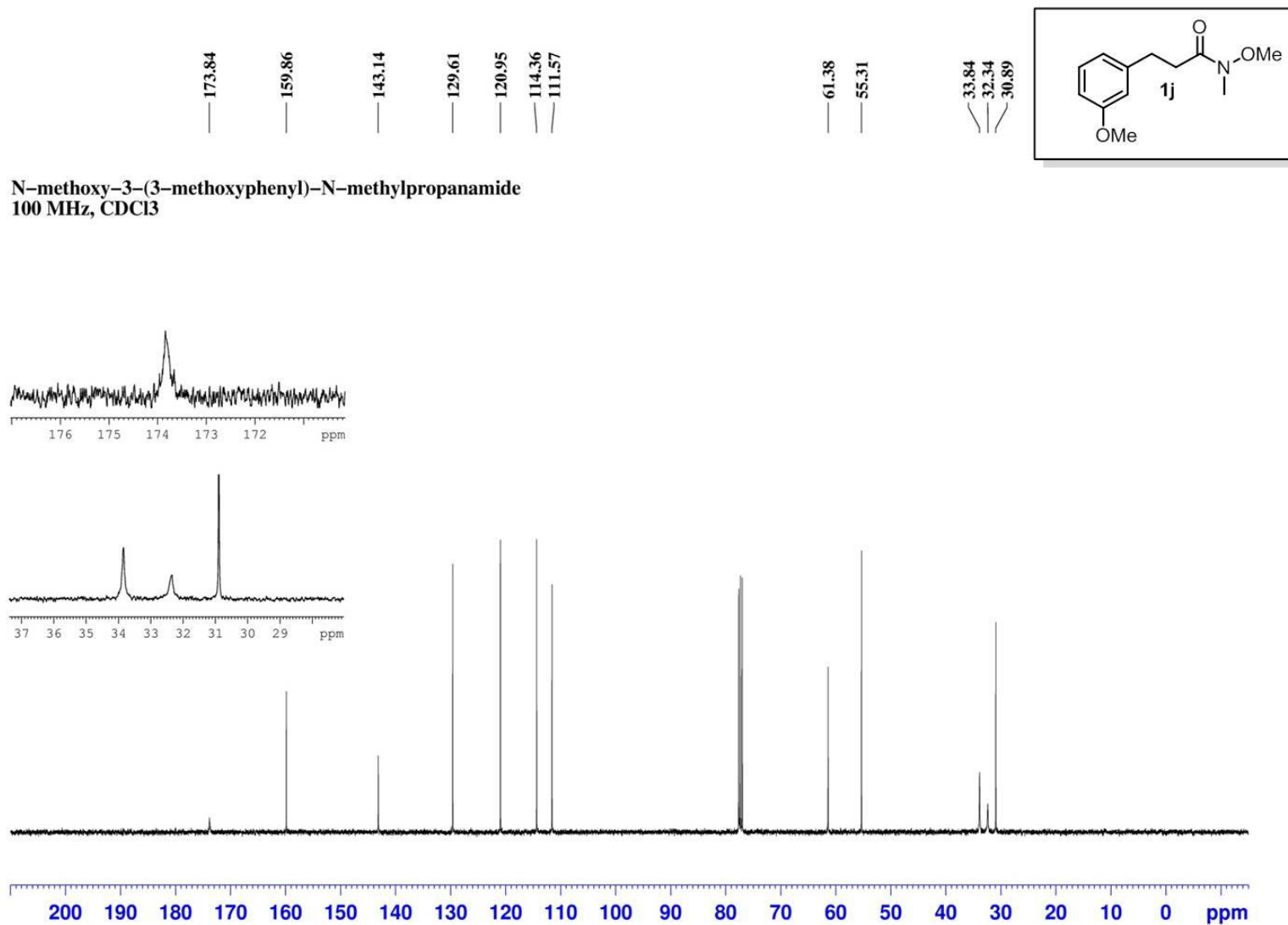


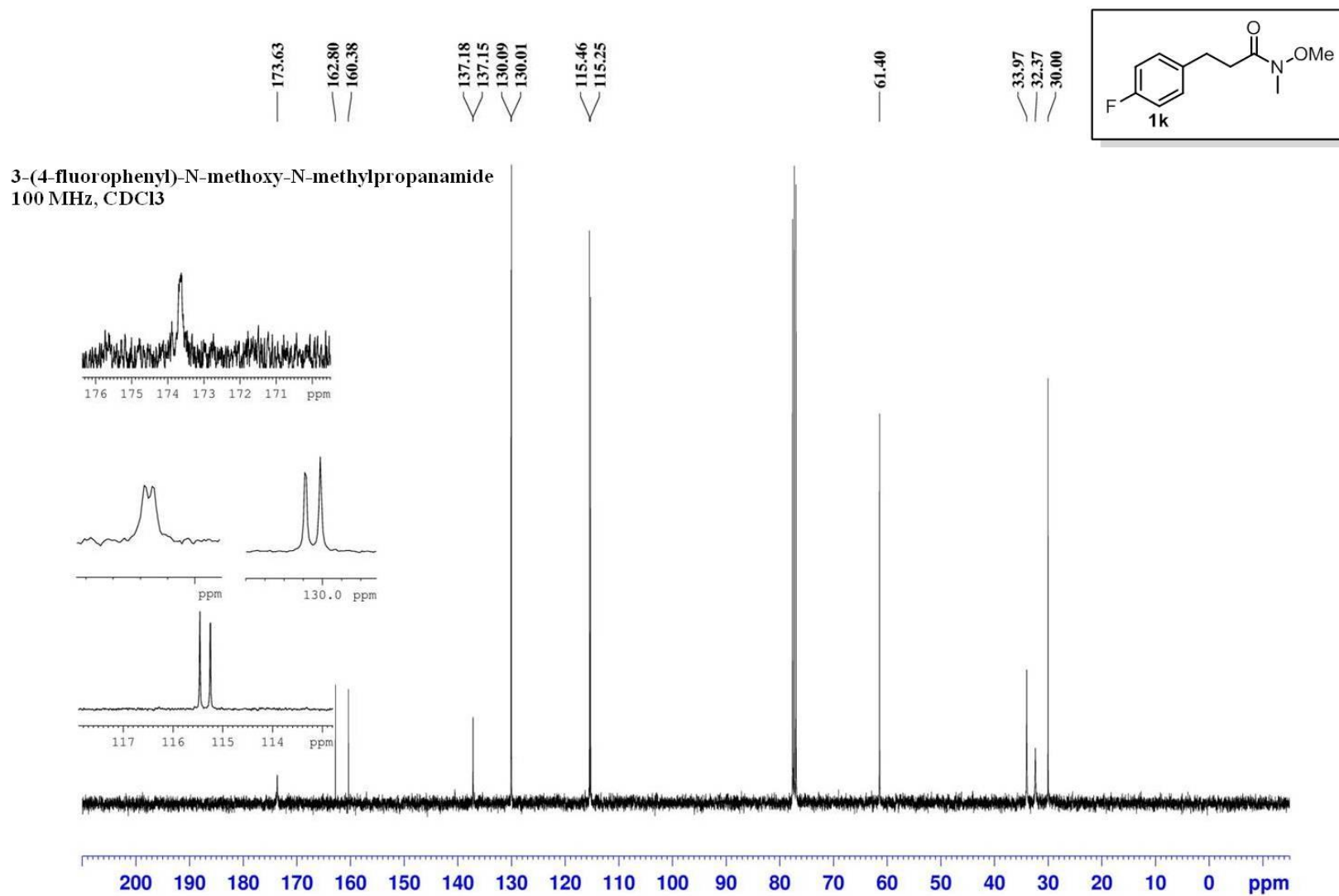


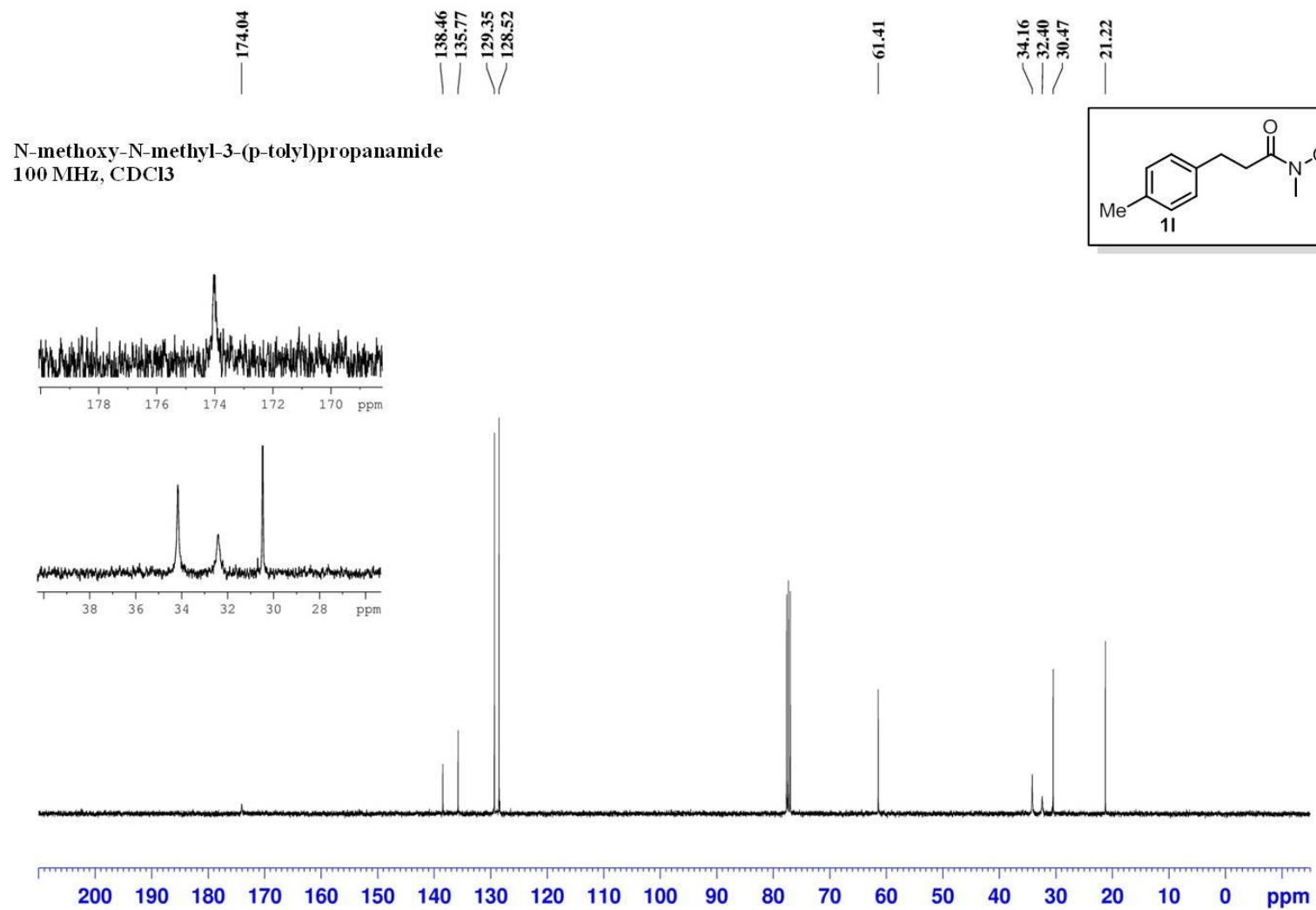
**N-methoxy-N-methyl-3-(3-methoxyphenyl)propanamide**  
100 MHz, CDCl<sub>3</sub>

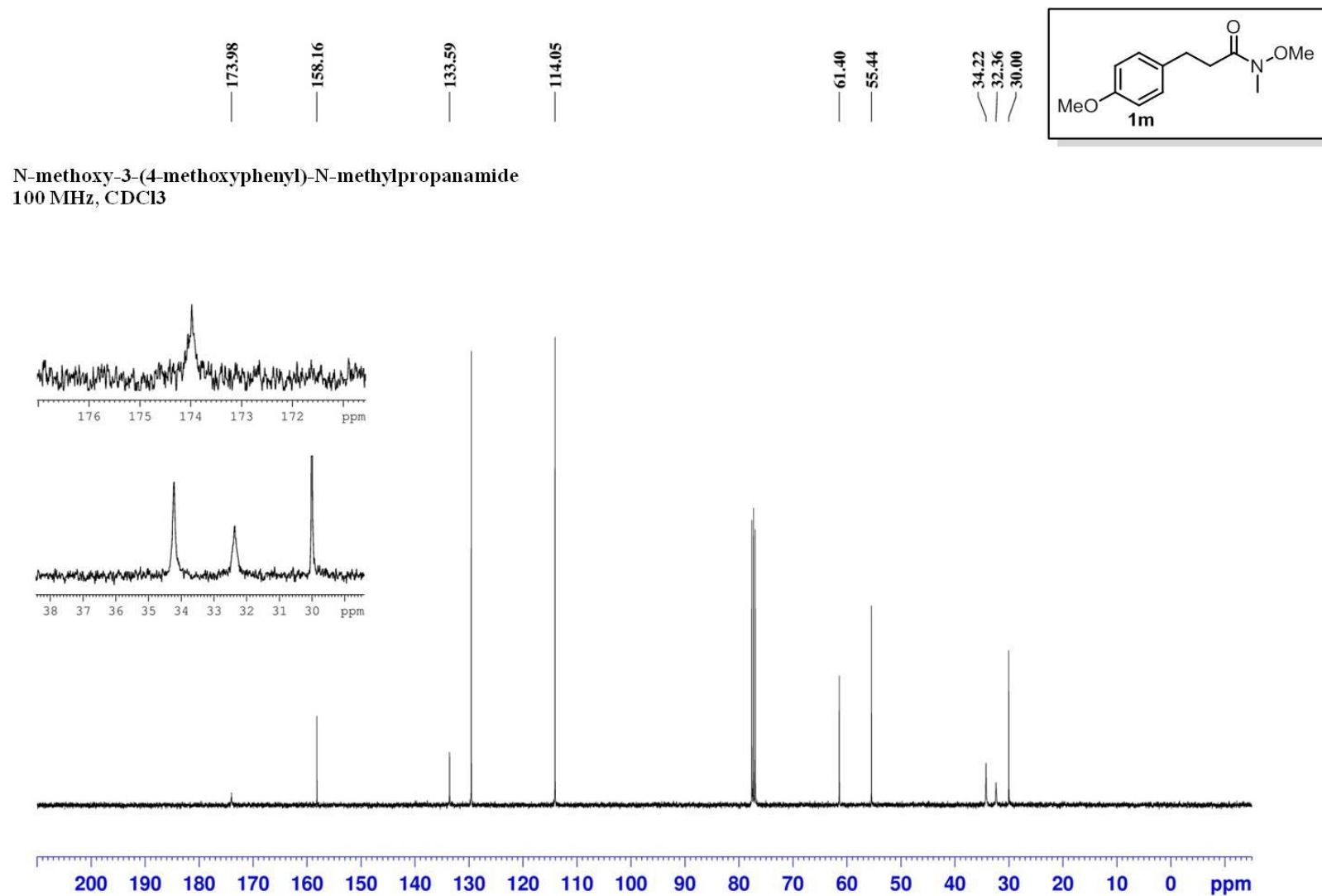






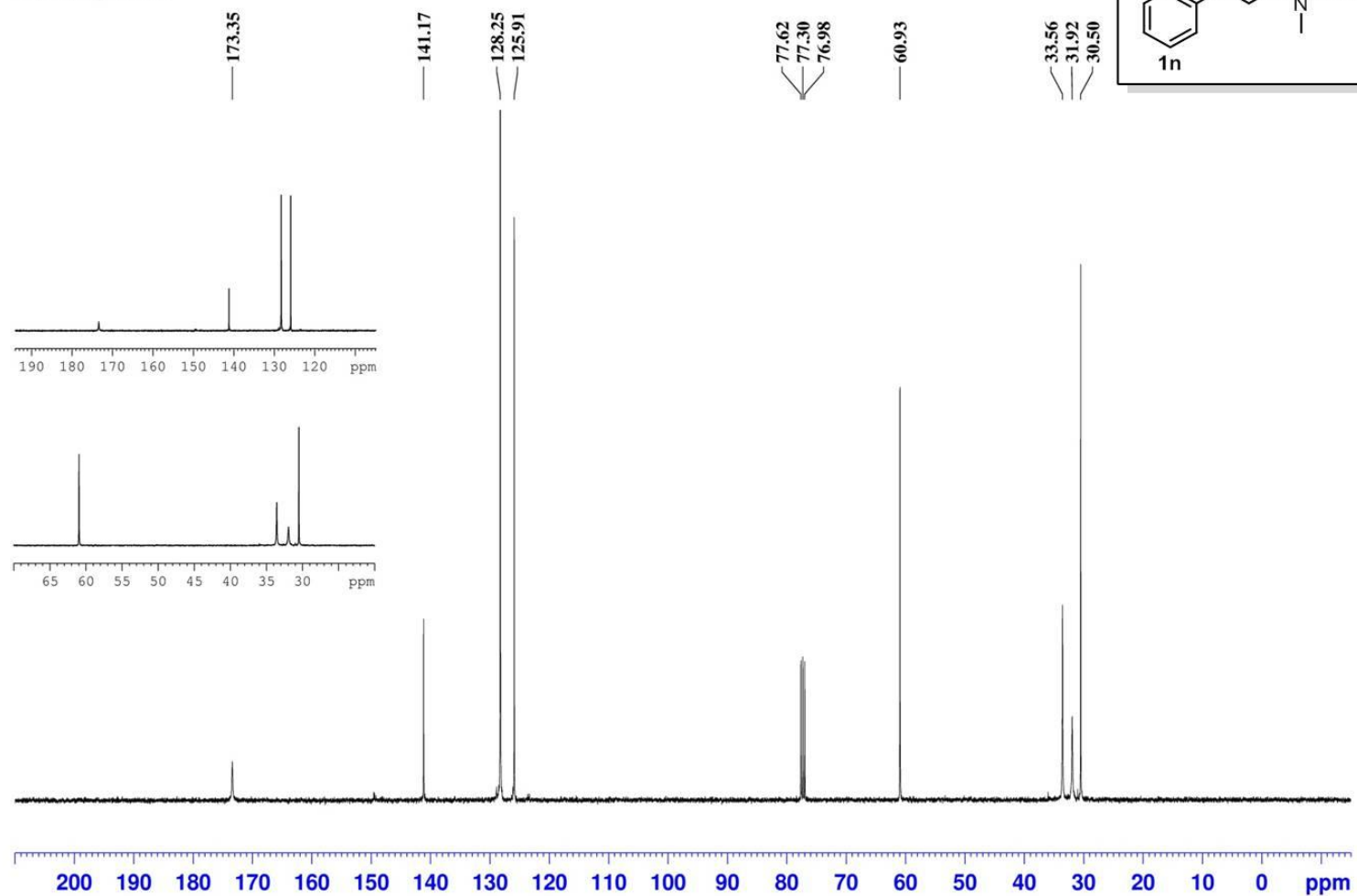




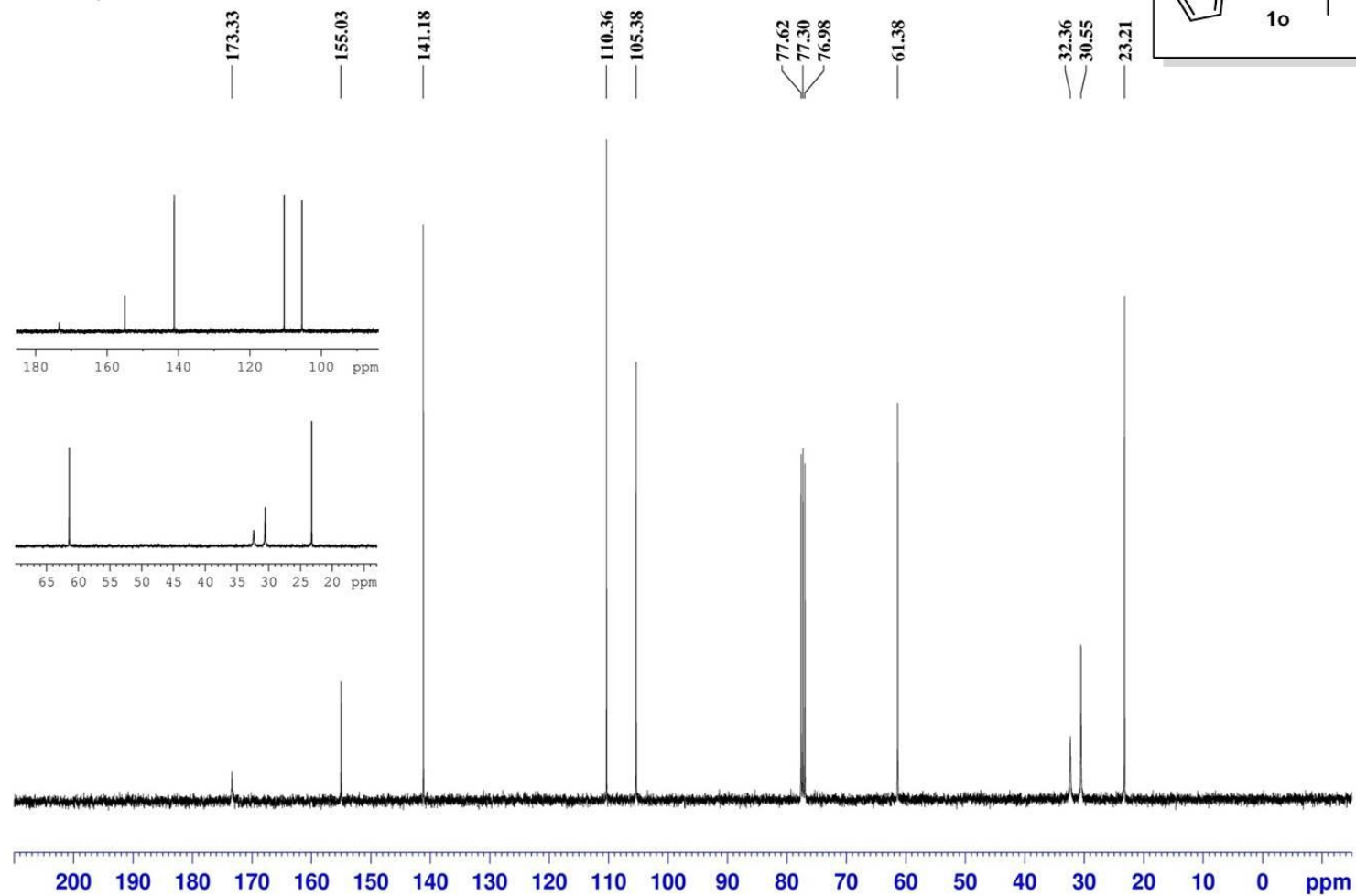




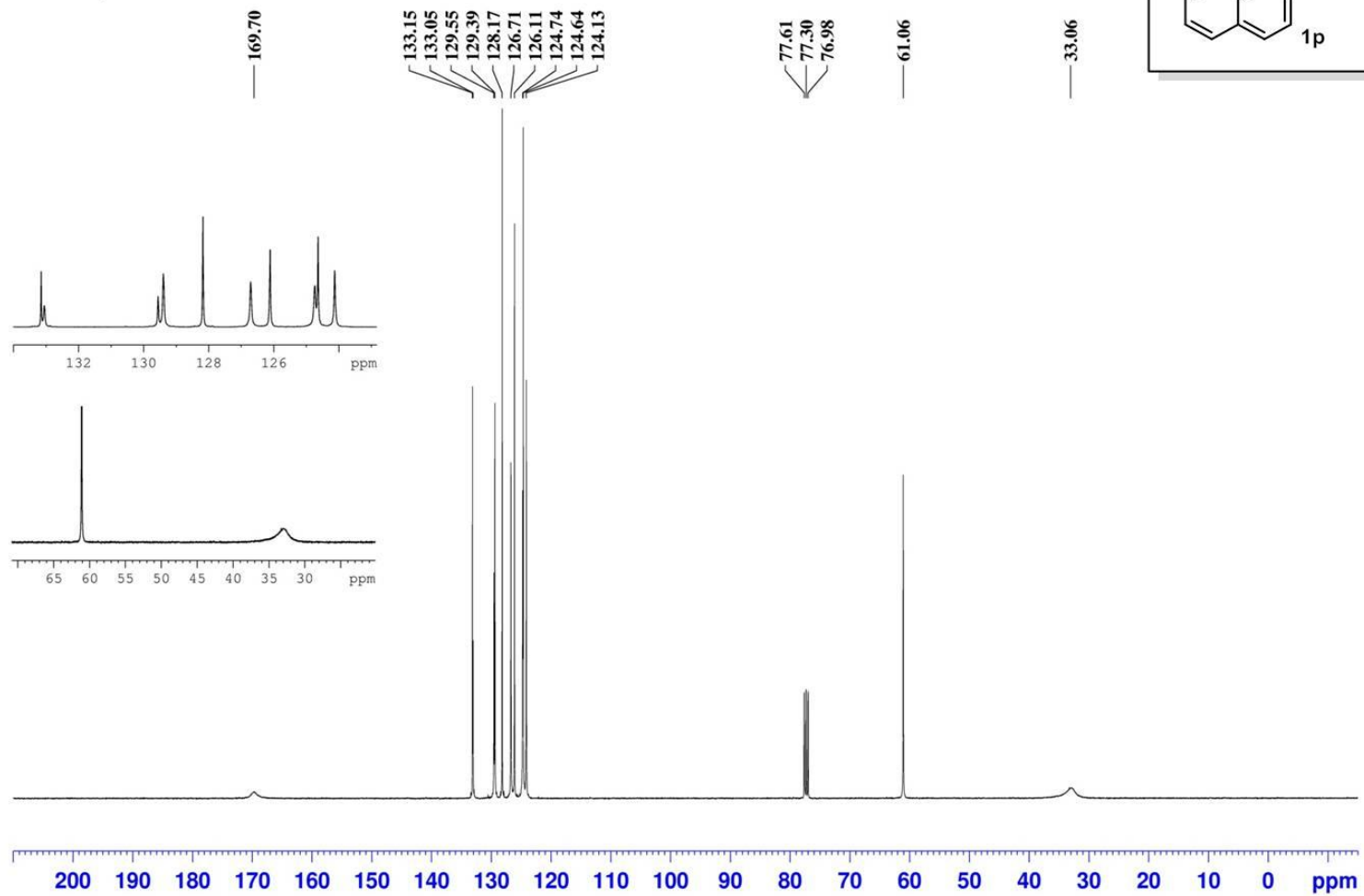
**N-methoxy-N-methyl-3-phenylpropanamide**  
100 MHz, CDCl<sub>3</sub>



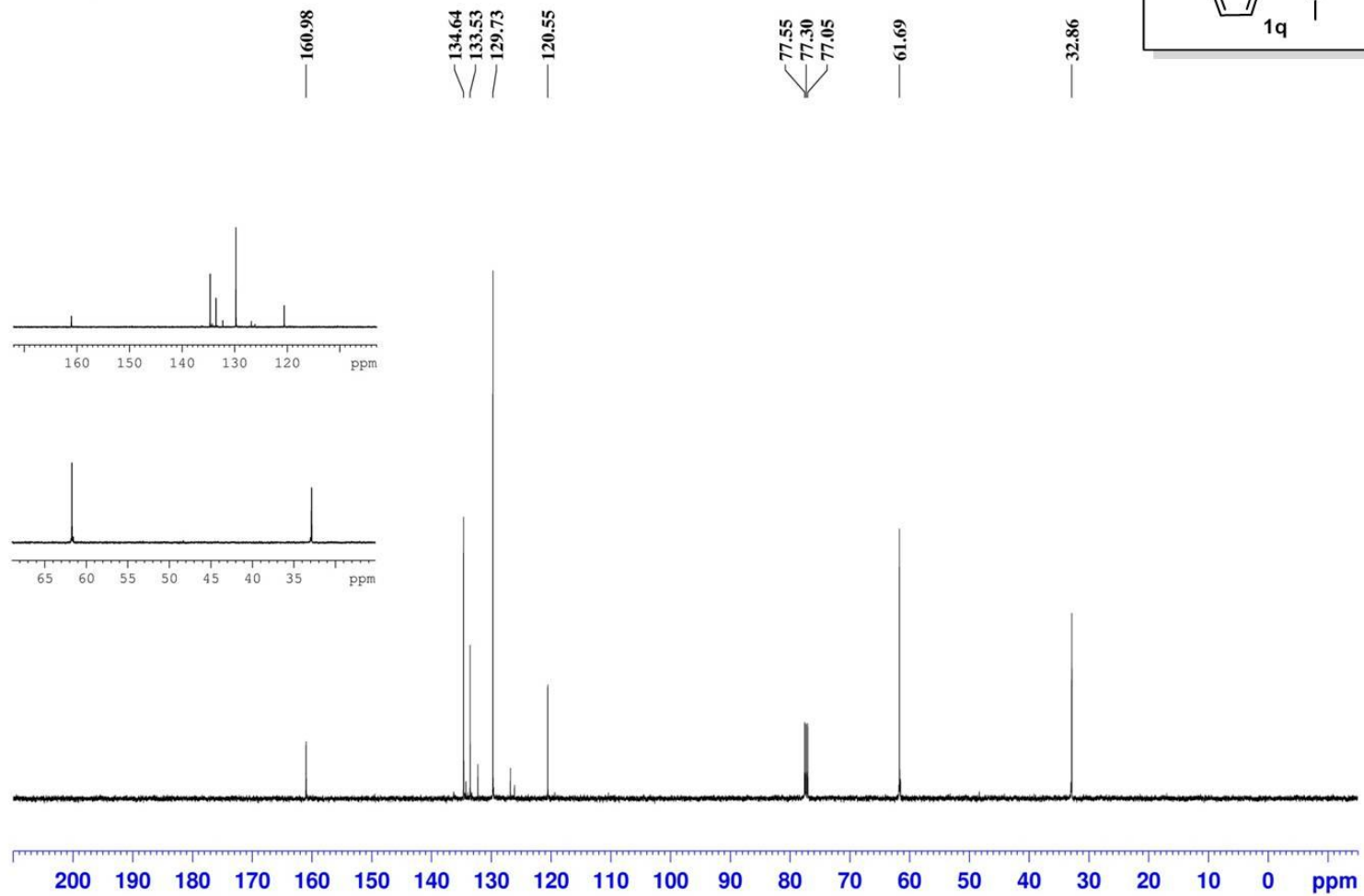
3-(furan-2-yl)-N-methoxy-N-methylpropanamide  
100 MHz, CDCl<sub>3</sub>



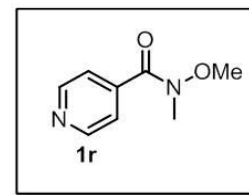
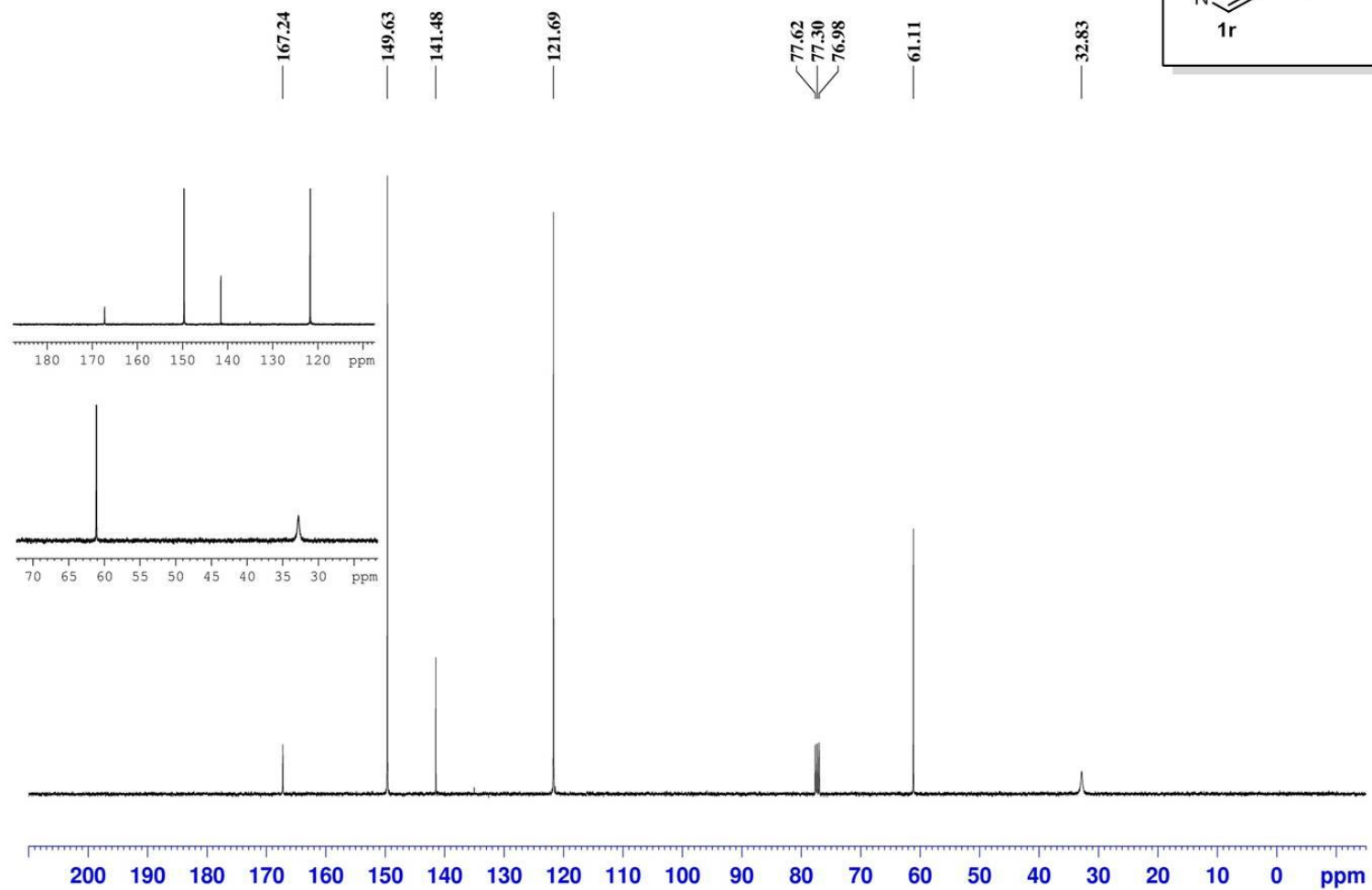
**N-methoxy-N-methyl-1-naphthamide**  
100 MHz, CDCl<sub>3</sub>



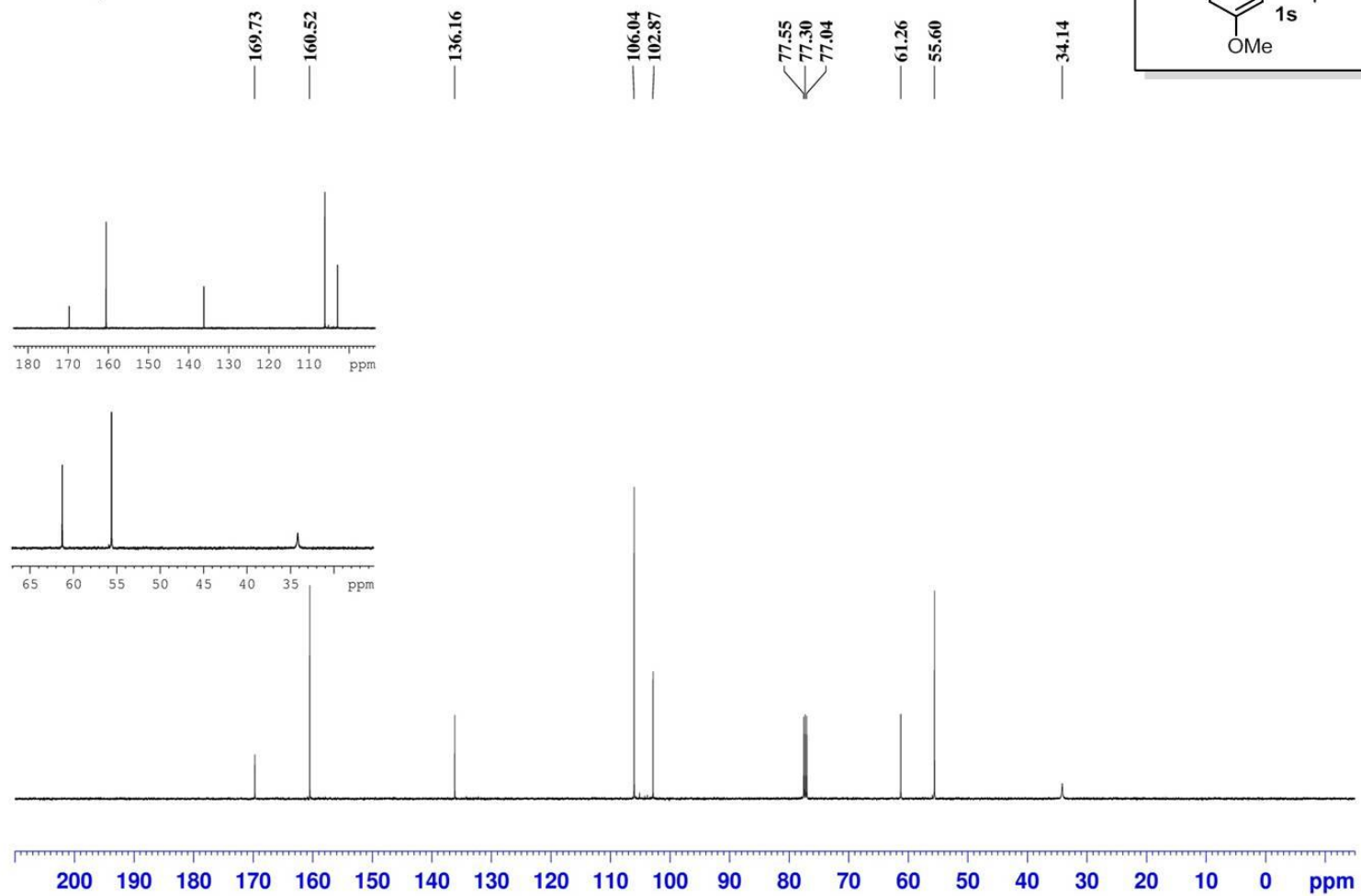
**5-bromo-N-methoxy-N-methylthiophene-2-carboxamide**  
125 MHz, CDCl<sub>3</sub>



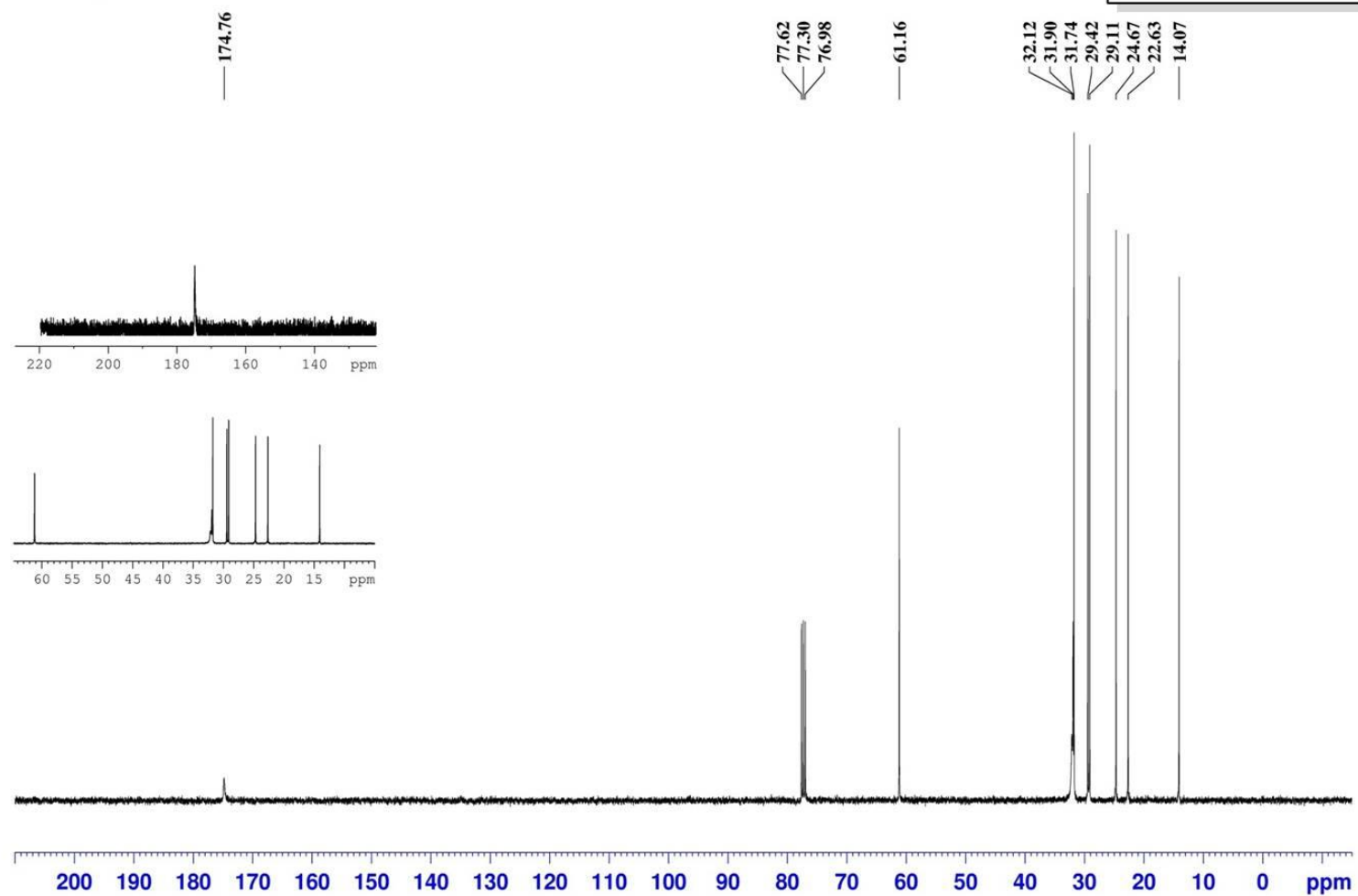
**N-methoxy-N-methylisonicotinamide**  
100 MHz, CDCl<sub>3</sub>



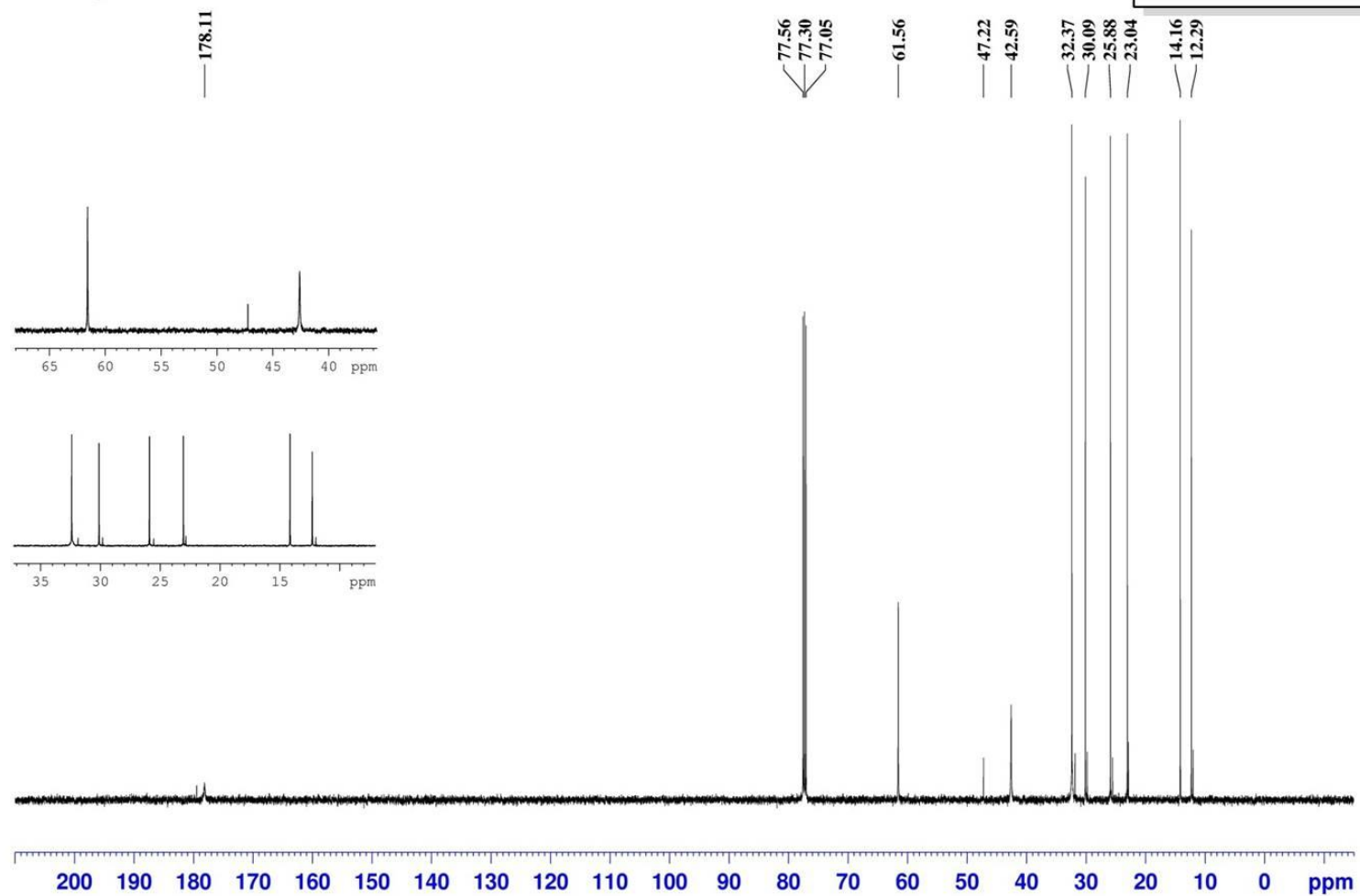
**N,3,5-trimethoxy-N-methylbenzamide**  
125 MHz, CDCl<sub>3</sub>



**N-methoxy-N-methyloctanamide**  
100 MHz, CDCl<sub>3</sub>

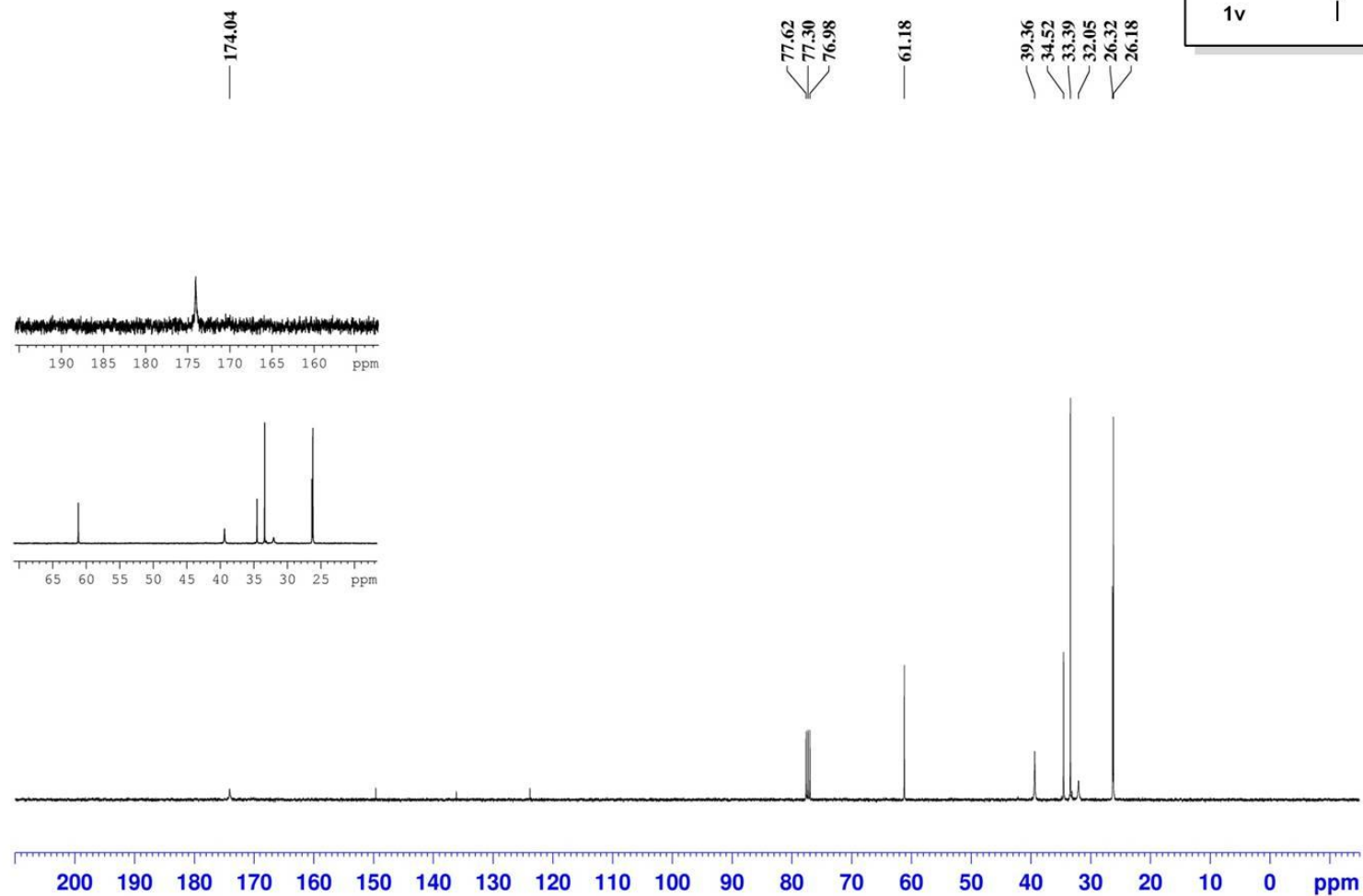


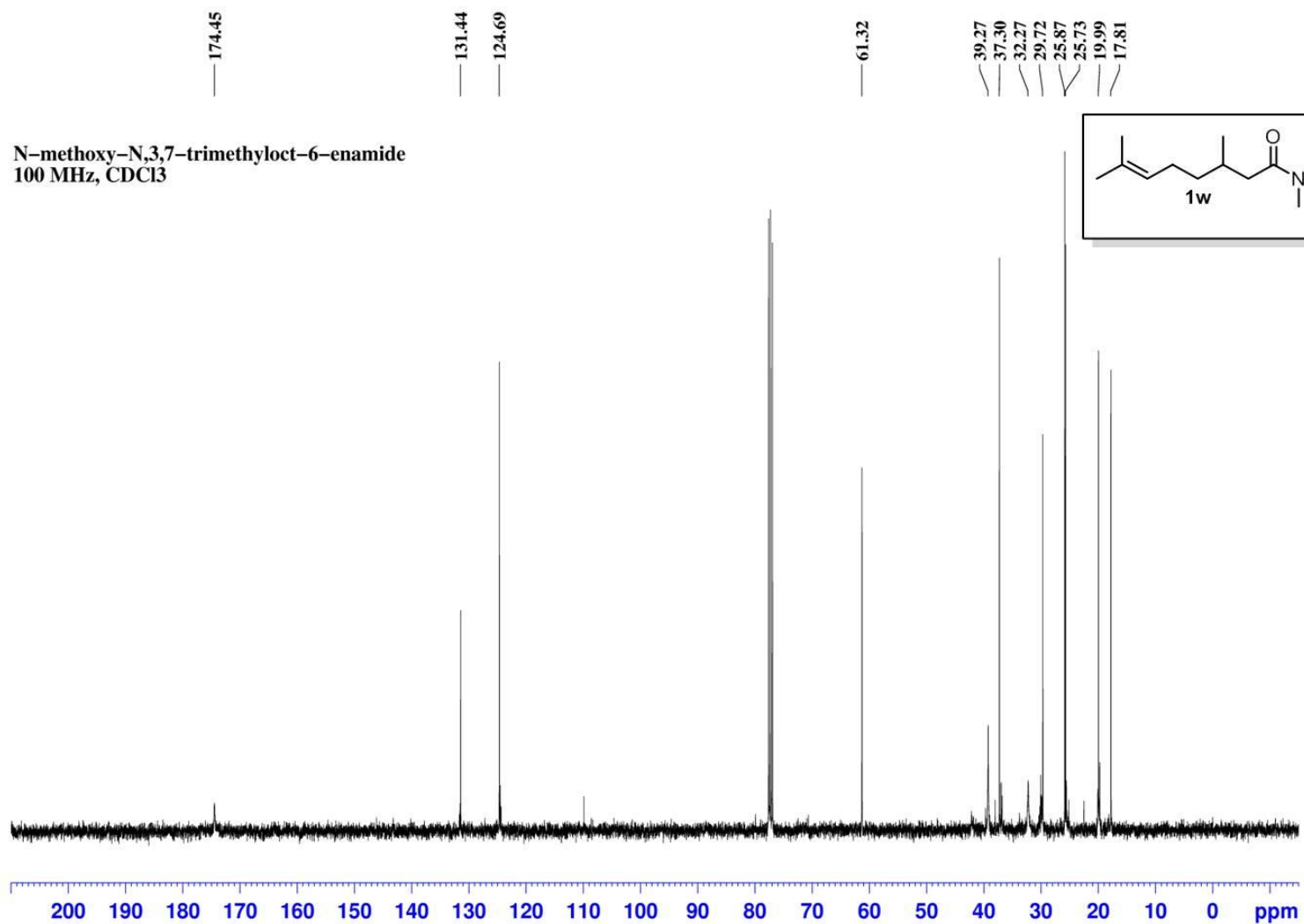
3-ethyl-N-methoxy-N-methylhexanamide  
125 MHz, CDCl<sub>3</sub>

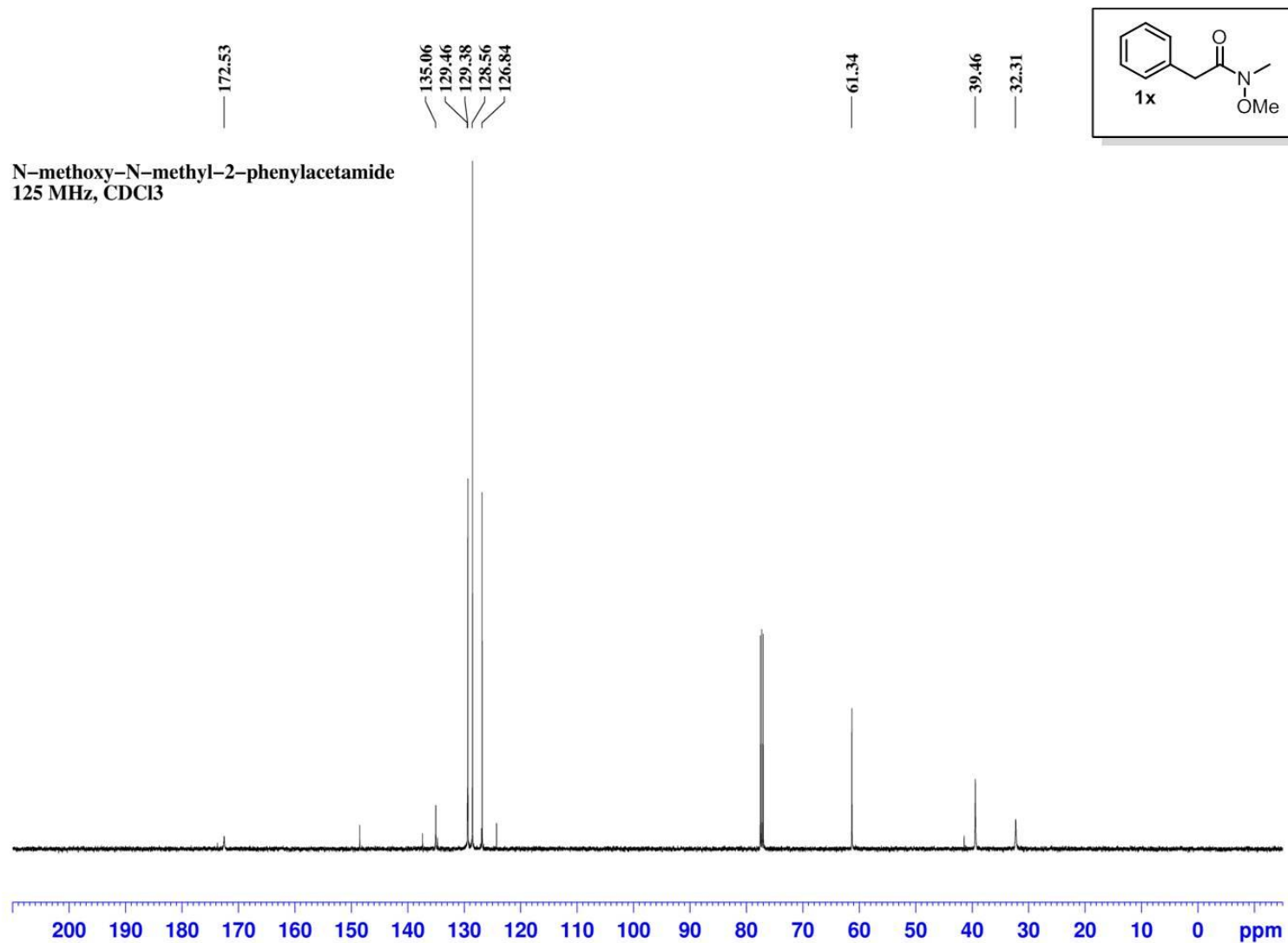


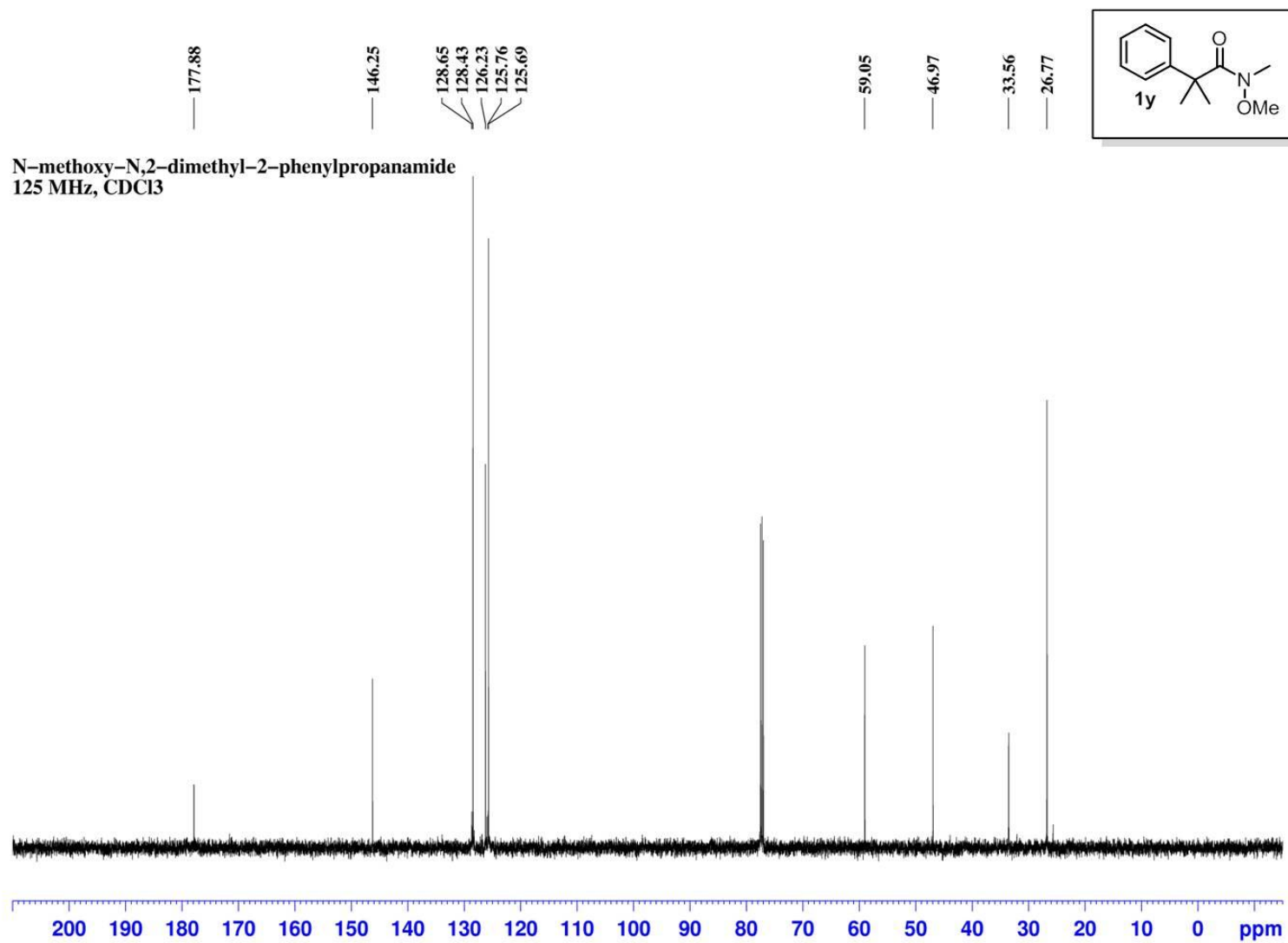


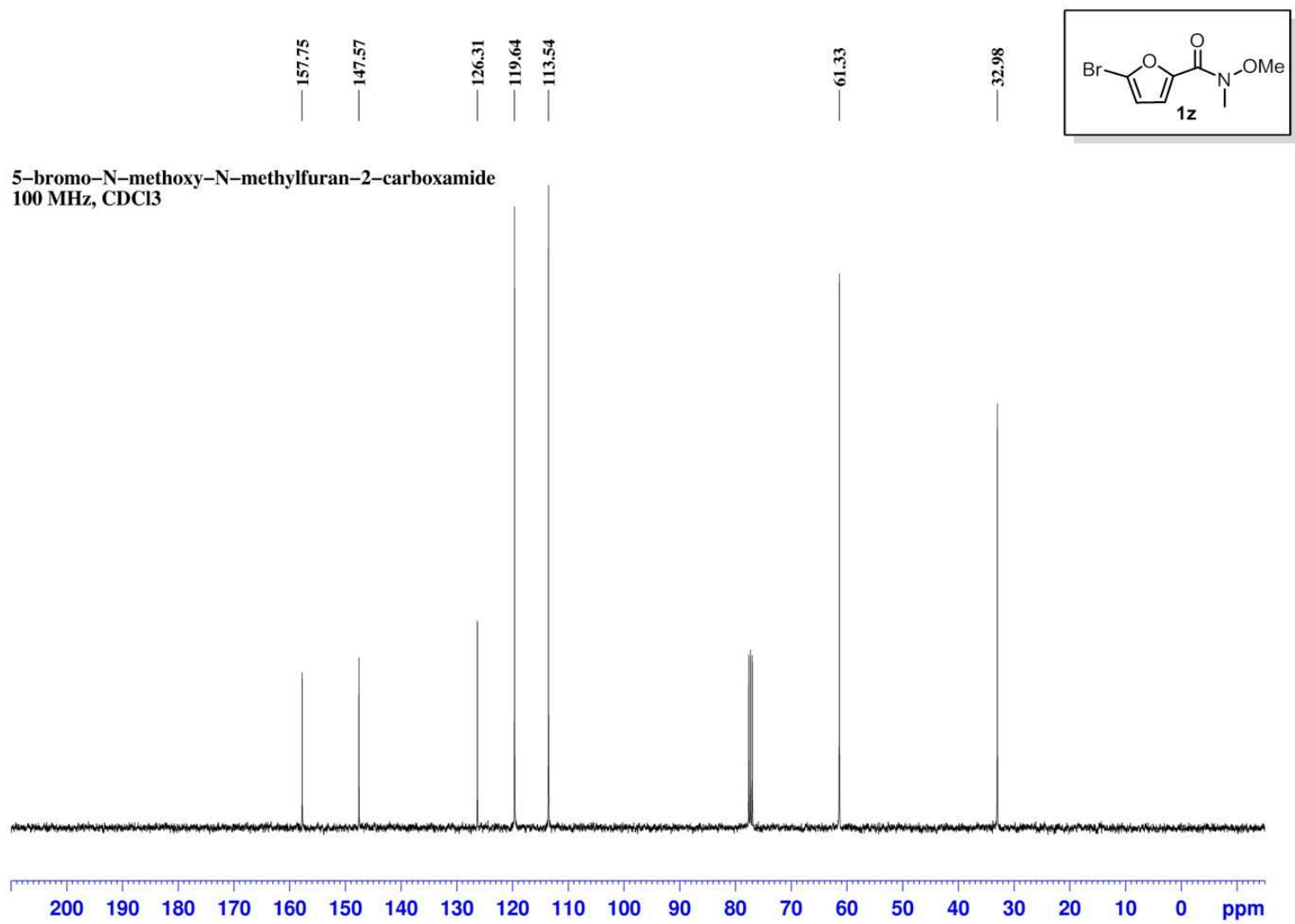
2-cyclohexyl-N-methoxy-N-methylacetamide  
100 MHz, CDCl<sub>3</sub>



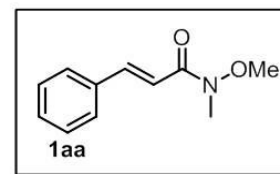
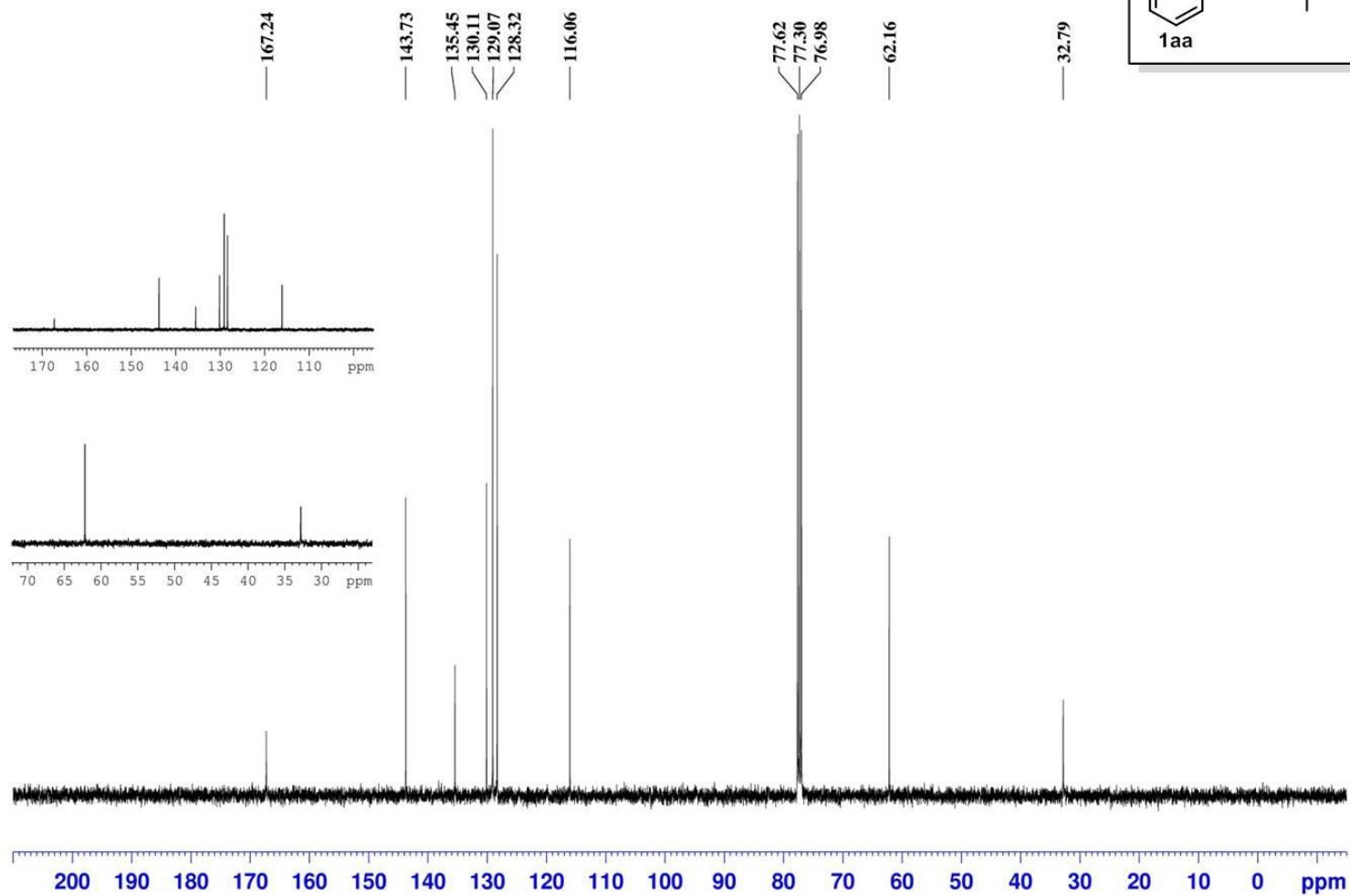




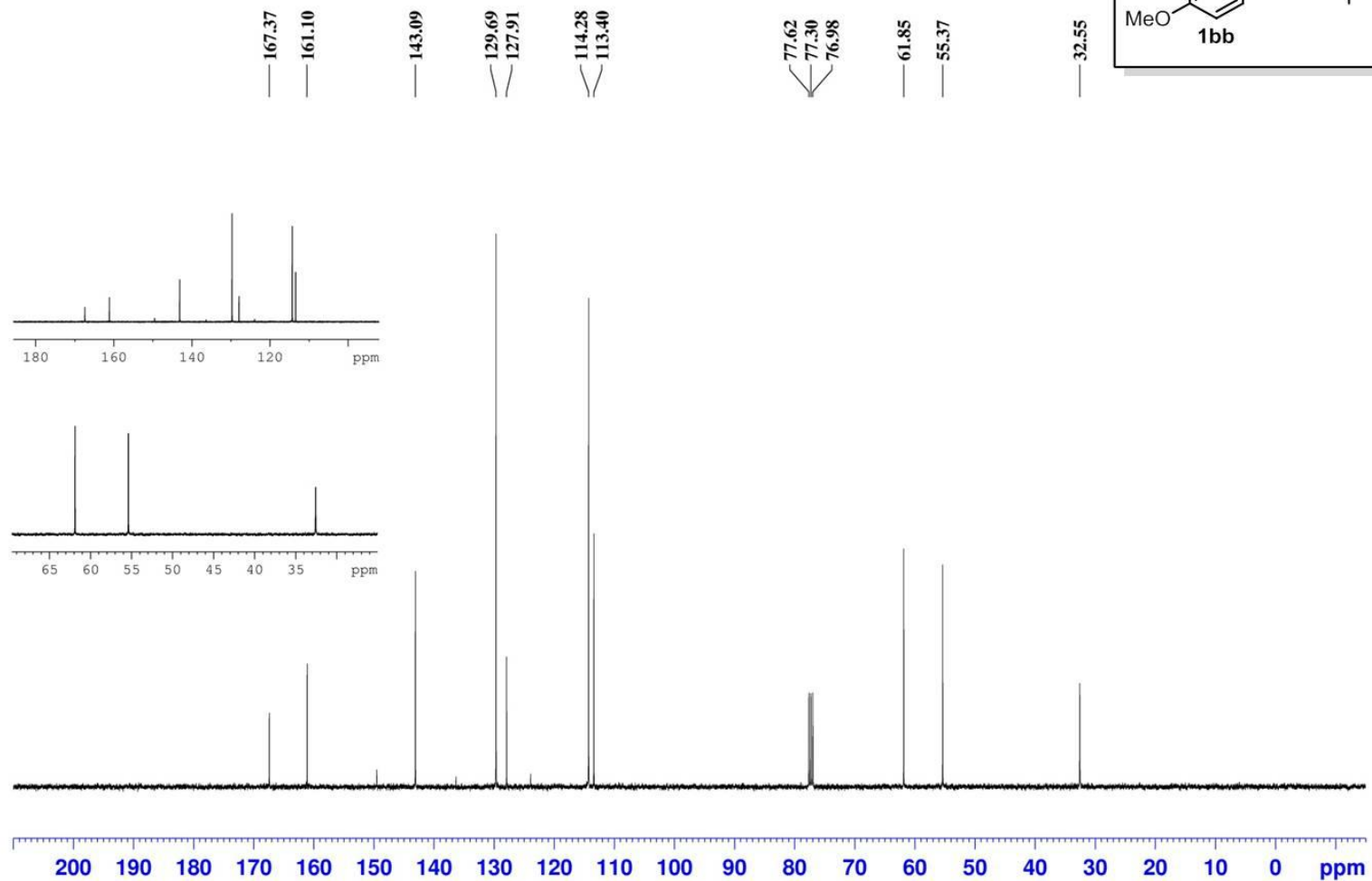




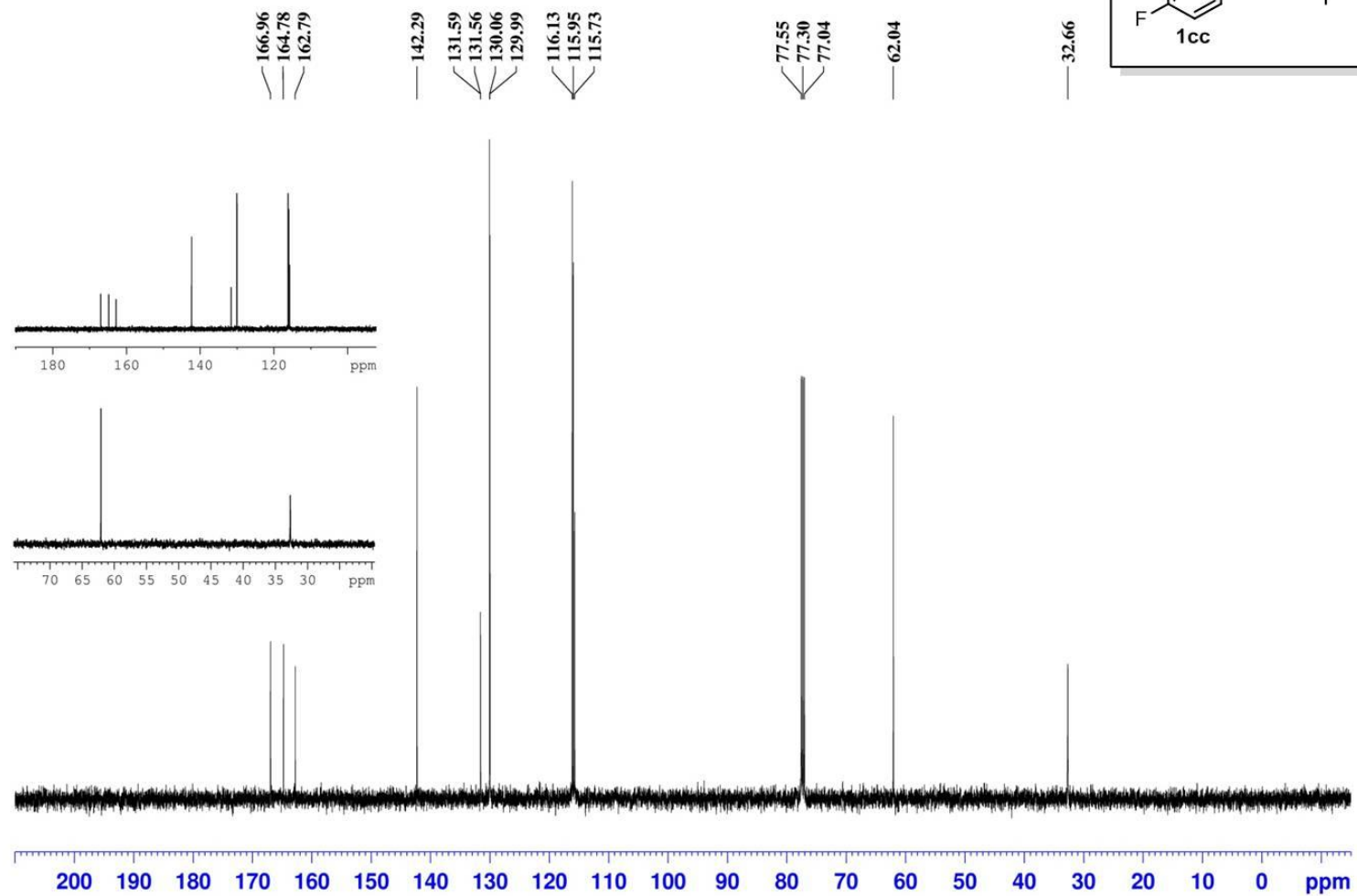
**N-methoxy-N-methylcinnamamide**  
100 MHz, CDCl<sub>3</sub>



(E)-N-methoxy-3-(4-methoxyphenyl)-N-methylacrylamide  
100 MHz, CDCl<sub>3</sub>

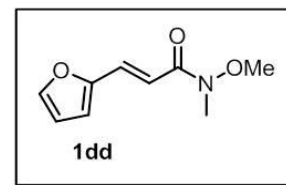
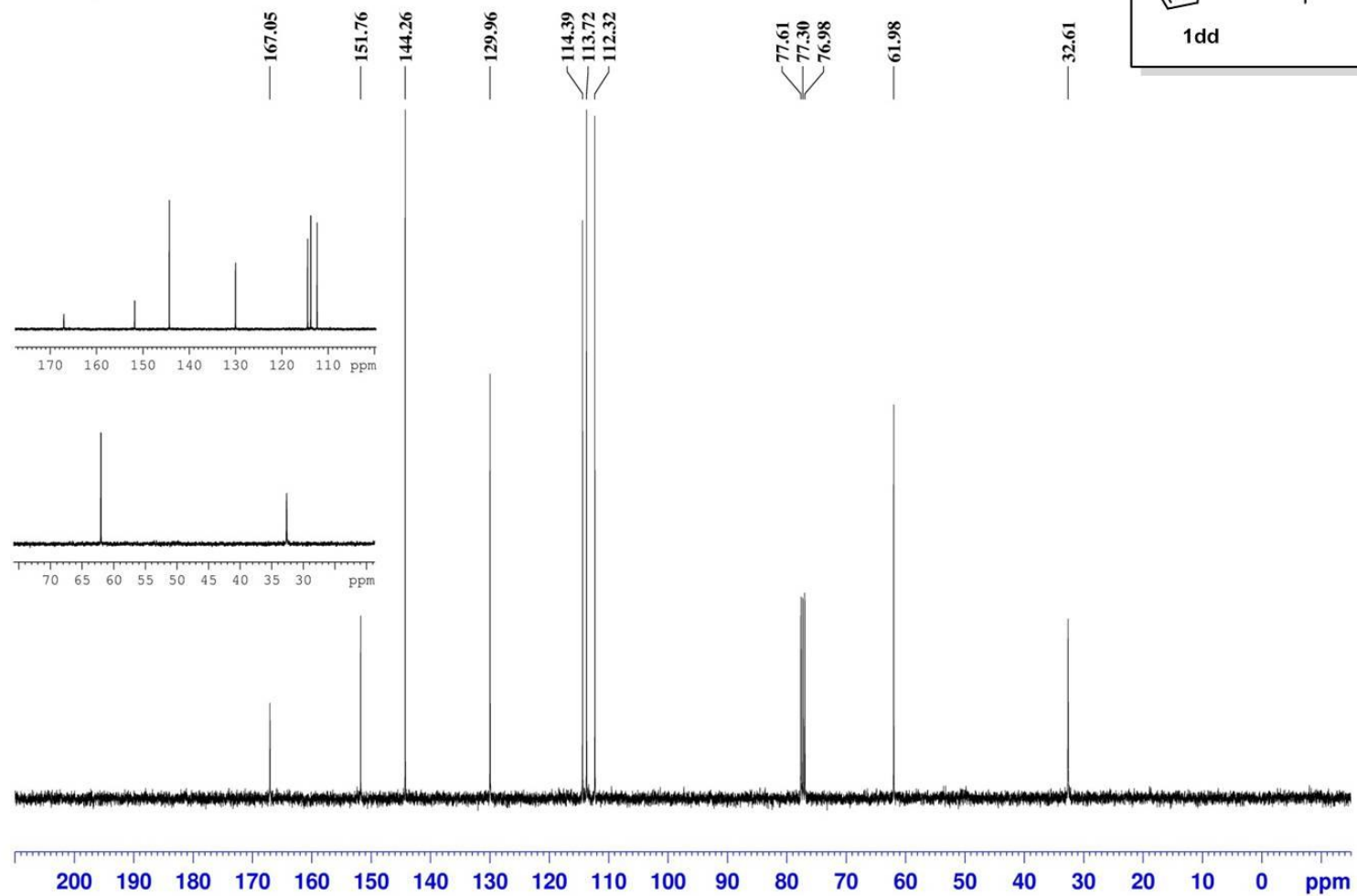


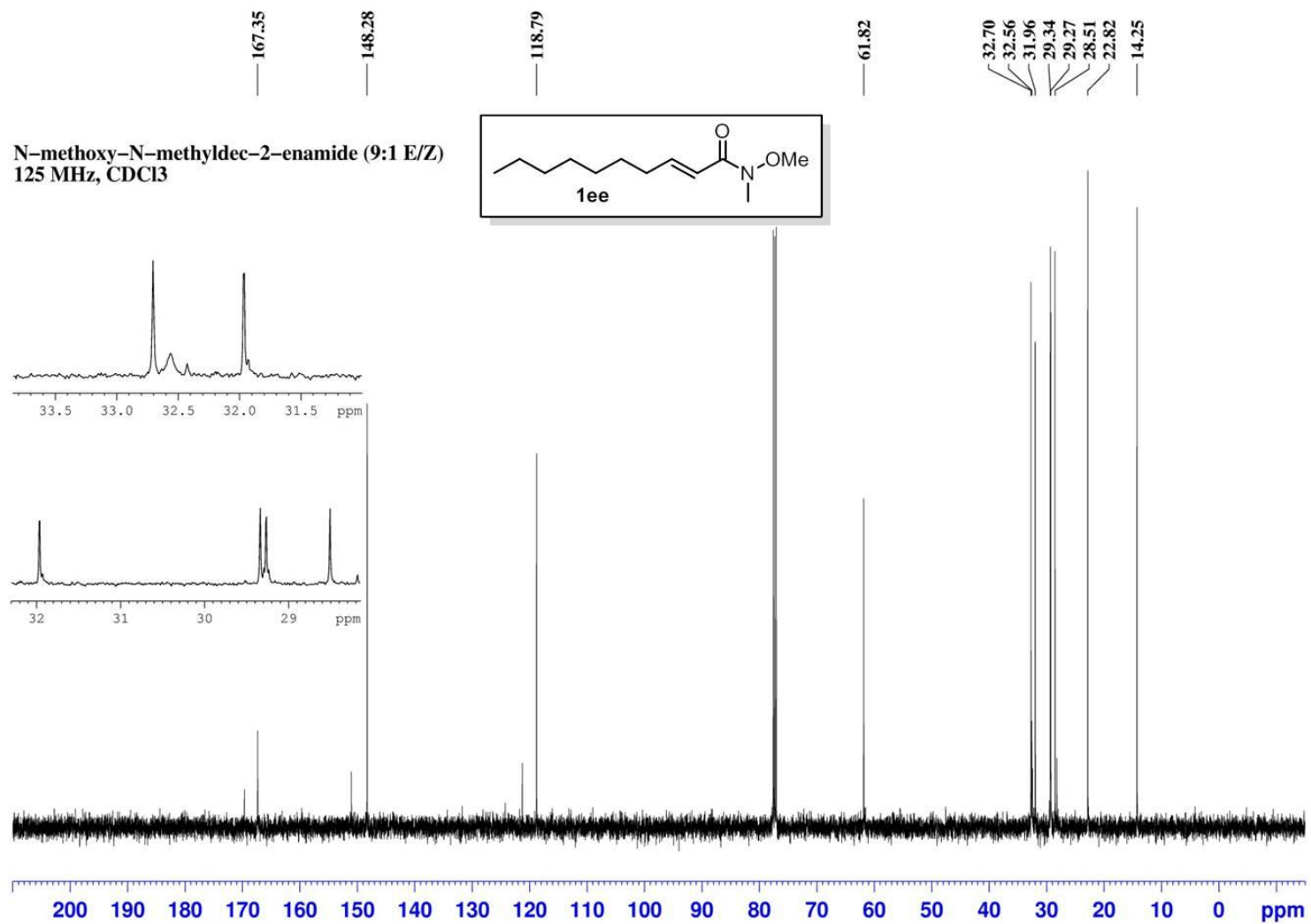
(E)-3-(4-fluorophenyl)-N-methoxy-N-methylacrylamide  
125 MHz, CDCl<sub>3</sub>

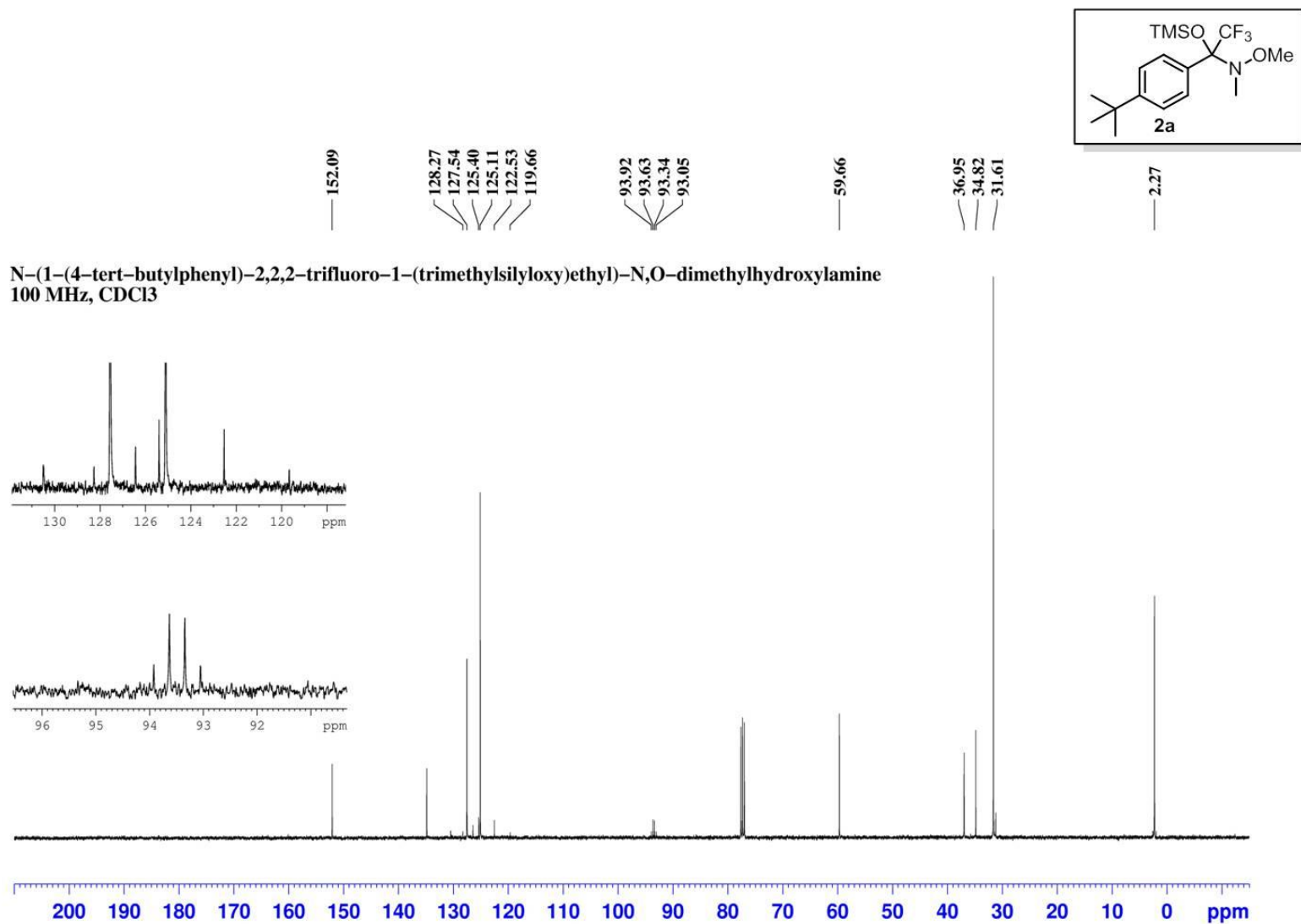


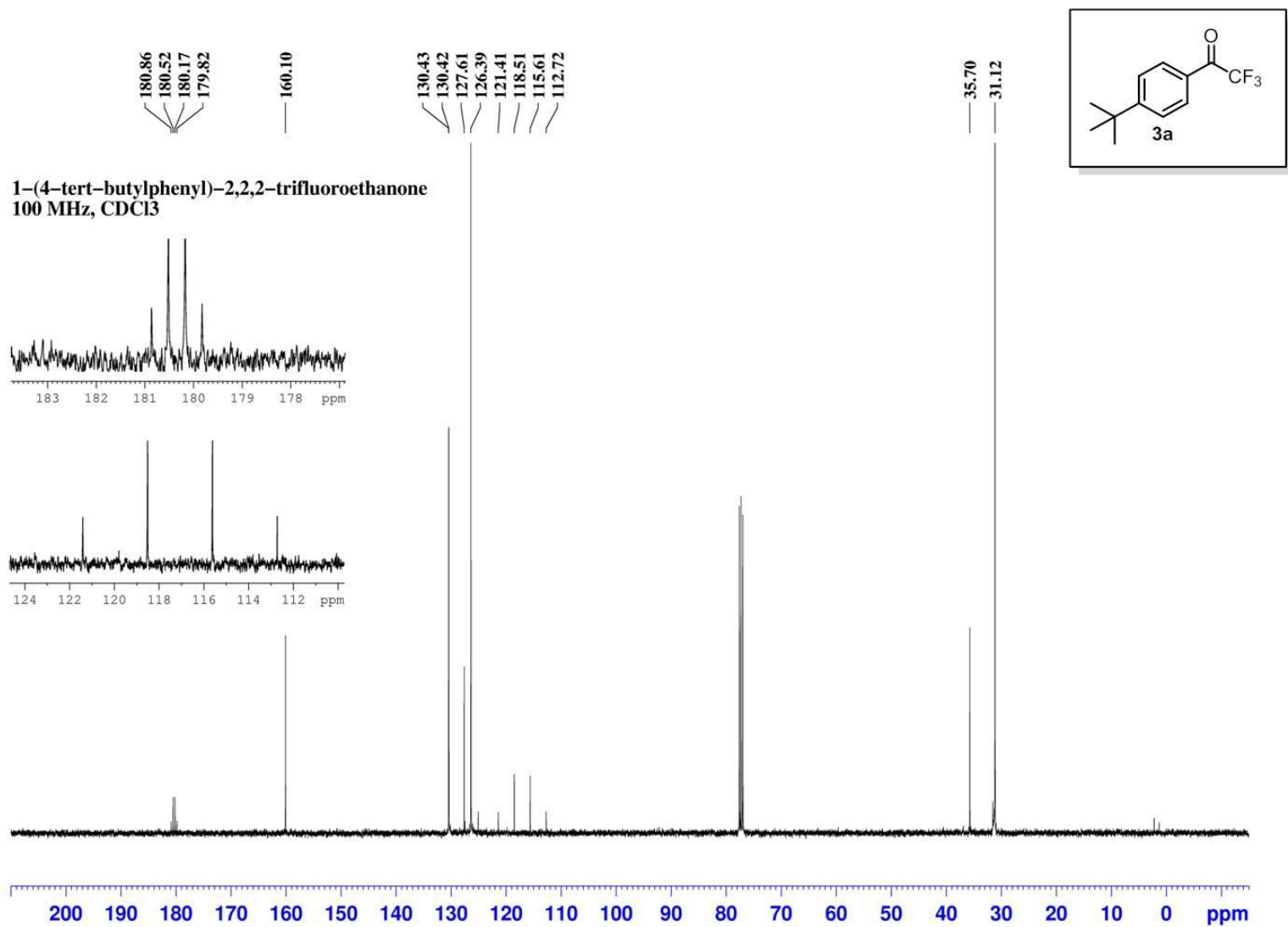


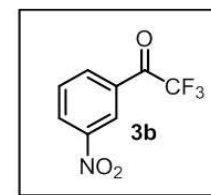
(E)-3-(furan-2-yl)-N-methoxy-N-methylacrylamide  
100 MHz, CDCl<sub>3</sub>



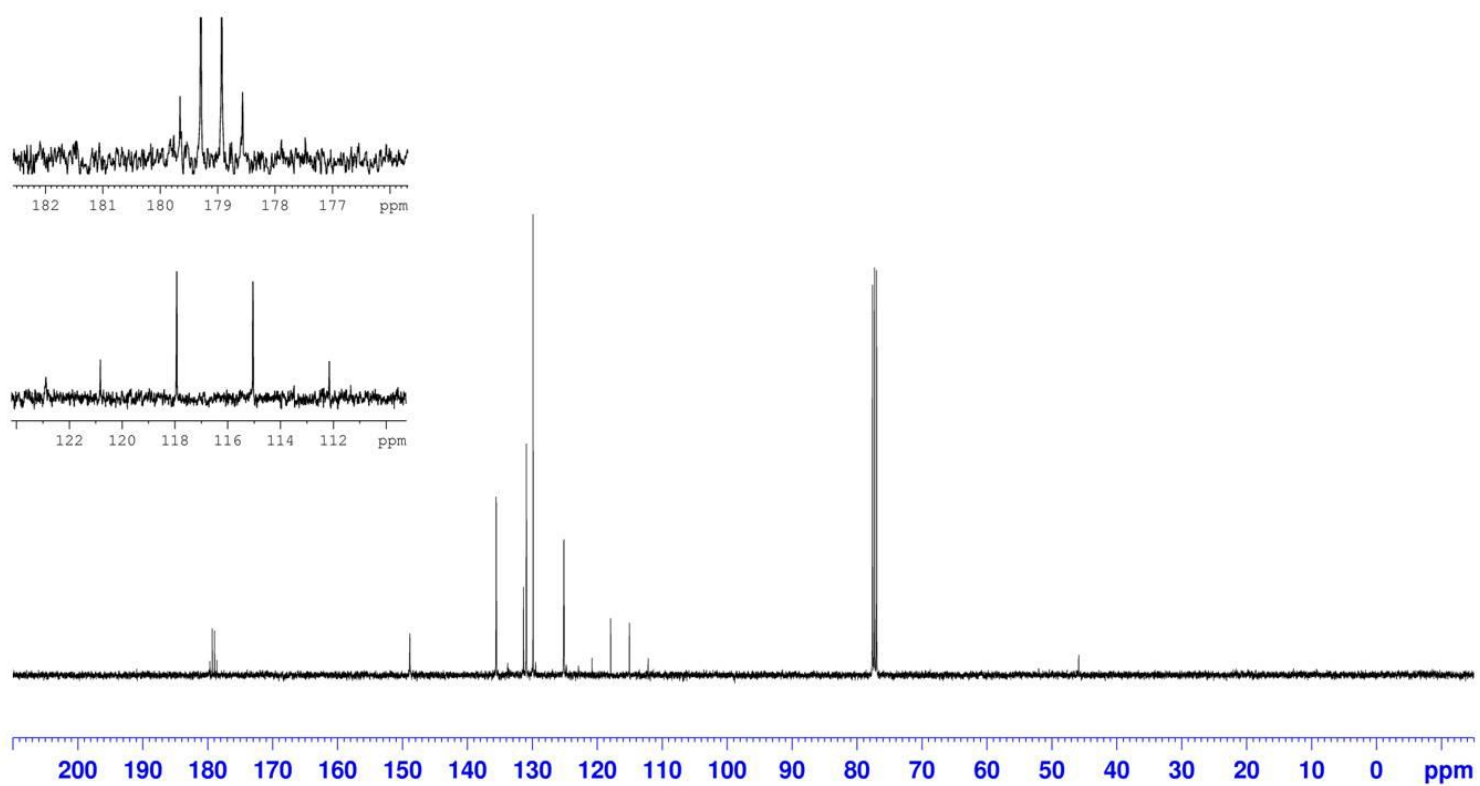






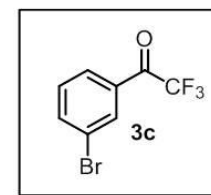
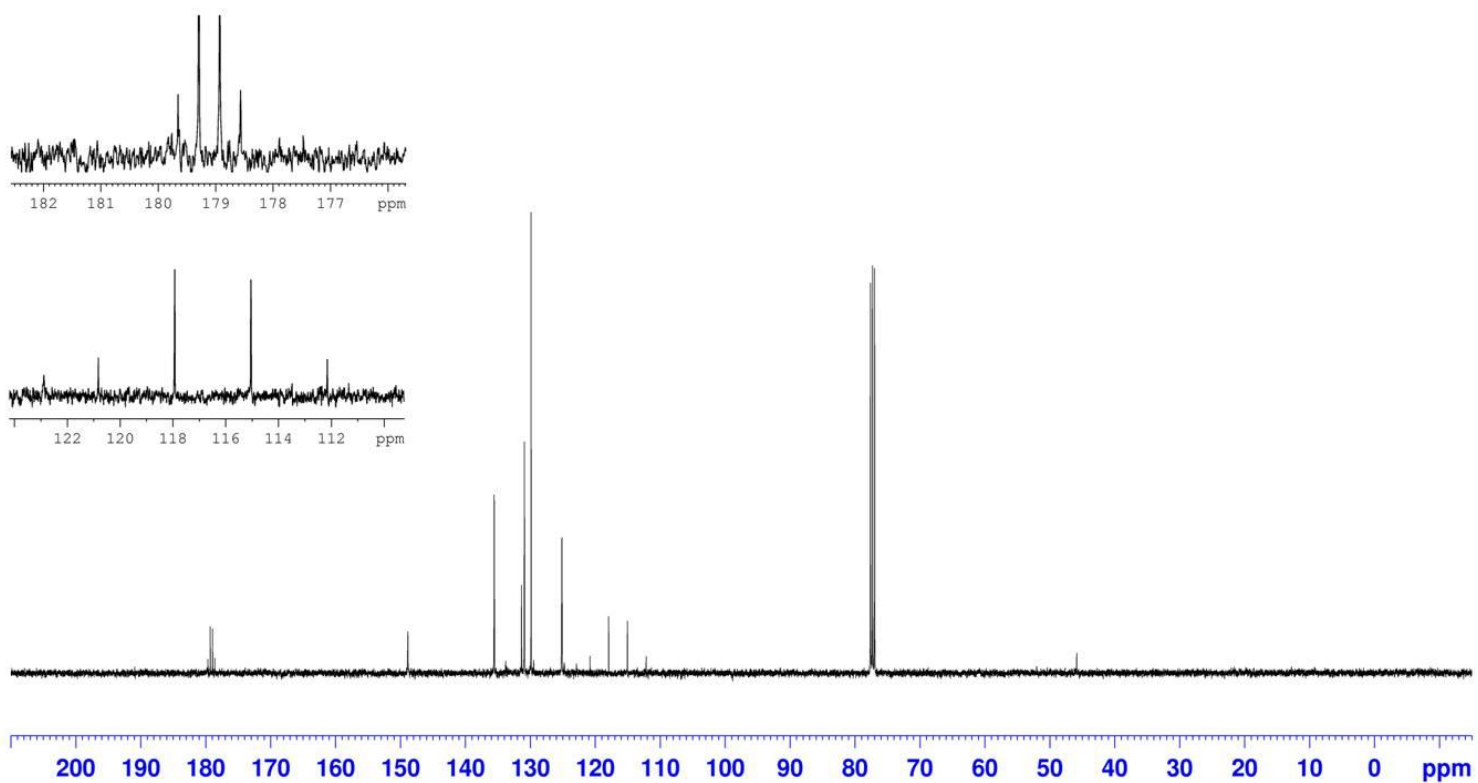


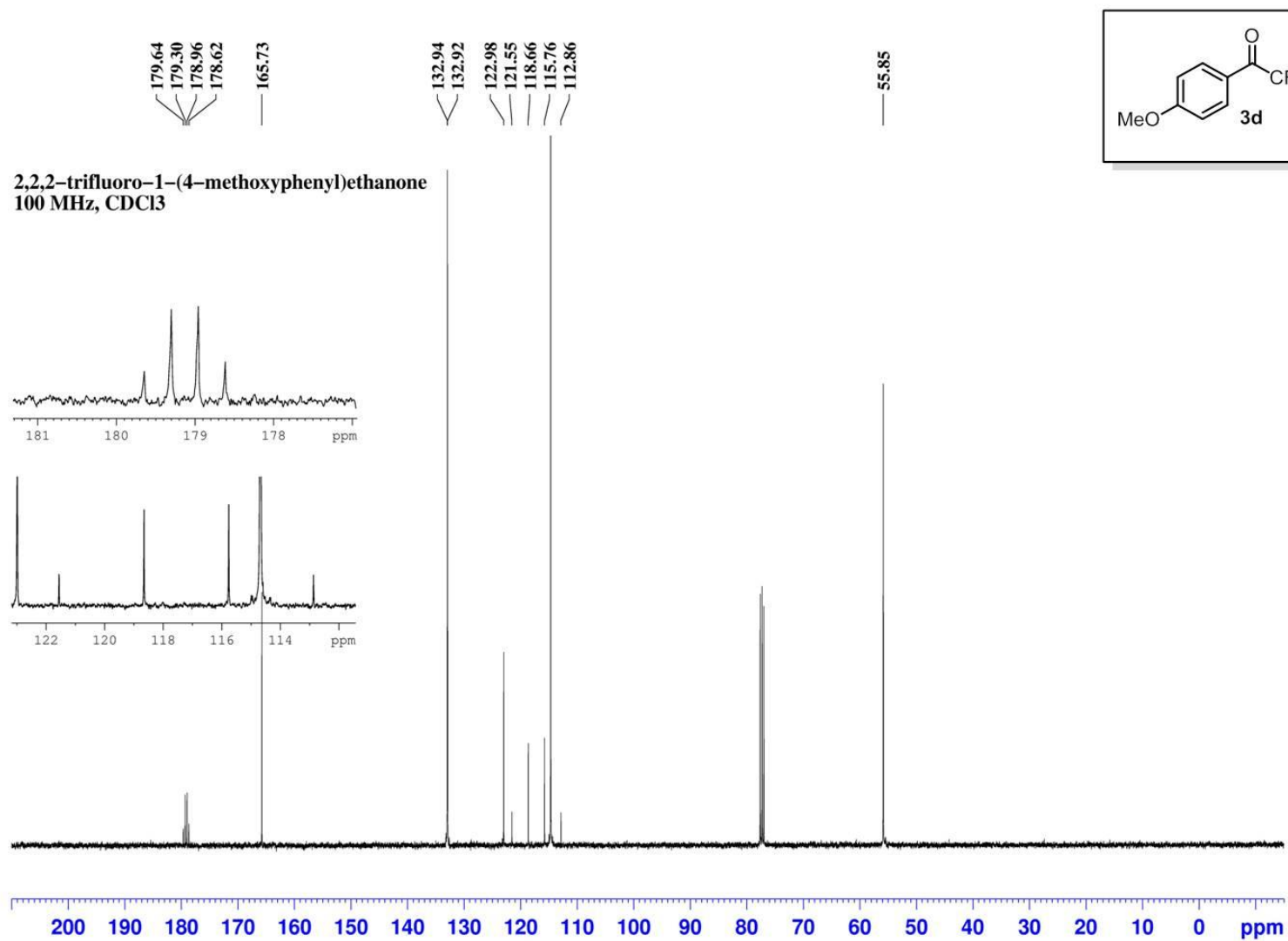
2,2,2-trifluoro-1-(3-nitrophenyl)ethanone  
100 MHz, CDCl<sub>3</sub>

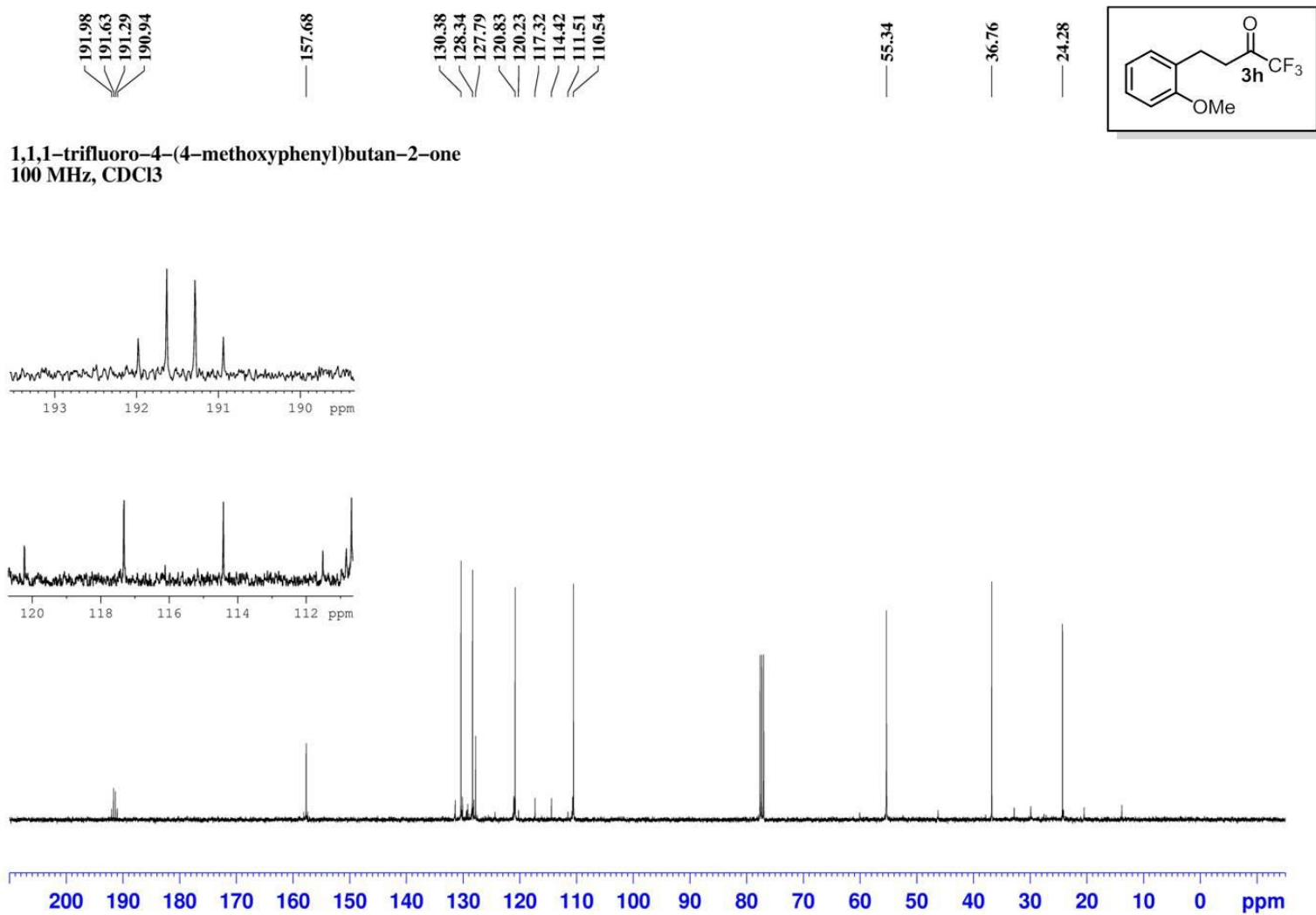




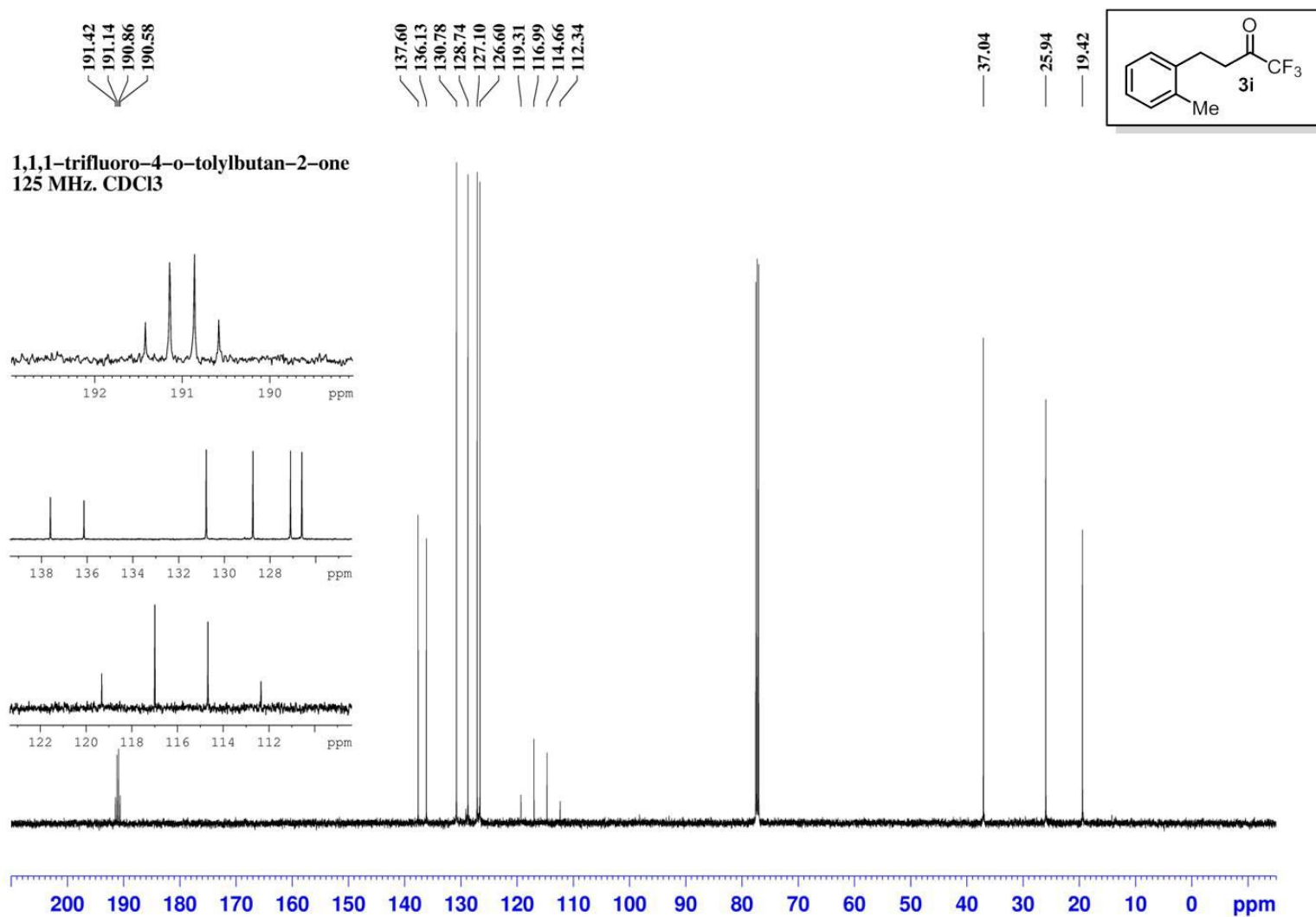
**2,2,2-trifluoro-1-(3-nitrophenyl)ethanone**  
100 MHz, CDCl<sub>3</sub>

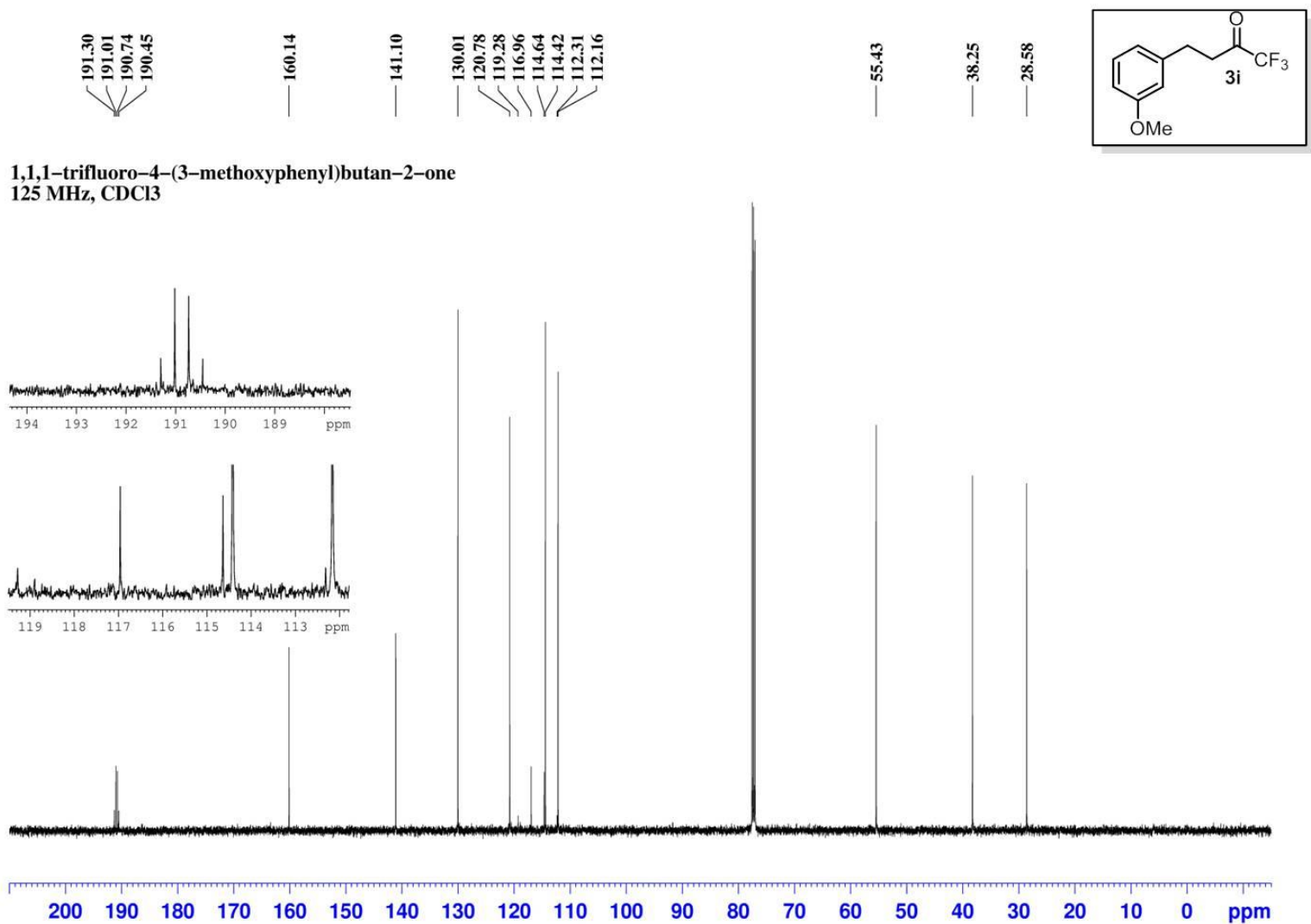


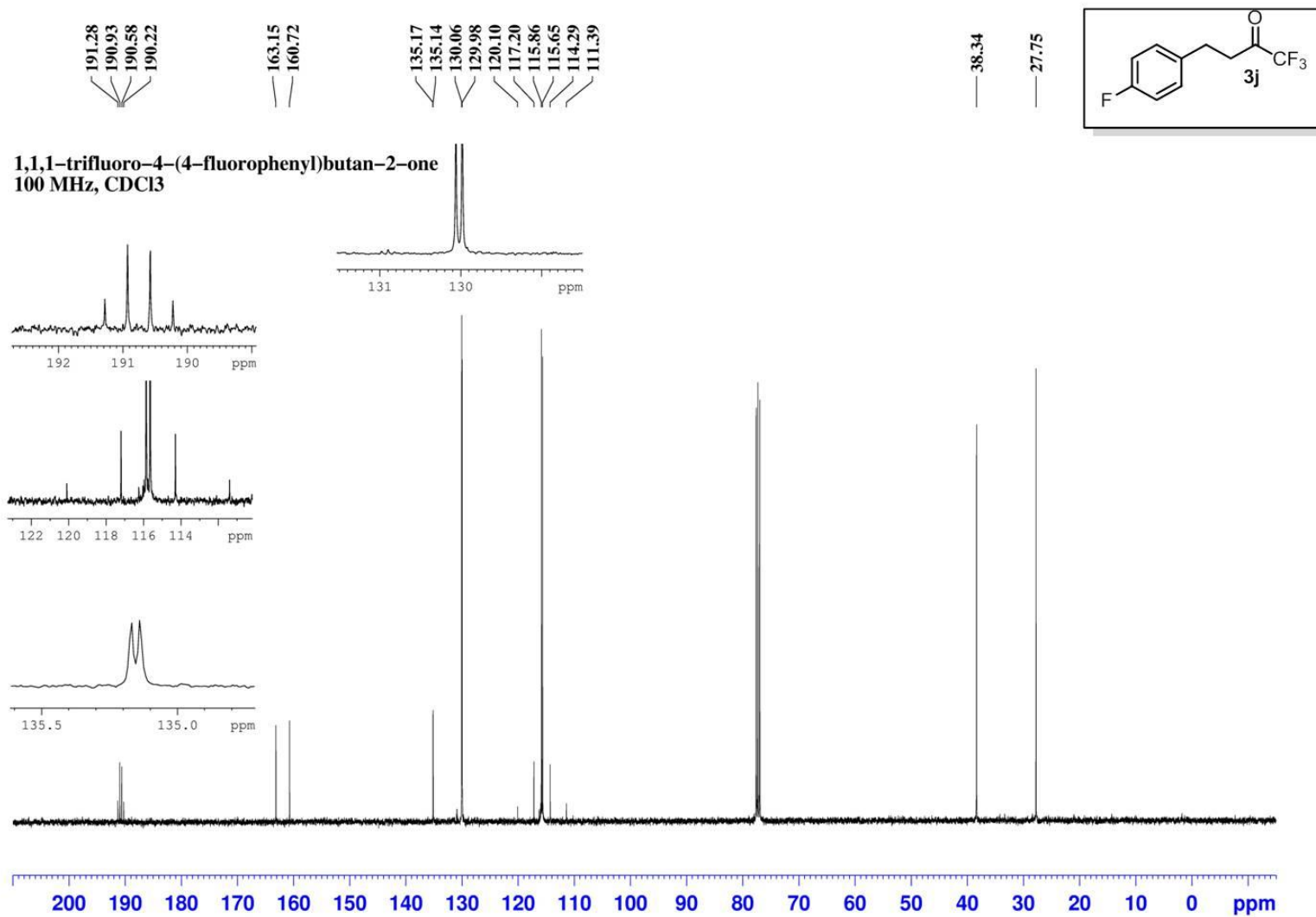


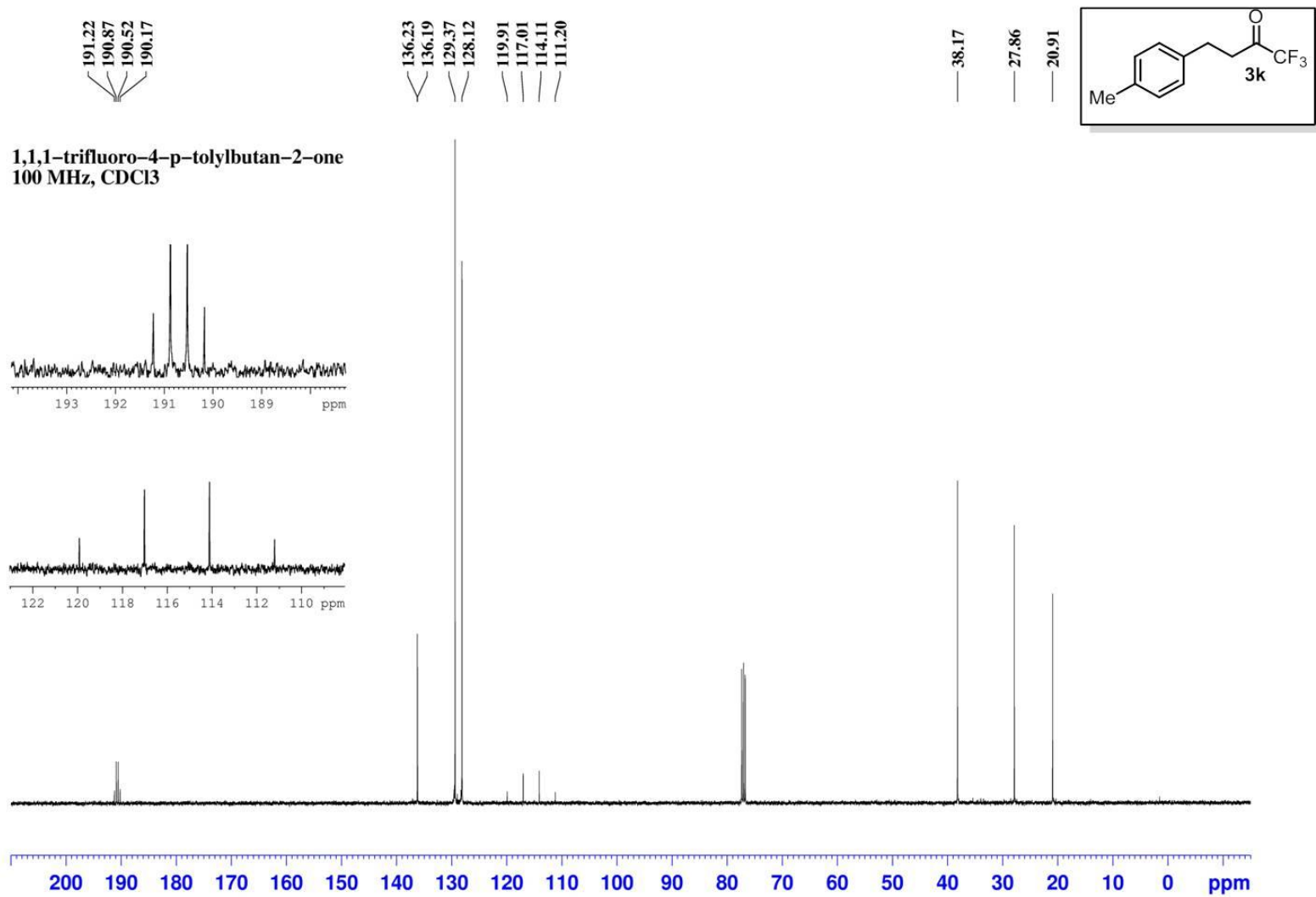


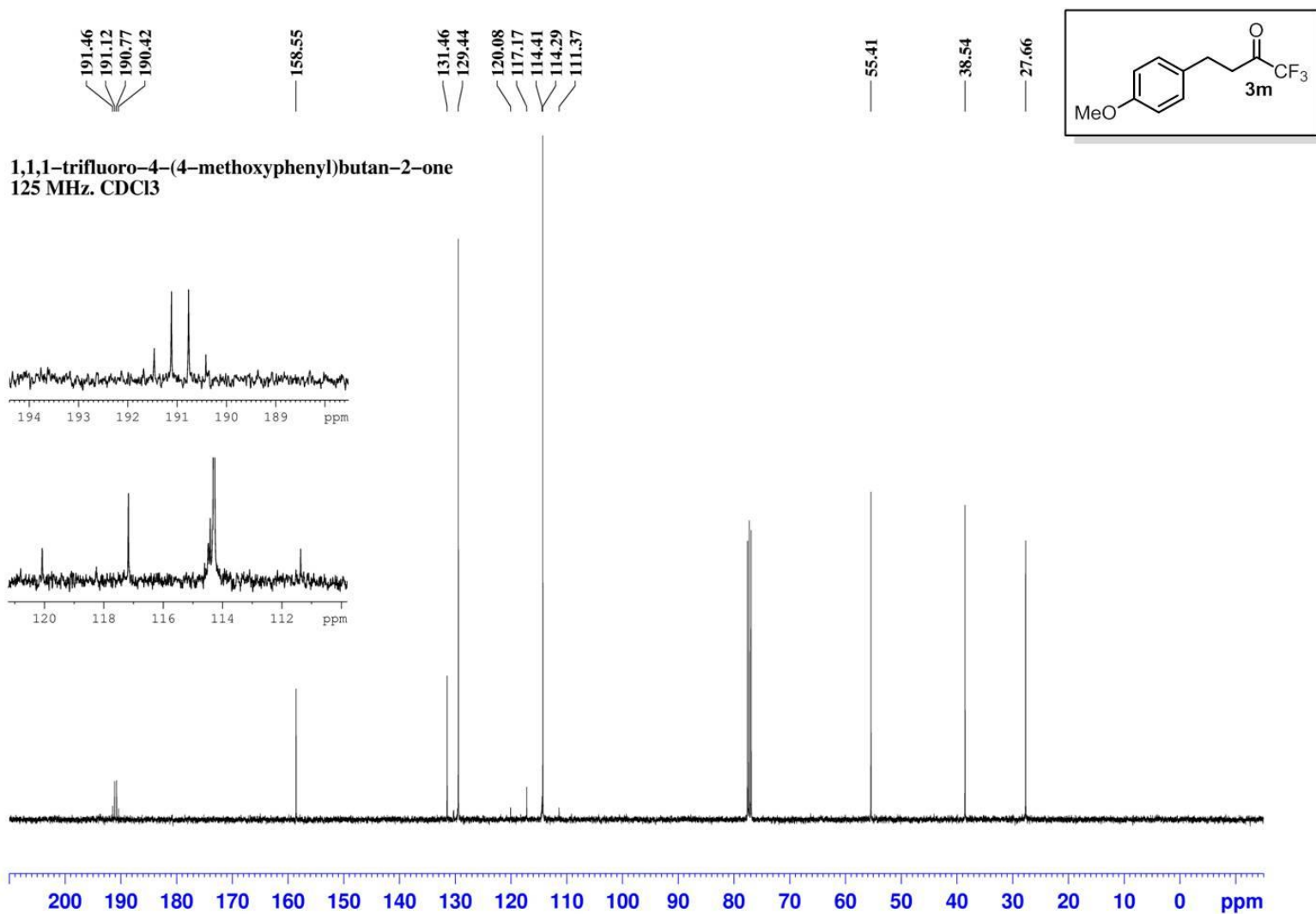


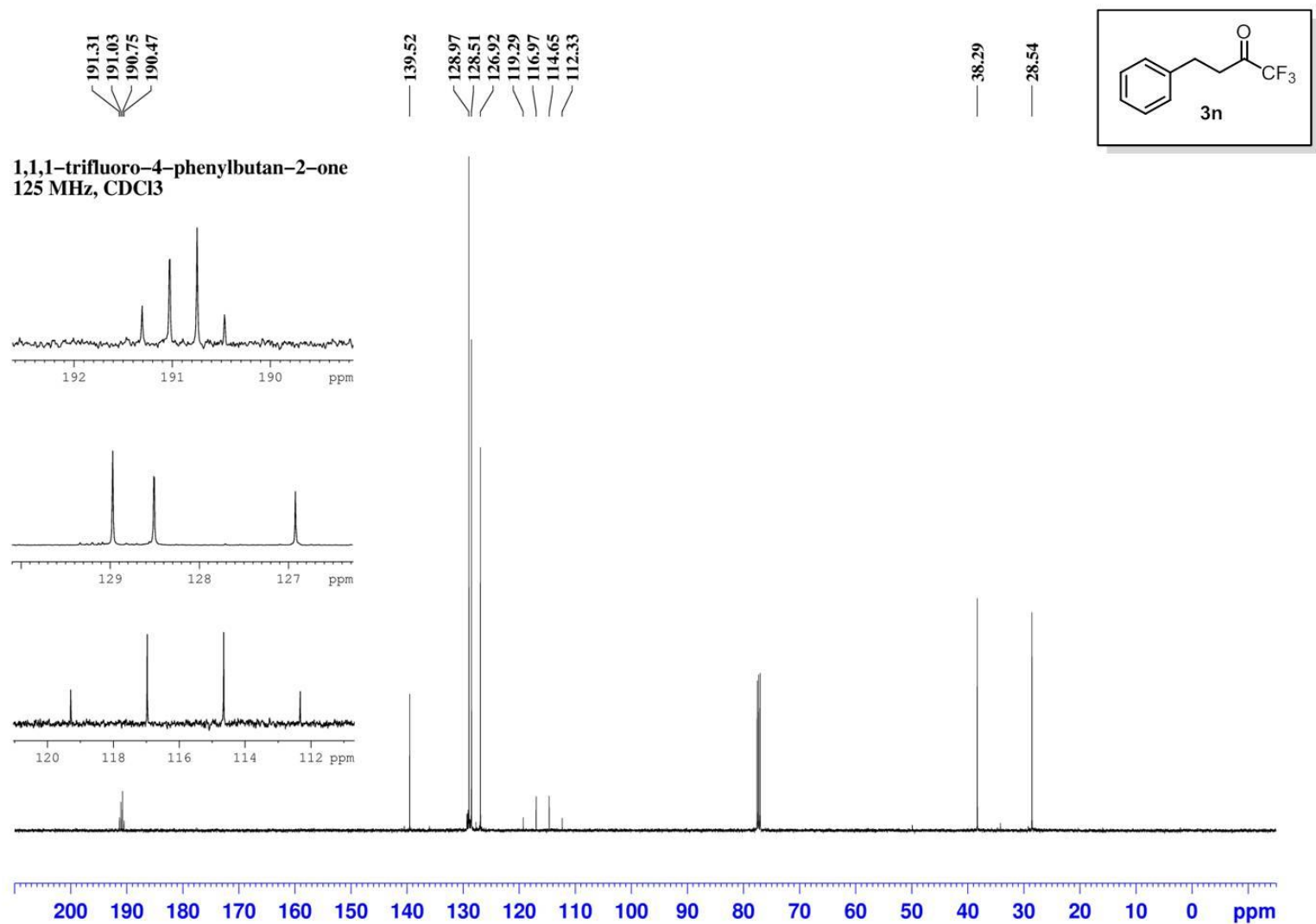


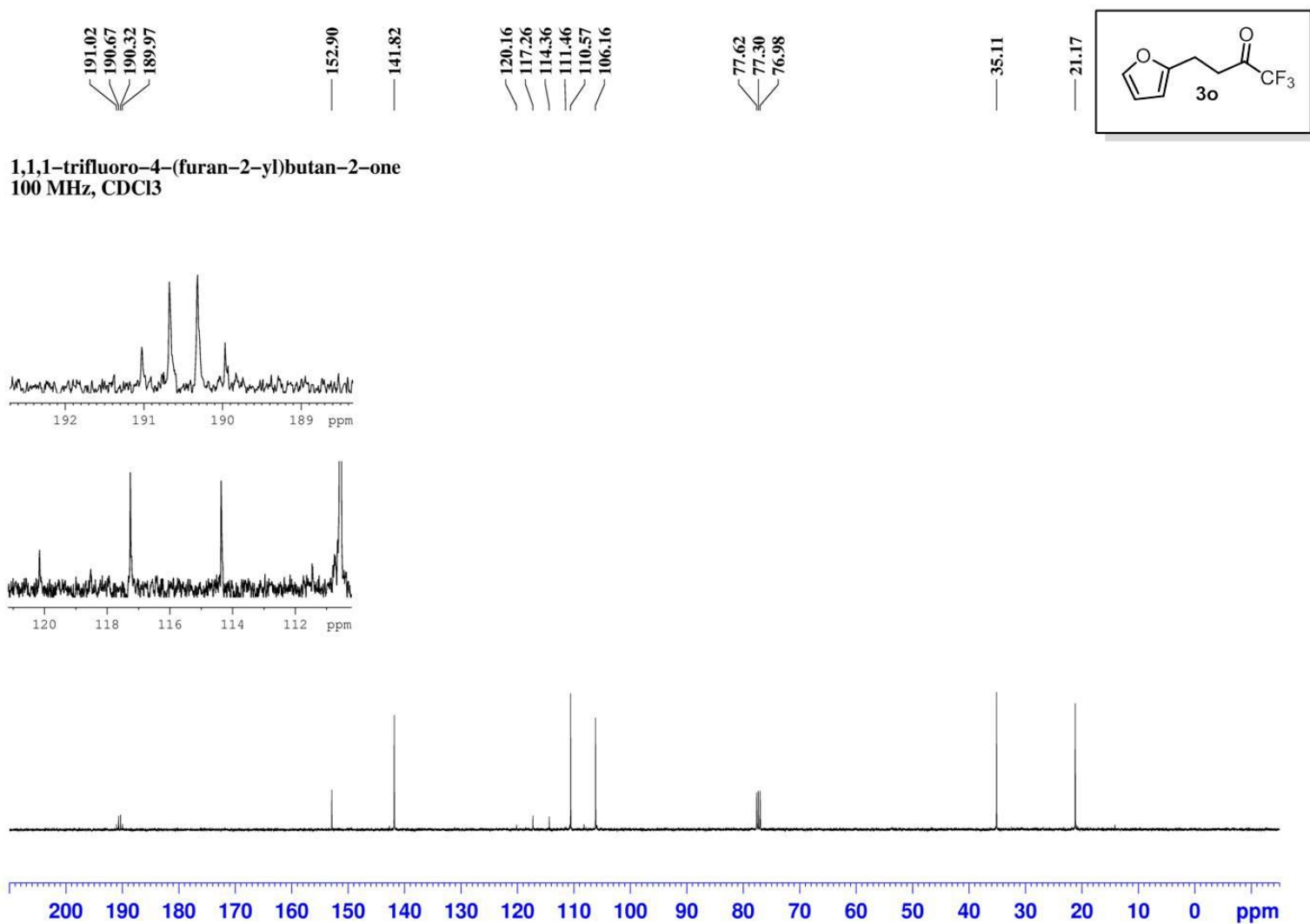


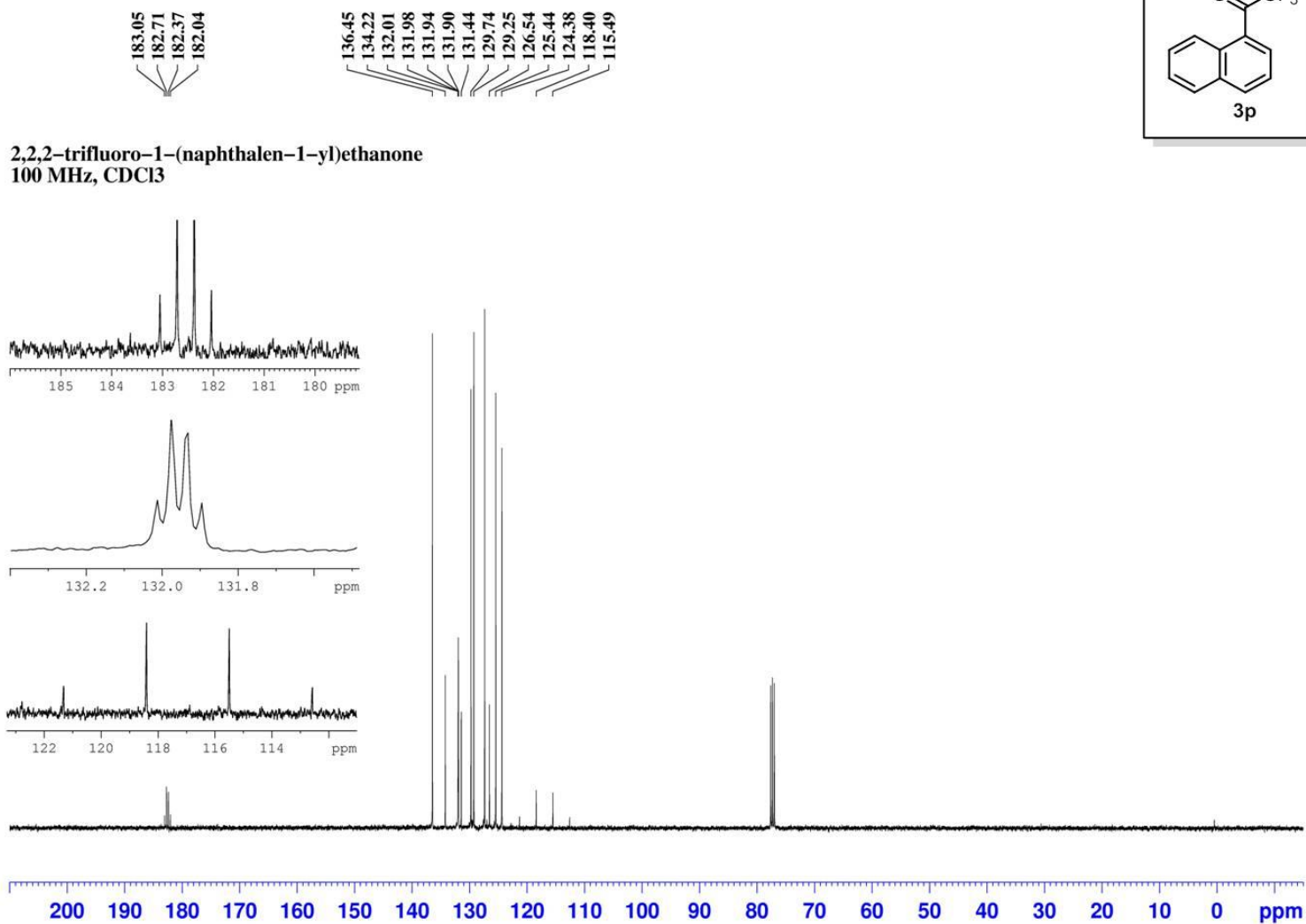




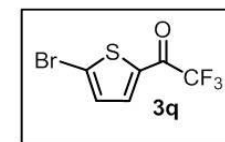




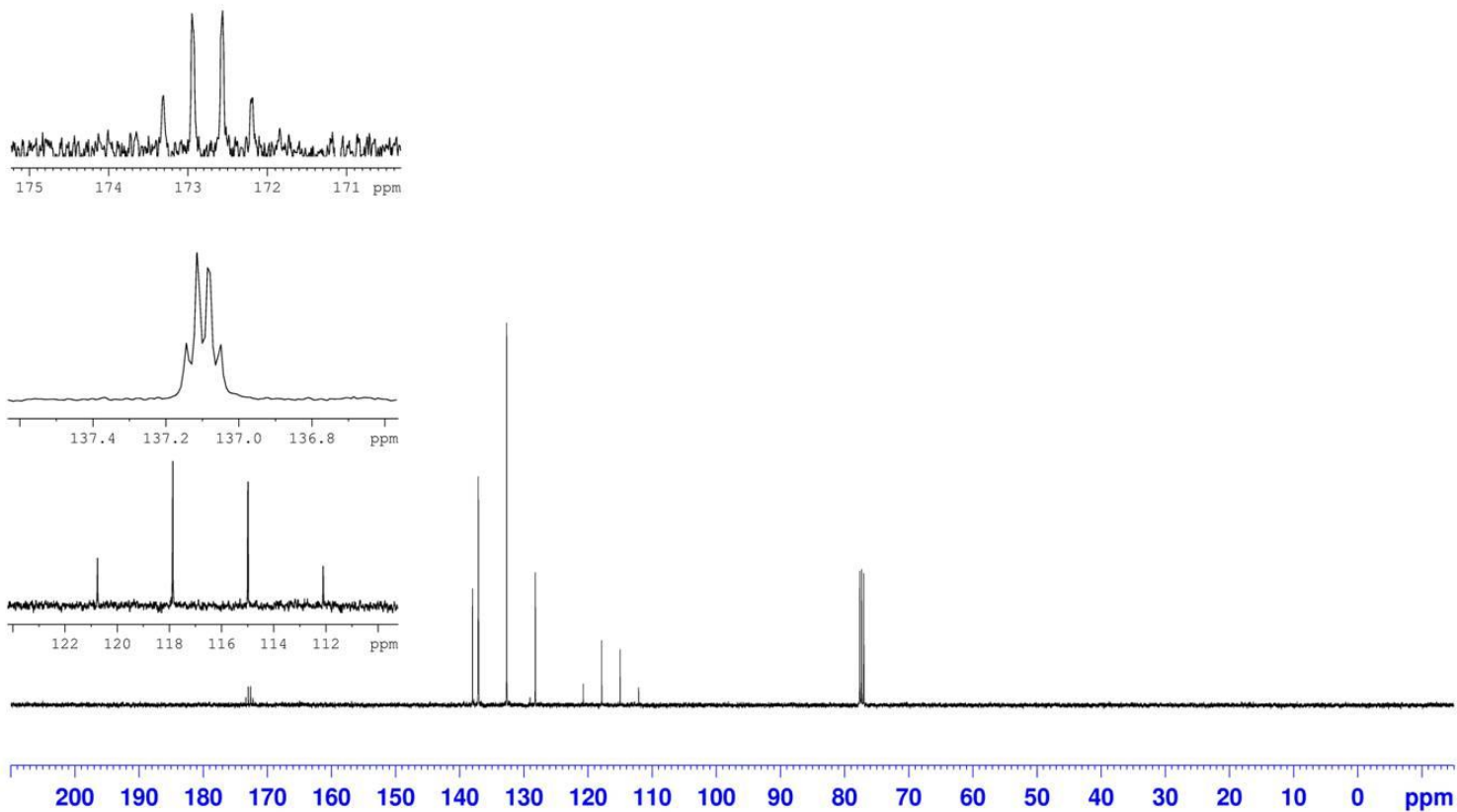


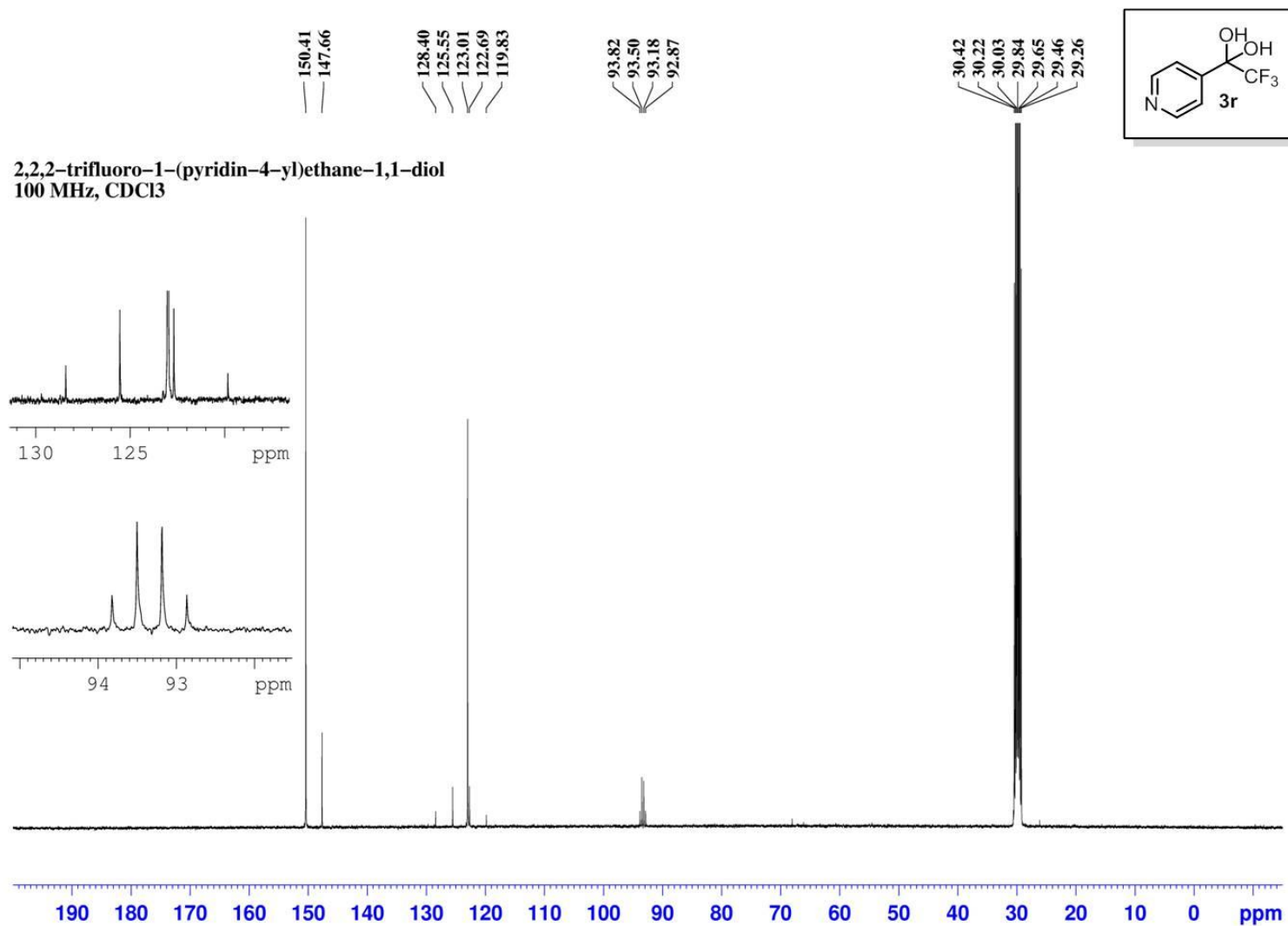


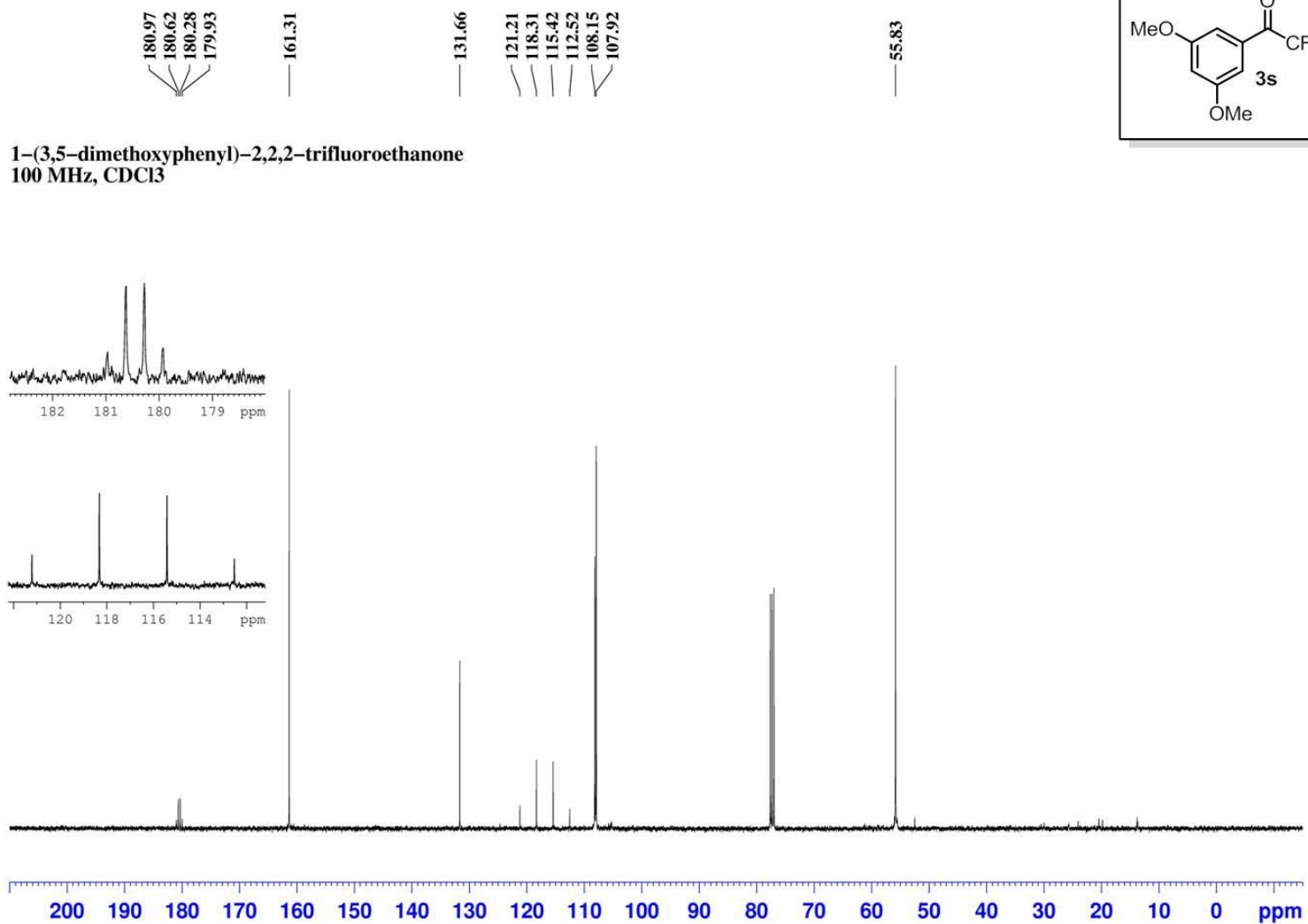


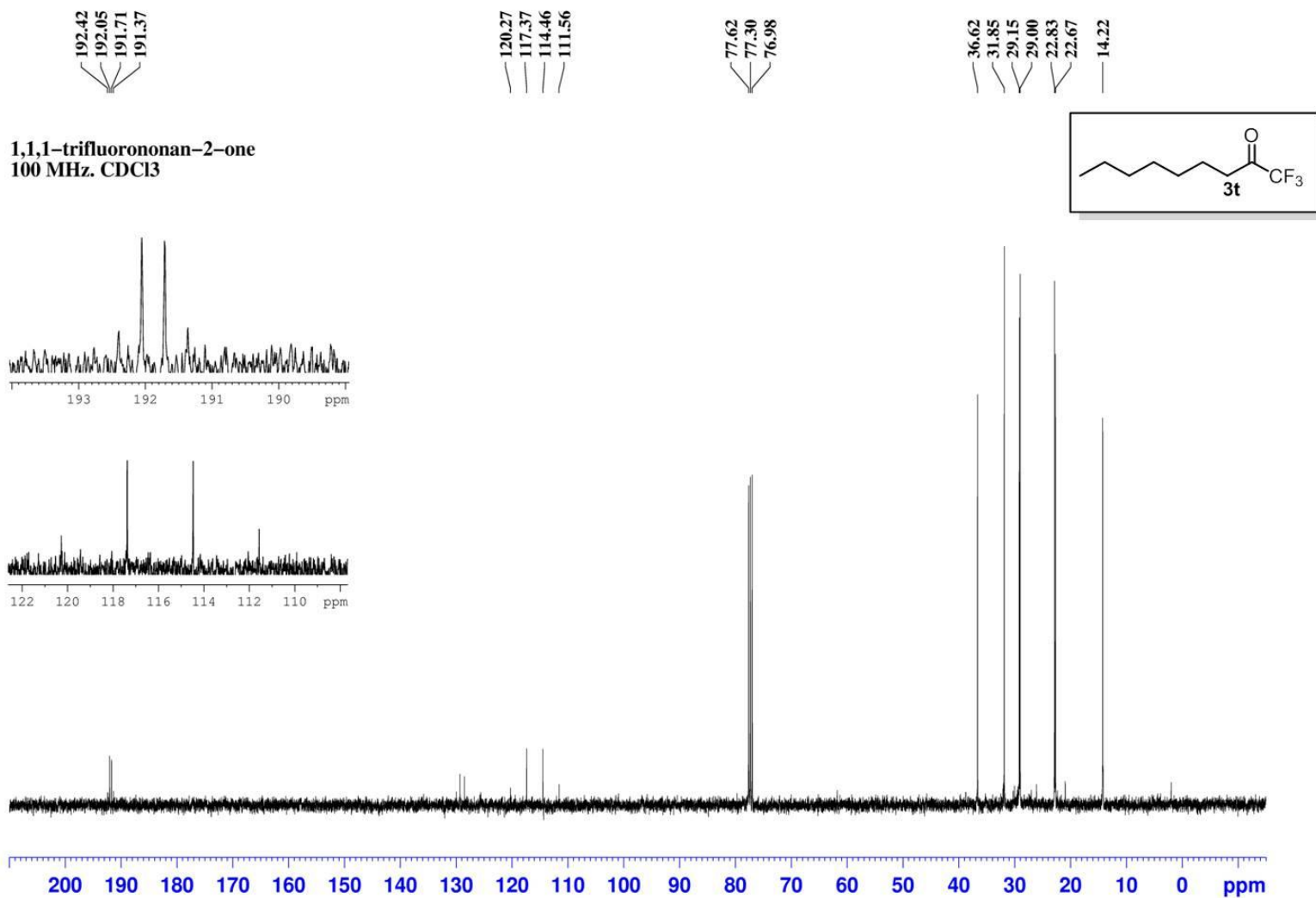


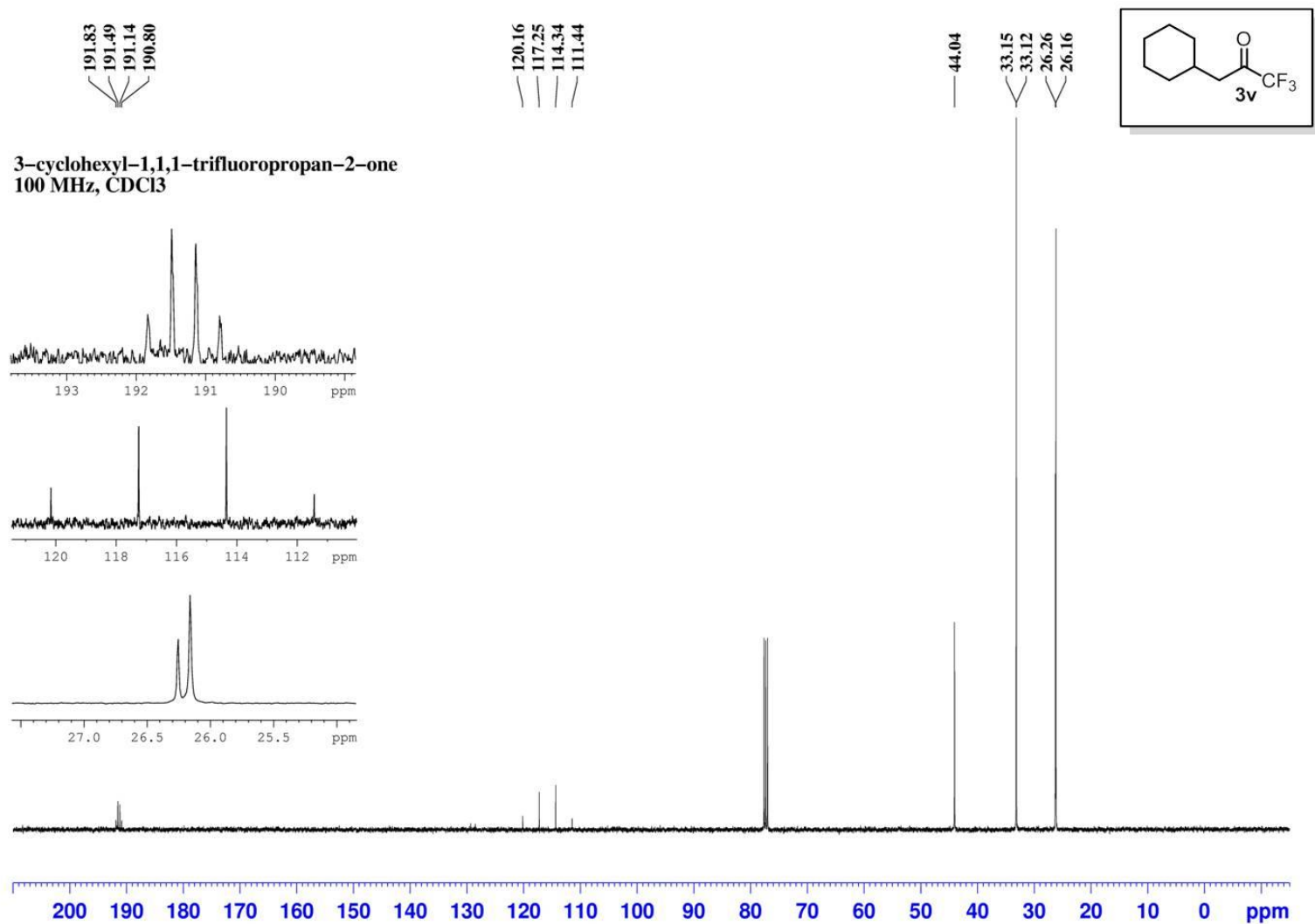
1-(5-bromothiophen-2-yl)-2,2,2-trifluoroethanone  
100 MHz, CDCl<sub>3</sub>

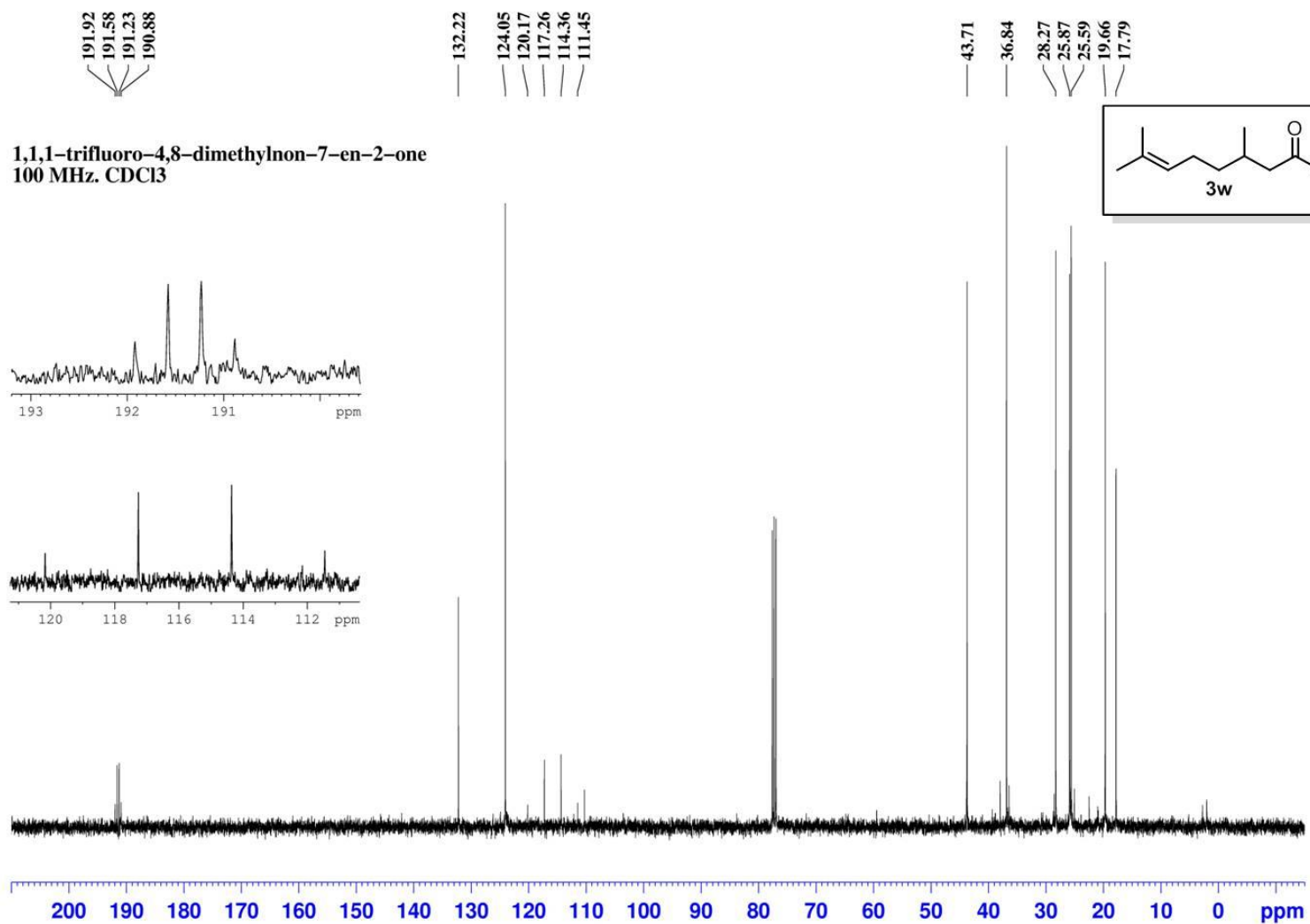






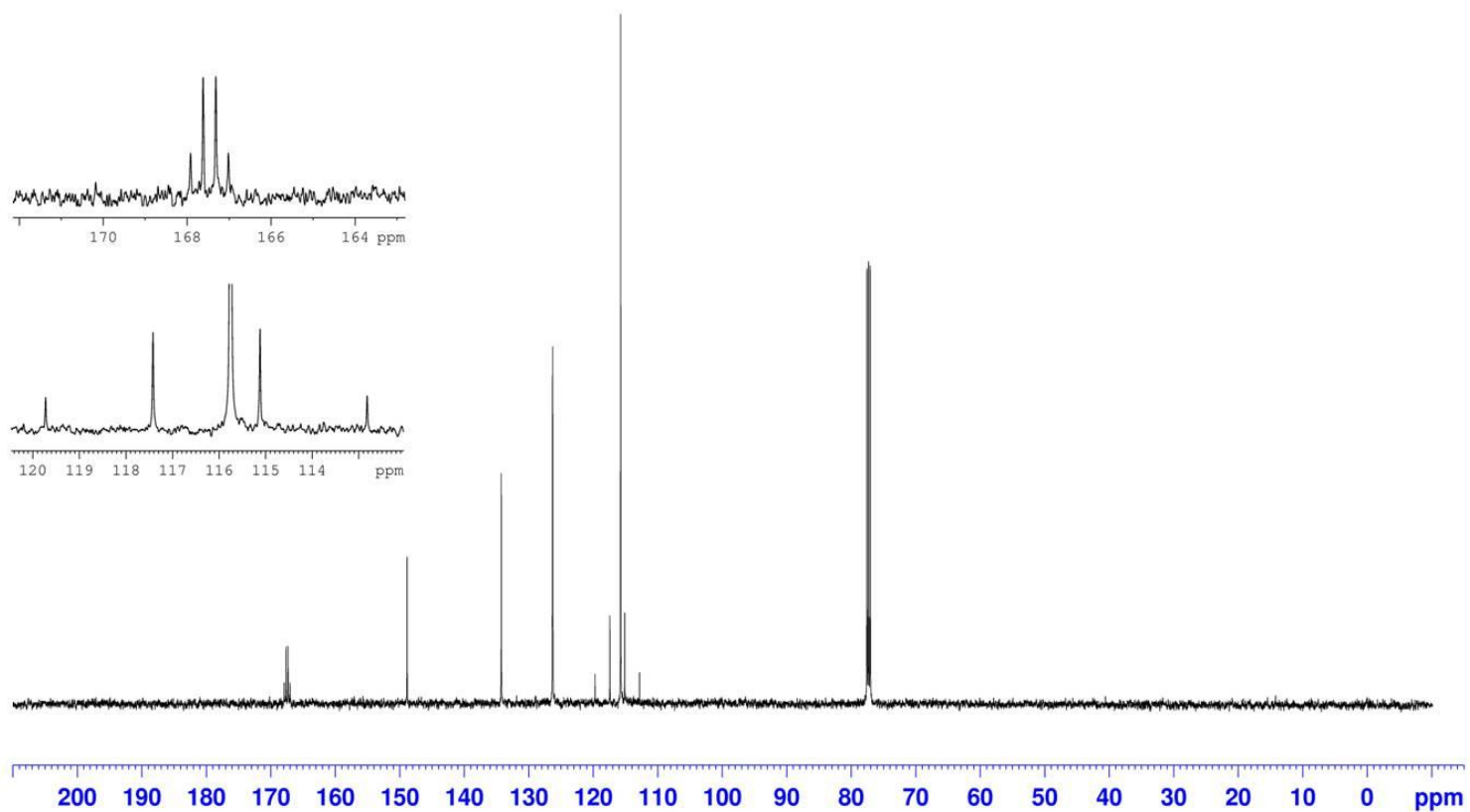
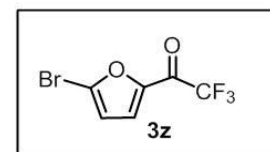


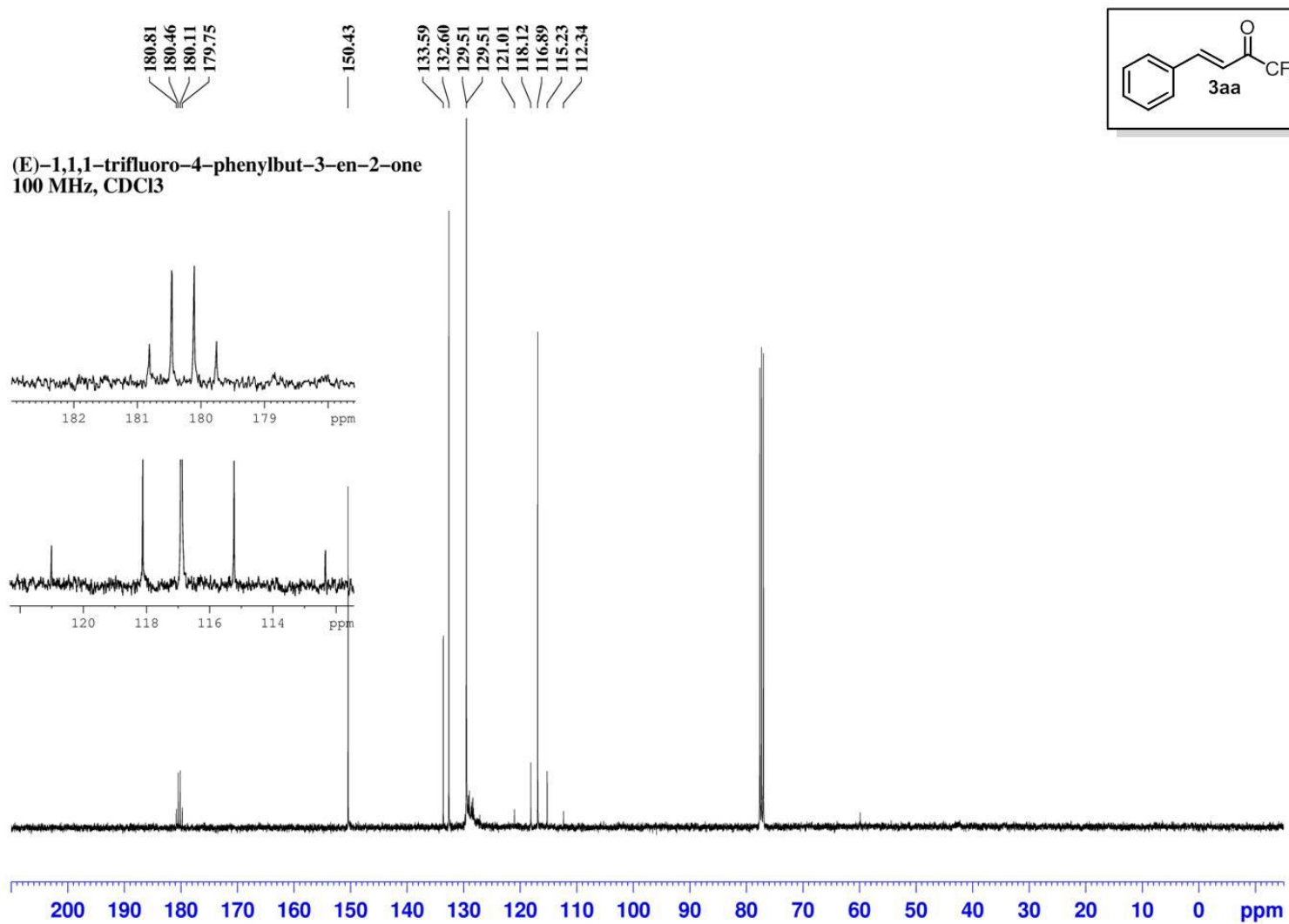




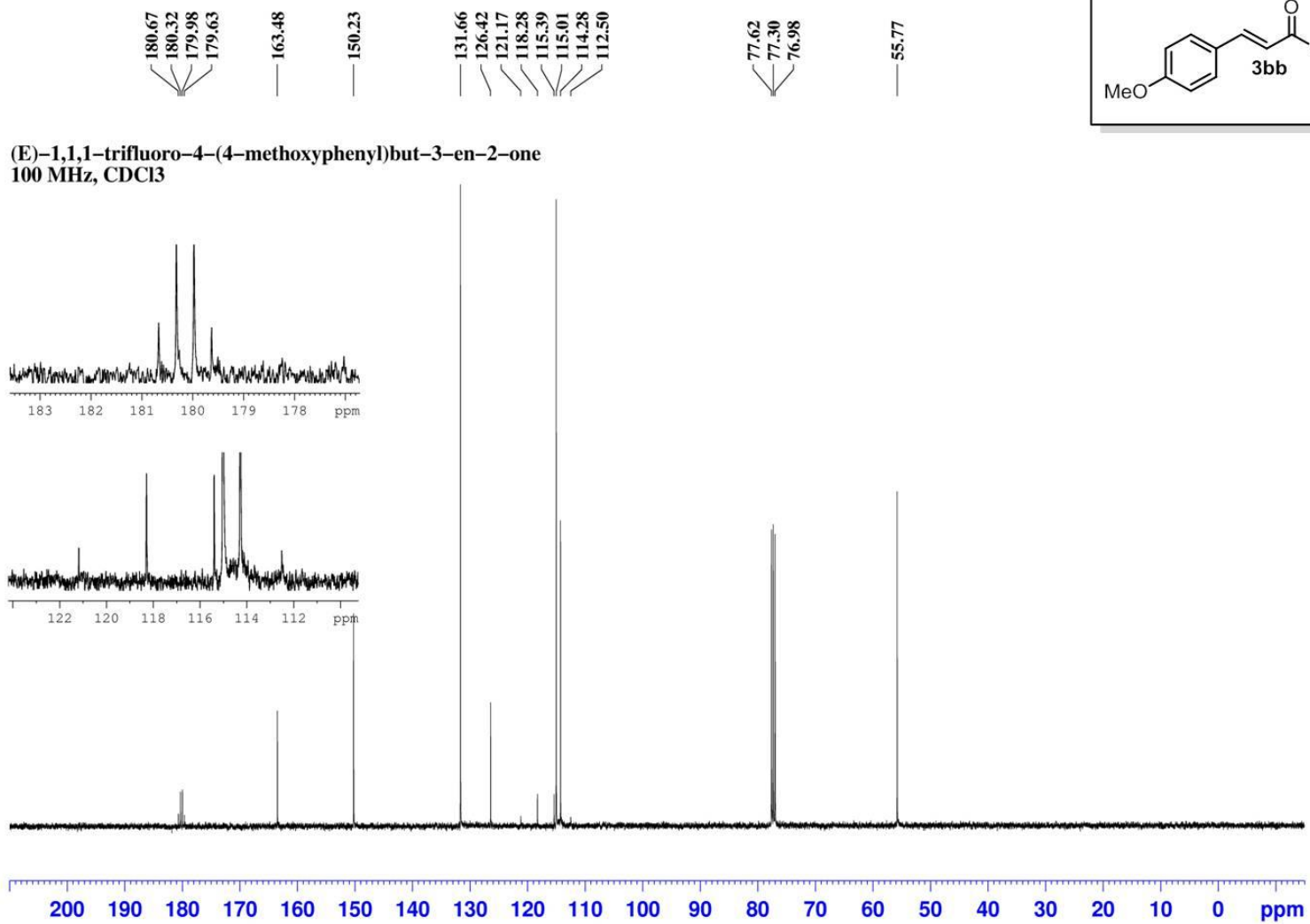
167.92  
167.62  
167.31  
167.01  
148.86  
134.25  
126.28  
119.72  
117.42  
115.75  
115.12  
112.82

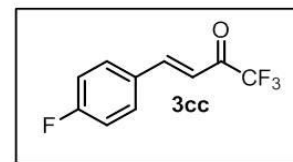
1-(5-bromofuran-2-yl)-2,2,2-trifluoroethanone  
125 MHz, CDCl<sub>3</sub>



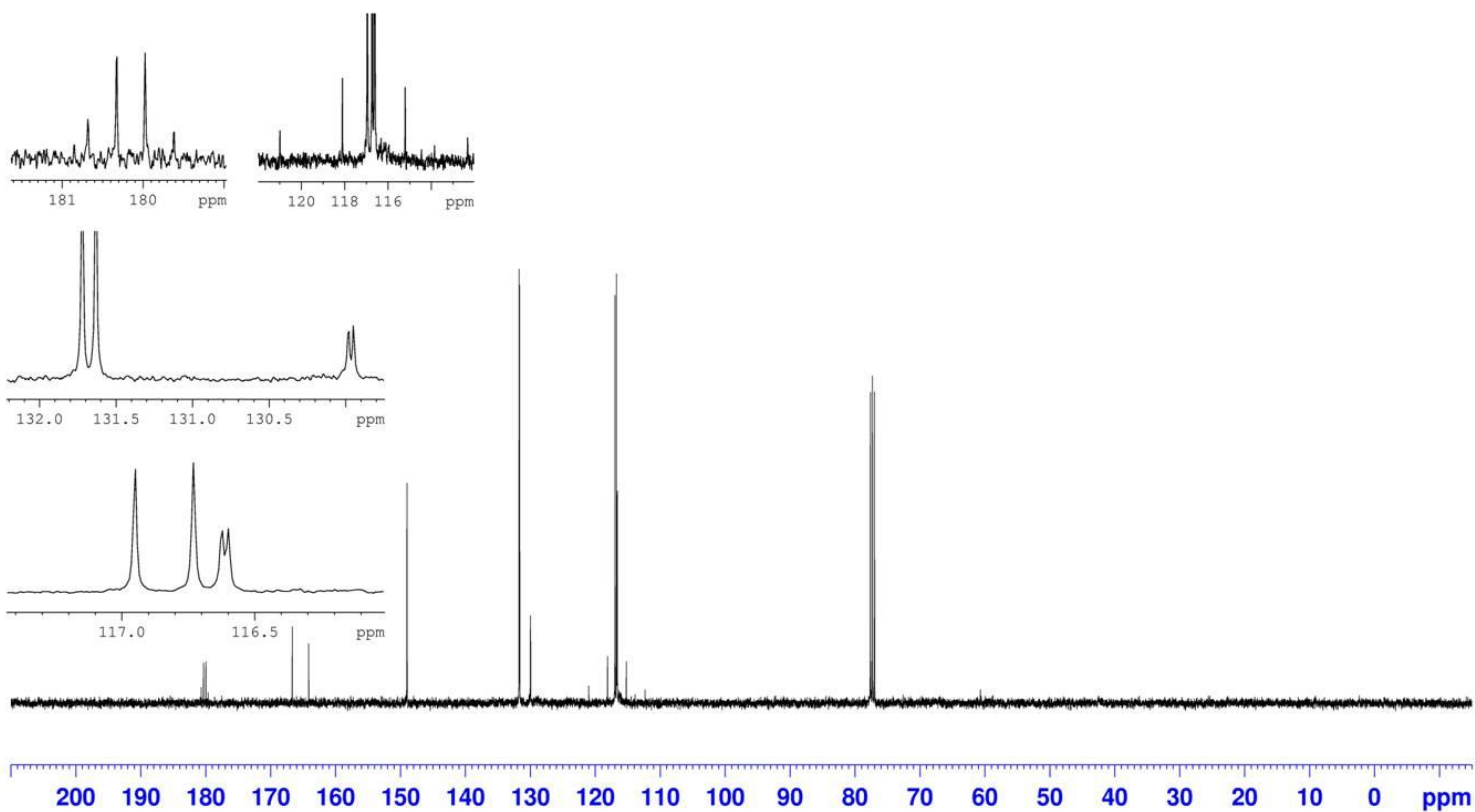


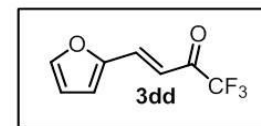
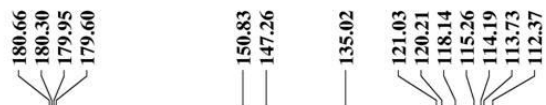




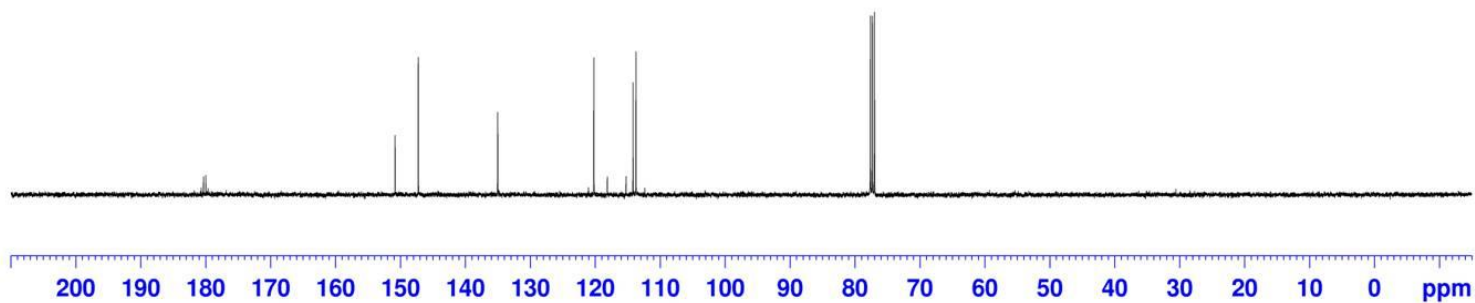
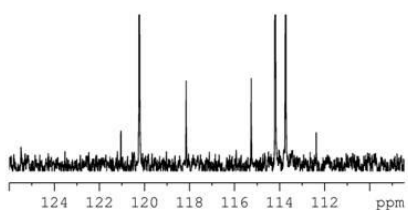
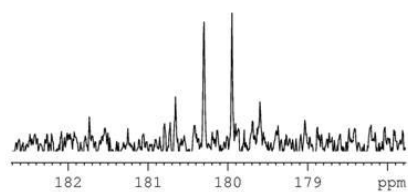


**(E)-1,1,1-trifluoro-4-(4-fluorophenyl)but-3-en-2-one**  
100 MHz, CDCl<sub>3</sub>

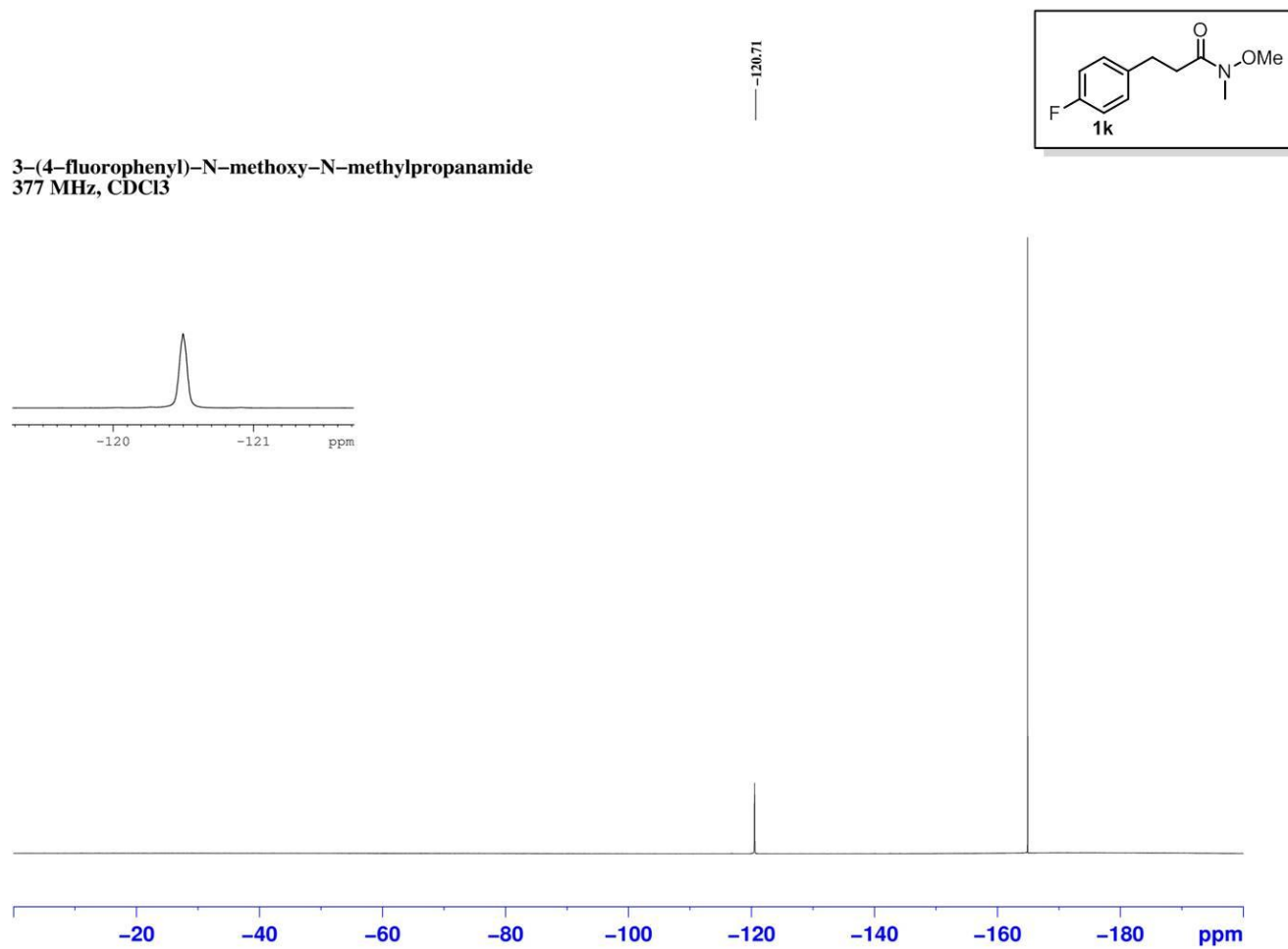




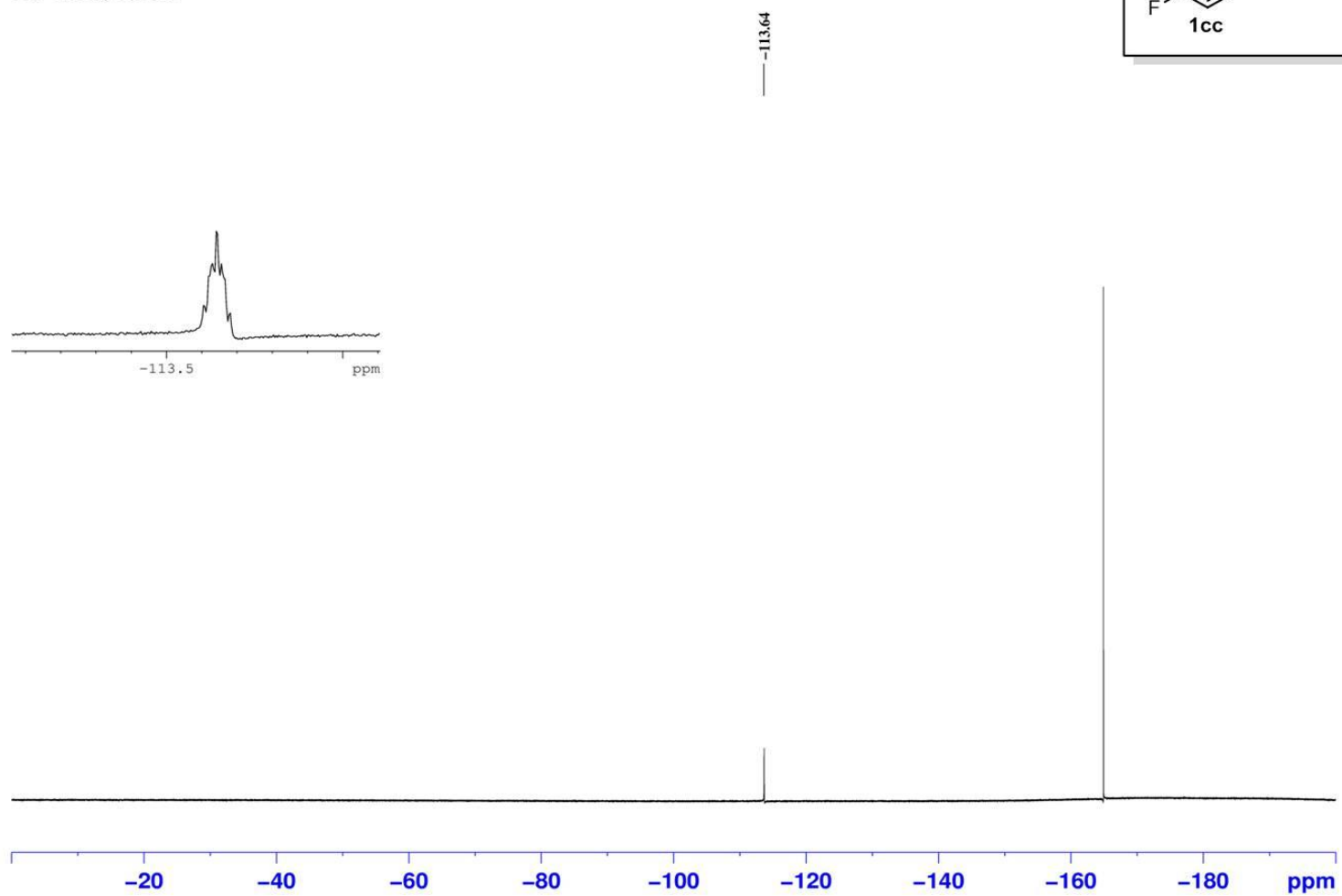
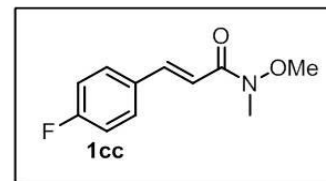
(E)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one  
100 MHz, CDCl<sub>3</sub>



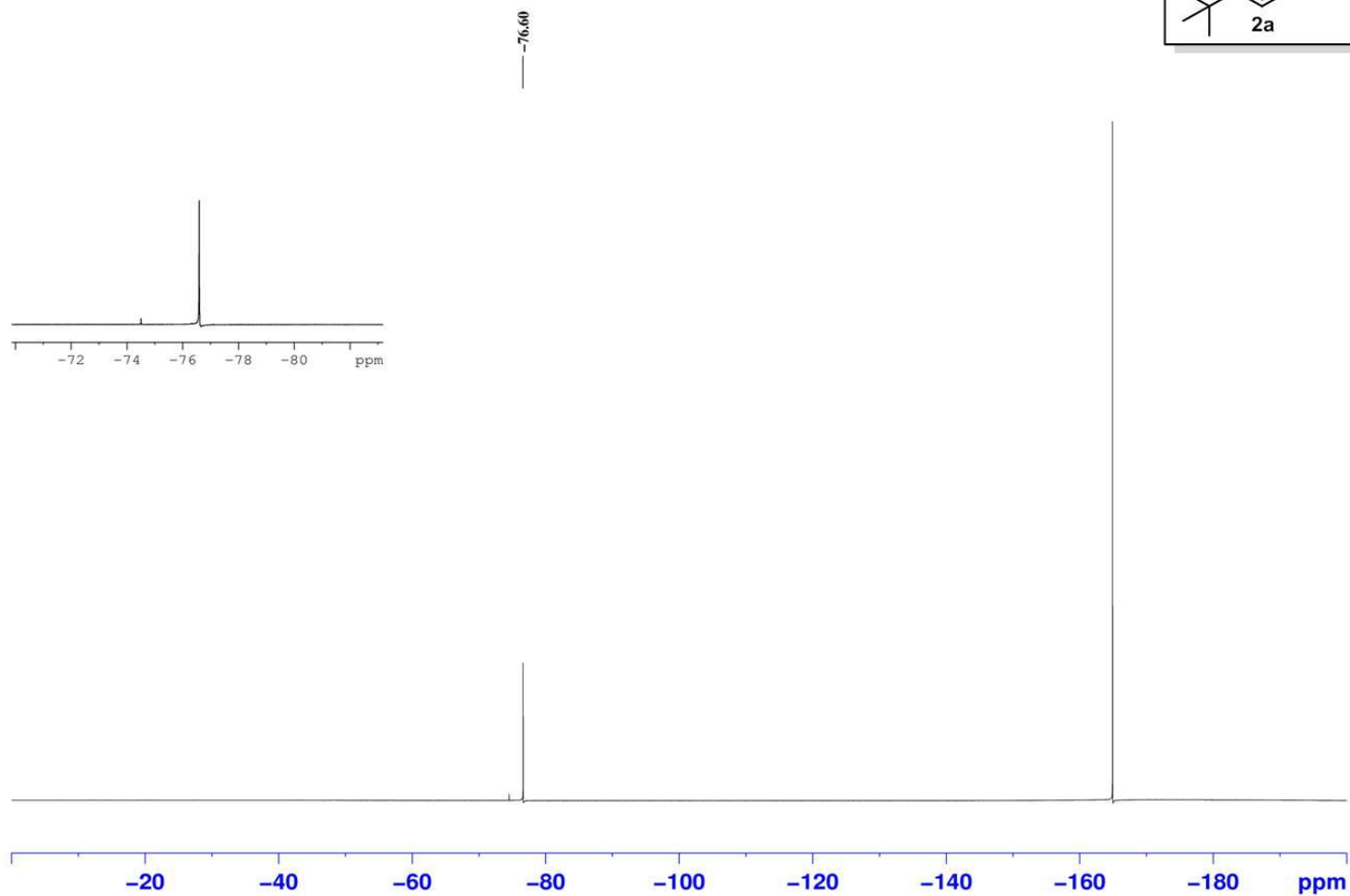
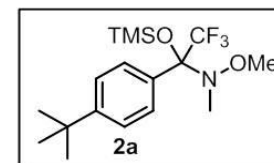
## <sup>19</sup>F-NMR Spectra of Synthesized Compounds



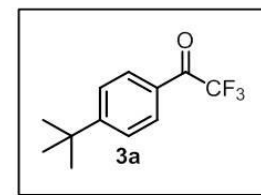
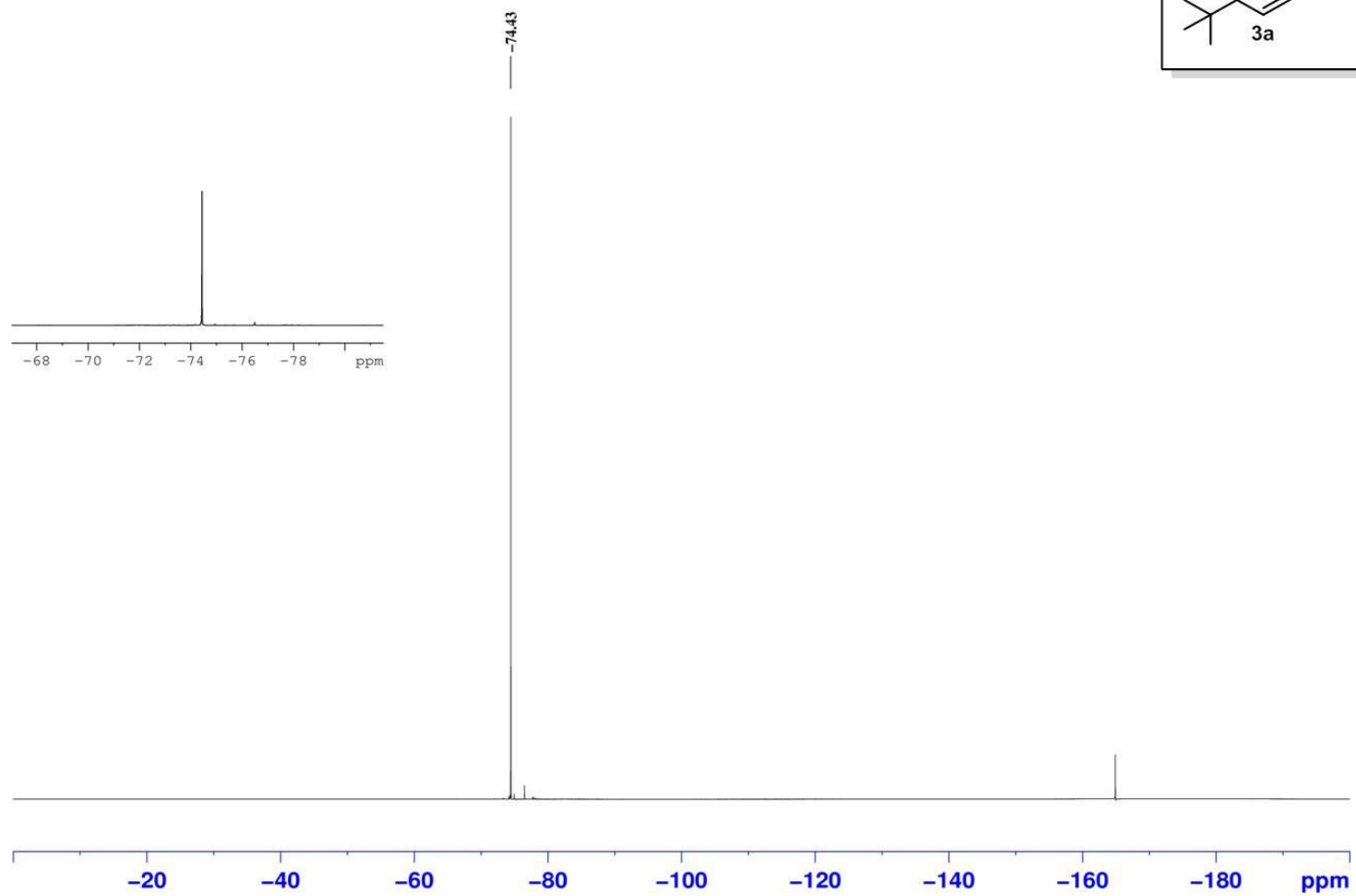
(E)-3-(4-fluorophenyl)-N-methoxy-N-methylacrylamide  
377 MHz, CDCl<sub>3</sub>



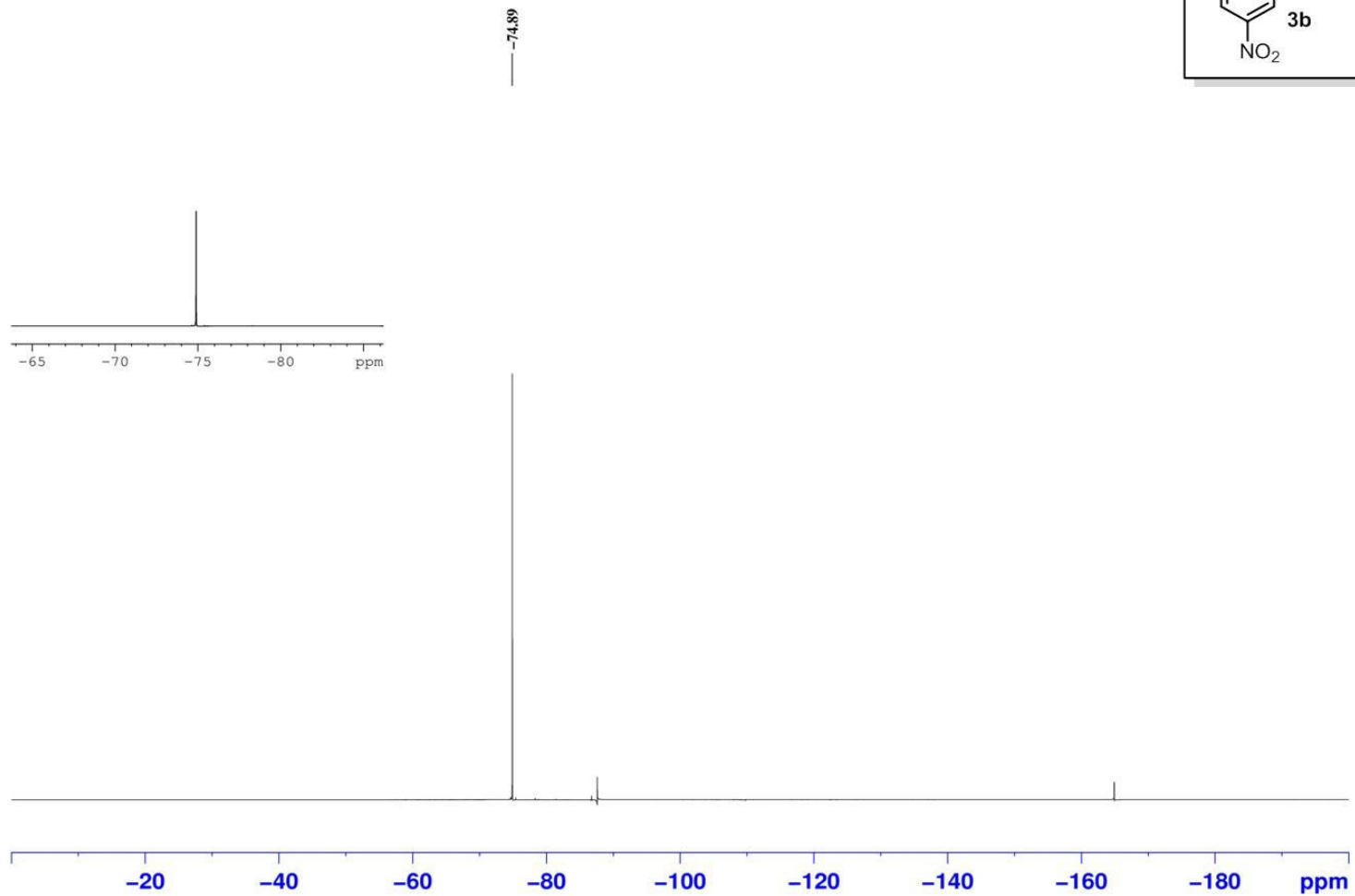
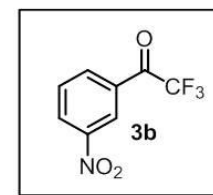
**N-(1-(4-tert-butylphenyl)-2,2,2-trifluoro-1-(trimethylsilyloxy)ethyl)-N,O-dimethylhydroxylamine**  
377 MHz, CDCl<sub>3</sub>



1-(4-*tert*-butylphenyl)-2,2,2-trifluoroethanone  
377 MHz, CDCl<sub>3</sub>

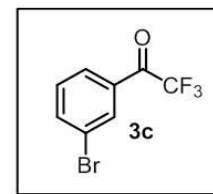
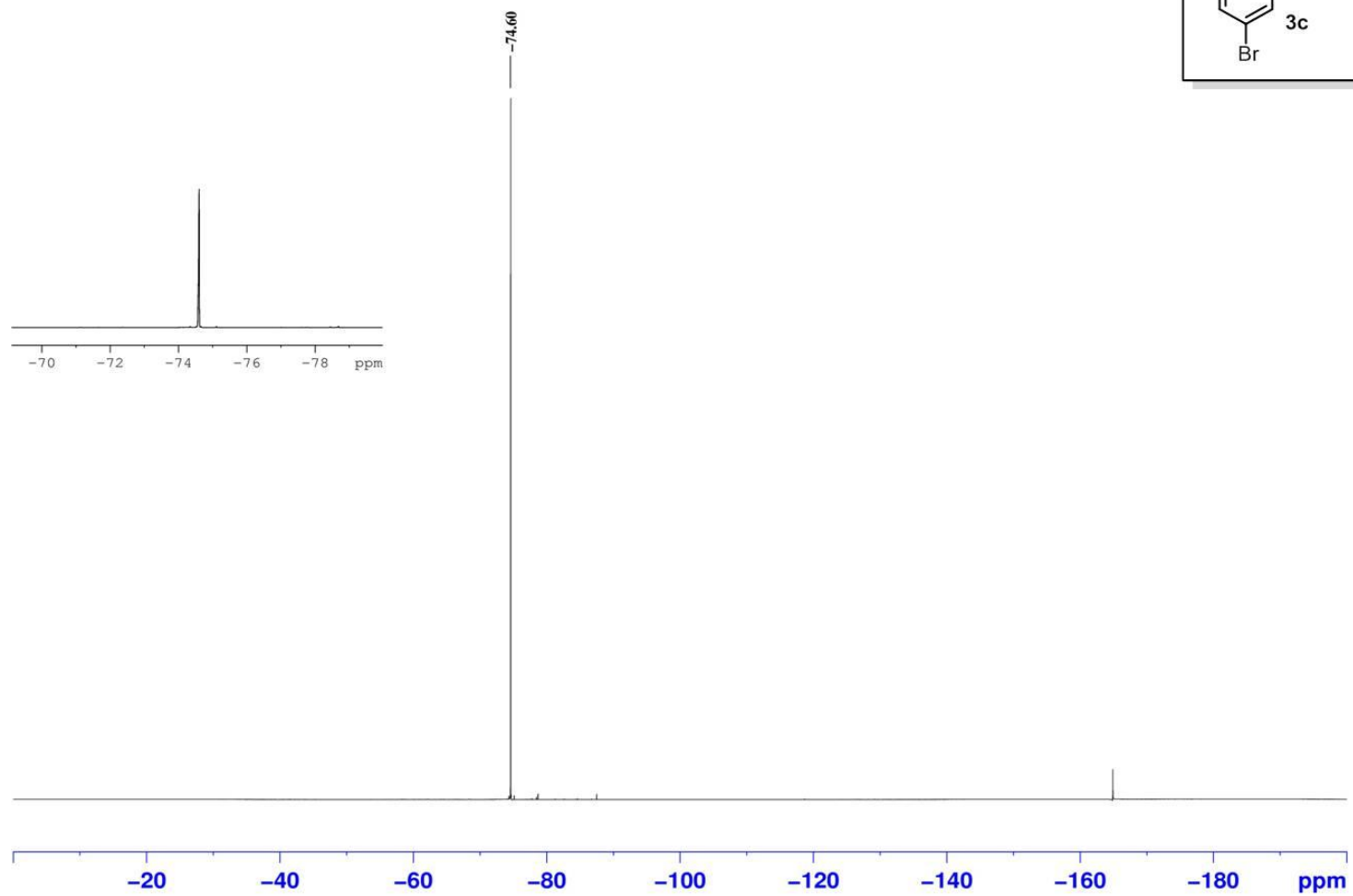


**2,2,2-trifluoro-1-(3-nitrophenyl)ethanone**  
377 MHz, CDCl<sub>3</sub>

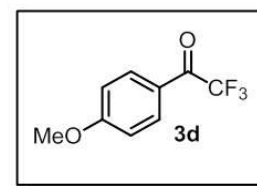
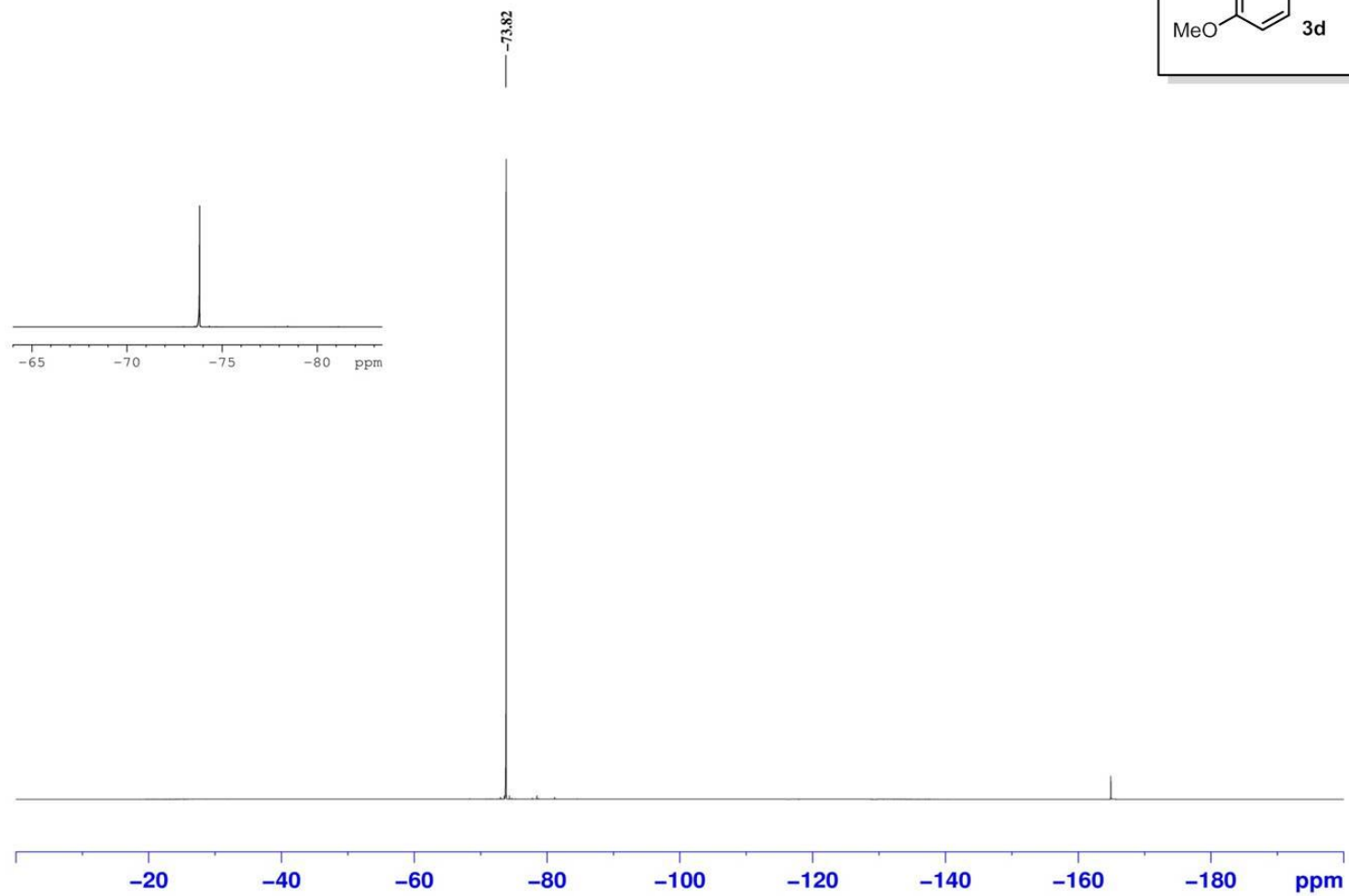




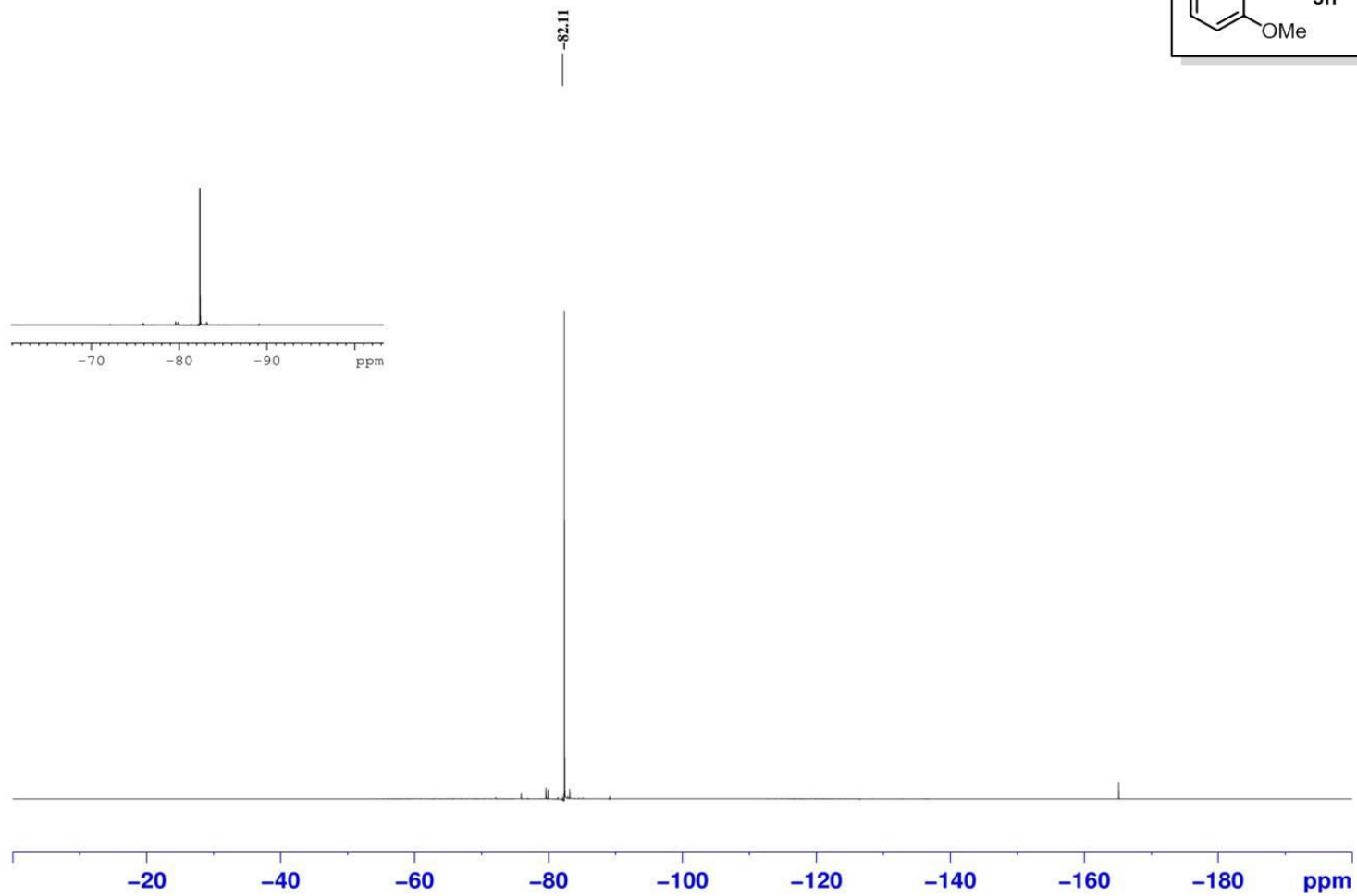
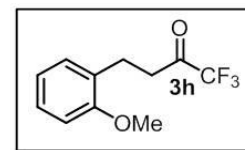
**1-(3-bromophenyl)-2,2,2-trifluoroethanone**  
377 MHz, CDCl<sub>3</sub>

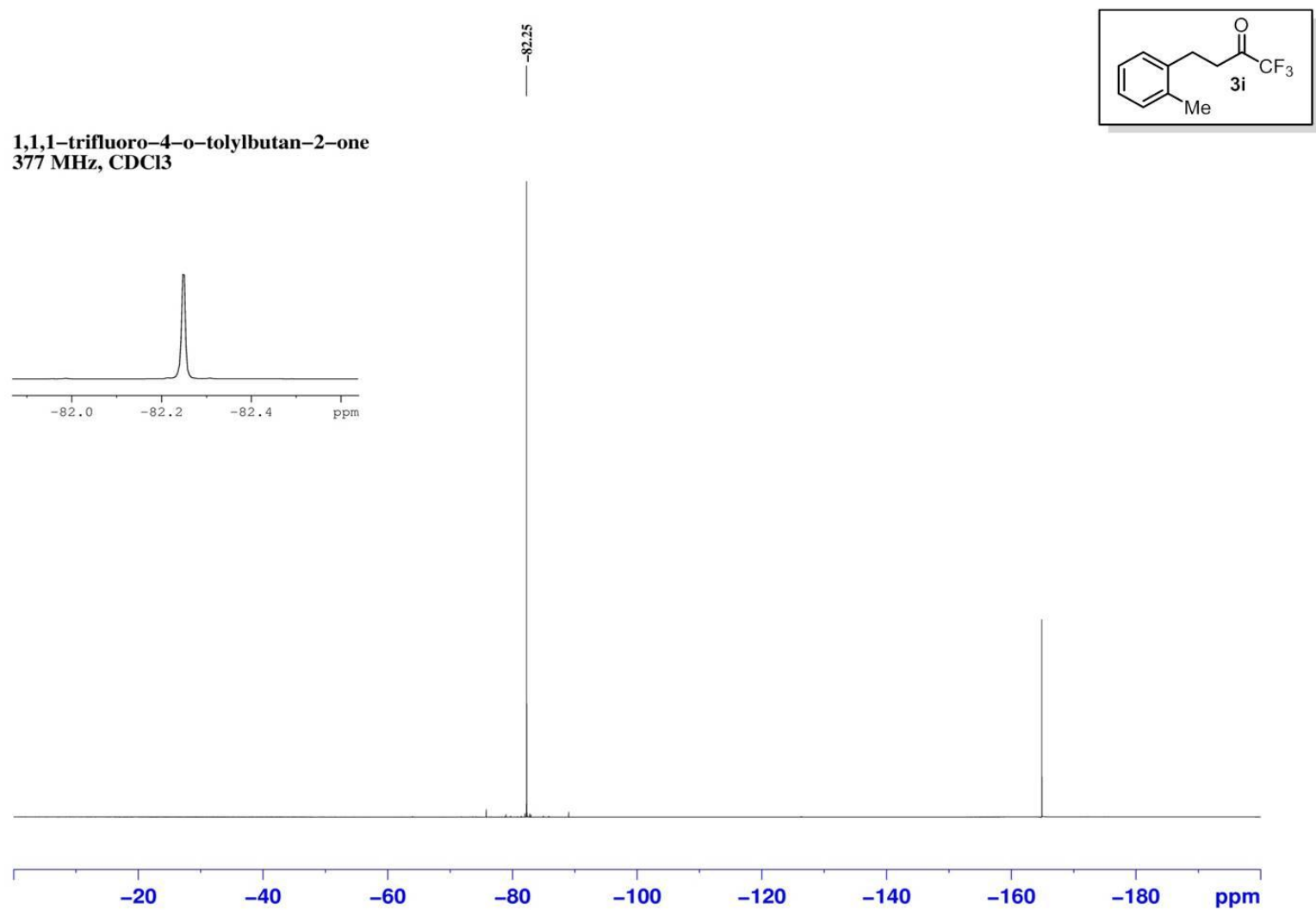


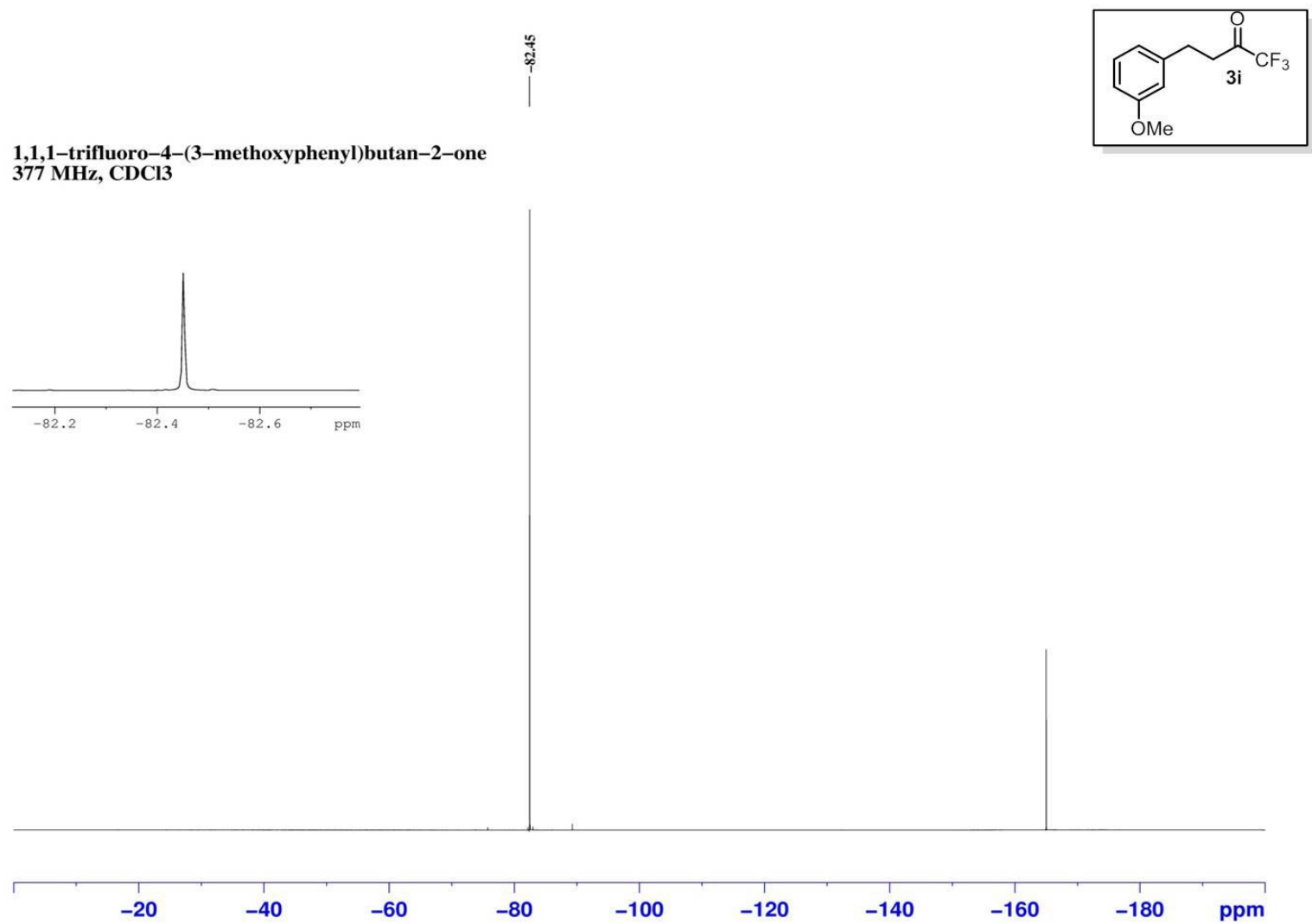
2,2,2-trifluoro-1-(4-methoxyphenyl)ethanone  
377 MHz, CDCl<sub>3</sub>

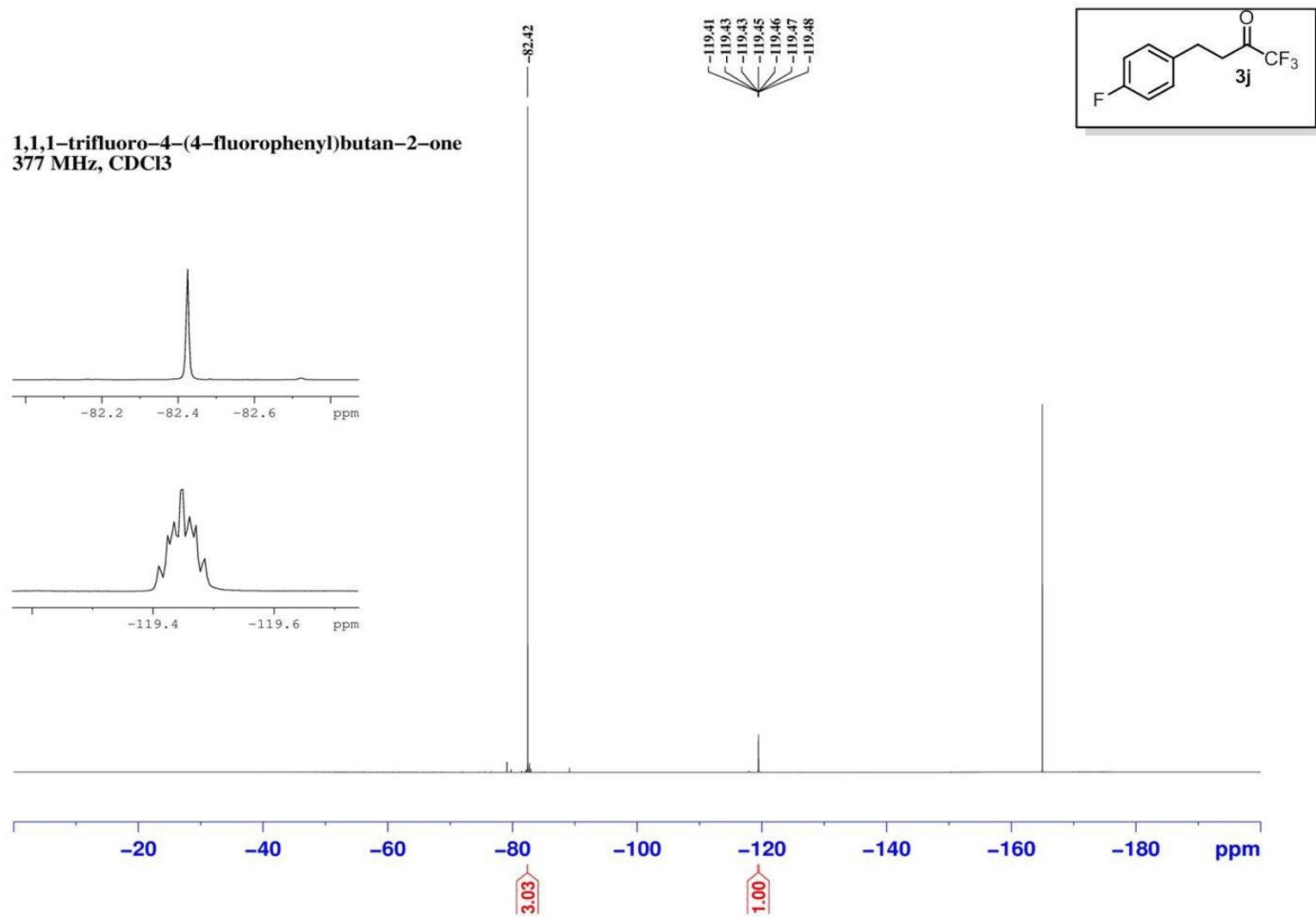


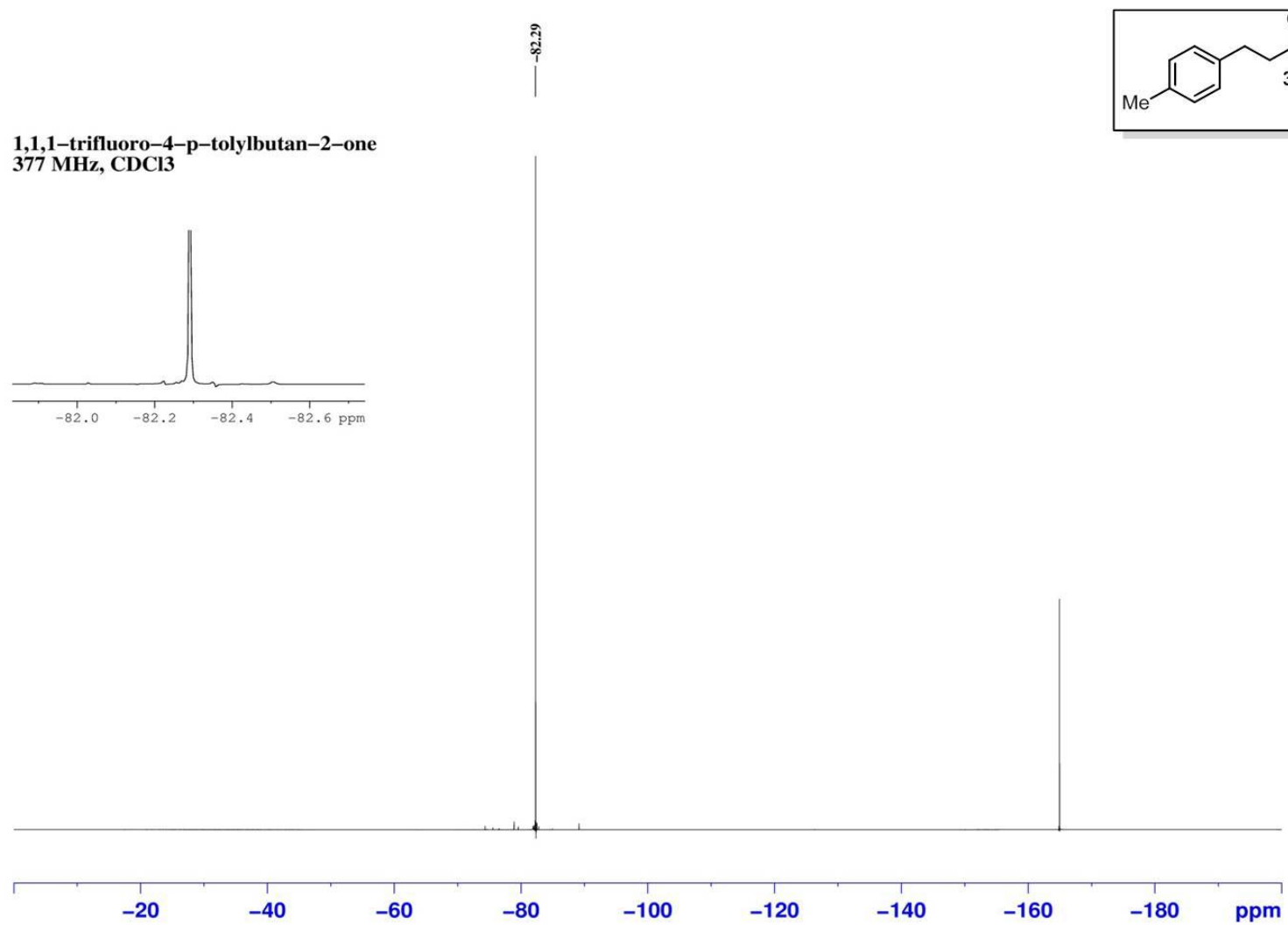
**1,1,1-trifluoro-4-(2-methoxyphenyl)butan-2-one**  
377 MHz, CDCl<sub>3</sub>

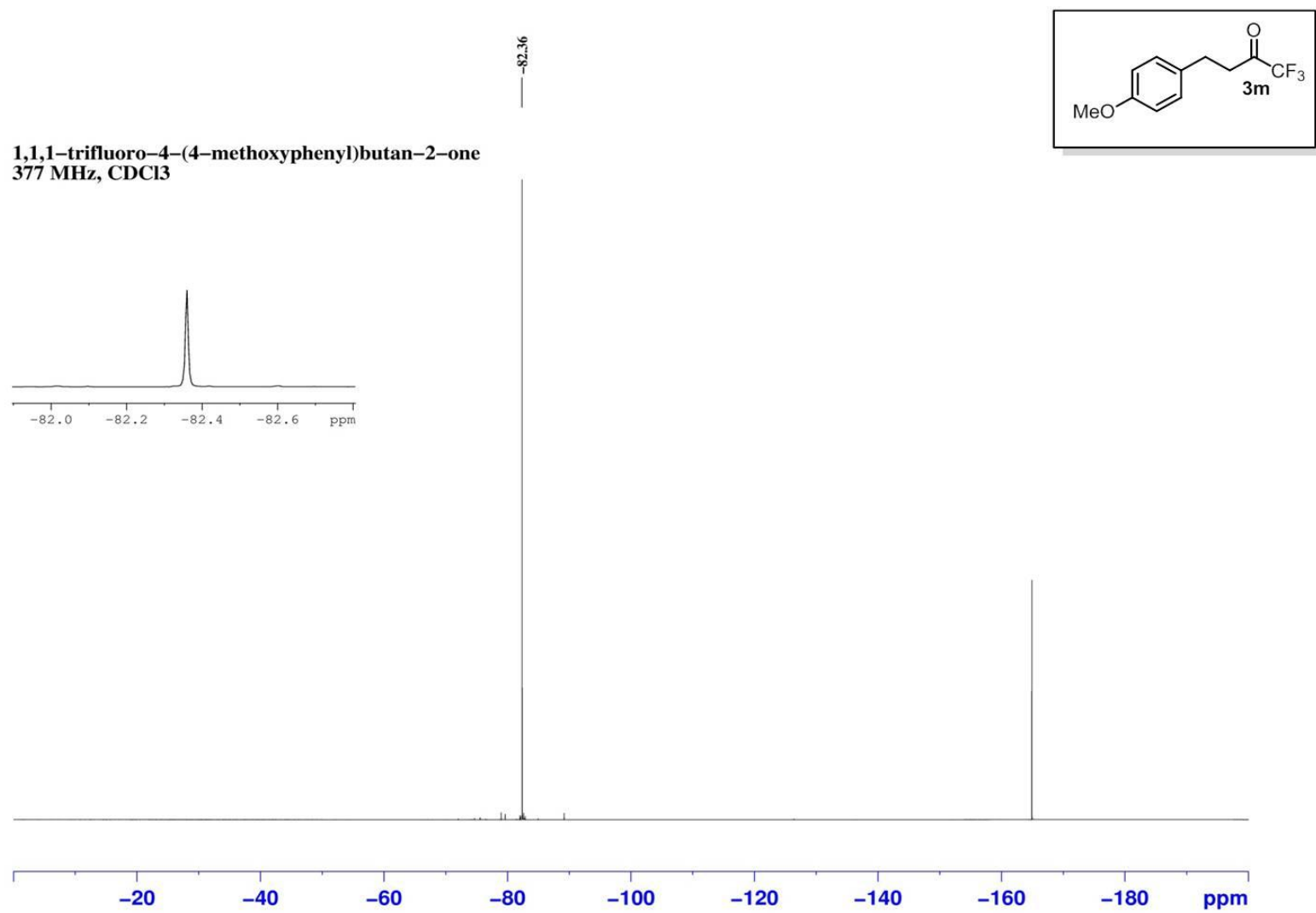






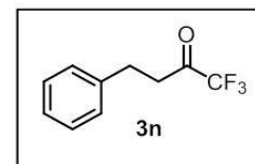
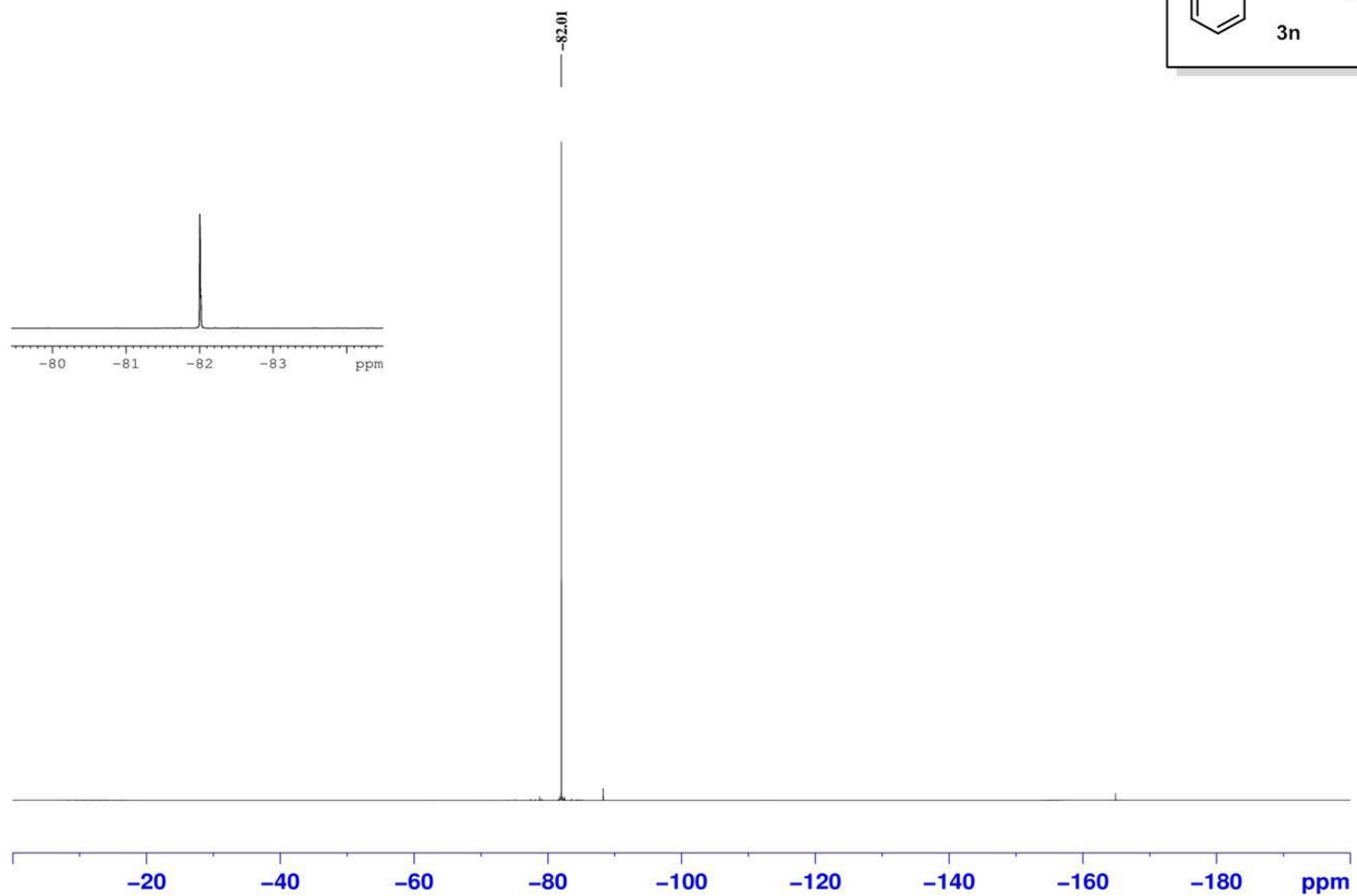




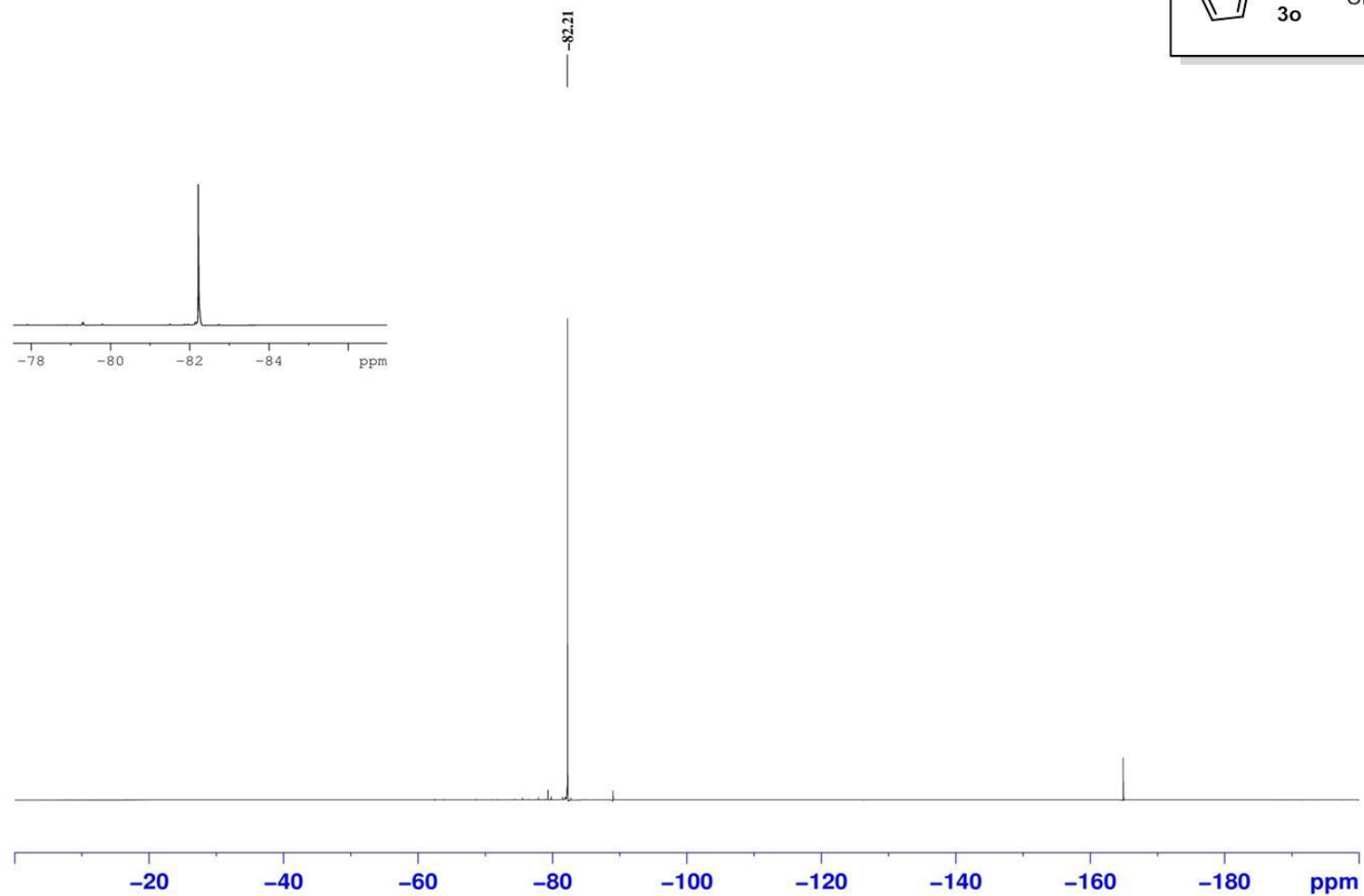
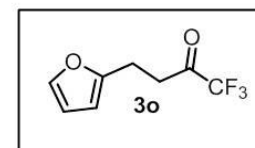




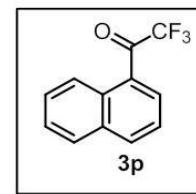
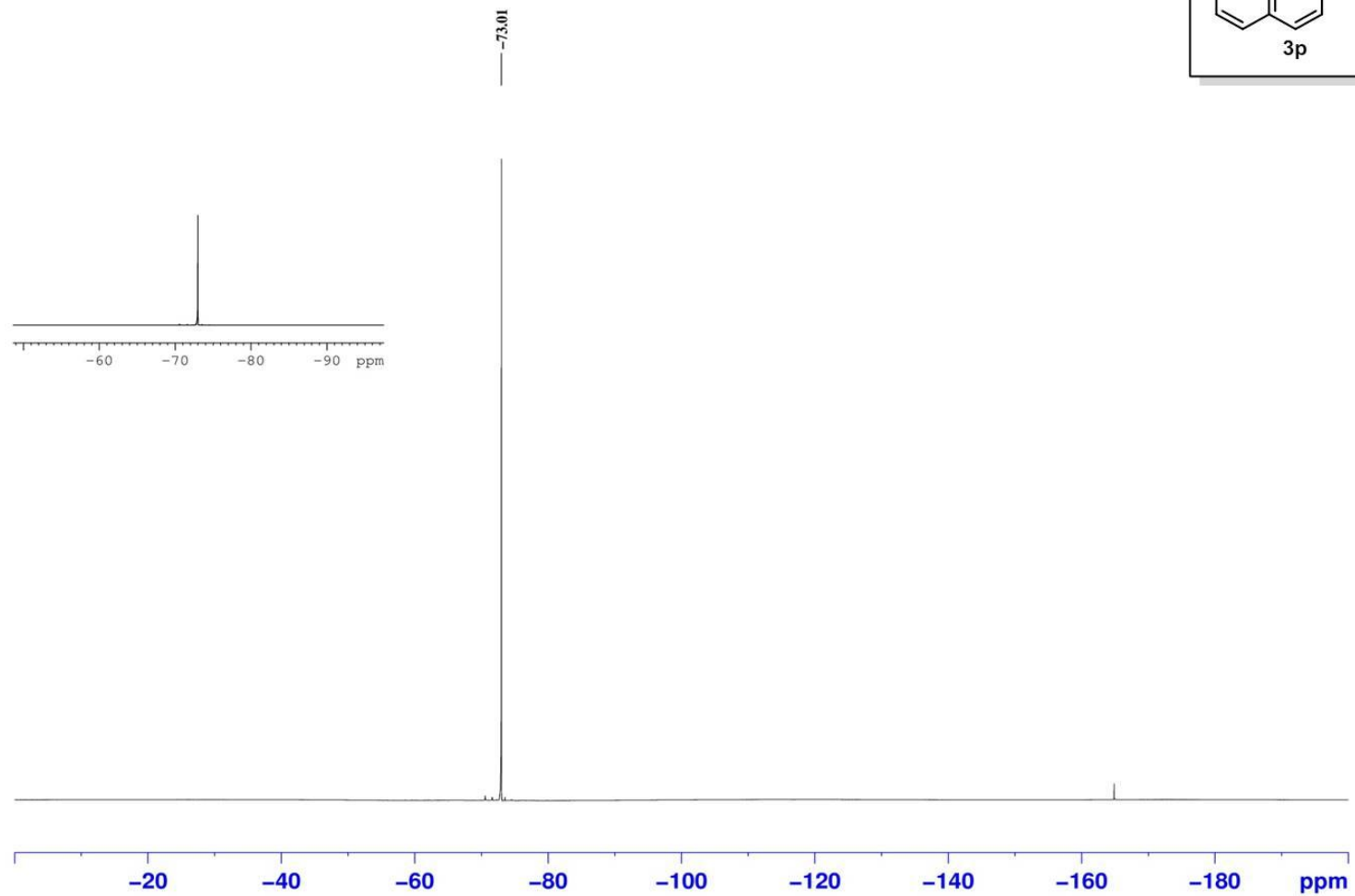
**1,1,1-trifluoro-4-phenylbutan-2-one**  
377 MHz, CDCl<sub>3</sub>



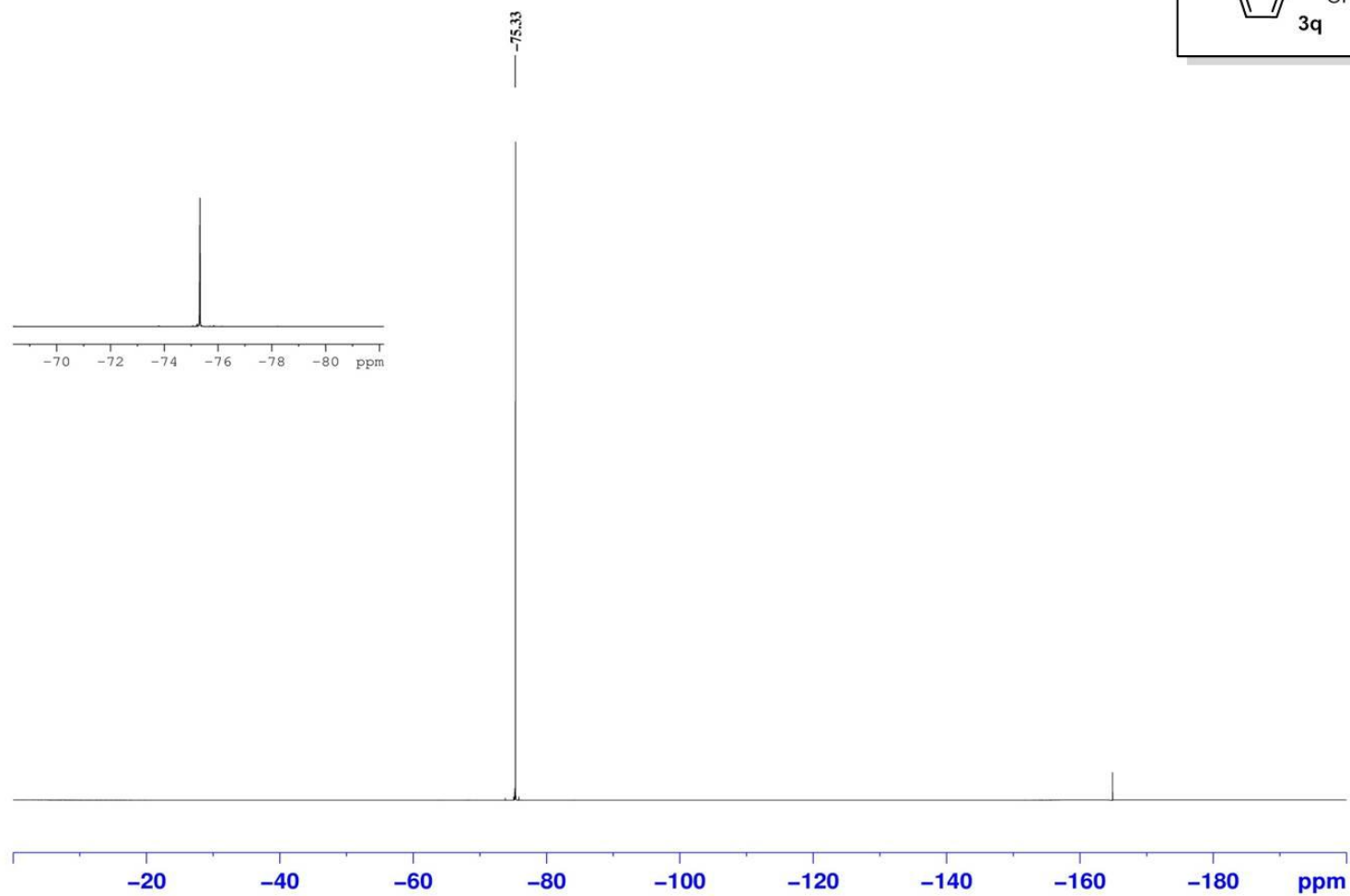
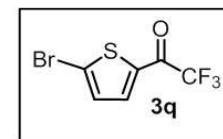
**1,1,1-trifluoro-4-(furan-2-yl)butan-2-one**  
377 MHz, CDCl<sub>3</sub>



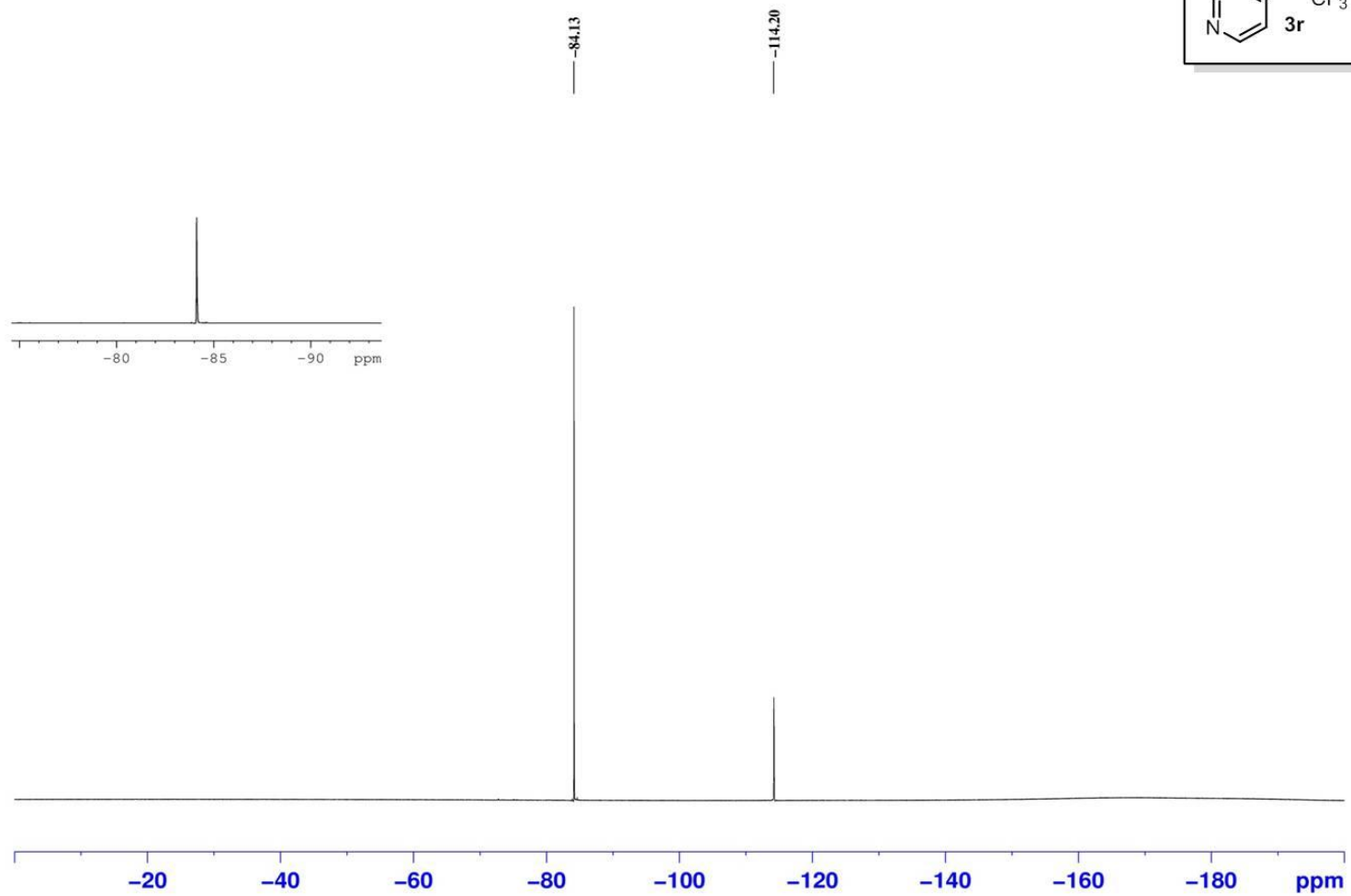
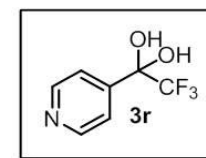
2,2,2-trifluoro-1-(naphthalen-1-yl)ethanone  
377 MHz, CDCl<sub>3</sub>



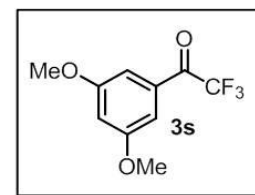
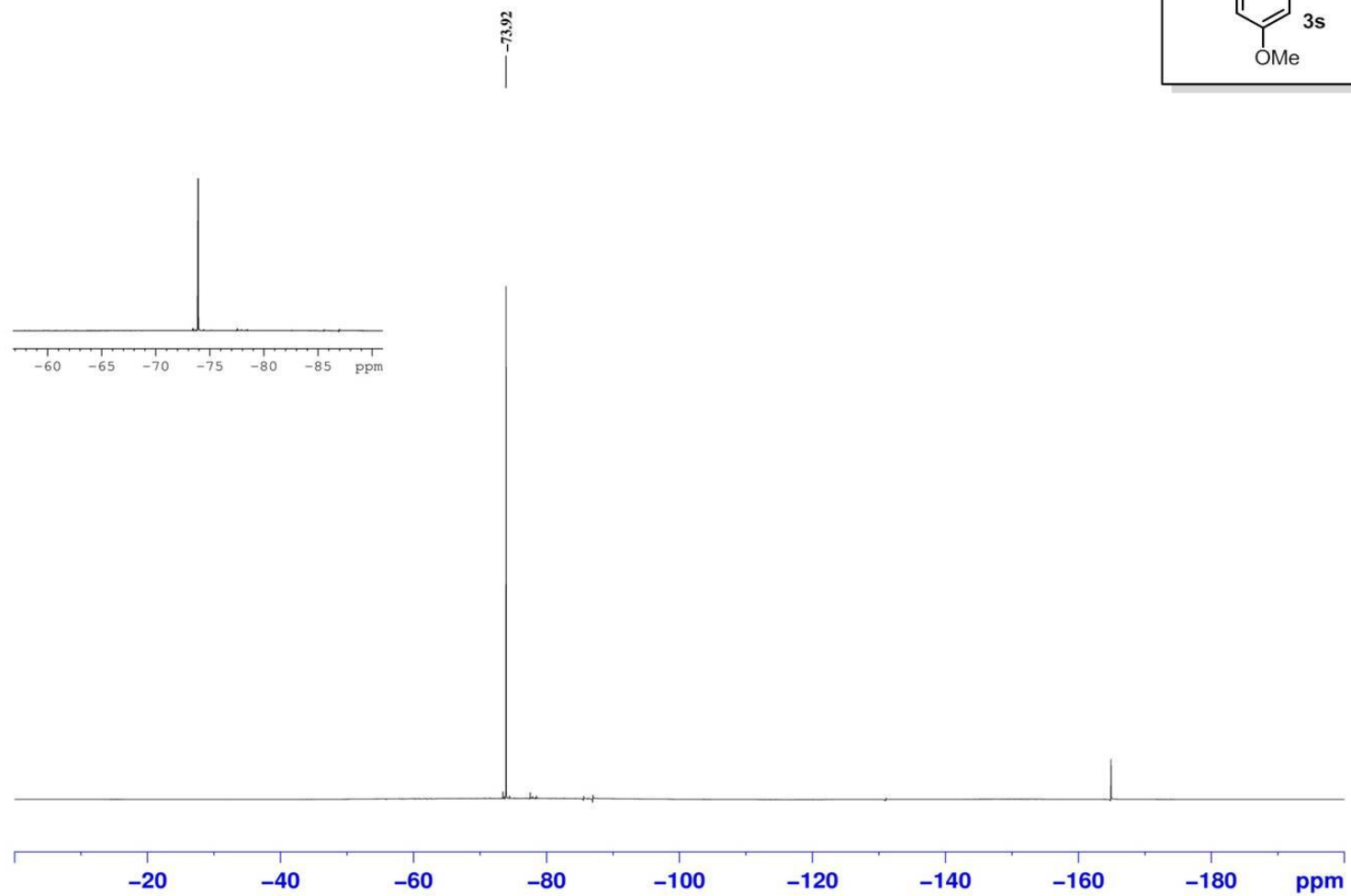
**1-(5-bromothiophen-2-yl)-2,2,2-trifluoroethanone**  
377 MHz, CDCl<sub>3</sub>



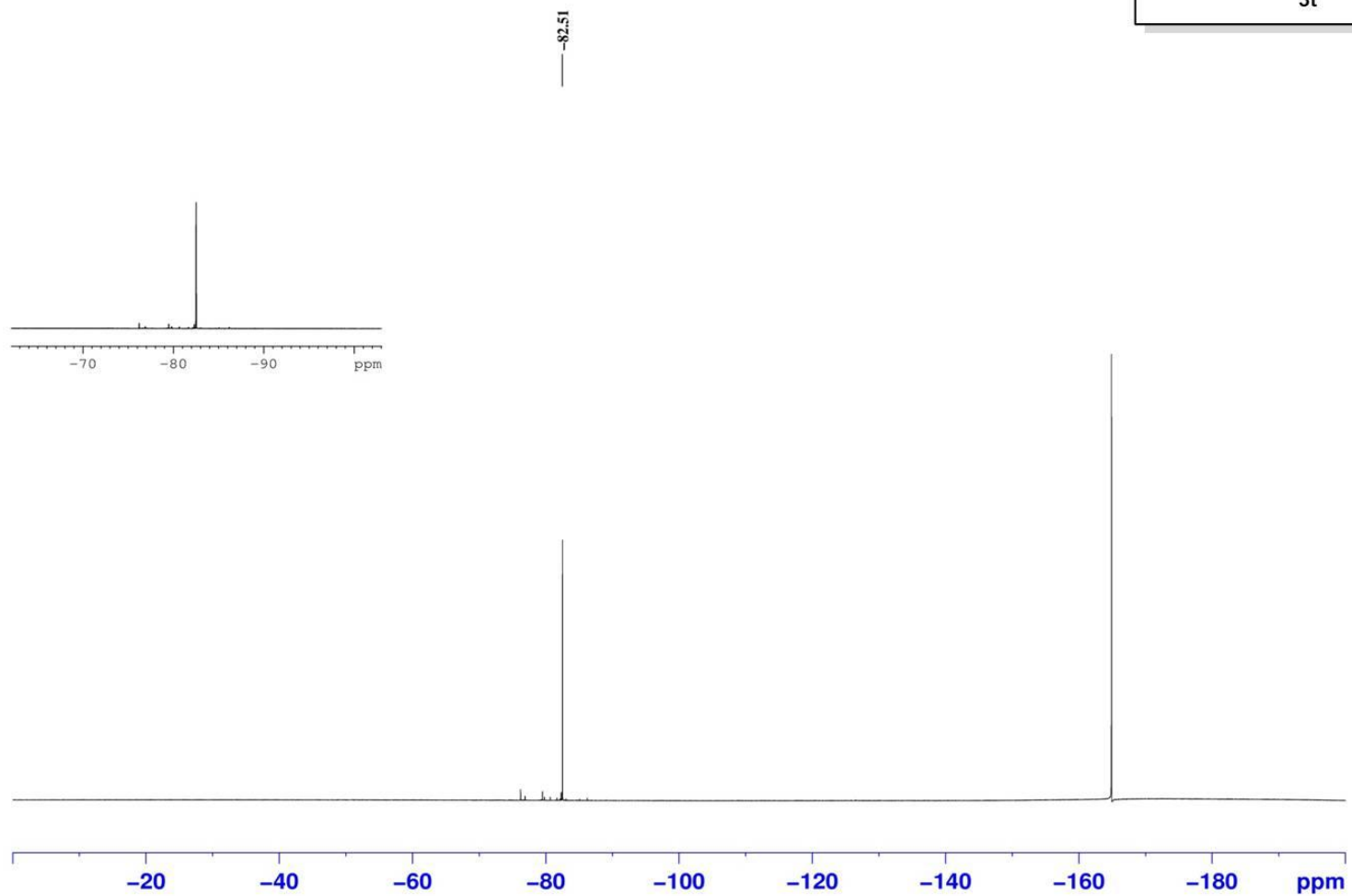
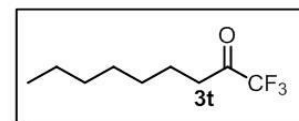
2,2,2-trifluoro-1-(pyridin-4-yl)ethane-1,1-diol  
377 MHz, Acetone-d<sub>6</sub>



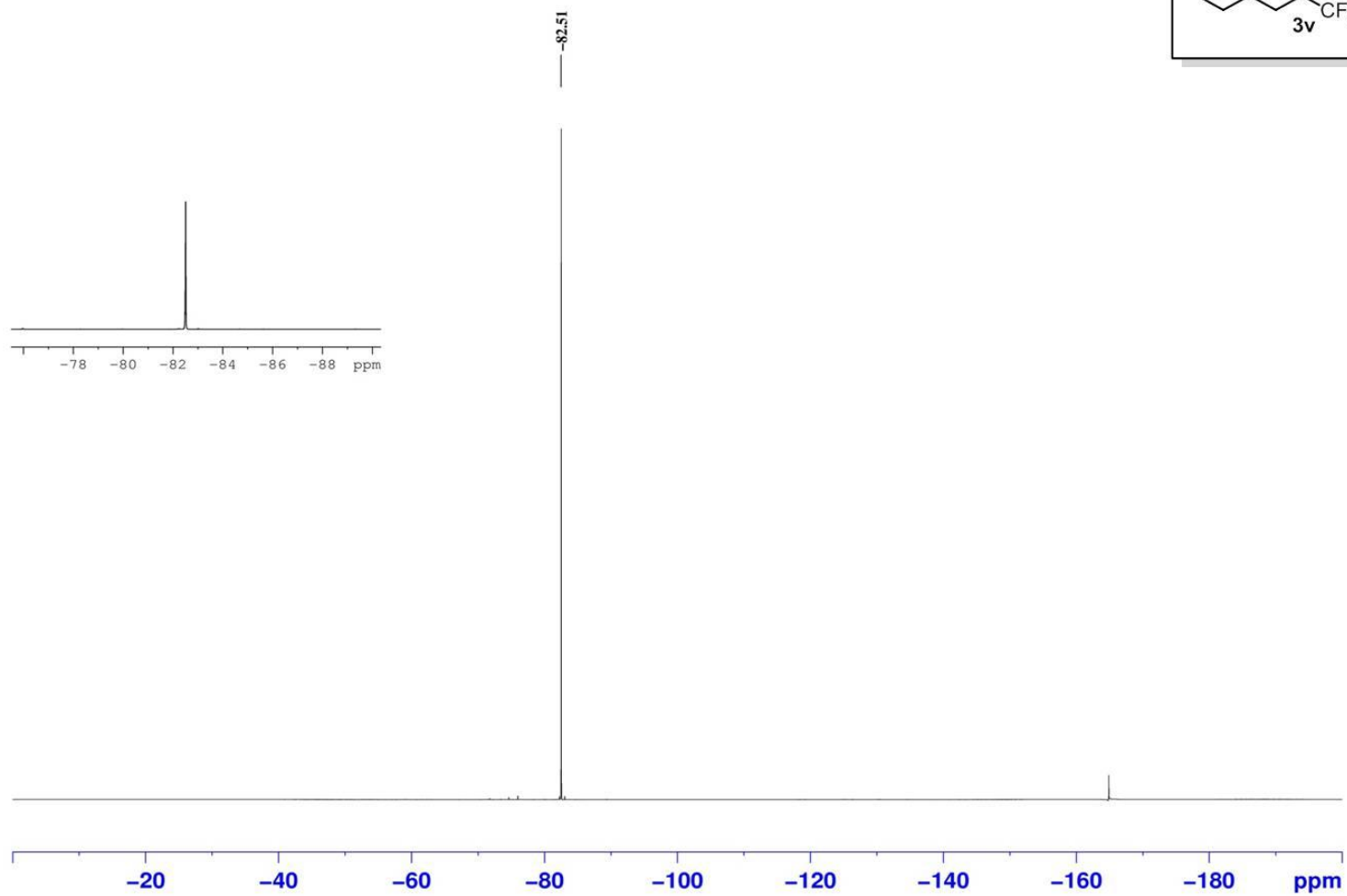
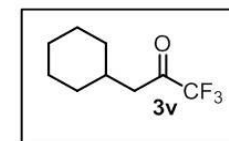
1-(3,5-dimethoxyphenyl)-2,2,2-trifluoroethanone  
377 MHz, CDCl<sub>3</sub>



**1,1,1-trifluorononan-2-one**  
377 MHz, CDCl<sub>3</sub>

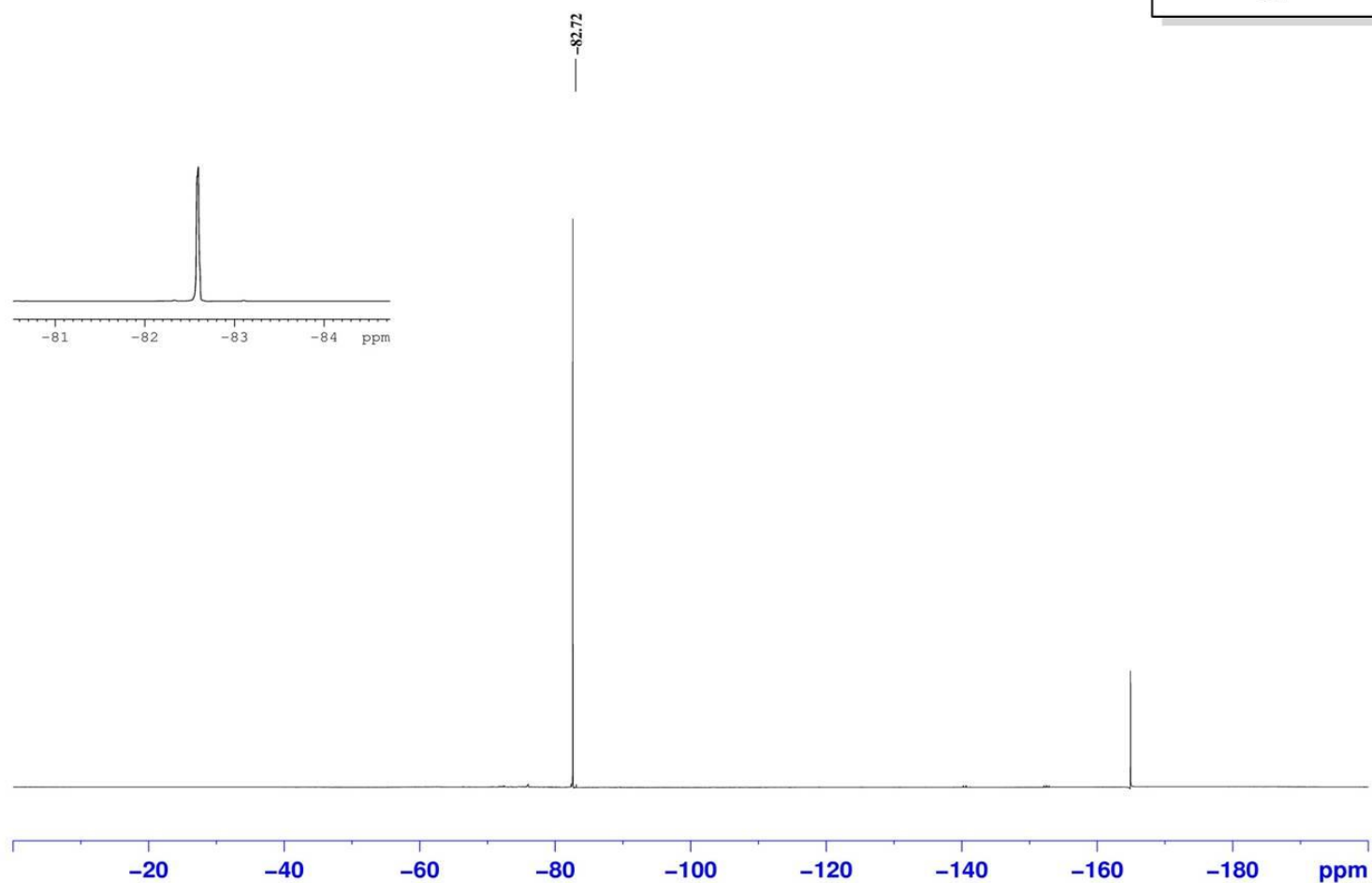
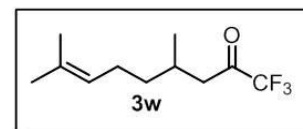


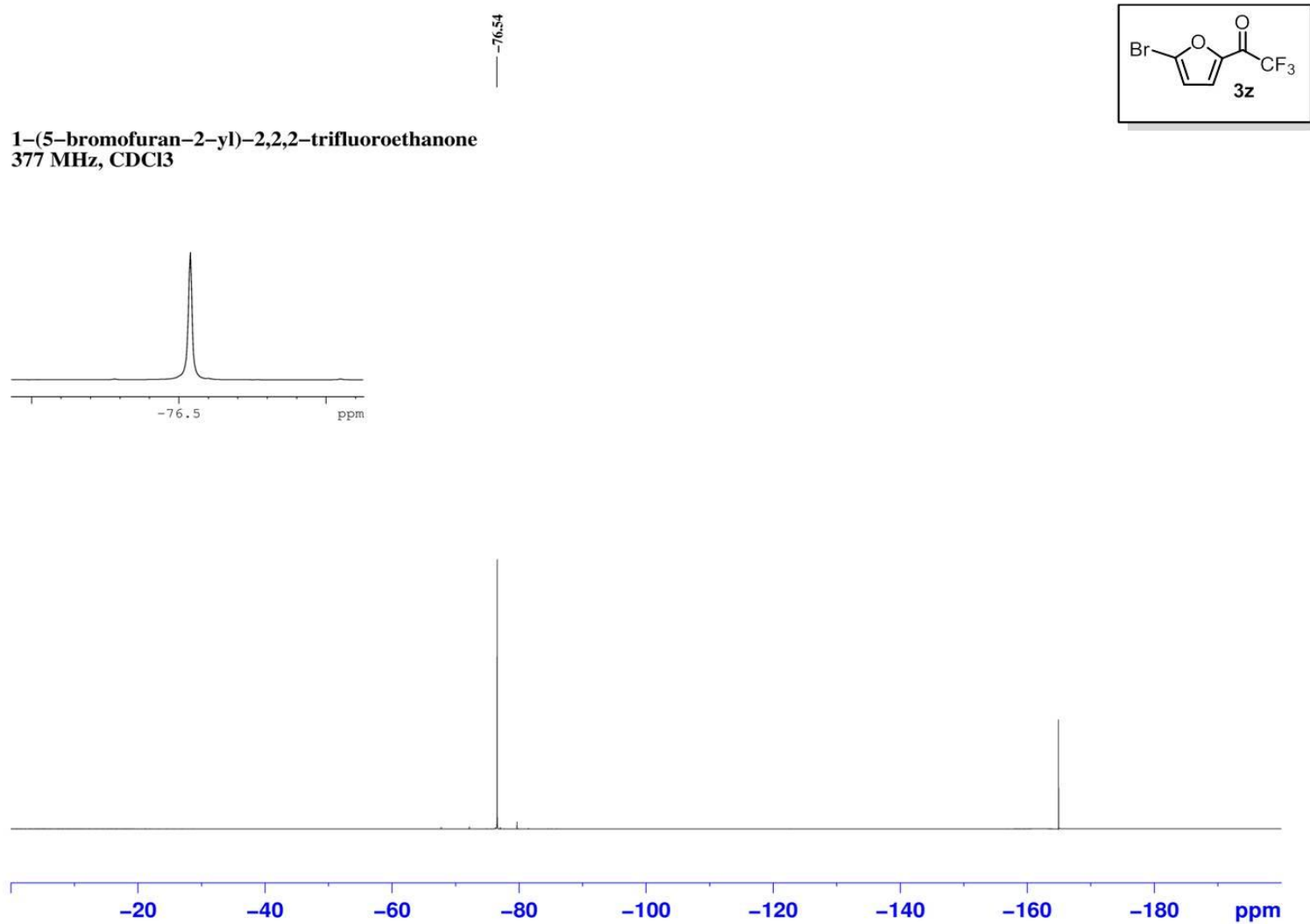
3-cyclohexyl-1,1,1-trifluoropropan-2-one  
377 MHz, CDCl<sub>3</sub>



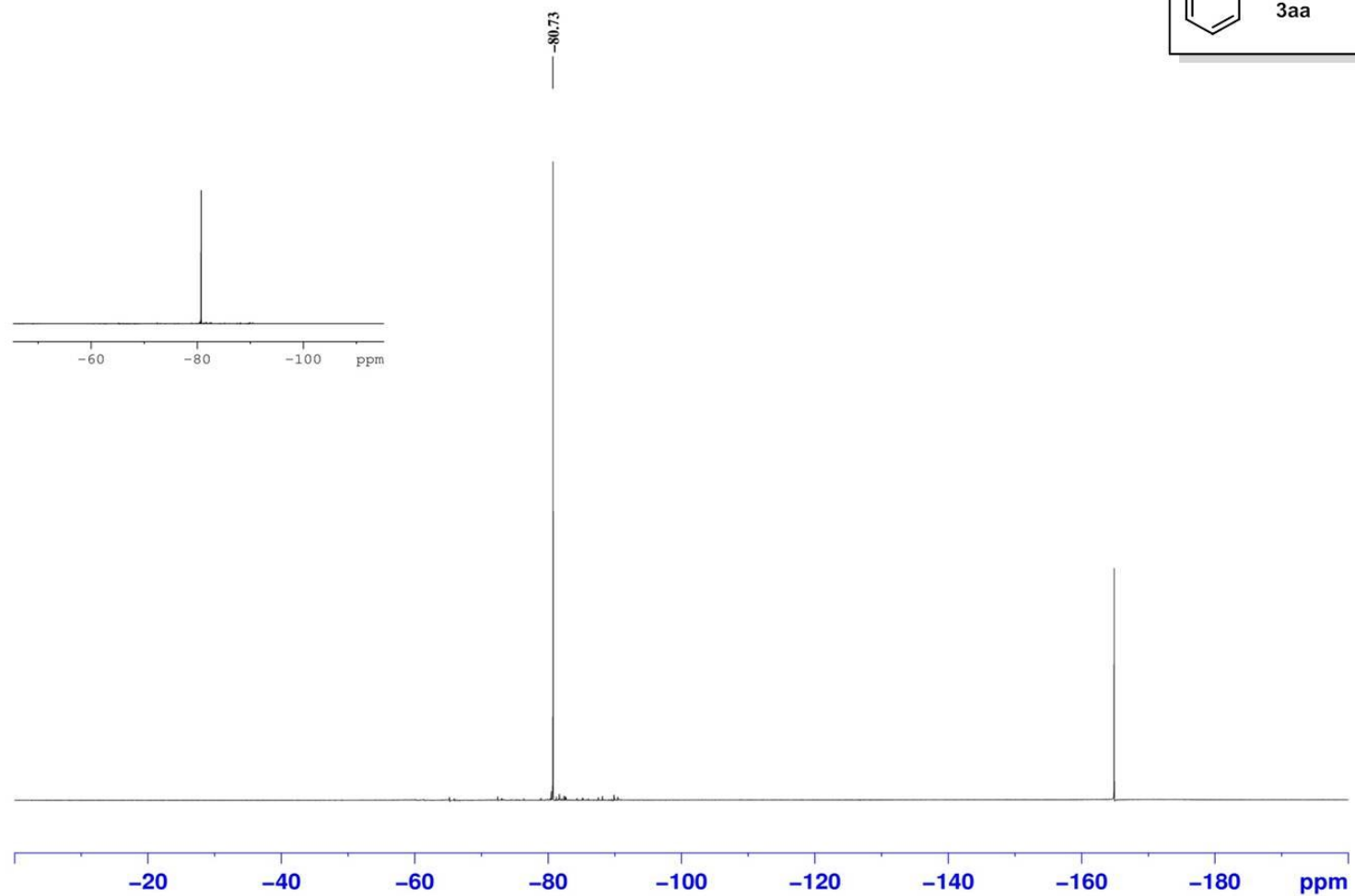
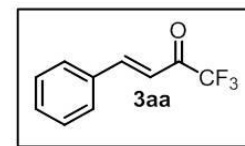


**1,1,1-trifluoro-4,8-dimethylnon-7-en-2-one**  
377 MHz, CDCl<sub>3</sub>

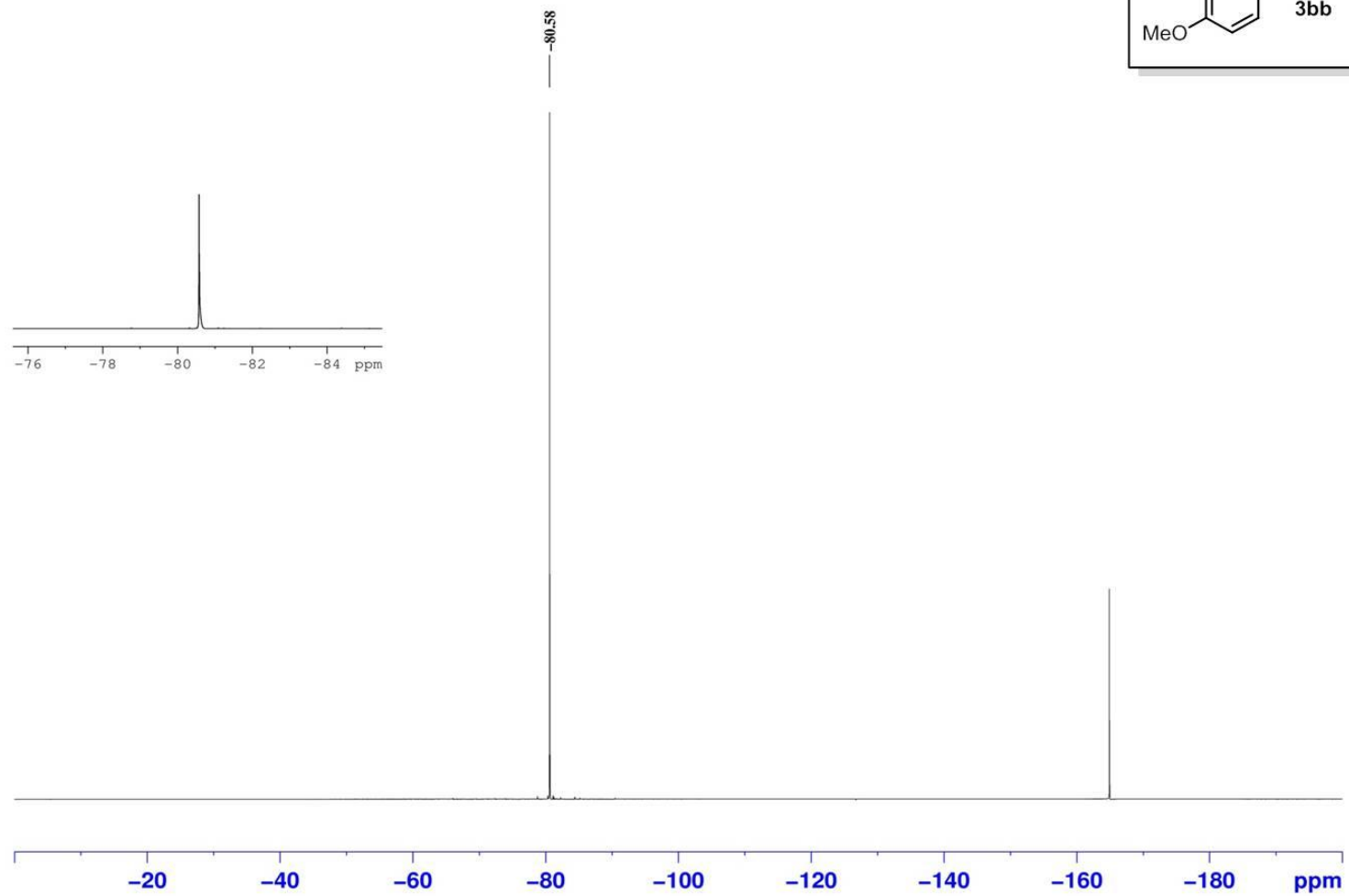
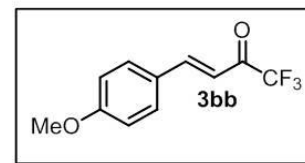


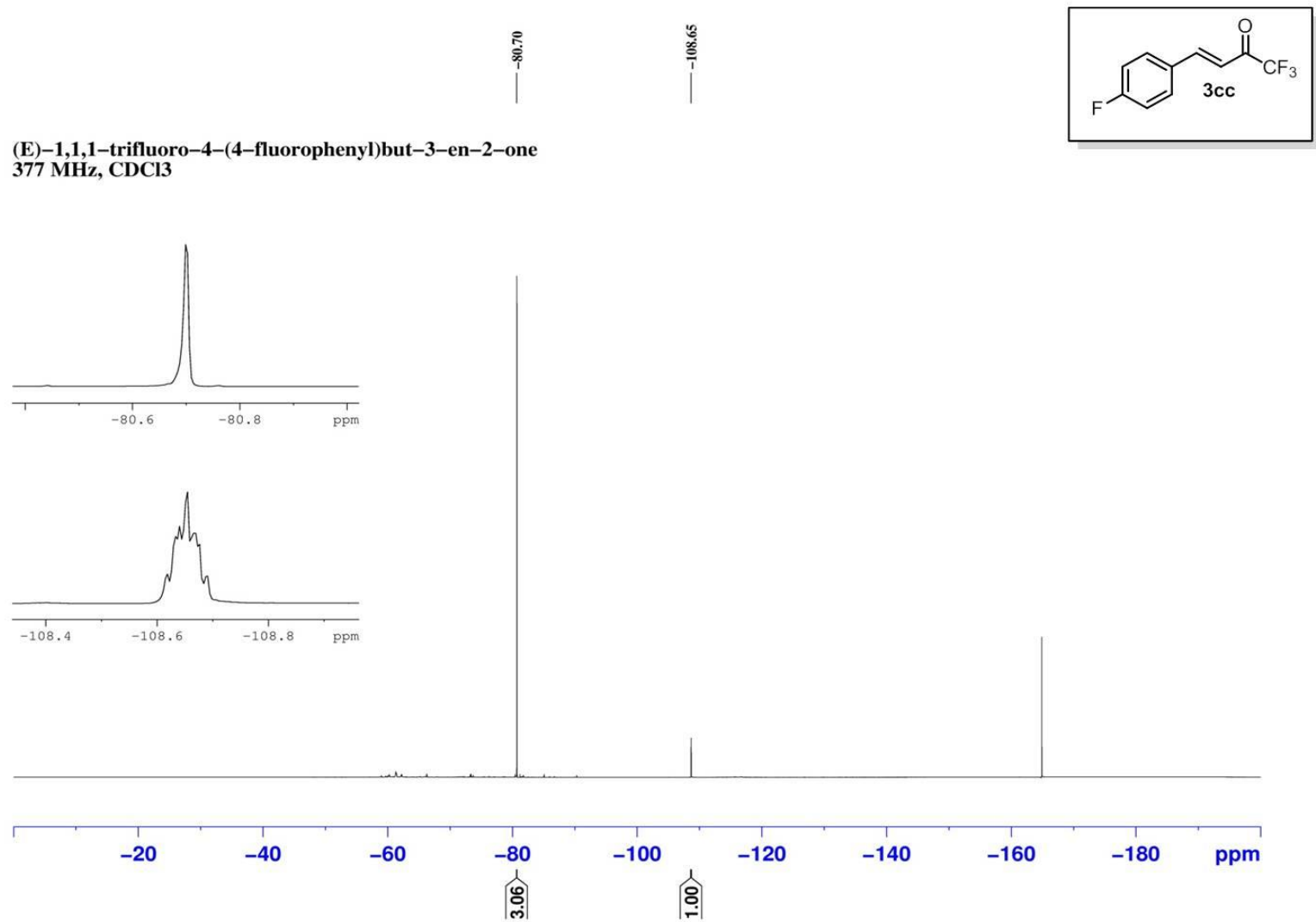


(E)-1,1,1-trifluoro-4-phenylbut-3-en-2-one  
377 MHz, CDCl<sub>3</sub>

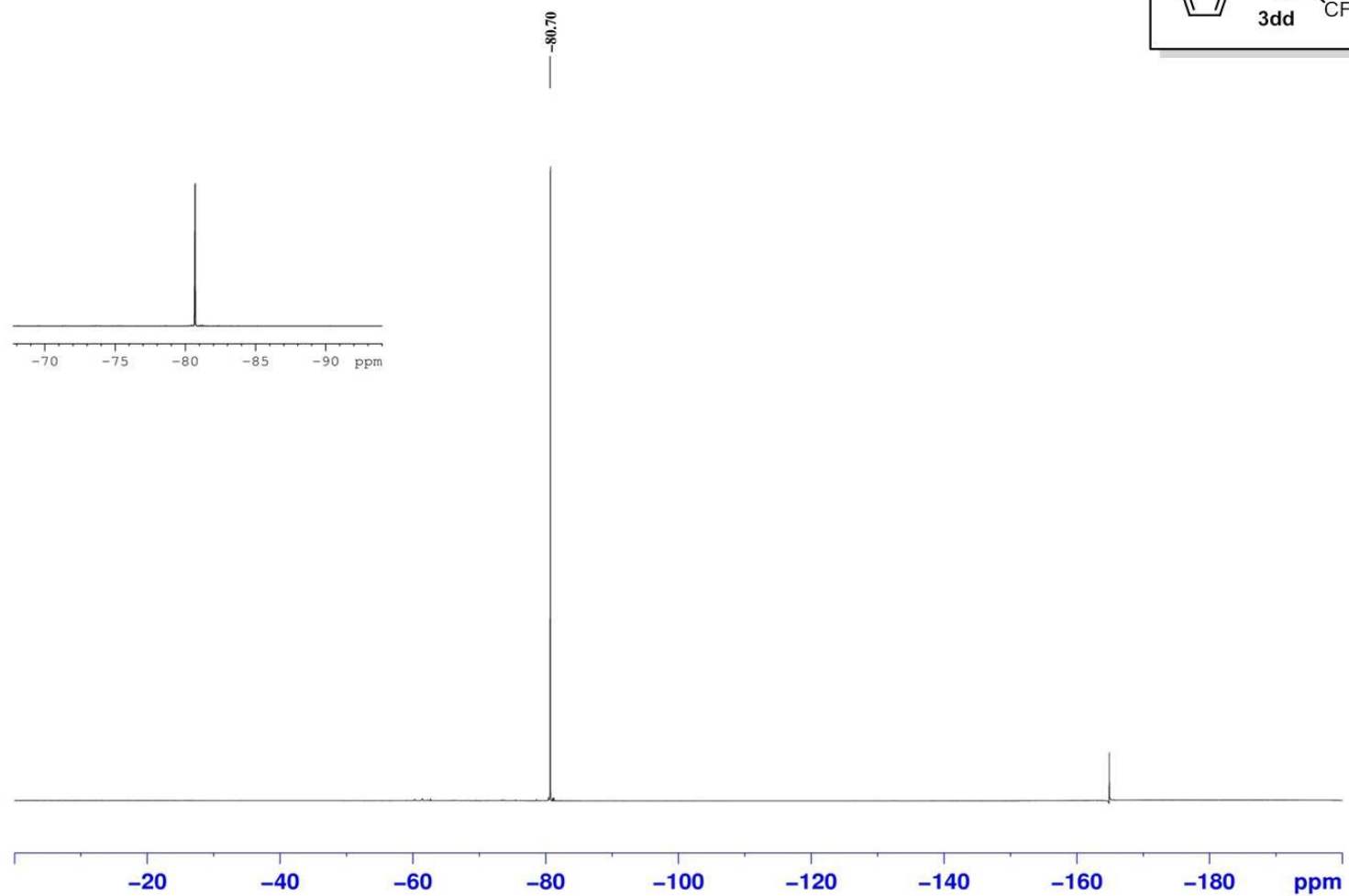
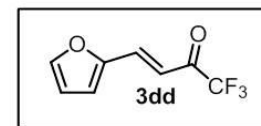


**(E)-1,1,1-trifluoro-4-(4-methoxyphenyl)but-3-en-2-one**  
377 MHz, CDCl<sub>3</sub>





(E)-1,1,1-trifluoro-4-(furan-2-yl)but-3-en-2-one  
377 MHz, CDCl<sub>3</sub>



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