Improved Cope-Type Hydroamination Reactivity of Hydrazine Derivatives

Francis Loiseau, Christian Clavette, Michaël Raymond, Jean-Grégoire Roveda, Alishya Burrell, André M. Beauchemin*

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Ontario, Canada, K1N 6N5

andre.beauchemin@uottawa.ca

Supporting Information

Table of Contents

General Information. All reactions were performed in oven-dried 0.5, 2, 5 or 20 mL Biotage sealed tubes under an argon atmosphere unless otherwise noted. Microwave reactions were run in a Biotage Initiator microwave. Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 μm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F_{254} (E. Merck), cut to size. Visualization was accomplished with UV light followed by dipping in a potassium permanganate solution and heating.

Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). ^{1}H NMR spectra were recorded on a Bruker Avance300 (300 MHz), Avance400 (400 MHz) or Varian500 (500 MHz) spectrometer at ambient temperature unless otherwise noted and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, C_6D_6 at 7.15 ppm, or $(CD_3)_2SO$ at 2.50 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance300 (75 MHz), Avance400 (100 MHz) or Varian500 (500 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard ($CDCl_3$ at 77.0 ppm, C_6D_6 at 128.02 ppm, $(CD_3)_2SO$ at 39.52 ppm). High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70ev at the Ottawa-Carleton Mass Spectrometry Centre.

Materials. Unless otherwise noted, all commercial materials were purchased from a supplier and used without further purification. Supporting information for previously reported compounds and precursors (Table 1, entries 1, 5-8) can be found in a previous communication.[1] The syntheses of 4-pentenal, 4-hexenal, 5-hexenal, 5-octenal[1] and 3-benzyloxypropionaldehyde can also be found in a recent publication.[2]

Procedures for the Scope of Intramolecular Hydroamination Using Hydrazine Derivatives (Table 1):

Note: *Procedure **A2** should be used for the preparation of 3,5-bistrifluoromethylbenzohydrazide derivatives. Reductions performed in t-BuOH typically minimize byproduct formation.[3]*

General Procedures A: Preparation of the Alkylhydrazides

A1: *Hydrazone Formation*: The corresponding aldehyde or ketone (1.25 equiv.) was dissolved in MeOH (0.2 M) at 25 ºC. The corresponding hydrazide was added to the reaction flask. The reaction was stirred at room temperature and monitored by TLC until consumption of the hydrazide was completed. Depending on substrates, the conditions varied from 30 min to 5 hours either at room temperature or at reflux, with aldehydes typically reacting faster than ketones and electron-poor hydrazides requiring longer or more forcing conditions to reach competion. The unpurified hydrazone was then dried over sodium sulfate, filtered over cotton, and used directly in the reduction to the alkyl hydrazide. (alternatively, silica-gel chromatography can be performed on certain hydrazones. Use of the unpurified reaction mixture was preferred, due to the lability of some hydrazones used)

Reduction of the Hydrazone: Performed via a modification of Lane's procedure.[4] The hydrazone was diluted further with MeOH (0.1 M) under argon and cooled to 30 ºC. $NaCNBH_3$ (2.4 equiv.) and methyl orange is added to the solution. A mixture of 1:1 HCl/MeOH was added fast via syringe until the solution was dark red (pH < 3), while keeping vigorous stirring. The reaction was monitored visually, and extra HCl solution was added if the solution loses its dark color within the first 30 minutes, while following the reaction by TLC. Upon completion (typically 1-3 hours), the reaction was diluted with 50 mL of CH_2Cl_2 and transferred to a separatory funnel. After adding 10 mL of water was added to the solution, the pH was raised slowly to 6.5-7.0 with saturated aq. $NaHCO_3$. The solution was extracted three times with CH_2Cl_2, the combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by column chromatography to give the corresponding alkyl or alkenyl hydrazide.

A2: *Hydrazone Formation*: The corresponding aldehyde or ketone (1.25 equiv.) was dissolved in *t*-BuOH (0.2 M) at 40 ºC. The corresponding hydrazide was added to the reaction flask. The reaction was monitored by TLC until consumption of the hydrazide was completed. The crude solution of hydrazone was then dried over sodium sulfate, filtered over cotton, and used directly in the reduction to the alkyl hydrazide. *Note: For supporting info on the synthesis of the aldehydes, see reference 1.

Reduction of the Hydrazone: Performed via a modification of Lane's procedure.[4] The crude hydrazone solution was diluted further with *t*-BuOH (0.1 M) under argon and cooled to 30 ºC. $NaCNBH_3$ (2.4 equiv.) and a pinch

---

1. Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

2. Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874.

3. For example during a solvent scan performed to minimize byproduct formation, attempted reduction in *i*-PrOH led to isolation of a small amount of isopropyl 3,5-bistrifluoromethylbenzoate.

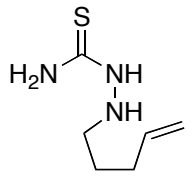
4. Lane, C. F. *Synthesis* **1975**, 135.

of methyl orange are added to the solution. A mixture of 1:1 HCl/MeOH was added fast via syringe until the solution was dark red (pH < 3), while keeping vigorous stirring. The reaction was monitored visually, and extra HCl solution was added if the solution loses its dark color within the first 30 minutes, while following the reaction by TLC. Upon completion (typically 1-3 hours), the reaction was diluted with 50 mL of CH_2Cl_2 and transferred to a separatory funnel. After adding 10 mL of water was added to solution, the pH was raised slowly to 6.5-7.0 with saturated aq. $NaHCO_3$. The solution was extracted three times with CH_2Cl_2, the combined organic layers are washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was then purified by column chromatography to give the corresponding alkyl or alkenyl hydrazide.

General Procedure B: Intramolecular Hydrohydrazidation

B1: *Microwave*: The corresponding hydrazide and α,α,α-trifluorotoluene (such that the concentration of the hydrazide was 0.05 M) were added to a Biotage Initator microwave vial (0.5, 2, 5 or 20 mL), while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated in a Biotage Initiator microwave for 10-16 hours at 70 °C to 195 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding hydrohydrazidation products.

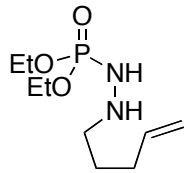
B2: *Standard Heating*: The corresponding hydrazide and α,α,α-trifluorotoluene (such that the concentration of the hydrazide was 0.05 M) were added to a Biotage Initator microwave vial (0.5, 2, 5 or 20 mL), while keeping it under an argon atmosphere. The septum was removed and the tube was then quickly sealed with a microwave cap and heated in a wax bath with constant stirring for 18-40 hours at 70 °C to 195 °C. The tube was cooled to ambient temperature, concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,4-dimethoxybenzene as an internal standard, then again concentrated under reduced pressure and purified by silica gel chromatography to give the corresponding hydrohydrazidation products.



1b

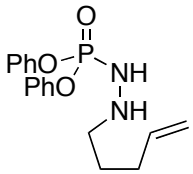
1-(Pent-4-enyl)thiosemicarbazide (1b) - (Table 1, entry 2). Synthesized following the general procedure **A1**. The hydrazone derived from the title compound was isolated as a white crystalline solid (0.997 g, 65 % yield) using flash chromatography (40 % EtOAc in toluene with 1 % Et_3N). TLC R_f 0.29 in 10 % MeOH in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) * denotes minor isomer δ ppm 10.58 (s, 1H), *9.13 (s, 1H), 7.44 (t, J = 4.8 Hz, 1H), 7.08 (s, 1H), 6.90 (s, 1H), *6.56 (t, J = 5.1 Hz, 1H), 5.78 (tdd, J = 16.4, 10.2, 6.2 Hz, 1H), 5.09-4.95 (m, 2H), 2.42-2.20 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 177.4, 148.0, 136.5, 115.7, 31.3, 29.9; IR (film) 3417, 3390, 3268, 3211, 3166, 2987, 2919, 1596, 1538, 1535, 1471, 1364, 1284, 1239, 1098, 912, 828 cm^{-1}; HRMS (EI): Exact mass calculated for $C_6H_{11}N_3S_1$ $[M]^+$: 157.0674. Found: 157.0690.The title compound, obtained after reduction of the thiosemicarbazone, was isolated (0.700 g, 74 %) as a white solid using flash chromatography (40-60 % EtOAc in hexanes with 1 % Et_3N). TLC R_f 0.49 in 10 % MeOH in CH_2Cl_2; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.80 (s, 1H), 7.10 (s, 1H), 6.36 (s, 1H), 5.77 (tdd, J = 16.9, 10.1, 6.7 Hz, 1H), 5.07-4.93 (m, 2H), 3.89 (t, J = 5.3 Hz, 1H), 2.91-2.82 (m, 2H), 2.15-2.05 (m, 2H), 1.58 (tt, J = 7.3, Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 182.1, 137.5, 115.4, 51.1, 31.1, 26.6; IR (film) 3412, 3287, 3204, 3169, 3101,

2991, 2934, 2892, 2846, 1637, 1595, 1561, 1459, 1265, 934, 889, 851, 801 cm^{-1}; HRMS (EI): Exact mass calculated for $C_6H_{13}N_3O$ $[M]^+$: 159.0830. Found: 159.0859.



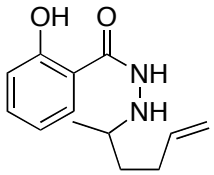
1c

Bis-ethoxyphospho-*N*'-(pent-4-enyl)-hydrazide (1c) - (Table 1, entry 3). Synthesized following the general procedure **A1**. Isolated 1.49 g (72% yield) of **1c** as a yellow oil. TLC R_f 0.69 in 10% MeOH/CH_2Cl_2. ^{1}H NMR ($CDCl_3$, 300 MHz)) δ ppm 5.78 (tdd, *J* = 16.9, 10.2, 6.6Hz, 1H), 5.05-4.91 (m, 2H), 4.48 (d, *J* = 30.2 Hz, 1H), 4.17-4.02 (m, 4H), 3.24 (s, 1H), 2.83 (t, *J* = 7.2 Hz, 2H), 2.07 (dd, *J* = 14.7, 6.9 Hz, 2H), 1.63-1.51 (m, 2H), 1.32 (dt, *J* = 7.07, 7.06, 0.60 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 138.0, 114.9, 62.8, 62.7, 53.0, 53.0, 31.1, 26.6, 16.2, 16.2; IR (film); 3473, 3272, 2983, 2914, 2858 cm^{-1}; HRMS (EI): Exact mass calculated for $C_9H_{21}N_2O_3P$ $[M]^+$: 236.129; found: 236.129.



1d

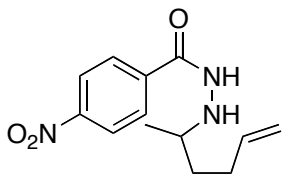
Bis-phenoxyphospho-*N*'-(pent-4-enyl)-hydrazide (1d) - (Table 1, entry 4). Synthesized following the general procedure **A1**. Isolated 0.419 g (82% yield) of **1d** as a white solid. TLC R_f 0.34 in 20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) 7.39-7.24 (m, 8H), 7.17 (t, *J* = 7.1 Hz, 2H), 5.75 (tdd, *J* = 16.9, 10.3, 6.7 Hz, 1H), 5.03-4.91 (m, 2H), 4.72 (d, *J* = 36.1 Hz, 1H), 3.50-3.35 (m, 1H), 2.79 (dd, *J* = 10.8, 6.6 Hz, 2H), 2.06 (q, *J* = 6.9, 6.7 Hz, 2H), 1.60-1.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 138.1, 129.8, 125.1, 120.5, 120.5, 115.2, 53.1, 53.1, 31.1, 26.7; IR (film); 2918, 2850, 1580, 1542, 1470 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{11}H_{21}N_2O_3P$ $[M]^+$: 332.129; found: 332.126.



1i

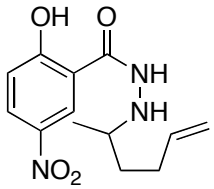
***N*'-(Hex-5-en-2-yl)-2-hydroxybenzohydrazide (1i) - (Table 1, entry 9):** Synthesized according to general procedure **A1**. The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30 % EtOAc in hexanes). The title compound was obtained as white solid (3.84 g, 88 %). TLC R_f 0.7 in 100 % EtOH; ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.48-7.31 (m, 2H), 6.99 (d, *J* = 8.7 Hz, 1H), 6.84 (t, *J* = 7.6 Hz, 1H), 5.80 (tdd, *J* = 16.8, 10.2, 6.6 Hz, 1H), 5.10-4.92 (m, 2H), 3.15-3.02 (m, 1H), 2.32-1.97 (m, 2H), 1.74-1.57 (m, 1H), 1.50-1.35 (m, 1H), 1.11 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm 169.5, 161.0, 138.0, 134.4, 125.2, 118.9, 118.5, 114.9, 113.1, 55.6, 34.0, 30.0, 18.4; IR (film) 3287, 3074, 2975,

2922, 2873, 1641, 1604, 1550, 1482, 1455, 1375, 1309, 1253, 1151, 1102, 1033, 991, 913, 824, 754 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{18}N_2O_2$ $[M]^+$: 234.1368. Found: 234.1362.



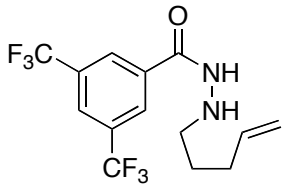
1j

***N*'-(Hex-5-en-2-yl)-4-nitrobenzohydrazide (1j) - (Table 1, entry 11).** Synthesized according to General Procedure **A2** using 4-nitrobenzhydrazide (1.25 g, 6.90 mmol) and 4-penten-2-one (0.879 mL, 7.59 mmol). Isolated 1.62 g (90 % yield) of the title compound following silica-gel chromatography (40 % EtOAc / hexanes); TLC R_f 0.49 (50 % EtOAc/hexanes). ^{1}H-NMR (400 MHz, DMSO-d_6): δ 10.30 (s, 1H), 8.32-8.29 (m, 2H), 8.07-8.04 (m, 2H), 5.82 (ddt, J = 17.0, 10.3, 6.6 Hz, 1H), 5.08-4.92 (m, 3H), 2.96 (sextet, J = 6.2 Hz, 1H), 2.18-2.02 (m, 2H), 1.64-1.55 (m, 1H), 1.38-1.29 (m, 1H), 1.02 (d, J = 6.3 Hz, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 163.9, 149.2, 138.9, 138.7, 128.6, 123.6, 114.7, 54.5, 33.7, 29.7, 18.5. IR (film): 3290, 3077, 2979, 2941, 2857, 1640, 1595, 1518, 1352, 1261, 764, 750 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{13}H_{17}N_3O_3$ [M]+: 263.12699. Found: 263.12899.



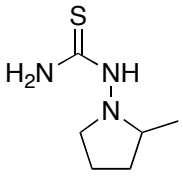
1k

***N*'-(Hex-5-en-2-yl)-2-hydroxy-5-nitrobenzohydrazide (1k) - (Table 1, entry 10).** Synthesized according to General Procedure **A2** using 2-hydroxy-5-nitrobenzhydrazide (1.00 g, 4.69 mmol) and 4-penten-2-one (0.598 mL, 5.16 mmol). Isolated 0.595 g (45 % yield) of the title compound following silica-gel chromatography (30 % EtOAc / hexanes); TLC R_f 0.52 (30% EtOAc/hexanes). ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.42 (d, J = 2.5 Hz, 1H), 8.29 (dd, J = 9.2, 2.6 Hz, 1H), 7.09 (d, J = 9.2 Hz, 1H), 5.83 (ddt, J = 16.9, 10.2, 6.6 Hz, 1H), 5.10-4.98 (m, 2H), 3.10 (sextet, J = 6.4 Hz, 1H), 2.17 (quintett, J = 13.6, 6.8 Hz, 2H), 1.73-1.61 (m, 1H), 1.48 (td, J = 14.7, 7.0 Hz, 1H), 1.15 (d, J = 6.3 Hz, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 167.9, 166.6, 139.4, 138.0, 129.4, 121.9, 119.5, 115.1, 112.6, 55.8, 34.0, 30.0, 18.5. IR (film): 3290, 3077, 2986, 1649, 1607, 1543, 1485, 1341, 1299, 1275, 1261, 764, 750 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{13}H_{17}N_3O_4$ [M]+: 279.12191. Found: 279.11942.



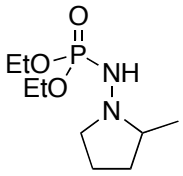
1l

3,5-Bis(trifluoromethyl)-*N*'-(pent-4-enyl)benzohydrazide (1l) - (Table 1, entry 12). The hydrazide was synthesized according to general procedure **A2** from 4-pentenal[5] (2.76 mmol) and using 3,5-bistrifluoromethylbenzhydrazide (0.500 g, 1.84 mmol). The compound was obtained as a white solid (0.225 g, 36% yield). TLC R_f 0.41 (20% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.23 (s, 2H), 8.06-7.99 (m, 1H), 5.81 (tdd, J = 16.9, 10.2, 6.7 Hz, 1H), 5.11-4.94 (m, 2H), 3.00 (t, J = 7.3 Hz, 2H), 2.22-2.09 (m, 2H), 1.75-1.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.5 (C), 137.8 (CH), 134.8 (C), 132.4 (q, J = 34.0 Hz, C), 127.3 (CH), 125.4 (CH), 122.8 (q, J = 273.0 Hz, C), 115.2 (CH_2), 51.7 (CH_2), 31.1 (CH_2), 27.1 (CH_2); IR (film) 3245, 3085, 2941, 2861, 1641, 1545, 1449, 1382, 1279, 1129, 908, 699, 680 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{14}H_{14}F_6N_2O$ $[M]^+$: 354.1010. Found 354.0995



2b

1-(2-Methylpyrrolidin-1-yl)thiourea (2b) - (Table 1, entry 2). Synthesized according to General Procedure **B1** using 1-(pent-4-enyl)thiosemicarbazide (**1b**) (0.0580 g, 0.364 mmol) and heated at 150 ºC for 16 h. Isolated 0.0477 g (82% yield) of the title compound as a white solid after column chromatography (40% EtOAc/hexanes). **13b**: TLC R_f 0.35 (60% EtOAc/hexanes). ^{1}H-NMR (300 MHz; $CDCl_3$): δ 7.80 (s, 1H), 7.09 (s, 1H), 6.36 (s, 1H), 5.84-5.70 (m, 1H), 5.05-4.96 (m, 2H), 3.89 (t, J = 5.3 Hz, 1H), 2.90-2.83 (m, 2H), 2.10 (q, J = 7.2 Hz, 2H), 1.60 (q, J = 7.3 Hz, 2H).^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 182.1, 137.5, 115.4, 51.1, 31.1, 26.6. IR (film): 3412, 3287, 3203, 3169, 3100, 2990, 2933, 2846, 1595, 1561, 1458, 1265, 934 cm^{-1}. HRMS (EI): Exact mass calculated for $C_6H_{13}N_3S$ [M]+: 159.083. Found: 159.08591.

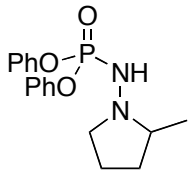


2c

1-(2-Methylpyrrolidin-1-yl)-bis-ethoxyphospho hydrazide (2c) - (Table 1, entry 3). Synthesized according to General Procedure **B1** (120 °C, 24 h) on 0.252 mmol of bisethoxyphospho-*N*'-(pent-4-enyl)-hydrazide (**1c**). Isolated 0.0584 g (98 % yield) of **2c** as a yellow oil and purified over column chromatography (6%

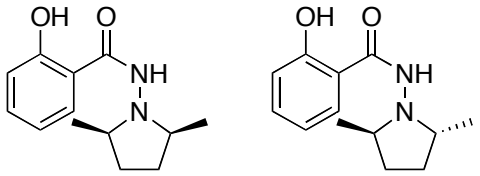
5. The 4-pentanal used was synthesized in a previous step through a Swern or Parikh-Doering oxidation from the respective alcohol, and used as an unpurified reaction mixture. Some examples of procedures can be found in previous publications, as outlined in the **starting materials** section of this supporting information. The quantity of aldehyde included in the condensation with hydrazides assumes a quantitative conversion.

MeOH/CH_2Cl_2). TLC R_f 0.64 (7.5 % MeOH/CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 4.24-4.00 (m, 4H), 3.58 (d, *J* = 29.8 Hz, 1H), 3.39 (dt, *J* = 8.5, 3.0 Hz, 1H), 2.50-2.39 (m, 1H), 2.36 (dd, *J* = 18.1, 9.0 Hz, 1H), 1.97-1.82 (m, 1H), 1.82-1.59 (m, 2H), 1.50-1.35 (m, 1H), 1.33 (t, *J* = 7.1 Hz, 6H), 1.15 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 63.8, 63.1, 63.0, 30.0, 19.9, 18.1, 16.4, 16.4, 16.4, 16.3; IR (film) 3488, 3184, 2976, 1645, 1444, 1.394, 1231, 1036 cm^{-1}; HRMS (EI): Exact mass calculated for $C_9H_{21}N_2O_3P[M]^+$: 236.1290; found: 236.1290.



2d

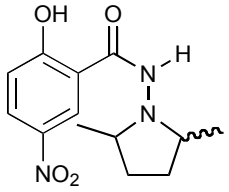
1-(2-Methylpyrrolidin-1-yl)-bis-phenoxyphospho hydrazide (2d) - (Table 1, entry 4). Synthesized according to General Procedure **B1** (110 °C, 18 h) on 0.250 mmol of bisphenoxyphospho-*N'*-(pent-4-enyl)-hydrazide (**1d**). Isolated 0.0837 g (99 % yield) of **2d** as a white solid. TLC R_f 0.92 (10 % MeOH/CH_2Cl_2). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC) δ ppm 7.36-7.23 (m, 8H), 7.20-7.10 (m, 2H), 4.26 (br s, 1H), 3.44-3.21 (m, 1H), 2.90-2.22 (m, 2H), 2.02-1.59 (m, 3H), 1.56-1.37 (m, 1H), 1.10 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 129.8, 129.7, 125.0, 124.9, 120.3, 64.1, 64.0, 58.5, 30.1, 20.0. Exact mass calculated for $C_{17}H_{21}N_2O_3P$ [M]+: 332.1290. Found: 332.1297.



2i

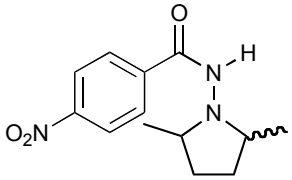
(±)-2-Hydroxy-*N*-((2*R*,5*S*)-2,5-dimethylpyrrolidin-1-yl)benzamide and (±)-2-hydroxy-*N*-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzamide (2i) - (Table 1, entry 9): Synthesized according to general procedure **A1** (90 ºC, 16 h) using 2-hydroxybenzhydrazide (0.207 g, 0.883 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 to 40% EtOAc/Hexanes). The title compounds were obtained as brown oils (0.036 g and 0.144 g, 87 % yield, 1:4 syn:anti). **5b-anti**: TLC R_f 0.4 in (40% EtOAc/Hexanes); ^{1}H NMR (300 MHz, $CDCl_3$)* denotes minor rotomer δ ppm *12.56 (s, 1H), 12.15 (s, 1H), 7.48-7.31 (m, 2H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.85 (t, *J* = 7.7 Hz, 2H), 6.57 (s, 1H), *3.54 (s, 1H), 2.83 (dd, *J* = 11.3, 5.9 Hz, 2H), *2.68-2.56 (m, 2H), 2.41-2.29 (m, 2H), 2.02-1.90 (m, 2H), 1.69-1.51 (m, 2H), *1.43-1.32 (m, 2H), 1.19 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 168.6, 159.7, 133.4, 127.5, 118.4, 117.2, 115.0, 59.9, 28.4, 18.8; IR (film) 3295, 3067, 2968, 2930, 2873, 2705, 2588, 1637, 1603, 1550, 1493, 1455, 1371, 1311, 1238, 1151, 1098, 1037, 908, 752 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{18}N_2O$ $[M]^+$: 234.1368. Found: 234.1377. **5b-syn**: TLC R_f 0.11 in (40% EtOAc/Hexanes); ^{1}H NMR (300 MHz, DMSO-d_6)* denotes minor rotomer δ ppm *12.40 (s, 1H), 12.10 (s, 1H), *7.94 (d, *J* = 7.6 Hz, 1H), 7.47-7.30 (m, 1H), 6.99 (d, *J* = 8.5 Hz, 1H), 6.94-6.77 (m, 2H), *4.04-3.79 (m, 1H), *3.71-3.49 (m, 1H), 3.44-3.26 (m, 2H), *2.44-2.21 (m, 2H), 2.20-2.04 (m, 2H), 1.62-1.44 (m, 2H), *1.44-1.27 (m, 1H), *1.26-1.21 (m, 6H), 1.10 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm 167.2, 159.2, 133.2, 127.9, 118.5, 117.1, 115.3, 55.7, 28.9, 17.1; IR (film) 3295, 3067, 2968, 2930, 2873, 2705, 2588, 1637, 1603, 1550, 1493, 1455, 1371,

1311, 1238, 1151, 1098, 1037, 908, 752 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{18}N_2O_2$ $[M]^+$: 234.1368. Found: 234.1377.



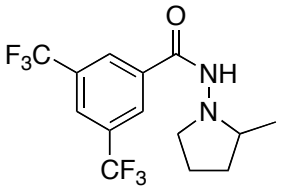
2j

(±)-2-Hydroxy-5-nitro-*N*-((2*R*,5*S*)-2,5-dimethylpyrrolidin-1-yl)benzamide and (±)-2-hydroxy-5-nitro-*N*-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzamide (2j) - (Table 1, entry 10). Synthesized according to general procedure **B2** (90 °C, 18 h) using *N*'-(hex-5-en-2-yl)-2-hydroxy-5-nitrobenzohydrazide (0.035 g, 0.13 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (55-70% EtOAc/Hexanes). The compound was obtained as a white solid (0.030 g, 88% yield, obtained as a mixture of diastereoisomers, 3.2:1 anti:syn). **Major product:** TLC R_f 0.20 in (50% EtOAc/Hexanes); ^{1}H NMR (300 MHz, DMSO-d_6, 120 ºC): δ 8.75 (s, 1H), 8.16 (d, J = 8.7, 1H), 7.00 (d, J = 9.1, 1H), 3.69-3.54 (m, 2H), 2.20-2.05 (m, 2H), 1.64-1.49 (m, 2H), 1.15 (d, J = 6.3, 7H). ^{13}C NMR (75 MHz, DMSO-d_6, 120 ºC): δ ppm 165.9, 139.4, 127.8, 125.3, 118.3, 60.2, 29.6, 16.7; IR (film) 2983, 2857, 1604, 1485, 1451, 1336, 1303, 1272, 1071, 824, 748 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{17}N_3O_4$ $[M]^+$: 279.1219 Found : 279.1223.



2k

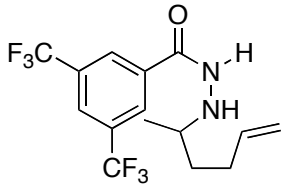
(±)-2-Hydroxy-4-nitro-*N*-((2*R*,5*S*)-2,5-dimethylpyrrolidin-1-yl)benzamide and (±)-2-hydroxy-4-nitro-*N*-((2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl)benzamide (2k) - (Table 1, entry 11). Synthesized according to general procedure **B2** (90 °C, 18 h) using *N*'-(hex-5-en-2-yl)-4-nitrobenzohydrazide (0.070 g, 0.266 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (40-65% EtOAc/Hexanes). The compound was obtained as a white solid (0.064 g, 91% yield, obtained as a mixture of diastereoisomers, 3:1 anti:syn). **Major product:** TLC R_f 0.36 in 50% EtOAc in hexanes; ^{1}H NMR (300 MHz; DMSO-d_6, 120 ºC): δ 8.79 (br s, 1H), 8.23 (d, J = 8.3, 2H), 7.98 (d, J = 7.9, 2H), 3.48-3.37 (m, 2H), 2.05-1.94 (m, 2H), 1.45-1.26 (m, 3H), 1.04 (d, J = 6.2, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz, 120 ºC): δ ppm 164.3, 149.5, 141.5, 129.2, 123.4, 47.3, 29.9, 17.5; IR (film) 3219, 2971, 2880, 1660, 1603, 1550, 1519, 1341, 1275, 1267, 764, 750 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{13}H_{17}N_3O_3$ $[M]^+$: 263.12699 Found : 263.12498.



2l

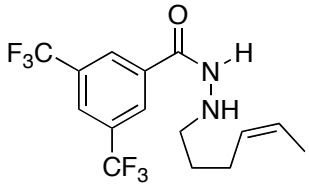
***N*-(2-Methylpyrrolidin-1-yl)-3,5-bis(trifluoromethyl)benzamide (2l and 3a) - (Table 1, entry 12 and Table 2, entry 1).** Synthesized according to general procedure **B1** (95 °C, 16 h) using 3,5-bis(trifluoromethyl)-*N*′-(pent-4-enyl)benzhydrazide (0.0770 g, 0.225 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (32% EtOAc/Hexanes). The compound was obtained as a white solid (0.0621 g, 81% yield). TLC R_f 0.14 (25% EtOAc/Hexanes); ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ ppm 9.34 (br s, 1H), 8.40 (s, 2H), 8.13 (s, 1H), 3.33-2.65 (m, 3H), 2.11-1.92 (m, 1H), 1.90-1.69 (m, 2H), 1.49-1.27 (m, 1H), 1.16-0.98 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C) δ ppm 162.6 (C), 136.5 (C), 129.9 (q, J = 33.5 Hz, C), 127.3 (CH), 123.0 (CH), 122.4 (q, J = 272.9 Hz, C), 58.8 (CH), 53.1 (CH_2), 29.9 (CH_2), 19.8 (CH_2), 17.5 (CH_3); IR (film) 3186, 3054, 2971, 2922, 2849, 2304, 1663, 1558, 1376, 1274, 1142, 908, 846, 747 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{14}H_{14}F_6N_2O$ $[M]^+$: 340.1010 Found : 340.1000

Procedures for the Scope of 3,5-*Bis*(trifluoromethyl)benzhydrazides Cyclizations (Table 2):



3b

3,5-Bis(trifluoromethyl)-*N*'-(hex-5-en-2-yl)benzohydrazide (3b) - (Table 2, entry 3). Synthesized according to General Procedure **A2** using 3,5-bistrifluoromethylbenzhydrazide (2.00 g, 7.34 mmol) and 5-hexen-2-one (1.21 mL, 10.3 mmol). Isolated 2.08 g (80% yield); TLC R_f 0.79 (40% EtOAc/hexanes). ^{1}H-NMR (400 MHz; $CDCl_3$): δ 8.21 (s, 2H), 8.00 (s, 1H), 5.79 (ddt, J = 17.0, 10.3, 6.7 Hz, 1H), 5.05-4.94 (m, 2H), 3.09 (sextet, J = 6.4 Hz, 1H), 2.22-2.04 (m, 2H), 1.69-1.60 (m, 1H), 1.43 (dddd, J = 13.5, 9.2, 7.4, 6.2 Hz, 1H), 1.11 (d, J = 6.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 400 MHz): δ ppm 164.5, 138.0, 134.8, 132.3 (q, J = 34.2 Hz, **C**CF_3), 127.3, 125.4, 122.8 (q, J = 273 Hz, **C**F_3), 115.0, 55.7, 34.0, 30.0, 18.4. IR (film): 3271, 3089, 2982, 2937, 1641, 1546, 1443, 1275, 1261, 1135, 907, 764, 750 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{15}H_{16}F_6N_2O$ [M]+: 354.11668. Found: 354.11556.

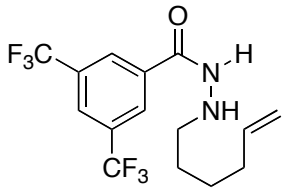


3c

3,5-Bis(trifluoromethyl)-*N*'-((*Z*)-hex-4-enyl)benzohydrazide (3c) - (Table 2, entry 5). The hydrazide was synthesized according to general procedure **A2** from *cis*-hex-4-enal[6] (4.13 mmol) and using 3,5-bistrifluoromethylbenzhydrazide (0.750 g, 2.76 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (15% EtOAc/Hexanes). The compound was obtained as a white solid (0.931 g, 36% yield). TLC R_f 0.40 (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.24

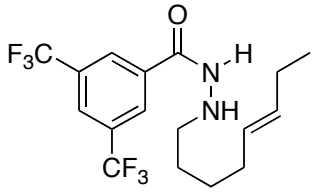
6. The *cis*-hex-4-enal, hex-5-enal and *trans*-oct-5-enal used were synthesized in previous steps through a Swern or Parikh-Doering oxidation of the respective alcohols, and used as unpurified reaction mixtures. Some examples of procedures can be found in previous publications,[1,2] as outlined in the **starting materials** section of this supporting information. The amount of aldehyde included in the condensation with hydrazides assumes a quantitative conversion.

(s, 2H), 8.02 (s, 1H), 5.64-5.21 (m, 2H), 2.97 (t, *J* = 7.3 Hz, 2H), 2.25-2.01 (m, 2H), 1.66-1.55 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.4 (C), 134.8 (C), 132.3 (q, *J* = 34.0 Hz, C), 129.4 (CH), 127.3 (CH), 125.3 (CH), 124.8 (CH), 122.8 (q, *J* = 272.9 Hz, C) 51.8 (CH_2), 27.8 (CH_2), 24.2 (CH_2), 12.7 (CH_3); IR (film) 3274, 3092, 3017, 2940, 2866, 1661, 1455, 1367, 1334, 1131, 928, 908, 848, 770, 696 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{15}H_{16}F_6N_2O$ $[M]^+$: 354.1167. Found : 354.1187



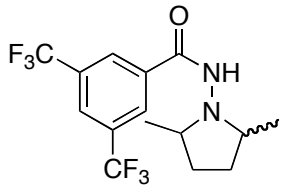
3d

3,5-Bis(trifluoromethyl)-*N*'-(hex-5-enyl)benzohydrazide (3d) - (Table 2, entry 7). The hydrazide was synthesized according to general procedure **A2** from hex-5-enal[6] (2.40 mmol), using 3,5-bistrifluoromethylbenzhydrazide (0.384 g, 1.41 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20% EtOAc/Hexanes). The title compound was obtained as a white solid (0.203 g, 57% yield). TLC R_f 0.38 in (30% EtOAc/Hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.26 (d, *J* = 12.0 Hz, 2H), 8.03 (s, 1H), 5.80 (tdd, *J* = 16.9, 10.1, 6.7 Hz, 1H), 5.02 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.96 (tdd, *J* = 10.2, 2.1, 1.2, 1.2 Hz, 1H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.14-2.05 (m, 2H), 1.66-1.55 (m, 2H), 1.55-1.44 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 164.4, 138.3, 134.7, 132.4 (d, *J* = 34.0 Hz, **C**CF_3), 127.3, 125.5, 122.8 (d, *J* = 272.98 Hz, **C**F_3), 114.9, 52.1, 33.4, 27.1, 26.1; IR (film) 3265, 3083, 2936, 2862, 1827, 1646, 1616, 1544, 1452, 1379, 1334, 1283, 1141, 909, 847, 778, 703, 678 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{15}H_{16}F_6N_2O$ $[M]^+$: 354.1167 Found : 354.1167



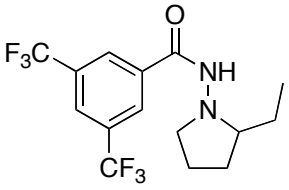
3e

3,5-Bis(trifluoromethyl)-*N*'-((*E*)-oct-5-enyl)benzohydrazide (3e) - (Table 2, entry 9). Synthesized according to general procedure **B1**, using 3,5-bistrifluoromethylbenzohydrazide (1.25 g, 4.63 mmol) and *trans*-oct-5-enal (7.84 mmol).[6] The reaction mixture was concentrated under reduced pressure. The title compound was isolated as a white solid (1.27 g, 72% yield) following flash chromatography (15% EtOAc/Hexanes). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (5% MeOH/DCM), TLC R_f 0.39 in 5% MeOH/CH_2Cl_2. ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 1H NMR (300 MHz, $CDCl_3$) δ ppm 8.24 (s, 2H), 8.02 (s, 1H), 5.33 (ddt, *J* = 17.8, 10.8, 7.0 Hz, 2H), 2.97 (t, *J* = 7.0 Hz, 2H), 2.10-1.95 (m, 4H), 1.62-1.50 (m, 2H), 1.48-1.36 (m, 2H), 0.93 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm **denotes minor traces of isomers* 164.4, 134.9, 132.3 (q, *J* = 33.9 Hz, 2C), 132.2, 128.4, 127.3, *124.6, 121.0, 52.1, 27.5, 27.1, 26.8, 20.5, 14.3; IR (film) 3443, 2097, 1653 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{17}H_{20}F_6N_2O$ $[M]^+$: 382.148; found: 382.1488.



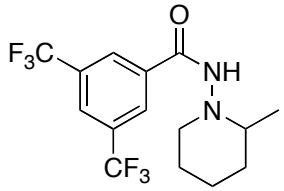
5b

3,5-Bis(trifluoromethyl)-*N*-(2,5-dimethylpyrrolidin-1-yl)benzamide (5b) - (Table 2, entry 3). Synthesized according to general procedure **B1** (90 °C, 10 h) using 3,5-bis(trifluoromethyl)-*N*′-(hex-5-enyl)benzohydrazide (0.100 g, 0.282 mmol, 1 equiv.). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (30% EtOAc/Hexanes). The compound was obtained as a white solid (0.098 g, 98% yield, obtained as a mixture of diastereoisomers, 3:1 anti:syn). **Major product:** TLC R_f 0.38 in (30% EtOAc/Hexanes); ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.06 (s, 1H), 8.39 (s, 2H), 8.10 (s, 1H), 3.45 (dq, J = 1.9, 0.6, 2H), 2.03-2.00 (m, 2H), 1.51-1.21 (m, 2H), 1.05 (d, J = 6.0, 6H) ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 162.5, 136.7, 129.9 (q, J = 33.8 Hz, **C**CF_3), 127.5, 123.0, 122.5 (q, J = 273.1 Hz, **C**F3), 55.9, 28.8, 16.4; IR (film) 3427, 3252, 3070, 2975, 2967, 1653, 1550, 1380, 1279, 1175, 1134, 907 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{15}H_{16}F_6N_2O$ $[M]^+$: 354.1167. Found : 354.1149.



5c

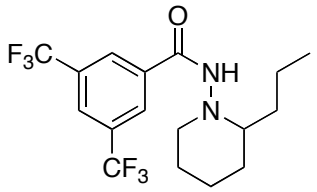
***N*-(2-Ethylpyrrolidin-1-yl)-3,5-bis(trifluoromethyl)benzamide (5c) - (Table 2, entry 5).** Synthesized according to general procedure **B1** (150 °C, 16 h) using 3,5-bis(trifluoromethyl)-*N*′-((*Z*)-hex-4-enyl)benzhydrazide (0.197 g, 0.565 mmol, 1 equiv.). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (25% EtOAc/Hexanes). The compound was obtained as a white solid (0.182 g, 91% yield). TLC R_f 0.27 in (30% EtOAc/Hexanes); ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ ppm 9.45 (br s, 1H), 8.40 (s, 2H), 8.13 (s, 1H), 3.39-2.68 (m, 3H), 2.12-1.16 (m, 6H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C) δ ppm 161.9 (C), 136.4 (C), 129.9 (q, J = 32.9 Hz, C), 127.4 (CH), 123.2 (CH), 122.5 (q, J = 273 Hz, C), 64.7 (CH_2), 53.6 (CH), 27.2 (CH_2), 25.1 (CH_2), 20.2 (CH_2), 9.0 (CH_3); IR (film) 3220, 3072, 2972, 2877, 1659, 1556, 1462, 1377, 1279, 1138, 905, 697, 682 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{15}H_{16}F_6N_2O$ $[M]^+$: 354.1167. Found : 354.1166.



5d

3,5-Bis(trifluoromethyl)-*N*-(2-methylpiperidin-1-yl)benzamide (5d) - (Table 2, entry 7). Synthesized according to general procedure **B1** (175 °C, 16 h) using 3,5-bis(trifluoromethyl)-*N*′-(hex-5-enyl)benzohydrazide (0.0950 g, 0.268 mmol, 1 equiv). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (26% EtOAc/Hexanes). The compound was obtained as a white solid (0.0816 g,

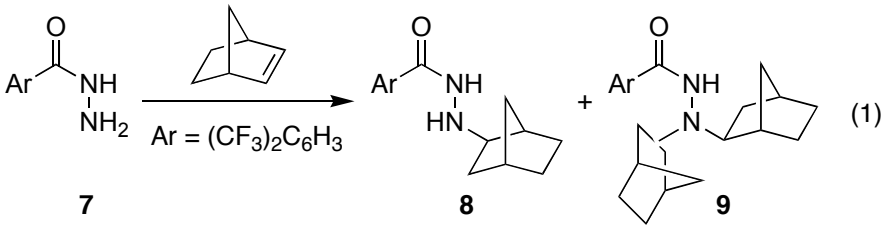
86% yield). TLC R_f 0.43 in 40% EtOAc in hexanes; ^{1}H NMR (300 MHz, DMSO-d_6, 120 °C) δ ppm 9.26 (br s, 1H), 8.40 (s, 2H), 8.09 (s, 1H), 3.18-2.63 (m, 3H), 1.79-1.47 (m, 4H), 1.40-1.15 (m, 2H), 1.12-0.93 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 120 °C) δ ppm 161.6 (C), 136.6 (C), 129.9 (q, J = 33.3 Hz, C), 127.4 (CH), 123.1 (CH), 122.4 (q, J = 272.9, C), 57.6 (CH), 54.9 (CH_2), 33.1 (CH_2), 24.8 (CH_2), 22.8 (CH_2), 18.4 (CH_3); IR (film) 3222, 3069, 2943, 2861, 1655, 1553, 1455, 1380, 1281, 1134, 906, 848, 702, 682 cm^{-1}; HRMS (EI): Exact mass calculated for $C_{15}H_{16}F_6N_2O$ $[M]^+$: 354.1167 Found : 354.1157



5e

3,5-Bis(trifluoromethyl)-*N*-(2-propylpiperidin-1-yl)benzamide (5e) - (Table 2, entry 9). Synthesized according to general procedure **B1** (195 ºC, 24 h) using 3,5-bis(trifluoromethyl)-*N*'-((*Z*)-oct-5-enyl)benzohydrazide (0.0968 g, 0.253 mmol). The reaction mixture was concentrated under reduced pressure and isolated using flash chromatography (20 % EtOAc in hexanes). The title compound was obtained as a brown crystal (0.0511 g, 53 % yield). TLC R_f 0.63 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm 9.28 (s, 1H), 8.38 (s, 2H), 8.12 (s, 1H), 3.10 (d, J = 10.3 Hz, 1H), 2.87 (m, 4H), 1.82-1.49 (m, 5H), 1.28 (m, 2H), 0.83 (t, J = 6.6 Hz, 3H), ;^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm * *denotes traces of minor isomers* 161.5, 136.5, 129.85 (q, J = 33.6 Hz, 2CCF_3), *127.8, 122.50 (q, J = 273 Hz,2 CF_3) 127.4, 123.1, 62.0, 55.1, 34.2, 29.9, 24.5, 22.8, 17.2, 13.2. HRMS (EI): Exact mass calculated for $C_{17}H_{20}F_6N_2O$ $[M]^+$: 382.148; found: 382.146.

Initial lead in intermolecular reactivity of hydrazides (eq 1):



7 **8** **9**

***N*'-(Bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)benzohydrazide (8) and *N*',*N*'-di(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)benzohydrazide (9) – (equation 1):** In a 2 mL Biotage sealed tube were transferred 3,5-bistrifluoromethylbenzhydrazide (0.356 g, 1.31 mmol) and norbornene (13.1 mmol), which following an argon purge for 5 min., were diluted with trifluorotoluene (0.65 mL). After heating for 10 hours at 160 ºC in the microwave, the solvent was evaporated and a NMR yield was taken (using dimethoxybenzene internal standard). The mono- and bis-hydroamination products (**8** and **9** respectively)[7] were obtained in a 59 % NMR yield (1:1.56 ratio). Some left over material (34%) and a condensation product (diacylhydrazine) derived from the starting material (7%) were also present. Column chromatography (8-12 %

7. Product **9**, resulting from 2 hydroamination events, is likely present as a mixture of diastereoisomers of the same R_f. The high temperature NMRs in DMSO-d_6 do not allow for differentiation between two diastereoisomers or residual rotomers being present.

EtOAc / hexanes) afforded the products for characterization purposes. **8:** TLC R_f 0.43 (20% EtOAc/hexanes). ^{1}H-NMR (300 MHz; DMSO-d_6, 120 ºC): δ 8.13 (s, 2H), 8.00 (s, 1H), 4.12-4.05 (m, 1H), 2.46-2.29 (m, 3H), 1.84 (t, J = 9.3, 2H), 1.66-1.29 (m, 4H), 1.22-1.07 (m, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz, 120 ºC): δ ppm 166.8, 139.8, 129.3 (q, J = 33.0 Hz, **C**CF_3), 127.9, 122.5 (q, J = 273 Hz, **C**F_3), 59.3, 40.7, 35.8, 35.6, 34.7, 27.4, 26.9. IR (film): 3351, 3241, 2958, 2875, 1635, 1340, 1279, 1170, 1134, 905, 763, 750. HRMS (EI): Exact mass calculated for $C_{16}H_{16}F_6N_2O$ [M]+: 366.11668. Found: 366.11836. **9:** TLC R_f 0.38 (20% EtOAc/hexanes). ^{1}H NMR (300 MHz; DMSO, 120 ºC): δ 9.01 (s, 1H), 8.40 (s, 2H), 8.13 (s, 1H), 3.10-2.92 (m, 2H), 2.36 (s, 2H), 2.20 (s, 2H), 1.71-1.25 (m, 10H), 1.21-0.91 (m, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz, 120 ºC): δ ppm 162.6, 136.4, 130.1 (q, J = 34.1 Hz, **C**CF_3), 127.3, 123.4, 122.5 (q, J = 273 Hz, **C**F_3), 65.6, 65.2, 38.5, 38.4, 36.2, 35.8, 34.9, 34.8, 34.7, 34.6, 27.5, 27.5, 27.0, 26.9. IR (film): 3309, 3252, 2960, 2876, 1656, 1276, 1176, 1134, 764, 750 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{23}H_{26}F_6N_2O$ [M]+: 460.19493. Found: 460.19104.

Optimization of the Reaction Conditions for Intermolecular Reactivity:

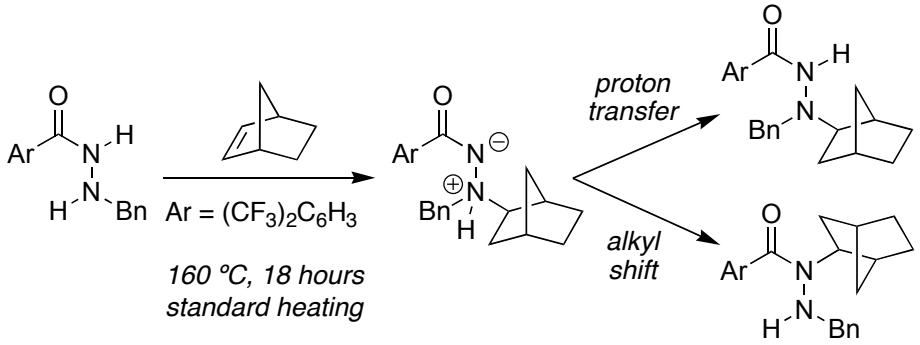


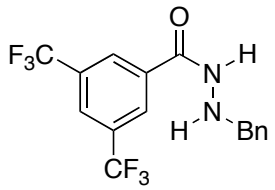
Table 3 Solvent scan for *N'*-benzyl-3,5-bis(trifluoromethyl)benzohydrazide

Entry	Solvent[a]	NMR Conversion[b]	Ratio Proton Transfer: [1,2] Rearrangement
1	**$PhCF_3$**	**63%**	**2.7 : 1**
2	$CHCl_3$	49%	2.3 : 1
3	MeCN	38%	2.8 : 1
4	DMSO	27%	2.9 : 1
5	Dioxane	42%	2.0 : 1
6	***t*-BuOH**	**64%**	**2.6 : 1**

[a] Solvents used as received from commercial supplier
[b] NMR Conversions determined by ^{1}H NMR (at 120 ºC) using 1,4-dimethoxybenzene as internal standard

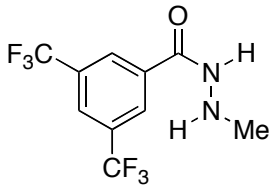
Procedures for the Intermolecular Hydrohydrazidation Scope (Table 3):

General Procedure C. Procedure for Intermolecular Hydrohydrazidation. To a Biotage sealed tube equipped with a magnetic stir bar was added the hydrazide, norbornene (10 equiv.), and trifluorotoluene (2 M).[8] The tube was sealed and heated in a wax bath at 160 ˚C for 18-40 h. After cooling to room temperature, the reaction was transferred to a round bottom flask through chloroform rinses. The reaction was concentrated in vacuo to give the crude products, which were then purified by flash chromatography to afford both hydroamination products.



10a

***N*'-Benzyl-3,5-bis(trifluoromethyl)benzohydrazide (10a) (Table 3, entry 1).** Synthesized according to General Procedure **A2** on 3,5-bistrifluoromethylbenzhydrazide (4.30 g, 15.2 mmol) and benzaldehyde (2.02 g, 19.0 mmol). Isolated 3.18 g (56 % yield) of the titled compound as a white solid after column chromatography (20% EtOAc/hexanes). TLC R_f 0.77 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.13 (s, 2H), 8.00 (s, 1H), 7.41-7.27 (m, 5H), 4.11 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 164.4, 136.8, 134.7, 132.2 (q, J = 34.0 Hz, **C**CF_3), 129.0, 128.6, 127.9, 127.4, 125.4, 122.8 (q, J = 273.0 Hz, **C**F3), 55.7. IR (film): 3268, 3097, 3070, 3032, 2930, 2861, 1645, 1542, 1447, 1375, 1333, 1140 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{16}H_{12}F_6N_2O$ [M]+: 362.0854. Not Found. HRMS (EI): Exact mass calculated for C_7H_8N [M–3,5-bis(trifluoromethyl)benzoamide]+: 106.0657. Found: 106.0652.

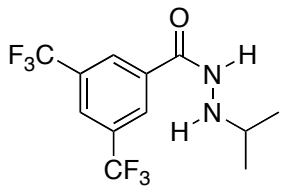


10b

3,5-Bis(trifluoromethyl)-*N*'-methylbenzohydrazide (10b) - (Table 3, entry 2). To *N*'-benzyl-3,5-bis(trifluoromethyl)benzohydrazide (0.400 g, 1.10 mmol) was dissolved in THF:DMF 4:1 (11 mL) and cooled to 0 ºC. While keeping constant stirring, sodium hydride 95 % (0.029 g, 1.2 mmol) was added to the reaction. Methyl iodide (0.34 mL, 5.5 mmol) was added and within 5 minutes, a solid crashed out of solution, and the solution became clear and colorless. Following a quench with water, the THF was evaporated over 20 minutes. The resulting slurry was taken in EtOAc, washed with brine:H_2O 1:1 (5 x 4 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the crude *N*'-benzyl-*N*'-methyl-3,5-bis(trifluoromethyl)benzohydrazide. *Benzyl Cleavage*: The unpurified hydrazide (1.00 g, 266 mmol) was added to a flame dried round-bottom flask and diluted with EtOAc (133 mL). Palladium on Carbon (10 wt%, 0.330 g) was added in 2 portions, followed by 5 subsequent purges with high vacuum and refilling with hydrogen

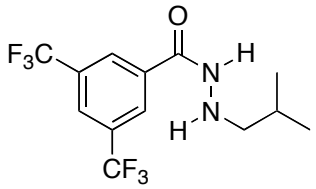
8. The size of the sealed tube is selected between 0.2, 2.0, 5.0 and 20 mL in order to minimize head space. Excess headspace in the reaction can lower the yield due to the volatility of norbornene.

atmosphere. The reaction was left to stir overnight under a hydrogen atmosphere and then showed complete conversion by TLC. Filtration over celite, followed by concentration under reduced pressure and silica-gel column chromatography (50% EtOAc/Hexanes) gave the title compound (0.501 g, 65 %), TLC R_f 0.24 (50% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 400 MHz): δ ppm 10.51 (br s, 1H), 8.47 (s, 2H), 8.32 (s, 1H), 5.28 (br s, 1H), 2.57 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ ppm 161.9, 135.5, 130.5 (q, J = 33.4 Hz, **C**CF_3), 127.8, 124.8, 123.1 (q, J = 273 Hz, **C**F_3), 38.3. IR (film): 3306, 3279, 3058, 2994, 2306, 1652, 1447, 1276, 1135, 915, 888, 748 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{10}H_8F_6N_2O$ [M]+: 286.05408. Found: 286.05267.



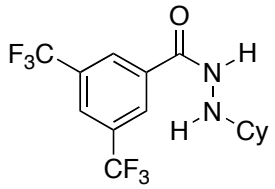
10c

3,5-Bis(trifluoromethyl)-*N*'-isopropylbenzohydrazide (10c) - (Table 3, entry 3). Synthesized according to General Procedure **A2** on 3,5-bistrifluoromethylbenzhydrazide (1.30 g, 4.77 mmol) and acetone (0.346 g, 5.96 mmol). Isolated 1.12 g (75% yield) of the title compound as a white solid after column chromatography (20% EtOAc/hexanes). TLC R_f 0.58 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.28 (s, 2H), 7.99 (s, 1H), 3.29-3.16 (m, 1H), 1.09 (dd, J = 6.2, 1.7 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.7, 134.9, 132.3 (q, J = 34.0 Hz, **C**CF3), 127.4, 125.3, 122.8 (q, J = 272.9 Hz, **C**F3), 51.6, 20.7. IR (film): 3747, 3283, 3093, 2975, 2937, 2873, 1649, 1546, 1451, 1379, 1341, 1284, 1136 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{12}H_{12}F_6N_2O$ [M]+: 314.0854. Found: 314.0856.



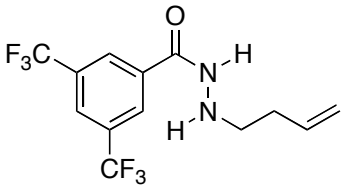
10d

3,5-Bis(trifluoromethyl)-*N*'-isobutylbenzohydrazide (10d) - (Table 3, entry 4). Synthesized according to General Procedure **A2** on 3,5-bistrifluoromethylbenzhydrazide (1.87 g, 6.87 mmol) and isobutyraldehyde (0.597 mL, 6.54 mmol). Isolated 1.17 g (54 % yield) of the title compound as a white solid after column chromatography (15% EtOAc/hexanes). TLC R_f 0.37 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 8.44 (s, 2H), 8.13 (s, 1H), 2.72 (d, J = 6.6 Hz, 2H), 1.84-1.77 (m, 1H), 0.97 (d, J = 6.7 Hz, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ ppm 162.1, 135.4, 130.5 (q, J = 33.0 Hz, **C**CF_3), 127.8, 124.8, 123.1 (q, J = 273 Hz, **C**F3), 58.9, 26.4, 20.5. IR (film): 3273, 3097, 2963, 2875, 1645, 1615, 1455, 1380, 1276, 1183, 1140, 937, 909, 846, 764, 750 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{13}H_{14}F_6N_2O$ [M]+: 328.10103. Found: 328.09771.



10e

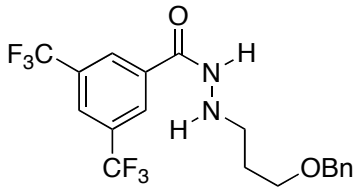
***N*'-Cyclohexyl-3,5-bis(trifluoromethyl)benzohydrazide (10e) (Table 3, entry 5).** Synthesized according to General Procedure **A2** on 3,5-bistrifluoromethylbenzhydrazide (1.17 g, 4.30 mmol) and cyclohexanone (0.527 g, 5.38 mmol). Isolated 0.820 g (54 % yield) of the title compound as a white solid after column chromatography (12% EtOAc/hexanes). TLC R_f 0.81 (50% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ ppm 8.20 (s, 2H), 8.01 (s, 1H), 2.98-2.87 (m, 1H), 1.97-1.87 (m, 2H), 1.82-1.72 (m, 2H), 1.67-1.59 (m, 1H), 1.36-1.09 (m, 5H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ ppm 164.4, 134.8, 132.1 (q, J = 33.99 Hz, **C**CF_3), 127.2, 125.2, 122.7 (q, J = 273.03 Hz, **C**F3), 59.2, 31.2, 25.7, 24.3. IR (film): 3747, 3276, 3089, 2934, 2854, 1641, 1539, 1451, 1371, 1276, 1136 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{15}H_{16}F_6N_2O$ [M]+: 354.1167. Found: 354.1149.



10f

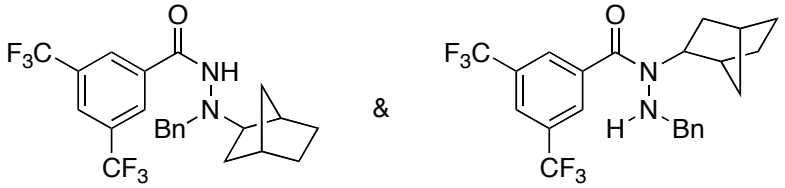
***N*'-(But-3-enyl)-3,5-bis(trifluoromethyl)benzohydrazide (10f) (Table 3, entry 6).** Prepared according to a modified procedure by Hansen.[9] 1-Bromobut-3-ene (0.600 mL, 5.92 mmol) and 3,5-bistrifluoromethyl-benzhydrazide (8.00 g, 29.6 mmol) were stirred in DMF (30 mL) at 100 °C for 15 hours. Ethyl actetate was added to the reaction mixture, and the resulting solution was washed with brine:H_2O 1:1 (5 x 60 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by silica gel chromatography (20 – 70 % EtOAc / Hexanes) gave the titled compound in 1.02 g (53 % yield). TLC R_f 0.68 (50% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 8.23 (s, 2H), 8.03 (s, 1H), 5.86 (ddt, J = 17.1, 10.2, 6.8 Hz, 1H), 5,19-5.08 (m, 2H), 3.08 (t, J = 6.9 Hz, 2H), 2.35 (q, J = 6.8 Hz, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 164.3, 135.4, 134.6, 132.4 (q, J = 33.9 Hz, **C**CF_3). 127.3, 125.4, 122.8 (q, J = 272.8 Hz, **C**F_3), 116.9, 51.1, 32.3. IR (film): 3233, 3085, 2929, 2868, 1648, 1561, 1386, 1277, 1169, 1140, 907 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{13}H_{12}F_6N_2O$ [M]+: 326.08538. Found: 326.08849.

9. Hansen, T. K. *Tetrahedron Lett.* **1999**, *40*, 9119.



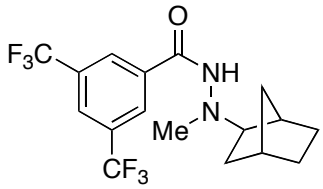
10g

***N*'-(3-(Benzyloxy)propyl)-3,5-bis(trifluoromethyl)benzohydrazide (10g) (Table 3, entry 7).** Synthesized according to General Procedure **A2** on 3,5-bistrifluoromethylbenzhydrazide (2.56 g, 9.41 mmol) and 3-benzyloxypropionaldehyde (1.70 g, 10.4 mmol). Isolated 2.04 g (52 % yield) of the titled compound as a white solid after column chromatography (30% EtOAc/hexanes). TLC R_f 0.18 (25% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz): δ ppm 8.45 (s, 2H), 8.12 (s, 1H), 7.33-7.25 (m, 5H), 4.50 (s, 2H), 3.60 (t, J = 6.3 Hz, 2H), 2.99 (t, J = 6.9 Hz, 2H), 1.82 (quintet, J = 6.6 Hz, 2H).^{13}C NMR (DMSO-d_6, 75 MHz): δ ppm 161.2, 138.3, 135.6, 130.3 (q, J = 33.1 Hz, **C**CF_3), 127.1, 126.6, 126.4, 125.8, 123.4, 123.4, 123.3, 122.5 (q, J = 272.7 Hz, **C**F_3), 71.5, 67.6, 48.0, 27.6. IR (film): 3280, 3096, 3039, 2937, 2861, 1652, 1616, 1450, 1379, 1275, 1267, 1137, 908, 845, 763, 749 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{19}H_{18}F_6N_2O_2$ [M]+: 420.12725. Found: 420.12952.



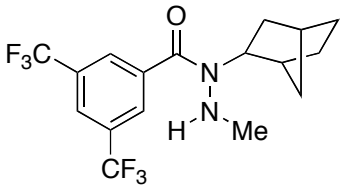
11a **12a**

***N*'-Benzyl-*N*'-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)benzohydrazide (11a) and *N*'-benzyl-*N*-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)benzohydrazide (12a) - (Table 3, entry 1).** Synthesized according to General Procedure **C** (160 °C, 40 h) on 0.636 mmol of the parent alkyl hydrazide. Isolated 0.153 g (61% yield) of **11a** as a white solid and 0.049 g (20% yield) of **12a** after column chromatography (12% EtOAc/hexanes). **11a**: TLC R_f 0.54 (20% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 9.30 (s, 1H), 8.17 (s, 2H), 8.04 (s, 1H), 7.38 (s, 2H), 7.30-7.12 (m, 3H), 4.08 (s, 2H), 3.17 (s, 1H), 2.88 (s, water), 2.38 (s, 1H), 2.27 (s, 1H), 1.80 (s, 1H), 1.64-1.37 (m, 4H), 1.20-1.02 (m, 3H). ^{13}C NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 162.2 (C), 137.8 (C), 136.4 (C), 129.9 (C), 128.1 (CH), 127.1 (CH), 127.0 (CH), 125.9 (CH), 123.1 (CH), 122.4 (CF_3), 67.8 (CH), 56.9 (CH_2), 39.0 (CH), 36.1 (CH_2), 35.2 (CH), 34.2 (CH_2), 27.7 (CH_2), 26.0 (CH_2). IR (film): 3238, 3070, 2953, 2867, 1652, 1550, 1447, 1379, 1349, 1276, 1185, 1128 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{23}H_{22}F_6N_2O$ [M]+: 456.1636. Not found. HRMS (EI): Exact mass calculated for $C_9H_5F_6N_2O$ [M-benzyl]+: 365.1089. Found: 365.1074. **12a**: TLC R_f 0.71 (20% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 7.95 (s, 3H), 7.18-7.12 (m, 3H), 7.03-6.98 (m, 2H), 5.29 (t, J = 5.3 Hz, 1H), 3.85 (d, J = 5.3 Hz, 2H), 3.77 (dd, J = 7.7, 5.3 Hz, 1H), 2.79 (s, water), 2.28 (s, 1H), 1.95-1.81 (m, 2H), 1.61 (ddd, J = 12.4, 8.2, 1.9 Hz, 1H), 1.51-1.44 (m, 2H), 1.27- 1.04 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 167.8 (C), 139.5 (C), 136.5 (C), 129.4 (q, J = 33.2 Hz, C), 128.0 (CH), 127.5 (CH), 127.5 (CH), 127.2 (CH), 126.4 (C), 122.4 (q, J = 273 Hz, CF_3), 121.5 (td, J = 7.6, 3.8 Hz, CH), 61.1 (CH), 53.7 (CH_2), 40.0 (CH), 36.1 (CH_2), 35.3 (CH_2), 34.9 (CH), 27.1 (CH_2), 26.9 (CH_2). IR (film): 2956, 2926, 2877, 1637, 1326, 1276, 1166, 1136, 1086 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{23}H_{22}F_6N_2O$ [M]+: 456.1636. Found: 456.1653.



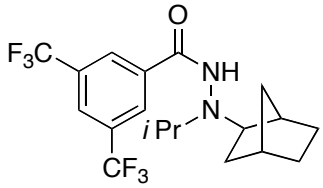
11b

&



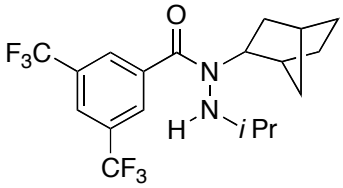
12b

***N*'-(Bicyclo-[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-methylbenzohydrazide (11b) and *N*-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-methylbenzohydrazide (12b) - (Table 3, entry 2).** Synthesized according to General Procedure **C** the parent alkyl hydrazide (0.139 g, 0.487 mmol) and norbornene, reacted for 18 hours at 160 °C. Isolated 0.128 g of **11b** as a white solid and 0.030 g of **12b** (85 % yield, 4.28:1) after column chromatography (10–20% EtOAc/hexanes). **11b**: TLC R_f 0.48 (25% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ 9.45 (br s, 1H), 8.40 (s, 2H), 8.13 (s, 1H), 2.94 (s, 1H), 2.61 (s, 3H), 2.27-2.21 (m, 2H), 1.64 (br s, 1H), 1.50-1.27 (m, 3H), 1.10-1.02 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 161.5, 136.5, 130.0 (q, J = 33.0 Hz, **C**CF_3), 127.4, 123.4, 122.0 (q, J = 272.9 Hz, **C**F_3), 69.0, 41.8, 38.8, 35.9, 35.2, 34.1, 27.7, 25.9. IR (film): 3418, 3104, 2963, 1870, 1652, 1557, 1284, 1131 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{17}H_{18}F_6N_2O$ [M]+: 380.13233. Found: 380.13307. **12b**: TLC R_f 0.87 (25% EtOAc/hexanes). ^{1}H NMR (300 MHz; DMSO-d_6, 120 ºC): δ 8.09 (s, 2H), 8.04 (s, 1H), 4.97 (q, J = 5.0 Hz, 1H), 3.72 (dd, J = 8.0, 5.5 Hz, 1H), 2.85 (s, 1H), 2.47 (d, J = 5.5 Hz, 4H), 2.29 (s, 1H), 1.89 (t, J = 8.3 Hz, 2H), 1.57 (t, J = 11.3 Hz, 1H), 1.47 (t, J = 4.6 Hz, 2H), 1.16 (d, J = 9.7 Hz, 1H), 1.09-1.05 (m, 2H).^{13}C NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 168.6, 140.9, 130.8 (q, J = 33.3 Hz, **C**CF_3), 128.3, 123.6 (q, J = 273.1 Hz, **C**F_3), 122.8, 62.0, 41.5, 38.0, 37.0, 36.4, 36.0, 28.2. IR (film): 3351, 3298, 2957, 2875, 1642, 1415, 1385, 1327, 1280, 1165, 1137, 906 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{17}H_{18}F_6N_2O$ [M]+: 380.13233. Found: 380.13184.



11c

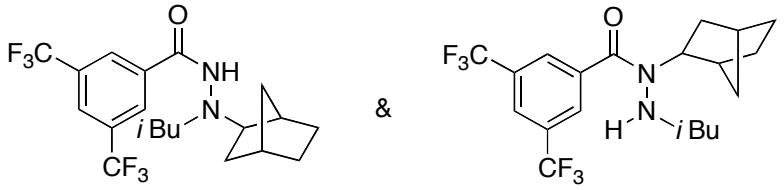
&



12c

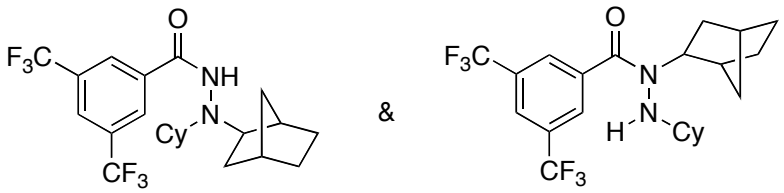
***N*'-(Bicyclo-[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-isopropylbenzohydrazide (11c) and *N*-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-isopropylbenzohydrazide (12c) - (Table 3, entry 3).** Synthesized according to General Procedure **C** (160 °C, 17 h) on *N*'-(but-3-enyl)-3,5-bis(trifluoromethyl)-benzohydrazide. (0.636 mmol). Isolated 0.123 g (47% yield) of **11c** as a white solid and 0.070 g (27% yield) of **12c** after column chromatography (12% EtOAc/hexanes). **11c**: TLC R_f 0.34 (20% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 8.82 (s, 1H), 8.41 (s, 2H), 8.08 (s, 1H), 3.45-3.20 (m, 1H), 2.24 (d, J = 19.9 Hz, 2H), 1.72 (d, J = 7.8 Hz, 1H), 1.57-1.20 (m, 5H), 1.16-0.94 (m, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 163.1, 136.7, 130.1 (q, J = 32.8 Hz, **C**CF_3), 127.3, 123.1, 122.5 (q, J = 273 Hz, **C**F_3), 64.4, 50.5, 38.8, 36.1, 35.1, 34.2, 27.7, 26.2, 17.7, 17.1. IR (film): 3264, 3074, 2960, 2873, 1653, 1550, 1466, 1447, 1387, 1341, 1280, 1174, 1132 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{19}H_{22}F_6N_2O$ [M]+: 408.1636. Found: 408.1632. **12c**: TLC R_f 0.66 (20% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 8.14 (s, 2H), 8.00 (s, 1H), 4.93 (s, 1H), 3.77-3.66 (m, 1H), 3.19-3.06 (m, 1H), 2.28 (s, 1H), 1.87 (t, J = 13.2 Hz, 2H), 1.60 (dd, J = 11.2, 9.6 Hz, 1H), 1.49 (d, J = 7.9 Hz, 2H), 1.13 (t, J = 10.4 Hz, 3H), 0.83 (t, J = 7.1 Hz, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 168.5, 139.8, 129.4 (q, J = 33.2 Hz, **C**CF_3), 128.1, 122.4

(q, J = 273 Hz, **C**F_3), 121.6, 61.7, 48.5, 39.8, 36.0, 35.2, 34.8, 27.0, 27.0, 19.6, 19.5. IR (film): 3325, 3276, 2964, 2876, 1641, 1447, 1325, 1280, 1177, 1135 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{19}H_{22}F_6N_2O$ [M]+: 408.1636. Found: 408.1643.



11d **12d**

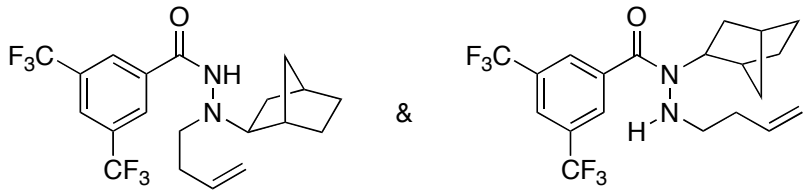
***N*'-(Bicyclo-[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-isobutylbenzohydrazide (11d) and *N*-(Bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-isobutylbenzohydrazide (12d) - (Table 3, entry 4).** Synthesized according to General Procedure **C** (160 °C, 17 h) on 3,5-bis(trifluoromethyl)-*N*'-isobutylbenzohydrazide (160 mg, 0.487 mmol). Isolated 0.115 g (53% yield) of **11d** as a white solid and 0.042 g (20% yield) of **12d** after column chromatography (5% EtOAc/hexanes). **11d**: TLC R_f 0.39 (10% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 9.19 (br s, 1H), 8.40 (s, 2H), 8.13 (s, 1H), 2.95-2.90 (m, 1H), 2.64-2.60 (m, 2H), 2.26-2.23 (m, 2H), 1.80-1.65 (m, 2H), 1.60-1.36 (m, 4H), 1.11-1.02 (m, 3H), 0.93-0.91 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 162.0, 136.4, 130.1 (1, J = 33.3 Hz, **C**CF_3), 127.2, 123.4, 122.5 (q, J = 273 Hz, **C**F_3), 68.1, 61.4, 39.5, 39.1, 36.1, 35.2, 34.1, 27.8, 25.9, 25.6, 19.9. IR (film): 3454, 3218, 3006, 2094, 1672, 1637, 1275, 1261, 764, 750 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{20}H_{24}F_6N_2O$ [M]+: 422.17928. Not Found. Exact mass calculated for $C_{17}H_{17}F_6N_2O$ [M-isopropyl]+: 379.1250. Found: 379.1183. **12d**: TLC R_f 0.55 (10% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 8.40 (br s, 1H), 8.10 (s, 2H), 8.02 (s, 1H), 4.84 (t, J = 5.9 Hz, 1H), 3.75 (dd, J = 7.8, 5.6 Hz, 1H), 2.59-2.55 (m, 2H), 2.29 (s, 1H), 1.91-1.87 (m, 2H), 1.63-1.60 (m, 1H), 1.53-1.47 (m, 3H), 1.18-1.09 (m, 3H), 0.71 (dd, J = 6.6, 2.6 Hz, 6H).. ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 167.8, 139.9, 129.6 (q, J = 33.3 Hz, **C**CF_3), 127.5, 122.5 (q, J = 273 Hz, **C**F_3), 121.5, 61.0, 57.9, 40.1, 36.0, 35.3, 34.9, 27.1, 27.1, 25.9, 19.3. IR (film): 2963, 2880, 1641, 1329, 1277, 1261, 1170, 1132, 764, 750 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{20}H_{24}F_6N_2O$ [M]+: 422.17928. Found: 422.1797.



11e **12e**

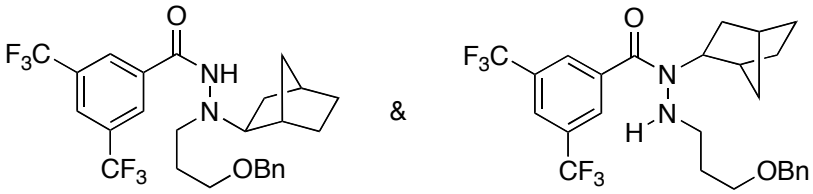
***N*'-Bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-cyclohexylbenzohydrazide (11e) and (*N*-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-cyclohexylbenzohydrazide (12e) - Table 3, entry 5).** Synthesized according to General Procedure **C** (160 °C, 40 h) on 0.565 mmol of the parent alkyl hydrazide. Isolated 0.169 g (67% yield) of **11e** as a white solid and 0.053 g (21% yield) of **12e** after column chromatography (10% EtOAc/hexanes). **11e**: TLC R_f 0.56 (20% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 8.91 (s, 1H), 8.41 (s, 2H), 8.10 (s, 1H), 3.10 (s, 1H), 2.24 (d, J = 22.9 Hz, 2H), 1.89 (s, 2H), 1.82-1.63 (m, 3H), 1.64-0.96 (m, 14H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 163.0, 136.5, 130.1, 127.4, 123.5, 122.6 (q, J = 273 Hz, **C**F_3), 63.7, 59.6, 38.7, 36.2, 35.2, 34.4, 28.5, 28.2, 27.8, 26.4, 25.2, 24.7. IR (film): 3241, 3067, 2941, 2861, 1656, 1561, 1550, 1451, 1379, 1345, 1280, 1159, 1132 cm^{-1}. HRMS

(EI): Exact mass calculated for $C_{22}H_{26}F_6N_2O$ [M]+: 448.1949. Found: 448.1949. **12e**: TLC R_f 0.85 (20% EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ ppm 8.15 (s, 2H), 8.00 (s, 1H), 4.90 (s, 1H), 3.70 (dd, J = 7.0, 5.9 Hz, 1H), 2.28 (s, 1H), 1.87 (t, J = 11.5 Hz, 2H), 1.64 (ap t, J = 9.3 Hz, 3H), 1.58-1.40 (m, 6H), 1.20-1.07 (m, 6H), 0.97-0.78 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 168.5, 139.8, 129.4 (q, J = 33.2 Hz, **C**CF_3), 128.2, 122.5 (q, J = 273 Hz, **C**F_3), 121.6, 61.7, 56.2, 39.8, 36.1, 35.2, 34.9, 29.9, 29.9, 27.1, 27.0, 24.8, 23.0, 22.9. IR (film): 3317, 3272, 2934, 2858, 1645, 1451, 1314, 1276, 1178, 1140 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{22}H_{26}F_6N_2O$ [M]+: 448.1949. Found: 448.1917.



11f **12f**

***N*'-(Bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-(but-3-enyl)benzohydrazide (11f) and *N*-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)-*N*'-(but-3-enyl)benzohydrazide (12f) - (Table 3, entry 6).** Synthesized according to General Procedure **C** on 0.487 mmol of the parent alkylated hydrazide and norbornene, reacted for 18 hours at 160 °C. Isolated 0.140 g of **11f** as a white solid and 0.038 g of **12f** (87 % yield, 3.68:1) after column chromatography (8% EtOAc/hexanes). **11f**: TLC R_f 0.31 (10% EtOAc/hexanes). ^{1}H NMR (300 MHz; DMSO-d_6, 120 ºC): δ 9.22 (br s, 1H), 8.42 (s, 2H), 8.12 (s, 1H), 5.93-5.84 (m, 1H), 4.99 (dd, J = 26.2, 13.7 Hz, 2H), 2.93 (dd, J = 12.9, 6.2 Hz, 3H), 2.27-2.22 (m, 4H), 1.69 (s, 1H), 1.50-1.34 (m, 4H), 1.07 (dd, J = 17.9, 8.8 Hz, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 162.2, 136.3, 130.1 (q, J = 33.9 Hz, CCF_3), 127.3, 123.4, 122.5 (q, J = 272.9 Hz, CF_3), 114.3, 67.7, 52.7, 38.9, 36.0, 35.2, 34.1, 30.8, 27.7, 26.0. IR (film): 3248, 2960, 2868, 1645, 1275, 1261, 1120, 763, 749 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{20}H_{22}F_6N_2O$ [M]+: 420.16363. Not found. Exact mass calculated for $C_{17}H_{17}F_6N_2O$ [M-allyl]+: 379.125. Found: 379.1259. **12f**: TLC R_f 0.51 (8% EtOAc/hexanes). ^{1}H NMR (500 MHz; benzene-d_6): δ ppm 7.93 (s, 2H), 7.73 (s, 1H), 5.65 (m, 1H), 5.01 (d, J = 17.1 Hz, 1H), 4.96 (d, J = 10.2 Hz, 1H), 4.35 (s, 1H), 3.45 (s, 1H), 2.81 (s, 1H), 2.71 (s, 1H), 2.03 (m, 4H), 1.85 (ap d, J = 6.6 Hz, 1H), 1.76 (ap d, J = 11.9 Hz, 1H), 1.24 (m, 3H), 0.95 (d, J = 9.1 Hz, 1H), 0.76 (d, J = 7.7 Hz, 2H). ^{13}C NMR (benzene-d_6, 125 MHz): δ ppm 168.5, 139.8, 135.7, 132.1 (q, J = 33.2 Hz, **C**CF_3), 128.5, 123.7 (q, J = 273 Hz, **C**F_3), 123.4, 116.5, 63.2, 50.8, 42.5, 37.2, 36.5, 36.4, 32.6, 28.5, 28.3. IR (film): 3336, 3279, 3086, 2957, 2875, 1643, 1414, 1327, 1280, 1169, 1138, 900, 840, 716, 705, 681 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{20}H_{22}F_6N_2O$ [M]+: 420.16363. Found: 420.16452.

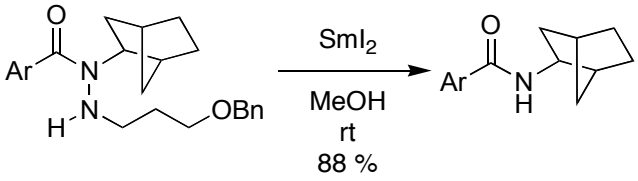


11g **12g**

***N*'-(3-(Benzyloxy)propyl)-*N*'-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)benzohydrazide (11g) and *N*'-(3-(benzyloxy)propyl)-*N*-(bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)benzohydrazide (12g) - (Table 3, entry 7).** Synthesized according to General Procedure **C** on 0.487 mmol of the parent alkylated hydrazide and norbornene, reacted for 18 hours at 160 °C. Isolated 0.166 g of **11g** as a white solid and 0.051 g of **12g** (86 % yield, 3.31:1) after column chromatography (15% EtOAc/hexanes). **11g**: TLC R_f 0.50 (25%

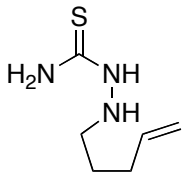
EtOAc/hexanes). ^{1}H NMR (DMSO-d_6, 300 MHz, 120 ºC): δ 9.31 (s, 1H), 8.43 (s, 2H), 8.17 (s, 1H), 7.37-7.20 (m, 5H), 4.45 (s, 2H), 3.59 (s, 2H), 2.93 (m, 3H), 2.30-2.17 (m, 2H), 1.78-1.65 (m, 3H), 1.45-1.37 (m, 4H), 1.09-1.03 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 162.2, 138.4, 136.2, 130.2 (q, J = 33.6 Hz, **C**CF_3), 127.5, 126.7, 126.5, 123.7, 122.6 (q, J = 273.0 Hz, **C**F_3), 71.5, 67.9, 67.4, 49.9, 39.1, 36.2, 35.3, 34.2, 27.9, 27.0, 26.0. IR (film): 3253, 3082, 2948, 2868, 2853, 1652, 1550, 1279, 1143, 1128 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{26}H_{28}F_6N_2O_2$ [M]+: 514.20550. Found: 514.19754. **12g**: TLC R_f 0.81 (25% EtOAc/hexanes). ^{1}H NMR (300 MHz; DMSO-d_6, 120 ºC): δ 8.10 (s, 2H), 8.03 (s, 1H), 7.34-7.24 (m, 5H), 4.94 (t, J = 5.9 Hz, 1H), 4.36 (s, 2H), 3.72 (dd, J = 7.4, 5.6 Hz, 1H), 3.33 (t, J = 6.3 Hz, 2H), 2.45 (s, 2H), 2.28 (s, 1H), 1.90-1.84 (m, 2H), 1.62-1.46 (m, 6H), 1.11 (dd, J = 19.5, 10.7 Hz, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 120 ºC): δ ppm 167.7, 139.7, 138.1, 129.6 (q, J = 33.1 Hz, **C**CF_3), 127.5, 127.3, 126.5, 126.4, 122.5 (q, J = 273.1 Hz, **C**F_3), 121.6, 71.4, 67.3, 61.1, 47.4, 40.2, 36.0, 35.3, 34.9, 27.2, 27.1. IR (film): 3282, 2955, 2873, 1641, 1326, 1279, 1268, 1169, 1137, 1101, 905, 848, 763, 749 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{26}H_{28}F_6N_2O_2$ [M]+: 514.20550. Found: 514.19897.

Cleavage of the *N*-*N* bond for proof of structure:



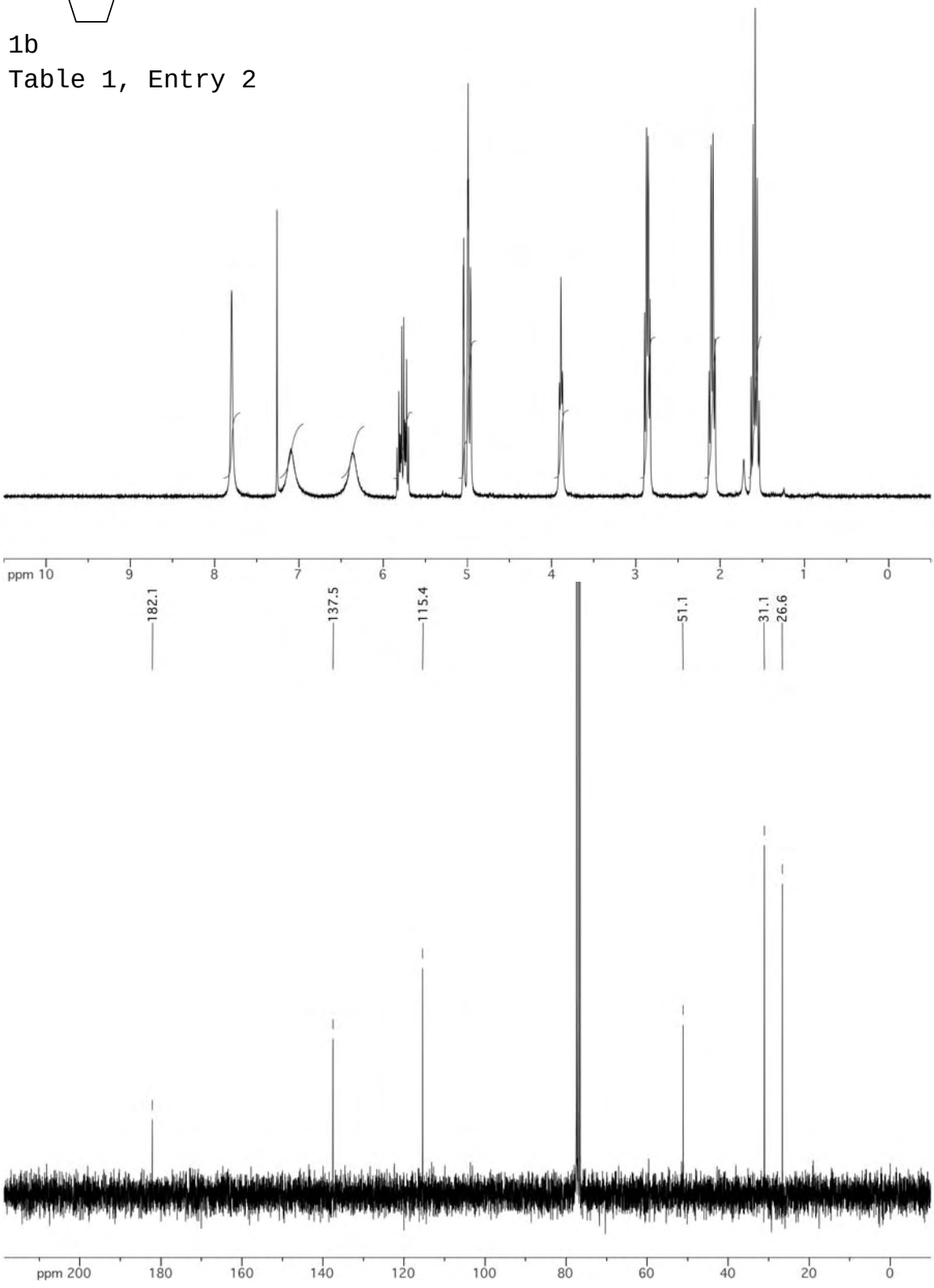
***N*-(Bicyclo[2.2.1]heptan-2-yl)-3,5-bis(trifluoromethyl)benzamide:** *SmI_2 preparation*: In a flame-dried round-bottom flask was added Sm powder (0.189 g, 1.28 mmol), which was stirred neat under high vacuum for 30 min. After purging with argon for 5 min, diiodoethane (freshly recrystallized, 0.282 g, 1.00 mmol) was added the resulting solid mixture was further purged for 15 min under high vacuum, and filled with argon. To the reaction flask was added freshly distilled THF (10 mL), to give a 0.1M solution of SmI_2. *Cleavage*: *Procedure adapted from the Maruoka group.*[10] To a stirred solution of the hydrazide (0.051 g, 0.10 mmol) in MeOH (0.5 mL) was added the SmI_2 in THF (0.1M) prepared above (4 mL) via syringe over 1 min. After 15 minutes of stirring at room temperature, the solution was shown to be complete by TLC analysis. The mixture was poured into sat. aq. $NaHCO_3$ and extracted 3 times with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Silica-gel chromatography (20% EtOAc/hexanes) afforded the cleaved amide (0.031 g, 88 %) as a colorless oil. TLC R_f 0.68 (25% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.16 (s, 2H), 7.99 (s, 1H), 5.95 (br s, 1H), 3.94 (t, J = 7.4, 3.7, 1H), 2.37-2.36 (m, 1H), 1.94 (ddd, J = 13.1, 8.0, 2.4, 2H), 1.62-1.51 (m, 2H), 1.44-1.19 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 163.9, 137.0, 132.1 (q, J = 33.3 Hz, **C**CF_3), 127.2, 124.8, 122.9 (q, J = 273 Hz, **C**F_3), 77.2, 53.9, 42.3, 40.3, 35.7, 28.0, 26.5. IR (film): 3295, 3074, 2959, 2880, 1641, 1616, 1549, 1279, 1176, 1134, 908, 702, 681 cm^{-1}. HRMS (EI): Exact mass calculated for $C_{16}H_{15}F_6NO$ [M]+: 351.10578. Found: 315.10766.

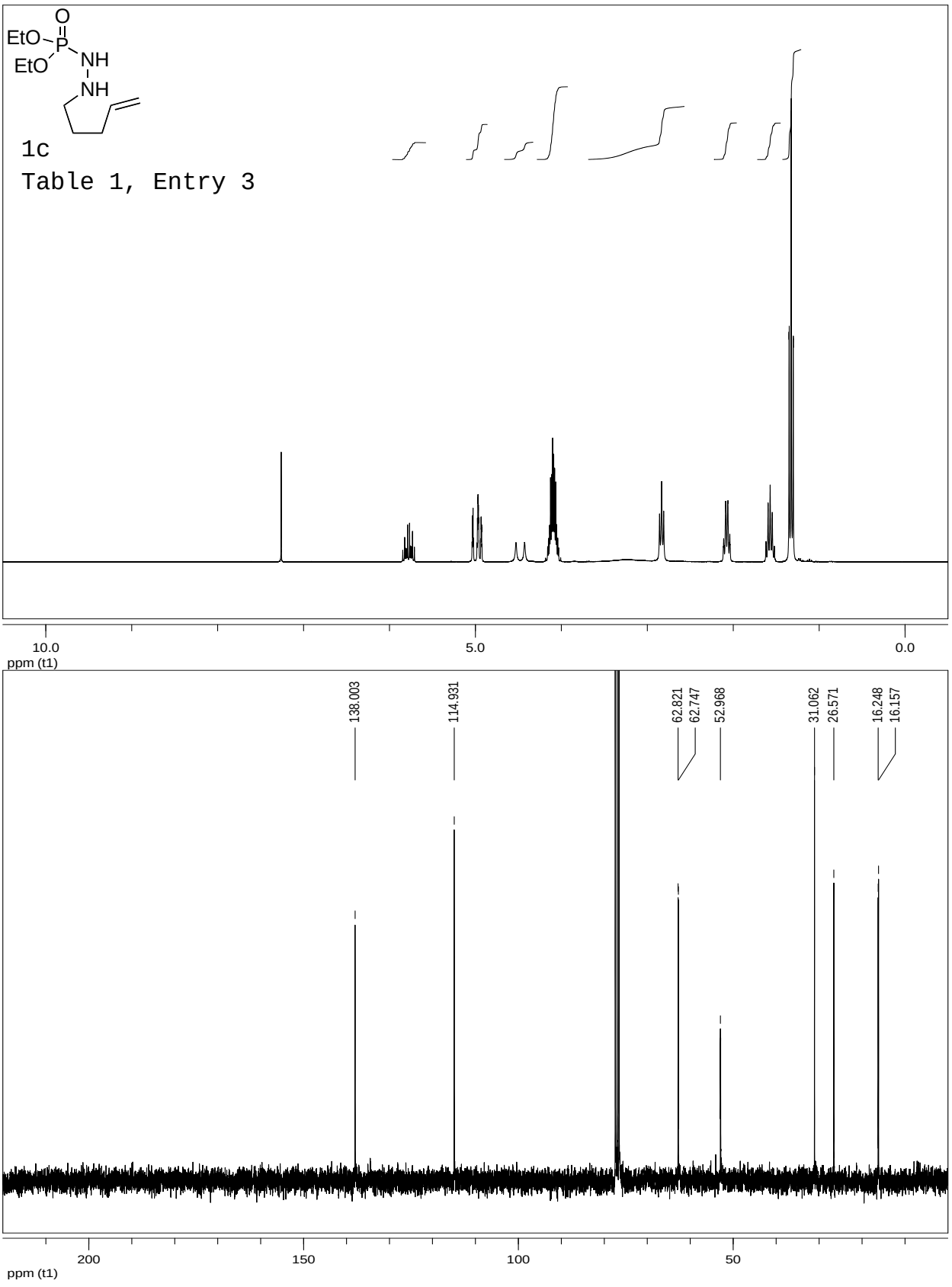
10. Hashimoto, T.; Maeda, Y.; Omote, M.; Nakatsu, H.; Maruoka, K. *J. Am. Chem. Soc.* **2010**, *132*, 4076

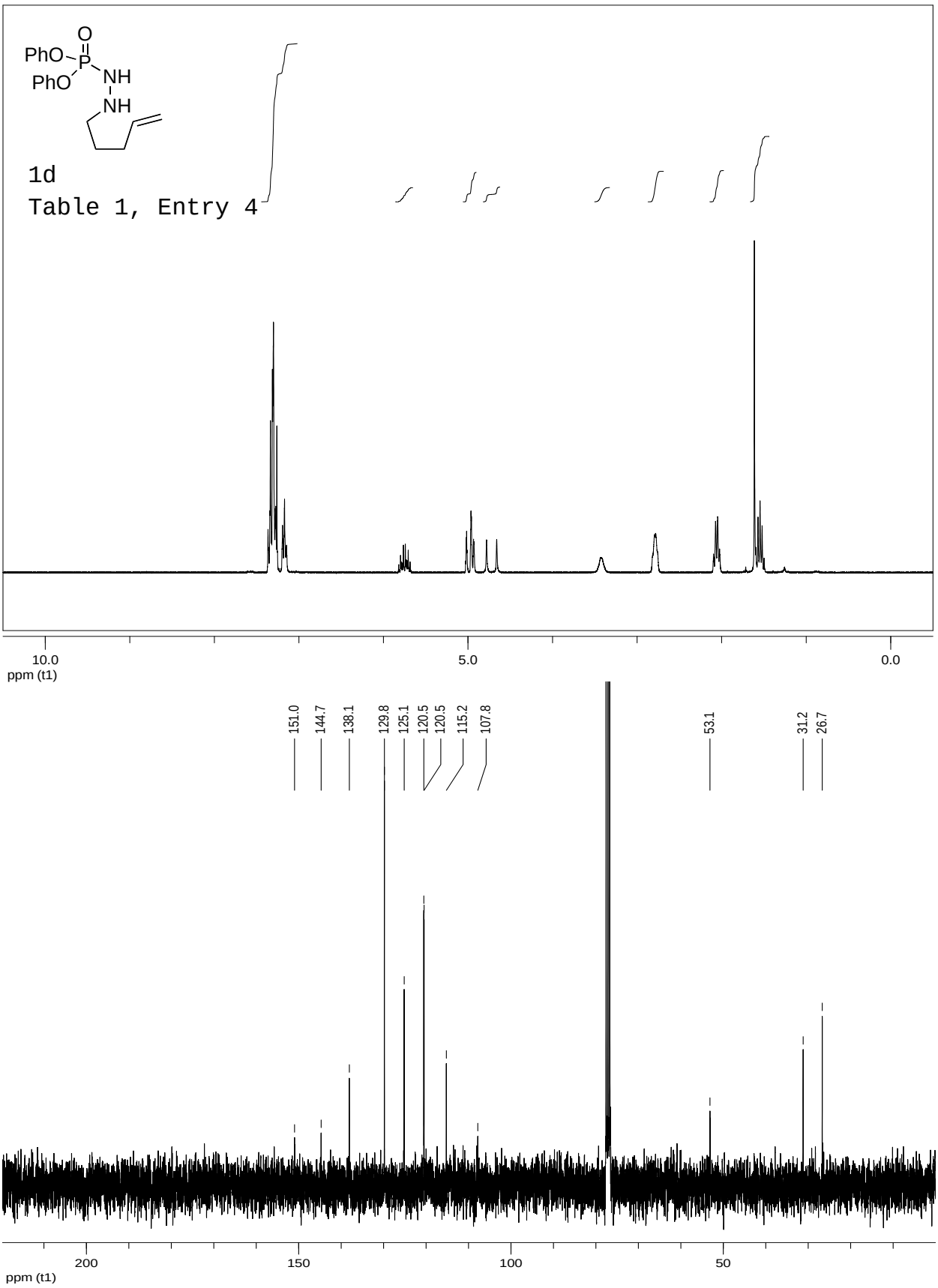


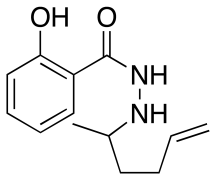
1b

Table 1, Entry 2



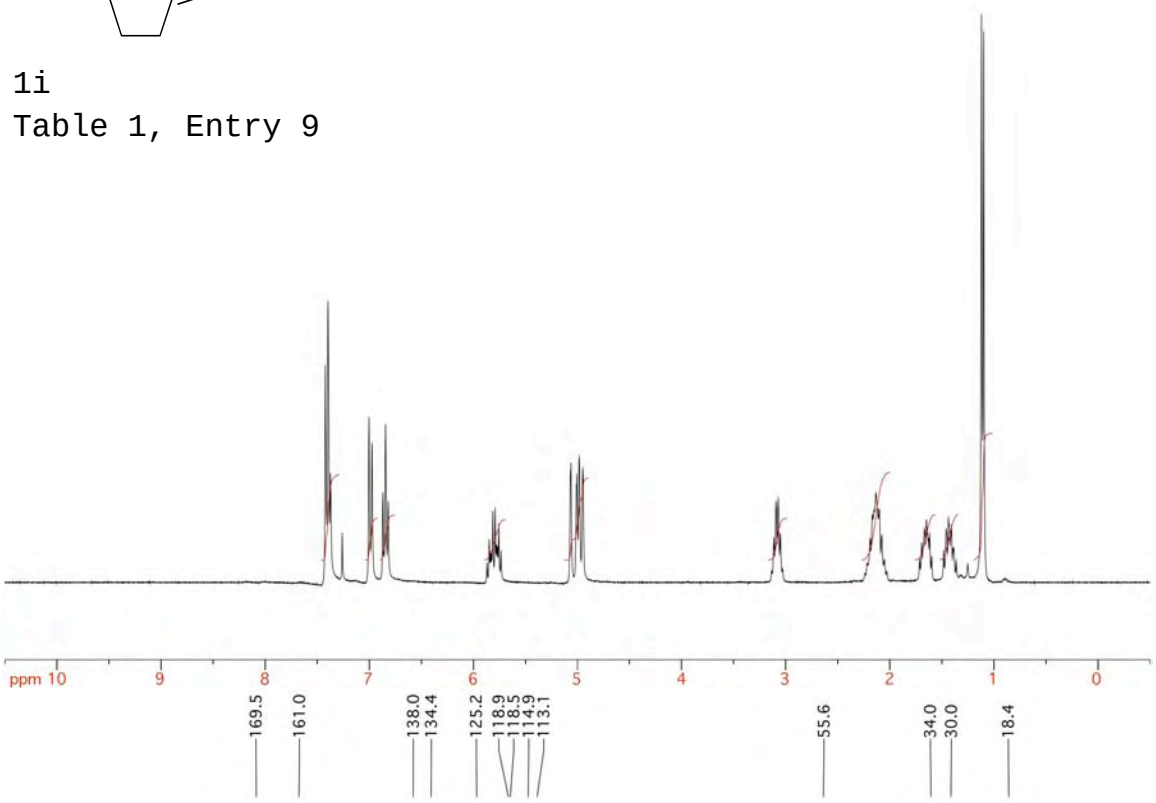

EtO
O
P
EtO
NH
NH
1c
Table 1, Entry 3
10.0
5.0
0.0
ppm (t1)
138.003
114.931
62.821
62.747
52.968
31.062
26.571
16.248
16.157
200
150
100
50
ppm (t1)

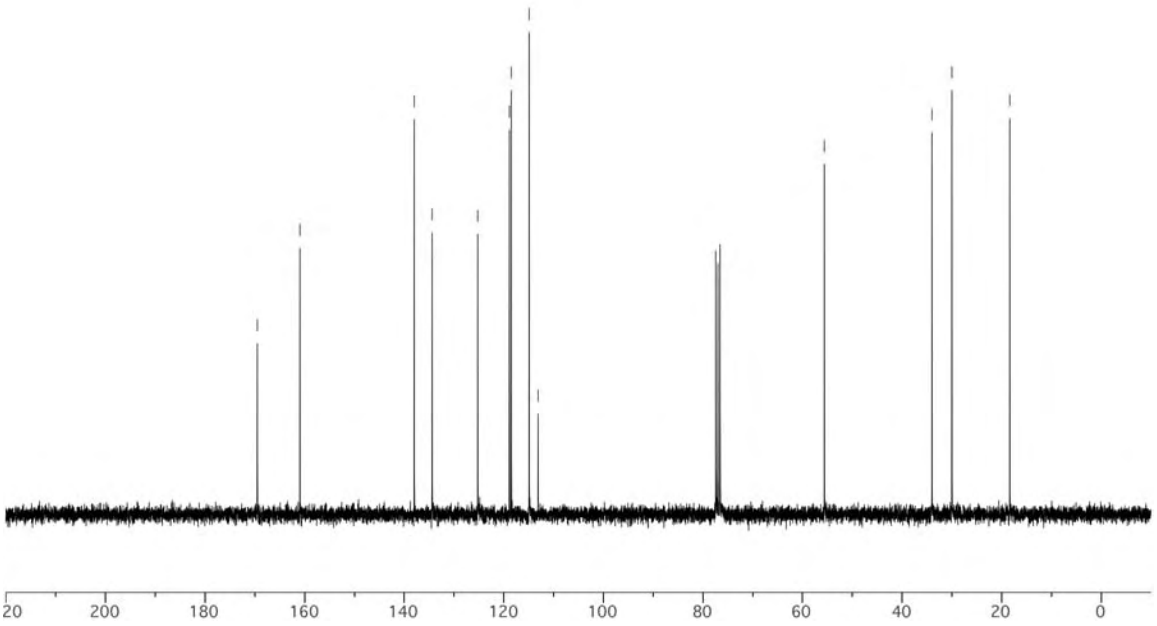

PhO
O
P
PhO
NH
NH
1d
Table 1, Entry 4
10.0
5.0
0.0
ppm (t1)
151.0
144.7
138.1
129.8
125.1
120.5
120.5
115.2
107.8
53.1
31.2
26.7
200
150
100
50
ppm (t1)

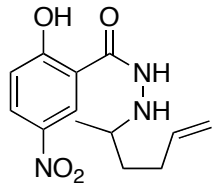


1i

Table 1, Entry 9

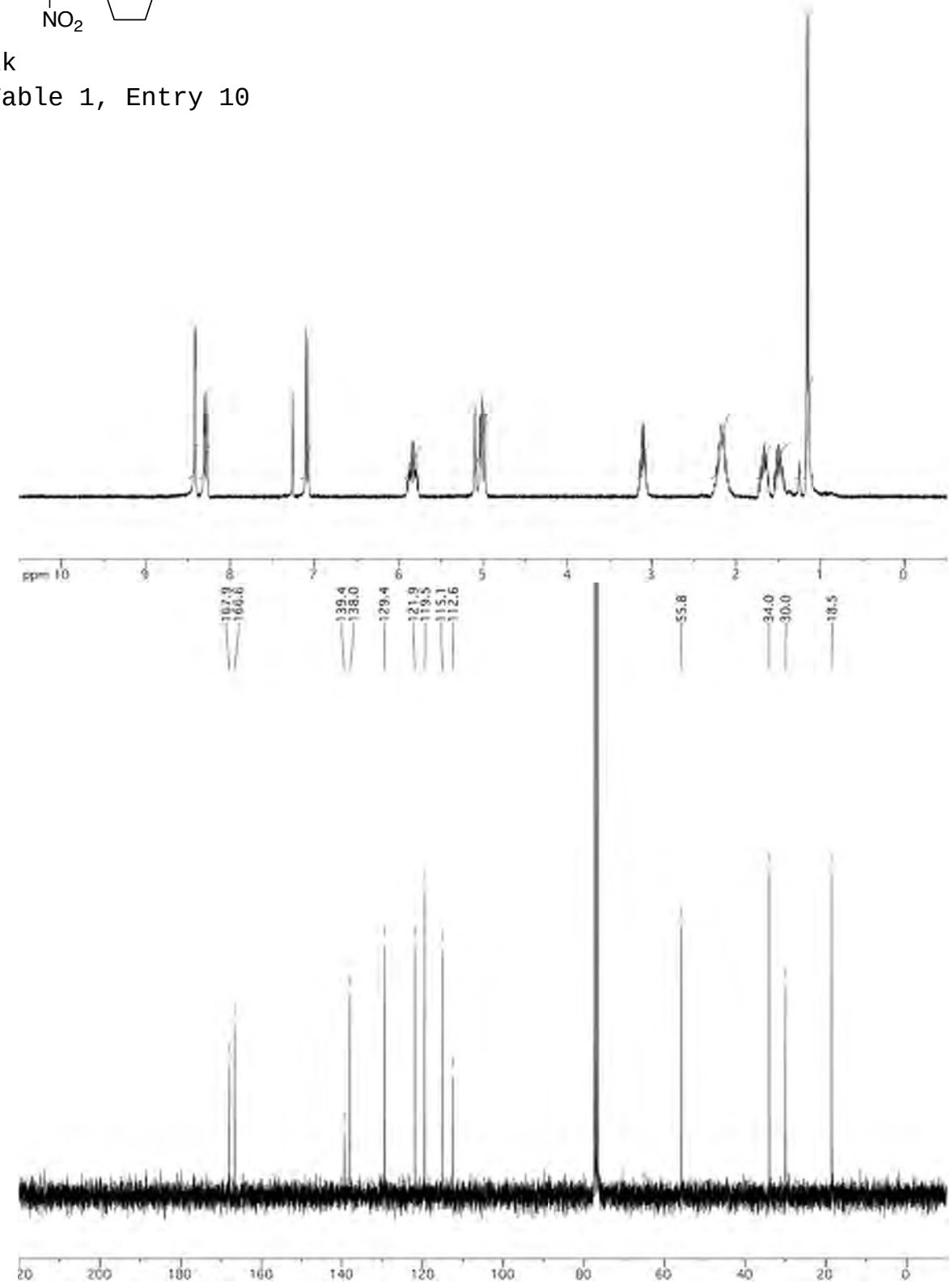


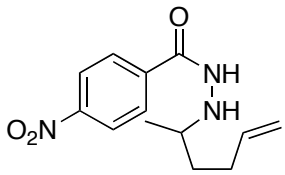




1k

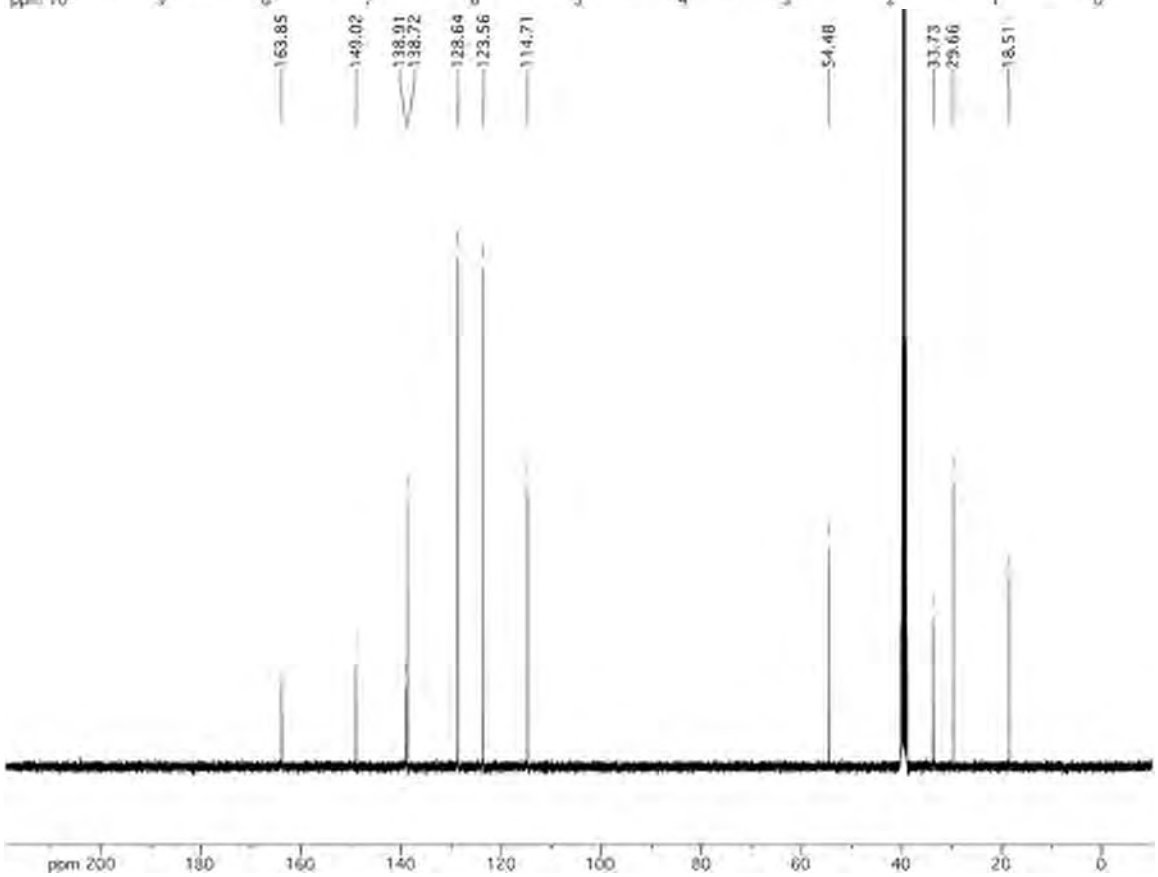
Table 1, Entry 10

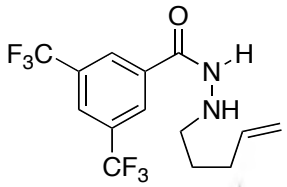




1j

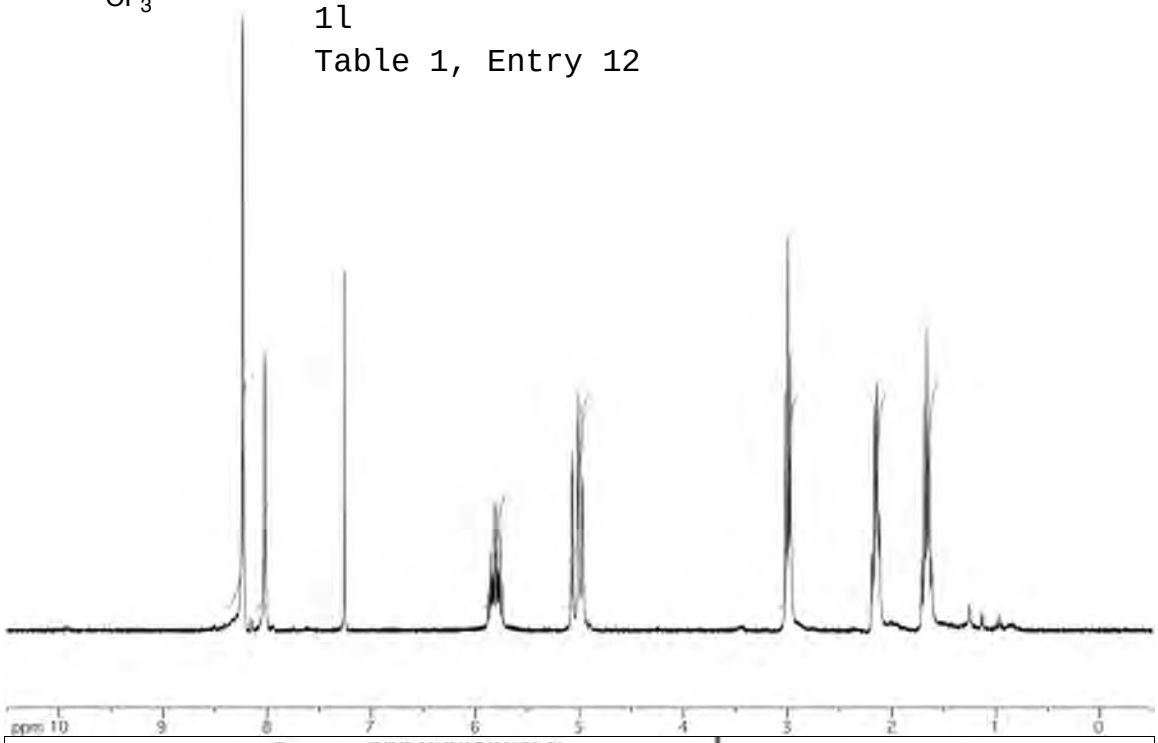
Table 1, Entry 11

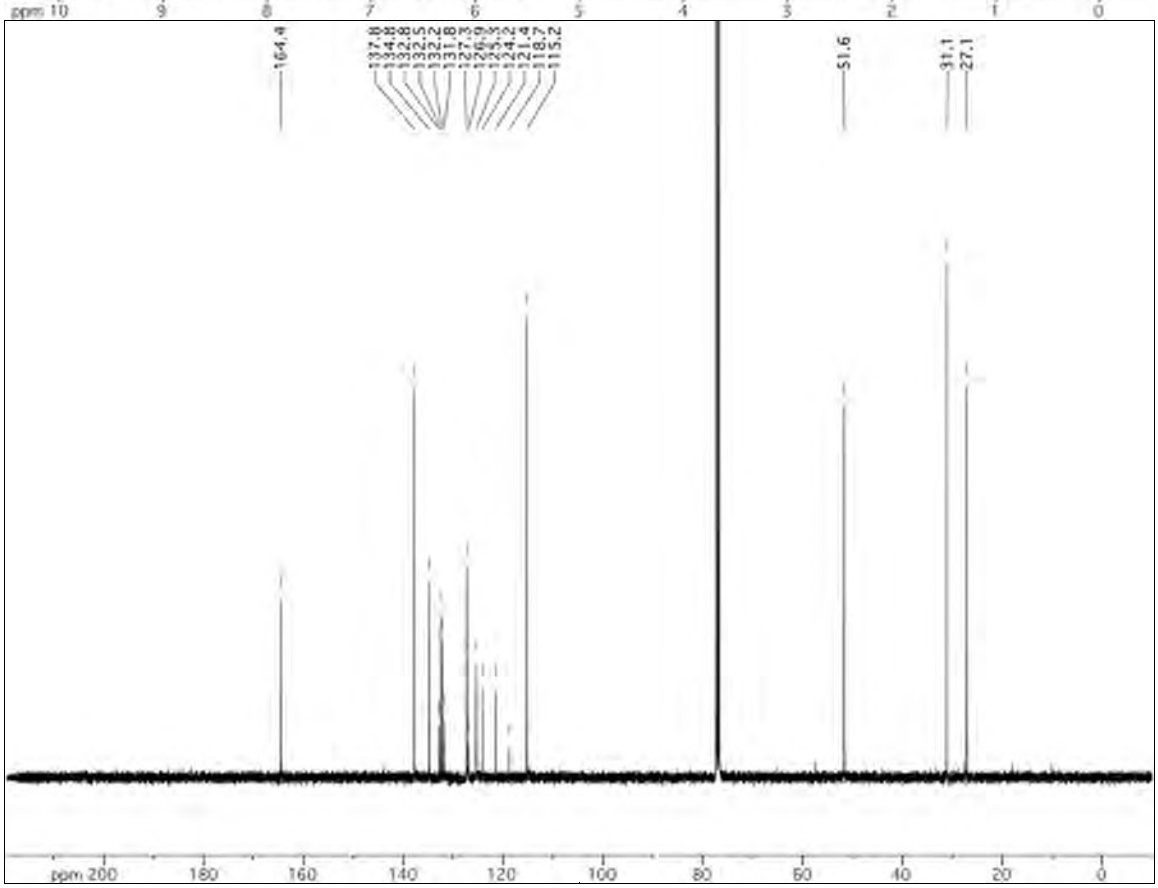


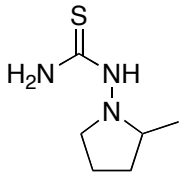


1l

Table 1, Entry 12

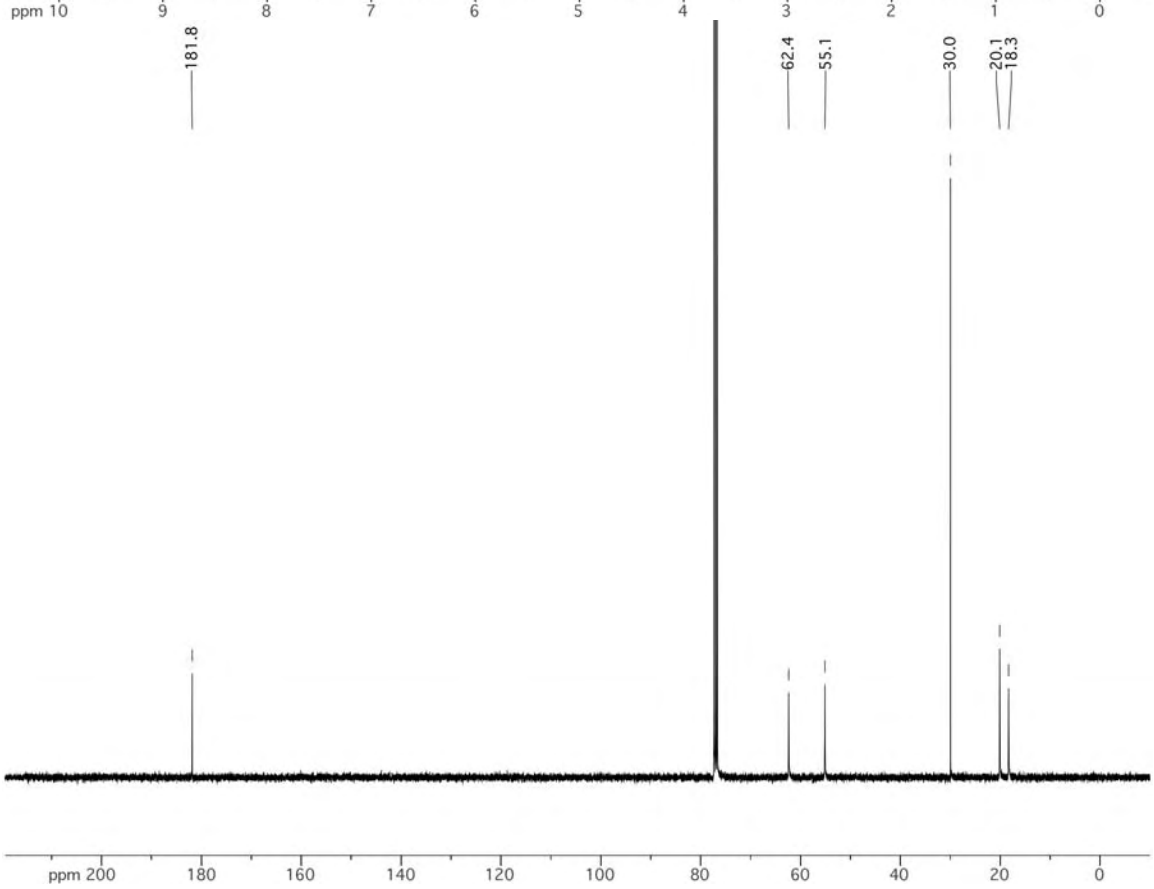


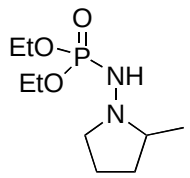




2b

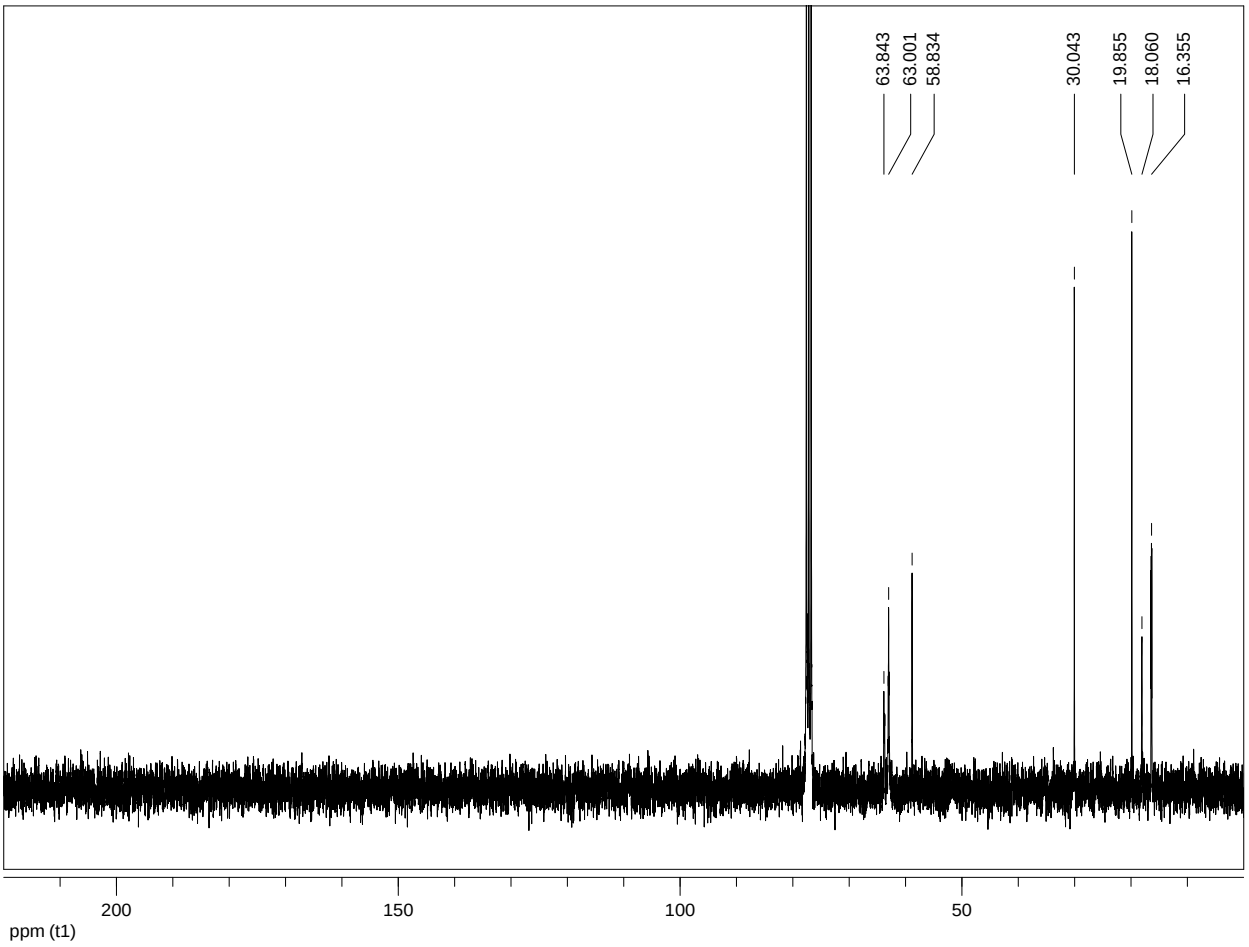
Table 1, Entry 2

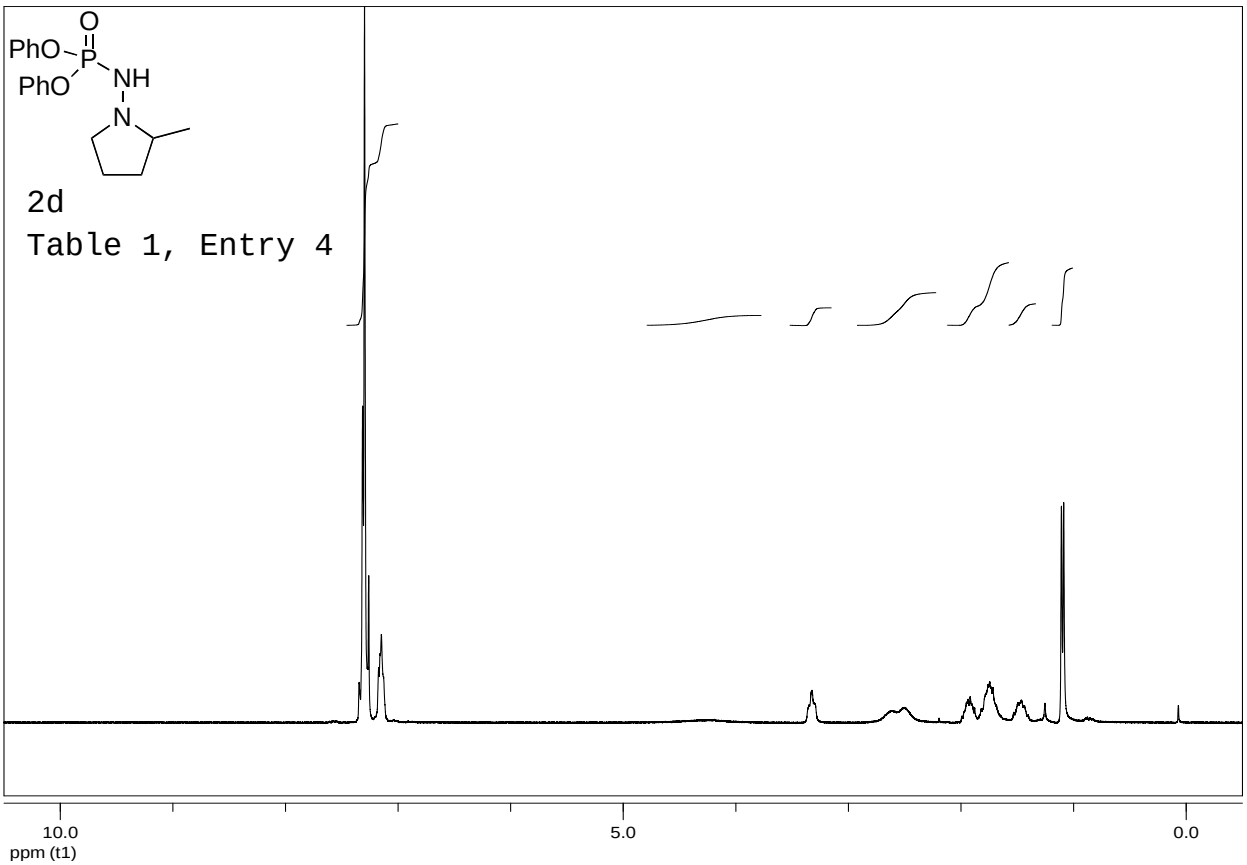


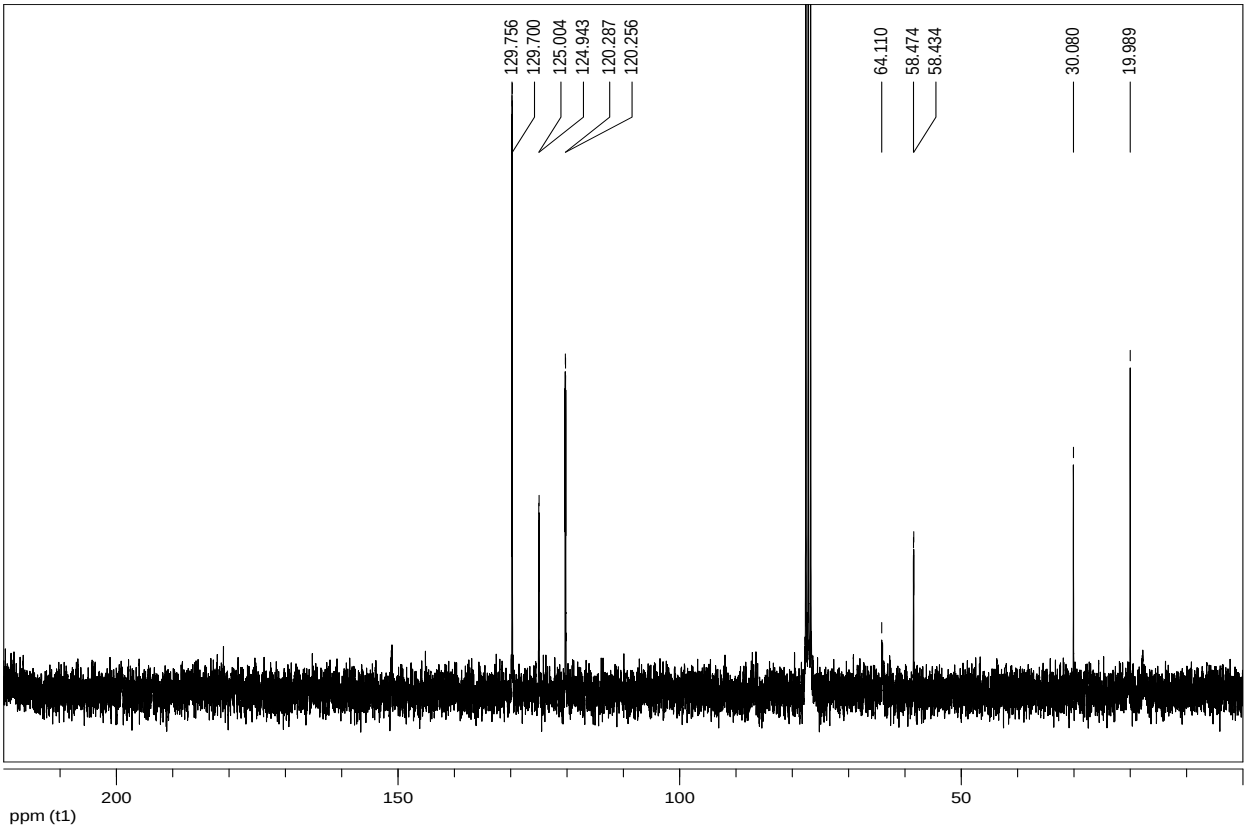


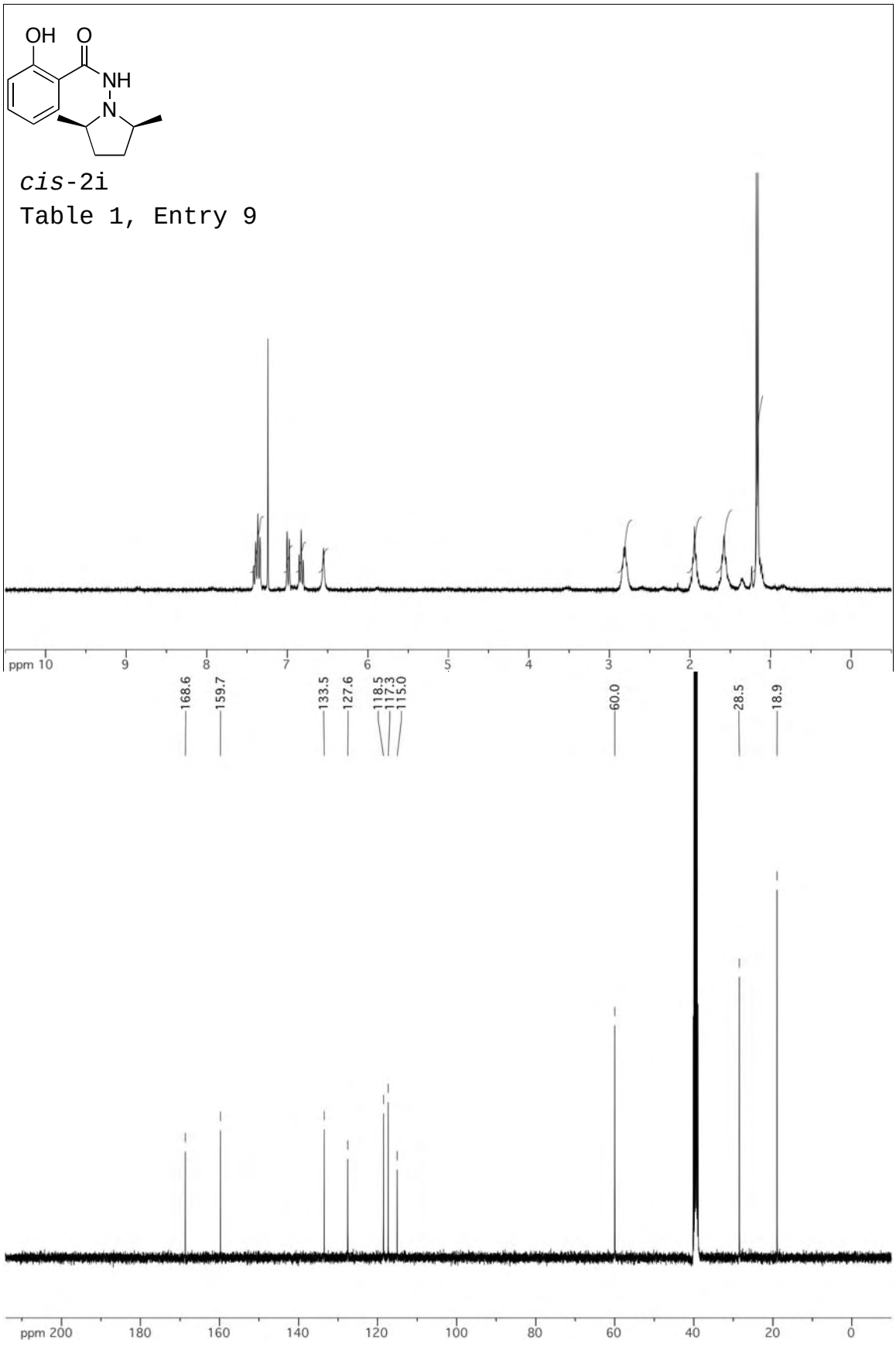
2c

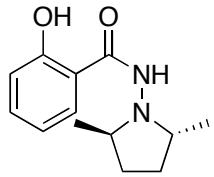
Table 1, Entry 3



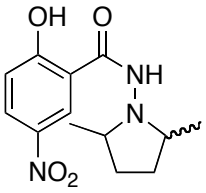

PhO
O
P
PhO
NH
N
2d
Table 1, Entry 4
10.0
5.0
0.0
ppm (t1)


129.756
129.700
125.004
124.943
120.287
120.256
64.110
58.474
58.434
30.080
19.989
200
150
100
50
ppm (t1)

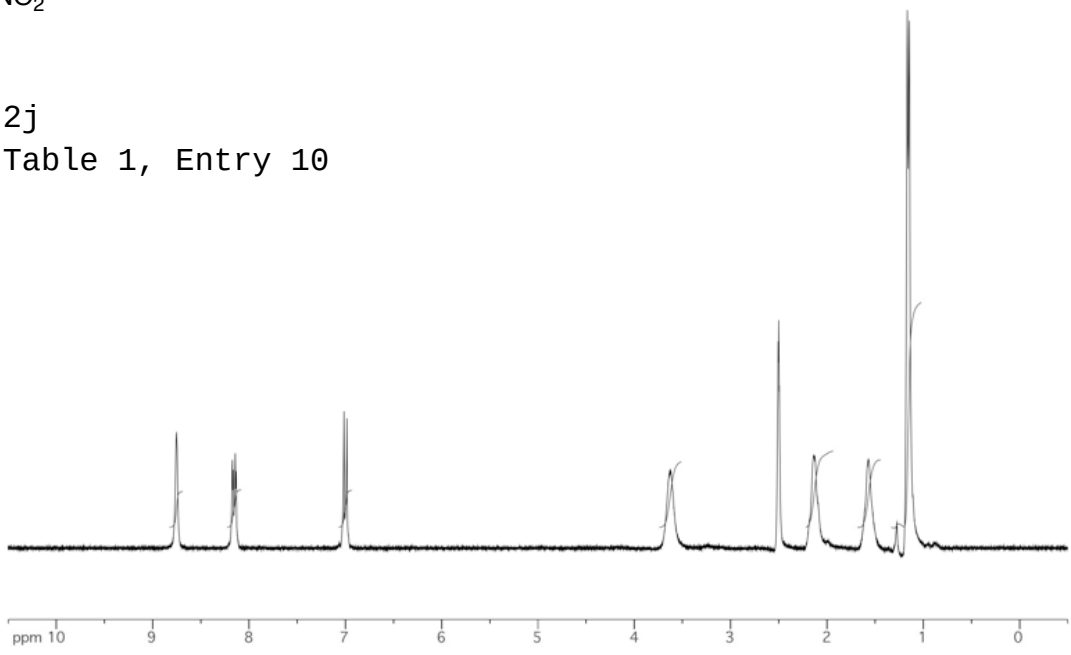

OH
O
NH
N
cis-2i
Table 1, Entry 9
ppm 10
9
8
7
6
5
4
3
2
1
0
168.6
159.7
133.5
127.6
118.5
117.3
115.0
60.0
28.5
18.9
ppm 200
180
160
140
120
100
80
60
40
20
0

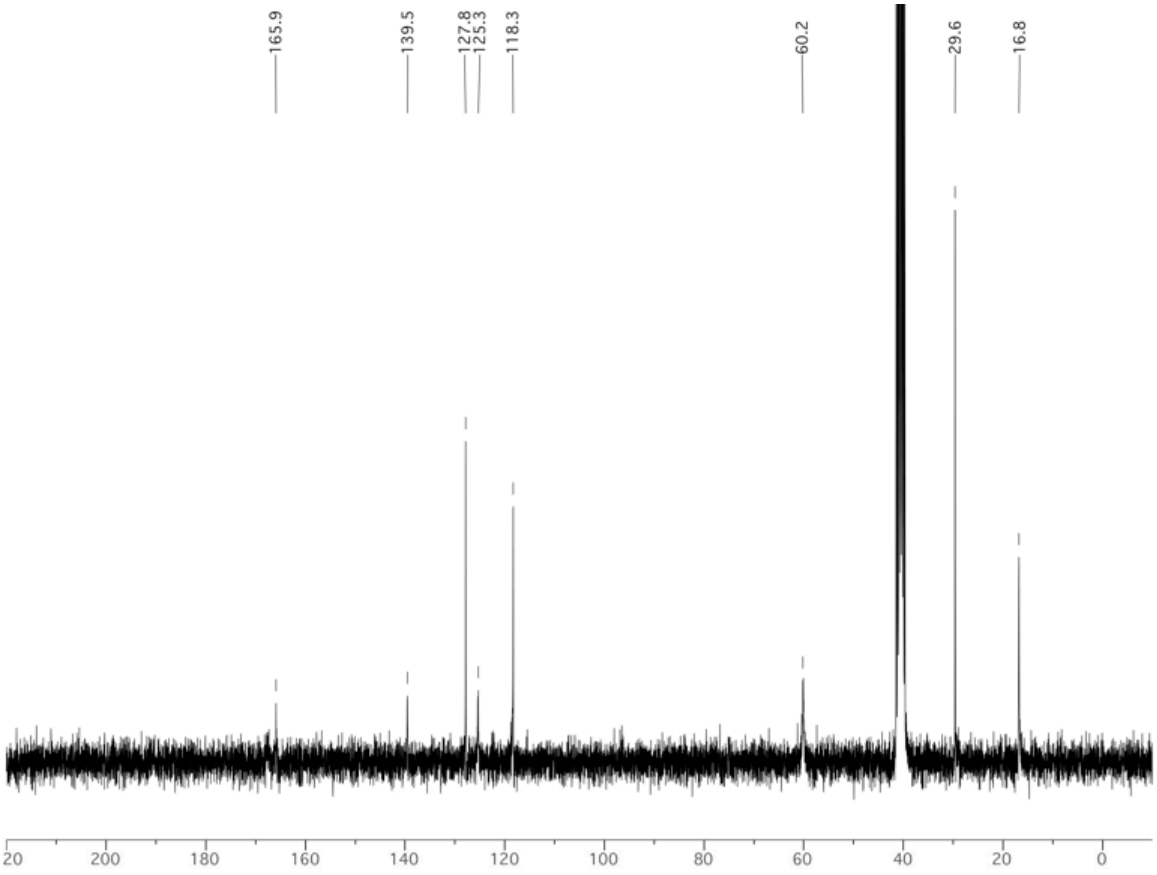


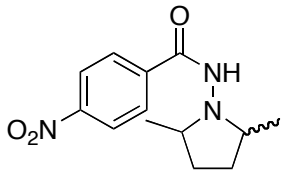
trans-2i
Table 1, Entry 9



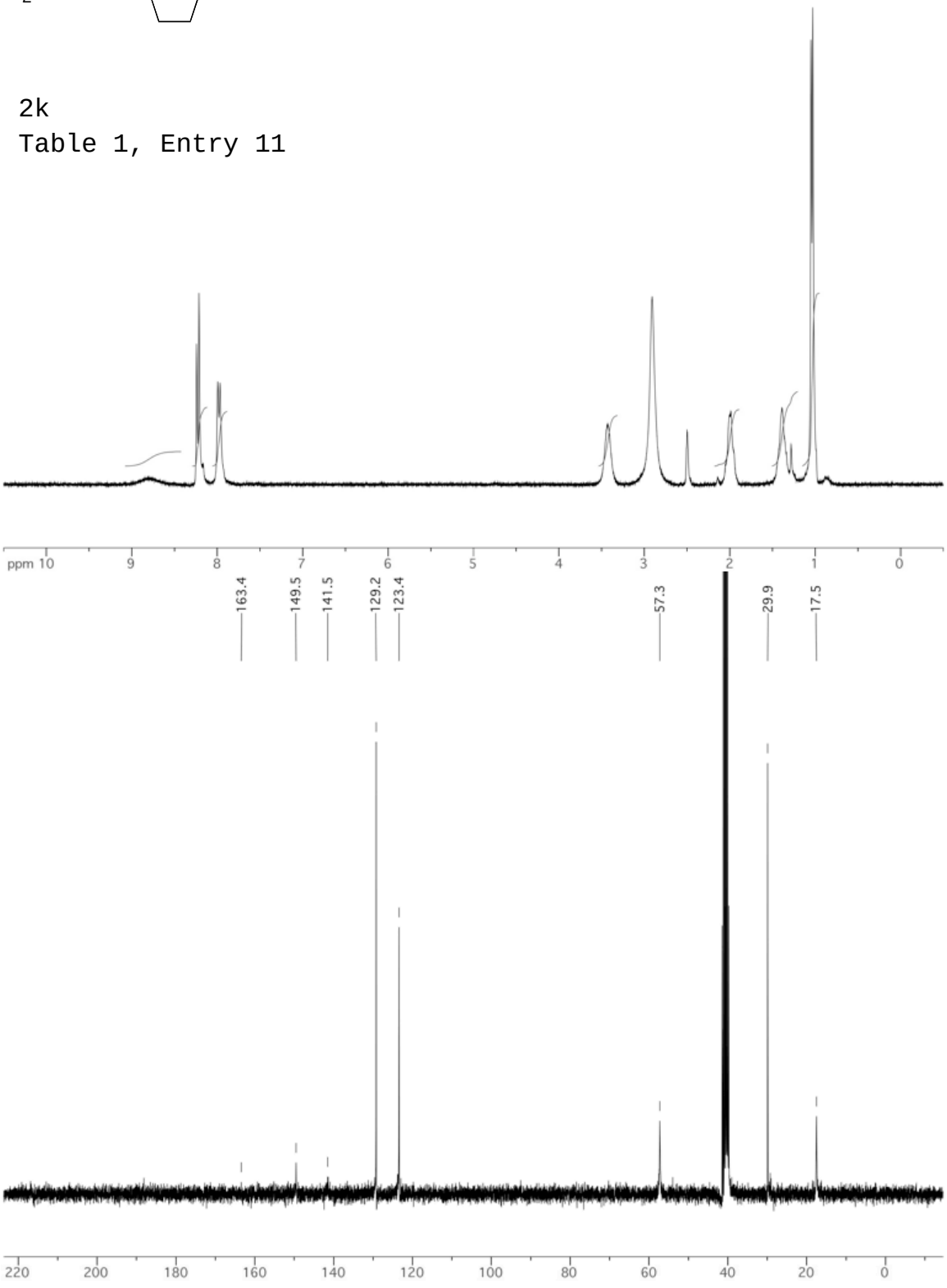
2j
Table 1, Entry 10

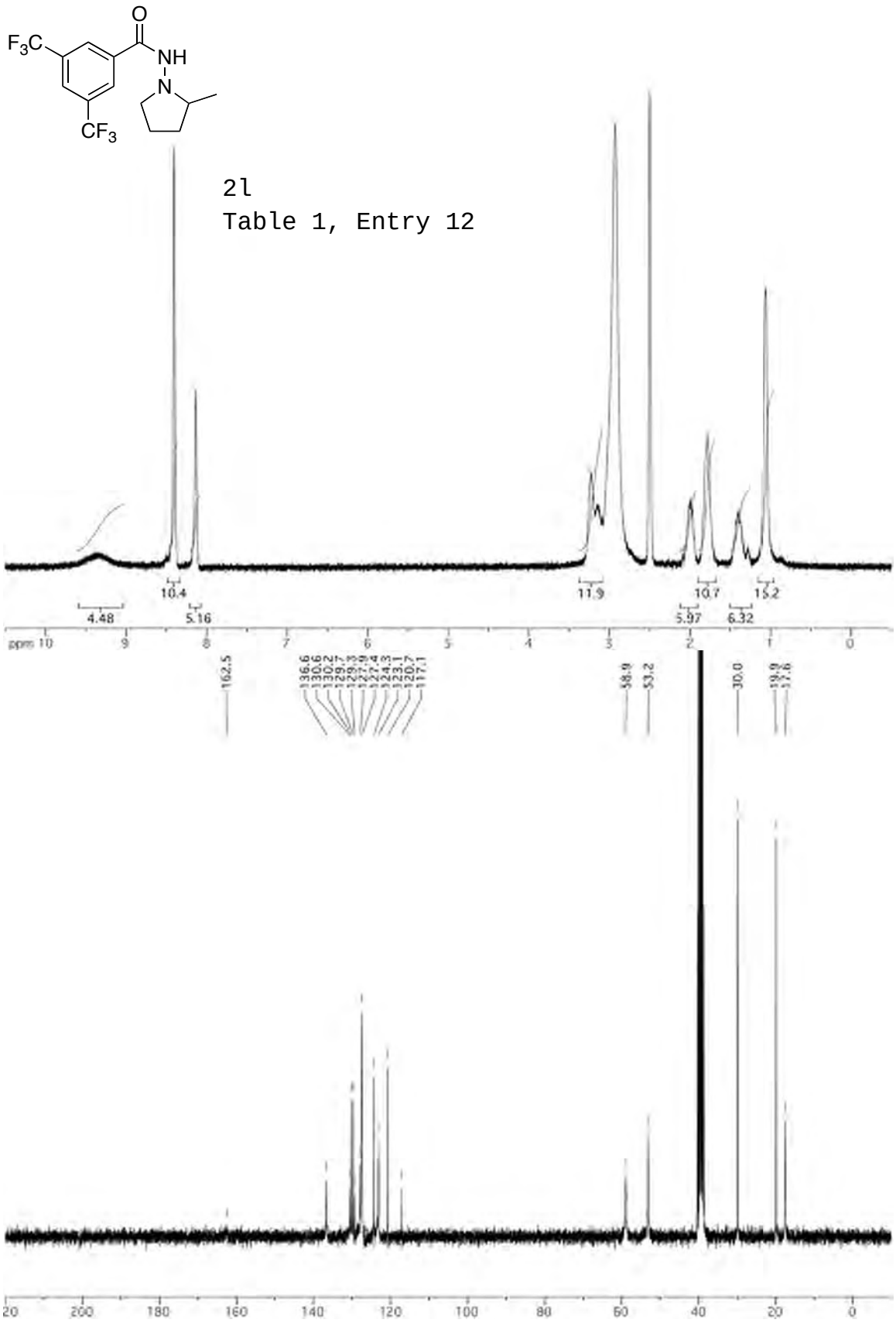


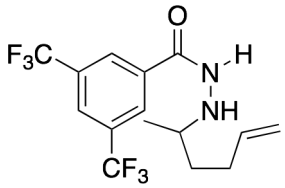




2k
Table 1, Entry 11

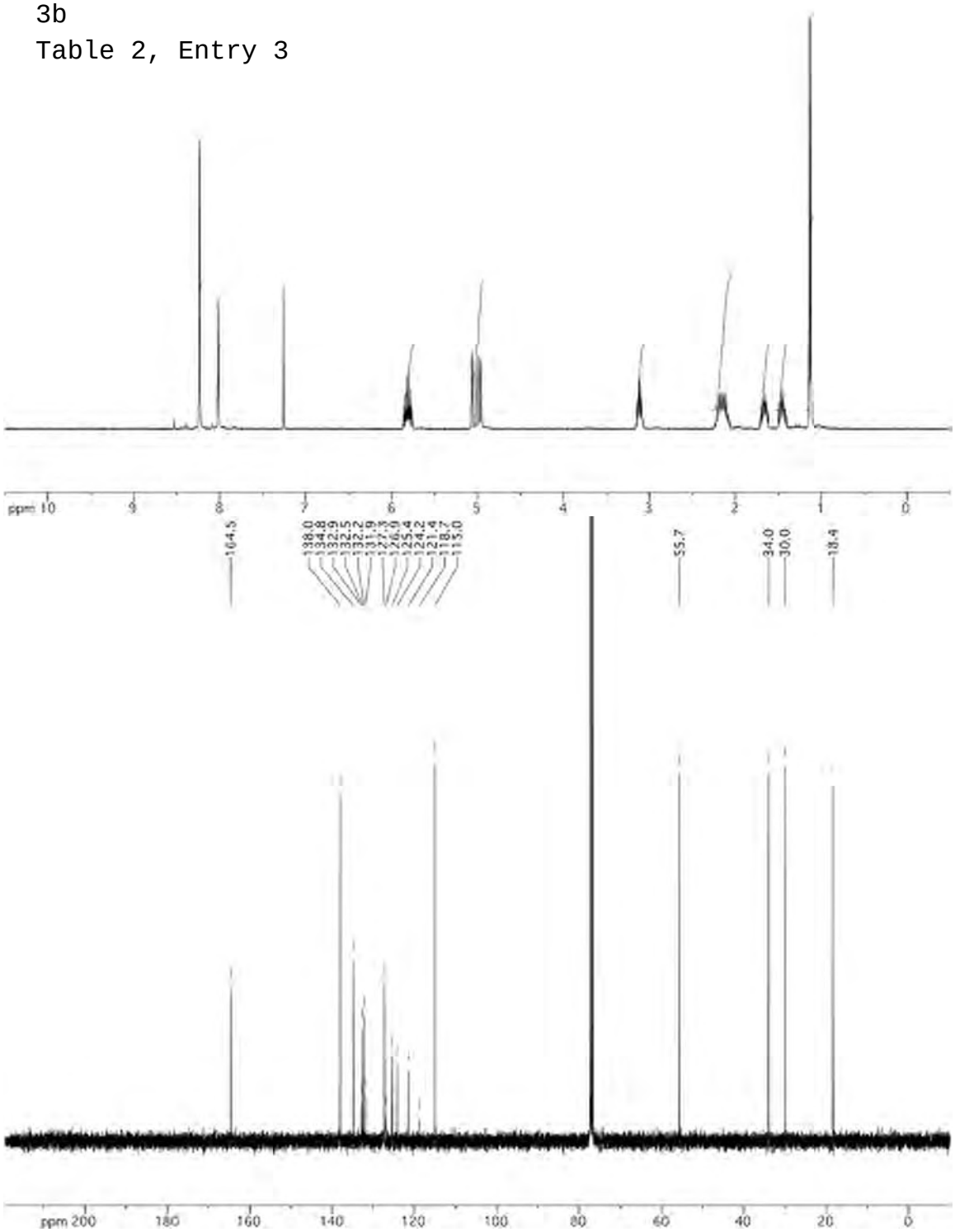


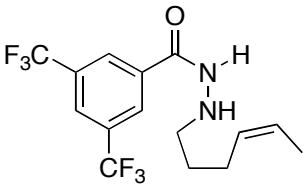

F3C
O
NH
N
CF3
2l
Table 1, Entry 12
10.4
4.48
5.16
11.9
10.7
5.97
15.2
6.32
ppm 10
9
8
7
6
5
4
3
2
1
0
162.5
136.6
130.6
130.2
129.3
127.9
127.4
124.3
123.1
120.7
117.1
58.9
53.2
30.0
19.9
17.6
220
200
180
160
140
120
100
80
60
40
20
0



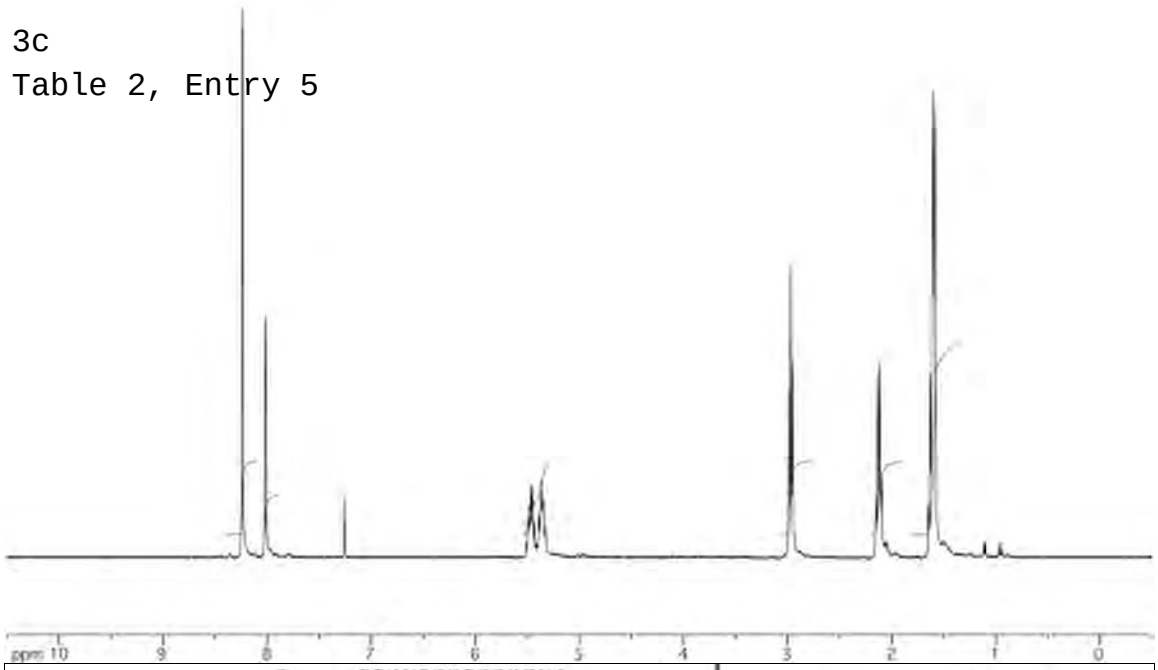
3b

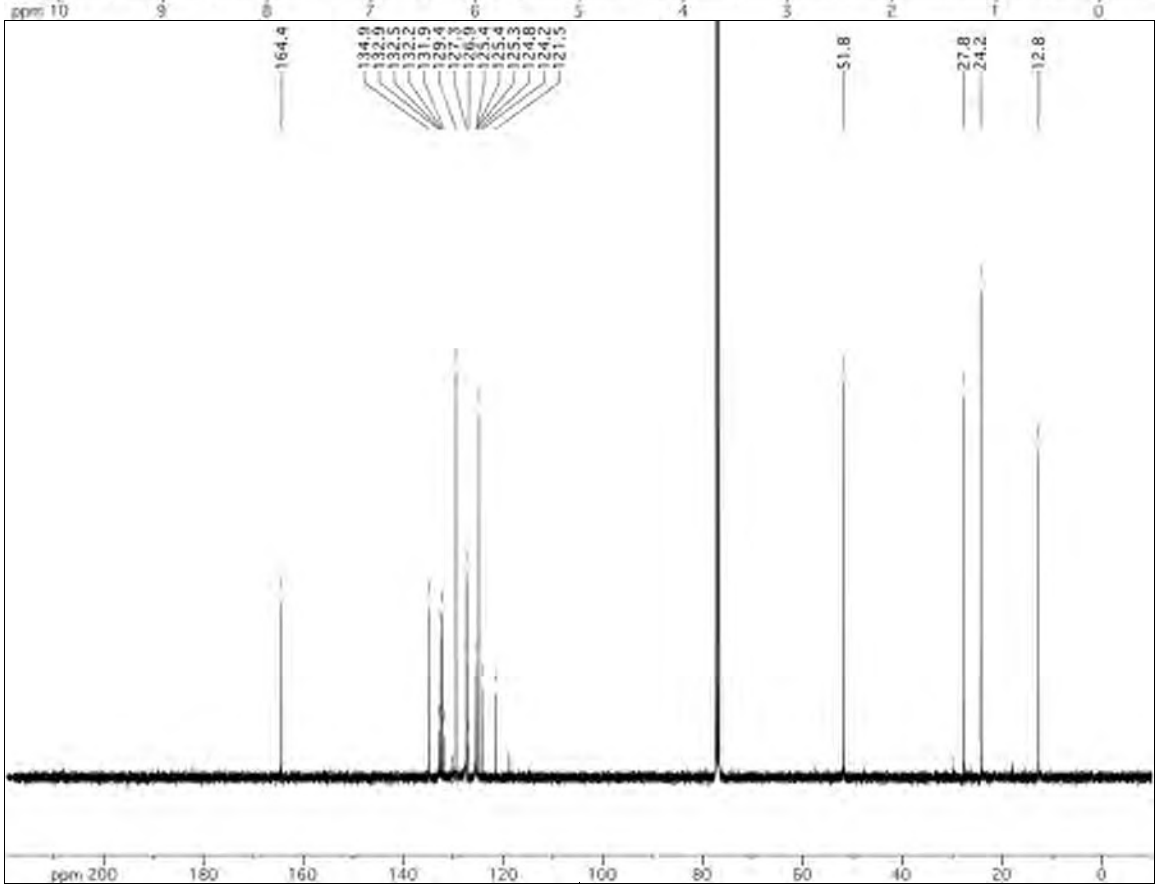
Table 2, Entry 3

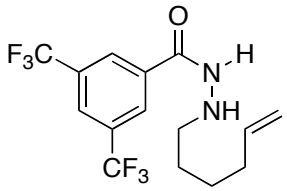




3c
Table 2, Entry 5

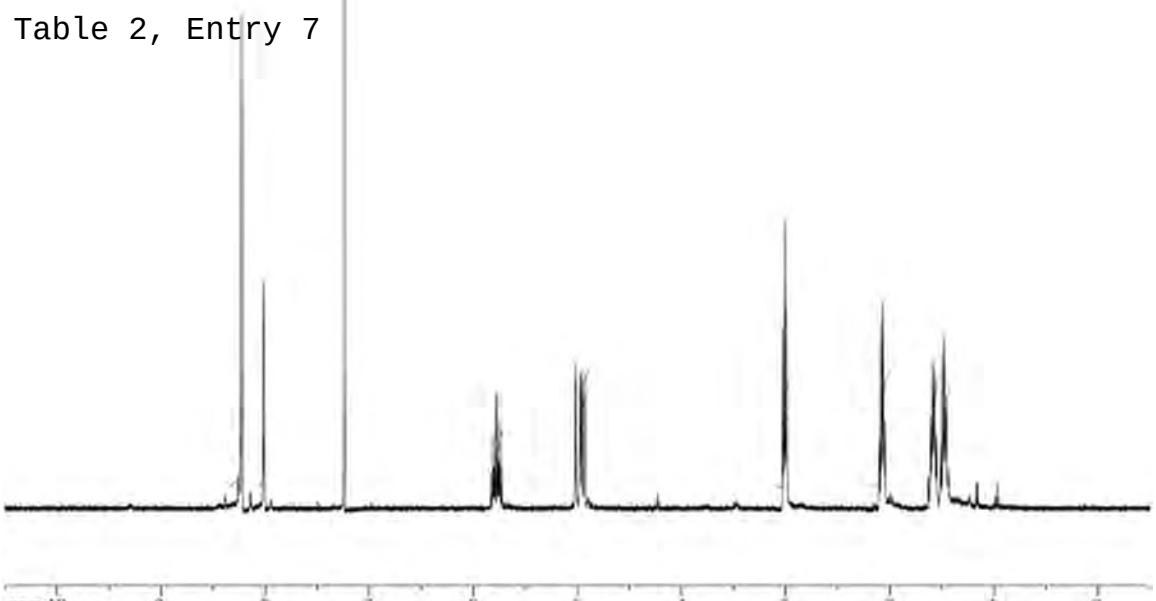


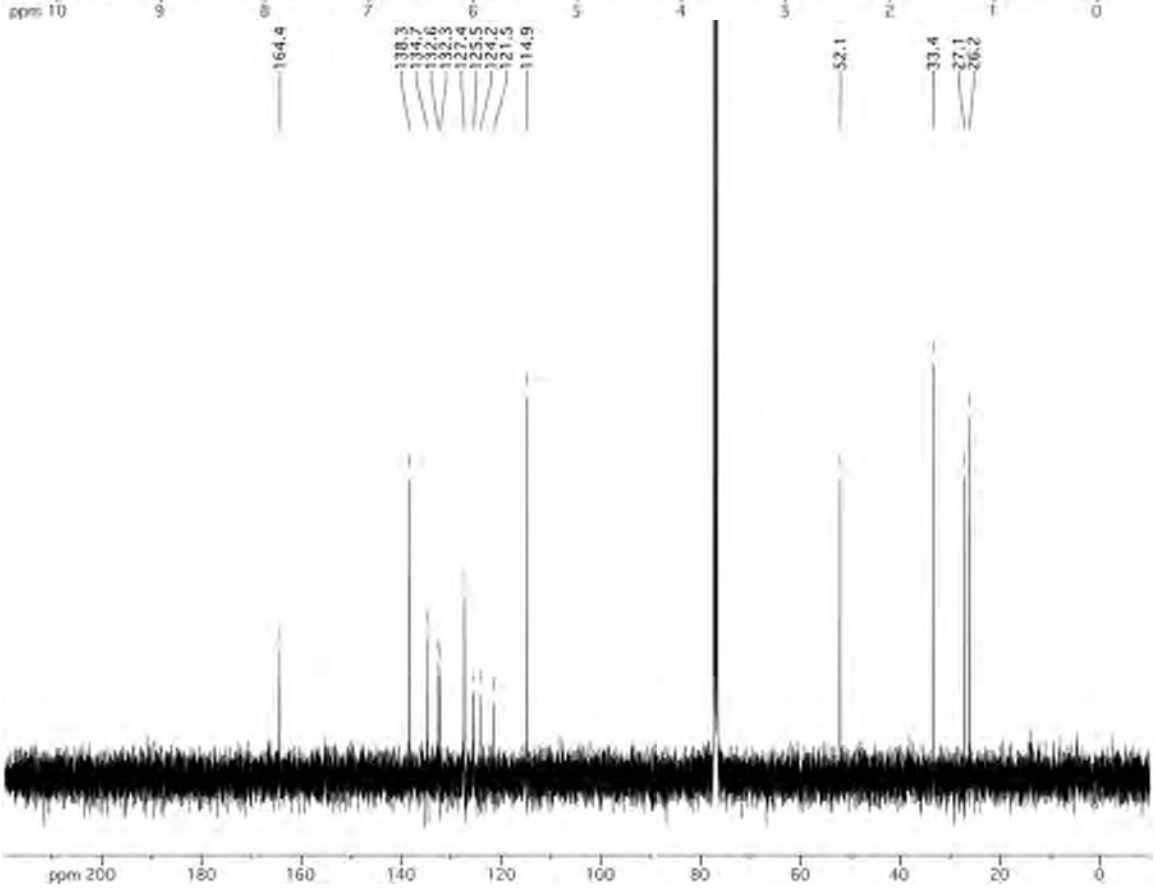


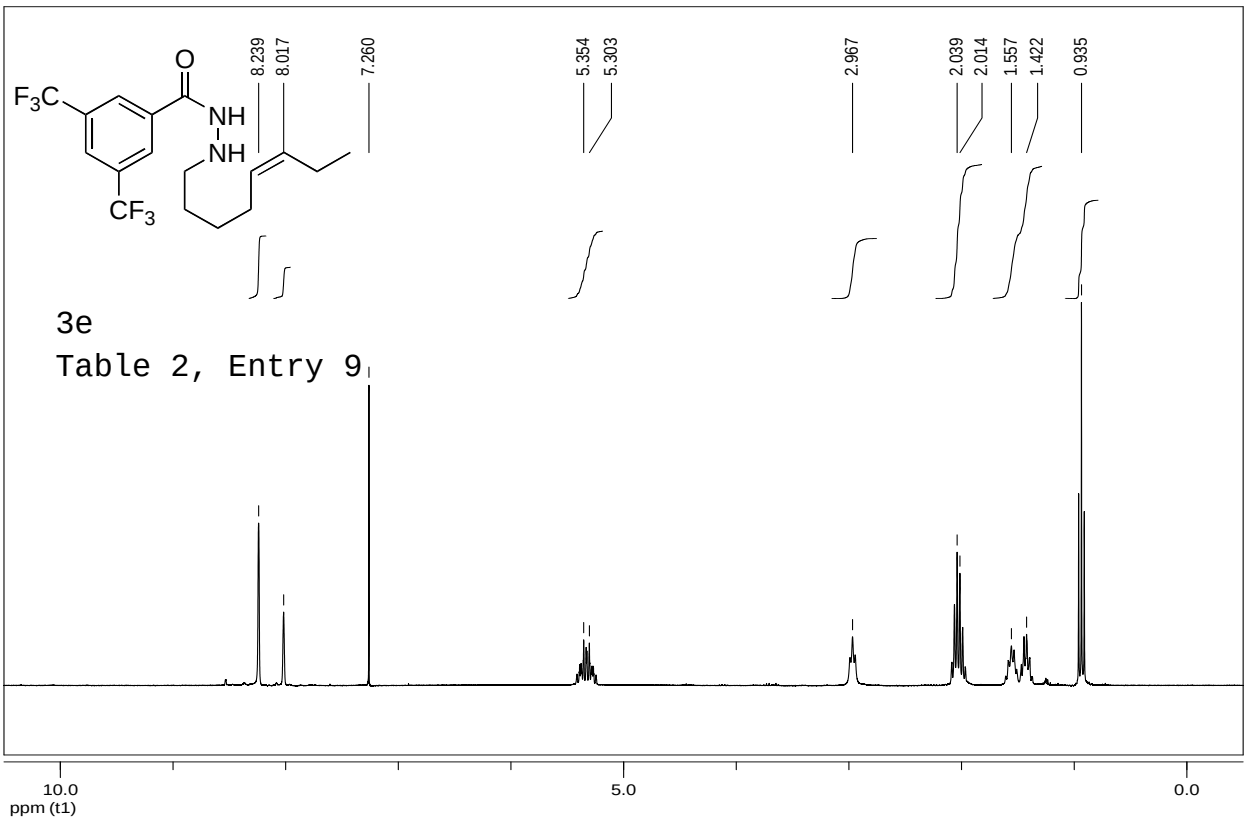


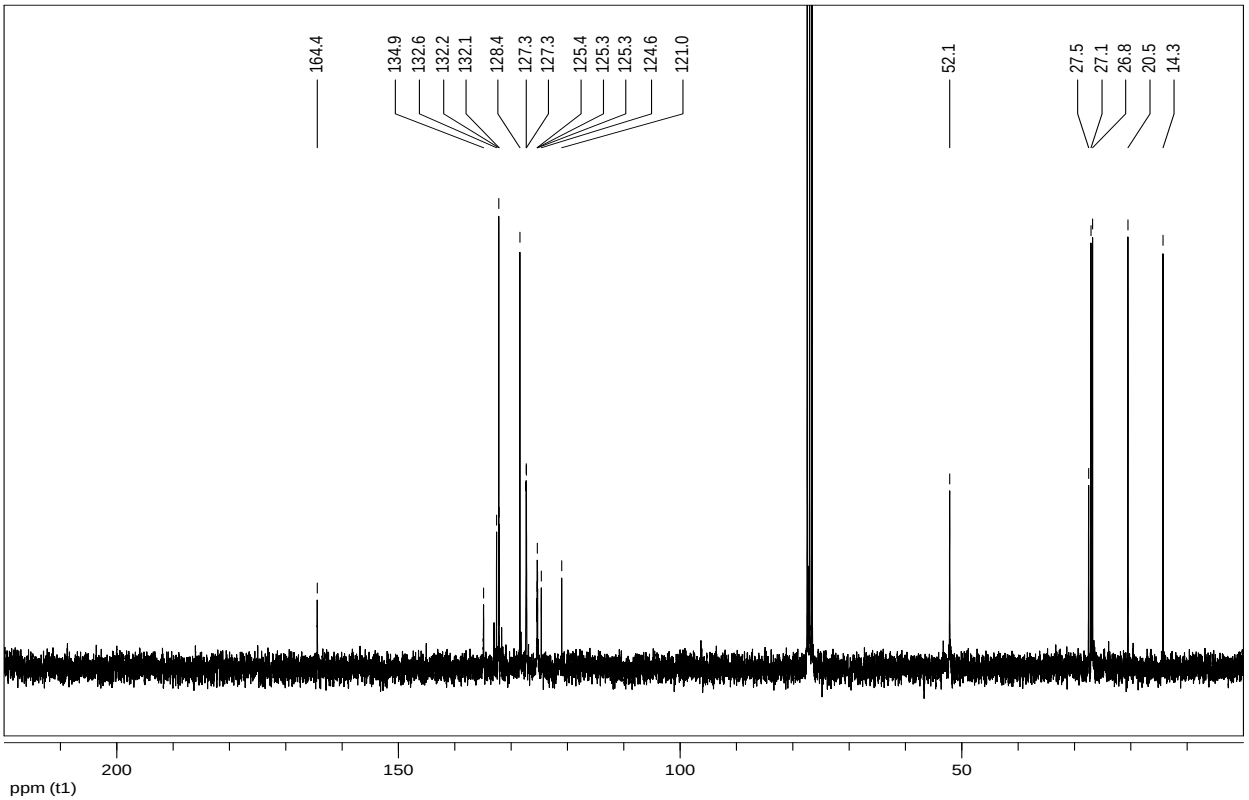
3d

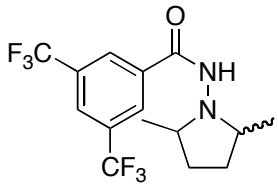
Table 2, Entry 7





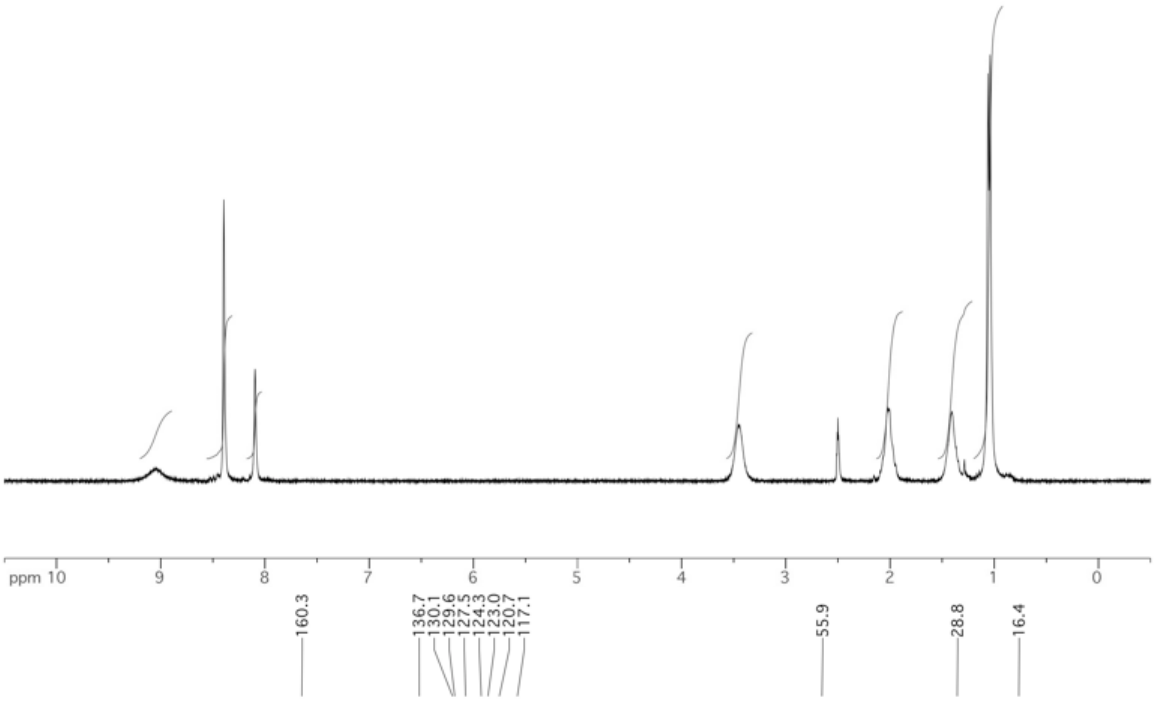

8.239
8.017
7.260
5.354
5.303
2.967
2.039
2.014
1.557
1.422
0.935
O
NH
NH
F3C
CF3
3e
Table 2, Entry 9
10.0
5.0
0.0
ppm (t1)

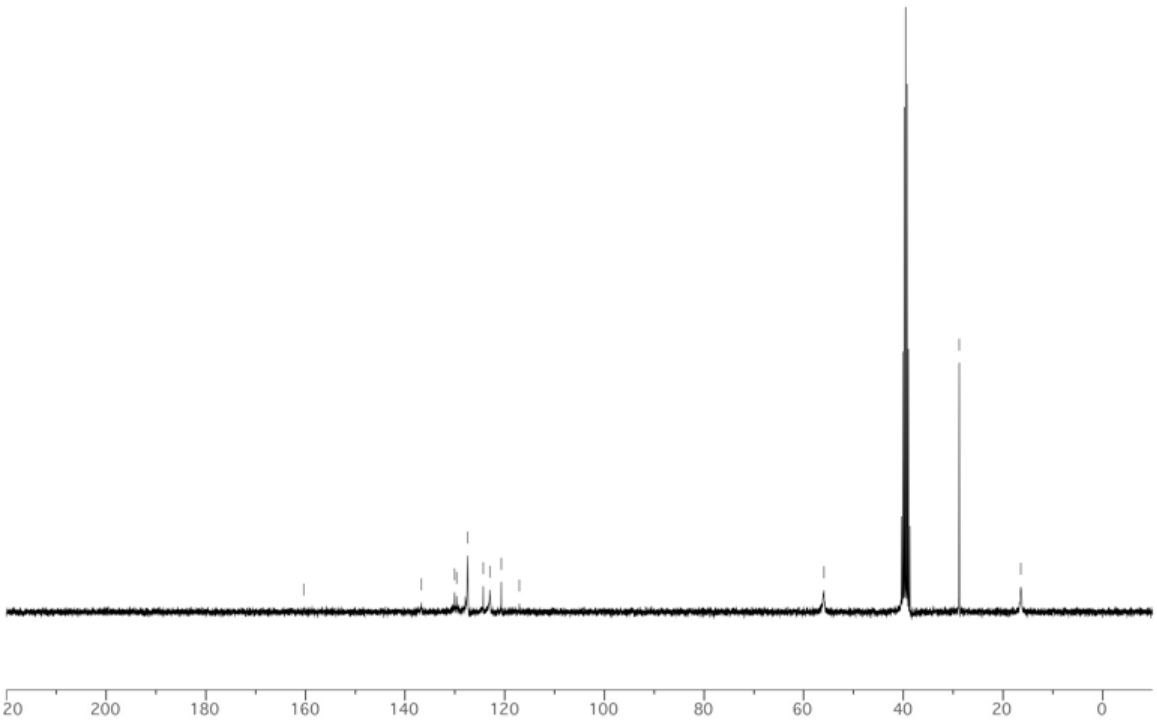

164.4
134.9
132.6
132.2
132.1
128.4
127.3
127.3
125.4
125.3
125.3
124.6
121.0
52.1
27.5
27.1
26.8
20.5
14.3
200
150
100
50
ppm (t1)

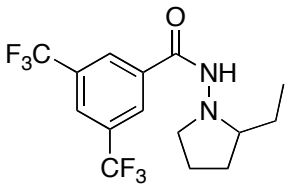


5b

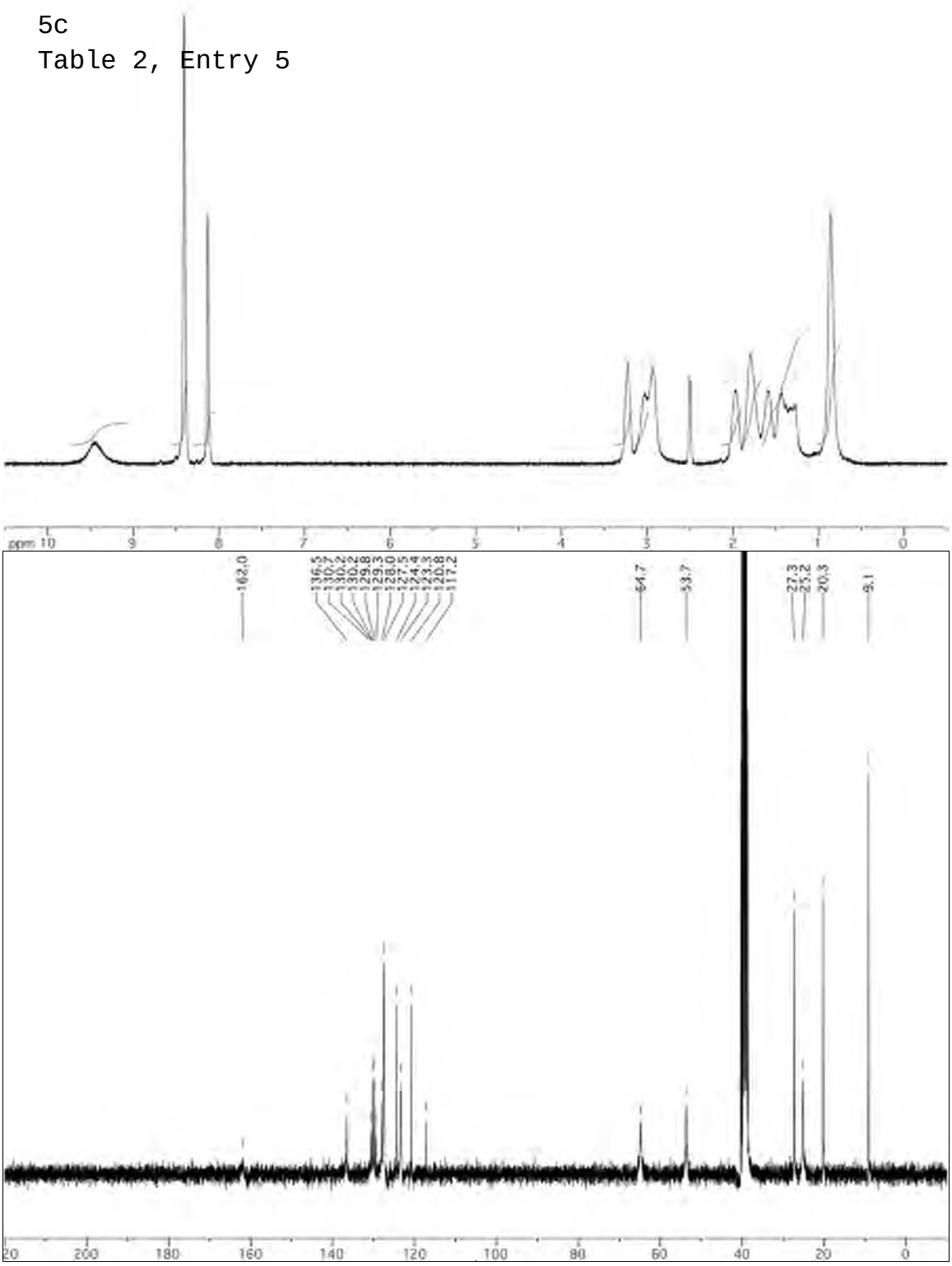
Table 2, Entry 3

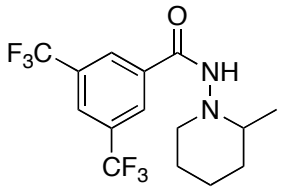






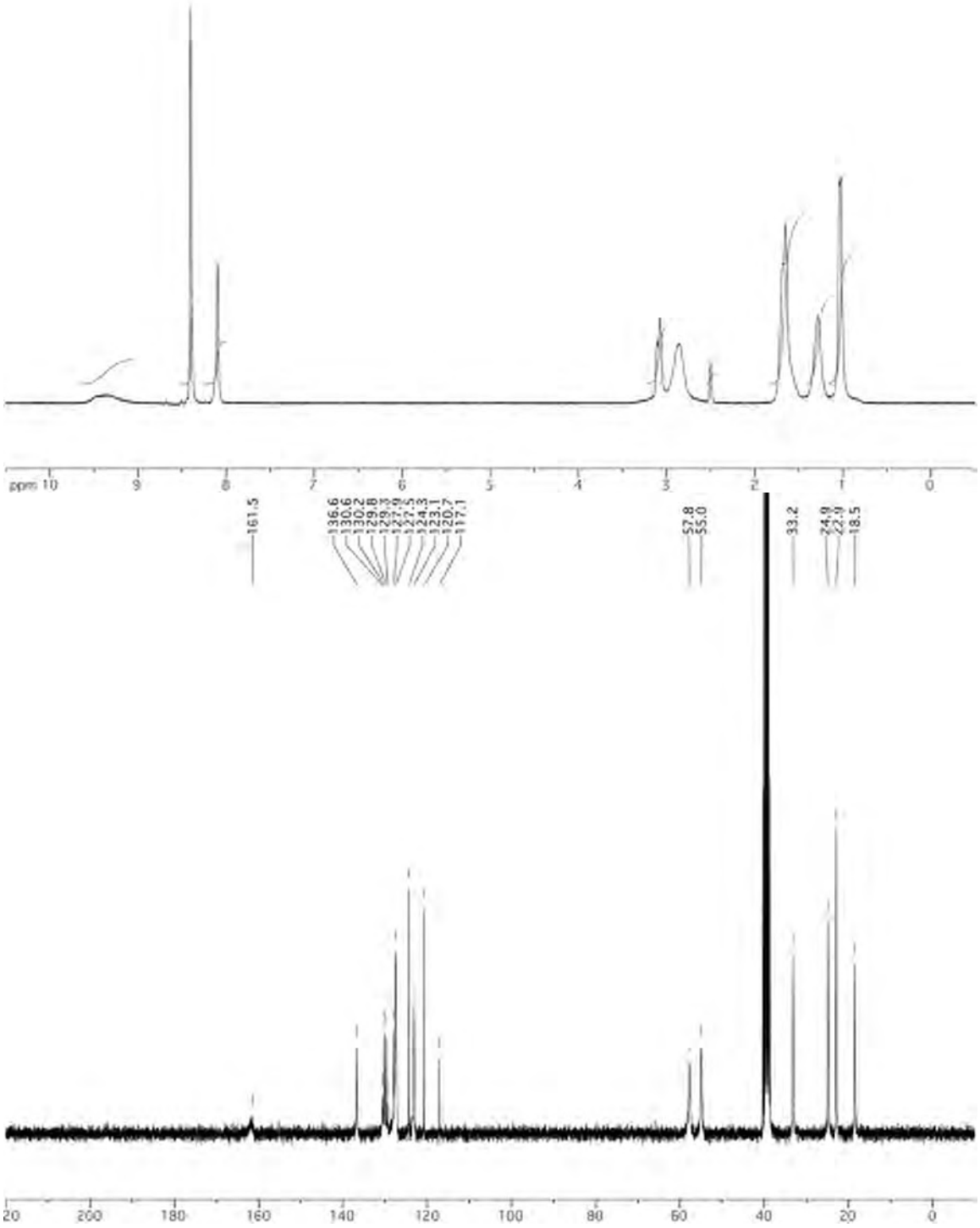
5c
Table 2, Entry 5

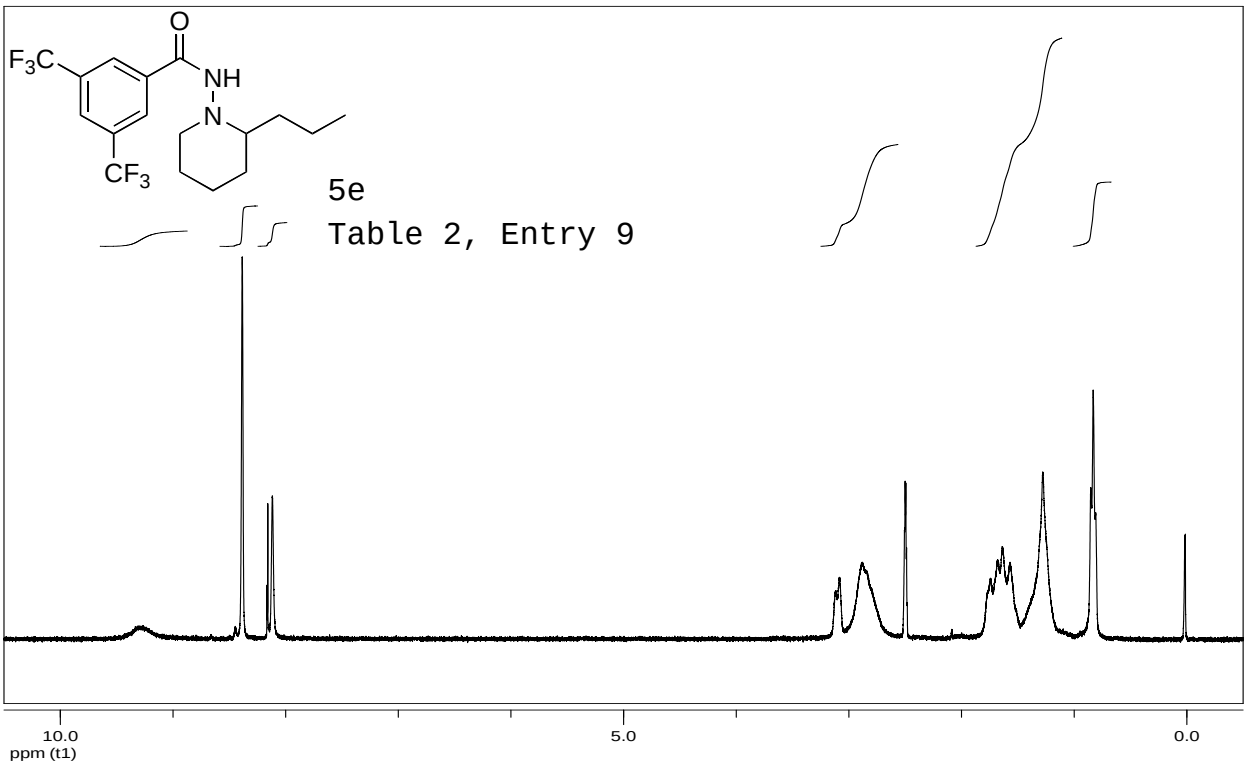


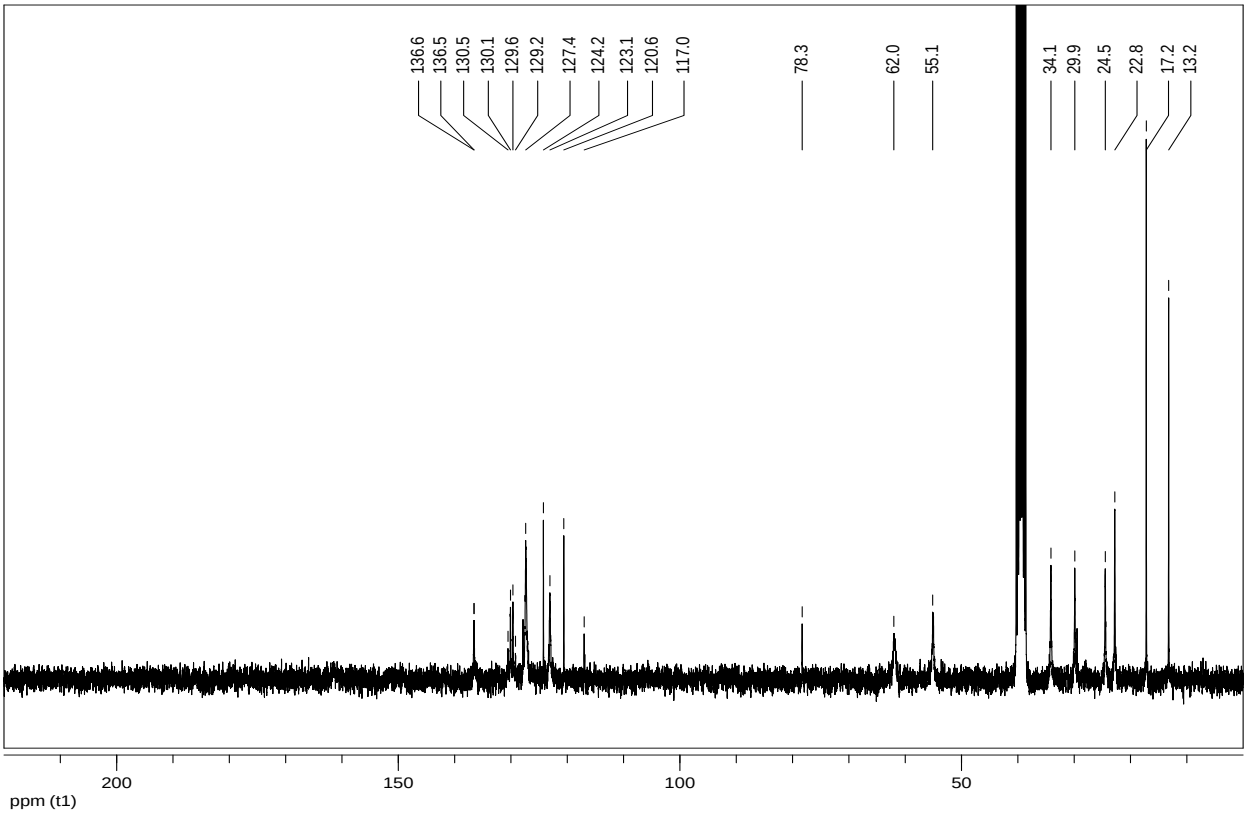


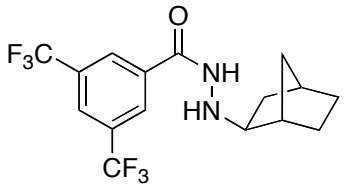
5d

Table 2, Entry 7

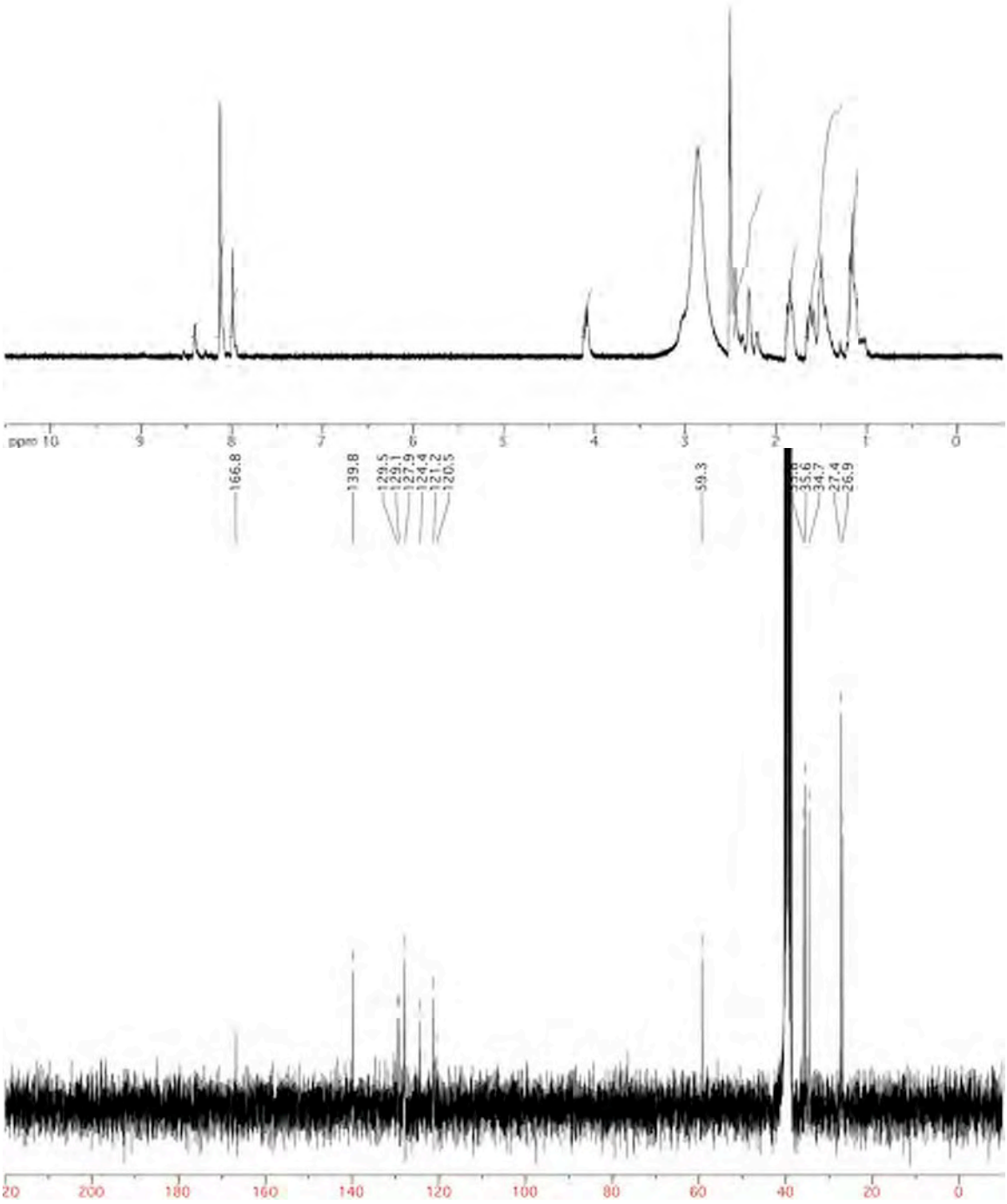


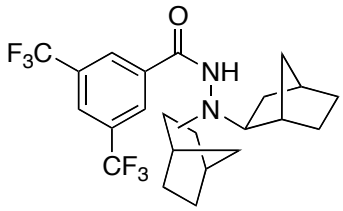

O
F3C
NH
N
CF3
5e
Table 2, Entry 9
10.0
5.0
0.0
ppm (t1)


136.6
136.5
130.5
130.1
129.6
129.2
127.4
124.2
123.1
120.6
117.0
78.3
62.0
55.1
34.1
29.9
24.5
22.8
17.2
13.2
200
150
100
50
ppm (t1)


O
F3C
NH
HN
CF3

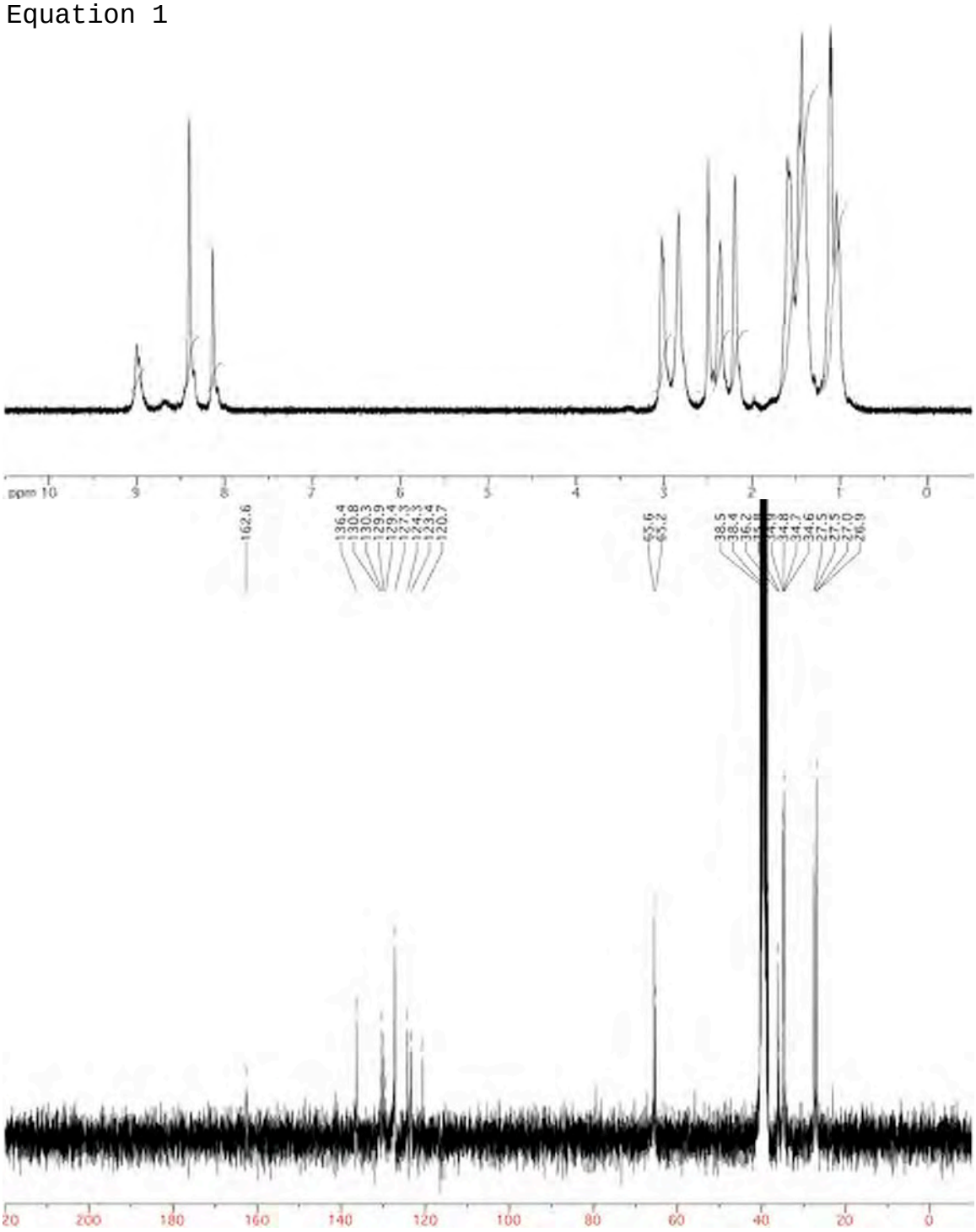
8
Equation 1

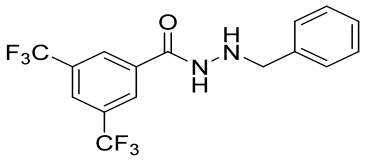

ppm 10
9
8
7
6
5
4
3
2
1
0
166.8
139.8
129.5
129.1
127.9
124.4
121.2
120.5
59.3
35.6
34.7
27.4
26.9
220
200
180
160
140
120
100
80
60
40
20
0


O
F3C
NH
N
CF3

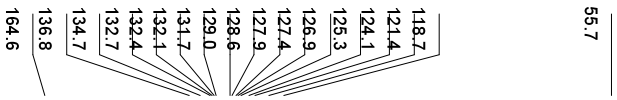
9

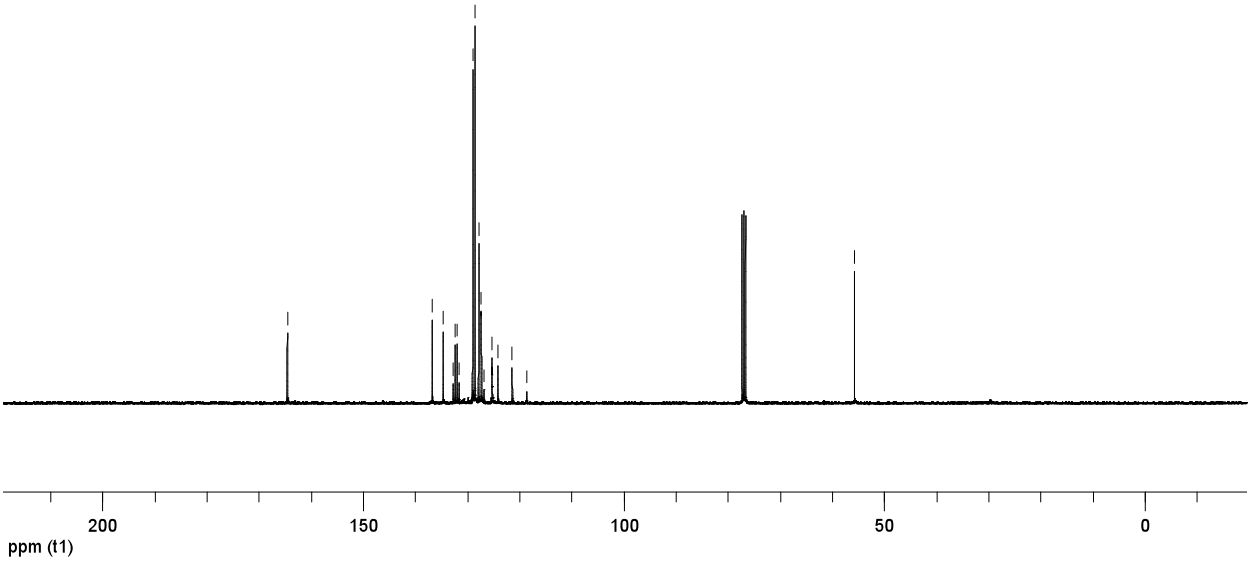
Equation 1

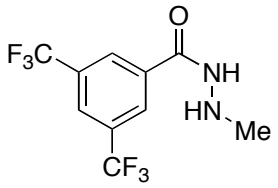

ppm 10
9
8
7
6
5
4
3
2
1
0
162.6
136.4
130.8
130.3
129.9
65.6
65.2
38.5
38.4
36.2
34.8
34.7
34.6
27.5
27.5
27.0
26.9
220
200
180
160
140
120
100
80
60
40
20
0



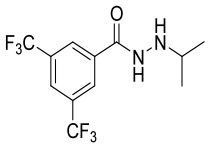
10a
Table 3, Entry 1





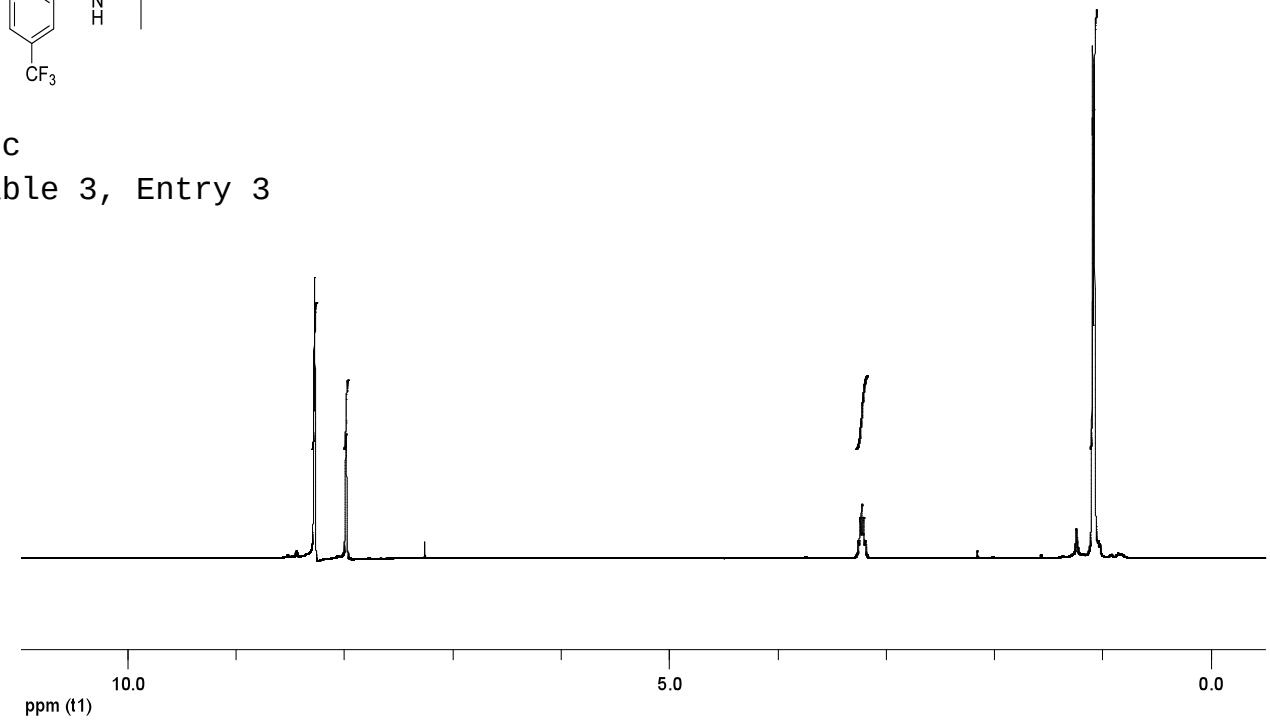


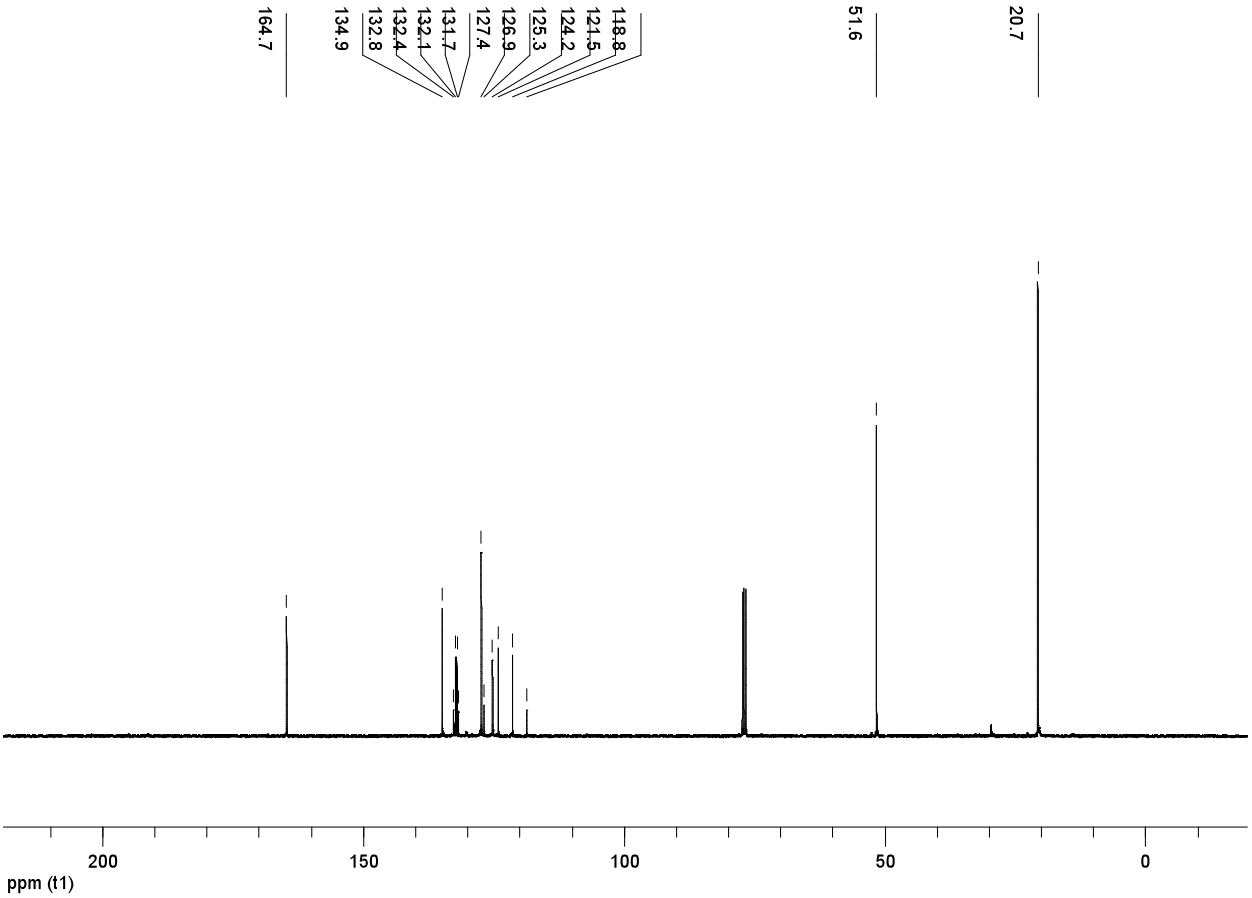
10b
Table 3, Entry 2

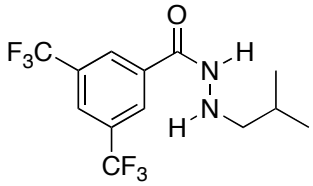


10c

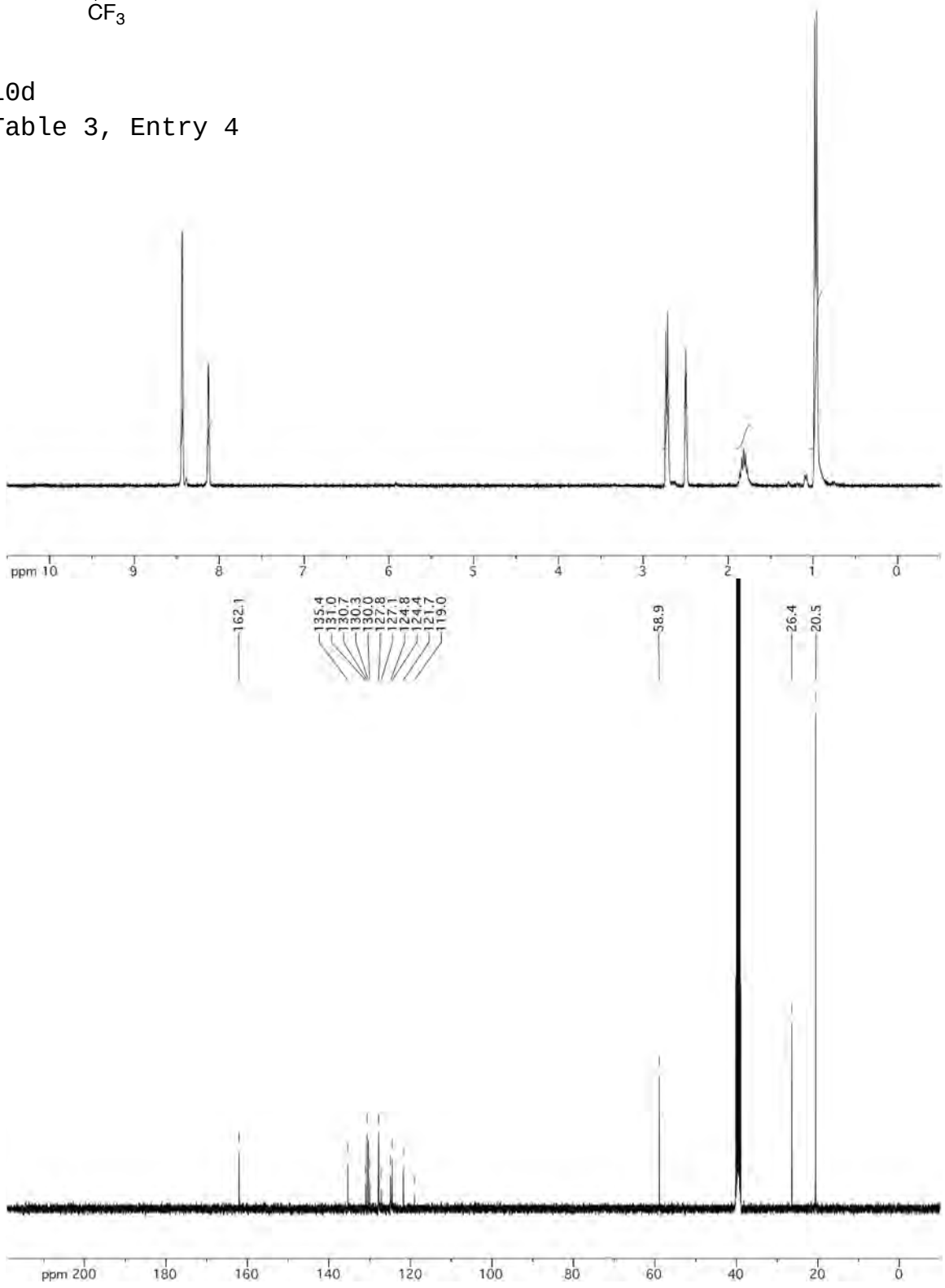
Table 3, Entry 3

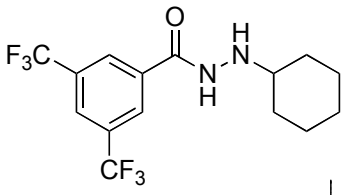




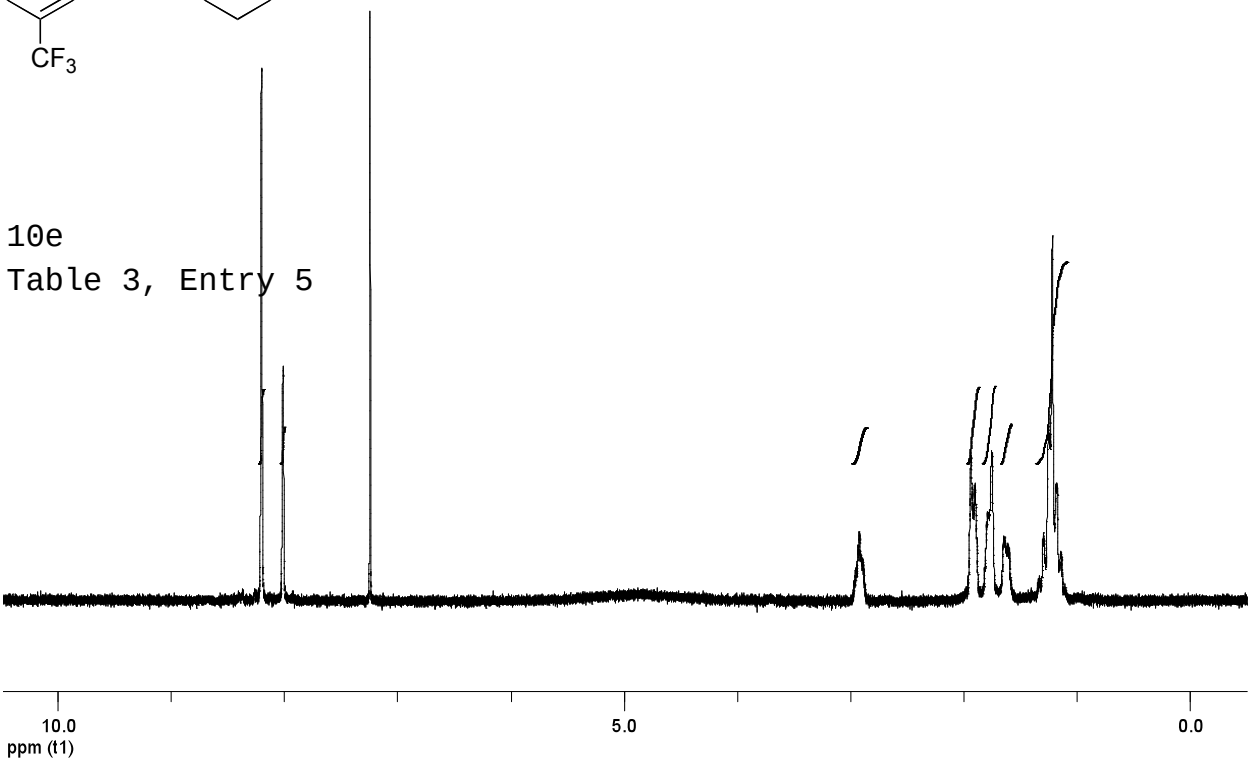


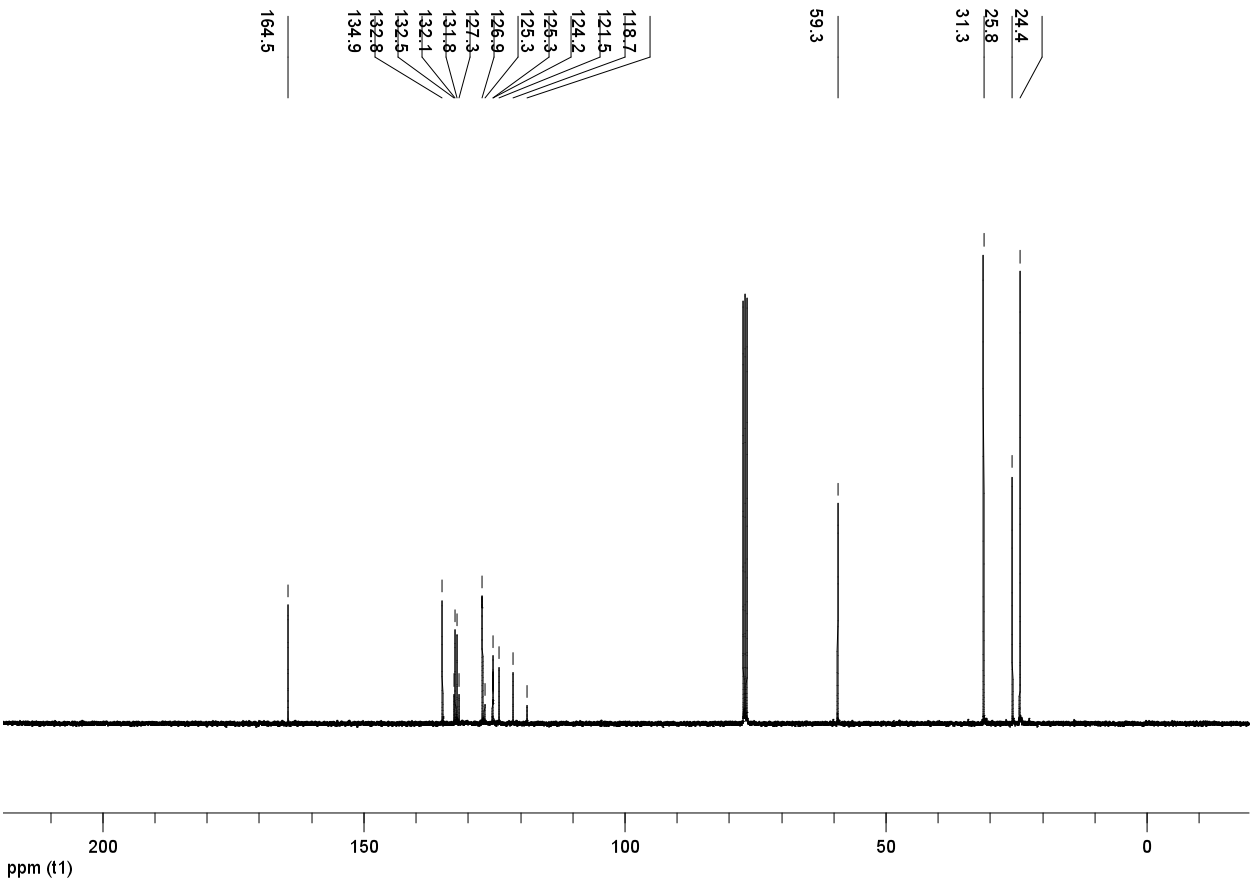
10d
Table 3, Entry 4

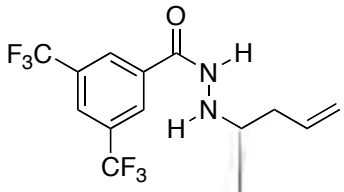




10e
Table 3, Entry 5

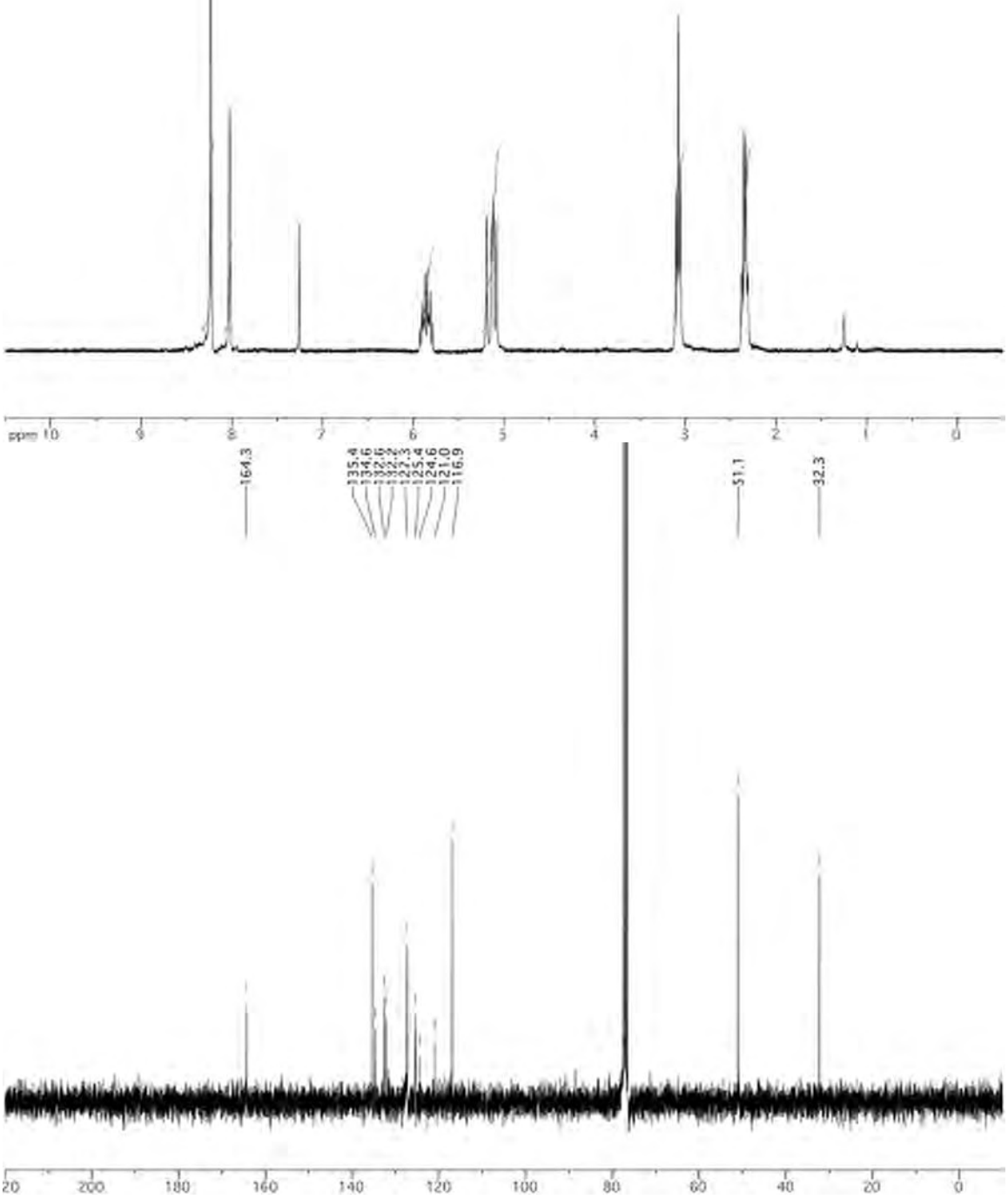


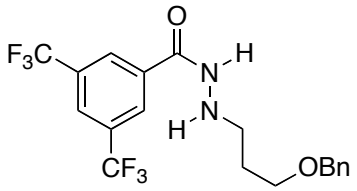




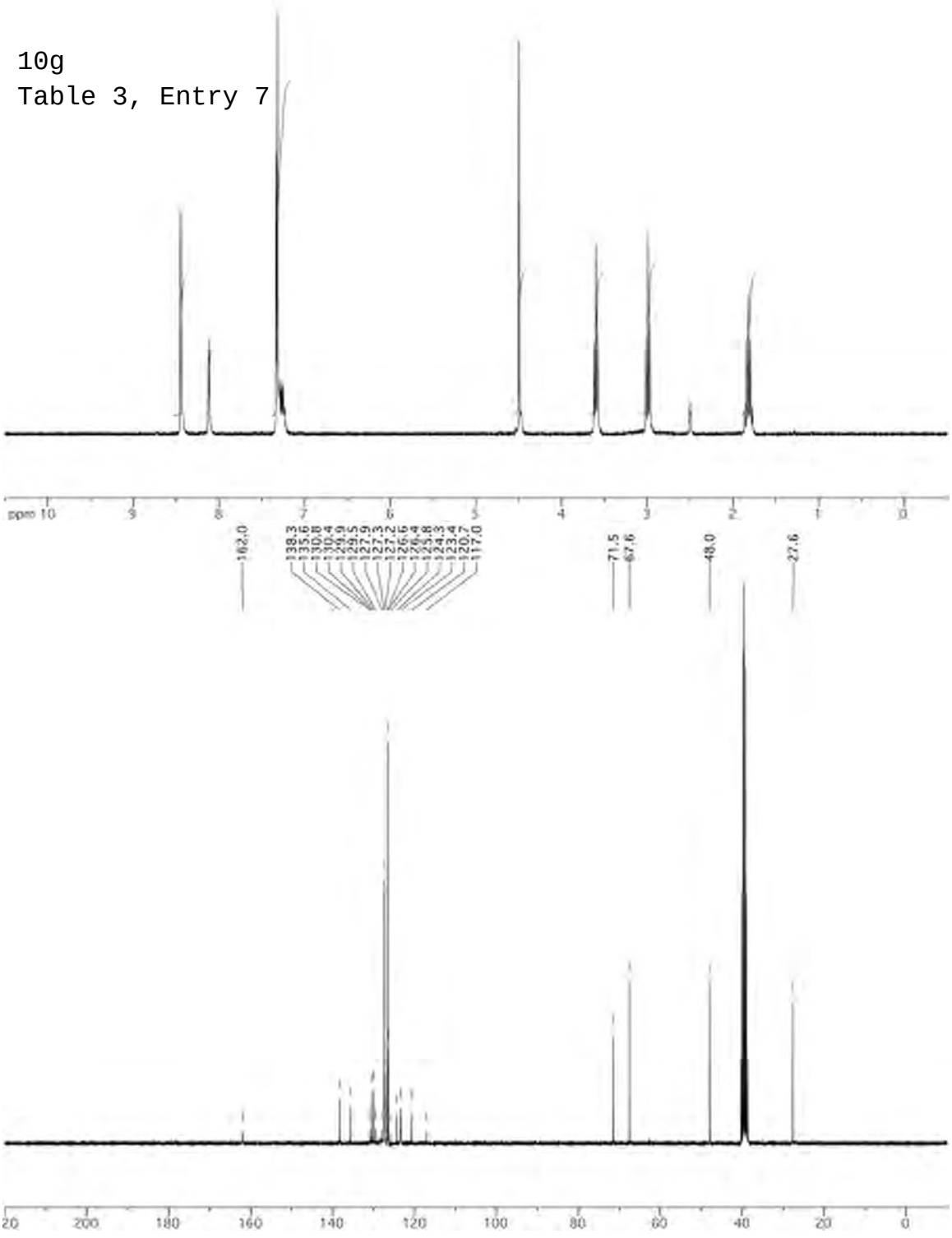
10f

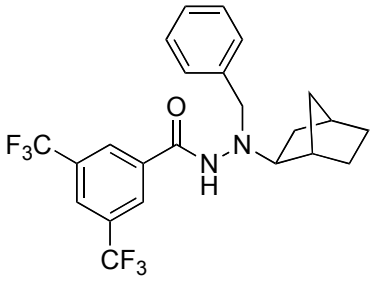
Table 3, Entry 6



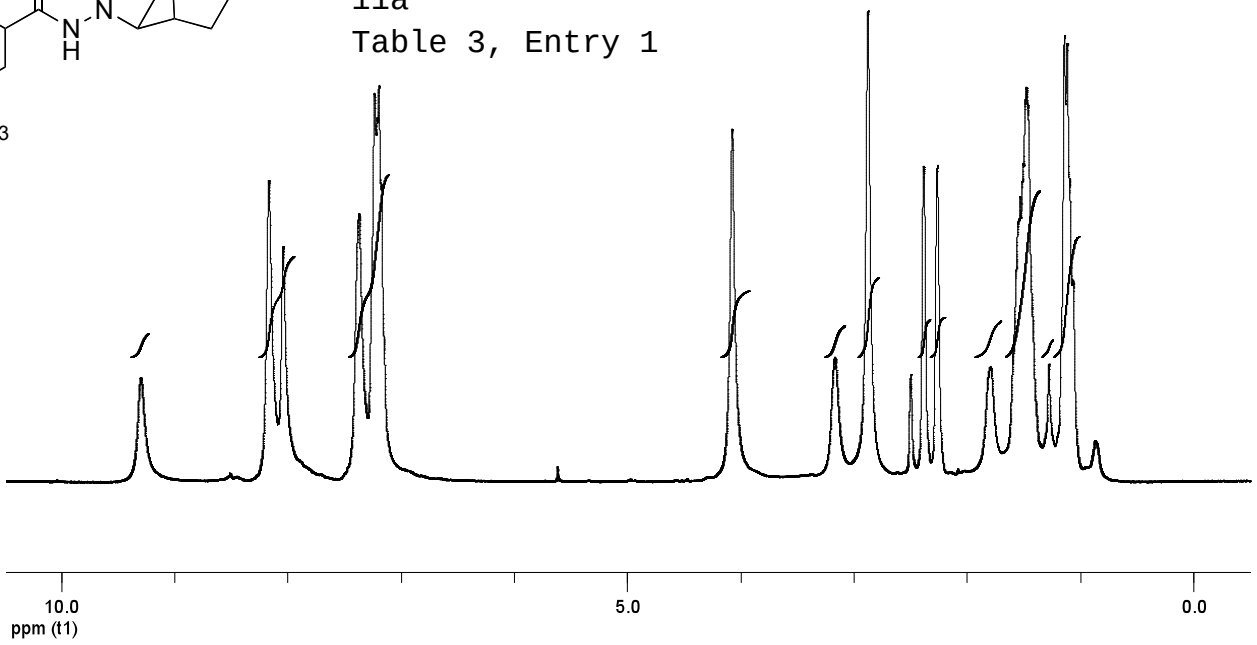


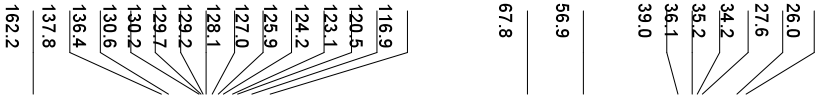
10g
Table 3, Entry 7

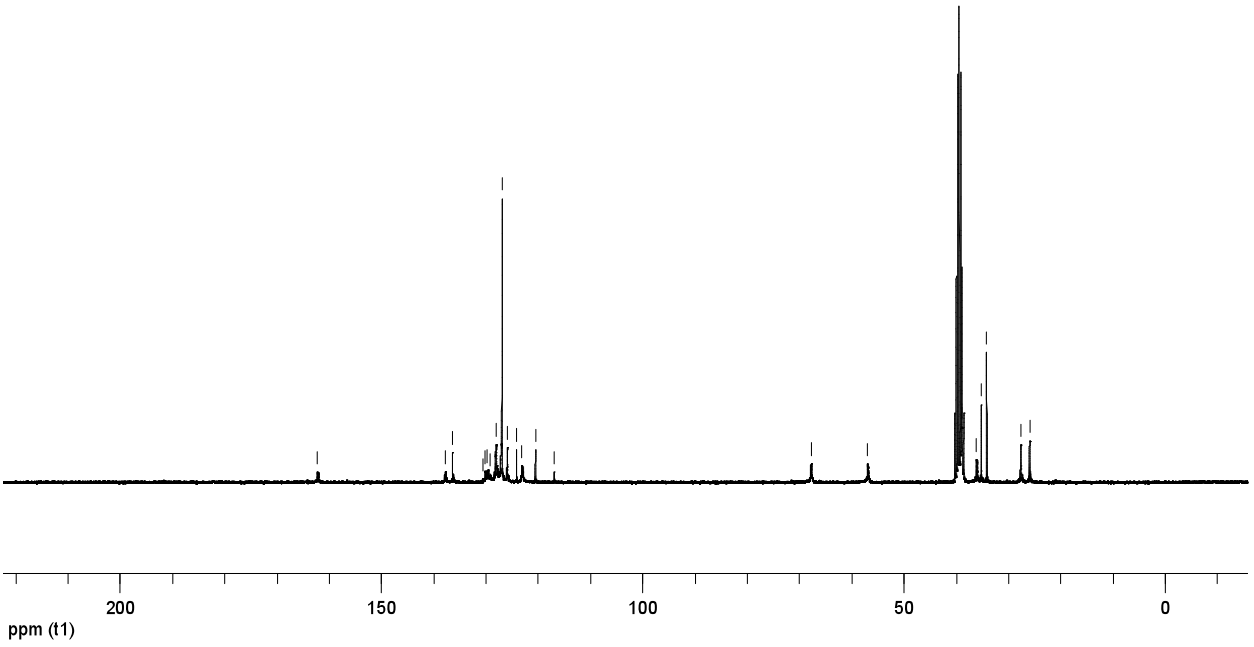


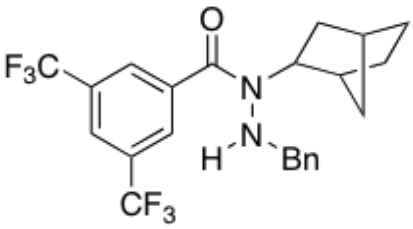


11a
Table 3, Entry 1



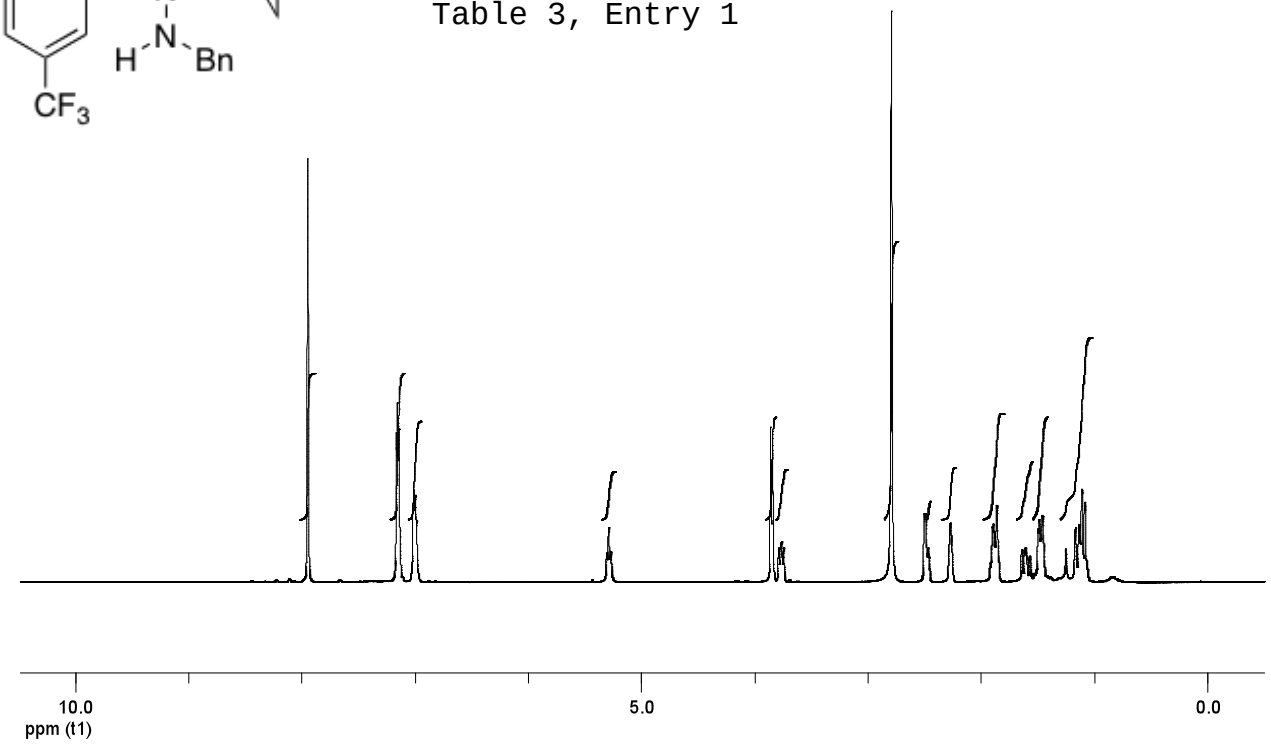


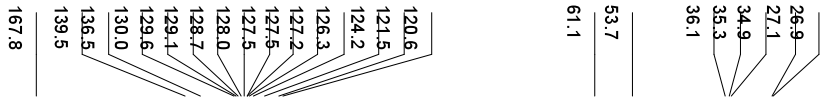


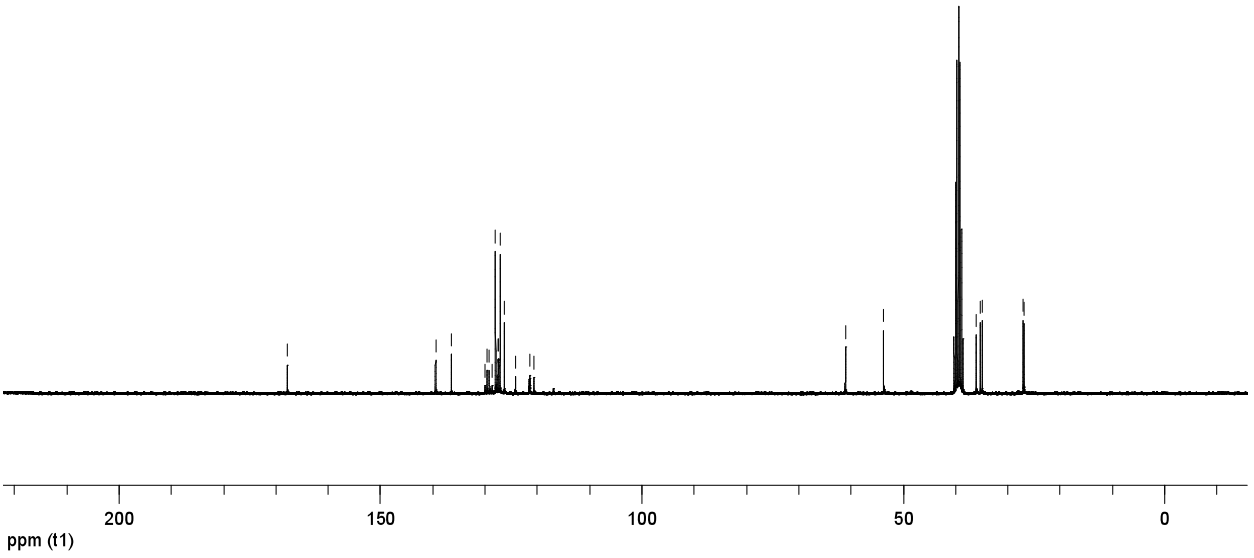


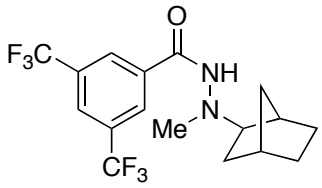
12a

Table 3, Entry 1



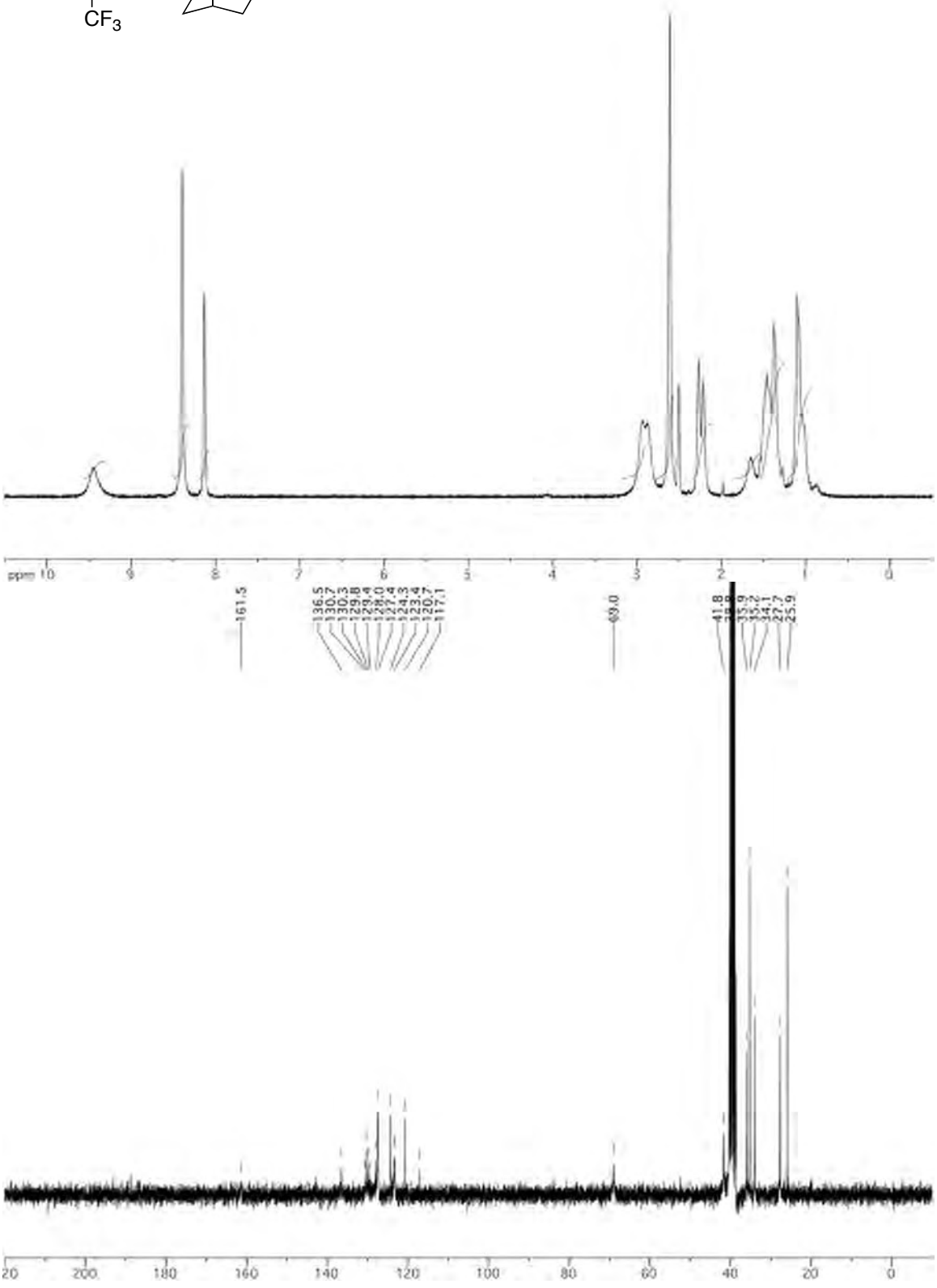


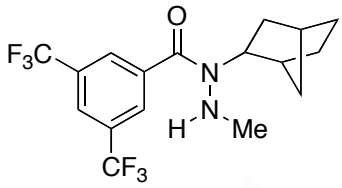




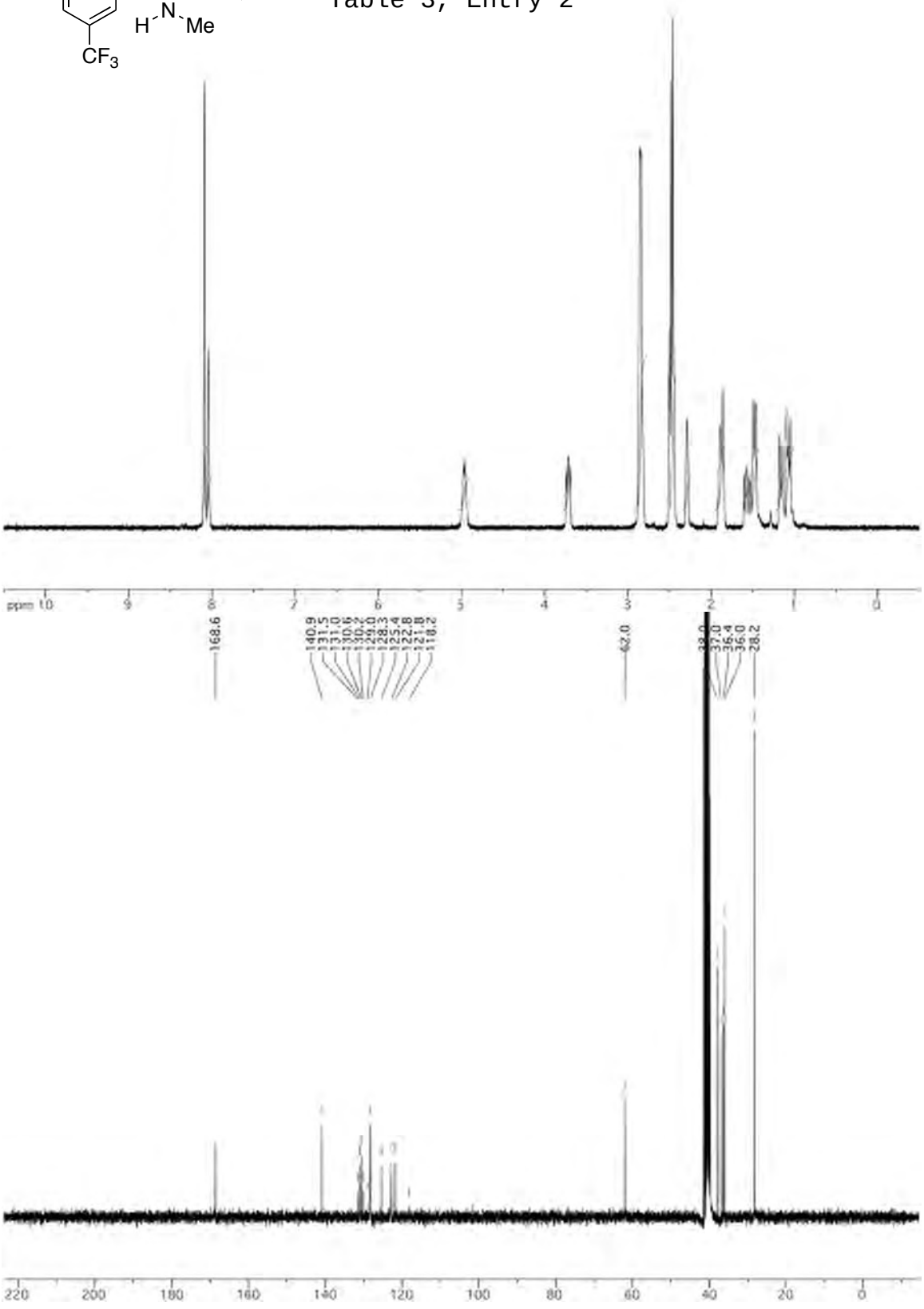
11b

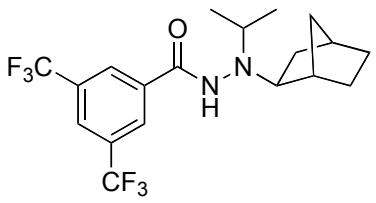
Table 3, Entry 2





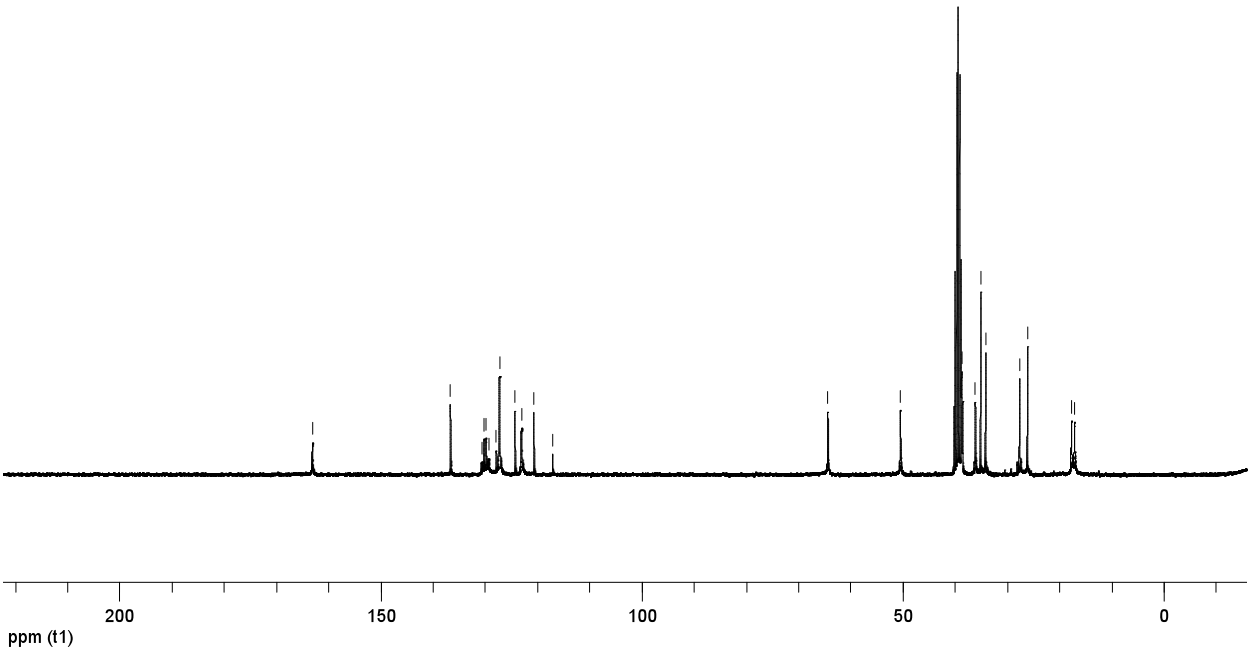
12b
Table 3, Entry 2

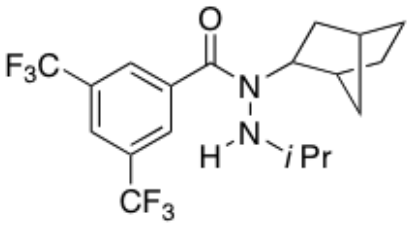




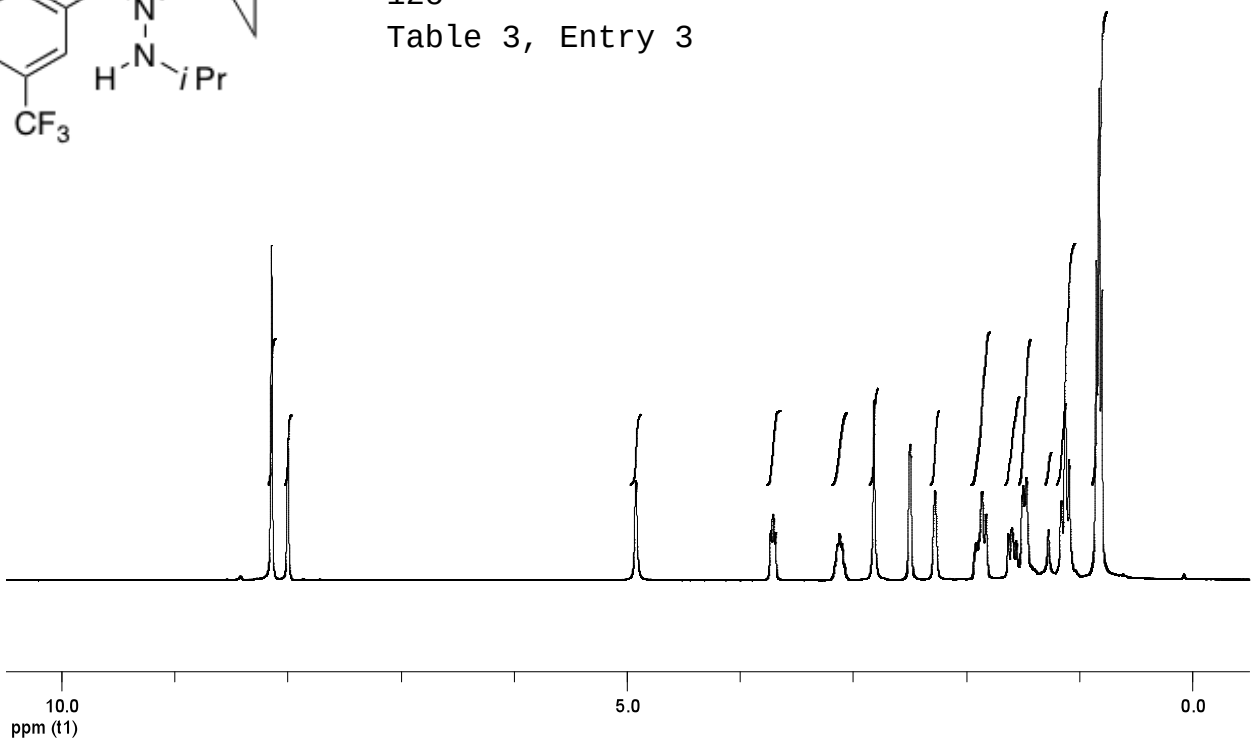
11c
Table 3, Entry 3

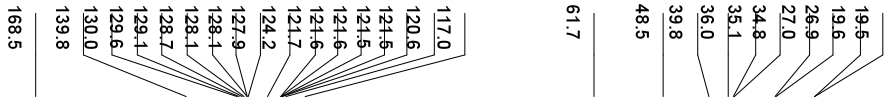
163.1
136.7
130.7
130.3
129.8
129.4
127.9
127.3
124.3
123.1
120.6
117.0
64.4
50.5
38.8
36.1
35.1
34.1
27.7
26.1
17.7
17.1

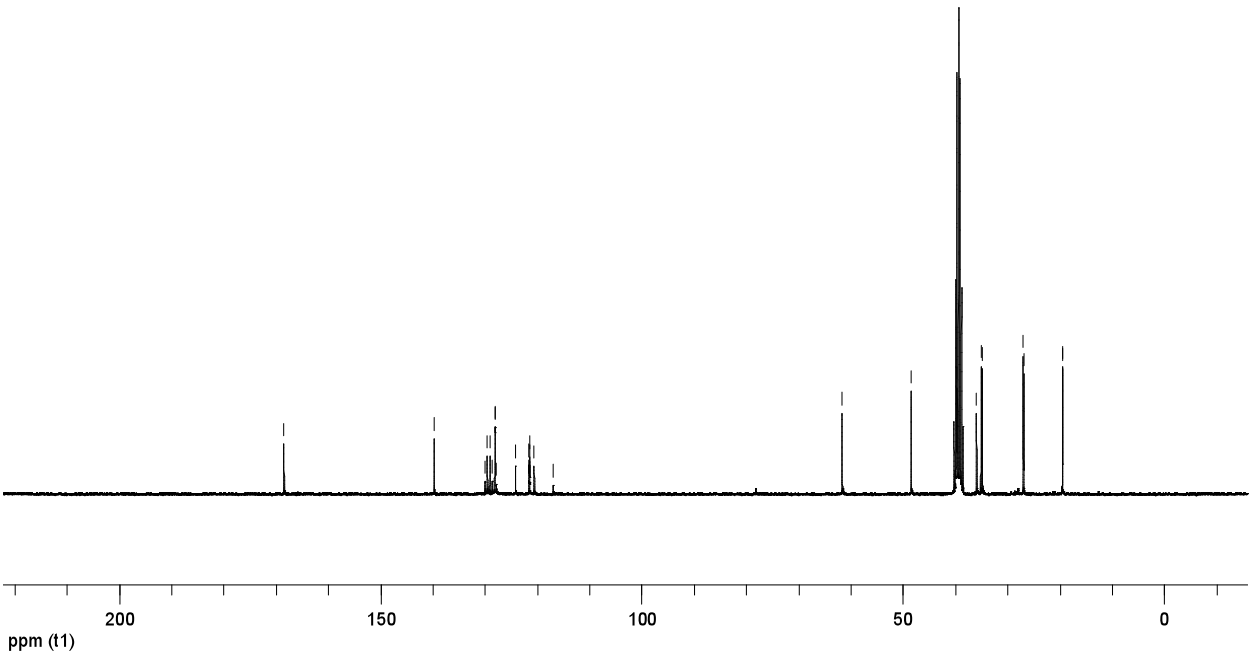


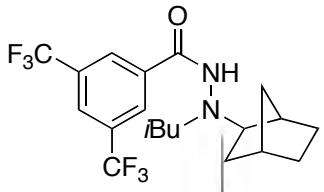


12c
Table 3, Entry 3

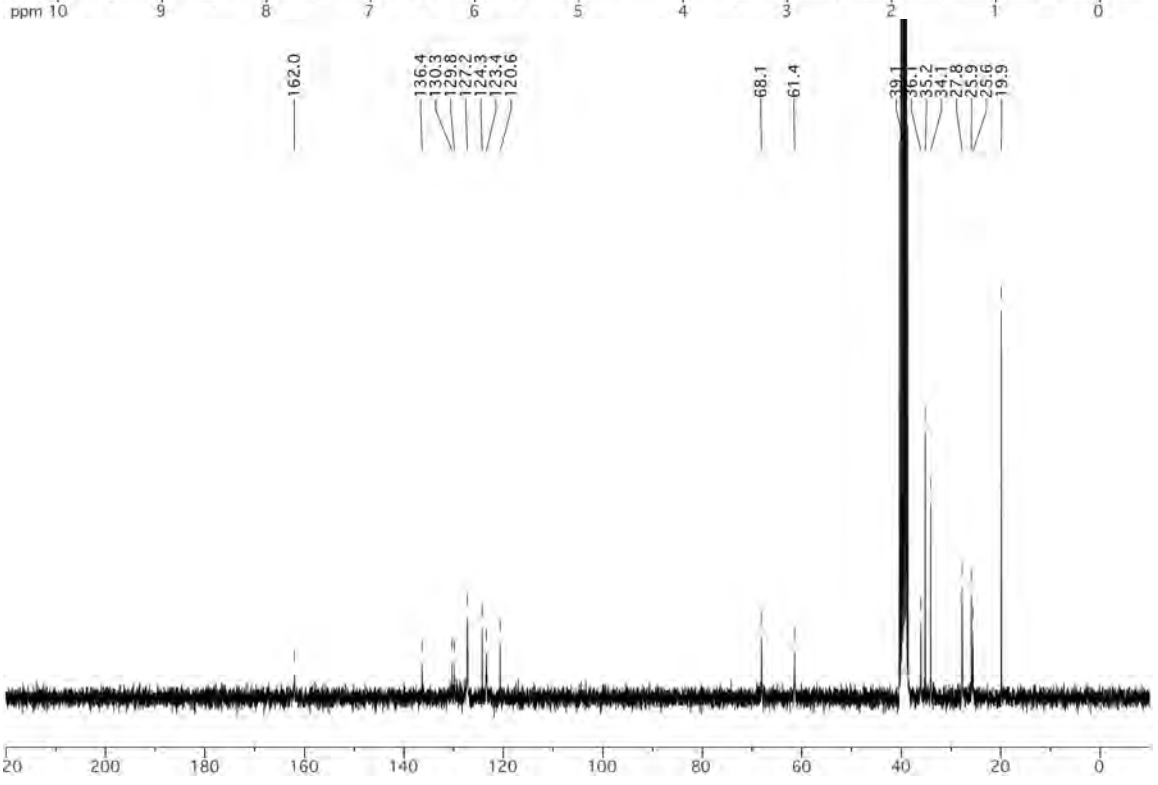


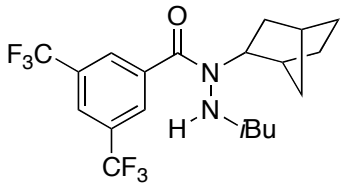




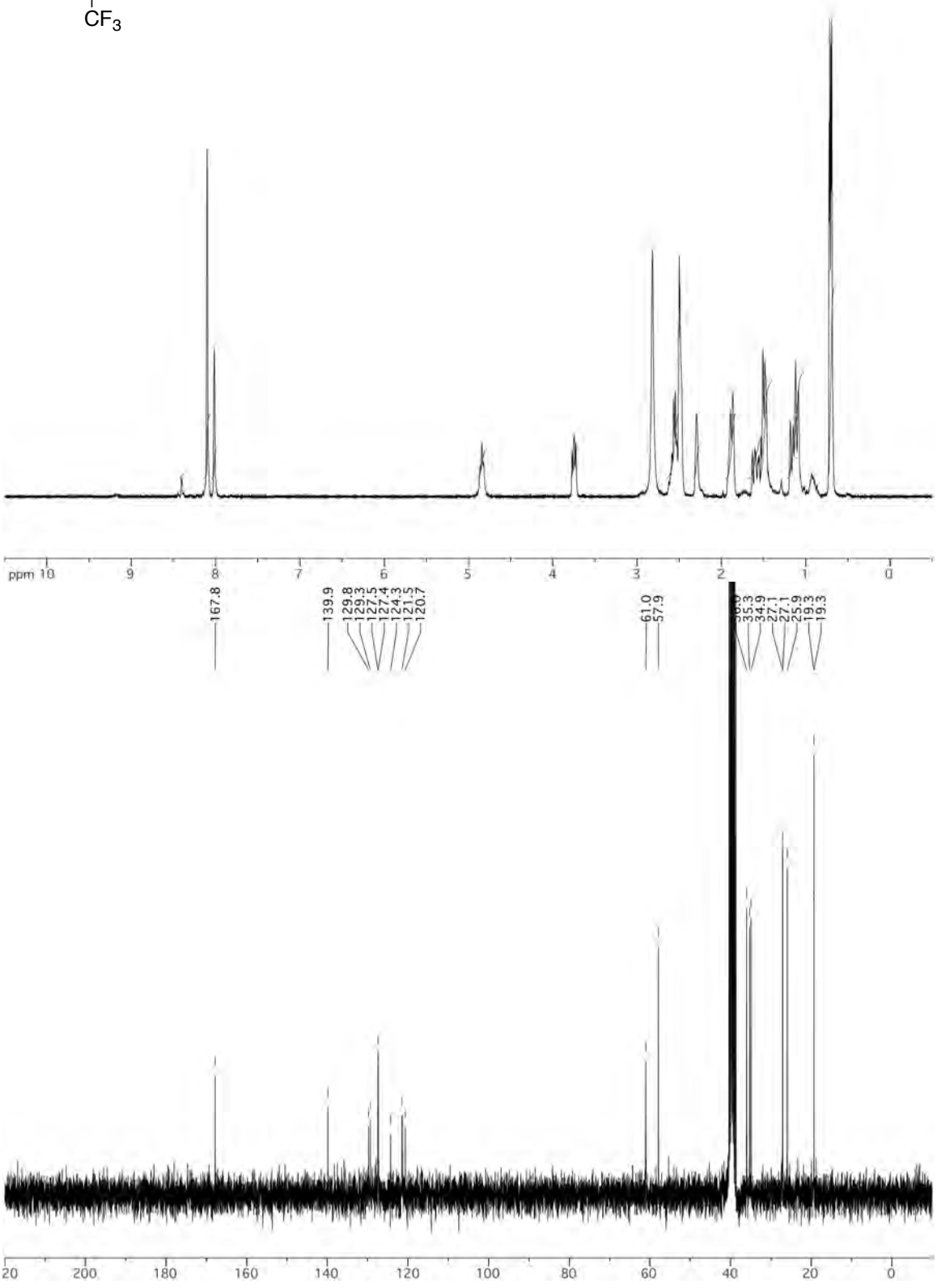


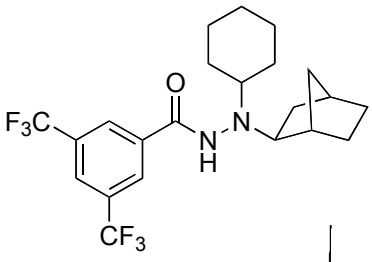
11d
Table 3, Entry 4



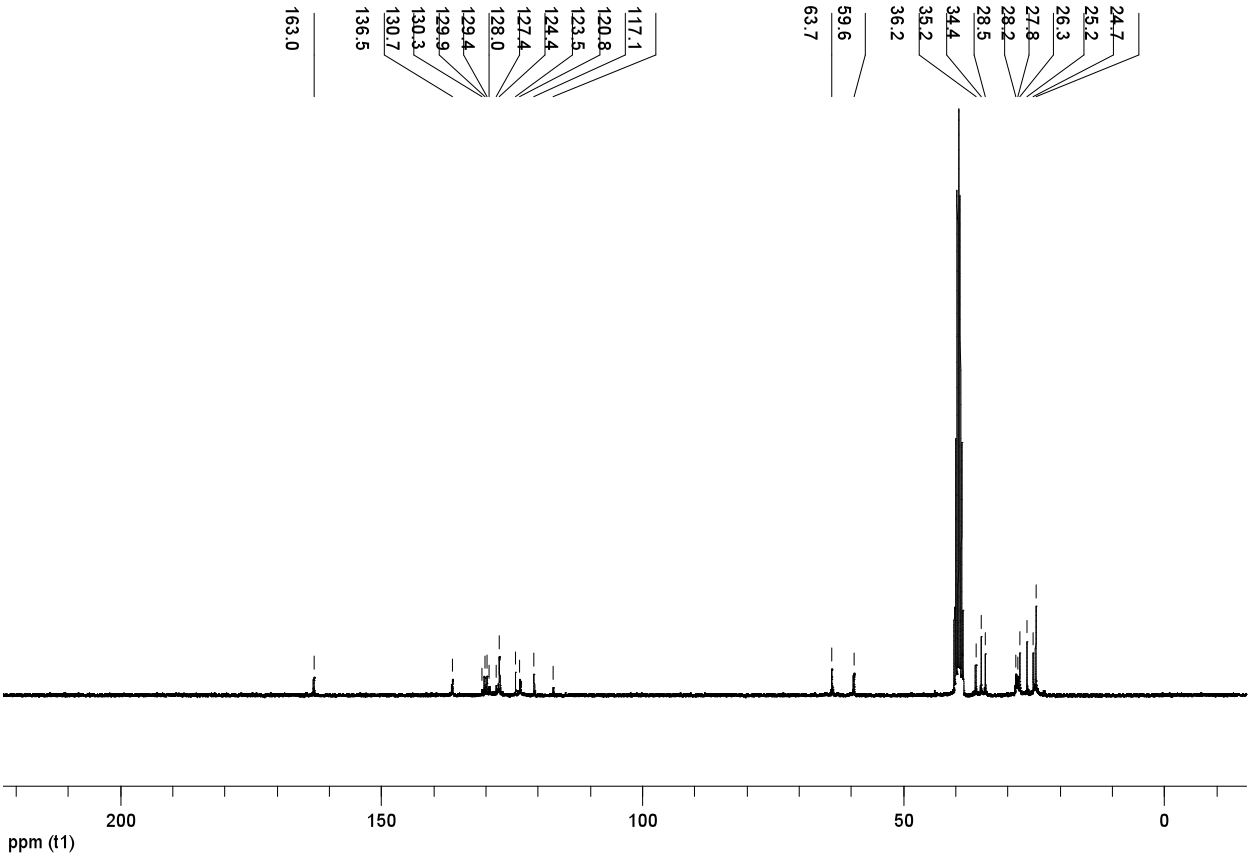


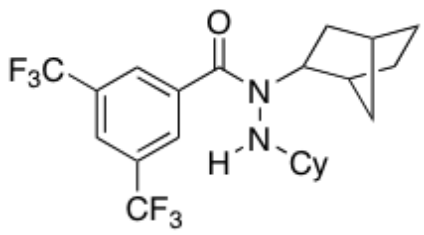
12d
Table 3, Entry 4



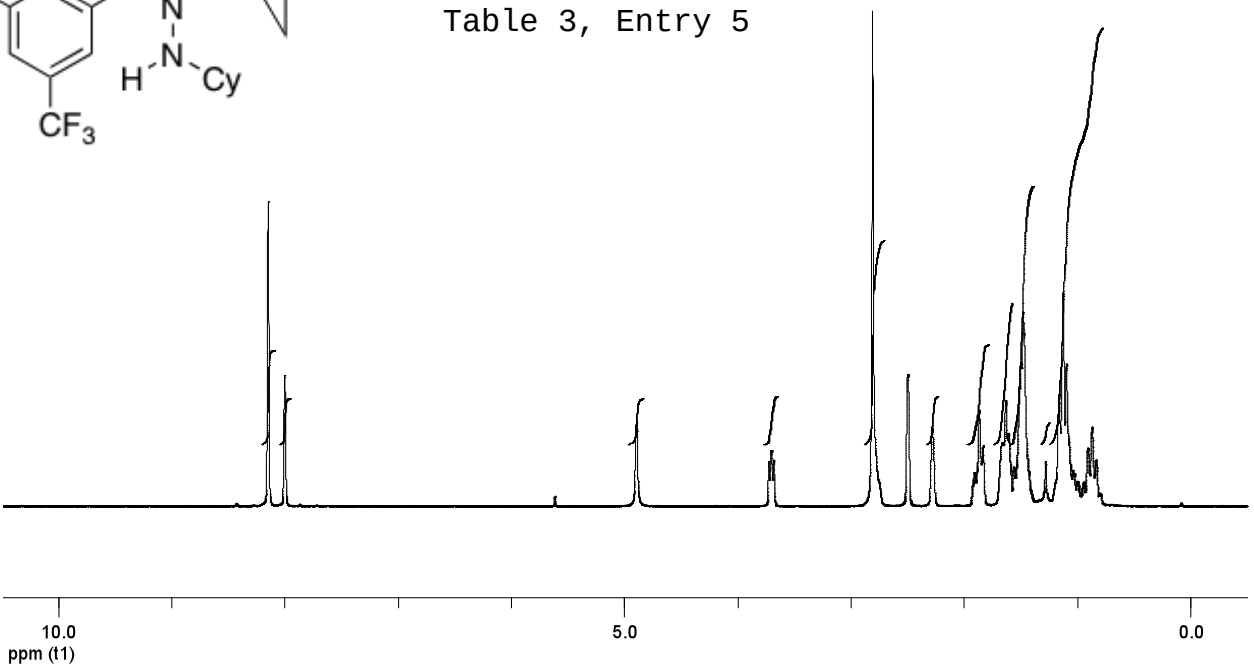


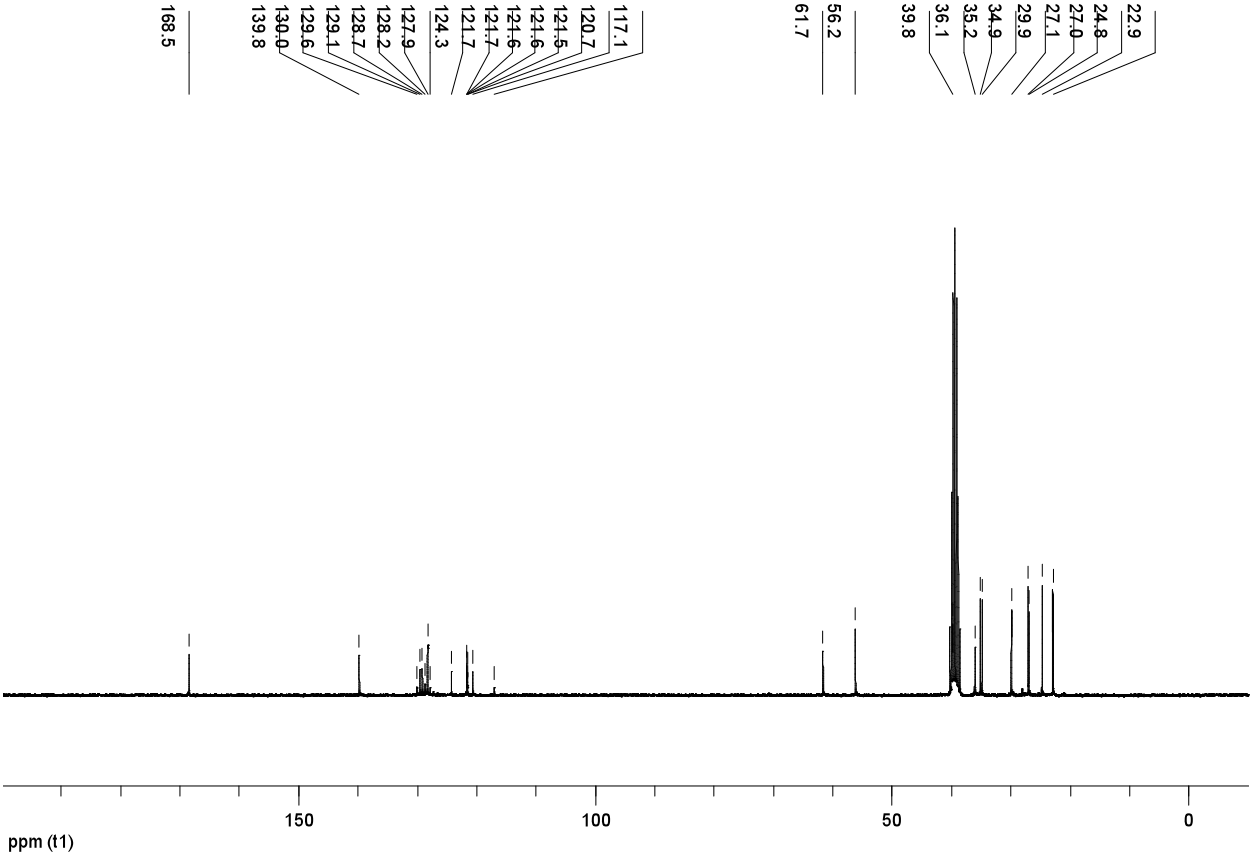
11e
Table 3, Entry 5

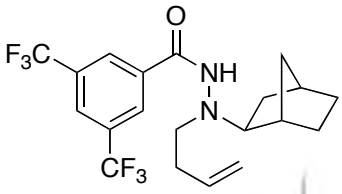




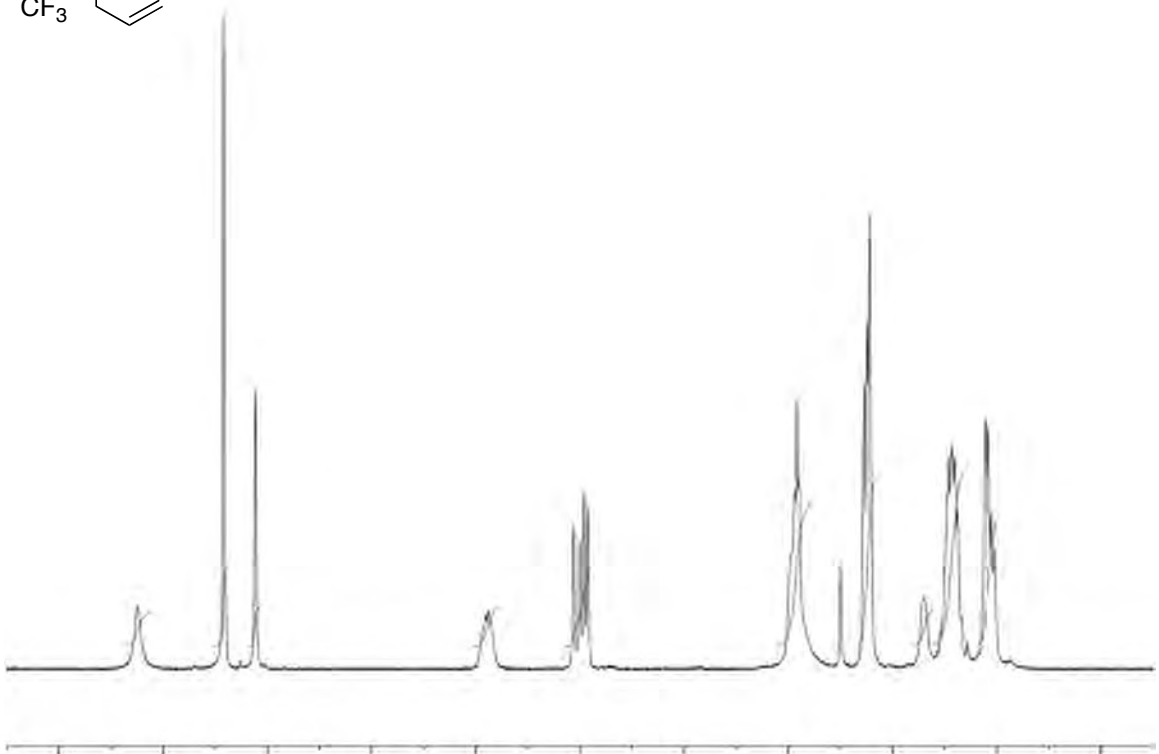
12e
Table 3, Entry 5

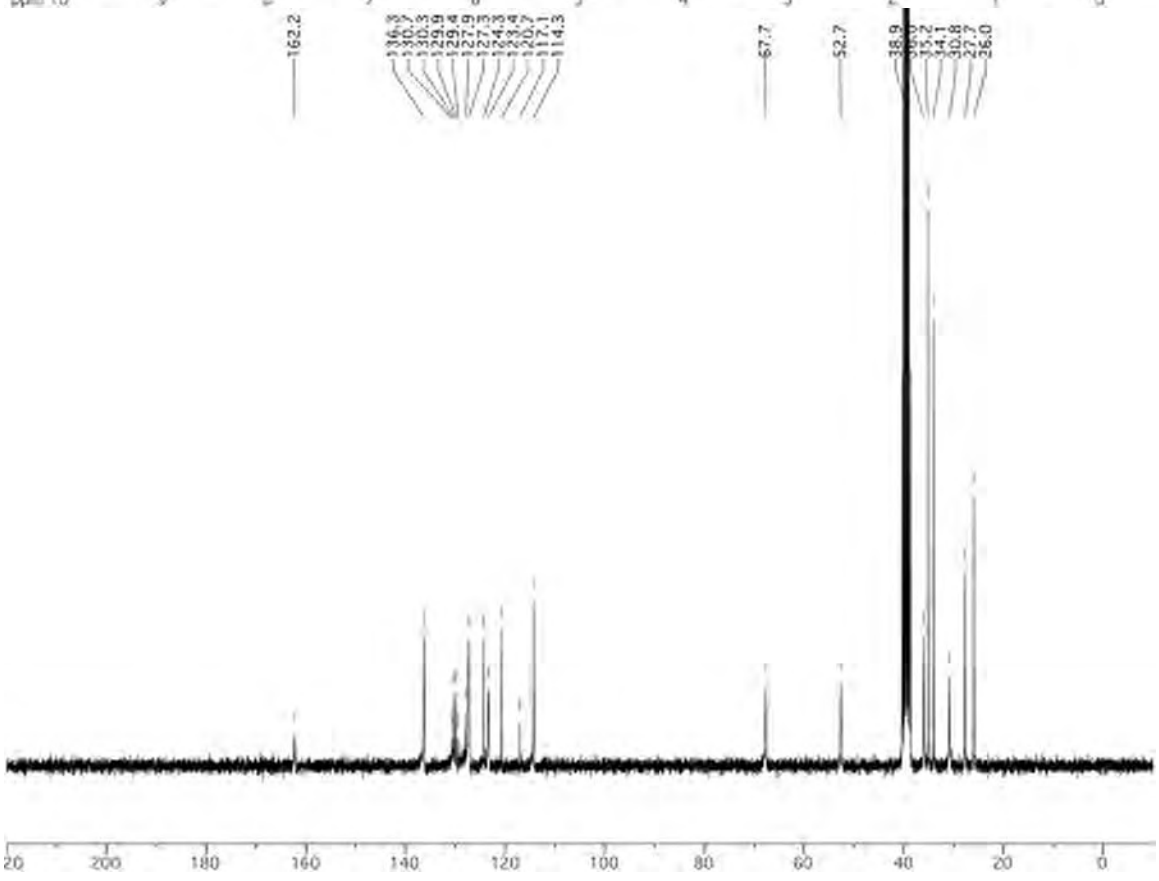


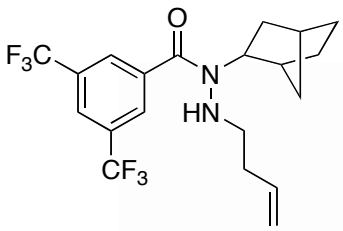




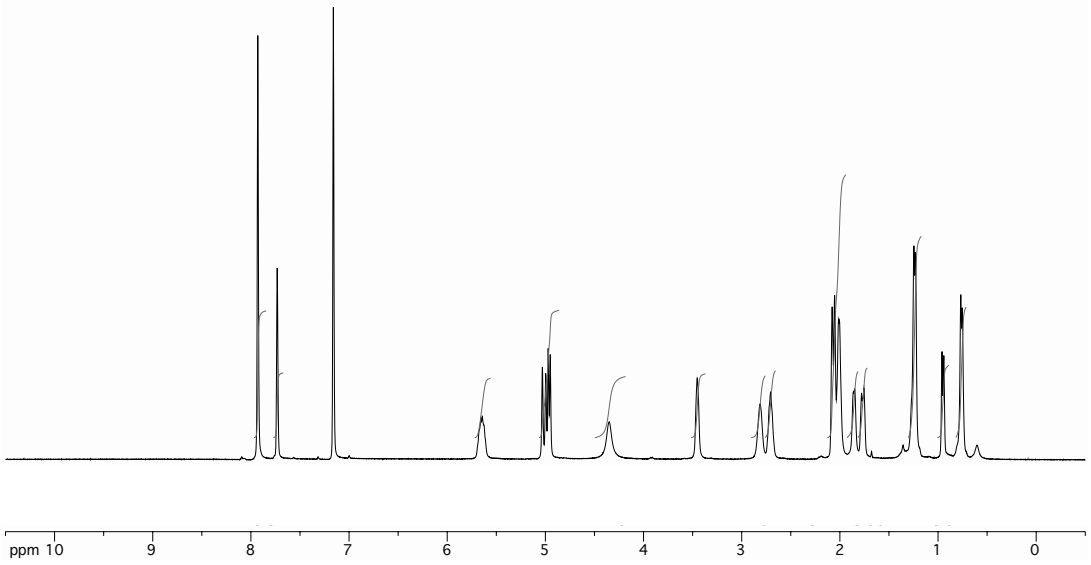
11f
Table 3, Entry 6

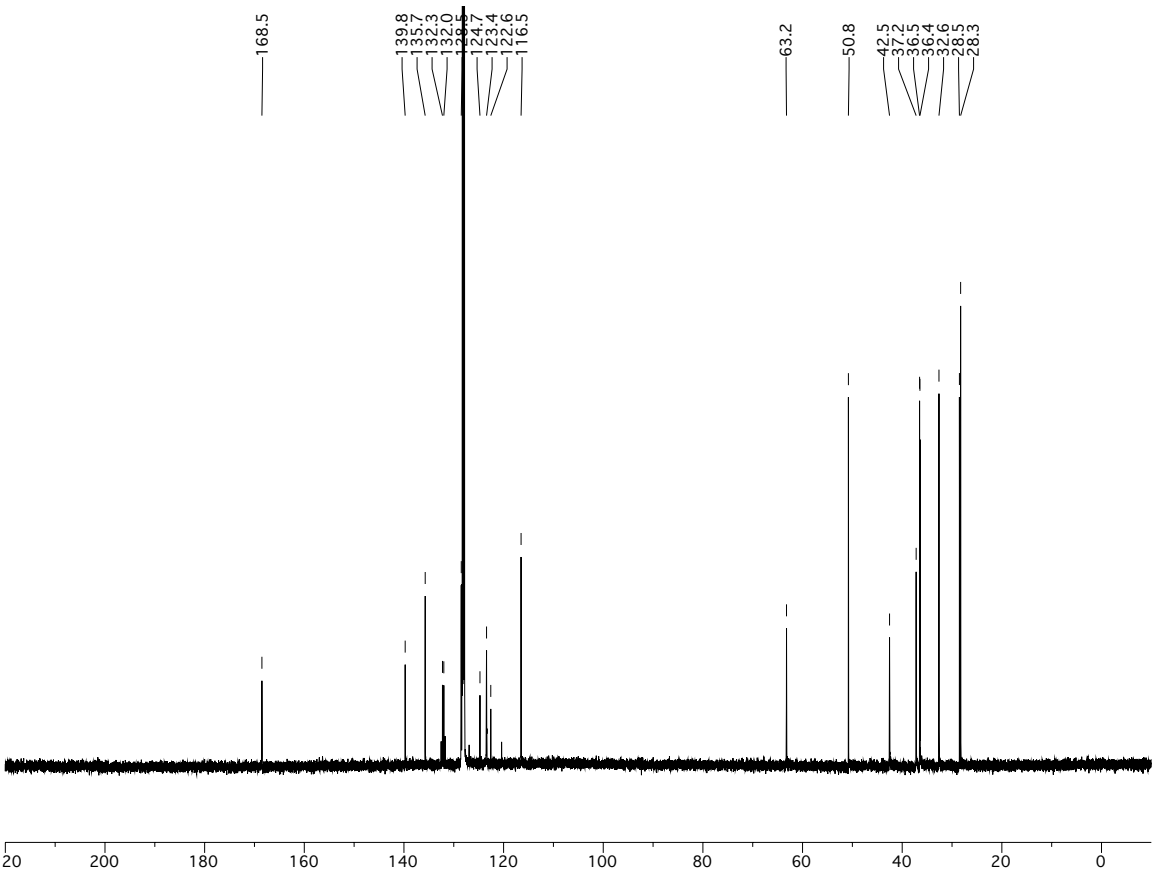


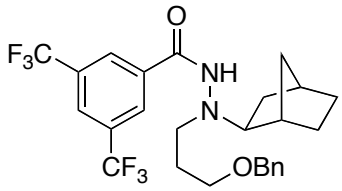




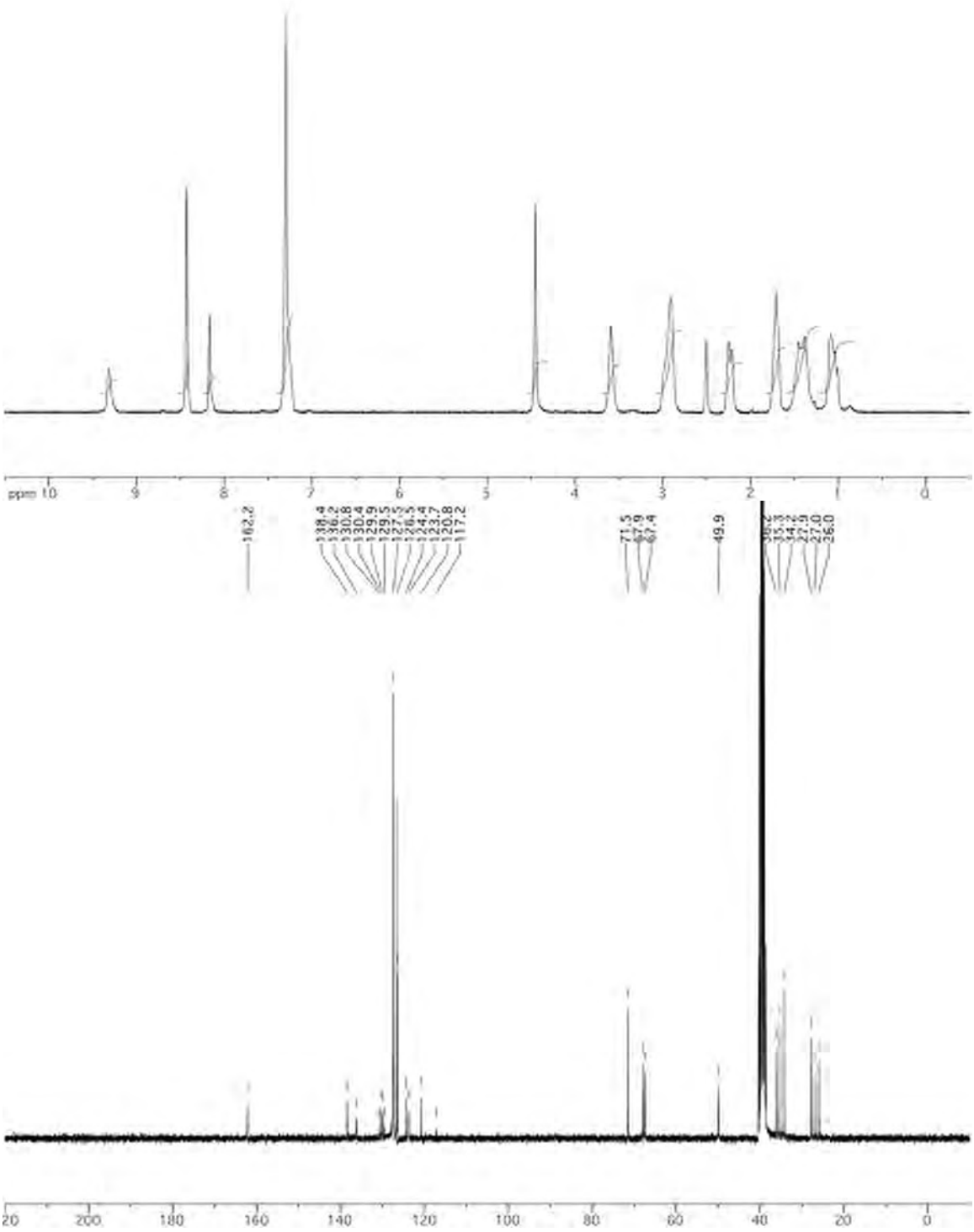
12 f
Table 3, entry 6

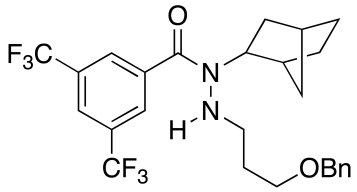




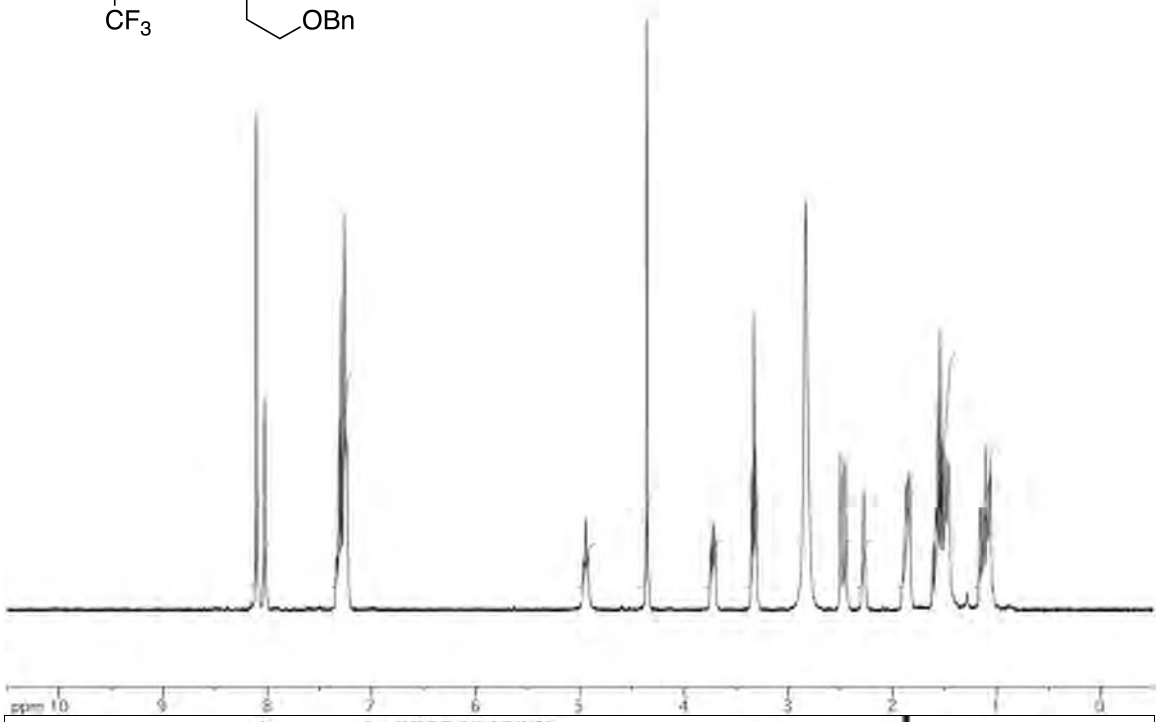


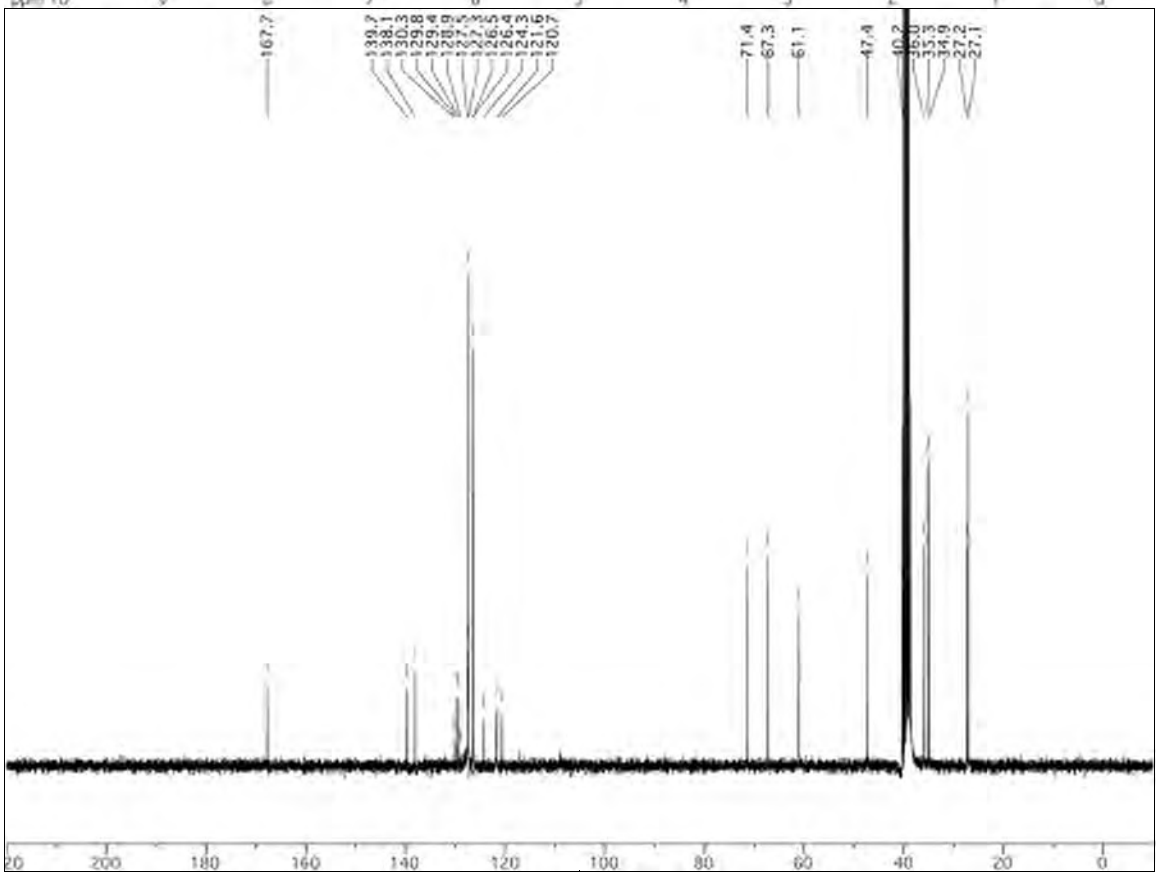
11g
Table 3, Entry 7

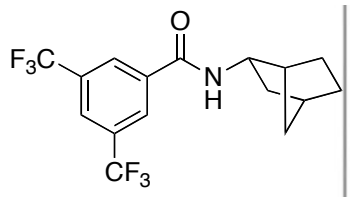




12g
Table 3, Entry 7







Cleavage of the N,N-Bond Product