Conversion of aryl carboxylic acids into aryl nitriles through multi-versions of Cu-mediated decarboxylative cyanation under aerobic conditions

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General considerations. The reagents used for experiments were commercially available and used as received unless otherwise noted. DMSO and DMF were distilled from CaH_2 under reduced pressure and stored under nitrogen. All reactions were performed under dioxygen with the strict exclusion of moisture using Schlenk techniques. Column chromatography was performed on silica gel 300-400 mesh. The yields reported are the isolated yields and the average of two runs. ^1H, ^{13}C and ^{19}F NMR spectra of all compounds were recorded at 400 and 100 MHz with $CDCl_3$ as solvent respectively, except for ^1H and ^{13}C NMR spectra of compounds **6p**, **16p**, **17p** and **18p** with d_6-DMSO as solvent. All coupling constants (*J* values) were reported in Hertz (Hz).

General procedure for Cu-catalyzed decarboxylative cyanation of aryl carboxylic acids using malononitrileor AMBN as cyanide source

Procedure A: An oven-dried Schlenk tube equipped with a stir bar was charged with aryl carboxylic acid (0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv) and K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. Under dioxygen, solvent (2 mL) was added via syringe. The rubber septum was replaced with a Teflon screwcap under dioxygen flow. With stirring, the reaction mixtures were heated at indicated temperature for 20 h, then cooled down to room temperature. The reaction mixtures were diluted with EtOAc and filtered through a short plug of silica gel that was then washed with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel to provide corresponding product.

Procedure B: An oven-dried Schlenk tube equipped with a stir bar was charged with aryl carboxylic acid (0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuX (0.24 mmol, 1.2 equiv) and potassium salt (0.2 mmol, 1.0 equiv). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. Under dioxygen, solvent (2 mL) was added via syringe. The rubber septum was replaced with a Teflon screwcap under dioxygen flow. With stirring, the reaction mixtures were heated at 160 ^oC for 20 h, then cooled down to room temperature. The reaction mixtures were diluted with EtOAc and filtered through a short plug of silica gel that was then washed with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel to provide corresponding product.

4,5-Dimethoxy-2-nitrobenzonitrile (1p)

Procedure A was followed using 4,5-dimethoxy-2-nitrobenzoic acid (45.4 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv) and DMF (2 mL). The reaction mixtures were purified by flash column chromatography on silica gel (25% ether in hexane) to afford 17.5 mg (42%) of the product as a yellow solid.

Procedure B was followed using 4,5-dimethoxy-2-nitrobenzoic acid (45.4 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv) and DMSO (2 mL). The reaction mixtures were purified by flash column chromatography on silica gel (25% ether in hexane) to afford 7.9 mg (19%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1,2] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1 H), 7.22 (s, 1 H), 4.02 (s, 3 H), 4.01 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.44, 152.23, 142.78, 115.49, 115.44, 107.95, 100.80, 56.99, 56.84.

5-Methoxy-2-nitrobenzonitrile (2p).

Procedure A was followed using 5-methoxy-2-nitrobenzoic acid (39.4 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (15% ether in hexane) to afford 18.9 mg (53%) of the product as a yellow solid.

Procedure B was followed using 5-methoxy-2-nitrobenzoic acid (39.4 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (15% ether in hexane) to afford 17.1 mg (48%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 9.3 Hz, 1 H), 7.32 (d, J = 2.7 Hz, 1 H), 7.21 (dd, J = 9.3, 2.8 Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.70, 141.43, 127.94, 120.62, 118.23, 115.10, 109.97, 56.68.

4-Methoxy-2-nitrobenzonitrile (3p)

Procedure A was followed using 4-methoxy-2-nitrobenzoic acid (39.4 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv) and DMF (2 mL). The reaction mixtures were heated at 170 ^{o}C for 20 h and purified by flash column chromatography on silica gel (20% ether in hexane) to afford 21.7 mg (61%) of the product as a yellow solid.

Procedure B was followed using 4-methoxy-2-nitrobenzoic acid (39.4 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv) and DMSO (2 mL). The reaction mixtures were heated at 160 ^{o}C for 20 h and purified by flash column chromatography on silica gel (20% ether in hexane) to afford 16.0 mg (45%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 - 7.78 (m, 2 H), 7.27 (dd, J = 8.8, 2.6 Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.21, 150.14, 136.66, 120.02, 115.34, 111.12, 99.39, 56.59.

4-Methyl-2-nitrobenzonitrile (4p).

Procedure A was followed using 4-methyl-2-nitrobenzoic acid (36.2 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were heated at 170 ^oC for 20 h and purified by flash column chromatography on silica gel (10% ether in hexane) to afford 23.0 mg (71%) of the product as a yellow solid.

Procedure B was followed using 4-methyl-2-nitrobenzoic acid (36.2 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 13.0 mg (40%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1] ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1 H), 7.79 (d, J = 7.9 Hz, 1 H), 7.61 (d, J = 7.8 Hz, 1 H), 2.56 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.49, 145.65, 135.31, 134.91, 126.06, 115.21, 105.10, 21.80.

2-Methyl-6-nitrobenzonitrile (5p).

Procedure A was followed using 2-methyl-6-nitrobenzoic acid (36.2 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were heated at 170 ^oC for 20 h and purified by flash column chromatography on silica gel (10% ether in hexane) to afford 22.7 mg (70%) of the product as a white solid.

Procedure B was followed using 2-methyl-6-nitrobenzoic acid (36.2 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 17.2 mg (53%) of the product as a white solid.

Exhibited spectral data in accordance with previous report.[1] ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 6.8, 2.6 Hz, 1 H), 7.72 - 7.67 (m, 2 H), 2.70 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.29, 145.79, 135.65, 132.77, 122.92, 113.81, 107.84, 21.09.

5-Amino-2-nitrobenzonitrile (6p).

Procedure A was followed using 5-amino-2-nitrobenzoic acid (36.4 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (20% ether in hexane) to afford 7.2 mg (22%) of the product as a yellow liquid.

Exhibited spectral data in accordance with previous report.[1,3] ^1H NMR (400 MHz, d_6-DMSO): δ 8.09 (d, J = 9.3 Hz, 1 H), 7.15 (s, 2 H), 7.01 (d, J = 2.5 Hz, 1 H), 6.83 (dd, J = 9.3, 2.6 Hz, 1 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 155.22, 135.13, 128.99, 119.17, 116.79, 116.01, 109.66.

2-Nitrobenzonitrile (7p).

Procedure A was followed using 2-nitrobenzoic acid (33.4 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 23.7 mg (80%) of the product as a yellow solid.

Procedure B was followed using 2-nitrobenzoic acid (33.4 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 15.4 mg (52%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1,2] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (dd, J = 6.3, 3.3 Hz, 1 H), 7.94 (dd, J = 7.6, 3.8 Hz, 1 H), 7.87 (dt, J = 6.1, 3.4, 2.7 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.48, 135.61, 134.44, 133.83, 125.57, 114.99, 107.93.

4-Chloro-2-nitrobenzonitrile (8p).

Procedure A was followed using 4-chloro-2-nitrobenzoic acid (40.3 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 15.7 mg (43%) of the product as a yellow solid.

Procedure B was followed using 4-chloro-2-nitrobenzoic acid (40.3 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 7.7 mg (21%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, J = 2.0 Hz, 1 H), 7.87 (d, J = 8.2 Hz, 1 H), 7.81 (dd, J = 8.2, 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.11, 140.45, 136.18, 134.42, 126.04, 114.06, 106.39.

5-Chloro-2-nitrobenzonitrile (9p).

Procedure A was followed using 5-chloro-2-nitrobenzoic acid (40.3 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 15.4 mg (42%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.9 Hz, 1 H), 7.89 (d, J = 2.2 Hz, 1 H), 7.80 (dt, J = 8.9, 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.78, 141.35, 135.23, 133.87, 126.90, 113.79, 109.64.

4-Fluoro-2-nitrobenzonitrile (10p)

Procedure A was followed using 4-fluoro-2-nitrobenzoic acid (37.0 mg, 0.2 mmol),

malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv) and DMSO (2 mL). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 9.3 mg (28%) of the product as a yellow solid.

Procedure B was followed using 4-fluoro-2-nitrobenzoic acid (37.0 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv) and DMSO (2 mL). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 8.3 mg (25%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, J = 7.9, 2.6 Hz, 1 H), 7.97 (dd, J = 8.6, 5.1 Hz, 1 H), 7.59 - 7.54 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.63, 163.02, 137.51 (d, J = 9.1 Hz), 121.99 (d, J = 22.2 Hz), 114.04 (d, J = 27.3 Hz), 114.11, 104.27 (d, J = 4.0 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ - 97.79 - - 97.84 (m, 1 F)

2-Nitro-4-(trifluoromethyl)benzonitrile (11p).

Procedure A was followed using 2-nitro-4-(trifluoromethyl)benzoic acid (47.0 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (10% ether in hexane) to afford 16.8 mg (39%) of the product as a yellow liquid.

Exhibited spectral data in accordance with previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1 H), 8.11 (d, J = 1.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.47, 130.94 - 130.87 (m), 123.16 - 122.84 (m), 122.44, 113.68, 111.40. ^{19}F NMR (377 MHz, $CDCl_3$): δ - 63.50 (s, 3 F)

2,4,6-Trimethoxylbenzonitrile (12p)

Procedure A was followed using 2,4,6-trimethoxylbenzoic acid (42.4 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv) and DMF (2 mL). The reaction mixtures were purified by flash column chromatography on silica gel (30% ether in hexane) to afford 15.1 mg (39%) of the product as a yellow solid.

Procedure B was followed using 2,4,6-trimethoxylbenzoic acid (42.4 mg, 0.2 mmol), AMBN (154 mg, 0.8 mmol, 4 equiv), CuBr (35 mg, 0.24 mmol, 1.2 equiv), K_2CO_3 (28 mg, 0.2 mmol, 1.0 equiv) and DMSO (2 mL). In addition, $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol%) was added as the catalyst. The reaction mixtures were purified by flash column chromatography on silica gel (30% ether in hexane) to afford 19.4 mg (50%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (s, 2 H), 3.88 (s, 6 H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.29, 163.77, 114.58, 90.32, 56.07, 55.66.

3-Methylbenzothiophene-2-nitrile (13p)

Procedure A was followed using 3-methylbenzothiophene-2-carboxylic acid (38.4

mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv) and DMF (2 mL). The reaction mixtures were heated at 170 ^oC for 20 h and purified by flash column chromatography on silica gel (1% ether in hexane) to afford 11.4 mg (33%) of the product as a white solid.

Procedure B was followed using 3-methylbenzothiophene-2-carboxylic acid (38.4 mg, 0.2 mmol), AMBN (153.6 mg, 0.8 mmol, 4 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv) and DMF (2 mL). The reaction mixtures were purified by flash column chromatography on silica gel (1% ether in hexane) to afford 22.4 mg (65%) of the product as a white solid.

Exhibited spectral data in accordance with previous report.[1,4,5] ^1H NMR (400 MHz, $CDCl_3$): δ 7.84 - 7.78 (m, 2H), 7.53 - 7.48 (m, 2H), 2.63 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.18, 140.75, 137.52, 127.87, 125.31, 123.48, 122.63, 114.53, 105.57, 13.72.

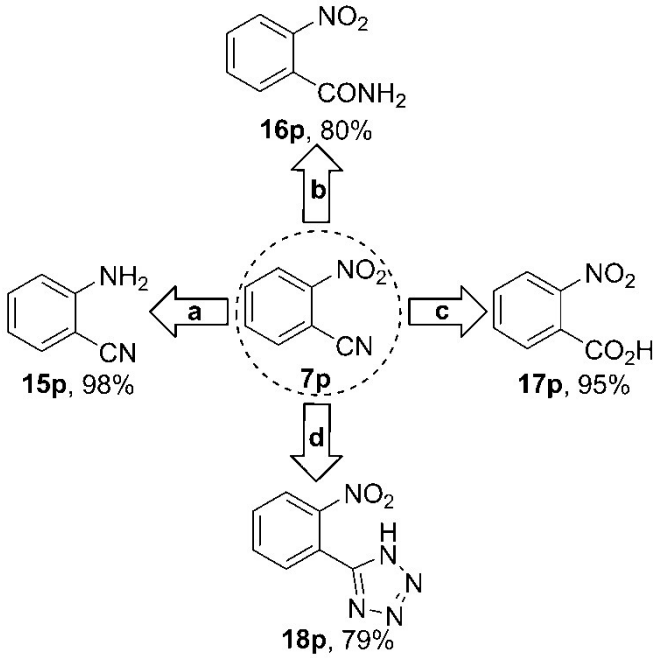
3-Methylbenzofuran-2-nitrile (14p).

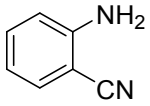
Procedure A was followed using 3-methylbenzofuran-2-carboxylic acid (35.2 mg, 0.2 mmol), malononitrile (26.4 mg, 0.4 mmol, 2 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv). The reaction mixtures were purified by flash column chromatography on silica gel (1% ether in hexane) to afford 15.1 mg (48%) of the product as a yellow solid.

Procedure B was followed using 3-methylbenzofuran-2-carboxylic acid (35.2 mg, 0.2 mmol), AMBN (153.6 mg, 0.8 mmol, 4 equiv), CuI (46 mg, 0.24 mmol, 1.2 equiv), K_3PO_4 (42.4 mg, 0.2 mmol, 1.0 equiv) and DMF (2 mL). The reaction mixtures were purified by flash column chromatography on silica gel (1% ether in hexane) to afford 14.8 mg (47%) of the product as a yellow solid.

Exhibited spectral data in accordance with previous report.[1,6] ^1H NMR (400 MHz, $CDCl_3$): δ 7.61 (dd, J = 8.0, 1.3 Hz, 1 H), 7.51 - 7.50 (m, 2 H), 7.38 - 7.34 (m, 1 H), 2.46 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.40, 129.79, 128.41, 126.92, 124.94, 123.97, 120.91, 112.10, 111.91, 8.78.

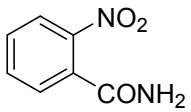
Diversification of 7p





2-Aminobenzonitrile (15p)

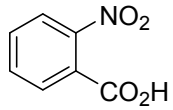
2-Aminobenzonitrile (**15p**) was synthesized according to literature.[7] An oven-dried flask equipped with a stir bar was charged with 2-nitrobenzonitrile **7p** (29.6 mg, 0.2 mmol), B_2Pin_2 (157.5 mg, 0.62 mmol, 3.1 equiv), KO*t*Bu (26.9 mg, 0.24 mmol, 1.2 equiv) and *i*PrOH (2 mL). With stirring, the reaction mixtures were heated at 110 °C for 2 h under air, followed by cooling down to room temperature. The reaction mixtures were diluted with EtOAc. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (15% EtOAc in petroleum ether) to afford 2-aminobenzonitrile **15p** in 98% yield (23.1 mg) as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (dd, J = 12.7, 8.1 Hz, 2 H), 6.73 - 6.66 (m, 2 H), 4.48 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.86, 134.05, 132.28, 117.84, 117.82, 115.26, 95.72.



2-Nitrobenzamide (16p)

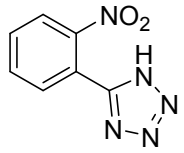
2-Nitrobenzamide (**16p**) was synthesized according to literature.[8] An oven-dried flask equipped with a stir bar was charged with 2-nitrobenzonitrile **7p** (29.6 mg, 0.2 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol, 5 mol%), 2,2'-bipyridyl (1.6 mg, 0.01 mmol, 5 mol%) and H_2O (2 mL). With stirring, the reaction mixtures were heated at 70 °C for 24 h under air, followed by cooling down to room temperature. The reaction mixtures

were diluted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (30% EtOAc in petroleum ether) to afford 2-nitrobenzamide **16p** in 80% yield (26.6 mg) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.14 (s, 1H), 7.99 (dd, J = 8.0, 1.2 Hz, 1 H), 7.76 (td, J = 7.5, 1.3 Hz, 1 H), 7.69 - 7.64 (m, 2 H), 7.63 (dd, J = 7.4, 1.5 Hz, 1 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 167.63, 147.69, 133.78, 133.04, 131.07, 129.29, 124.39.



2-Nitrobenzoic acid (17p)

2-Nitrobenzoic acid (**17p**) was synthesized according to literature.[9] An oven-dried flask equipped with a stir bar was charged with 2-nitrobenzonitrile **7p** (29.6 mg, 0.2 mmol), hydrobromic acid 33% in acetic acid (4 mL) and H_2O (2 mL). With stirring, the reaction mixtures were heated under reflux for 24 h, followed by cooling down to room temperature. The reaction mixtures were diluted with EtOAc. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (EtOAc) to afford 2-nitrobenzoic acid **17p** in 95% yield (31.7 mg) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 13.85 (s, 1 H), 7.97 (dq, J = 8.4, 1.7 Hz, 1 H), 7.87 - 7.84 (m, 1 H), 7.79 - 7.75 (m, 2 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 166.37, 148.84, 133.55 (d, J = 2 Hz), 132.84 (t, J = 2 Hz), 130.34, 127.73, 124.15.



5-(2-Nitrophenyl)-1-H-tetrazole (18p)

5-(2-Nitrophenyl)-1-H-tetrazole (**18p**) was synthesized according to literature.[10] An oven-dried flask equipped with a stir bar was charged with 2-nitrobenzonitrile **7p** (148 mg, 1.0mmol), $Cu(NO_3)_2 \cdot 3H_2O$ (24.2 mg, 0.1 mmol, 10 mol%), NaN_3 (130 mg, 2.0 mmol, 2 equiv.) and DMF (1 mL). With stirring, the reaction mixtures were heated at 120 ^{o}C for 16 h under air, followed by cooling down to room temperature. After acidified by HCl (3 M, pH 1.0), the reaction mixtures were diluted with EtOAc. Stirring was continued until there are no solid was present. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (EtOAc) to afford 2-nitrobenzamide **18p** in 79% yield (150.9 mg) as a white solid. ^{1}H NMR (400 MHz, d_6-DMSO): δ 8.19 (dt, J = 8.1, 0.9 Hz, 1 H), 7.94 - 7.85 (m, 3 H). ^{13}C NMR (100 MHz, d_6-DMSO): δ 154.20, 148.65, 134.14, 132.87, 132.01, 125.32, 119.70.

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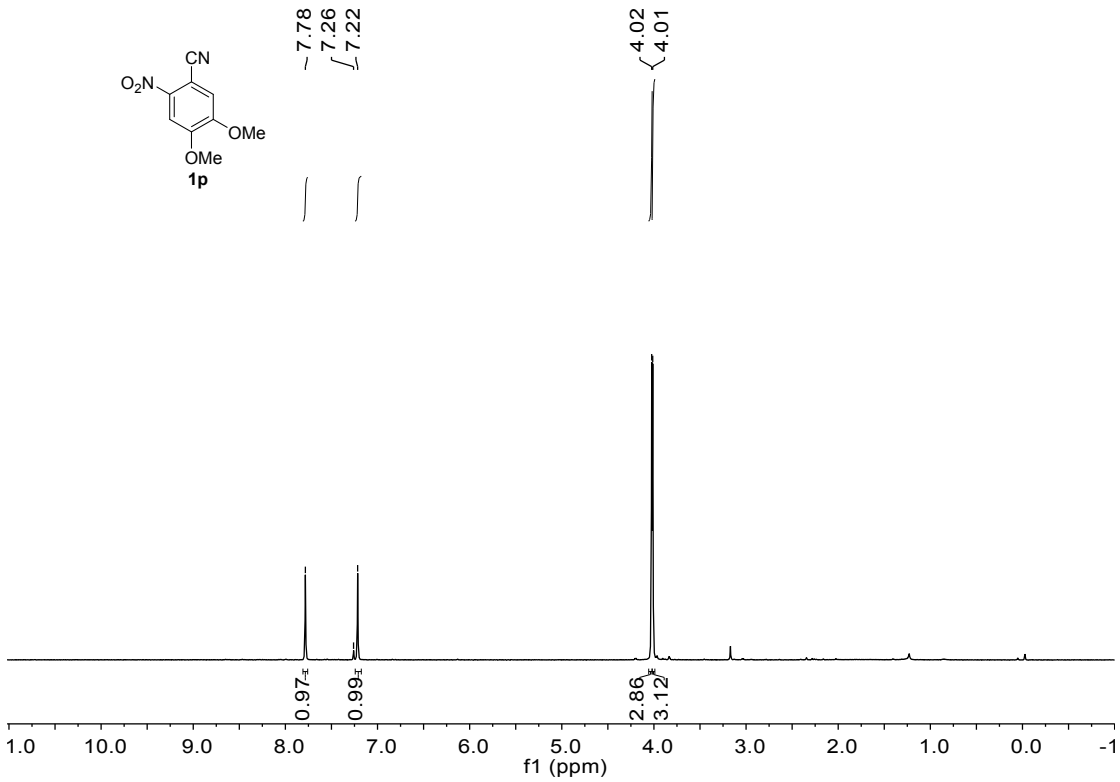
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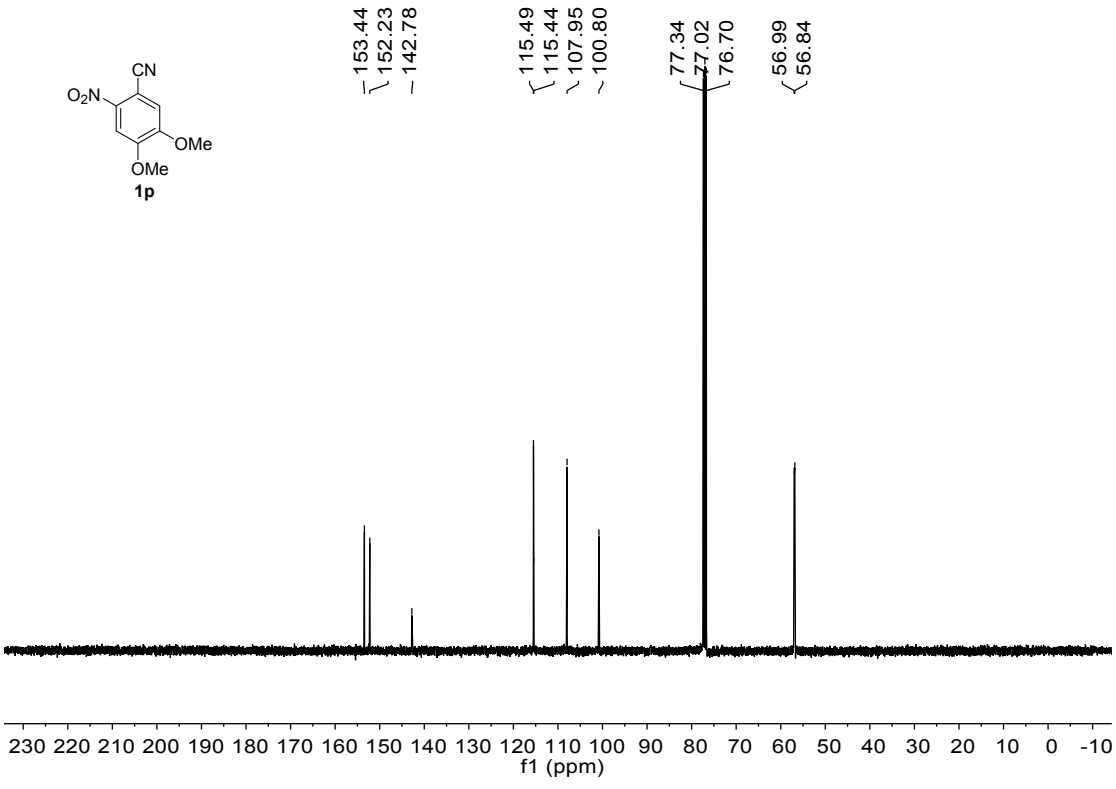
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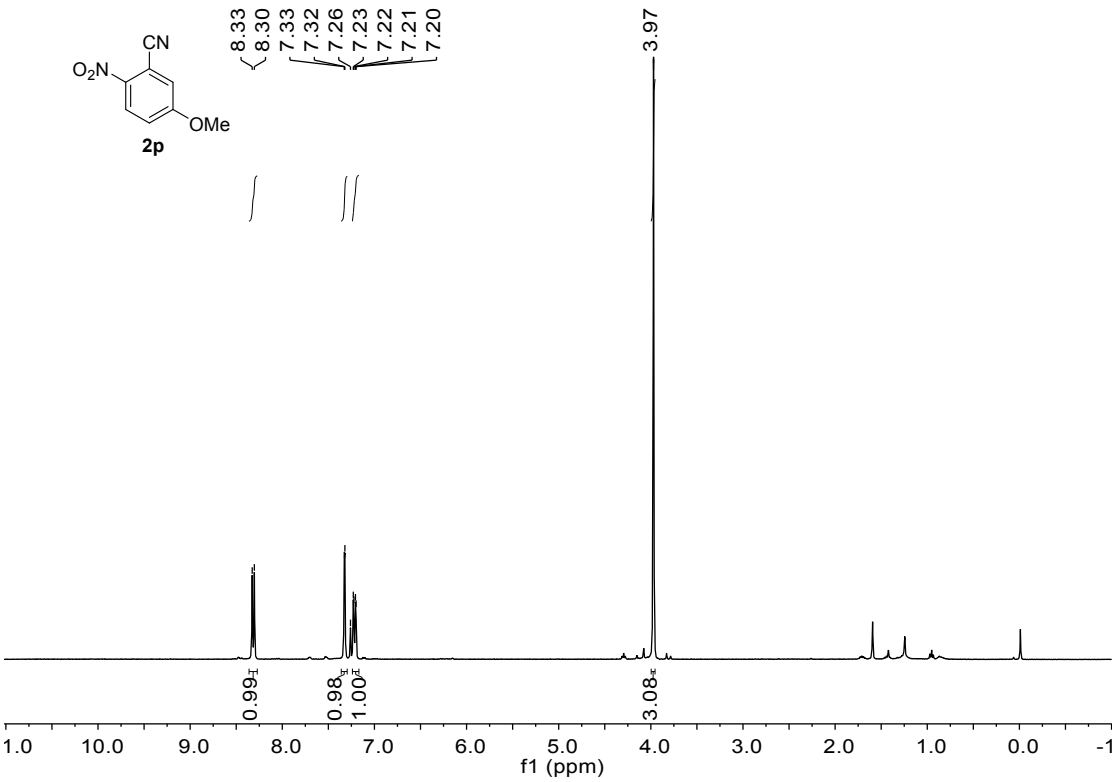
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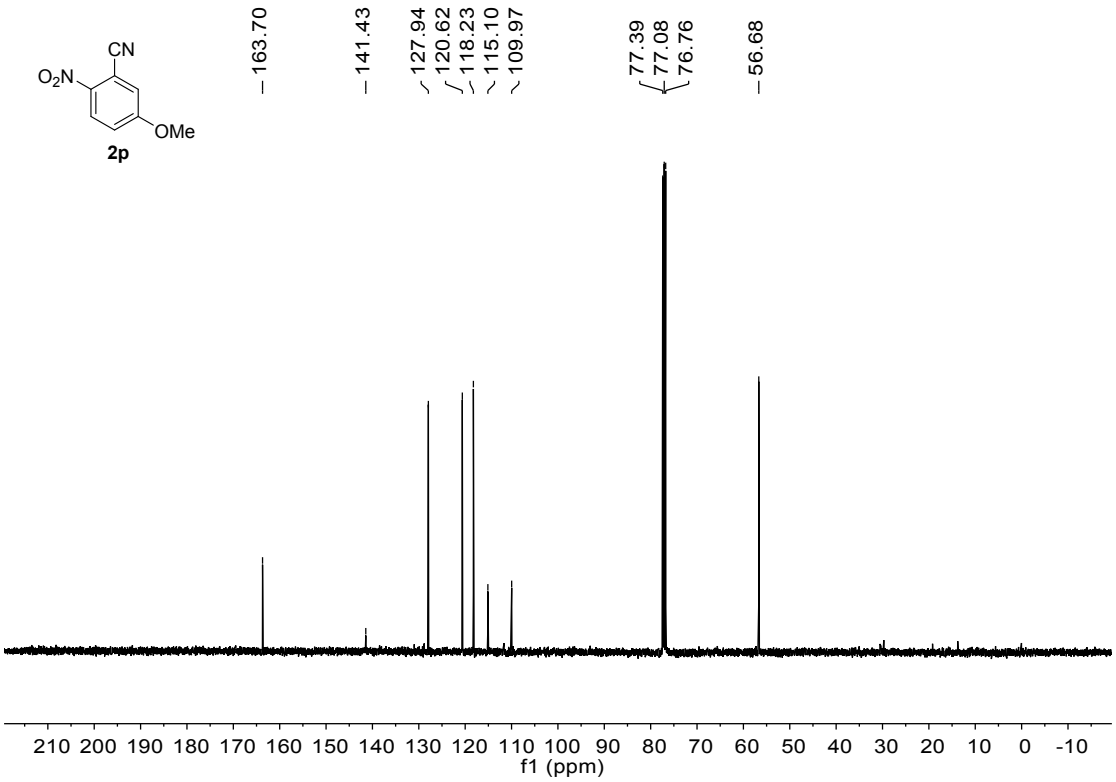
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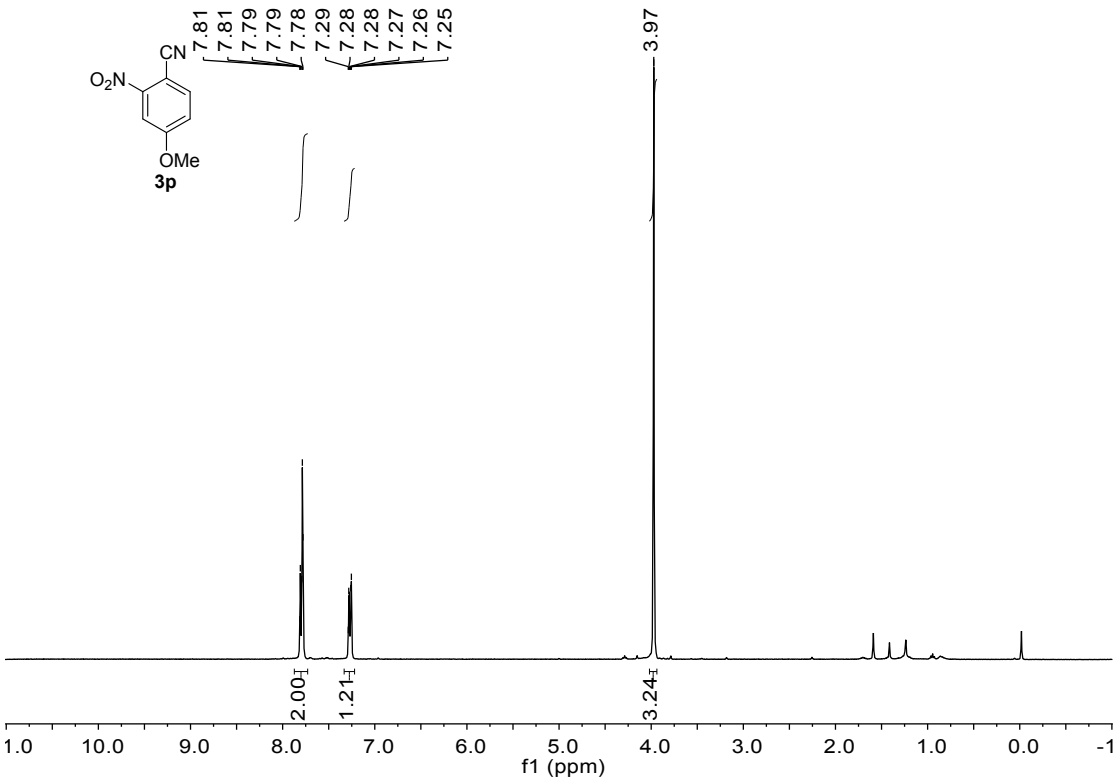
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OMe
3p
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1.21
3.24
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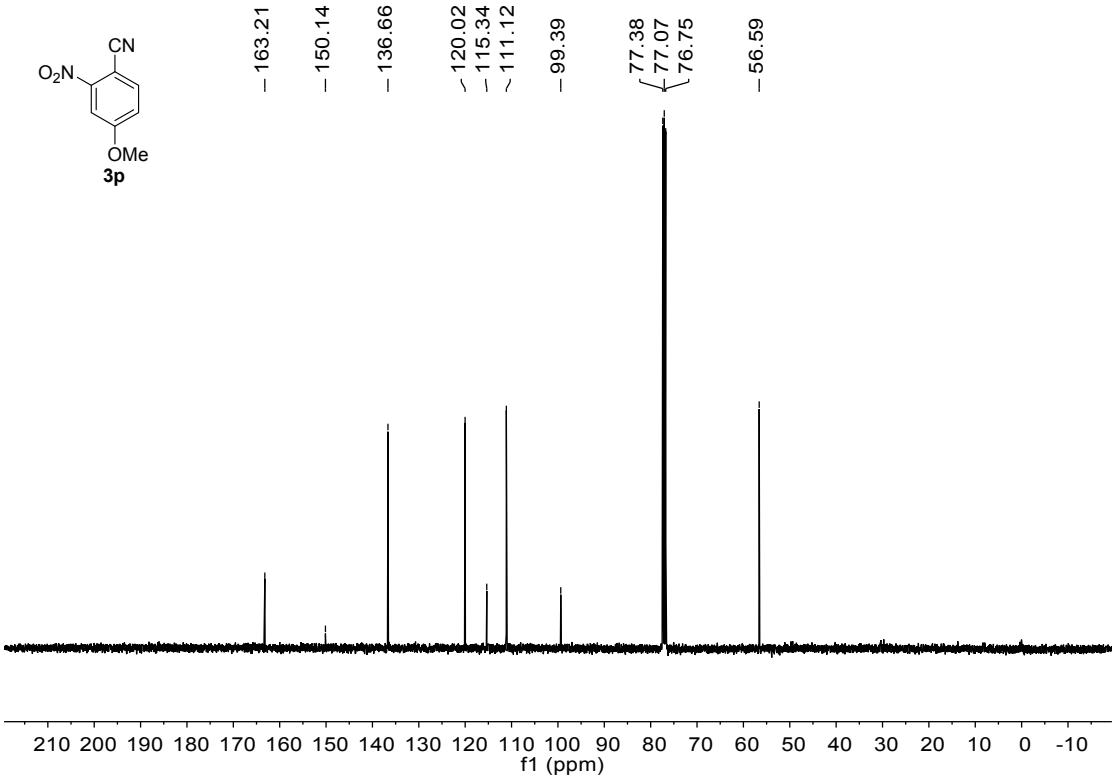
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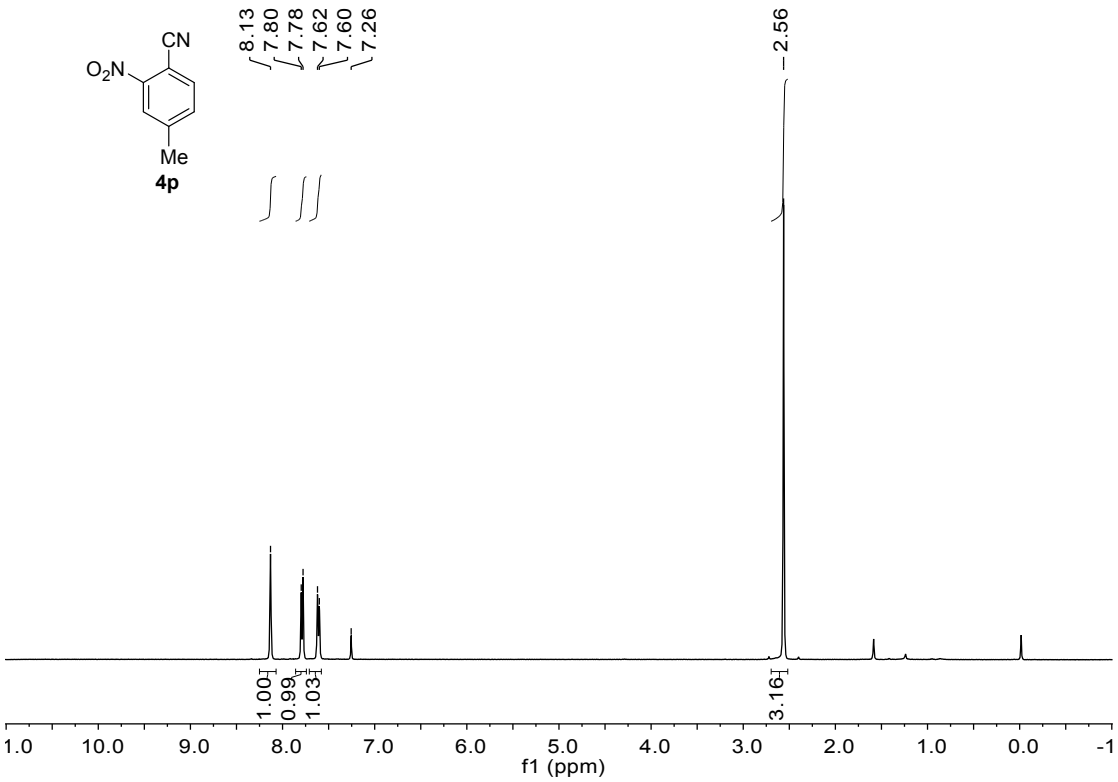
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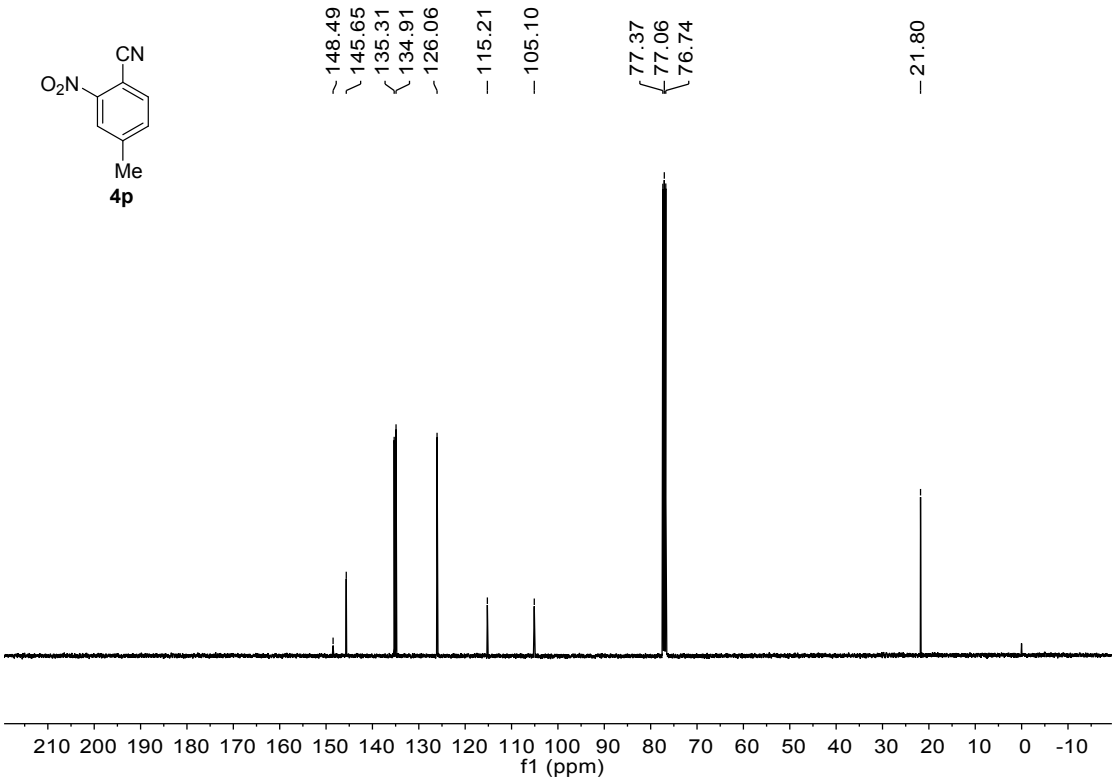
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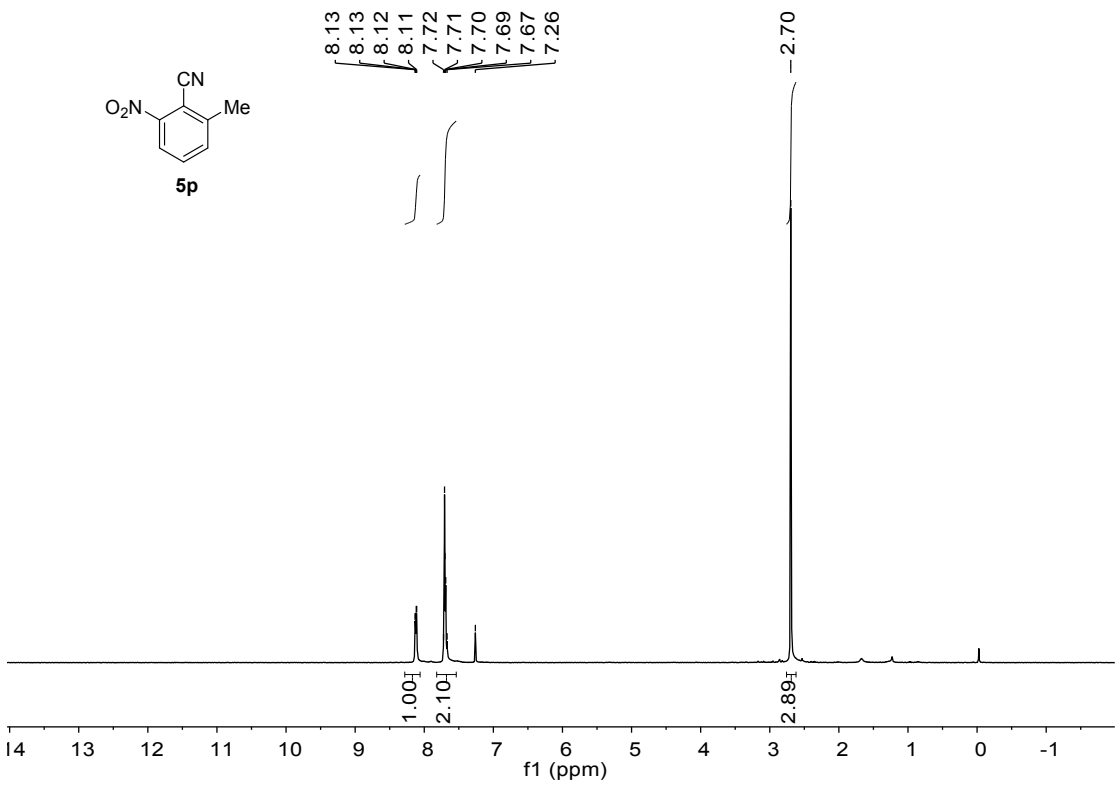
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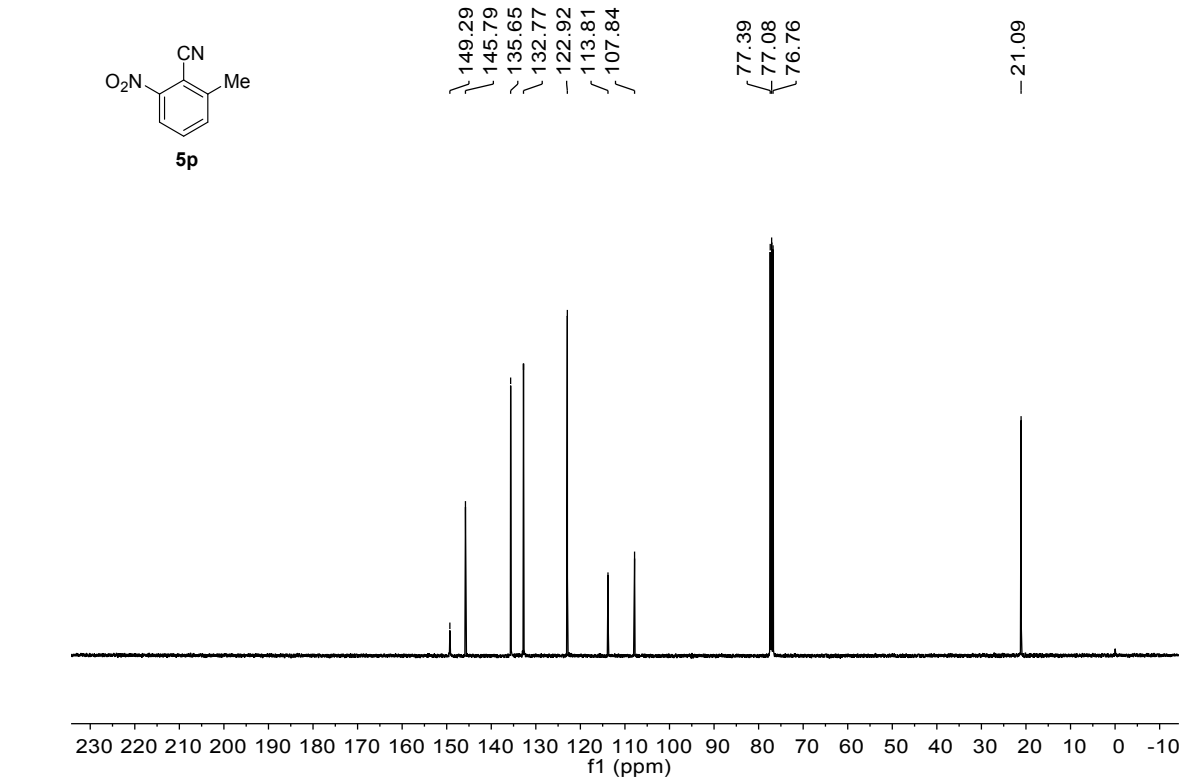
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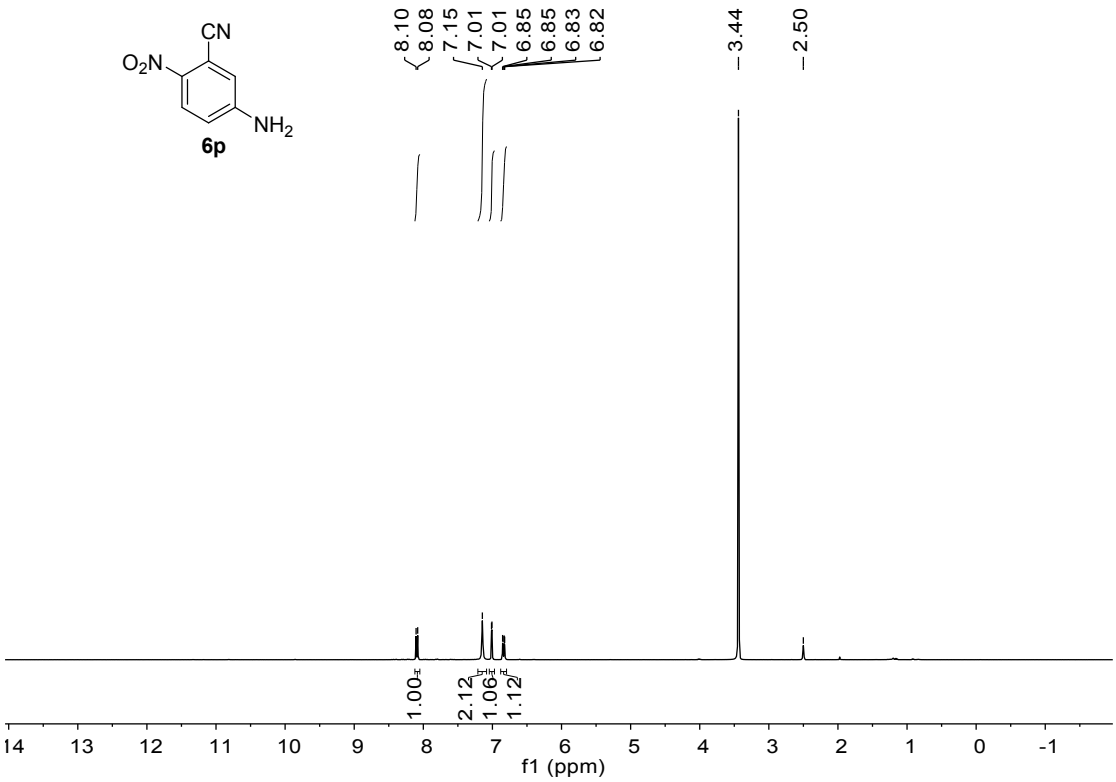
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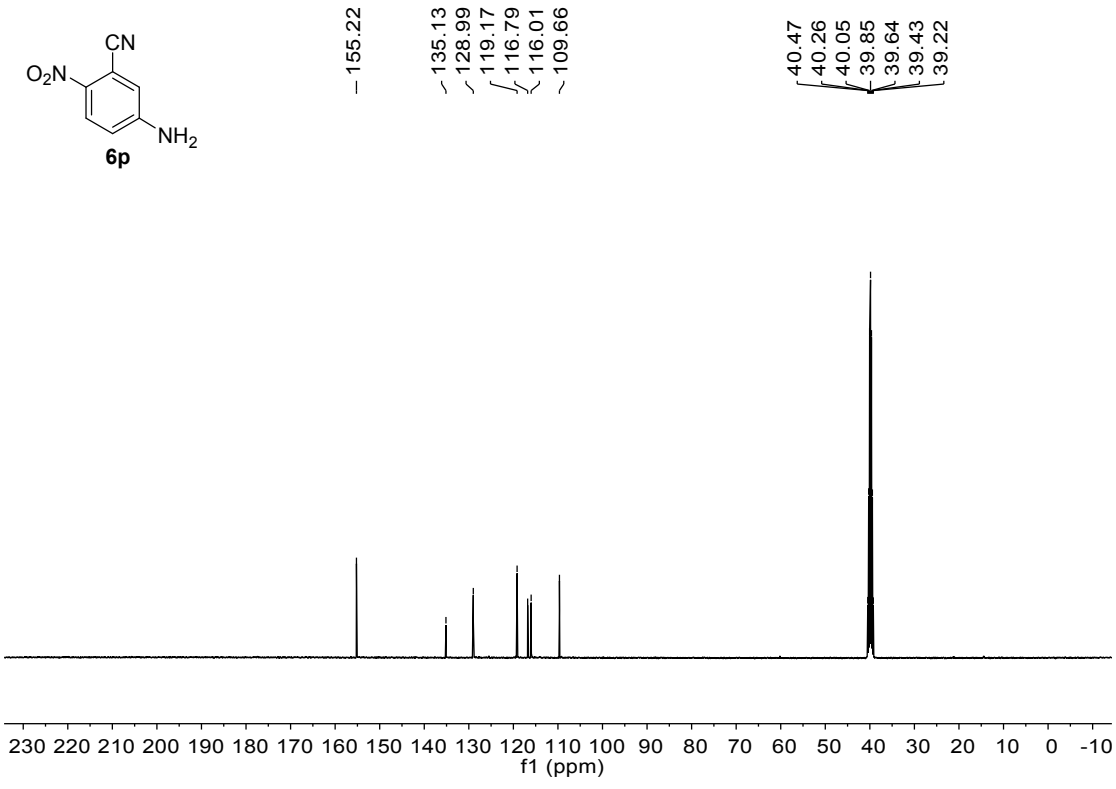
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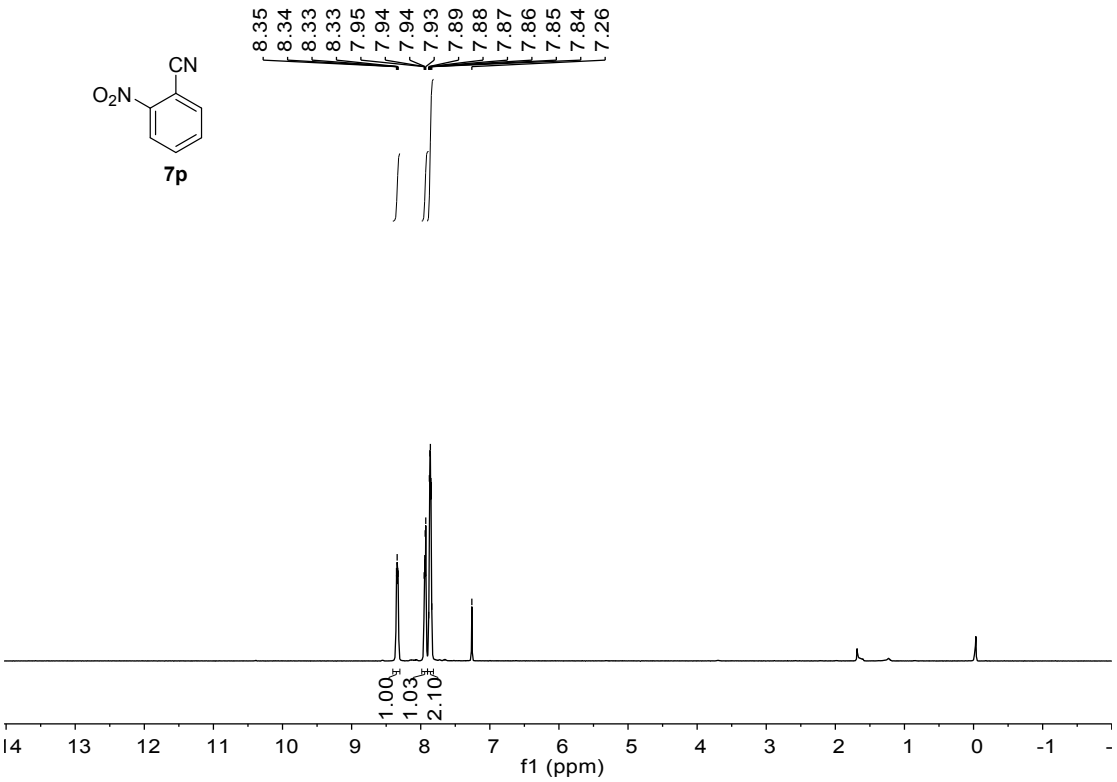
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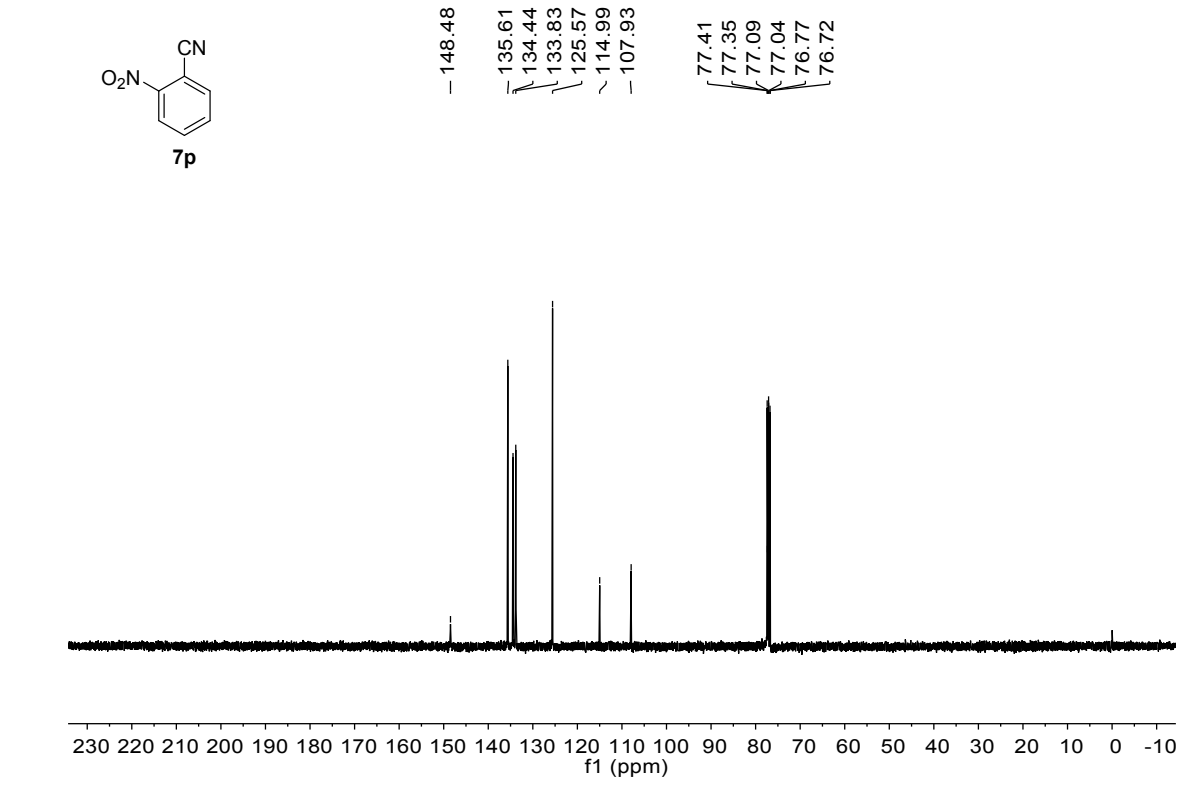
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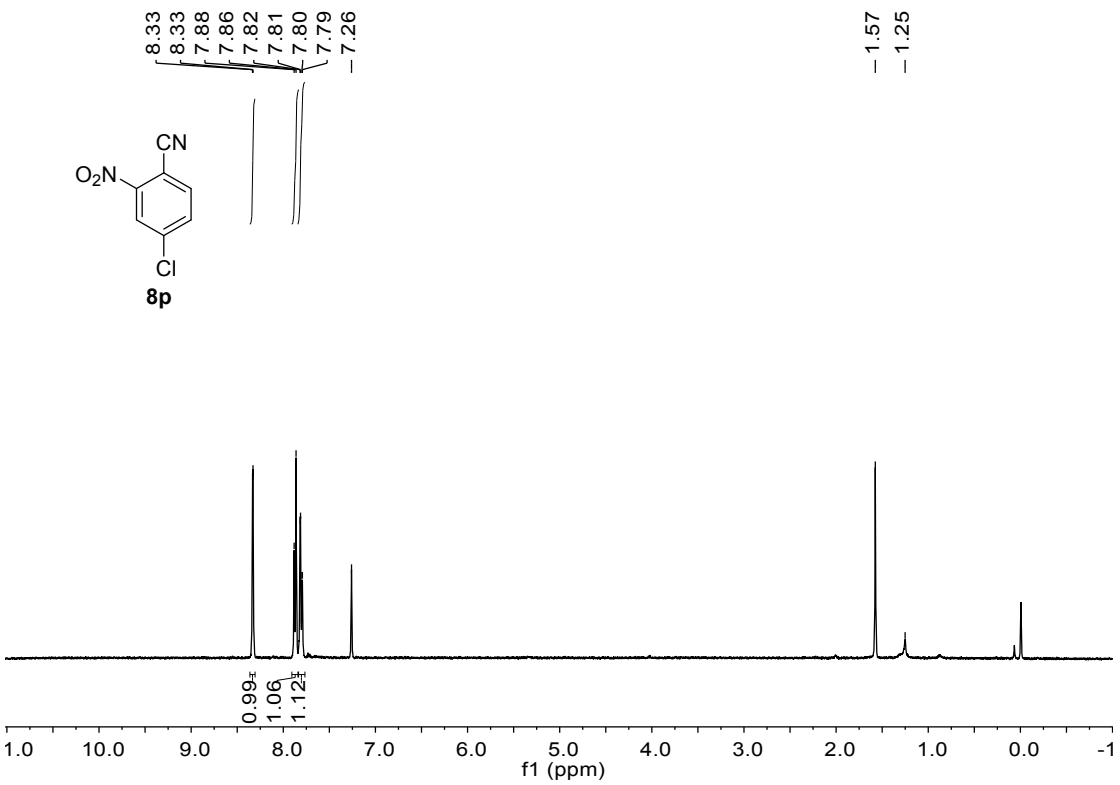
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Cl
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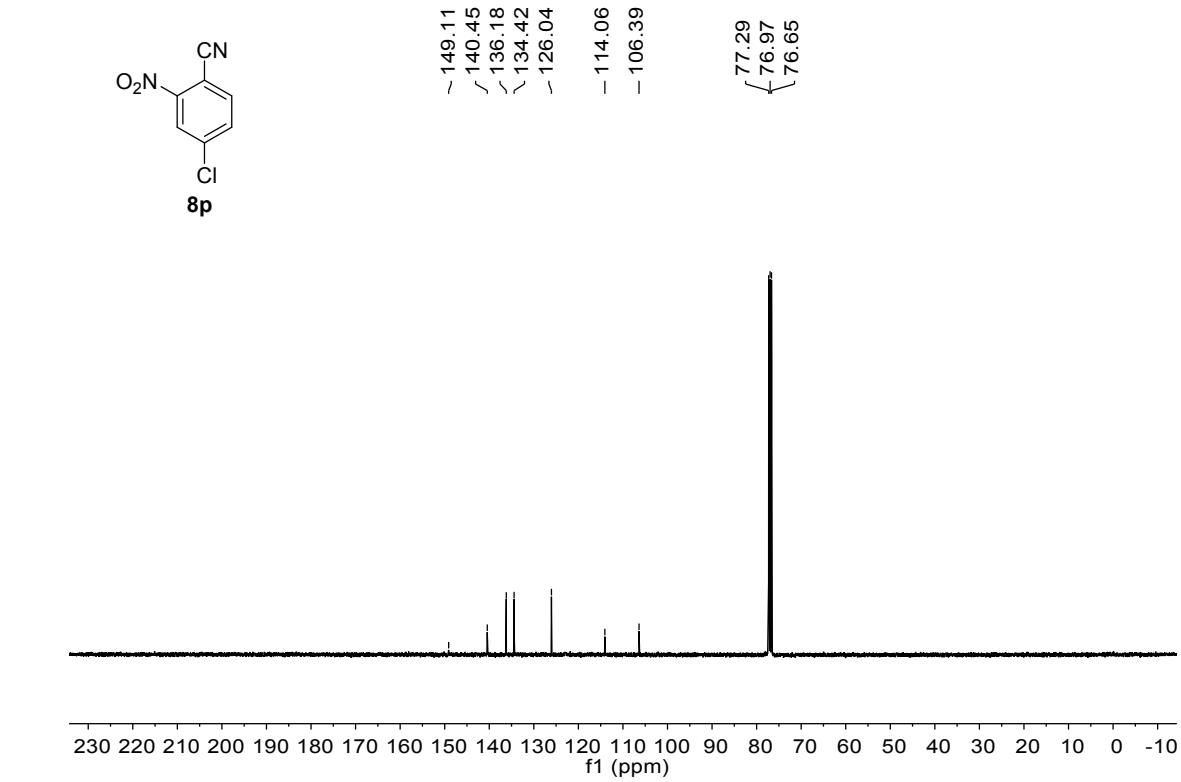
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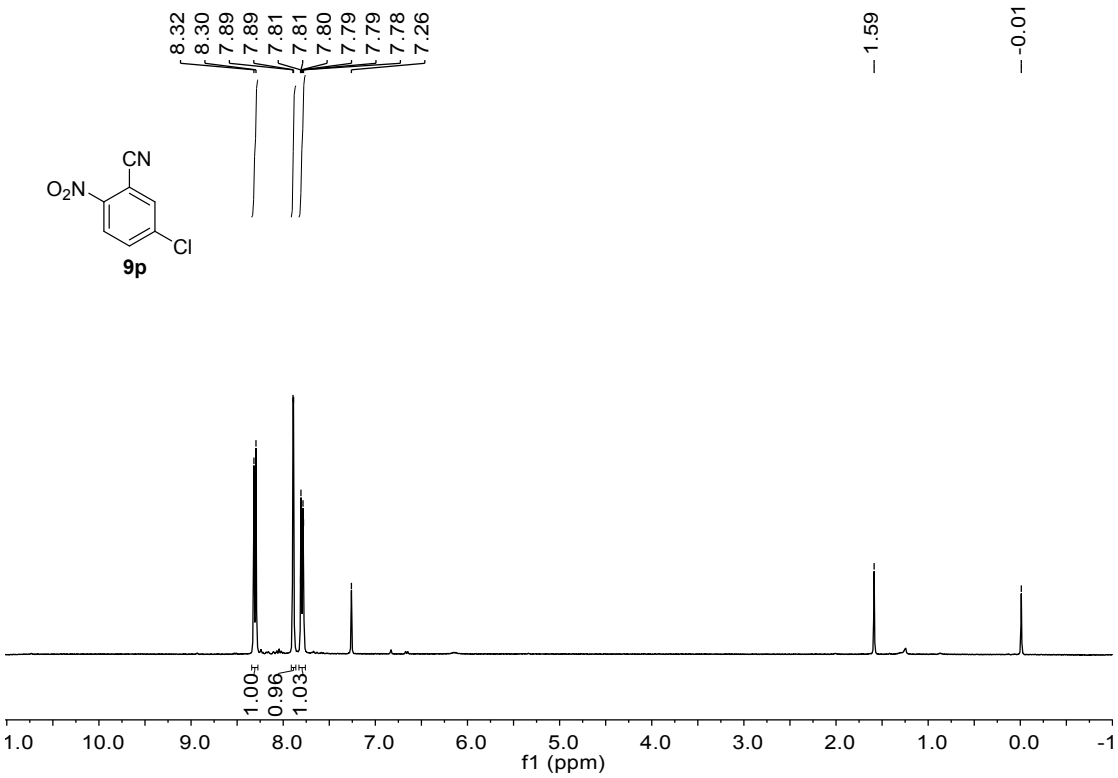
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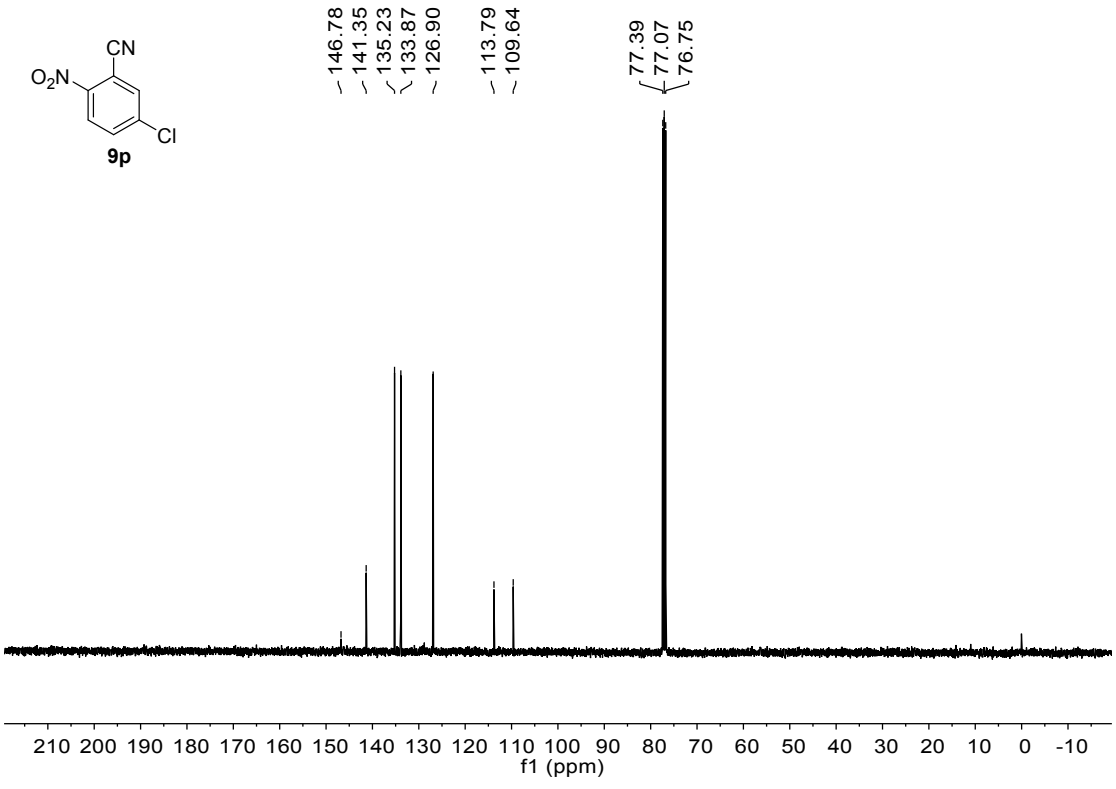
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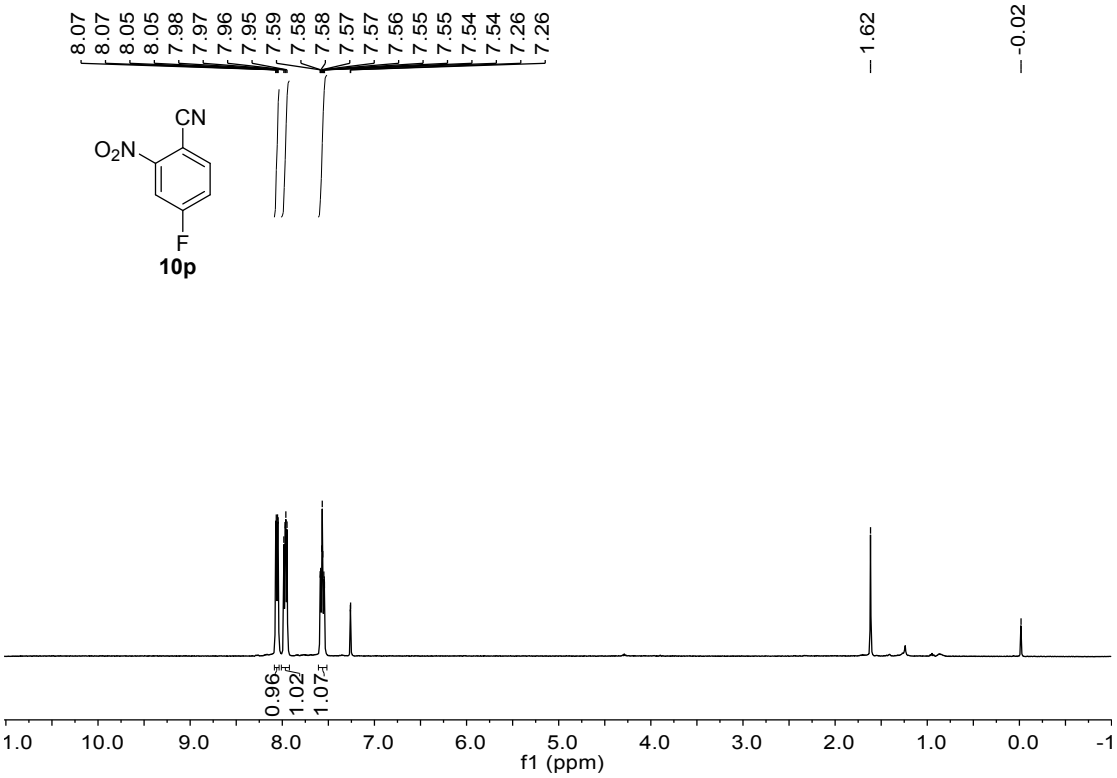
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CN
O2N
F
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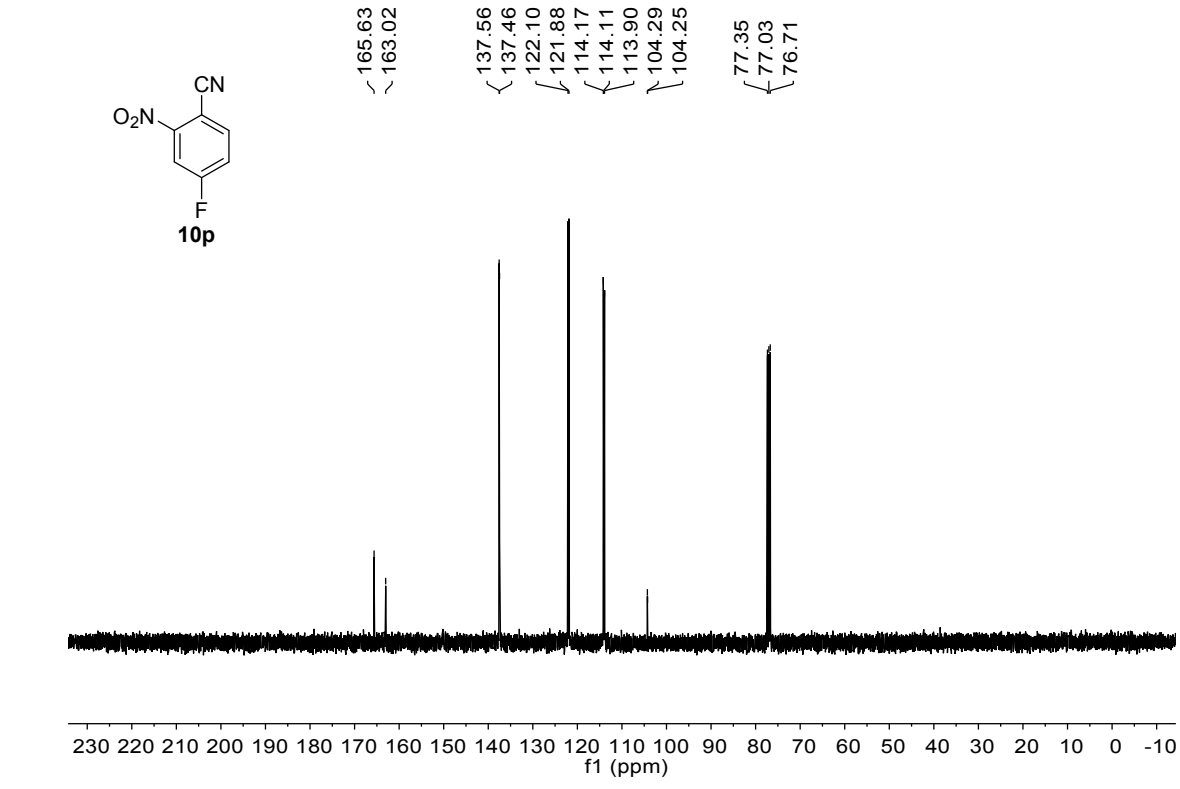
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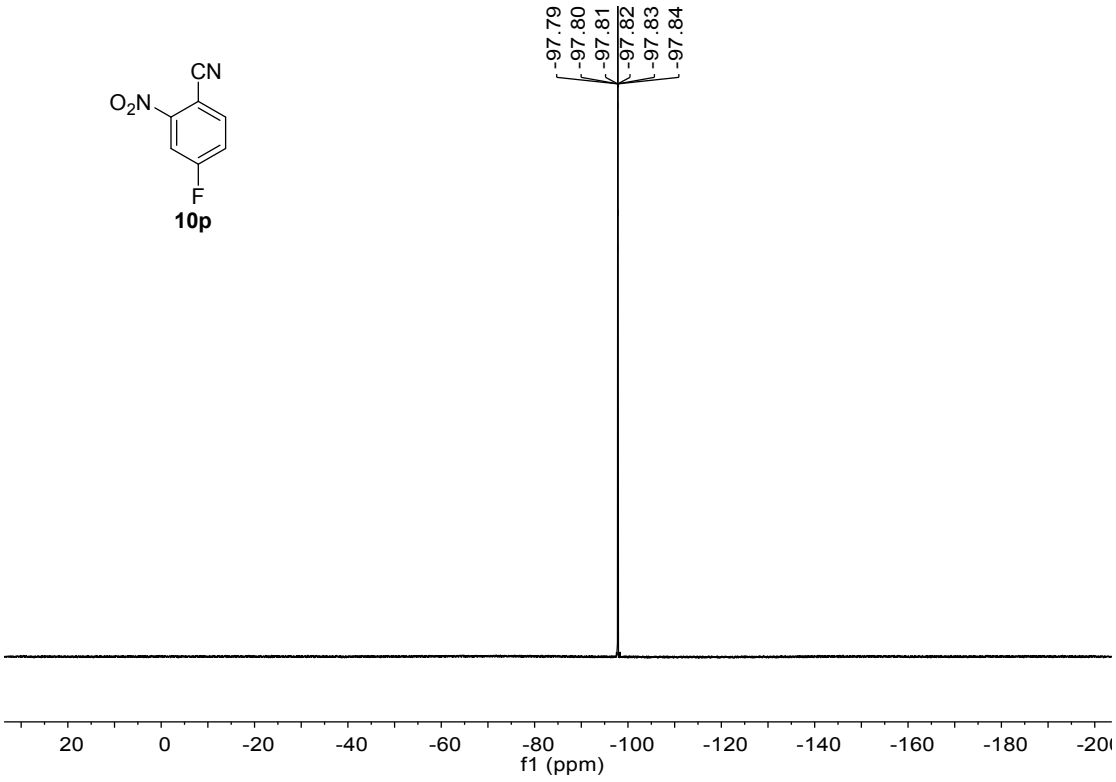
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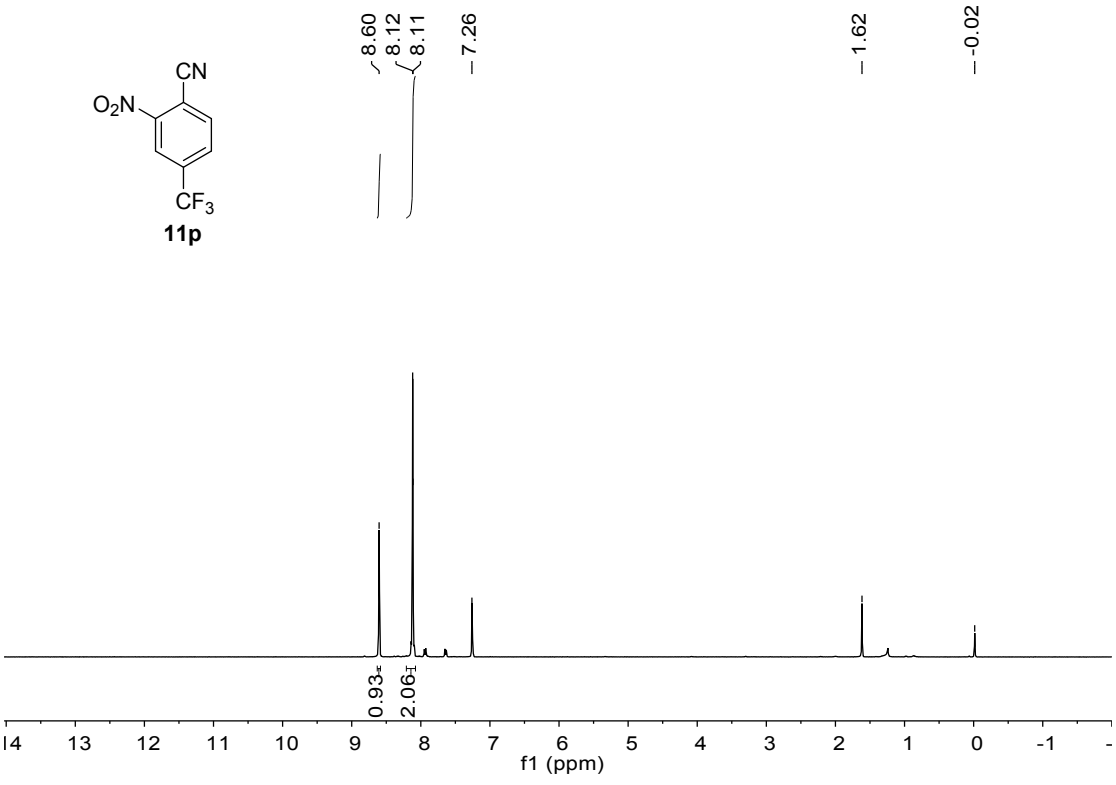
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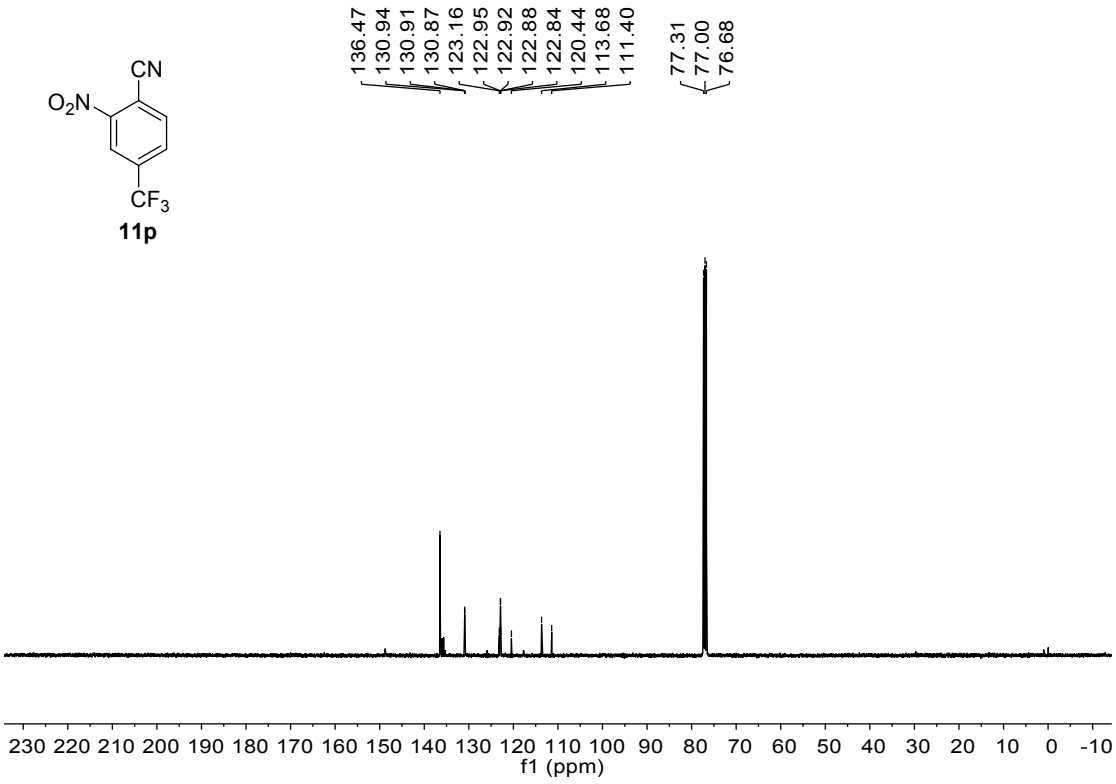
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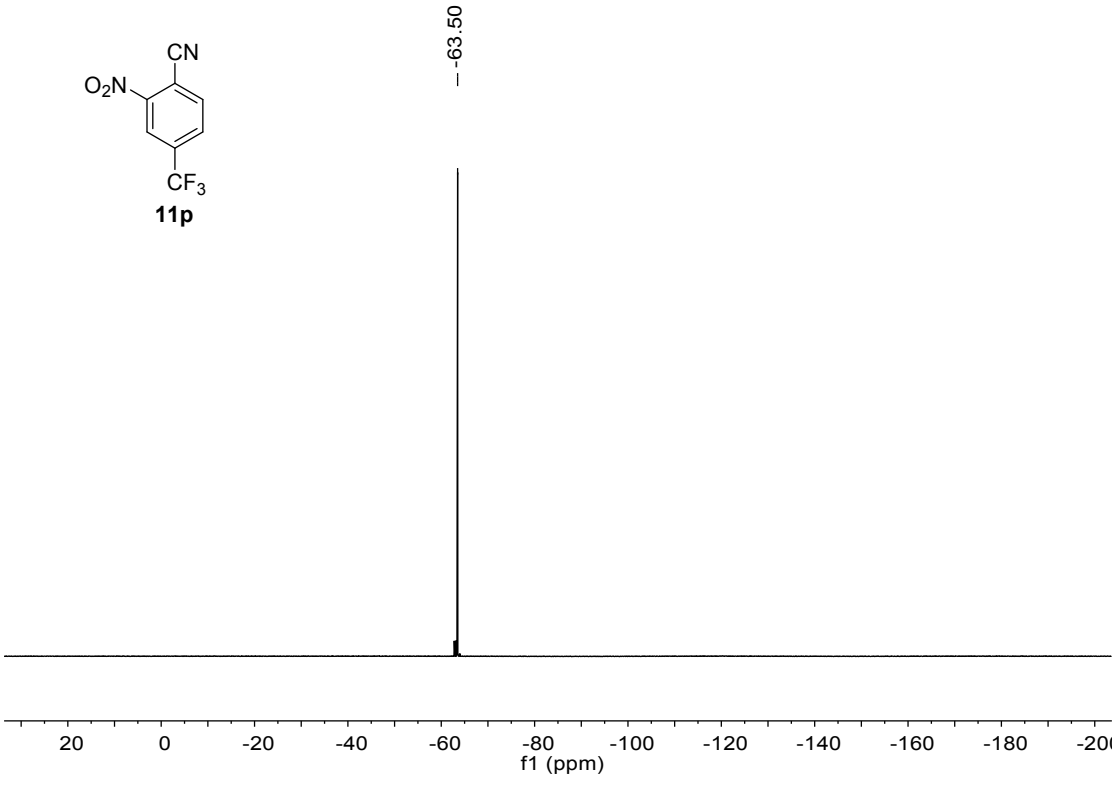
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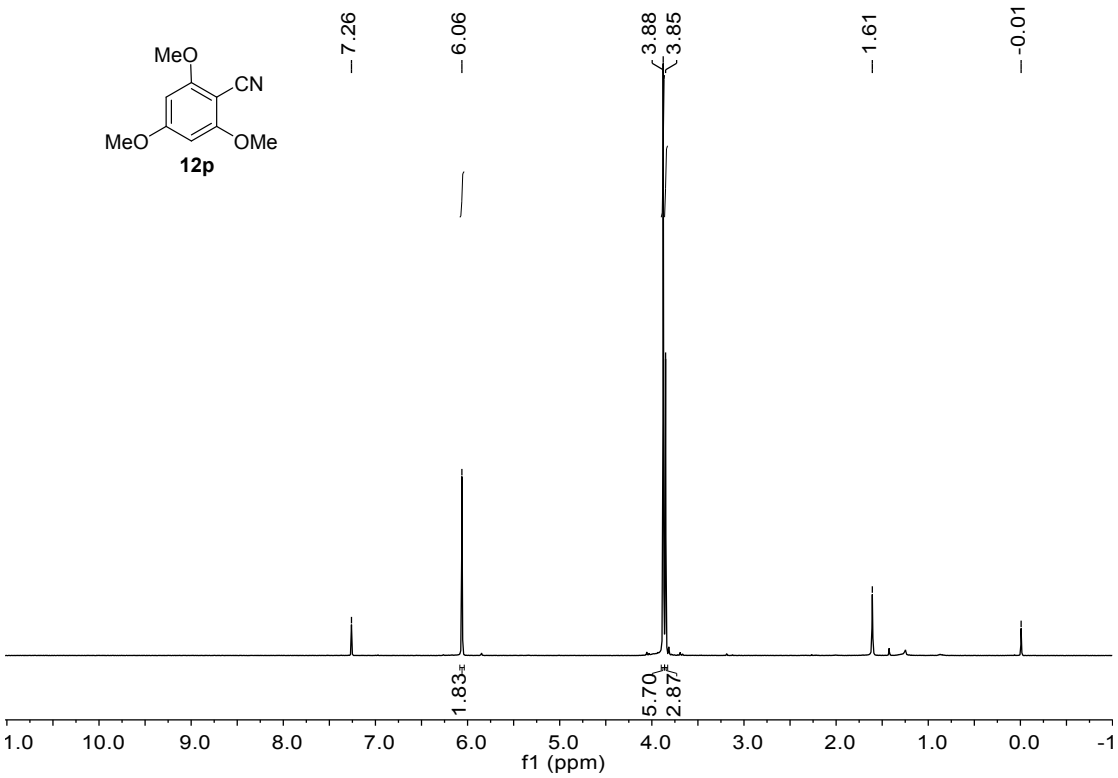
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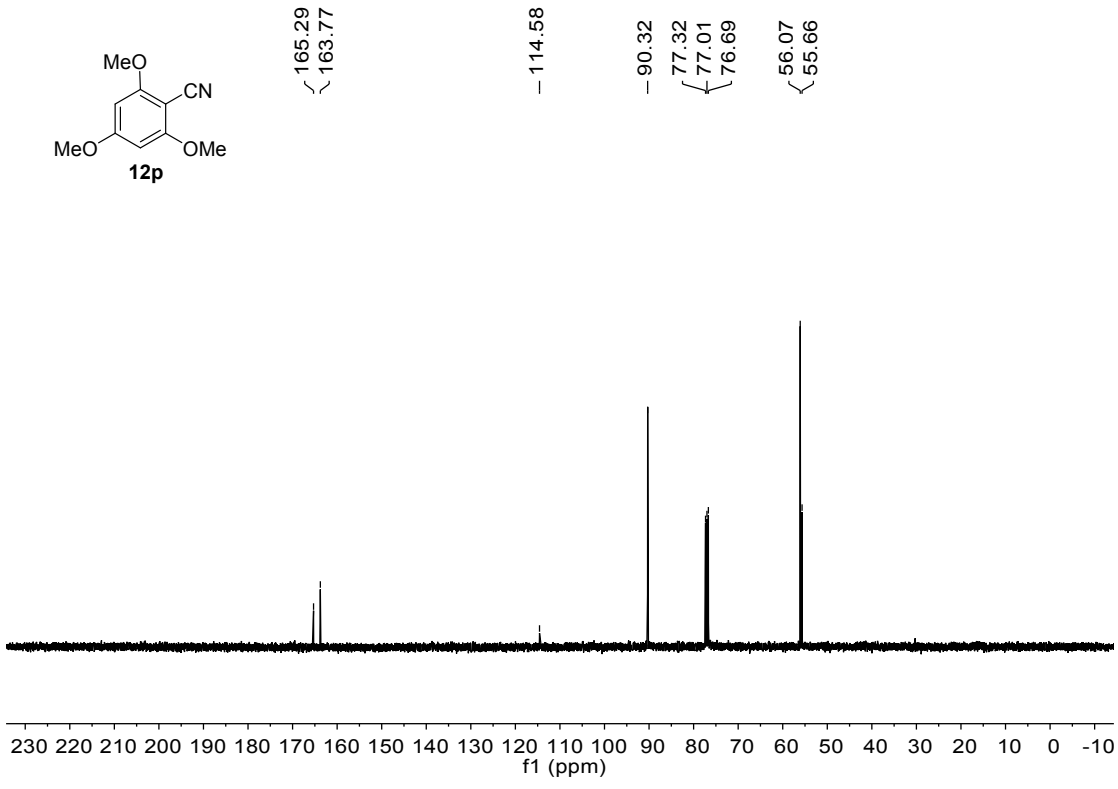
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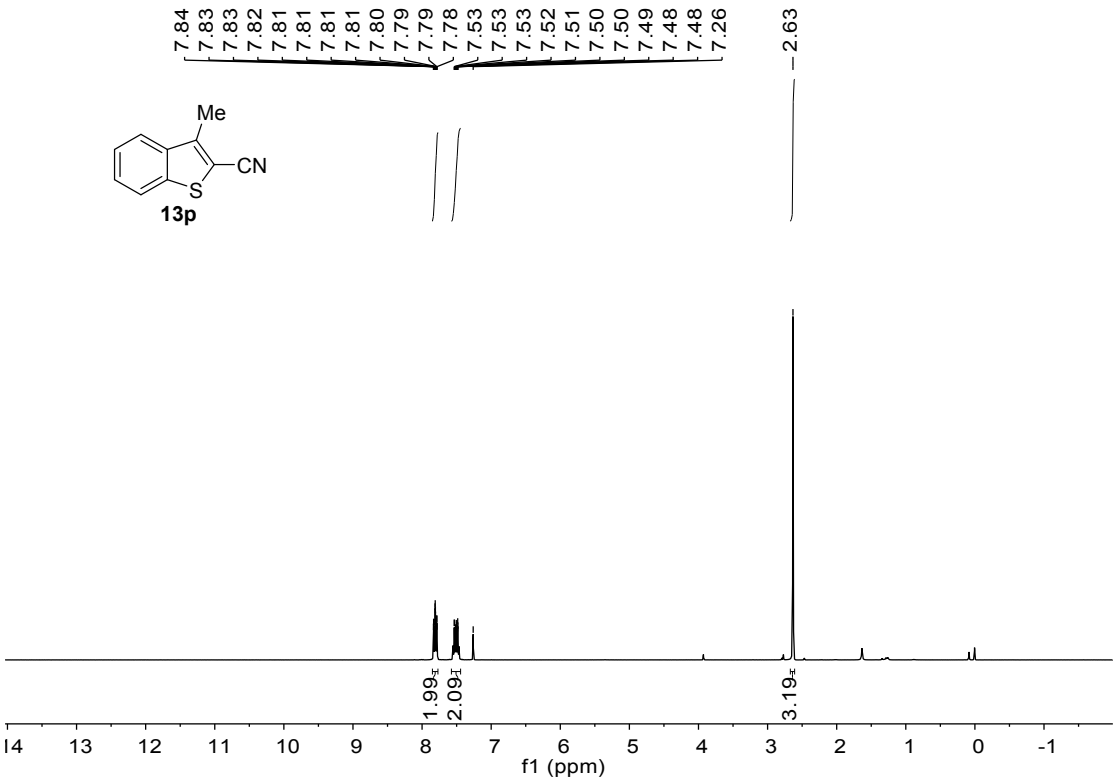
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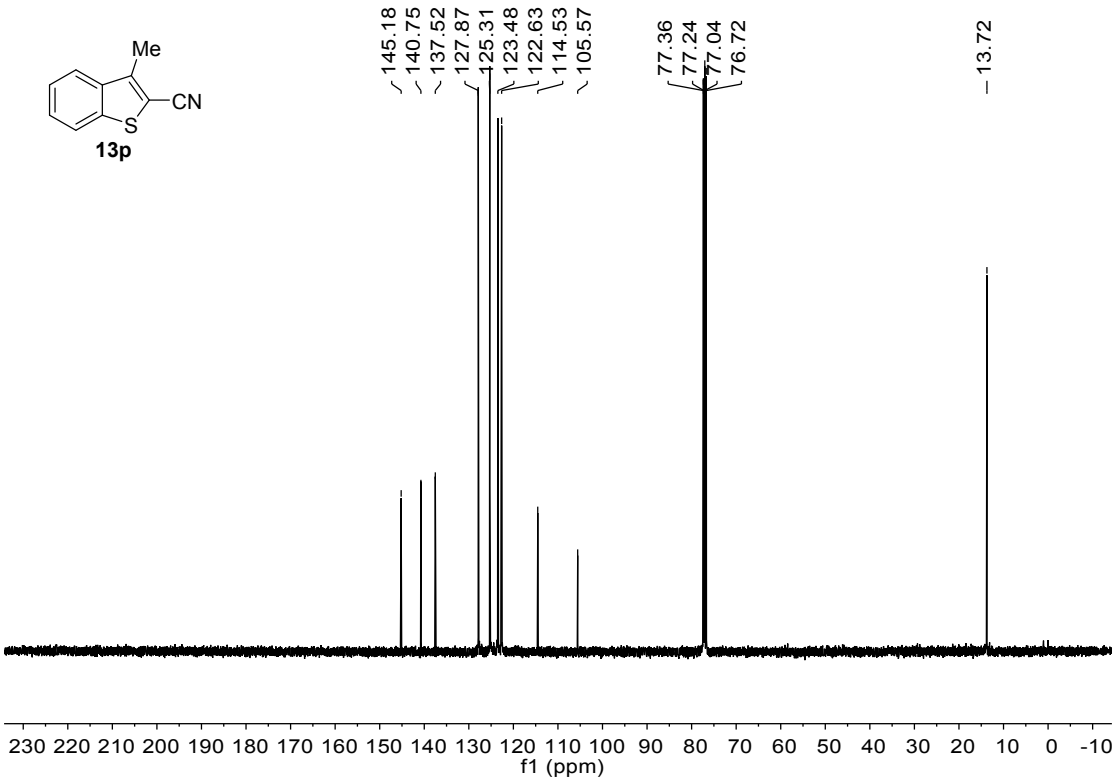
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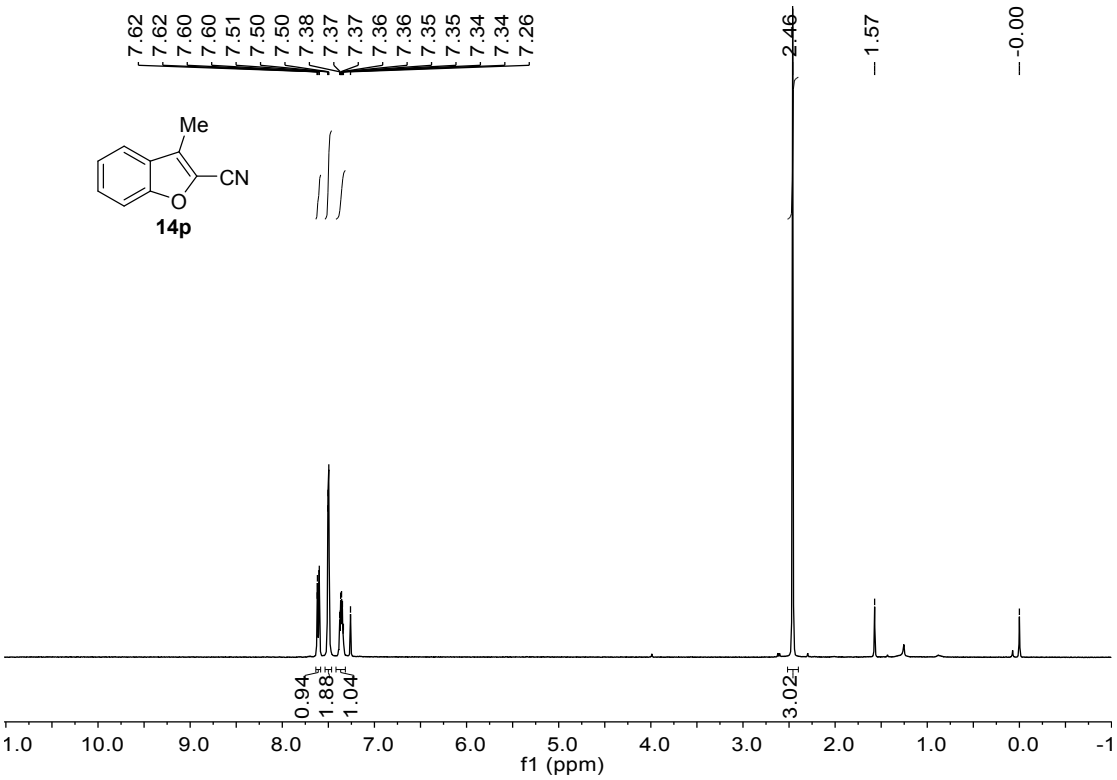
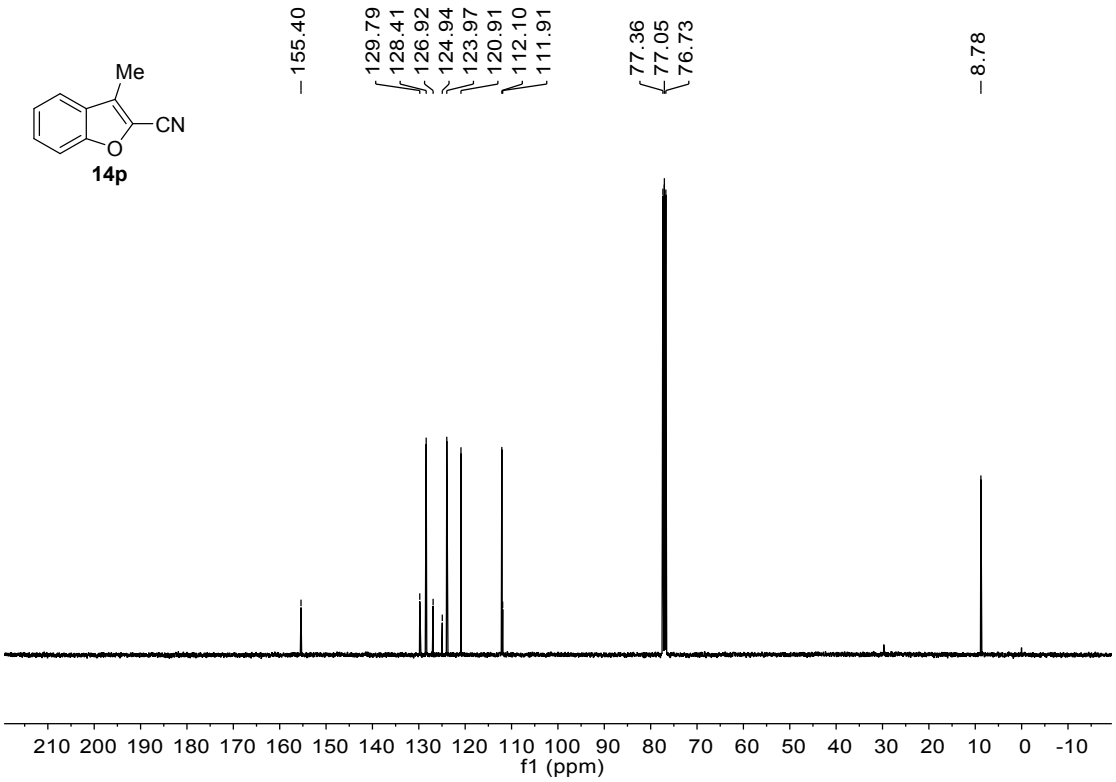
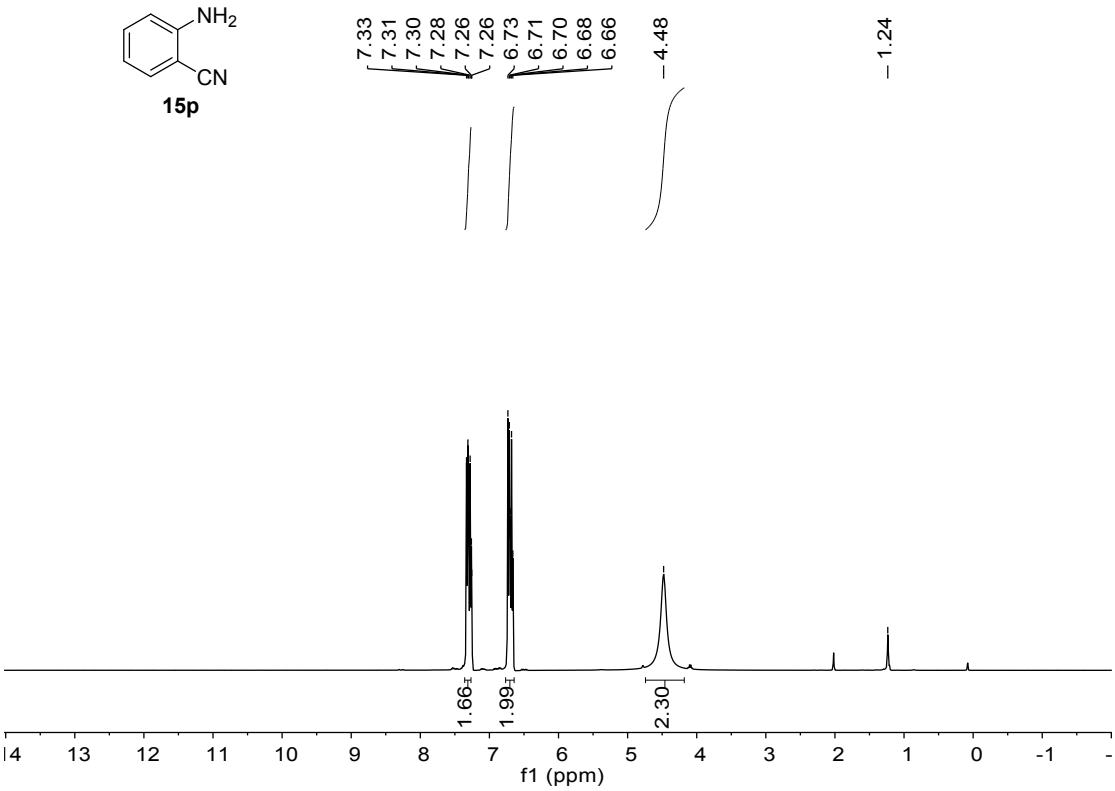
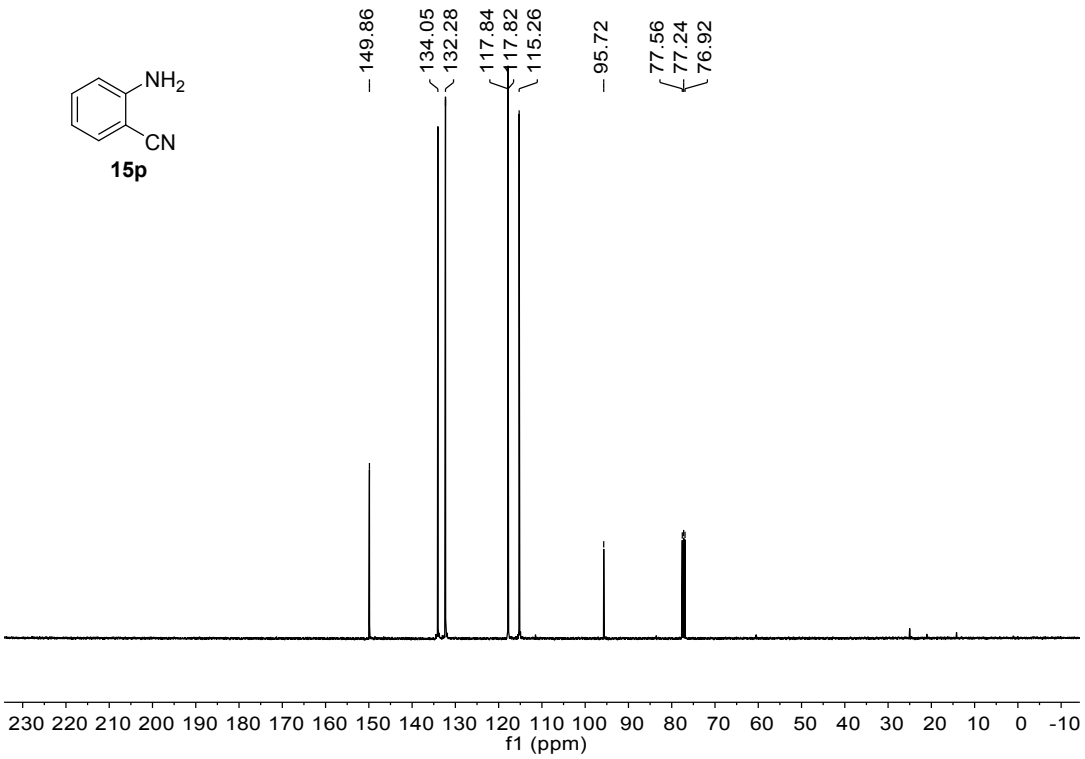
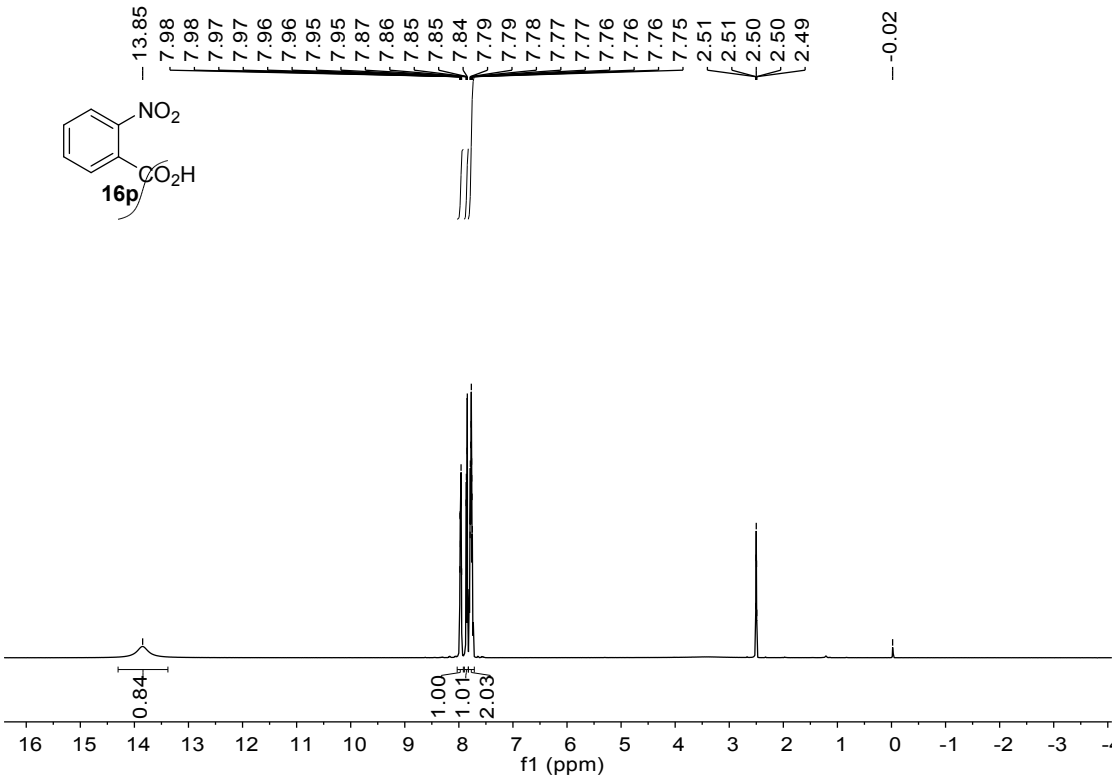
f1 (ppm)

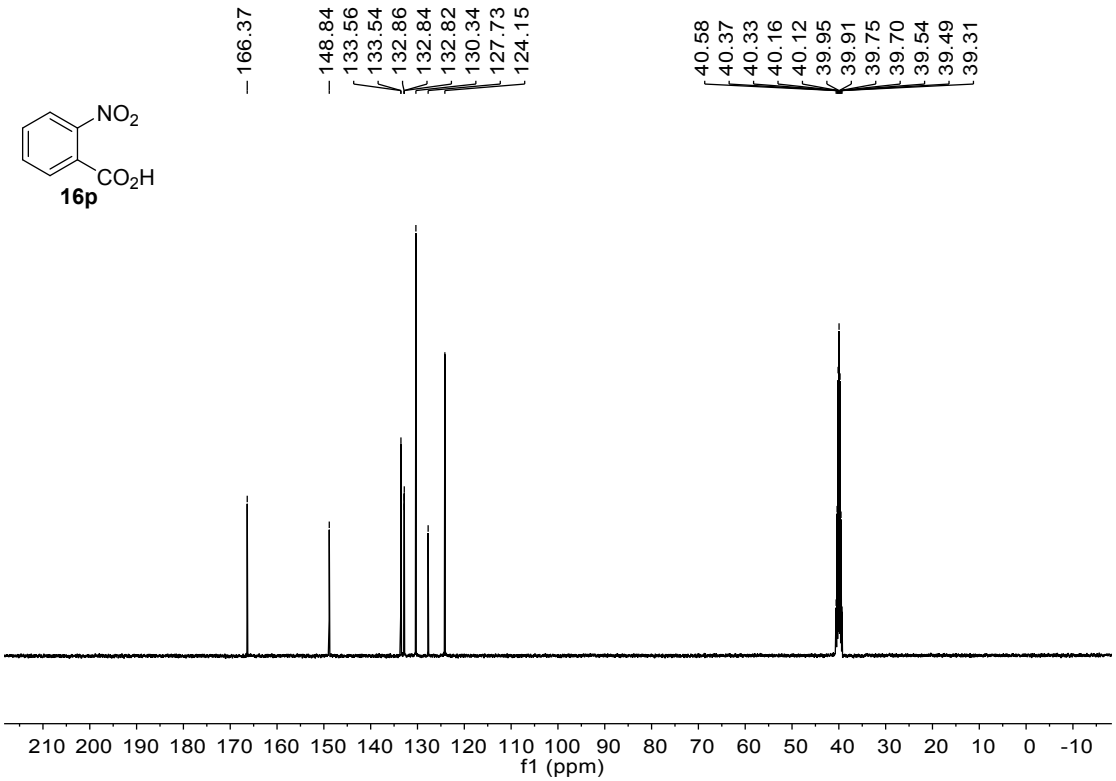

7.62
7.62
7.60
7.60
7.51
7.50
7.50
7.38
7.37
7.37
7.36
7.36
7.35
7.35
7.34
7.34
7.26
2.46
1.57
0.00
Me
CN
O
14p
0.94
1.88
1.04
3.02
1.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1
f1 (ppm)

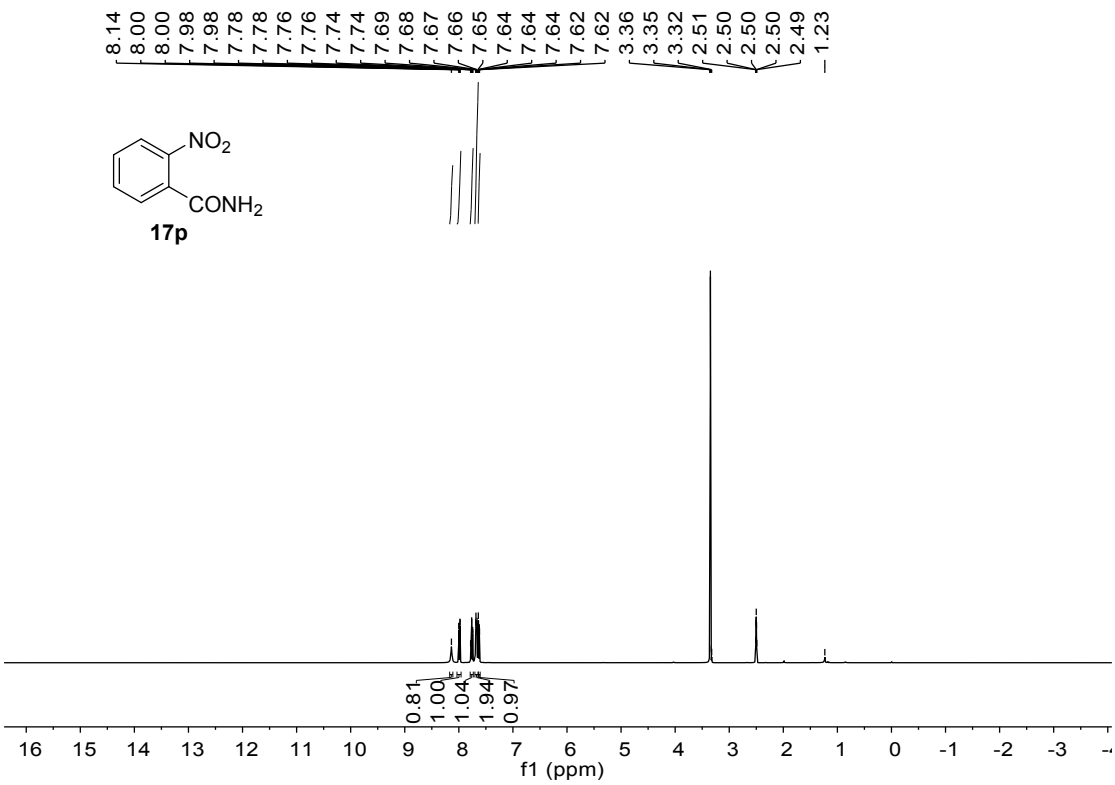

155.40
129.79
128.41
126.92
124.94
123.97
120.91
112.10
111.91
77.36
77.05
76.73
8.78
Me
CN
O
14p
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

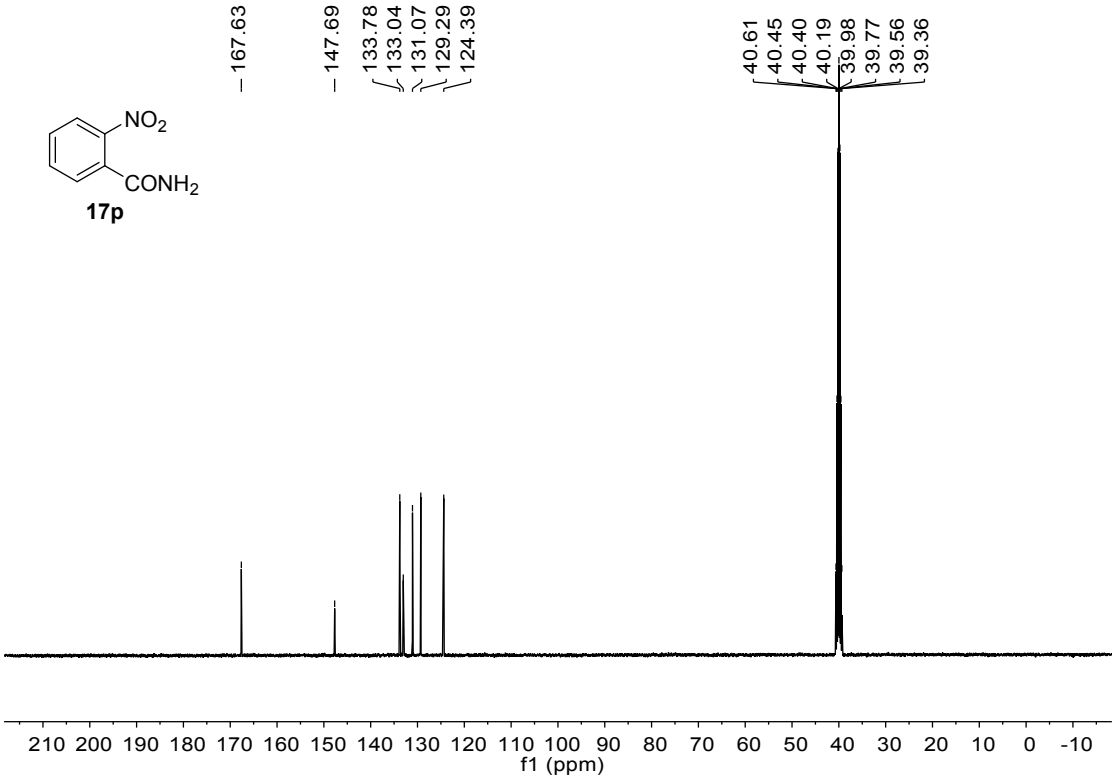

NH2
CN
15p
7.33
7.31
7.30
7.28
7.26
7.26
6.73
6.71
6.70
6.68
6.66
4.48
1.24
1.66
1.99
2.30
f1 (ppm)

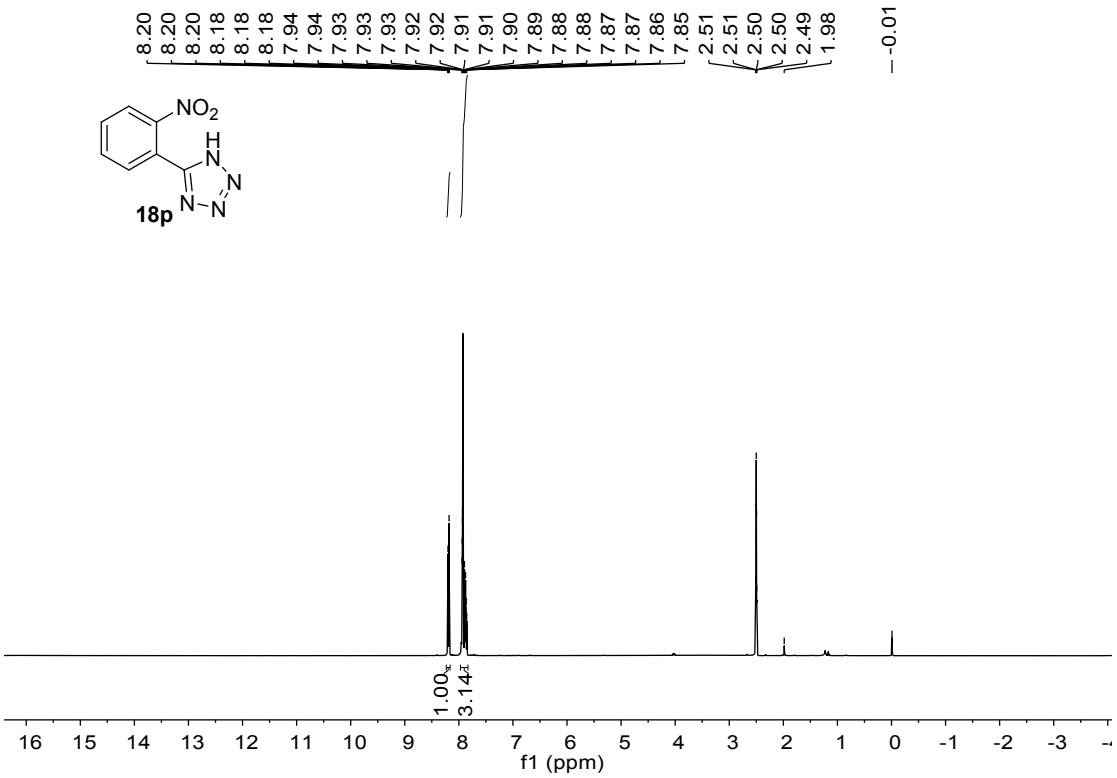

NH2
CN
15p
149.86
134.05
132.28
117.84
117.82
115.26
95.72
77.56
77.24
76.92
f1 (ppm)

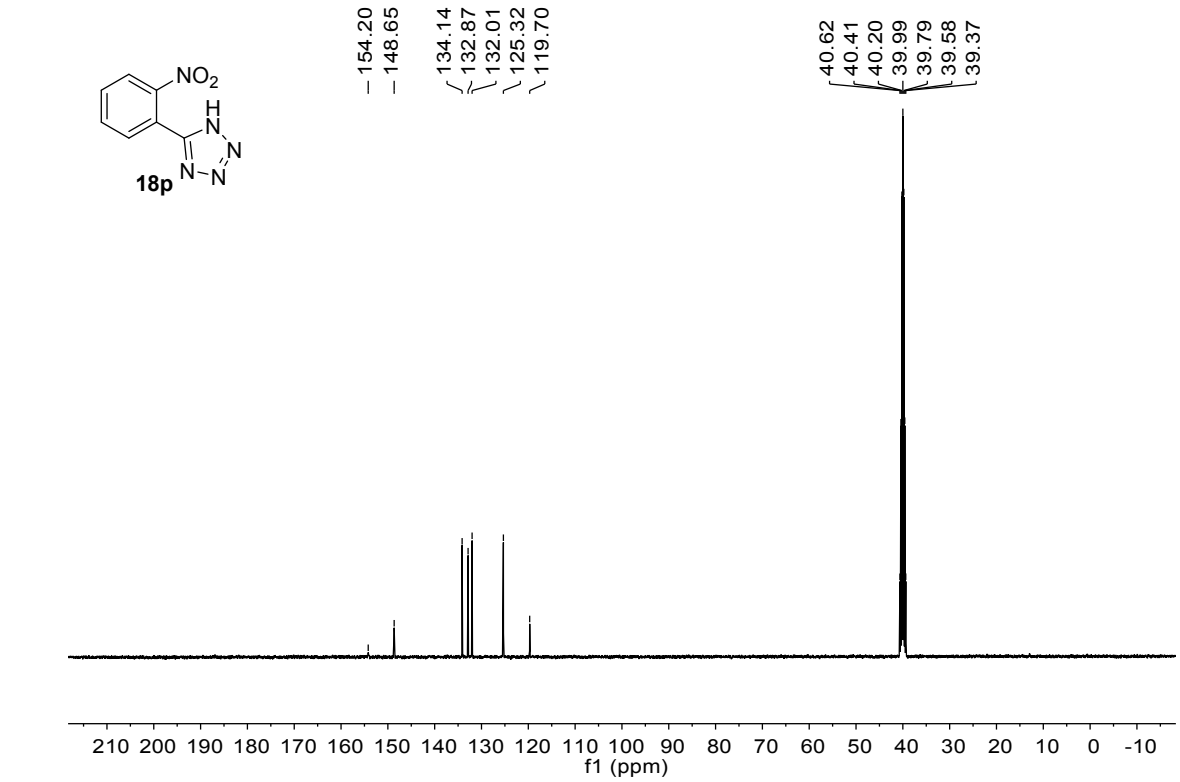

13.85
7.98
7.98
7.97
7.97
7.96
7.96
7.95
7.95
7.87
7.86
7.85
7.85
7.84
7.79
7.79
7.78
7.77
7.77
7.76
7.76
7.76
7.75
2.51
2.51
2.50
2.50
2.49
-0.02
NO2
CO2H
16p
0.84
1.00
1.01
2.03
f1 (ppm)


166.37
148.84
133.56
133.54
132.86
132.84
132.82
130.34
127.73
124.15
40.58
40.37
40.33
40.16
40.12
39.95
39.91
39.75
39.70
39.54
39.49
39.31
NO2
CO2H
16p
f1 (ppm)


8.14
8.00
8.00
7.98
7.98
7.78
7.78
7.76
7.76
7.74
7.74
7.69
7.68
7.67
7.66
7.65
7.64
7.64
7.64
7.62
7.62
3.36
3.35
3.32
2.51
2.50
2.50
2.49
1.23
NO2
CONH2
17p
0.81
1.00
1.04
1.94
0.97
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


167.63
147.69
133.78
133.04
131.07
129.29
124.39
40.61
40.45
40.40
40.19
39.98
39.77
39.56
39.36
NO2
CONH2
17p
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)


8.20
8.20
8.20
8.18
8.18
8.18
7.94
7.94
7.93
7.93
7.93
7.92
7.92
7.91
7.91
7.90
7.89
7.88
7.88
7.87
7.87
7.86
7.85
2.51
2.51
2.50
2.50
2.49
1.98
-0.01
NO2
H
N
N
N
N
18p
1.00
3.14
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
f1 (ppm)


154.20
148.65
134.14
132.87
132.01
125.32
119.70
40.62
40.41
40.20
39.99
39.79
39.58
39.37
NO2
H
N
N
N
N
18p
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)