Electronic Supplementary Material (ESI) for RSC Mechanochemistry.

Supporting Information

Al_2O_3 promoted mechanochemical nucleophilic aromatic substitution

Luca Vaghi, Eva Palomba, Antonio Papagni

University of Milano-Bicocca, Department of Materials Science, via R. Cozzi 55, 20125 Milano.

Table of Contents

Images of the work-up procedure

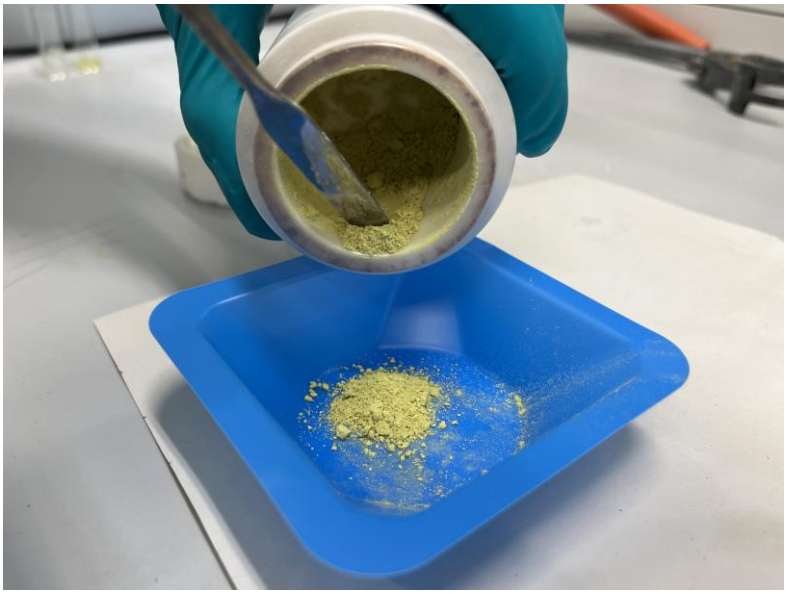


Figure S1. Crude recovery from the milling reactor.

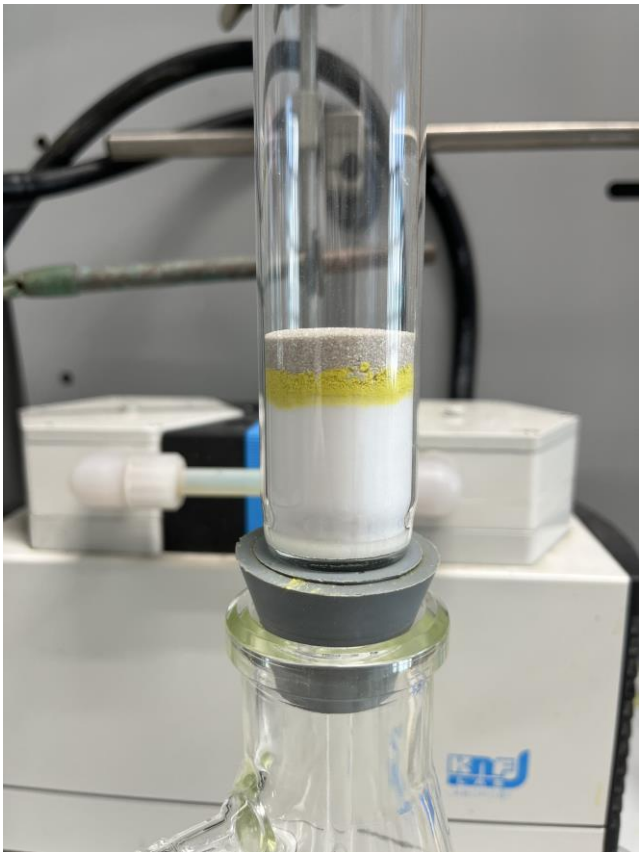


Figure S2. Setup for the purification on silica pad.

Synthetic procedures and compounds characterization

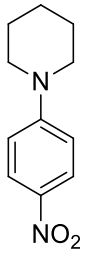
General information

All reagents and solvents were purchased from commercial sources and used without further purification. Reactions were performed in a SPEX® 8000M mixer/mill using 50 mL grinding reactor (ZrO_2) and 4 milling balls (1 cm diameter, ZrO_2). The following materials were used as milling auxiliaries: SiO_2 (Sigma-Aldrich 717177); TiO_2 (Sigma-Aldrich 14021); Al_2O_3 (Sigma-Aldrich 11028). Chromatographic purifications were performed using Merck 9385 silica gel, pore size 60 Å (230–400 mesh). Melting points were measured with a Stanford Research Systems Optimelt apparatus. ^{1}H, ^{13}C and ^{19}F spectra were recorded with a Bruker AVANCE III HD 400 MHz spectrometer (^{1}H: 400 MHz, ^{13}C: 101 MHz, ^{19}F 376 MHz) chemical shifts (δ) are expressed in parts per million (ppm), and coupling constants are given in Hz. Splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded with a PerkinElmer Spectrum 100 FT-IR spectrometer equipped with universal ATR sampling accessory. Elemental analyses were obtained with an Elementar vario MICRO cube instrument.

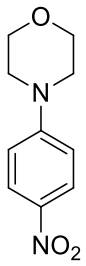
General Procedure for the mechanochemical S_NAr of aryl fluorides

Aryl fluoride (2 mmol), nucleophile (equivalents stated in the text) and auxiliary (5 g) were added to the zirconia reactor equipped with four zirconia milling balls (d=1 cm). The mixture was shaken at 15 Hz for the time stated in the text. The powdery residue was recovered and directly put over a short pad of silica gel (a small amount of silica gel can be mixed before to the residue if elution results difficult), vacuum-aided elution with the proper solvent mixture and subsequent removal of the volatiles under reduced pressure afforded the desired product in a pure form.

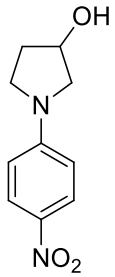
Isolated compounds



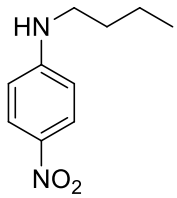
1-(4-nitrophenyl)piperidine (**3a**). 376 mg, 91%; yellow solid; mp 103-105°C; R_f = 0.35 (SiO_2, *n*-heptane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.07 (m, 2H), 6.82 – 6.75 (m, 2H), 3.46 – 3.41 (m, 4H), 1.73 – 1.65 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 137.4, 126.1, 112.3, 48.3, 25.3, 24.2. The physical and spectroscopic data are in accordance with those reported in the literature.[1]



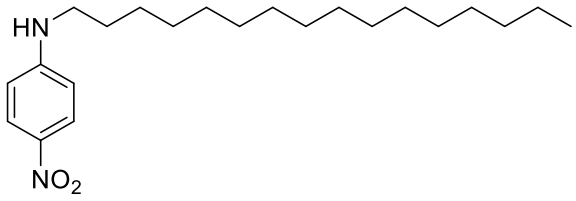
4-(4-nitrophenyl)morpholine (**3b**). 401 mg, 96%; yellow solid; mp 150-151 °C; R_f = 0.33 (SiO_2, EtOAc/*n*-heptane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 2H), 6.85 – 6.79 (m, 2H), 3.88 – 3.83 (m, 4H), 3.39 – 3.34 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 138.9, 125.9, 112.6, 66.3, 47.1. The physical and spectroscopic data are in accordance with those reported in the literature.[2]



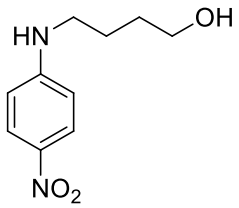
1-(4-nitrophenyl)pyrrolidin-3-ol (**3c**). 333 mg, 80%; yellow solid; mp 180-181 °C; R_f = 0.55 (SiO_2, *n*-heptane/EtOAc 8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 – 8.02 (m, 2H), 6.64 – 6.58 (m, 2H), 5.10 (d, *J* = 3.6 Hz, 1H), 4.47 – 4.40 (m, 1H), 3.54 – 3.43 (m, 3H), 3.25 (d, J = 11.2 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.99 – 1.90 (m, 1H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.0, 135.3, 126.0, 110.8, 69.0, 56.2, 45.9, 33.4; IR (ATR): 3436, 3110, 3089, 2949, 2921, 2857, 2666, 2556, 2391, 1603, 1570, 1522, 1471, 1438, 1406, 1365, 1293, 1225, 1194, 1163, 1100, 977, 952, 868, 820, 753, 728, 693, 681, 625, 544 cm^{-1}; Anal. Calcd. for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.58; H, 5.83; N, 13.50.



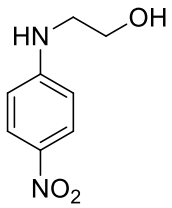
N-butyl-4-nitroaniline (**3d**). 124 mg, 32%; yellow solid; mp 55-56 °C; R_f = 0.26 (SiO_2, *n*-heptane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.04 (m, 2H), 6.54 – 6.47 (m, 2H), 4.50 (s, 1H), 3.21 (td, *J* = 7.1, 5.5 Hz, 2H), 1.69 – 1.56 (m, 2H), 1.50 – 1.38 (m, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 137.5, 126.5, 110.9, 43.1, 31.1, 20.1, 13.8. The physical and spectroscopic data are in accordance with those reported in the literature.[3]



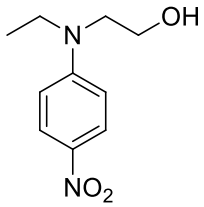
N-hexadecyl-4-nitroaniline (**3e**). 24 mg, 3%; yellow solid; mp 74-75 °C; R_f = 0.38 (SiO_2, *n*-heptane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.05 (m, 2H), 6.54 – 6.48 (m, 2H), 4.46 (s, 1H), 3.25 – 3.16 (m, 2H), 1.72 – 1.57 (m, 4H), 1.43 – 1.20 (m, 24H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.4, 137.8, 126.5, 110.9, 43.4, 31.9, 29.91 – 29.20 (m, 10C), 29.1, 27.0, 22.7, 14.1; IR (ATR): 3348, 2956, 2915, 2848, 1637, 1603, 1541, 1469, 1439, 1362, 1319, 1294, 1284, 1270, 1186, 1153, 1134, 1108, 1000, 839, 753, 723, 700, 662, 546 cm^{-1}; Anal. Calcd. for $C_{22}H_{38}N_2O_2$: C, 72.88; H, 10.56; N, 7.73. Found: C, 73.01; H, 10.64; N, 7.68.



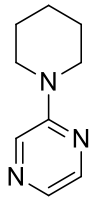
4-[(4-nitrophenyl)amino]butan-1-ol (**3h**). 220 mg, 52%; yellow solid; mp 135-136 °C; R_f = 0.40 (SiO_2, EtOAc/*n*-heptane 8:2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.3 Hz, 2H), 7.28 (t, *J* = 5.4 Hz, 1H), 6.66 – 6.59 (m, 2H), 4.45 (t, *J* = 5.1 Hz, 1H), 3.44 (dd, *J* = 11.4, 6.3 Hz, 2H), 3.14 (dd, *J* = 12.5, 6.9 Hz, 2H), 1.65 – 1.46 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.1, 135.9, 126.7, 111.1, 60.8, 42.7, 30.4, 25.5; IR (ATR): 3440, 3274, 3174, 3124, 2936, 2892, 2863, 1599, 1590, 1542, 1506, 1476, 1462, 1286, 1270, 1178, 1132, 1104, 1057, 1030, 996, 833, 753, 742, 697, 662, 628, 544 cm^{-1}; Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.22; H, 6.68; N, 13.31.



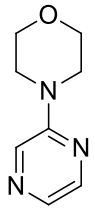
2-[(4-nitrophenyl)amino]ethanol (**3i**). 227 mg, 62%; yellow solid; mp 109-110 °C; R_f = 0.34 (SiO_2, EtOAc/*n*-heptane 1:1); ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.98 (d, *J* = 9.3 Hz, 2H), 7.29 (t, *J* = 5.5 Hz, 1H), 6.66 (d, *J* = 9.4 Hz, 2H), 4.82 (t, *J* = 5.4 Hz, 1H), 3.58 (q, *J* = 5.7 Hz, 2H), 3.24 (q, *J* = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 155.2, 136.0, 126.7, 111.2, 59.7, 45.5. The physical and spectroscopic data are in accordance with those reported in the literature.[4]



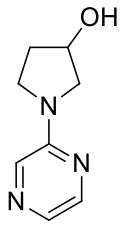
2-[ethyl(4-nitrophenyl)amino]ethanol (**3j**). 17 mg, 4%; yellow solid; mp 67-68 °C; R_f= 0.29 (SiO_2, EtOAc/*n*-heptane 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.90 (m, 2H), 6.60 – 6.54 (m, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 3.53 (t, *J* = 6.0 Hz, 2H), 3.48 (q, *J* = 7.3 Hz, 2H), 2.86 (s, 1H), 1.17 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 136.1, 126.4, 110.3, 59.7, 52.3, 46.0, 11.8; IR (ATR): 3398, 3155, 2971, 2933, 2903, 2873, 2681, 2406, 1594, 1579, 1517, 1490, 1478, 1468, 1438, 1412, 1391, 1374, 1355, 1305, 1280, 1224, 1198, 1188, 1134, 1113, 1081, 1073, 1035, 1021, 997, 951, 848, 823, 809, 796, 778, 750, 695, 633, 619, 564, 532 cm^{-1}; Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.33. Found: C, 57.27; H, 6.70; N, 13.28.



2-piperidin-1-ylpyrazine (**5a**). 274 mg, 84%; yellow solid; mp 35-36 °C; R_f = 0.20 (SiO_2, *n*-heptane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 1.5 Hz, 1H), 8.00 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.74 (d, *J* = 2.6 Hz, 1H), 3.58 – 3.50 (m, 4H), 1.68 – 1.57 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 141.7, 131.9, 131.1, 45.5, 25.3, 24.5. The physical and spectroscopic data are in accordance with those reported in the literature.[5]

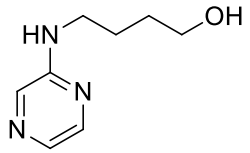


4-pyrazin-2-ylmorpholine (**5b**). 227 mg, 69%; pale grey solid; mp 46-47 °C, R_f = 0.23 (SiO_2, *n*-heptane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 1.5 Hz, 1H), 8.06 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.88 (d, *J* = 2.6 Hz, 1H), 3.84 – 3.79 (m, 4H), 3.57 – 3.52 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 141.7, 133.5, 130.9, 66.5, 44.7. The physical and spectroscopic data are in accordance with those reported in the literature.[6]

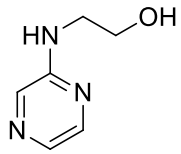


1-pyrazin-2-ylpyrrolidin-3-ol (**5c**). 284 mg, 86%; pale grey solid; mp 87-88 °C; R_f = 0.17 (SiO_2, EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (dd, *J* = 2.7, 1.5 Hz, 1H), 7.80 (d, *J* = 1.5 Hz, 1H), 7.72 (d, *J* = 2.7 Hz, 1H), 4.63 – 4.57 (m, 1H), 3.66 – 3.48 (m, 4H), 3.38 (s, 1H),

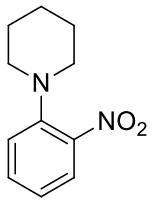
2.15 – 2.07 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.0, 142.2, 131.0, 130.3, 70.3, 54.8, 44.4, 33.9; IR (ATR): 3235, 3048, 2954, 2919, 2861, 1580, 1516, 1493, 1465, 1438, 1379, 1352, 1319, 1296, 1255, 1224, 1204, 1180, 1128, 1109, 1075, 1009, 994, 968, 915, 871, 826, 716, 623, 536 cm^{-1}; Anal. Calcd. for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.17; H, 6.70; N, 25.42.



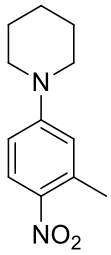
4-(pyrazin-2-ylamino)butan-1-ol (**5h**). 209 mg, 63%; Colorless oil; R_f = 0.28 (SiO_2, EtOAc/EtOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.78 (d, *J* = 1.4 Hz, 1H), 7.62 (d, *J* = 2.8 Hz, 1H), 5.48 (t, *J* = 5.4 Hz, 1H), 3.99 (s, 1H), 3.59 (t, *J* = 6.1 Hz, 2H), 3.32 – 3.23 (m, 2H), 1.69 – 1.52 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.8, 141.8, 132.2, 132.0, 62.0, 41.1, 29.8, 25.9; IR (ATR): 3289, 2936, 2864, 1596, 1519, 1464, 1434, 1397, 1342, 1292, 1204, 1179, 1151, 1105, 1057, 1001, 914, 872, 822, 753, 623, 536 cm^{-1}; Anal. Calcd. for $C_8H_{13}N_3O$: C, 57.46; H, 7.84; N, 25.13. Found: C, 57.61; H, 7.78; N, 25.09.



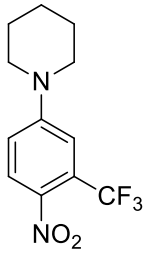
2-(pyrazin-2-ylamino)ethanol (**5i**). 168 mg, 61%; pale ochre solid; mp 55-56 °C; R_f = 0.31 (SiO_2, EtOAc/EtOH 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 2.8, 1.5 Hz, 1H), 7.84 (d, *J* = 1.5 Hz, 1H), 7.68 (d, *J* = 2.8 Hz, 1H), 5.59 (s, 1H), 4.49 (s, 1H), 3.80 – 3.74 (m, 2H), 3.51 – 3.44 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 141.4, 132.9, 132.3, 61.8, 44.0; IR (ATR): 3272, 2925, 2864, 1595, 1519, 1464, 1434, 1397, 1342, 1292, 1204, 1179, 1151, 1105, 1057, 1001, 914, 872, 822, 753, 623, 536 cm^{-1}; Anal. Calcd. for $C_6H_9N_3O$: C, 51.79; H, 6.52; N, 30.20. Found: C, 51.88; H, 6.59; N, 30.07.



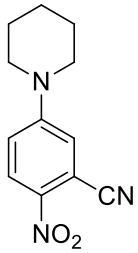
1-(2-nitrophenyl)piperidine (**6a**). 405 mg, 98%; orange solid; mp 78-79 °C; R_f = 0.47 (SiO_2, *n*-heptane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.46 – 7.40 (m, 1H), 7.11 (dd, *J* = 8.3, 0.8 Hz, 1H), 6.98 – 6.92 (m, 1H), 3.05 – 2.97 (m, 4H), 1.76 – 1.66 (m, 4H), 1.63 – 1.55 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.0, 142.7, 133.3, 126.0, 120.8, 120.6, 52.9, 25.9, 24.0. The physical and spectroscopic data are in accordance with those reported in the literature.[7]



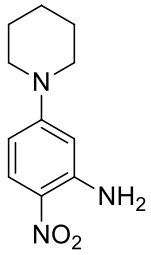
1-(3-methyl-4-nitrophenyl)piperidine (**8a**). 416 mg, 95%; yellow solid; mp 53-54 °C; R_f = 0.36 (SiO_2, *n*-heptane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 9.3 Hz, 1H), 6.64 (dd, *J* = 9.3, 2.9 Hz, 1H), 6.58 (d, *J* = 2.8 Hz, 1H), 3.42 – 3.35 (m, 4H), 2.60 (s, 3H), 1.69 – 1.62 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 137.9, 137.4, 127.9, 115.8, 110.9, 48.3, 25.3, 24.6, 22.7. The physical and spectroscopic data are in accordance with those reported in the literature.[8]



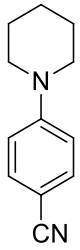
1-[4-nitro-3-(trifluoromethyl)phenyl]piperidine (**9a**). 544 mg, 99%; yellow solid; mp 71-72 °C; R_f = 0.44 (SiO_2, *n*-heptane/EtOAc 8:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 9.3 Hz, 1H), 7.10 (d, *J* = 2.7 Hz, 1H), 6.87 (dd, *J* = 9.3, 2.9 Hz, 1H), 3.48 – 3.40 (m, 4H), 1.73 – 1.64 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 135.7, 128.9, 126.3 (q, *J* = 32.7 Hz), 122.46 (q, *J* = 273.3 Hz),114.2, 111.8 (q, *J* = 6.4 Hz), 48.3, 25.2, 24.0; ^{19}F NMR (376 MHz, $CDCl_3$) δ -60.20. The physical and spectroscopic data are in accordance with those reported in the literature.[9]



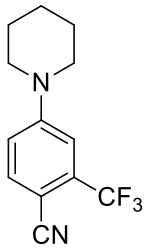
2-nitro-5-(1-piperidinyl)benzonitrile (**10a**). 447 mg, 97%; yellow solid; mp 127-128 °C; R_f = 0.38 (SiO_2, *n*-heptane/EtOAc 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 9.6 Hz, 1H), 7.08 (d, *J* = 3.0 Hz, 1H), 6.93 (dd, *J* = 9.6, 3.0 Hz, 1H), 3.51 – 3.44(m, 4H), 1.78 – 1.63 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.3, 136.1, 128.0, 118.5, 116.4, 114.9, 110.3, 48.2, 25.2, 23.9. The physical and spectroscopic data are in accordance with those reported in the literature.[10]



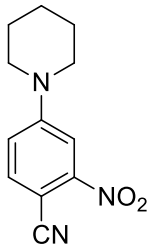
2-nitro-5-(1-piperidinyl)aniline (**11a**). 385 mg, 87%; orange solid; mp 104-105 °C; R_f = 0.41 (SiO_2, *n*-heptane/EtOAc 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 9.7 Hz, 1H), 6.25 (dd, *J* = 9.8, 2.7 Hz, 1H), 6.16 (br s, 2H), 5.92 (d, *J* = 2.7 Hz, 1H), 3.45 – 3.26 (m, 4H), 1.73 – 1.55 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 147.4, 128.3, 124.0, 105.8, 97.5, 48.2, 25.3, 24.3. The physical and spectroscopic data are in accordance with those reported in the literature.[11]



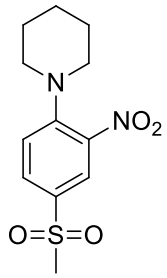
4-(1-piperidinyl)benzonitrile (**13a**). 140 mg, 38%; white solid; mp 52-53 °C; R_f = 0.32 (SiO_2, *n*-heptane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 3.41 – 3.25 (m, 4H), 1.77 – 1.55 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 133.5, 120.4, 114.0, 98.9, 48.4, 25.2, 24.2. The physical and spectroscopic data are in accordance with those reported in the literature.[12]



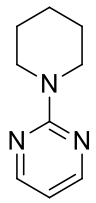
4-(1-piperidinyl)-2-(trifluoromethyl)benzonitrile (**14a**). 504 mg, 99%; white solid; mp 68-69 °C; R_f = 0.35 (SiO_2, *n*-heptane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 2.6 Hz, 1H), 6.92 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.47 – 3.33 (m, 4H), 1.77 – 1.62 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8, 136.0, 134.0 (q, *J* = 31.7 Hz), 122.8 (q, *J* = 274.1 Hz), 117.1, 115.4, 111.2 (q, *J* = 4.6 Hz), 95.2, 48.2, 25.1, 24.1; ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.41. The physical and spectroscopic data are in accordance with those reported in the literature.[13]



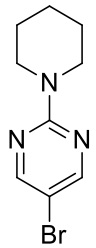
2-nitro-4-(1-piperidinyl)benzonitrile (**15a**). 413 mg, 89%; orange solid; mp 142-143 °C; R_f = 0.33 (SiO_2, *n*-heptane/EtOAc 6:4); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 2.7 Hz, 1H), 7.58 (d, *J* = 8.9 Hz, 1H), 7.02 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.52 – 3.35 (m, 4H), 1.79 – 1.64 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 150.3, 136.2, 116.9, 116.6, 109.2, 92.7, 48.2, 25.1, 23.9. The physical and spectroscopic data are in accordance with those reported in the literature.[14]



1-[4-(methylsulfonyl)-2-nitrophenyl]piperidine (**19a**). 548 mg, 96%; orange solid; mp 124-125 °C; R_f = 0.45 (SiO_2, *n*-heptane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, *J* = 2.3 Hz, 1H), 7.83 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.14 (d, *J* = 9.0 Hz, 1H), 3.23 – 3.10 (m, 4H), 3.03 (s, 3H), 1.75 – 1.59 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 138.6, 131.7, 128.9, 127.3, 120.2, 51.8, 44.7, 25.4, 23.6. The physical and spectroscopic data are in accordance with those reported in the literature.[15]

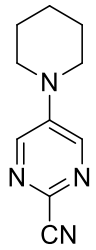


2-(1-piperidinyl)pyrimidine (**20a**). 311 mg, 95%; colourless oil; R_f = 0.35 (SiO_2, *n*-heptane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 4.7 Hz, 2H), 6.33 (t, *J* = 4.7 Hz, 1H), 3.75 – 3.66 (m, 4H), 1.65 – 1.45 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 157.9, 109.0, 44.7, 25.7, 24.8. The physical and spectroscopic data are in accordance with those reported in the literature.[16]



5-bromo-2-(1-piperidinyl)pyrimidine (**21a**). 478 mg, 99%; white solid; mp 55-56 °C; R_f = 0.65 (SiO_2, *n*-heptane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 2H), 3.73 – 3.63

(m, 6H), 1.67 – 1.45 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.8, 157.7, 104.8, 45.0, 25.6, 24.7. The physical and spectroscopic data are in accordance with those reported in the literature.[17]



5-(1-piperidinyl)-2-pyrimidinecarbonitrile (**22a**). 335 mg, 89%; white solid; mp 96-97 °C; R_f = 0.30 (SiO_2, *n*-heptane/EtOAc 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 3.45 – 3.31 (m, 2H), 1.75 – 1.58 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.3, 141.5, 131.6, 116.8, 47.0, 24.9, 23.7; IR (ATR): 2939, 2850, 2229, 1558, 1523, 1465, 1451, 1442, 1371, 1291, 1239, 1211, 1128, 1023, 917, 890, 855, 800, 769, 654, 556 cm^{-1}; Anal. Calcd. for $C_{10}H_{12}N_4$: C, 63.81; H, 6.43; N, 29.77. Found: C, 63.90; H, 6.42; N, 29.71.

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Scale-up experiment

Procedure for the mechanochemical S_NAr on 10 mmol of 1-fluoro-2-nitrobenzene ***6***

1-Fluoro-2-nitrobenzene **6** (1.41 g, 10 mmol), piperidine **2a** (1.28 g, 15 mmol) and Al_2O_3 (15 g) were added to the zirconia reactor (50 mL) equipped with four zirconia milling balls (d=1 cm). The mixture was shaken at 15 Hz for 1 h. The powdery residue was recovered, mixed with a small amount of silica gel and put directly over a pad of silica gel. Vacuum-aided elution with *n*-eptane/EtOAc 8:2 and subsequent removal of the volatiles under reduced pressure afforded **6a** (1.87 g, 91%) in a pure form.

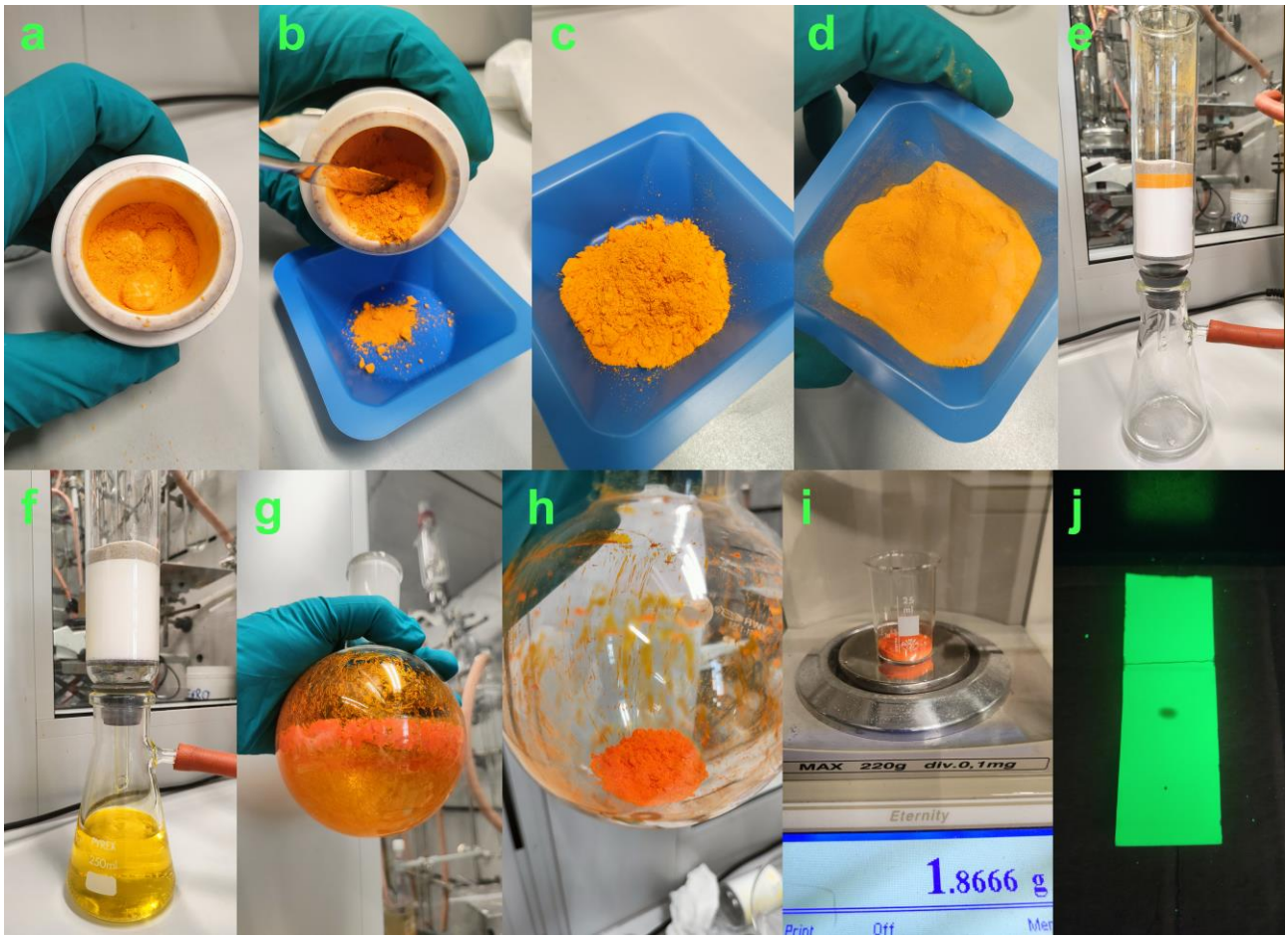
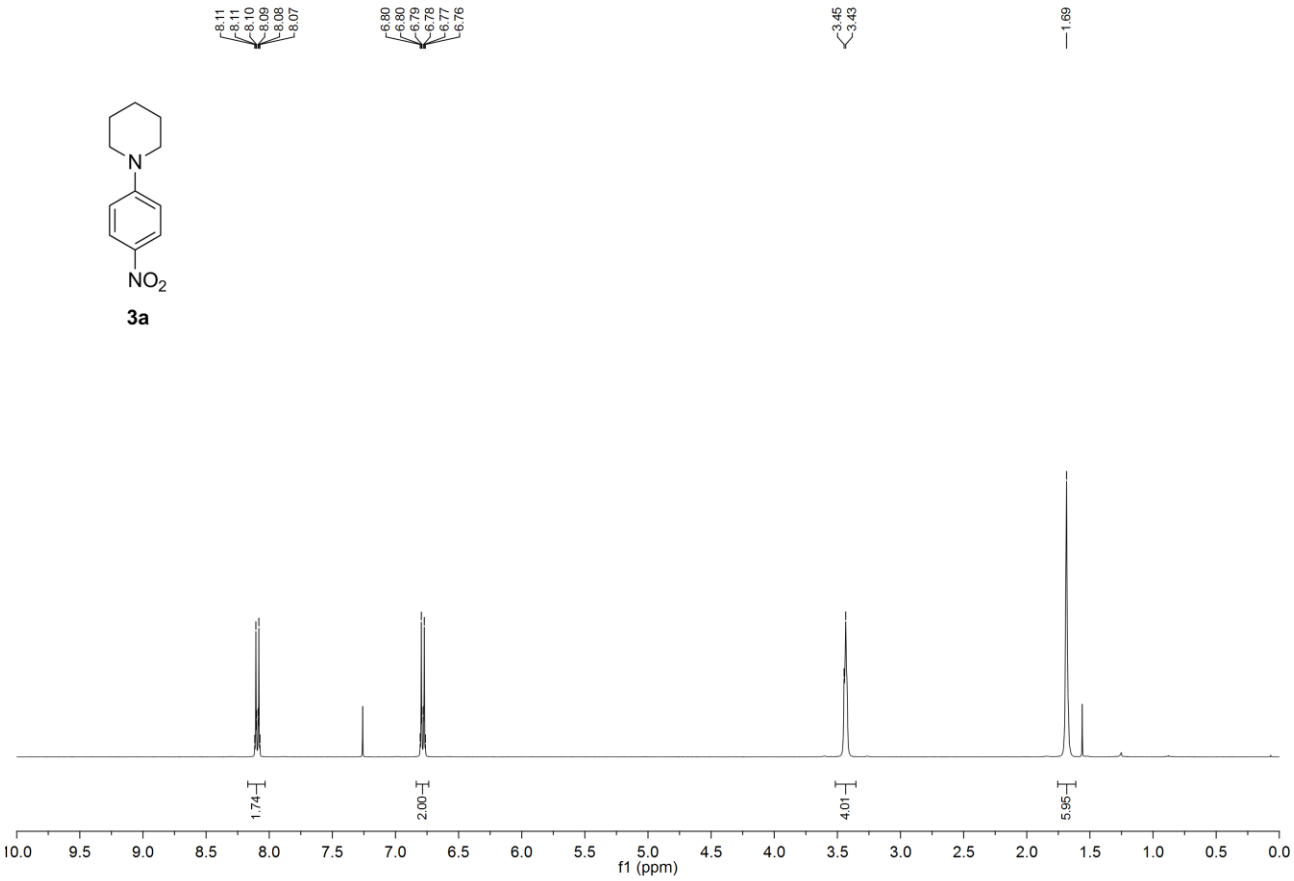
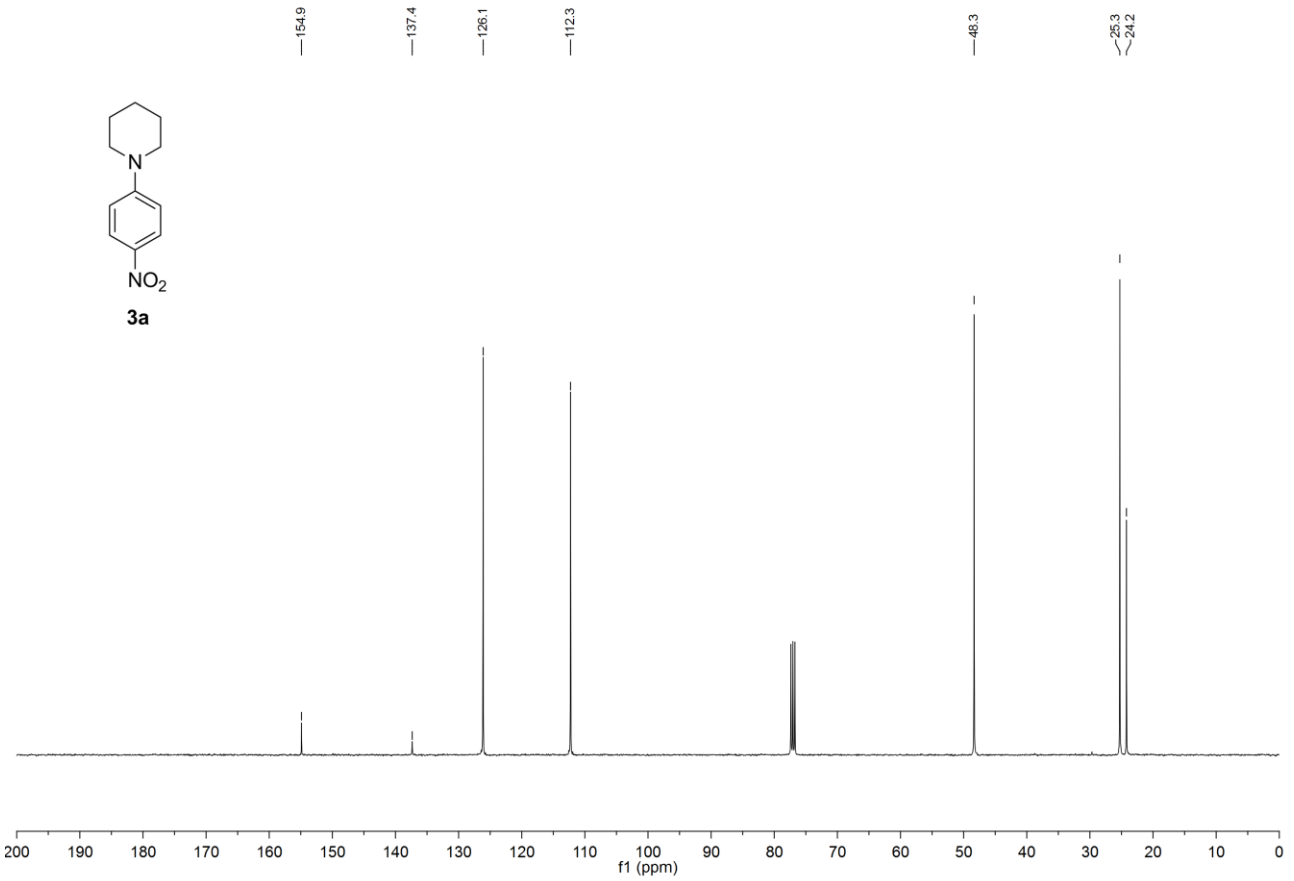
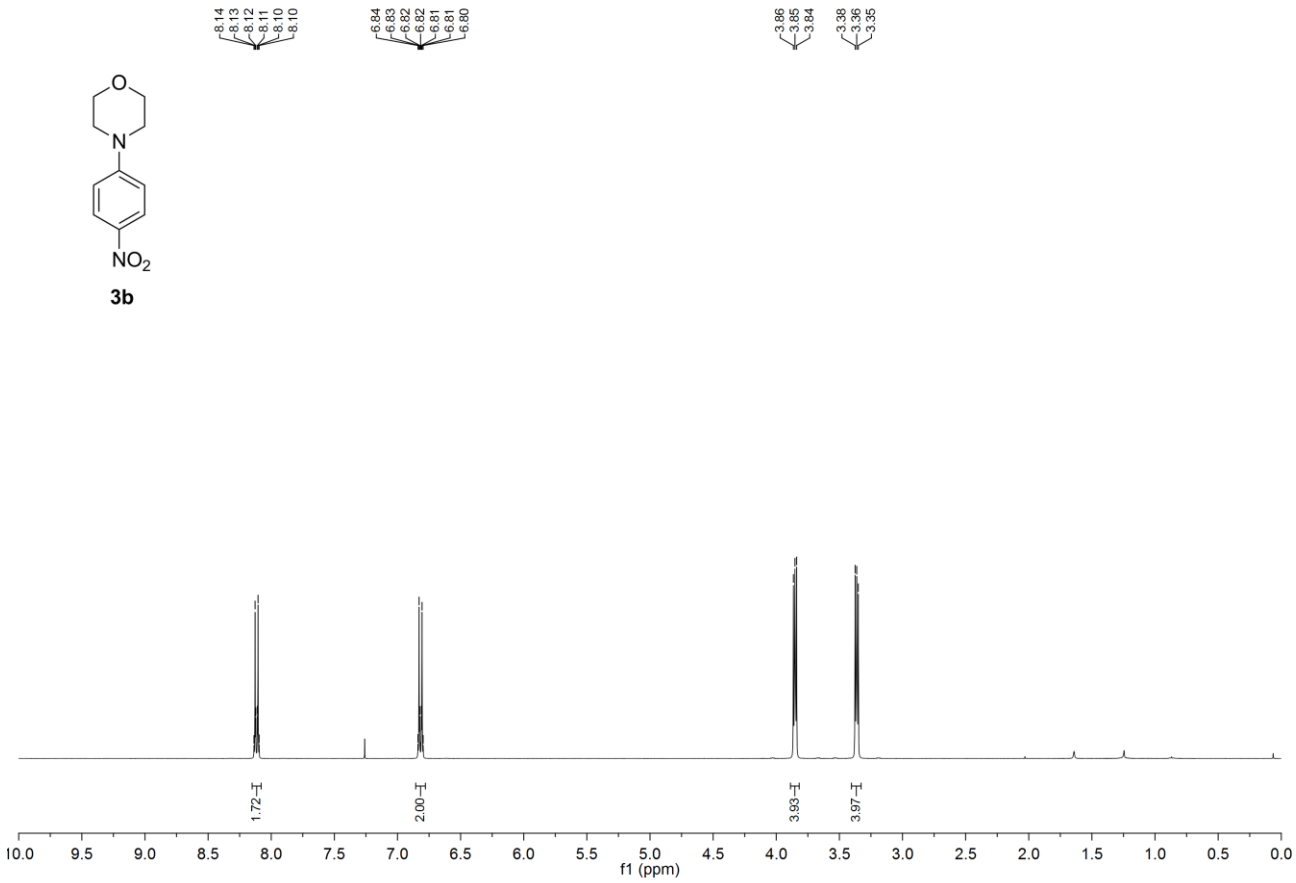


Figure S3. Image sequence of the scale-up experiment. a) aspect of the reactor at the end of the experiment; b) recovery of the crude from the jar; c) aspect of the crude; d) aspect of the crude after mixing with a small amount of silica gel; e) setup for purification via dry column chromatography; f) eluted fraction containing the product **6a**; g,h) aspect of the product **6a** after removal of the volatiles under reduced pressure; i) weighing; j) purity check via TLC analysis.

NMR and IR spectra



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8.10
8.10
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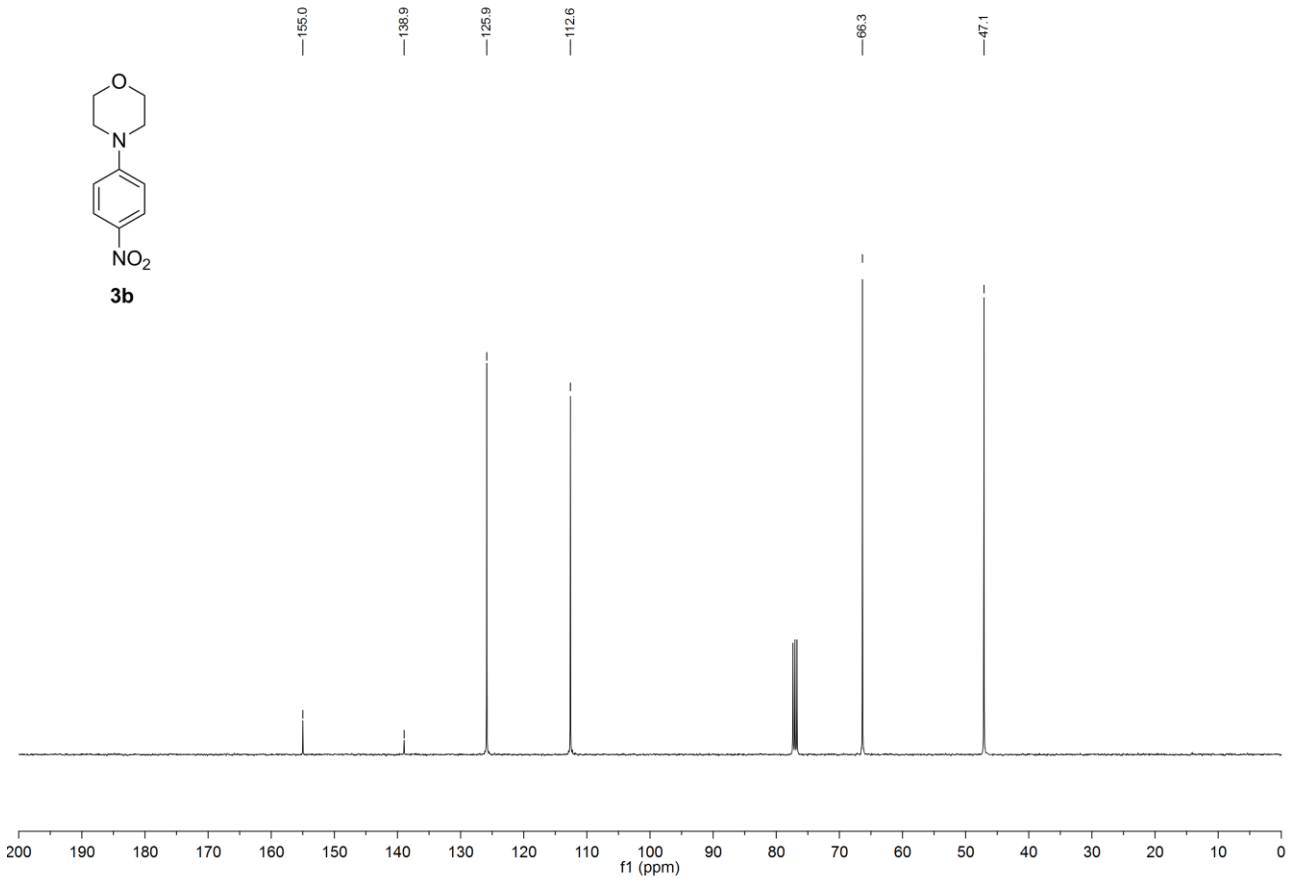
6.83
6.82
6.82
6.81
6.81
6.80
3.86
3.85
3.84
3.38
3.36
3.35
O
N
NO2
3b
1.72
2.00
3.93
3.97
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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47.1
O
N
NO2
3b
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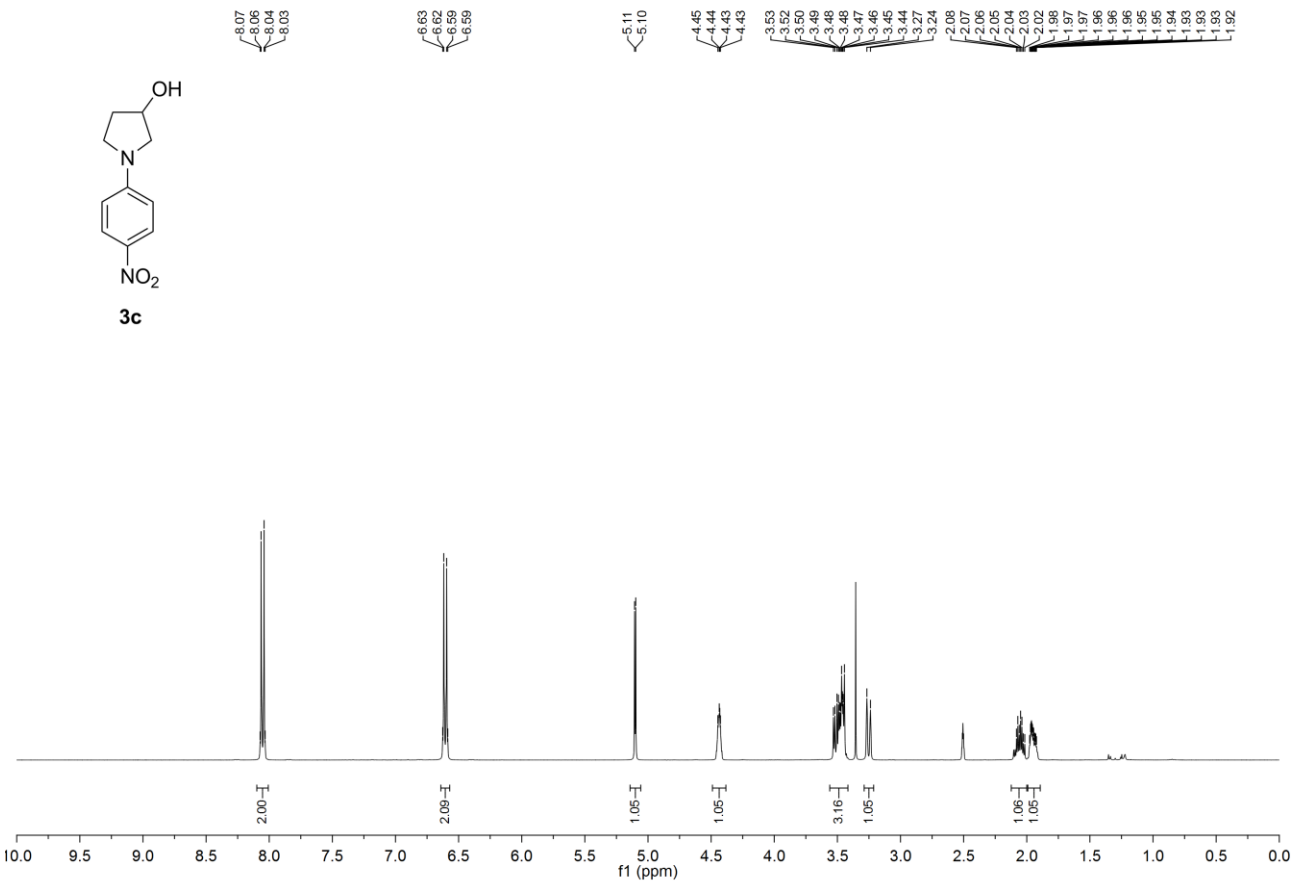
f1 (ppm)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3.44
3.27
3.24
2.08
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1.97
1.96
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1.94
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OH
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3c
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2.09
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1.05
3.16
1.05
1.06
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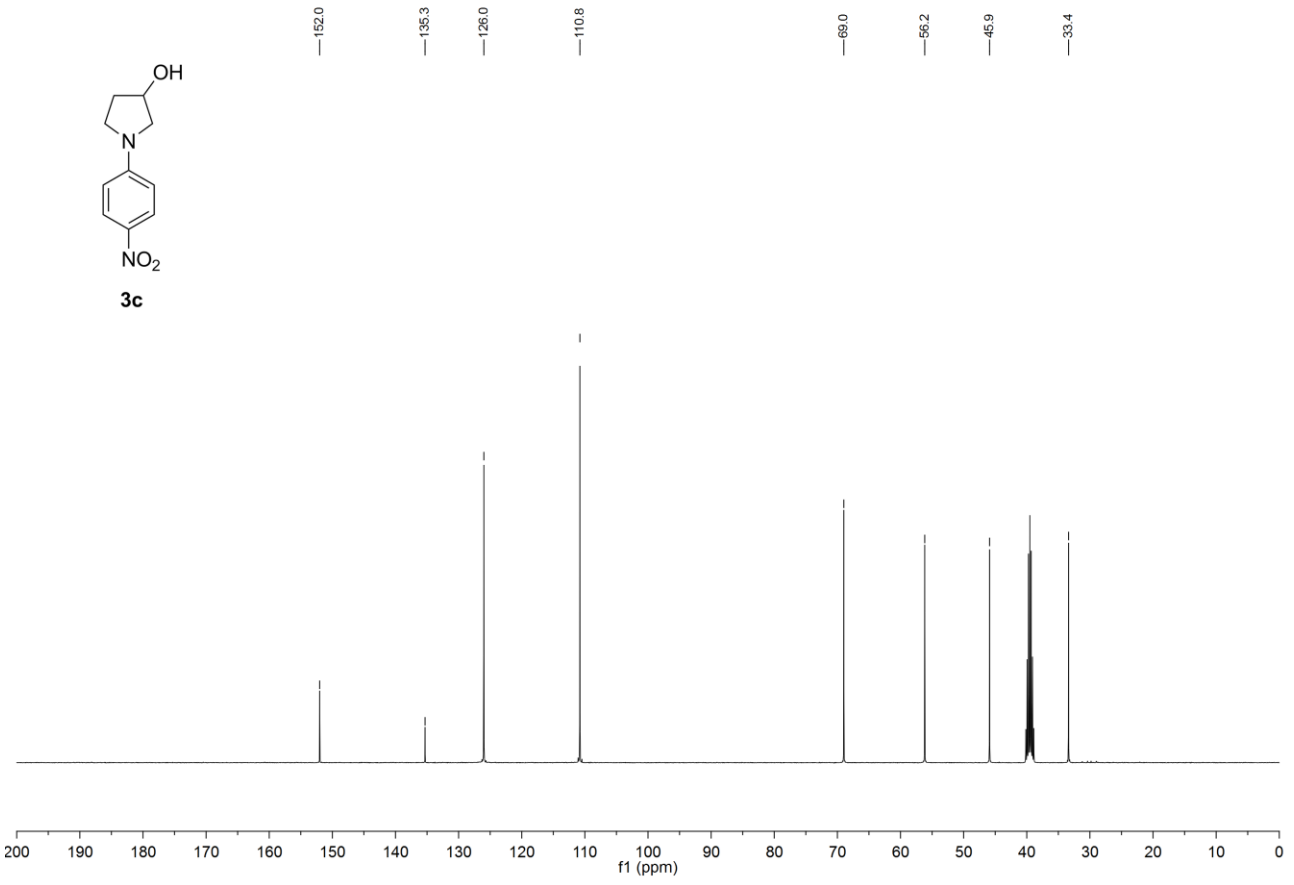
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NO2
3c
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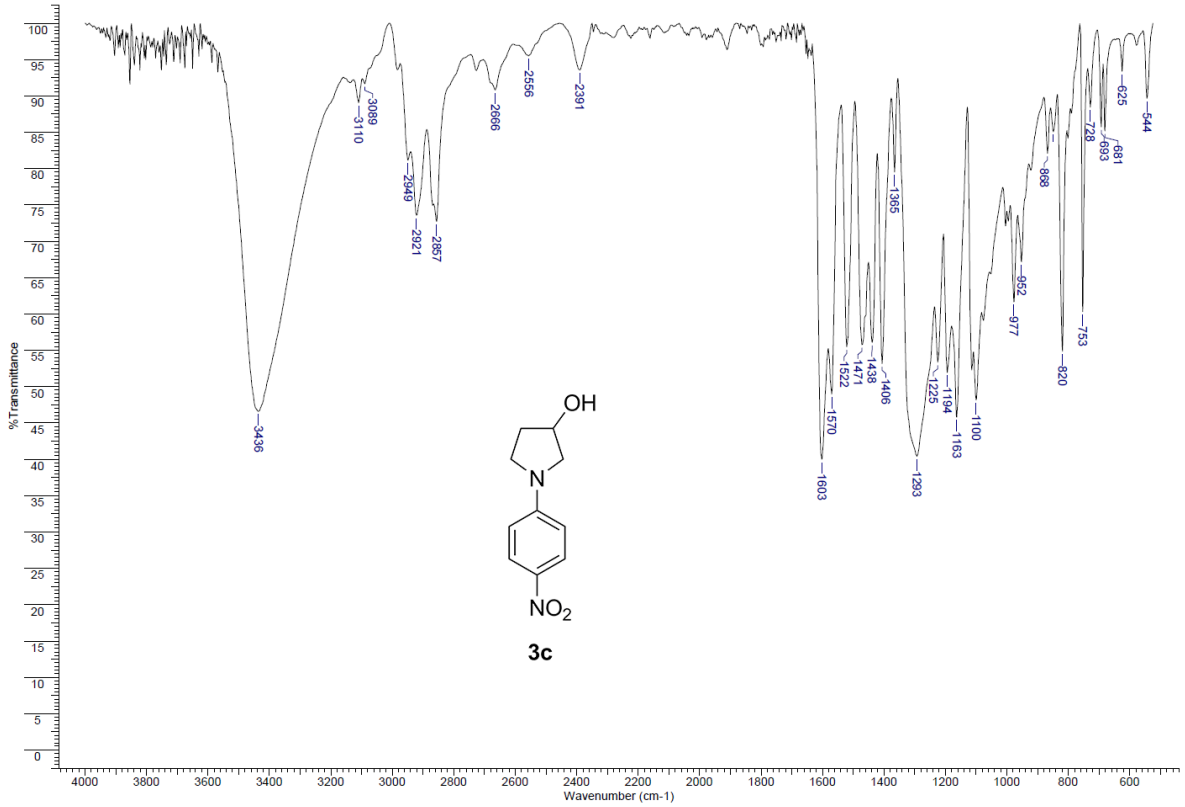
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Wavenumber (cm-1)
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1406
1365
1293
1225
1194
1163
1100
977
952
868
820
753
728
693
681
625
544
OH
N
NO2

3c


8.09
8.08
8.08
8.07
8.06
8.05
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6.52
6.52
6.50
6.50
6.49
4.50
3.23
3.22
3.21
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3.20
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1.66
1.65
1.64
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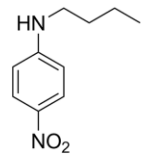
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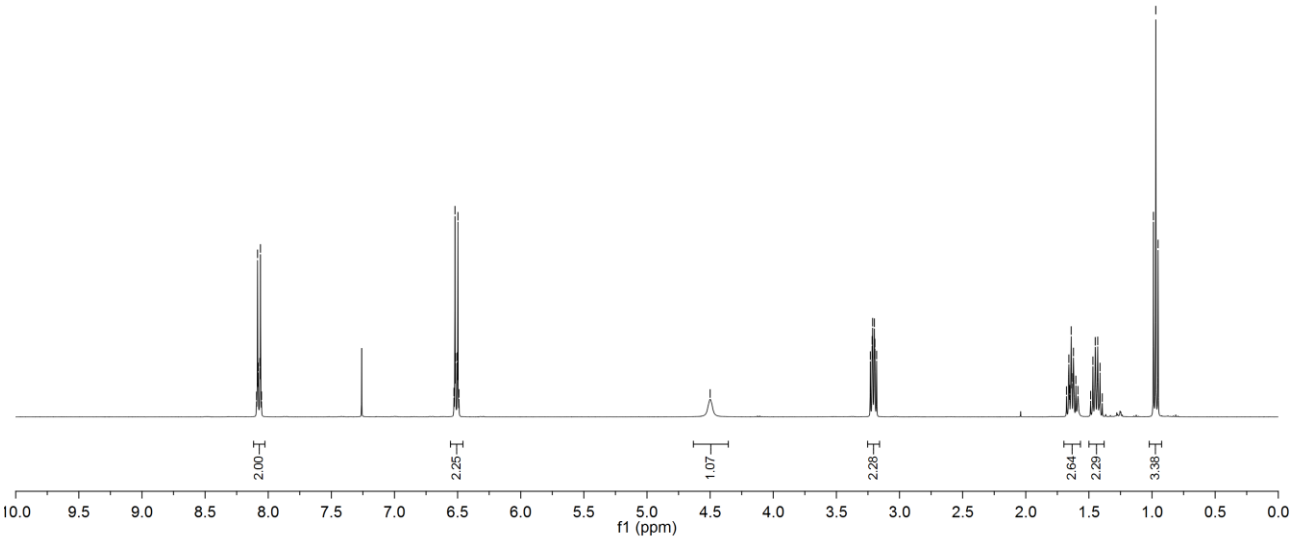
NO2

3d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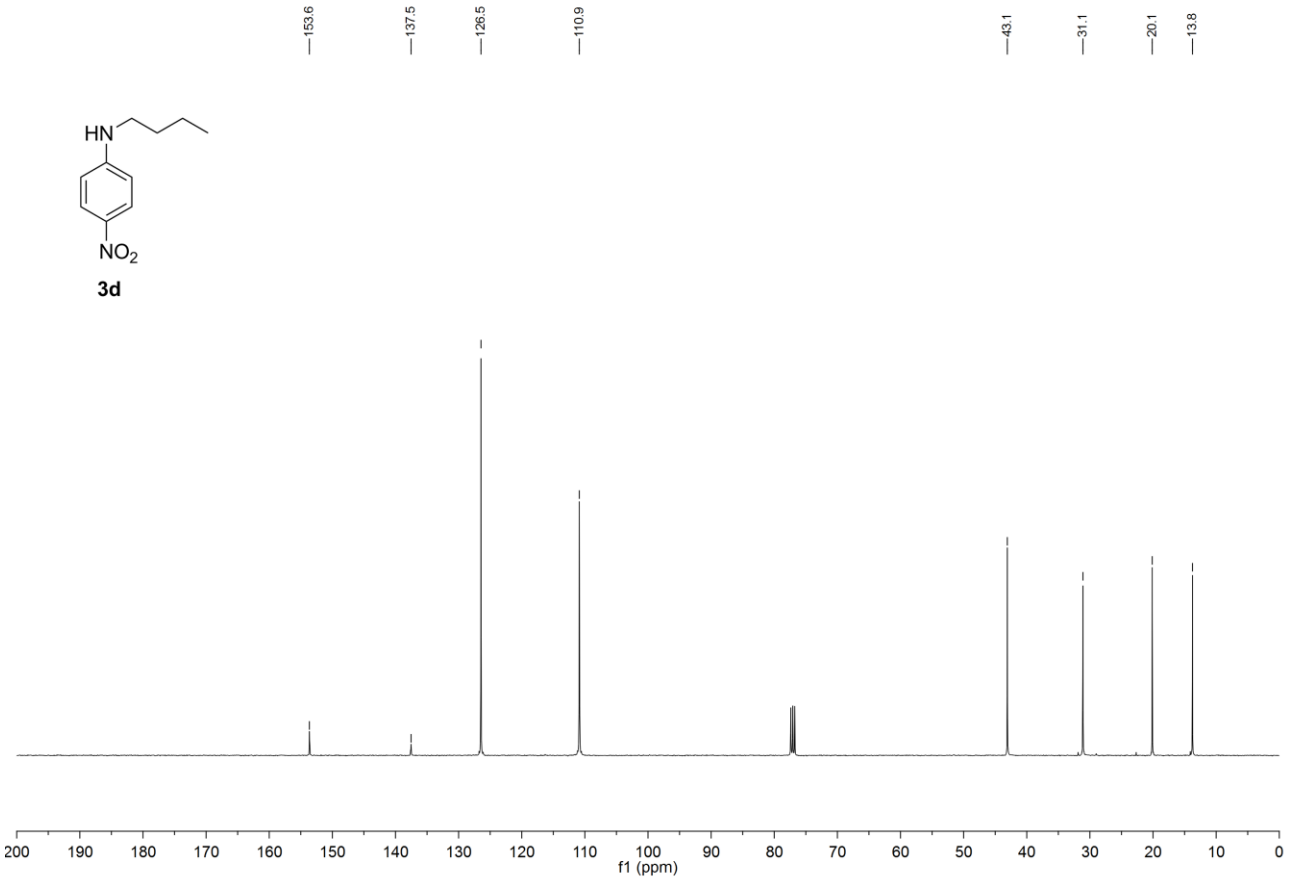
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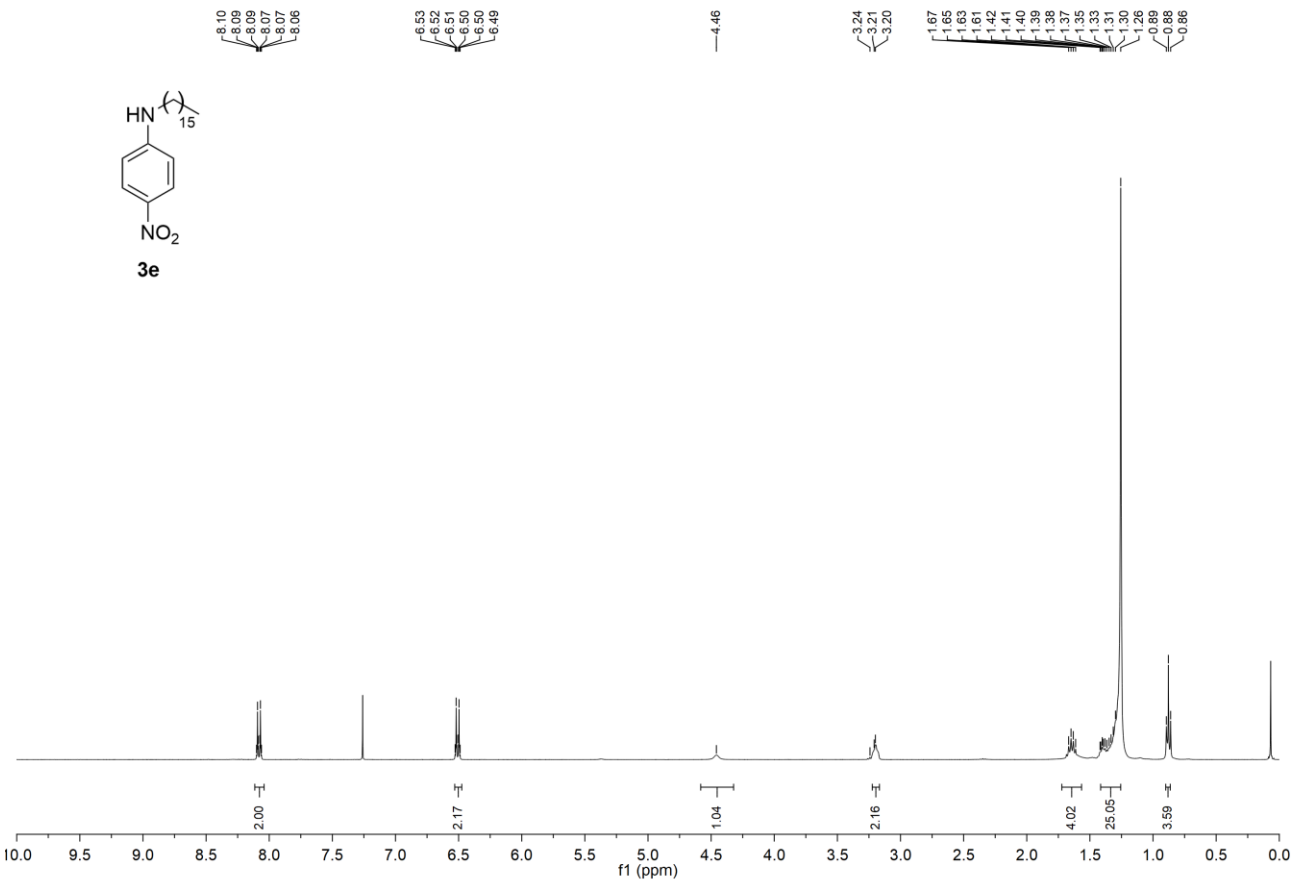
f1 (ppm)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0.88
0.86
HN
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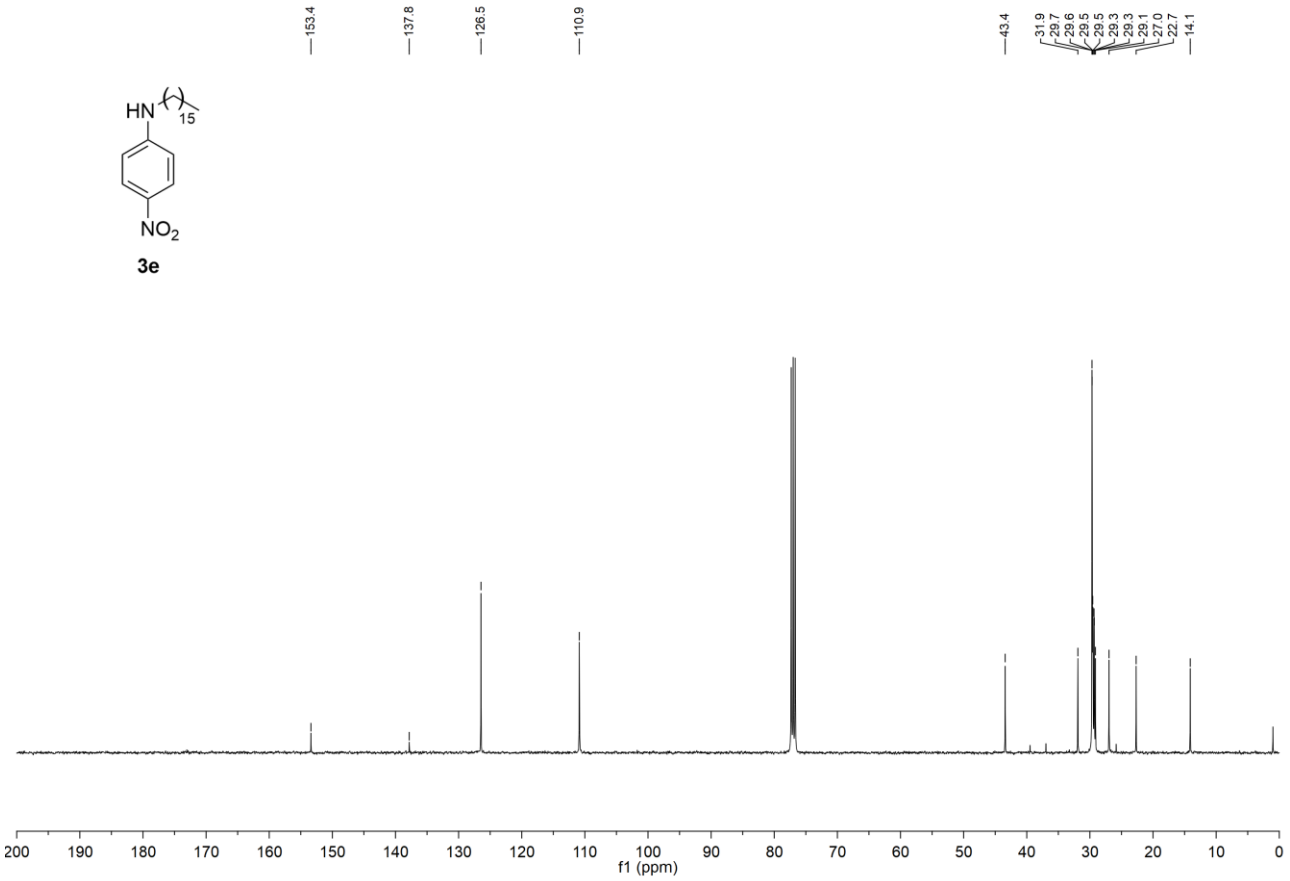
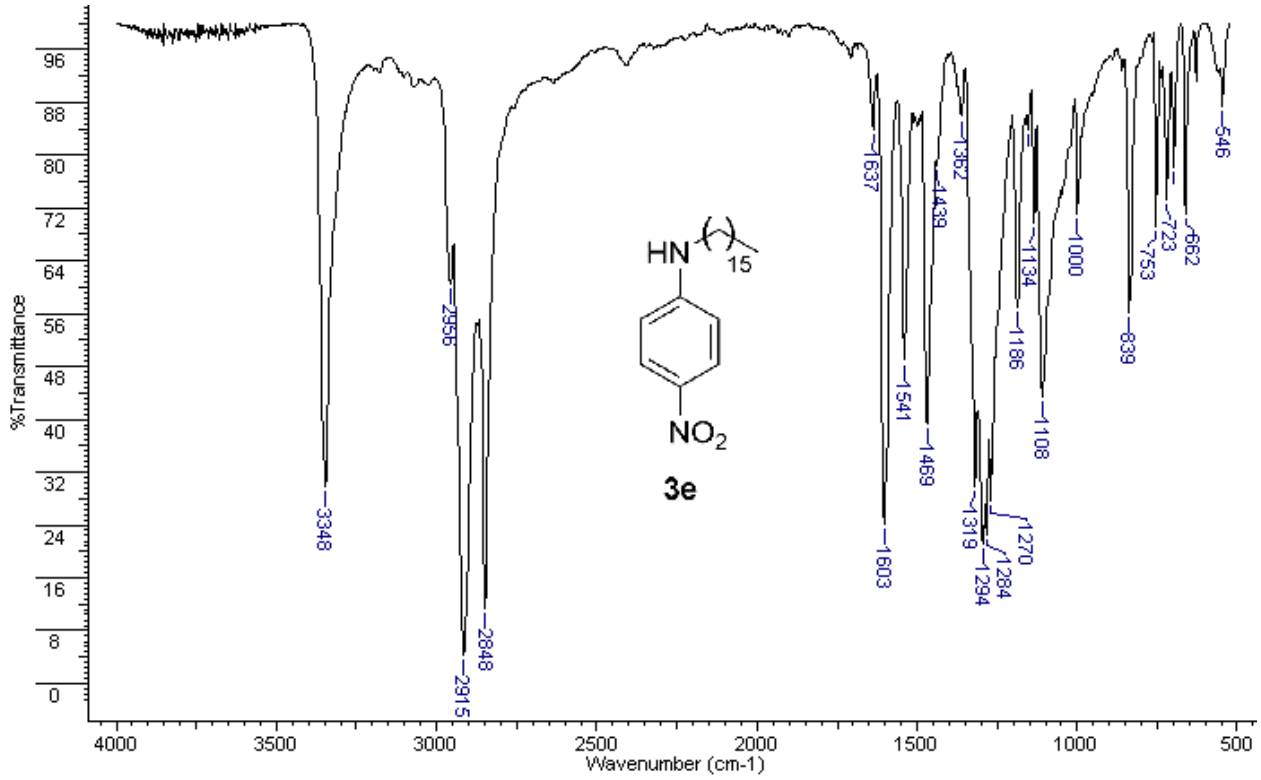
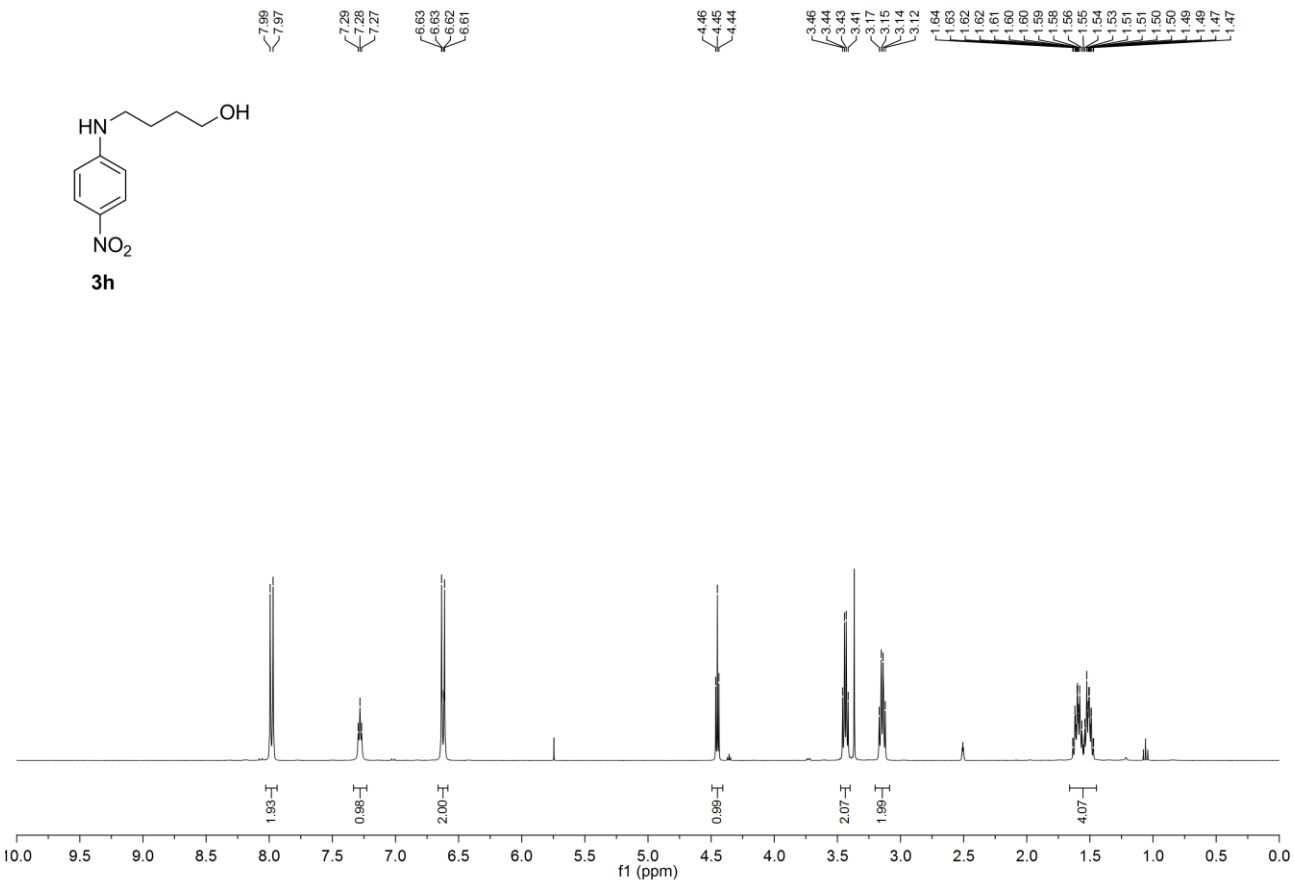
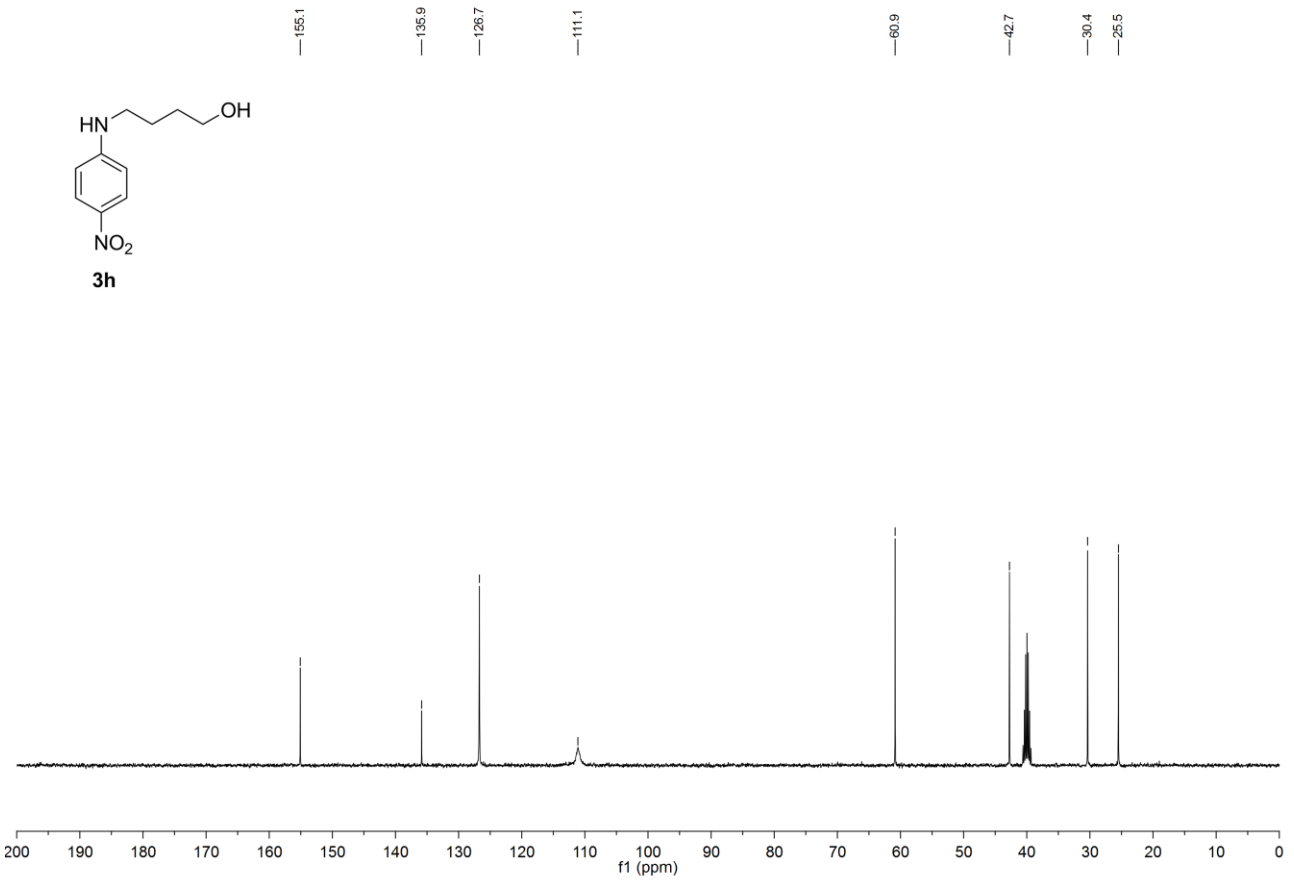
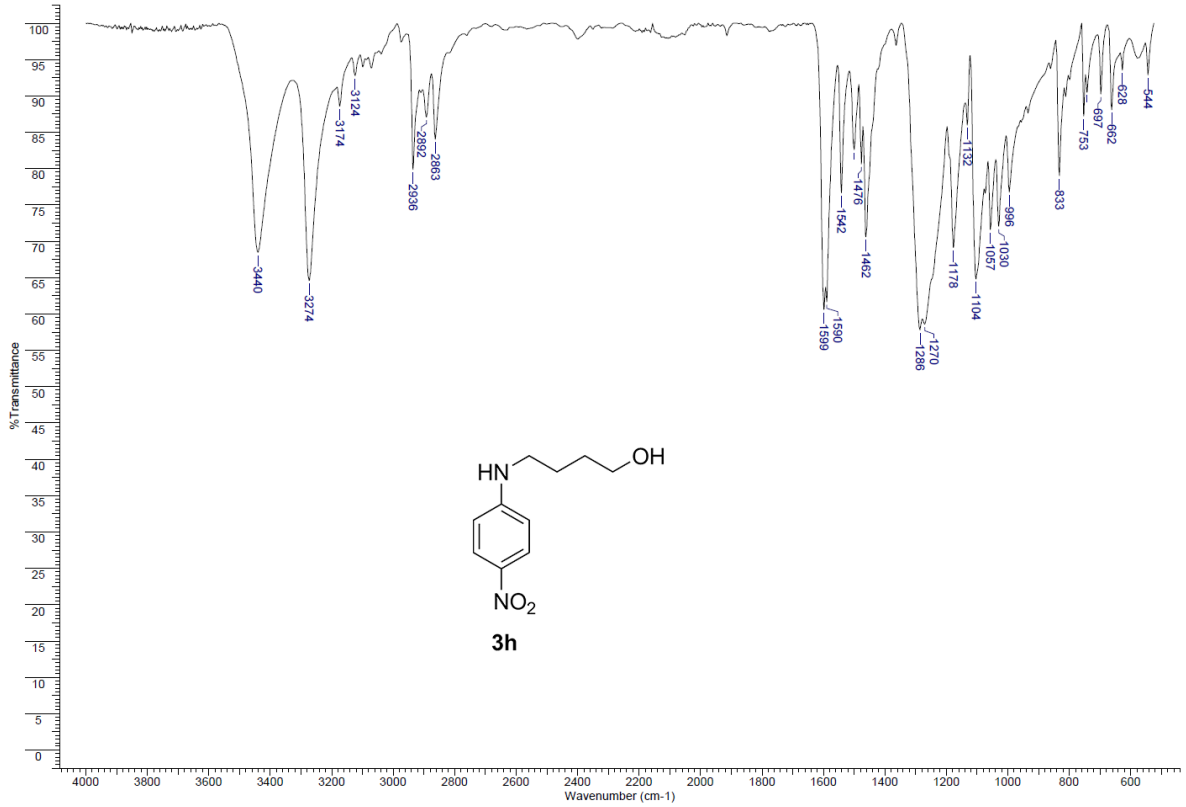
NO2
3e
2.00
2.17
1.04
2.16
4.02
25.05
3.59
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


153.4
137.8
126.5
110.9
43.4
31.9
29.7
29.6
29.5
29.5
29.3
29.3
29.1
27.0
22.7
14.1
HN
15
NO2
3e
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

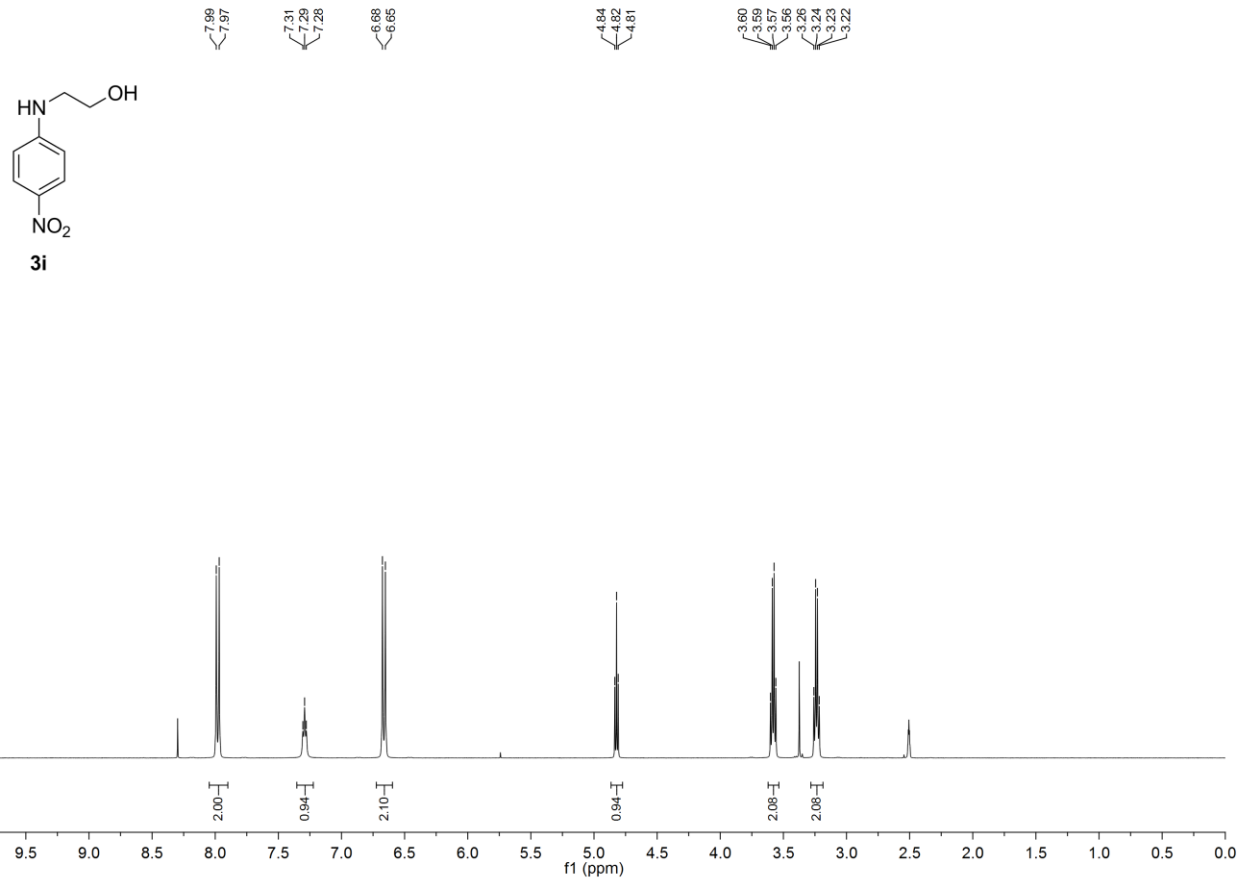

%Transmittance
96
88
80
72
64
56
48
40
32
24
16
8
0
3348
2956
2915
2848
1637
1603
1541
1469
1439
1362
1319
1294
1284
1270
1186
1134
1108
1000
839
753
723
662
546
HN
15
NO2
3e
4000
3500
3000
2500
2000
1500
1000
500
Wavenumber (cm-1)


7.99
7.97
7.29
7.28
7.27
6.63
6.63
6.62
6.61
4.46
4.45
4.44
3.46
3.44
3.43
3.41
3.17
3.15
3.14
3.12
1.64
1.63
1.62
1.62
1.61
1.60
1.60
1.59
1.58
1.56
1.55
1.54
1.53
1.51
1.51
1.50
1.50
1.49
1.49
1.47
1.47
HN
OH
NO2
3h
1.93
0.98
2.00
0.99
2.07
1.99
4.07
f1 (ppm)

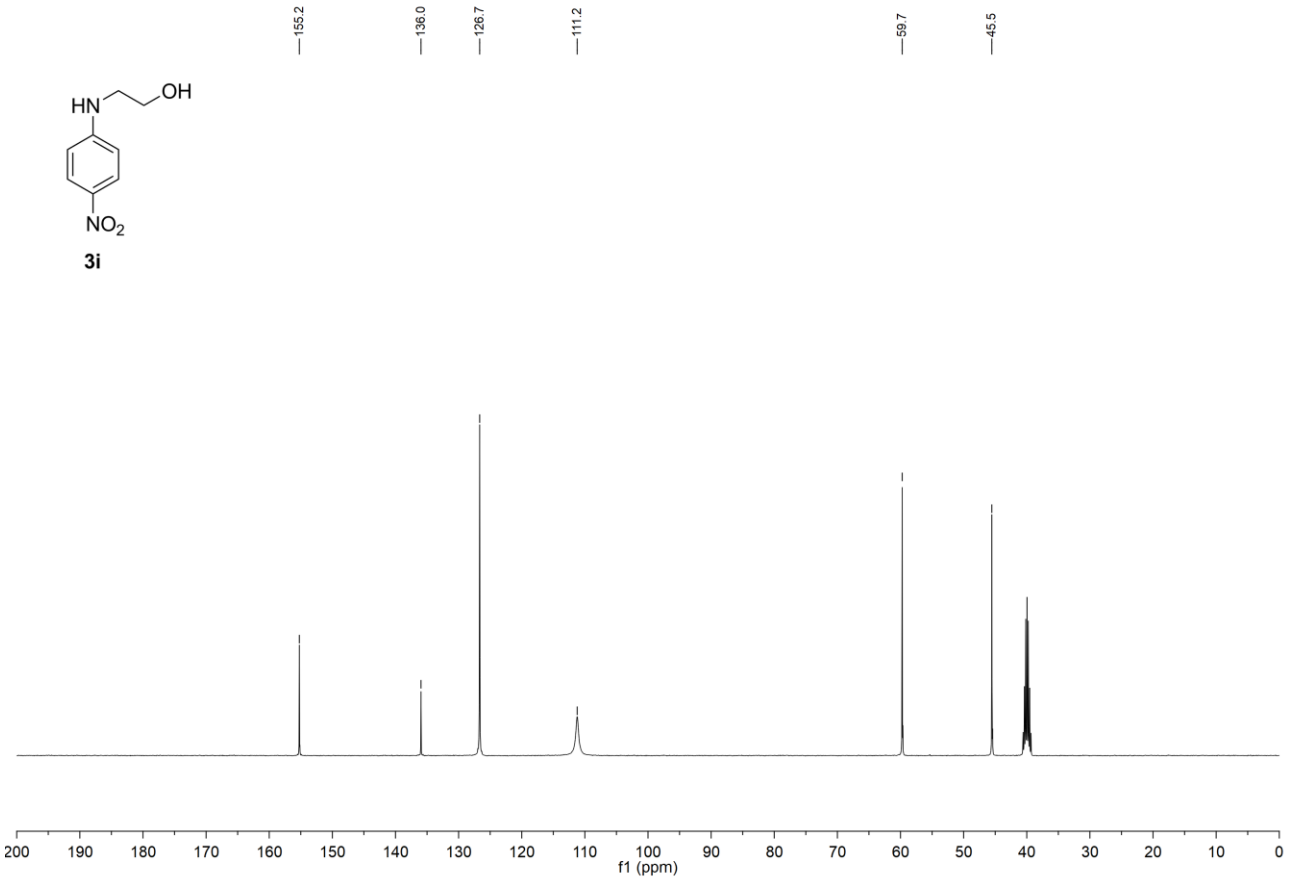

155.1
135.9
126.7
111.1
60.9
42.7
30.4
25.5
HN
OH
NO2
3h
f1 (ppm)

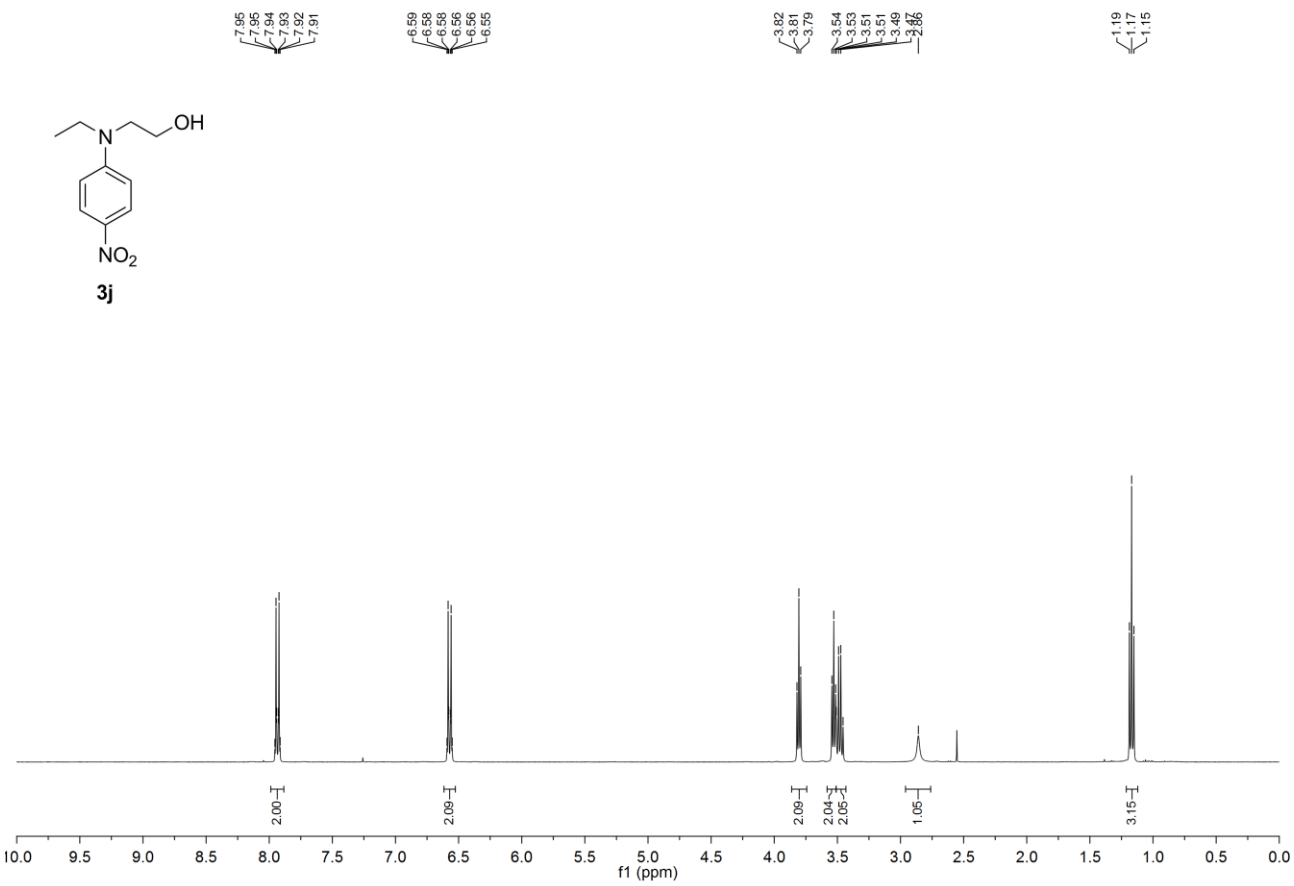

%Transmittance
Wavenumber (cm-1)
3440
3274
3174
3124
2936
2892
2863
1599
1590
1542
1476
1462
1286
1270
1178
1132
1104
1057
1030
996
833
753
697
662
628
544
HN
OH
NO2

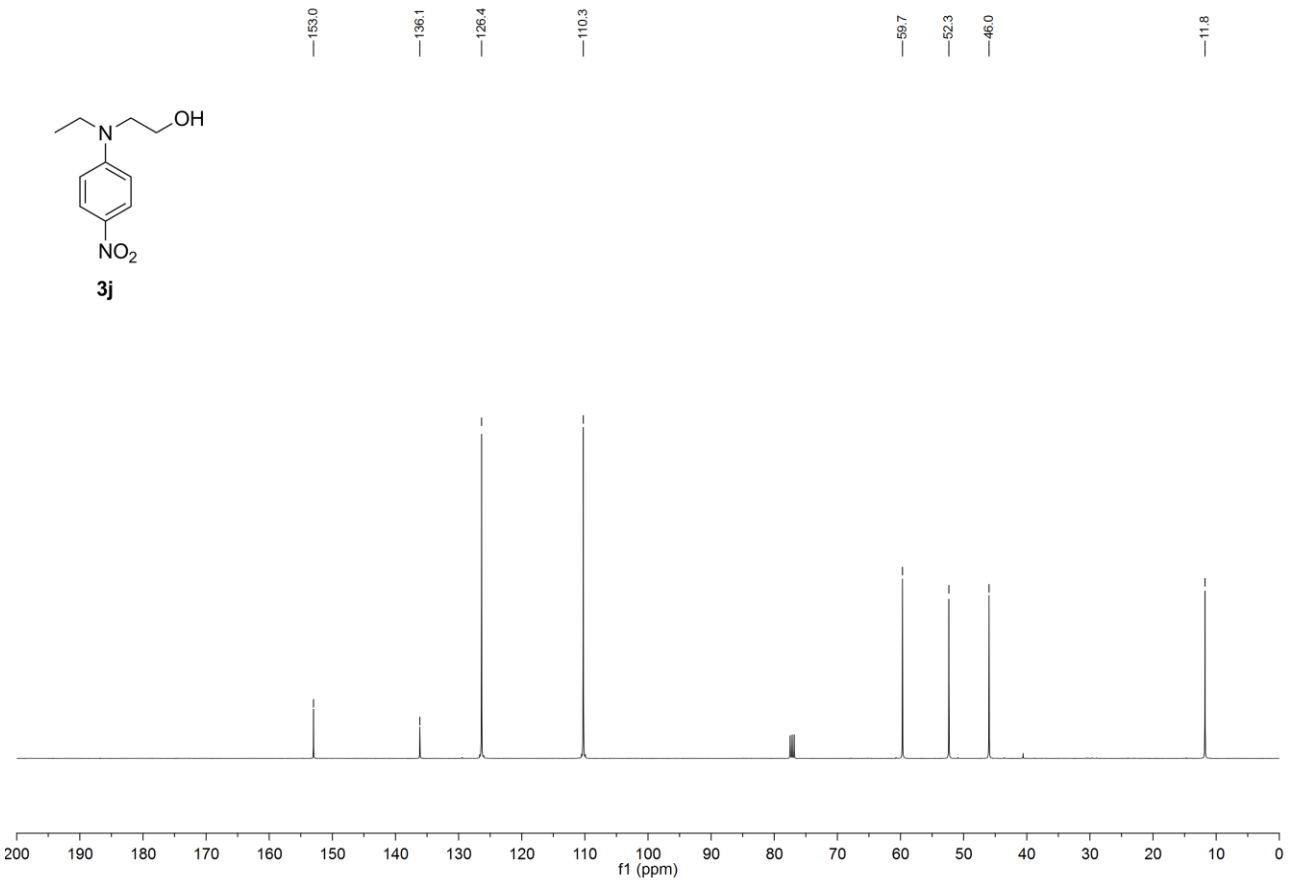
3h

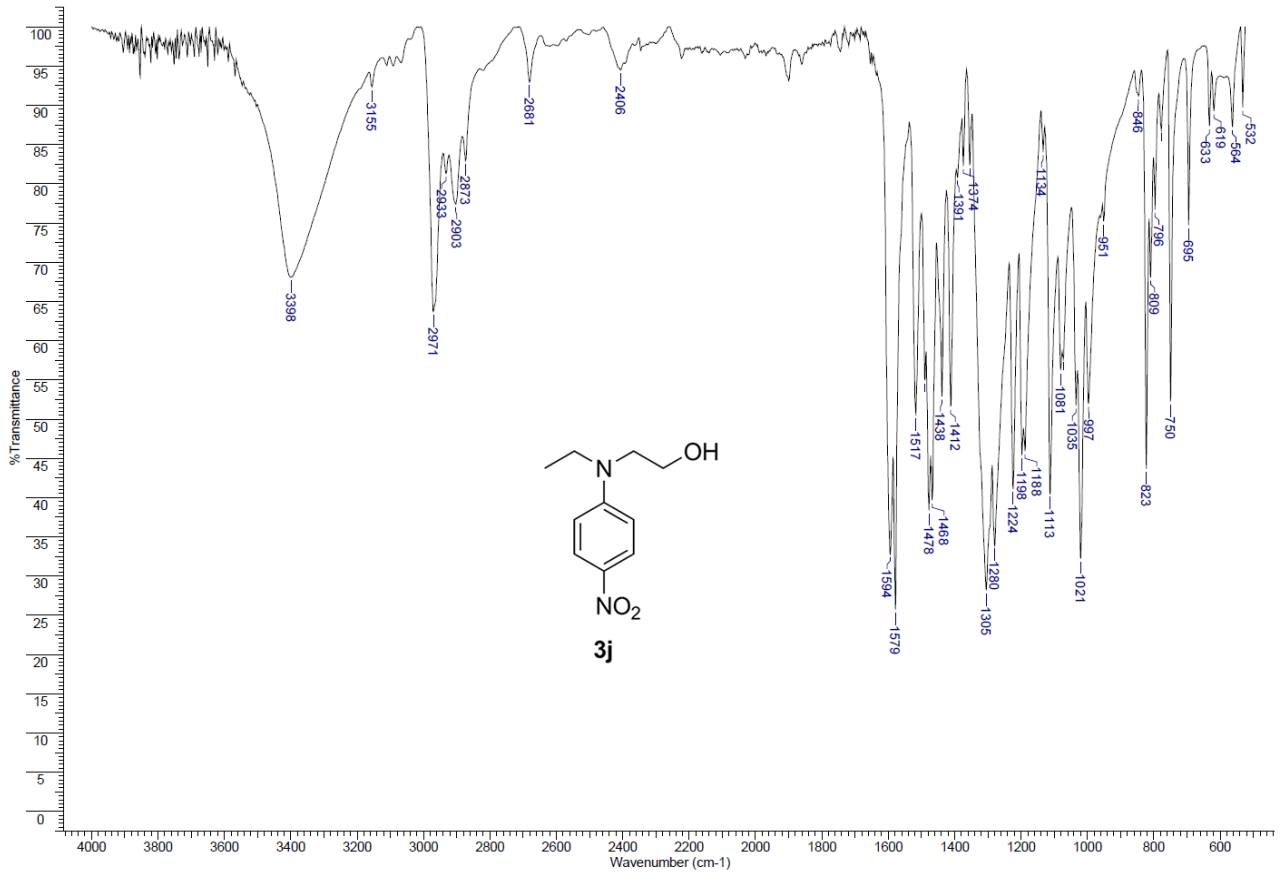

7.99
7.97
7.31
7.29
7.28
6.68
6.65
4.84
4.82
4.81
3.60
3.59
3.57
3.56
3.26
3.24
3.23
3.22
HN
OH
NO2
2.00
0.94
2.10
0.94
2.08
2.08
f1 (ppm)

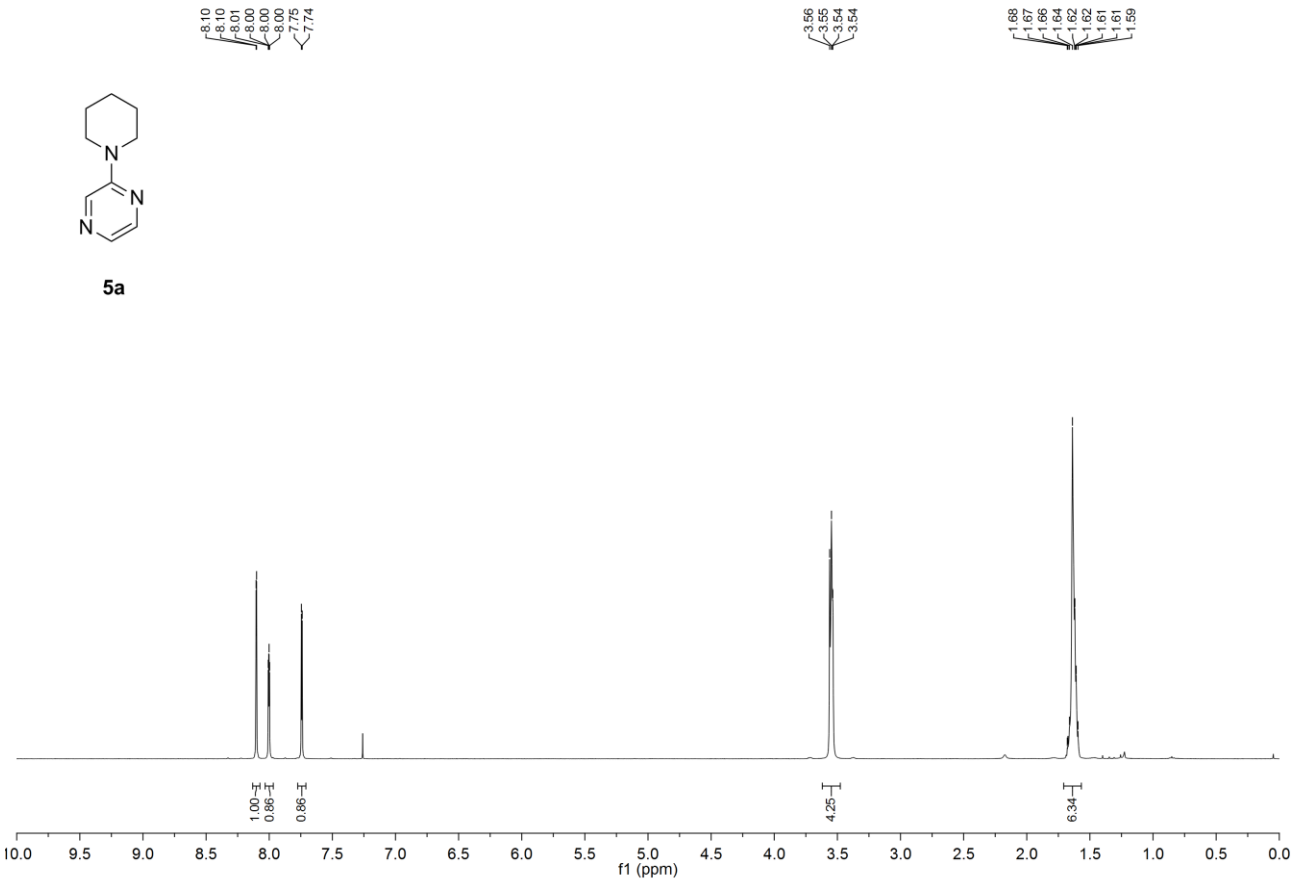
3i

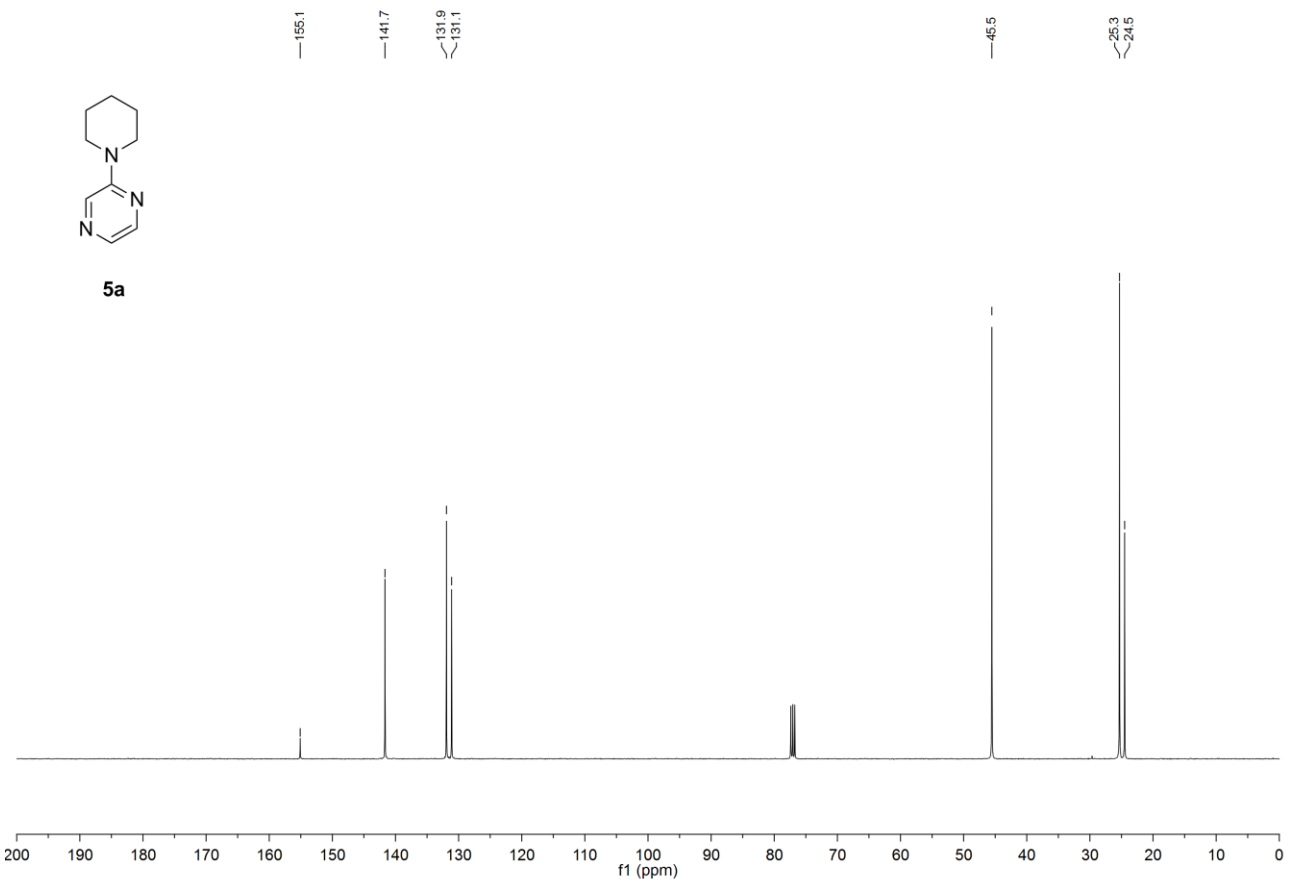

155.2
136.0
126.7
111.2
59.7
45.5
HN
OH
NO2
3i
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

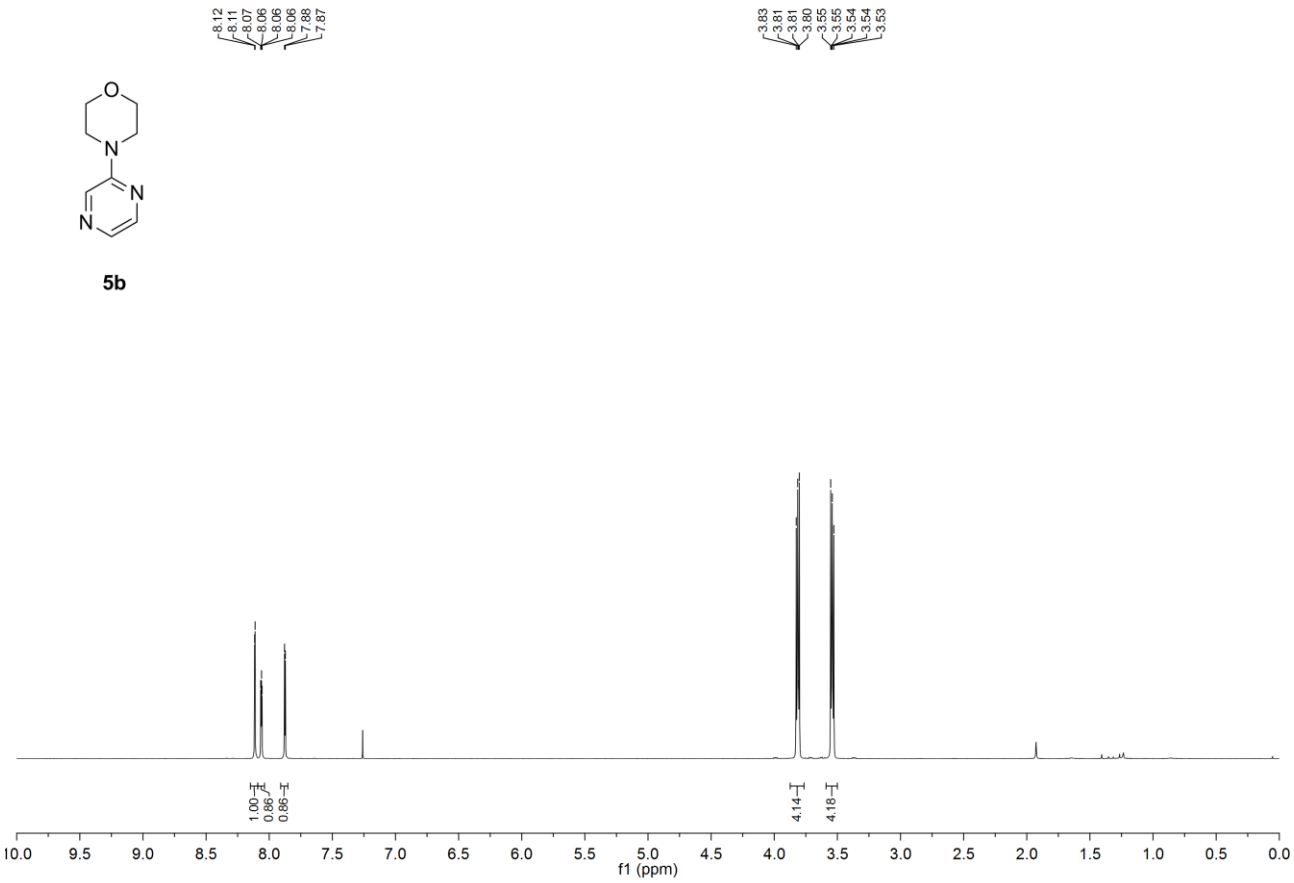

7.95
7.95
7.94
7.93
7.92
7.91
6.59
6.58
6.58
6.56
6.56
6.55
3.82
3.81
3.79
3.54
3.53
3.51
3.51
3.49
2.86
1.19
1.17
1.15
N
OH
NO2
3j
2.00
2.09
2.09
2.04
2.05
1.05
3.15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


153.0
136.1
126.4
110.3
59.7
52.3
46.0
11.8
OH
N
NO2
3j
f1 (ppm)

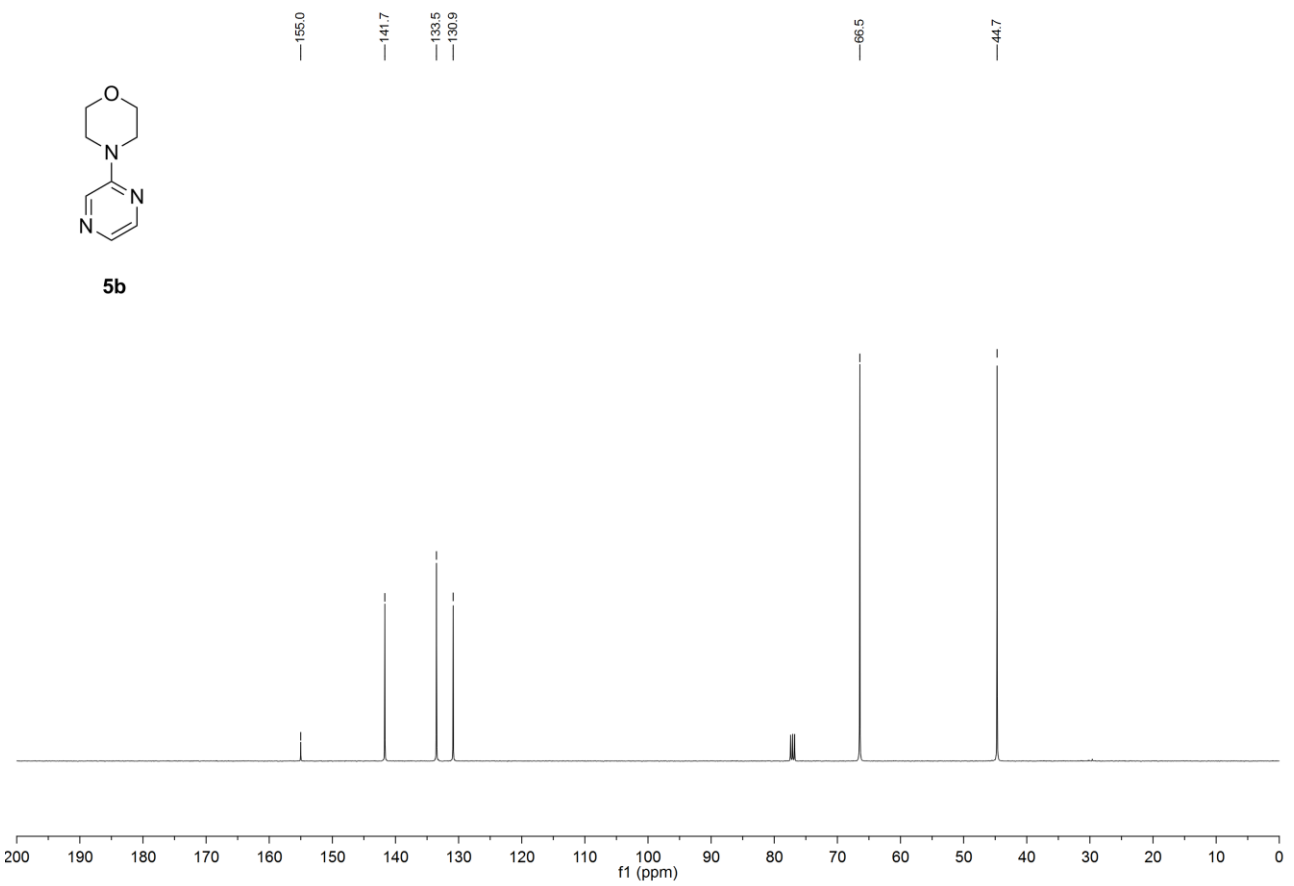

%Transmittance
Wavenumber (cm-1)
3398
3155
2971
2933
2903
2873
2681
2406
1594
1579
1517
1478
1468
1438
1412
1391
1374
1305
1280
1224
1198
1188
1134
1113
1081
1035
1021
997
951
846
823
809
796
750
695
633
619
564
532
OH
N
NO2
3j


8.10
8.10
8.01
8.00
8.00
8.00
7.75
7.74
3.56
3.55
3.54
3.54
1.68
1.67
1.66
1.64
1.62
1.62
1.61
1.61
1.59
N
N
N
5a
1.00
0.86
0.86
4.25
6.34
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

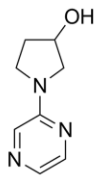

155.1
141.7
131.9
131.1
45.5
25.3
24.5
N
N
N
5a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.12
8.11
8.07
8.06
8.06
8.06
7.88
7.87
3.83
3.81
3.81
3.80
3.55
3.55
3.54
3.54
3.53
O
N
N
N
1.00
0.86
0.86
4.14
4.18
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

5b

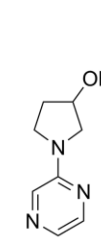

155.0
141.7
133.5
130.9
66.5
44.7
O
N
N
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

5b


OH
N
N
N

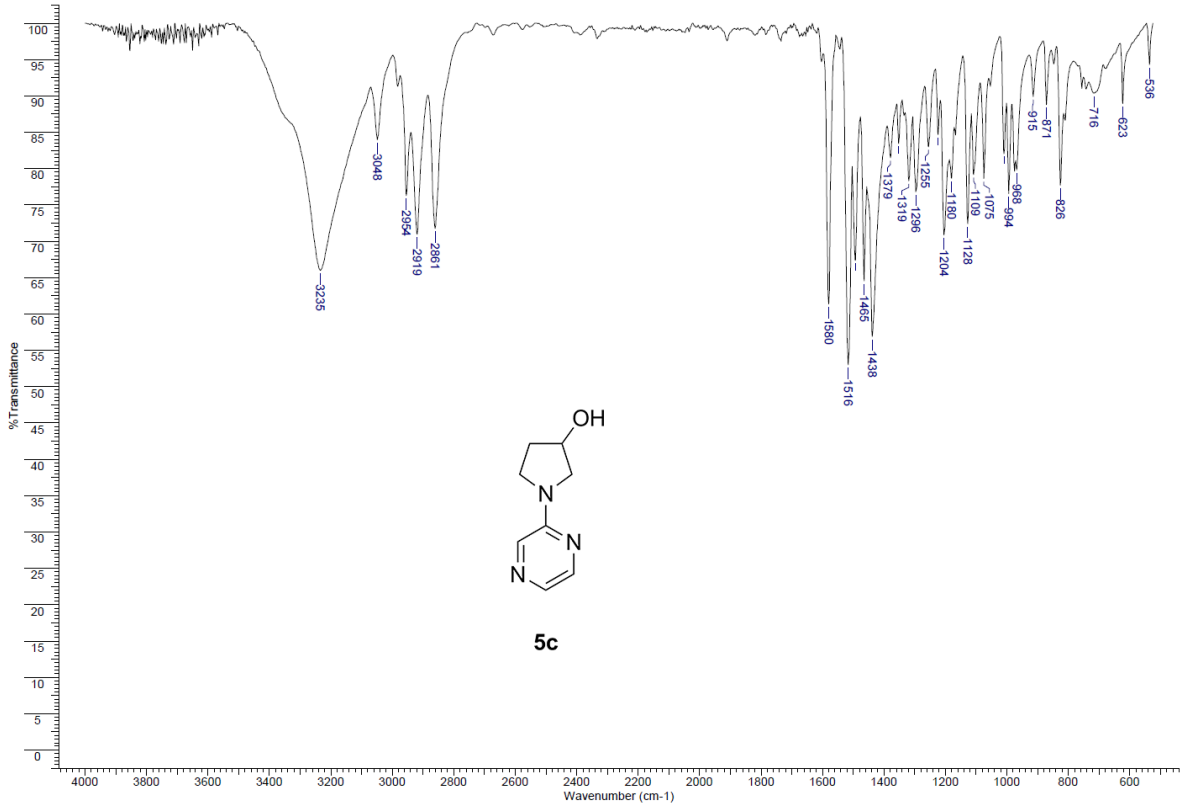
5c

7.98
7.98
7.97
7.97
7.80
7.80
7.72
7.72
4.62
4.61
4.60
4.60
4.60
4.59
3.61
3.60
3.60
3.59
3.58
3.57
3.56
3.56
3.55
3.55
3.52
2.16
2.15
2.14
2.13
2.12
2.12
2.11
2.10
2.10
2.10
2.09
2.09
2.09
2.08
2.08
2.07
2.07
2.06
2.06
1.00
1.07
1.00
1.09
4.58
0.94
2.25
f1 (ppm)


OH
N
N
N

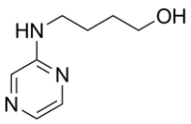
5c

153.0
142.2
131.0
130.3
70.2
54.8
44.3
33.9
f1 (ppm)

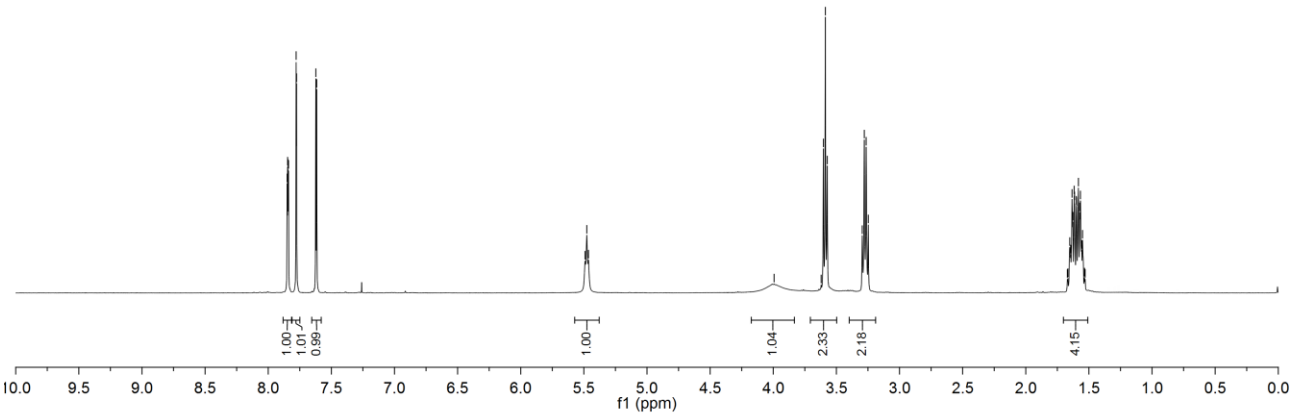

%Transmittance
Wavenumber (cm-1)
3235
3048
2954
2919
2861
1580
1516
1465
1438
1379
1319
1296
1255
1204
1180
1128
1109
1075
994
969
915
871
826
716
623
536
OH
N
N
N

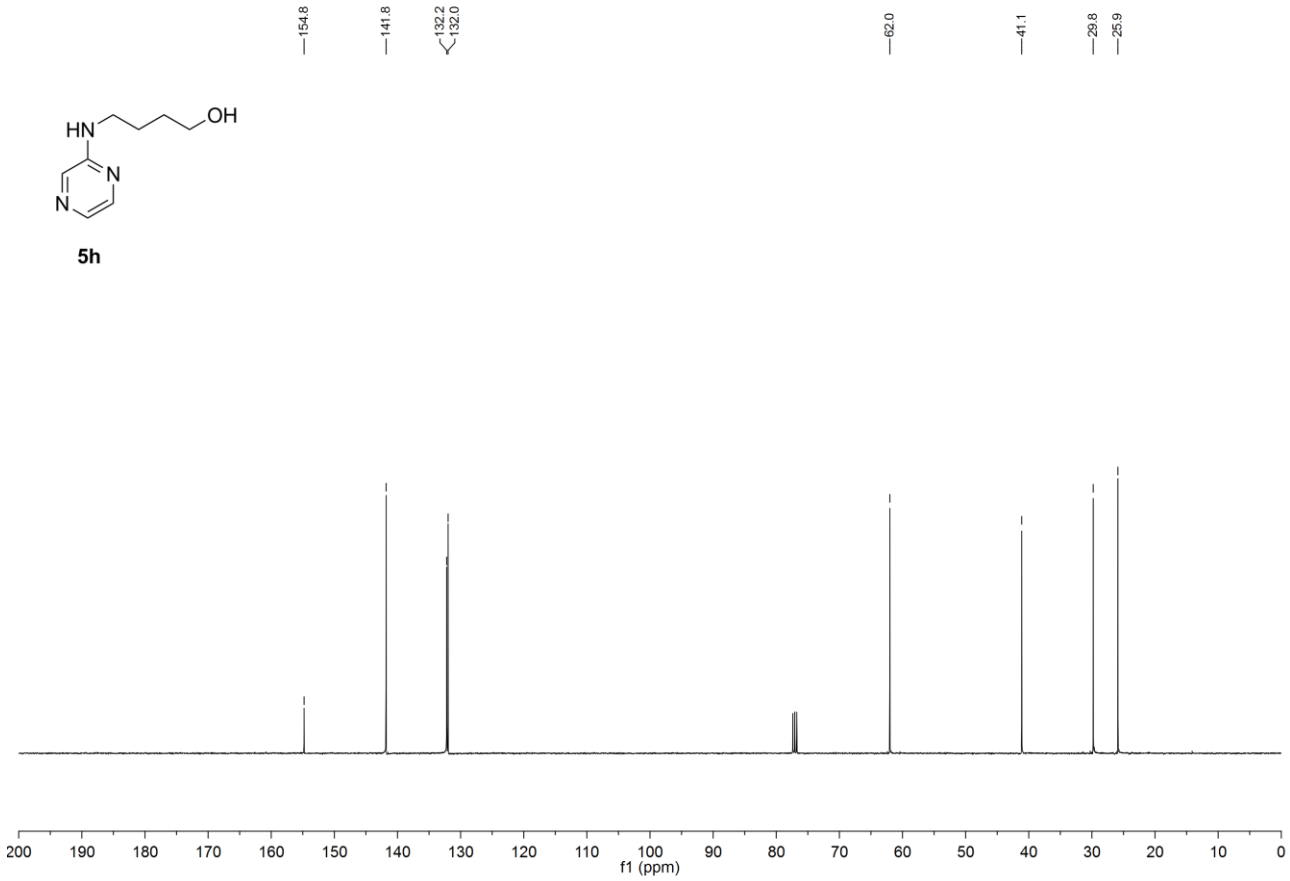
5c

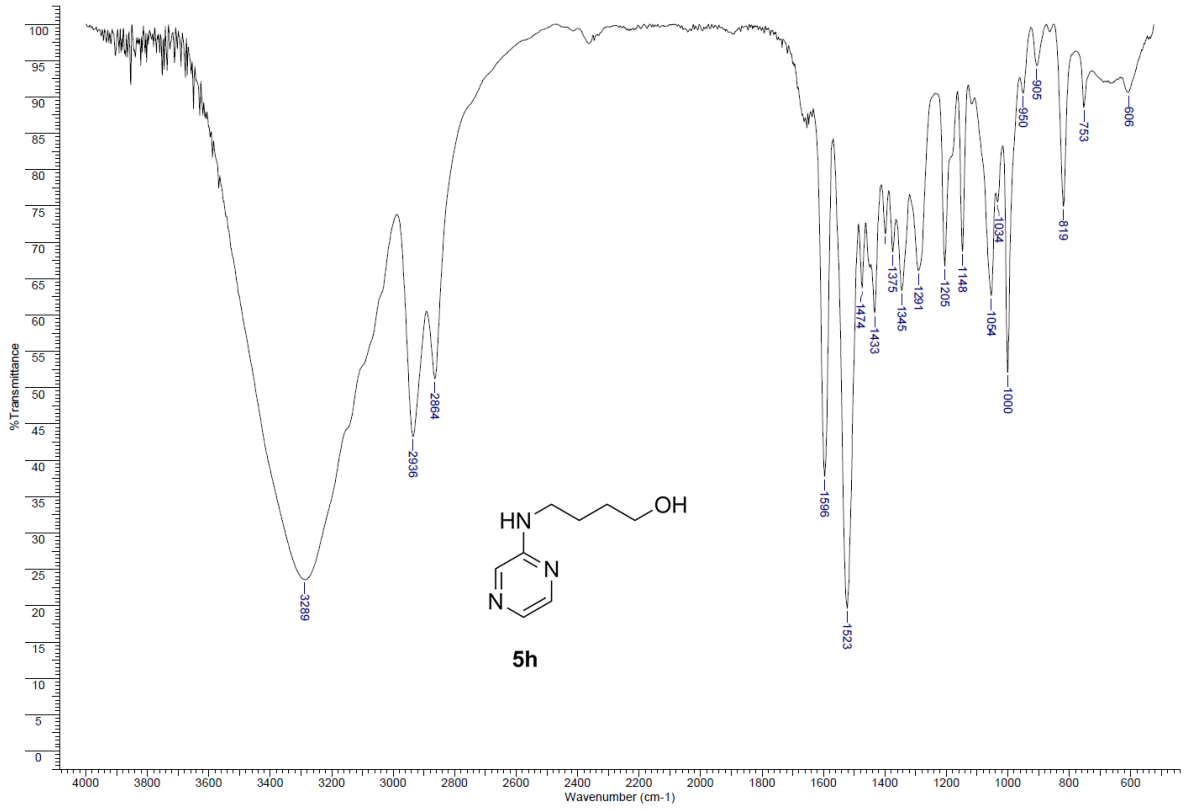

7.85
7.85
7.84
7.84
7.78
7.78
7.62
7.62
5.49
5.48
5.46
3.99
3.62
3.60
3.59
3.57
3.30
3.28
3.26
3.25
1.67
1.67
1.65
1.64
1.63
1.63
1.62
1.61
1.60
1.60
1.58
1.57
1.57
1.56
1.55
1.53
1.53

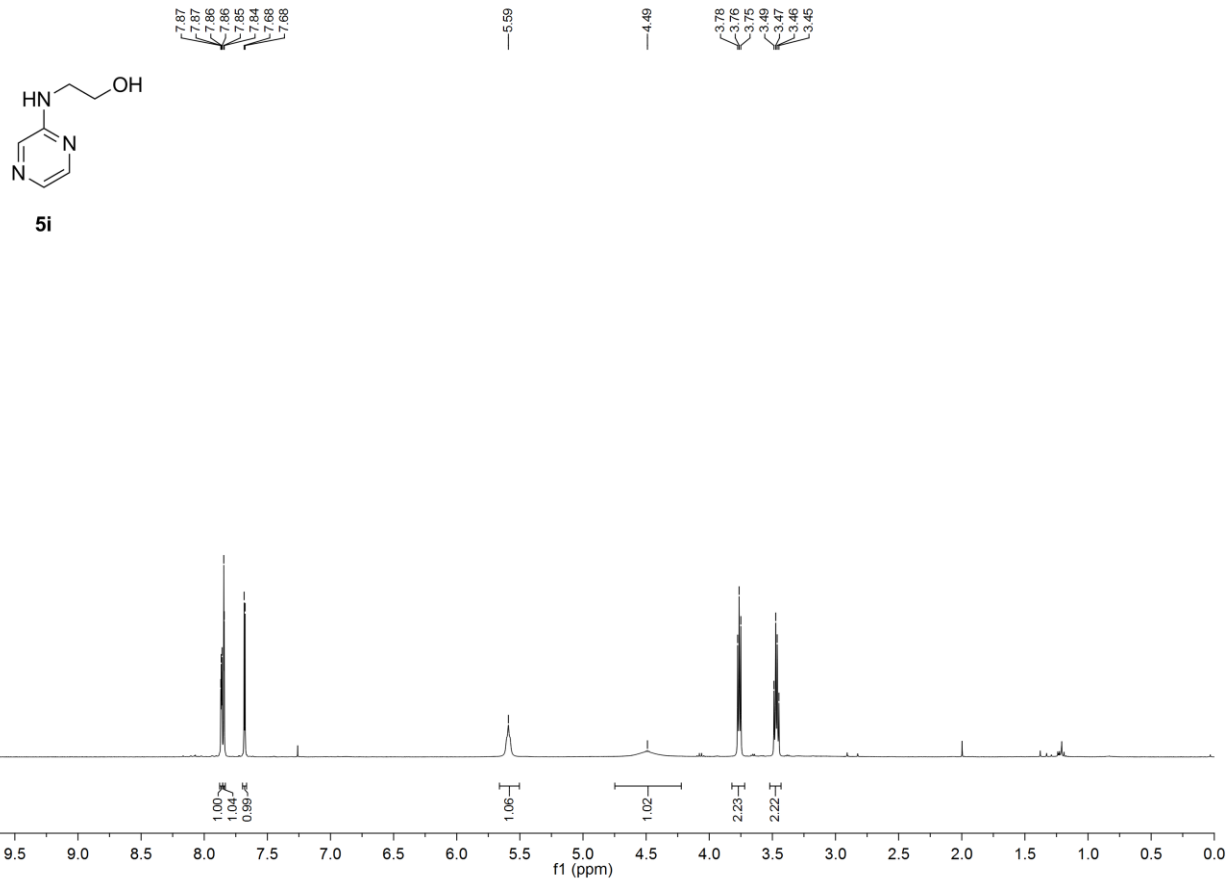

HN
OH
N
N

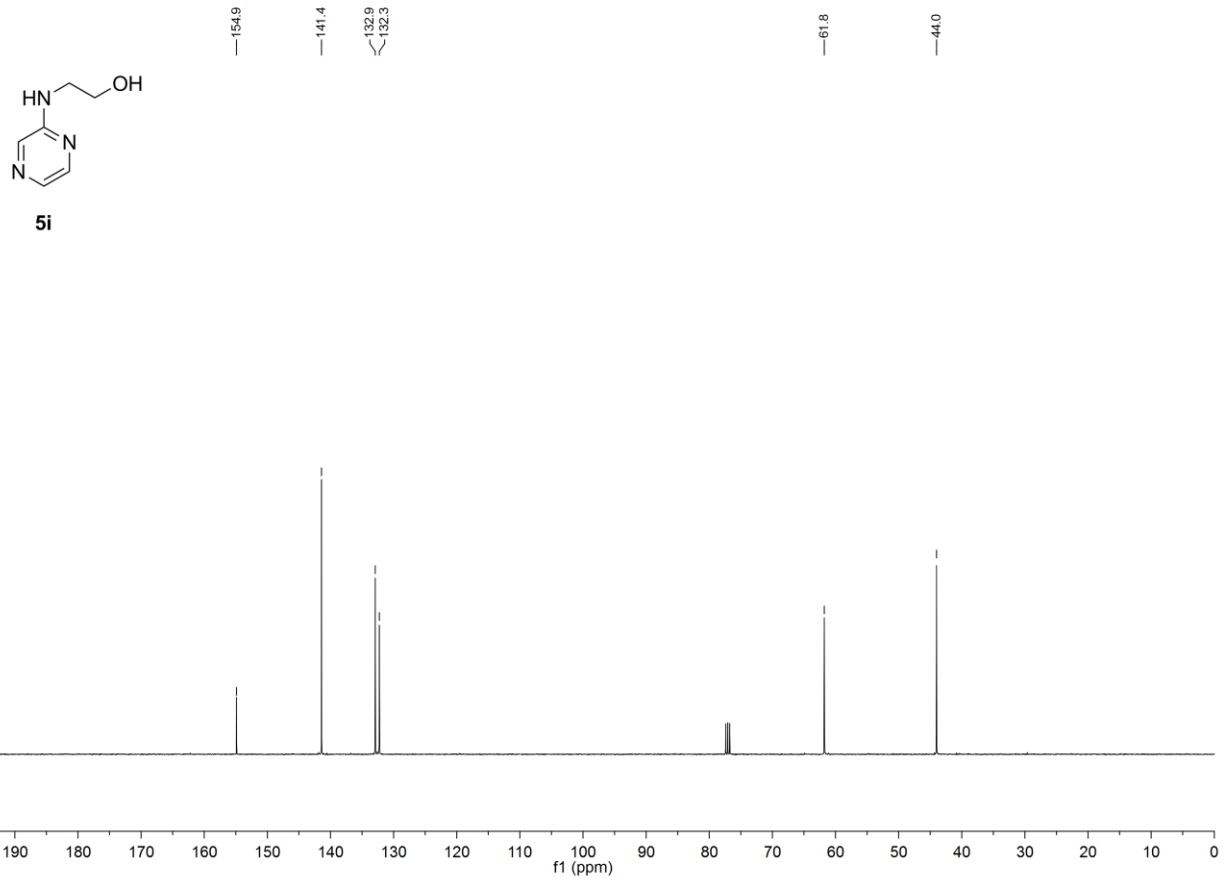
5h

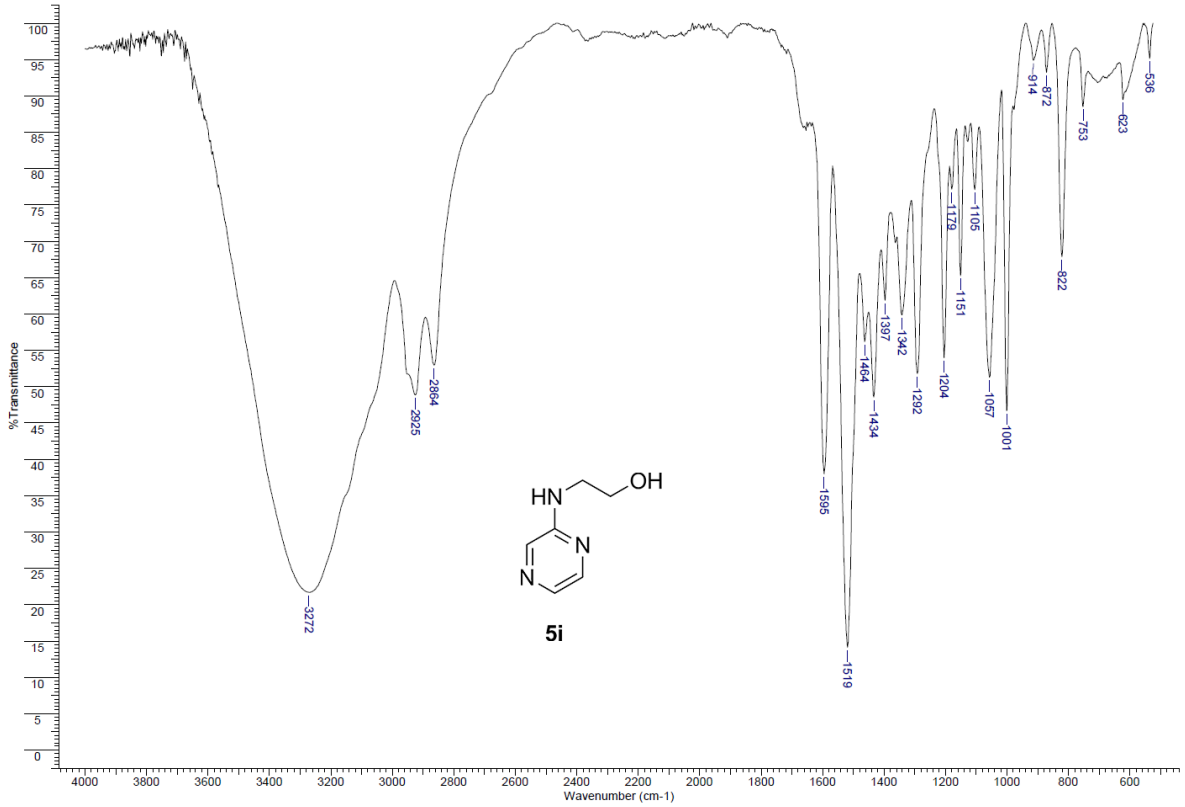

1.00
1.01
0.99
1.00
1.04
2.33
2.18
4.15
f1 (ppm)


154.8
141.8
132.2
132.0
62.0
41.1
29.8
25.9
HN
OH
N
N
5h
f1 (ppm)

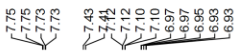

%Transmittance
Wavenumber (cm-1)
3289
2936
2864
1596
1523
1474
1433
1375
1345
1291
1205
1148
1054
1034
1000
950
905
819
753
606
HN
OH
N
N
5h

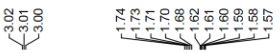

7.87
7.87
7.86
7.86
7.85
7.84
7.68
7.68
5.59
4.49
3.78
3.76
3.75
3.49
3.47
3.46
3.45
HN
OH
N
N
5i
1.00
1.04
0.99
1.06
1.02
2.23
2.22
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

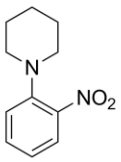

154.9
141.4
132.9
132.3
61.8
44.0
HN
OH
N
N
5i
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


%Transmittance
Wavenumber (cm-1)
3272
2925
2864
1595
1519
1464
1434
1397
1342
1292
1204
1179
1151
1105
1057
1001
914
872
822
753
623
536
HN
OH
N
N

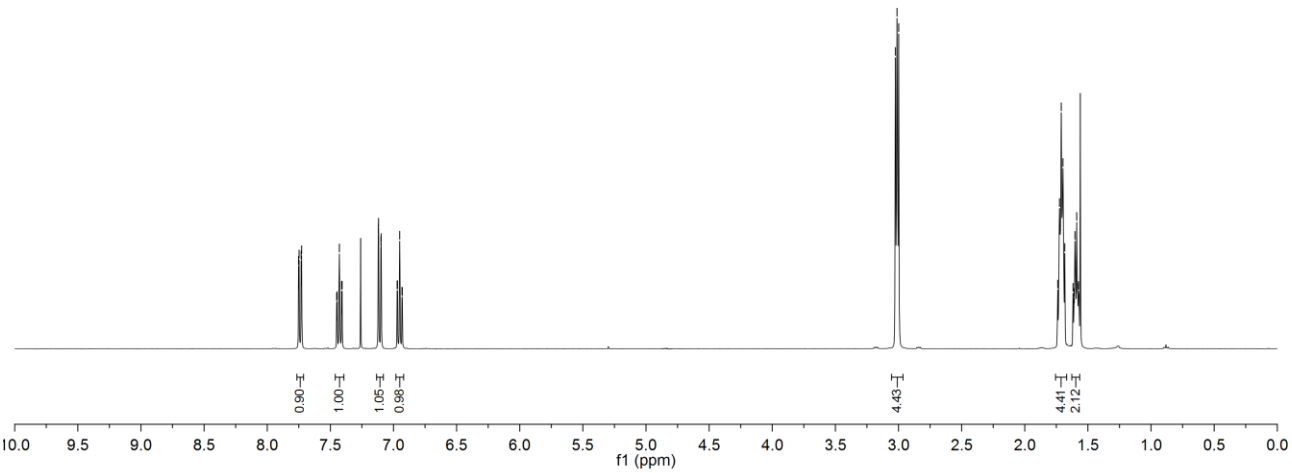
5i

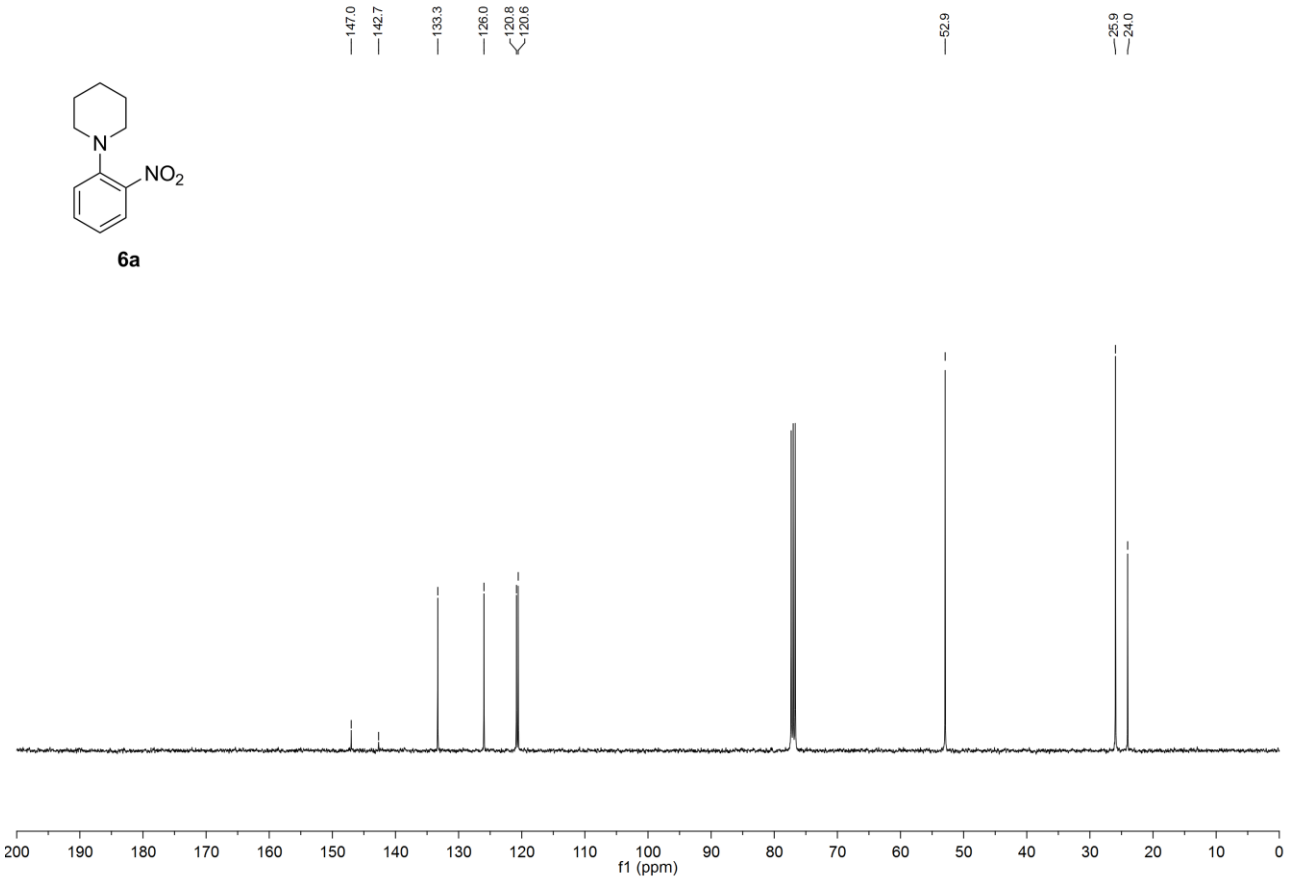

7.75
7.75
7.73
7.73
7.43
7.12
7.10
6.97
6.95
6.93
6.93

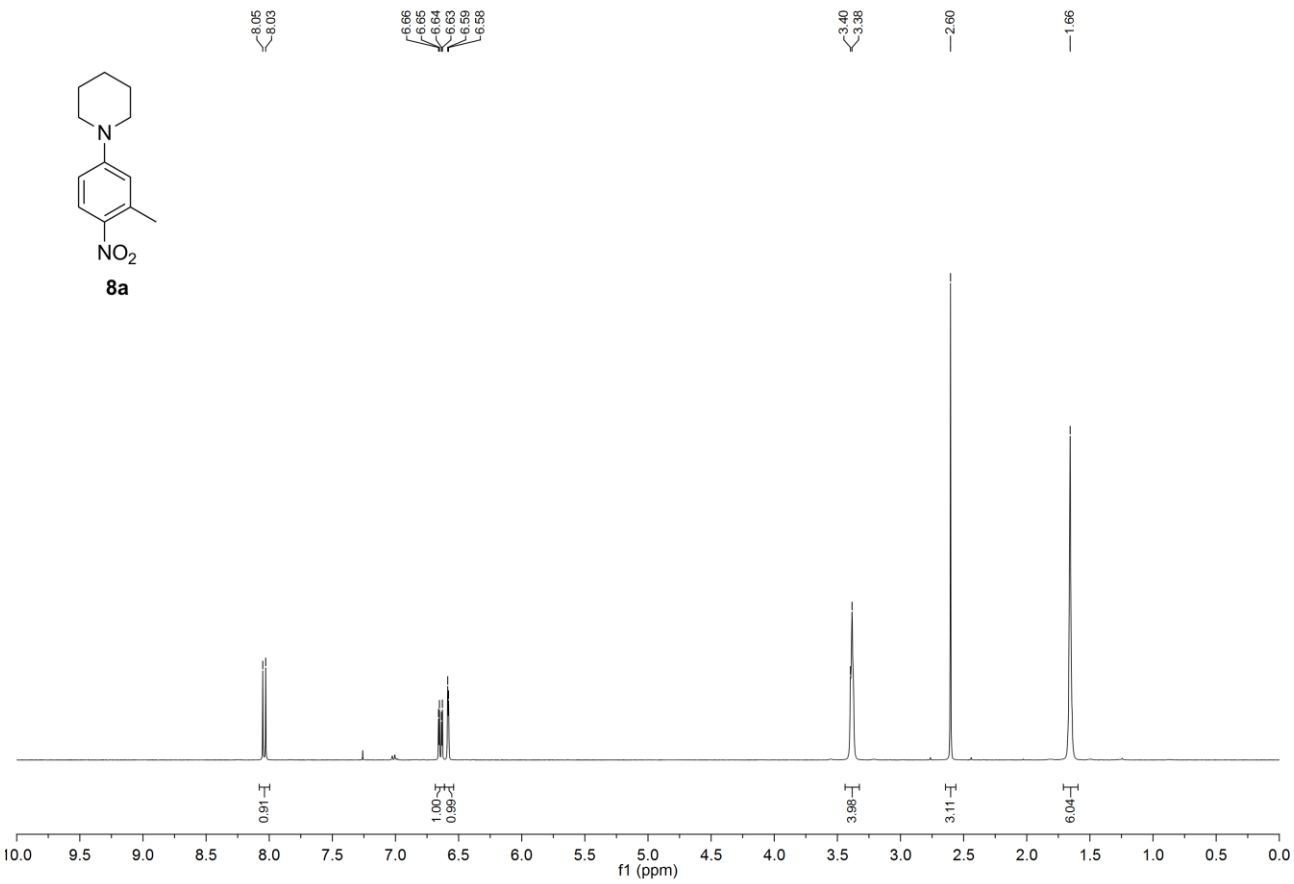

3.02
3.01
3.00
1.74
1.73
1.71
1.70
1.68
1.62
1.61
1.60
1.59
1.58
1.57

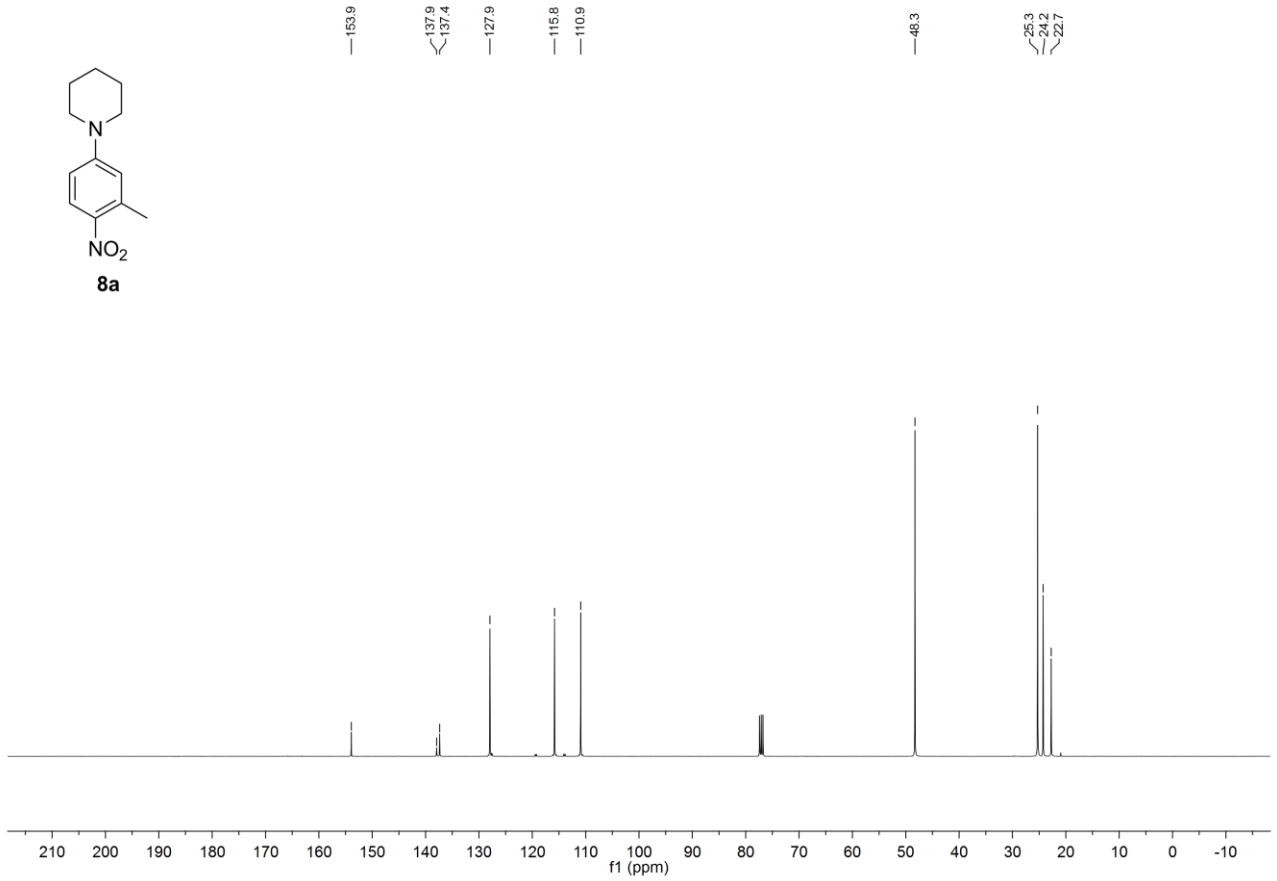

N
NO2

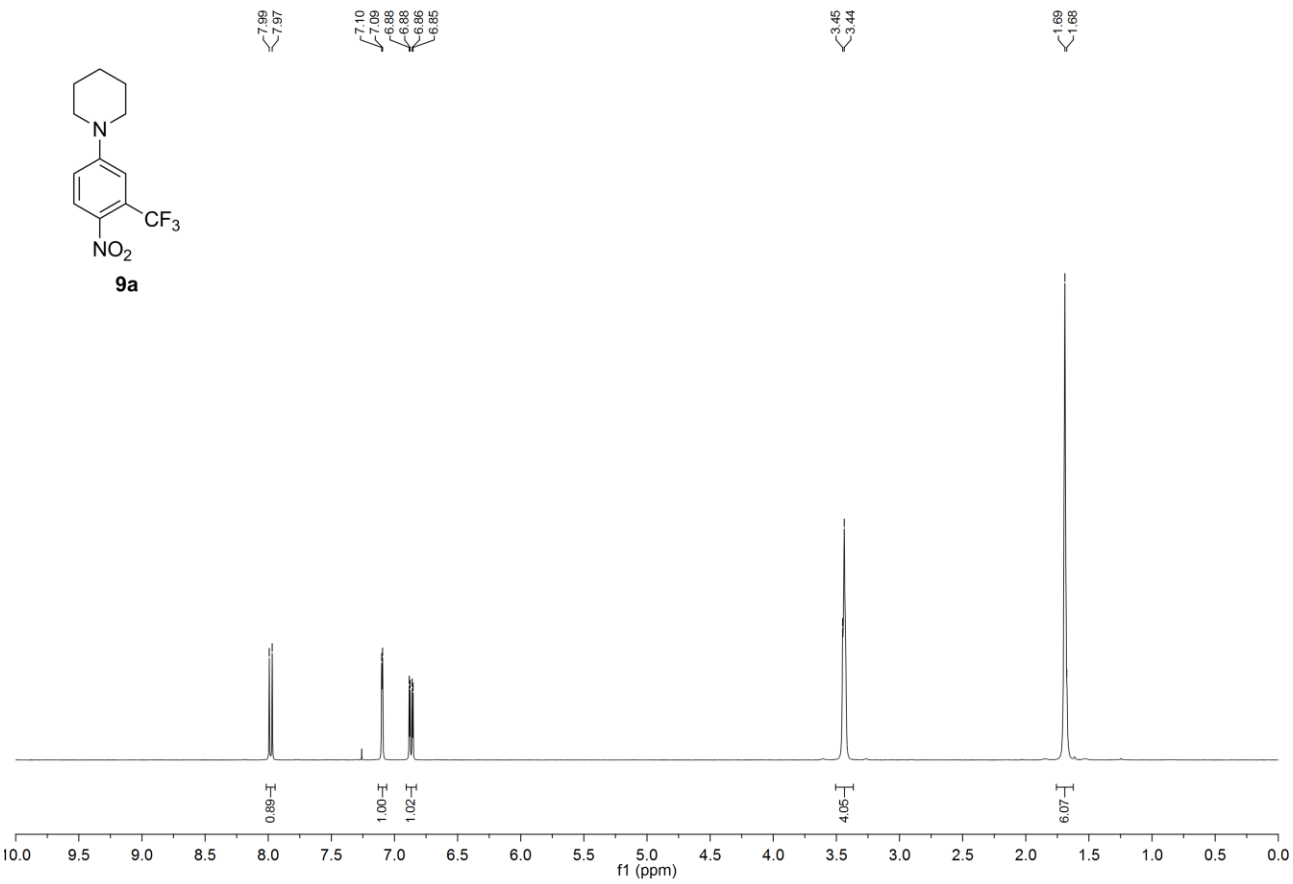
6a

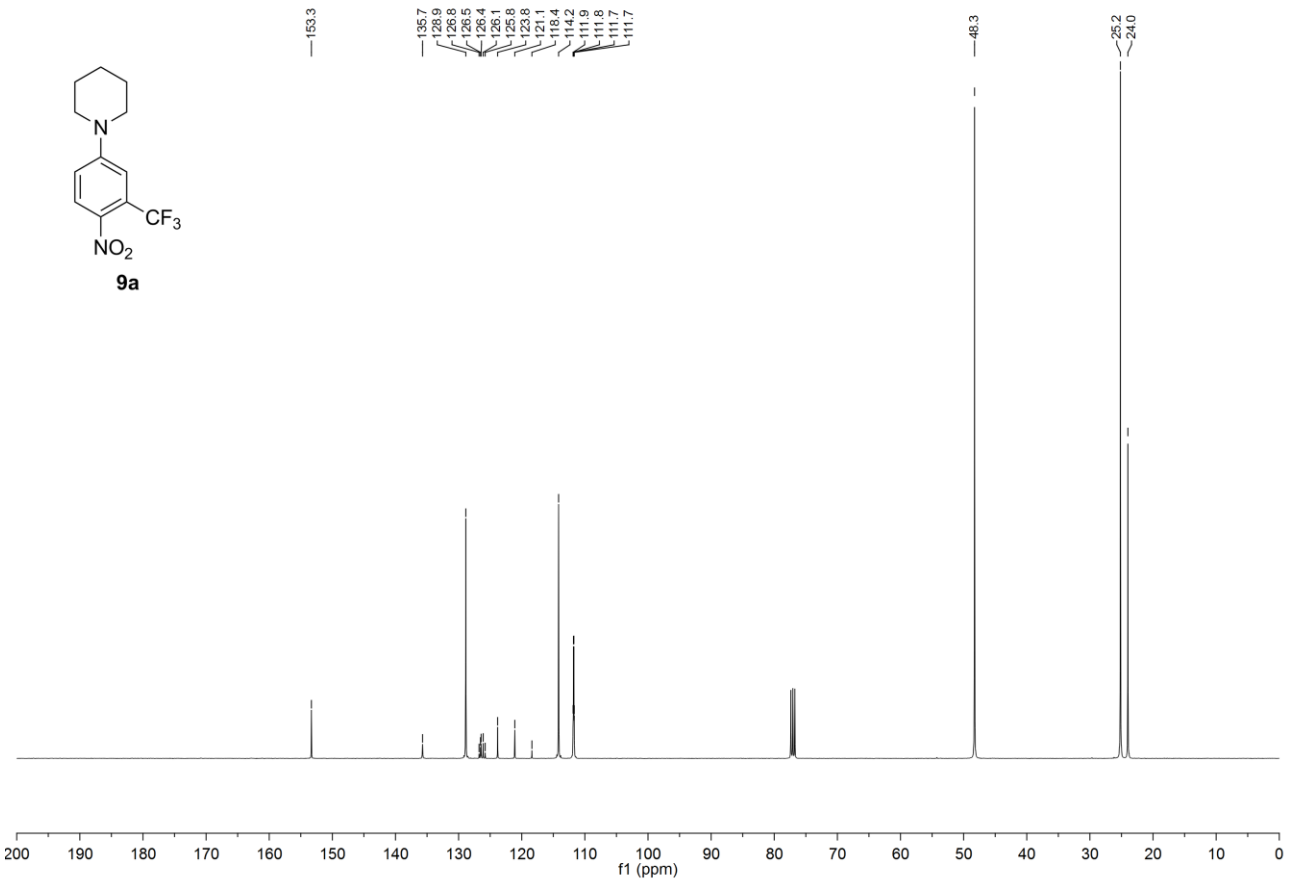

0.90
1.00
1.05
0.98
4.43
4.41
2.12
f1 (ppm)

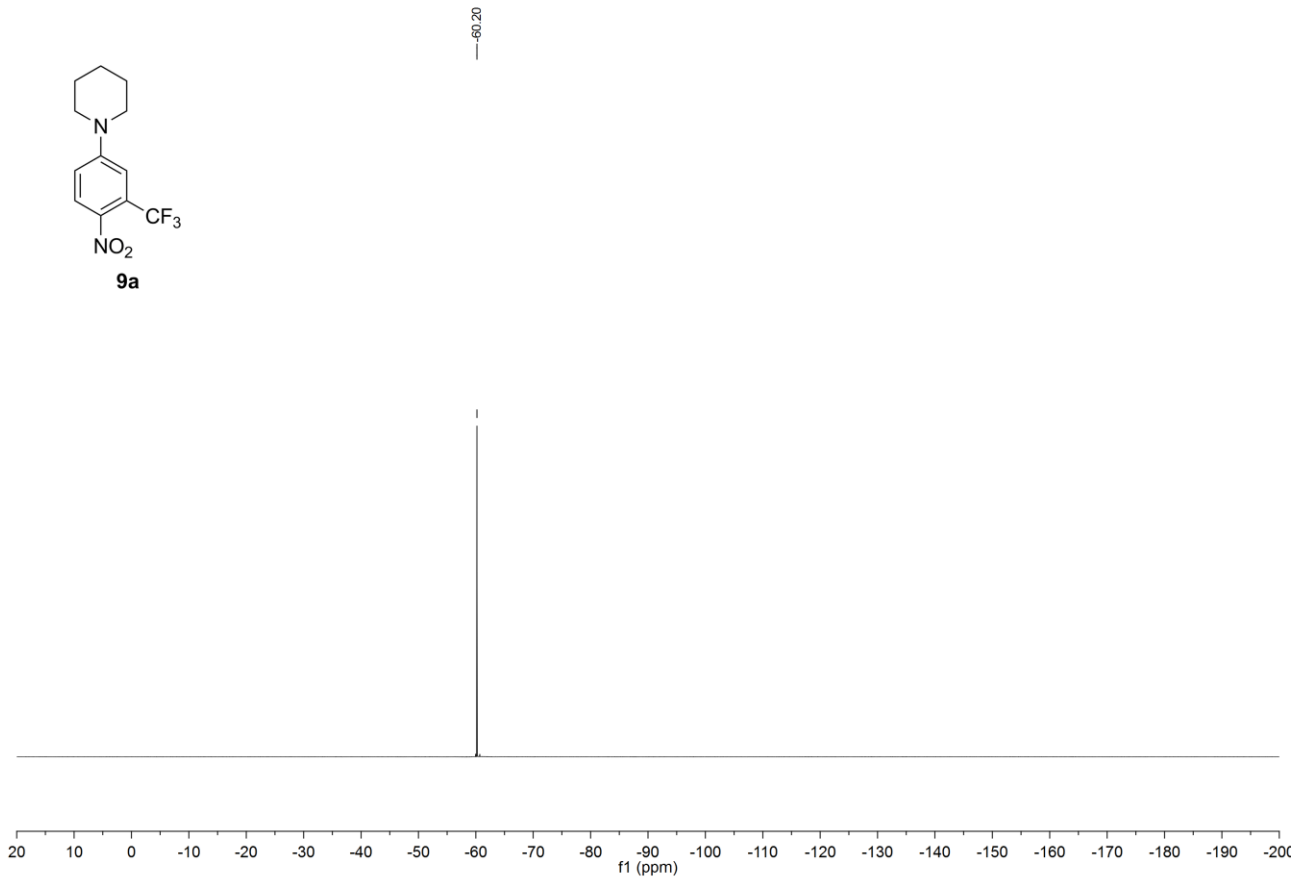

147.0
142.7
133.3
126.0
120.8
120.6
52.9
25.9
24.0
N
NO2
6a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

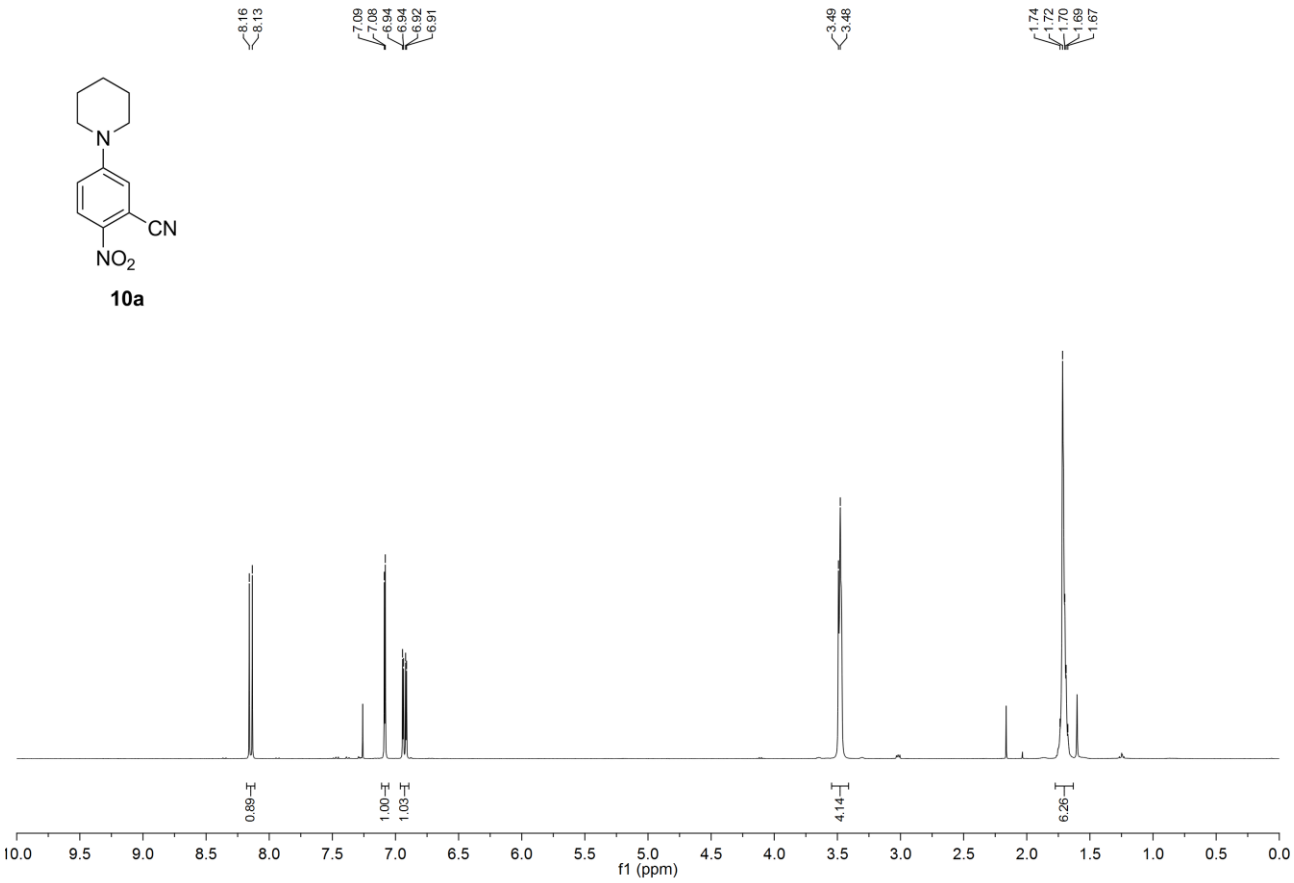

8.05
8.03
6.66
6.65
6.64
6.63
6.59
6.58
3.40
3.38
2.60
1.66
N
NO2
8a
0.91
1.00
0.99
3.98
3.11
6.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


153.9
137.9
137.4
127.9
115.8
110.9
48.3
25.3
24.2
22.7
N
NO2
8a
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

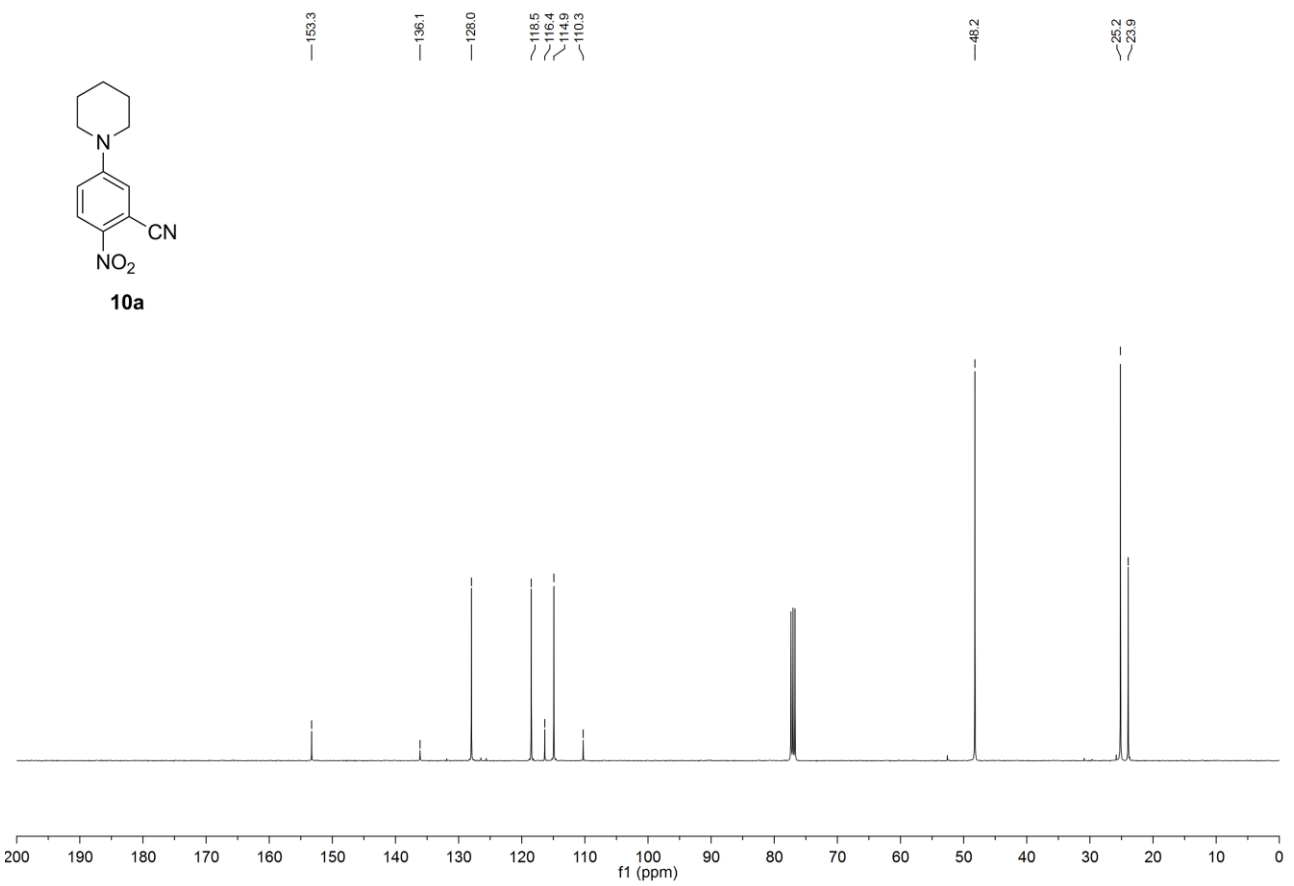

7.99
7.97
7.10
7.09
6.88
6.88
6.86
6.85
3.45
3.44
1.69
1.68
N
CF3
NO2
9a
0.89
1.00
1.02
4.05
6.07
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


153.3
135.7
128.9
126.8
126.5
126.4
126.1
125.8
123.8
121.1
118.4
114.2
111.9
111.8
111.7
111.7
48.3
25.2
24.0
N
CF3
NO2
9a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

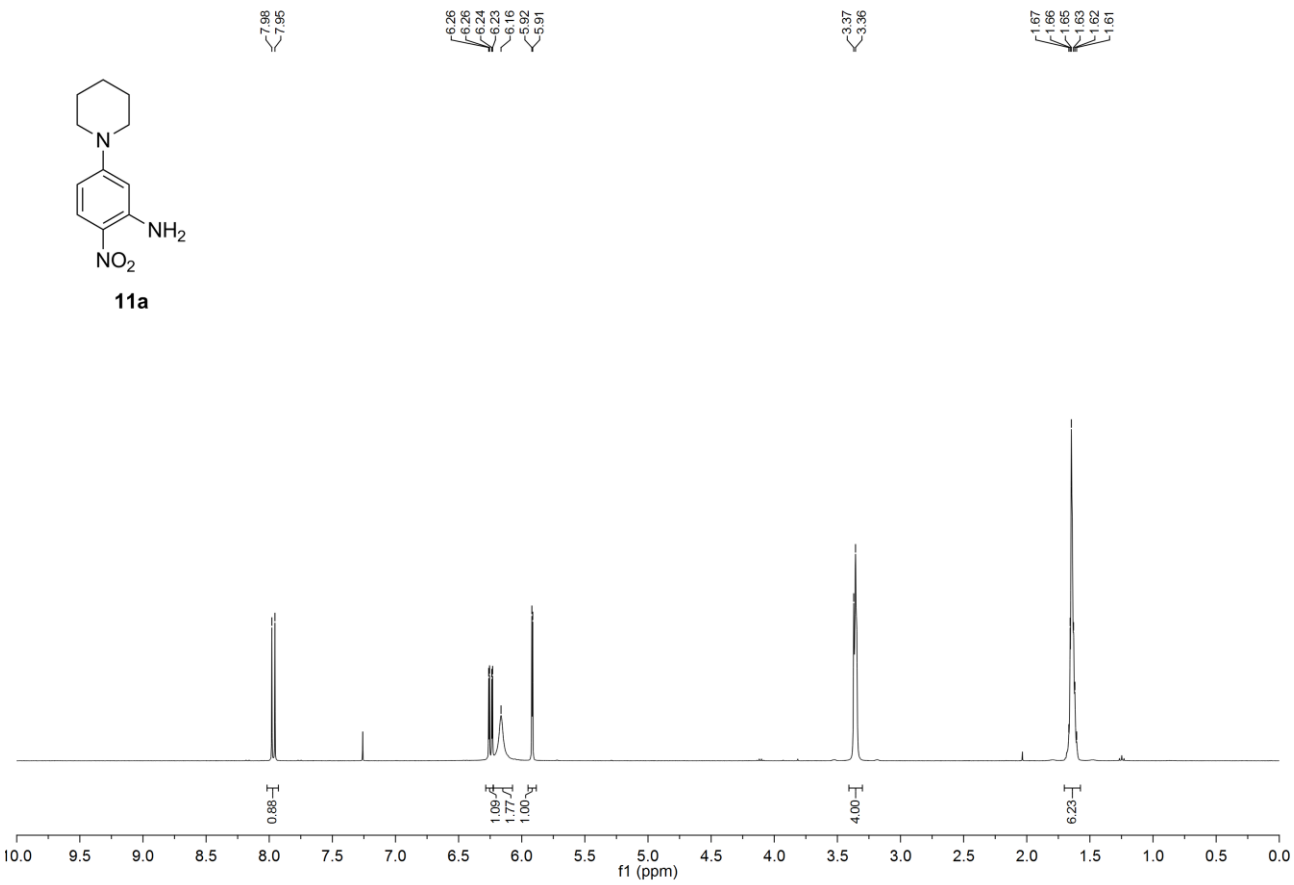

-60.20
N
CF3
NO2
9a
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200
f1 (ppm)

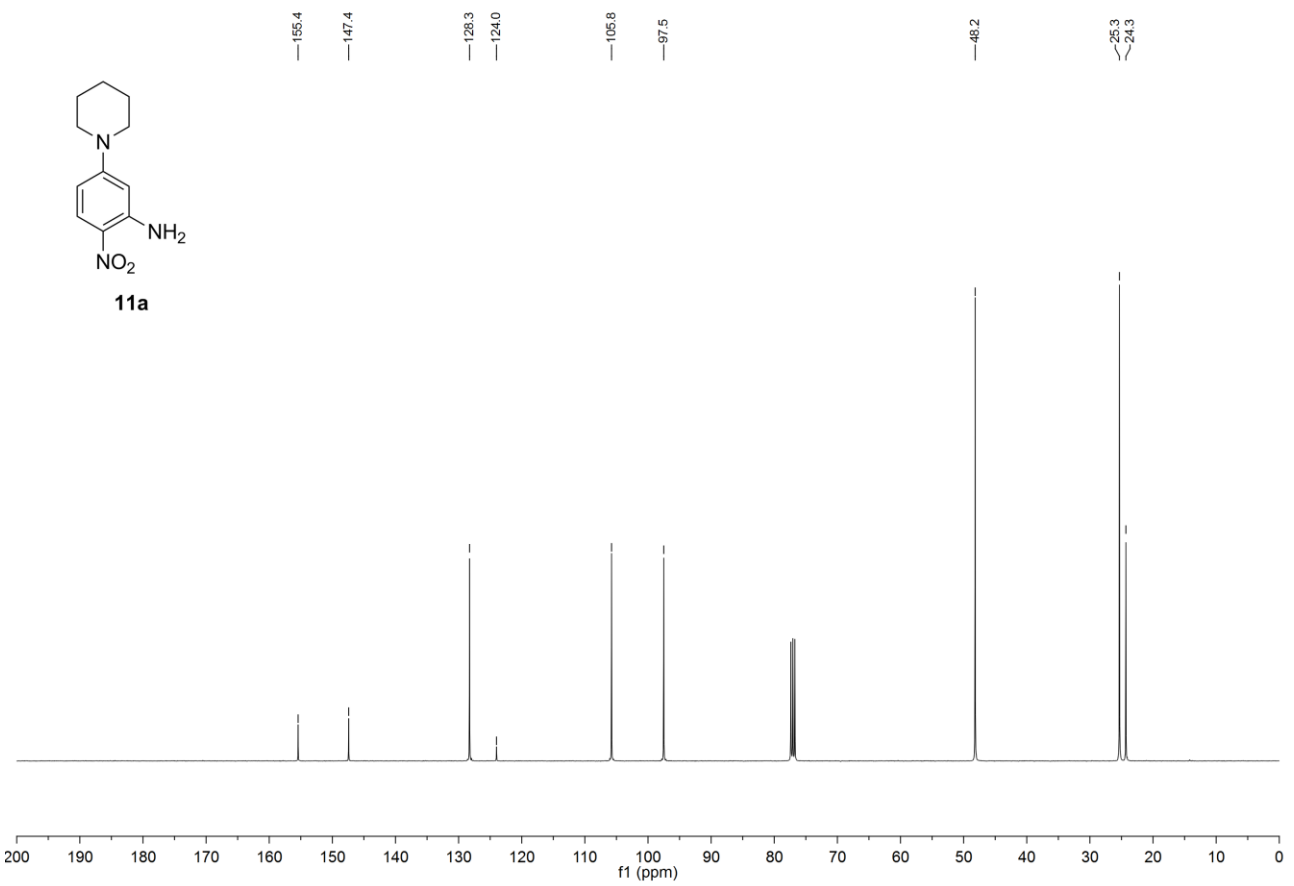

8.16
8.13
7.09
7.08
6.94
6.94
6.92
6.91
3.49
3.48
1.74
1.72
1.70
1.69
1.67
N
CN
NO2
0.89
1.00
1.03
4.14
6.26
f1 (ppm)

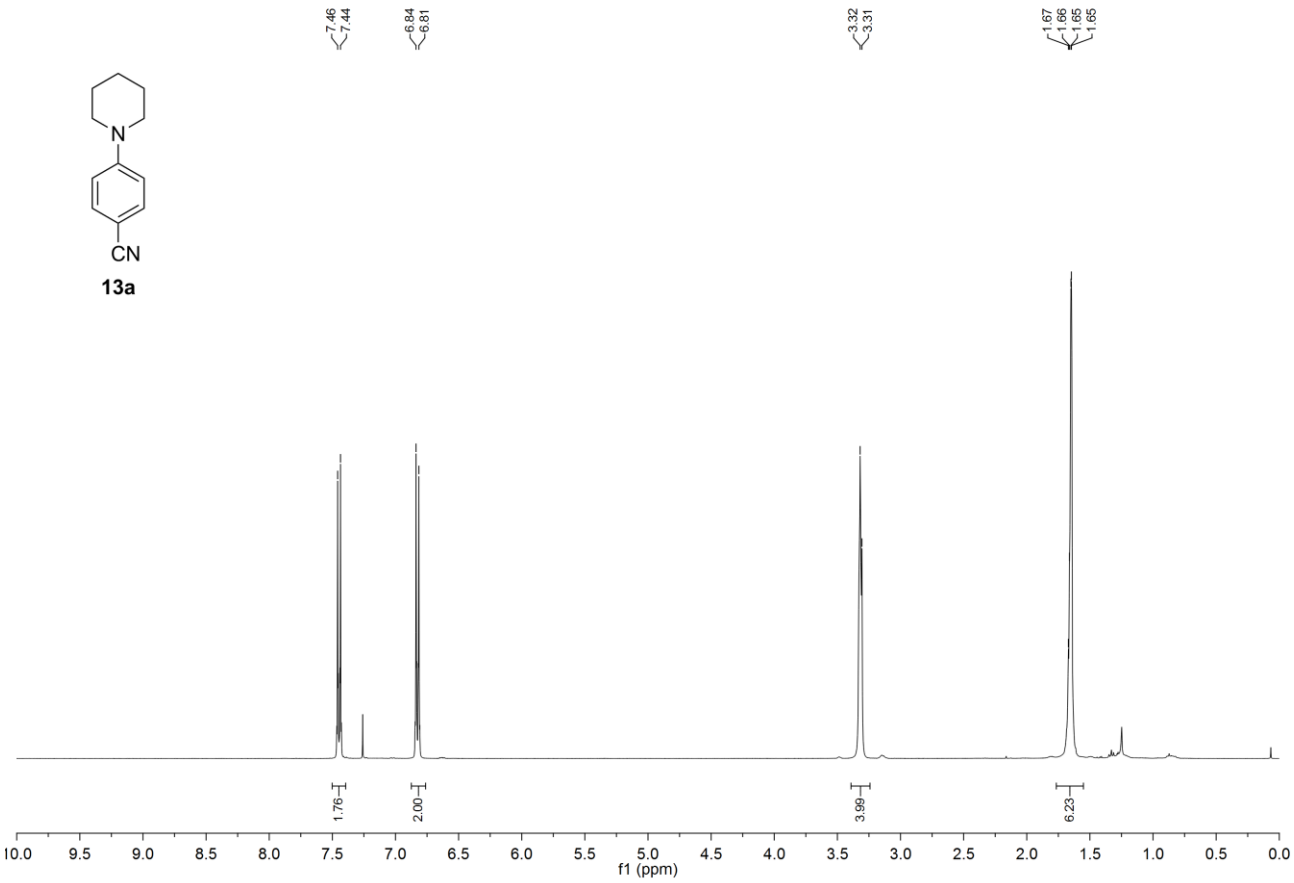
10a

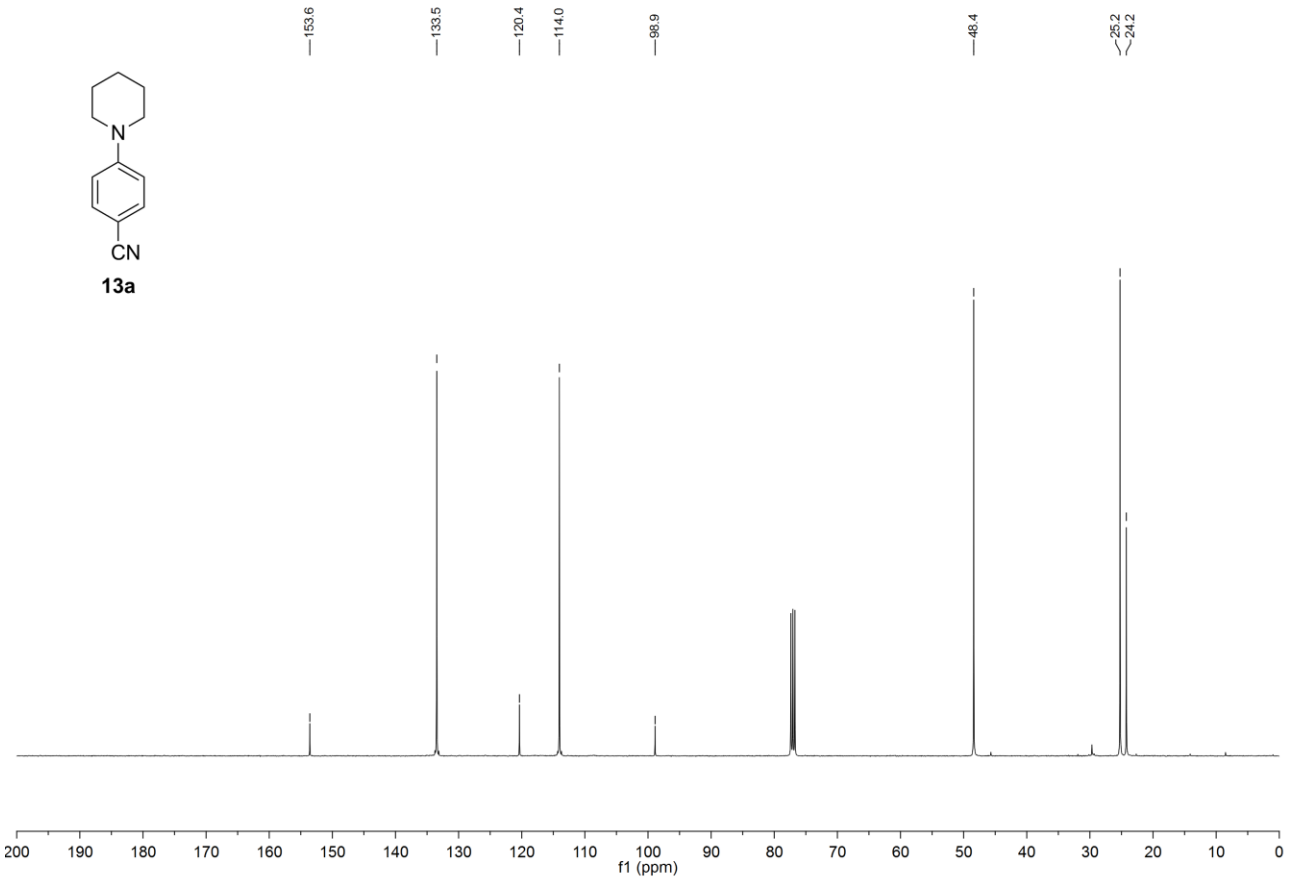

153.3
136.1
128.0
118.5
116.4
114.9
110.3
48.2
25.2
23.9
N
CN
NO2
f1 (ppm)

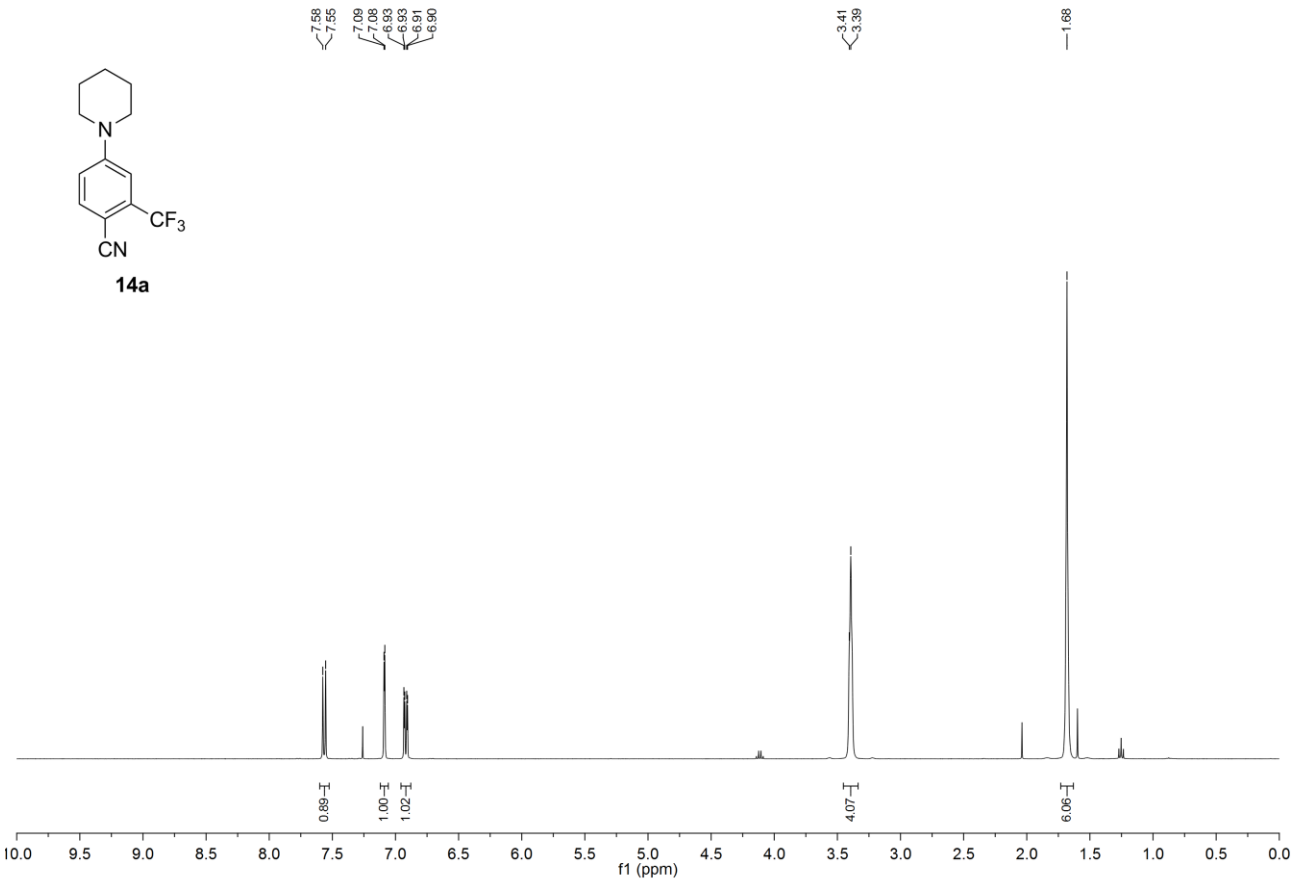
10a

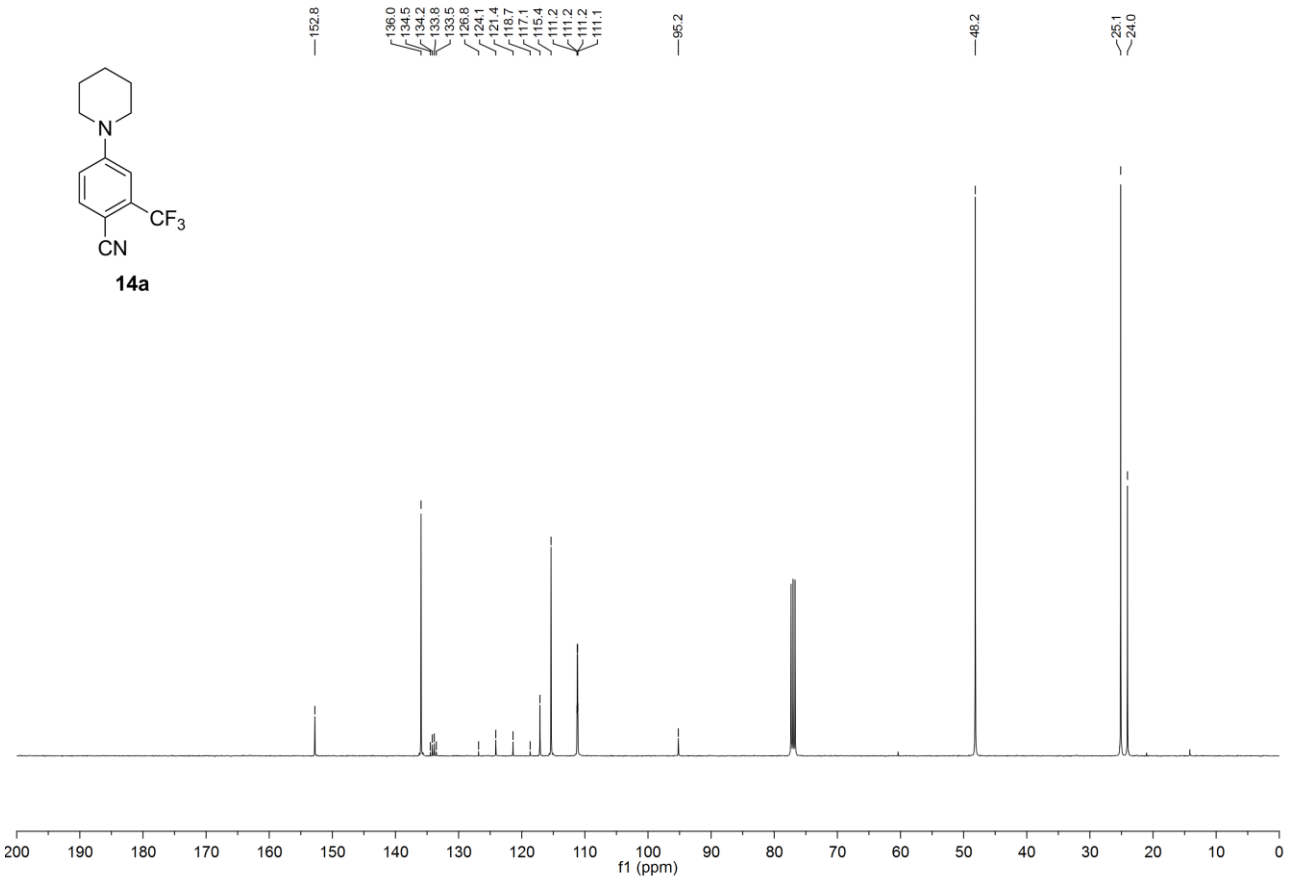

7.98
7.95
6.26
6.26
6.24
6.23
6.16
5.92
5.91
3.37
3.36
1.67
1.66
1.65
1.63
1.62
1.61
N
NH2
NO2
11a
0.88
1.09
1.77
1.00
4.00
6.23
f1 (ppm)

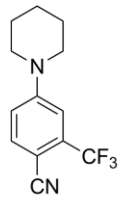

155.4
147.4
128.3
124.0
105.8
97.5
48.2
25.3
24.3
N
NH2
NO2
11a
f1 (ppm)


7.46
7.44
6.84
6.81
3.32
3.31
1.67
1.66
1.65
1.65
N
CN
13a
1.76
2.00
3.99
6.23
f1 (ppm)


153.6
133.5
120.4
114.0
98.9
48.4
25.2
24.2
N
CN
13a
f1 (ppm)

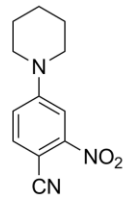

7.58
7.55
7.09
7.08
6.93
6.93
6.91
6.90
3.41
3.39
1.68
N
CF3
CN
14a
0.89
1.00
1.02
4.07
6.06
f1 (ppm)


152.8
136.0
134.5
134.2
133.8
133.5
126.8
124.1
121.4
118.7
117.1
115.4
111.2
111.2
111.2
111.1
95.2
48.2
25.1
24.0
N
CF3
CN
14a
f1 (ppm)


N
CF3
CN

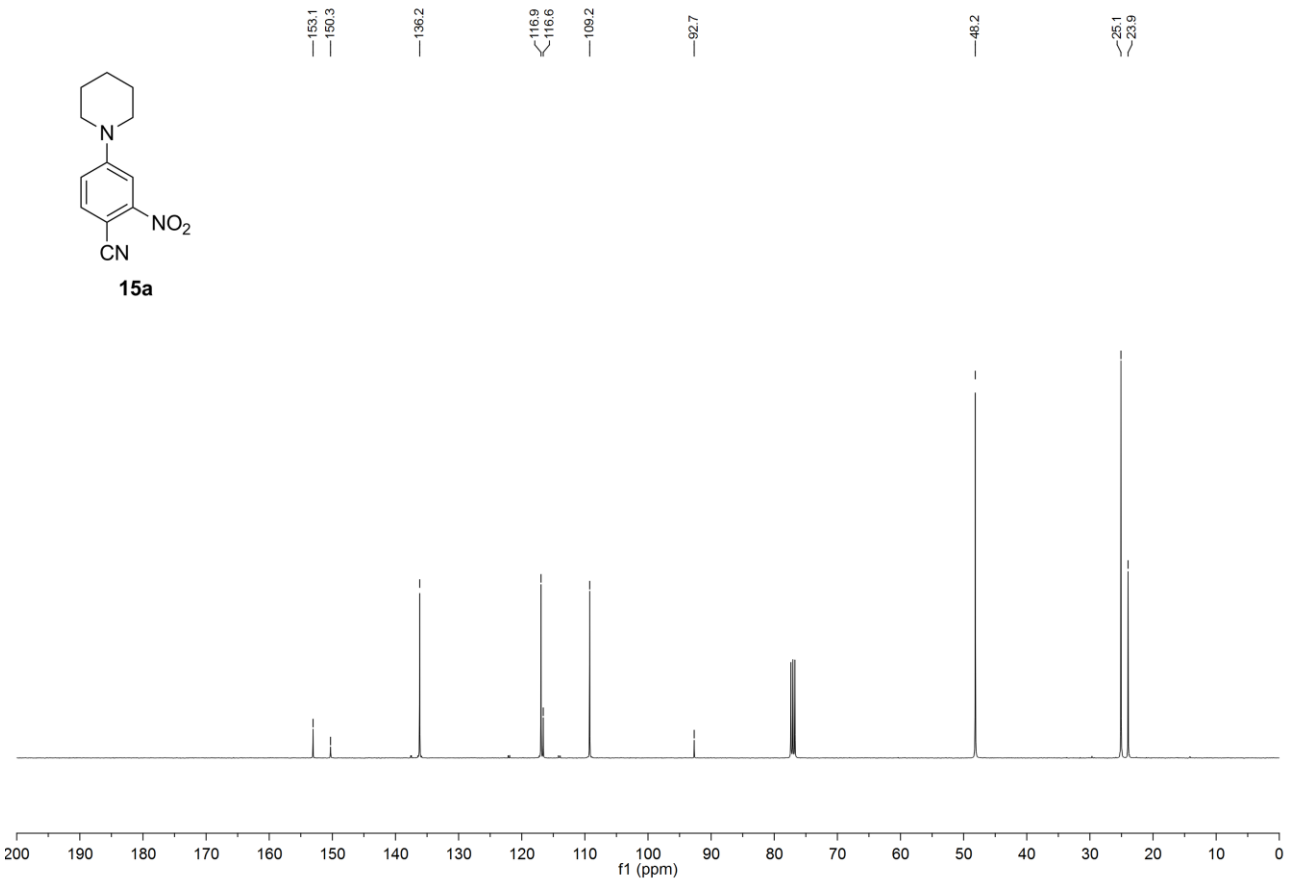
14a

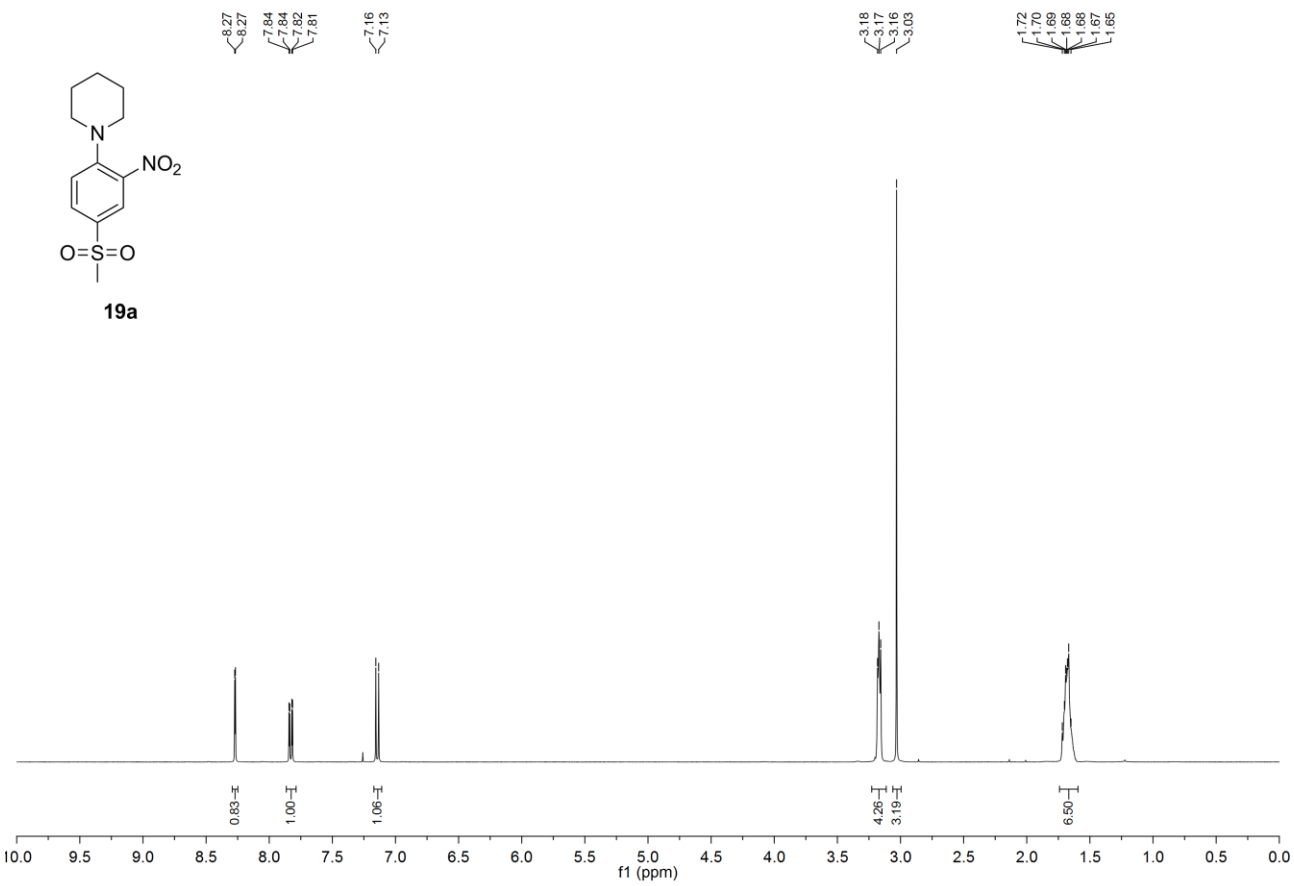
-62.41
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
f1 (ppm)

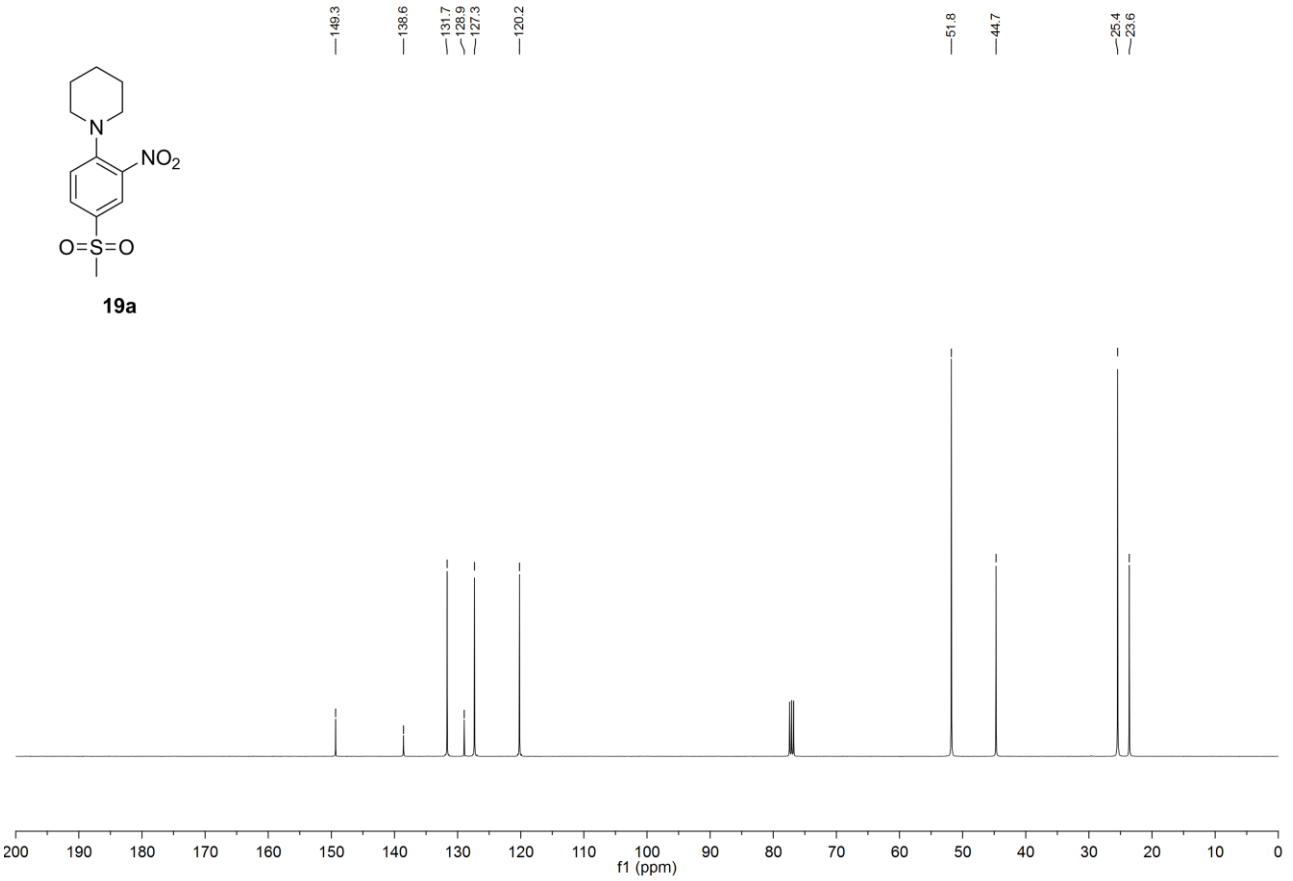

N
NO2
CN

15a

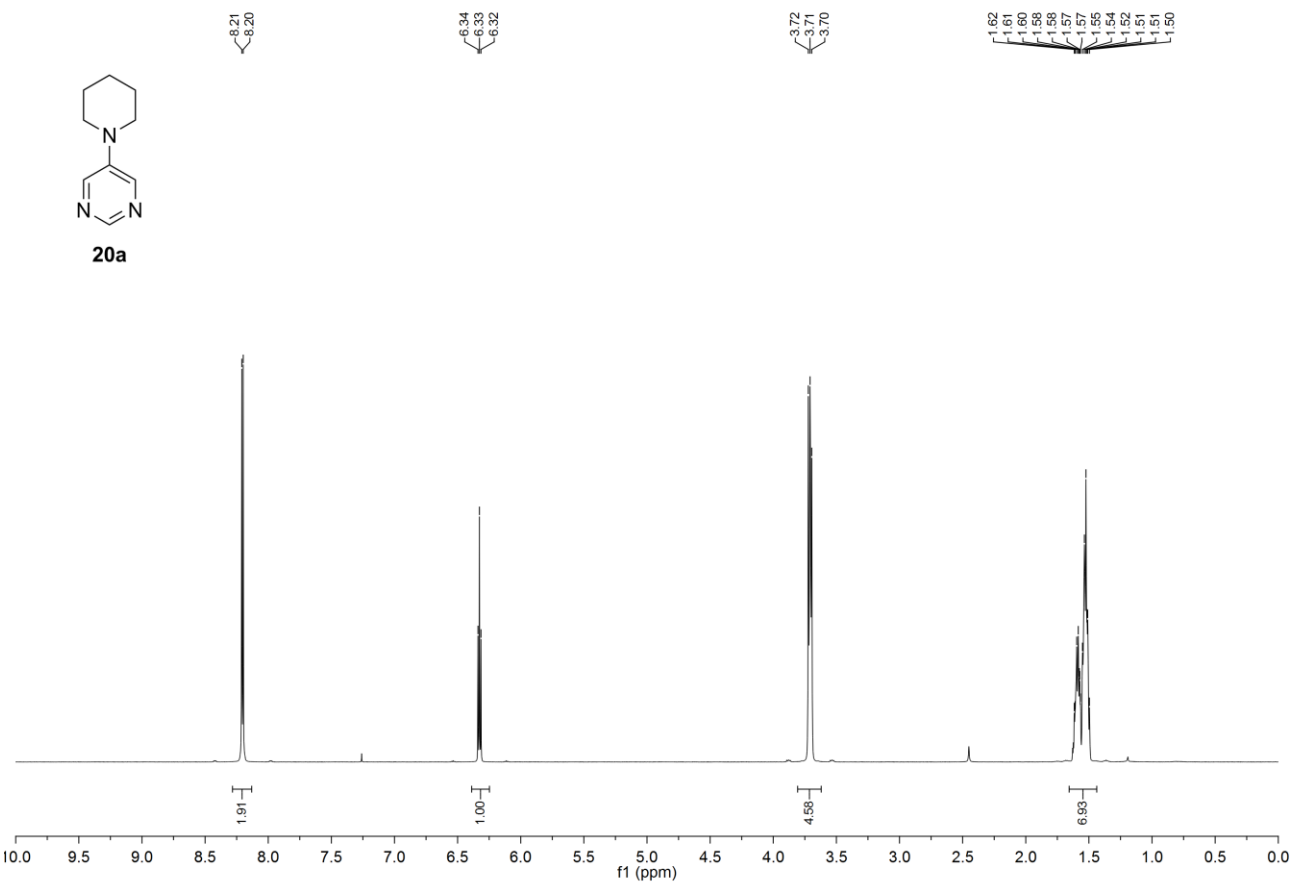
7.60
7.59
7.59
7.57
7.03
7.03
7.01
7.00
3.46
3.45
1.70
1.89
1.00
4.00
5.99
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


153.1
150.3
136.2
116.9
116.6
109.2
92.7
48.2
25.1
23.9
N
NO2
CN
15a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

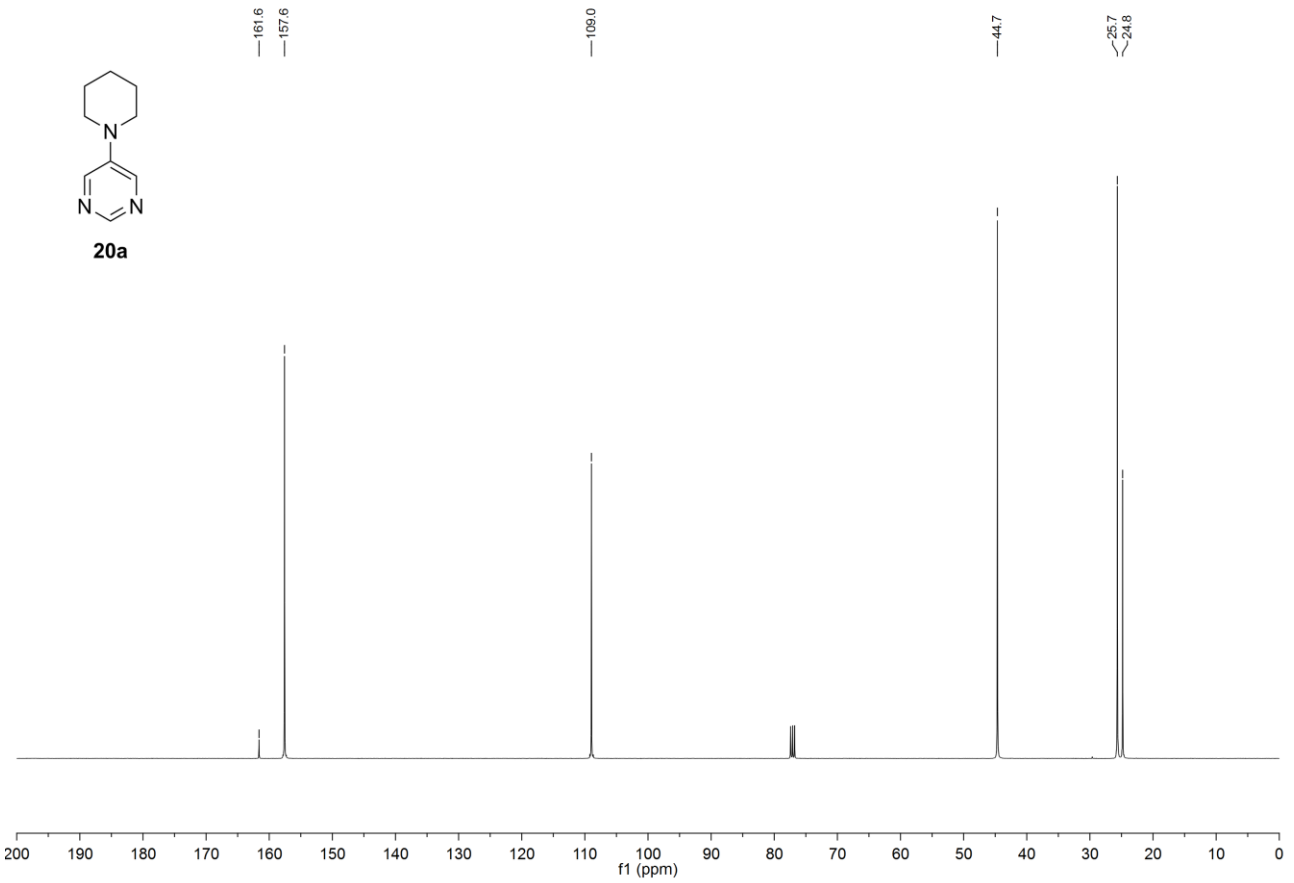

8.27
8.27
7.84
7.84
7.82
7.81
7.16
7.13
3.18
3.17
3.16
3.03
1.72
1.70
1.69
1.68
1.68
1.67
1.65
N
NO2
O=S=O
19a
0.83
1.00
1.06
4.26
3.19
6.50
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

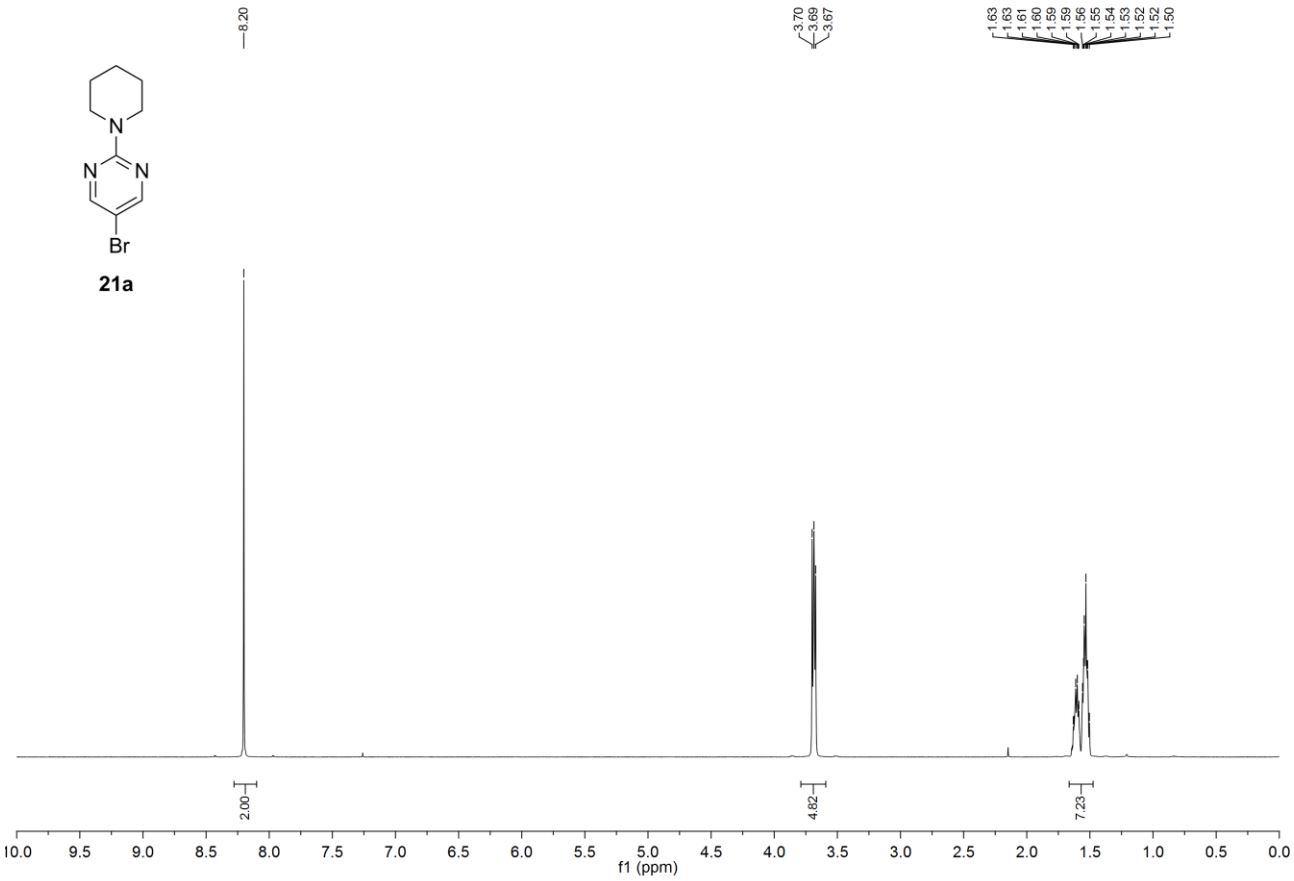

149.3
138.6
131.7
128.9
127.3
120.2
51.8
44.7
25.4
23.6
N
NO2
O=S=O
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

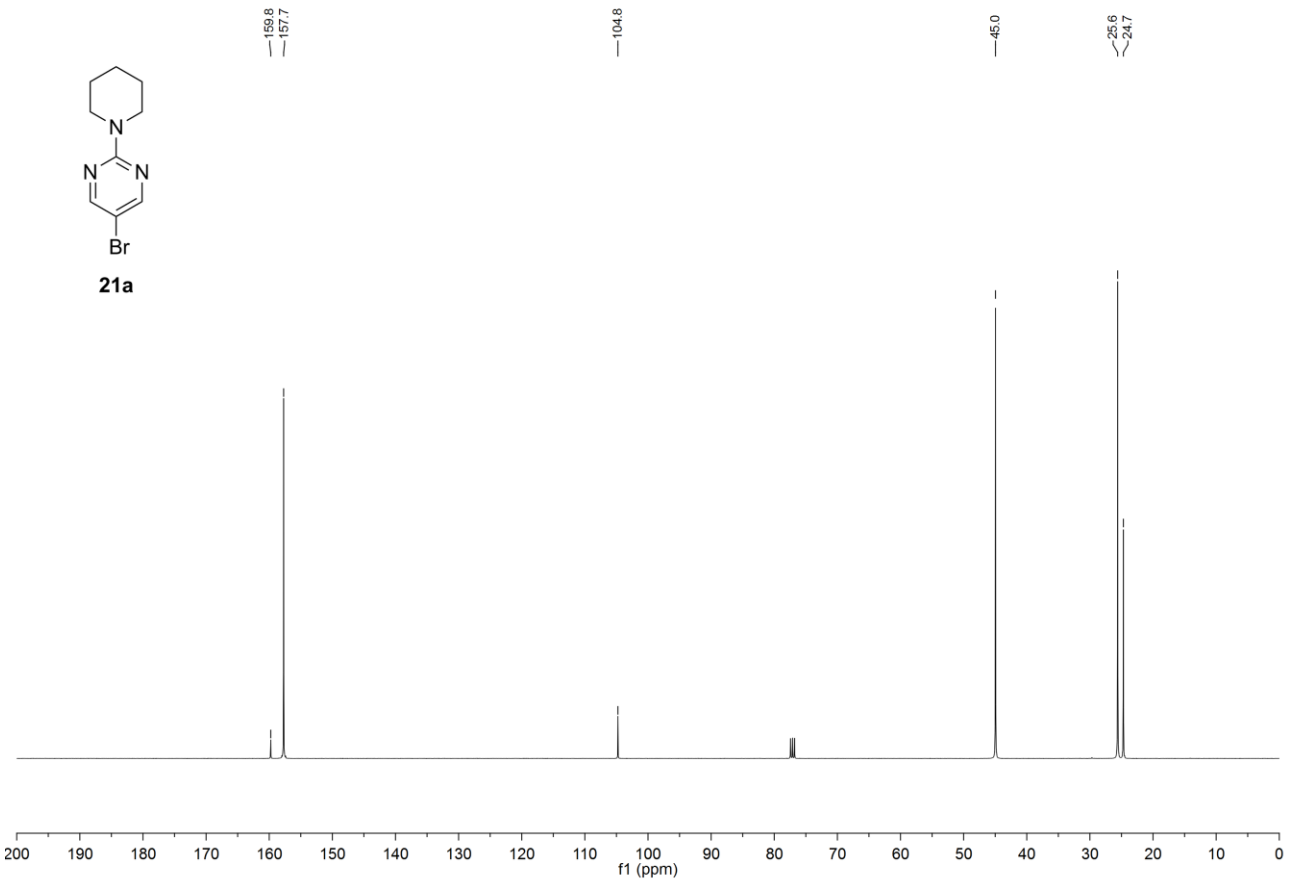
19a

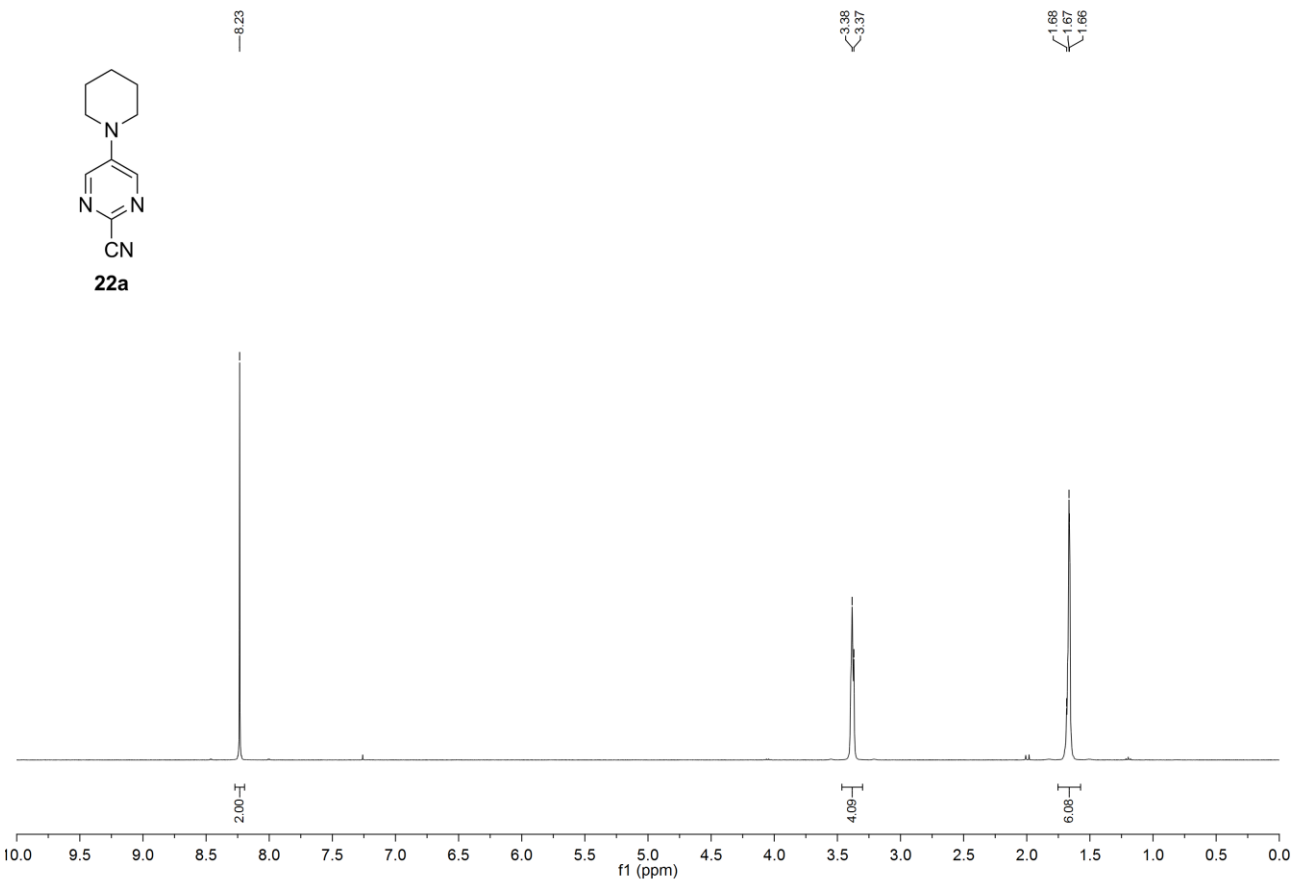

8.21
8.20
6.34
6.33
6.32
3.72
3.71
3.70
1.62
1.61
1.60
1.58
1.58
1.57
1.57
1.55
1.54
1.52
1.51
1.51
1.50
N
N N
1.91
1.00
4.58
6.93
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

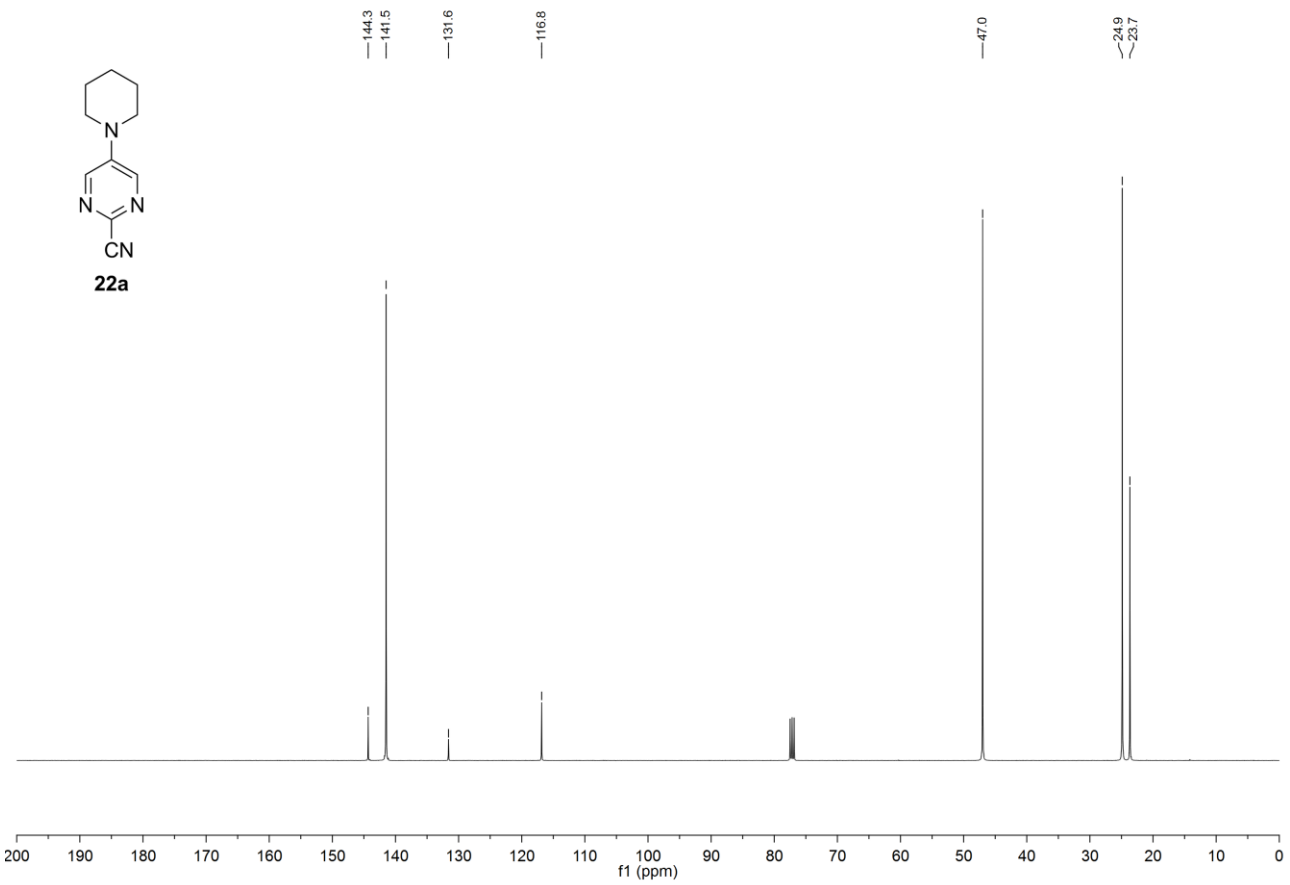
20a

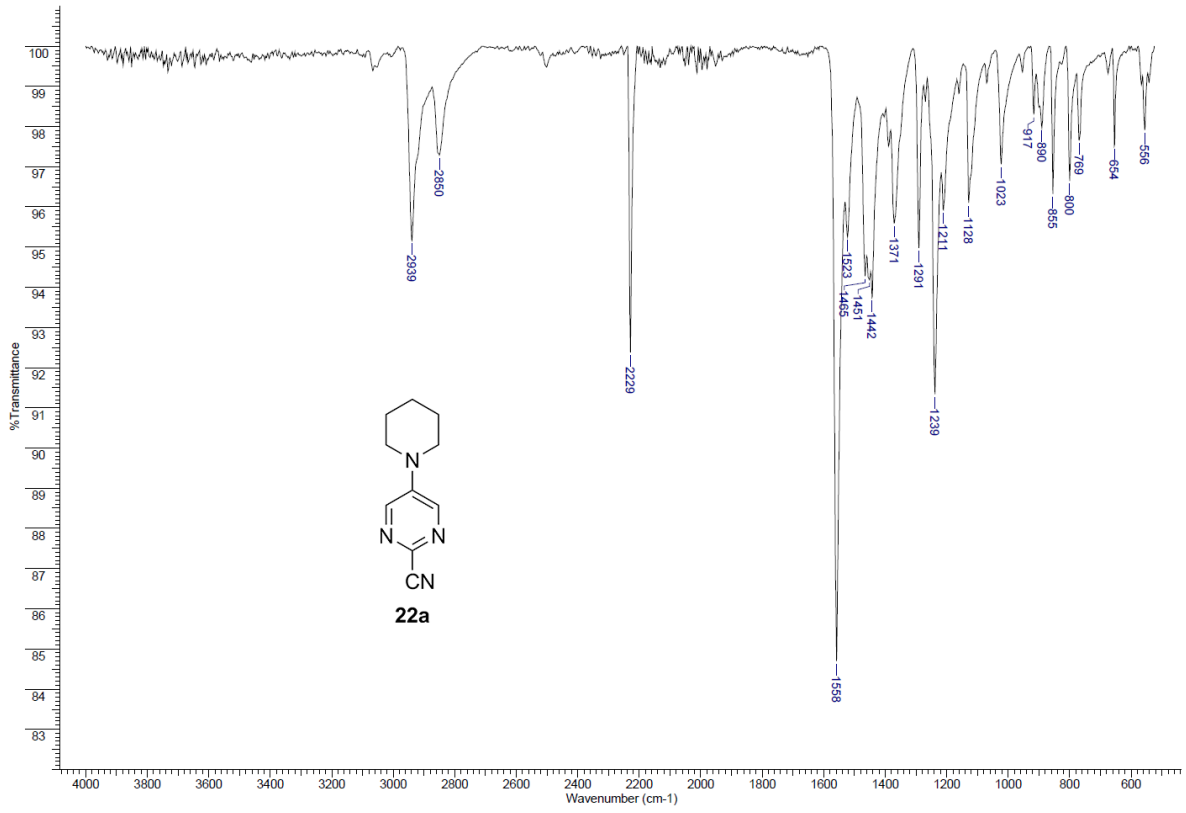

161.6
157.6
109.0
44.7
25.7
24.8
N
N
N
20a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.20
3.70
3.69
3.67
1.63
1.63
1.61
1.60
1.59
1.59
1.56
1.55
1.54
1.53
1.52
1.52
1.50
N
N
N
Br
21a
2.00
4.82
7.23
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


159.8
157.7
104.8
45.0
25.6
24.7
N
N
N
Br
21a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


8.23
3.38
3.37
1.68
1.67
1.66
N
N
N
CN
22a
2.00
4.09
6.08
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


144.3
141.5
131.6
116.8
47.0
24.9
23.7
22a
f1 (ppm)


%Transmittance
Wavenumber (cm-1)
2939
2850
2229
1558
1523
1465
1451
1442
1371
1291
1239
1211
1128
1023
917
890
855
800
769
654
556
22a