Rotational Spectra of Five Cyano Derivatives of Fluorene

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Contents

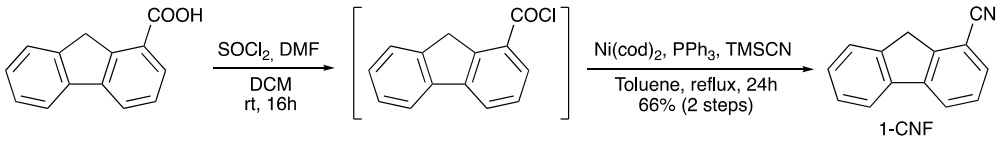
1. Synthesis of cyanofluorenes: experimental details and spectroscopic data

1.1. General methods

All reactions were carried out under argon using oven-dried glassware. Anhydrous DMSO, CH_2Cl_2, Et_2O, toluene and DMF were taken from a MBraun SPS-800 Solvent Purification System. Commercial reagents were purchased from ABCR GmbH, Sigma-Aldrich or Fluorochem, and were used without further purification. TLC was performed on Merck silica gel 60 F_{254} and chromatograms were visualized with UV light (254 and 360 nm). Column chromatography was performed on Merck silica gel 60 (ASTM 230-400 mesh). Centrifugation was performed in a Hettich EBA21 centrifuge. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz (Varian Mercury-300 instrument), 400 and 101 MHz (Varian Inova 400) or 500 and 125 MHz (Varian Inova 500) respectively. Low resolution mass spectra (EI) were obtained at 70 eV on a HP-5988A instrument, while high-resolution mass spectra (HRMS) were obtained on a Micromass Autospec spectrometer. Atmospheric pressure chemical ionisation (APCI) HRMS were obtained on a Bruker Microtof, using either Direct Inlet Probe (DIP) or Flow Injection Analysis (FIA) for sample introduction.

1.2. Experimental procedures and characterization data.

1.2.1. Synthesis of 9*H*-fluorene-1-carbonitrile (1-cyanofluorene, 1-CNF).

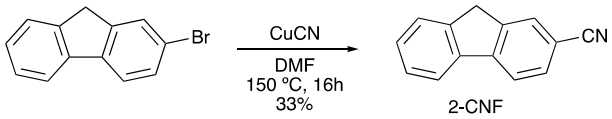


The compound was prepared accorded to an adapted literature procedure.[1]

In an oved-dried 25 mL double neck round bottom flask 9*H*-fluorene-1-carboxylic acid (504 mg, 2.39 mmol) was added. The flask was purged with Ar and then anhydrous CH_2Cl_2 (9.6 mL), DMF (0.05 mL) and $SOCl_2$ (0.350 mL, 4.795 mmol) were added. The mixture was stirred at room temperature overnight and then, solvent, and unreacted $SOCl_2$ were removed under reduced pressure. The crude acyl chloride was used without any further purification. $Ni(cod)_2$ (6.6 mg, 0.024 mmol, 10 mol %) and PPh_3 (12.6 mg, 0.048 mmol, 20 mol%) were added and the flask was purged with Ar. The mixture was dissolved in 12 mL of toluene, TMSCN (0.360 mL, 2.877 mmol) was added and the resulting mixture was stirred under reflux for 24h. Et_3N was added to quench the remaining TMSCN and, subsequently, organics were removed under reduced pressure and the product was purified by column chromatography on SiO_2 (hexane/CH_2Cl_2, 4:1) yielding 1-CNF

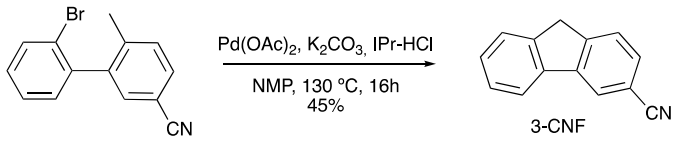
as pale yellow solid (305 mg, 66%). [1] **H-NMR** (300 MHz, $CDCl_3$) δ: 7.99 – 7.90 (d, *J* = 6.6 1H), 7.78 (d, *J* = 6.6, 1H), 7.62 – 7.53 (m, 2H), 7.50 – 7.34 (m, 3H), 4.02 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 146.98 (C), 142.91 (C), 142.23 (C), 139.95 (C), 129.65 (CH), 128.08 (CH), 127.61 (CH), 127.29 (CH), 125.28 (CH), 123.92 (CH), 120.37 (CH), 117.64 (C), 109.33 (C), 36.64 (CH_2). **HRMS (APCI-DIP-TOF)** for $C_{14}H_9N$ ([M+H$^+$]) Calcd.: 191.0808; Found: 191.0805.

1.2.2. Synthesis of 9*H*-fluorene-2-carbonitrile (2-cyanofluorene, 2-CNF).



To a solution of 2-bromo-9*H*-fluorene (1 g, 4.08 mmol) in dry DMF (40.8 mL), cuprous cyanide (1.462 g, 16.31 mmol) was added, and the mixture was heated at 150 ºC for 16h. Then, aqueous ammonia was added and the product was extracted with CH_2Cl_2 (3x15 mL). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (Hexane/ EtOAc, 4:1) yielding 2-CNF as a pale yellow solid (257 mg, 33%). [1] **H-NMR** (300 MHz, $CDCl_3$) δ: 7.88 – 7.80 (m, 3H), 7.67 (m, 1H), 7.60 (m, 1H), 7.46 – 7.37 (m, 2H), 3.95 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 146.23 (C), 143.90 (C), 143.63 (C), 139.91 (C), 131.18 (CH), 128.62 (CH), 128.57 (CH), 127.30 (CH), 125.31 (CH), 120.96 (CH), 120.37 (CH), 119.62 (C), 109.72 (C), 36.77 (CH_2). **HRMS (APCI-DIP-TOF)** for $C_{14}H_9N$ ([M+H$^+$]) Calcd.: 191.0808; Found: 191.0802.

1.2.3. Synthesis of 9*H*-fluorene-3-carbonitrile (3-cyanofluorene, 3-CNF).

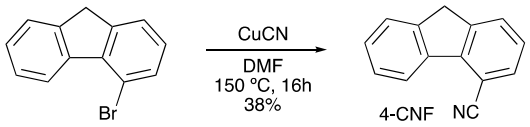


The compound was prepared accorded to an adapted literature procedure.[2]

2'-Bromo-6-methyl-[1,1'-biphenyl]-3-carbonitrile (720 mg, 2.64 mmol), K_2CO_3 (365.6 mg, 2.64 mmol), $Pd(OAc)_2$ (11.9 mg, 0.053 mmol), IPr-HCl (45 mg, 0.106 mmol) were placed in a 25 mL Schlenk tube and purged with Ar. Then, dry NMP (8 mL) was added and the mixture was stirred at 150ºC for 16h. After that, the solution was extracted with hexane and washed with water. The organic phase was dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The

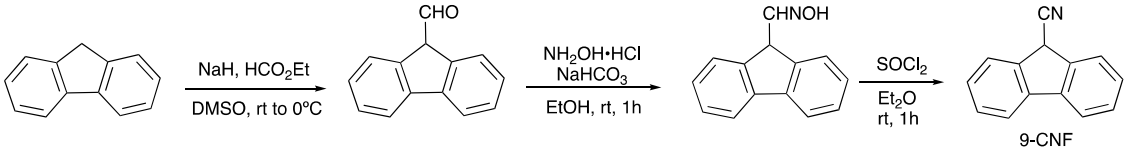
residue was purified by column chromatography on silica gel (Hexane/ EtOAc, 4:1) yielding 3-CNF as a pale yellow solid (230 mg, 45%).[1] **H-NMR** (300 MHz, $CDCl_3$) δ: 8.03 (s, 1H), 7.81 (d, *J* = 7.6, 1H), 7.64 – 7.57 (m, 3H), 7.46 – 7.36 (m, 2H), 3.98 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 148.12 (C), 142.99 (C), 142.76 (C), 139.69 (C), 130.31 (CH), 128.14 (CH), 127.30 (CH), 125.78 (CH), 125.23 (CH), 123.42 (CH), 120.43 (CH), 119.42 (C), 110.77 (C), 37.32 (CH_2). **HRMS (APCI-DIP-TOF)** for $C_{14}H_9N$ ([M+H$^+$]) Calcd.: 191.0808; Found: 191.0814.

1.2.4. Synthesis of 9*H*-fluorene-4-carbonitrile (4-cyanofluorene, 4-CNF).



To a solution of 4-bromo-9*H*-fluorene (0.5 g, 2.04 mmol) in dry DMF (20.4 mL), cuprous cyanide (0.73 g, 8.159 mmol) was added, and the mixture was heated at 150 ºC for 16h. Then, aqueous ammonia was added and the product was extracted with CH_2Cl_2 (3x15 mL). The combined organic layers were dried with Na_2SO_4, filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography on silica gel (Hexane/ EtOAc, 4:1) yielding 4-CNF as a pale yellow solid (147 mg, 38%). [1] **H-NMR** (300 MHz, $CDCl_3$) δ: 8.49 (d, *J* = 7.6, 1H), 7.75 (d, *J* = 7.6, 1H), 7.67 – 7.58 (m, 2H), 7.51 – 7.40 (m, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 3.93 (s, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 144.47 (C), 143.74 (C), 143.22 (C), 138.94 (C), 131.44 (CH), 129.21 (CH), 128.57 (CH), 127.42 (CH), 126.50 (CH), 125.02 (CH), 122.42 (CH), 118.44 (C), 104.37 (C), 36.62 (CH_2). **HRMS (APCI-DIP-TOF)** for $C_{14}H_9N$ ([M+H$^+$]) Calcd.: 191.0730; Found: 191.0722.

1.2.5. Synthesis of 9*H*-fluorene-9-carbonitrile (9-cyanofluorene, 9-CNF).

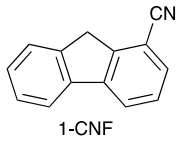


The compound was prepared accorded to an adapted literature procedure.[3]

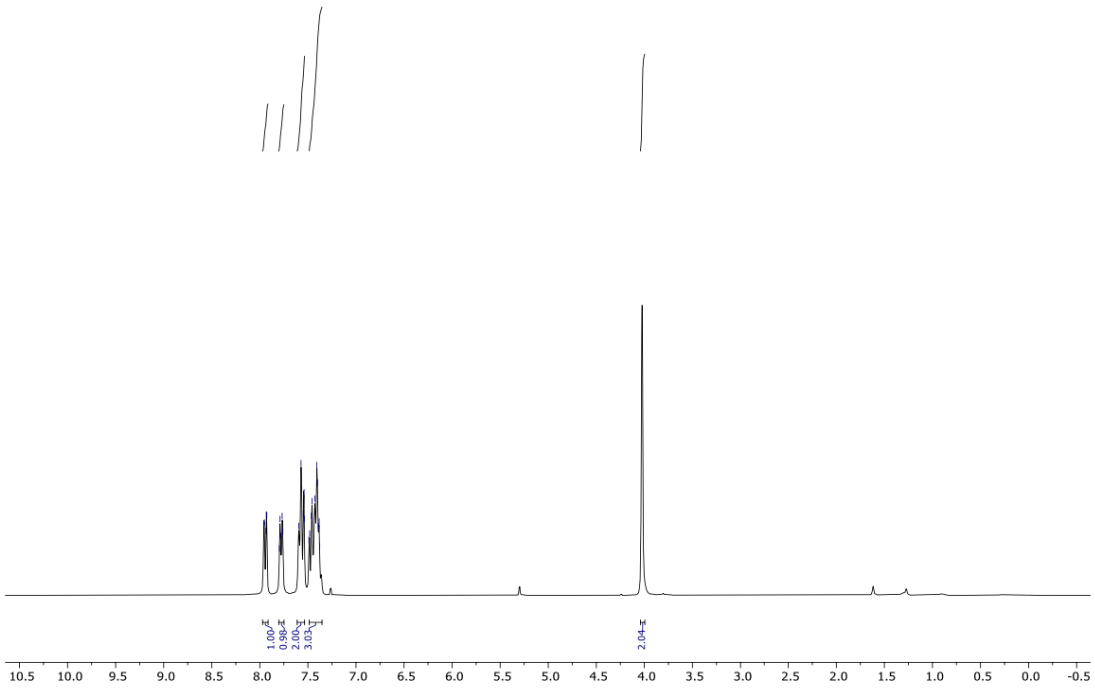
To a stirred solution of fluorene (2 g, 12.03 mmol) in dry DMSO (40.1) mL, NaH (5.29 g, 132.35 mmol, 60% dispersion in mineral oil) was added and stirred at room temperature for 30 minutes.

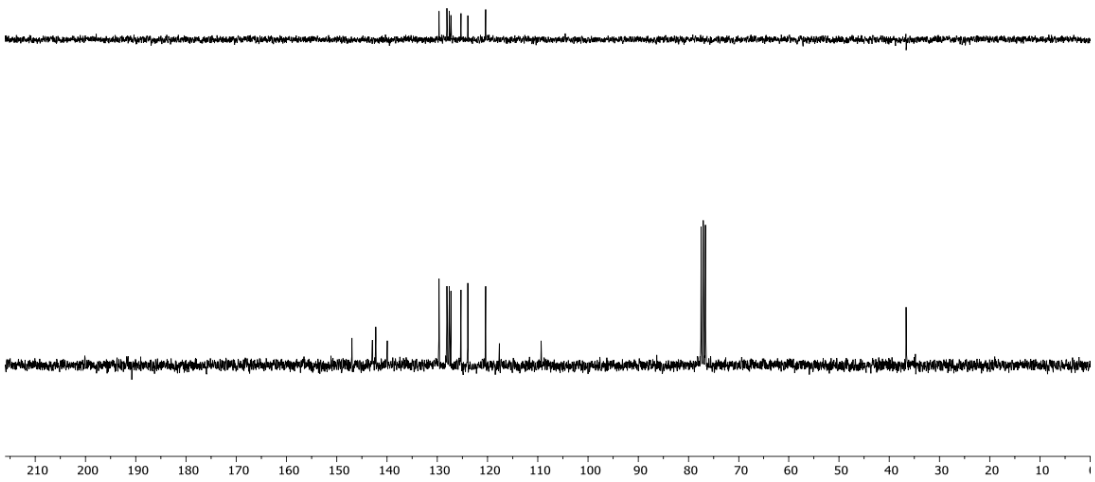
Then, ethyl formiate (6 mL, 74.6 mmol) was added at 0ºC and stirred overnight allowing the mixture to reach rt. The reaction was quenched with H_2O and the pH adjusted to 1 with HCl. Organics were extracted with Et_2O, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude aldehyde was mixed with NH_2OH-HCl (1.25 g, 18.04 mmol) and $NaHCO_3$ (2.02 g, 24.06 mmol) in 60 mL of EtOH and stirred at room temperature for 2h. The reaction crude was filtered, and the filtrate was concentrated under reduced pressure. The crude oxime was dissolved in 40 mL of Et_2O and $SOCl_2$ (0.87 mL, 12.03 mmol) was added, and the mixture stirred overnight. Then, H_2O was added, and organics extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude compound was purified by column chromatography on SiO_2 (hexane/CH_2Cl_2, 4:1) yielding 9-CNF as a pale yellow solid (1.23g, 56%). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ: 7.80 – 7.77 (m, 2H), 7.74 – 7.70 (m, 2H), 7.53 – 7.46 (m, 2H), 7.41 (td, J = 7.5, 1.3 Hz, 2H), 4.93 (s, 1H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ: 140.89 (2xC), 137.85 (2xC), 129.28 (2xCH), 128.18 (2xCH), 125.10 (2xCH), 120.58 (2xCH), 118.10 (C), 37.07 (CH). **HRMS (APCI-DIP-TOF)** for $C_{14}H_9N$ ([M^+]) Calcd.: 191.0730; Found: 191.0729.

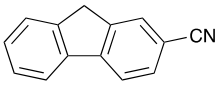
2. ^{1}H and ^{13}C NMR spectra



1-CNF



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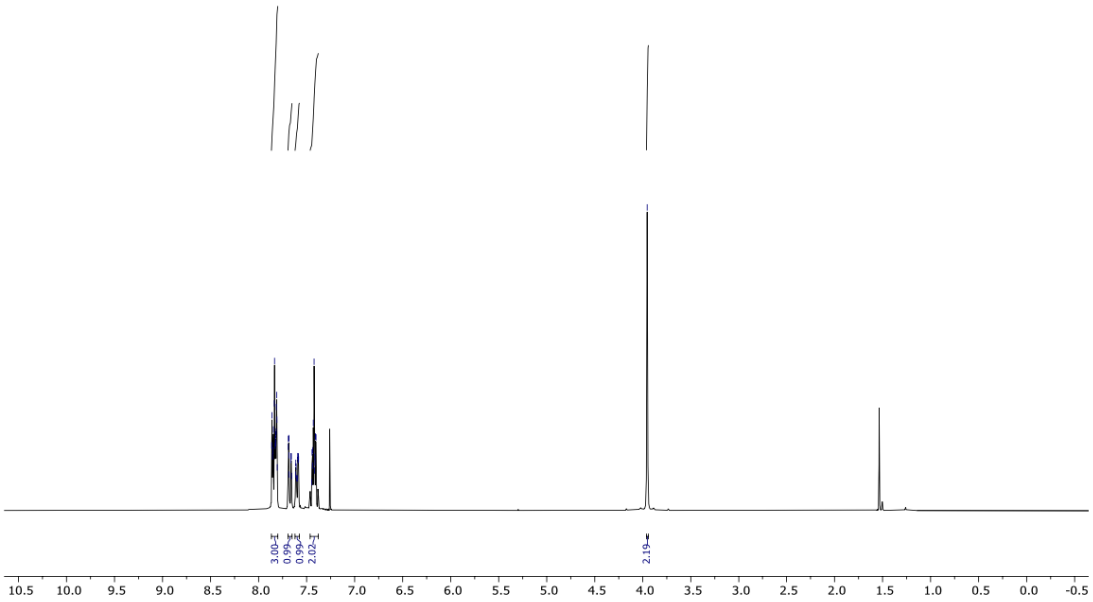
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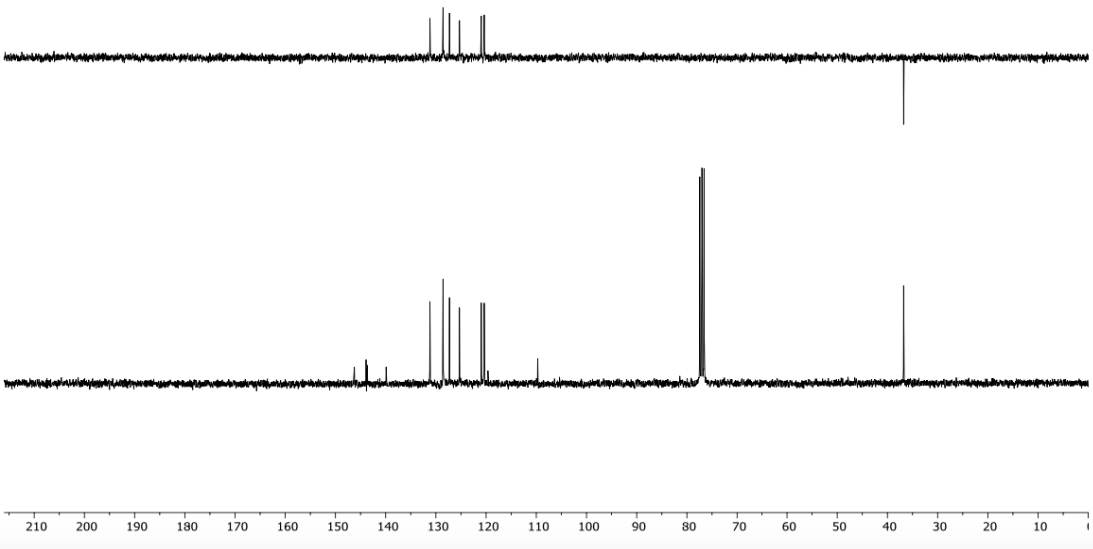
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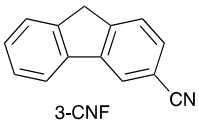
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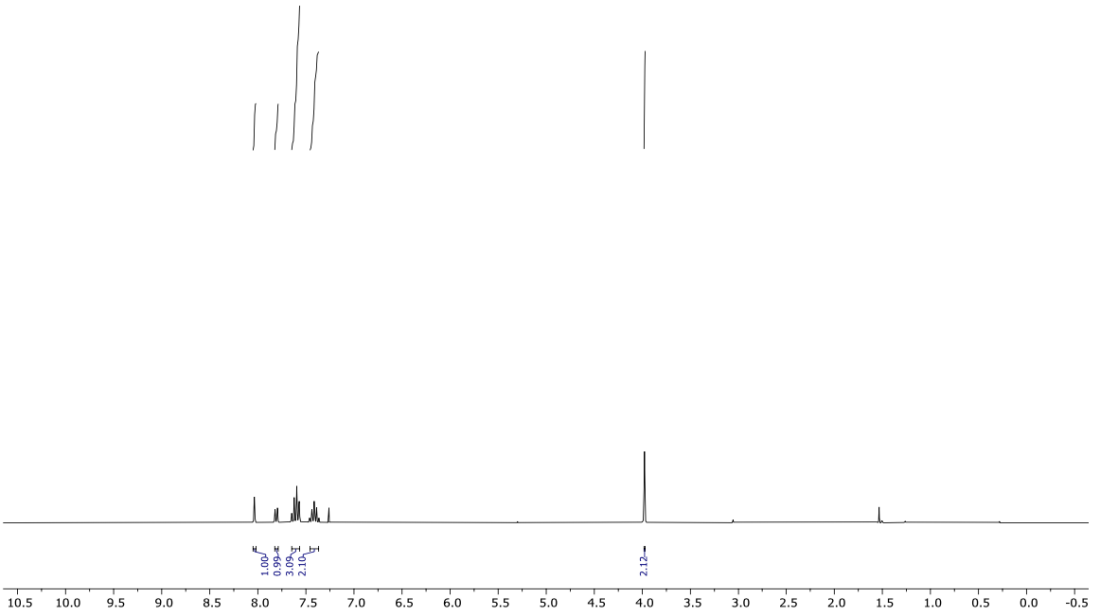
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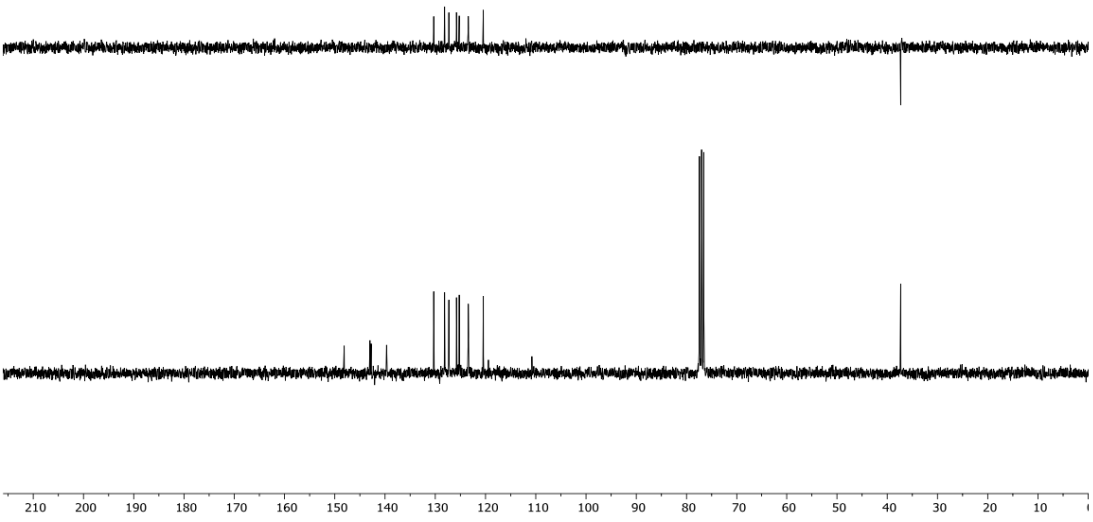
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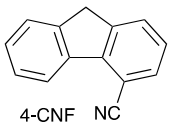
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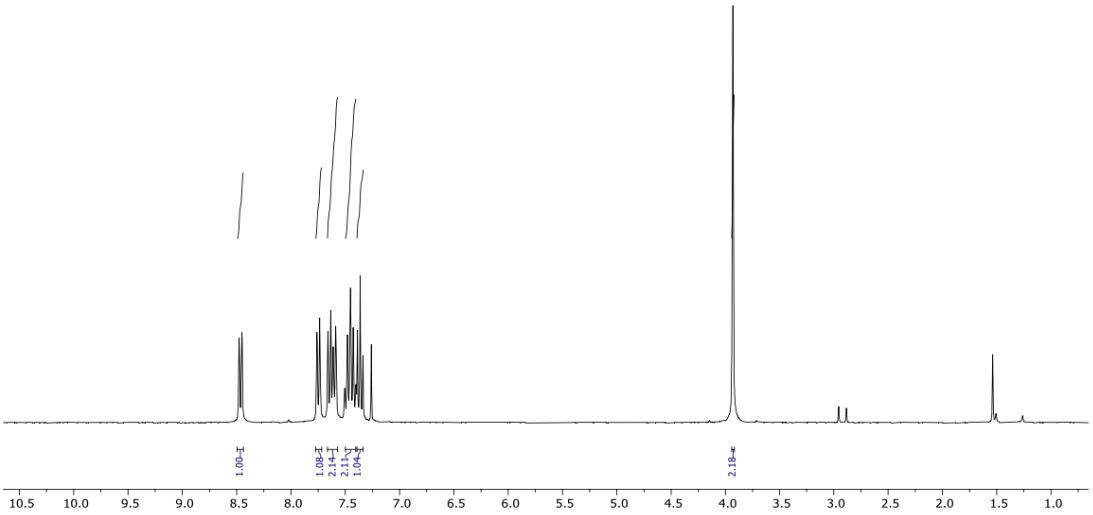
4-CNF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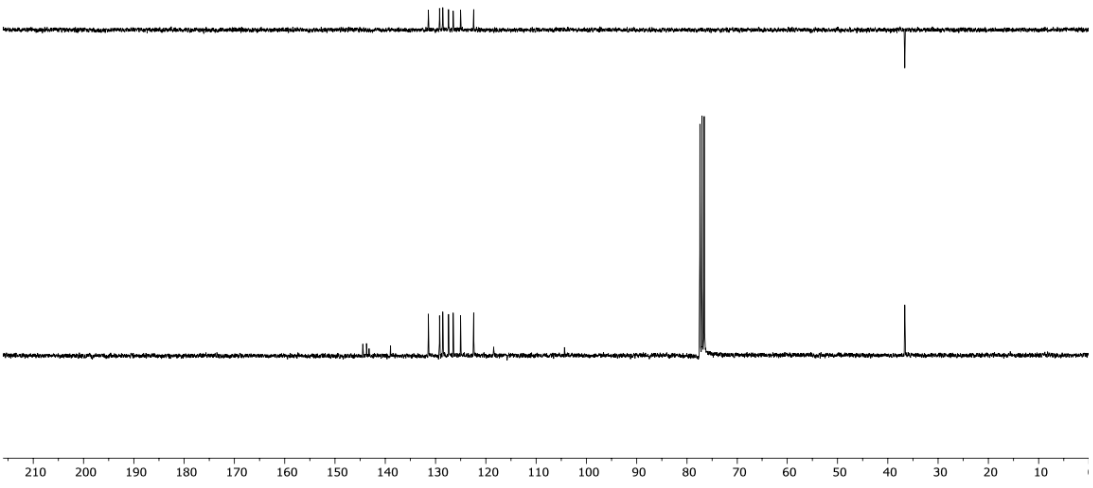
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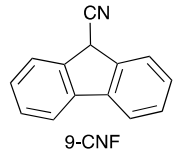
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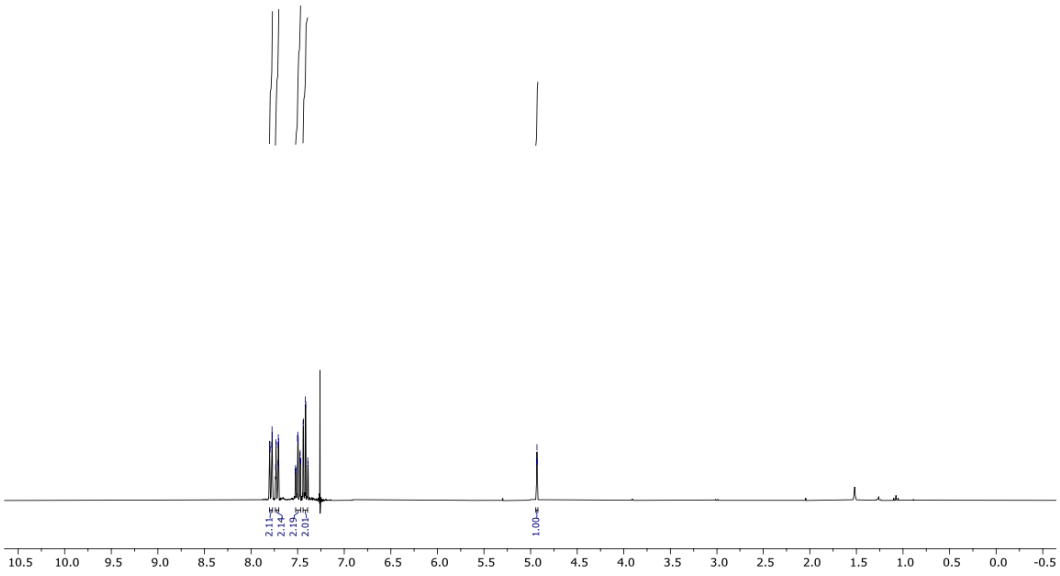
9-CNF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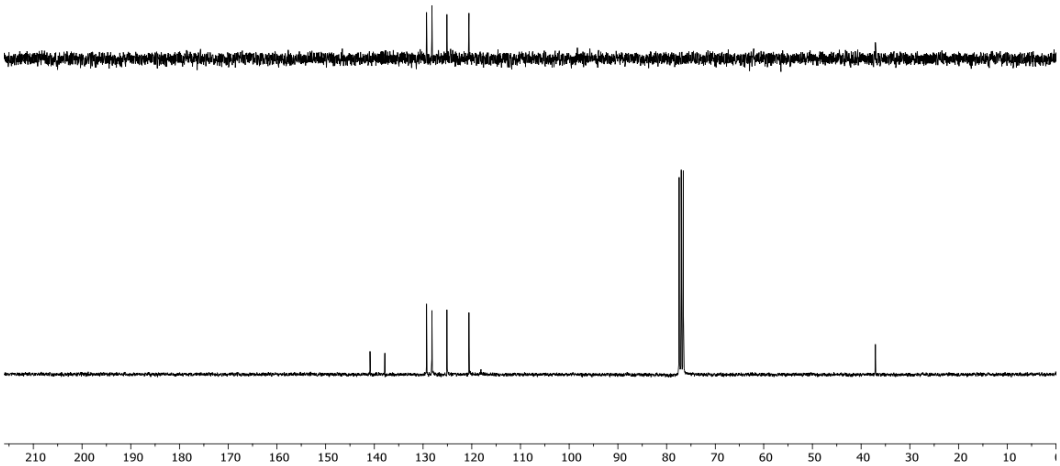
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3. X. Hou, Z. Ge. T. Wang, W. Guo J. Wu, J. Cui, C. Lai, R. Li. Synthesis and Structure-Activity Relationships of A Novel Class of Dithiocarbamic Acid Esters as Anticancer Agent, *Arch. Pharm. Chem. Life Sci*., 2011, **11**, 320–332.