Water-Mediated Preactivation: An Efficient Protocol for C-N Cross-Coupling Reactions

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Supporting Information

General Reagent Information

All reactions were carried out under an argon atmosphere. The 1,4-dioxane and *tert*-butanol were purchased from Aldrich Chemical Co. in Sure-Seal bottles and were used as recieved. $Pd(OAc)_2$ was a gift from BASF and aryl halides and amines were purchased from Aldrich Chemical Co., Alfa Aesar, or TCI America. All amines that were a liquid were distilled from calcium hydride and stored under argon. Amines that were a solid and all aryl halides were used as purchased without furthur purification. Distilled water was degassed by brief (30 sec) sonication under vacuum. Anhydrous tribasic potassium phosphate was purchased from Fluka Chemical Co. and both potassium carbonate and sodium *tert*-butoxide were purchased from Aldrich Chemical Co. and used as received. Ligands **1**[1] and **2**[2] were synthesized using literature procedures.

General Analytical Information

All compounds were characterized by ^1H NMR, ^{13}C NMR, IR spectroscopy, and elemental analysis. Copies of the ^1H and ^{13}C spectra can be found at the end of the Supporting Information. Nuclear Magnetic Resonance spectra were recorded on a Varian 300 MHz instrument. All ^1H 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 ^1H decoupling. All IR spectra was taken on a Perkin – Elmer 2000 FTIR. All GC analyses were performed on a Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA.

General Procedure A

An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a teflon septum, was charged with $Pd(OAc)_2$ (1 mol%) and ligand (3 mol%). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and the solvent (2 mL) and degassed H_2O (4 mol%) were added via syringe. After addition of the water, the solution was heated to 110 °C for 1.5 min.

A second oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon septum, was charged with base (1.4 mmol) (aryl chlorides or amines that were solids at room temperature were added with the base). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and then the aryl chloride (1.0 mmol) and amine (1.2 mmol) were added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula. The solution was heated to 110 °C until the aryl chloride had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, washed with water, concentrated in vacuo, and purified via flash chromatography on silica gel.

General Procedure B

General procedure A was used with the following modification: 1.4 mmol of amine was used.

General Procedure C

General procedure A was used with the following modification: after addition of the water the solution was heated to 80 °C for 1 min.

General Procedure D

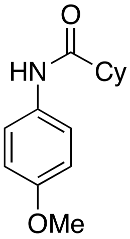
General procedure A was used with the following modification: after addition of the water the solution was heated to 80 °C for 1 min and 2.5 mmol of the base was used.

General Procedure E

An oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a teflon septum, was charged with a pre-milled 1:3 mixture of $Pd(OAc)_2$ and XPhos (0.05 mol% Pd).* The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and the solvent (1 mL) and degassed H_2O (2 mol%) were added via syringe. After addition of the water, the solution was heated to 80 °C for 1 min.

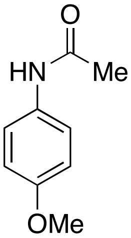
A second oven-dried test tube, which was equipped with a magnetic stir bar and fitted with a Teflon septum, was charged with base (2.4 mmol) (aryl chlorides or amines that were solids at room temperature were added with the base). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times) and then the aryl chloride (2.0 mmol), amine (2.4 mmol) and solvent (1 mL) were added via syringe and the activated catalyst solution was transferred from the first reaction vessel into the second via cannula. The solution was heated to 110 °C until the aryl chloride had been completely consumed as judged by GC analysis. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate, washed with water, concentrated in vacuo, and purified via flash chromatography on silica gel.

*The $Pd(OAc)_2$ (1 equiv) and XPhos (3 equiv) were ground together in a mortar and pestle and stored in a desicator.

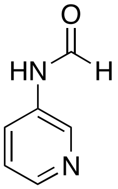


***N*-(4-Methoxyphenyl)cyclohexanecarboxamide** (Table 1, entry 1) Following general procedure A, a mixture of 4-chloroanisole (123 μL, 1.0 mmol), cyclohexanecarboxamide (153 mg, 1.2 mmol), K_3PO_4 (297 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **2** (14.6 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 3

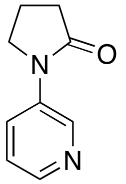
h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 10-50% EtOAc/hexanes) to provide the title compound as a white solid (227 mg, 97%), mp 147-149 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55, (s, 1H), 7.42 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0 Hz, 2H), 3.76 (s, 3H), 2.20 (tt, *J* = 3.5 Hz, *J* = 11.5 Hz, 1H), 1.91 (m, 2H), 1.80 (m, 2H), 1.68 (m, 1H), 1.51 (m, 2H), 1.25 (m, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.8, 156.4, 131.6, 122.0, 114.2, 55.7, 46.5, 29.9, 25.9 ppm. IR (neat, cm^{-1}): 3295, 2922, 2852, 1528, 1514, 1384, 1247, 1031, 824. Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21. Found: C, 71.96; H, 8.24.



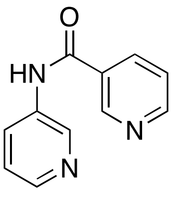
***N*-(4-Methoxyphenyl)ethanamide** (Table 1, entry 2) Following general procedure A, a mixture of 4-chloroanisole (123 μL, 1.0 mmol), acetamide (71 mg, 1.2 mmol), K_3PO_4 (297 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **2** (14.6 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 3 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 10-50% EtOAc/hexanes) to provide the title compound as a white solid (138 mg, 84%), mp 126-128 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (s, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 3.77 (s, 3H), 2.12 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.8, 156.6, 131.3, 122.2, 114.3, 55.7, 24.5 ppm. IR (neat, cm^{-1}): 3240, 3066, 1604, 1514, 1410, 1029, 838, 775. Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.44; H, 6.71. Found: C, 65.37; H, 6.78.



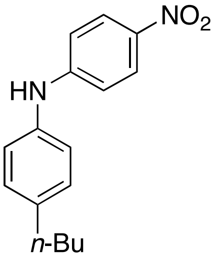
***N*-(pyridin-3-yl)methanamide** (Table 1, entry 3) Following general procedure B, a mixture of 3-chloropyridine (95 μL, 1.0 mmol), formamide (56 μL, 1.4 mmol), K_3PO_4 (297 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **2** (14.6 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 3 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 7-9% MeOH/CH_2Cl_2) to provide the title compound as a white solid (102 mg, 84%), mp 93-94 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.60 (bm, 0.25H), 9.44 (s, 0.75H), 8.72 (d, *J* = 11.0 Hz, 0.25H), 8.67 (d, *J* = 2.5 Hz, 0.75H), 8.49 (d, *J* = 2.5 Hz, 0.25H), 8.43 (m, 1H), 8.33, (d, *J* = 4.5 Hz, 0.75H), 8.20 (d, *J* = 8.0 Hz, 0.75H), 7.50 (d, *J* = 8.0 Hz, 0.25H), 7.29 (m, 1H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.7, 160.2, 146.5, 145.3, 141.0, 140.8, 134.8, 134.3, 128.0, 126.3, 124.6, 124.3 ppm. IR (neat, cm^{-1}): 3244, 3131, 1648, 1606, 1370, 1247, 1031, 839. Anal. Calcd. for $C_6H_6N_2O$: C, 59.01; H, 4.95. Found: C, 59.06; H, 5.03.



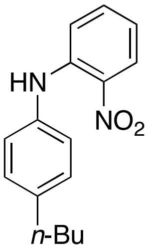
1-(Pyridin-3-yl)pyrrolidin-2-one (Table 1, entry 4) Following general procedure A, a mixture of 3-chloropyridine (95 μL, 1.0 mmol), 3-pyrrolidinone (102 mg, 1.2 mmol), K_3PO_4 (297 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **2** (14.6 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 3 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 7-9% MeOH/CH_2Cl_2) to provide the title compound as a white solid (135 mg, 83%), mp 39-41 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.61 (d, *J* = 2.5 Hz), 8.22 (dd, *J* = 1.5 Hz, *J* = 5.0 Hz, 1H), 8.02 (qd, *J* = 1.5 Hz, *J* = 8.5 Hz, 1H), 7.14 (m, 1H), 3.73 (t, *J* = 7.0 Hz, 2H), 2.46 (t, *J* = 8.0 Hz, 2H), 2.06 (p, *J* = 7.0 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.9, 145.3, 140.7, 136.2, 126.9, 123.5, 48.1, 32.5, 18.1 ppm. IR (neat, cm^{-1}): 3384, 2976, 1698, 1486, 1390, 1308, 1231, 806, 707. Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21. Found: C, 66.56; H, 6.23.



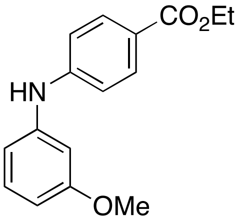
***N*-(Pyridin-3-yl)pyridine-3-carboxamide** (Table 1, entry 5) Following general procedure A, a mixture of 3-chloropyridine (95 μL, 1.0 mmol), nicotinamide (146 mg, 1.2 mmol), K_3PO_4 (297 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), **2** (14.6 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 3 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 7-9% $MeOH/CH_2Cl_2$) to provide the title compound as a white solid (199 mg, 99%), mp 189-190 °C. ^1H NMR (300 MHz, DMSO) δ: 10.65 (s, 1H), 9.12 (s, 1H), 8.92 (s, 1H), 8.77 (d, *J* = 5.0 Hz, 1H), 8.31 (m, 2H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.57 (q, *J* = 5.0 Hz, 1H), 7.40 (q, *J* = 5.0 Hz, 1H) ppm. ^{13}C NMR (75 MHz, DMSO) δ: 165.2, 153.1, 149.4, 145.5, 142.6, 136.3, 136.2, 130.7, 128.1, 124.3, 124.2 ppm. IR (neat, cm^{-1}): 3309, 2922, 2852, 1680, 1590, 1429, 1384, 1117. Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55. Found: C, 66.22; H, 4.57.



***N*-(4-Butylphenyl)-4-nitroaniline** (Table 2, entry 1) Following general procedure C, a mixture of 1-butyl-4-chlorobenzene (169 mg, 1.0 mmol), 4-nitroaniline (166 mg, 1.2 mmol), K_2CO_3 (193 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), XPhos (14.3 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-20% EtOAc/Hexane) to provide the title compound as an orange solid (258 mg, 96%), mp 76-77 °C. ^1H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.43 (s, 1H), 2.62 (t, *J* = 7.5 Hz, 2H), 1.62 (p, *J* = 7.5 Hz, 2H), 1.38 (sextet, *J* = 7.0 Hz, 2H), 0.95 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.2, 140.0, 139.4, 137.1, 129.9, 126.6, 122.7, 113.5, 35.3, 33.9, 22.6, 14.2 ppm. IR (neat, cm^{-1}): 3344, 2928, 1593, 1502, 1182, 1112, 834, 751. Anal. Calcd. for $C_{16}H_{19}N_2O_2$: C, 71.09; H, 6.71. Found: C, 71.35; H, 6.87.

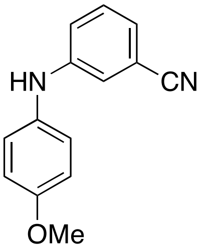


N-(4-Butylphenyl)-2-nitroaniline (Table 2, entry 2) Following general procedure C, a mixture of 1-butyl-4-chlorobenzene (169 mg, 1.0 mmol), 2-nitroaniline (166 mg, 1.2 mmol), K_2CO_3 (193 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), XPhos (14.3 mg, 0.03 mmol), H_2O (1 µL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 2 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-20% EtOAc/Hexane) to provide the title compound as an red oil (252 mg, 93%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.48 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 7.34 (t, J = 7.0 Hz, 1H), 7.21 (m, 5H), 6.73 (t, J = 7.0 Hz, 1H), 2.63 (t, J = 7.5 Hz, 2H), 1.62 (p, J = 7.0 Hz, 2H), 1.38 (sextet, J = 7.0 Hz, 2H), 0.94 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 143.9, 141.0, 136.3, 135.9, 133.0, 129.9, 126.8, 124.9, 117.3, 116.2, 35.4, 33.9, 22.6, 14.3 ppm. IR (neat, cm^{-1}): 3353, 2929, 2858, 1607, 1573, 1348, 1262, 1147, 740. Anal. Calcd. for $C_{16}H_{19}N_2O_2$: C, 71.09; H, 6.71. Found: C, 71.34; H, 6.97.

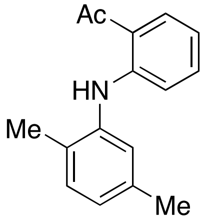


Ethyl 4-(3-methoxyphenylamino)benzoate (Table 2, entry 3) Following general procedure C, a mixture of 3-chloroanisole (123 µL, 1.0 mmol), ethyl-4-aminobenzoate (198 mg, 1.2 mmol), K_2CO_3 (193 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), XPhos (14.3 mg, 0.03 mmol), H_2O (1 µL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-30% EtOAc/Hexane) to provide the title compound as a white solid (232 mg, 86%), mp 87-88 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.93 (d, J = 8.5 Hz, 2H), 7.23 (t, J = 8.0 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.75 (m, 2H), 6.61 (d, J = 8.0 Hz, 1H), 6.30 (s, 1H), 4.34 (q, J = 7.0 Hz, 2H), 3.78 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ:

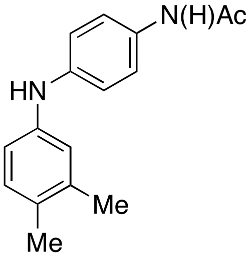
166.9, 160.9, 148.0, 142.6, 131.7, 130.5, 121.7, 115.2, 112.7, 108.4, 106.0, 60.8, 55.5, 14.7 ppm. IR (neat, cm^{-1}): 3351, 2980, 1688, 1523, 1493, 1278, 1175, 1108, 769. Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.89; H, 6.23.



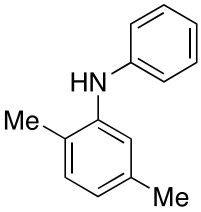
3-(4-methoxyphenylamino)benzonitrile (Table 2, entry 4) Following general procedure C, a mixture of 4-chloroanisole (123 μL, 1.0 mmol), 3-aminobenzonitrile (142 mg, 1.2 mmol), K_2CO_3 (193 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), XPhos (14.3 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-30% EtOAc/Hexane) to provide the title compound as a yellow oil (209 mg, 93%), mp 87-89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (t, *J* = 6.5 Hz, 1H), 7.06 (m, 5H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.82 (s, 1H), 3.81 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.4, 149.2, 138.7, 136.6, 134.9, 132.8, 131.2, 130.3, 126.1, 125.6, 118.7, 116.1, 114.3, 28.3, 21.3, 18.0 ppm. IR (neat, cm^{-1}): 3377, 2226, 1601, 1524, 1330, 1237, 1034, 778. Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39. Found: C, 75.10; H, 5.40.



1-(2-(2,5-Dimethylphenylamino)phenyl)ethanone (Table 2, entry 5) Following general procedure C, a mixture of 2-chloro-1,4-dimethylbenzene (134 μL, 1.0 mmol), 2'-aminoacetophenone (146 μL, 1.2 mmol), K_2CO_3 (193 mg, 1.4 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), XPhos (14.3 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-30% EtOAc/Hexane) to provide the title compound as a yellow oil (227 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.46 (s, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.21 (m, 2H), 6.97 (m, 2H), 6.73 (t, *J* = 7.0 Hz, 1H), 2.70 (s, 3H), 2.37 (s, 3H), 2.30 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.4, 149.2, 138.7, 136.6, 134.9, 132.8, 131.2, 130.3, 126.1, 125.6, 118.7, 116.1, 114.3, 28.3, 21.3, 18.0 ppm. IR (neat, cm^{-1}): 3256, 2922, 1639, 1578, 1453, 1246, 1233, 1164, 745. Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16. Found: C, 80.44; H, 7.30.

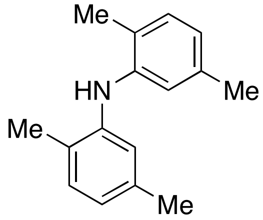


***N*-(4-(3,4-Dimethylphenylamino)phenyl)ethanamide** (Table 2, entry 6) Following general procedure D, a mixture of 4-chloro-1,2-dimethylbenzene (141 mg, 1.0 mmol), 4'-aminoacetanilide (180 mg, 1.2 mmol), K_2CO_3 (345 mg, 2.5 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), XPhos (14.3 mg, 0.03 mmol), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 50-100% EtOAc/Hexane) to provide the title compound as a white solid (223 mg, 88%), mp 116-117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86 (s, 1H), 7.35 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.81 (m, 2H), 5.61 (s, 1H), 2.21 (s, 6H), 2.13 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.0, 141.3, 140.8, 137.8, 130.6, 129.5, 122.2, 119.8, 118.1, 115.7, 24.5, 20.3, 19.3 ppm. IR (neat, cm^{-1}): 3308, 2920, 1659, 1606, 1556, 1370, 1317, 814. Anal. Calcd. for $C_{16}H_{19}N_2O$: C, 75.56; H, 7.13. Found: C, 75.26; H, 7.17.

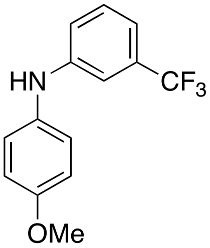


2,5-Dimethyl-*N*-phenylaniline (Table 3, entry 1) Following general procedure E, a mixture of 2-chloro-1,4-dimethylbenzene (268 μL, 2.0 mmol), aniline (220 μL, 2.4

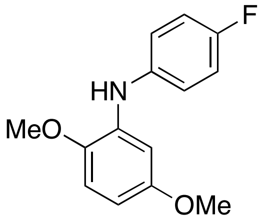
mmol), NaO*t*-Bu (230 mg, 2.4 mmol), 1:3 Pd(OAc)$_2$:XPhos (1.7 mg, 0.05 mol% Pd), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-30% EtOAc/Hexane) to provide the title compound as a yellow oil (375 mg, 95%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.48 (t, *J* = 8.5 Hz, 2H), 7.31 (m, 2H), 7.15 (m, 3H), 7.01 (d, *J* = 7.5 Hz, 1H), 5.51 (s, 1H), 2.51 (s, 3H), 2.42 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 144.5, 141.3, 136.8, 131.2, 129.7, 125.7, 123.2, 120.7, 120.0, 117.8, 21.6, 17.9 ppm. IR (neat, cm^{-1}): 3388, 3048, 2920, 1601, 1578, 1519, 1311, 748, 694. Anal. Calcd. for $C_{14}H_{15}N$: C, 85.24; H, 7.66. Found: C, 85.17; H, 7.64.



Bis(2,5-dimethylphenyl)amine (Table 3, entry 2) Following general procedure E, a mixture of 2-chloro-1,4-dimethylbenzene (268 μL, 2.0 mmol), 2,5-dimethylaniline (298 μL, 2.4 mmol), NaO*t*-Bu (230 mg, 2.4 mmol), 1:3 Pd(OAc)$_2$:XPhos (1.7 mg, 0.05 mol% Pd), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-30% EtOAc/Hexane) to provide the title compound as a yellow oil (436 mg, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (d, *J* = 7.5 Hz, 2H), 7.11 (s, 2H), 7.01 (d, *J* = 7.5 Hz, 2H), 5.33 (s, 1H), 2.55 (s, 6H), 2.49 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.4, 136.9, 131.2, 125.0, 122.6, 119.6, 21.7, 17.9 ppm. IR (neat, cm^{-1}): 3399, 2921, 2859, 1579, 1459, 1415, 1293, 1003, 798. Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50. Found: C, 84.99; H, 8.46.



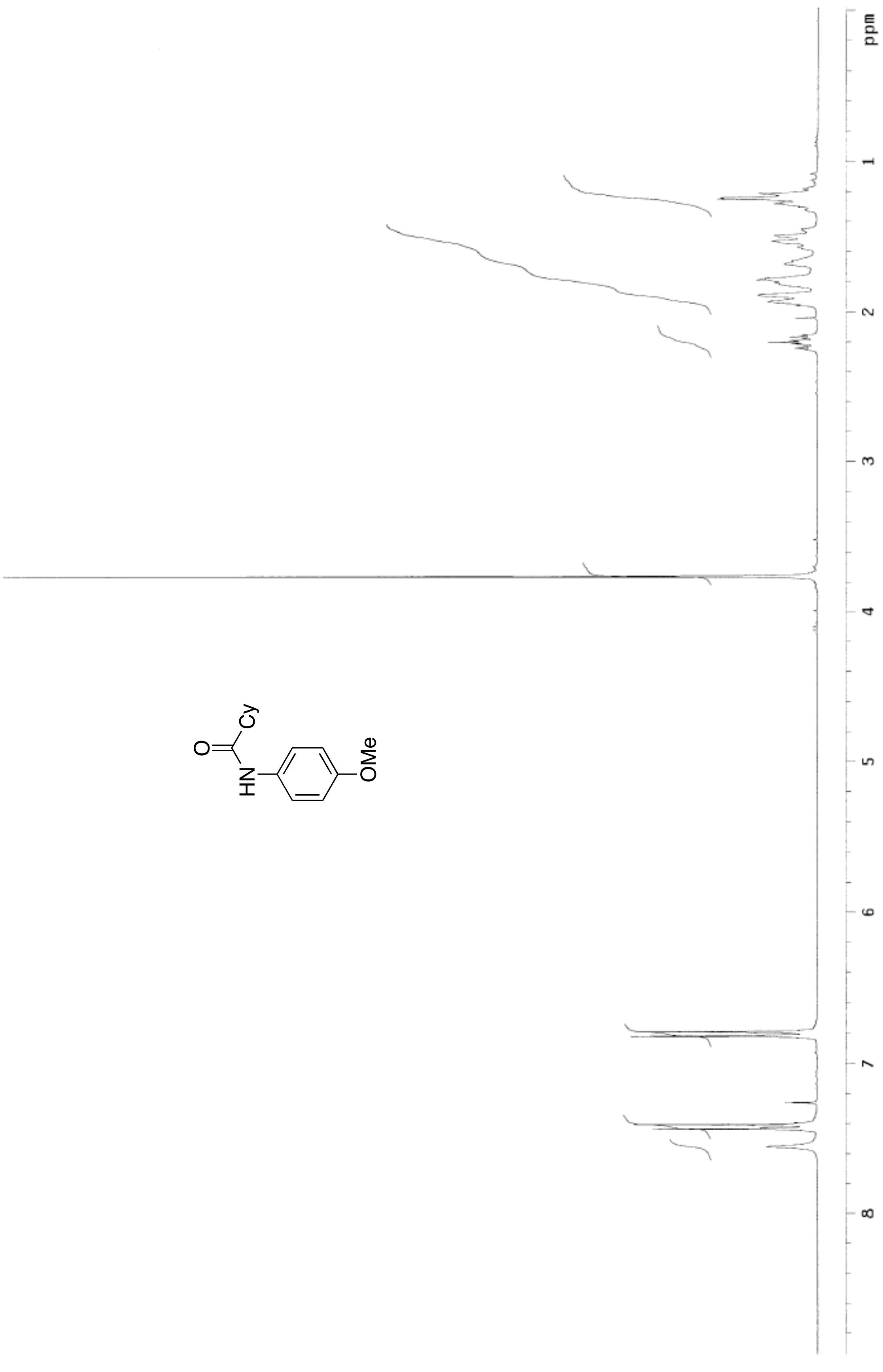
***N*-(4-methoxyphenyl)-3-(trifluoromethyl)aniline** (Table 3, entry 3) Following general procedure E, a mixture of 2-chloro-1,4-dimethoxybenzene (286 μL, 2.0 mmol), 4-fluoroaniline (286 μL, 2.4 mmol), NaO*t*-Bu (230 mg, 2.4 mmol), 1:3 $Pd(OAc)_2$:XPhos (1.7 mg, 0.05 mol% Pd), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-30% EtOAc/Hexane) to provide the title compound as a white solid (523 mg, 98%), mp 58-60 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.30 (t, J = 8.0 Hz, 1H), 7.06 (m, 5H), 6.93 (d, J = 9.0 Hz, 2H), 5.66 (s, 1H), 3.84 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.4, 146.3, 134.5, 132.1, 131.7, 130.1, 130.0, 129.9, 126.3, 123.7, 122.7, 118.1, 118.1, 115.9, 115.8, 115.8, 115.7, 115.1, 111.5, 111.5, 111.4, 111.4, 55.8 ppm. IR (neat, cm^{-1}): 3367, 2968, 2843, 1506, 1217, 1164, 1112, 1071, 1027, 788. Anal. Calcd. for $C_{14}H_{12}F_3NO$: C, 62.92; H, 4.53. Found: C, 63.01; H, 4.56.



***N*-(4-Fluorophenyl)-2,5-dimethoxyaniline** (Table 3, entry 4) Following general procedure E, a mixture of 2-chloro-1,4-dimethoxybenzene (286 μL, 2.0 mmol), 4-fluoroaniline (286 μL, 2.4 mmol), NaO*t*-Bu (230 mg, 2.4 mmol), 1:3 $Pd(OAc)_2$:XPhos (1.7 mg, 0.05 mol% Pd), H_2O (1 μL, 0.04 mmol) and *t*-BuOH (2 mL) was heated to 110 °C for 1 h. The crude product was purified via the Biotage SP4 (silica-packed 25+M; 0-30% EtOAc/Hexane) to provide the title compound as a yellow oil (492 mg, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.16 (m, 2H), 7.03 (m, 2H), 6.79 (m, 2H), 6.37 (dd, J = 3.0 Hz, J = 8.5 Hz, 1H), 6.15 (s, 1H), 3.87 (s, 3H), 3.76 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ: 160.2, 157.0, 154.5, 122.1, 122.0, 116.3, 116.0, 111.3, 102.5, 101.1, 56.3, 55.8 ppm. IR (neat, cm^{-1}): 3413, 2939, 1605, 1523, 1215, 1050, 829, 785. Anal. Calcd. for $C_{14}H_{14}FNO_2$: C, 68.00; H, 5.71. Found: C, 68.07; H, 5.74.

References

1) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapers, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
2) Anderson, K. W.; Tundel, R. E.; Ikawa, T.; Altman, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2006**, *45*, 6523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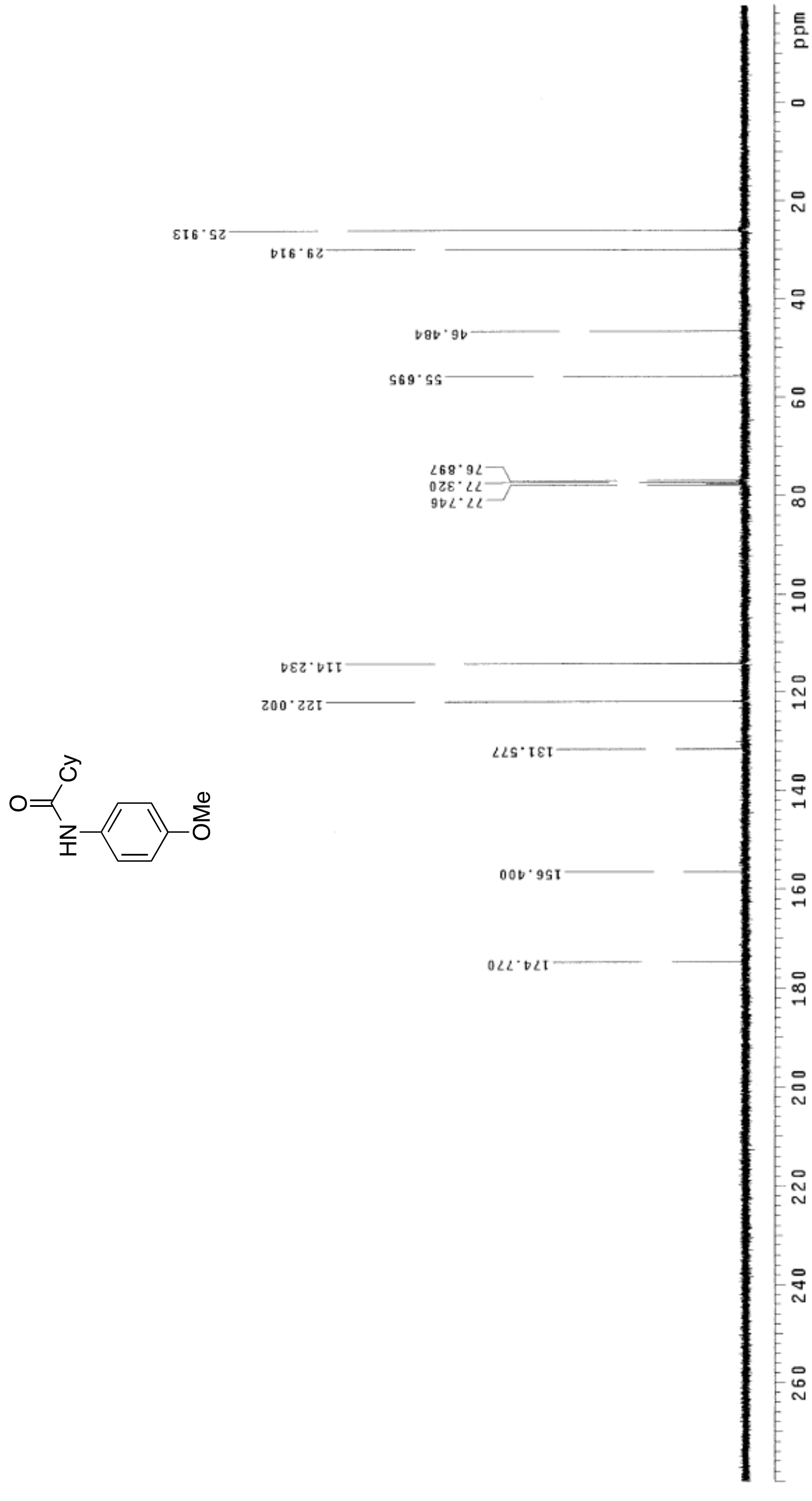
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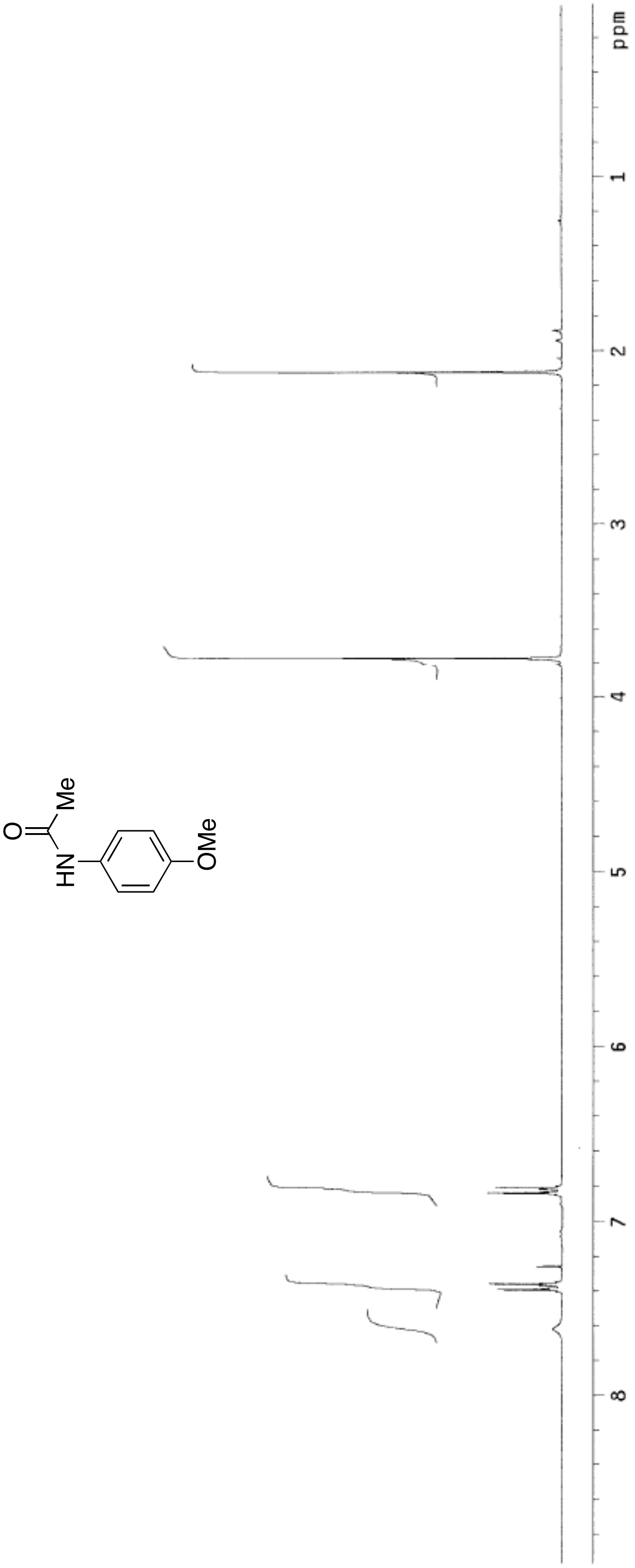
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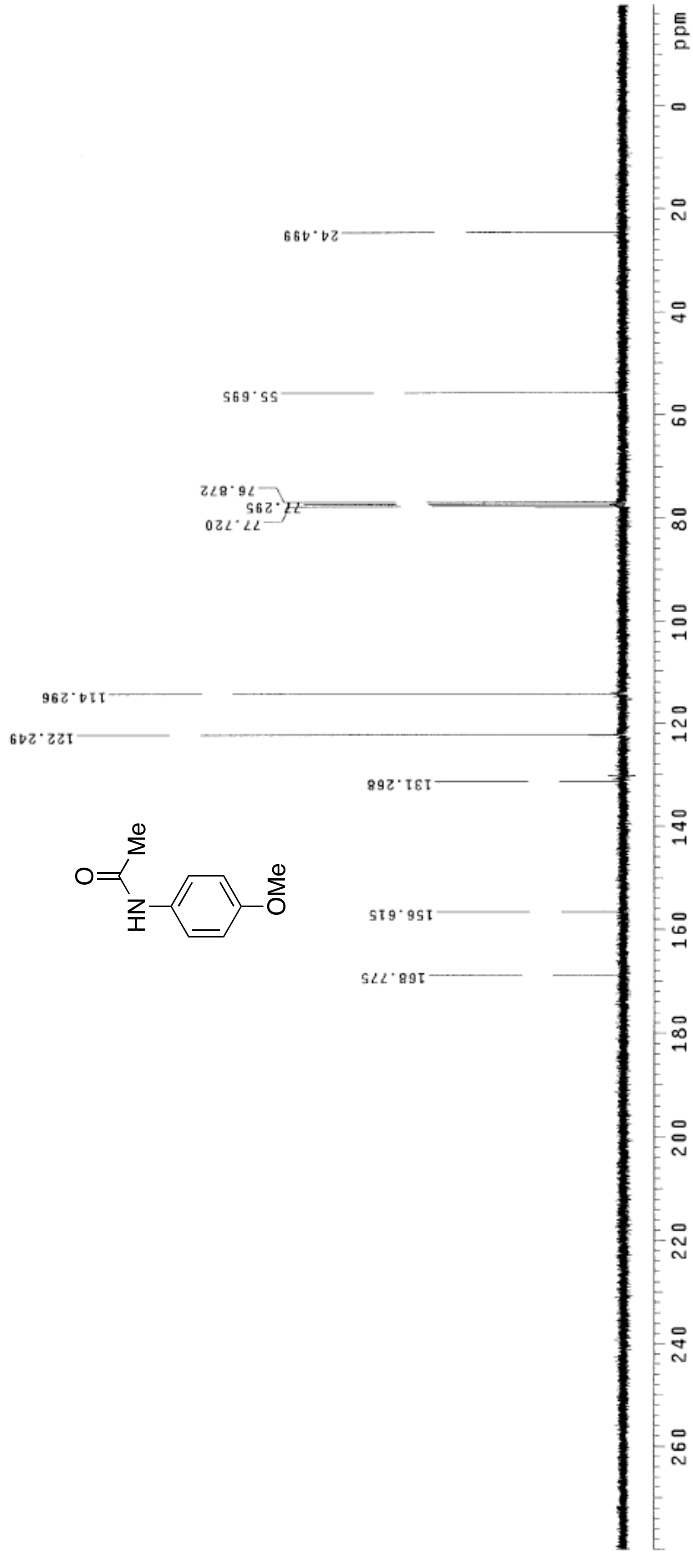
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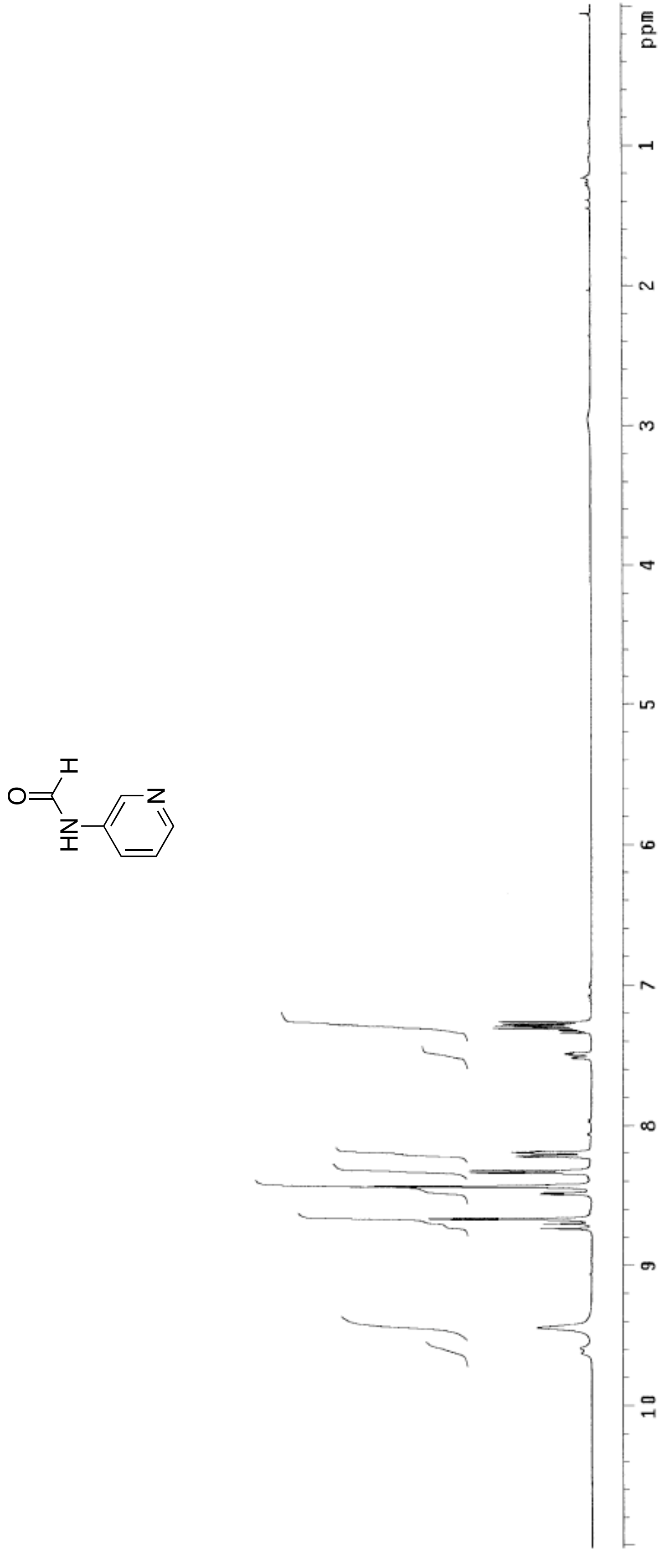
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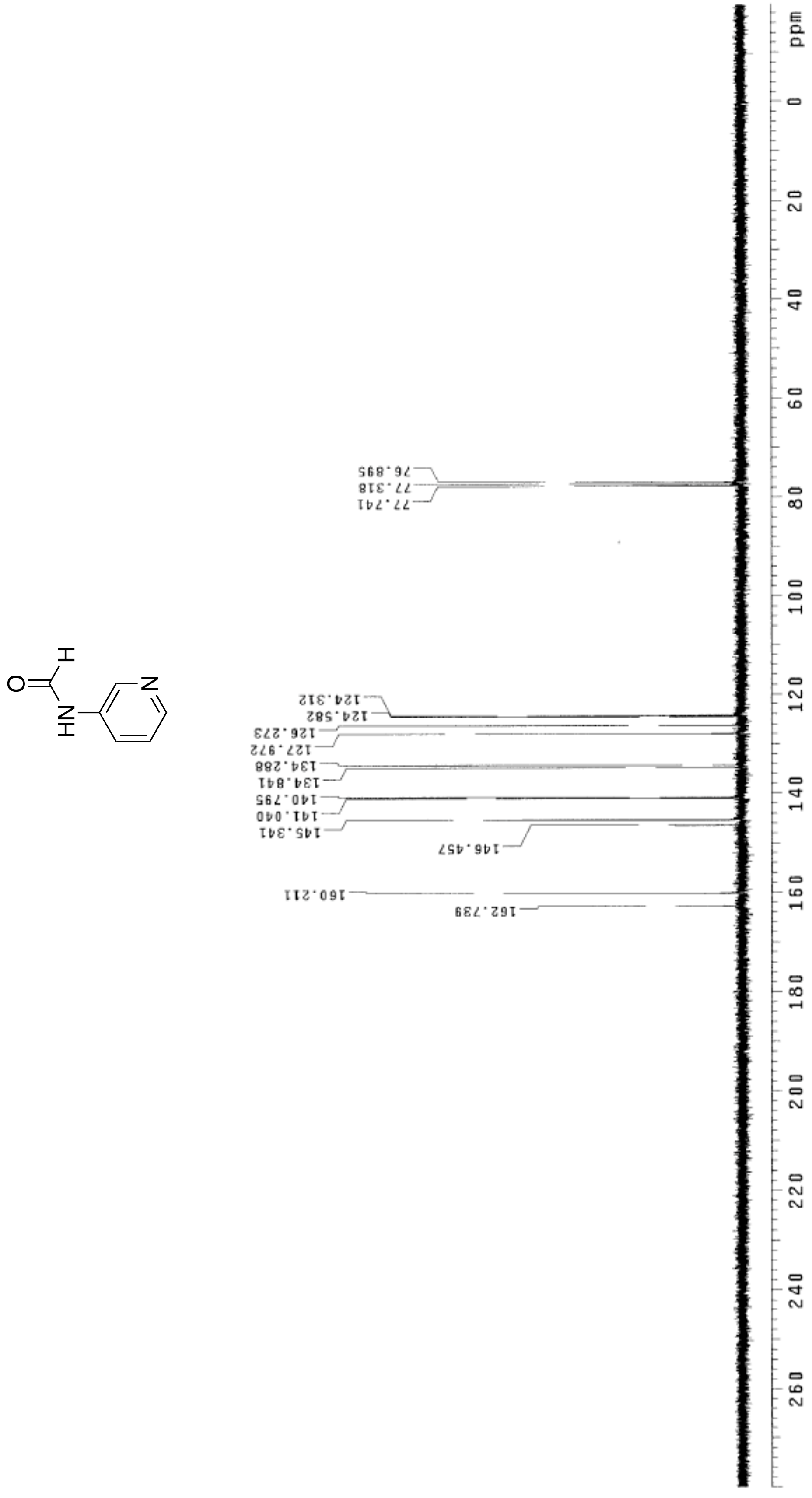
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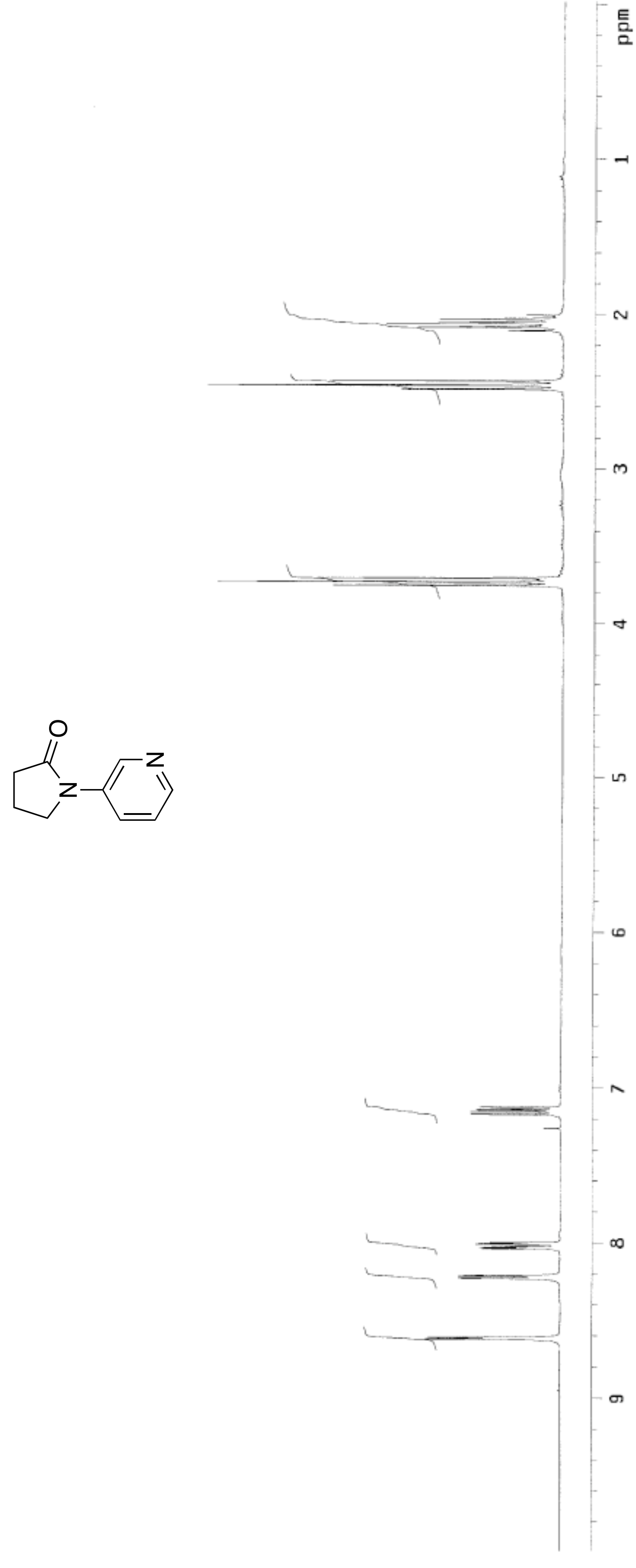
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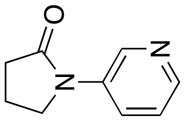
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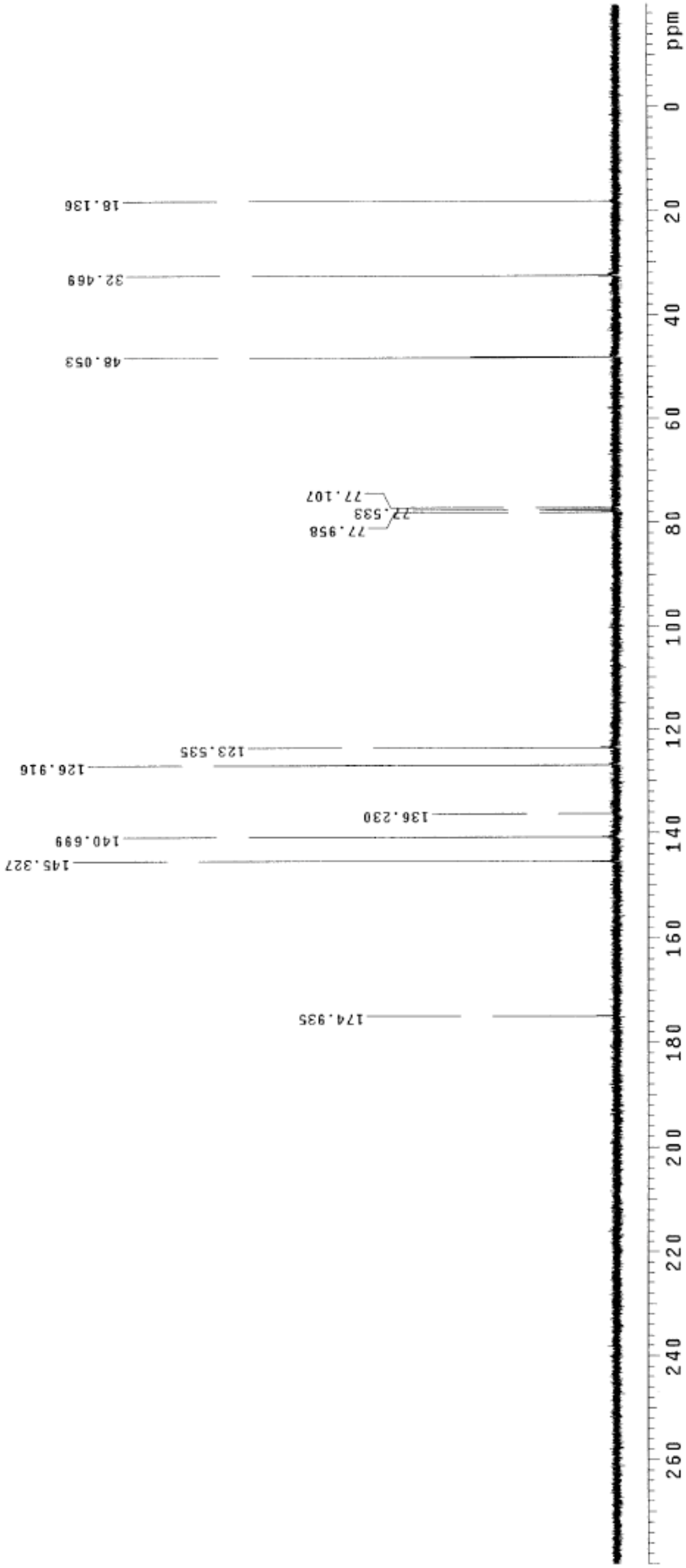
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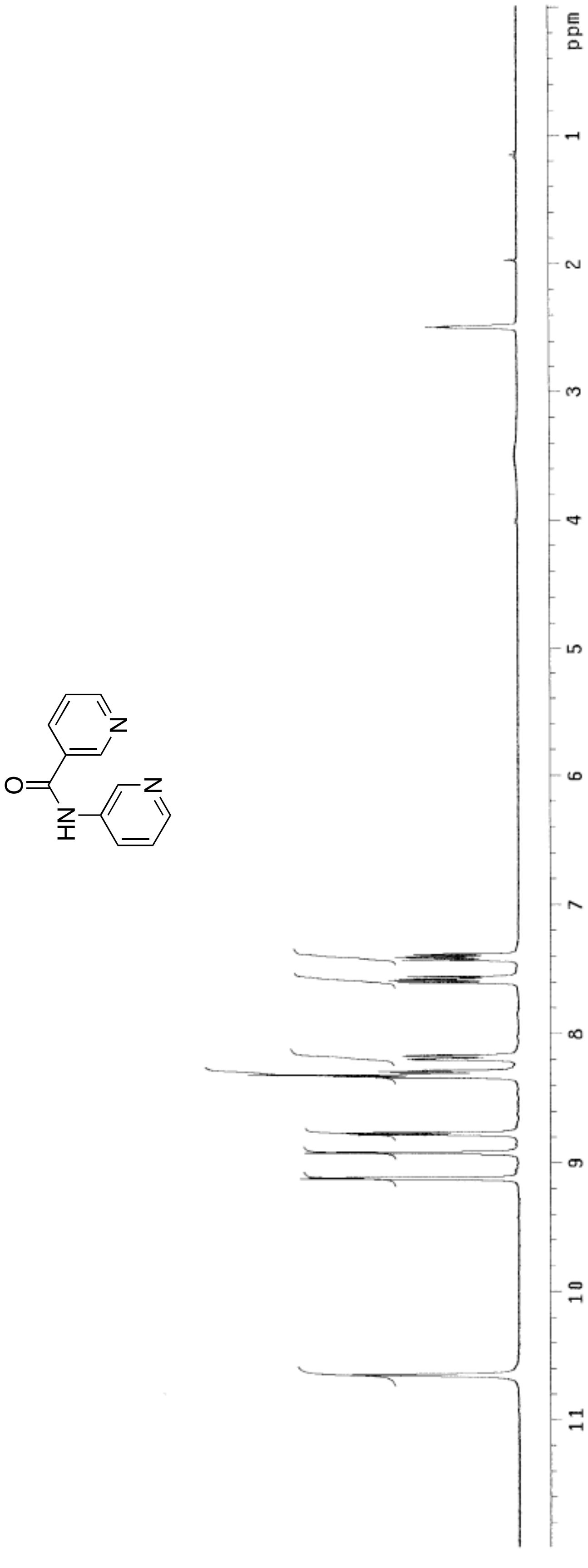
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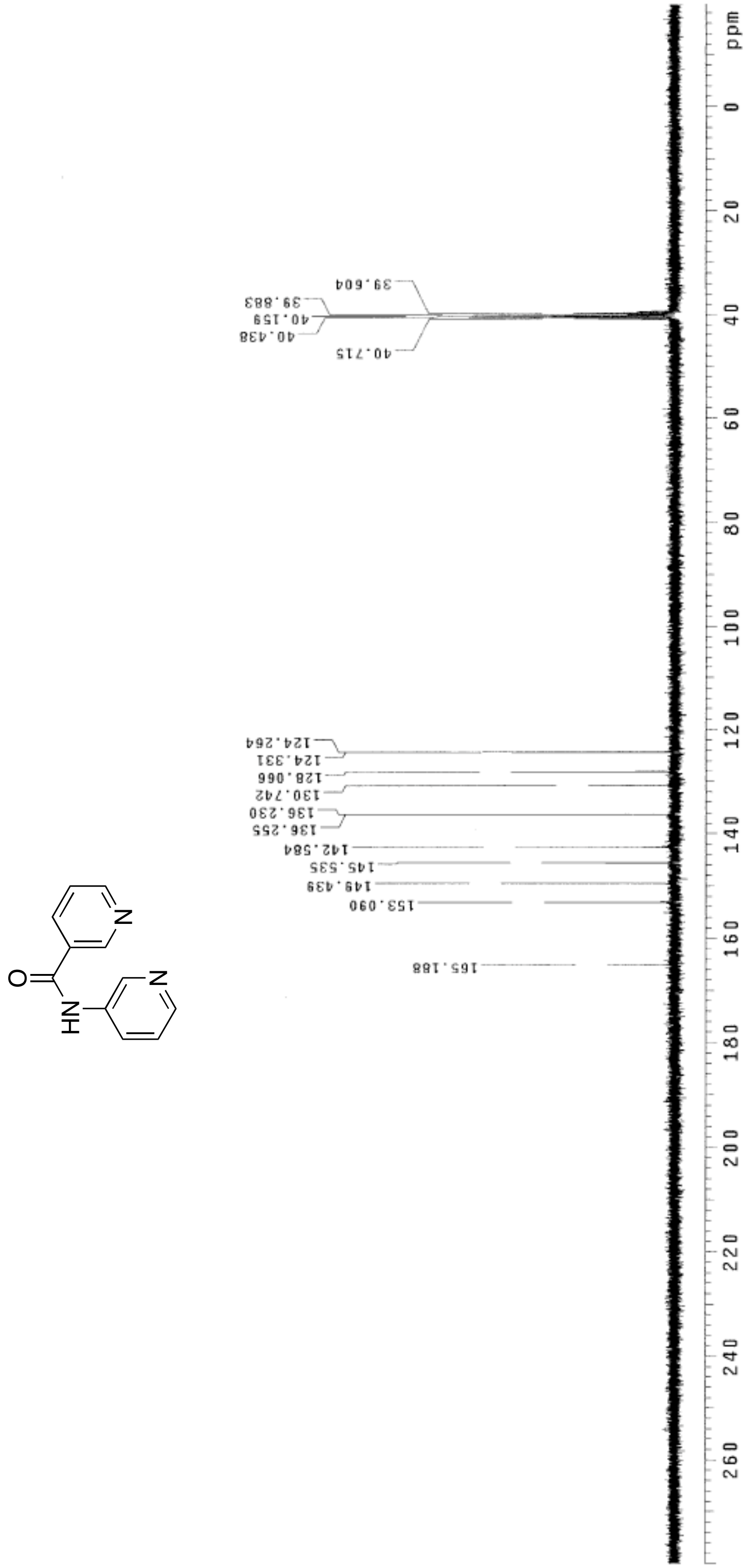
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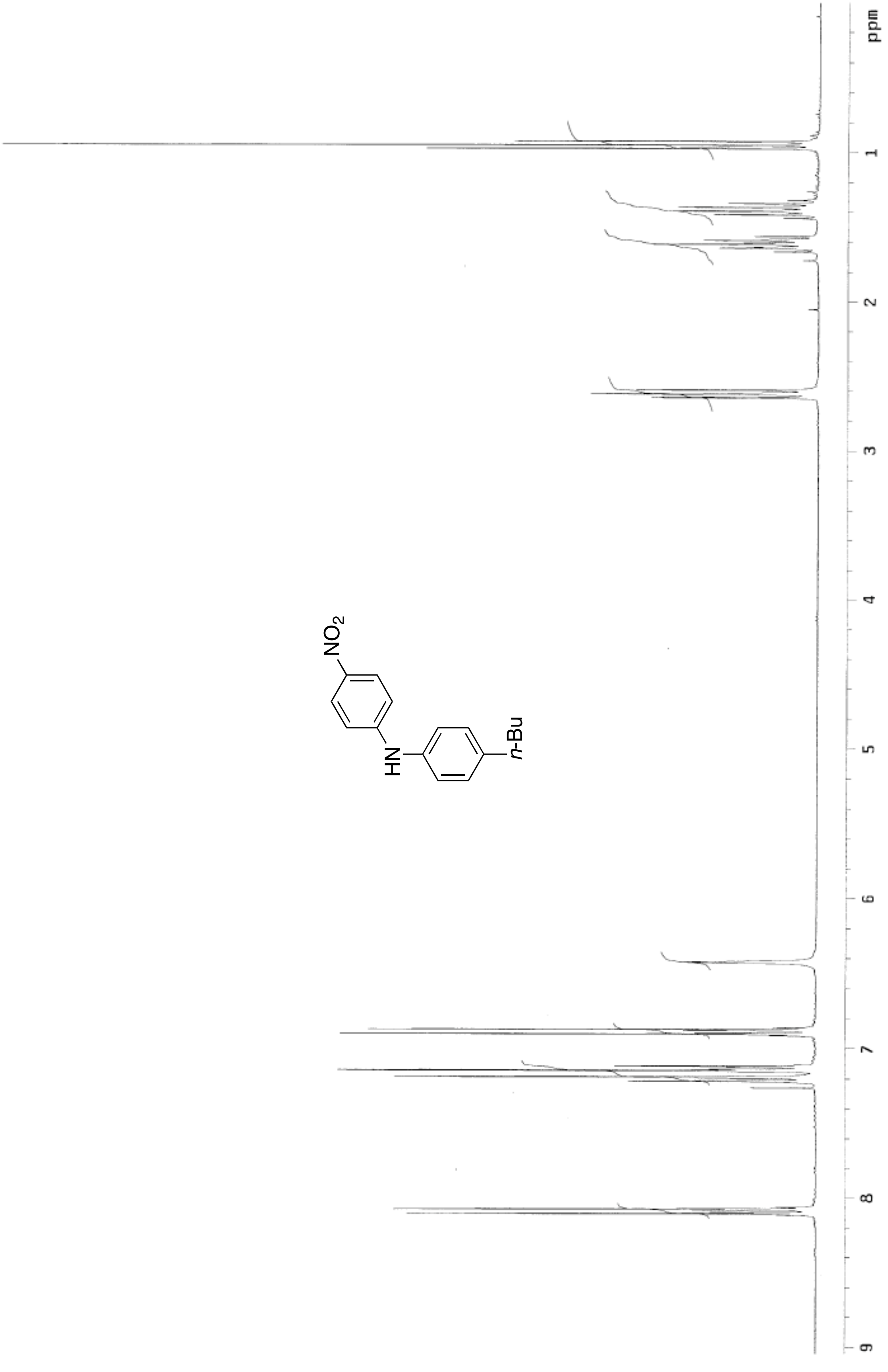

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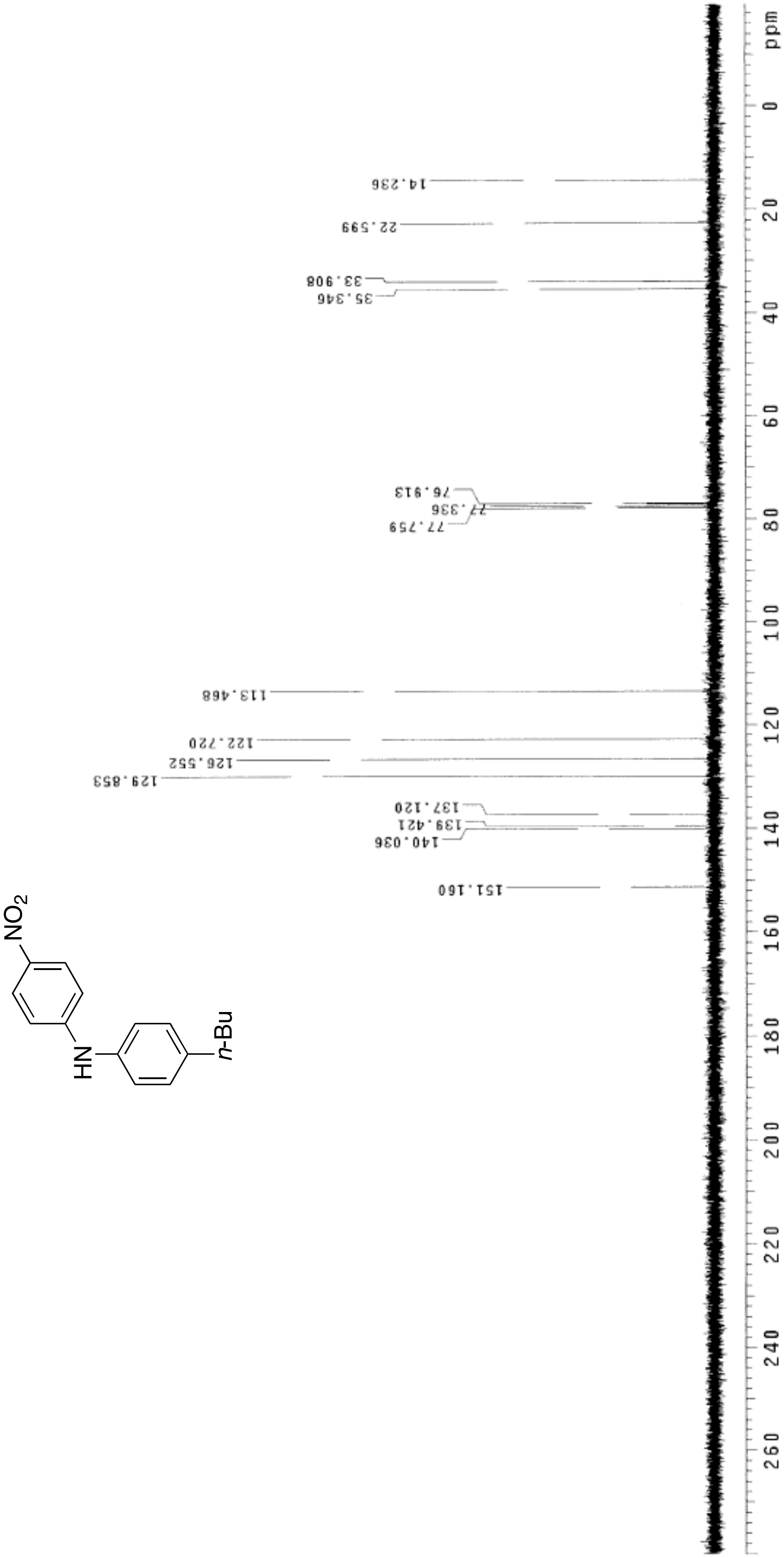

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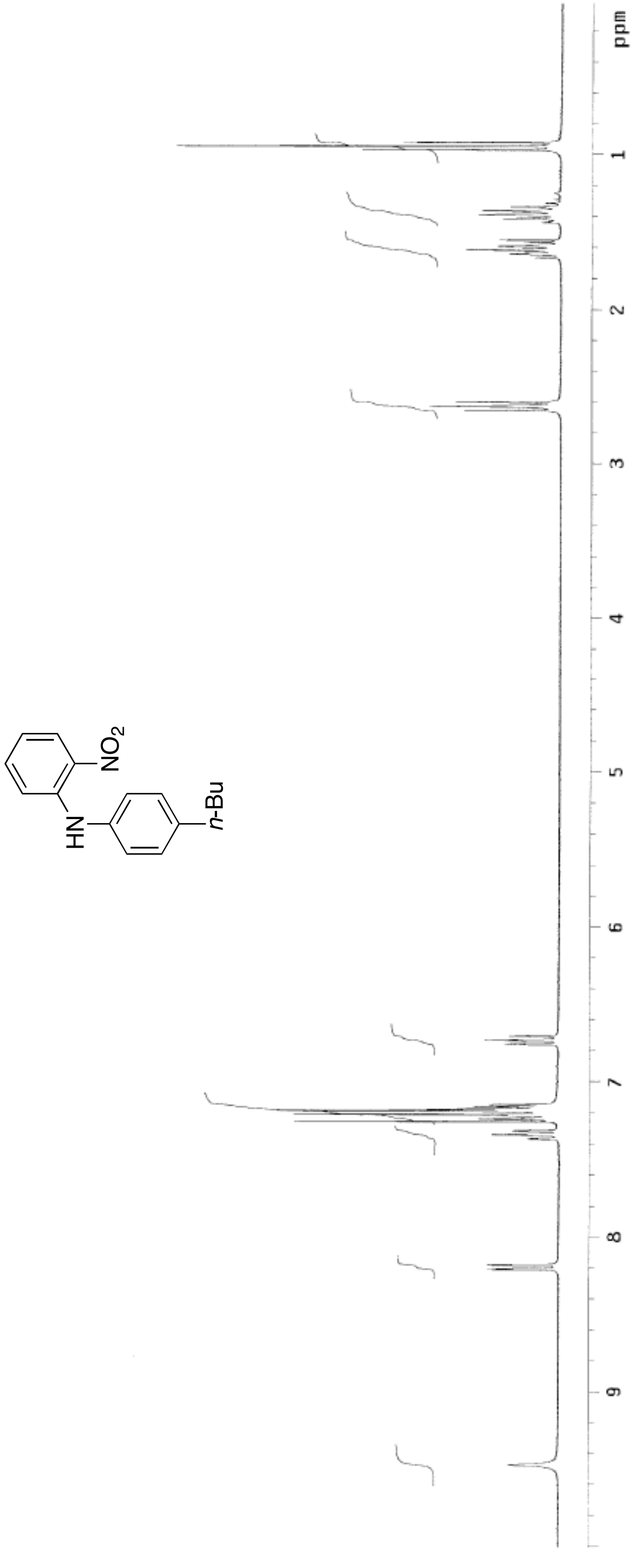
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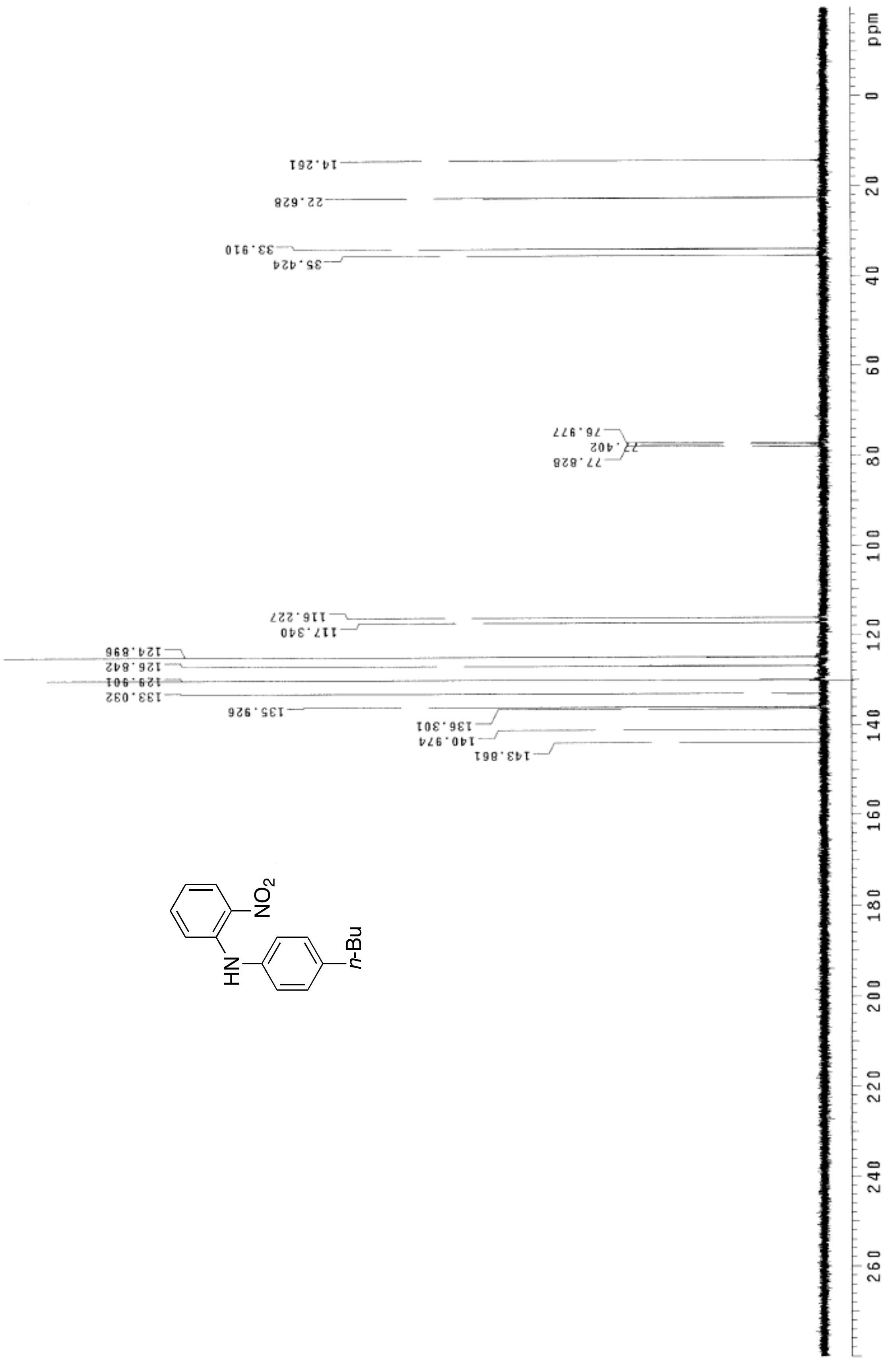
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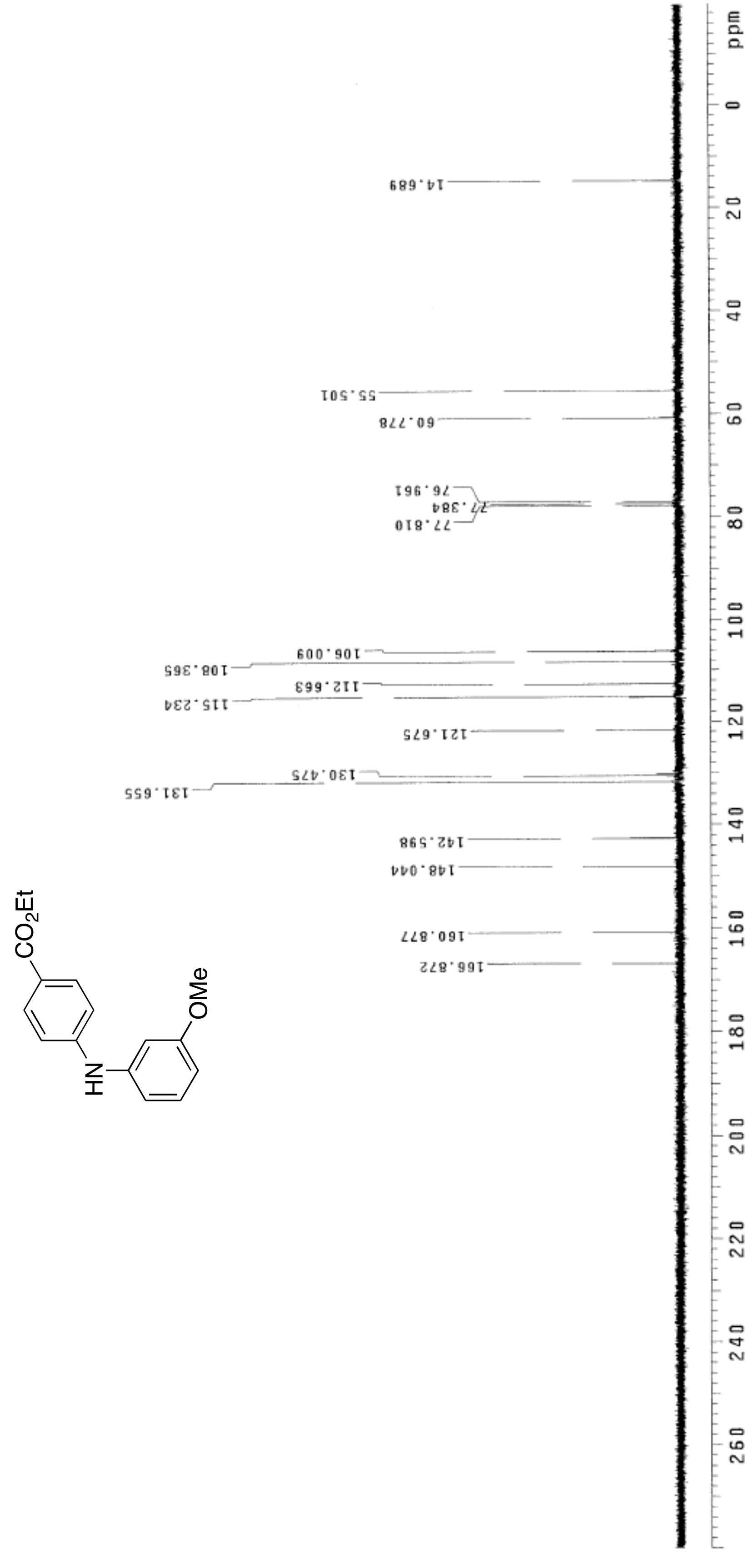
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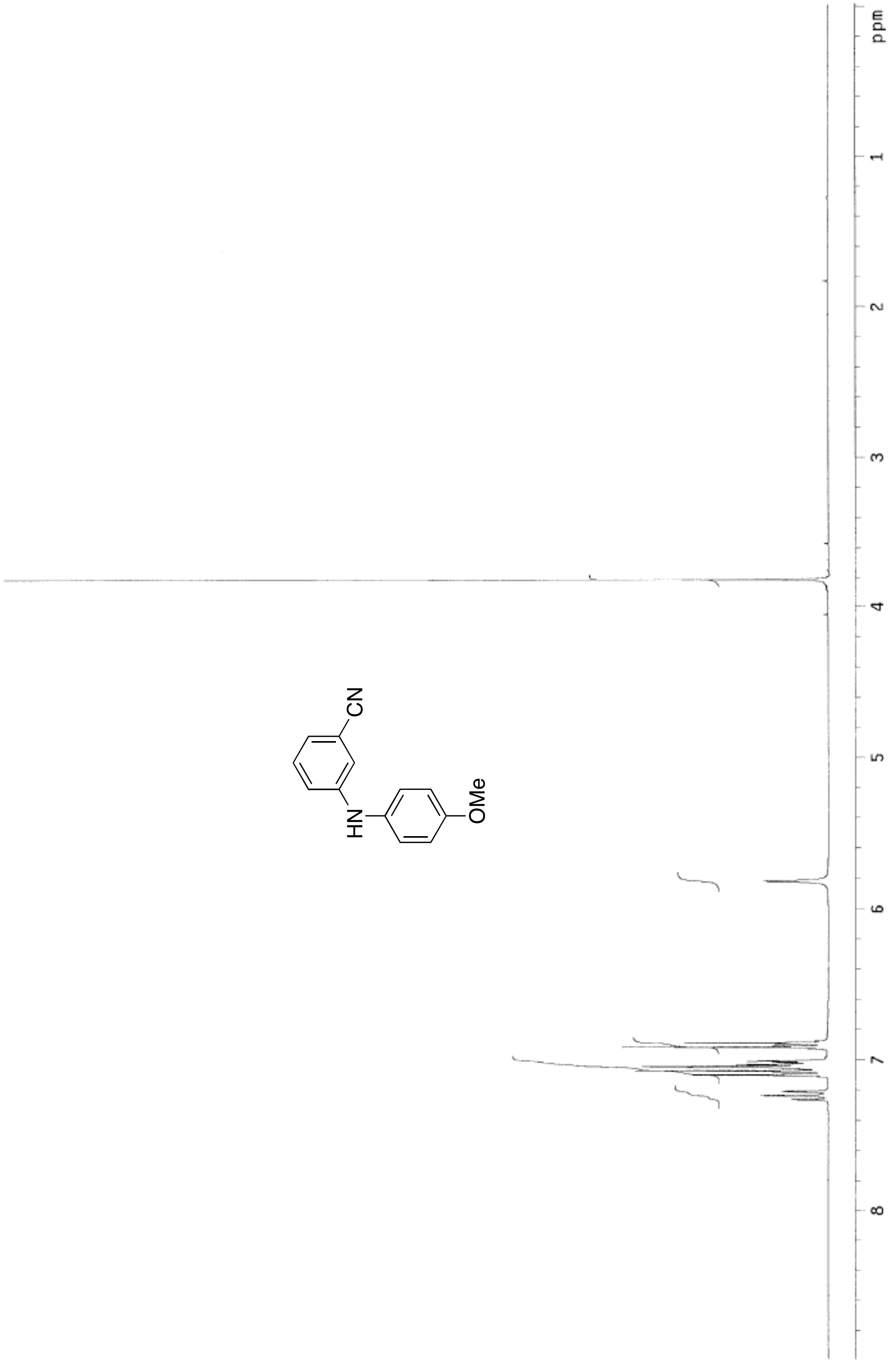
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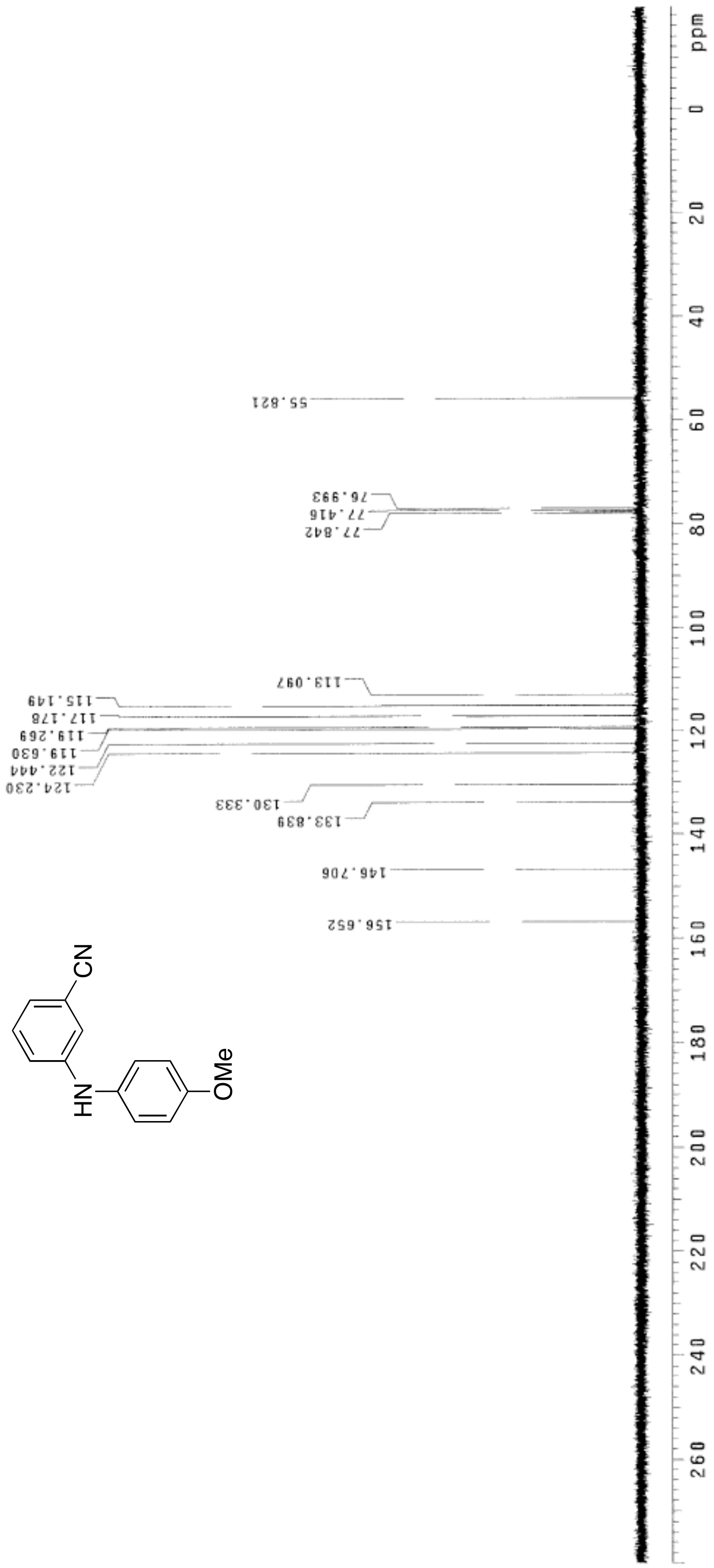
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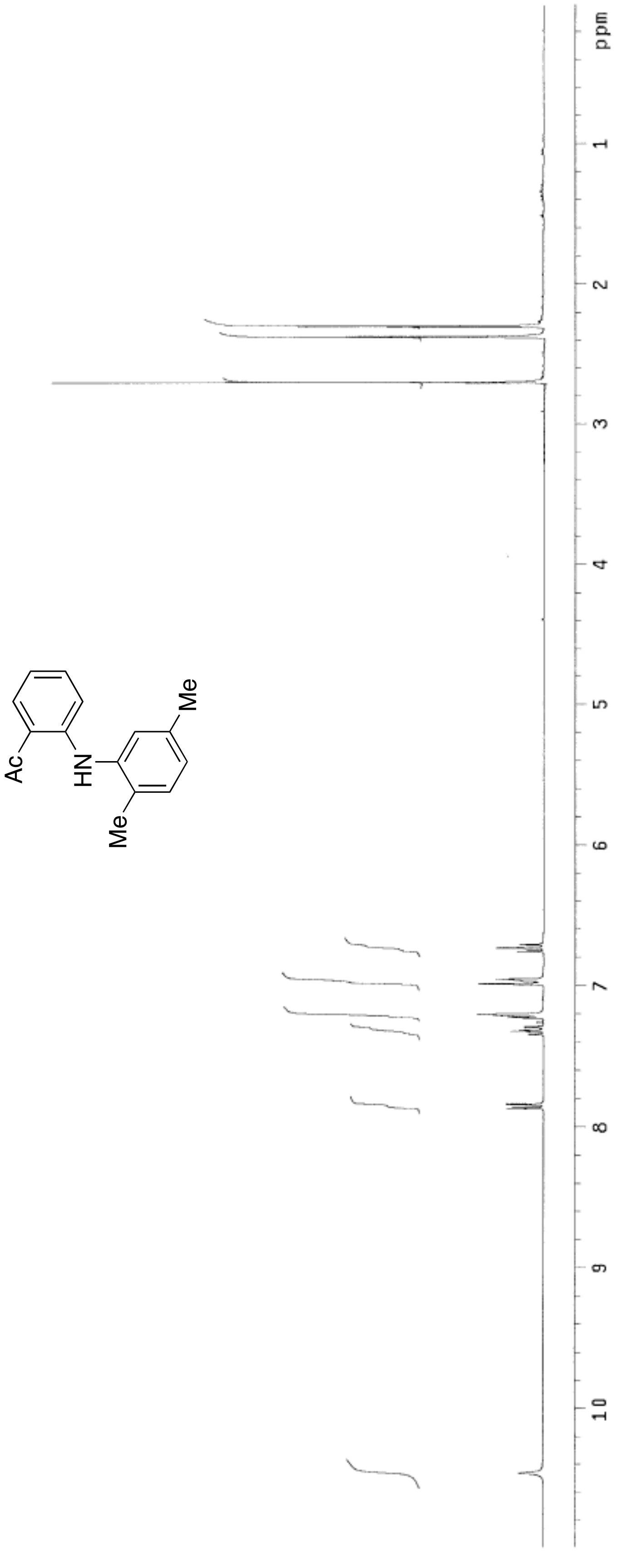
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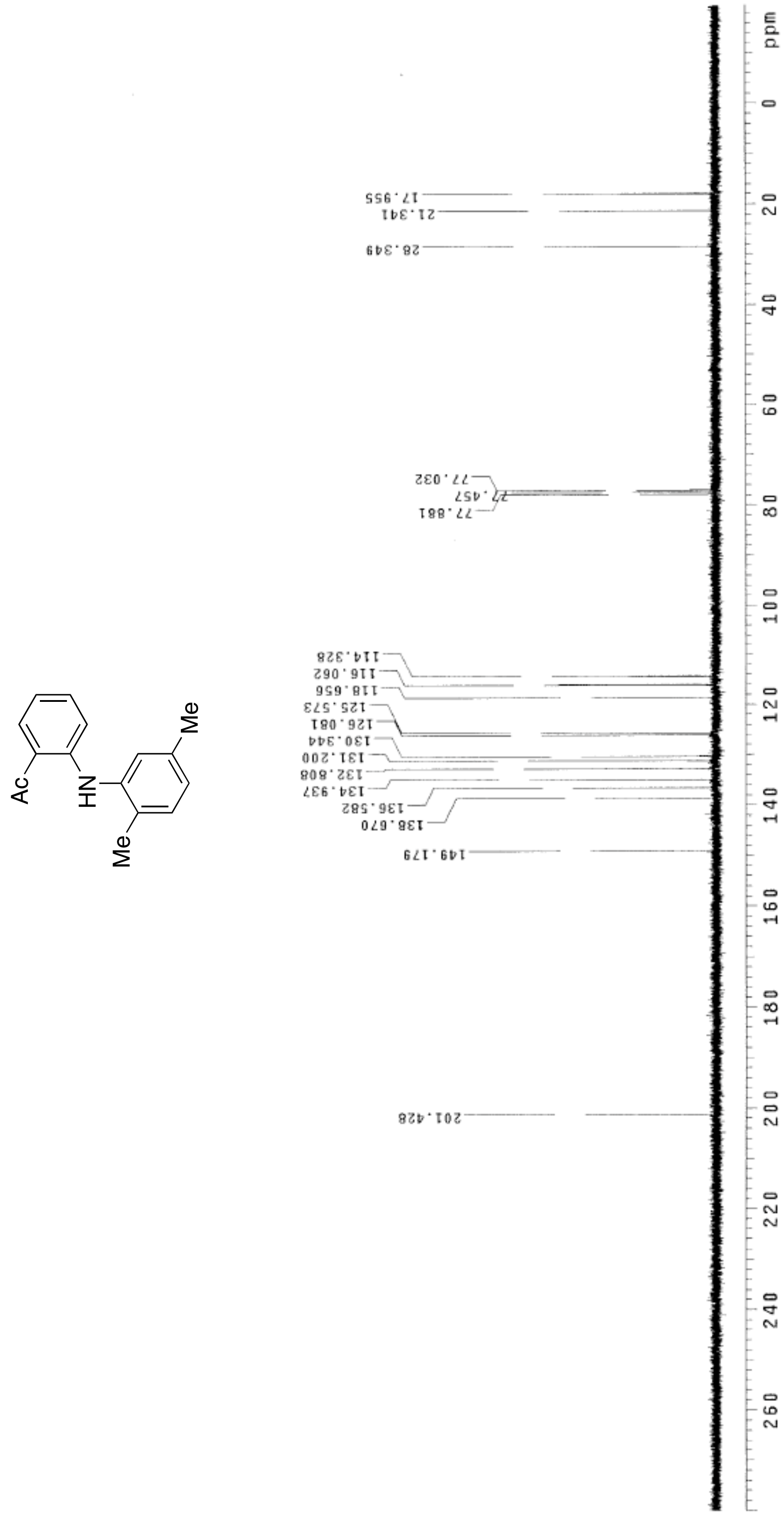
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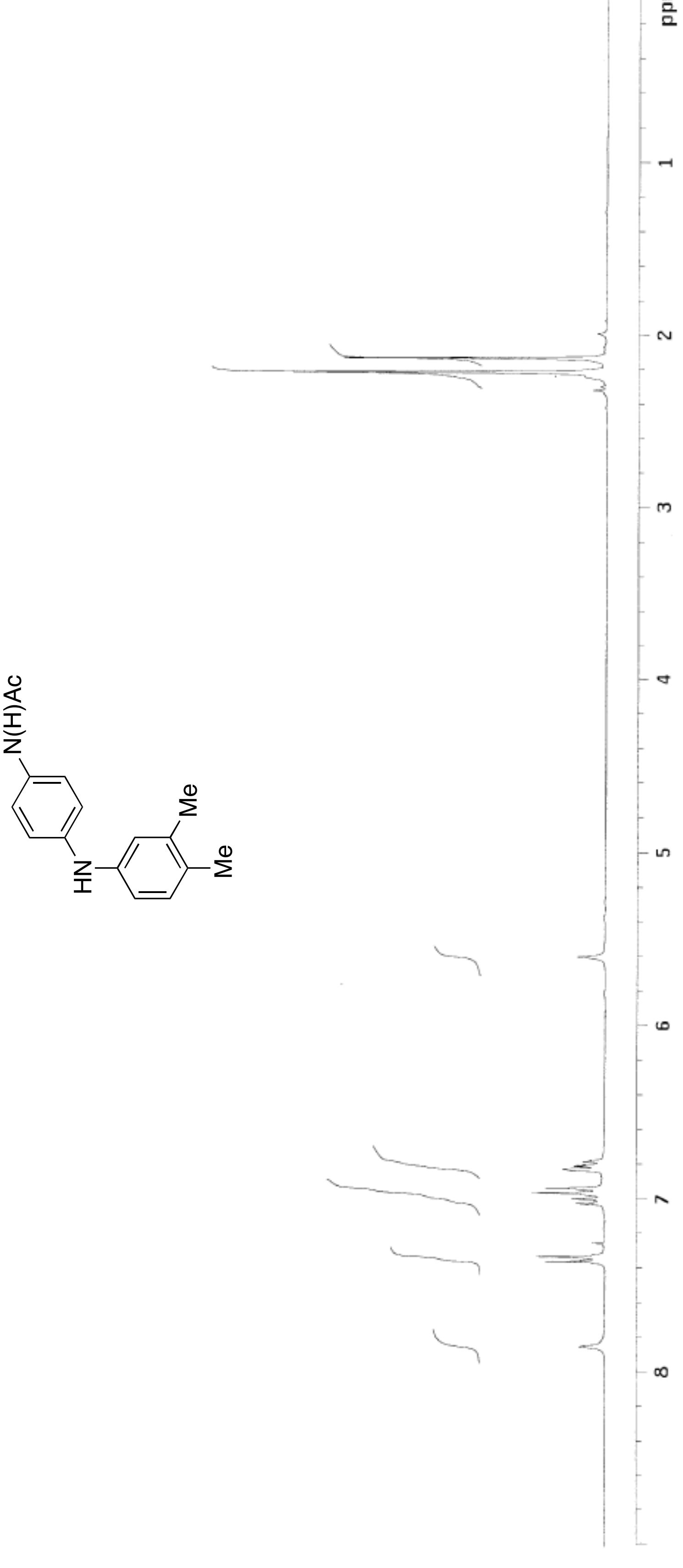
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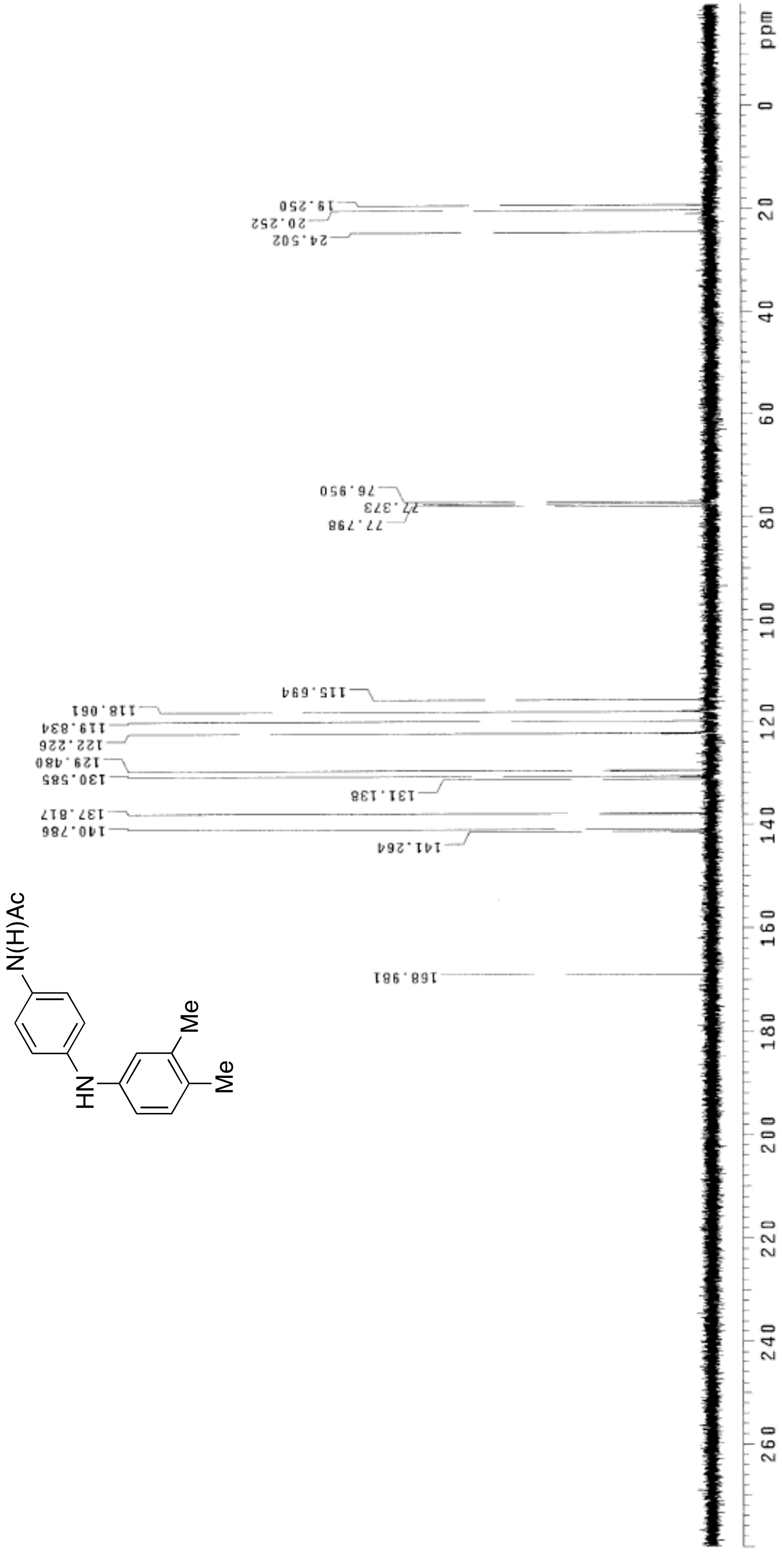
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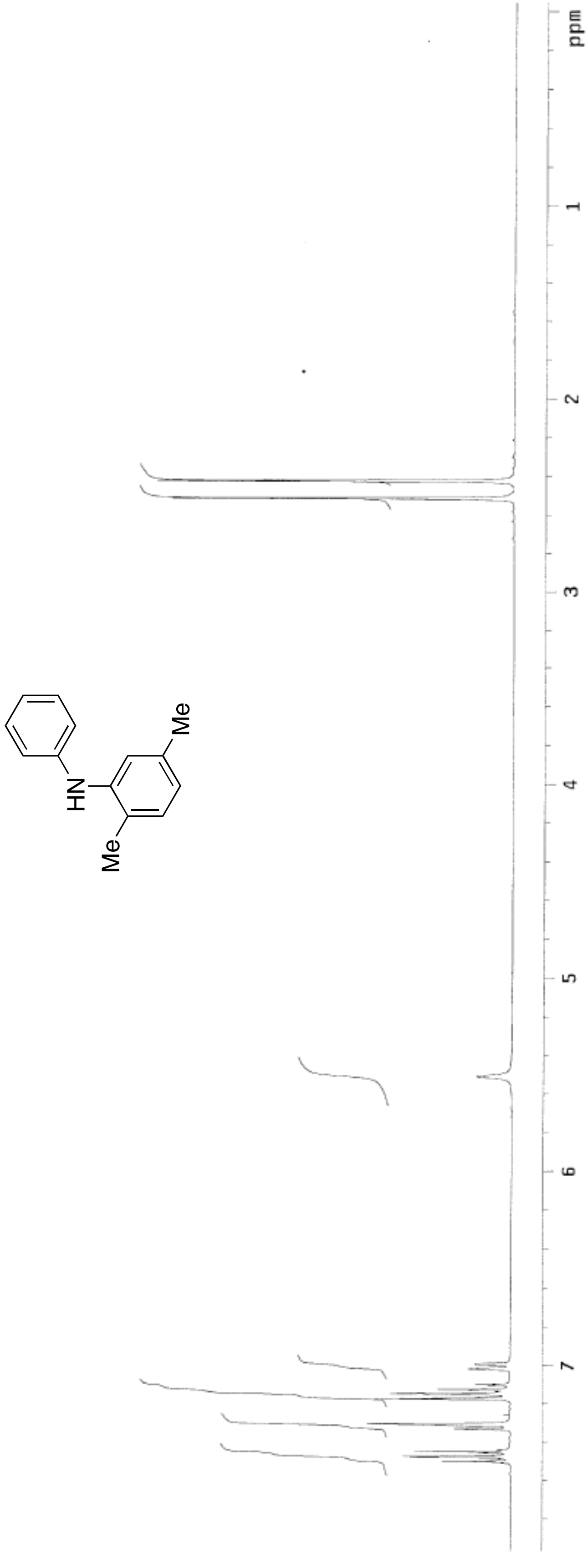
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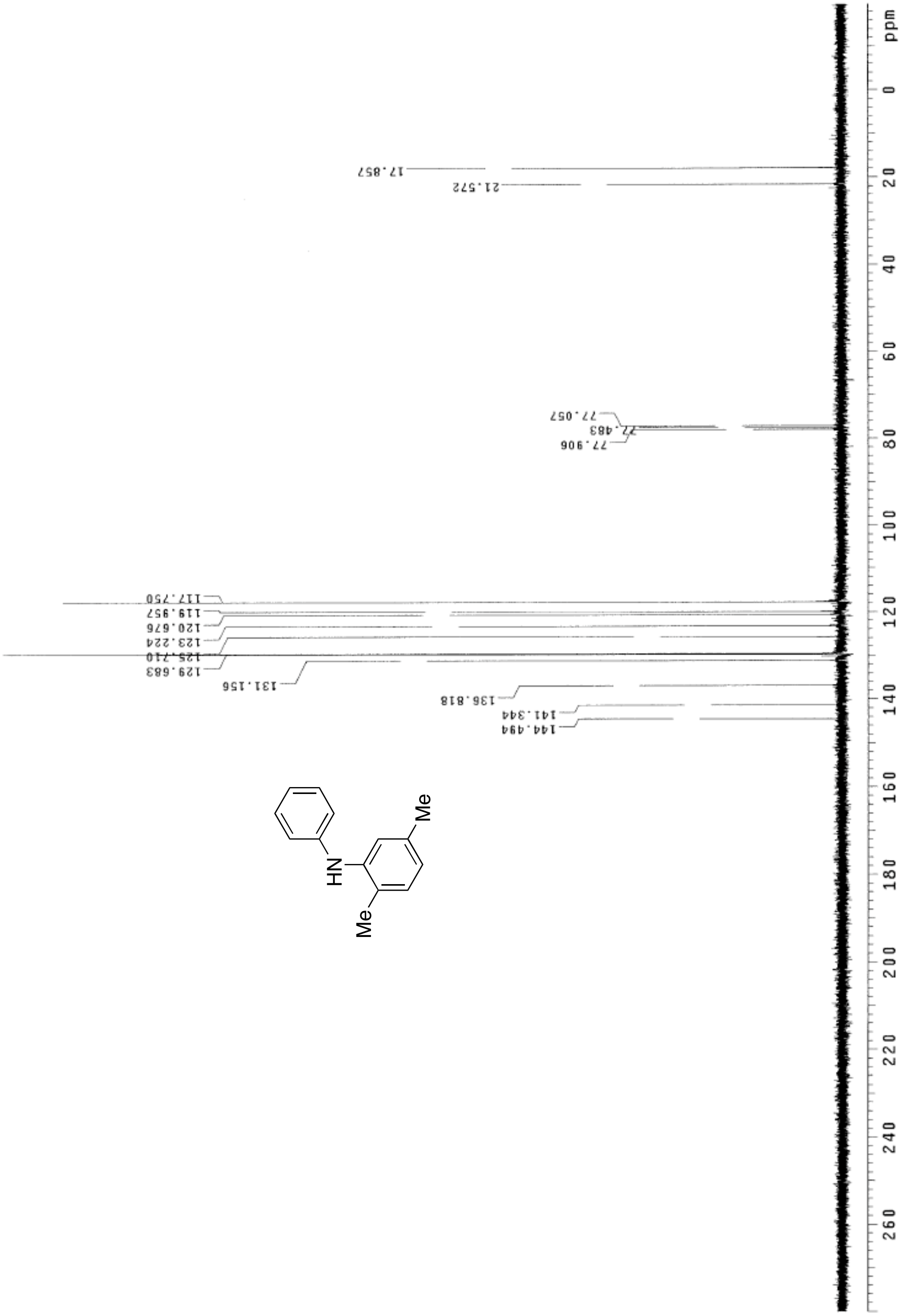
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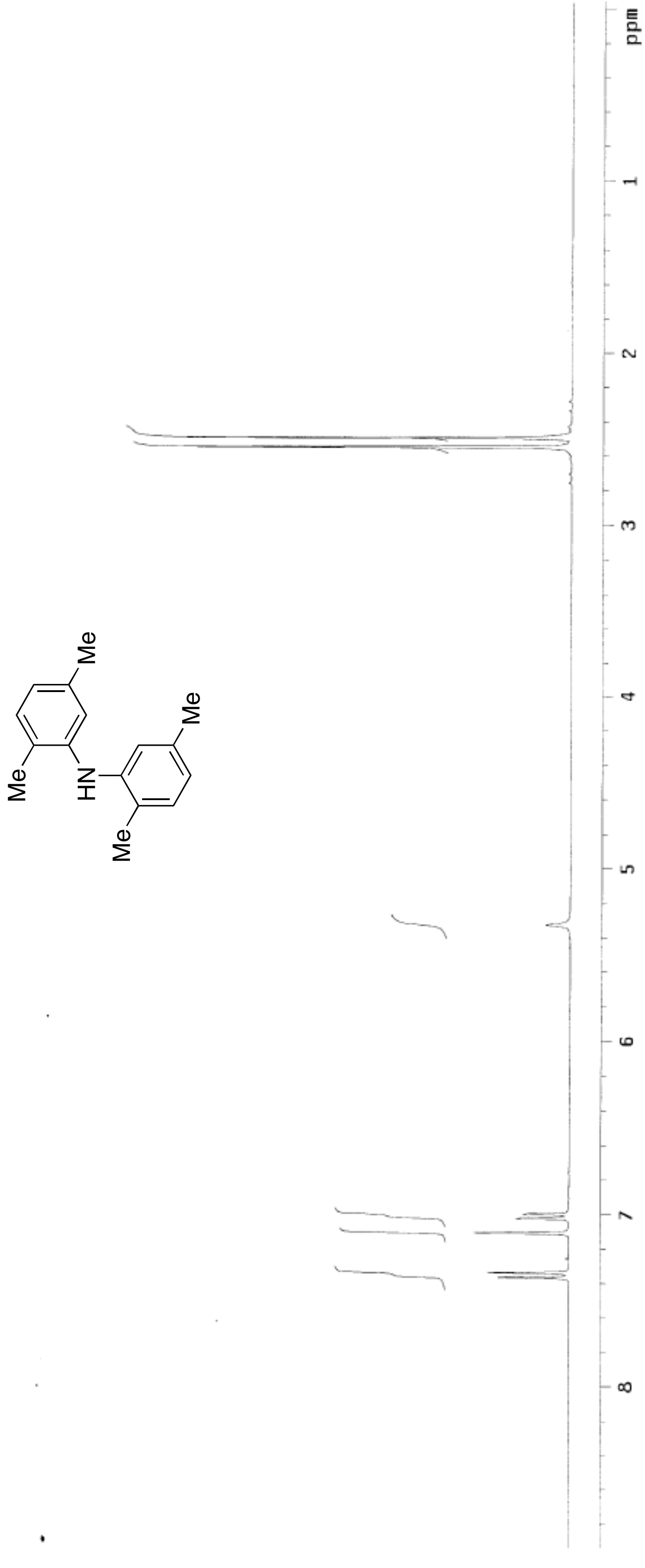
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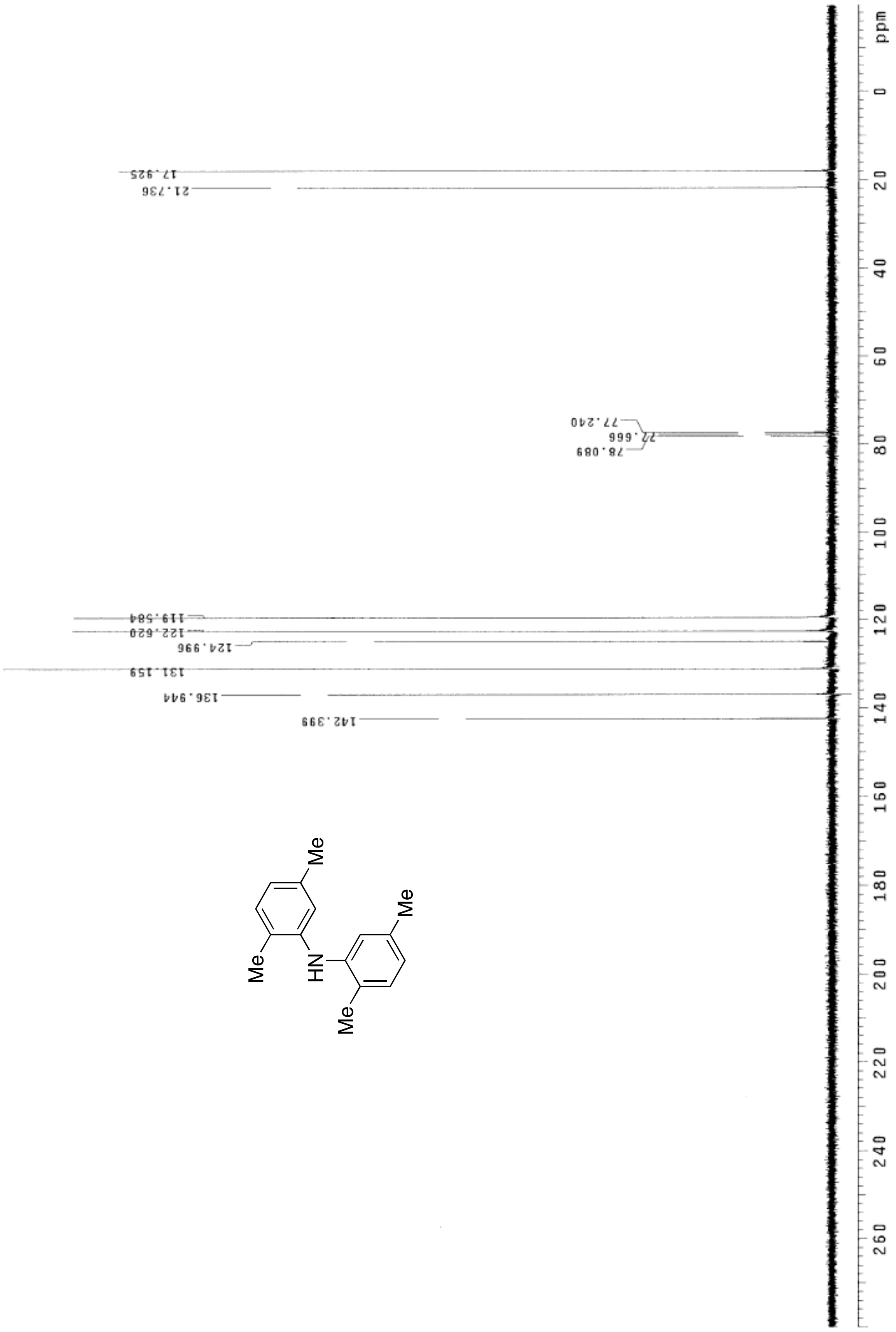
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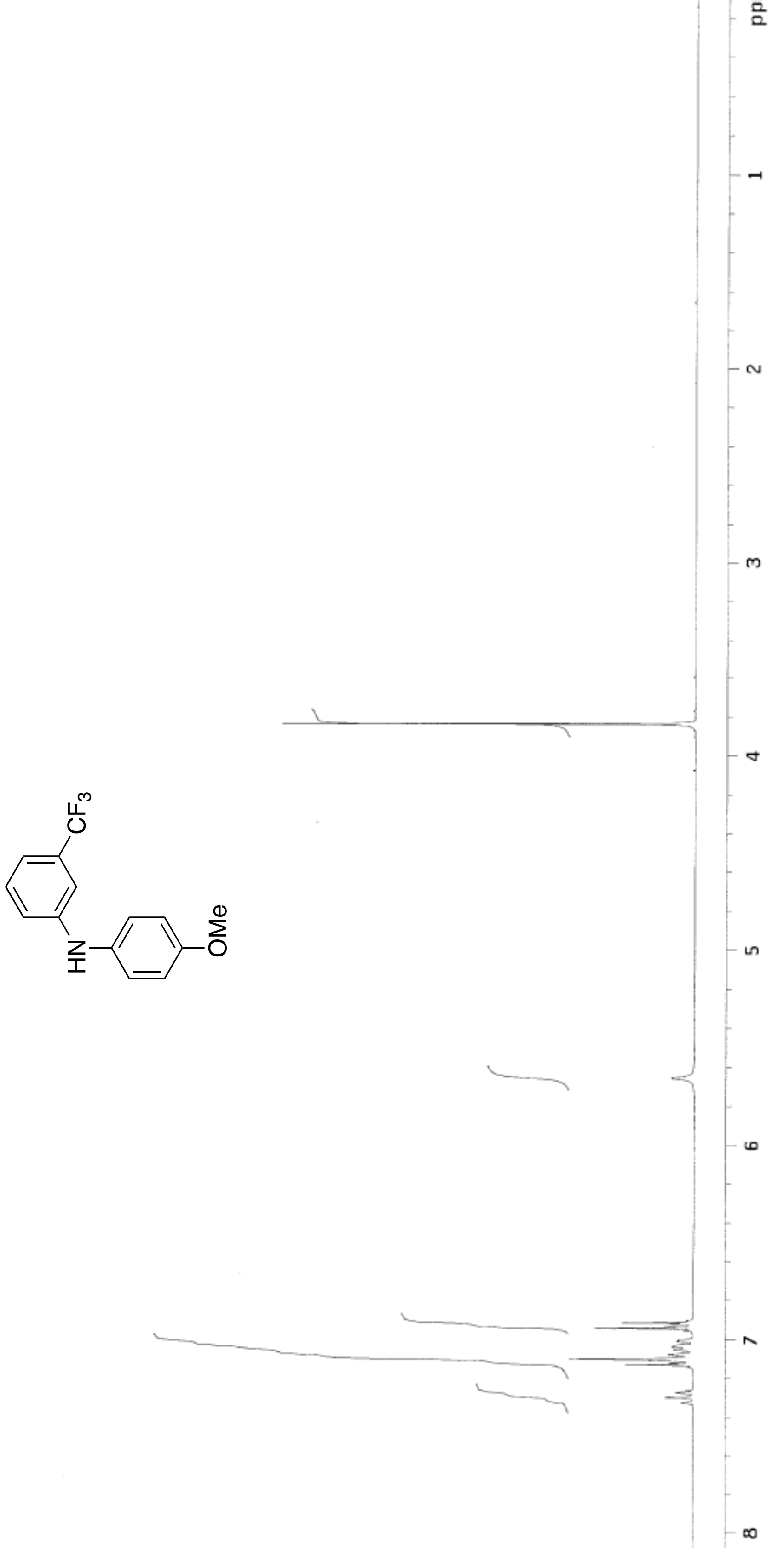
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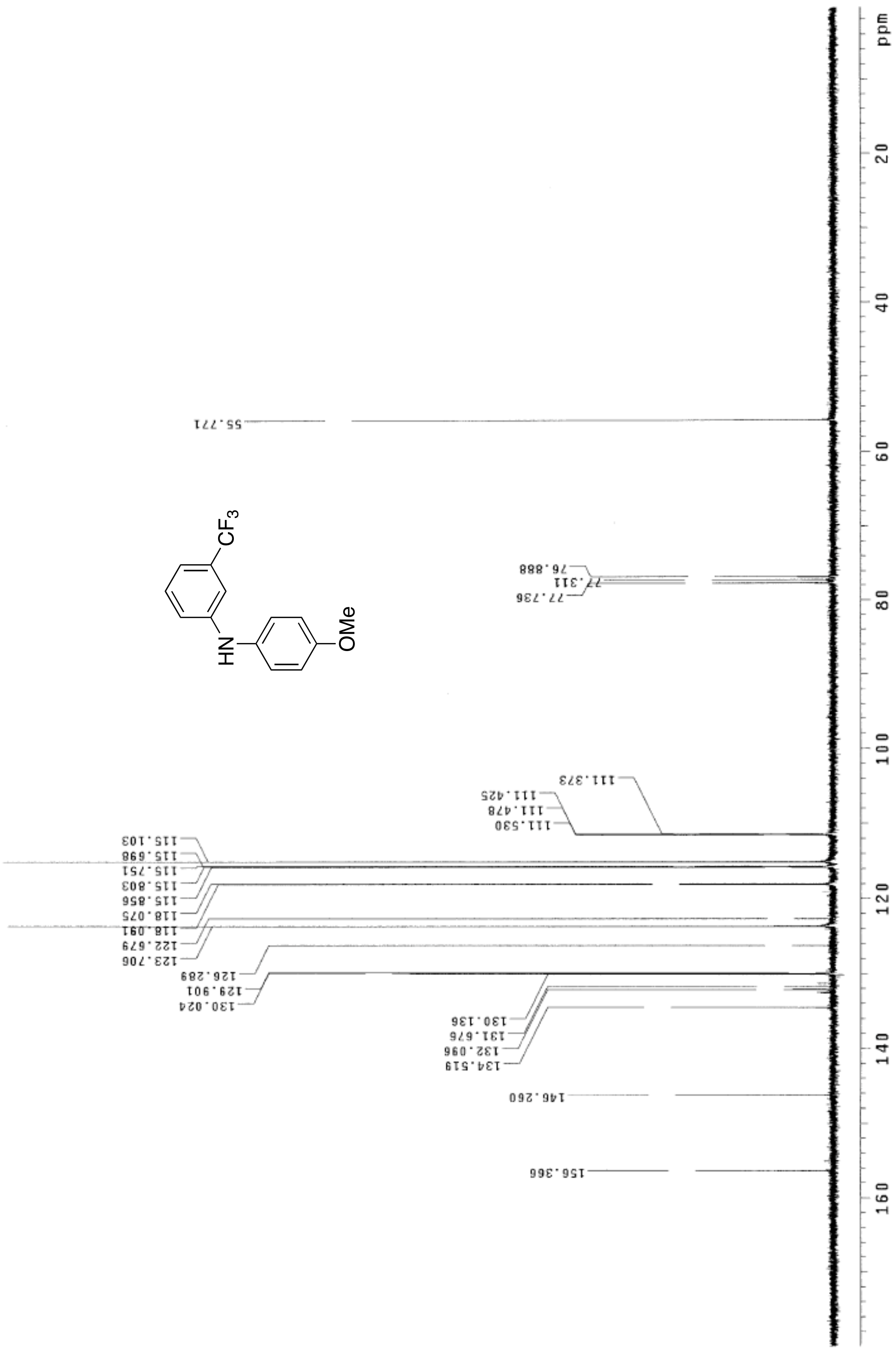
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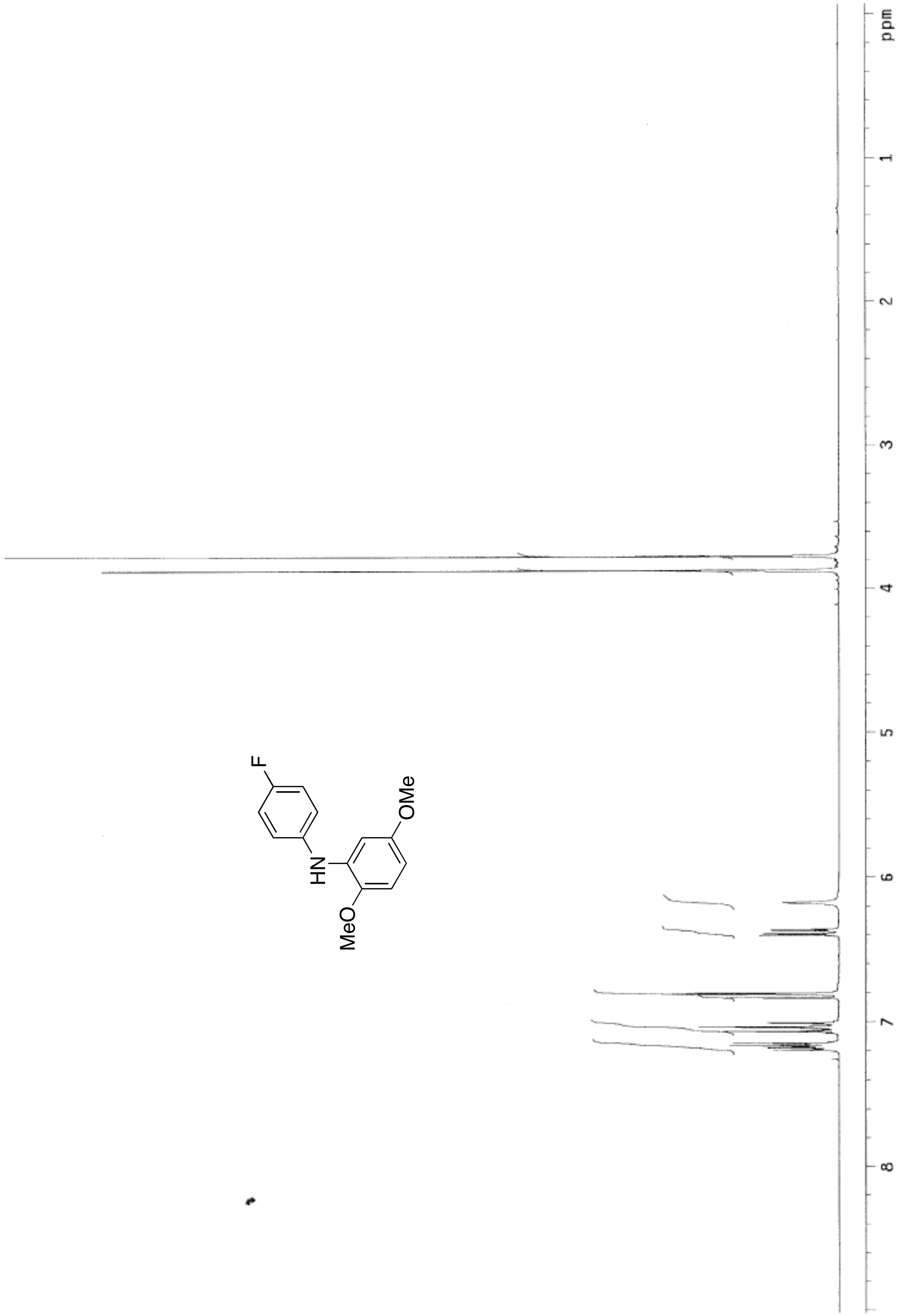
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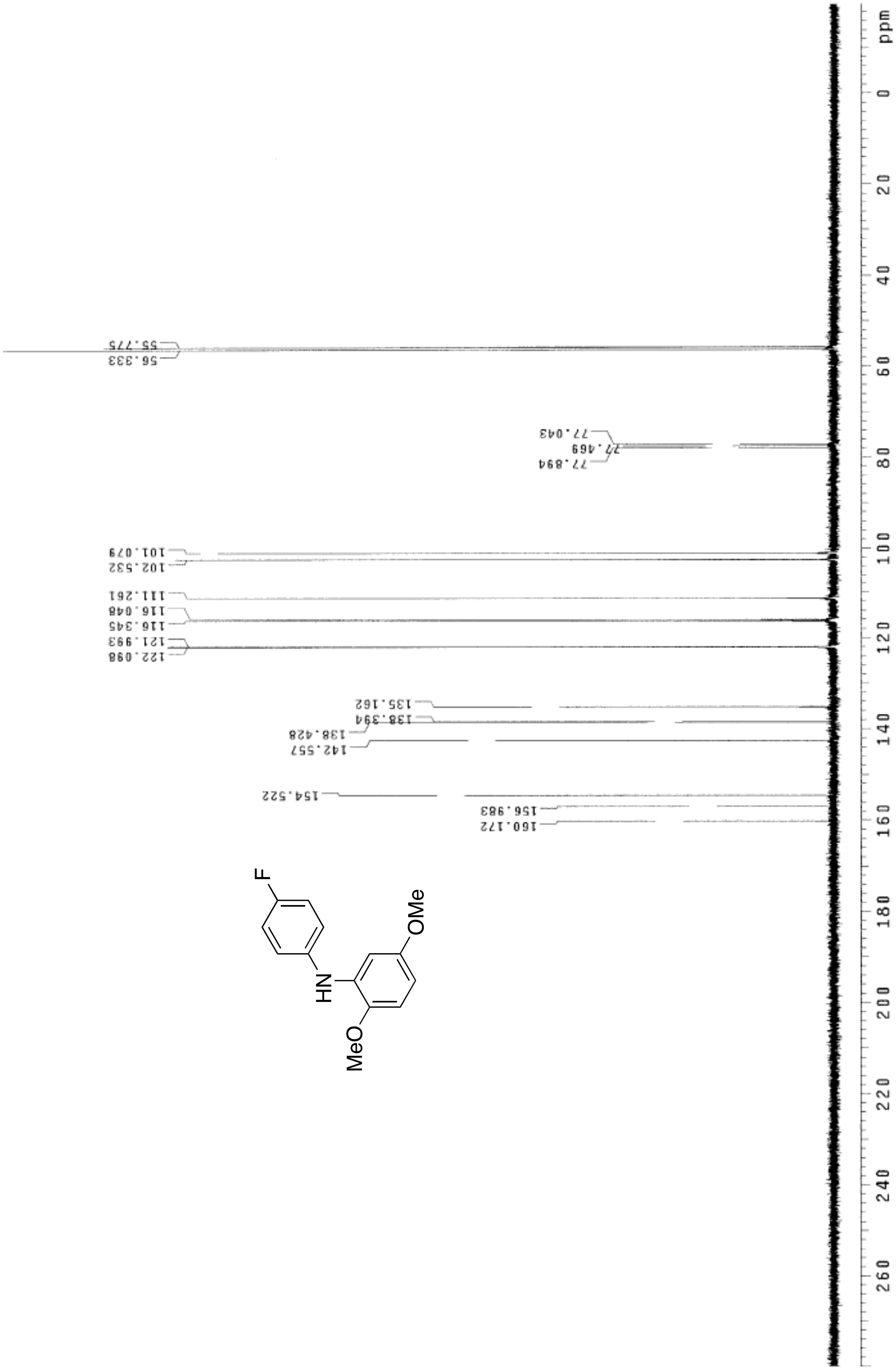
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