Supporting Information for

A New Method for the Cleavage of Nitrobenzyl Amides and Ethers

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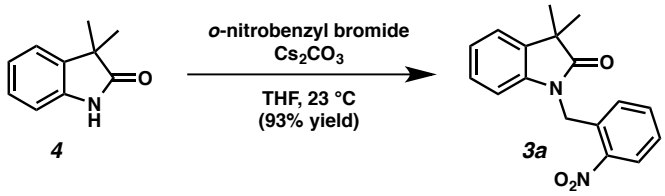
Materials and Methods.

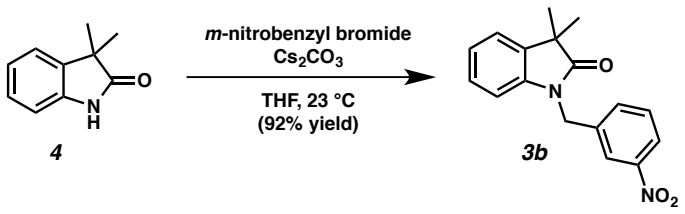
Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF, Et_2O, CH_2Cl_2, toluene, benzene, CH_3CN, and dioxane were dried by passage through an activated alumina column under argon. Triethylamine was distilled over CaH_2 prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. Commercially available reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator unless otherwise indicated. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N_2 atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, *p*-anisaldehyde, or PMA (phosphomolybdic acid) staining. Silicycle Silia*Flash* P60 Academic Silica gel (particle size 0.040-0.064 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on a Varian Inova 500 MHz spectrometer and are reported relative to residual $CHCl_3$ (δ 7.26 ppm), or $(CD_3)_2CO$ (δ 2.05 ppm). ^{13}C NMR spectra are recorded on a Varian Inova 500 MHz spectrometer (125MHz) and are reported relative to $CHCl_3$ (δ 77.16 ppm), or $(CD_3)_2CO$ (δ 29.84 ppm). Data for ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d= broad doublet, app = apparent. Data for ^{13}C are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were obtained from Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

Experimental Procedures and Spectroscopic Data



***N*–2-nitrobenzyloxindole 3a.** To a mixture of 3,3-dimethyloxindole **4**[1] (150 mg, 0.93 mmol, 1.00 equiv) and Cs_2CO_3 (606 mg, 1.86 mmol, 2.00 equiv) in THF (4.70 mL) was added *o*-nitrobenzyl bromide (302 mg, 1.40 mmol, 1.50 equiv). The reaction mixture was stirred overnight. Then, the reaction mixture was extracted with EtOAc (3 x 6 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 → 1:2 EtOAc:hexanes) on silica gel to afford *N*–2-nitrobenzyl-3,3-dimethyloxindole **3a** (258 mg, 93% yield).

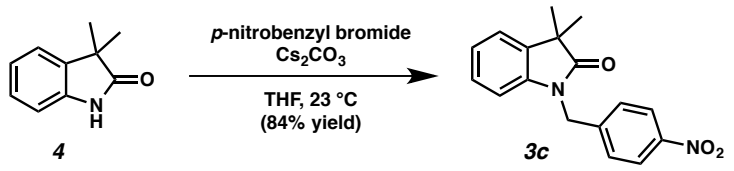
R_f = 0.35 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.51 (td, *J* = 7.6, 1.4 Hz, 1H), 7.44 (dddt, *J* = 8.1, 7.4, 1.4, 0.7 Hz, 1H), 7.28 (ddd, *J* = 7.3, 1.3, 0.6 Hz, 1H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 7.12 (dq, J = 7.8, 1.0 Hz, 1H), 7.09 (td, *J* = 7.5, 1.1 Hz, 1H), 6.61 (dt, *J* = 7.8, 0.8 Hz, 1H), 5.33 (d, *J* = 0.8 Hz, 2H), 1.48 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.8, 148.2, 141.4, 135.8, 134.2, 132.0, 128.5, 128.0, 127.6, 125.7, 123.2, 122.8, 108.8, 77.2, 44.5, 41.2, 24.8; IR (Neat Film NaCl) 2968, 1721, 1615, 1524, 1489, 1385, 1338, 1177, 1008, 858, 761 cm^{-1}; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1234; found: 297.1236.



[1] Vu, A. T.; Cohn, S. T.; Zhang, P.; Kim, C. Y. Mahaney, P. E.; Bray, J. A.; Johnston, G. H.; Koury, E. J.; Cosmi, S. A.; Deecher, D. C.; Smith, V. A.; Harrison, J. E.; Leventhal, L.; Whiteside, G. T.; Kennedy, J. D.; Trybulski, E. J. *J. Med. Chem.* **2010**, *53*, 2051–2062.

***N*–3-nitrobenzyloxindole 3b.** To a mixture of 3,3-dimethyloxindole **4**[1] (100 mg, 0.62 mmol, 1.00 equiv) and Cs_2CO_3 (403 mg, 1.24 mmol, 2.00 equiv) in THF (3.10 mL) was added *m*-nitrobenzyl bromide (335 mg, 1.55 mmol, 2.50 equiv). The reaction mixture was stirred overnight. Then, the reaction mixture was extracted with EtOAc (3 x 4 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 → 1:2 EtOAc:hexanes) on silica gel to afford *N*–3-nitrobenzyl-3,3-dimethyloxindole **3b** (170 mg, 92% yield).

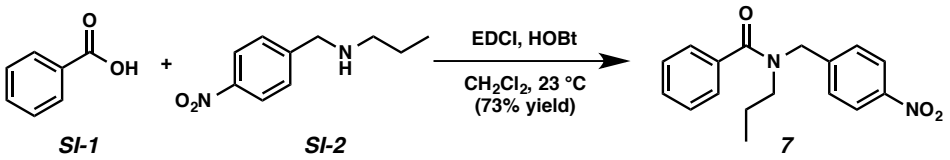
R_f = 0.35 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 – 8.11 (m, 2H), 7.60 (ddt, *J* = 7.7, 1.8, 0.9 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.26 – 7.24 (m, 1H), 7.17 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (td, *J* = 7.5, 1.0 Hz, 1H), 5.01 (s, 2H), 1.46 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.7, 148.6, 141.1, 138.5, 135.9, 133.3, 130.1, 127.9, 123.2, 122.9, 122.8, 122.2, 108.7, 77.2, 44.4, 43.0, 24.7; IR (Neat Film NaCl) 2969, 1652, 1538, 1348, 1011, 933, 761; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1234; found: 297.1241.



***N*–4-nitrobenzyloxindole 3c.** To a mixture of 3,3-dimethyloxindole **4**[1] (50 mg, 0.31 mmol, 1.00 equiv) and Cs_2CO_3 (202 mg, 0.62 mmol, 2.00 equiv) in THF (1.60 mL) was added *p*-nitrobenzyl bromide (101 mg, 0.47 mmol, 1.50 equiv). The reaction mixture was stirred overnight. Then, the reaction mixture was extracted with EtOAc (3 x 3 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:4 → 1:2 EtOAc:hexanes) on silica gel to afford *N*–4-nitrobenzyl-3,3-dimethyloxindole **3c** (77.5 mg, 84% yield).

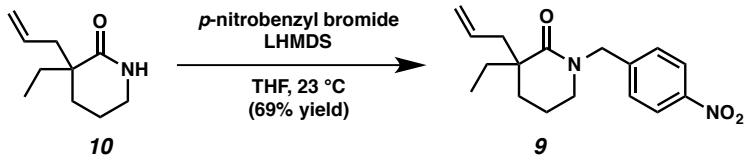
R_f = 0.35 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.43 (d, *J* = 10.0 Hz, 2H), 7.25 (ddd, *J* = 7.3, 1.5, 0.7 Hz, 1H), 7.16 (td, *J* = 7.7, 1.3 Hz, 1H), 7.07 (td, *J* = 7.5, 1.1 Hz, 1H), 6.65 (dt, *J* = 7.7, 0.7 Hz, 1H), 5.01 (s, 2H),

1.45 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.6, 147.6, 143.7, 141.1, 135.8, 128.0, 127.9, 124.2, 123.2, 122.8, 108.7, 77.2, 44.4, 43.1, 24.7; IR (Neat Film NaCl) 2968, 1707, 1613, 1522, 1343, 1173, 1111, 1009, 760; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{17}N_2O_3$ $[M+H]^+$: 297.1234; found: 297.1239.



Benzamide 7. To a solution of benzoic acid **SI-1** (57.0 mg, 0.463 mmol, 1.00 equiv) and propylamine **SI-2**[2] (90.0 mg, 0.463 mmol, 1.00 equiv) in CH_2Cl_2 (2.30 mL) were added EDCI (90.0 mg, 0.579 mmol, 1.25 equiv) and HOBt (78.0 mg, 0.579, 1.25 equiv). The reaction mixture was stirred overnight at 23 °C. Then, the reaction mixture was extracted with CH_2Cl_2 (3 x 3 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:8 → 1:2 EtOAc:hexanes) on silica gel to afford *N*–3-nitrobenzyl-3,3-dimethyloxindole **7** (101 mg, 73% yield).

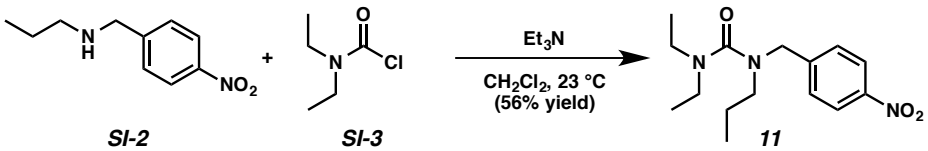
R_f = 0.32 (1:2 EtOAc:hexanes); (Due to the distinct presence of rotameric isomers, the ^{1}H NMR and ^{13}C NMR contained extra peaks. See the attached spectrum); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 10 Hz 2H), 7.53 – 7.35 (m, br, 7H), 4.84 – 4.61 (m, br, 2H), 3.43 – 3.18 (m, br, 2H), 1.68 –1.53 (m, br, 2H), 0.95 – 0.73 (m, br, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.47, 147.44, 145.42, 136.17, 129.84, 128.71, 127.49, 126.61, 124.06, 77.16, 52.29, 50.82, 47.59, 46.85, 21.87, 20.34, 11.07; IR (Neat Film NaCl) 3060, 2963, 2874, 1633, 1519, 1461, 1412, 1344, 1258, 1098, 859, 791, 736; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{19}N_2O_3$ $[M+H]^+$: 299.1390; found: 299.1396.



[2] Hajipour, A. R.; Fontanilla, D.; Chu, U. B.; Arbabian, M.; Ruoho, A. E. *Bioorg. Med. Chem*. **2010**, *18*, 4397–4404.

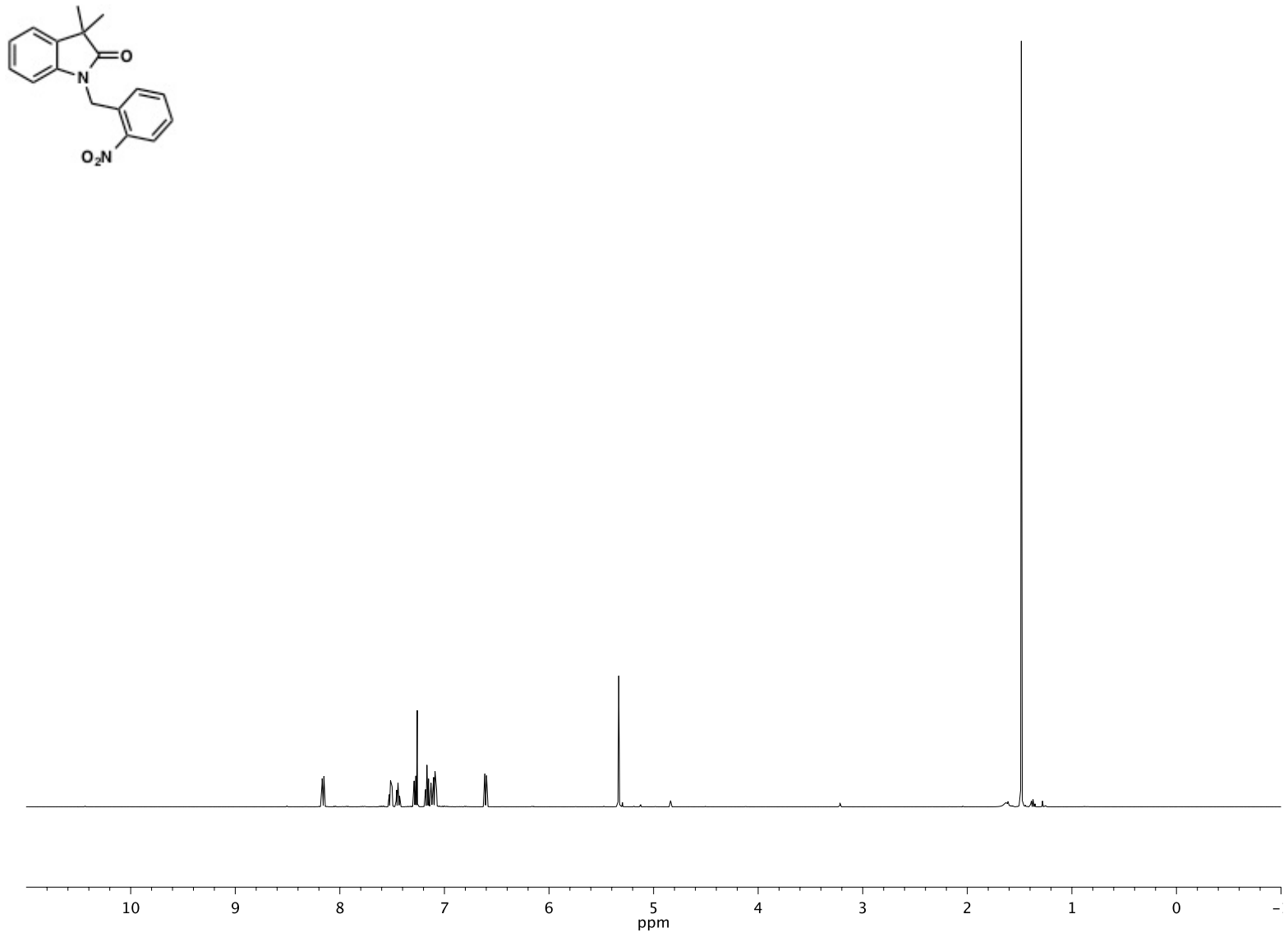
***N*–4-nitrobenzylpiperidin-2-one 9.** To a solution of lactam **10** (34.0 mg, 0.203 mmol, 1.00 equiv) in THF (1.40 mL) was added LHMDS (41.0 mg, 0.244 mmol, 1.20 equiv) at 0 °C. The reaction mixture was stirred for 1 h, and then, *p*-nitrobenzyl bromide (66.0 mg, 0.305 mmol, 1.50 equiv) was added. The reaction mixture was stirred overnight at 23 °C. Then, the reaction mixture was extracted with EtOAc (3 x 3 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:2 EtOAc:hexanes) on silica gel to afford *N*–4-nitrobenzylpiperidin-2-one **9** (42.0 mg, 69% yield).

R_f = 0.25 (1:2 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.7 Hz, 2H), 7.41 (d, *J* = 8.7 Hz, 2H), 5.80 – 5.71 (m, 1H), 5.11 – 5.04 (m, 2H), 4.65 (d, *J* = 3.8 Hz, 2H), 3.22 (td, *J* = 6.1, 1.3 Hz, 2H), 2.54 (ddt, *J* = 13.5, 6.9, 1.3 Hz, 1H), 2.21 (ddt, *J* = 13.4, 8.0, 1.1 Hz, 1H), 1.81 (dddd, *J* = 11.9, 6.8, 2.9, 1.4 Hz, 3H), 1.76 – 1.72 (m, 2H), 1.55 (dq, *J* = 13.5, 7.4 Hz, 1H), 0.88 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 147.4, 145.6, 134.7, 128.7, 124.0, 118.3, 77.2, 50.5, 48.6, 45.5, 43.3, 31.6, 28.9, 19.9, 8.9; IR (Neat Film NaCl) 2939, 1633, 1519, 1344, 1196, 1109; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{17}H_{23}N_2O_3$ $[M+H]^+$: 303.1703; found: 303.1707.

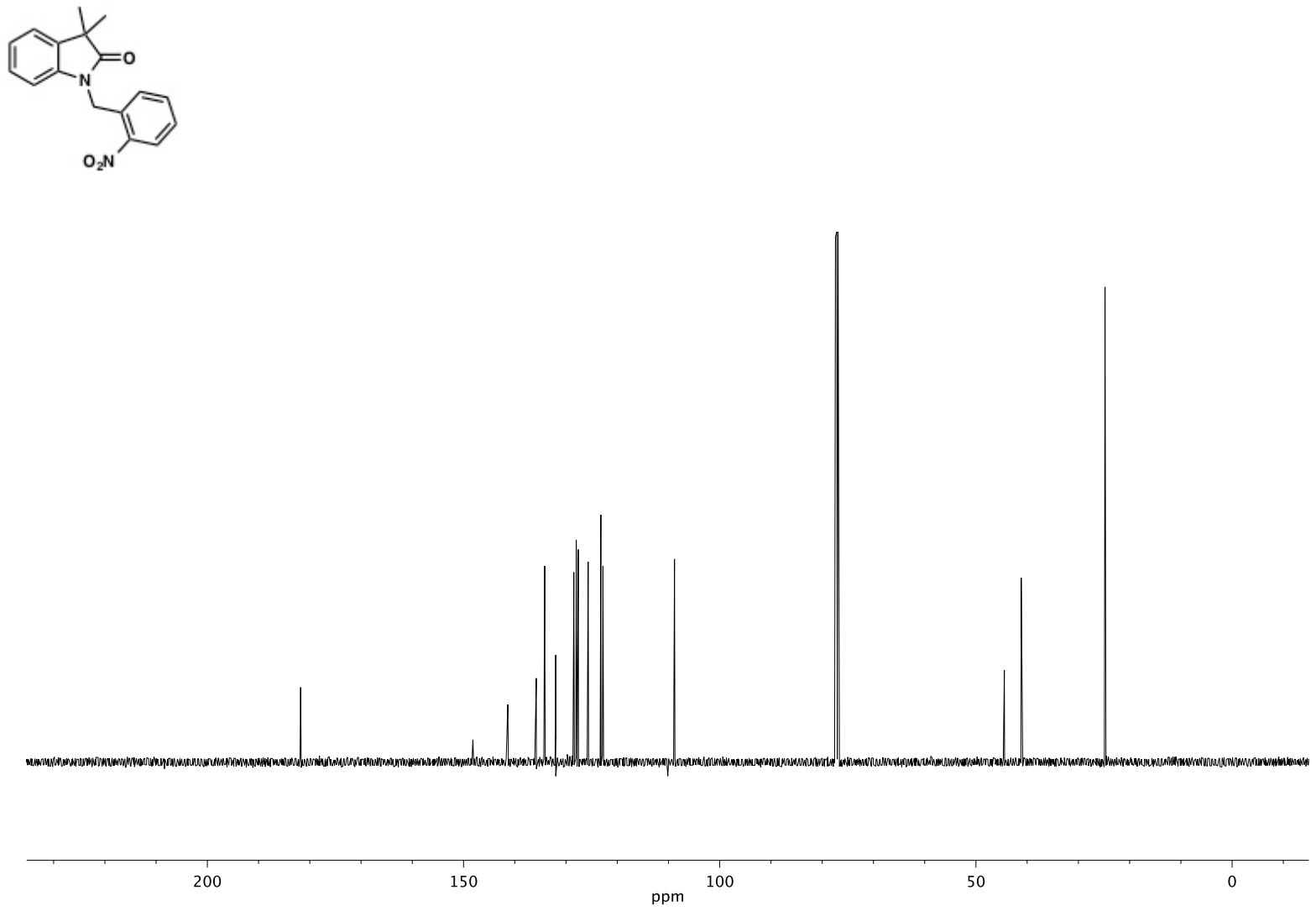


Urea 11. To a solution of propylamine **SI-2**[2] (100 mg, 0.515 mmol, 1.00 equiv) and Et_3N (0.18 mL, 1.29 mmol, 2.50 equiv) in CH_2Cl_2 (2.60 mL) was added diethylcarbamoyl chloride **SI-3** (72.0 μL, 0.566 mmol, 1.10 equiv) at 0 °C. The solution was warmed to 23 °C and stirred overnight. Then, the reaction mixture was extracted with CH_2Cl_2 (3 x 3.5 mL) and washed with brine. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography (1:8 → 1:4 EtOAc:hexanes) on silica gel to afford urea **11** (85 mg, 56% yield).

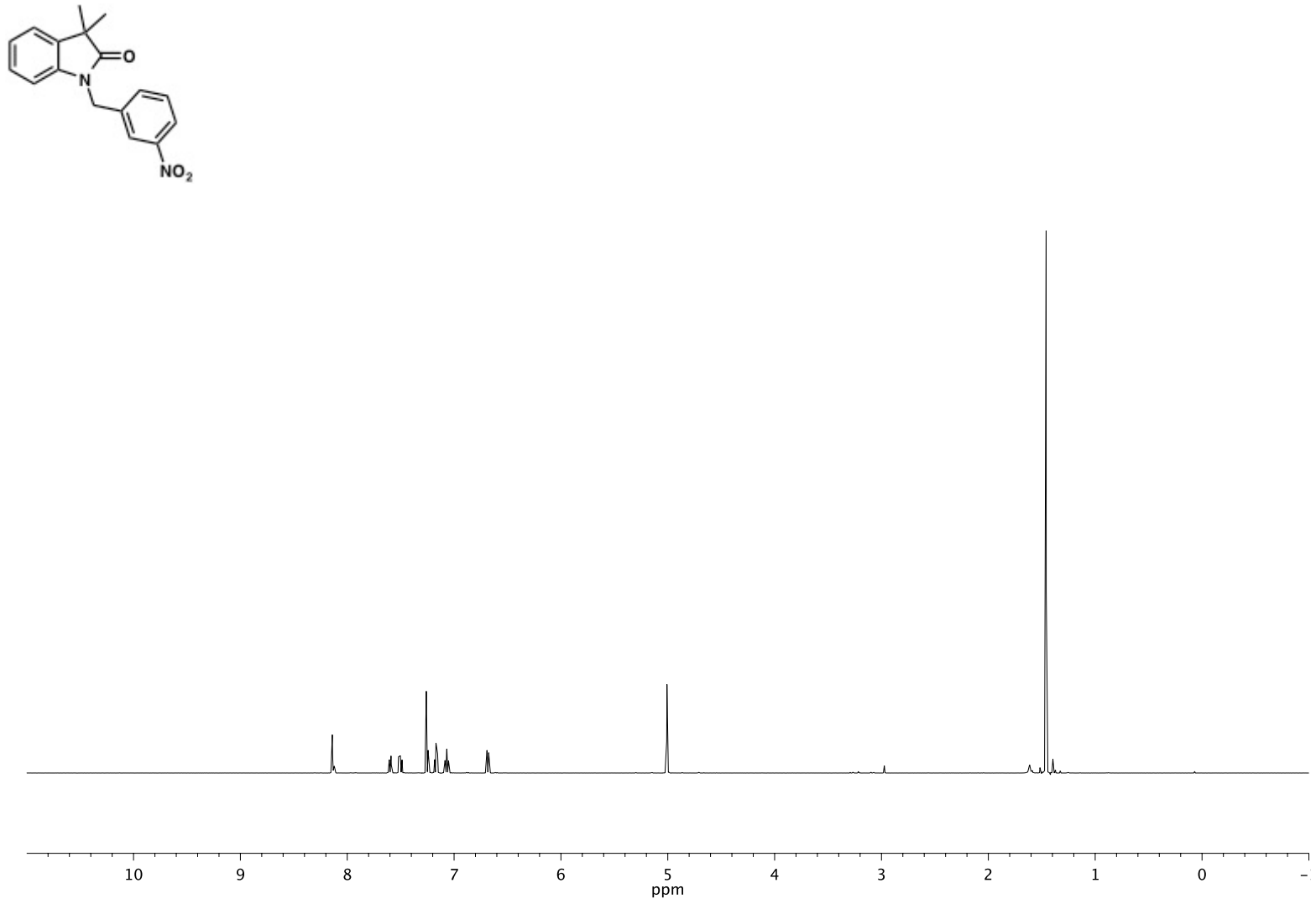
R_f = 0.32 (1:4 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.6 Hz, 2H), 7.42 (d, *J* = 8.6 Hz, 2H), 4.42 (s, 2H), 3.22 (q, *J* = 7.1 Hz, 4H), 3.06 – 3.01 (m, 2H), 1.61 – 1.52 (m, 2H), 1.11 (t, *J* = 7.1 Hz, 6H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 164.9, 147.2, 146.9, 128.4, 123.8, 51.4, 51.2, 42.5, 21.1, 13.4, 11.4; IR (Neat Film NaCl) 2967, 1644, 1520, 1410, 1344, 1251, 1132, 1108; HRMS (MM: ESI-APCI+) *m/z* calc'd for $C_{15}H_{24}N_3O_3$ $[M+H]^+$: 294.1812; found: 294.1863.



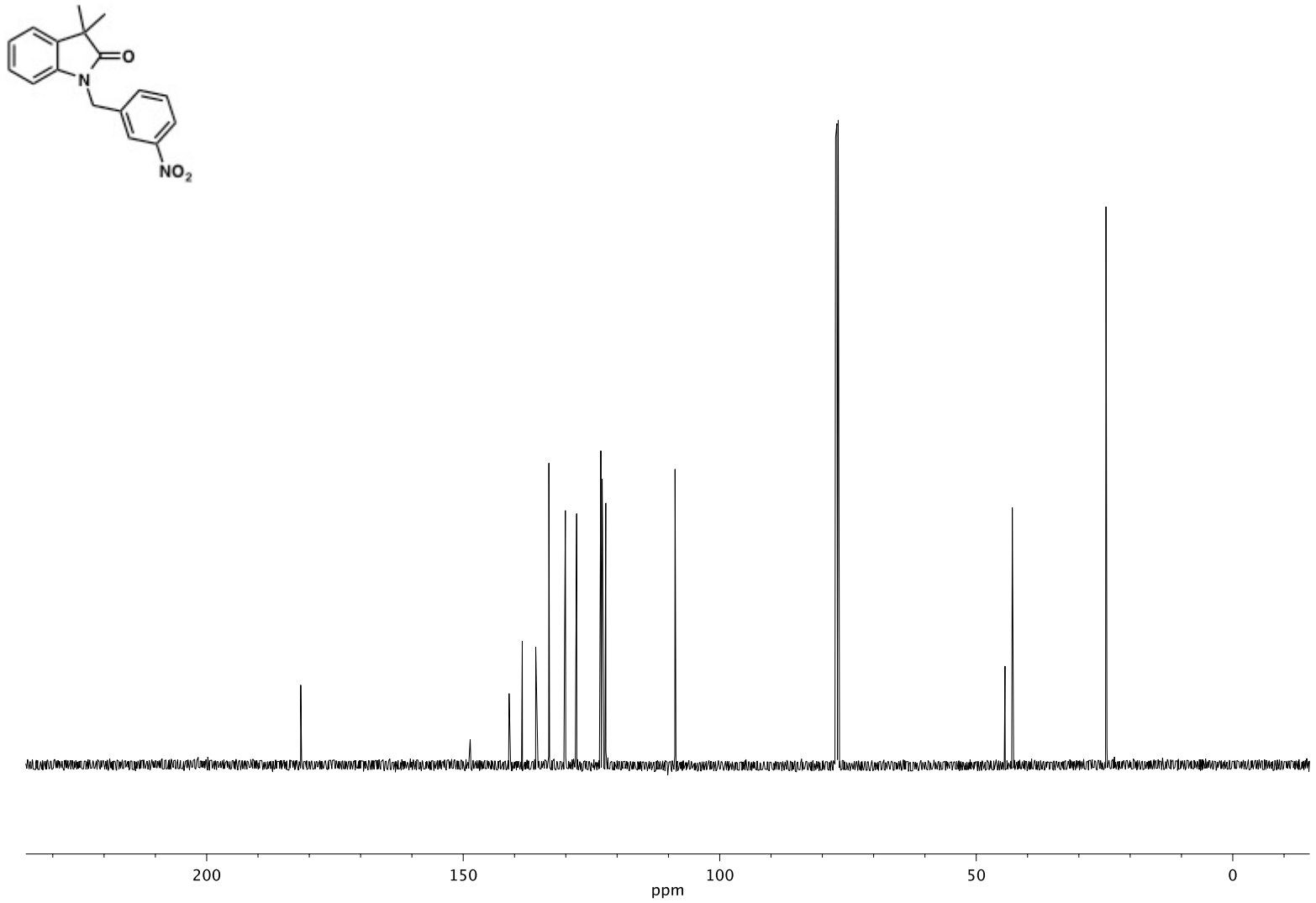
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3a**.



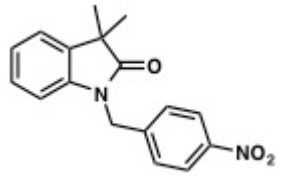
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3a**.

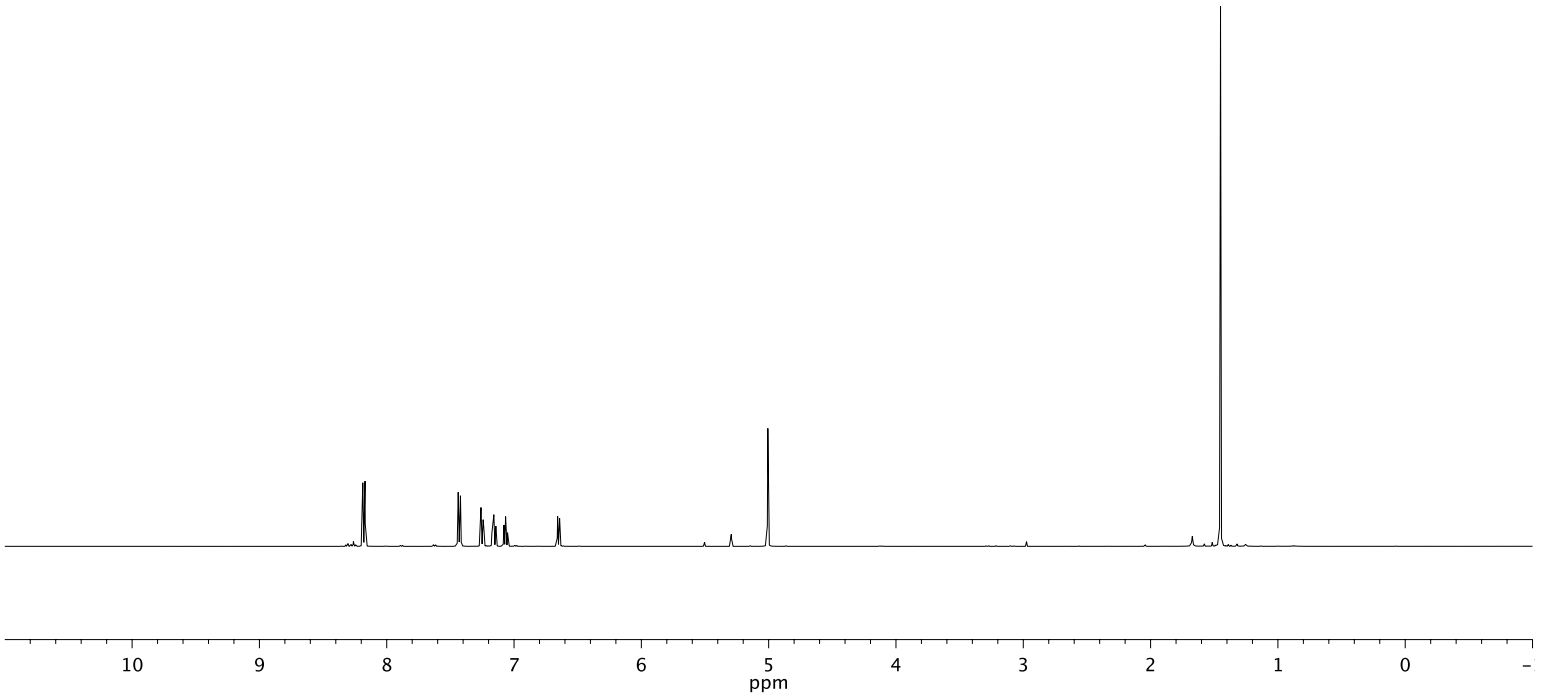


^{1}H NMR (500 MHz, $CDCl_3$) of compound **3b**.

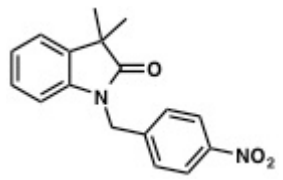


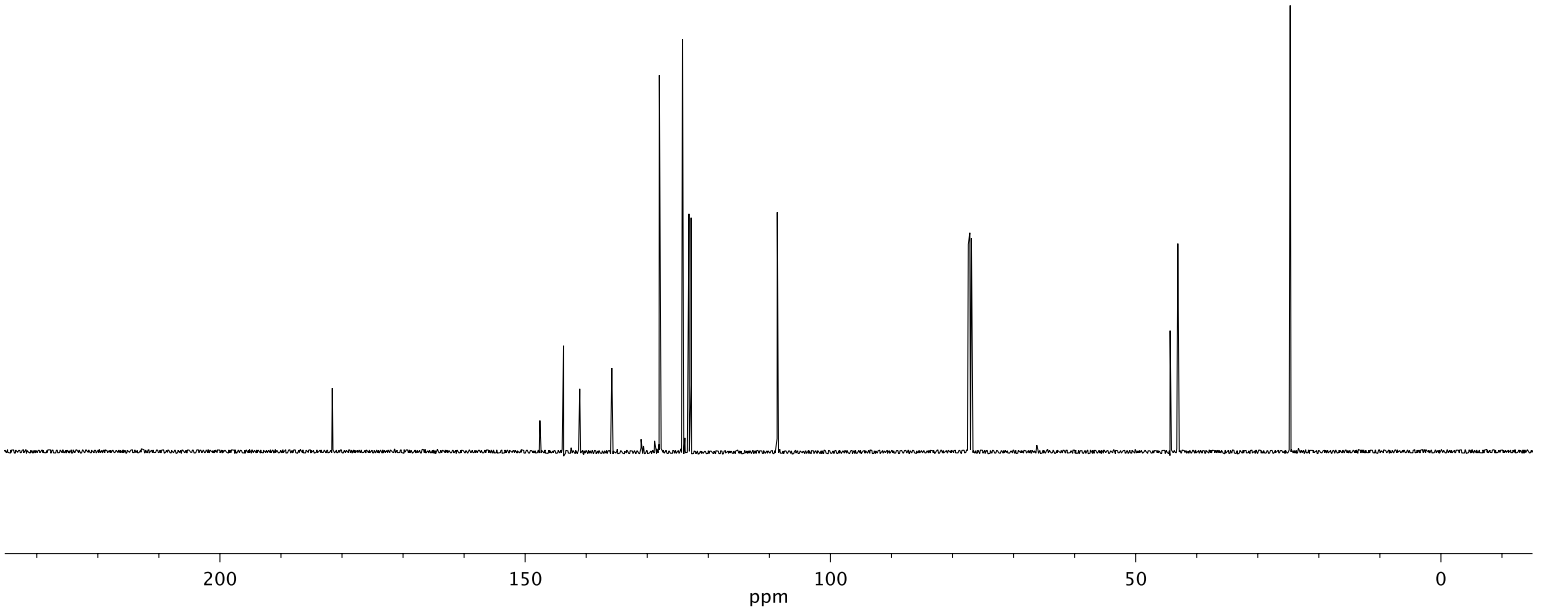
^{13}C NMR (126 MHz, $CDCl_3$) of compound **3b**.



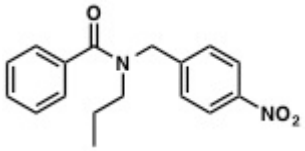


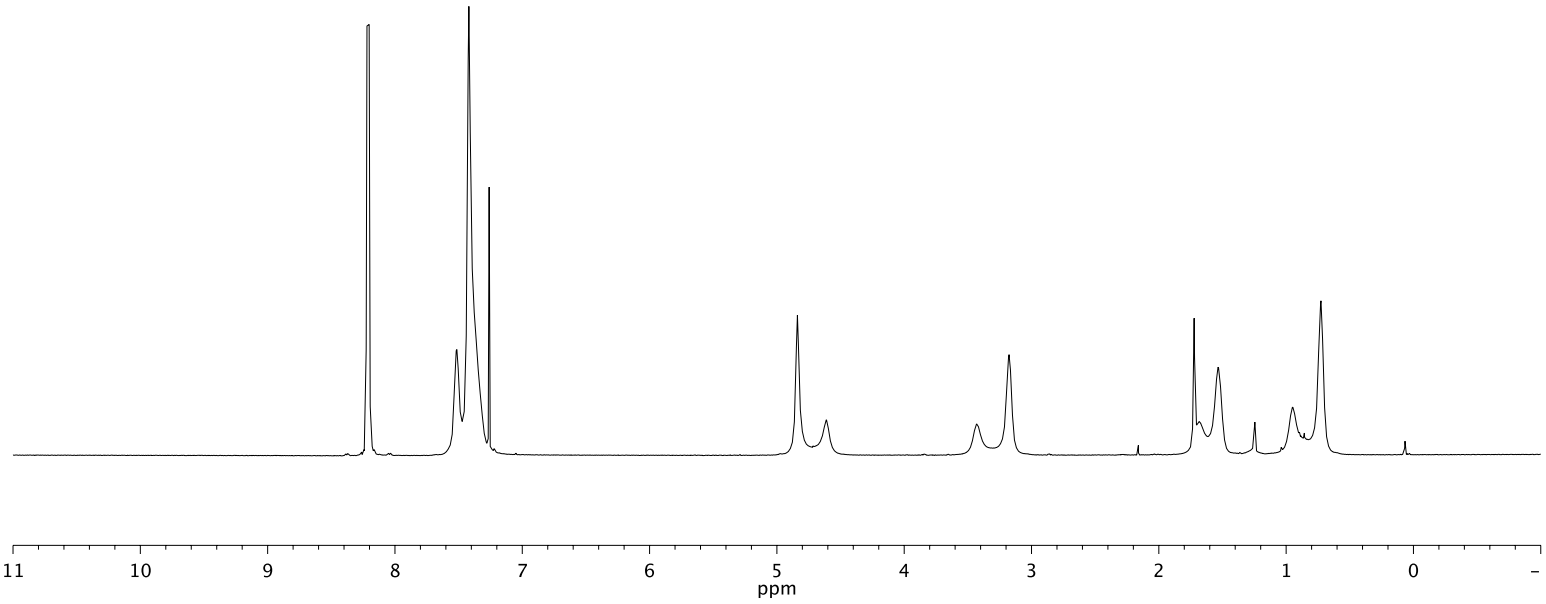
^{1}H NMR (500 MHz, $CDCl_3$) of compound **3c**.



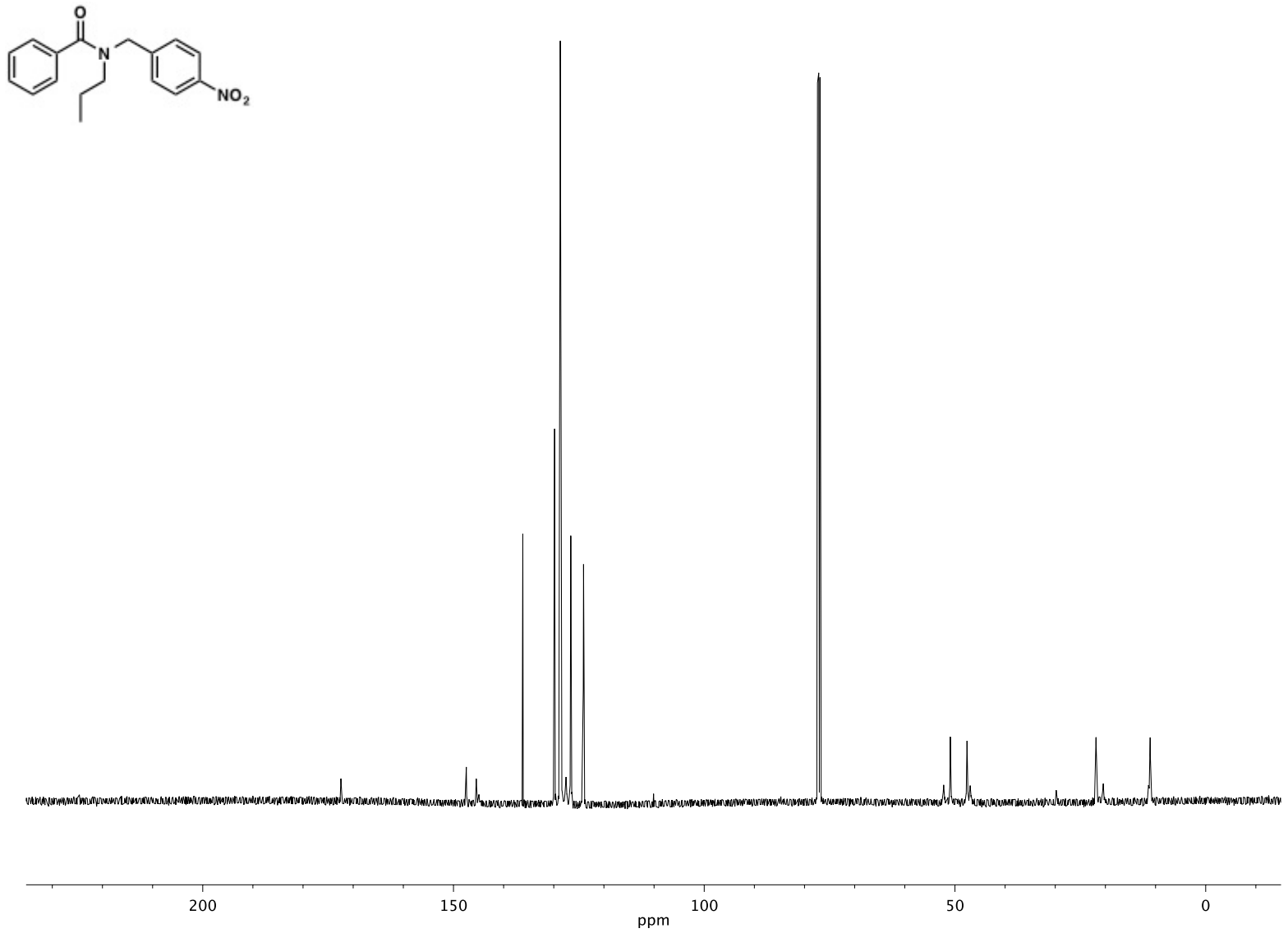


^{13}C NMR (126 MHz, $CDCl_3$) of compound **3c**.

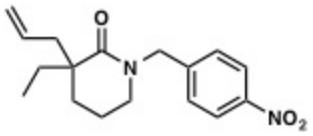


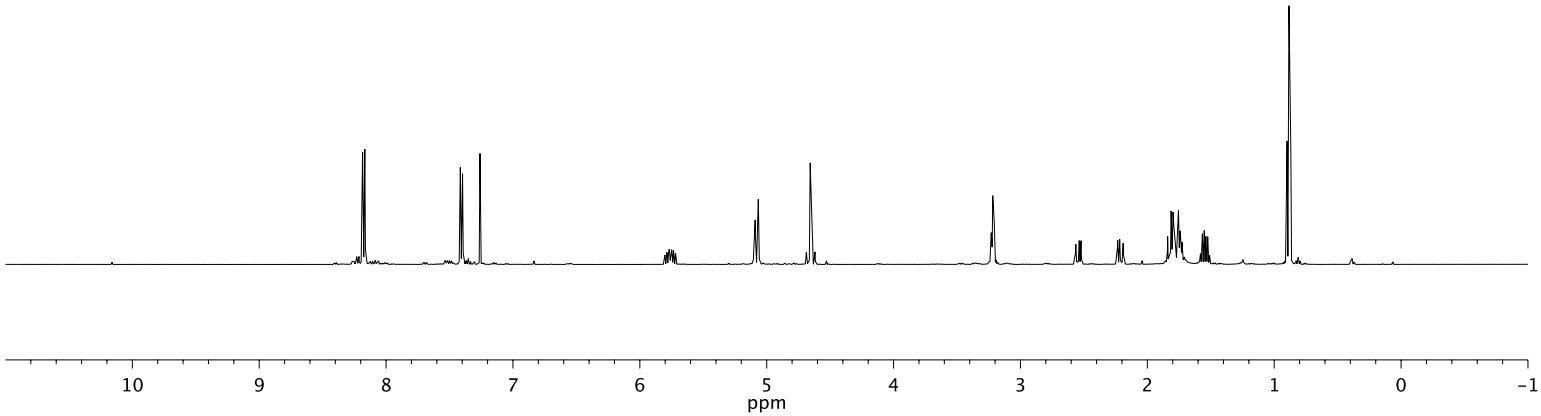


^{1}H NMR (500 MHz, $CDCl_3$) of compound **7**.

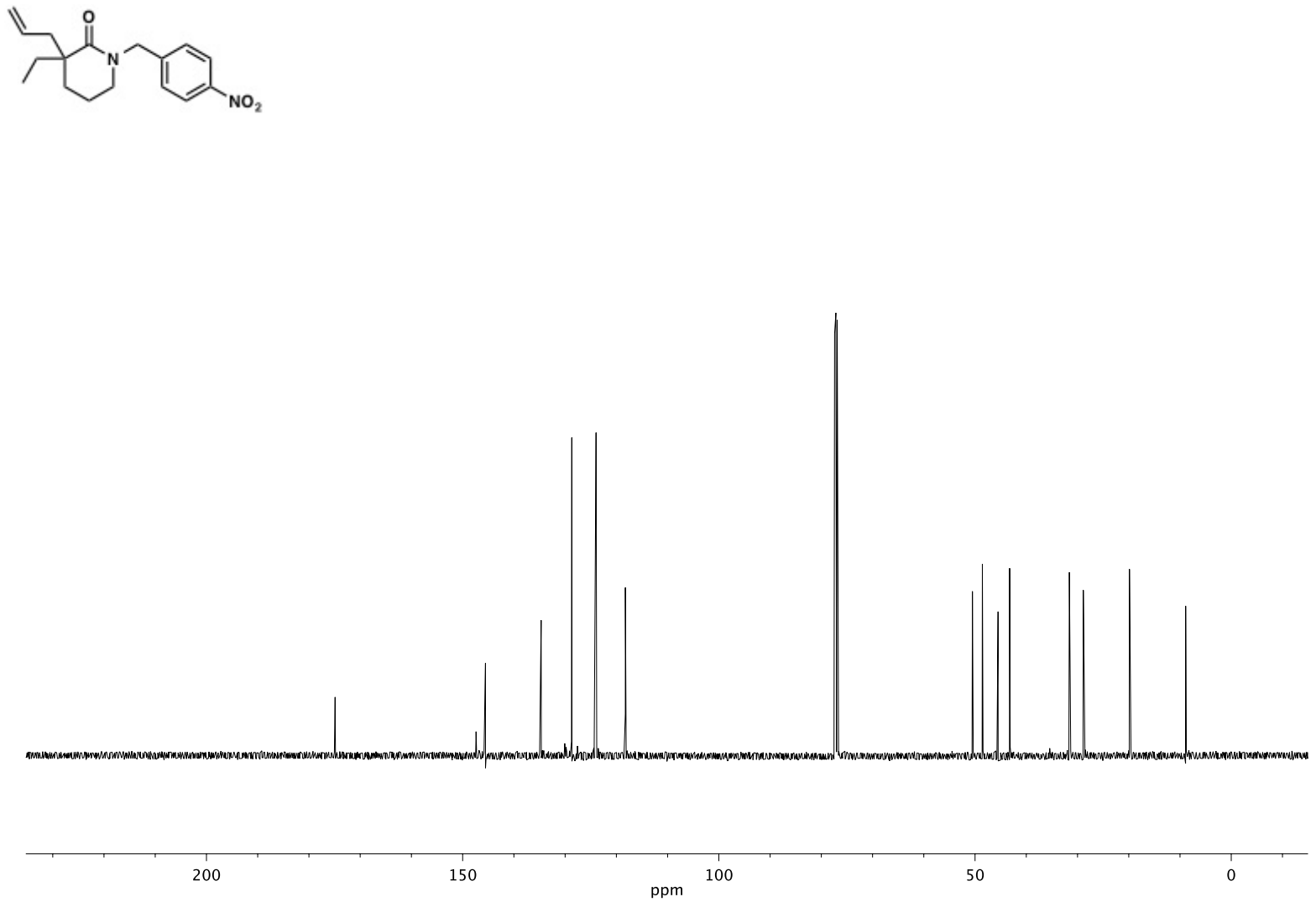


^{13}C NMR (126 MHz, $CDCl_3$) of compound **7**.

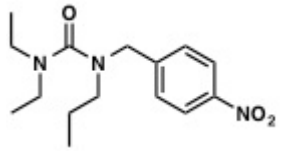


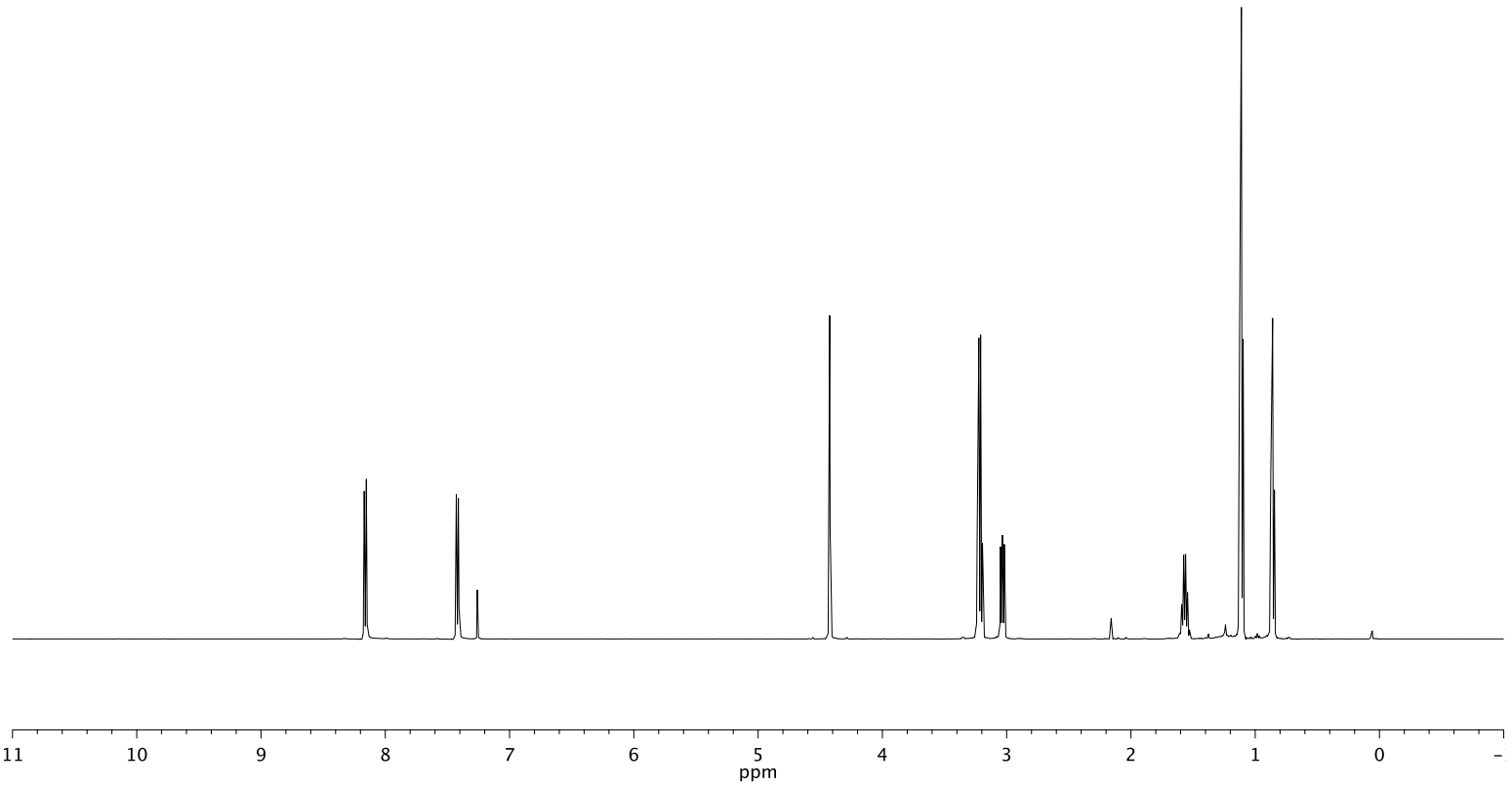


^{1}H NMR (500 MHz, $CDCl_3$) of compound **9**.

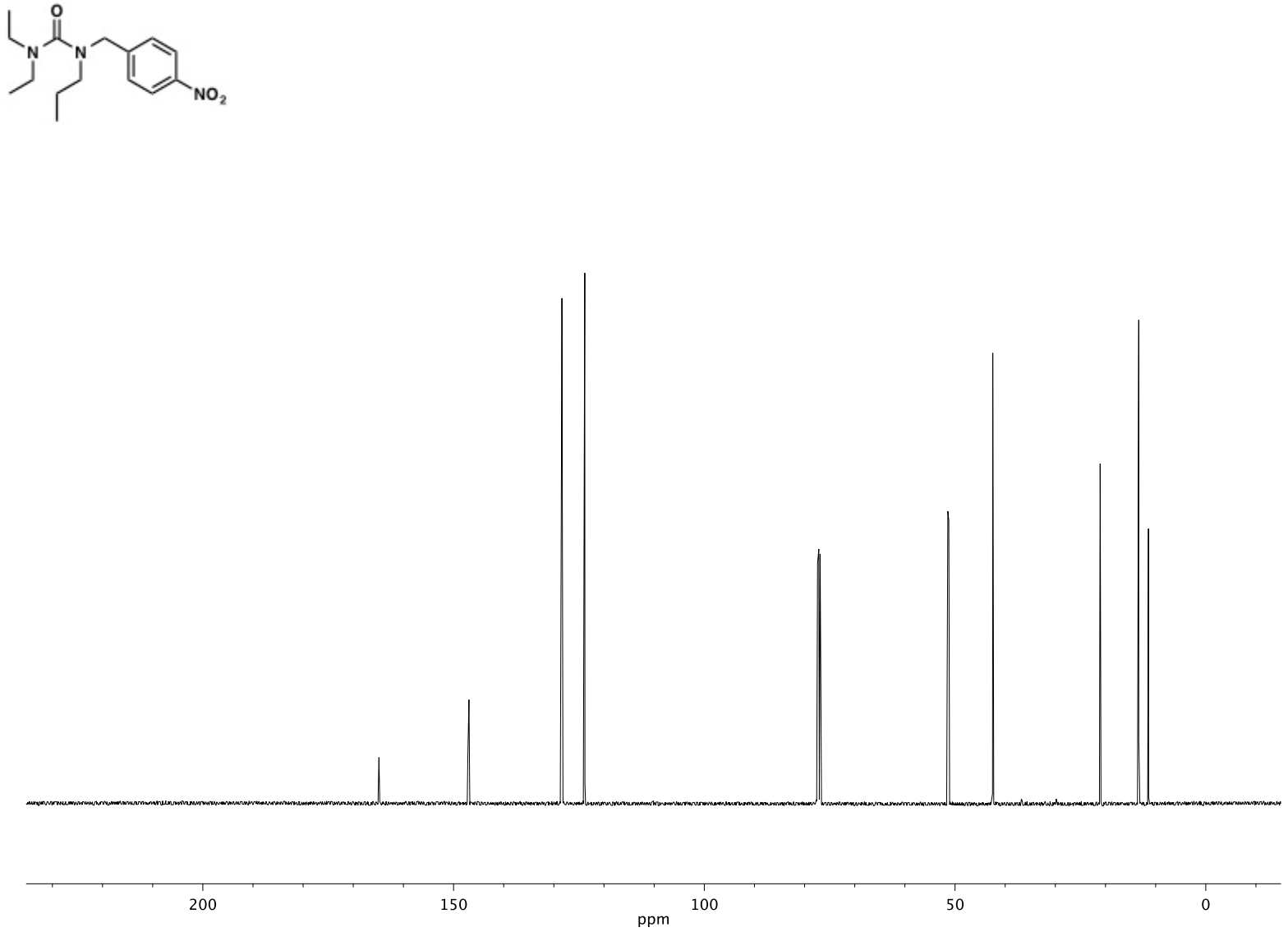


^{13}C NMR (125 MHz, $CDCl_3$) of compound **9**.





^{1}H NMR (500 MHz, $CDCl_3$) of compound **11**.



^{13}C NMR (126 MHz, $CDCl_3$) of compound **11**.