The Selective Monoarylation of Acetate Esters and Aryl Methyl Ketones Using Aryl Chlorides

Mark R. Biscoe and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, 77 Massachusetts Avenue, Cambridge Massachusetts 02139

Supporting Information

General: Reagent Information. THF, Et_2O, CH_2Cl_2 and toluene were purchased from J.T. Baker in CYCLE-TAINER® solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF and Et_2O) or through neutral alumina and copper (II) oxide (for toluene and CH_2Cl_2). All reagents and solvents were used as received unless otherwise noted. Precatalyst **3** was prepared as described in ref. 1. *t*-Butyl acetate (Aldrich) was distilled from CaH_2. 1M solutions of LHMDS in toluene were purchased from Aldrich. XPhos was received as a gift from Shasun. *t*-BuXPhos was purchased from Strem. KO*t*-Bu (Acros) was stored in a glovebox under an atmosphere of N_2; scintillation vials of KO*t*-Bu were removed from the glovebox and stored in a benchtop desiccator for use (ca. 2 months). Flash chromatography was performed using Silicycle silica gel (ultra pure grade).

General Analytical Information. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR (where applicable) spectroscopy. Copies of the ^{1}H, ^{13}C, and ^{31}P NMR spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Bruker 400 MHz instrument. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm) in the deuterated solvent, unless otherwise stated. All ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), unless otherwise stated, and all were obtained with ^{1}H decoupling. All ^{31}P NMR spectra are reported in ppm relative to H_3PO_4 (0 ppm – external standard). All GC analyses were performed on a Hewlett-Packard 6890 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase.

General Procedural Information.

Representative procedure for the monoarylation of *t*-butyl acetate:

t-BuXPhos precatalyst **3** (4 mg, 0.005 mmol) was added to a test tube equipped with a stirbar. The test tube was sealed with a teflon septum-lined screw cap and evacuated/backfilled with argon. 4-Chlorotoluene (59 μL, 0.5 mmol), *t*-butyl acetate

(101 μL, 0.75 mmol) and 1M LHMDS/toluene solution (1.5 mL, 1.5 mmol) were added in succession via syringe. The reaction mixture was allowed to stir for 30 min at room temperature. At this point, saturated aqueous NH_4Cl (ca. 1 mL) was added to the reaction solution, and the resulting mixture was vigorously shaken. This mixture was then poured into a separatory funnel and extracted three times with EtOAc. The combined organic washes were dried over Na_2SO_4. After column chromatography (2:98 to 4:96 gradient of EtOAc:Hexanes), the desired product was obtained as a colorless liquid (102 mg, 98 %).

Representative procedures for the monoarylation of aryl acetyls:

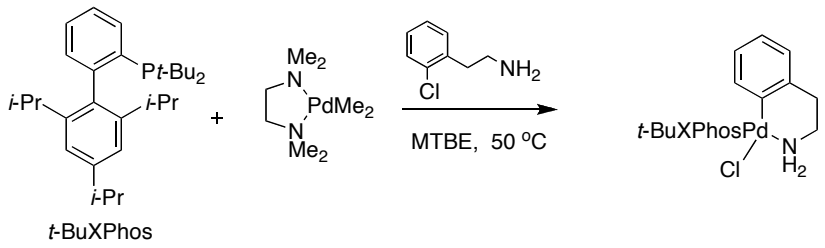
Procedure A: (generally with non-heteroaryl chlorides):

XPhos precatalyst **4** (4 mg, 0.005 mmol) and KO*t*-Bu (112 mg, 1 mmol) were added to a test tube equipped with a stirbar. The test tube was sealed with a teflon septum-lined screw cap and evacuated/backfilled with argon. 4-Butyl chlorobenzene (0.089 g, 0.525 mmol), 2-acetylthiophene (54 μL, 0.5 mmol) and toluene (2.0 mL) were added to the reaction vessel in succession via syringe. The reaction mixture was heated to 60 ºC for 4 h. After cooling to room temperature, saturated aqueous NH_4Cl (ca. 1 mL) was added to the reaction solution, and the resulting mixture was vigorously shaken. This mixture was then poured into a separatory funnel and extracted three times with EtOAc. The combined organic washes were dried over Na_2SO_4. After column chromatography (90:10 Hex:EtOAc), the desired product was obtained as a colorless liquid (114 mg, 88 %).

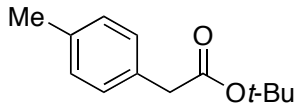
Procedure B (generally with heteroaryl chlorides):

XPhos precatalyst **4** (4 mg, 0.005 mmol) and KO*t*-Bu (132 mg, 1.2 mmol) were added to a test tube equipped with a stirbar. The test tube was sealed with a teflon septum-lined screw cap and evacuated/backfilled with argon. 3-Chloropyridine (48 μL, 0.5 mmol), 3-acetylpyridine (66 μL, 0.6 mmol) and toluene (2.0 mL) were added to the reaction vessel in succession via syringe. The reaction mixture was heated to 60 ºC for 4 h. After cooling to room temperature, saturated aqueous NH_4Cl (ca. 1 mL) was added to the reaction solution, and the resulting mixture was vigorously shaken. This mixture was then poured into a separatory funnel and extracted three times with EtOAc. The combined organic washes were dried over Na_2SO_4. After column chromatography (94:6 CH_2Cl_2:MeOH), the desired product was obtained as a pale yellow solid (84 mg, 85 %).

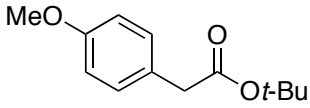
Preparation of *t*-BuXPhos precatalyst:



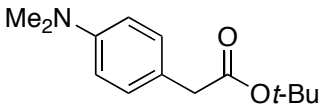
To a Schlenk tube equipped with a stirbar and a teflon screw valve, $Me_2Pd(II)(tmeda)$ (0.48 g, 1.9 mmol) was added. The Schlenk tube was evacuated and back-filled with argon; this sequence was repeated a total of 3 times. Under a positive pressure of argon, the teflon screw valve was replaced with a rubber septum, through which MTBE (4 mL) and 2-chloro phenethylamine (0.3 g, 1.9 mmol) (Aldrich) were added via syringe. Still under a positive pressure of argon, the rubber septum was removed and *t*-BuXPhos (0.8 g, 1.9 mmol) was added. The reaction mixture was then resealed with the Teflon screw valve. The mixture was heated to 50 ºC for 2 h. As the reaction progressed, it became milky-white in appearance. After cooling to room temperature, the reaction mixture was transferred to an Erlenmeyer flask using hexanes and then placed in a -20 ºC freezer for 1 h. Using suction filtration, **6** was isolated as a white powder (0.98 g, 76 %). ^{1}H NMR (400 MHz, $CDCl_3$) is very complex (see below). ^{31}P NMR (162 MHz, $CDCl_3$): δ 57.5.



***tert*-Butyl 2-*p*-tolylacetate** (Table 1, Entry 1). The general procedure was employed as described. A colorless oil (102 mg, 98 %) was isolated by column chromatography (gradient from 98:2 to 96:4 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.16 (m, 4 H), 3.49 (s, 2 H), 2.34 (s, 3 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 136.5, 131.8, 129.3, 129.2, 80.9, 42.4, 28.2, 21.3. IR (neat, cm^{-1}): 3051, 3006, 2979, 2927, 2871, 1734, 1516, 1368, 1258, 1142. Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.97; H, 9.03.

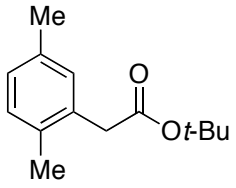


***tert*-Butyl 2-(4-methoxyphenyl)acetate** (Table 1, Entry 2). The general procedure was employed as described. A colorless oil (100 mg, 90 %) was isolated by column chromatography (85:15 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.18 (d, J = 8.7 Hz, 2 H), 6.85 (d, J = 8.7 Hz, 2 H), 3.79 (s, 3 H), 3.46 (s, 2 H), 1.44 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 158.7, 130.4, 127.0, 114.1, 80.9, 55.4, 41.9, 28.2. IR (neat, cm^{-1}): 3036, 3003, 2978, 2935, 2837, 1733, 1614, 1514, 1368, 1036. Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 70.24; H, 8.16. Found: C, 70.21; H, 8.35.

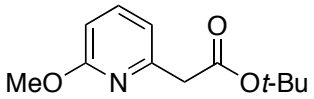


***tert*-Butyl 2-(4-(dimethylamino)phenyl)acetate** (Table 1, Entry 3). The general procedure was employed as described. A colorless liquid (106 mg, 90 %) was isolated by column chromatography (gradient from 90:10 to 85:15 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.13 (d, J = 8.6 Hz, 2 H), 6.70 (d, J = 8.6 Hz, 2 H), 3.42 (s, 2 H), 2.93 (s,

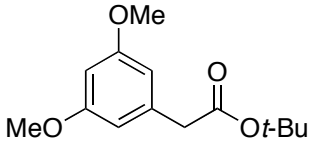
6 H), 1.43 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.9, 149.8, 130.0, 122.9, 113.0, 80.6, 41.8, 41.0, 28.3. IR (neat, cm^{-1}): 3074, 2978, 2931, 2802, 1733, 1617, 1524, 1367, 1141, 948. Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.46; H, 8.99. Found: C, 71.49; H, 8.94.



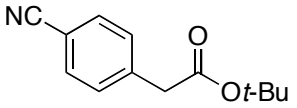
***tert*-Butyl 2-(2,5-dimethylphenyl)acetate** (Table 1, Entry 4). The general procedure was employed as described. A colorless oil (104 mg, 95 %) was isolated by column chromatography (97:3 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.06 (d, J = 7.6 Hz, 1 H), 6.97-7.01 (m, 2 H), 3.51 (s, 2 H), 2.30 (s, 3 H), 2.26 (s, 3 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 135.6, 133.7, 133.4, 131.1, 130.3, 128.0, 80.9, 40.7, 28.5, 21.1, 19.3. IR (neat, cm^{-1}): 3004, 2978, 2927, 2870, 1734, 1506, 1457, 1368, 1145. Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.10; H, 9.28.



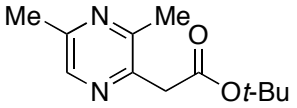
***tert*-Butyl 2-(6-methoxypyridin-2-yl)acetate** (Table 1, Entry 5). The general procedure was employed as described, but using an ice bath instead of at rt. A colorless liquid (103 mg, 92 %) was isolated by column chromatography (90:10 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.50 (dd, J = 8.2, 7.3 Hz, 1 H), 6.80 (d, J = 7.2 Hz, 1 H), 6.59 (d, J = 8.3 Hz, 1 H), 3.90 (s, 3 H), 3.63 (s, 2 H), 1.45 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 163.8, 152.9, 139.0, 116.3, 108.8, 81.1, 53.5, 45.1, 28.2. IR (neat, cm^{-1}): 3069, 3005, 2979, 2952, 2872, 1734, 1602, 1580, 1469, 1036.



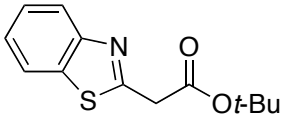
***tert*-Butyl 2-(3,5-dimethoxyphenyl)acetate** (Table 1, Entry 6). The general procedure was employed as described. A colorless oil (112 mg, 89 %) was isolated by column chromatography (85:15 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.43 (d, J = 2.2 Hz, 2 H), 6.36 (t, J = 2.2 Hz, 1 H), 3.78 (s, 6 H), 3.46 (s, 2 H), 1.4 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 160.9, 137.0, 107.4, 99.2, 81.1, 55.5, 43.1, 28.2. IR (neat, cm^{-1}): 3002, 2977, 2937, 2839, 1734, 1598, 1458, 1207, 1068, 686. Anal. Calcd. for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.89; H, 8.12.



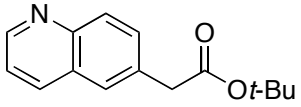
***tert*-Butyl 2-(4-cyanophenyl)acetate** (Table 1, Entry 7).[2] The general procedure was employed as described, but using an ice bath instead of at rt. A white powder (94 mg, 87 %) containing < 5 % diarylated product was isolated by column chromatography (80:20 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 8.4 Hz, 2 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 3.58 (s, 2 H), 1.42 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169,7, 140.2, 132.4, 130.3, 119.0, 111.0, 81.8, 42.7, 28.1. IR (neat, cm^{-1}): 3067, 3052, 3008, 2981, 2227, 1734, 1609, 1510, 1339, 1150.



***tert*-Butyl 2-(3,5-dimethylpyrazin-2-yl)acetate** (Table 1, Entry 8). The general procedure was employed as described. A yellow liquid (93 mg, 84 %) was isolated by column chromatography (50:50 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.21 (s, 1 H), 3.76 (s, 2 H), 2.48 (s, 6 H), 1.42 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 150.4, 149.8, 148.3, 142.2, 81.8, 43.0, 28.2, 21.3, 21.1. IR (neat, cm^{-1}): 3046, 2979, 2929, 1733, 1457, 1369, 1280, 1153. Anal. Calcd. for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16. Found: C, 65.04; H, 8.31.

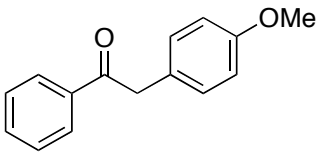


***tert*-Butyl 2-(benzo[*d*]thiazol-2-yl)acetate** (Table 1, Entry 9). The general procedure was employed as described, but with 4 h reaction time. A pale yellow liquid (118 mg, 95 %) was isolated by column chromatography (80:20 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.00 (d, *J* = 8.1 Hz, 1 H), 7.86 (d, *J* = 8.1 Hz, 1 H), 7.46 (td, *J* = 7.1, 1.2 Hz, 1 H), 7.37 (td, *J* = 7.1, 1.2 Hz, 1 H), 4.09 (s, 2 H), 1.49 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 163.5, 152.8, 136.0, 126.2, 125.3, 123.1, 121.7, 82.7, 41.3, 28.2. IR (neat, cm^{-1}): 3064, 2979, 2933, 1734, 1507, 1370, 1151, 761. Anal. Calcd. for $C_{13}H_{15}NO_2S$: C, 62.62; H, 6.06. Found: C, 62.06; H, 5.86.

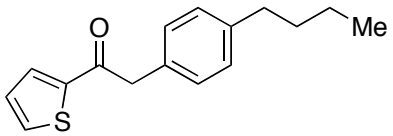


***tert*-Butyl 2-(quinolin-6-yl)acetate** (Table 1, Entry 10). The general procedure was employed as described, but with 14 h reaction time. A yellow liquid (103 mg, 85 %) was isolated by column chromatography (95:5 CH_2Cl_2:MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.88 (dd, *J* = 4.2, 1.7 Hz, 1 H), 8.11 (d, *J* = 8.3 Hz, 1 H), 8.05 (d, *J* = 8.6 Hz, 1 H), 7.69 (s, 1 H), 7.64 (dd, *J* = 8.6, 2.0 Hz, 1 H), 7.38 (dd, *J* = 8.3, 4.2 Hz, 1 H), 3.71 (s, 2 H), 1.44 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 150.4, 147.6, 136.0, 133.3,

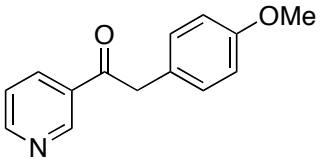
131.3, 129.7, 128.4, 127.9, 121.4, 81.4, 42.8, 28.2. IR (neat, cm^{-1}): 3074, 3003, 2979, 2933, 1729, 1596, 1501, 1368, 1148. Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04. Found: C, 73.89; H, 7.00.



2-(4-Methoxyphenyl)-1-phenylethanone (Table 2, Entry 1). General procedure A was employed as described. A white powder (101 mg, 89 %) was isolated by column chromatography (gradient from 95:5 to 90:10 Hex:EtOAc). Mp: 97-98 ºC (lit mp:[3] 94-96 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.02 (m, 2 H), 7.56 (tt, *J* = 7.0, 1.3 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2 H), 7.20 (d, *J* = 8.7 Hz, 2 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.24 (s, 2 H), 3.78 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.1, 158.6, 136.7, 133.2, 130.6, 128.8, 128.7, 126.6, 114.3, 55.3, 44.7. IR (neat, cm^{-1}): 3055, 3024, 3000, 2928, 1692, 1514, 1447, 1035, 793, 756. Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.62; H, 6.24. Found: C, 79.58; H, 6.19.

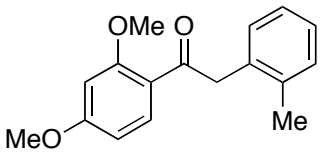


2-(4-Butylphenyl)-1-(thiophen-2-yl)ethanone (Table 2, Entry 2). General procedure A was employed as described. A colorless liquid (114 mg, 88 %) was isolated by column chromatography (90:10 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.77 (dd, *J* = 3.8, 1.1 Hz, 1 H), 7.63 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.22 (m, 2 H), 7.12 (m, 3 H), 4.16 (s, 2 H), 2.59 (t, *J* = 7.7 Hz, 2 H), 1.60 (m, 2 H), 1.36 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 144.1, 141.9, 134.2, 132.8, 131.6, 129.4, 128.9, 128.3, 46.2, 35.4, 33.8, 22.6, 14.1. IR (neat, cm^{-1}): 3052, 3023, 2956, 2928, 2857, 1659, 1515, 1414, 1356, 1059, 724.

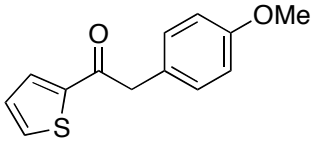


2-(4-Methoxyphenyl)-1-(pyridin-3-yl)ethanone (Table 2, Entry 3). General procedure A was employed as described with the exception that 3 mL of toluene were used. A white powder was isolated (92 mg, 81 %) was isolated by column chromatography (97:3:1 CH_2Cl_2:MeOH:NEt_3). Mp: 91-93 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.22 (s, 1 H), 8.75 (dd, *J* = 4.8, 1.8 Hz, 1 H), 8.24 (dt, *J* = 8.0, 1.8 Hz, 1 H), 7.39 (dd, *J* = 8.0, 4.8 Hz, 1 H), 7.39 (d, *J* = 8.4 Hz, 2 H) 6.85 (d, *J* = 8.4 Hz, 2 H), 4.22 (s, 2 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.8, 158.9, 153.5, 150.1, 136.2, 132.0, 130.6, 125.6, 123.9, 114.4, 55.4, 45.1. IR (neat, cm^{-1}): 2958, 2936, 2836, 1691,

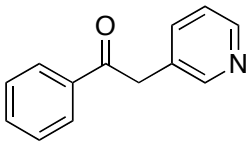
1584, 1516, 1030, 797, 705. Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77. Found: C, 73.30; H, 5.69.



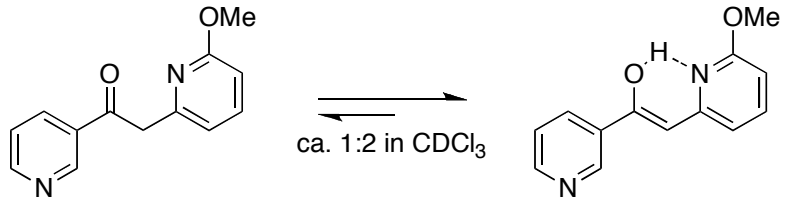
1-(2,4-Dimethoxyphenyl)-2-*o*-tolylethanone (Table 2, Entry 4). General procedure B was employed as described. A colorless oil (131 mg, 97 %) was isolated by column chromatography (70:30 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.82 (d, *J* = 8.7 Hz, 1 H), 7.11-7.18 (m, 4 H), 6.54 (dd, *J* = 8.7, 2.3 Hz, 1 H), 6.48 (d, *J* = 2.3 Hz, 1 H), 4.30 (s, 2 H), 3.91 (s, 3 H), 3.86 (s, 3 H), 2.24 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.8, 164.6, 160.8, 137.2, 134.9, 133.1, 130.4, 130.2, 127.0, 126.0, 121.3, 105.4, 98.5, 55.73, 55.67, 48.6, 20.0. IR (neat, cm^{-1}): 3064, 3015, 2967, 2943, 2840, 1667, 1601, 1464, 1257, 1214, 835, 745.



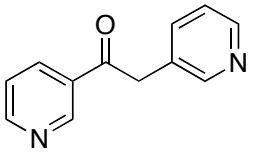
2-(4-Methoxyphenyl)-1-(thiophen-2-yl)ethanone (Table 2, Entry 5). General procedure A was employed as described. A white solid (108 mg, 93 %) was isolated by column chromatography (85:15 Hex:EtOAc). Mp: 78-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (dd, *J* = 3.8, 1.1 Hz, 1 H), 7.63 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.22 (m, 2 H), 7.12 (m, 1 H), 6.85 (m, 2 H), 4.13 (s, 2 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 158.8, 144.0, 134.1, 132.8, 130.6, 128.4, 126.5, 114.3, 55.5, 45.7. IR (neat, cm^{-1}): 3102, 3000, 2955, 2933, 2908, 2835, 1657, 1611, 1512, 1414, 1248, 1179. Anal. Calcd. for $C_{13}H_{12}O_2S$: C, 67.21; H, 5.21. Found: C, 67.47; H, 5.27.



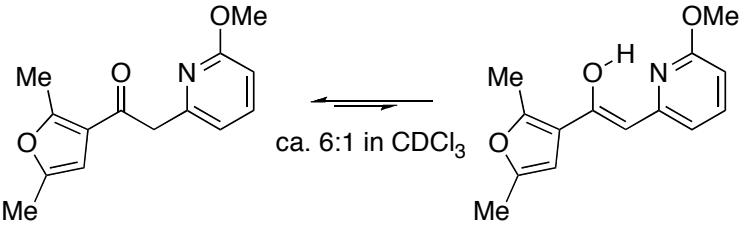
1-Phenyl-2-(pyridin-3-yl)ethanone (Table 2, Entry 6).[4] General procedure B was employed as described. A colorless liquid (88 mg, 90 %) was isolated by column chromatography (90:10 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.52 (m, 2 H), 8.01 (d, *J* = 6.3 Hz, 2 H), 7.58 (app. t, *J* = 7.5 Hz, 2 H), 7.48 (app. t, *J* = 7.8 Hz, 2 H), 7.26 (m, 1 H), 4.30 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.6, 150.8, 148.6, 137.4, 136.4, 133.8, 130.3, 129.0, 128.6, 123.6, 42.5.



2-(6-Methoxypyridin-2-yl)-1-(pyridin-3-yl)ethanone (Table 2, Entry 7). General procedure B was employed as described with the exception that 4 mL of toluene were used. A yellow oil (87 mg, 76 %) was isolated by column chromatography (95:5:1 CH_2Cl_2:MeOH;NEt_3) as a 1:2 mixture of tautomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 14.12 (s, 2.1 H), 9.33 (dd, *J* = 2.2, 0.8 Hz, 1.0 H), 9.03 (dd, *J* = 2.3, 0.7 Hz, 2.1 H), 8.74 (dd, *J* = 4.8, 1.7 Hz, 1.0 H), 8.58 (dd, *J* = 4.8, 1.6 Hz, 2.1 H), 8.33 (dt, *J* = 8.0, 1.9 Hz, 1.0 H), 8.05 (dt, *J* = 8.0, 1.9 Hz, 2.1 H), 7.56 (dd, *J* = 8.2, 7.5 Hz, 2.1 H), 7.52 (dd, *J* = 8.2, 7.2 Hz, 1.0 H), 7.39 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 1.0 H), 7.32 (ddd, *J* = 8.0, 4.8, 0.8 Hz, 2.1 H), 6.86 (d, *J* = 7.2 Hz, 1.0 H), 6.71 (d, *J* = 7.2 Hz, 2.1 H), 6.59 (d, *J* = 8.2 Hz, 1.0 H), 6.55 (d, *J* = 8.2 Hz, 2.1 H), 6.08 (s, 2.1 H), 4.36 (s, 2.0 H), 4.00 (s, 6.6 H), 3.80 (s, 3.0 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.2, 163.9, 162.0, 158.0, 155.5, 153.6, 152.0, 151.0, 150.1, 147.1, 140.0, 139.4, 136.4, 132.7, 132.1, 131.7, 123.7, 123.4, 116.7, 114.5, 109.3, 107.4, 97.0, 53.8, 53.5, 48.6. IR (neat, cm^{-1}): 3410, 3035, 2979, 2910, 1690, 1584, 1440.

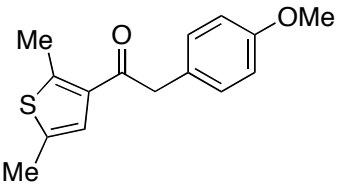


1,2-Di(pyridin-3-yl)ethanone (Table 2, Entry 8). General procedure B was employed as described. A pale yellow solid (84 mg, 85 %) was isolated by column chromatography (94:6 CH_2Cl_2:MeOH). Mp: 82-84 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.24 (m, 1 H), 8.80 (dd, *J* = 4.8, 1.7 Hz, 1 H), 8.53 (dd, *J* = 4.8, 1.6 Hz, 1 H), 8.51 (d, *J* = 1.9 Hz, 1 H), 8.26 (dt, *J* = 8.0, 2.0 Hz, 1 H), 7.59 (dt, *J* = 7.9, 2.0 Hz, 1 H), 7.44 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1 H), 7.28 (dd, *J* = 7.4, 4.8 Hz, 1 H), 4.32 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 154.1, 150.8, 150.0, 148.9, 137.4, 135.9, 131.7, 129.4, 124.0, 123.7, 42.8. IR (neat, cm^{-1}): 3035, 2915, 1692, 1586, 1481, 1421, 1336, 704. Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08. Found: C, 72.52; H, 5.13.

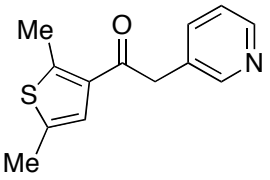


1-(2,5-Dimethylfuran-3-yl)-2-(6-methoxypyridin-2-yl)ethanone (Table 2, Entry 9). General procedure B was employed as described with the exception that 3 mL of toluene were used. A colorless oil (95 mg, 78 %) was isolated by column chromatography (85:15 Hex:EtOAc) as a 6:1 mixture of tautomers. ^{1}H NMR (400 MHz,

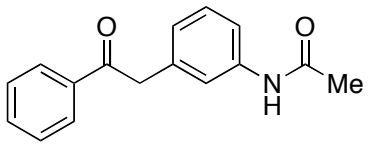
$CDCl_3$) δ: 13.8 (s, 0.15 H), 7.45-7.51 (m, 1.0 H), 6.81, (d, *J* = 7.6 Hz, 0.85 H), 6.58 (d, *J* = 8.4 Hz, 0.85 H), 6.56 (d, *J* = 7.6 Hz, 0.15 H), 6.43 (d, *J* = 8.4 Hz, 0.15 H), 6.34 (s, 0.85 H), 6.08 (s, 0.15 H), 5.57 (s, 0.15 H), 4.05 (s, 1.70 H), 3.96 (s, 0.45 H), 3.87 (s, 2.55 H), 2.54 (s, 2.55 H), 2.53 (s, 0.45 H), 2.23 (s, 0.45 H), 2.22 (s, 2.55 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.4, 163.9, 161.9, 158.0, 157.8, 156.7, 153.0, 150.1, 149.9, 139.7, 139.1, 121.7, 117.8, 116.7, 113.4, 108.7, 106.4, 106.2, 105.7, 104.9, 95.7, 53.7, 53.4, 50.7, 14.5, 14.2, 13.5, 13.3. IR (neat, cm^{-1}): 3402, 3073, 2981, 2950, 2923, 1677, 1600, 1577, 1468, 1033, 736.



1-(2,5-Dimethylthiophen-3-yl)-2-(4-methoxyphenyl)ethanone (Table 2, Entry 10). General procedure A was employed as described with the exception that 3 mL of toluene were used. A colorless liquid that solidified into a white solid (107 mg, 82 %) was isolated by column chromatography (90:10 Hex:EtOAc) (Mp: 42-43 ºC). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.15 (d, *J* = 8.7 Hz, 2 H), 7.07 (s, 1 H), 6.88 (d, *J* = 8.7 Hz, 2 H), 4.03 (s, 2 H), 3.79 (s, 3 H), 2.66 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.1, 158.6, 148.6, 135.3, 135.2, 130.7, 126.9, 126.3, 114.2, 55.4, 47.7, 16.3, 15.2. IR (neat, cm^{-1}): 3033, 2996, 2954, 2920, 2834, 1665, 1613, 1512, 1479, 1248, 1126, 1035. Anal. Calcd. for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19. Found: C, 69.49; H, 6.24.



1-(2,5-Dimethylthiophen-3-yl)-2-(pyridin-3-yl)ethanone (Table 2, Entry 11). General procedure B was employed as described with the exception that 3 mL of toluene were used. A pale yellow oil (98 mg, 85 %) was isolated by column chromatography (50:50 Hex:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.50 (dd, *J* = 4.8, 1.4 Hz, 1 H), 8.46 (d, *J* = 1.7 Hz, 1 H), 7.57 (dt, *J* = 7.8, 1.8 Hz, 1 H), 7.26 (m, 1 H), 7.07 (s, 1 H), 4.09 (s, 2 H), 2.64 (s, 3 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 192.4, 150.8, 149.2, 148.4, 137.4, 135.7, 134.7, 130.5, 125.9, 123.5, 45.3, 16.3, 15.2. IR (neat, cm^{-1}): 3030, 2953, 2920, 2859, 1669, 1577, 1549, 1479, 1360, 1130, 1028. Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.50; H, 5.66. Found: C, 67.11; H, 5.67.

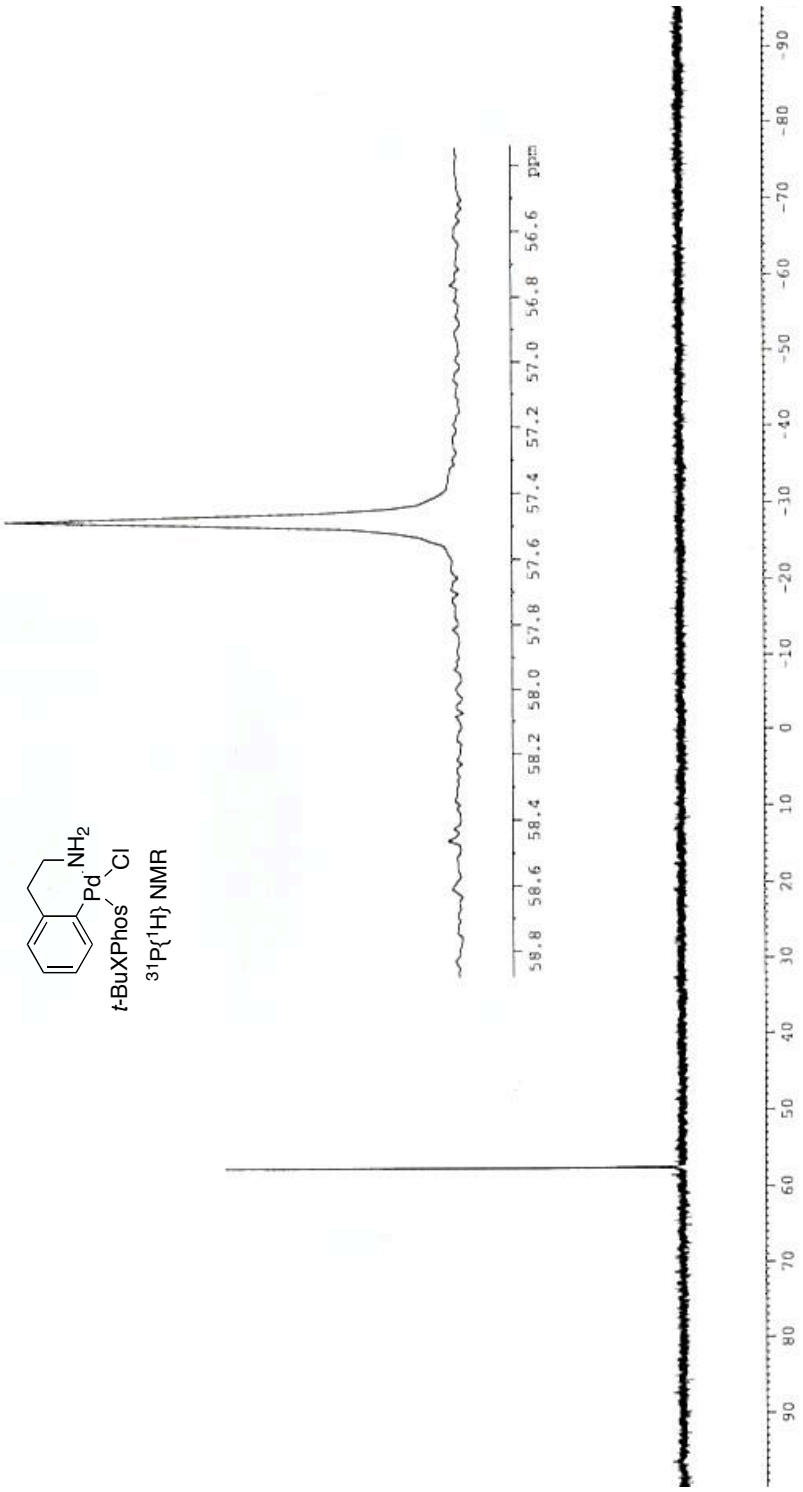


***N*-(3-(2-Oxo-2-phenylethyl)phenyl)acetamide** (Table 2, Entry 12). General procedure B was employed as described with the exception that 3 mL of toluene were used. A white powder (108 mg, 86 %) was isolated by column chromatography (gradient from 50:50 to 25:75 Hex:EtOAc). Mp: 126-128 ºC. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.15 (s, 1 H), 7.98 (d, *J* = 7.2 Hz, 2 H), 7.54 (t, *J* = 7.8 Hz, 1 H), 7.44 (app. t, *J* = 7.8 Hz, 3 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.19 (t, *J* = 7.8 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 4.22 (s, 2 H), 2.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 169.1, 138.7, 136.5, 135.2, 133.6, 129.2, 128.9, 128.7, 125.3, 121.3, 118.7, 45.5, 24.5. IR (neat, cm^{-1}): 3313, 3151, 3087, 2919, 1676, 1612, 1595, 1581, 1553, 1491, 1210, 691. Anal. Calcd. for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97. Found: C, 75.32; H, 6.00.

References:

1) Biscoe, M. R.; Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 6686.
2) Hama, T.; Hartwig, J. F. *Org. Lett.* **2008**, *10*, 1549.
3) Dittmer, D. C. *J. Org. Chem.* **1959**, *24*, 651.
4) Raynolds, S. *J. Am. Chem. Soc.* **1960**, *82*, 472.

Compound **4**


NH2
Pd
Cl
t-BuXPhos
31P{1H} NMR
58.8 58.6 58.4 58.2 58.0 57.8 57.6 57.4 57.2 57.0 56.8 56.6 ppm
90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90

Compound **4**

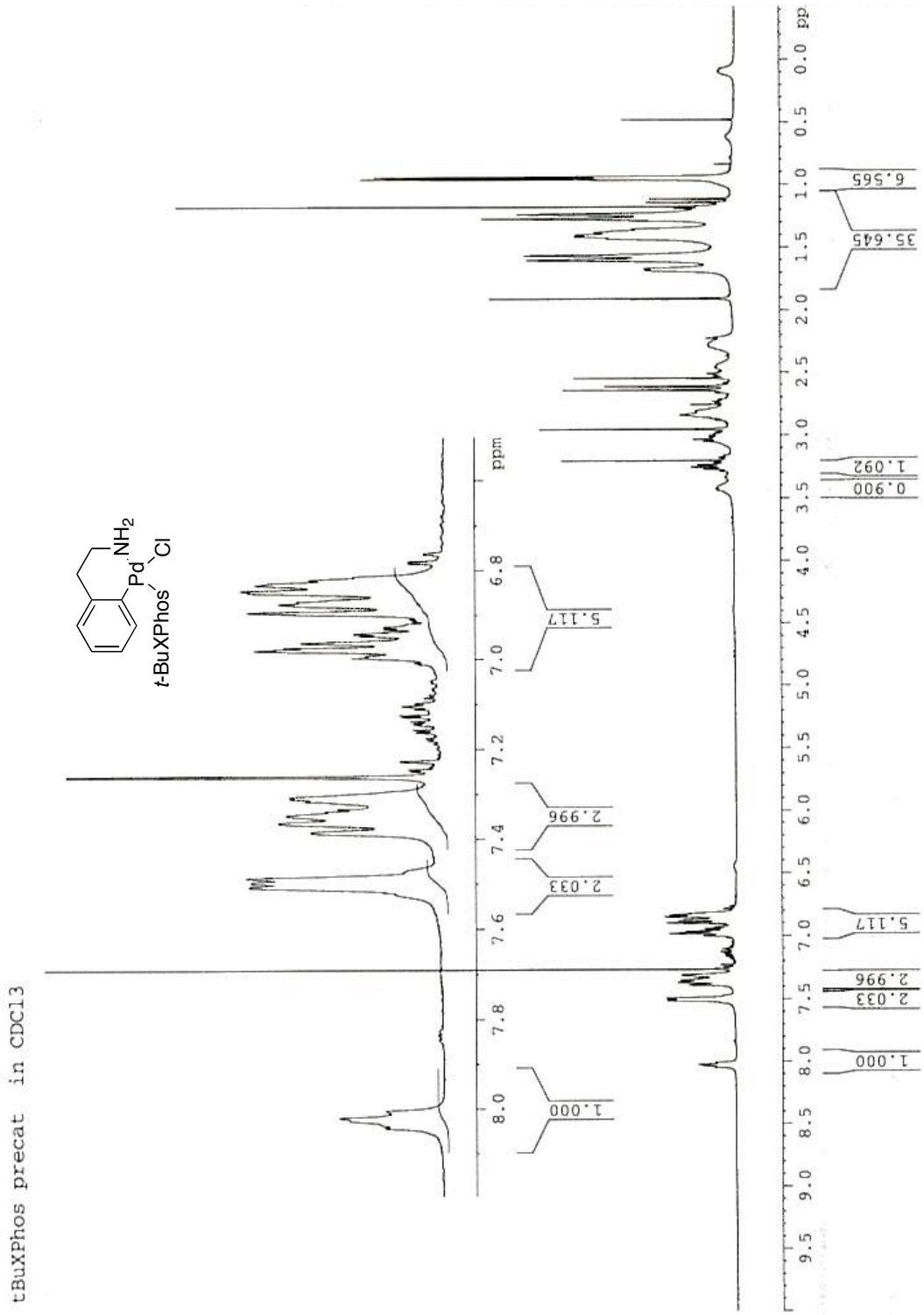

tBuXPhos precat in CDCl3
NH2
Pd
Cl
t-BuXPhos
ppm
1.000
2.033
2.996
5.117
6.565
35.645
1.092
0.900

Table 1, Entry 1

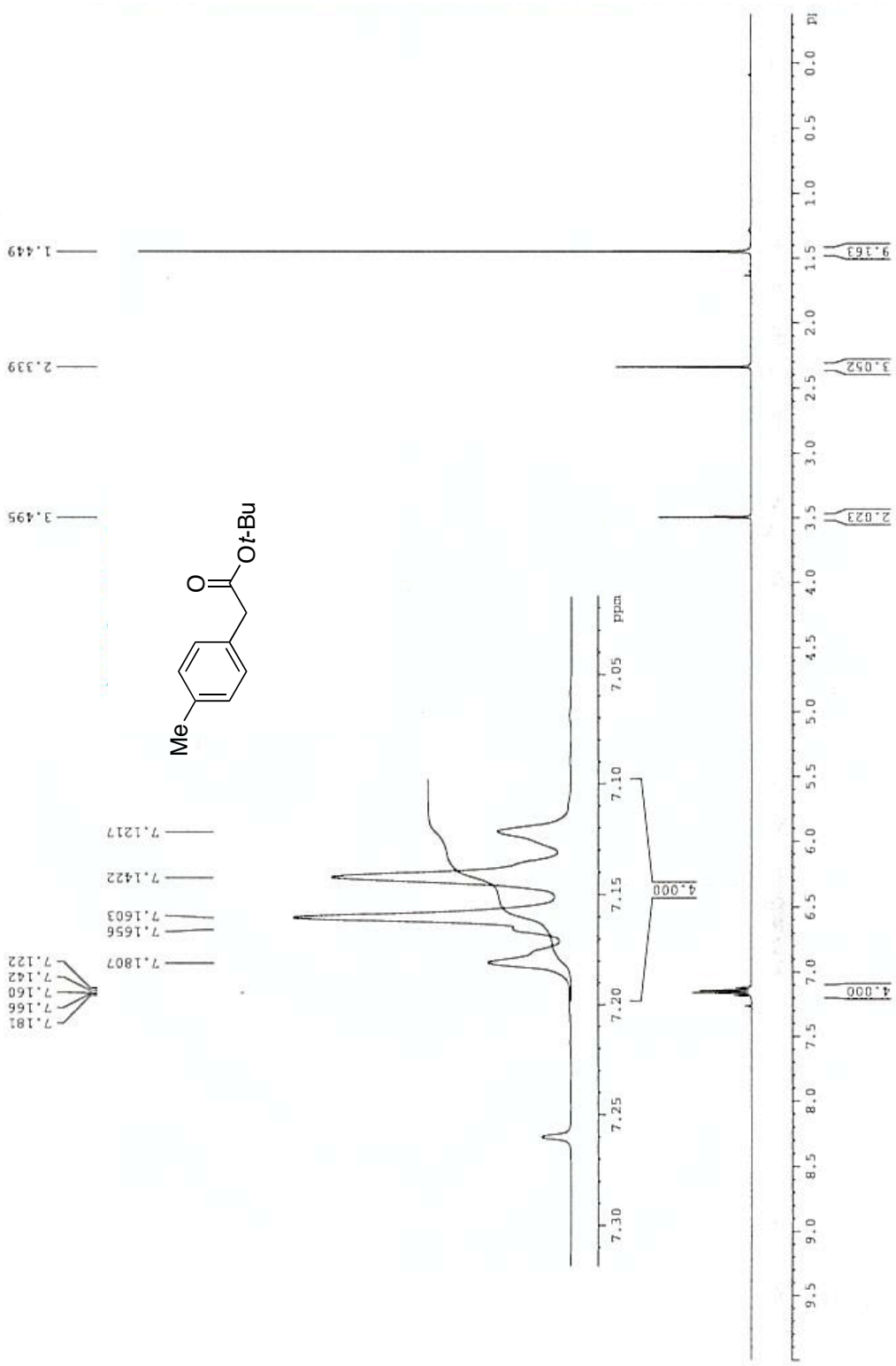


Table 1, Entry 1

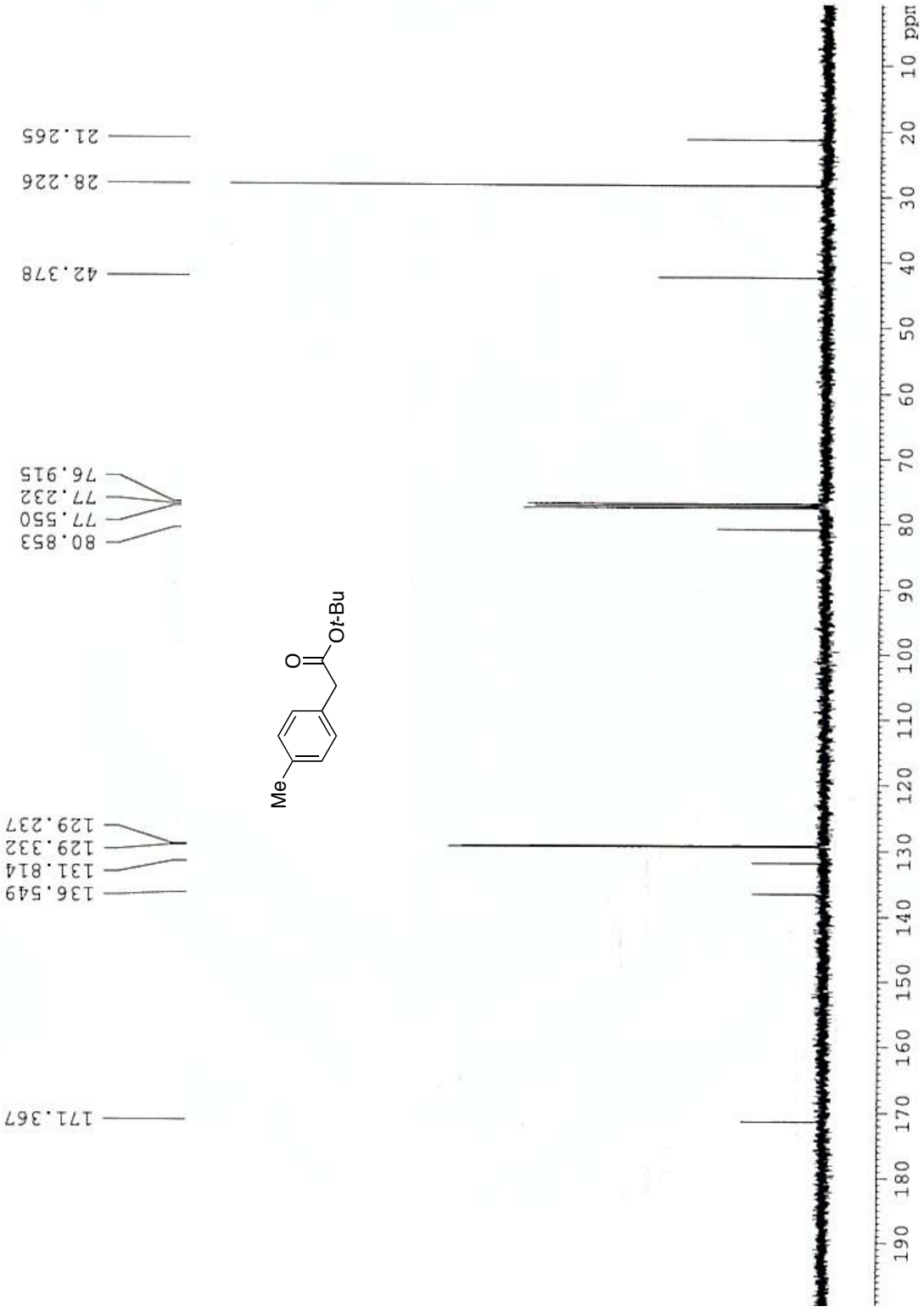


Table 1, Entry 2

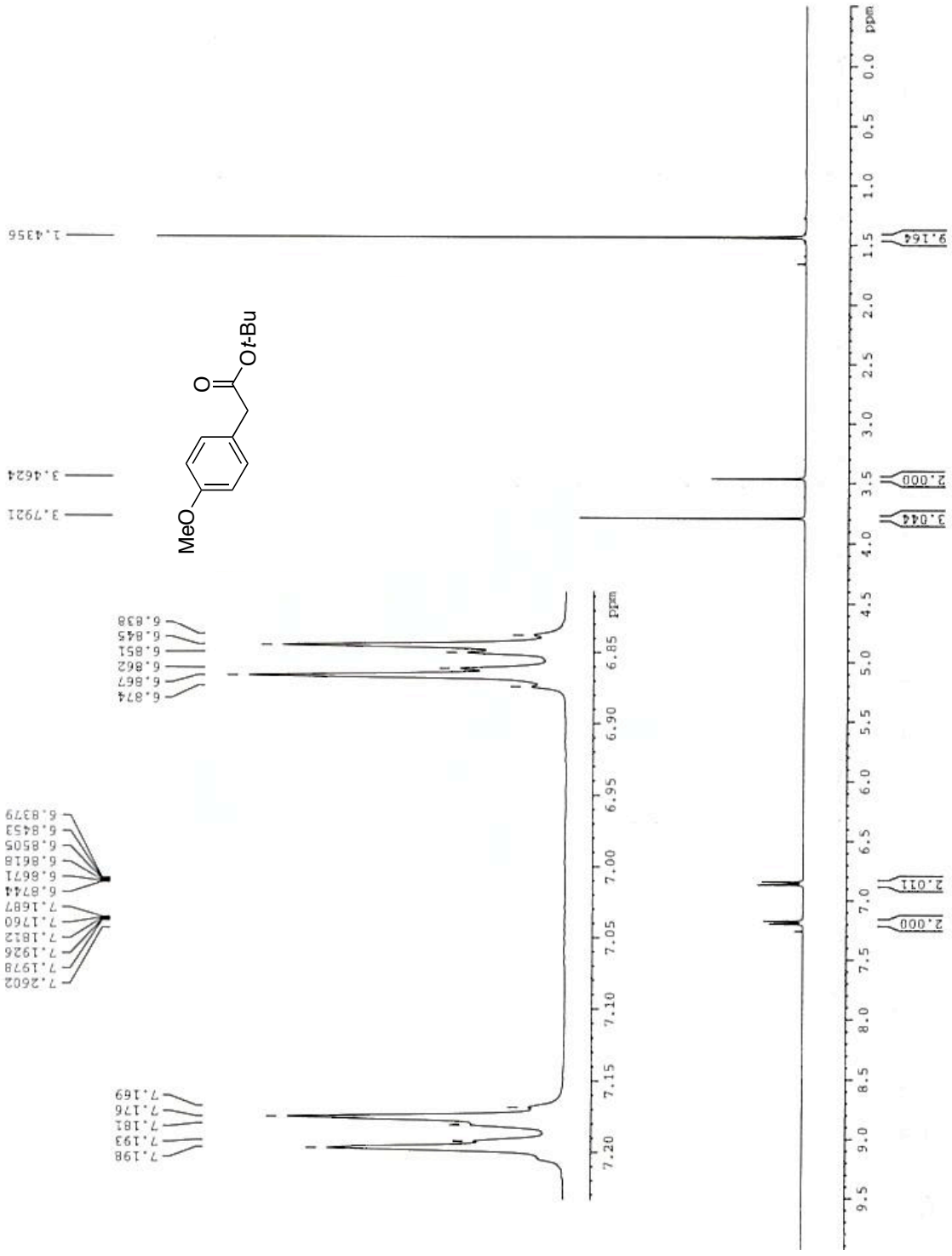


Table 1, Entry 2

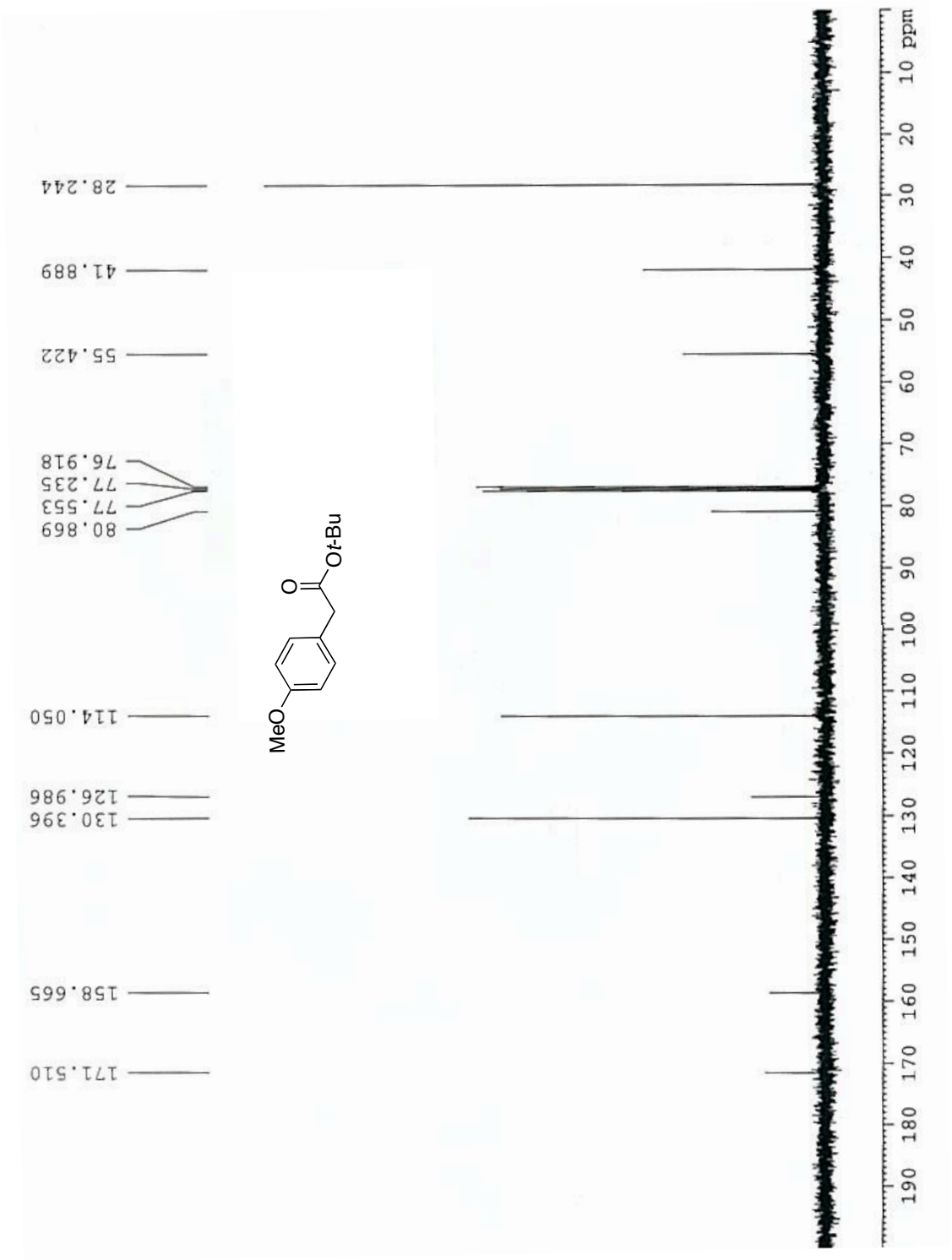


Table 1, Entry 3

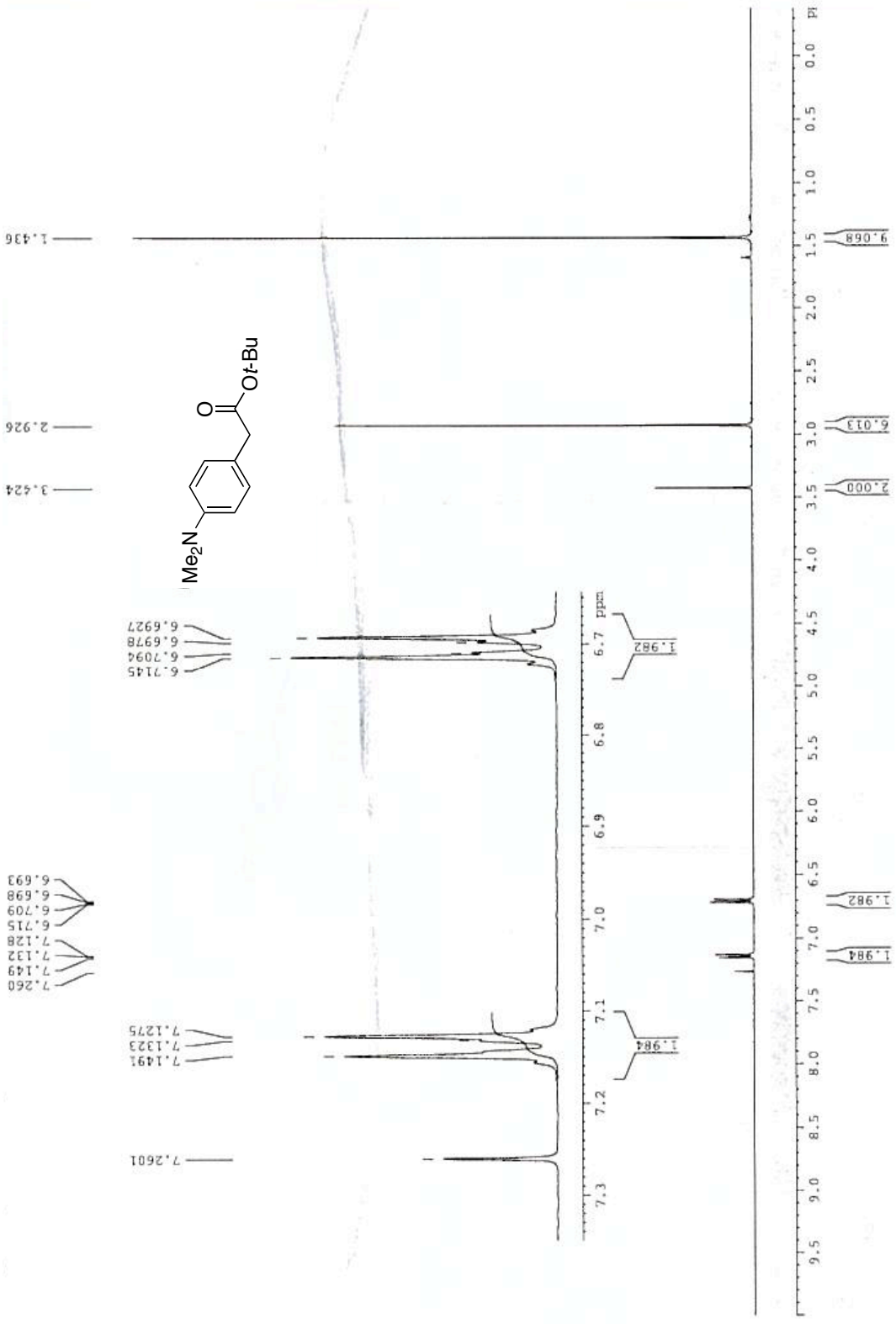


Table 1, Entry 3

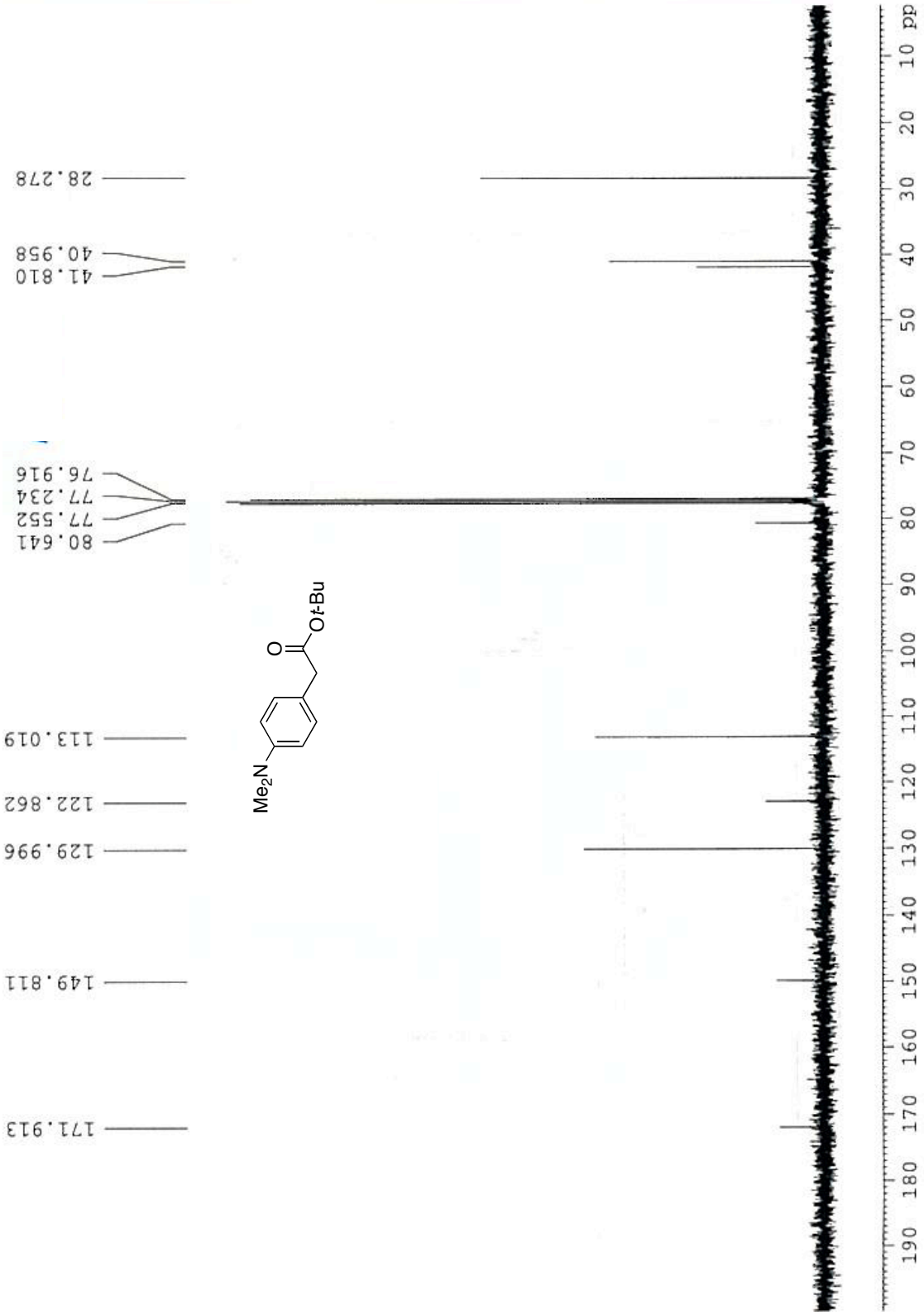


Table 1, Entry 4

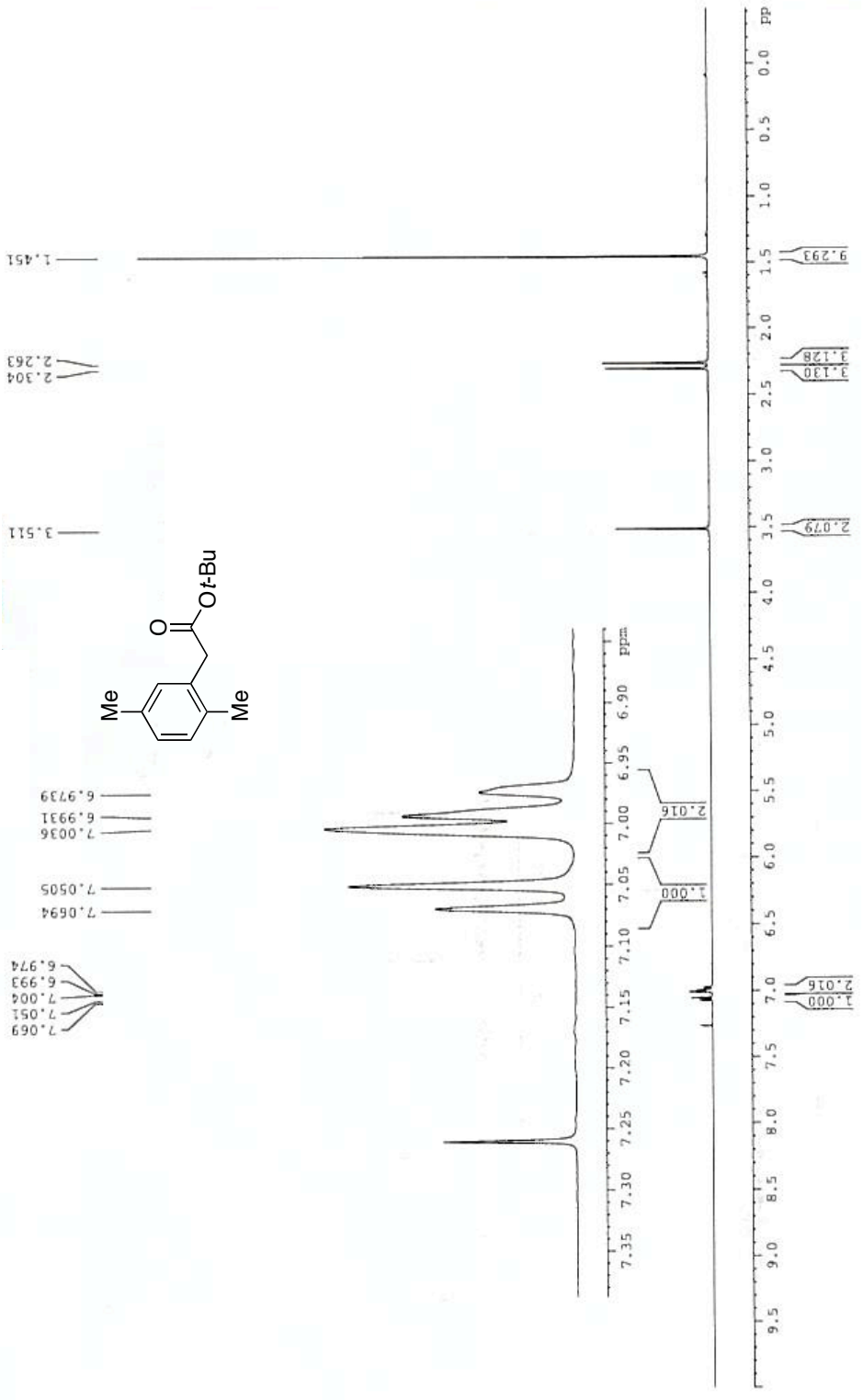


Table 1, Entry 4

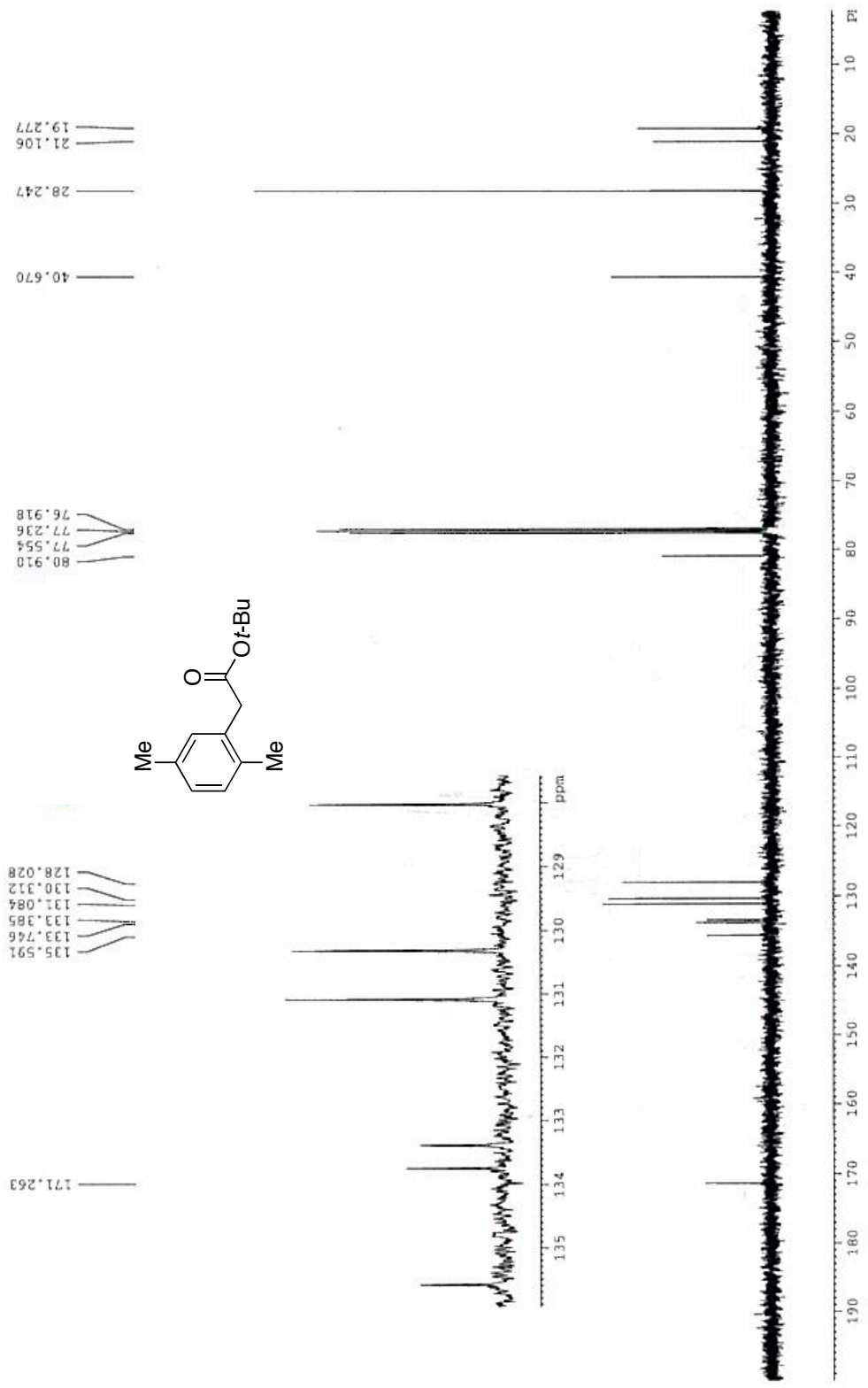


Table 1, Entry 5

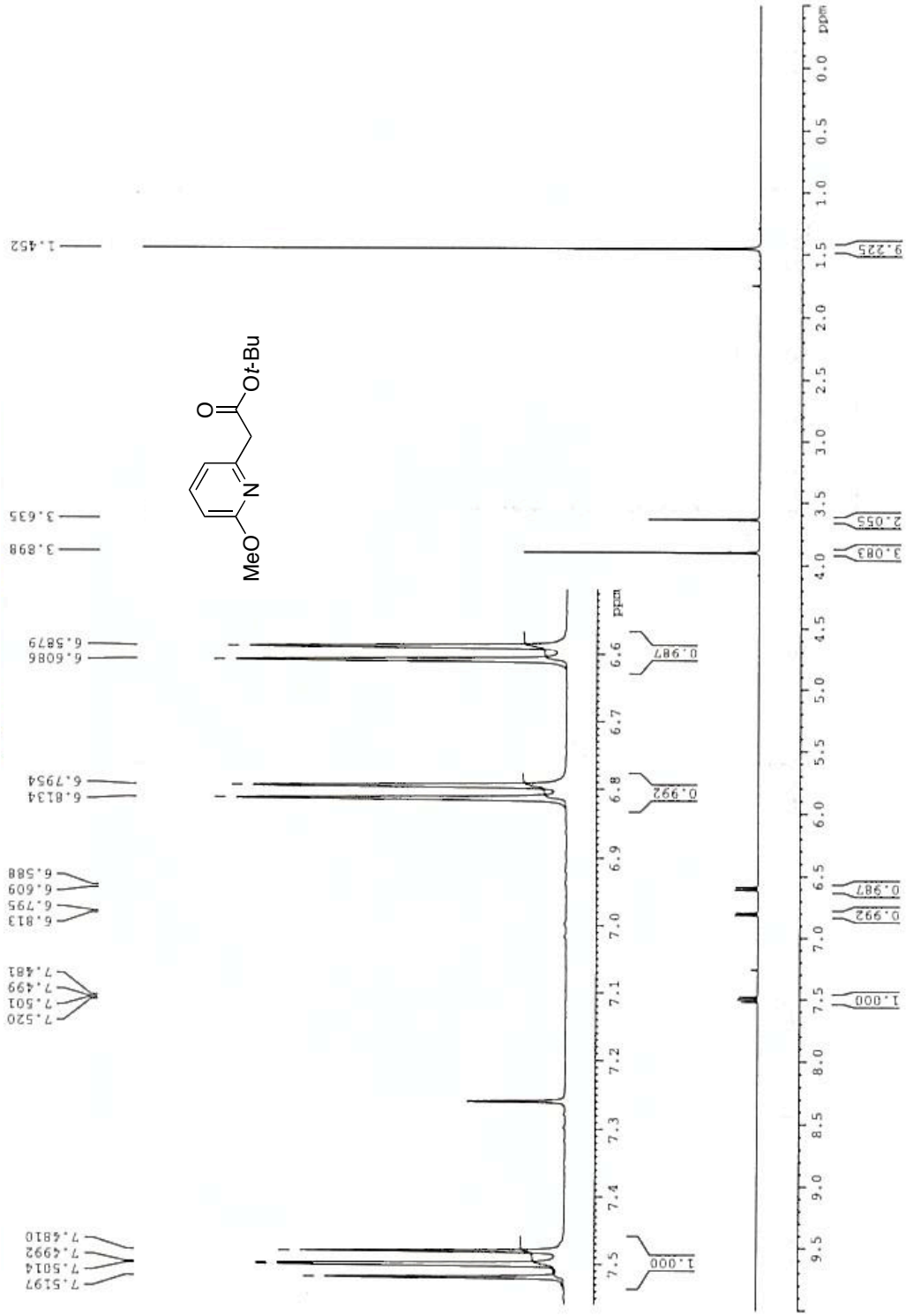


Table 1, Entry 5

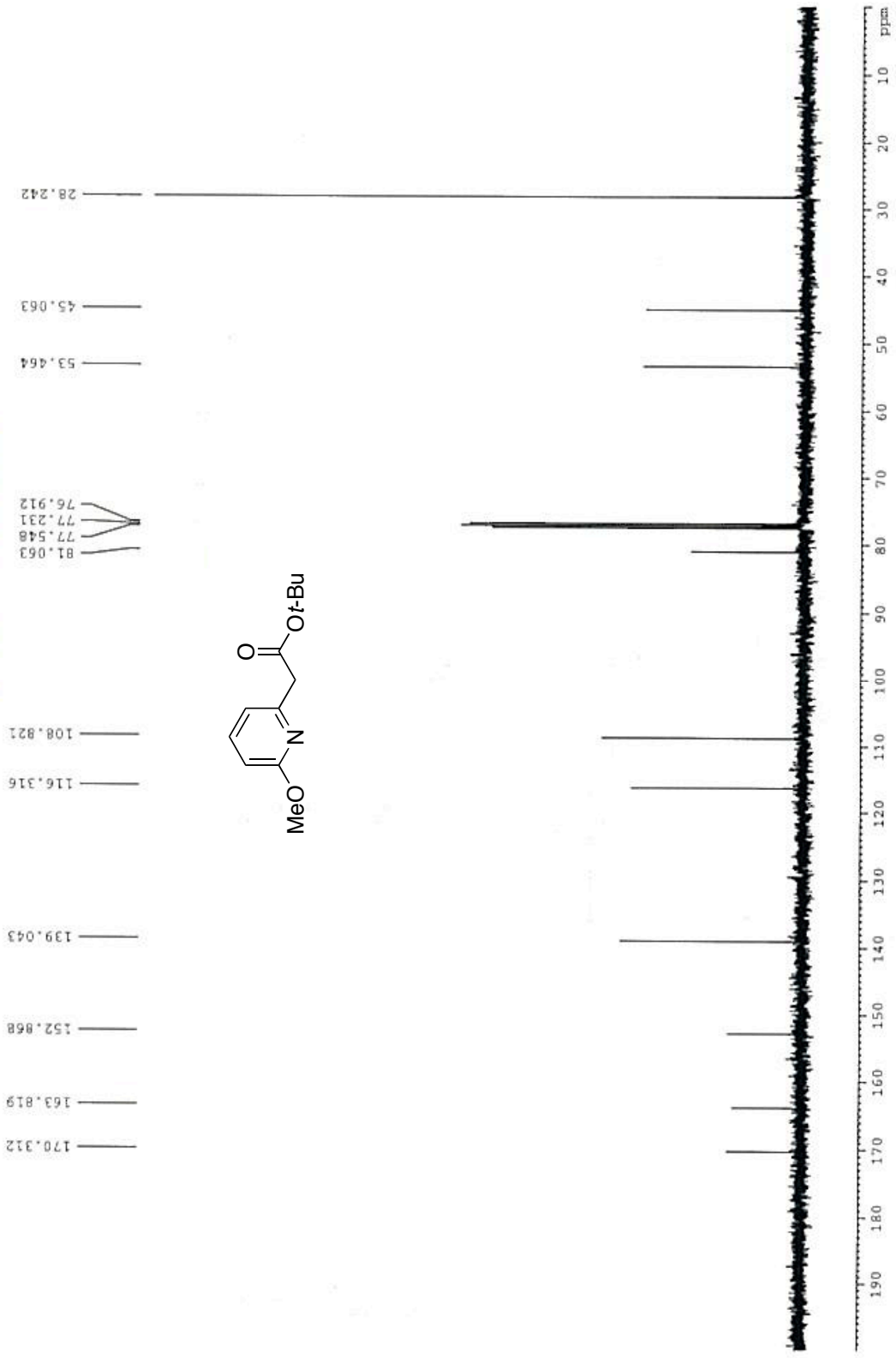


Table 1, Entry 6

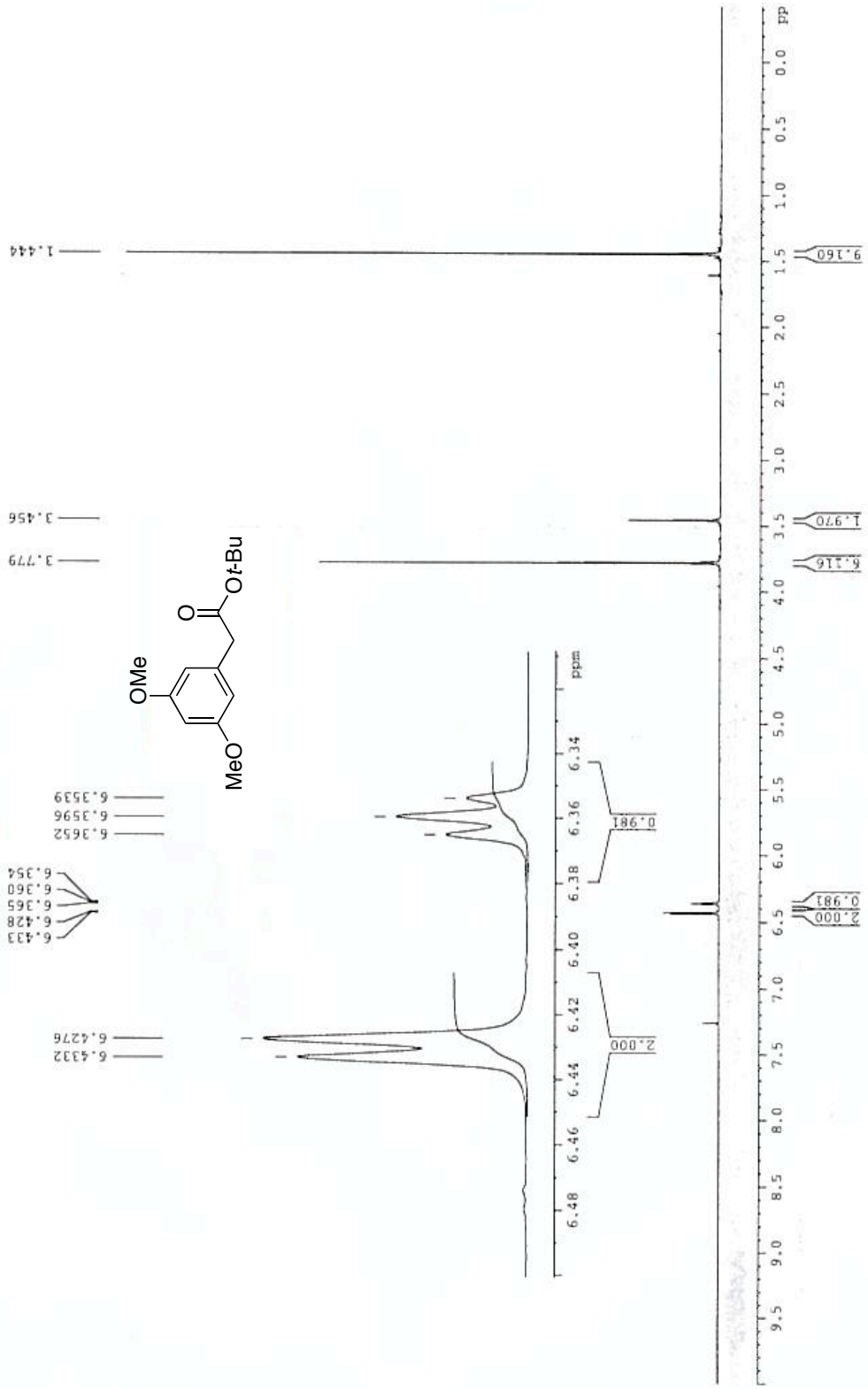


Table 1, Entry 6

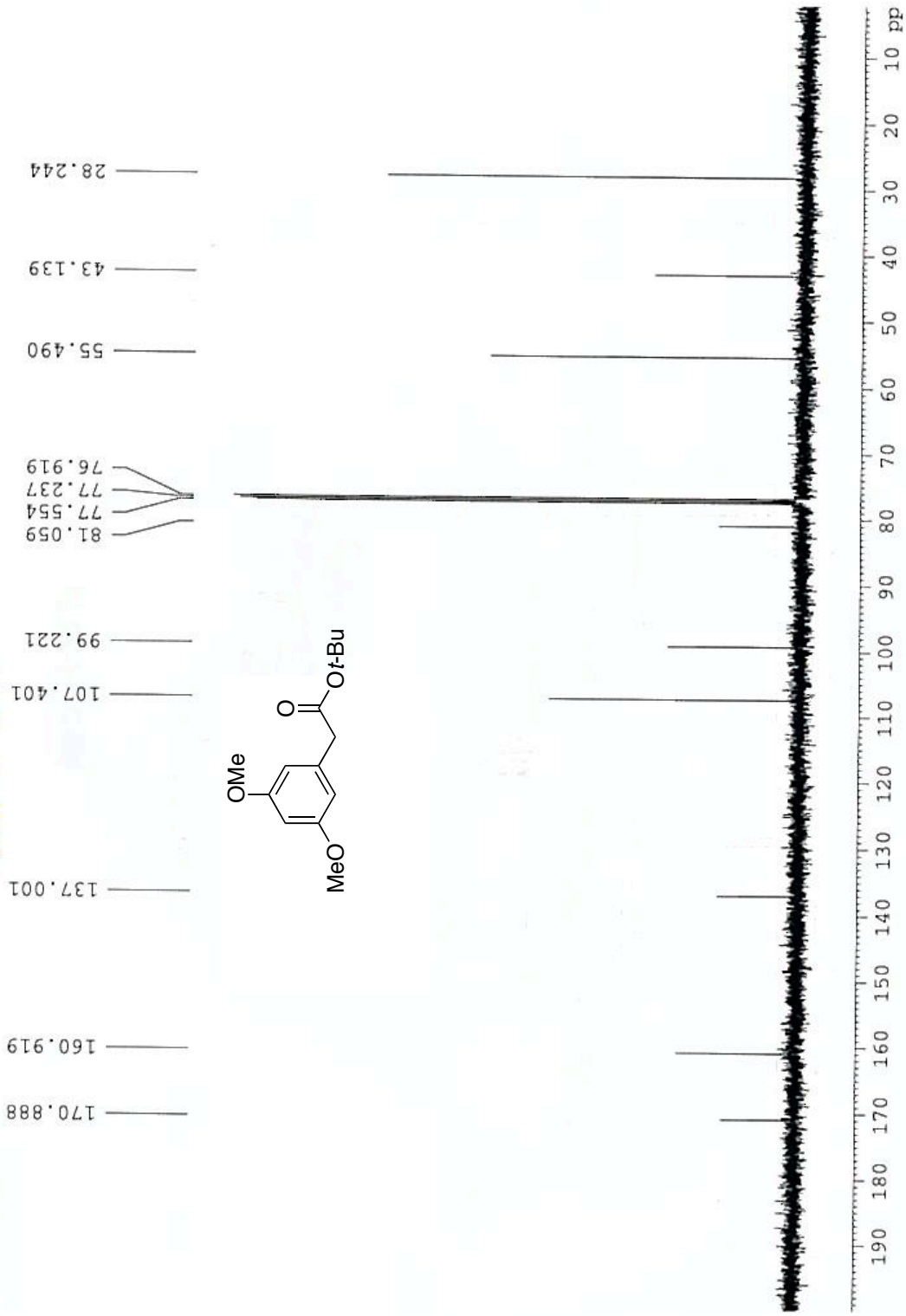


Table 1, Entry 7

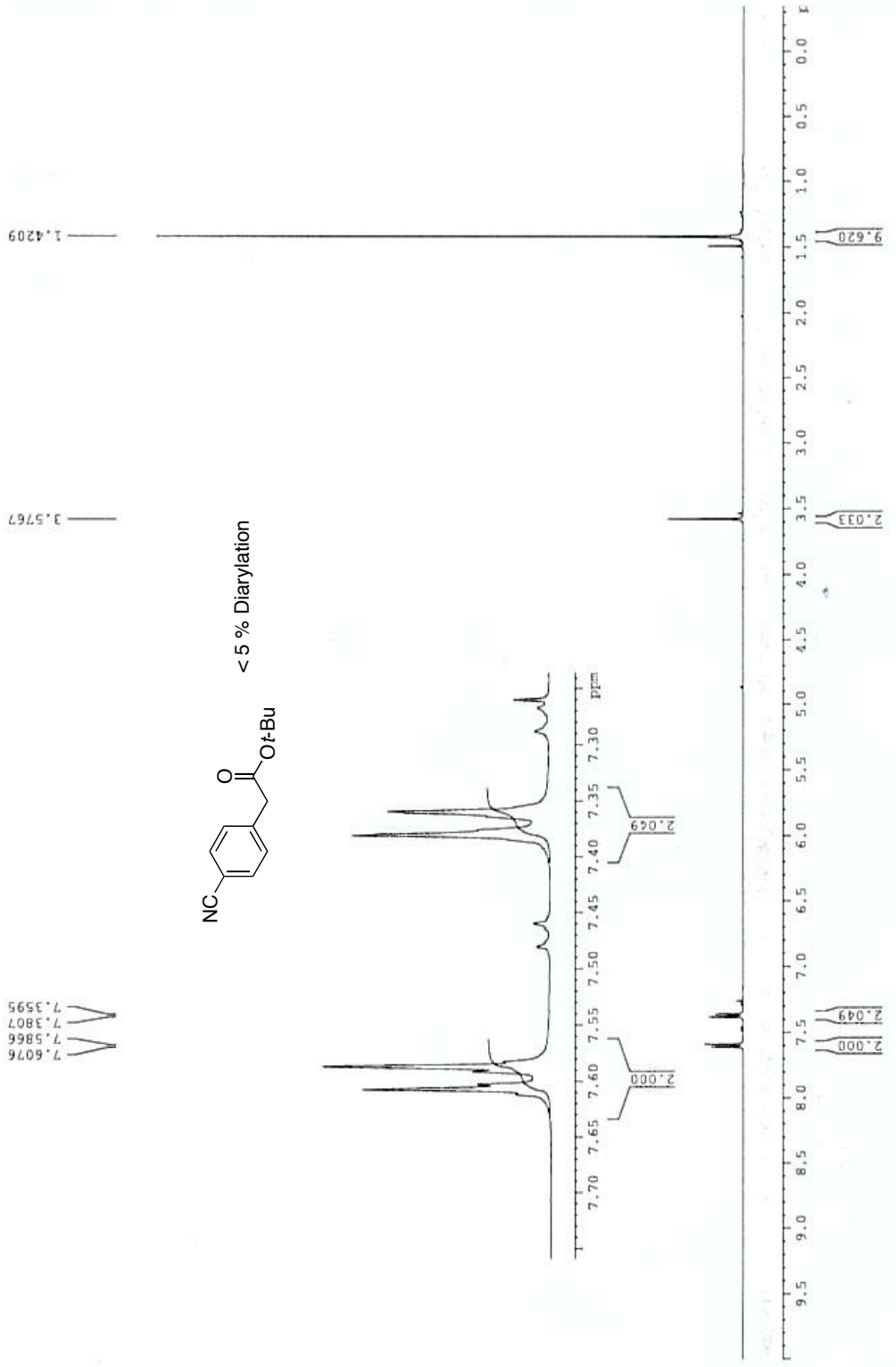


Table 1, Entry 7

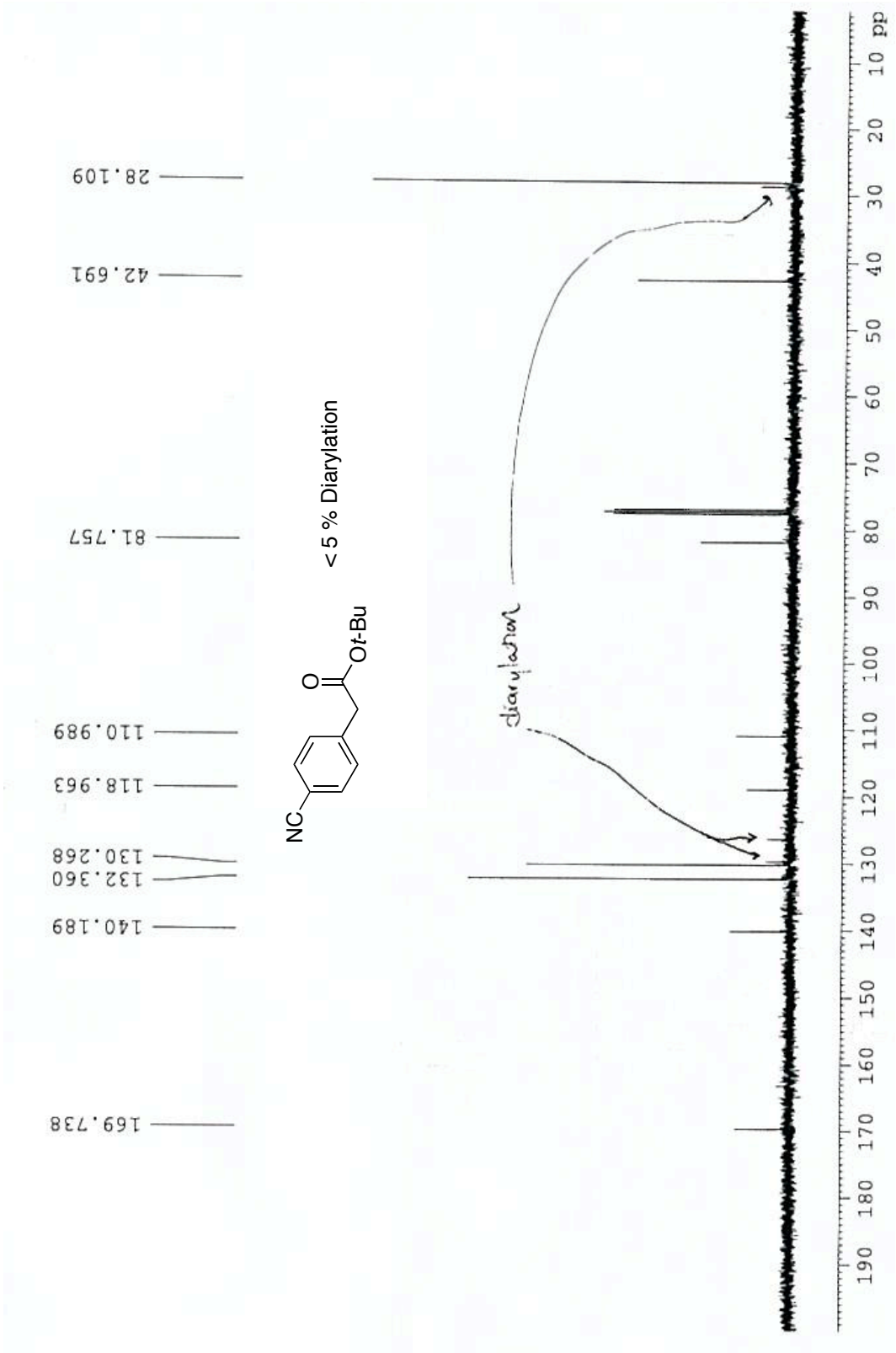


Table 1, Entry 8

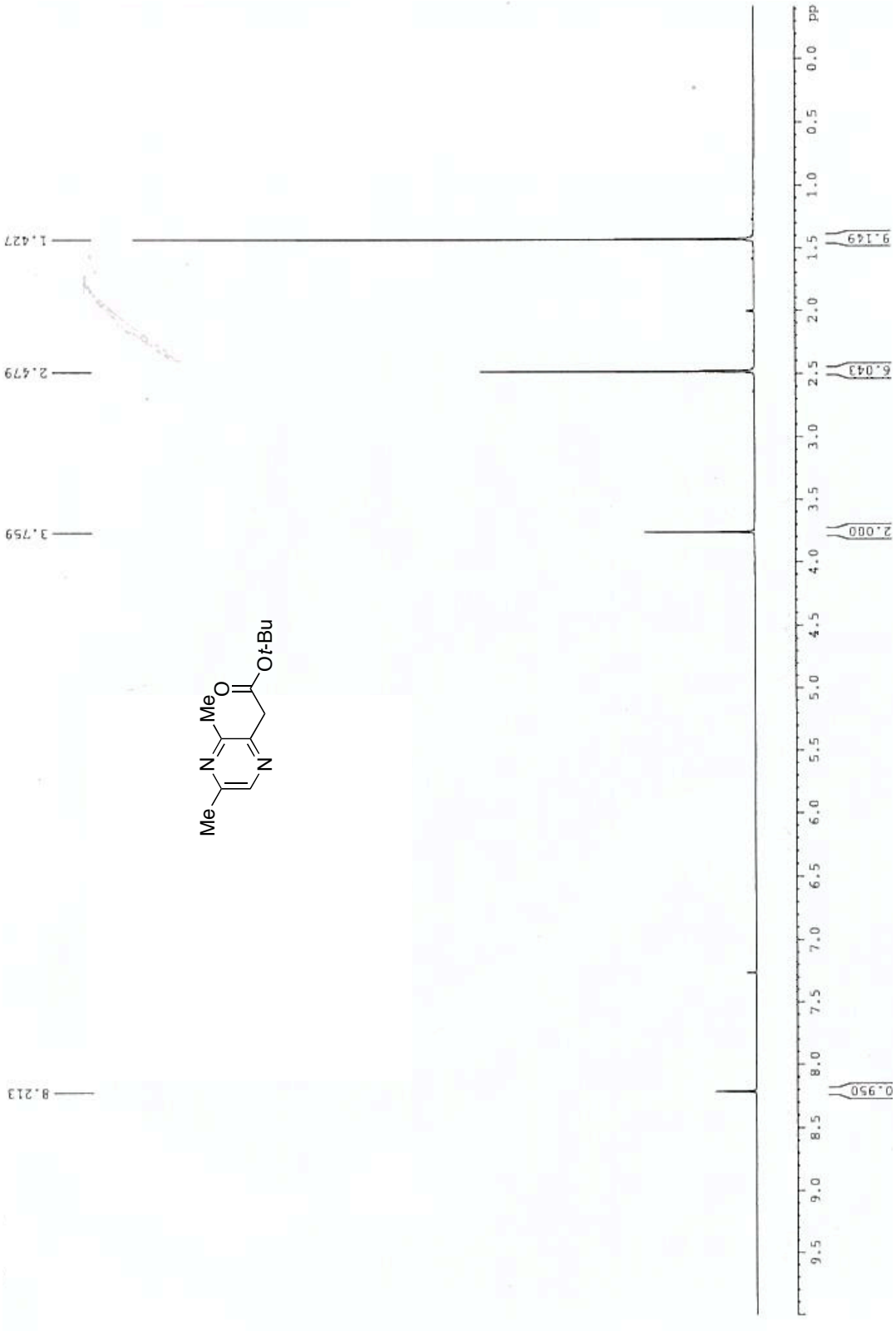


Table 1, Entry 8

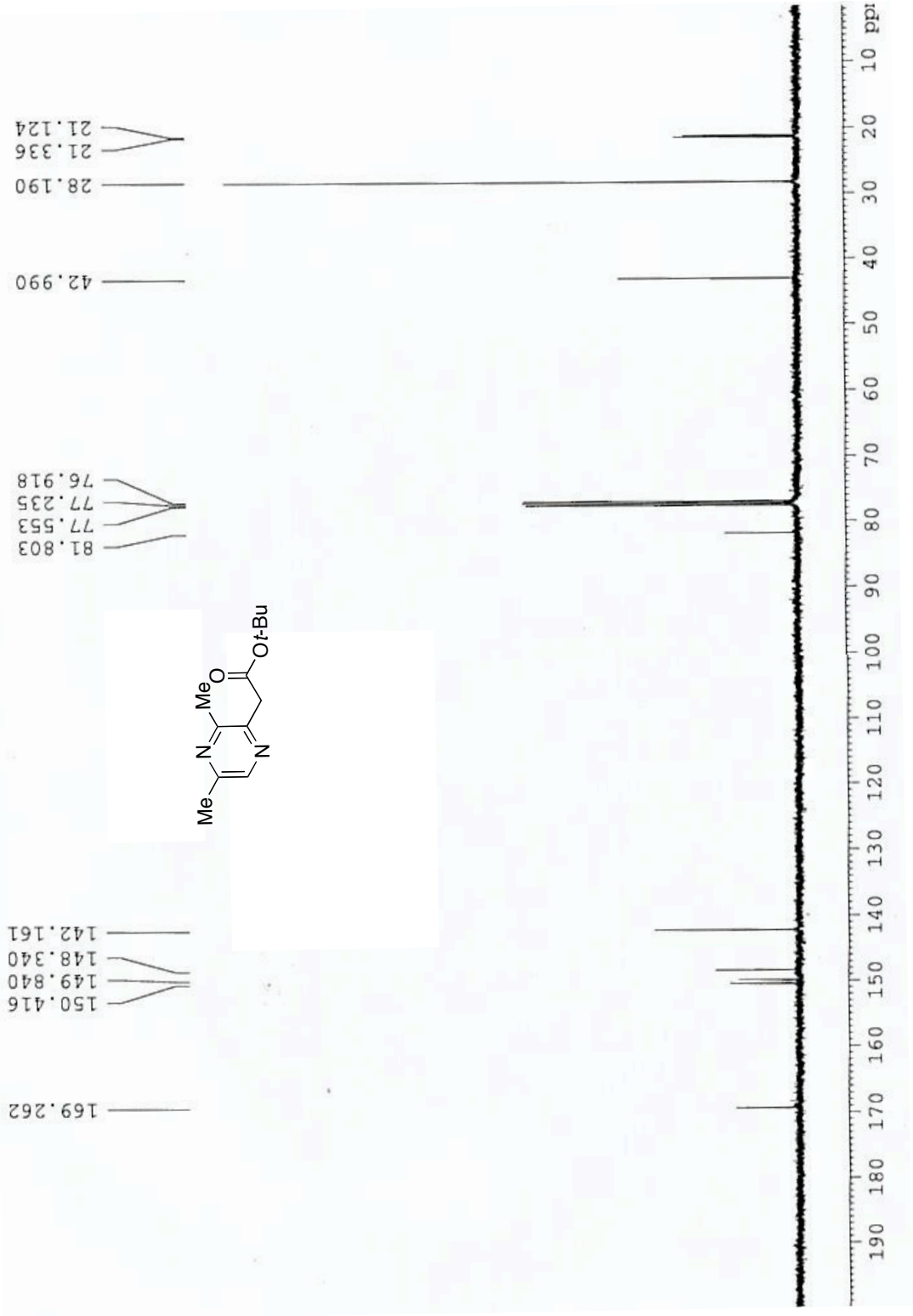


Table 1, Entry 9

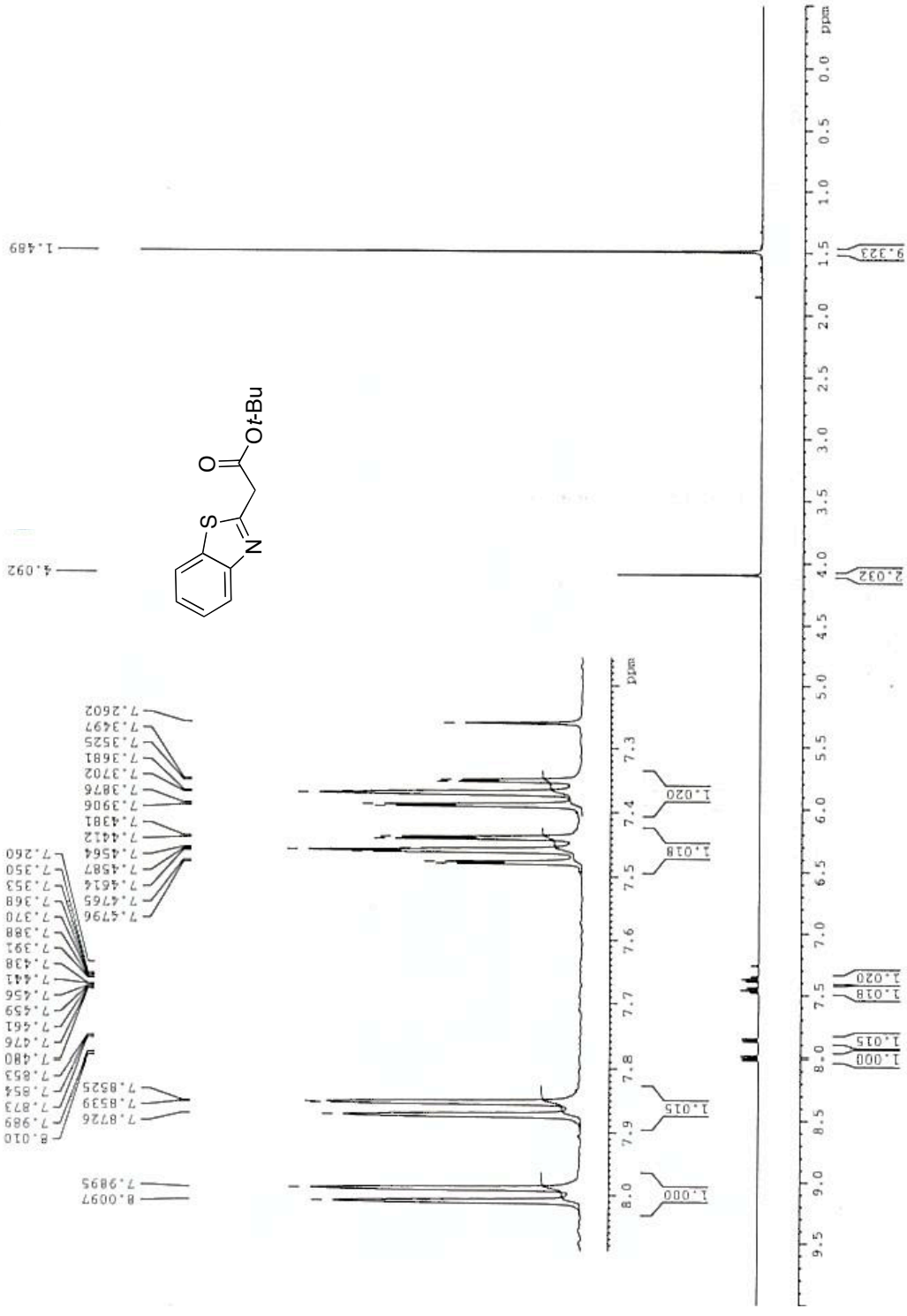


Table 1, Entry 9

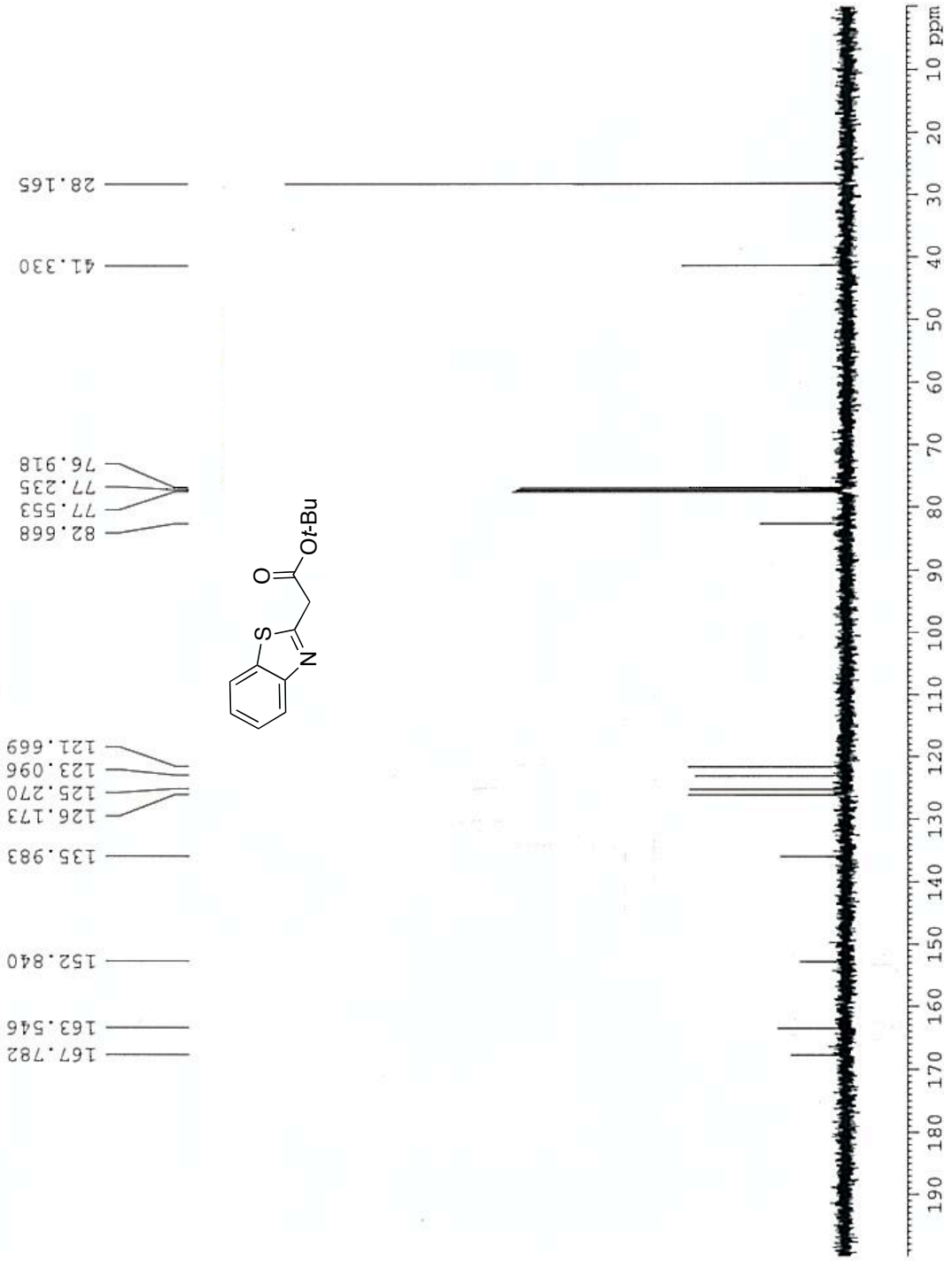


Table 1, Entry 10

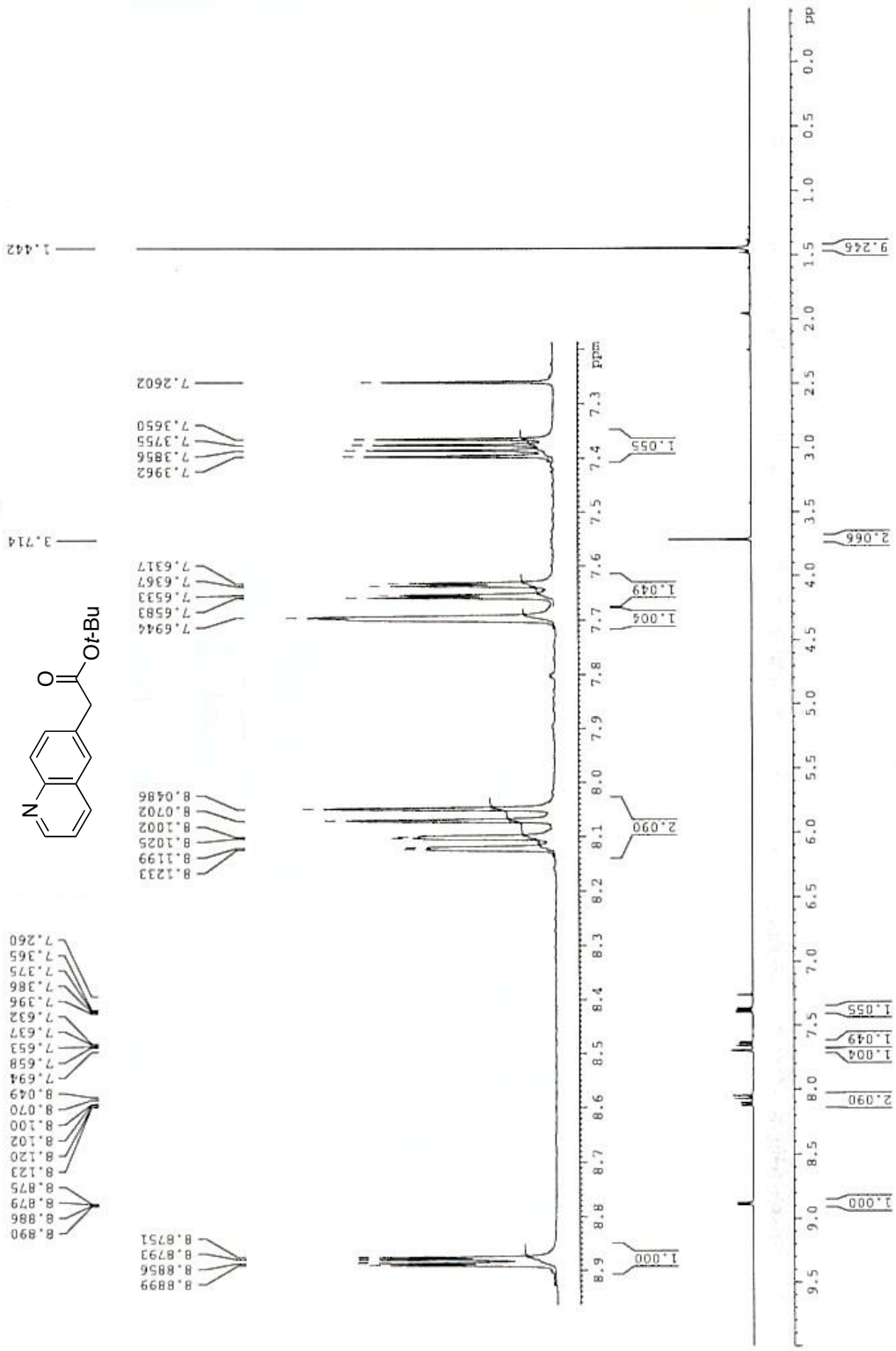


Table 1, Entry 10

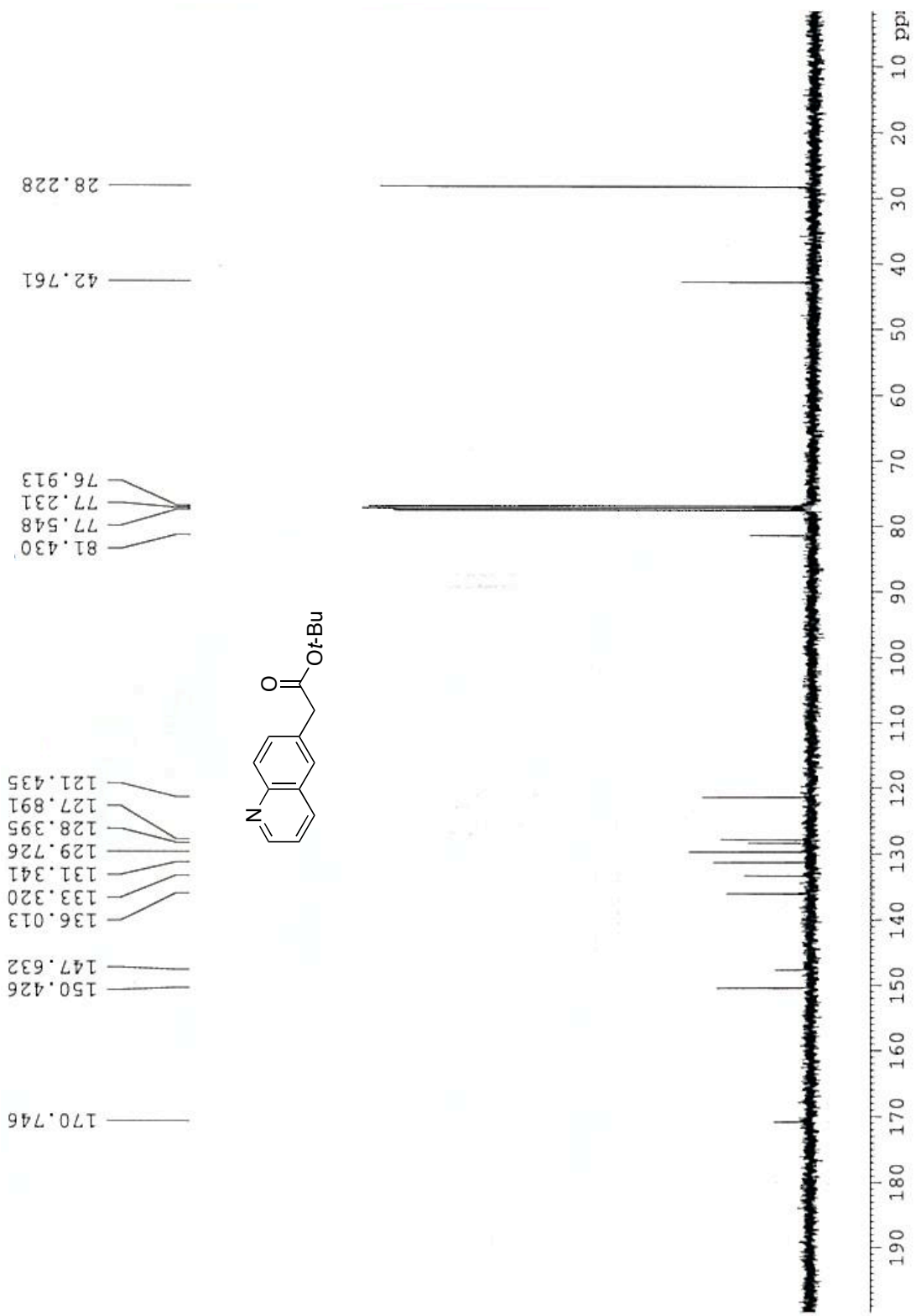


Table 2, Entry 1

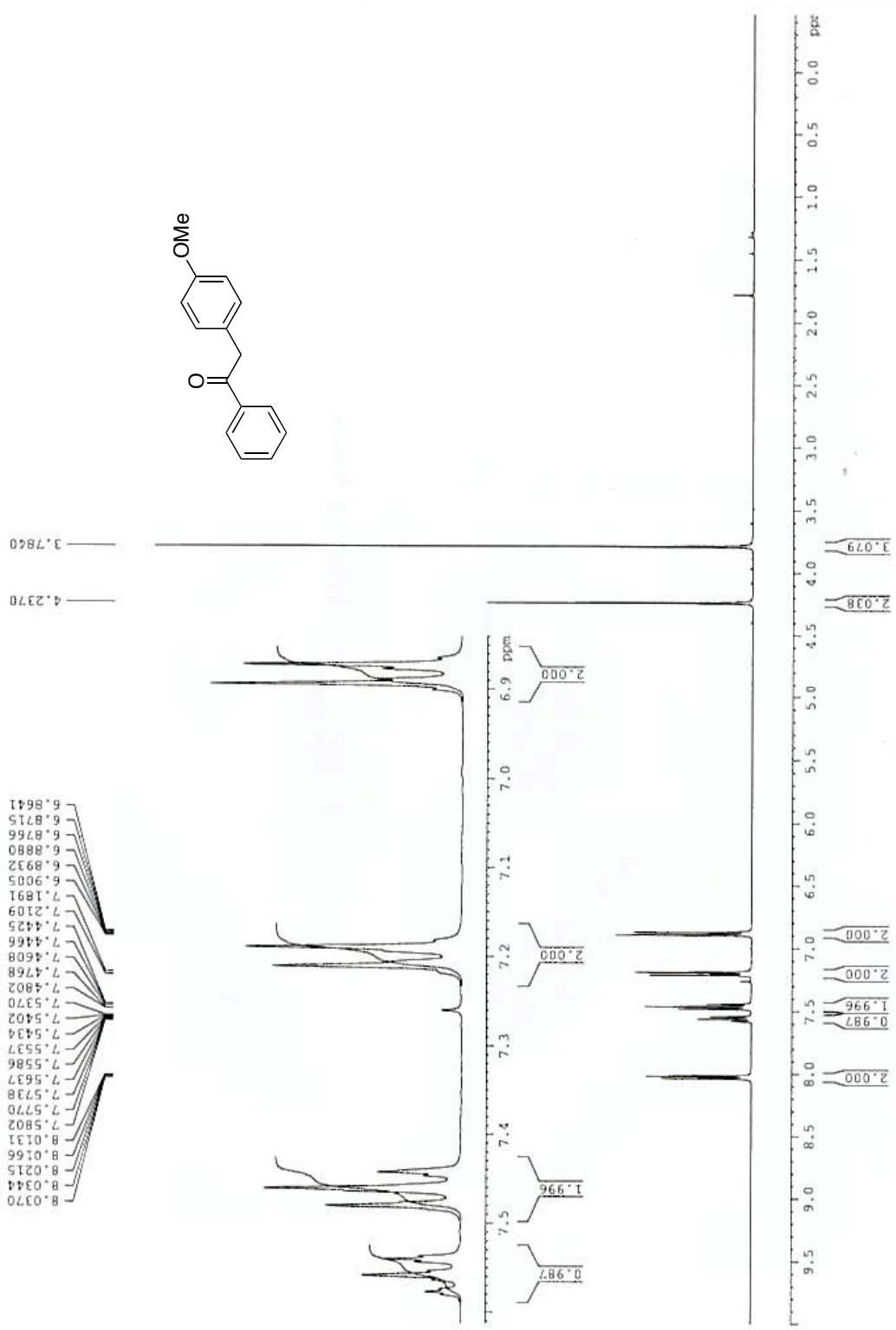


Table 2, Entry 1

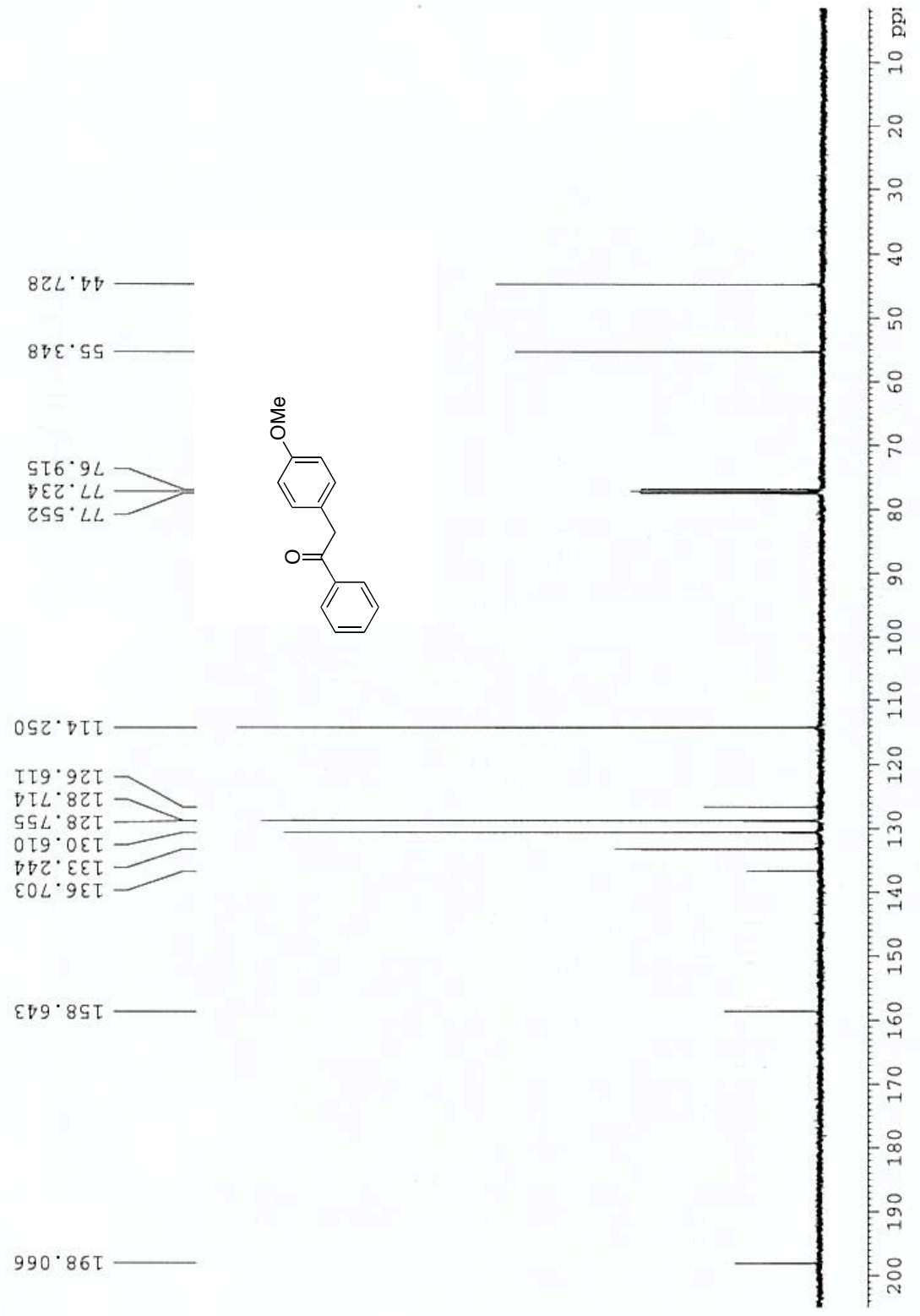


Table 2, Entry 2

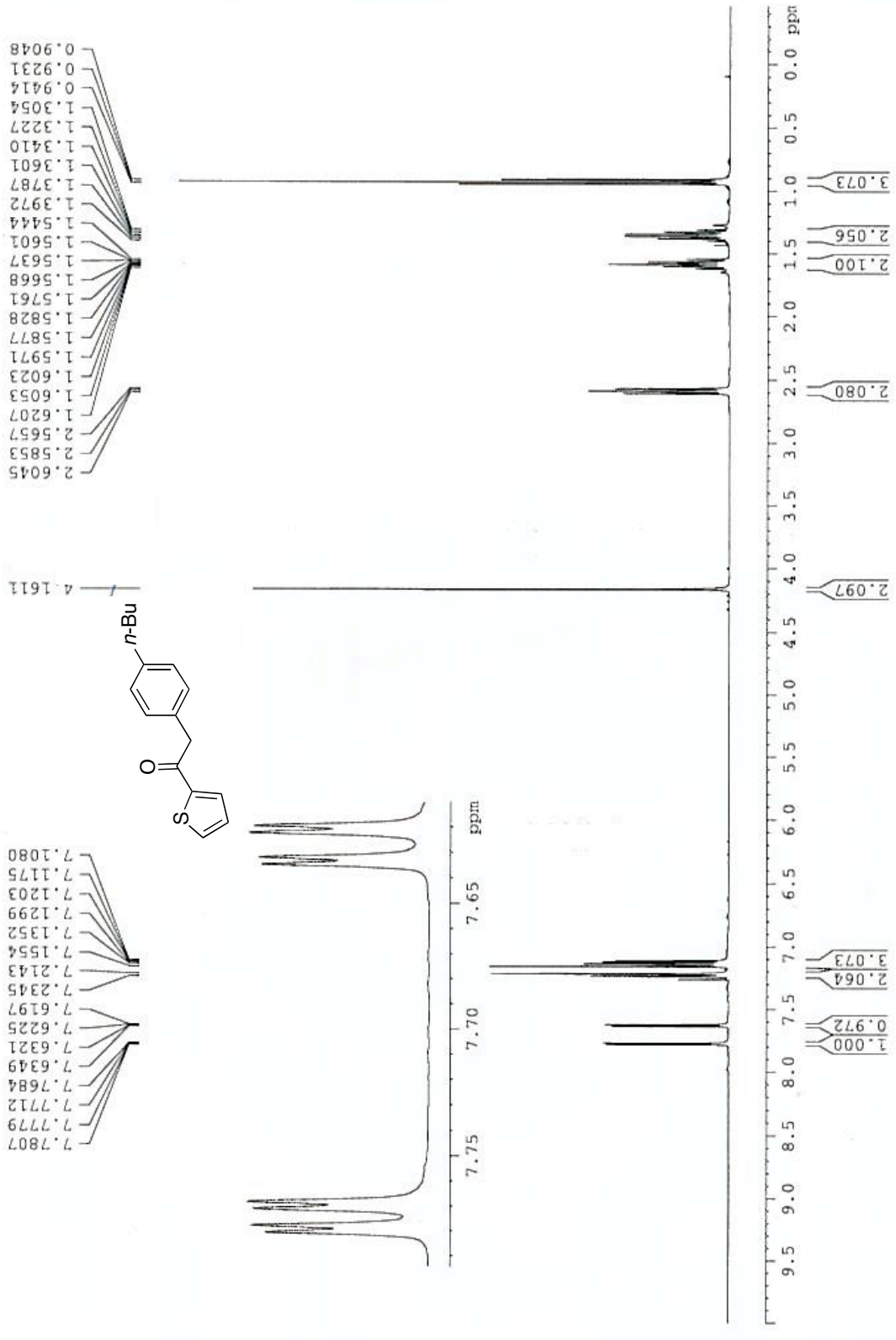


Table 2, Entry 2

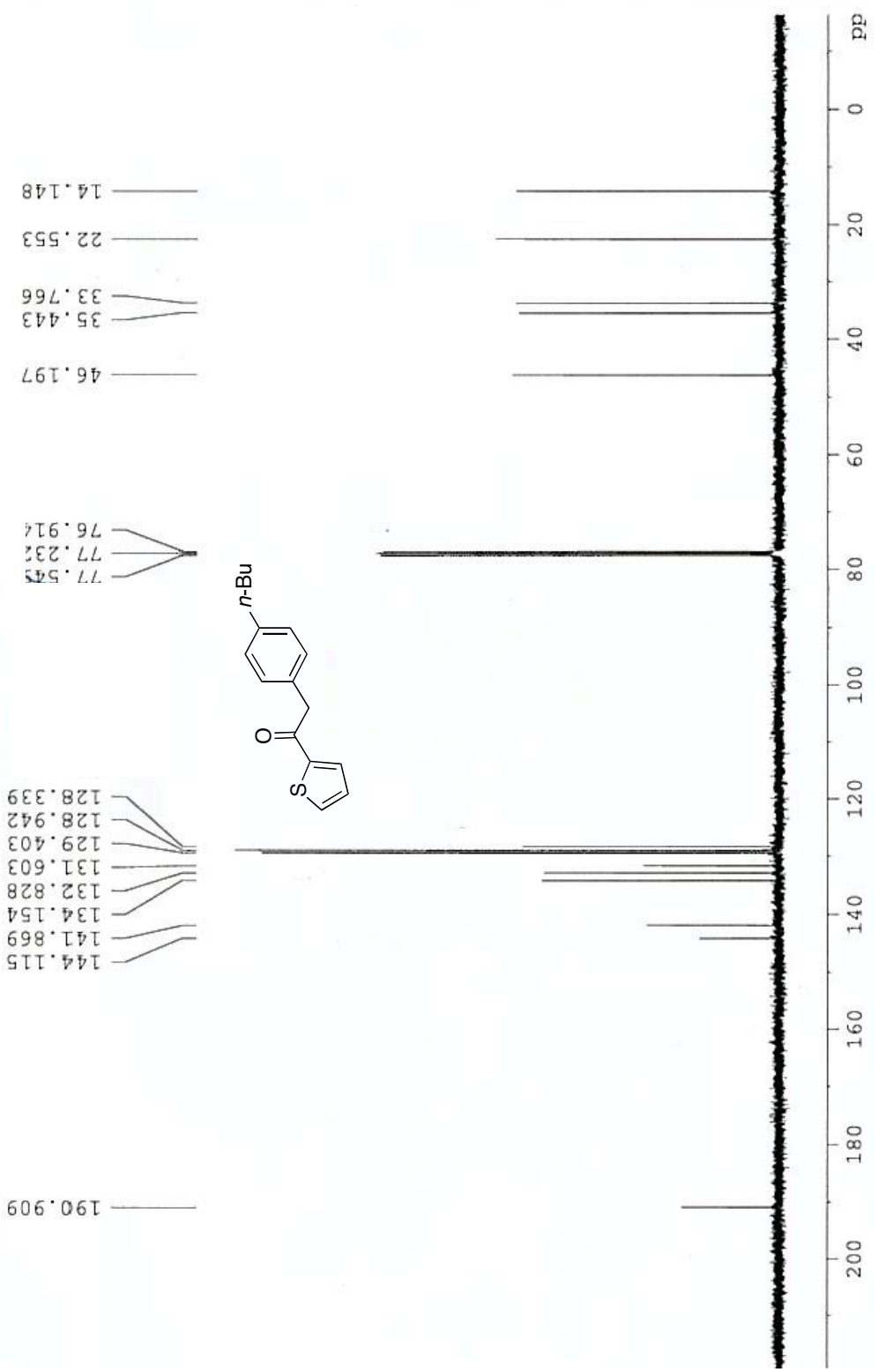


Table 2, Entry 3

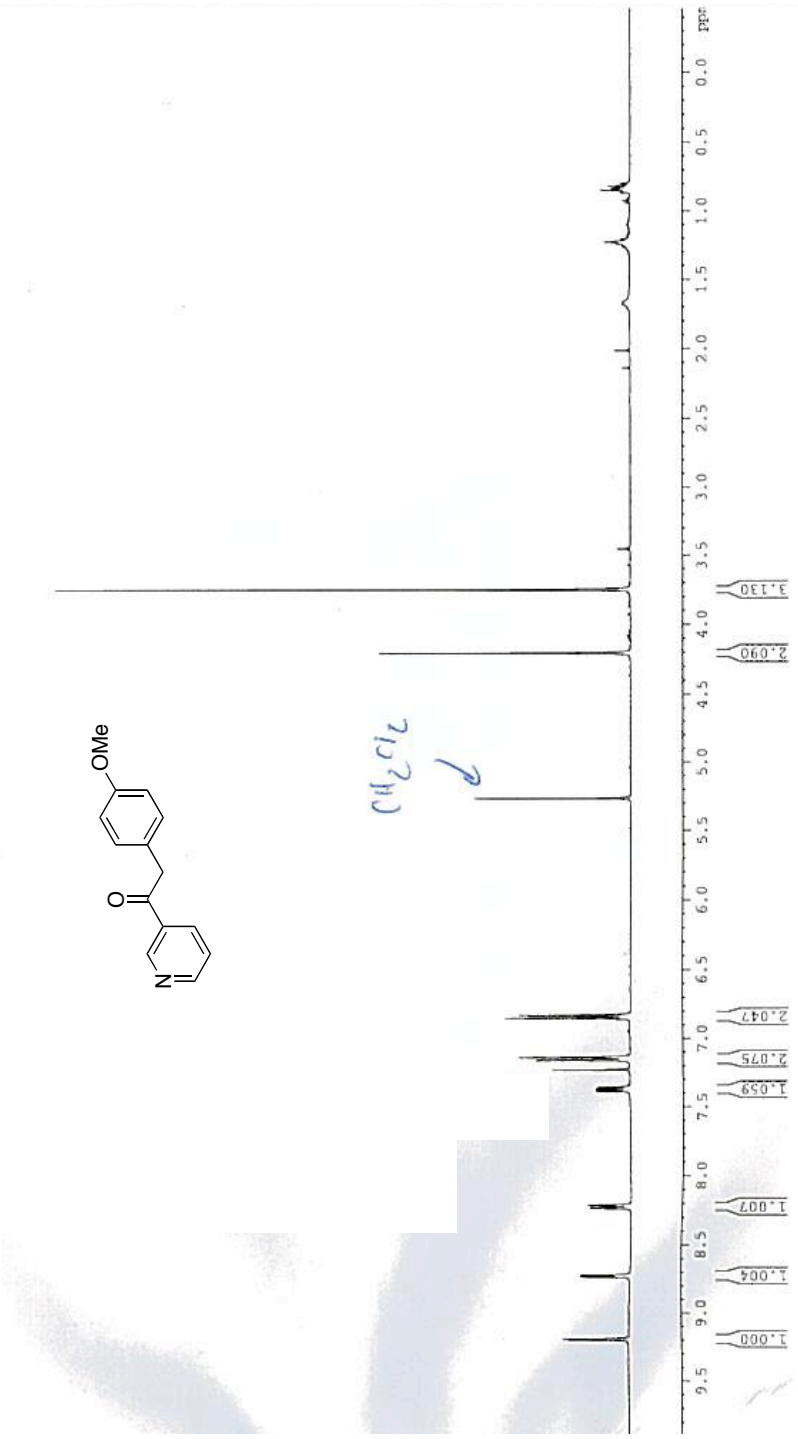


Table 2, Entry 3

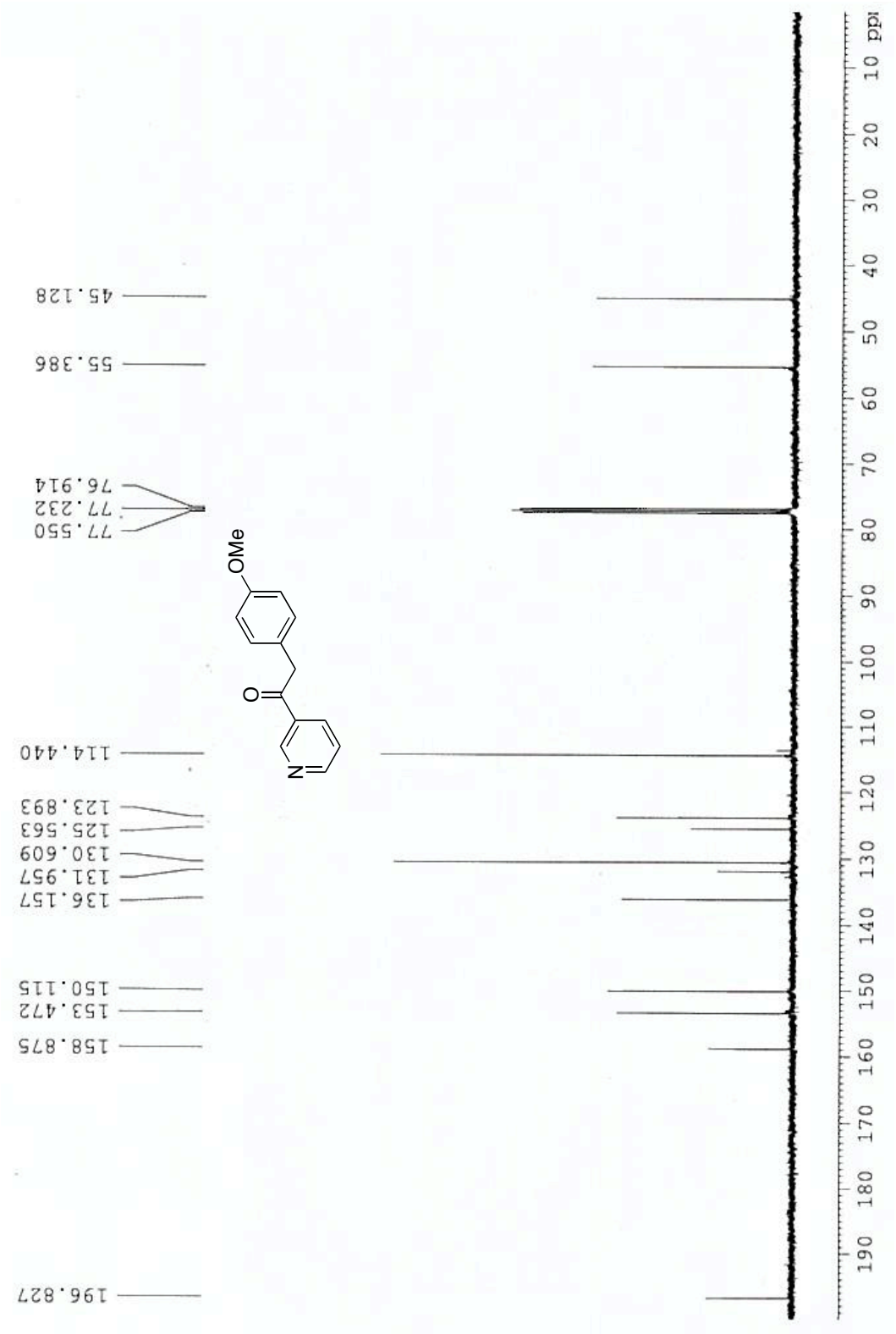


Table 2, Entry 4

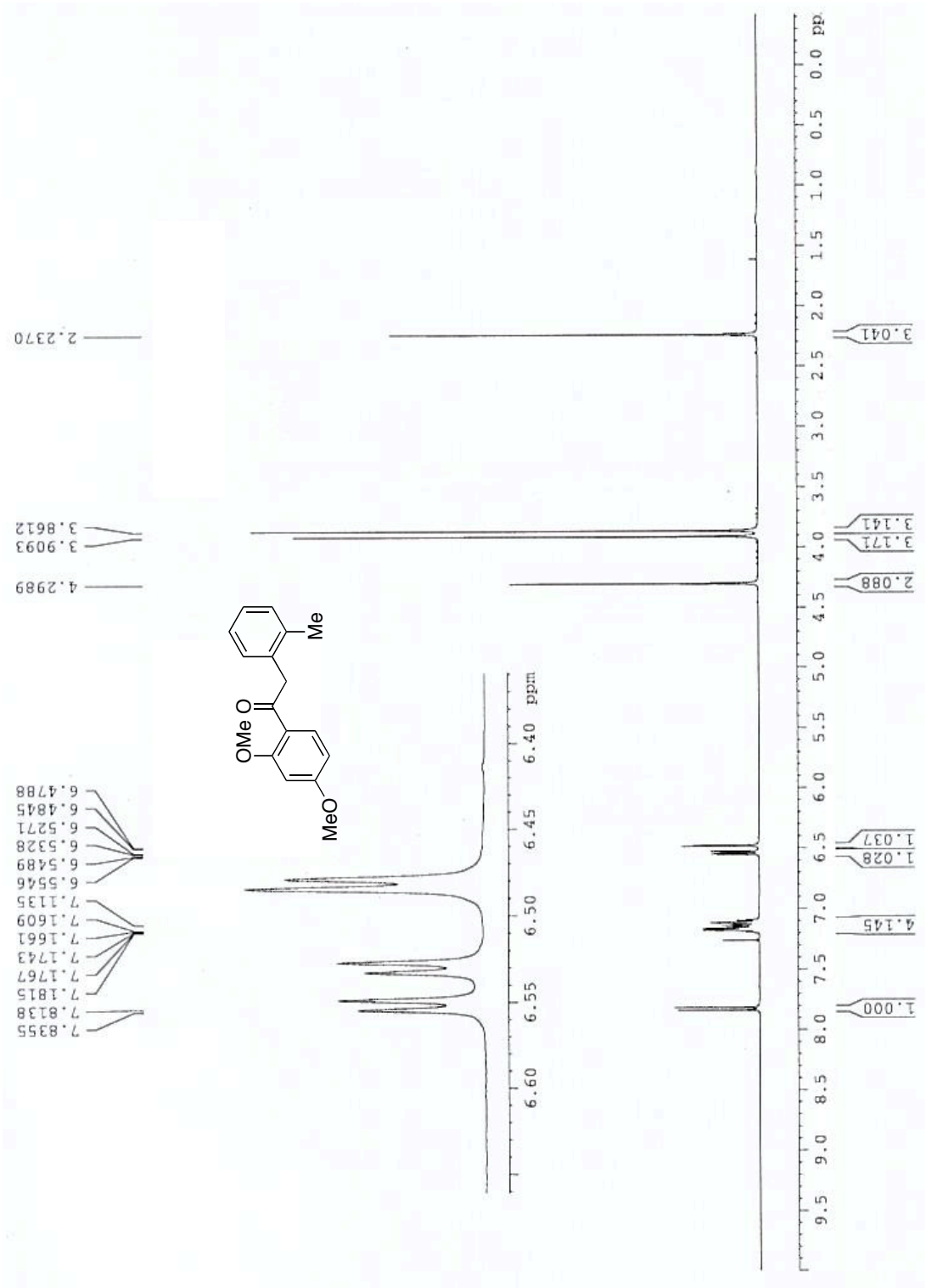


Table 2, Entry 4

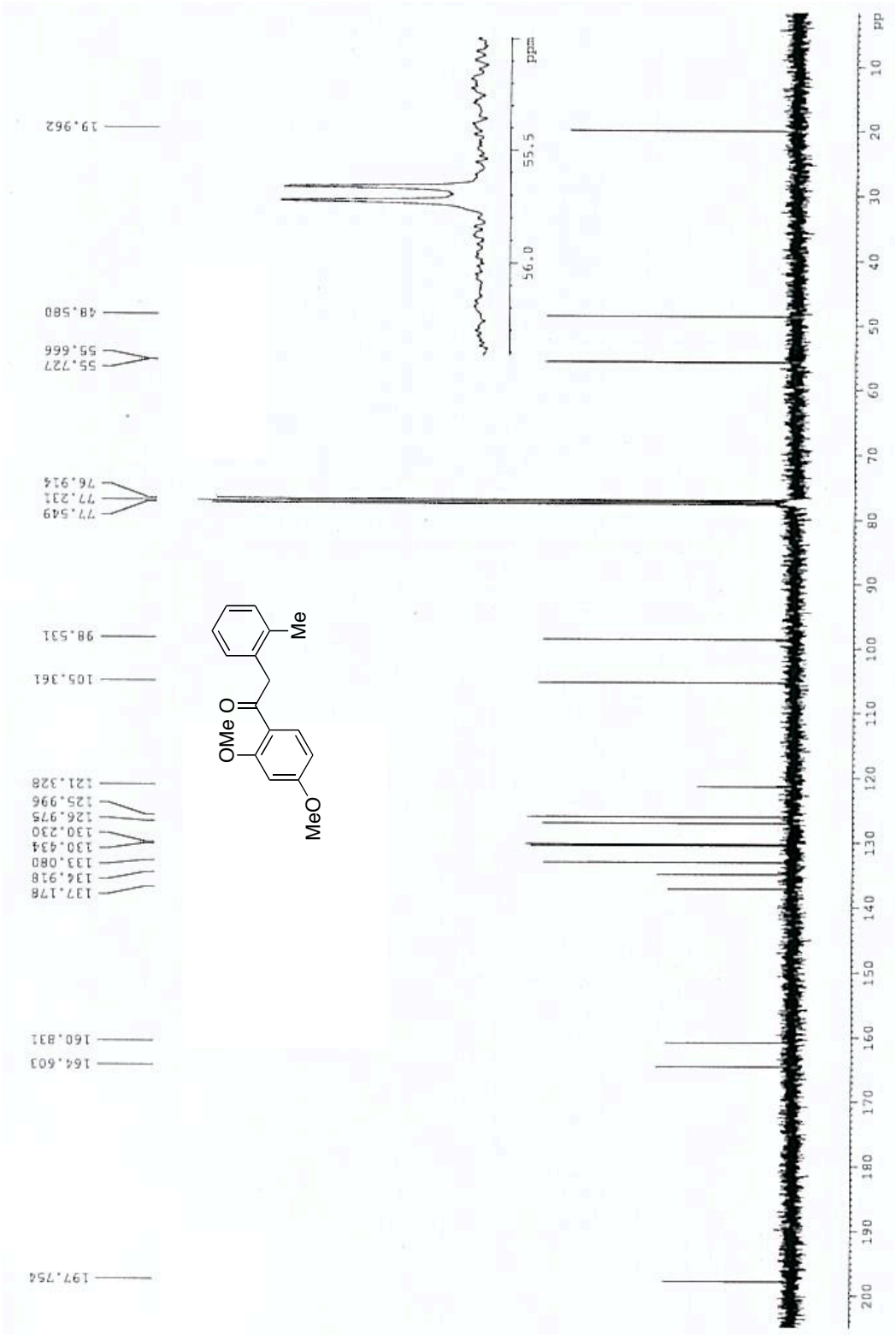


Table 2, Entry 5

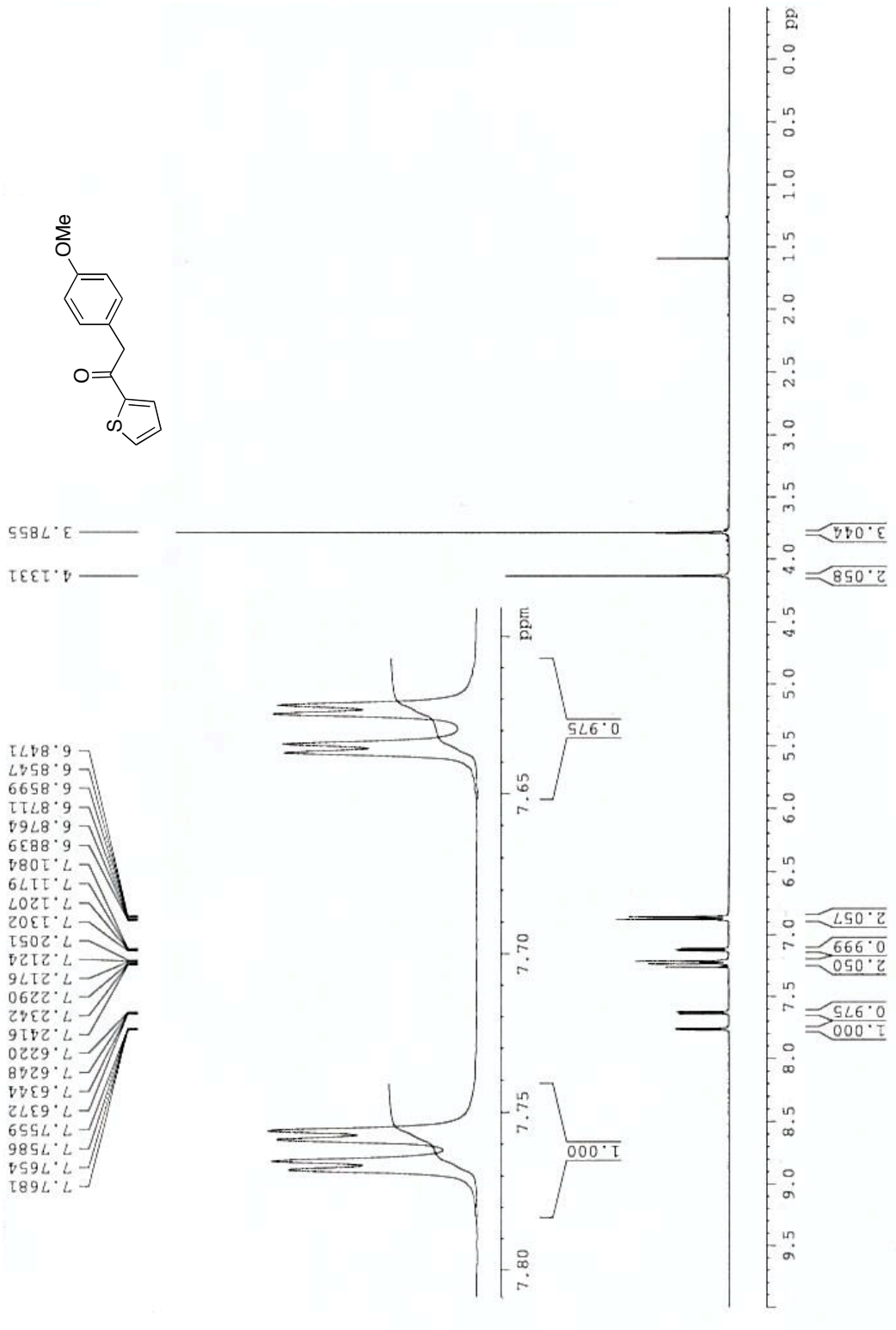


Table 2, Entry 5

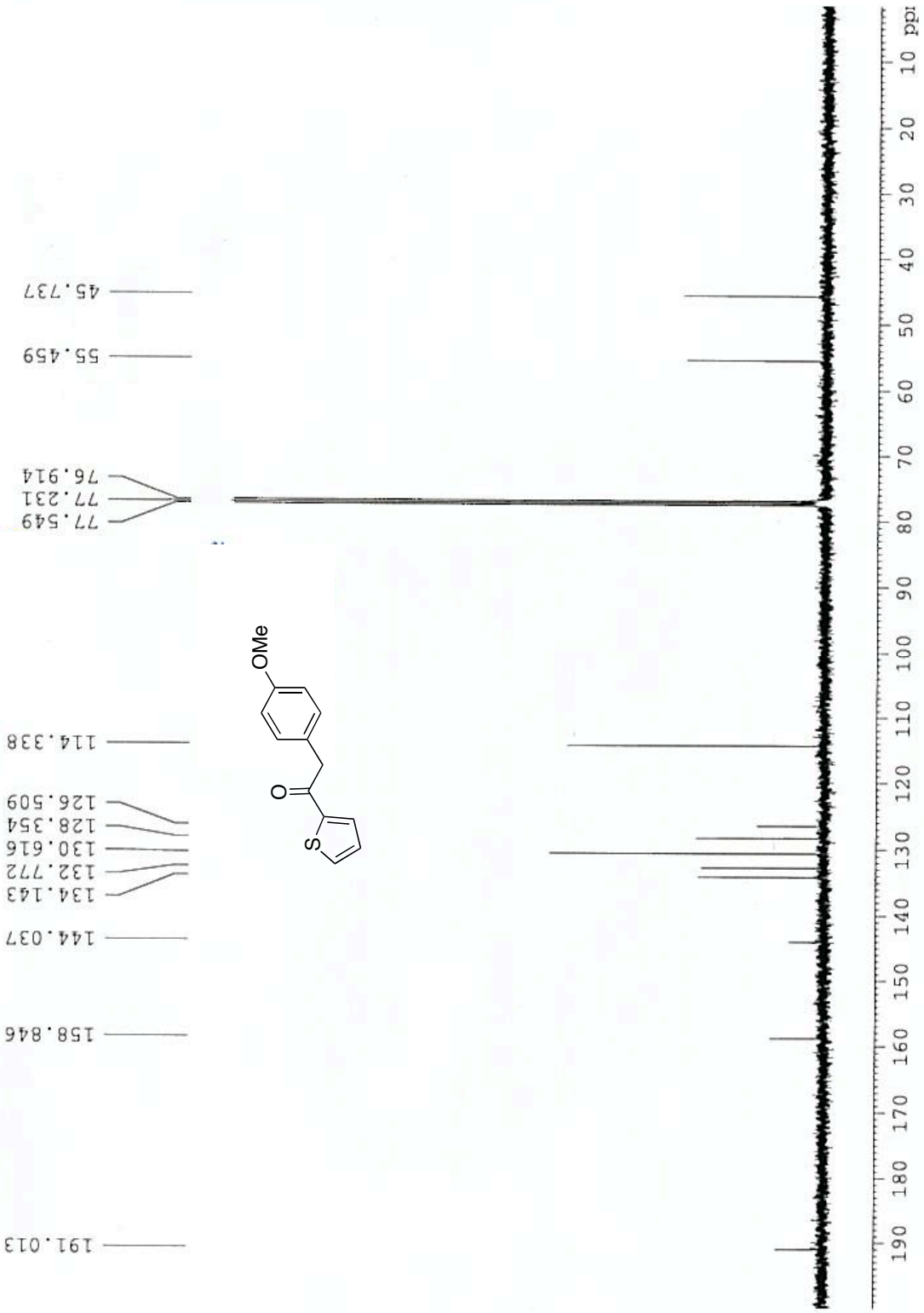


Table 2, Entry 6

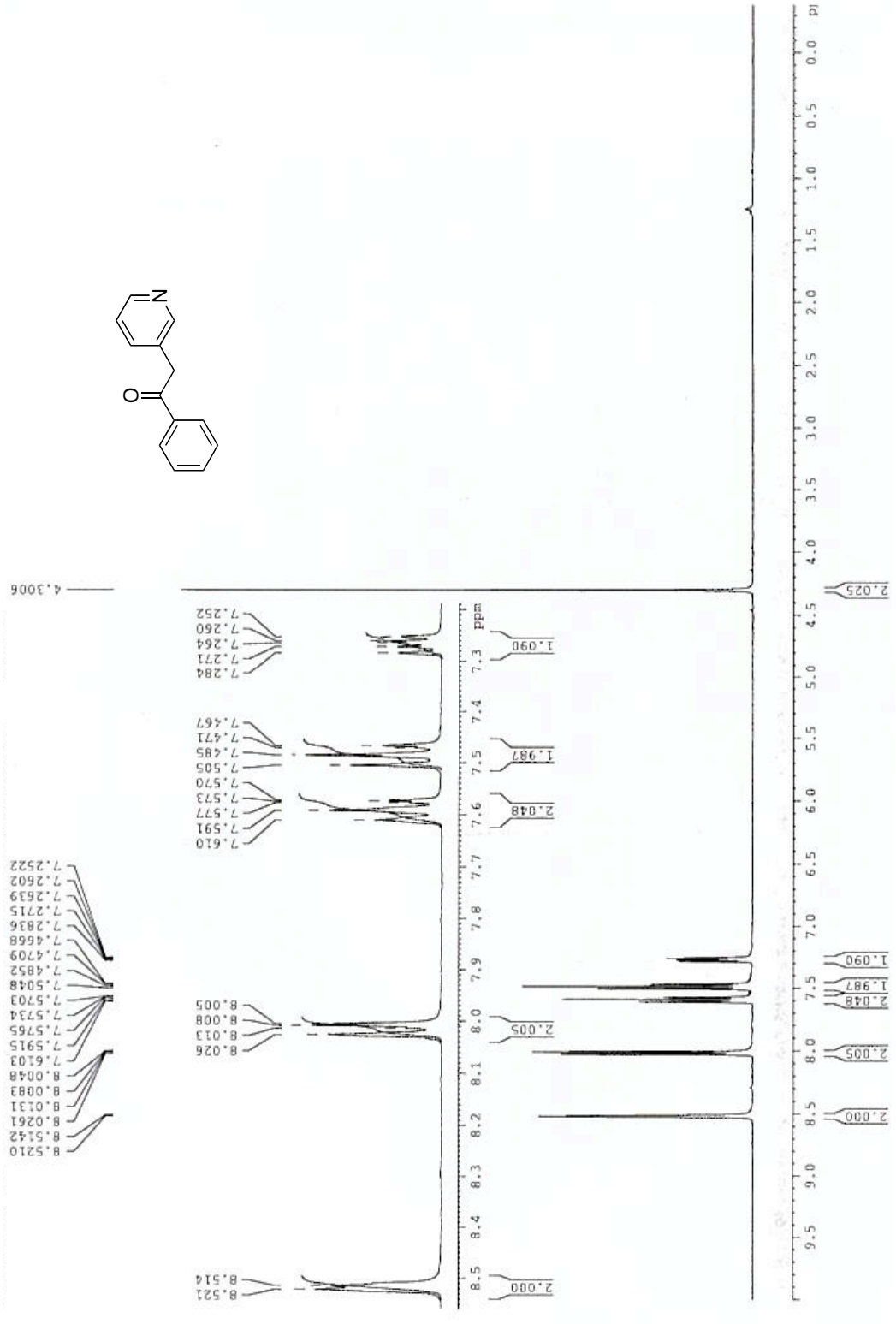


Table 2, Entry 6

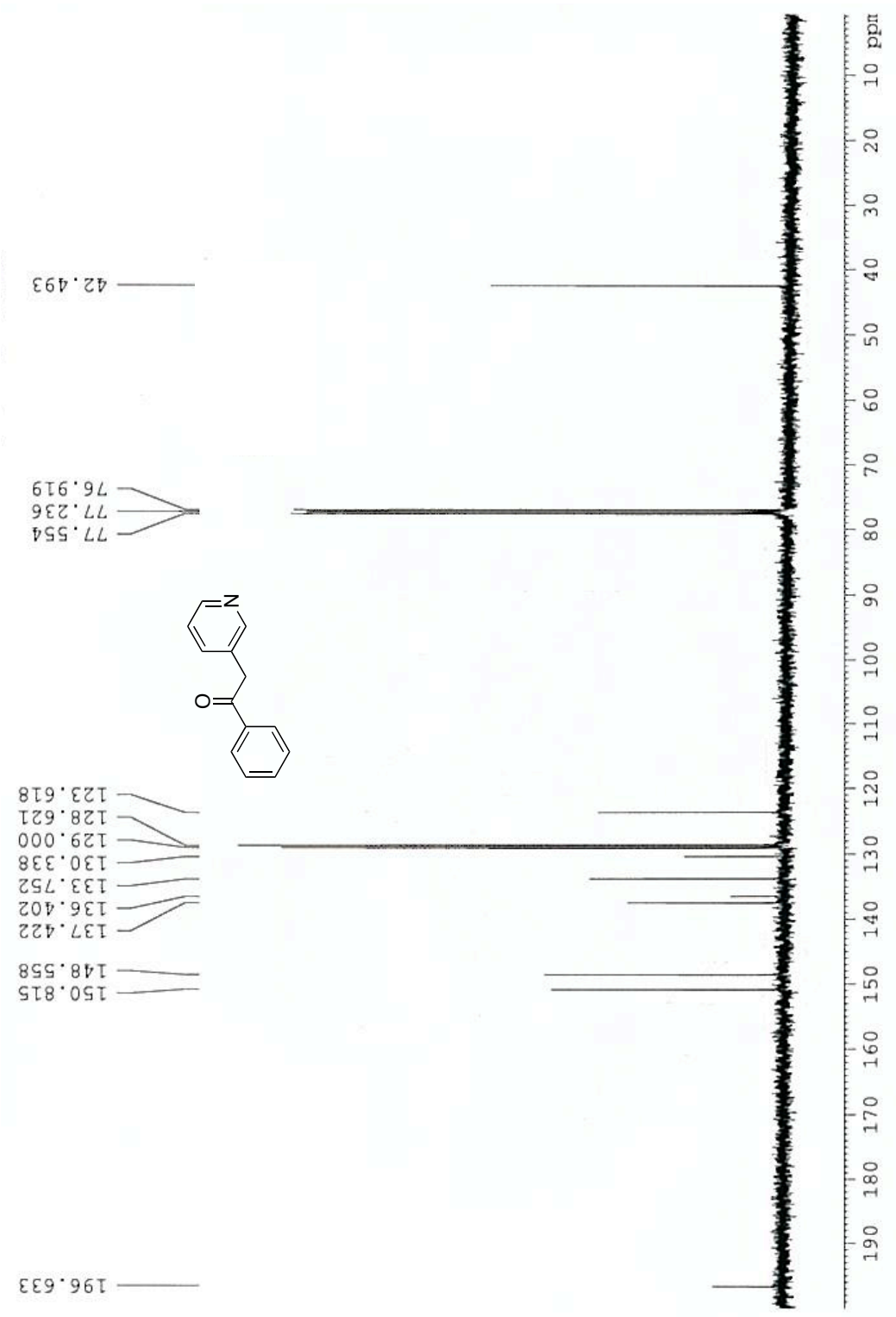


Table 2, Entry 7

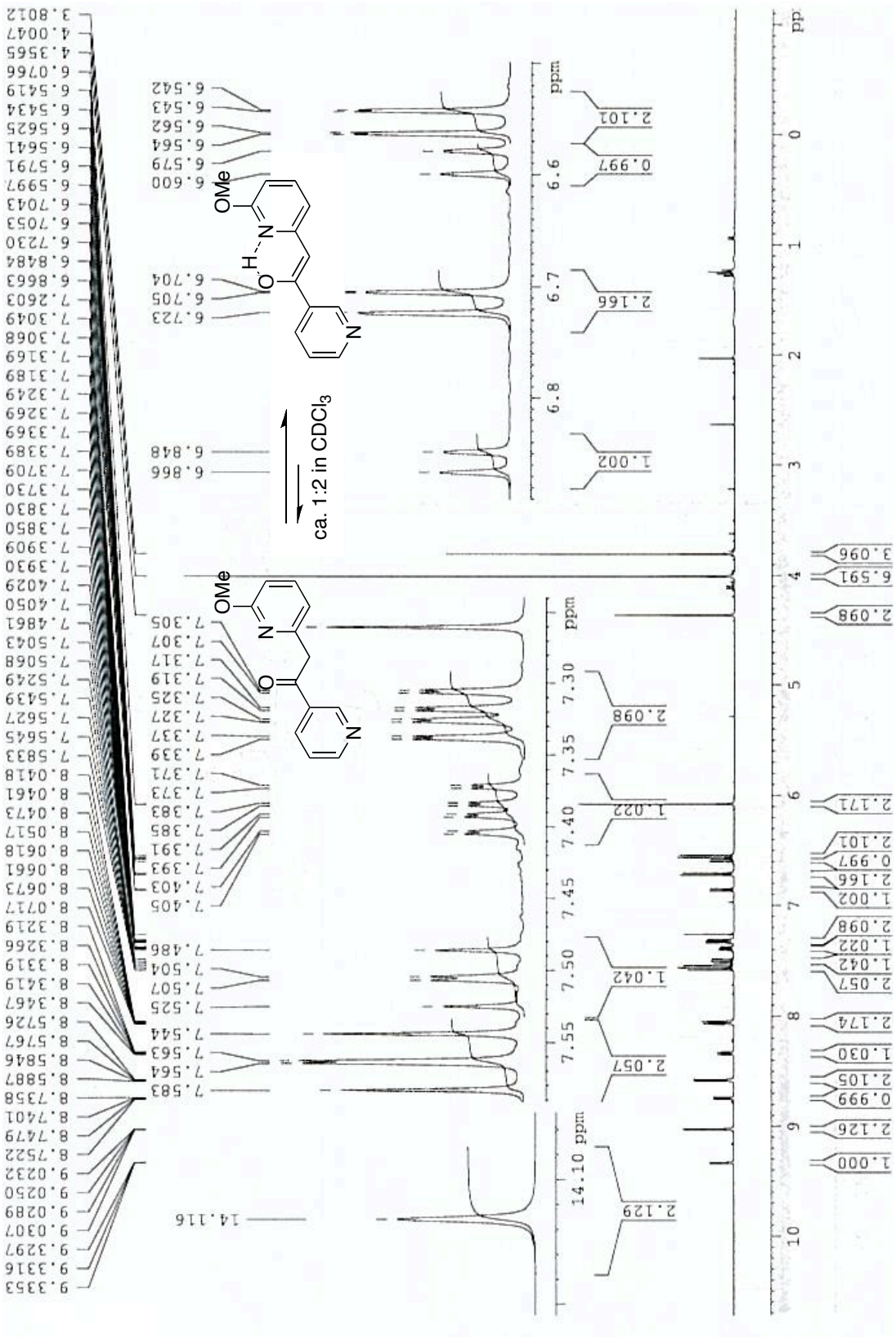


Table 2, Entry 7

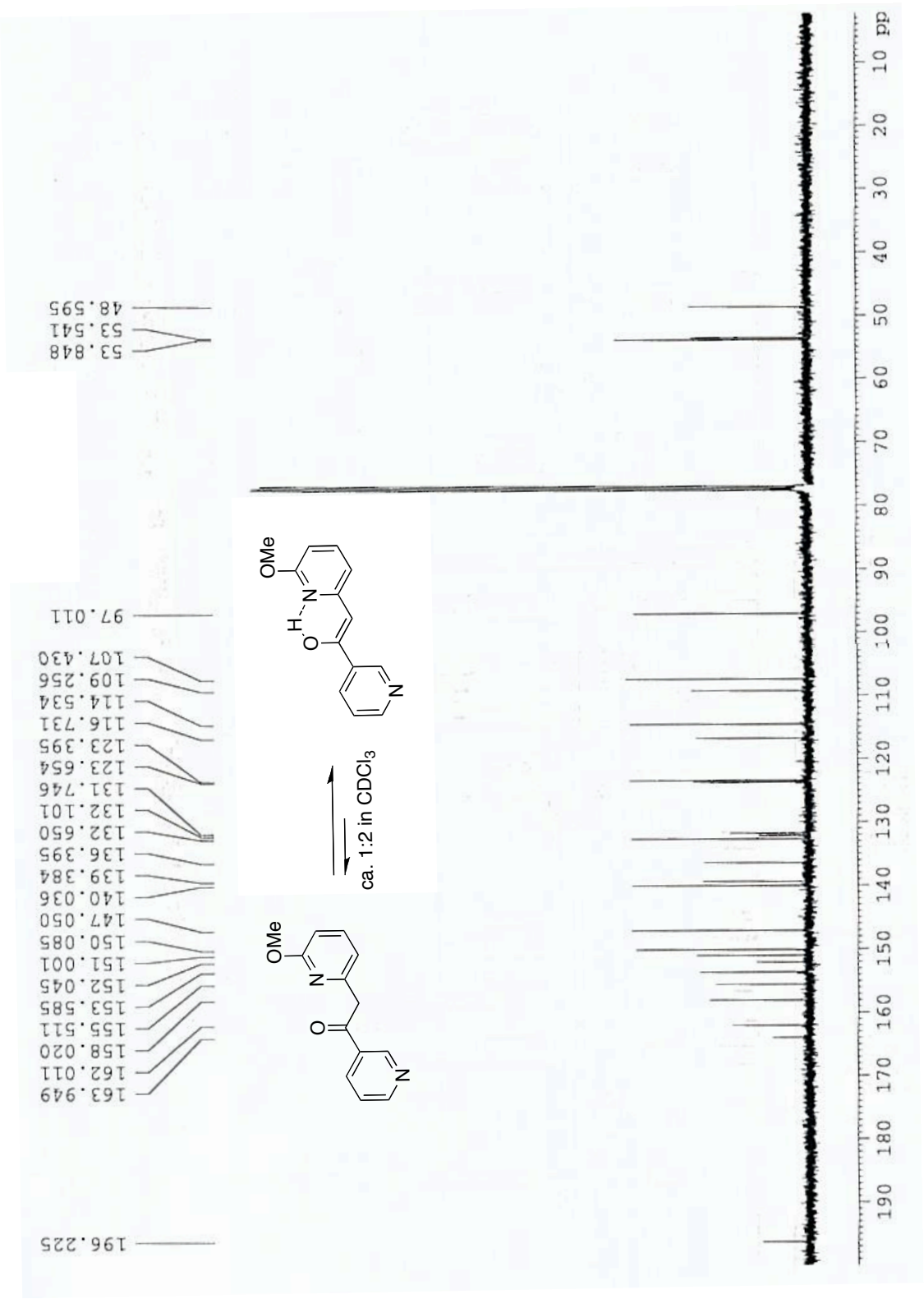


Table 2, Entry 8

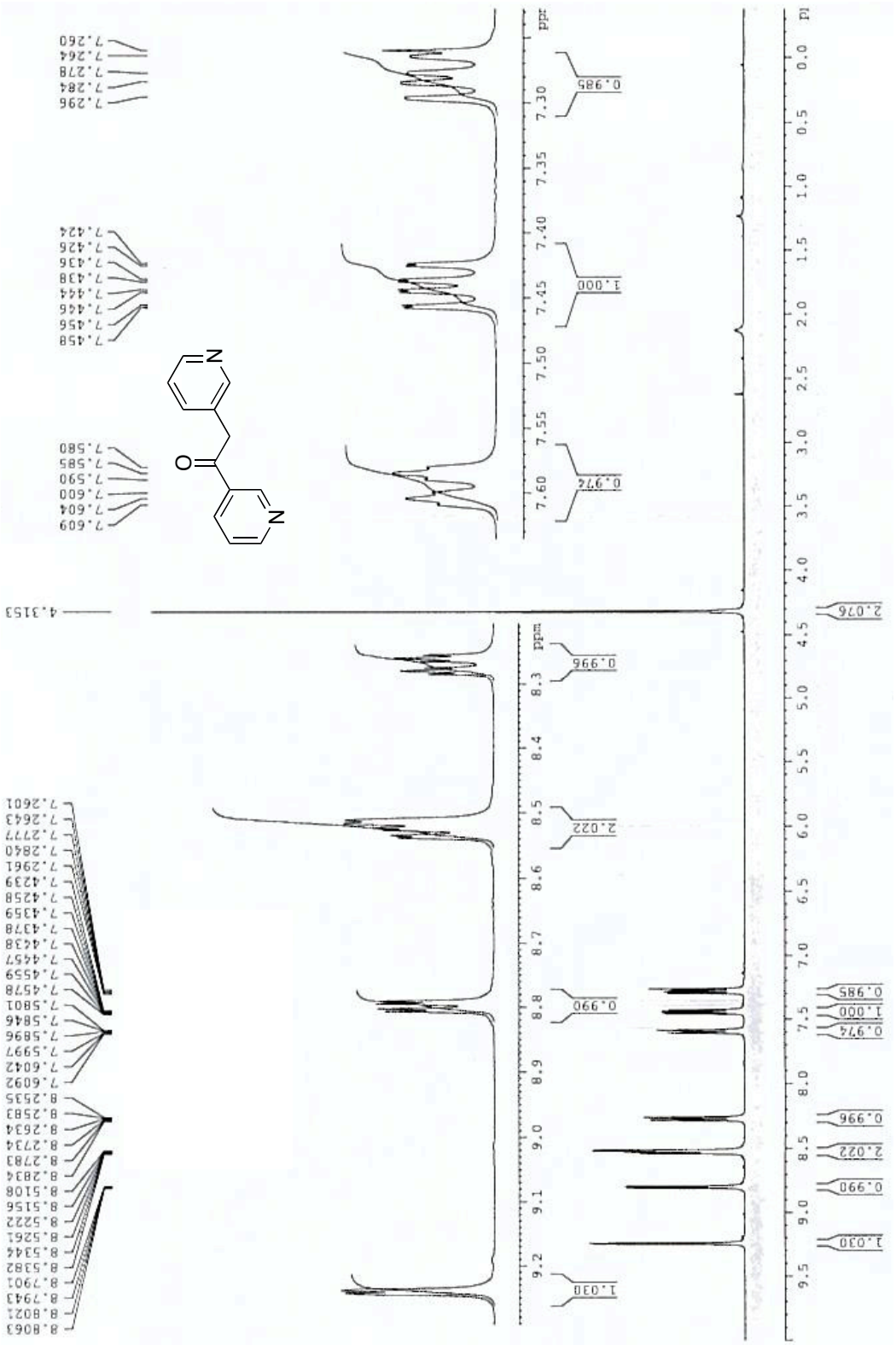


Table 2, Entry 8

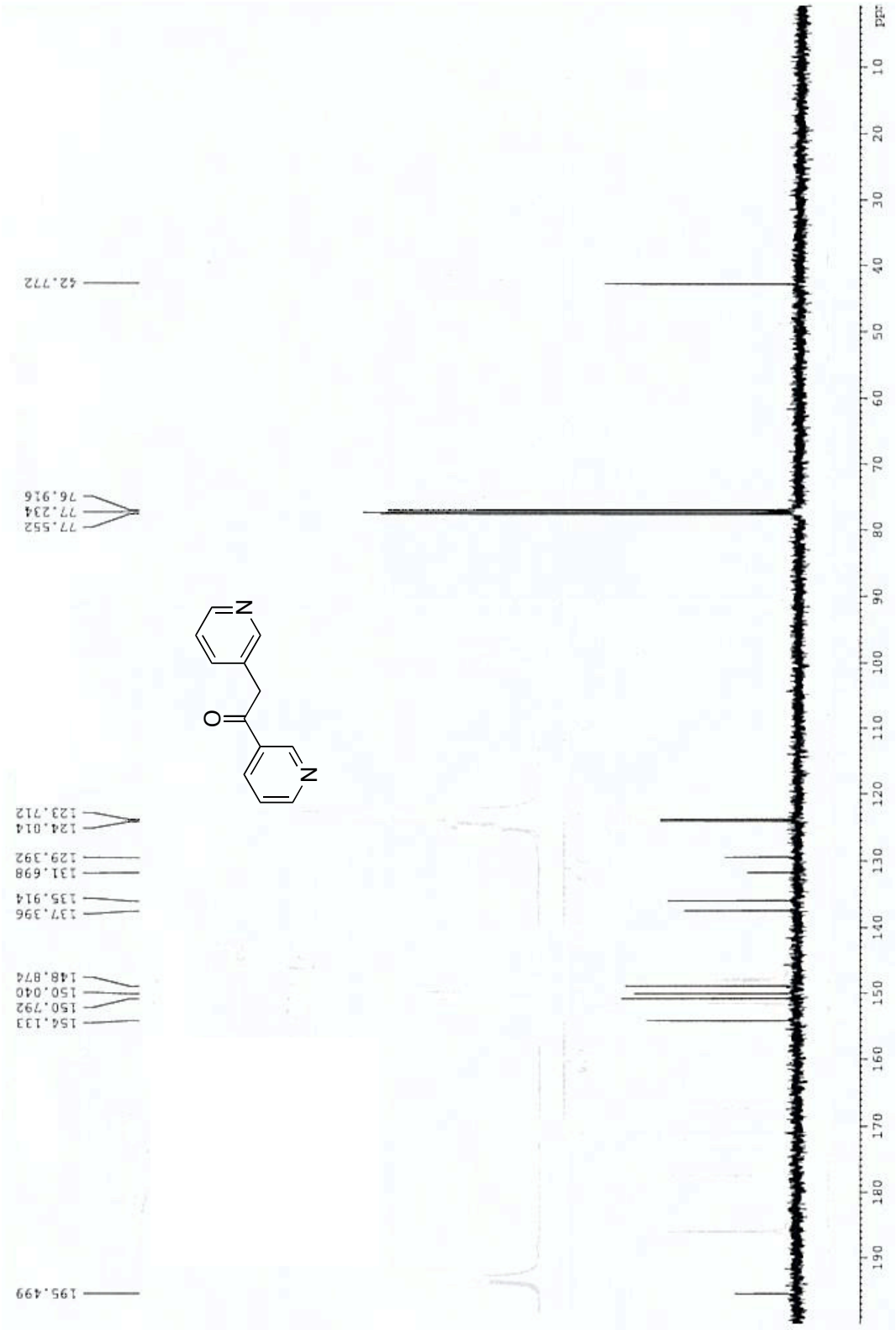


Table 2, Entry 9

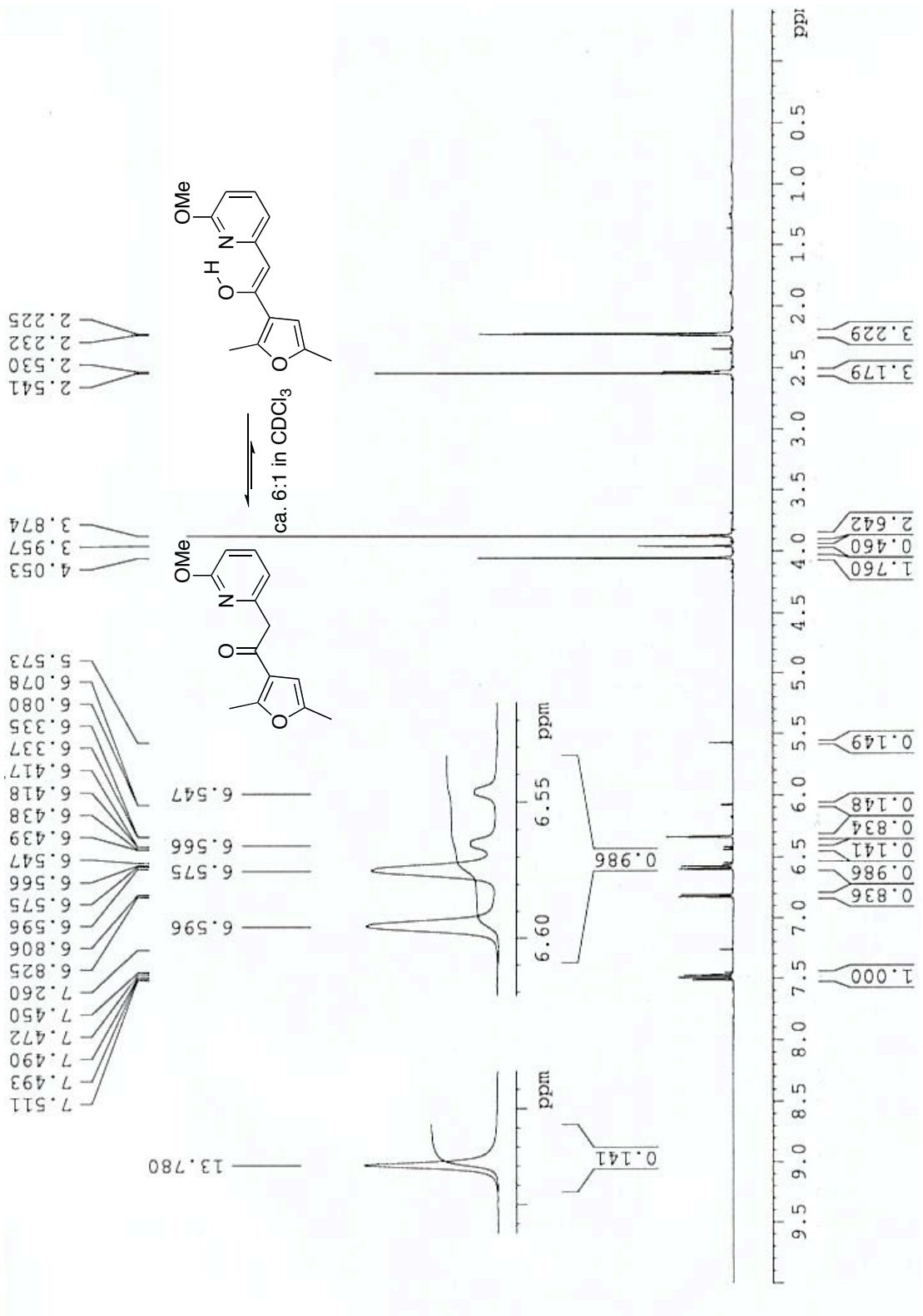


Table 2, Entry 9

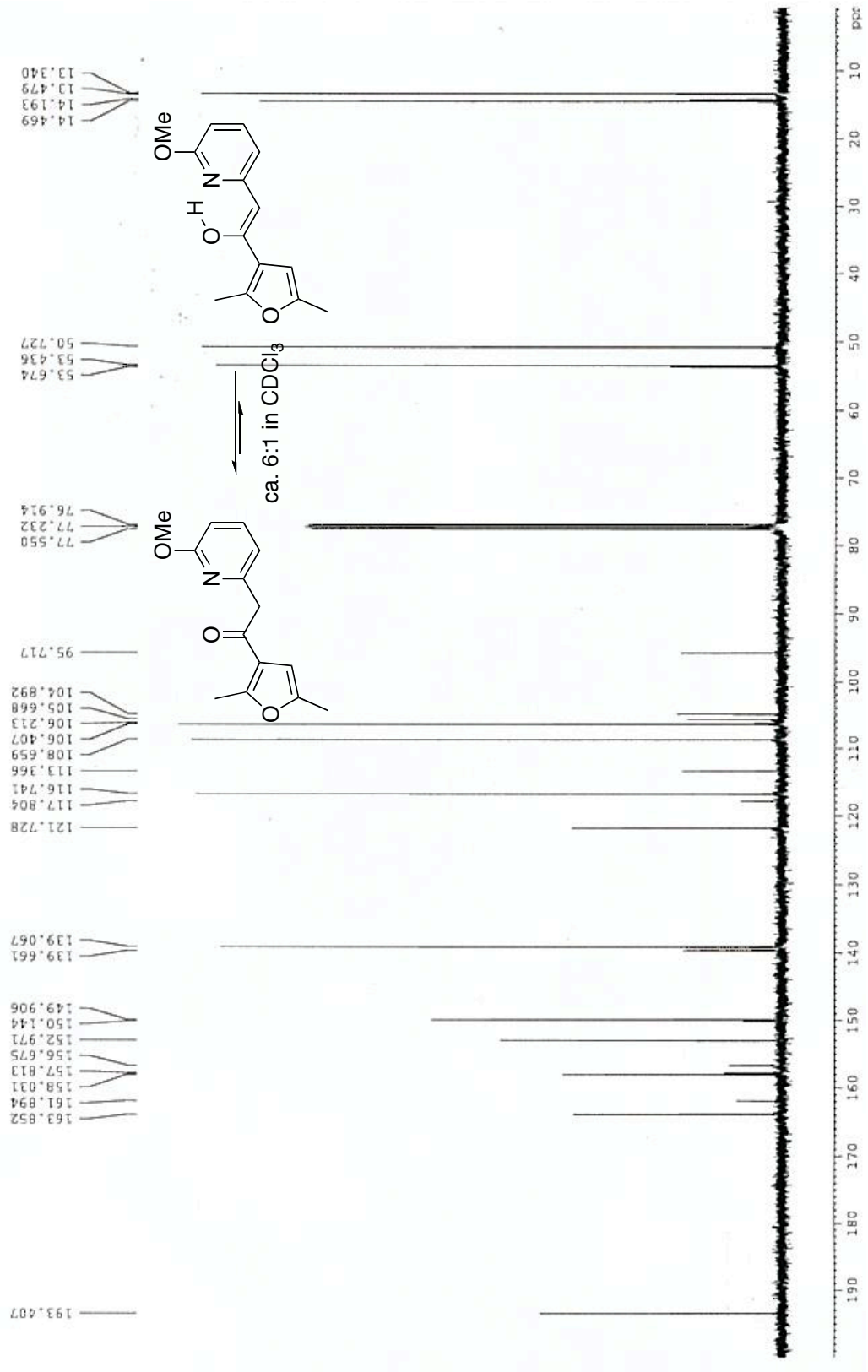


Table 2, Entry 10

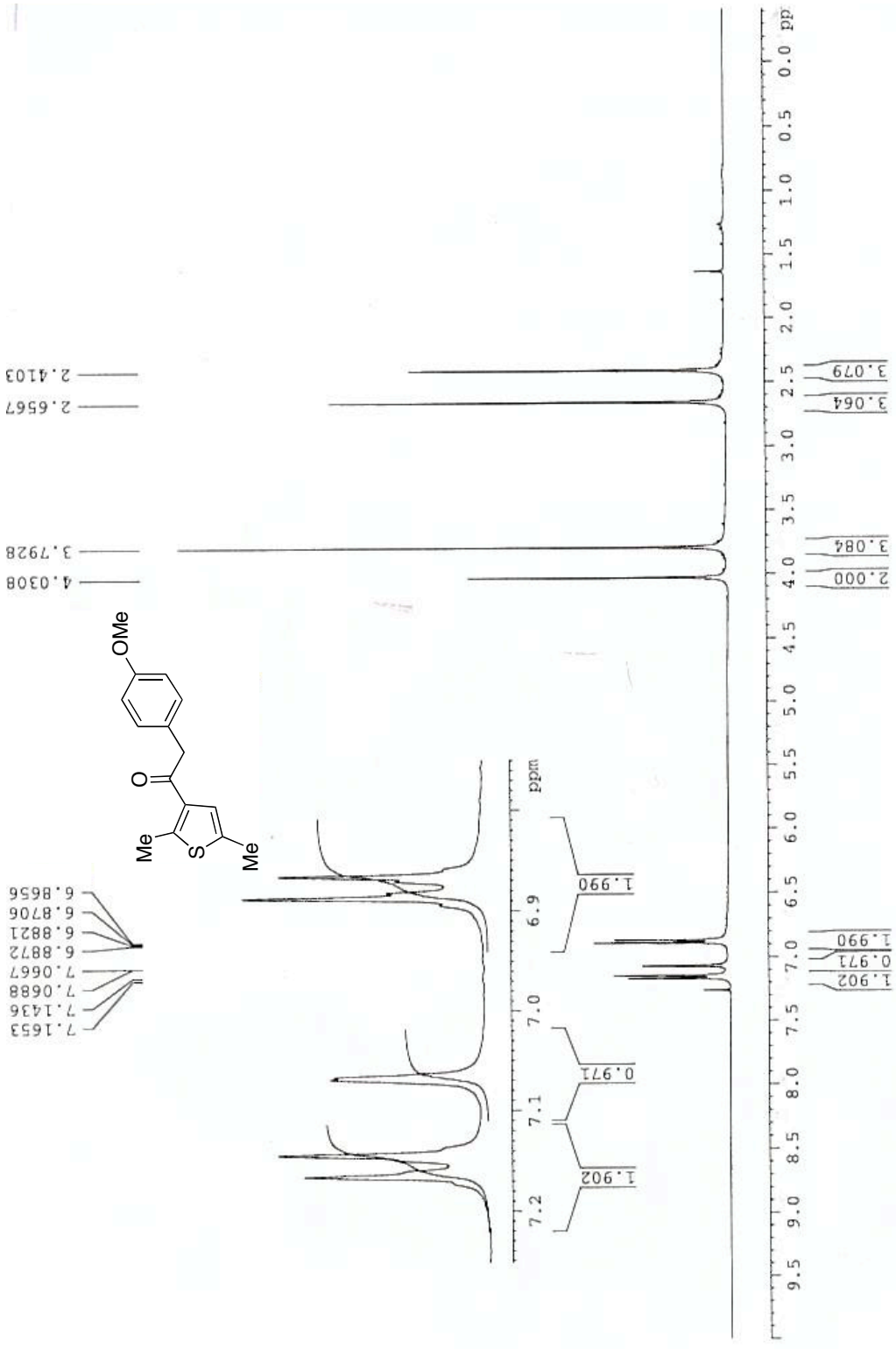


Table 2, Entry 10

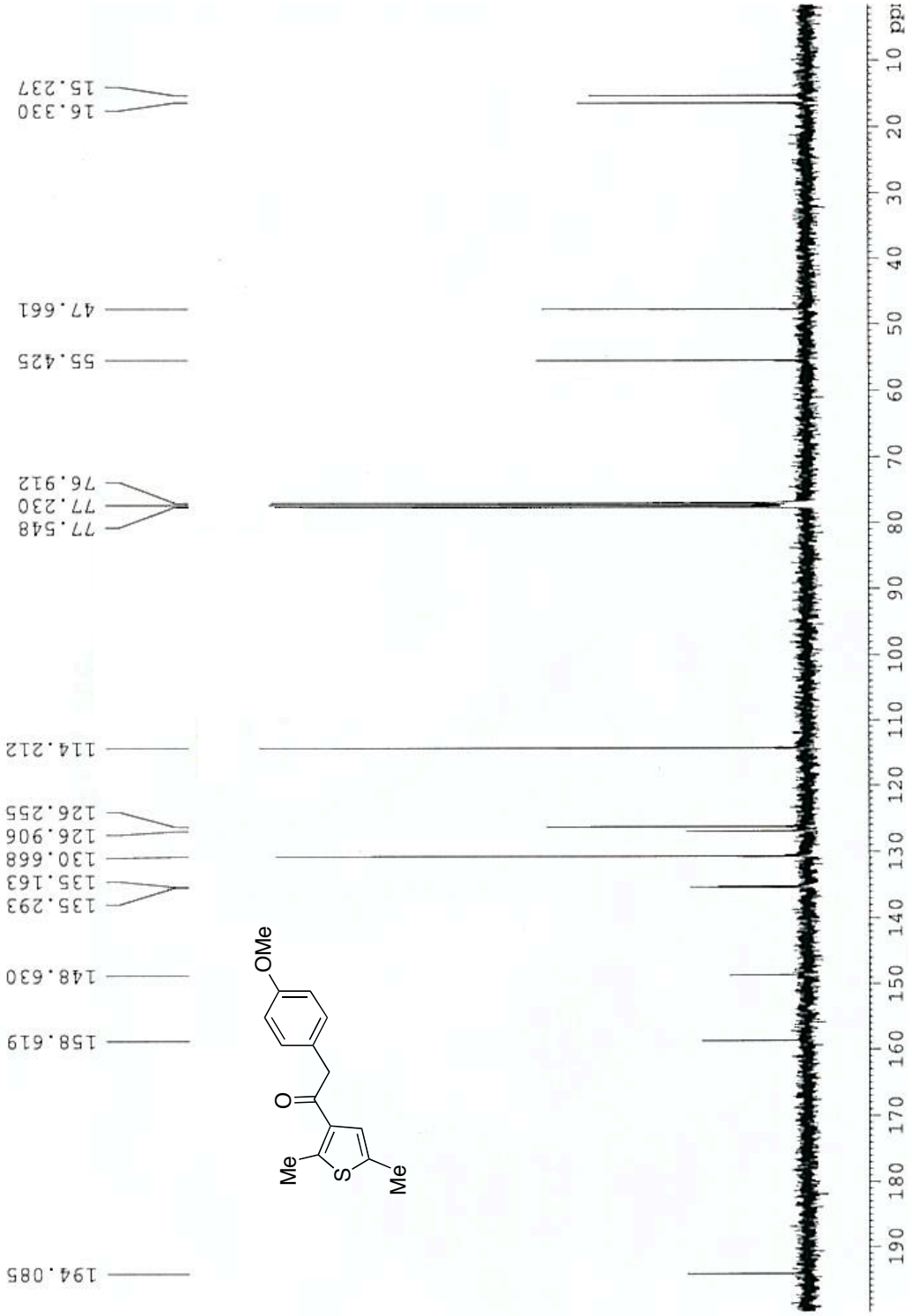


Table 2, Entry 11

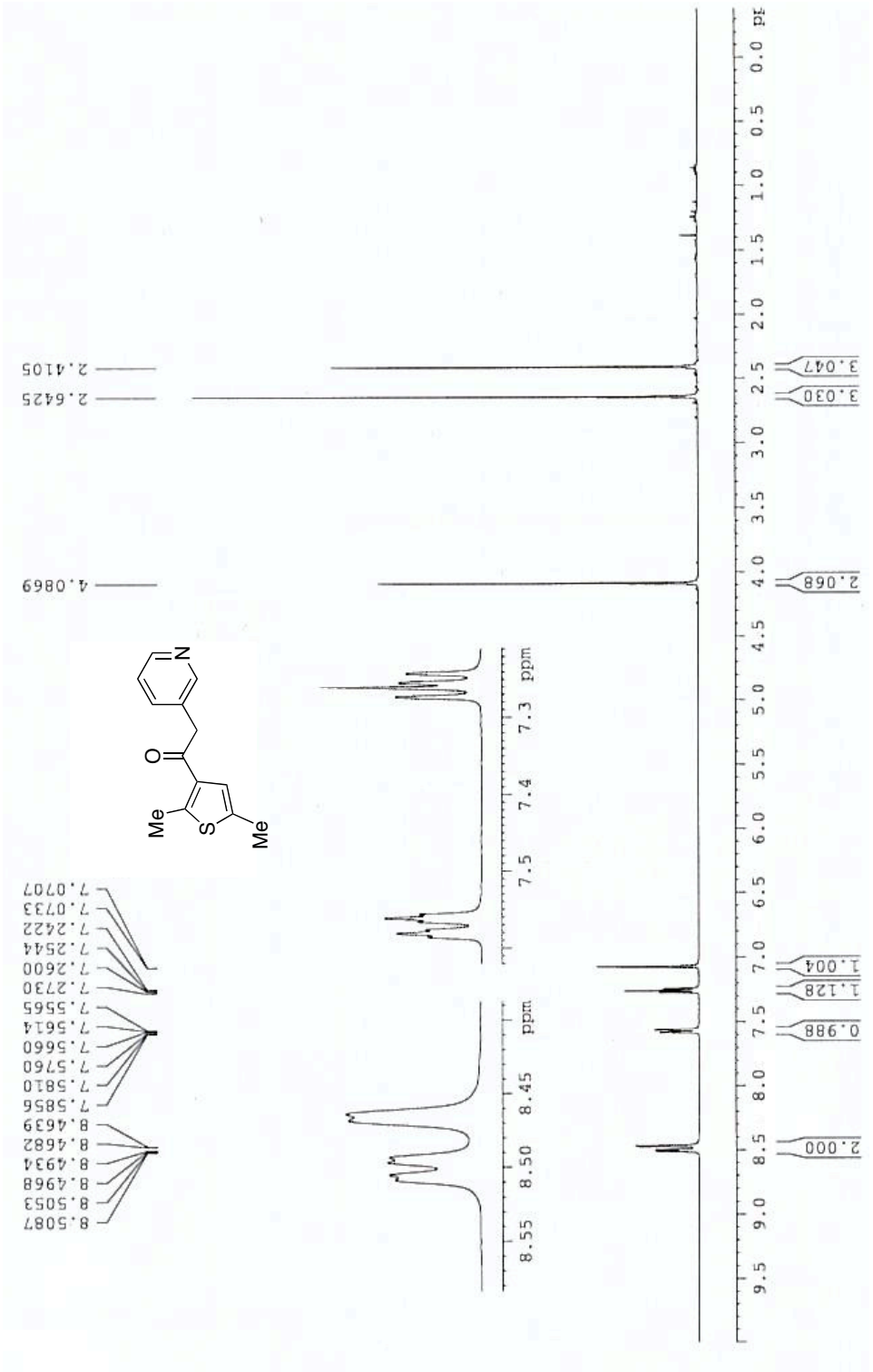


Table 2, Entry 11

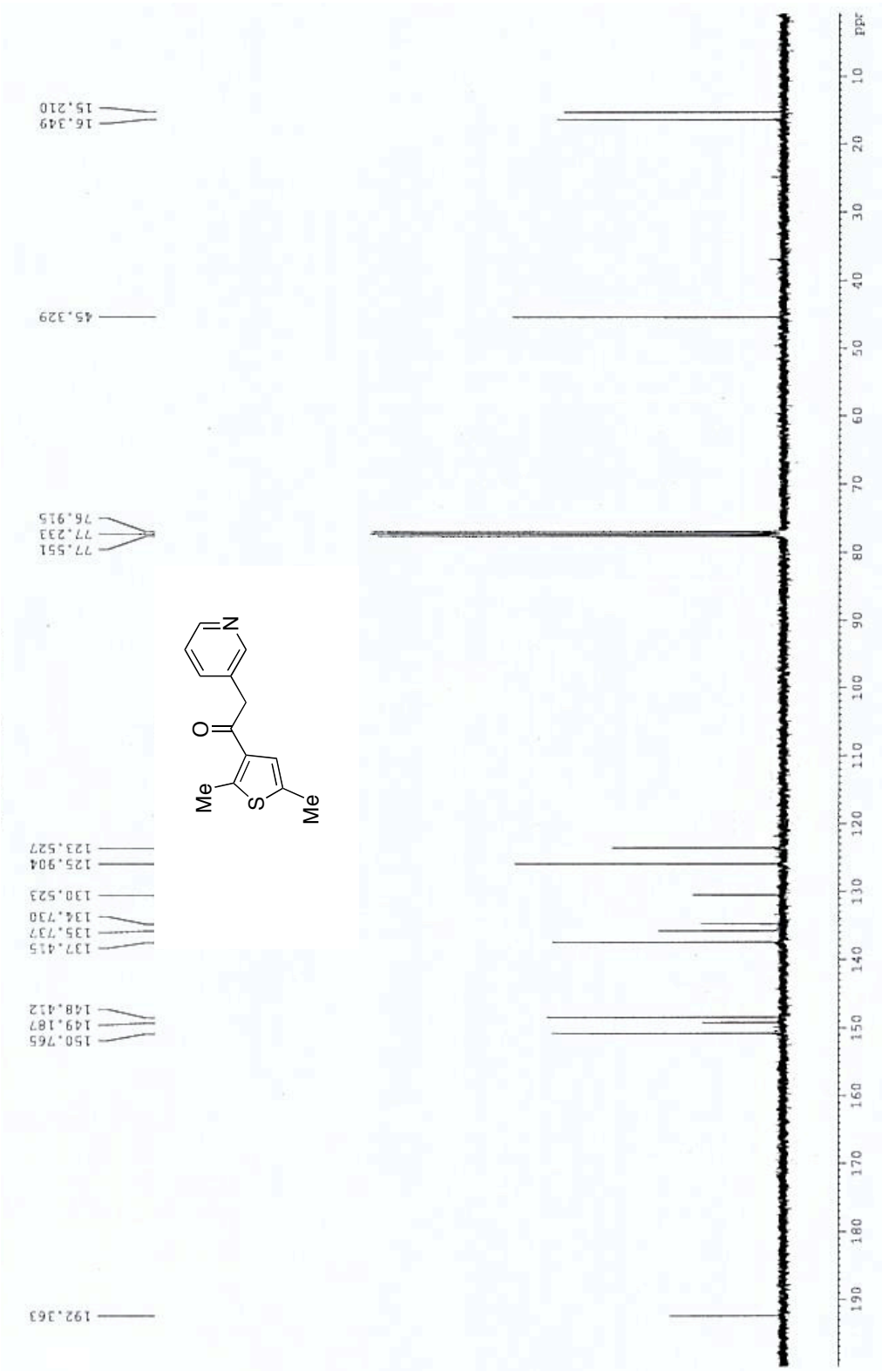


Table 2, Entry 12

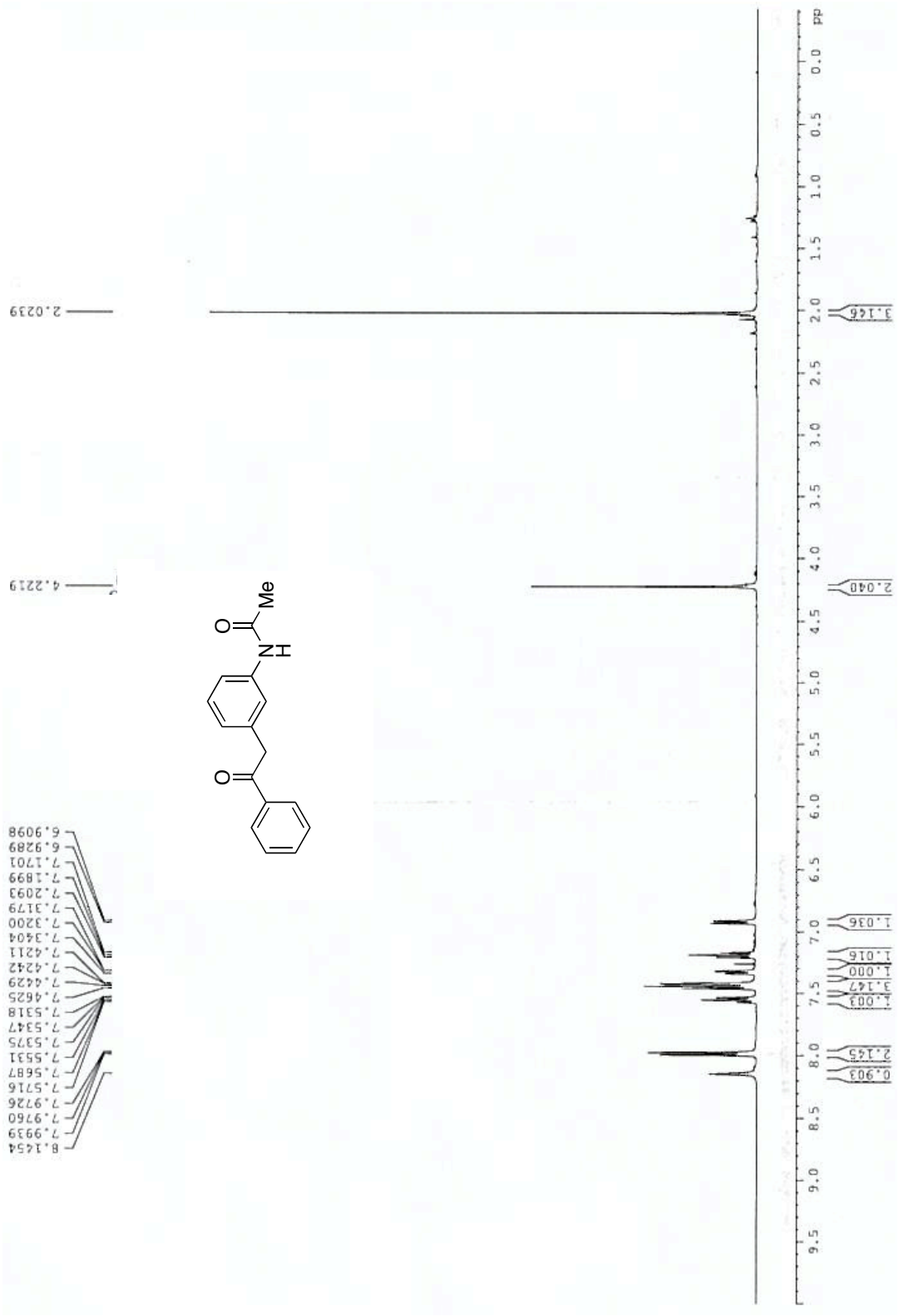


Table 2, Entry 12