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SUPPORTING INFORMATION

Acetic Acid as a Catalyst for the *N*-Acetylation of Amines Using Acetate Esters as the Acyl Source

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Materials and Methods

Unless preparative details are provided, all reagents were purchased from Alfa Aesar, Acros Organics, Aldrich, Fluka or Lancaster and used without further purification. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F254 aluminium or plastic plates, purchased from Fisher. The organic compounds were visualised under UV (254 nm) irradiation and stained with potassium permanganate dip, followed by gentle heating. Purification of the final products was performed by flash chromatography using the indicated solvent on Aldrich silica gel 60 (230-400 mesh).

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance 250 (250 MHz), a Bruker Avance 300 (300 MHz) or an Agilent 500 (500 MHz) in $CDCl_3$ or DMSO-d_6 as solvents. Chemical shifts (δ) are reported as parts per million (ppm) and are referenced internally to the residual protic solvent signal for $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.50 ppm). Coupling constants (*J*) are reported in Hertz (Hz) and signal multiplicities are reported as singlet (s) , doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), doublet of doublets (dd), multiplet (m), or broad singlet (br s). HRMS-ESI were run on an Agilent 1200 series LC/MSD coupled to a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik).

Infra-red spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with relevant absorbances quoted as ν in cm^{-1}. Optical rotation ($[\alpha]_D$) values were measured at room temperature using an Optical Activity AA-10 Automatic Polarimeter (*c* = 1, $CHCl_3$). Enantiomeric excesses were measured by HPLC using an Agilent 1260 Infinity Quaternary LC System fitted with a Chiralcel OD column (25 cm, 0.8 cm diameter), eluting with HPLC grade hexane and isopropylalcohol. Melting points were determined using Stuart SMP10 melting point equipment using closed end glass capillary tubes and are uncorrected.

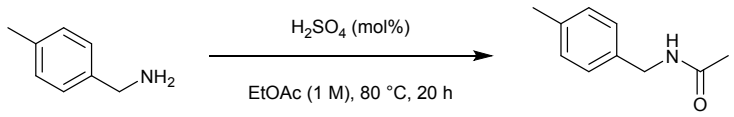
Acetylations

Investigations into the Effect of Sulfuric Acid on Acetylation Reactions

General Procedure I – Sulfuric Acid Catalyst Screen

To an oven dried Radleys carousel tube containing 4-methylbenzylamine (127 µL, 1 mmol) was added ethyl acetate (1 mL, 1 M) followed by the appropriate amount of H_2SO_4 (Table S1). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-(4-methylbenzyl)acetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 3.85 ppm (2H, 4-methylbenzylamine) and 4.39 ppm (2H, *N*-(4-methylbenzyl)acetamide).

Table S1. Effect of sulfuric acid on acetylation reactions.



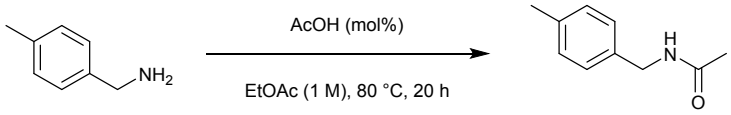
Entry	H_2SO_4 (mol%)	Conversion (%)
1	100	0
2	5	6

Optimisation of the Reaction Conditions - Primary Amines

General Procedure II – Catalyst Loading Screen

To an oven dried Radleys carousel tube containing 4-methylbenzylamine (127 µL, 1 mmol) was added ethyl acetate (1 mL, 1 M) followed by the appropriate amount of acetic acid (Table S2). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-(4-methylbenzyl)acetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 3.85 ppm (2H, 4-methylbenzylamine) and 4.39 ppm (2H, *N*-(4-methylbenzyl)acetamide).

Table S2. Optimisation of the catalyst loading for the acetylation of primary amines.

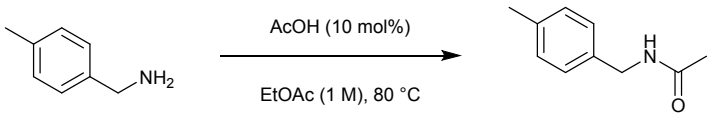


Entry	AcOH (mol%)	Conversion (%)
1	100	100
2	50	100
3	20	100
4	10	100
5	5	98
6	-	Traces

General Procedure III – Reaction Time Screen

To an oven dried Radleys carousel tube containing 4-methylbenzylamine (127 µL, 1 mmol) was added ethyl acetate (1 mL, 1 M) followed by acetic acid (5.7 µL, 10 mol%). The carousel tube was then sealed and the reaction mixture heated at 80 °C for the appropriate number of hours (Table S3). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-(4-methylbenzyl)acetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 3.85 ppm (2H, 4-methylbenzylamine) and 4.39 ppm (2H, *N*-(4-methylbenzyl)acetamide).

Table S3. Optimisation of the reaction time for the acetylation of primary amines.



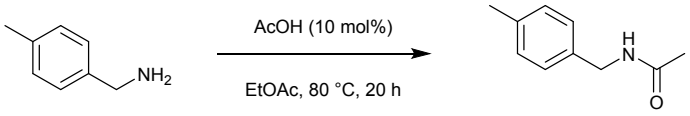
Entry	Time (h)	Conversion (%)
1	20	100
2	16	96
3	12	95
4	8	85

General Procedure IV – Ethyl Acetate Solvent Screen

To an oven dried Radleys carousel tube containing 4-methylbenzylamine (127 µL, 1 mmol) was added the appropriate amount of ethyl acetate (Table S4) followed by acetic acid (5.7 µL, 10 mol%). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary

evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-(4-methylbenzyl)acetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 3.85 ppm (2H, 4-methylbenzylamine) and 4.39 ppm (2H, *N*-(4-methylbenzyl)acetamide).

Table S4. Optimisation of the solvent concentration for the acetylation of primary amines.

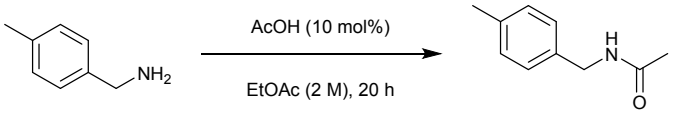


Entry	EtOAc (mL)	Conversion (%)
1	2	100
2	1	100
3	0.5	100
4	0.25	90

General Procedure V – Reaction Temperature Screen

To an oven dried Radleys carousel tube containing 4-methylbenzylamine (127 µL, 1 mmol) was added ethyl acetate (0.5 mL, 2 M) followed by acetic acid (5.7 µL, 10 mol%). The carousel tube was then sealed and the reaction mixture heated at the appropriate temperature for 20 hours (Table S5). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-(4-methylbenzyl)acetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 3.85 ppm (2H, 4-methylbenzylamine) and 4.39 ppm (2H, *N*-(4-methylbenzyl)acetamide).

Table S5. Optimisation of the reaction temperature for the acetylation of primary amines.



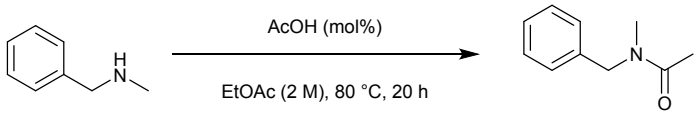
Entry	Temperature (°C)	Conversion (%)
1	80	100
2	60	53
3	40	10

Optimisation of the Reaction Conditions – Secondary Amines

General Procedure VI – Catalyst Loading Screen With Ethyl Acetate

To an oven dried Radleys carousel tube containing *N*-benzylmethylamine (129 µL, 1 mmol) was added ethyl acetate (0.5 mL, 2 M) followed by the appropriate amount of acetic acid (Table S6). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-Benzyl-*N*-methylacetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks of *N*-benzylmethylamine (2H, 3.78 ppm) and *N*-benzyl-*N*-methylacetamide (2H, 4.46 and 4.53 ppm, major and minor rotamers).

Table S6. Optimisation of the catalyst loading for the acetylation of secondary amines, using ethyl acetate as the solvent.

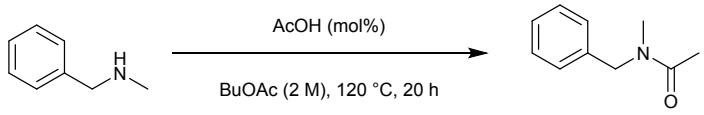


Entry	AcOH (mol%)	Conversion (%)
1	50	32
2	100	45
3	250	31

General Procedure VII – Catalyst Loading Screen With Butyl Acetate

To an oven dried Radleys carousel tube containing *N*-benzylmethylamine (129 µL, 1 mmol) was added butyl acetate (0.5 mL, 2 M) followed by the appropriate amount of acetic acid (Table S7). The carousel tube was then sealed and the reaction mixture heated at 120 °C for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-Benzyl-*N*-methylacetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks of *N*-benzylmethylamine (2H, 3.78 ppm) and *N*-benzyl-*N*-methylacetamide (2H, 4.46 and 4.53 ppm, major and minor rotamers).

Table S7. Optimisation of the catalyst loading for the acetylation of secondary amines, using butyl acetate as the solvent.

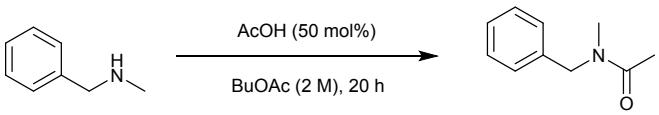


Entry	AcOH (mol%)	Conversion (%)
1	-	Traces
2	10	76
3	25	94
4	50	100
5	100	100

General Procedure VIII – Reaction Temperature Screen

To an oven dried Radleys carousel tube containing *N*-benzylmethylamine (129 µL, 1 mmol) was added butyl acetate (0.5 mL, 2 M) followed by acetic acid (28.6 µL, 50 mol%). The carousel tube was then sealed and the reaction mixture heated at the appropriate temperature for 20 hours (Table S8). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-Benzyl-*N*-methylacetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks of *N*-benzylmethylamine (2H, 3.78 ppm) and *N*-benzyl-*N*-methylacetamide (2H, 4.46 and 4.53 ppm, major and minor rotamers).

Table S8. Optimisation of the reaction temperature for the acetylation of secondary amines.



Entry	Temperature (°C)	Conversion (%)
1	80	44
2	110	96
3	120	100

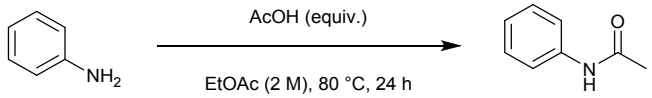
Optimisation of the Reaction Conditions - Anilines

General Procedure IX – Catalyst Loading Screen

To an oven dried Radleys carousel tube containing aniline (91 µL, 1 mmol) was added ethyl acetate (0.5 mL, 2 M) followed by the appropriate amount of acetic acid (Table S9). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 24 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting

crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-phenylacetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 6.50-6.66 ppm (3H, aniline) and 7.28 ppm (2H, *N*-phenylacetamide).

Table S9. Optimisation of the catalyst loading for the acetylation of aniline derivatives.

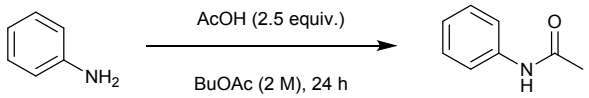


Entry	AcOH (equiv.)	Conversion (%)
1	0.5	16
2	1	37
3	2.5	58

General Procedure X – Reaction Temperature Screen

To an oven dried Radleys carousel tube containing aniline (91 µL, 1 mmol) was added butyl acetate (0.5 mL, 2 M) followed by acetic acid (143 µL, 2.5 equiv.). The carousel tube was then sealed and the reaction mixture heated at the appropriate temperature for 24 hours (Table S10). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-phenylacetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 6.50-6.66 ppm (3H, aniline) and 7.28 ppm (2H, *N*-phenylacetamide).

Table S10. Optimisation of the reaction temperature for the acetylation of aniline derivatives.



Entry	Temperature (°C)	Conversion (%)
1	80	60
2	100	86
3	110	>99
4	120	96
5	130	93

Synthesis of Acetamides

General Procedure XI – Acetylation of Primary Amines

To an oven dried Radleys carousel tube containing the appropriate primary amine (2 mmol) was added ethyl acetate (1 mL, 2 M) followed by acetic acid (11.4 µL, 10 mol%). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude amide product was purified by silica column chromatography.

General Procedure XII – Acetylation of Secondary Amines

To an oven dried Radleys carousel tube containing the appropriate secondary amine (2 mmol) was added butyl acetate (1 mL, 2 M) followed by acetic acid (57.2 µL, 50 mol%). The carousel tube was then sealed and the reaction mixture heated at 120 °C for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude amide product was purified by silica column chromatography.

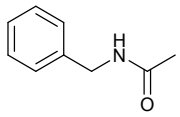
General Procedure XIII – Acetylation of Anilines

To an oven dried Radleys carousel tube containing the appropriate aniline (2 mmol) was added butyl acetate (1 mL, 2 M) followed by acetic acid (286 µL, 2.5 equiv.). The carousel tube was then sealed and the reaction mixture heated at 110 °C for 24 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude amide product was purified by silica column chromatography.

General Procedure XIV - Scale-up Example

To a round bottomed flask containing benzylamine (7.3 mL, 67 mmol) was added ethyl acetate (34 mL, 2 M) followed by acetic acid (0.38 mL, 10 mol%). The round bottomed flask was then sealed and the reaction mixture heated at 80 °C for 22 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude amide product was purified by silica column chromatography.

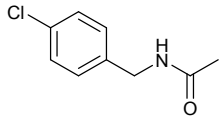
***N*-Benzylacetamide**[1] **(1a)**



Following general procedure XI, benzylamine (218 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (95:5, DCM/MeOH, R_f 0.37) as an off-white solid (283 mg, 95%).

mp 61-63 °C (lit.[1] 61 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.22 (m, 5H, *Ph*), 6.14 (s, 1H, N*H*), 4.39 (d, *J* = 4.4 Hz, 2H, CH_2), 1.98 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 138.3, 128.6, 127.8, 127.4, 43.7, 23.2; HRMS-ESI calcd for $[C_9H_{11}NONa]^+$: 172.0738 $[M+Na]^+$. Found: 172.0758; FT-IR (neat) ν in cm^{-1}: 1640 (C=O stretch).

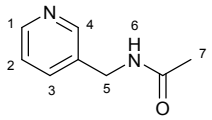
***N*-(4-Chlorobenzyl)acetamide**[2] **(1b)**



Following general procedure XI, 4-chlorobenzylamine (243 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (94:6, DCM/MeOH, R_f 0.31) as a beige solid (343 mg, 93%).

mp 107-108 °C (lit.[2] 106-108 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 (d, *J* = 8.4 Hz, 2H, *m*-CH_{Ar}), 7.21 (d, *J* = 8.3 Hz, 2H, *o*-CH_{Ar}), 5.80 (s, 1H, N*H*), 4.39 (d, *J* = 5.9 Hz, 2H, CH_2), 2.02 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.0, 136.8, 133.3, 129.1, 128.8, 43.0, 23.2; HRMS-ESI calcd for $[C_9H_{10}ClNONa]^+$: 206.0349 $[M+Na]^+$. Found: 206.0376; FT-IR (neat) ν in cm^{-1}: 1638 (C=O stretch).

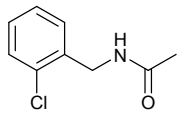
***N*-(Pyridin-3-ylmethyl)acetamide**[3] **(1c)**



Following general procedure XI, 3-picolylamine (204 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (88:12, DCM/MeOH, R_f 0.32) as a yellow oil (271 mg, 90%).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.52 – 8.47 (m, 2H, *1* & *4*), 7.63 (d, *J* = 7.8 Hz, 1H, *3*), 7.28 – 7.21 (m, 1H, *2*), 6.19 (br s, 1H, *6*), 4.43 (d, *J* = 5.9 Hz, 2H, *5*), 2.02 (s, 3H, *7*) ; ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.4, 149.1, 148.8, 135.8, 134.3, 123.7, 41.1, 23.2; HRMS-ESI calcd for $[C_8H_{11}N_2O]^+$: 151.0871 $[M+H]^+$. Found: 151.0871; FT-IR (neat) ν in cm^{-1}: 1648 (C=O stretch).

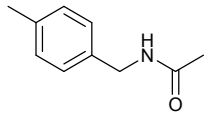
***N*-(2-Chlorobenzyl)acetamide[4] (1d)**



Following general procedure XI, 2-chlorobenzylamine (241 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (96:4, DCM/MeOH, R_f 0.30) as a white solid (348 mg, 95%).

mp 72-74 °C (lit.[4] 71-73 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.35 (m, 2H, CH_{Ar}), 7.25-7.22 (m, 2H, CH_{Ar}), 5.87 (s, 1H, N*H*), 4.53 (d, *J* = 6.0 Hz, 2H, CH_2), 2.02 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1, 135.7, 133.5, 130.0, 129.4, 128.8, 127.0, 41.5, 23.1; HRMS-ESI calcd for $[C_9H_{10}ClNONa]^+$: 206.0348 $[M+Na]^+$. Found: 206.0359; FT-IR (neat) ν in cm^{-1}: 1639 (C=O stretch).

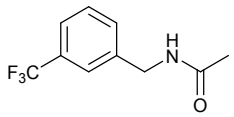
***N*-(4-Methylbenzyl)acetamide[1] (1e)**



Following general procedure XI, 4-methylbenzylamine (255 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (94:6, DCM/MeOH, R_f 0.32) as a beige solid (323 mg, 99%).

mp 112-114 °C (lit.[1] 111 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 – 7.12 (m, 4H, CH_{Ar}), 5.76 (s, 1H, N*H*), 4.38 (d, *J* = 5.6 Hz, 2H, CH_2), 2.33 (s, 3H, PhCH_3), 2.00 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 137.3, 135.2, 129.4, 127.9, 43.5, 23.3, 21.1; HRMS-ESI calcd for $[C_{10}H_{13}NONa]^+$: 186.0895 $[M+Na]^+$. Found: 186.0910; FT-IR (neat) ν in cm^{-1}: 1633 (C=O stretch).

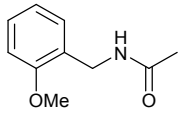
***N*-(3-(Trifluoromethyl)benzyl)acetamide[5] (1h)**



Following general procedure XI, 3-(trifluoromethyl)benzylamine (287 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (93:7, DCM/MeOH, R_f 0.31) as a yellow-white solid (420 mg, 97%).

mp 56-57 °C (lit.[5] 56-57 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 – 7.35 (m, 4H, CH_{Ar}), 6.67 (s, 1H, N*H*), 4.39 (d, *J* = 6.0 Hz, 2H, CH_2), 1.95 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 170.5, 139.6, 131.1, 131.0 (q, J_{CF} = 32.2 Hz), 129.2, 124.3 (q, J_{CF} = 3.8 Hz), 124.2 (q, J_{CF} = 3.8 Hz), 124.1 (q, J_{CF} = 272.2 Hz), 43.1, 23.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -62.67; HRMS-ESI calcd for $[C_{10}H_{10}F_3NONa]^+$: 240.0612 $[M+Na]^+$. Found: 240.0605; FT-IR (neat) ν in cm^{-1}: 1628 (C=O stretch).

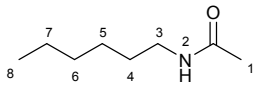
***N*-(2-Methoxybenzyl)acetamide[4] (1i)**



Following general procedure XI, 2-methoxybenzylamine (261 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (95:5, DCM/MeOH, R_f 0.26) as a yellow solid (333 mg, 93%).

mp 93-95 °C (lit.[4] 91-93 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 – 7.21 (m, 2H, *o*-C*H*$_{Ar}$ and *p*-C*H*$_{Ar}$), 6.94 – 6.83 (m, 2H, *m*-C*H*$_{Ar}$), 6.12 (s, 1H, N*H*), 4.40 (d, *J* = 5.8 Hz, 2H, C*H*$_2$), 3.84 (s, 3H, OC*H*$_3$), 1.95 (s, 3H, C(O)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 157.5, 129.8, 128.9, 126.3, 120.7, 110.3, 55.3, 39.4, 23.4; HRMS-ESI calcd for $[C_{10}H_{13}NO_2Na]^+$: 202.0844 $[M+Na]^+$. Found: 202.0851; FT-IR (neat) ν in cm^{-1}: 1646 (C=O stretch).

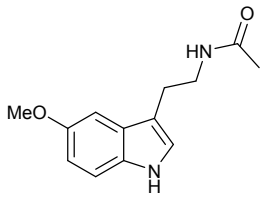
***N*-Hexylacetamide[6] (1j)**



Following general procedure XI, hexylamine (264 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (96:4, DCM/MeOH, R_f 0.36) as a colourless oil (276 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.86 (s, 1H, *2*), 3.18 (td, *J* = 7.2, 5.9 Hz, 2H, *3*), 1.93 (s, 3H, *1*), 1.47 – 1.42 (m, 2H, *4*), 1.29 – 1.22 (m, 6H, *5-7*), 0.84 (t, *J* = 6.7 Hz, 3H, *8*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.2, 39.7, 31.4, 29.5, 26.6, 23.2, 22.5, 13.9; HRMS-ESI calcd for $[C_8H_{16}NO]^+$: 142.1226 $[M-H]^-$. Found: 142.1251; FT-IR (neat) ν in cm^{-1}: 1649 (C=O stretch).

***N*-(2-(5-Methoxy-1H-indol-3-yl)ethyl)acetamide[7] (1k)**

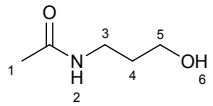


Following general procedure XI, 5-methoxytryptamine (380 mg, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (94:6, DCM/MeOH, R_f 0.31) as a dark brown oil (324 mg, 70%).

^{1}H NMR (500 MHz, DMSO-d^6): δ 10.63 (br s, 1H, CHN*H*), 7.92 (br s, 1H, CH$_2$N*H*), 7.22 (d, *J* = 8.7 Hz, 1H, NHCC*H*), 7.09 (s, 1H, C*H*$_{Ar}$), 7.01 (s, 1H, C*H*$_{Ar}$), 6.71 (d, *J* = 8.7 Hz, 1H, CH$_3$OCC*H*), 3.78 (s, 3H,

OCH_3), 3.30 (q, *J* = 7.0 Hz, 2H, CH_2NH), 2.77 (t, *J* = 7.4 Hz, 2H, CCH_2), 1.81 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, DMSO-d^6): δ 169.4, 153.4, 131.8, 128.0, 123.7, 112.4, 112.1, 111.5, 100.6, 55.8, 40.2, 25.7, 23.2; HRMS-ESI calcd for $[C_{13}H_{16}N_2O_2Na]^+$: 255.1109 $[M+Na]^+$. Found: 255.1116; FT-IR (neat) ν in cm^{-1}: 1627 (C=O stretch).

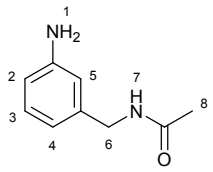
_N_-(3-Hydroxypropyl)acetamide[8] (1m)



Following general procedure XI, 3-amino-1-propanol (150 mg, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (90:10, DCM/MeOH) as a colourless oil (209 mg, 89%).

R_f (80:20, DCM/MeOH) 0.24; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.01 (br s, 1H, *2*), 3.64 (t, 2H, *5*), 3.40 (q, *J* = 6.1 Hz, 2H, *3*), 3.25 (br s, 1H, *6*), 2.00 (s, 3H, *1*), 1.71 – 1.65 (m, 2H, *4*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 171.4, 59.3, 36.4, 32.2, 23.1; HRMS-ESI calcd for $[C_5H_{12}NO_2]^+$: 118.0868 $[M+H]^+$. Found: 118.0881; FT-IR (neat) ν in cm^{-1}: 1625 (C=O stretch), 3287 (O-H stretch).

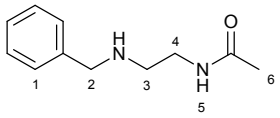
_N_-(3-Aminobenzyl)acetamide[9] (1n)



Following general procedure XI, 3-aminobenzylamine (244 mg, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (91:9, DCM/MeOH, R_f 0.28) as a orange-brown solid (308 mg, 94%).

mp 97-99 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (t, *J* = 7.6 Hz, 1H, *3*), 6.68 – 6.63 (m, 1H, *5*), 6.63 – 6.57 (m, 2H, *2* & *4*), 5.66 (s, 1H, *7*), 4.34 (d, *J* = 5.6 Hz, 2H, *6*), 3.69 (s, 2H, *1*), 2.02 (s, 3H, *8*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 169.8, 146.8, 139.4, 129.6, 117.9, 114.4, 114.2, 43.8, 23.3; HRMS-ESI calcd for $[C_{18}H_{24}N_4O_2Na]^+$: 351.1797 $[2M+Na]^+$. Found: 351.1747; FT-IR (neat) ν in cm^{-1}: 1617 (C=O stretch).

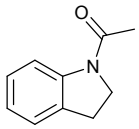
***N*-(2-(Benzylamino)ethyl)acetamide[10] (1o)**



Following general procedure XI, *N*-benzylethylenediamine (300 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (90:10, DCM/MeOH) as a viscous yellow oil (346 mg, 90%).

R_f (85:15, DCM/MeOH) 0.28; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.24 (m, 5H, *1*), 6.05 (br s, 1H, *5*), 3.79 (s, 2H, *2*), 3.34 (q, *J* = 5.5 Hz, 2H, *4*), 2.78 (t, *J* = 5.8 Hz, 2H, *3*), 1.97 (s, 3H, *6*); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.6, 139.7, 128.5, 128.1, 127.1, 53.5, 48.0, 39.1, 23.1; HRMS-ESI calcd for $[C_{11}H_{17}N_2O]^+$: 193.1341 $[M+H]^+$. Found: 193.1324; FT-IR (neat) ν in cm^{-1}: 1638 (C=O stretch).

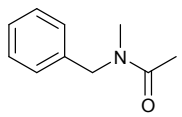
1-(Indolin-1-yl)ethan-1-one[11] (2a)



Following general procedure XII, indoline (224 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (97:3, DCM/MeOH, R_f 0.31) as a brown solid (251 mg, 78%).

mp 98-100 °C (lit.[11] mp 100-102 °C); ^{1}H NMR (500 MHz, DMSO-d^6): δ 8.03 (d, *J* = 8.0 Hz, 1H, CH_{Ar}), 7.21 (d, *J* = 7.2 Hz, 1H, CH_{Ar}), 7.13 (t, *J* = 7.6 Hz, 1H, CH_{Ar}), 6.97 (t, *J* = 7.4 Hz, 1H, CH_{Ar}), 4.07 (t, *J* = 8.5 Hz, 2H, NCH_2), 3.12 (t, *J* = 8.5 Hz, 2H, NCH_2CH_2), 2.14 (s, 3H, CH_3); ^{13}C NMR (126 MHz, DMSO-d^6): δ 168.5, 142.9, 131.7, 126.9, 124.7, 123.0, 115.8, 48.1, 27.3, 24.0; HRMS-ESI calcd for $[C_{10}H_{11}NONa]^+$: 184.0738 $[M+Na]^+$. Found: 184.0737; FT-IR (neat) ν in cm^{-1}: 1642 (C=O stretch).

***N*-Benzyl-*N*-methylacetamide[12] (2b)**

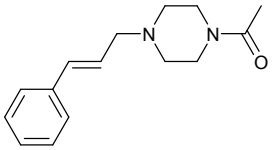


Following general procedure XII, *N*-benzylmethylamine (258 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (96:4, DCM/MeOH, R_f 0.33) as a yellow-brown oil (296 mg, 91%). The product was observed as two rotamers in its ^{1}H and ^{13}C NMR spectra.

^{1}H NMR (500 MHz, DMSO-d^6): δ 7.36 – 7.16 (m, 5H, *Ph*), 4.53 (s, 2H, minor rotamer, CH_2), 4.46 (s, 2H, major rotamer, CH_2), 2.88 (s, 3H, major rotamer, NCH_3), 2.77 (s, 3H, minor rotamer, NCH_3), 2.04 (s, 3H, major rotamer, C(O)CH_3), 2.02 (s, 3H, minor rotamer, C(O)CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ

170.3 (major rotamer), 170.3 (minor rotamer), 138.3 (major rotamer), 138.0 (minor rotamer), 129.2 (minor rotamer), 128.8 (major rotamer), 127.9 (major rotamer), 127.6 (minor rotamer), 127.4 (minor rotamer), 127.0 (major rotamer), 53.7 (minor rotamer), 50.1 (major rotamer), 35.8 (major rotamer), 33.6 (minor rotamer), 22.0 (major rotamer), 21.7 (minor rotamer); HRMS-ESI calcd for $[C_{10}H_{13}NONa]^+$: 186.0895 $[M+Na]^+$. Found: 186.0897; FT-IR (neat) ν in cm^{-1}: 1638 (C=O stretch).

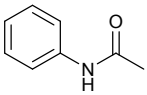
1-(4-Cinnamylpiperazin-1-yl)ethan-1-one (2c)



Following general procedure XII, 1-cinnamylpiperazine (405 mg, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (88:12, DCM/MeOH, R_f 0.31) as a dark brown oil (451 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45-7.42 (m, 2H, *m*-CH_{Ar}), 7.35 – 7.29 (m, 2H, *o*-CH_{Ar}), 7.26 – 7.21 (m, 1H, *p*-CH_{Ar}), 6.53 (d, *J* = 16.0 Hz, 1H, PhC*H*), 6.30 (dt, *J* = 15.9, 6.6 Hz, 1H, PhCHC*H*), 3.48 – 3.39 (m, 4H, C(O)NCH_2), 3.13 – 3.07 (m, 2H, CHCH_2), 2.39 (t, *J* = 5.0 Hz, 2H, CH_2NCH_2), 2.34 (t, *J* = 5.1 Hz, 2H, CH_2NCH_2), 1.98 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.1, 136.6, 132.3, 128.5, 127.4, 126.7, 126.2, 60.0, 52.8, 52.3, 45.6, 40.8, 21.2; HRMS-ESI calcd for $[C_{15}H_{20}N_2ONa]^+$: 267.1473 $[M+Na]^+$. Found: 267.1480; FT-IR (neat) ν in cm^{-1}: 1627 (C=O stretch).

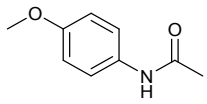
***N*-Phenylacetamide[13] (3a)**



Following general procedure XIII, aniline (182 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (95:5, DCM/MeOH, R_f 0.30) as a pale brown solid (249 mg, 92%).

mp 114-116 °C (lit.[13] 114-115 °C); ^{1}H NMR (500 MHz, DMSO-d^6): δ 9.90 (br s, 1H, N*H*), 7.57 (d, *J* = 8.0 Hz, 2H, *o*-CH_{Ar}), 7.28 (t, *J* = 7.7 Hz, 2H, *m*-CH_{Ar}), 7.01 (t, *J* = 7.4 Hz, 1H, *p*-CH_{Ar}), 2.04 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, DMSO-d^6): δ 168.2, 139.3, 128.6, 122.9, 118.9, 23.98; HRMS-ESI calcd for $[C_8H_{10}NO]^+$: 136.0762 $[M+H]^+$. Found: 136.0773; FT-IR (neat) ν in cm^{-1}: 1662 (C=O stretch).

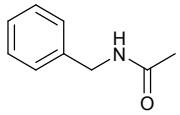
***N*-(4-Methoxyphenyl)acetamide**[13] **(3b)**



Following general procedure XIII, *p*-anisidine (246 mg, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (95:5, DCM/MeOH, R_f 0.26) as a brown solid (290 mg, 88%).

mp 129-130 °C (lit.[13] 128-129 °C); ^{1}H NMR (500 MHz, DMSO-d^6): δ 9.76 (br s, 1H, N*H*), 7.48 (d, *J* = 8.9 Hz, 2H, *o*-CH_{Ar}), 6.86 (d, *J* = 8.9 Hz, 2H, *m*-CH_{Ar}), 3.71 (s, 3H, OCH_3), 2.00 (s, 3H, C(O)CH_3); ^{13}C NMR (126 MHz, DMSO-d^6): δ 167.7, 155.0, 132.5, 120.5, 113.8, 55.1, 23.8; ESI-MS of $[C_9H_{11}NO_2]^+$; HRMS-ESI calcd for $[C_9H_{12}NO_2]^+$: 166.0868 $[M+H]^+$. Found: 166.0887; FT-IR (neat) ν in cm^{-1}: 1646 (C=O stretch).

***N*-Benzylacetamide**[14] **(1a)**



Following general procedure XIV, benzylamine (7.3 mL, 67 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (95:5, DCM/MeOH, R_f 0.37) as an off-white solid (9.18 g, 92%).

mp 61-63 °C (lit.[14] 61 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.21 (m, 5H, *Ph*), 6.18 (s, 1H, N*H*), 4.37 (d, *J* = 4.4 Hz, 2H, CH_2), 1.97 (s, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.1, 138.4, 128.7, 127.9, 127.5, 43.8, 23.2; HRMS-ESI calcd for $[C_9H_{11}NONa]^+$: 172.0738 $[M+Na]^+$. Found: 172.0752; FT-IR (neat) ν in cm^{-1}: 1642 (C=O stretch).

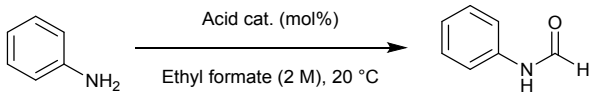
Formamides and Other Amides

Optimisation of the Reaction Conditions – Ethyl Formate

General Procedure XV

To an oven dried Radleys carousel tube containing aniline (91 µL, 1 mmol) was added ethyl formate (0.5 mL, 2 M) followed by the appropriate amount of either formic acid or acetic acid. The carousel tube was then sealed and the reaction mixture heated at 20 °C for the appropriate amount of hoursm (Table S11). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-phenylformamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 6.50-6.66 ppm (3H, aniline) and 7.26-7.37 ppm (2H, major and minor rotamers, *N*-phenylformamide).

Table S11. Optimisation for the formylation of aniline.



Entry	Acid	Acid (mol%)	Time (h)	Conversion (%)
1	-	-	20	36
2	Formic acid	10	20	94
3	Formic acid	20	20	97
4	Formic acid	50	20	100
5	Acetic acid	50	20	100
6	Formic acid	50	16	100
7	Acetic acid	50	16	100

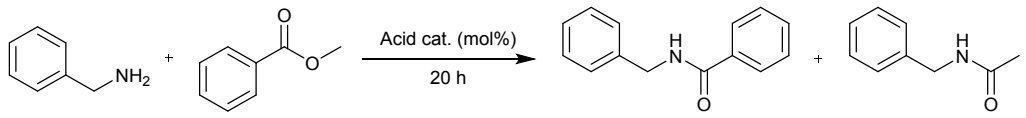
Optimisation of the Reaction Conditions – 4-Methyl Benzoate

General Procedure XVI

To an oven dried Radleys carousel tube containing benzylamine (109 µL, 1 mmol) was added methyl benzoate followed by the appropriate amount of acetic acid. The carousel tube was then sealed and the reaction mixture heated at the appropriate temperature for 20 hours (Table S12). After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude reaction mixture was analysed by ^{1}H NMR. Percentage conversion into *N*-benzylbenzamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 3.92 ppm (2H, benzylamine) and 4.66 ppm (2H, *N*-benzylbenzamide). Percentage conversion into *N*-benzylacetamide was calculated from the crude ^{1}H NMR spectra by comparison of the peaks at 3.92

ppm (2H, benzylamine) and 4.44 ppm (2H, *N*-benzylacetamide). Total conversion was calculated by the addition of the percentage conversions into *N*-benzylbenzamide and *N*-benzylacetamide.

Table S12. Optimisation for the reaction of methyl benzoate and benzylamine.



8a **8b**

Entry	Acid (mol%)	Temperature (°C)	Equivalents of Ester	Conversion into 8a (%)	Conversion into 8b (%)	Total Conversion (%)
1	10	110	1	23	5	28
2	10[a]	110	1	6	3	9
3	50	110	1	17	21	38
4	50[a]	110	1	7	13	20
5	10[a]	110	3	5	1	6
6	10	120	3	17	3	20
7	10	120	4	16	2	8
8	20	120	4	11	3	14
9	10	150	1	32	6	38
10	10	150	3	18	2	20

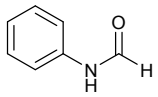
[a] Reaction performed in toluene (2M).

Synthesis of Formamides

General Procedure XVII

To an oven dried Radleys carousel tube containing the appropriate aniline (2 mmol), was added ethyl formate (1 mL, 2 M) followed by acetic acid (28.6 µL, 50 mol%). The carousel tube was then sealed and the reaction mixture heated at 20 °C for 16 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude amide product was purified by silica column chromatography.

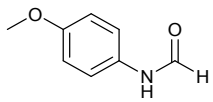
N-Phenylformamide[15] (7d)



Following general procedure XVII, aniline (182 µL, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (95:5, DCM/MeOH, R_f 0.30) as a colourless oil (228 mg, 94%).

^{1}H NMR (300 MHz, DMSO-d^6): δ 10.16 (m, 1H, minor and major rotamers, N*H*), 8.79 (d, *J* = 11.0 Hz, 1H, minor rotamer, *CHO*), 8.27 (d, *J* = 1.9 Hz, 1H, major rotamer, C*H*O), 7.59 (d, *J* = 7.6 Hz, 2H, major rotamer, *o*-CH_{Ar}), 7.37 – 7.26 (m, 2H, minor and major rotamers, *m*-CH_{Ar}), 7.19 (d, *J* = 7.5 Hz, 2H, minor rotamer, *o*-CH_{Ar}), 7.11 – 7.02 (m, 1H, minor and major rotamers, *p*-CH_{Ar}); ^{13}C NMR (75 MHz, DMSO-d^6): δ 162.6 (minor rotamer), 159.6 (major rotamer), 138.4 (minor rotamer), 138.3 (major rotamer), 129.4 (minor rotamer), 128.9 (major rotamer), 123.7 (minor rotamer), 123.6 (major rotamer), 119.1 (major rotamer), 117.5 (minor rotamer); HRMS-ESI calcd for $[C_7H_7NONa]^+$: 144.0425 $[M+Na]^+$. Found: 144.0481; FT-IR (neat) ν in cm^{-1}: 1670 (C=O stretch).

N-(4-Methoxyphenyl)formamide[15] (7e)



Following general procedure XVII, *p*-anisidine (246 mg, 2 mmol) was used as the amine species. The title compound was recovered after purification by column chromatography (95:5, DCM/MeOH, R_f 0.25) as a white-yellow solid (278 mg, 92%).

mp 79-81 °C (lit.[15] 79-81 °C); ^{1}H NMR (500 MHz, DMSO-d^6): δ 10.00 (br s, 1H, minor and major rotamers, N*H*), 8.59 (d, *J* = 11.1 Hz, 1H, minor rotamer, C*H*O), 8.20 (d, *J* = 1.6 Hz, 1H, major rotamer, C*H*O), 7.50 (d, *J* = 9.0 Hz, 2H, major rotamer, *o*-CH_{Ar}), 7.11 (d, *J* = 8.9 Hz, 2H, minor rotamer, *o*-CH_{Ar}), 6.91 – 6.86 (m, 2H, minor and major rotamers, *m*-CH_{Ar}), 3.72 (s, 3H, OCH_3); ^{13}C NMR (126 MHz, DMSO-d^6): δ 162.5 (minor rotamer), 159.0 (major rotamer), 156.0 (minor rotamer), 155.4 (major rotamer), 131.4 (major rotamer), 131.3 (minor rotamer), 120.6 (major rotamer), 119.7 (minor

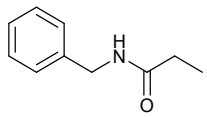
rotamer), 114.6 (minor rotamer), 114.0 (major rotamer), 55.3 (minor rotamer), 55.2 (major rotamer); HRMS-ESI calcd for $[C_8H_9NO_2Na]^+$: 174.0531 $[M+Na]^+$. Found: 174.0546; FT-IR (neat) ν in cm^{-1}: 1655 (C=O stretch).

Synthesis of Other Amides

General Procedure XVIII

To an oven dried Radleys carousel tube containing the appropriate amine (2 mmol), was added the appropriate ester followed by acetic acid (11.4 µL, 10 mol%), unless otherwise stated. The carousel tube was then sealed and the reaction mixture heated at 110 °C, unless otherwise stated, for 20 hours. After being allowed to cool to room temperature, the solvent was removed *in vacuo* on a rotary evaporator and the resulting crude amide product was purified by silica column chromatography.

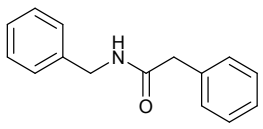
N-Benzylpropionamide[16] (7a)



Following general procedure XVIII, benzylamine (218 µL, 2 mmol) and ethyl propionate (461 µL, 4 mmol) were used as the amine and ester species, respectively. The title compound was recovered after purification by column chromatography (100% DCM) as a yellow oil (300 mg, 92%).

R_f (96:4, DCM/MeOH) 0.34; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 – 7.24 (m, 5H, *Ph*), 5.71 (br s, 1H, N*H*), 4.45 (d, *J* = 5.7 Hz, 2H, PhCH_2), 2.25 (q, *J* = 7.6 Hz, 2H, CH_3CH_2), 1.19 (t, *J* = 7.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 138.4, 128.8, 127.9, 127.6, 43.6, 29.8, 9.9; HRMS-ESI calcd for $[C_{10}H_{13}NONa]^+$: 186.0895 $[M+Na]^+$. Found: 186.0949; FT-IR (neat) ν in cm^{-1}: 1641 (C=O stretch).

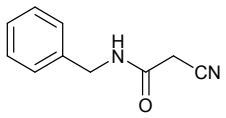
N-Benzyl-2-phenylacetamide[17] (7b)



Following general procedure XVIII, benzylamine (218 µL, 2 mmol) and ethyl phenylacetate (638 µL, 4 mmol) were used as the amine and ester species, respectively. The title compound was recovered after purification by column chromatography (from 100% DCM to 96:4, DCM/MeOH) as a white solid (419 mg, 93%).

R_f (99:1, DCM/MeOH) 0.34; mp 123-124 °C (lit.[17] 121-123 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.21 (m, 8H, *Ph*), 7.20 – 7.15 (m, 2H, *Ph*), 6.05 (br s, 1H, N*H*), 4.38 (d, *J* = 5.9 Hz, 2H, NHCH_2), 3.58 (s, 2H, C(O)CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.9, 138.2, 134.9, 129.4, 129.0, 128.6, 127.5, 127.4, 127.3, 43.8, 43.6; HRMS-ESI calcd for $[C_{15}H_{15}NONa]^+$: 248.1051 $[M+Na]^+$. Found: 248.1108; FT-IR (neat) ν in cm^{-1}: 1636 (C=O stretch).

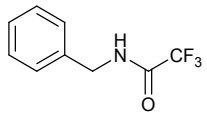
***N*-Benzyl-2-cyanoacetamide**[18] **(7c)**



Following general procedure XVIII, benzylamine (218 µL, 2 mmol) and ethyl cyanoacetate (426 µL, 4 mmol) were used as the amine and ester species, respectively. The title compound was recovered after purification by column chromatography (from 100% DCM to 96:4, DCM/MeOH) as a white solid (327 mg, 94%).

R_f (96:4, DCM/MeOH) 0.31; mp 124-126 °C (lit.[18] 124 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 – 7.17 (m, 5H, *Ph*), 6.54 (br s, 1H, N*H*), 4.45 (d, *J* = 5.7 Hz, 2H, PhCH_2), 3.36 (s, 2H, CNCH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 160.8, 136.8, 128.9, 128.0, 127.9, 114.6, 44.4, 25.8; HRMS-ESI calcd for $[C_{10}H_{10}N_2ONa]^+$: 197.0691 $[M+Na]^+$. Found: 197.0696; FT-IR (neat) ν in cm^{-1}: 1643 (C=O stretch), 2257 (C≡N stretch).

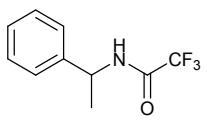
***N*-Benzyl-2,2,2-trifluoroacetamide**[19] **(7f)**



Following general procedure XVIII, benzylamine (218 µL, 2 mmol) and ethyl trifluoroacetate (238 µL, 2 mmol) were used as the amine and ester species, respectively, and the reaction was performed at room temperature (25 °C) with no acid catalyst present. The title compound was recovered after purification by column chromatography (100% DCM, R_f 0.36) as a white solid (406 mg, 100%).

mp 74-75 °C (lit.[20] 74-75 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.46 – 7.19 (m, 5H, *Ph*), 6.82 (br s, 1H, N*H*), 4.51 (d, *J* = 5.8 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.2 (q, J_{CF} = 37.1 Hz), 135.9, 129.1, 128.3, 128.0, 115.9 (q, J_{CF} = 287.7 Hz), 43.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ -75.84; HRMS-ESI calcd for $[C_9H_7F_3NO]^+$: 202.0480 $[M+H]^+$. Found: 202.0486; FT-IR (neat) ν in cm^{-1}: 1699 (C=O stretch).

2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide[21] **(7g)**

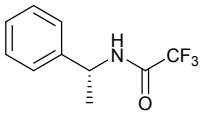


Following general procedure XVIII, *racemic*-methylbenzylamine (255 µL, 2 mmol) and ethyl trifluoroacetate (238 µL, 2 mmol) were used as the amine and ester species, respectively, and the reaction was performed at room temperature (25 °C) with no acid catalyst present. The title

compound was recovered after purification by column chromatography (100% DCM, R_f 0.30) as a white solid (433 mg, 100%).

mp 89-90 °C (lit.[22] 88 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 2H, *Ph*), 7.35 – 7.30 (m, 3H, *Ph*), 6.43 (br s, 1H, N*H*), 5.15 (quint, *J* = 7.1 Hz, 1H, NHC*H*), 1.60 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.3 (q, J_{CF} = 37.0 Hz), 140.9, 129.0, 128.1, 126.1, 115.8 (q, J_{CF} = 288.1 Hz), 49.8, 21.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -75.92; HRMS-ESI calcd for $[C_{10}H_{11}F_3NO]^+$: 218.0793 $[M+H]^+$. Found: 218.0789; FT-IR (neat) ν in cm^{-1}: 1693 (C=O stretch); $[\alpha]_D^{20}$ + 0 (*c* 1.0 in $CHCl_3$); HPLC: Chiracel OD column (25 cm), 1.0 mL min^{-1}, 98:2 Hexane:IPA, (*S*)-enantiomer retention time 11.20 minutes, (*R*)-enantiomer retention time 19.40 minutes.

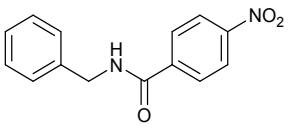
(*R*)-2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide[22] (7h)



Following general procedure XVIII, (*R*)-(+)-α-methylbenzylamine (255 µL, 2 mmol) and ethyl trifluoroacetate (238 µL, 2 mmol) were used as the amine and ester species, respectively, and the reaction was performed at room temperature (25 °C) with no acid catalyst present. The title compound was recovered after purification by column chromatography (100% DCM, R_f 0.30) as a white solid (434 mg, 100%).

mp 89 °C (lit.[22] 88 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.36 (m, 2H, *Ph*), 7.35 – 7.30 (m, 3H, *Ph*), 6.43 (br s, 1H, N*H*), 5.15 (quint, *J* = 7.1 Hz, 1H, NHC*H*), 1.60 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.3 (q, J_{CF} = 37.0 Hz), 140.9, 129.0, 128.1, 126.1, 115.8 (q, J_{CF} = 288.1 Hz), 49.8, 21.0; ^{19}F NMR (470 MHz, $CDCl_3$): δ -75.92; HRMS-ESI calcd for $[C_{10}H_{11}F_3NO]^+$: 218.0793 $[M+H]^+$. Found: 218.0797; FT-IR (neat) ν in cm^{-1}: 1697 (C=O stretch); $[\alpha]_D^{20}$ + 138 (*c* 1.0 in $CHCl_3$) (lit.[23] $[\alpha]_D^{25}$ + 137 (*c* 1.0 in $CHCl_3$)); HPLC: Chiracel OD column (25 cm), 1.0 mL min^{-1}, 98:2 Hexane:IPA, (*R*)-enantiomer retention time 18.81 minutes, no peak observed for (*S*)-enantiomer at 11.20 minutes, *ee* > 99%.

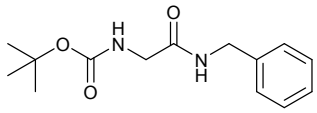
***N*-Benzyl-4-nitrobenzamide[24] (7i)**



Following general procedure XVIII, benzylamine (218 µL, 2 mmol) and methyl 4-nitrobenzoate (362 mg, 2 mmol) were used as the amine and ester species, respectively, and the reaction was performed at 150 °C. The title compound was recovered after purification by column chromatography (from 100% DCM to 96:4, DCM/MeOH) as an off-white solid (307 mg, 60%).

R_f (98:2, DCM/MeOH) 0.33; mp 140-142 °C (lit.[25] 139-140 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.9 Hz, 2H, *m*-CH_{Ar}), 7.94 (d, *J* = 8.9 Hz, 2H, *o*-CH_{Ar}), 7.40 – 7.29 (m, 5H, *Ph*), 6.59 (br s, 1H, N*H*), 4.65 (d, *J* = 5.7 Hz, 2H, CH_2); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.3, 149.6, 139.9, 137.4, 128.9, 128.2, 128.0, 127.9, 123.8, 44.5; HRMS-ESI calcd for $[C_{14}H_{12}N_2O_3Na]^+$: 279.0746 $[M+Na]^+$. Found: 279.0726; FT-IR (neat) ν in cm^{-1}: 1629 (C=O stretch).

tert-Butyl (2-(benzylamino)-2-oxoethyl)carbamate[26] (7j)



Following general procedure XVIII, benzylamine (218 µL, 2 mmol) and *N*-Boc-glycine methyl ester (351 µL, 2 mmol) were used as the amine and ester species, respectively. The title compound was recovered after purification by column chromatography (94:6, DCM/MeOH, R_f 0.32) as an off-white solid (512 mg, 97%).

mp 66-68 °C (lit.[26] 65 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 – 7.16 (m, 5H, *Ph*), 6.93 (br s, 1H, $PhCH_2NH$), 5.50 (t, *J* = 5.6 Hz, 1H, OC(O)N*H*), 4.39 (d, *J* = 5.8 Hz, 2H, PhCH_2), 3.79 (d, *J* = 5.1 Hz, 2H, C(O)CH_2), 1.39 (s, 9H, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.6, 156.2, 138.0, 128.7, 127.6, 127.5, 80.2, 44.4, 43.3, 28.3; HRMS-ESI calcd for $[C_{14}H_{20}N_2O_3Na]^+$: 287.1372 $[M+Na]^+$. Found: 287.1346; FT-IR (neat) ν in cm^{-1}: 1655 (amide C=O stretch), 1703 (carbamate C=O stretch).

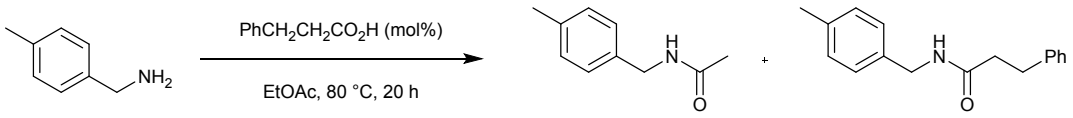
Investigations into the Reaction Mechanism

Use of 3-Phenylpropionic Acid as the Catalyst

General Procedure XIX – $PhCH_2CH_2CO_2H$ Catalyst Screen

To an oven dried Radleys carousel tube containing 4-methylbenzylamine (127 µL, 1 mmol) was added the appropriate amount of ethyl acetate, followed by the appropriate amount of 3-phenylpropionic acid (Table S13). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 20 hours. After being allowed to cool to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with $NaHCO_3$ (3 x 20 mL). The organics were dried with $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator. The resulting crude reaction mixture was analysed by ^1H NMR. Percentage conversion into *N*-(4-methylbenzyl)acetamide and *N*-(4-methylbenzyl)-3-phenylpropanamide was calculated from the crude ^1H NMR spectra by comparison of the peaks at 3.85 ppm (2H, 4-methylbenzylamine), 4.39 ppm (2H, *N*-(4-methylbenzyl)acetamide and *N*-(4-methylbenzyl)-3-phenylpropanamide). Product ratios were also calculated from the crude ^1H NMR spectra by comparison of the peaks at 3.00 ppm (2H, *N*-(4-methylbenzyl)-3-phenylpropanamide) and 2.02 ppm (3H, *N*-(4-methylbenzyl)acetamide).

Table S13. Investigations into the reaction mechanism using 3-phenylpropionic acid as the catalyst.



4a 4b

Entry[a]	Acid (mol%)	EtOAc (mL)	Conversion into 4a & 4b (%)[b]	4a : 4b[b]
1	-	1	2	-
2	100	1	100	95 : 5
3	50	1	100	96 : 4
4	20	1	100	97 : 3
5	10	1	100	98 : 2
6	5	1	97	99 : 1
7	2	1	76	99 : 1
8	100	0.5	100	93 : 7
9	100	0.25	97	91 : 9
10[*]	100	0.098	62	84 : 16

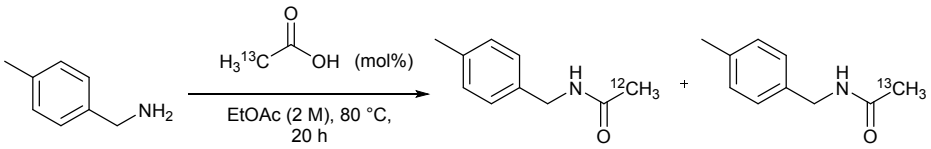
[*] Low solvent volume may have resulted in inefficient stirring.

Acetic Acid ^{13}C-Labelling Study

General Procedure XX – ^{13}C-Labelled Acetic Acid Screen

To an oven dried Radleys carousel tube containing 4-methylbenzylamine (127 µL, 1 mmol) was added ethyl acetate (0.5 mL, 2 M) followed by the appropriate amount of acetic acid-2-^{13}C (Table S14 and S15). The carousel tube was then sealed and the reaction mixture heated at 80 °C for 20 hours. After being allowed to cool to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and washed with $NaHCO_3$ (3 x 20 mL). The organics were dried with $MgSO_4$, filtered and concentrated *in vacuo* on a rotary evaporator. The resulting crude reaction mixture was analysed by ^{1}H and ^{13}C NMR. Percentage incorporation of labelled acetic acid was calculated using (i) the integrals of the two methyl peaks in each of the quantitative ^{13}C NMR spectra; (ii) the integrals of the arene methyl satellite peaks and the acetyl methyl satellite peaks in each of the ^{1}H NMR spectra.

Table S14. Investigations into catalyst incorporation using ^{13}C-labelled AcOH (Quantitative ^{13}C NMR spectra).

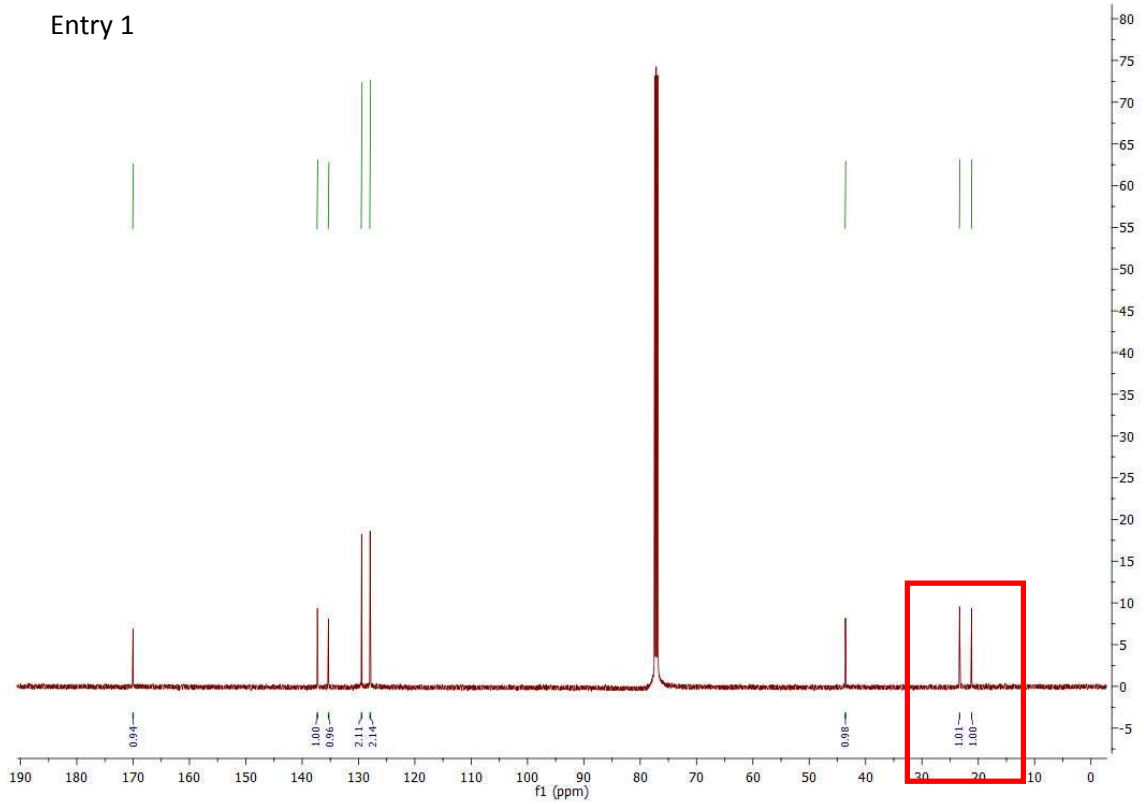


5a **5b**

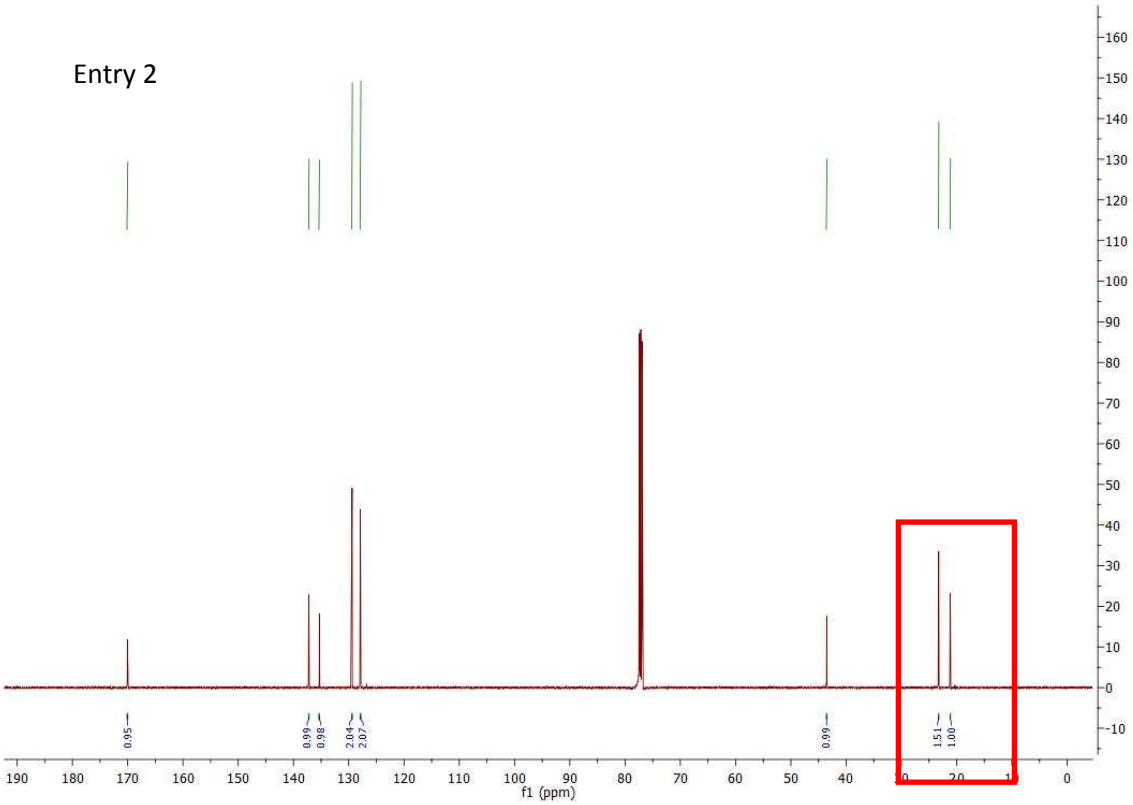
Entry	AcOH-2-^{13}C (mol%)	AcOH-2-^{13}C Incorporation (%)[a]
1[b]	-	0
2	10	0.52
3	50	3.01

[a] Percentage incorporation calculated using the integrals of the two methyl peaks in each of the quantitative ^{13}C NMR spectra; [b] Unlabelled 10 mol% AcOH used.

Entry 1



Entry 2



Entry 3

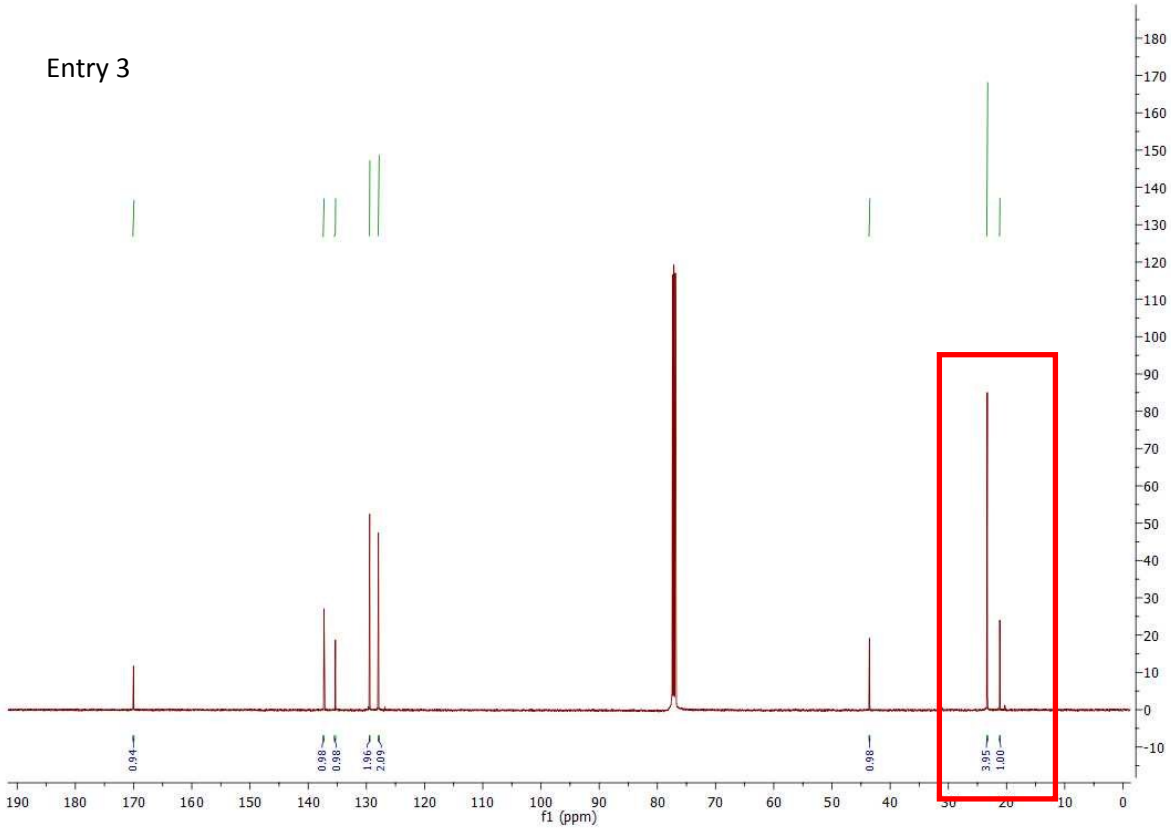
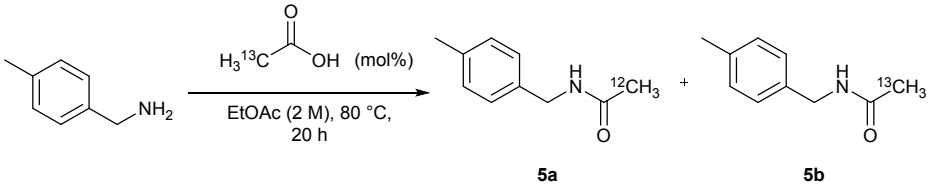


Table S15. Investigations into catalyst incorporation using ^{13}C-labelled AcOH (^{1}H NMR spectra).

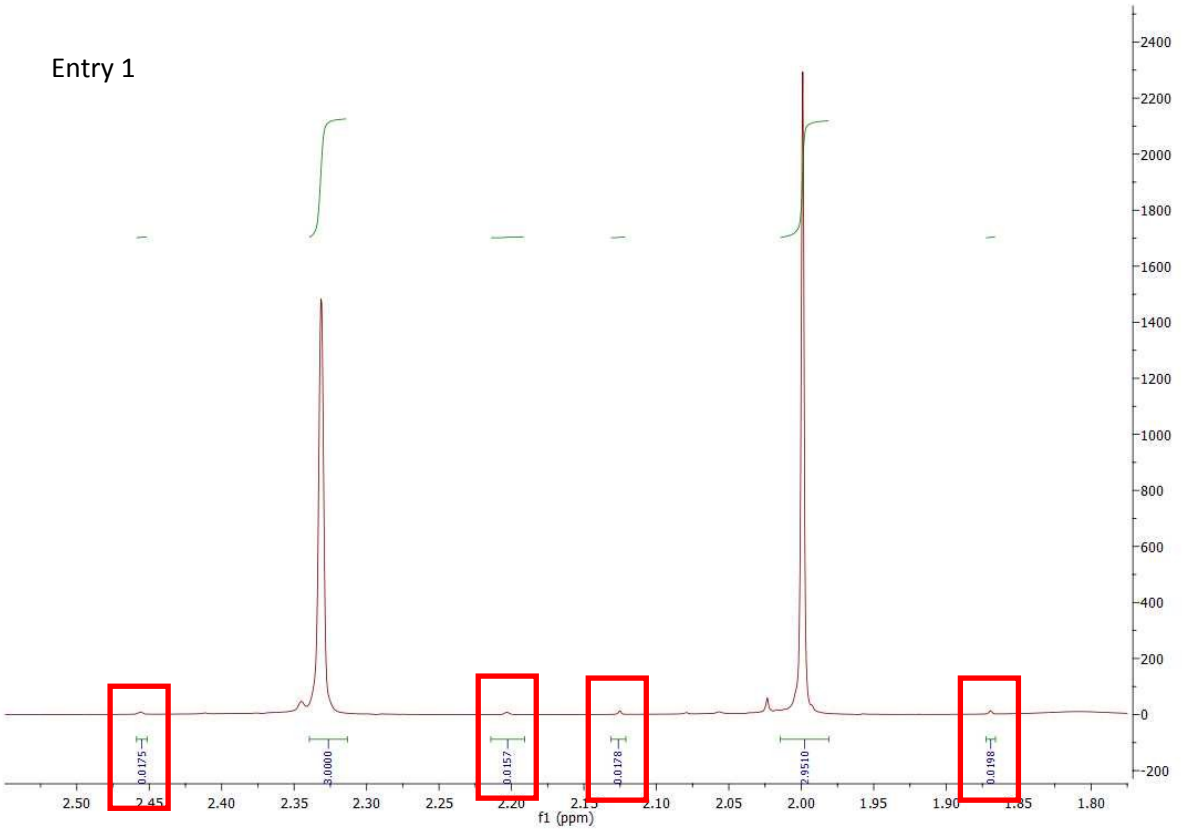


5a **5b**

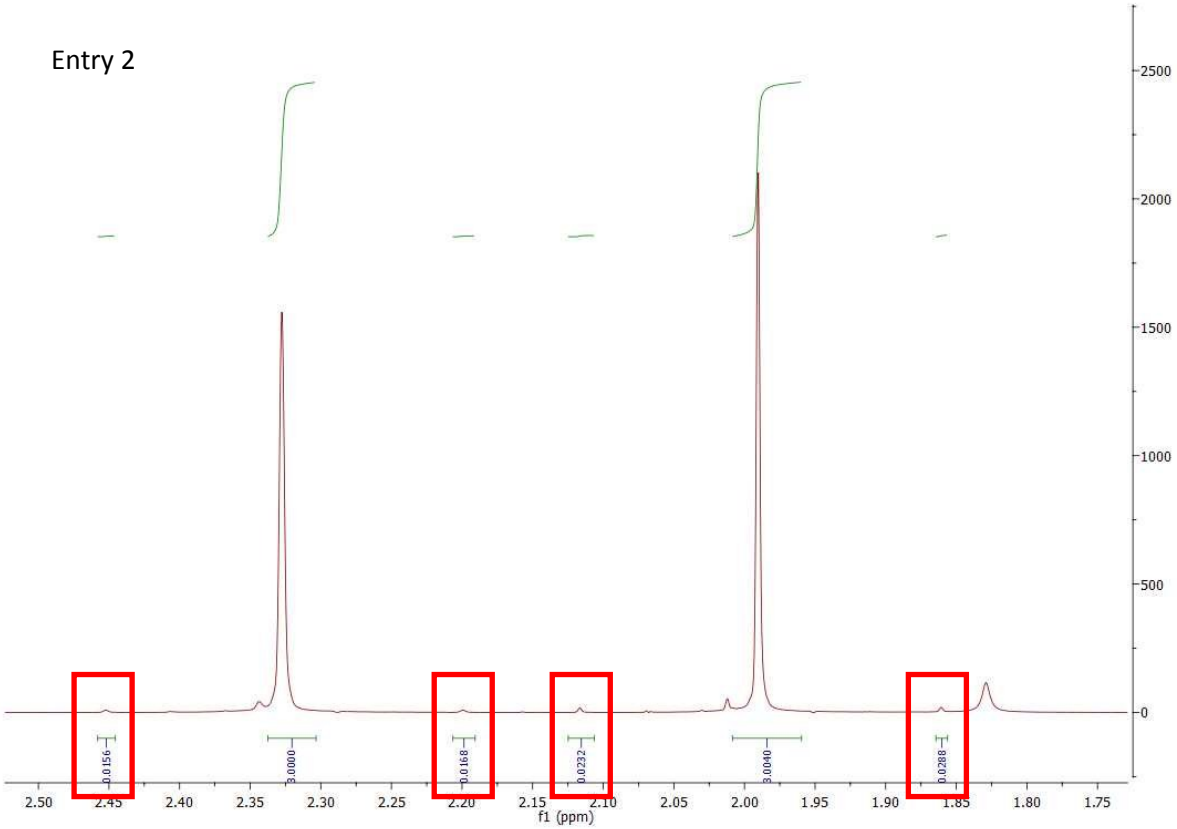
Entry	AcOH-2-^{13}C (mol%)	AcOH-2-^{13}C Incorporation (%)[a]
1[b]	-	0
2	10	0.51
3	50	3.03

[a] Percentage incorporation calculated using the integrals of the arene methyl satellite peaks and the acetyl methyl satellite peaks in each of the ^{1}H NMR spectra; [b] Unlabelled AcOH used.

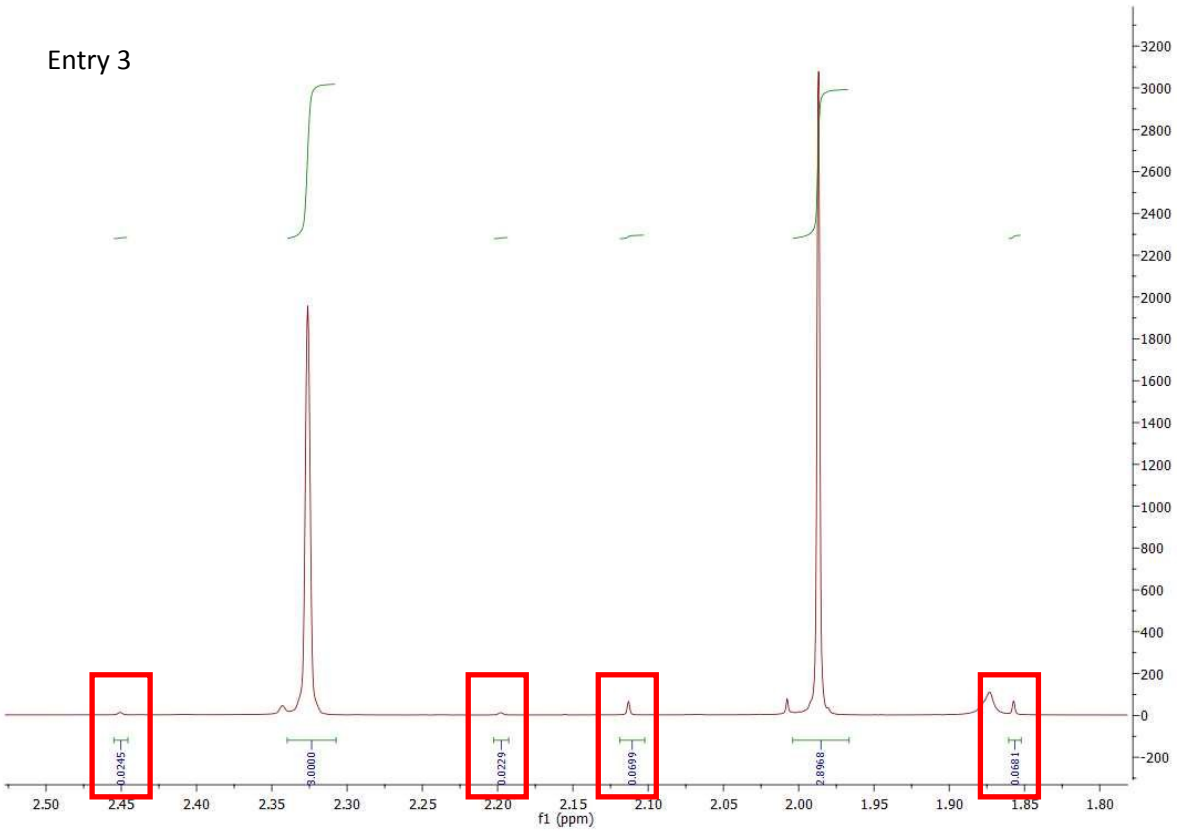
Entry 1



Entry 2

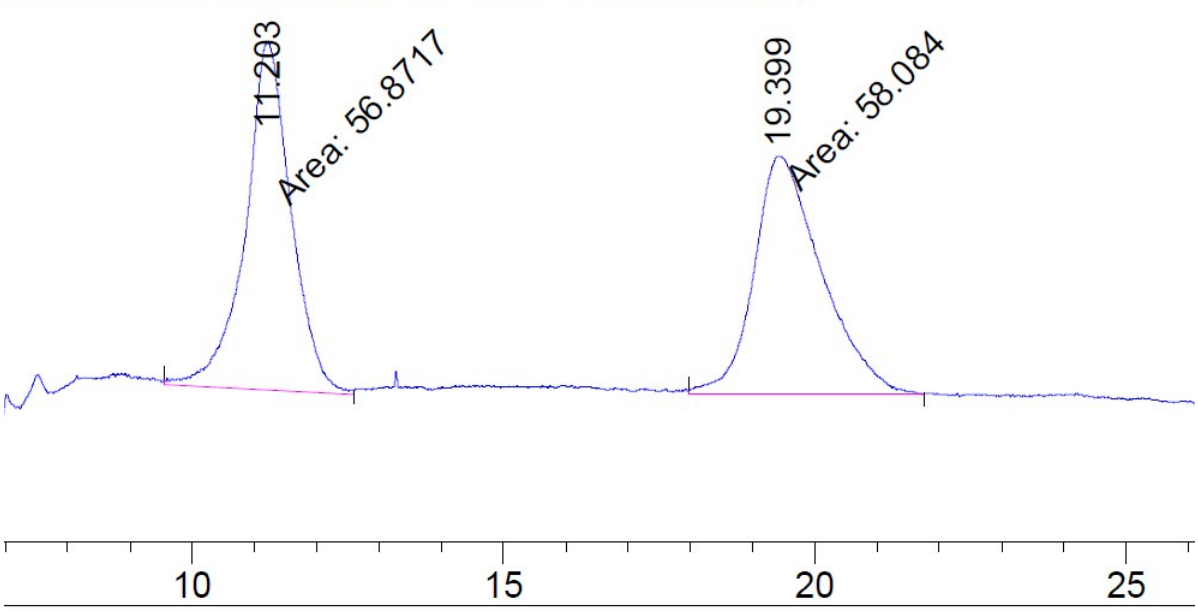


Entry 3

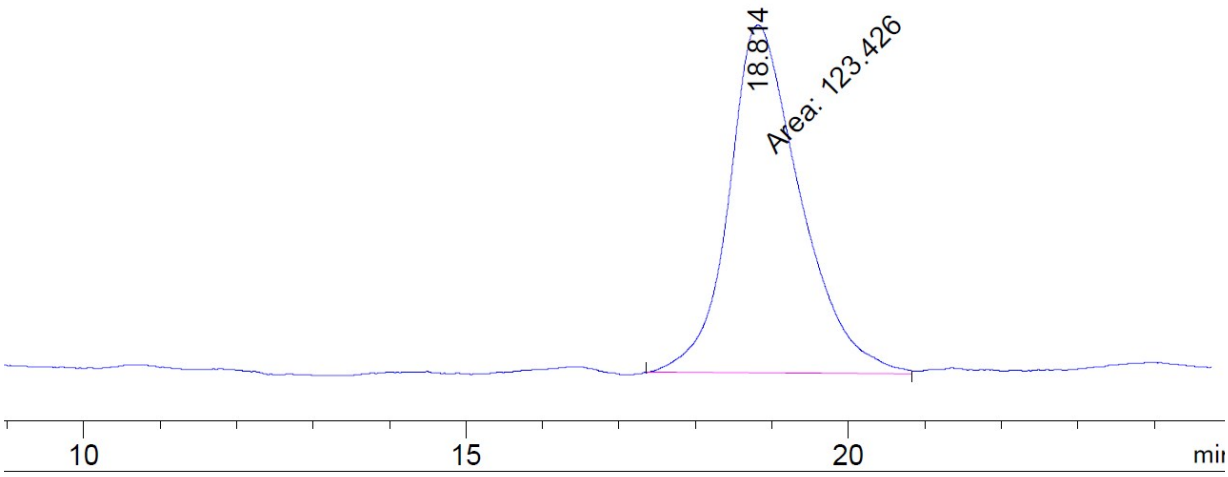


HPLC Traces

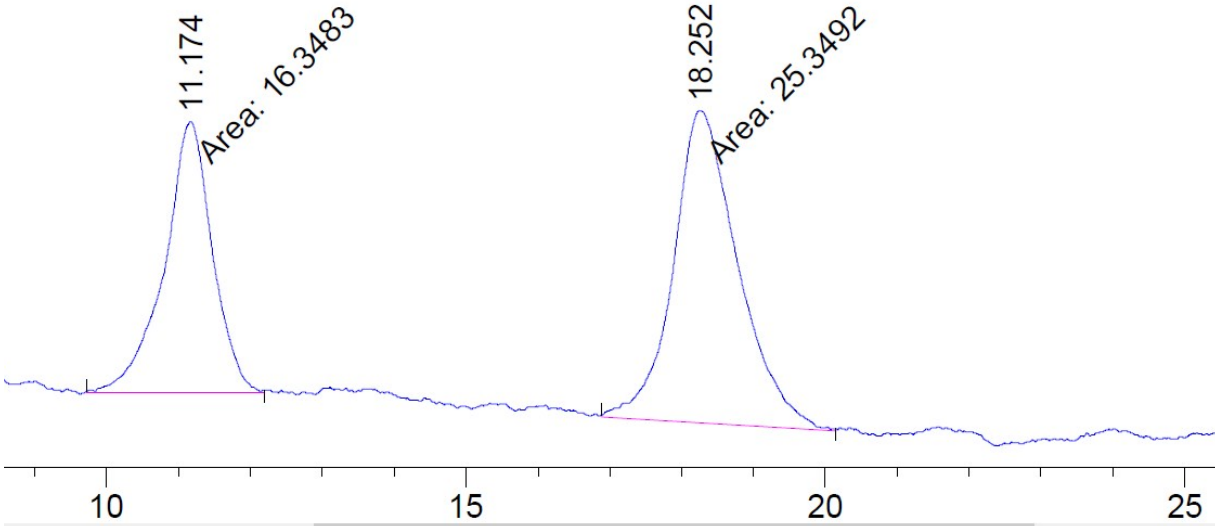
***Racemic*-2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide**

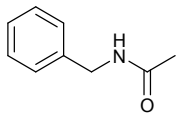


(*R*)-2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide

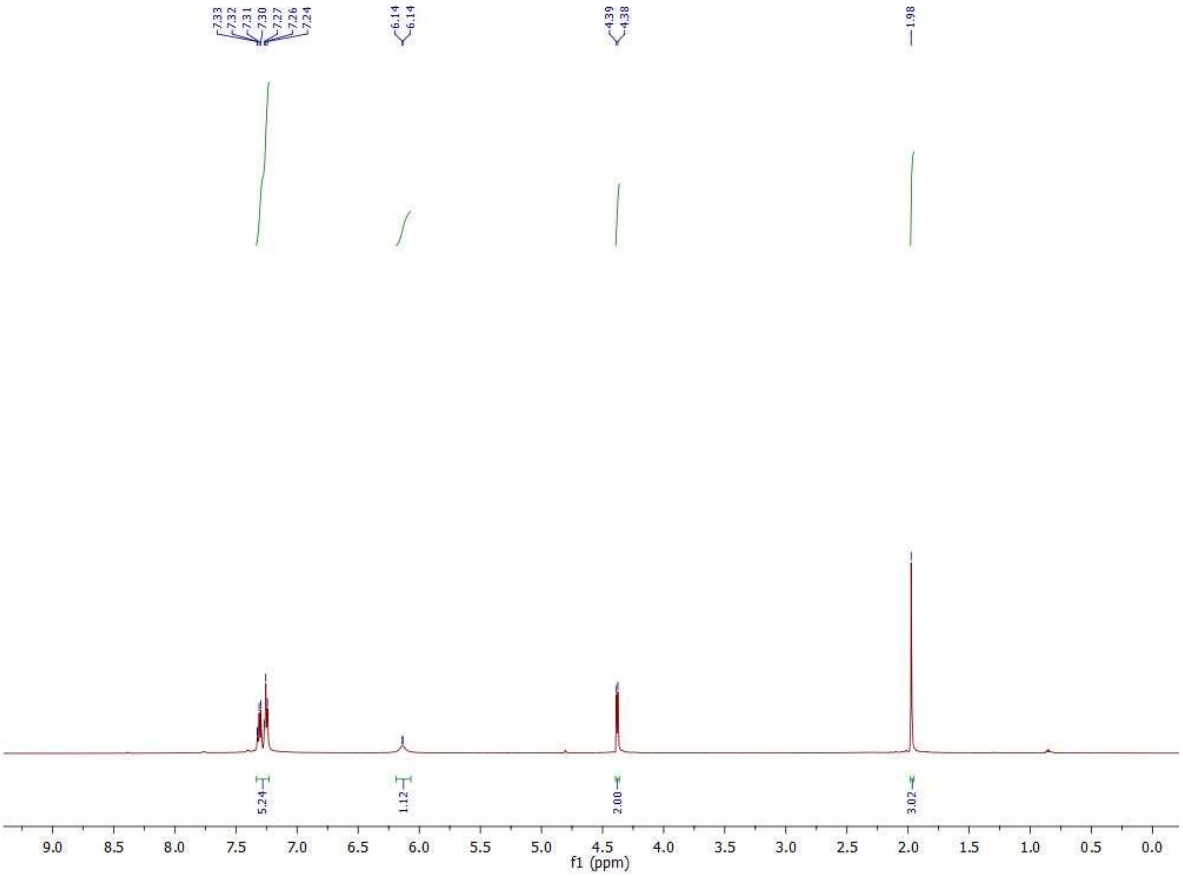


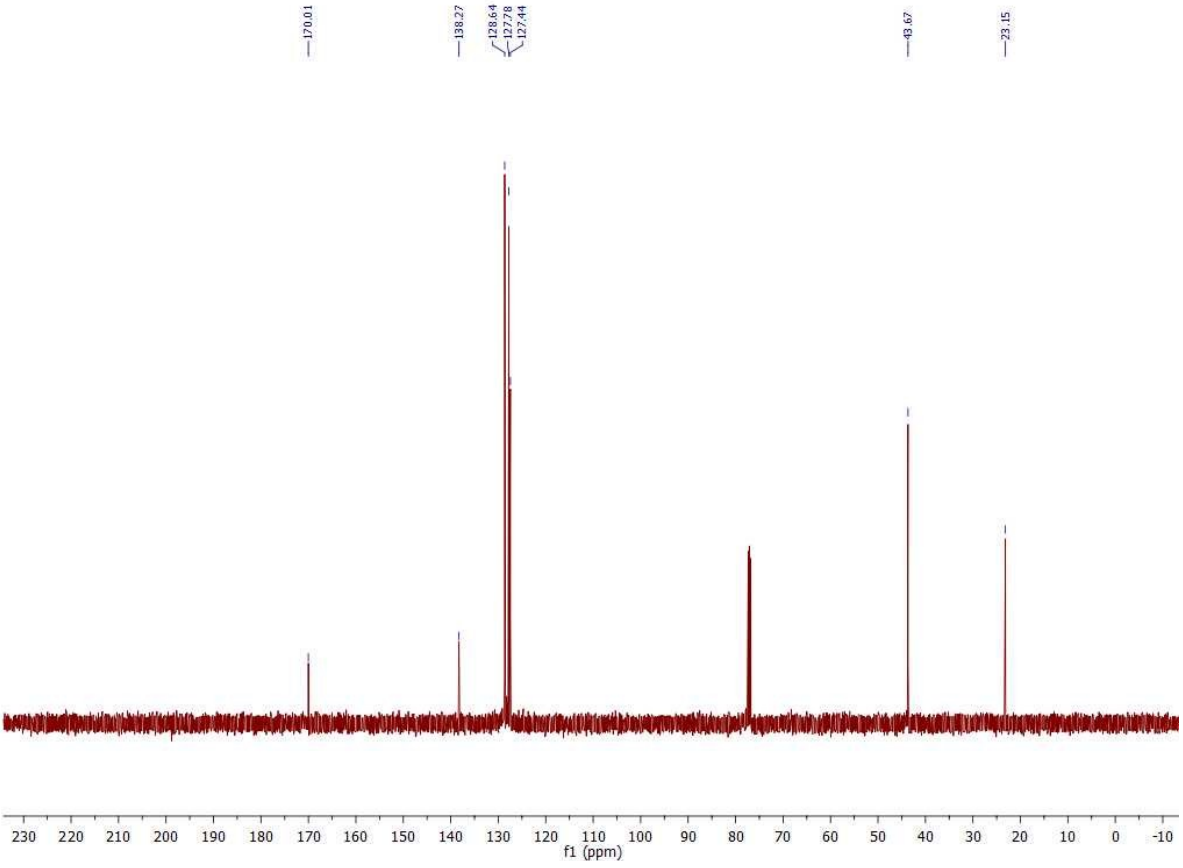
(*R*)-2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide + 2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide

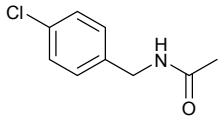




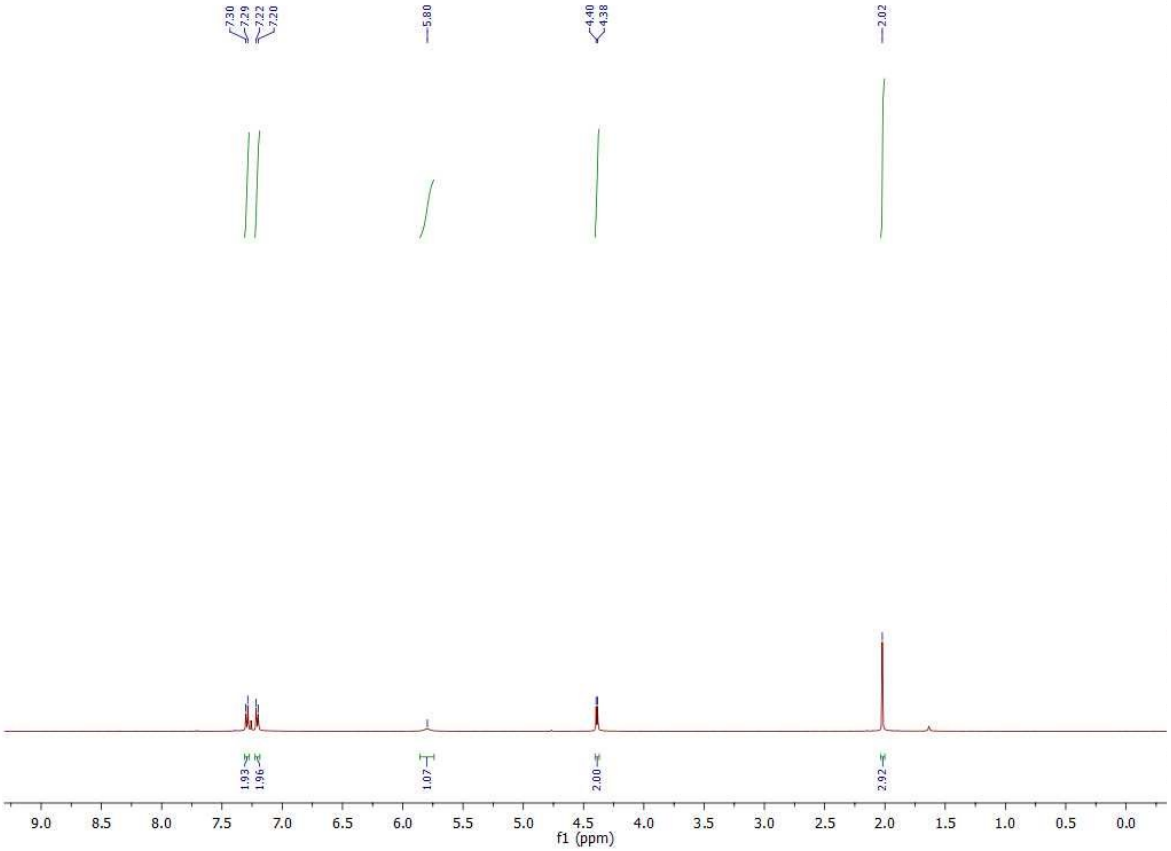
_N_-Benzylacetamide[1] (1a)

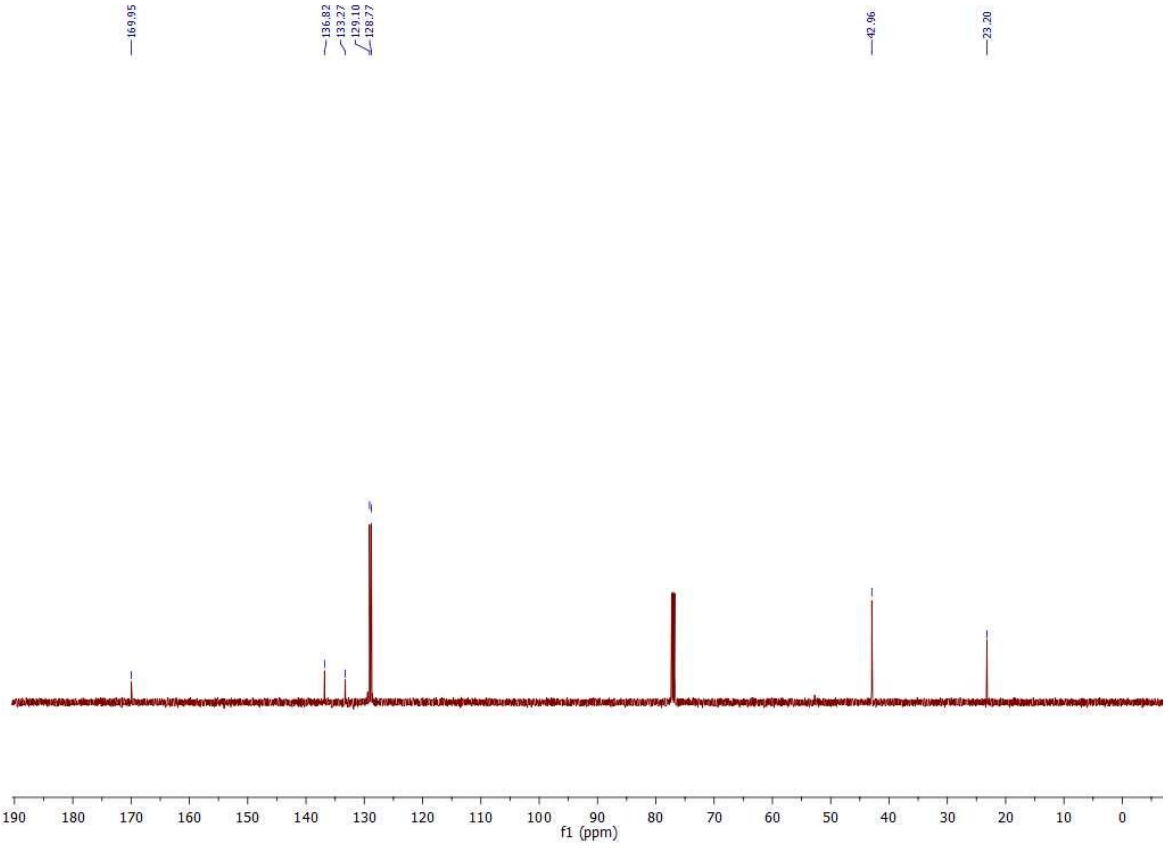


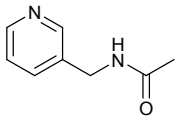




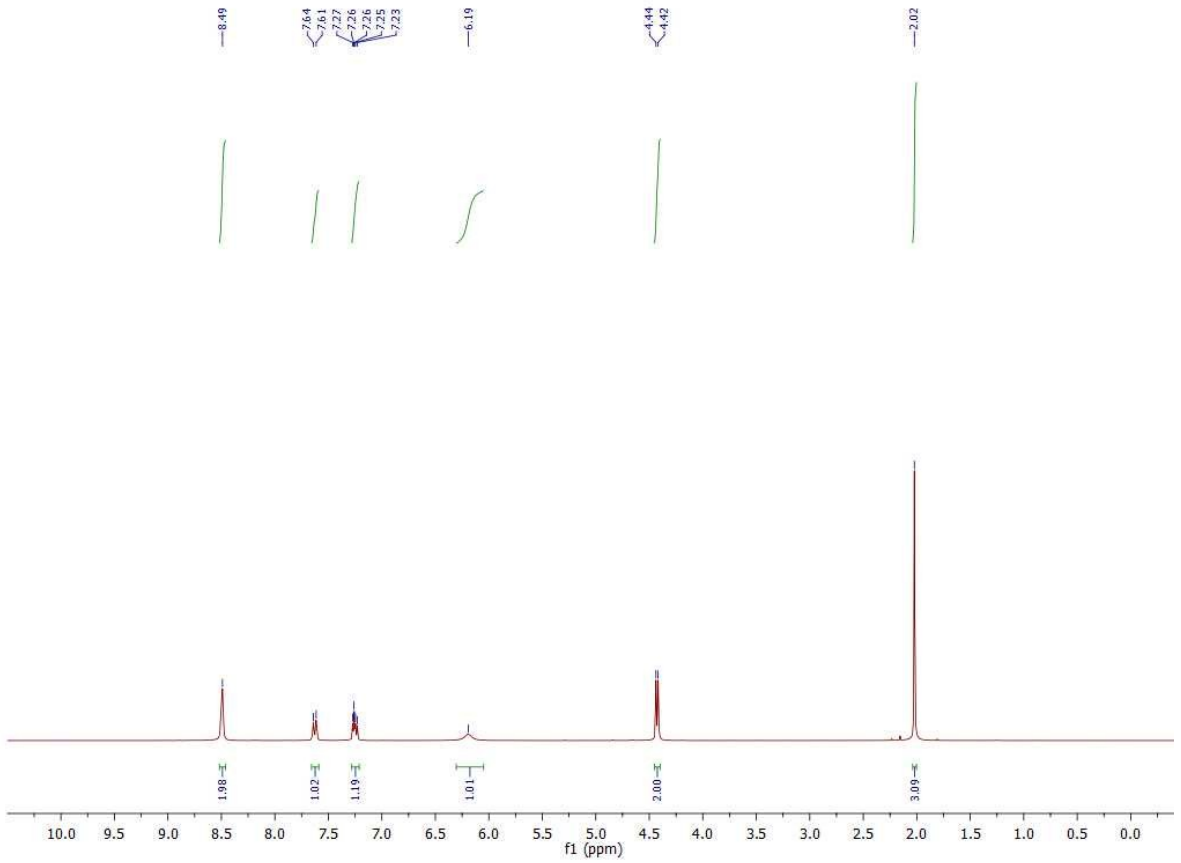
***N*-(4-Chlorobenzyl)acetamide[2] (1b)**

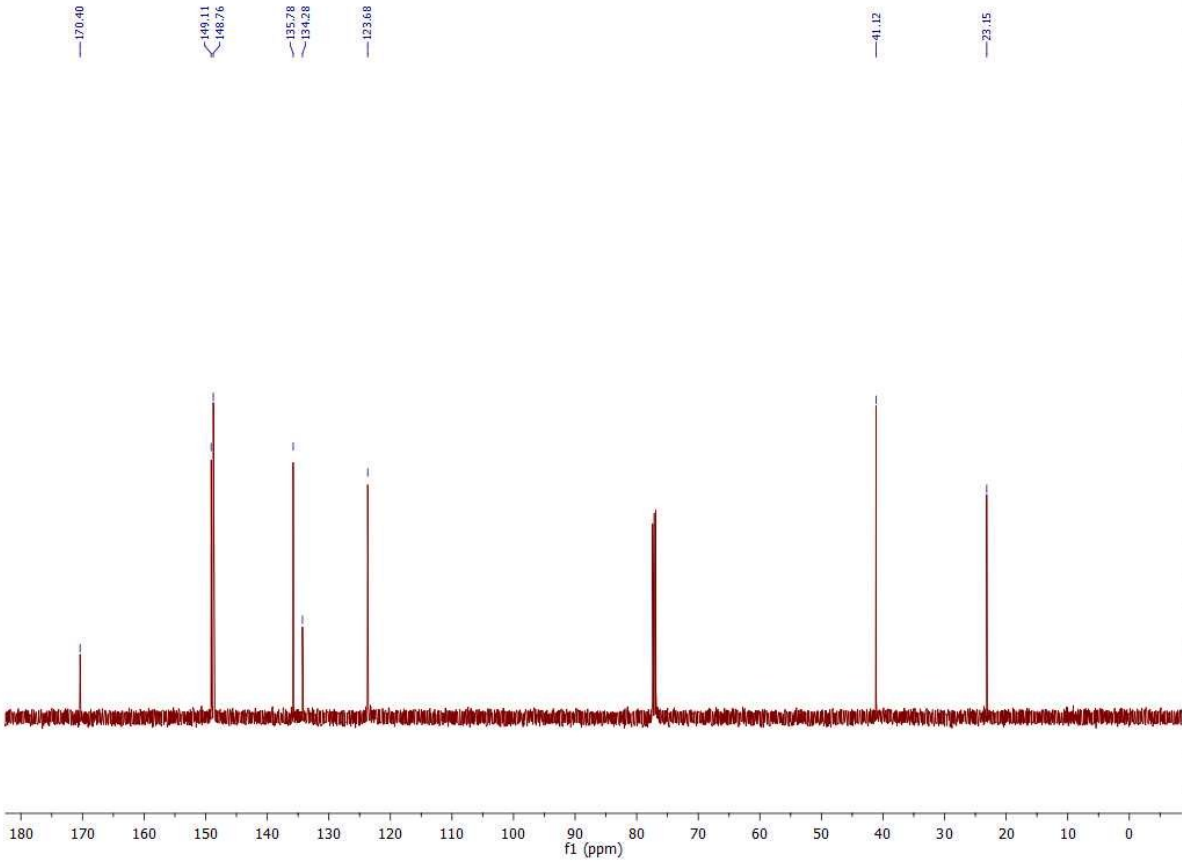


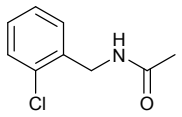




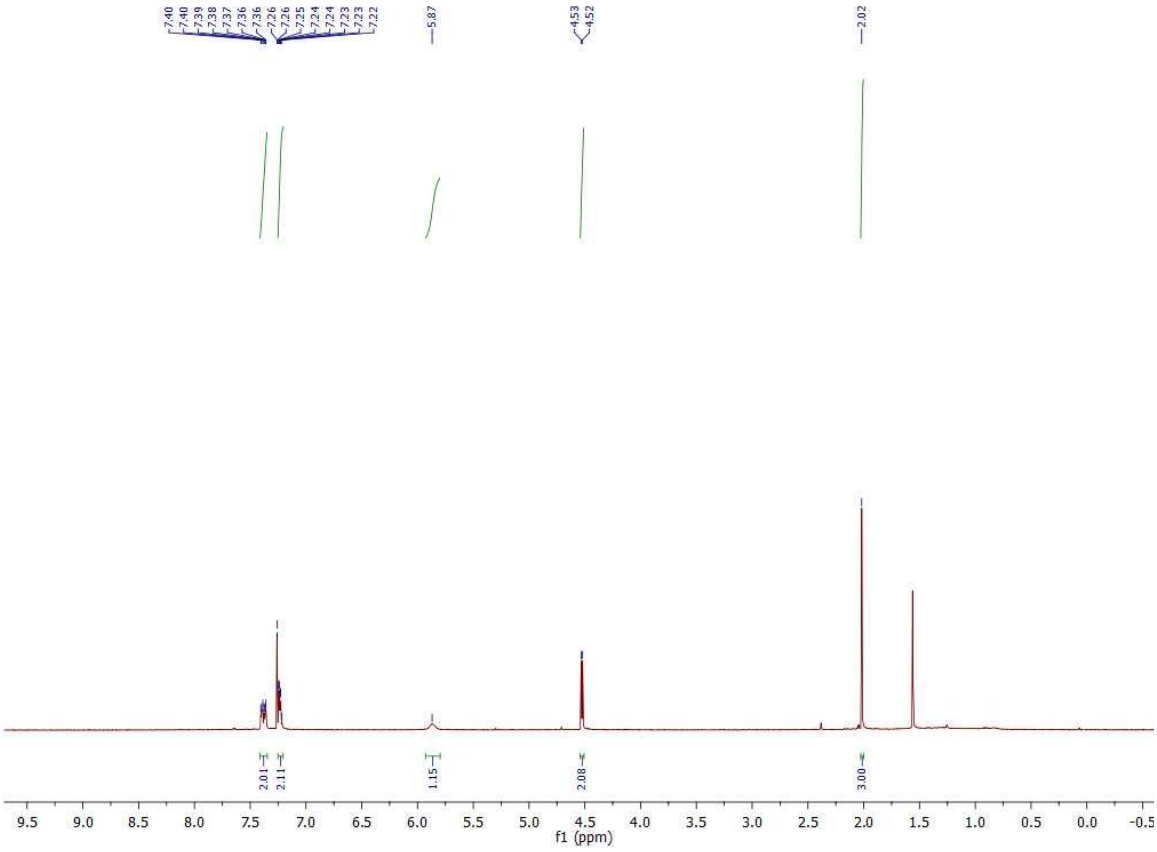
_N_-(Pyridin-3-ylmethyl)acetamide[3] (1c)

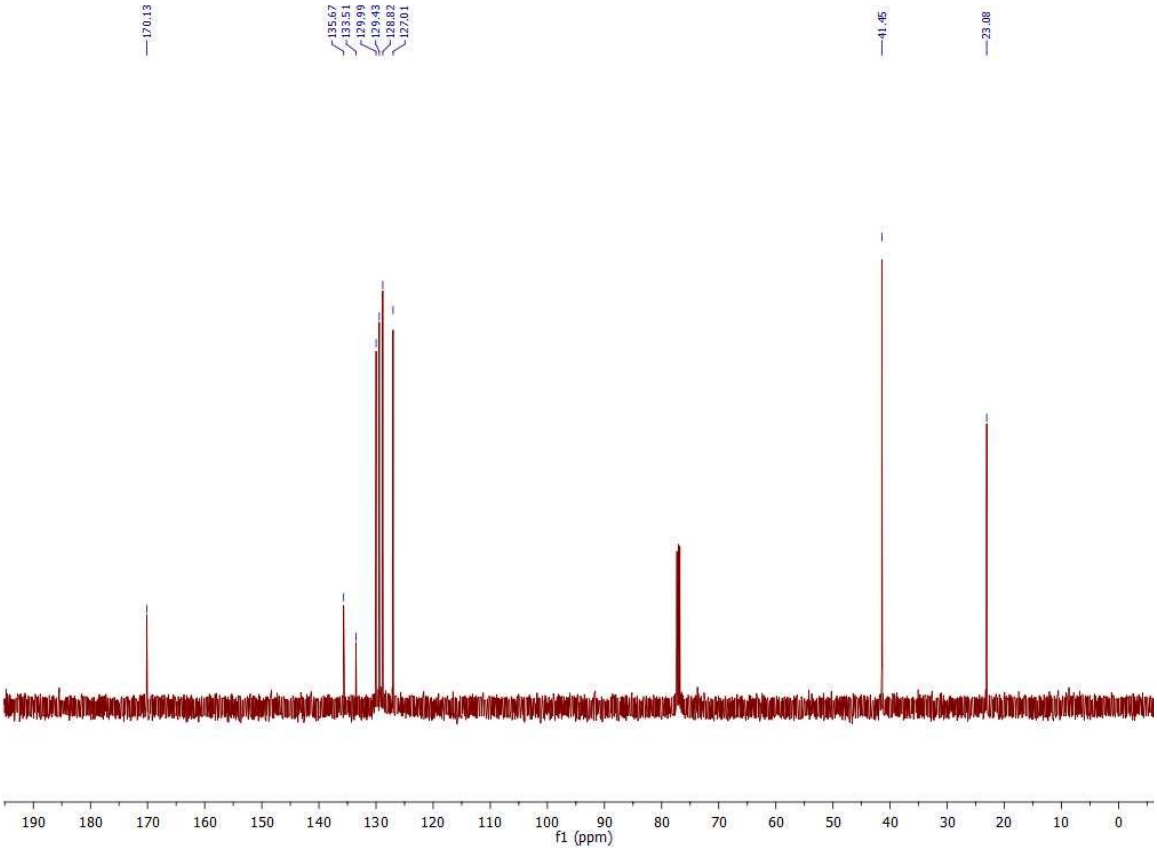


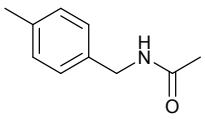




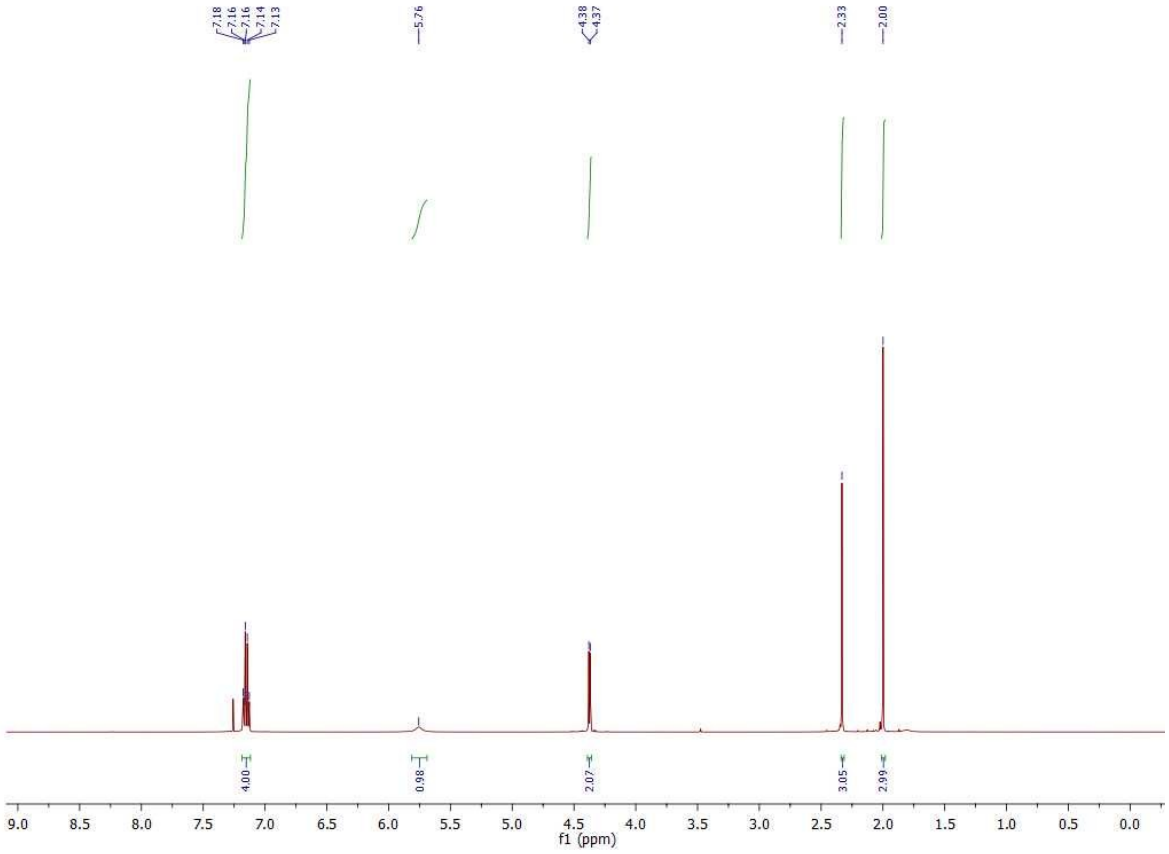
_N_-(2-Chlorobenzyl)acetamide[4] (1d)

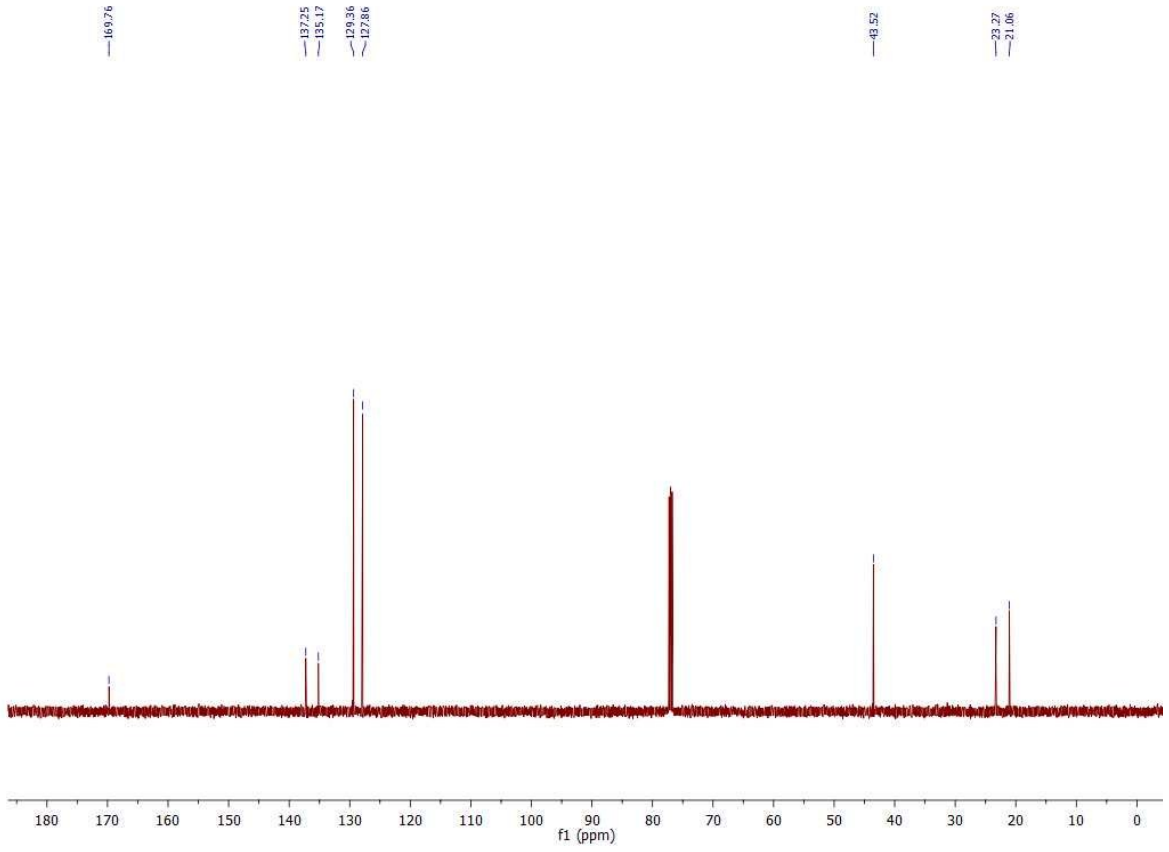


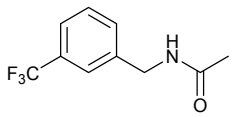




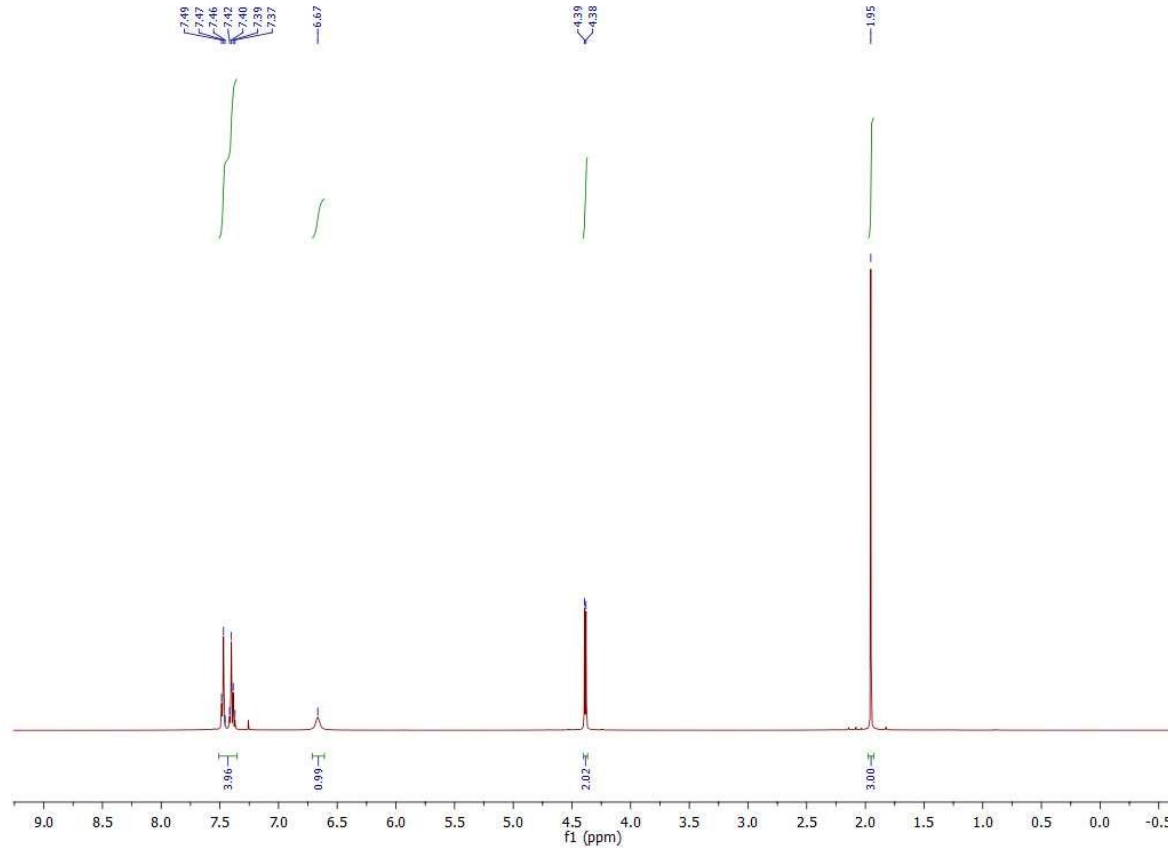
_N_-(4-Methylbenzyl)acetamide[1] (1e)

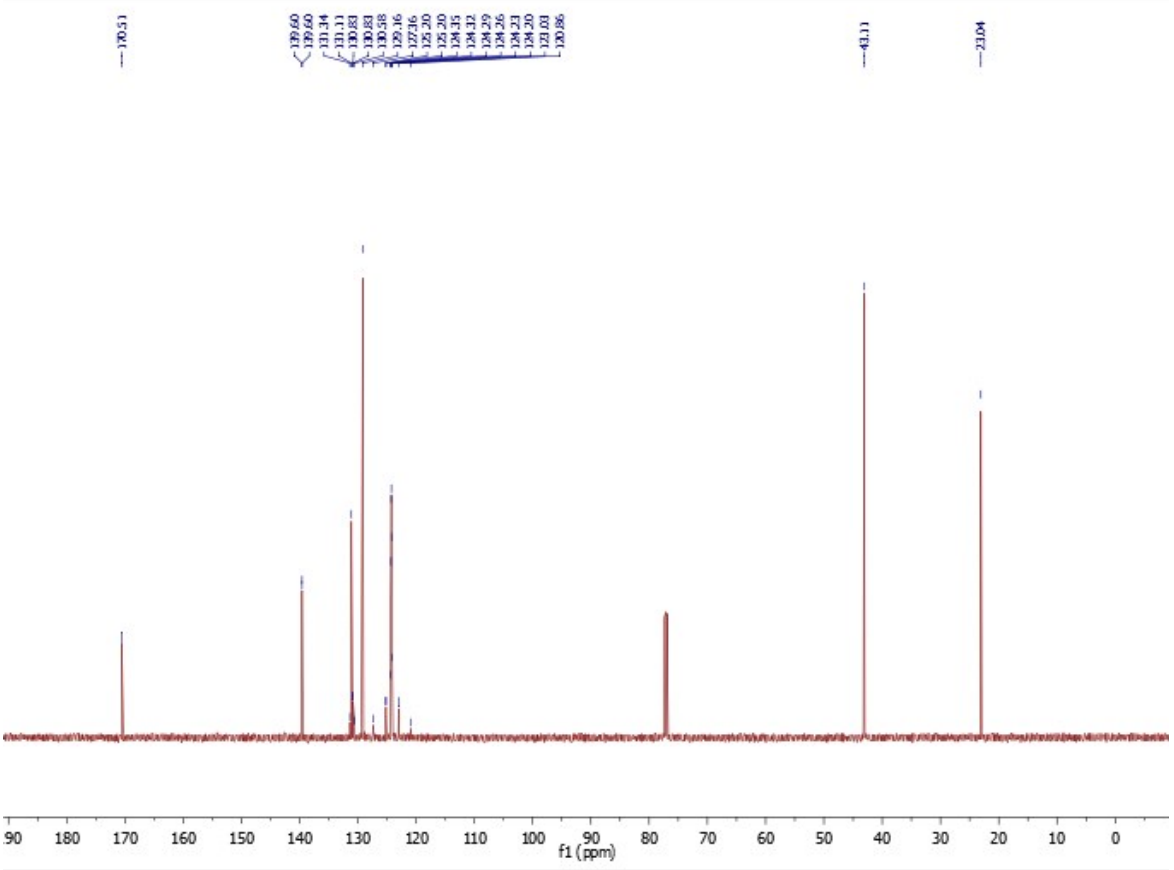


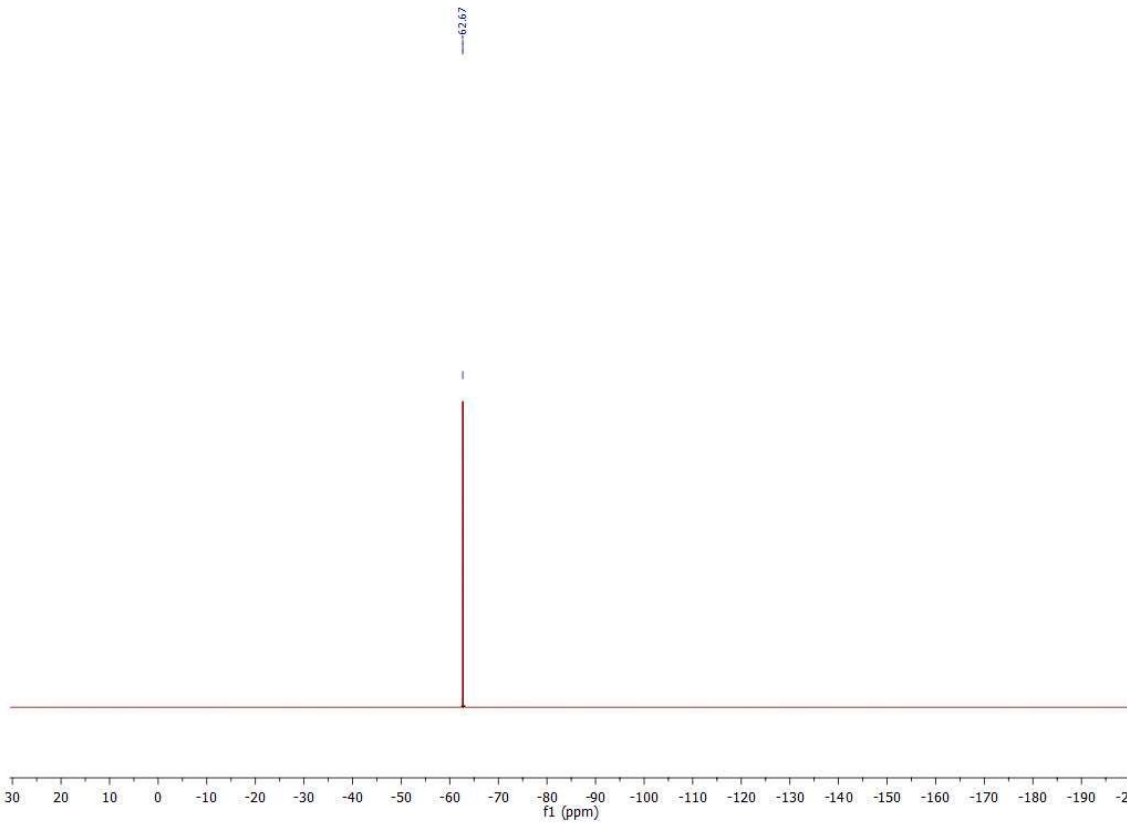




***N*-(3-(Trifluoromethyl)benzyl)acetamide[5] (1h)**



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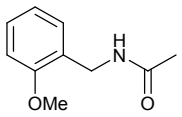
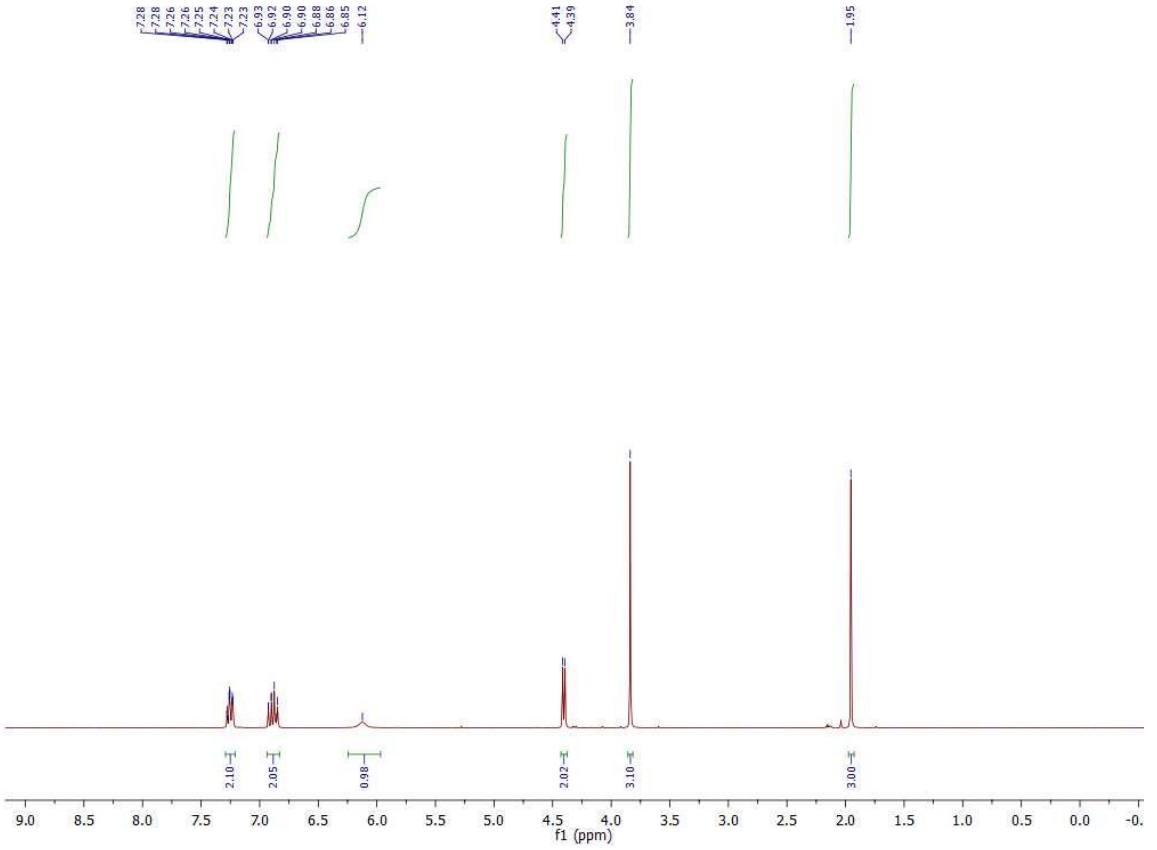
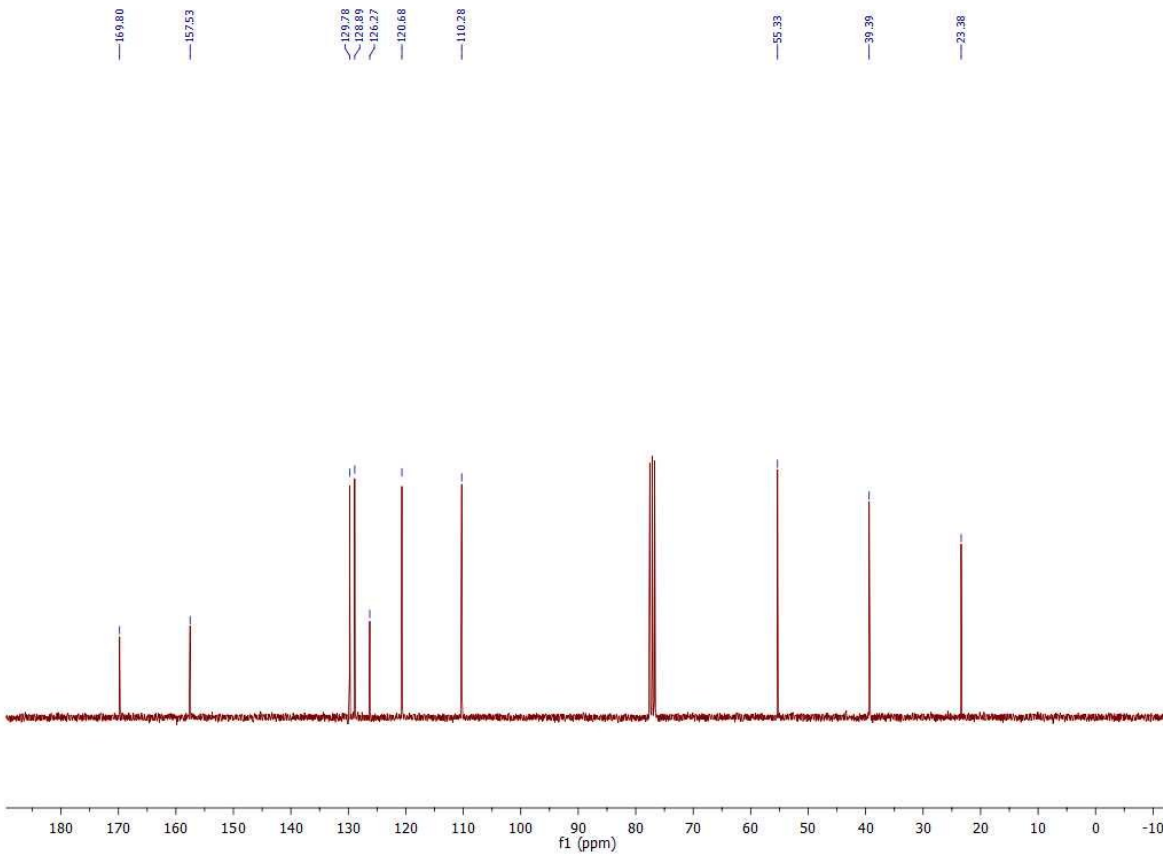
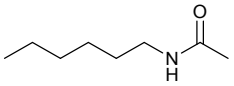
f1 (ppm)



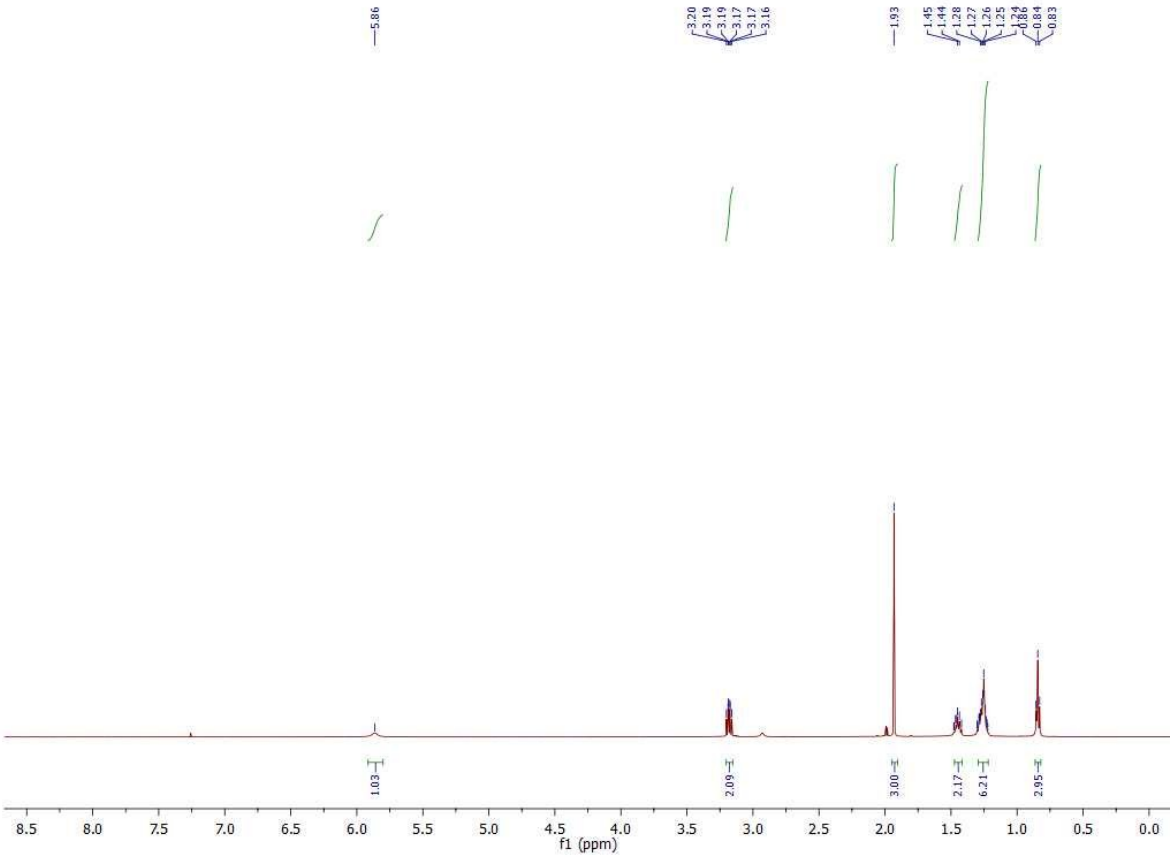
_N_-(2-Methoxybenzyl)acetamide[4] (1i)

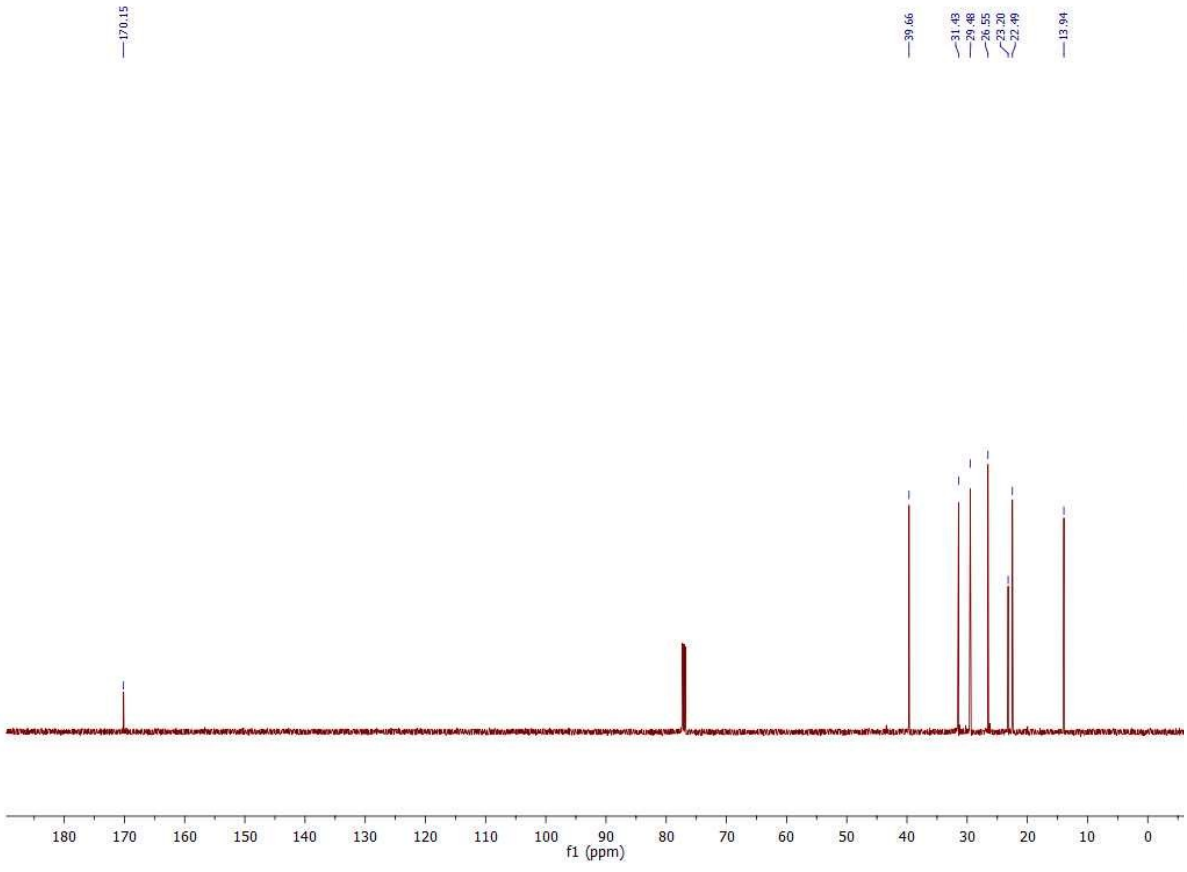


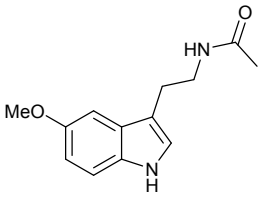




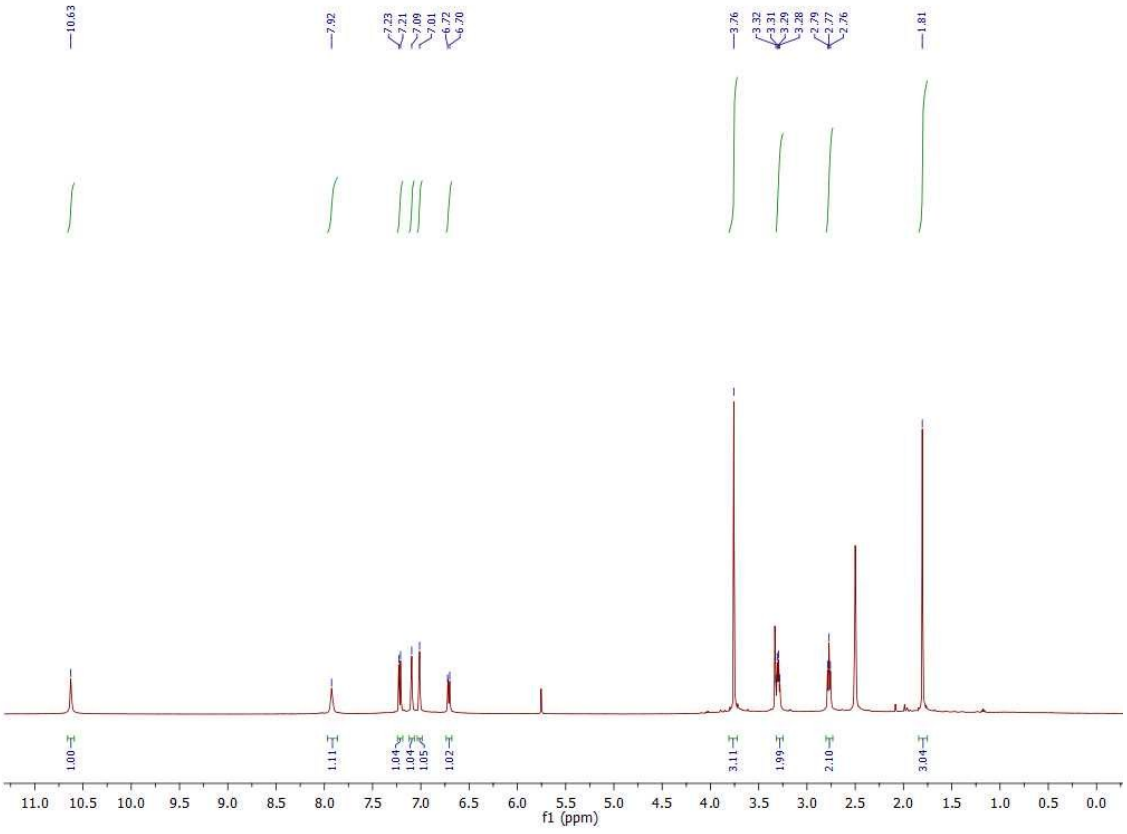
_N_-Hexylacetamide[6] (1j)

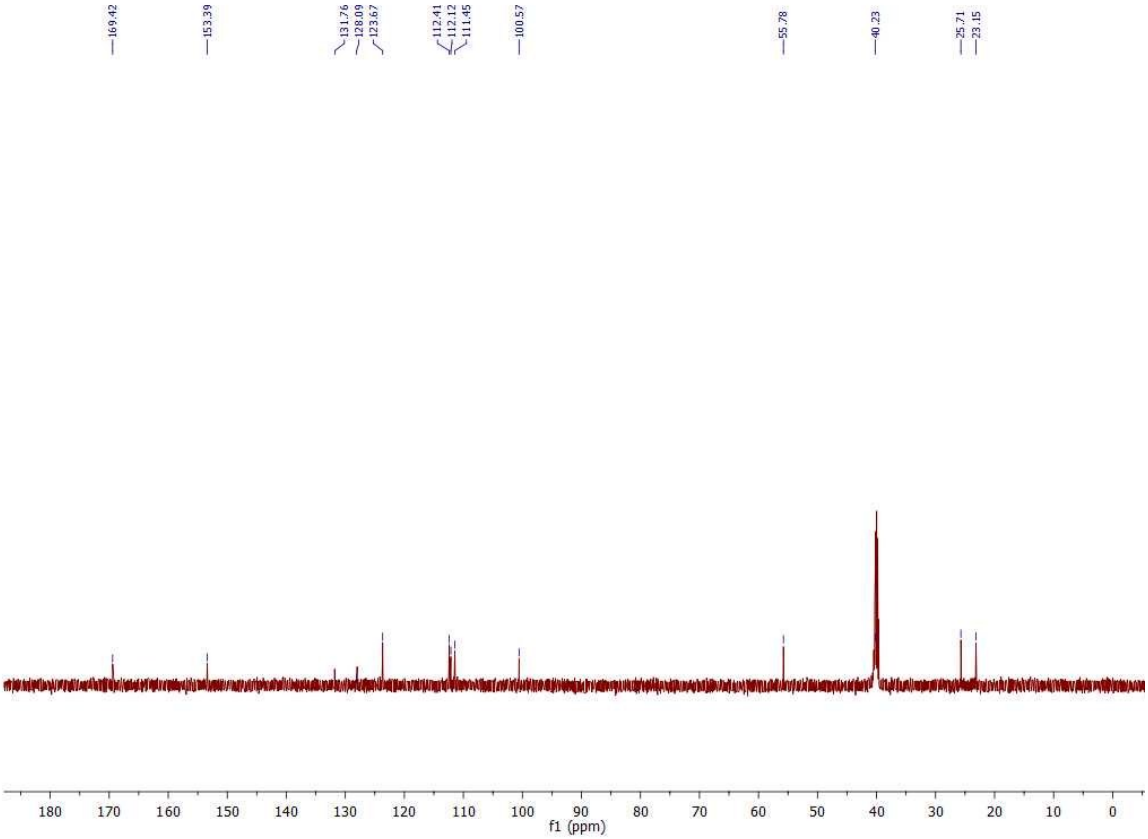


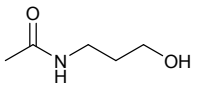




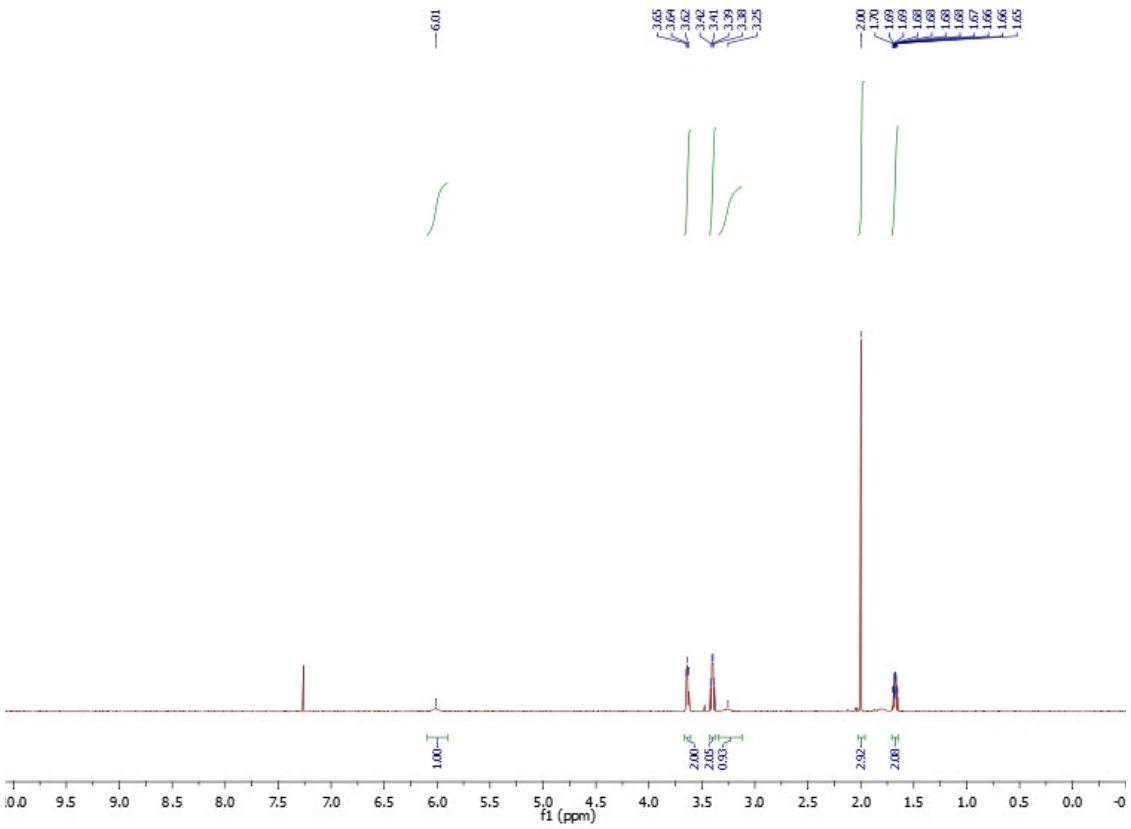
***N*-(2-(5-Methoxy-1H-indol-3-yl)ethyl)acetamide[7] (1k)**

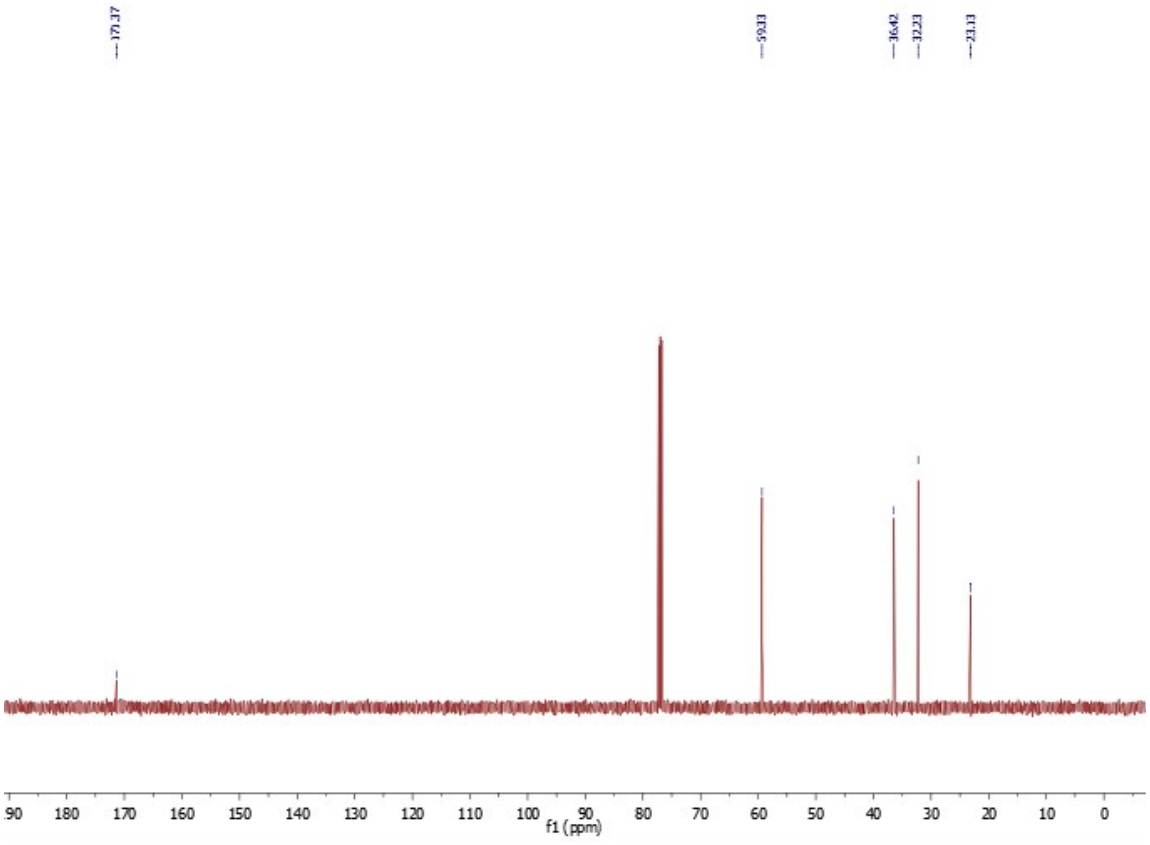


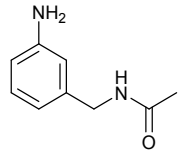




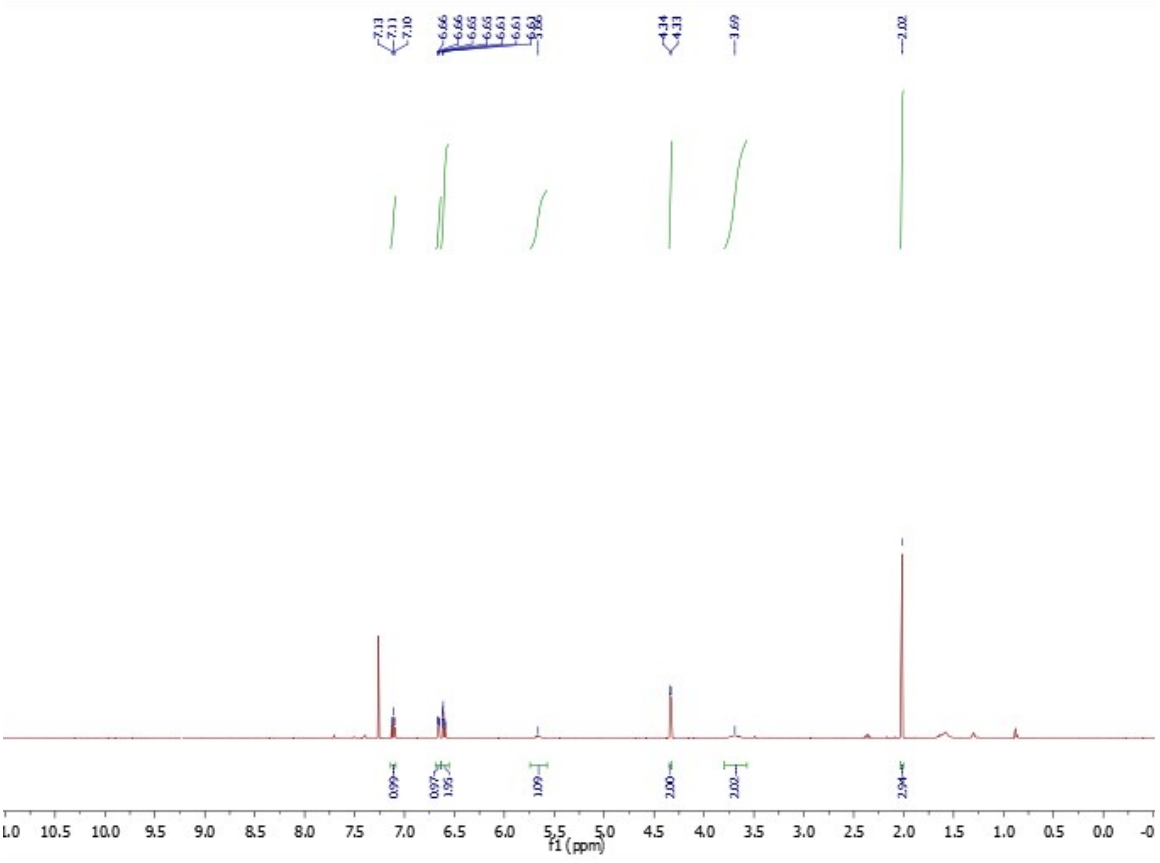
***N*-(3-Hydroxypropyl)acetamide[8] (1m)**

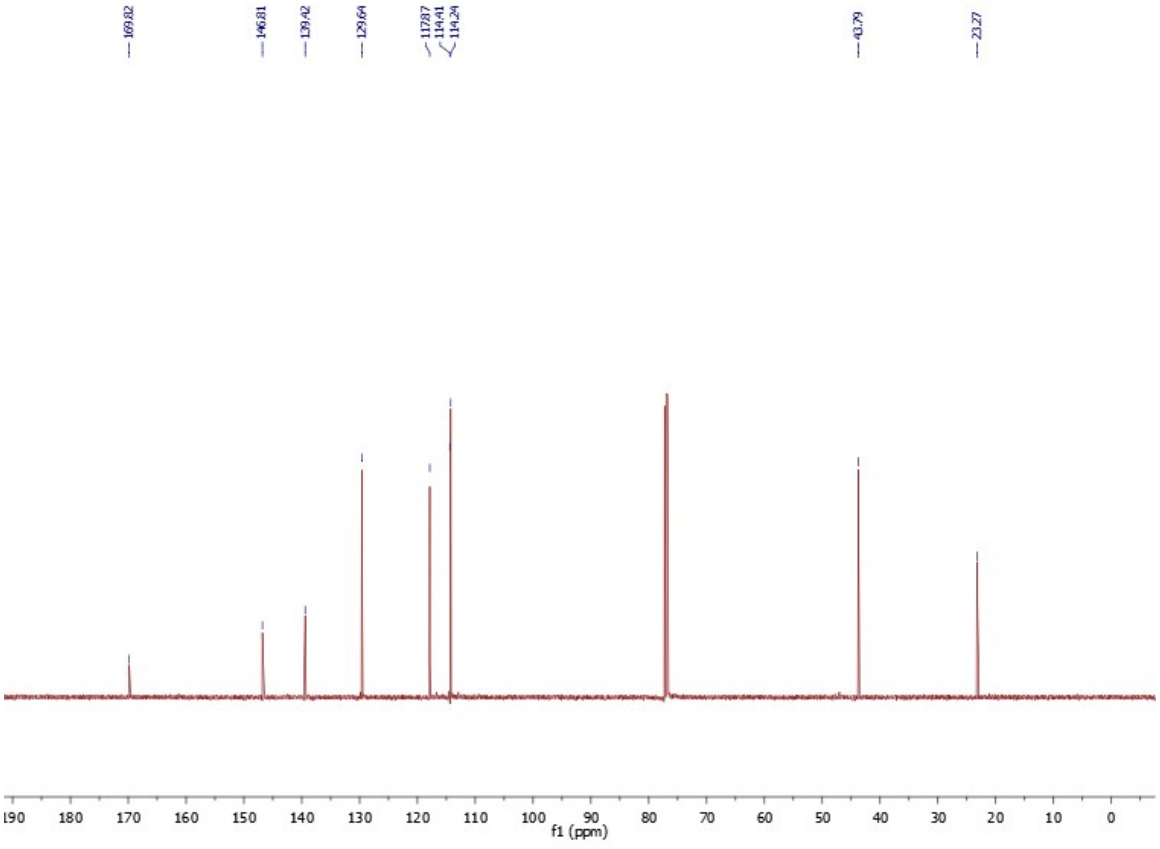


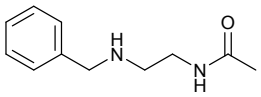




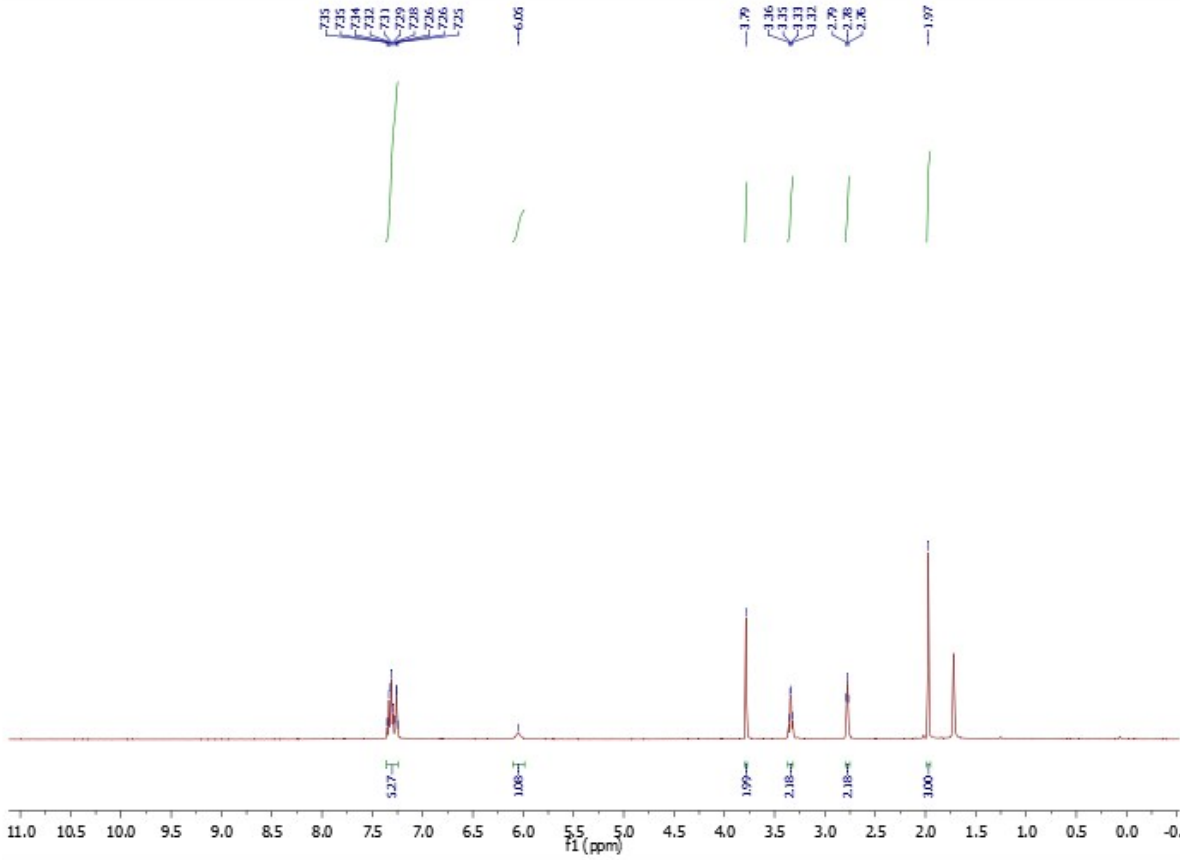
***N*-(3-Aminobenzyl)acetamide[9] (1n)**

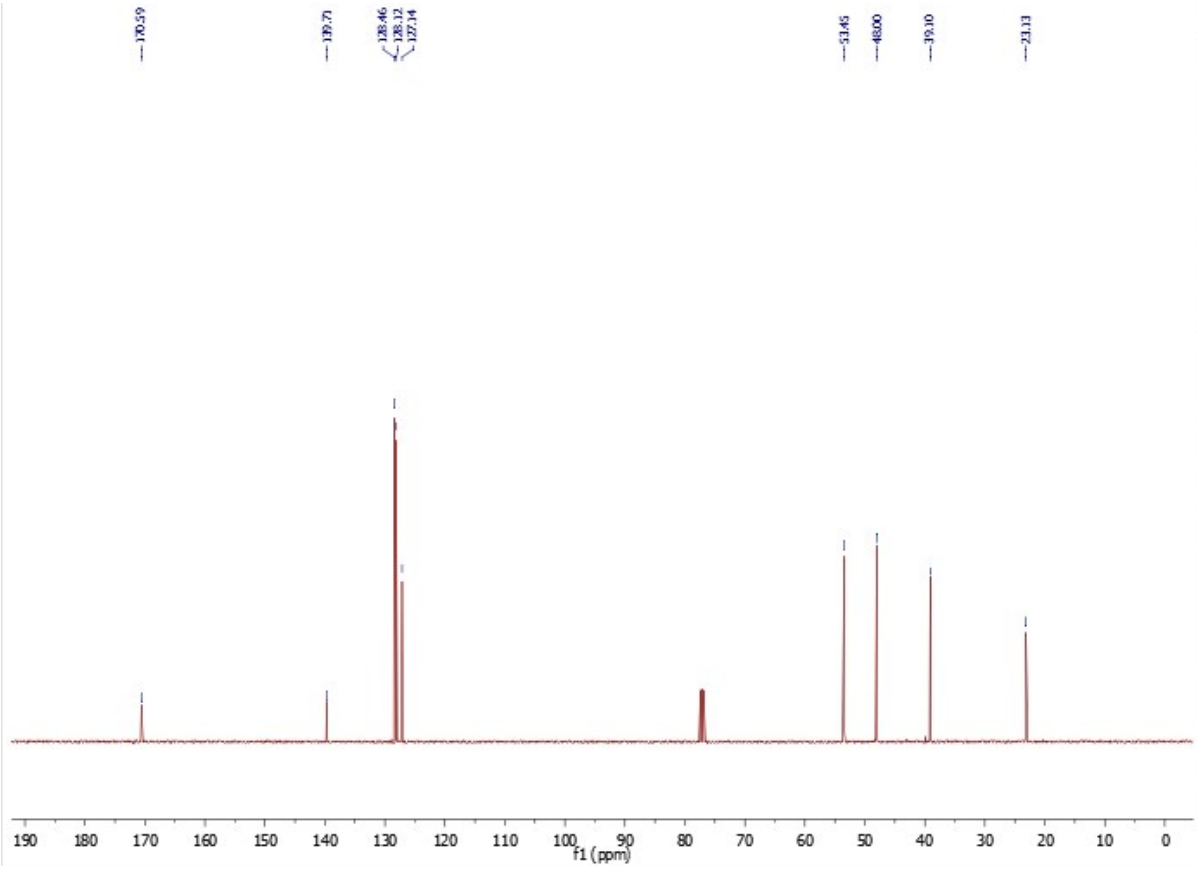


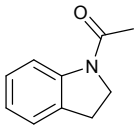




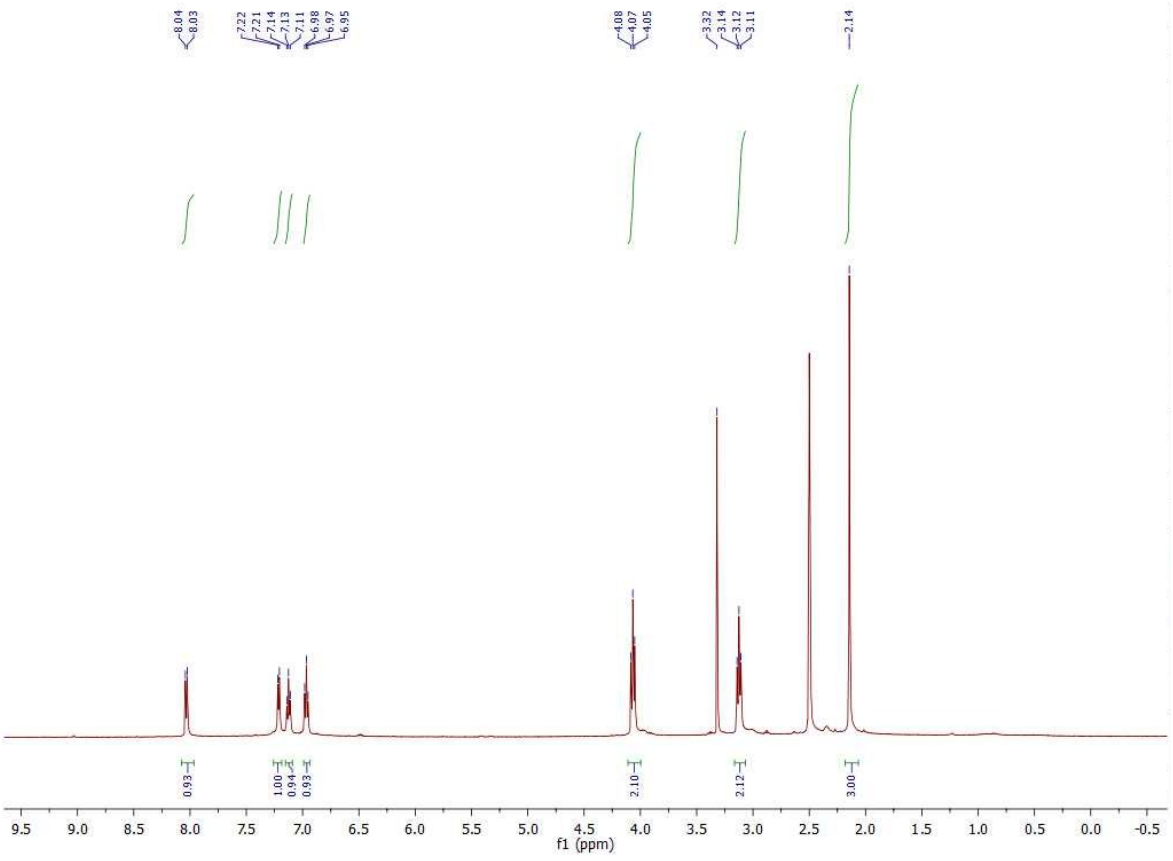
_N_-(2-(Benzylamino)ethyl)acetamide[10] (1o)

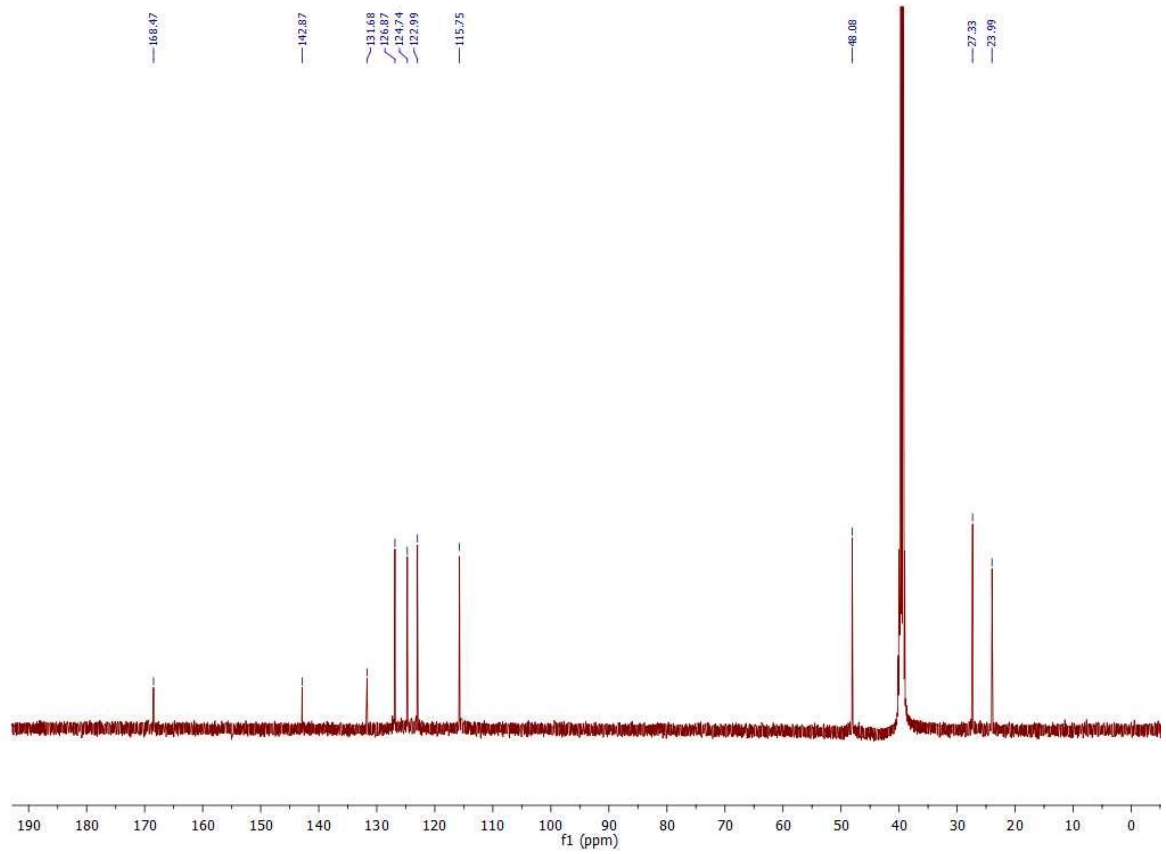


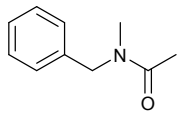




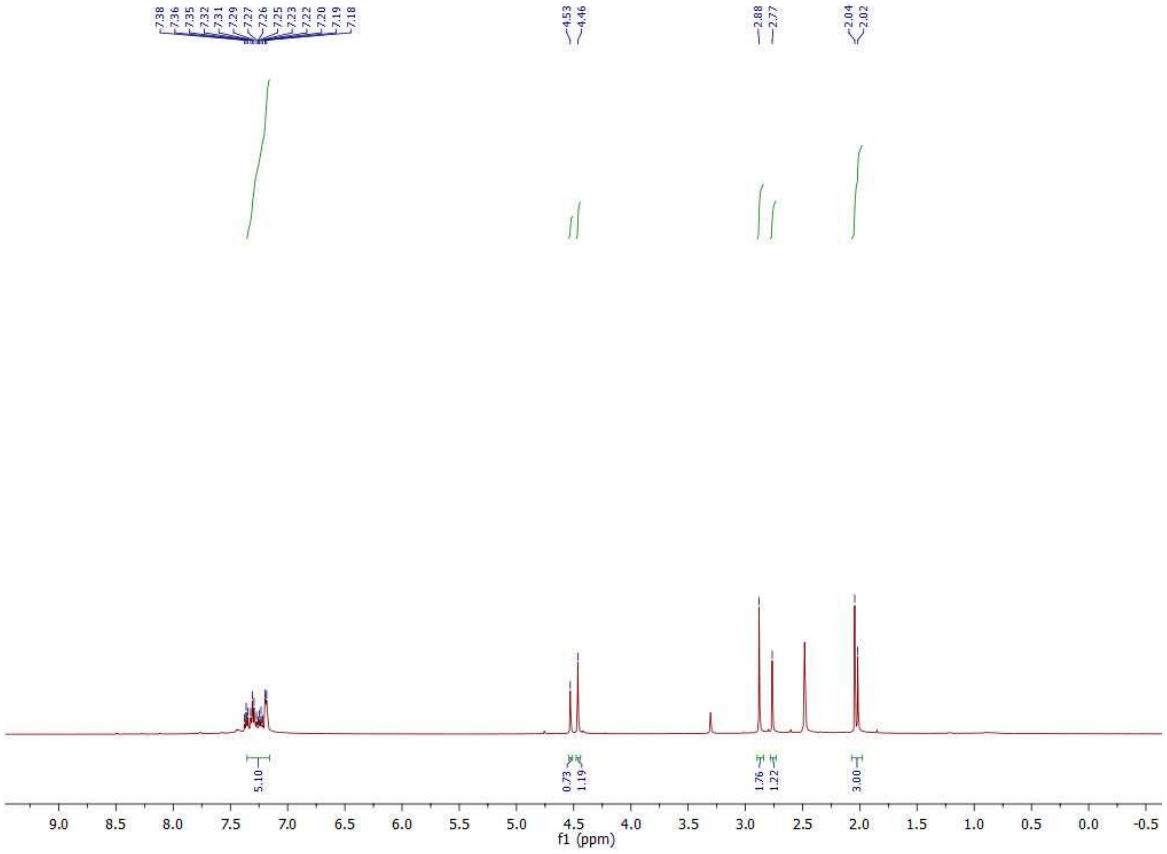
1-(Indolin-1-yl)ethan-1-one[11] (2a)

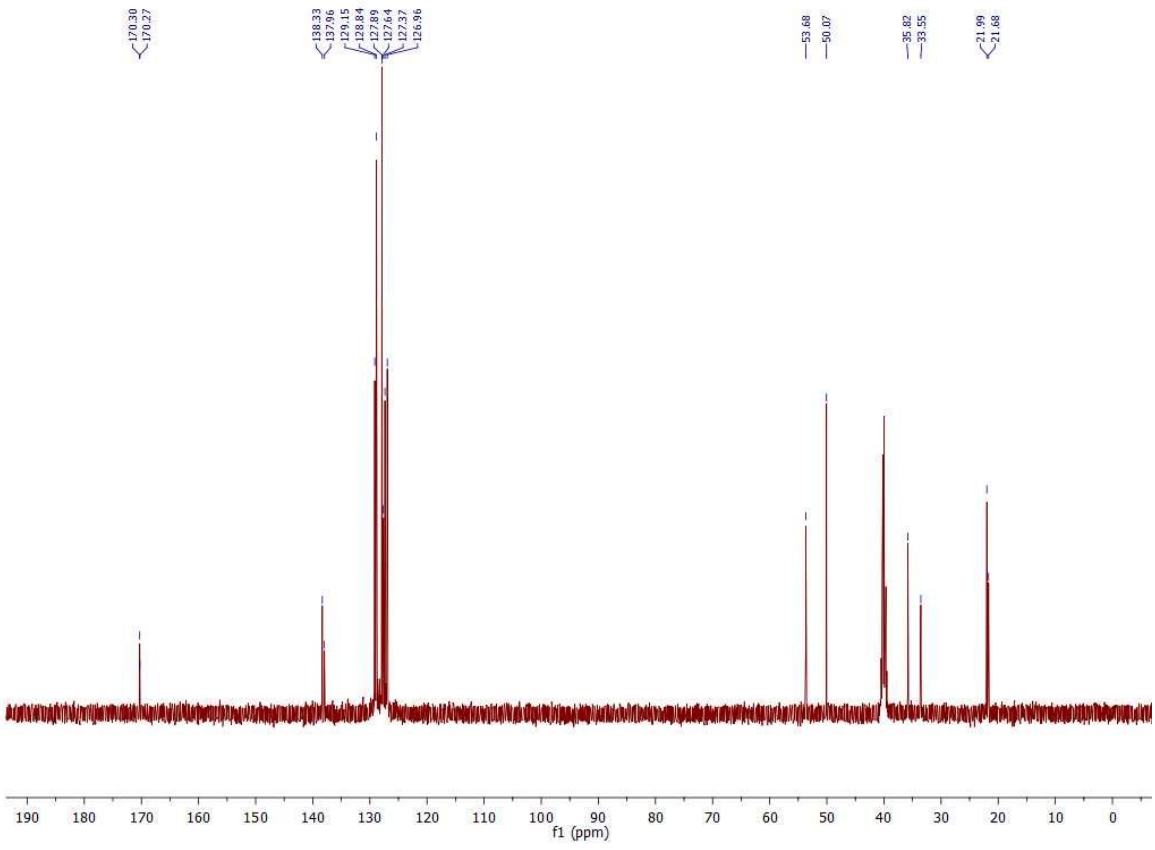


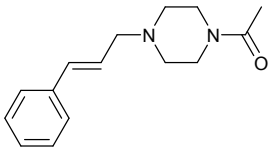




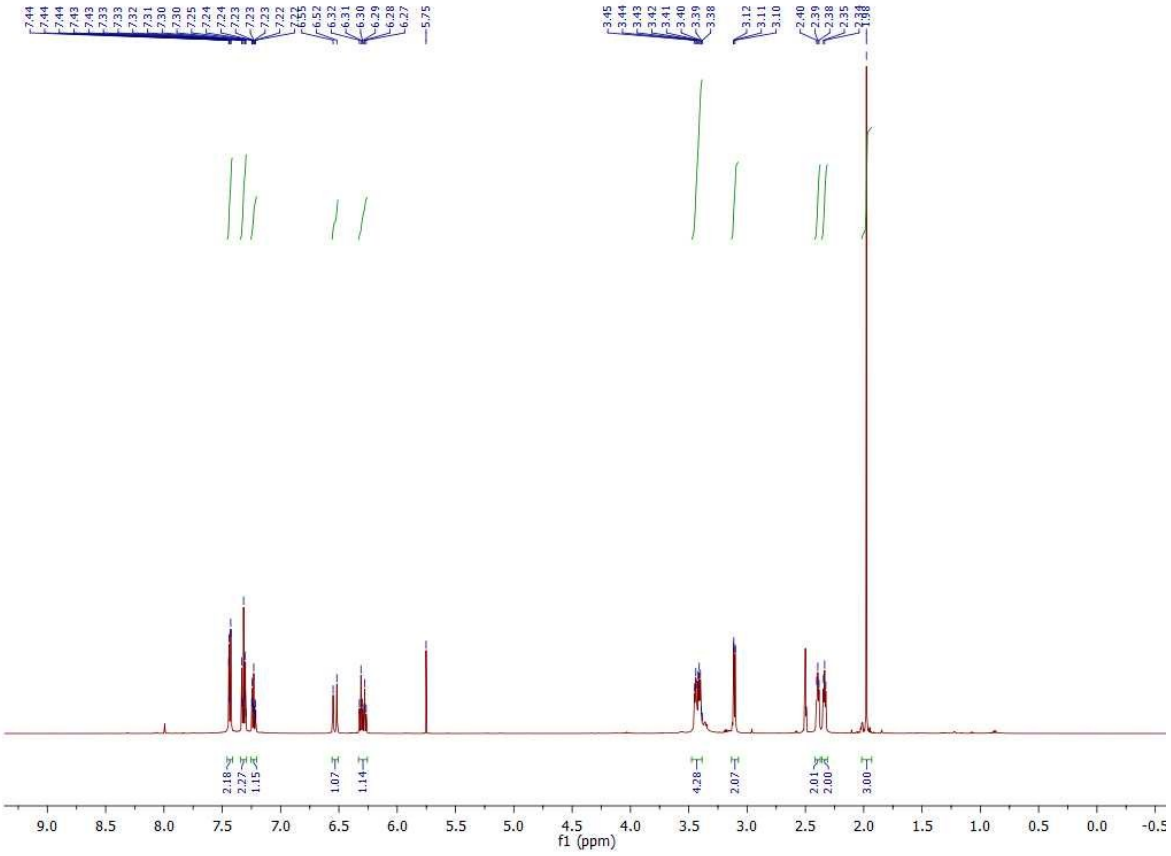
_N_-Benzyl-_N_-methylacetamide[12] (2b)

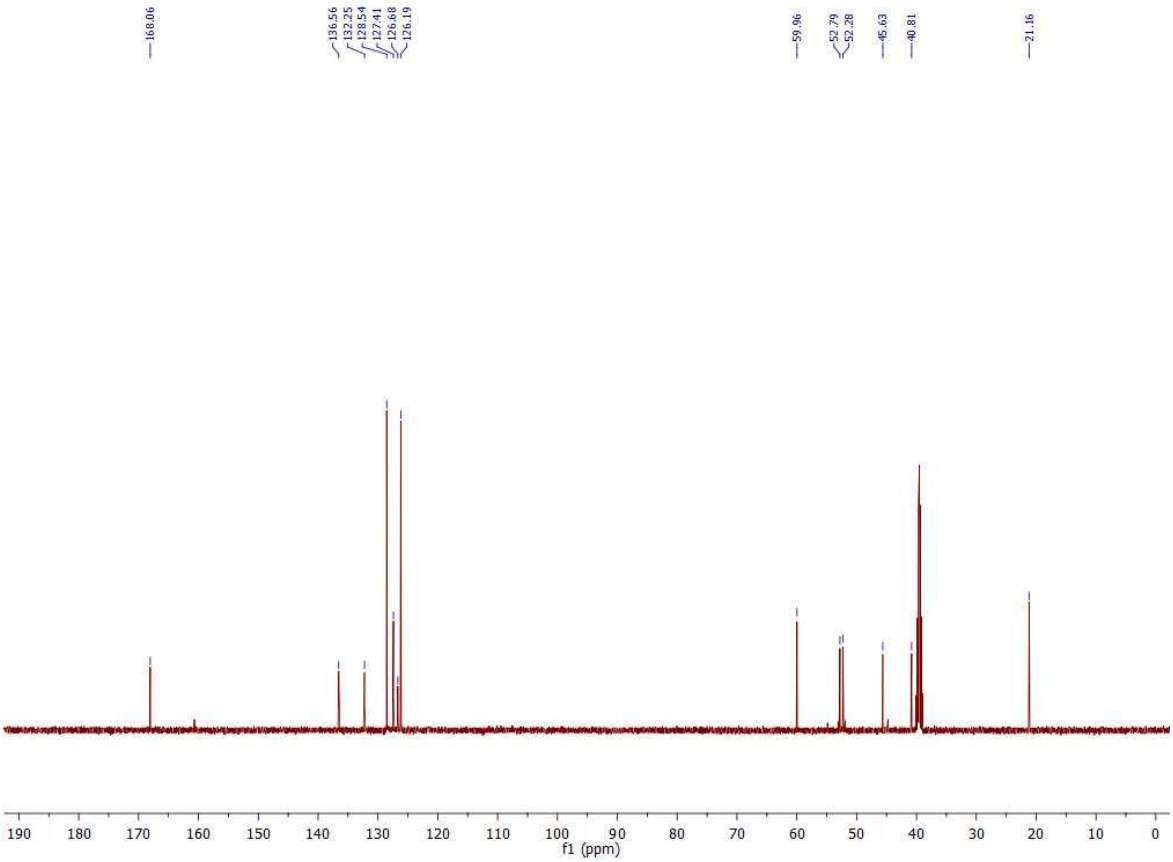


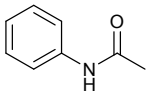




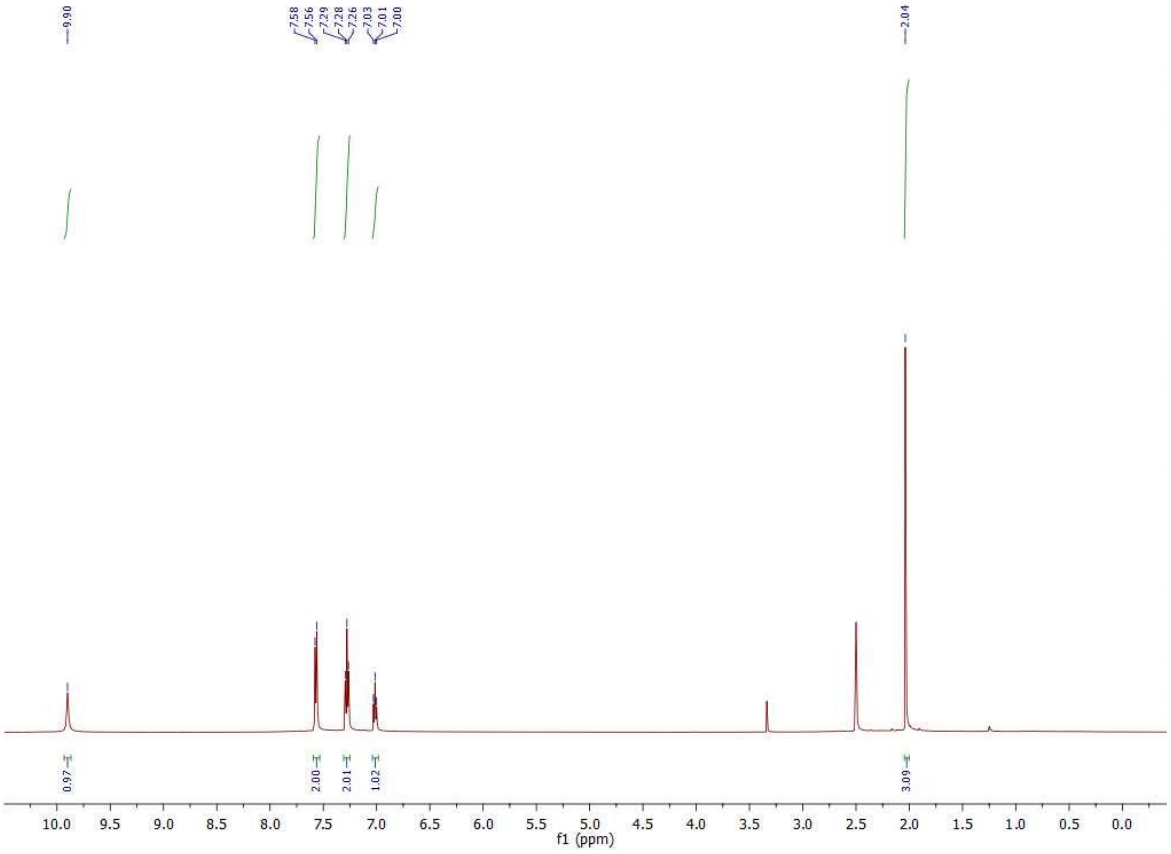
1-(4-Cinnamylpiperazin-1-yl)ethan-1-one (2c)

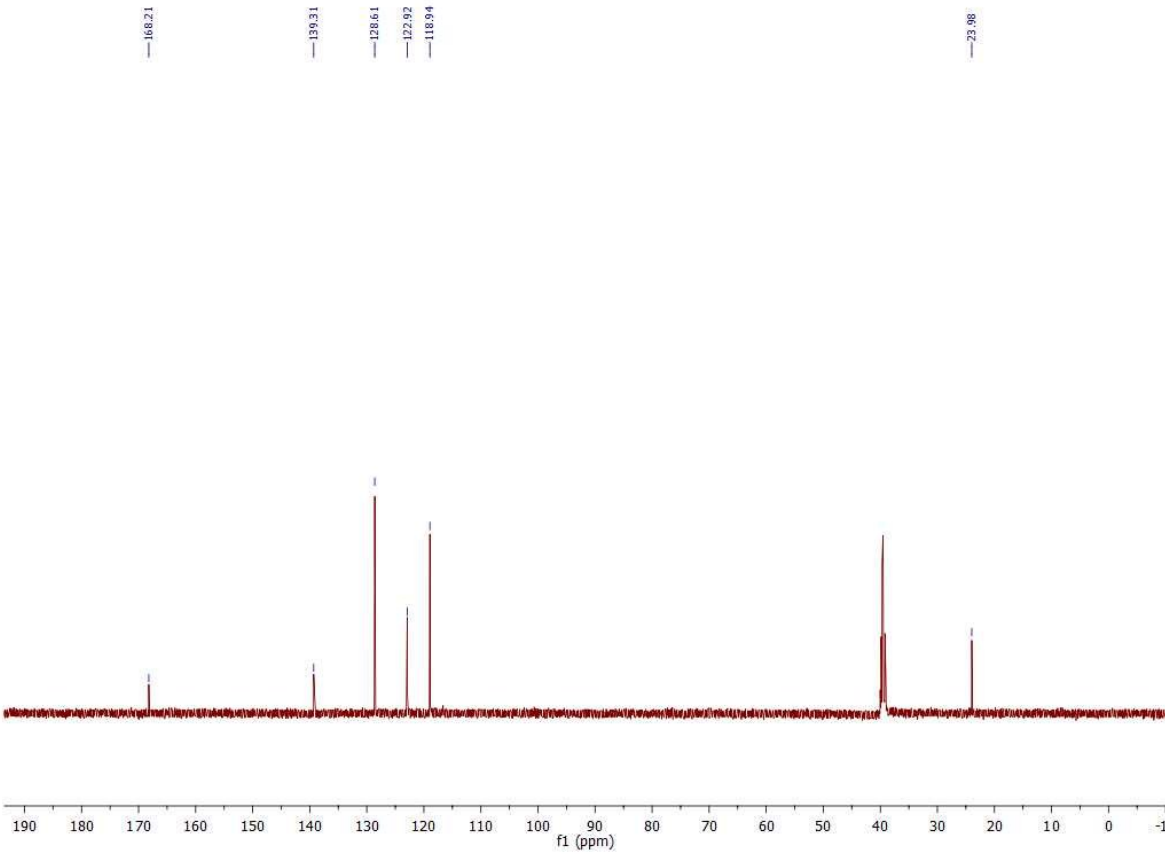


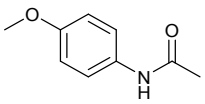




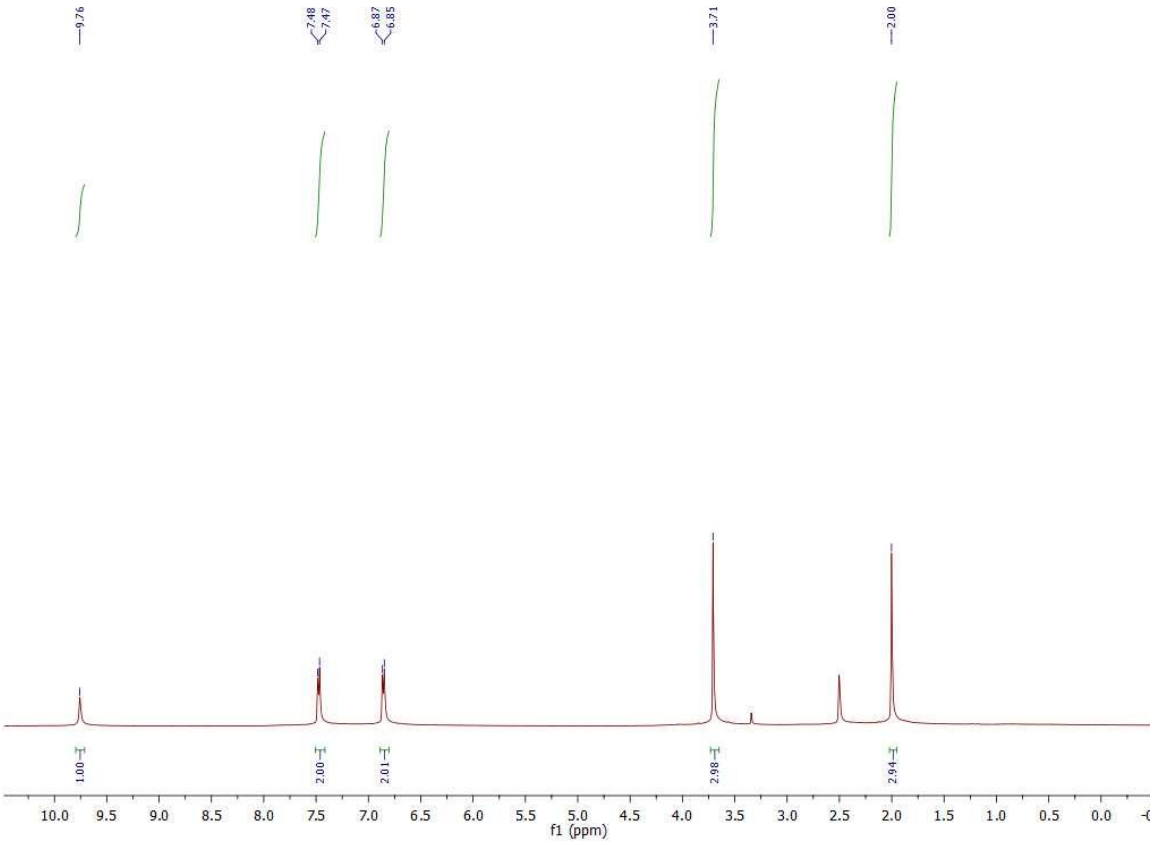
_N_-Phenylacetamide[13] (3a)

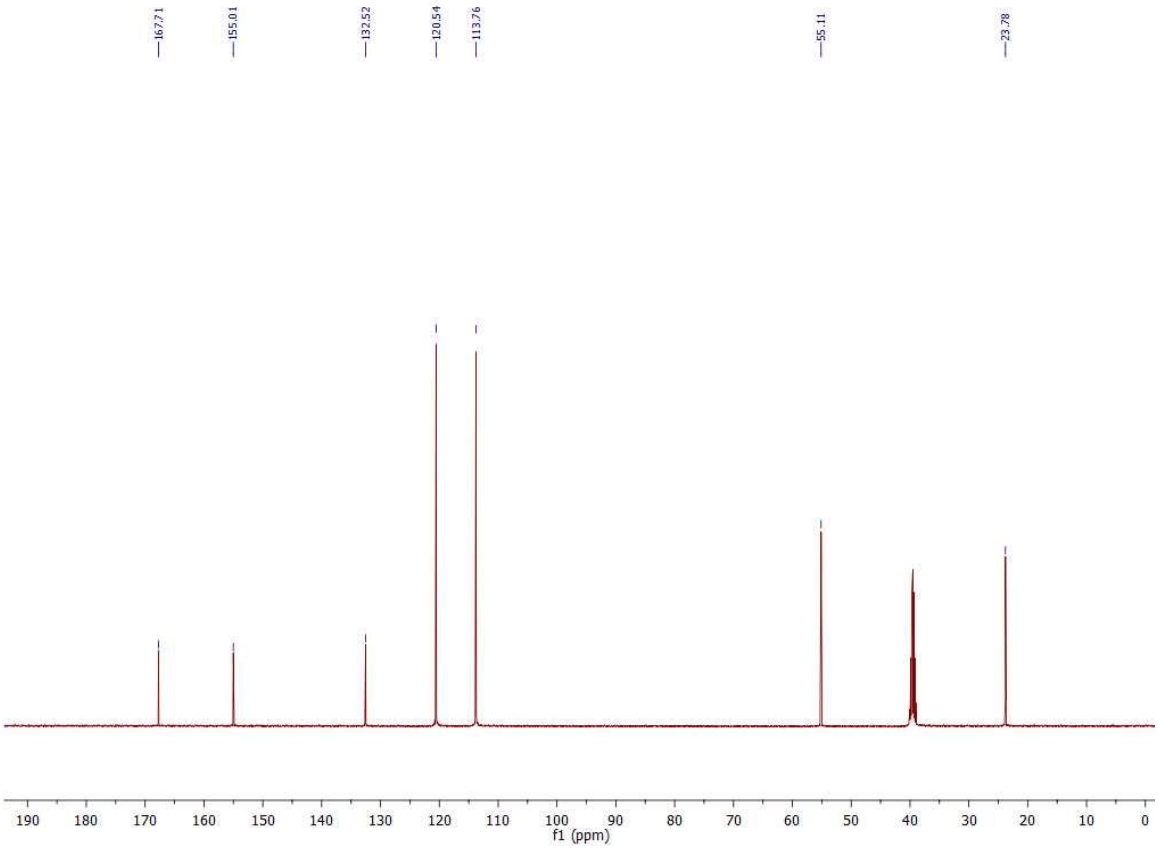


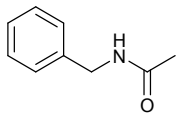




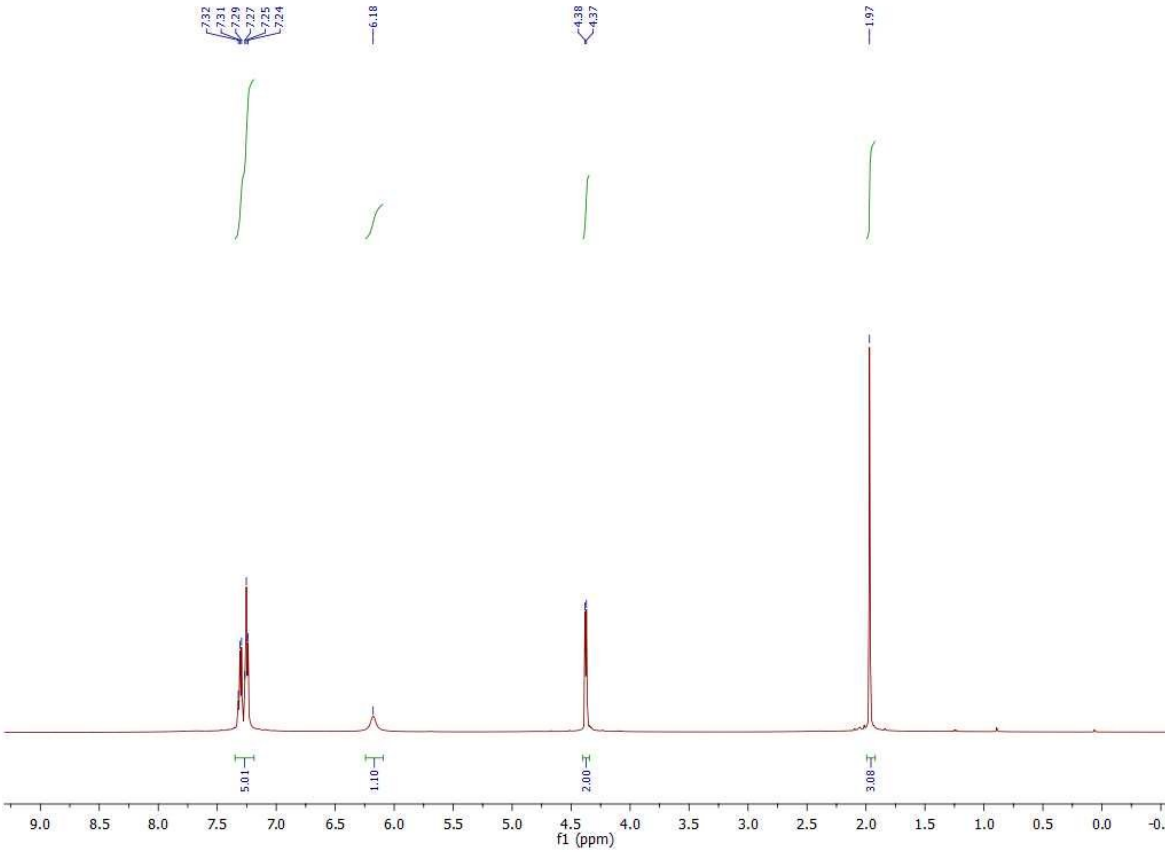
_N_-(4-Methoxyphenyl)acetamide[13] (3b)

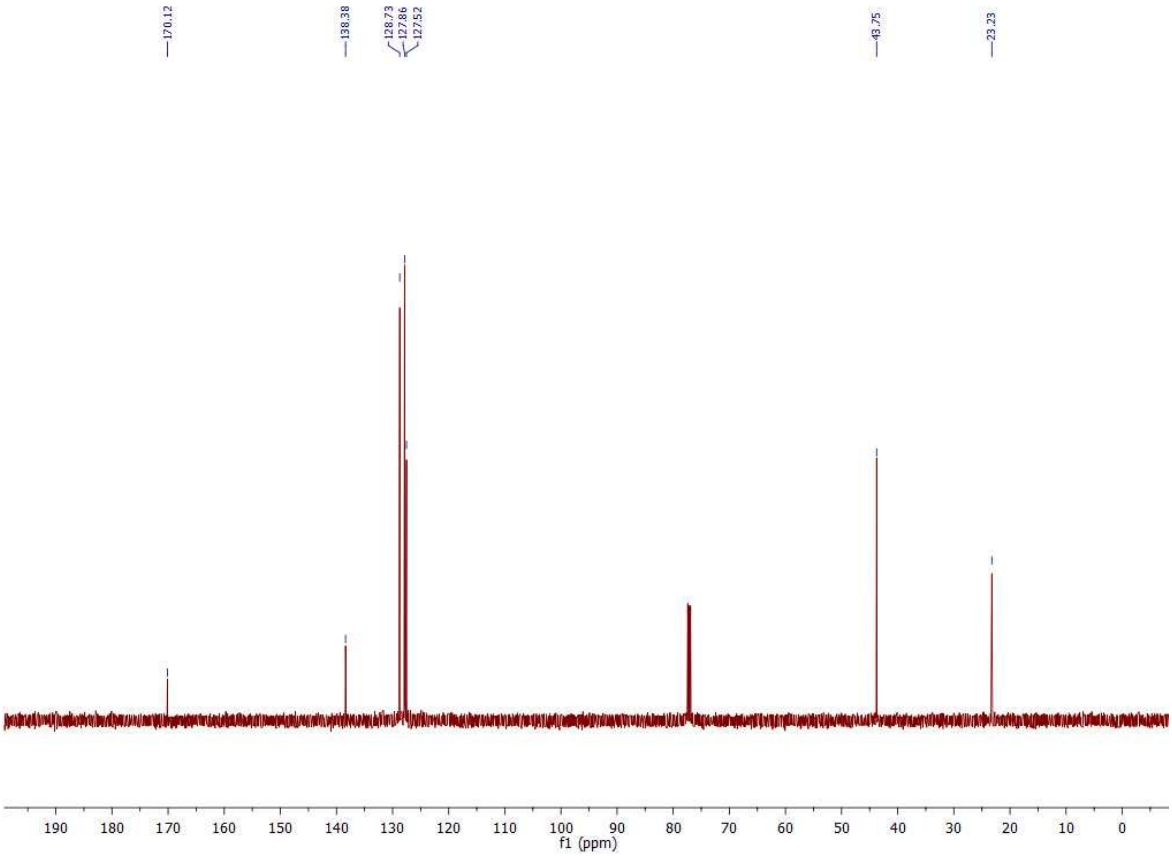


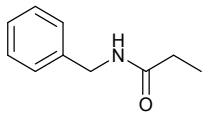




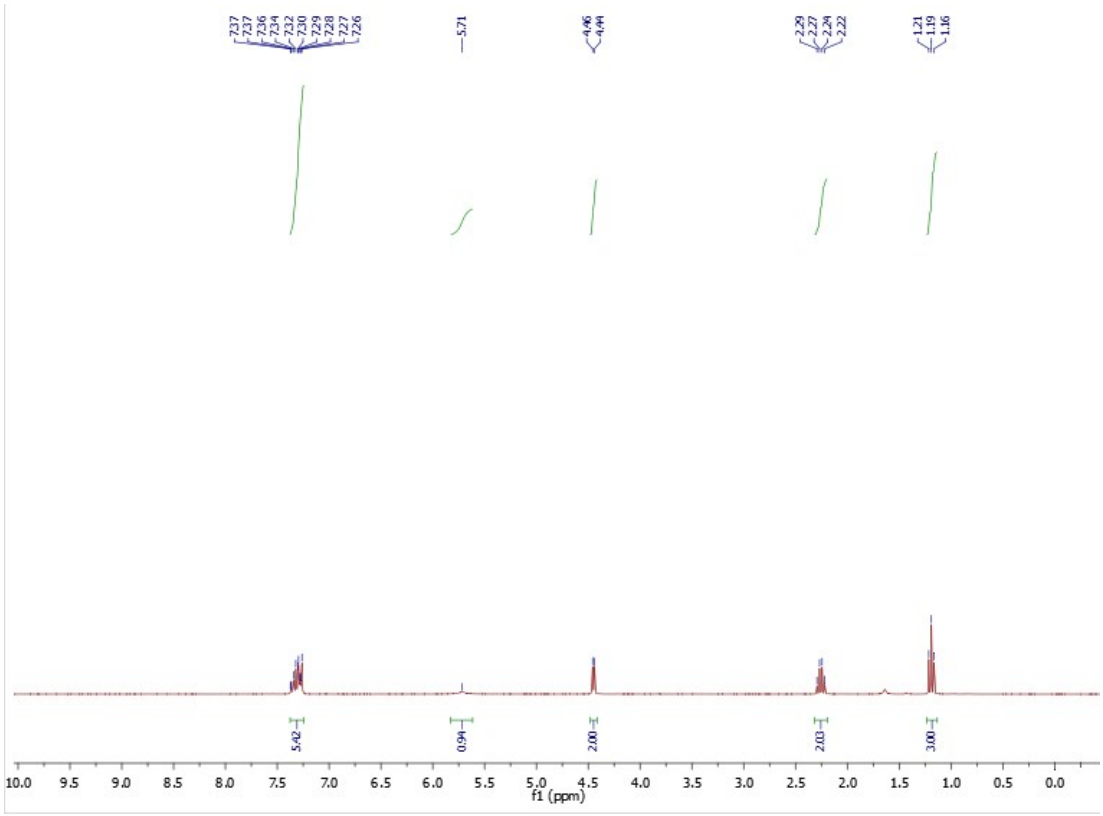
_N_-Benzylacetamide Scale-Up[14] (1a)

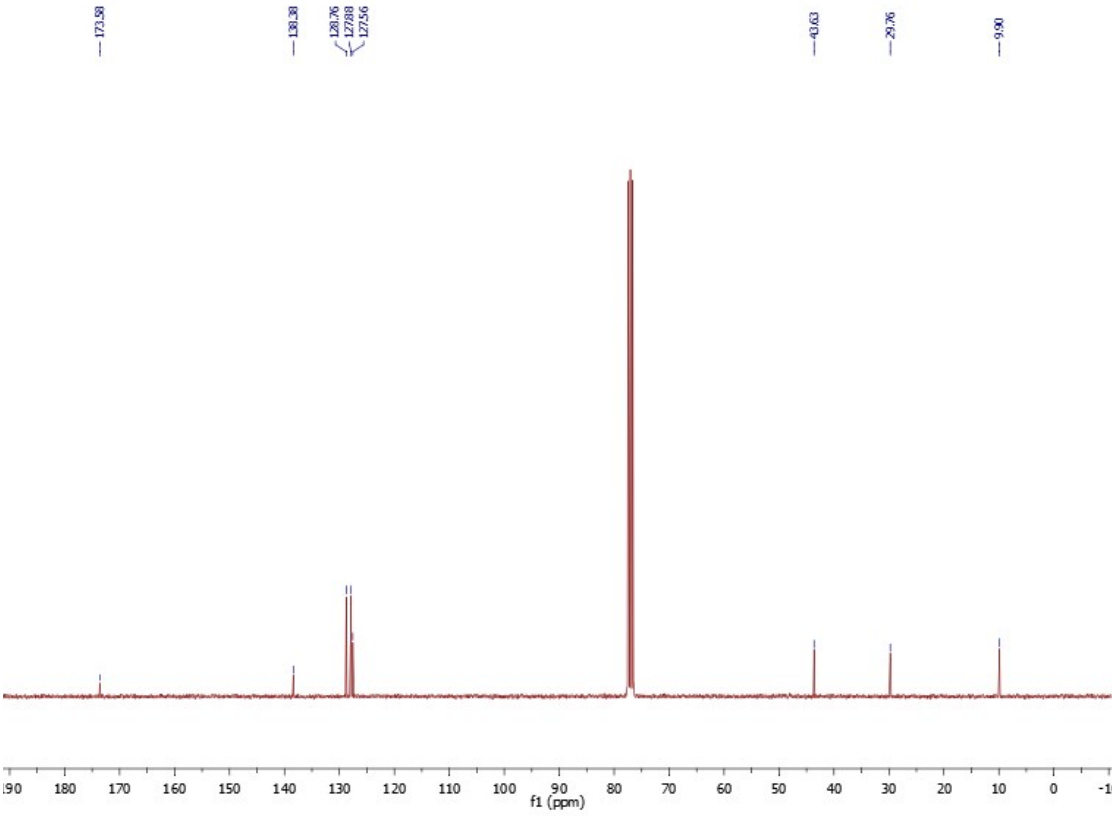


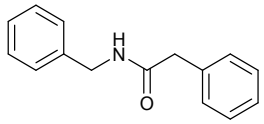




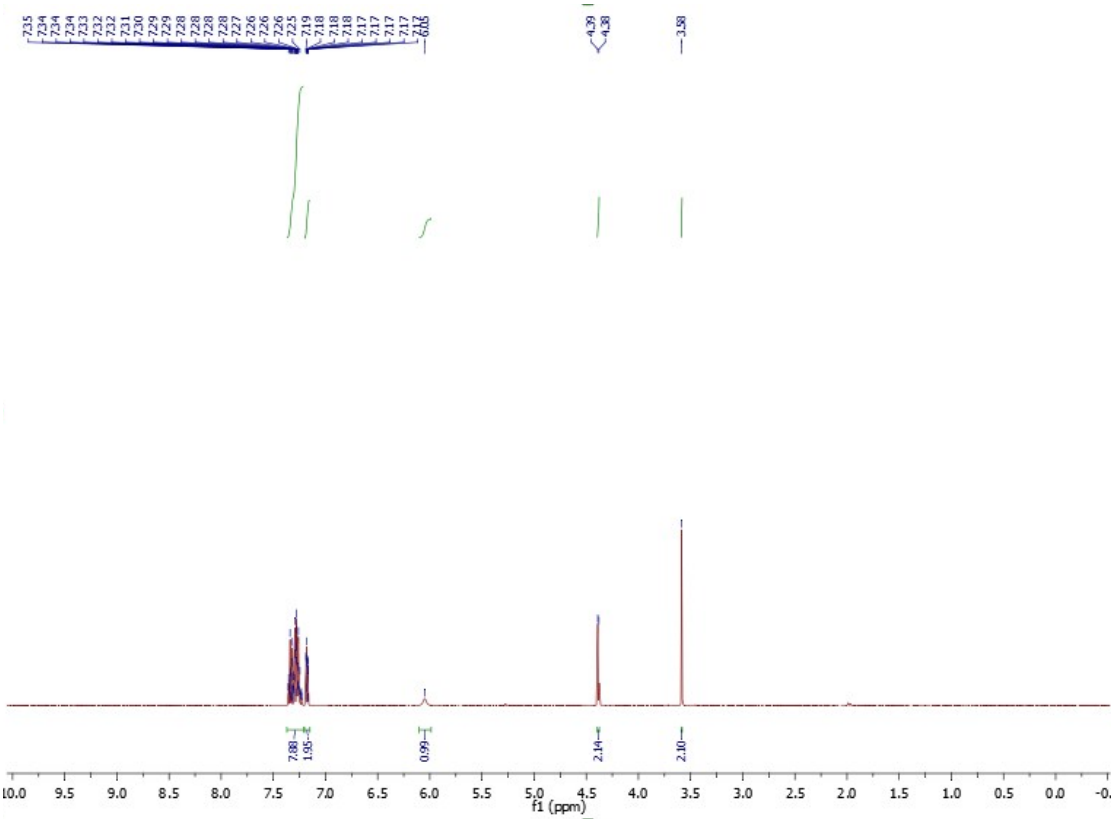
_N_-Benzylpropionamide[16] (7a)

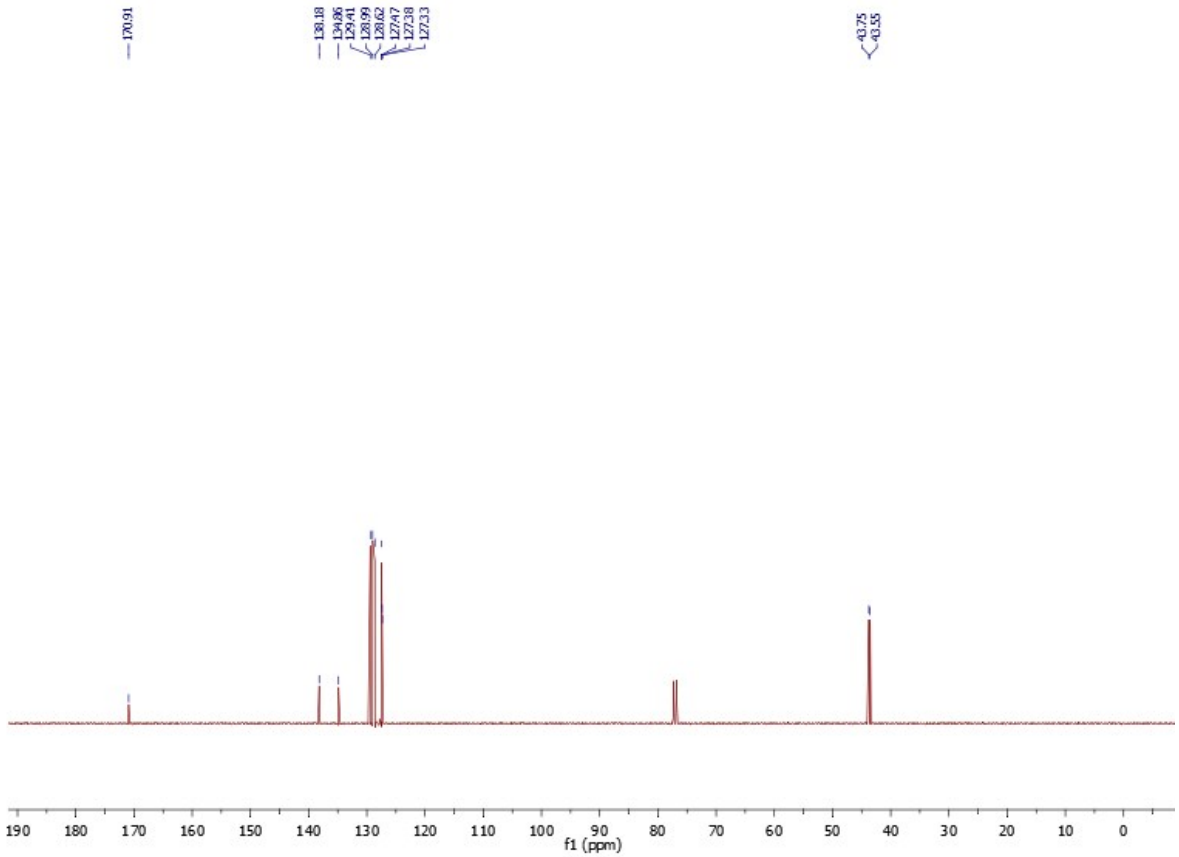


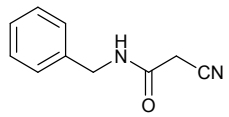




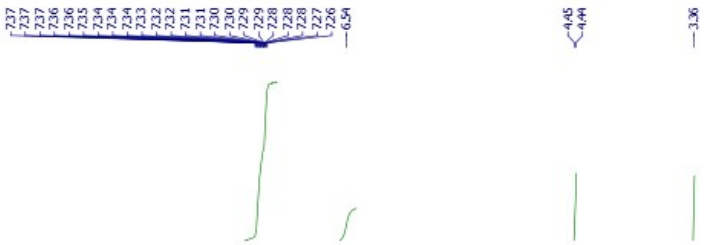
_N_-Benzyl-2-phenylacetamide[17] (7b)

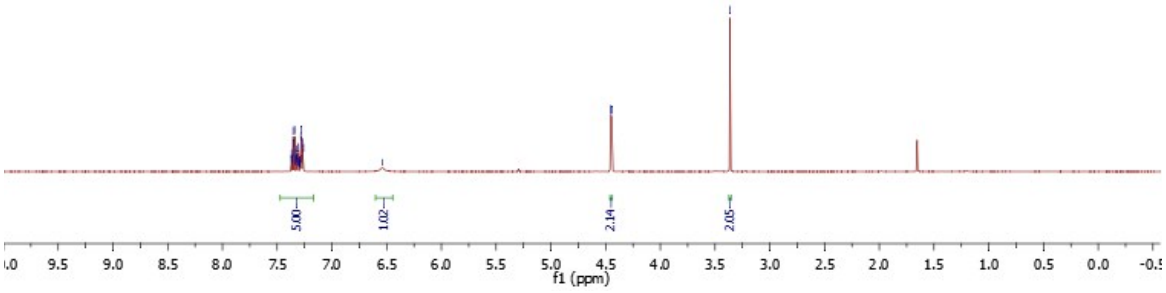


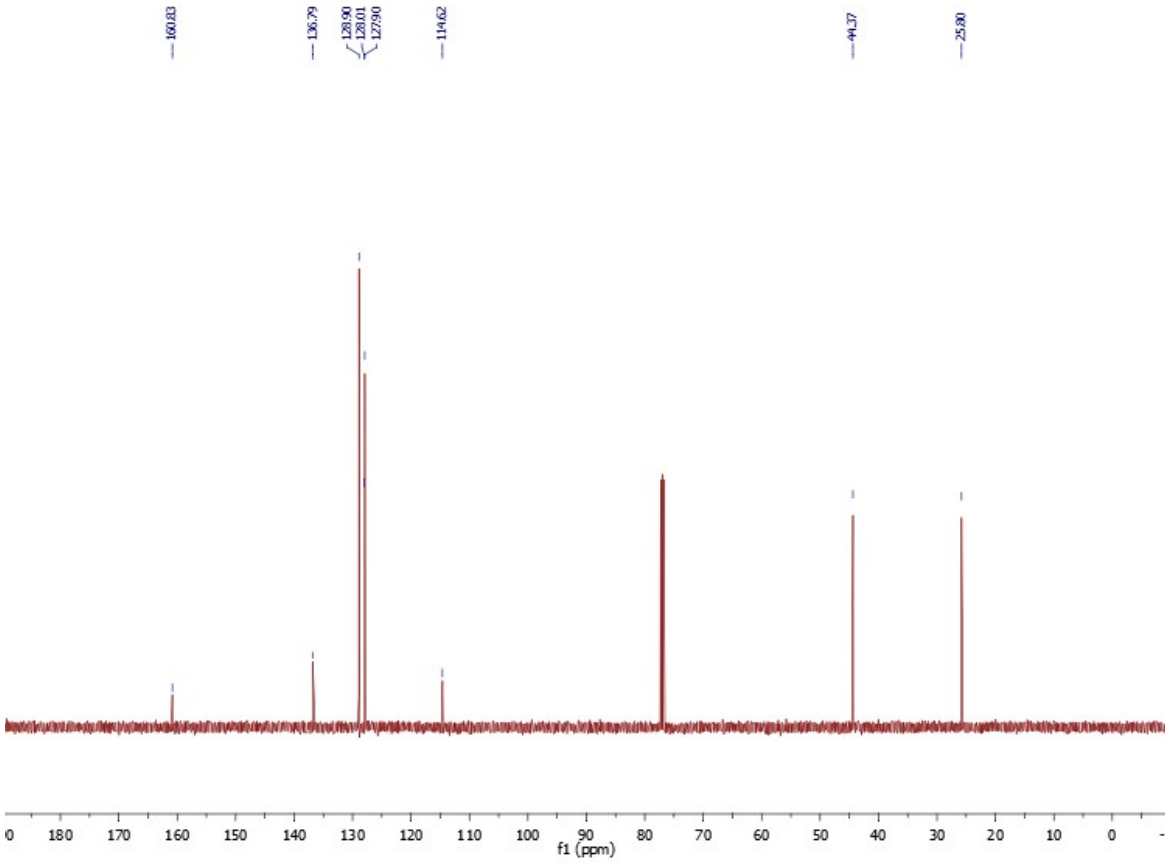


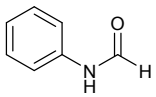


***N*-Benzyl-2-cyanoacetamide**[18] **(7c)**

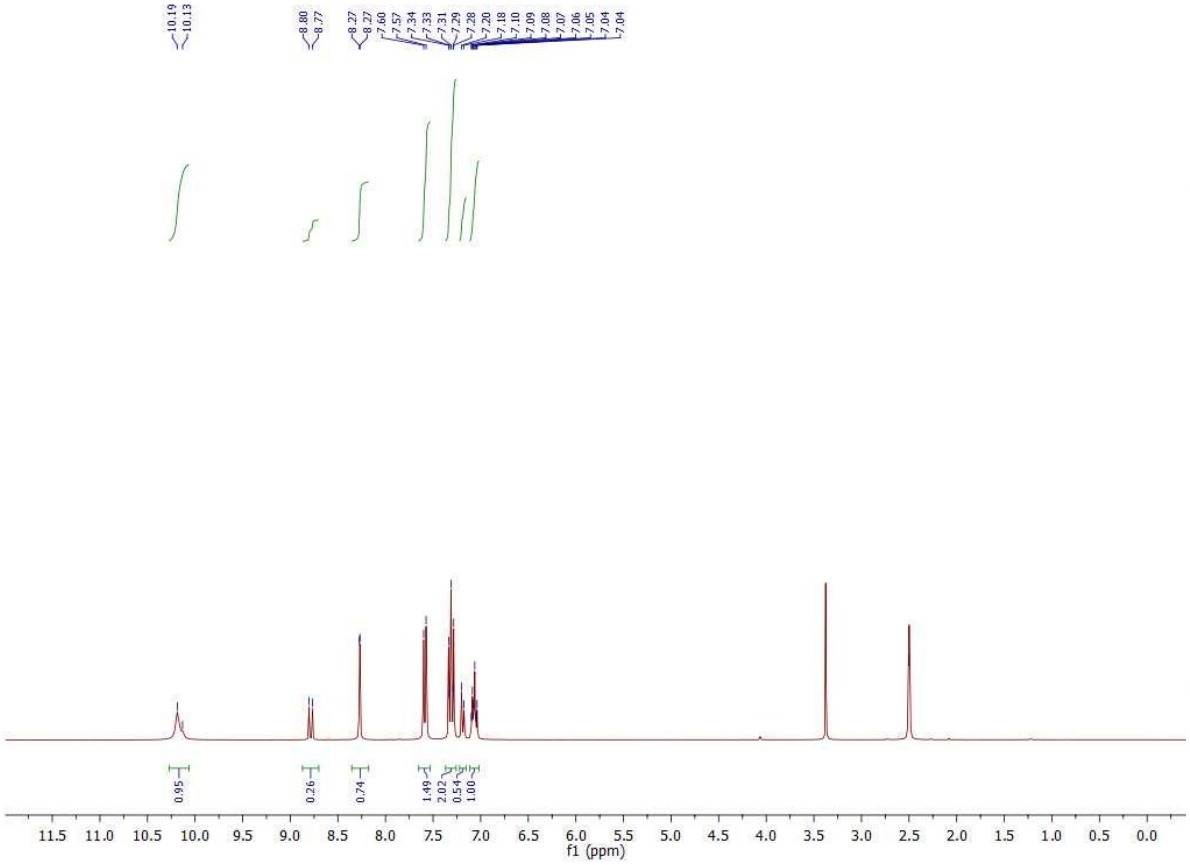


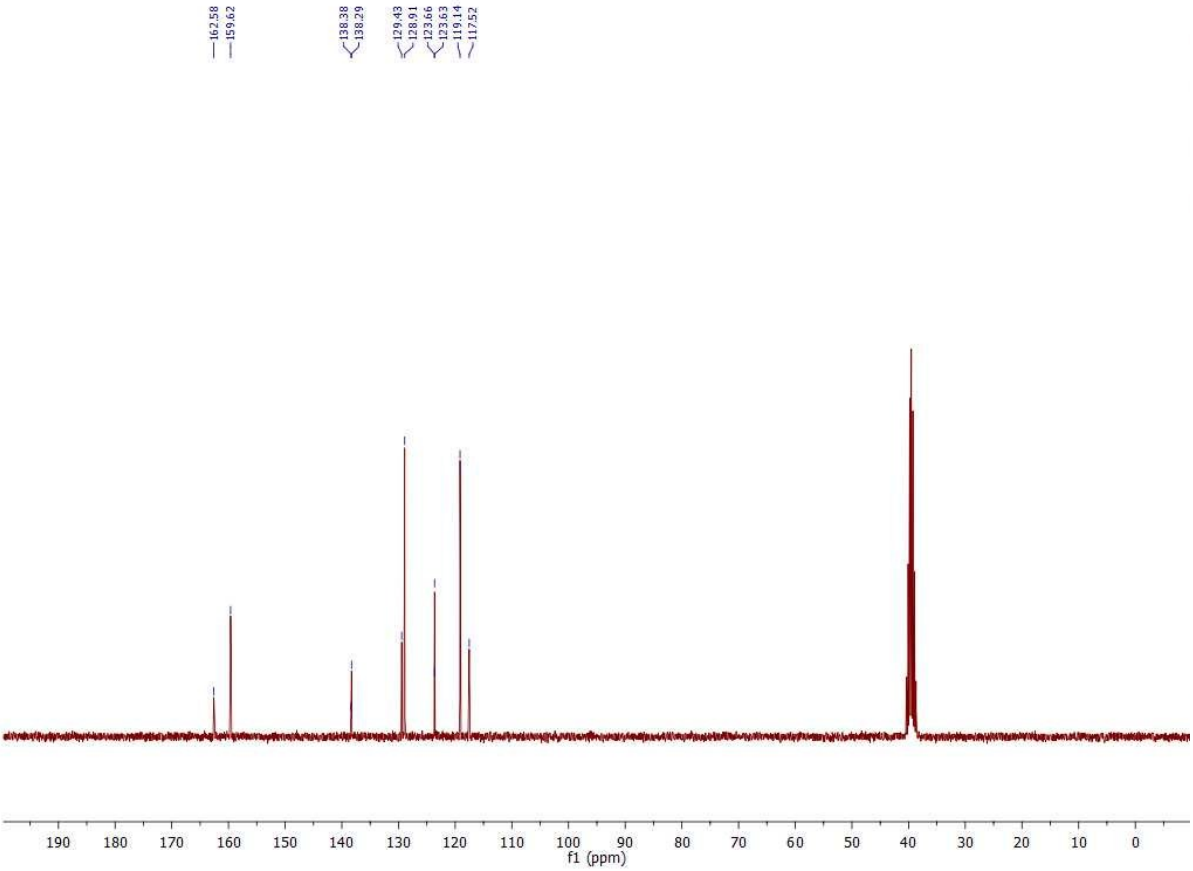


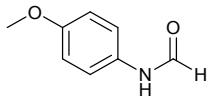




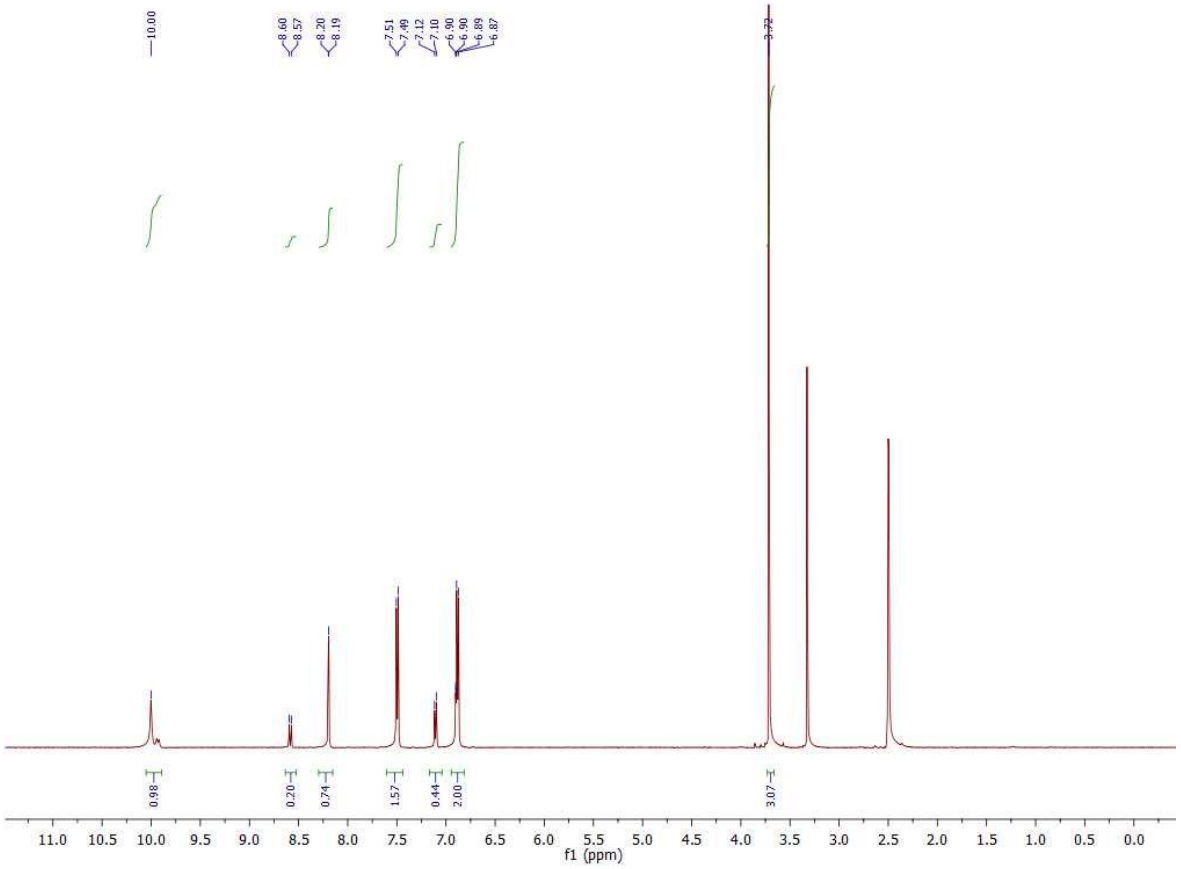
_N_-Phenylformamide[15] (7d)

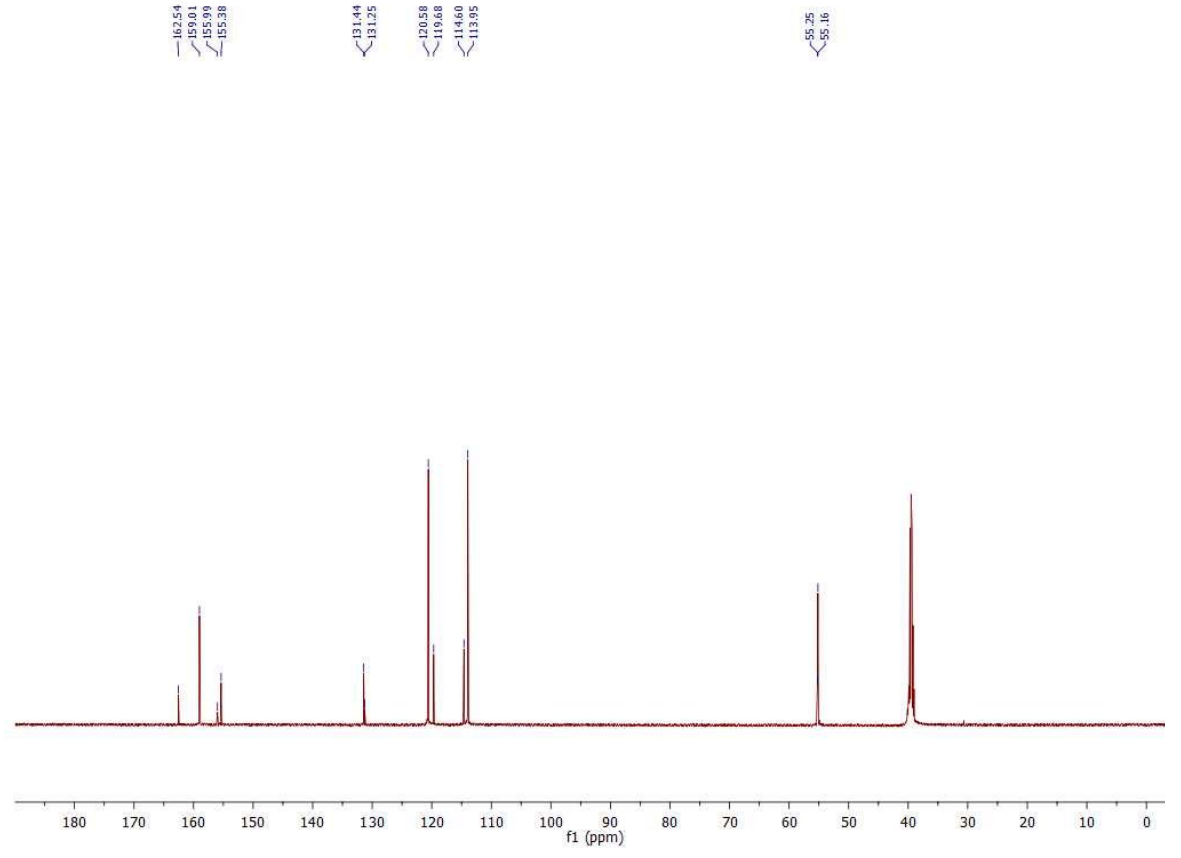


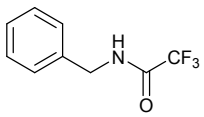




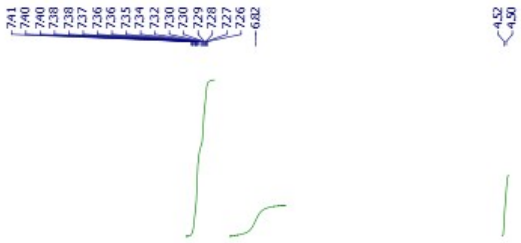
_N_-(4-Methoxyphenyl)formamide[15] (7e)

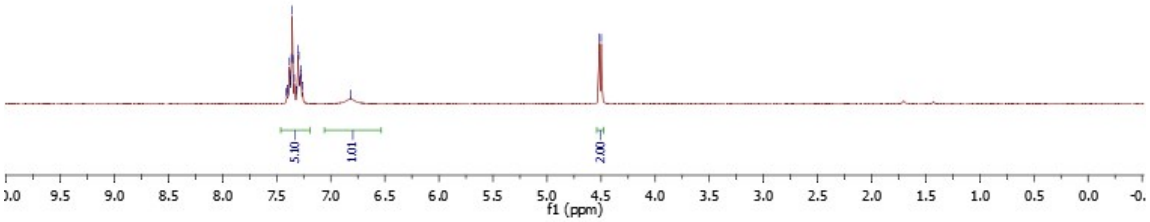


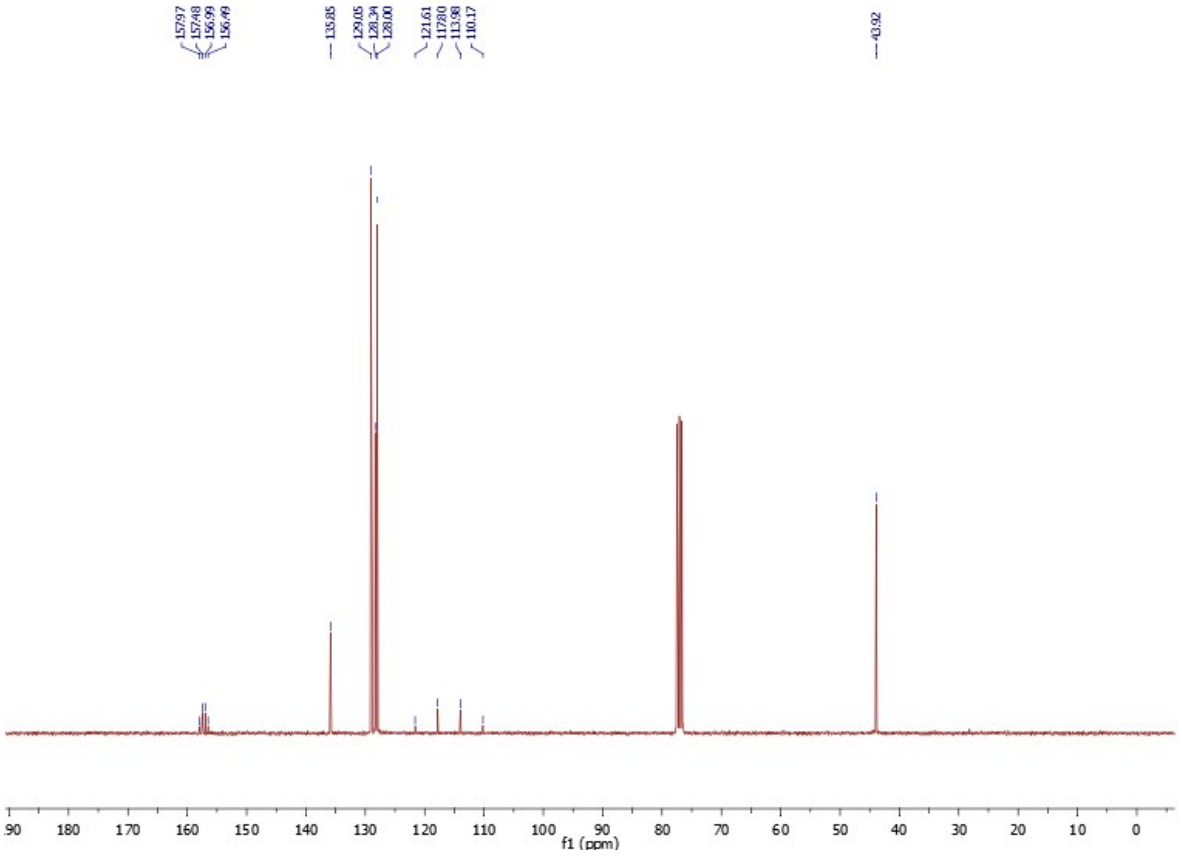


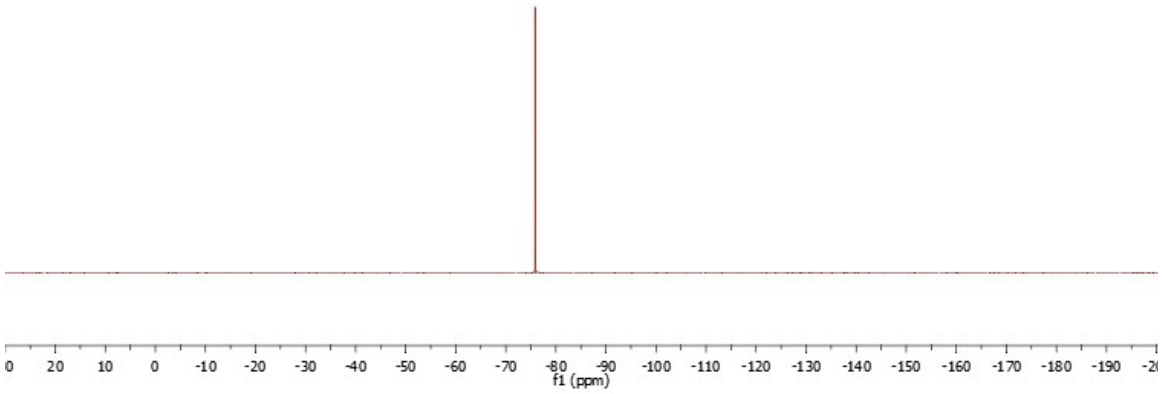


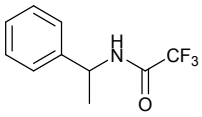
***N*-Benzyl-2,2,2-trifluoroacetamide**[19] **(7f)**



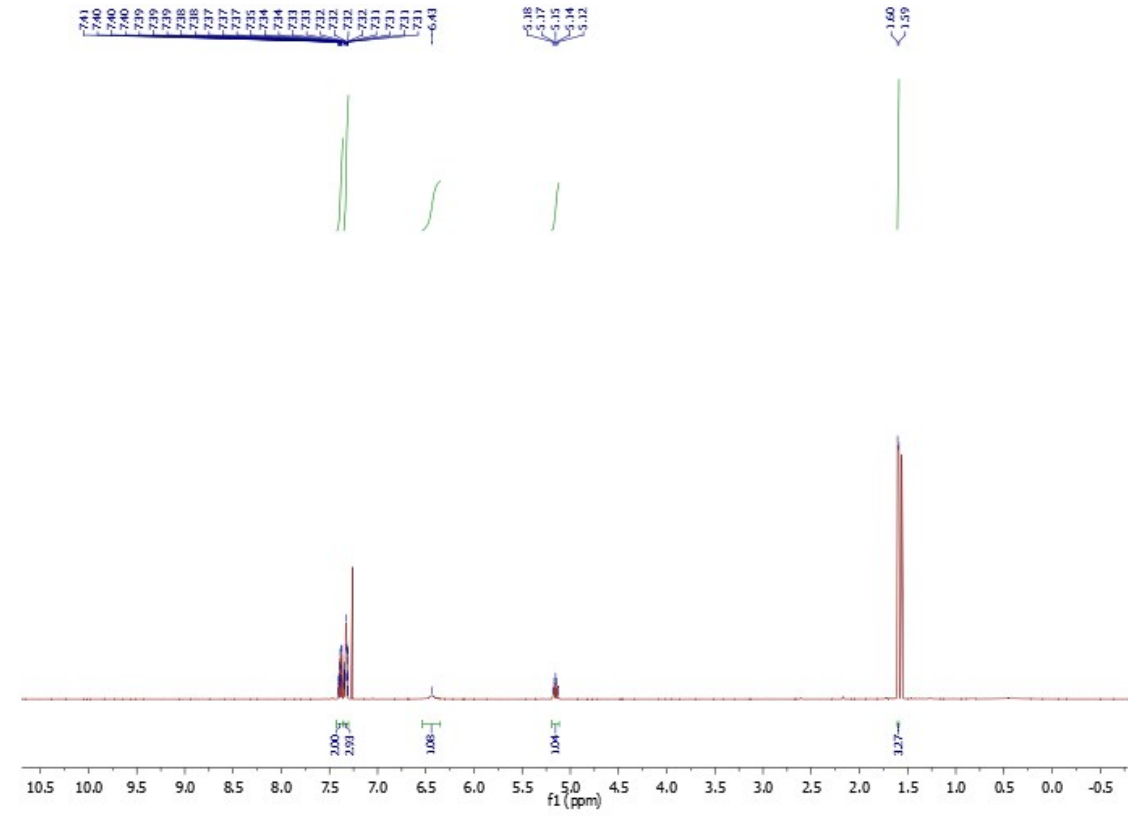


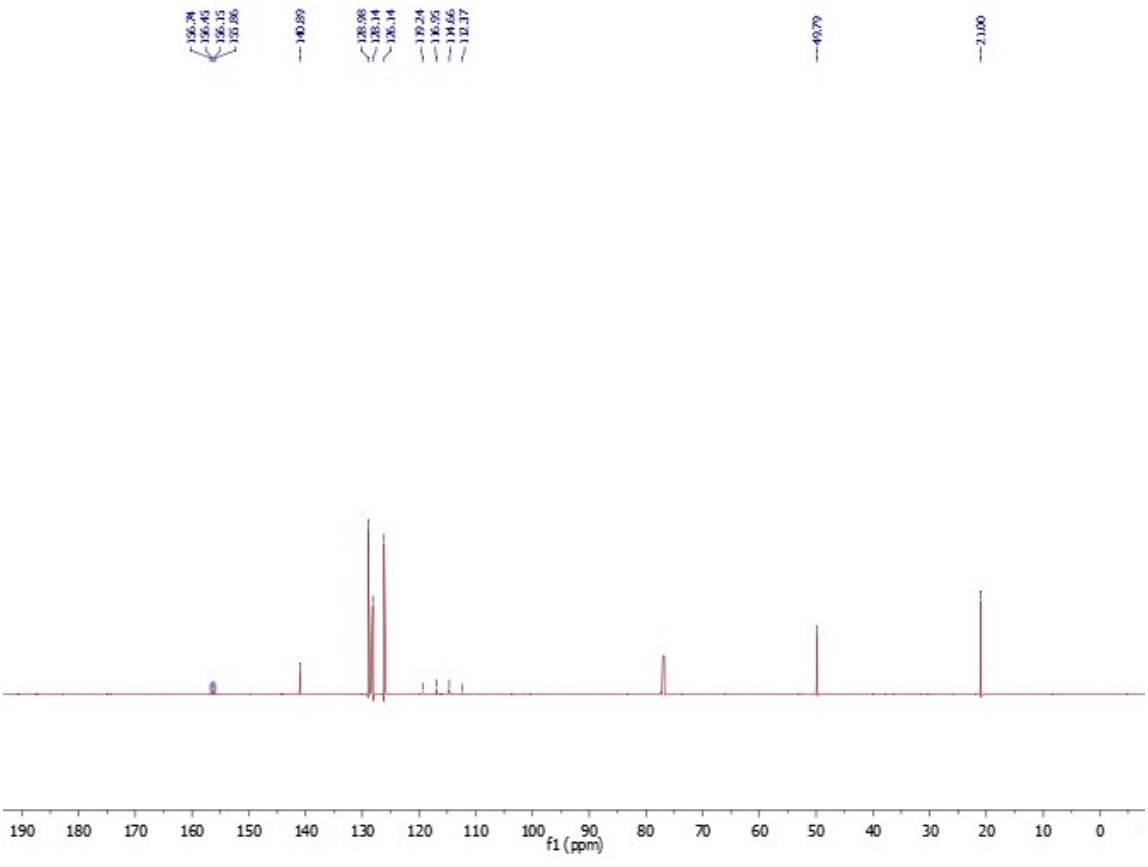


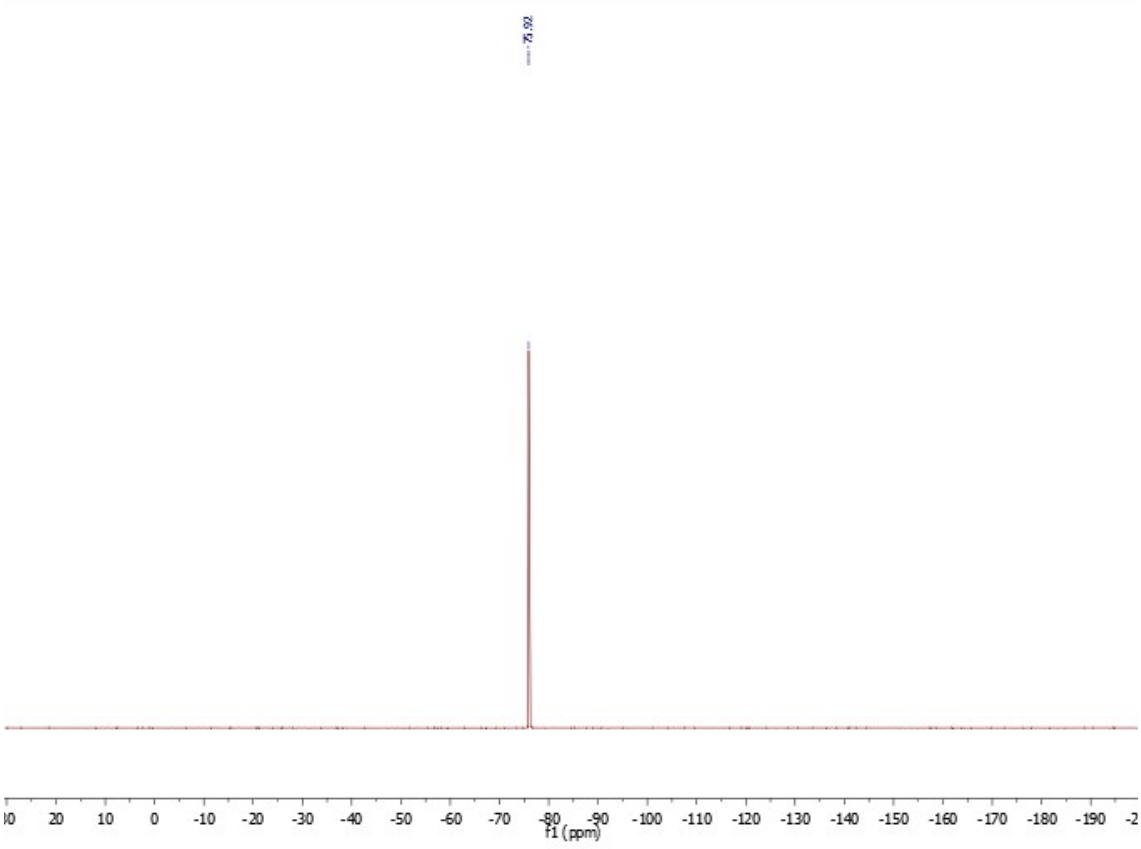

20
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
f1 (ppm)



2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide[21] (7g)



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20
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0
-10
-20
-30
-40
-50
-60
-70
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-90
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-130
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-150
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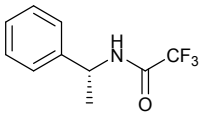
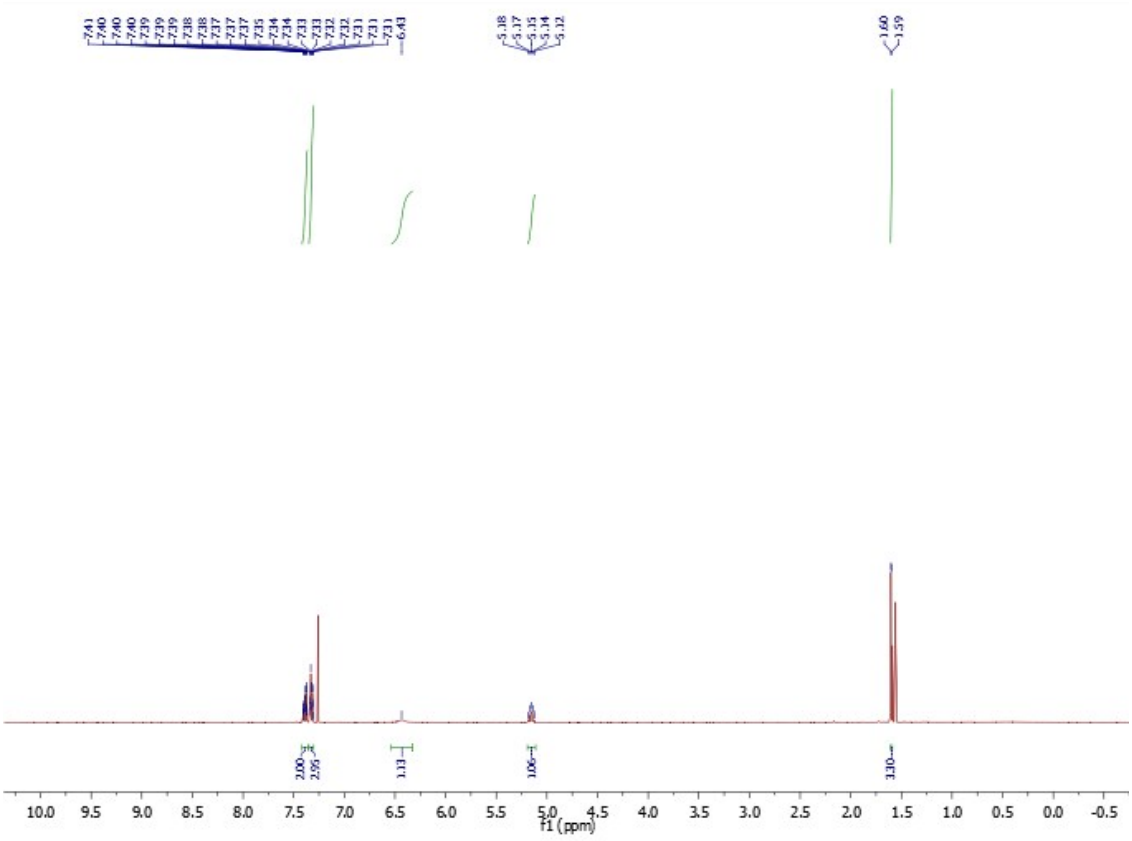
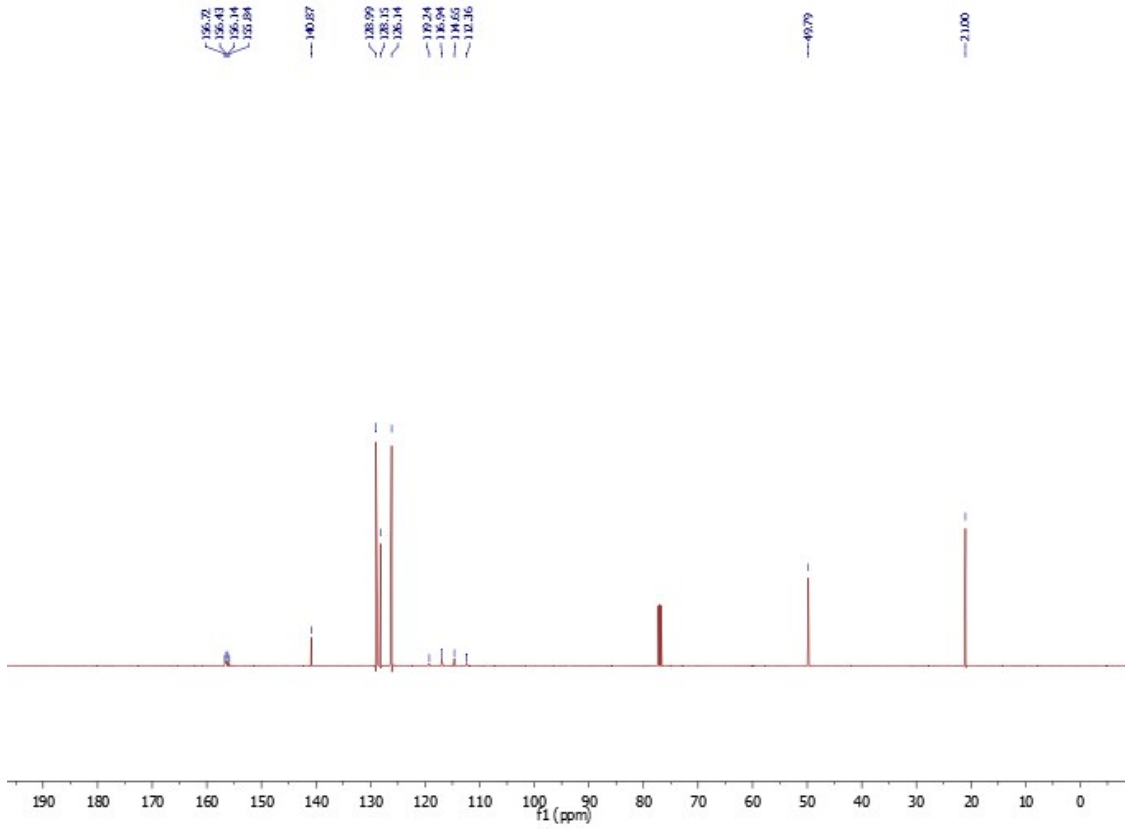
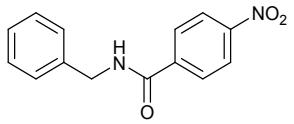
-170
-180
-190
f1 (ppm)



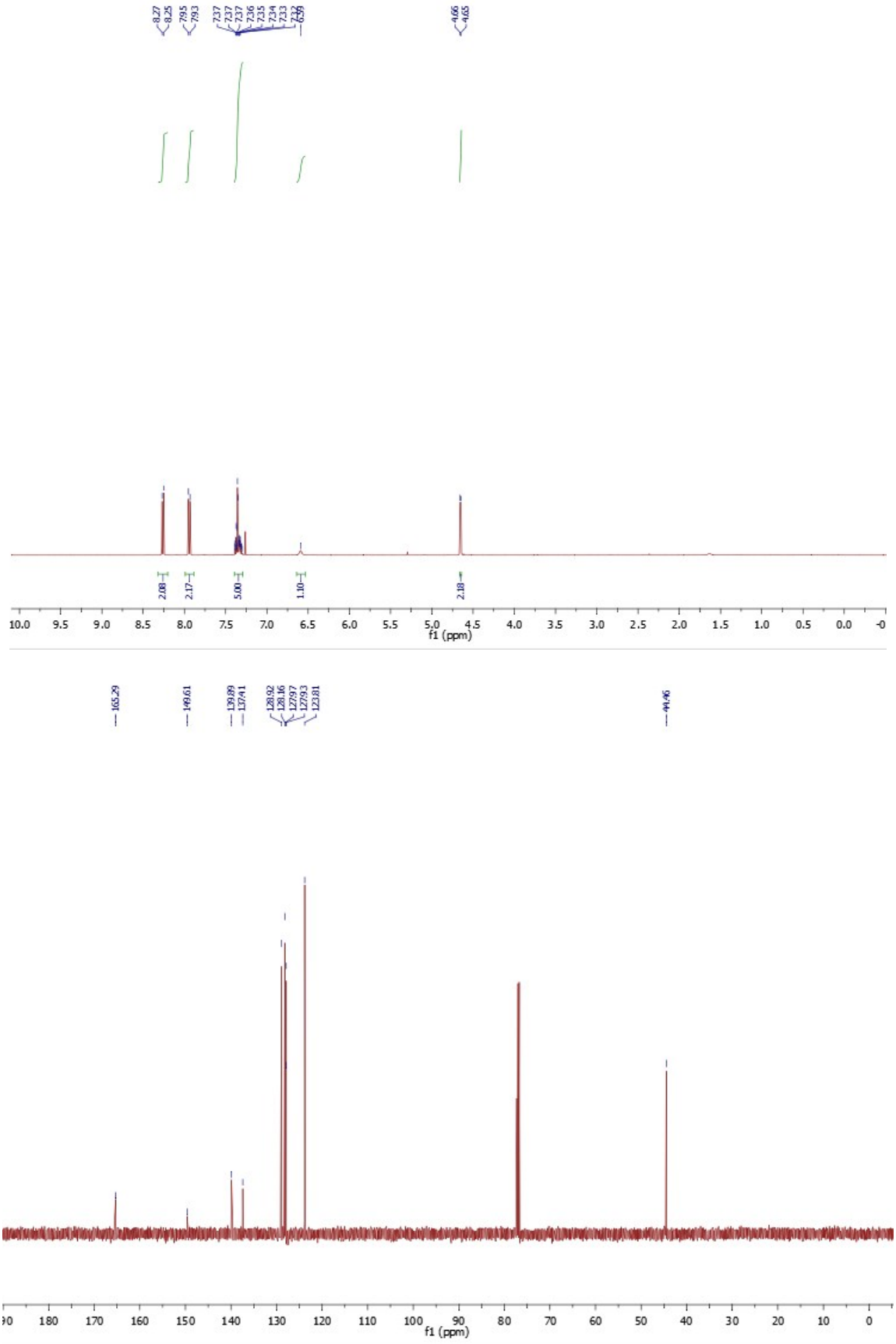
(*R*)-2,2,2-Trifluoro-*N*-(1-phenylethyl)acetamide[22] (7h)

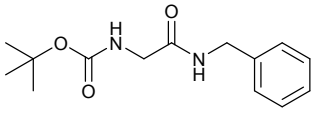




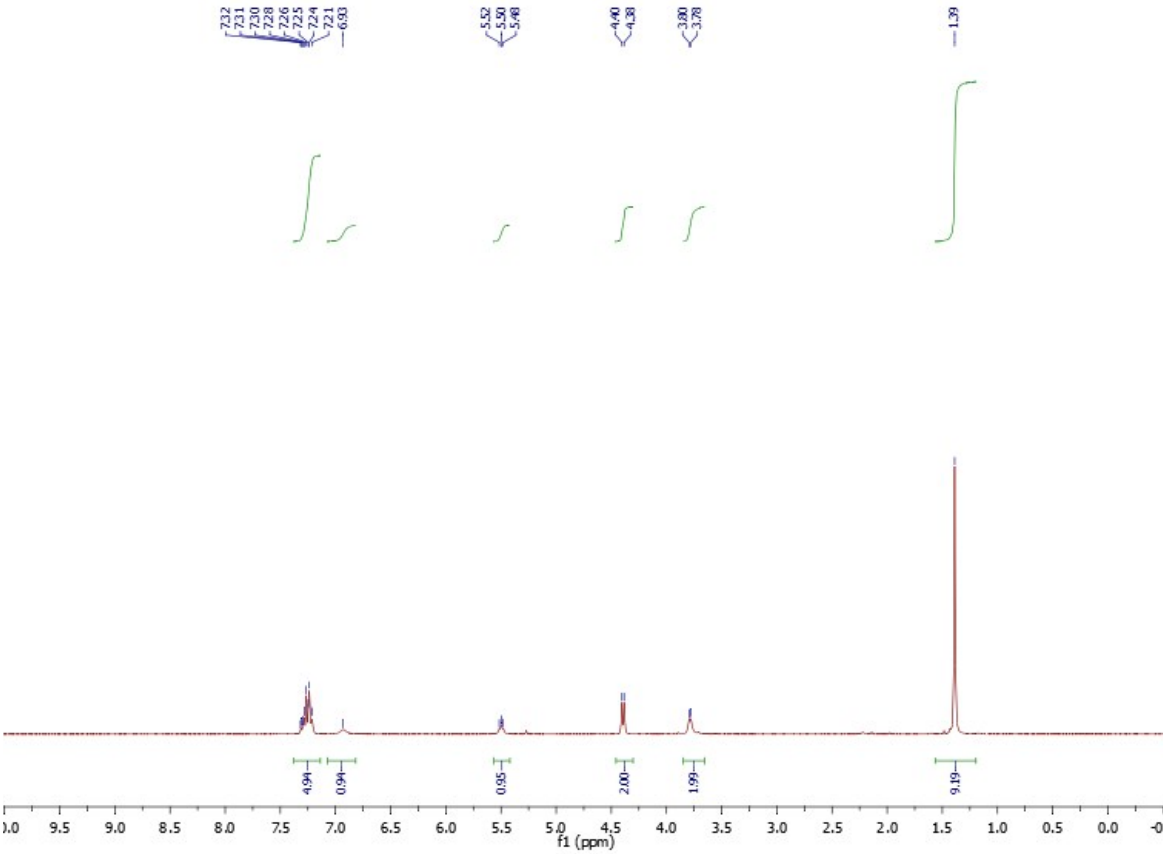


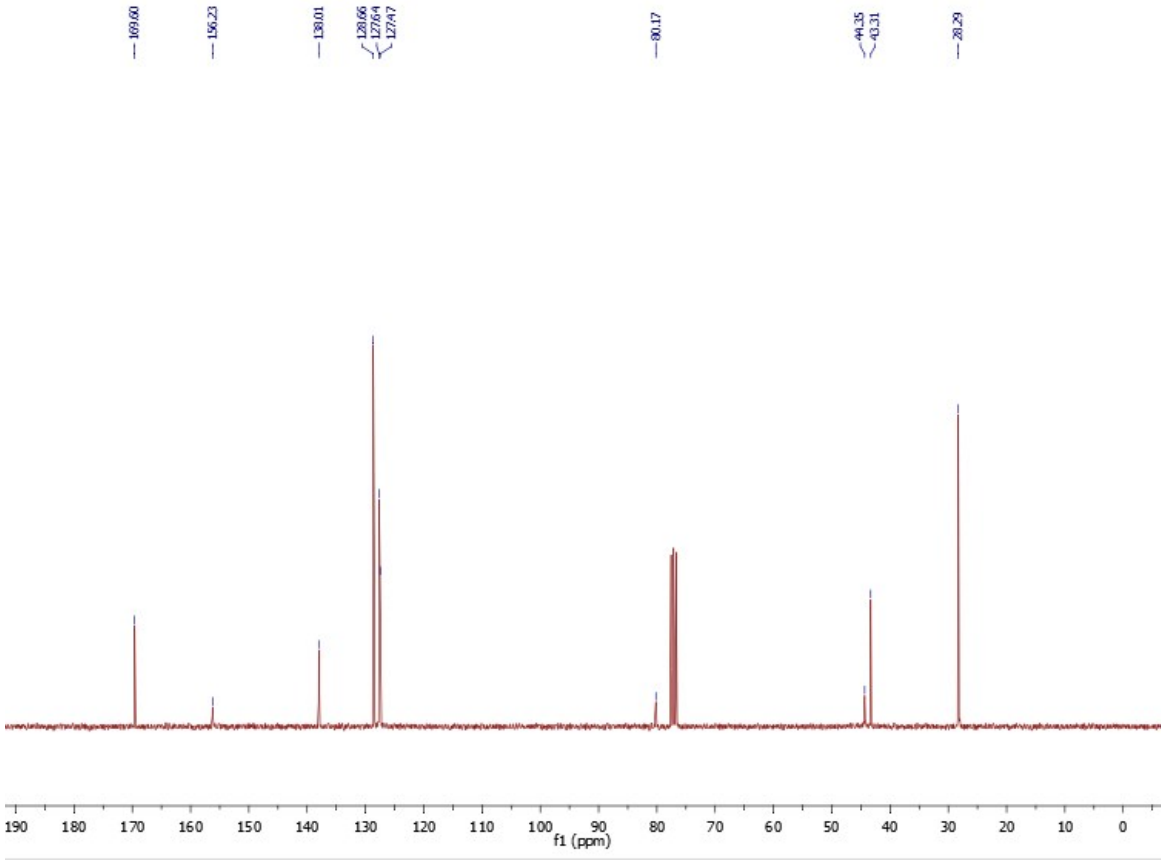
***N*-Benzyl-4-nitrobenzamide**[24] **(7*i*)**





***tert*-Butyl (2-(benzylamino)-2-oxoethyl)carbamate[26] (7j)**





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