Electronic Supplementary Material (ESI) for Chemical Communications

Copper/TEMPO Catalysed Synthesis of Nitriles from Aldehydes or Alcohols using Aqueous Ammonia and with Air as the Oxidant

Supporting Information

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1. General Considerations

Unless otherwise stated, all reagents were purchased from Sigma-Aldrich and used without further purification, apart from diethyl ether, which was distilled prior to use. 2,2,6,6-tetramethylpiperidinyloxy and 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy were purchased from Fluorochem. 4-sulfantooxy-2,2,6,6-tetramethylpiperidinyloxy (**4c**) was synthesised from 4-hydroxy-2,2,6,6-tetramethylpiperidinyloxy (**4b**) using a literature procedure.[1] O_2:N_2 (8:92) high pressure premixed gas cylinder (β standard) were purchased from BOC Industrial Gases UK. All reactions were carried out in oven-dried glassware. Flash column chromatography (FCC) was performed on Davisil silica gel 60 as the stationary phase and the solvents employed were of analytical grade. Thin layer chromatography (TLC) was carried out using Merck TLC silica gel 60 sheets, and visualised with ultraviolet light, potassium permanganate or iodine stain. ^{1}H NMR spectra were recorded on a Bruker AVX400 (400 MHz) spectrometer at ambient temperature. ^{13}C NMR spectra were recorded on a Bruker AVX400 (101 MHz) spectrometer at ambient temperature.

Gas chromatography analyses were carried out using Agilent 6890N series gas chromatograph.
A Phenomen 7HG-G007-11 ZB-WAX column (30.0 m x 320 µm x 0.25 µm nominal) was employed for all the separations using the following conditions: initial column temperature, 50°C; initial hold time, 1 min; next temperature, 200 °C; hold time, 0 min; rate of temperature ramp 1, 25 °C/min, final temperature 230 °C; hold time, 18 min;rate of temperature ramp 2, 3 °C/min; injection temperature, 250 °C; injection volume 1 µL; detection temperature, 250 °C; split mode. The effluent was combusted in a H_2/Airflame and detected using an FID (flame ionization detector).

2. Experimental details

2.1 General procedure for "open flask" catalytic reactions

To a 100ml two-neck round bottomed flask, a solution of copper (II) salt (0.3 mmol, 10 mol %), 2,2'-bipyridine (0.3 mmol, 46.8 mg, 10 mol %) and TEMPO derivative (0.3 mmol, 10 mol %) in 10 mL of acetonitrile was added. If TEMPO (**4a**) or HO-TEMPO (**4b**) were used, 0.05 M sodium hydroxide solution was added (6 mL, 10 mol %) to the catalyst solution. If HSO_3O-TEMPO (**4c**) is used, then 0.1 M sodium hydroxide solution was added (6 mL, 20 mol %) to the catalyst solution. The desired substrate (3 mmol) was then added to the flask, equipped with a magnetic stirrer bar and the flask was fitted with a water cooled condenser. The solution was stirred and the condenser was left open to the air to allow the air to act as the oxidant. The reaction was heated to the desired to temperature on a hot plate stirrer. A syringe pump delivered 35 w.t. % aqueous NH_3 at a specified flow rate; *via* a Suba-Seal® septum fitted to the flask's second neck. The reaction mixture was then left for a specified time.

2.2 Initial optimization experiments

Benzaldehyde and benzyl alcohol were used as substrates in initial optimisation studies to explore factors such as copper salt, base effects and rate of NH_3 addition. In these preliminary experiments, yields were determined by GC and calculated as P/(P+SM) and not accounting for response factors. Control experiments demonstrated that both the copper complex and TEMPO were necessary for the reaction to proceed.

2.3 Product Purification Procedures

Method A

When HSO_3O-TEMPO (**4c**) was employed as the radical it was possible to purify the product as follows:

Upon completion of the reaction, sodium chloride was added to the reaction mixture. The mixture was then transferred to a 250 mL separating funnel and the product was extracted with diethyl ether (3 x 20 mL). The organic layers were combined and then concentrated to a volume of approximately 20 mL by evaporating the solvent under vacuum at 0 °C. In order to separate any remaining aldehyde 1 M sodium metabisulfite solution (20 mL) was added to the organic layer and stirred for 2-3 hours. The reaction mixture was then transferred to a 250 mL separating funnel. $CuCl_2$ (50 mg) was then added into the separating funnel which ensured any remaining 2,2'-bipyridine became water soluble. The aqueous phase was then extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over magnesium sulphate. The solvent was then removed under vacuum at 0 °C to yield the product which was pure by ^{1}H and ^{13}C NMR spectroscopy .

Method B

The procedure was the similar to *Method A* except that and the product was purified by silica column chromatography at the end of the steps described in *Method A*. Additionally, in some cases the dichloromethane was used in the extractions. In the cases of **2j** and **2k** , diethyl ether was used as the solvent for the extractions and for **2h** and **2i** dichloromethane was used as extraction solvent. For **2j** and **2k** silica column chromatography used a solvent system of diethyl ether/petroleum ether (1:5). For **2h** silica column chromatography used a solvent system of ethyl acetate/petroleum ether (1:10). For **2i** the silica column chromatography used a solvent system of diethyl ether/petroleum ether (3:2).

2.4 Accurate yield determination *via* GC analysis

In some cases we found that it was impossible to remove all the residual traces of solvent without losing some of the product and lowering the yield. In these cases we also utilised GC and employed a standard. In order to obtain an accurate yield we carried out calibrations to obtain the relative response factor of the product compared to the standard. In all cases (other than **2i**) nonane was used as the standard and this was added to the combined organic layers there were used to extract the product from the aqueous phase. In the case of **2i**, we were also concerned about the water solubility of the product and in this case we used methyl benzoate as the standard. This was added to the reaction mixture at the end of the reaction.

2.5 Primary amide by-products

As discussed in the manuscript we found that in the case of **1j** and **1l** small quantities of primary amide were also produced. In both cases, the amide products by isolated *via* silica column chromatography (ethanol: dichloromethane 1:10) allowing us to confirm these products by ^{1}H and ^{13}C NMR, which had data consistent with literature values.[2,3] Due to the volatility of the nitrile products, the accurate yield of nitrile and amide was determined using GC with nonane as a standard.

2.6 Example of nitrile synthesis using a pressurised reactor under *limiting oxygen conditions (8%O_2)*

The reaction was carried out in Parr Instrument Company 50 mL stainless steel reactor, fitted with a safety pressure-relief valve. The reaction mixture was placed in a glass liner along with a magnetic stirrer. The reactor was then placed in an aluminium heating block, on a hotplate stirrer.

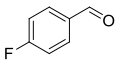
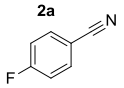
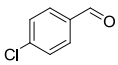
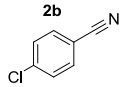
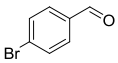
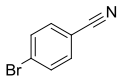
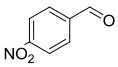
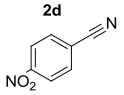
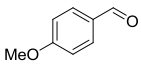
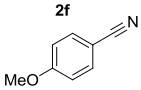
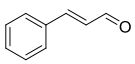
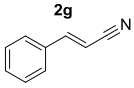
To the glass liner a solution of copper(II) chloride(4.0 mg, 0.03 mmol, 1 mol %), 2,2'-bipyridine (0.03 mmol, 4.7 mg, 1 mol %), and HSO_3O-TEMPO (**4c**) (7.6 mg, 0.03 mmol, 1 mol %) in 6 mL acetonitrile was added. To this catalyst solution, 0.1M sodium hydroxide solution was added (0.6 mL, 0.06 mmol, 2 mol %). Then 4-chlorobenzaldehyde (427 mg, 3 mmol) and 35 w.t. % aqueous ammonia solution (6 equivalents with regard to the substrate, 18 mmol, 1 mL) was added into the reactor vessel. The reactor vessel was pressurised to 40 bar with a O_2:N_2 (8:92) gas mixture. The reaction was then stirred in the heating block at 120 °C for 16 hours. Purification Method A afforded 4-chlorobenzonitrile **2c** (347 mg, 83%) as a colourless solid.

2.7 Modified method for aliphatic substrates

To a 100ml one-neck round bottomed flask, a solution of tetrakisacetonitrile copper(I) triflate (114.5 mg, 0.3 mmol, 10 mol %), 2,2'-bipyridine (0.3 mmol, 46.8 mg, 10 mol %) and TEMPO (46.8 mg, 0.3 mmol, 10 mol %) in 10 mL of acetonitrile was added. Octanal (**1m**) (385 mg, 3 mmol) or 1-octanol (**1n**) (391 mg, 3 mmol) and 35 w.t. % aqueous ammonia solution (0.42 mL, 7.5 mmol, 2.5 equivalents with regard to the substrate) was then added to the flask, equipped with a magnetic stirrer bar. The flask was fitted with a water cooled condenser which had a Suba-Seal® septum fitted to the top and then a balloon filled with house compressed air was connected. For octanal, the reaction was stirred at 25 °C for 24 hours and in the case of 1-octanol the reaction was maintained at 50 °C for 24 hours.

When the reaction was finished, as judged by GC, brine (20 mL) and diethyl ether (25 mL) were added to the mixture. The phases were separated and nonane (0.1 g, 0.78 mmol) was added to the organic phase as an internal standard for quantative GC yield determination. A sample of the organic phase was taken for GC analysis. Due to volatility of the product, the yield was determined by GC using nonane as the internal standard. The remainder of the organic phase was then concentrated on a rotary evaporator and analysed by ^{1}H and ^{13}C NMR, where the crude spectra was in agreement with the literature.[4]

2.8 Substrate scope table with further experimental details

Entry	Substrate	Radical	Aqueous NH_3 flow rate	Temperature	Time	Purification method	Product	Yield (%)
1	 **1a**	HO-TEMPO	1 mL/h	25 °C	16 h	B	 **2a**	95[a]
2	 **1b**	HO-TEMPO HO_3SO-TEMPO	1 mL/h 1.5 mL/h	25 °C 70 °C	24 h 8 h	B A	 **2b**	72[a] 72[a], 95[b]
3	 **1c**	HO_3SO-TEMPO HO_3SO-TEMPO	1.5 mL/h 1 mL/h	70 °C 40 °C	8 h 16 h	A A	 **2c**	88[a] 93[a]
4	 **1d**	HO_3SO-TEMPO	1.5 mL/h	70 °C	8 h	A	 **2d**	90[a]
5	 **1e**	HO_3SO-TEMPO	1.5 mL/h	70 °C	8 h	A	 **2e**	96[a]
6	 **1f**	HO_3SO-TEMPO	1 mL/h	40 °C	16 h	A	 **2f**	95[a]
7	 **1g**	HO_3SO-TEMPO	1.5 mL/h	70 °C	16 h	A	 **2g**	70[a]
8	 **1h**	HO-TEMPO HO_3SO-TEMPO	1 mL/h 1.5 mL/h	25 °C 70 °C	16 h 8 h	B B	 **2h**	71[a] 75[a]
9	 **1i**	HO_3SO-TEMPO	1 mL/h	40 °C	16 h	B	 **2i**	78[a], 90[b]
10	 **1j**	HO_3SO-TEMPO	1 mL/h	40 °C	16 h	B	 **2j**	76[a], 93[b]
11	 **1k**	HO_3SO-TEMPO	1 mL/h	40 °C	16 h	B	 **2k**	76[a], 95[b]
12	 **1l**	HO_3SO-TEMPO	1 mL/h	40 °C	6 h	A	 **2l**	63[a], 92[b]

a = isolated yield. b = GC yield.

Benzonitrile 2a

The title compound was prepared from benzaldehyde **1a** (318 mg, 3 mmol) using the general procedure and purified using method B to afford benzonitrile **2a** (293 mg, 95%) as a colourless oil. Data is consistent with literature values.[5]

4-Fluorobenzonitrile 2b

The title compound was prepared from 4-fluorobenzaldehyde **2b** (372 mg, 3 mmol) using the general procedure and purified using method A to afford 4-fluorobenzonitrile **2b** (262 mg, 72%) as a colourless solid. Data is consistent with literature values.[6]

4-Chlorobenzonitrile 2c

The title compound was prepared from 4-chlorobenzaldehyde **1c** (422 mg, 3 mmol) using the general procedure and purified using method A to afford 4-chlorobenzonitrile **2c** (384 mg, 93%) as a colourless solid. Data is consistent with literature values.[5]

4-Bromobenzonitrile 2d

The title compound was prepared from 4-bromobenzaldehyde **1d** (555 mg, 3 mmol) using the general procedure and purified using method A to afford 4-bromobenzonitrile **2d** (491 mg, 90% yield) as an off-white sold. Data is consistent with literature values.[7]

4-Nitrobenzonitrile 2e

The title compound was prepared from 4-nitrobenzaldehyde **1e** (453 mg, 3 mmol) using the general procedure and purified using method A to afford 4-nitrobenzonitrile **2e** (427 mg, 96%) as a yellow solid. Data is consistent with the literature values.[5]

2-nitrobenzonitrile 2f

The title compound was prepared from 2-nitrobenzaldehyde **1f** (453 mg, 3 mmol) using the general procedure and purified using method A to afford 2-nitrobenzonitrile **2f** (423 mg, 95%) as a yellow solid. Data is consistent with the literature values.[8]

4-methoxybenzonitrile 2g

The title compound was prepared from 4-methoxybenzaldehyde **1g** (408 mg, 3 mmol) using the general procedure and purified using method A to afford 4-methoxybenzonitrile **2g** (280 mg, 70%) as a colourless solid. Data is consistent with literature values. [5]

Cinnamyl nitrile 2h

The title compound was prepared from cinnamaldehyde **1h** (396 mg, 3 mmol) using the general procedure and purified using method B to afford cinnamyl nitrile **2h** (291 mg, 75%) as a colourless oil. Data is consistent with literature values. [5]

3-pyridinecarbonitrile 2i

The title compound was prepared from 3-pyridinecarboxaldehyde **1i** (321 mg, 3 mmol) using the general procedure and purified using method B to afford 3-pyridinecarbonitrile **2i** (244 mg, 78%) as a colourless solid. Data is consistent with literature values.[9]

2-thiophenecarbonitrile 2j

The title compound was prepared from 2-thiophenecarboxaldehyde **1j** (336 mg, 3 mmol) using the general procedure and purified using method B to afford 2-thiophenecarbonitrile **2j** (237 mg, 76%) as a colourless oil. Data is consistent with literature values.[10]

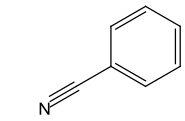
3-thiophenecarbonitrile 2k

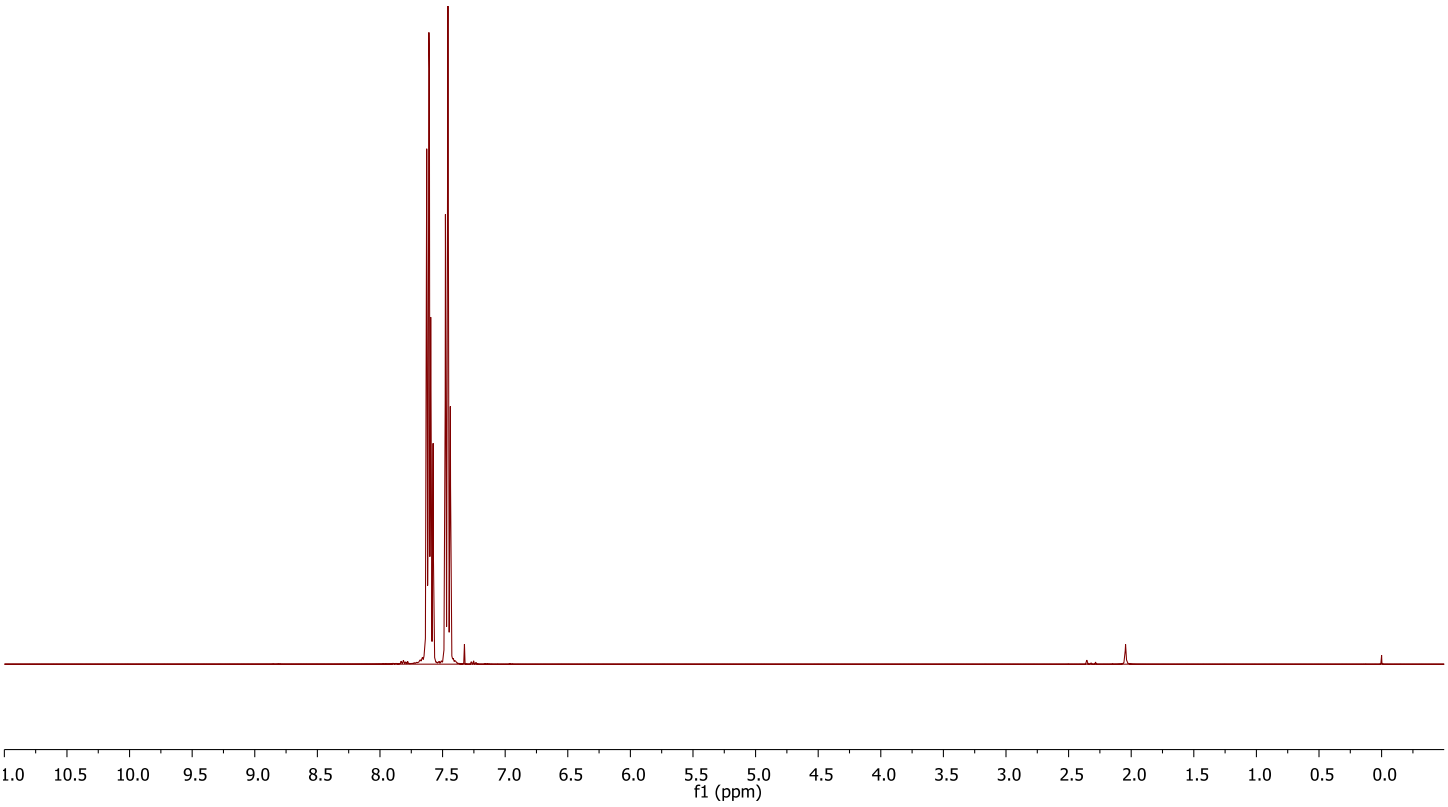
The title compound was prepared from 3-thiophenecarboxaldehyde **1k** (336 mg, 3 mmol) using the general procedure and purified using method B to afford 3-thiophenecarbonitrile **2k** (237 mg, 76%) as a colourless oil. Data is consistent with literature values. [10]

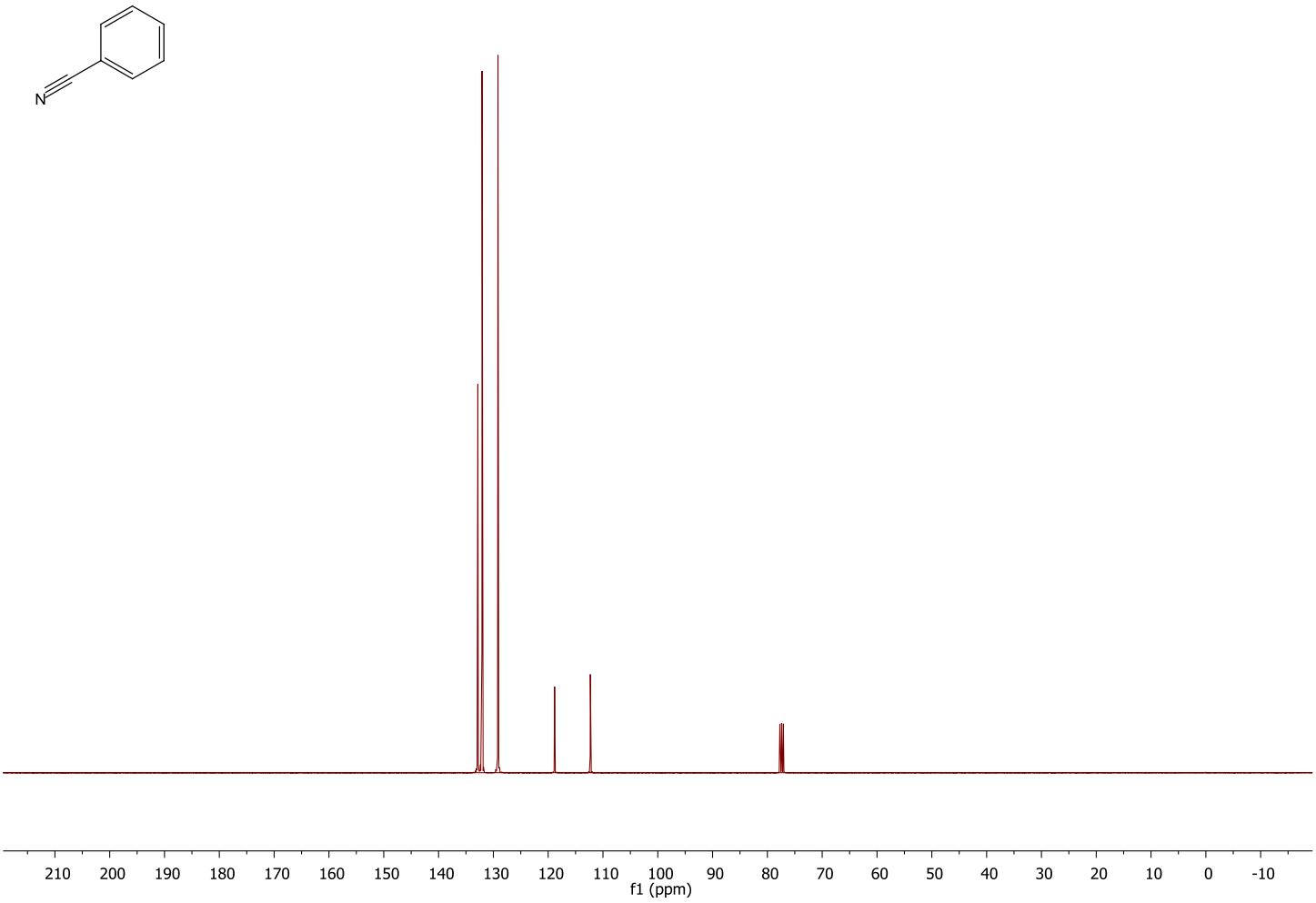
2-furancarbonitrile 2l

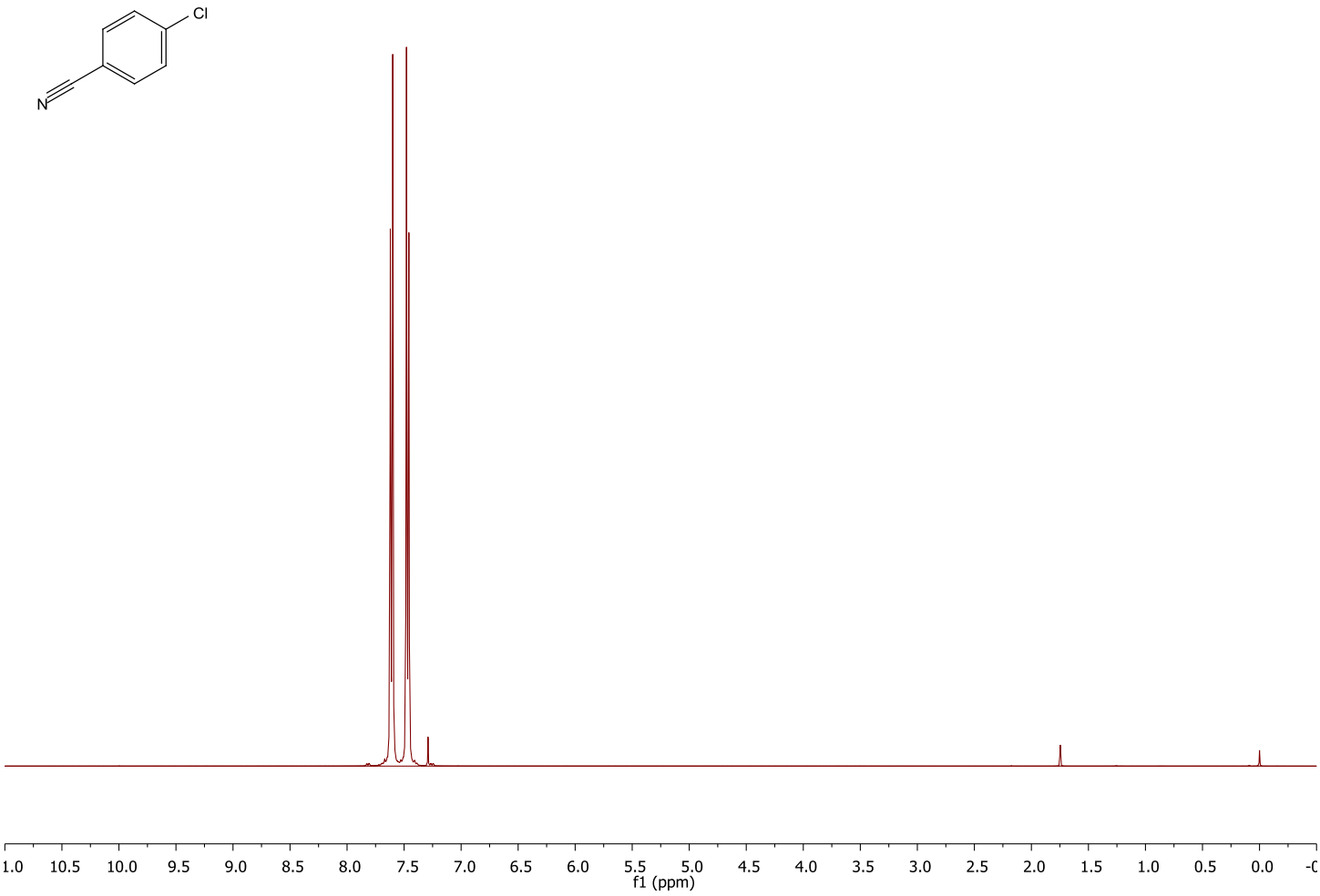
The title compound was prepared from furfural **1l** (288 mg, 3 mmol) using the general procedure and purified using method A to afford 2-furancarbonitrile **2l** (176 mg, 63%) as a yellow oil. Data is consistent with literature values.[11]

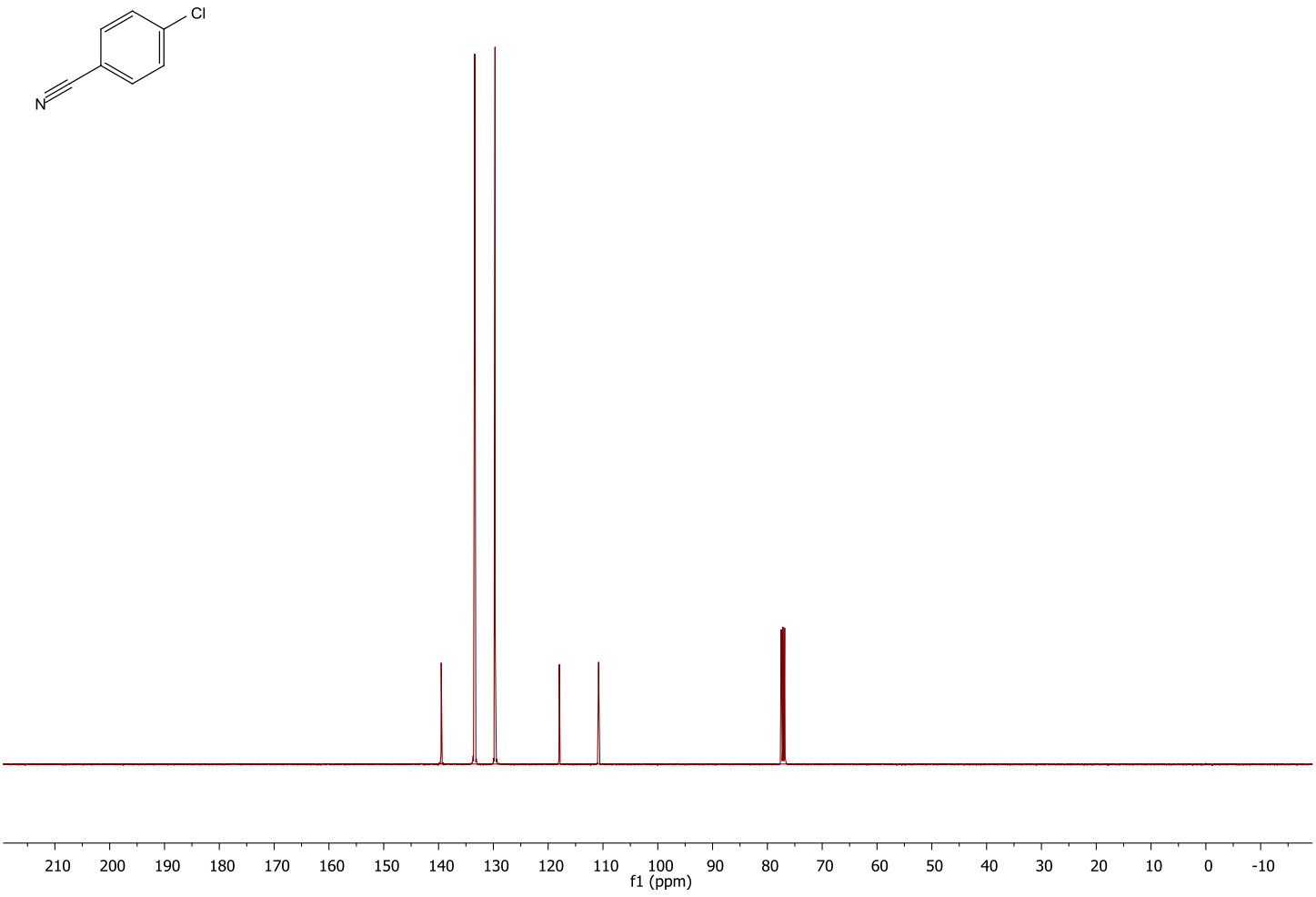
NMR Spectra

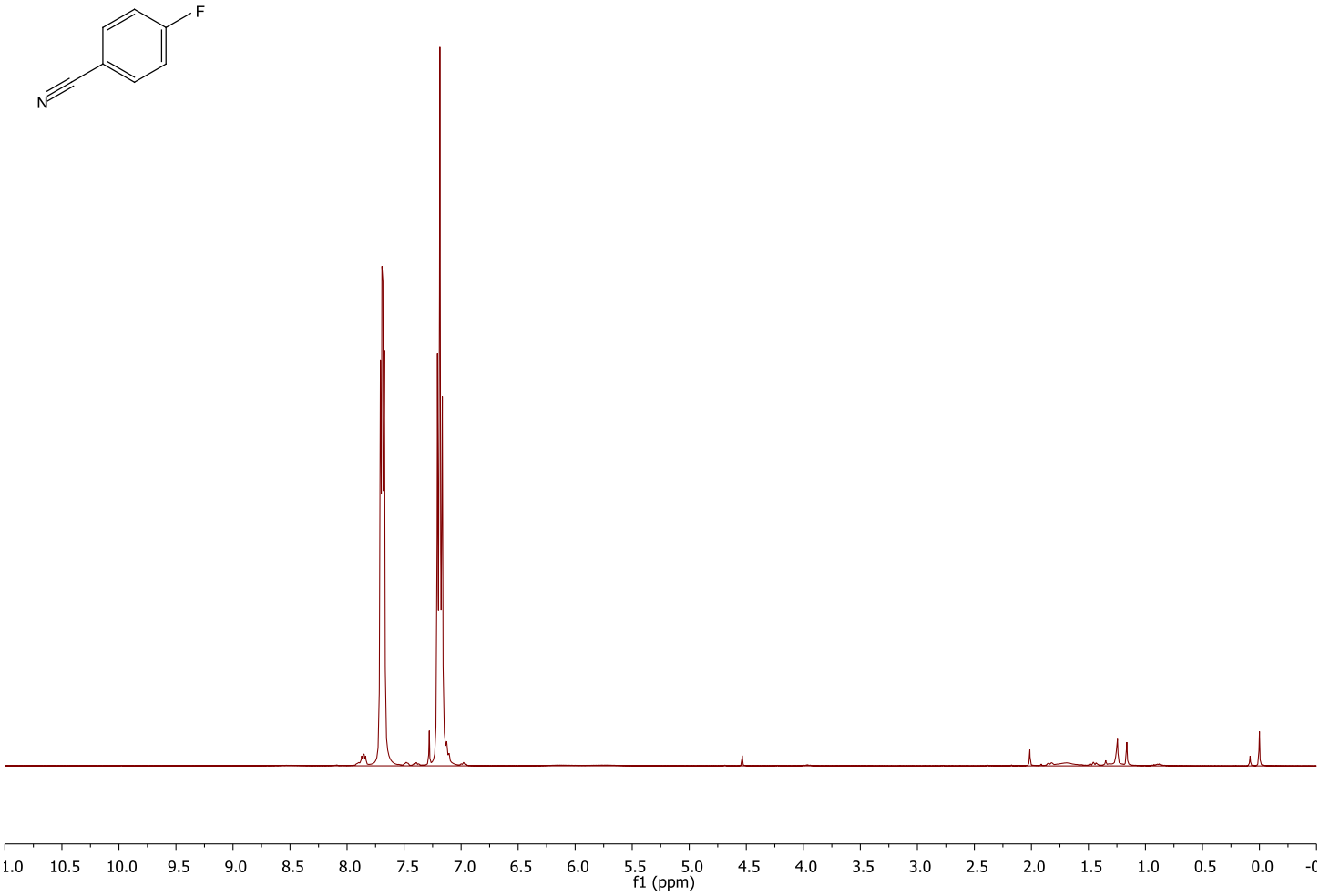


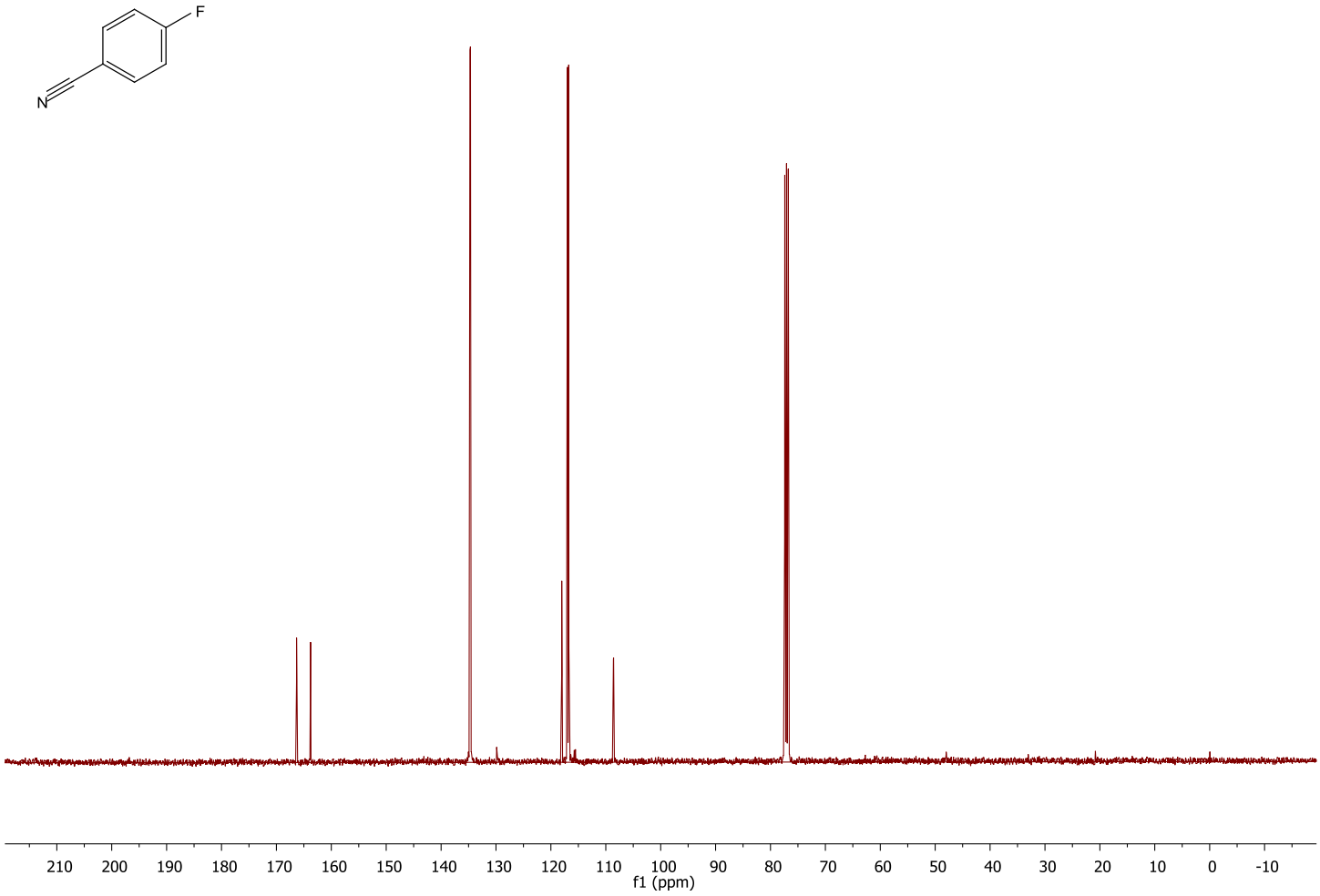


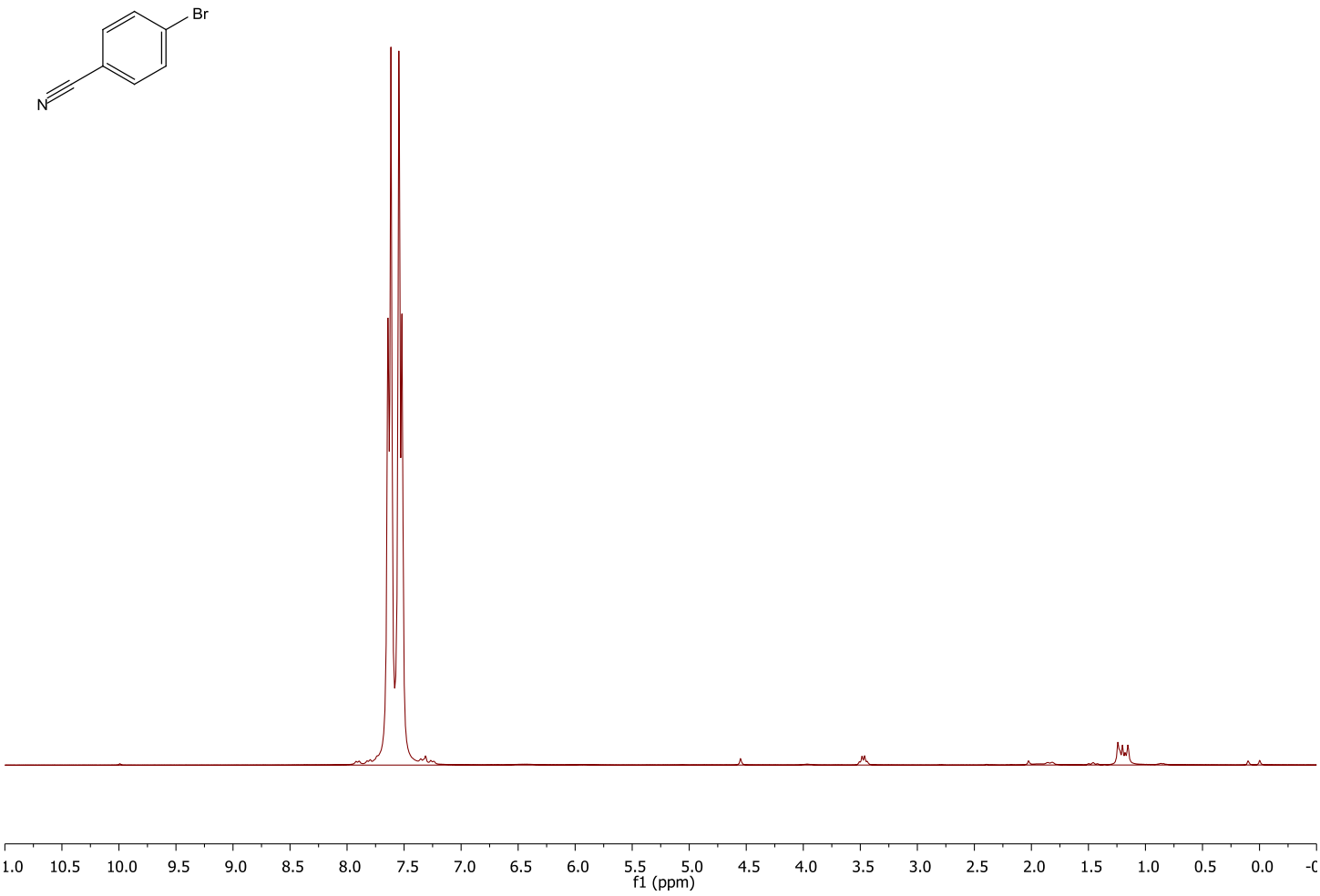


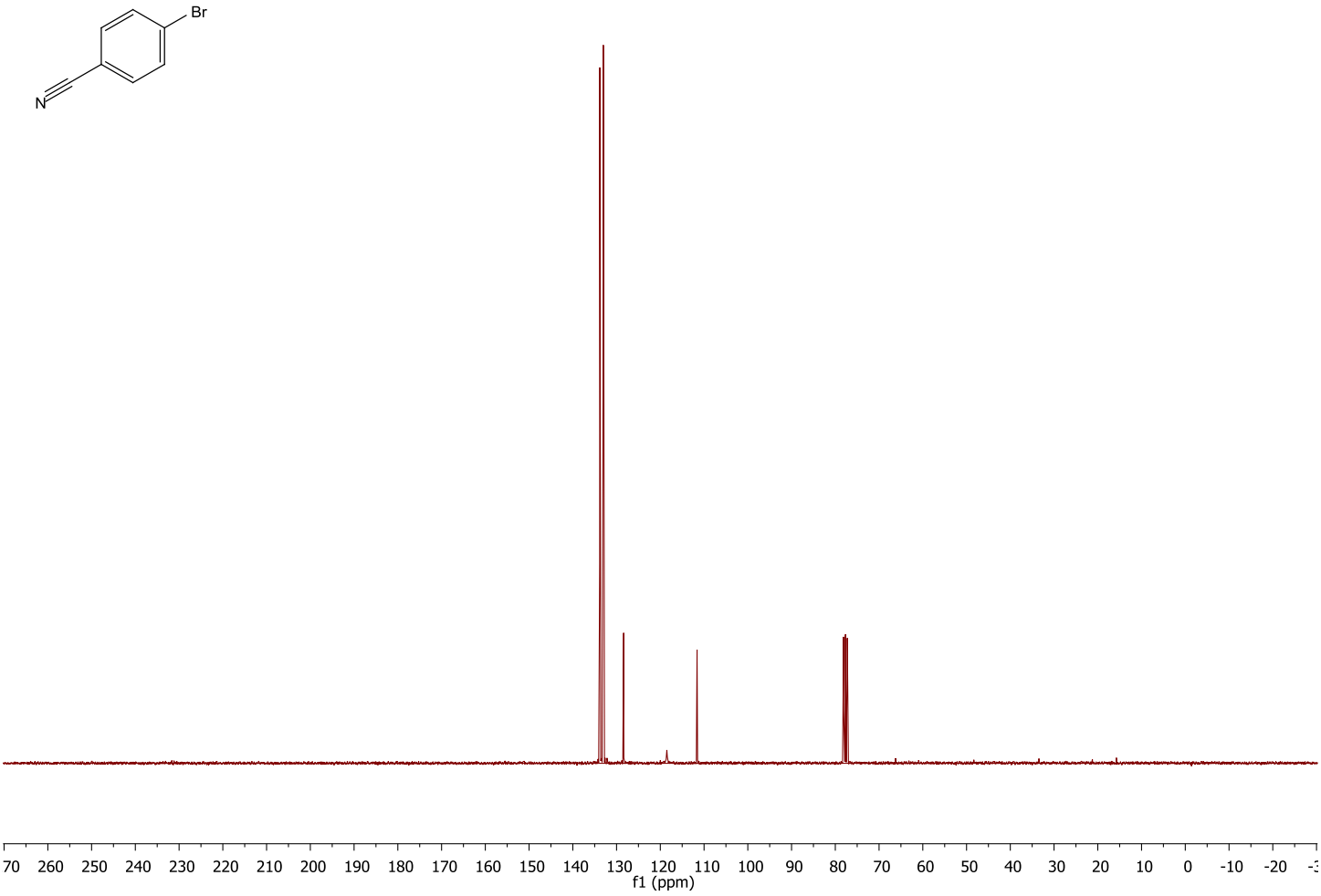


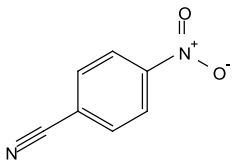


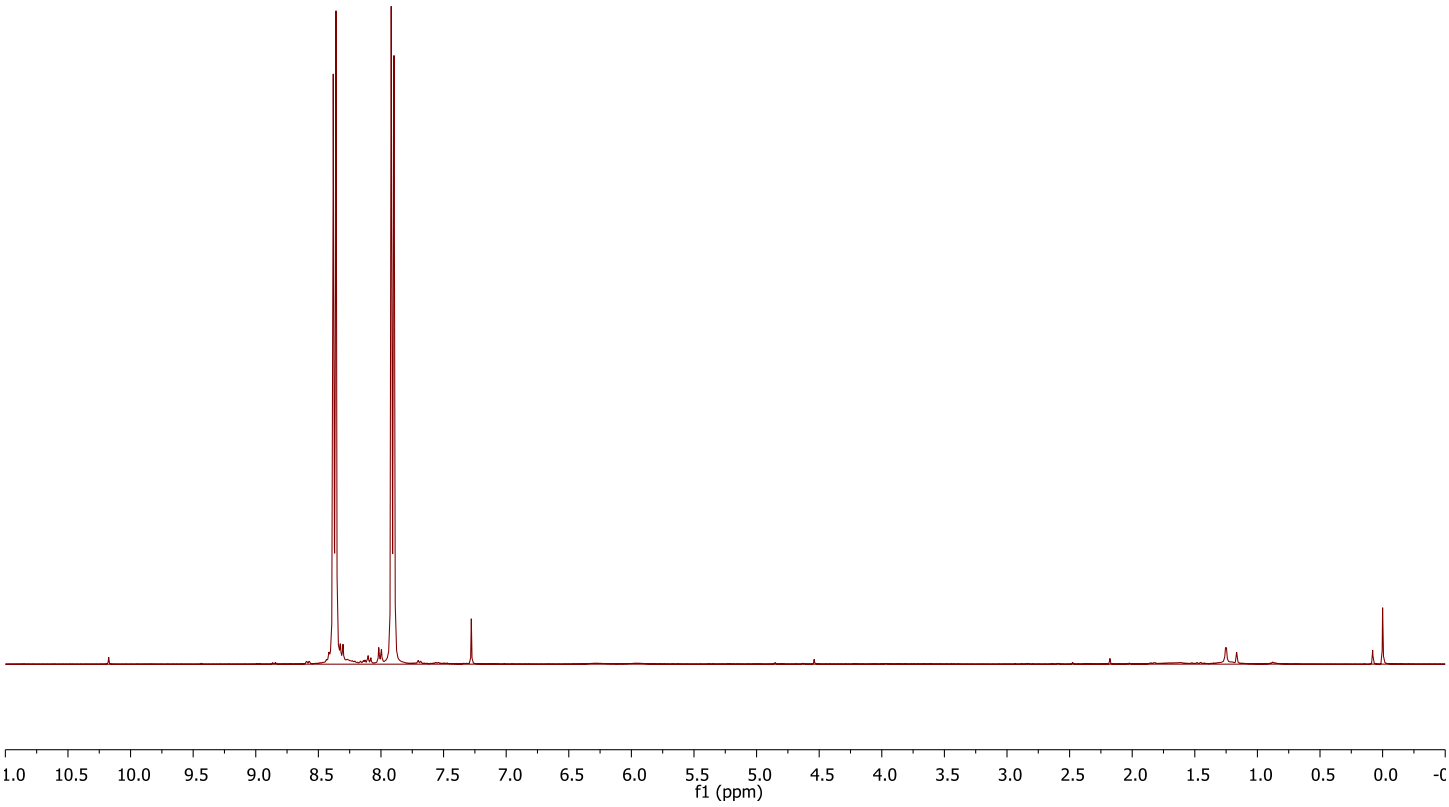


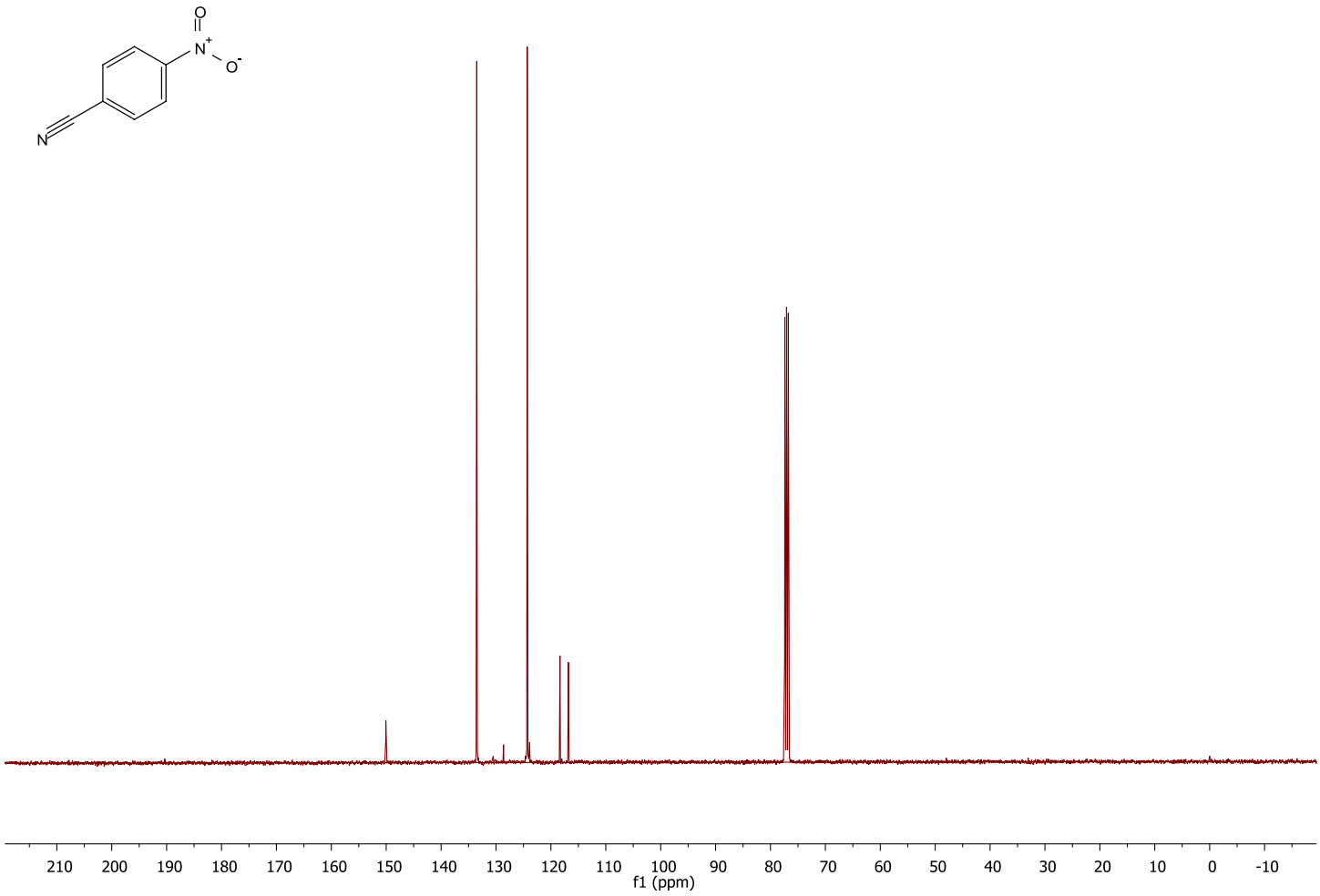


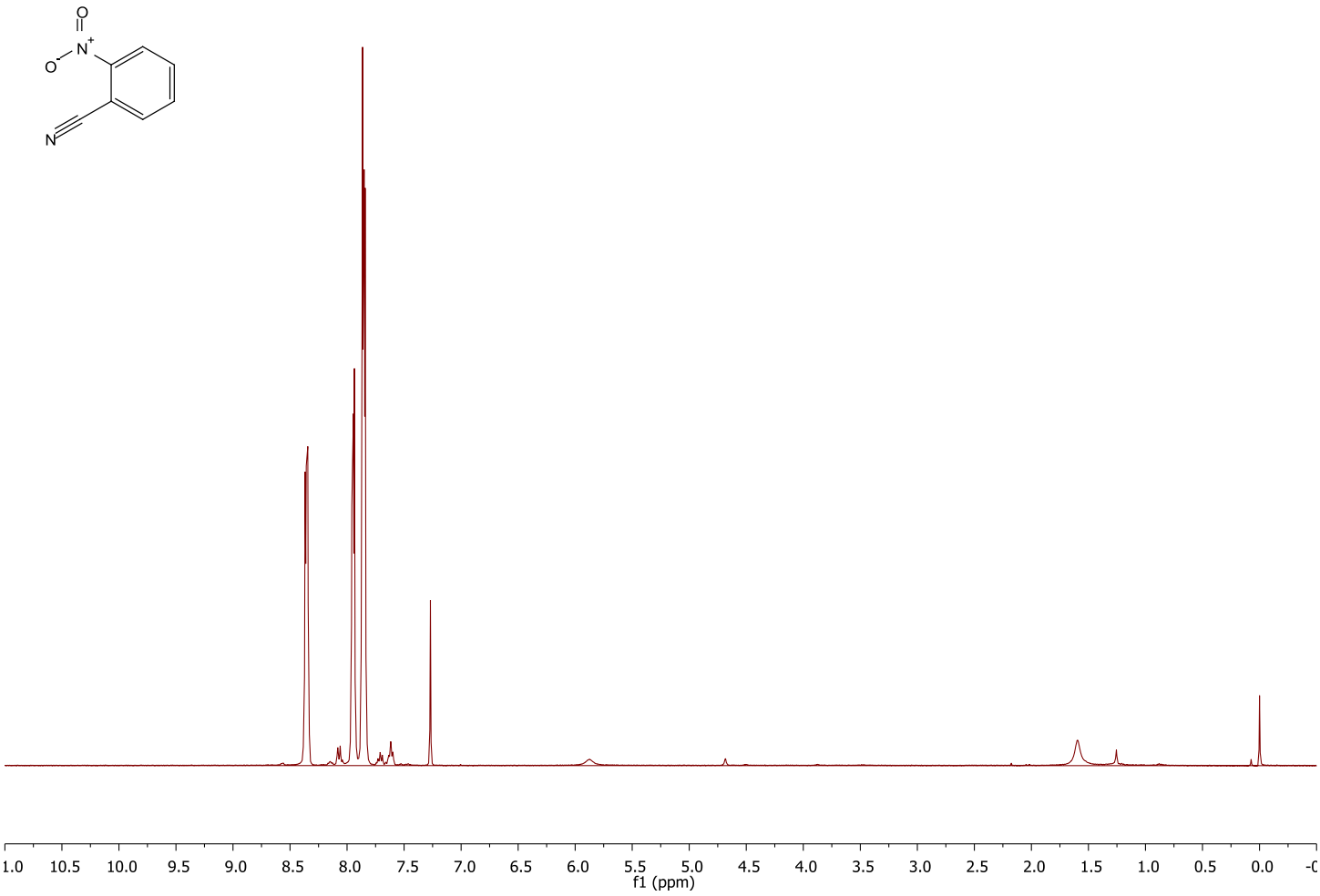


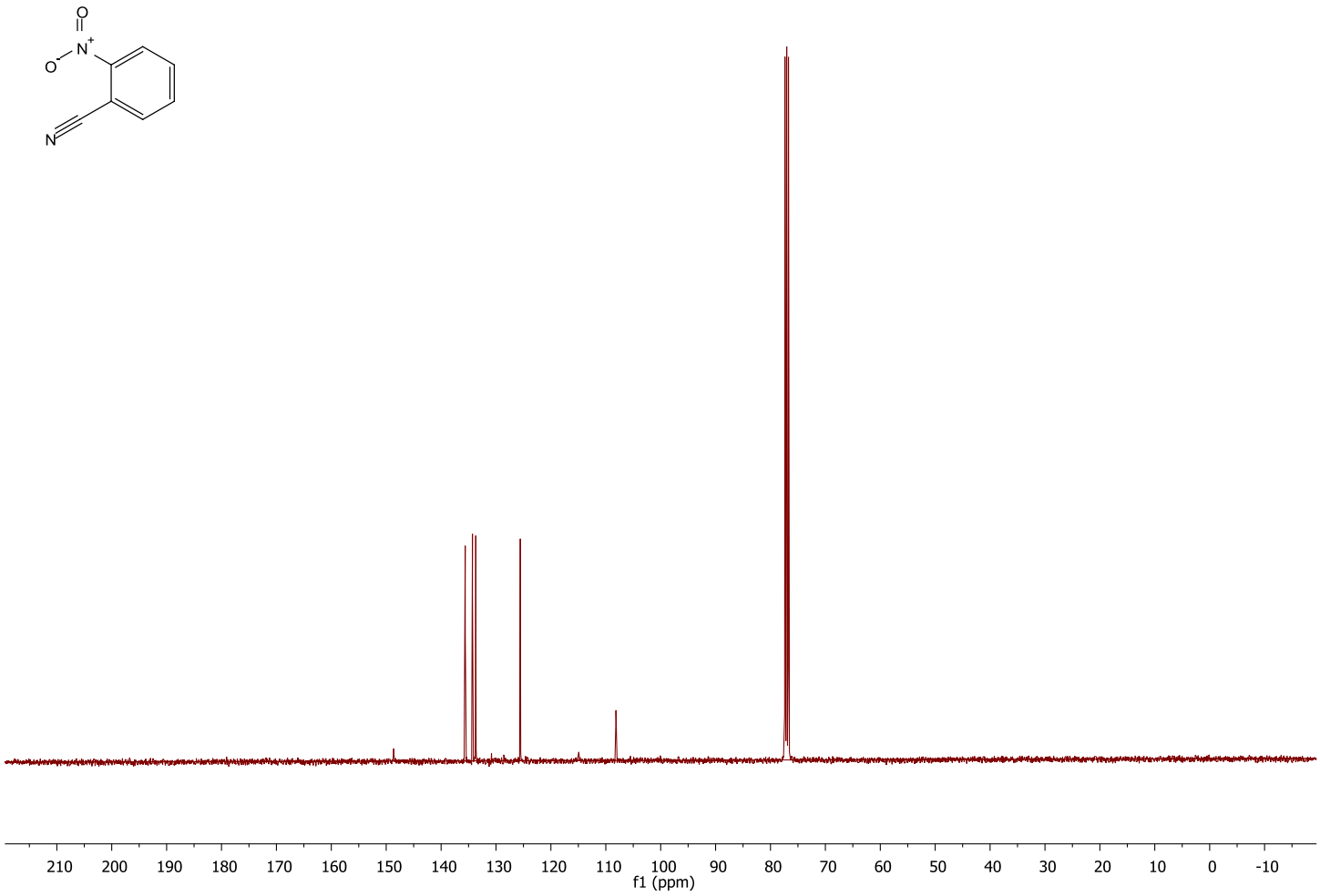


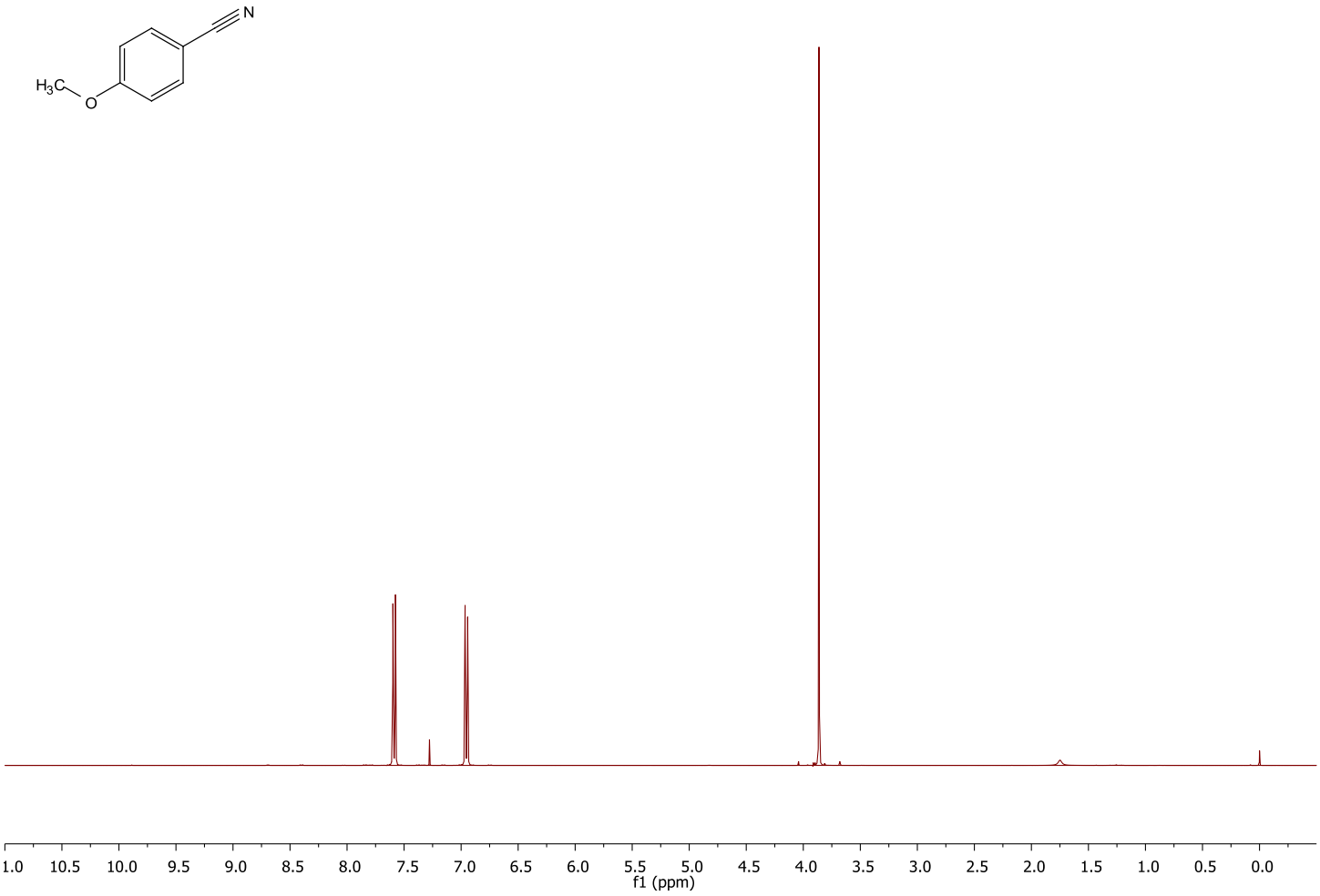


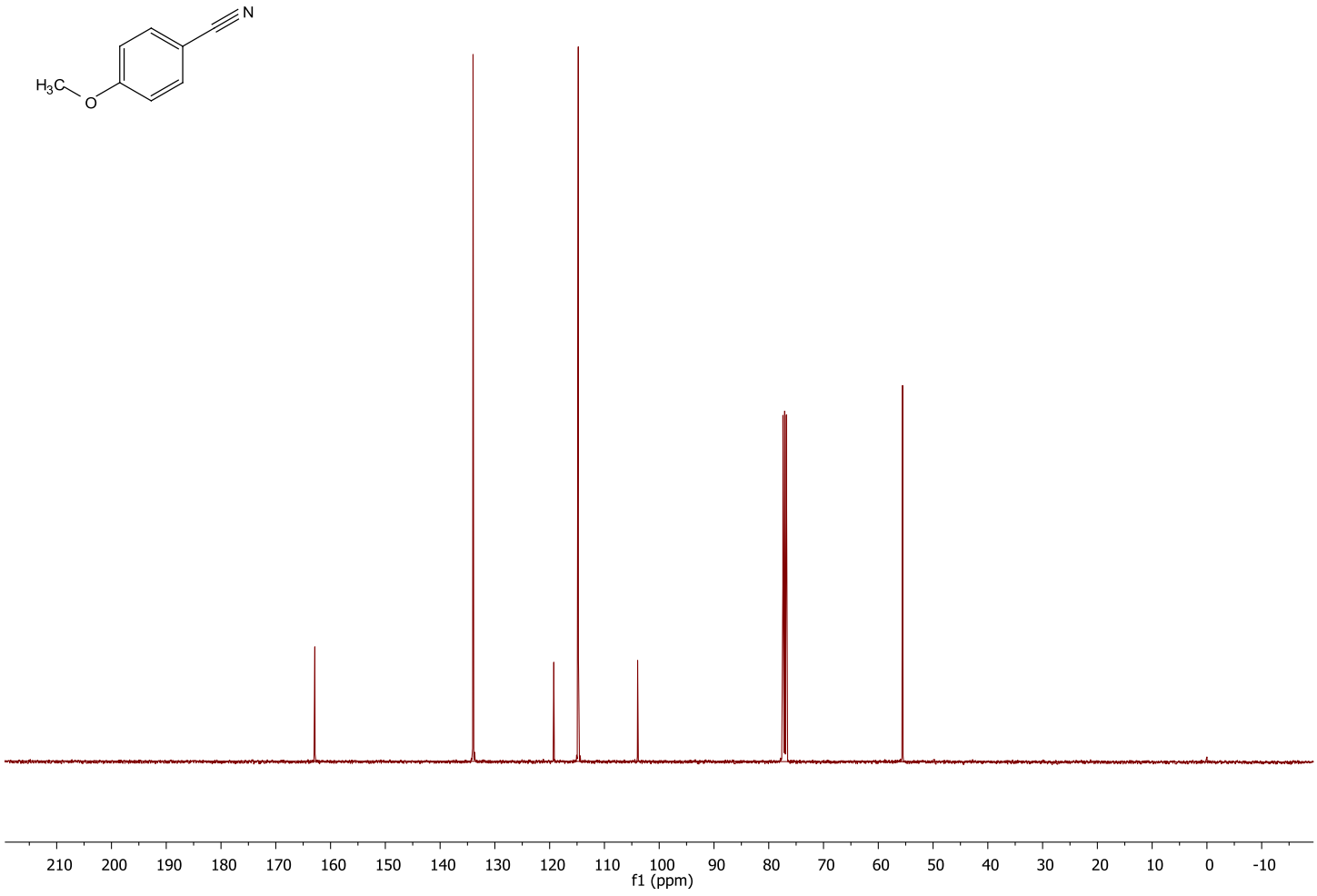


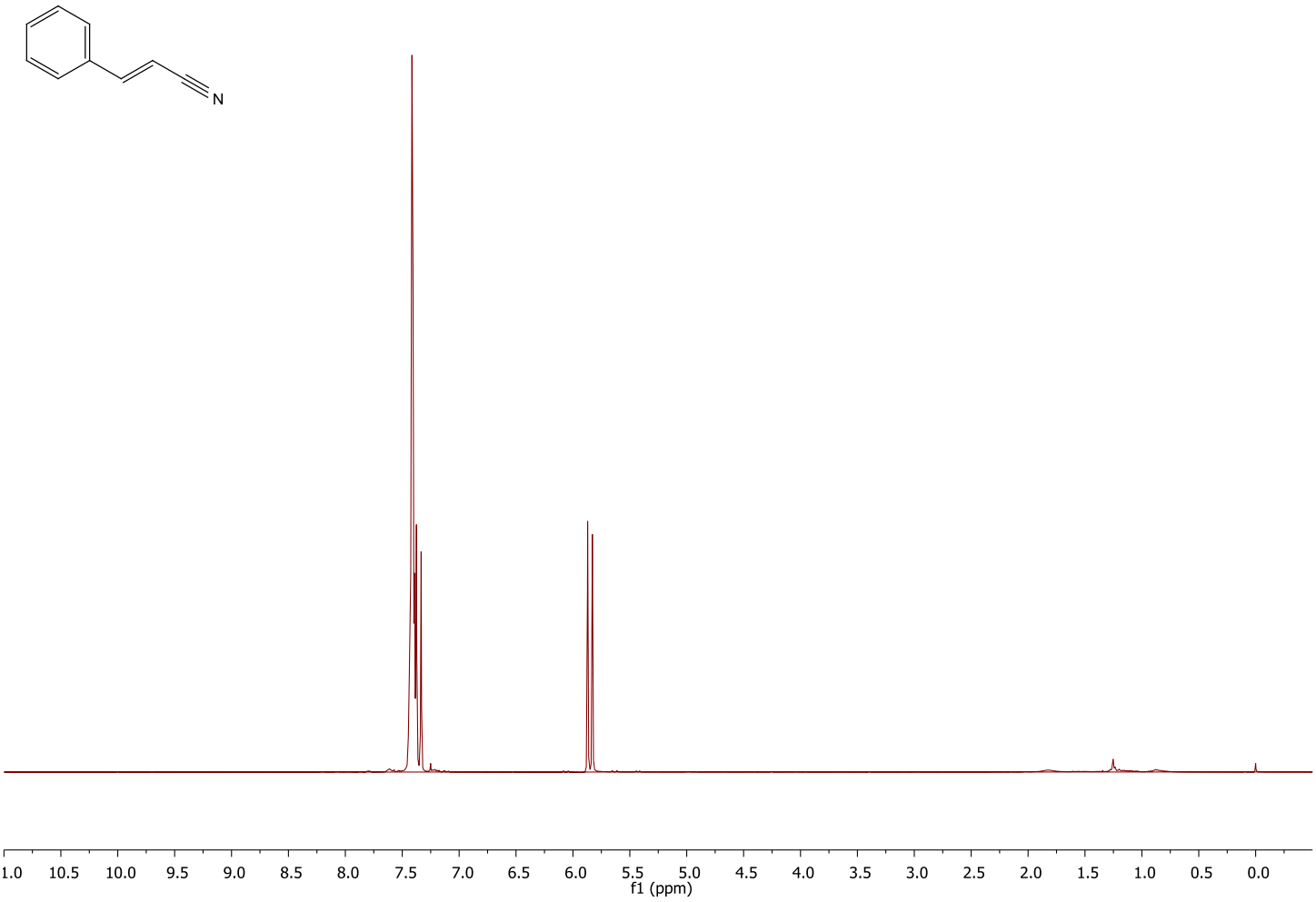


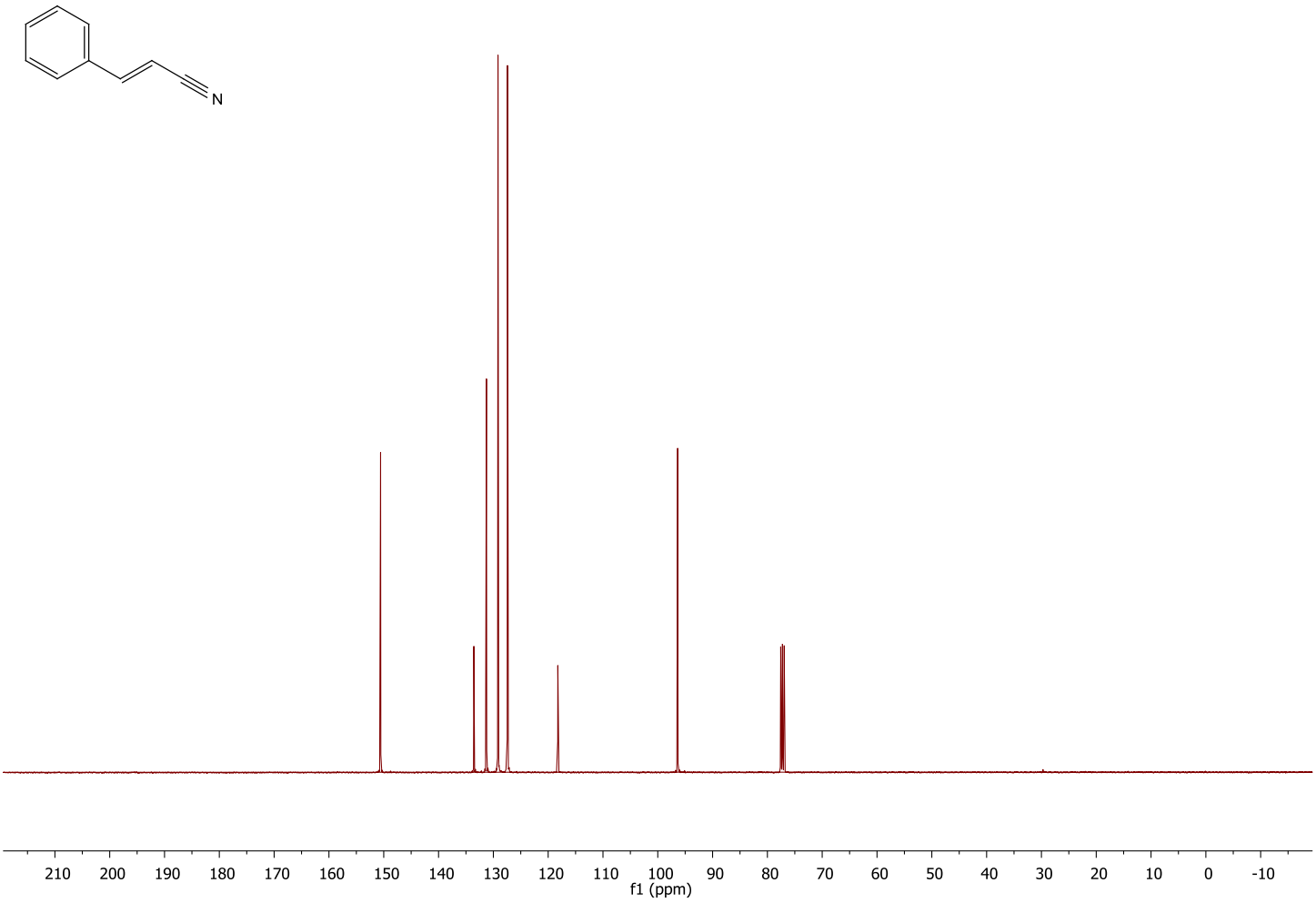


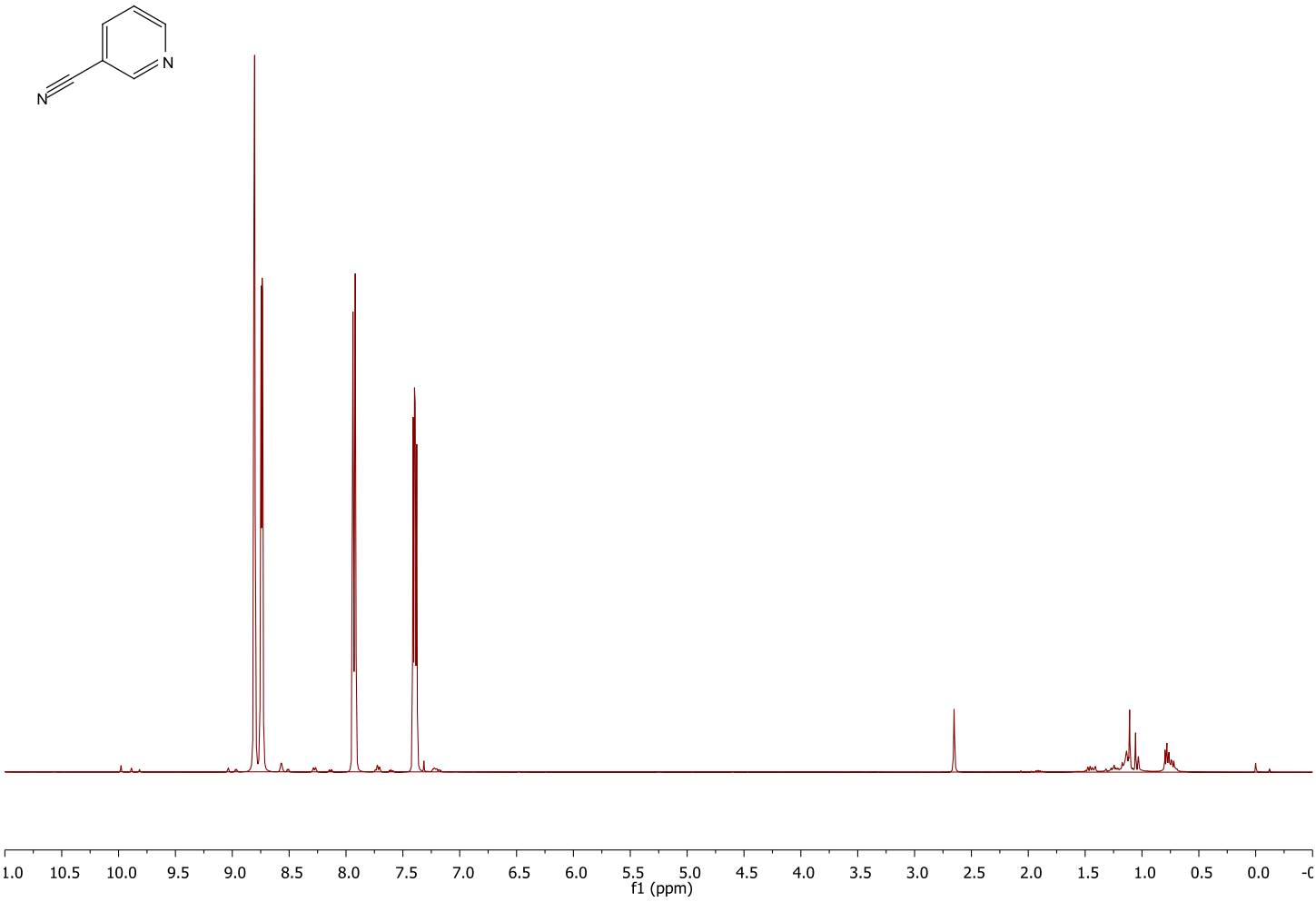


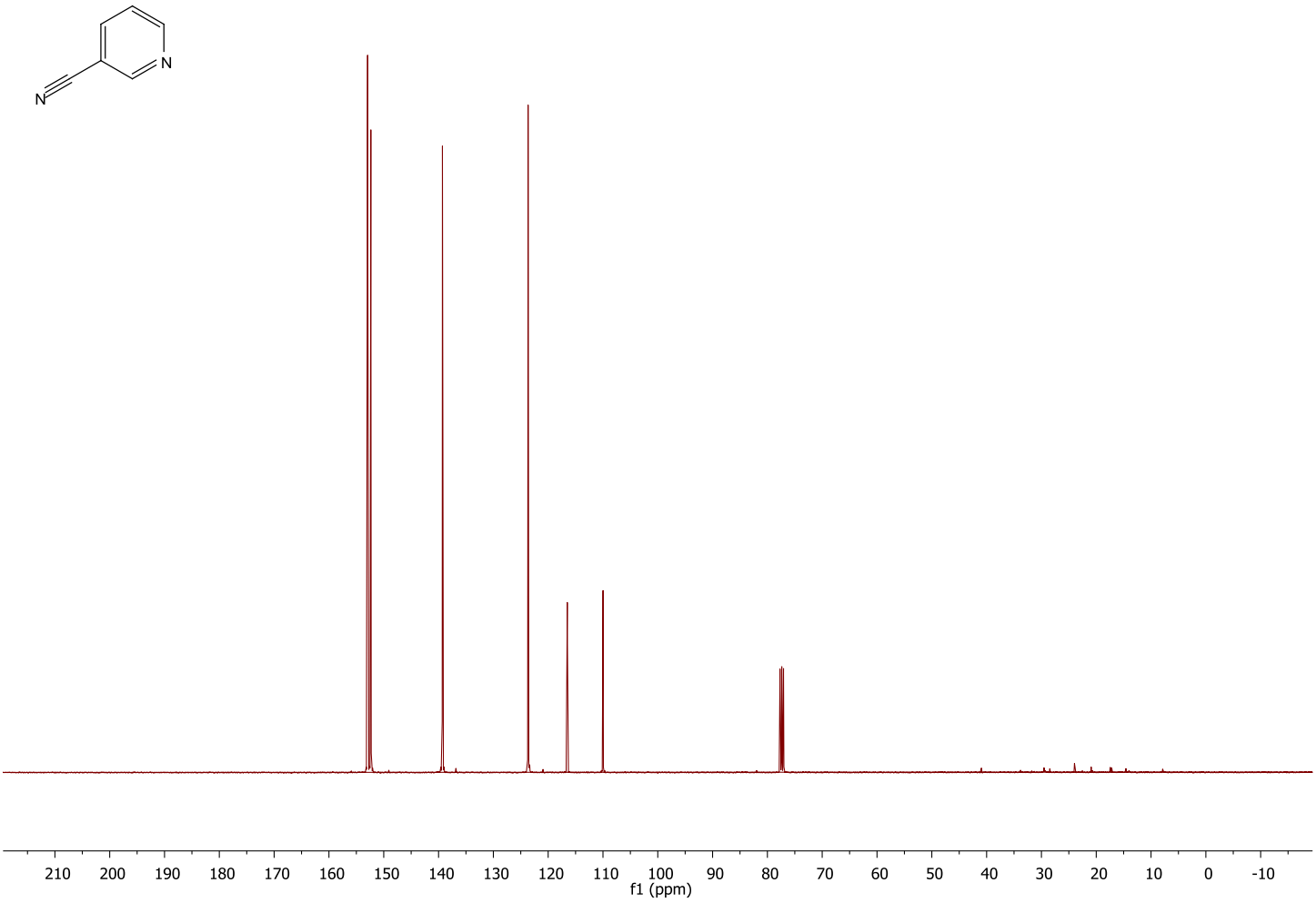


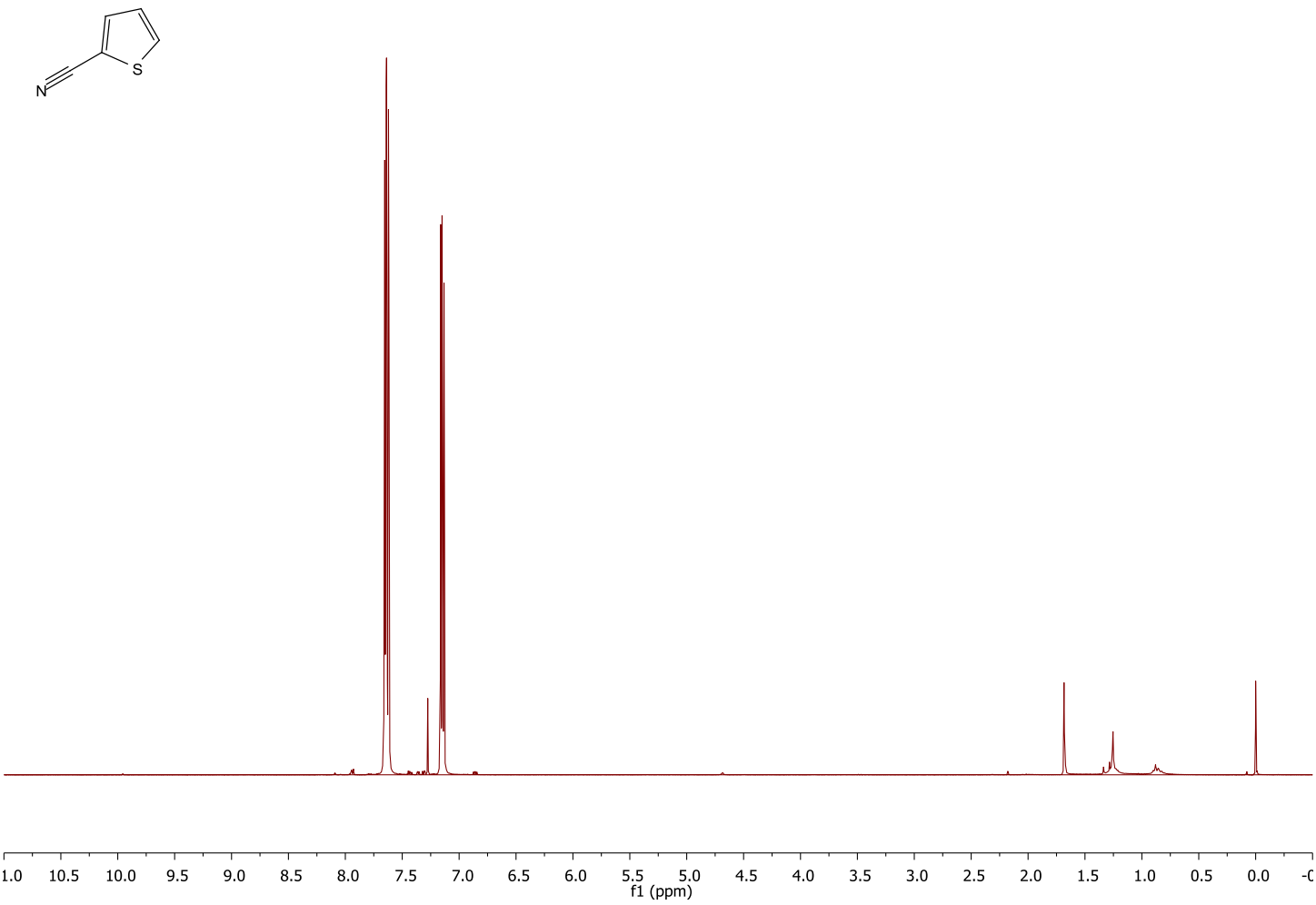


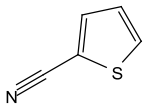


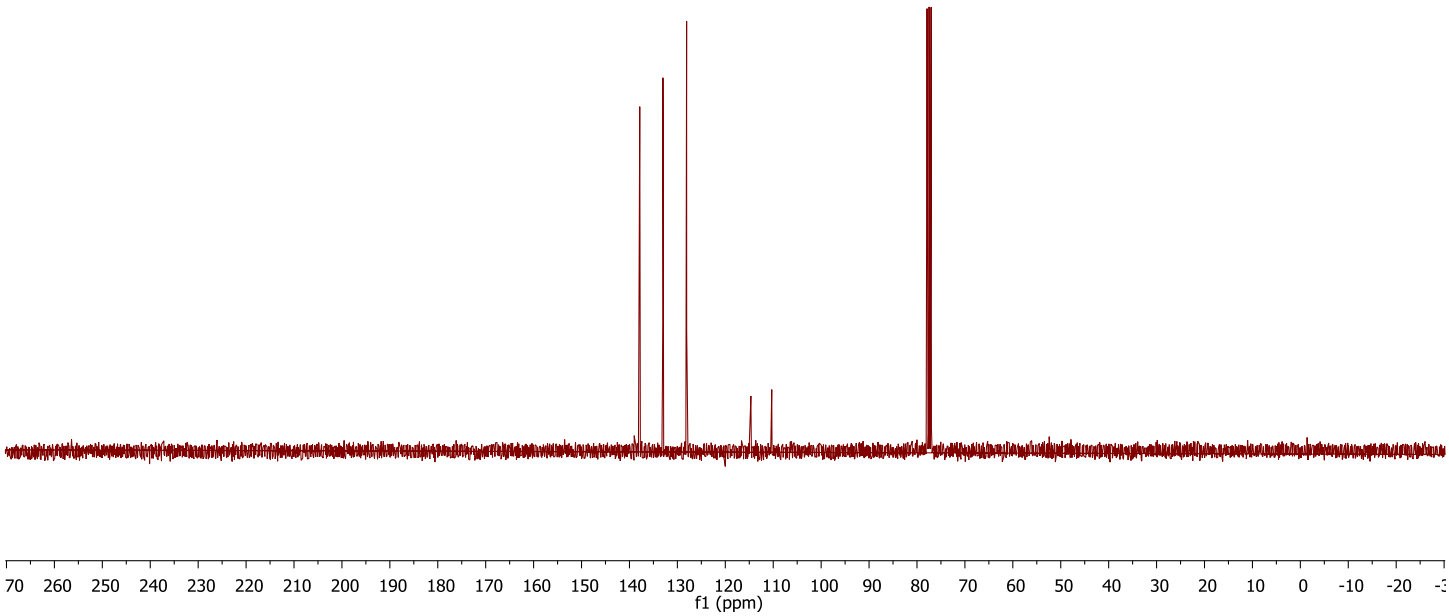


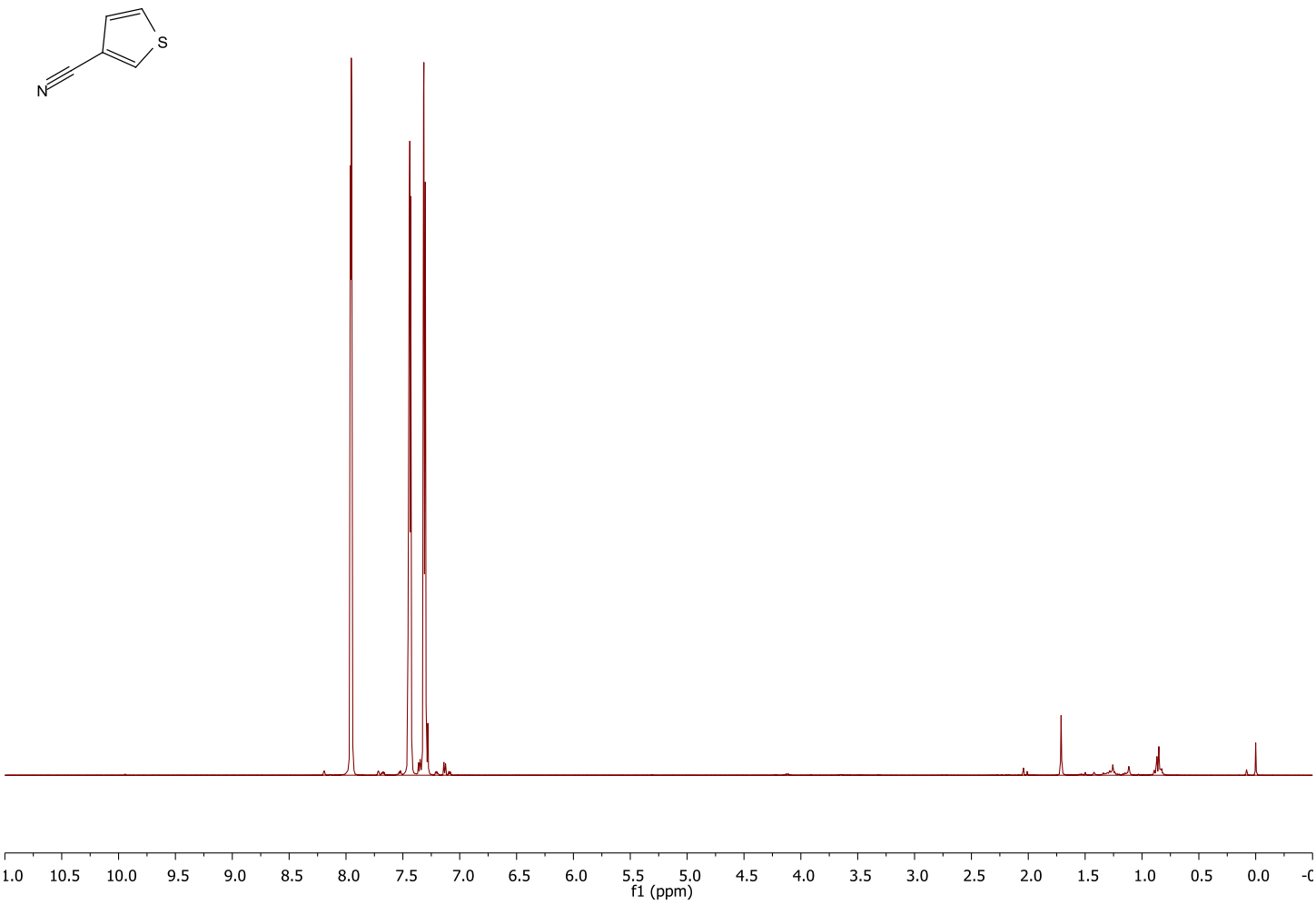


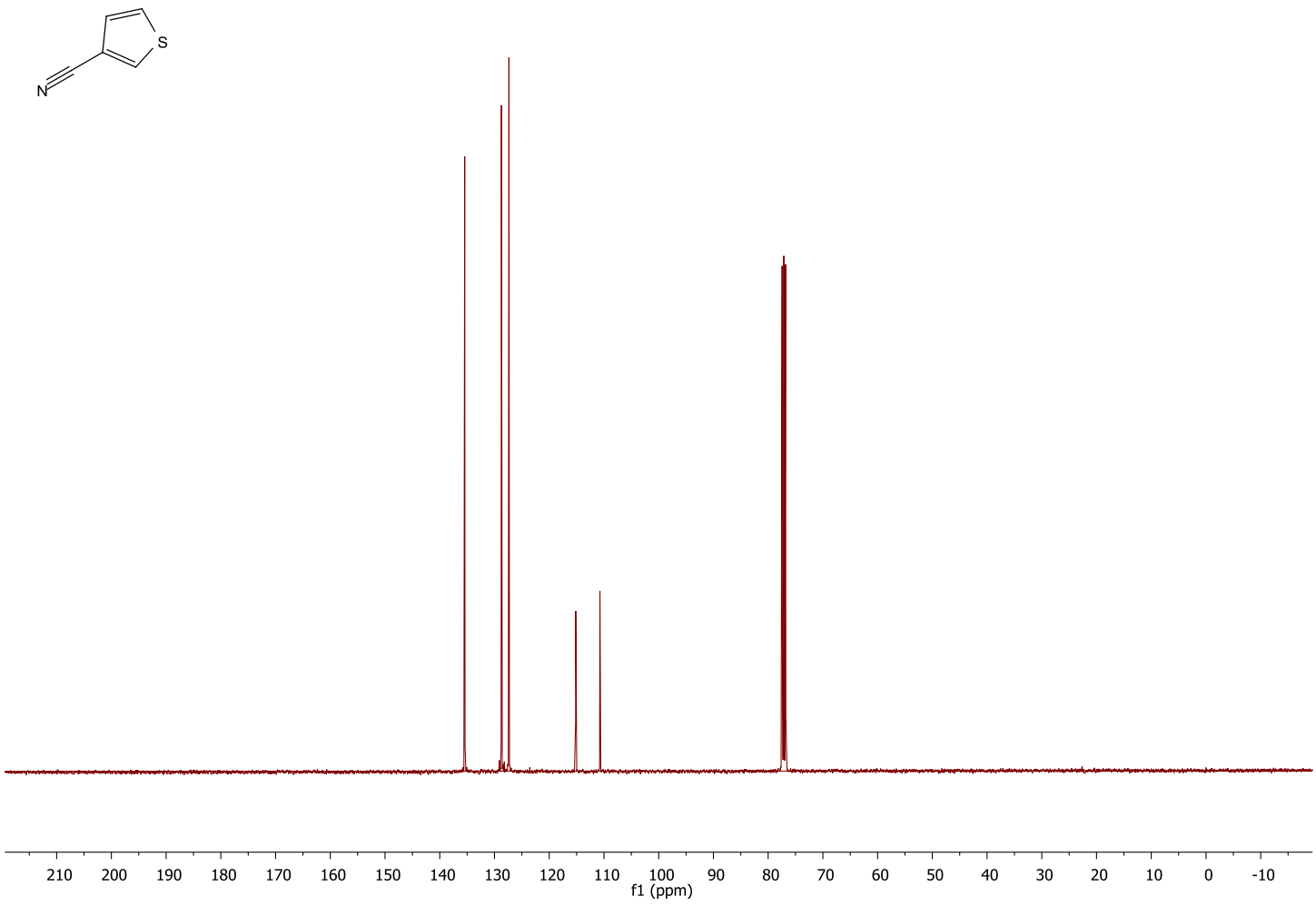


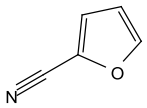


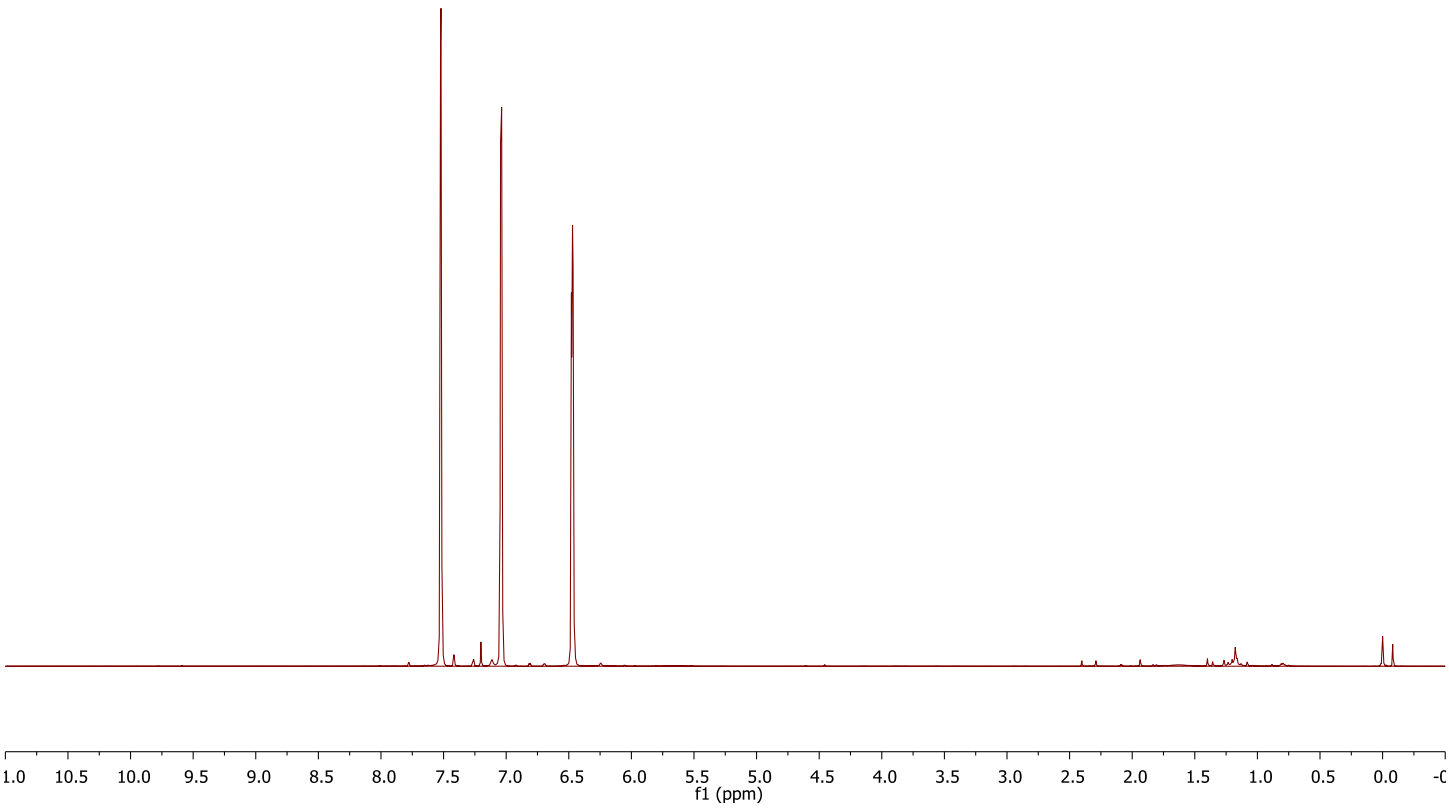


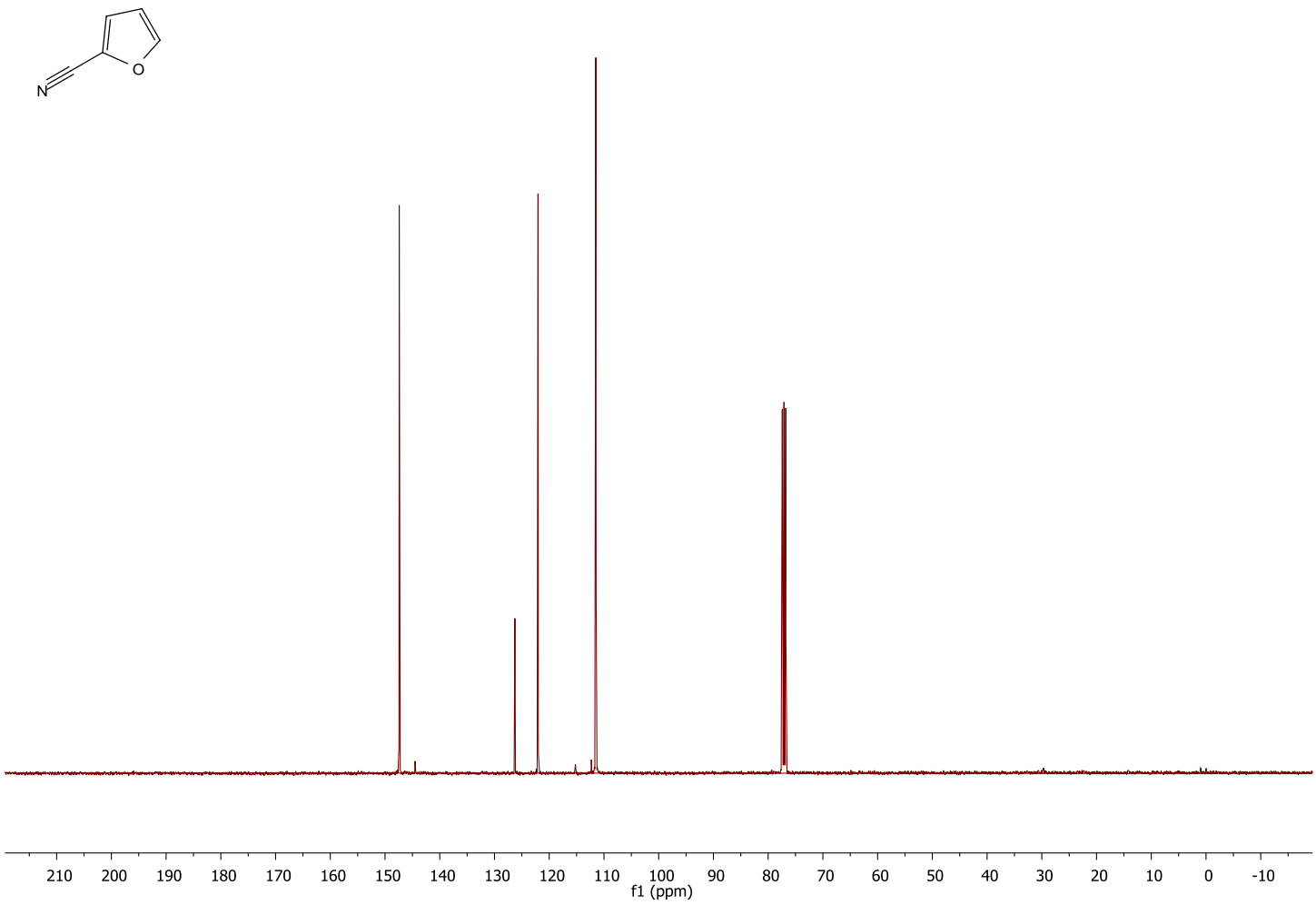


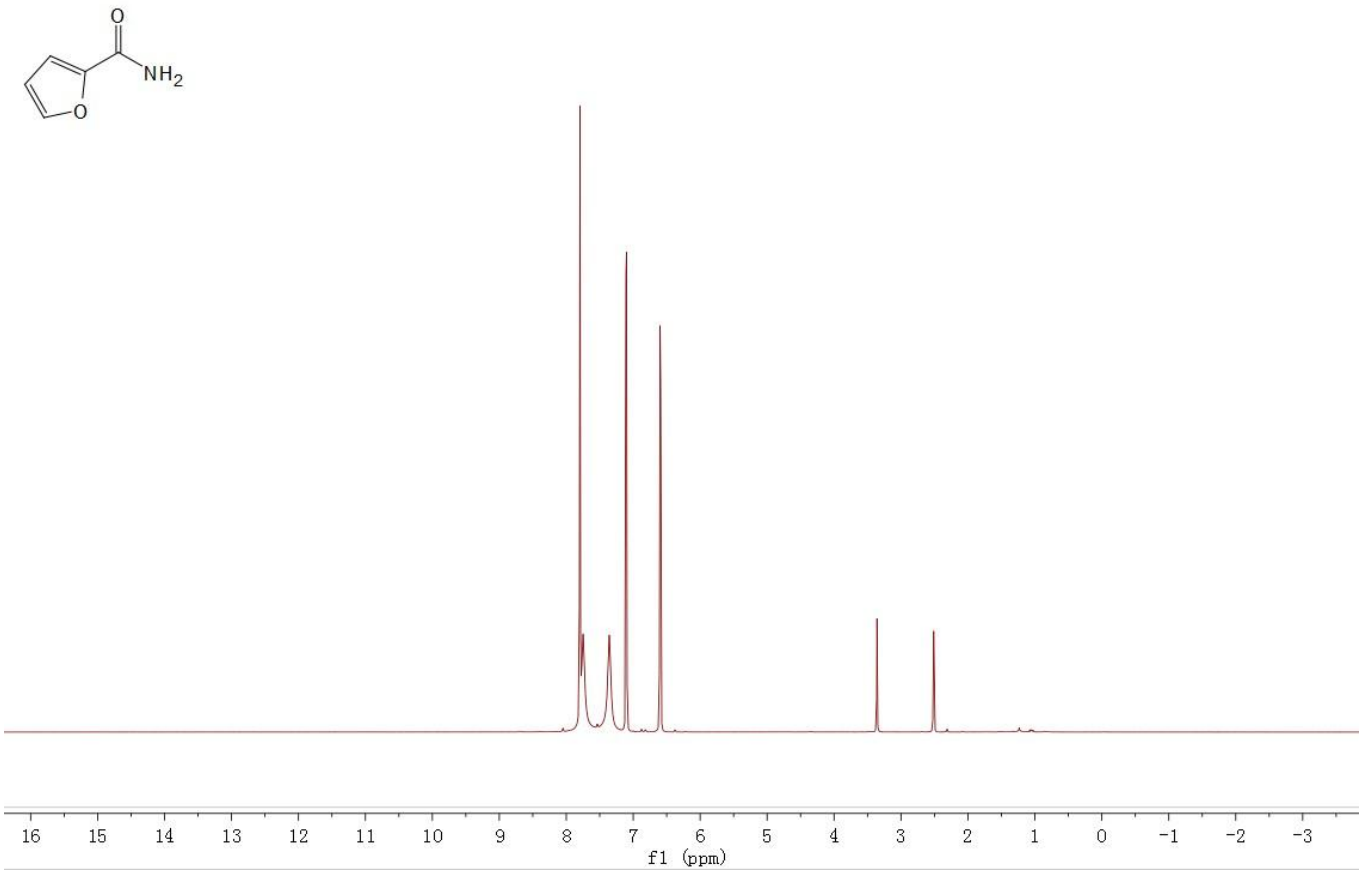


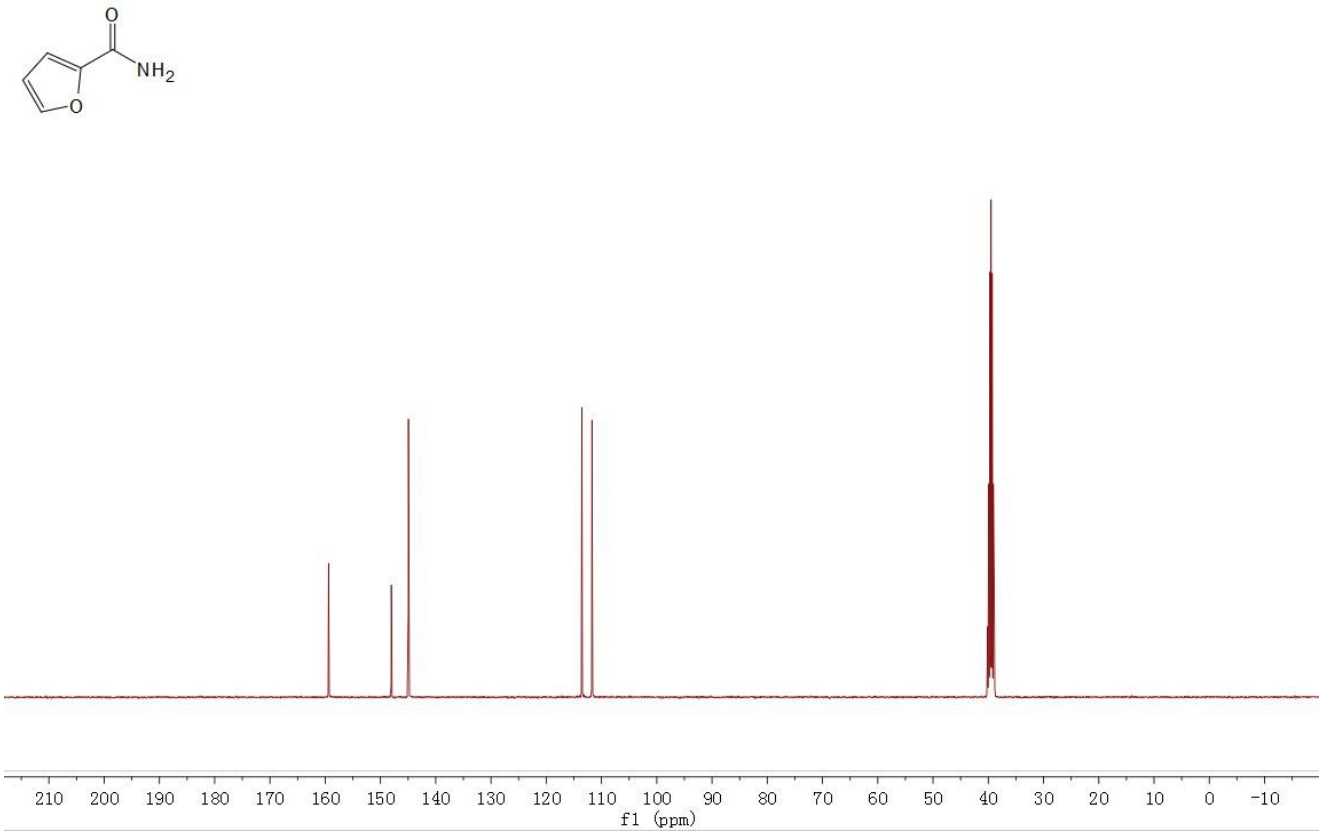


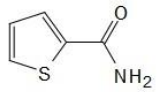


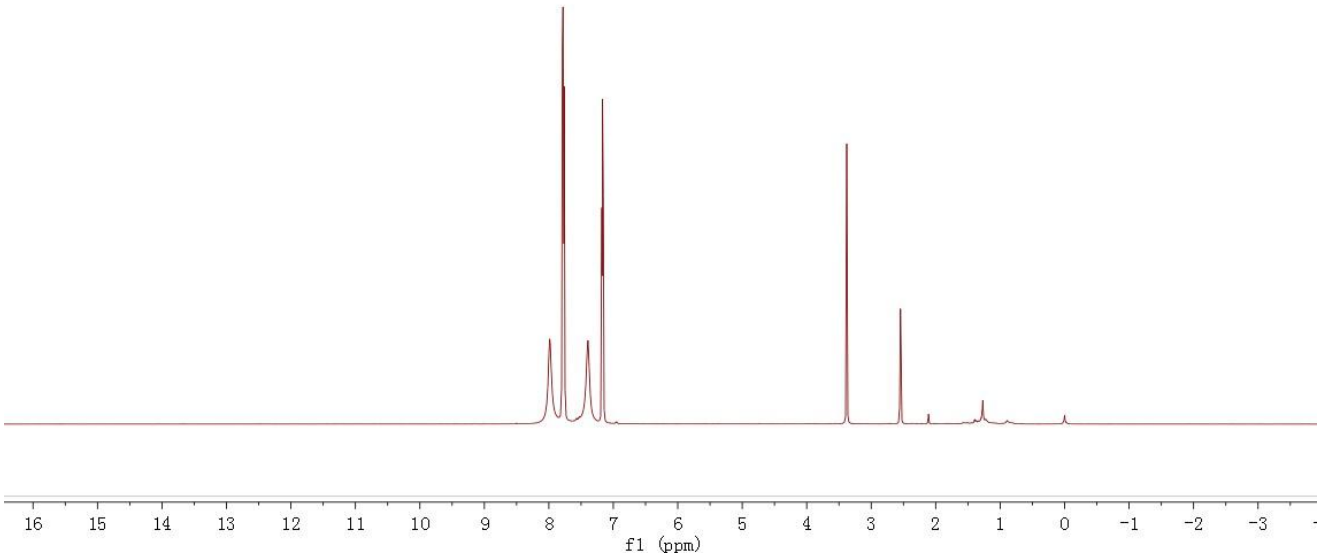


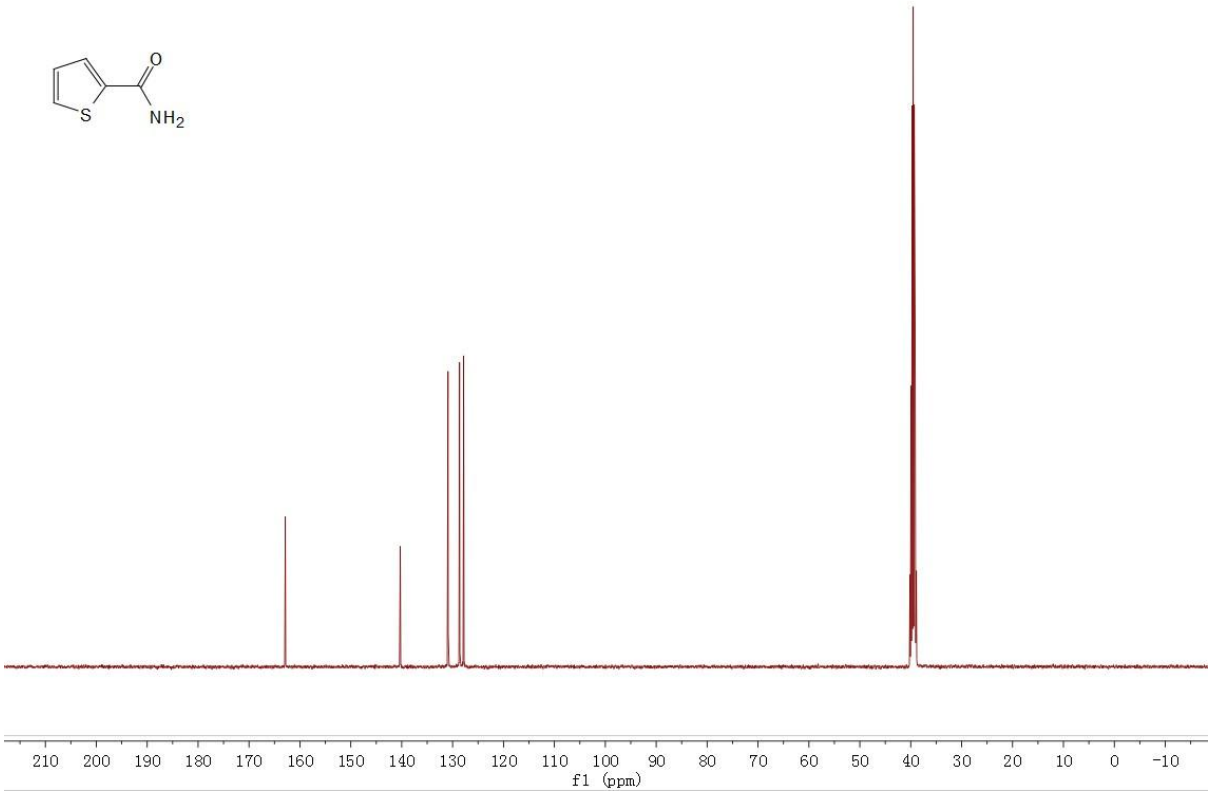


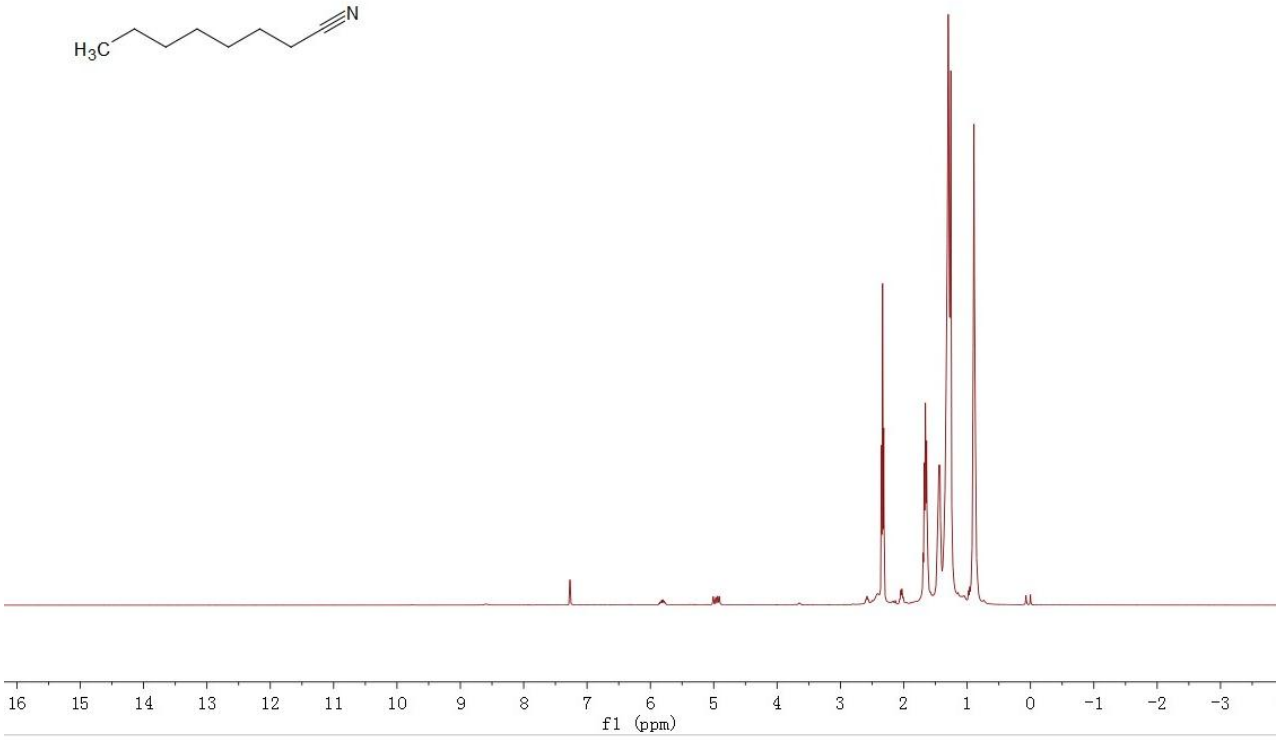


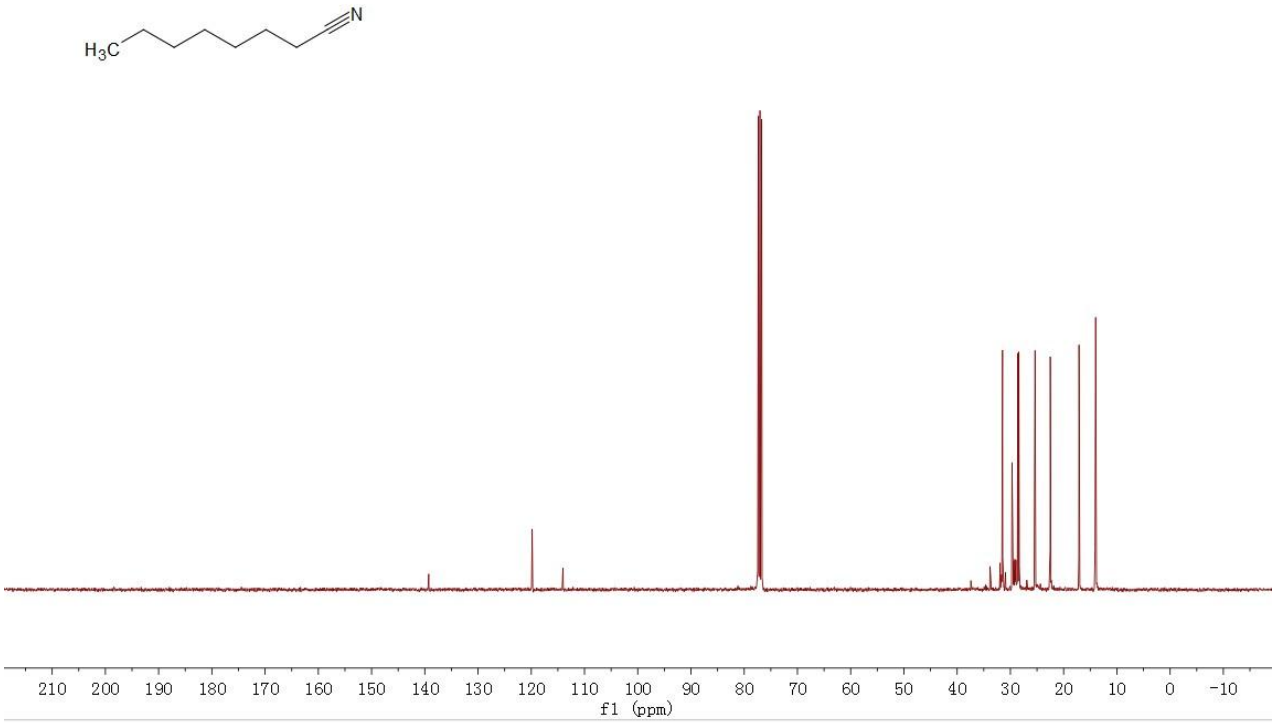












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