Rapid Wolff-Kishner Reductions in a Silicon Carbide Microreactor

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Supporting Information

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General Experimental Information.

Caution: Hydrazine hydrate is a toxic, volatile, and potentially explosive compound. While no issues were encountered during this study, proper precautions should be taken before carrying out these high temperature reactions, particularly if the scale is to be increased.

Carbitol (99%) was purchased from Sigma Aldrich and used as received. Hydrazine monohydrate (98+%) was purchased from Alfa Aesar and used as received. Yields were noticeably affected by the age and quality of hydrazine hydrate. All other solvents and reagents were purchased from Sigma Aldrich, Alfa Aesar, or Combi-Blocks and used as received.

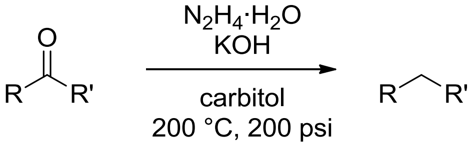
Organic solutions were concentrated by rotary evaporation at reduced pressure (100 mbar) at 25-50 °C. Flash chromatography was performed using 60Å commercial grade 40-63 μm silica gel purchased from BDH. ^{1}H spectra were obtained using either a Varian XL 300 MHz spectrometer. ^{1}H NMR spectra were internally referenced to residual $CHCl_3$ (7.26 ppm). Spectral features are tabulated in the following order: chemical shift (δ, ppm); multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m =

multiplet, br = broad); coupling constant (*J*, Hz); number of protons.

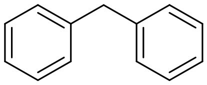
The microreactor was prepared by ESK Ceramics GmbH & Co out of EKasic® C silicon carbide. The isosceles trapezoid-shaped channels have approximately 300 μm and 700 μm width bases and 600 μm height. The reactor was connected to a machined compression chuck with standard 10-32 ports and PEEK fittings. Viton ETP o-rings were used to seal the connection between the chuck and reactor. The chuck was cooled with a steady stream of water. The reaction zone was enclosed in a machined aluminum block containing a hole for a 200 watt ¼ in. high temperature cartridge heater, purchased from McMaster-Carr. Temperature was controlled and monitored by a J-KEM Scientific Gemini PID controller with an Omega K-type thermocouple. The thermocouple is contacted directly to the microreactor through a small hole on the heating block, aided by a small amount of Chemplex 1381 thermally conductive heat sink grease.

A commercially available Syrris Asia syringe pump was used to deliver reactants to the microreactor through 0.03 inch inner diameter, 1/16 inch outer diameter PFA tubing from Idex® Health and Science. The second inlet and quench line of the reactor were connected to closed needle valves which allowed depressurizing of the system in the event of a clog. The outlet of the reactor was connected to an adjustable back pressure regulator prepared in-house. Alternatively, back pressure regulators from Idex® Health and Science could be used. Some variation in the pressure of the system due to inconsistent action of the back pressure regulators in gas-liquid flow is expected.

General Procedure

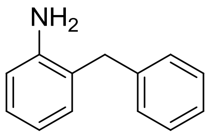


The substrate, KOH (3 equiv), and 4 mL of diethylene glycol monoethyl ether (carbitol) were combined in a 5 mL volumetric flask. The contents were placed in an ultrasonic cleaning bath and sonicated until the mixture became homogeneous. Hydrazine monohydrate (1.5 equiv) was added and the flask was brought to 5 mL total volume by dropwise addition of carbitol. The reactor was connected to a 200 psi back pressure regulator and brought to 200 °C. The reacting solution was pumped through using a Syrris Asia syringe pump with 500/250 μL glass syringes. The syringe pump was set to stop pumping if the pressure exceeded 20 bar. After waiting for the reactor to reach steady state (~3 residence times), a sample vial was placed at the outlet and the product was collected for ~2 residence times. The sample was worked up and purified by flash column chromatography. Concentrations and residence times were optimized case-by-case, with the highest concentration used that allowed continuous operation without clogging. In the event of a clog, the reactor was depressurized and washed with clean carbitol and water.

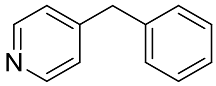


diphenylmethane (2a). The general procedure was followed at 0.8 M concentration with a flow rate of 94 μL/min (t_{res} = 5 min). After collecting sample for 20 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 0-5% Et_2O/hexane to provide **2a** as a clear oil (207 mg, 82%). Characterization data match commercially available material. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.16 - 7.32 (m, 10 H), 3.98 (s, 2 H).

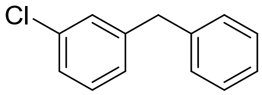
The reaction could also be done with the addition of an extra 3 equivalents (216 uL) of water at a flow rate of 47 μL/min (t_{res} = 10 min), providing **2a** as a clear oil after collection for 45 minutes (237 mg, 84%).



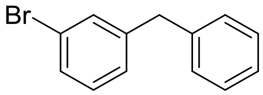
2-benzylaniline (2b). The general procedure was followed at 0.8 M concentration with a flow rate of 31.3 μL/min (t_{res} = 15 min). After collecting sample for 38 minutes, the material was diluted with water and extracted with ethyl acetate. The organic phase was washed 5 times with water and once with brine. After drying with sodium sulfate, the sample was filtered, evaporated to dryness, and loaded onto a packed silica gel column. Elution with 10-30% EtOAc/hexane provided **2b** as a slightly yellow oil (174 mg, 82%). Characterization data match commercially available material. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.17 - 7.34 (m, 5 H), 7.04 - 7.14 (m, 2 H), 6.78 (td, *J*=7.8, 1.0 Hz, 1 H), 6.69 (dd, *J*=7.8, 1.2 Hz, 1 H), 3.92 (s, 2 H), 3.51 (br. s., 2 H)



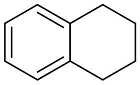
4-benzylpyridine (2c). The general procedure was followed at 0.5 M concentration with a flow rate of 156 μL/min (t_{res} = 3 min). After collecting 9 minutes of sample, the material was diluted with water and extracted with ethyl acetate. The organic phase was washed 5 times with water and once with brine. After drying with sodium sulfate, the sample was filtered, evaporated to dryness, and loaded onto a packed silica gel column. Elution with 30-60% EtOAc/hexane provided **2c** as a yellow oil (112 mg, 94%). Characterization data match commercially available material. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 8.51 (d, *J*=5.5 Hz, 2 H), 7.06 - 7.38 (m, 7 H), 3.97 (s, 2 H).



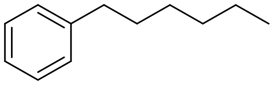
1-benzyl-3-chlorobenzene (2d). The general procedure was followed at 0.4 M concentration with a flow rate of 156 μL/min (t_{res} = 3 min). After collecting sample for 12 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 0-5% Et_2O/hexane to provide **2d** as a clear oil (127 mg, 84%). Characterization data match those observed by Sarkar *et. al.*,[1] albeit each peak is shifted downfield by ~0.2 ppm. A publication by Martins and Lautens[2] provides an image of the NMR spectrum which is in agreement with our data. We thus expect the listed NMR signals be Sarkar *et. al.* are improperly referenced. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.31 - 7.38 (m, 2 H), 7.19 - 7.29 (m, 6 H), 7.11 (m, 1 H), 3.99 (s, 2 H).



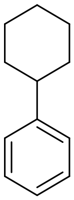
1-benzyl-3-bromobenzene (2e). The general procedure was followed at 0.4 M concentration with a flow rate of 47 μL/min (t_{res} = 10 min). After collecting sample for 30 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 0-5% Et_2O/hexane to provide **2e** as a clear oil (79 mg, 76%). Characterization data match the literature.[3] **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.09 - 7.36 (m, 9 H), 3.94 (s, 2 H).



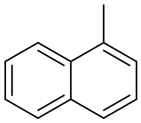
1,2,3,4-tetrahydronaphthalene (2f). The general procedure was followed at 0.8 M concentration with a flow rate of 31.3 μL/min (t_{res} = 15 min). After collecting sample for 76 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 0-5% Et_2O/hexane to provide **2f** as a clear oil (196 mg, 78%). Characterization data match commercially available material. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.01 - 7.09 (m, 4 H), 2.76 (m, 4 H), 1.78 (m, 4 H).



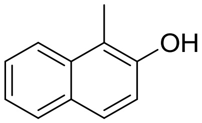
hexylbenzene (2g). The general procedure was followed at 0.8 M concentration with a flow rate of 47 μL/min (t_{res} = 10 min) and a reactor temperature of 220 °C. After collecting sample for 40 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 0-5% Et_2O/hexane to provide **2g** as a clear oil (235 mg, 96%). Characterization data match commercially available material. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.12 - 7.31 (m, 5 H), 2.60 (t, *J* = 7.6, 2 H), 1.55 - 1.67 (m, 2 H), 1.22 - 1.38 (m, 6 H), 0.83 - 0.92 (m, 3 H).



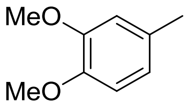
cyclohexylbenzene (2h). The general procedure was followed at 0.8 M concentration with a flow rate of 234 µL/min (t_{res} = 2 min). After collecting sample for 25 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 0-5% Et_2O/hexane to provide **2h** as a clear oil (249 mg, 83%). Characterization data match commercially available material. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.11 - 7.35 (m, 5 H), 2.50 (m, 1 H), 1.68 - 1.96 (m, 5 H), 1.22 - 1.54 (m, 5 H).



1-methylnaphthalene (2i). The general procedure was followed at 0.1 M concentration with a flow rate of 156 µL/min (t_{res} = 3 min). After collecting sample for 55 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 0-5% Et_2O/hexane to provide **2i** as a clear oil (127 mg, 91%). Characterization data match commercially available material. **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.95 (d, *J*=7.5 Hz, 6 H), 7.80 (d, *J*=7.7 Hz, 6 H), 7.66 (d, *J*=7.7 Hz, 6 H), 7.22 - 7.51 (m, 25 H), 2.65 (d, *J*=1.5 Hz, 3 H).



1-methylnaphthalen-2-ol (2j). The general procedure was followed at 0.8 M concentration with a flow rate of 94 µL/min (t_{res} = 5 min). After collecting sample for 20 minutes, the material was diluted with saturated ammonium chloride and extracted with ethyl acetate. The organic phase was washed 5 times with water and once with brine. After drying with sodium sulfate, the sample was filtered, evaporated to dryness, and loaded onto a packed silica gel column. Elution with 0-5% EtOAc/hexane provided **2j** as a yellow solid (213 mg, 90%). Characterization data match the literature.[4] **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 7.93 (d, *J*=8.4 Hz, 5 H), 7.78 (d, *J*=8.1 Hz, 5 H), 7.63 (d, *J*=8.8 Hz, 5 H), 7.51 (td, *J*=7.7, 1.3 Hz, 5 H), 7.32 - 7.39 (m, 5 H), 7.07 (d, *J*=8.8 Hz, 5 H), 4.91 (s, 5 H), 2.55 (s, 15 H).



1,2-dimethoxy-4-methylbenzene (2k). Due to crystallization of hydrazone from the volumetric flask when the aldehyde and hydrazine are combined, an alternative procedure was used. The starting aldehyde (4 mmol) was added to a 5 mL volumetric flask which was filled to 5 mL with carbitol. To a second 5 mL volumetric flask was added KOH (12 mmol), hydrazine monohydrate (6 mmol) and carbitol to the 5 mL mark, and the flask was sonicated until homogeneous. The two solutions were fed at 47 µL/min each (t_{res} = 5 min) into the two separate inlets of the microreactor. The on-chip mixing in the high temperature reactor prevented clogging due to hydrazone formation. After collecting sample for 40 minutes, the material was diluted with water, extracted with a small amount of hexanes, and loaded directly onto a packed silica gel column. Elution with 5-10% Et_2O/hexane to provide **2k** as a clear oil (200 mg, 87%). Characterization data match the literature.[6] **^{1}H NMR** ($CDCl_3$, 300 MHz): δ = 6.69 - 6.80 (m, 3 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 2.31 (s, 3 H).

References

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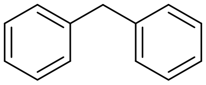
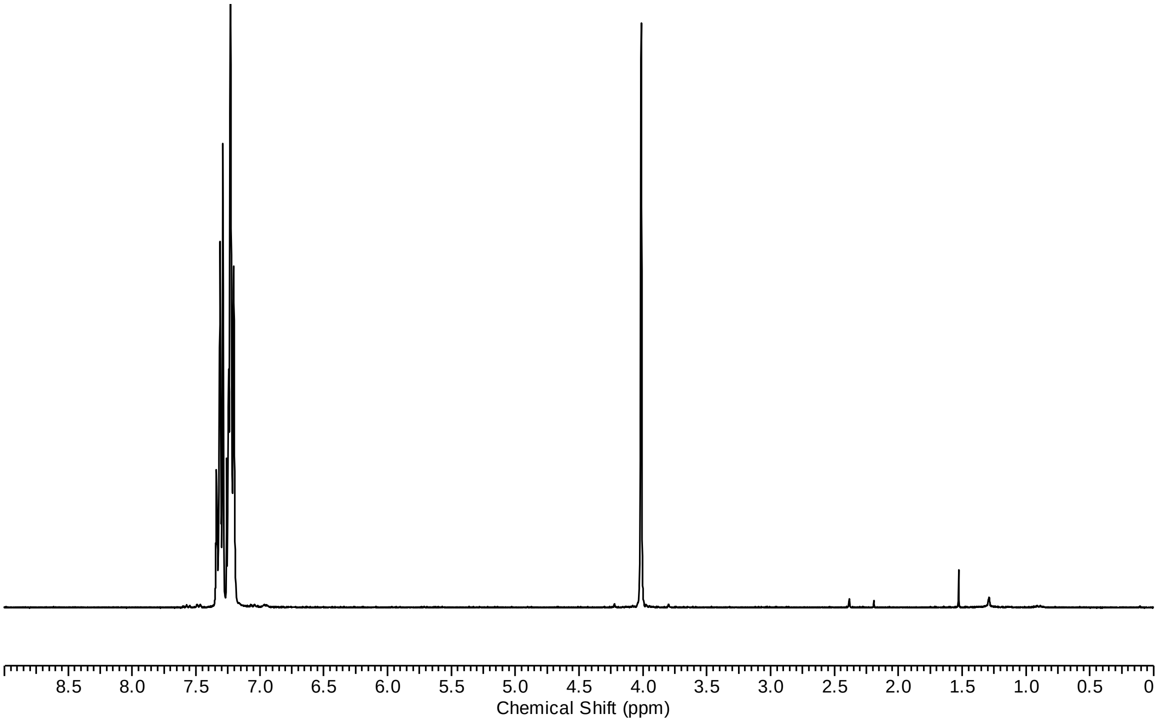
Spectra

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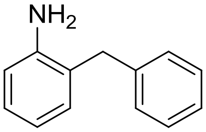
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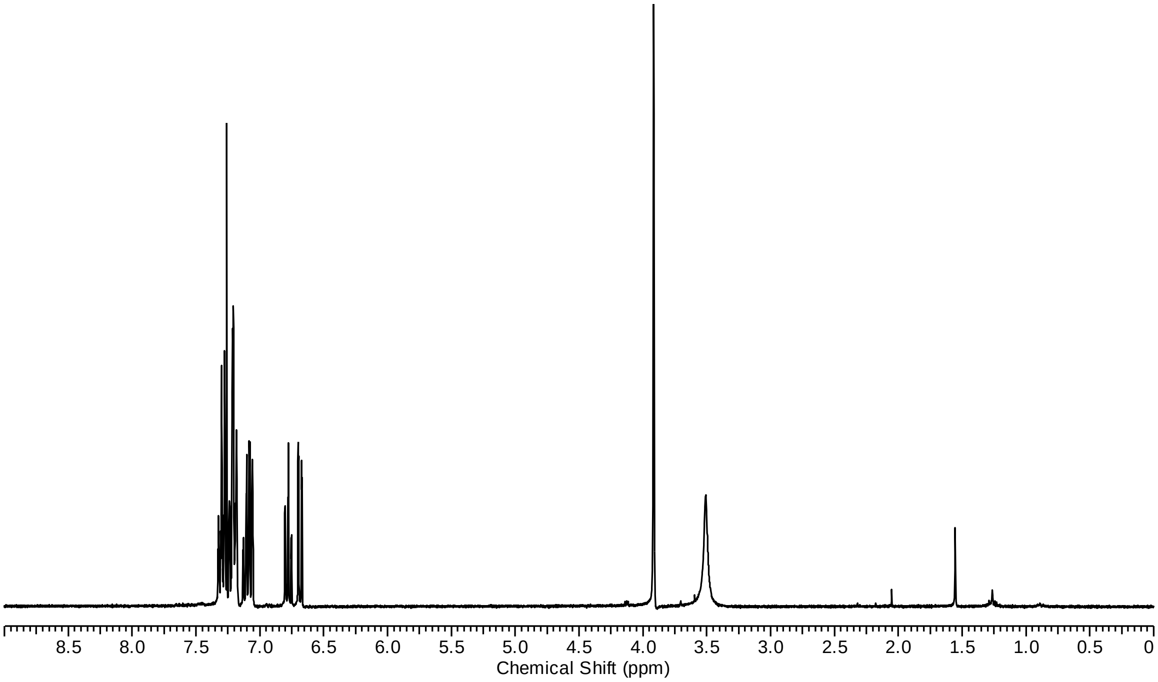
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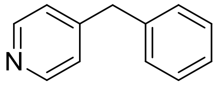
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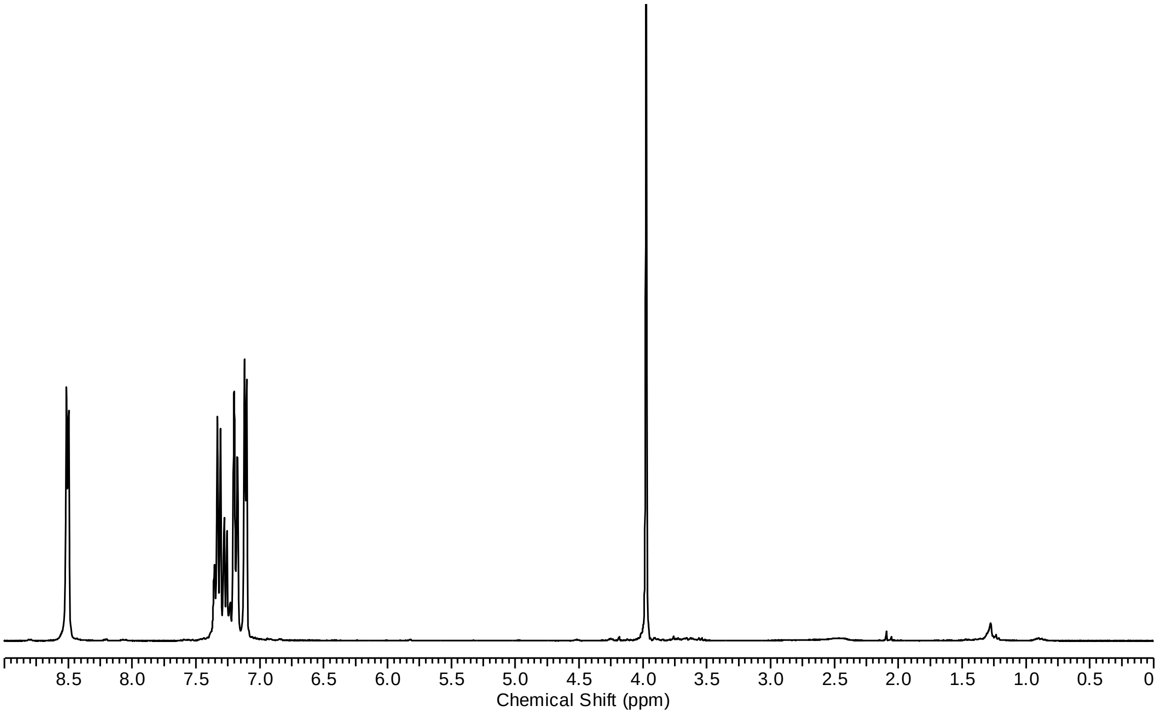
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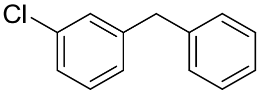
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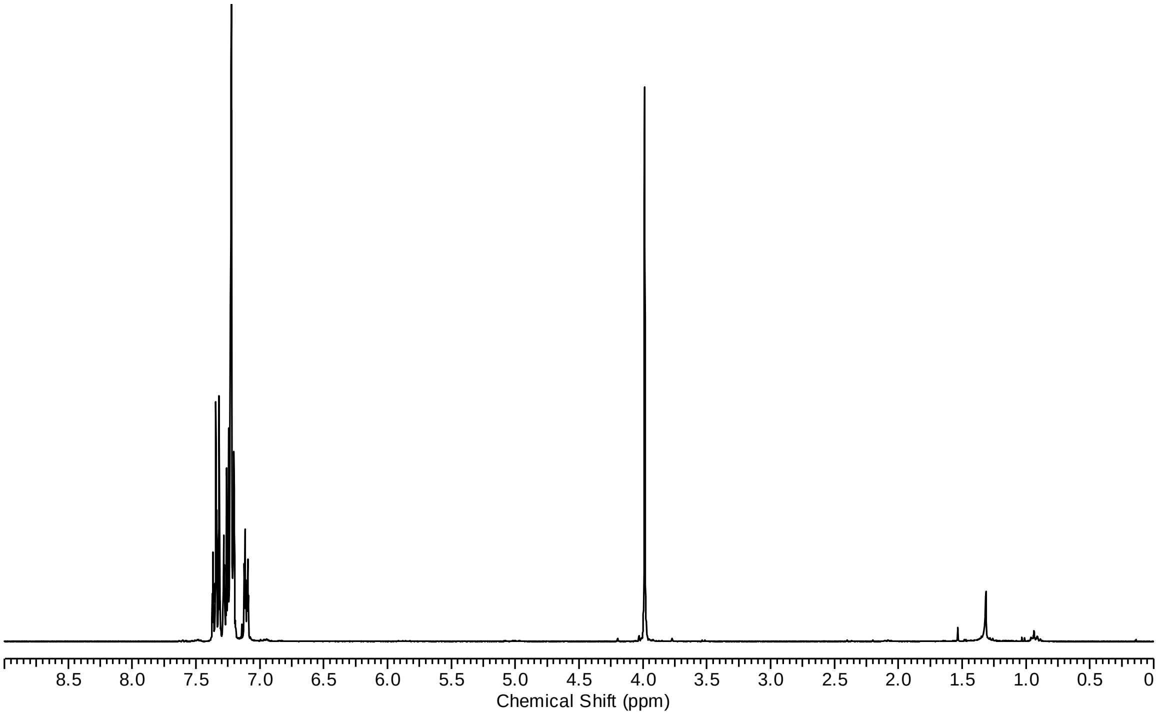
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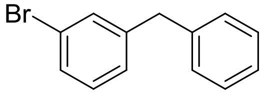
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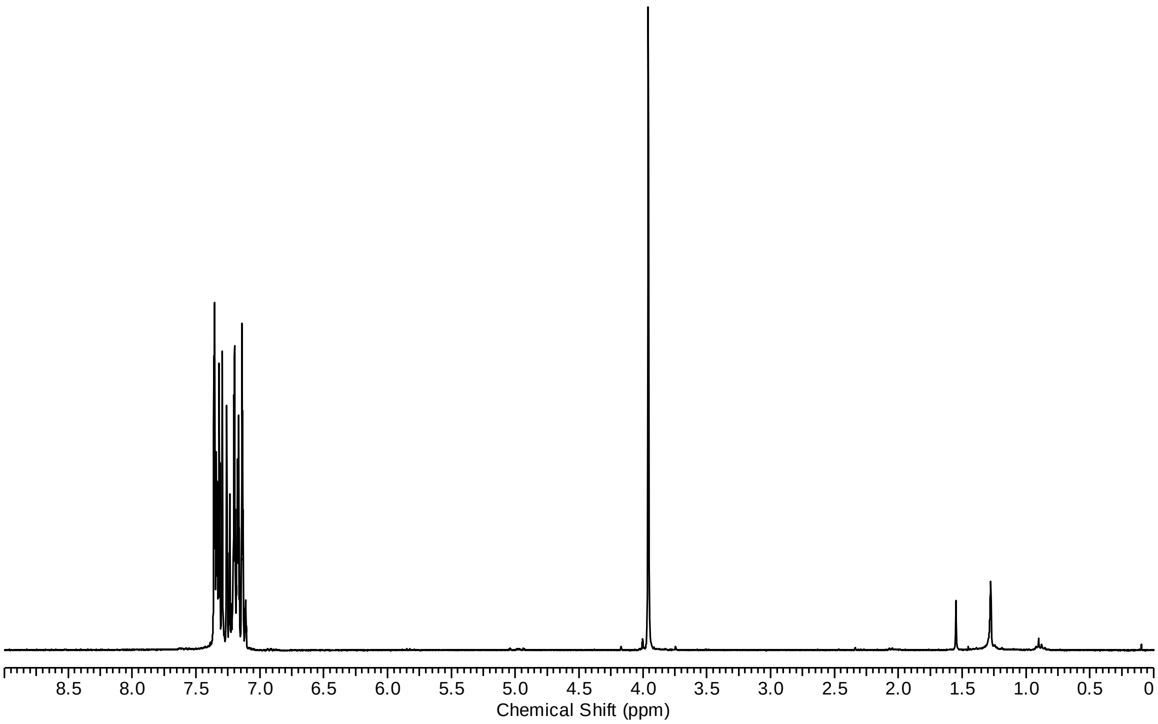
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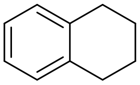

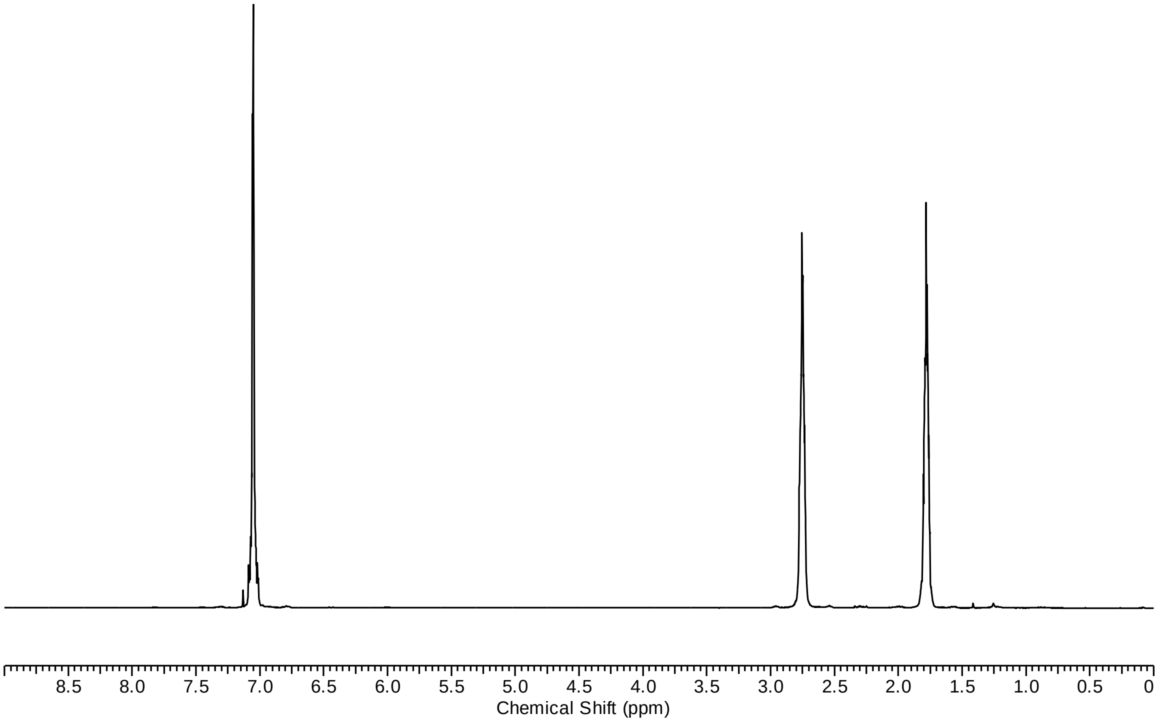
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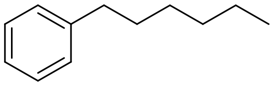

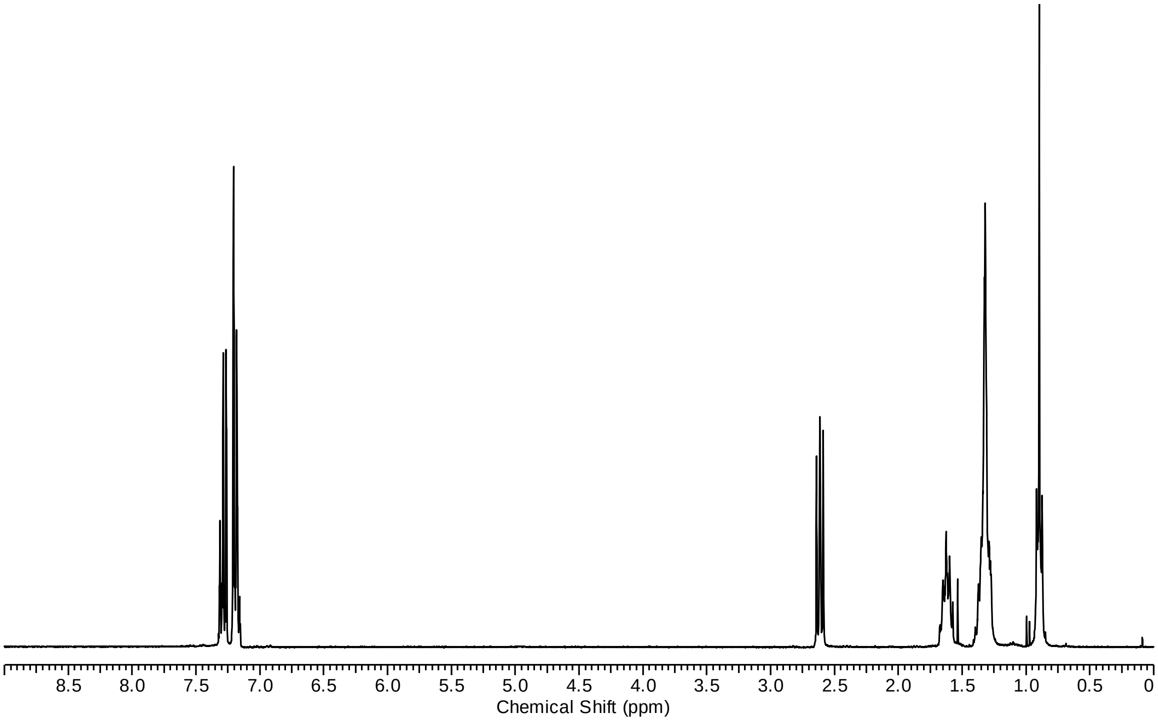
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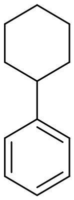

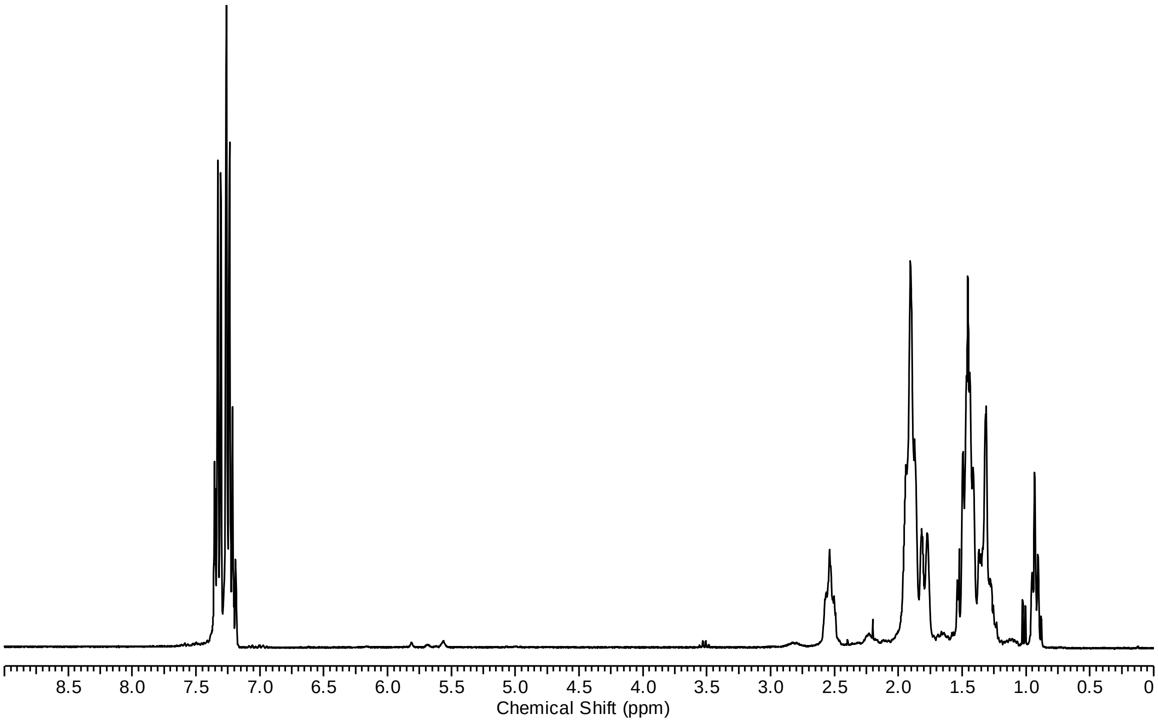
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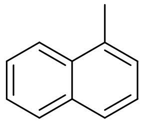

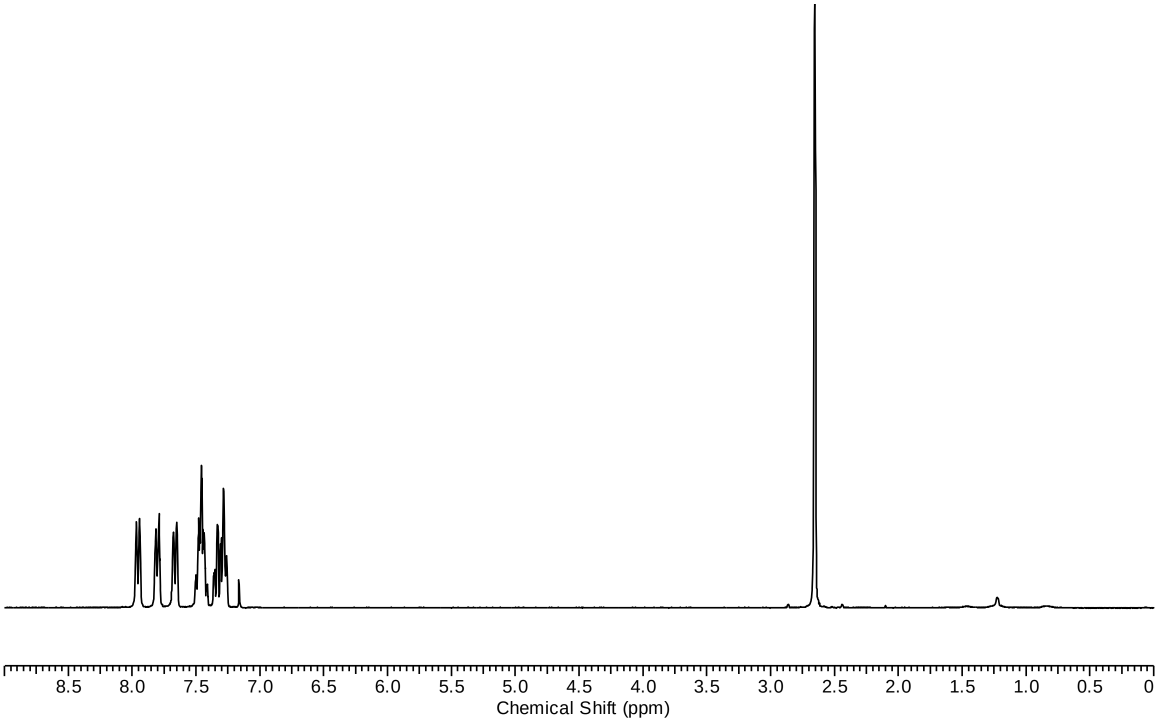
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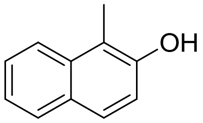
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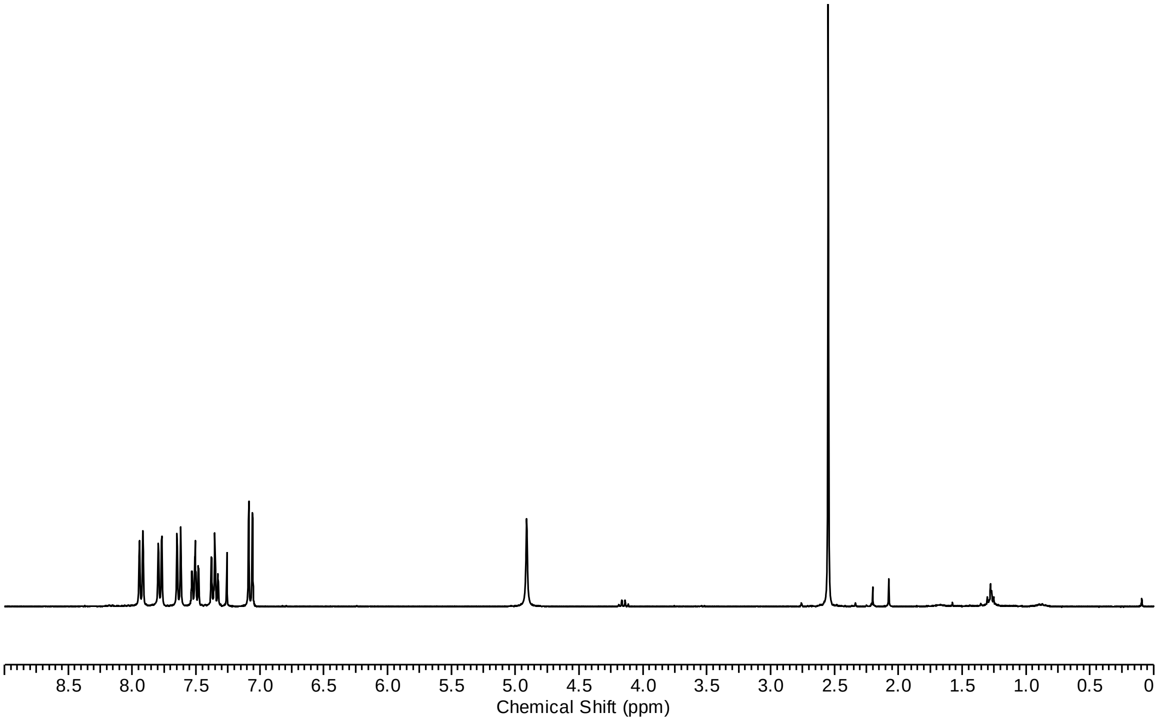
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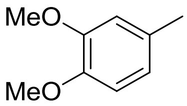
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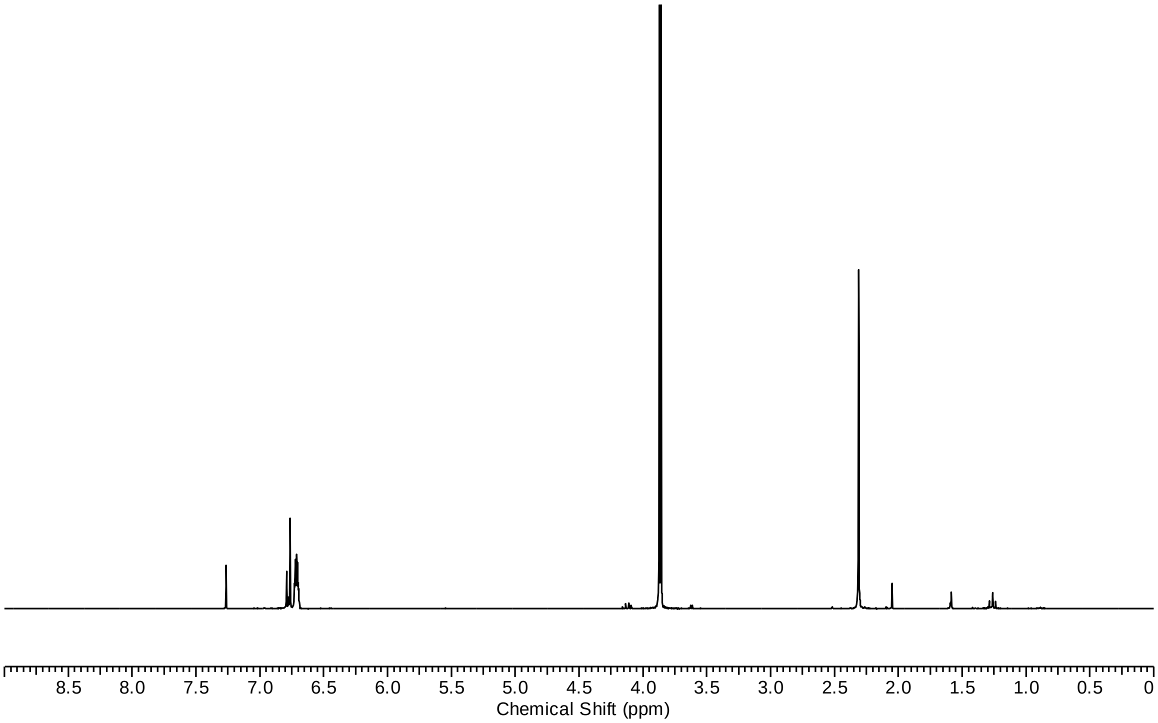
MeO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6.0
5.5
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2.0
1.5
1.0
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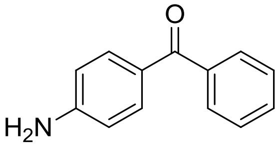
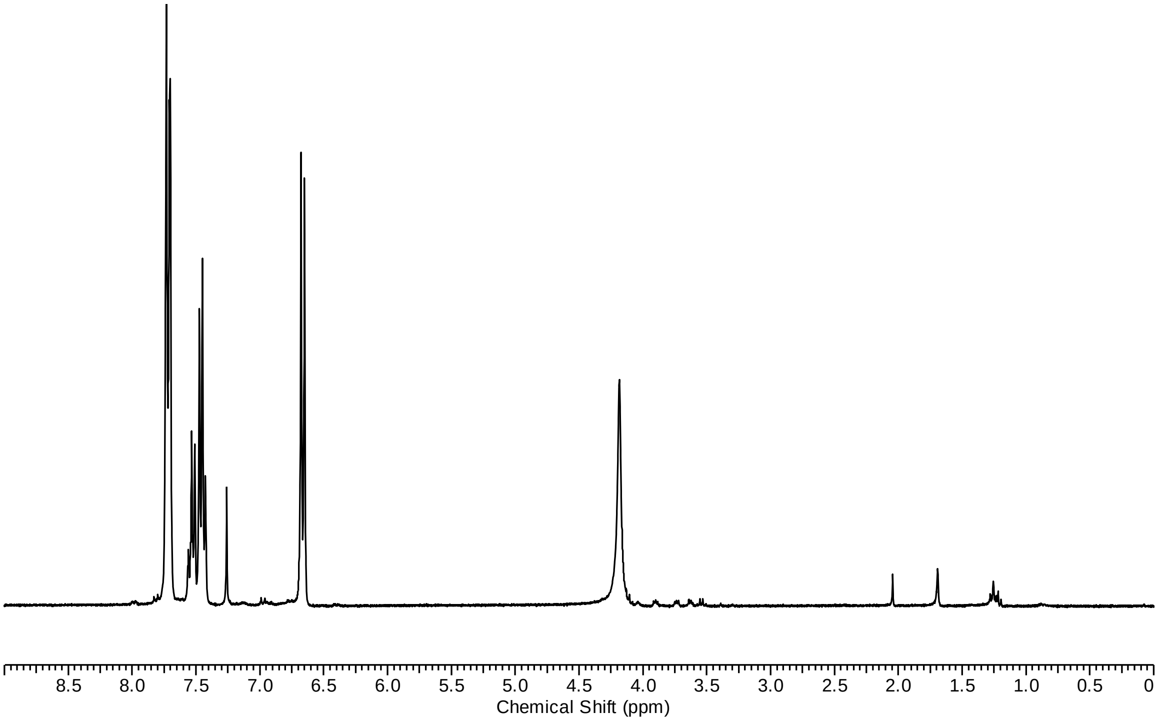
Chemical Shift (ppm)


O
H2N


8.5
8.0
7.5
7.0
6.5
6.0
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5.0
4.5
4.0
3.5
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2.5
2.0
1.5
1.0
0.5
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Chemical Shift (ppm)