

One-pot preparation of methyl 2-diazo-3-oxopropionates comprising an aqueous ‘sulfonyl-azide-free’ (SAFE) diazo transfer step

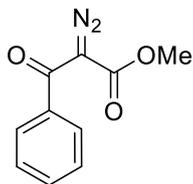
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Experimental Procedures and Characterization Data	S1
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Copies of ¹ H and ¹³ C NMR spectra	S7

General Information. Substrates for methoxycarbonylation reactions were purchased from commercial sources and used as received. NMR spectroscopic data were recorded with a 400 MHz spectrometer (400.13 MHz for ¹H and 100.61 MHz for ¹³C) in CDCl₃ and were referenced to residual solvent proton signal ($\delta_{\text{H}} = 7.26$) and solvent carbon signal ($\delta_{\text{C}} = 77.0$). All chemical shifts are reported in parts per million (ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Mass spectra were recorded with a HRMS-ESI-qTOF spectrometer (electrospray ionization mode). Melting point was determined with a melting point apparatus Stuart SMP 50 in open capillary tubes. Flash column chromatography was carried out on silica gel grade 60 (0.040–0.063 mm) 230–400 mesh. 3-(Chlorosulfonyl)benzoic acid was synthesized as reported [S1] and was used for the preparation of “SAFE-cocktail” without any further purification.

Preparation of “SAFE-cocktail” solution. To a stirred solution of sodium azide (0.99 g, 15 mmol) and potassium carbonate (3.11 g, 22.5 mmol) in water (40 ml) was added 3-(chlorosulfonyl)benzoic acid (3.66 g, 16.5 mmol), and the mixture was stirred at ambient temperature for 10 minutes. The resulting aqueous solution was divided into 5 equal portions.

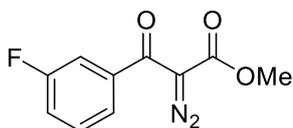
General methoxycarbonylation/diazo transfer two-step procedure. Synthesis of methyl 2-diazo-3-oxopropionates. To a stirred suspension of sodium *tert*-butoxide (336 mg, 3.5 mmol) in THF (4 ml) or 1,4-dioxane (4 ml) were added the corresponding methyl ketone **1** (2 mmol) and dimethyl carbonate (3 mmol, 0.25 ml). The mixture was then heated (temperature is specified below for each example), and the reaction progress was monitored by TLC. When no more ketone was detectable (2–16 h), the mixture was cooled to room temperature, and freshly prepared “SAFE-cocktail” (1/5 part containing 3 mmol of diazo transfer reagent) was added in one portion. The mixture was stirred at ambient temperature for 2 hours. Upon completion of diazo transfer reaction, the product was extracted with dichloromethane or diethyl ether (2×8 ml), the organic phase was dried over sodium sulfate and evaporated to dryness to afford methyl 2-diazo-3-oxopropionates **3**. Usually the purity of thus isolated substance was above 95%. In some cases further purification by flash chromatography on silica gel was applied as indicated.



Methyl 2-diazo-3-oxo-3-phenylpropanoate (3a)

Conditions for methoxycarbonylation: THF, 60 °C

Yield 312 mg (76%). Pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ = 7.62 (d, *J* = 7.0 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 3.78 (s, 3H) ppm. ¹H NMR spectra are in accordance with literature data [S2].



Methyl 2-diazo-3-(3-fluorophenyl)-3-oxopropanoate (3b)

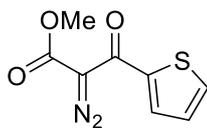
Conditions for methoxycarbonylation: THF, 60 °C

Yield 315 mg (71%). Pale yellow oil.

¹H NMR (400 MHz, , CDCl₃) δ = 7.44 – 7.37 (m, 2H), 7.33 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.23 (ddt, *J* = 8.5, 6.8, 2.7 Hz, 1H), 3.80 (s, 3H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 185.4 (d, *J* = 2.5 Hz), 162.1 (d, *J* = 247.5 Hz), 161.1, 138.9 (d, *J* = 7.0 Hz), 129.5 (d, *J* = 7.7 Hz), 124.1 (d, *J* = 3.1 Hz), 119.2 (d, *J* = 21.2 Hz), 115.4 (d, *J* = 23.1 Hz), 76.4, 52.4 ppm.

HRMS (ESI+ve) Exact mass calculated for C₁₀H₇FN₂NaO₃⁺ [M+Na]⁺ : 245.0333, found 245.0335.

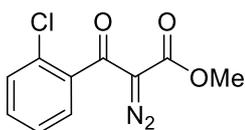


Methyl 2-diazo-3-oxo-3-(thiophen-2-yl)propanoate (3c)

Conditions for methoxycarbonylation: THF, 60 °C

Yield 316 mg (75%) Dark brown oil.

¹H NMR (400 MHz, CDCl₃) δ = 8.03 (d, *J* = 3.8 Hz, 1H), 7.64 (d, *J* = 4.9 Hz, 1H), 7.09 (t, *J* = 4.5 Hz, 1H), 3.83 (s, 3H) ppm. ¹H NMR spectra are in accordance with literature data [S3].



Methyl 3-(2-chlorophenyl)-2-diazo-3-oxopropanoate (3d)

Conditions for methoxycarbonylation: THF, 60 °C

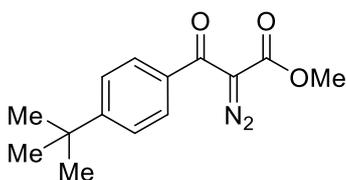
Yield 312 mg (65%). Pale yellow oil.

¹H NMR (400 MHz, , CDCl₃) δ = 7.40 – 7.37 (m, 2H), 7.35 – 7.27 (m, 2H), 3.73 (s, 3H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 185.7, 160.6, 137.66, 131.3, 130.7, 129.4, 127.9, 126.8, 52.4 ppm.

(C=N signal is overlapped with CDCl₃ solvent peak)

HRMS (ESI+ve) Exact mass calculated for C₁₀H₇ClN₂NaO₃⁺ [M+Na]⁺ : 261.0038, found 261.0045.



Methyl 3-(4-*tert*-butylphenyl)-2-diazo-3-oxopropanoate (3e)

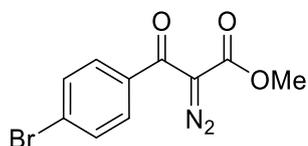
Conditions for methoxycarbonylation: 1,4-dioxane, 75 °C

Yield 354 mg (67%). Dark orange oil.

^1H NMR (400 MHz, CDCl_3) δ = 7.60 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 1.34 (s, 9H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 186.1, 161.6, 156.2, 134.1, 128.5, 124.9, 75.7, 52.3, 35.09, 31.1 ppm.

HRMS (ESI+ve) Exact mass calculated for $\text{C}_{14}\text{H}_{16}\text{N}_2\text{NaO}_3^+$ [$\text{M}+\text{Na}$] $^+$: 283.1053, found 283.1049.



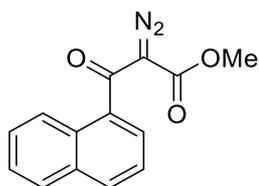
Methyl 3-(4-bromophenyl)-2-diazo-3-oxopropanoate (3f)

Conditions for methoxycarbonylation: $(\text{MeO})_2\text{CO}$ (5 mmol, 0.42 ml), THF, 60 °C. Yield 416 mg (73%) Beige solid; m.p. 95–98 °C (decomp.).

^1H NMR (400 MHz, CDCl_3) δ = 7.56 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 185.7, 161.2, 135.7, 131.2, 130.0, 127.2, 76.4, 52.4 ppm.

HRMS (ESI+ve) Exact mass calculated for $\text{C}_{10}\text{H}_7\text{BrN}_2\text{NaO}_3^+$ [$\text{M}+\text{Na}$] $^+$: 304.9532 and 306.9512, found 304.9532 and 306.9512



Methyl 2-diazo-3-(naphthalen-1-yl)-3-oxopropanoate (3g)

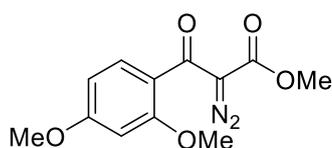
Conditions for methoxycarbonylation: THF, 60 °C

Yield 379 mg (75%). Pale yellow oil.

^1H NMR (400 MHz, CDCl_3) δ = 8.04 (dd, J = 6.7, 2.4 Hz, 1H), 7.96 (d, J = 7.9 Hz, 1H), 7.89 (dd, J = 6.3, 3.1 Hz, 1H), 7.57 – 7.47 (m, 4H), 3.68 (s, 3H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 187.7, 160.9, 135.2, 133.5, 131.3, 129.9, 128.55, 127.3, 126.4, 125.7, 124.5, 124.4, 52.3 ppm. (C=N signal is overlapped with CDCl_3 solvent peak)

HRMS (ESI+ve) Exact mass calculated for $\text{C}_{14}\text{H}_{10}\text{N}_2\text{NaO}_3^+$ [$\text{M}+\text{Na}$] $^+$: 277.0584, found 277.0589.



Methyl 2-diazo-3-(2,4-dimethoxyphenyl)-3-oxopropanoate (3h)

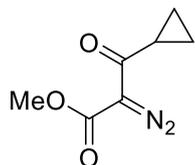
Conditions for methoxycarbonylation: 1,4-dioxane, 90 °C

Yield 416 mg (78%). Beige oil.

^1H NMR (400 MHz, CDCl_3) δ = 7.34 (d, J = 8.5 Hz, 1H), 6.52 (dd, J = 8.5, 2.2 Hz, 1H), 6.42 (d, J = 2.2 Hz, 1H), 3.83 (s, 3H), 3.78 (s, 3H), 3.75 (s, 3H).

^{13}C NMR (101 MHz, CDCl_3) δ = 184.6, 163.7, 161.8, 158.8, 130.9, 120.7, 104.9, 98.2, 55.6, 55.5, 52.1 ppm. (C=N signal is overlapped with CDCl_3 solvent peak)

HRMS (ESI+ve) Exact mass calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_5^+$ [$\text{M}+\text{Na}$] $^+$: 287.0635, found 287.0638 and exact mass calculated for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_5^+$ [$\text{M}+\text{H}$] $^+$: 265.0819, found 265.0816



Methyl 3-cyclopropyl-2-diazo-3-oxopropanoate (3i)

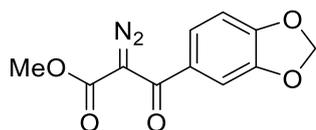
Conditions for methoxycarbonylation: THF, 60 °C

Yield 150 mg (45%). Pale brown oil

^1H NMR (400 MHz, CDCl_3) δ = 3.86 (s, 3H), 3.14-3.06 (m 1H), 1.26-1.16 (m, 2H), 1.06-0.9 (m, 2H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 192.1, 162.1, 76.2, 52.1, 17.6, 11.7 ppm.

HRMS (ESI+ve) Exact mass calculated for $\text{C}_7\text{H}_8\text{N}_2\text{NaO}_3^+$ $[\text{M}+\text{Na}]^+$: 191.0428, found 191.0430.



Methyl 3-(1,3-benzodioxol-5-yl)-2-diazo-3-oxopropanoate (3j)

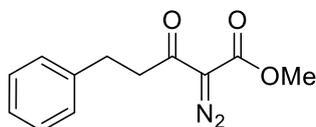
Conditions for methoxycarbonylation: 1,4-dioxane, 90 °C

The product was subjected to a flash chromatography on silica gel (eluent: CH_2Cl_2 -*n*-hexane = 1:3 \rightarrow 1:1 \rightarrow 1:0). Yield 248 mg (50%). R_f = 0.43 (CH_2Cl_2). Beige oil.

^1H NMR (400 MHz, CDCl_3) δ = 7.26 (dd, J = 8.1, 1.7 Hz, 1H), 7.15 (s, 1H), 6.83 (d, J = 8.1 Hz, 1H), 6.03 (s, 2H), 3.81 (s, 3H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 184.7, 161.6, 151.4, 147.4, 130.8, 124.7, 109.0, 107.6, 101.8, 75.5, 52.3 ppm.

HRMS (ESI+ve) Exact mass calculated for $\text{C}_{11}\text{H}_{18}\text{N}_2\text{NaO}_5^+$ $[\text{M}+\text{Na}]^+$: 271.0325, found 271.0323.



Methyl 2-diazo-3-oxo-5-phenylpentanoate (3k)

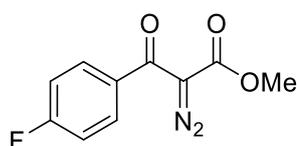
Conditions for methoxycarbonylation: THF, 60 °C

The product was subjected to a flash chromatography on silica gel (eluent: CH_2Cl_2 -*n*-hexane = 1:3 \rightarrow 1:1 \rightarrow 1:0). Yield 205 mg (44%). R_f = 0.55 (CH_2Cl_2). Dark brown oil.

^1H NMR (400 MHz, CDCl_3) δ = 7.32 – 7.15 (m, 5H), 3.83 (s, 3H), 3.18 (t, J = 7.7 Hz, 2H), 2.97 (t, J = 7.7 Hz, 2H) ppm.

^{13}C NMR (101 MHz, CDCl_3) δ = 191.7, 161.7, 140.8, 128.5, 128.4, 126.1, 75.8, 52.2, 41.8, 30.2 ppm.

HRMS (ESI+ve) Exact mass calculated for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{NaO}_3^+$ $[\text{M}+\text{Na}]^+$: 255.0740, found 255.0746 and exact mass calculated for $\text{C}_{12}\text{H}_{13}\text{N}_2\text{O}_3^+$ $[\text{M}+\text{H}]^+$: 233.0921, found 233.0927



Methyl 2-diazo-3-(3-fluorophenyl)-3-oxopropanoate (3l)

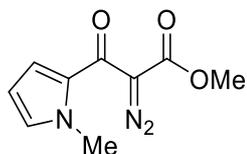
Conditions for methoxycarbonylation: 1,4-dioxane, 75 °C

The product was subjected to a flash chromatography on silica gel (eluent: CH_2Cl_2 -hexane = 1:3 \rightarrow 1:1 \rightarrow 1:0). Yield 233 mg (52%). R_f = 0.34 (CH_2Cl_2). Pale yellow oil.

^1H NMR (400 MHz, CDCl_3) $\delta = 7.67$ (dd, $J = 8.8, 5.4$ Hz, 2H), 7.10 (t, $J = 8.7$ Hz, 2H), 3.80 (s, 3H) ppm.

^{19}F NMR (376 MHz, CDCl_3) $\delta = -106.04$ ppm.

^1H NMR spectra are in accordance with literature data [S2].



Methyl 2-diazo-3-(1-methyl-1H-pyrrol-2-yl)-3-oxopropanoate (3m)

Conditions for methoxycarbonylation: Bu^tONa (672 mg, 7 mmol), $(\text{MeO})_2\text{CO}$ (8 mmol, 0.68 ml), THF, 60°C , overnight.

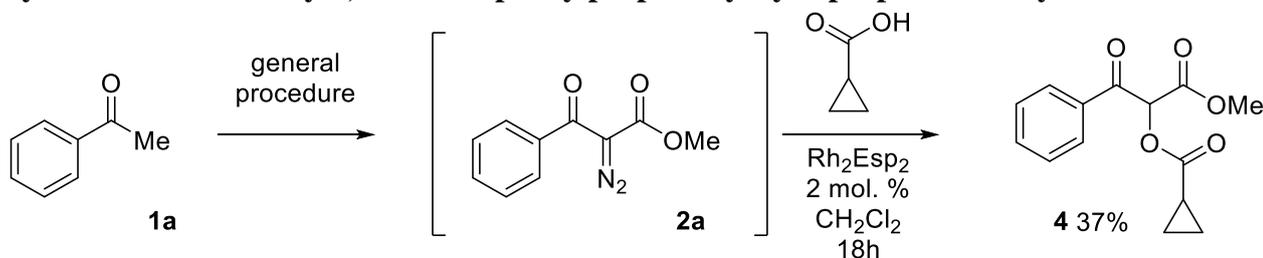
^1H NMR (400 MHz, CDCl_3) $\delta = 6.94$ (dd, $J = 4.2, 1.7$ Hz, 1H), 6.84 (t, $J = 2.1$ Hz, 1H), 6.14 (dd, $J = 4.1, 2.5$ Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H) ppm.

^{13}C NMR (101 MHz, CDCl_3) $\delta = 173.7, 162.4, 131.2, 128.1, 119.9, 108.1, 73.6, 52.3, 37.0$ ppm.

HRMS (ESI+ve) Exact mass calculated for $\text{C}_9\text{H}_9\text{N}_3\text{NaO}_3^+ [\text{M}+\text{Na}]^+$: 230.0536, found 230.0537

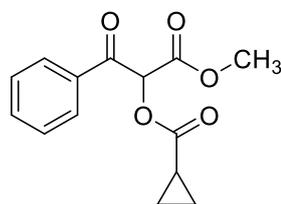
Methoxycarbonylation/diazo transfer/ O-H insertion three-step procedure.

Synthesis of 1-methoxy-1,3-dioxo-3-phenylprop-2-yl cyclopropanecarboxylate



Methyl 2-diazo-3-oxo-3-phenylpropanoate 2a was synthesized by general procedure from acetophenone (2 mmol) and was used directly for the next step without further purification.

To a stirred solution of $\text{Rh}_2(\text{esp})_2$ (30 mg, 40 μmol , 2 mol %) and cyclopropanecarboxylic acid (159 μl , 2 mmol) in anhydrous dichloromethane (5 ml) was added **2b** dissolved in anhydrous dichloromethane (5 ml), and the mixture was stirred at ambient temperature for 18 h, evaporated and subjected to flash column chromatography on silica gel (eluent: dichloromethane –hexane = 1:3 \rightarrow 1:1 \rightarrow 1:0).



1-Methoxy-1,3-dioxo-3-phenylprop-2-yl cyclopropanecarboxylate (4).

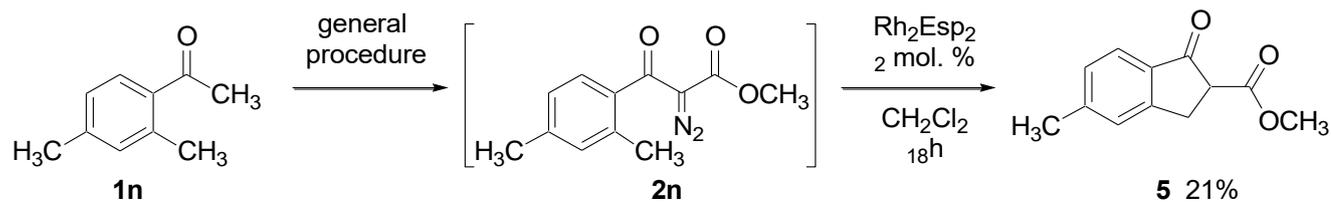
Yield 196 mg (37% from acetophenone). Pale yellow oil. $R_f = 0.46$ (CH_2Cl_2).

^1H NMR (400 MHz, CDCl_3) $\delta = 8.00$ (d, $J = 7.3$ Hz, 2H), 7.62 (t, $J = 7.4$ Hz, 1H), 7.49 (t, $J = 7.7$ Hz, 2H), 6.35 (s, 1H), 3.79 (s, 3H), 1.80 (tt, $J = 8.0, 4.6$ Hz, 1H), $1.12 - 1.07$ (m, 2H), 0.96 (tt, $J = 6.0, 2.0$ Hz, 2H) ppm.

^{13}C NMR (101 MHz, CDCl_3) $\delta = 189.7, 173.4, 165.8, 134.2, 134.2, 129.2, 128.8, 74.2, 53.1, 12.7, 9.4$ and 9.3 ppm.

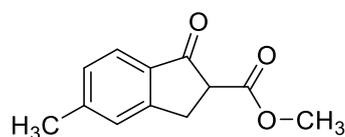
HRMS (ESI+ve) Exact mass calculated for $\text{C}_{14}\text{H}_{15}\text{O}_5^+ [\text{M}+\text{H}]^+$: 263.0914, found 263.0910

Methoxycarbonylation/diazo transfer/ intramolecular C-H insertion three-step procedure. Synthesis of methyl 5-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate.



To a stirred suspension of sodium *tert*-butoxide (336 mg, 3.5 mmol) in THF (4 ml) were added 2,4-dimethylacetophenone **1n** (591 μl , 2 mmol) and dimethyl carbonate (6 mmol, 0.5 ml). The mixture was then heated at 60 °C and the reaction progress was monitored by TLC. When no more ketone was detectable, the mixture was cooled to room temperature, and freshly prepared “SAFE-cocktail” (containing 3 mmol of diazo transfer reagent) was added in one portion. The mixture was stirred at ambient temperature for 2 hours. Upon completion of the diazo transfer reaction, the product was extracted with dichloromethane (2 \times 8 ml), the organic phase was dried over sodium sulfate and evaporated to dryness to afford diazo keto ester **2n**, which was used directly for the next step without further purification.

To a stirred solution of $\text{Rh}_2(\text{esp})_2$ (30 mg, 40 μmol , 2 mol.%) in anhydrous dichloromethane (5 ml) was added diazo keto ester (solution in 5 ml of CH_2Cl_2), and the mixture was stirred at ambient temperature for 18 h, evaporated and subjected to flash column chromatography on silica gel (eluent: dichloromethane –hexane = 1:3 \rightarrow 1:1 \rightarrow 1:0).



Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **5**

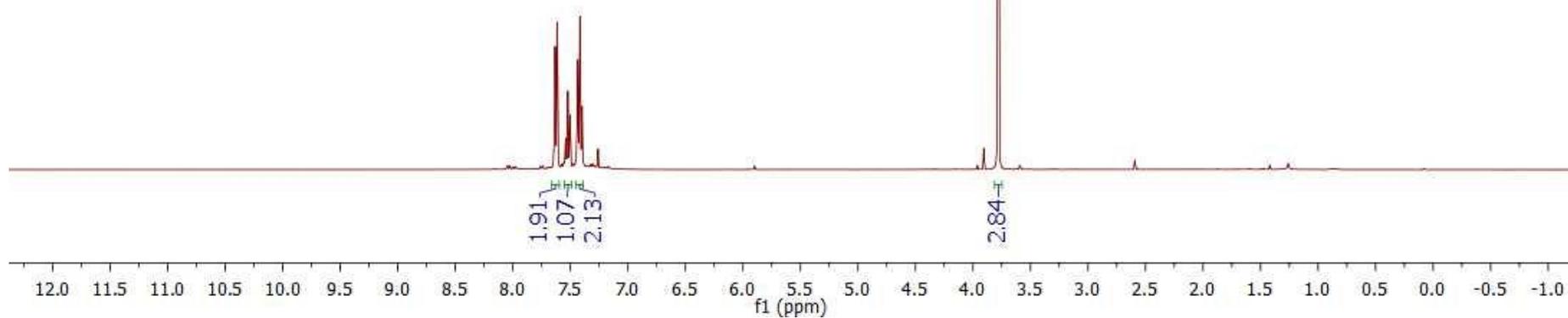
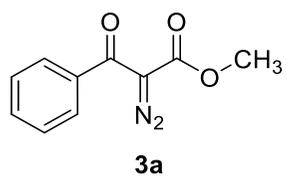
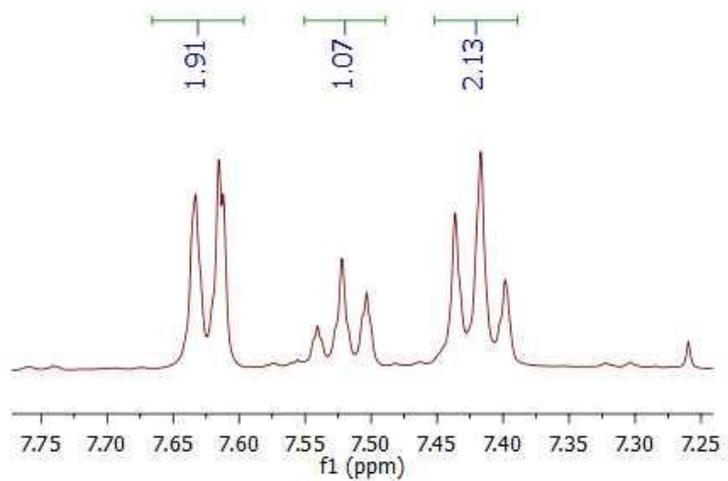
Yield 83 mg (21% from 2,4-dimethylacetophenone). Colorless oil. $R_f = 0.44$ (hexane/EtOAc 3:1)

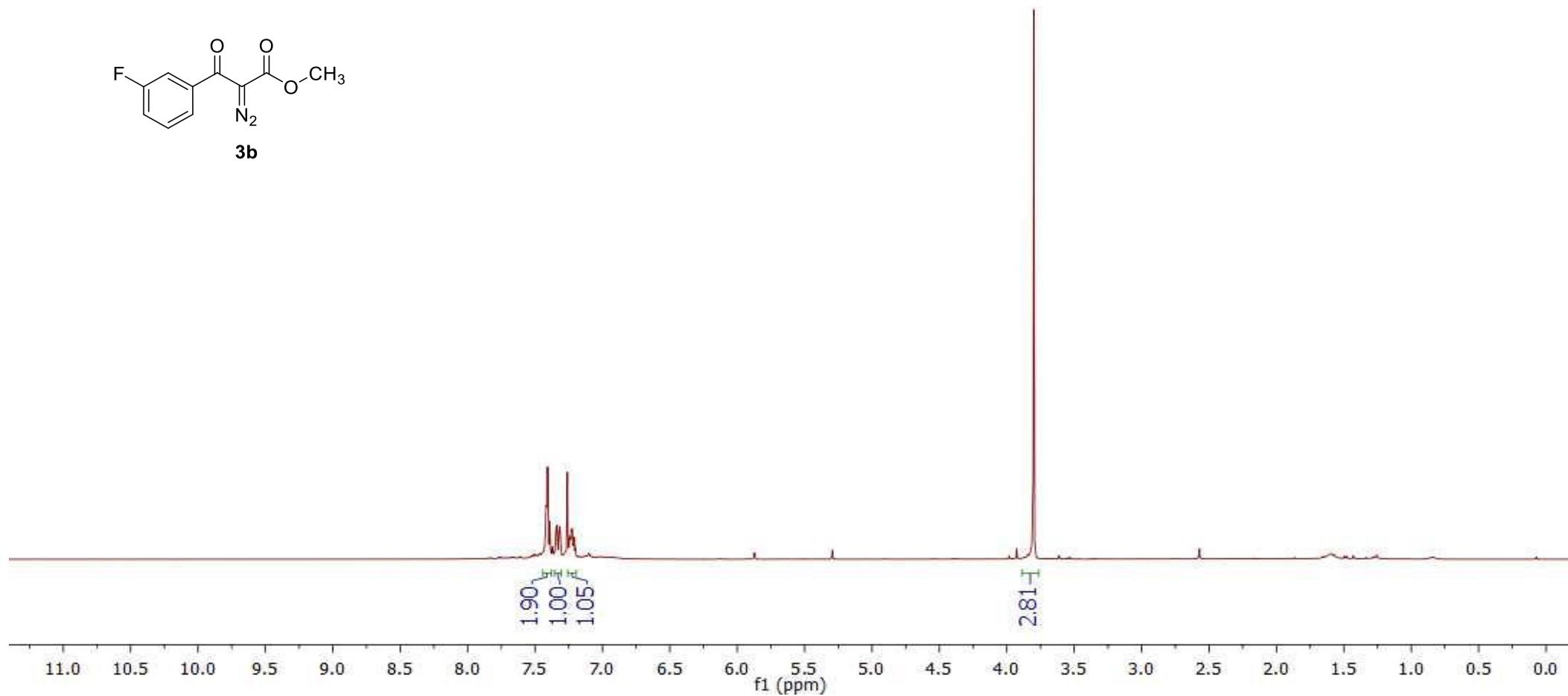
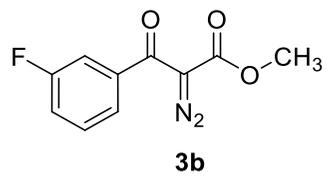
$^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 7.66$ (d, $J = 7.9$ Hz, 1H), 7.29 (s, 1H), 7.20 (d, $J = 7.9$ Hz, 1H), 3.78 (s, 3H), 3.71 (dd, $J = 8.2, 4.0$ Hz, 1H), 3.50 (dd, $J = 17.3, 3.9$ Hz, 1H), 3.31 (dd, $J = 17.2, 8.2$ Hz, 1H), 2.44 (s, 3H) ppm. $^1\text{H NMR}$ spectra are in accordance with literature data [S4]. HRMS (ESI+ve) Exact mass calculated for $\text{C}_{12}\text{H}_{12}\text{NaO}_3^+$ $[\text{M}+\text{Na}]^+$: 227.0679, found 227.0689

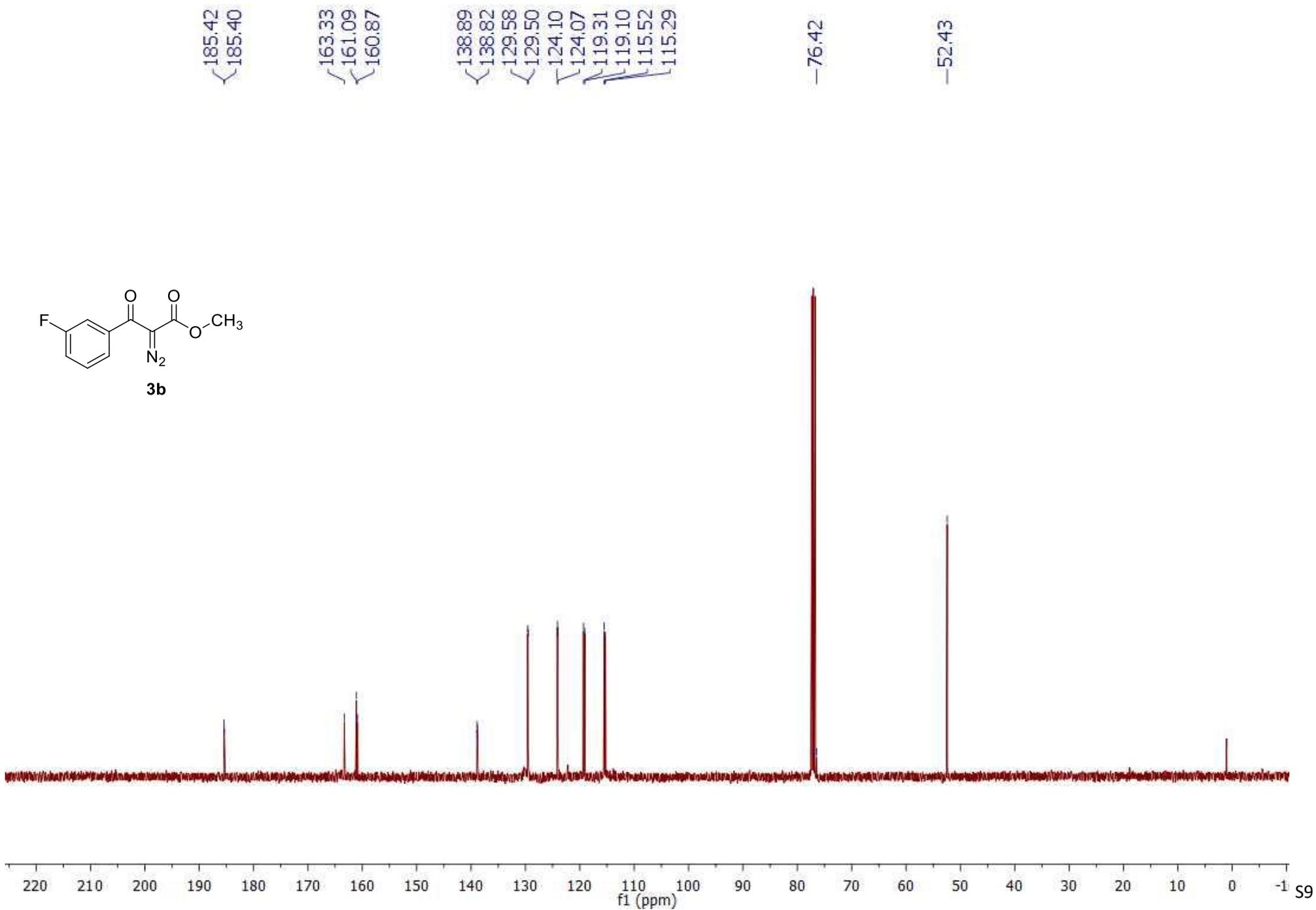
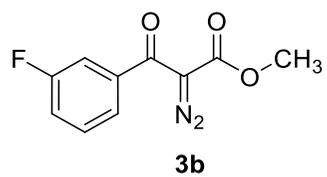
References

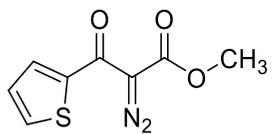
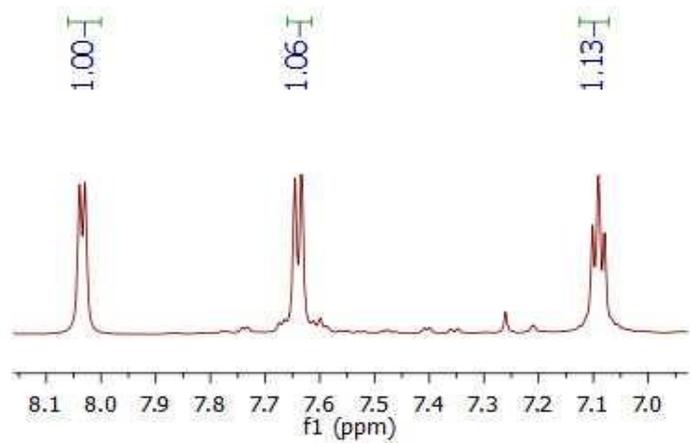
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NMR Spectra

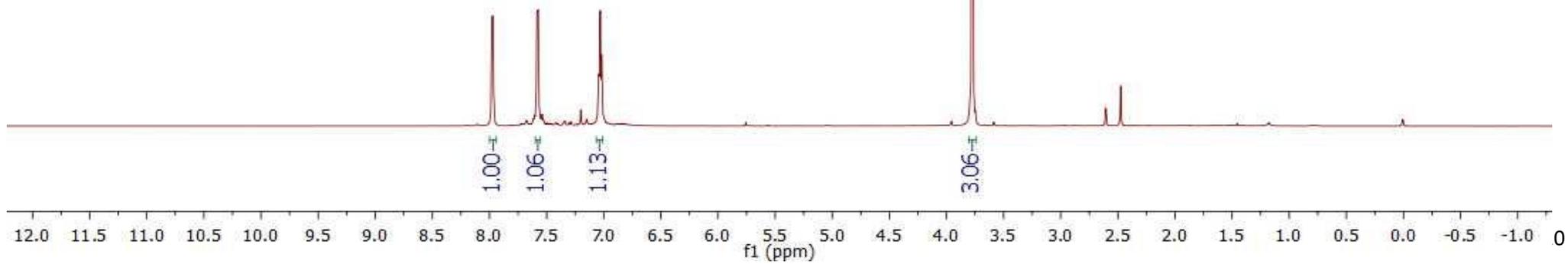


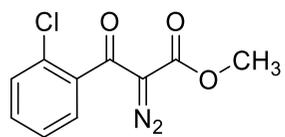
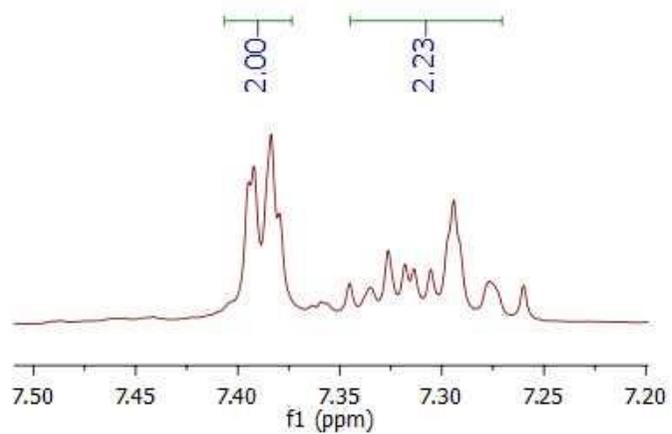




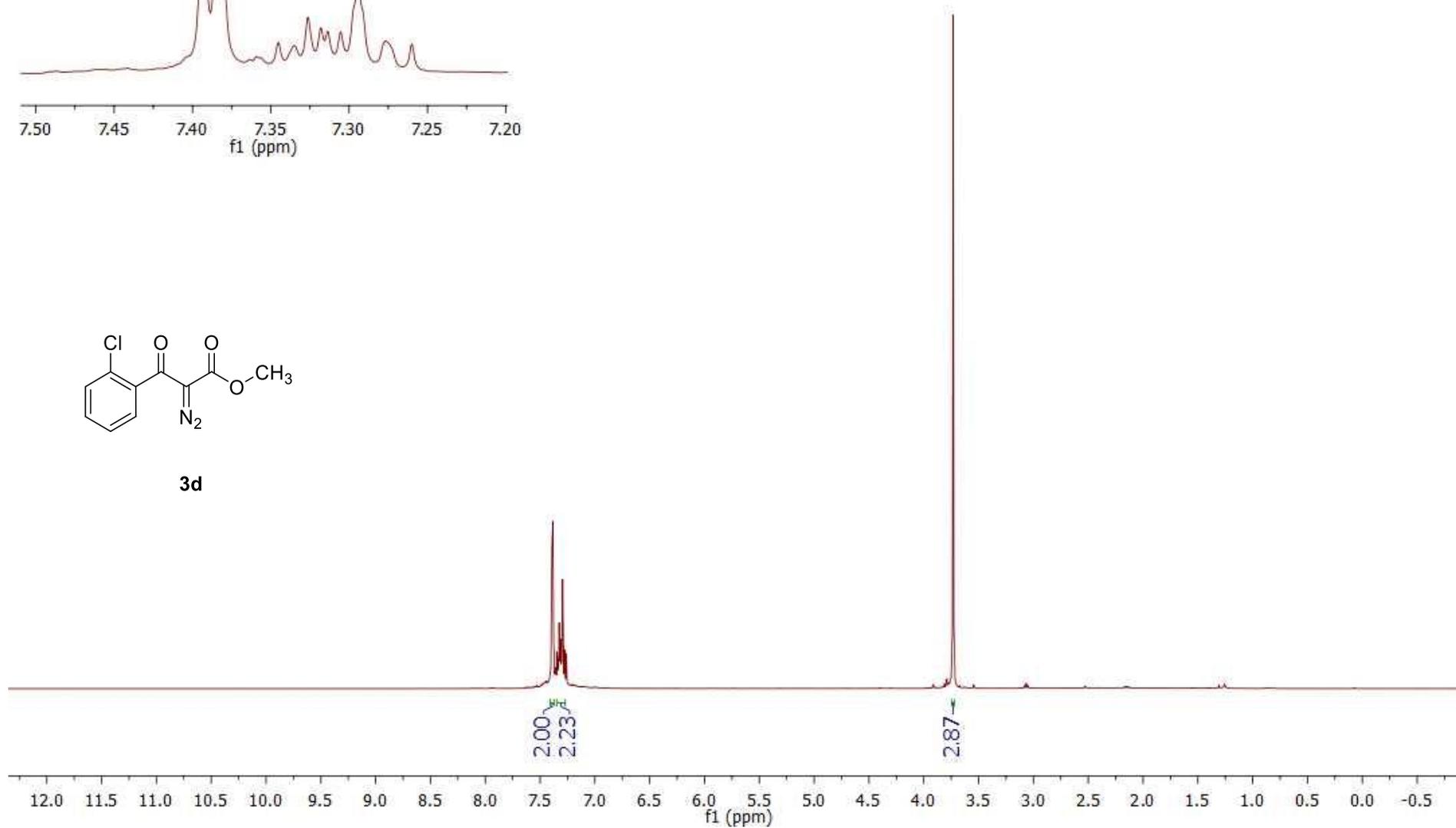


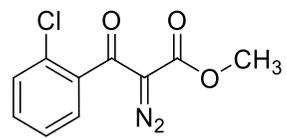
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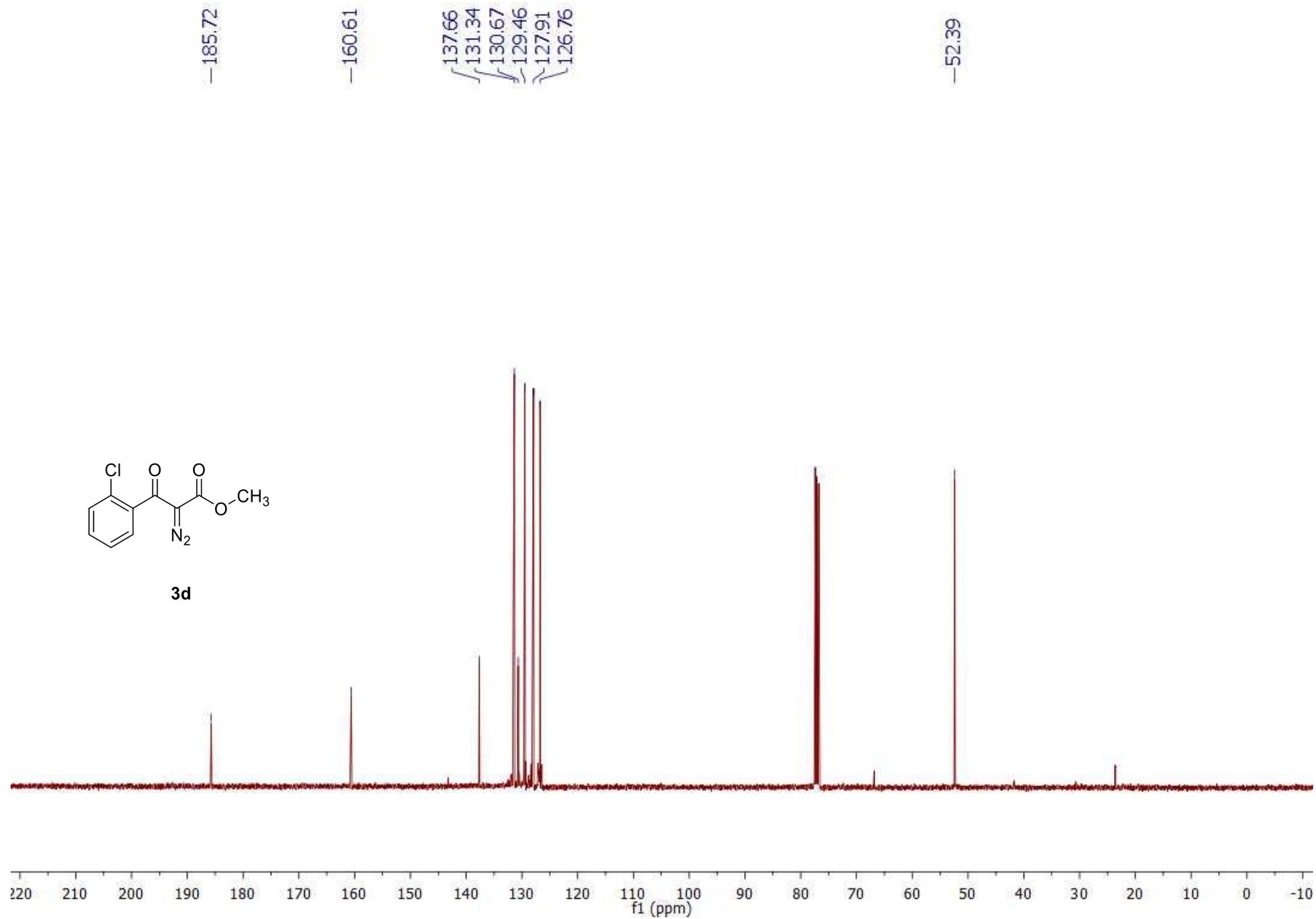


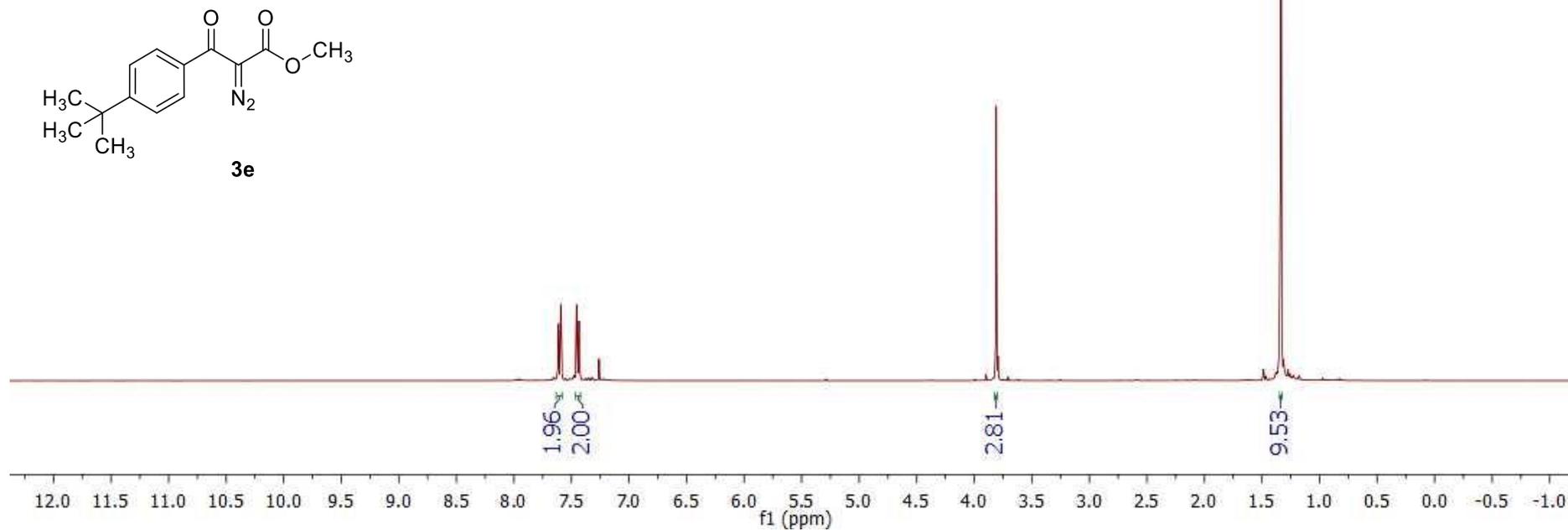
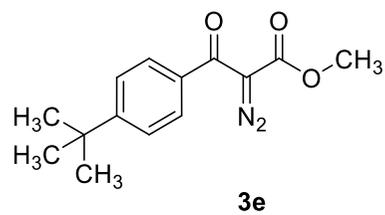
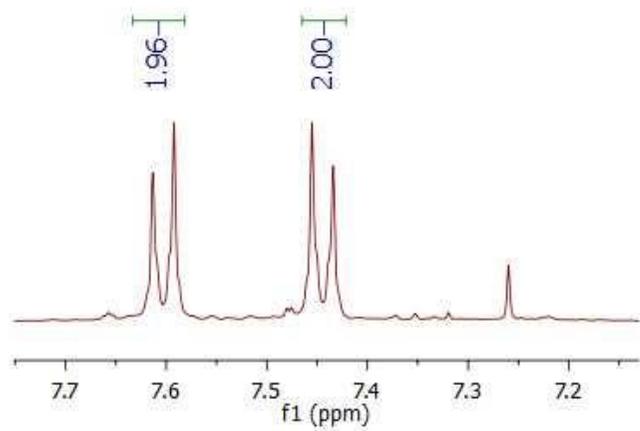
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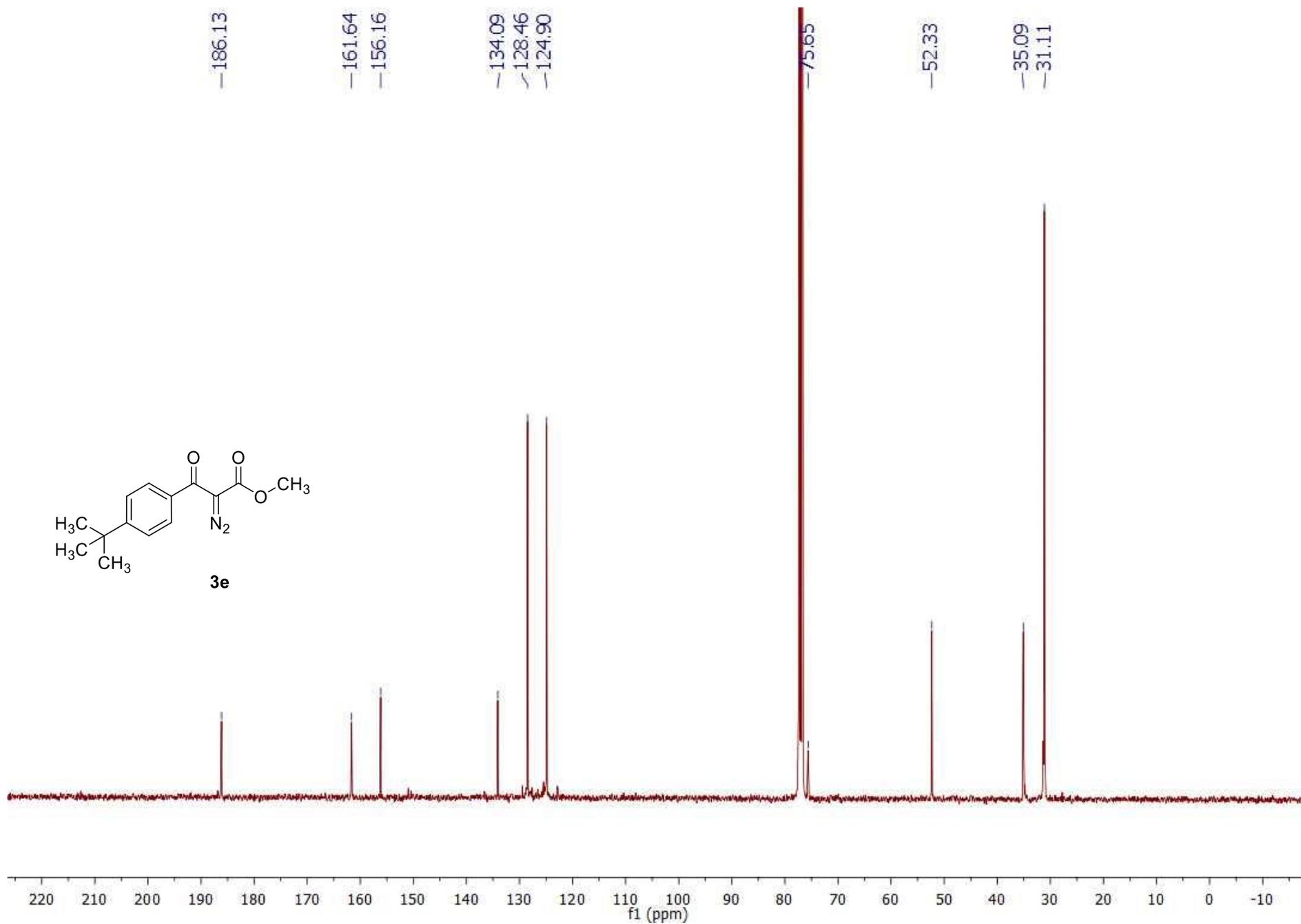


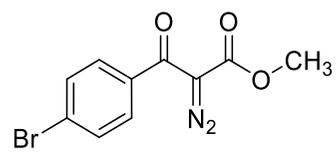
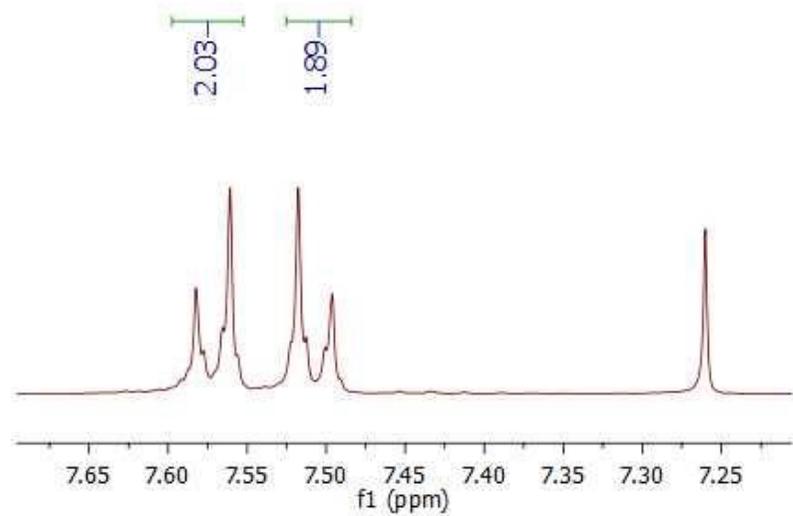


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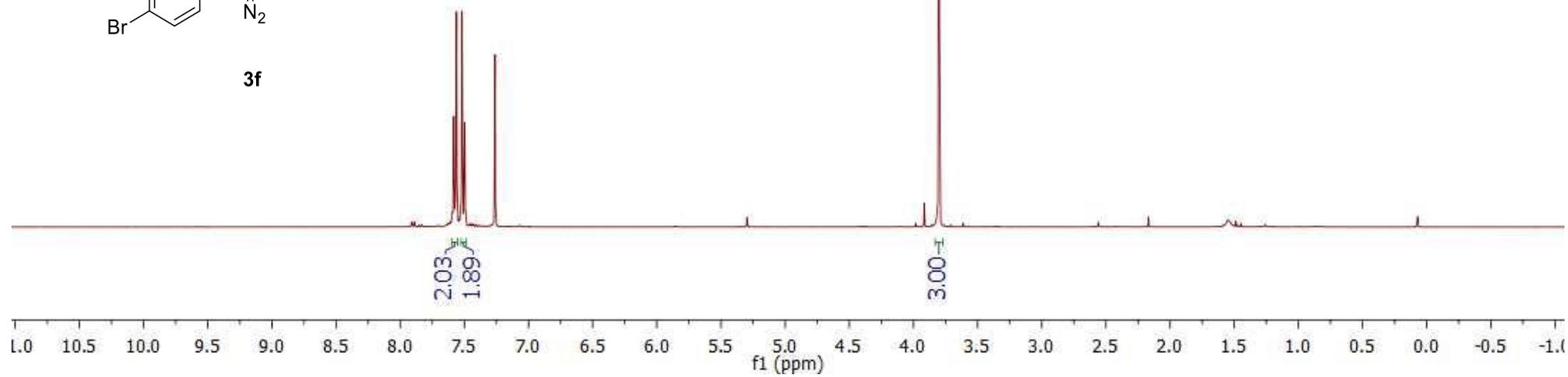


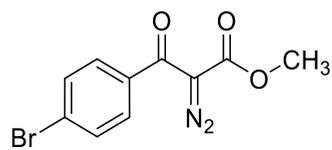




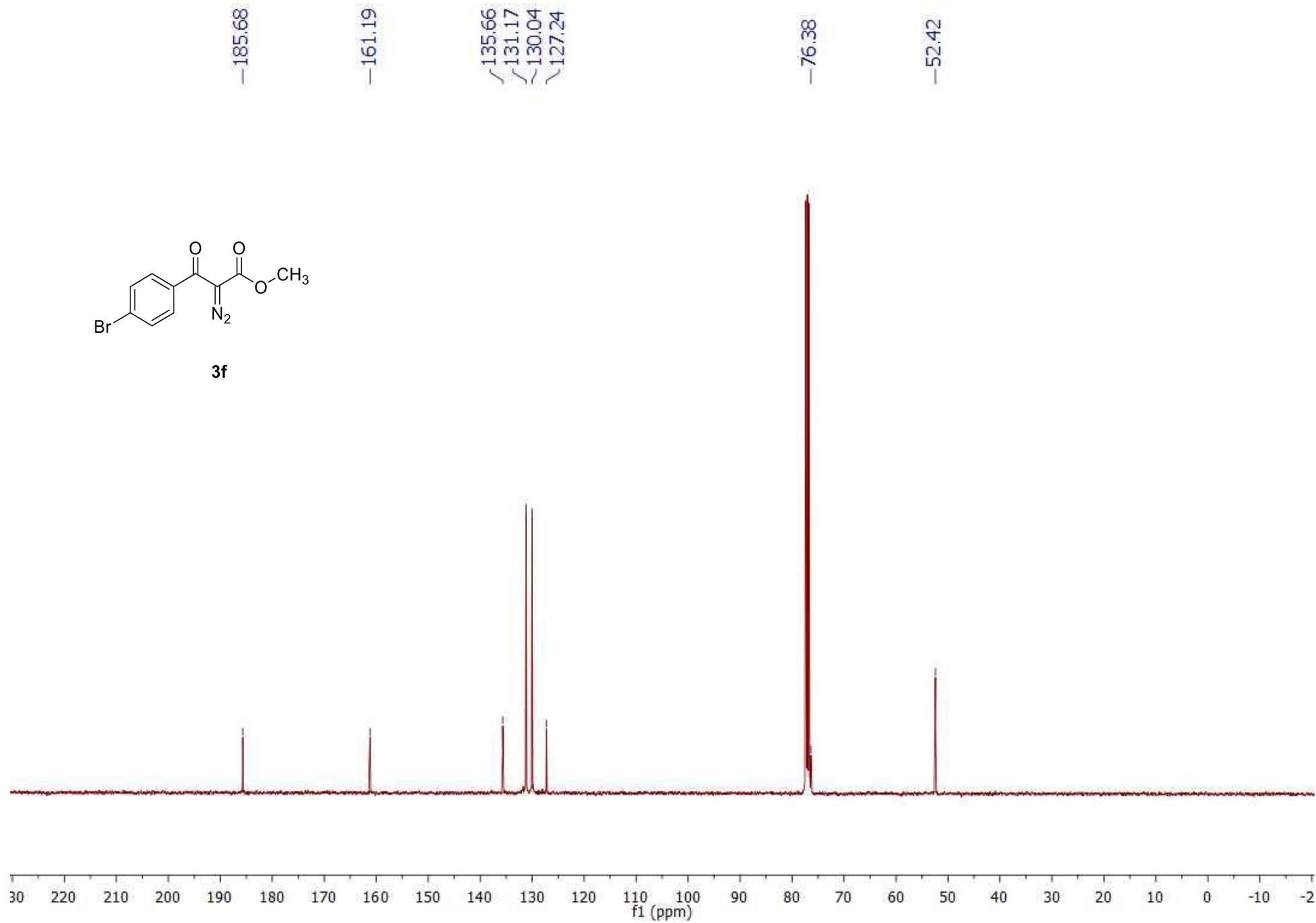


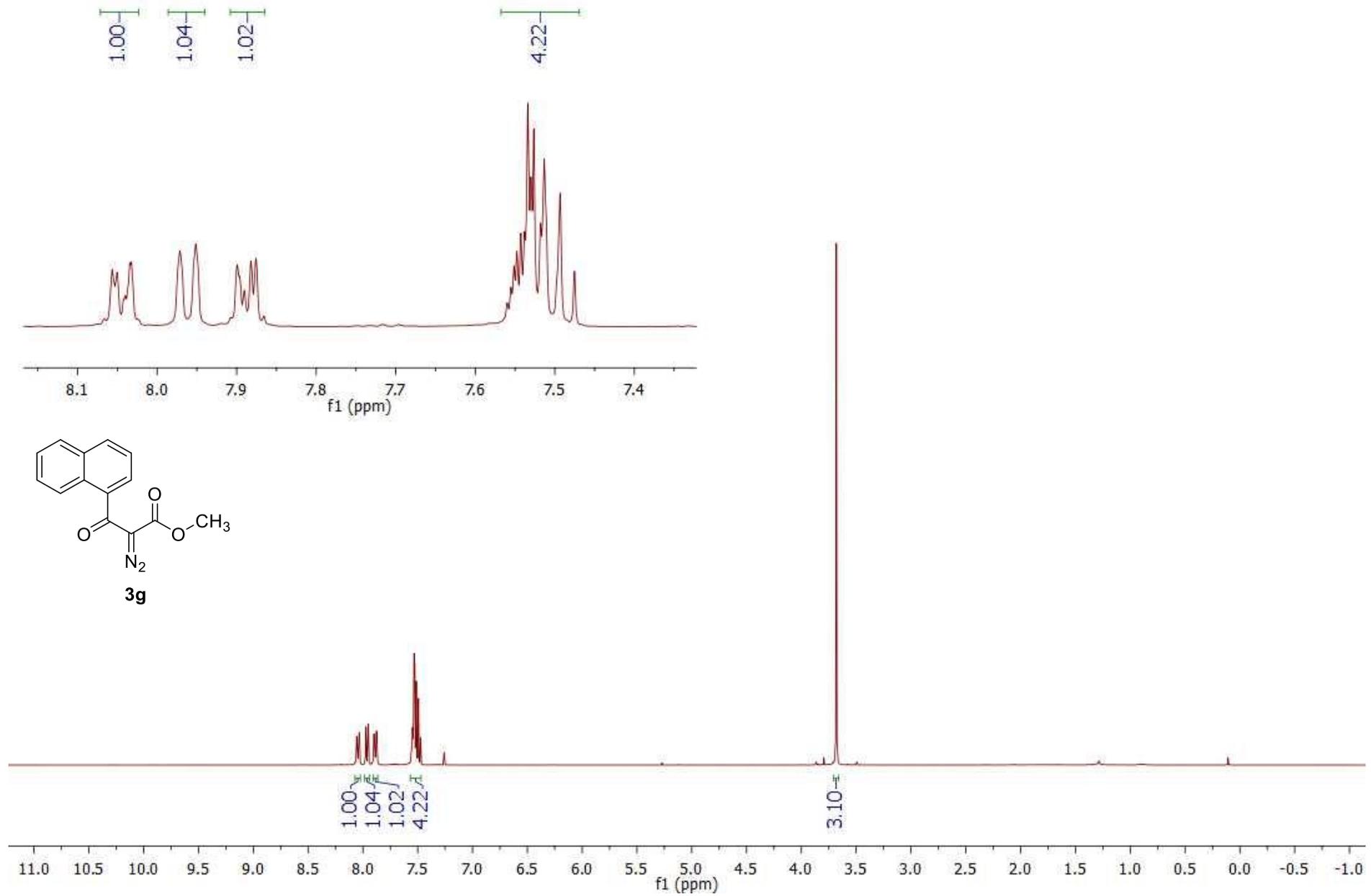
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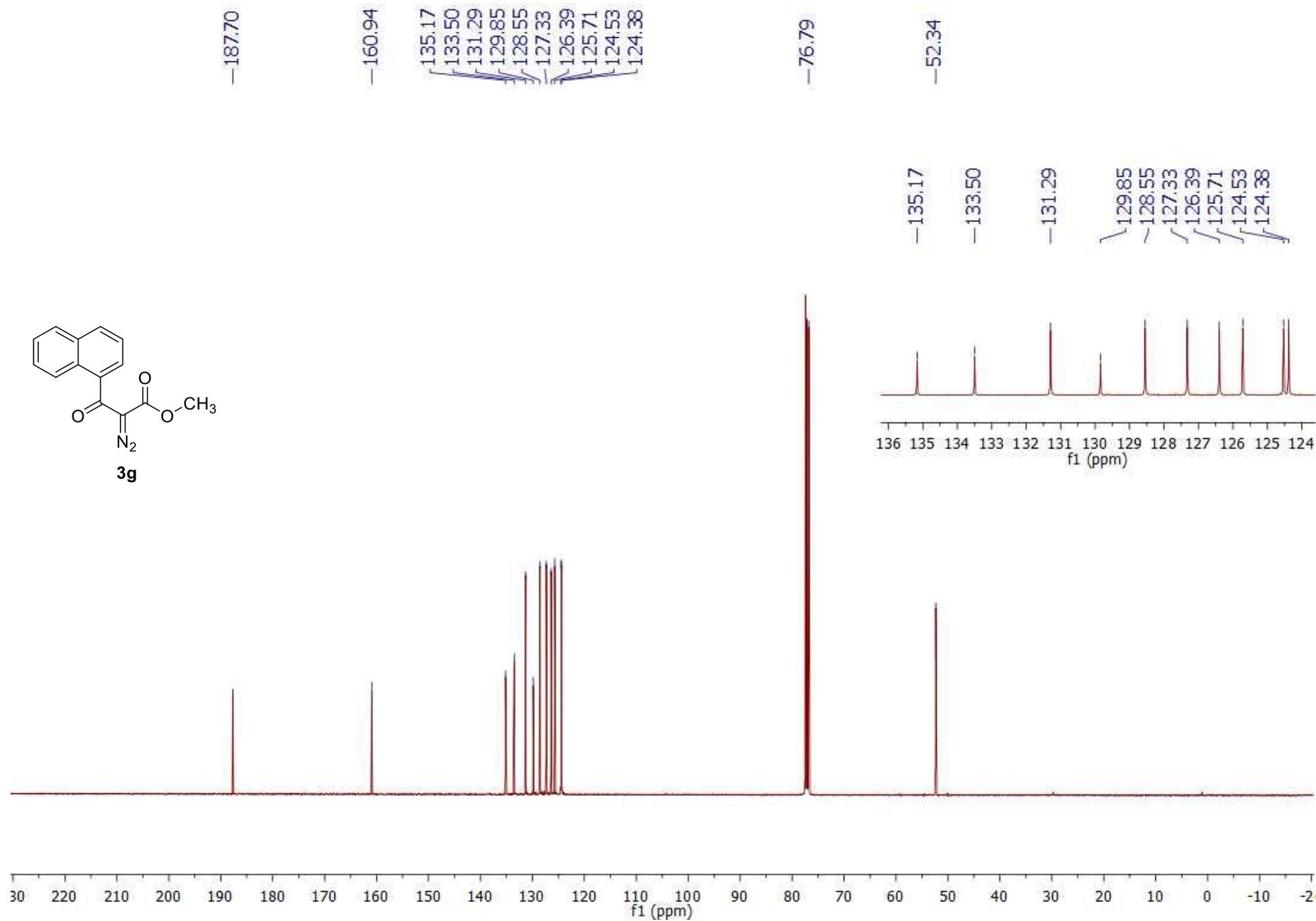
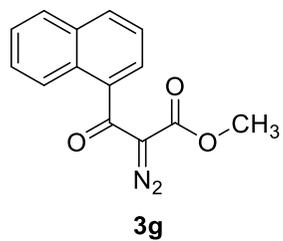


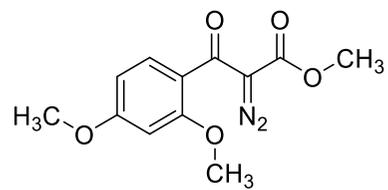
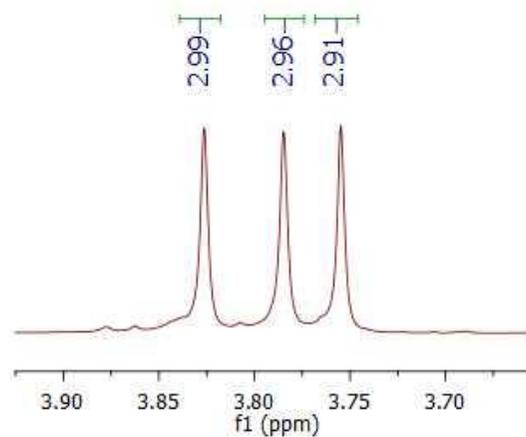
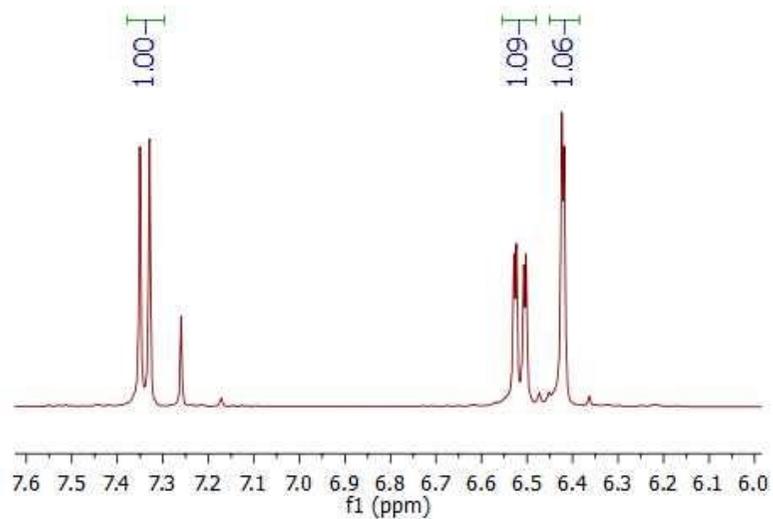


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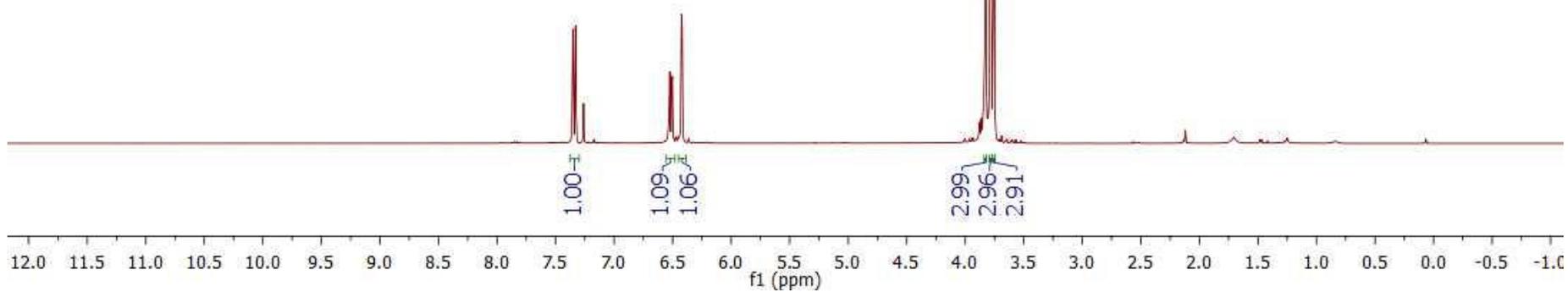


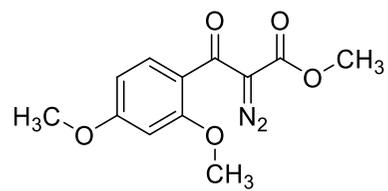






3h





3h

-184.61

163.74

161.78

158.84

-130.86

-120.73

-104.91

-98.21

55.58

55.47

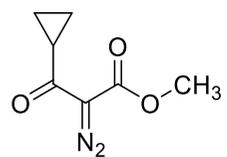
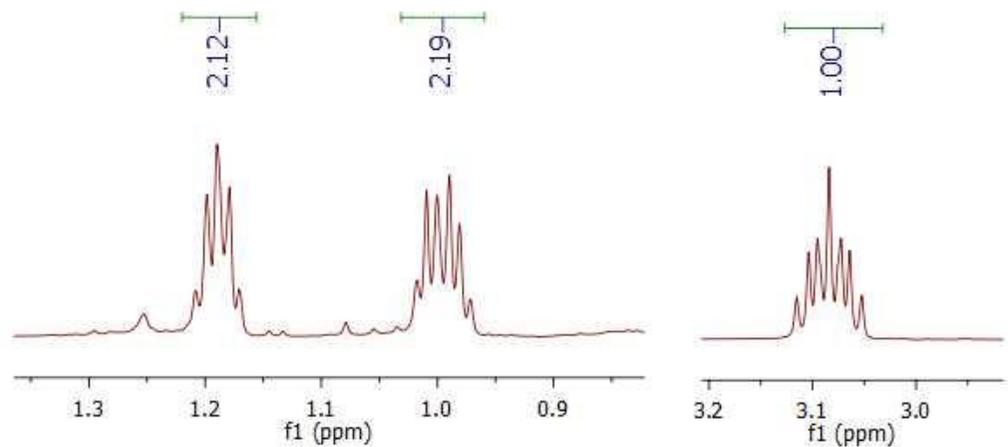
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-55.58

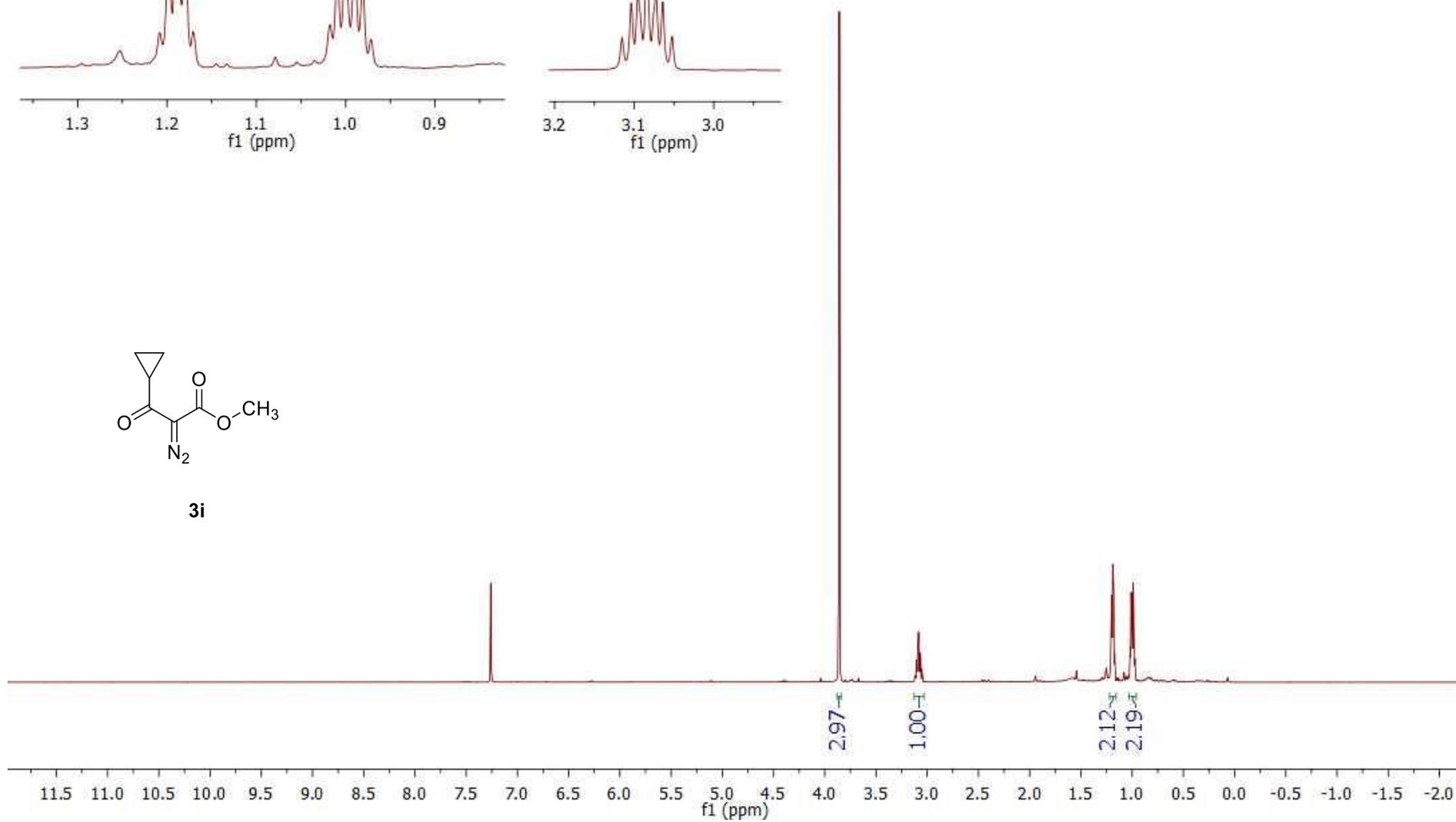
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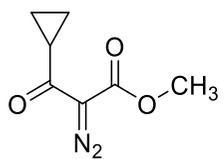
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f1 (ppm)

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f1 (ppm)

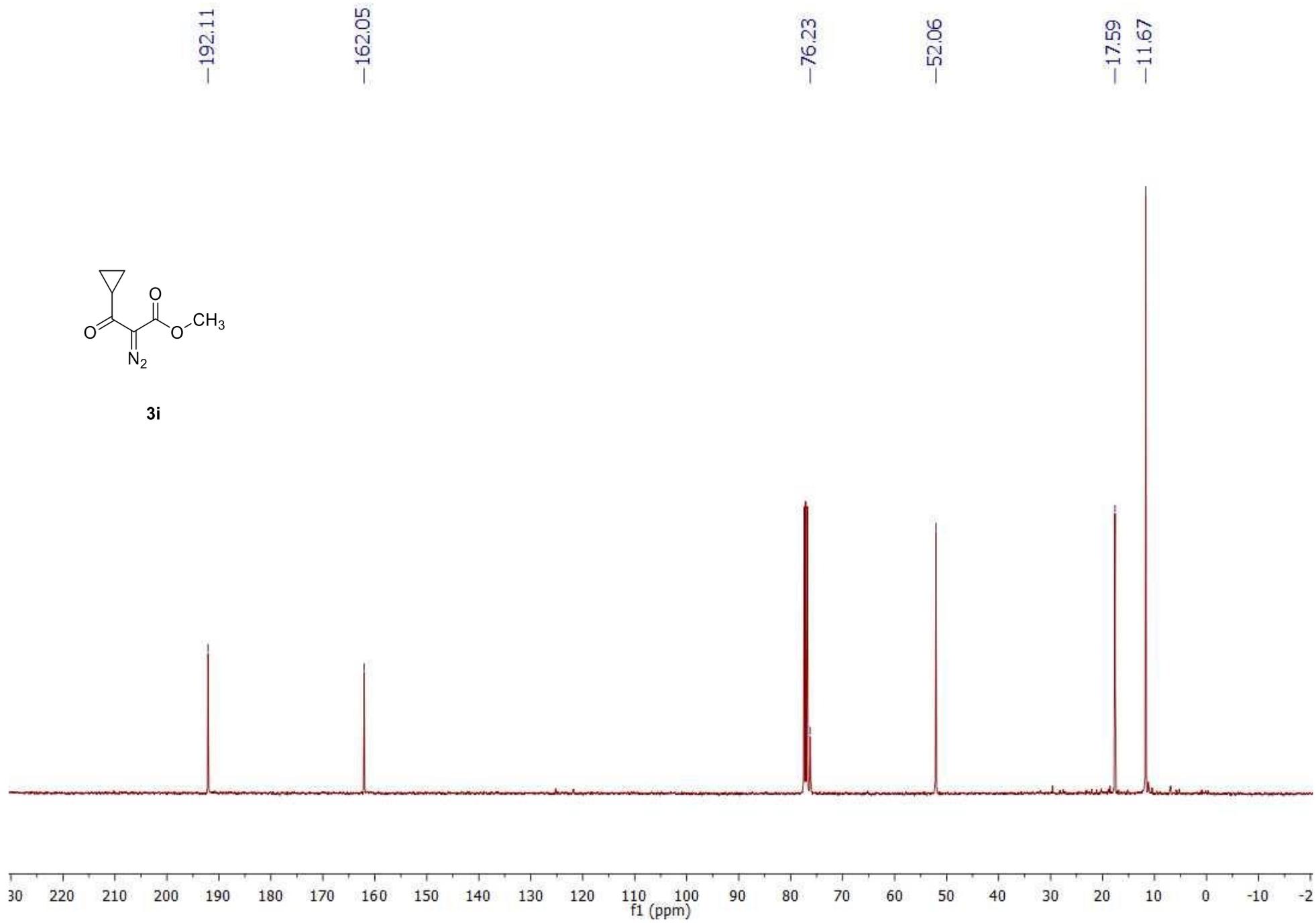


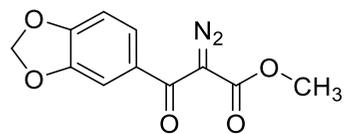
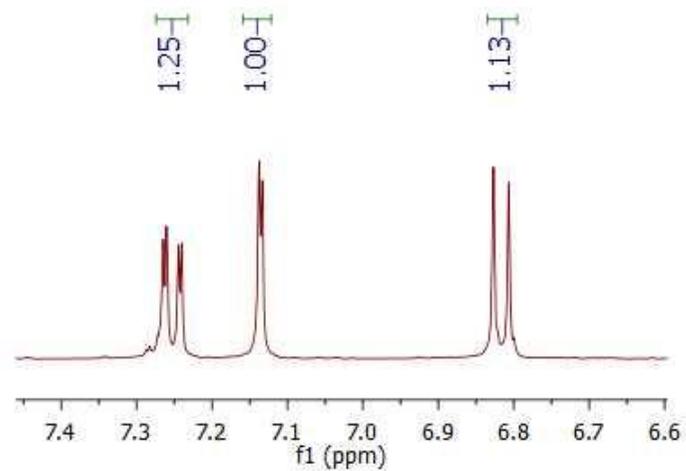
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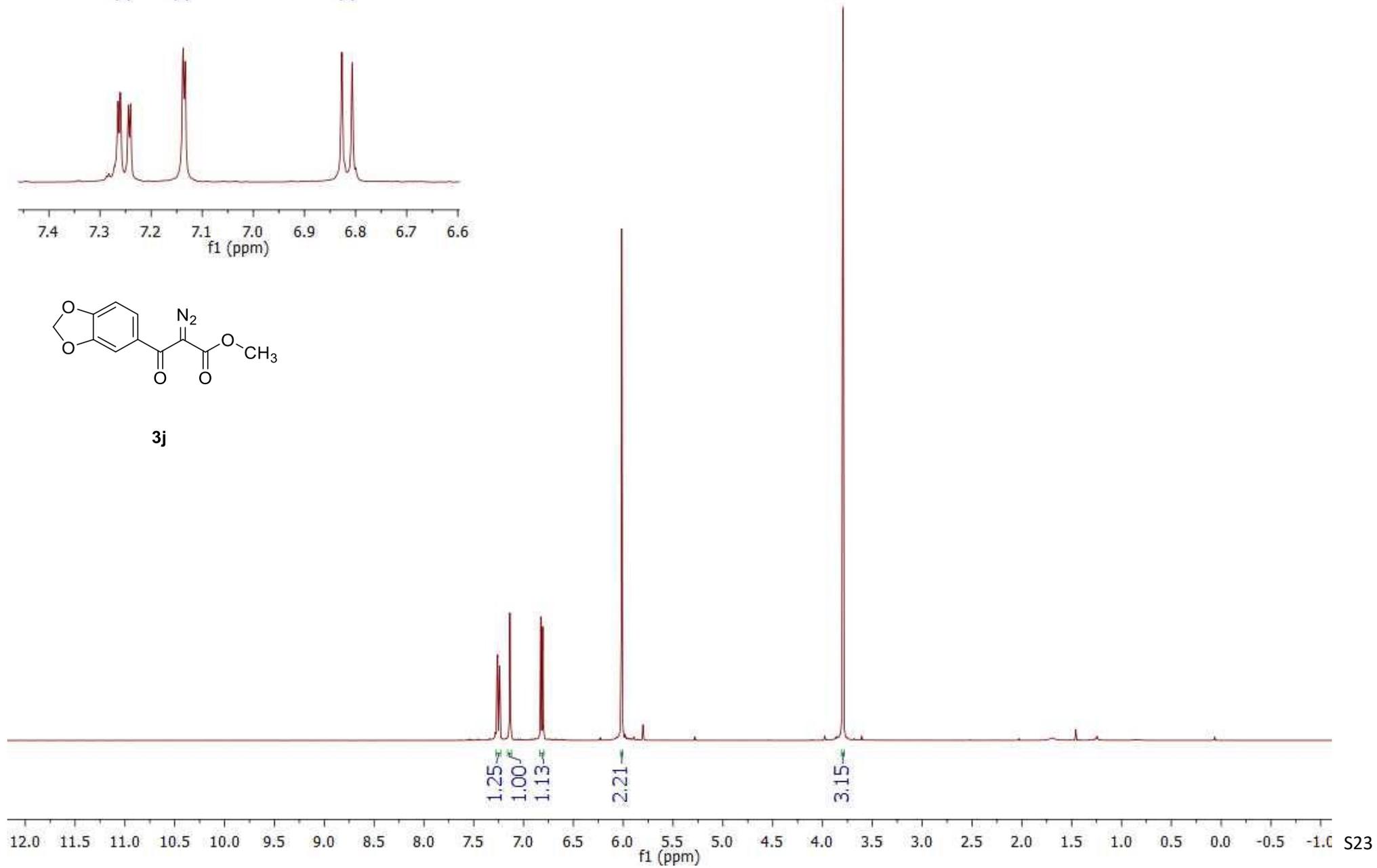


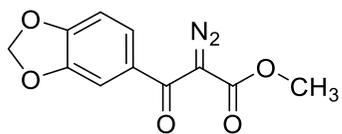
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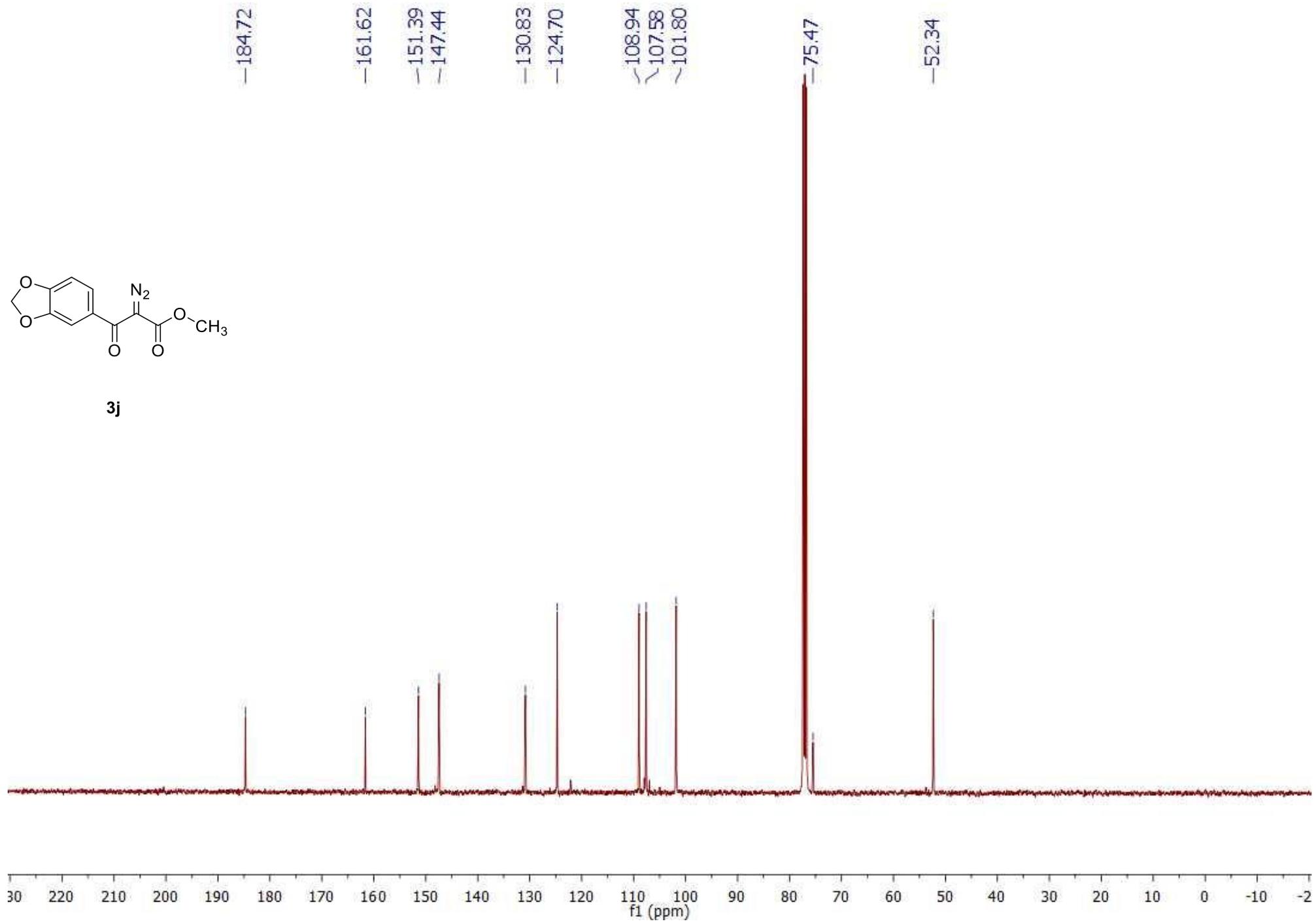


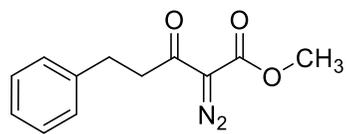
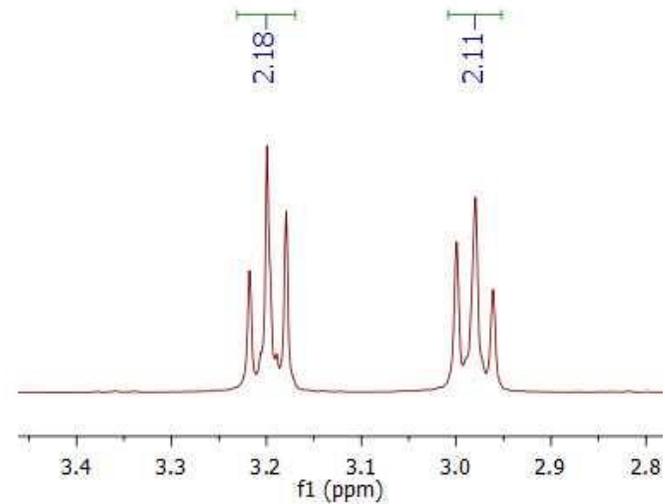
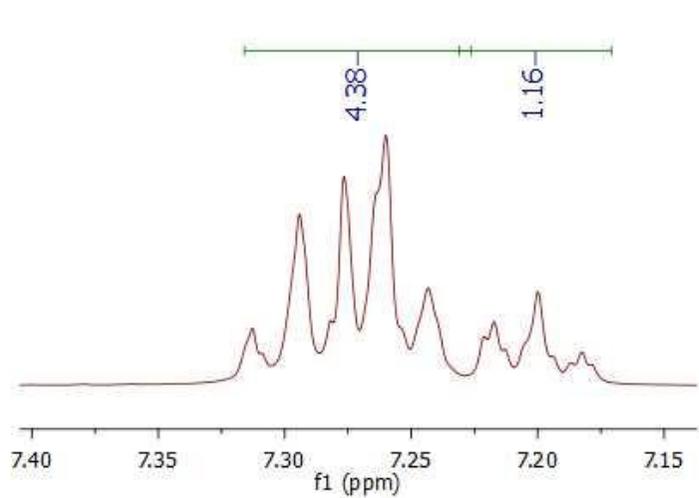
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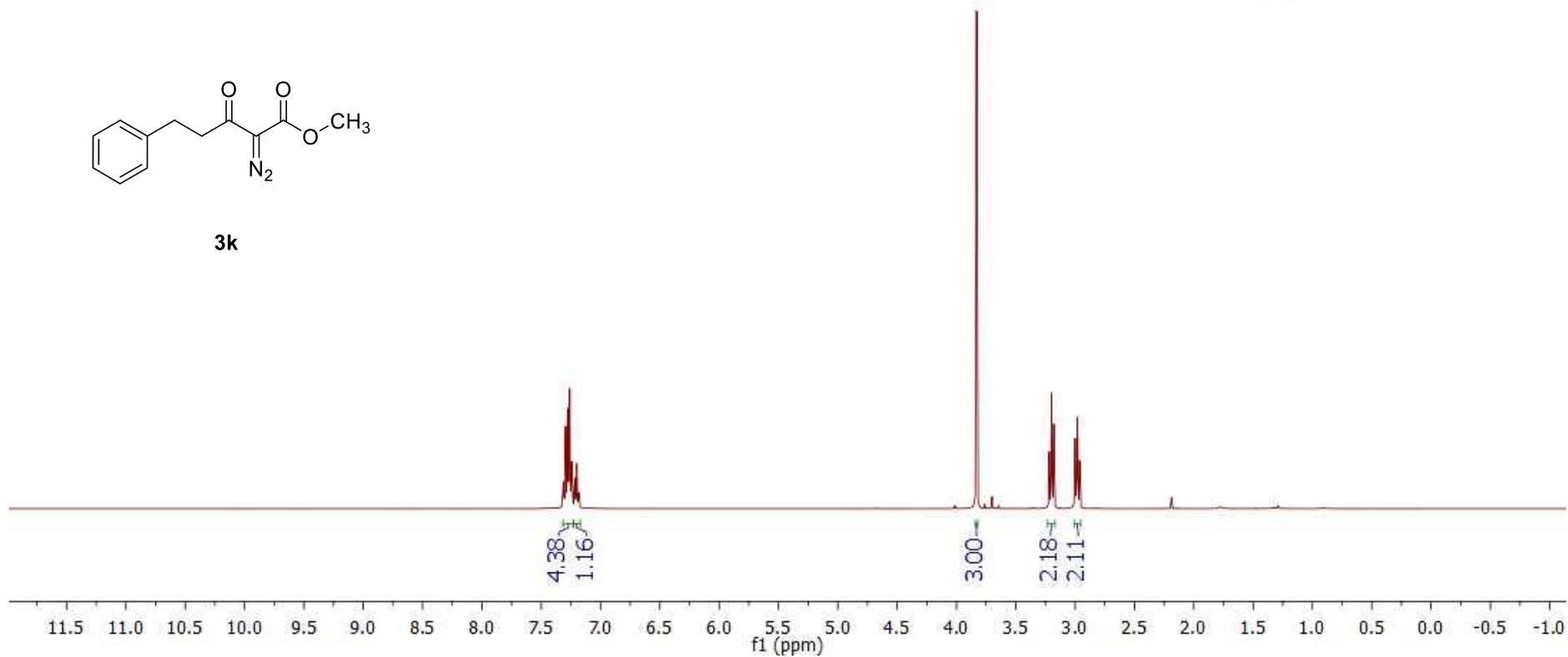


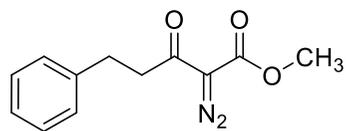
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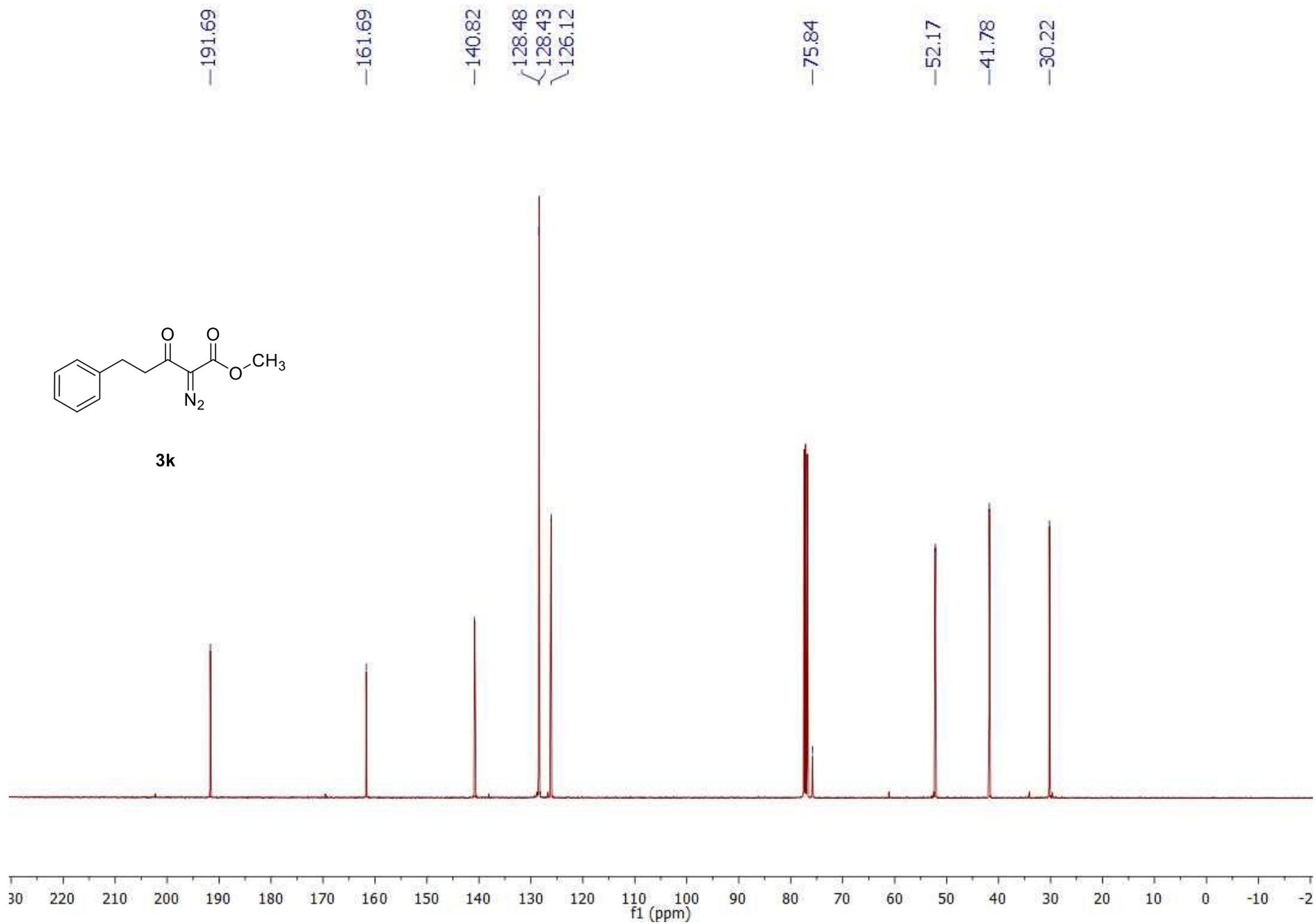


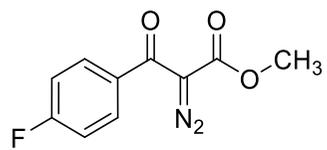
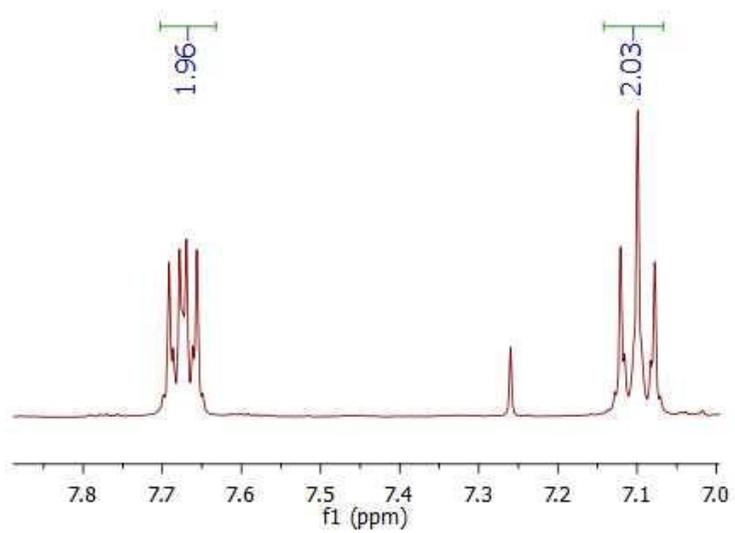
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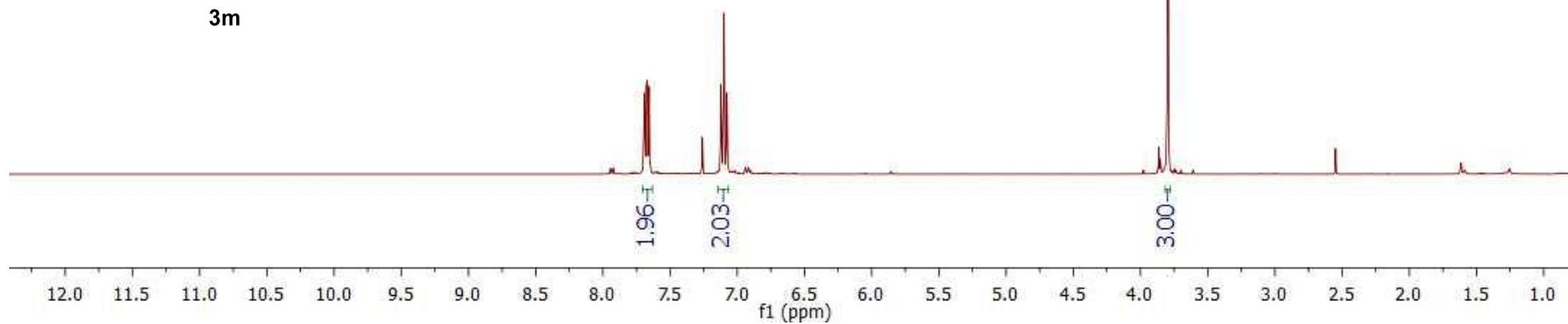


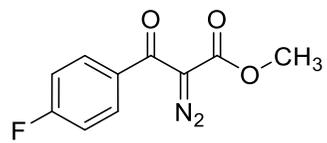
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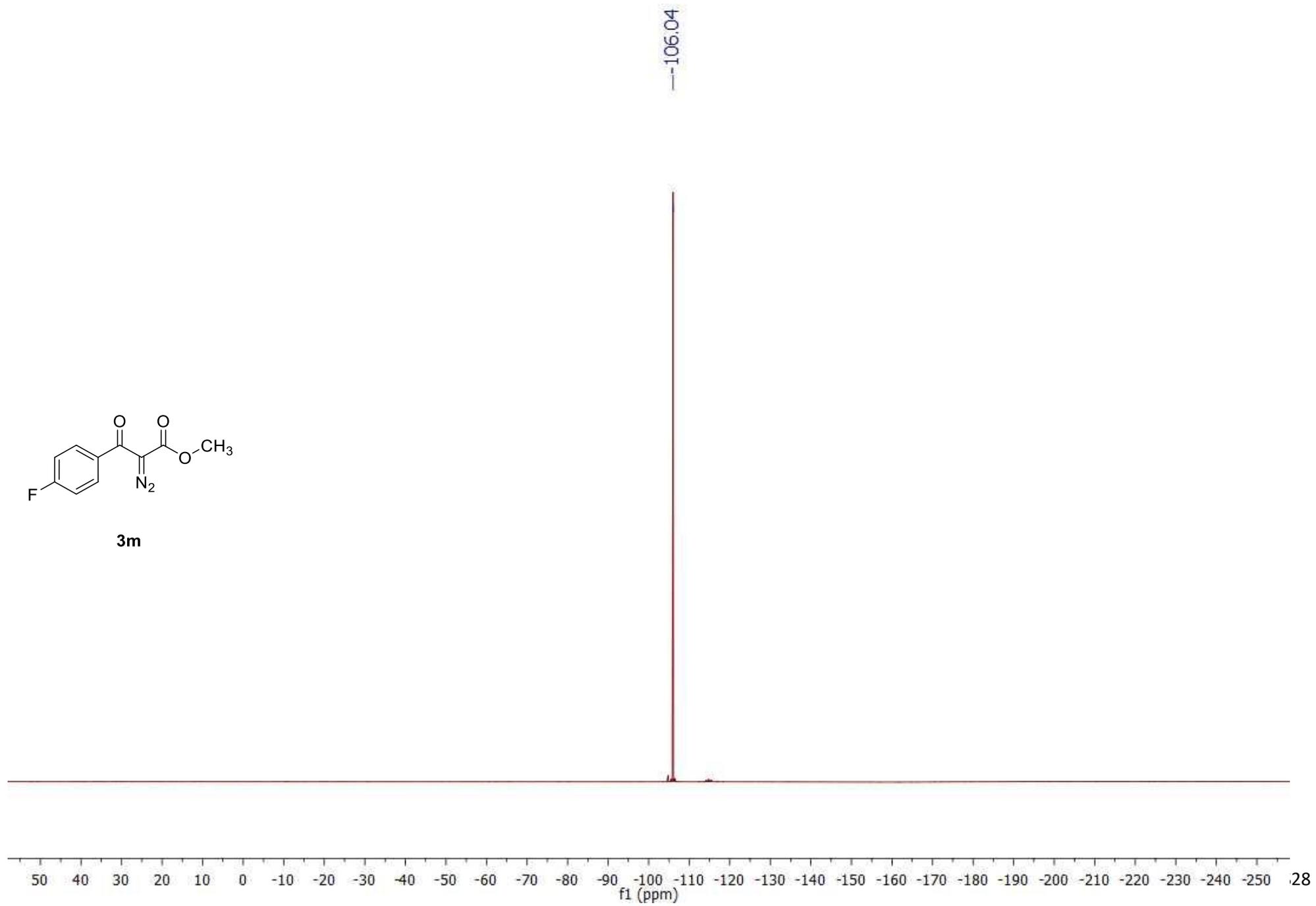


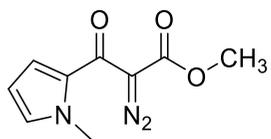
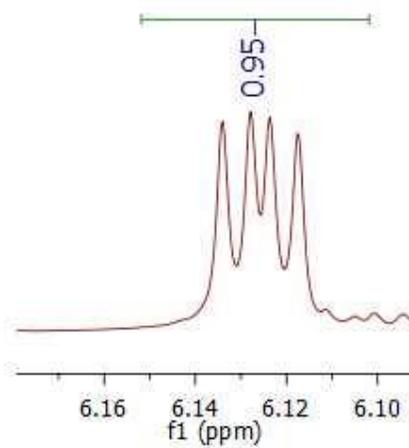
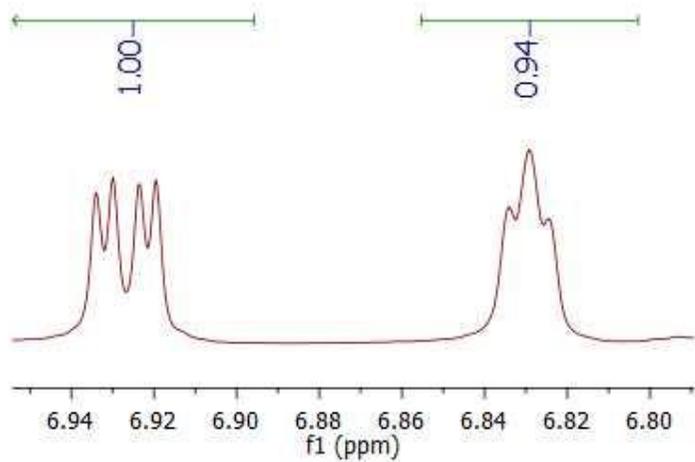
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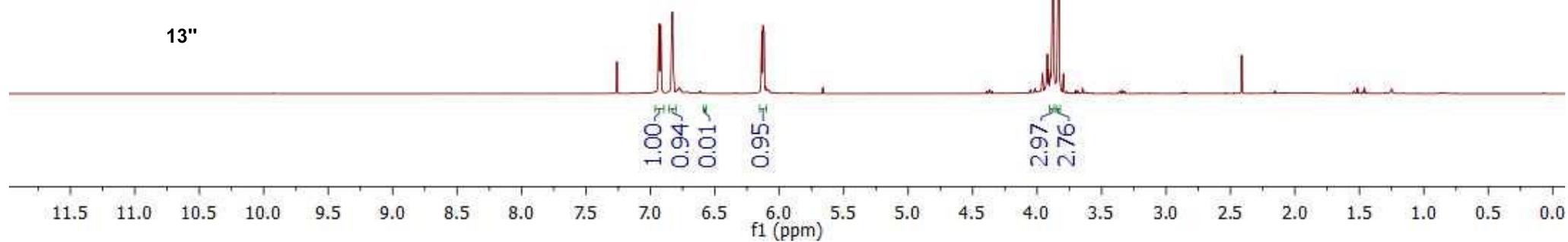


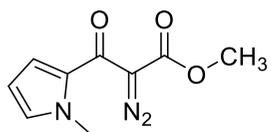
3m





13"





13"

-173.68

-162.36

131.18

128.12

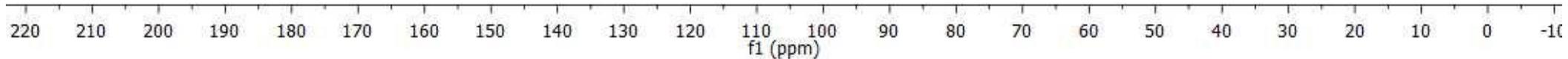
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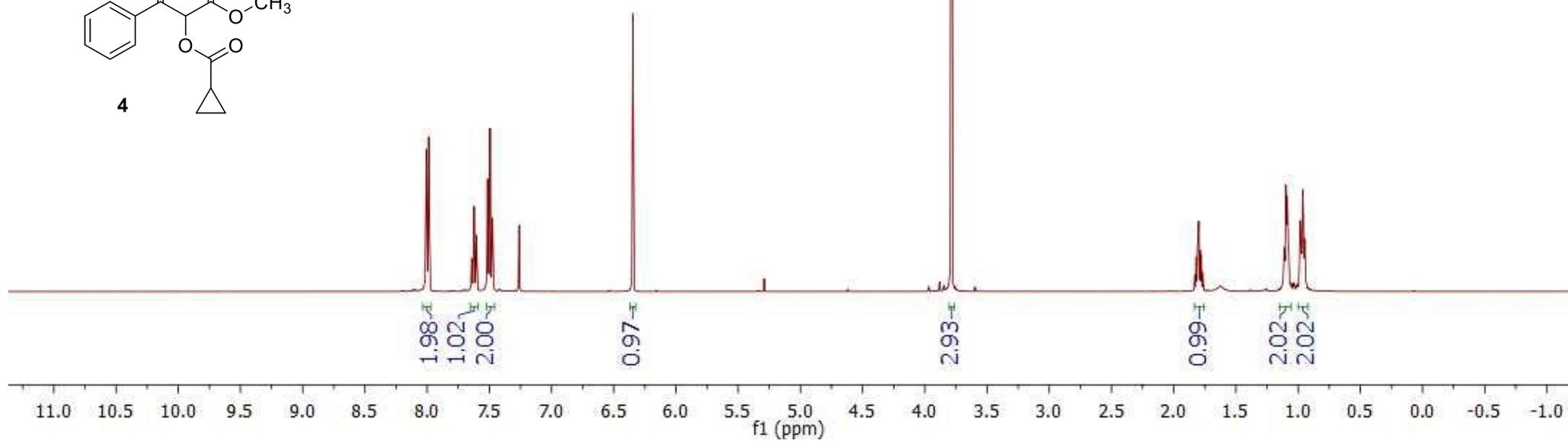
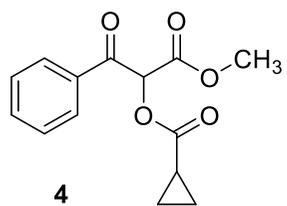
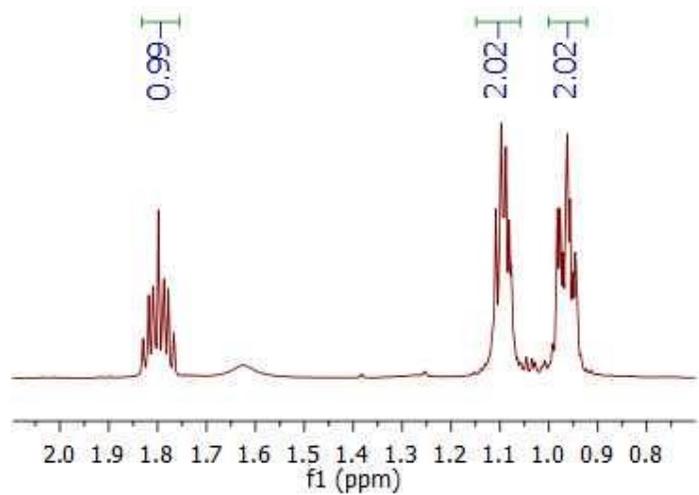
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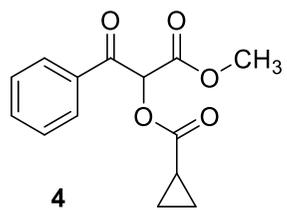
-73.55

-52.32

-37.03







-189.74

-173.44

-165.79

134.21

134.19

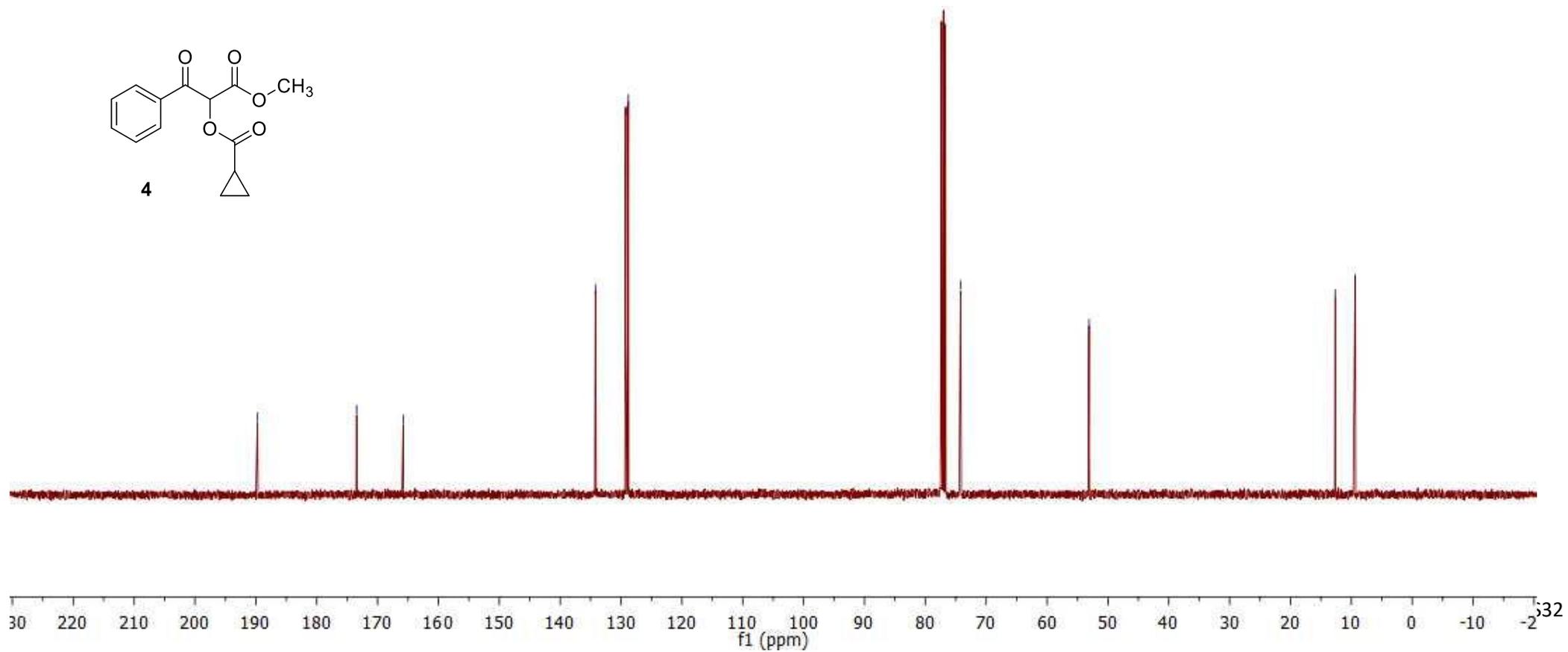
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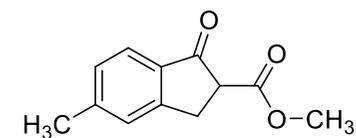
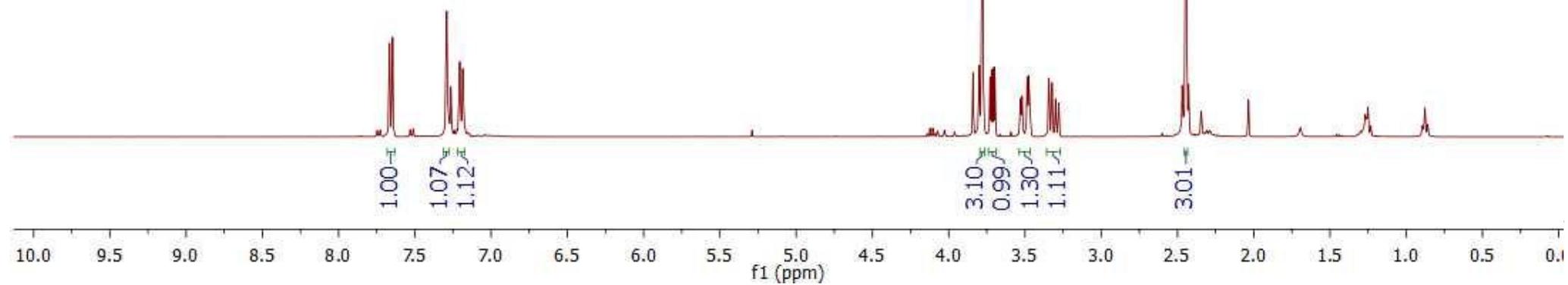
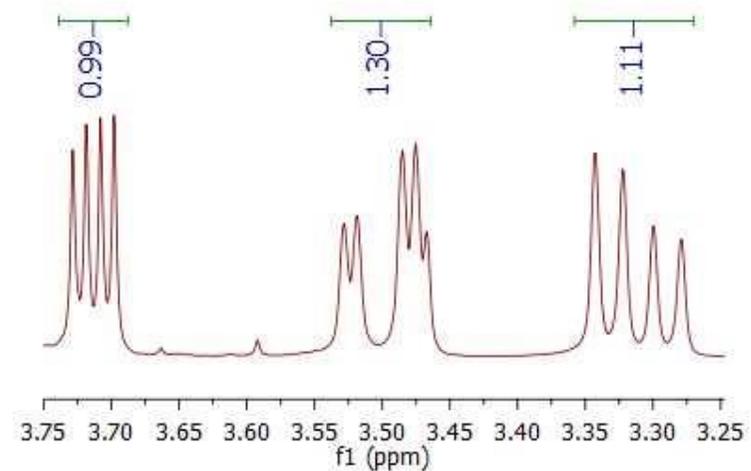
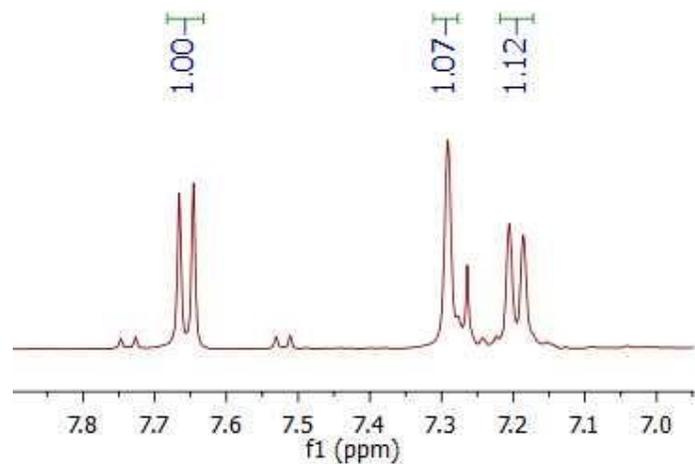
128.80

-74.21

-53.10

-12.66





5