Pd-Catalysis in Cyanide-free Synthesis of Nitriles from Haloarenes via Isoxazolines

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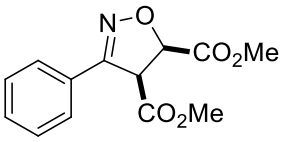
General remarks

Ethyl nitroacetate is an energetic material and should be handled carefully and stored away from strong oxidants and bases. According to SDS of commercial suppliers, it has a flash point of 92 °C. No other hazard sentences are reported.

Reagents were obtained from commercial sources and used as received. 10-Methoxy-2a,2a[1]-dihydroxantheno[9,1-cd]isoxazole **8** was prepared according to the procedure reported in the literature.[1] DMF was dried and stored over microwave activated 4 Å molecular sieves, degassed by bubbling argon for at least 30 minutes, and stored under an inert atmosphere. Reactions were carried out under nitrogen or argon using standard Schlenk technique. Flash column chromatography was performed on Merck Geduran SI 60 Å silica gel (40−63 μm) and thin-layer chromatography on Merck 60 F254 plates. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 AVANCE spectrometer fitted with a QNP probehead using the solvent as internal standard (7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR for $CDCl_3$, 3.31 ppm for ^{1}H NMR and 49.0 ppm for ^{13}C NMR for CD_3OD and 2.5 ppm for ^{1}H NMR and 39.5 ppm for ^{13}C NMR for DMSO-d_6). The signal patterns were indicated as follows: s = singlet, d = doublet, t = triplet, m = multiplet or br = broad. Exact mass analyses were recorded on Waters LCT Premier XE mass spectrometer equipped with an electrospray ionization source and a time of flight analyzer. All prepared benzonitriles are known compounds and their spectroscopic data correspond to those reported in the literature.

Preparation of isoxazoline 5[2]

To a solution of *N*-hydroxybenzimidoyl chloride (0.150 g, 0.965 mmol) in 10 mL of DMF, dimethyl maleate (0.121 mL, 0.965 mmol) and Et_3N (0.132 mL, 0.965 mmol) were added. The reaction mixture was stirred at room temperature for 30 minutes. The salt was filtered off and the filtrate was concentrated under vacuum to obtain a yellow oil. The resulting crude product was purified by flash chromatography on silica gel (hexane: EtOAc, 8:2) to afford product **5** (0.172 g, 68 %) as a colorless oil and 14% of the *E*-isomer.



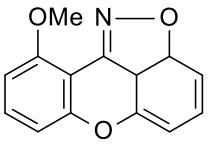
Z-Dimethyl 3-phenyl-4,5-dihydroisoxazole-4,5-dicarboxylate (**5**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71-7.63 (m, 2H), 7.42-7.35 (m, 3H), 5.37 (d, *J* = 11.4 Hz, 1H), 4.78 (d, *J* = 11.4 Hz, 1H), 3.79 (s, 3H), 3.64 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.9, 167.7, 154.6, 130.8, 128.9, 127.4, 126.9, 81.8, 56.5, 53.1, 52.9. HRMS (ESI-TOF) calculated for $C_{13}H_{14}NO_5$ $[M+H]^+$ 264.0866, found: 264.0864.

Ring opening of isoxazoline 5 to benzonitrile (Table 3, entry 7)

Under nitrogen, a Schlenk-type flask equipped with a magnetic bar was charged with K_2CO_3 (58 mg, 0.42 mmol), PhOK (8 mg, 0.06 mmol), PPh_3 (44 mg, 0.168 mmol), **5** mg, 0.21 mmol) and DMF (4.0 mL). The mixture was heated in an oil bath at 120 ˚C for 3h. At the end of the reaction the mixture was allowed to cool to room temperature, diluted with EtOAc (30 mL), washed three times (3 × 30 mL) with a 5% solution of H_2SO_4 and dried over $MgSO_4$. The crude mixture was analyzed by GC and benzonitrile was quantified by using the internal standard method. The other reaction reported in 3 were performed in a similar way.

Preparation of isoxazoline 8[1]

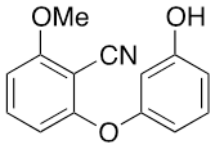
To a solution of 2-phenoxy-6-methoxybenzaldoxime (500 mg, 2.06 mmol) in $CHCl_3$ (410 mL) at 0 ºC were added Et_3N (0.429 mL, 3.08 mmol) and *N*-chlorosuccinimide (412 mg, 3.08 mmol). The mixture was refluxed for 4.5 h and then cooled to room temperature, washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by flash column chromatography on silica gel (hexane: EtOAc, 3:1) to give product **8** (260 mg, 52%) as a white solid.



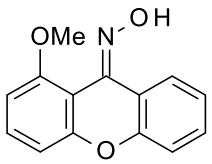
10-Methoxy-2a,2a[1]-dihydroxantheno[9,1-cd]isoxazole (**8**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 1H), 6.65 (dd, *J* = 8.4, 0.5 Hz, 1H), 6.59 (dd, *J* = 8.4, 0.5 Hz, 1H), 6.12 (dd, *J* = 9.6, 6.5 Hz, 1H), 5.76 (ddd, *J* = 9.6, 4.5, 1.5 Hz, 1H), 5.56-5-52 (m, 2H), 4.33 (d, *J* = 15.5 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 154.5, 146.1, 145.2, 132.0, 126.0, 117.9, 109.2, 104.9, 103.5, 102.2, 77.0, 56.4, 46.9. HRMS (ESI-TOF) calculated for $C_{14}H_{12}NO_3$ $[M+H]^+$ 242.0812, found: 242.0774.

Ring opening of isoxazoline 8 to 2-(3-hydroxyphenoxy)-6-methoxybenzonitrile (9) and 1-methoxy-9H-xanthen-9-one oxime (10)

To a 10 mL round bottom flask were added under argon isoxazoline **8** (20 mg, 0.082 mmol), $Pd(dba)_2$ (1.2 mg, 0.002 mmol), K_2CO_3 (34.4 mg, 0.24 mmol) and PPh_3 (1.0 mg, 0.004 mmol). DMF (2.5 mL) was then added *via* syringe. The resulting suspension was stirred at room temperature for 1h, then diluted with AcOEt (5 mL), washed with a saturated solution of $NaHCO_3$ (3 x 5 mL) and dried over Na_2SO_4. The solvent was removed under vacuum and the product was isolated by flash column chromatography on silica gel using DCM:MeOH (9.8:0.2) as eluent. Product **9** was isolated as a white solid (2.7 mg, 14%). From the same reaction mixture product **10**[1] was obtained as a white solid in 31% yield (6 mg).



2-(3-Hydroxyphenoxy)-6-methoxybenzonitrile (**9**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.29 (s, 1H), 7.91 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.49-7,38 (m, 2H), 7.33-7,21 (m, 2H), 6.99 (d, *J* = 8.3 Hz, 1H), 6.82 (d, *J* = 8.3 Hz, 1H), 4.05 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.9, 155.3, 151.9, 144.1, 132.0, 130.2, 125.2, 124.3, 122.1, 116.3, 111.1, 107.7, 106.5, 57.0. HRMS (ESI-TOF) calculated for $C_{14}H_{12}NO_3$ $[M+H]^+$ 242.0812, found: 242.0818.

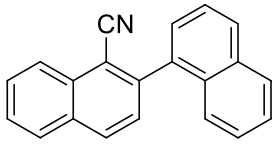


1-Methoxy-9H-xanthen-9-one oxime (**10**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (d, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 7.32 (t, *J* = 8.3 Hz, 1H), 7.24-7.17 (m, 2H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.3, 153.6, 152.7, 131.9, 131.5, 130.9, 130.2, 122.6, 117.0, 116.7, 110.01, 108.9, 106.1, 56.3. HRMS (ESI-TOF) calculated for $C_{14}H_{12}NO_3$ $[M+H]^+$ 242.0812, found: 242.0840.

Catalytic reaction of Scheme 2: synthesis of 2'a

Under nitrogen, a Schlenk-type flask equipped with a magnetic bar was charged with K_2CO_3 (100 mg, 0.72 mmol), PhOK (10 mg, 0.072 mmol), a DMF solution (4 mL) of $Pd(OAc)_2$ (4 mg, 0.018 mmol) and a DMF solution (4 mL) of 1-iodonaphthalene (183 mg, 0.72 mmol), norbornene (55 mg, 0.58 mmol) and ethyl nitroacetate (0.4 mL, 475 mg,

3.57 mmol). The resulting mixture was heated at 120 ˚C under stirring for 48 h. After cooling to room temperature, the mixture was diluted with EtOAc (30 mL), washed three times (3 × 30 mL) with a 10% solution of H_2SO_4 and dried over Na_2SO_4. Compounds **2a** and **2'a**[3] were isolated in 5 and 30% yield, respectively, by flash column chromatography on silica gel using a 9:1 mixture of hexane-EtOAc as eluent.

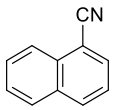


2-(1-Naphthyl)-1-naphthonitrile (**2'a**): Yield: 30% (30 mg); pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (further split d, *J* = 8.2 Hz, 1H), 8.16 (br d, *J* = 8.2 Hz, 1H), 8.05–7.94 (m, 3H), 7.77 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.69 (ddd, *J* = 8.2, 6.9, 1.3 Hz, 1H), 7.65–7.51 (m, 5H), 7.44 (ddd, *J* = 8.3, 6.9, 1.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 136.3, 133.7, 132.9, 132.2, 132.0, 131.4, 129.3, 128.9, 128.5 (× 2), 128.4, 127.8, 127.5, 126.6, 126.2, 125.6, 125.3, 125.2, 116.9, 110.4. MS: *m/z* 279 (M^+, 100), 252 (14), 250 (12), 139 (10), 126 (20).

General procedure for the catalytic synthesis of aryl nitriles 2

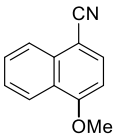
A Schlenk-type flask equipped with a magnetic bar was charged under nitrogen with K_2CO_3 (300 mg, 2.17 mmol), PhOK (28 mg, 0.21 mmol), PPh_3 (37.5 mg, 0.14 mmol), a DMF solution (4 mL) of $Pd(OAc)_2$ (4 mg, 0.0179 mmol), a DMF solution (4 mL) containing the desired aryl halide (0.72 mmol), dimethyl maleate (256 mg, 1.78 mmol) and ethyl nitroacetate (0.4 mL, 475 mg, 3.56 mmol). The mixture was heated in an oil bath at 120 ˚C for 24h. At the end of the reaction the mixture was allowed to cool to room temperature, diluted with EtOAc (30 mL), washed three times (3 × 30 mL) with a 10% aqueous solution of H_2SO_4 (or a saturated $NaHCO_3$ solution when bromopyridines were used) and dried over $MgSO_4$. All products were isolated by flash column chromatography on silica gel using a 9:1 mixture of hexane-EtOAc as eluent.

1-Naphthonitrile (**2a**)[4]



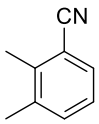
White solid (97 mg, 0.63 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.95-7.84 (m, 2H), 7.73-7.44 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.3, 132.9, 132.6, 132.4, 128.7, 128.6, 127.6, 125.1, 124.9, 117.9, 110.2.

4-Methoxynaphthonitrile (**2b**)[5]



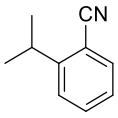
White solid (55 mg, 0.30 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32 (d, *J* = 8.4 Hz, 1H), 8.16 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.65 (td, *J* = 6,9, 1,1 Hz, 1H), 7.54 (t, *J* = 6,9 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 4.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 134.2, 133.6, 129.1, 126.8, 125.4, 125.1, 122.9, 118.6, 103.5, 102.1, 56.1.

2,3-Dimethylbenzonitrile (**2c**)[6]



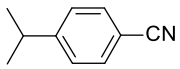
Pale yellow oil (76 mg, 0.58 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7 Hz, 1H), 7.34 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 2.46 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.0, 134.1, 130.34, 126.2, 118.8, 113.1, 20.1, 17.9.

1-Isopropylbenzonitrile (**2d**)[7]



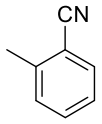
Pale yellow oil (78 mg, 0.54 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.54 (td, *J* = 7.8, 1.3 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.27 (td, *J* = 7.7, 1.1 Hz, 1H), 3.38 (hept, *J* = 6.9 Hz, 1H), 1.32 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.6, 133.1, 133.0, 126.4, 126.3, 126.1, 126.0, 32.5, 23.4.

4-Isopropylbenzonitrile (**2e**)[6]



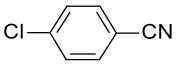
Pale yellow oil (74 mg, 0.51 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 2.96 (hept, *J* = 6.9 Hz, 1H), 1.32 (s, 3H), 1,30 (s, 3H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.5, 132.4, 127.4, 119.3, 109.8, 34.5, 23.6.

o-Tolunitrile (**2f**)[8]



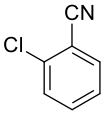
Colorless oil (47 mg, 0.40 mmol). ^{1}H NMR (300 MHz, CD_3OD δ 7.63 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.54 (td, *J* = 7.6, 1.2 Hz, 1H), 7.43-7.37 (m, 1H), 7.36-7.28 (m, 1H), 2.51 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ 143.0, 134.1, 133.5, 131.4, 127.6, 118.9, 1136, 20.4.

4-Chlorobenzonitrile (**2g**)[6]



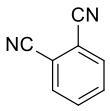
White solid (85 mg, 0.62 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.8 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 133.4, 129.7, 117.9, 110.8.

2-Chlorobenzonitrile (**2h**)[6]



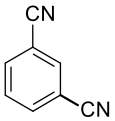
White solid (93 mg, 0.68 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (ddd, *J* = 7.8, 1.6, 0.5 Hz, 1H), 7.59-7.48 (m, 2H), 7.37 (ddd, *J* = 7.8, 6.9, 1.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 134.1, 133.9, 130.1, 127.3, 116.0, 113.4.

1,2-Dicyanobenzene (**2i**)[8]



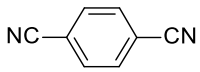
White solid (87 mg, 0.68 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.14 (dd, *J* = 5.8, 3.3 Hz, 2H), 7.93 (dd, *J* = 5.8, 3.3 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 134.0, 133.9, 115.9, 114.5.

1,3-Dicyanobenzene (**2j**)[4]



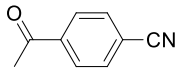
White solid (56 mg, 0.44 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, *J* = 1.0 Hz, 1H), 7.92-7,89 (m, 2H), 7.66 (t, *J* = 7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.12, 135.54, 130.46, 116.71, 114.29.

1,4-Dicyanobenzene (**2k**)[6]



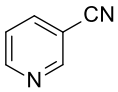
White solid (78 mg, 0.61 mmol). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.08 (s, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 133.2, 117.5, 115.7.

4-Acetylbenzonitrile (**2l**)[4]



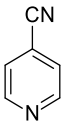
White solid (91 mg, 0.63 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.5 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 2.63 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.6, 140.0, 132.6, 128.8, 118.0, 116.5, 26.9.

3-Pyridinecarbonitrile (**2m**)[8]



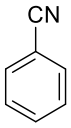
White solid (60 mg, 0.58 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.89 (d, *J* = 2.0 Hz, 1H), 8.82 (dd, *J* = 5.0, 2 Hz, 1H), 7,96 (d, *J* = 5.0 Hz, 1H), 7.44 (ddd, *J* = 8.0, 5.0, 0.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.1, 152.6, 139.3, 123.7, 116.6, 110.3.

4-Pyridinecarbonitrile (**2n**)[6]



White solid (54 mg, 0.52 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (dd, *J* = 4.4, 1.5 Hz, 2H), 7.46 (dd, *J* = 4.4, 1.5 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 125.2, 120.3, 116.4.

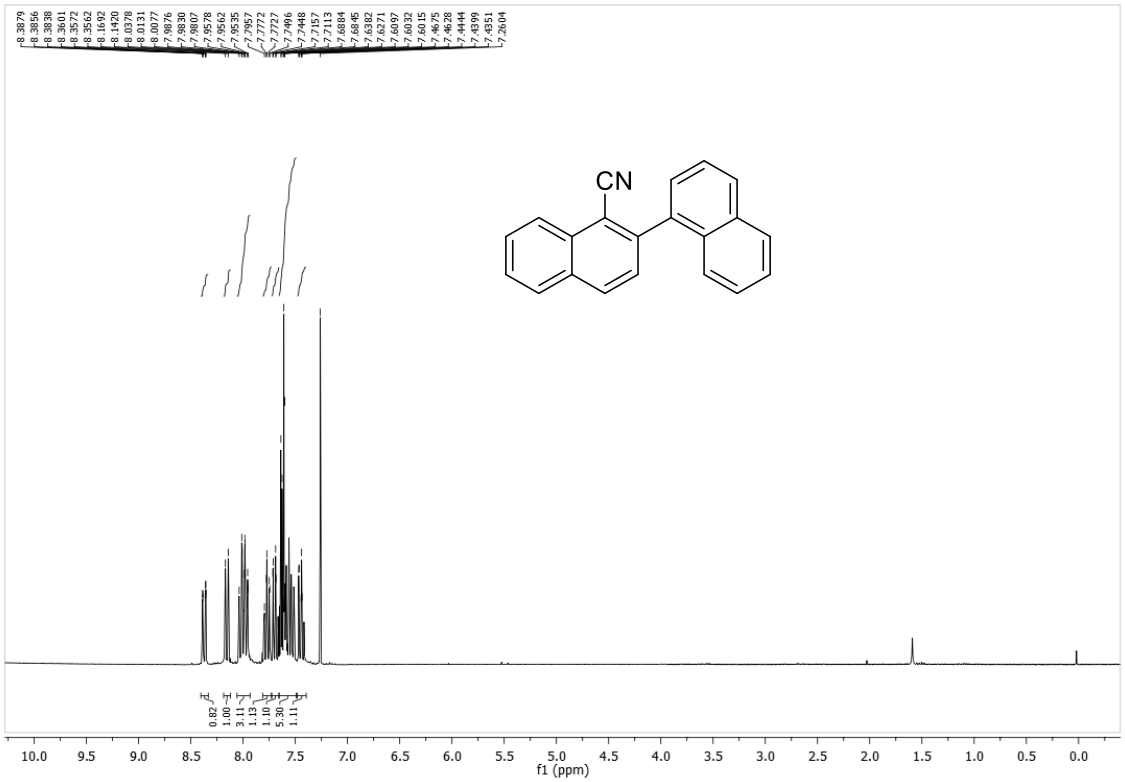
Benzonitrile (**2o**)[6]

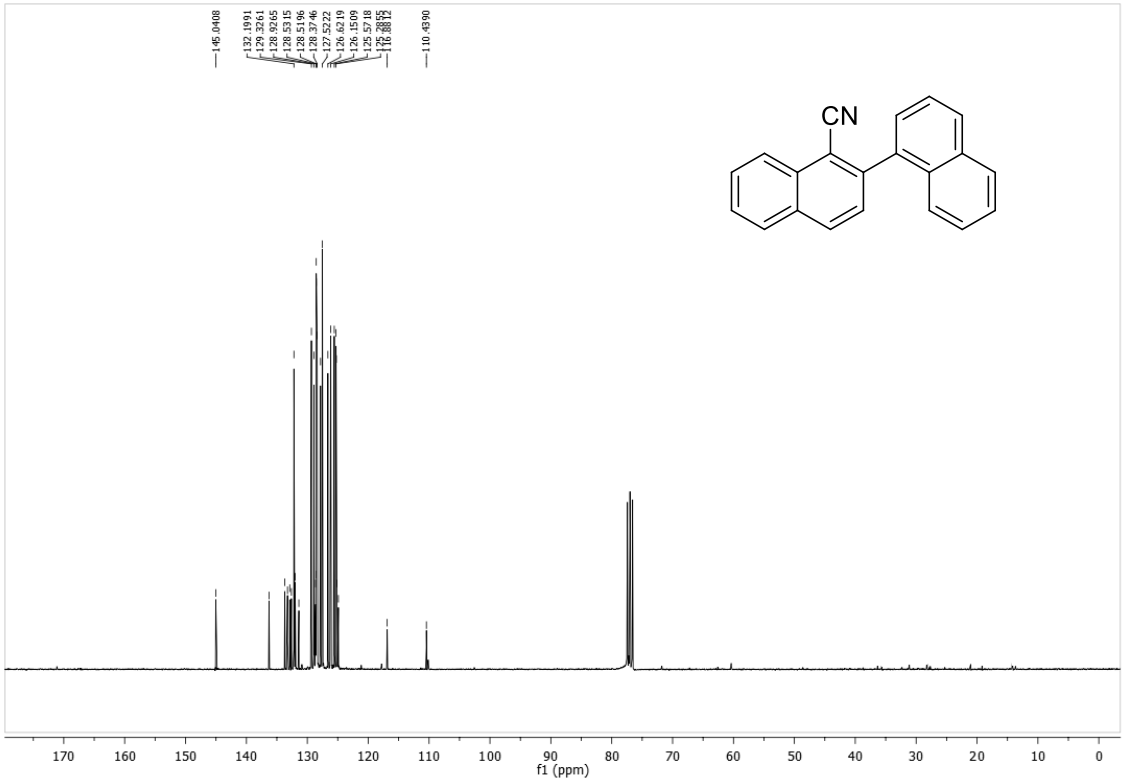


Colorless oil (59 mg, 0.57 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69-7.55 (m, 3H), 7.52-7.41 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8, 132.2, 129.2, 118.9, 112.5.

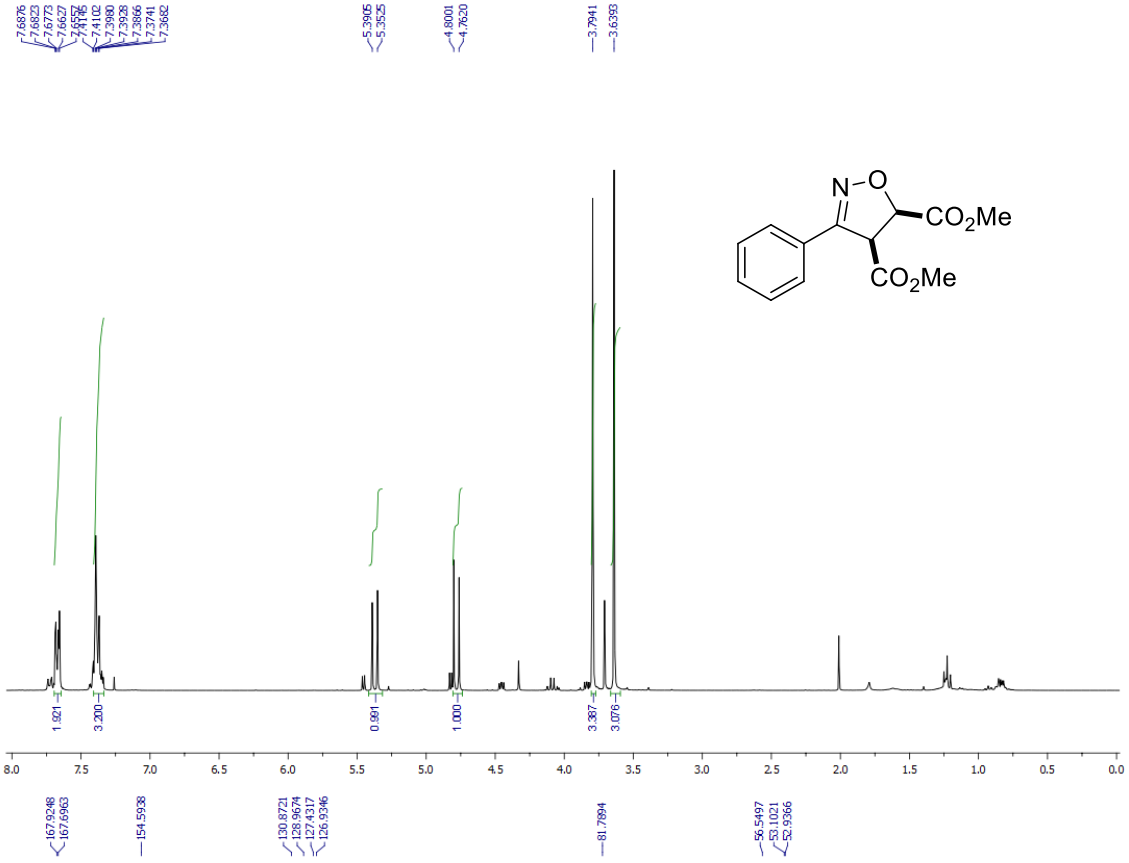
NMR spectra

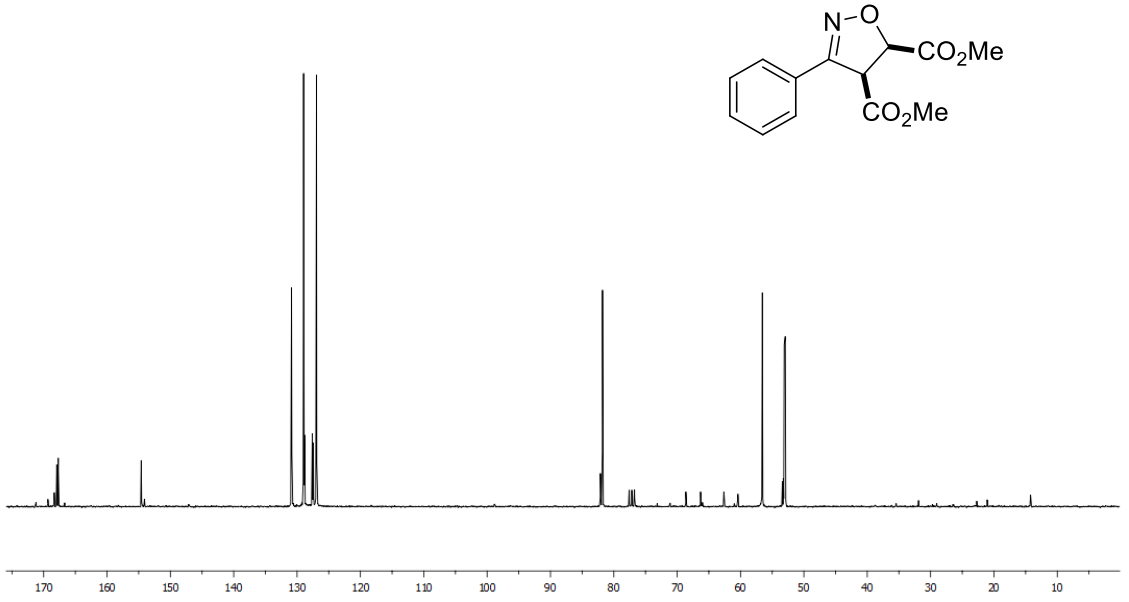
2-(1-Naphthyl)-1-naphthonitrile (**2'a**)



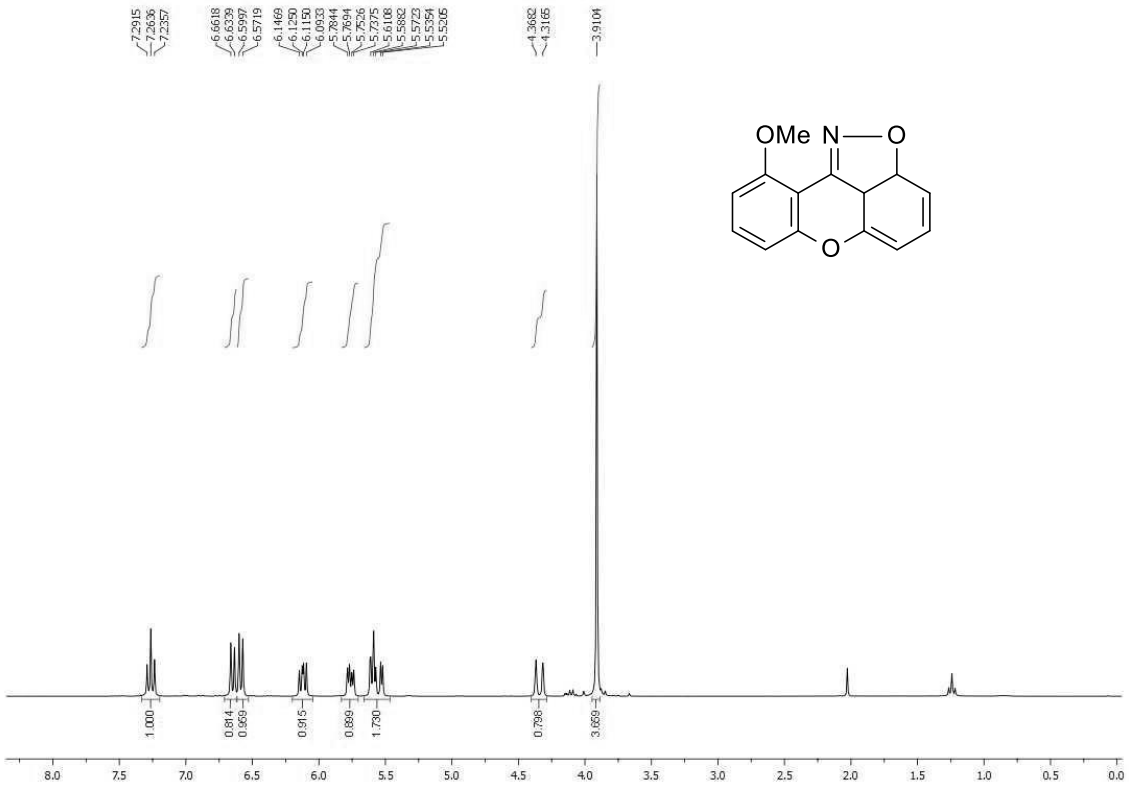


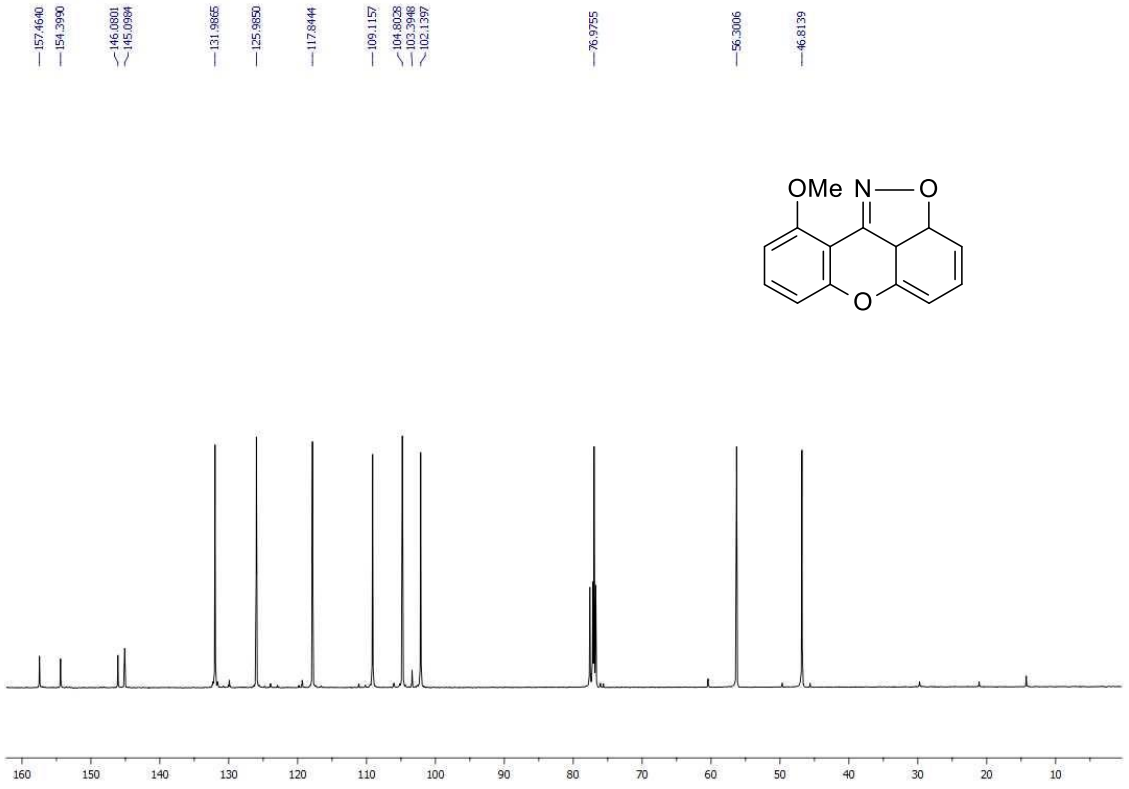
Z-Dimethyl 3-phenyl-4,5-dihydroisoxazole-4,5-dicarboxylate (**5**)



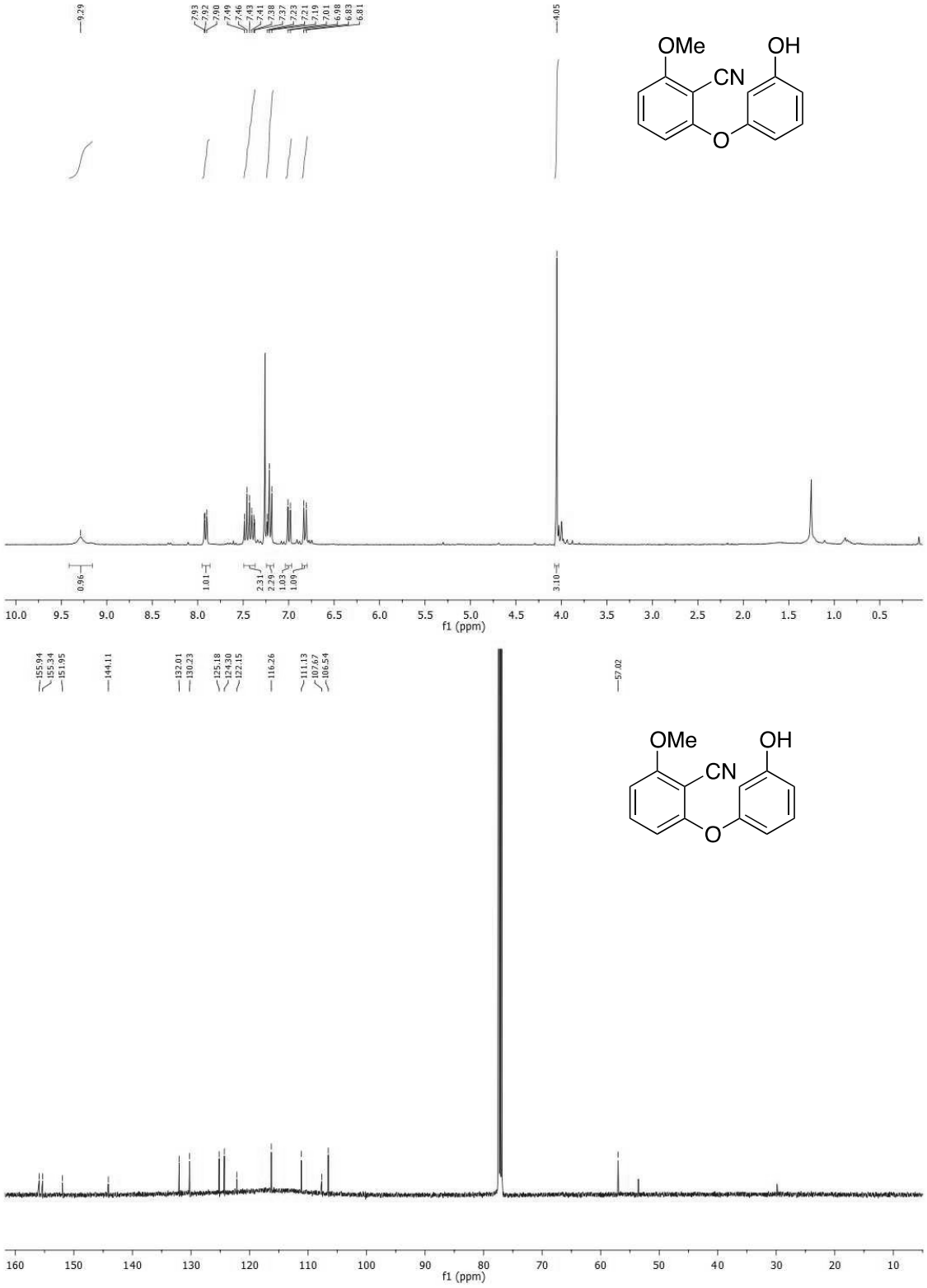


10-Methoxy-2a,2a^1-dihydroxantheno[9,1-cd]isoxazole (**8**)

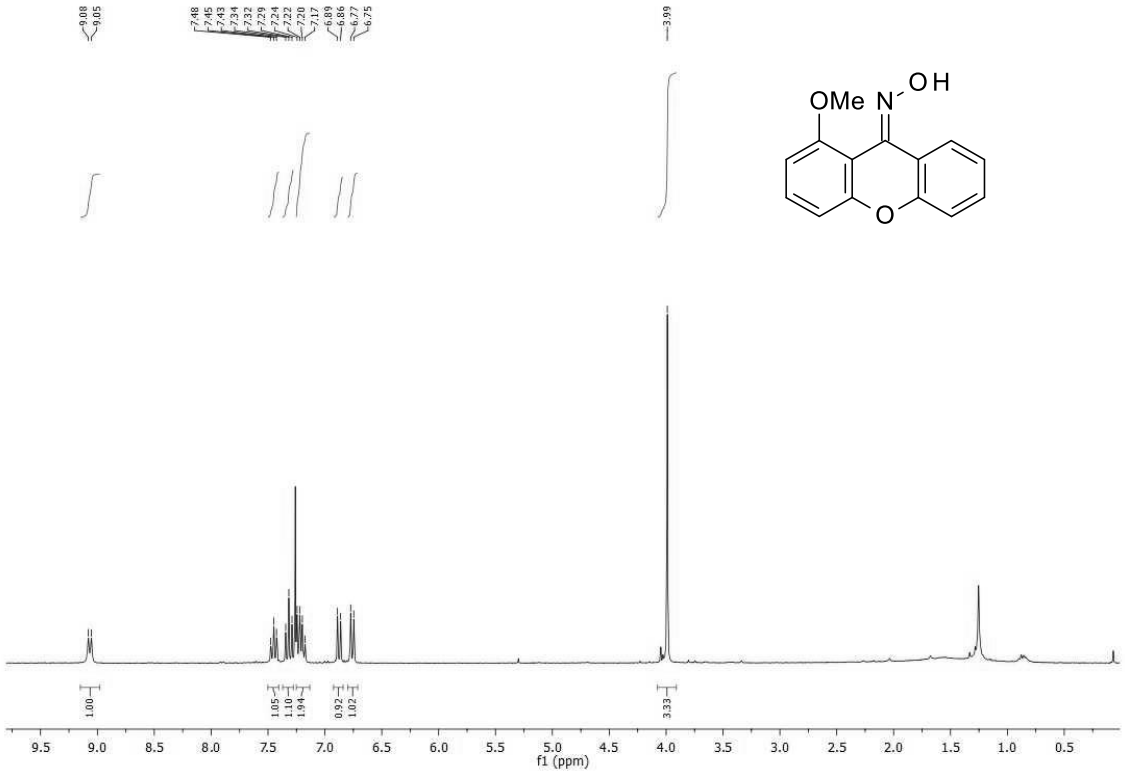


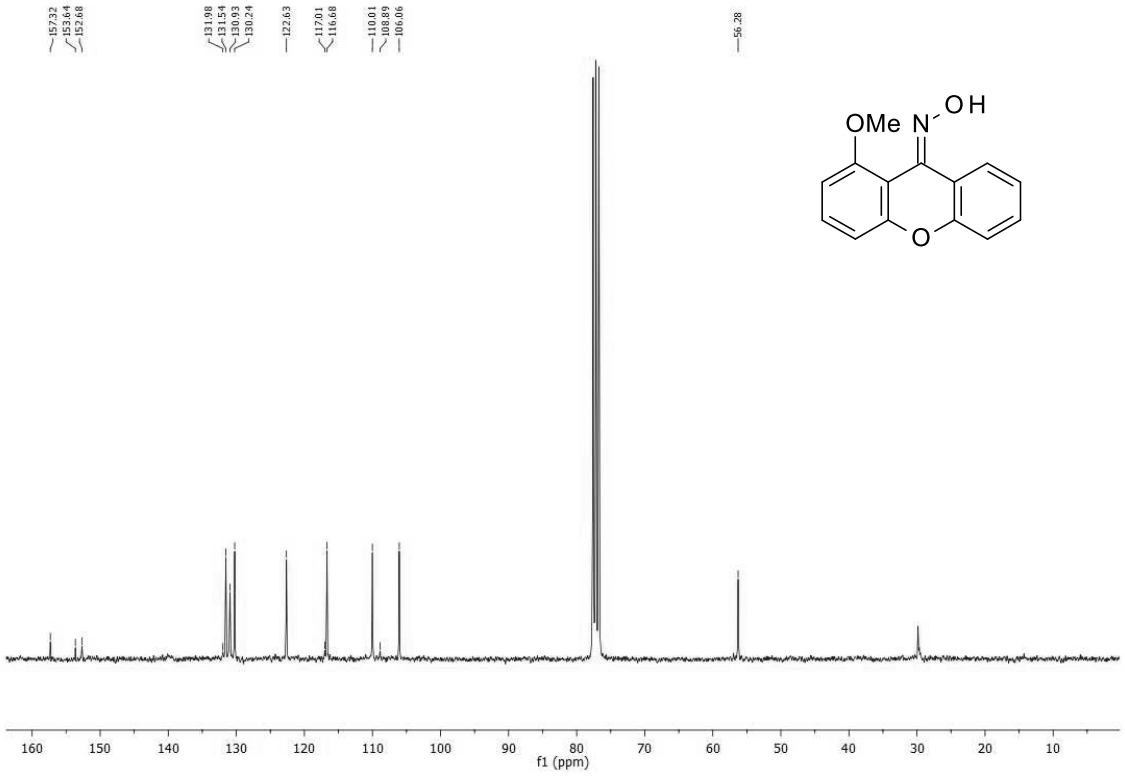


2-(3-Hydroxyphenoxy)-6-methoxybenzonitrile (**9**)

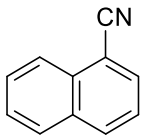


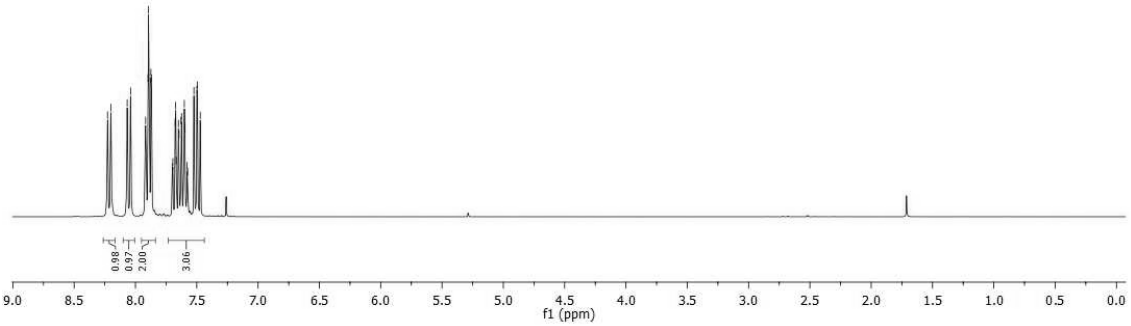
1-Methoxy-9H-xanthen-9-one oxime (**10**)

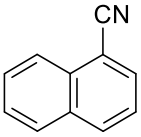


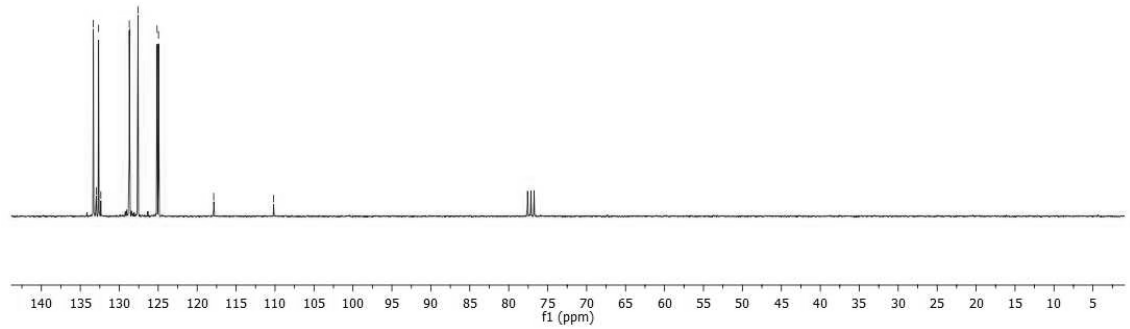


1-Naphthonitrile (**2a**)

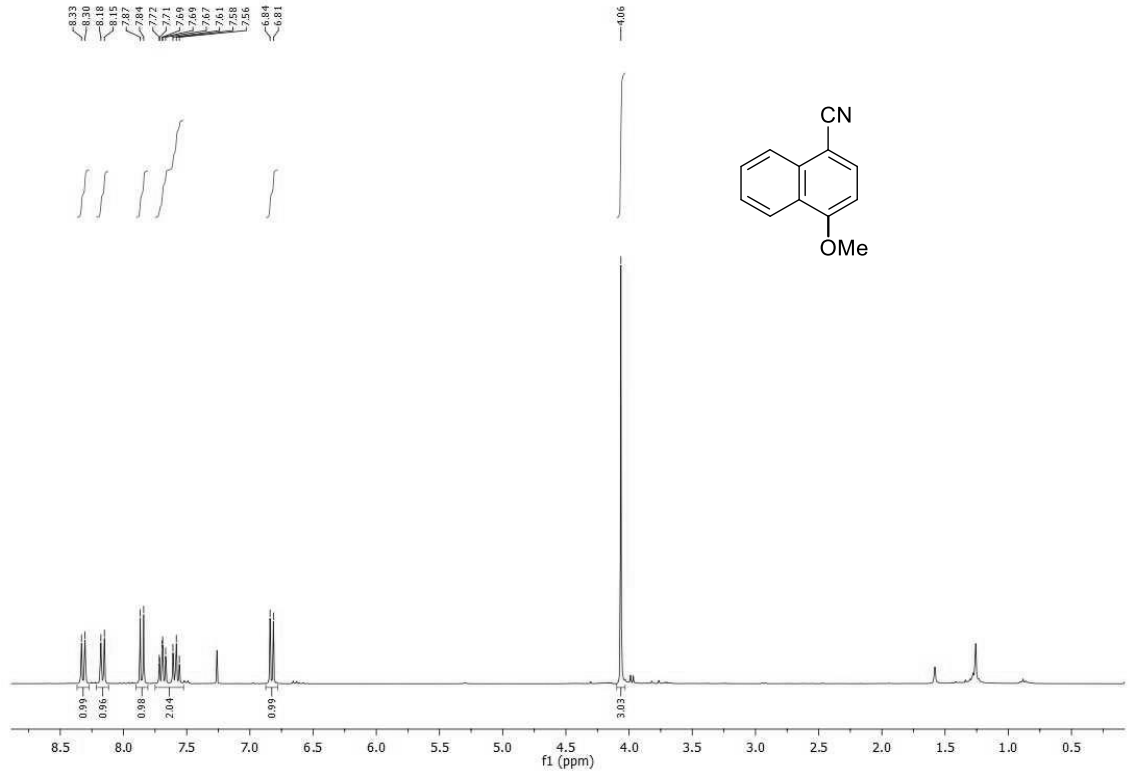


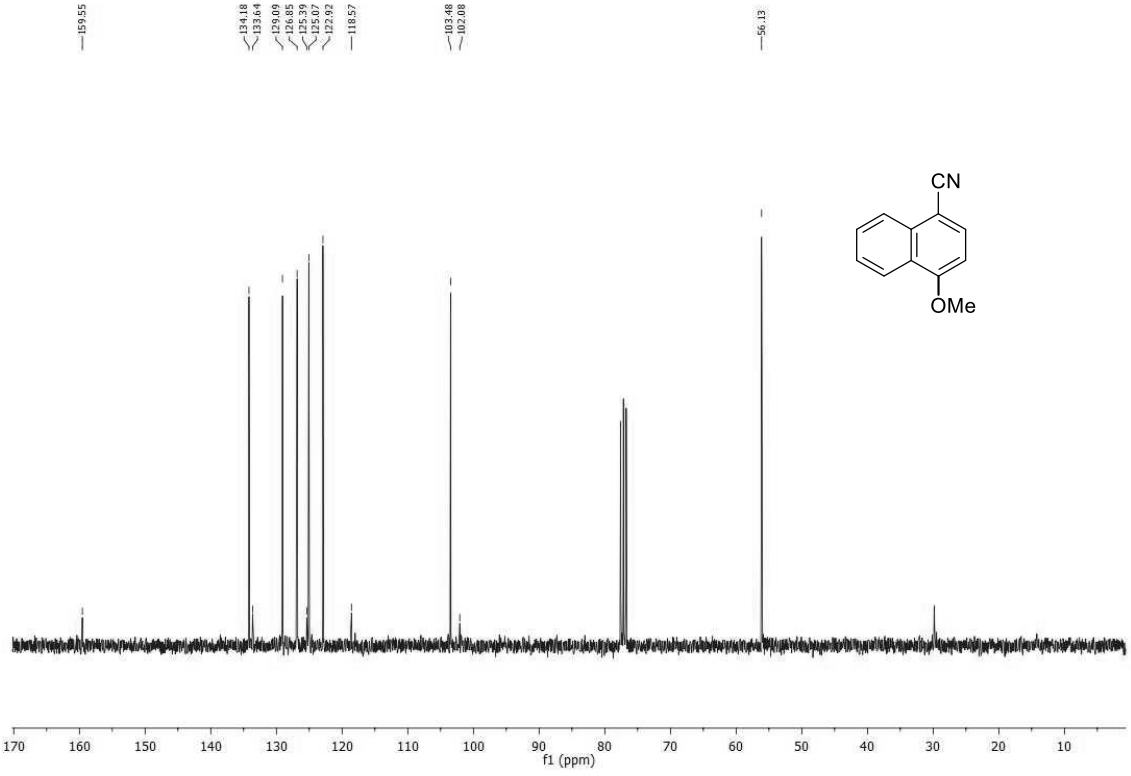




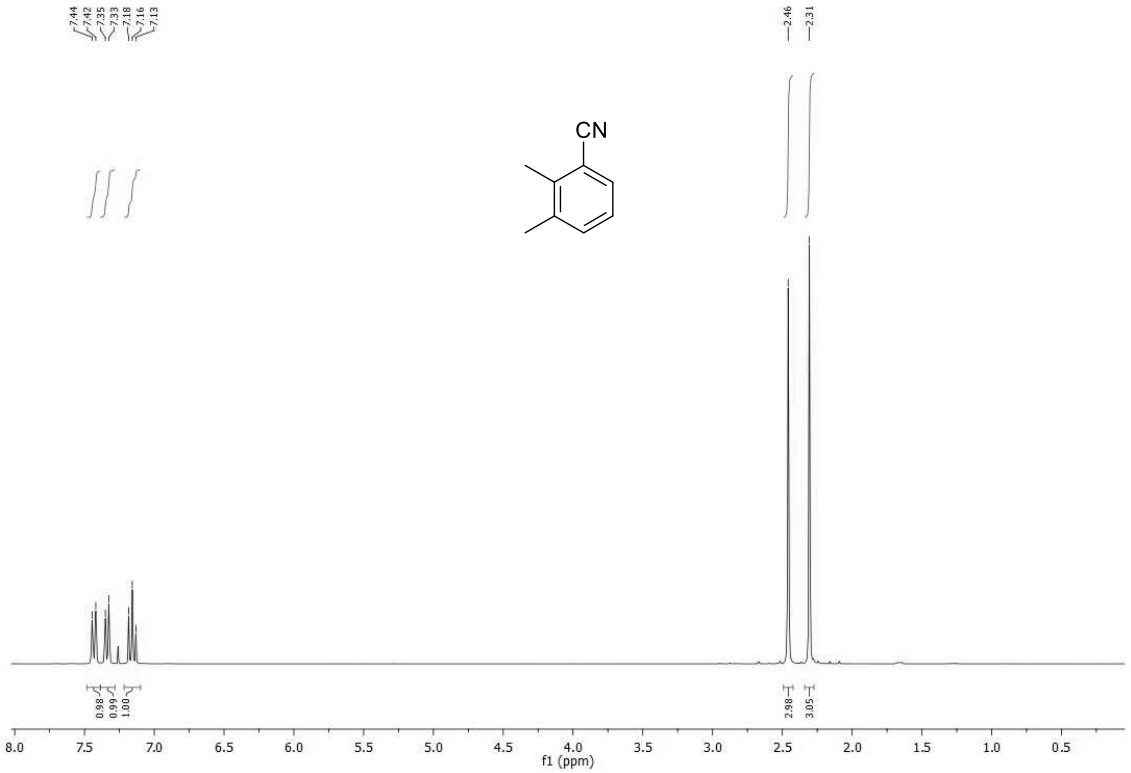


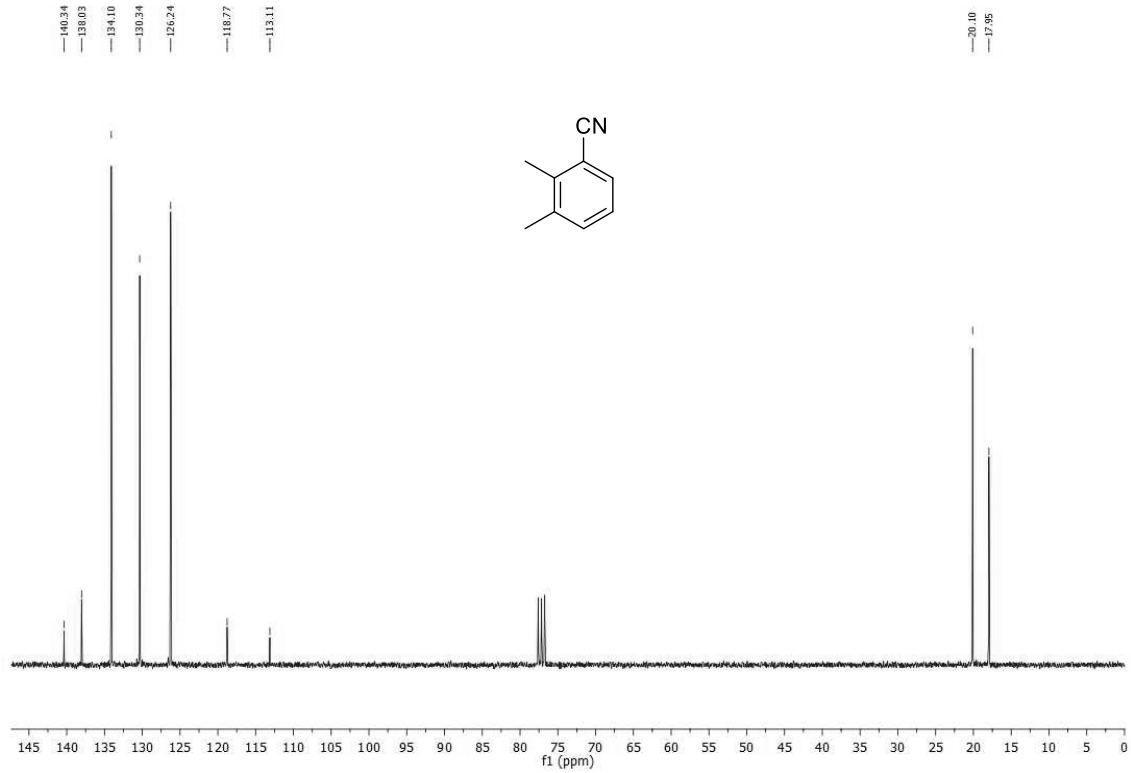
4-Methoxynaphthonitrile (**2b**)



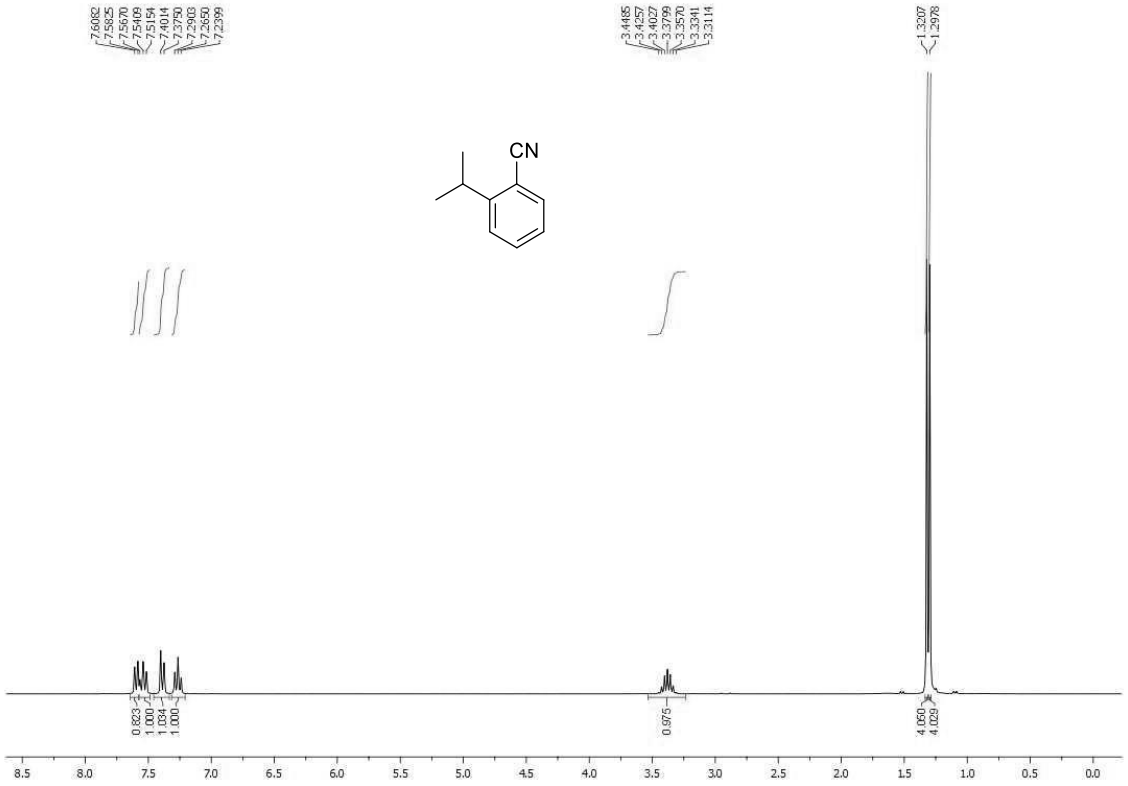


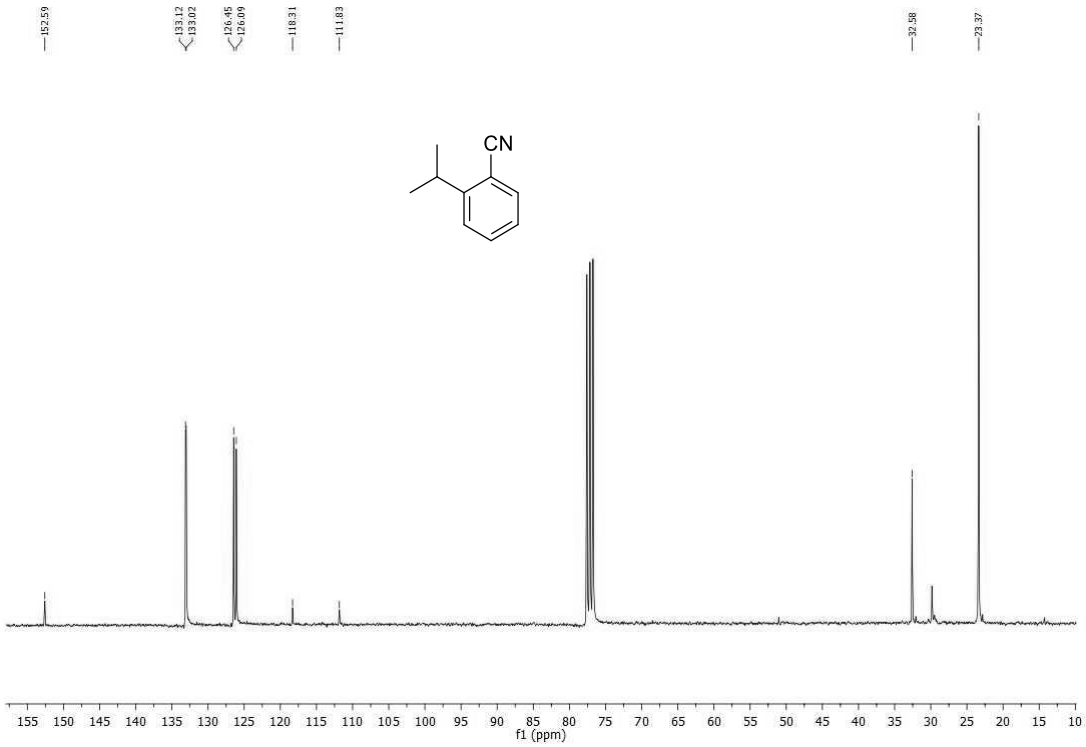
2,3-Dimethylbenzonitrile (**2c**)



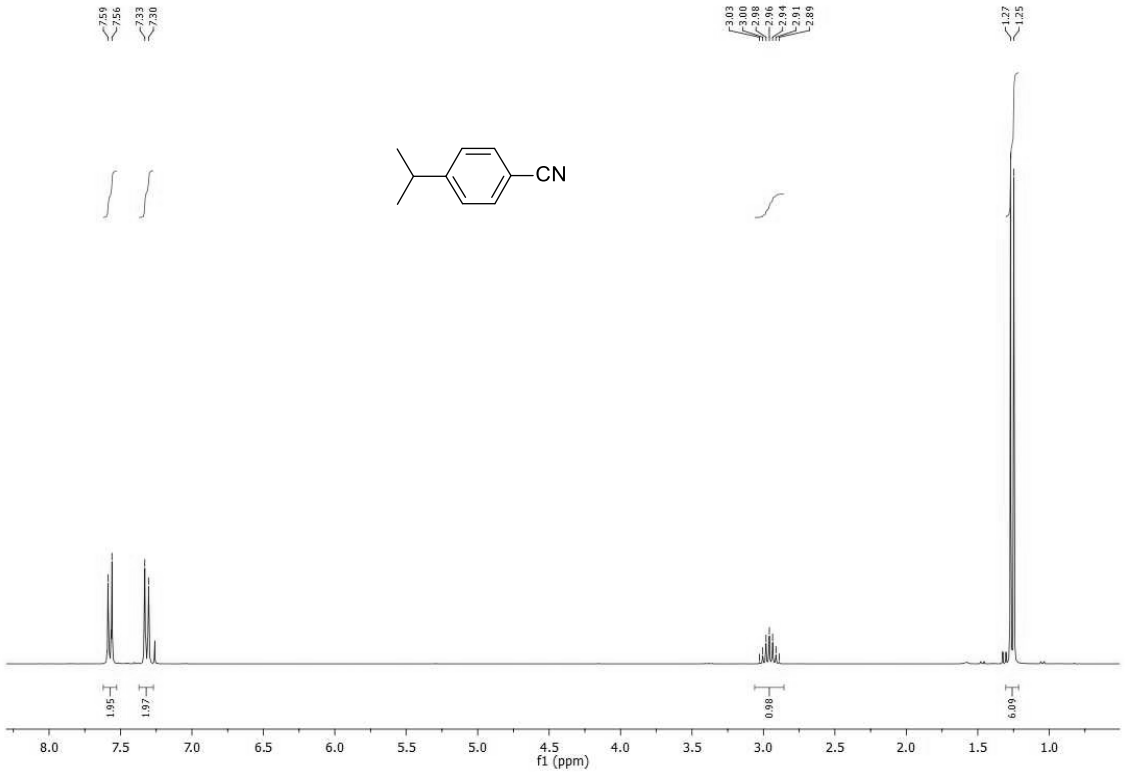


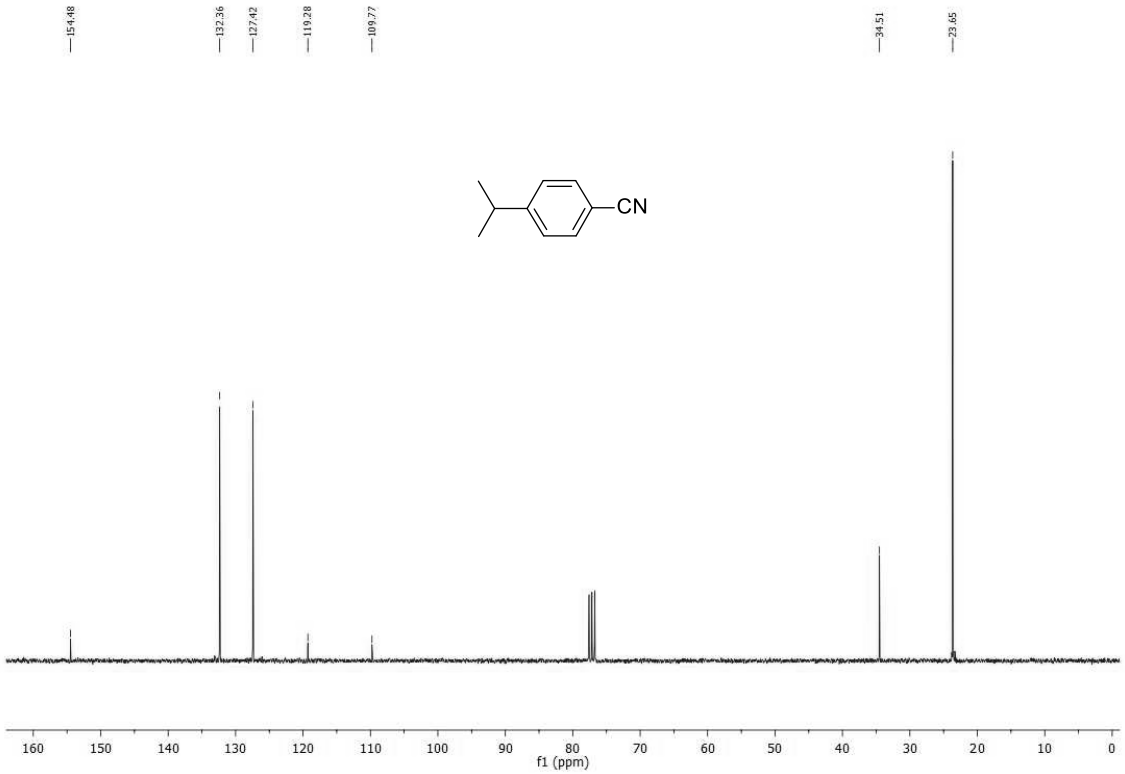
2-Isopropylbenzonitrile (**2d**)



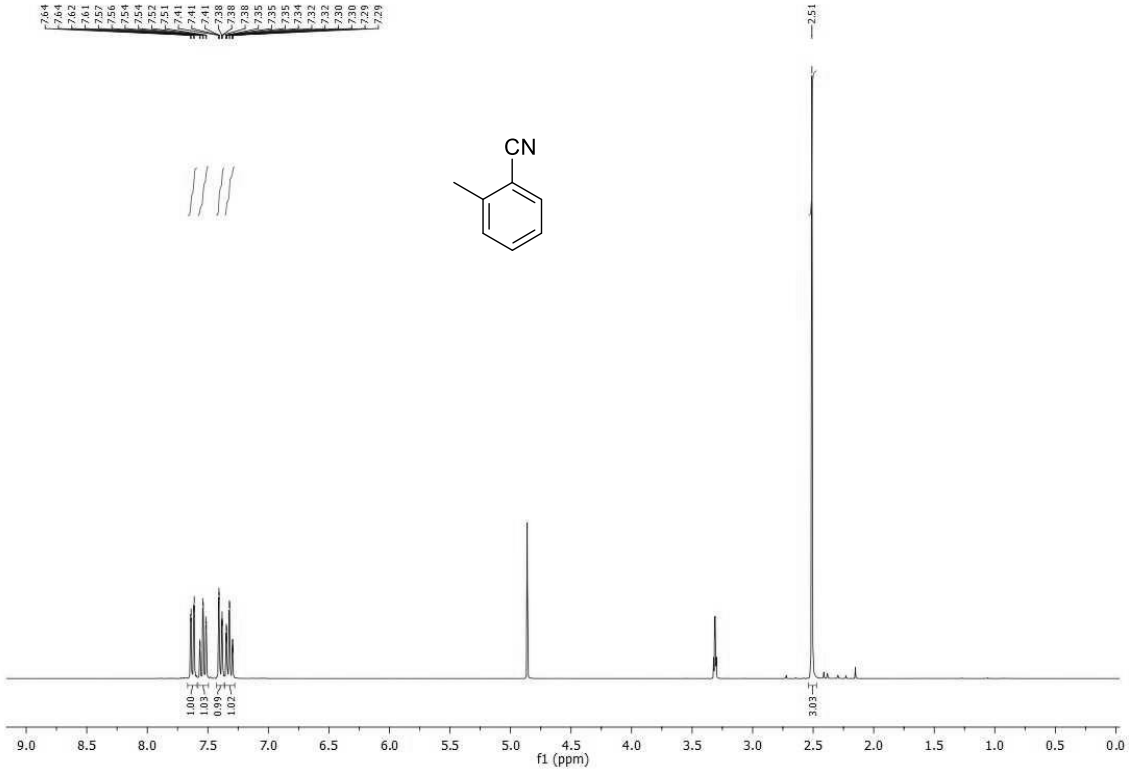


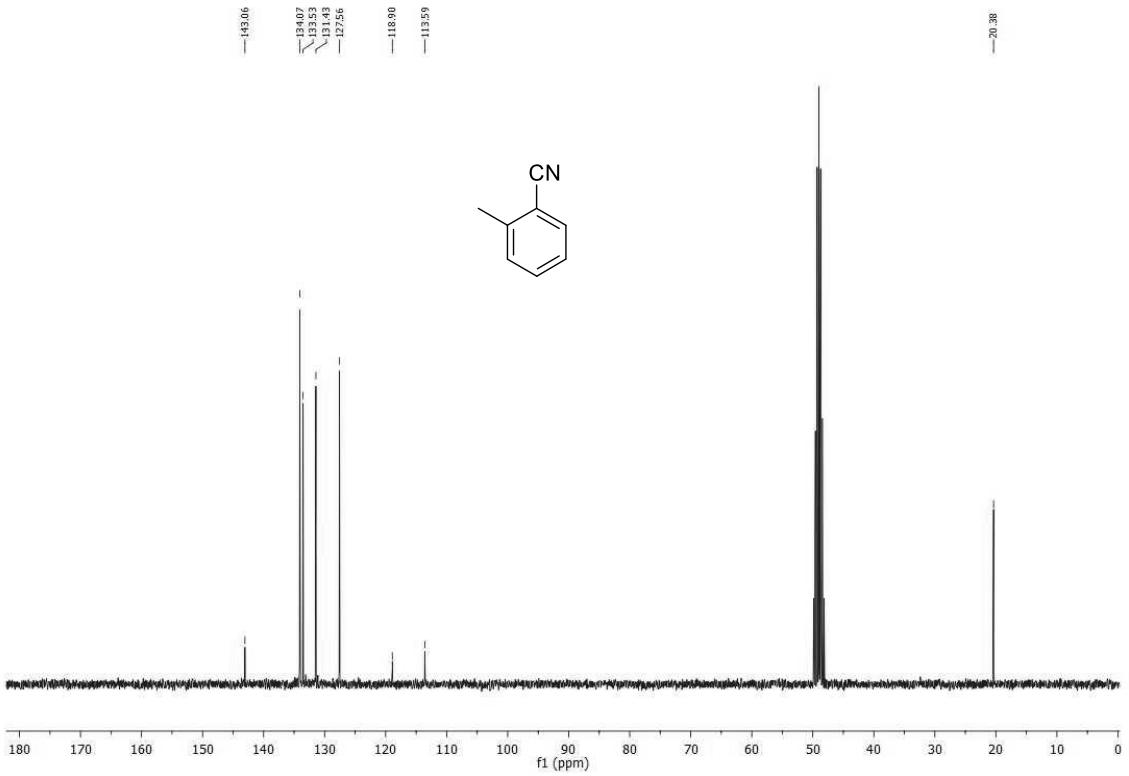
4-Isopropylbenzonitrile (**2e**)



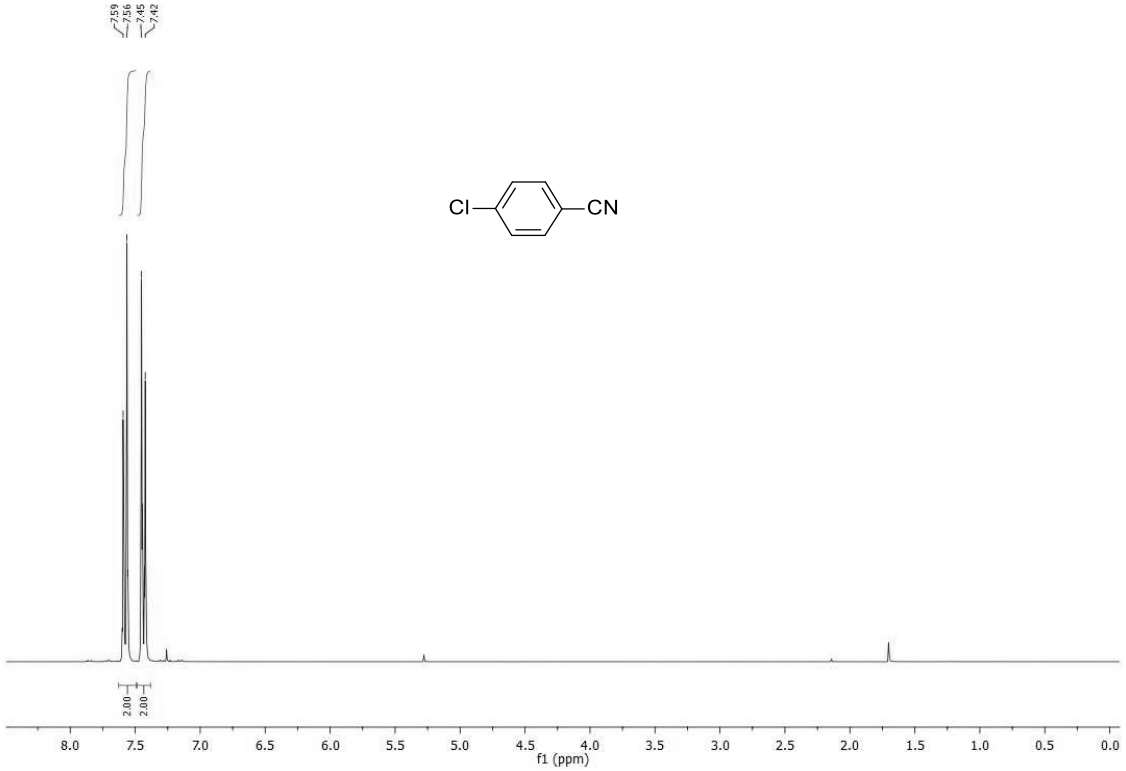


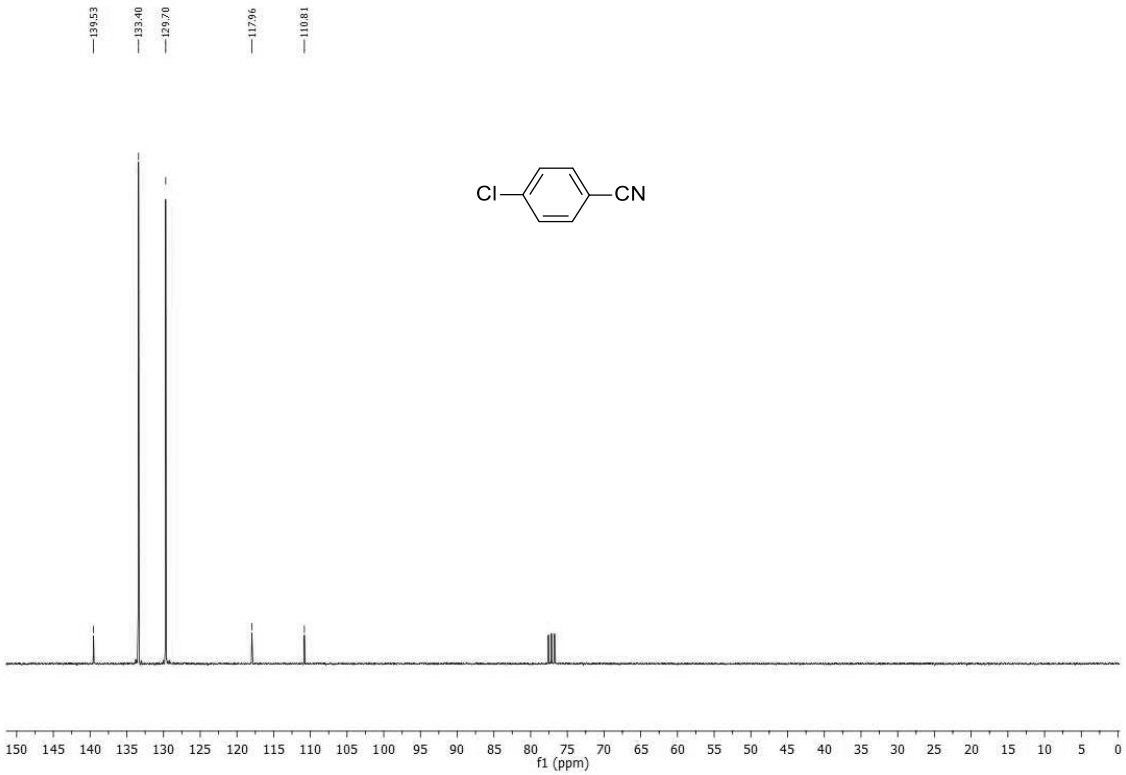
o-Tolunitrile (**2f**)



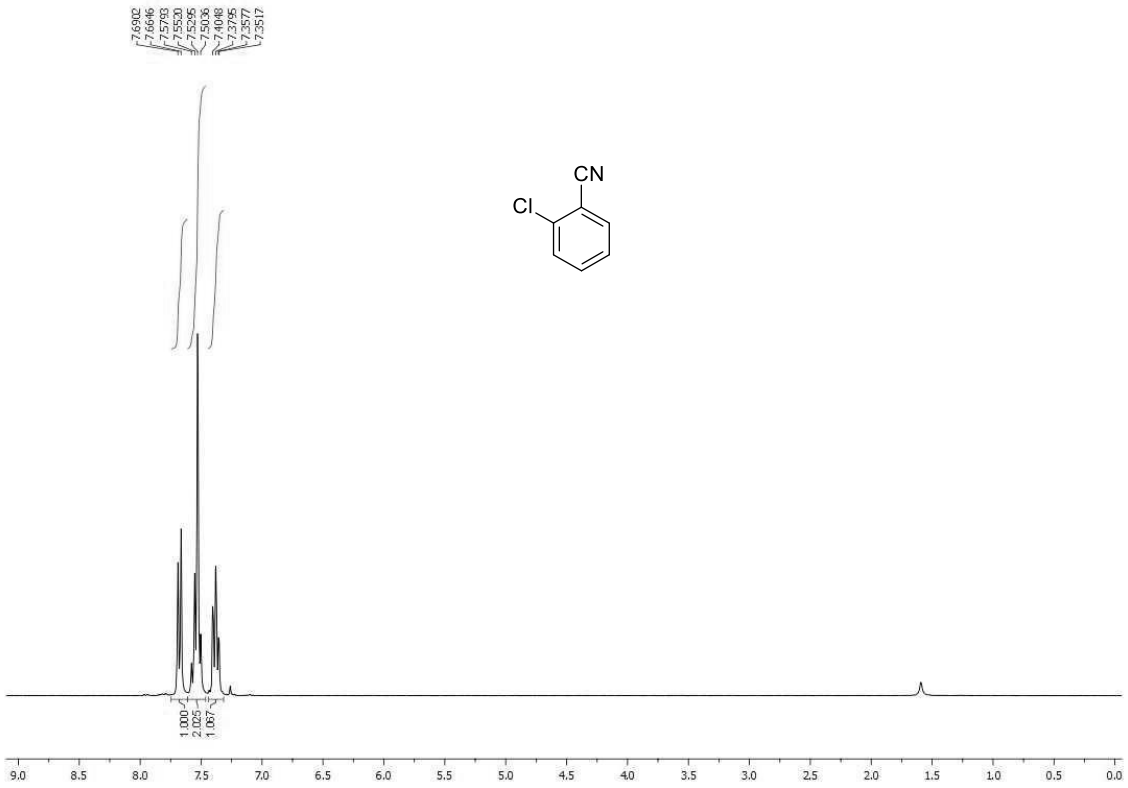


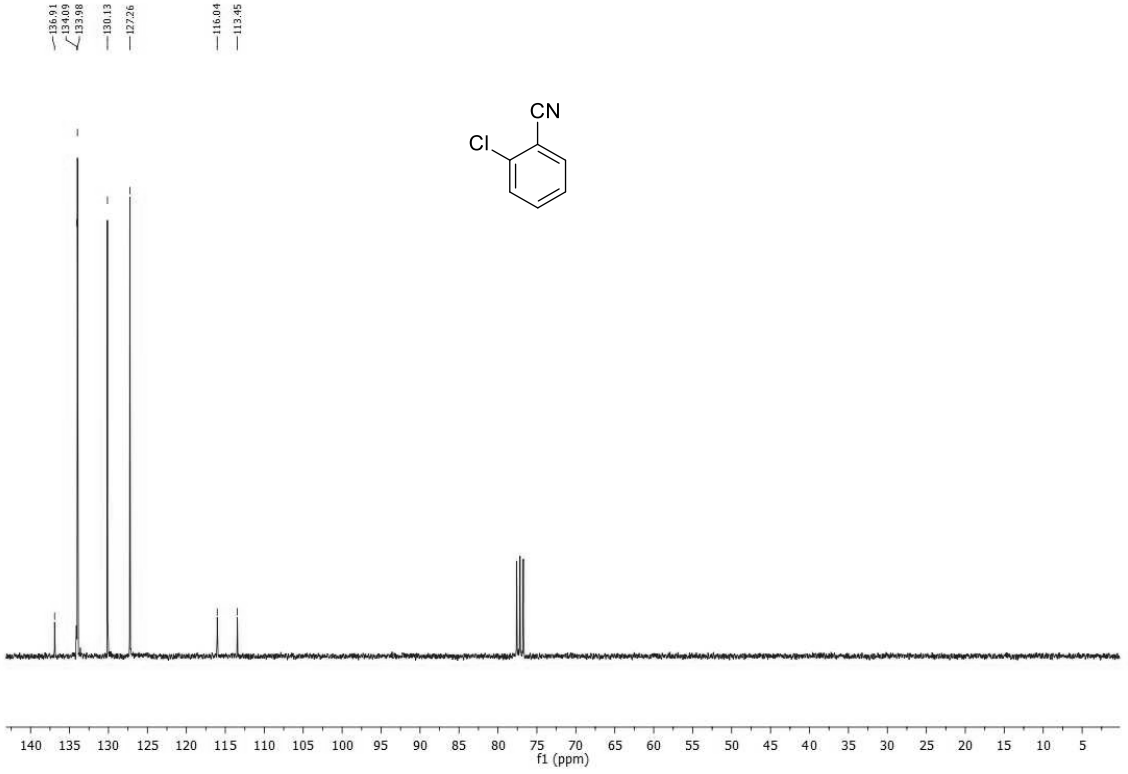
4-Chlorobenzonitrile (**2g**)



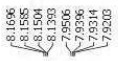


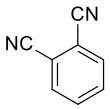
2-Chlorobenzonitrile (**2h**)

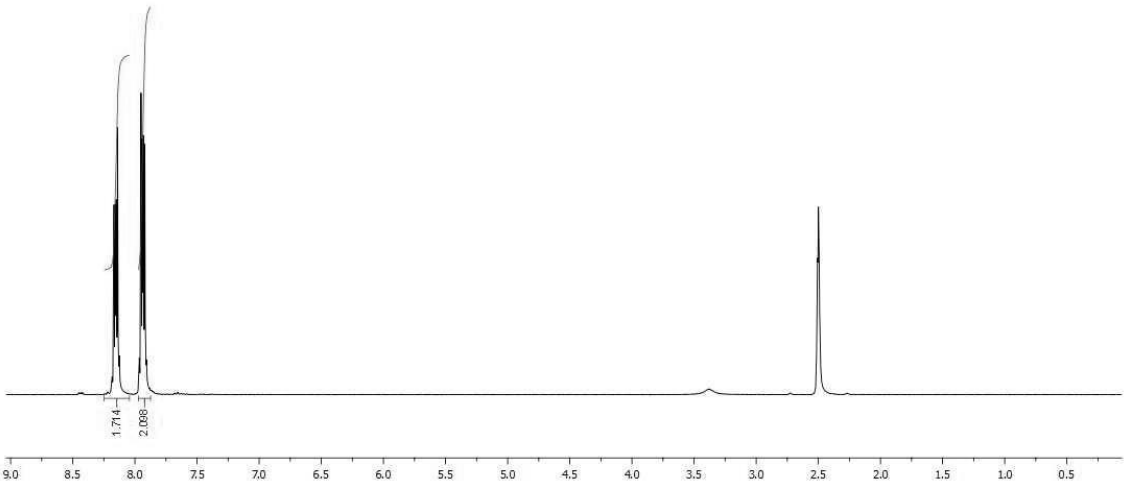


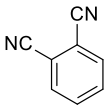


1,2-Dicyanobenzene (**2i**)

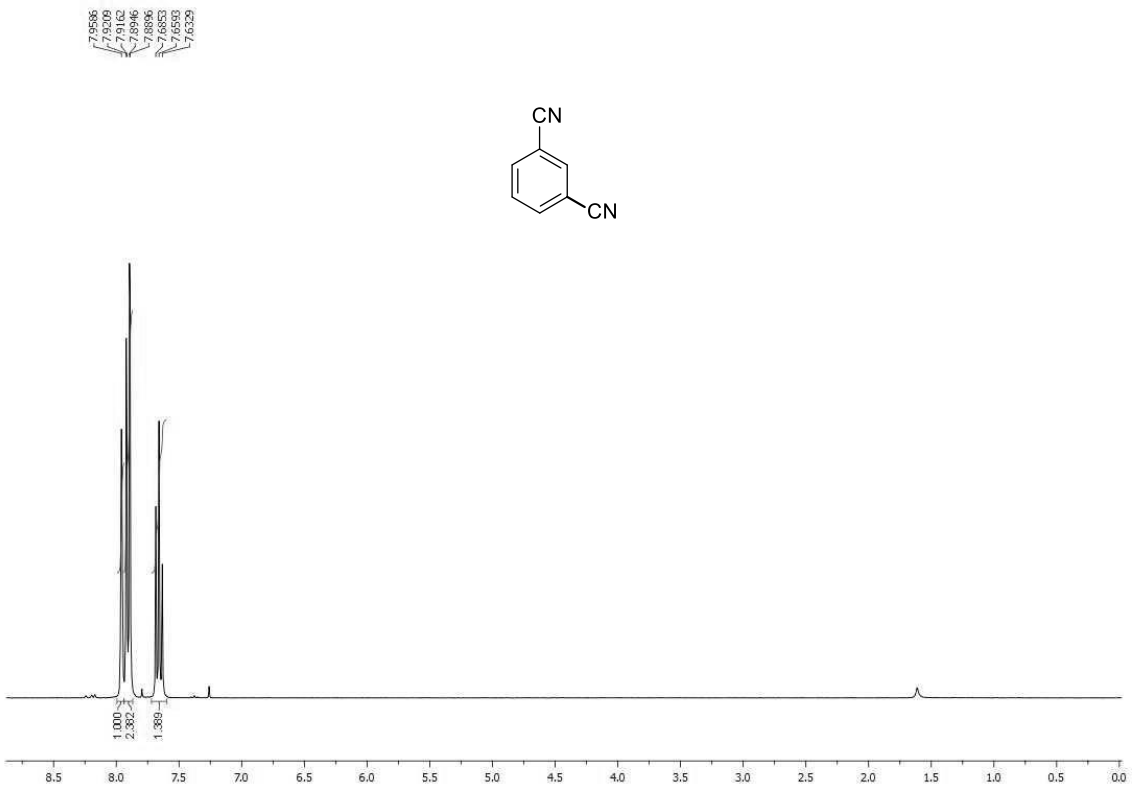


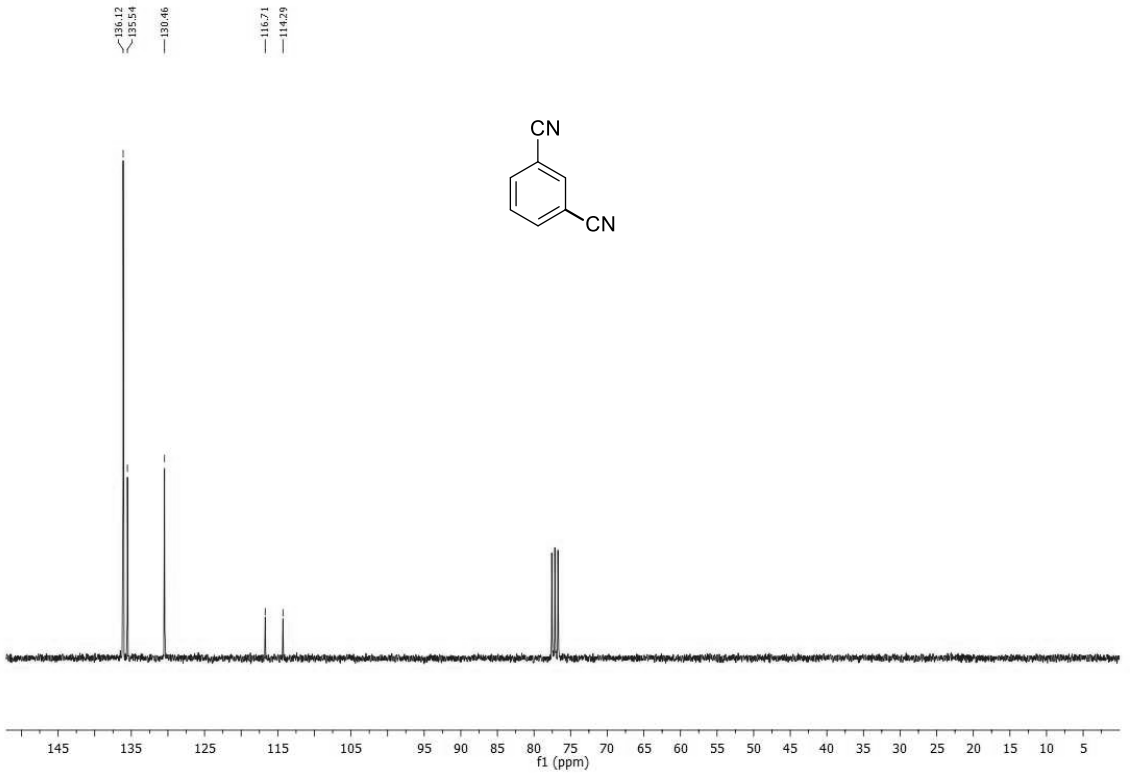




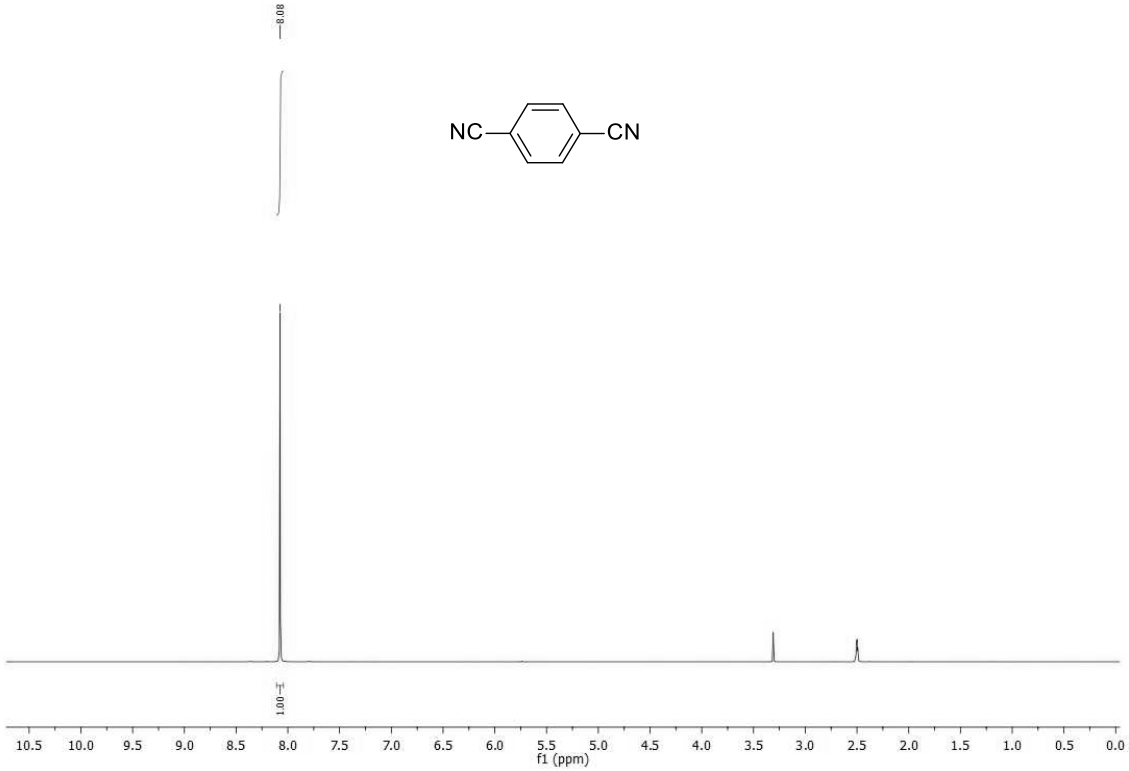


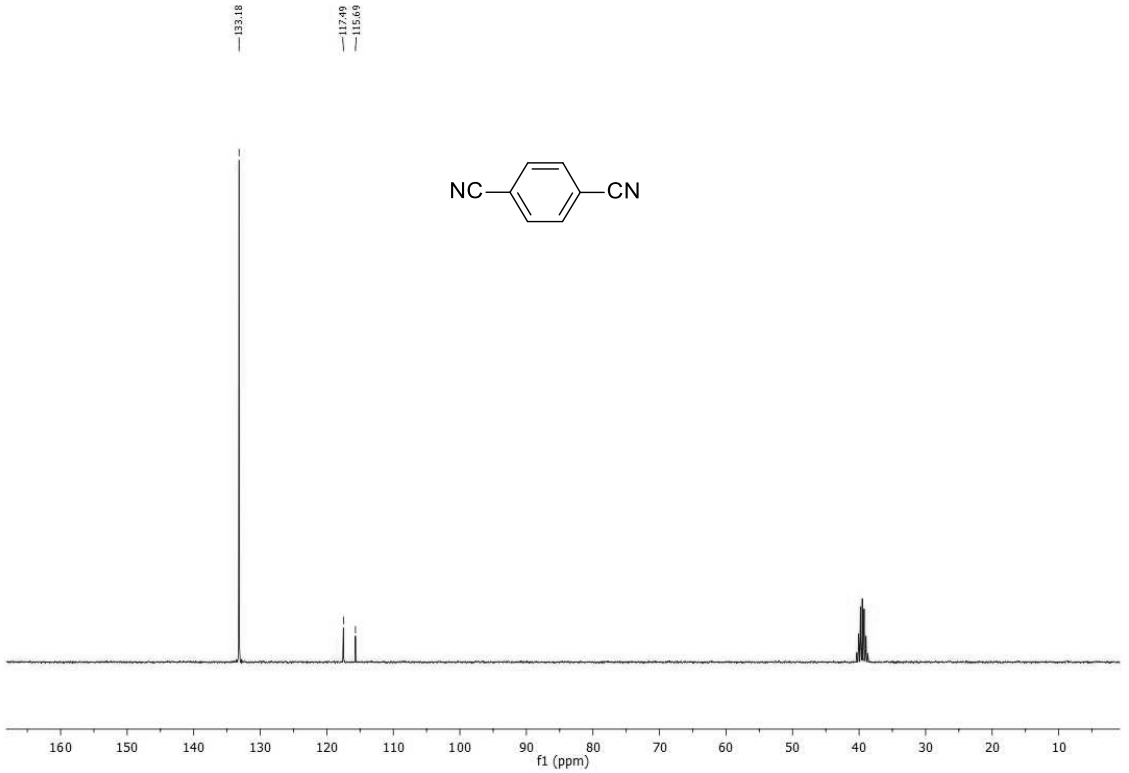
1,3-Dicyanobenzene (**2j**)



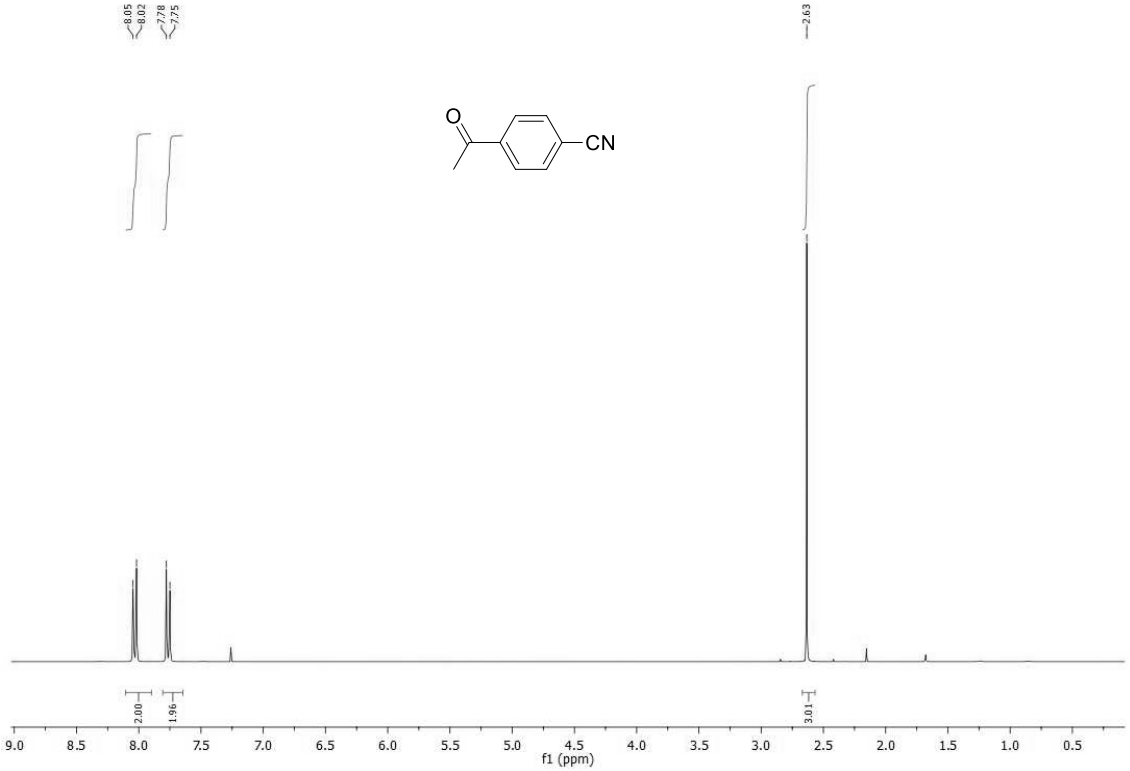


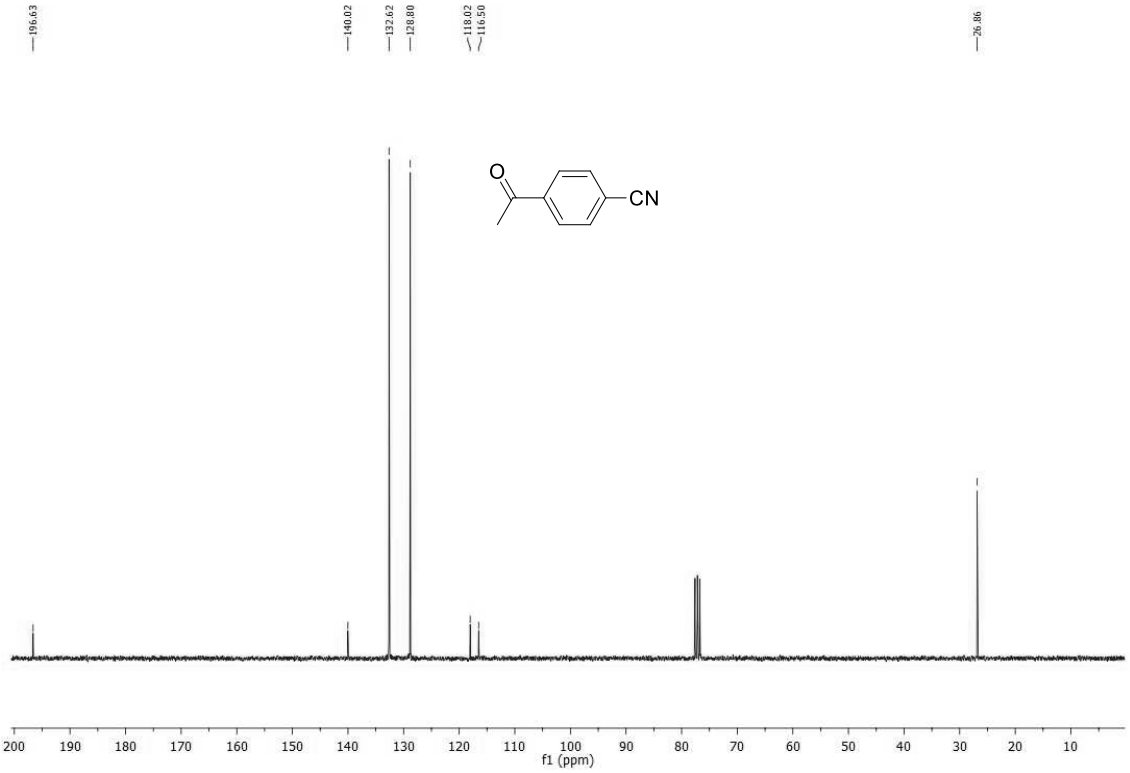
1,4-Dicyanobenzene (**2k**)



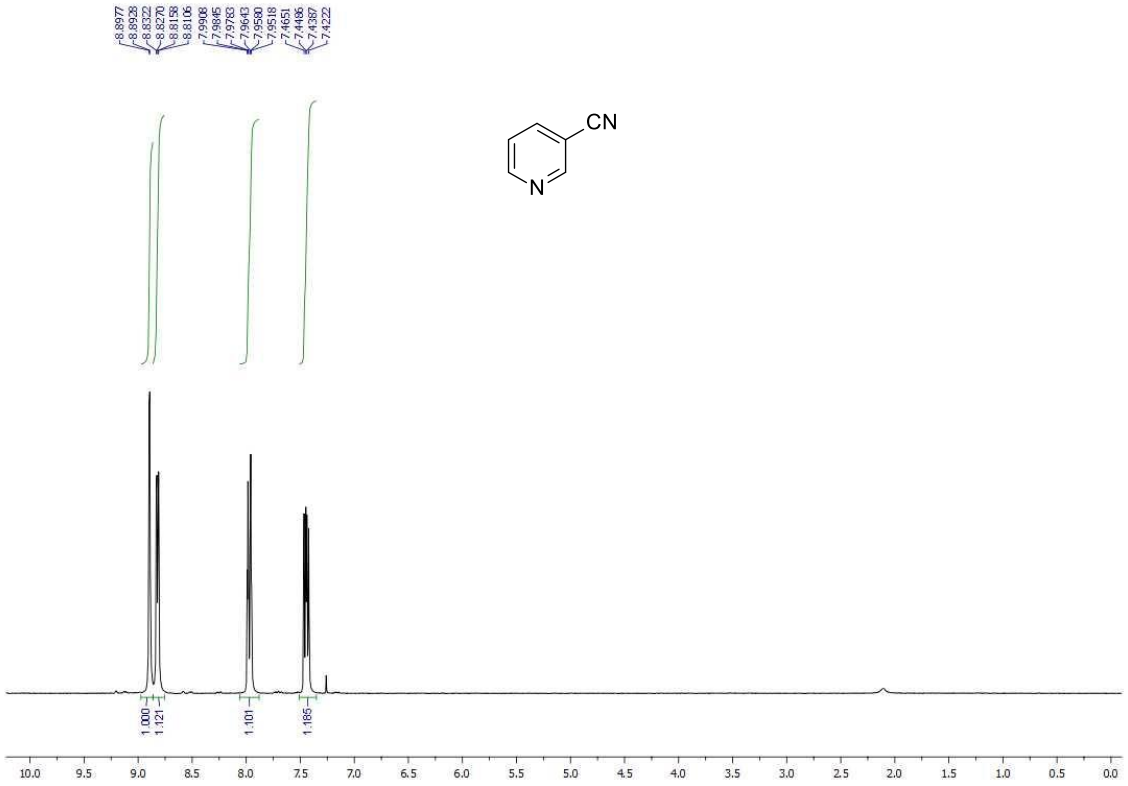


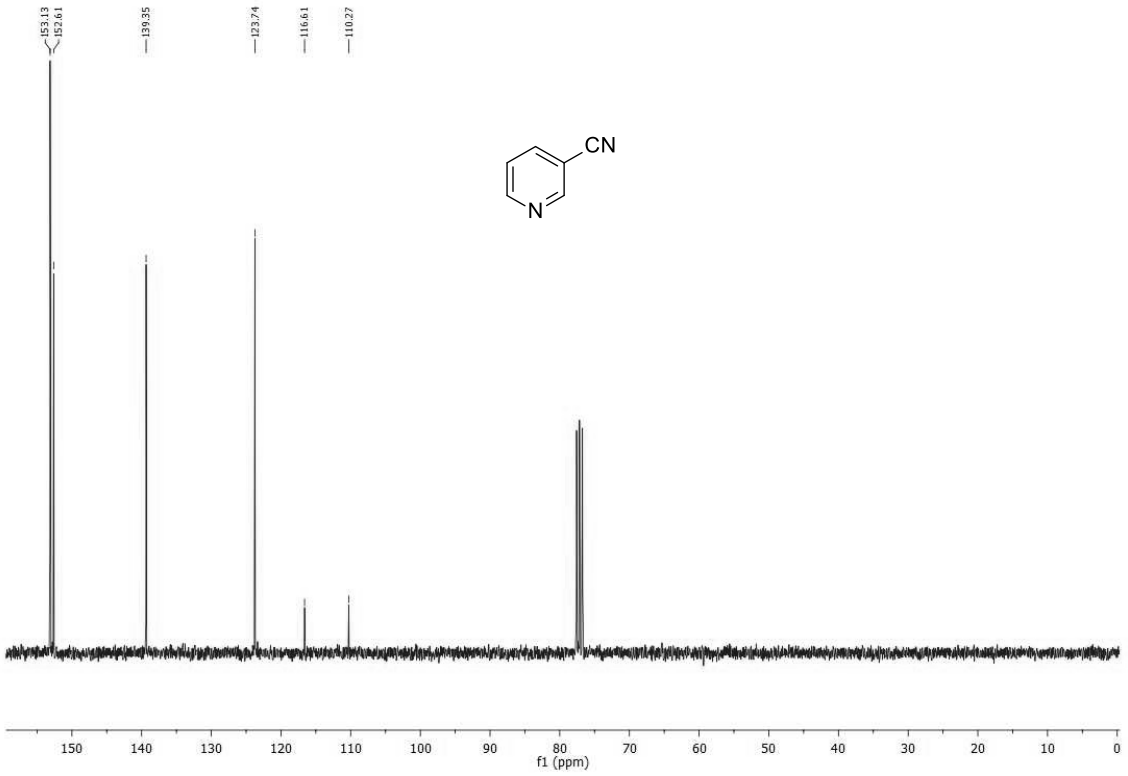
4-Acetylbenzonitrile (**2l**)



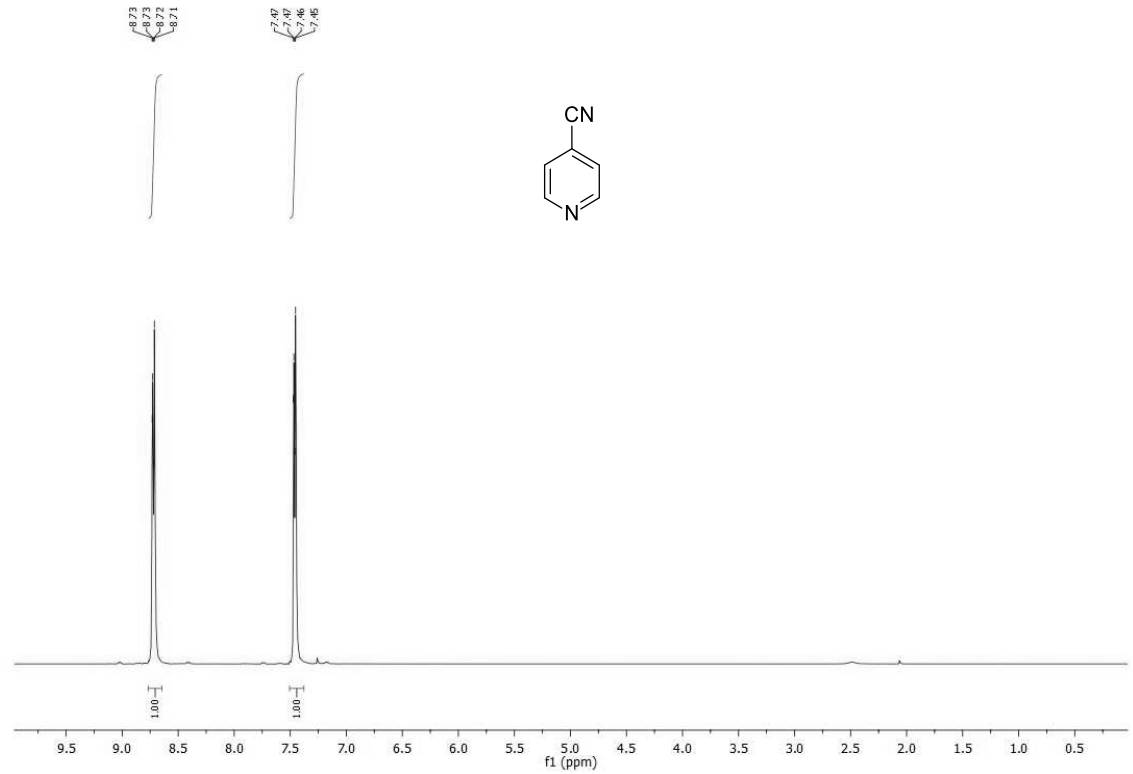


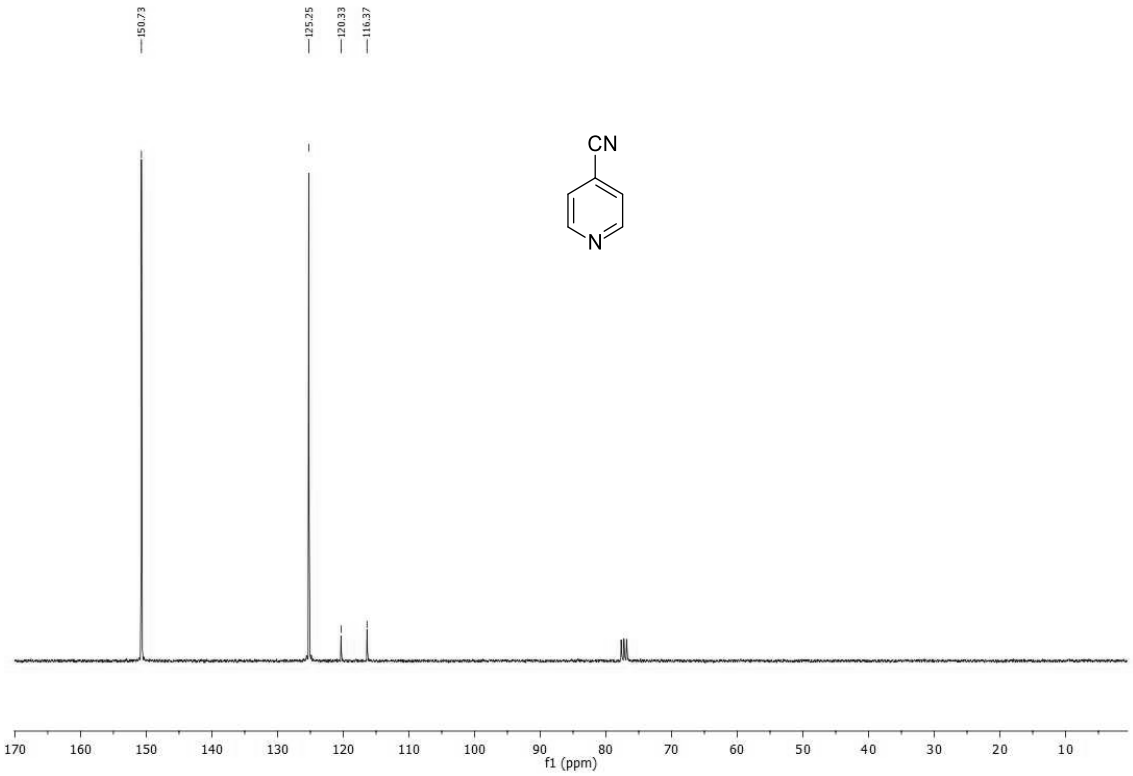
3-Pyridinecarbonitrile (**2m**)



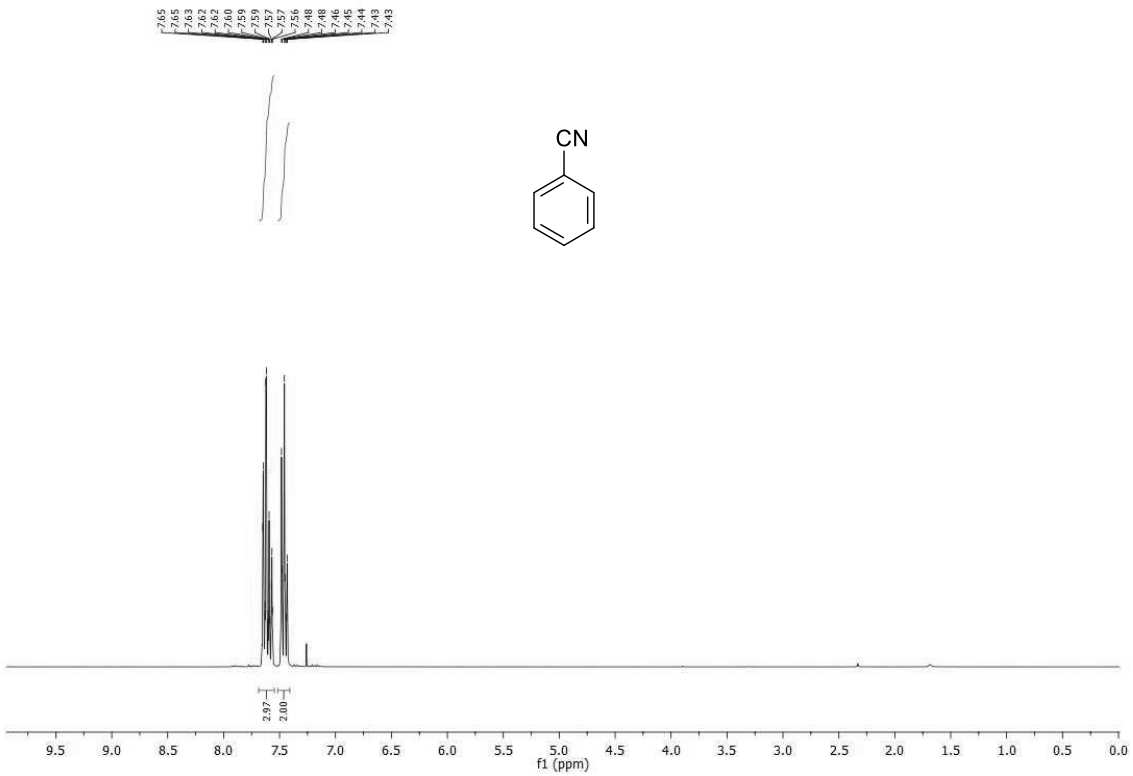


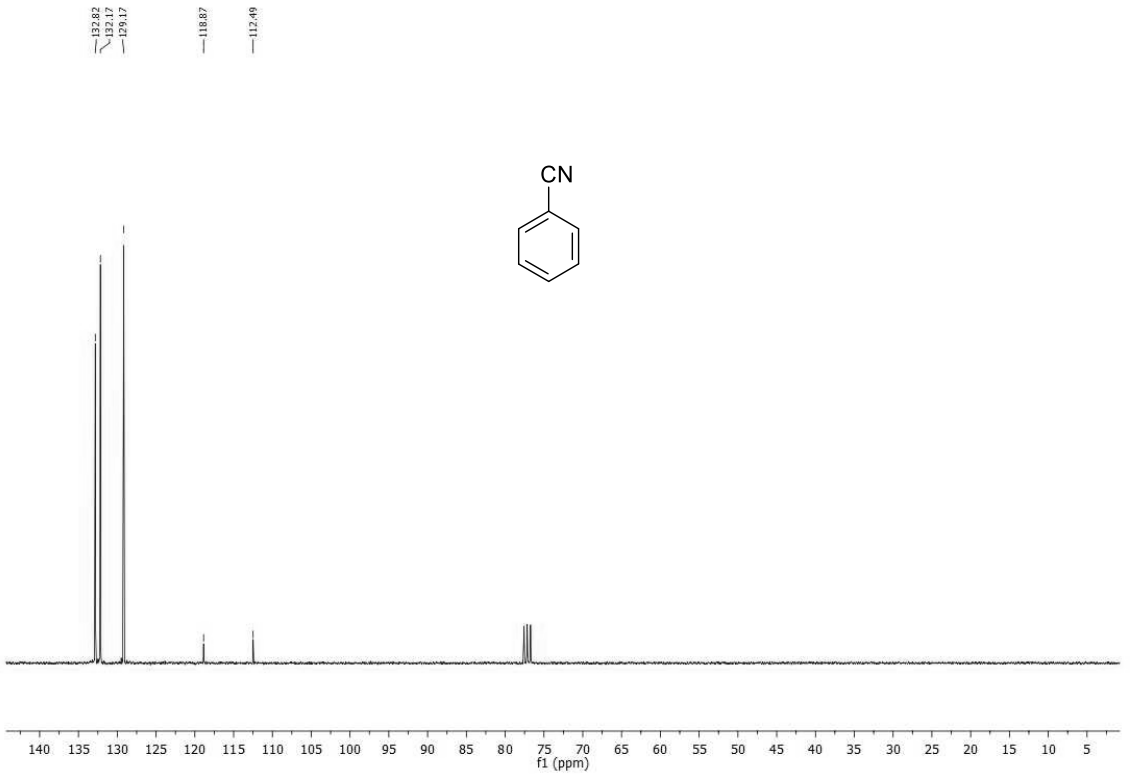
4-Pyridinecarbonitrile (**2n**)





Benzonitrile (**2o**)





References and notes

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