Supporting Information for

A Trustworthy Mechanochemical Route to Isocyanides: The Handyman of Chemistry

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1. General information

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, TCI Europe and used as received. All reactions were monitored by thi*n*-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade. Mechanochemical reactions were carried out using a FormTech FTS-1000 Shaker Mill® apparatus. The reagents were milled using a zirconia SmartSnap™ grinding jar (15 mL) equipped with balls (ϕ = 8 mm) of the same material. Precisely, the zirconium oxide of the vessels and balls used for all reactions accomplished in the mixer mill is yttrium oxide stabilized (ZrO_2-Y). These parameters were applied if not stated otherwise. ^1H and ^{13}C liquid NMR spectra were recorded on a Varian 500 MHz and Bruker Avance III HD 600 MHz NMR spectrometer at 298 K and were calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to as the residual hydrogen in the solvent ($CHCl_3$, 7.26 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet, and combination of thereof), coupling constant (J) in Hertz (Hz) and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm). Deuterated NMR solvents were obtained from Aldrich. Samples were analyzed using an Agilent 5977B MS interfaced to the GC 7890B equipped with a DB-5ms column (J & W), injector temperature at 230 °C, detector temperature at 280 °C, helium carrier gas flow rate of 1 ml/min. The GC oven temperature program was 60°C initial temperature with 4 min hold time and ramping at 15°C/min to a final temperature of 270°C with 7 min hold time. 1 µL of each sample was injected in split (1:20) mode. After a solvent delay of 3 minutes mass spectra were acquired in full scan mode using 2.28 scans/s with a mass range of 50–500 Amu. Retention times were determined by injecting pure compounds under identical conditions. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data. Yields refer to pure isolated materials.

2. Mechanochemical synthesis of 2a-i

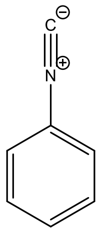
General procedure for isocyanide synthesis

A 15 mL ZrO_2-Y jar equipped with two ZrO_2-Y milling balls (ϕ = 8 mm) was filled with formamide **1a-i** (1 mmol), *p*-tosyl chloride (1.5 mmol), triethylamine (1 mmol) and Na_2CO_3 (6 mmol). The vessel was then closed, and the mechanochemical reaction was conducted for 60 min at a frequency of 18 Hz. At the end of the reaction, an additional 15 min grinding with H_2O (0.5 eq.) was performed. After this step, the crude was recovered as a solid in a beaker and dissolved in heptane (10 mL). A short silica pad (1 g) was required for further purification. Lastly, the organic layer was dried over Na_2SO_4, and the solvent was removed under pressure to afford the pure isocyanide compound.

General procedure for isocyanide gram scale synthesis

A 35 mL ZrO_2-Y jar equipped with three ZrO_2-Y milling balls (ϕ = 10 mm) was filled with formamide **1a-i** (5 mmol), *p*-tosyl chloride (7.5 mmol), triethylamine (5 mmol) and Na_2CO_3 (30 mmol). The vessel was then closed, and the mechanochemical reaction was conducted for 60 min at a frequency of 18 Hz. At the end of the reaction, an additional 15 min grinding with H_2O (0.5 eq.) was performed. After this step, the crude was recovered as a solid in a beaker and dissolved in *n*-heptane (50 mL). A short silica pad (5 g) was required for further purification. Lastly, the organic layer was dried over Na_2SO_4, and the solvent was removed under pressure to afford the pure isocyanide compound.

Isocyanobenzene (**2a**).



The title compound was synthesized according to the general procedure stated above. **1a** (121.1 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2a** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a yellowish oil (72.2 mg, 0.7 mmol, 70%).

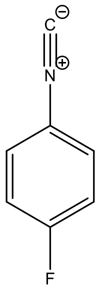
R_f = 0.60 (*n*-heptane:EtOAc 9:1 v/v).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.40-7.36 (m, 5H).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 164.1, 129.6, 129.5, 126.6.

The spectroscopic data closely match the ones previously reported in the literature.[1]

1-fluoro-4-isocyanobenzene (**2b**).



The title compound was synthesized according to the general procedure stated above. **1b** (139.1 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2b** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a brownish solid (81.1 mg, 0.67 mmol, 67%).

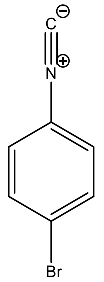
R_f = 0.64 (*n*-heptane:EtOAc 9:1 v/v).

^{1}H NMR (600 MHz, CDCl$_3$): δ = 7.38-7.36 (d, J = 8.5 Hz, 2H), 7.32-7.31 (d, J = 8.4 Hz, 2H).

^{13}C NMR (151 MHz, CDCl$_3$): δ = 165.8, 135.5, 129.9, 127.8, 125.3, 125.2, 125.1.

The spectroscopic data closely match the ones previously reported in the literature.[2]

1-Bromo-4-isocyanobenzene (**2c**).



The title compound was synthesized according to the general procedure stated above. **1c** (200.0 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2c** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a yellowish solid (131.0 mg, 0.72 mmol, 72%).

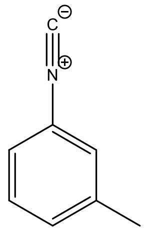
R*f* = 0.61 (*n*-heptane:EtOAc 9:1 v/v)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.55 – 7.53 (m, 2H), 7.26-7.25 (d, *J* = 2.1 Hz, 2H).

^{13}C NMR (151 MHz, CDCl3):δ = 132.9, 128.0, 123.6.

The spectroscopic data closely match the ones previously reported in the literature.[3]

1-Isocyano-3-methylbenzene (**2d**).



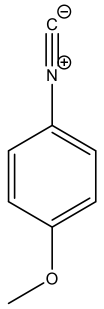
The title compound was synthesized according to the general procedure stated above. **1d** (135.2 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 mg, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2d** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a brown oil (83.2 mg, 0.71 mmol, 71%).

R*f* = 0.57 (*n*-heptane:EtOAc 9:1 v/v)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.27 – 7.25 (m, 1H), 7.21 – 7.17 (m, 3H), 2.36 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 163.7, 139.8, 130.3, 129.3, 127.0, 123.6, 21.2.

1-Isocyano-4-methoxybenzene (**2e**).



The title compound was synthesized according to the general procedure stated above. **1e** (151.2 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2e** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a yellow solid (109.2 mg, 0.82 mmol, 82%)

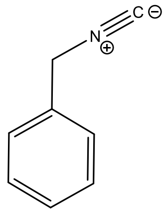
R$_f$ = 0.45 (*n*-exane:EtOAc 9:1 v/v)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.31 (d, 2H), 6.93 – 6.83 (m, 2H), 3.82 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 160.0, 127.9, 114.7, 55.7.

The spectroscopic data closely match the ones previously reported in the literature.[1]

Benzyl isocyanide (**2f**).



The title compound was synthesized according to the general procedure stated above. **1f** (135.2 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2f** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a brown oil (110.2 mg, 0.94 mmol, 94%)

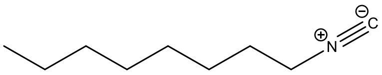
R_f = 0.55 (*n*-heptane:EtOAc 9:1 v/v)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.44 – 7.38 (m, 2H), 7.38 – 7.32 (m, 3H), 4.65 (t, J = 2.3 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 157.8, 132.35, 129.00, 128.44, 126.62, 45.6.

The spectroscopic data closely match the ones previously reported in the literature.[1]

1-Isocyanooctane (**2g**).



The title compound was synthesized according to the general procedure stated above. **1g** (157.3 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2g** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a colourless oil (125.3 mg, 0.9 mmol, 90%)

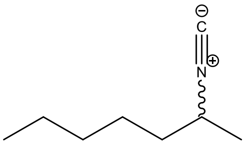
R_f = 0.53 (*n*-heptane:EtOAc 9:1 v/v)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.37 (ddt, 2H), 1.67 (dddd, 2H), 1.43 (td, 2H), 1.35 – 1.21 (m, 8H), 0.89 (t, 3H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 155.7, 41.8, 41.7, 41.6, 31.8, 29.3, 29.2, 28.8, 26.5, 22.7, 14.2.

The spectroscopic data closely match the ones previously reported in the literature.[1]

2-isocyanoheptane (**2h).**



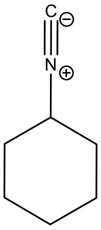
The title compound was synthesized according to the general procedure stated above. **1h** (143.1 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2h** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a yellow oil (107,6 mg, 0.86 mmol, 86%)

R_f = 0.50 (*n*-heptane:EtOAc 9:1 v/v)

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.62-3.58 (m, 1H), 1.70-1.69 (m, 2H), 1.36-1.34 (m, 6H), 0.91-0.88 (m, 6H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.2, 50.4, 36.9, 31.3, 25.5, 22.6, 21.8, 14.1.

Isocyanocyclohexane (**2i**).



The title compound was synthesized according to the general procedure stated above. **1i** (127.2 mg, 1 mmol), *p*-tosyl chloride (285.9 mg, 1.5 mmol), triethylamine (139 µl, 1 mmol), and Na_2CO_3 (635.9 mg, 6 mmol) were used, to afford **2i** after a short silica pad (SiO_2/*n*-heptane 100% v/v) as a yellowish oil (96.1 mg, 0.88 mmol, 88%)

R_f = 0.60 (*n*-heptane:EtOAc 9:1 v/v)

^{1}H NMR (600 MHz, $CDCl_3$): *δ* = 3.61-3.58 (tt, *J* = 8.2, 3.4 Hz, 1H), 1.90 – 1.86 (m, 2H), 1.77 – 1.64 (m, 4H), 1.49-1.34 (m, 4H).

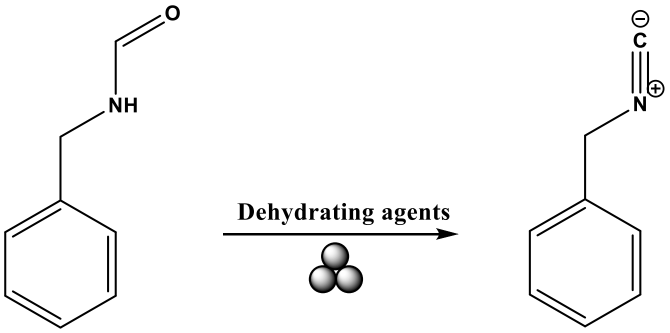
^{13}C NMR (151 MHz, $CDCl_3$): *δ* = 154.1, 52.0, 51.9, 51.8, 32.8, 25.1, 22.9.

The spectroscopic data closely match the ones previously reported in the literature.[1]

Procedure for the optimization of the reaction (Table T1)

A 15 mL ZrO_2-Y jar equipped with two ZrO_2-Y milling balls (8 mm diameter) was filled with formamide **1f** (1 mmol), dehydrating combo reagents. The vessel was then closed, and the mechanochemical reaction was conducted at different times in a diverse range of frequencies (from 18 to 36 Hz). At the end of the reaction, the crude was recovered as a solid in a beaker, dissolved in *n*-hexane (15 mL). A silica pad (2 g) was required for purification. Lastly, the organic layer was dried over Na_2SO_4 and the solvent was removed under pressure to afford the pure isocyanide compound.

Table T1. Optimization of the reaction conditions for isocyanide **2f** synthesis in the presence of different dehydrating agents.



Entry	**Dehydrating agents**	**Additive**	**Yield (%)**[g]
1	Ac_2O	Triethylamine[a]	60%
2	TFAA	Triethylamine[a]	67%
3	Isatoic Anhydride	Triethylamine[a]	< 1%
4	CDI	$NaHSO_4$	traces
5	DIC	Triethylamine[a]	18%
6	*p*-Ts imidazole	$NaHSO_4$	traces
7	*p*-Ts imidazole	$NaHSO_4$[a]	traces
8	***p*-TsCl**	**Triethylamine**[d,e]	**quant.**
9	*p*-TsCl	*N*-methyl imidazole	43%
10	*p*-TsCl	*N*-methyl imidazole[b,c,e]	75%
11	*p*-TsCl	Imidazole[b,c]	20%
12	*p*-TsCl	Na_2CO_3 anhydrous + triethylamine	70%
13	***p*-TsCl**	**Na_2CO_3 anhydrous + Triethylamine**[e,f]	**94%**
14	*p*-TsCl	Na_2CO_3 anhydrous	2%
15	*p*-TsCl	Na_2CO_3	< 1%
16	*p*-TsCl	K_2CO_3	traces
17	*p*-TsCl	Cs_2CO_3	traces
18	*p*-TsCl	MgO	traces
19	*p*-TsCl	BaO	traces
20	*p*-TsCl	LiCl	traces
21	*p*-TsCl	$BF_3{\cdot}Et_2O$	traces

Reaction conditions: formamide **1a** (1 mmol), dehydrating agents (1 mmol), additive (10 mol%), 60 min, 36 Hz. [a] Additive (1 mmol). [b] Additive (2 mmol). [c] 120 min reaction. [d] additive (7 mmol), NaCl (400 mg), 0.5 h, 36 Hz. [e] Frequency of 18 Hz. [f] Na_2CO_3 (6 mmol), triethylamine (1 mmol). [g] GC-MS calculated yields.

3. References

1. Mocci, R.; Murgia, S.; De Luca, L.; Colacino, E.; Delogu, F.; Porcheddu, A. *Org. Chem. Front.* **2018**, *5*, 531–538. doi:10.1039/c7qo01006k

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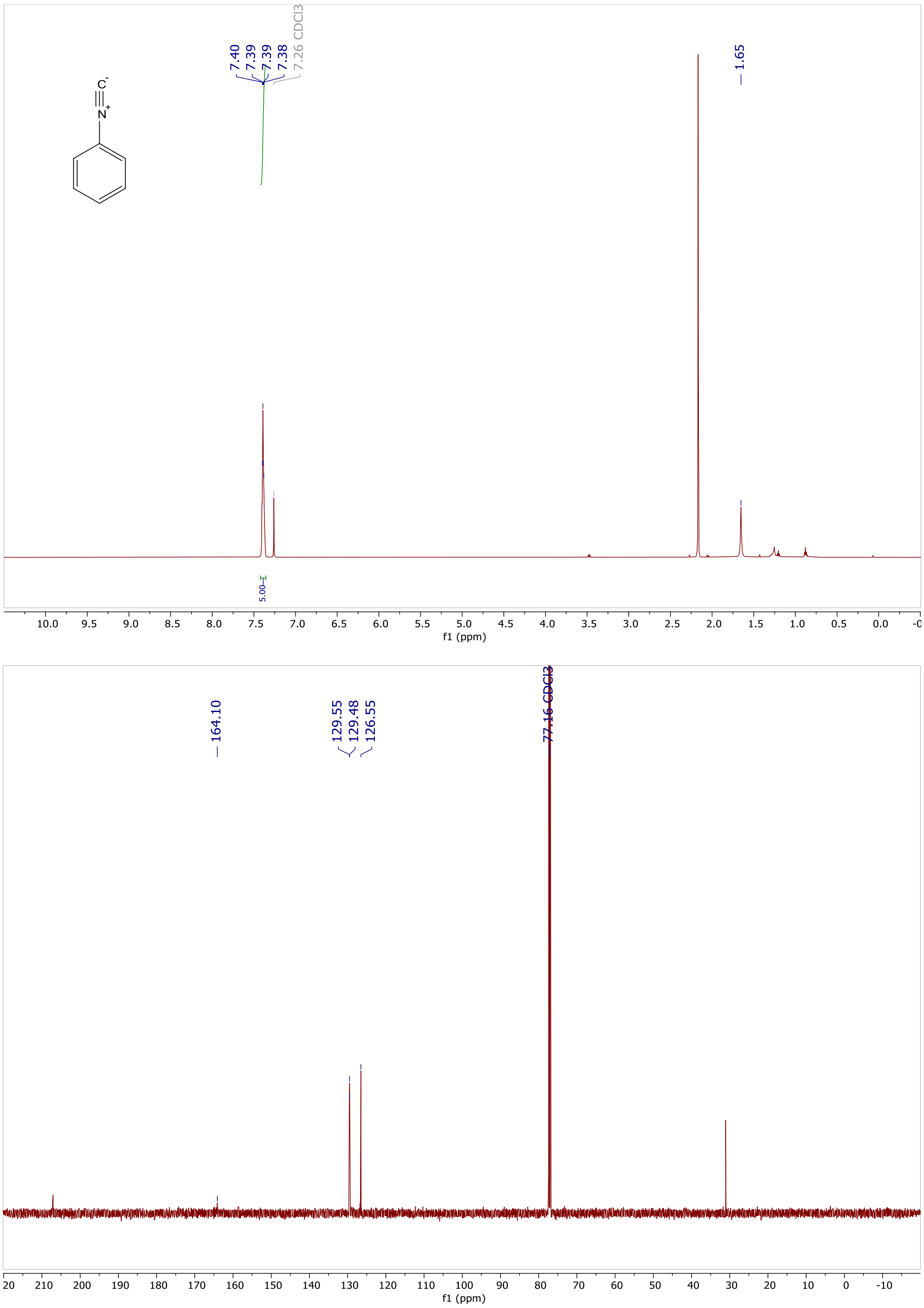
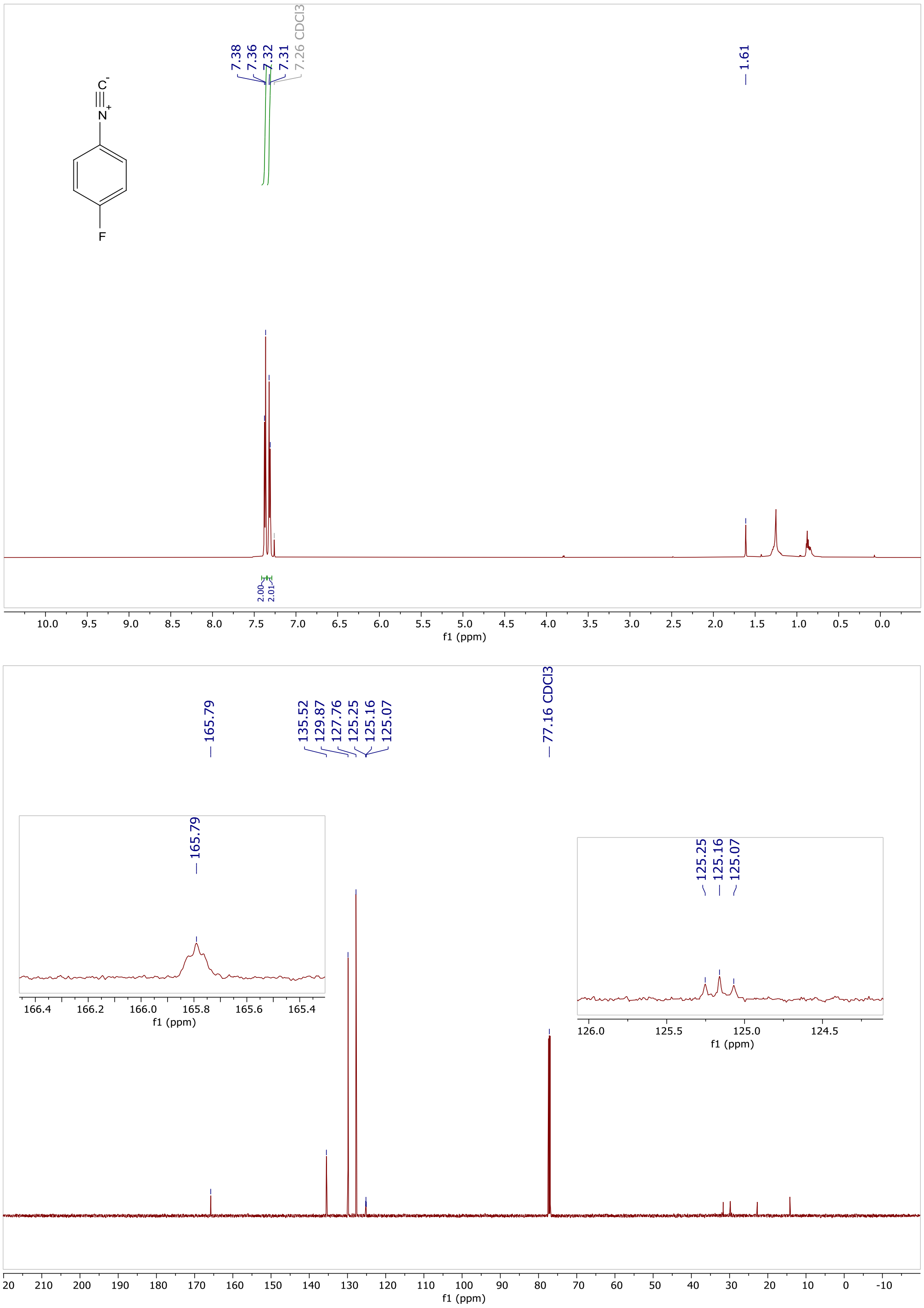
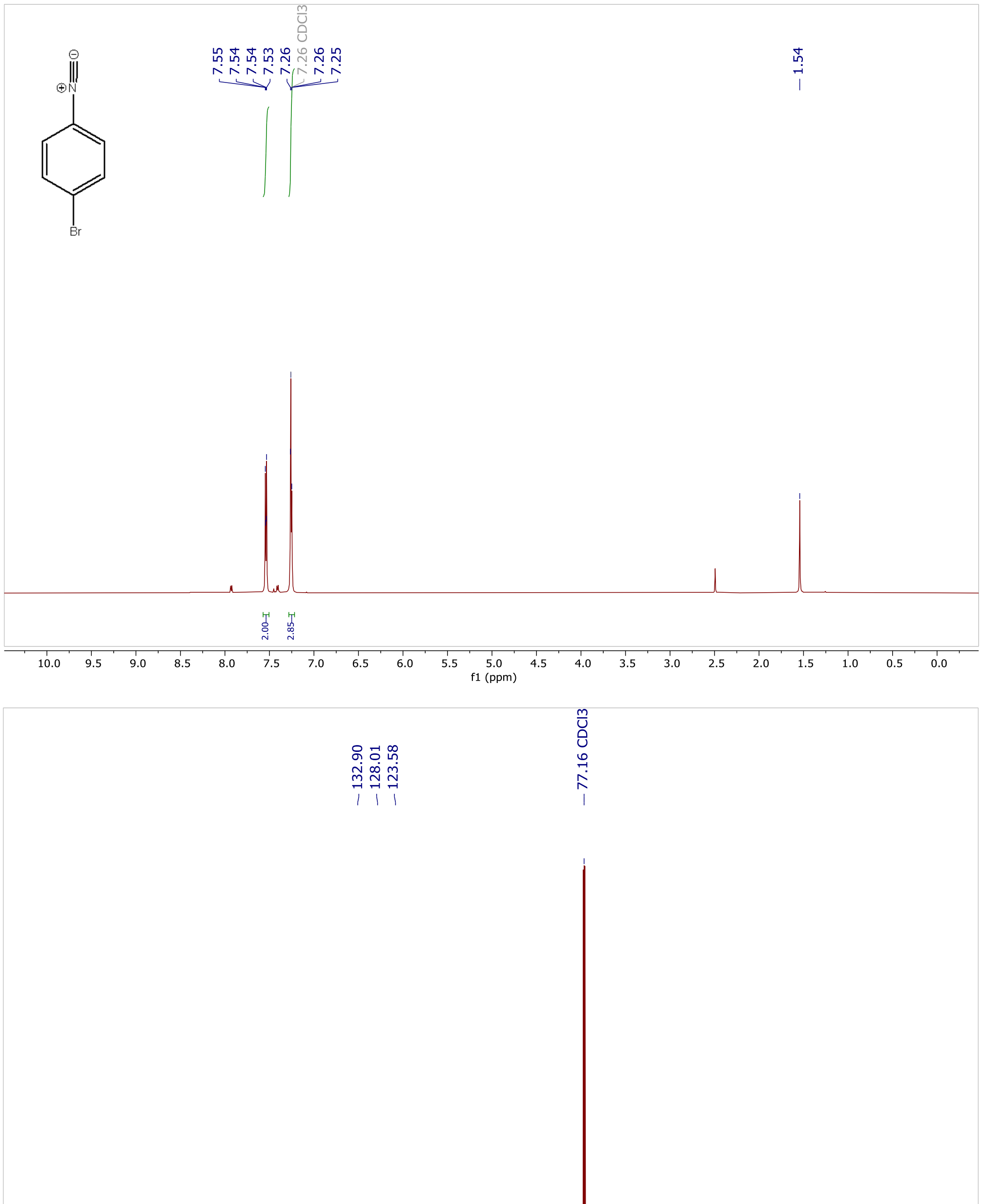
4. Spectra



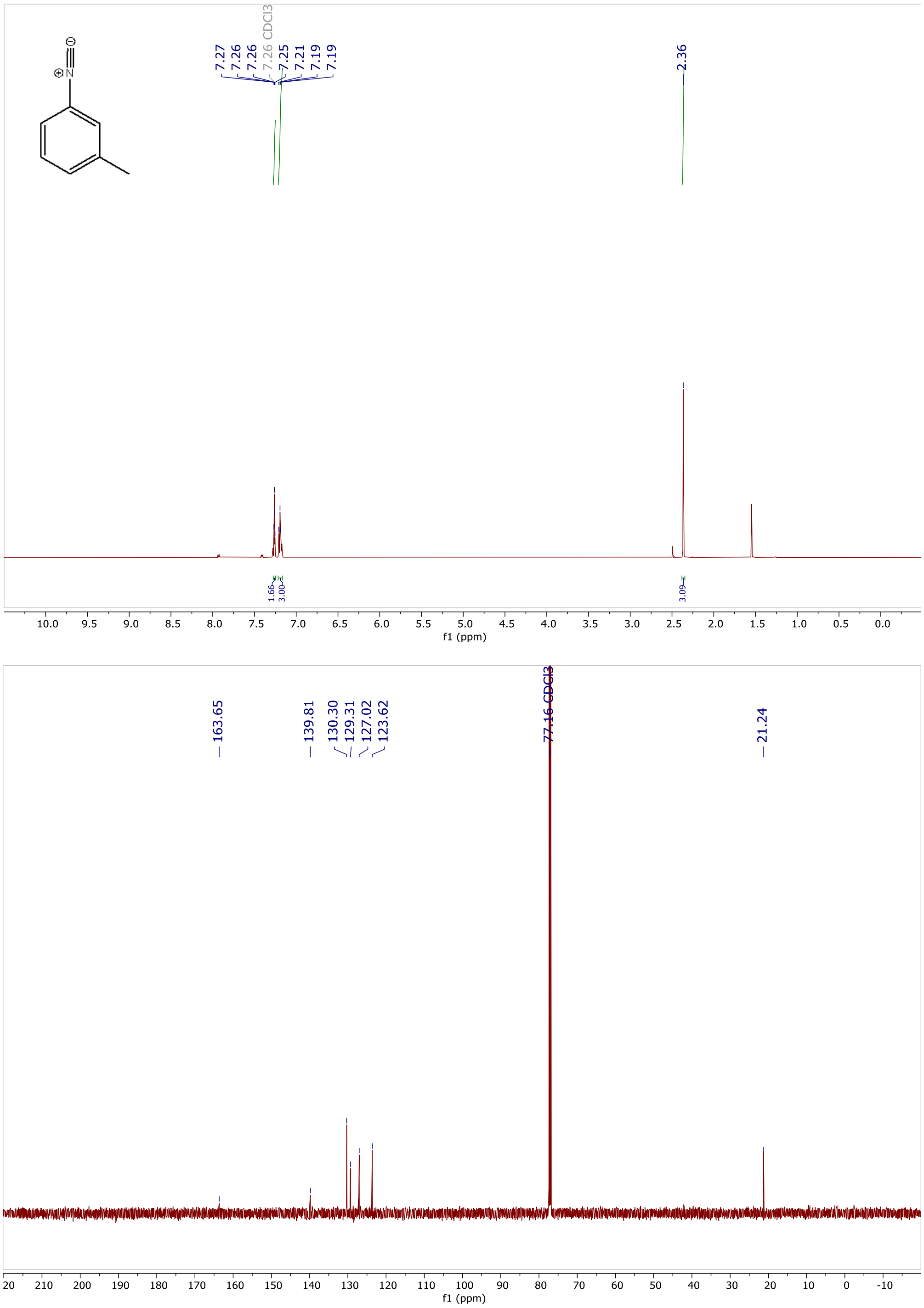
^{1}H and ^{13}C of Isocyanide **2a**



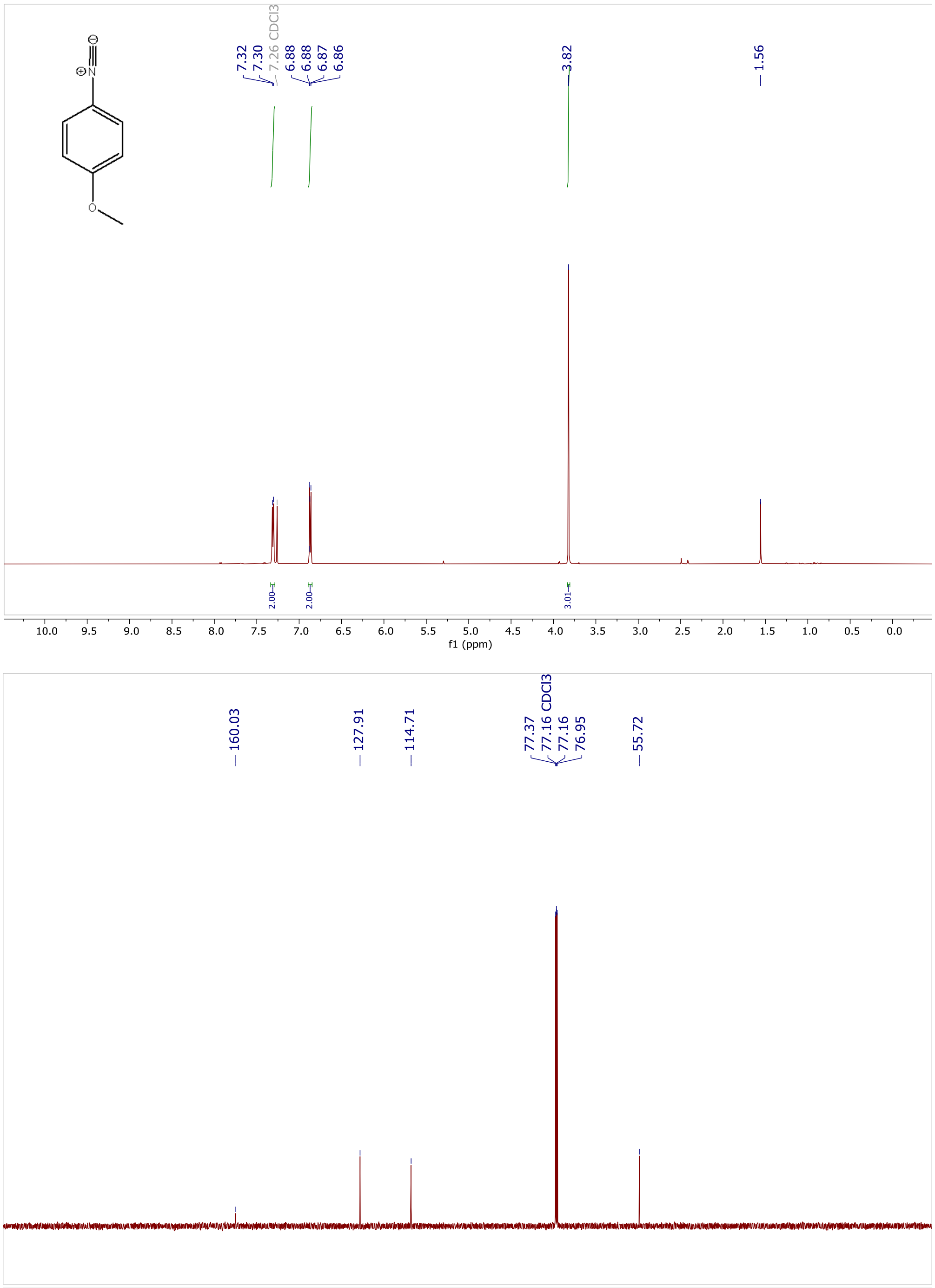
^{1}H and ^{13}C of Isocyanide **2b**



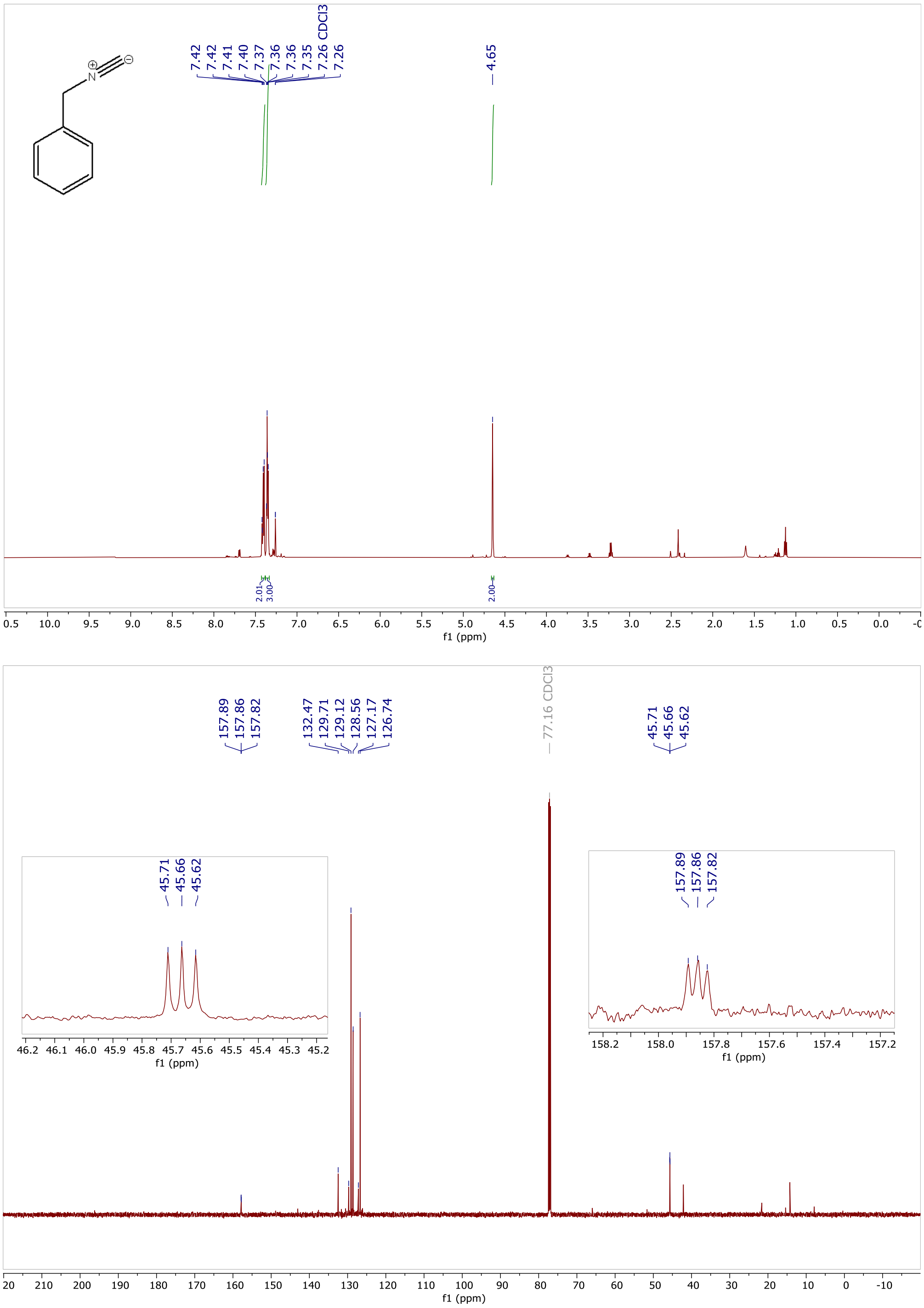
^{1}H and ^{13}C of Isocyanide **2c**



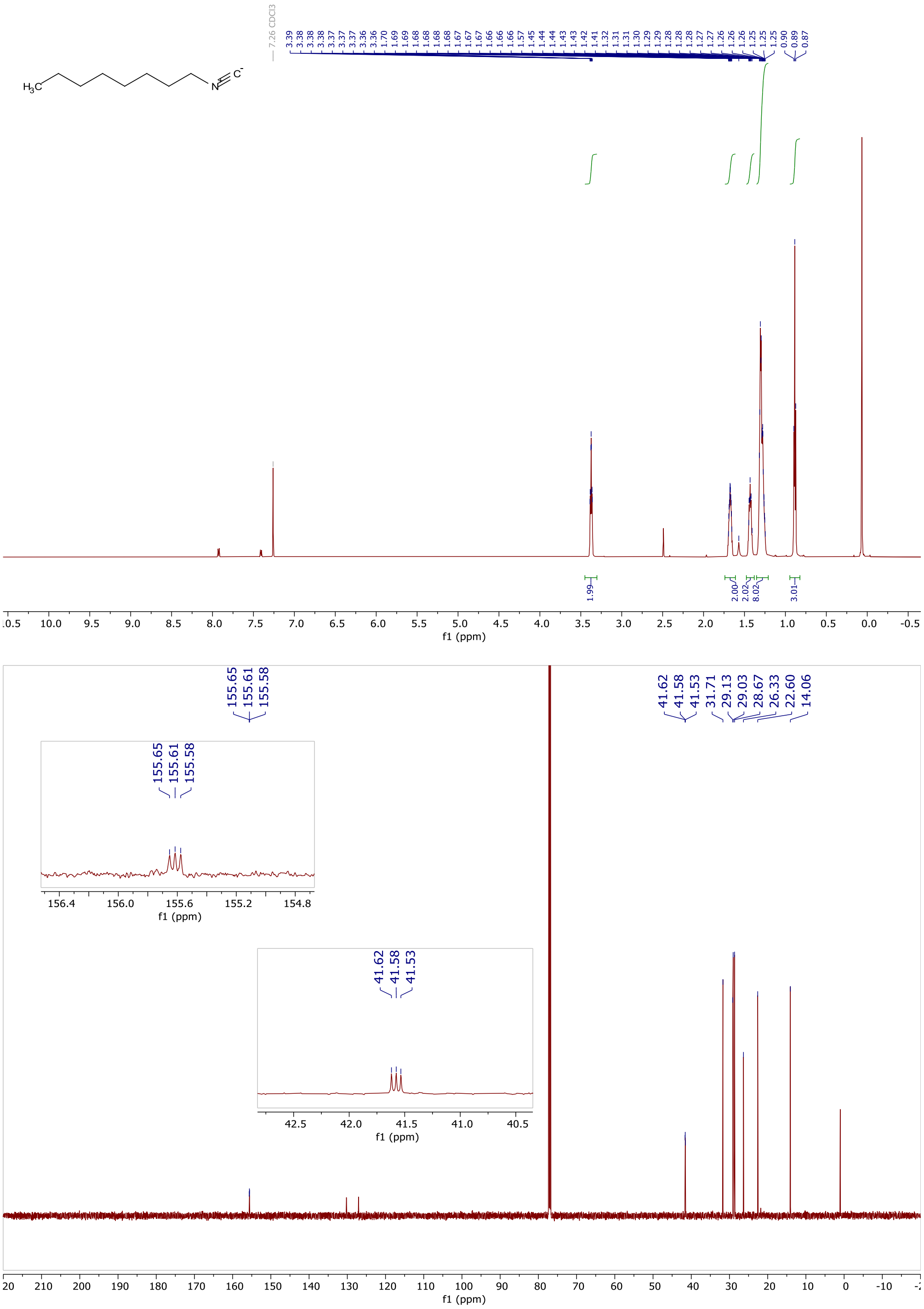
^{1}H and ^{13}C of Isocyanide **2d**



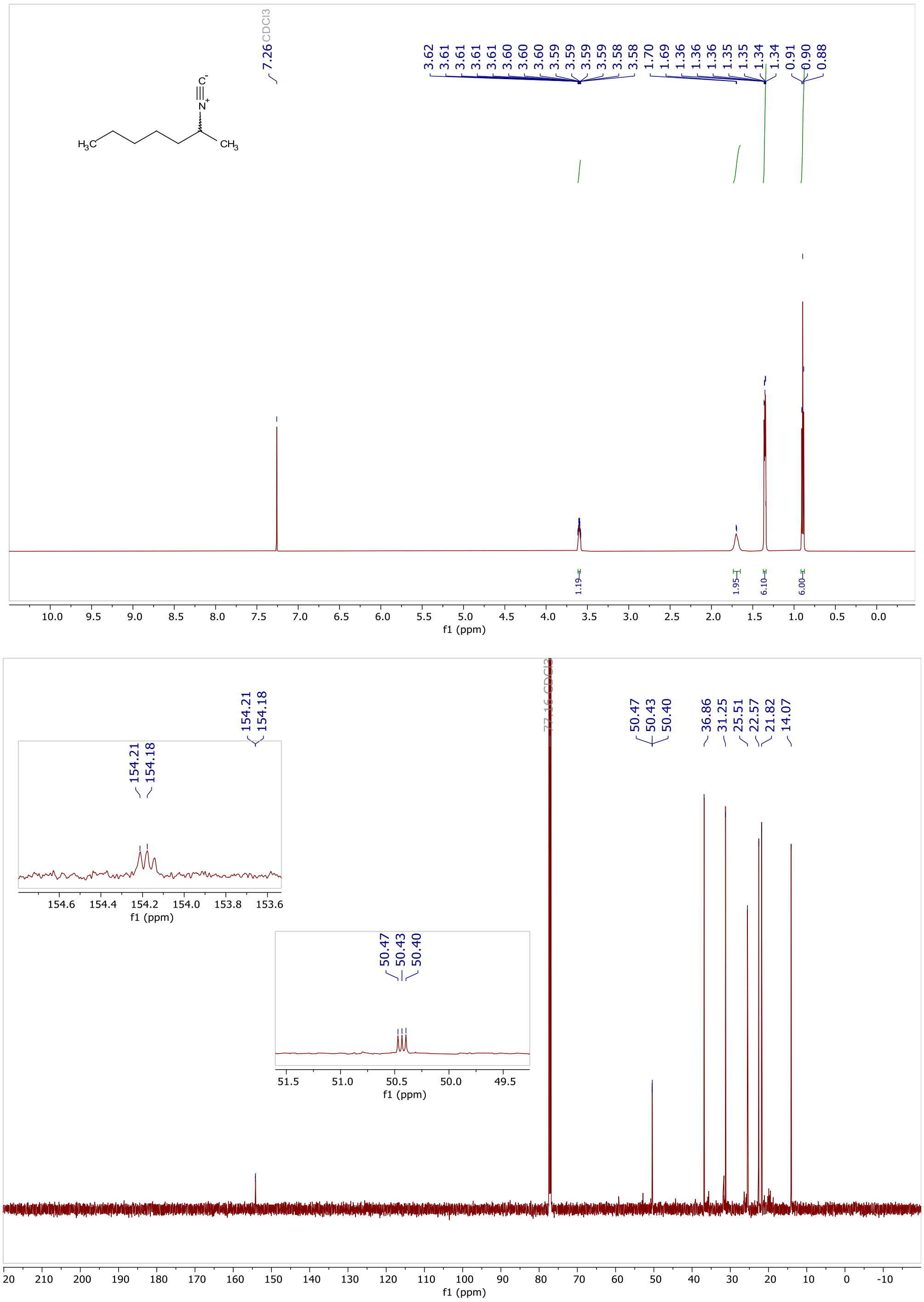
^{1}H and ^{13}C of Isocyanide **2e**



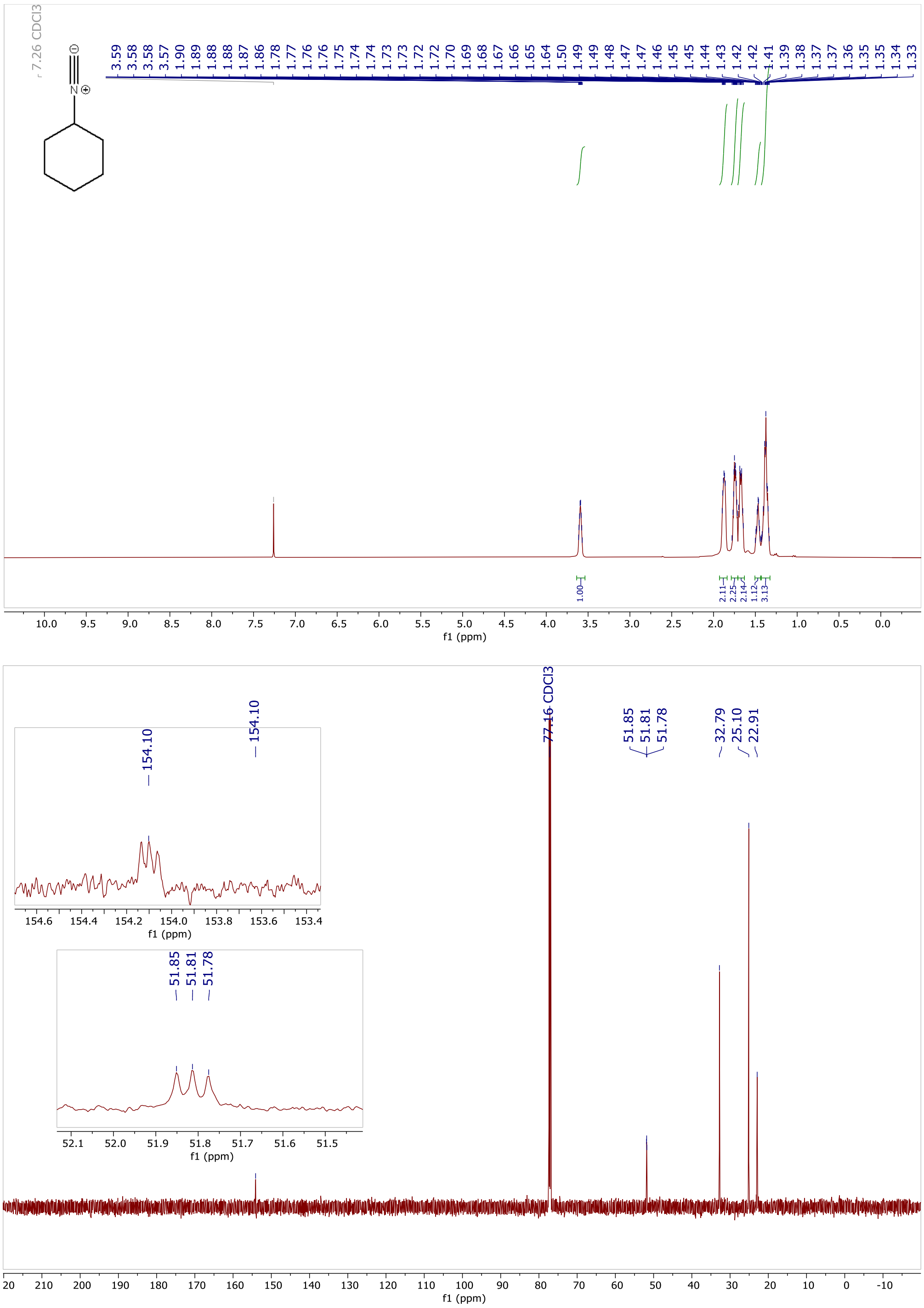
^{1}H and ^{13}C of Isocyanide **2f**



^{1}H and ^{13}C of Isocyanide **2g**



^{1}H and ^{13}C of Isocyanide **2h**



^{1}H and ^{13}C of Isocyanide **2i**