Probing the Hydrolytic Reactivity of 2-Difluoromethyl Pyrroles

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Supporting Information

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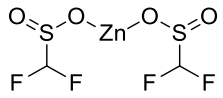
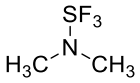
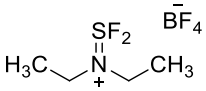
Structures of fluorinating agents



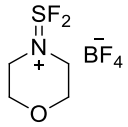
Zinc difluoromethanesulfinate (ZnDFMS)



(Dimethylamino)sulfur trifluoride (DAST)



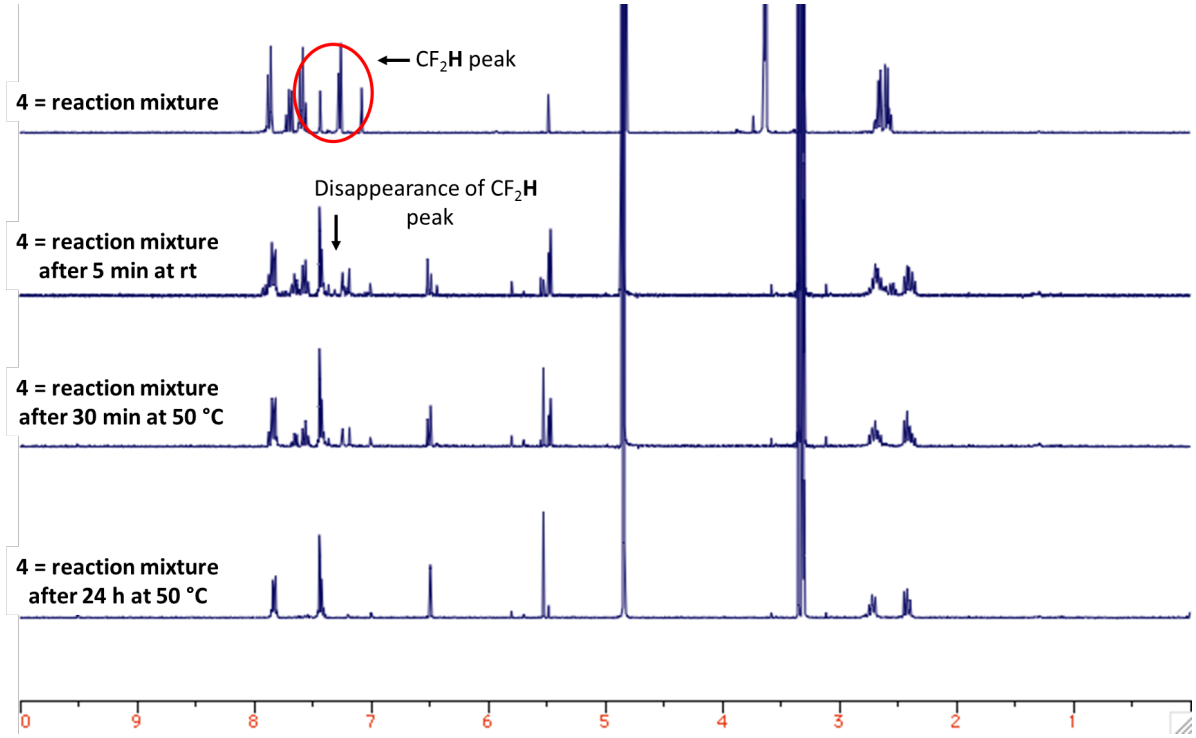
(Diethylamino)difluorosulfonium tetrafluoroborate
(Xtalfluor-E)



Difluoro(morpholino)sulfonium tetrafluoroborate
(Xtalfluor-M)

NMR-study of deprotection of 4

(A)



(B)

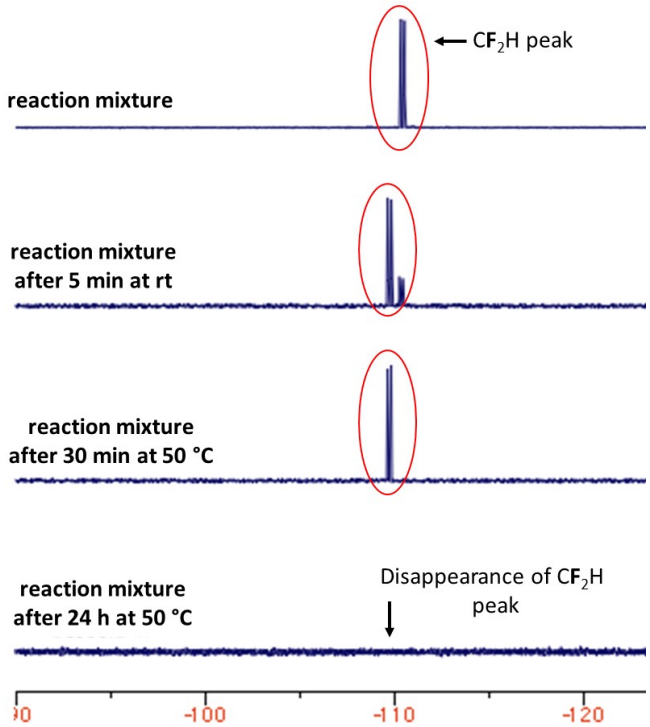
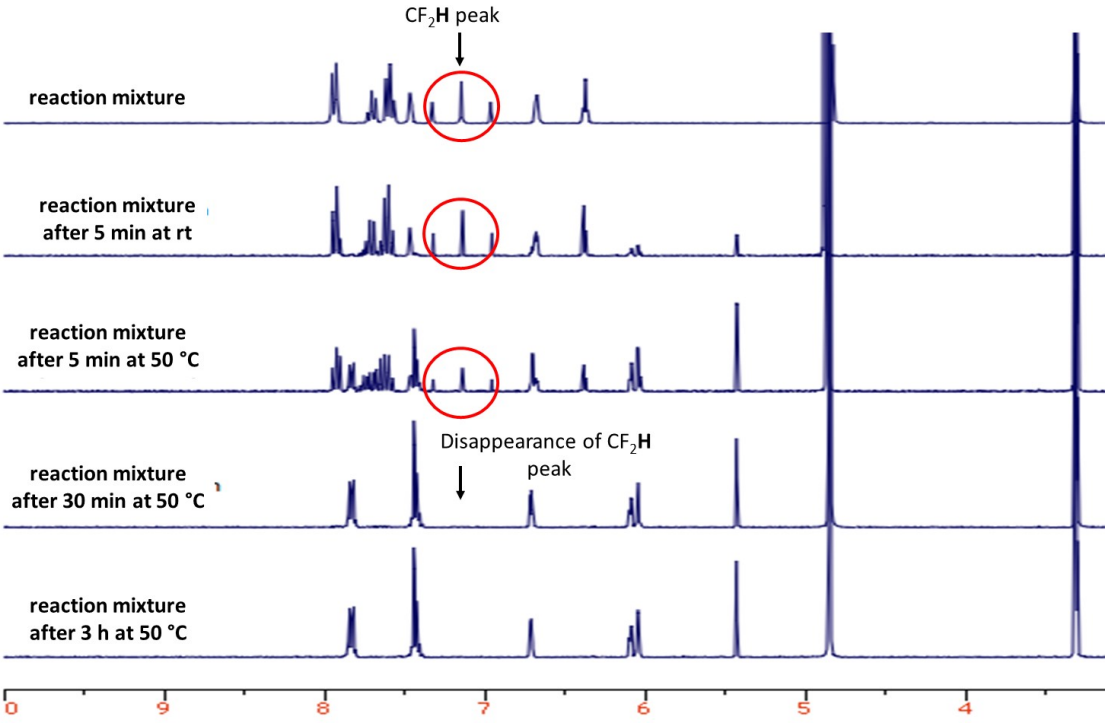


Figure 1. (A) ^{1}H NMR (MeOD, 300 MHz); (B) ^{19}F NMR (MeOD, 470 MHz).

NMR-study of deprotection of 10

(A)



(B)

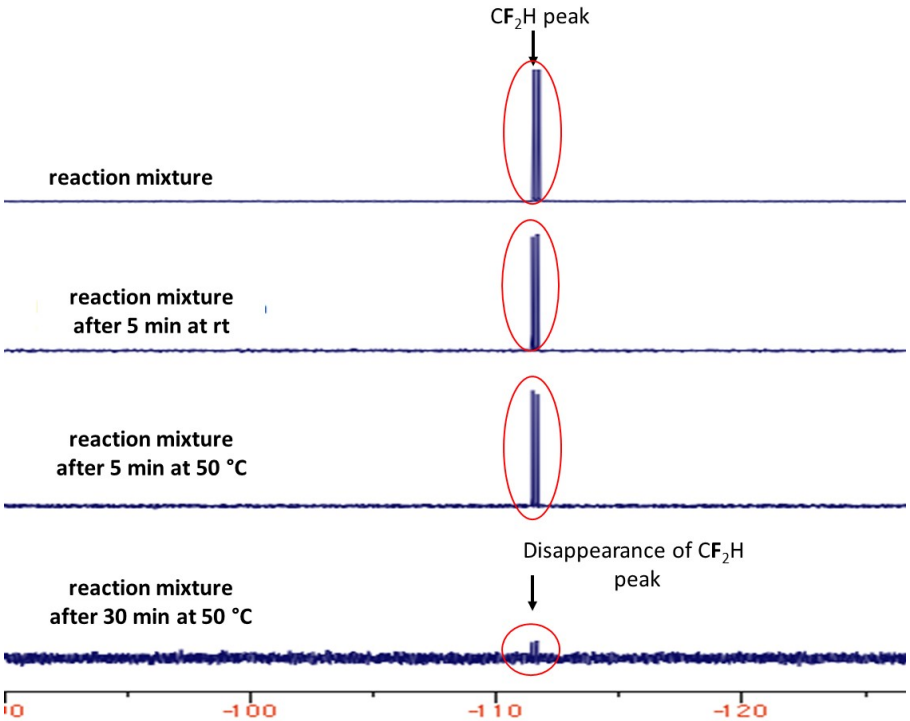


Figure 2. (A) ^{1}H NMR (MeOD, 500 MHz); (B) ^{19}F NMR (MeOD, 470 MHz).

General procedure for studying the *N*-deprotection of 19a-e

The deprotection of *N*-2-nosyl α-difluoromethyl pyrroles **19a-e** was recorded in a Varian CARY 100 BIO UV-Visible spectrophotometer. The cuvette holders were equipped with a circulating cooling bath set at -10 ºC. A steady flow of dry N_2 gas was piped into the sample chamber. The cuvette holders were cooled for 3 hours before testing their refrigeration capacity on a blank sample. It was found that the temperature of a blank sample containing CH_3CN took 10 minutes to equilibrate to 0 ºC.

Cuvettes were equipped with a septum, sealed using both Teflon tape on the thread of the cuvette and parafilm around the septum cover. The sealed cuvette was flushed with N_2 for 10 minutes, and then charged with 3 mL of an anhydrous solution of the pyrrole (1 equiv.) and PhSH (400 equiv.) in CH_3CN. The charged cuvette was cooled to 0 ºC over 10 minutes, and manual baseline correction was performed. The deprotection reaction was initiated by the injection of 0.5 mL of a stock solution of anhydrous NEt_3 (560 equiv.) through the septum of the cuvette. A stock solution of anhydrous NEt_3 was prepared using NEt_3 (2.19 mL, 1.57×10^{-2} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2. The solution was bubbled with N_2 for 10 minutes.

The reaction was monitored for 60 seconds at a wavelength of 368 nm, collecting data points at 1×10^{-1} second intervals. The concentration of deprotected pyrrole (**19a-e**) forming was calculated from each absorbance value over time, to produce rate constants. UV-absorbing compounds **14** and **17** were treated as forming at the same rate with a combined bimolecular extinction coefficient of 5850 L mol^{-1} cm^{-1}. Kinetic analysis was run in triplicates.

Table 1. Theoretical change in absorbance at 368 nm produced by 100% conversion of fluorinated *N*-2-nosyl protected pyrroles to 14 compared to the experimental absorbance.

Compound	Substituent (R)	Final concentration of pyrrole (M)	Expected absorbance by 100% conversion to 14	Average[a] final absorbance at Equilibrium (Discrepancy)	% Overproduction
19a	CF_3	4.033×10^{-4}	1.613	2.378 (0.765)	47
19b	F	4.109×10^{-4}	1.644	2.456 (0.812)	49
19c	H	4.078×10^{-4}	1.631	2.370 (0.739)	45
19d	CH_3	4.150×10^{-4}	1.660	2.360 (0.700)	42
19e	$OOCH_3$	3.568×10^{-4}	1.427	2.094 (0.667)	47

[a]Average absorbance reading at equilibrium in the duplicated experiments.

In order to account for the overproduction the corrected extinction coefficients were calculated using the Beer-Lambert equation:

$$A = c\,\ell\,\mathcal{E}$$

A = absorbance; c = concentration (M); l = pathlength (cm); ε = extinction coefficient ($Lmol^{-1}cm^{-1}$)

Table 2. Corrected Extinction Coefficients of the Multichromophore System at 368 nm

R	Expected Final Concentration of [14] (M)	Average Total Absorbance Achieved at Equilibrium	Corrected Extinction Coefficient of the Multichromophore System at Equilibrium (ε)
CF_3	4.033×10^{-4}	2.378	Applying Beer-Lambert to obtain corrected extinction coefficient $\varepsilon = \frac{2.378}{(1\ cm)(4.033X10^{-4})}$ =5896 L mol^{-1} cm^{-1}
F	4.109×10^{-4}	2.456	5977 L mol^{-1} cm^{-1}
H	4.078×10^{-4}	2.370	5812 L mol^{-1} cm^{-1}
CH_3	4.150×10^{-4}	2.360	5687 L mol^{-1} cm^{-1}
OCH_3	3.568×10^{-4}	2.094	5869 L mol^{-1} cm^{-1}

Consequently, the Beer-Lambert law was used to transform the absorbance readings to the concentration of *N*-deprotected α-difluoromethyl pyrroles **24** from the corrected extinction coefficients. The product concentration was then applied to the first order rate equation:

$$[P]_t = -([P]_\infty - [P]_o)e^{-kt} + [P]_\infty$$

[P] = concentration of product; $[P]_t$= concentration of product at time "t"; $[P]_\infty$= concentration of product at equilibrium; $[P]_o$= concentration of product at time 0

First order rate equations are usually based on the consumption of starting material, rather than the production of product. Therefore the above equation derives from:

$$[SM]_t = [SM]_0 e^{-kt}$$

[SM] = concentration of starting material; $[SM]$ = concentration of starting material at time "t"; $[SM]$ = concentration of starting material at time 0

$$\ln[\mathrm{SM}]_t = -\mathrm{kt} + \ln[SM]_0$$

$$\ln[\mathrm{SM}]_t - \ln[SM]_0 = -\mathrm{kt}$$

$$\ln\frac{[SM]_t}{[SM]_0} = -\mathrm{kt}$$

$$\frac{[SM]_t}{[SM]_0} = e^{-\mathrm{kt}}$$

Since:

$$[SM]_t = [P]_\infty - [P]_t \text{ and } [SM]_0 = [P]_\infty - [P]_0$$

$$-[P]_t = ([P]_\infty - [P]_o)e^{-kt} - [P]_\infty$$

$$[P]_t = -([P]_\infty - [P]_o)e^{-kt} + [P]_\infty$$

The rate constants of each substrate are calculated using Kaleidagraph v 4.1.3 by plotting concentration of product over time.

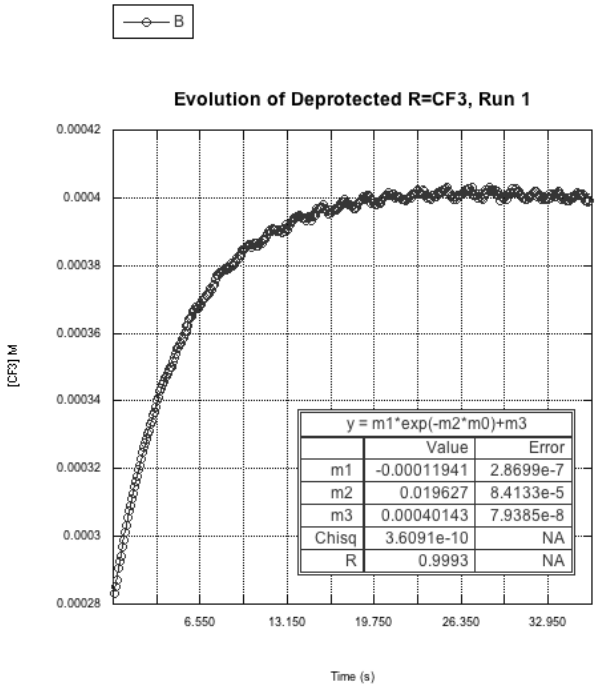
Line of Best Fit: $y = [(m1) * \exp(-m2 * m0)] + m3$

Variable 'm2' is the rate constant 'k' at the concentrations employed.

Rate constant afforded from the production of 22a, replicate #1

An initial stock was prepared using **19a** (0.021 g, 4.71×10^{-5} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2. After bubbling the solution with N_2 for 10 minutes, an aliquot of the first stock (1.000 mL, 4.71×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N_2. The second stock was then charged with PhSH (0.20 mL, 404 equiv., 1.90×10^{-3} mmol) and the remaining volume consisted of CH_3CN. After bubbling the solution with

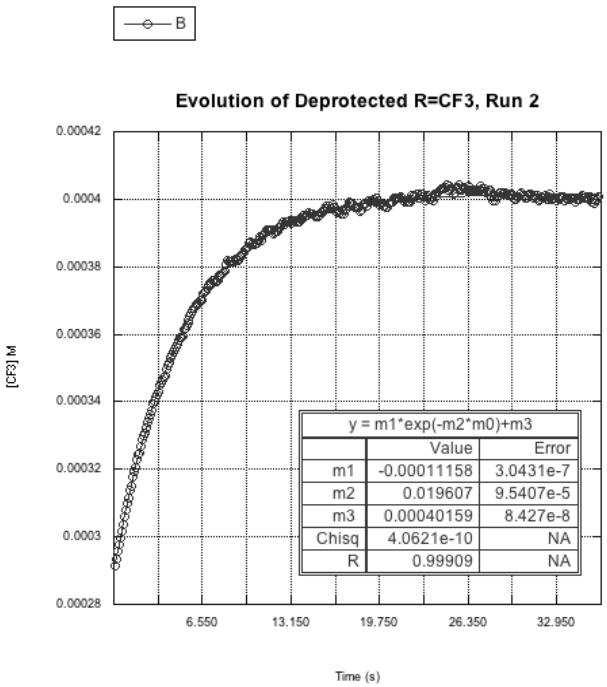
N_2 for 10 minutes, an aliquot of the second stock (3.00 mL, 1.41×10^{-6} mol of **19a**, 5.71×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.50 mL, 555 equiv., 7.84×10^{-4} mol) of the NEt_3 stock solution was added to a cuvette charged with **19a** and PhSH, resulting in a final concentration of 1.63×10^{-1} M of NEt_3, 2.24×10^{-1} M of PhSH and 4.03×10^{-4} M of **19a** in the monitored reaction. The reaction was monitored until it reached equilibrium (36 seconds).



$$k = 1.96\times10^{-2}\ s^{-1}$$

Rate constant afforded from the production of 22a, replicate #2

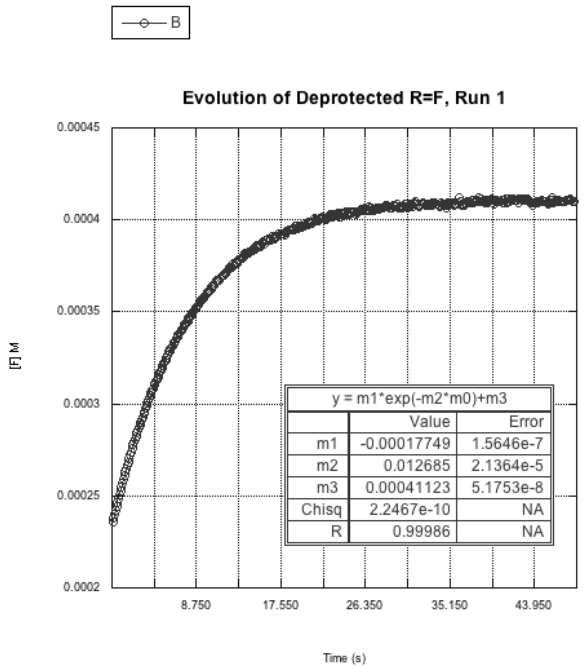
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (36 seconds).



$k = 1.96\times10^{-2}\ s^{-1}$

Rate Constant Afforded from the Production of 22b, replicate#1

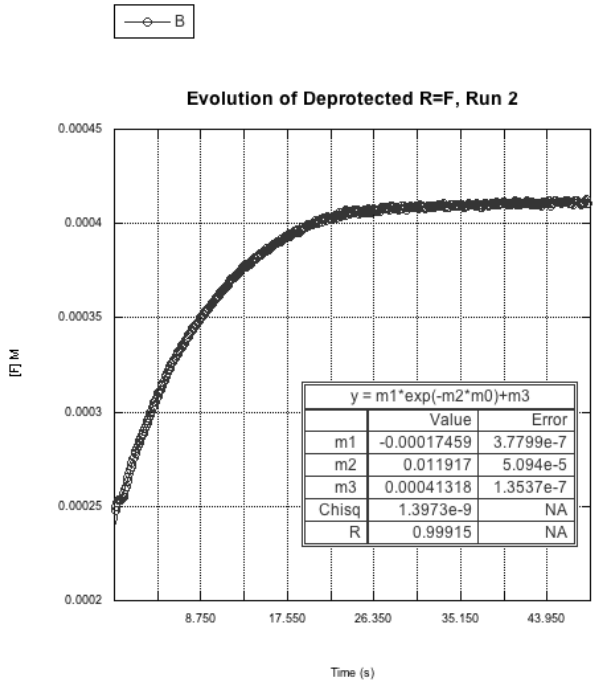
An initial stock was prepared using **19b** (0.19 g, 4.79×10^{-5} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2. After bubbling the solution with N_2 for 10 minutes, an aliquot of the first stock (1.0 mL, 4.79×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N_2. The second stock was then charged with PhSH (0.20 mL, 397 equiv., 1.90×10^{-3} mol) and the remaining volume consisted of CH_3CN. After bubbling the solution with N_2 for 10 minutes, an aliquot of the second stock (3.0 mL, 1.44×10^{-6} mol of **19b**, 5.71×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 545 equiv., 7.84×10^{-4} mol) of the NEt_3 stock solution was added to a cuvette charged with **19b** and PhSH, resulting in a final concentration of 1.63×10^{-1} M of NEt_3, 2.24×10^{-1} M of PhSH and 4.11×10^{-4} M of **19b** in the monitored reaction. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.27\times10^{-2}\ s^{-1}$$

Rate Constant Afforded from the Production of 22b, replicate #2

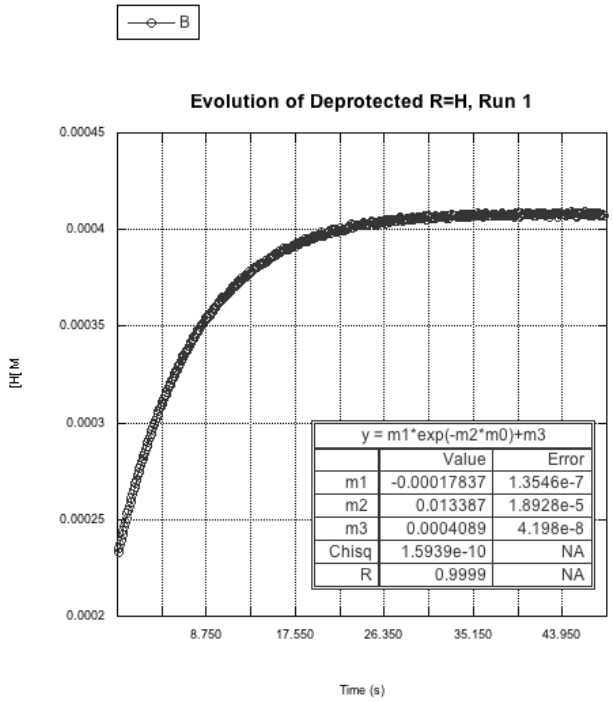
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.19\times10^{-2}s^{-1}$$

Rate Constant Afforded from the Production of 22c, replicate#1

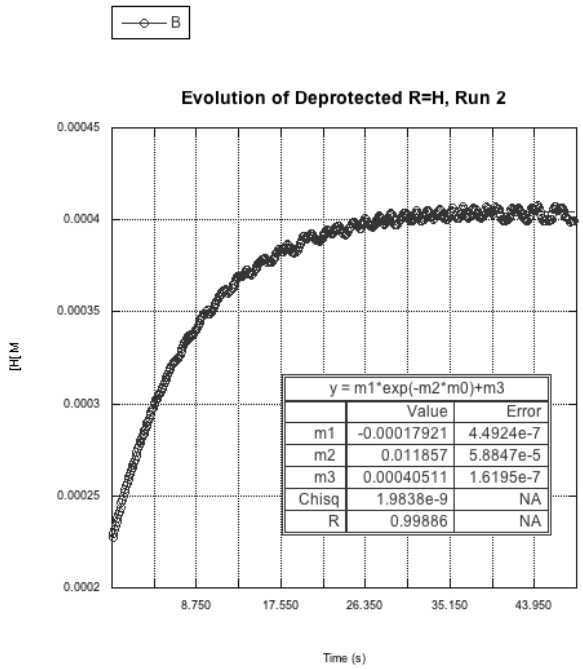
An initial stock was prepared using **19c** (0.018 g, 4.76×10^{-5} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2. After bubbling the solution with N_2 for 10 minutes, an aliquot of the first stock (1.0 mL, 4.76×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N_2. The second stock was then charged with PhSH (0.20 mL, 400 equiv., 1.90×10^{-3} mol) and the remaining volume consisted of CH_3CN. After bubbling the solution with N_2 for 10 minutes, an aliquot of the second stock (3.0 mL, 1.43×10^{-6} mol of **19c**, 5.71×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate N-deprotection, an aliquot (0.5 mL, 550 equiv., 7.84×10^{-4} mol) of the NEt_3 stock solution was added to a cuvette charged with **19c** and PhSH, resulting in a final concentration of 1.63×10^{-1} M of NEt_3, 2.24×10^{-1} M of PhSH and 4.08×10^{-4} M of **19c** in the monitored reaction. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.34\times10^{-2}\ s^{-1}$$

Rate Constant Afforded from the Production of 22c, replicate #2

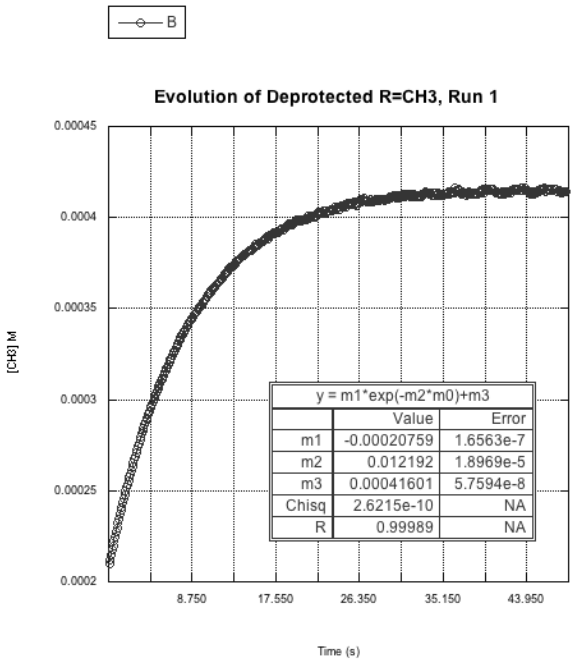
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (48 seconds).



$k = 1.19\times10^{-2}\ s^{-1}$

Rate Constant Afforded from the Production of 22d, replicate#1

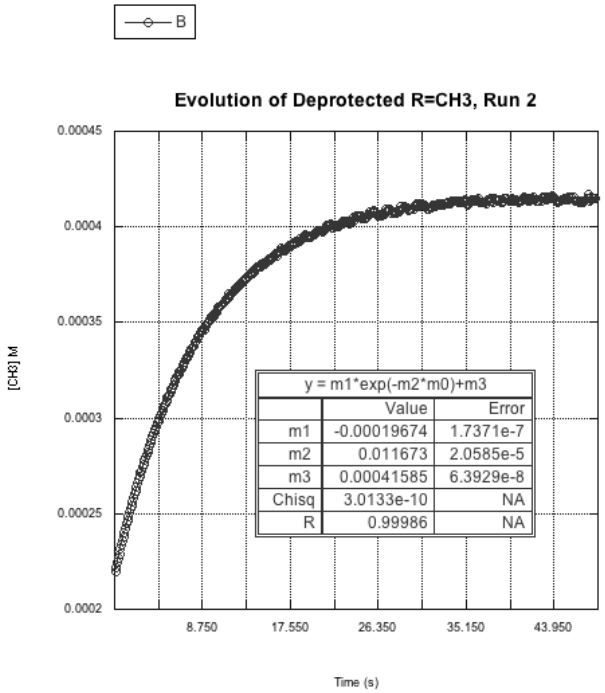
An initial stock was prepared using **19d** (0.019 g, 4.84×10^{-5} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2. After bubbling the solution with N_2 for 10 minutes, an aliquot of the first stock (1.0 mL, 4.84×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N_2. The second stock was then charged with PhSH (0.20 mL, 395 equiv., 1.90×10^{-3} mol) and the remaining volume consisted of CH_3CN. After bubbling the solution with N_2 for 10 minutes, an aliquot of the second stock (3.0 mL, 1.45×10^{-6} mol of **19d**, 5.71×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 540 equiv., 7.84×10^{-4} mol) of the NEt_3 stock solution was added to a cuvette charged with **19d** and PhSH, resulting in a final concentration of 1.63×10^{-1} M of NEt_3, 2.24×10^{-1} M of PhSH and 4.15×10^{-4} M of **19d** in the monitored reaction. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.22\times10^{-2}\ s^{-1}$$

Rate Constant Afforded from the Production of 22d, replicate #2

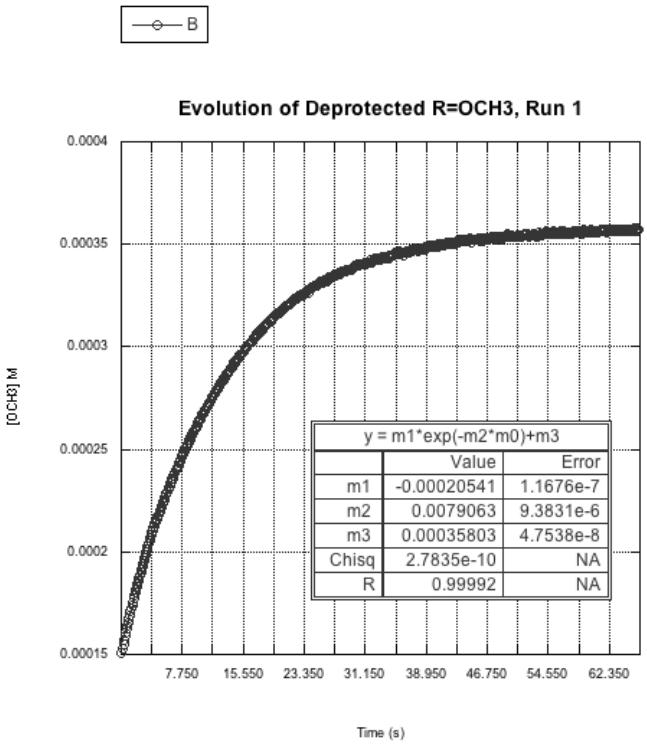
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (48 seconds).



$$k = 1.17\times10^{-2}\ s^{-1}$$

Rate Constant Afforded from the Production of 22e, replicate#1

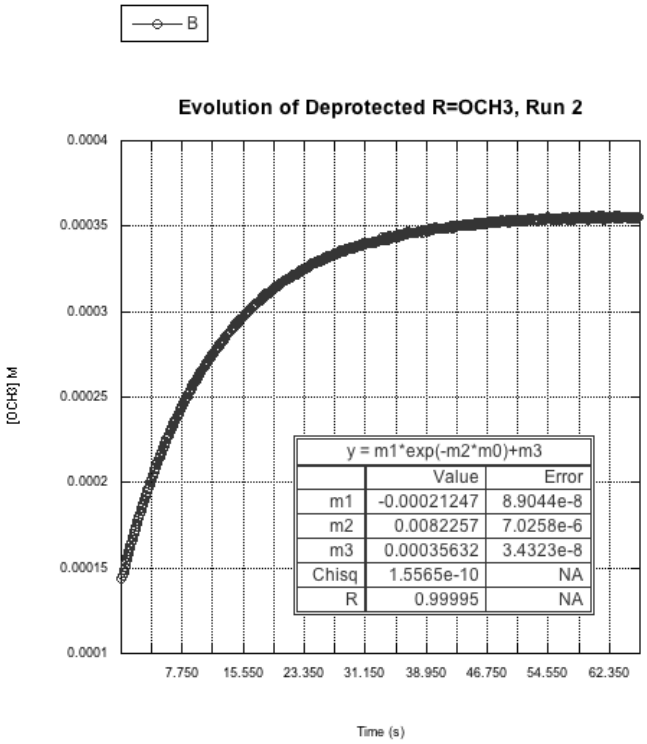
An initial stock was prepared using **19e** (0.017 g, 4.16×10^{-5} mol) in CH_3CN using a 10.000 mL volumetric flask equipped with a septum under N_2. After bubbling the solution with N_2 for 10 minutes, an aliquot of the first stock (1.0 mL, 4.16×10^{-6} mol) was transferred to a second 10.000 mL volumetric flask equipped with a septum under N_2. The second stock was then charged with PhSH (0.20 mL, 457 equiv., 1.90×10^{-3} mol) and the remaining volume consisted of CH_3CN. After bubbling the solution with N_2 for 10 minutes, an aliquot of the second stock (3.0 mL, 1.25×10^{-6} mol of **19e**, 5.71×10^{-4} mol of PhSH) was transferred to a sealed cuvette equipped with a septum cover. To initiate *N*-deprotection, an aliquot (0.5 mL, 627 equiv., 7.84×10^{-4} mol) of the NEt_3 stock solution was added to a cuvette charged with **19e** and PhSH, resulting in a final concentration of 1.63×10^{-1} M of NEt_3, 2.24×10^{-1} M of PhSH and 3.57×10^{-4} M of **19e** in the monitored reaction. The reaction was monitored until it reached equilibrium (66 seconds).



$k = 7.91\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Production of 22e, replicate #2

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (66 seconds).



$$k = 8.23\times10^{-3}\ s^{-1}$$

General Procedure for the kinetics of α-difluromethyl hydrolysis of 19a-f

The deprotection of each *N*-2-nosyl α-difluoromethyl pyrroles **19a-f** to form **22a-f** was performed as a stock solution, at the concentrations indicated for each substrate (*vide infra*), using PhSH (1.8 equiv.) and NEt_3 (2.5 equiv.) in CD_3CN (purging and bubbling with N_2). Hexafluorobenzene (0.5 equiv.) was added as an internal standard at a known concentration.

A stock solution was freshly prepared prior to *N*-deprotection of the samples. The stock solution was produced at a concentration of ~0.02 M. Between 0.5 mL and 1 mL of stock solution was prepared each time. The solution was bubbled with N_2 for 10 minutes for the removal of any residual oxygen. The amount of the hexafluorobenzene from the stock solution (0.4 M in CD_3CN), which was added to each sample stock solution, is indicated in the procedures below. Upon complete deprotection, as noted by use of ^1H and ^{19}F NMR spectroscopy, the stock solution was transferred to three separate dry and N_2-flushed NMR tubes (0.5 mL each). The NMR tubes were equipped with septum, sealed with both Teflon tape and parafilm.

The starting concentration of deprotected pyrrole is confirmed by use of the internal standard before beginning hydrolysis. The instrument bore temperature was increased to 40 ºC and the sample was allowed to equilibrate for 5 minutes, at which point a t0 spectrum was collected. The sample was ejected from the bore, and hydrolysis was initiated by the injection of H_2O (~1000 equiv.) through the septum cap. The sample was then briefly agitated using a vortex mixer and re-inserted into the probe. The first spectrum was collected immediately (^{19}F NMR, $t \approx 2$ minutes). Subsequent data points were collected at 1 minute and 13 second intervals (32 scans), to a total collection time of 25 minutes. The decreasing concentration of fluorinated pyrrole was calculated by use of the integration of the peaks arising from the internal standard and the α-difluoromethyl group. Samples were run in triplicates, and the rate constants were calculated.

Line of Best Fit in Relation to the Rate Equation

Rate constants of each substrate are calculated using Kaleidagraph v 4.1.3 by plotting concentration of starting material over time.

Rate Equation: $[SM]_t = [SM]_0 e^{-kt}$

Where:

$$[SM]_t = \frac{\int SM_t}{\int SM_0}[SM]_o$$

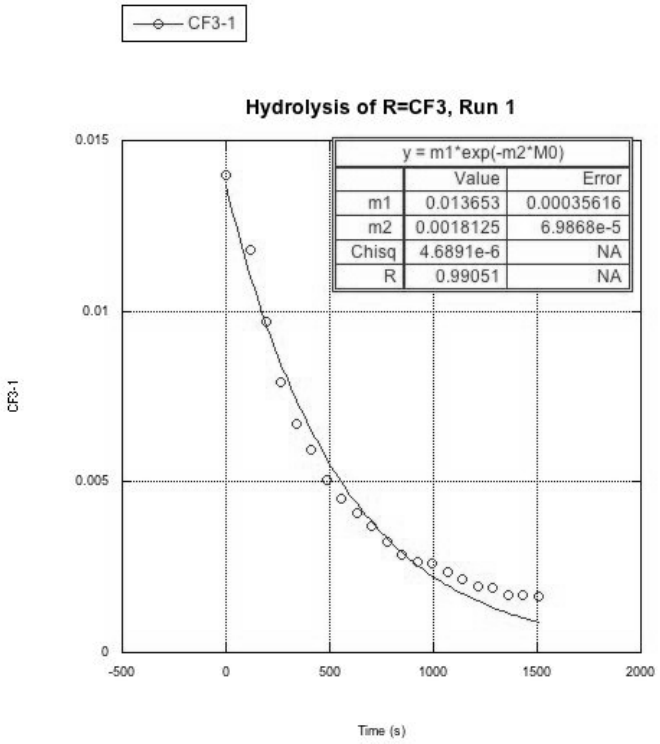
$\int SM_t$ = peak integral of the starting material at time *t*; $\int SM_0$' = peak integral of the starting material the reaction was initiated.

Line of Best Fit: y = [(m1) * exp(-m2 * m0)]

Variable 'm2' is the rate constant 'k' at the concentrations employed

Rate Constant Afforded from the Hydrolysis of 22a, replicate #1

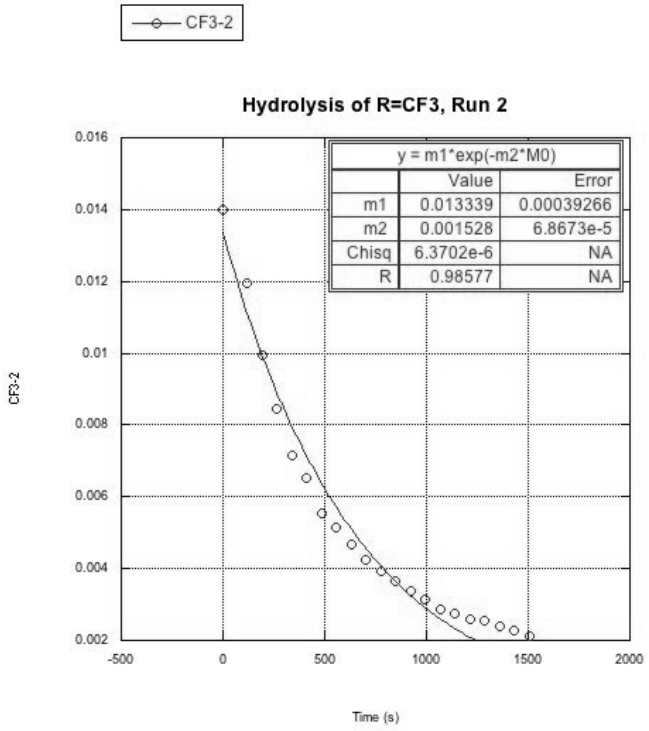
An initial stock was prepared using **19a** (0.022 g, 4.93×10^{-5} mol) and PhSH (0.01 mL, 8.87×10^{-5} mol) in CD_3CN (2.5 mL) under N_2. After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.017 mL, 1.23×10^{-4} mol) and hexafluorobenzene from stock solution (0.06 mL, containing 2.46×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.90×10^{-2} M of **22a**. An aliquot of the reaction mixture (0.5 mL, containing 9.52×10^{-6} mol of **22a**) was transferred to a dry and N_2-flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.18 mL, 1000 equiv.) through the septum cap, resulting in a total concentration of 1.40×10^{-2} M of **22a** in the monitored reaction initially. The reaction was monitored via use of ^{19}F NMR spectroscopy for 25 minutes.



$$k_{CF3\text{-}1} = 1.81\times10^{-3}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22a, replicate #2

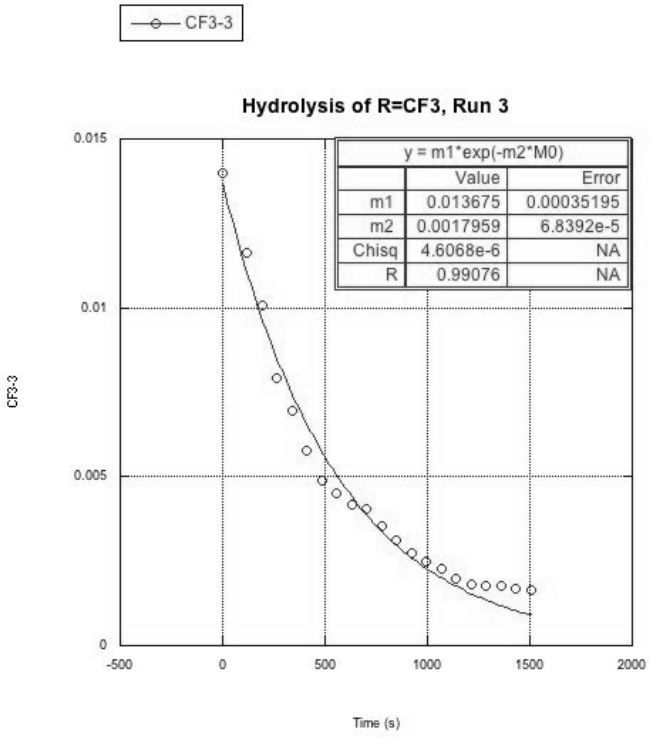
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$$k_{CF3\text{-}2} = 1.53\times10^{-3}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22a, replicate #3

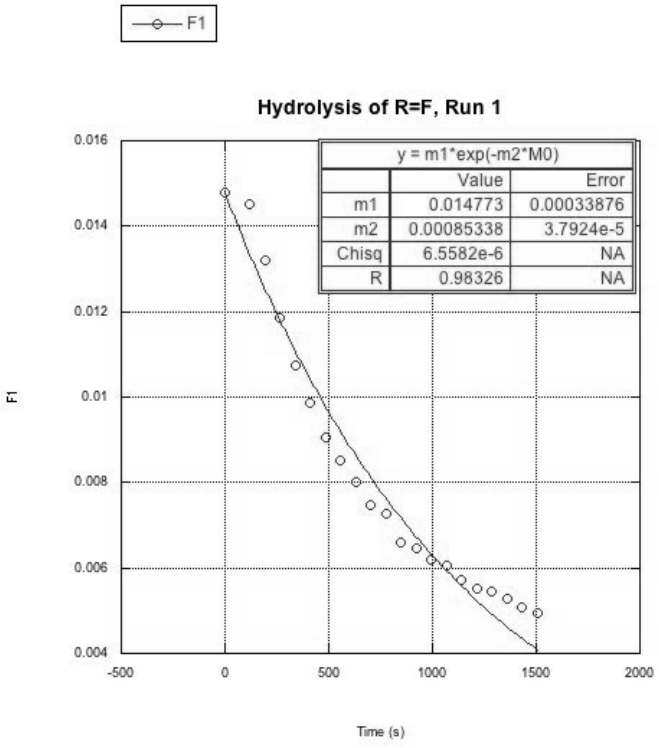
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{CF3\text{-}3} = 1.80\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22b, Replicate #1

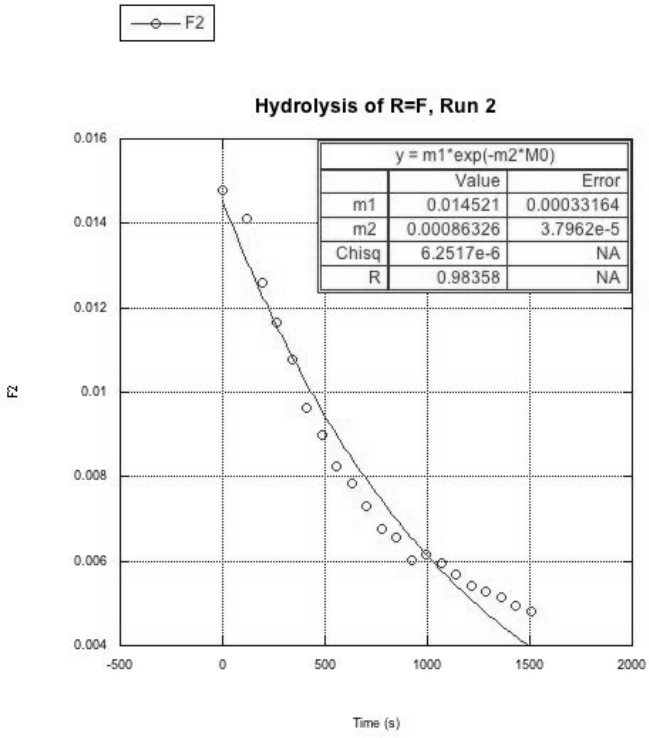
An initial stock was prepared using **19b** (0.022 g, 5.55×10^{-5} mol) and PhSH (0.01 mL, 9.99×10^{-5} mol) in CD_3CN (2.8 mL) under N_2. After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.019 mL, 1.39×10^{-4} mol) and hexafluorobenzene stock (0.07 mL, containing 2.77×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.96×10^{-2}M **22b**. An aliquot of the reaction mixture (0.5 mL, containing 9.82×10^{-6} mol of **22b**) was transferred to a dry and N_2-flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.18 mL, 1000 equiv.) through the septum cap, resulting in a total concentration of 1.41×10^{-2} M of **22b** in the monitored reaction initially. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes.



$$k_{F\text{-}1} = 8.53\times10^{-4}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22b, replicate #2

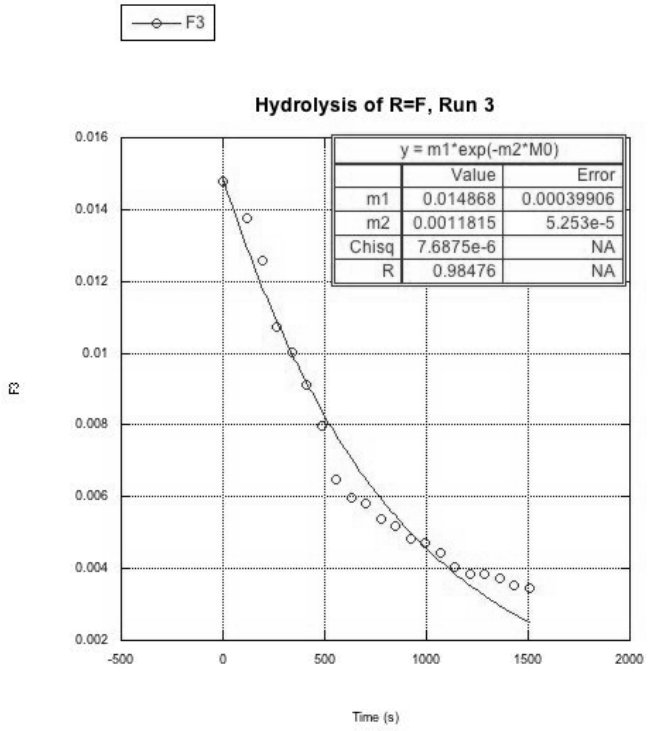
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$$k_{F\text{-}2} = 8.63\times10^{-4}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22b, replicate #3

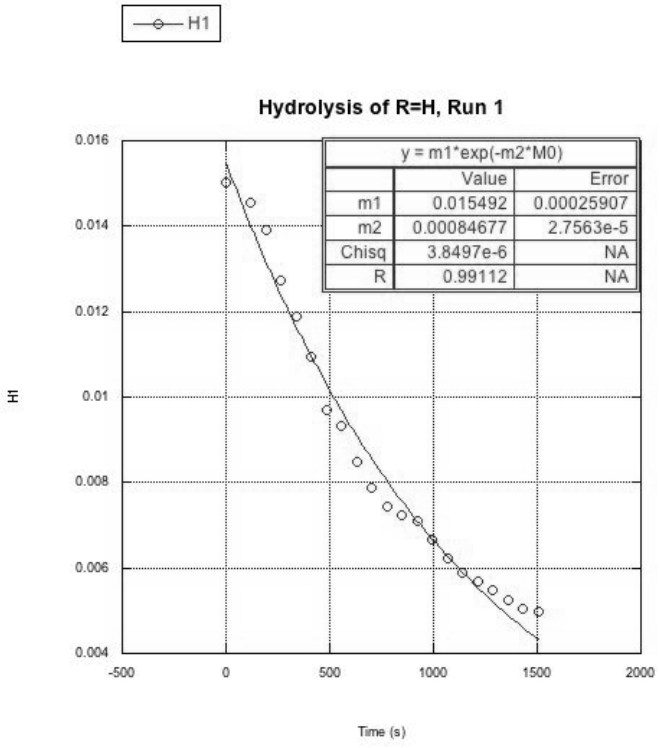
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$$k^{F\text{-}3} = 1.18\times10^{-3}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22c, replicate #1

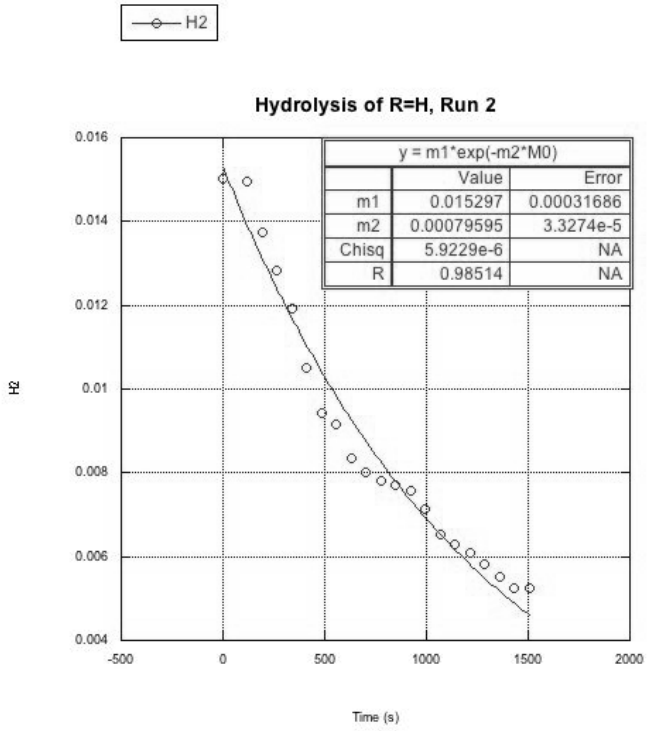
An initial stock was prepared using **19c** (0.020 g, 5.29×10^{-5} mol) and PhSH (0.01 mL, 9.51×10^{-5} mol) in CD_3CN (2.5 mL) under N_2. After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.018 mL, 1.32×10^{-4} mol) and hexafluorobenzene stock (0.07 mL, containing 2.64×10^{-5} mol of hexafluorobenzene) were added, resulting in 2.03×10^{-2} M of **22c**. An aliquot of the reaction mixture (0.5 mL, containing 1.02×10^{-5} mol of **22c**) was transferred to a dry and N_2-flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.18 mL, 979 equiv.) through the septum cap, resulting in a total concentration of 1.50×10^{-2} M of **22c** in the monitored reaction initially. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes.



$$k_{H\text{-}1} = 8.47\times10^{-4}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22c, replicate #2

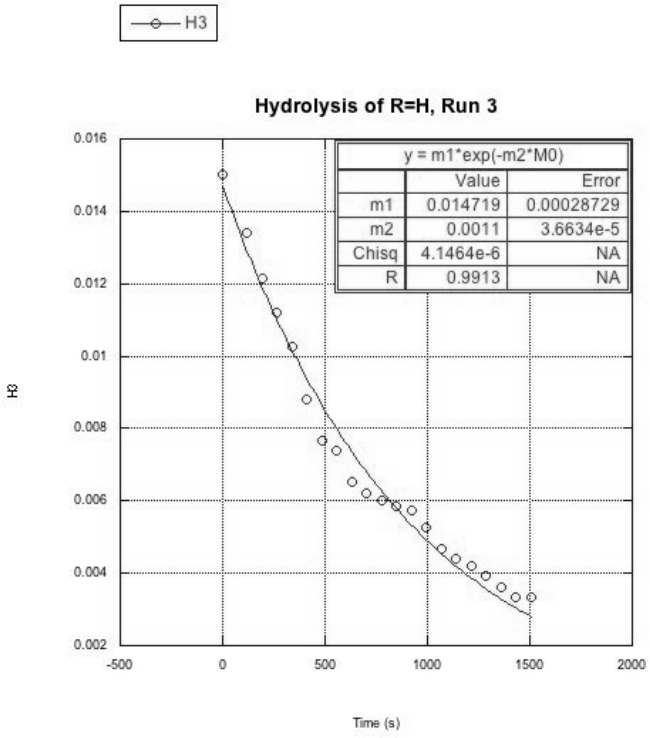
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{H\text{-}2} = 7.96\times10^{-4}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22c, replicate #3

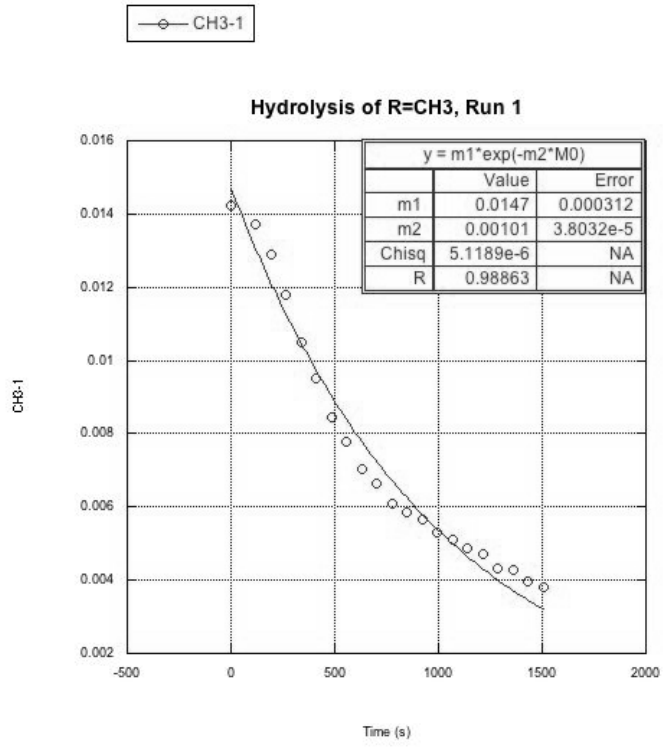
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{H\text{-}3} = 1.10\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22d, replicate #1

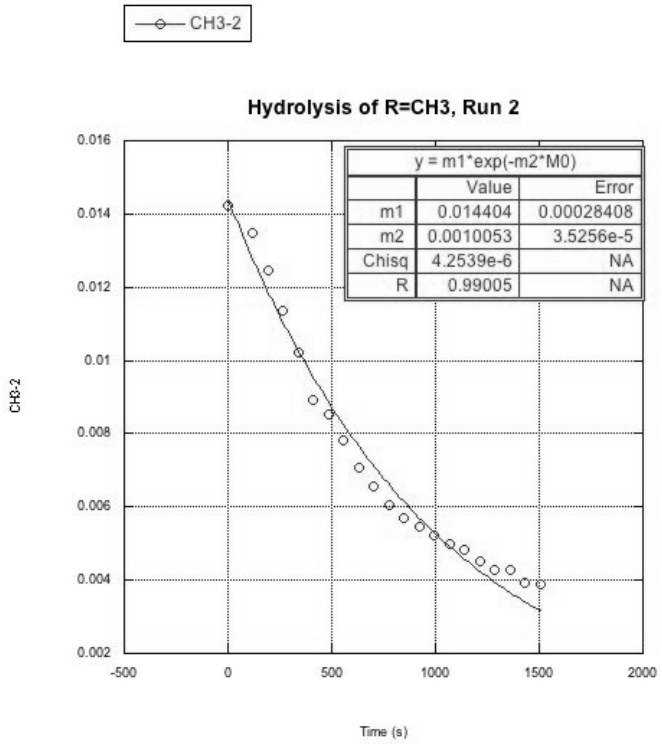
An initial stock was prepared using **19d** (0.022 g, 5.61×10^{-5} mol) and PhSH (0.01 mL, 1.00×10^{-4} mol) in CD_3CN (2.8 mL) under N_2. After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.019 mL, 1.40×10^{-4} mol) and hexafluorobenzene stock (0.07 mL, containing 2.80×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.93×10^{-2} M of **22d**. An aliquot of the reaction mixture (0.5 mL, containing 9.67×10^{-6} mol of **22d**) was transferred to a dry and N_2-flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.18 mL, 1032 equiv.) through the septum cap, resulting in a total concentration of 1.42×10^{-2} M of **22d** in the monitored reaction initially. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes.



$$k_{CH3\text{-}1} = 1.01\times10^{-3}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22d, replicate #2

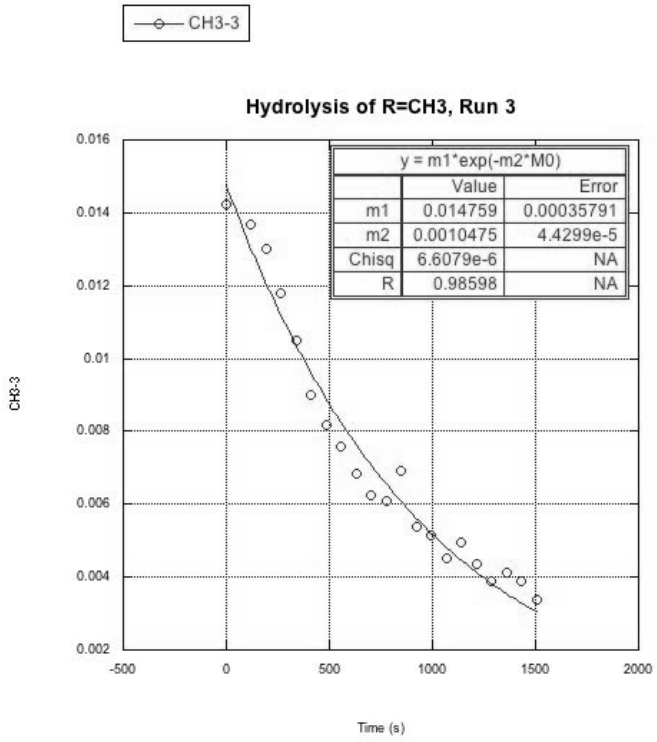
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{CH3\text{-}2} = 1.01\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22d, replicate #3

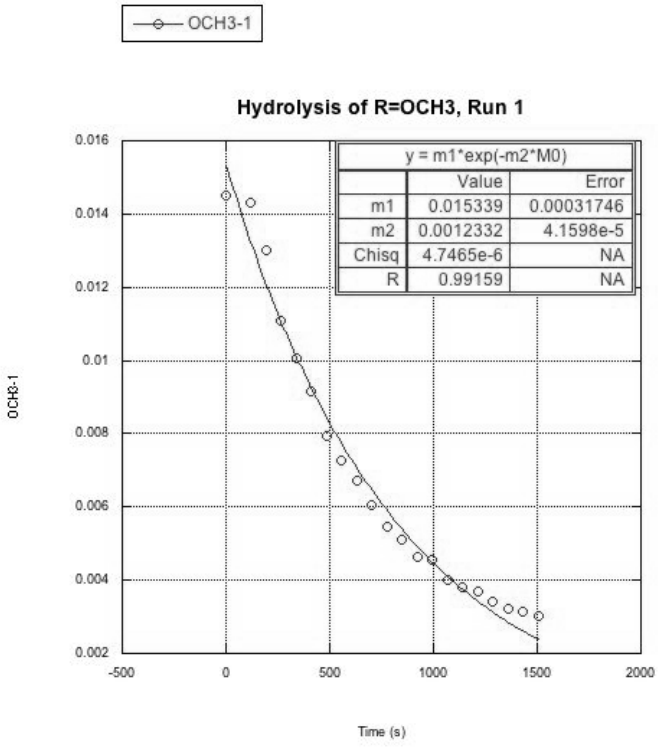
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{CH3\text{-}3} = 1.05\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22e, replicate #1

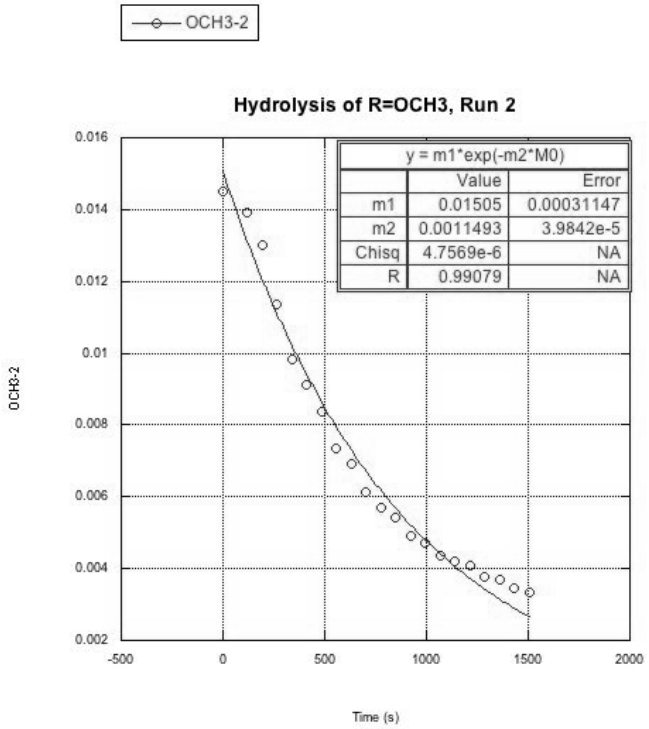
An initial stock was prepared using **19e** (0.025 g, 6.12×10^{-5} mol) and PhSH (0.01 mL, 1.10×10^{-4} mol) in CD_3CN (3.0 mL) under N_2. After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.021 mL, 1.53×10^{-4} mol) and hexafluorobenzene stock (0.072 mL, containing 3.06×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.96×10^{-2} M concentration of **22e**. An aliquot of the reaction mixture (0.5 mL, containing 9.81×10^{-6} mol of **22e**) was transferred to a dry and N_2-flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.18 mL, 1013 equiv.) through the septum cap, resulting in a total concentration of 1.45×10^{-2} M of **22e** in the monitored reaction initially. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes.



$$k_{OCH3\text{-}1} = 1.23\times10^{-3}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22e, replicate #2

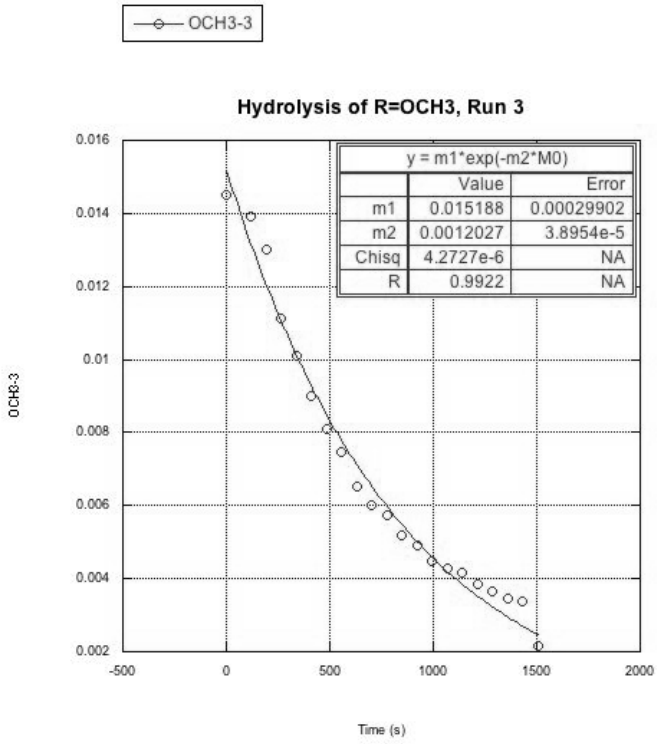
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{OCH3\text{-}2} = 1.15\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22e, replicate #3

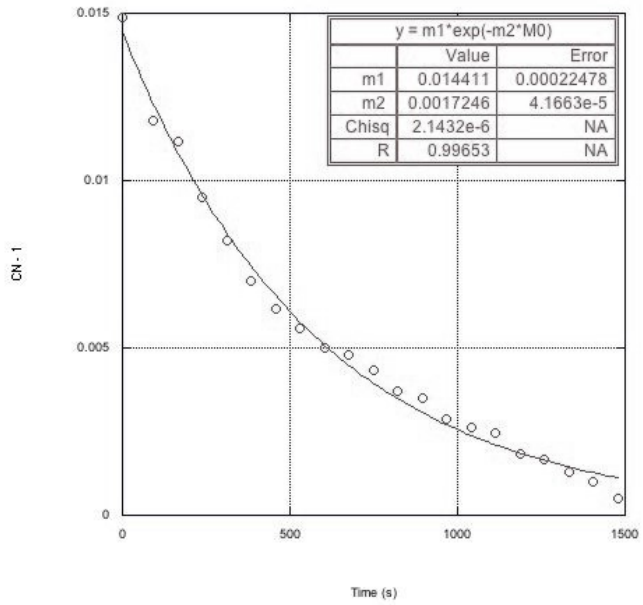
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{OCH3\text{-}3} = 1.20\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22f, replicate #1

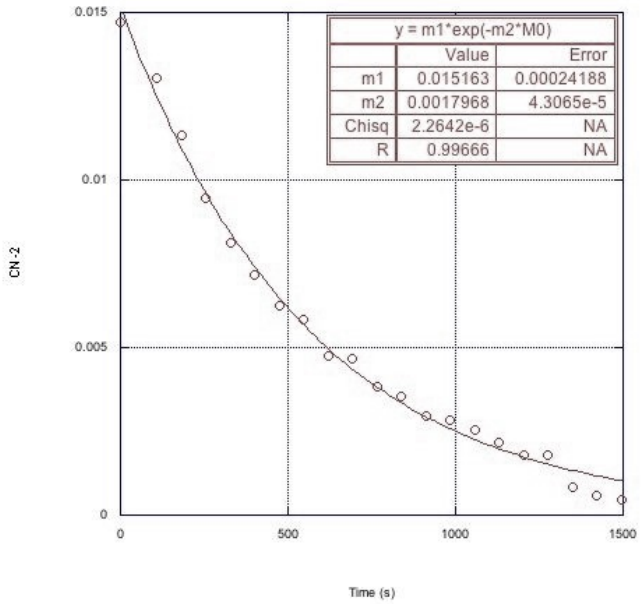
An initial stock was prepared using **19f** (0.010 g, 2.48×10^{-5} mol) and PhSH (0.0047 mL, 4.46×10^{-5} mol) in CD_3CN (1.21 mL) under N_2. After bubbling the solution with N_2 for 10 minutes, anhydrous NEt_3 (0.0087 mL, 6.20×10^{-5} mol) and hexafluorobenzene stock (0.031 mL, containing 1.23×10^{-5} mol of hexafluorobenzene) were added, resulting in 1.98×10^{-2} M concentration of **22f**. An aliquot of the reaction mixture (0.5 mL, containing 9.92×10^{-6} mol of **22f**) was transferred to a dry and N_2-flushed NMR tube equipped with septum cap once *N*-deprotection was complete. Hydrolysis was initiated by the injection of H_2O (0.18 mL, 1000 equiv.) through the septum cap, resulting in a total concentration of 1.49×10^{-2} M of **22f** in the monitored reaction initially. The reaction was monitored by use of ^{19}F NMR spectroscopy for 25 minutes.



$k_{CN} = 1.72\times10^{-3}\ s^{-1}$

Rate Constant Afforded from the Hydrolysis of 22f, replicate #2

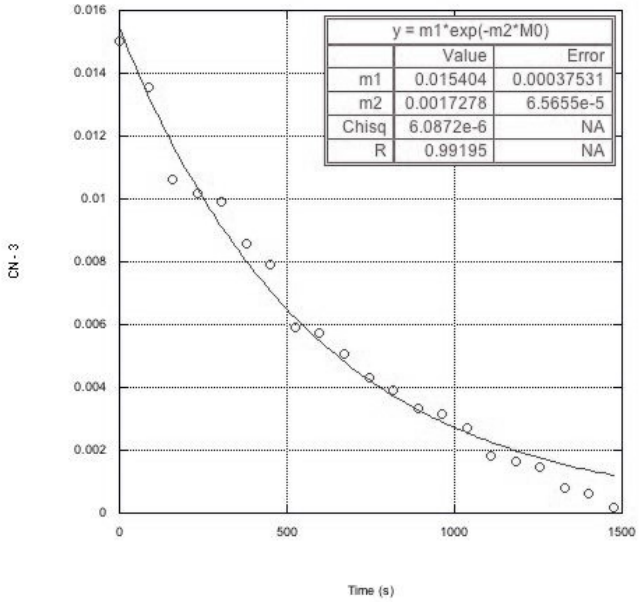
Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$$k_{CN} = 1.80\times10^{-3}\ s^{-1}$$

Rate Constant Afforded from the Hydrolysis of 22f, replicate #3

Followed procedure for replicate # 1. The reaction was monitored until it reached equilibrium (25 minutes).



$k_{CN} = 1.73 \times 10^{-3}\ s^{-1}$

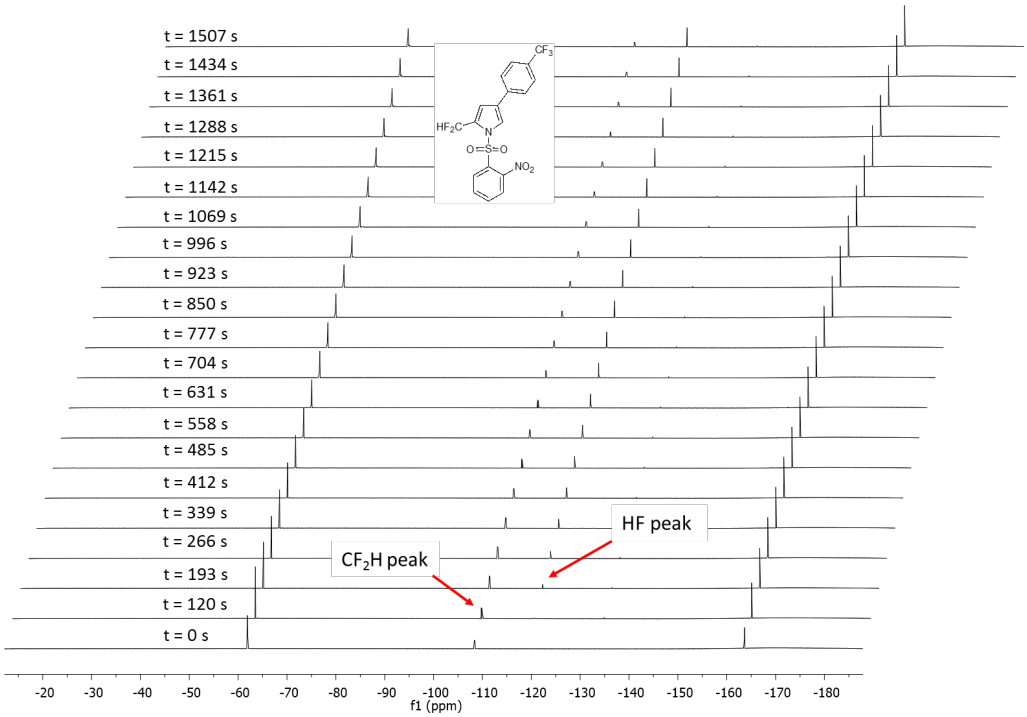


Figure 3. ^{19}F NMR spectra during the hydrolysis of the difluoromethyl group in 19a.

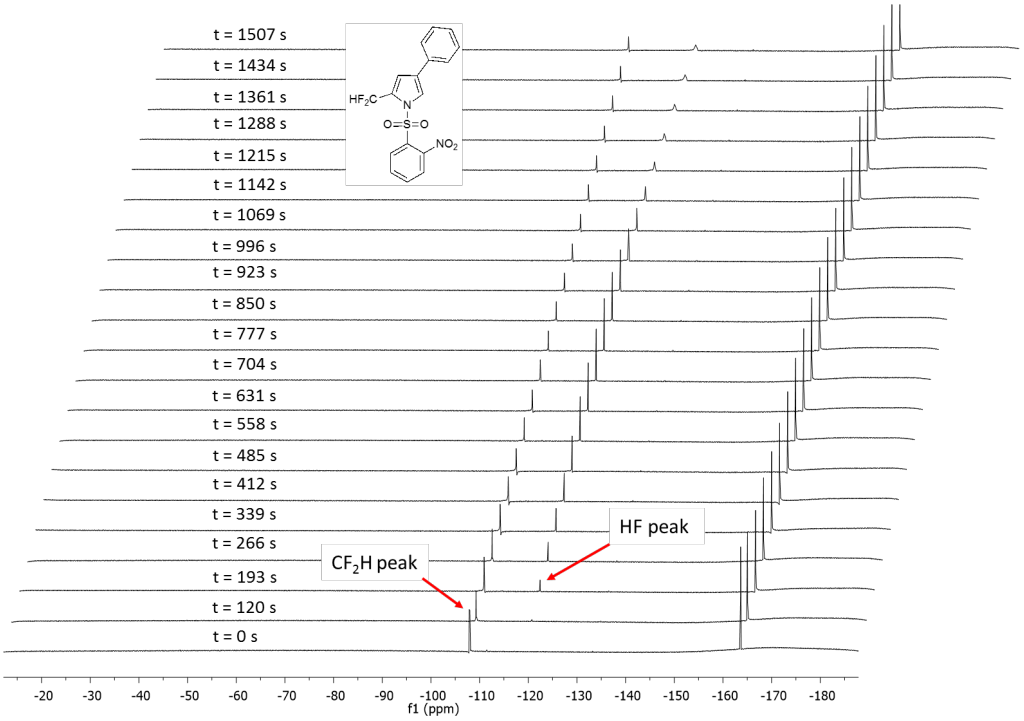


Figure 4. ^{19}F NMR spectra during the hydrolysis of the difluoromethyl group in 19c.

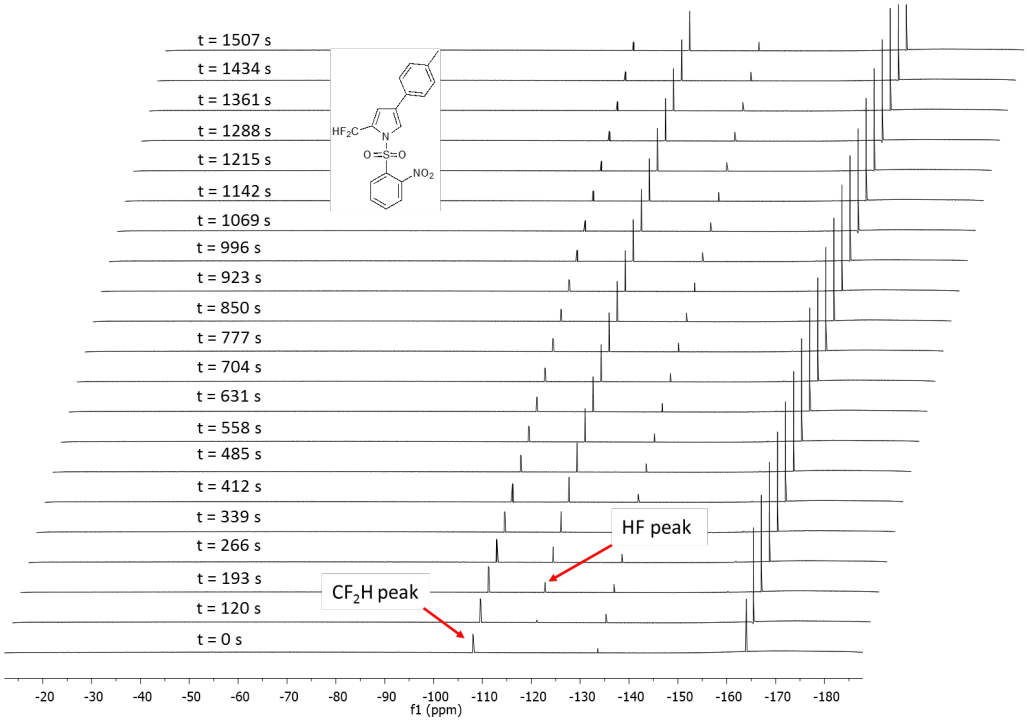


Figure 5. ^{19}F NMR spectra during the hydrolysis of the difluoromethyl group in 19d.

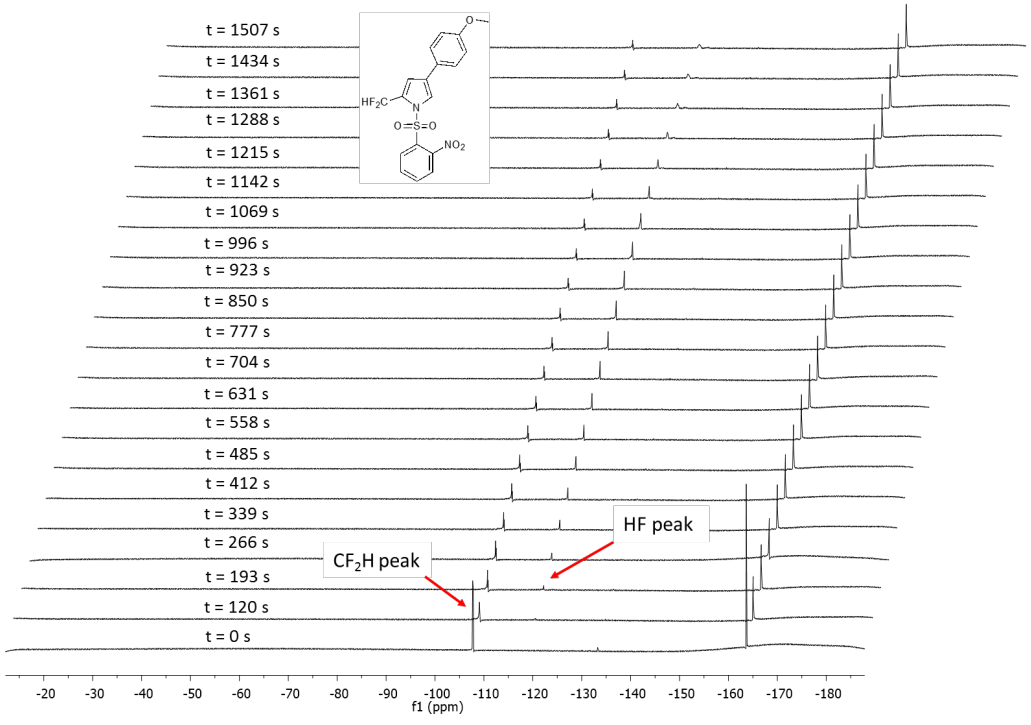


Figure 6. ^{19}F NMR spectra during the hydrolysis of the difluoromethyl group in 19e.

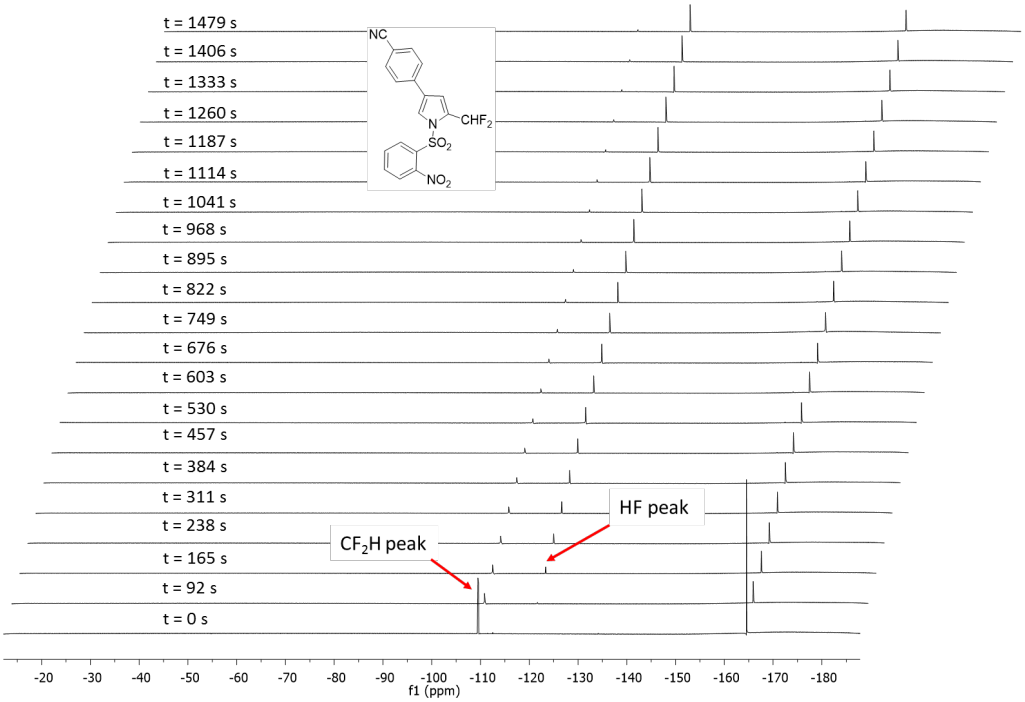
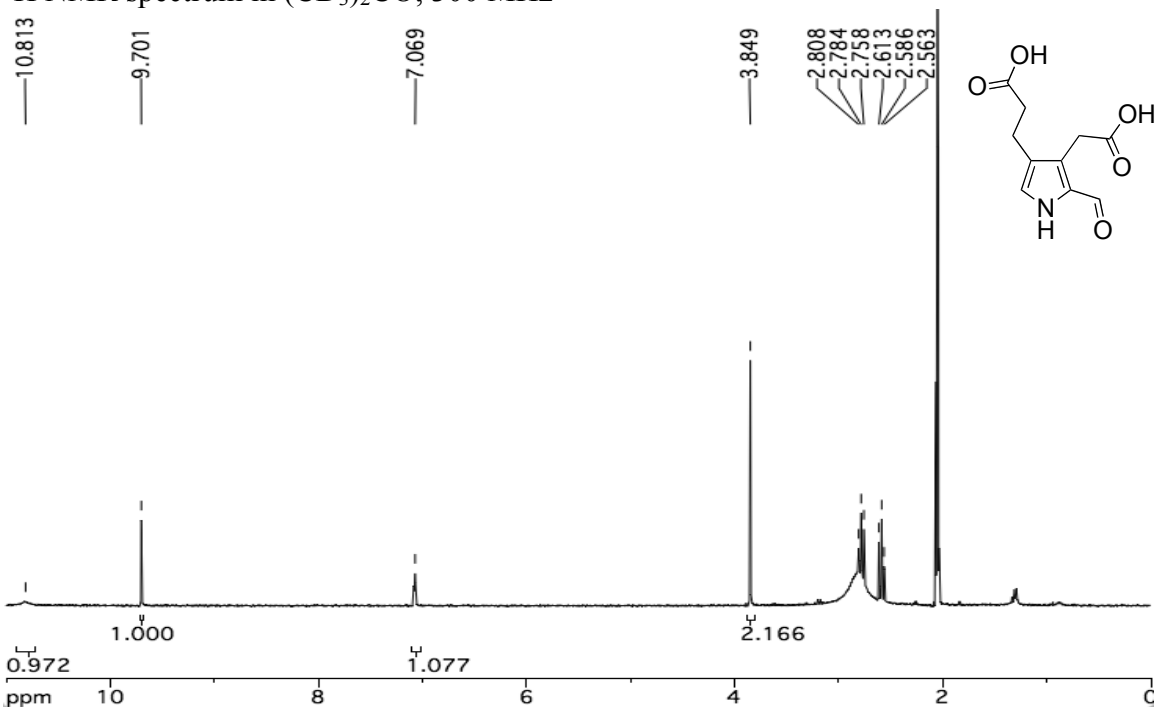


Figure 7. ^{19}F NMR spectra during the hydrolysis of the difluoromethyl group in 19f.

NMR spectra

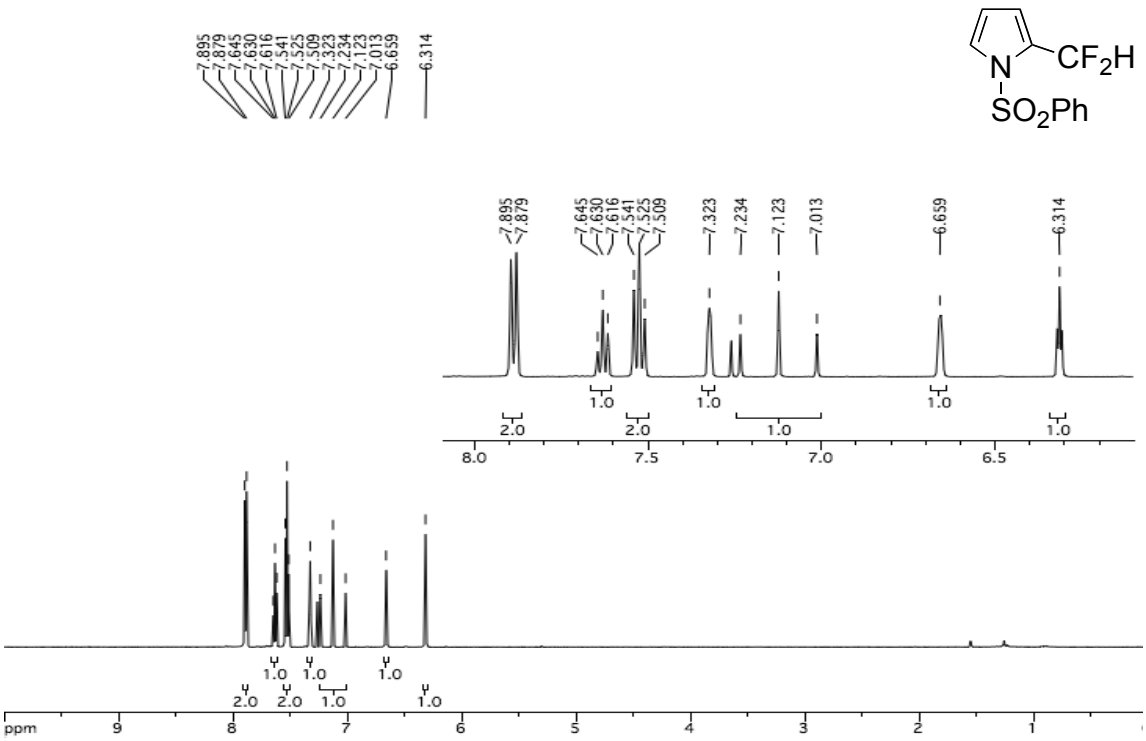
3-(4-(Carboxymethyl)-5-formyl-1H-pyrrol-3-yl)propanoic acid (8)

^{1}H NMR spectrum in $(CD_3)_2CO$, 300 MHz

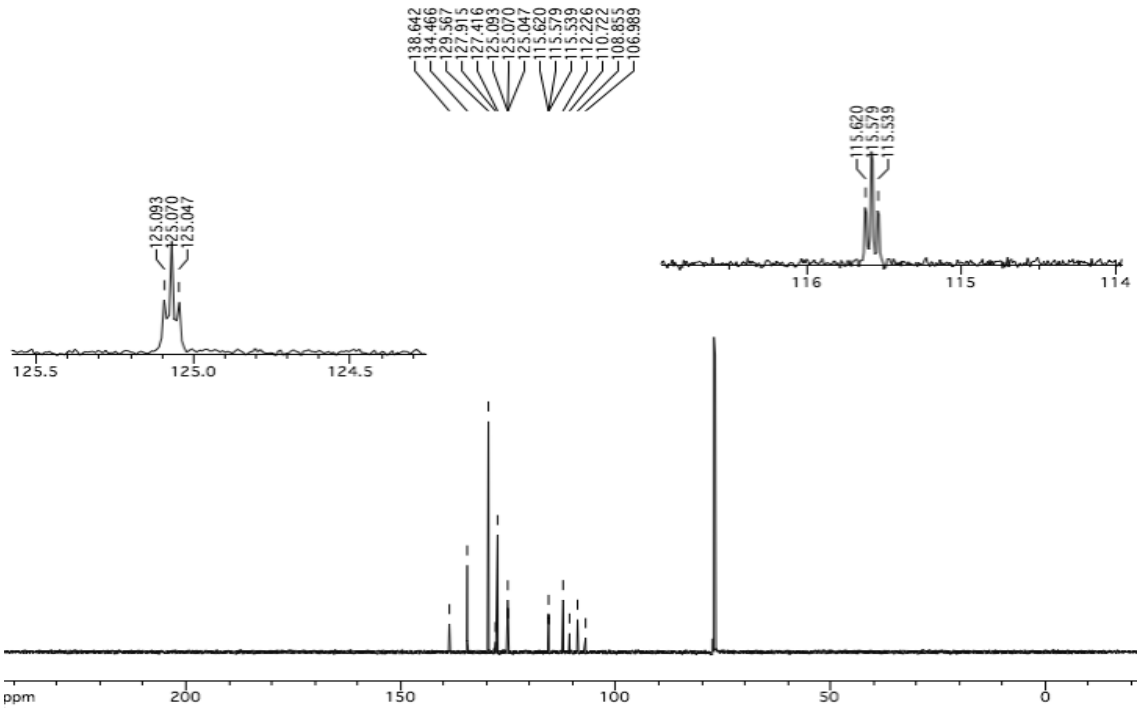


2-(Difluoromethyl)-1-(phenylsulfonyl)-pyrrole (10)

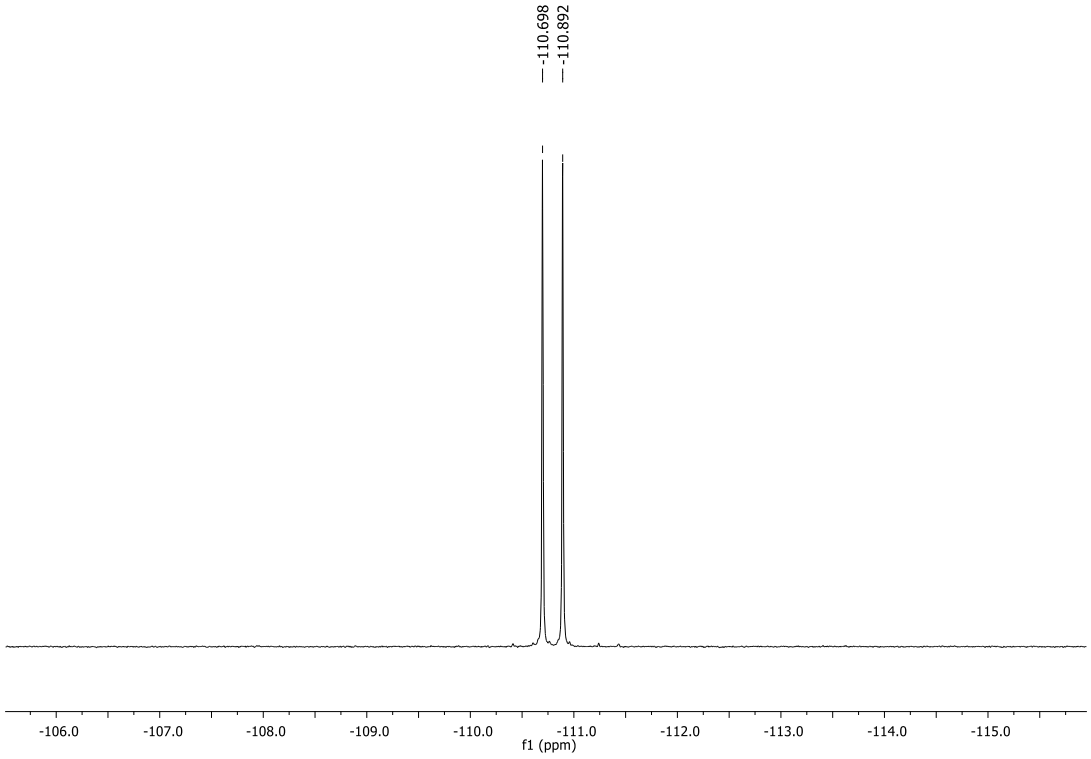
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

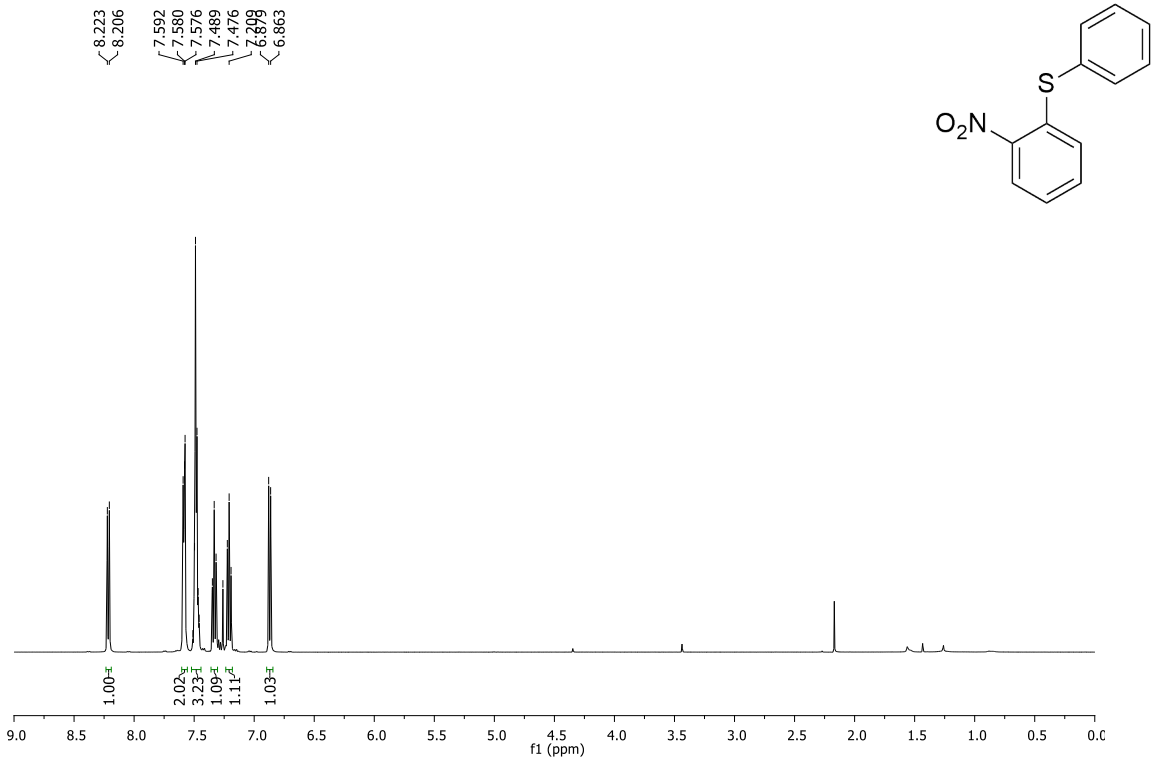


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

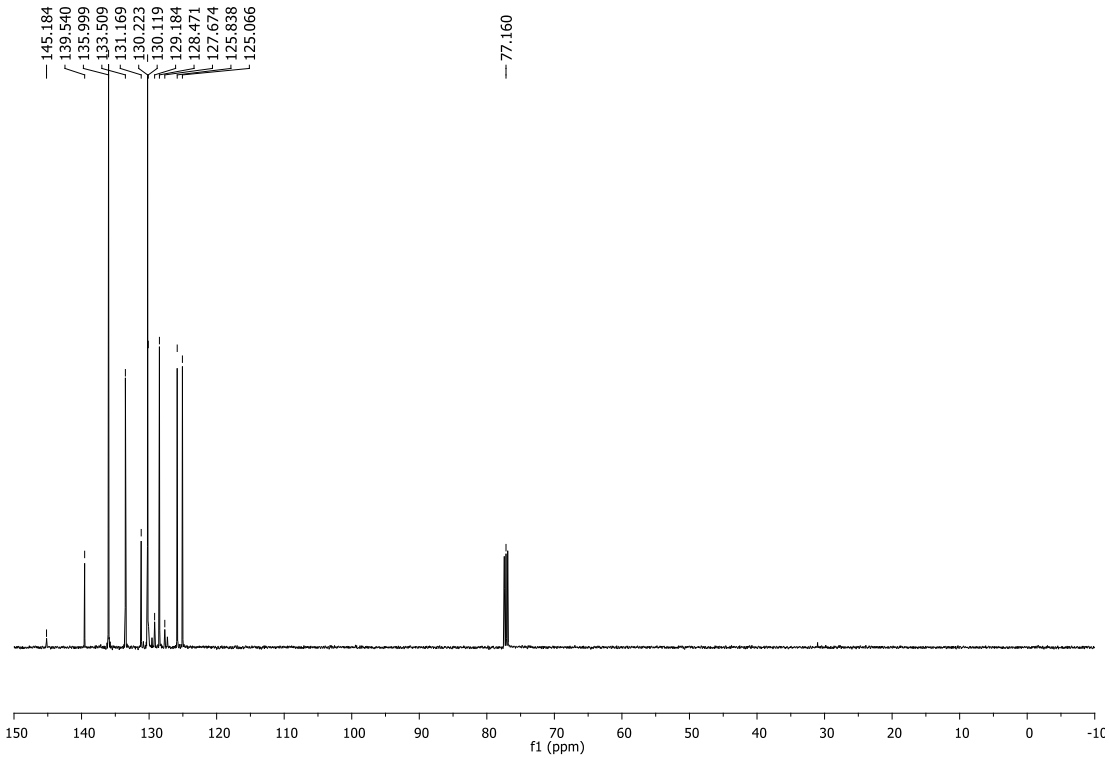


(2-Nitrophenyl)(phenyl) sulfide (14)

^{1}H NMR spectrum in $CDCl_3$, 500 MHz

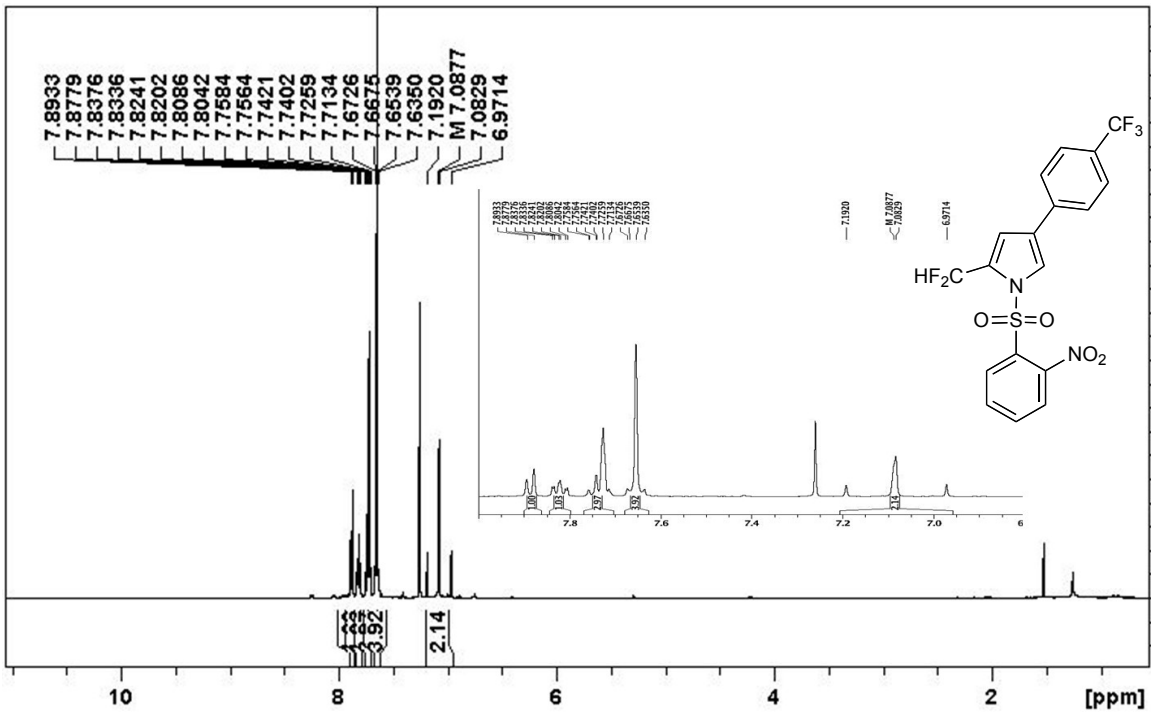


^{13}C NMR spectrum in $CDCl_3$, 125 MHz

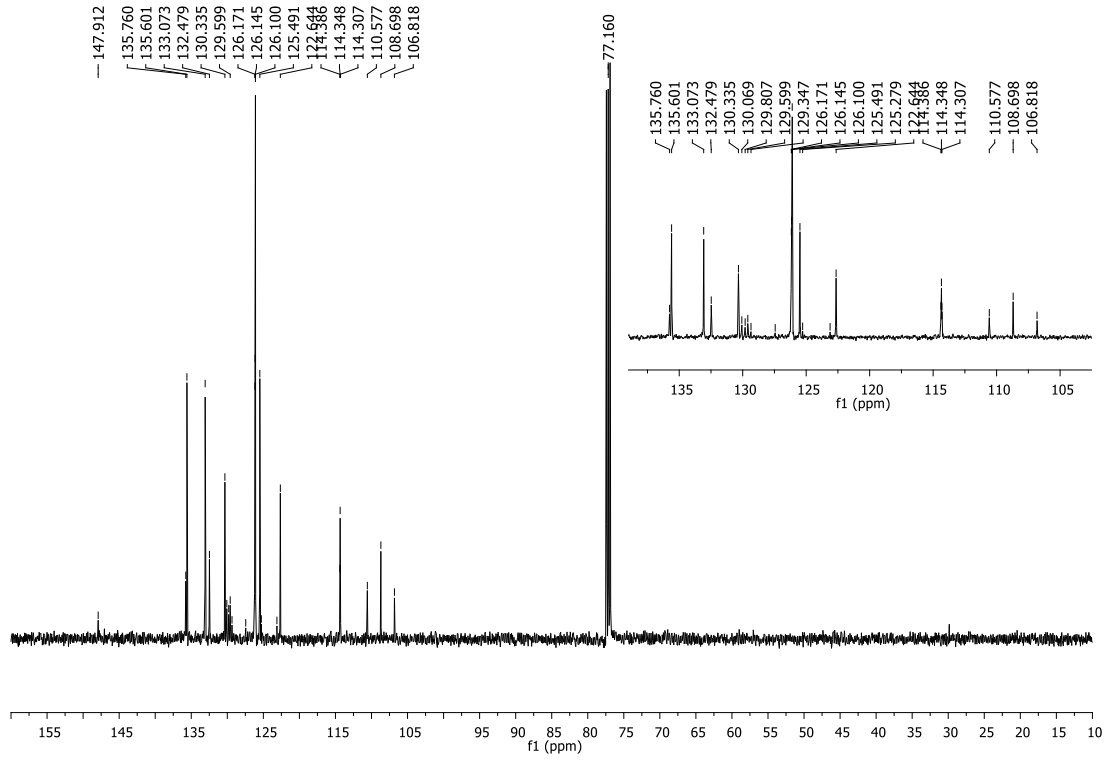


2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-pyrrole (19a)

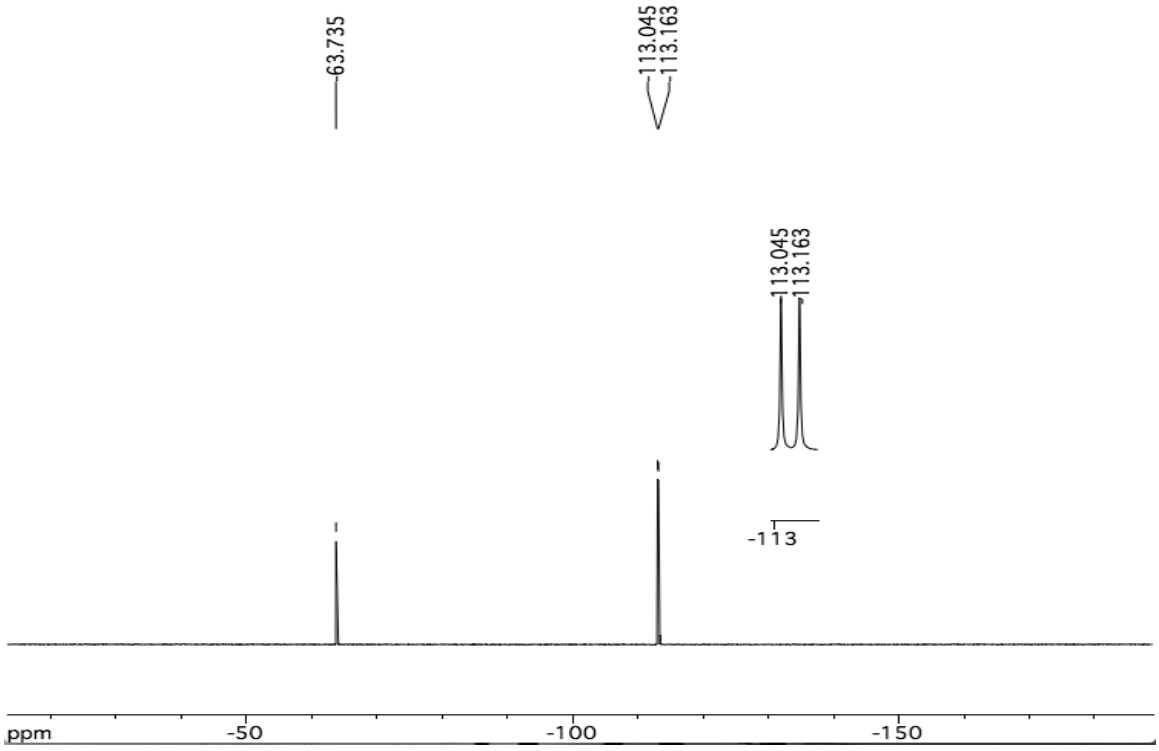
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

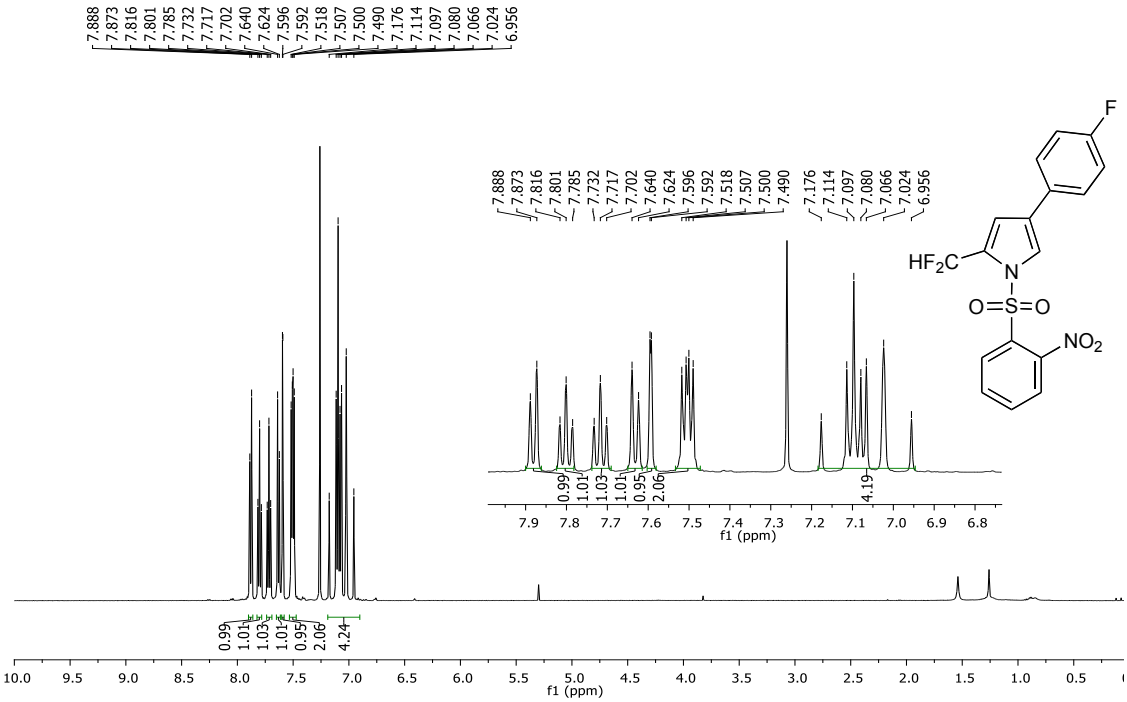


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

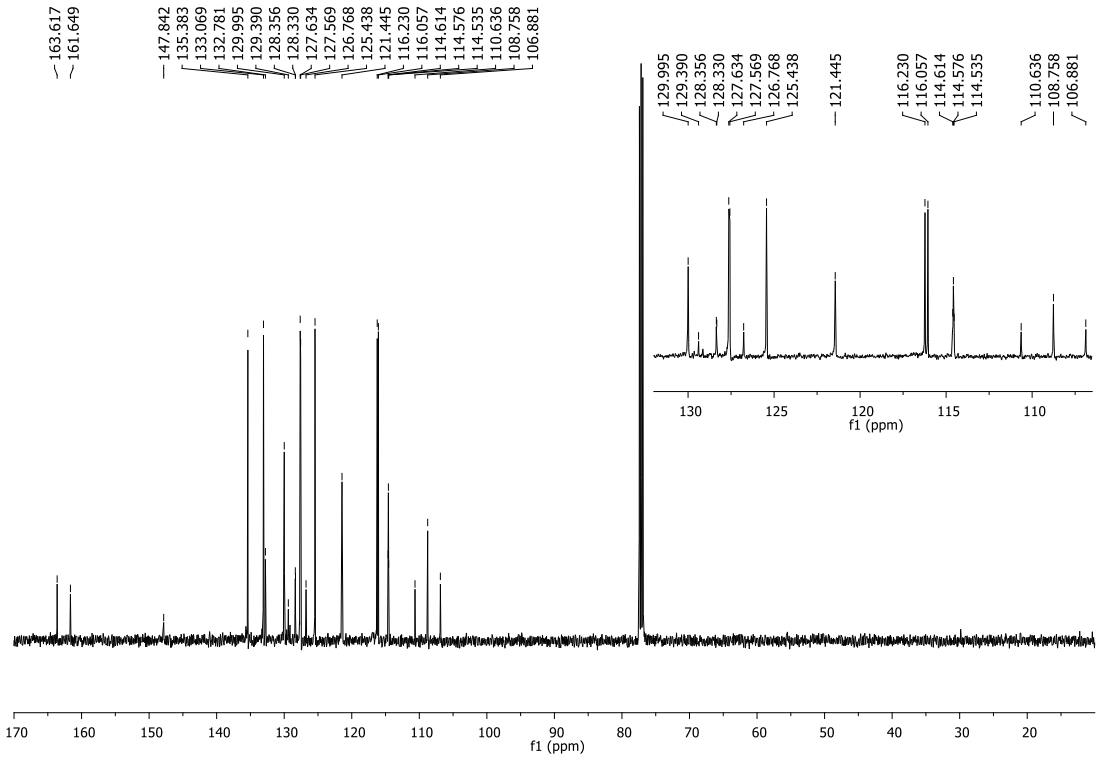


2-(Difluoromethyl)-4-(4-fluorophenyl)-1-(2-nitrophenylsulfonyl)-pyrrole (19b)

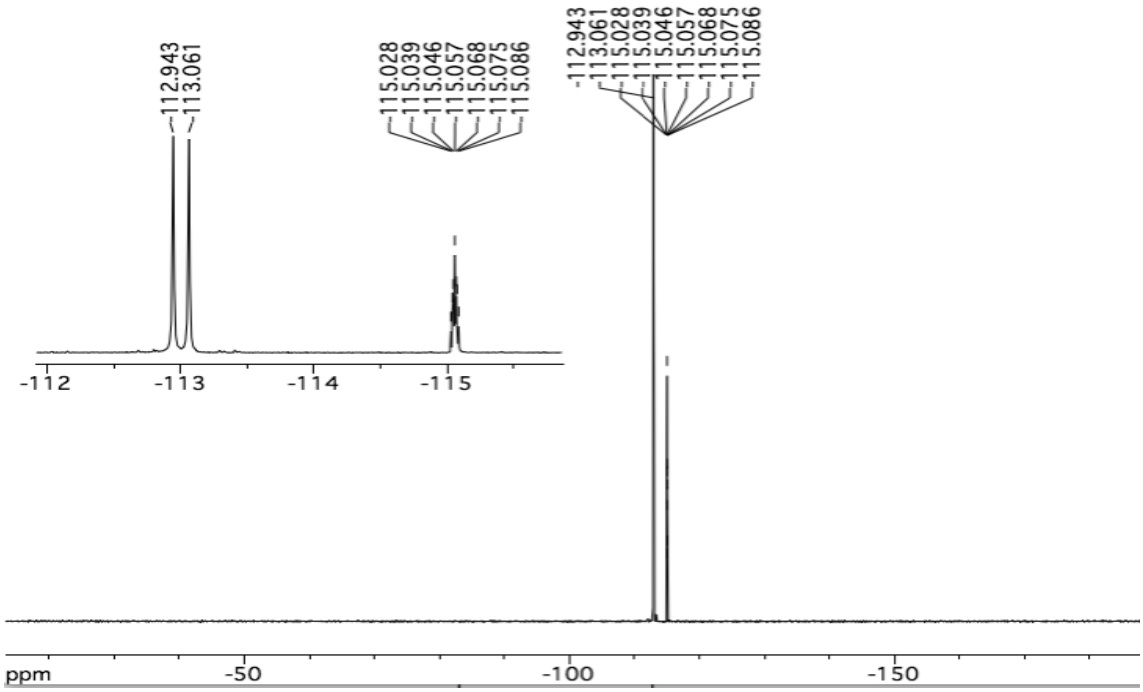
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

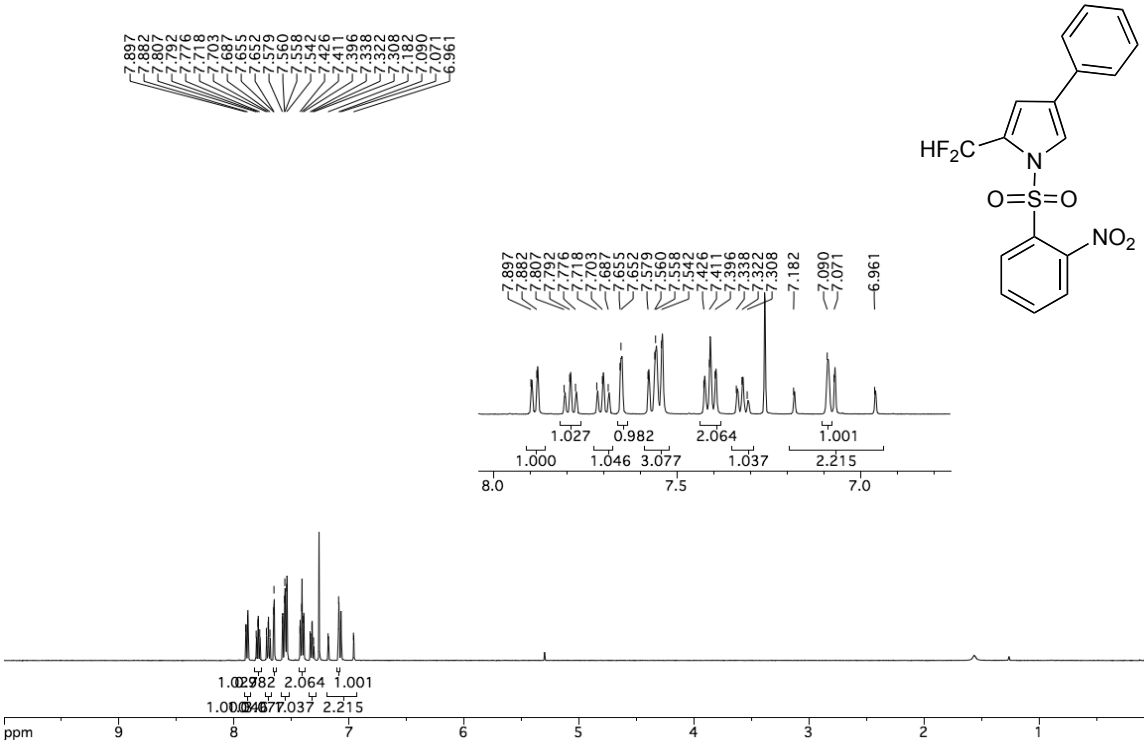


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

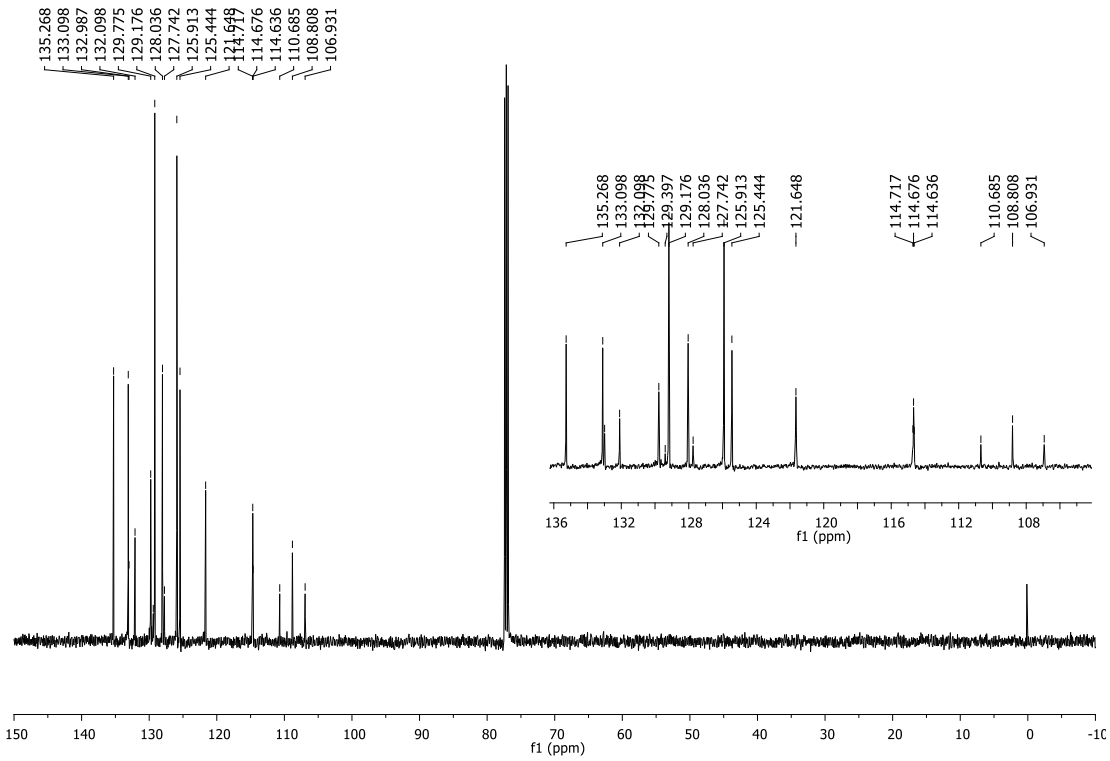


2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-phenyl-pyrrole (19c)

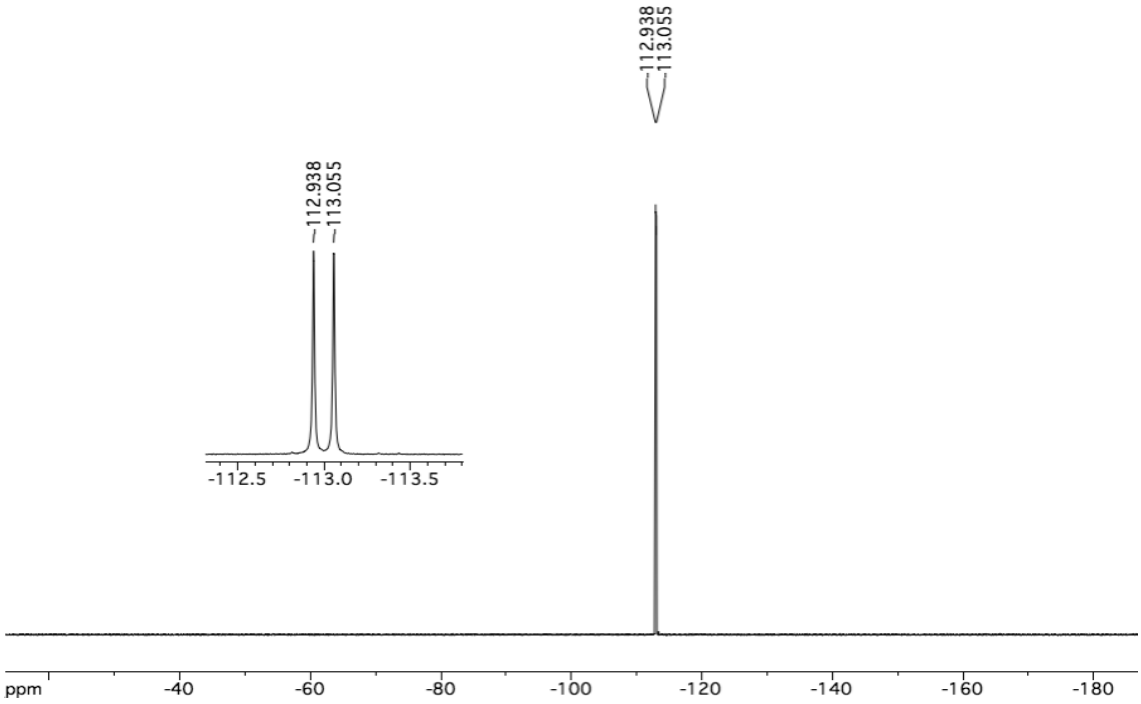
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

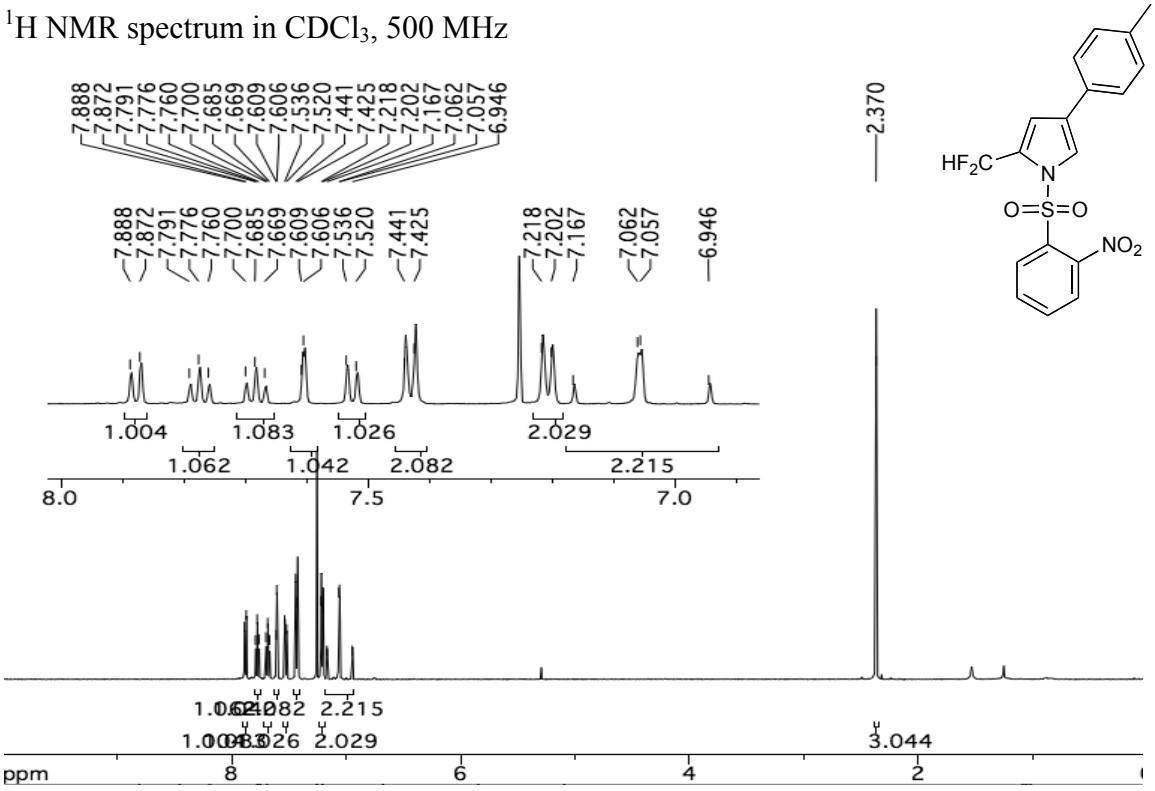


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

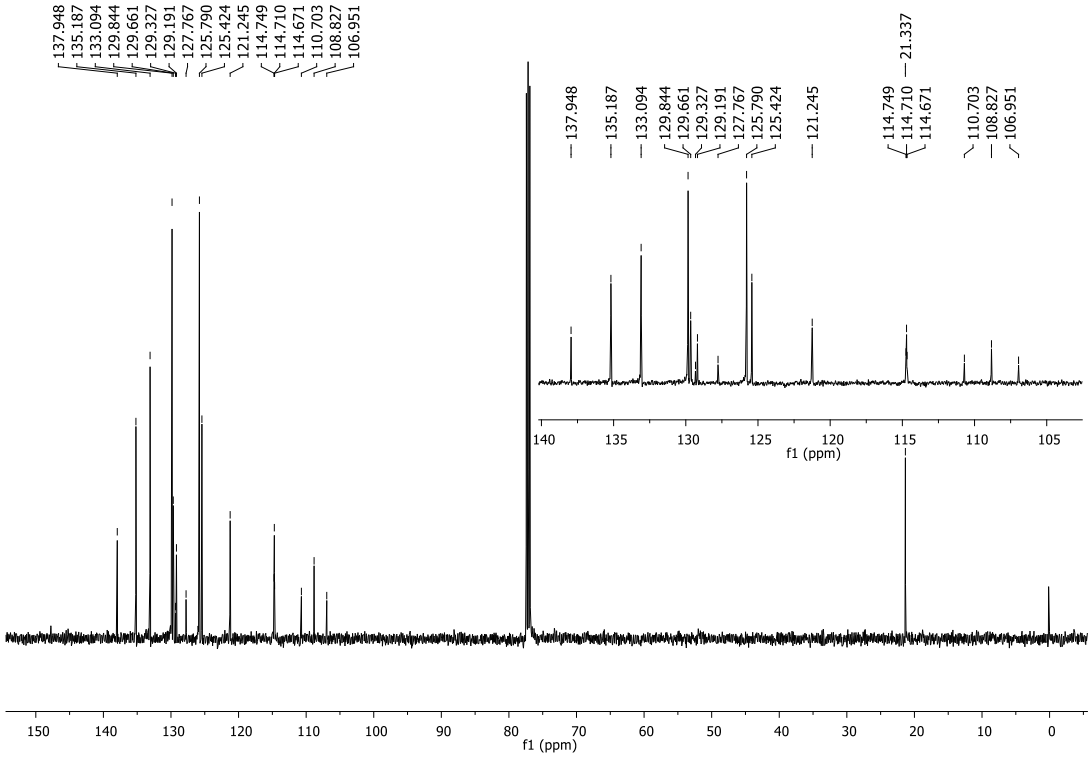


2-(Difluoromethyl)-1-(2-nitrophenylsulfonyl)-4-*p*-tolyl-pyrrole (19d)

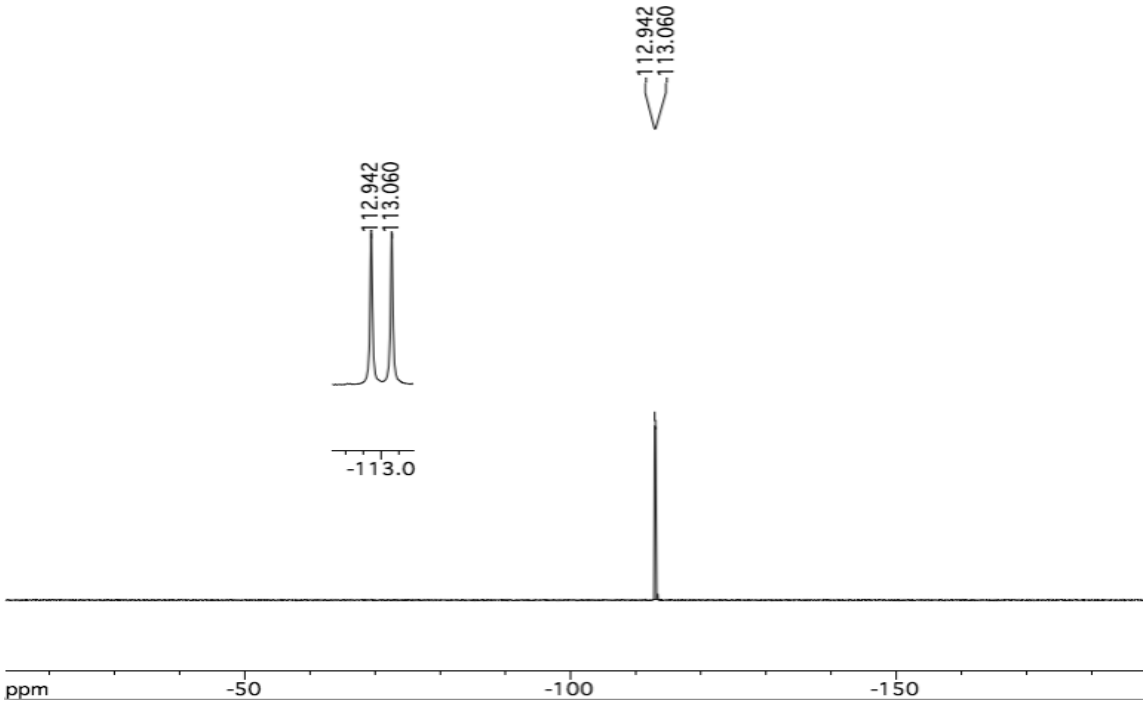
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

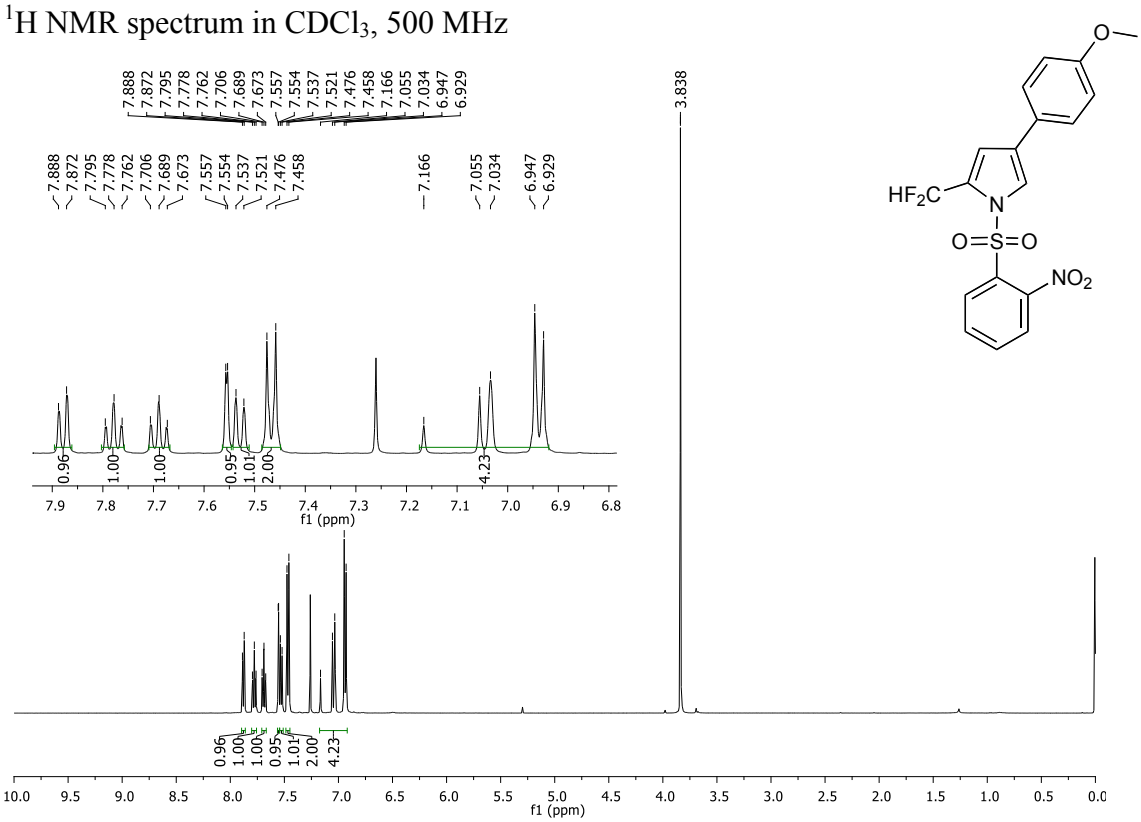


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

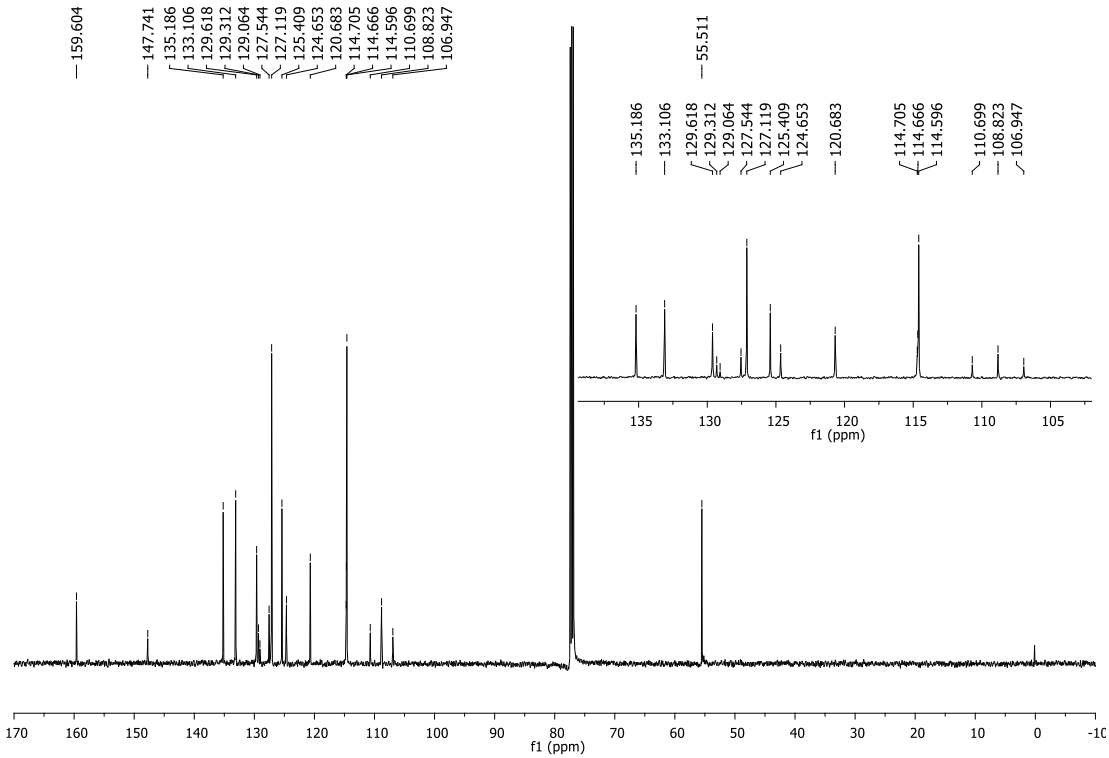


2-(Difluoromethyl)-4-(4-metho×yphenyl)-1-(2-nitrophenylsulfonyl)-pyrrole (19e)

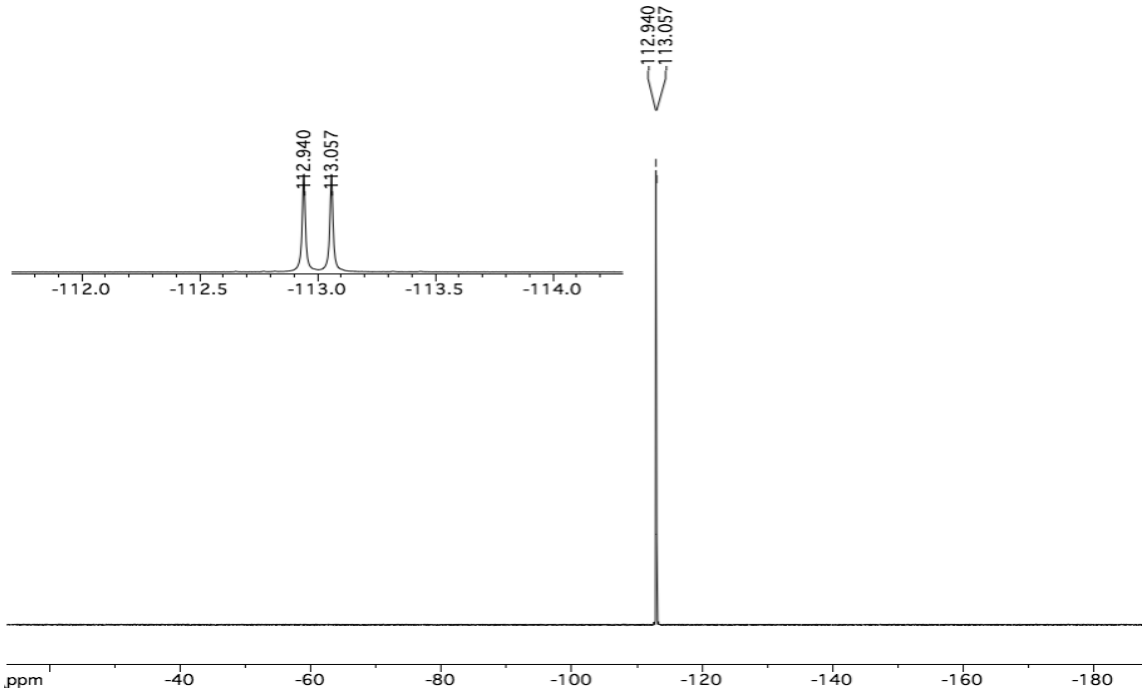
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

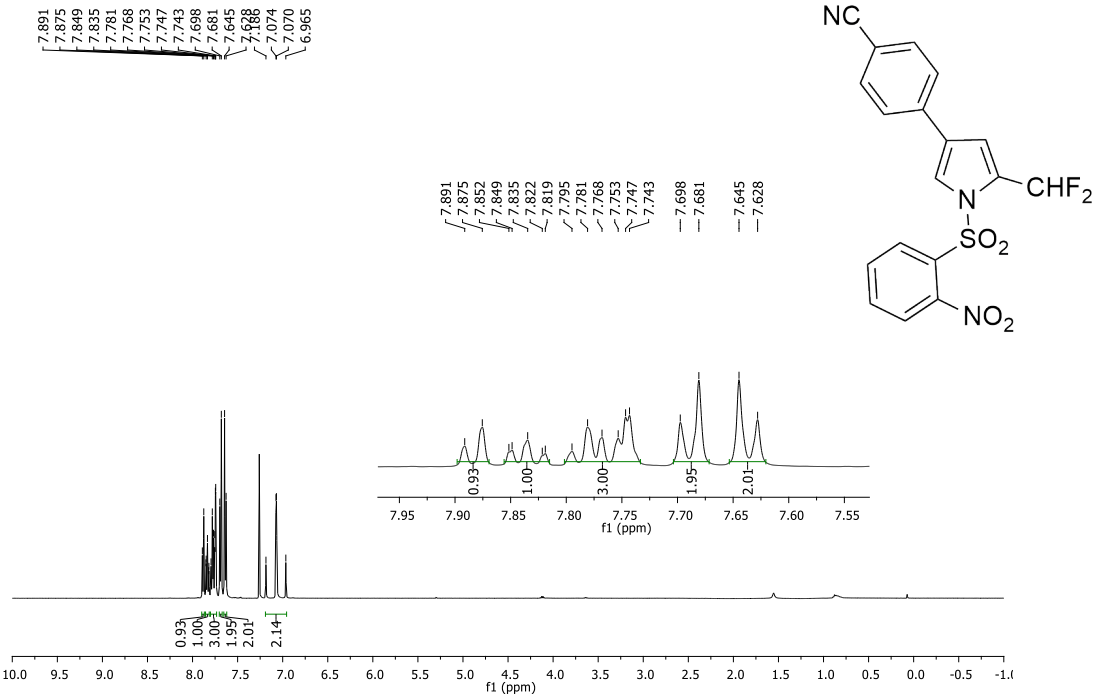


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

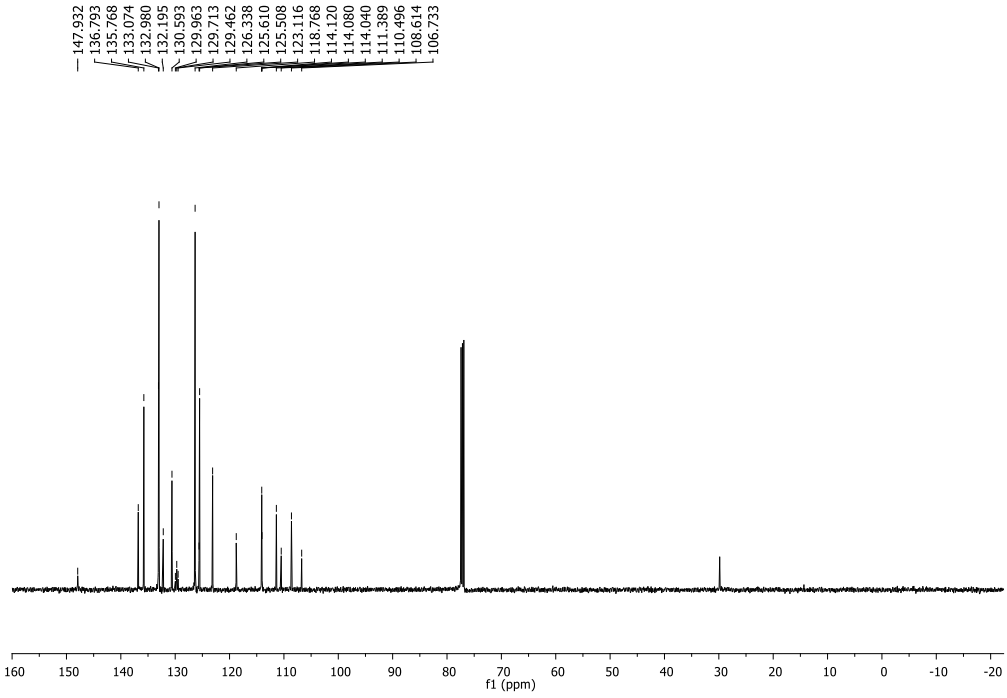


2-(Difluoromethyl)-4-(4-cyanoyphenyl)-1-(2-nitrophenylsulfonyl)-pyrrole (19f)

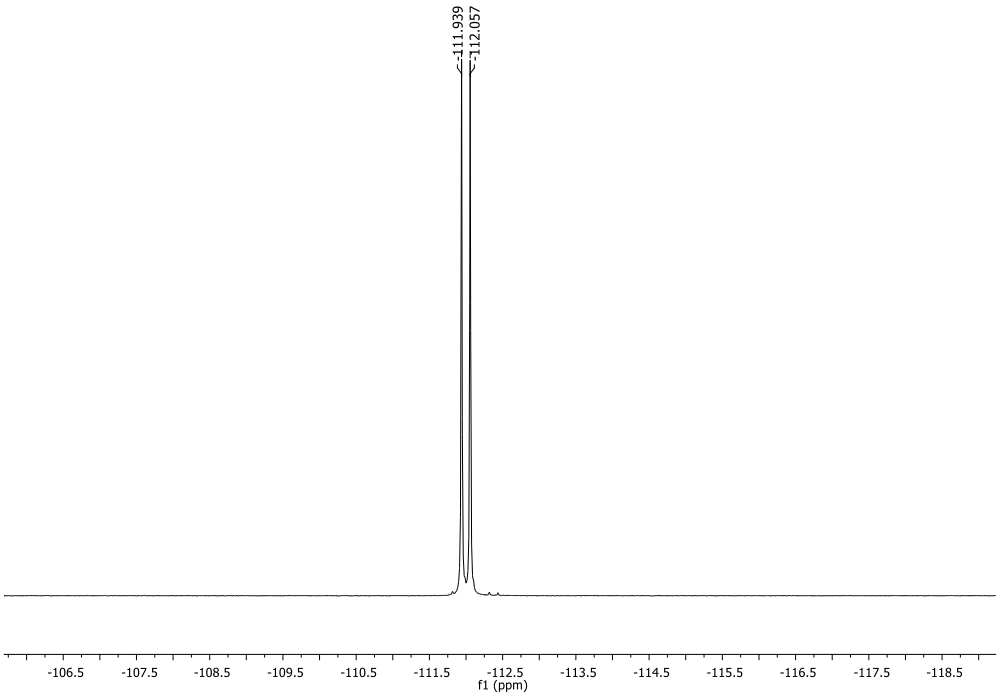
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

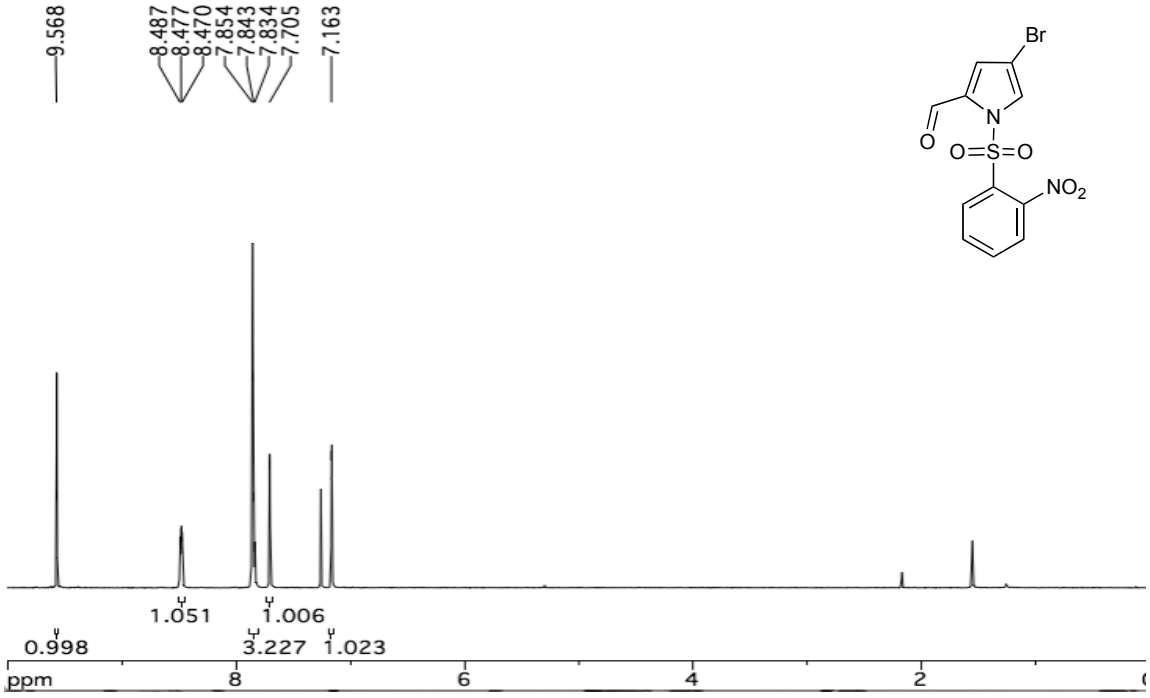


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

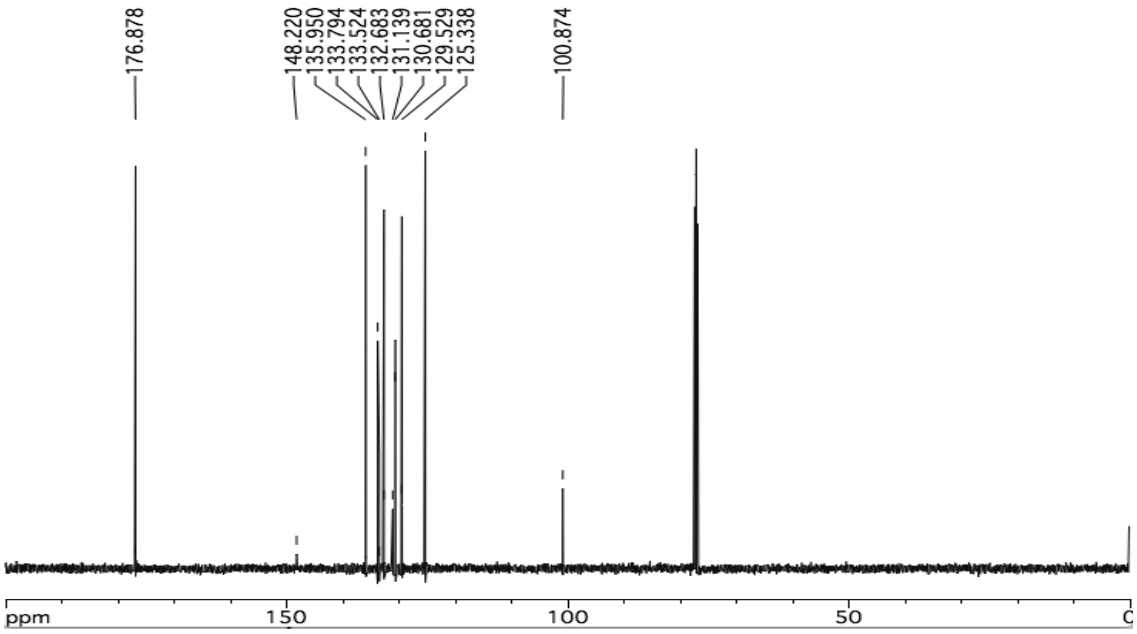


4-Bromo-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (20)

^{1}H NMR spectrum in $CDCl_3$, 500 MHz

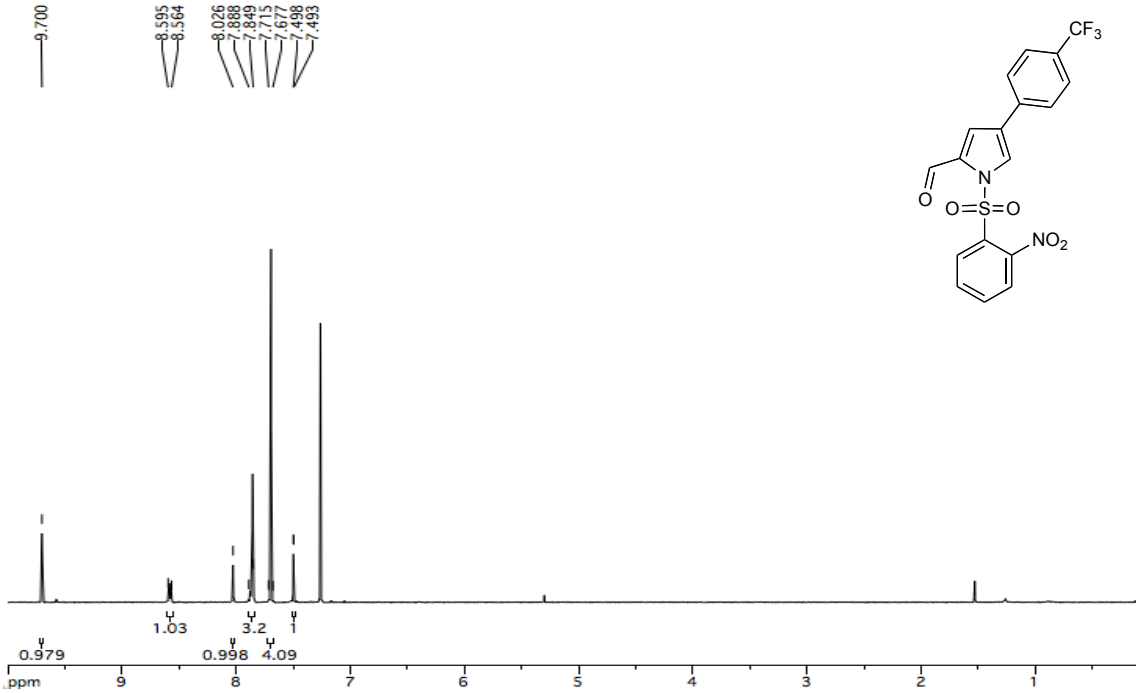


^{13}C NMR spectrum in $CDCl_3$, 125 MHz

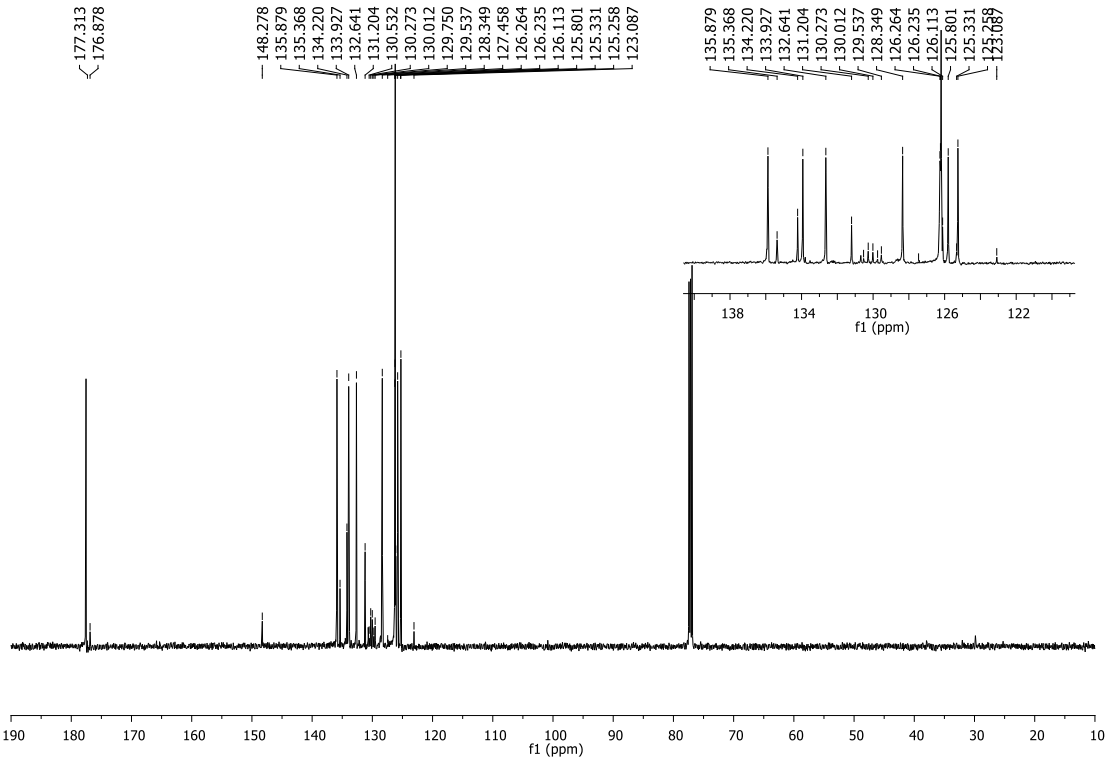


1-(2-Nitrophenylsulfonyl)-4-(4-(trifluoromethyl)phenyl)-pyrrole-2-carbaldehyde (21a)

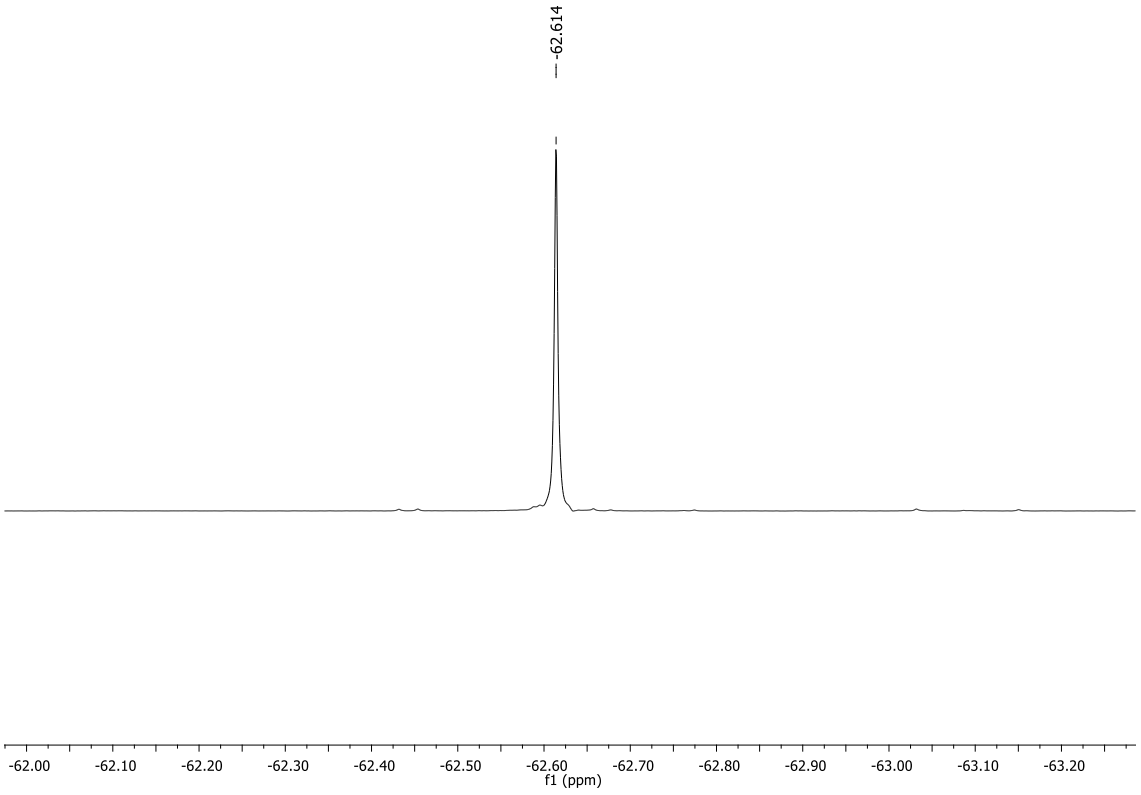
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

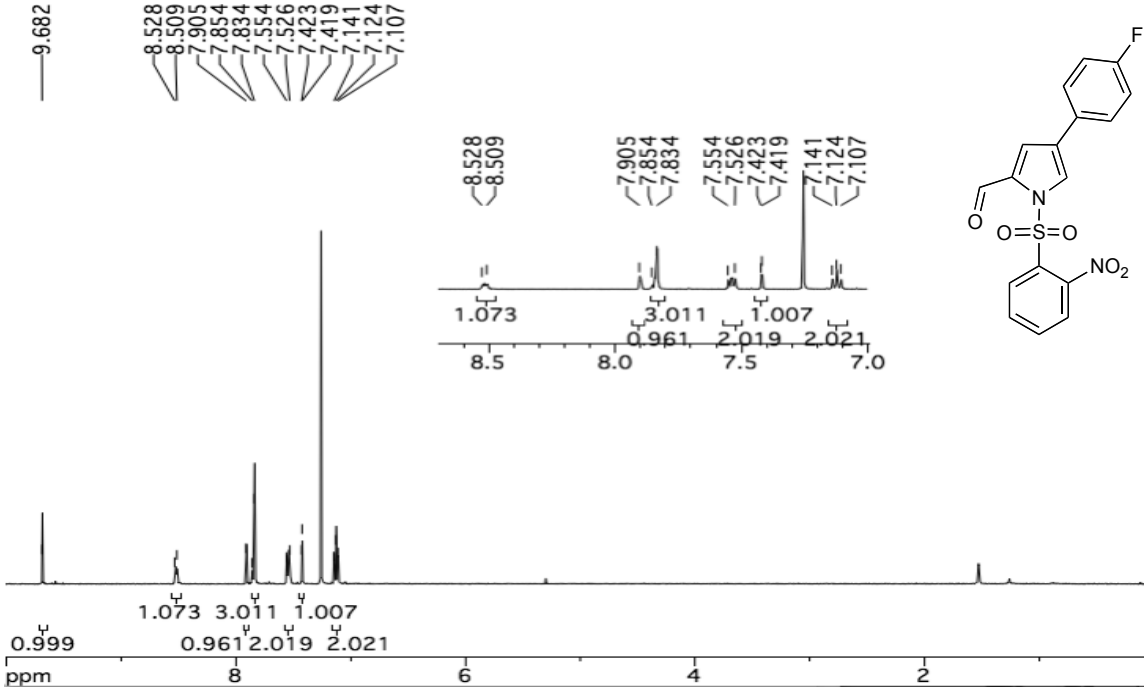


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

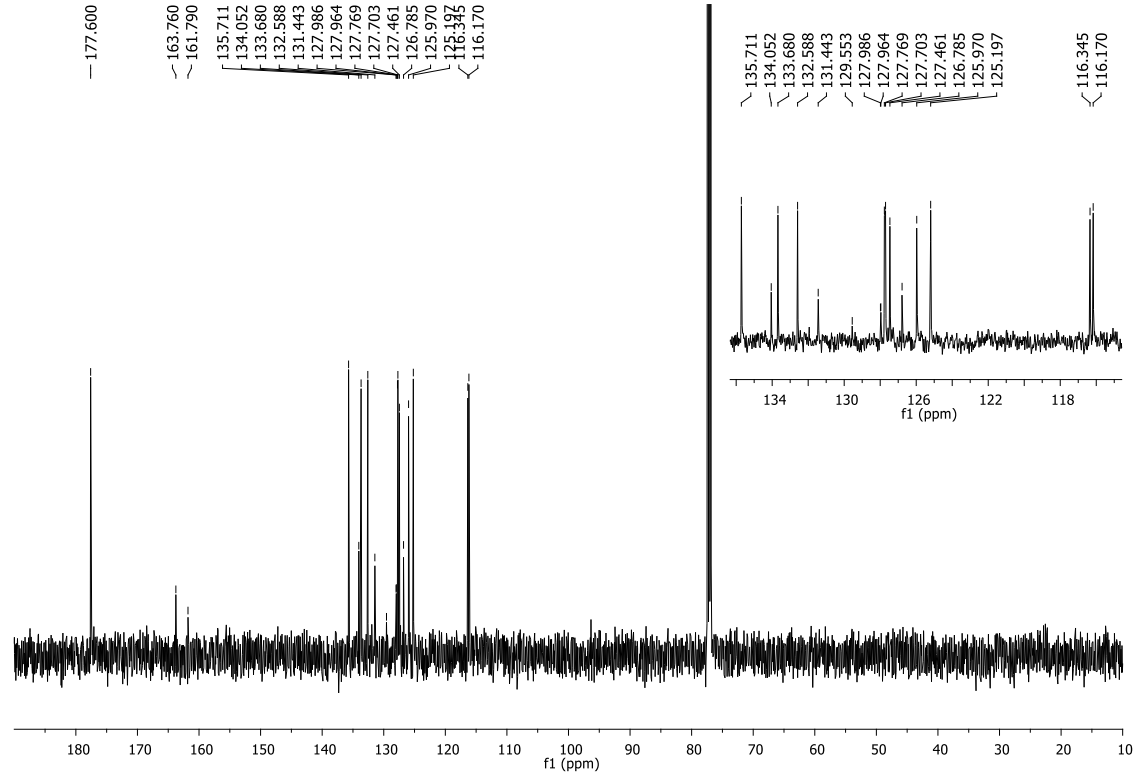


4-(4-Fluorophenyl)-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (21b)

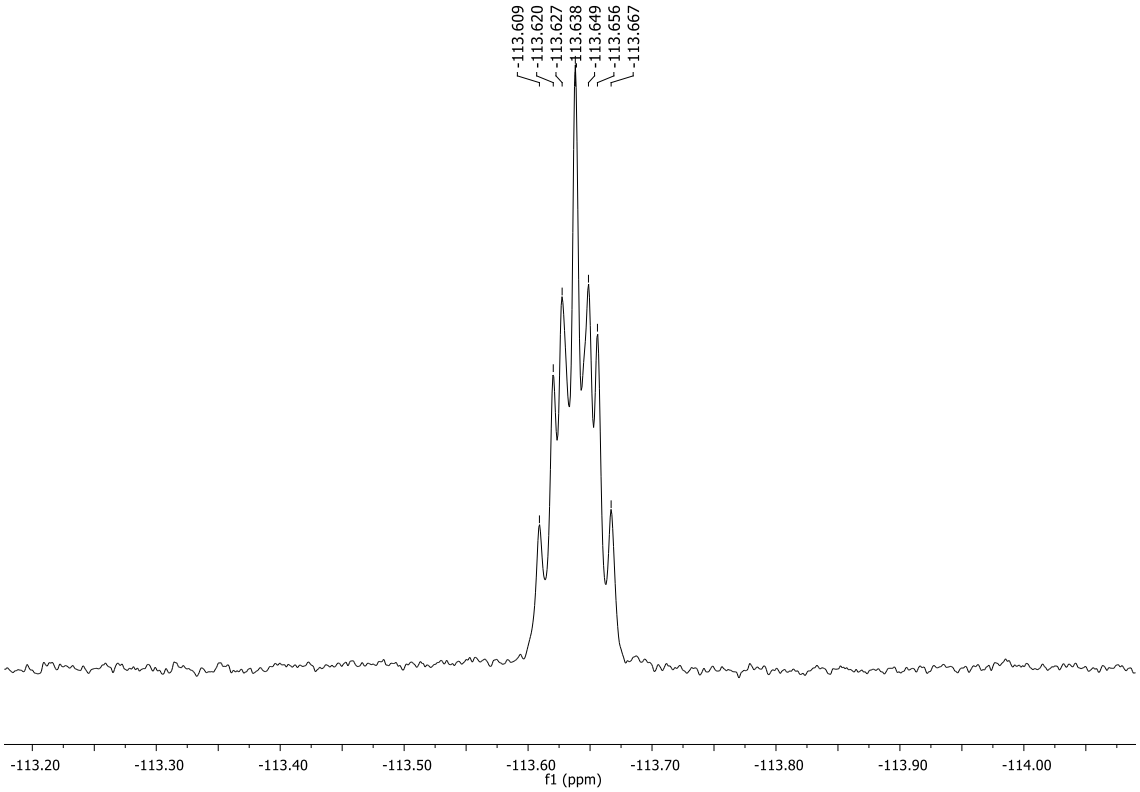
^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz

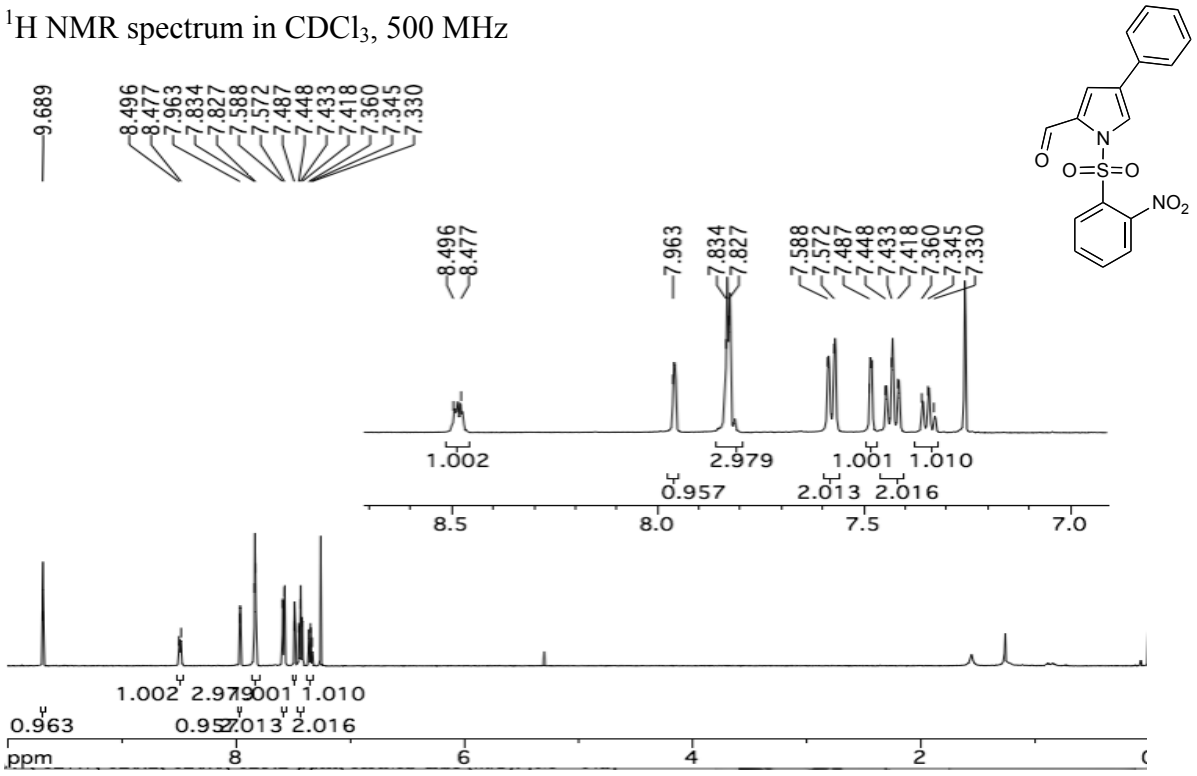


^{19}F NMR spectrum in $CDCl_3$, 470 MHz

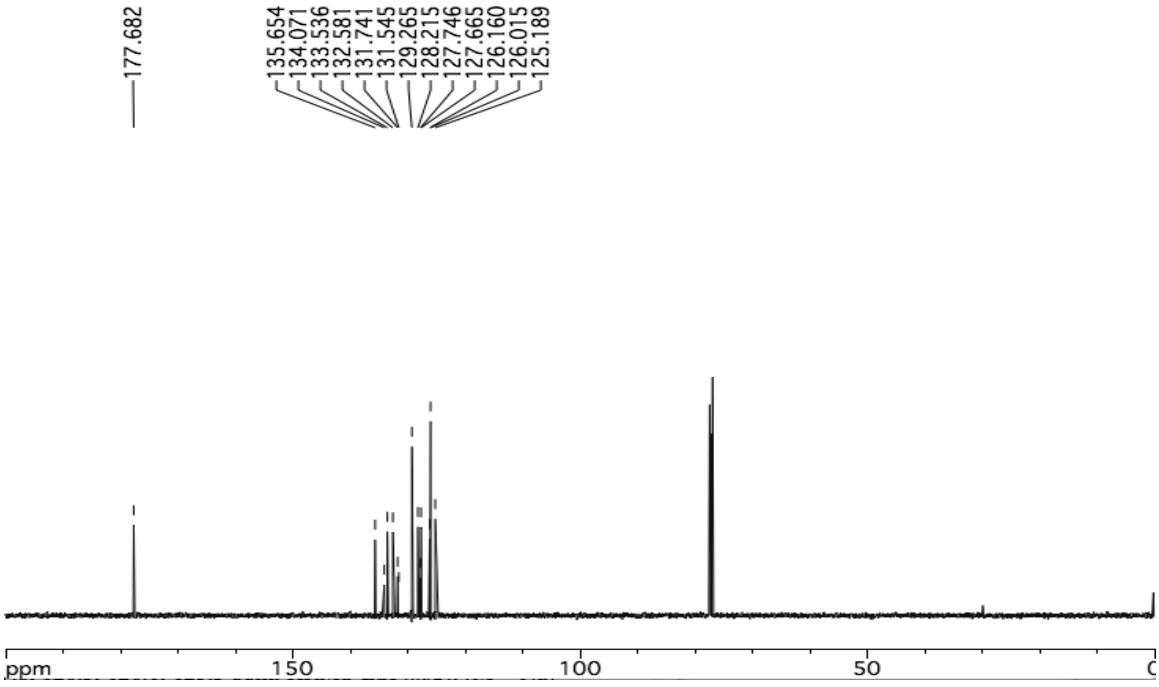


1-(2-Nitrophenylsulfonyl)-4-phenyl-pyrrole-2-carbaldehyde (21c)

^{1}H NMR spectrum in $CDCl_3$, 500 MHz

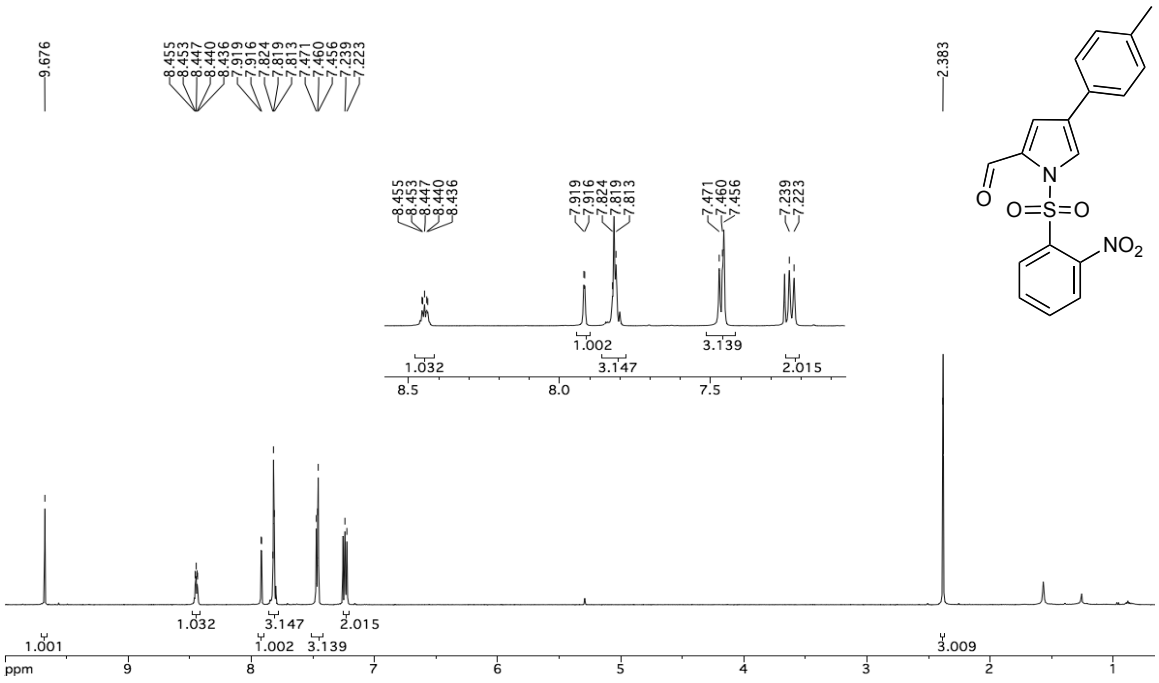


^{13}C NMR spectrum in $CDCl_3$, 125 MHz

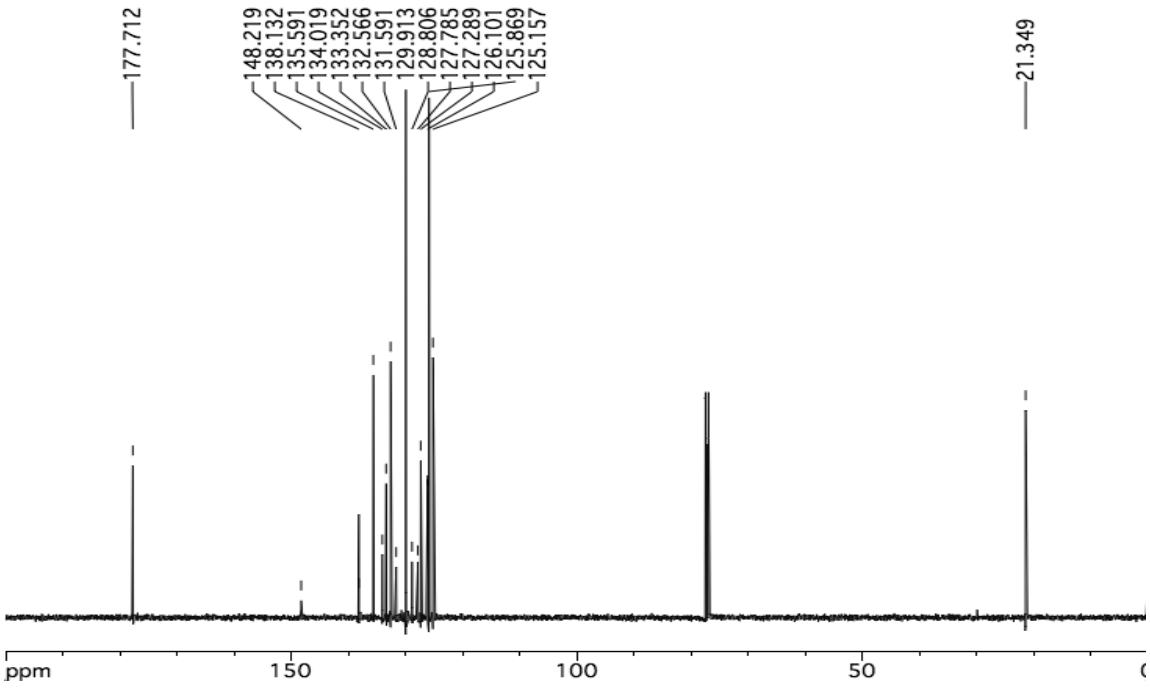


1-(2-Nitrophenylsulfonyl)-4-*p*-tolyl-pyrrole-2-carbaldehyde (21d)

^{1}H NMR spectrum in $CDCl_3$, 500 MHz

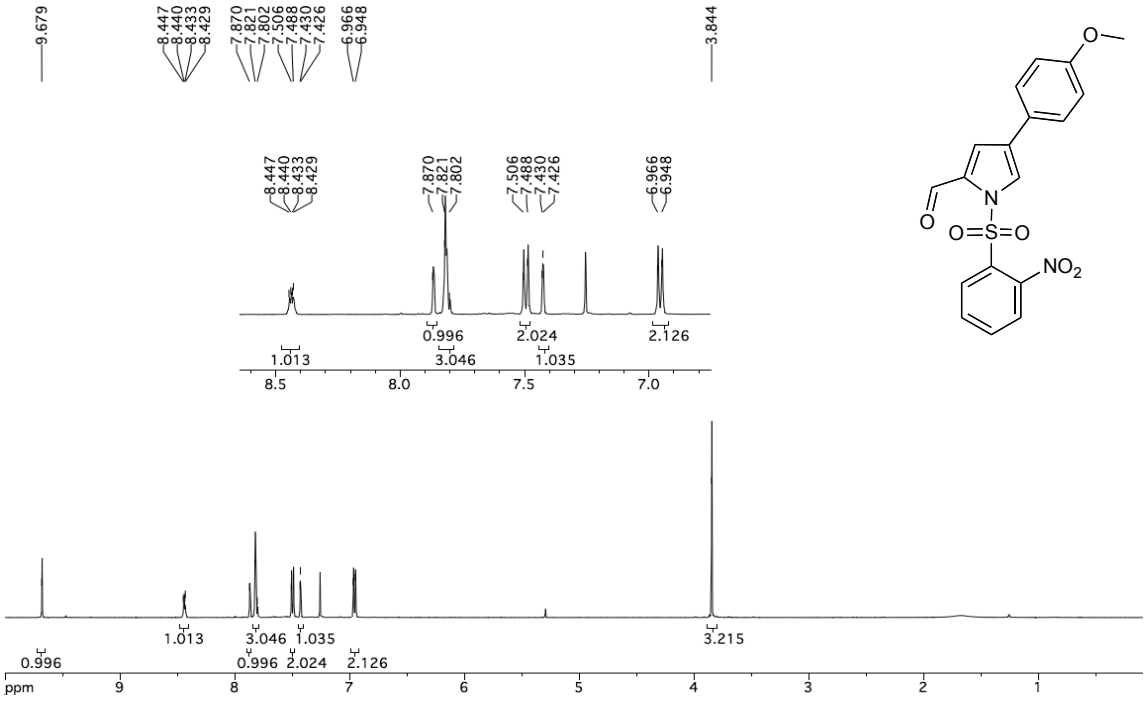


^{13}C NMR spectrum in $CDCl_3$, 125 MHz

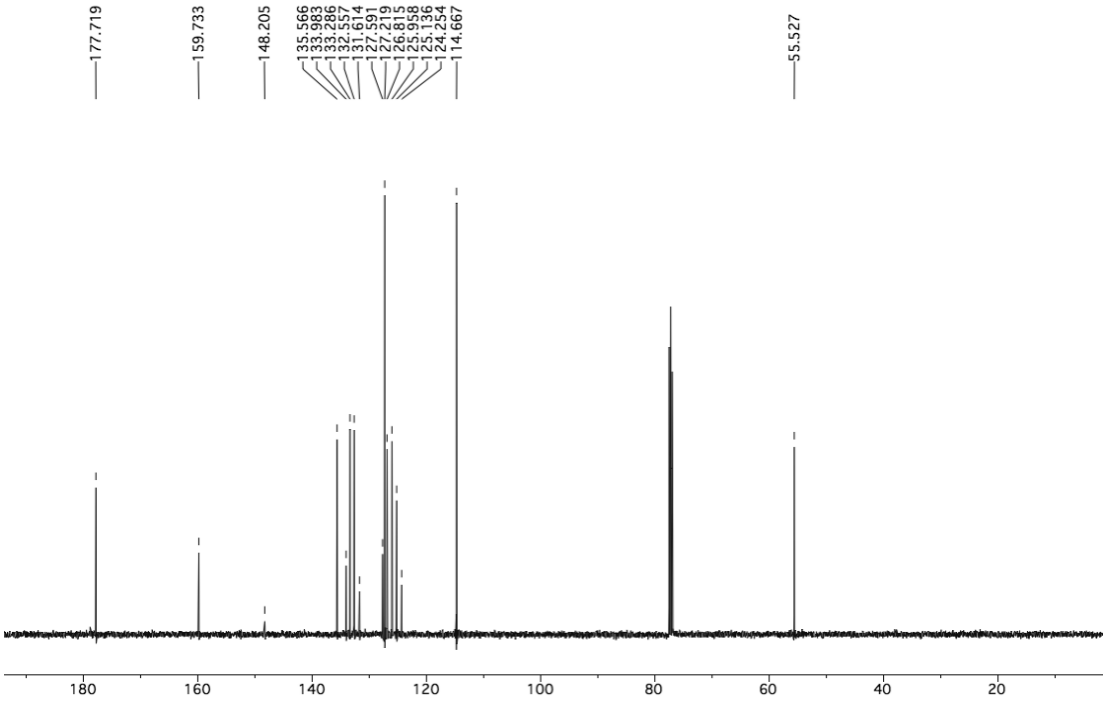


4-(4-Methoxyphenyl)-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (21e)

^{1}H NMR spectrum in $CDCl_3$, 500 MHz

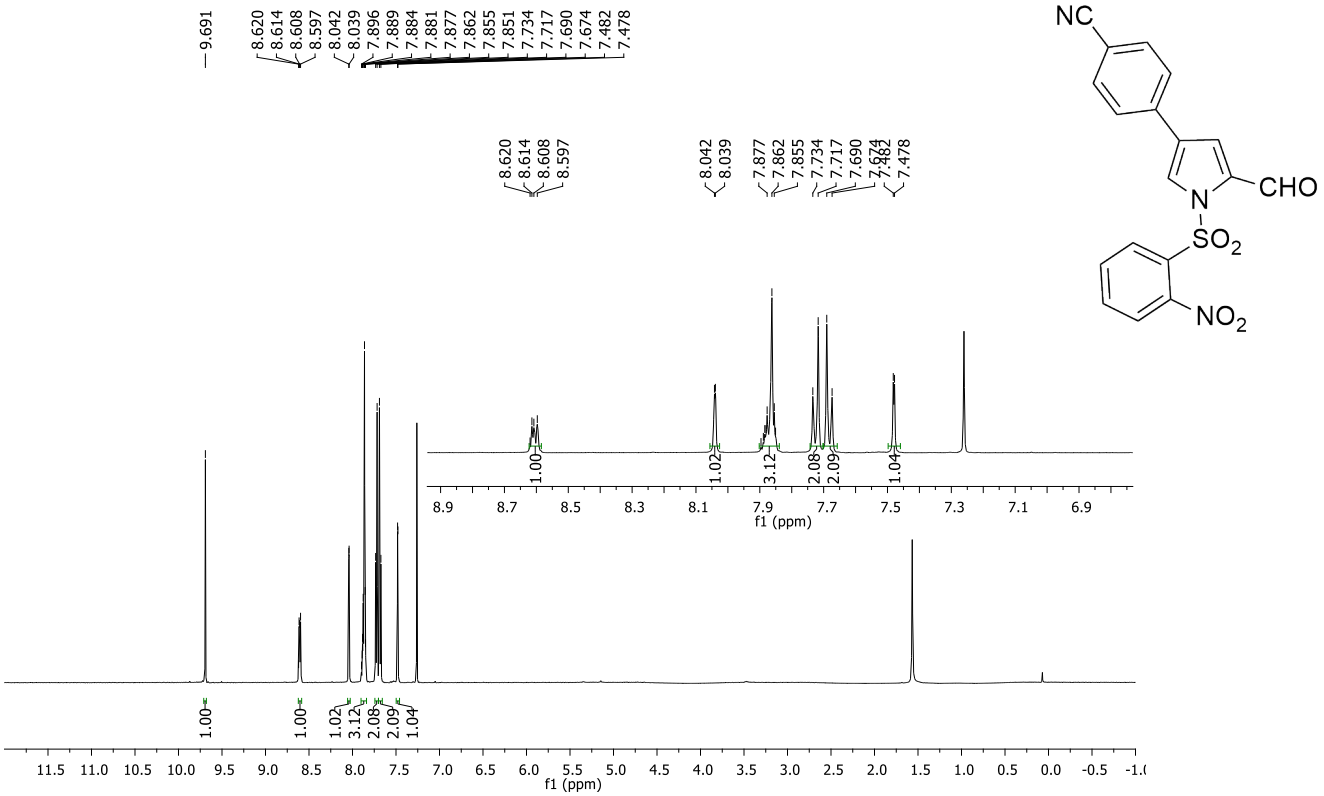


^{13}C NMR spectrum in $CDCl_3$, 125 MHz



4-(4-Cyanophenyl)-1-(2-nitrophenylsulfonyl)-pyrrole-2-carbaldehyde (21f)

^{1}H NMR spectrum in $CDCl_3$, 500 MHz



^{13}C NMR spectrum in $CDCl_3$, 125 MHz