Iodide as an Activating Agent for Acid Chlorides in Acylation Reactions.

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Supporting information

Contents:

Materials and Methods

All reactions requiring an anhydrous, inert atmosphere were carried out under a nitrogen atmosphere using evacuated carousel or ampules. Unless preparative details are provided, all reagents were purchased from commercial suppliers Acros Organics, Aldrich, Alfa Aesar, Fluka, Lancaster, Maybridge, Strem or TCI UK and used without further purification. Thin layer chromatography was carried out on aluminium or plastic backed silica plates, purchased from Aldrich. The plates were visualised under UV (254 nm) light, followed by staining with phosphomolybdic acid dip or potassium permanganate and gentle heating. During compound separations, column chromatography was carried out using 60 micron dry silica purchased from Aldrich. Organic layers were routinely dried with anhydrous MgSO4 and concentrated using a Büchi rotary evaporator.

^{1}H NMR / ^{13}C NMR spectra were run in deuterated (≥99.5%) solvents purchased from Fluorochem unless stated otherwise, on either a Bruker Avance 500 (500 MHz) or a Bruker Avance 300 (300 MHz). Any chemical shifts (δ) are reported as parts per million (ppm) with reference to tetramethylsilane (TMS) (δH = 0.00 ppm) unless otherwise stated. The coupling constants (J) are reported in Hz and signal multiplicities are reported as singlet (s), doublet (d), triplet (t), quartet (q), quintet (qu), doublet of doublets (dd), doublet of triplets (dt), triplet of triplets (tt), multiplet (m), or broad singlet (br. s).

For mass spectrometry data acquisition a micrOTOF electrospray time-of-flight (ESI-TOF) mass spectrometer (Bruker Daltonik, GmbH, Bremen, Germany) was used; this was coupled to an Agilent 1200 LC system (Agilent Technologies, Waldbronn, Germany). The LC system was used as an auto sampler only. 10 µL of sample was injected into a 30:70 flow of water:acetonitrile at 0.3 mL/min to the mass spectrometer. For each acquisition 10 µL of a calibrant of 5 mM sodium formate was injected after the sample. The observed mass and isotope pattern matched the corresponding theoretical values as calculated from the expected elemental formula.

Infrared spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer, using a Universal ATR accessory for sampling, with relevant absorbance quoted as ν in cm-1. Optical rotations were measured on an AA-10 Automatic Polarimeter. HPLC traces were measured using a Perkin Elmer 200 Series HPLC system. Enantiomeric excess measurements were carried out using a Chiracel column as specified for each compound, eluting with HPLC grade hexane and isopropyl alcohol. All other HLPC experiments were carried out using a Phenomenex Prodigy 5 µm column and an acetonitrile (0.05% TFA): water (0.05% TFA) gradient elution system. Melting points were determined using Stuart SMP10 melting point equipment using closed end glass capillary tubes and are uncorrected.

Iodide source screening and optimization procedure I:

To oven dried Radleys carousel tubes an iodide source (0.2 mmol) and *p*-toluenesulfonamide (171 mg, 1 mmol) were added, 1 mL of anhydrous acetonitrile dissolved the reagents, benzoyl chloride (140 μL, 1.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ^{o}C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. The resulting crude products were analysed by their ^{1}H NMR spectra against an internal standard of 2,5-dimethylfuran (0.5 mmol).

General procedure II:

To oven dried Radleys carousel tubes potassium iodide (299 mg, 1.8 mmol) and sulfonamide (3 mmol) were added, 3 mL of anhydrous MeCN dissolved the reagents, acid chloride (3.6 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ^{o}C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. Purification by column chromatography or recrystallization were carried out as necessary.

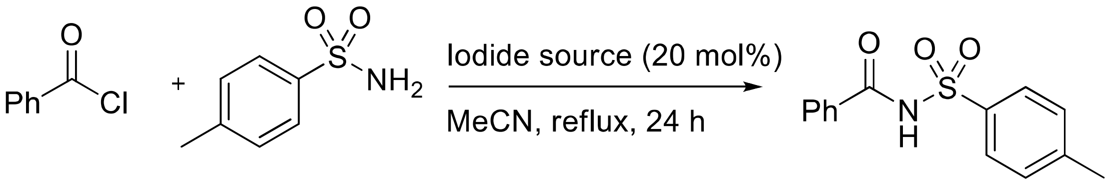
General procedure III:

To oven dried Radleys carousel tubes lithium iodide (402 mg, 3 mmol) and *N*-methylpyrrole (3.9 mmol) were added, 3 mL of anhydrous MeCN dissolved the reagents (4 Å molecular sieves), acid chloride (3 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ^{o}C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. Purification by column chromatography or recrystallization were carried out as necessary.

General procedure IV:

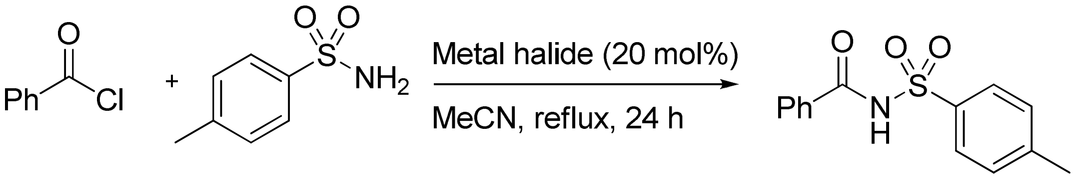
To oven dried Radleys carousel tubes potassium iodide (598 mg, 3.6 mmol) and a hindered phenol (3 mmol) were added, 3 mL of anhydrous MeCN dissolved the reagents, acid chloride (7.2 mmol) was added to the solution using a micropipette. The tube was then sealed and the reaction mixture was immediately heated to 82 ^{o}C and stirred for 24 hours. The resulting reaction mixture was then cooled to room temperature and washed with DCM and sodium thiosulfate solution. The organic components were then dried and concentrated *in vacuo*. Purification by column chromatography or recrystallization were carried out as necessary.

Iodide optimization



Iodide Source 20 mol %	**% conversion into acyl sulfonamide[a]**
No Iodide	9
LiI	13
NaI	78
KI	69
RbI	46
CsI	18
NH_4I	61
Bu_4NI	10

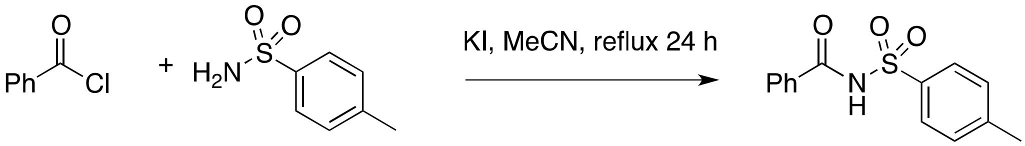
[a] Conversions determined by ^{1}H NMR using 2,5 dimethylfuran as an internal standard

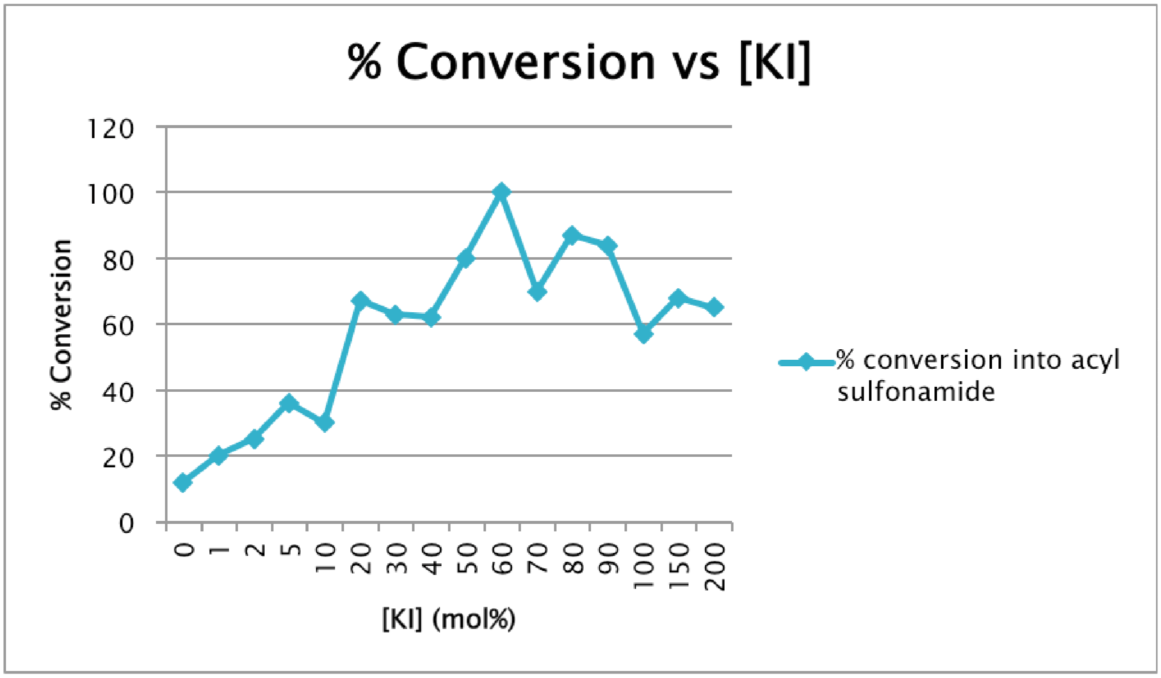


Salt 20 mol %	% conversion into acyl sulfonamide[a]
NaCl	41
KCl	8
KBr	44
KI	72

1 mmol p-toluenesulfonamide, 1.2 mmol benzoyl chloride, reflux, MeCN 1 mL, 24 hours.

[a]Conversions determined by ^{1}H NMR using 2,5 dimethylfuran as an internal standard

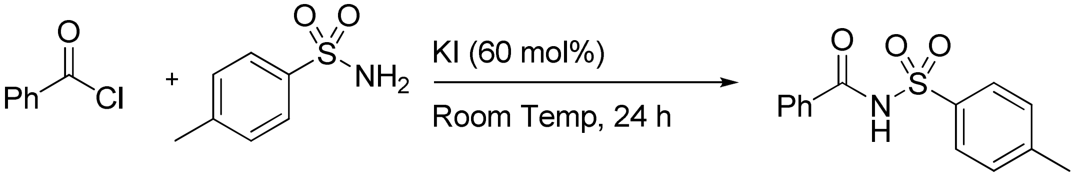




1 mmol p-toluenesulfonamide, 1.2 mmol benzoyl chloride, reflux, MeCN 1 mL, 24 hours.

Conversions determined by ^{1}H NMR using 2,5 dimethylfuran as an internal standard

Solvent Screen:

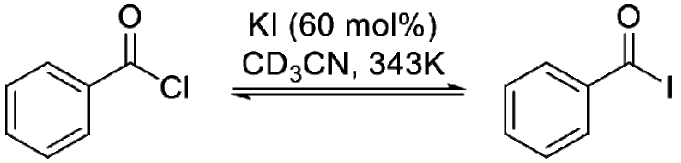


Solvent (1mL)	% conversion into acyl sulfonamide[a]
Toluene	0
Acetonitrile	46
Hexane	0
THF	0
DCM	0
EtOAc	14
DMSO	0
DMF	0

1 mmol p-toluenesulfonamide, 1.2 mmol benzoyl chloride, 0.6 mmol KI, room temperature, 24 hours.

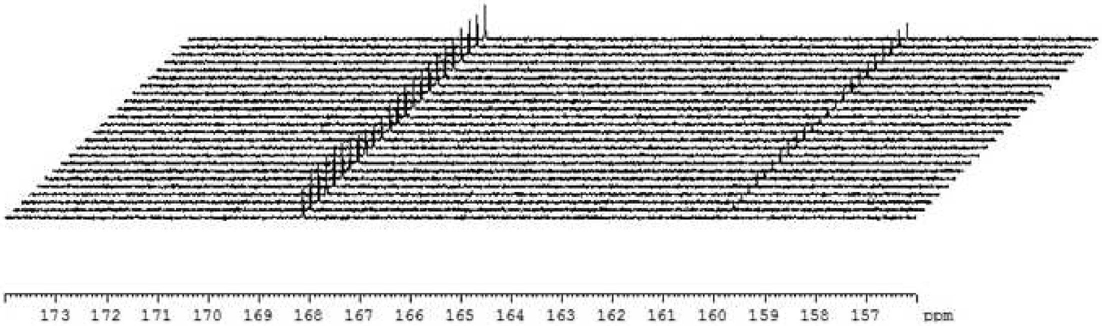
[a]Conversions determined by ^{1}H NMR using 2,5 dimethylfuran as an internal standard

NMR Studies



^{13}C NMR (Bruker Advance 500 MHz) heated to 343 K, a spectrum was taken every hour over a 24 hour period, the diagram below shows the first spectrum to the last, bottom to top.

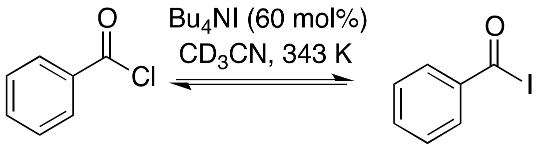
Benzoyl chloride and potassium iodide in deuterated acetonitrile at 343 K, each spectrum represents 1 hour



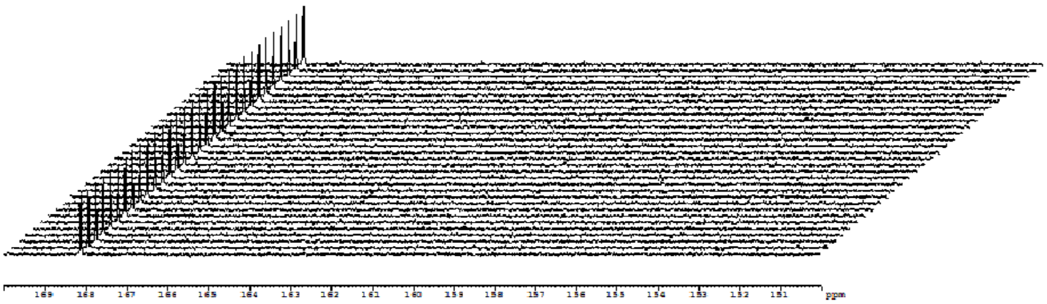
peak at 168.3 ppm represents acid chloride carbonyl carbon shift

peak at 159.6 ppm represents acid iodide carbonyl carbon shift

1.2 mmol benzoyl chloride, 1 mL CD_3CN, 60 mol % KI.



^{13}C NMR (Bruker Advance 500 MHz) heated to 343 K, a spectrum was taken every hour over a 24 hour period, the diagram below shows the first spectrum to the last, bottom to top.

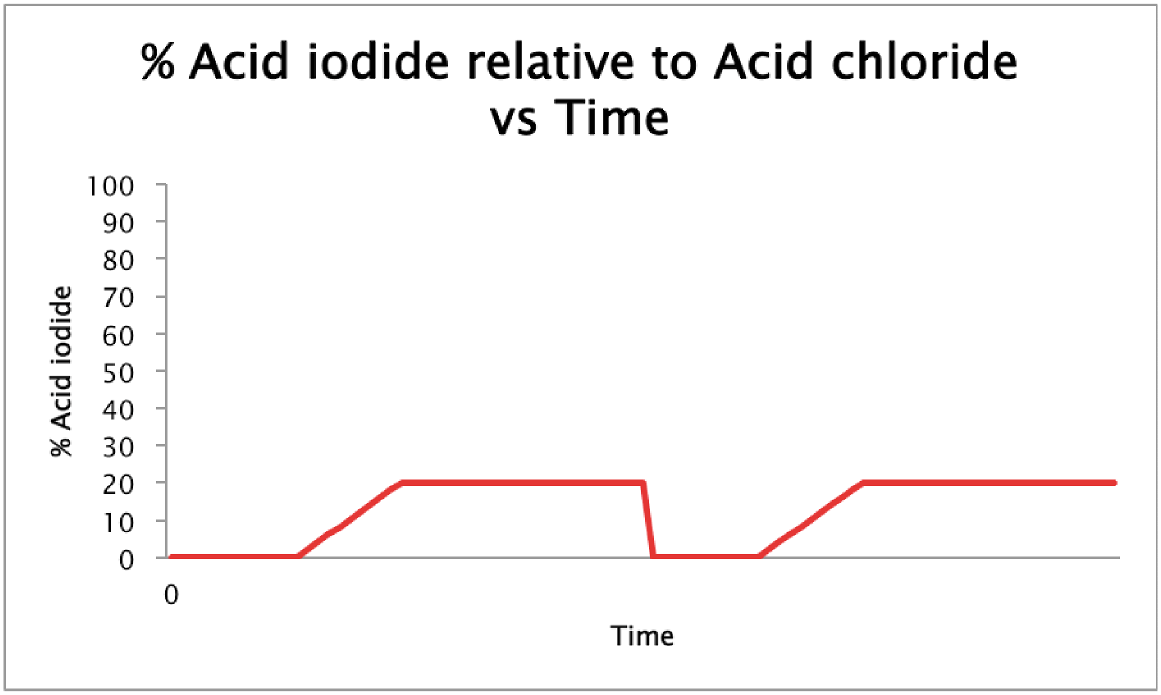

Carbonyl region shows no acid iodide peak with nBu4NI

343 K, CD3CN, each spectrum taken at 20 min intervals, earliest in the foreground. Benzoyl chloride and nBu4NI

1.2 mmol benzoyl chloride, 1 mL CD_3CN, 60 mol % Bu_4NI.

Acid iodide vs Acid chloride NMR experiment:

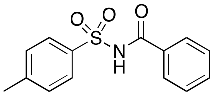
- benzoyl chloride and KI allowed to equilibrate at 343K in 1 mL deuterated MeCN.
- Estimated 20% average acid iodide at equilibrium
- Add 20 mol % of benzylamine and triethylamine
- Acid iodide carbonyl peak (159.7 ppm) disappears
- After 3 hours the equilibrium returns and 20% of acid iodide is observed



% Acid iodide calculated by the relative intensities of acid chloride C=O peak versus acid iodide C=O peak in the ^{13}C NMR.

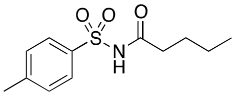
Characterization of products:

N-tosylbenzamide (Table 1, Entry 1)



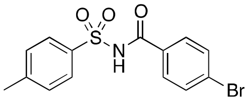
Following **general procedure II**, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (739 mg, 89% yield) after column chromatography eluting with 3:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 9.36 (1H, br.s, MePhSO$_2$N$\underline{H}$COPh), 7.97 (2H, d, *J* = 8.4 Hz, Ar), 7.75 (2H, d, *J* = 8.6 Hz, Ar), 7.56-7.40 (1H, m, Ar), 7.34 (2H, t, *J* = 7.6 Hz, Ar), 7.27 (2H, d, *J* = 8.1 Hz, Ar), 2.36 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 164.4, 145.3, 135.5, 133.5, 131.1, 129.7, 128.7, 127.9, 21.75. IR (film, cm^{-1}): ν_{max} = 1703 (C=O). ESI-MS of [C$_{14}$H$_{12}$NO$_3$S]$^-$; theoretical m/z of [M-H]$^-$ = 274.0537, measured m/z of [M-H]$^-$ = 274.0537.

N-tosylpentanamide (Table 1, Entry 2)



Following **general procedure II**, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and valeroyl chloride (434 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (676 mg, 88% yield) after column chromatography eluting with 3:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 9.13 (1H, br.s, NH), 7.94 (2H, d, *J* = 8.4 Hz, Ar), 7.34 (2H, d, *J* = 8.0 Hz, Ar), 2.43 (3H, s, CH$_3$), 2.31-2.20 (2H, m, CH$_2$), 1.52 (2H, dt, *J* = 15.2, 7.4 Hz, CH$_2$), 1.24 (2H, dq, *J* = 14.5, 7.3 Hz, CH$_2$), 0.82 (3H, t, *J* = 7.3 Hz, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 171.5, 145.2, 135.6, 129.7, 128.3, 36.0, 26.3, 22.0, 21.7, 13.7. IR (film, cm^{-1}): ν_{max} = 1704 (C=O). ESI-MS of [C$_{12}$H$_{16}$NO$_3$S]$^-$; theoretical m/z of [M-H]$^-$ = 254.0850, measured m/z of [M-H]$^-$ = 254.0854.

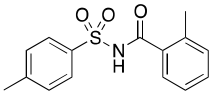
4-bromo-*N*-tosylbenzamide (Table1, Entry 3)



Following **general procedure II**, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and 4-bromobenzoyl chloride (790 mg, 3.6 mmol) as the acid chloride species. The title compound was recovered as a grey solid (711 mg, 67% yield) after column chromatography eluting with 3:1

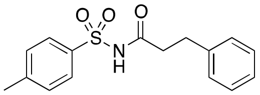
Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 9.09 (1H, br.s, NH), 8.03 (2H, d, *J* = 8.4 Hz, Ar), 7.66 (2H, d, *J* = 8.7 Hz, Ar), 7.58 (2H, d, *J* = 8.8 Hz, Ar), 7.36 (2H, d, *J* = 8.0 Hz, Ar), 2.45 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 163.4, 145.5, 135.3, 132.3, 130.1, 129.7, 129.3, 128.7, 126.5, 21.7. IR (film, cm^{-1}): ν_{max} = 1703 (C=O). ESI-MS of [$C_{14}H_{11}BrNO_3S$]$^-$; theoretical m/z of [M-H]$^-$ = 351.9643, measured m/z of [M-H]$^-$ = 351.9649.

N-tosyl-*p*-toluamide (Table 1, Entry 4)



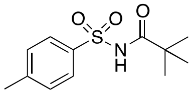
Following **general procedure II**, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and *o*-toluoyl chloride (470 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (800 mg, 92% yield) after column chromatography eluting with 3:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 8.75 (1H, br.s, NH), 7.93 (2H, d, *J* = 8.4 Hz, Ar), 7.39-7.21 (4H, m, Ar), 7.12(2H, d, *J* = 7.5 Hz, Ar), 2.37 (3H, s, CH$_3$), 2.27 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 166.3, 145.2, 138.0, 135.5, 132.1, 131.8, 131.7, 129.7, 128.5, 127.3, 126.0, 21.8, 20.1. IR (film, cm^{-1}): ν_{max} = 1698 (C=O). ESI-MS of [$C_{15}H_{14}NO_3S$]$^-$; theoretical m/z of [M-H]$^-$ = 288.0694, measured m/z of [M-H]$^-$ = 288.0688.

N-tosylhydrocinnamide (Table 1, Entry 5)



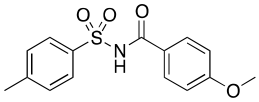
Following **general procedure II**, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and hydrocinnamoyl chloride (535 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (829 mg, 92% yield) after column chromatography eluting with 3:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 9.03 (1H, br.s, NH), 7.89 (2H, d, *J* = 8.4 Hz, Ar), 7.31 (2H, d, *J* = 8.1 Hz, Ar), 7.25-7.13 (3H, m, Ar), 7.06 (2H, dd, *J* = 7.5, 1.9 Hz, Ar), 2.86 (2H, t, *J* = 7.7 Hz, CH$_2$), 2.56 (2H, t, *J* = 7.7 Hz, CH$_2$), 2.45 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 170.5, 145.2, 139.7, 135.4, 129.7, 128.6, 128.4, 128.3, 126.4, 37.9, 30.3, 21.8. IR (film, cm^{-1}): ν_{max} = 1680 (C=O). ESI-MS of [$C_{16}H_{16}NO_3S$]$^-$; theoretical m/z of [M-H]$^-$ = 302.0851, measured m/z of [M-H]$^-$ = 302.0855.

N-tosylpivalamide (Table 1, Entry 6)



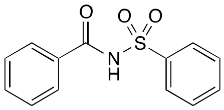
Following **general procedure II**, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and pivaloyl chloride (445 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as an off-white solid (614 mg, 80% yield) after column chromatography eluting with 3:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 8.74 (1H, br.s, NH), 7.88 (2H, d, *J* = 8.4 Hz, Ar), 7.27 (2H, d, *J* = 8.0 Hz, Ar), 2.37 (3H, s, CH$_3$), 1.07 (9H, s, CH$_3$).^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 176.2, 145.0, 135.5, 129.6, 128.4, 40.0, 26.7, 21.7. IR (film, cm^{-1}): ν_{max} = 1708 (C=O). ESI-MS of [C$_{16}$H$_{16}$NO$_3$S]$^-$; theoretical m/z of [M-H]$^-$ = 254.0851, measured m/z of [M-H]$^-$ = 254.0846.

4-methoxy-*N*-tosylbenzamide (Table 1, Entry 7)



Following **general procedure II**, *p*-toluenesulfonamide (514 mg, 3 mmol) was used as the sulfonamide species and 4-methoxybenzoyl chloride (487 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (893 mg, 97% yield) after column chromatography eluting with 9:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 9.28 (1H, br.s, NH), 8.04 (2H, d, *J* = 8.4 Hz, Ar), 7.79 (2H, d, *J* = 8.9 Hz, Ar), 7.34 (2H, d, *J* = 8.1 Hz, Ar), 6.89 (2H, d, *J* = 8.9 Hz, Ar), 3.82 (3H, s, CH$_3$), 2.43 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 163.8, 145.1, 135.6, 130.1, 129.6, 128.6, 123.3, 114.2, 55.6, 21.7. IR (film, cm^{-1}): ν_{max} = 1766 (C=O). ESI-MS of [C$_{15}$H$_{16}$NO$_4$S]$^+$; theoretical m/z of [M+H]$^+$ = 306.0800, measured m/z of [M+H]$^+$ = 306.0781.

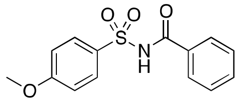
N-benzenesulfonamide benzoyl (Table 1, Entry 8)



Following **general procedure II**, benzenesulfonamide (471 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a yellow solid (752 mg, 96% yield) after column chromatography eluting with 2:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 9.10(1H, br.s, NH), 8.10 (2H, d, *J* = 7.1 Hz, Ar), 7.73 (2H, d, *J* = 7.1 Hz, Ar), 7.59 (1H, 1, *J* = 7.4 Hz, Ar), 7.49 (3H, t, *J* = 7.5 Hz, Ar), 7.36 (2H, t, *J* = 7.6 Hz, Ar). ^{13}C NMR (75.5

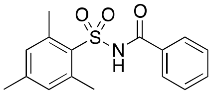
MHz, $CDCl_3$, 298K), (δ ppm): 164.2, 138.5, 134.1, 133.6, 131.1, 129.0, 129.0, 128.6, 127.8. IR (film, cm^{-1}): ν_{max} = 1694 (C=O). ESI-MS of $[C_{13}H_{10}NO_3S]^-$; theoretical m/z of $[M-H]^-$ = 260.0381, measured m/z of $[M-H]^-$ = 260.0374.

benzoyl *N*-4-methoxy-benzenesulfonamide (Table 1, Entry 9)



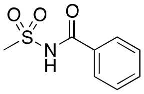
Following **general procedure II**, 4-methoxybenzenesulfonamide (562 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (728 mg, 83% yield) after column chromatography eluting with 9:1 Hexane:EtOAc. ^1H NMR: ($CDCl_3$, 300 MHz) δ 9.32 (1H, br.s, NH), 8.10 (2H, d, *J* = 9.1 Hz, Ar), 7.82 (2H, d, *J* = 7.2 Hz, Ar), 7.55 (1H, t, *J* = 8.0 Hz, Ar), 7.42 (2H, t, *J* = 7.6 Hz, Ar), 7.01 (2H, d, *J* = 9.1 Hz, Ar), 3.87 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 164.4, 164.1, 133.5, 131.2, 131.1, 129.7, 128.9, 127.8, 114.2, 55.8. IR (film, cm^{-1}): ν_{max} = 1695 (C=O). ESI-MS of $[C_{14}H_{12}NO_4S]^-$; theoretical m/z of $[M-H]^-$ = 290.0487, measured m/z of $[M-H]^-$ = 290.0479.

N-benzoyl-2,4,6-trimethylbenzenesulfonamide (Table 1, Entry 10)



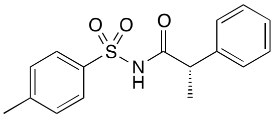
Following **general procedure II**, 2,4,6-trimethylbenzenesulfonamide (598 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a pale yellow solid (664 mg, 73% yield) after column chromatography eluting with 8:1 Hexane:EtOAc, mp 174-176 °C, ^1H NMR: ($CDCl_3$, 300 MHz) δ 9.41 (1H, br.s, NH), 7.76 (2H, dd, *J* = 8.4, 1.2 Hz, Ar), 7.50 (1H, t, *J* = 8.0 Hz, Ar), 7.37 (2H, t, *J* = 8.0 Hz, Ar), 6.93 (2H, s, Ar), 2.71 (6H, s, CH_3); 2.23 (3H, s, CH_3). ^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 164.8, 143.9, 140.7, 133.5, 132.2, 131.2, 129.0, 127.8, 22.9, 21.1. IR (film, cm^{-1}): ν_{max} = 2986, 1696 (C=O), 1600, 1452, 1337, 1156, 1054, 708. ESI-MS of $[C_{16}H_{16}NO_3S]^-$; theoretical m/z of $[M-H]^-$ = 304.34, measured m/z of $[M-H]^-$ = 304.2 Requires C 63.34%; H 5.65%; N 4.62%, found: C 63.40%; H 5.66%; N 4.49%

N-benzoyl-methanesulfonamide (Table 1, Entry 11)



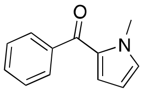
Following **general procedure II**, 2,4,6-trimethylbenzenesulfonamide (285 mg, 3 mmol) was used as the sulfonamide species and benzoyl chloride (418 µL, 3.6 mmol) as the acid chloride species. The title compound was recovered as a white solid (496 mg, 83% yield) recrystallized after layering hexane on DCM solution. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 8.98 (1H, br.s, NH), 7.81 (2H, d, *J* = 7.1 Hz, Ar), 7.56 (1H, t, *J* = 7.4 Hz, Ar), 7.43 (2H, t, *J* = 7.6 Hz, Ar), 3.37 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 165.5, 133.9, 130.9, 129.1, 127.9, 41.8. IR (film, cm^{-1}): ν_{max} = 1678 (C=O). ESI-MS of [$C_8H_8NO_3S$]$^-$; theoretical m/z of [M-H]$^-$ = 198.0225, measured m/z of [M-H]$^-$ = 198.0228.

(S)-2-phenyl-N-tosylpropanamide (Table 1, Entry 12)



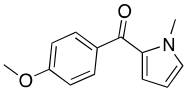
Following **general procedure II**, *p*-toluenesulfonamide (171 mg, 1 mmol) was used as the sulfonamide species and (s)-2-phenylpropoyl chloride (205 µL, 1.2 mmol, >99% enantiomeric excess) as the acid chloride species. The title compound was recovered as an off-white solid (164 mg, 54% yield, 80% enantiomeric excess) after preparative chiral HPLC. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 8.17 (1H, br.s, NH), 7.72 (2H, d, *J* = 8.4 Hz, Ar), 7.19 (5H, d, *J* = 6.2 Hz, Ar), 7.00 (2H, d, *J* = 3.6 Hz, Ar), 3.48 (1H, q, CH$_3$), 2.37 (3H, s, CH$_3$), 1.30 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 171.5, 145.1, 139.0, 135.2, 130.0, 129.3, 128.4, 127.9, 127.6, 47.4, 21.7, 18.0. IR (film, cm^{-1}): ν_{max} = 1709 (C=O). ESI-MS of [$C_{16}H_{16}NO_3S$]$^-$; theoretical m/z of [M-H]$^-$ = 302.0851, measured m/z of [M-H]$^-$ = 302.0841.

N-methyl-2-benzoylpyrrole (Table 2, Entry 1)



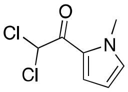
Following **general procedure III**, *N*-methylpyrrole (350 µL, 3.9 mmol) and benzoyl chloride (354 µL, 3 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (376 mg, 68% yield) after column chromatography eluting with 9:1 Hexane:EtOAc. ^{1}H NMR: (CDCl$_3$, 300 MHz) δ 7.80 (2H, d, *J* = 6.8 Hz, Ar), 7.59-7.49 (1H, m, Ar), 7.45 (2H, t, *J* = 7.2 Hz, Ar), 6.92 (1H, t, *J* = 2.0 Hz, Ar), 6.74 (1H, dd, *J* = 4.1, 1.7 Hz, Ar), 4.04 (3H, s, CH$_3$). ^{13}C NMR (75.5 MHz, CDCl$_3$, 298K), (δ ppm): 186.2, 140.0, 131.4, 130.5, 129.2, 128.1, 122.9, 108.1, 37.4. IR (film, cm^{-1}): ν_{max} = 1621 (C=O). ESI-MS of $[C_{12}H_{12}NO]^+$; theoretical m/z of $[M+H]^+$ = 186.0919, measured m/z of $[M+H]^+$ = 186.0905.

4-methoxy-(*N*-methyl-1H-2-pyrrolyl)methanone (Table 2, Entry 2)



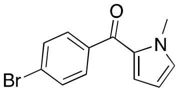
Following **general procedure III**, *N*-methylpyrrole (350 μL, 3.9 mmol) and 4-methoxybenzoyl chloride (406 μL, 3 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (370 mg, 58% yield) after column chromatography eluting with 9:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.84 (2H, d, *J* = 8.9 Hz Ar), 6.95 (2H, d, *J* = 8.9 Hz, Ar), 6.90 (1H, t, *J* = 2.0 Hz, Ar), 6.73 (1H, dd, *J* = 4.0, 1.7 Hz, Ar), 6.15 (1H, dd, *J* = 4.0, 2.5 Hz, Ar), 4.01 (3H, s, CH_3), 3.88 (3H, s, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 185.2, 162.5, 132.5, 131.5, 130.9, 130.7, 122.0, 113.3, 107.9, 55.5, 37.2. IR (film, cm^{-1}): ν_{max} = 1620 (C=O). ESI-MS of $[C_{13}H_{14}NO_2]^+$; theoretical m/z of $[M+H]^+$ = 216.1025, measured m/z of $[M+H]^+$ = 216.1065.

2,2 dichloro-1-(*N*-methyl-1H-2-pyrrolyl)-ethanone (Table 2, Entry 3)



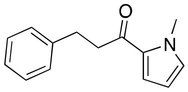
Following **general procedure III**, *N*-methylpyrrole (350 μL, 3.9 mmol) and dichloroacetyl chloride (290 μL, 3 mmol) as the acid chloride species. The title compound was recovered as a yellow solid (423 mg, 73% yield) after column chromatography eluting with 9:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.07 (1H, dd, *J* = 4.3, 1.5 Hz, Ar), 6.95-6.89 (1H, m, Ar), 6.16 (1H, dd, *J* = 4.3, 2.4 Hz, Ar), 3.91 (3H, s, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 176.6, 134.0, 125.1, 121.3, 109.3, 68.0, 38.0. IR (film, cm^{-1}): ν_{max} = 1660 (C=O). ESI-MS of $[C_7H_8Cl_2NO]^+$; theoretical m/z of $[M+H]^+$ = 191.9983, measured m/z of $[M+H]^+$ = 191.9982.

(4-bromophenyl)(1-methyl-1*H*-pyrrol-2-yl)methanone (Table 2, Entry 4)



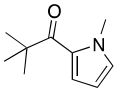
Following **general procedure III**, *N*-methylpyrrole (350 μL, 3.9 mmol) and 4-bromobenzoyl chloride (658 mg, 3 mmol) as the acid chloride species. The title compound was recovered as a brown solid (482 mg, 61% yield) after column chromatography eluting with 9:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.60 (2H, d, *J* = 8.6, Ar), 7.51 (2H, d, *J* = 8.6 Hz, Ar), 6.85 (1H, t, *J* = 2.0 Hz, Ar), 6.62 (1H, dd, *J* = 4.1, 1.7 Hz, Ar), 6.08 (1H, dd, *J* = 4.1, 2.5 Hz, Ar), 3.94 (3H, s, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 184.9, 138.7, 131.9, 131.3, 130.7, 130.2, 122.9, 108.4, 37.4. IR (film, cm^{-1}): ν_{max} = 1623 (C=O). ESI-MS of $[C_{12}H_{11}BrNO]^+$; theoretical m/z of $[M+H]^+$ = 264.0024, measured m/z of $[M+H]^+$ = 264.0006.

1-(*N*-methyl-1H-2-pyrrolyl)-3-phenyl-1-propanone (Table 2, Entry 5)



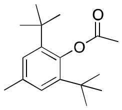
Following **general procedure III**, *N*-methylpyrrole (350 μL, 3.9 mmol) and hydrocinnamoyl chloride (445 μL, 3 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (318 mg, 50% yield) after column chromatography eluting with 9:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.26-7.07 (5H, m, Ar), 6.87 (1H, dd, *J* = 4.1, 1.7 Hz, Ar), 6.73 (1H, t, *J* = 2.0 Hz, Ar), 6.04 (1H, dd, *J* = 4.1, 2.5 Hz, Ar), 3.88 (3H, s, CH_3), 3.08-2.99 (2H, m, CH_2), 2.94 (2H, ddd, *J* = 9.1, 6.3, 1.8 Hz, CH_2).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 197.9, 129.8, 128.5, 118.7, 107.1, 43.7, 38.6, 28.9. IR (film, cm^{-1}): ν_{max} = 1643 (C=O). ESI-MS of $[C_{14}H_{16}NO]^+$; theoretical m/z of $[M+H]^+$ = 214.1232, measured m/z of $[M+H]^+$ = 214.1240.

1,1-dimethyl(*N*-methyl-1H-2-pyrrolyl)propanone (Table 2, Entry 6)



Following **general procedure III**, *N*-methylpyrrole (350 μL, 3.9 mmol) and pivaloyl chloride (370 μL, 3 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (200 mg, 40% yield) after column chromatography eluting with 19:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.03 (1H, dd, *J* = 4.2, 1.6 Hz, Ar), 6.78-6.71 (1H, m, Ar), 6.11 (1H, dd, *J* = 4.2, 2.5 Hz, Ar), 3.90 (3H, s, CH_3), 1.36 (9H, s, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 197.9, 129.8, 128.5, 118.7, 107.1, 43.7, 38.6, 28.9. IR (film, cm^{-1}): ν_{max} = 1635 (C=O). ESI-MS of $[C_{10}H_{16}NO]^+$; theoretical m/z of $[M+H]^+$ = 166.1232, measured m/z of $[M+H]^+$ = 166.1236.

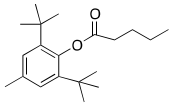
2,6-di-*tert*-butyl-4-methylphenyl acetate (Table 3, Entry 1)



Following **general procedure IV**, 2,6-di-*tert*-butyl-4-methylphenol (661 mg, 3 mmol) as the hindered phenol and acetyl chloride (510 μL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow solid (746 mg, 95% yield) after column chromatography eluting with 99:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.17-7.12 (2H, m, Ar), 2.36 (3H, s, CH_3), 2.35 (3H, s, CH_3), 1.37

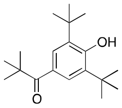
(18H, s, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 171.4, 145.7, 142.0, 134.6, 127.1, 35.3, 31.5, 22.7, 21.6. IR (film, cm^{-1}): ν_{max} = 1759 (C=O). ESI-MS of $[C_{17}H_{26}O_2]^+$; theoretical m/z of $[M+H]^+$ = 285.1831, measured m/z of $[M+H]^+$ = 285.1829.

2,6-di-*tert*-butyl-4-methylphenyl pentanoate (Table 3, Entry 2)



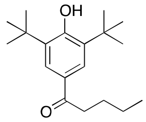
Following **general procedure IV**, 2,6-di-*tert*-butyl-4-methylphenol (661 mg, 3 mmol) as the hindered phenol and valeroyl chloride (855 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (882 mg, 97% yield) after column chromatography eluting with 99:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.12 (2H, s, Ar), 2.68-2.53 (2H, m, CH_2), 2.32 (3H, s, CH_3), 1.76 (2H, dt, *J* = 15.6, 7.5 Hz, CH_2), 1.46 (2H, dq, *J* = 14.5, 7.3 Hz, CH_2), 1.33 (18H, s, CH_3), 0.98 (3H, t, *J* = 7.3 Hz, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 173.8, 145.9, 142.0, 134.4, 127.0, 35.2, 31.5, 30.2, 26.4, 22.4, 21.6, 13.8. IR (film, cm^{-1}): ν_{max} = 1758 (C=O). ESI-MS of $[C_{17}H_{23}O_2]^+$; theoretical m/z of $[M+H]^+$ = 305.2481, measured m/z of $[M+H]^+$ = 305.2485. C H N requires C 78.90%; H 10.59%; N 0%, found: C 78.60%; H 10.50%; N 0%

1-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,2-dimethylpropan-1-one (Table 3, entry 3)



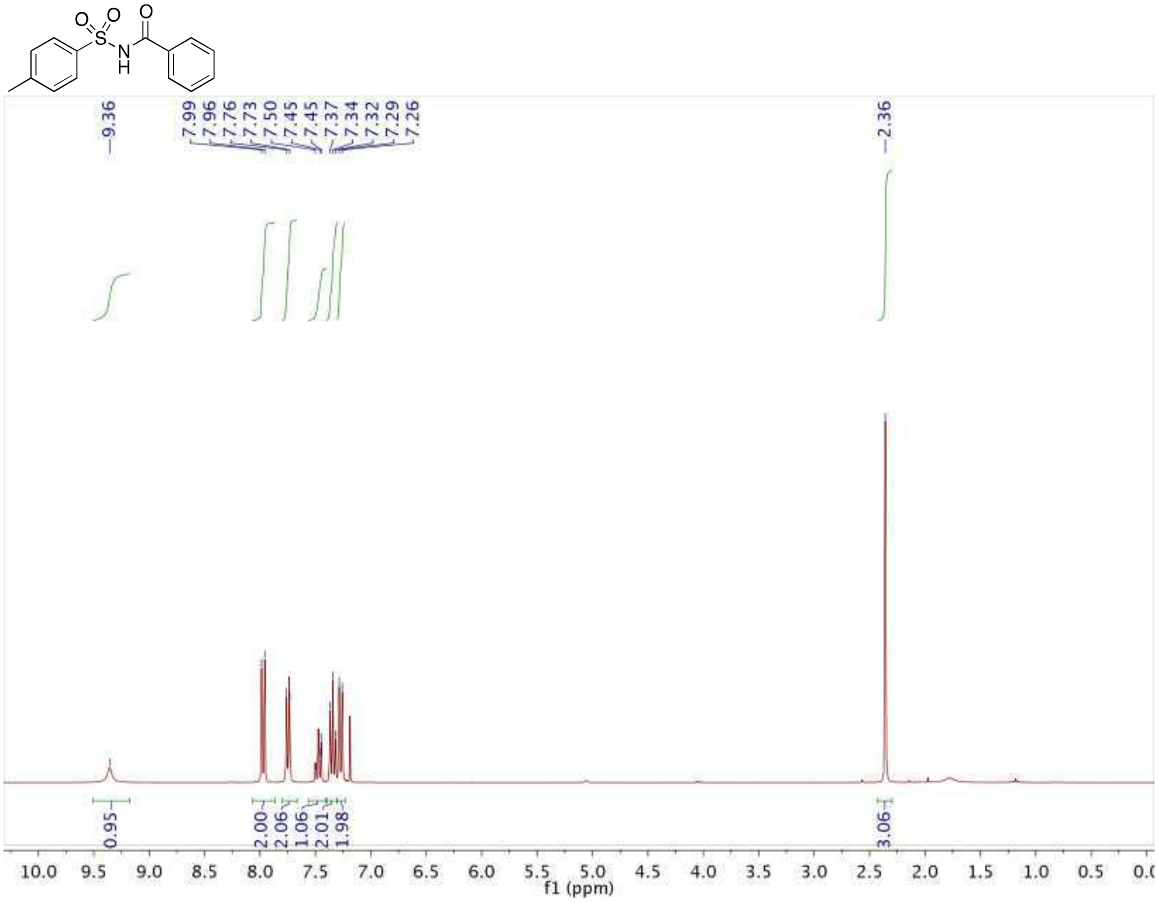
Following **general procedure IV**, 2,6-di-*tert*-butyl-phenol (617 mg, 3 mmol) as the hindered phenol and pivaloyl chloride (890 µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (502 mg, 58% yield) after column chromatography eluting with 99:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.72 (2H, s, Ar), 5.54 (1H, s, OH), 1.39 (18H, s, CH_3), 1.31 (9H, s, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 206.8, 157.0, 128.5, 126.7, 43.7, 34.4, 30.2, 28.7. IR (film, cm^{-1}): ν_{max} = 1748 (C=O). ESI-MS of $[C_{19}H_{29}O_2]^-$; theoretical m/z of $[M-H]^-$ = 289.2200, measured m/z of $[M-H]^-$ = 289.2194.

1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)pentan-1-one (Table 3, entry 4)

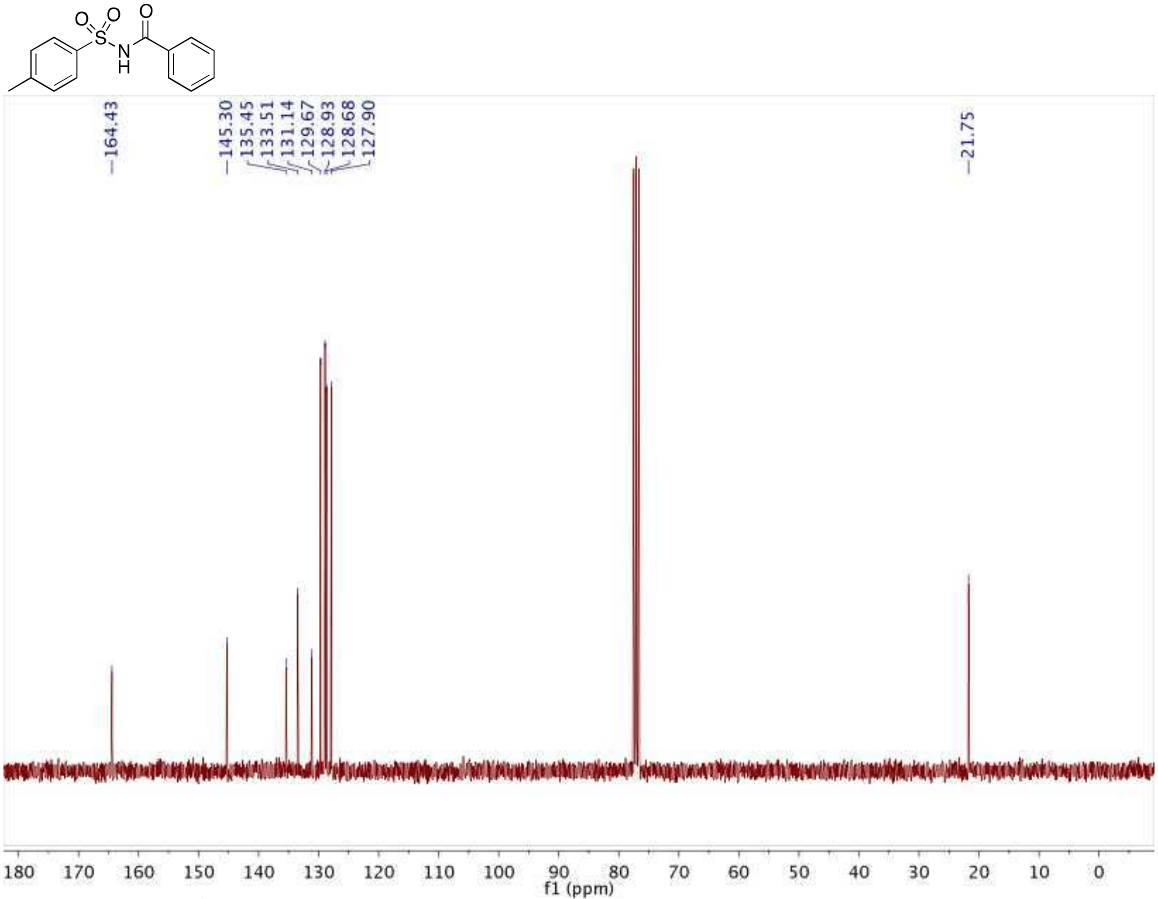


Following **general procedure IV**, 2,6-di-*tert*-butyl-phenol (617 mg, 3 mmol) as the hindered phenol and valeroyl chloride (855µL, 7.2 mmol) as the acid chloride species. The title compound was recovered as a yellow oil (847mg, 97% yield) after column chromatography eluting with 99:1 Hexane:EtOAc. ^{1}H NMR: ($CDCl_3$, 300 MHz) δ 7.87 (2H, s, Ar), 5.62 (1H, s, OH), 2.94 – 2.76, (2H, m, CH_2), 2.68 - 2.49 (2H, m, CH_2), 1.29 (20H, m, (18H)CH_3, (2H)CH_2), 0.94 – 0.90 (3H, m, CH_3).^{13}C NMR (75.5 MHz, $CDCl_3$, 298K), (δ ppm): 200.2, 173.1, 143.1, 134.0, 126.4, 38.2, 35.6, 31.3, 26.2, 22.5, 14.0. IR (film, cm^{-1}): ν_{max} = 1761 (C=O). ESI-MS of $[C_{19}H_{29}O_2]^-$; theoretical m/z of $[M\text{-}H]^-$ = 289.2168, measured m/z of $[M\text{-}H]^-$ = 289.2181.

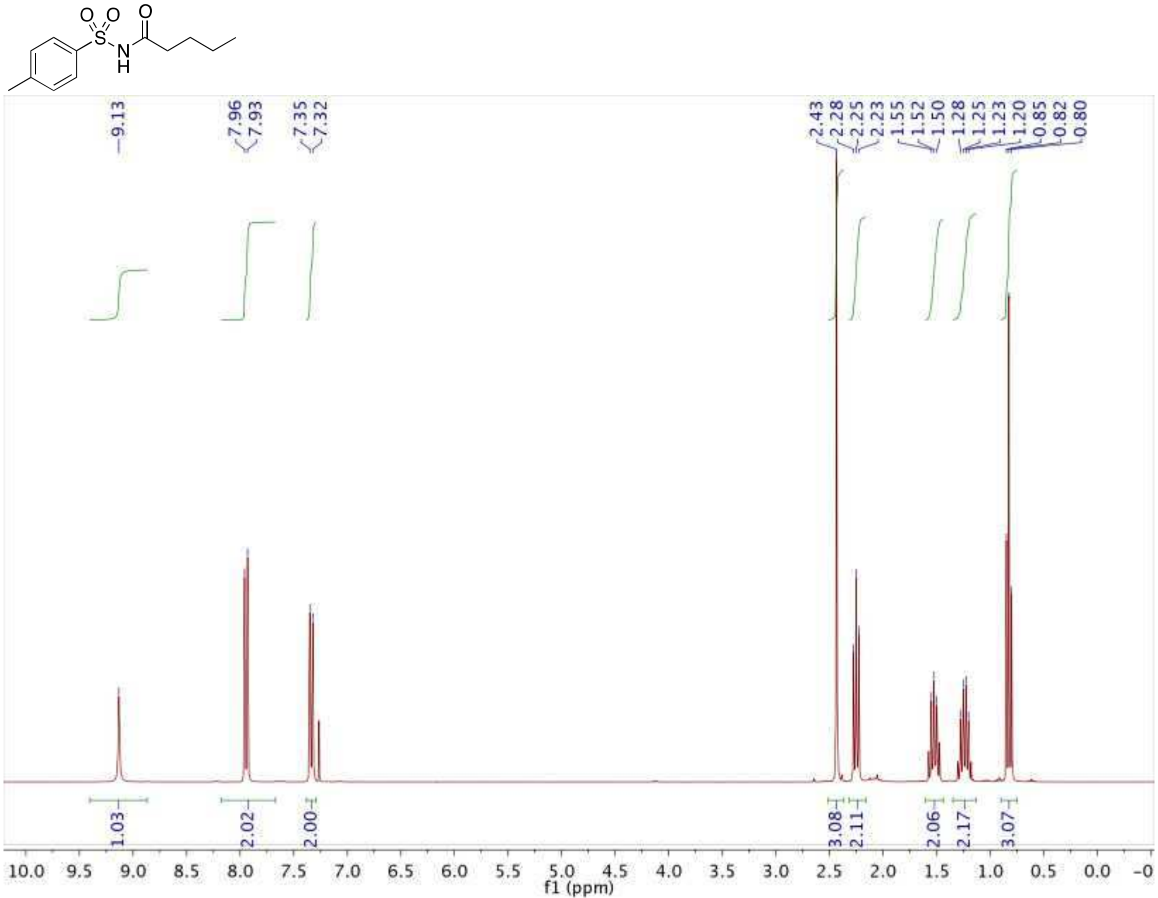
NMR Spectra:



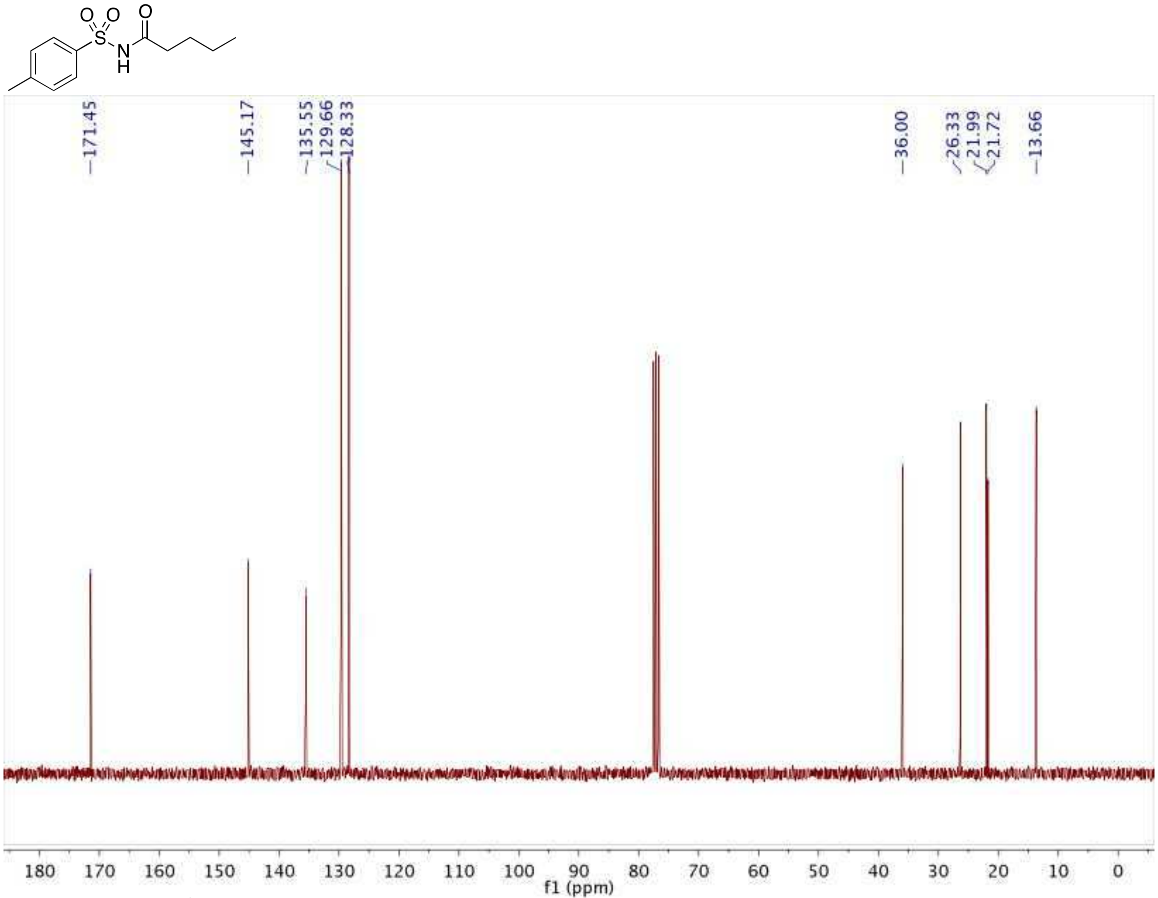
^{1}H NMR: (CDCl$_3$, 300 MHz) of *N*-tosylbenzamide (Table 1, Entry 1)



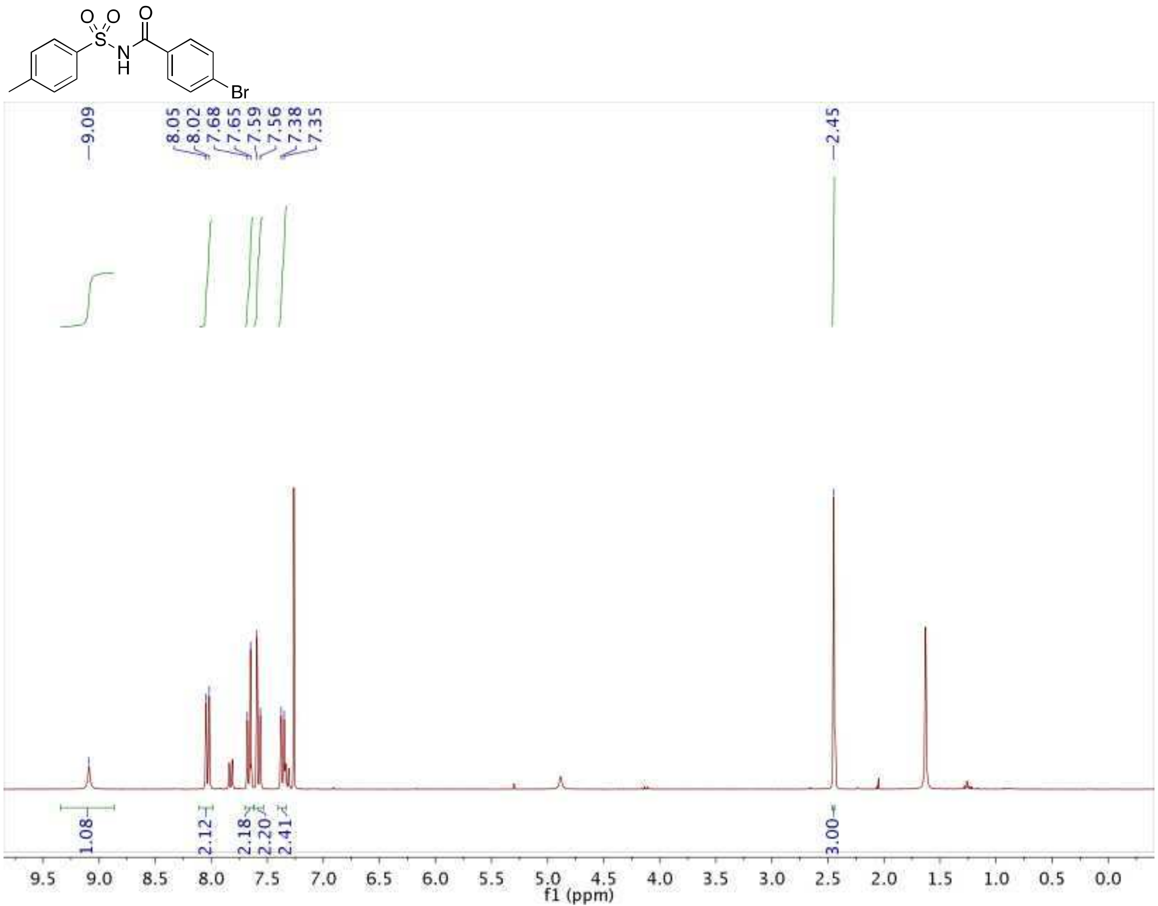
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of *N*-tosylbenzamide (Table 1, Entry 1)



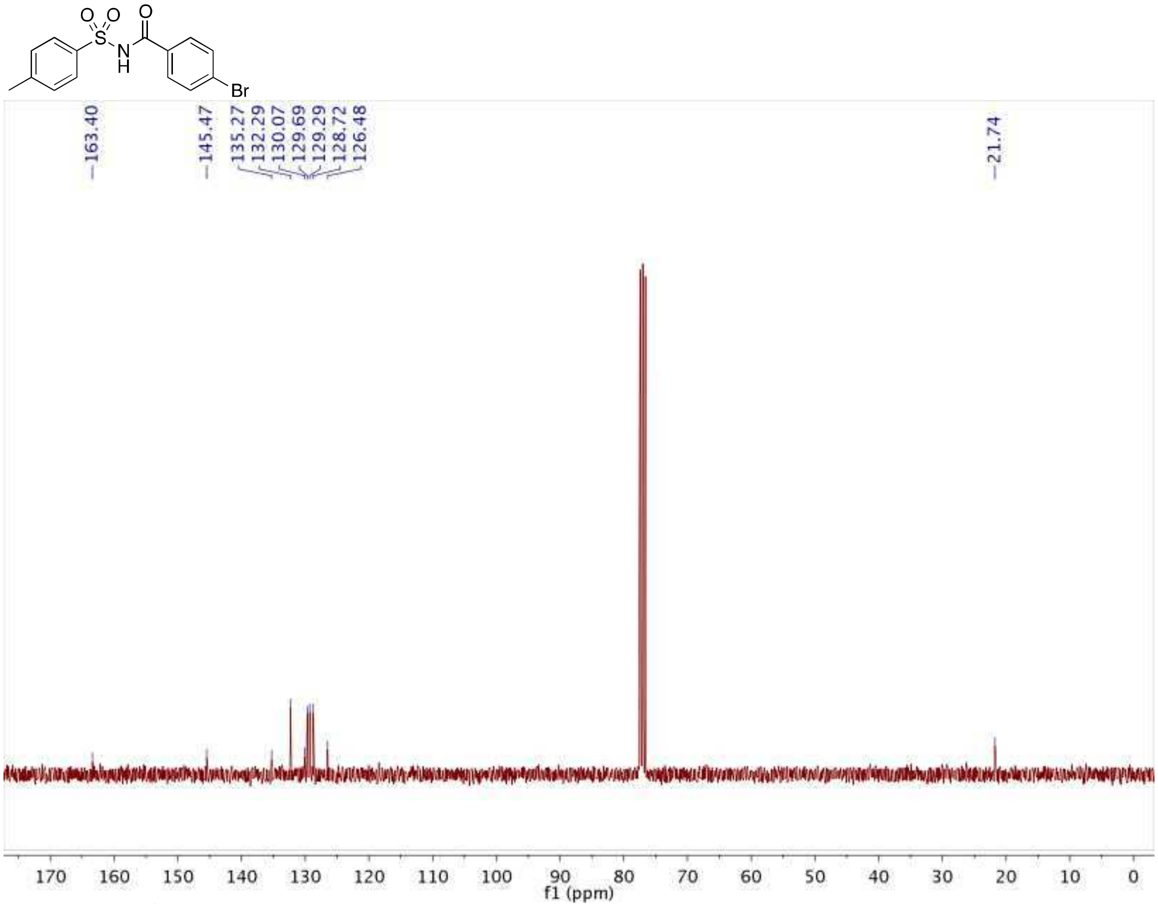
^{1}H NMR: ($CDCl_3$, 300 MHz) of *N*-tosylpentanamide (Table 1, Entry 2)



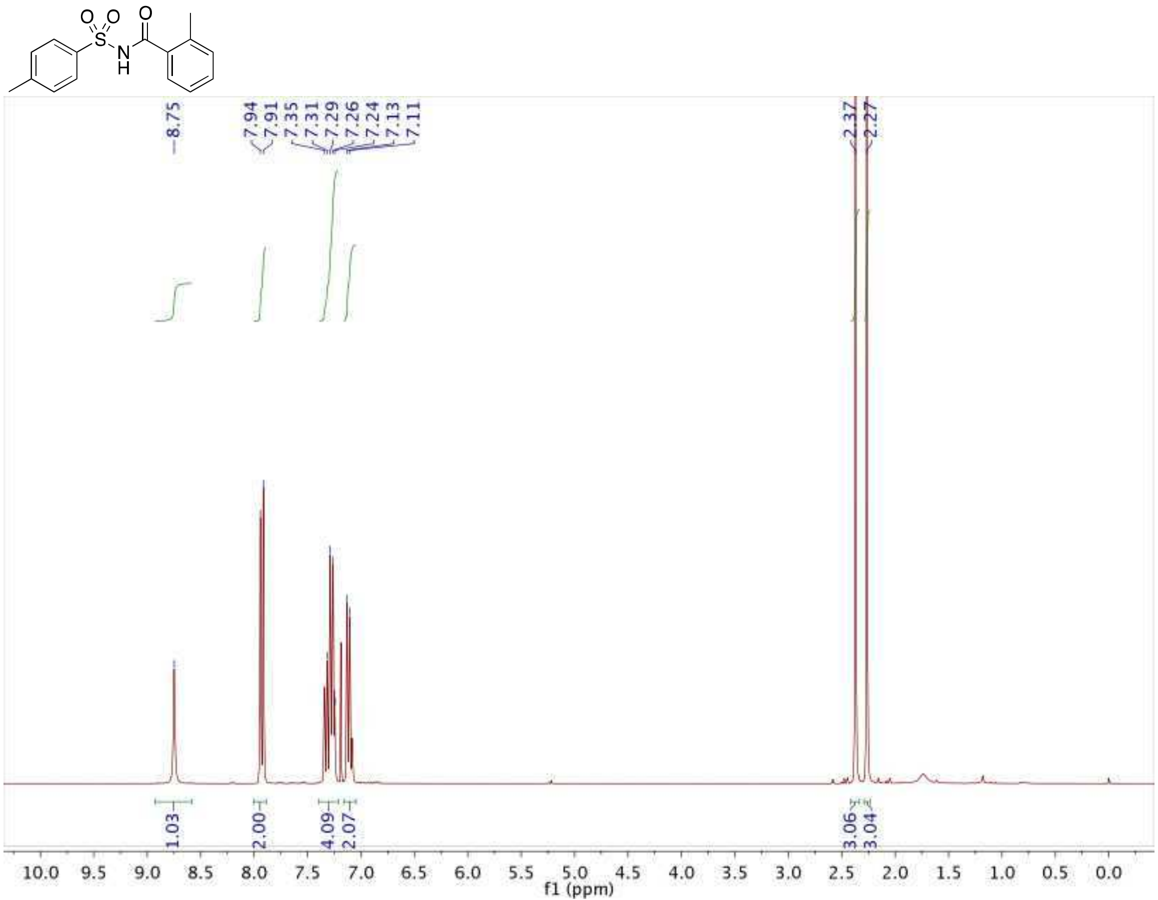
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of *N*-tosylpentanamide (Table 1, Entry 2)



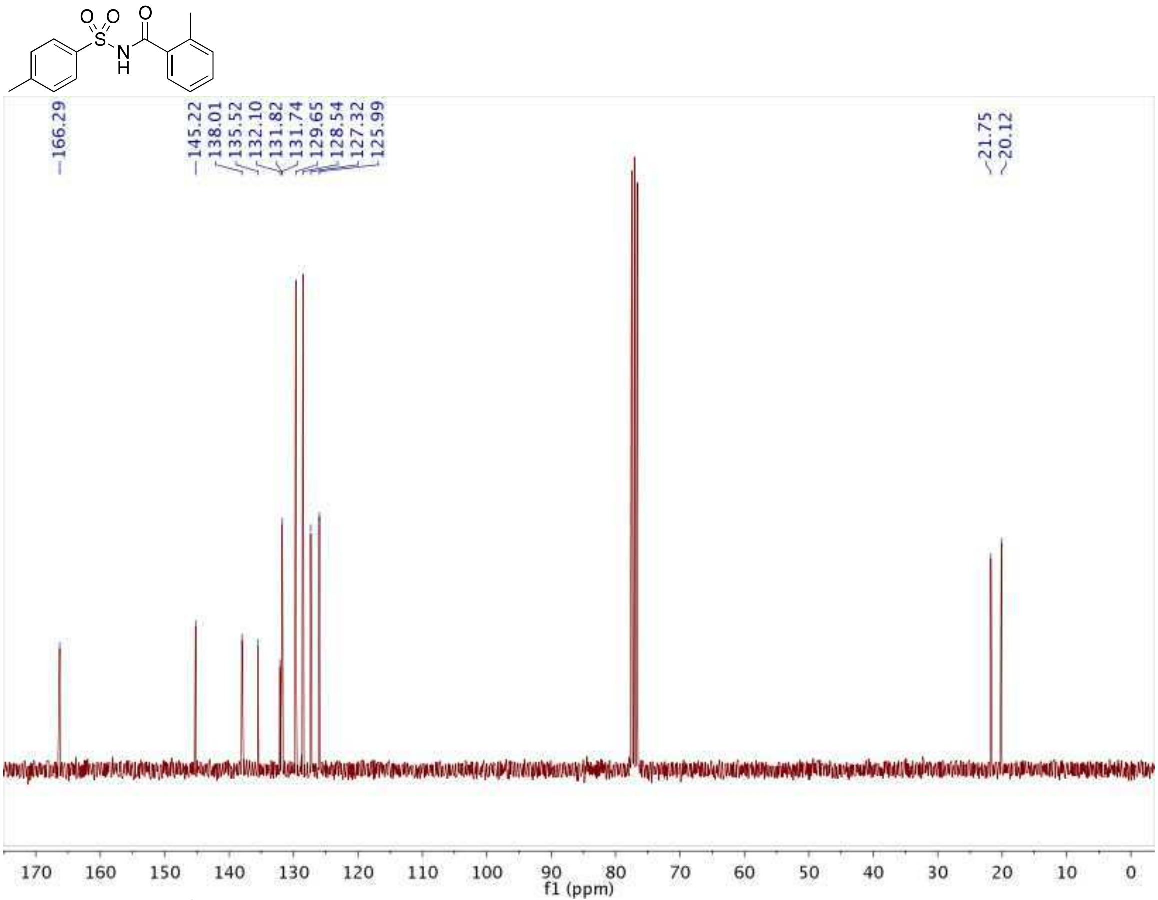
^{1}H NMR: ($CDCl_3$, 300 MHz) of 4-bromo-*N*-tosylbenzamide (Table1, Entry 3)



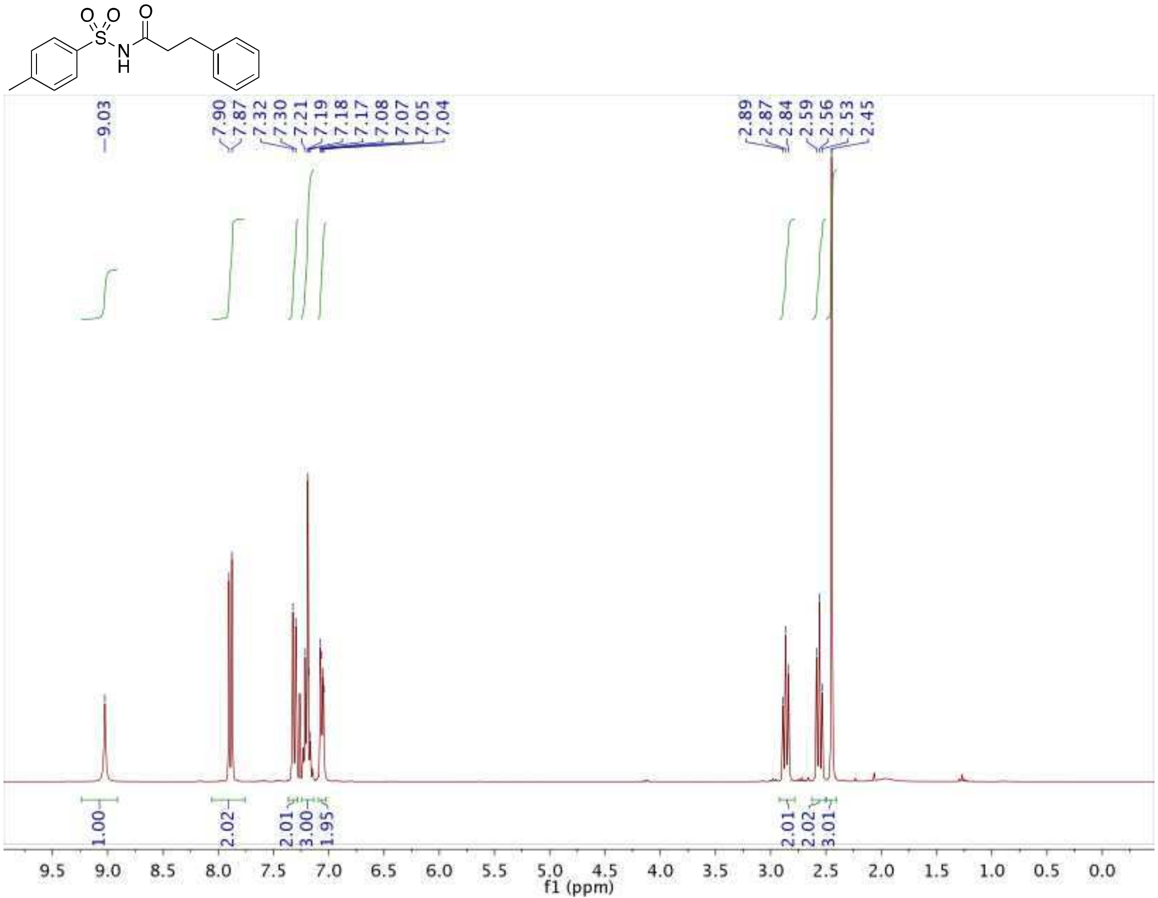
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of 4-bromo-*N*-tosylbenzamide (Table1, Entry 3)



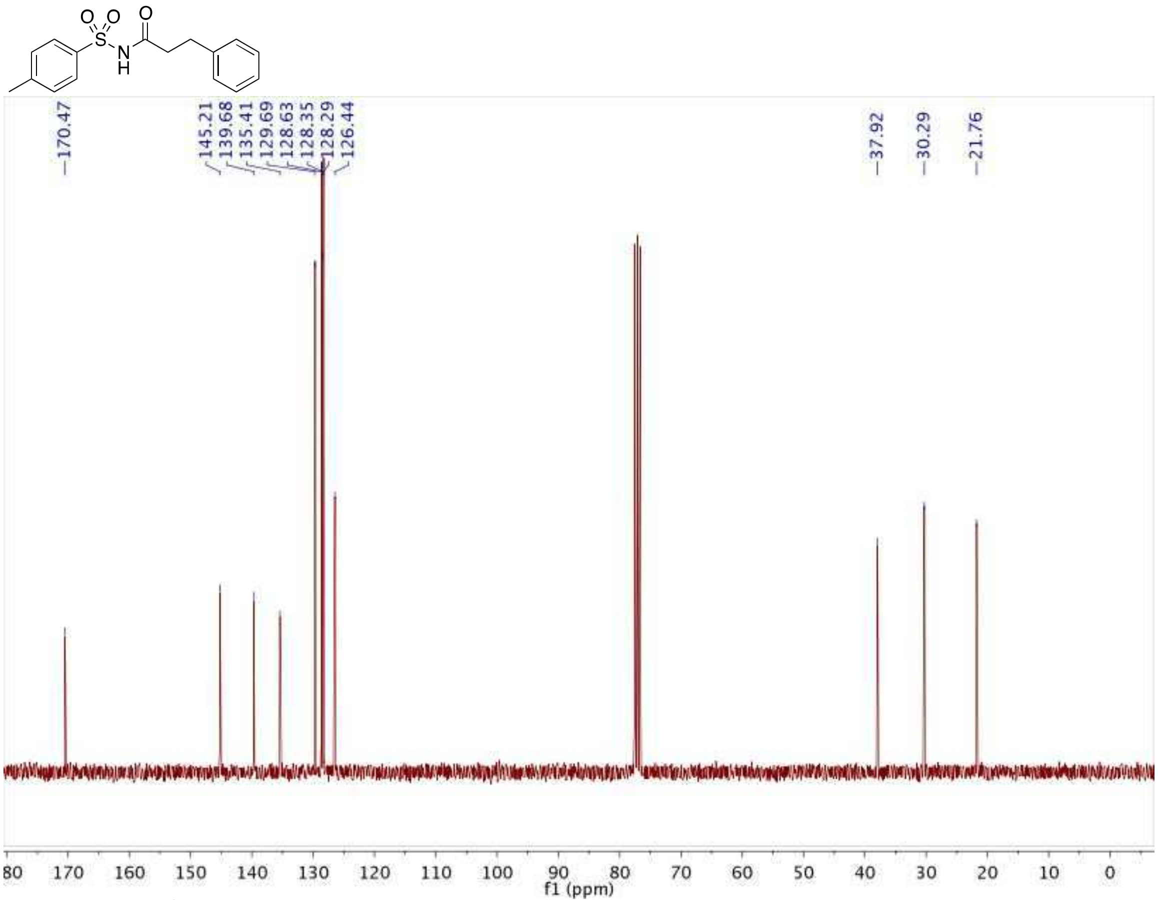
^{1}H NMR: ($CDCl_3$, 300 MHz) of *N*-tosyl-*p*-toluamide (Table 1, Entry 4)



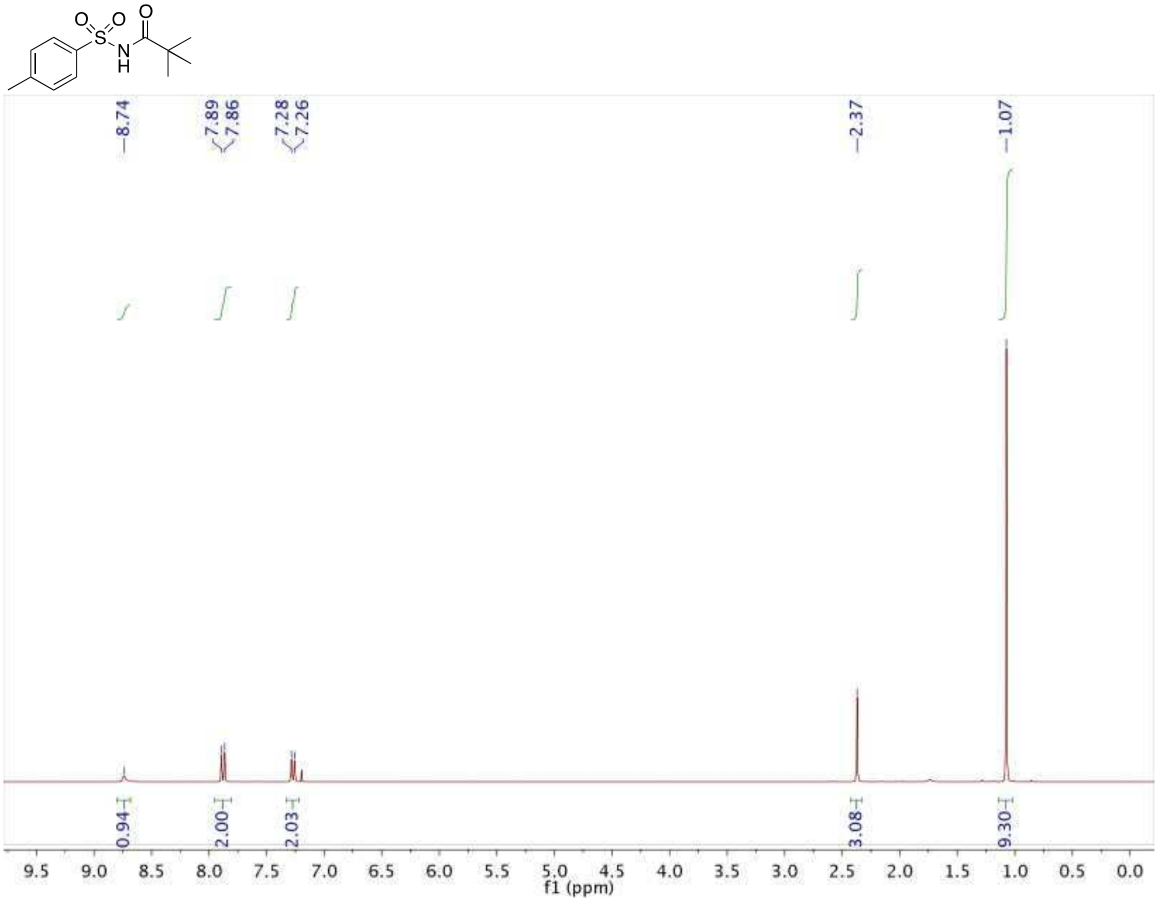
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of *N*-tosyl-*p*-toluamide (Table 1, Entry 4)



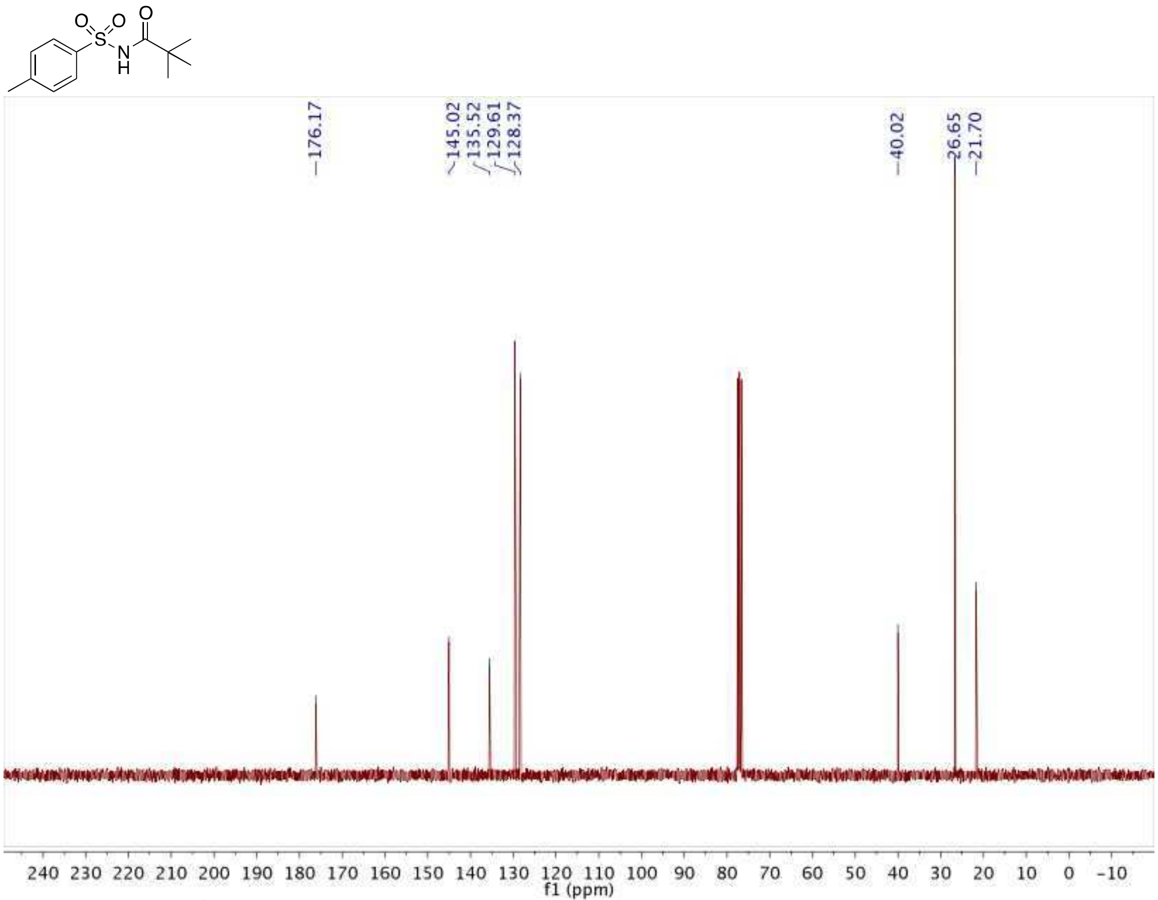
^{1}H NMR: ($CDCl_3$, 300 MHz) of *N*-tosylhydrocinnamide (Table 1, Entry 5)



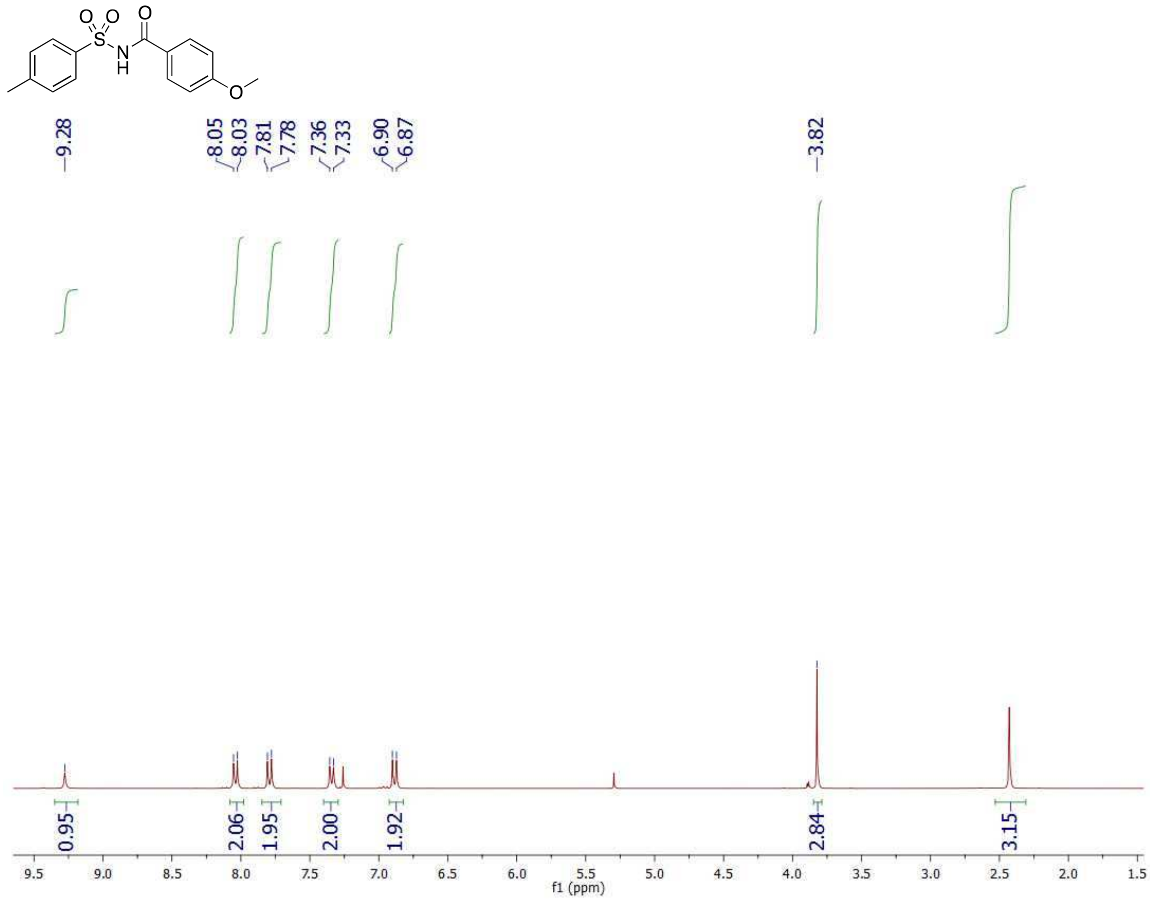
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of *N*-tosylhydrocinnamide (Table 1, Entry 5)



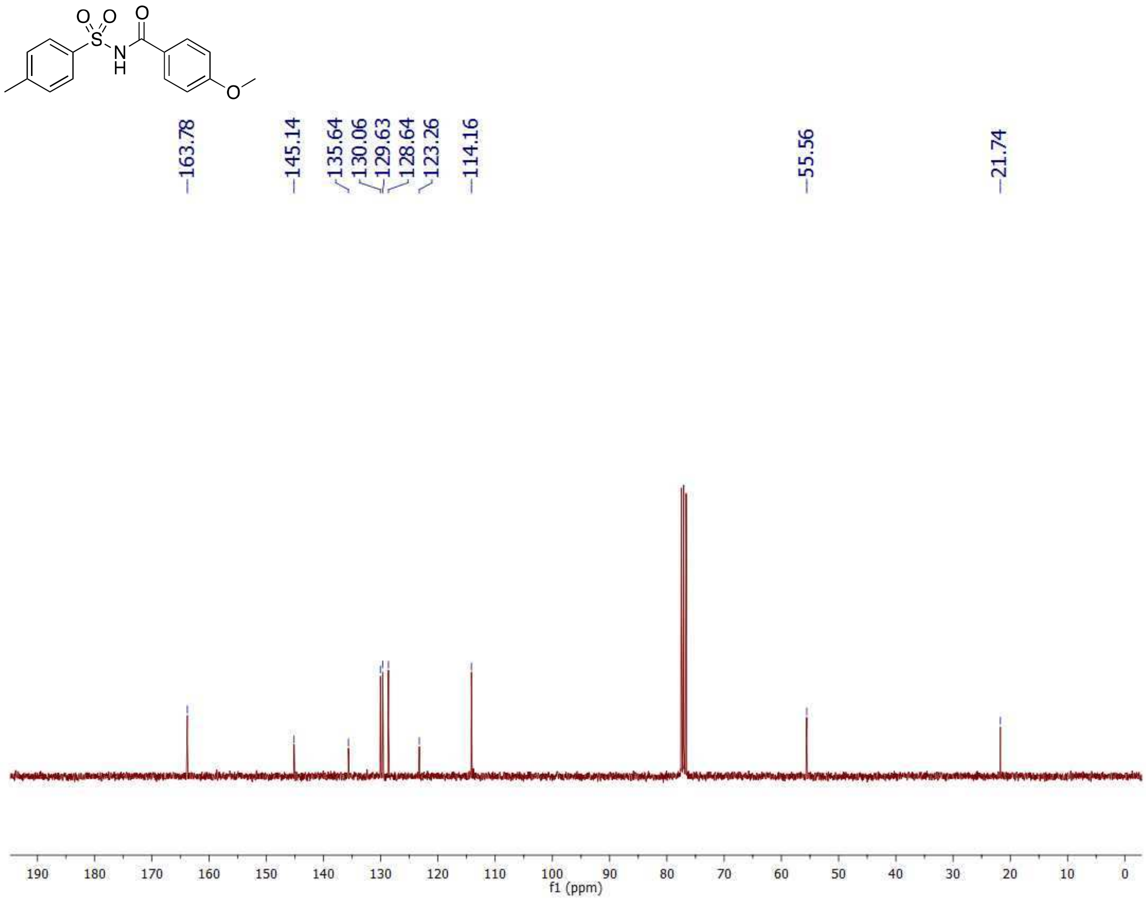
^{1}H NMR: ($CDCl_3$, 300 MHz) of *N*-tosylpivalamide (Table 1, Entry 6)



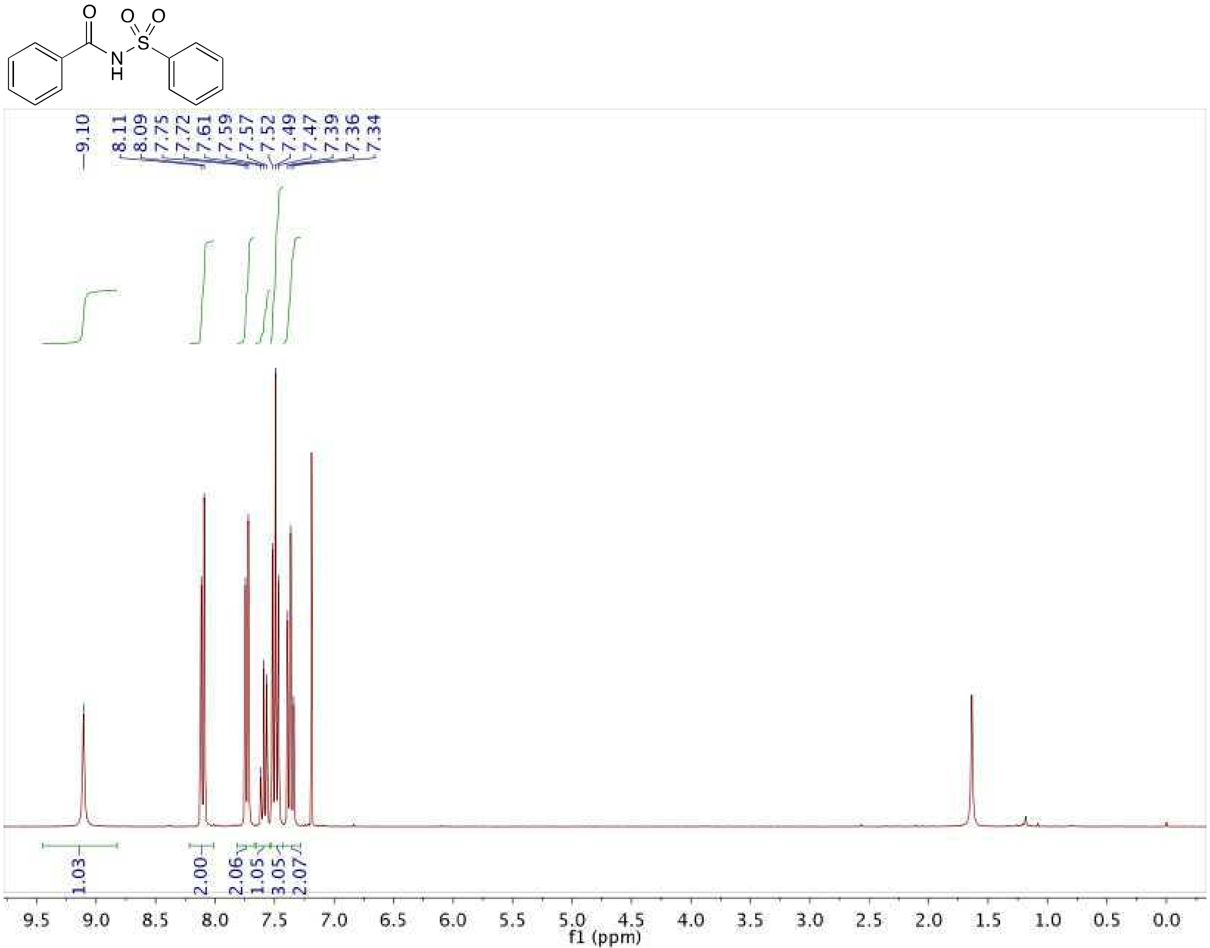
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of *N*-tosylpivalamide (Table 1, Entry 6)



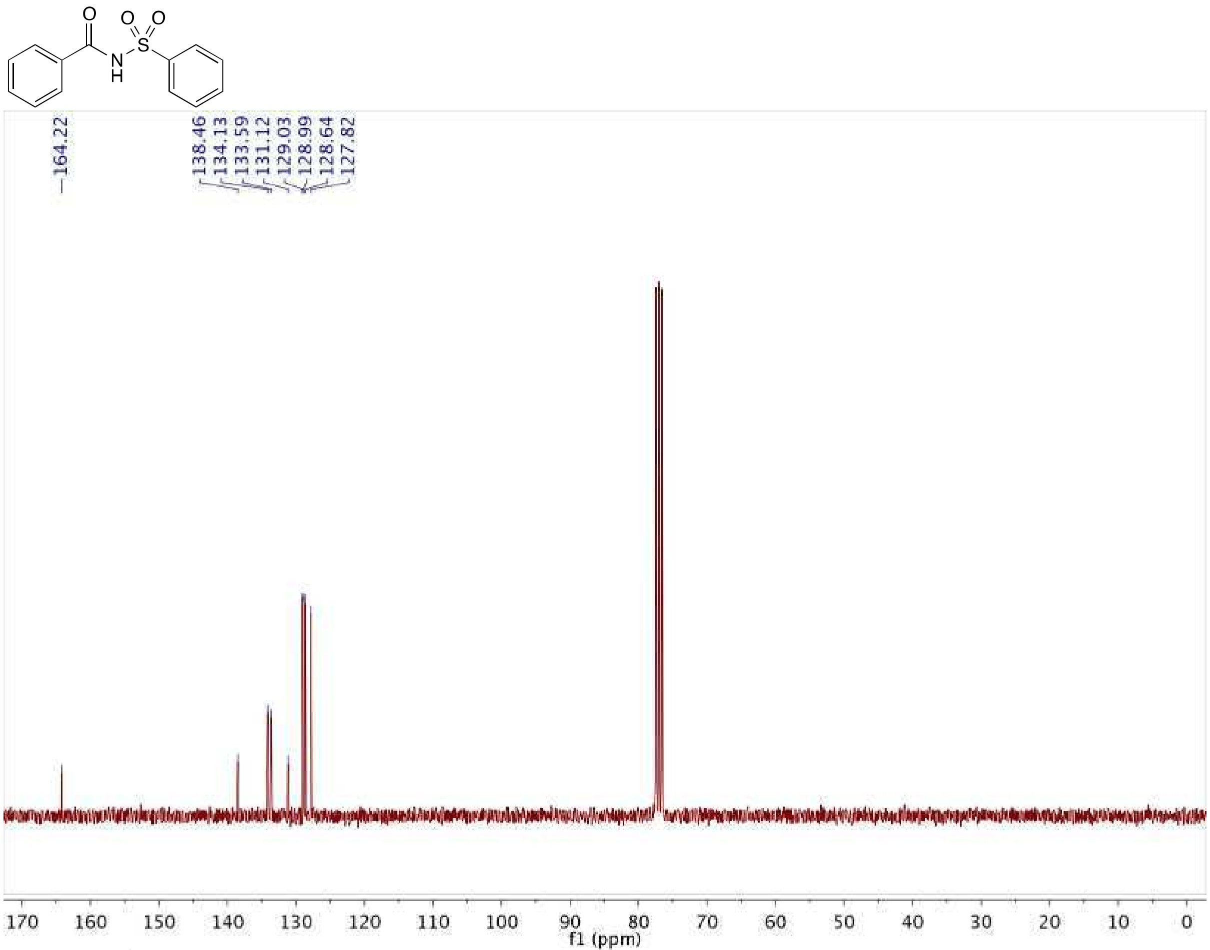
^{1}H NMR: ($CDCl_3$, 300 MHz) of 4-methoxy-*N*-tosylbenzamide (Table 1, Entry 7)



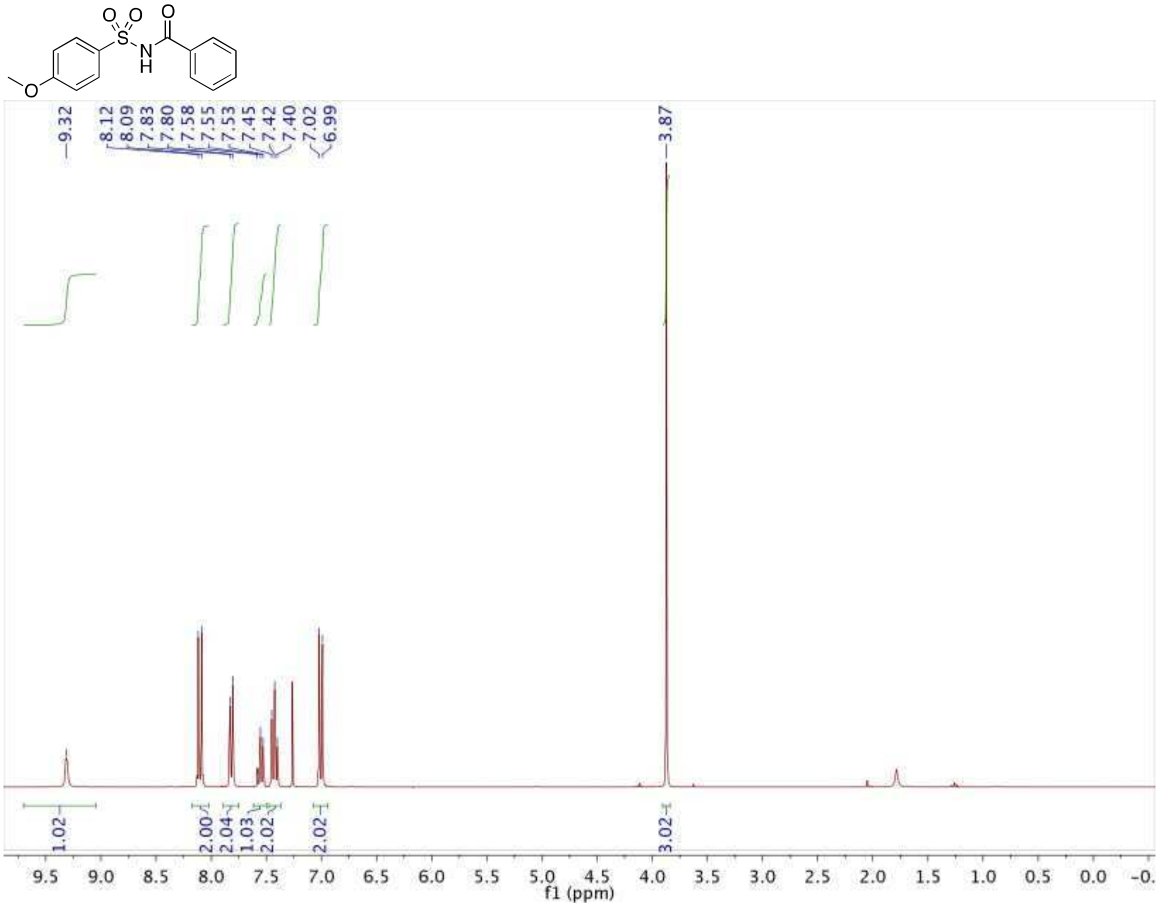
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of 4-methoxy-*N*-tosylbenzamide (Table 1, Entry 7)



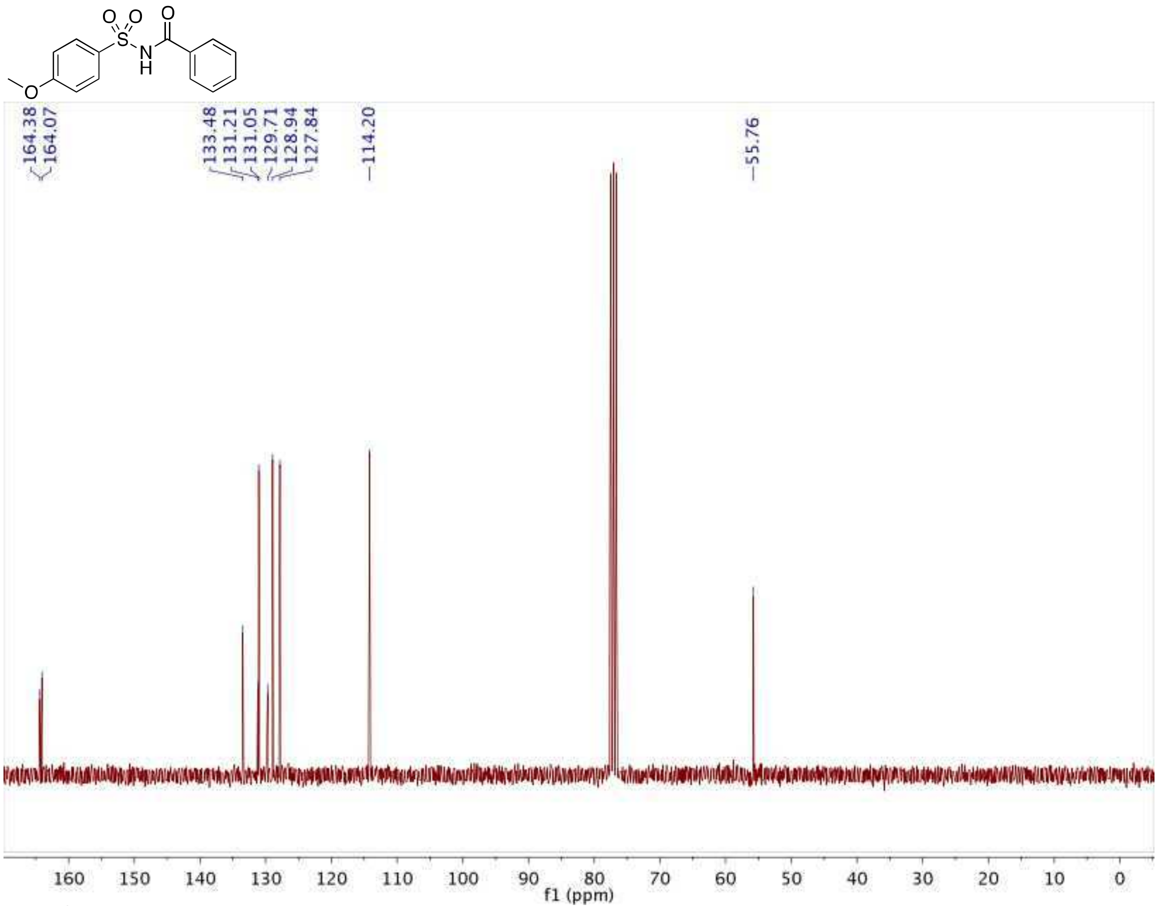
^{1}H NMR: ($CDCl_3$, 300 MHz) of *N*-benzenesulfonamide benzoyl (Table 1, Entry 8)



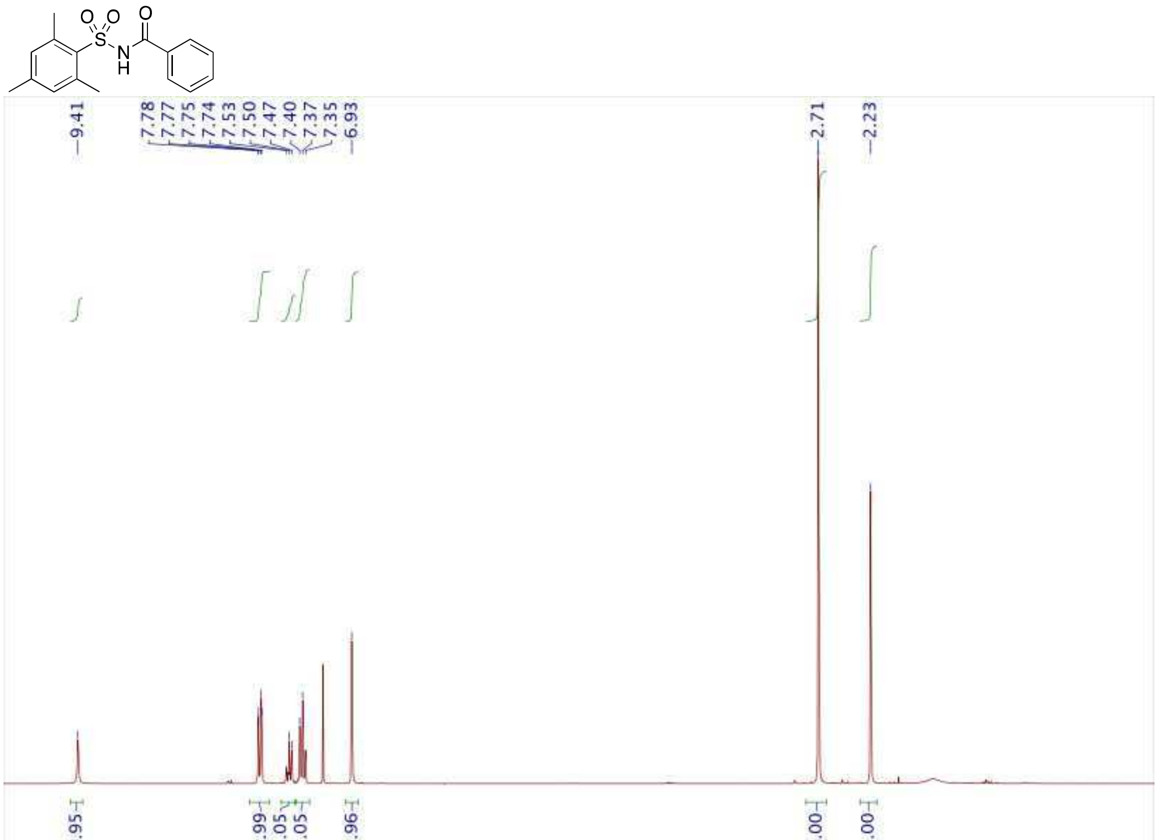
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of *N*-benzenesulfonamide benzoyl (Table 1, Entry 8)



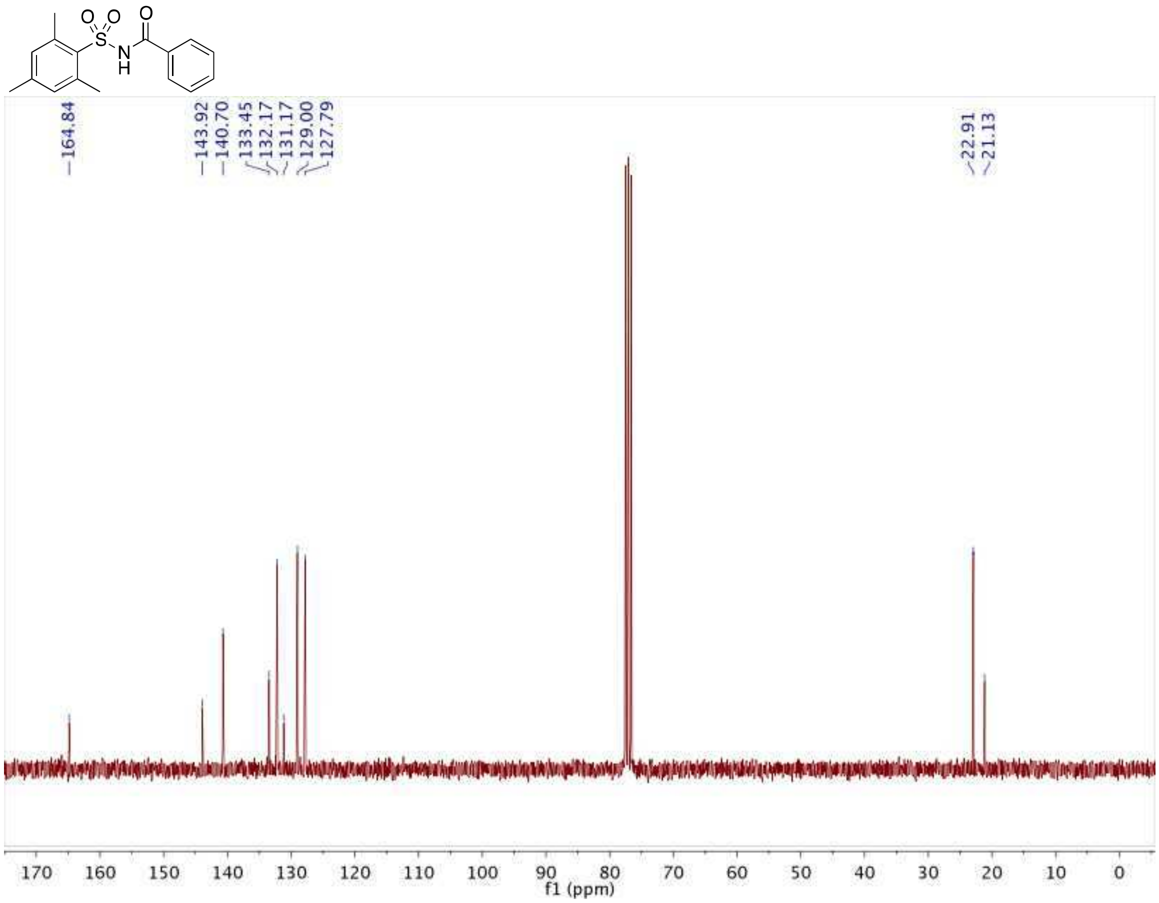
^{1}H NMR: (CDCl$_3$, 300 MHz) of benzoyl *N*-4-methoxy-benzenesulfonamide (Table 1, Entry 9)



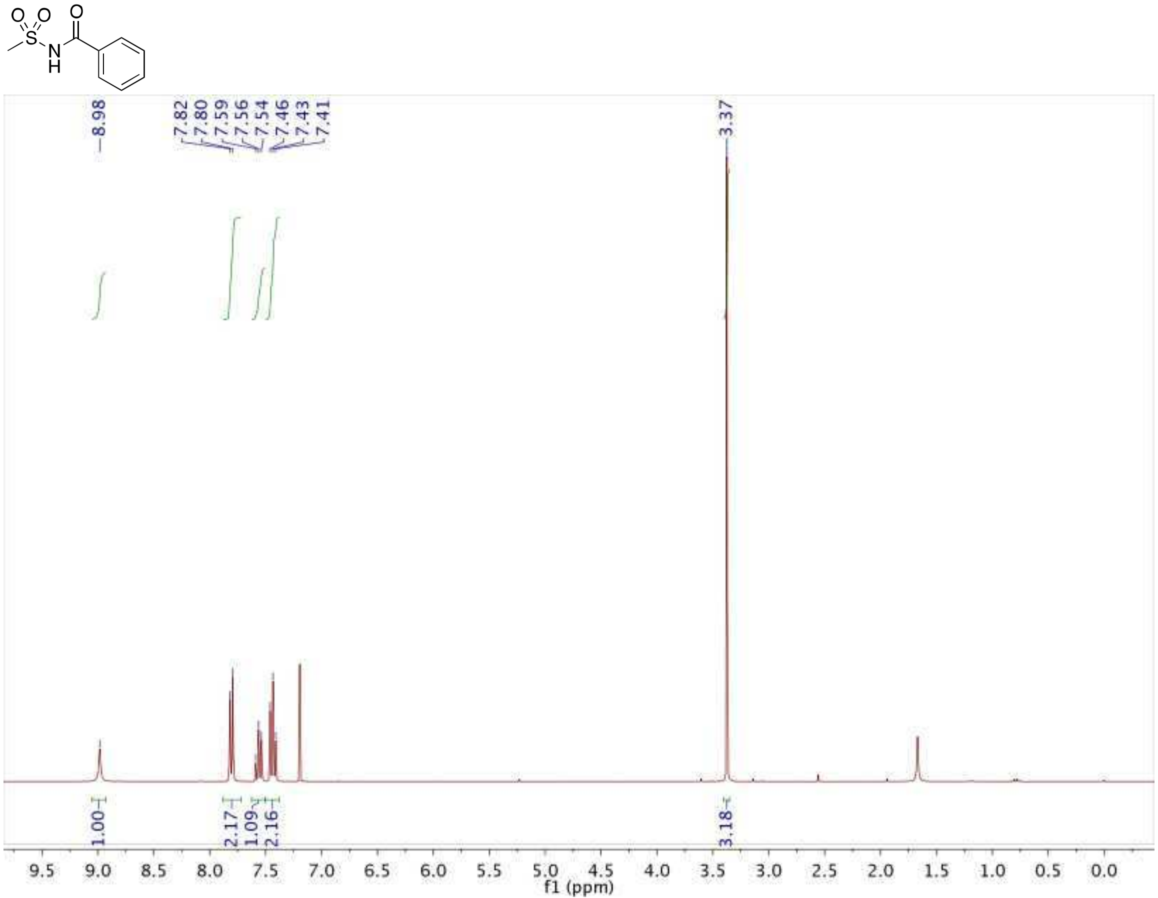
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of benzoyl *N*-4-methoxy-benzenesulfonamide (Table 1, Entry 9)



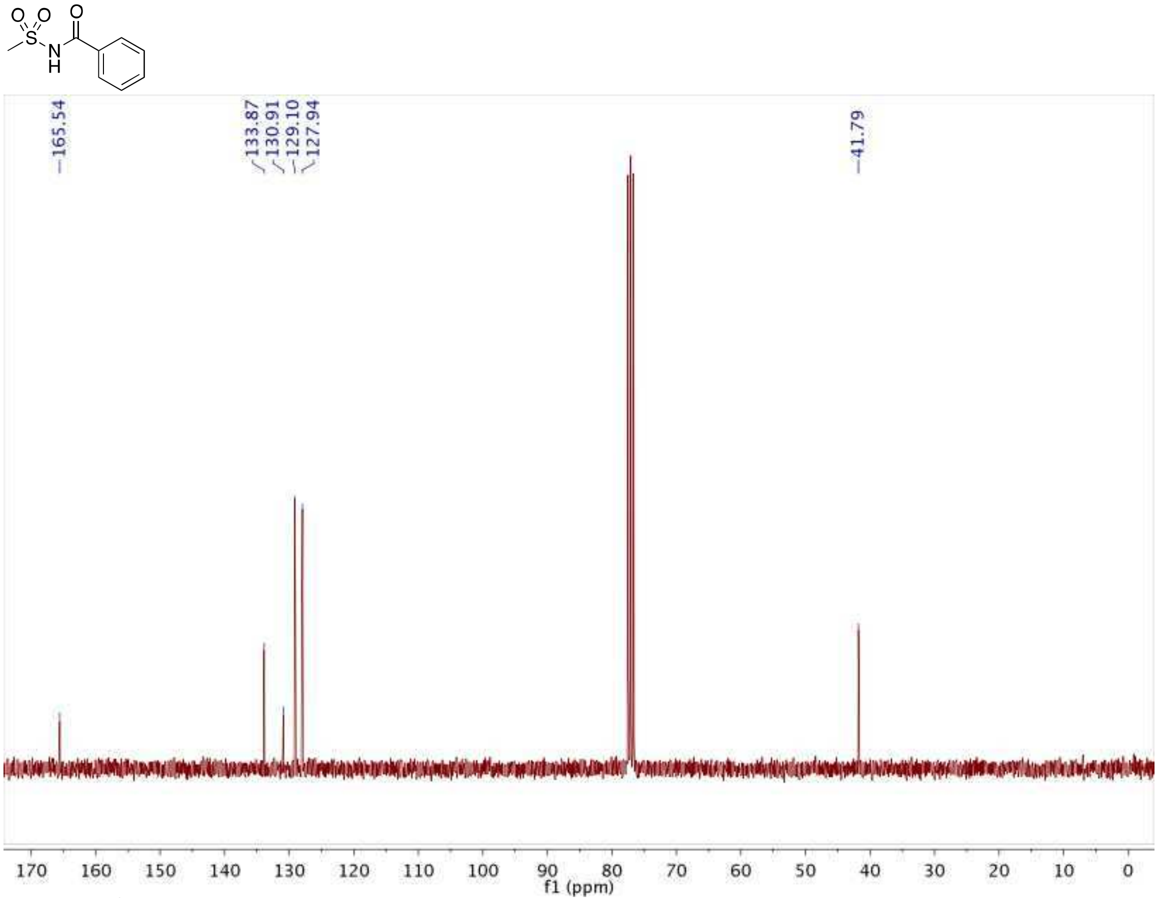
^{1}H NMR: ($CDCl_3$, 300 MHz) of *N*-benzoyl-2,4,6-trimethylbenzenesulfonamide (Table 1, Entry 10)



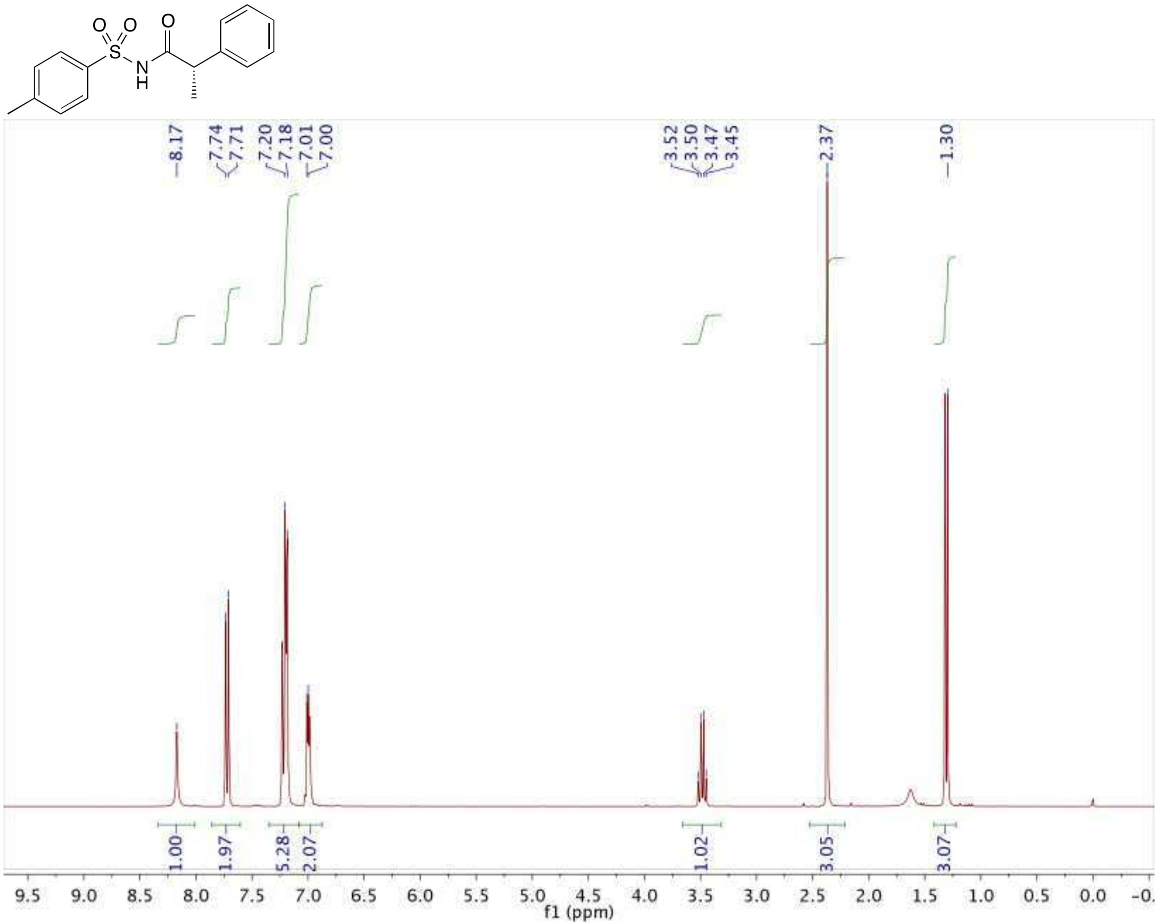
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of *N*-benzoyl-2,4,6-trimethylbenzenesulfonamide (Table 1, Entry 10)



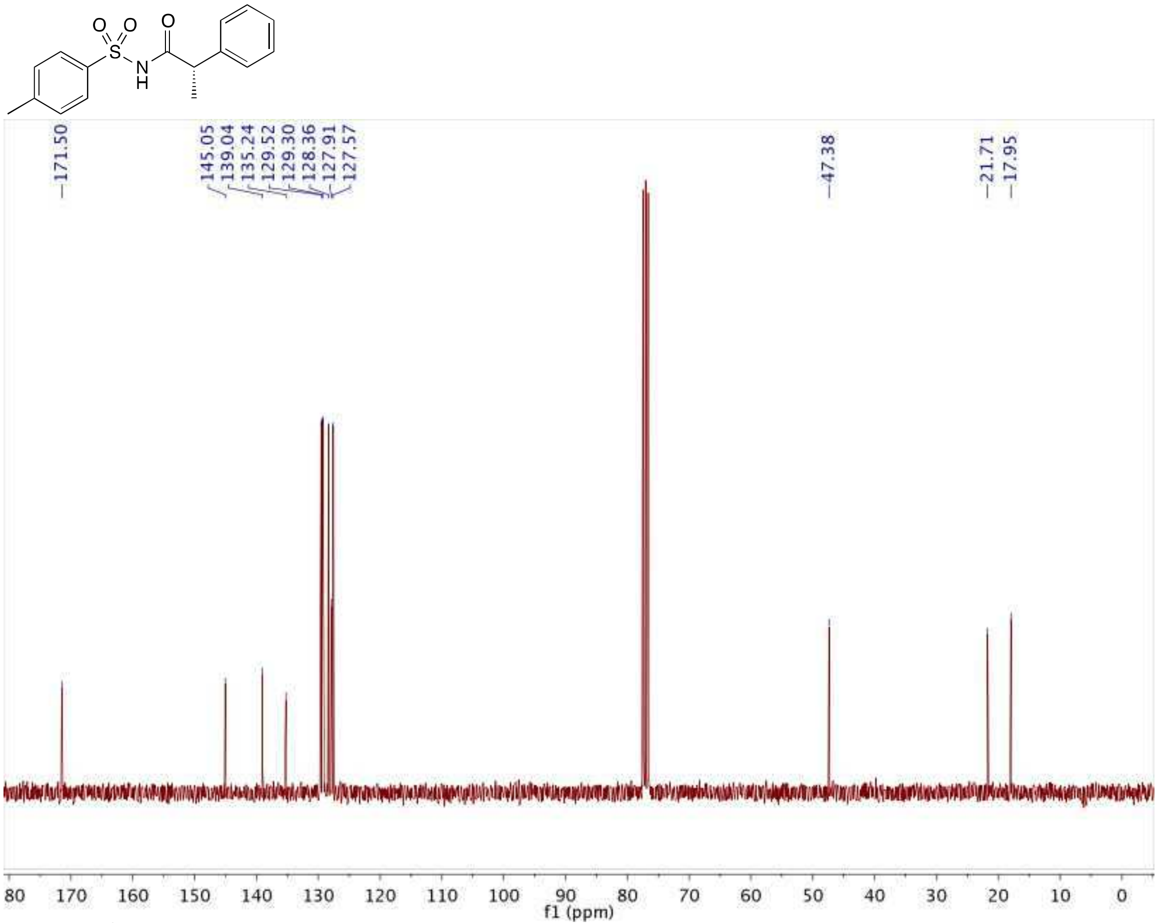
^{1}H NMR: (CDCl$_3$, 300 MHz) of *N*-benzoyl-methanesulfonamide (Table 1, Entry 11)



^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of *N*-benzoyl-methanesulfonamide (Table 1, Entry 11)



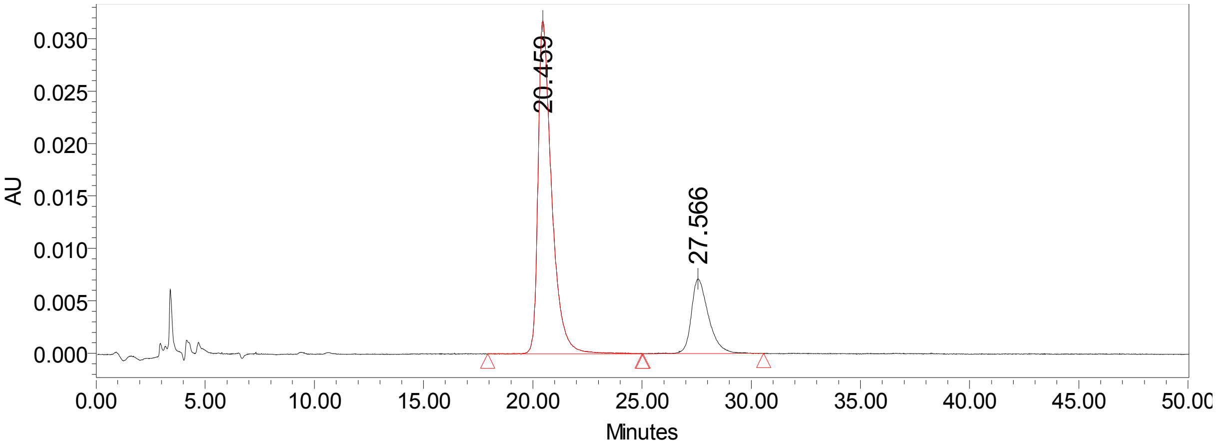
^{1}H NMR: ($CDCl_3$, 300 MHz) of (S)-2-phenyl-N-tosylpropanamide (Table 1, Entry 12)



^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of (S)-2-phenyl-N-tosylpropanamide (Table 1, Entry 12)

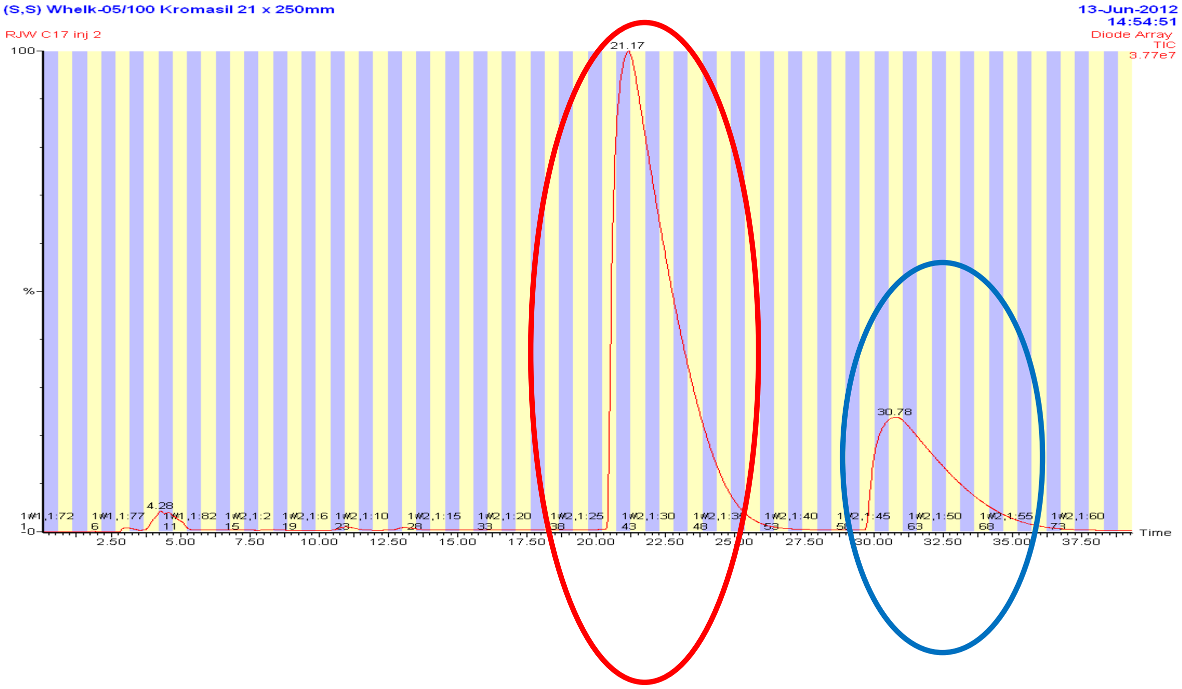
HPLC Analysis:

Isocratic *iso*-Hexane/ *iso*-Propanol 80:20 - both containing 0.1% glacial acetic acid.
Column: (S,S) – Whelk 4.6 x 250mm
Flow rate – 1ml/min

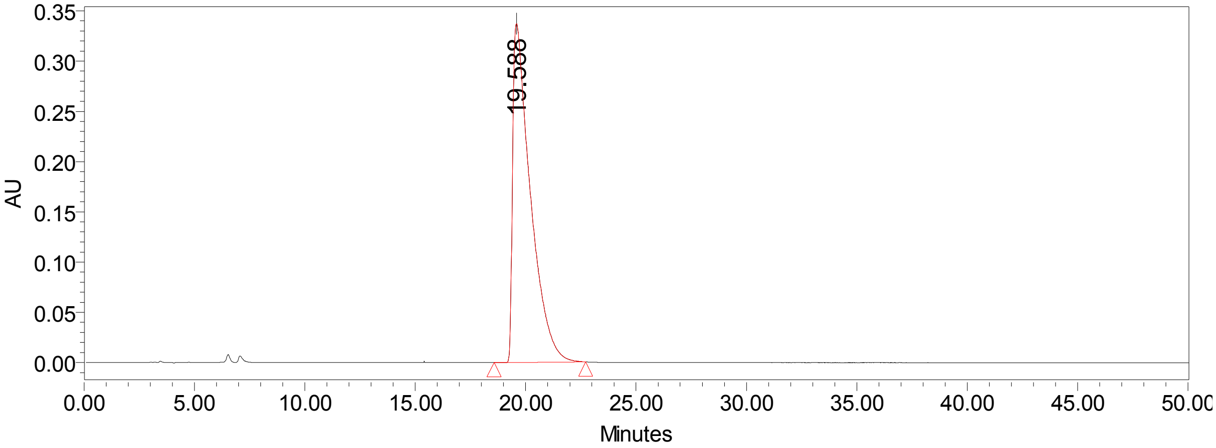


Prep:

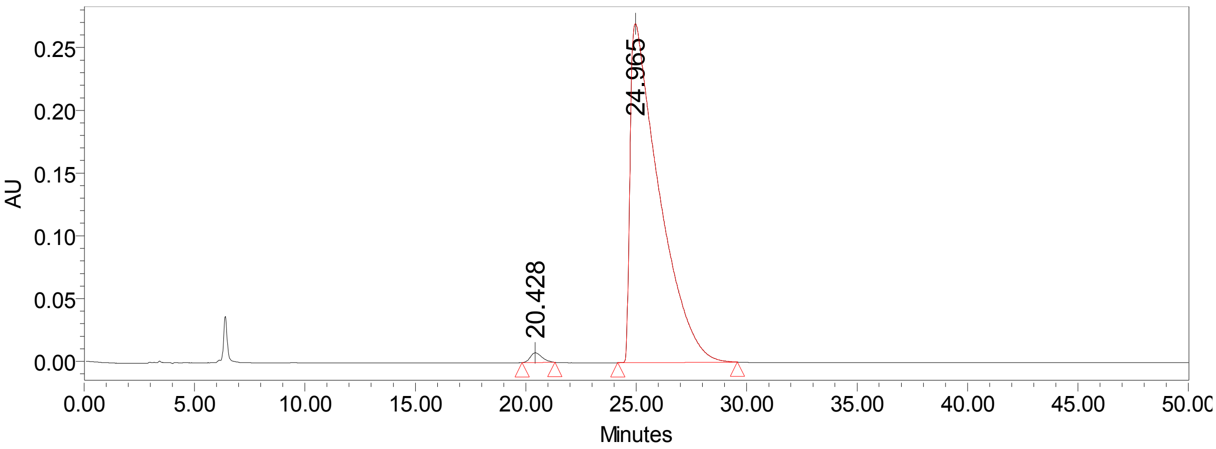
Isocratic *iso*-Hexane/*iso*-Propanol 80:20 - both containing 0.1% glacial acetic acid.
Column: (S,S) – Whelk 21 x 250mm
Flow rate – 20ml/min

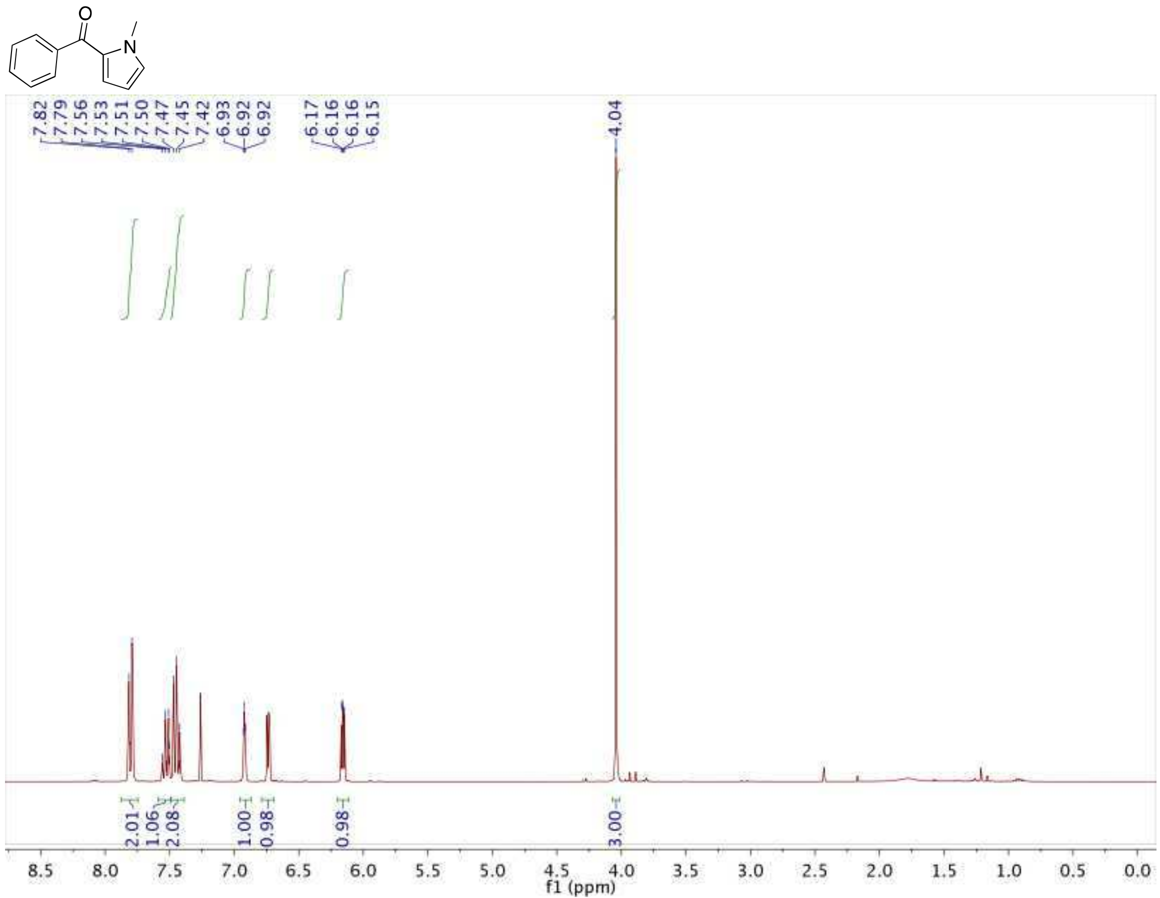


Enantiomer A: 46mg

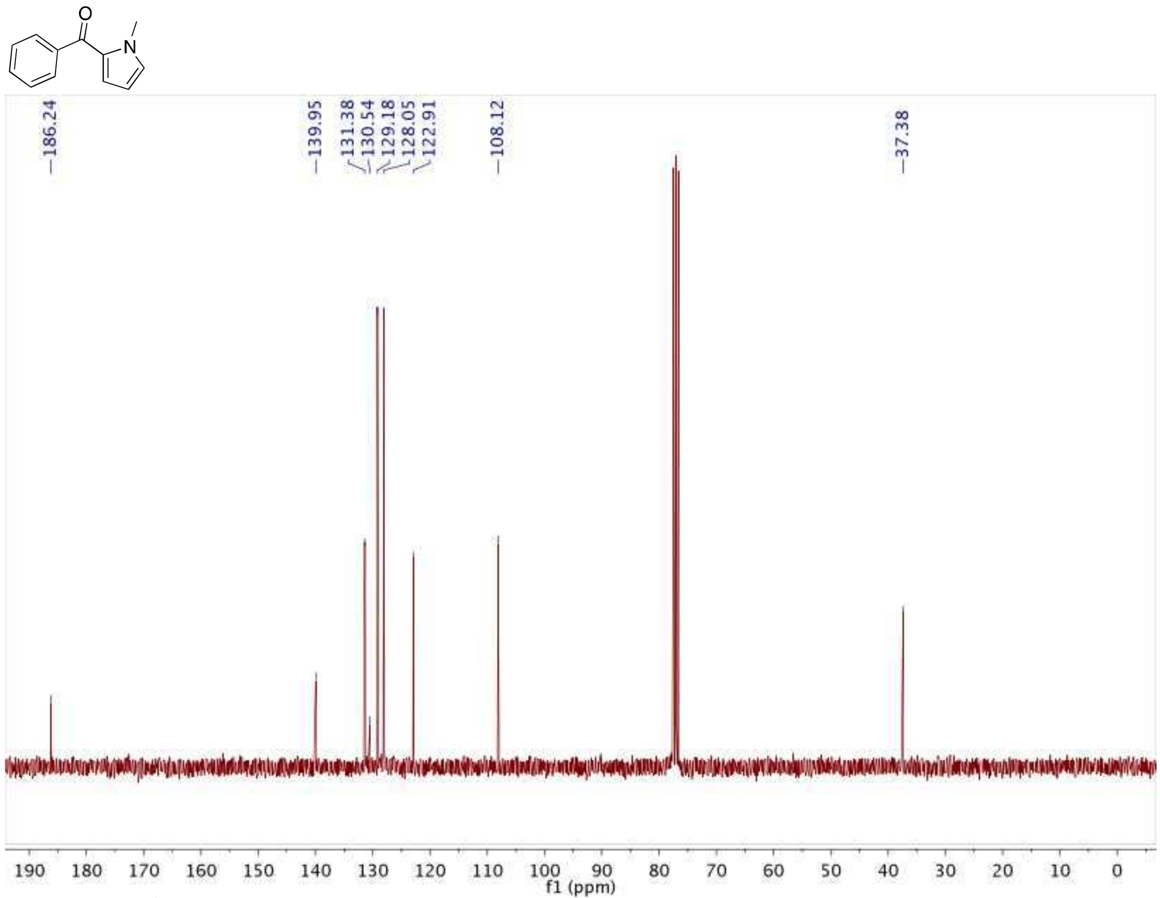


Enantiomer B: 6.5mg

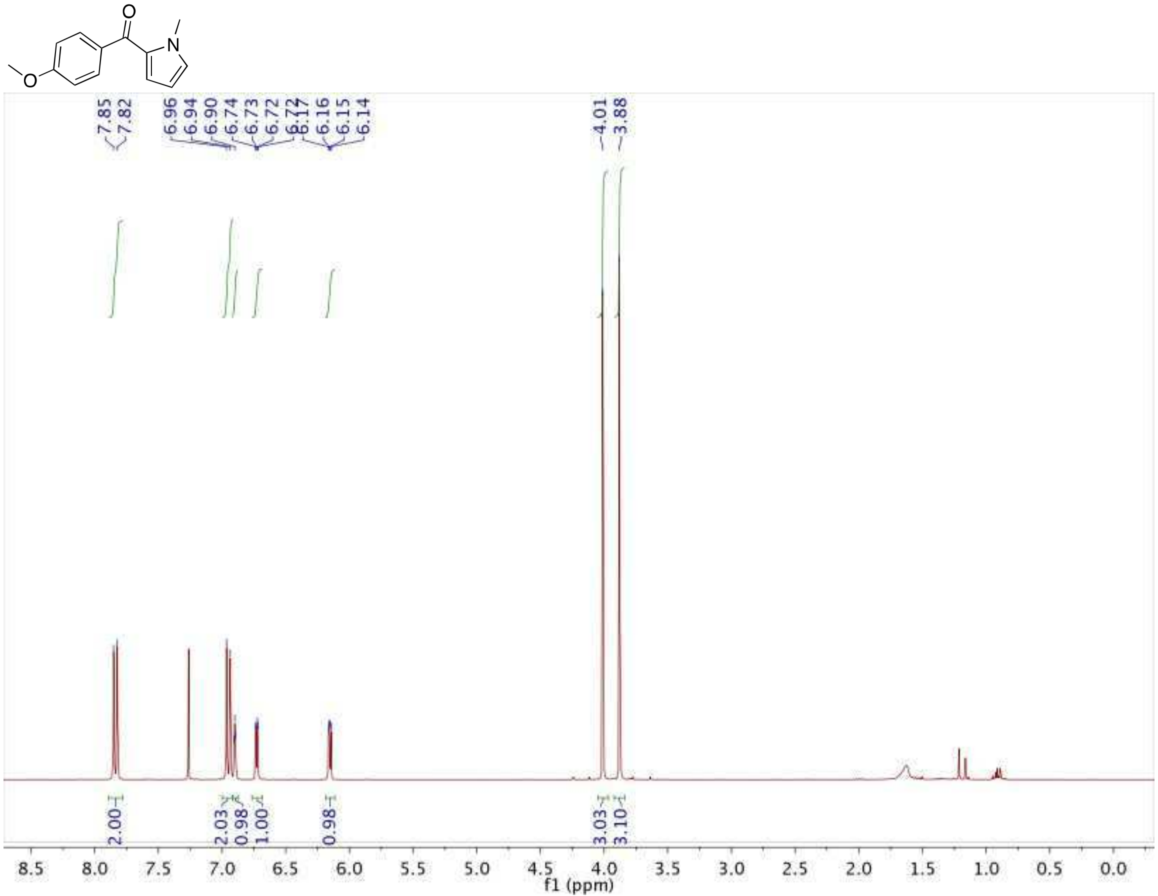




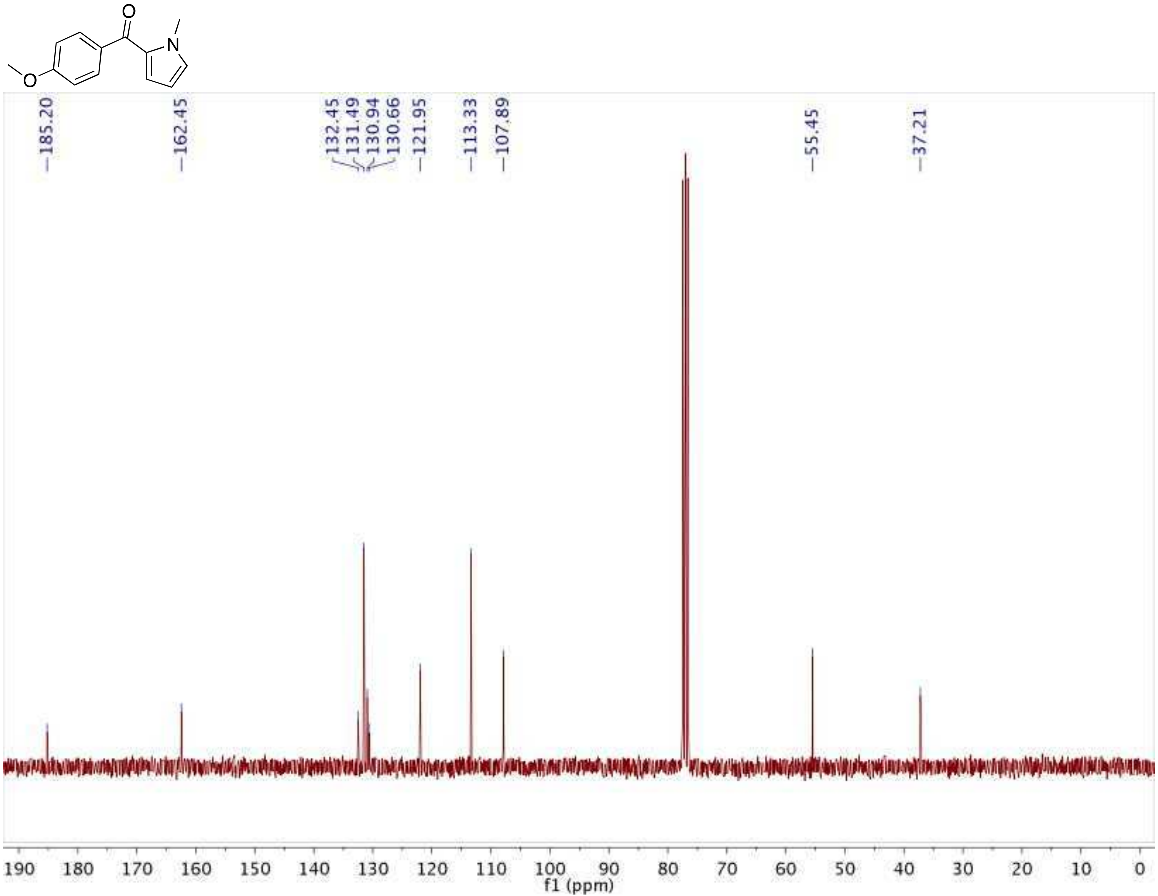
^{1}H NMR: ($CDCl_3$, 300 MHz) of *N*-methyl-2-benzoylpyrrole (Table 2, Entry 1)



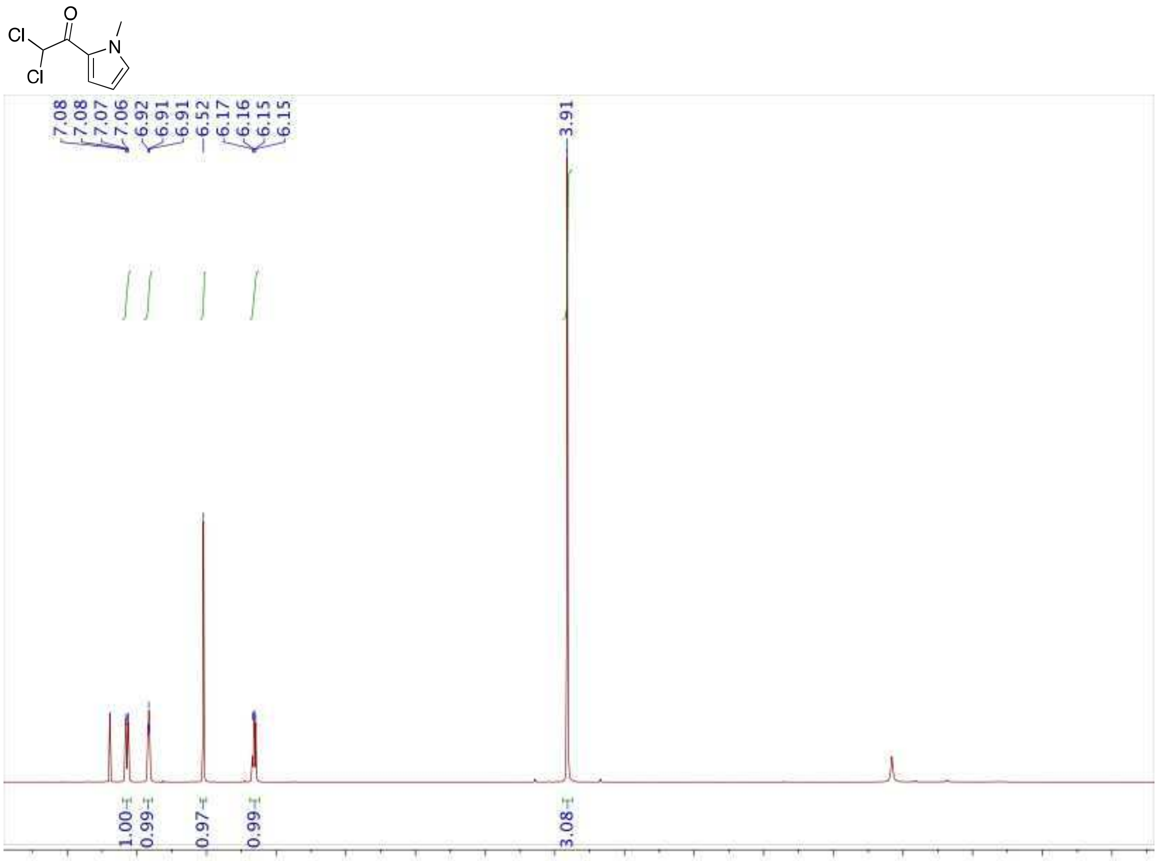
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of *N*-methyl-2-benzoylpyrrole (Table 2, Entry 1)



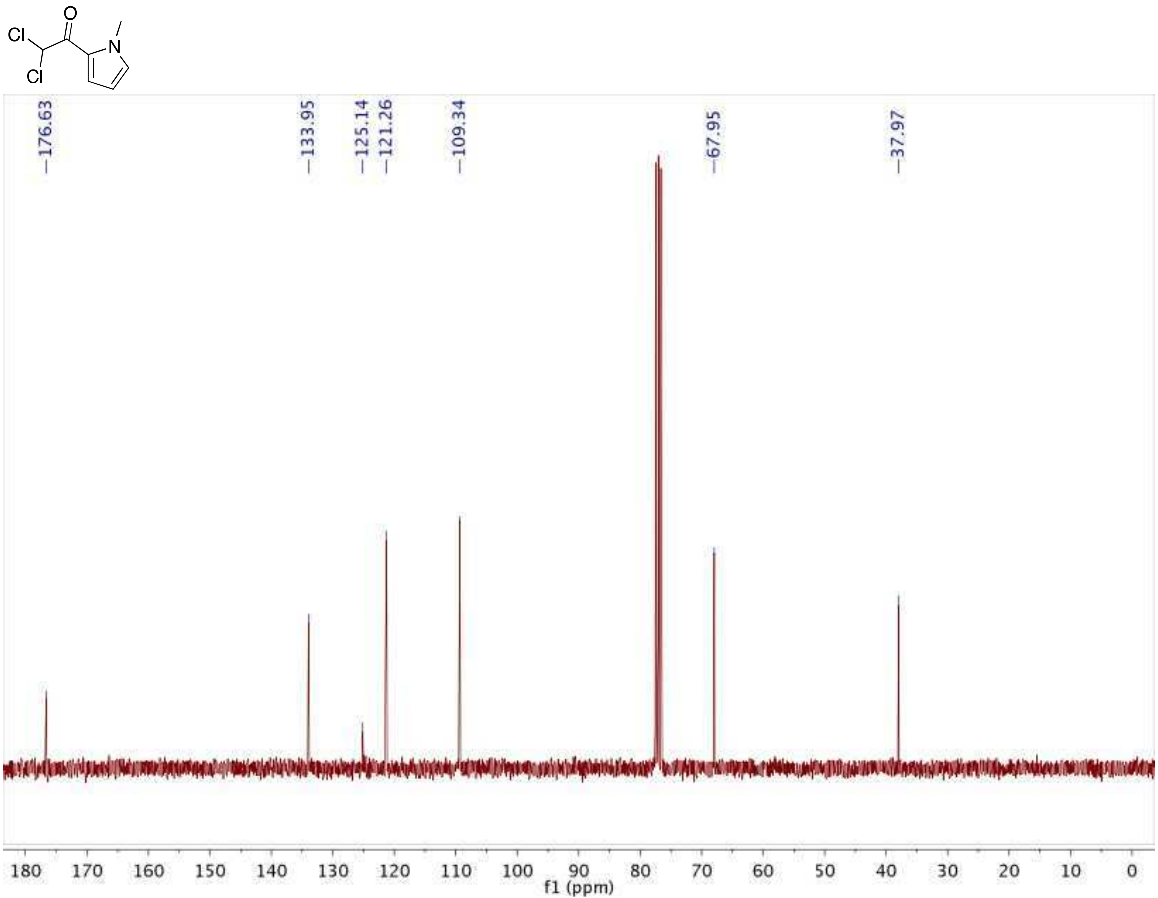
^{1}H NMR: ($CDCl_3$, 300 MHz) of 4-methoxy-(*N*-methyl-1H-2-pyrrolyl)methanone (Table 2, Entry 2)



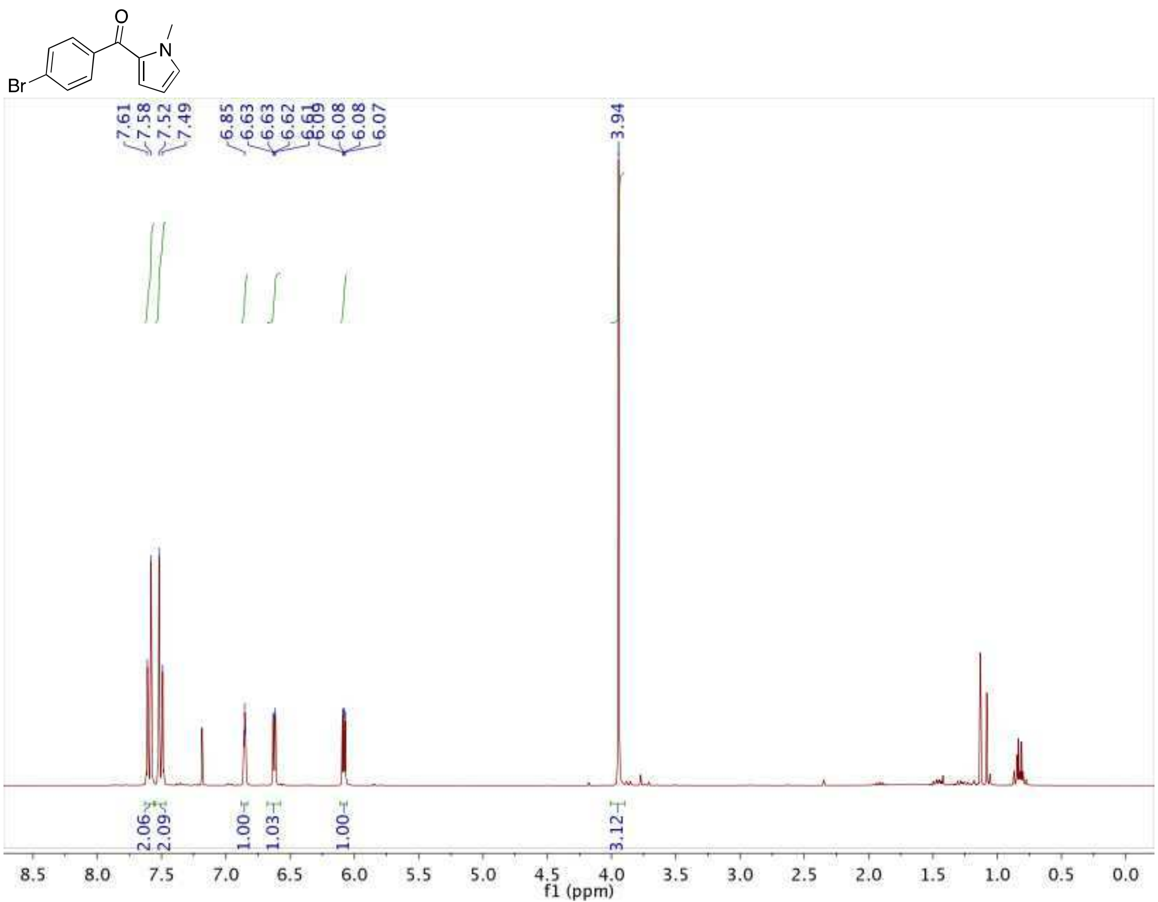
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of 4-methoxy-(*N*-methyl-1H-2-pyrrolyl)methanone (Table 2, Entry 2)



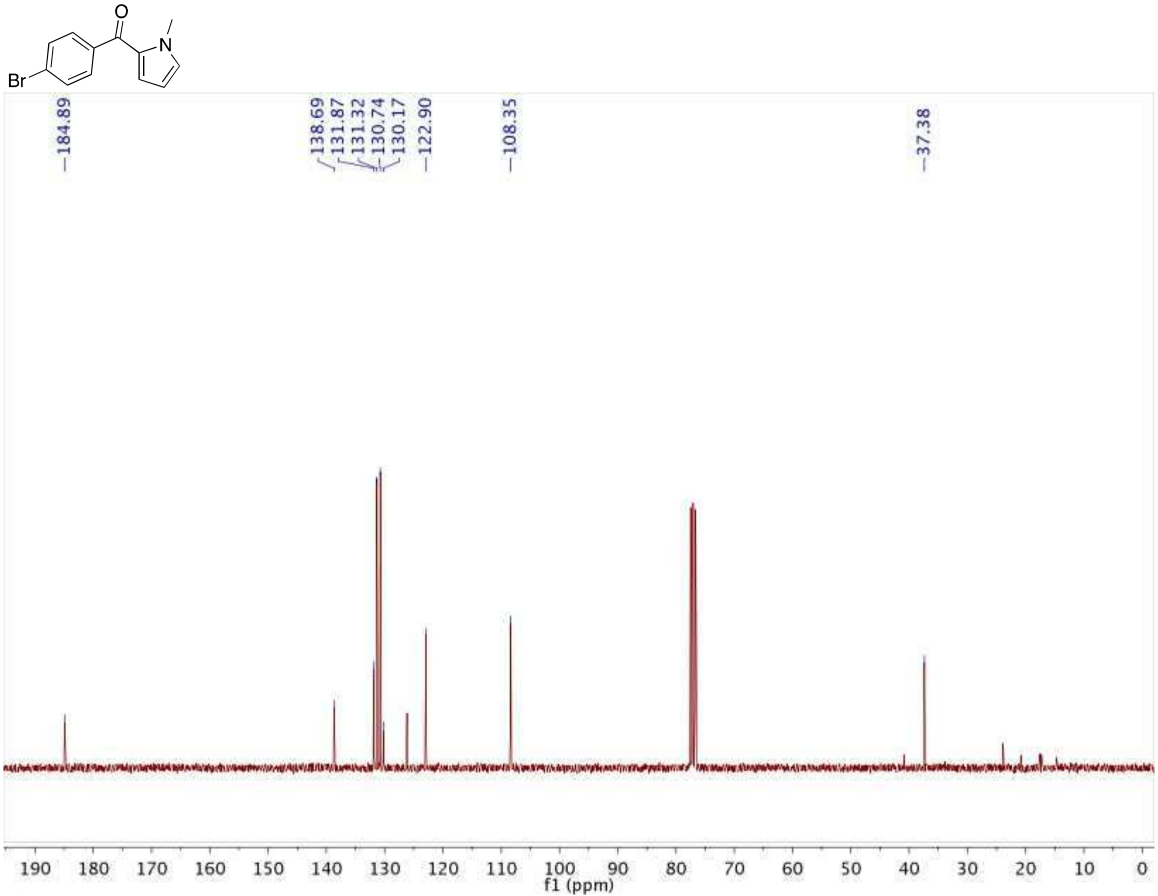
^{1}H NMR: ($CDCl_3$, 300 MHz) of 2,2 dichloro-1-(*N*-methyl-1H-2-pyrrolyl)-ethanone (Table 2, Entry 3)



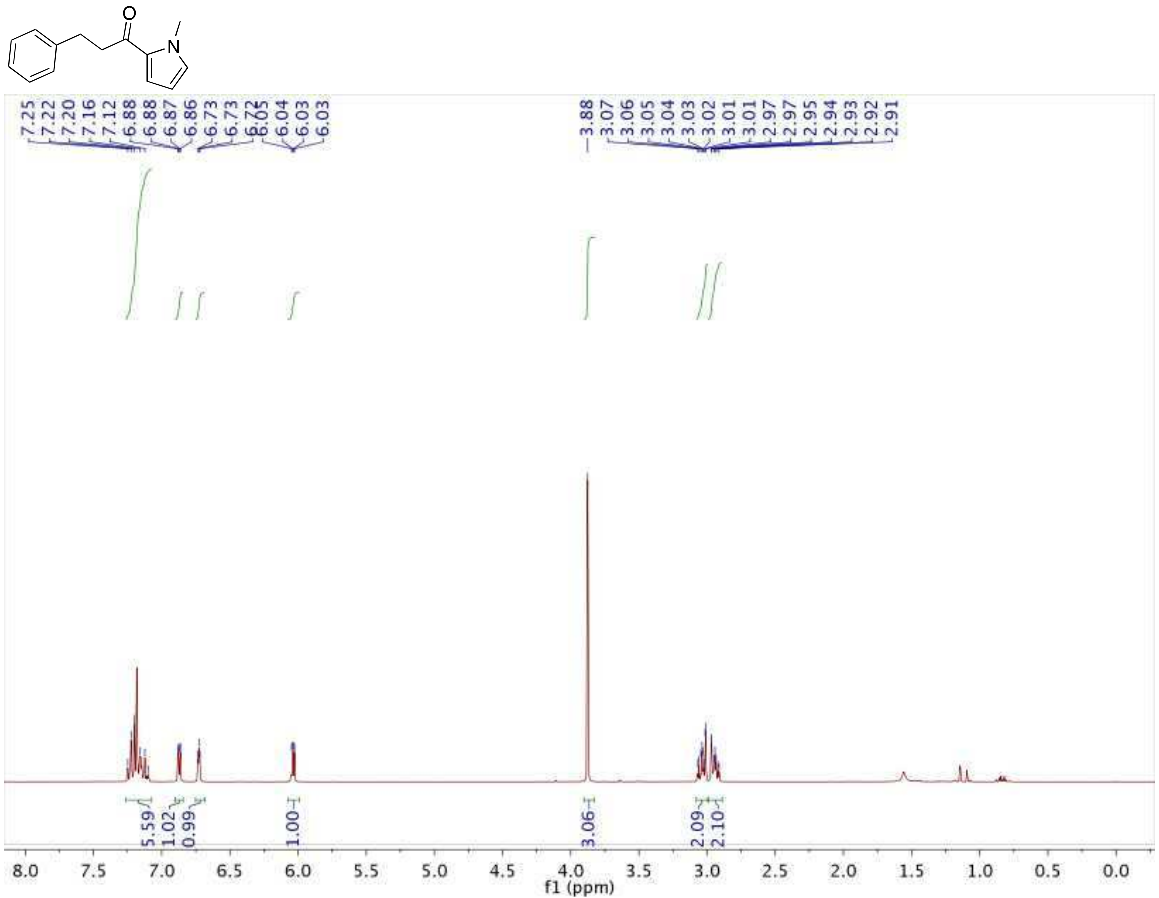
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of 2,2 dichloro-1-(*N*-methyl-1H-2-pyrrolyl)-ethanone (Table 2, Entry 3)



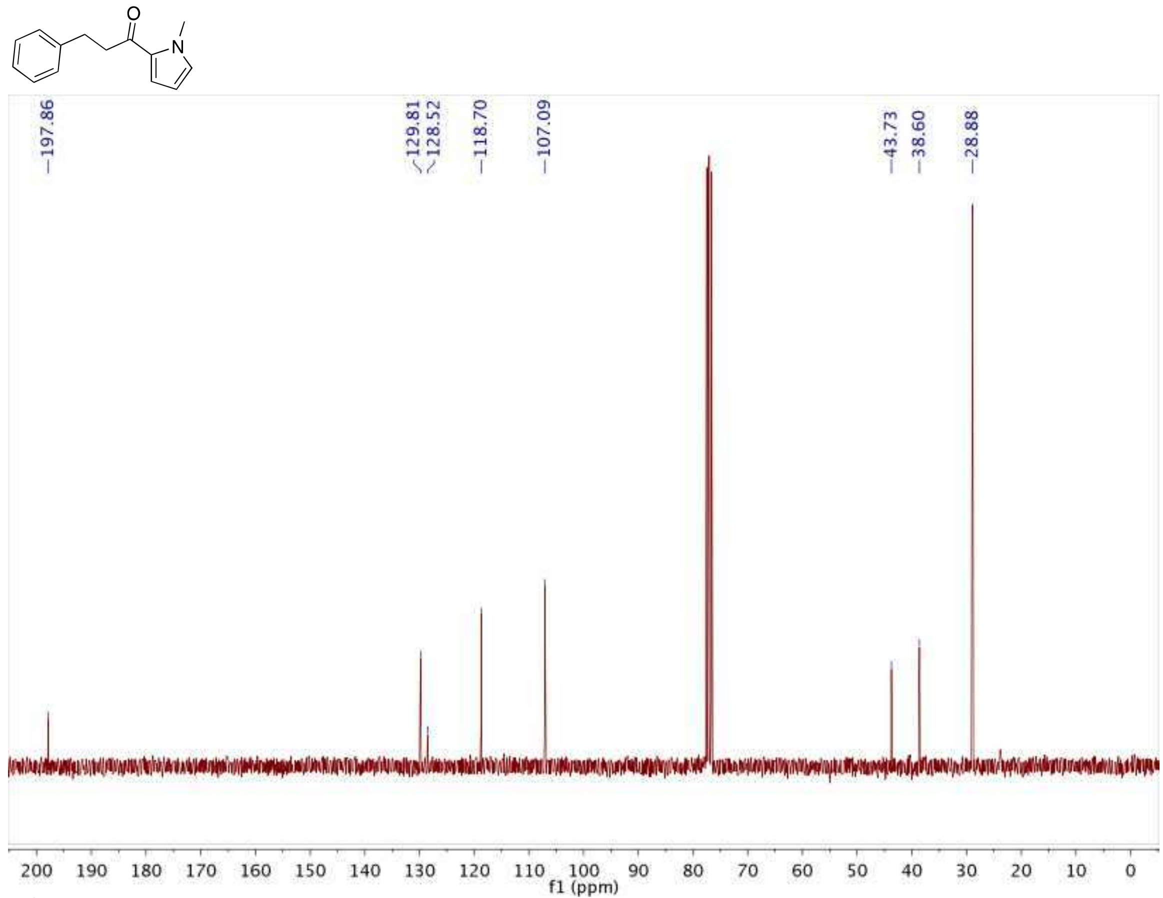
^{1}H NMR: ($CDCl_3$, 300 MHz) of 4-bromophenyl(1-methyl-1*H*-pyrrol-2-yl)methanone (Table 2, Entry 4)



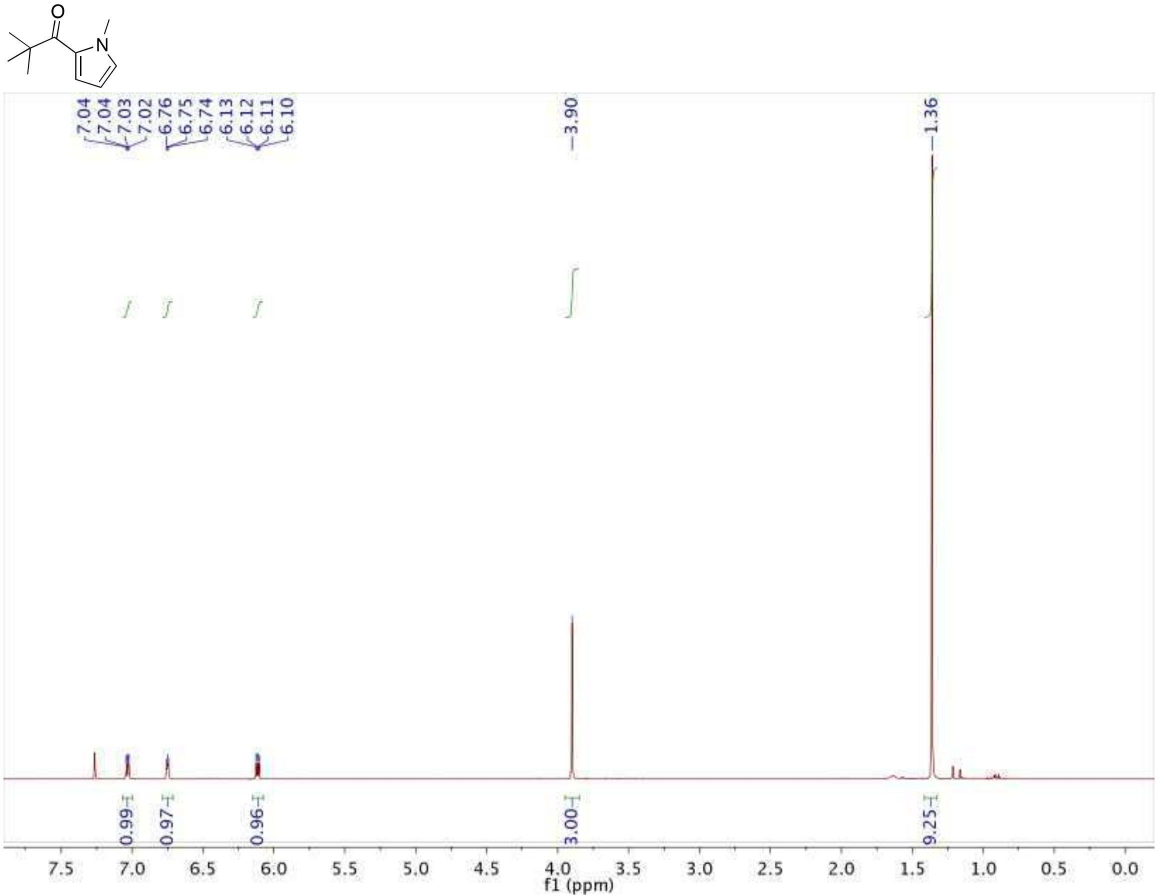
^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of 4-bromophenyl(1-methyl-1*H*-pyrrol-2-yl)methanone (Table 2, Entry 4)



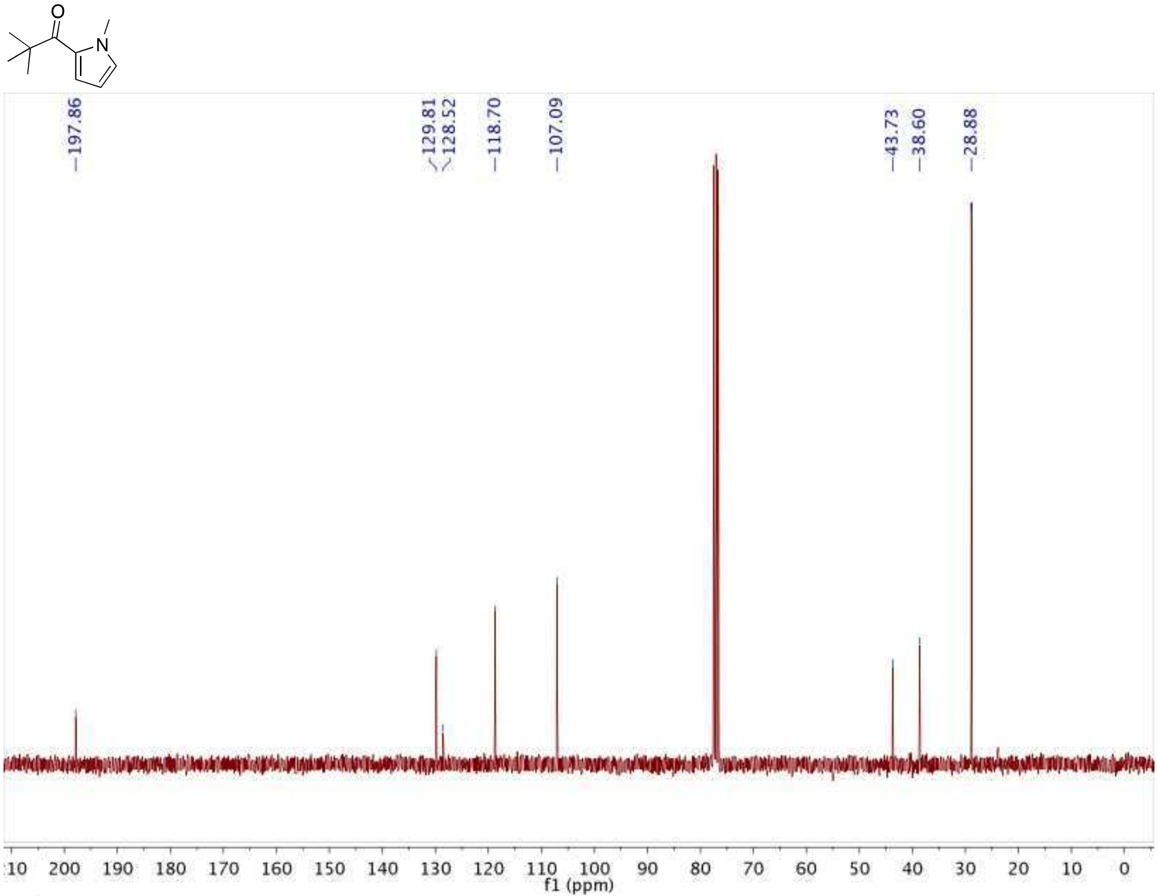
^{1}H NMR: ($CDCl_3$, 300 MHz) of 1-(*N*-methyl-1H-2-pyrrolyl)-3-phenyl-1-propanone (Table 2, Entry 5)



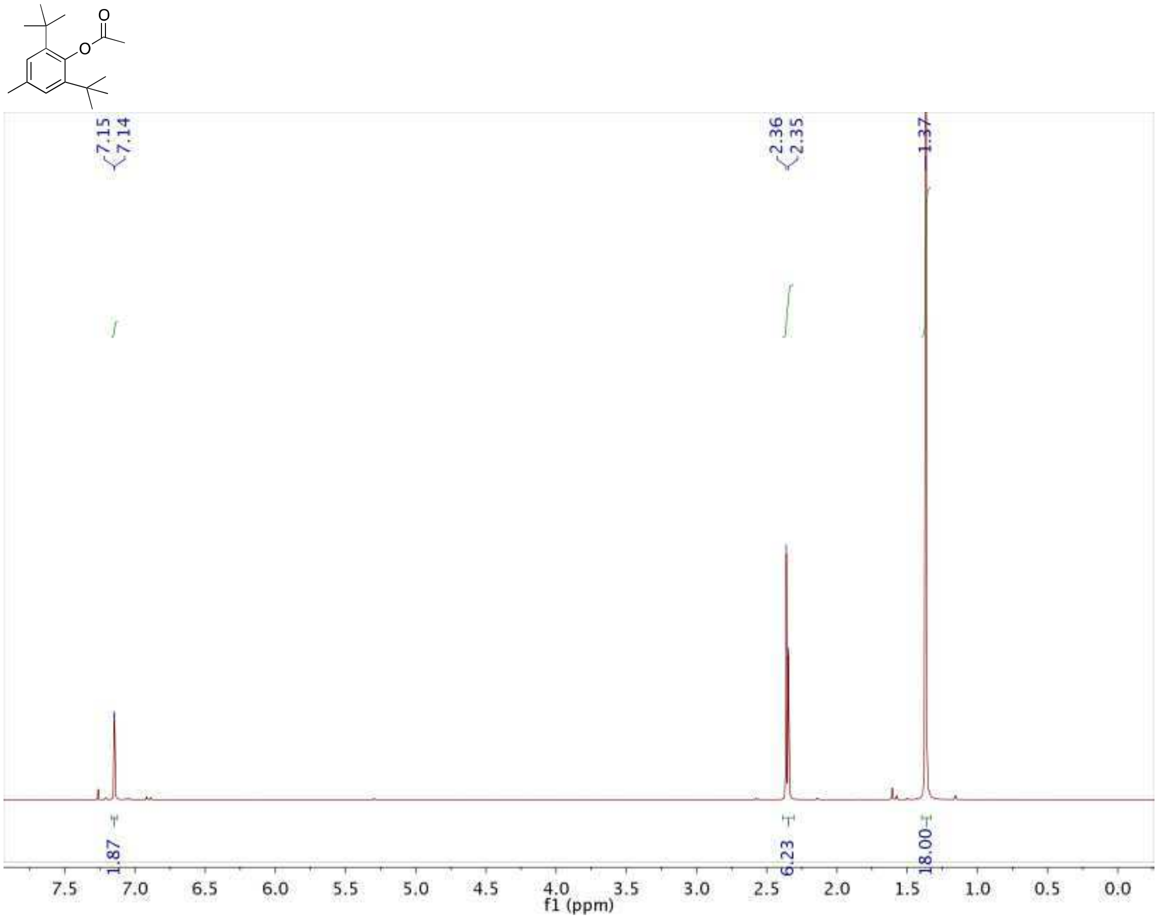
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of 1-(*N*-methyl-1H-2-pyrrolyl)-3-phenyl-1-propanone (Table 2, Entry 5)



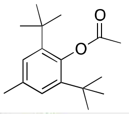
^{1}H NMR: (CDCl$_3$, 300 MHz) of 1,1-dimethyl(*N*-methyl-1H-2-pyrrolyl)propanone (Table 2, Entry 6)

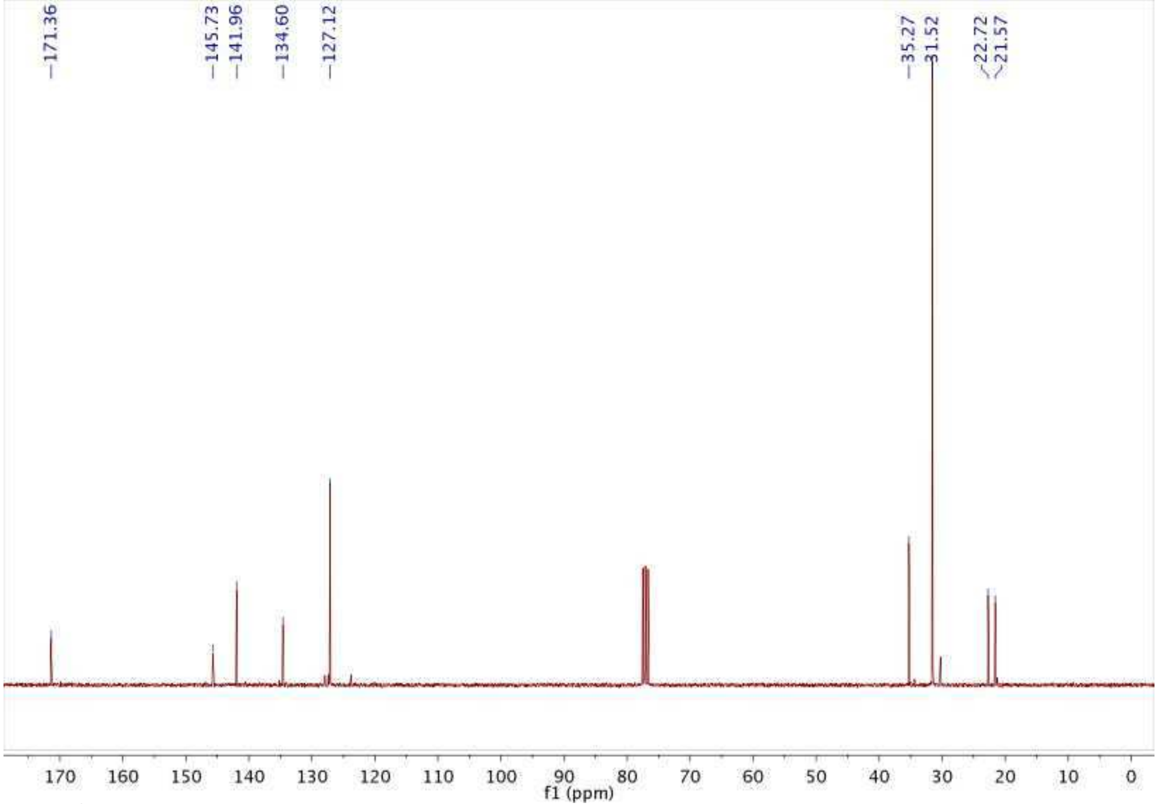


^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of 1,1-dimethyl(*N*-methyl-1H-2-pyrrolyl)propanone (Table 2, Entry 6)

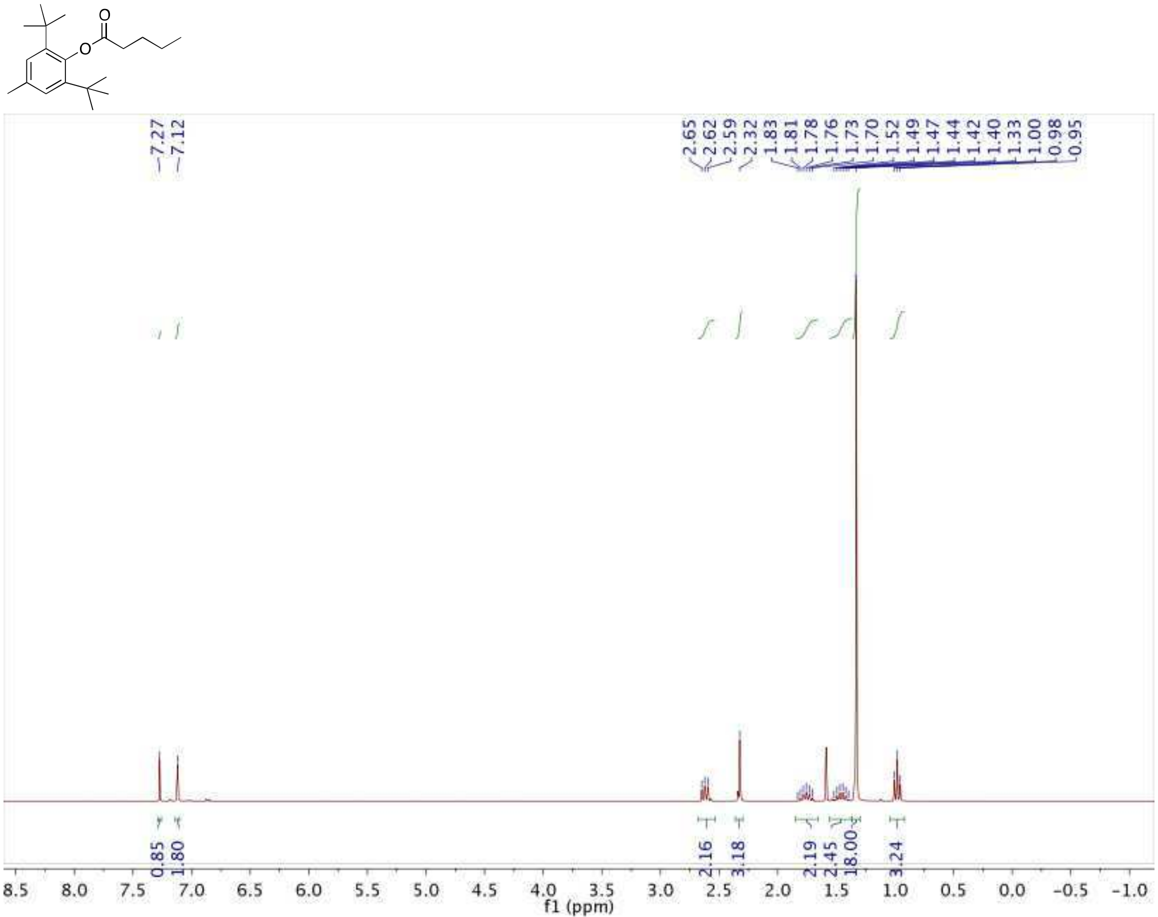


^{1}H NMR: ($CDCl_3$, 300 MHz) of 2,6-di-*tert*-butyl-4-methylphenyl acetate (Table 3, Entry 1)

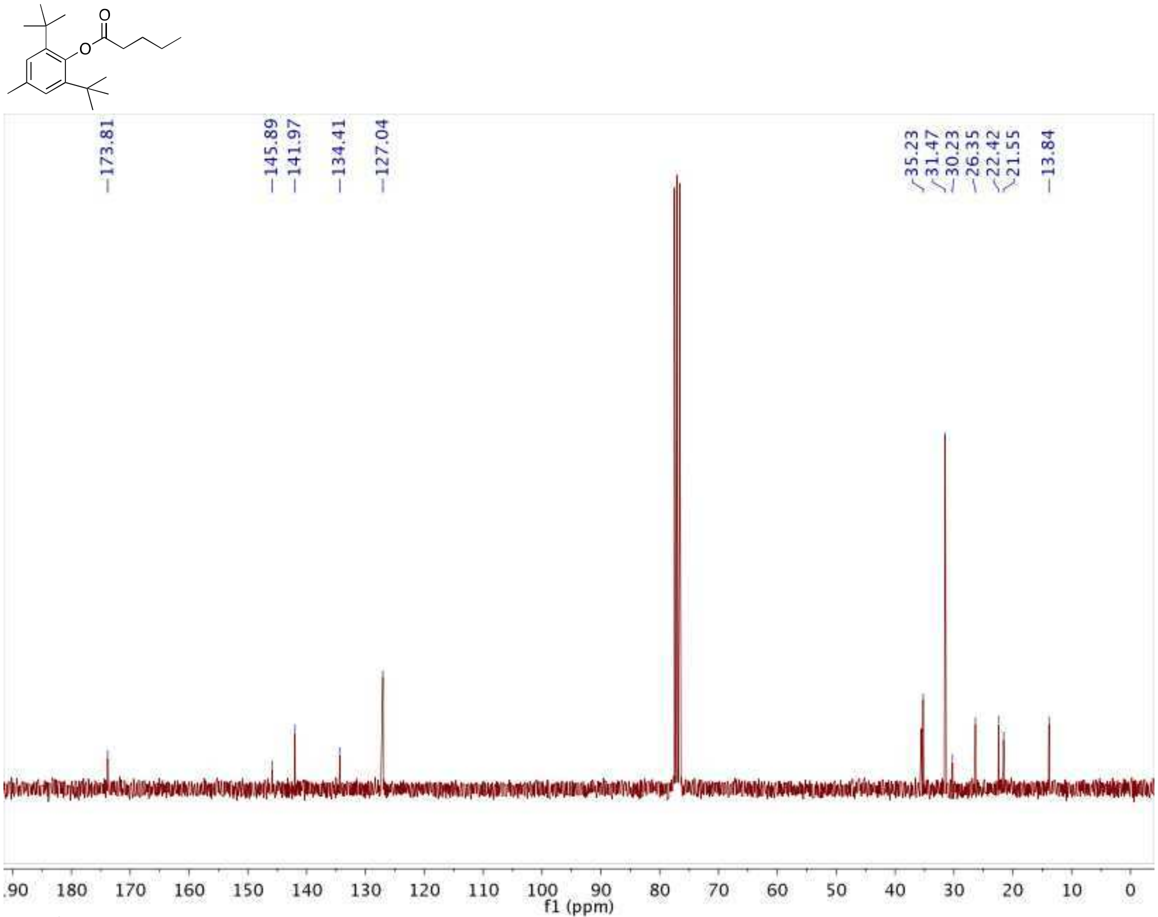




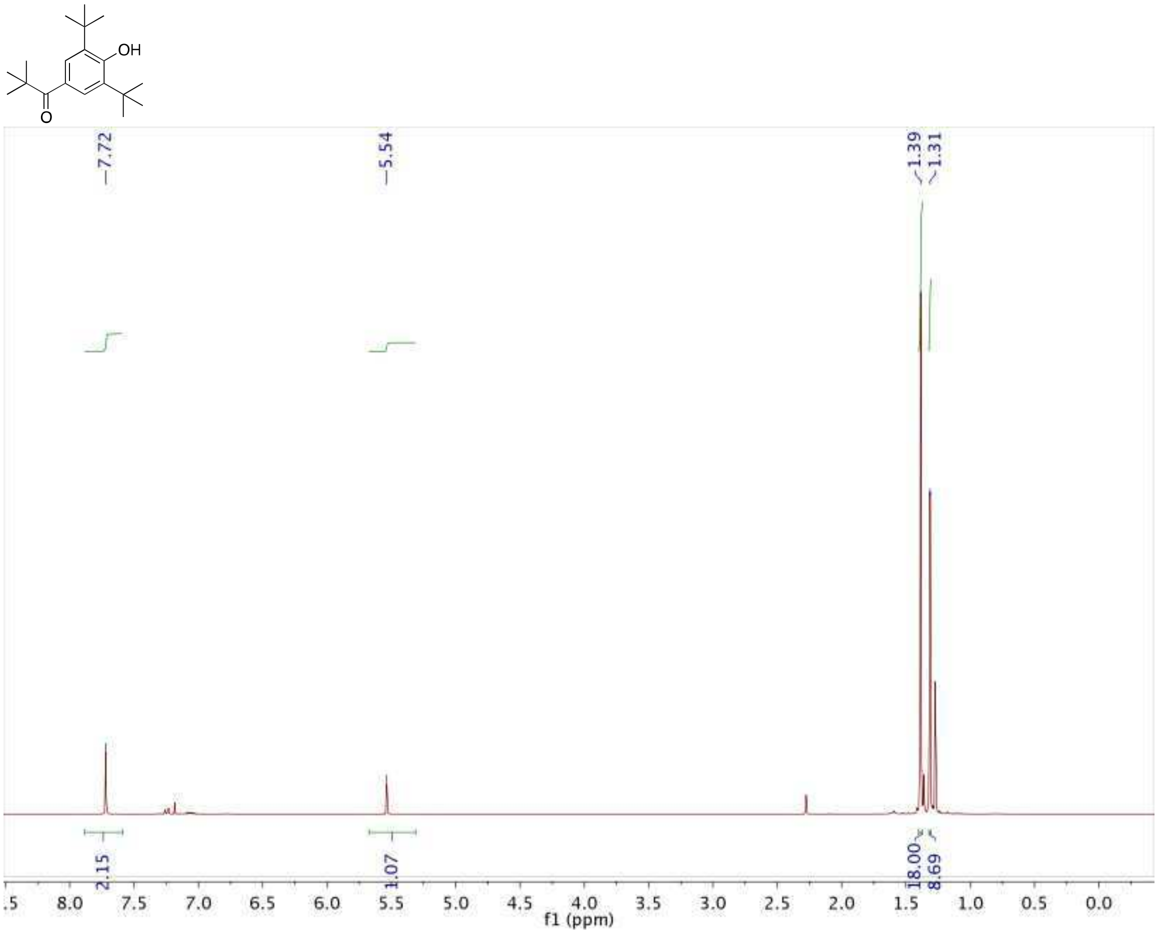
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of 2,6-di-*tert*-butyl-4-methylphenyl acetate (Table 3, Entry 1)



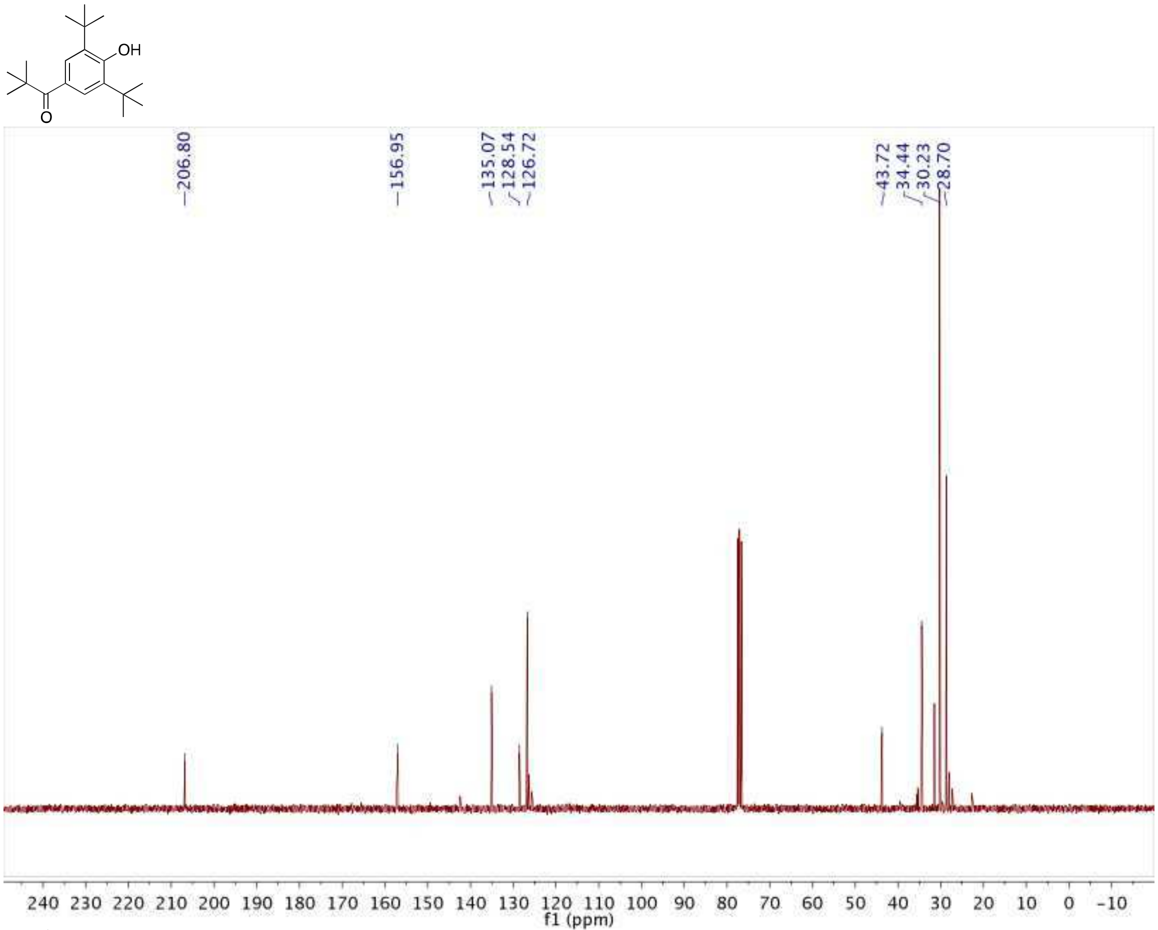
^{1}H NMR: ($CDCl_3$, 300 MHz) of 2,6-di-*tert*-butyl-4-methylphenyl pentanoate (Table 3, Entry 2)



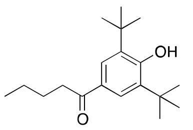
^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of 2,6-di-*tert*-butyl-4-methylphenyl pentanoate (Table 3, Entry 2)

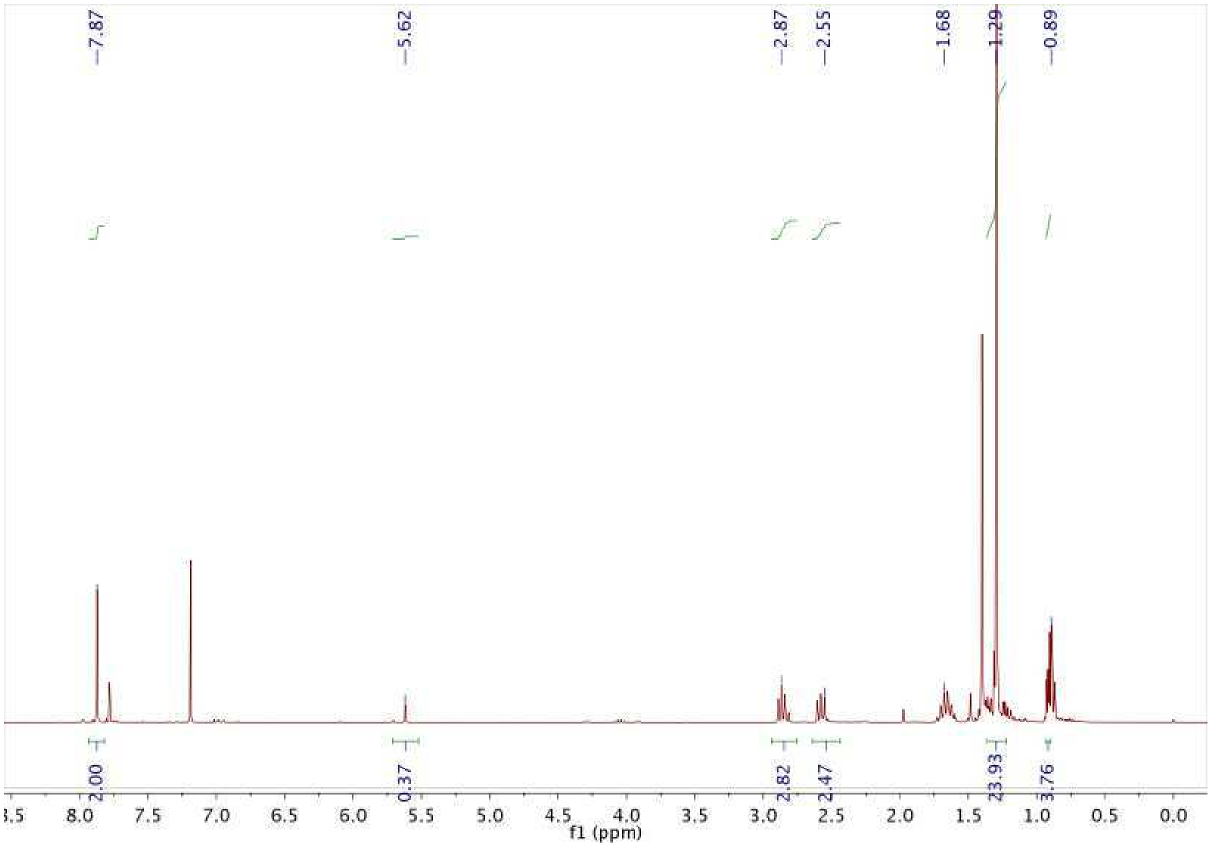


^{1}H NMR: (CDCl$_3$, 300 MHz) of 1-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,2-dimethylpropan-1-one (Table 3, entry 3)

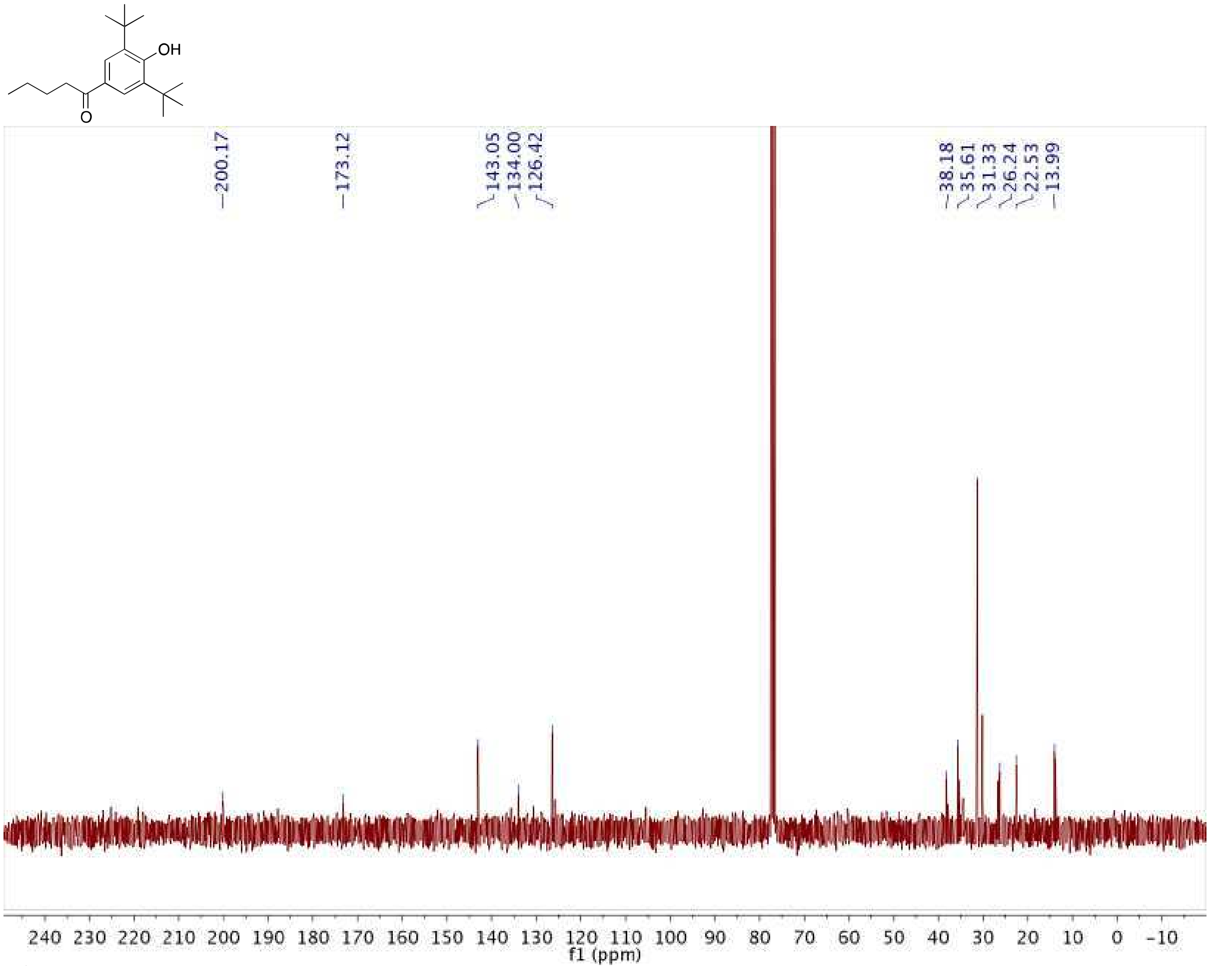


^{13}C NMR (75.5 MHz, $CDCl_3$, 298K) of 1-(3,5-di-tert-butyl-4-hydroxyphenyl)-2,2-dimethylpropan-1-one (Table 3, entry 3)





^{1}H NMR: ($CDCl_3$, 300 MHz) of 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)pentan-1-one (Table 3, entry 4)



^{13}C NMR (75.5 MHz, CDCl$_3$, 298K) of 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)pentan-1-one (Table 3, entry 4)