Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

A Cyanide-Free Synthesis of Nitriles in Exploiting Flow Chemistry

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Materials and Methods

Unless otherwise stated, all solvents were purchased from Fisher Scientific and used without further purification. Substrates and reagents were purchased from Fluorochem or Sigma Aldrich and used as received.

^{1}H-NMR spectra were recorded on 400 MHz and 500 MHz instruments and are reported relative to residual solvent: $CDCl_3$ (δ 7.26 ppm). ^{13}C-NMR spectra were recorded on the same instruments (100 and 125 MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm).

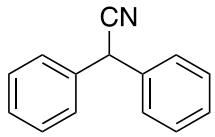
Data for ^{1}H-NMR are reported as follows: chemical shift (δ/ ppm) (integration, multiplicity, coupling constant (Hz)). Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, sext = sextet, sept = septet, m = multiplet. Data for ^{13}C-NMR are reported in terms of chemical shift (δ/ ppm) and multiplicity (C, CH, CH_2 or CH_3). COSY, HSQC, and HMBC experiments were used in the structural assignment. IR spectra were obtained by use of a Bruker Platinum spectrometer (neat, ATR sampling) with the intensities of the characteristic signals being reported as weak (w, <20% of tallest signal), medium (m, 21-70% of tallest signal) or strong (s, >71% of tallest signal).

High-resolution mass spectrometry was performed using the indicated techniques on a micromass LCT orthogonal time-of-flight mass spectrometer with leucine-enkephalin (Tyr-Gly-Phe-Leu) as an internal lock mass.

Continuous flow experiments were performed using Chemyx Inc Fusion 100 syringe pumps. The flow reactor consisted of a Teflon T-piece, 1/8” PFA tubing, or 1/16” PFA tubing with a Teflon helical static mixer. The reaction scale-up was performed on a Vapourtec E-series system equipped with a peristaltic pump.

General Experimental Procedures

2.1 Synthesis of 2,2-diphenylacetonitrile (**2a**)



Chemical Formula: $C_{14}H_{11}N$
Exact Mass: 193.0891

General batch procedure A:

To an ice-cooled solution of TosMIC (215 mg, 1.1 mmol) in DMSO (7 mL) was added KO^{t}Bu (392 mg, 3.5 mmol). After stirring for 5 min in a nitrogen-enriched environment, MeOH (0.7 mL) was added, then benzophenone (182 mg, 1.0 mmol). The reaction mixture was stirred at room temperature. At 1 h, a second portion of TosMIC (195 mg, 1.0 mmol) and KO^{t}Bu (224 mg, 2.0 mmol) was added and a nitrogen-enriched environment was established again in the flask using a nitrogen balloon. The reaction mixture was extracted with aqueous NH_4Cl and EtOAc. The EtOAc layer was then washed twice with brine. The recovered EtOAc layer was evaporated *in vacuo* to give a colourless solid. Silica was used for all chromatography columns.

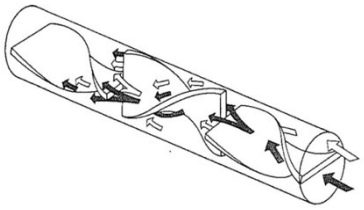
General continuous flow procedure B:

1. **Reaction with KO^{t}Bu**

Line A: Benzophenone (182 mg, 1 mmol) was added to a vial along with TosMIC (234 mg, 1.2 mmol), MeOH (0.5 mL) and DMSO (2.5 mL). The solution was taken up into a 5 mL syringe which was then loaded onto a syringe pump.

Line B: KO^{t}Bu (280 mg, 2.5 mmol) and DMSO (3 mL) were added to a separate vial. The viscous solution was taken up into a 5 mL syringe, which was then loaded onto a separate syringe pump.

A static mixer coil (22.4 mL)(Image 1) was used and an overall flow rate of 1.12 mL/min was set. After both solutions had been dispensed, a 25 mL syringe containing MeOH replaced the T-piece and was set to the same flow rate of 1.12 mL/min. Aqueous NH_4Cl (0.3 mL, 2.5 mmol) was kept in the collection flask to quench the reaction. The reaction was extracted in the same way as detailed in the batch procedure above.



SI Image 1. The static mixer coil used in the continuous flow setup for the reactions with KO^{t}Bu and NaOMe (left). A schematic of the internal helical structure of the reactor coil which increases reaction mixing (right).

2. Reaction with NaOMe

Line A: Benzophenone (182 mg, 1 mmol) was added to a vial along with TosMIC (292.5 mg, 1.5 mmol), and THF (1.0 mL). The solution was taken up into a 5 mL syringe which was then loaded onto a syringe pump.

Line B: NaOMe (25% in MeOH)(0.43 mL, 2 mmol) was taken up into a 5 mL syringe, which was then loaded onto a separate syringe pump.

A static mixer coil (11.2 mL)(Image 1) was used and an overall flow rate of 11.2 mL/min was set. After both solutions had been dispensed, a 20 mL syringe containing MeOH (15 mL) replaced the T-piece and was set to the same flow rate of 1.12 mL/min. Citric acid (384 mg, 2 mmol) was kept in the collection flask to quench the reaction. The reaction was extracted in the same way as the batch procedure.

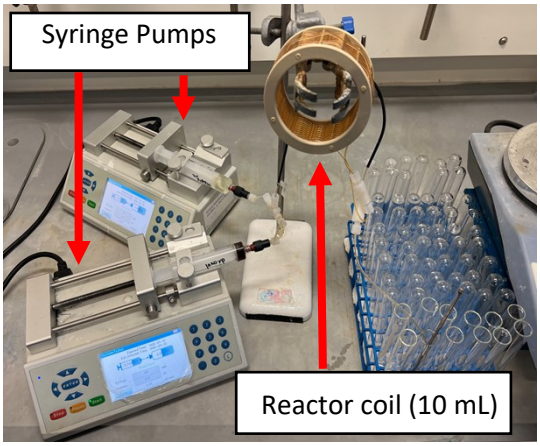
3. Reaction with NaO^{t}Bu

Line A: Benzophenone (546 mg, 3 mmol) was added to a vial along with TosMIC (1.46 g, 7.5 mmol), and 2:1 DMSO:MeOH (4.5 mL). The solution was taken up into a 15 mL syringe which was then loaded onto a syringe pump.

Line B: NaO^{t}Bu (2 M in THF)(7.5 mL, 15 mmol) was taken up into a 15 mL syringe. Additional THF (6 mL) was taken up into the syringe to prevent NaO^{t}Bu crashing out of solution and causing clogging of the inlet connectors. The syringe was then loaded onto a separate syringe pump.

A standard PFA coil (10 mL)(Image 2) was used and an overall flow rate of 6.67 mL/min was set. After both solutions had been dispensed, a 10 mL syringe filled with MeOH replaced the T-piece and was set to the same flow rate of 6.67 mL/min.

The reaction output was collected in test tubes containing citric acid (960 mg, 8.57 mmol). The output tubing was transferred to a new test tube every 1 min. The output collected between 3 - 5 min was combined and extracted in the same way as in the batch procedure.

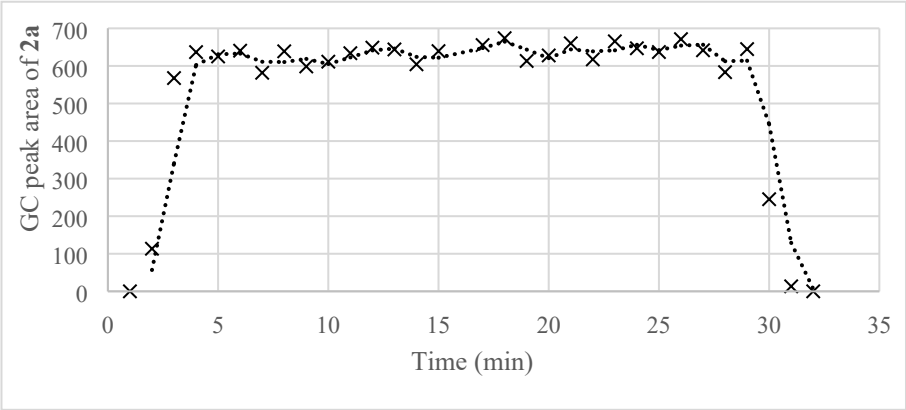


SI Image 2. Continuous flow reaction setup for the reaction with NaO^{t}Bu.

4. Scaled-up reaction with NaO^{t}Bu

If the setup shown in Image 2 were to be scaled up, several syringe swaps would be required over the course of the 30 min run. To avoid this disruption and therefore obtain a smoother steady state graph, a Vapourtec E-series flow reactor equipped with a peristaltic pump was used to carry out the reaction scale-up.

The reaction output was collected in test tubes at 1-minute intervals and quenched with citric acid (960 mg, 8.57 mmol). The contents of each test tube were extracted with EtOAc /water and washed twice with brine. A sample was taken for GC analysis and the results are plotted below (Graph 1); where x = 1 min, this represents the reaction output collected between 0 – 1 min. The material collected between x = 4 min and x = 29 min was combined and the concentrated crude material was purified by column chromatography. 2,2-diphenylacetonitrile (**2a**) (3.81 g, 19.7 mmol) was isolated. This corresponds to a throughput of 8.8 g/h.

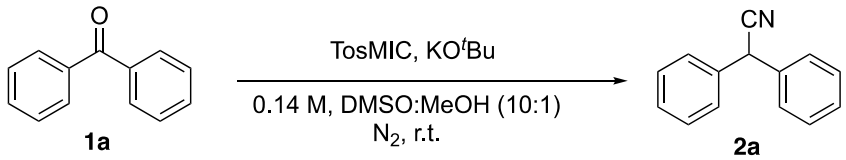


SI Graph 1. Steady state plot of the scaled-up reaction (30 mmol). The peak area (plotted on y-axis) was determined *via* GC analysis.

Reaction Optimisation

3.1 Batch setup

SI Table 1. Full optimisation study for the batch setup



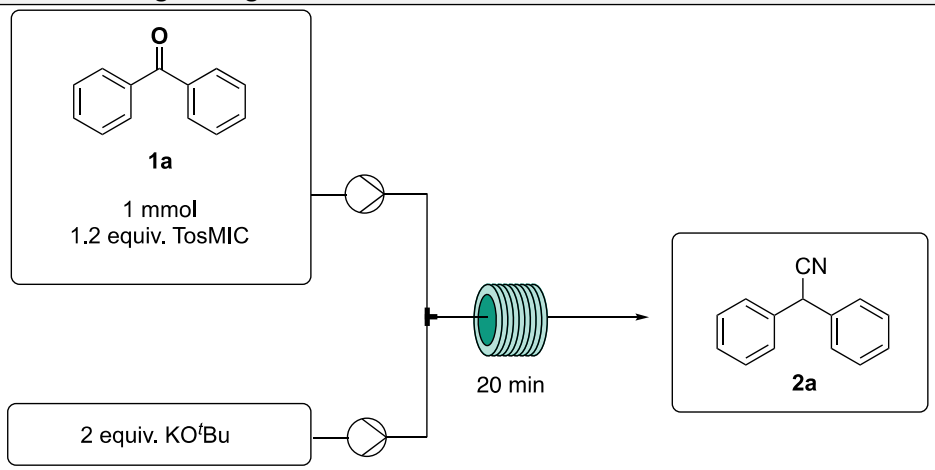
1a **2a**

Entry	TosMIC (equiv.) [a]	[c]	KO^{t}Bu (equiv.) [b]	[d]	Time (h)	Conversion to 2a (%)[e]
1	1.3	-	3.0	-	1	58
2	1.3	-	3.0	-	2	63
3	1.3	-	3.0	-	19	11
4	1.3	1.0	3.5	-	2	73
5	1.3	1.0	3.5	-	3	69
6	1.3	1.0	3.5	2.0	4	91
7	1.4	1.0	3.5	2.0	3	76
8	1.3	1.0	3.5	3.5	4	93
9	1.1	1.0	3.5	2.0	4	93
10	1.1	3.5	3.5	4.0	4	95
11	1.3	1.0	3.5	2.0	1	70
12[f]	1.3	1.0	3.5	2.0	2	71
13[f]	1.3	1.0	3.5	2.0	3	63

[a][b]Addition made at start of reaction. [c][d]Addition made 1 h after start of reaction. [e]Determined by ^{1}H-NMR. [f]gradient used: r.t. for 1 h, then 30°C for 30 min, then 50°C for 30 min, then 70°C for 30 min, then 90°C for 30 min

3.2 Continuous Flow Setup

SI Table 2. Mixing strategies tested for the reaction with KO^{t}Bu

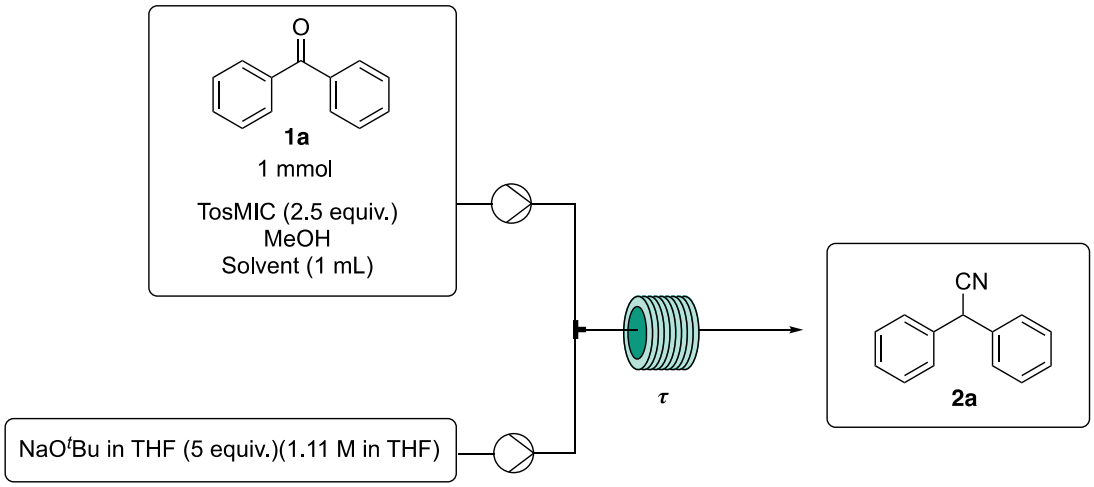


Entry	Pump type	Reactor type	Conversion to 2a (%)[a]
1	Syringe	Static mixer coil	52
2[b]	Syringe	Sand column	-
3	Peristaltic	Static mixer reactor	24

[a]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

[b]Build-up of pressure in sand column tripped the syringe pumps.

SI Table 3. Linear optimisation experiments for the reaction with NaO^{t}Bu. These results follow on from the DOE studies detailed in Table 3.



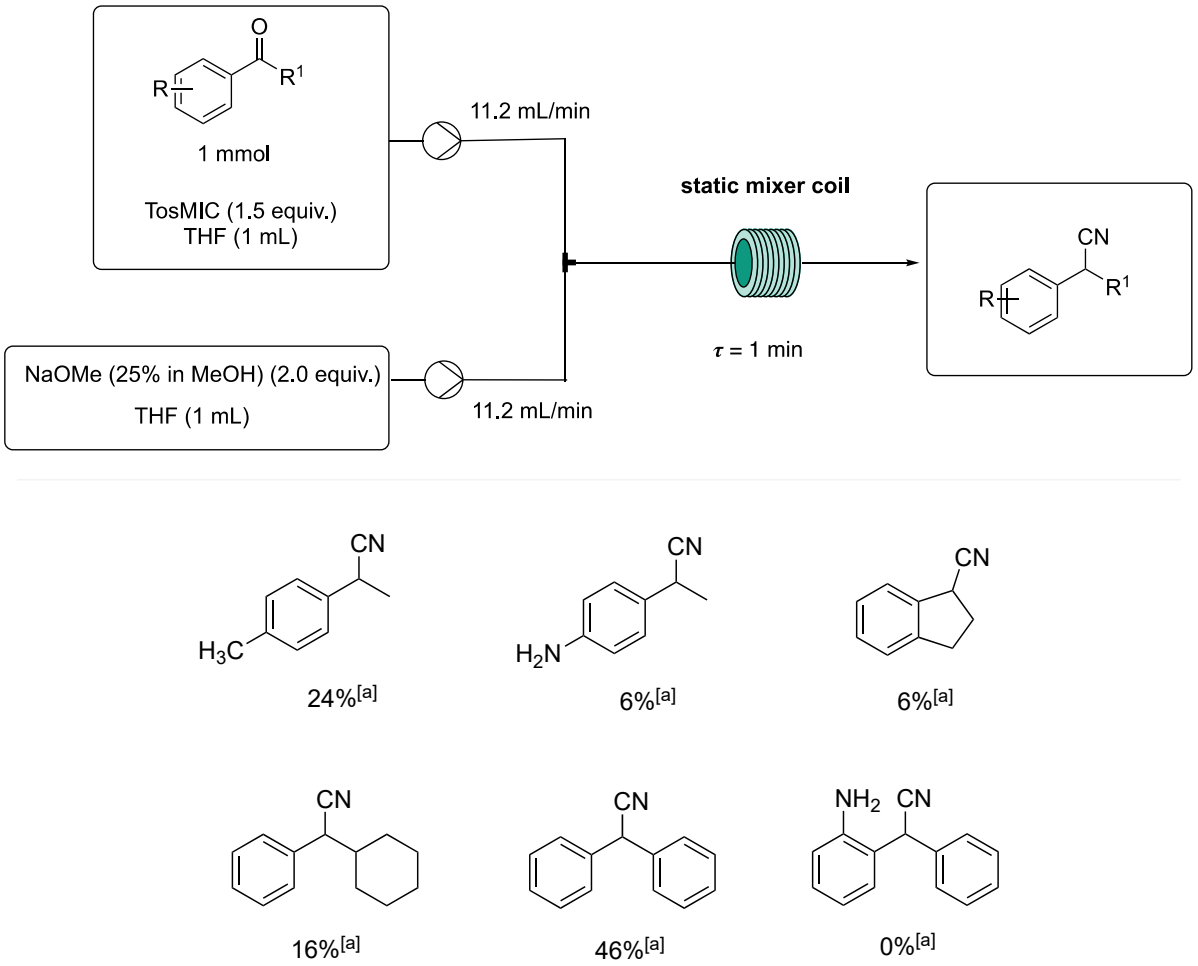
Entry	τ (min)	MeOH (mL)	Solvent	Yield (%)[a]
1	0.5	0.5	DMSO	58
2	1.0	0.5	DMSO	72
3	1.5	0.5	DMSO	55
4	1.0	0.2	DMSO	67
5	1.0	0.5	ACN	23
6[b]	1.0	0.5	THF	-
7[b]	1.0	0.5	Toluene	-

[a]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard. [b]Blocked reactor coil.

3.3 Unsuccessful substrate scopes

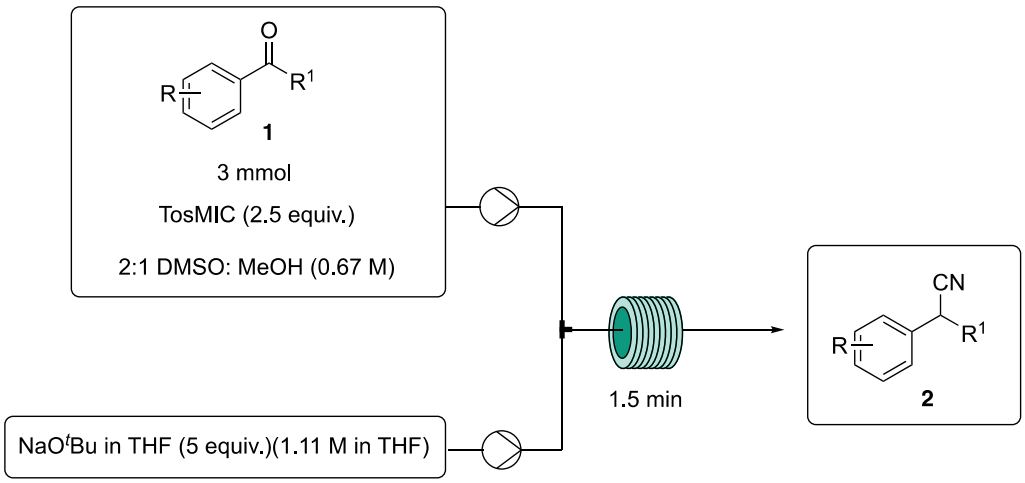
1. Reaction with NaOMe

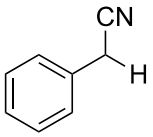
Although NaOMe precipitated in the presence of excess THF (reaction solvent), the wider tubing diameter of the static mixer coil prevented any clogging issues by allowing the reaction mixture and the precipitate to progress as a suspension through the coil. This may still present issues upon scale-up, however, as the projected throughput of the reaction was excellent efforts to broaden the substrate scope were made. Despite these further experiments with NaOMe this was ultimately unsuccessful as poor product yields were obtained along with several unidentified side products.



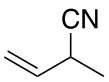
SI Scheme 1. Unsuccessful substrate scope using conditions that were optimised using NaOMe and a benzophenone substrate (**1a**). [a]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

2. Reaction with NaO^{t}Bu

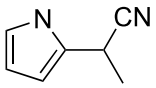




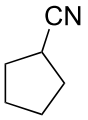
2p, NP[a]



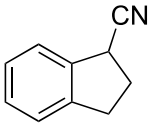
2q, NP[a]



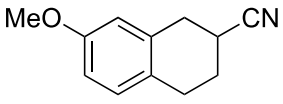
2r, NP[a]



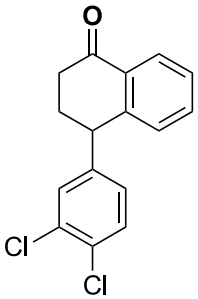
2s, NP[a]

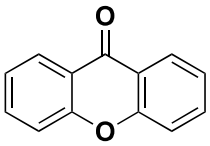


2t, < 5%[a]



2u, NP[a]





2w, Insoluble in DMSO:MeOH

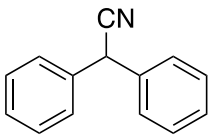
2v, Crashed out in reactor

SI Scheme 2. Unsuccessful substrate scope using the optimised conditions for the NaO^{t}Bu reaction. [a]Determined by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard.

Spectroscopic Data

2,2-Diphenylacetonitrile (2a)

Following the general continuous flow procedure B (4. Scaled-up reaction with NaO^{t}Bu), compound **2a** was obtained in 83% yield (3.81 g, 19.74 mmol).



Chemical Formula: $C_{14}H_{11}N$
Exact Mass: 193.0891

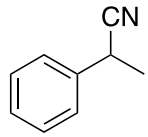
Appearance: colourless solid

Rf: 0.44 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.41 – 7.30 (m, 10 H), 5.14 (s, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 136.0 (2x C), 129.3 (4x CH), 128.4 (2x CH), 127.9 (4x CH), 119.8 (CN), 42.8 (CH). **IR** (neat) ν/cm^{-1}: 3063 (w), 3032 (w), 2248 (w), 1599 (w), 1493 (m), 1454 (m), 1080 (w), 1031 (w), 756 (m), 735 (m), 696 (s), 649 (w), 628 (w), 534 (w), 460 (w). **HR-MS** (TOF ES): calculated for $C_{14}H_{12}N$ 194.0969, found 194.0960 ($M+H^+$). Data is in agreement with reported data. [1]

2-Phenylpropanenitrile (2b)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2b** was obtained in 58% yield (206 mg, 1.57 mmol).



Chemical Formula: C_9H_9N
Exact Mass: 131.0735

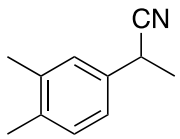
Appearance: colourless oil

Rf: 0.33 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.42 – 7.30 (m, 5H), 3.90 (q, *J* = 7.3 Hz, 1H), 1.65 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 137.2 (C), 129.2 (2x CH), 128.2 (CH), 126.8 (2x CH), 121.7 (CN), 31.4 (CH), 21.6 (CH_3). **IR** (neat) ν/cm^{-1}: 3031 (w), 2986 (w), 2938 (w), 2241 (w), 1494 (m), 1452 (s), 1078 (w), 758 (s), 698 (s), 510 (m). Data is in agreement with reported data. [2]

2-(3,4-Dimethylphenyl)propanenitrile (2c)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2c** was obtained in 65% yield (280.6 mg, 1.77 mmol).



Chemical Formula: $C_{11}H_{13}N$
Exact Mass: 159.1048

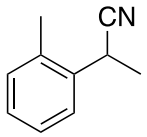
Appearance: colourless oil

Rf: 0.30 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.16 (d, J = 8.1 Hz, 2H), 7.09 (m, 1H), 3.85 (q, J = 7.3 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 1.64 (d, J = 7.3 Hz, 3H).**^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 137.5 (C), 136.5 (C), 134.6 (C), 130.3 (CH), 128.0 (CH), 124.1 (CH), 122.0 (CN), 30.9 (CH), 21.6 (CH_3), 19.8 (CH_3), 19.4 (CH_3). **IR** (neat) ν/cm^{-1}: 2982 (m), 2938 (m), 2240 (m), 1505 (s), 1451 (s), 1385 (m), 1063 (w), 1022 (m), 987 (m), 921 (m), 820 (s), 597 (m). **HR-MS** (TOF ES): calculated for $C_{11}H_{14}N$, found 160.1120 $(M+H)^+$.

2-(*o*-Tolyl)propanenitrile (2d)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2d** was obtained in 58% yield (153.2 mg, 1.06 mmol).



Chemical Formula: $C_{10}H_{11}N$
Exact Mass: 145.0891

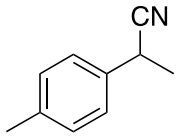
Appearance: colourless oil

Rf: 0.22 (DCM/cyclohexane = 2/3)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.47 – 7.43 (m, 1H), 7.28 – 7.18 (m, 3H), 4.05 (q, *J* = 7.2 Hz, 1H), 2.37 (s, 3H), 1.62 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 135.4 (C), 134.9 (C), 131.1 (CH), 128.3 (CH), 127.1 (CH), 126.9 (CH), 121.9 (CN), 28.3 (CH), 20.2 (CH_3), 19.1 (CH_3). **IR** (neat) ν/cm^{-1}: 2984 (w), 2938 (w), 2240 (m), 1491 (s), 1455 (s), 1082 (m), 762 (s), 724 (m). **HR-MS** (TOF ES): calculated for $C_{10}H_{12}N$, found 146.0965 $(M+H)^+$. Data is in agreement with reported data.[2]

2-(p-Tolyl)propanenitrile (2e)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2e** was obtained in 96% yield (252.5 mg, 1.74 mmol).



Chemical Formula: $C_{10}H_{11}N$
Exact Mass: 145.0891

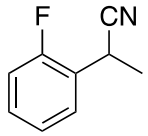
Appearance: colourless oil

Rf: 0.30 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.30 – 7.24 (m, 2H), 7.22 (d, J = 8.0 Hz, 2H), 3.89 (q, J = 7.3 Hz, 1H), 2.38 (s, 3H), 1.65 (d, J = 7.2 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 138.0 (C), 134.2 (C), 129.9 (2x CH), 126.7 (2x CH), 121.9 (CN), 30.9 (CH), 21.6 (CH_3), 21.2 (CH_3). **IR** (neat) ν/cm^{-1}: 2984 (w), 2924 (w), 2240 (w), 1514 (s), 1453 (m), 1084 (w), 816 (s), 570 (m), 514 (m). **HR-MS** (TOF ES): calculated for $C_{10}H_{12}N$, found 146.0964 $(M+H)^+$. Data is in agreement with reported data.[2]

2-(2-Fluorophenyl)propanenitrile (2f)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2f** was obtained in 60% yield (81 mg, 0.54 mmol).



Chemical Formula: C_9H_8FN
Exact Mass: 149.0641

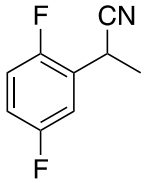
Appearance: colourless oil

Rf: 0.25 (DCM/cyclohexane = 3/2)

^{1}H-NMR (400 MHz, $CDCl_3$) δ/ppm 7.48 (m, 1H), 7.36 – 7.28 (m, 1H), 7.19 (m, 1H), 7.09 (m, 1H), 4.19 (q, J = 7.2 Hz, 1H), 1.64 (d, J = 7.2 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ/ppm 159.8 (d, *J* = 248.0 Hz, CF), 130.1 (d, *J* = 8.1 Hz, CH), 128.4 (d, *J* = 3.4 Hz, CH), 125.0 (d, *J* = 3.5 Hz, CH), 124.4 (d, *J* = 14.0 Hz, C), 120.8 (CN), 116.0 (d, *J* = 21.3 Hz, CH), 25.5 (d, *J* = 4.0 Hz, CH), 20.2 (d, *J* = 1.1 Hz, CH_3). **^{19}F-NMR** (375 MHz, $CDCl_3$) δ/ppm -118.6. **IR** (neat) v/cm^{-1}: 2990 (w), 2942 (w), 2244 (w), 1589 (w), 1493 (s), 1454 (s), 1235 (s), 1109 (m), 815 (m), 762 (s). Data is in agreement with reported data.[2]

2-(2,5-Difluorophenyl)propanenitrile (2g)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2g** was obtained in 70% yield (104.7 mg, 0.63 mmol)



Chemical Formula: $C_9H_7F_2N$
Exact Mass: 167.0547

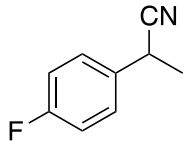
Appearance: colourless oil

Rf: 0.22 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.23 – 7.16 (m, 1H), 7.10 – 6.96 (m, 2H), 4.16 (q, *J* = 7.2 Hz, 1H), 1.64 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 158.9 (dd, *J* = 244.3, 2.4 Hz, CF), 155.8 (dd, *J* = 242, 2.6 Hz, CF), 126.0 (dd, *J* = 16.65, 7.61 Hz, C), 120.2 (CN), 117.2 (dd, *J* = 24.2, 8.6 Hz, CH), 116.6 (dd, *J* = 23.9, 8.6 Hz, CH), 115.2 (dd, *J* = 25.5, 3.6 Hz, CH), 25.5 (d, *J* = 3.5 Hz, CH), 20.0 (CH_3). **^{19}F-NMR** (375 MHz, $CDCl_3$) δ/ppm -116.7, -125.0 **IR** (neat) v/cm^{-1}: 2993 (w), 2944 (w), 2246 (w), 1499 (s), 1427 (w), 1247 (w), 1187 (s), 873 (m), 820 (m), 474 (w).

2-(4-Fluorophenyl)propanenitrile (2h)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2h** was obtained in 81% yield (90 mg, 0.6 mmol).



Chemical Formula: C_9H_8FN
Exact Mass: 149.0641

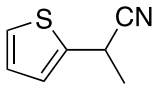
Appearance: colourless oil

Rf: 0.21 (DCM/cyclohexane = 1/1)

^{1}H-NMR (00 MHz, $CDCl_3$) δ/ppm 7.36 – 7.29 (m, 2H), 7.11 – 7.03 (m, 2H), 3.89 (q, *J* = 7.3 Hz, 1H), 1.63 (d, *J* = 7.3 Hz, 3H). **^{13}C-NMR** (100 MHz, $CDCl_3$) δ/ppm 162.7 (d, *J* = 247.3 Hz, CF), 133.2 (d, *J* = 3.4 Hz, C), 128.8 (d, *J* = 8.3 Hz, 2x CH), 121.8 (CN), 116.4 (d, *J* = 21.9 Hz, 2x CH), 30.9 (CH), 21.8 (CH_3). **^{19}F-NMR** (375 MHz, $CDCl_3$) δ/ppm -114.0. **IR** (neat) ν/cm^{-1}: 2988 (w), 2940 (w), 2242 (w), 1604 (m), 1509 (s), 1455 (w), 1228 (s), 1162 (m), 836 (s), 523 (m). Data is in agreement with reported data.[2]

2-(Thiophen-2-yl)propanenitrile (2i)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2i** was obtained in 45% yield (120 mg, 0.88 mmol).



Chemical Formula: C_7H_7NS
Exact Mass: 137.0299

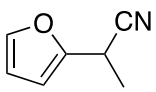
Appearance: colourless oil

Rf: 0.28 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.25 (m, 1H), 7.06 (m, 1H), 6.96 (m, 1H), 4.16 (q, *J* = 7.2 Hz, 1H), 1.72 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 139.7 (C), 127.5 (CH), 126.0 (CH), 125.8 (CH), 121.1 (CN), 27.0 (CH), 21.9 (CH_3). **IR** (neat) ν/cm^{-1}: 3107 (w), 2987 (w), 2938 (w), 2241 (w), 2102 (w), 1453 (m), 1379 (w), 1237 (m), 830 (m), 705 (s). Data is in agreement with reported data. [3]

2-(Furan-2-yl)propanenitrile (2j)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2j** was synthesised in 78% yield. This was determined by ^{1}H-NMR only, using 1,3,5-trimethoxybenzene as an internal standard. An isolated yield value for compound **2j** was not obtained due to its high volatility. The following chemical shift and peak integration values of compound **2j** were identified in the crude reaction ^{1}H-NMR. These values align with those reported for the same compound in the literature,[4] and are detailed below.



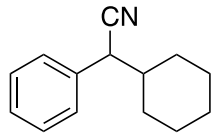
Chemical Formula: C_7H_7NO
Exact Mass: 121.0528

Rf: 0.15 (DCM/cyclohexane = 15/100)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.29 (m, 2H), 7.18 (m, 1H), 3.99 (q, J = 6.9 Hz, 1H), 1.67 (d, J = 7.2 Hz, 3H).

2-Cyclohexyl-2-phenylacetonitrile (2k)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2k** was obtained in 20% yield (39 mg, 0.2 mmol).



Chemical Formula: $C_{14}H_{17}N$
Exact Mass: 199.1361

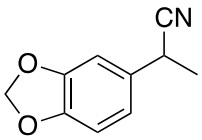
Appearance: colourless oil

Rf: 0.26 (Et_2O/pentane = 1/100)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.41 – 7.21 (m, 5H), 3.61 (d, *J* = 6.7 Hz, 1H), 1.74 (m, 6H), 1.22 – 1.07 (m, 5H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 135.2 (C), 129.3 (2x CH), 128.4 (2x CH), 128.4 (CH), 120.6 (CN), 44.8 (CH), 43.2 (CH), 31.7 (CH_2), 30.0 (CH_2), 26.4 (CH_2), 26.3 (CH_2), 26.3 (CH_2). **IR** (neat) ν/cm^{-1}: 3031 (w), 2925 (s), 2853 (s), 2238 (w), 1493 (w), 1451 (s), 754 (m), 715 (s). Data is in agreement with reported data. [5]

2-(Benzo[*d*][1,3]dioxol-5-yl)propanenitrile (2l)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2l** was obtained in 76% yield (120 mg, 0.69 mmol).



Chemical Formula: $C_{10}H_9NO_2$
Exact Mass: 175.0633

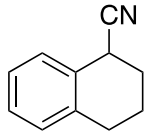
Appearance: pale pink oil

Rf: 0.16 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 6.82 – 6.77 (m, 3H), 5.97 (s, 2H), 3.81 (q, *J* = 7.3 Hz, 1H), 1.60 (d, *J* = 7.2 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 148.1 (C), 147.2 (C), 130.6 (C), 121.4 (CN), 119.8 (CH), 108.4 (CH), 107.0 (CH), 101.2 (CH_2), 30.7 (CH), 21.4 (CH_3). **IR** (neat) ν/cm^{-1}: 2985 (w), 2898 (w), 2240 (w), 1610 (w), 1488 (s), 1441 (s), 1248 (s), 1039 (s), 936 (m), 812 (m). **HR-MS** (TOF ES): calculated for $C_{10}H_{10}NO_2$, found 176.0707 $(M+H)^+$. Data is in agreement with reported data. [6]

1,2,3,4-Tetrahydronaphthalene-1-carbonitrile (2m)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2m** was obtained in 84% yield (358 mg, 2.28 mmol).



Chemical Formula: $C_{11}H_{11}N$
Exact Mass: 157.0891

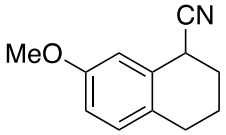
Appearance: colourless oil

Rf: 0.22 (DCM/cyclohexane = 2/3)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.41 – 7.38 (m, 1H), 7.29 – 7.23 (m, 2H), 7.19 – 7.16 (m, 1H), 4.02 (t, *J* = 6.3 Hz, 1H), 2.87 (m, 2H), 2.19 (m, 2H), 2.13 – 2.01 (m, 1H), 1.95 – 1.82 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 136.8 (C), 130.2 (C), 130.2 (CH), 129.2 (CH), 128.4 (CH), 126.9 (CH), 122.2 (CN), 31.2 (CH), 28.8 (CH_2), 27.8 (CH_2), 21.2 (CH_2). **IR** (neat) v/cm^{-1}: 3061 (w), 3020 (m), 2934 (w), 2865 (w), 2235 (m), 1580 (w), 1492 (m), 1450 (s), 767 (s), 740 (s), 432 (w). **HR-MS** (TOF ES): calculated for $C_{11}H_{12}N$, found 158.0964 $(M+H)^+$. Data is in agreement with reported data. [7]

7-Methoxy-1,2,3,4-tetrahydronaphthalene-1-carbonitrile (2n)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2n** was obtained in 75% yield (126.8 mg, 0.68 mmol).



Chemical Formula: $C_{12}H_{13}NO$
Exact Mass: 187.0997

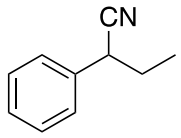
Appearance: colourless oil

Rf: 0.30 (DCM/cyclohexane = 3/2)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.03 (m, 1H), 6.88 (m, 1H), 6.80 (m, 1H), 3.95 (t, *J* = 6.3 Hz, 1H), 3.80 (s, 3H), 2.83 – 2.66 (m, 2H), 2.19 – 2.06 (m, 2H), 2.06 – 1.96 (m, 1H), 1.82 (m, 1H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 158.1 (C), 130.8 (CH), 130.7 (C), 128.4 (C), 121.8 (CN), 114.8 (CH), 113.2 (CH), 55.5 (CH_3), 31.2 (CH), 27.7 (CH_2), 27.4 (CH_2), 21.1 (CH_2). **IR** (neat) v/cm^{-1}: 2943 (m), 2837 9 (w), 2236 (w), 1611 (m), 1504 (s), 1249 (s), 1037 (m), 829 (w), 708 (w). **HR-MS** (TOF ES): calculated for $C_{12}H_{14}NO$, found 188.1069 $(M+H)^+$. Data is in agreement with reported data. [8]

2-Phenylbutanenitrile (2o)

Following the general continuous flow procedure B (3. Reaction with NaO^{t}Bu), compound **2o** was obtained in 88% yield (178.3 mg, 1.2 mmol).



Chemical Formula: $C_{10}H_{11}N$
Exact Mass: 145.0891

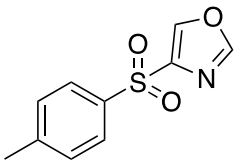
Appearance: colourless oil

Rf: 0.40 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 7.41 – 7.29 (m, 5H), 3.74 (t, *J* = 7.2 Hz, 1H), 1.99 – 1.90 (m, 2H), 1.08 (t, *J* = 7.4 Hz, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 135.8 (C), 129.1 (2x CH), 128.1 (CH), 127.2 (2x CH), 120.8 (CN), 39.0 (CH), 29.3 (CH_2), 11.5 (CH_3). **IR** (neat) ν/cm^{-1}: 2969 (w), 2869 (w), 2237 (w), 1493 (m), 1454 (s), 760 (m), 699 (s). Data is in agreement with reported data. [9]

4-Tosyloxazole (9)

Following the general continuous flow procedure B (4. Scaled-up reaction with NaO^{t}Bu), compound **9** was obtained in 40% yield (2.00 g, 9.27 mmol).

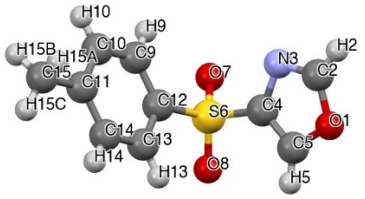


Chemical Formula: $C_{10}H_9NO_3S$
Exact Mass: 223.0303

Appearance: colourless solid

Rf: 0.04 (DCM/cyclohexane = 1/1)

^{1}H-NMR (500 MHz, $CDCl_3$) δ/ppm 8.28 (m, 1H), 7.93 (d, *J* = 8.3 Hz, 2H), 7.88 (d, *J* = 0.9 Hz, 1H), 7.37 – 7.32 (m, 2H), 2.42 (s, 3H). **^{13}C-NMR** (125 MHz, $CDCl_3$) δ/ppm 152.14 (CH), 145.29 (C), 142.75 (C), 141.84 (CH), 136.21 (C), 129.98 (2x CH), 128.35 (2x CH), 21.68 (CH_3). **IR** (neat) ν/cm^{-1}: 3144 (m), 1593 (w), 1504 (w), 1318 (s), 1203 (w), 1142 (s), 1055 (s), 909 (m), 862 (m), 811 (s), 690 (s), 652 (s), 596 (s), 529 (s), 488 (w). **HR-MS** (TOF ES): calculated for $C_{10}H_{10}NO_3S$, found 224.0376 $(M+H)^+$. Data is consistent with that reported.[10] **Crystal data (CCDC-2288150):** $C_{10}H_9NO_3S$, f.w. 223.03, T = 100.3 K, triclinic, space group P $2_1/c$ (14), a 7.3626(2) b 18.2561(6) c 7.9316(3), Å, α = 90, β = 110.701(4), γ = 90, V = 997.275 Å3 , Z = 4, Dx = 1.485 g cm-3 , R-factor (%) 3.75



Short contact < (sum of vdW radii)

Number	Atom 1	Atom 2	Length	Length - VdW

1	H14	O7	2.443	-0.277
2	O8	C2	3.046	-0.174
3	O8	H2	2.538	-0.182
4	H13	O8	2.557	-0.163
5	H5	O7	2.521	-0.199

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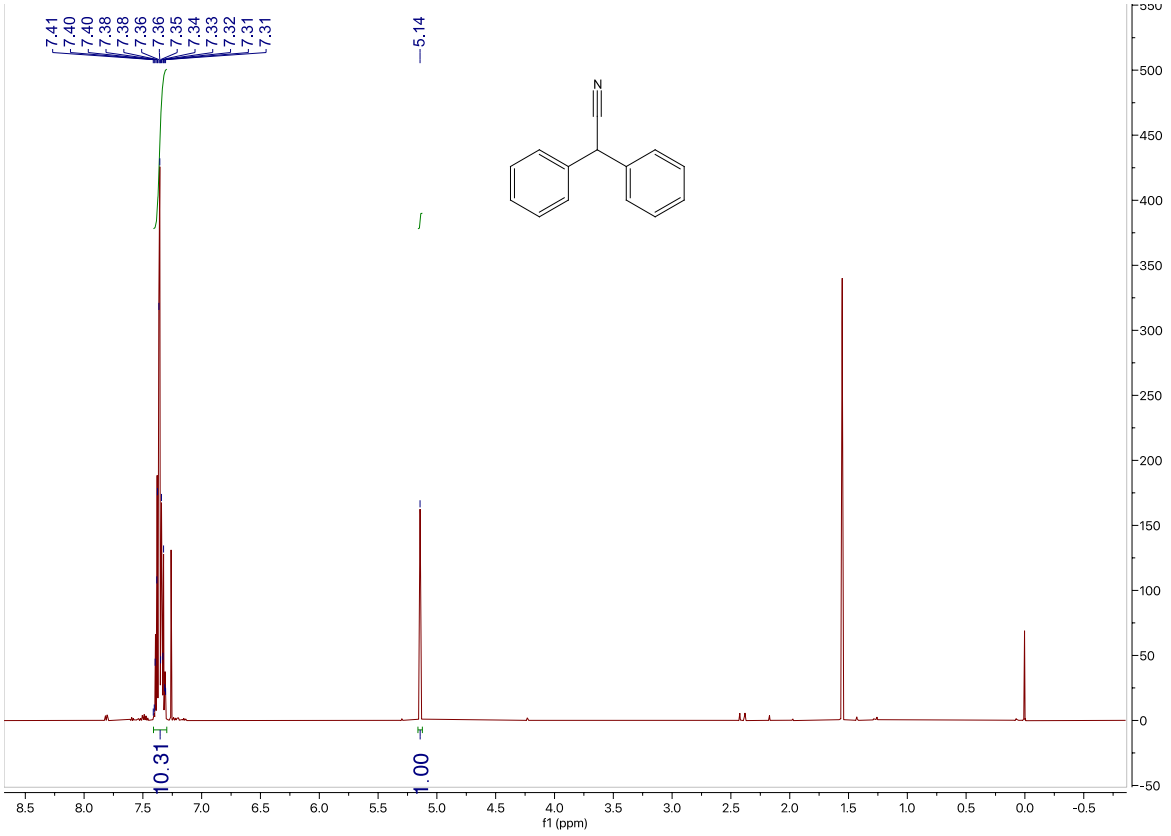
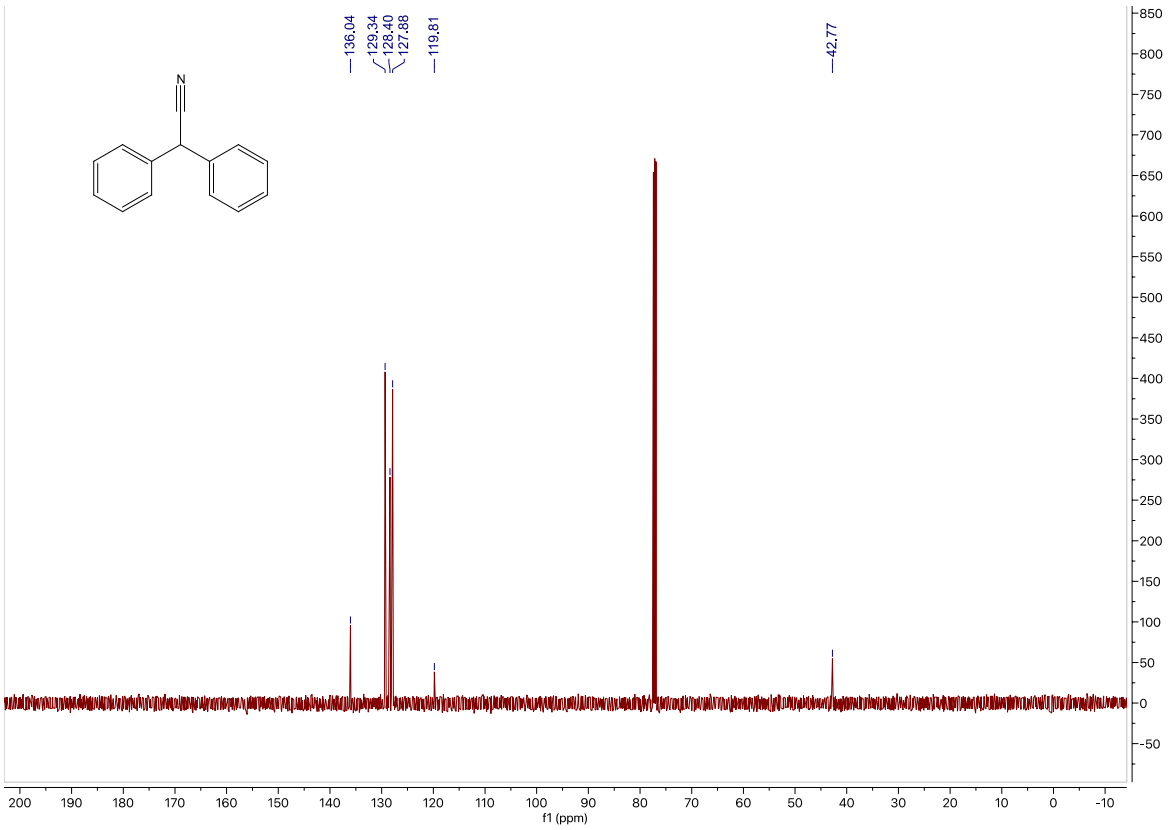
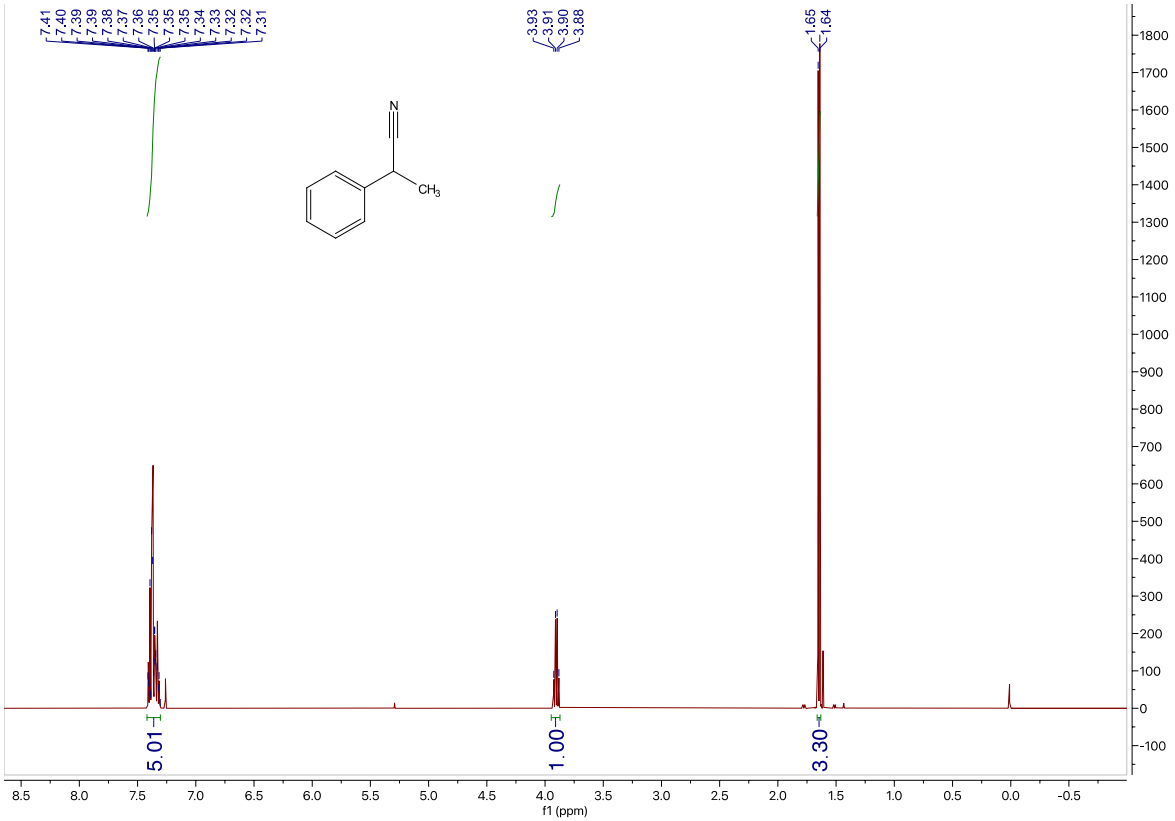
Copies of NMR spectra of compounds:

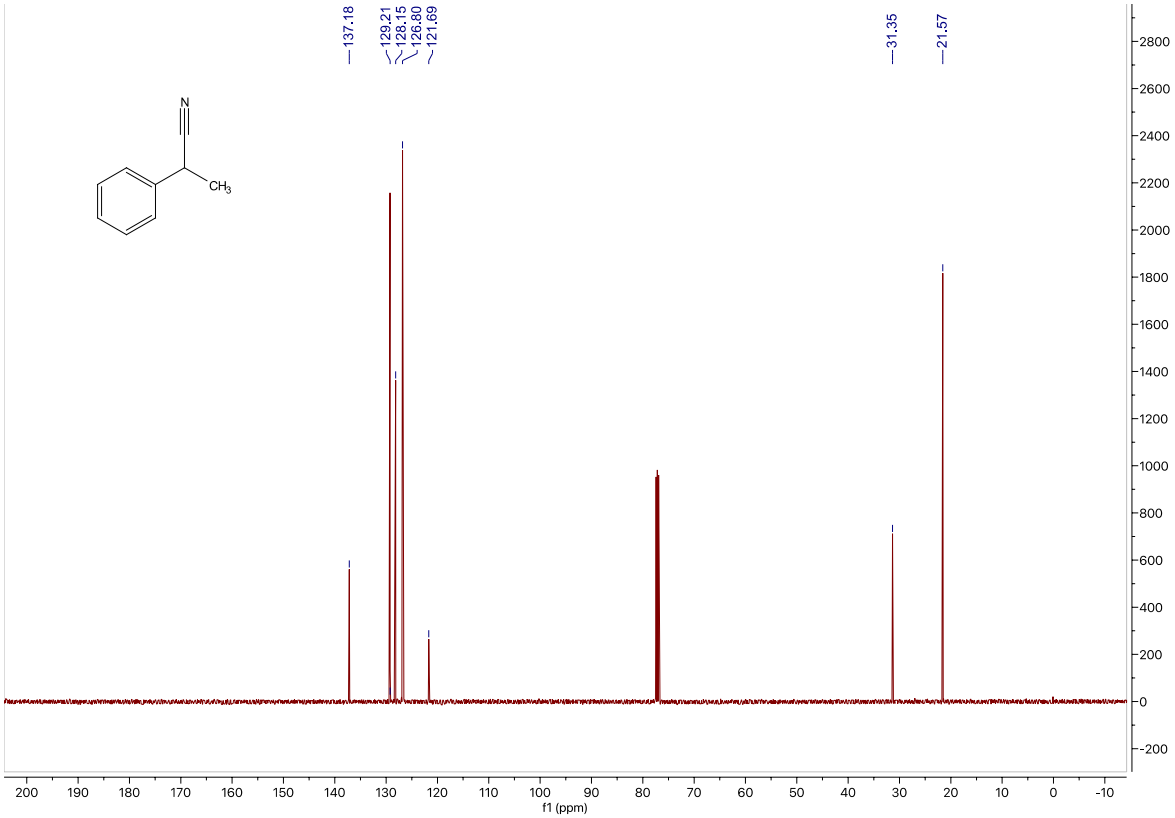
^{1}H and ^{13}C NMR of compound 2a



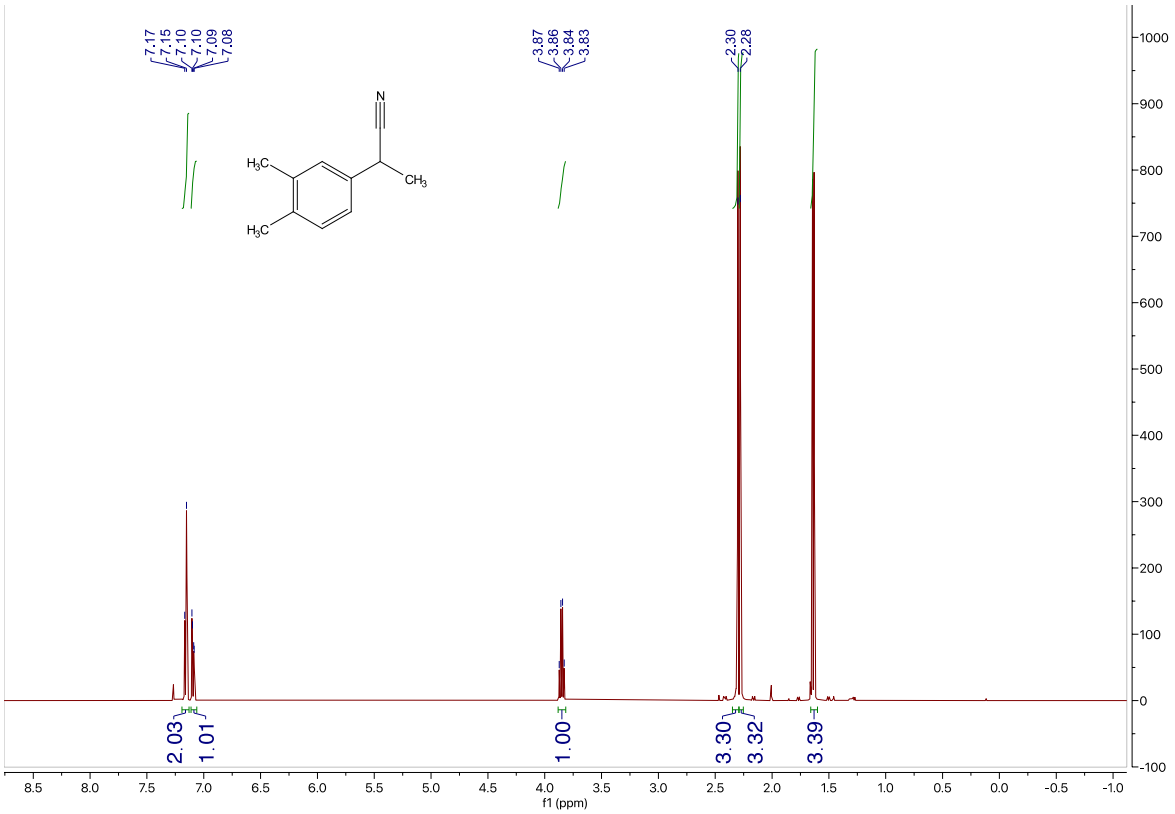


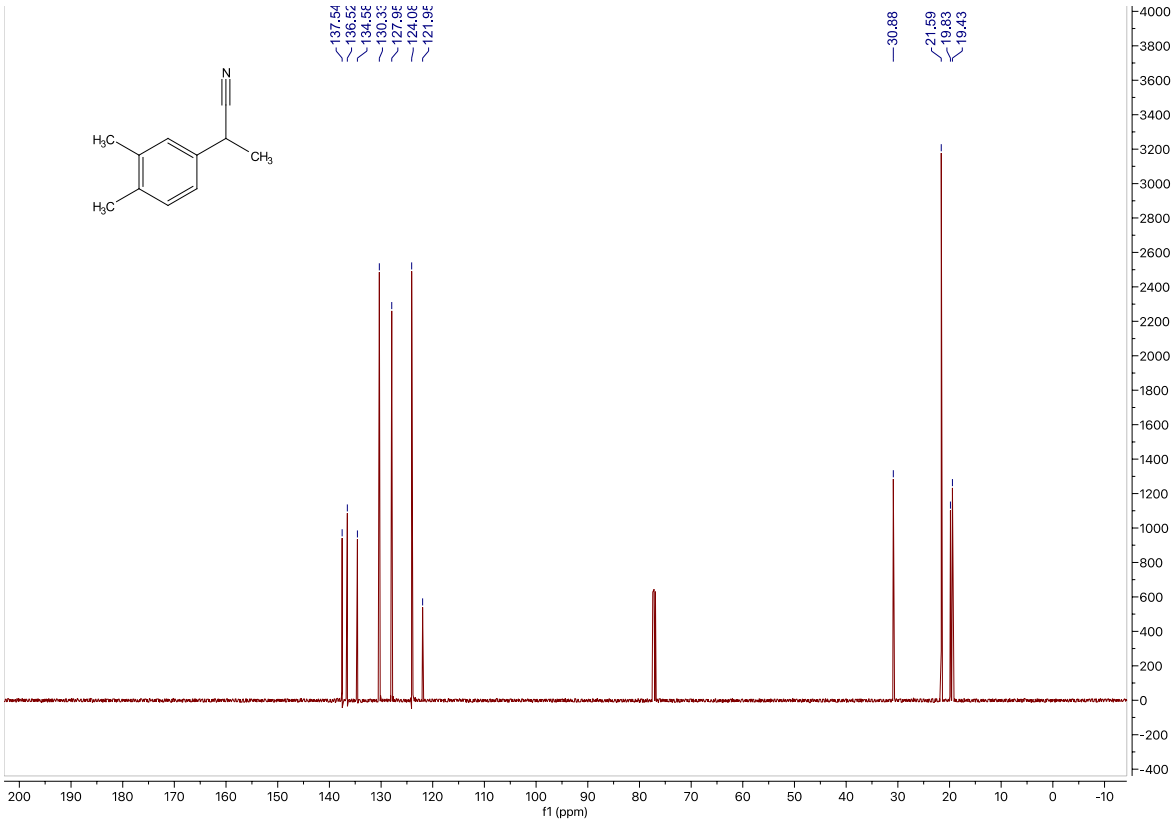
^{1}H and ^{13}C NMR of compound 2b



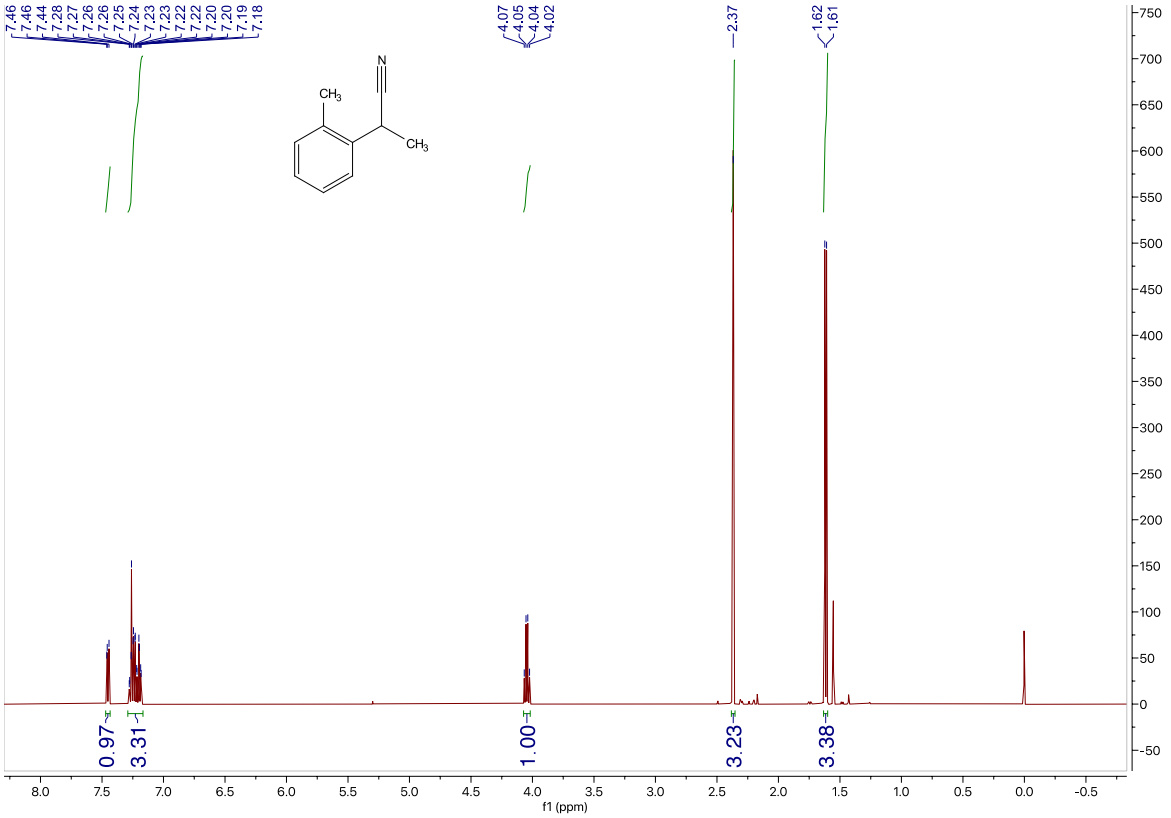


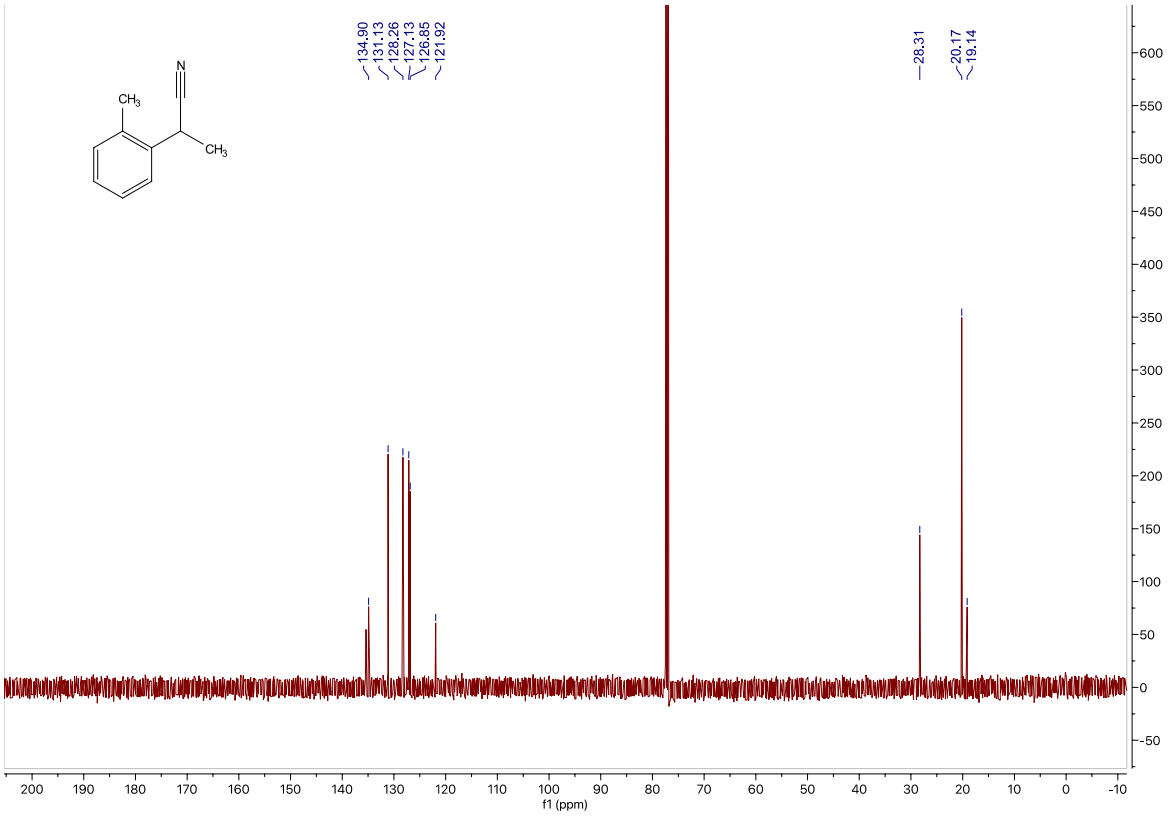
^{1}H and ^{13}C NMR of compound 2c



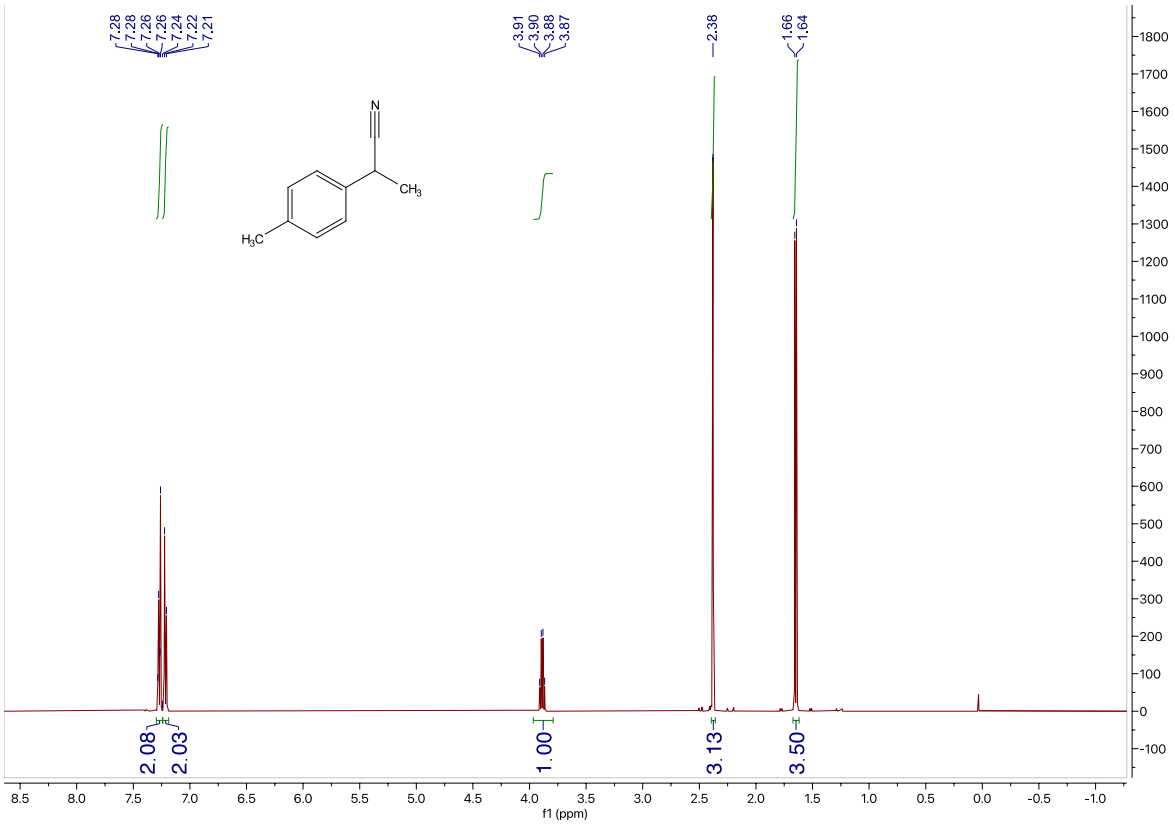


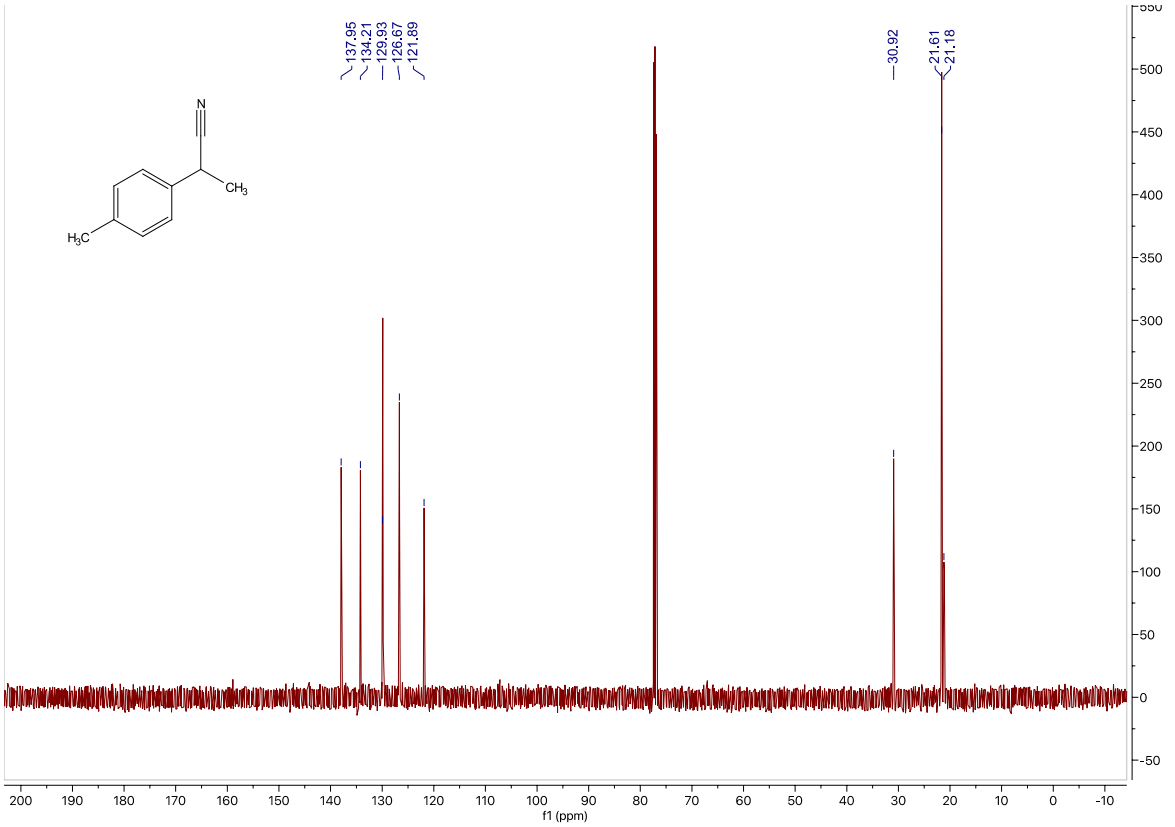
^{1}H and ^{13}C NMR of compound 2d



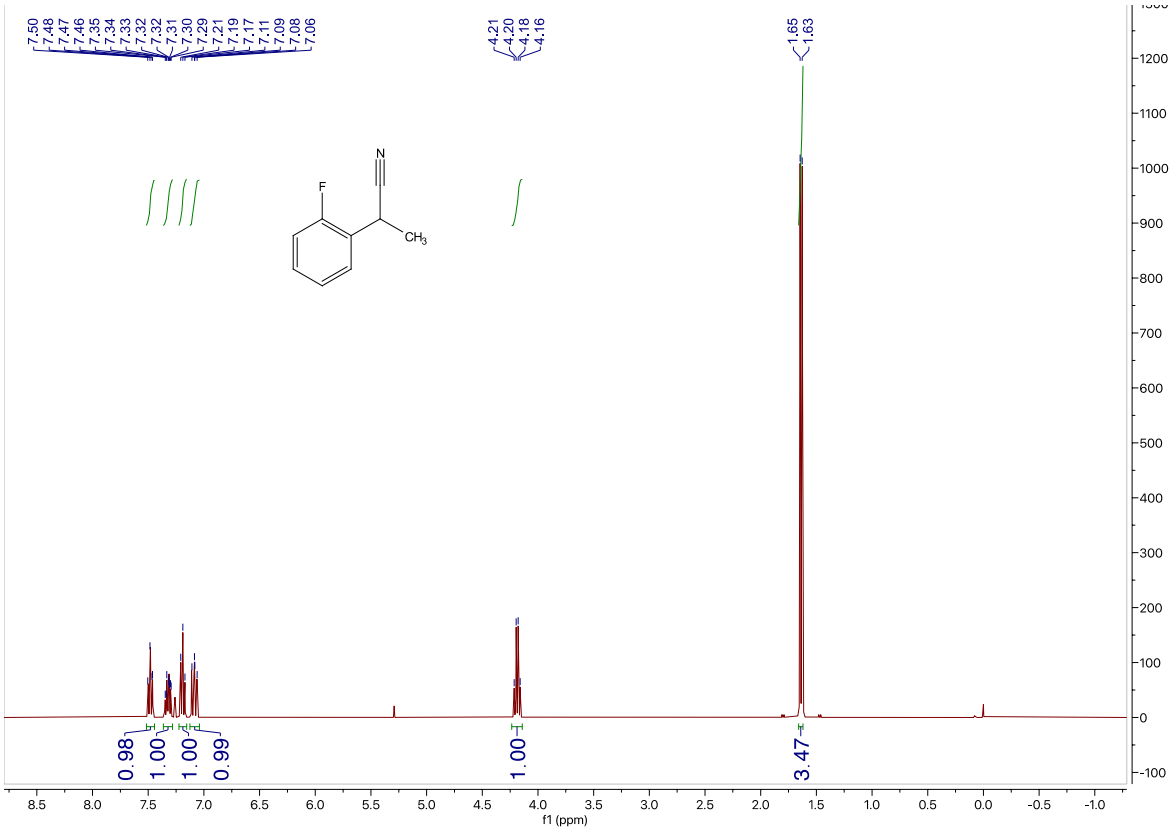


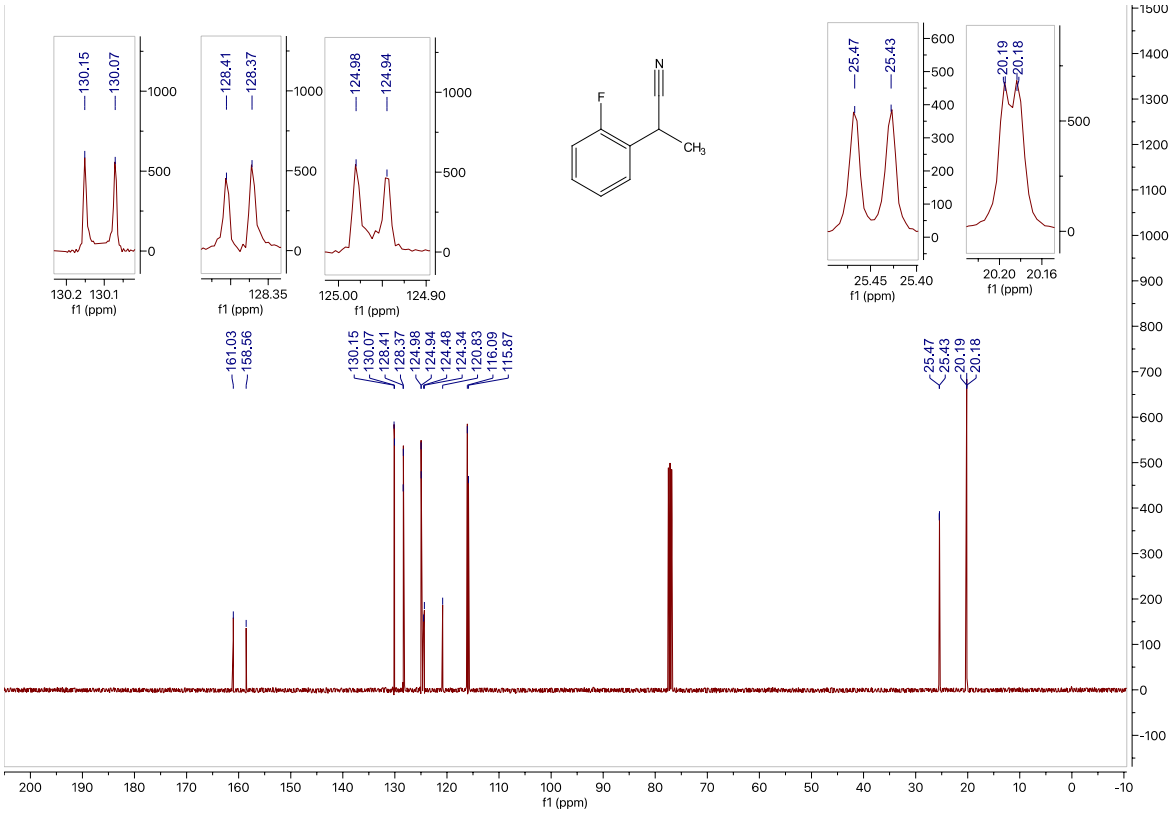
^{1}H and ^{13}C NMR of compound 2e

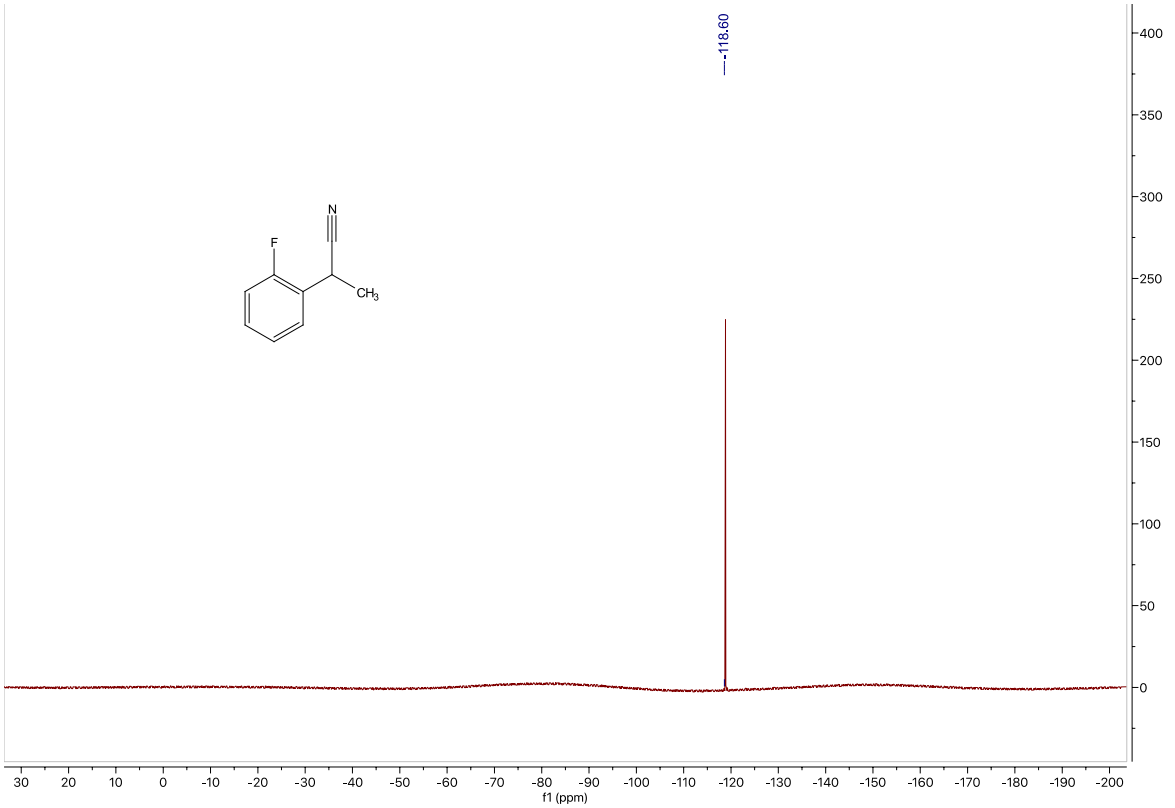




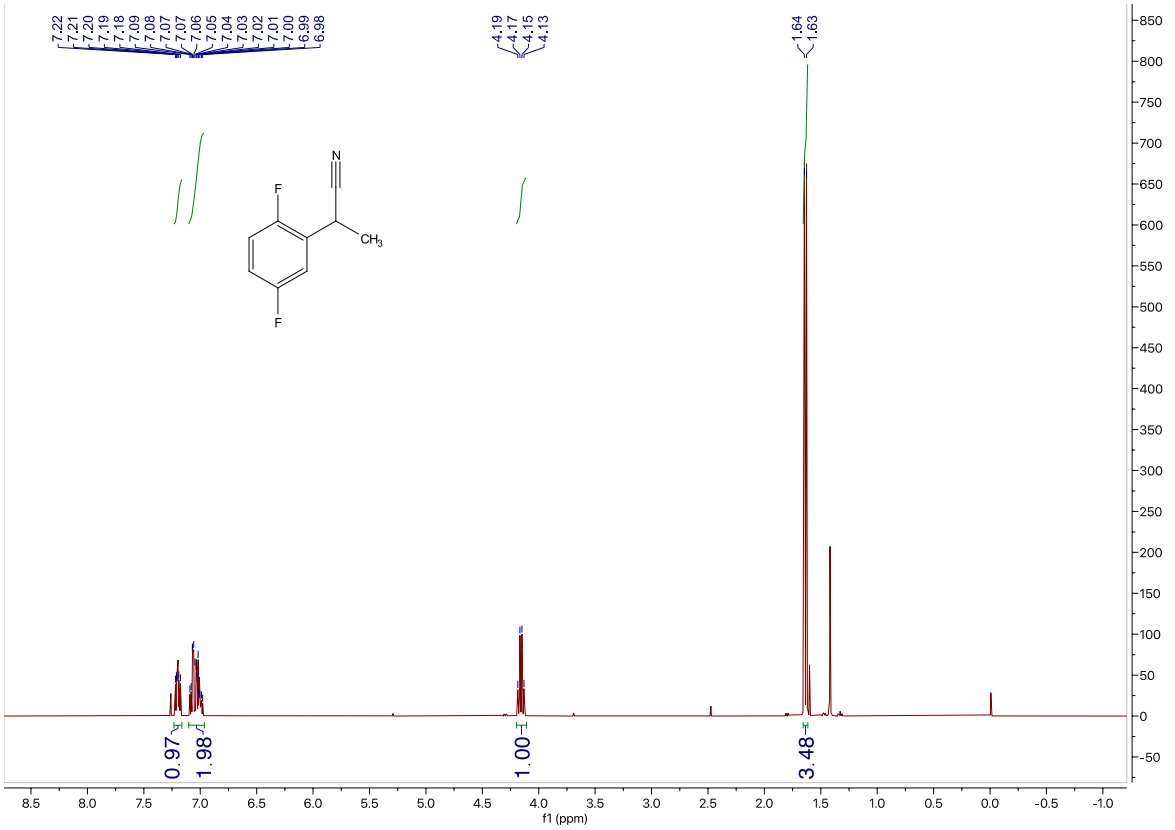
^{1}H, ^{13}C and ^{19}F NMR of compound 2f

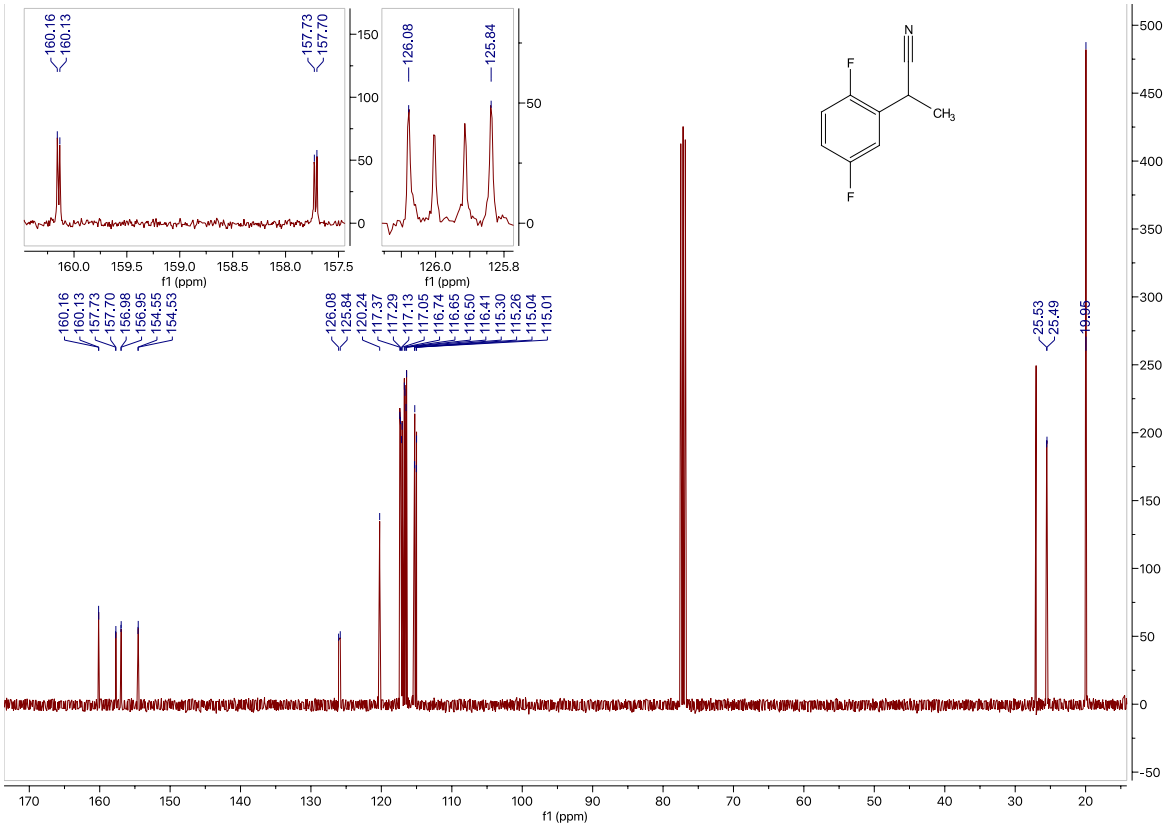


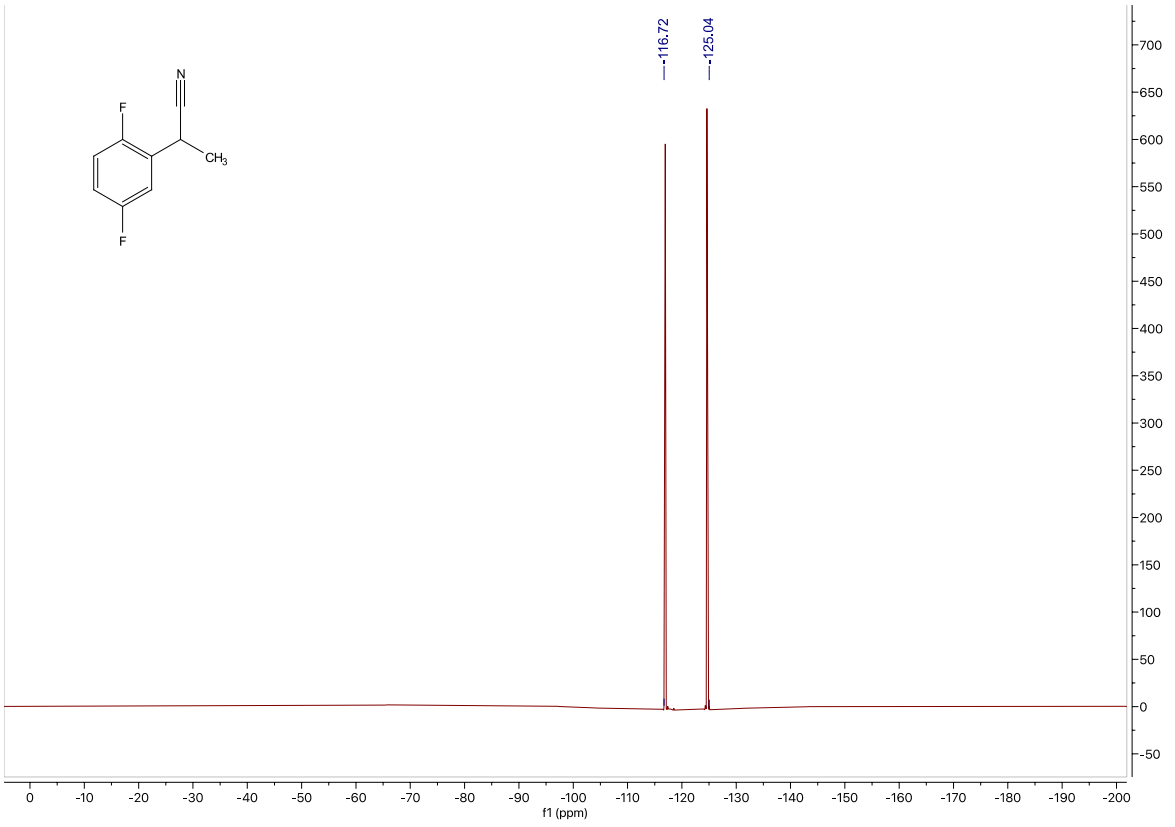




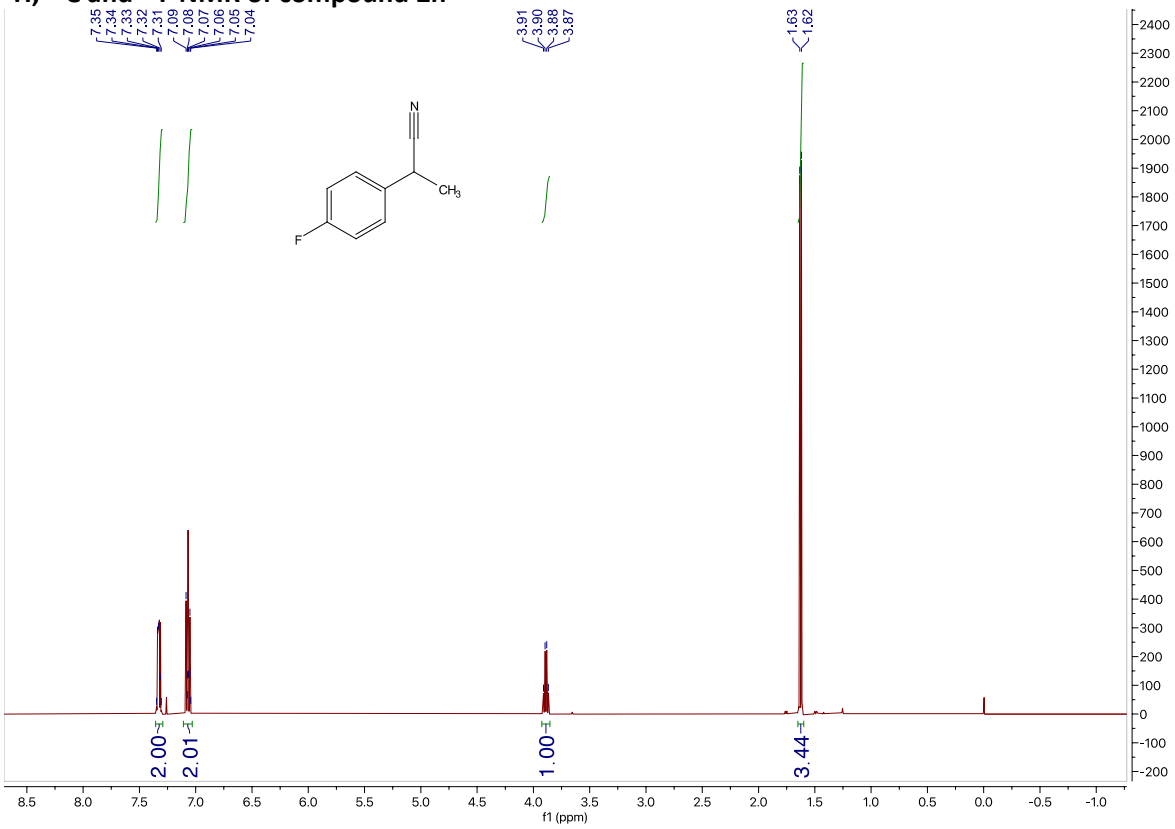
^{1}H, ^{13}C NMR and ^{19}F NMR of compound 2g

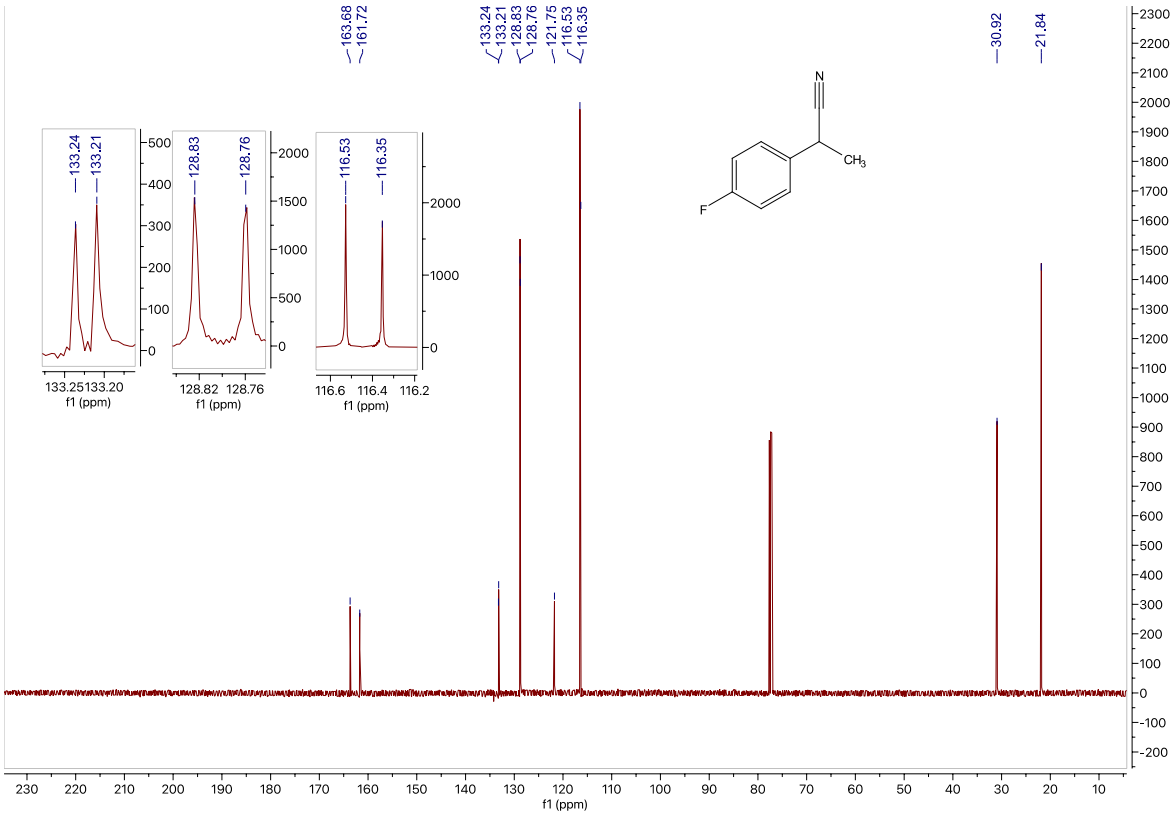


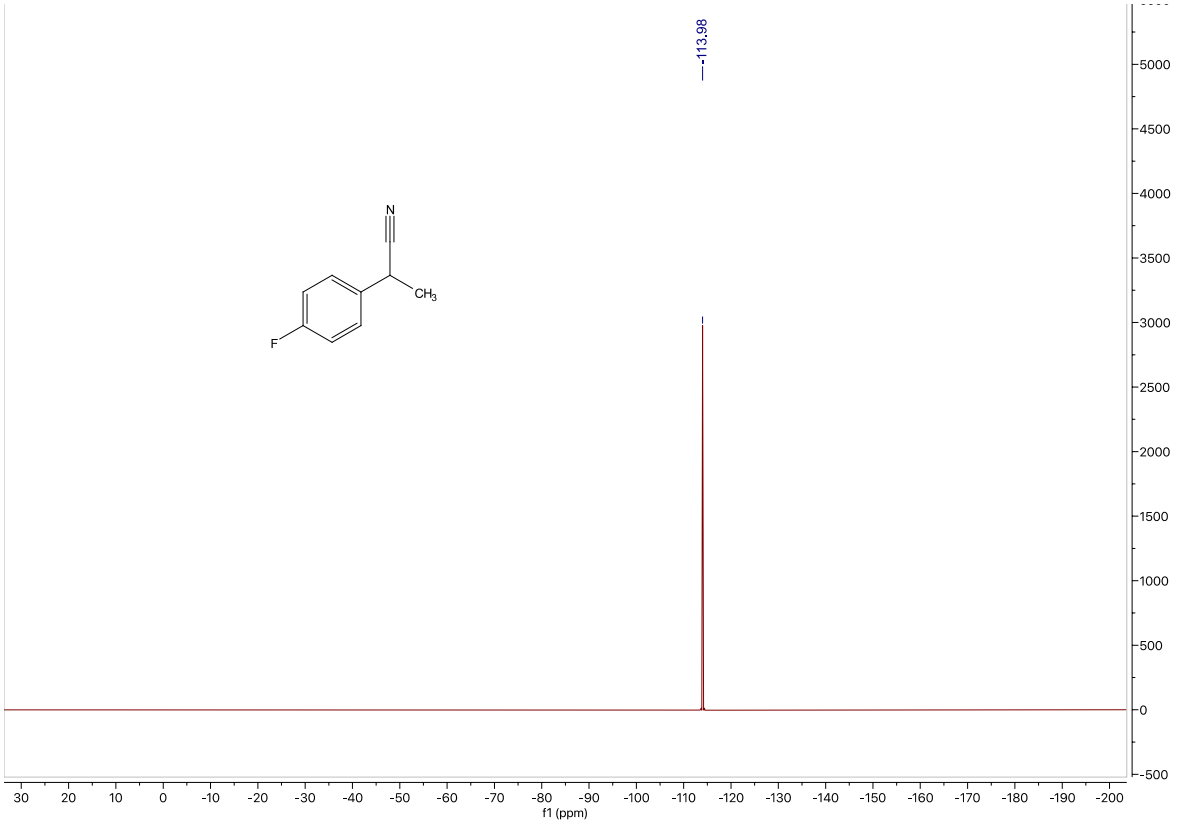

160.16
160.13
157.73
157.70
126.08
125.84
160.16
160.13
157.73
157.70
156.98
156.95
154.55
154.53
126.08
125.84
120.24
117.37
117.29
117.13
117.05
116.74
116.65
116.50
116.41
115.30
115.26
115.04
115.01
25.53
25.49
19.96
f1 (ppm)
f1 (ppm)
f1 (ppm)
N
F
CH3
F


-116.72
-125.04
f1 (ppm)
N
F
CH3
F

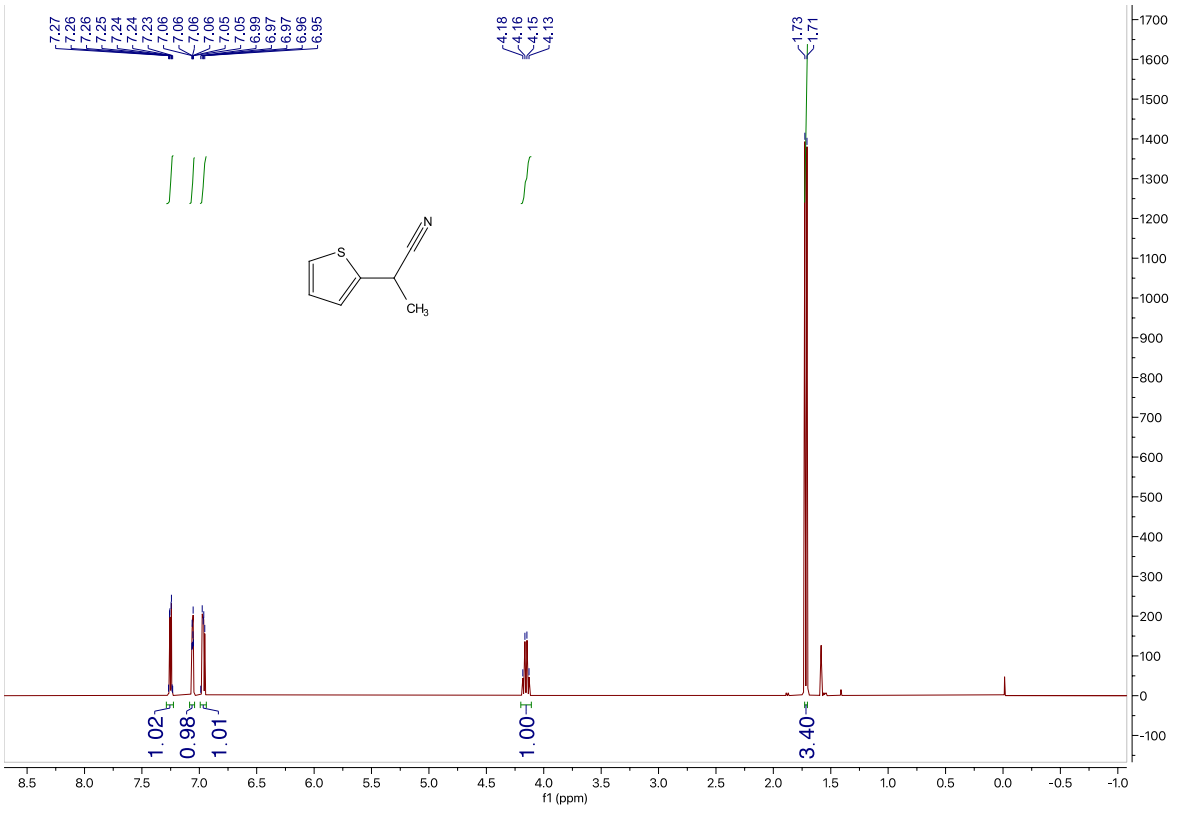
^{1}H, ^{13}C and ^{19}F NMR of compound 2h

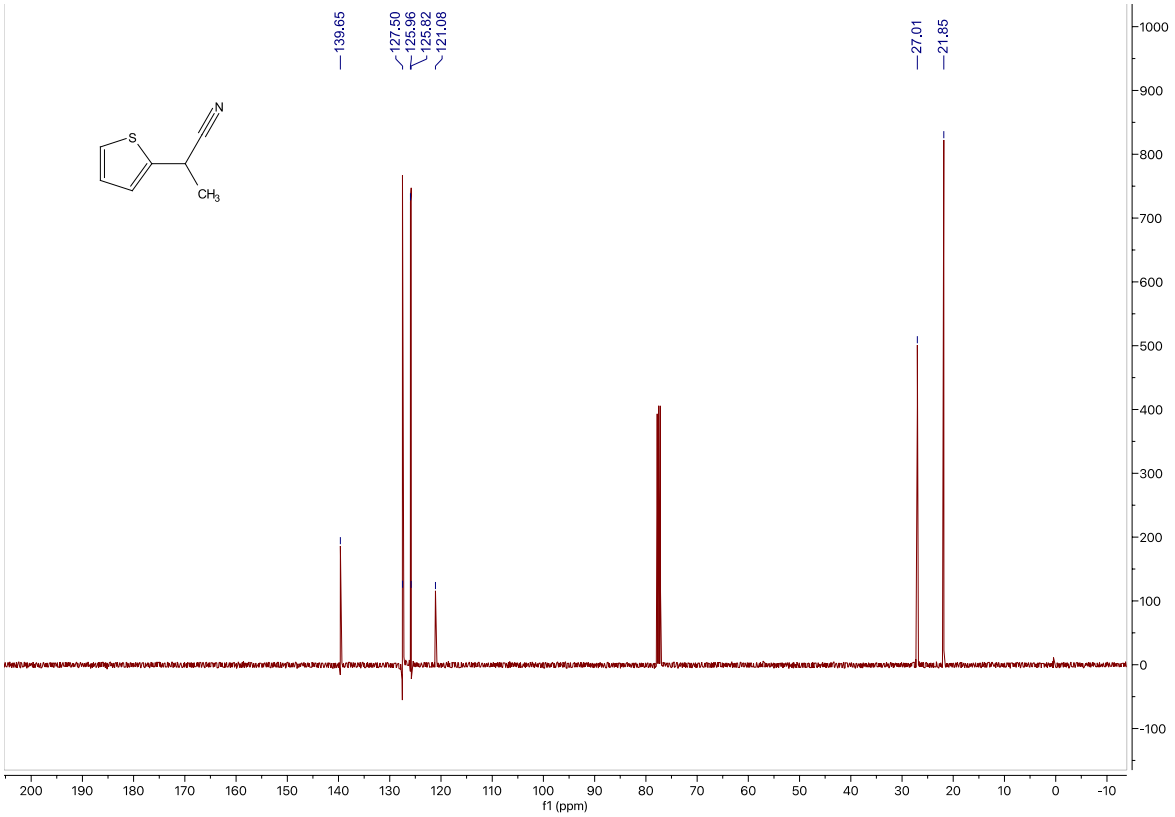




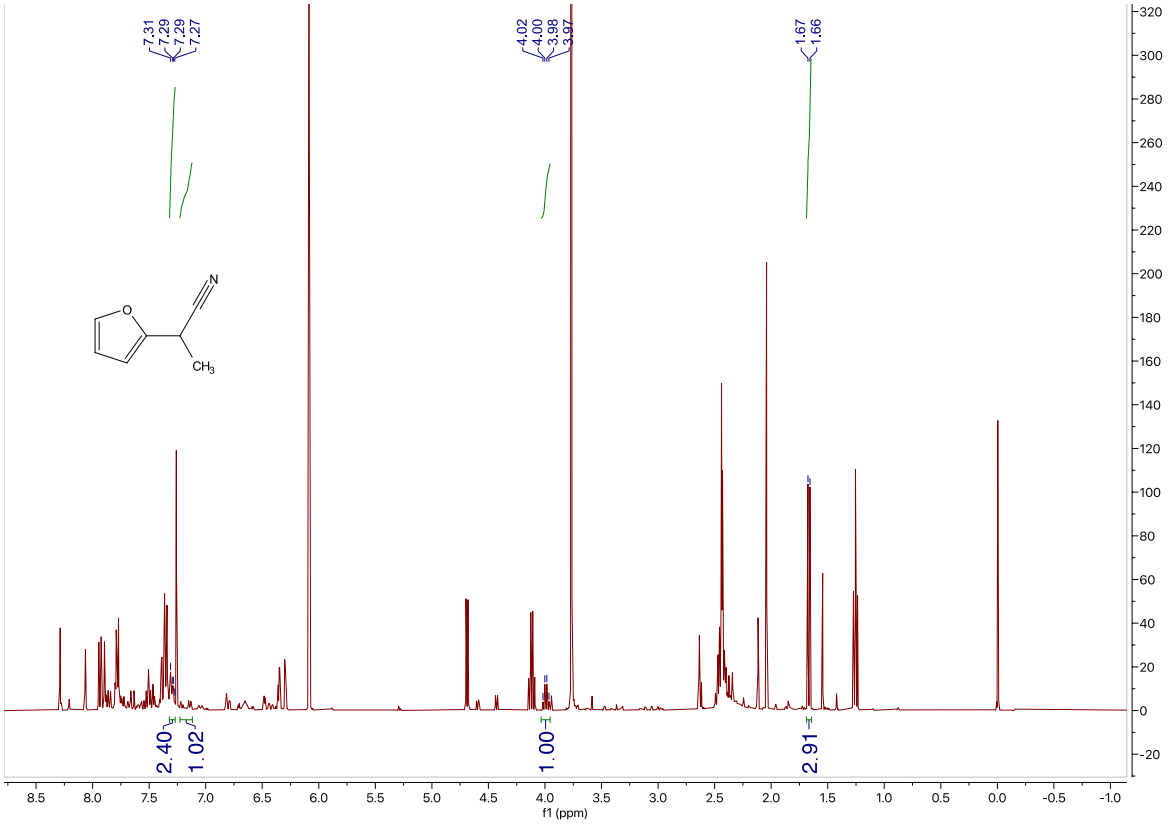


^{1}H and ^{13}C NMR of compound 2i

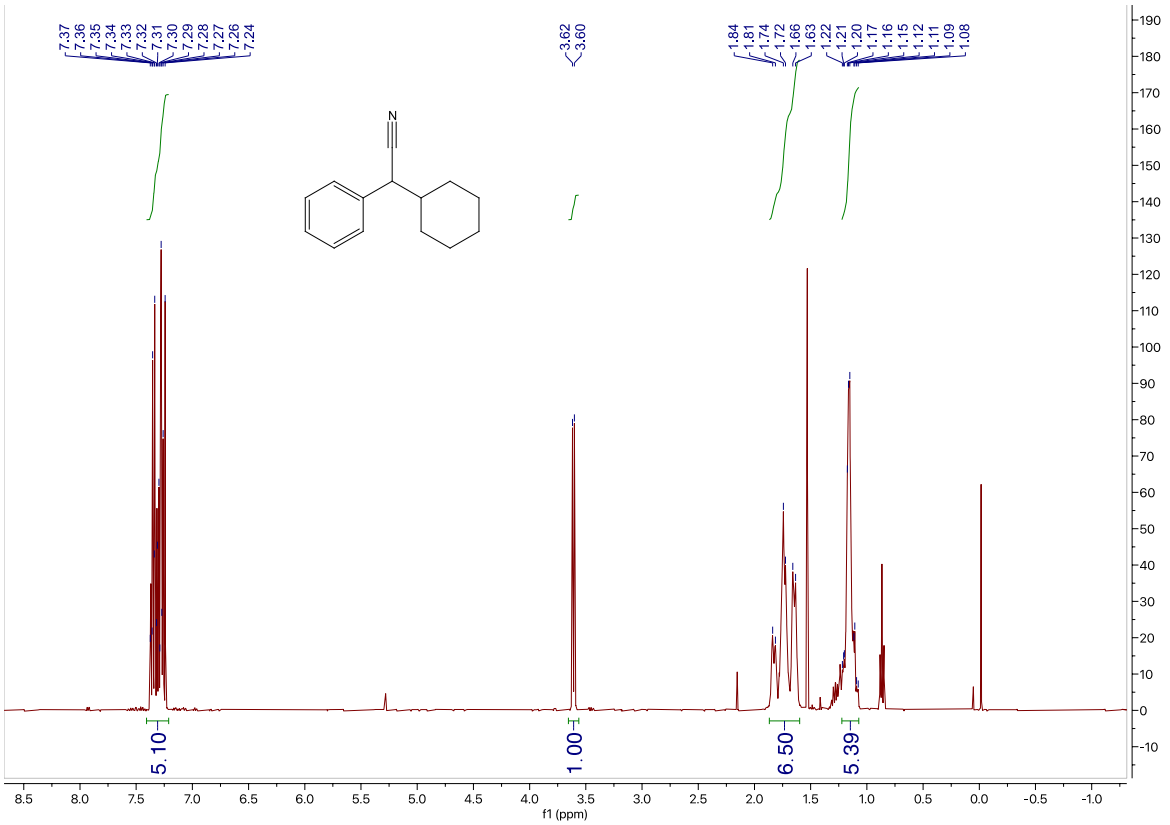


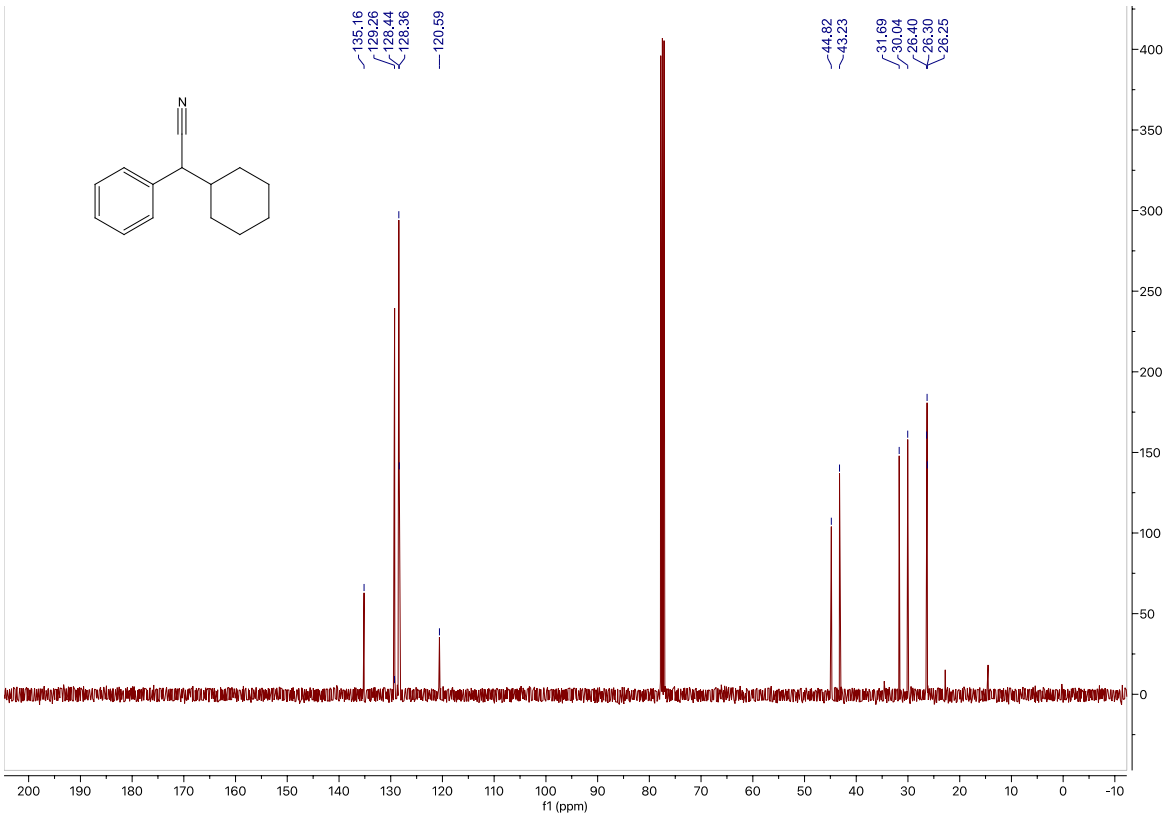


^{1}H and ^{13}C NMR of compound 2j – *Compound is volatile (qNMR spectrum shown below)*

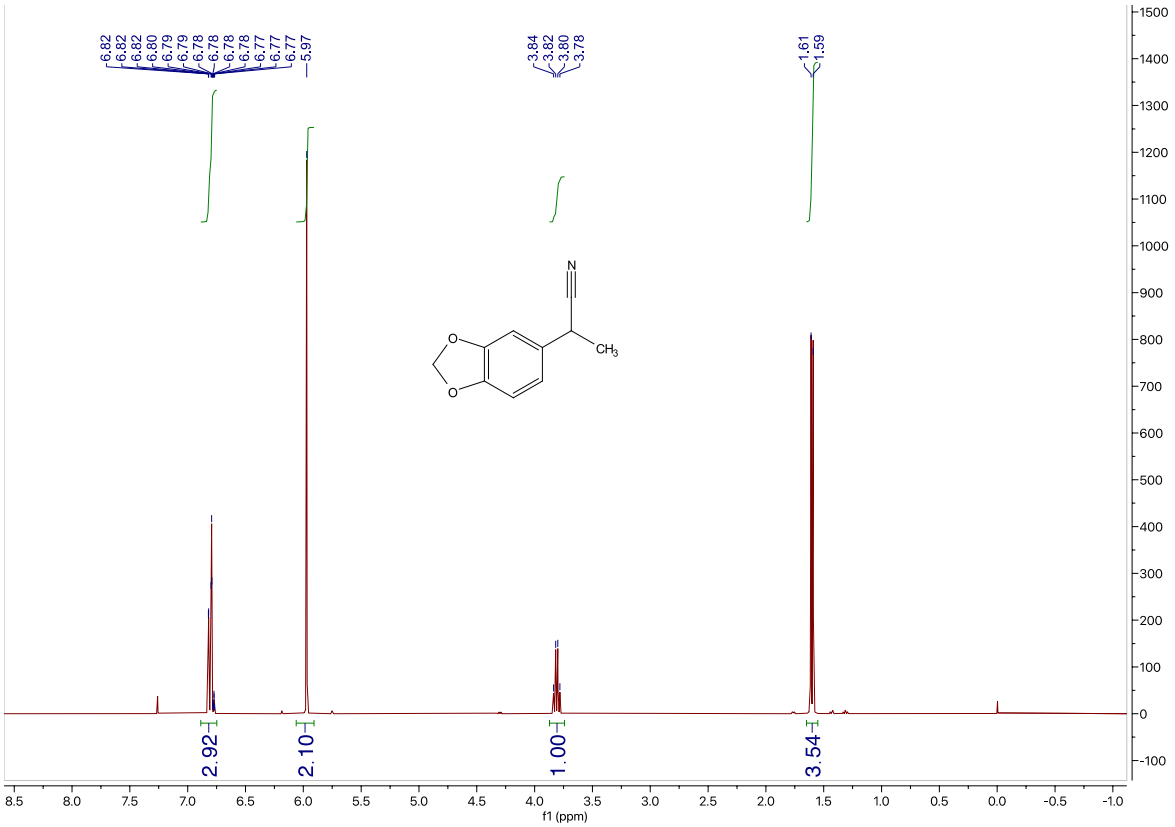


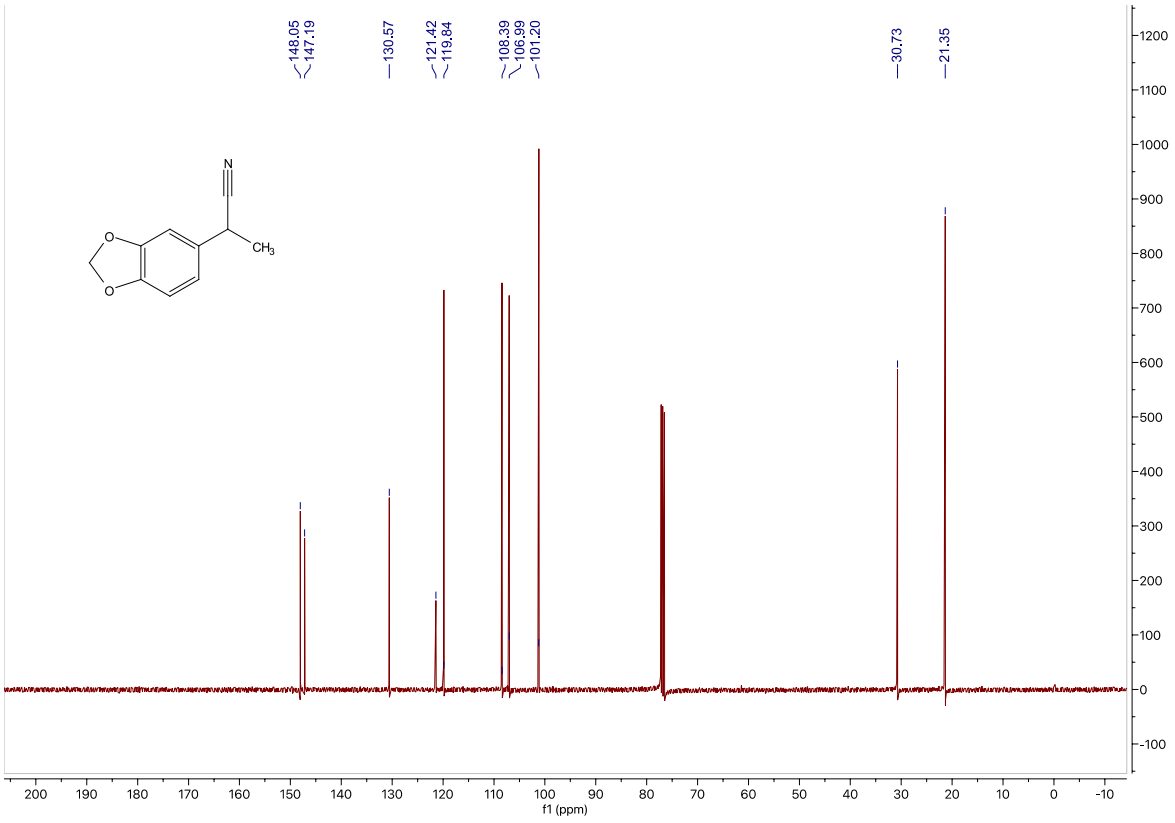
^{1}H and ^{13}C NMR of compound 2k



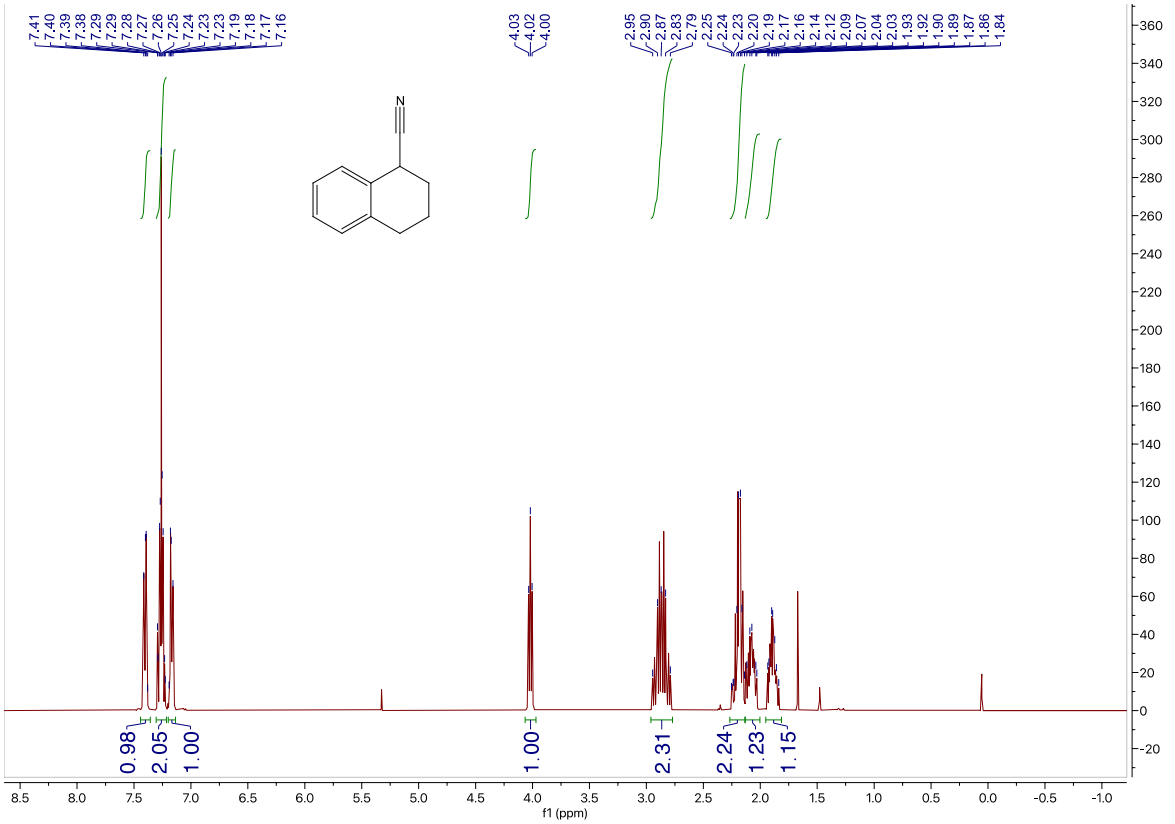


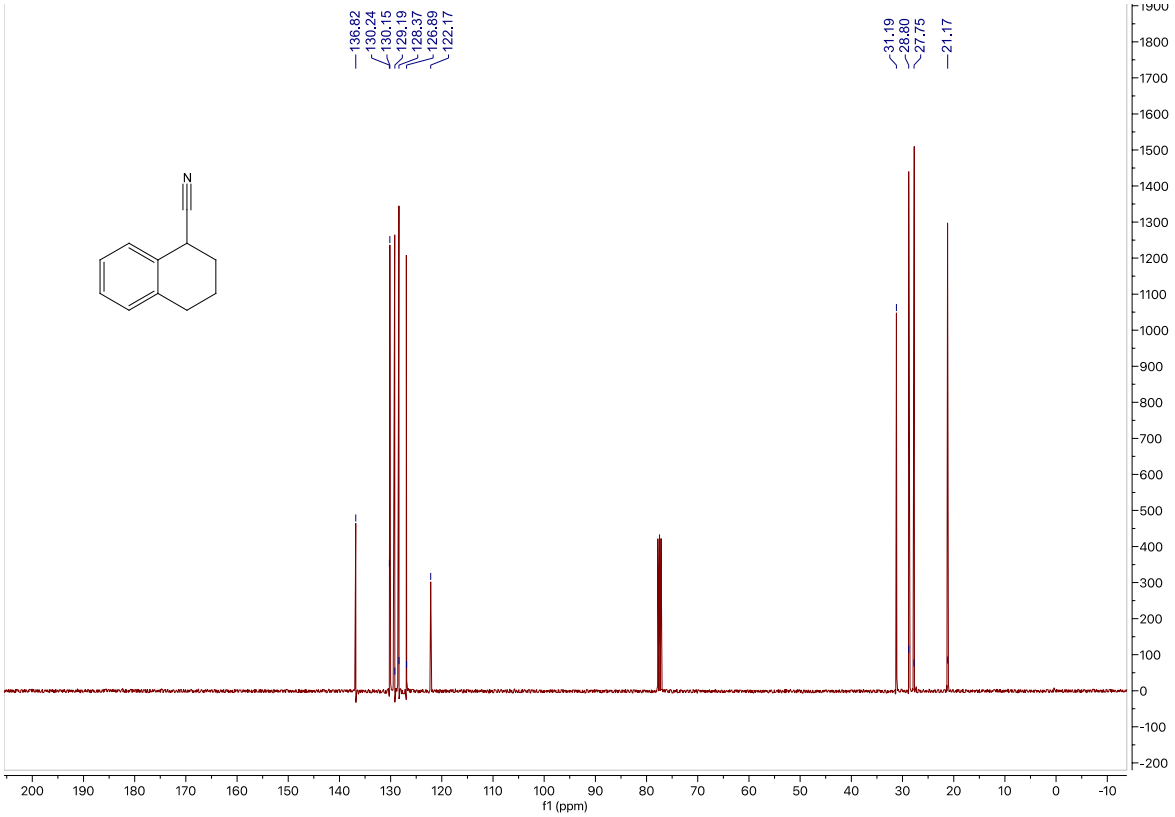
^{1}H and ^{13}C NMR of compound 2l



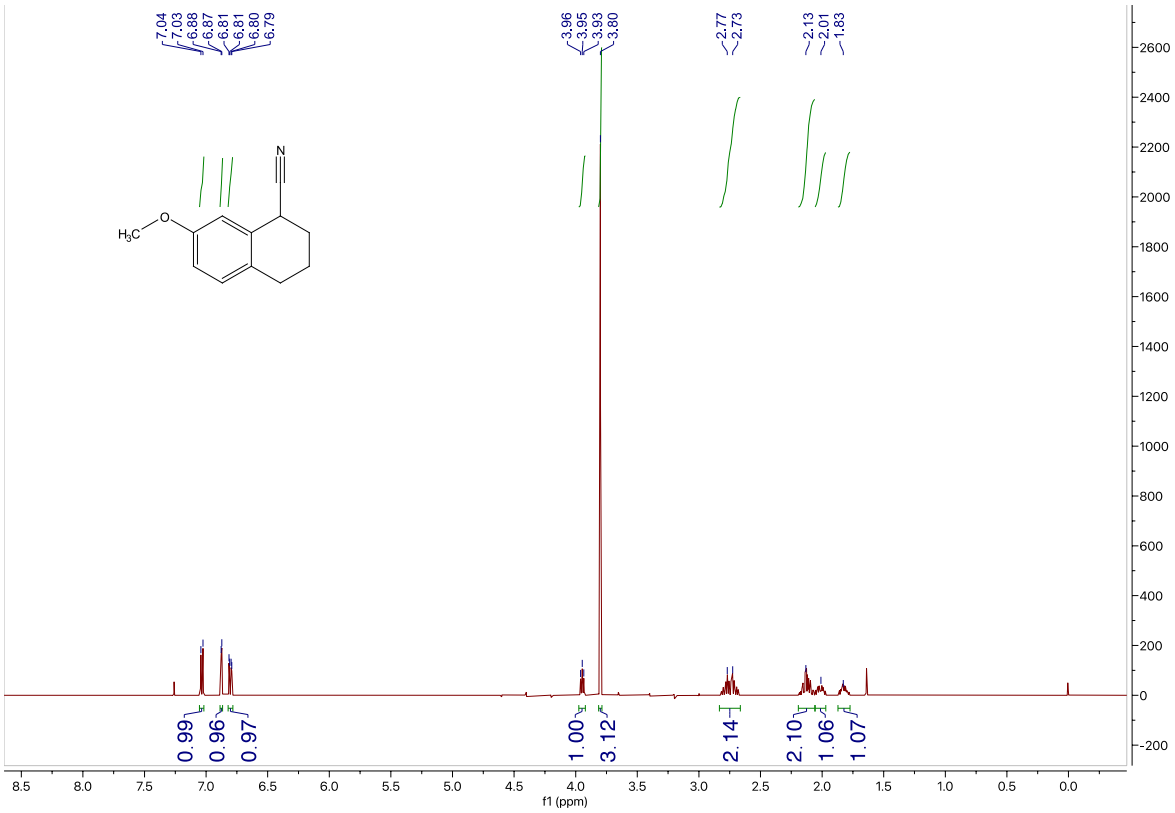


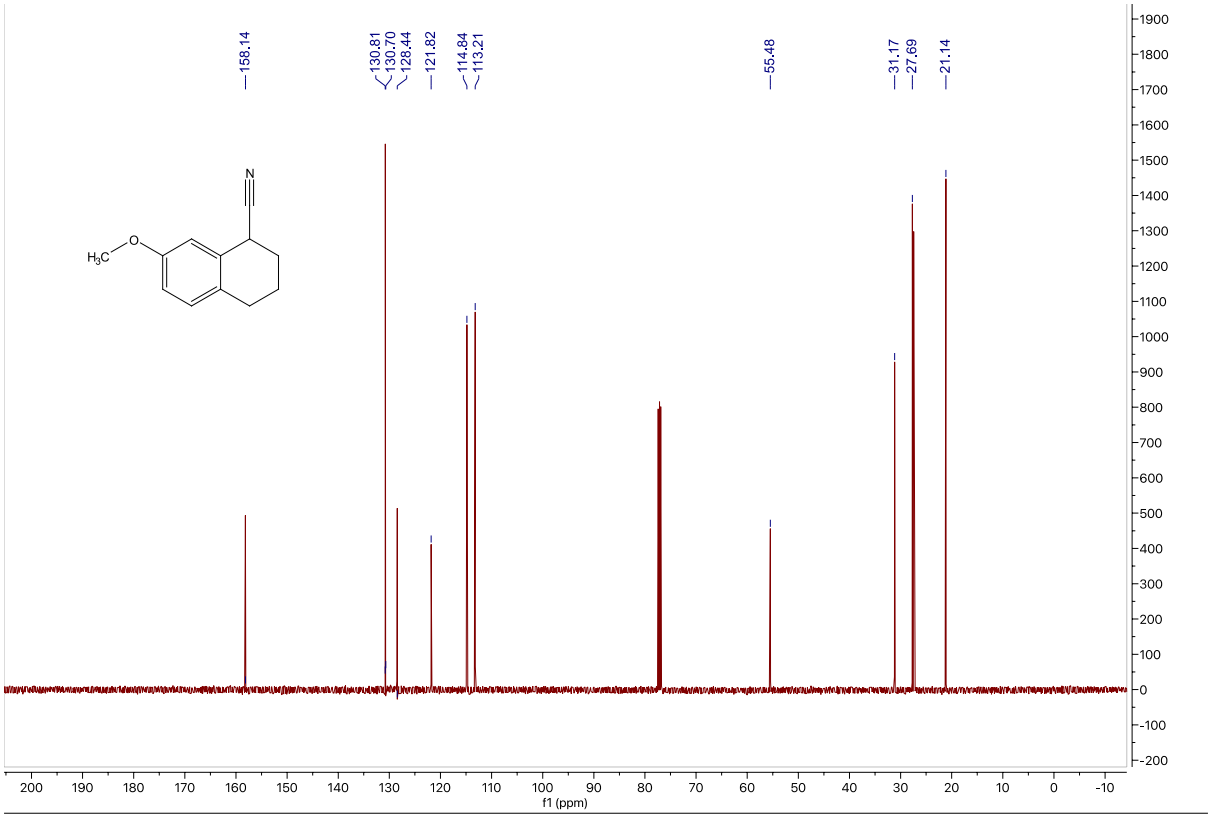
^{1}H and ^{13}C NMR of compound 2m



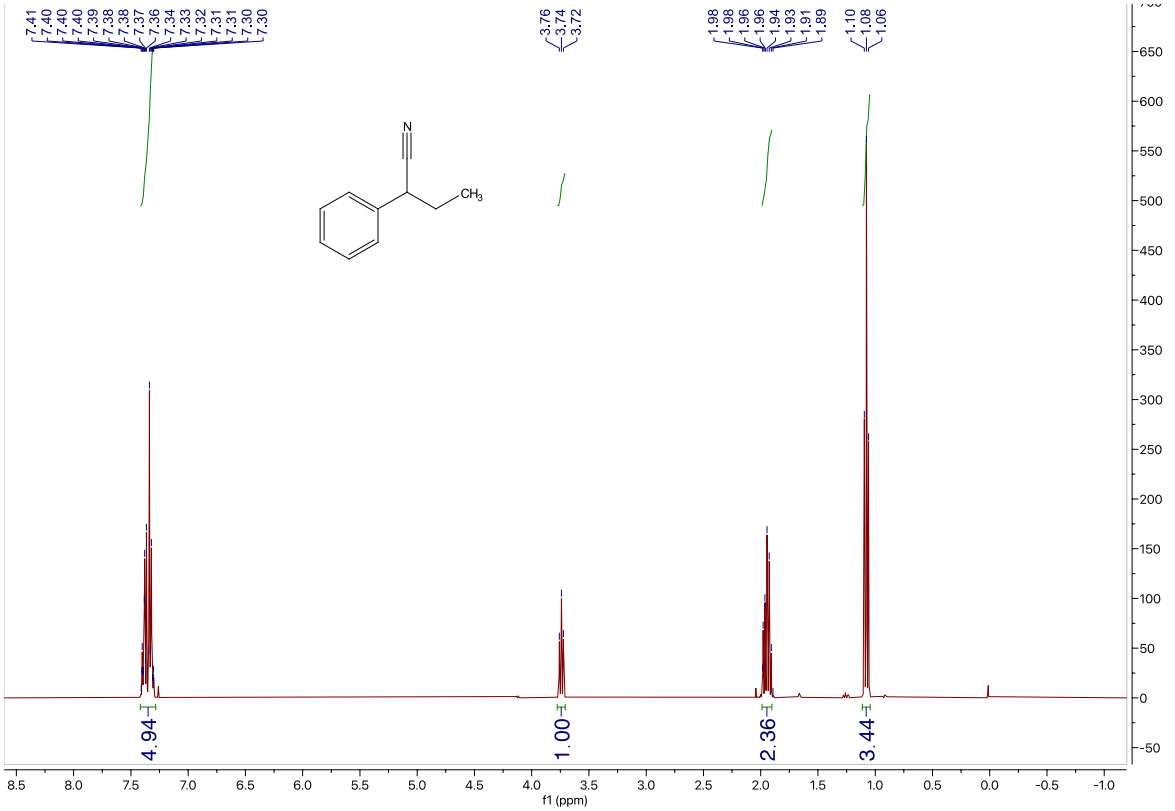


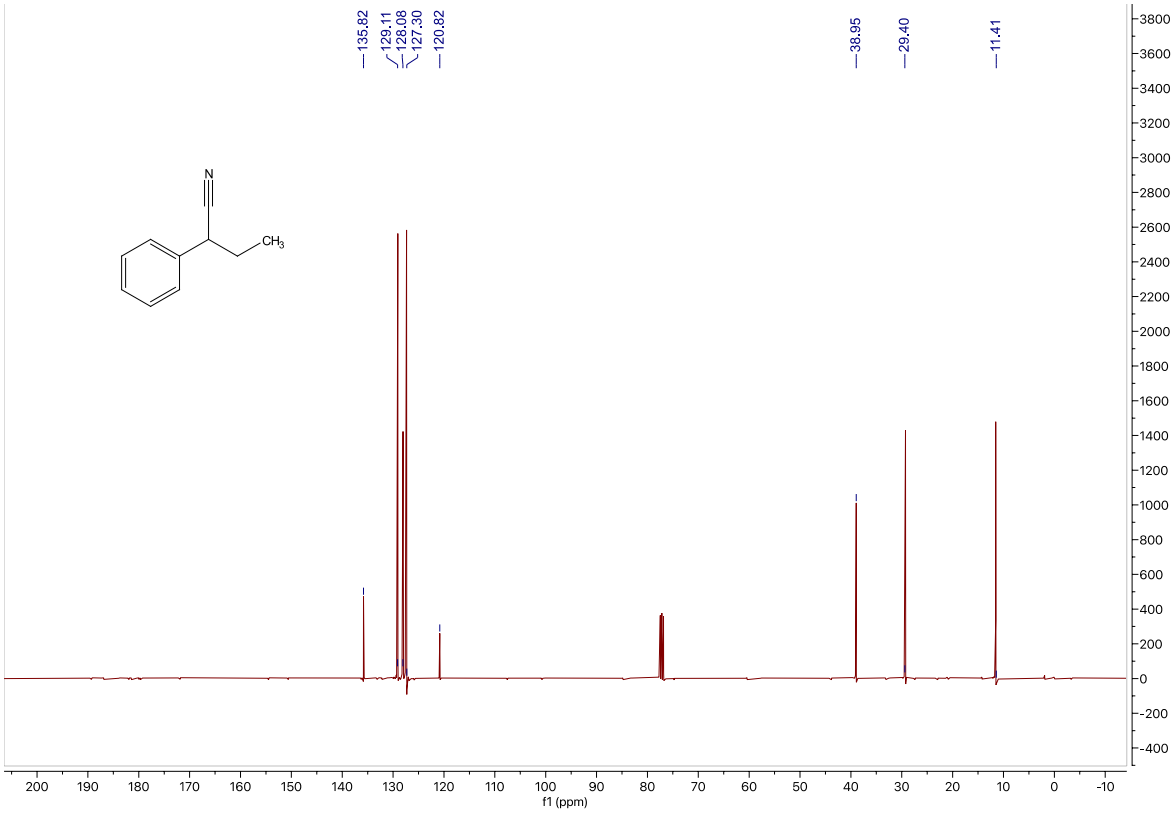
^{1}H and ^{13}C NMR of compound 2n





^{1}H and ^{13}C NMR of compound 2o





^{1}H and ^{13}C NMR of compound 9