Supplementary Information

Catalyst-free amidation of aldehyde with amine under mild conditions

Contents

1. *Experimental*

All chemicals were commercially available and purchased from Aladdin (Shanghai, China) and were used as received without any further purification. All chemicals used were of analytical grade. ^{1}H NMR and ^{13}C NMR spectrum were recorded on a Bruker Avance 400 MHz or a Bruker Avance 500 MHz spectrometer. For a Bruker Avance 400 MHz instrument, samples were run at 400 MHz and 100.6 MHz respectively for ^{1}H NMR and ^{13}C NMR spectrum, and for the Bruker Avance 500 MHz instrument, samples were run at 500 MHz and 125.8 MHz respectively for ^{1}H NMR and ^{13}C NMR spectrum. All chemical shifts (δ) were quoted in parts per million (ppm) and reported relative to an internal tetramethylsilane (TMS, δ 0.00) standard. The following abbreviations were used to define the multiplicities: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; p, pentet and m, multiplet. Yields of products were measured by HPLC analysis using an Agilent1100 instrument equipped with a Vertex column (250mm x 4.6mm x 5μm), or GC-analysis on a GC-4000A instrument equipped with a Agilent DB-624 column (25 m x 0.32 mm x 0.25mm).

2. General procedures

2.1 General procedures for reaction conditions optimization

To a solution of **4 mL** solvent (H_2O, CH_2Cl_2, CH_3CN, or CH_3OH), benzyaldehyde of 0.5 mmol together with 0.1mL DMSO were introduced and well dissolved. After then, varied ratios of substrates listed in Table 1 were added into the previous solution and stirred at varied temperatures. Amine dissolved in **2mL** solvent was slowly dropwised into the solution in 5 hours and incubated overnight. Yields were determined by HPLC analysis equipped with a Vertex column (250mm x 4.6mm x 5μm)

2.2 General procedure for amidation of aldehyde with secondary amines

To a solution of **4 mL** H_2O, aldehyde of 0.5 mmol together with 0.1mL DMSO were introduced and well dissolved. After then, TCCA of 0.2 mmol(0.046g) were added into the previous solution and stirred at varied temperatures. Secondary amine of 1.5 mmol dissolved in **2mL** solvent was dropwised slowly into the solution in 5 hours and incubated overnight.

After reaction, pH value of the solution was made at 8.0, the solution was added into ethyl acetate of 5 mL and extracted three times with a total amount of 15 mL. The organic solution was isolated and combined together. After that, the organic solution was washed by saturated brine twice and isolated. The organic solution was then distilled under evacuation to remove the organic solvent ethyl acetate. And the residues were chromatographed to afford pure product amides.

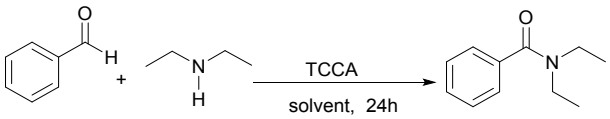
2.3 General procedure for amidation of aldehyde with primary amines

To a solution of **2 mL** solvent CH_2Cl_2, TCCA of 0.2 mmol (0.046g) was introduced, stirred and well dissolved. Aldehyde of 0.5 mmol was dissolved in **2 mL** $CH_2Cl_2$was dropwised into the solution in 0.5h. After that, primary amine 1.5 mmol dissolved in **2 mL** CH_2Cl_2 were dropwised slowly into the solution in 5 hours and incubated overnight.

After reaction, 10 mL H_2O was added to the reaction solution, the organic solvent was isolated and washed three times with 15 mL saturated brine and isolated. The organic solution was then distilled under evacuation to remove CH_2Cl_2. And the residues were chromatographed to afford pure product amides.

3. Optimization of reaction conditions

Table S1 Optimization of the reaction conditions [a]



Entry	Ratio [b] (mol)	Ratio [c] (mol)	T(°C)	Solvent	Yield [d] (%)
1	1:1	1: 1.2/3	25	H_2O	*n.d*
2	1:1.5	1: 1.2/3	25	H_2O	52
3	1:2	1: 1.2/3	25	H_2O	64 (70 [e])
4	1:2.5	1: 1.2/3	25	H_2O	88 (89[e])
5	1:3	1: 1.2/3	25	H_2O	95 (96[e])
6	1:3.5	1: 1.2/3	25	H_2O	95 (95[e])
7	1:4	1: 1.2/3	25	H_2O	87 (88[e])
8	1:4.5	1: 1.2/3	25	H_2O	84
9	1:5	1: 1.2/3	25	H_2O	80
10	1:3	1: 0.5/3	25	H_2O	49
11	1:3	1: 0.7/3	25	H_2O	68
12	1:3	1: 0.9/3	25	H_2O	80
13	1:3	1: 1.0/3	25	H_2O	87 (90[e])
14	1:3	1: 1.1/3	25	H_2O	93 (94[e])
15	1:3	1: 1.3/3	25	H_2O	88
16	1:3	1: 1.5/3	25	H_2O	72
17	1:3	1: 1.7/3	25	H_2O	*Trace*
18	1:3	1: 1.2/3	50	H_2O	74
19	1:3	1: 1.2/3	75	H_2O	*Trace*
20	1:3	1: 1.2/3	90	H_2O	*n.d*
21	1:3	1: 1.2/3	25	DCM	73
22	1:3	1: 1.2/3	25	CH_3OH	59
23	1:3	1: 1.2/3	25	CH_3CN	64
24[f]	1:3	1: 1.2/3	25	DCM	74
25[f]	1:3	1: 1.2/3	25	CH_3OH	59
26[f]	1:3	1: 1.2/3	25	CH_3CN	66

[a] Reaction were carried out on a 6 mL scale, conditions: benzaldehyde, 0.5 mmol, and veried ratios of substrates listed in Table 1; [b] Ratio = benzaldehyde: diethylamine; [c] Ratio = benzaldehyde: TCCA; [d] Yields were determined by HPLC analysis based on the aldehyde; [e] Yields were measured after the addition of 0.1 mL DMSO; [f] Yields were measured after the addition of 1 mmol triethylamine to the reaction solution; n.d., not detected; DCM, dichloromethane.

4. Proposed mechanism

A possible pathway for the reaction is suggested in Fig.S1. It is proposed that the introduced TCCA can react with the previously dissolved aldehyde in reaction media

fast with priority to result the corresponding acid chloride, and the generated acid chloride will be spontaneously consumed by the existing substrate amine in aqueous solution to generate the desired product amide. Due to fast formation of C-N bond and more stability of C-N bond in amide compound, the majority of the formed acid chloride choose amine with priority to form amide while not H_2O resulting in by-product acid. The reaction can thus proceed smoothly and efficiently at room temperature.

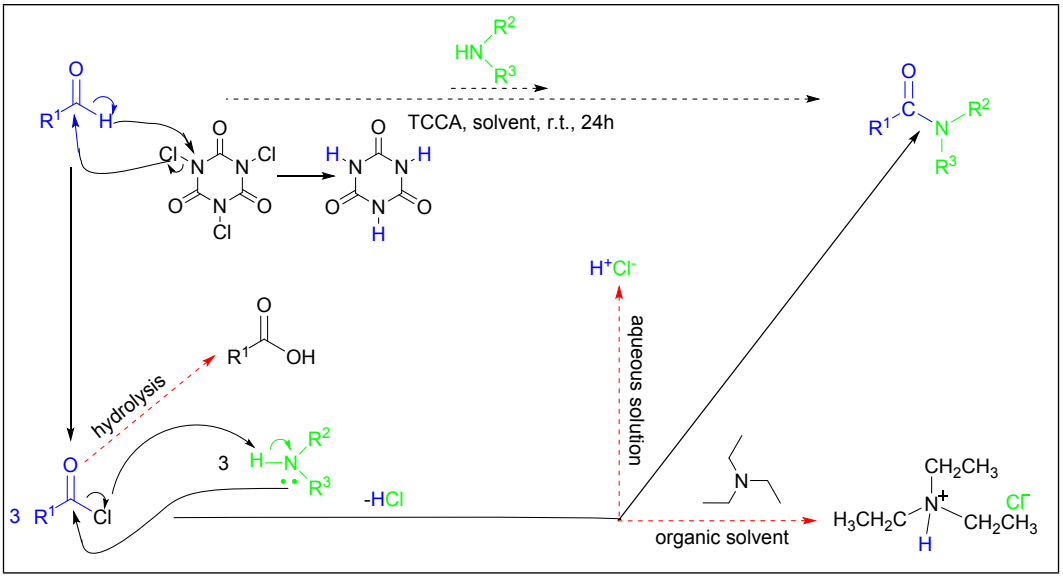
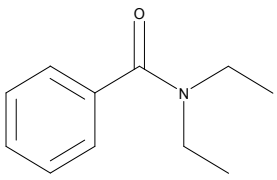


Fig.S1 Proposed pathway for the cascade reaction

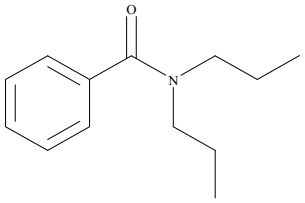
5. ^{1}H NMR and ^{13}C NMR spectrum for isolated products

N, N- diethylbenzamide **(Entry 1, Table 1)**



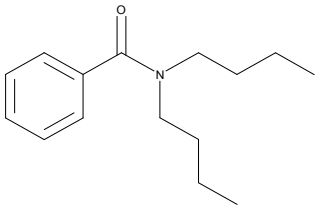
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.10 (t, 3H), δ = 1.25 (t, 3H), δ = 3.25 (q, 2H), δ = 3.54 (q, 2H), δ = 7.26 - 7.57 (m, 3H), δ = 8.05 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 13.0, 41.5, 43.0, 126.3, 128.4, 129.1, 137.3, 171.4.

N, N-(di-n-propyl)-benzamide **(Entry 2, Table 1)**



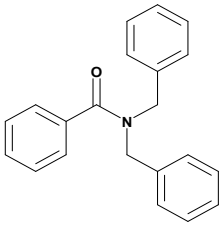
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.73 (br s, 3H), δ = 0.97 (br s, 3H), δ =1.52 (br d, *J* = 6.4Hz, 2H), δ = 1.69 (br d, *J* = 6.8Hz, 2H), δ = 3.15 (br s, 2H), δ = 3.46 (br s, 2H), δ = 7.30-7.42 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 11.4, 20.7, 21.9, 46.3, 50.7, 126.4, 128.3, 129.0, 137.3, 171.8.

N, N-(di-n-butyl)-benzamide **(Entry 3, Table 1)**



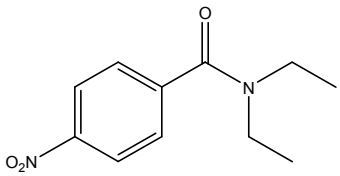
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.77 (*br* s, 3H), δ = 0.97 (br s, 3H), δ =1.05-1.20 (m, 2H), δ = 1.32-1.53 (m, 4H), δ = 1.64 (br s, 2H), δ = 3.18 (br s, 2H), δ = 3.48 (br s, 2H), δ = 7.31-7.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.6, 13.9, 19.7, 20.3, 29.6, 30.8, 44.5, 48.8, 126.4, 128.3, 129.0, 137.3, 171.7.

N, N-dibenzylbenzamide **(Entry 4, Table 1)**



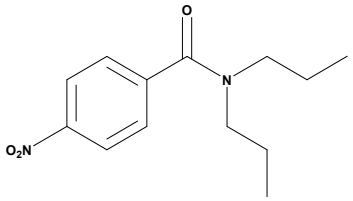
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.40 (s, 2H), δ = 4.70 (s, 2H), δ = 7.15 (d, *J* = 6.0Hz, 2H), δ = 7.26-7.40 (m, 11H), δ = 7.46-7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.4, 55.6, 126.7, 127.1, 127.6, 128.5, 128.6, 128.7, 128.9, 128.9, 129.7, 134.9, 136.2, 137.5, 172.3.

4-nitryl-N, N-didiethylbenzamide **(Entry 5, Table 1)**



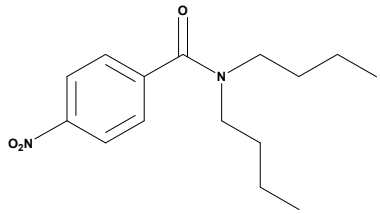
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.14 (t, *J* = 6.8Hz, 3H), δ = 1.28 (t, *J* = 6.8Hz, 3H), δ = 3.23 (dd, *J* = 13.6, 6.8Hz, 2H), δ = 3.58 (dd, *J* = 13.2, 6.4Hz, 2H), δ = 7.57 (d, *J* = 8.4Hz, 2H), δ = 8.28 (d, *J* = 8.4Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 14.2, 39.5, 43.3, 123.8, 127.4, 143.4, 148.0, 168.9.

4-nitryl-N, N-(di-n-propyl)-benzamide **(Entry 6, Table 1)**



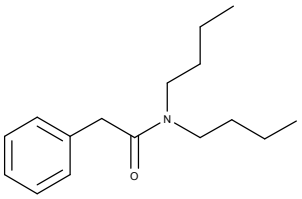
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.61 (br s, 3H), δ = 0.84 (br s, 3H), δ =1.41 (br s, 2H), δ = 1.56 (br s, 2H) δ = 3.00 (br s, 2H), δ = 3.34 (br s, 2H), δ = 7.33-7.50 (m, 2H) , δ = 8.02-8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8, 11.3, 20.6, 21.8, 46.3, 50.5, 123.7, 127.5, 143.5, 147.8, 169.3.

4-nitryl-N, N-(di-n-butyl)-benzamide **(Entry 7, Table 1)**



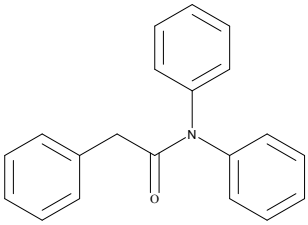
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.66 (br s, 3H), δ = 0.84 (br s, 3H), δ =1.00 (br s, 2H), δ = 1.27 (br s, 2H), δ = 1.37 (br s, 2H), δ = 1.52 (br s, 2H) , δ = 3.03 (br d, *J* = 6.0 Hz, 2H), δ = 3.38 (br d, *J* = 5.6Hz, 2H), δ = 7.42 (t, *J* = 8.0 Hz, 2H) , δ = 8.02 - 8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 13.8, 19.6, 20.1, 29.4, 30.6, 44.5, 48.6, 123.6, 127.5, 143.5, 147.8, 169.1.

N, N-(di-n-butyl)- phenylacetamide **(Entry 8, Table 1)**



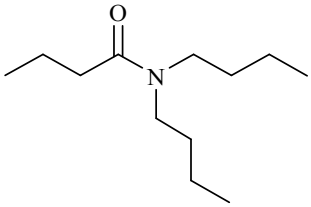
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (td, *J* = 6.8 Hz, 2.4Hz, 6H), δ = 1.19-1.35 (m, 4H), δ = 1.39-1.57 (m, 4H), δ = 3.19 (t, *J* = 8.0Hz, 2H), δ = 3.31 (t, *J* = 7.6Hz, 2H), δ = 3.69 (s, 2H), δ = 7.18 - 7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 13.9, 20.1, 20.3, 29.7, 31.1, 41.0, 45.7, 48.1, 126.6, 128.6, 128.7, 135.6, 170.5.

N, N-diphenylphenylacetamide **(Entry 9, Table 1)**



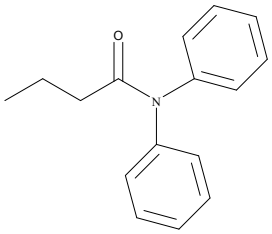
^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.65 (s, 2H), δ = 7.11 (d, *J* = 6.4 Hz, 2H), δ = 7.16-7.40 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 42.2, 116.8, 116.9, 119.6, 119.7, 126.5, 126.8, 128.4, 129.0, 129.1, 137.9, 142.7, 142.8, 171.1.

N, N-(di-n-butyl)-butylamide **(Entry 10, Table 1)**



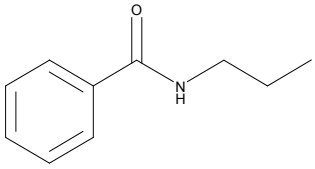
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88-0.96 (m, 9H), δ = 1.23 - 1.34 (m, 4H), δ = 1.43 - 1.55 (m, 4H), δ = 1.60 - 1.68 (m, 2H) , δ = 2.25 (t, *J* = 7.4 Hz, 2H) , δ = 3.19 (t, *J* = 7.8Hz, 2H) , δ = 3.28 (t, *J* = 7.6Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 13.9, 14.0, 18.9, 20.1, 20.2, 29.9, 31.2, 35.0, 45.7, 47.8, 172.8.

N, N-diphenylbutylamide **(Entry 11, Table 1)**



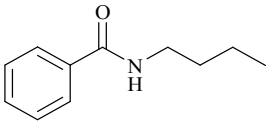
^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.0Hz, 3H), δ = 1.67-1.76 (m, 2H), δ = 2.27 (t, *J* = 7.4Hz, 2H), δ = 7.22 - 7.64 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.8, 19.0, 37.2, 117.8, 126.9, 129.3, 143.0, 173.2.

N-(n-propyl)-benzamide **(Entry 1, Table 2)**



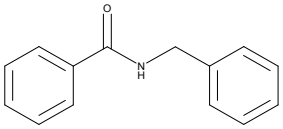
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2Hz, 3H), δ = 1.51-1.65 (m, 2H), δ = 3.33 (dd, *J* = 13.2, 6.8Hz, 2H), δ = 7.33 (t, *J*=7.2Hz, 3H), δ = 7.42 (t, J=7.6Hz, 1H), δ = 7.81 (d, *J* = 7.6Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.5, 22.8, 41.8, 127.1, 128.3, 131.2, 134.8, 167.9.

N-(n- butyl)-benzamide **(Entry 2, Table 2)**



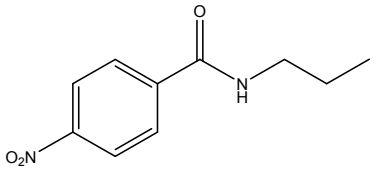
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (t, *J*=7.6Hz, 3H), δ = 1.36-1.47 (m, 2H), δ = 1.56-1.65 (m, 2H), δ = 3.46 (dd, *J* =13.2, 6.4Hz, 2H), δ = 6.22 (s, 1H), δ = 7.42 (t, *J* = 6.8Hz, 2H) , δ = 7.46-7.53 (m, 1H) , δ = 7.76 (d, *J* = 7.6Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 20.2, 31.8, 39.8, 126.9, 128.5, 131.3, 134.9, 167.6.

N-benzylbenzamide **(Entry 3, Table 2)**



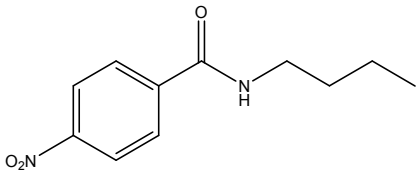
^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.94 (s, 2H), δ = 7.36-7.55 (m, 8H), δ = 7.91-7.998 (m, 2H), δ = 8.46 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.1, 127.0, 127.6, 127.9, 128.6, 128.8, 131.6, 134.4, 138.2, 167.5.

4-nitryl-N-(n-propyl)-benzamide **(Entry 4, Table 2)**



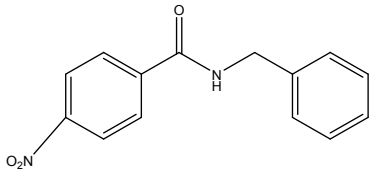
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.2Hz, 3H), δ = 1.60-1.72 (m, 2H), δ = 3.43 (dd, J_1 = 7.0 Hz, J_2 = 6.8Hz, 2H), δ = 6.69 (s, 1H), δ = 7.95 (d, J = 8.4Hz, 2H), δ = 8.26 (d, J = 8.4Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =11.5, 22.8, 42.1, 123.8, 128.2, 140.5, 149.4, 165.7.

4-nitryl-N-(n-butyl)-benzamide **(Entry 5, Table 2)**



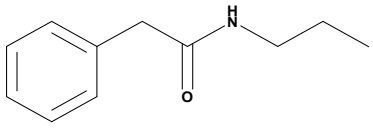
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (t, J = 7.2Hz, 3H), δ = 1.34-1.47 (m, 2H), δ = 1.56-1.67 (m, 2H), δ = 3.46 (dd, J_1 = 6.8Hz, J_2 = 6.4Hz, 2H), δ = 6.79 (s, 1H), δ =7.95 (d, J = 8.8Hz, 2H), δ = 8.18 - 8.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 20.2, 31.5, 40.2, 123.7, 128.2, 140.5, 149.4, 165.7.

4-nitryl-N-benzylbenzamide **(Entry 6, Table 2)**



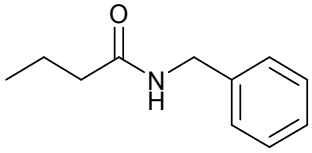
^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.63 (d, J = 5.6Hz, 2H), δ = 6.80 (s, 1H), δ = 7.18-7.47 (m, 5H), δ = 7.94 (d, J = 8.8Hz, 2H), δ = 8.24 (d, J = 8.4Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 44.5, 123.8, 128.0, 128.0, 128.3, 129.0, 137.5, 139.9, 149.6, 165.5.

N-(n-propyl)-phenylacetamide **(Entry 7, Table 2)**



^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83 (t, *J* = 7.2Hz, 3H), δ = 1.38-1.50 (m, 2H), δ = 3.16 (dd, *J* = 13.6, 6.8Hz, 2H), δ = 3.57 (s, 2H), δ = 5.51 (s, 1H), δ = 7.25 - 7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 22.7, 41.3, 43.9, 127.3, 129.0, 129.5, 135.1, 171.0.

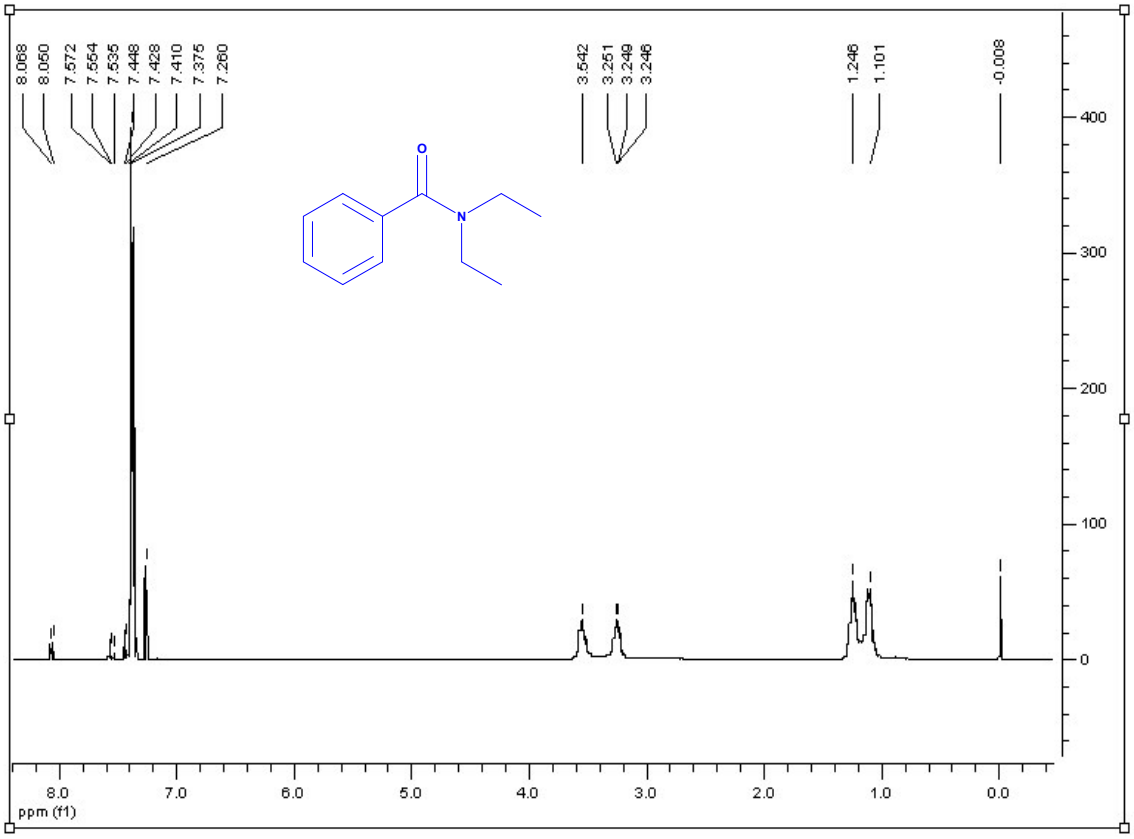
*N-**benzylbutyramide*** **(Entry 8, Table 2)**



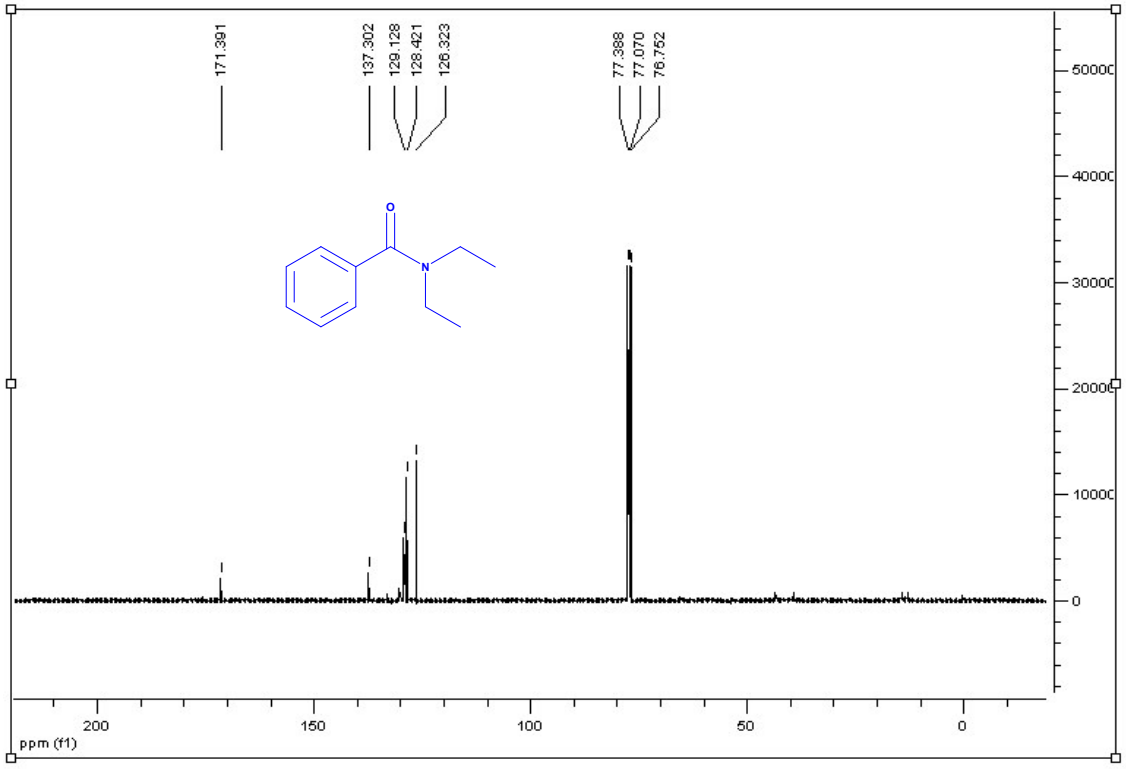
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.2Hz, 3H), δ = 1.55 - 1.67 (m, 2H), δ = 2.13 (t, *J* = 7.2Hz, 2H), δ = 4.33 (d, *J* = 6.0Hz, 2H), δ = 6.67 (s, 1H), δ = 7.16 - 7.7.32 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 19.2, 38.5, 43.3, 127.3, 127.7, 128.6, 138.7, 173.3.

6. *^{1}H NMR and ^{13}C NMR spectra of product amides*

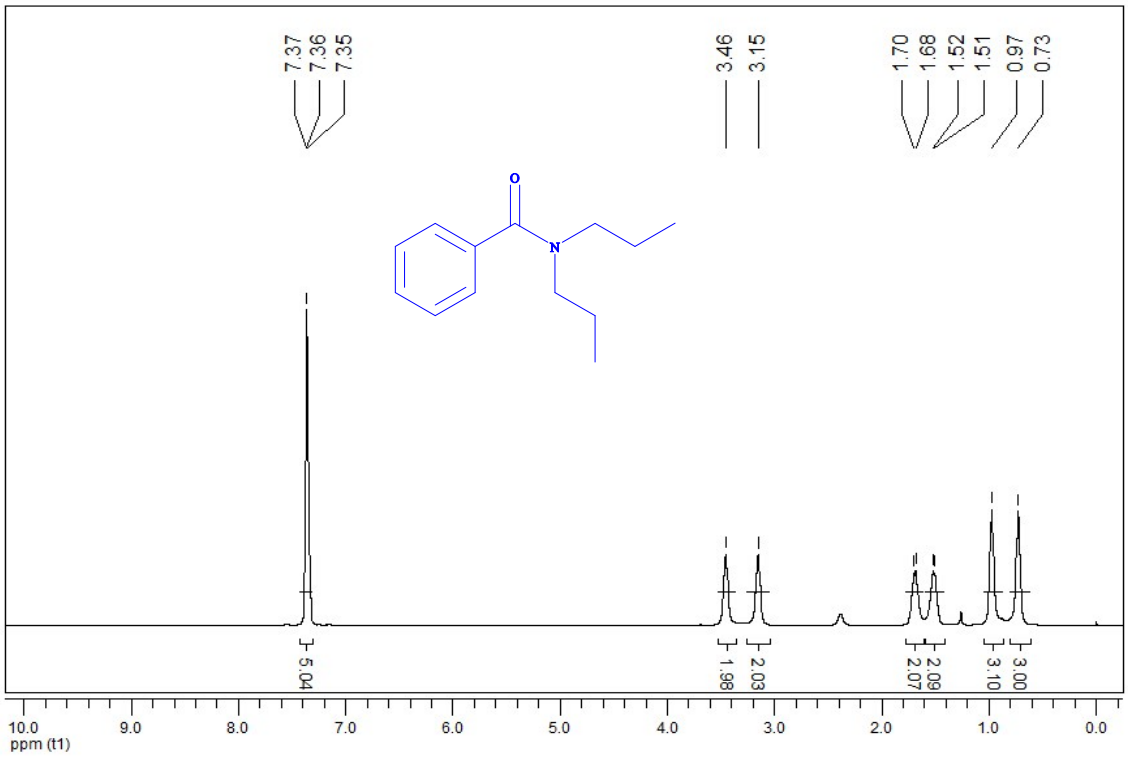
[1]H NMR for N, N- diethylbenzamide



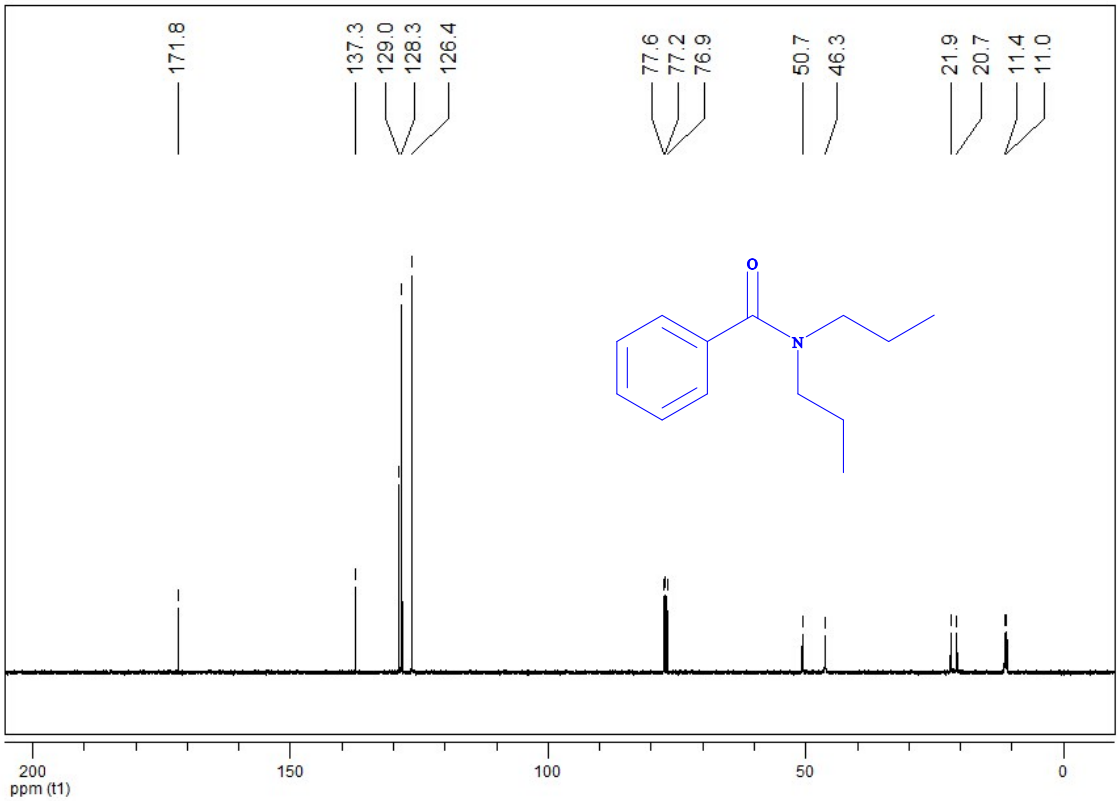
[13]C NMR for N, N- diethylbenzamide



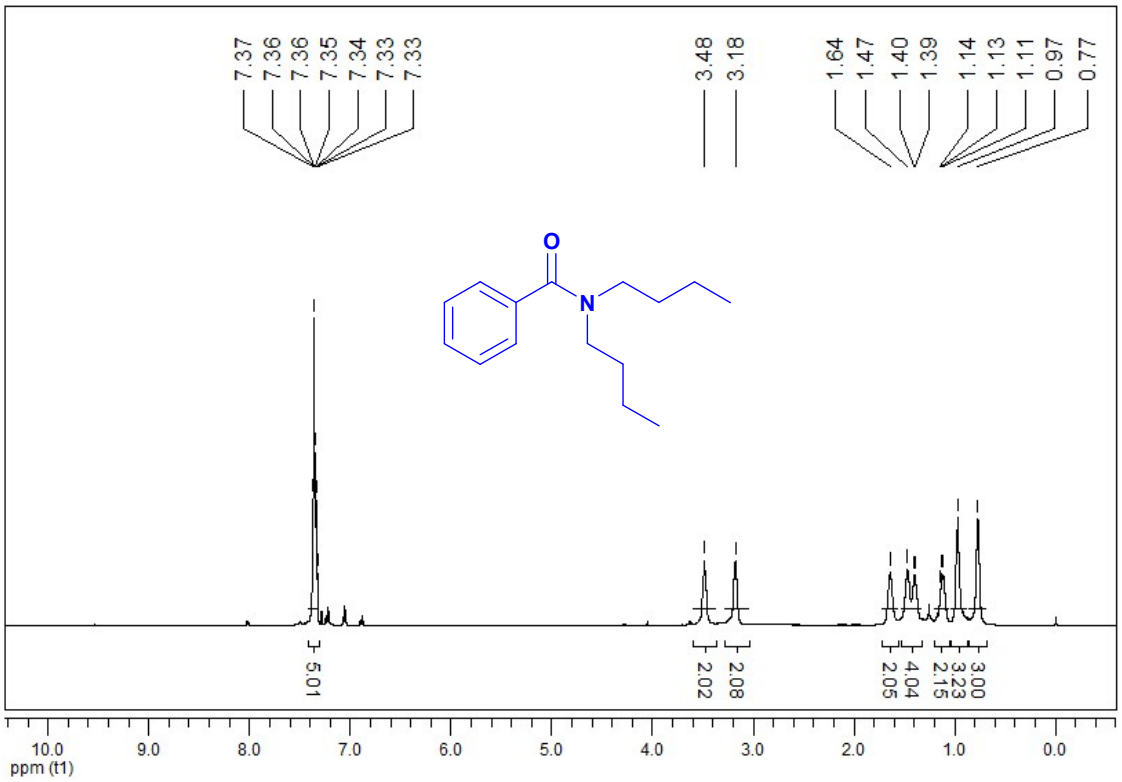
[1]H NMR for N, N-(di-n-propyl)-benzamide



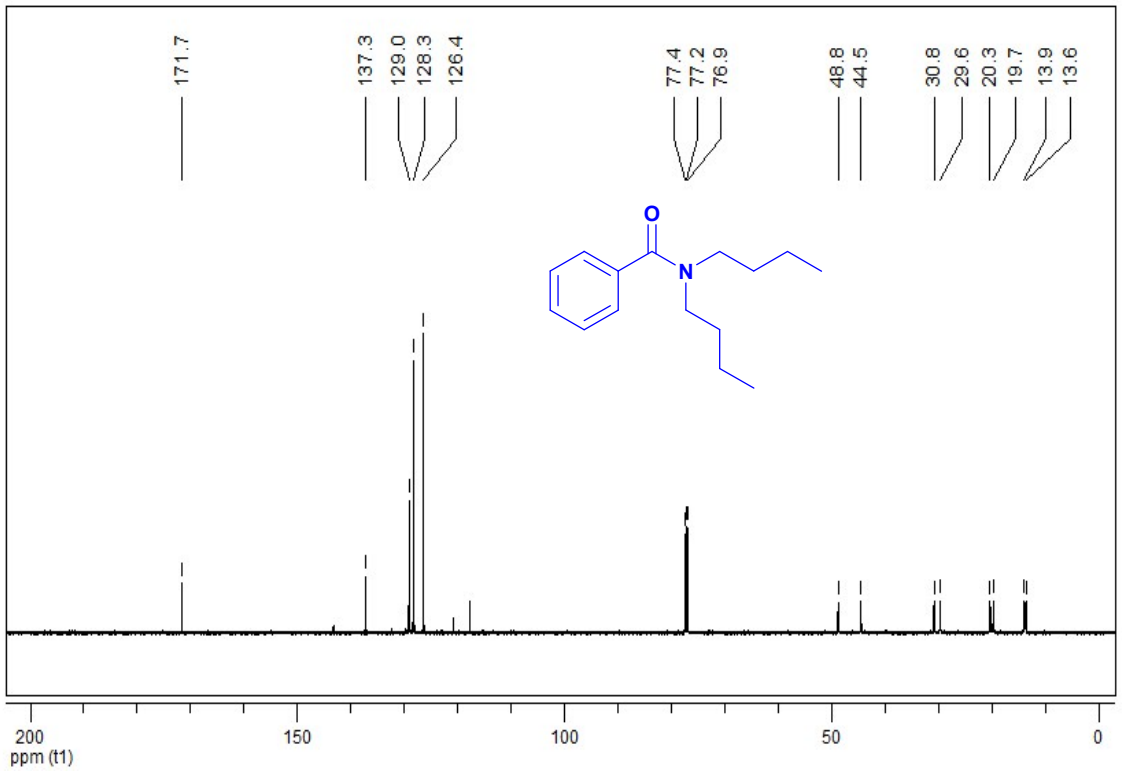
[13]C NMR for N, N-(di-n-propyl)-benzamide



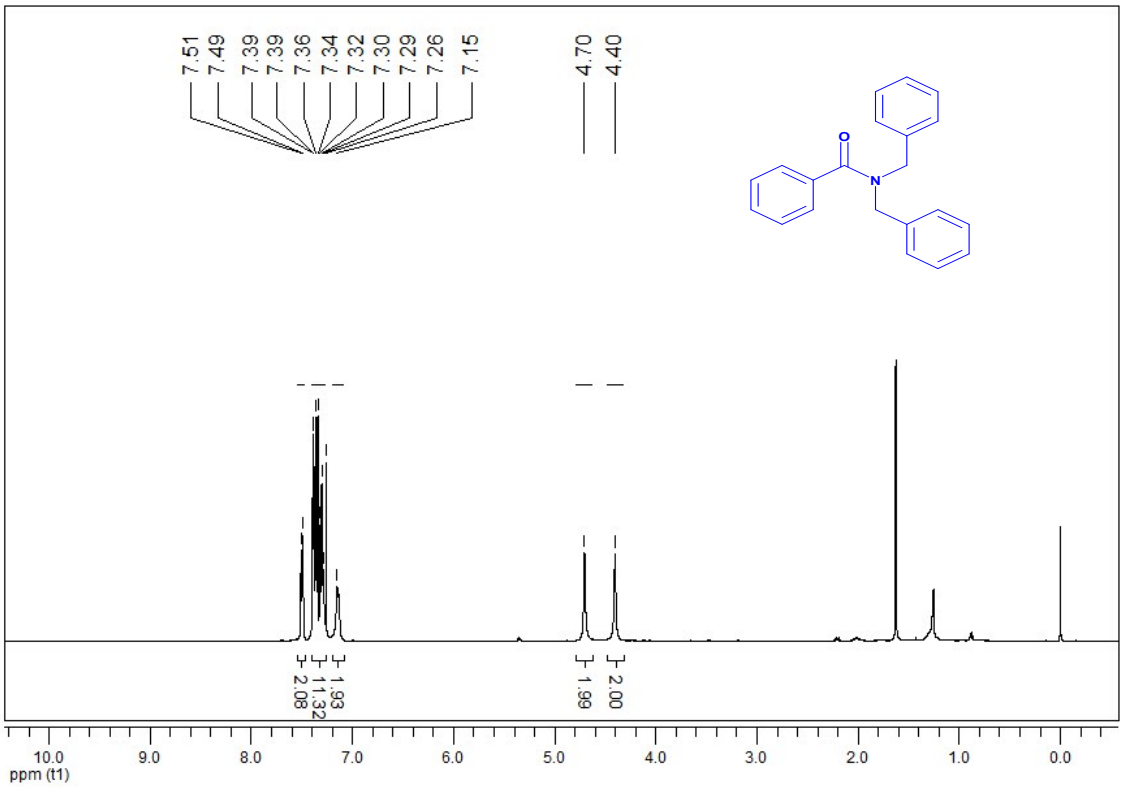
[1]H NMR for N, N-(di-n-butyl)-benzamide



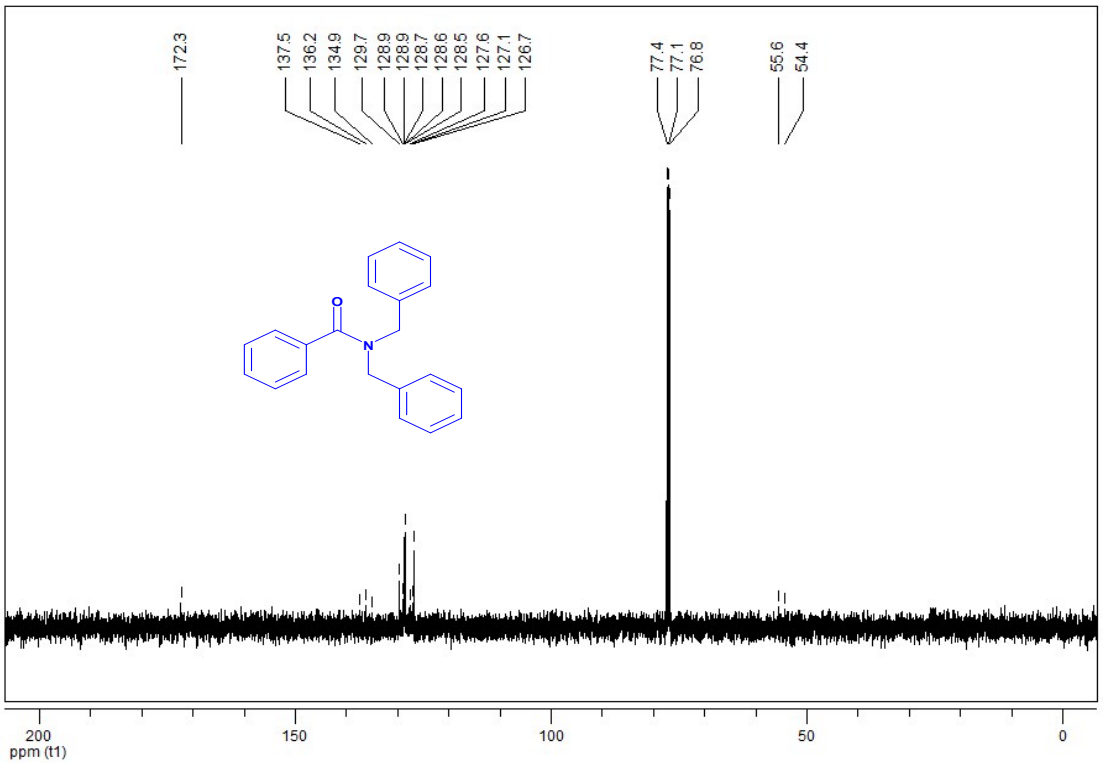
[13]C NMR for N, N-(di-n-butyl)-benzamide



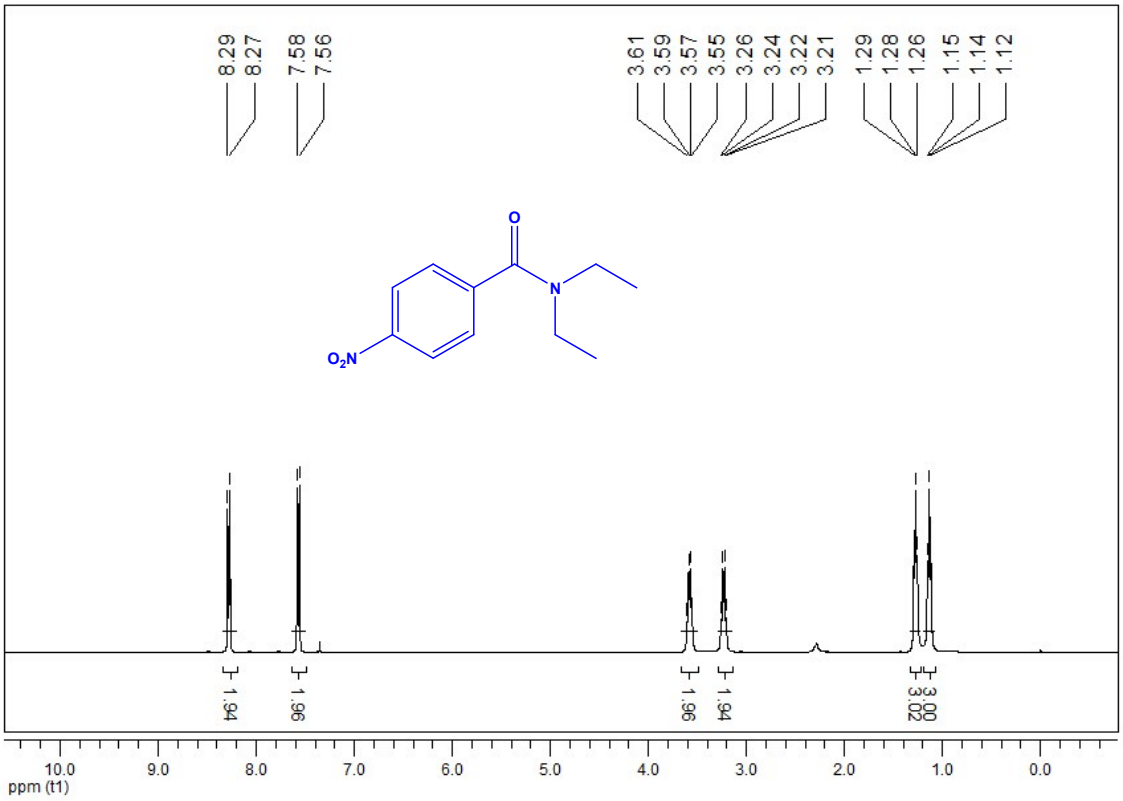
[1]H NMR for N, N-dibenzylbenzamide



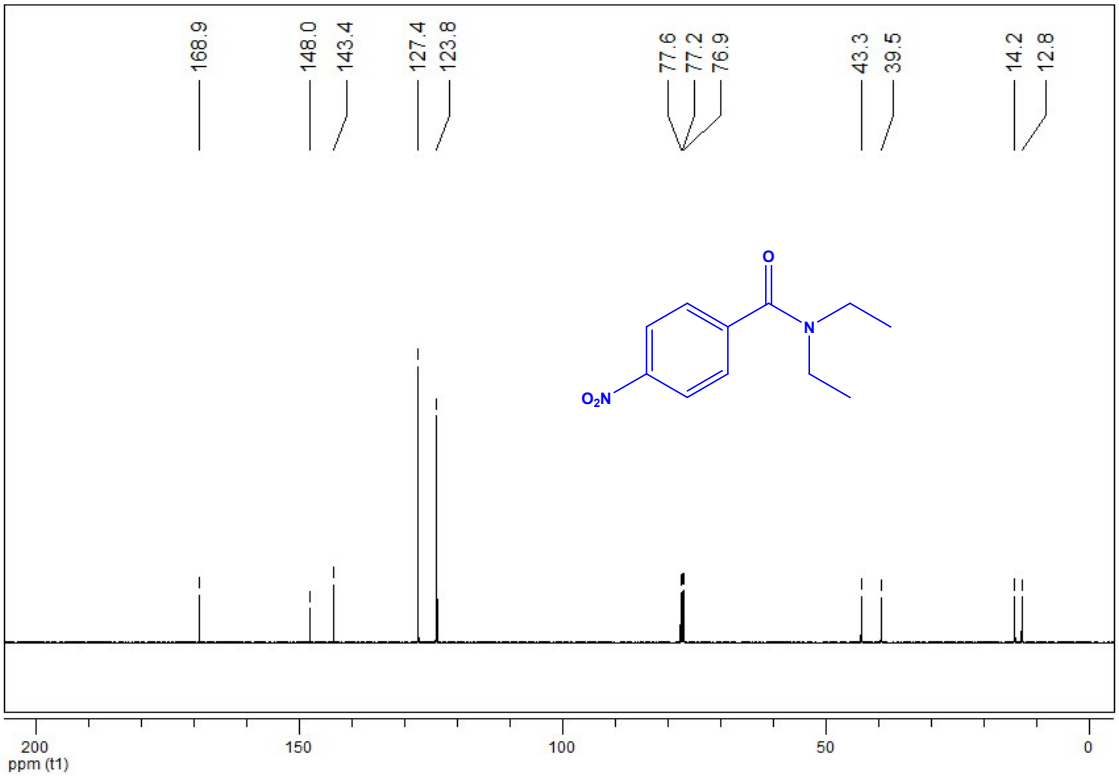
[13]C NMR for N, N-dibenzylbenzamide



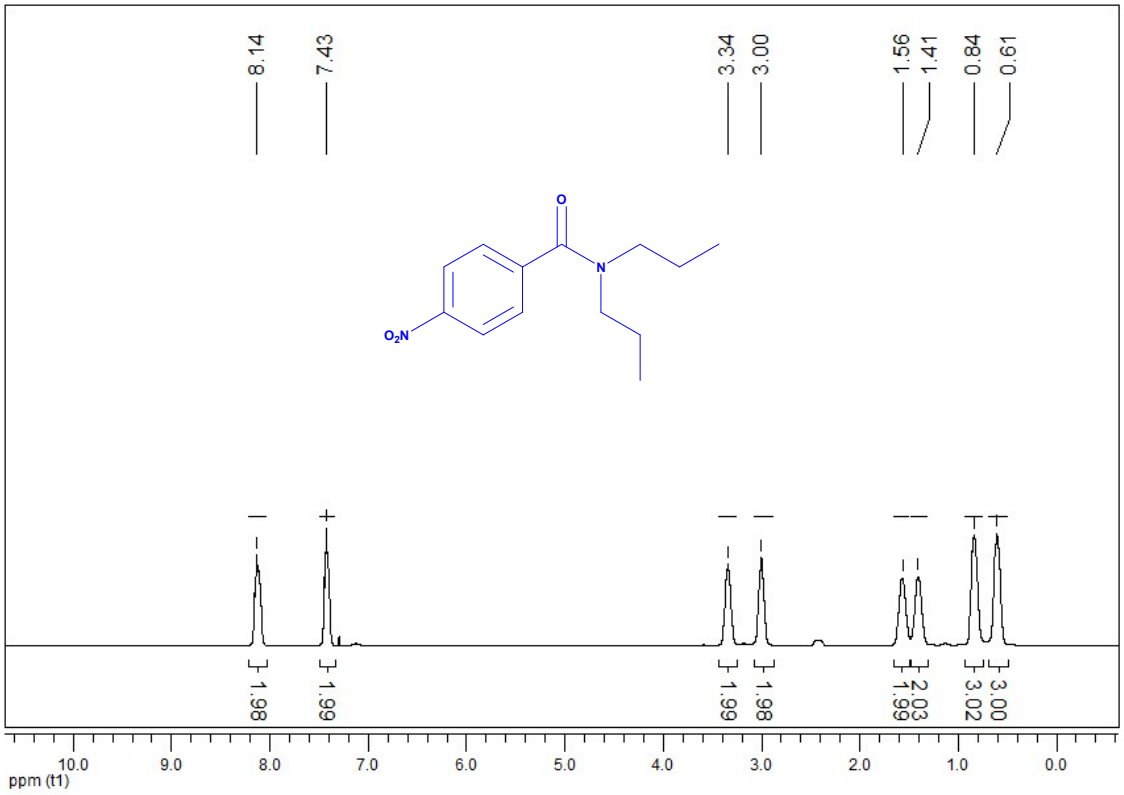
[1]H NMR for 4-nitryl-N-didiethylbenzamide



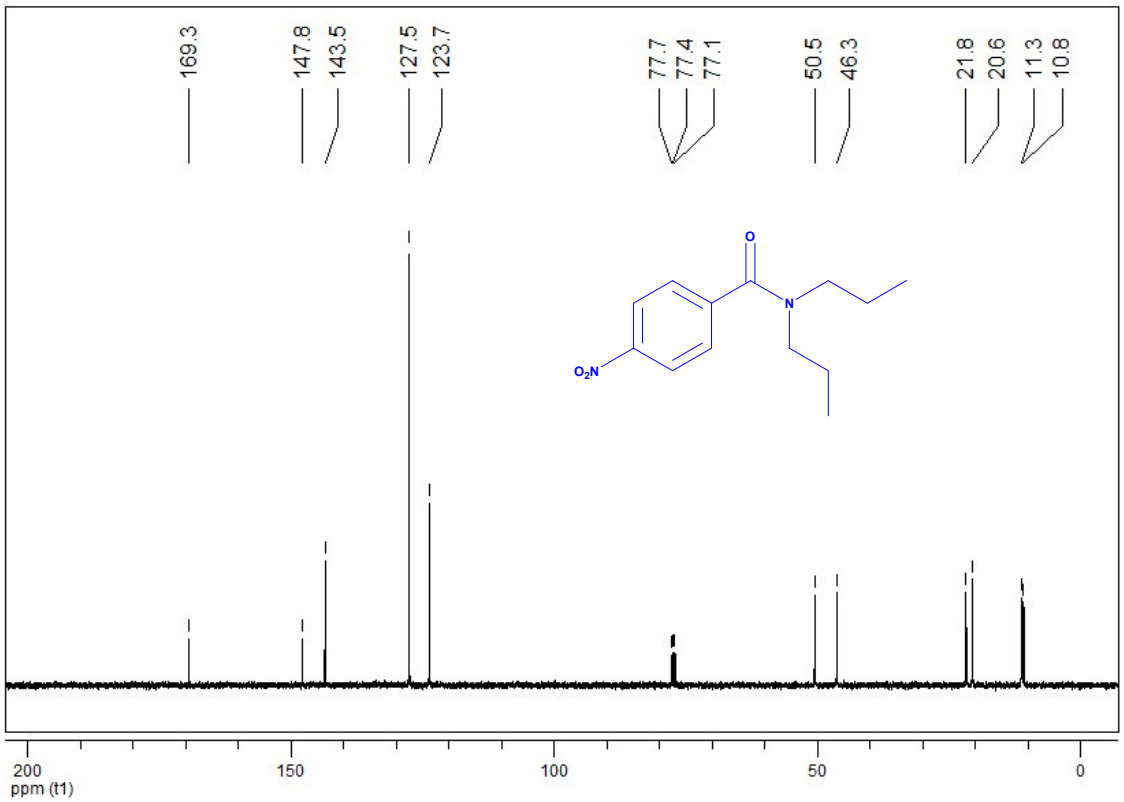
[13]C NMR for 4-nitryl-N-didiethylbenzamide



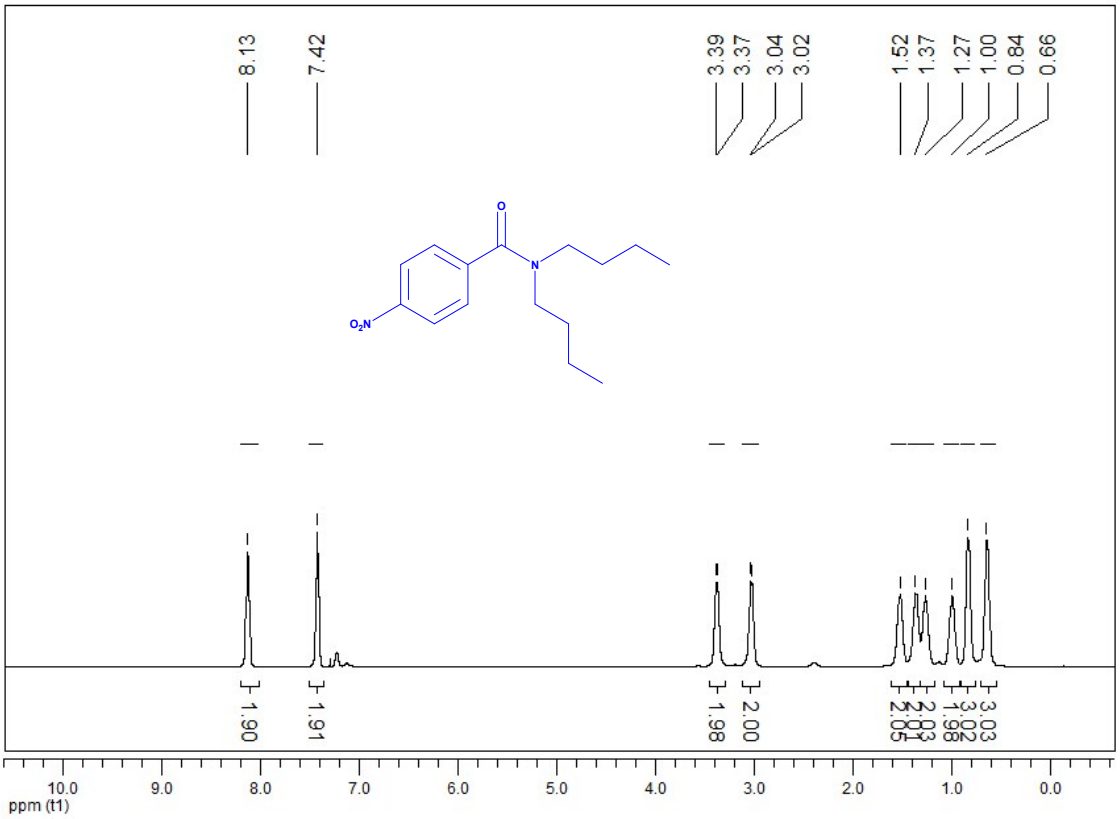
[1]H NMR for 4-nitryl-N, N-(di-n-propyl)-benzamide



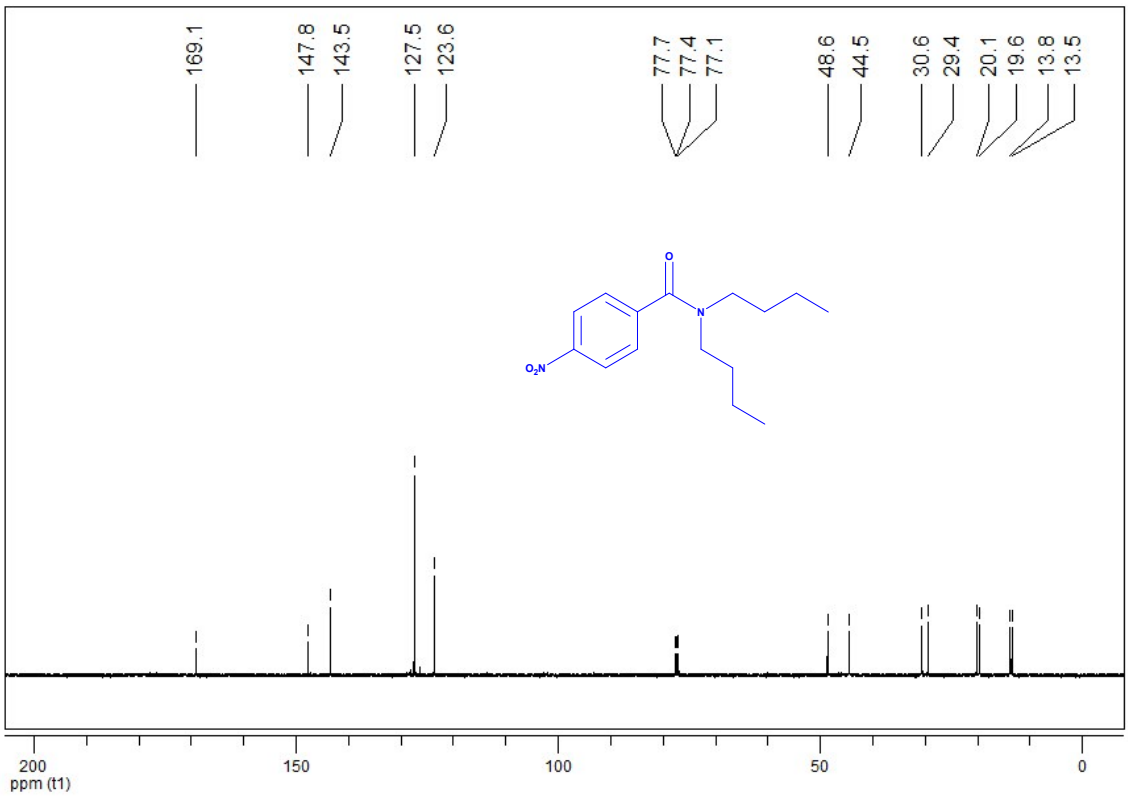
[13]C NMR for 4-nitryl-N, N-(di-n-propyl)-benzamide



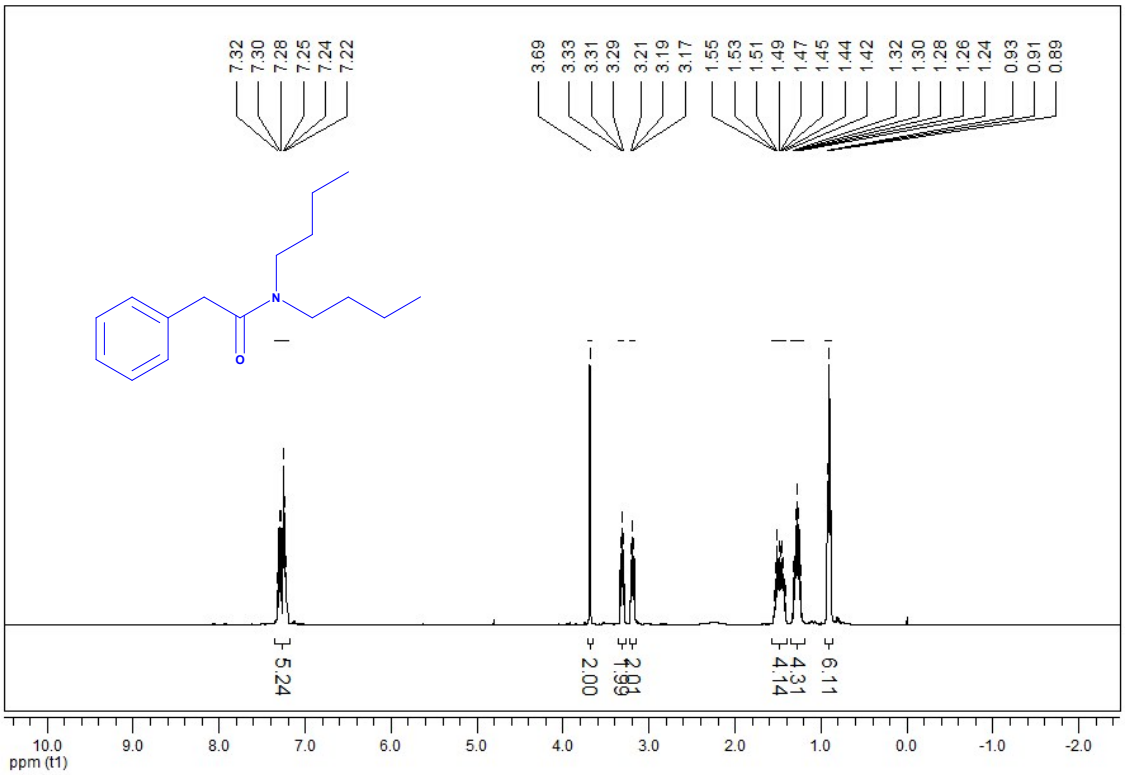
[1]H NMR for 4-nitryl-N, N-(di-n-butyl)-benzamide



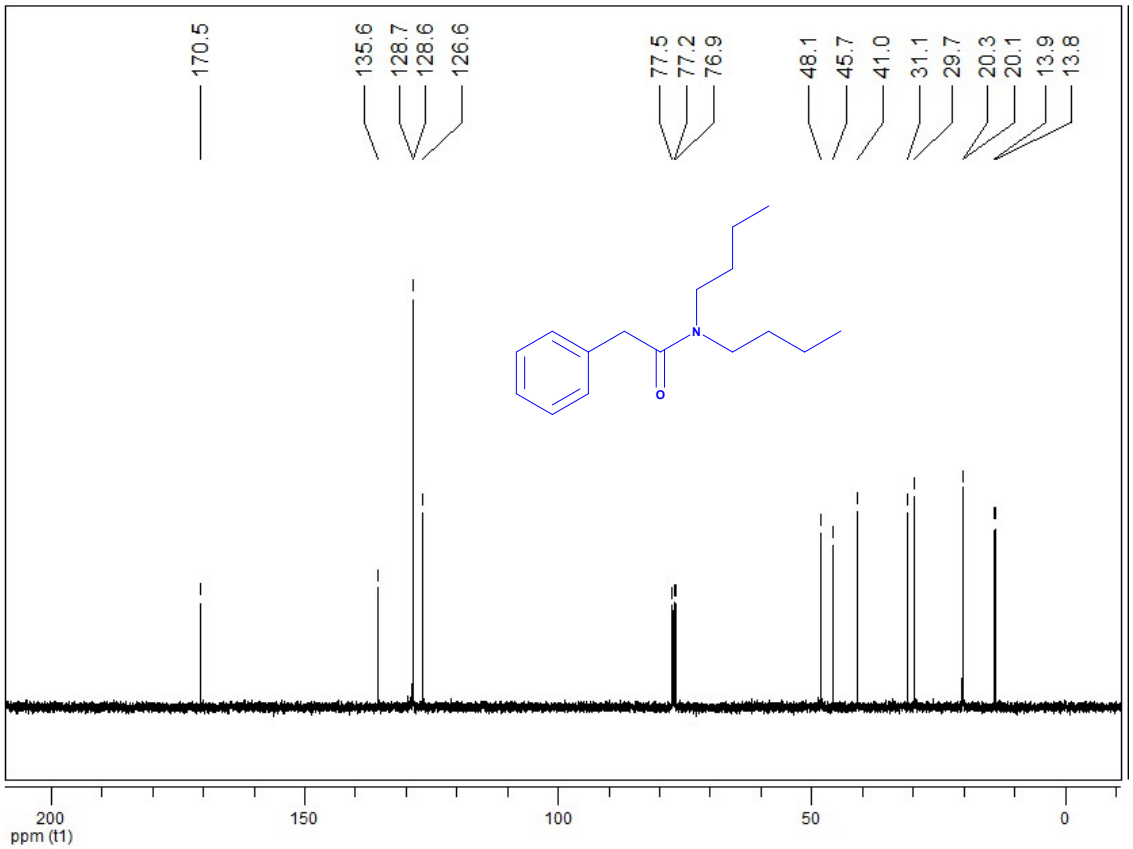
[13]C NMR for 4-nitryl-N, N-(di-n-butyl)-benzamide



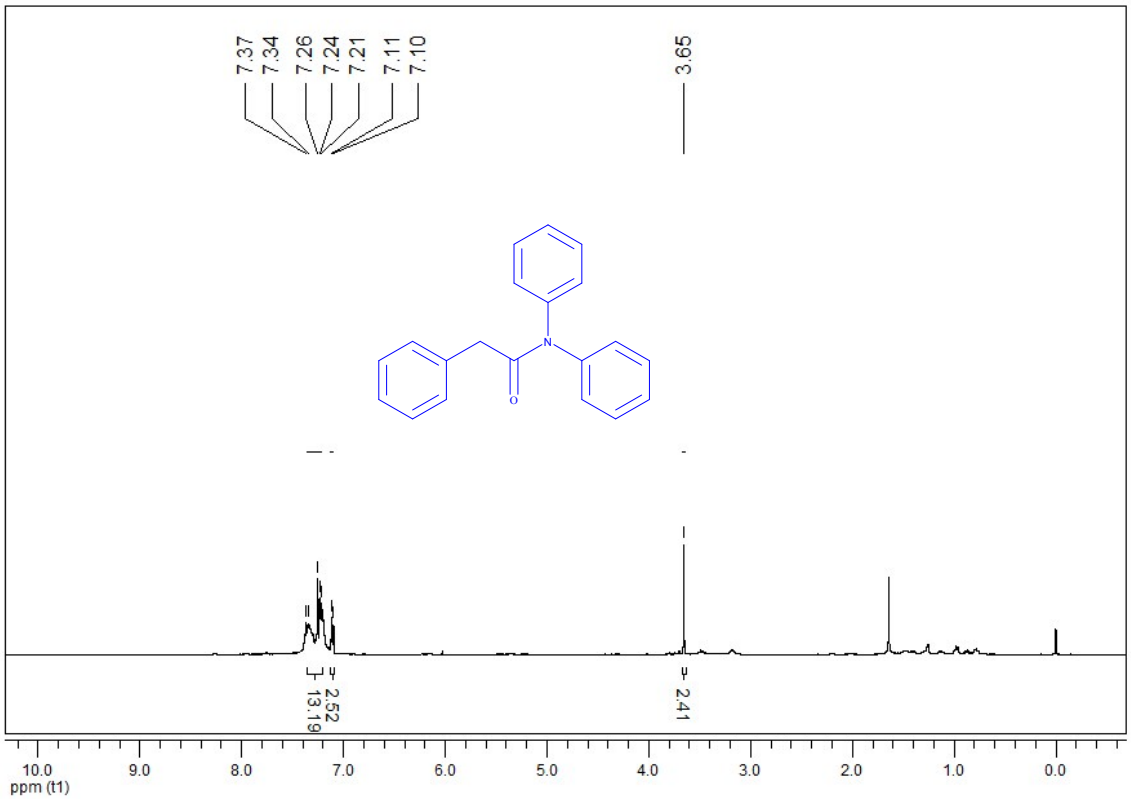
[1]H NMR for N, N-(di-n-butyl)-phenylacetamide



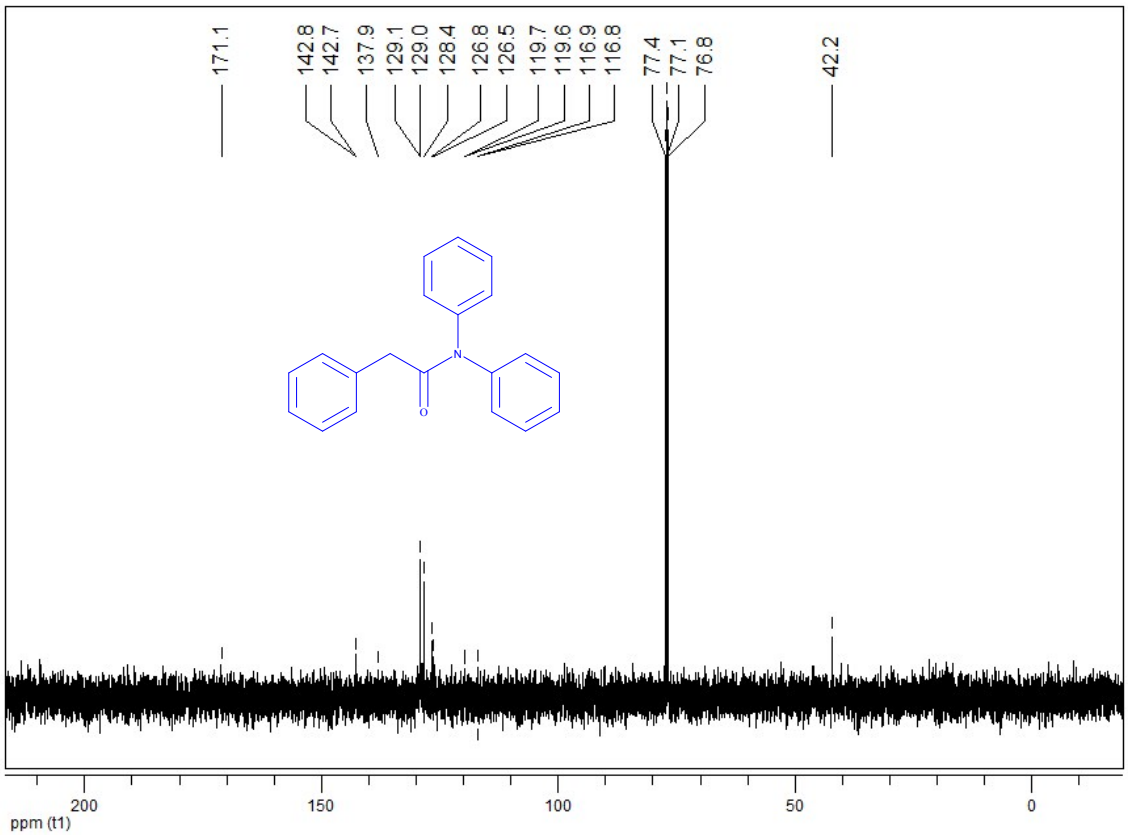
[13]C NMR for N, N-(di-n-butyl)-phenylacetamide



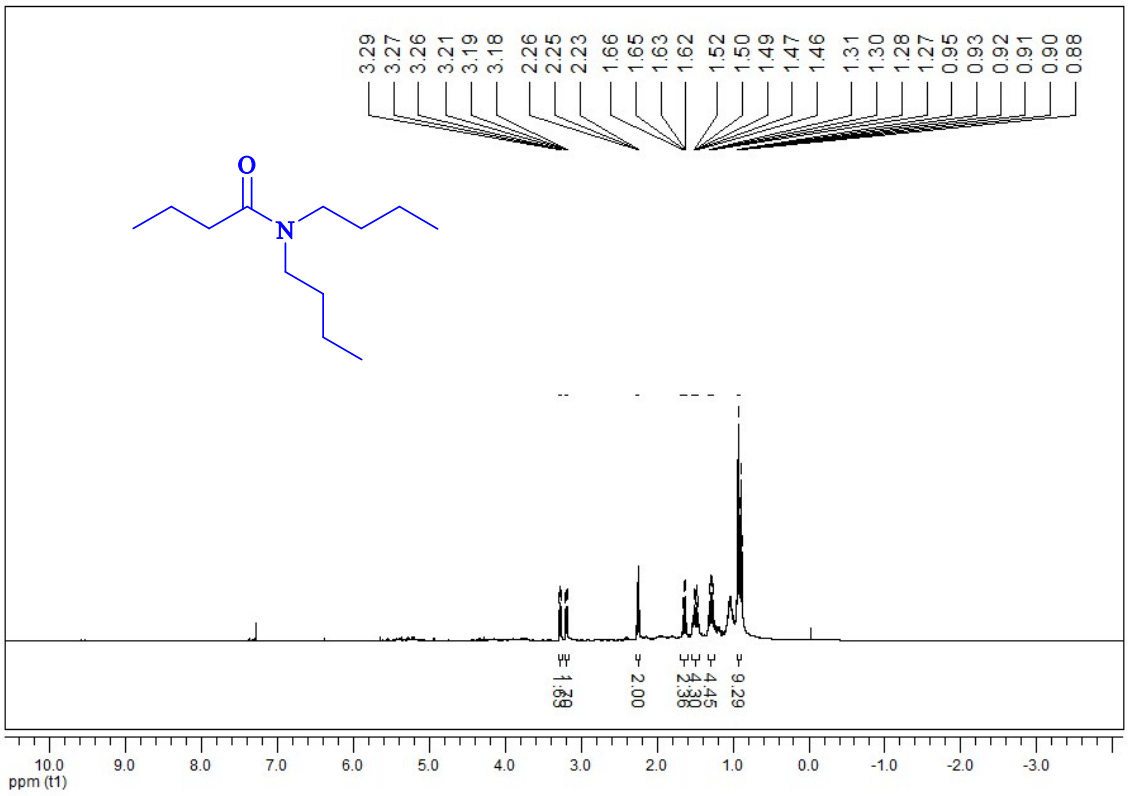
[1]H NMR for N, N-diphenylphenylacetamide



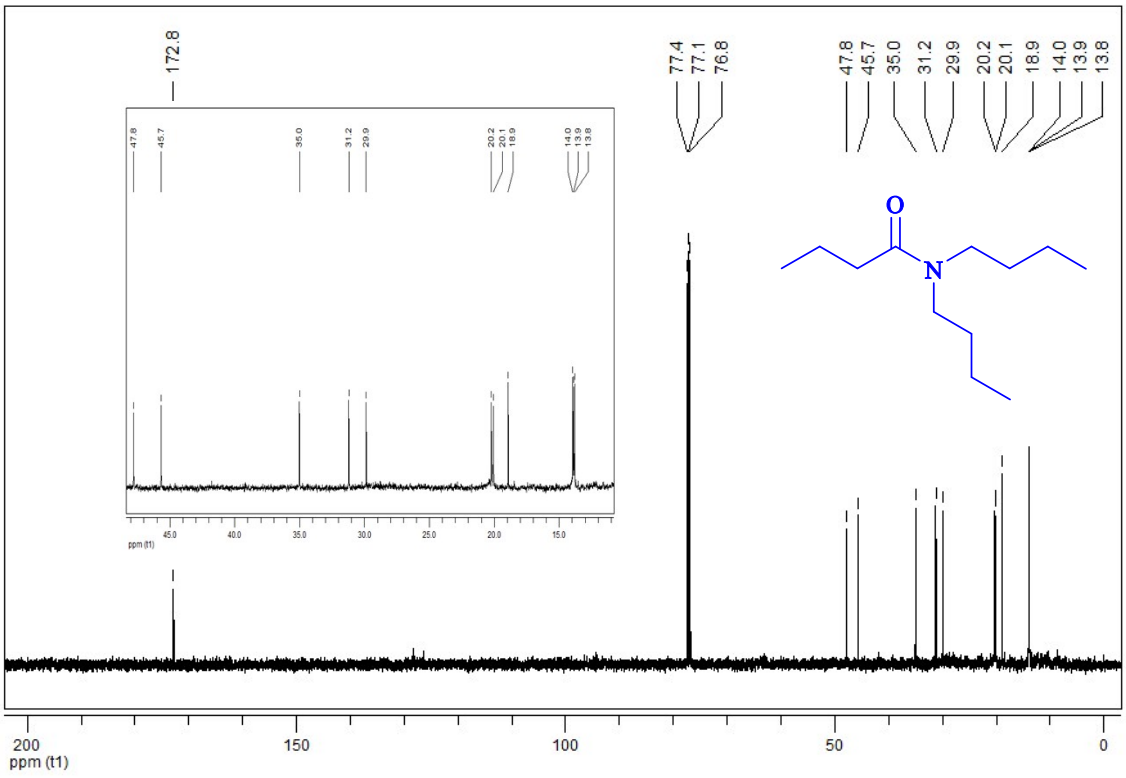
[13]C NMR for N, N-diphenylphenylacetamide



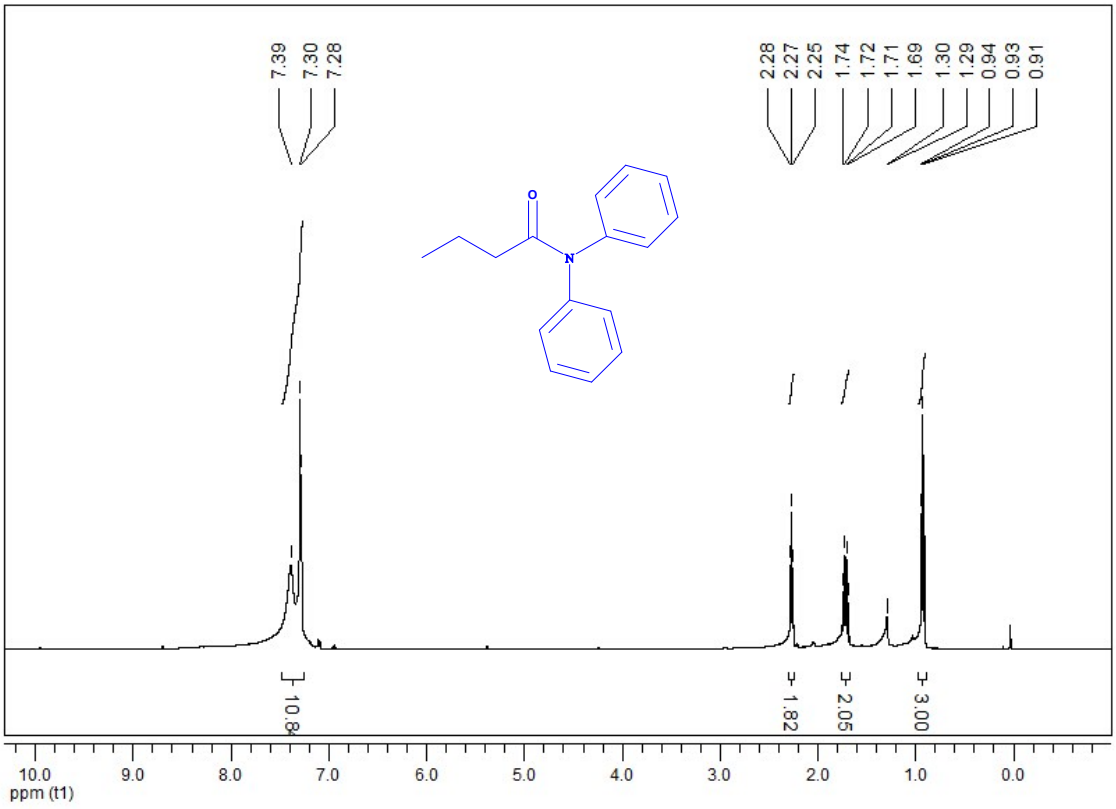
[1]H NMR for N, N-(di-n-butyl)-butylamide



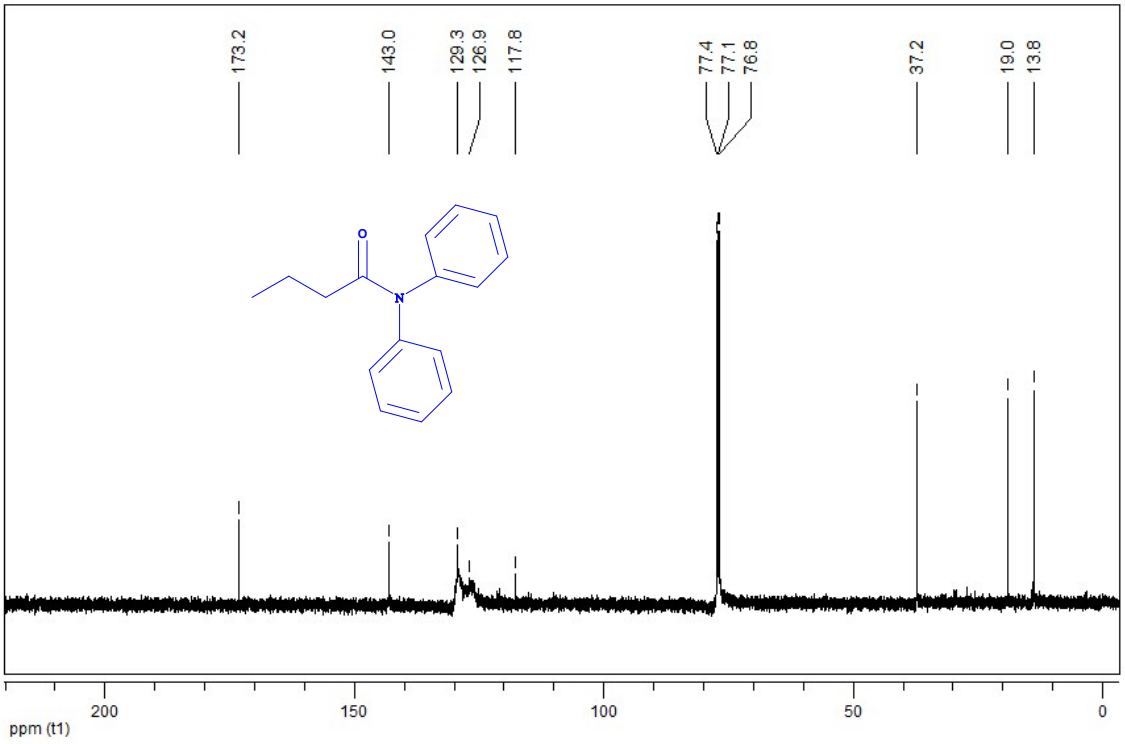
[13]C NMR for N, N-(di-n-butyl)-butylamide



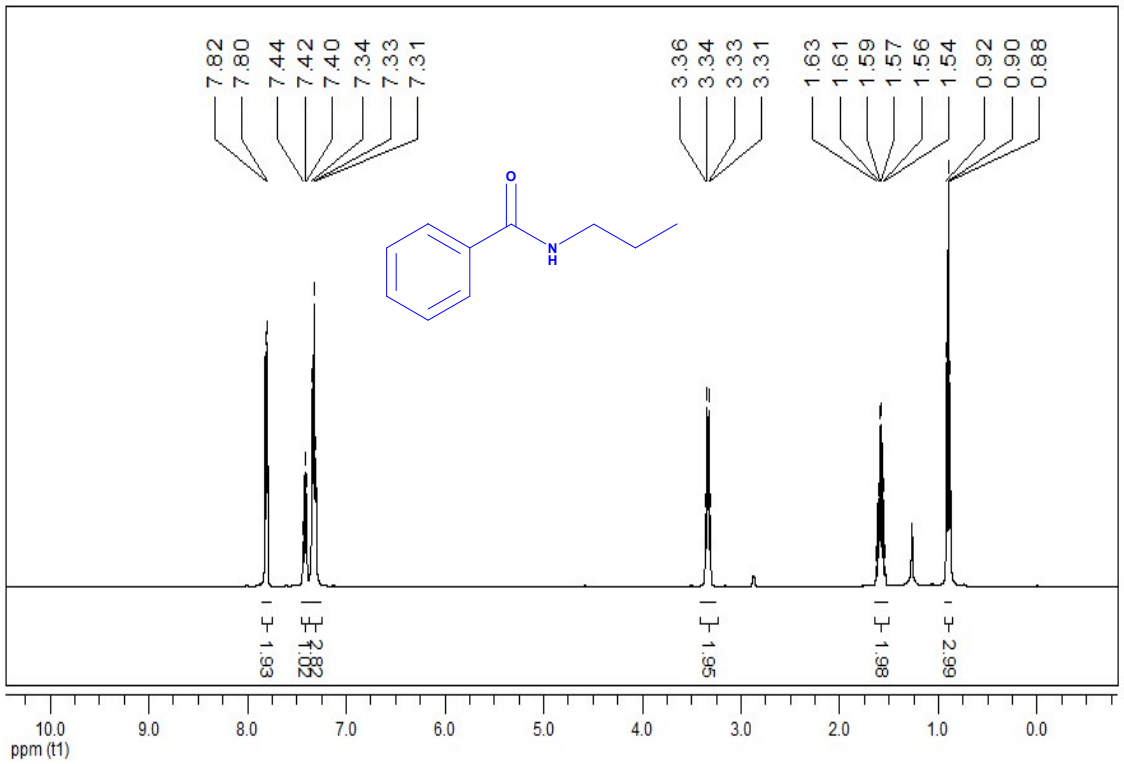
[1]H NMR for N, N-diphenylbutylamide



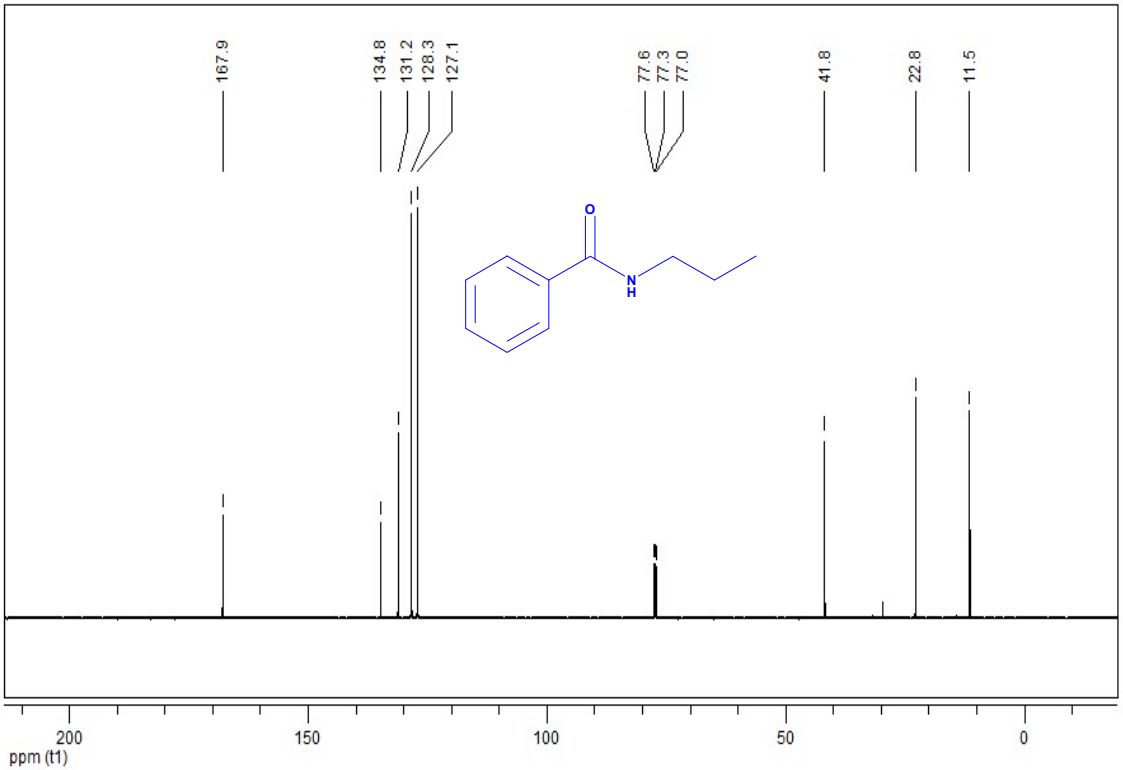
[13]C NMR for N, N-diphenylbutylamide



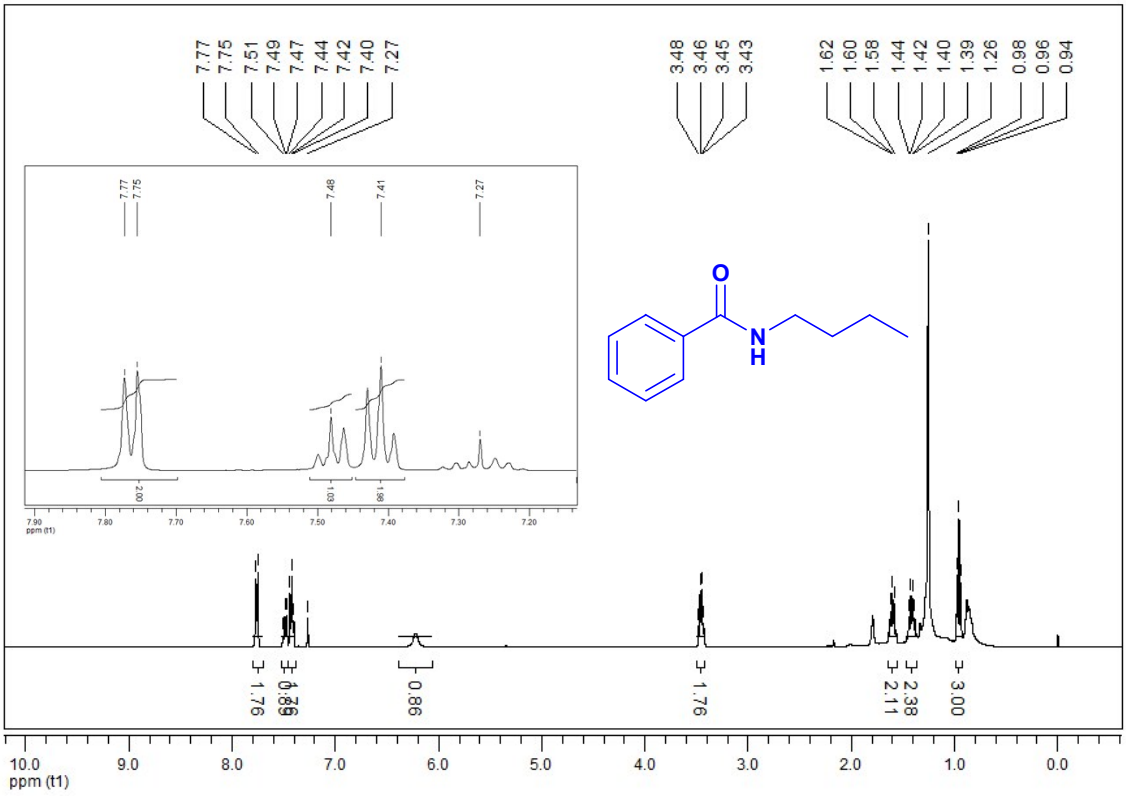
[1]H NMR for N-(n-propyl)-benzamide



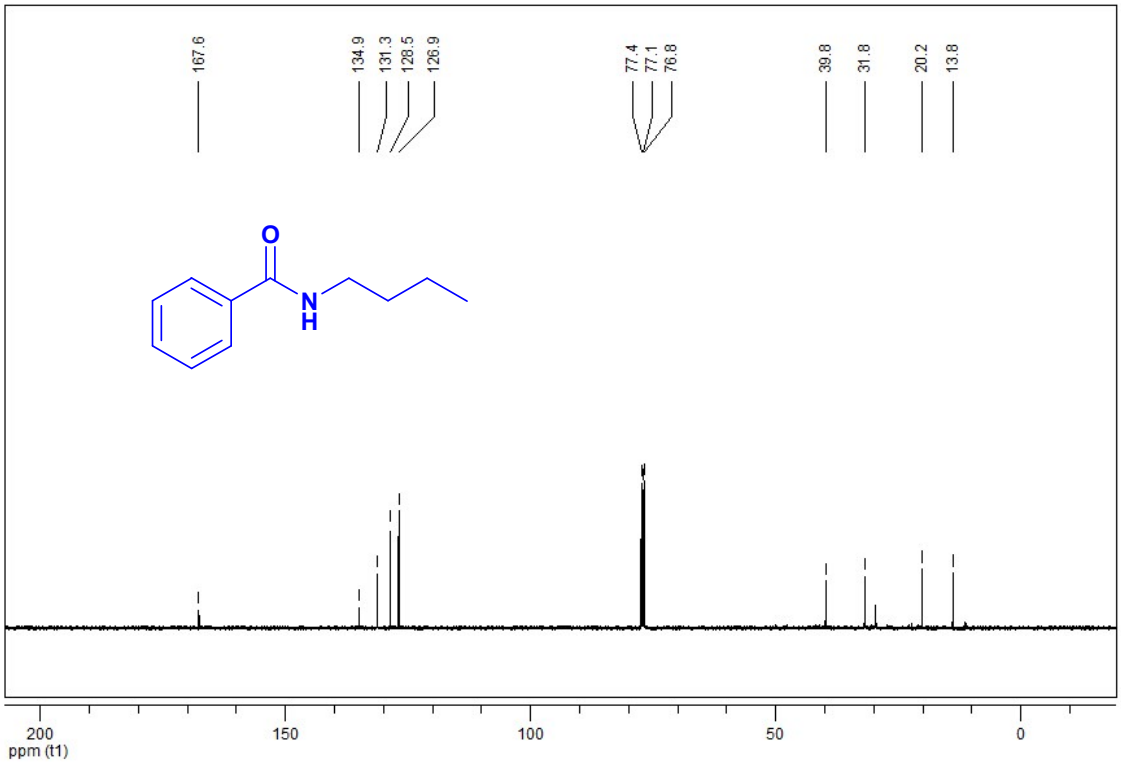
[13]C NMR for N-(n-propyl)-benzamide



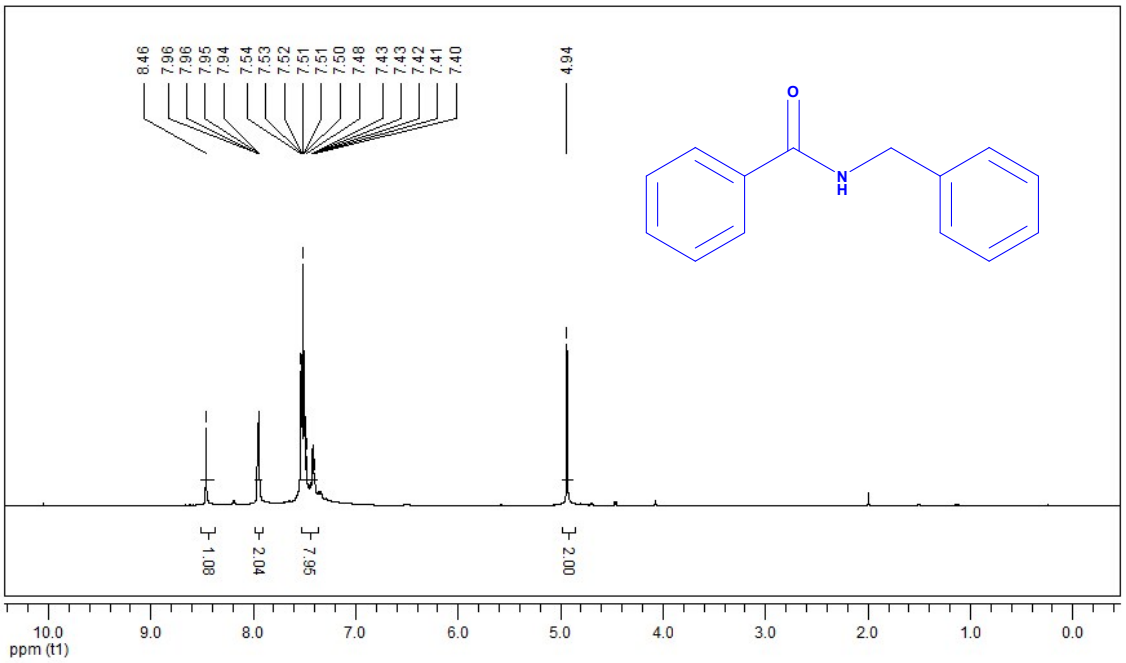
[1]H NMR for N-(n- n-butyl)-benzamide



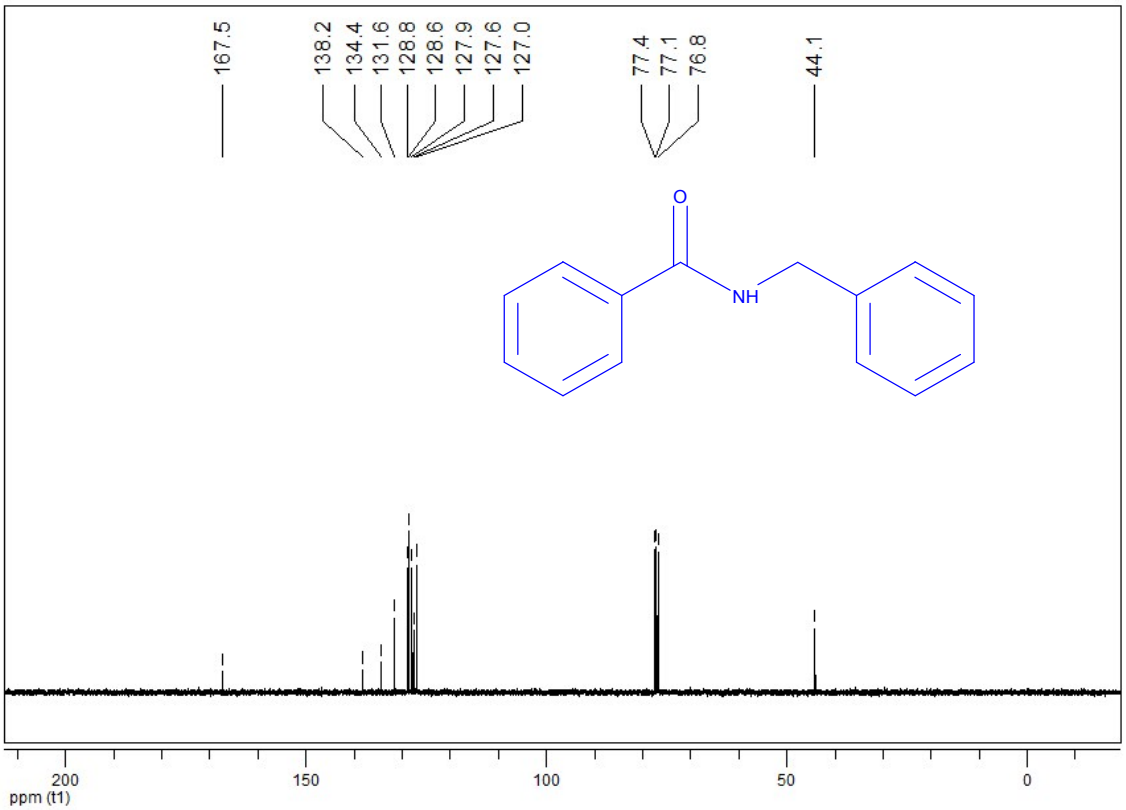
[13]C NMR for N-(n- n-butyl)-benzamide



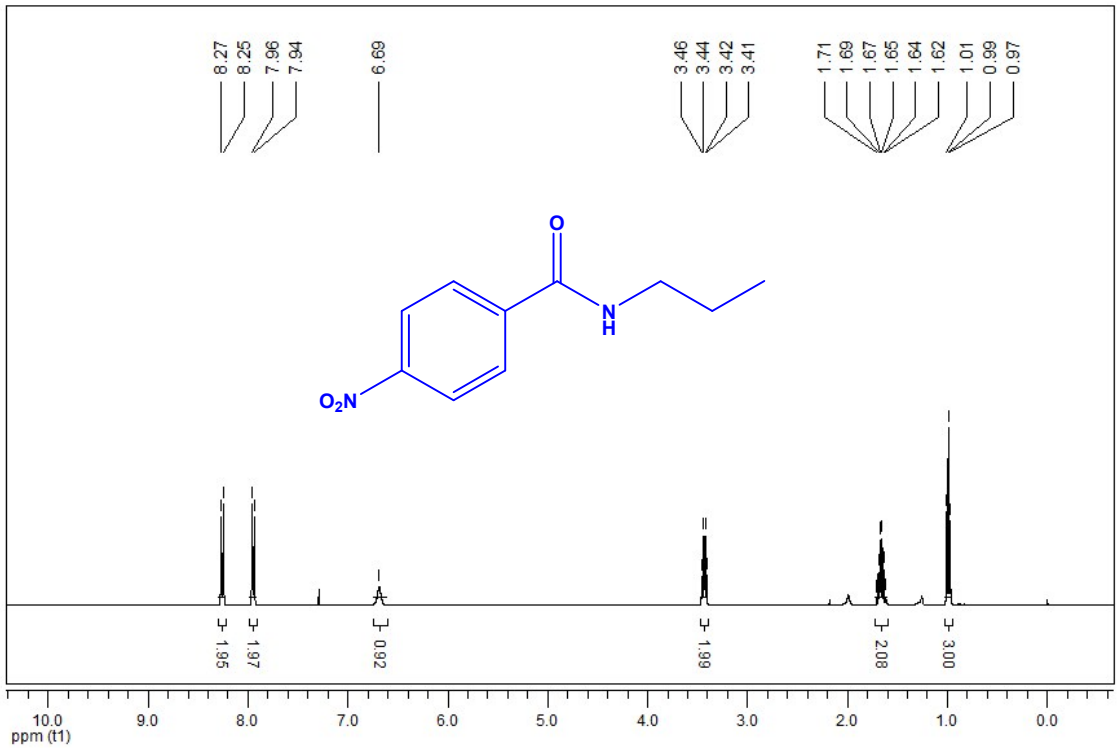
[1]H NMR for N- benzylbenzamide



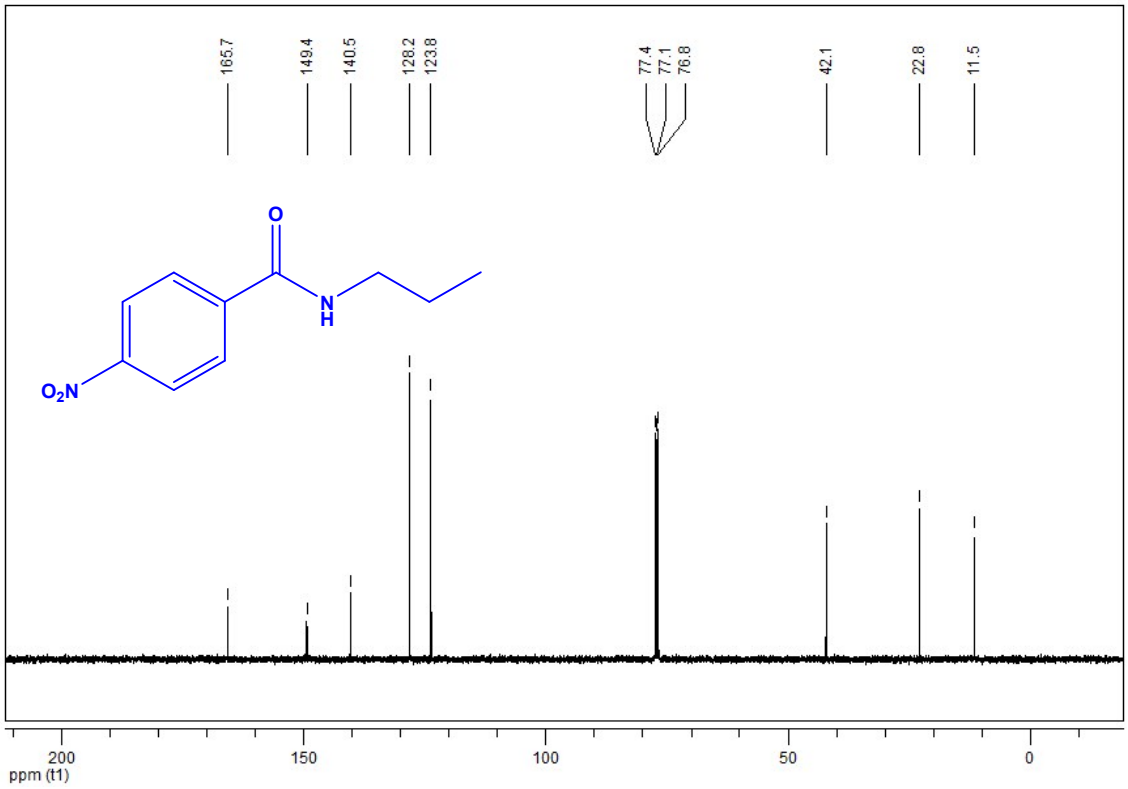
[13]C NMR for N- benzylbenzamide



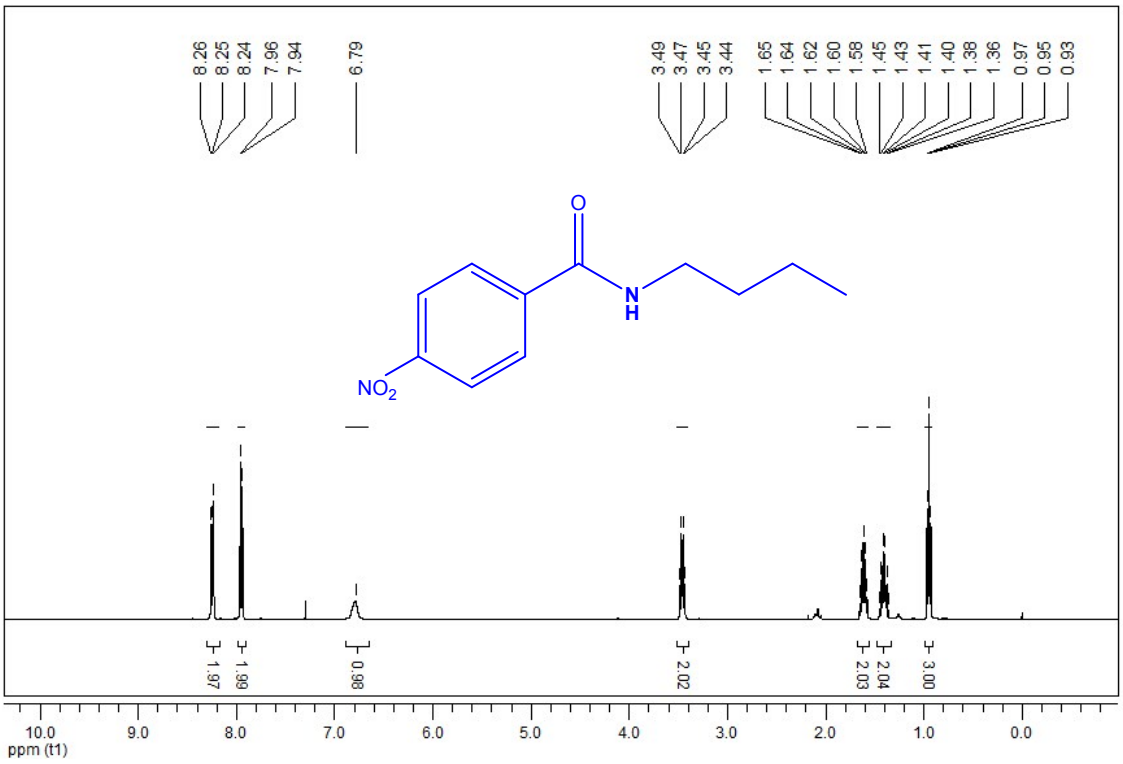
[1]H NMR for 4-nitryl-N-(n-butyl)-benzamide



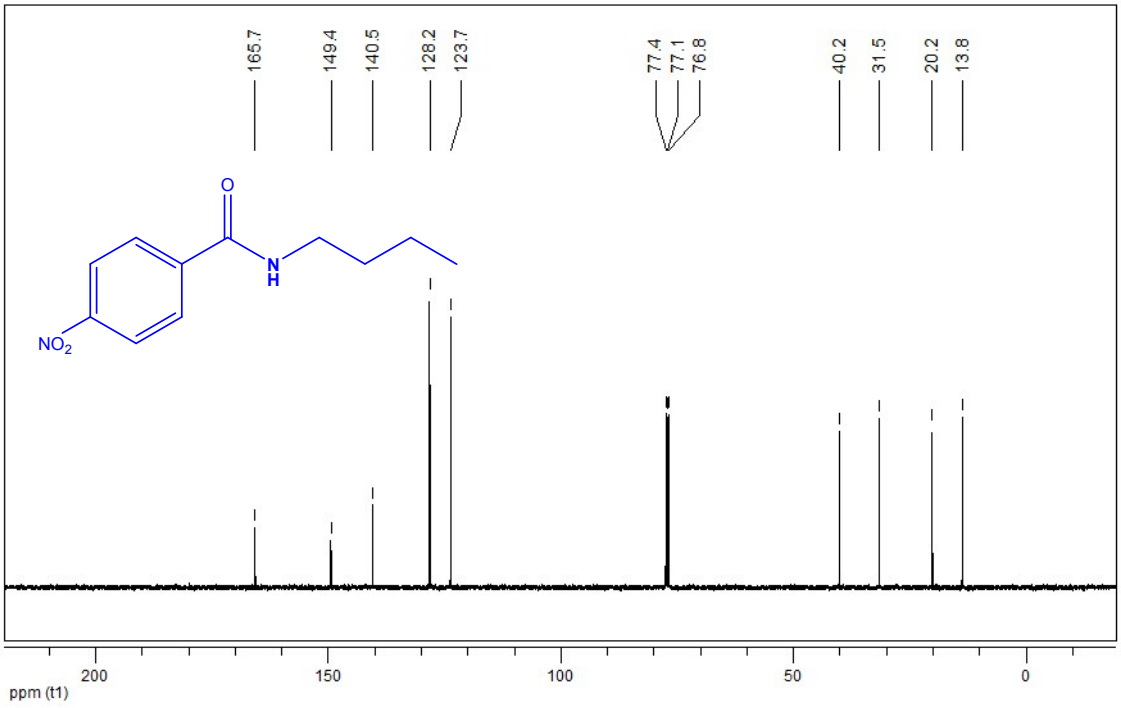
[13]C NMR for 4-nitryl-N-(n-butyl)-benzamide



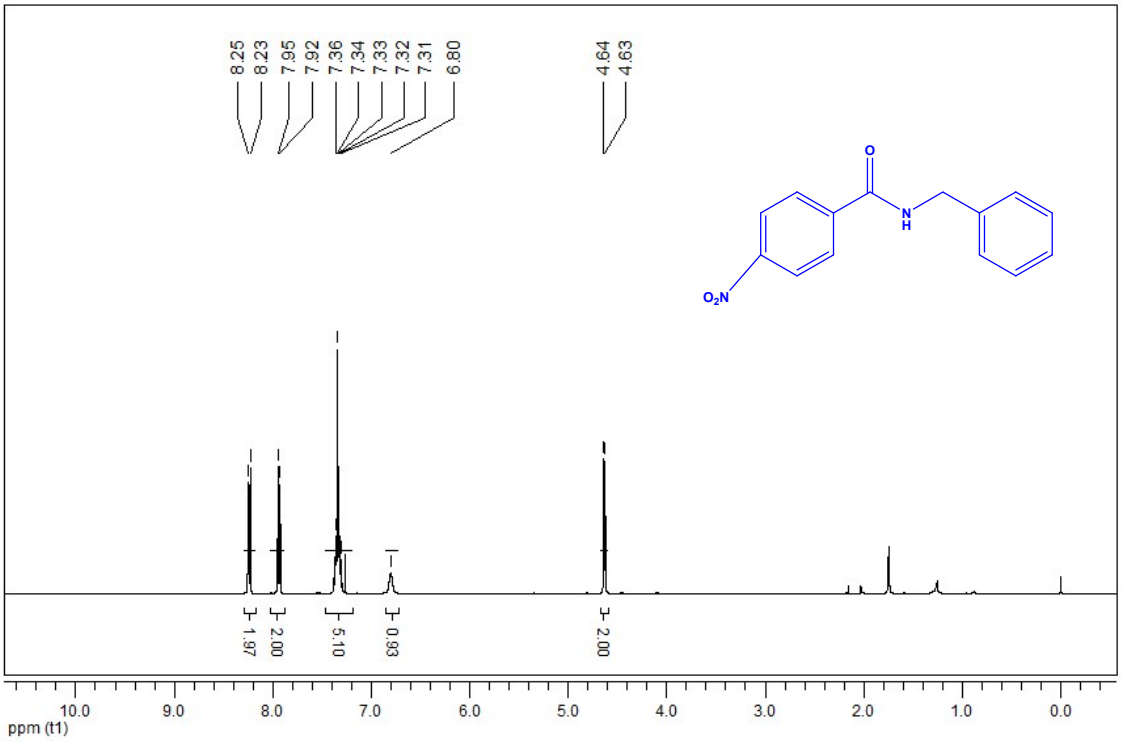
[1]H NMR for 4-nitryl-N-(n-butyl)-benzamide



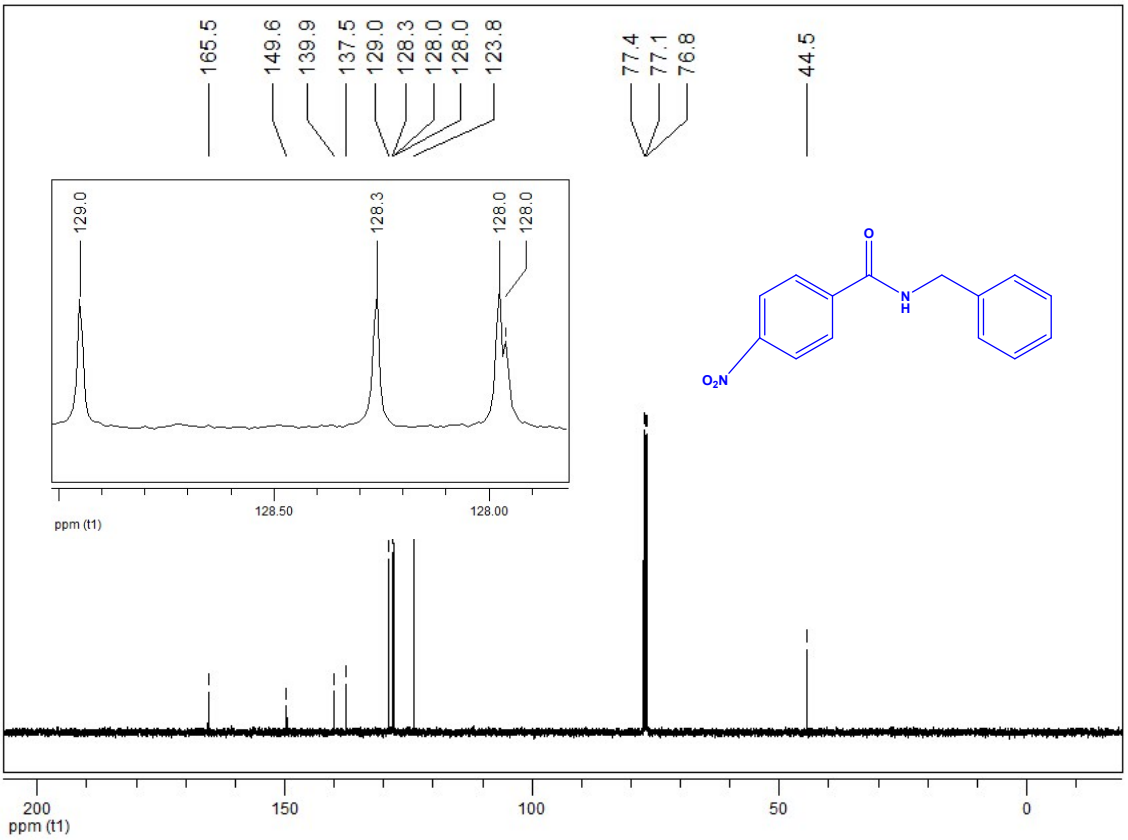
[13]C NMR for 4-nitryl-N-(n-butyl)-benzamide



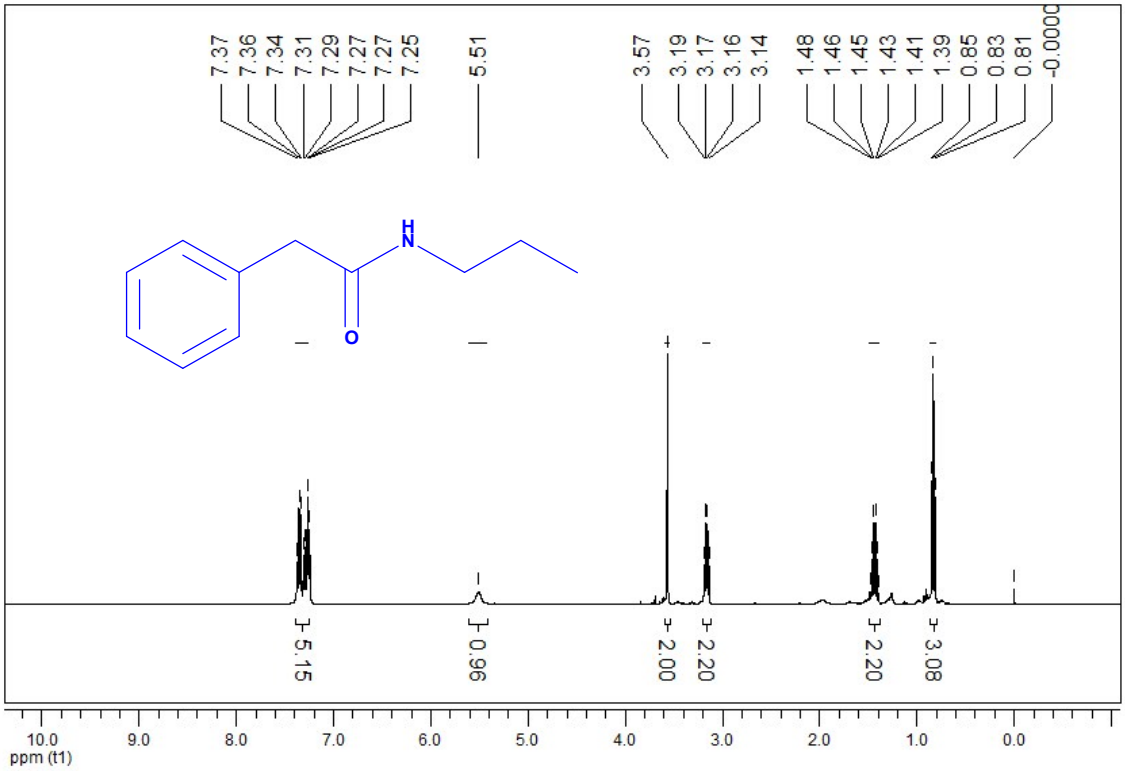
[1]H NMR for 4-nitryl-N-benzylbenzamide



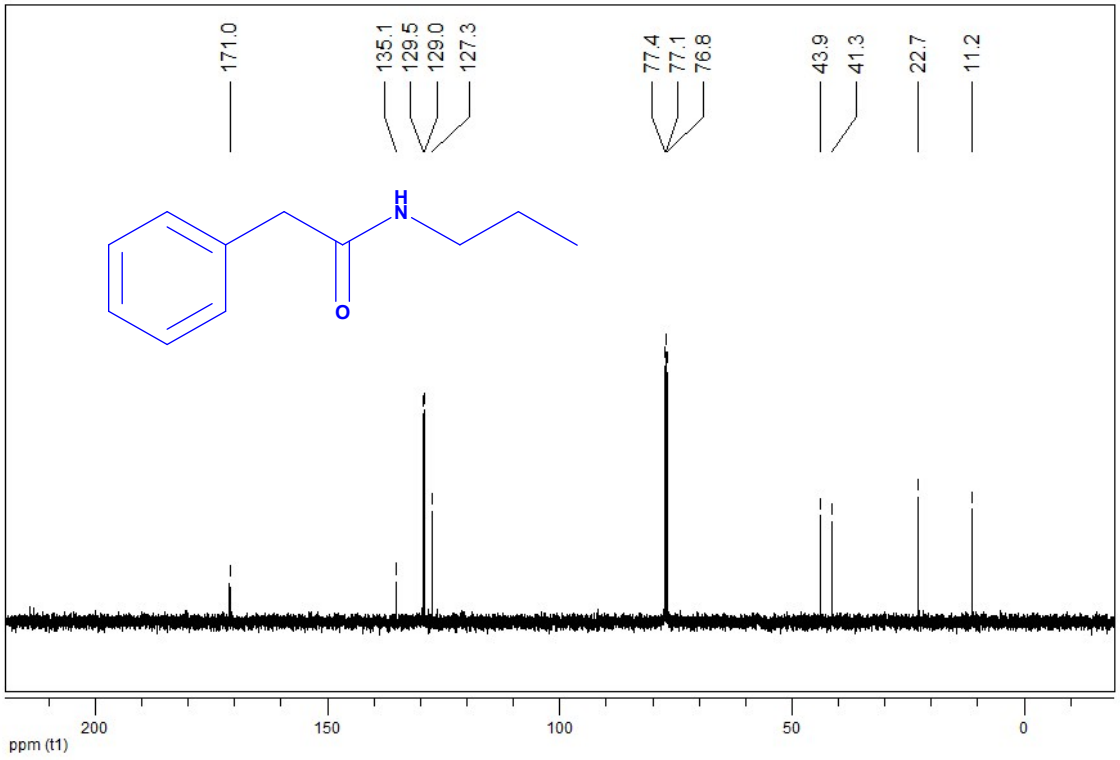
[13]C NMR for 4-nitryl-N-benzylbenzamide



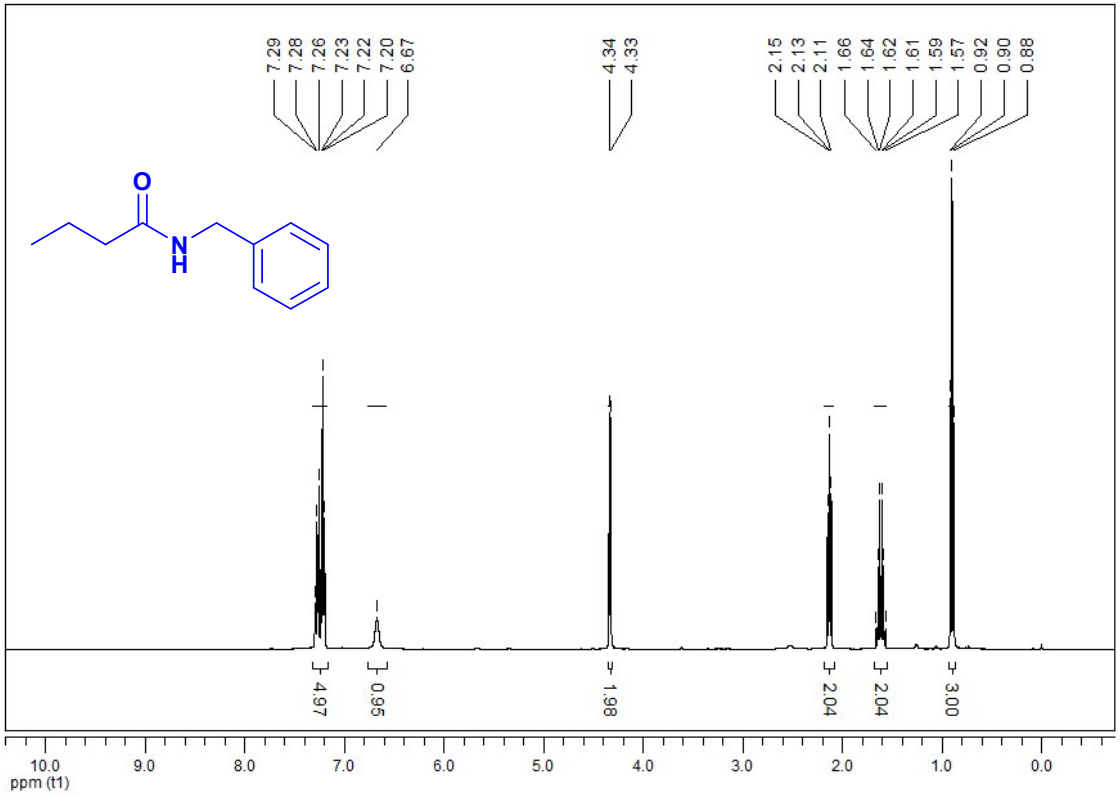
[1]H NMR for N-(n-propyl)- phenylacetamide



[13]C NMR for N-(n-propyl)- phenylacetamide



[1]H NMR for N-benzylbutyramide



[13]C NMR for N-benzylbutyramide