Zinc-Mediated Allylation and Alkylation of Aminals in the Presence of TMSCl and Diisopropylamine

Bunpei Hatano,* Keita Nagahashi, and Tatsuro Kijima

Division of Chemistry, Graduate School of Science and Engineering, Yamagata University, 4-3-16 Jonan, Yonezawa, 992-8510, Japan

hatano@yz.yamagata-u.ac.jp

Supporting Information

Table of Contents

General Methods

All melting points were measured on a capillary point apparatus and are uncorrected. IR spectra were recorded using sodium chloride plates (liquid compounds) or a pressed potassium bromide disc (solid compounds). Frequencies were given in reciprocal centimeters (cm^{-1}) and only selected absorbance was reported. NMR spectra were recorded in chloroform-*d* with TMS for ^{1}H (500 MHz) and ^{13}C (125 MHz) as an internal reference. MS analyses were performed by electron impact ionization method at 70 eV. High-resolution mass spectra were obtained under electron spray ionization conditions. Analytical thin layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel. Visualization on TLC was achieved by use of UV light (254 nm) and treatment with anisaldehyde or molybdatophosphoric acid stain followed by heating. Column chromatography was undertaken on silica gel (63–210

μm). All solvents were freshly distilled under nitrogen atmosphere over an appropriate drying agent before use. Zinc powder was activated according to literature procedure.[1] Chlorotrimethylsilane (TMSCl) was distilled from CaH_2 and stored under nitrogen. Diisopropylamine was distilled from NaOH and stored under nitrogen over molecular sieves 4 Å. Other reagents are of commercial quality. All reactions were carried out under nitrogen atmosphere in well-dried glassware.

Preparation of Aminals 1

Method A (1a–h). To the suspension of aldehyde (30.0 mmol) and dried chromatographic alumina (10 g) in ether (20 mL) was added the secondary amine (75.0 mmol) for three portions at 0 °C. The reaction mixture was stirred at room temperature overnight. The resulting suspension was then filtrated in suction, and the filtered alumina was washed with ether (3×20 mL). The combined ethereal solution was evaporated to give crude **1**. After recrystallization in petroleum ether or Kugelrohr distillation in vacuum conditions, pure aminals (**1a–h**) were obtained in 80–95% yields, respectively.

Method B (1i and 1j).[2] A mixture of benzotriazole (6.0 g, 50 mmol), benzamide (6.1 g, 50 mmol) and the aldehyde (10 mL) was refluxed for 24 h in dry toluene (40 mL). Water formed during the reaction was removed azeotropically by a Dean-Stark apparatus. Toluene and excess aldehyde were then removed under reduced pressure (60 °C/30 mmHg) and the residue was treated with ether (100 mL). The resulting solid was recrystallized from MeOH, giving pure aminals (**1i** and **1j**) in 73% and 75% yields, respectively.

Representative Procedures

Representative procedure for homoallylamines (3). To a suspension of zinc (392 mg, 6.0 mmol) in benzene (10 mL) was added allyl bromide (6.0 mmol) followed by diisopropylamine (1.7 mL, 12 mmol) and **1** (2.0 mmol) at room temperature under nitrogen atmosphere. After cooling in an ice-water bath, chlorotrimethylsilane (761 μL, 6.0 mmol) was added to mixture in one portion. The reaction mixture was stirred for 10 min in an ice bath, and then allowed to warm to room temperature. After stirring for 6 h at room temperature, aqueous NaOH (1N, 30 mL) was added. The mixture was stirred for additional 30 min, during which zinc hydroxide precipitated. The resulting suspension was filtered in suction, and the filtered solid was washed with ether (3×10 mL). The ethereal solution was separated and washed with aqueous

NaOH (1N, 30 mL), water (30 mL), and brine (30 mL). After drying over Na_2SO_4, and subsequent evaporation, the residue was purified using column chromatography on silica gel (30 g; eluent, CH_2Cl_2/MeOH = 100:0, 98:2, 96:4, 94:6, 92:8, 90:10, 100 mL × each). The results are presented in Table 1, Table 2, and Table 3.

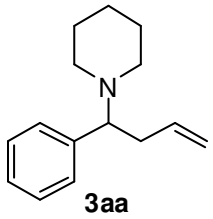
Representative procedure for homoallylamide (3ia and 3ja). The same procedure as that described above was followed except that benzene was replaced by THF, because aminals (**1i** and **1j**) did not dissolve enough in benzene. After stirring 6 h at room temperature, the reaction mixture was poured into a saturated NH_4Cl (30 mL). The mixture was extracted with ether (2×30 mL), and the combined organic extracts was washed with aqueous NaOH (1N, 30 mL), water (30 mL), and brine (30 mL). After drying over Na_2SO_4, and subsequent evaporation, the residue was purified using column chromatography on silica gel (30 g; eluent, haxane/AcOEt = 75:25, 300 mL). The results are presented in Table 2.

Representative procedure for β-amino derivatives (3af, 3ag, and 3ah). The same procedure as that described above was followed except that allyl bromide was replaced by benzyl bromide (713 μL, 6.0 mmol), ethyl α-bromoacetate (662 μL, 6.0 mmol), or α-bromonitrile (400 μL, 6.0 mmol). In the case of ethyl α-bromoacetate, work-up was performed by the addition of saturated $NaHCO_3$ (30 mL) instead of aqueous NaOH to prevent possible de-esterification. The results are presented in Table 3.

Synthesis of butaverine (3ai) using alkylation of 1a with organozinc reagents. To a suspension of zinc (392 mg, 6.0 mmol) in benzene (10 mL) was added *n*-butyl α-bromoacetate[3] (867 μL, 6.0 mmol) followed by diisopropylamine (1.7 mL, 12 mmol) and **1a** (2.0 mmol) at room temperature under nitrogen atmosphere. After cooling in an ice-water bath, chlorotrimethylsilane (761 μL, 6.0 mmol) was added to the mixture in one portion. The reaction mixture was stirred for 10 min in an ice bath and then allowed to warm to room temperature. After stirring for 6 h at room temperature, saturated $NaHCO_3$ (30 mL) was added. The mixture was stirred for additional 30 min. Then the resulting suspension was filtered in suction, and the filtered solid was washed with ether (3×10 mL). The ethereal solution was separated and washed with saturated $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL). After drying over Na_2SO_4, and evaporation, the residue was purified using column chromatography on silica gel (30 g; eluent, CH_2Cl_2/MeOH = 100:0, 98:2, 96:4, 94:6, 92:8, 90:10, 100 mL × each). Pure butaverine was obtained in 74% yield (427 mg, 1.49 mmol).

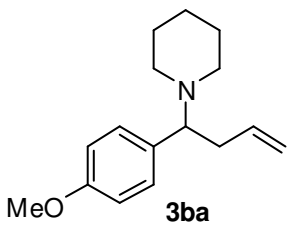
Analytical Data of Compounds 3

4-phenyl-4-piperidino-1-butene (3aa): colorless oil; IR (neat) ν_{max} 2933, 1639, 1446, 1111, 991, 914, 758, 710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.35 (dd, 2H, *J* = 7.3, 7.3 Hz), 7.24 (d, 1H, *J* = 7.3 Hz), 7.21 (d, 2H, *J* = 7.3Hz), 5.67–5.56 (m, 1H), 4.96 (dd, 1H, *J* = 17.0, 3.7 Hz), 4.89 (dd, 1H, *J* = 10.5, 3.7 Hz), 3.39 (dd, 1H, *J* = 9.3, 5.3 Hz), 2.66 (ddd, 1H, *J* = 14.5, 7.0, 5.3 Hz), 2.57 (ddd, 1H, *J* = 14.5, 9.3, 7.5 Hz), 2.36–2.33 (m, 4H), 1.59–1.48 (m, 4H), 1.35 (ddd, 2H, *J* = 15.0, 7.5, 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.8, 136.1, 128.8, 127.8, 126.8, 116.0, 70.2, 51.2, 37.1, 26.3, 24.6; MS (EI) *m/z* (%): 175 (17), 174 ([M–C_3H_5], 100), 91 (56); HRMS (ESI) calcd. for $C_{15}H_{22}N_1$ = 216.1752 $[M+H]^+$, found: 216.1746.



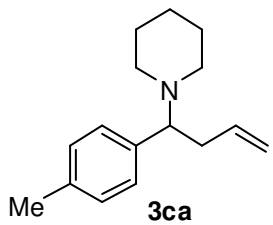
3aa

4-(4-methoxyphenyl)-4-piperidino-1-butene (3ba): light yellow oil; IR (neat) ν_{max} 2931, 1610, 1512, 1243, 1174, 1036, 908, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, 2H, *J* = 8.5 Hz), 6.84 (d, 2H, *J* = 8.5 Hz), 5.66–5.58 (m, 1H), 4.96 (dd, 1H, *J* = 17.0, 4.0 Hz), 4.89 (dd, 1H, *J* = 10.5, 4.0 Hz), 3.79 (s, 3H), 3.36 (dd, 1H, *J* = 9.5, 5.5 Hz), 2.64 (ddd, 1H, *J* = 14.0, 6.6, 5.5 Hz), 2.55 (ddd, 1H, *J* = 14.0, 9.5, 7.6 Hz), 2.35–2.28 (m, 4H), 1.59–1.48 (m, 4H), 1.34 (ddd, 2H, *J* = 12.0, 6.0, 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.4, 136.1, 131.7, 129.7, 115.9, 113.0, 69.5, 55.1, 51.1, 37.2, 26.3, 24.6; MS (EI) m/z (%): 205 (13), 204 ([M–C_3H_5, 100), 121 (23); HRMS (ESI) calcd. for $C_{16}H_{24}N_1O_1$ = 246.1858 [M + H]$^+$, found: 246.1846.



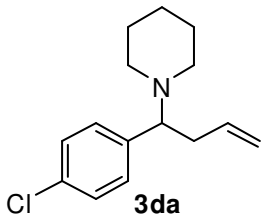
3ba

4-(4-methylphenyl)-4-piperidino-1-butene (3ca): light yellow oil; IR (neat) ν_{max} 2931, 1639, 1512, 1443, 1111, 991, 906, 825 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.12 (d, 2H, *J* = 8.5 Hz), 7.09 (d, 2H, *J* = 8.5 Hz), 5.67–5.58 (m, 1H), 4.97 (dd, 1H, *J* = 15.0, 2.0 Hz), 4.89 (dd, 1H, *J* = 9.5, 2.0 Hz), 3.37 (dd, 1H, *J* = 9.3, 5.4 Hz), 2.64 (ddd, 1H, *J* = 15.0, 7.9, 5.4 Hz), 2.57 (ddd, 1H, *J* = 15.0, 9.3, 7.5 Hz), 2.37 - 2.33 (m, 4H), 2.33 (s, 3H), 1.56–1.48 (m, 4H), 1.33 (ddd, 2H, *J* = 12.0, 6.0, 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.5, 136.3, 136.3, 128.7, 128.5, 115.9, 69.9, 51.1, 37.1, 26.3, 24.5, 21.1; MS (EI) *m/z* (%) 189 (16), 188 ([M–C_3H_5], 100), 105 (42); HRMS (ESI) calcd. for $C_{16}H_{24}N_1$ = 230.1909 $[M+H]^+$, found: 230.1905.



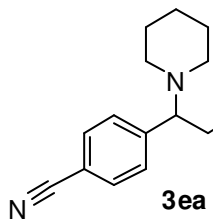
3ca

4-(4-chlorophenyl)-4-piperidino-1-butene (3da): colorless oil; IR (neat) ν_{max} 2933, 1639, 1492, 1093, 914, 837, cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, 2H, *J* = 8.5 Hz), 7.16 (d, 2H, *J* = 8.5 Hz), 5.63–5.55 (m, 1H), 4.94 (dd, 1H, *J* = 17.0, 3.5 Hz), 4.90 (dd, 1H, *J* = 10.3 Hz, 3.5 Hz), 3.36 (dd, 1H, *J* = 9.0, 5.0 Hz), 2.63 (ddd, 1H, *J* = 14.0, 6.6, 5.0 Hz), 2.51 (ddd, 1H, *J* = 14.0, 9.0, 7.6 Hz), 2.37–2.27 (m, 4H), 1.55–1.49 (m, 4H), 1.35 (ddd, 2H, *J* = 12.0, 6.0, 6.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 138.6, 135.6, 132.4, 130.0, 128.0, 116.4, 69.5, 51.2, 37.1, 26.3, 24.6; MS (EI) *m/z* (%): 210 ([M–C_3H_5], 31), 209 (12), 208 ([M–C_3H_5], 100), 127 (15), 125 (37), 69 (11); HRMS (ESI) calcd. for $C_{15}H_{21}Cl_1N_1$ = 250.1363 $[M+H]^+$, found 250.1363.



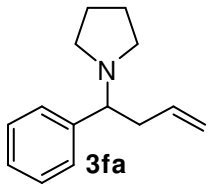
3da

4-(4-cyanophenyl)-4-piperidino-1-butene (3ea): light yellow oil; IR (neat) ν_{max} 2933, 2227, 1606, 1441, 1111, 991, 914, 841 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, 2H, *J* = 8.5 Hz), 7.35 (d, 2H, *J* = 8.5 Hz), 5.61–5.53 (m, 1H), 4.92 (dd, 1H, J 17.0, 1.2 Hz), 4.92 (dd, 1H, *J* = 10.0, 1.2 Hz), 3.42 (dd, 1H, *J* = 8.8, 5.3 Hz), 2.64 (ddd, 1H, *J* = 14.0, 7.0, 5.3 Hz), 2.51 (ddd, 1H, *J* = 14.0, 8.8, 7.8 Hz), 2.36–2.32 (m, 4H), 1.54–1.51 (m, 4H), 1.37 (ddd, 2H, *J* = 11.4, 5.8, 5.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.5, 134.9, 131.7, 129.3, 119.0, 117.0, 110.6, 69.9, 51.4, 36.9, 26.2, 24.5; MS (EI) *m/z* (%): 200 (13), 199 ([M–C_3H_5], 100), 116 (31), 69 (11), 55 (11); HRMS (ESI) calcd. for $C_{16}H_{21}N_2$ = 241.1705 $[M+H]^+$, found 241.1694.



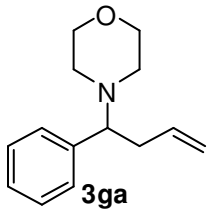
3ea

4-phenyl-4-pyrrolidino-1-butene (3fa): light yellow oil; IR (neat) ν_{max} 2966, 2780, 1641, 1491, 1456, 1136, 995, 914, 760, 701 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29–7.27 (m, 4H), 7.24–7.21 (m, 1H), 5.57–5.49 (m, 1H), 4.92 (dd, 1H, *J* = 17.0, 3.4 Hz), 4.88 (dd, 1H, *J* = 10.2, 3.4 Hz), 3.15 (dd, 1H, *J* = 9.5, 4.3 Hz), 2.67 (ddd, 1H, *J* = 13.0, 6.4, 4.3 Hz) 2.57–2.50 (m, 3H), 2.40–2.36 (m, 2H), 1.74–1.63 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.6, 135.4, 128.2, 128.0, 126.9, 116.3, 70.9, 52.6, 40.6, 23.2; MS (EI) *m/z* (%): 161 (12), 160 ([M–C_3H_5], 100), 91 (43); HRMS (ESI) calcd. for $C_{14}H_{20}N_1$ = 202.1596 $[M+H]^+$, found 202.1602.



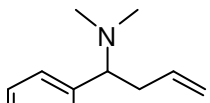
3fa

4-morpholyl-4-phenyl-1-butene (3ga): colorless oil; IR (neat) ν_{max} 2958, 2852, 1452, 1118, 1004, 914, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, 2H, *J* = 6.1 Hz), 7.29–7.24 (m, 3H), 5.63–5.55 (m, 1H), 4.95 (dd, 1H, *J* = 17.0, 3.3Hz), 4.91 (dd, 1H, *J* = 10.0, 3.3 Hz), 3.67 (dd, 4H, *J* = 4.8, 4.8 Hz), 3.30 (dd, 1H, *J* = 9.0, 5.1 Hz), 2.65 (ddd, 1H, *J* = 14.0, 6.6, 5.1 Hz) 2.53–2.42 (m, 3H), 2.41–2.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.1, 135.4, 128.6, 128.0, 127.1, 116.5, 70.2, 67.2, 51.1, 37.1; MS (EI) *m/z* (%) 177 (12), 176 ([M–C_3H_5], 100), 105 (21), 91 (34); HRMS (ESI) calcd. for $C_{14}H_{20}N_1O_1$ = 218.1545 $[M+H]^+$, found 218.1547.



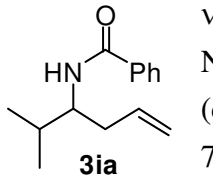
3ga

4-dimethylamino-4-phenyl-1-butene (3ha): (Reg. No. = 20599-34-2); colorless oil; ^1H NMR (500 MHz, $CDCl_3$): δ 7.30–7.27 (m, 2H), 7.23–7.18 (m, 3H), 5.61–5.53 (m, 1H), 4.95 (dd, 1H, *J* = 17.0, 3.0 Hz), 4.89 (dd, 1H, *J* = 8.0, 3.0 Hz), 3.23 (dd, 1H, *J* = 9.0, 5.5 Hz), 2.62 (ddd, 1H, *J* = 14.0, 7.0, 7.0 Hz), 2.45 (ddd, 1H, *J* = 14.0, 7.0, 7.0 Hz), 2.16 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.0, 135.7, 128.6, 127.9, 127.0, 116.4, 70.5, 42.7, 37.8; ; MS (EI) *m/z* (%): 135 (10), 134 ([M–C_3H_5], 100), 91 (22), 42 (37); HRMS (ESI) calcd. for $C_{12}H_{18}N_1$ = 176.1439 $[M+H]^+$, found 176.1439.



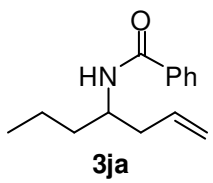
3ha

4-benzoylamino-5-methyl-1-hexene (3ia): white solid; mp 109.0–110.2 °C; IR (KBr) ν_{max} 3322, 3069, 2964, 1636, 1546, 1322, 1289, 1152, 914, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.75–7.73 (m, 2H), 7.50–7.47 (m, 1H), 7.42 (dd, 2H, *J* = 7.5, 7.5 Hz), 5.91 (br, 1H), 5.83 (dddd, 1H, *J* = 17.2, 10.2, 7.1, 7.1 Hz), 5.10 (dd, 1H, *J* = 17.2, 1.6 Hz), 5.07 (dd, 1H, *J* = 10.2, 1.6 Hz), 4.09 (ddd, 1H, *J* = 7.8, 6.1, 5.0 Hz), 2.40 (ddd, 1H, *J* = 12.8, 7.1, 5.0 Hz), 2.26 (ddd, 1H, *J* = 12.8, 7.8, 7.1 Hz), 1.92–1.83 (m, 1H), 0.99 (d, 3H, *J* = 6.8 Hz), 0.97 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.2, 135.1, 134.8, 131.3, 128.5, 126.7, 117.6, 53.9, 36.6, 31.5, 19.3, 18.2; MS (EI) *m/z* (%): 176 ([M–C_3H_5], 17), 105 (100), 77 (35), 51 (10); HRMS (ESI) calcd. for $C_{14}H_{20}N_1O_1$ = 218.1545 $[M+H]^+$, found 218.1549.



3ia

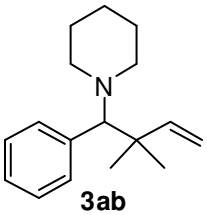
4-benzoylamino-1-heptene (3ja): white solid; mp 87.8–88.6 °C; IR (KBr) ν_{max} 3313, 3067, 2954, 2866, 1635, 1534, 1311, 1152, 991, 913, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.75–7.73 (m, 2H), 7.51–7.47 (m, 1H), 7.44–7.41 (m, 2H), 5.90 (br, 1H), 5.84 (dddd, 1H, *J* = 17.5, 10.3, 7.2, 7.2 Hz), 5.12 (dd, 1H, *J* = 17.5, 1.4 Hz), 5.11 (dd, 1H, *J* = 10.3, 1.4



3ja

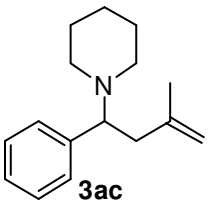
Hz), 4.24 (dddd, 1H, *J* = 6.0, 6.0, 6.0, 6.0 Hz), 2.39 (ddd, 1H, *J* = 14.0, 7.2, 6.0 Hz), 2.30 (ddd, 1H, *J* = 14.0, 7.2, 6.0 Hz), 1.62–1.55 (m, 1H), 1.54–1.46 (m, 1H), 1.46–1.39 (m, 1H), 0.94 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 167.0, 135.0, 134.4, 131.2, 128.5, 126.7, 117.9, 48.7, 39.2, 36.6, 19.3, 14.0; MS (EI) *m/z* (%): 176 ([M–C_3H_5], 17), 105 (100), 77 (37), 51 (10); HRMS (ESI) calcd. for $C_{14}H_{20}N_1O_1$ = 218.1545 $[M+H]^+$, found 218.1547.

3,3-dimethyl-4-phenyl-4-piperidino-1-butene (3ab): colorless oil; IR (neat) ν_{max} 2931, 1641, 1448, 1365, 1248, 1153, 1093, 997, 912, 752, 702 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27–7.19 (m, 5H), 6.24 (dd, 1H, *J* = 17.7 10.8 Hz), 5.03 (dd, 1H, *J* = 17.7, 2.0 Hz), 5.00 (dd, 1H, *J* = 10.8, 2.0 Hz), 3.22 (s, 1H), 2.57 - 2.54 (m, 2H), 2.14–2.06 (m, 2H), 1.54–1.48 (m, 4H), 1.28–1.26 (m, 2H), 1.18 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.0, 138.4, 130.3, 127.2, 126.4, 110.9, 80.1, 41.8, 28.7, 26.9, 24.9, 24.5; MS (EI) *m/z* (%):175 (14), 174 ([M–C_5H_9], 100), 91 (37); HRMS (ESI) calcd. for $C_{17}H_{26}N_1$ = 244.2065 $[M+H]^+$, found 244.2057.



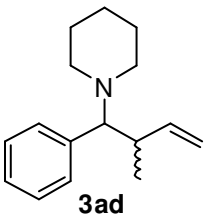
3ab

2-methyl-4-phenyl-4-piperidino-1-butene (3ac): light yellow oil; IR (neat) ν_{max} 2933, 1649, 1450, 1112, 983, 885, 703 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 (dd, 2H, *J* = 7.3, 7.3 Hz), 7.23 (d, 1H, *J* = 7.3Hz), 7.19 (d, 2H, *J* = 7.3Hz), 4.62 (s, 1H), 4.56 (s, 1H), 3.59 (dd, 1H, *J* = 9.6, 5.5 Hz), 2.67 (dd, 1H, *J* = 14.0, 5.5 Hz), 2.54 (dd, 1H, *J* = 14.0, 9.6 Hz), 2.38–2.33 (m, 4H), 1.63 (s, 3H), 1.58–1.48 (m, 4H), 1.32 (ddd, 2H, *J* = 12.0, 6.0, 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.3, 139.1, 128.8, 127.6, 126.8, 112.3, 68.6, 51.0, 40.7, 26.4, 24.6, 22.7; MS (EI) *m/z* (%): 175 (14), 174 ([M–C_4H_7], 100), 91 (38); HRMS (ESI) calcd. for $C_{16}H_{24}N_1$ = 230.1909 $[M+H]^+$, found 230.1900.



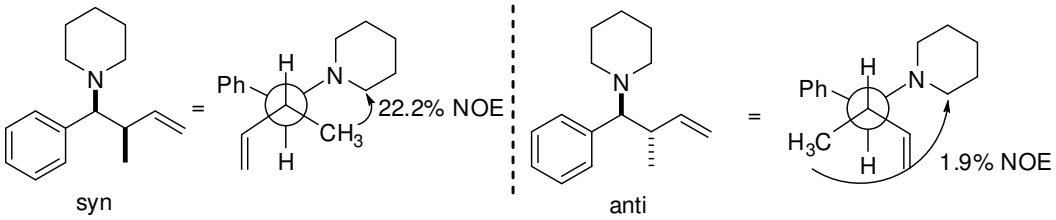
3ac

3-methyl-4-phenyl-4-piperidino-1-butene (3ad) (mixture, *syn : anti = 61 : 39*): colorless oil; IR (neat) ν_{max} 2931, 1741, 1641, 1448, 1373, 1097, 997, 908, 701 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.19 (m, 3H), 7.14–7.10 (m, 2H), 5.94–5.87 (m, 0.39H, *anti*), 5.67–5.60 (m, 0.61H, *syn*), 5.03–5.02 (m, 0.39H, *anti*), 5.00 (ddd, 0.39H, *J* = 11.0, 2.7, 1.6 Hz, *anti*), 4.86 (dd, 0.61 H, *J* = 17.0, 1.6 Hz, *syn*), 4.82 (dd, 0.61H, *J* = 10.5, 1.6 Hz, *syn*), 3.17 (d, 0.39H, *J* = 9.6 Hz, *anti*), 3.12 (d, 0.61H, *J* = 9.6 Hz, *syn*), 2.93–2.81 (m, 1H), 2.37–2.31 (m, 2H), 2.26–2.19 (m, 2H), 1.55–1.44 (m, 4H), 1.31–1.27 (m, 2H), 1.09 (d, 1.83H, *J* = 6.7 Hz, *syn*), 0.61 (d, 1.17H, *J* = 6.7 Hz, *anti*);

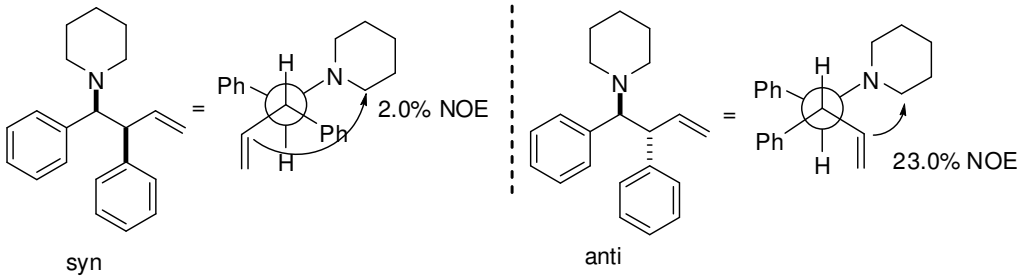


3ad

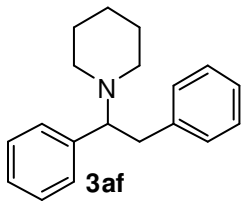
^{13}C NMR (125 MHz, $CDCl_3$): δ 145.5, 141.8, 137.6 137.5, 129.4, 129.2, 127.5, 127.3, 126.7, 126.6, 114.8, 112.4, 75.4, 75.1, 50.9, 50.6, 38.2, 37.7, 26.5, 26.4, 24.8, 24.7, 17.8, 17.2 : MS (EI) *m/z* (%): 175 (14), 174 ([M–C_4H_7], 100), 91 (42); HRMS (ESI) calcd. for $C_{16}H_{24}N_1$ = 230.1909 $[M+H]^+$, found 230.1901.



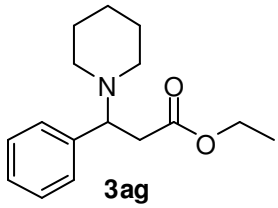
3,4-diphenyl-4-piperidino-1-butene (3ae) (mixture, *syn : anti = 45 : 55*): light yellow oil; IR (neat) ν_{max} 2931, 1738, 1452, 1238, 1101, 989, 912, 744, 700 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–6.96 (m, 10H), 6.42–6.35 (m, 0.45H, *syn*), 5.86–5.79 (m, 0.55H, *anti*), 5.06 (dd, 0.45H, *J* = 10.2, 1.8 Hz, *syn*), 4.95 (dd, 0.45H, *J* = 17.0, 1.8 Hz, *syn*), 4.87 (dd, 0.55H, *J* = 10.2, 1.8 Hz, *anti*), 4.83 (dd, 0.55H, *J* = 17.0, 1.8 Hz, *anti*), 4.06–3.98 (m, 1H), 3.87 (d, 0.45H, *J* = 11.5 Hz, *syn*), 3.73 (d, 0.55H, *J* = 11.5 Hz, *anti*), 2.60–2.45 (m, 0.90H, *syn*), 2.39–2.36 (m, 1.10H, *anti*), 2.27–2.21 (m, 0.90H, *syn*), 2.17–2.16 (m, 1.10H, *anti*), 1.59–1.55 (m, 0.90H, *syn*), 1.51–1.47 (m, 1.10H, *anti*), 1.31–1.26 (m, 1.80H, *syn*), 1.22–1.15 (m, 2.20H, *anti*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 142.5, 141.7, 139.7, 136.8, 135.8, 129.3, 129.2, 128.5, 128.4, 128.0, 127.8, 127.5, 127.2, 126.8, 126.5, 125.8, 125,8, 116.1, 114.1, 74.0, 73.9, 51.0, 51.0, 26.5, 26.2, 24.7, 24.6; MS (EI) *m/z* (%): 175 (12), 174 ([M–C_9H_9], 100), 91 (41); HRMS (ESI) calcd. for $C_{21}H_{26}N_1$ = 292.2065 $[M+H]^+$, found 292.2054.



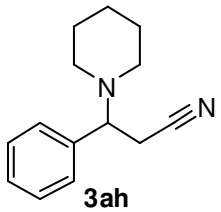
1,2-diphenyl-1-piperidinoethane (3af): (Reg. No. = 36794-52-2 or 127529-18-4 or 127529-17-3); light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25–7. 21 (m, 2H), 7.18 (dd, 1H, J = 7.0, 7.0 Hz), 7.14–7.11 (m, 4H), 7.07 (dd, 1H, *J* = 7.3, 7.3 Hz), 6.99 (d, 2H, *J* = 7.5 Hz), 3.58 (dd, 1H, *J* = 9.5, 5.5 Hz), 3.30 (dd, 1H, *J* = 13.5, 5.5 Hz), 2.99 (dd, 1H, *J* = 13.5, 9.5 Hz), 2.48–2.34 (m, 4H), 1.60–1.53 (m, 4H), 1.36 (ddd, 2H, *J* = 12.0, 6.0, 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 139.4, 129.3, 128.9, 127.8, 127.6, 126.8, 125.6, 72.3, 51.4, 39.2, 26.4, 24.6; MS (EI) *m/z* (%): 175 (12), 174 ([M–C_7H_7], 100), 91 (32); HRMS (ESI) calcd. for $C_{19}H_{24}N_1$ = 266.1909 $[M+H]^+$, found 266.1899



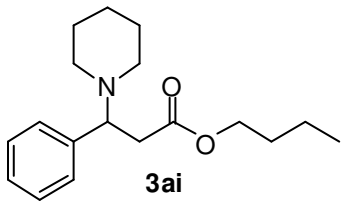
ethyl 3-phenyl-3-piperidinopropanoate (3ag): (120173-16-2); light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (dd, 2H, *J* = 7.5, 6.7 Hz), 7.25 (d, 1H, *J* = 6.7 Hz), 7.23 (d, 2H, *J* = 7.5 Hz), 4.05 (q, 2H, *J* = 7.1 Hz), 3.98 (dd, 1H, *J* = 7.7, 7.7 Hz), 3.00 (dd, 1H, *J* = 14.6, 7.7 Hz), 2.68 (dd, 1H, *J* = 14.6, 7.7 Hz), 2.46–2.35 (m, 2H), 2.34–2.29 (m, 2H), 1.57–1.45 (m, 4H), 1.32 (ddd, 2H, *J* = 11.7, 5.8, 5.8 Hz), 1.15 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 138.6, 128.4, 127.9, 127.2, 66.4, 60.2, 50,8, 38.1, 26.3, 24.5, 14.1; MS (EI) *m/z* (%): 175 (13), 174 ([M–$C_4H_7O_2$], 100), 91 (22), 84 (10), 42 (13), 41 (26); HRMS (ESI) calcd. for $C_{16}H_{24}N_1O_2$ = 262.1807 $[M+H]^+$, found 262.1802.



3-phenyl-3-piperidinopropanenitrile (3ah): (Reg. No. = 73067-30-8); light yellow solid; mp 58.6–59.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (dd, 2H, *J* = 7.5, 7.2 Hz), 7.32 (d, 1H, *J* = 7.2 Hz), 7.29 (d, 2H, *J* = 7.5 Hz), 3.69 (dd, 1H, *J* = 7.4, 6.1 Hz), 2.86 (dd, 1H, *J* = 16.8, 6.1 Hz), 2.79 (dd, 1H, *J* = 16.8, 7.4 Hz), 2.43–2.32 (m, 4H), 1.59–1.54 (m, 4H), 1.38 (ddd, 2H, *J* = 12.0, 6.0, 6.0 Hz); ^{13}C-NMR (125 MHz, $CDCl_3$): δ 138,3 128.5, 128.0, 127.8, 118.2, 66.1, 51.2, 26.1, 24.3, 22.0; MS (EI) *m/z* (%): 175 (13), 174 ([M–$C_2H_2N_1$], 100), 103 (10), 91 (38), 77 (15), 51 (10), 42 (16), 41 (44); HRMS (ESI) calcd. for $C_{14}H_{19}N_2$ = 215.1548 $[M+H]^+$, found 215.1550.



butaverine (*n*-butyl 3-phenyl-3-piperidinopropanoate) (3ai): (Reg. No. = 55837-14-4); light yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.29 (m, 2H), 7.26–7.22 (m, 3H), 4.03–3.96 (m, 3H), 2.97 (dd, 1H, *J* = 15.0, 7.5 Hz), 2.70 (dd, 1H, *J* = 15.0, 7.5 Hz), 2.43–2.38 (m, 2H), 2.32–2.27 (m, 2H), 1.54–1.47 (m, 6H), 1.34–1.26 (m, 4H), 0.88 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 138.6, 128.4, 127.9, 127.2, 66.4, 64.1, 50.8, 38.1, 30.6, 26.3, 24.5, 19.0, 13.6; MS (EI) *m/z* (%): 175 (13), 174 ([M–$C_6H_{11}O_2$], 100), 91 (15), 42 (10), 41 (36); HRMS (ESI) calcd. for $C_{18}H_{28}N_1O_2$ = 290.2120 $[M+H]^+$, found 290.2112.

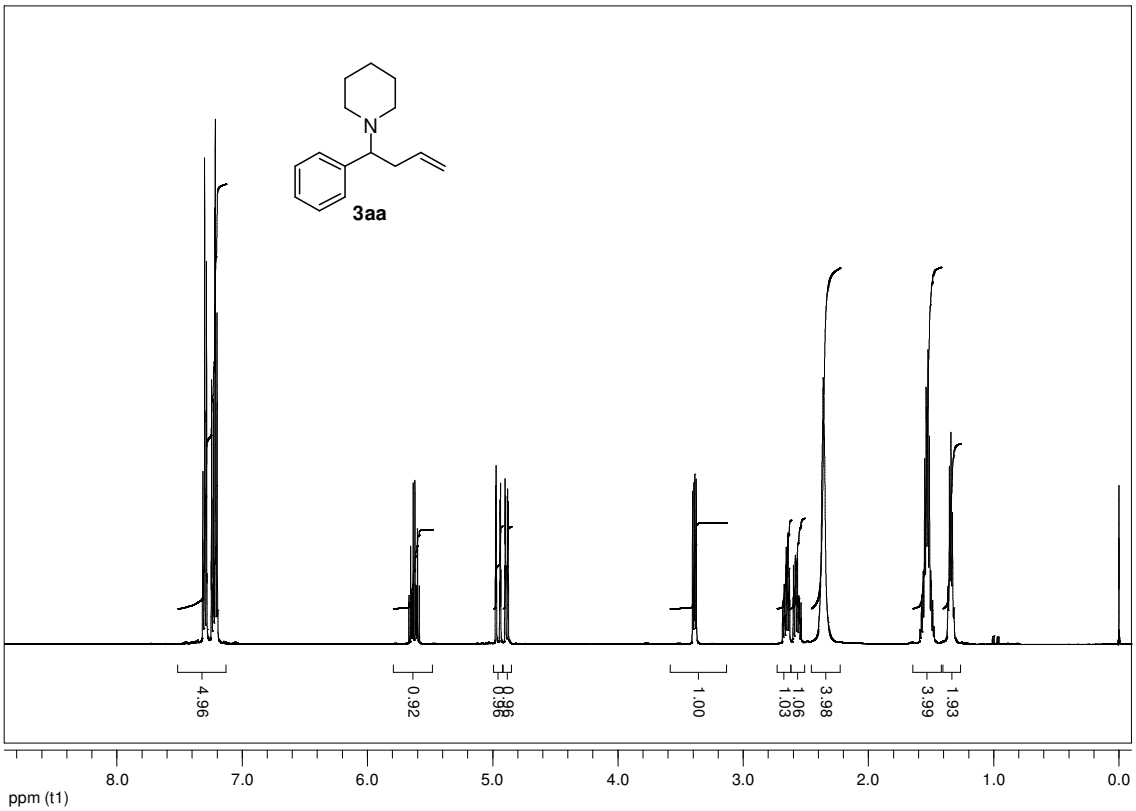


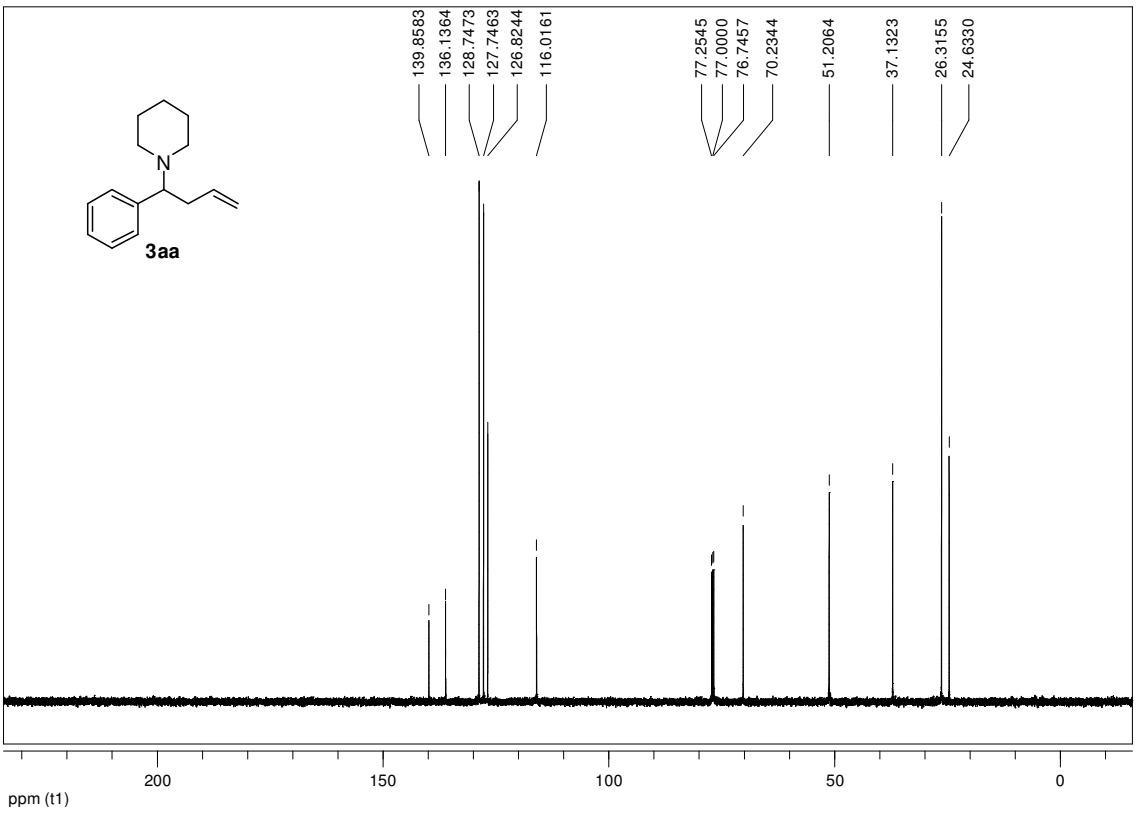
3ai

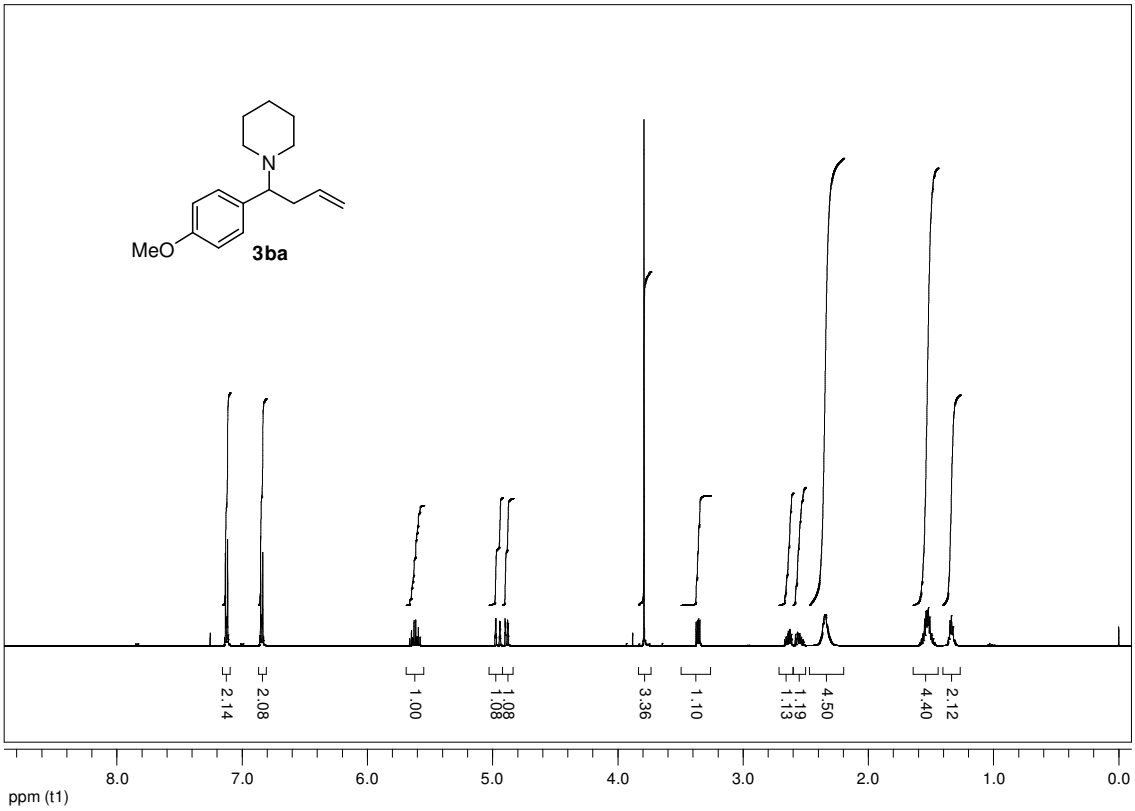
References and Notes

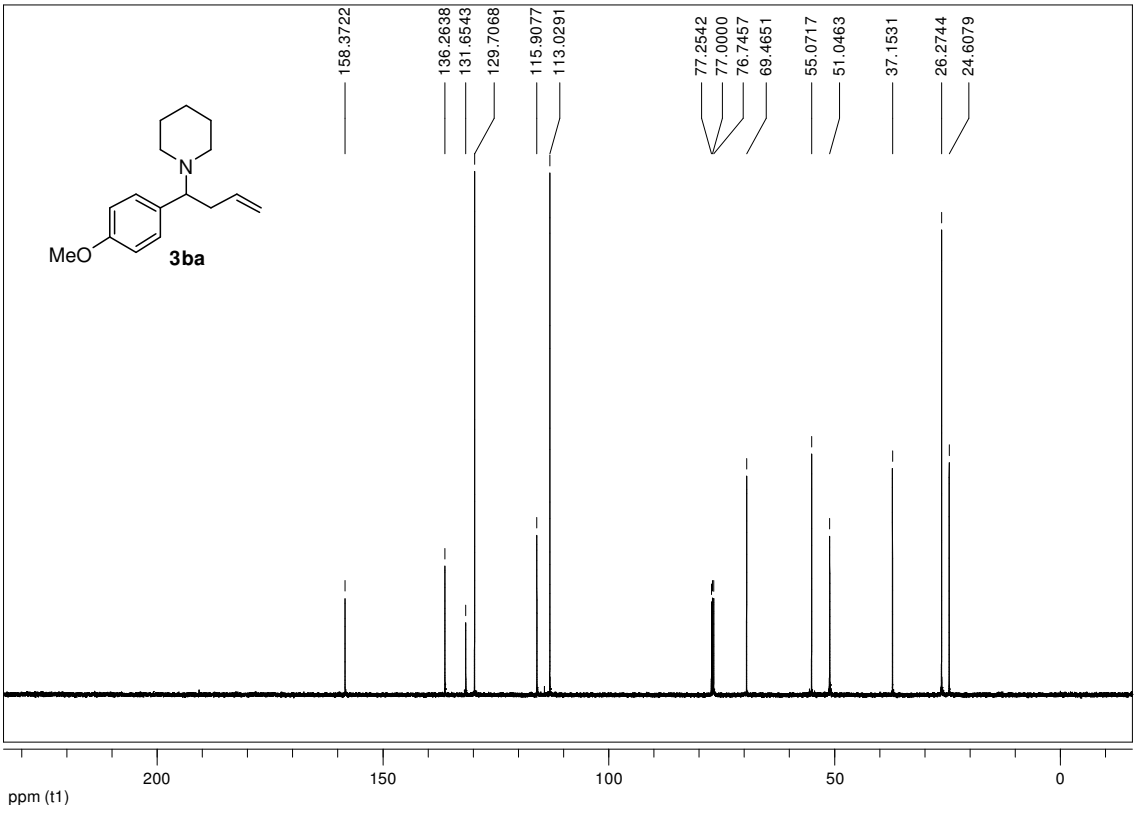
(1) Newman, M. S.; Evans, F. J. *J. Am. Chem. Soc.* **1955**, *77*, 946–947.
(2) Aminals (**1i** and **1j**) were prepared according to a modified procedure of a known method, see: Katritzky, A. R; Drewniak, M. J. *Chem. Soc., Perkin Trans. 1* **1988**, 2339–2344.
(3) Preparation of butyl α-bromoacetate, see: Zhu, X-F.; Schaffrer, A-P.; Li, R. C.; Kwon, O. *Org. Lett.* **2005**, *7*, 2977–2980.

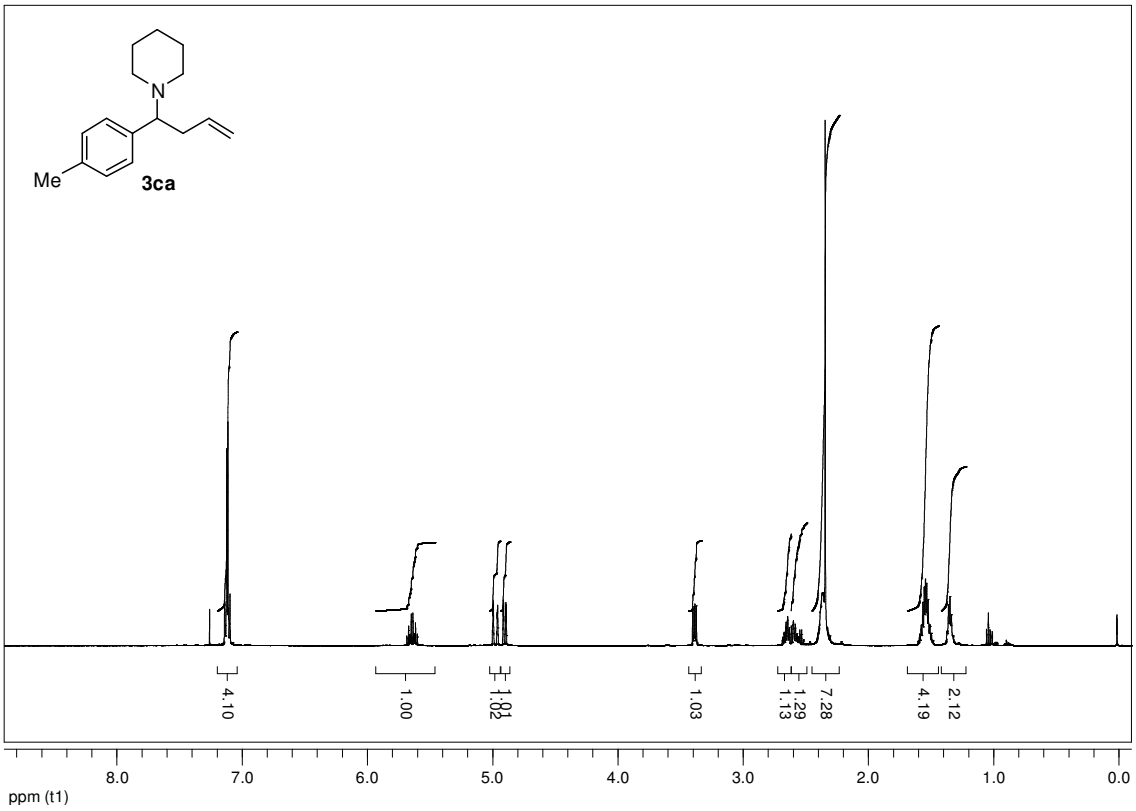
^{1}H and ^{13}C NMR Spectra of Compound 3

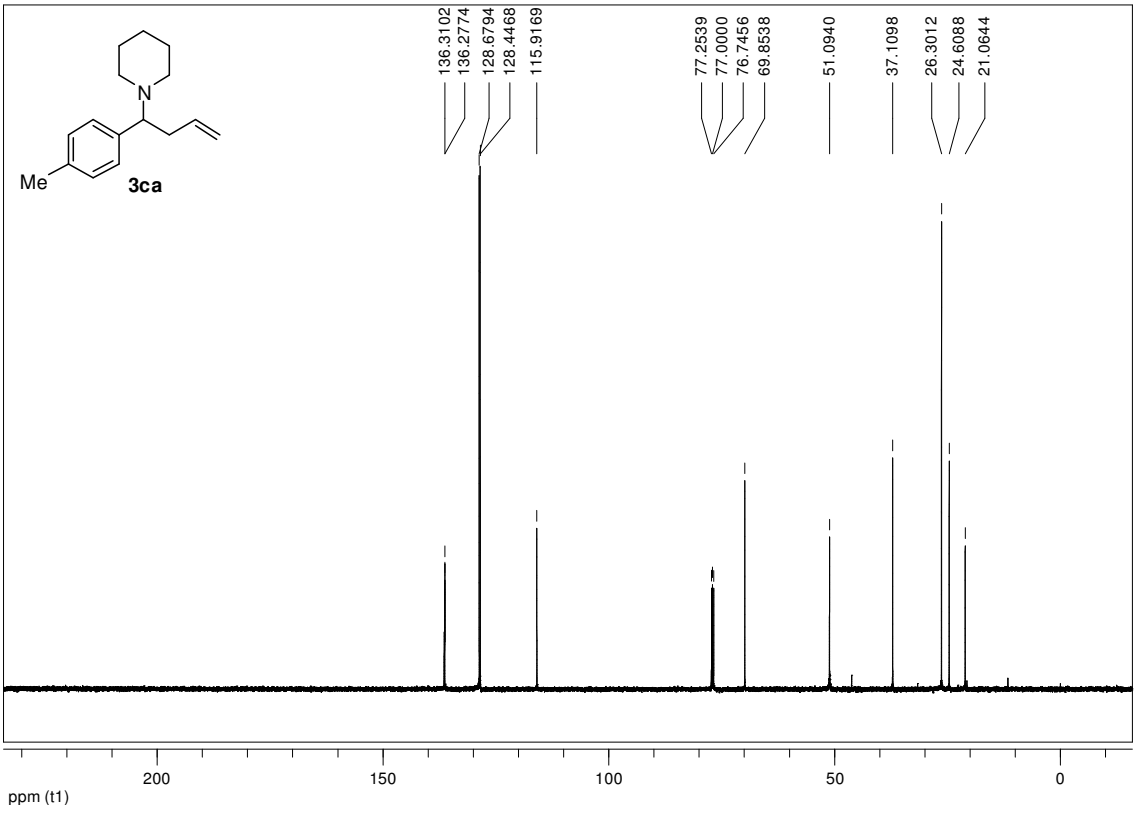


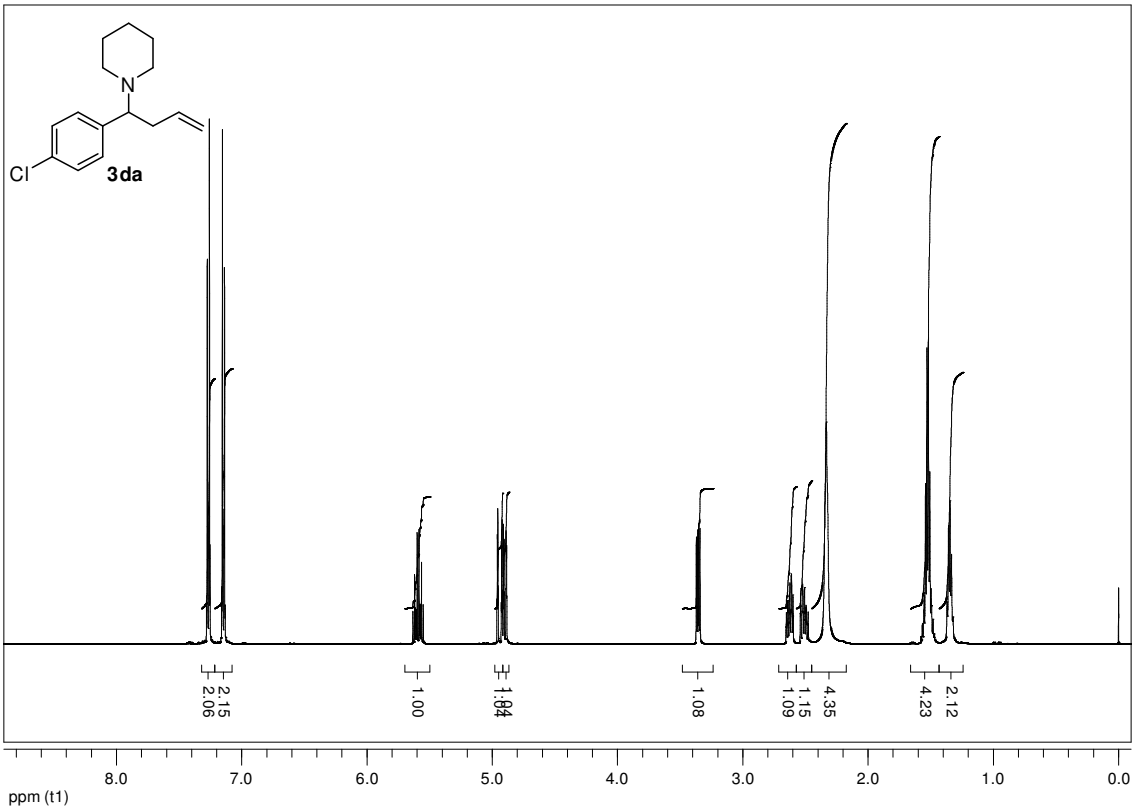


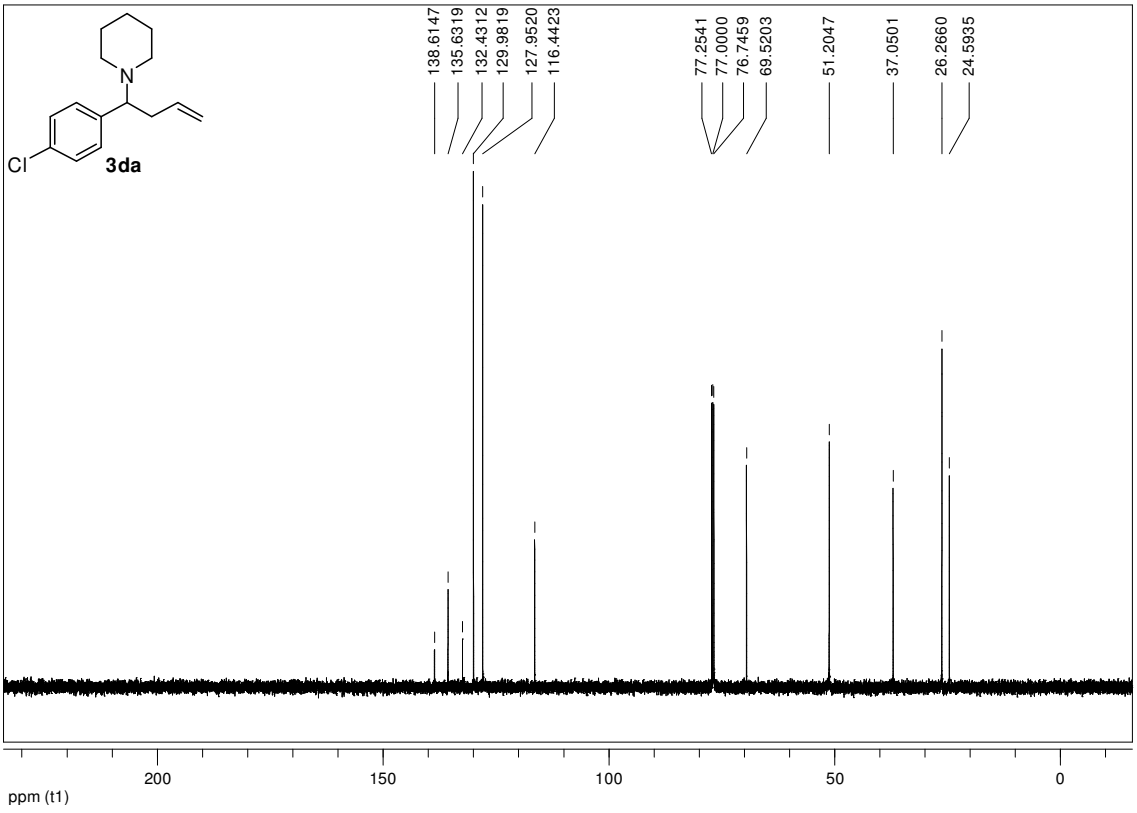

MeO
3ba
2.14
2.08
1.00
1.08
1.08
3.36
1.10
1.13
1.19
4.50
4.40
2.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

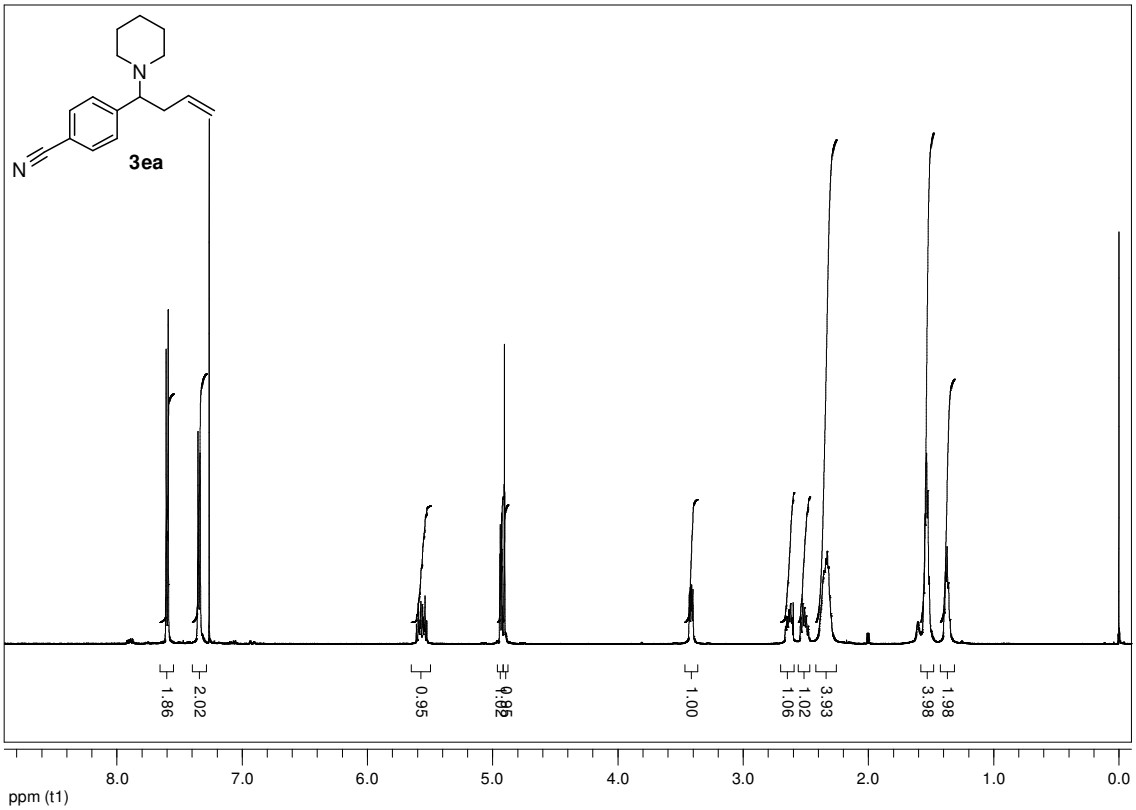

158.3722
136.2638
131.6543
129.7068
115.9077
113.0291
77.2542
77.0000
76.7457
69.4651
55.0717
51.0463
37.1531
26.2744
24.6079
MeO
3ba
200
150
100
50
0
ppm (t1)

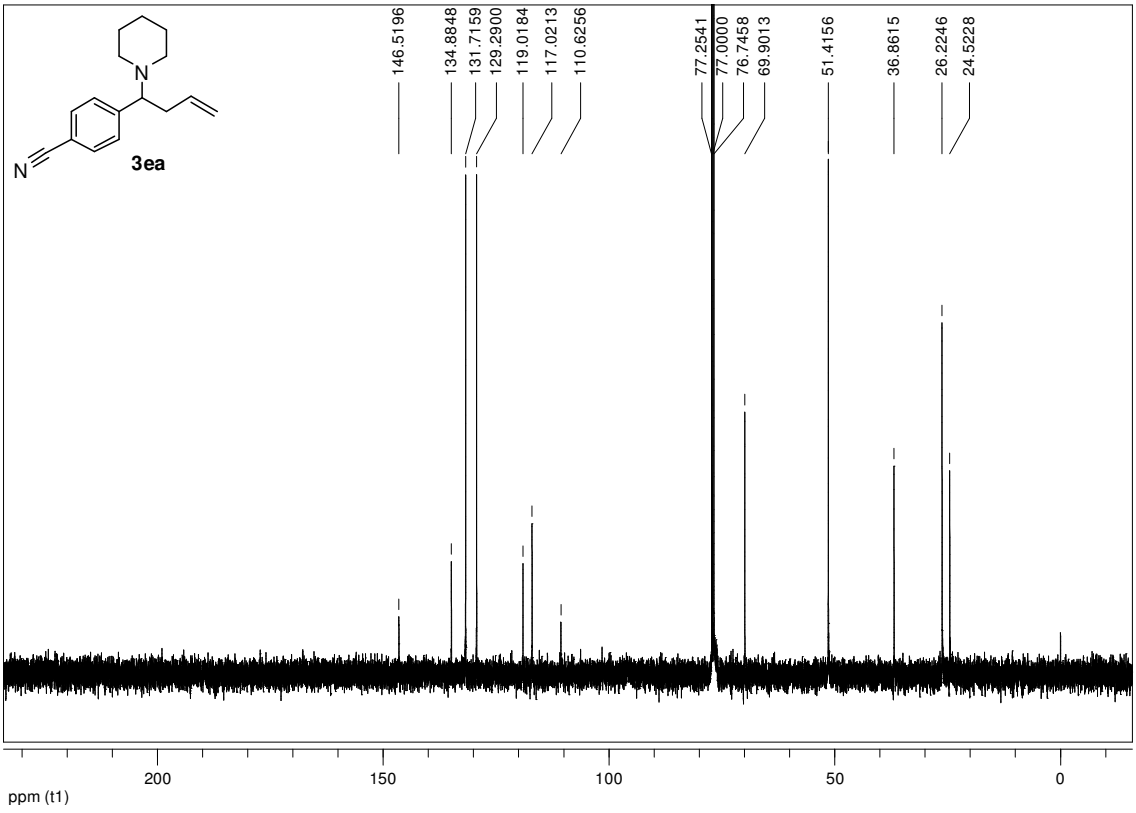

N
Me
3ca
4.10
1.00
1.01
1.02
1.03
1.13
1.29
7.28
4.19
2.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

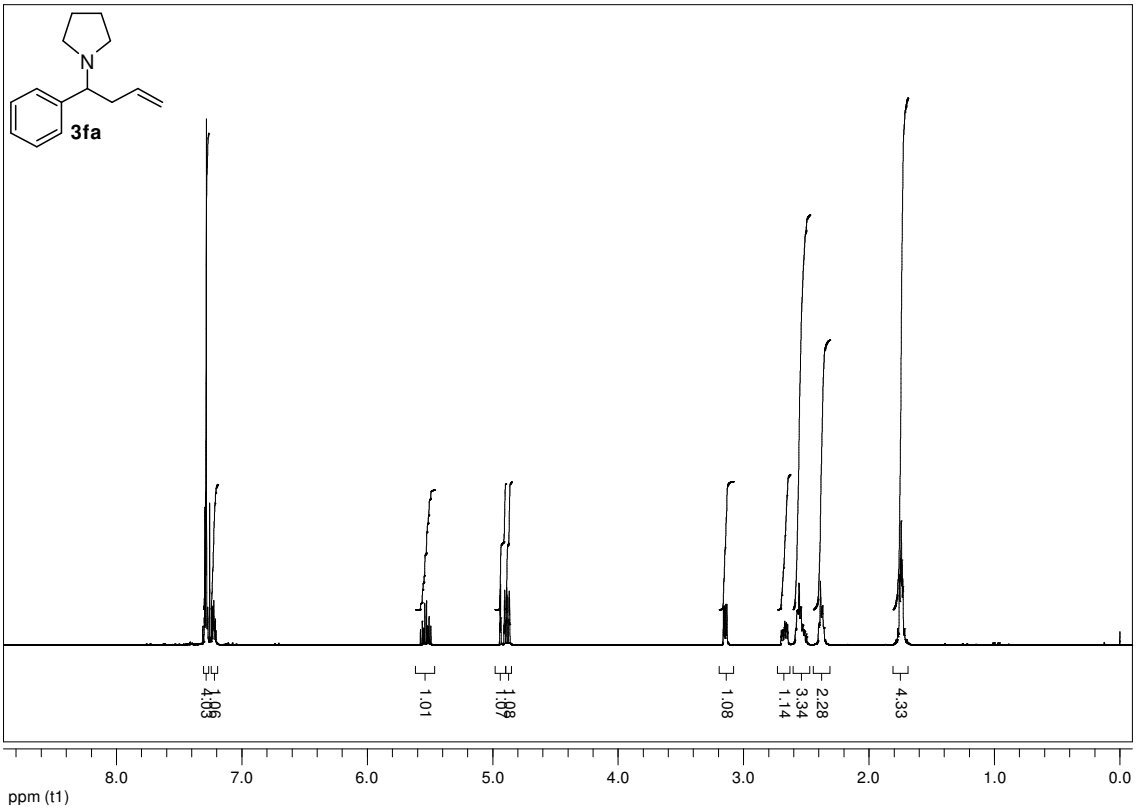

N
Me
3ca
136.3102
136.2774
128.6794
128.4468
115.9169
77.2539
77.0000
76.7456
69.8538
51.0940
37.1098
26.3012
24.6088
21.0644
200
150
100
50
0
ppm (t1)

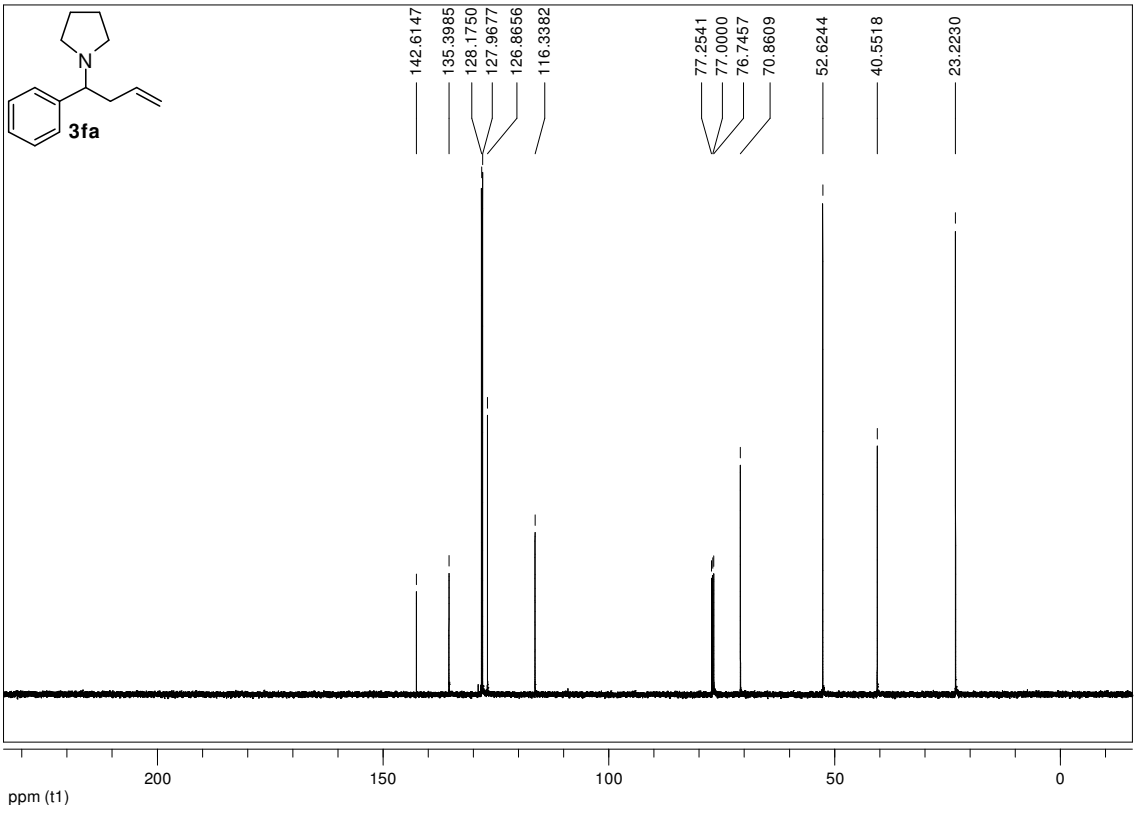

N
Cl
3da
2.06
2.15
1.00
1.04
1.08
1.09
1.15
4.35
4.23
2.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

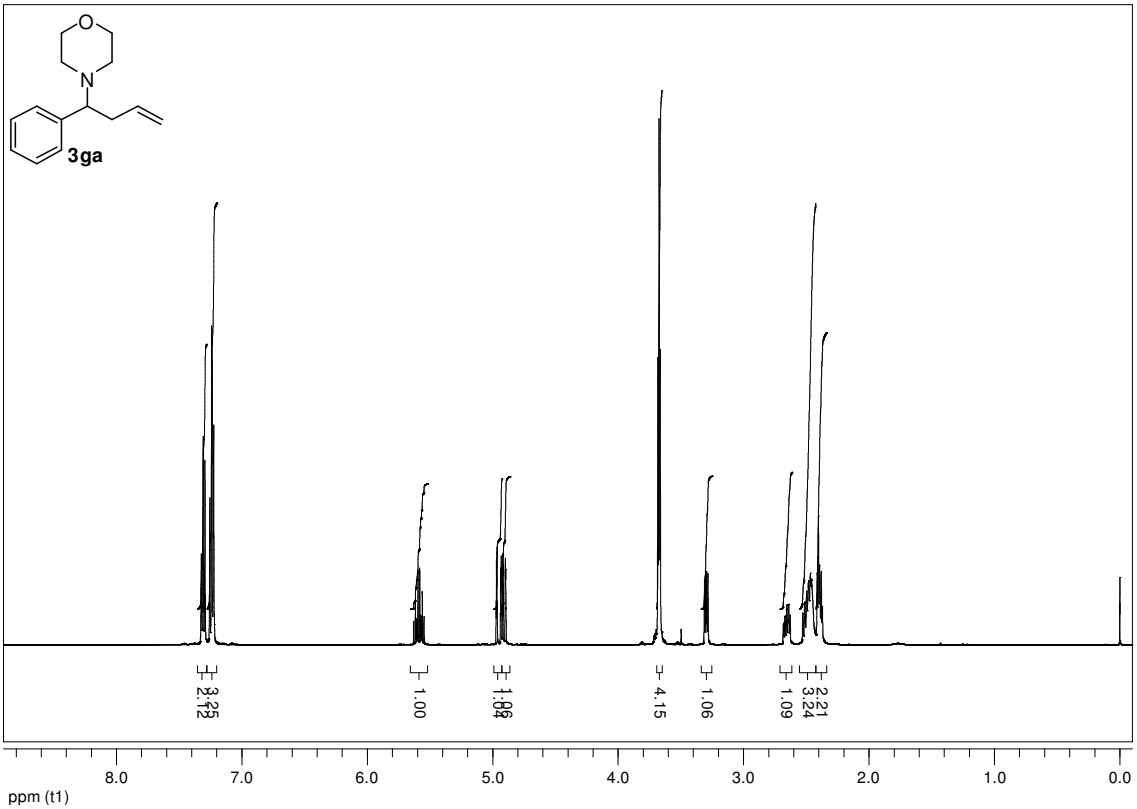

N
Cl
3da
138.6147
135.6319
132.4312
129.9819
127.9520
116.4423
77.2541
77.0000
76.7459
69.5203
51.2047
37.0501
26.2660
24.5935
200
150
100
50
0
ppm (t1)

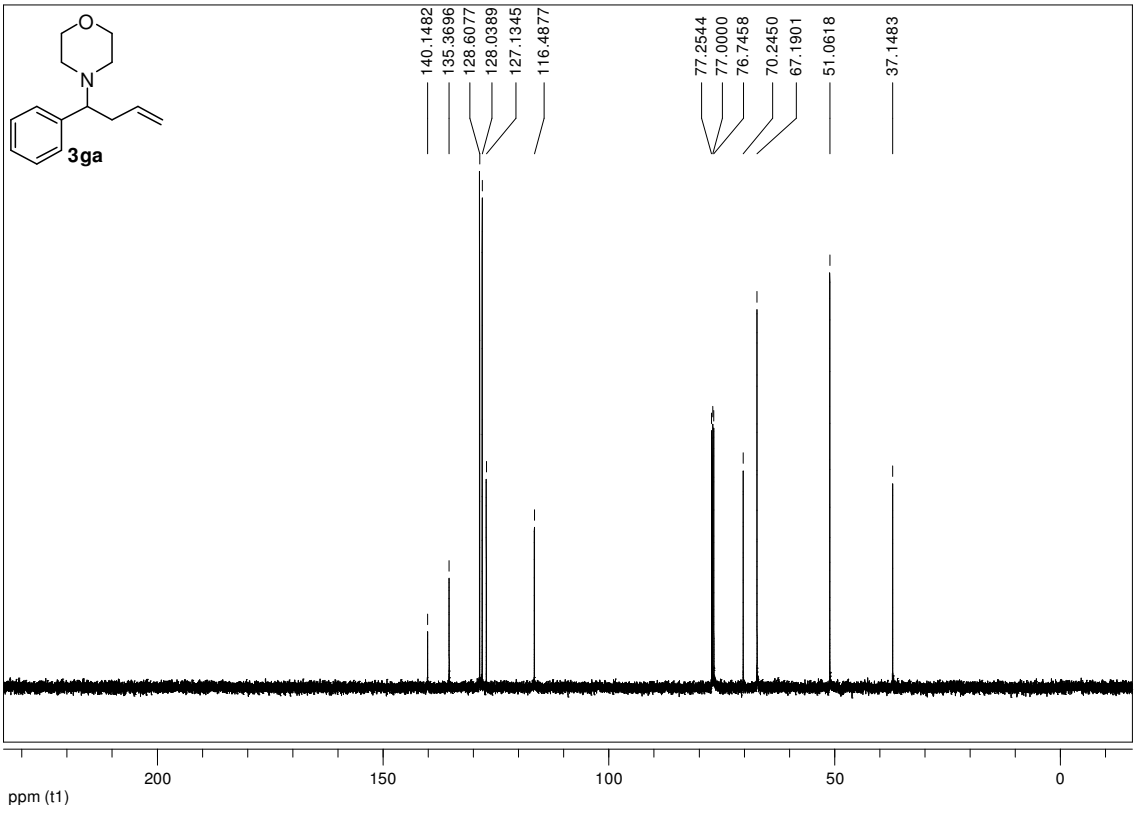

3ea
1.86
2.02
0.95
1.00
1.06
1.02
3.33
3.98
1.98
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

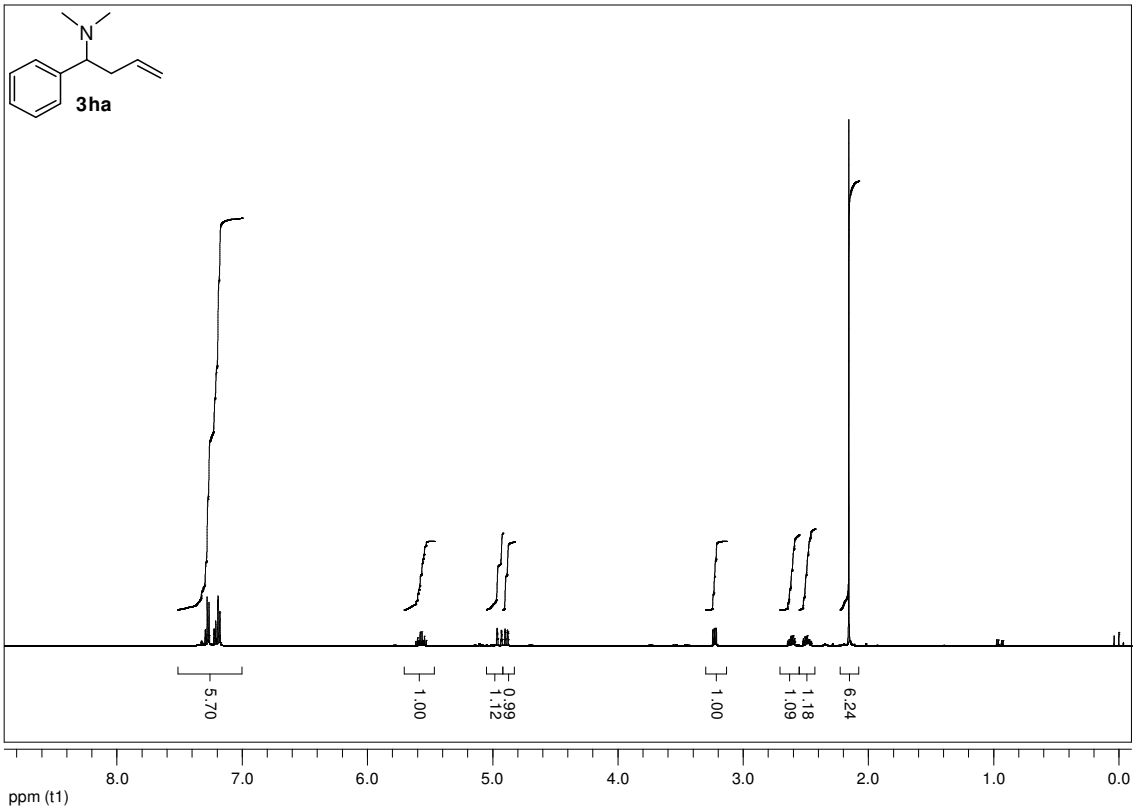

3ea
146.5196
134.8848
131.7159
129.2900
119.0184
117.0213
110.6256
77.2541
77.0000
76.7458
69.9013
51.4156
36.8615
26.2246
24.5228
200
150
100
50
0
ppm (t1)

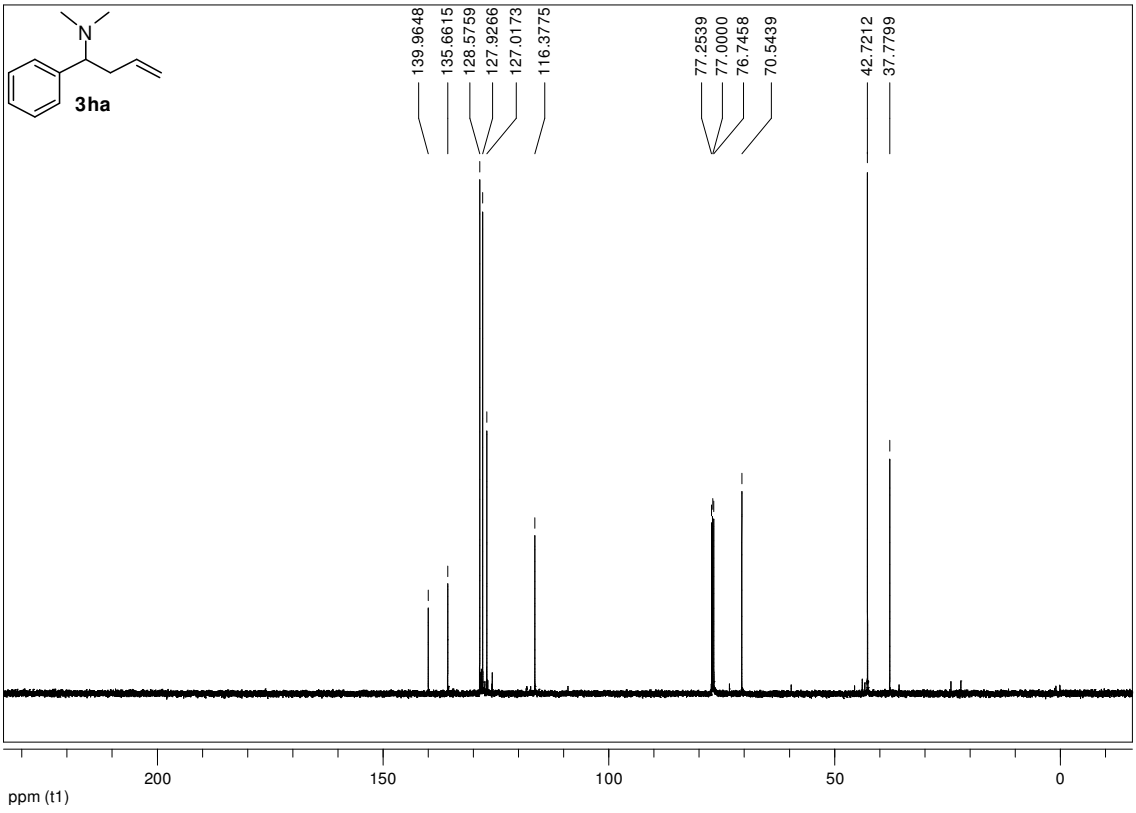

3fa
4.03
1.01
1.08
1.14
3.34
2.28
4.33
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

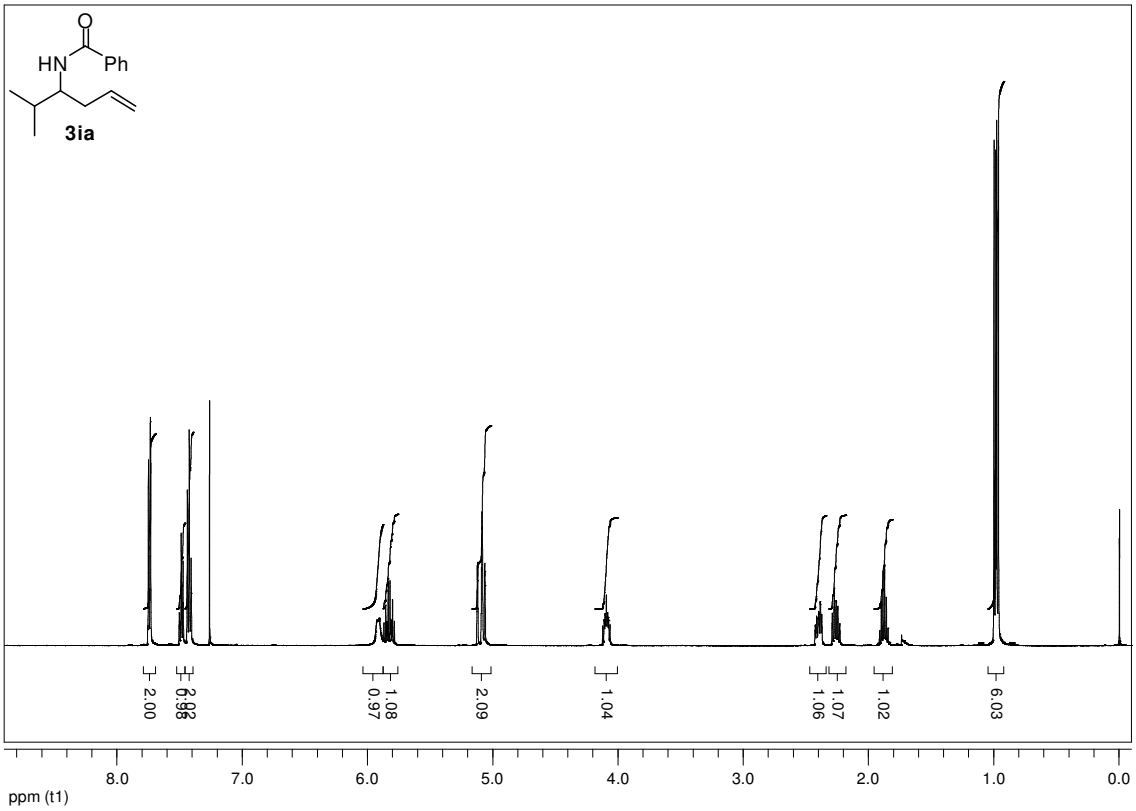

3fa
142.6147
135.3985
128.1750
127.9677
126.8656
116.3382
77.2541
77.0000
76.7457
70.8609
52.6244
40.5518
23.2230
200
150
100
50
0
ppm (t1)

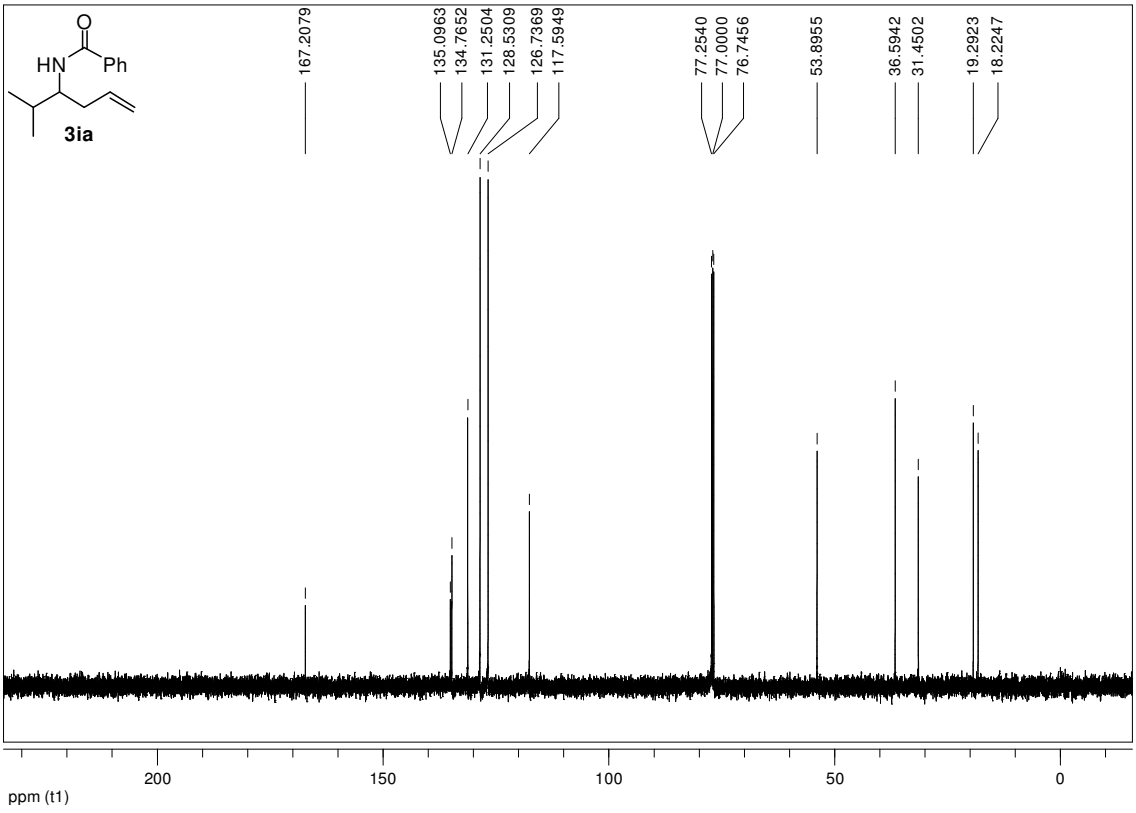

3ga
3.25
2.12
1.00
1.06
1.04
4.15
1.06
1.09
3.24
2.21
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

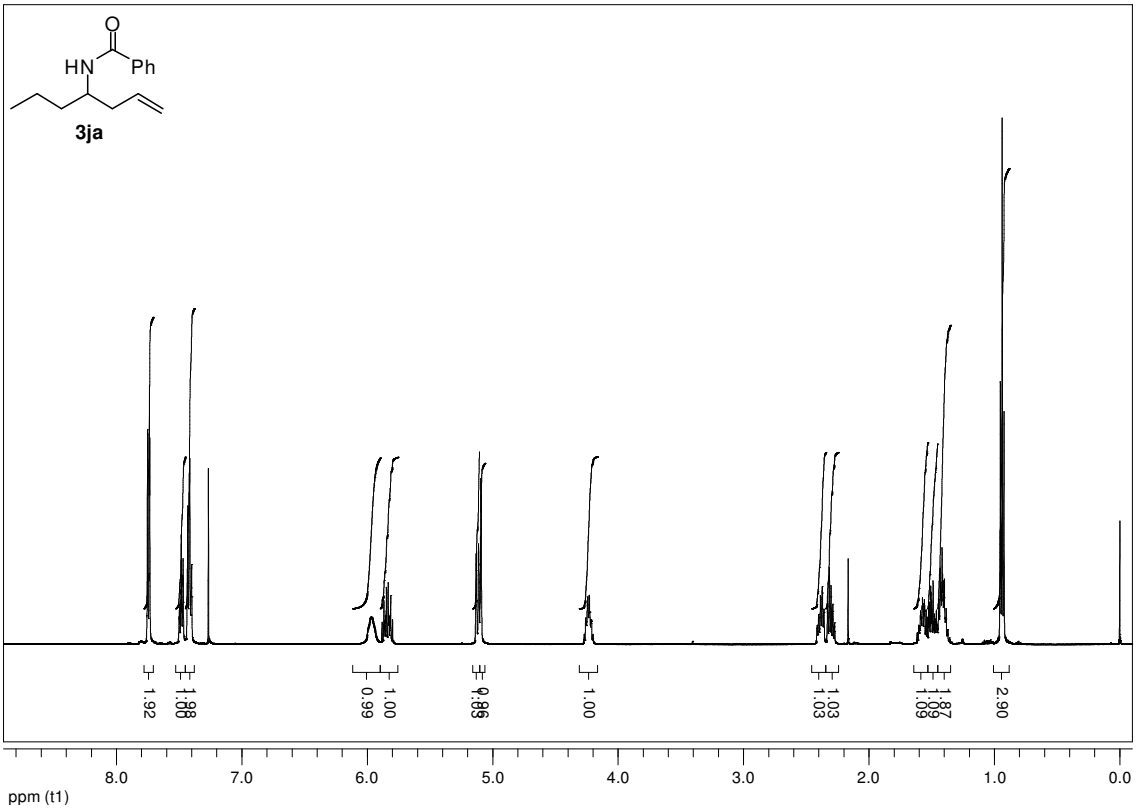

3ga
140.1482
135.3696
128.6077
128.0389
127.1345
116.4877
77.2544
77.0000
76.7458
70.2450
67.1901
51.0618
37.1483
200
150
100
50
0
ppm (t1)

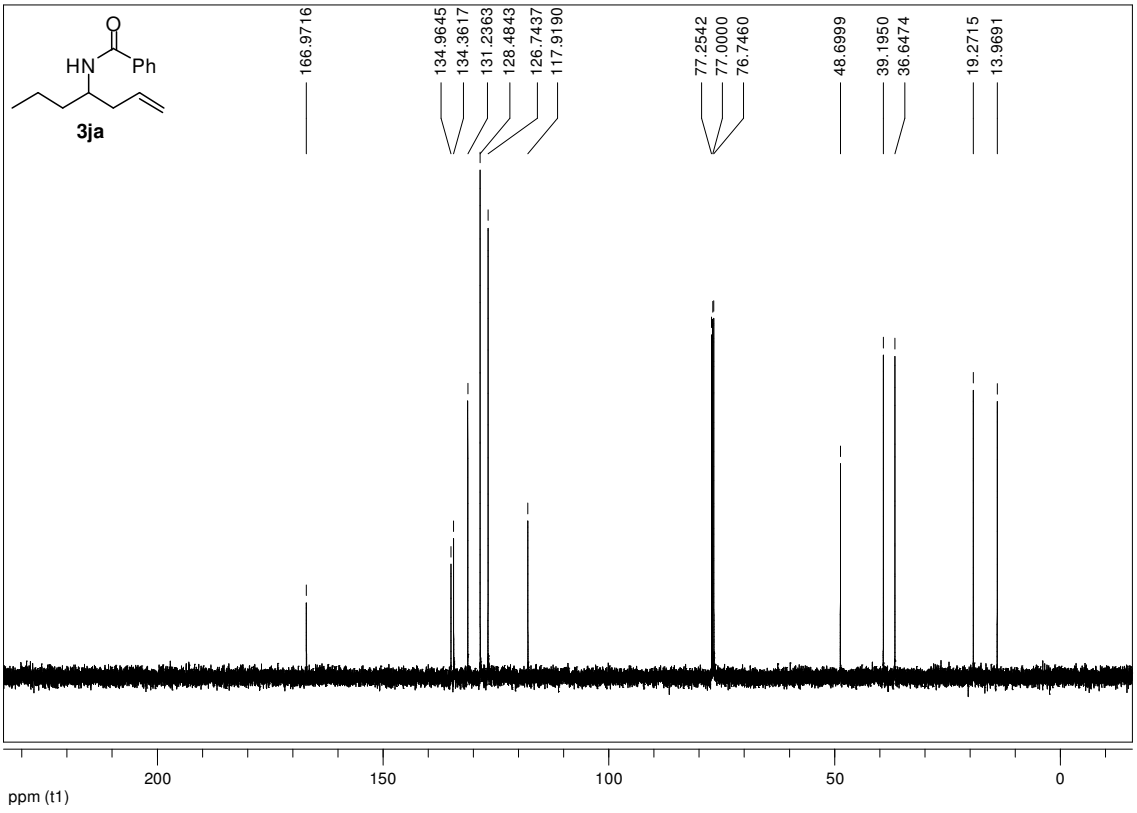

3ha
5.70
1.00
0.69
1.12
1.00
1.09
1.18
6.24
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

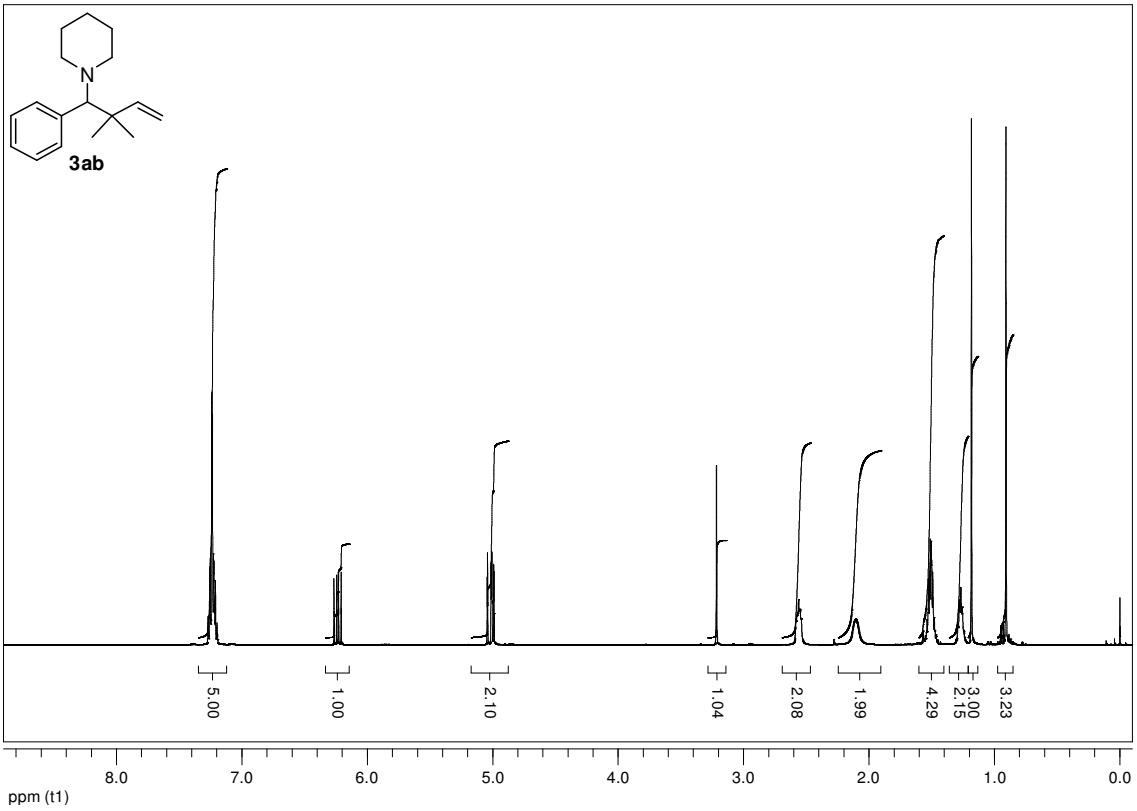

3ha
139.9648
135.6615
128.5759
127.9266
127.0173
116.3775
77.2539
77.0000
76.7458
70.5439
42.7212
37.7799
200
150
100
50
0
ppm (t1)

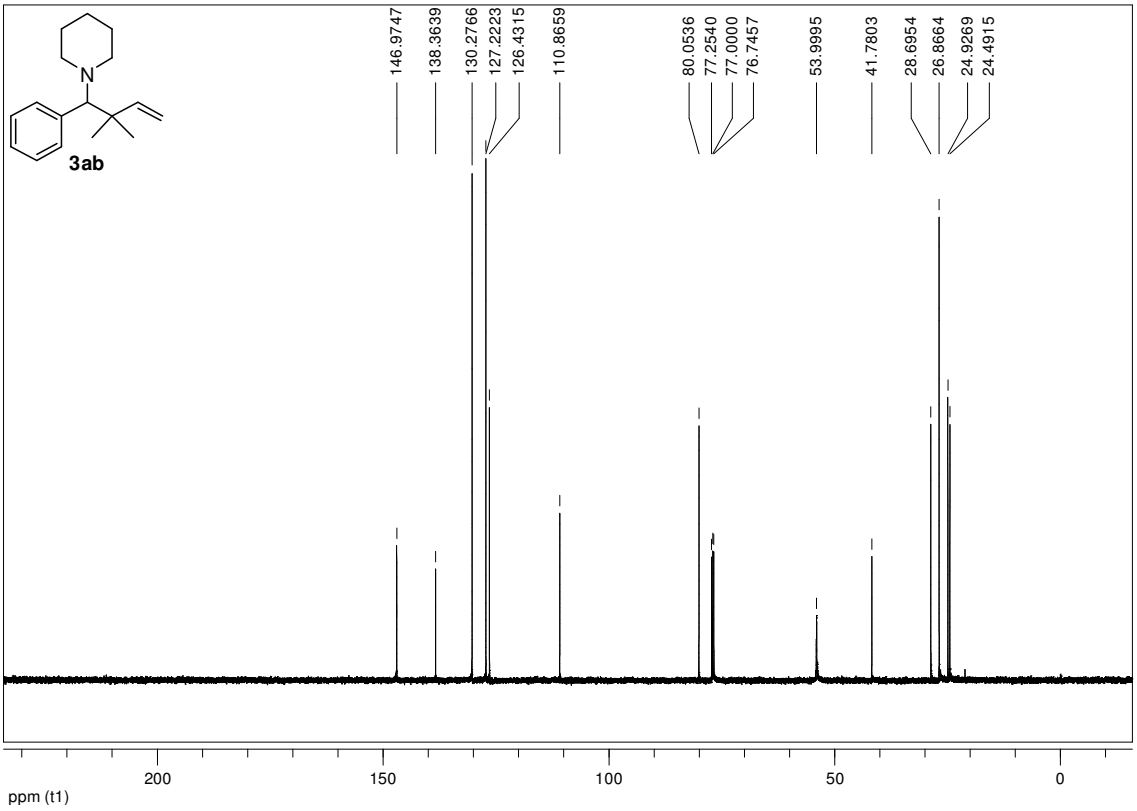

HN
O
Ph
3ia
2.00
2.06
0.98
1.08
0.97
2.09
1.04
1.06
1.07
1.02
6.03
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

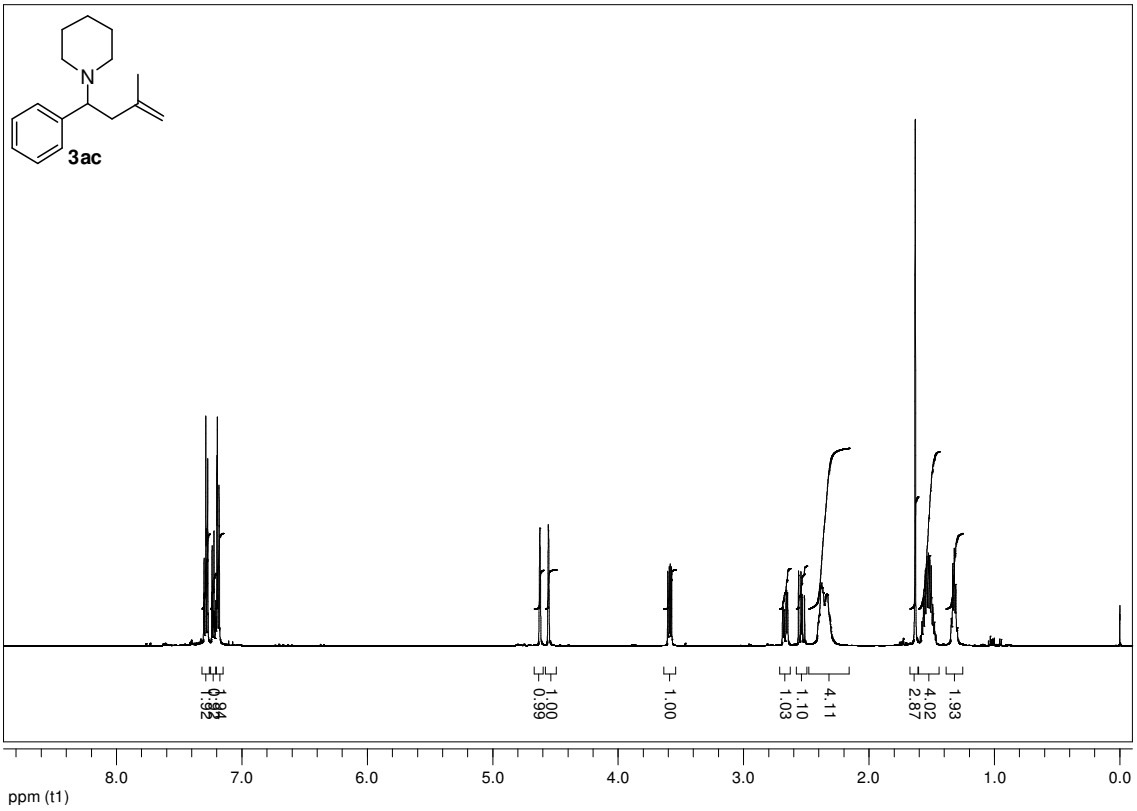

HN
O
Ph
3ia
167.2079
135.0963
134.7652
131.2504
128.5309
126.7369
117.5949
77.2540
77.0000
76.7456
53.8955
36.5942
31.4502
19.2923
18.2247
200
150
100
50
0
ppm (t1)

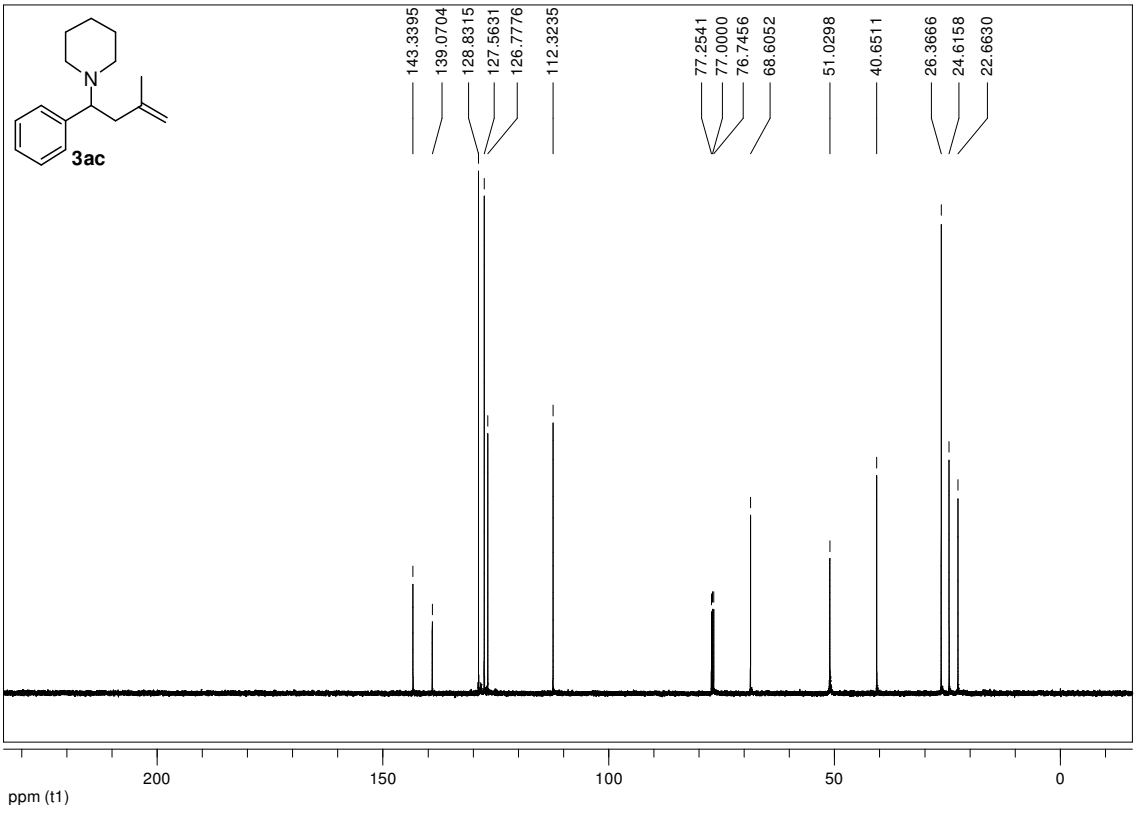

HN
O
Ph
3ja
1.92
1.98
1.00
0.99
1.00
1.00
1.03
1.03
1.09
1.87
2.90
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

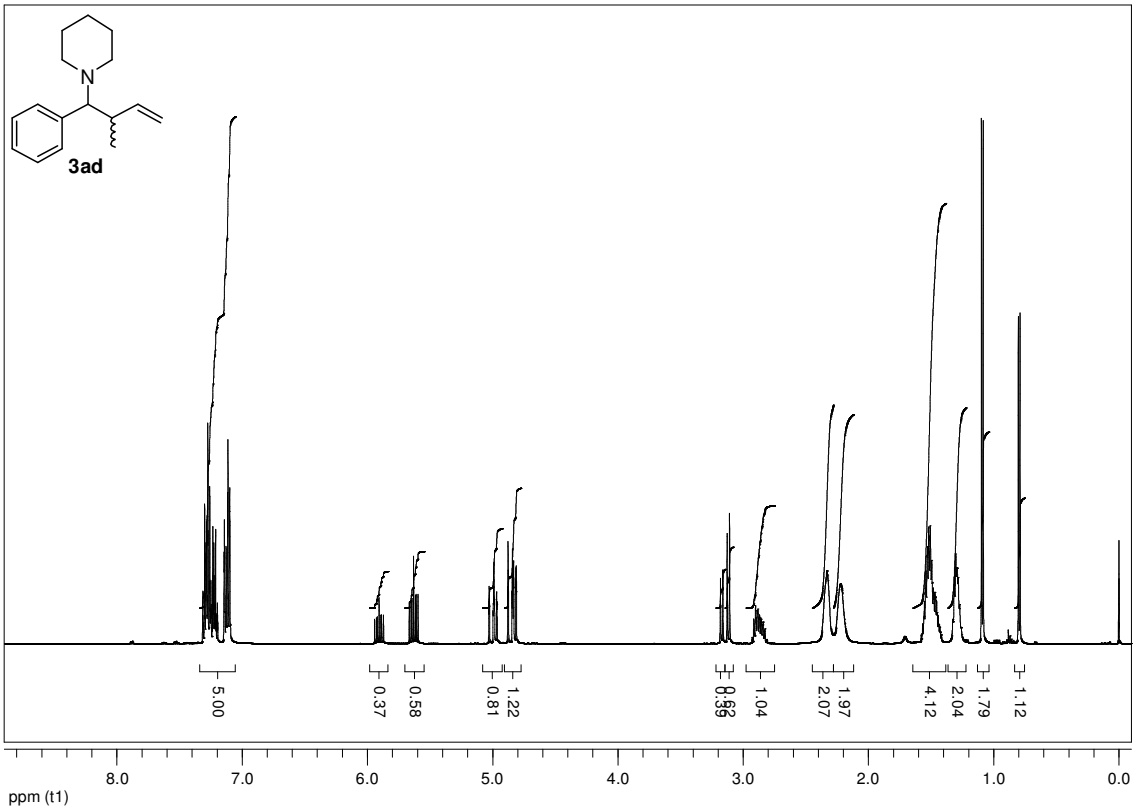

HN
O
Ph
3ja
166.9716
134.9645
134.3617
131.2363
128.4843
126.7437
117.9190
77.2542
77.0000
76.7460
48.6999
39.1950
36.6474
19.2715
13.9691
200
150
100
50
0
ppm (t1)

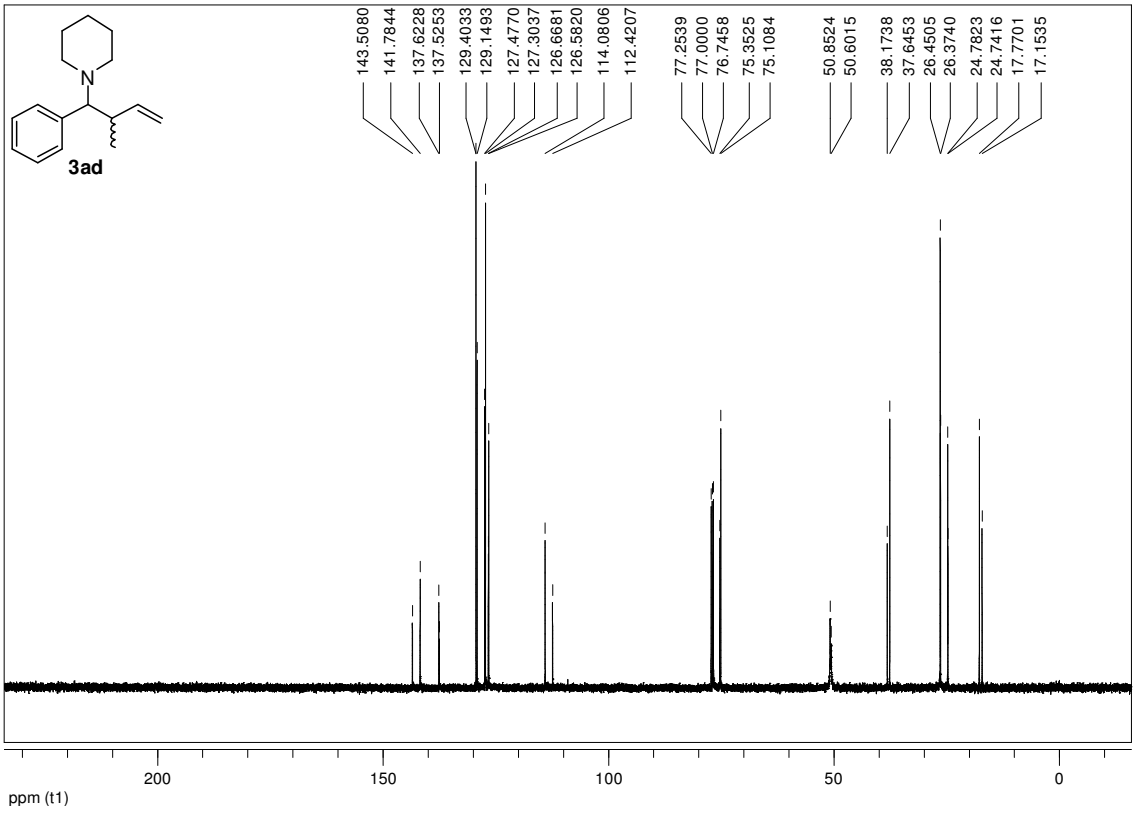

3ab
5.00
1.00
2.10
1.04
2.08
1.99
4.29
3.00
2.15
3.23
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

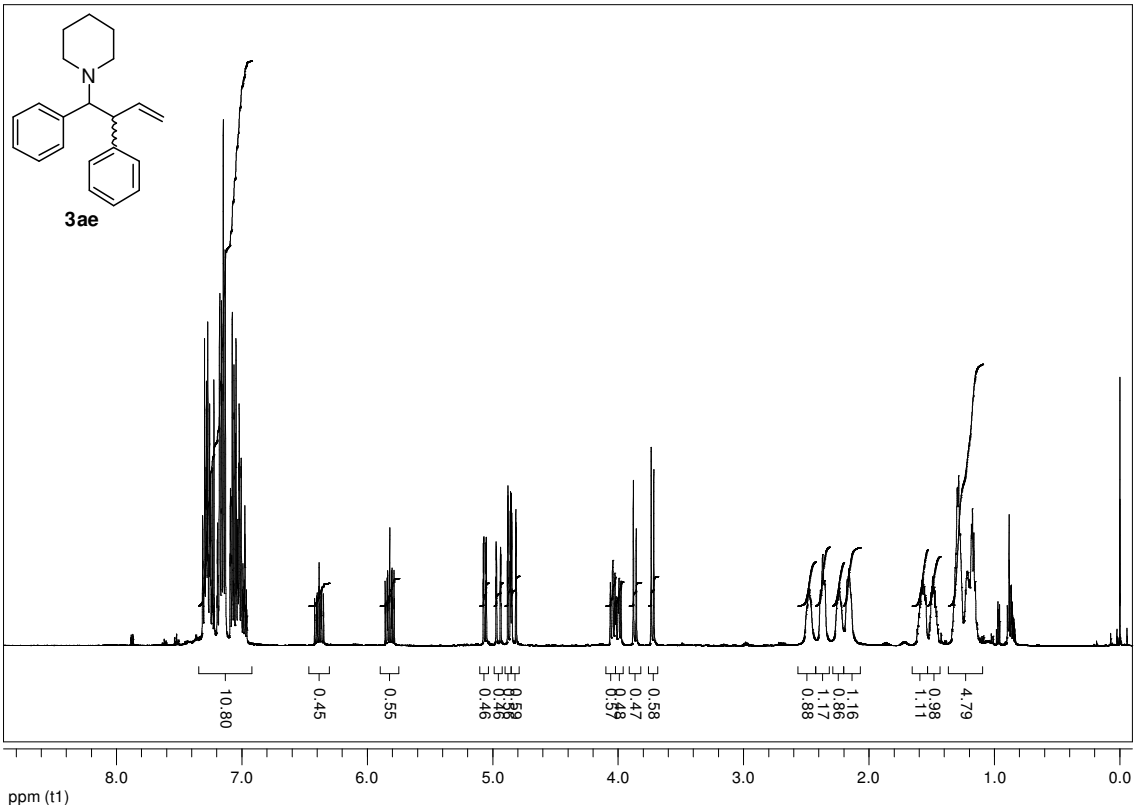

3ab
146.9747
138.3639
130.2766
127.2223
126.4315
110.8659
80.0536
77.2540
77.0000
76.7457
53.9995
41.7803
28.6954
26.8864
24.9269
24.4915
200
150
100
50
0
ppm (t1)

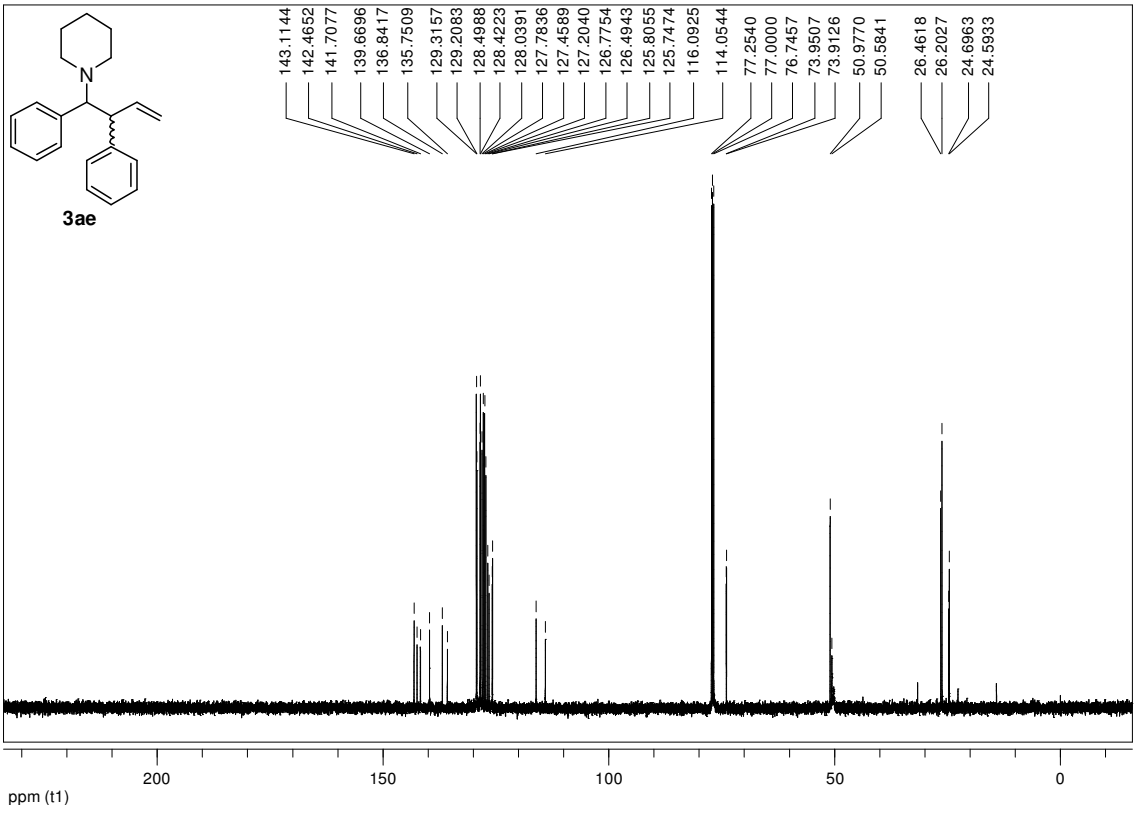

3ac
1.92
1.84
0.96
1.00
1.00
1.03
1.10
4.11
2.87
4.02
1.93
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

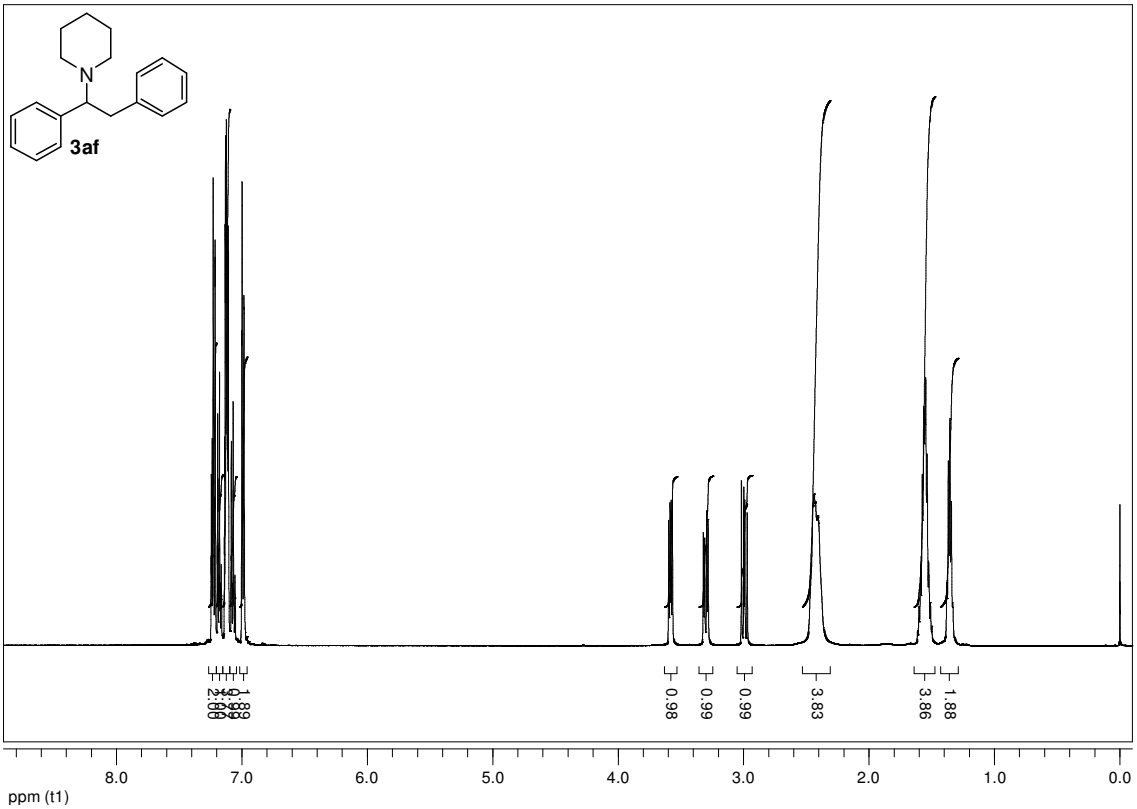

3ac
143.3395
139.0704
128.8315
127.5631
126.7776
112.3235
77.2541
77.0000
76.7456
68.6052
51.0298
40.6511
26.3666
24.6158
22.6630
200
150
100
50
0
ppm (t1)

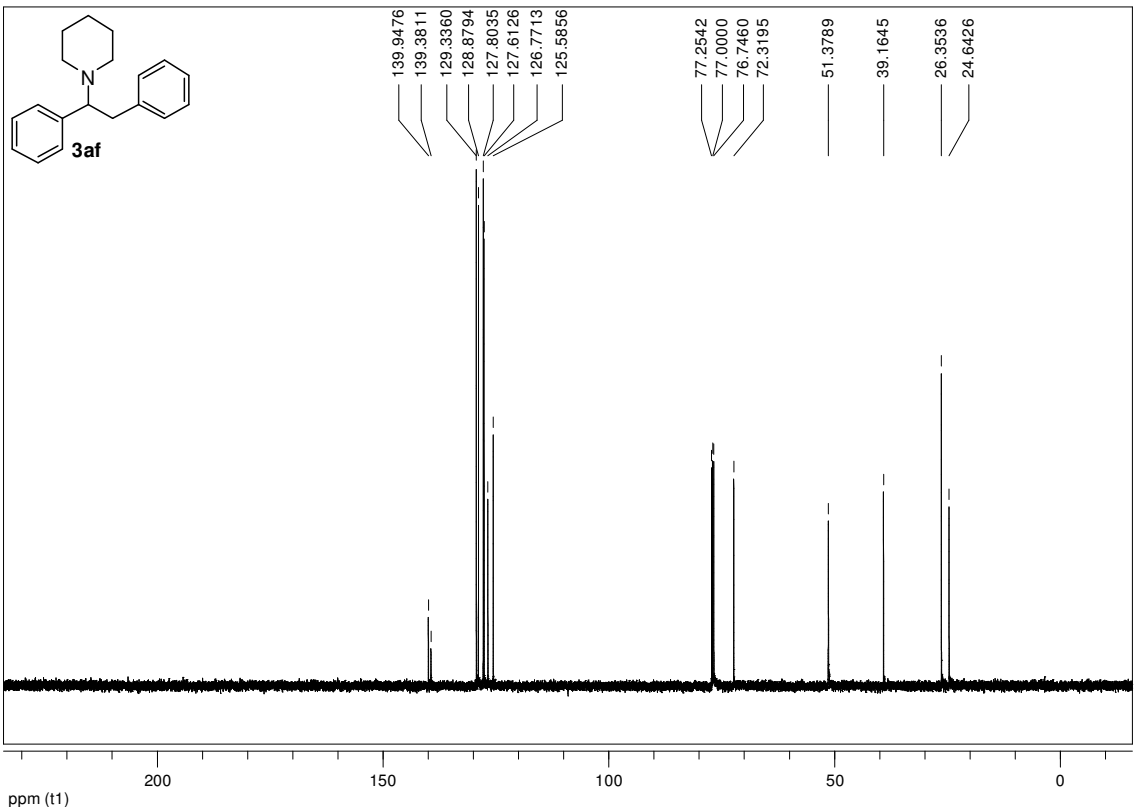

3ad
5.00
0.37
0.58
0.81
1.22
1.04
2.07
1.97
4.12
2.04
1.79
1.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

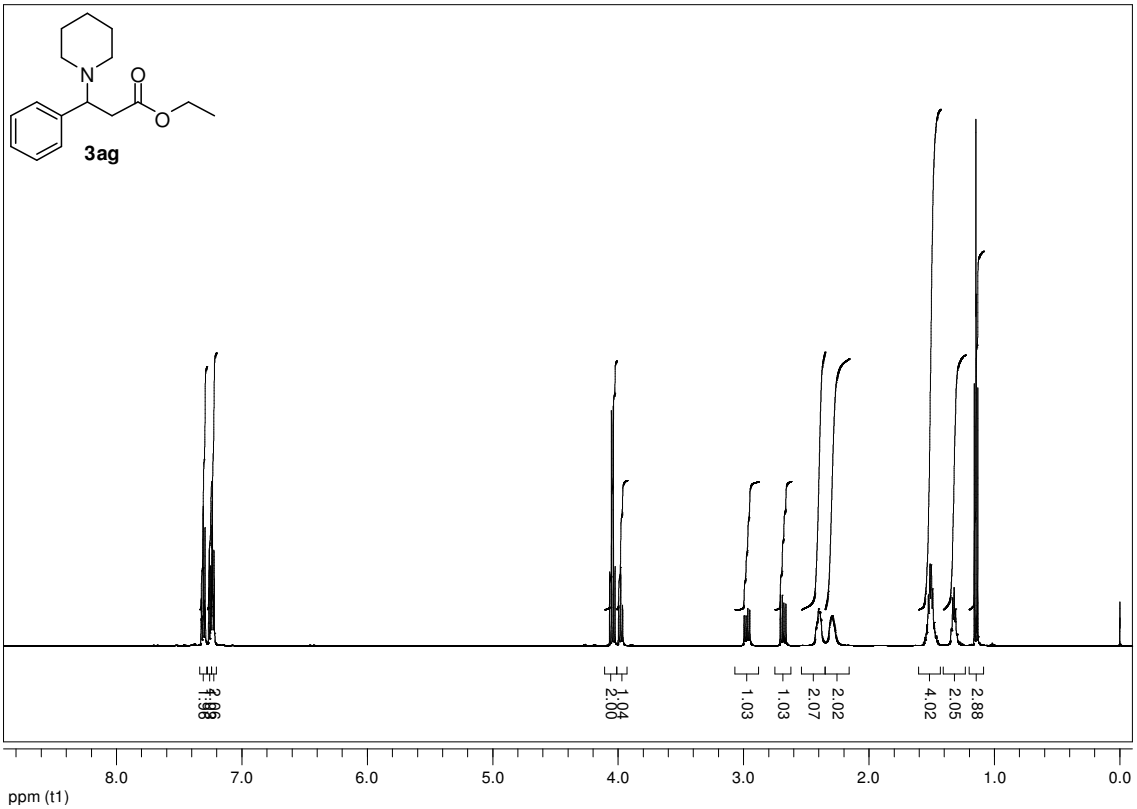

3ad
143.5080
141.7844
137.6228
137.5253
129.4033
129.1493
127.4770
127.3037
126.6681
126.5820
114.0806
112.4207
77.2539
77.0000
76.7458
75.3525
75.1084
50.8524
50.6015
38.1738
37.6453
26.4505
26.3740
24.7823
24.7416
17.7701
17.1535
200
150
100
50
0
ppm (t1)

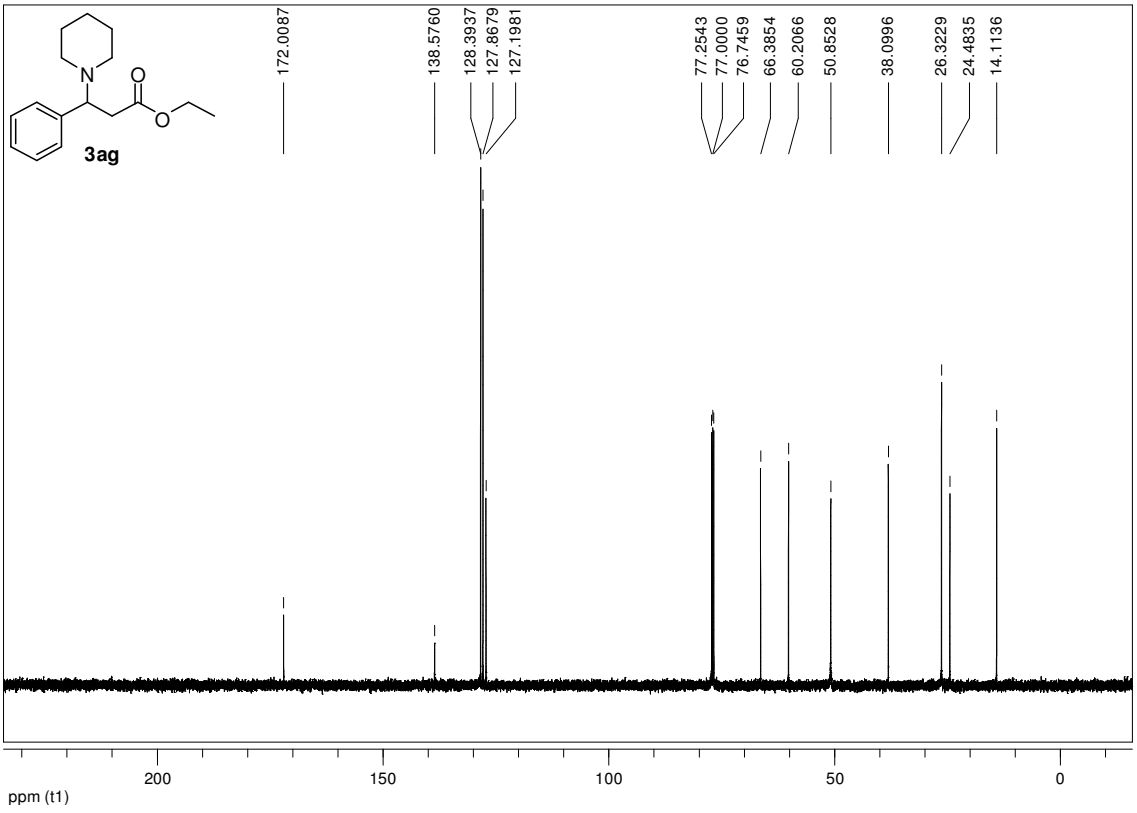

3ae
10.80
0.45
0.55
0.46
0.58
0.47
0.58
0.88
1.17
1.16
0.86
1.11
0.98
4.79
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

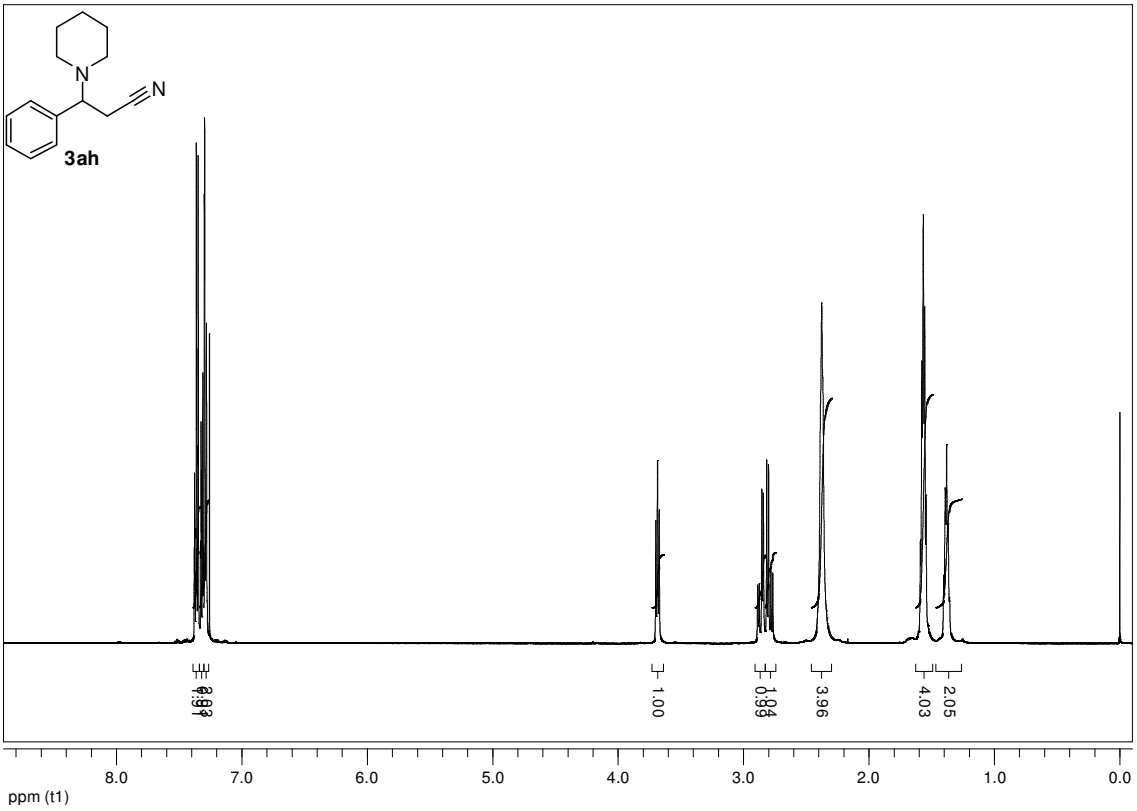

3ae
143.1144
142.4652
141.7077
139.6696
136.8417
135.7509
129.3157
129.2083
128.4988
128.4223
128.0391
127.7836
127.4589
127.2040
126.7754
126.4943
125.8055
125.7474
116.0925
114.0544
77.2540
77.0000
76.7457
73.9507
73.9126
50.9770
50.5841
26.4618
26.2027
24.6963
24.5933
200
150
100
50
0
ppm (t1)

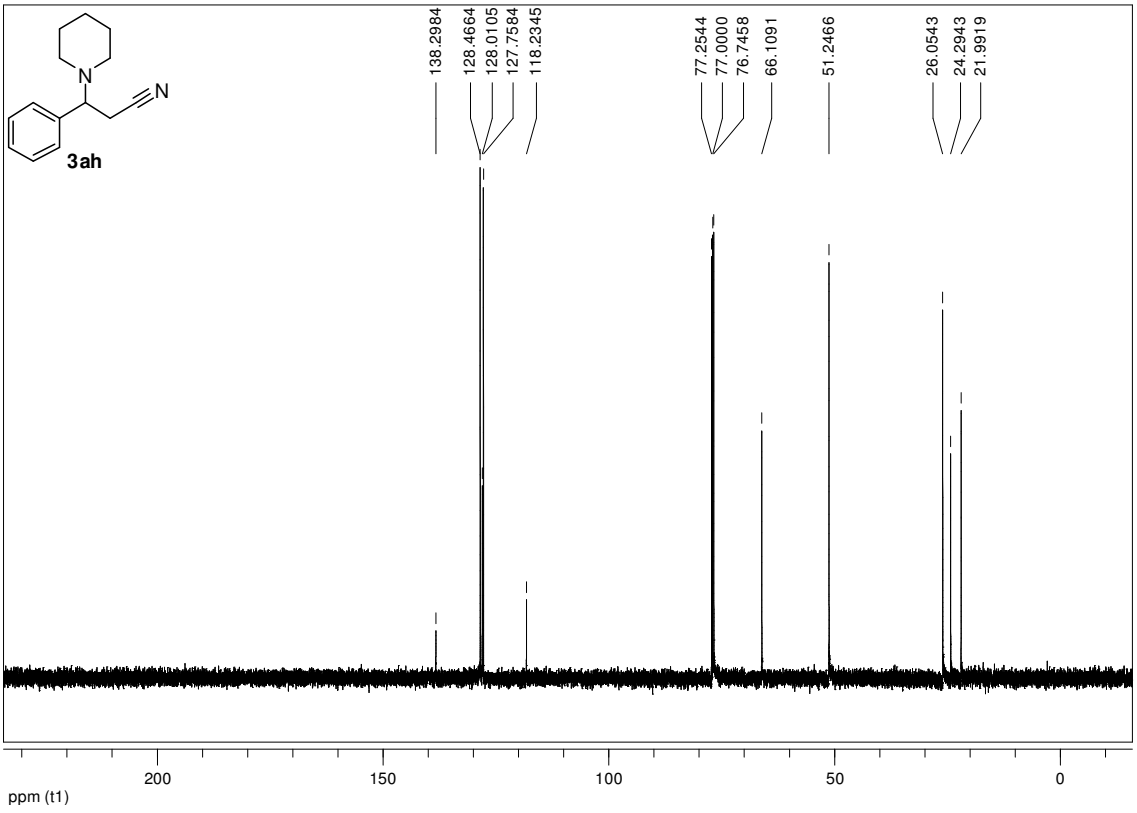

3af
0.98
0.99
0.99
3.83
3.86
1.88
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

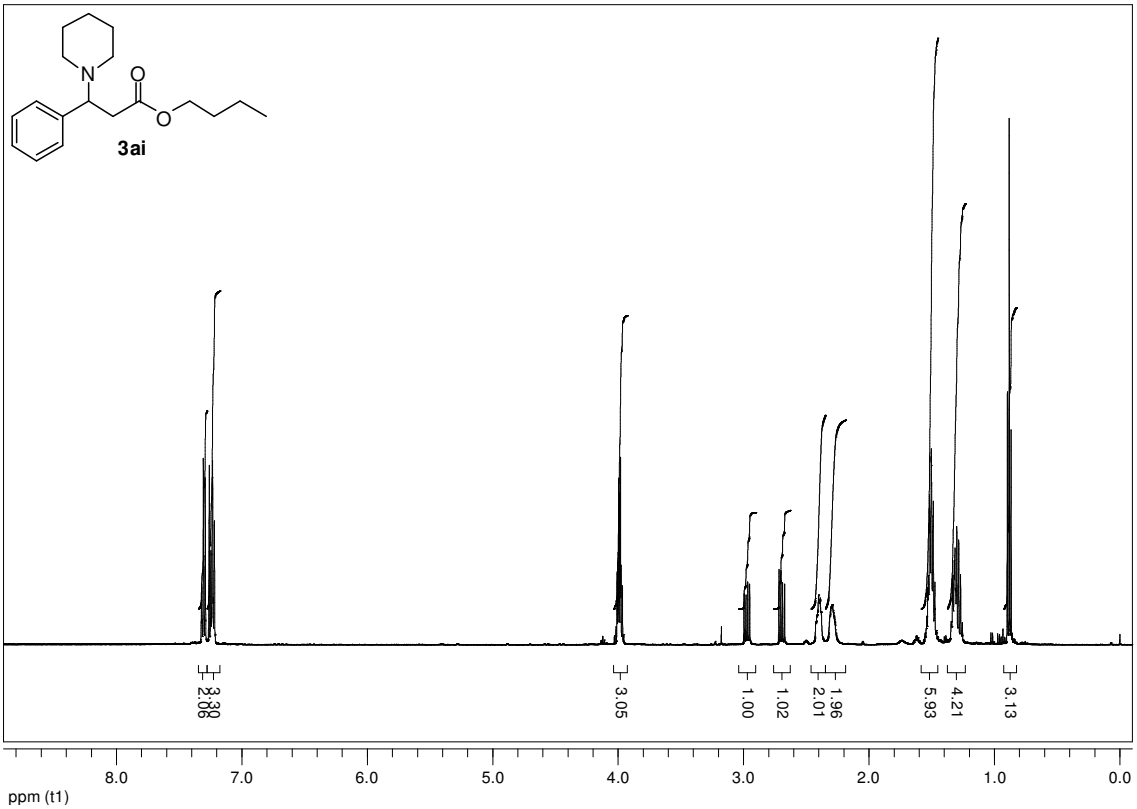

3af
139.9476
139.3811
129.3360
128.8794
127.8035
127.6126
126.7713
125.5856
77.2542
77.0000
76.7460
72.3195
51.3789
39.1645
26.3536
24.6426
200
150
100
50
0
ppm (t1)

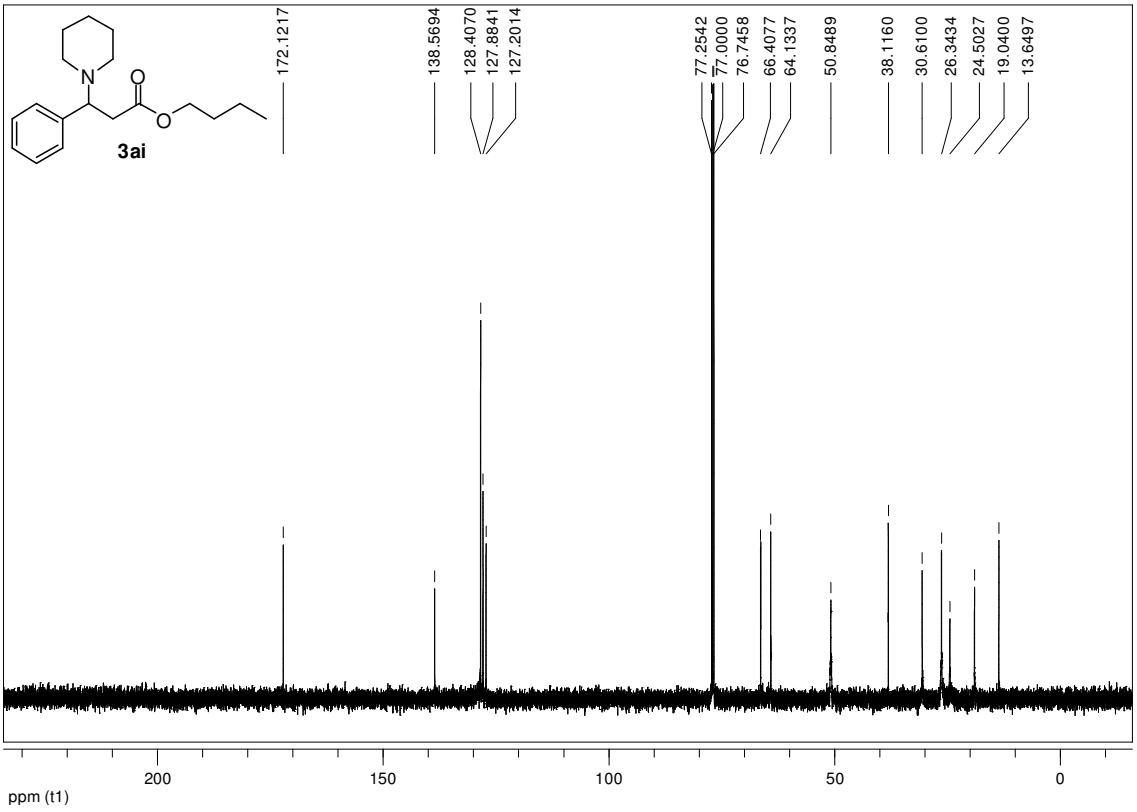

3ag
1.03
1.03
2.07
2.02
4.02
2.05
2.88
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


3ag
172.0087
138.5760
128.3937
127.8679
127.1981
77.2543
77.0000
76.7459
66.3854
60.2066
50.8528
38.0996
26.3229
24.4835
14.1136
200
150
100
50
0
ppm (t1)


3ah
1.00
1.04
3.96
4.03
2.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


3ah
138.2984
128.4664
128.0105
127.7584
118.2345
77.2544
77.0000
76.7458
66.1091
51.2466
26.0543
24.2943
21.9919
200
150
100
50
0
ppm (t1)


3ai
2.80
2.86
3.05
1.00
1.02
2.01
1.96
5.93
4.21
3.13
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


3ai
172.1217
138.5694
128.4070
127.8841
127.2014
77.2542
77.0000
76.7458
66.4077
64.1337
50.8489
38.1160
30.6100
26.3434
24.5027
19.0400
13.6497
200
150
100
50
0
ppm (t1)