Micelle-Guided Morita-Baylis-Hillman Reaction of Ketones in Water

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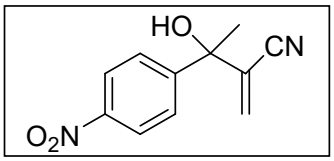
General information:

All the reactions were carried out by using standard syringe-septum technique. Thin layer chromatography (TLC) was employed to monitor the reactions. UV active spots were analysed under UV- light and TLC plates were exposed to $KMnO_4$ -solution for spot visualisation. For column chromatography commercial silica gel of mesh particle size (100-200) was used. ^1H and ^{13}C NMR of samples were recorded in $CDCl_3$ and CD3OD solvents and the chemical shifts were reported in parts per million on δ-scale using tetramethylsilane as an internal standard. Singlet (*s*), doublet (*d*), triplet (*t*), quartet (*q*), doublet of doublet (*dd*) and multiplet (*m*) standard abbreviations were used. Coupling constant (*J*) was reported in Hz. HRMS (ESI-TOF analyser**)** equipment was used to record mass spectra.

Micellar medium preparation: Cetyltrimethylammonium bromide (CTAB) surfactant (164 mg, 0.0045 M, 5 times above CMC) was added to 100 ml distilled water on constant stirring in a 250 ml round bottom flask. To form CTAB micellar assemblies, the solution was constantly stirred for an hour at/above Kraft's temperature (Kraft temp. of CTAB is 25 ˚C). Same procedure was adopted to form the stock solutions of micelles with other surfactants also.

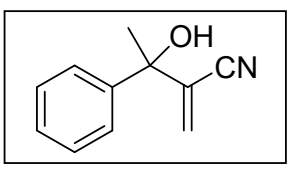
General procedure for the synthesis of compounds 3-20: To carry out the reaction, the micellar stock solution (40 equiv.) was taken in a neat and clean RB. To this, reactants ketone (1 equiv.) and acrynonitrile or methyacrylate (1.2 equiv.) were added on constant stirring at or above the Kraft's temperature of the surfactant. DABCO (0.2 equiv.) and scandium triflate (0.2 equiv.) were also added to the reaction mixture on constant stirring. The reaction progress was monitored by TLC. Ethylacetate and water were added to reaction mixture in the ratio of 2:1 followed by brine solution. Organic layer was partitioned and aqueous layer was further extracted with ethylacetate and dried over sodium sulphate. Rotatory evaporation of the organic solvents and subsequent column chromatography using hexane and ethylacetate resulted in purifications of compounds **3-20**.

3-hydroxy-2-methylene-3-(4-nitrophenyl)butanenitrile (3):



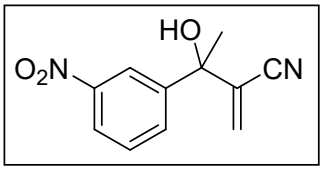
^1H NMR ($CDCl_3$, 500 MHz): δ 1.91 (s, 3H), 6.10 (s, 1H), 6.18 (s, 1H), 7.70 (d, *J* = 5.0 Hz, 2H), 8.25 (d, *J* = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 28.2, 74.5, 116.9, 123.8, 126.6, 129.6, 129.9, 147.6, 150.0; HRMS calcd. for $C_{11}H_{11}N_2O_3$ $[M+H]^+$: 219.0764; Found 219.0659.

3-hydroxy-2-methylene-3-phenylbutanenitrile (4):



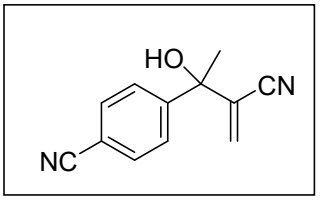
^1H NMR ($CDCl_3$, 400 MHz): δ 1.88 (s, 3H), 6.04 (s, 1H), 6.11 (s, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.42 (t, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 28.0, 74.9, 117.4, 125.4, 128.0, 128.3, 128.7, 130.9, 142.9; HRMS calcd. for $C_{11}H_{12}NO$ $[M+H]^+$: 174.0913; Found 174.0921.

3-hydroxy-2-methylene-3-(3-nitrophenyl)butanenitrile (5):



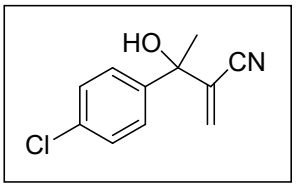
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.22 (s, 3H), 6.09 (s, 1H), 6.19 (s, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 8.20 (d, J = 8 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 28.2, 74.4, 116.9, 120.7, 123.2, 129.6, 129.7, 129.9, 131.7, 145.2, 148.4; HRMS calcd. for $C_{11}H_{11}N_2O_3$ $[M+H]^+$: 219.0764; Found 219.0659

4-(3-cyano-2-hydroxy-3-en-2-yl)benzonitrile (6):



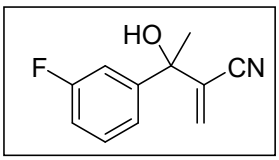
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.85 (s, 3H), 6.06 (s, 1H), 6.14 (s, 1H), 7.62 (d, J = 4.0 Hz, 2H), 7.68 (d, J =4.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 28.0, 74.5, 111.9, 117.0, 118.5, 126.3, 129.5, 130.0, 132.5, 148.3; HRMS calcd. for $C_{12}H_{11}N_2O$ $[M+H]^+$: 199.0866; Found 199.0864.

3-(4-chlorophenyl)-3-hydroxy-2-methylenebutanenitrile (7):



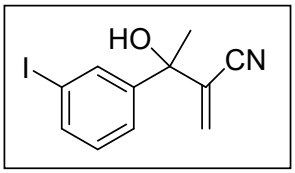
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.14 (s, 3H), 6.02 (s, 1H), 6.09 (s, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 28.1, 74.5, 117.2, 127.0, 128.8, 128.9, 130.6, 134.2, 141.4; HRMS calcd. for $C_{11}H_{10}ClNONa$ $[M+Na]^+$: 230.0343; Found 230.0360.

3-(3-fluorophenyl)-3-hydroxy-2-methylenebutanenitrile (8):



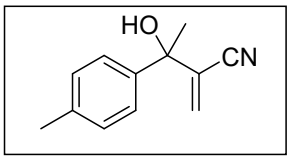
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.84 (s, 3H), 6.01 (s, 1H), 6.09 (s, 3H), 7.06 (t, J = 8.0 Hz, 1H), 7.15 (t, J = 8.0 Hz, 1H), 7.46 (q, J = 8.0 Hz, 1H), 8.00 (q, J = 4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 22.7, 74.5, 115.5 (d, J = 21.2 Hz), 115.8 (d, J = 22.2 Hz), 117.3, 119.4, 127.4 (d, J = 9.1 Hz), 128.6, 130.6 (d, J = 9.1 Hz), 132.9, 161.0; HRMS calcd. for $C_{11}H_{10}FNONa$ $[M+Na]^+$: 214.0639; Found 214.0629.

3-hydroxy-3-(3-iodophenyl)-2-methylenebutanenitrile (9):



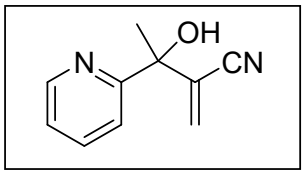
^{1}H NMR (CDCl3, 400 MHz): δ 1.85 (s, 3H), 6.05 (s, 1H), 6.11 (s, 1H), 7.27 (t, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 28.2, 74.4, 117.1, 122.9, 124.1, 128.7, 129.1, 130.3, 131.4, 133.8, 145.0; HRMS calcd. for $C_{11}H_{10}INONa$ $[M+Na]^+$: 321.9699; Found 321.9690.

3-hydroxy-2-methylene-3-(p-tolyl)butanenitrile (10):



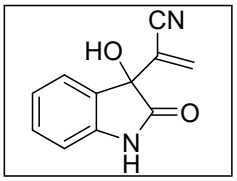
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.89 (s, 3H), 3.51 (s, 3H), 6.04 (s, 1H), 6.11 (s, 1H), 7.42 (m, 2H), 7.50 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 28.3, 51.0, 74.9, 117.6, 125.4, 128.3, 128.6, 128.7, 131.0, 143; HRMS calcd. for $C_{12}H_{13}NONa$ $[M+Na]^+$: 210.0889; Found 210.0883

3-hydroxy-2-methylene-3-(pyridin-2-yl)butanenitrile (11):



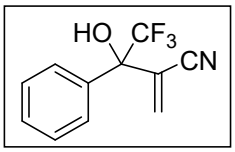
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.80 (s, 3H), 5.99 (s, 1H), 6.06 (s, 1H), 7.31 (t, J = 5.0 Hz, 1H), 7.58 (d, J = 10.0 Hz, 1H), 7.80 (t, J = 5.0 Hz, 1H), 8.55 (d, J = 5.0 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 26.7, 74.0, 119.3, 120.1, 123.3, 129.4, 133.5, 137.8, 147.8, 159.8; HRMS calcd. for $C_{10}H_{10}N_2O$ [M] : 174.0793; Found 174.0735.

2-(3-hydroxy-2-oxoindolin-3-yl)acrylonitrile (12):



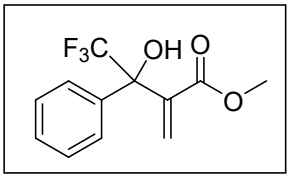
^{1}H NMR (CD_3OD, 500 MHz): δ 6.26 (s, 1H), 6.36 (s, 1H), 6.97 (d, J = 5.0 Hz, 1H), 7.12 (t, J = 5.0 Hz, 1H), 7.33 (d, J = 10.0 Hz, 1H), 7.37 (d, J = 5.0 Hz, 1H); ^{13}C NMR (MeOD, 101 MHz): δ 76.6, 110.4, 115.6, 122.8, 123.4, 124.4, 128.9, 130.5, 130.9, 141.8, 176.6; HRMS calcd. for $C_{11}H_8N_2NaO_2$ $[M+Na]^+$: 223.0478; Found 223.0473

4,4,4-trifluoro-3-hydroxy-2-methylene-3-phenylbutanenitrile (13):



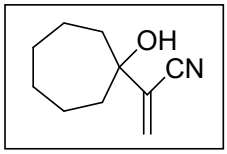
^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.37 (s, 1H), 6.42 (s, 1H), 7.47 (m, 3H), 7.62 (d, J = 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 77.8 (q, J = 30.2 Hz), 115.8, 122.6 (d, J = 25.2 Hz), 125.1, 126.5, 126.6, 129.0, 130.0, 134.8 (d, J = 37.8 Hz); HRMS calcd. for $C_{11}H_8F_3NONa$ $[M+Na]^+$: 250.0450; Found 250.0453.

Methyl-4,4,4-trifluoro-3-hydroxy-2-methylene-3-phenylbutan (14):



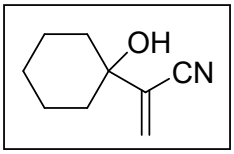
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.66 (s, 3H), 5.67 (s, 1H), 6.12 (s, 1H), 6.61 (s, 1H), 7.35 (m, 3H), 7.56 (d, J = 4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 52.7, 79.3 (q, J = 28.3 Hz), 122.8, 125.6, 126.9, 128.3, 129.1 (t, J = 7.1 Hz), 136.0, 137.1, 167.5; HRMS calcd. for $C_{12}H_{12}F_3O_3$ $[M+H]^+$: 261.0733; Found 261.0731.

2-(1-hydroxycycloheptyl)acrylonitrile (15):



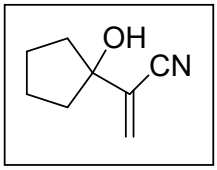
^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.58-1.78 (m, 12H), 5.90 (s, 1H), 6.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 21.9, 28.7, 40.4, 75.9, 118.0, 127.2, 132.9; HRMS calcd. for $C_{10}H_{16}NO$ $[M+H]^+$: 166.1226; Found 166.1232.

2-(1-hydroxycyclohexyl)acrylonitrile (16):



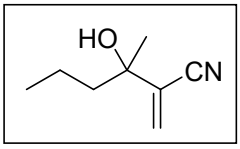
^{1}H NMR (CDCl3, 400 MHz): δ 1.64-1.76 (m, 10H), 5.95 (s, 1H), 6.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 21.3, 24.9, 35.9, 72.5, 117.9, 128.4, 132.2; HRMS calcd. for $C_9H_{13}NONa$ $[M+Na]^+$: 174.0889; Found 174.0878.

2-(1-hydroxycyclopentyl)acrylonitrile (17):



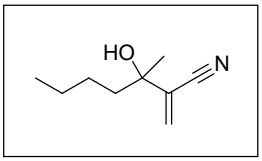
1H NMR ($CDCl_3$, 400 MHz): δ 1.72-1.85 (m, 4H), 1.90-2.02 (m, 4H) 5.98 (s, 1H), 6.15 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 23.8, 39.7, 87.0, 117.9, 128.4, 129.8; HRMS calcd. for $C_8H_{11}NONa$ $[M+Na]^+$: 160.0733; Found 160.0732.

3-hydroxy-3-methyl-2-methylenehexanenitrile (18):



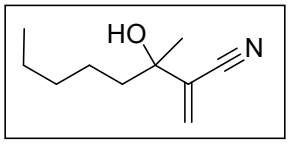
^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.96 (t, J = 8.0 Hz, 3H), 1.26 (s, 3H), 1.31-1.56 (m, 4H), 5.97 (s, 1H), 6.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 14.2, 16.8, 27.5, 43.1, 73.9, 117.8, 128.6, 130.6; HRMS calcd. for $C_8H_{13}NONa$ $[M+Na]^+$: 162.0889; Found 162.0881.

3-Hydroxy-3-methyl-2-methyleneheptanenitrile (19):



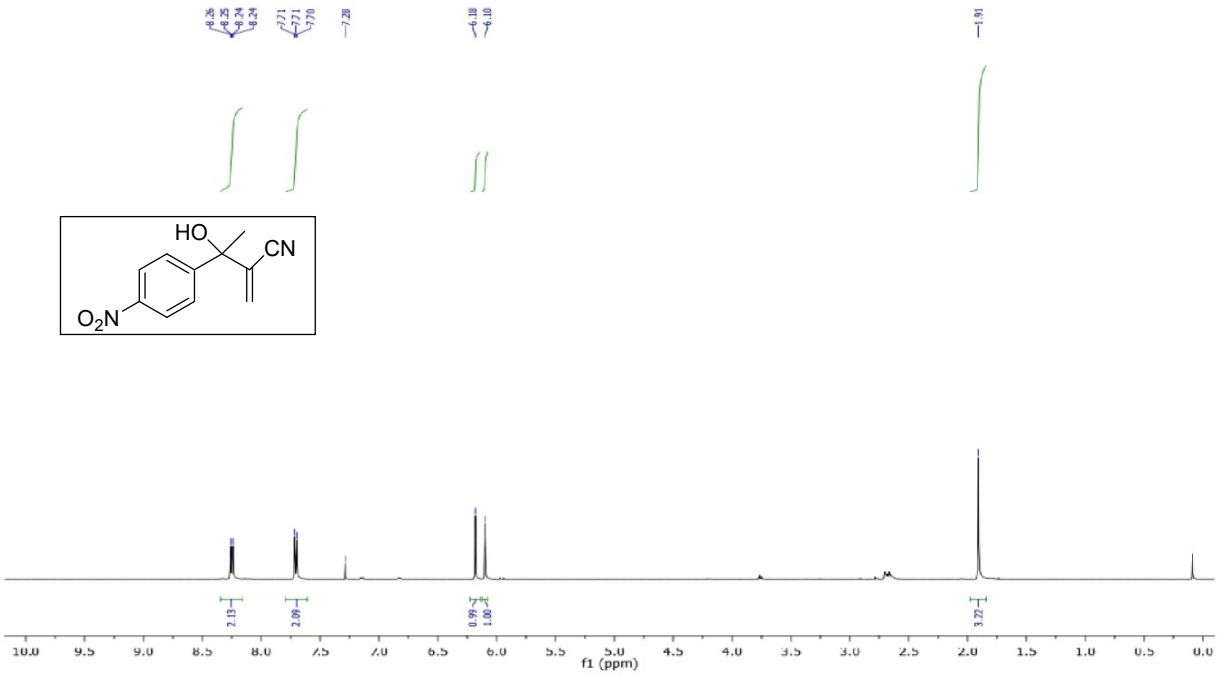
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.95 (t, J = 8.0 Hz, 3H), 1.25-1.35 (m, 9H), 5.97 (s, 1H), 6.07 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.2, 16.8, 27.5, 29.7, 43.0, 73.9, 117.7, 128.6, 130.6; HRMS calcd. for $C_9H_{15}NONa$ $[M+Na]^+$: 176.1046; Found 176.1043.

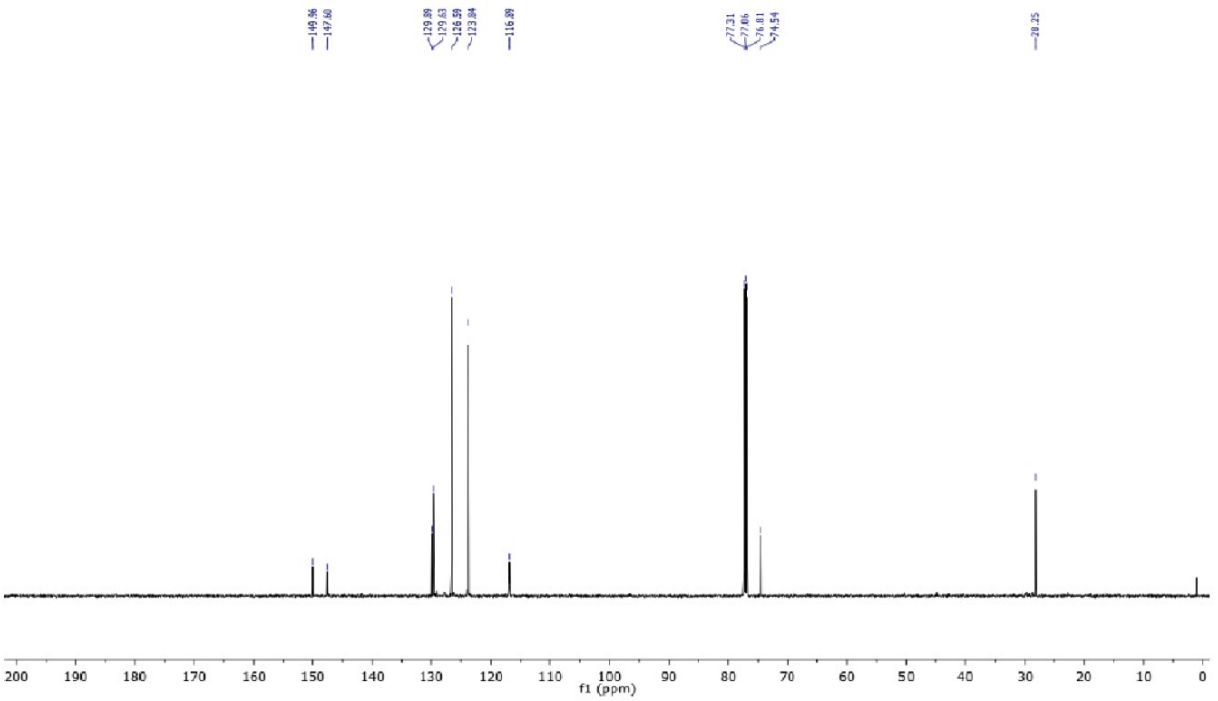
3-hydroxy-3-methyl-2-methyleneoctanenitrile (20):



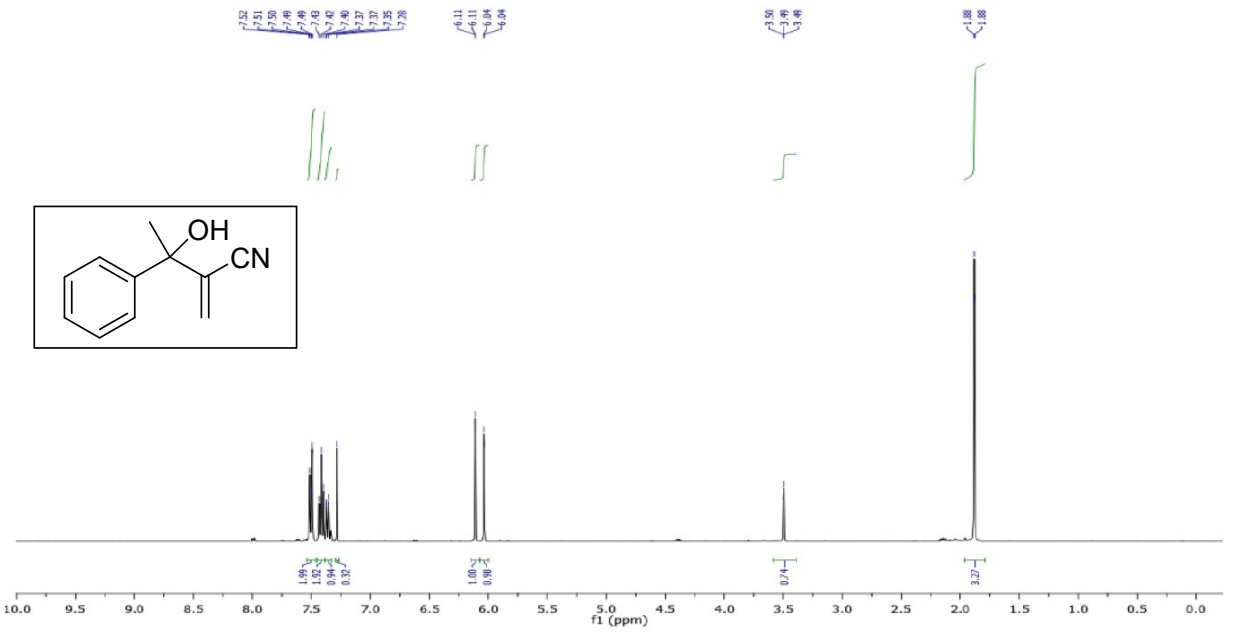
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.91 (t, J = 4 Hz, 3H), 1.27-1.34 (m, 11H), 5.99 (s, 1H), 6.09 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.0, 22.7, 27.6, 29.7, 31.8, 40.8, 74.0, 117.8, 128.7, 130.6; HRMS calcd. for $C_{10}H_{17}NONa$ $[M+Na]^+$: 190.1202; Found 190.1203

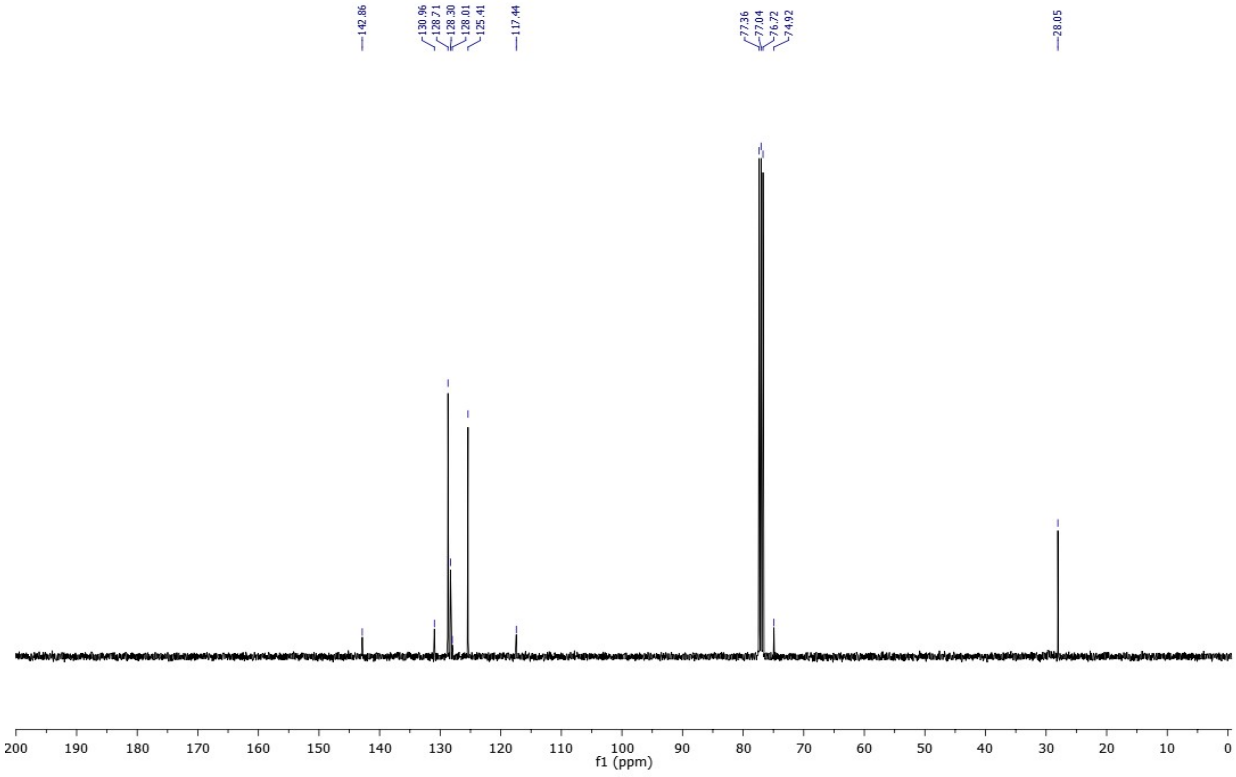
^{1}H and ^{13}C NMR in $CDCl_3$ of compound **3**



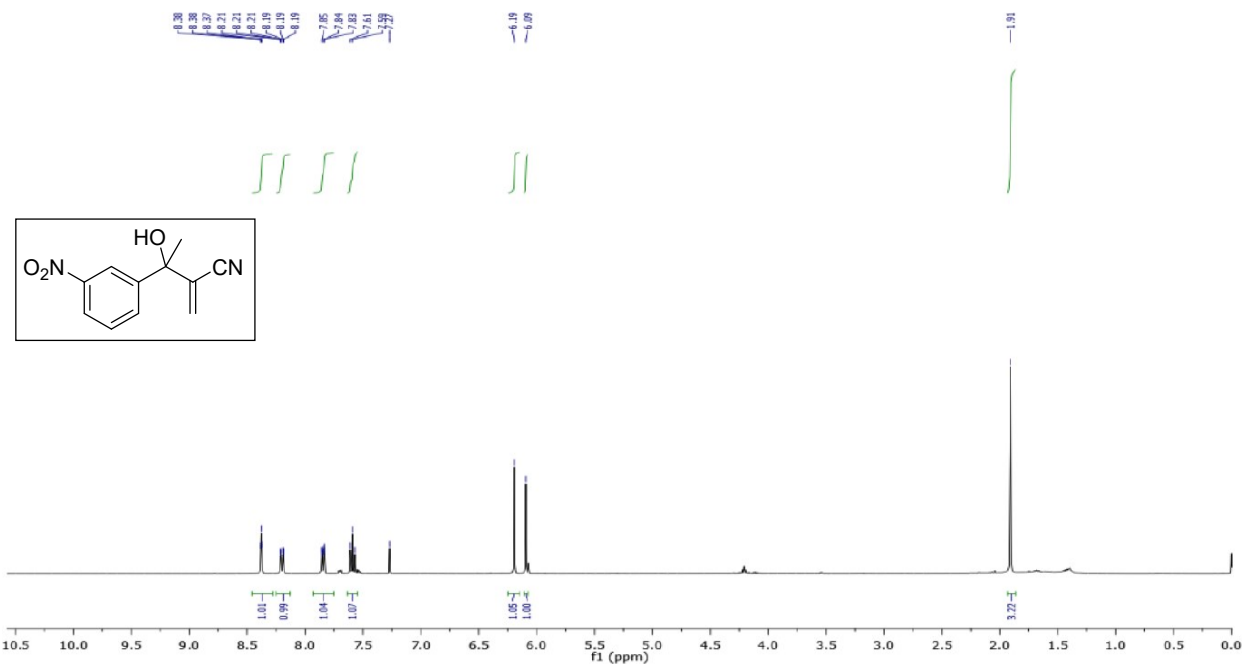


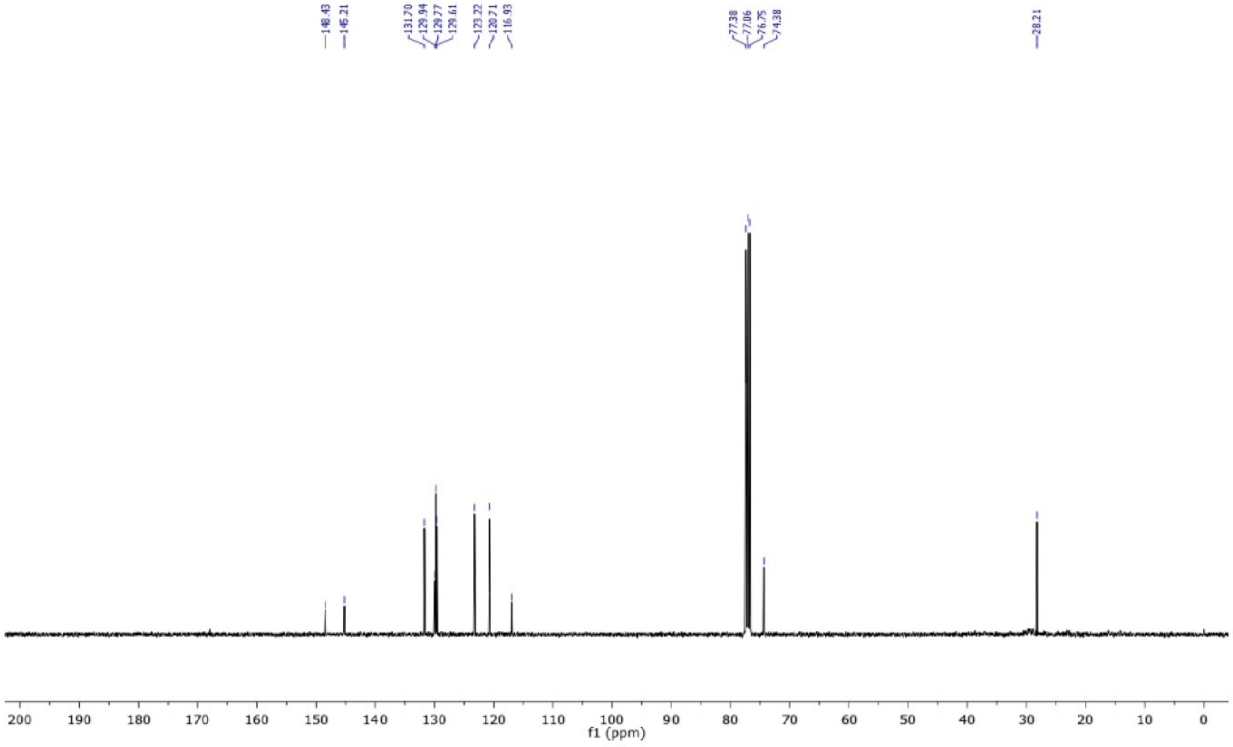
^{1}H and ^{13}C NMR in $CDCl_3$ of compound **4**



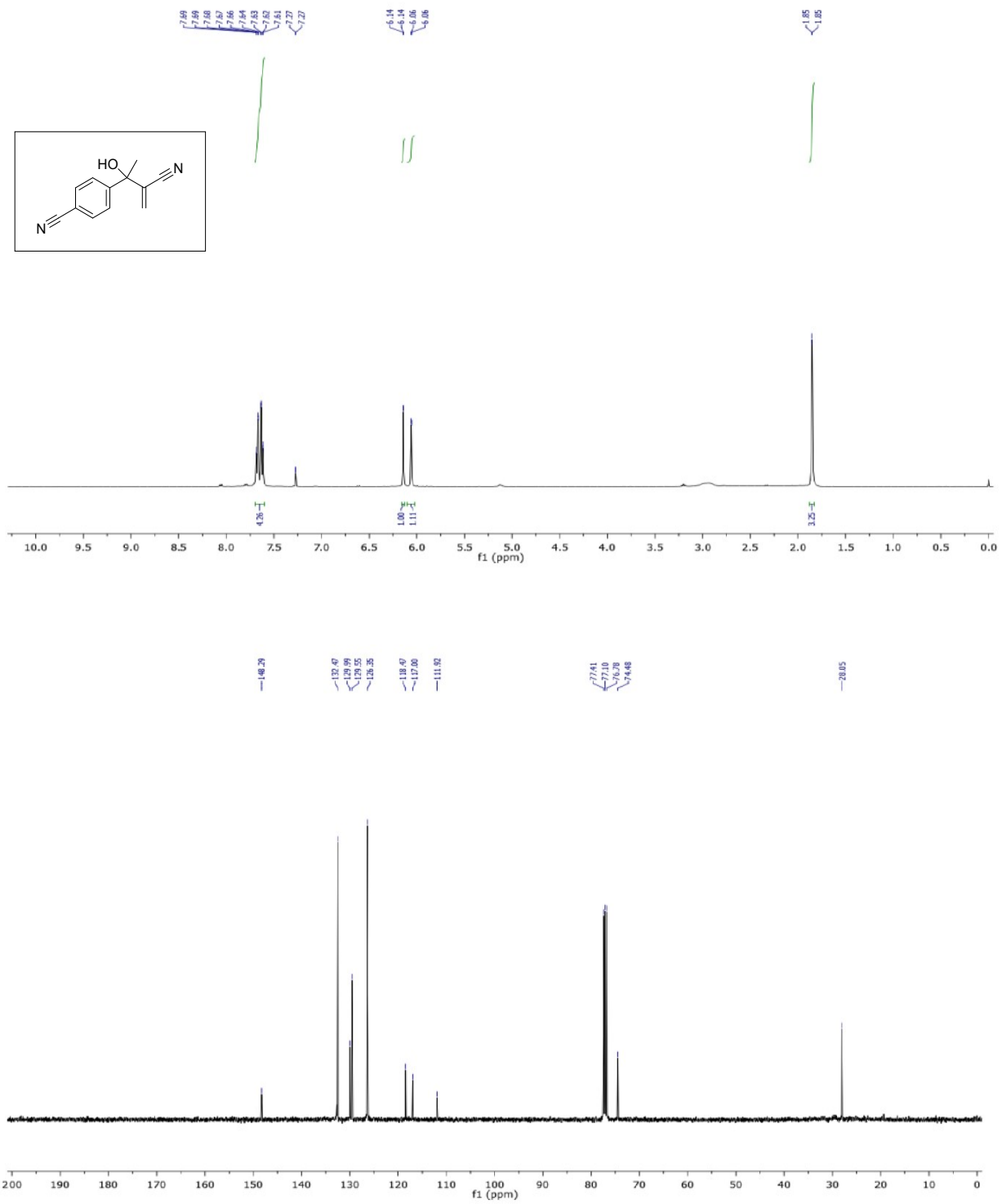


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **5**

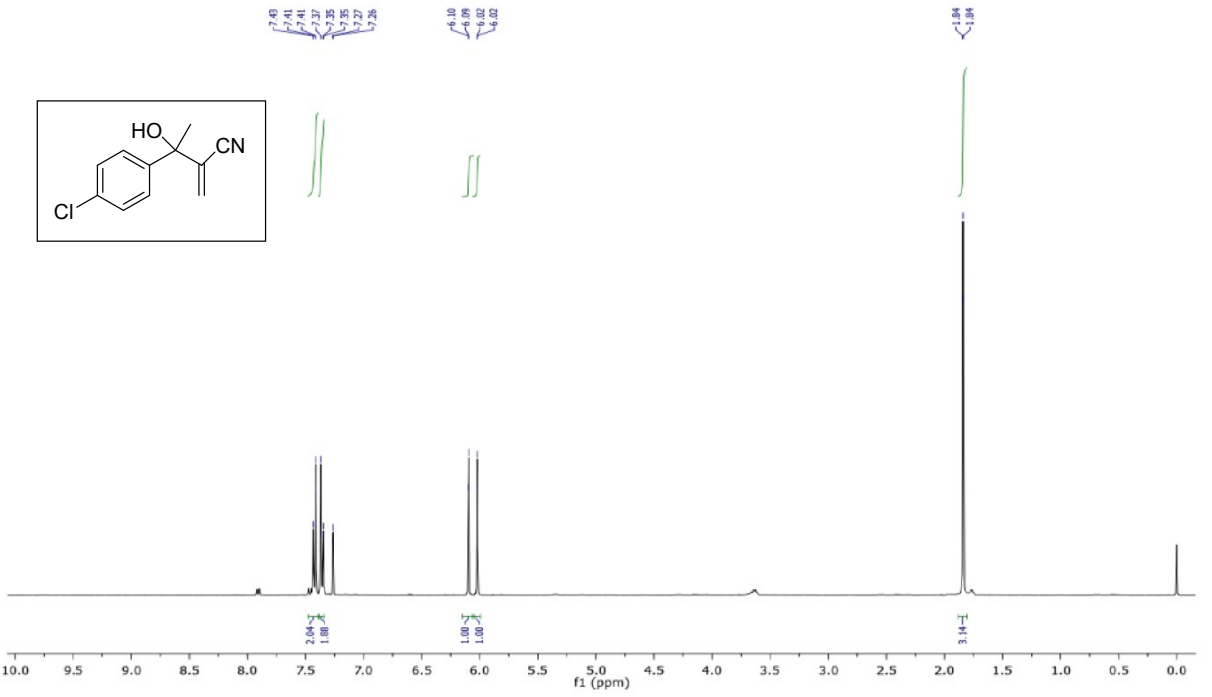


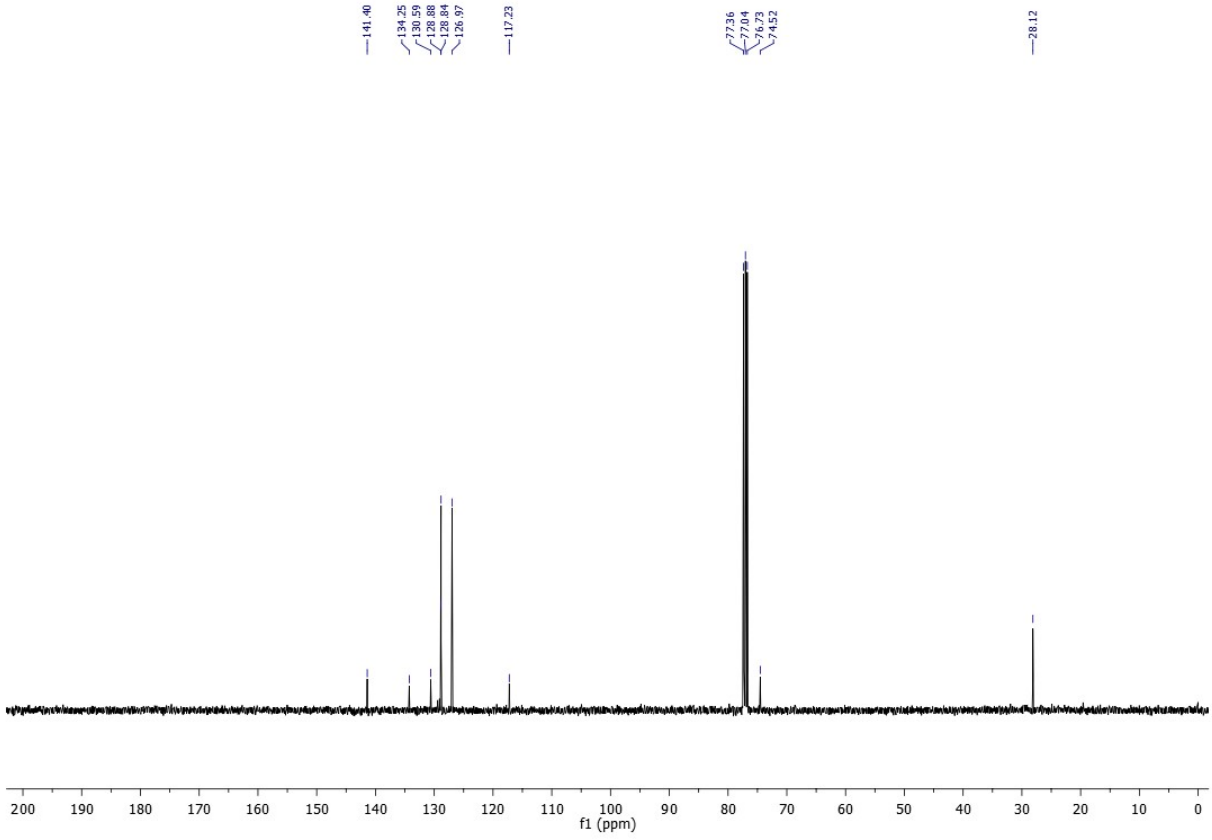


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **6**

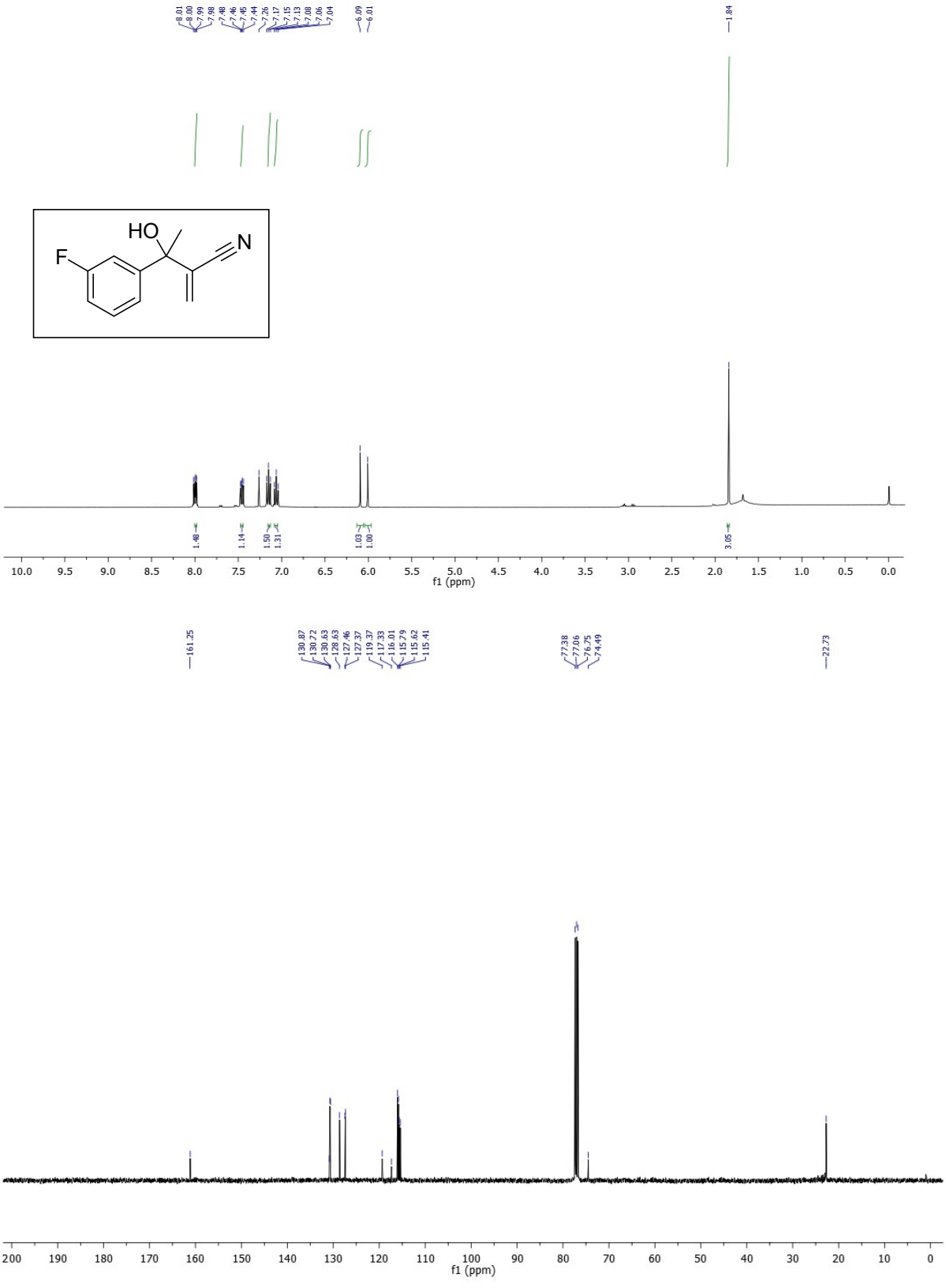


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **7**

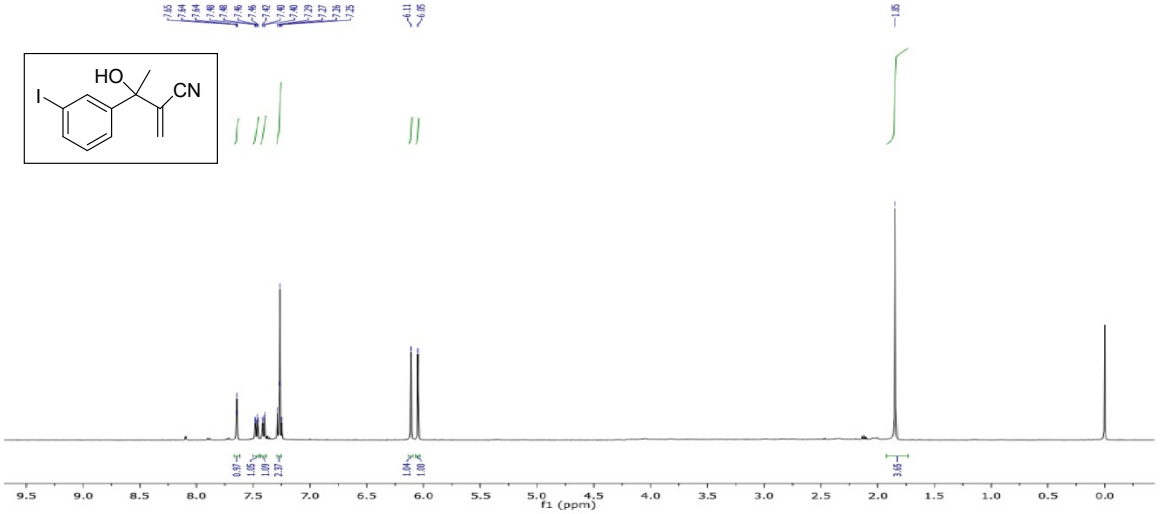


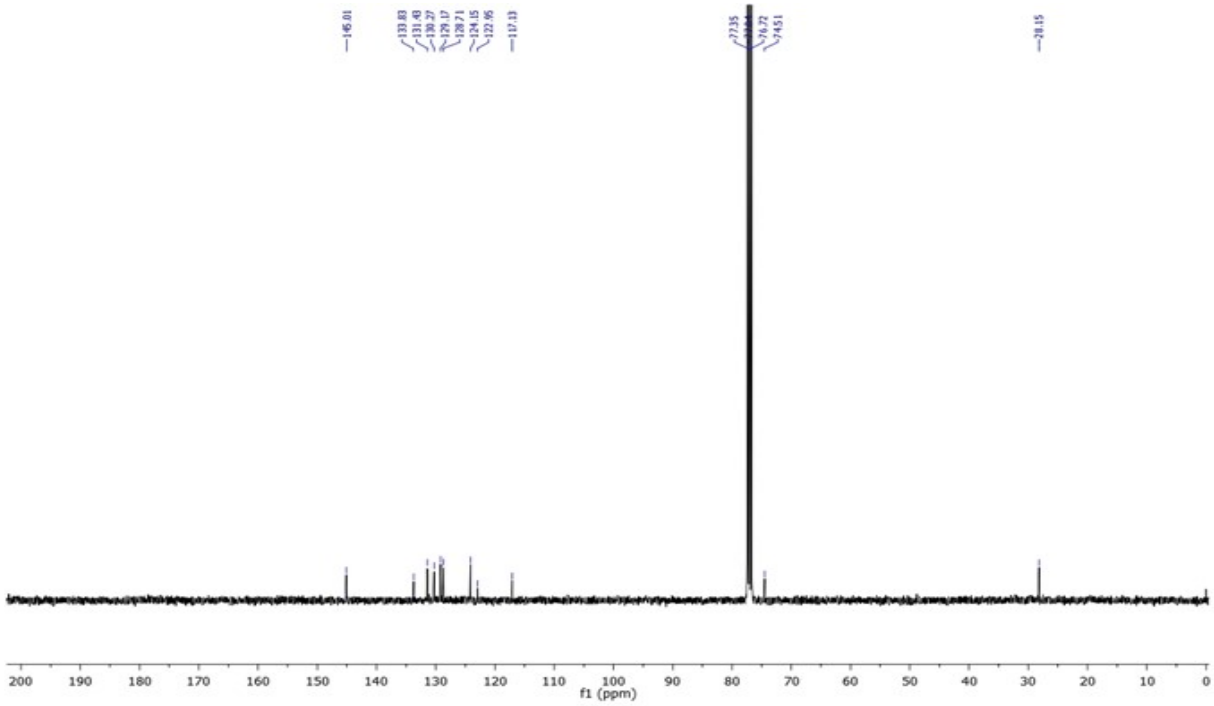


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **8**

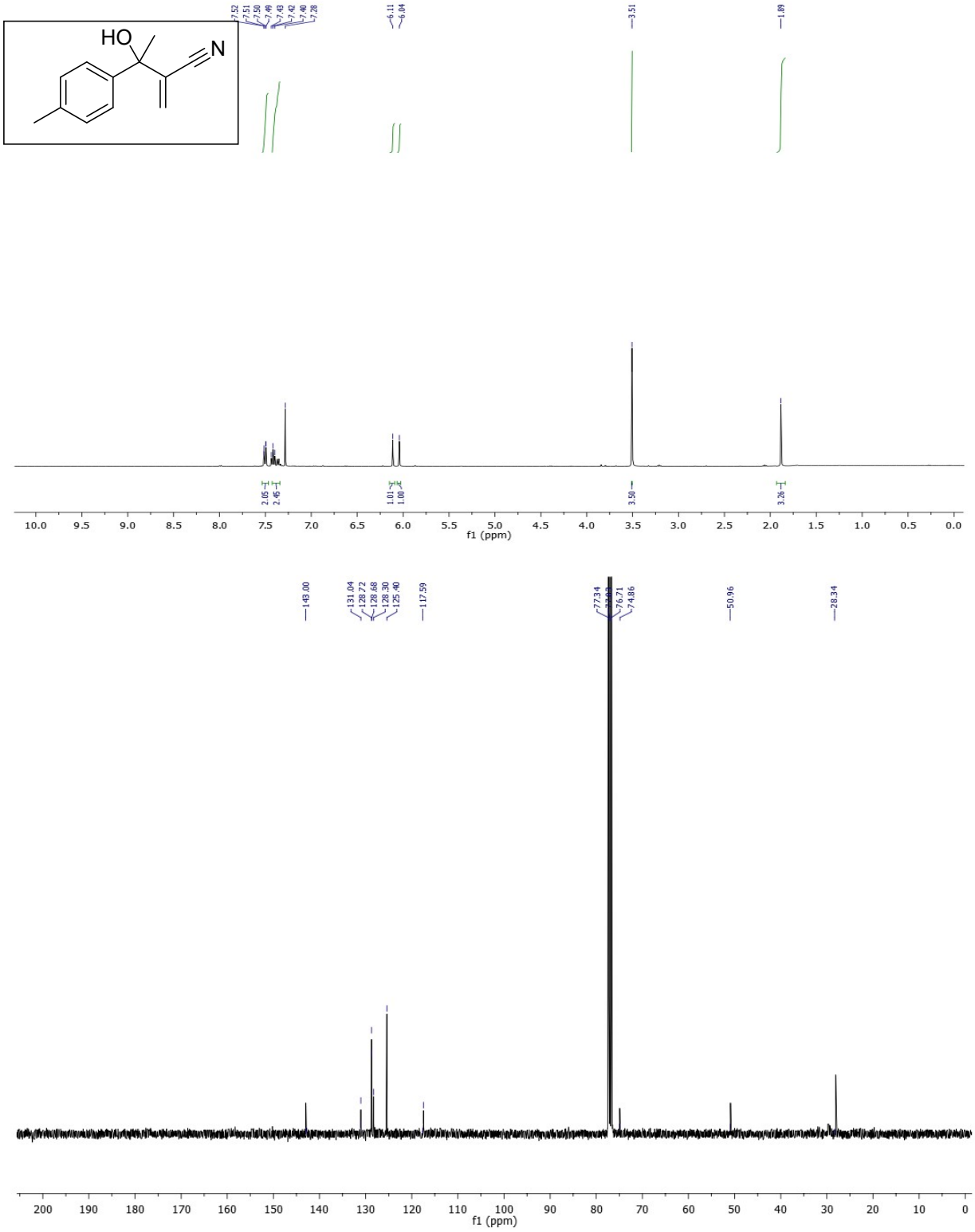


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **9**

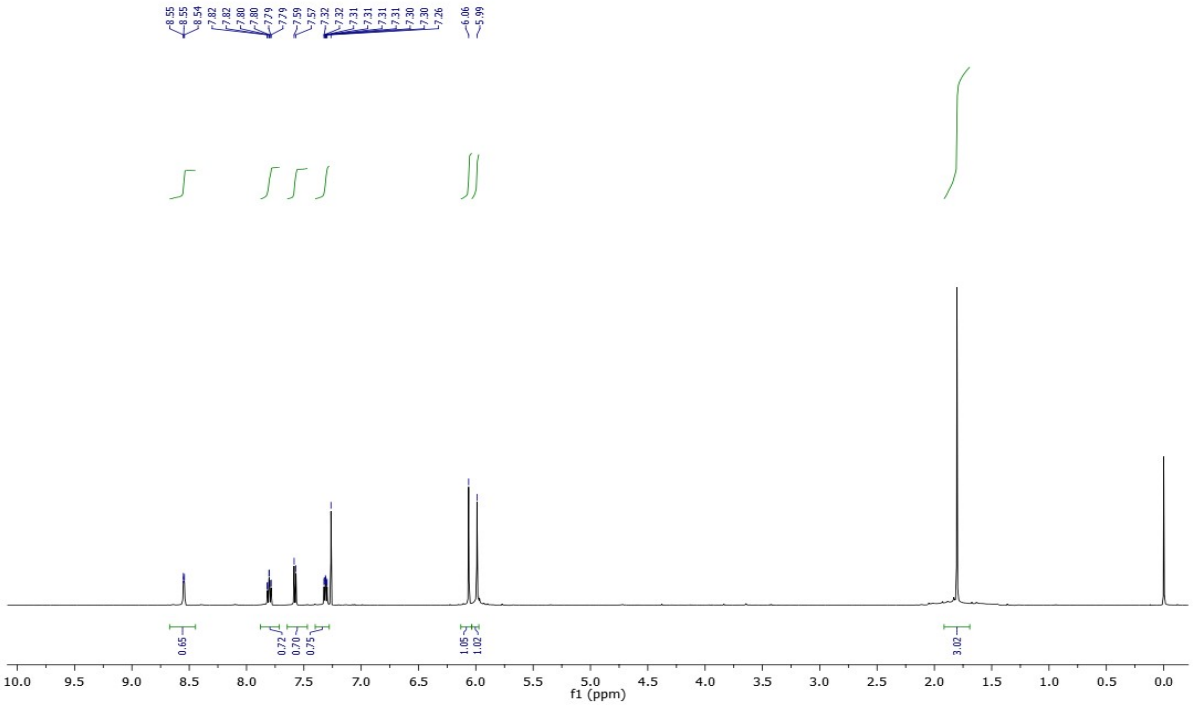


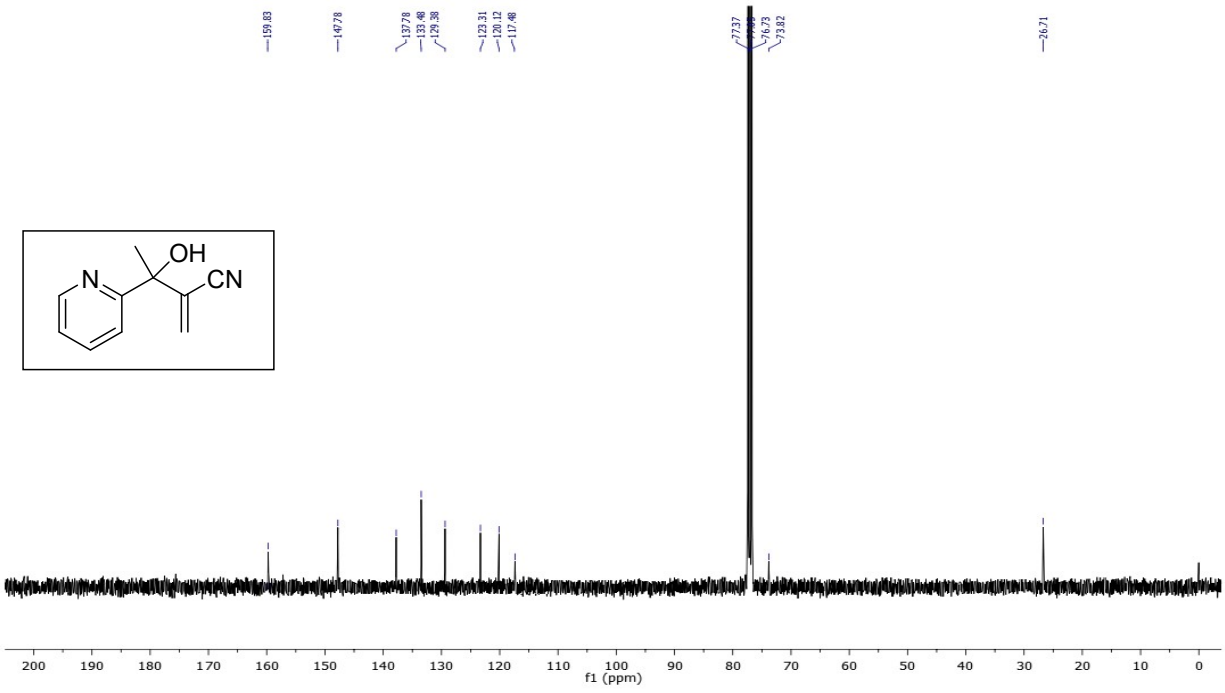


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **10**

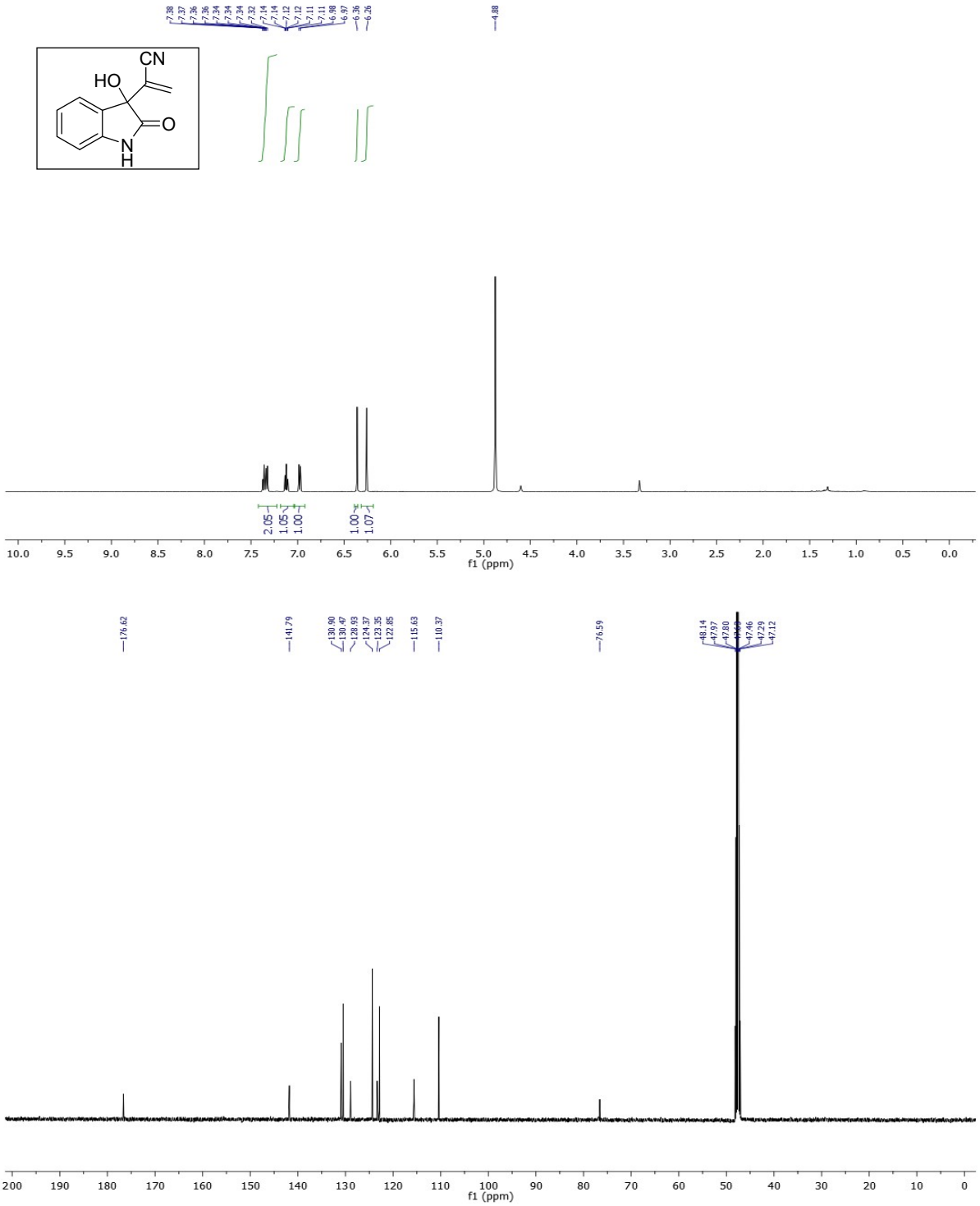


^{1}H and ^{13}C NMR in $CDCl_3$ of Compound **11**

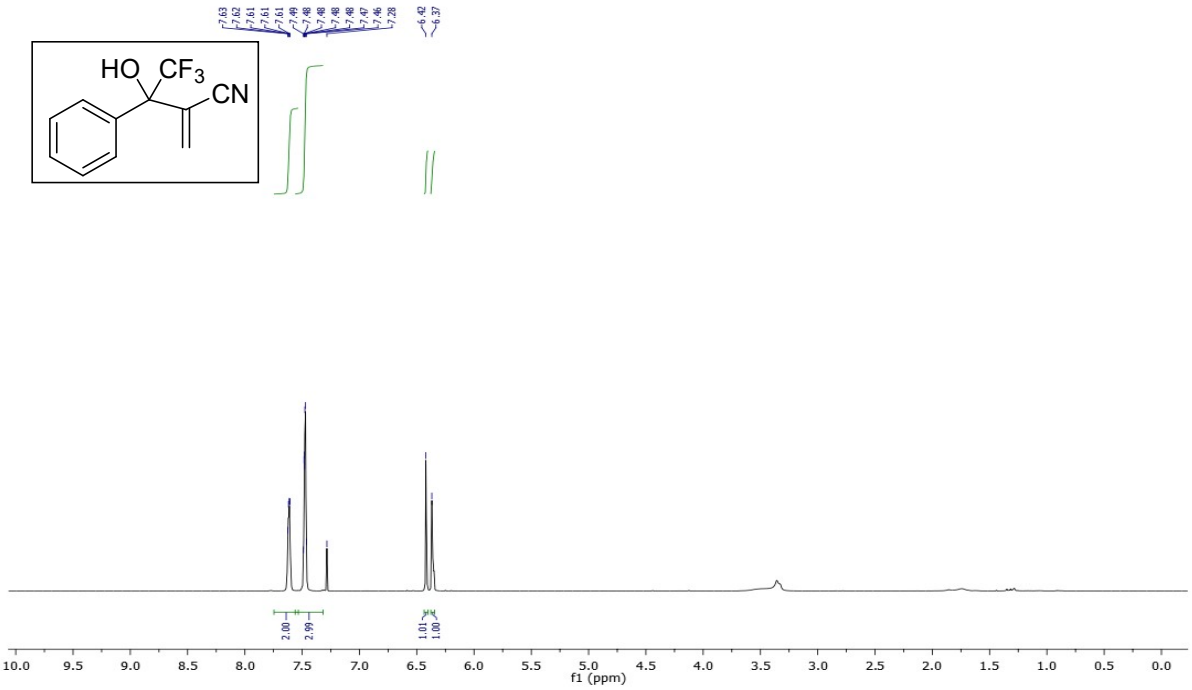


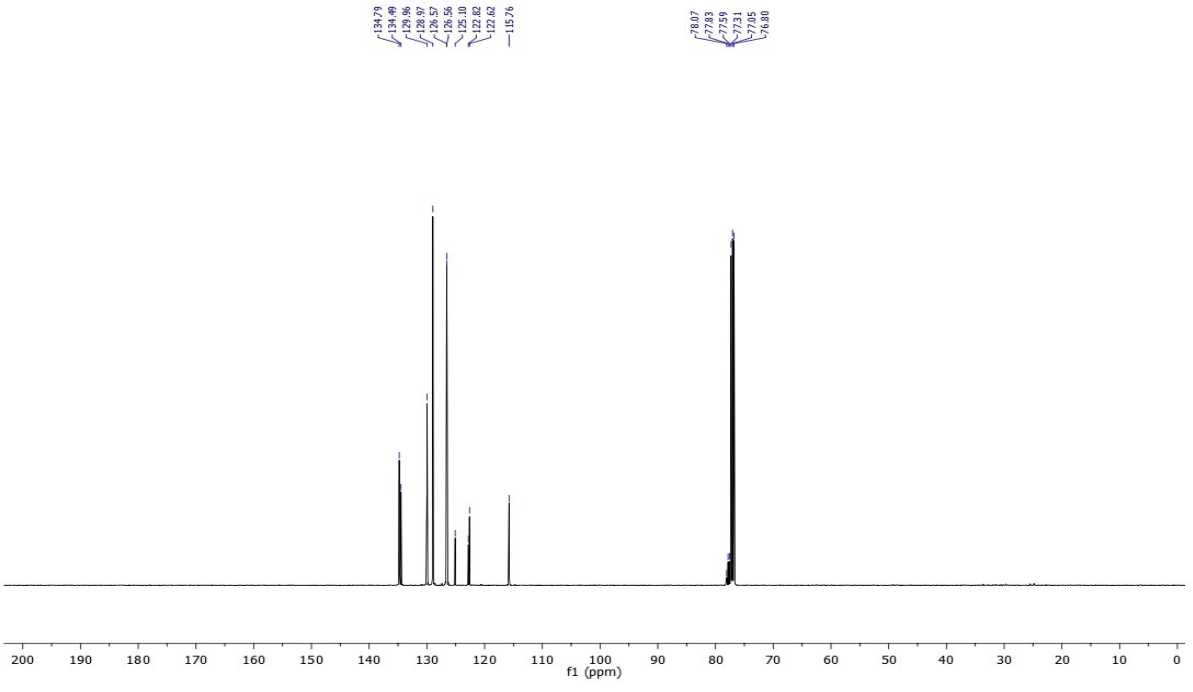


^{1}H & ^{13}C NMR in CD_3OD of compound **12**

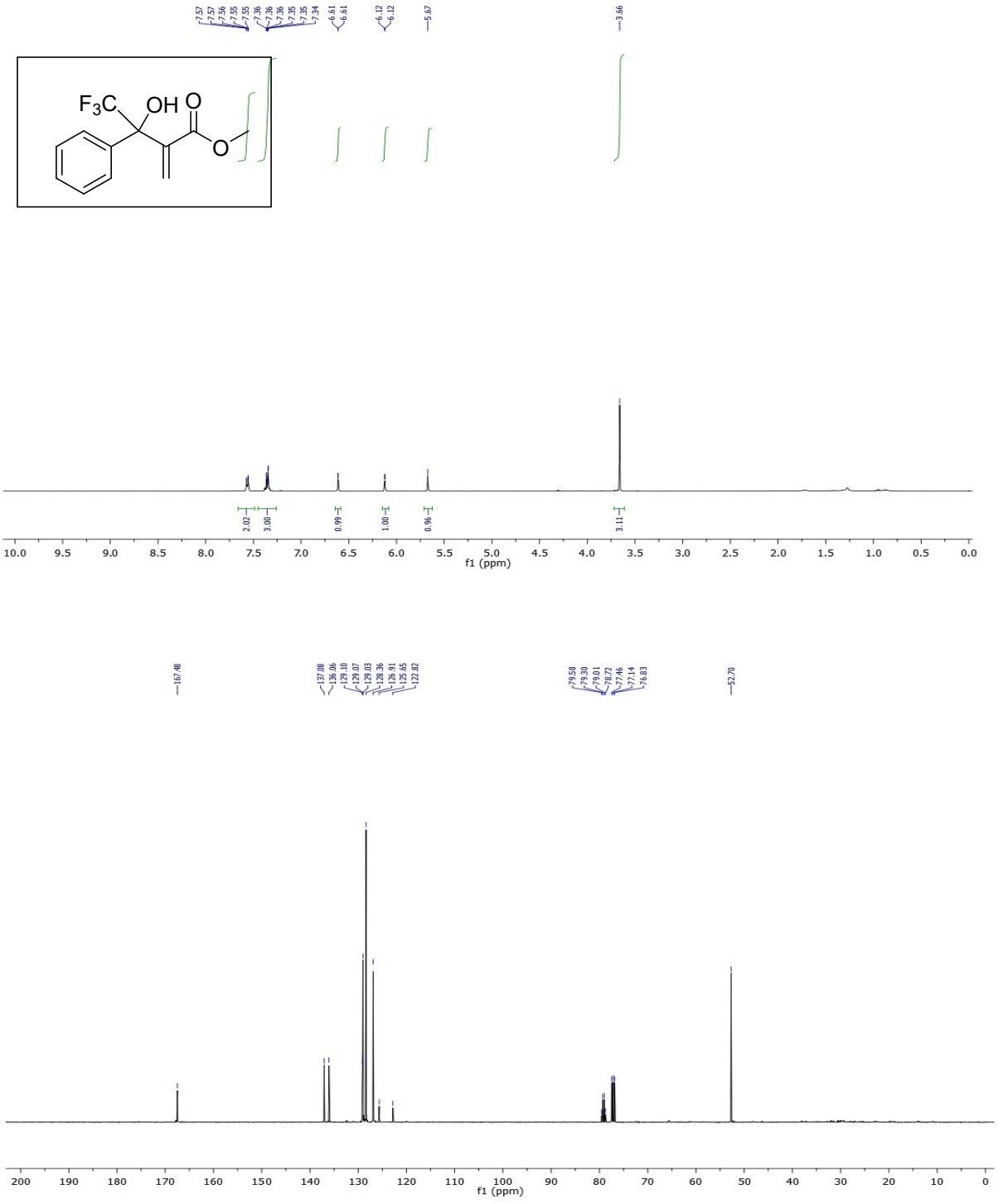


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **13**

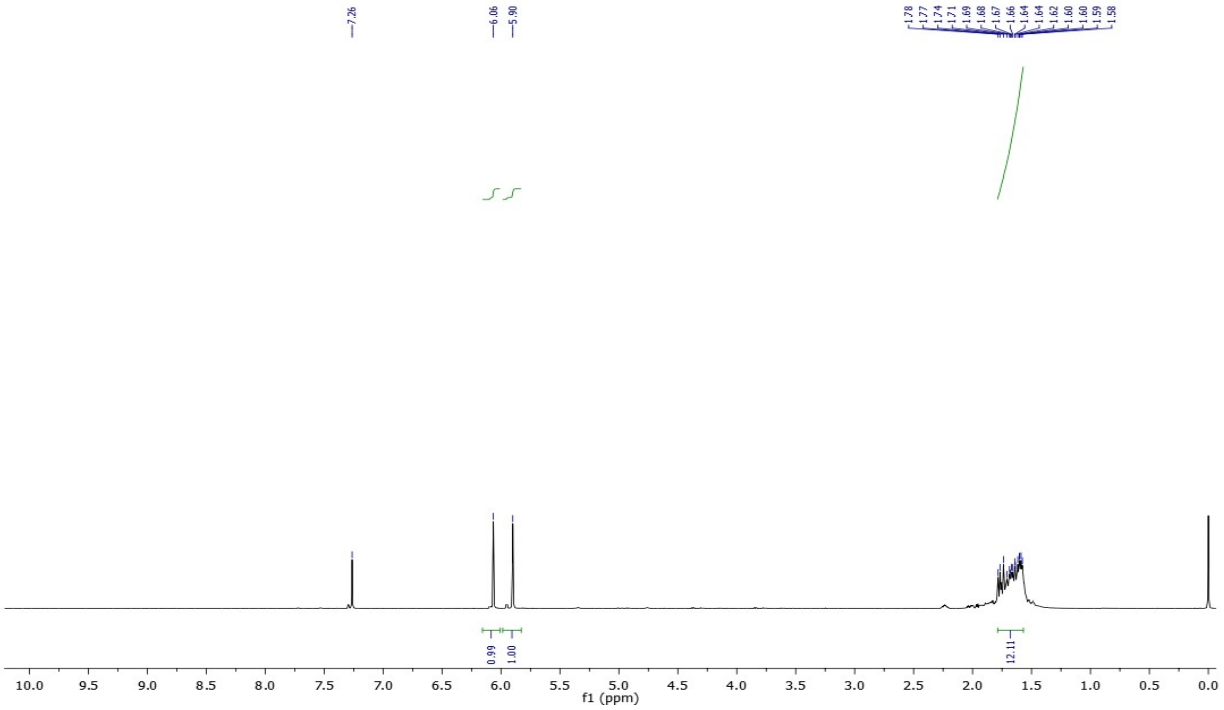


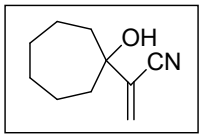


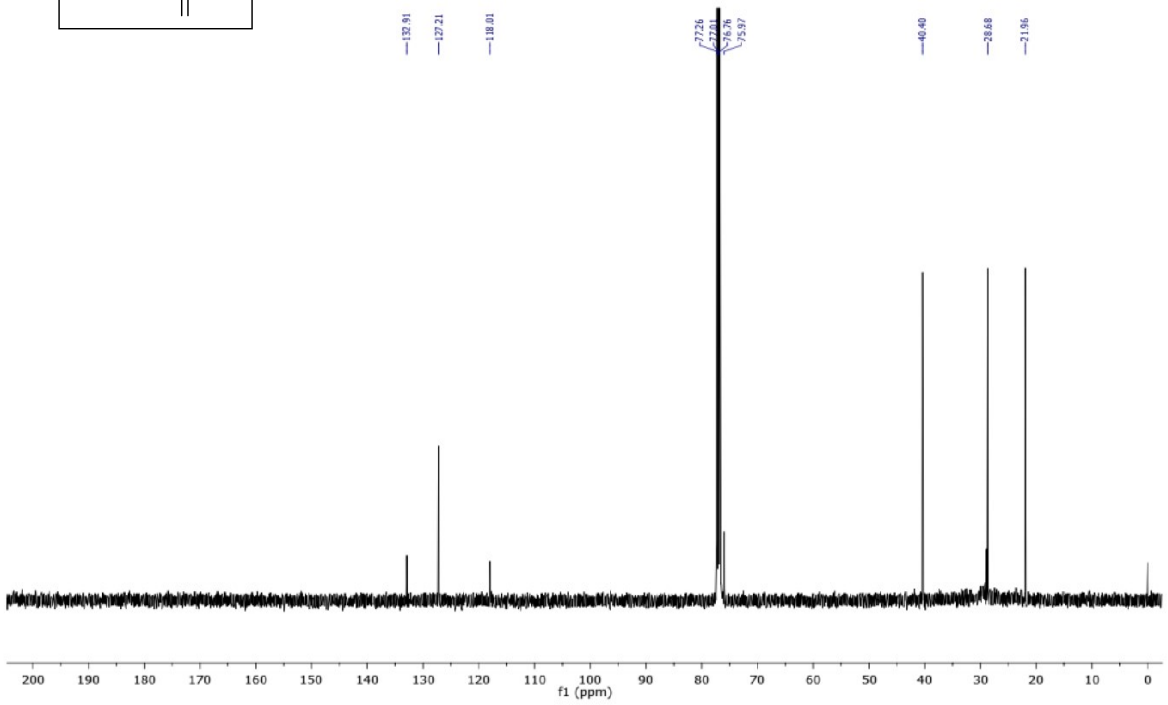
^{1}H and ^{13}C NMR in $CDCl_3$ of compound **14**



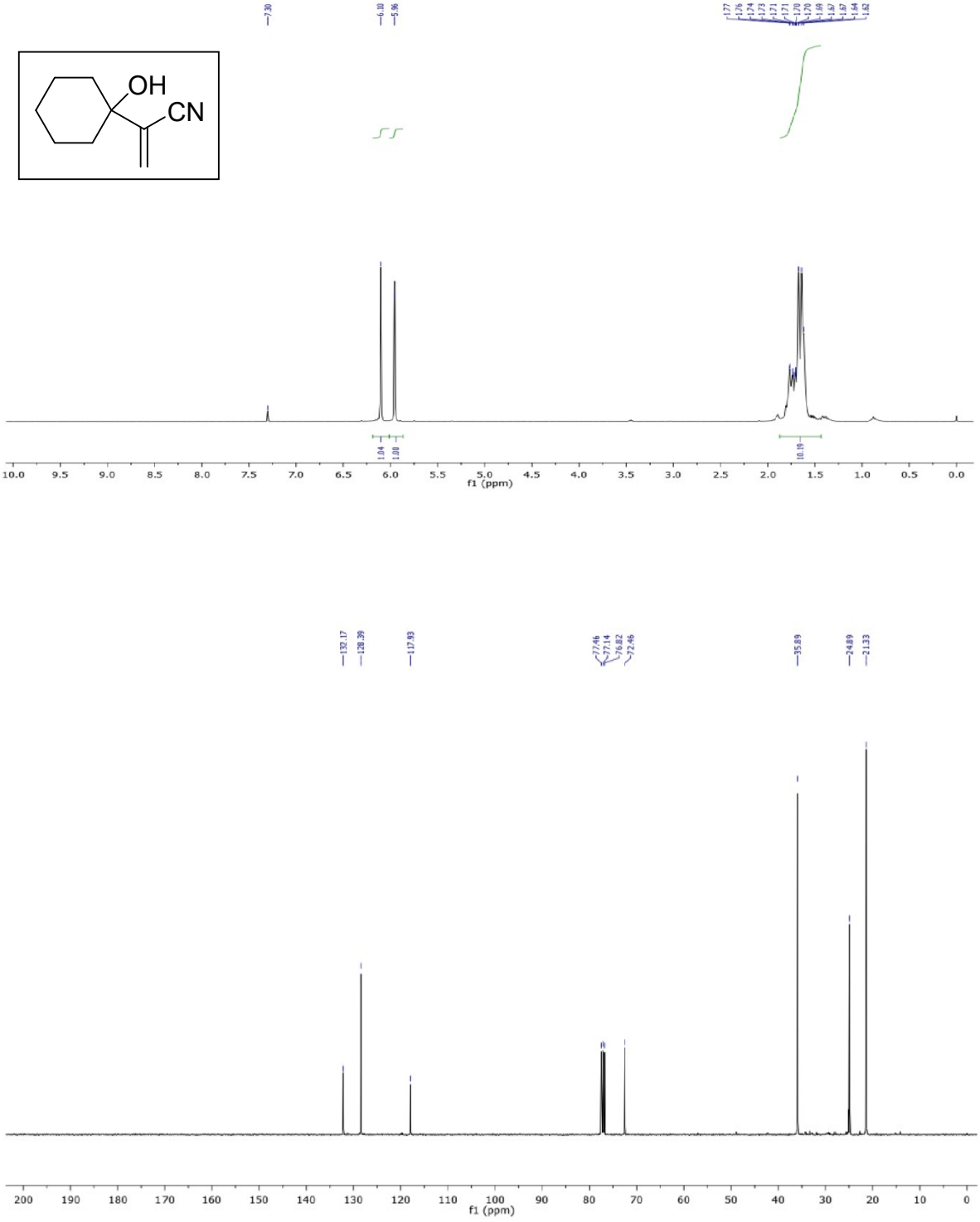
^{1}H and ^{13}C NMR in $CDCl_3$ of compound **15**



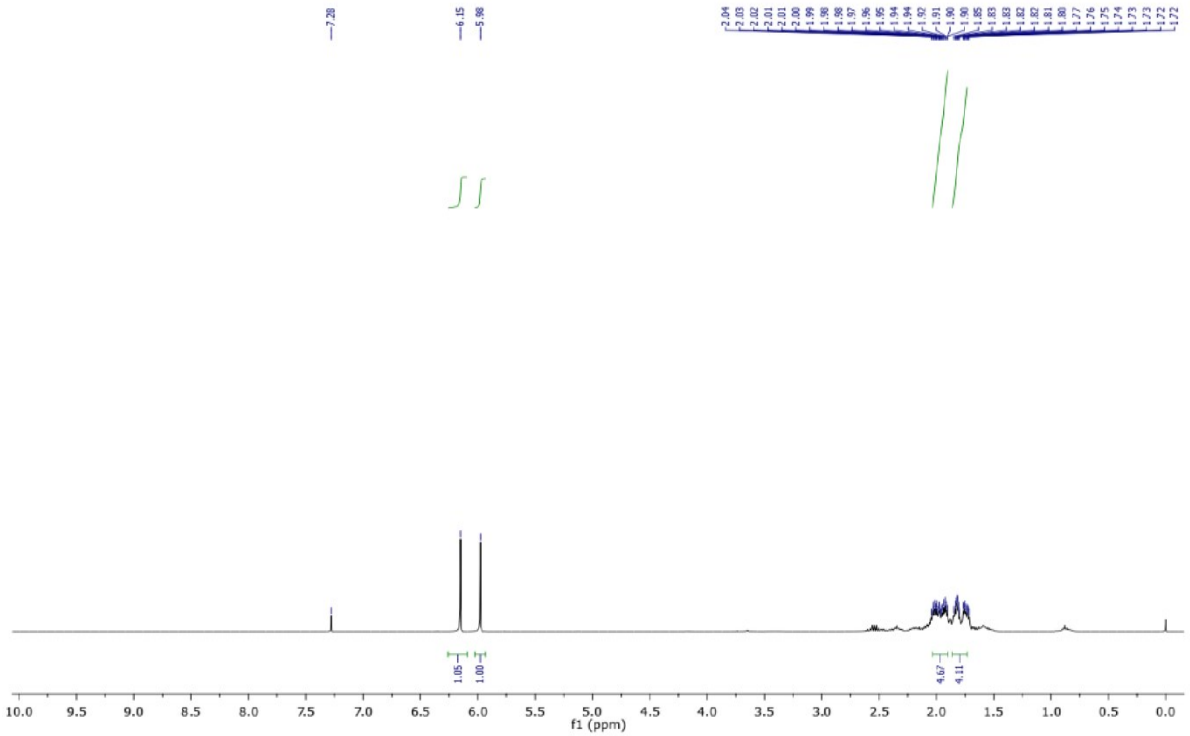




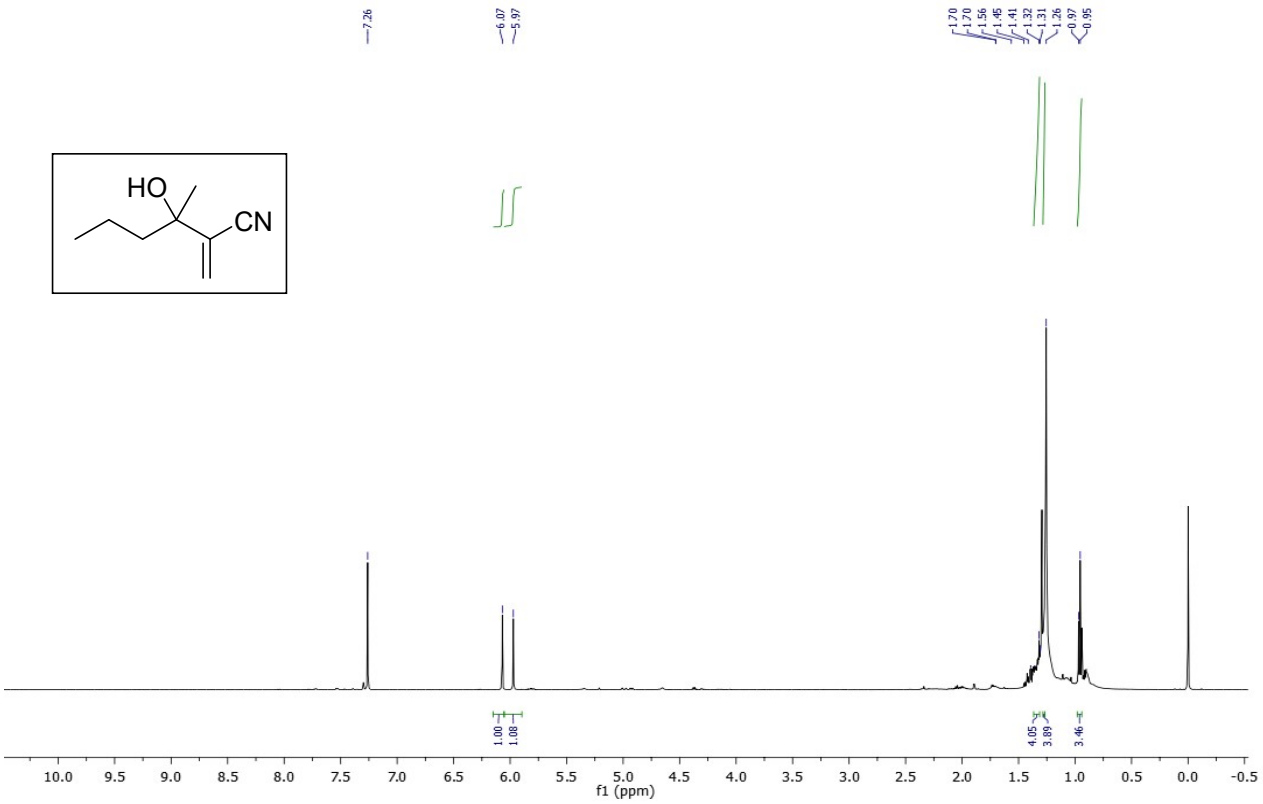
^{1}H and ^{13}C NMR in $CDCl_3$ of compound **16**

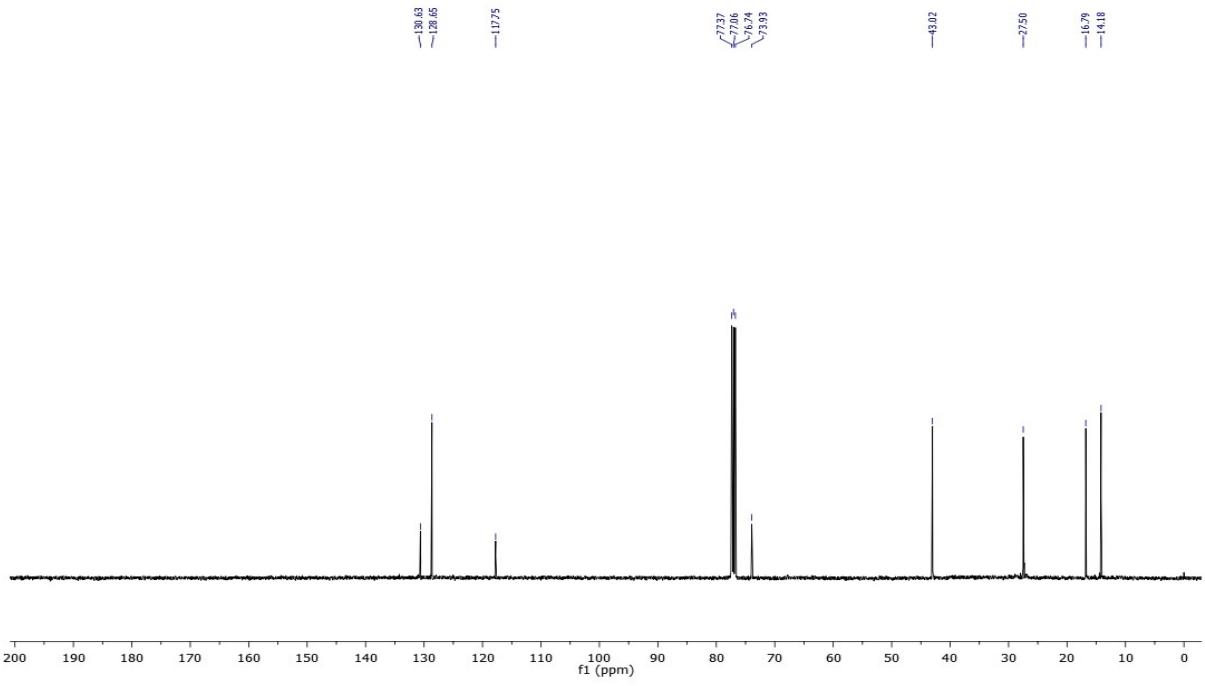


^{1}H and ^{13}C NMR in $CDCl_3$ of compound **17**

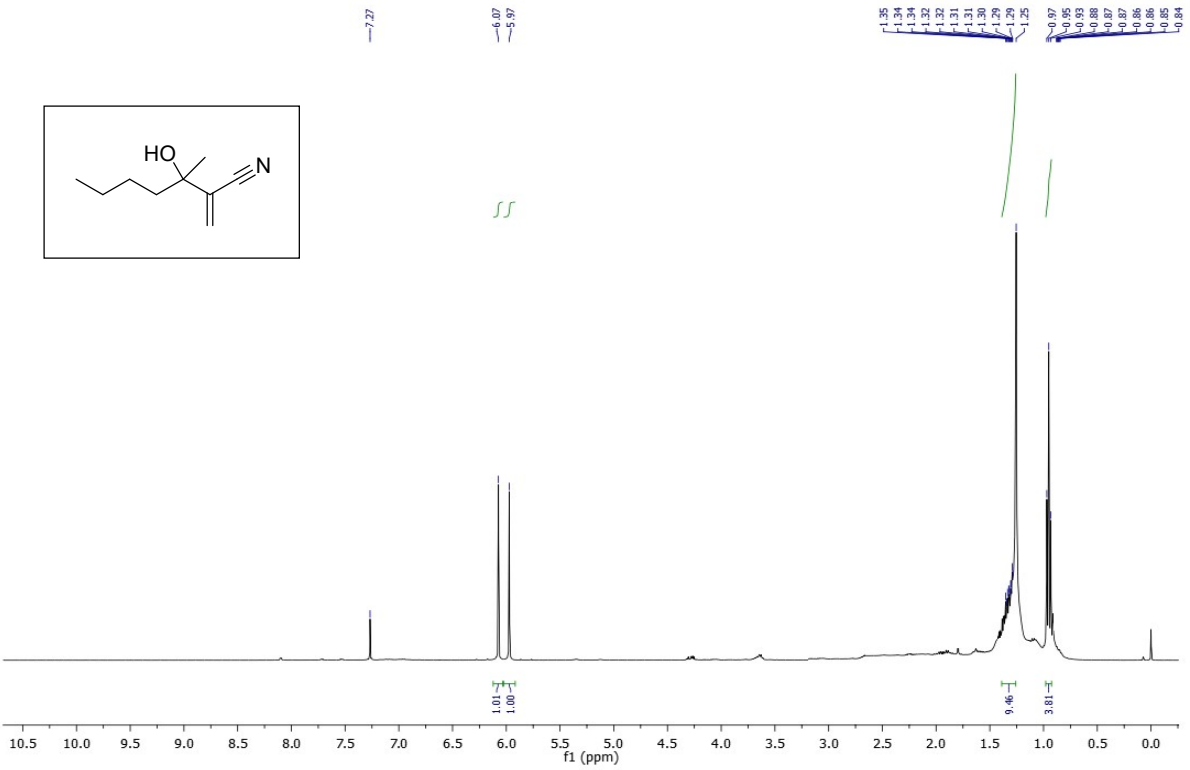


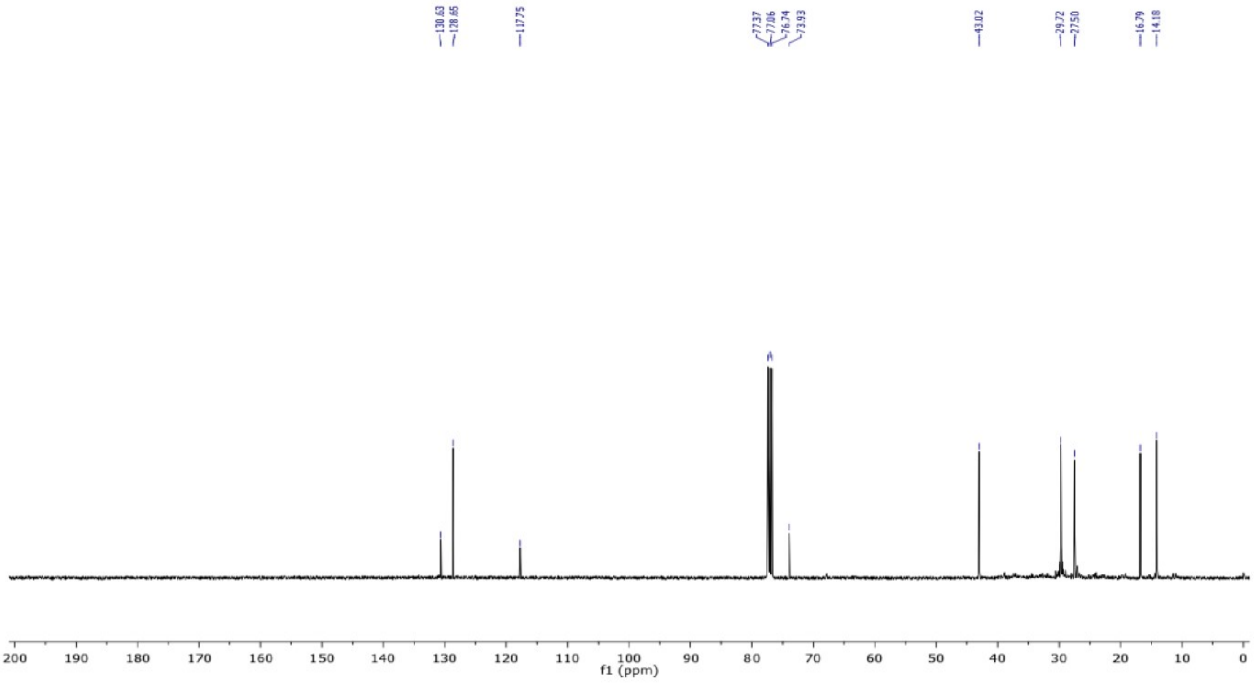
^{1}H and ^{13}C NMR in $CDCl_3$ of compound **18**





^{1}H and ^{13}C NMR in $CDCl_3$ of compound **19**

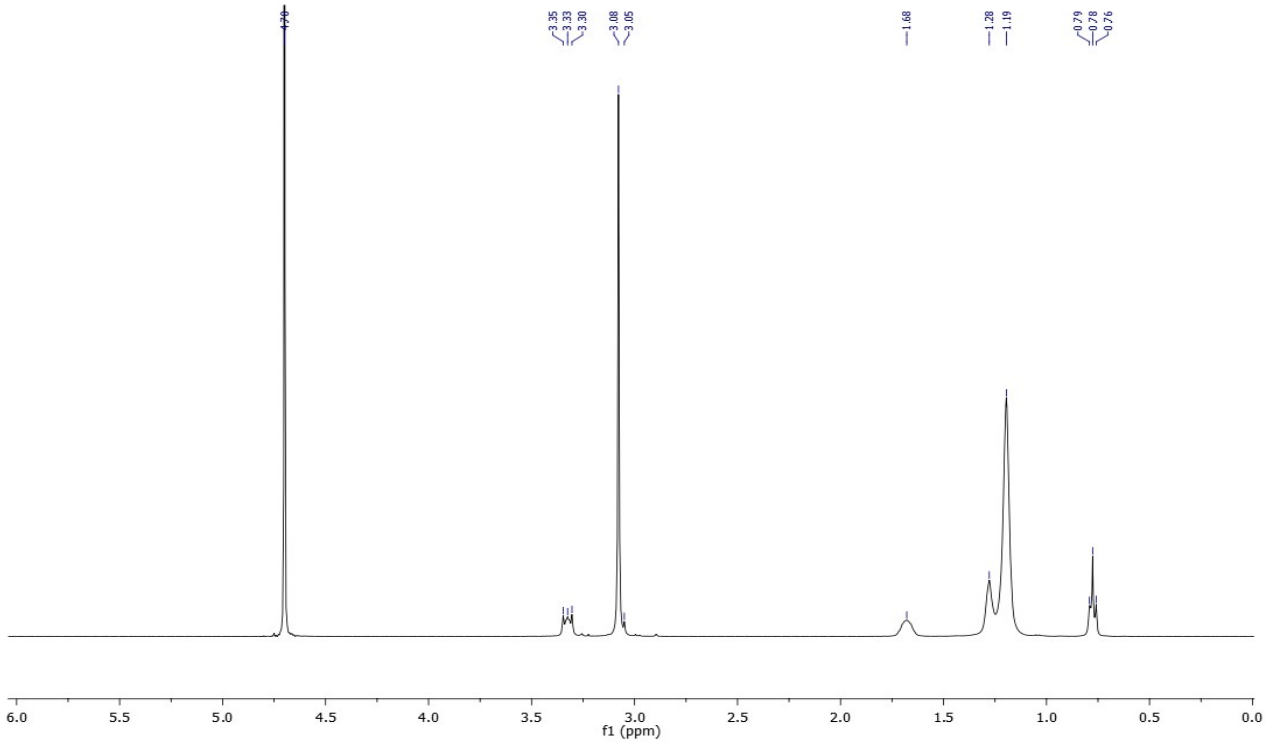




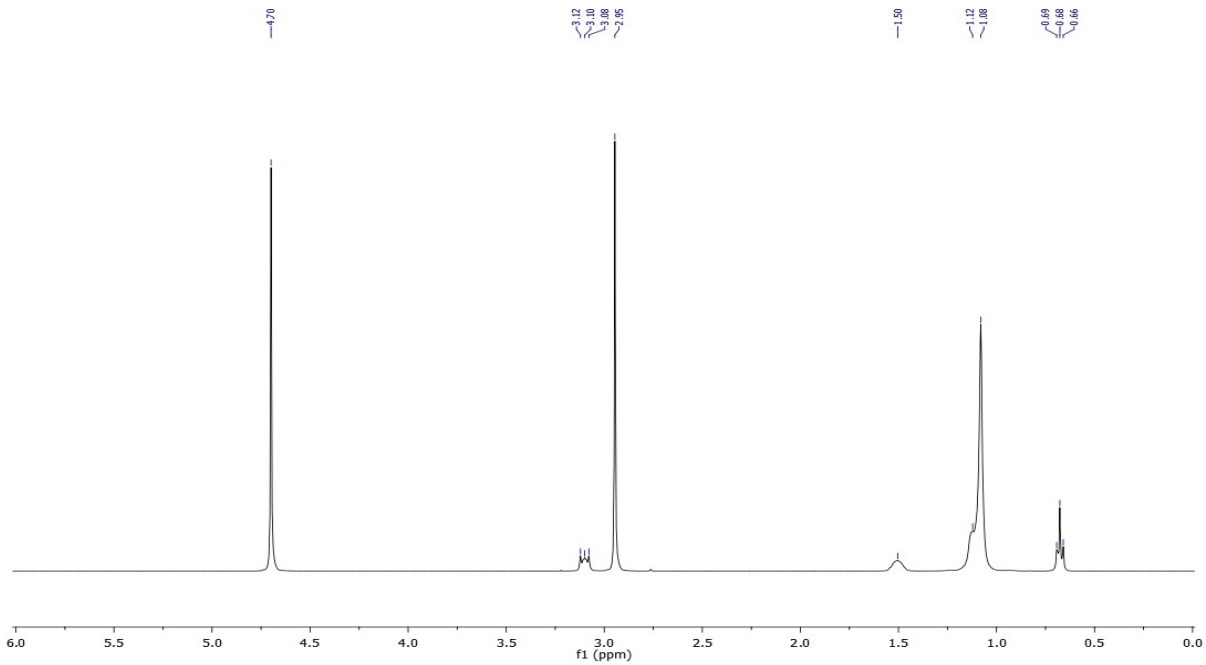
Proton NMR studies to establish the reaction site:

A micellar stock solution (0.01M) of surfactant CTAB was prepared by adding 72.8 mg of CTAB to 20 ml of D_2O on constant stirring in a clean glass vial. The solution was continuously stirred for an hour at 25°C. From this stock solution, a figurate of 3 ml each was added into a clean and well labelled glass vials. The concentrations of 0.00, 0.004, 0.008, 0.016 and 0.032 M were prepared by adding *p*-nitroacetophenone into these glass vials under vigorous stirring. ^{1}H NMR of all these solutions were recorded from Bruker 400 MHz instrument in one series to minimize the temperature and dilution effects.

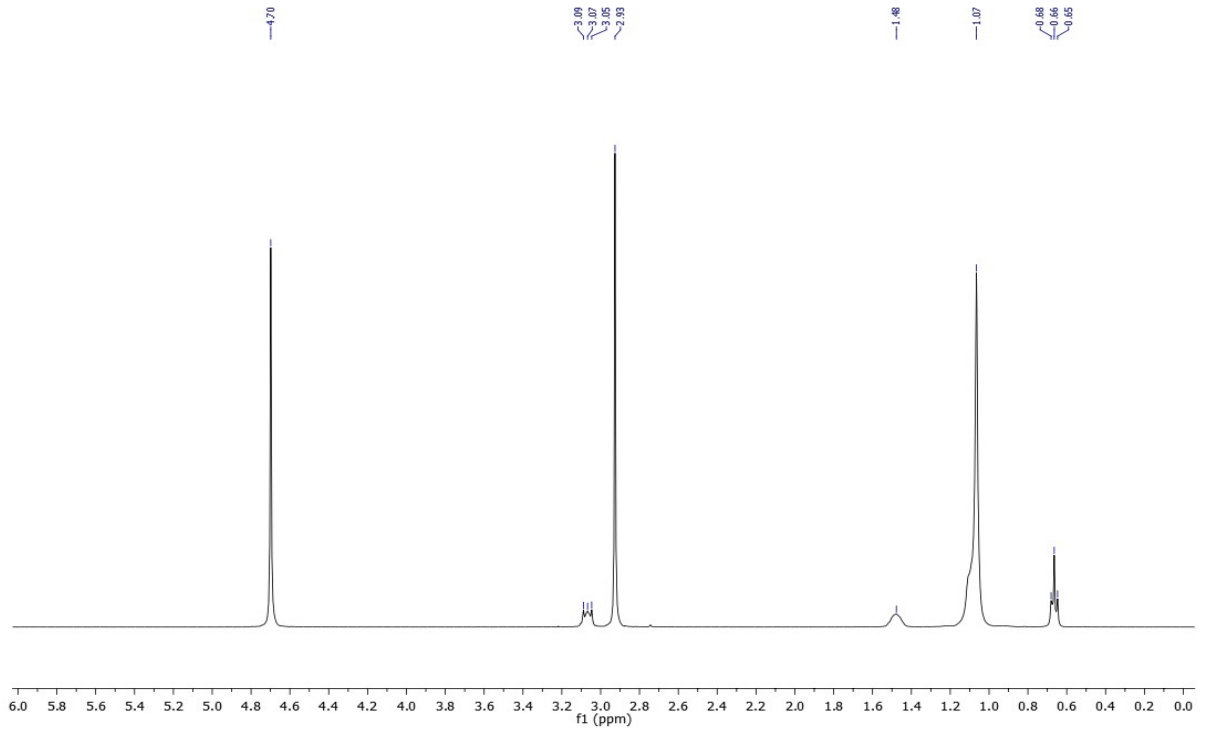
^{1}H NMR (D_2O, 400 MHz) at a conc. of 0.00M



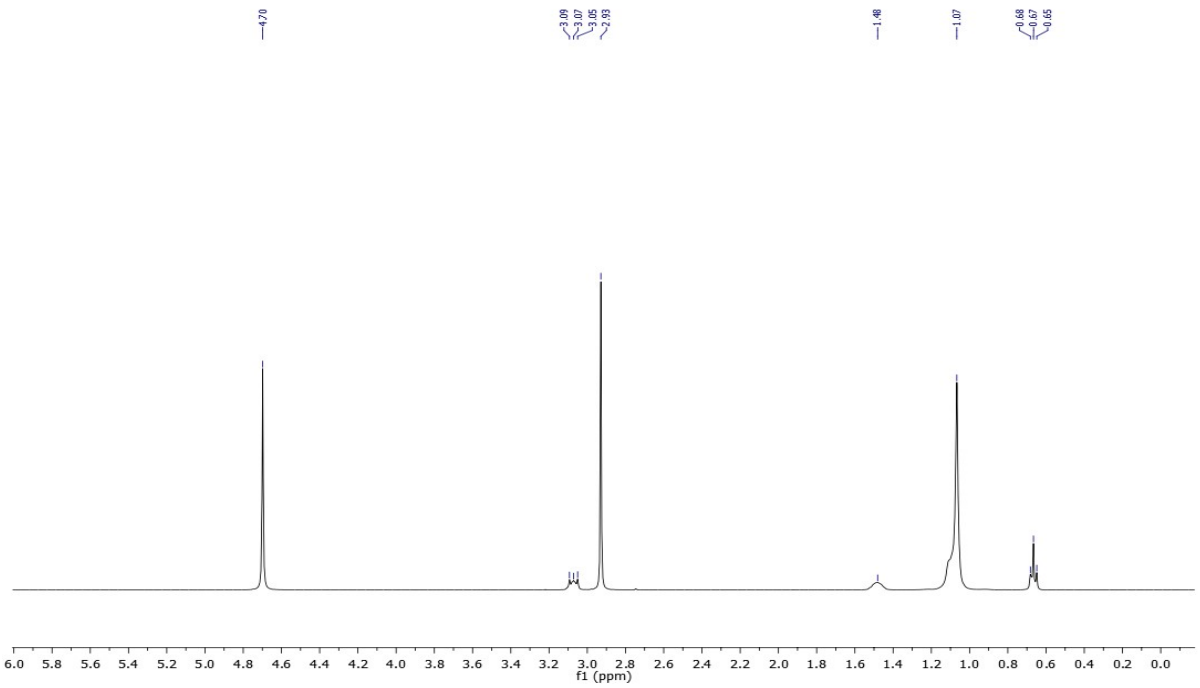
^{1}H NMR (D_2O, 400 MHz) at a conc. of 0.04M



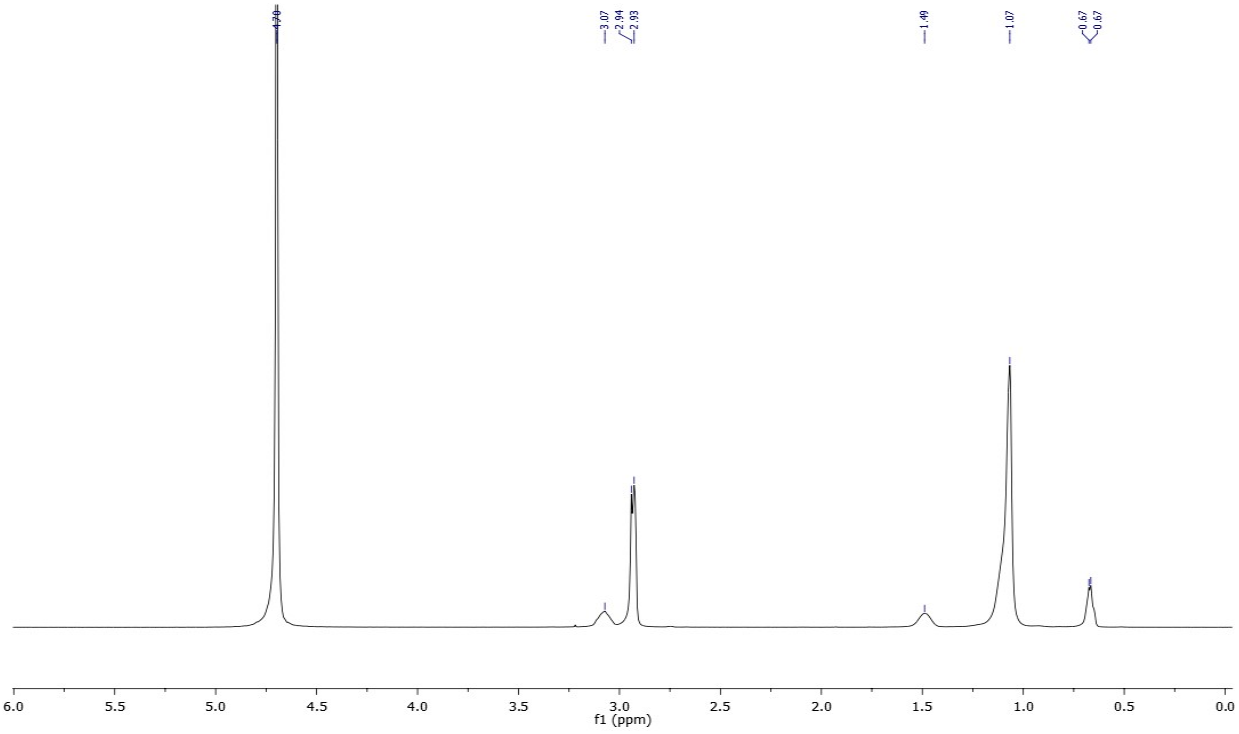
^{1}H NMR (D_2O, 400 MHz) at a conc. of 0.08M



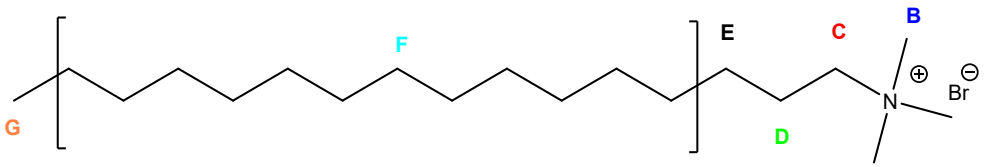
^{1}H NMR (D_2O, 400 MHz) at a conc. of 0.016M



^{1}H NMR (D_2O, 400 MHz) at a conc. of 0.032M



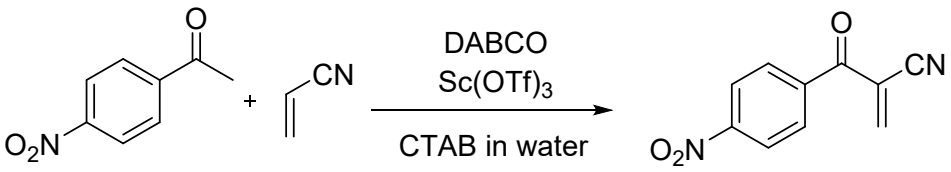
Chemical shifts (ppm) of CTAB (0.025M) surfactant with *p*-nitroacetophenone in D_2O



CTAB

Conc. of ketone(M)	B δ[N-$(CH_3)_3$]	C δ(α-CH_2-)	D δ(β-CH_2-)	E δ(γ-CH_2-)	F δ[Δ-$(CH_2)_{12}$]	G δ(ω-CH_3)
0.000	3.08	3.30	1.68	1.28	1.19	0.78
0.002	3.06	3.27	1.65	1.26	1.17	0.75
0.004	2.95	3.08	1.50	1.12	1.08	0.68
0.008	2.93	3.05	1.48	_	1.07	0.66
0.016	2.94	3.06	1.49	_	1.07	0.67
0.032	2.93	3.07	1.49	_	1.07	0.67

Effect of temperature and concentration on a reaction between *p*-nitroacetophenone and acrylonitrile in CTAB solutions.

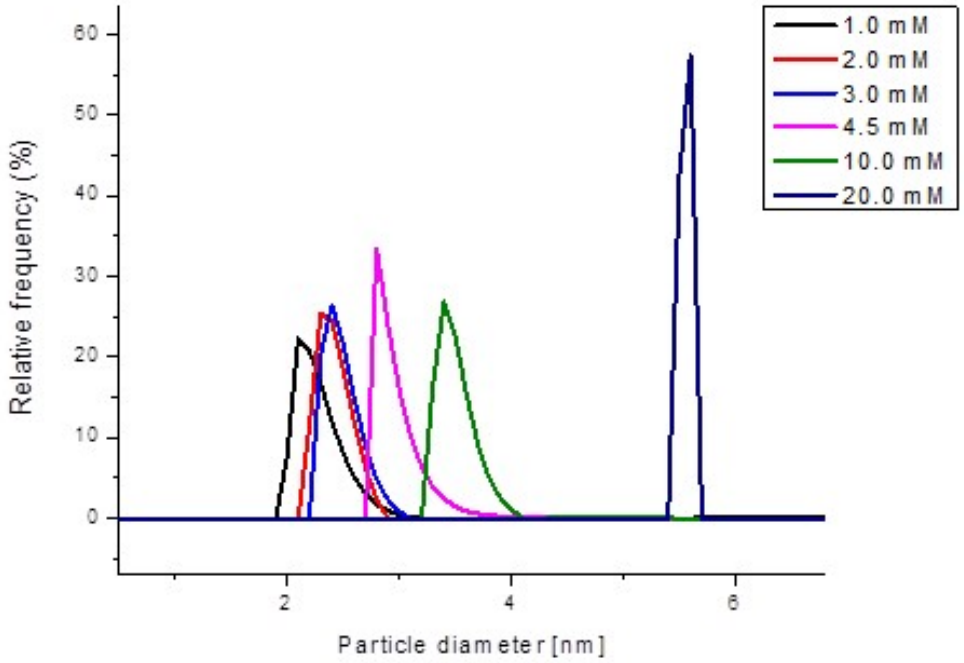


CTAB solution (mM) in water	Temperature (°C)	Yield (%) after 3 days
4.5	25	66
4.5	30	58
4.5	35	50
4.5	40	35
4.5	50	20
4.5	60	Traces
9.0	25	55-60
18.0	25	50-55
27.0	25	45-50
36.0	25	30-40

Dynamic Light Scattering (DLS) experiment to study the effect of concentration and temperature on CTAB micellar assembly size:

Effect of Concentration.

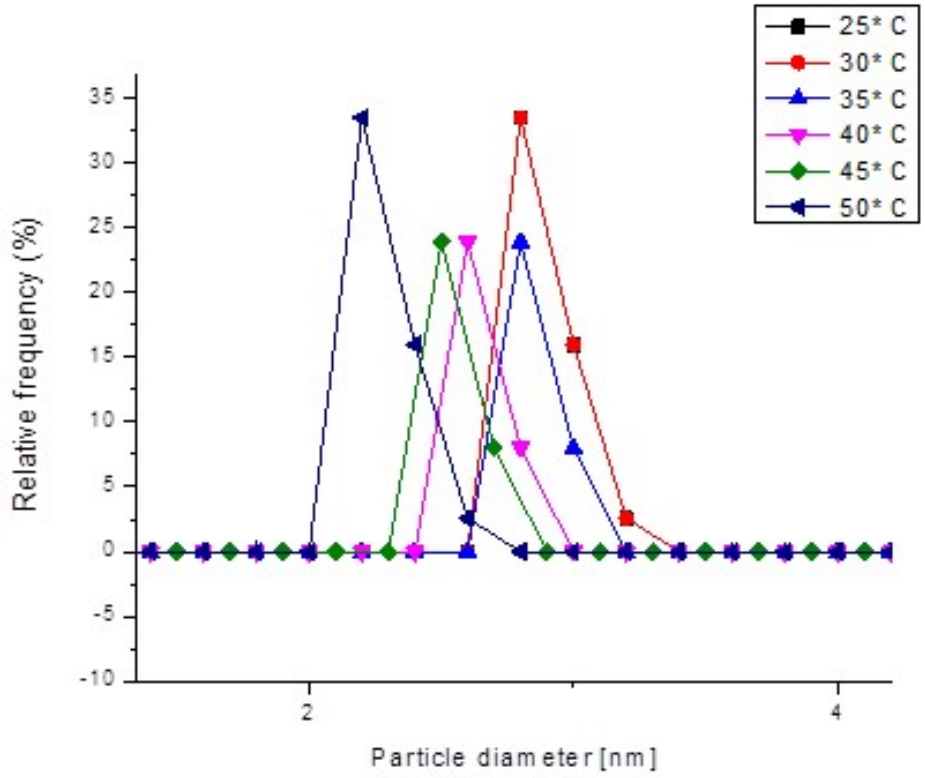
To study the effect of concentration of surfactant over the micellar size different concentration 1.0 mM (1.1 times CMC), 2.0 mM (2.2 times CMC), 3.0 mM (3.3 times CMC), 4.5 mM (5 times CMC), 10.0 mM (11.1 times CMC), 20.0 mM (22.2 times CMC) of CTAB surfactant were prepared in double distilled water. DLS (Litesizer 500) was used to record the particle size of above mentioned concentrations at 25° C temperature. The recorded data is shown in graphical and tabulated form below.



CTAB Concentration (mM)	Particle diameter (nm)
1.0	2.1
2.0	2.3
3.0	2.4
4.5	2.8
10.0	3.4
20.0	5.6

Effect of Temperature.

To study the effect of temperature on micellar size, a solution of CTAB (4.5 mM) was prepared in double distilled water and its particle diameter was recorded at different temperatures. The results are mentioned below in graphical and tabular form below.



Temperature (°C)	Particle diameter (nm)
25	2.8
30	2.8
35	2.7
40	2.5
45	2.4
50	2.2