Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supplementary Information

Copper-Catalyzed Aerobic Nitrogen-Migration Cyanation and Oxygenation of Unsaturated Keto Oximes via C=C Bond Cleavage: Facile Access to 4-Oxobutanenitriles

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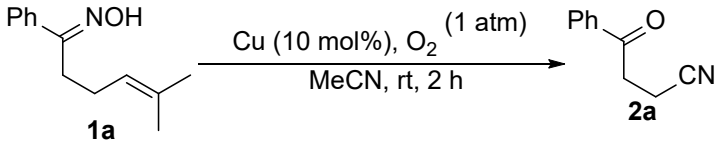
Contents

(A) General Information

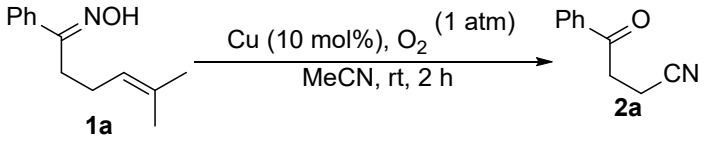
^{1}H-NMR and ^{13}C-NMR spectra were recorded at room temperature using a Bruker Avance-500 instruments or Avance-400 instruments (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz), NMR spectra of all products were reported in ppm with reference to solvent signals [^{1}H NMR: $CD(H)Cl_3$ (7.26 ppm), ^{13}C NMR: $CD(H)Cl_3$ (77.00 ppm)]. Highresolution mass spectra (HRMS) was recorded on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry. Melting Points were recorded on Hanon MP100 Apparatus and were uncorrected. All the substrates 1 were prepared according to the known procedures.1 Unless otherwise noted, all reactions were carried out using standard Schlenk techniques, and the starting materials and solvents were commercially available and were used without further purification. Column chromatography was performed on silica gel (200-300 mesh) using petroleum ether (PE)/ethyl acetate (EA). The unsaturated oximes **1** were prepared according to the literatures.[1]

(a) Typical Procedure for the Copper-Catalyzed Aerobic Nitrogen-Migration Cyanation and Oxygenation of Unsaturated Keto Oximes



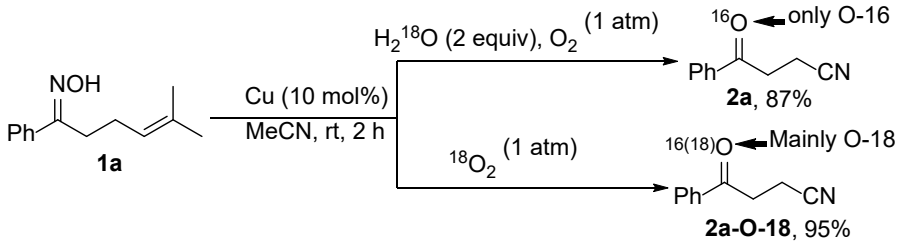
To a Schlenk tube were added 5-methyl-1-phenylhex-4-en-1-one oxime **1a** (40.6 mg, 0.2 mmol), Cu powder (0.02 mmol; 10 mol%), and CH_3CN (2 mL). Then the tube was charged with O_2 three times, and was stirred at room temperature for 2 h until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. After the reaction was finished, the reaction mixture was washed by saturated NaCl solution (5 mL × 3), and diluted in diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to provide **2a**.

(b) General Procedure for 1 mmol Scale of 1a.

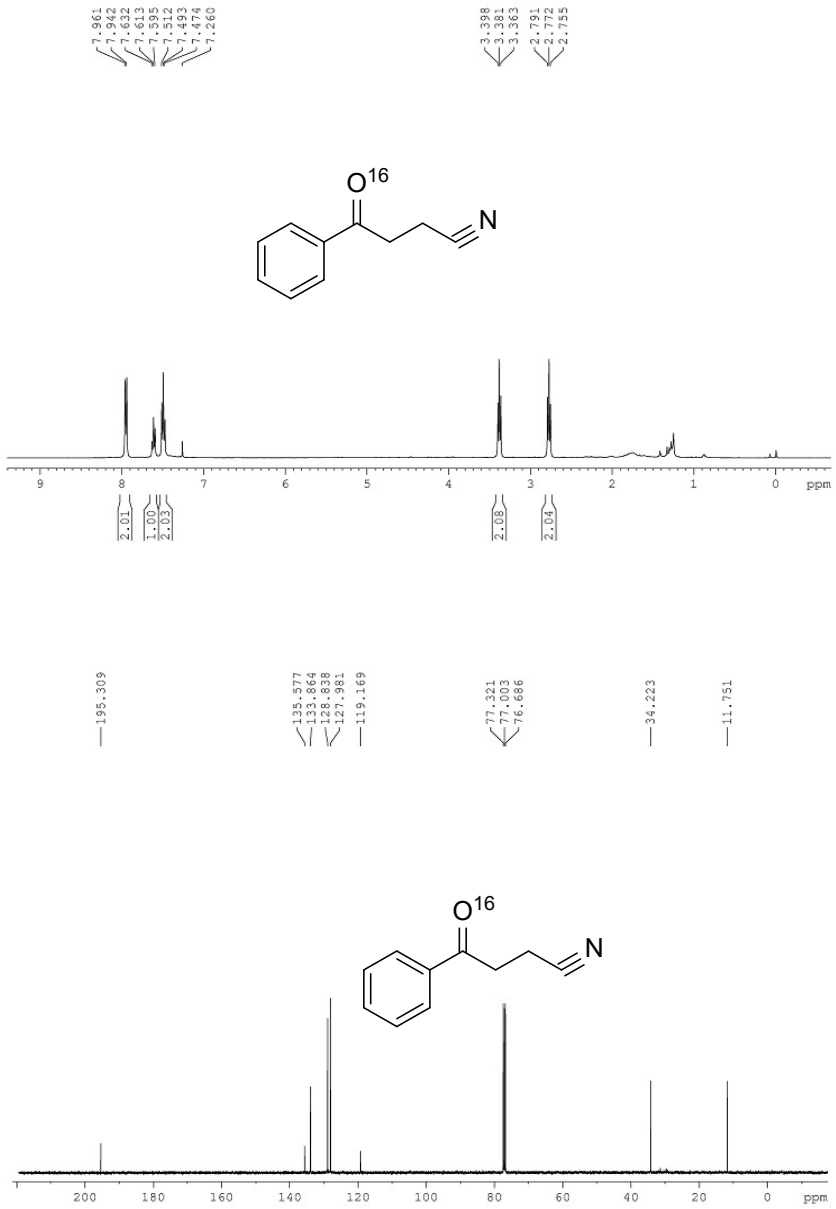


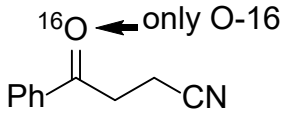
To a Schlenk tube were added 5-methyl-1-phenylhex-4-en-1-one oxime **1a** (203 mg, 1 mmol), Cu powder (0.1 mmol; 10 mol%), and CH_3CN (5 mL). Then the tube was charged with O_2 three times, and was stirred at room temperature for 2 h until complete consumption of starting material as monitored by TLC and/or GC-MS analysis. After the reaction was finished, the reaction mixture was washed by saturated NaCl solution (5 mL × 3), and diluted in diethyl ether. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate = 10:1) to provide **2a** (143.1 mg; 90% yield).

(c) Isotope-Labelled Experiments

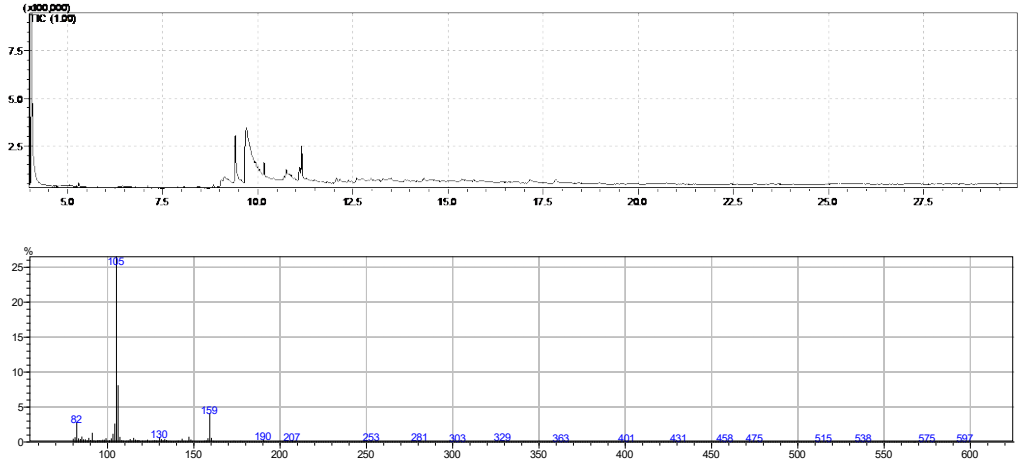


The product **2a** was purified by flash chromatography to give 27.7 mg (87%) as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.95 (d, *J* = 9.5 Hz, 2H), 7.63 (t, *J* = 9.5 Hz, 1H), 7.49 (t, *J* = 9.5 Hz, 1H), 3.38 (t, *J* = 8.5 Hz, 2H), 2.78 (t, *J* = 9.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 195.309, 135.6, 133.9, 128.8, 128.0, 119.2, 34.2, 11.8.





(MW=159)



[MS Spectrum]

# of Peaks 521

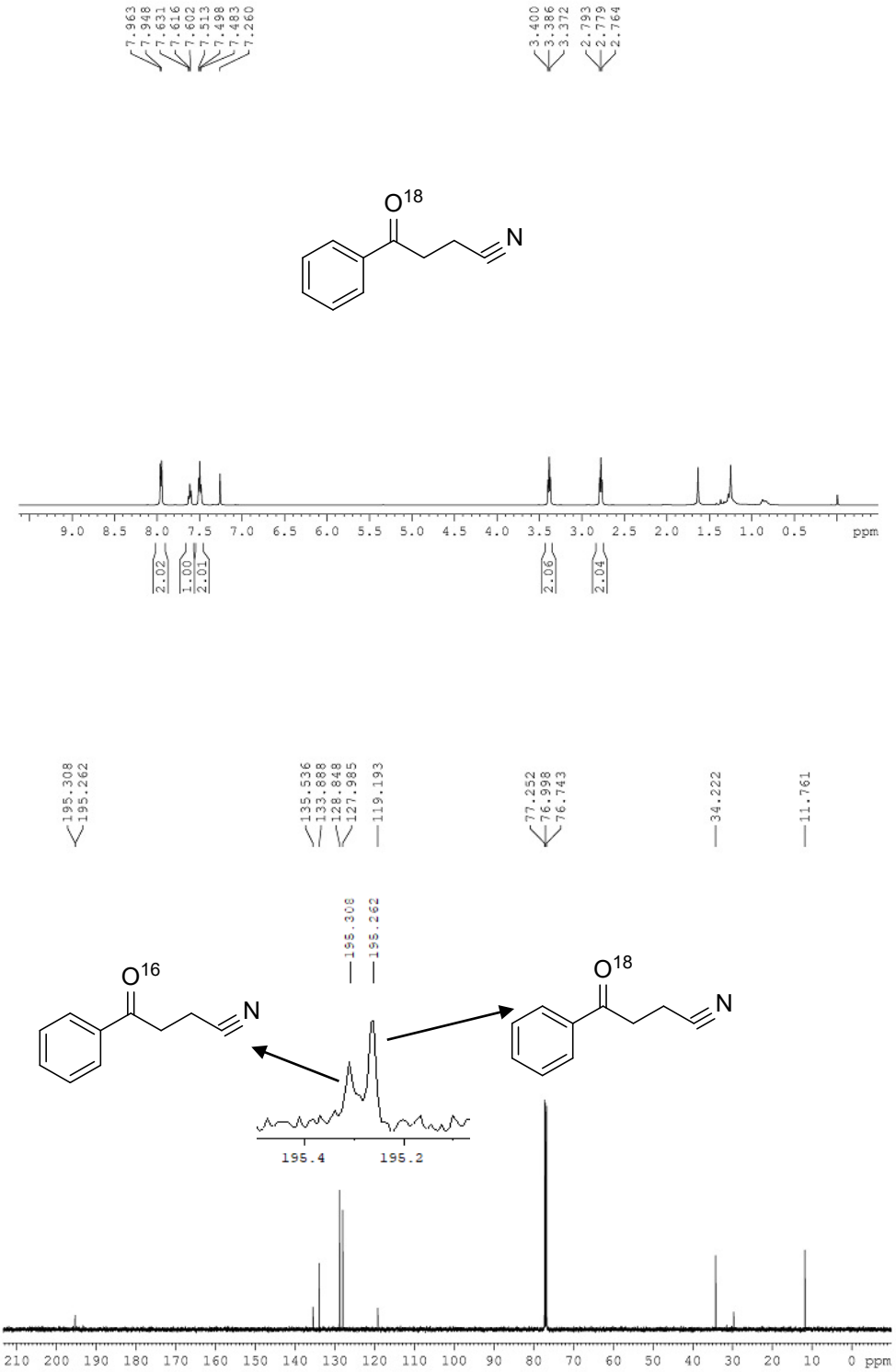
Raw Spectrum 9.730 (scan : 1147) Base Peak m/z 105.15 (Inten : 199,519)

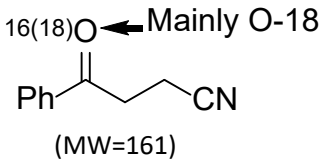
Background No Background Spectrum

m/z Absolute Intensity Relative Intensity

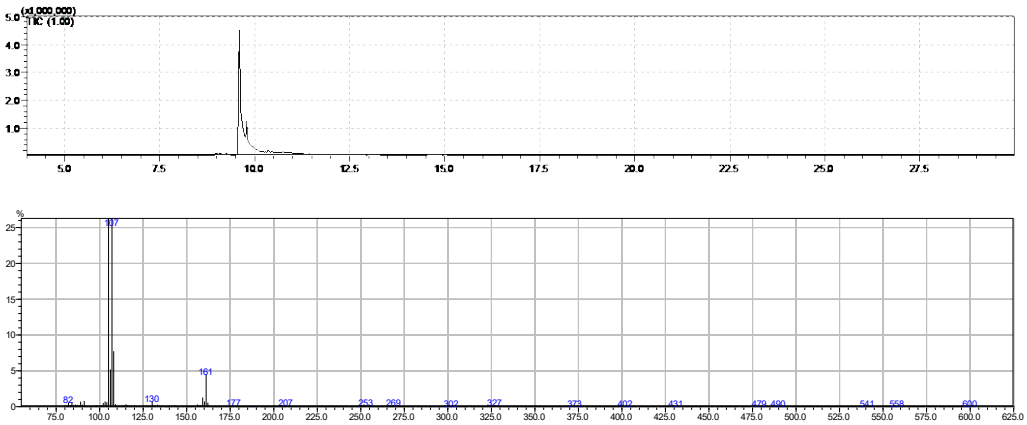
80.10	815	0.41	100.20	223	0.11	127.30	391	0.20
81.20	1220	0.61	101.10	310	0.16	128.30	279	0.14
82.15	5519	2.77	102.15	886	0.44	129.20	252	0.13
83.20	870	0.44	103.15	2196	1.10	130.20	1247	0.63
84.20	694	0.35	104.15	5125	2.57	131.20	646	0.32
85.15	1400	0.70	105.15	199519	100.00	132.20	311	0.16
86.10	606	0.30	106.15	16071	8.05	133.15	640	0.32
87.10	590	0.30	107.15	1325	0.66	134.20	439	0.22
88.15	339	0.17	108.20	358	0.18	143.25	776	0.39
89.15	1039	0.52	113.15	721	0.36	147.15	1339	0.67
90.15	441	0.22	114.10	215	0.11	148.25	557	0.28
91.15	2468	1.24	115.15	1043	0.52	149.30	191	0.10
92.10	316	0.16	116.15	510	0.26	156.30	231	0.12
94.10	343	0.17	117.25	378	0.19	157.20	290	0.15
95.10	402	0.20	118.20	417	0.21	158.20	930	0.47
96.10	342	0.17	120.20	252	0.13	**159.20**	**8030**	**4.02**
97.20	502	0.25	122.20	220	0.11	**160.20**	**1038**	**0.52**
98.15	533	0.27	123.20	502	0.25	**161.20**	**198**	**0.10**
99.15	947	0.47	126.20	279	0.14	162.20	71	0.04

The product **2a-O-18** was purified by flash chromatography to give 30.2 mg (95%) as yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.95 (d, *J* = 9.5 Hz, 2H), 7.63 (t, *J* = 9.5 Hz, 1H), 7.49 (t, *J* = 9.5 Hz, 1H), 3.38 (t, *J* = 8.5 Hz, 2H), 2.78 (t, *J* = 9.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 195.308, 195.262, 135.5, 133.9, 128.8, 128.0, 119.2, 34.2, 11.8.





(MW=161)



[MS Spectrum]

# of Peaks 505

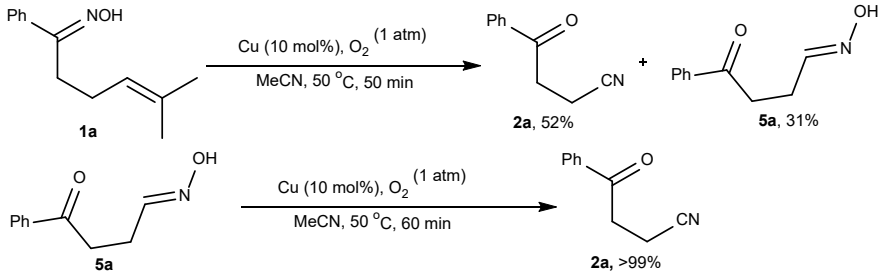
Raw Spectrum 9.645 (scan : 1130) Base Peak m/z 107.10 (Inten : 893,447)

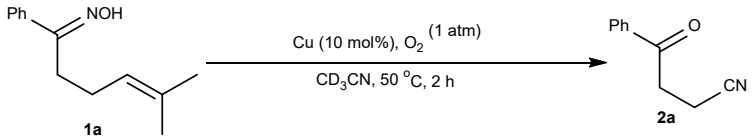
Background No Background Spectrum

m/z Absolute Intensity Relative Intensity

80.05	1156	0.13	92.10	618	0.07	130.15	5259	0.59
81.10	535	0.06	97.20	950	0.11	131.15	1095	0.12
82.10	3942	0.44	98.10	900	0.10	132.20	980	0.11
83.15	1365	0.15	101.10	1198	0.13	133.20	1841	0.21
84.10	4764	0.53	102.10	4151	0.46	134.20	970	0.11
85.10	1510	0.17	103.15	5786	0.65	**159.15**	**10816**	**1.21**
86.10	1887	0.21	104.15	4943	0.55	**160.15**	**5917**	**0.66**
87.10	1679	0.19	105.10	246516	27.59	**161.15**	**39408**	**4.41**
88.15	1095	0.12	106.15	45786	5.12	162.15	4432	0.50
89.10	5652	0.63	107.10	893447	100.00	163.15	298	0.03
90.10	1682	0.19	108.10	68662	7.69	164.10	103	0.01
91.15	6593	0.74	109.10	2551	0.29			

(d) The Reaction Process Monitored by ^{1}H NMR Analysis.





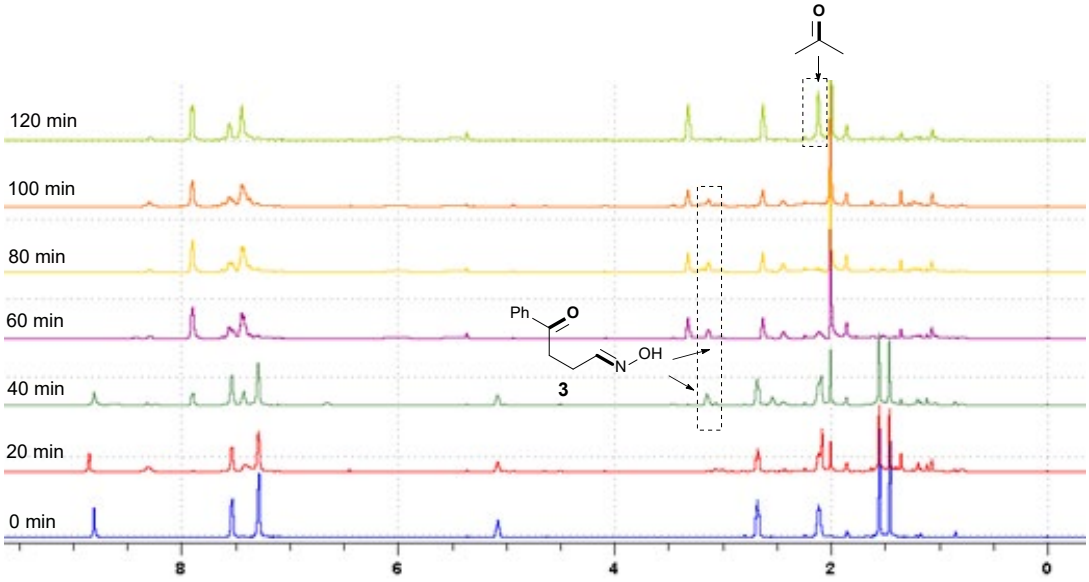
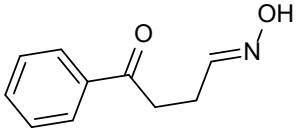
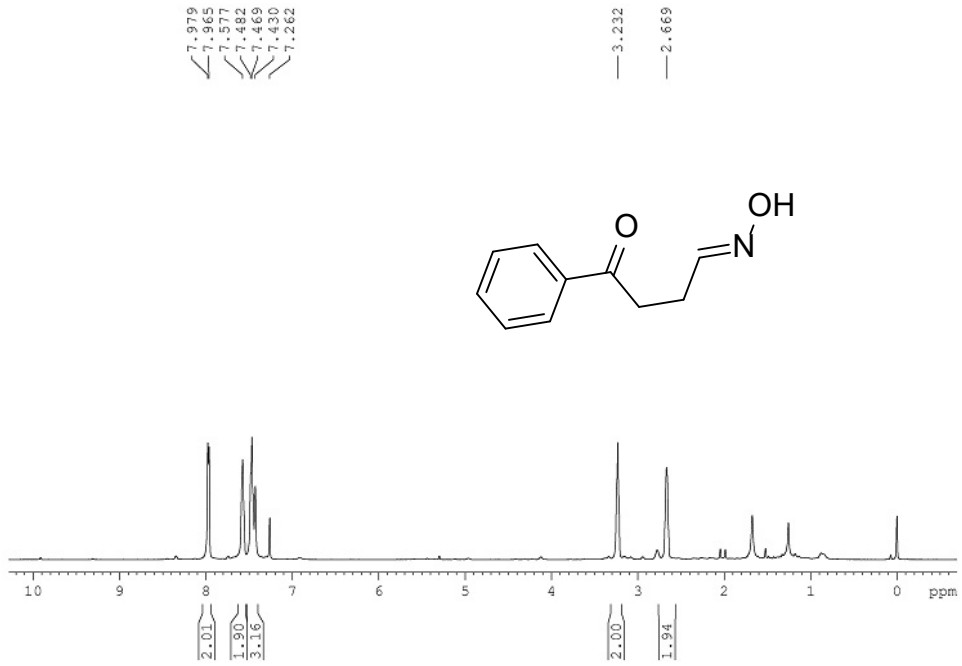


Figure S1. Control Experiments and Reaction Process Monitored by 1H NMR Analysis.

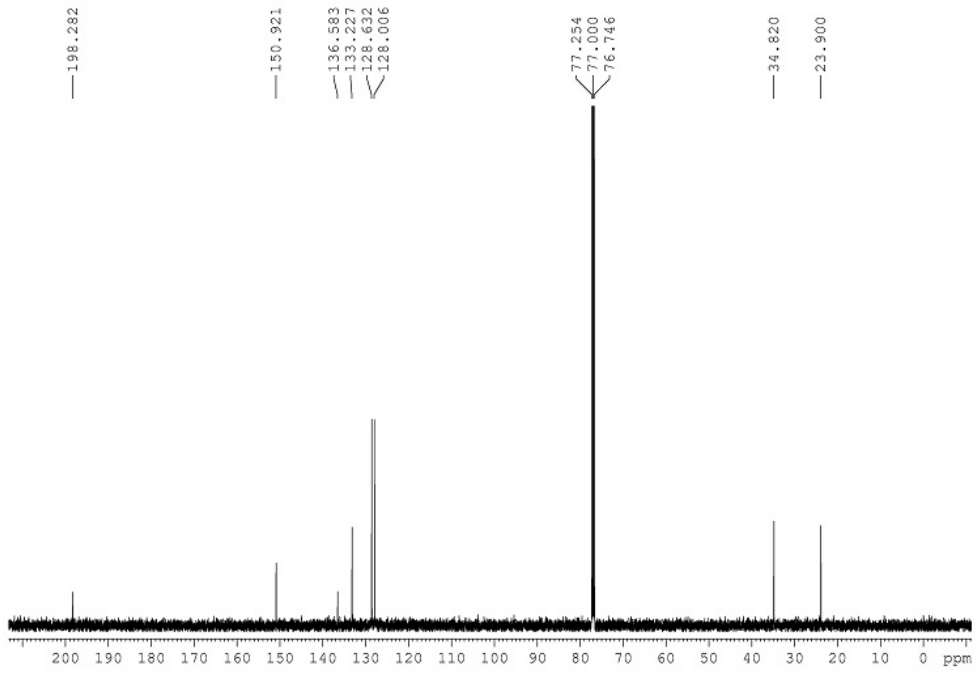
4-oxo-4-phenylbutanal oxime (5a)



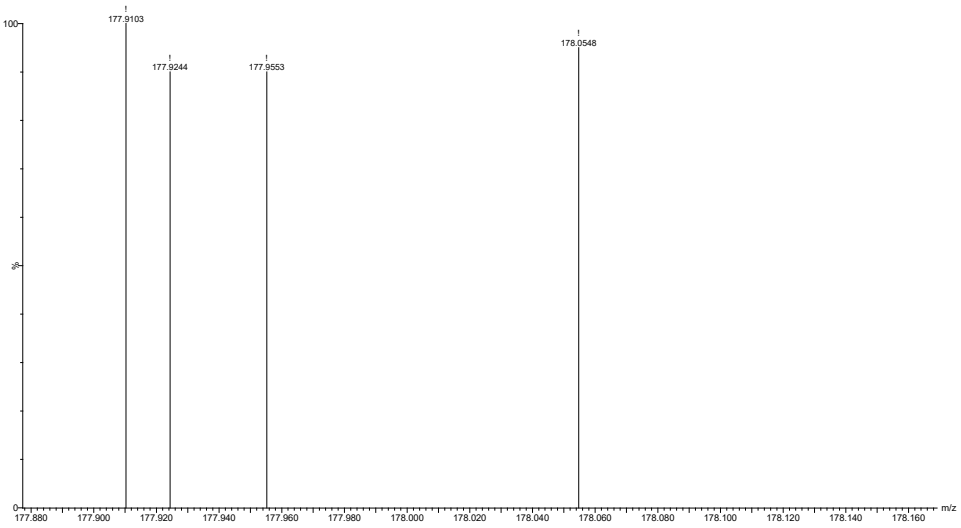
The product was purified by flash chromatography to give as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.98 (d, *J* = 7.0 Hz, 2H), 7.58 (s, 2H), 7.43-7.48 (m, 3H), 3.23 (s, 2H), 2.67 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 198.3, 150.9, 136.6, 133.2, 128.6, 128.0, 34.8, 23.9. HRMS (ESI) m/z calcd for $C_{10}H_{12}NO_2^+$ $(M+H)^+$ 178.0863, found 178.0548.



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)


177.9103
177.9244
177.9553
178.0548
100
%
0
177.880
177.900
177.920
177.940
177.960
177.980
178.000
178.020
178.040
178.060
178.080
178.100
178.120
178.140
178.160
m/z

HRMS (ESI)

(e) EPR Spectra Experiments

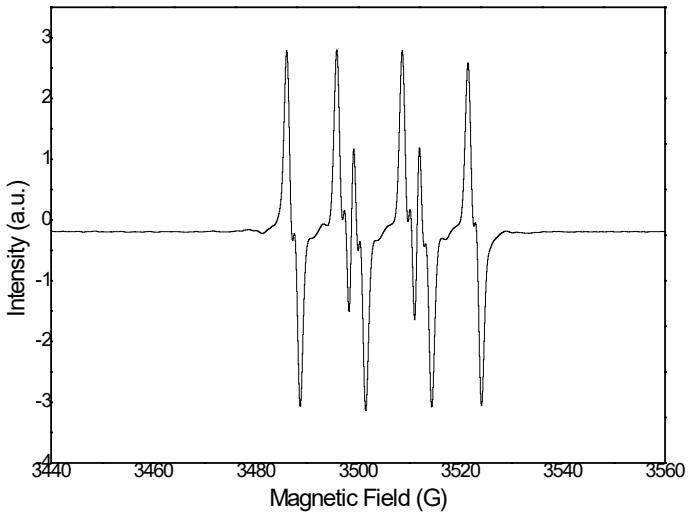


Figure S2 EPR Spectra of Reaction System: **1a** (0.20 mmol), Cu powder (0.020 mmol), CH_3CN (2 mL), stirred at 50 °C under O_2 (1 atm), 0.5 h. 0.01 mL of this reaction solution was taken out into a small tube, followed by the addition of 0.01 mL DMPO (5*10-2 M). Then, this mixture was analyzed by EPR. There are classical six peaks the signals corresponding to (DMPO–$O_2^{\cdot-}$).

In the EPR spectra monitored with the addition of the radical trap 5-,5-dimethyl-1-pyrroline N-oxide (DMPO), the signal corresponding to DMPO–$O_2^{\cdot-}$ has been identified which are classical six peaks. Furthermore, these EPR results demonstrate that the Superoxide radical is generated from O_2.

(f) Hammett Studies of the Reaction

To a Schlenk tube were added Cu power (0.02 mmol; 10 mol%), 5-methyl-1-phenylhex-4-en-1-one oxime **1a** (0.2 mmol; 1.0 equiv), and CD_3CN (2 mL). Then the tube was charged with oxygen three times, was stirred at room temperature, six groups were carried out in parallel and stop the one of reaction every ten minute. After that, the reaction system through followed by addition of 1,4-Diazine as an internal standard determine the yields. As the results shown in Figure S3, substituents on benzene have not a impact on the reaction rate and the ρ value (0.49) in Hammett plot was given in below. These results suggest that there is a buildup of negative charge on the benzene ring in the transition state.

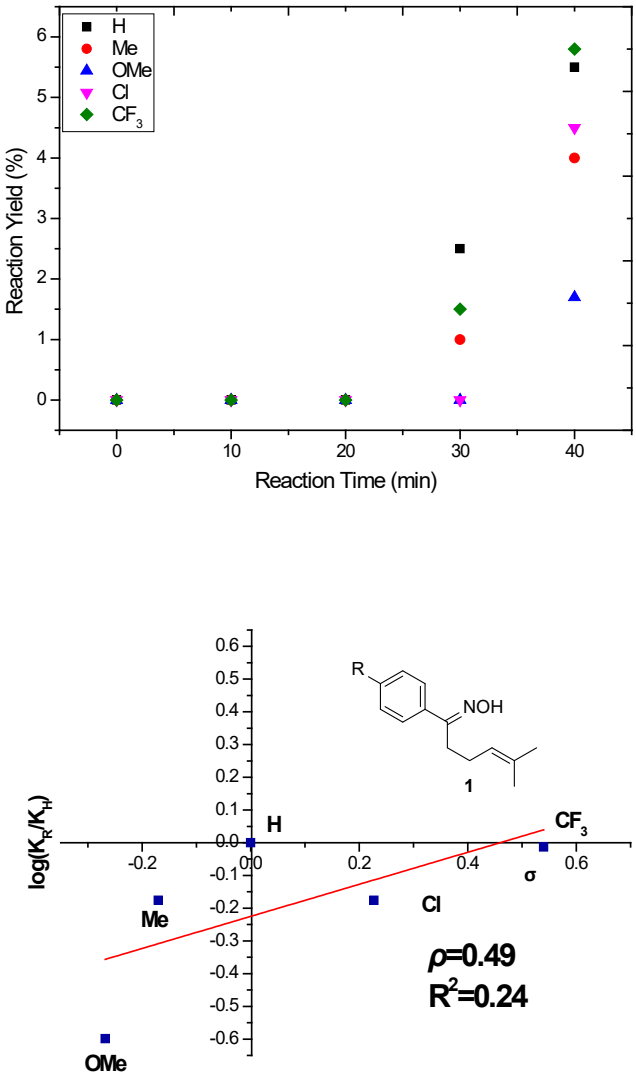


Figure S3 The Electronic Effect of 1 for the Reaction (TOP: Time course of reaction; Bottom: Hammett plot, log(kR/kH) vs σ).

(g) The UV-Visible Spectroscopic Analysis of the Effect of CH_3CN, 1a and [Cu] Catalyst.

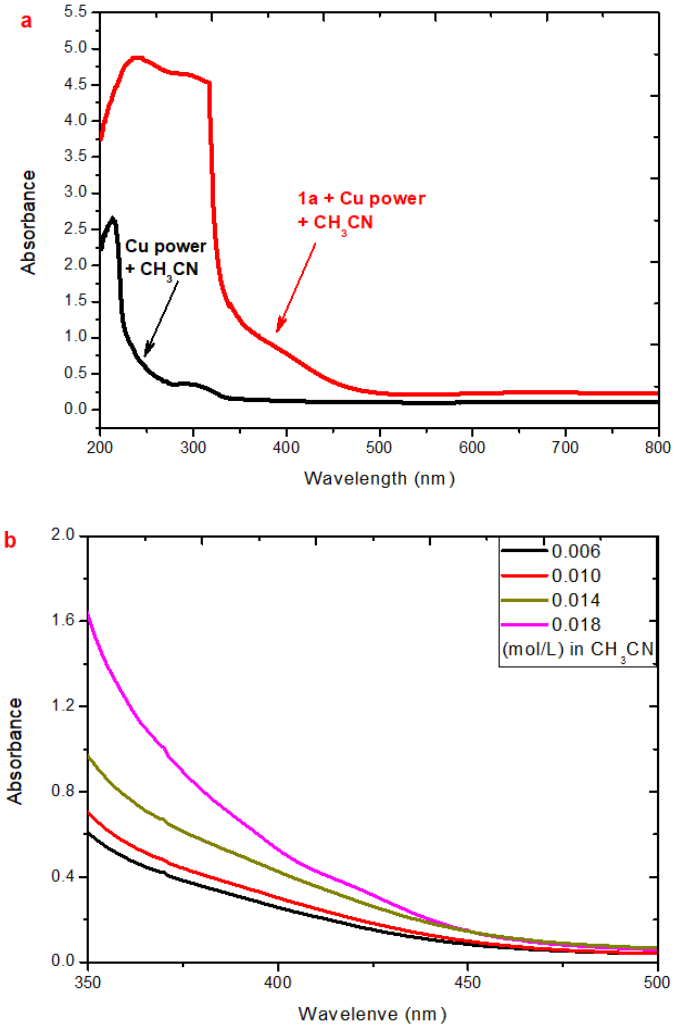
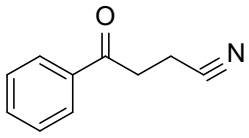


Figure S4 The UV-Visible Spectroscopic Experiment. **a:** Cu power (0.01 mmol/mL) in CH_3CN (dark line); both Cu power (0.01 mmol/mL) and **1a** (0.01 mmol/mL) in CH_3CN (red line). **b:** Cu power (0.01 mmol/mL) and various concentrations of **1a** in CH_3CN.

An obvious red shift of both Cu and CH_3CN were observed upon the addition of **1a** (Figure S4-a), suggesting that the reaction involves the Cu as the radical initiator (Figure S4-a). The UV−vis analysis reveals shows that **1a** and Cu had no obvious absorption peaks in the UV-vis spectra. Meanwhile, a variation of the absorbance was also along with the solution concentration of **1a** changing, suggesting that the Cu was involved in the reaction as a radical initiator**.**

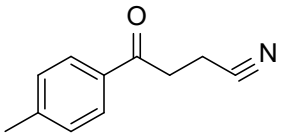
(B) Characterization Data

4-oxo-4-phenylbutanenitrile (2a)[2]



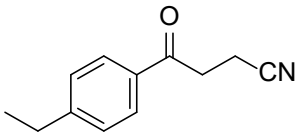
The product was purified by flash chromatography to give 30.2 mg (95%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.95 (d, *J* = 9.5 Hz, 2H), 7.63 (t, *J* = 9.5 Hz, 1H), 7.49 (t, *J* = 9.5 Hz, 1H), 3.38 (t, *J* = 8.5 Hz, 2H), 2.78 (t, *J* = 9.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 195.3, 135.6, 133.9, 128.8, 128.0, 119.2, 34.2, 11.8.

4-oxo-4-p-tolylbutanenitrile (2b)[2]



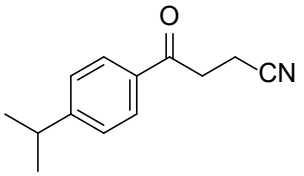
The product was purified by flash chromatography to give 31.8 mg (92%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.85 (d, *J* = 10.0 Hz, 2H), 7.29 (d, *J* = 10.0 Hz, 2H), 3.36 (t, *J* = 9.0 Hz, 2H), 2.77 (t, *J* = 9.0 Hz, 2H), 2.43 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.9, 144.9, 133.2, 129.5, 128.1, 119.3, 34.1, 21.7, 11.8.

4-(4-ethylphenyl)-4-oxobutanenitrile (2c)



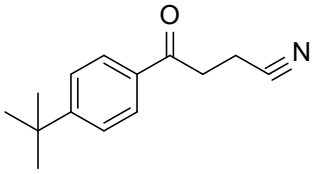
The product was purified by flash chromatography to give 31.8 mg (85%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.88 (d, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 7.5 Hz, 2H), 3.35 (t, *J* = 7.0 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.71 (t, *J* = 7.5 Hz, 2H), 1.27 (t, *J* = 8.0 Hz, 3H),. ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.9, 150.9, 133.3, 128.2, 128.1, 119.3, 34.0, 28.9, 15.0, 11.7. HRMS (ESI) m/z calcd for $C_{12}H_{14}NO^{+}$ $(M+H)^{+}$ 188.1070, found188.1088.

4-(4-isopropylphenyl)-4-oxobutanenitrile (2d)



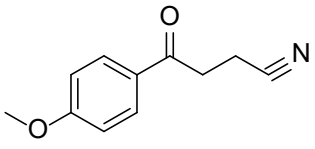
The product was purified by flash chromatography to give 33.4 mg (83%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.89 (d, *J* = 8.0 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 3.35 (t, *J* = 7.0 Hz, 2H), 2.95-3.00 (m, 1H), 2.75 (t, *J* = 7.0 Hz, 2H), 1.27 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.9, 155.4, 133.4, 128.2, 126.8, 119.3, 34.1, 34.0, 23.5, 11.7. HRMS (ESI) m/z calcd for $C_{13}H_{16}NO^{+}$ $(M+H)^{+}$ 202.1226, found202.1229.

4-(4-tert-butylphenyl)-4-oxobutanenitrile (2e)[2]



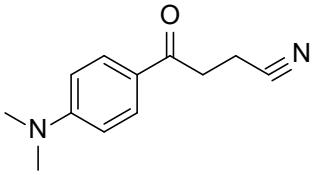
The product was purified by flash chromatography to give 38.7 mg (90%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.89 (d, *J* = 9.5 Hz, 2H), 7.50 (d, *J* = 9.5 Hz, 2H), 3.36 (t, *J* = 8.5 Hz, 2H), 2.77 (t, *J* = 8.5 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.9, 157.8, 133.0, 128.0, 125.8, 119.3, 35.2, 34.1, 31.0, 11.8.

4-(4-methoxyphenyl)-4-oxobutanenitrile (2f)[2]



The product was purified by flash chromatography to give 35.2 mg (93%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.93 (d, *J* = 11.0 Hz, 2H), 6.96 (d, *J* = 11.0 Hz, 2H), 3.88 (s, 3H), 3.33 (t, *J* = 9.0 Hz, 2H), 2.76 (t, *J* = 9.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.7, 164.1, 130.3, 128.7, 119.3, 114.0, 55.5, 33.9, 11.8.

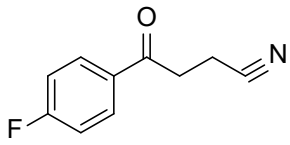
4-(4-(dimethylamino)phenyl)-4-oxobutanenitrile (2g)



The product was purified by flash chromatography to give 31.8 mg (53%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.85 (d, *J* = 8.5 Hz, 2H), 6.66 (d, *J* = 9.0 Hz, 2H), 3.28 (t, *J* = 7.0 Hz, 2H), 3.08 (s, 6H), 2.75 (t, *J* = 7.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.0, 153.8,

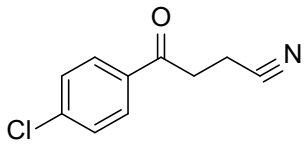
130.2, 123.5, 119.7, 110.7, 40.0, 33.4, 12.0. HRMS (ESI) m/z calcd for $C_{12}H_{15}N_2O^+$ $(M+H)^+$ 203.1179, found203.1179.

4-(4-fluorophenyl)-4-oxobutanenitrile (2h)[2]



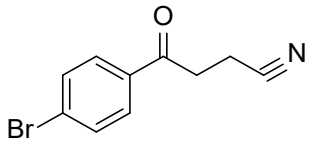
The product was purified by flash chromatography to give 30.8 mg (87%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.97-8.00 (m, 2H), 7.17 (t, *J* = 10.5 Hz, 2H), 3.36 (t, *J* = 9.0 Hz, 2H), 2.77 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.7, 166.2 (d, *J* = 318.3 Hz), 132.0 (d, *J* = 3.75 Hz), 130.7 (d, *J* = 11.75 Hz), 119.1, 116.0 (d, *J* = 27.5 Hz), 34.2, 11.8. ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -103.5.

4-(4-chlorophenyl)-4-oxobutanenitrile (2i)[2]



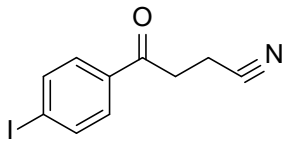
The product was purified by flash chromatography to give 32.8 mg (85%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.90 (d, *J* = 10.5 Hz, 1H), 7.48 (d, *J* = 10.5 Hz, 1H), 3.36 (t, *J* = 9.0 Hz, 2H), 2.78 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.1, 140.5, 133.9, 129.4, 129.2, 119.0, 34.3, 11.8.

4-(4-bromophenyl)-4-oxobutanenitrile (2j)[2]



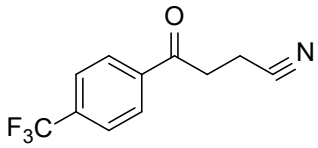
The product was purified by flash chromatography to give 39.6 mg (84%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.82 (d, *J* = 10.5 Hz, 2H), 7.65 (d, *J* = 10.5 Hz, 2H), 3.35 (t, *J* = 9.0 Hz, 2H), 2.78 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.4, 133.7, 132.2, 130.1, 128.4, 119.0, 34.2, 11.7.

4-(4-iodophenyl)-4-oxobutanenitrile (2k)



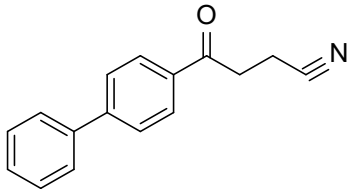
The product was purified by flash chromatography to give 31.8 mg (79%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.86 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 3.33 (t, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.6, 138.2, 134.8, 129.3, 119.0, 102.0, 34.1, 11.7. HRMS (ESI) m/z calcd for $C_{10}H_9INO^+$ $(M+H)^+$ 285.9723, found285.9727.

4-oxo-4-(4-(trifluoromethyl)phenyl)butanenitrile (2l)[3]



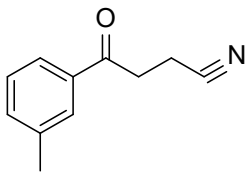
The product was purified by flash chromatography to give 38.6 mg (85%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.06 (d, *J* = 10.0 Hz, 2H), 7.75 (d, *J* = 10.0 Hz, 2H), 3.39-3.43 (m, 2H), 2.78-2.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.5, 138.1, 135.1 (q, *J* = 41.0 Hz), 128.4, 125.9 (q, *J* = 4.6 Hz), 123.4 (q, *J* = 338.9 Hz), 118.9, 34.5, 11.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -63.2.

4-([1,1'-biphenyl]-4-yl)-4-oxobutanenitrile (2m)



The product was purified by flash chromatography to give 31.8 mg (86%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.03 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.0 Hz, 2H), 7.49 (t, *J* = 7.0 Hz, 2H), 7.43 (t, *J* = 7.5 Hz, 1H), 3.42 (t, *J* = 7.0 Hz, 2H), 2.81 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.9, 146.6, 139.5, 134.2, 129.0, 128.6, 128.5, 127.4, 127.3, 119.2, 34.3, 11.8.

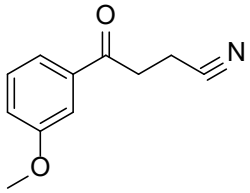
4-oxo-4-m-tolylbutanenitrile (2n)[2]



The product was purified by flash chromatography to give 31.8 mg (92%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.75 (d, *J* = 14.5 Hz, 2H),

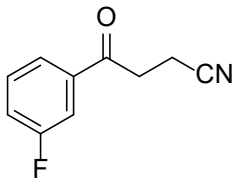
7.63 (m, 2H), 3.37 (t, *J* = 8.5 Hz, 2H), 2.77 (t, *J* = 9.0 Hz, 2H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 195.3, 138.7, 135.6, 134.6, 128.7, 128.5, 125.2, 119.2, 34.3, 21.3, 11.8.

4-(3-methoxyphenyl)-4-oxobutanenitrile (2o)[2]



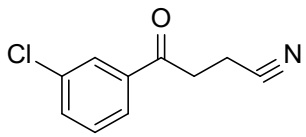
The product was purified by flash chromatography to give 34.4 mg (91%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.48-7.53 (m, 2H), 7.40 (t, *J* = 10.0 Hz, 1H), 7.14-7.17 (m, 1H), 3.86 (s, 3H), 3.38 (t, *J* = 9.0 Hz, 2H), 2.78 (t, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 195.2, 160.0, 136.9, 129.9, 120.6, 120.3, 119.1, 112.3, 55.5, 34.4, 11.8.

4-(3-fluorophenyl)-4-oxobutanenitrile (2p)



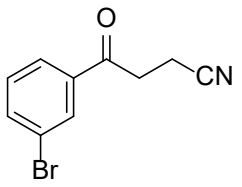
The product was purified by flash chromatography to give 23.0 mg (65%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.73 (d, *J* = 7.5 Hz, 1H), 7.63 (d, *J* = 9.0 Hz, 2H), 7.48 (q, *J* = 8.0 Hz, *J* = 13.5 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 3.36 (t, *J* = 7.0 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.1, 162.9(d, *J* = 123.6 Hz), 137.6(d, *J* = 3.1 Hz), 130.6(d, *J* = 3.9 Hz), 123.8(d, *J* = 1.6 Hz), 121.0(d, *J* = 10.9 Hz), 118.9, 114.8(d, *J* = 11.2 Hz), 34.4, 11.7. ^{19}F NMR (471 MHz, $CDCl_3$) δ (ppm) -111.1.

4-(3-chlorophenyl)-4-oxobutanenitrile (2q)[2]



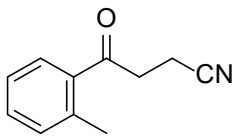
The product was purified by flash chromatography to give 33.6 mg (87%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.93 (s, 1H), 7.83 (d, *J* = 9.5 Hz, 1H), 7.59 (d, *J* = 9.5 Hz, 1H), 7.45 (t, *J* = 10.0 Hz, 1H), 3.36 (t, *J* = 9.0 Hz, 2H), 2.78 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.1, 137.1, 135.3, 133.8, 130.2, 128.1, 126.1, 118.9, 34.4, 11.7.

4-(3-bromophenyl)-4-oxobutanenitrile (2r)



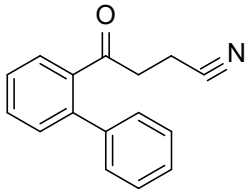
The product was purified by flash chromatography to give 36.8 mg (78%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.07 (s, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 3.35 (t, *J* = 7.0 Hz, 2H), 2.77 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 194.0, 137.2, 136.7, 131.1, 130.4, 126.5, 123.2, 118.9, 34.3, 11.7.

4-oxo-4-(o-tolyl)butanenitrile (2s)



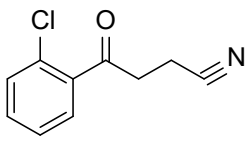
The product was purified by flash chromatography to give 27.3 mg (79%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.69 (d, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.5 Hz, 1H), 7.28-7.31 (m, 2H), 3.32 (t, *J* = 7.0 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H), 2.54 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 198.4, 139.2, 135.6, 132.4, 132.3, 128.8, 125.9, 119.2, 36.4, 21.7,12.0.

4-(biphenyl-2-yl)-4-oxobutanenitrile (2t)



The product was purified by flash chromatography to give 41.8 mg (89%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.52-7.58 (m, 2H), 7.42-7.48 (m, 5H), 7.31-7.33 (m, 2H), 2.56 (t, *J* = 8.5 Hz, 2H), 2.46 (t, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 202.6, 140.4, 140.1, 139.1, 131.1, 130.3, 129.0, 128.7, 128.3, 128.0, 127.7, 118.7, 37.7, 12.0. HRMS (ESI) m/z calcd for $C_{16}H_{15}NO^+$ $(M+H)^+$ 236.1070, found 236.1087.

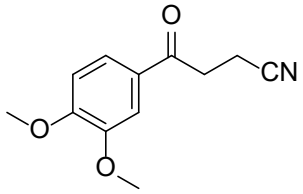
4-(2-chlorophenyl)-4-oxobutanenitrile (2u)[2]



The product was purified by flash chromatography to give 32.0 mg (83%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.59 (d, *J* = 9.5 Hz, 1H), 7.47

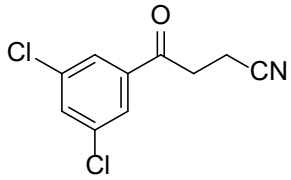
(d, *J* = 5.0 Hz, 2H), 7.38-7.41 (m, 1H), 3.41 (t, *J* = 9.0 Hz, 2H), 2.80 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 198.0, 137.3, 132.7, 131.3, 130.8, 129.5, 127.2, 118.8, 38.2, 11.9.

4-(3,4-dimethoxyphenyl)-4-oxobutanenitrile (2v)



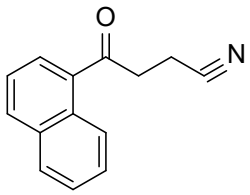
The product was purified by flash chromatography to give 35.5 mg (81%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.55 (d, *J* = 8.5 Hz, 1H), 7.49 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.33 (t, *J* = 7.0 Hz, 2H), 2.75 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.8, 153.8, 149.2, 128.8, 122.7, 119.3, 110.1, 109.9, 56.1, 55.9, 33.7, 11.9. HRMS (ESI) m/z calcd for $C_{12}H_{14}NO_3^+$ $(M+H)^+$ 220.0968, found220.0968.

4-(3,5-dichlorophenyl)-4-oxobutanenitrile (2w)



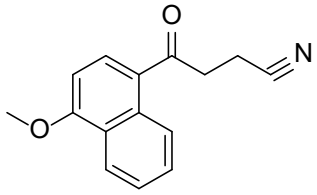
The product was purified by flash chromatography to give 35.1 mg (77%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.80 (s, 1H), 7.59 (s, 1H), 7.38-7.41 (m, 1H), 3.33 (t, *J* = 7.0 Hz, 2H), 2.78 (t, *J* = 7.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.0, 137.8, 136.0, 133.5, 126.4, 118.6, 34.5, 11.7. HRMS (ESI) m/z calcd for $C_{10}H_8Cl_2NO^+$ $(M+H)^+$ 227.9977, found227.9978.

4-(naphthalen-1-yl)-4-oxobutanenitrile (2x)[4]



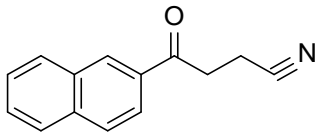
The product was purified by flash chromatography to give 37.6 mg (90%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.78 (d, *J* = 10.5 Hz, 1H), 8.17 (d, *J* = 10.0 Hz, 1H), 8.09 (d, *J* = 10.0 Hz, 1H), 7.95 (t, *J* = 10.0 Hz, 1H),7.64-7.69 (m, 1H), 7.60-7.62 (m, 1H), 7.50-7.58 (m, 1H), 3.51 (t, *J* = 9.0 Hz, 2H), 2.88 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 198.7, 133.9, 133.7, 130.1, 128.5, 128.5, 128.4, 128.4, 126.7, 125.6, 1242, 119.2, 36.8, 12.2.

4-(4-methoxynaphthalen-1-yl)-4-oxobutanenitrile (2y)



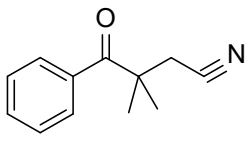
The product was purified by flash chromatography to give 43.5 mg (91%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 9.02 (d, *J* = 11.0 Hz, 1H), 8.33 (d, *J* = 10.5 Hz, 1H), 8.01 (d, *J* = 10.0 Hz, 1H), 7.65 (t, *J* = 9.0 Hz, 1H), 7.54 (t, *J* = 9.0 Hz, 1H), 6.81 (t, *J* = 10.0 Hz, 1H), 4.08 (s, 3H), 3.46 (t, *J* = 9.0 Hz, 2H), 2.82 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 196.5, 160.0, 132.0, 131.6, 129.2, 1261, 125.9, 125.8, 125.5, 122.2, 119.5, 102.1, 55.9, 35.9, 12.3. HRMS (ESI) m/z calcd for $C_{15}H_{15}NO_2^+$ $(M+H)^+$ 240.1019, found 240.1029.

4-(naphthalen-2-yl)-4-oxobutanenitrile (2z)[2]



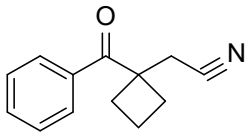
The product was purified by flash chromatography to give 34.7 mg (83%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.47 (s, 1H), 7.97-8.02 (m, 2H), 7.88-7.93 (m, 2H), 7.57-7.66 (m, 2H), 3.53 (t, *J* = 9.0 Hz, 2H), 2.84 (t, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 195.2, 135.9, 132.9, 132.4, 129.9, 129.6, 129.6, 128.9, 128.8, 127.9, 127.1, 123.4, 119.2, 34.3, 11.9.

3,3-dimethyl-4-oxo-4-phenylbutanenitrile (2aa)[3]



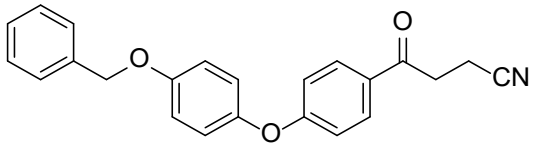
The product was purified by flash chromatography to give 34.0 mg (91%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.74 (d, *J* = 9.0 Hz, 2H), 7.51-7.53 (m, 1H), 7.42-7.46 (m, 2H), 2.71 (s, 2H), 1.57 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 204.5, 136.5, 131.9, 128.4, 128.1, 118.2, 46.4, 29.1, 25.3.

2-(1-benzoylcyclobutyl)acetonitrile (2ab)



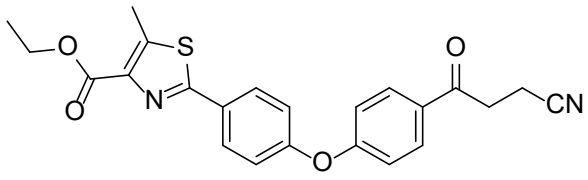
The product was purified by flash chromatography to give 35.0 mg (88%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.80 (d, *J* = 8.0 Hz, 2H), 7.56-7.61 (m, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 2.94 (s, 2H), 2.83-2.89 (m, 2H), 2.33-2.35 (m, 2H), 2.16-2.25 (m, 1H), 1.92-1.98 (m, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 200.8, 133.6, 133.2, 128.9, 128.8, 116.9, 49.5, 30.3, 26.9, 15.2. HRMS (ESI) m/z calcd for $C_{13}H_{15}NO^{+}$ $(M+H)^{+}$ 200.1070, found 200.1078.

4-(4-(4-(benzyloxy)phenoxy)phenyl)-4-oxobutanenitrile (2ac)



The product was purified by flash chromatography to give 46.4 mg (65%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.91 (d, *J* = 11.0 Hz, 2H), 7.35-7.46 (m, 5H), 7.01 (m, 4H), 6.97 (d, *J* = 11.0 Hz, 2H), 5.08 (s, 2H), 3.33 (t, *J* = 9.0 Hz, 2H), 2.77 (t, *J* = 9.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.7, 163.5, 156.1, 148.5, 136.8, 130.3, 129.8, 128.6, 128.1, 127.5, 121.7, 119.3, 116.6, 116.2, 70.5, 34.0, 11.8. HRMS (ESI) m/z calcd for $C_{23}H_{21}NO_3^{+}$ $(M+H)^{+}$ 358.1438, found 358.1447.

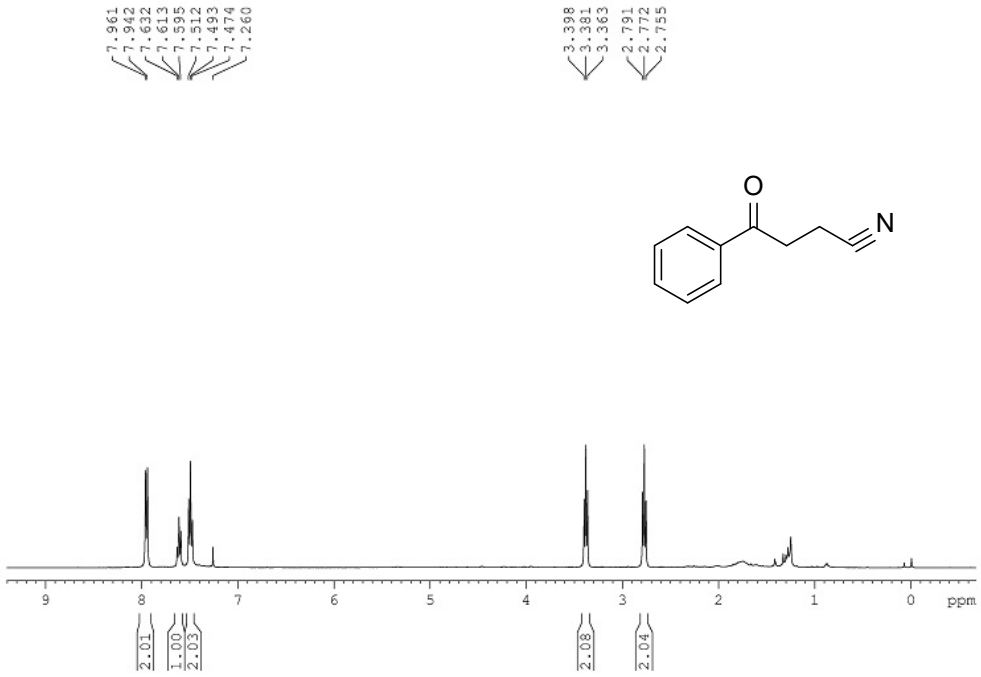
ethyl 2-(4-(4-(3-cyanopropanoyl)phenoxy)phenyl)-5-methylthiazole-4-carboxylate (2ad)



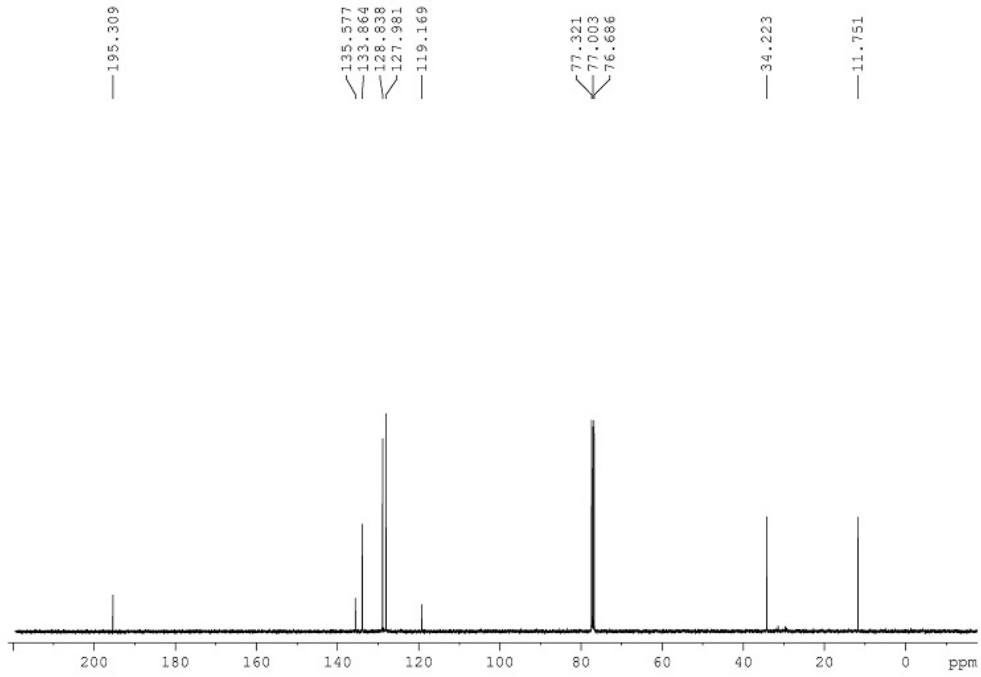
The product was purified by flash chromatography to give 51.2 mg (61%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.98 (t, *J* = 11.0 Hz, 4H), 7.08-7.13 (m, 4H), 4.36 (q, *J* = 17.5 Hz, *J* = 8.5 Hz, 2H), 3.36 (t, *J* = 8.5 Hz, 2H), 2.76-2.80 (m, 5H), 1.39 (t, *J* = 9.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ = 193.8, 168.7, 162.2, 161.5, 161.0, 157.8, 131.0, 130.4, 129.5, 128.8, 121.9, 120.2, 119.1, 118.2, 61.3, 34.1, 17.5, 14.3, 11.8. HRMS (ESI) m/z calcd for $C_{23}H_{22}N_2O_4S^{+}$ $(M+H)^{+}$ 421.1217, found 421.1211.

(C) NMR Spectra of Compounds 2

4-oxo-4-phenylbutanenitrile (2a)

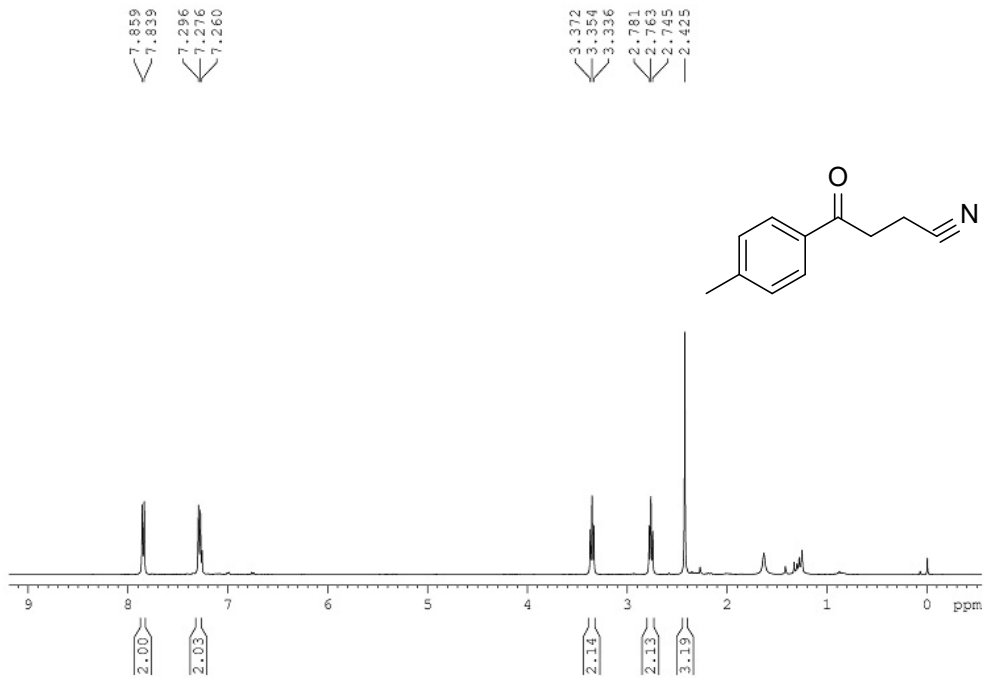


^{1}H NMR (500 MHz, $CDCl_3$)

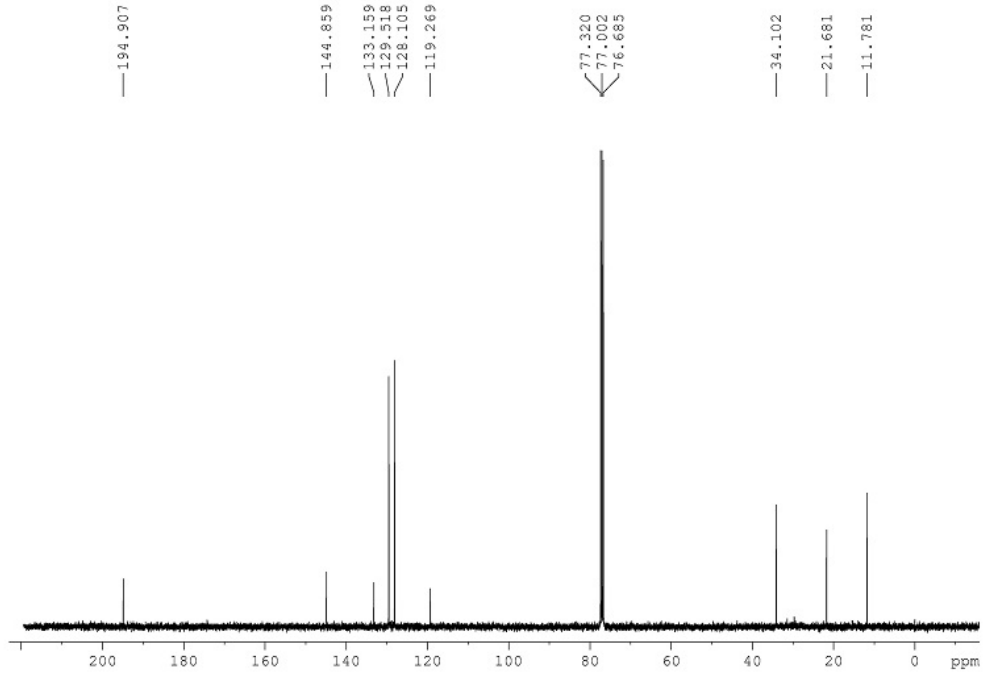


^{13}C NMR (125 MHz, $CDCl_3$)

4-oxo-4-p-tolylbutanenitrile (2b)

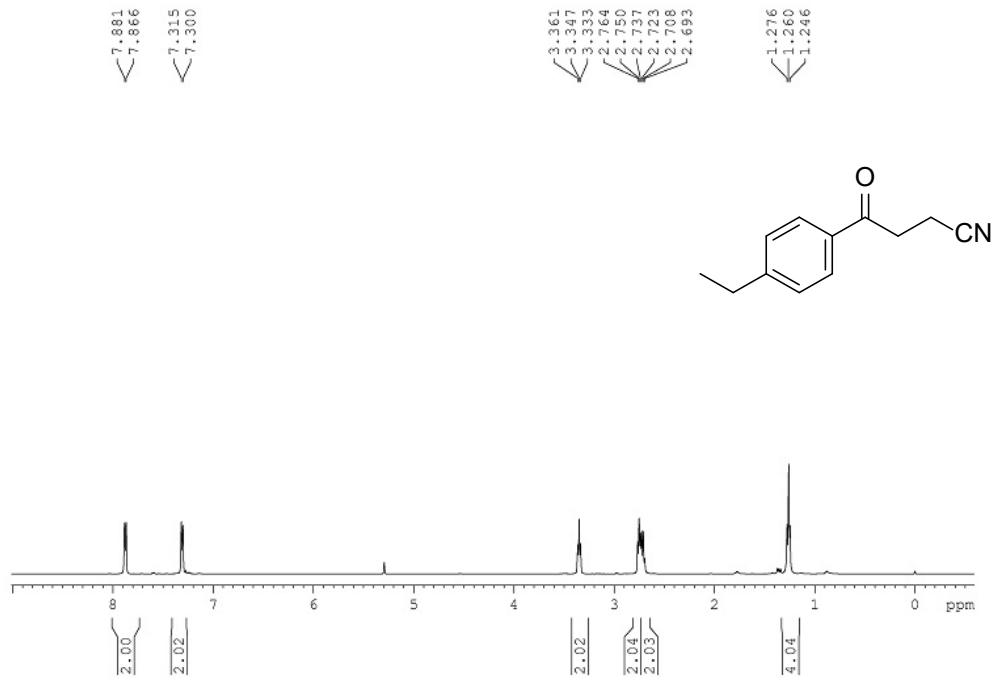


^{1}H NMR (500 MHz, $CDCl_3$)

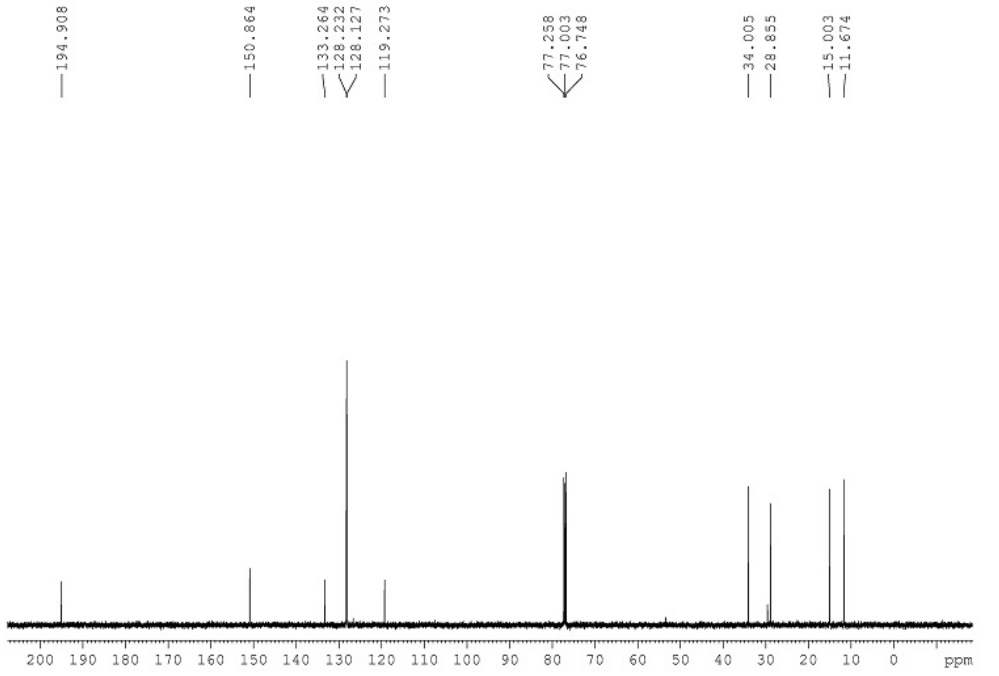


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-ethylphenyl)-4-oxobutanenitrile (2c)

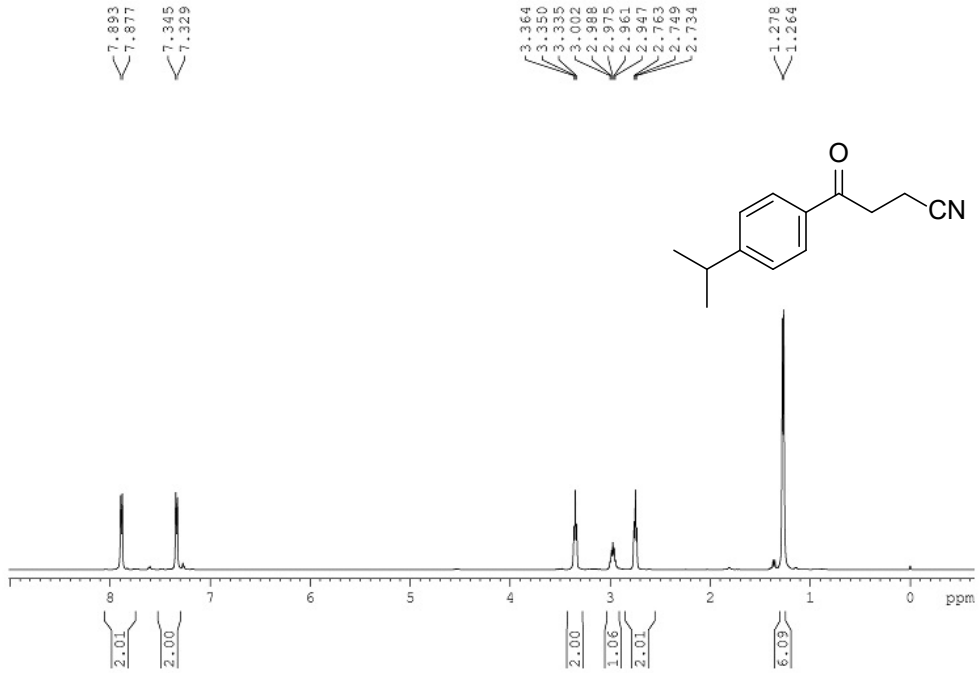


^{1}H NMR (500 MHz, $CDCl_3$)

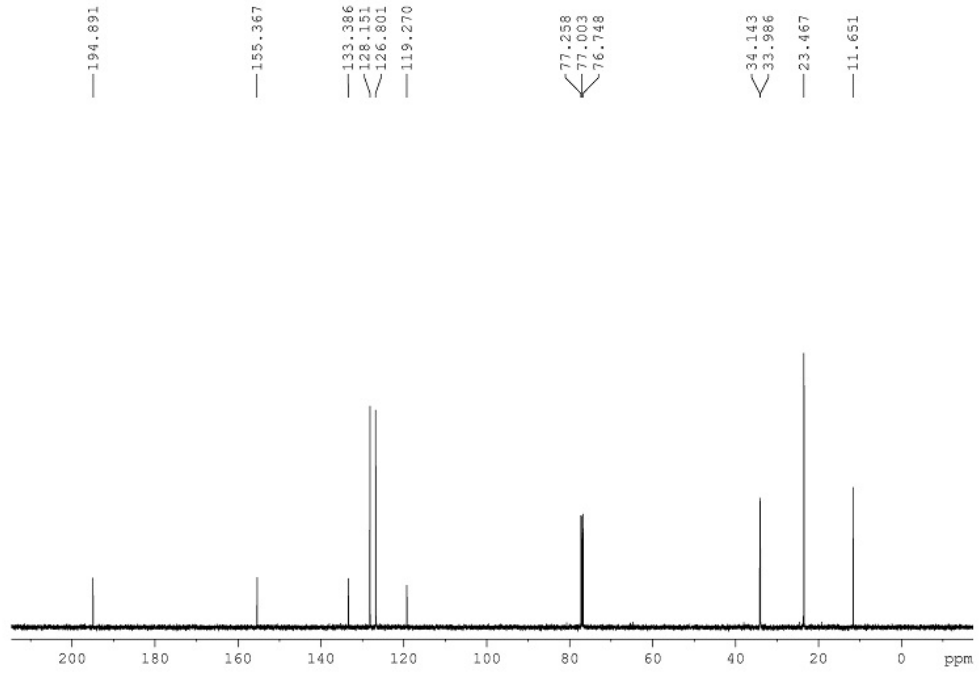


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-isopropylphenyl)-4-oxobutanenitrile (2d)

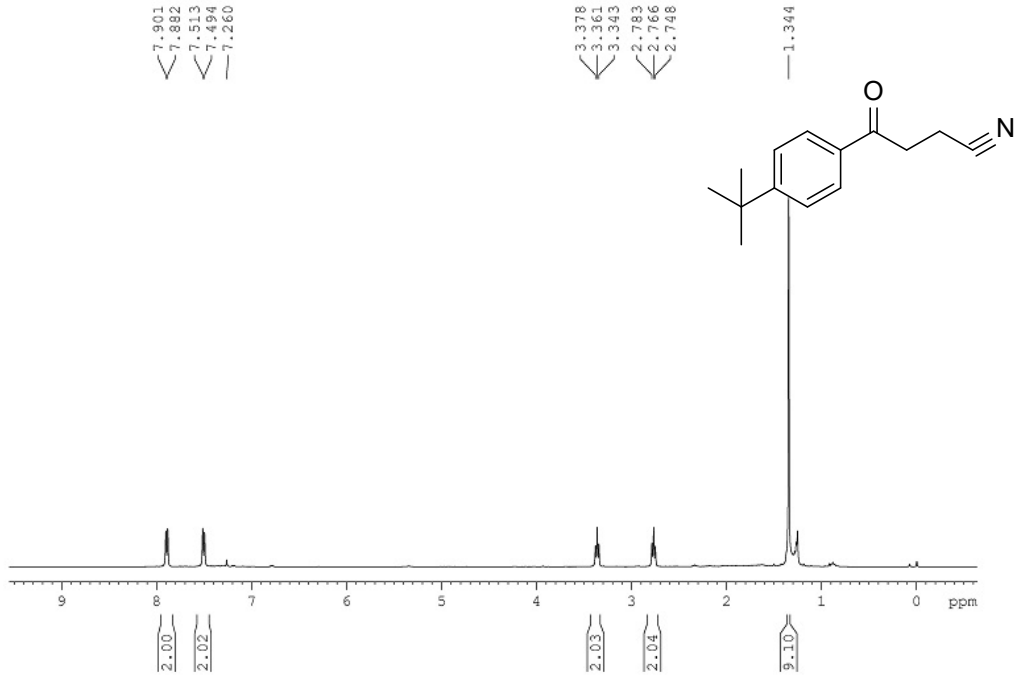


^{1}H NMR (500 MHz, $CDCl_3$)

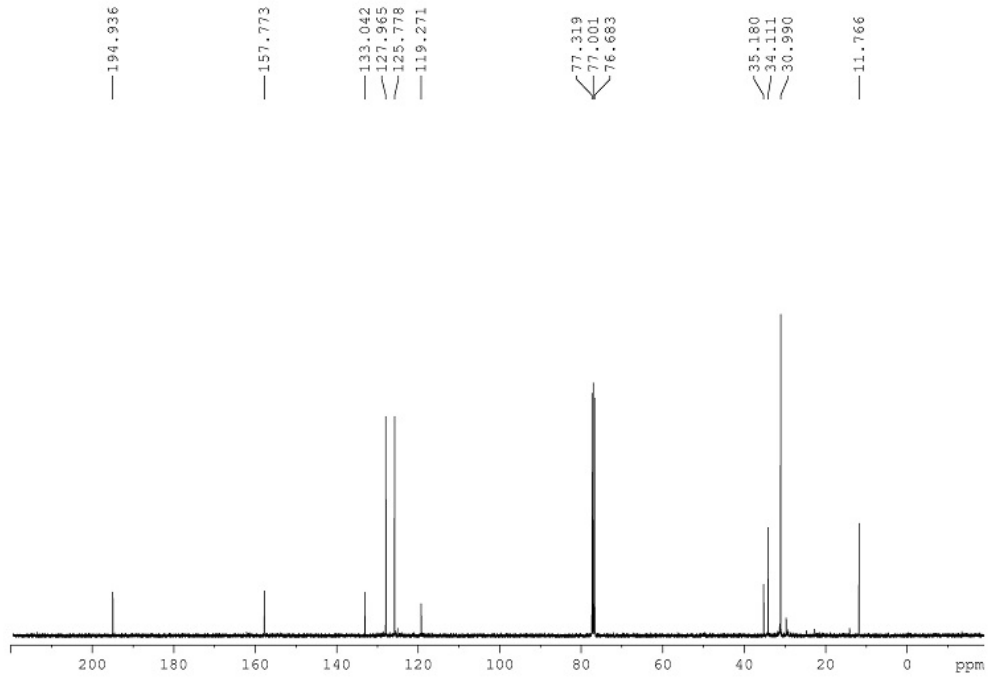


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-tert-butylphenyl)-4-oxobutanenitril (2e)

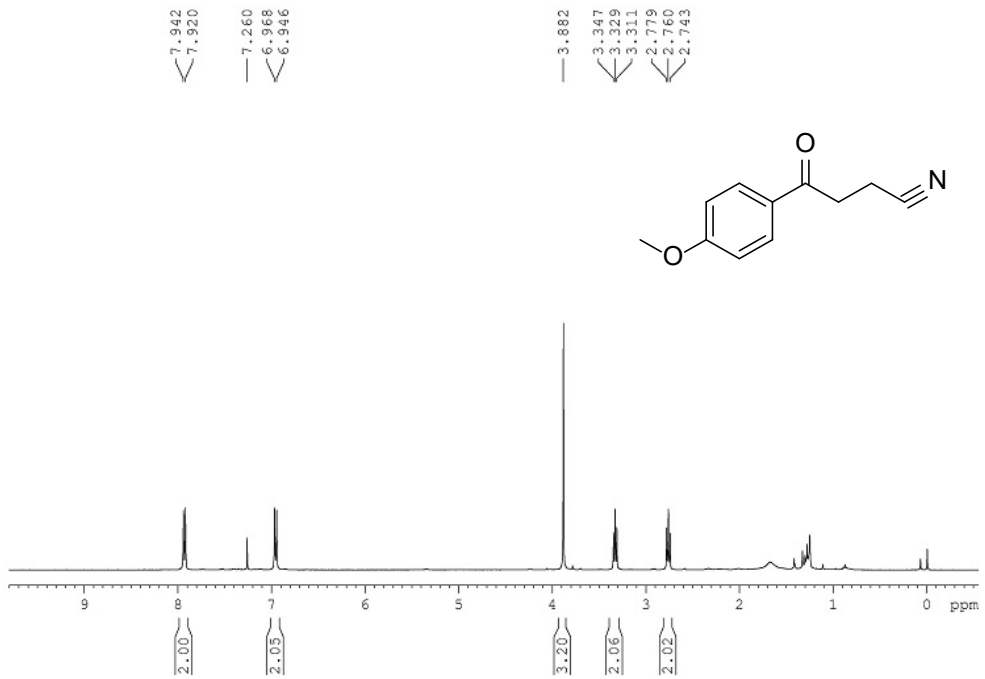


^{1}H NMR (500 MHz, $CDCl_3$)

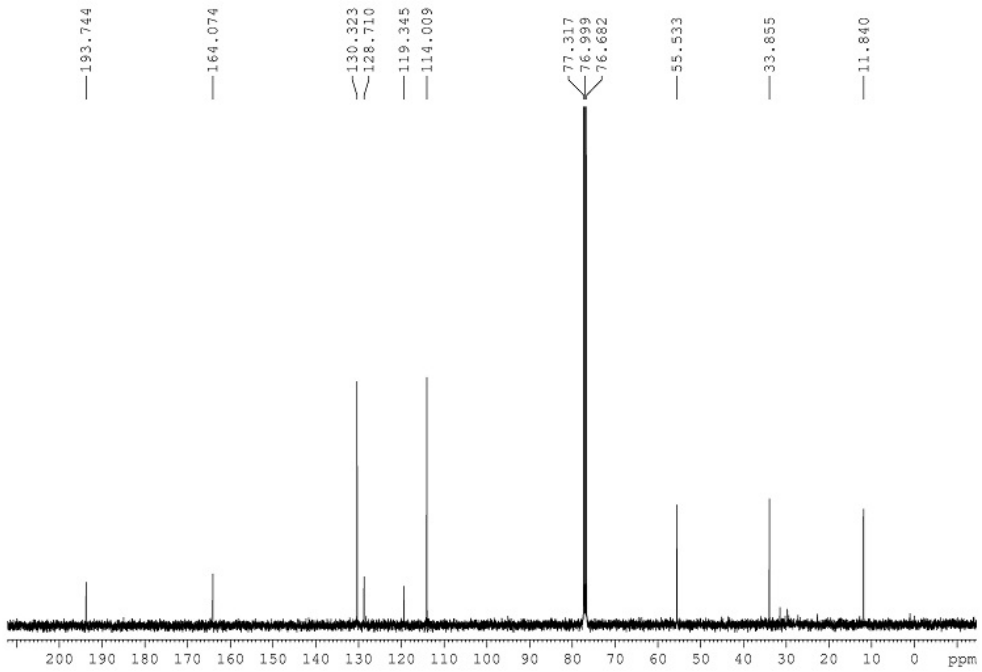


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-methoxyphenyl)-4-oxobutanenitrile (2f)

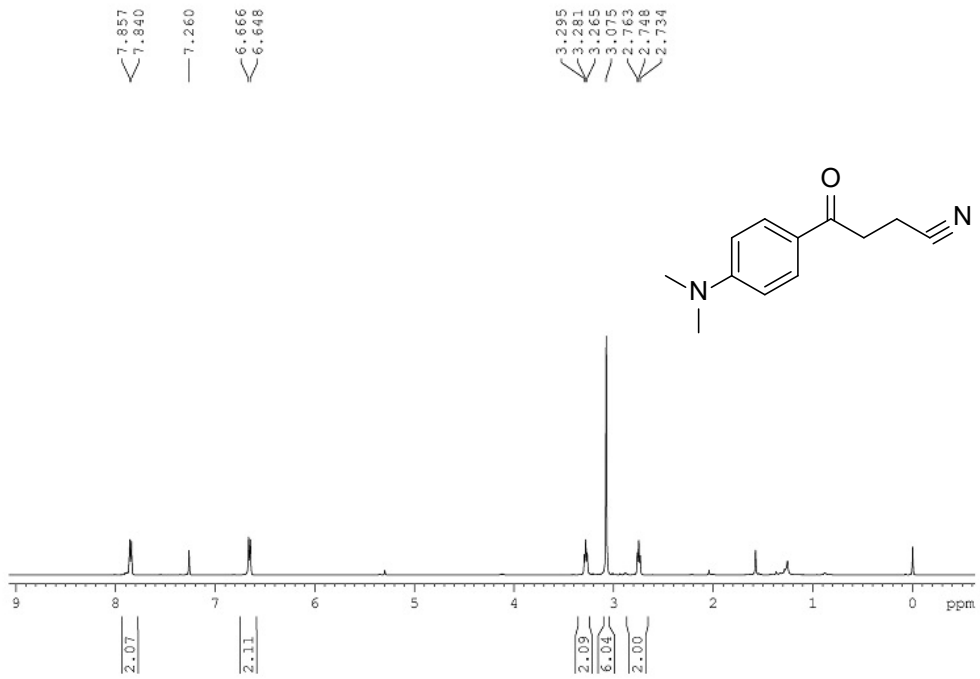


^{1}H NMR (500 MHz, $CDCl_3$)

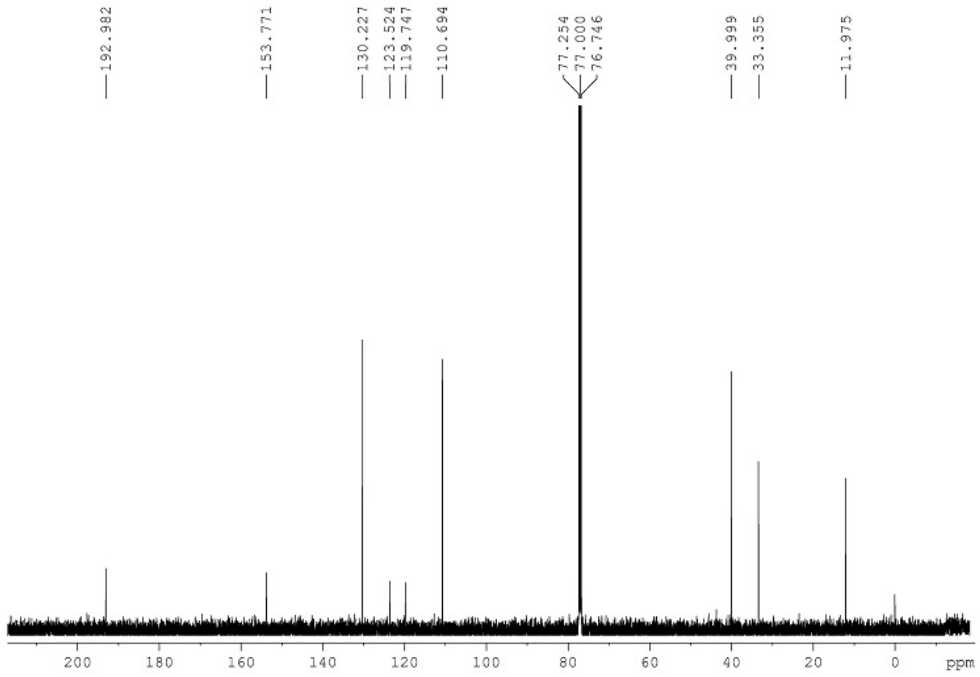


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-(dimethylamino)phenyl)-4-oxobutanenitrile (2g)

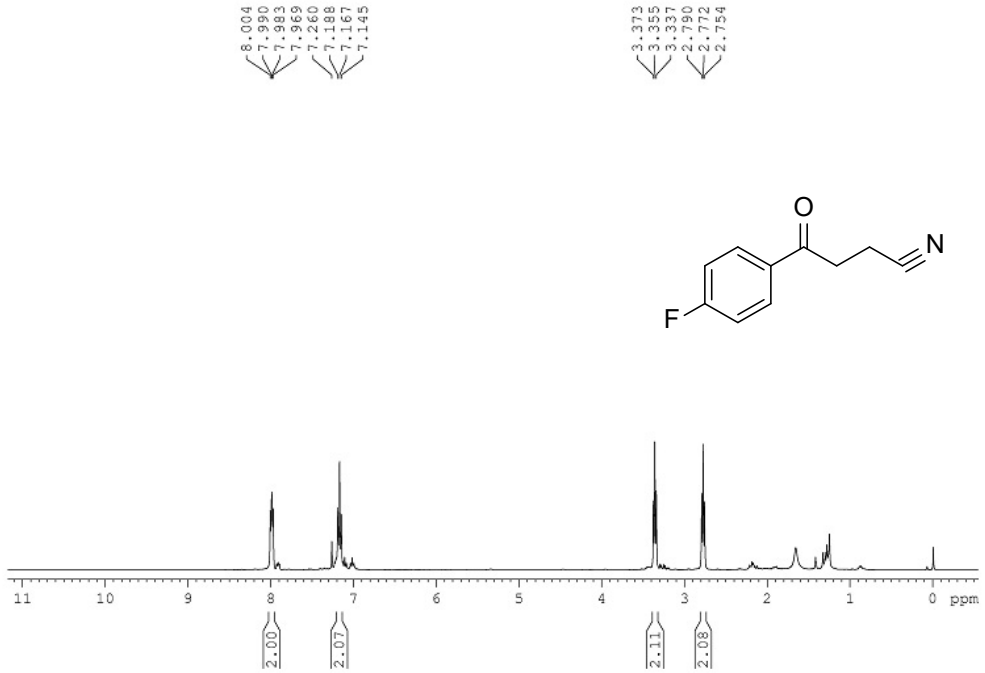


^{1}H NMR (500 MHz, $CDCl_3$)

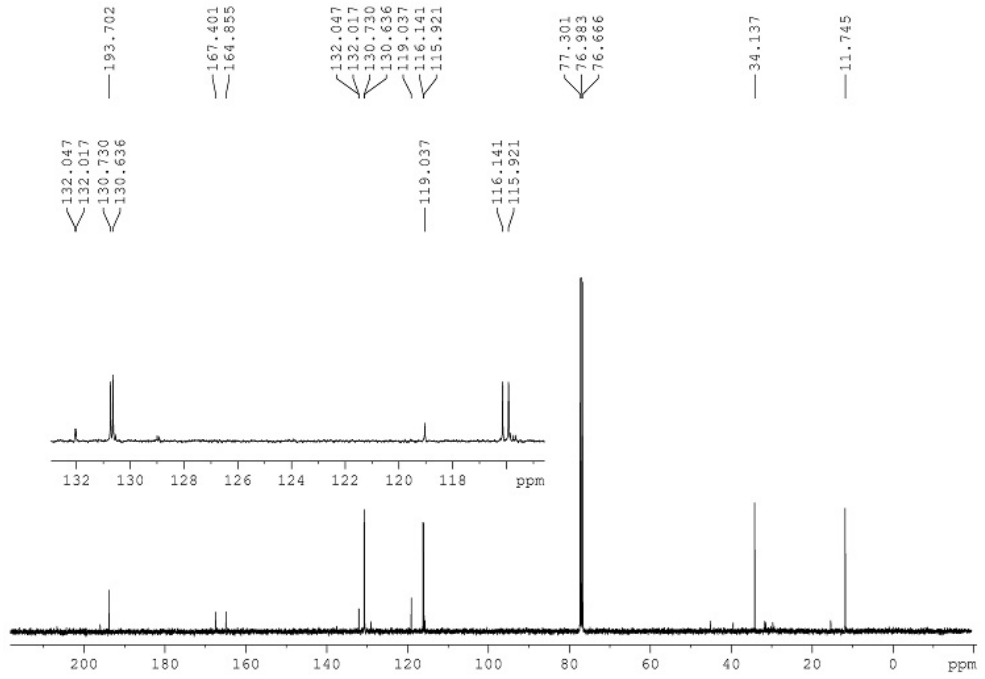


^{13}C NMR (125 MHz, $CDCl_3$)

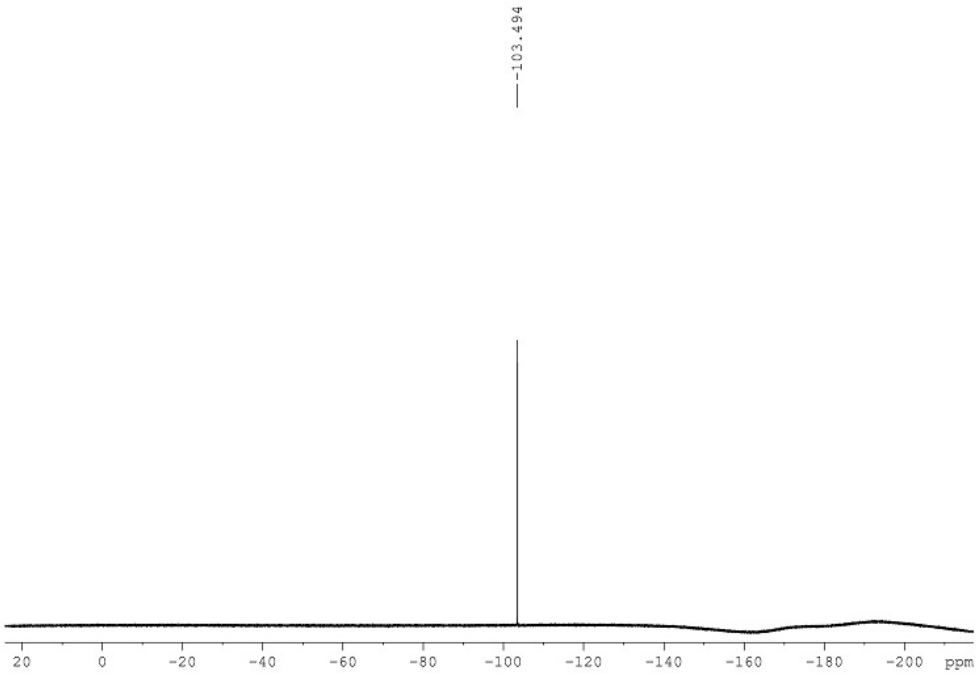
4-(4-fluorophenyl)-4-oxobutanenitrile (2h)



^{1}H NMR (500 MHz, $CDCl_3$)

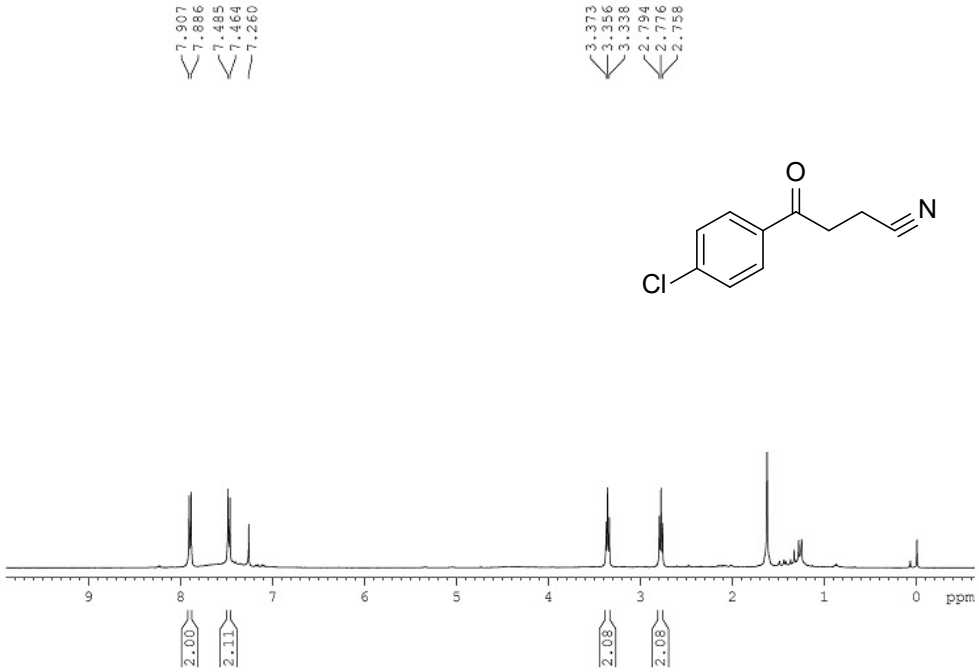


^{13}C NMR (125 MHz, $CDCl_3$)

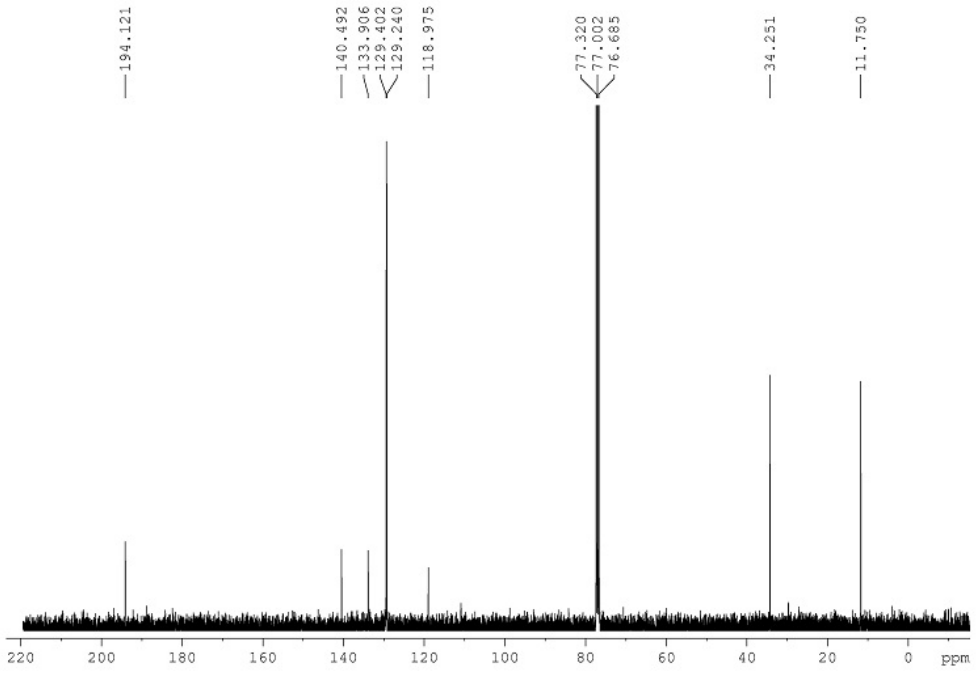


^{19}F NMR (471 MHz, $CDCl_3$)

4-(4-chlorophenyl)-4-oxobutanenitrile (2i)

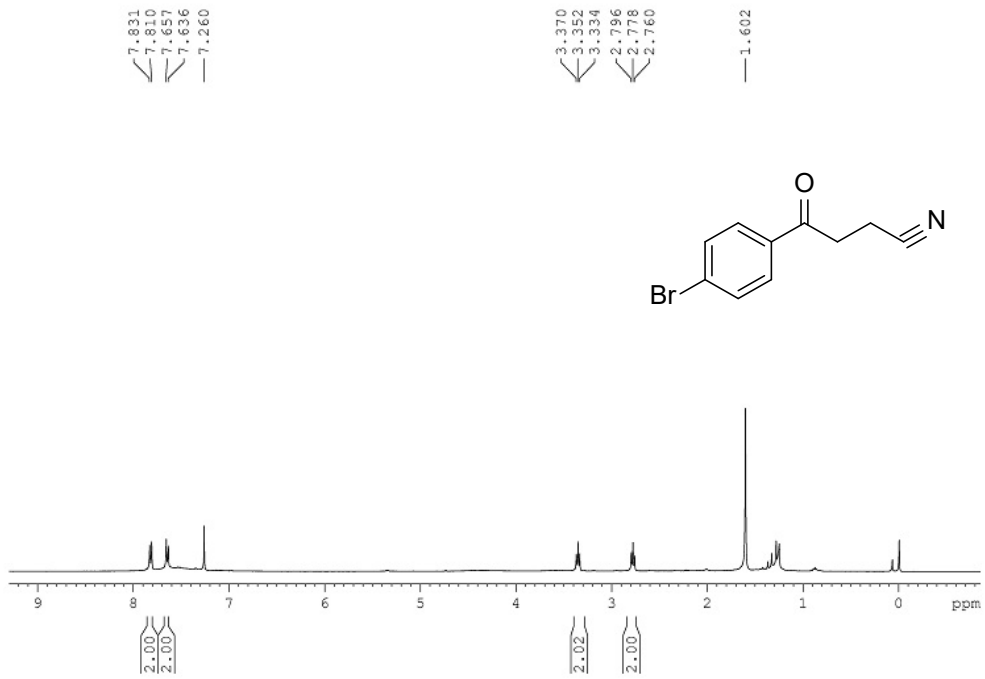


^{1}H NMR (500 MHz, $CDCl_3$)

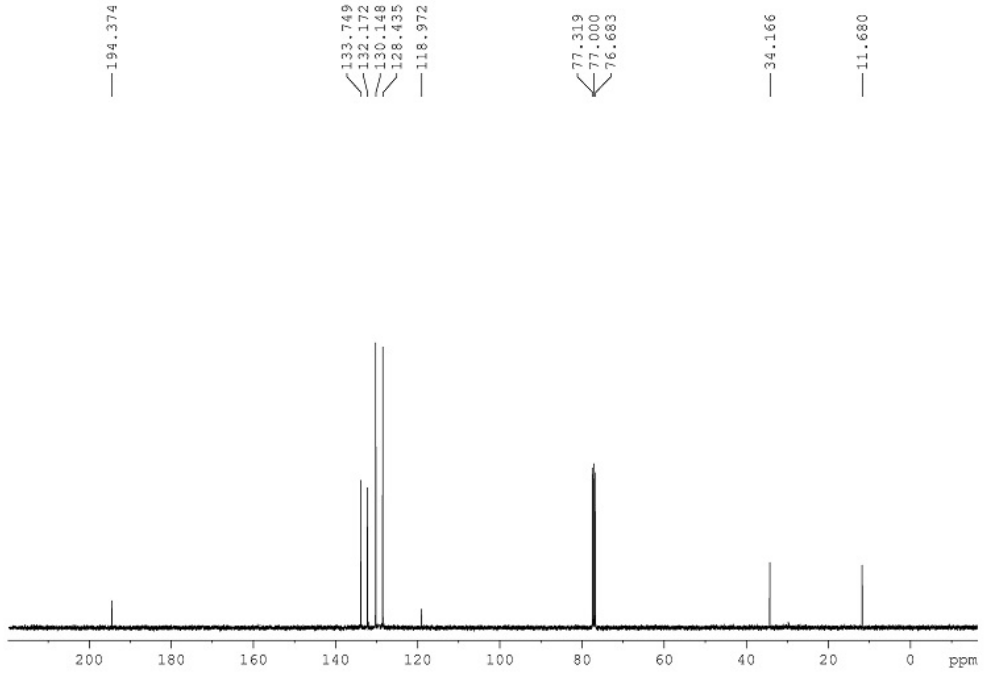


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-bromophenyl)-4-oxobutanenitrile (2j)

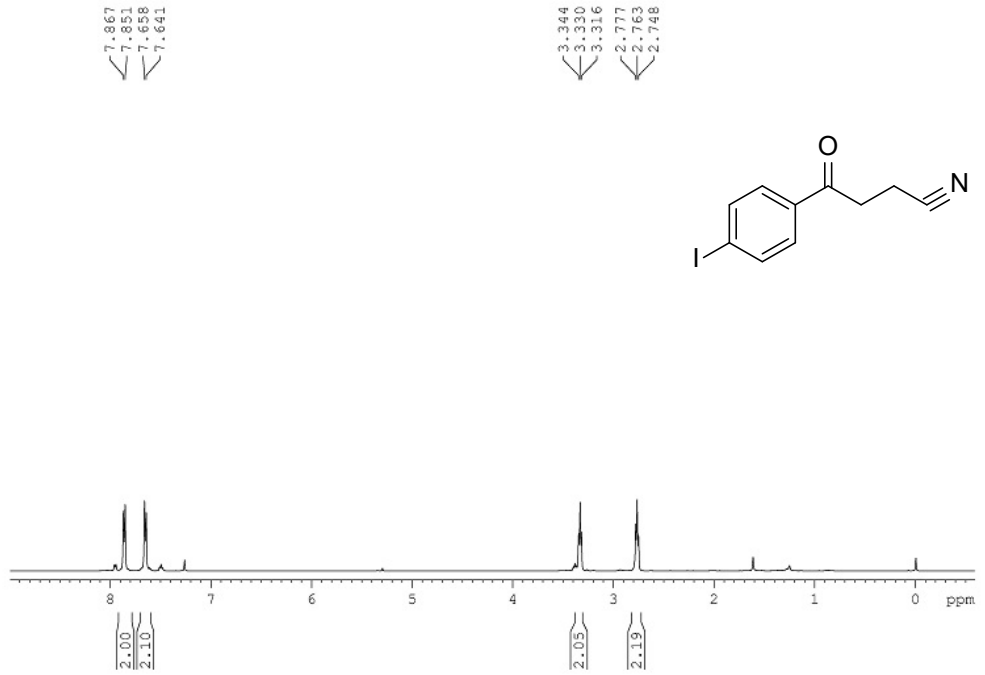


^{1}H NMR (500 MHz, $CDCl_3$)

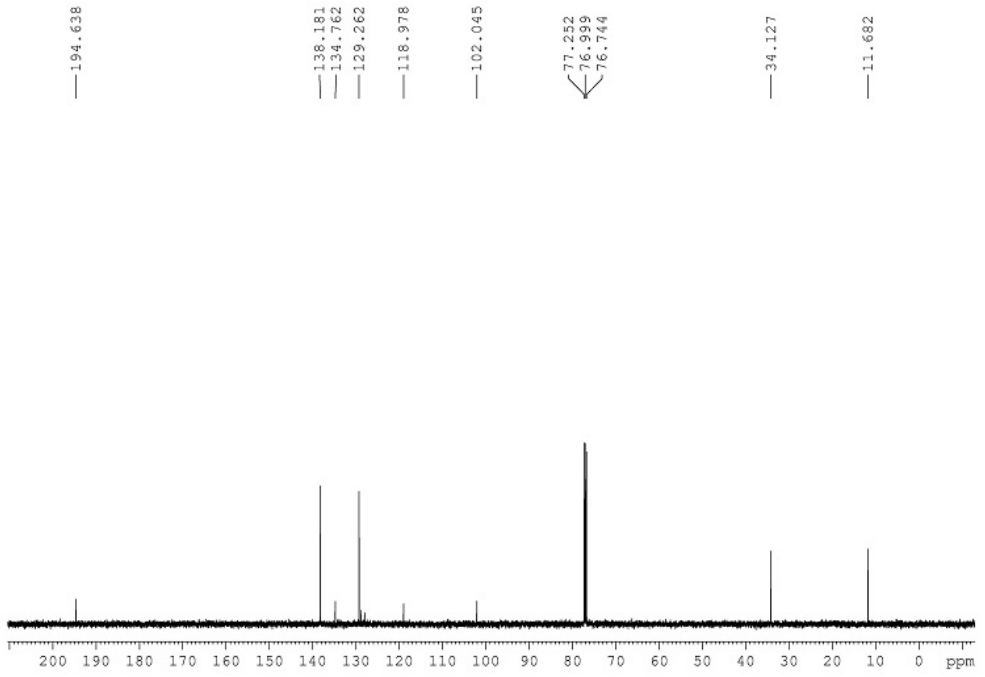


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-iodophenyl)-4-oxobutanenitrile (2k)

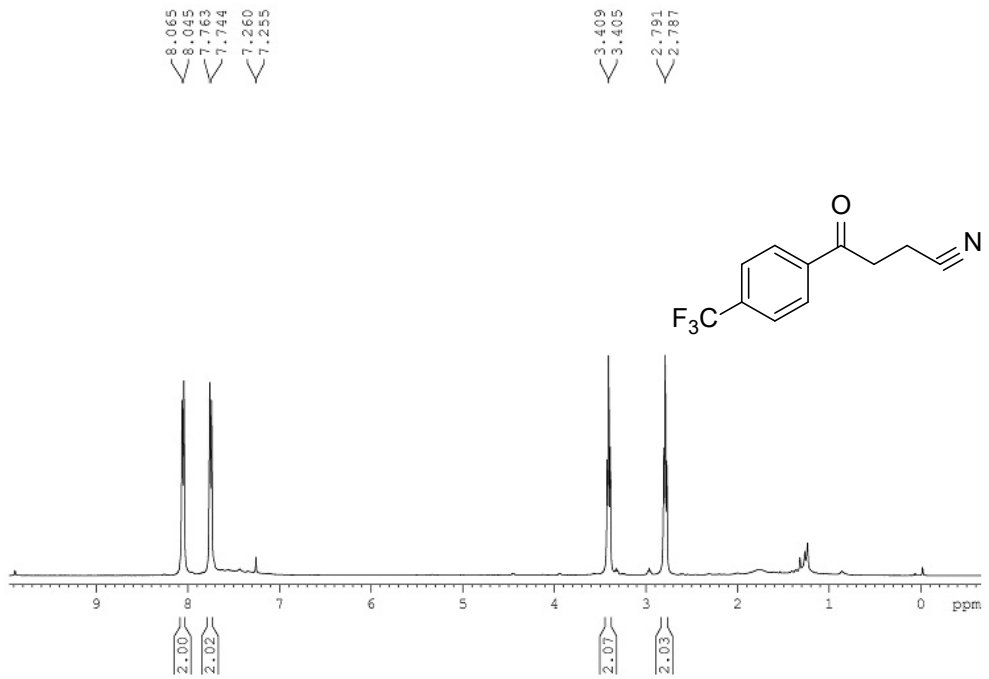


^{1}H NMR (500 MHz, $CDCl_3$)

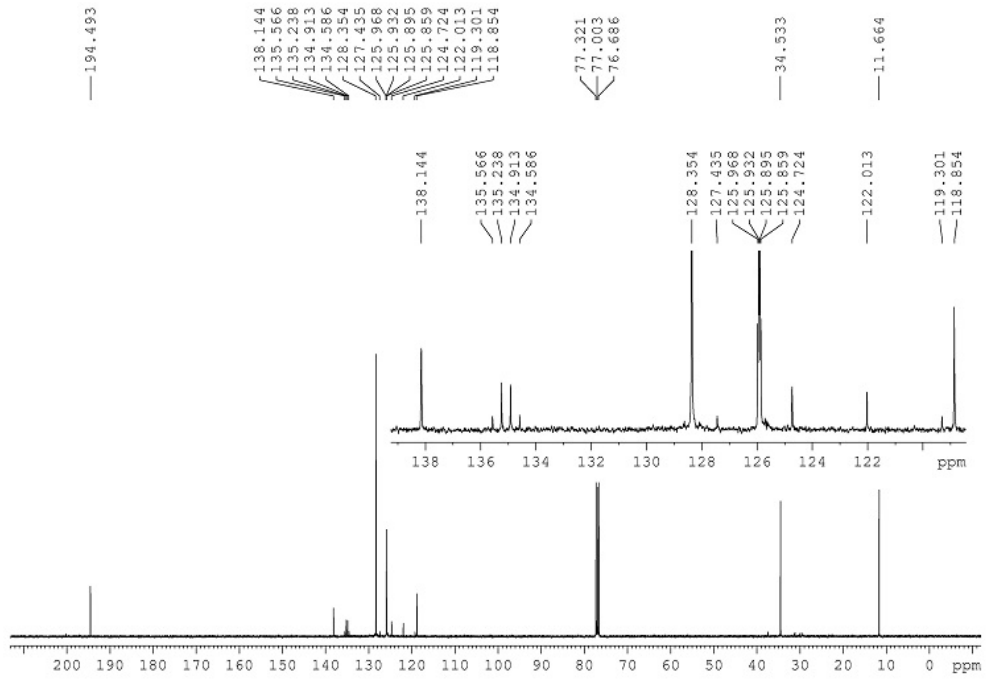


^{13}C NMR (125 MHz, $CDCl_3$)

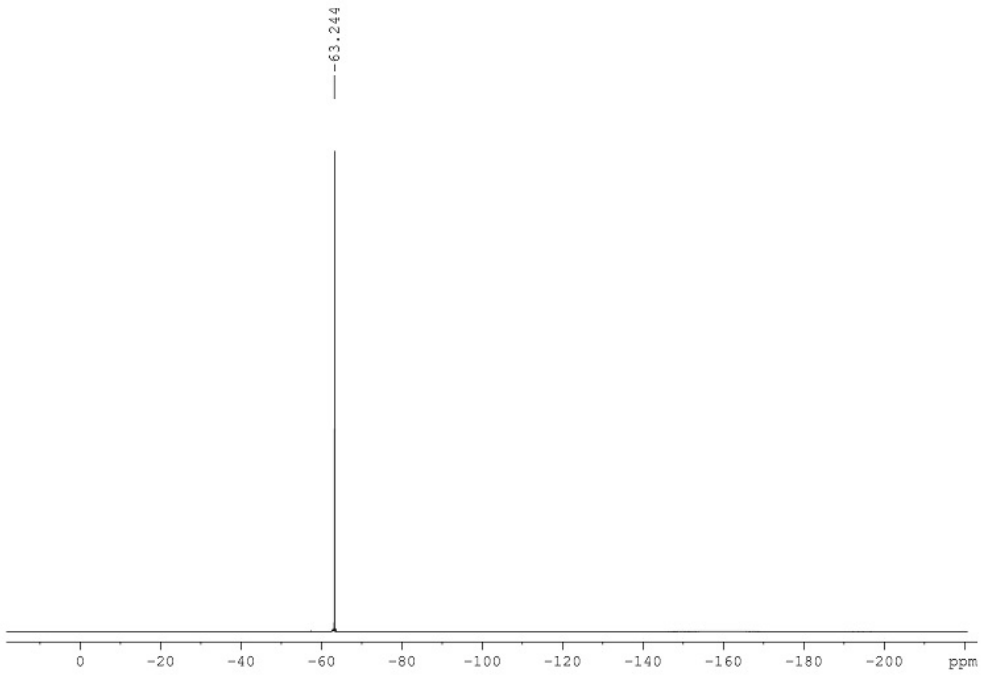
4-oxo-4-(4-(trifluoromethyl)phenyl)butanenitrile (2l)



^{1}H NMR (500 MHz, $CDCl_3$)

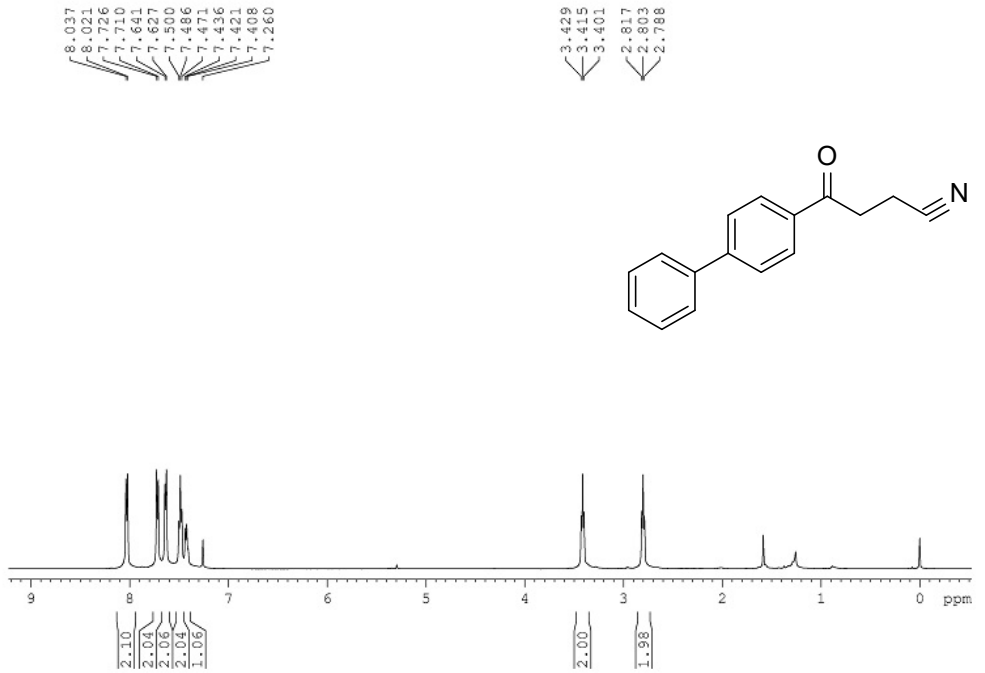


^{13}C NMR (125 MHz, $CDCl_3$)

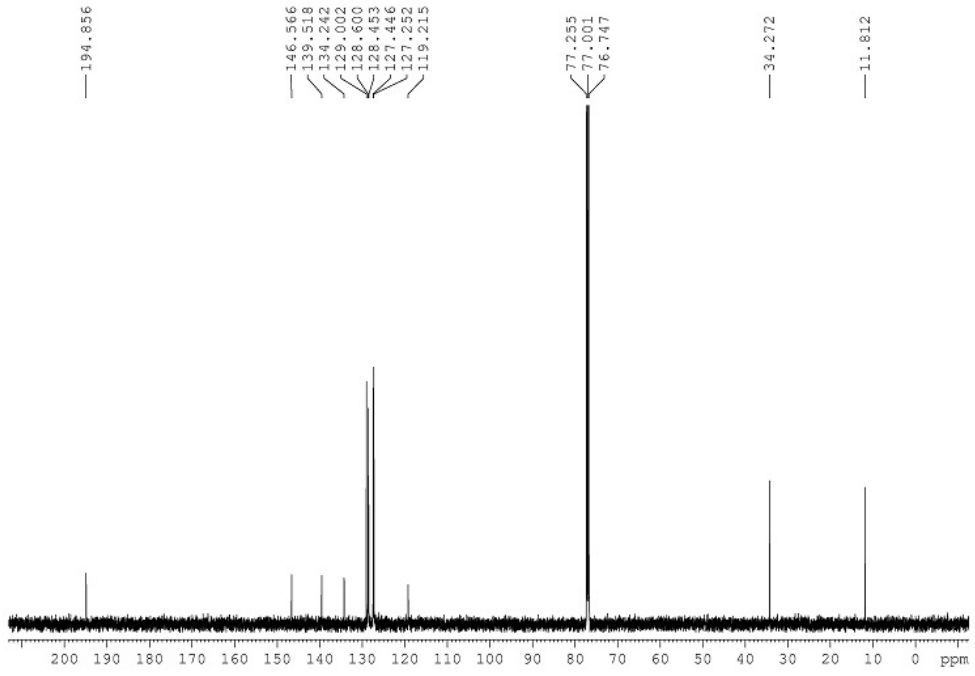


^{19}F NMR (471 MHz, $CDCl_3$)

4-([1,1'-biphenyl]-4-yl)-4-oxobutanenitrile (2m)

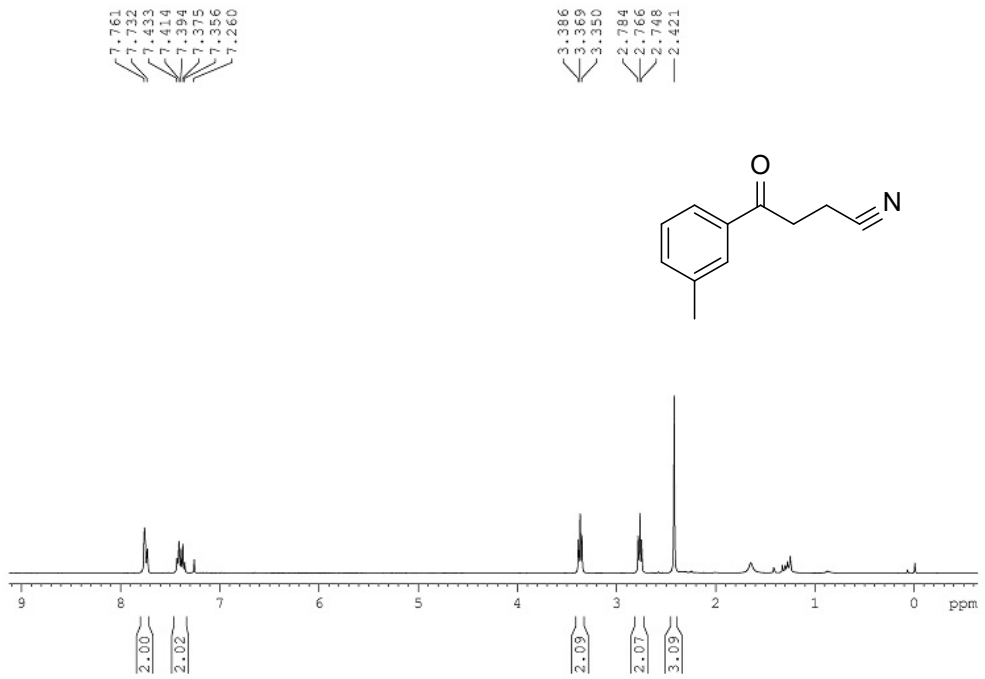


^{1}H NMR (500 MHz, $CDCl_3$)

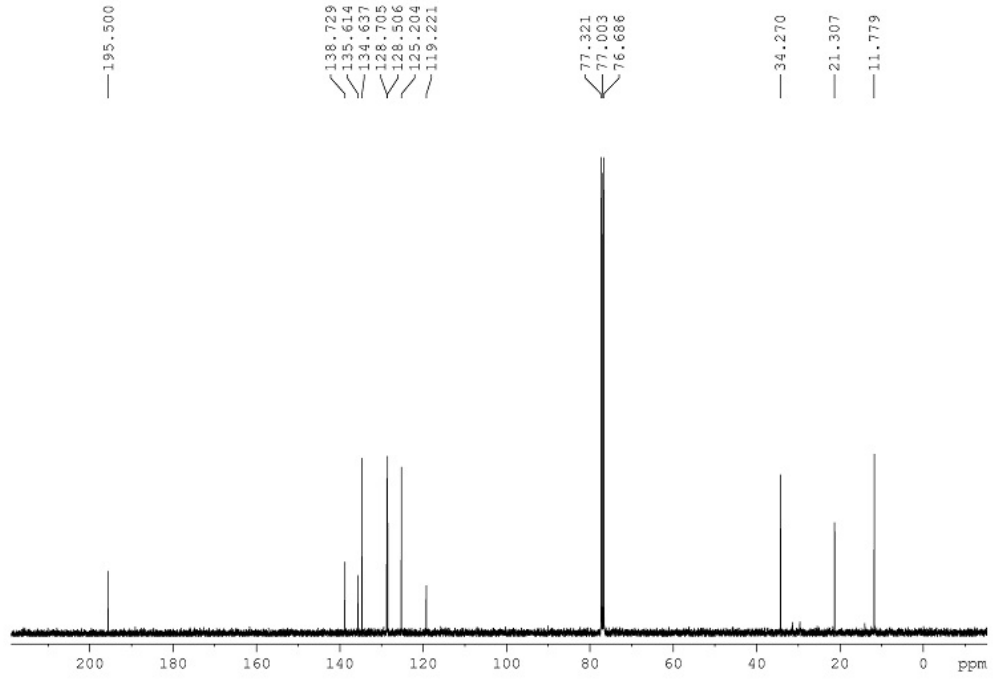


^{13}C NMR (125 MHz, $CDCl_3$)

4-oxo-4-m-tolylbutanenitrile (2n)

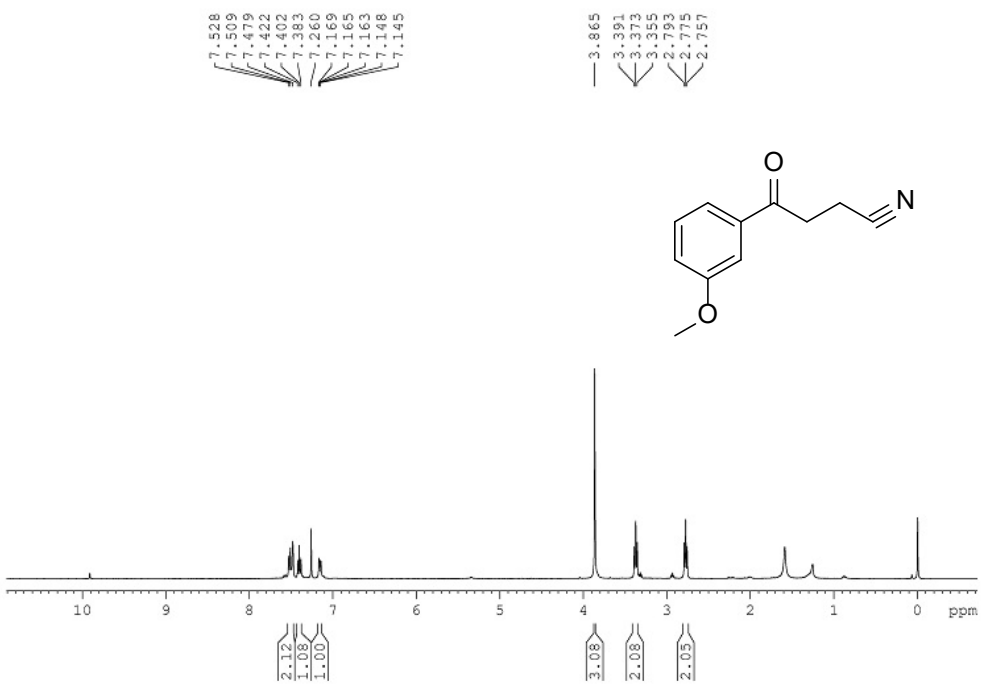


^{1}H NMR (500 MHz, $CDCl_3$)

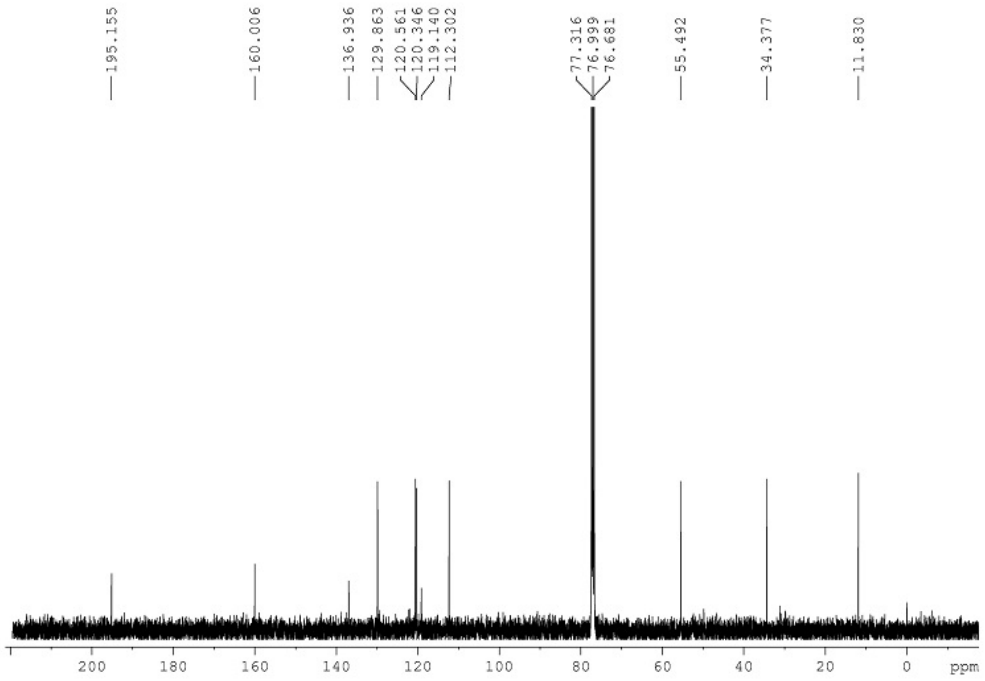


^{13}C NMR (125 MHz, $CDCl_3$)

4-(3-methoxyphenyl)-4-oxobutanenitrile (2o)

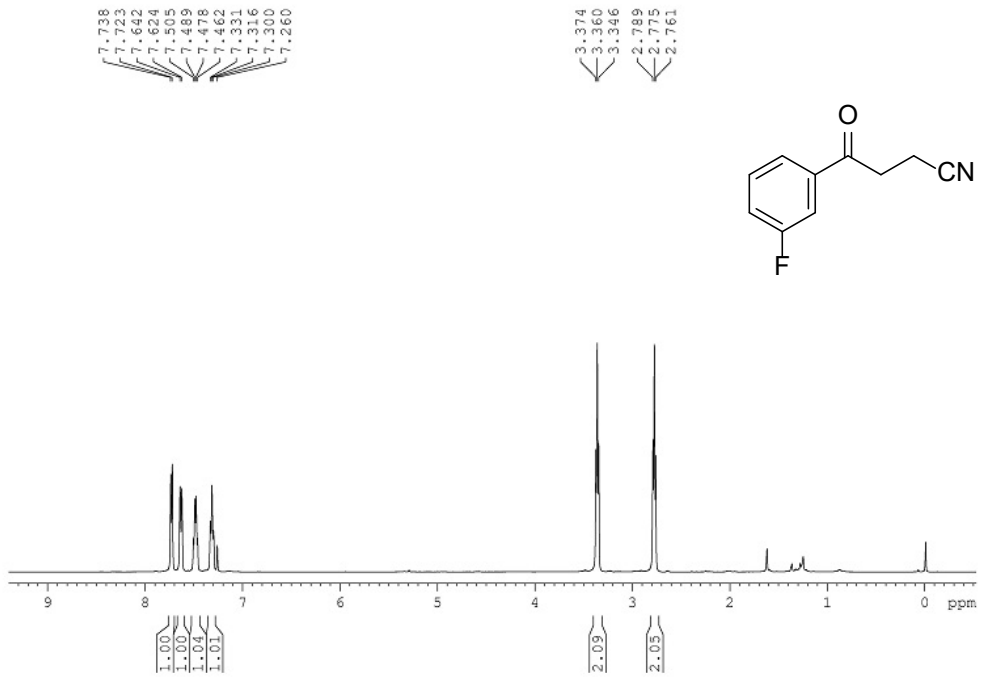


^{1}H NMR (500 MHz, $CDCl_3$)

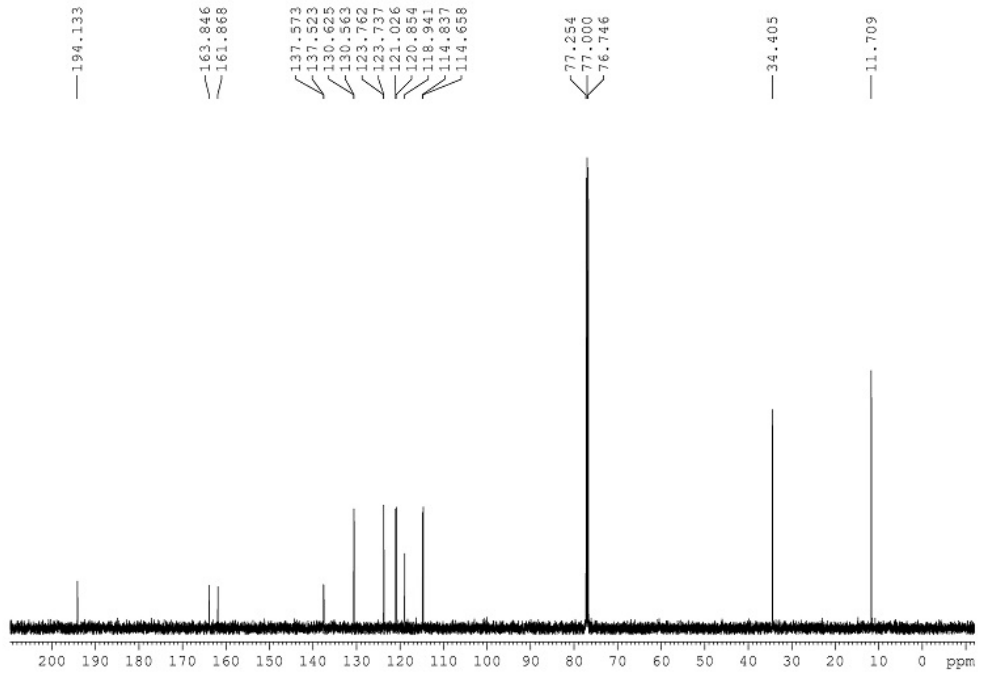


^{13}C NMR (125 MHz, $CDCl_3$)

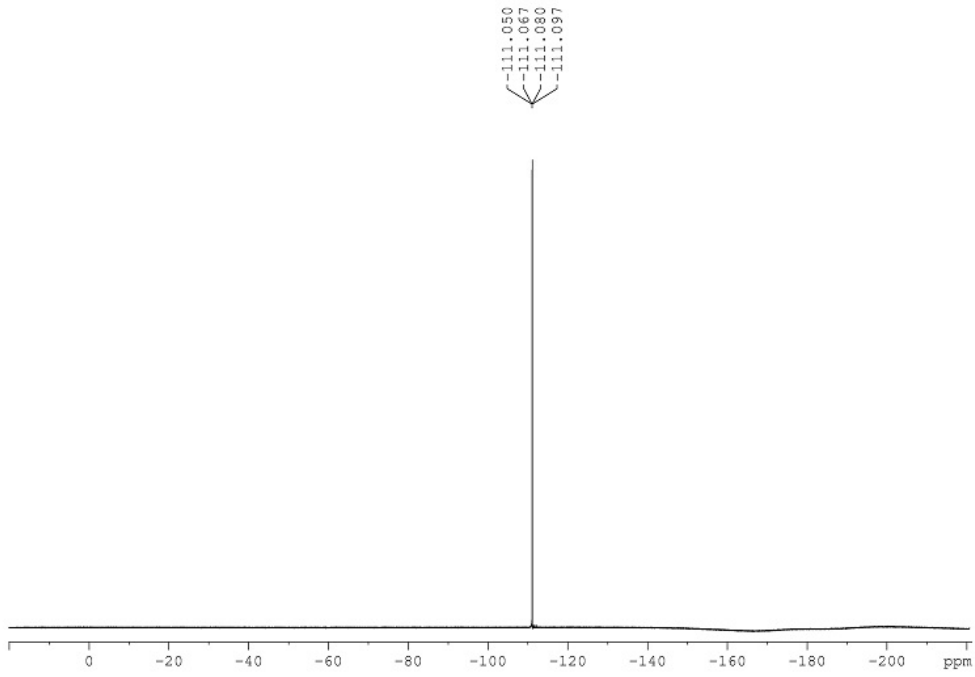
4-(3-fluorophenyl)-4-oxobutanenitrile (2p)



^{1}H NMR (500 MHz, $CDCl_3$)

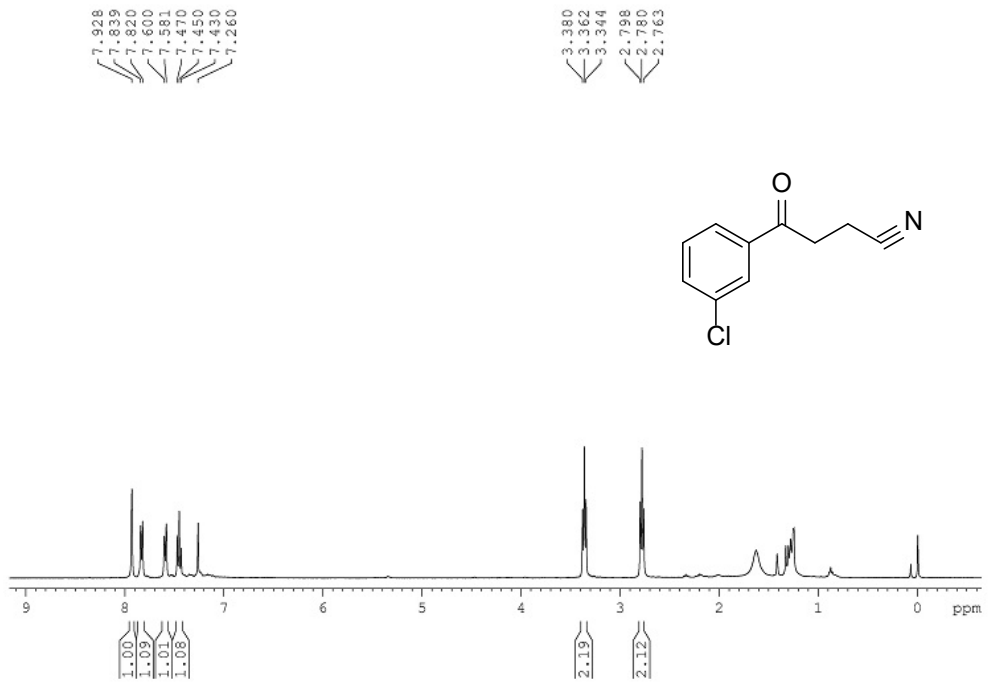


^{13}C NMR (125 MHz, $CDCl_3$)

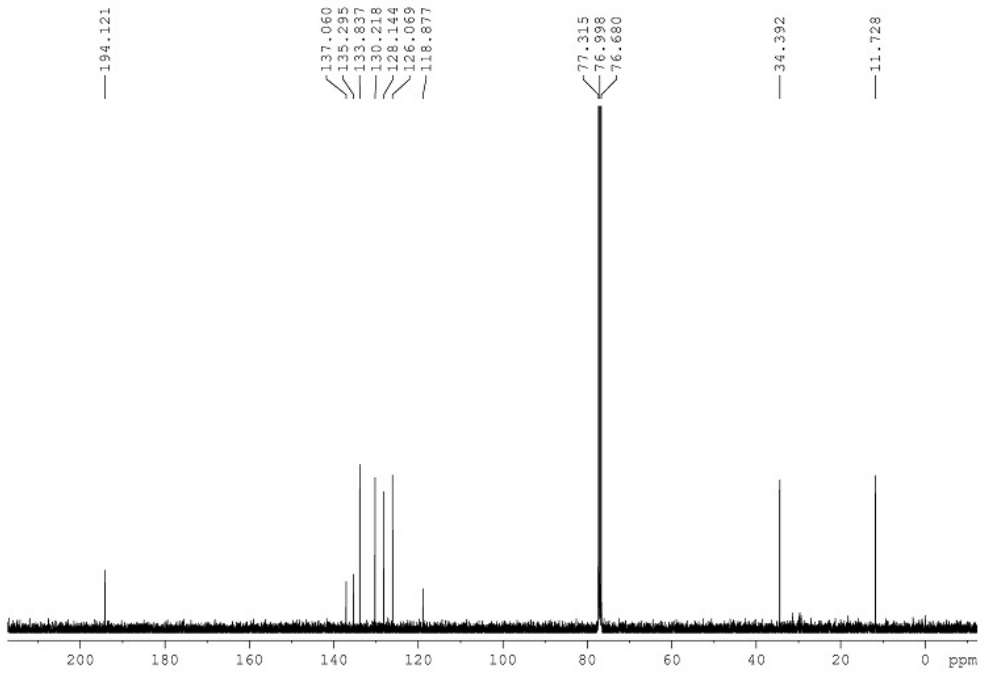


^{19}F NMR (471 MHz, $CDCl_3$)

4-(3-chlorophenyl)-4-oxobutanenitrile (2q)

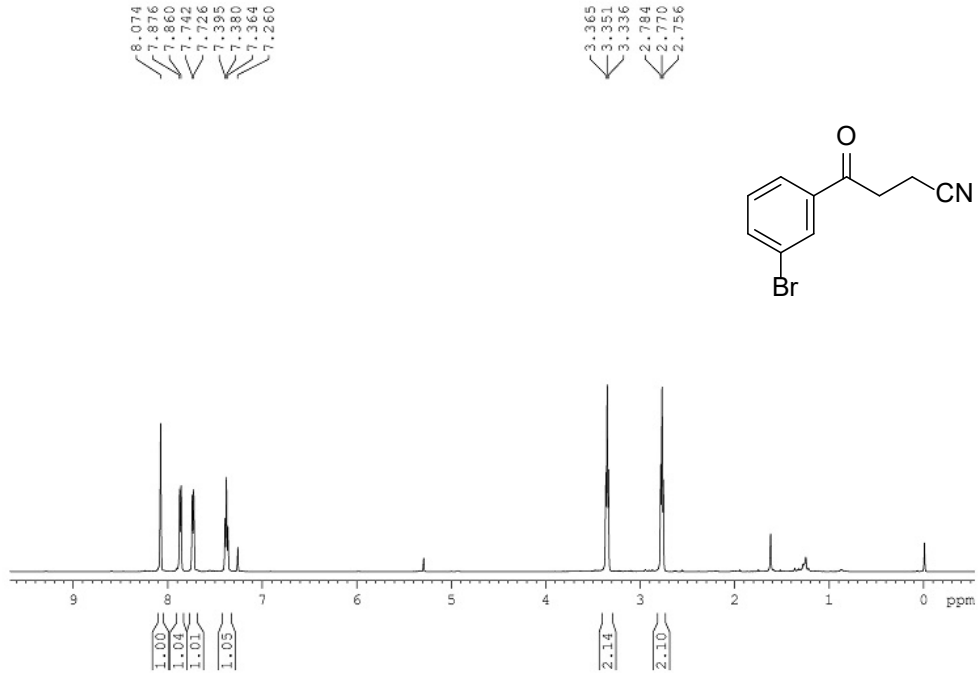


^{1}H NMR (500 MHz, $CDCl_3$)

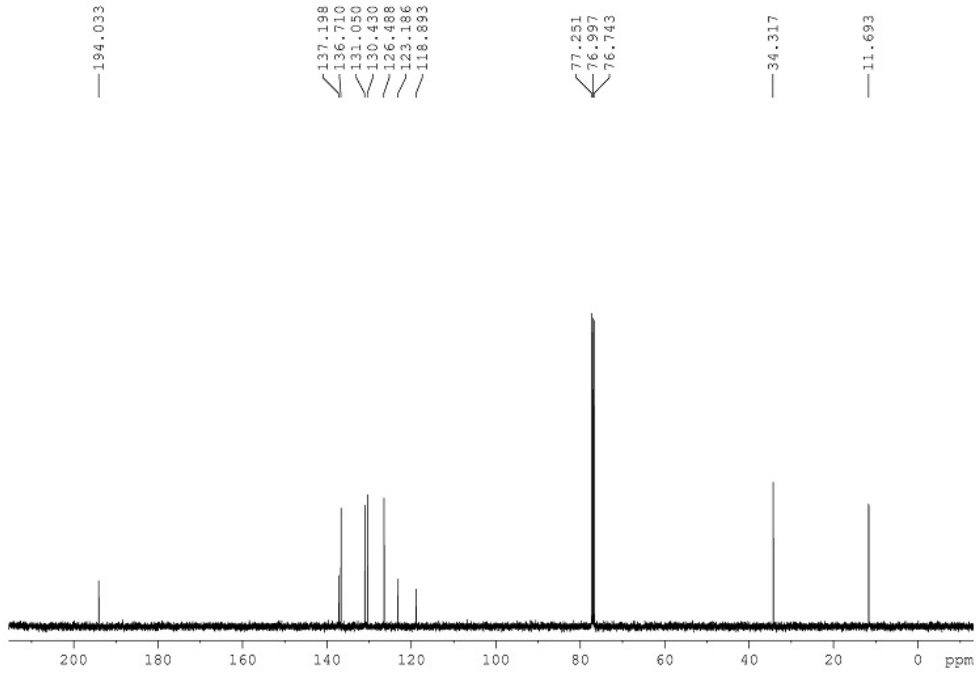


^{13}C NMR (125 MHz, $CDCl_3$)

4-(3-bromophenyl)-4-oxobutanenitrile (2r)



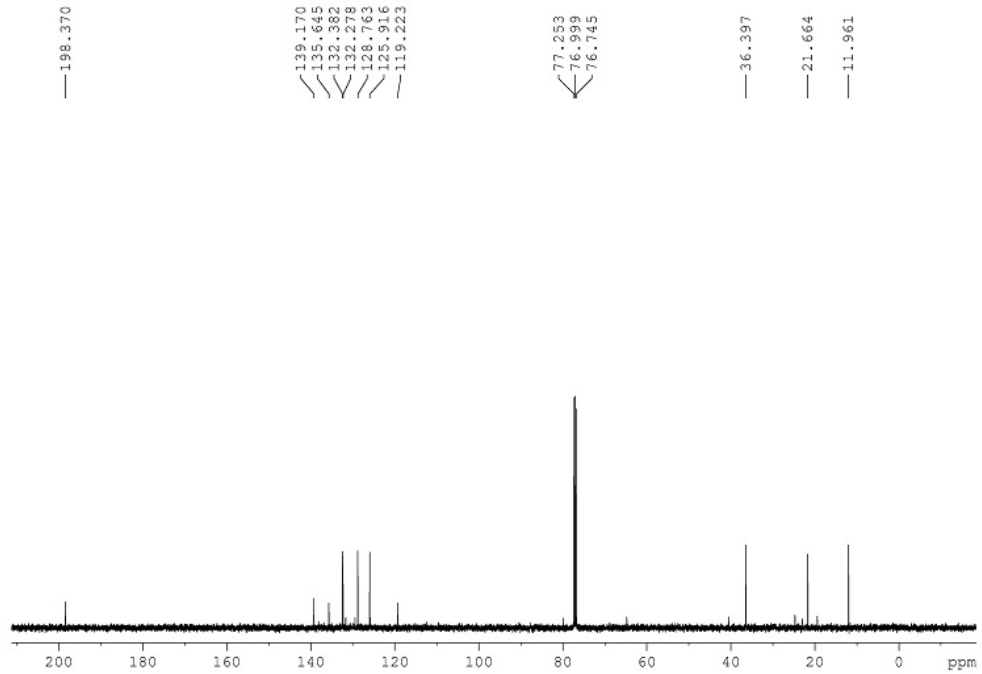
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

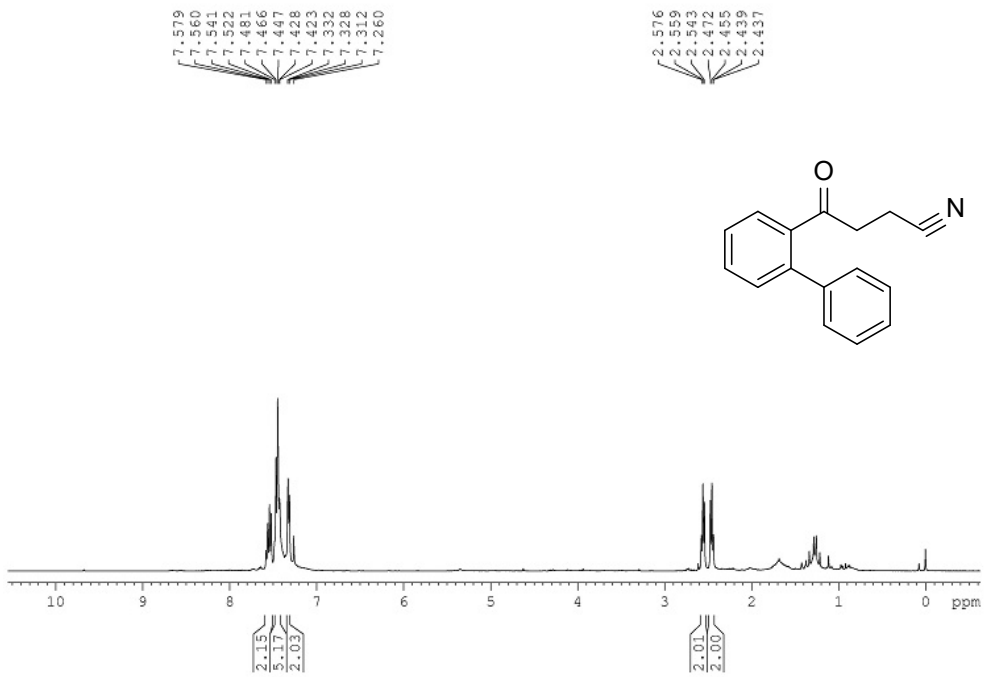
4-oxo-4-(o-tolyl)butanenitrile (2s)

^{1}H NMR (500 MHz, $CDCl_3$)

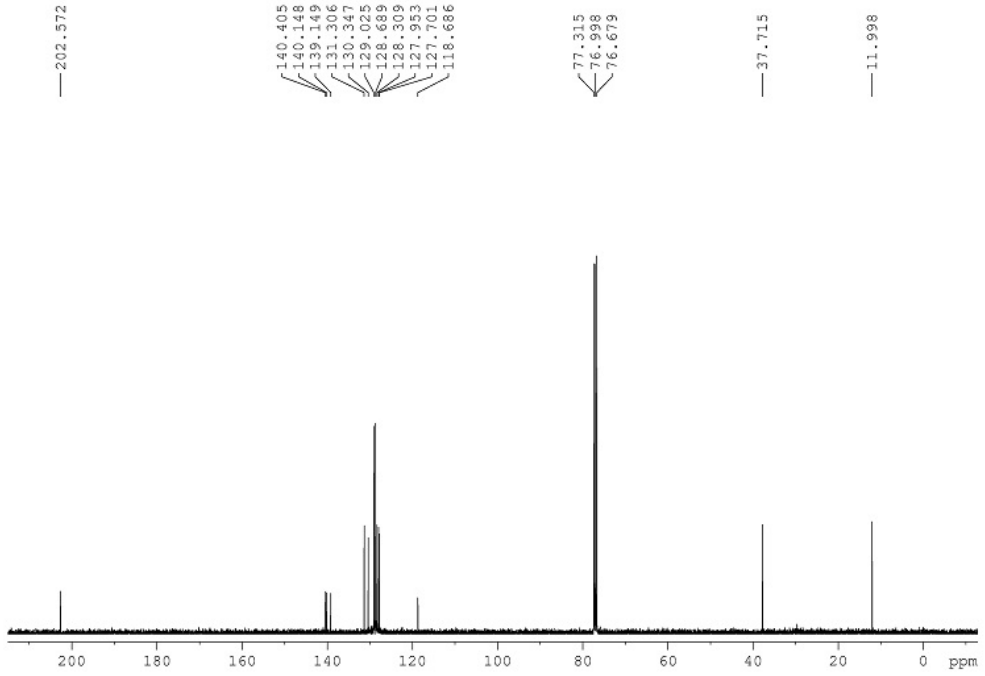


^{13}C NMR (125 MHz, $CDCl_3$)

4-(biphenyl-2-yl)-4-oxobutanenitrile (2t)

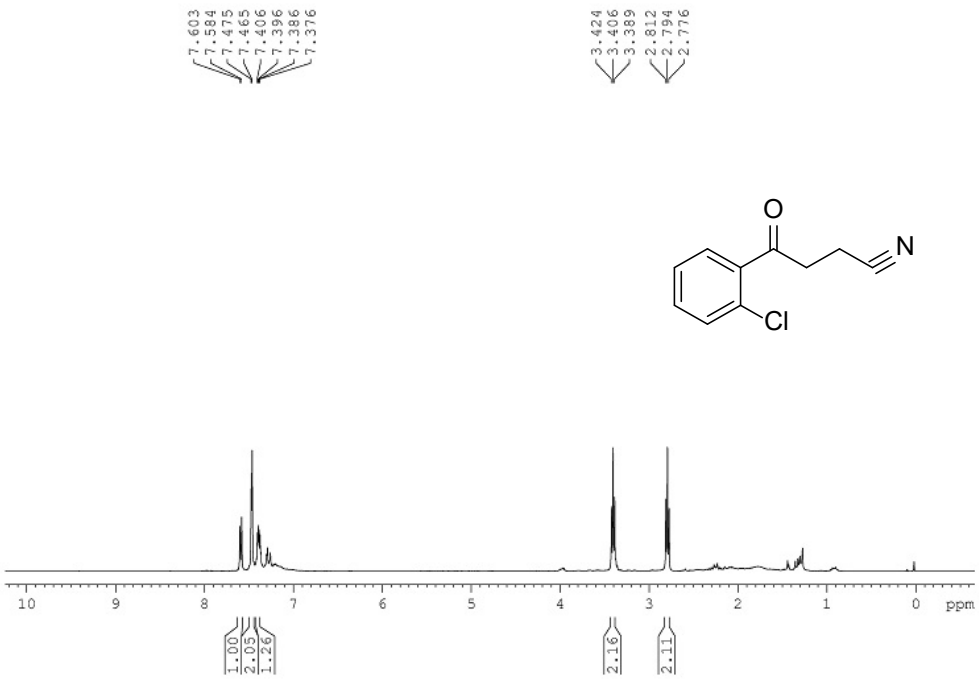


^{1}H NMR (500 MHz, $CDCl_3$)

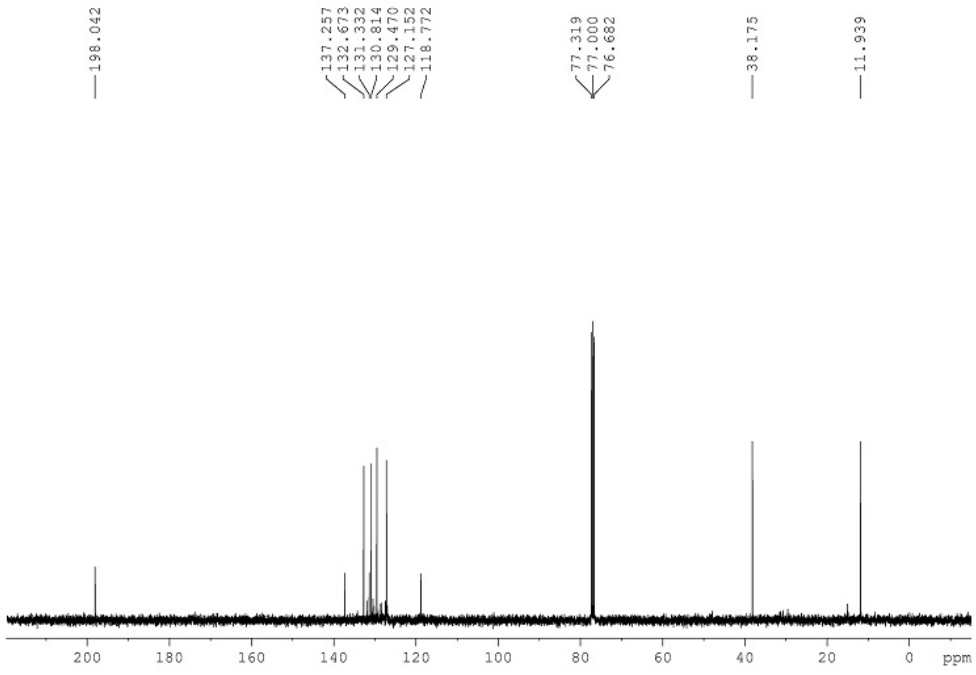


^{13}C NMR (125 MHz, $CDCl_3$)

4-(2-chlorophenyl)-4-oxobutanenitrile (2u)

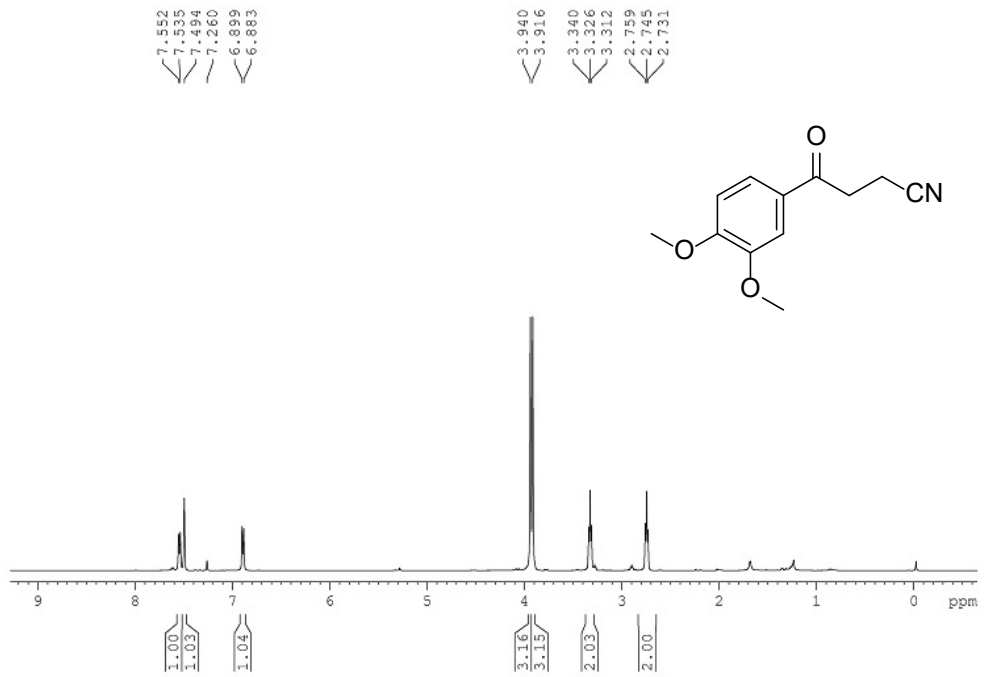


^{1}H NMR (500 MHz, $CDCl_3$)

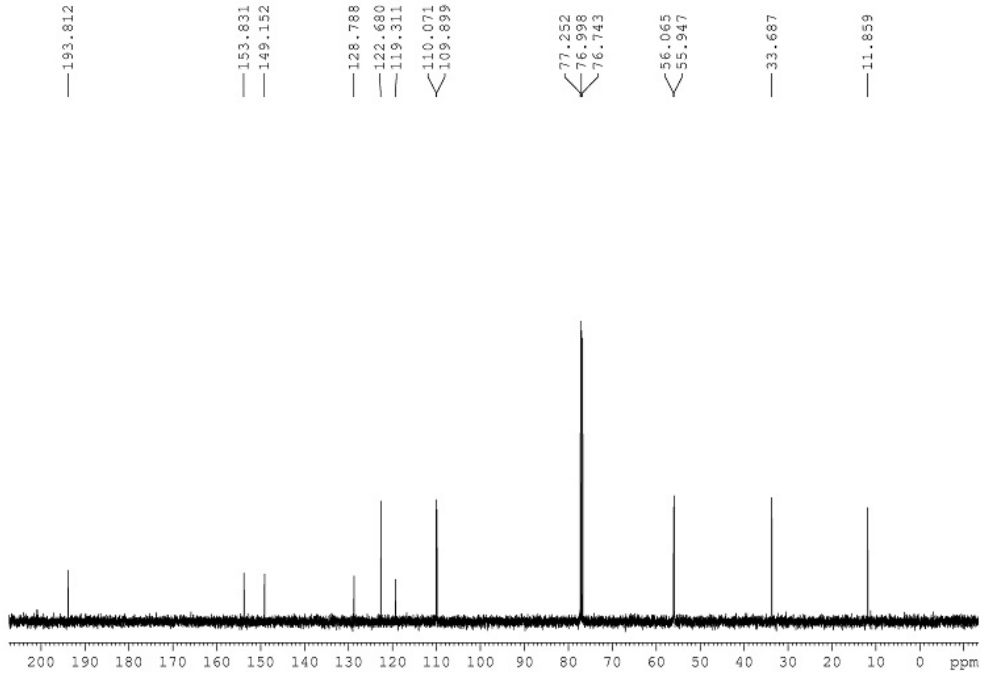


^{13}C NMR (125 MHz, $CDCl_3$)

4-(3,4-dimethoxyphenyl)-4-oxobutanenitrile (2v)

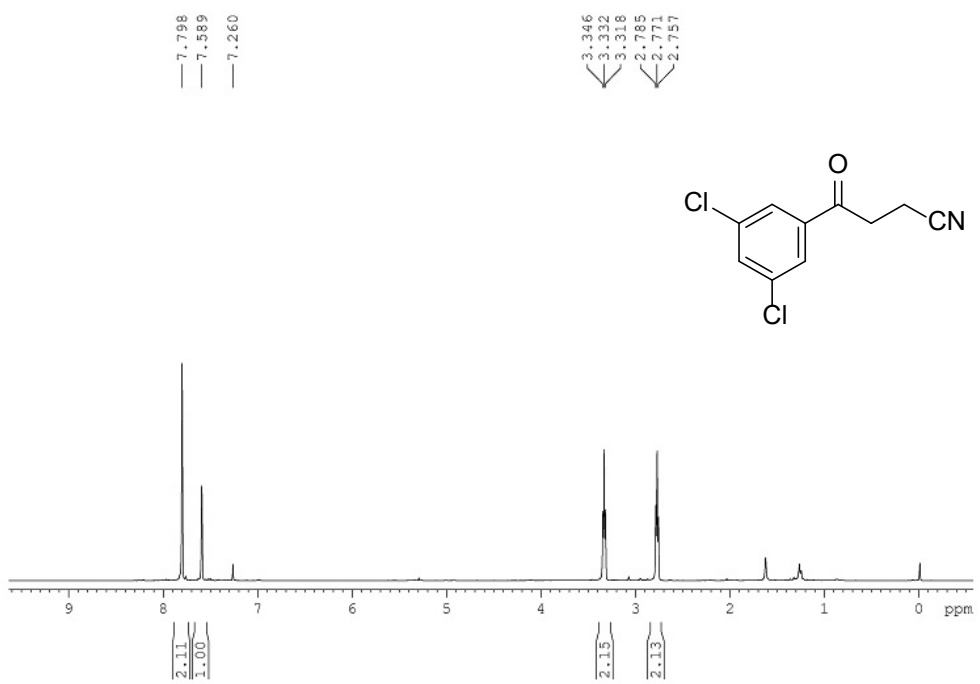


^{1}H NMR (500 MHz, $CDCl_3$)

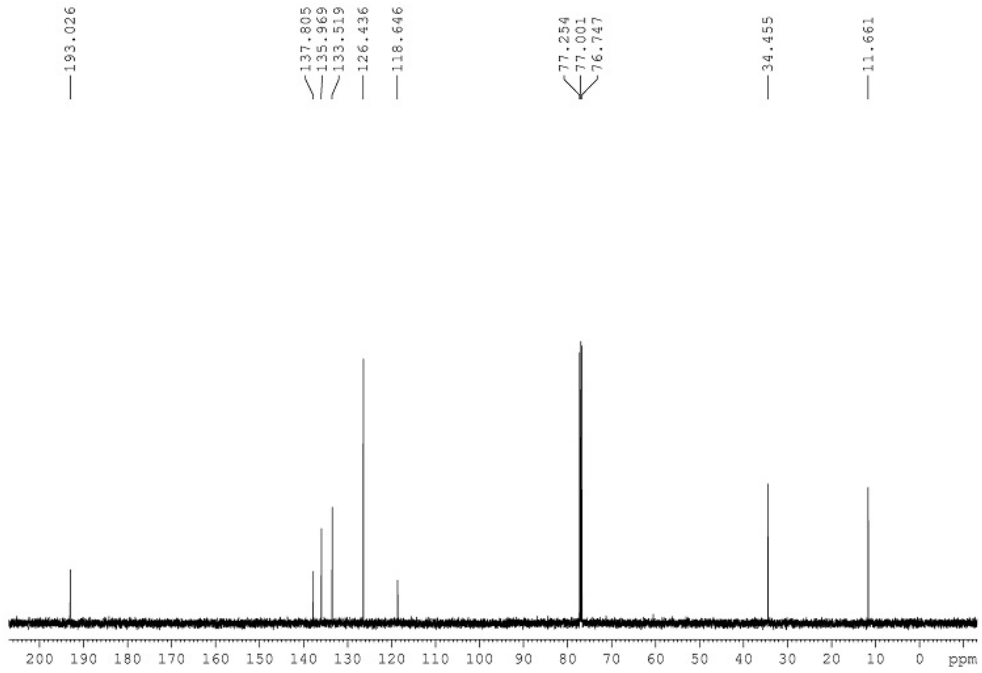


^{13}C NMR (125 MHz, $CDCl_3$)

4-(3,5-dichlorophenyl)-4-oxobutanenitrile (2w)

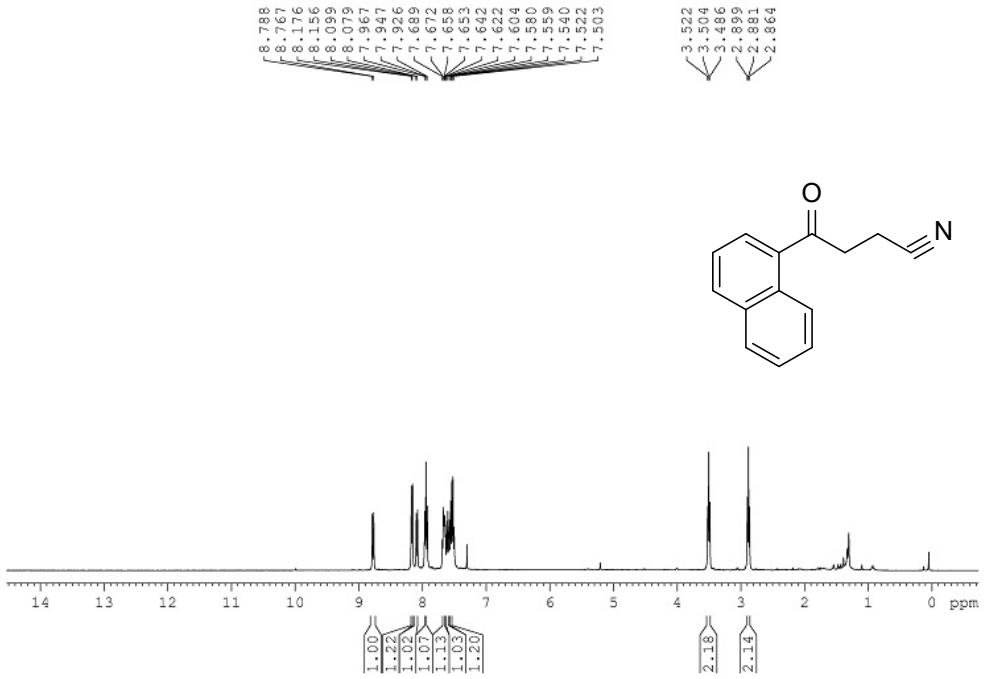


^{1}H NMR (500 MHz, $CDCl_3$)

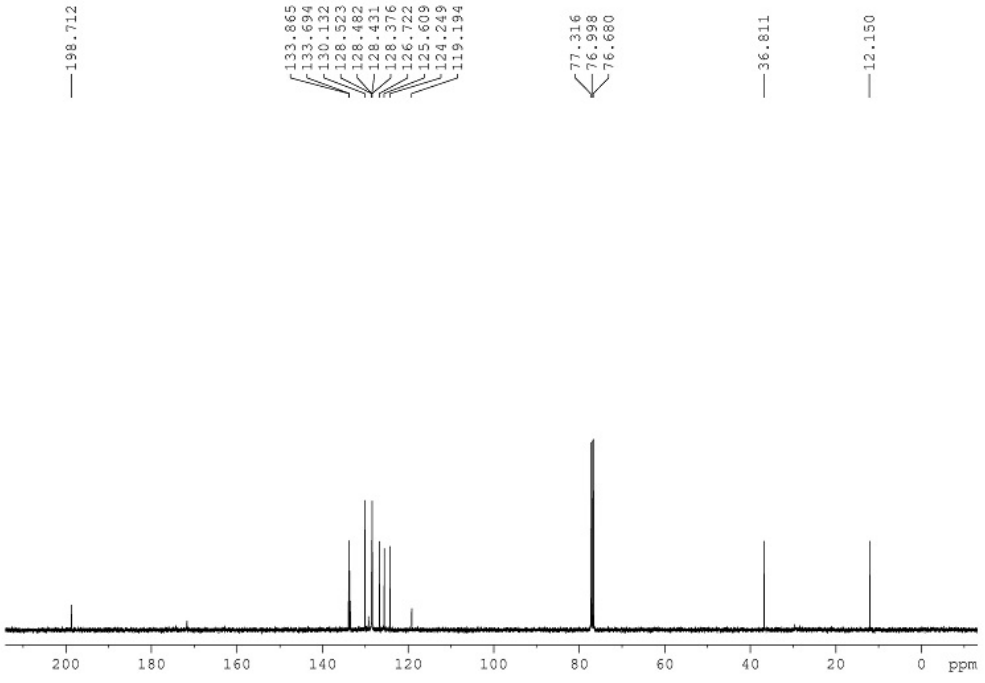


^{13}C NMR (125 MHz, $CDCl_3$)

4-(naphthalen-1-yl)-4-oxobutanenitrile (2x)

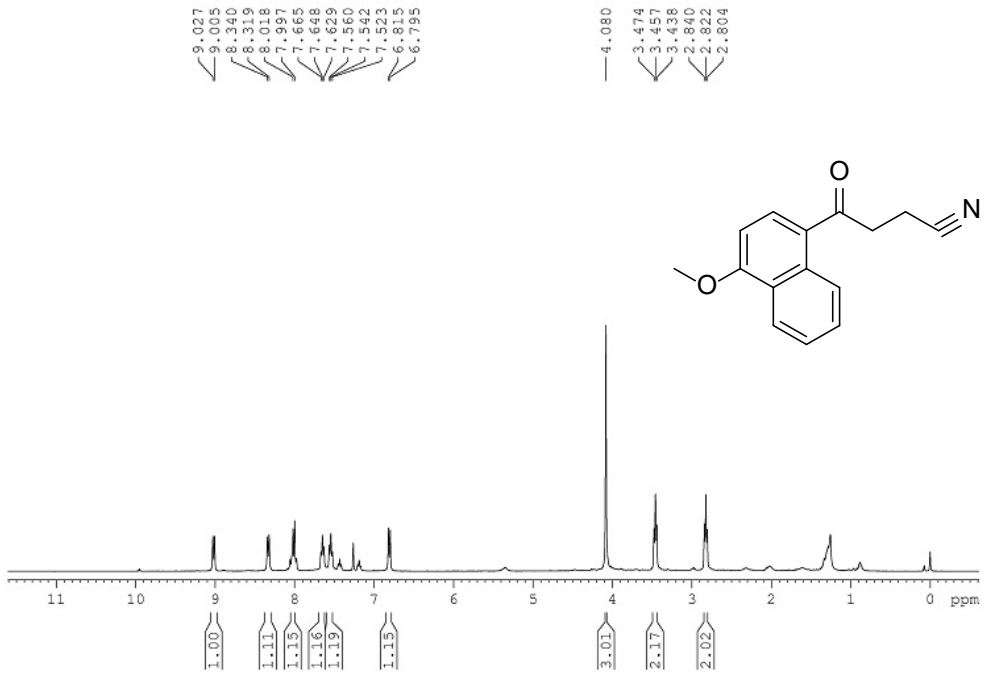


^{1}H NMR (500 MHz, $CDCl_3$)

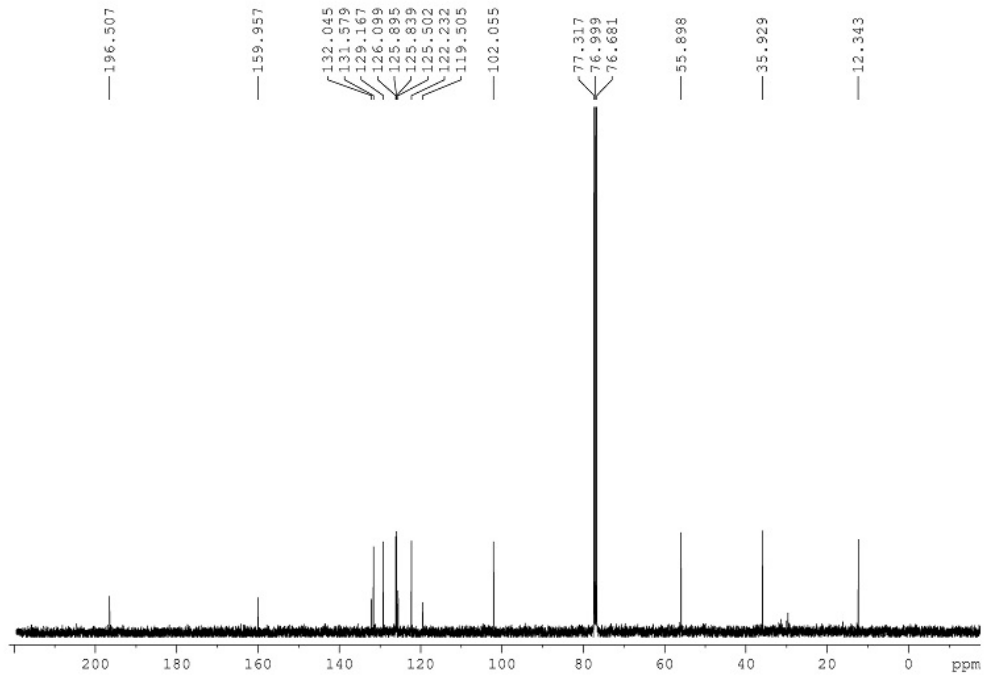


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-methoxynaphthalen-1-yl)-4-oxobutanenitrile (2y)



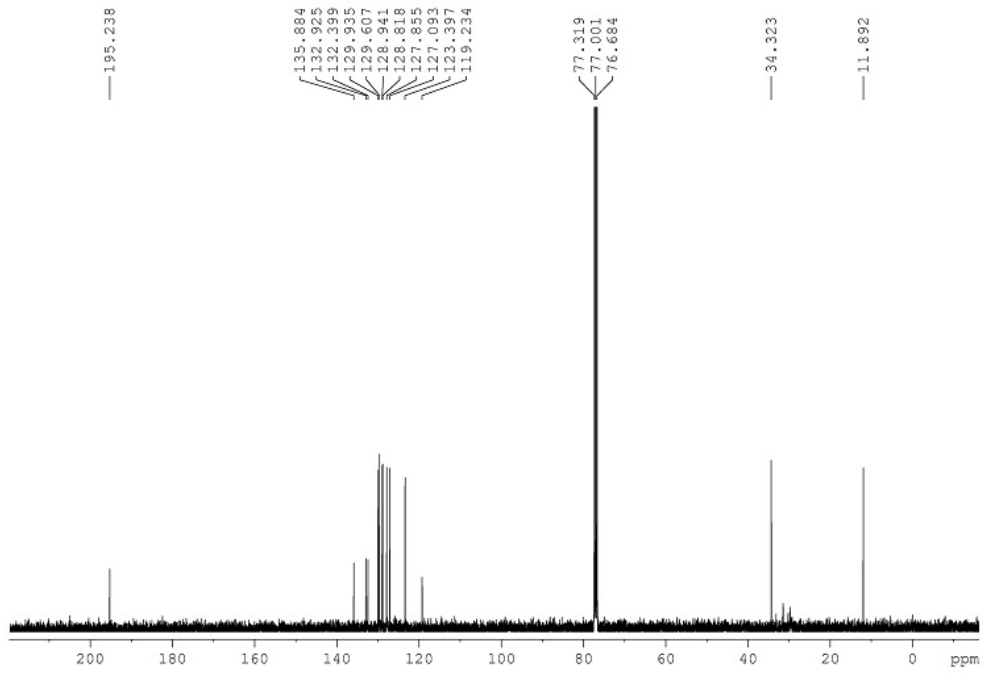
^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

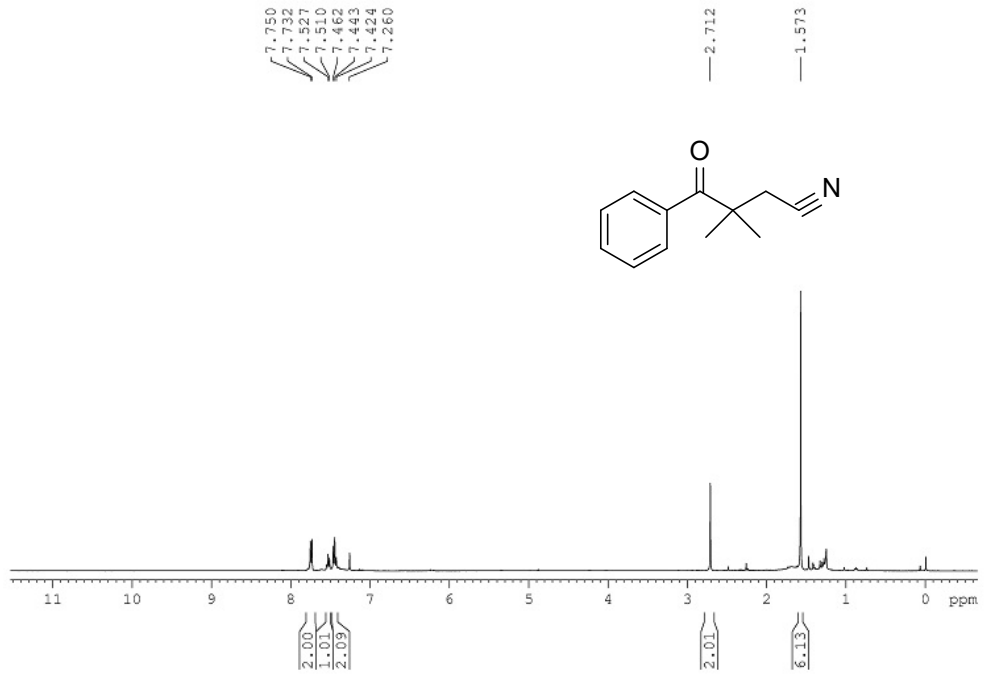
4-(naphthalen-2-yl)-4-oxobutanenitrile (2z)

^{1}H NMR (500 MHz, $CDCl_3$)

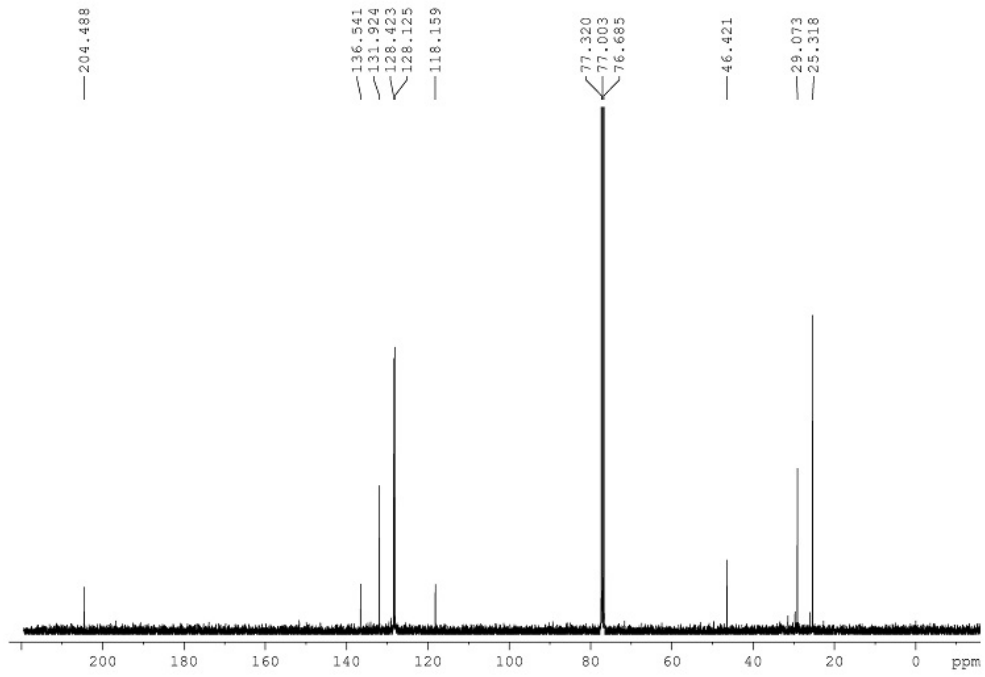


^{13}C NMR (125 MHz, $CDCl_3$)

3,3-dimethyl-4-oxo-4-phenylbutanenitrile (2aa)

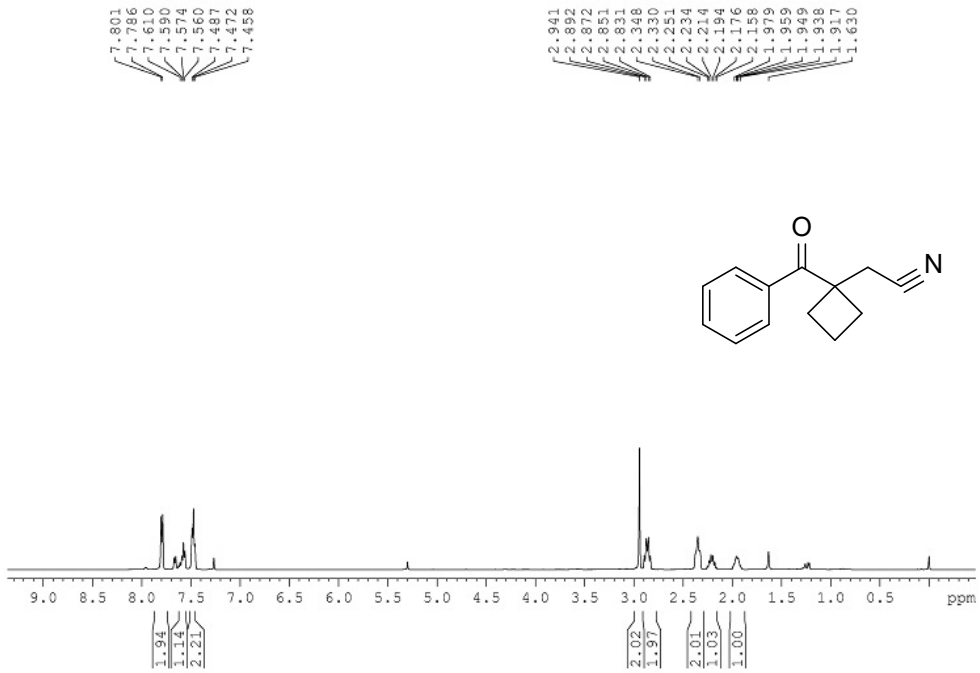


^{1}H NMR (500 MHz, $CDCl_3$)

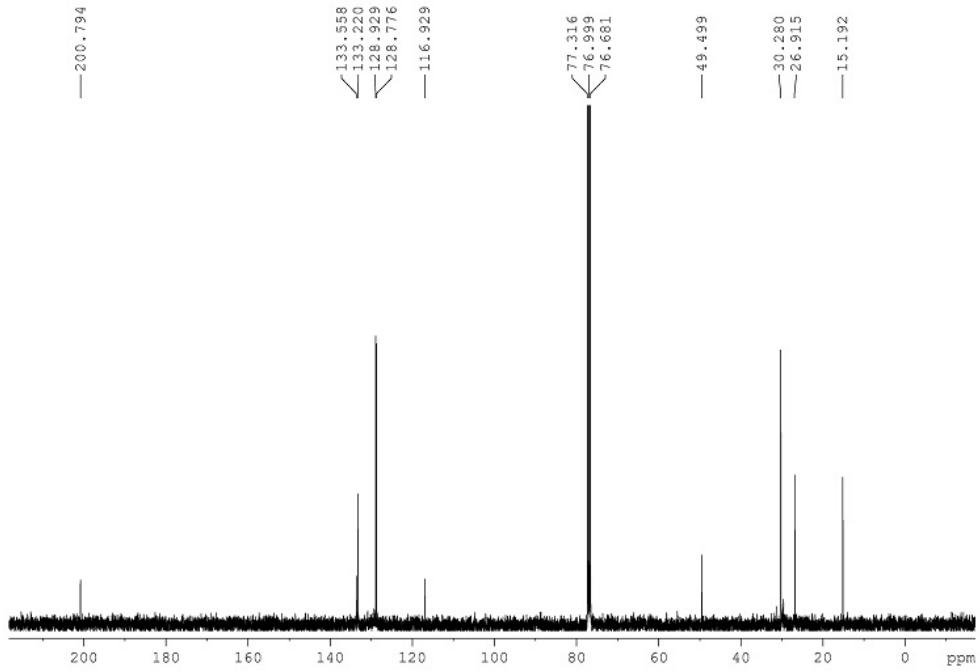


^{13}C NMR (125 MHz, $CDCl_3$)

2-(1-benzoylcyclobutyl)acetonitrile (2ab)

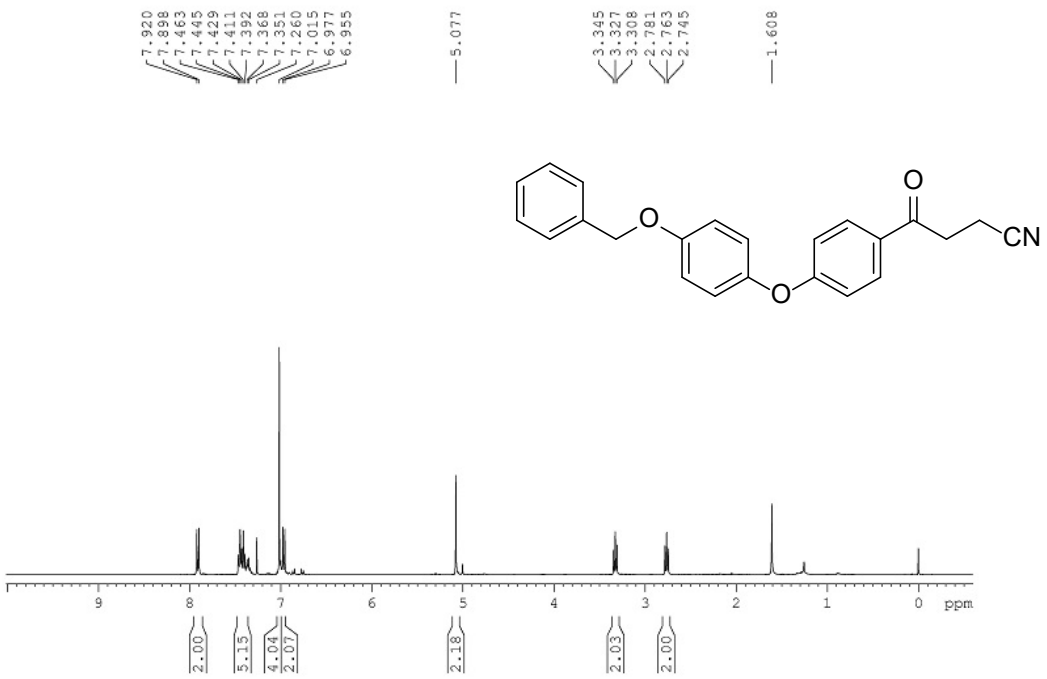


^{1}H NMR (500 MHz, $CDCl_3$)

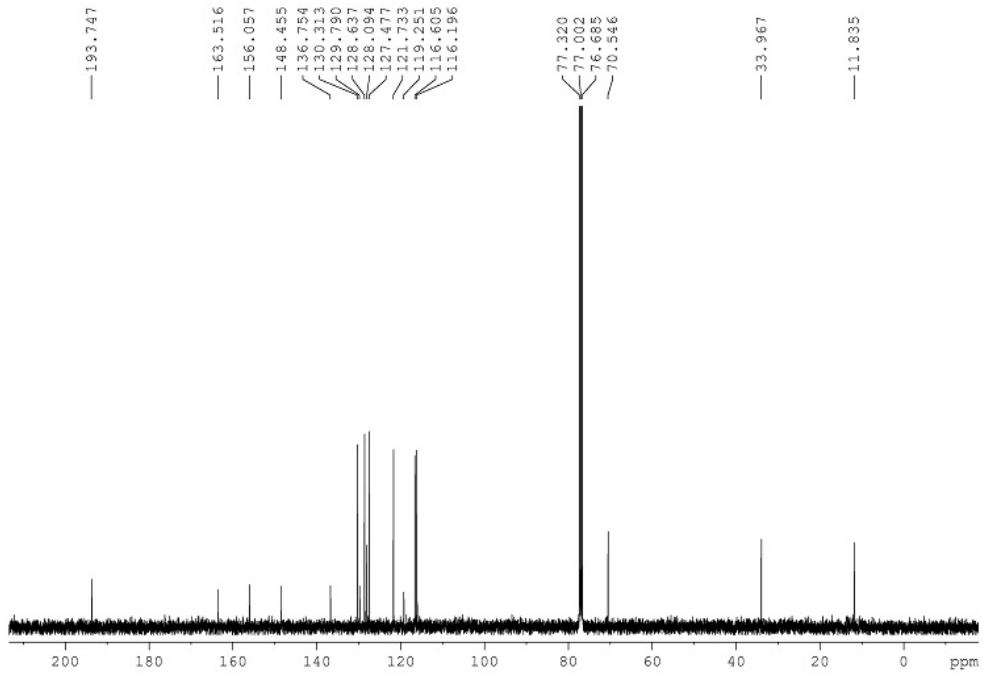


^{13}C NMR (125 MHz, $CDCl_3$)

4-(4-(4-(benzyloxy)phenoxy)phenyl)-4-oxobutanenitrile (2ac)

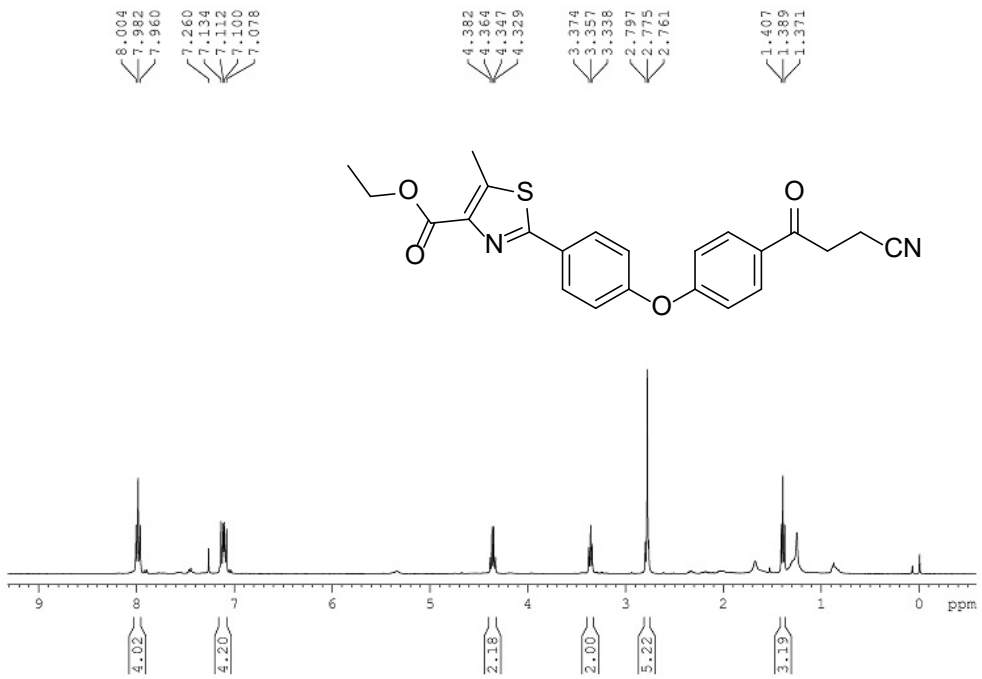


^{1}H NMR (500 MHz, $CDCl_3$)

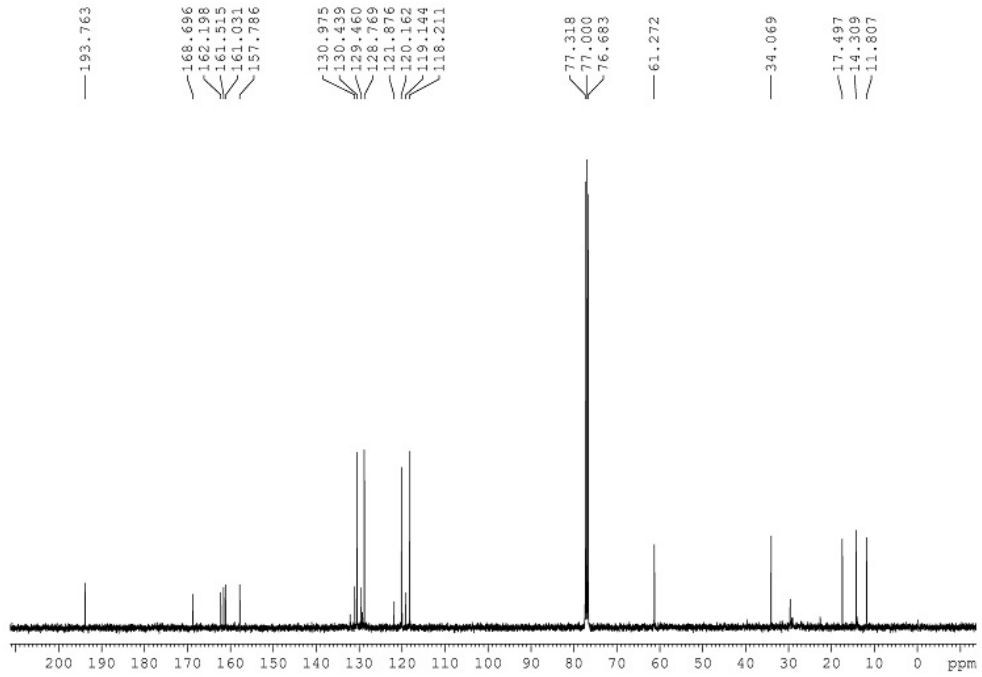


^{13}C NMR (125 MHz, $CDCl_3$)

ethyl 2-(4-(4-(3-cyanopropanoyl)phenoxy)phenyl)-5-methylthiazole-4-carboxylate (2ad)



^{1}H NMR (500 MHz, $CDCl_3$)



^{13}C NMR (125 MHz, $CDCl_3$)

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