Arylation using sulfonamides: Phenylacetamide synthesis through tandem acylation-Smiles rearrangement

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Supporting Information

1. General Remarks

All reactions were carried out under an atmosphere of N_2 unless otherwise specified. Any reagents not listed as an experimental protocol were bought from commercial sources and were used as received. Yields of all the compounds refer to isolated compounds unless otherwise stated. Anhydrous THF was distilled from sodium/benzophenone ketyl immediately before use. Other solvents were purchased in anhydrous quality and used as received or obtained from a Innotative Technologies PureSolv MD 5 Solvent Purification System.

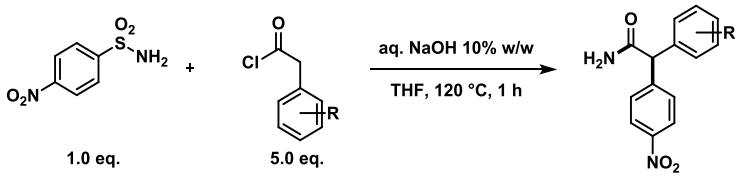
Thin layer chromatography (TLC) was performed on commercially available pre-coated TLC plates (Merck Silica gel 60 F_{254} aluminium sheets). Visualisation was either achieved under UV light at 254 nm or with a $KMnO_4$ stain. Melting points were recorded on a Griffen melting point apparatus and were uncorrected. Column chromatography was conducted on silica gel (Sigma Aldrich, 40-63 μm, 60 Å) or Biotage KP-Sil or Snap Ultra cartridges on a Biotage Isolera automated columning machine.

^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 298 K on either 500 or 400 MHz Bruker NMR spectrometers as stated. Signal positions were recorded in δ ppm and measured from the centre of the signal excluding multiplets which are given as a range. Splitting patterns are reported using the abbreviations s, br. s, d, t, q, quin, sept and m (or combinations thereof) denoting singlet, broad singlet, doublet, triplet, quartet, quintet, septet and multiplet respectively. The use of *app*, Ar, α abbreviations refer to apparent, aromatic, and quaternary, respectively. All ^1H NMR and ^{13}C chemical shifts were referenced to the residual solvent peak of $CDCl_3$ (^1H referenced to 7.26 ppm and ^{13}C referenced to 77.16 ppm), $(CD_3)_2SO$ (^1H referenced to 2.50 ppm and ^{13}C referenced to 39.52 ppm), methanol (^1H referenced to 3.31 ppm and ^{13}C referenced to 49.00 ppm) and acetone (^1H referenced to 2.05 ppm and ^{13}C referenced to 29.84 ppm). All ^{19}F chemical shifts were unadjusted from raw data. All coupling constants, *J*, are quoted in Hz and reported to the nearest 0.1 Hz. Assignment of spectra was aided by DEPT 135 and 2D NMR spectroscopy (COSY, HSQC and HMBC). Assignments are provided in the following format: chemical shift (multiplicity, coupling constant, integration, description of functional group, letter referenced to molecule drawn above).

All mass spectrometry was carried out by a mass spectrometry service at the University of Manchester. High resolution mass spectrometry (HRMS) was completed on a Waters QTOF micro with ESI/APCI ionisation. Low resolution mass spectrometry was performed on Waters SQD2 Q-MS, Agilent 5975C Triple Axis GCMS or Hewlet Packard 5971 MSD

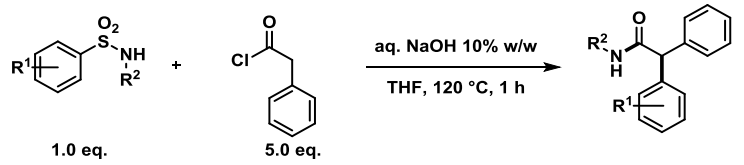
2. General procedures

General procedure A for the Smiles rearrangement with variation of the acyl chloride



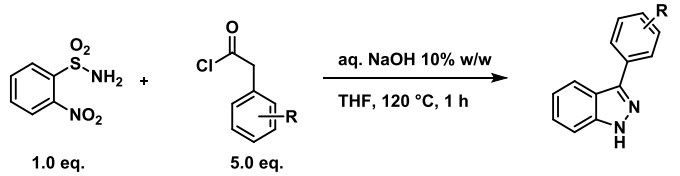
In a 5 mL microwave vial, 4-nitrobenzenesulfonamide (40 mg, 0.20 mmol, 1.0 eq.) was dissolved in THF (1.0 mL) and cooled to 0 ºC. Aqueous NaOH (1.0 mL, 10% w/w) was added slowly followed by dropwise addition of acyl chloride (1.0 mmol, 5.0 eq.). The vial was sealed and the reaction mixture was stirred at 120 ºC in a pre-warmed oil bath for one hour. H_2O (20 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

General procedure B for the Smiles rearrangement with variation of the sulfonamide



In a 5 mL microwave vial, sulfonamide (0.20 mmol, 1.0 eq.) was dissolved in THF (1.0 mL) and cooled to 0 ºC. Aqueous NaOH (1.0 mL, 10% w/w) was added slowly followed by dropwise addition of phenylacetyl chloride (132 µL, 1.0 mmol, 5.0 eq.). The vial was sealed and the reaction mixture was stirred at 120 ºC in a pre-warmed oil bath for one hour. H_2O (20 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

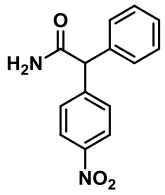
General procedure C for 1H-indazole synthesis



In a 5 mL microwave vial, 2-nitrobenzenesulfonamide (40 mg, 0.20 mmol, 1.0 eq.) was dissolved in THF (1.0 mL) and cooled to 0 ºC. Aqueous NaOH (1.0 mL, 10% w/w) was added slowly followed by dropwise addition of acyl chloride (1.0 mmol, 5.0 eq.). The vial was sealed and the reaction mixture was stirred at 120 ºC in a pre-warmed oil bath for one hour. H_2O (20 mL) and EtOAc (10 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by column chromatography.

3. Compound Data

2-(4-nitrophenyl)-2-phenylacetamide ***9a***

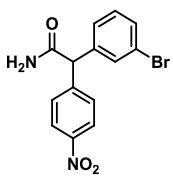


Prepared following General Procedure A using phenylacetyl chloride (132 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained as a white solid (45 mg, 0.17 mmol, 87% yield).

1.0 mmol scale procedure: In a 20 mL microwave vial, 4-nitrobenzenesulfonamide (202.2 mg, 1.0 mmol, 1.0 eq.) was dissolved in THF (5.0 mL) and cooled to 0 ºC. Aqueous NaOH (5.0 mL, 10% w/w) was added dropwise followed by slow addition of phenylacetyl chloride (661 µL, 5.0 mmol, 5.0 eq.). The vial was sealed and the reaction mixture was stirred at 120 ºC in a prewarmed oil bath for one hour. H_2O (50 mL) and EtOAc (30 mL) were added and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by column chromatography (eluent: 30 to 100% ethyl acetate in hexane) to give the title compound as a yellow solid (228.7 mg, 0.892 mmol, 89% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.08 (d, *J* = 8.8 Hz, 2 H), 7.39 (d, *J* = 8.8 Hz, 2 H), 7.32–7.22 (m, 3 H), 7.19 (d, *J* = 6.3 Hz, 2 H), 6.22 (br. s, 1 H), 5.66 (br. s, 1 H), 4.93 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 173.1, 147.2, 146.5, 137.9, 130.0, 129.4, 128.9, 128.3, 123.9, 58.3; HRMS (APCI) $C_{14}H_{12}O_3N_2K^+$ ($[M+K]^+$) requires 295.0480; found 295.0477; m.p. 92–94 ºC.

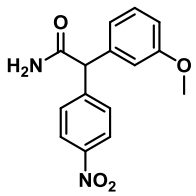
2-(3-bromophenyl)-2-(4-nitrophenyl)acetamide ***9b***



Prepared following General Procedure A using 2-(3-bromophenyl)acetyl chloride (151 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an orange solid (54.0 mg, 0.16 mmol, 81% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.21 (d, *J* = 8.4 Hz, 2 H), 7.51–7.42 (m, 4 H), 7.26 (m, 2 H), 5.81 (br. s, 1 H), 5.63 (br. s, 1 H), 4.96 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 172.0, 147.4, 145.7, 140.0, 131.9, 131.4, 130.9, 130.0, 127.5, 124.1, 123.4, 57.6; HRMS (APCI) $C_{14}H_{12}O_3N_2Br^+$ ($[M+H]^+$) requires 335.0026; found 335.0031; m.p. 102–104 ºC.

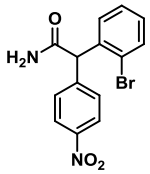
2-(3-methoxyphenyl)-2-(4-nitrophenyl)acetamide ***9c***



Prepared following General Procedure A using 2-(3-methoxyphenyl)acetyl chloride (156 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off white solid (49.0 mg, 0.17 mmol, 86% yield).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.17 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.8 Hz, 2 H), 7.29 (*app* t, *J* = 8.0 Hz, 1 H), 6.88–6.80 (m, 3 H), 6.07 (br. s, 1 H), 5.70 (br. s, 1 H), 4.98 (s, 1 H), 3.78 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 173.0, 160.3, 147.2, 146.4, 139.4, 130.5, 130.0, 123.9, 121.1, 115.0, 113.2, 58.2, 55.4; HRMS (APCI) $C_{15}H_{15}O_4N_2^+$ ($[M+H]^+$) requires 287.1026; found 287.1027; m.p. 85–87 ºC.

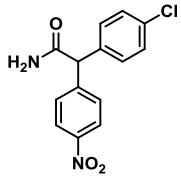
2-(2-bromophenyl)-2-(4-nitrophenyl)acetamide ***9d***



Prepared following General Procedure A using 2-(2-bromophenyl)acetyl chloride (149 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an orange solid (47.1 mg, 0.14 mmol, 70% yield), containing a minor inseparable co-running impurity.

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.18 (d, *J* = 8.7 Hz, 2 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.47 (d, *J* = 8.7 Hz, 2 H), 7.37–7.30 (m, 2 H), 7.20 (ddd, *J* = 8.0, 6.1, 3.0 Hz, 1 H), 6.26 (br. s, 1 H), 5.77 (br. s, 1H), 5.49 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 172.4, 147.3, 145.3, 137.4, 133.6, 130.3, 130.2, 129.8, 128.3, 125.3, 123.9, 57.0; HRMS (APCI) $C_{14}H_{12}O_3N_2Br^+$ ($[M+H]^+$) requires 335.0026; found 335.0031; m.p. 92–94 ºC.

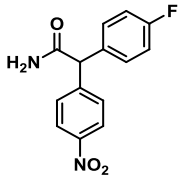
2-(4-chlorophenyl)-2-(4-nitrophenyl)acetamide ***9e***



Prepared following General Procedure A using 2-(4-chlorophenyl)acetyl chloride (146 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off white solid (52.0 mg, 0.18 mmol, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.20 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.24 (d, *J* = 8.1 Hz, 2 H), 5.76 (br. s, 1 H), 5.60 (br. s, 1 H), 4.98 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 172.3, 147.4, 146.0, 136.4, 134.4, 130.2, 129.9 , 129.6, 124.1, 57.5; HRMS (APCI) $C_{14}H_{11}O_3N_2ClK^+$ ($[M+H]^+$) requires 329.0090; found 329.0089; m.p. 124–125 ºC.

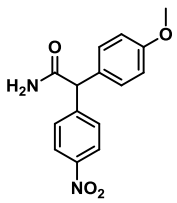
2-(4-fluorophenyl)-2-(4-nitrophenyl)acetamide ***9f***



Prepared following General Procedure A using 2-(4-fluorophenyl)acetyl chloride (137 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as a colourless oil (46.0 mg, 0.17 mmol, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.19 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.26 (*app* t, *J* = 6.8 Hz, 2 H), 7.07 (*app* t, *J* = 8.4 Hz, 2 H), 6.12 (br. s, 1 H), 5.65 (br. s, 1 H), 4.99 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 172.9, 162.4 (d, *J* = 248.4 Hz), 147.2, 146.1, 133.5 (d, *J* = 3.5 Hz), 130.4 (d, *J* = 8.1 Hz), 129.8, 123.9, 116.2 (d, *J* = 21.6 Hz), 57.2; ^{19}F NMR (376 MHz, $CDCl_3$, ppm): δ −113; HRMS (APCI) $C_{14}H_{12}O_3N_2F^+$ ($[M+H]^+$) requires 275.0826; found 275.0825.

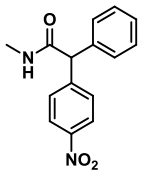
2-(4-methoxyphenyl)-2-(4-nitrophenyl)acetamide ***9g***



Prepared following General Procedure A using 2-(4-methoxyphenyl)acetyl chloride (153 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off white solid (47.0 mg, 0.16 mmol, 82% yield).

^{1}H NMR (500 MHz, $(CD_3)_2CO$, ppm): δ 8.17 (d, *J* = 8.4 Hz, 2 H), 7.64 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.6 Hz, 2 H), 7.20 (br. s, 1 H), 6.90 (d, *J* = 8.6 Hz, 2 H), 6.58 (br. s, 1 H), 5.16 (s, 1H), 3.77 (s, 3 H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$, ppm): δ 173.3, 159.9, 149.6, 147.7, 132.3, 130.8, 130.6, 124.0, 114.8, 56.9, 55.5; HRMS (APCI) $C_{15}H_{14}O_4N_2K^+$ ($[M+K]^+$) requires 325.0585; found 325.0581; m.p. 125–127 ºC.

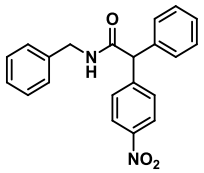
N-methyl-2-(4-nitrophenyl)-2-phenylacetamide ***9h***



Prepared following General Procedure B using *N*-methyl-4-nitrobenzenesulfonamide (43 mg, 0.20 mmol, 1.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off white solid (45 mg, 0.17 mmol, 83% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.17 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 7.39–7.29 (m, 3 H), 7.26–7.22 (m, 2 H), 5.70 (s, 1H), 4.96 (s, 1 H), 2.85 (d, *J* = 4.8 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 171.2, 147.1, 147.0, 138.2, 130.0, 129.4, 128.9 , 128.1 , 123.9, 58.8, 27.0; HRMS (APCI) $C_{15}H_{15}O_3N_2^+$ ($[M+H]^+$) requires 271.1077; found 271.1078; m.p. 85–87 ºC.

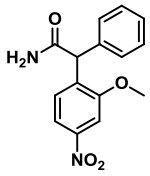
N-benzyl-2-(4-nitrophenyl)-2-phenylacetamide ***9i***



Prepared following General Procedure B using *N*-benzyl-4-nitrobenzenesulfonamide (58 mg, 0.20 mmol, 1.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off white solid (65 mg, 0.18 mmol, 91% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.15 (d, *J* = 8.8 Hz, 2 H), 7.45 (d, *J* = 8.8 Hz, 2 H), 7.38–7.24 (m, 8 H), 7.21–7.18 (m, 2 H), 6.00 (t, *J* = 5.8 Hz, 1 H), 4.97 (s, 1 H), 4.45 (d, *J* = 5.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 170.5, 147.1, 146.9, 138.1, 137.8, 130.0, 129.3, 128.9, 128.8, 128.1, 127.8, 127.8, 123.8, 58.6, 44.1; HRMS (APCI) $C_{21}H_{19}O_3N_2^+$ ($[M+H]^+$) requires 347.1390; found 347.1400; m.p. 85–87 ºC.

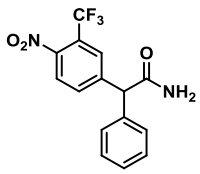
2-(2-methoxy-4-nitrophenyl)-2-phenylacetamide ***9j***



Prepared following General Procedure B using 2-methoxy-4-nitrobenzenesulfonamide (46 mg, 0.20 mmol, 1.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off white solid (42 mg, 0.15 mmol, 74% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 7.80 (dd, *J* = 8.5, 2.1 Hz, 1 H), 7.73 (d, *J* = 2.1 Hz, 1 H), 7.41–7.35 (m, 2 H), 7.36–7.30 (m, 3 H), 7.28 (d, *J* = 8.5 Hz, 1 H), 5.64 (br. s, 1 H), 5.57 (br. s, 1 H,), 5.28 (s, 1 H), 3.94 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 173.4, 157.4, 148.3, 137.3, 135.6, 130.2, 129.3, 129.1, 128.1, 116.1 , 105.7, 56.4, 52.2; HRMS (APCI) $C_{15}H_{14}O_4N_2Na^+$ ([M+Na]$^+$) requires 309.0846; found 309.0843; m.p. 85–87 ºC.

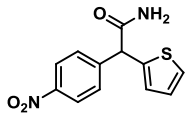
2-(4-nitro-3-(trifluoromethyl)phenyl)-2-phenylacetamide ***9k***



Prepared following General Procedure B using 4-nitro-3-(trifluoromethyl)benzene-sulfonamide (54.0 mg, 0.20 mmol, 1.0 eq.). The title compound was obtained (Elution: 20-100% EtOAc in hexane) as an off white solid (56.3 mg, 0.17 mmol, 87% yield).

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.07-8.00 (m, 2 H), 7.94 (dd, *J* = 8.4, 1.7 Hz, 1 H), 7.48-7.43 (m, 2 H), 7.40-7.34 (m, 2 H), 7.34-7.28 (m, 2 H), 6.71 (br. s, 1 H), 5.34 (s, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 172.6, 147.5, 139.9, 135.2, 129.7, 129.5, 129.2 (q, *J* = 5.2 Hz), 128.3, 126.2, 123.3 (q, *J* = 273.2 Hz), 123.0 (q, *J* = 33.6 Hz), 57.2, aromatic carbon next to NO_2 not observed; ^{19}F NMR (376 MHz, $(CD_3)_2CO$, ppm): δ −60.5; HRMS (ESI) $C_{15}H_{10}O_3N_2F_3^-$ ([M−H]$^-$) requires 323.0649; found 323.0649; m.p.120-122 °C.

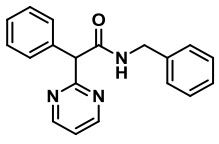
2-4-nitrophenyl)-2-(thiophen-2-yl)acetamide ***9l***



Prepared following General Procedure A using 2-thiophenyl acetyl chloride (123 µL, 1 mmol, 5 eq.). The title compound was obtained (Elution: 0-80% EtOAc in hexane) as a brown solid (35.1 mg, 0.134 mmol, 67% yield).

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 8.20 (dt, *J* = 8.9, 1.9 Hz, 2 H), 7.73 (dt, *J* = 8.8, 2 Hz, 2 H), 7.38 (dd, *J* = 5.3, 1.0 Hz, 2 H), 7.09 (dt, *J* = 3.5, 1.0 Hz, 1 H), 6.98 (dd, *J* = 5.2, 3.5 Hz, 1 H), 6.72 (br. s 1 H), 5.50 (s, 1 H) ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 172.3, 148.8, 148.0, 142.2, 130.3, 127.3, 127.2, 126.5, 124.2, 52.95, 52.91 V_{max} (neat) /cm^{-1}: 3367, 3194, 1670 (C=O), 1605, 1516, 1390, 1344, 701; HRMS (ESI): $C_{12}H_9O_3N_2S^-$ ([M-H]$^-$) requires 261.0339; found 261.0343; m.p. 138-140°C.

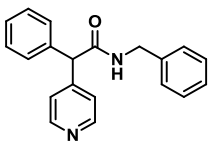
N-benzyl-2-phenyl-2-(pyrimidin-2-yl)acetamide ***9m***



Prepared following General Procedure B using *N*-benzylpyrimidine-2-sulfonamide (49.9 mg, 0.20 mmol, 1.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as a sticky yellow solid (43.6 mg, 0.14 mmol, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.73 (d, *J* = 4.9 Hz, 2 H), 7.83 (br. s, 1 H), 7.47 (d, *J* = 7.2 Hz, 2 H), 7.35-7.23 (m, 8 H), 7.21 (t, *J* = 4.9 Hz, 1 H), 5.34 (s, 1 H), 4.60-4.47 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 169.8, 168.3, 157.4, 138.4, 137.8, 129.0, 128.7, 128.7, 127.8, 127.6, 127.4, 119.5, 62.6, 43.8; HRMS (APCI) $C_{19}H_{18}ON_3^+$ ($[M+H]^+$) requires 304.1444; found 304.1446; m.p. 83-87 °C.

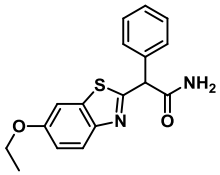
N-benzyl-2-phenyl-2-(pyridin-4-yl)acetamide ***9n***



Prepared following General Procedure B using *N*-benzylpyridine-4-sulfonamide (49.7 mg, 0.20 mmol, 1.0 eq.). The title compound was obtained (Elution: 20-100% EtOAc in hexane) as a white solid (25.5 mg, 0.084 mmol, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 8.53 (d, *J* = 5.4 Hz, 2 H), 7.38-7.25 (m, 8 H), 7.24-7.18 (m, 4 H), 6.04 (br. s, 1 H), 4.87 (s, 1 H), 4.48 (d, *J* = 5.8 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 170.4, 150.2, 148.3, 137.9, 137.8, 129.3, 128.9, 128.9, 128.1, 127.8, 124.2, 58.5, 44.1; HRMS (APCI) $C_{20}H_{19}ON_2^+$ ($[M+H]^+$) requires 303.1492; found 303.1488; m.p. 128-130 °C.

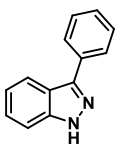
2-(6-ethoxybenzo[d]thiazol-2-yl)-2-phenylacetamide ***9o***



Prepared following General Procedure B using 6-ethoxybenzo[*d*]thiazole-2-sulfonamide (51.7 mg, 0.20 mmol, 1.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off-white solid (39.5 mg, 0.13 mmol, 63% yield).

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 7.80 (d, *J* = 8.9 Hz, 1 H), 7.61-7.55 (m, 2 H), 7.52 (br. s, 1 H), 7.50 (d, *J* = 2.5 Hz, 2 H), 7.39-7.33 (m, 2 H), 7.33-7.27 (m, 1 H), 7.05 (dd, *J* = 8.9, 2.5 Hz, 1 H), 6.71 (br. s, 1 H), 5.47 (s, 1 H), 4.10 (q, *J* = 7.0 Hz, 2 H), 1.38 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 171.8, 167.7, 157.9, 150.0, 139.3, 138.1, 129.4, 129.4, 128.5, 124.0, 116.5, 105.5, 64.6, 57.2, 15.1; HRMS (APCI) $C_{17}H_{17}O_2N_2S^+$ ($[M+H]^+$) requires 313.1005; found 313.1010; m.p. 131-134°C.

3-phenyl-1H-indazole ***12a***

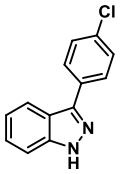


Prepared following General Procedure C using and phenylacetyl chloride (130 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as a colourless solid (21 mg, 0.11 mmol, 54% yield).

^{1}H NMR (500 MHz, $(CD_3)_2CO$, ppm): δ 12.38 (br. s, 1 H), 8.11 (d, *J* = 8.6 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 2H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.53 (t, *J* = 7.56 Hz, 2H), 7.41 (q, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $(CD_3)_2CO$, ppm): δ 145.0, 143.0, 135.2, 129.6, 128.5, 128.0, 127.0, 121.9, 121.60, 121.58, 111.3; LRMS (EI): 194 ($[M+H]^+$).

Spectral data is in accordance with that previously reported in the literature.[1]

3-(4-chlorophenyl)-1H-indazole ***12b***

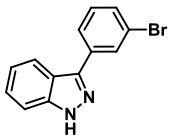


Prepared following General Procedure C using and 4-chlorophenylacetyl chloride (146 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off-white solid (23.7 mg, 0.11 mmol, 52% yield).

^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 10.55 (br. s, 1 H), 8.00 (d, *J* = 8.2 Hz, 1 H), 7.93 (d, *J* = 8.4 Hz, 2 H), 7.53-7.40 (m, 4 H), 7.29-7.22 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 144.8, 141.7, 134.2, 132.1, 129.2, 128.9, 127.2, 121.8, 121.0, 120.9, 110.2; MS (ESI): 227 $[(M-H)]^-$; m.p. 124-126 °C.

Spectral data is in accordance with that previously reported in the literature.1

3-(3-bromophenyl)-1H-indazole ***12c***

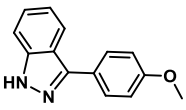


Prepared following General Procedure C using and 3-bromophenylacetyl chloride (151 µL, 1.0 mmol, 5.0 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as an off-white solid (36.1 mg, 0.13 mmol, 66% yield).

^{1}H NMR (500 MHz, $CDCl_3$, ppm): δ 10.40 (br. s, 1H), 8.16 (s, 1 H), 8.02 (d, *J* = 7.9 Hz, 1 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 7.55 (d, *J* = 7.9 Hz, 1 H), 7.51 (d, *J* = 8.3 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 1 H), 7.39 (t, *J* = 7.8 Hz, 1 H), 7.23-7.16 (m, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm): δ 144.5, 141.8, 135.7, 131.2, 130.6, 130.5, 127.2, 126.2, 123.1, 122.0, 121.0, 121.0, 110.2; HRMS (ESI) $C_{13}H_8N_2Br^-$ ($[M-H]^-$) requires 270.9876; found 270.9873; m.p. 109-110 °C.

Spectral data is in accordance with that previously reported in the literature.[2]

3-(4-methoxyphenyl)-1H-indazole ***12d***



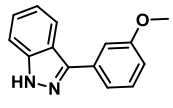
Prepared following General Procedure C using 4-methoxyphenyl acetyl chloride (152 µL, 1mmol, 5 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as a yellow oil (23.9 mg, 0.106 mmol, 53% yield)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 12.26 (br. s, 1 H), 8.08 (dt, *J* = 8.2, 0.8 Hz, 1 H), 8.00 (dt, *J* = 8.9, 2.1 Hz, 2 H), 7.61 (dt, *J* = 9.4, 0.8 Hz, 1 H), 7.40 (ddd, *J* = 8.4, 6.9, 1.0 Hz, 1 H), 7.21 (ddd, *J* = 8.1, 6.9 0.9 Hz, 1 H), 7.09 (dt, *J* = 8.9, 6.7 Hz, 2 H), 3.86 (s, 3 H) ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 160.4, 144.9, 142.9, 129.2, 127.8, 126.9, 121.64, 121.62, 121.5, 115.0, 111.2, 55.6; LRMS (ESI): 225 ($[M+H]^+$), 247 ($[M+Na]^+$), 263 ($[M+K]^+$), 487 ($[2M+K]^+$).

Spectral data is in accordance with that previously reported in the literature.1

[1] Yu, D.-G.; Suri, M.; Glorius, F. *J. Am. Chem. Soc.* **2013**, *135*, 8802-8805.
[2] Shamsabadi, A.; Chudasama, V. *Chem. Commun.* **2018**, *54*, 11180-11183.

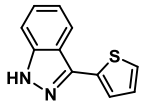
Preparation of 3-(3-methoxyphenyl)-1H-Indazole ***12e***



Prepared following General Procedure C using 3-methoxyphenyl acetyl chloride (155 µL, 1mmol, 5 eq.). The title compound was obtained (Elution: 0-100% EtOAc in hexane) as a yellow oil (27.3 mg, 0.122 mmol, 61% yield)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 12.40 (br. s, 1 H), 8.10 (dt, *J* = 8.3, 0.9 Hz, 1 H), 7.66-7.59 (m, 3 H), 7.46-7.39 (m, 2 H), 7.24 (ddd, *J* = 8.9, 6.9 0.9 Hz, 1 H), 6.98 (dd, *J* = 8.3, 2.6 Hz, 1 H), 3.89 (s, 3 H) ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 161.0, 144.9, 143.0, 136.5, 130.6, 127.0, 122.0, 121.6, 120.3, 114.3, 113.1, 111.3, 55.5; LRMS (ESI): 225 ($[M+H]^+$), 247 ($[M+Na]^+$) 263 ($[M+K]^+$).
Spectral data is in accordance with that previously reported in the literature.[3]

3-(thiophen-2-yl)-1H-Indazole ***12f***

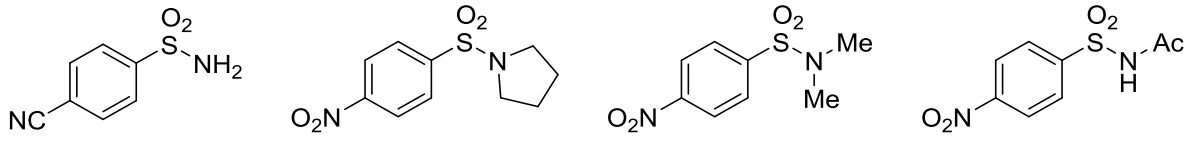


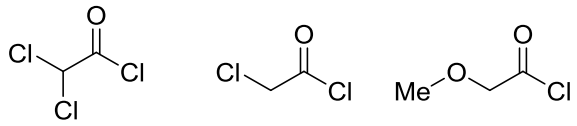
Prepared following General Procedure C using 2-thiophenyl acetyl chloride (74 µL, 0.6 mmol, 3 eq.). The title compound was obtained (Elution: 10-80% EtOAc in hexane) as a yellow micro crystalline solid (34.3 mg, 0.171 mmol, 71% yield)

^{1}H NMR (400 MHz, $(CD_3)_2CO$, ppm): δ 12.32 (br. s, 1 H), 8.14-8.10 (m, 1 H), 7.75 (dd, *J* = 3.6, 1Hz, 1 H), 7.64-7.60 (m, 1 H), 7.49 (dd, *J* = 5.1, 1 Hz, 1 H) 7.45 – 7.40 (m, 1 H) 7.28 – 7.23 (m, 1 H), 7.20 (dd, *J* = 5.1, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $(CD_3)_2CO$, ppm): δ 142.8, 140.5, 137.6, 128.5, 127.4, 125.6, 125.1, 122.1, 121.3, 121.0, 111.33; LRMS (ESI): 199 ($[M-H]^-$); m.p. 139-141°C.
Spectral data is in accordance with that previously reported in the literature.[4]

4. Unsuccessful Substrates

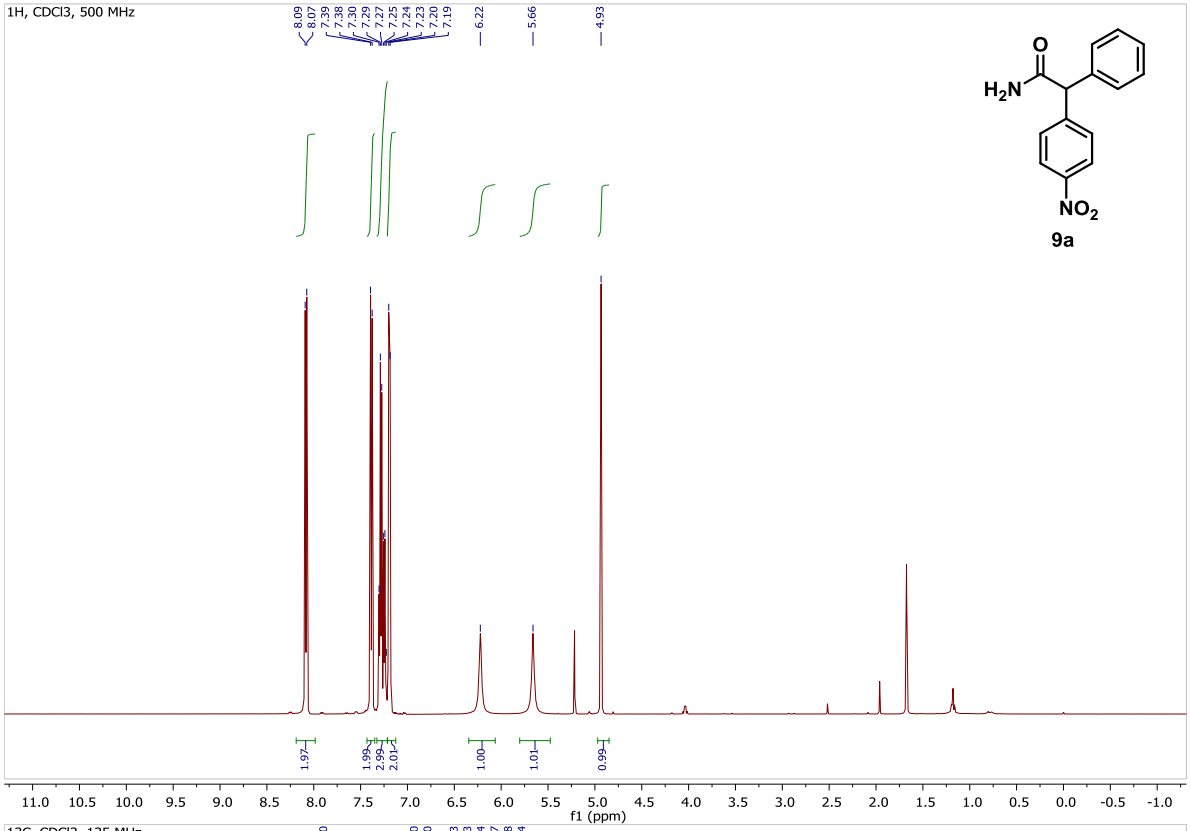
The following sulfonamides and acyl chlorides were unsuccessful in the reaction under the standard conditions.

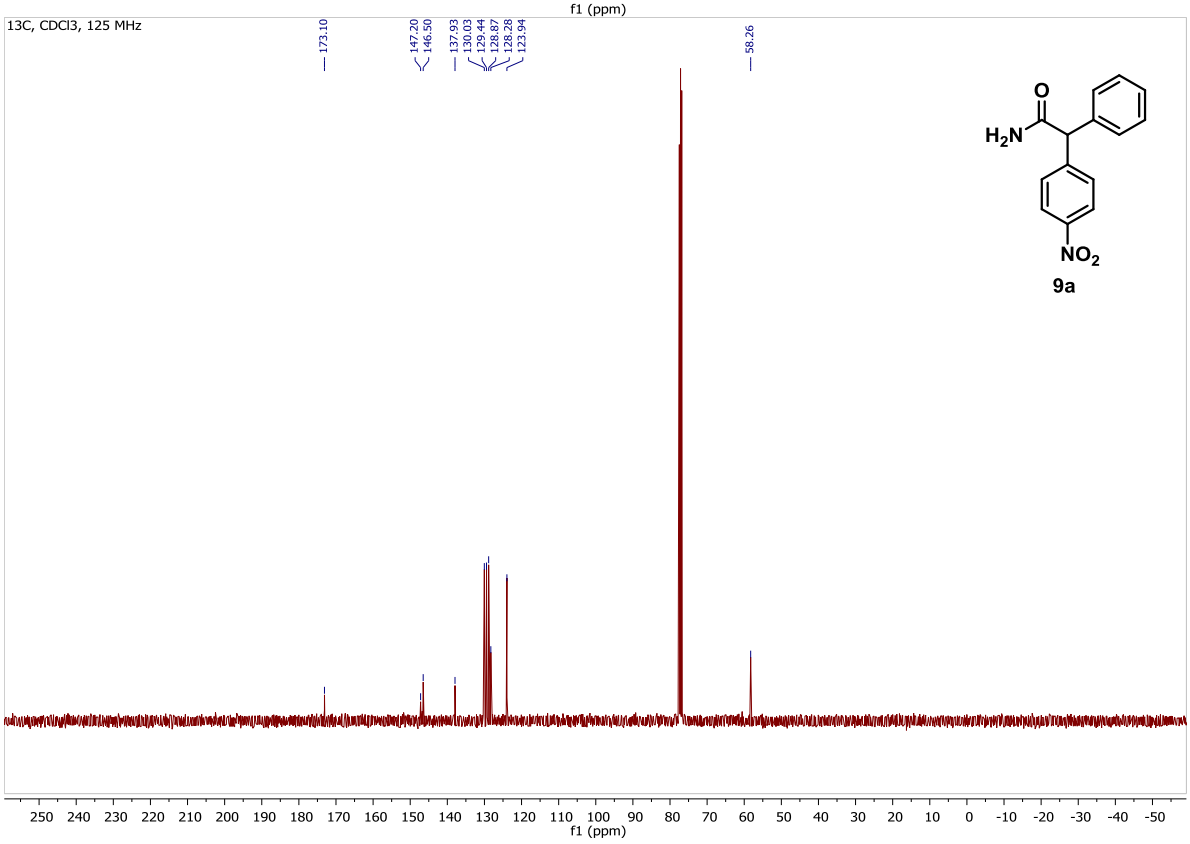


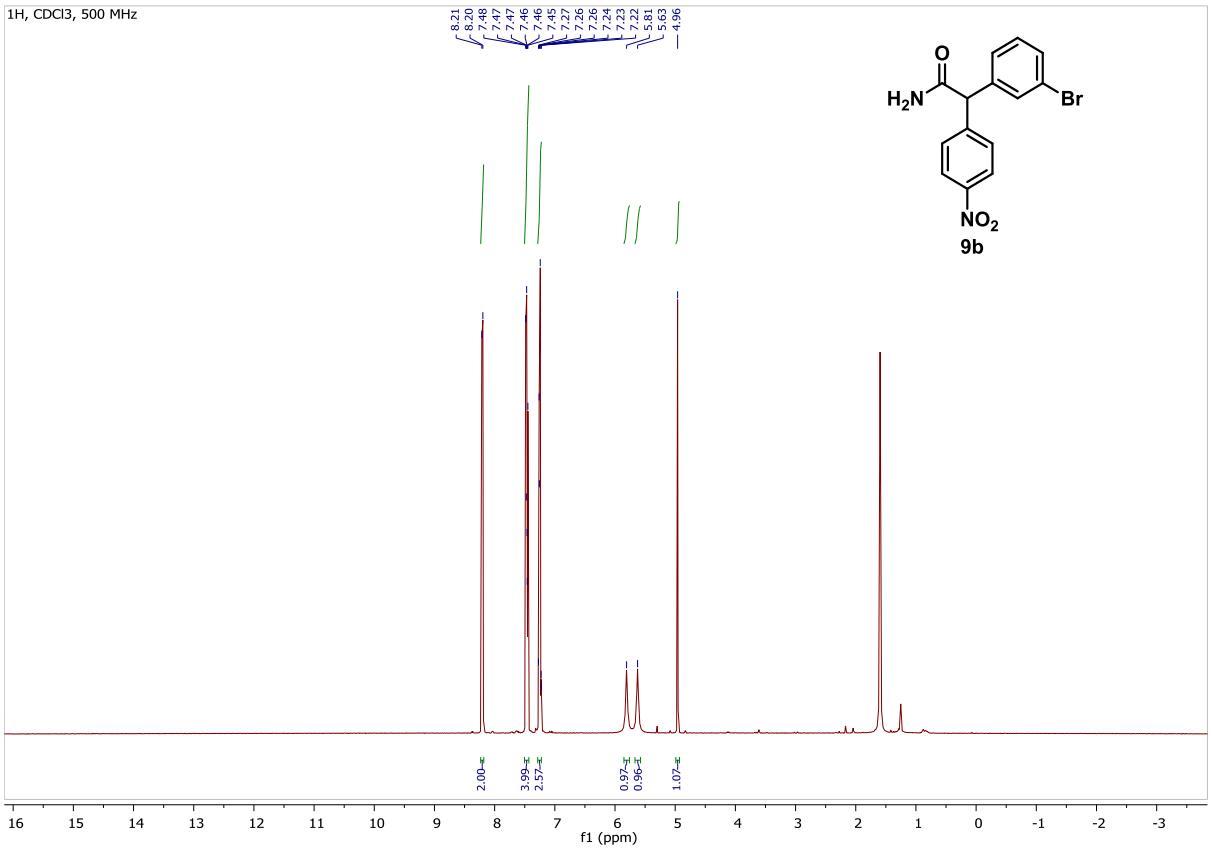


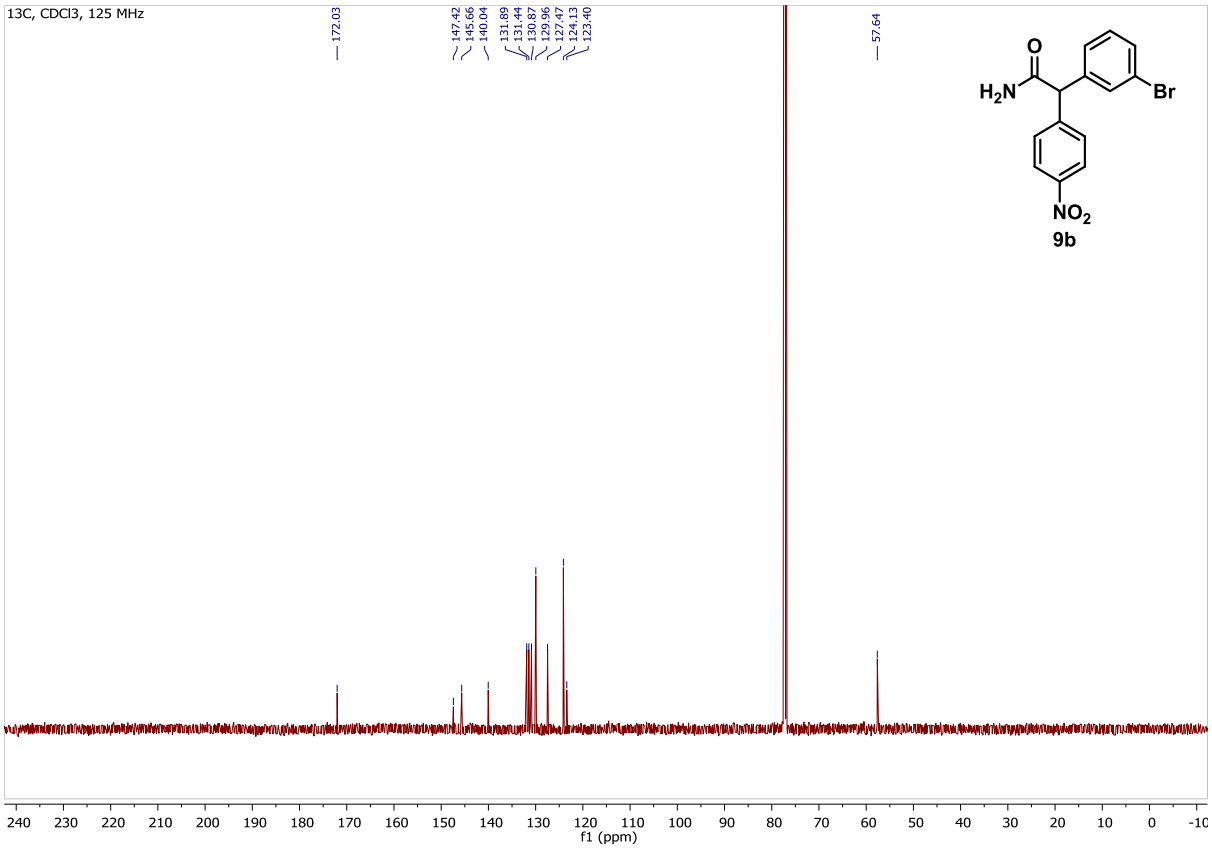
[3] Youngaye, W.; Hartland, C. L.; Morgan, B. J.; Ting, A.; Nag, P. P.; Vincent, B.; Mosher, C. A.; Bittker, J. A.; Dandpani, S.; Palmer, M.; Whitesell, L.; Lindquist, S.; Schreiber, S. L.; Munoz, B. *Beilstein J. Org. Chem.* **2013**, *9*, 1501-1507.
[4] Li, L.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340-3343.

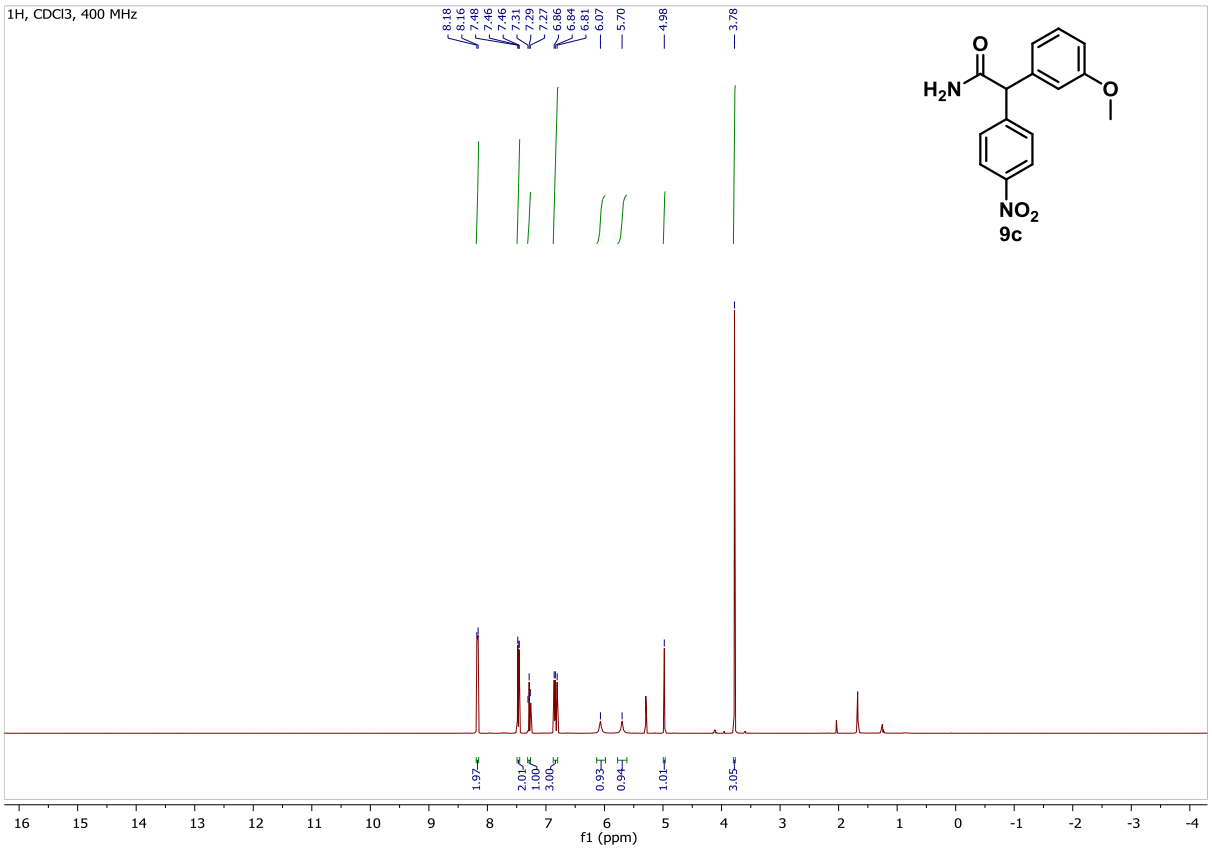
5. NMR Spectra

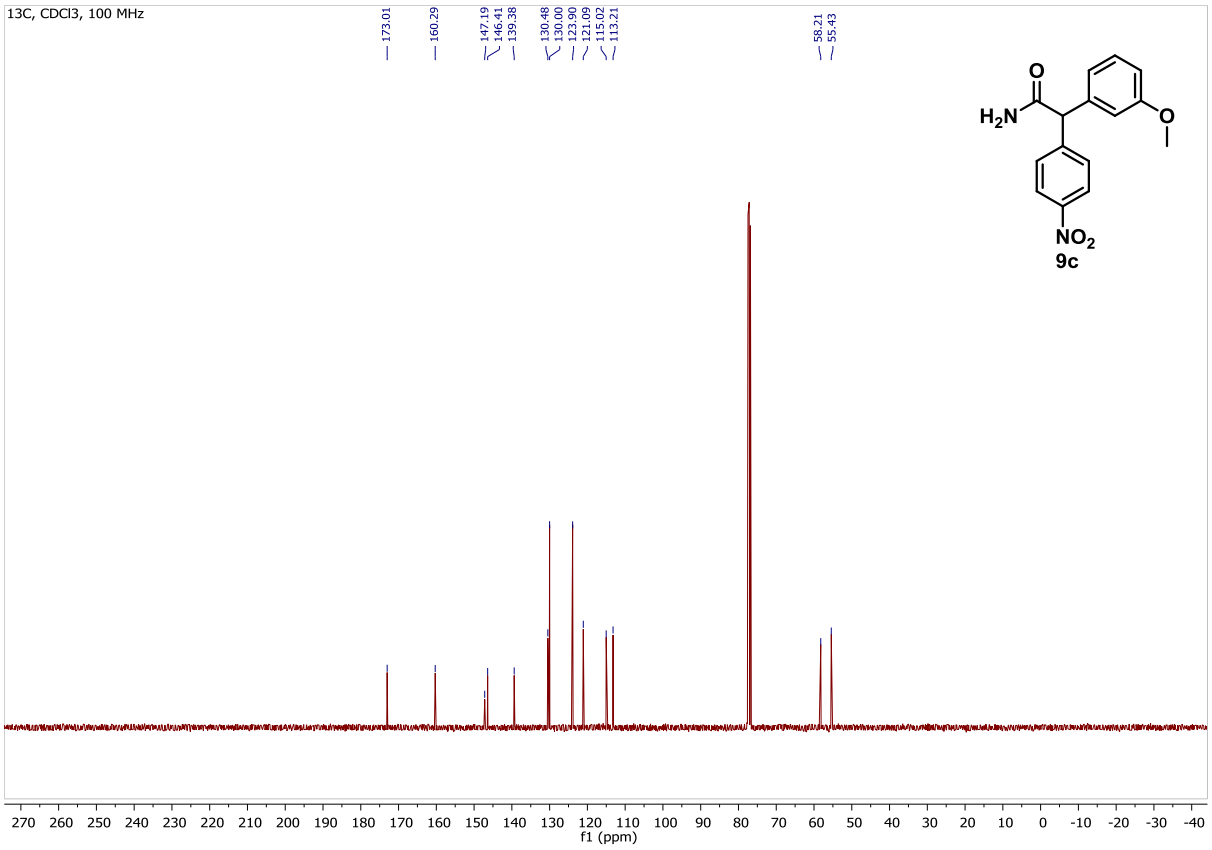


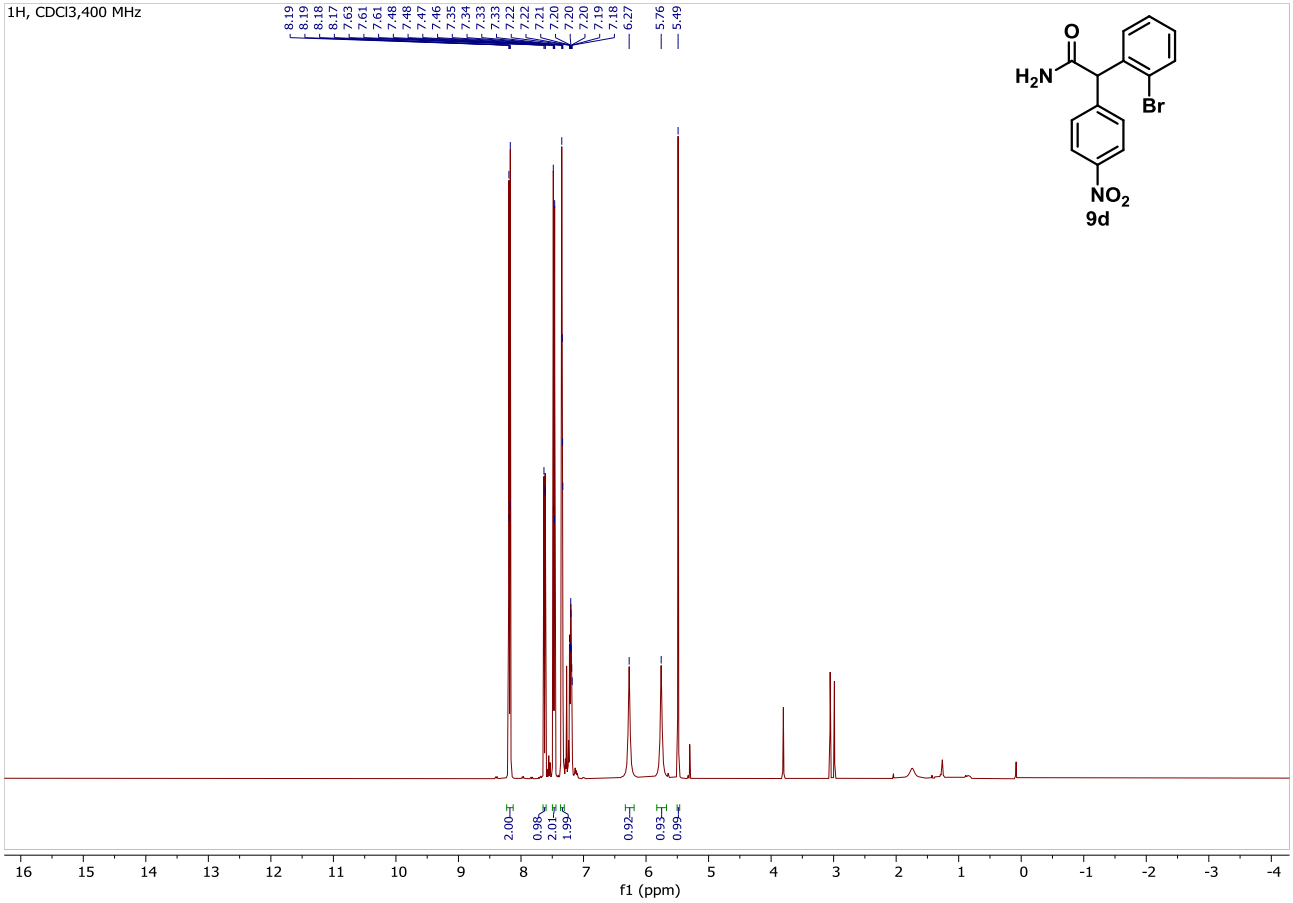


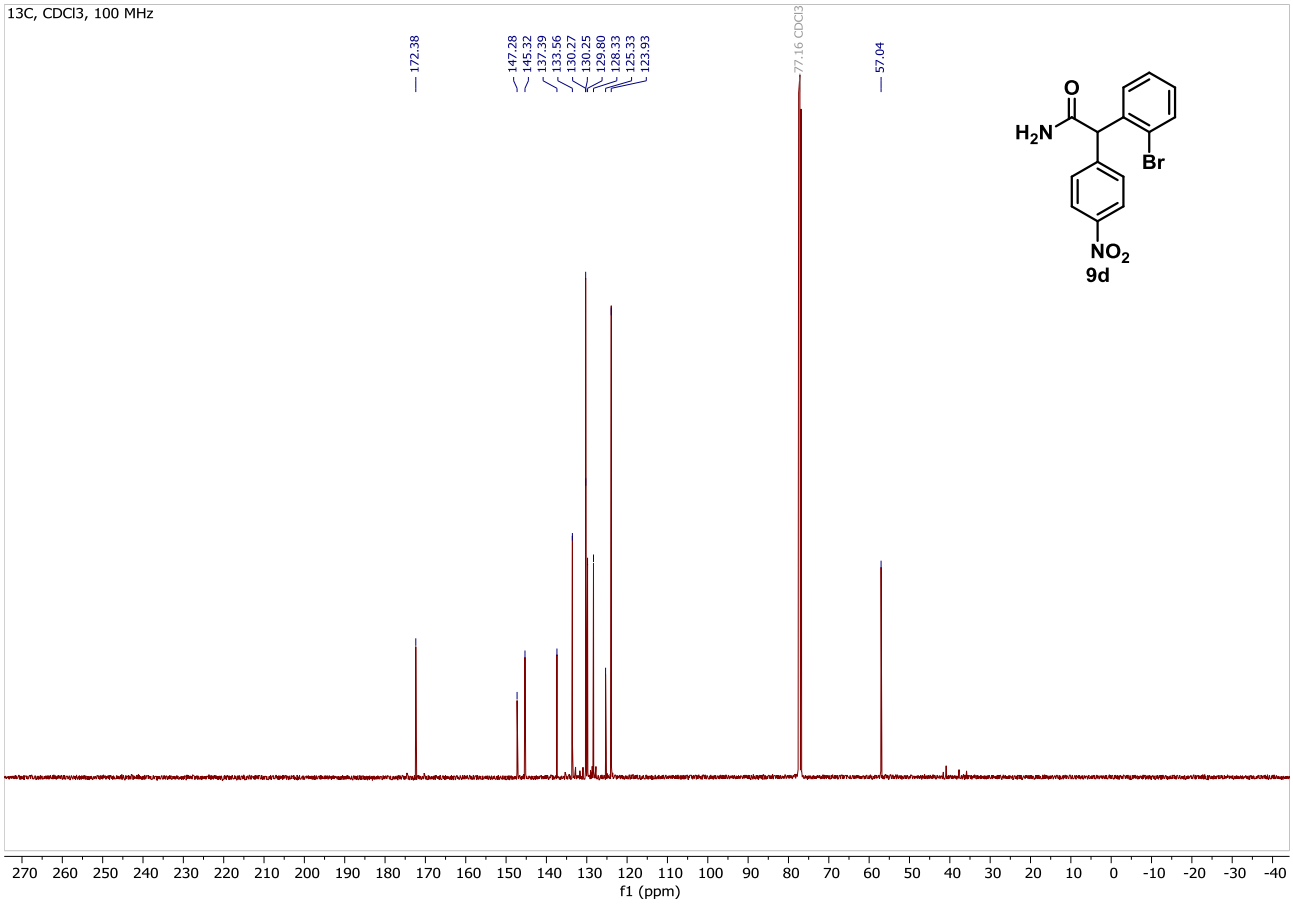

1H, CDCl3, 500 MHz
8.21
8.20
8.48
7.47
7.47
7.46
7.46
7.45
7.27
7.26
7.26
7.24
7.23
7.22
5.81
5.63
4.96
O
H2N
Br
NO2
9b
2.00
3.99
2.57
0.97
0.96
1.07
f1 (ppm)

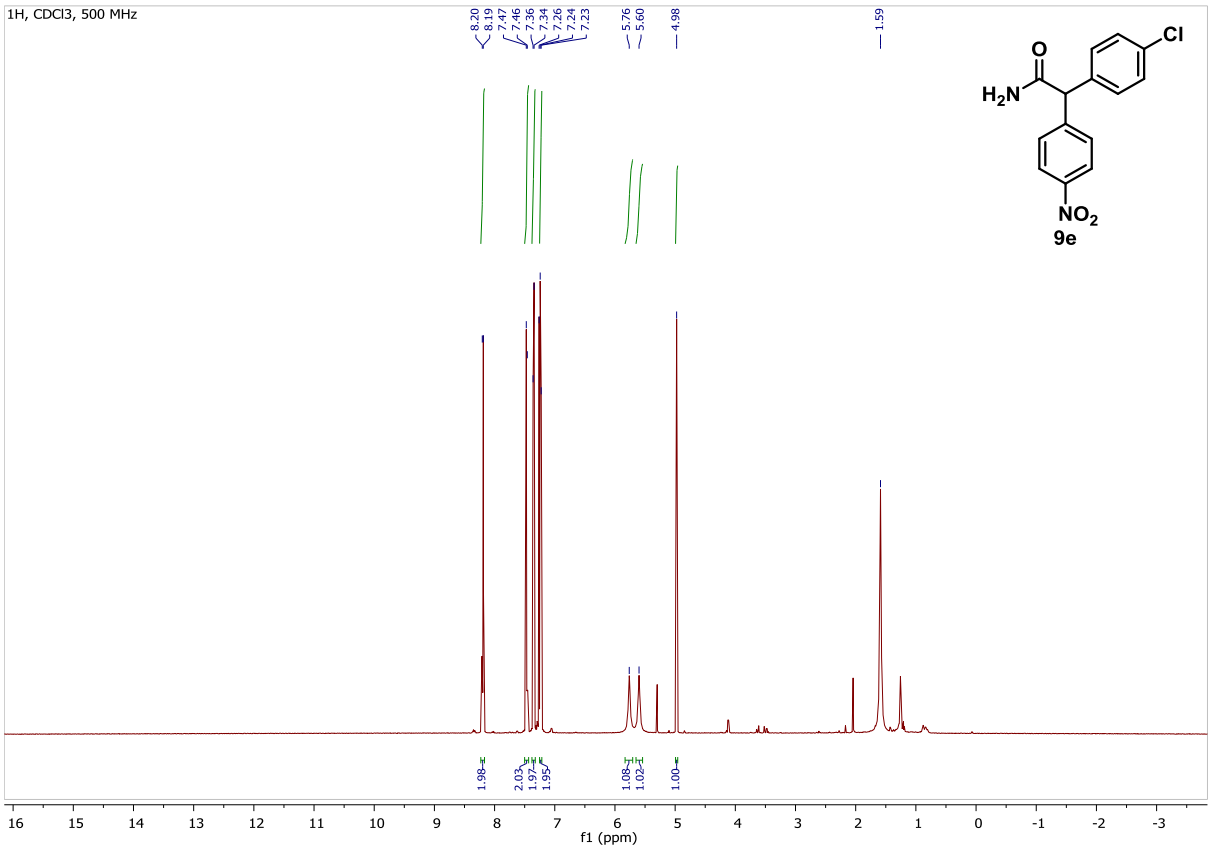

13C, CDCl3, 125 MHz
172.03
147.42
145.66
140.04
131.89
131.44
130.87
129.96
127.47
124.13
123.40
57.64
O
H2N
Br
NO2
9b
f1 (ppm)

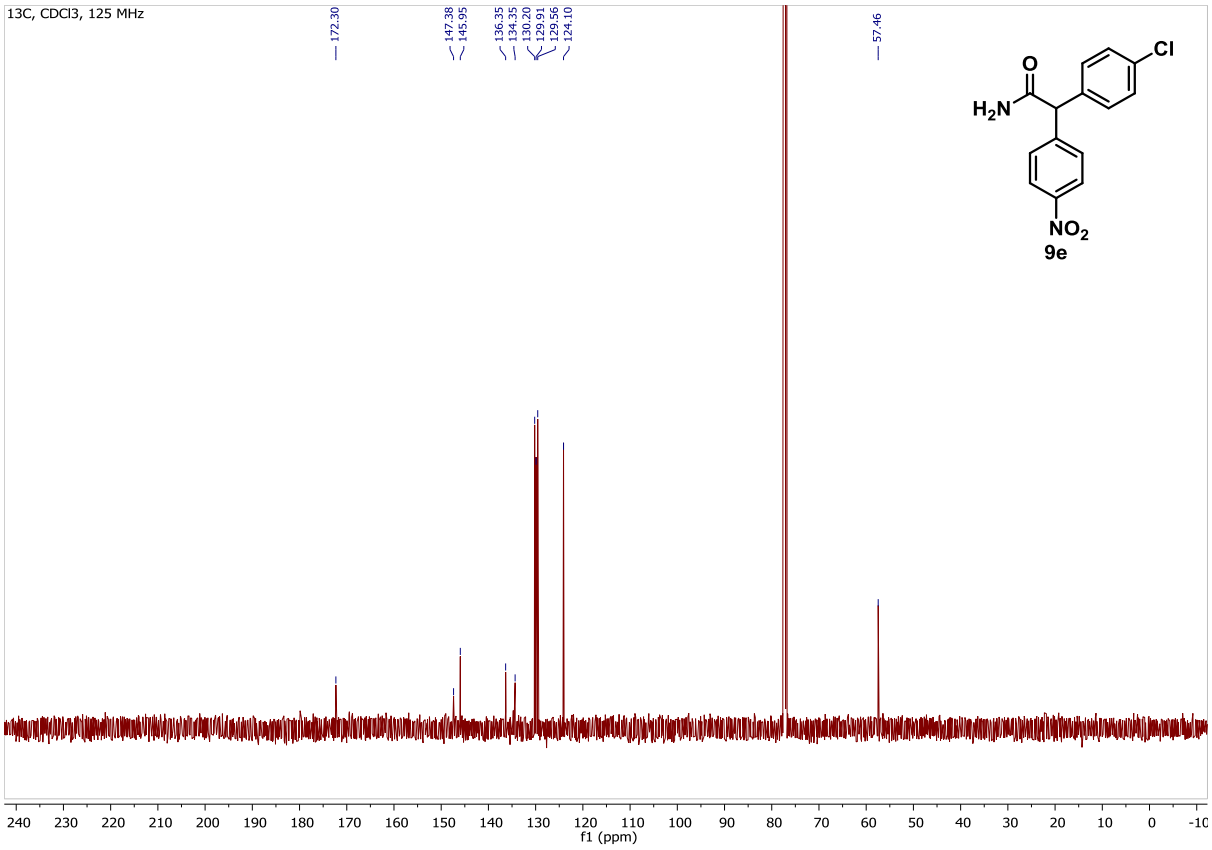

1H, CDCl3, 400 MHz
8.18
8.16
7.48
7.46
7.46
7.31
7.29
7.27
6.86
6.84
6.81
6.07
5.70
4.98
3.78
1.97
2.01
1.00
3.00
0.93
0.94
1.01
3.05
f1 (ppm)
O
H2N
O
NO2
9c

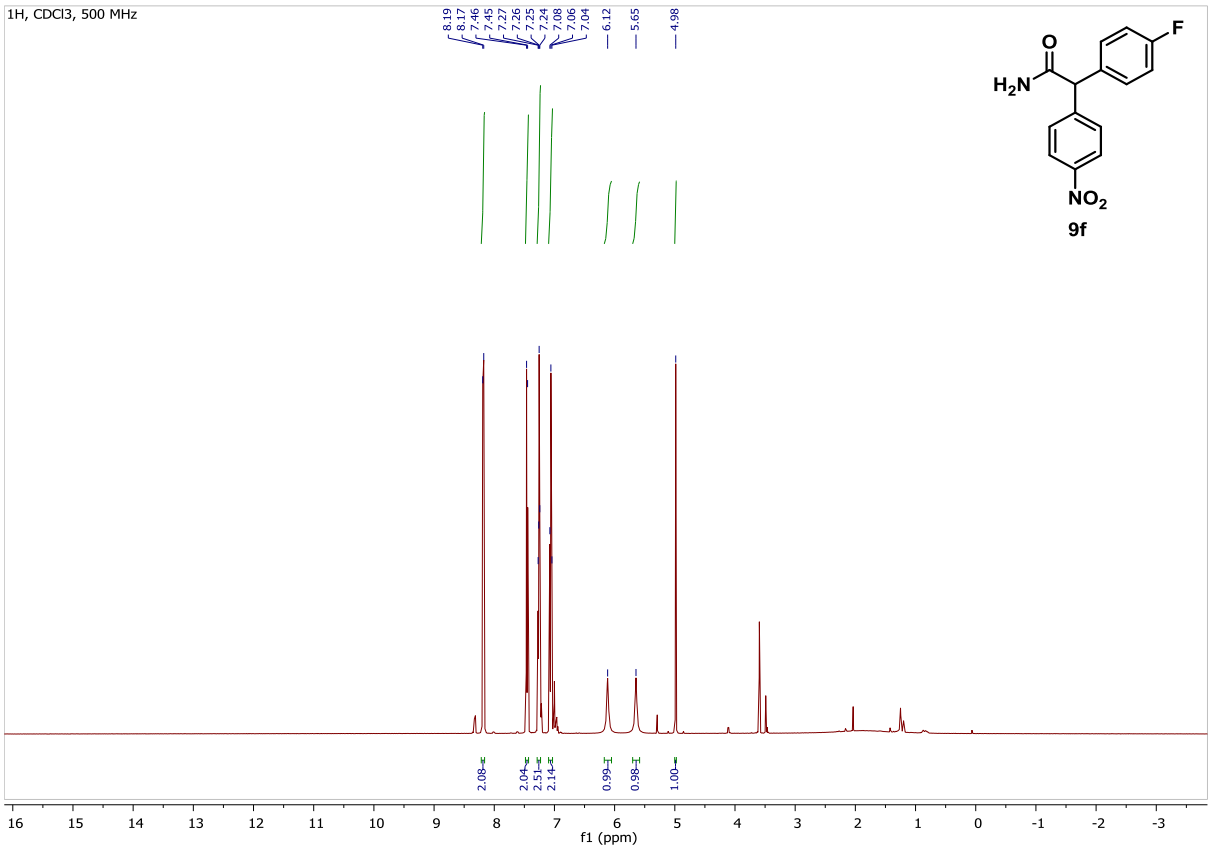

13C, CDCl3, 100 MHz
173.01
160.29
147.19
146.41
139.38
130.48
130.00
123.90
121.09
115.02
113.21
58.21
55.43
f1 (ppm)
O
H2N
O
NO2
9c

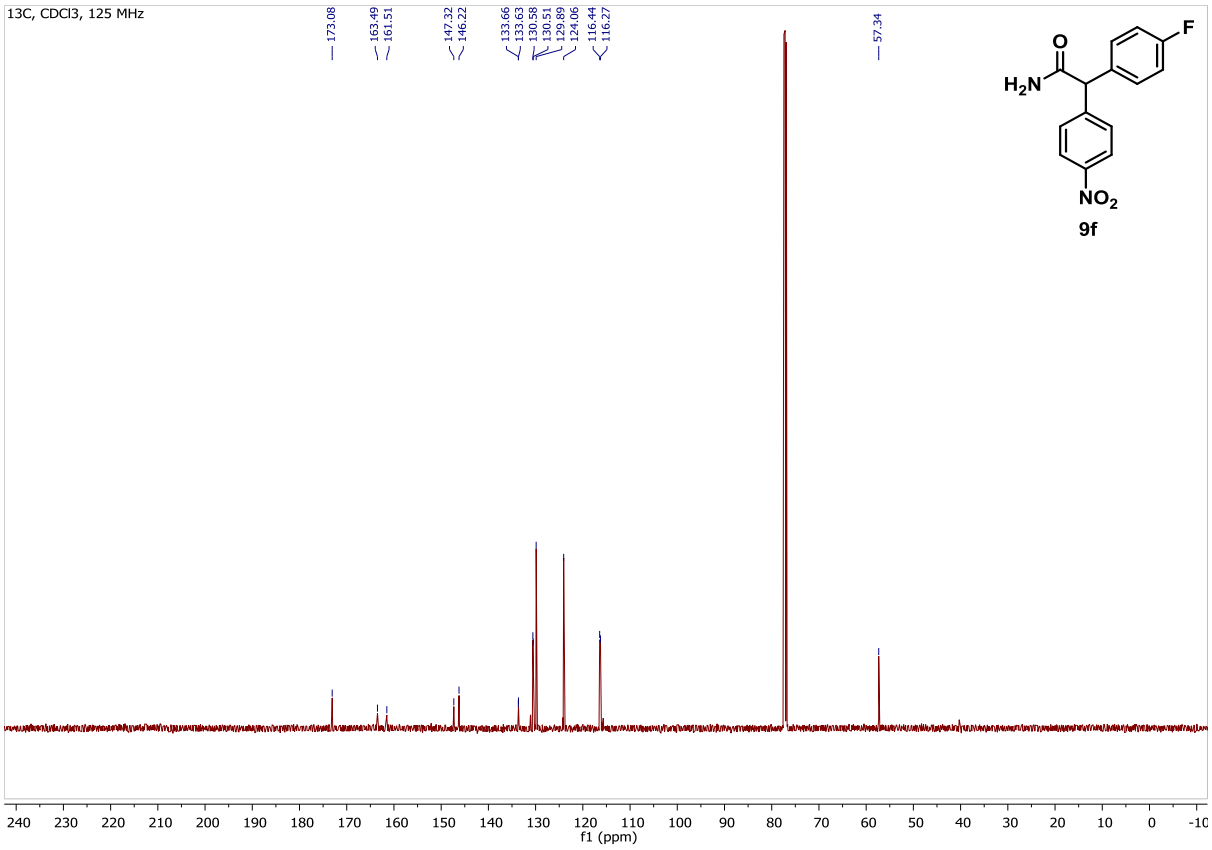

1H, CDCl3,400 MHz
8.19
8.19
8.18
8.17
7.63
7.61
7.61
7.48
7.48
7.47
7.46
7.35
7.34
7.33
7.33
7.22
7.22
7.21
7.20
7.20
7.20
7.19
7.18
6.27
5.76
5.49
O
H2N
Br
NO2
9d
2.00
0.98
2.01
1.99
0.92
0.93
0.99
16 15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3 -4
f1 (ppm)

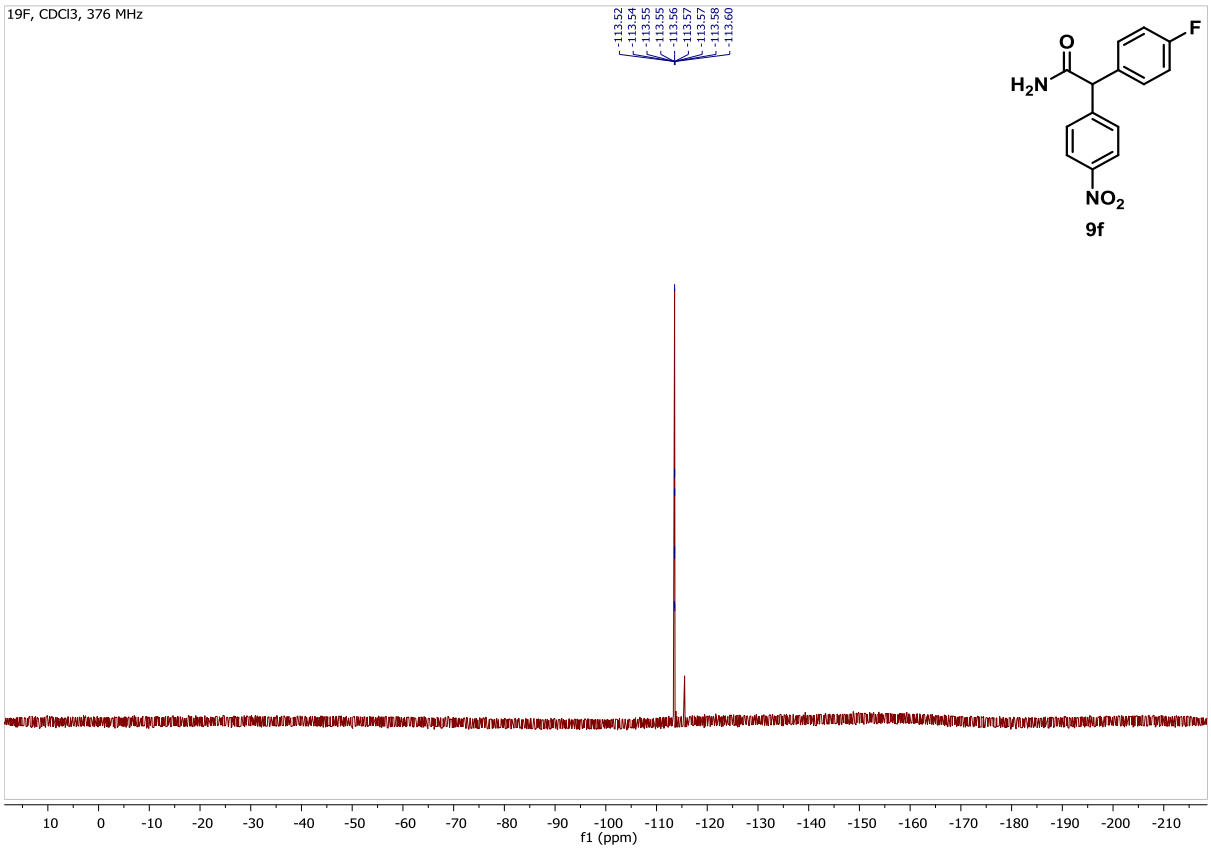

13C, CDCl3, 100 MHz
172.38
147.28
145.32
137.39
133.56
130.27
130.25
129.80
128.33
125.33
123.93
77.16 CDCl3
57.04
O
H2N
Br
NO2
9d
270 260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40
f1 (ppm)

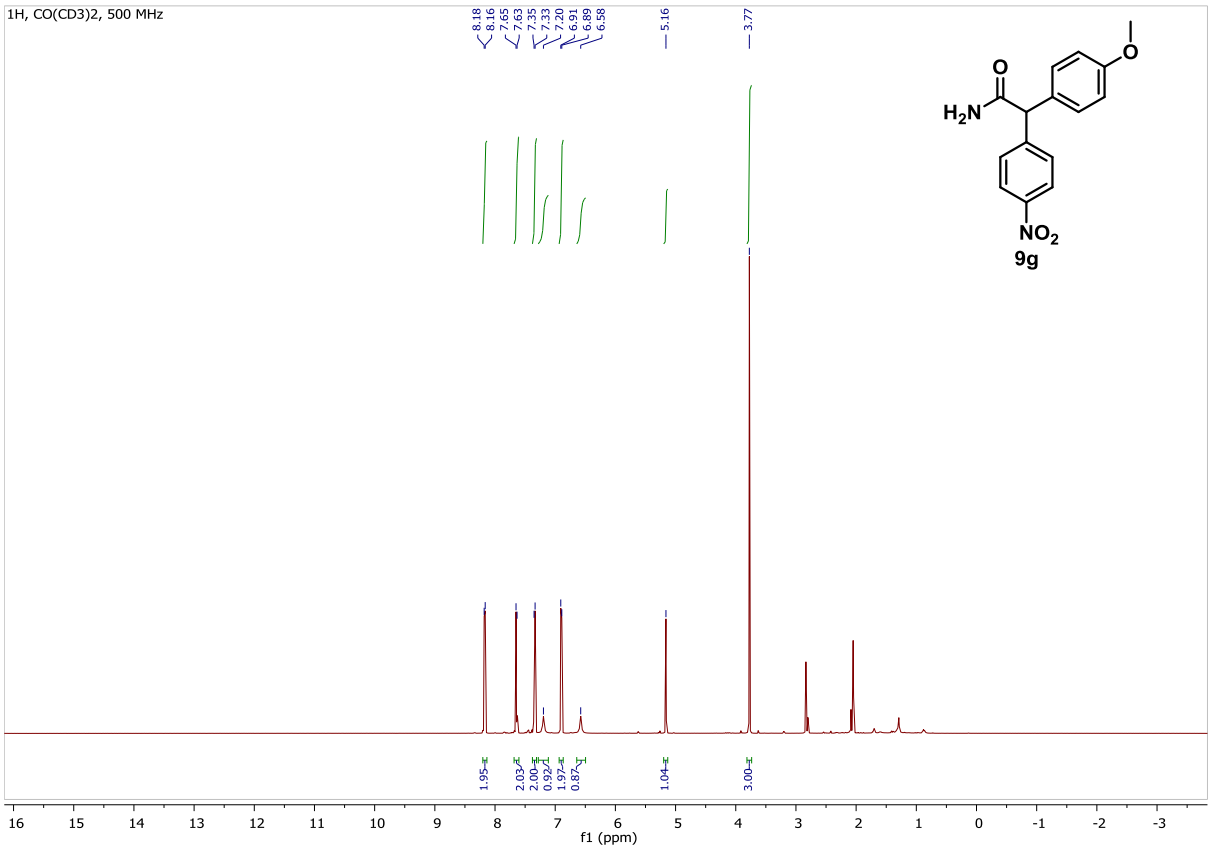

1H, CDCl3, 500 MHz
8.20
8.19
7.47
7.46
7.36
7.34
7.26
7.24
7.23
5.76
5.60
4.98
1.59
1.98
2.03
1.97
1.95
1.08
1.02
1.00
f1 (ppm)
O
H2N
Cl
NO2
9e

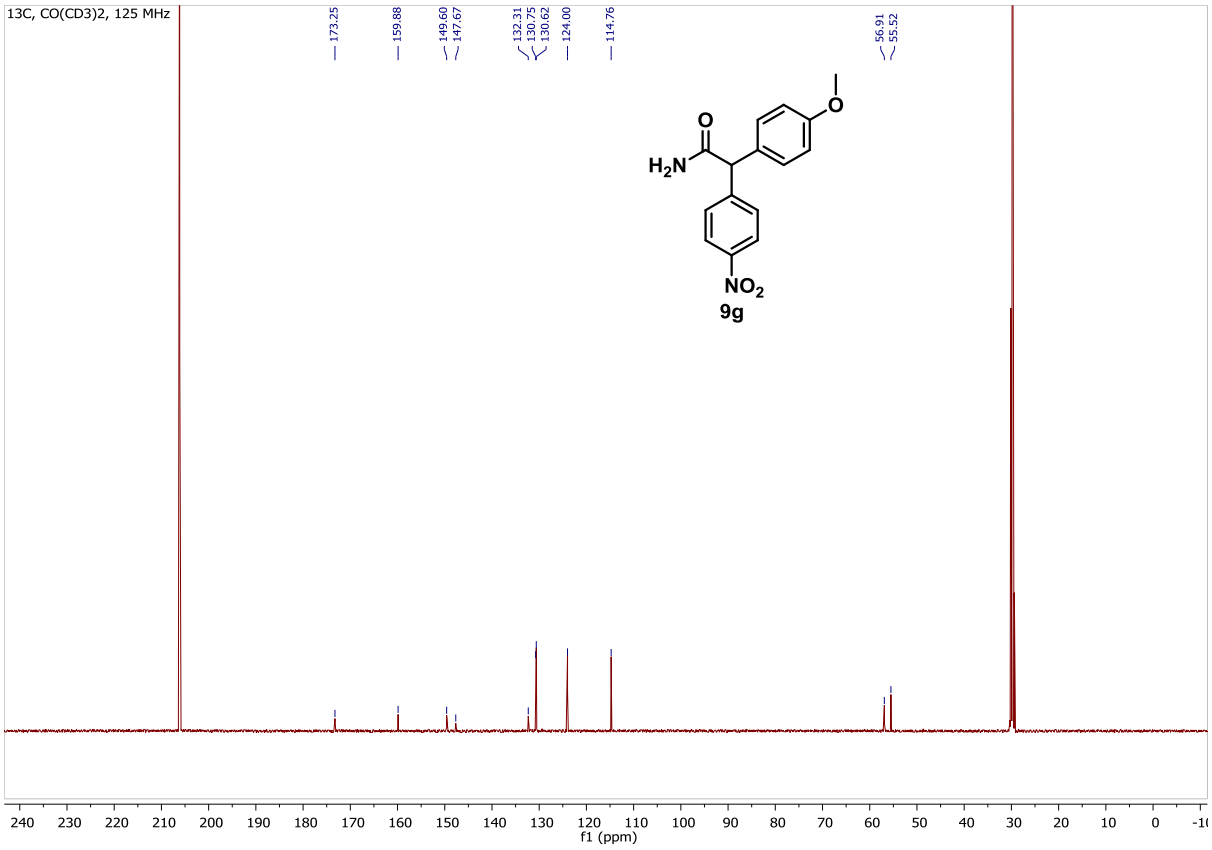

13C, CDCl3, 125 MHz
172.30
147.38
145.95
136.35
134.35
130.20
129.91
129.56
124.10
57.46
f1 (ppm)
O
H2N
Cl
NO2
9e

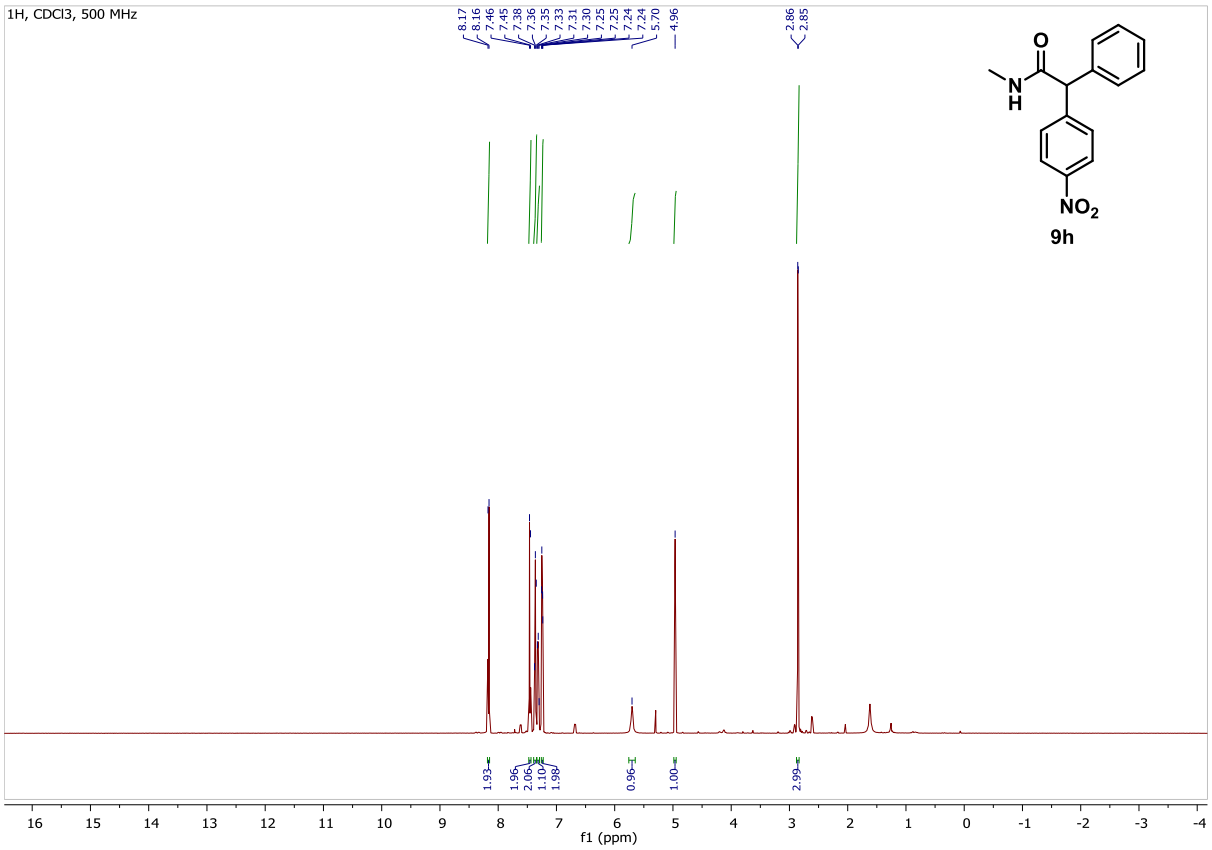

1H, CDCl3, 500 MHz
8.19
8.17
7.46
7.45
7.27
7.26
7.25
7.24
7.08
7.06
7.04
6.12
5.65
4.98
2.08
2.04
2.51
2.14
0.99
0.98
1.00
f1 (ppm)
O
F
H2N
NO2
9f

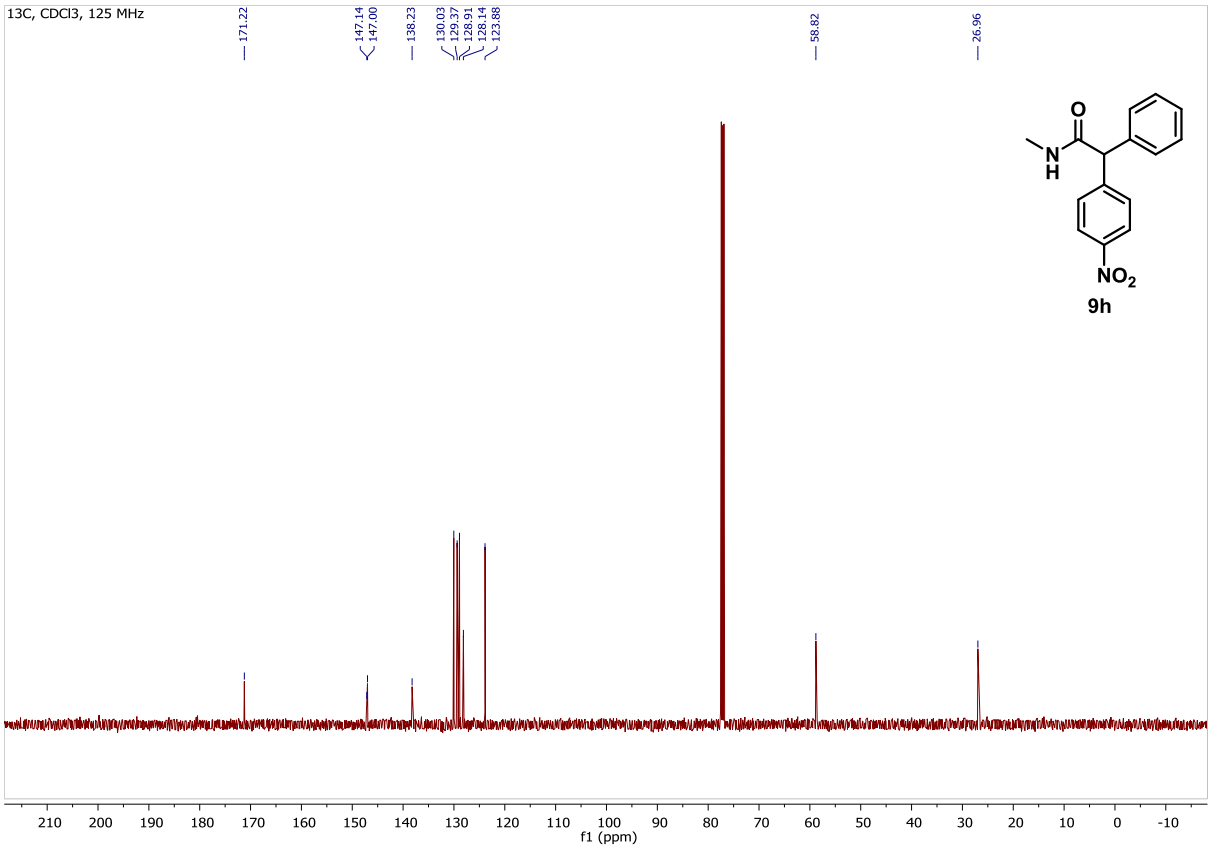

13C, CDCl3, 125 MHz
173.08
163.49
161.51
147.32
146.22
133.66
133.63
130.58
130.51
129.89
124.06
116.44
116.27
57.34
f1 (ppm)
O
F
H2N
NO2
9f

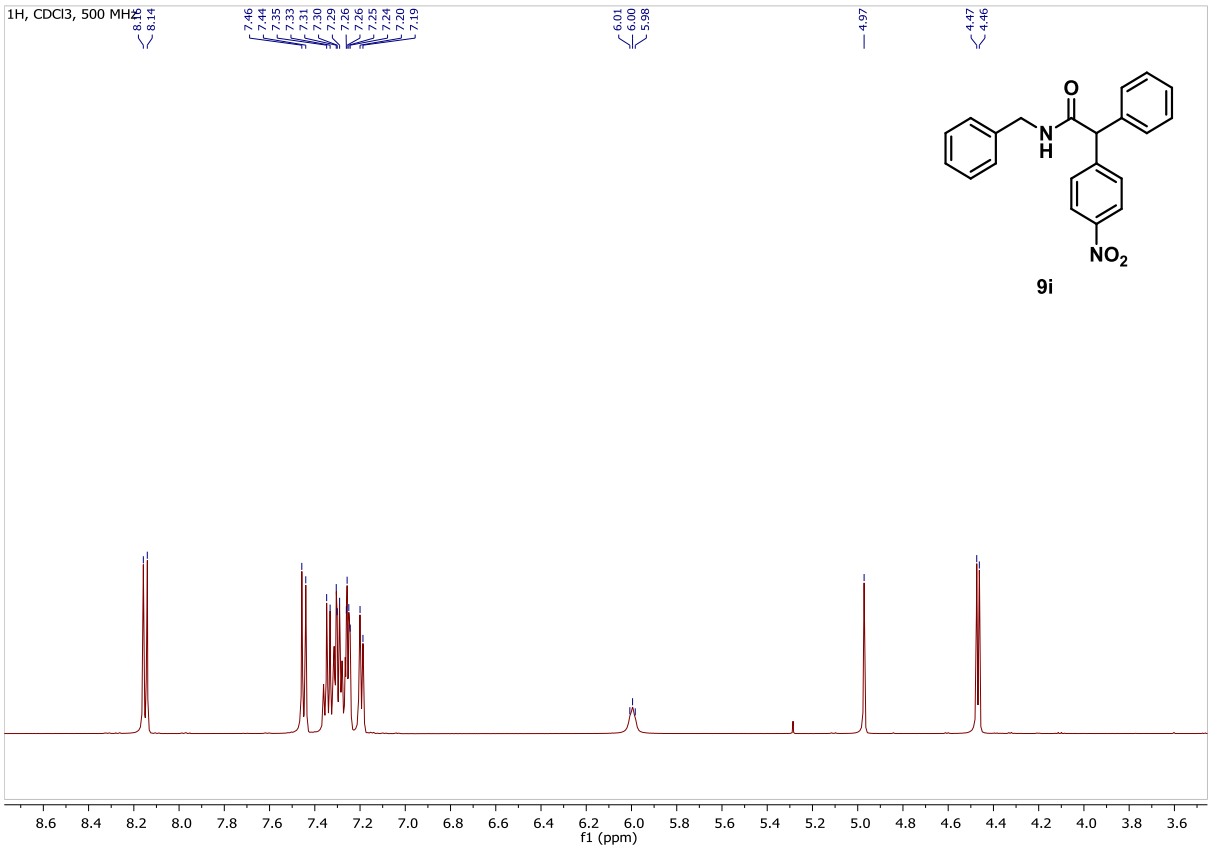

19F, CDCl3, 376 MHz
-113.52
-113.54
-113.55
-113.55
-113.56
-113.57
-113.57
-113.58
-113.60
O
H2N
F
NO2
9f
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

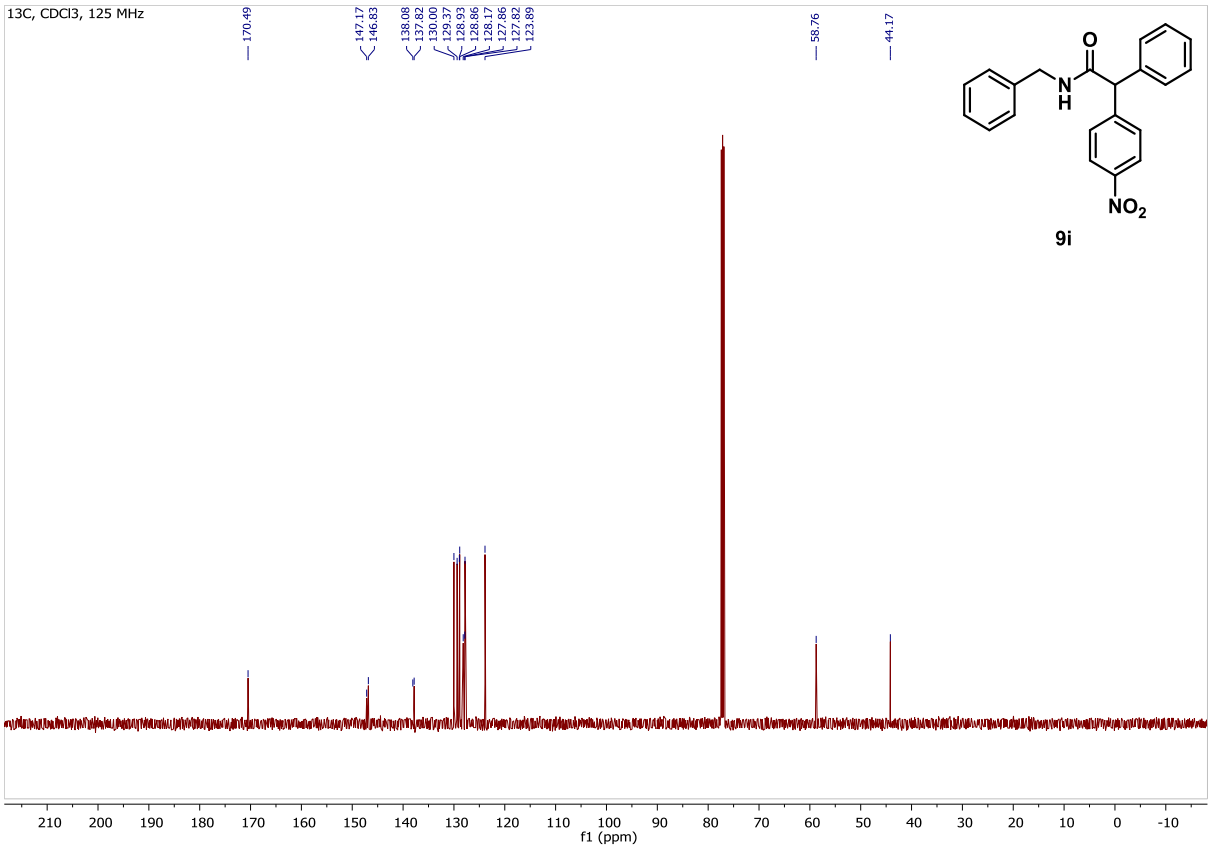

1H, CO(CD3)2, 500 MHz
8.18
8.16
7.65
7.63
7.35
7.33
7.20
6.91
6.89
6.58
5.16
3.77
1.95
2.03
2.00
0.92
1.97
0.87
1.04
3.00
O
H2N
O
NO2
9g
f1 (ppm)

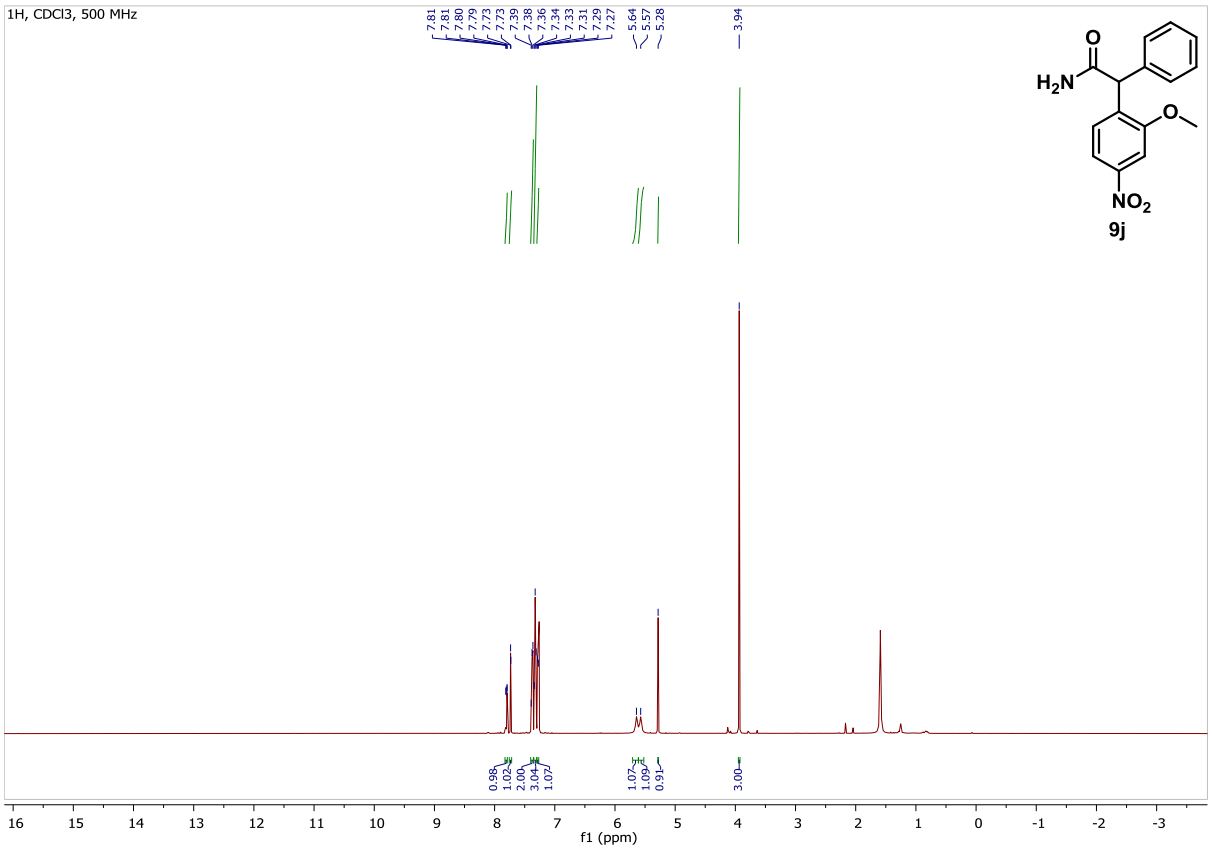

13C, CO(CD3)2, 125 MHz
173.25
159.88
149.60
147.67
132.31
130.75
130.62
124.00
114.76
56.91
55.52
O
H2N
O
NO2
9g
f1 (ppm)

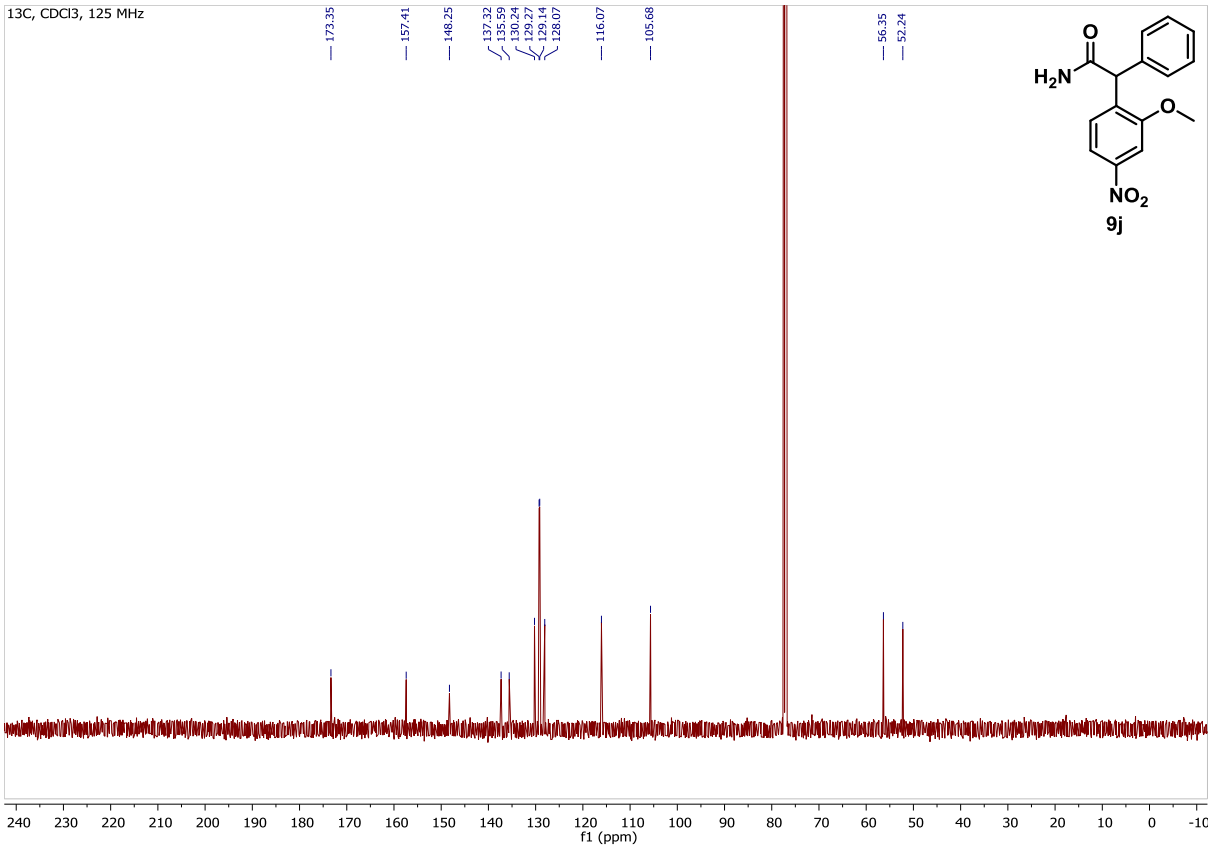

1H, CDCl3, 500 MHz
8.17
8.16
7.46
7.45
7.38
7.36
7.35
7.33
7.31
7.30
7.25
7.25
7.24
7.24
5.70
4.96
2.86
2.85
1.93
1.96
2.06
1.10
1.98
0.96
1.00
2.99
f1 (ppm)
O
N
H
NO2
9h

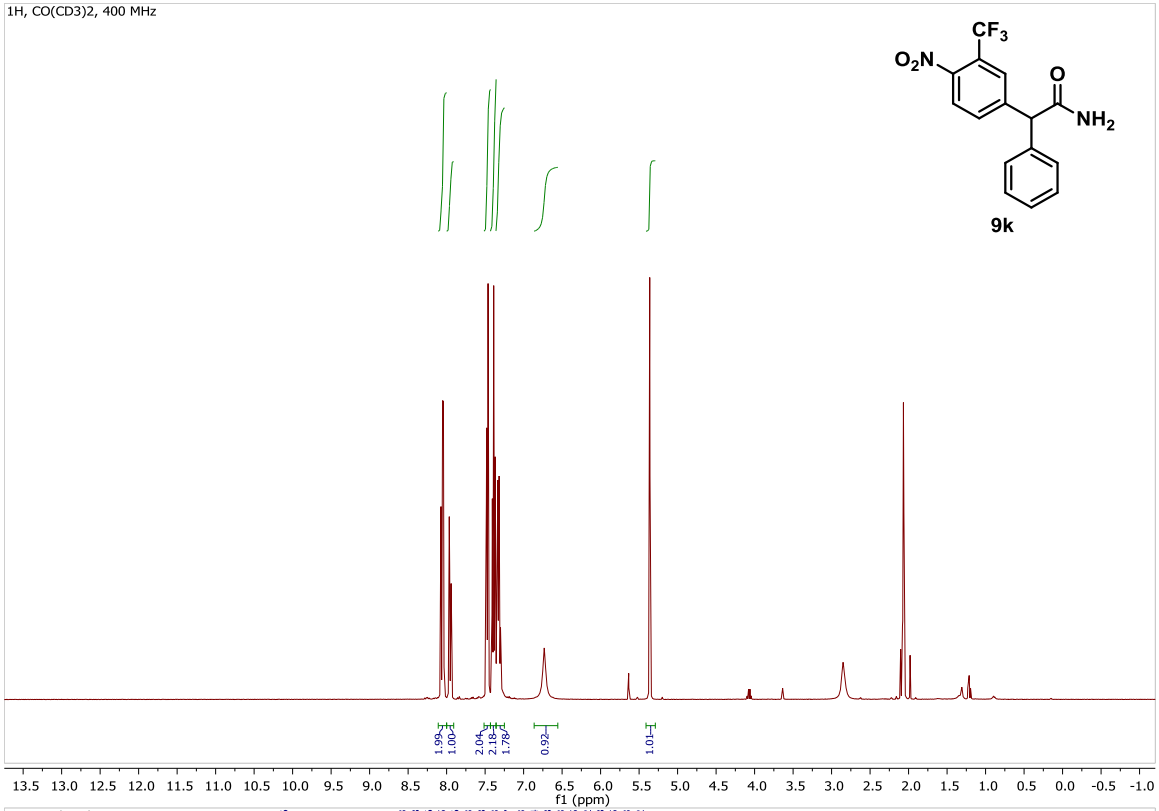

13C, CDCl3, 125 MHz
171.22
147.14
147.00
138.23
130.03
129.37
128.91
128.14
123.88
58.82
26.96
f1 (ppm)
O
N
H
NO2
9h

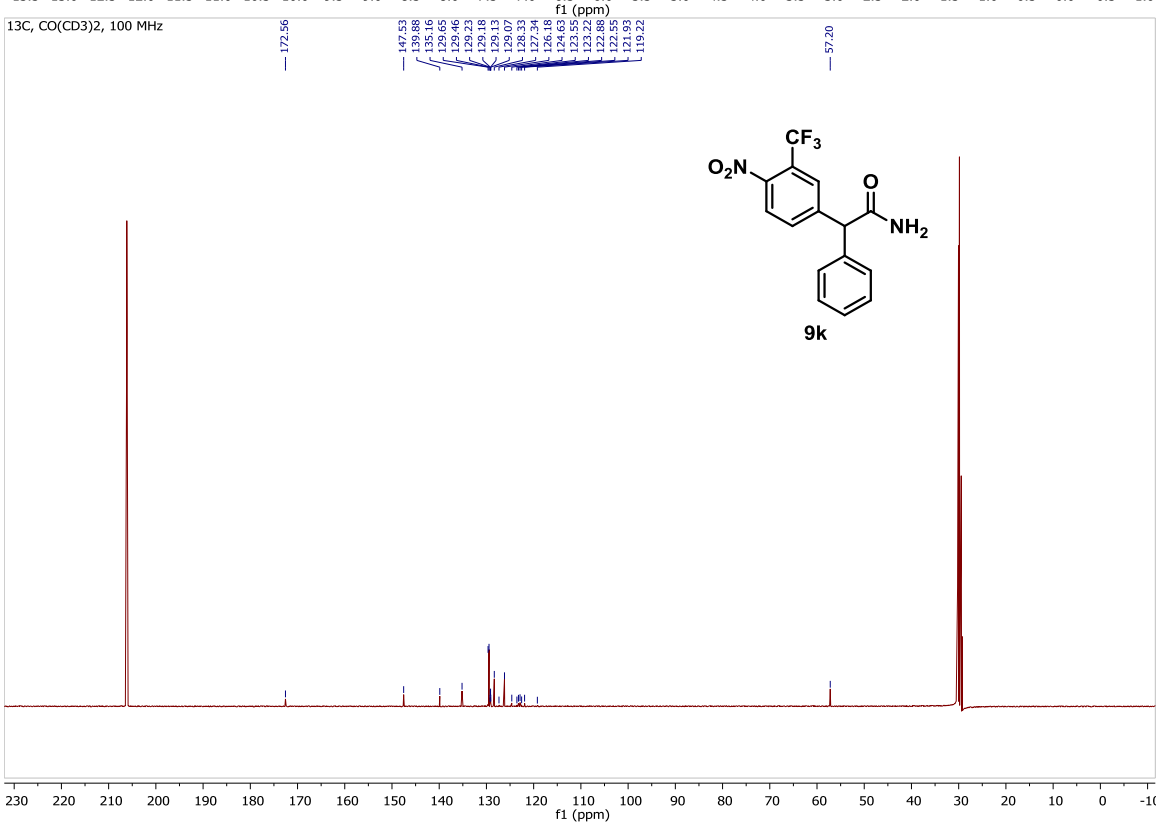

1H, CDCl3, 500 MHz
8.16
8.14
7.46
7.44
7.35
7.33
7.31
7.30
7.29
7.26
7.26
7.25
7.24
7.20
7.19
6.01
6.00
5.98
4.97
4.47
4.46
O
N
H
NO2
9i
8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6
f1 (ppm)

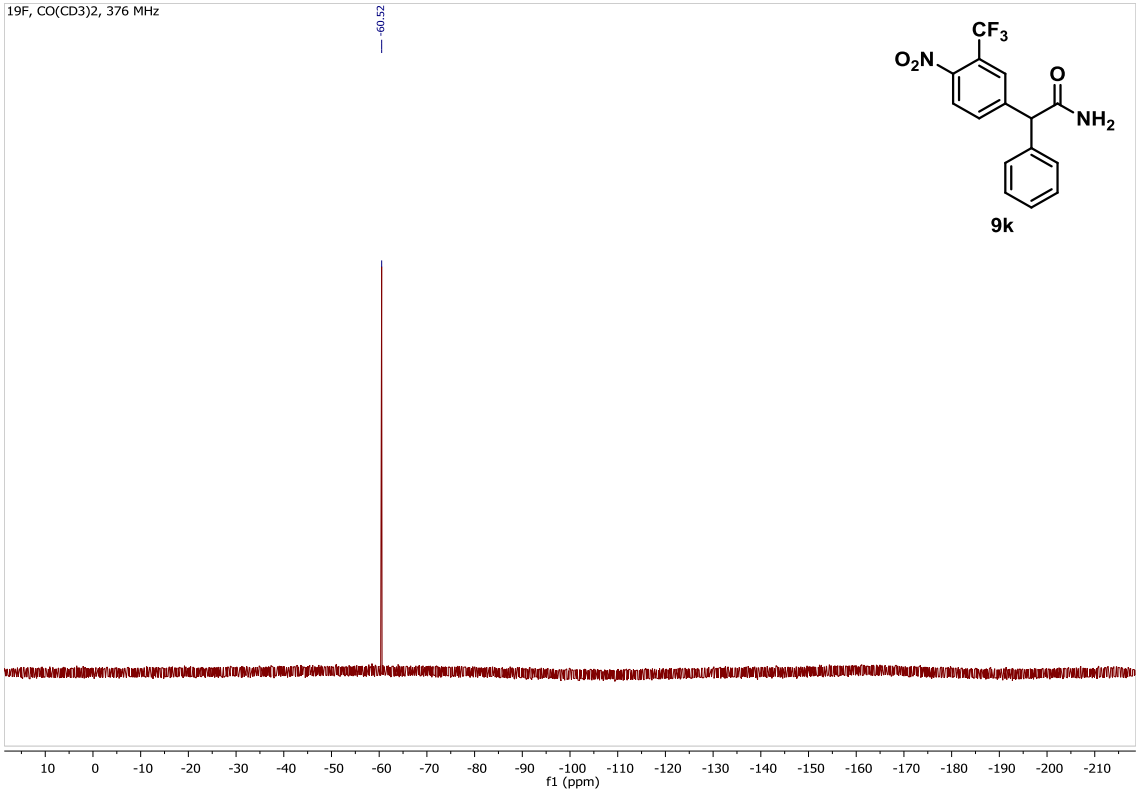

13C, CDCl3, 125 MHz
170.49
147.17
146.83
138.08
137.82
130.00
129.37
128.93
128.86
128.17
127.86
127.82
123.89
58.76
44.17
O
N
H
NO2
9i
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

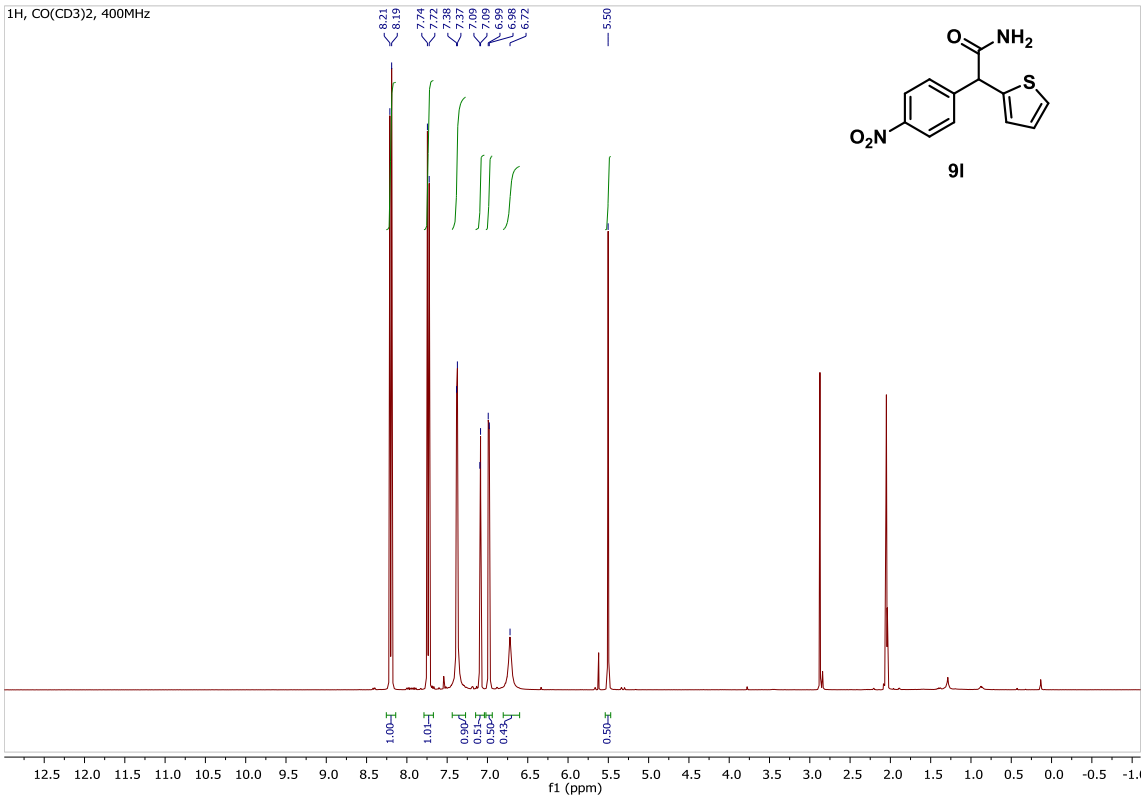

1H, CDCl3, 500 MHz
7.81
7.81
7.80
7.79
7.73
7.73
7.39
7.38
7.36
7.34
7.33
7.31
7.29
7.27
5.64
5.57
5.28
3.94
0.98
1.02
2.00
3.04
1.07
1.07
1.09
0.91
3.00
f1 (ppm)
O
H2N
O
NO2
9j

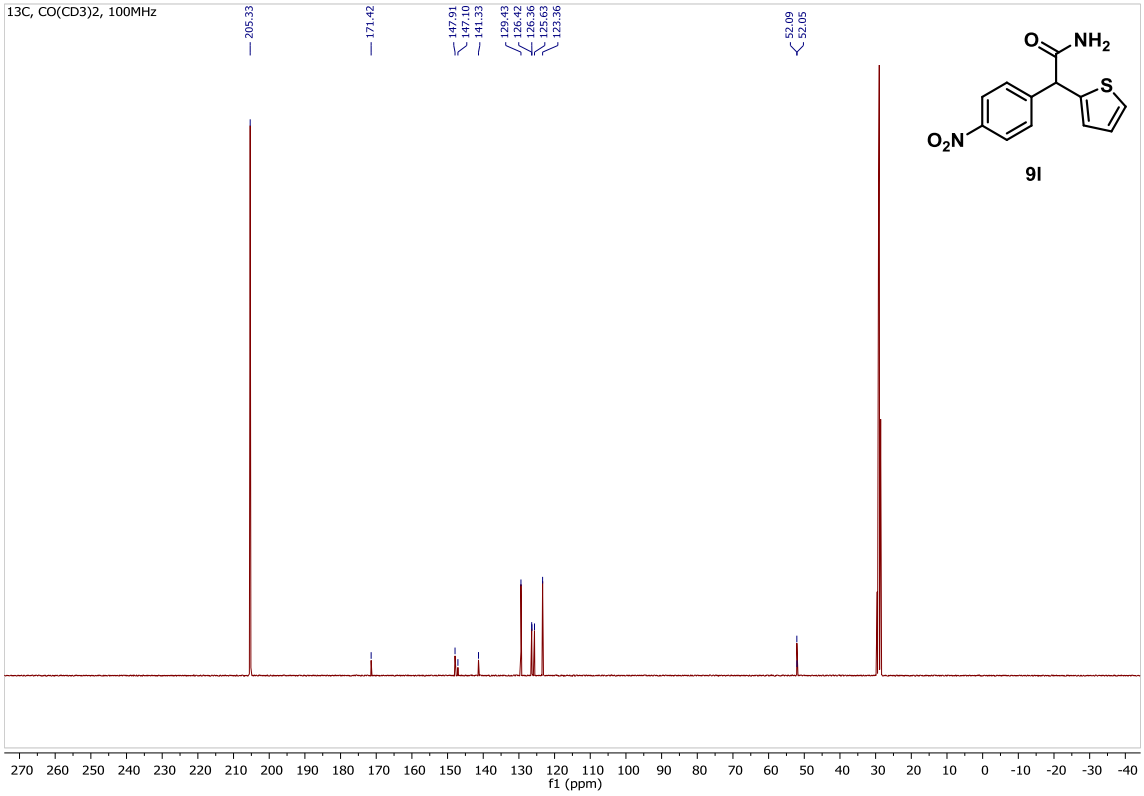

13C, CDCl3, 125 MHz
173.35
157.41
148.25
137.32
135.59
130.24
129.27
129.14
128.07
116.07
105.68
56.35
52.24
f1 (ppm)
O
H2N
O
NO2
9j

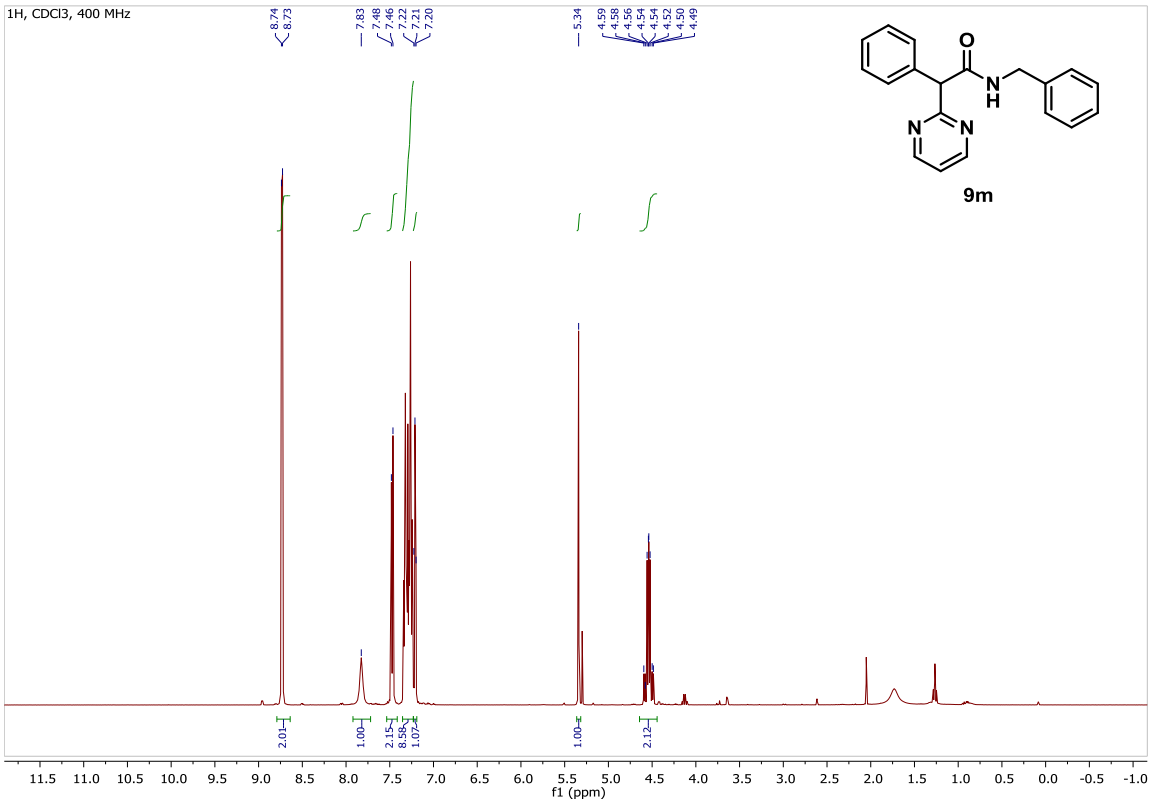

1H, CO(CD3)2, 400 MHz
CF3
O2N
O
NH2
9k
1.99
1.00
2.04
2.18
1.78
0.92
1.01
f1 (ppm)

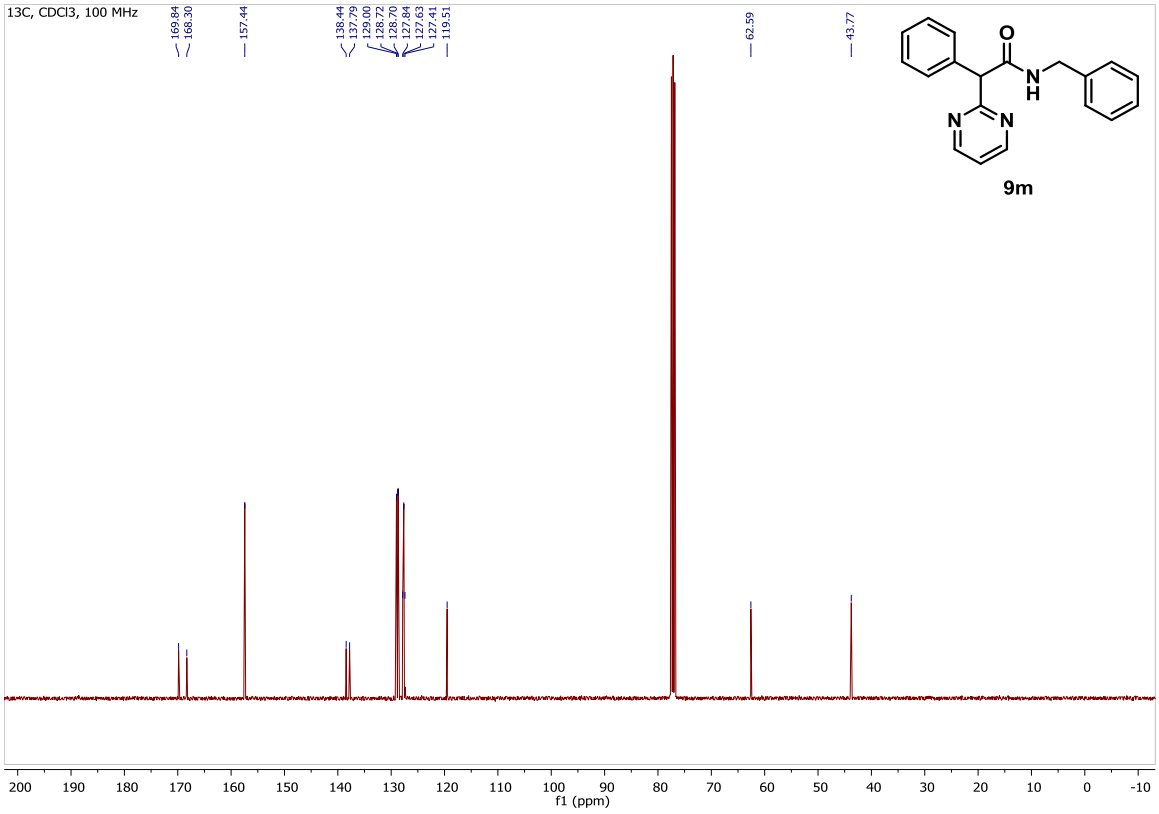

13C, CO(CD3)2, 100 MHz
172.56
147.53
139.88
135.16
129.65
129.46
129.33
129.18
129.13
129.07
128.33
127.34
126.18
124.63
123.55
123.22
122.88
122.55
121.93
119.22
57.20
CF3
O2N
O
NH2
9k
f1 (ppm)

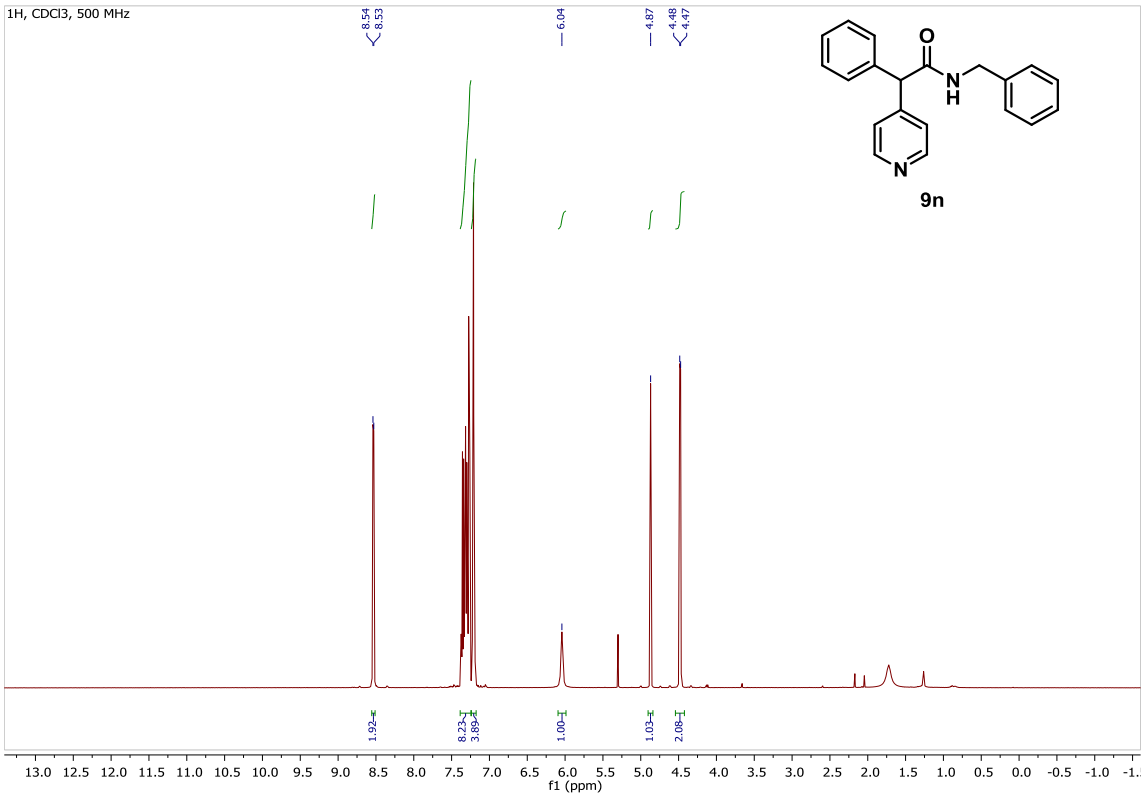

19F, CO(CD3)2, 376 MHz
-60.52
CF3
O2N
O
NH2
9k
10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210
f1 (ppm)

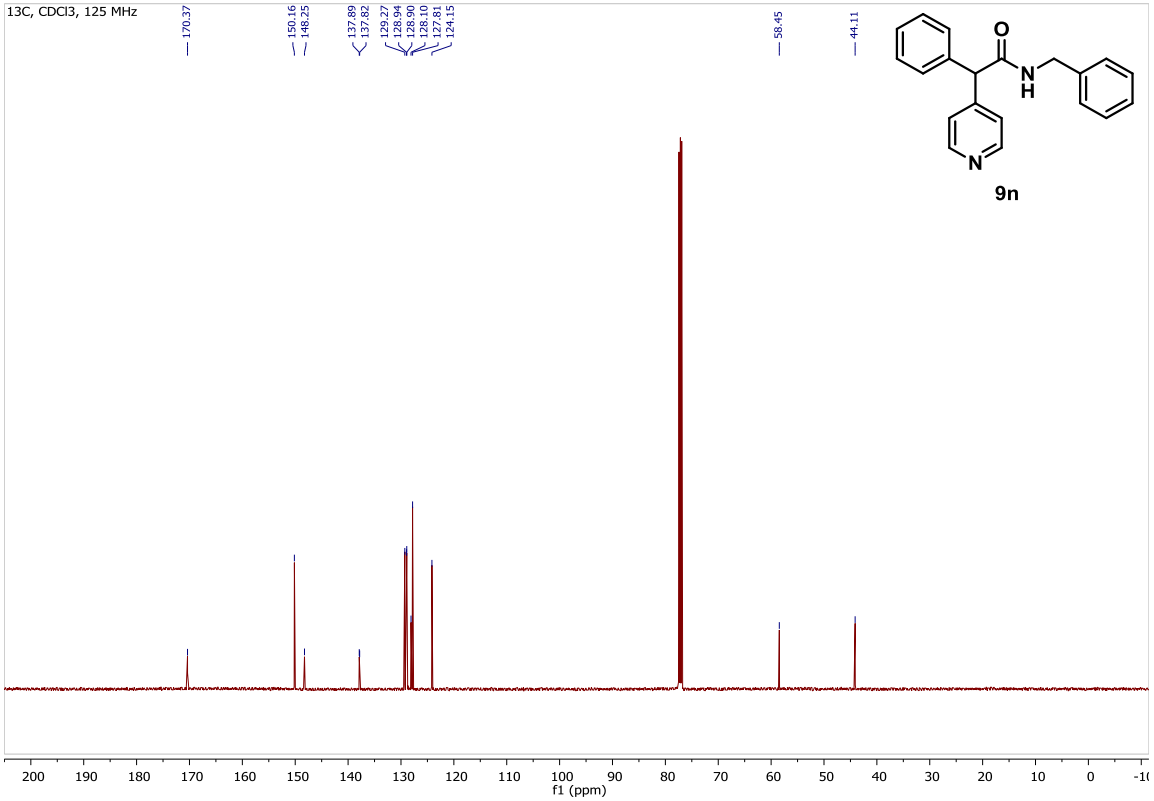

1H, CO(CD3)2, 400MHz
8.21
8.19
7.74
7.72
7.38
7.37
7.09
7.09
6.99
6.98
6.72
5.50
1.00
1.01
0.90
0.51
0.50
0.43
0.50
f1 (ppm)
9l

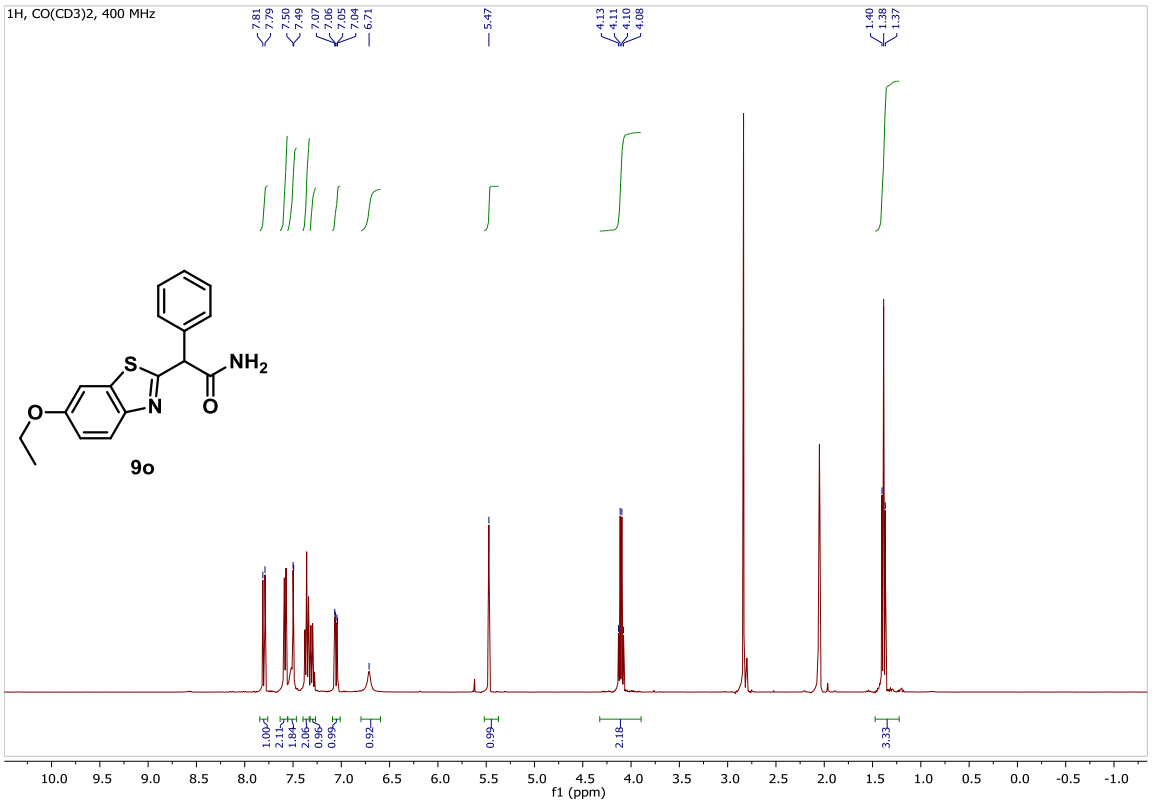

13C, CO(CD3)2, 100MHz
205.33
171.42
147.91
147.10
141.33
129.43
126.42
126.36
125.63
123.36
52.09
52.05
f1 (ppm)
9l

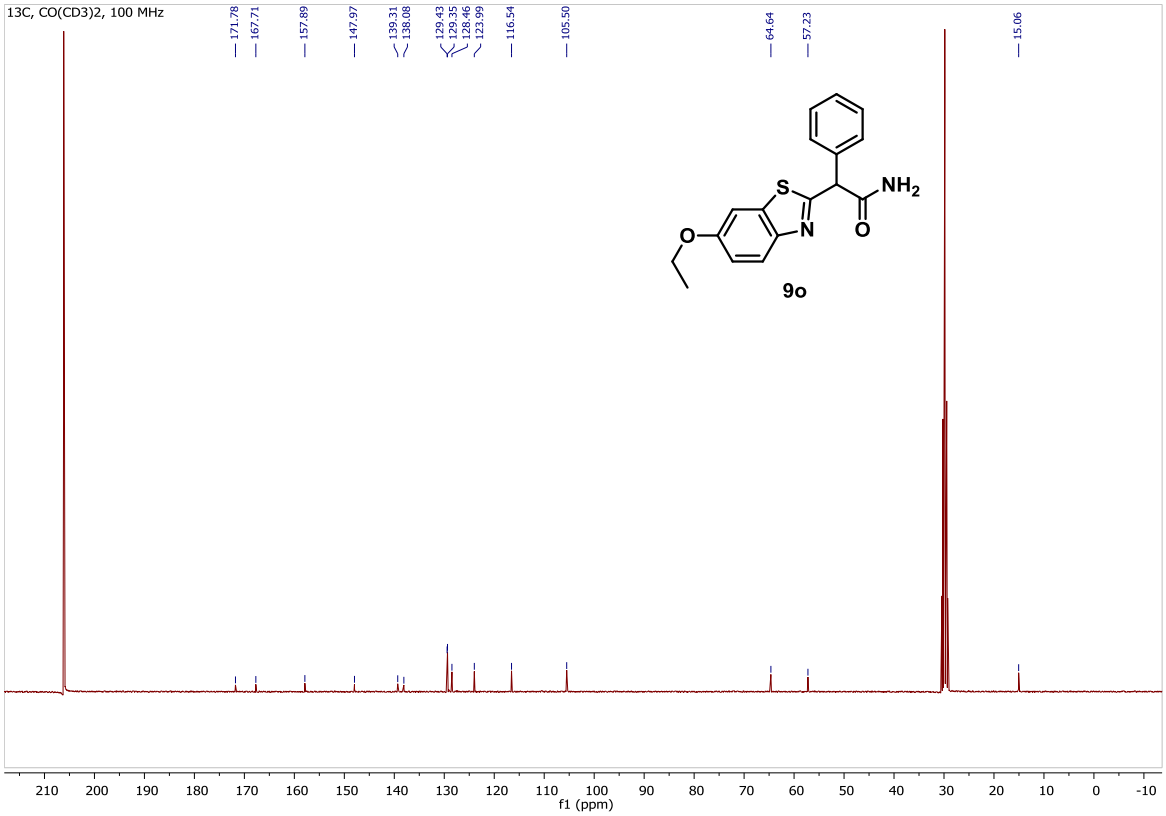

1H, CDCl3, 400 MHz
8.74
8.73
7.83
7.48
7.46
7.22
7.21
7.20
5.34
4.59
4.58
4.56
4.54
4.54
4.52
4.50
4.49
2.01
1.00
2.15
8.58
1.07
1.00
2.12
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)
O
N
H
N
N
9m

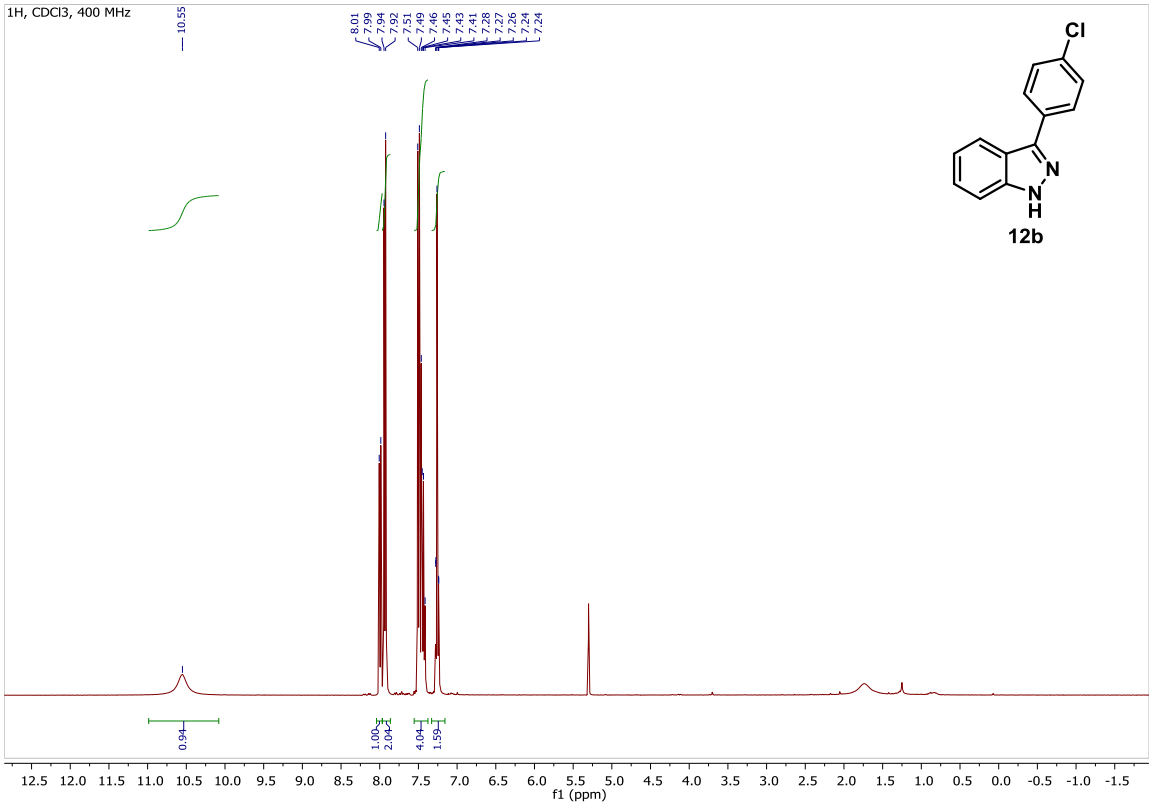

13C, CDCl3, 100 MHz
169.84
168.30
157.44
138.44
137.79
129.00
128.72
128.70
127.84
127.63
127.41
119.51
62.59
43.77
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)
O
N
H
N
N
9m

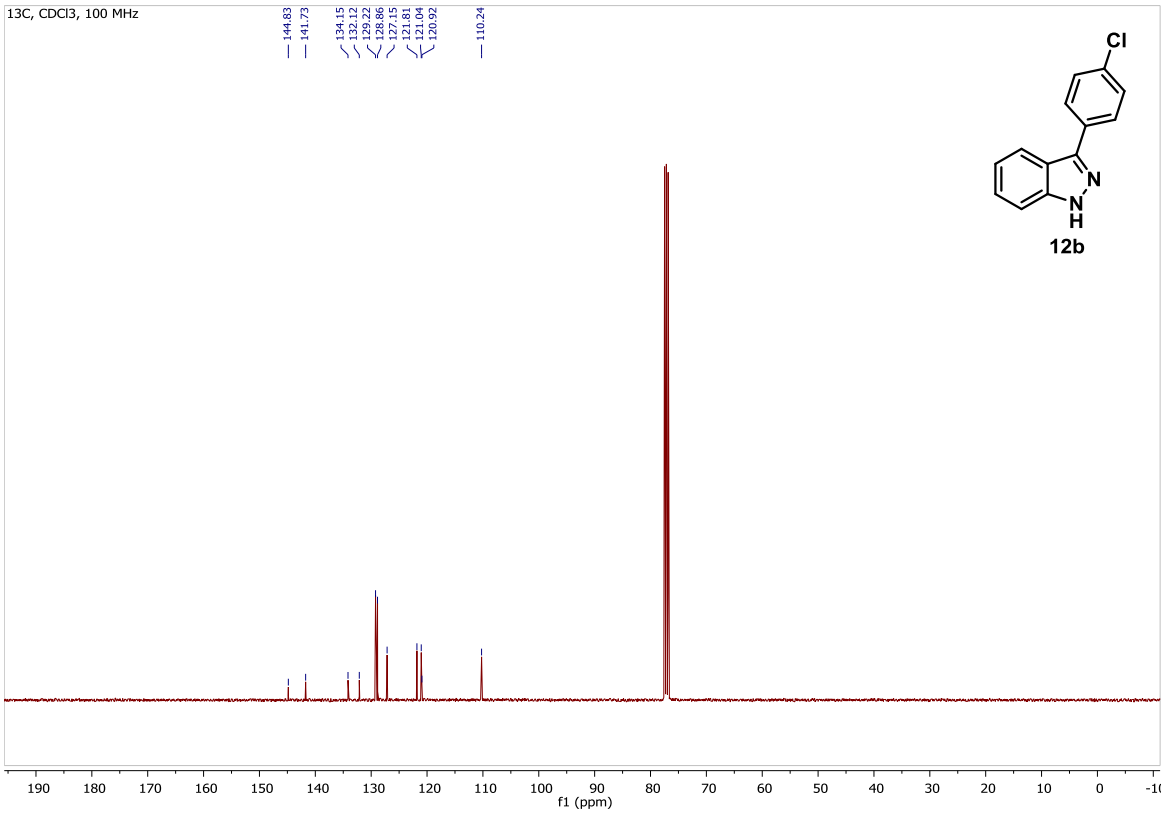

1H, CDCl3, 500 MHz
8.54
8.53
6.04
4.87
4.48
4.47
O
N
H
N
9n
1.92
8.23
3.89
1.00
1.03
2.08
f1 (ppm)

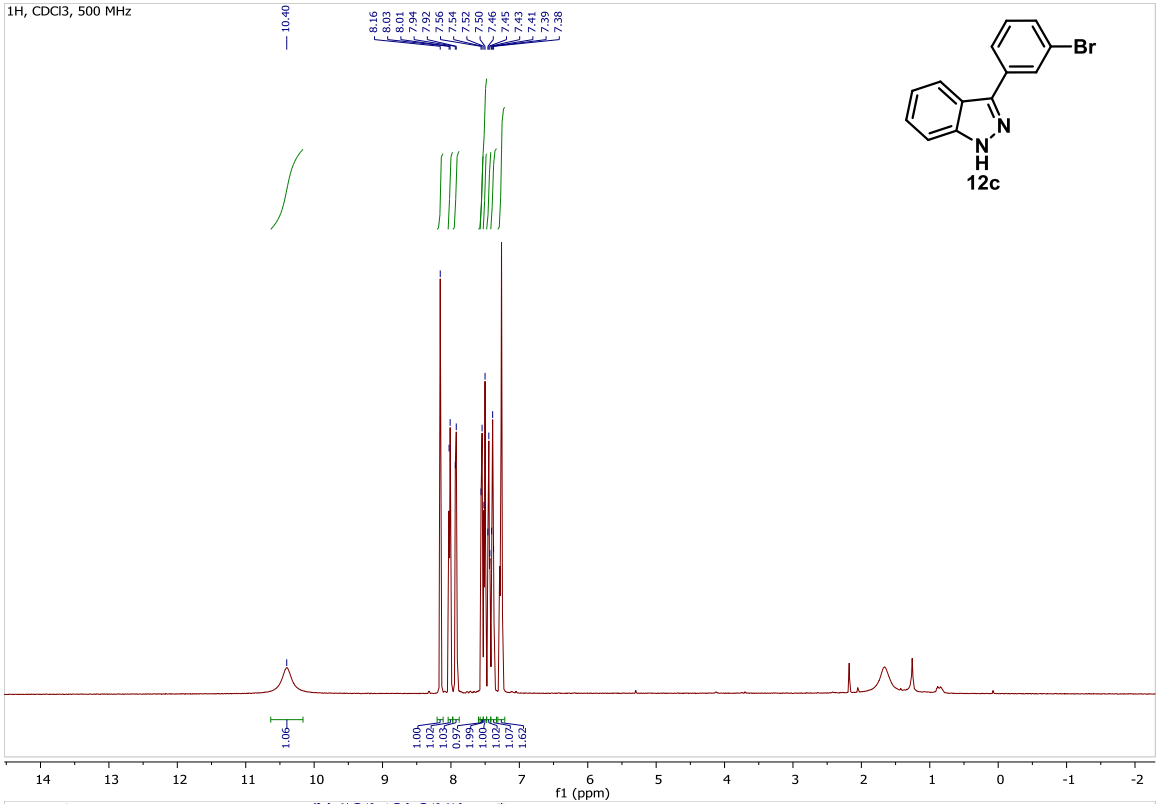

13C, CDCl3, 125 MHz
170.37
150.16
148.25
137.89
137.82
129.27
128.94
128.90
128.10
127.81
124.15
58.45
44.11
O
N
H
N
9n
f1 (ppm)

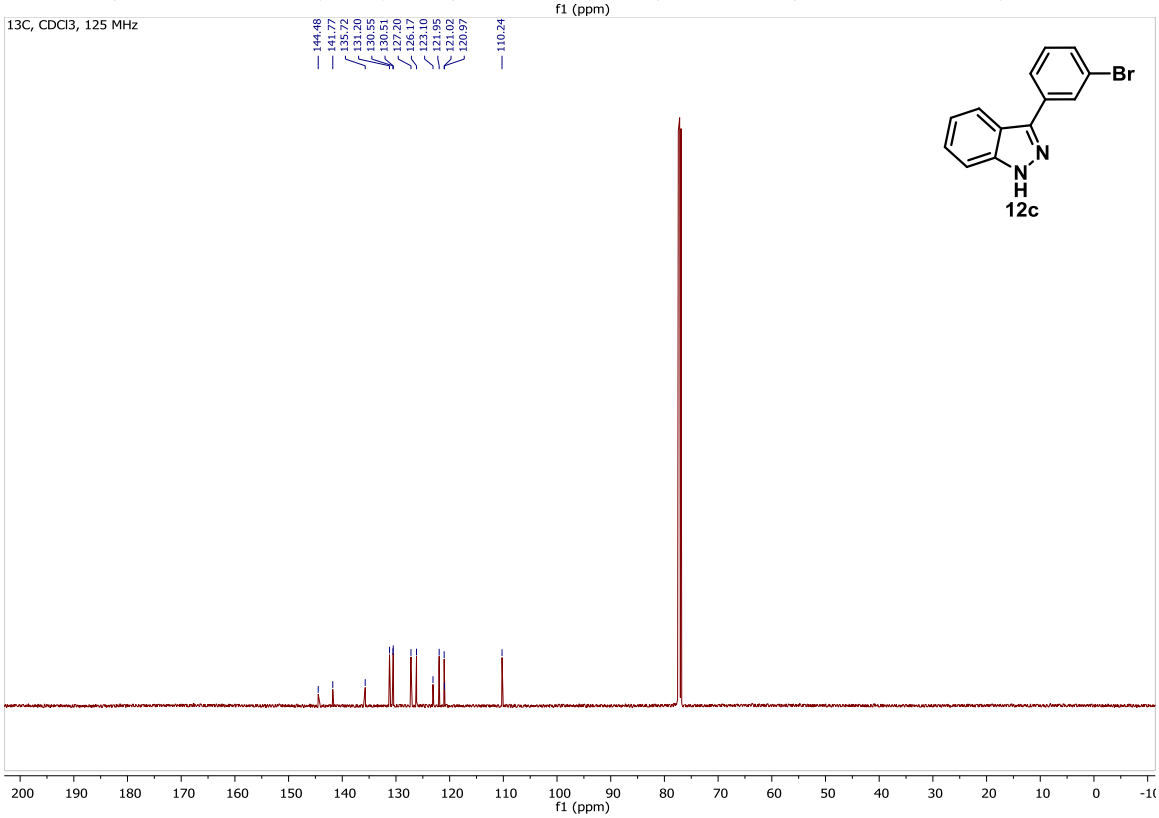

1H, CO(CD3)2, 400 MHz
7.81
7.79
7.50
7.49
7.07
7.06
7.05
7.04
6.71
5.47
4.13
4.11
4.10
4.08
1.40
1.38
1.37
1.00
2.11
1.84
2.06
0.96
0.99
0.92
0.99
2.18
3.33
S
N
O
NH2
O
9o
f1 (ppm)

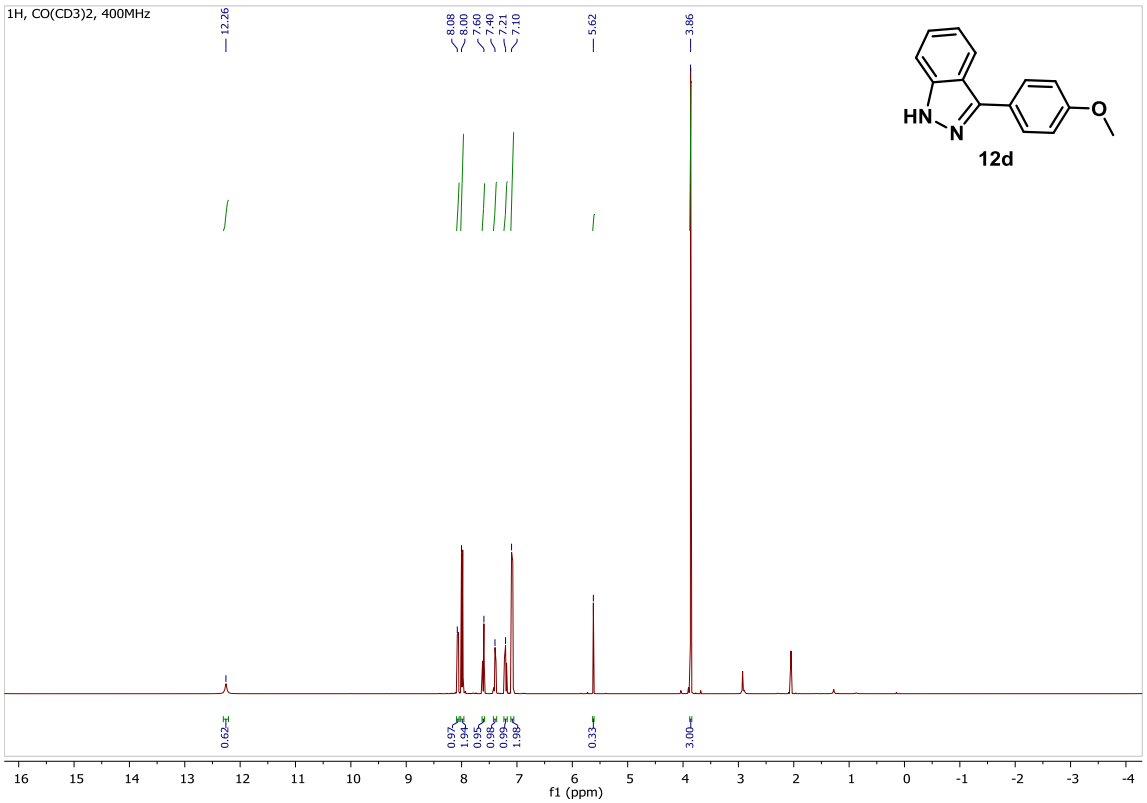

13C, CO(CD3)2, 100 MHz
171.78
167.71
157.89
147.97
139.31
138.08
129.43
129.35
128.46
123.99
116.54
105.50
64.64
57.23
15.06
S
N
O
NH2
O
9o
f1 (ppm)

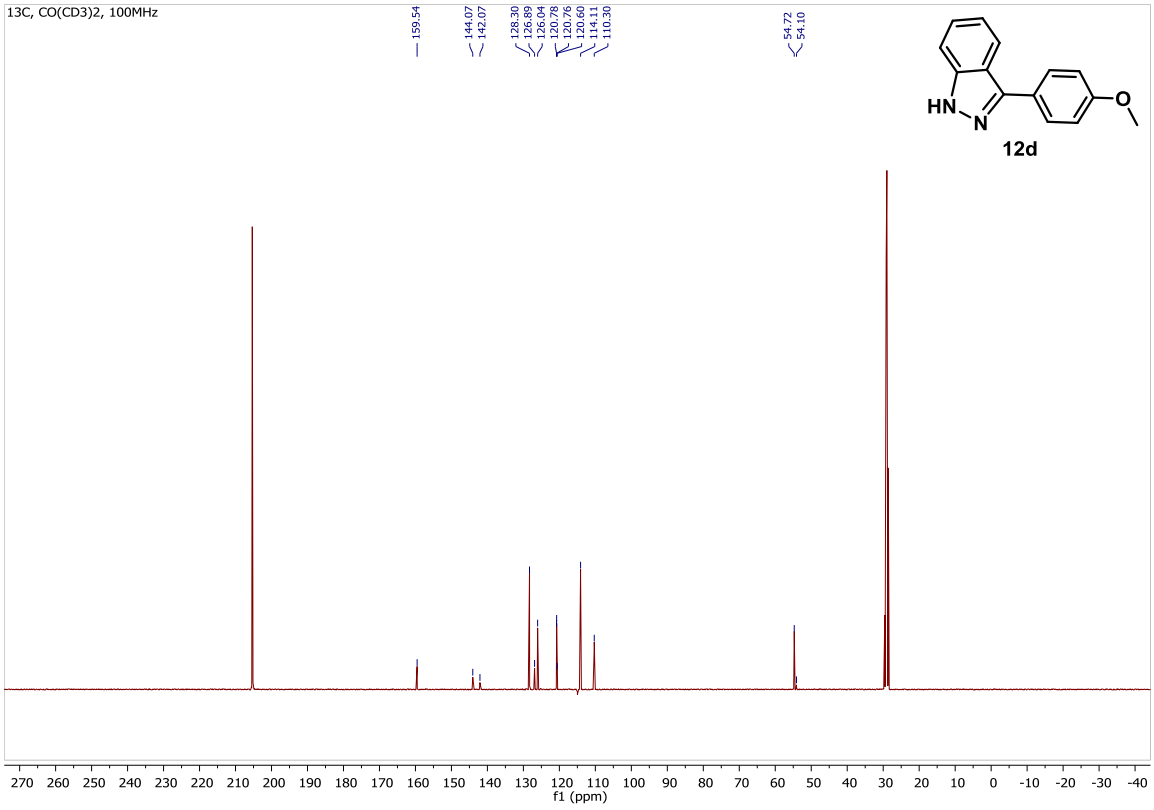

1H, CDCl3, 400 MHz
10.55
8.01
7.99
7.94
7.92
7.51
7.49
7.46
7.45
7.43
7.41
7.28
7.27
7.26
7.24
7.24
Cl
N
N
H
12b
0.94
1.00
2.04
4.04
1.59
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)

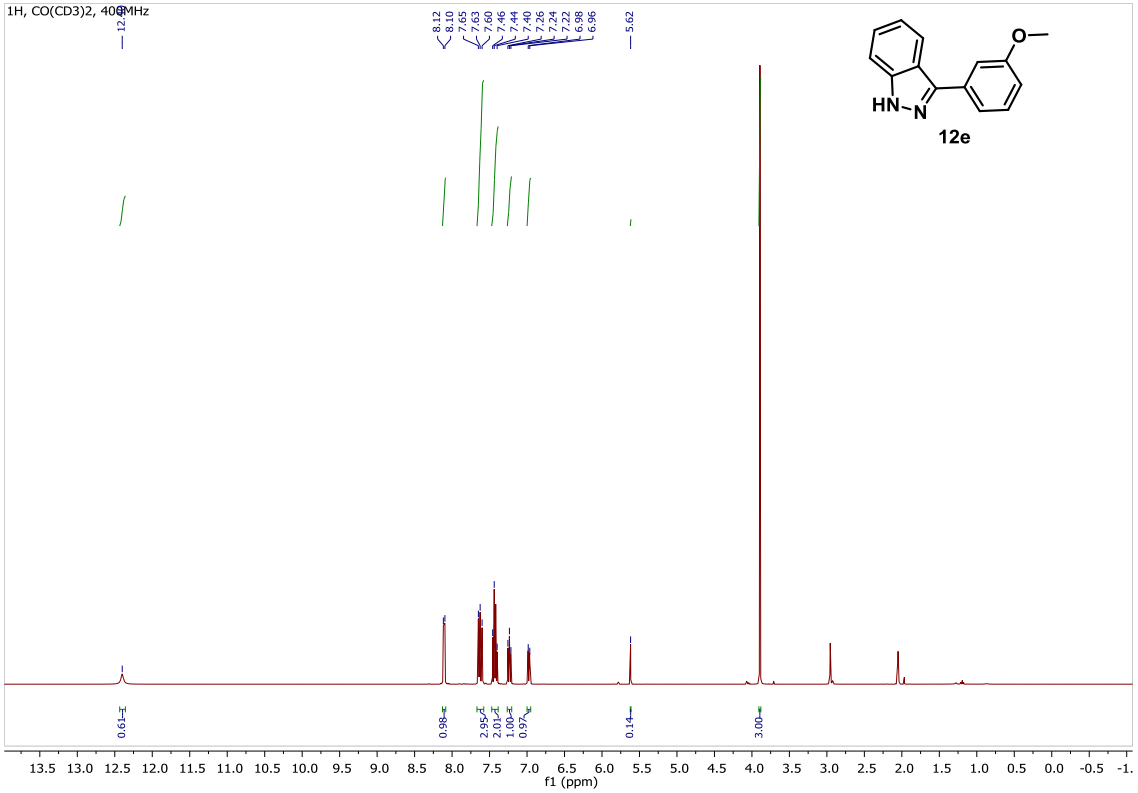

13C, CDCl3, 100 MHz
144.83
141.73
134.15
132.12
129.22
128.86
127.15
121.81
121.04
120.92
110.24
Cl
N
N
H
12b
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

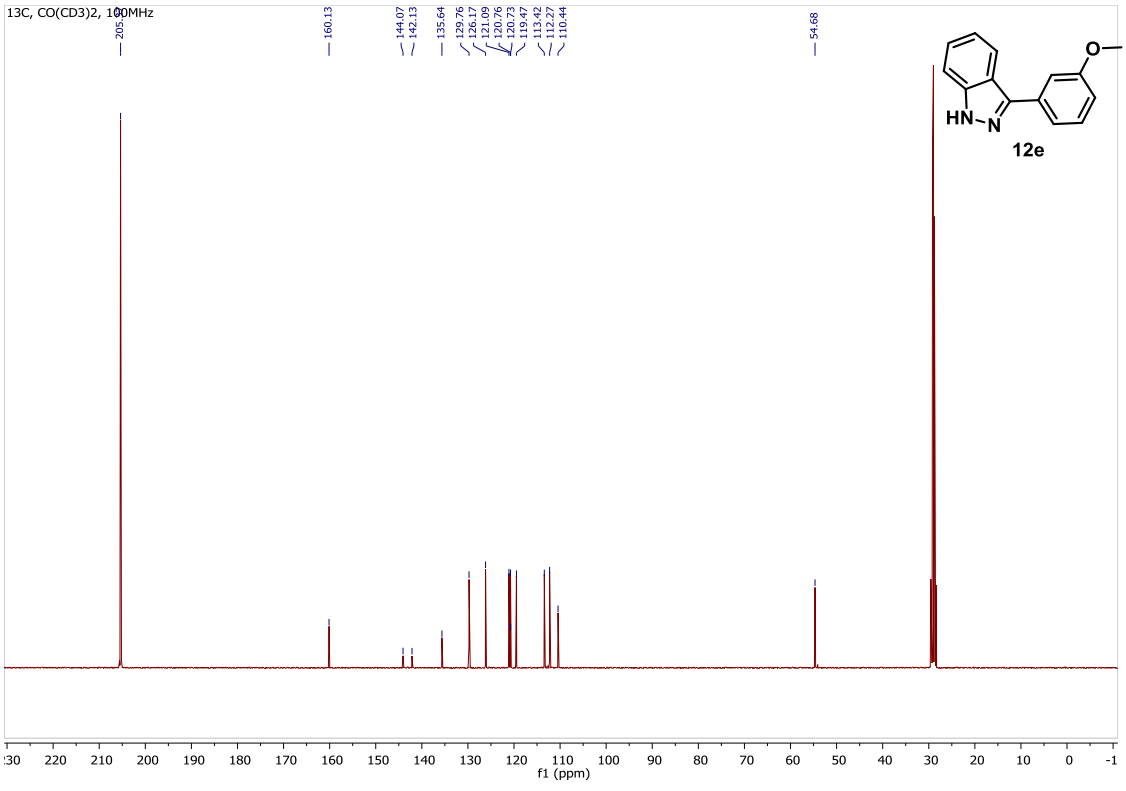

1H, CDCl3, 500 MHz
10.40
8.16
8.03
8.01
7.94
7.92
7.56
7.54
7.52
7.50
7.46
7.45
7.43
7.41
7.39
7.38
Br
N
N
H
12c
1.06
1.00
1.02
1.03
0.97
1.99
1.00
1.02
1.07
1.62
f1 (ppm)

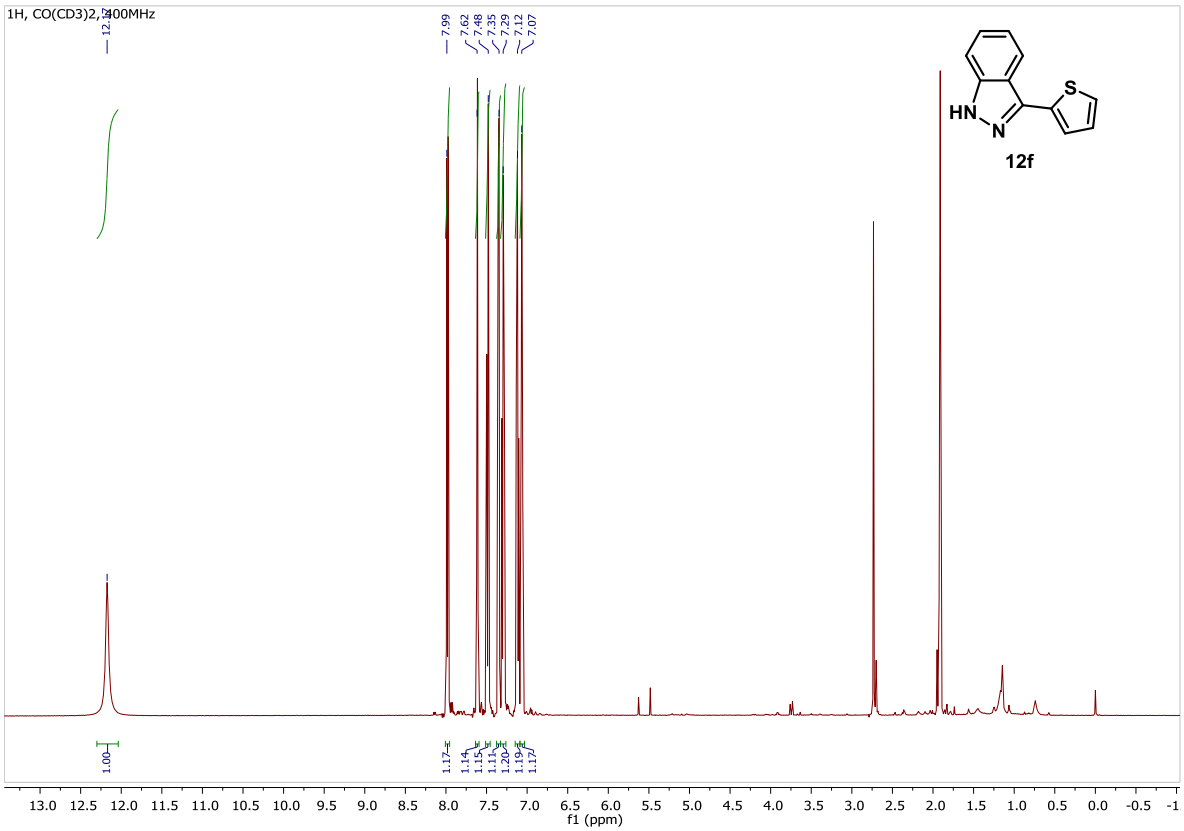

13C, CDCl3, 125 MHz
144.48
141.77
135.72
131.20
130.55
130.51
127.20
126.17
123.10
121.95
121.02
120.97
110.24
Br
N
N
H
12c
f1 (ppm)

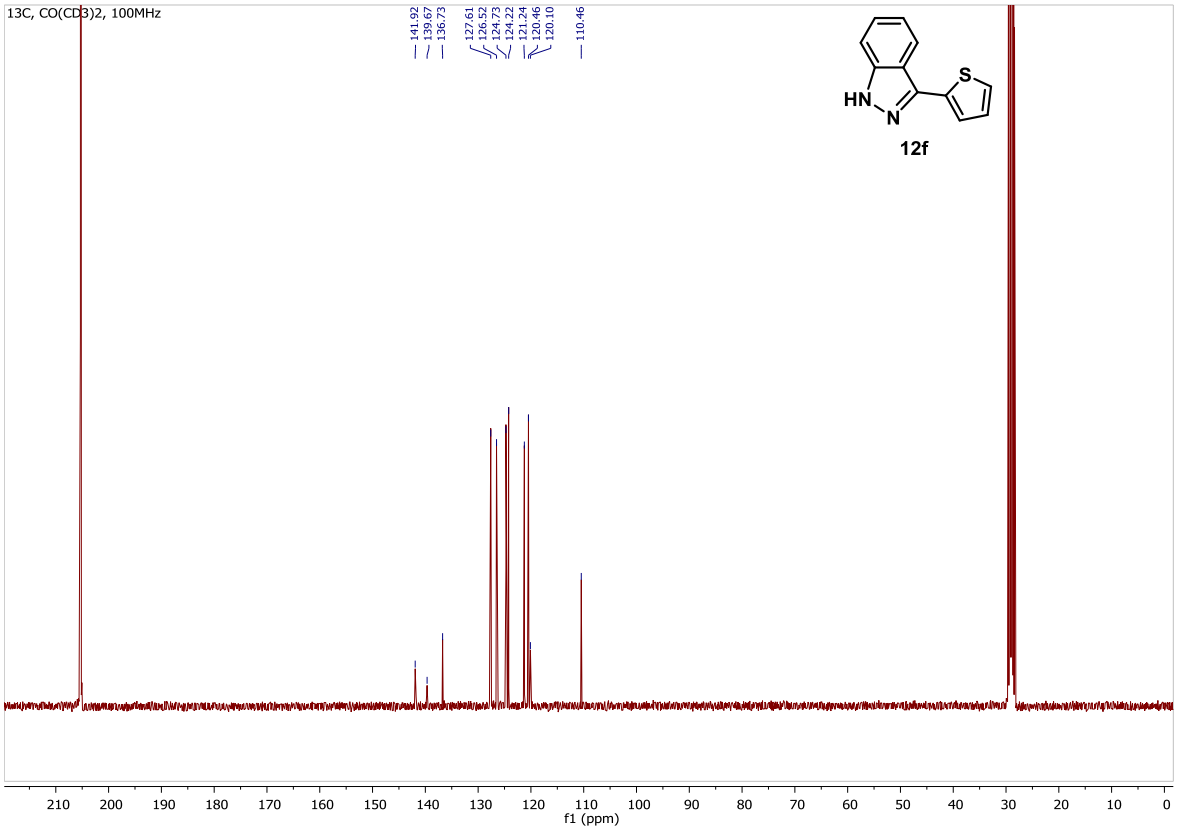

1H, CO(CD3)2, 400MHz
12.26
8.08
8.00
7.60
7.40
7.21
7.10
5.62
3.86
HN
N
O
12d
0.62
0.97
1.94
0.95
0.98
0.99
1.98
0.33
3.00
f1 (ppm)


13C, CO(CD3)2, 100MHz
159.54
144.07
142.07
128.30
126.89
126.04
120.78
120.76
120.60
114.11
110.30
54.72
54.10
HN
N
O
12d
f1 (ppm)


1H, CO(CD3)2, 400MHz
12.61
8.12
8.10
7.65
7.63
7.60
7.46
7.44
7.40
7.26
7.24
7.22
6.98
6.96
5.62
0.61
0.98
2.95
1.01
1.00
0.97
0.14
3.00
HN
N
O
12e
f1 (ppm)


13C, CO(CD3)2, 100MHz
205.5
160.13
144.07
142.13
135.64
129.76
126.17
121.09
120.76
120.23
119.47
113.42
112.27
110.44
54.68
HN
N
O
12e
f1 (ppm)


1H, CO(CD3)2, 400MHz
12.14
7.99
7.62
7.48
7.35
7.29
7.12
7.07
HN
N
S
12f
1.00
1.17
1.14
1.15
1.11
1.20
1.19
1.17
13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


13C, CO(CD3)2, 100MHz
141.92
139.67
136.73
127.61
126.52
124.73
124.22
121.24
120.46
120.10
110.46
HN
N
S
12f
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)