Expedient Synthesis of α-(2-Azaheteroaryl) Acetates via the Addition of Silyl Ketene Acetals to Azine-*N*-oxides

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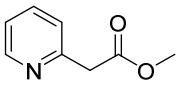
GENERAL EXPERIMENTAL DETAILS

All chemicals, reagents and solvents were purchased from commercial sources when available and used without further purification. Proton (1H NMR) and carbon (13C NMR) nuclear magnetic spectroscopy were recorded with 400 and 500 MHz Varian spectrometers. Chemical shifts are expressed in parts per million downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad singlet. Mass spectrometry (MS) was performed via atmospheric pressure chemical ionization (APCI) or electron scatter (ES) ionization sources. Liquid chromatography mass spectrometry (LCMS) was performed on an Agilent 1100 Series (Waters Atlantis C18 column, 4.6 x 50 mm, 5 μm; 95% water/acetonitrile linear gradient to 5% water/acetonitrile over 4 min, hold at 5% water / 95% acetonitrile to 5.0 min, trifluoroacetic acid modifier (0.05%); flow rate of 2.0 mL/ min). Gas chromatography mass spectrometry (GCMS) was performed on a HP6890 Series GC System (Agilent 19091 capillary column, 0.2 x 12 m, 0.33 μm; 10.5 psi; flow rate of 40.0 mL/min; temperature 105-250^{o}C.) High resolution mass spectroscopy (HRMS) was performed on an Agilent (6220) LC-MS TOF using a Xbridge C18 2.5 μm 3.0 X 5.0 mm at 60^{o}C; ammonium formate: water as mobile phase A1 and 50:50 Methanol:Acetonitrile as mobile Phase B1. Silica gel chromatography was performed using a medium pressure Biotage or ISCO system using columns pre-packaged by various commercial vendors including Biotage and ISCO. Whatman pre-coated silica gel plates (250 μm) were used for analytical TLC. The terms “concentrated” and “evaporated” refer to the removal of solvent at reduced pressure on a rotary evaporator with a bath temperature less than 35^{o}C.

NOTE: Older or impure PyBroP can be contaminated with pyrrolidine, which can act as an effective nucleophile in this transformation. It is imperative to have new commercial PyBroP or to recrystallize the impure material from CH_2Cl_2/Et_2O. All reactions were performed in 2 dram vials under normal atmospheric conditions with no special precautions.

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION FOR COMPOUNDS FOUND IN TABLE 1:

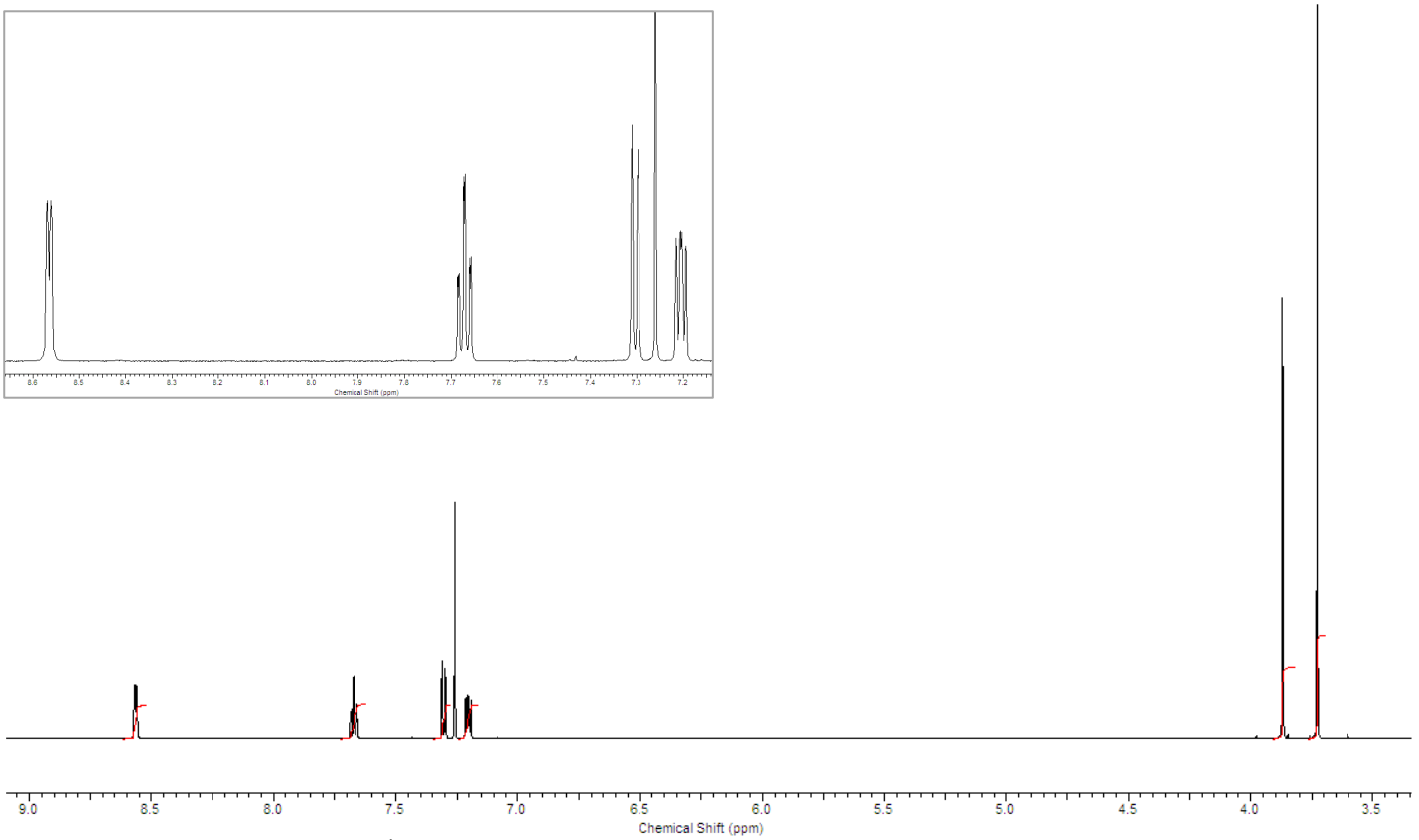
Unless otherwise noted, all reactions were prepared according to the general procedure for compound **3**, with the appropriate azine-*N*-oxide. Most reactions, although complete, were allowed to stir overnight for convenience.



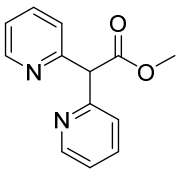
methyl 2-(pyridin-2-yl)acetate

3: In a 2-dram vial equipped with a magnetic stir bar, pyridine-*N*-oxide (100 mg, 1.05 mmol), *i*Pr_2EtN (567 µL, 3.16 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (461 µL, 2.10 mmol) and PyBroP (550 mg 1.16 mmol) were sequentially combined in THF (5 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, a mild exotherm was evident with considerable darkening of the solution. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-80% EtOAc: Heptanes) to afford the desired product as a colorless oil (128 mg, 81%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J=4.1 Hz, 1H), 7.67 (dt, J=1.8, 7.6 Hz, 1H), 7.30 (d, J=7.6 Hz, 1H), 7.20 (dd, J=5.3, 7.0 Hz, 1H), 3.87 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 154.3, 149.4, 136.8, 122.9, 52.1, 43.7. m/z = 152.0 $(M+H)^+$.

The data for this compound is consistent with commercially available material (Sigma Aldrich).

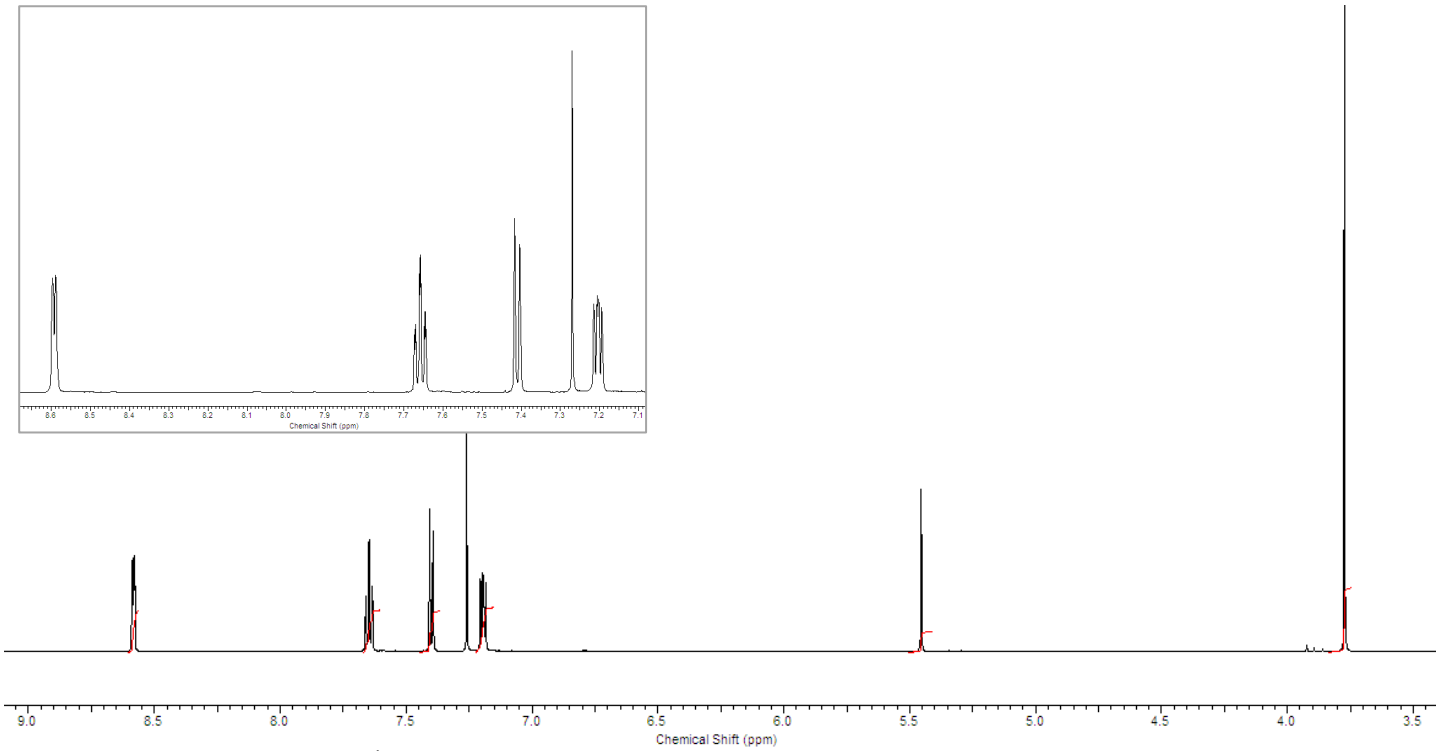


^{1}H NMR Spectrum of methyl 2-(pyridin-2-yl)acetate (**3**)

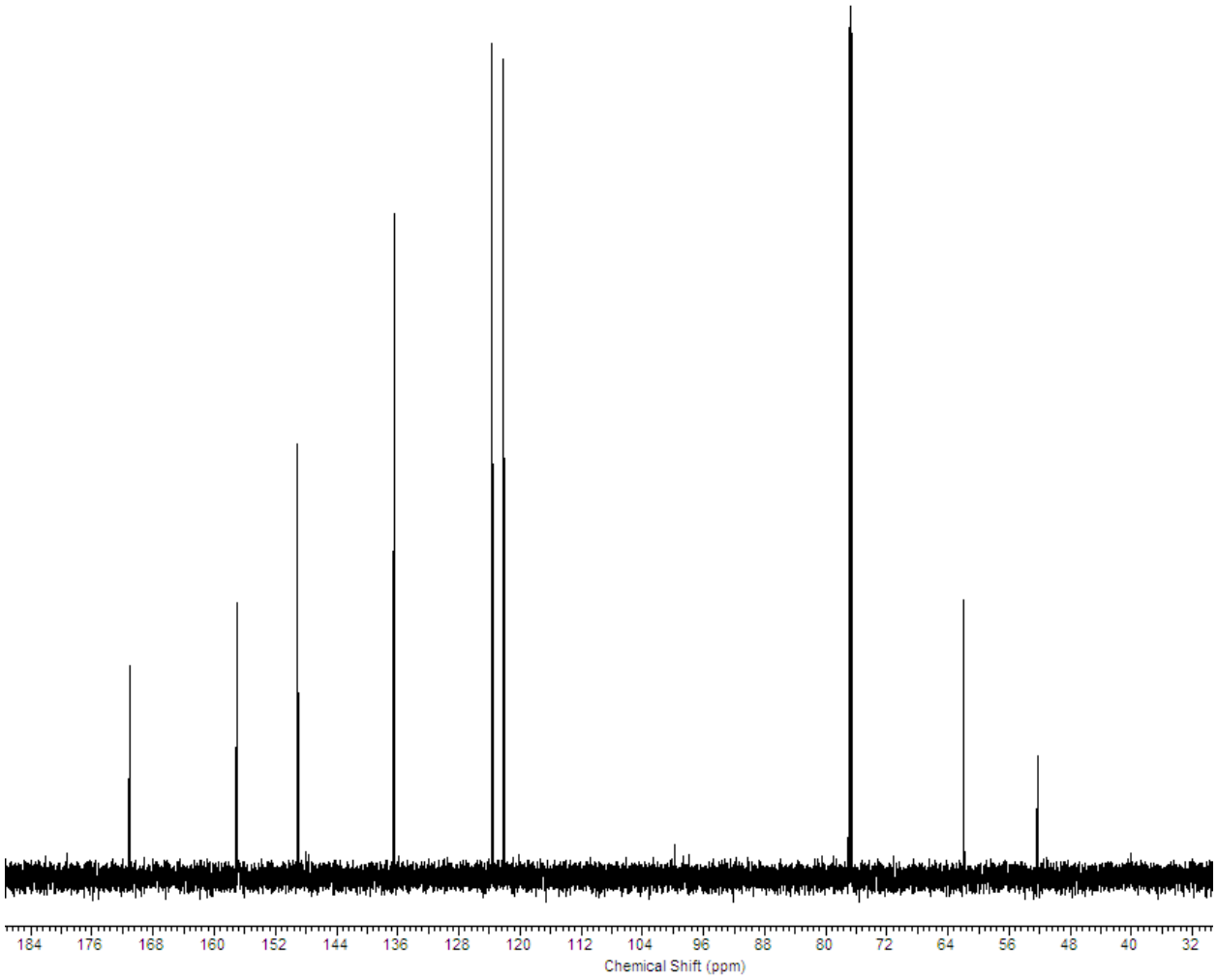


methyl 2,2-di(pyridin-2-yl)acetate

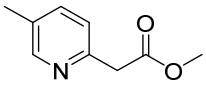
4: yellow oil – pooled from multiple reaction optimization runs.
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J=4.1 Hz, 2H), 7.66 (dt, J=1.8, 7.6 Hz, 2H), 7.41 (d, J=7.6 Hz, 2H), 7.18-7.22 (m, 2H), 5.46 (s, 1H), 3.78 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 157.3, 149.4, 136.4, 123.9, 122.4, 62.1, 51.9. HRMS Calculated for $C_{13}H_{13}N_2O_2$ $(M+H)^+$ 229.0972; Found 229.0972. FTIR (cm^{-1}) = 1739, 1588, 1433.



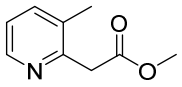
^{1}H NMR Spectrum of methyl 2,2-di(pyridin-2-yl)acetate (**4**)



^{13}C NMR Spectrum of methyl 2,2-di(pyridin-2-yl)acetate (**4**)



methyl 2-(5-methylpyridin-2-yl)acetate

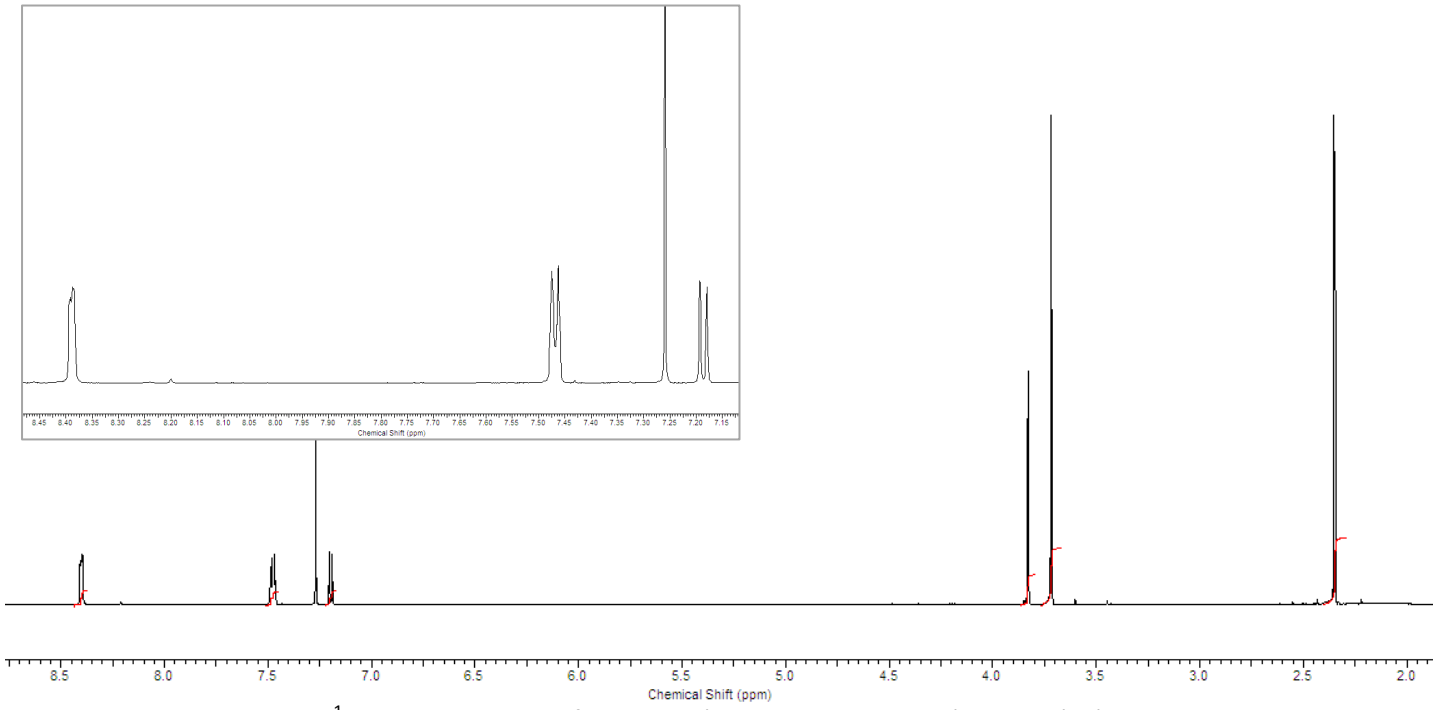


methyl 2-(3-methylpyridin-2-yl)acetate

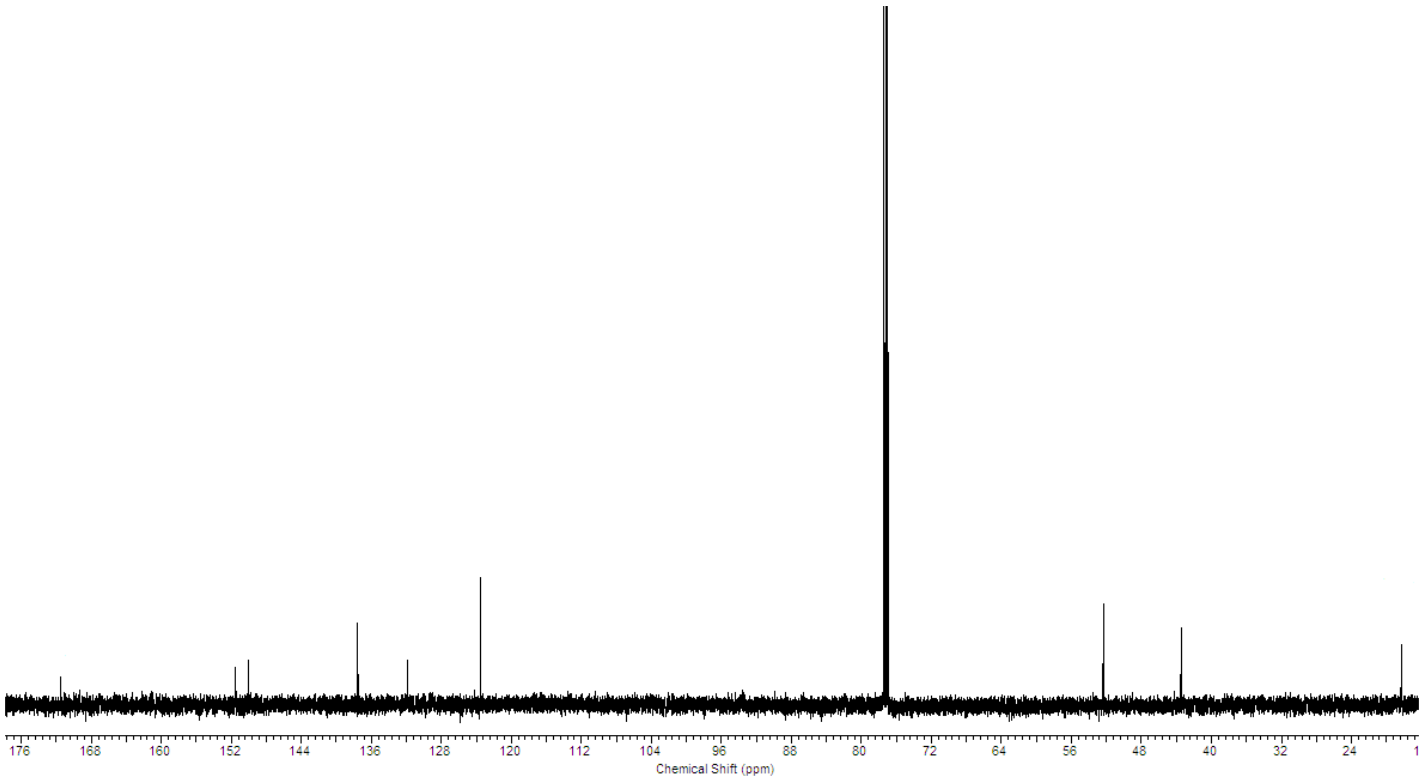
6a and **6b.** In a 2-dram vial equipped with a magnetic stir bar, 3-picoline-*N*-oxide (115 mg, 1.05 mmol), *i*Pr_2EtN (567 μL, 3.16 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (461 μL, 2.10 mmol) and PyBroP (550 mg 1.16 mmol) were sequentially combined in THF (5 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, a mild exotherm was evident with considerable darkening of the solution. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-10% EtOAc: Heptanes, with slow gradient) to afford the desired products as colorless oils.

Methyl 2-(5-methylpyridin-2-yl)acetate (63 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (m, 1H), 7.47 (d, J=8.2 Hz, 1H), 7.19 (d, J=8.2 Hz, 1H), 3.82 (s, 2H), 3.72 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 151.5, 150.0, 137.5, 131.8, 123.5, 52.3, 43.5, 18.0. HRMS Calculated for $C_9H_{12}NO_2$ $(M+H)^+$ 166.0823; Found 166.0825. FTIR (cm^{-1}) = 1732, 1160.

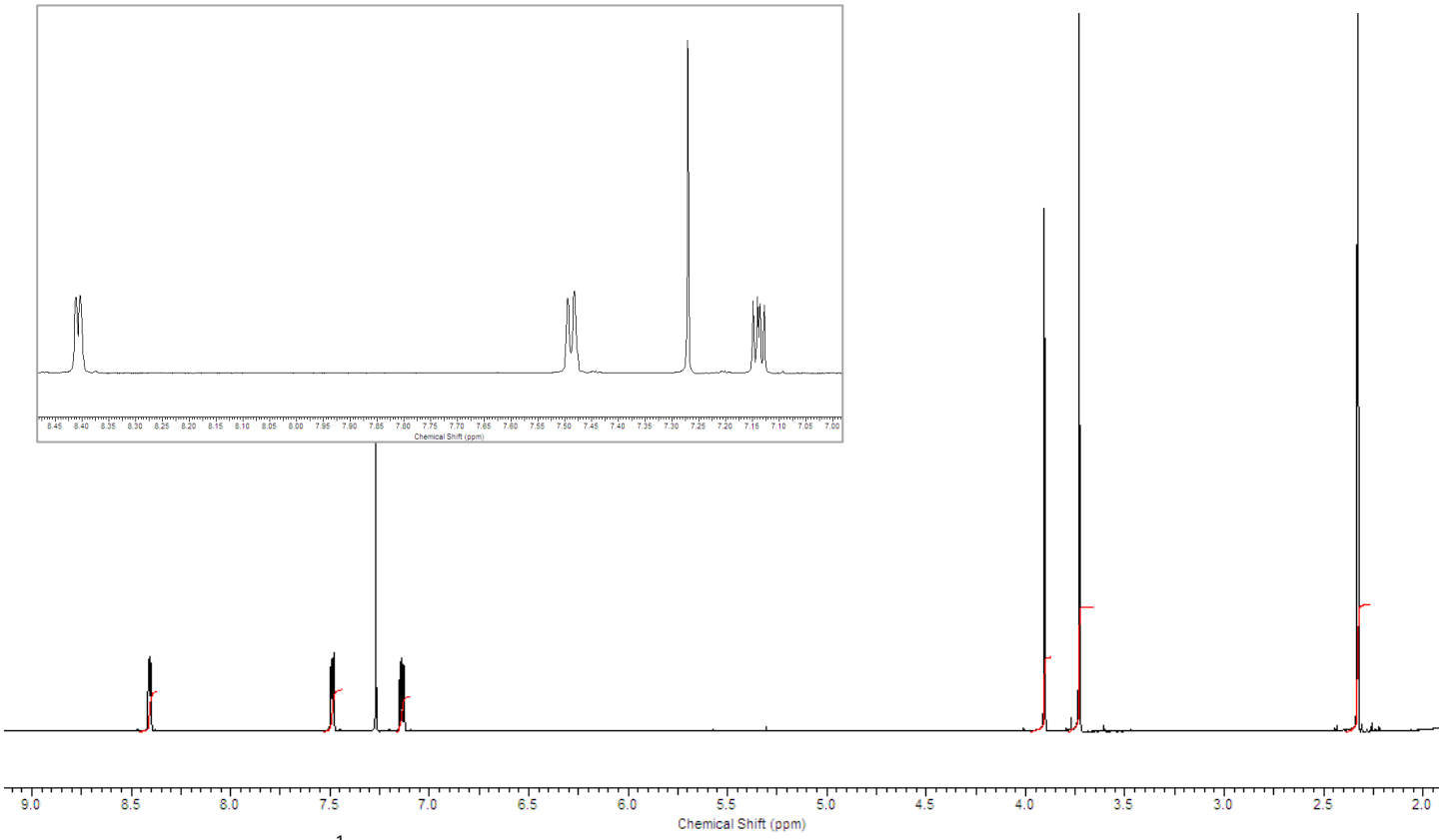


^{1}H NMR Spectrum of methyl 2-(5-methylpyridin-2-yl)acetate (**6a**)

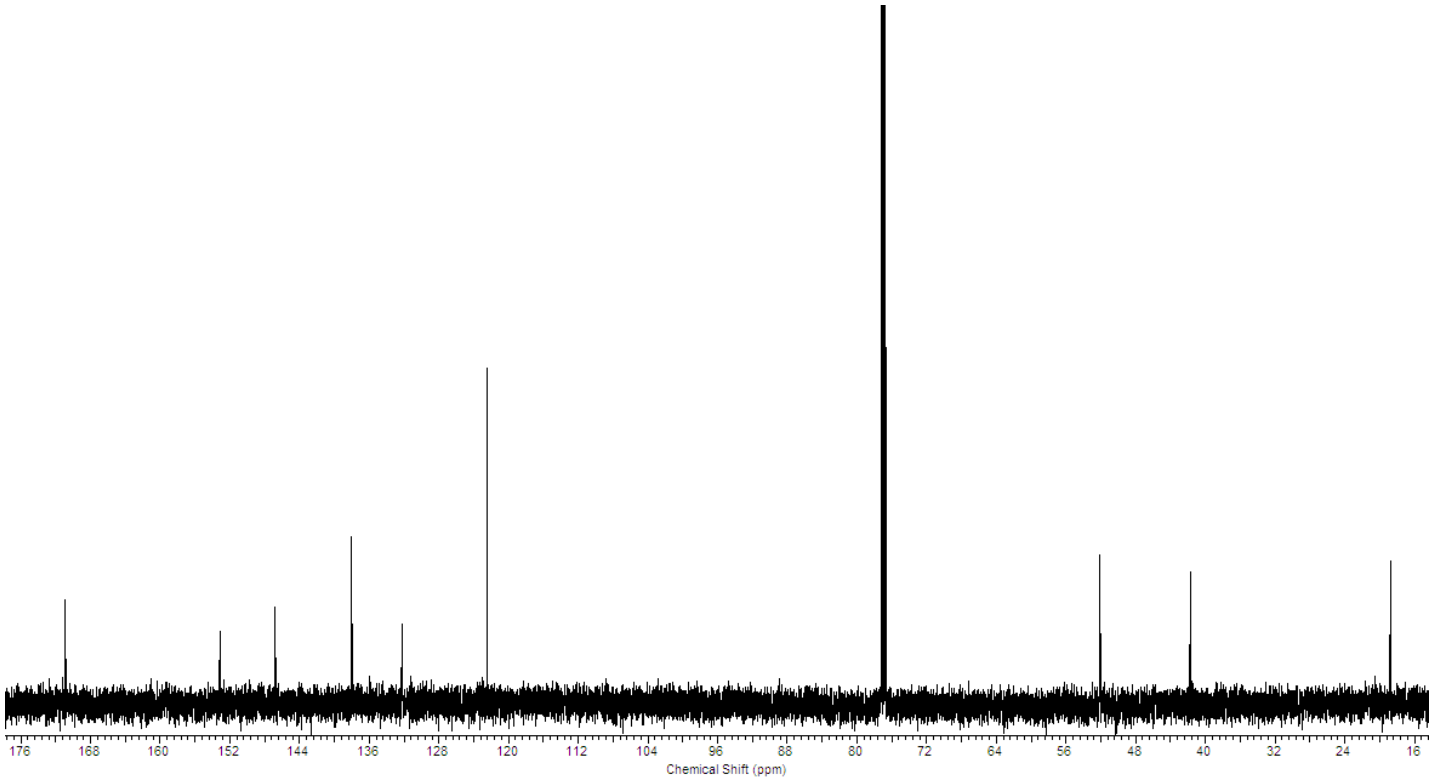


^{13}C NMR Spectrum of methyl 2-(5-methylpyridin-2-yl)acetate (**6a**)

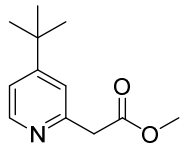
Methyl 2-(3-methylpyridin-2-yl)acetate (70 mg, 40%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J=4.1 Hz, 1H), 7.49 (d, J=7.6 Hz, 1H), 7.14 (dd, J=4.7, 7.6 Hz, 1H), 3.90 (s, 2H), 3.76 - 3.70 (m, 3H), 2.33 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 153.1, 146.8, 138.0, 132.2, 122.5, 52.1, 41.7, 18.8. HRMS Calculated for $C_9H_{12}NO_2$ $(M+H)^+$ 166.0823; Found 166.0821. FTIR (cm^{-1}) = 1735, 1158.



^{1}H NMR Spectrum of methyl 2-(3-methylpyridin-2-yl)acetate (**6b**)



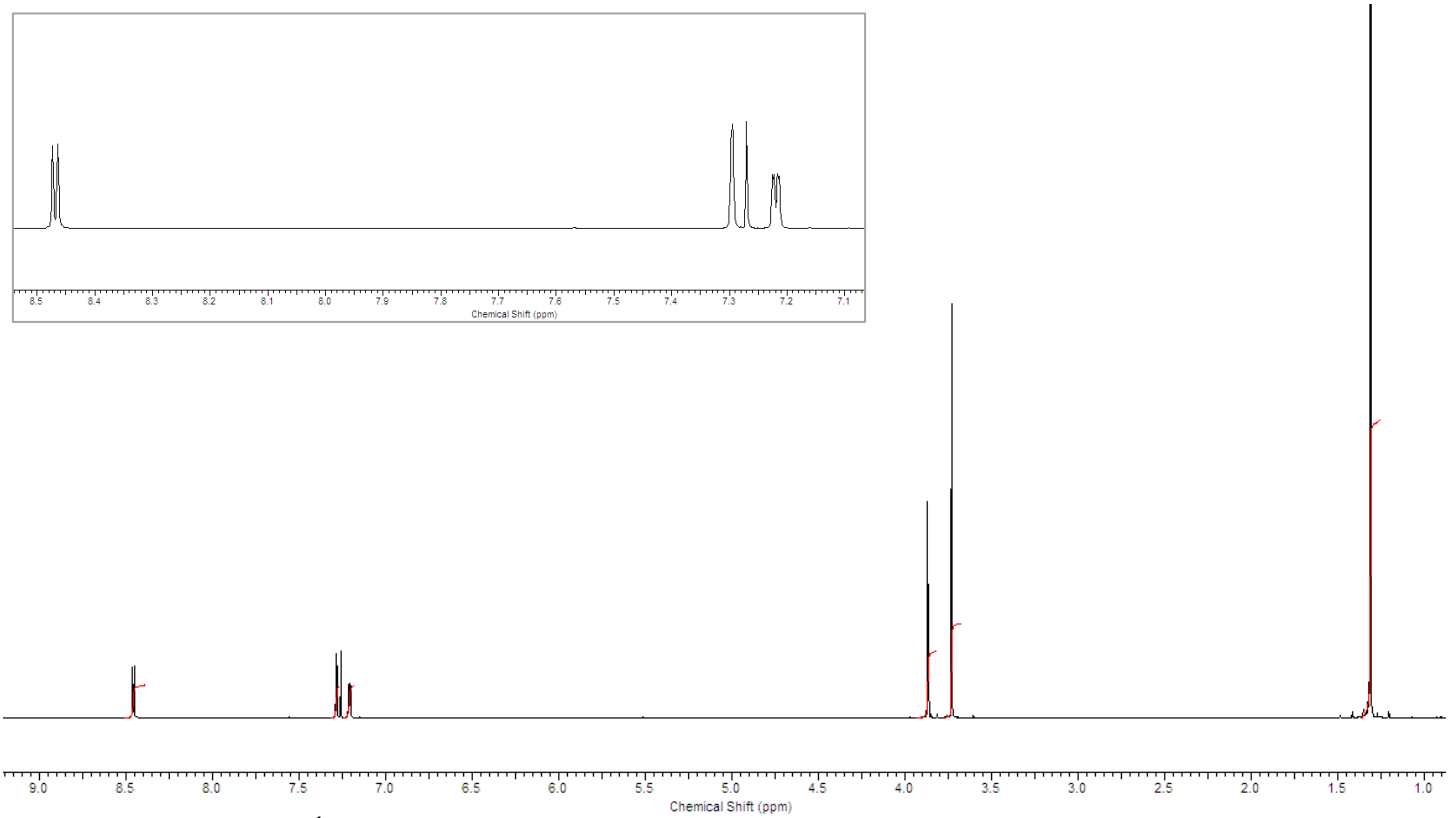
^{13}C NMR Spectrum of methyl 2-(3-methylpyridin-2-yl)acetate (**6b**)



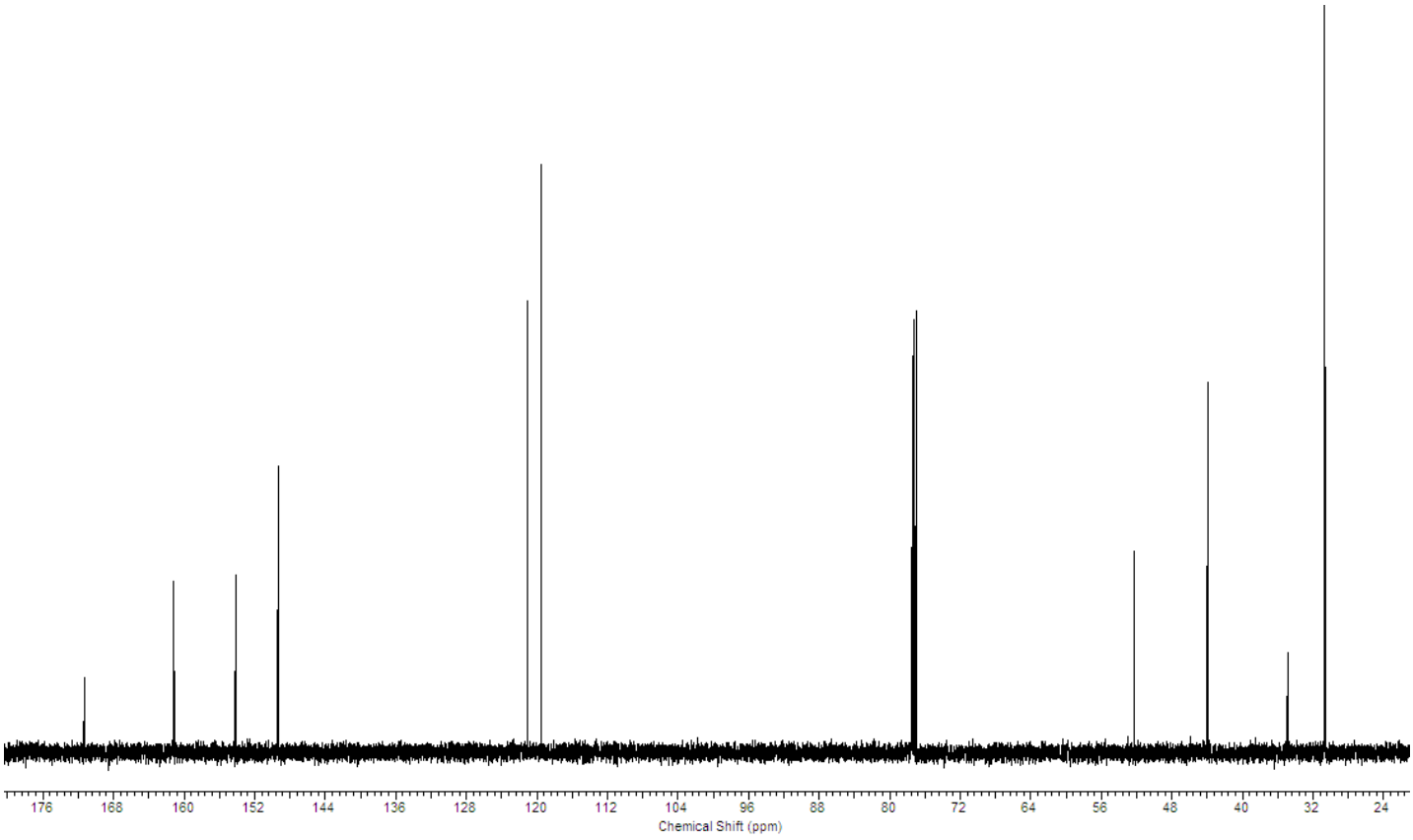
methyl 2-(4-(*tert*-butyl)pyridin-2-yl)acetate

6c: In a 2-dram vial equipped with a magnetic stir bar, 4-*tert*-butylpyridine-*N*-oxide (95.0 mg, 0.63 mmol), *i*Pr_2EtN (338 μL, 1.88 mmol), 1-(tert-butyldimethylsilyloxy)-1-methoxyethene (275 μL, 1.26 mmol) and PyBroP (329 mg 0.69 mmol) were sequentially combined in THF (4 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, a mild exotherm was evident with darkening of the solution. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product a clear oil (95 mg, 73%).

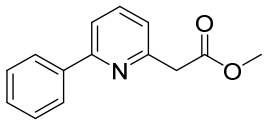
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, J=5.9 Hz, 1H), 7.29 (s, 1H), 7.22 (dd, J=1.5, 5.6 Hz, 1H), 3.88 (s, 2H), 3.74 (s, 3H), 1.32 (s, 9H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 161.2, 154.2, 149.3, 121.1, 119.5, 52.3, 43.9, 34.9, 30.7. HRMS Calculated for $C_{12}H_{18}NO_2$ $(M+H)^+$ 208.1332; Found 208.1333. FTIR (cm^{-1}) = 1740, 1600, 1195.



^{1}H NMR Spectrum of methyl 2-(4-(*tert*-butyl)pyridin-2-yl)acetate (**6c**)



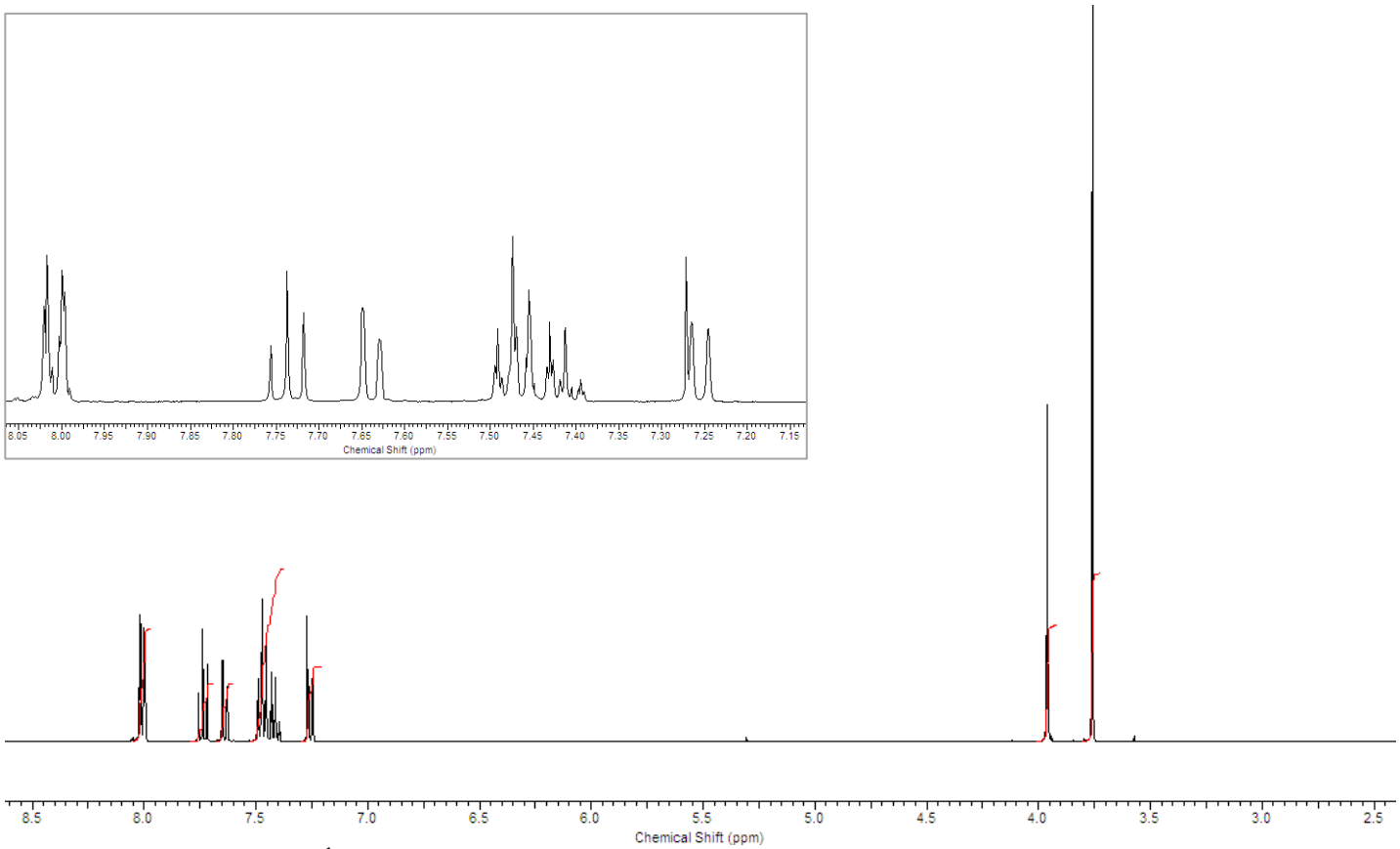
^{13}C NMR Spectrum of methyl 2-(4-(*tert*-butyl)pyridin-2-yl)acetate (**6c**)



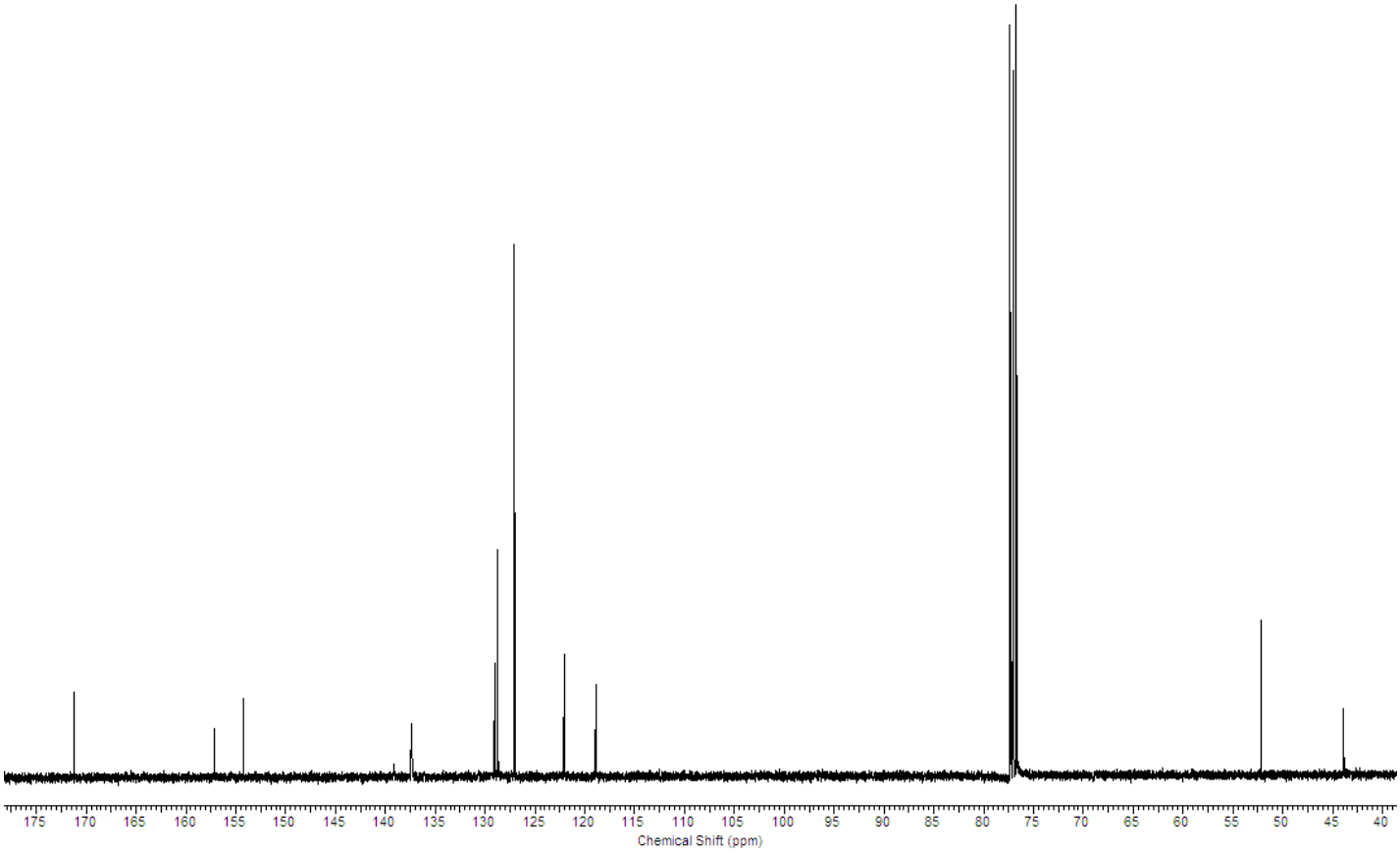
methyl 2-(6-phenylpyridin-2-yl)acetate

6d: In a 2-dram vial equipped with a magnetic stir bar, 6-phenylpyridine-*N*-oxide (45.0 mg, 0.26 mmol), *i*Pr_2EtN (140 μL, 0.78 mmol), 1-(tert-butyldimethylsilyloxy)-1-methoxyethene (114 μL, 0.52 mmol) and PyBroP (136 mg 0.29 mmol) were sequentially combined in THF (2 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, a mild exotherm was evident with darkening of the solution. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as an off-white oil (40 mg, 68%),

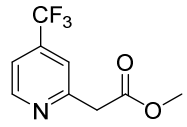
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 - 7.97 (m, 2H), 7.74 (t, J=8.2 Hz, 1H), 7.64 (d, J=7.4 Hz, 1H), 7.51 - 7.38 (m, 3H), 7.27 (dd, J=1.0, 8.2 Hz, 1H), 3.96 (s, 2H), 3.76 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 157.4, 154.5, 139.4, 137.7, 129.3, 129.0, 127.3, 122.4, 119.2, 52.4, 44.2. HRMS Calculated for $C_{14}H_{14}NO_2$ $(M+H)^+$ 228.1018; Found 228.1019. FTIR (cm^{-1}) = 1740, 1454.



^{1}H NMR Spectrum of methyl 2-(6-phenylpyridin-2-yl)acetate (**6d**)



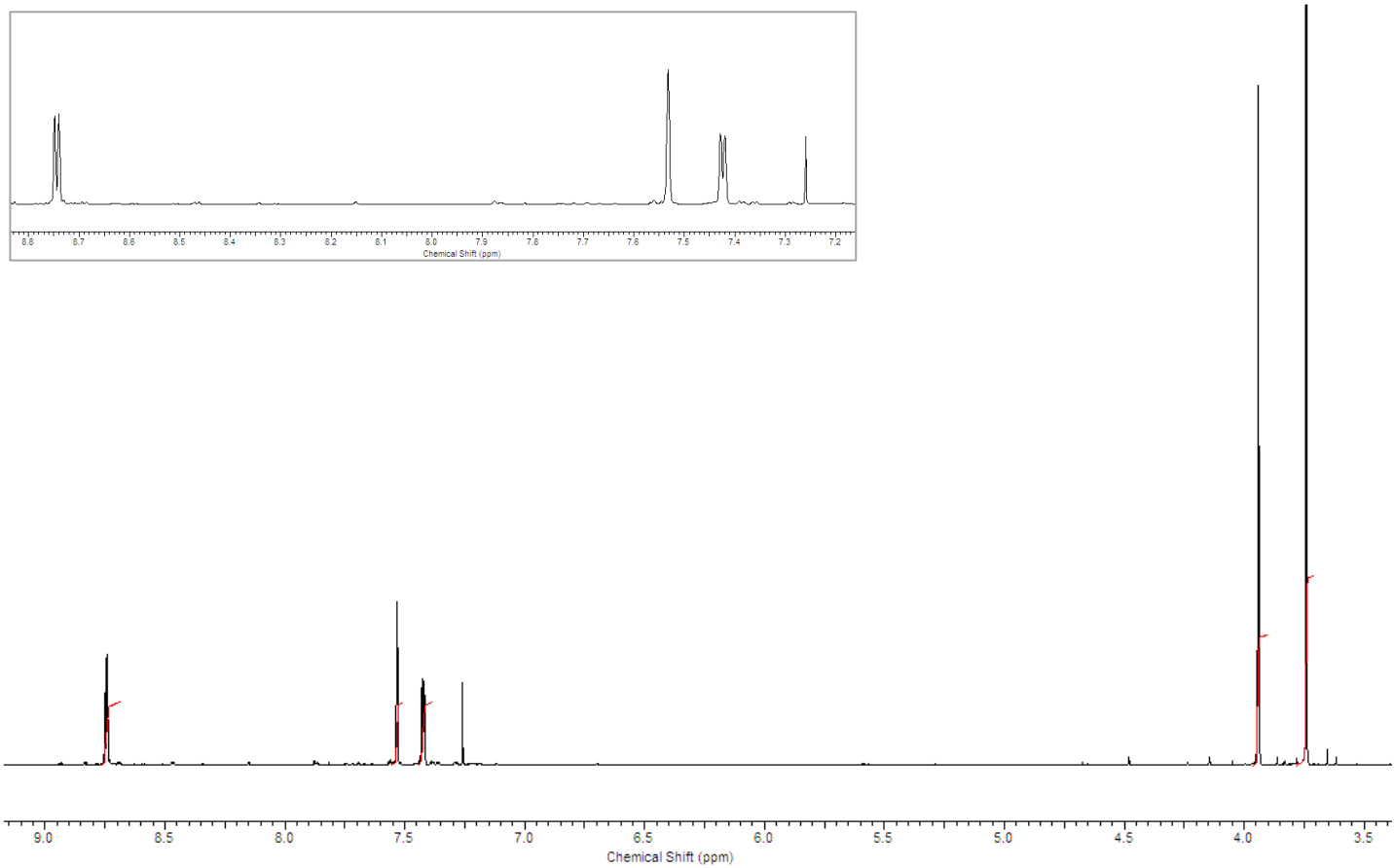
^{13}C NMR Spectrum of methyl 2-(6-phenylpyridin-2-yl)acetate (**6d**)



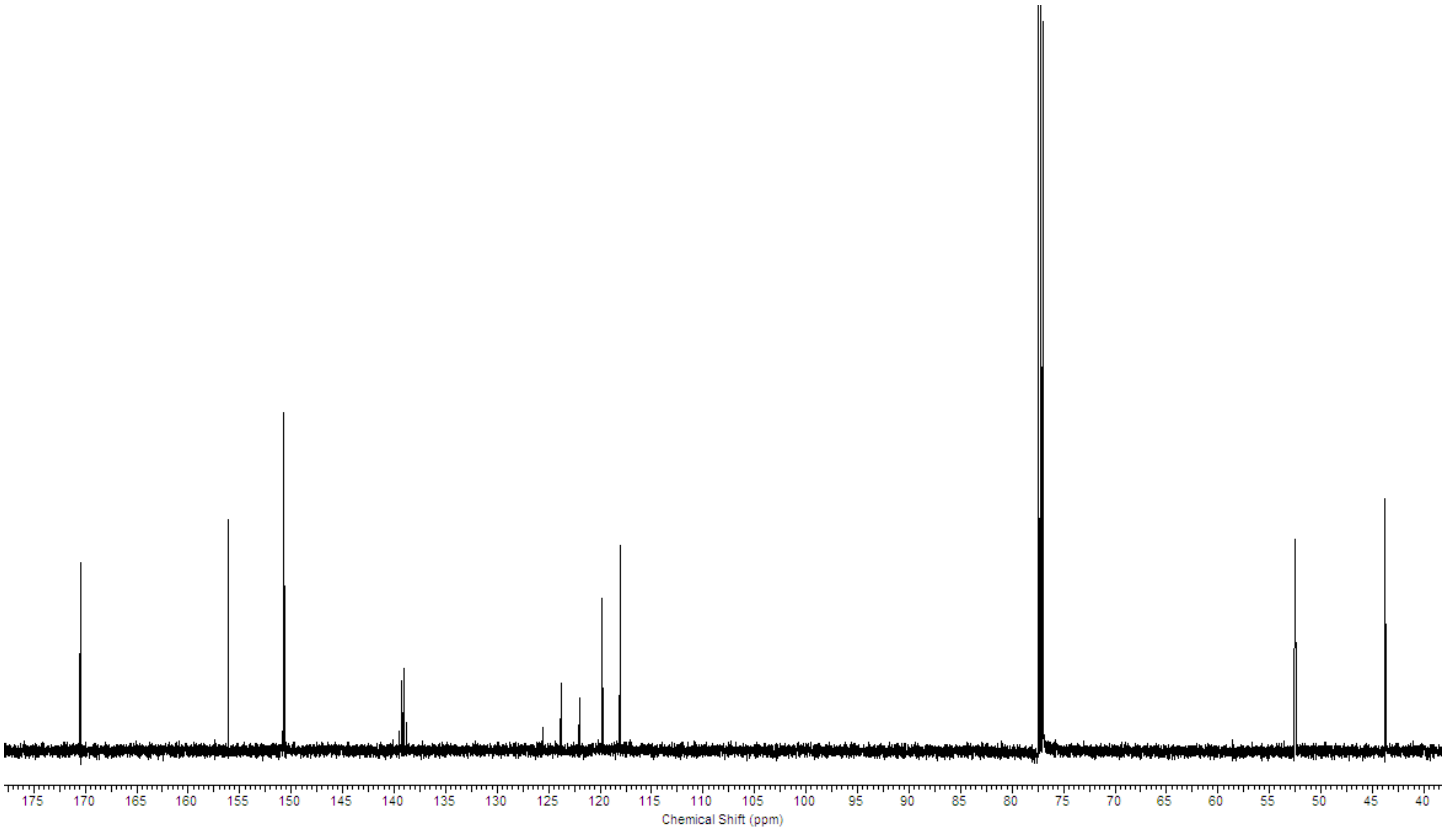
methyl 2-(4-(trifluoromethyl)pyridin-2-yl)acetate

6e: In a 2-dram vial equipped with a magnetic stir bar, 4-trifluoromethylpyridine-*N*-oxide (171 mg, 1.05 mmol), *i*Pr_2EtN (567 μL, 3.16 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (461 μL, 2.10 mmol) and PyBroP (550 mg 1.16 mmol) were sequentially combined in THF (5 mL). After stirring for 2 minutes, the reaction was heated to 45°C for 2 hours. The reaction was cooled, poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as a brown oil (113 mg, 48%).

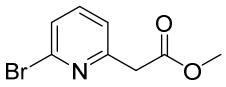
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J=4.7 Hz, 1H), 7.54 (s, 1H), 7.44 (d, J=4.7 Hz, 1H), 3.95 (s, 2H), 3.75 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 155.9, 150.5, 139.0 (q), 125.4, 123.6, 121.8, 119.6, 117.9, 52.3, 43.1. HRMS Calculated for $C_9H_9F_3NO_2$ $(M+H)^+$ 220.0580; Found 220.0573. FTIR (cm^{-1}) = 1642, 1343



^{1}H NMR Spectrum of methyl 2-(4-(trifluoromethyl)pyridin-2-yl)acetate (**6e**)



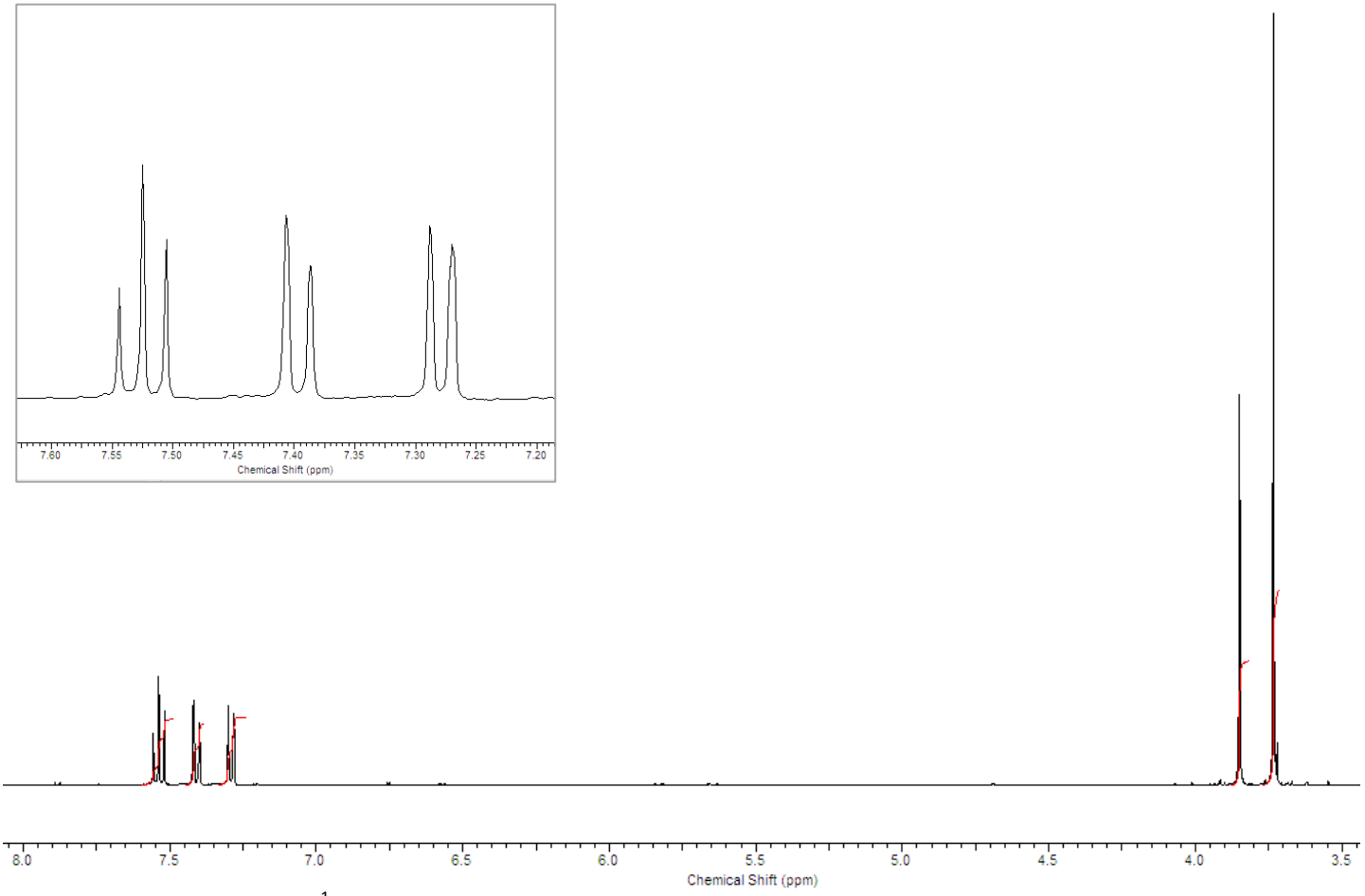
^{13}C NMR Spectrum of methyl 2-(4-(trifluoromethyl)pyridin-2-yl)acetate (**6e**)



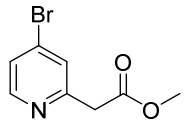
methyl 2-(6-bromopyridin-2-yl)acetate

6f: In a 2-dram vial equipped with a magnetic stir bar, 6-bromopyridine-*N*-oxide (174 mg, 1.00 mmol), *i*Pr_2EtN (557 μL, 3.10 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (438 μL, 2.00 mmol) and PyBroP (523 mg 1.10 mmol) were sequentially combined in THF (5 mL). After stirring for 2 minutes, the reaction was heated to 45°C for 2 hours. The reaction was cooled, poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as an orange oil (80 mg, 35%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (t, J=8.0 Hz, 1H), 7.41 (d, J=8.0 Hz, 1H), 7.29 (d, J=8.0 Hz, 1H), 3.85 (s, 2H), 3.73 (s, 3H).
^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 155.5, 141.5, 138.9, 126.6, 122.9, 52.3, 43.1. m/z = 231.9 $(M+H)^+$.

The data for this compound is consistent with commercially available material (D-L Chiral Chemicals).



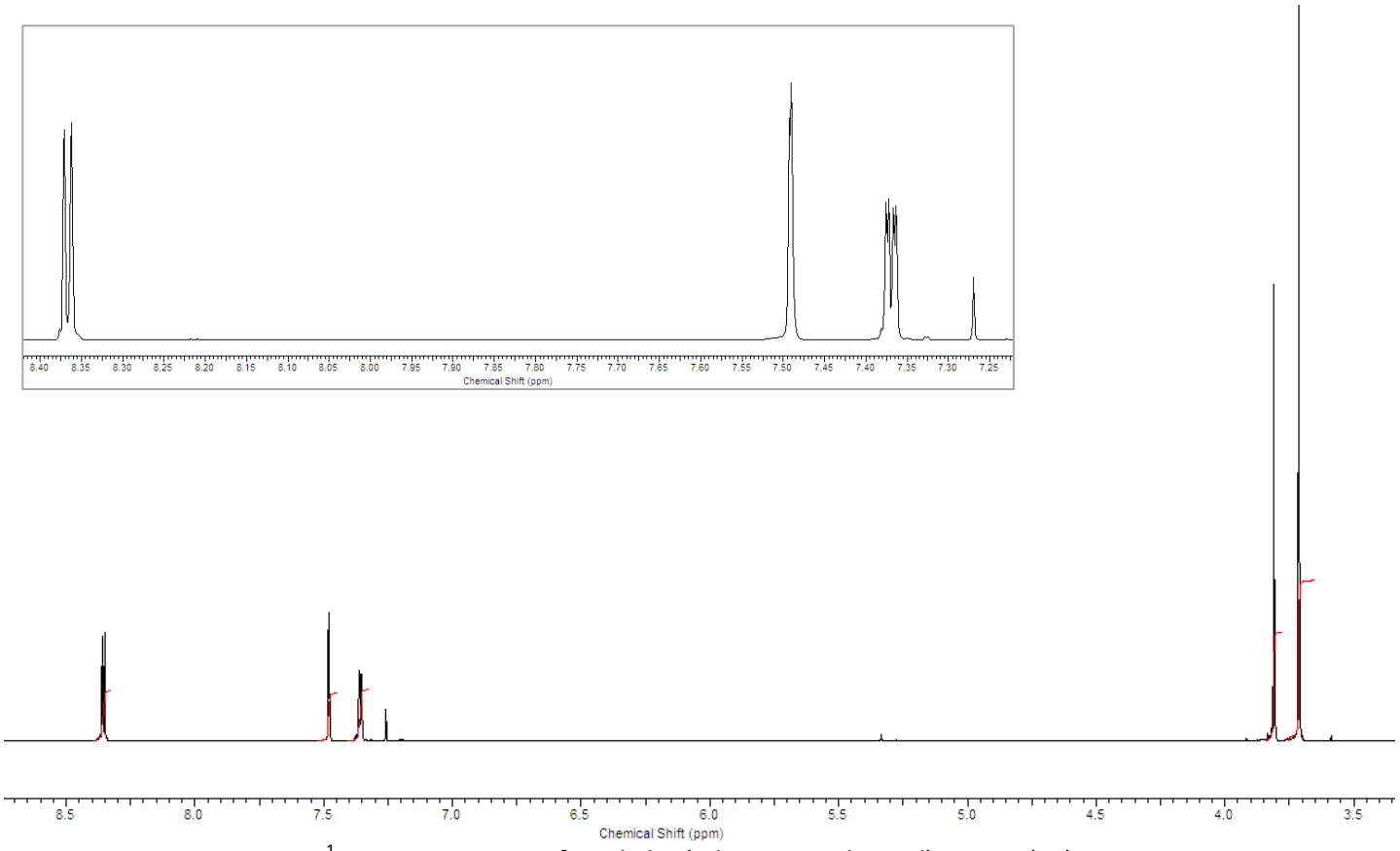
^{1}H NMR Spectrum of methyl 2-(6-bromopyridin-2-yl)acetate (**6f**)



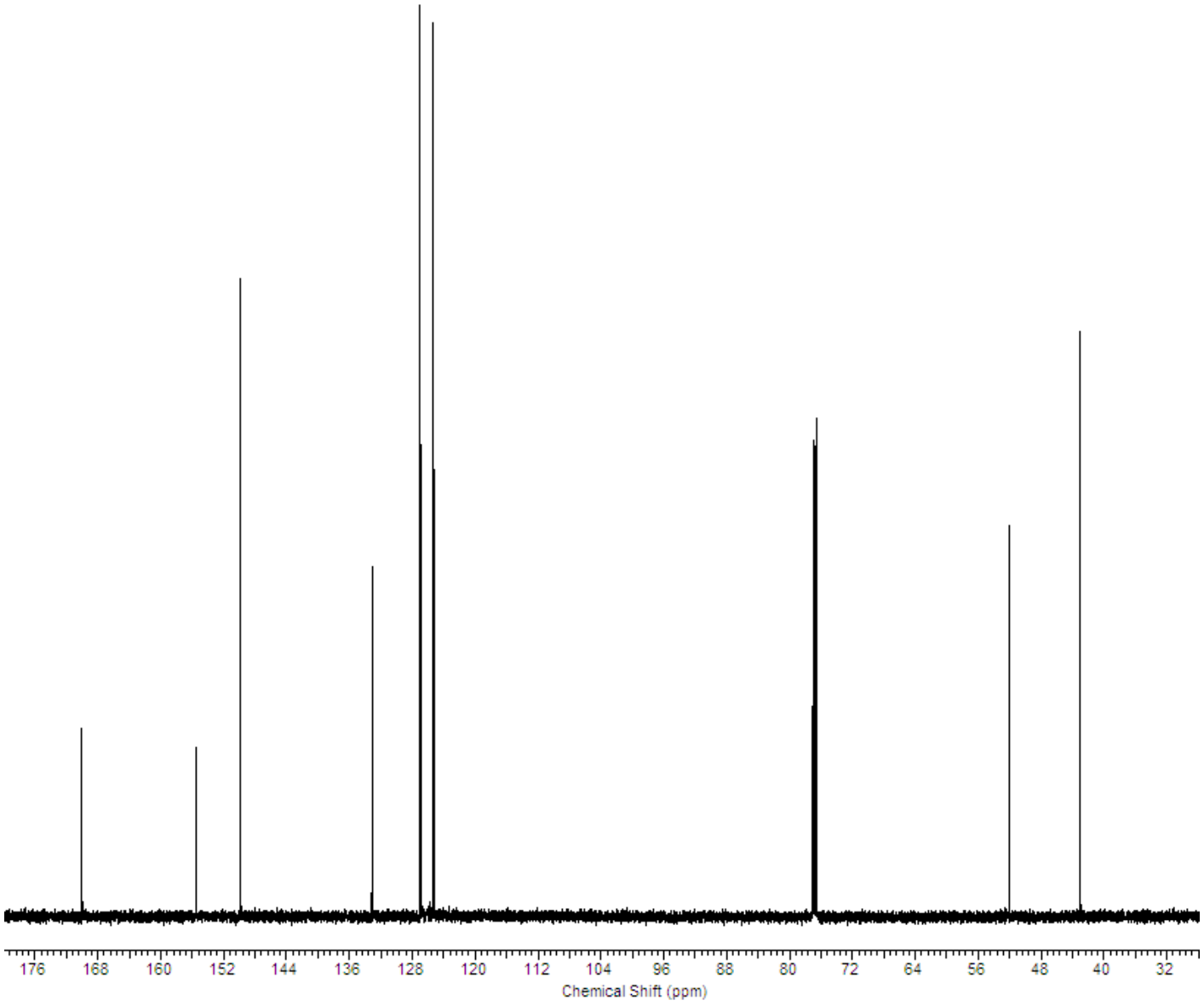
methyl 2-(4-bromopyridin-2-yl)acetate

6g: In a 2-dram vial equipped with a magnetic stir bar, 4-bromopyridine-*N*-oxide (100 mg, 0.58 mmol), *i*Pr_2EtN (310 µL, 1.72 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (252 µL, 1.15 mmol) and PyBroP (301 mg 0.63 mmol) were sequentially combined in THF (3 mL). The vial was capped and stirred vigorusly at room temperature. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as an off-white oil (95 mg, 73%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, J=5.3 Hz, 1H), 7.49 (d, J=1.8 Hz, 1H), 7.37 (dd, J=1.8, 5.3 Hz, 1H), 3.82 (s, 2H), 3.72 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 155.5, 149.9, 133.0, 127.0, 125.3, 52.0, 43.0. HRMS Calculated for $C_8H_9BrNO_2$ $(M+H)^+$ 229.9807; Found 229.9811. FTIR (cm^{-1}) = 1735, 1175.



^{1}H NMR Spectrum of methyl 2-(4-bromopyridin-2-yl)acetate (**6g**)



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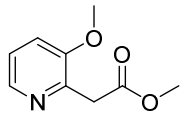
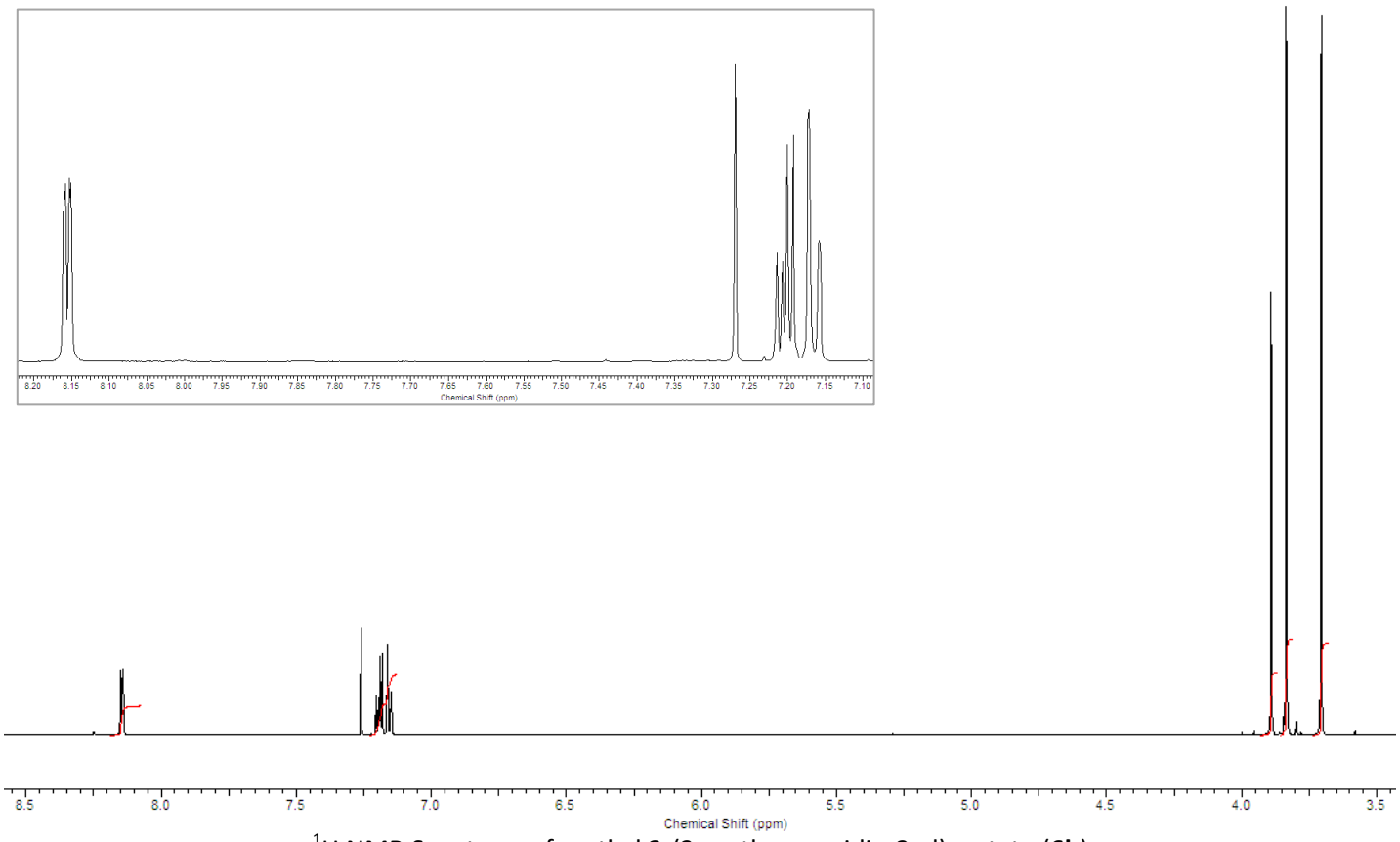
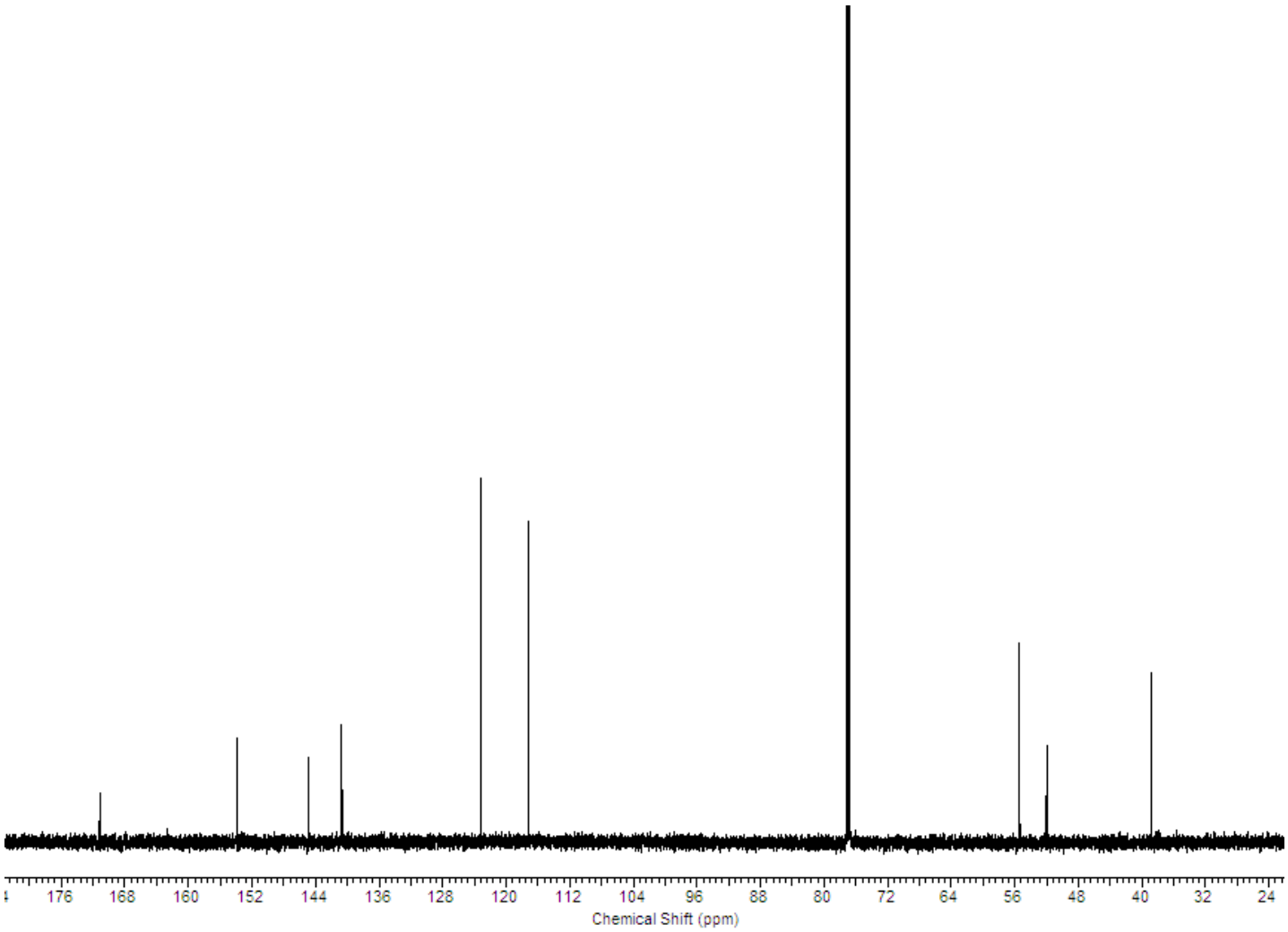


methyl 2-(3-methoxypyridin-2-yl)acetate

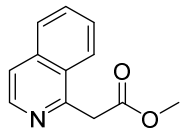
6h: In a 2-dram vial equipped with a magnetic stir bar, 3-methoxypyridine-*N*-oxide (75 mg, 0.60 mmol), *i*Pr_2EtN (323 μL, 1.80 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (262 μL, 1.20 mmol) and PyBroP (314 mg 0.66 mmol) were sequentially combined in THF (3 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, the reaction was heated to 45°C for 2 hours. The reaction was cooled, poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as an off-white oil (52 mg, 48%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (dd, J=1.2, 4.7 Hz, 1H), 7.19 (dd, J=4.7, 8.2 Hz, 1H), 7.15 (d, J=7.6 Hz, 1H), 3.89 (s, 2H), 3.84 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 154.1, 145.1, 141.0, 123.4, 117.5, 55.6, 52.2, 39.0. HRMS Calculated for $C_9H_{11}NNaO_3$ $(M+Na)^+$ 204.0632; Found 204.0631. FTIR (cm^{-1}) = 1740, 1429, 1270.



^{1}H NMR Spectrum of methyl 2-(3-methoxypyridin-2-yl)acetate (**6h**)

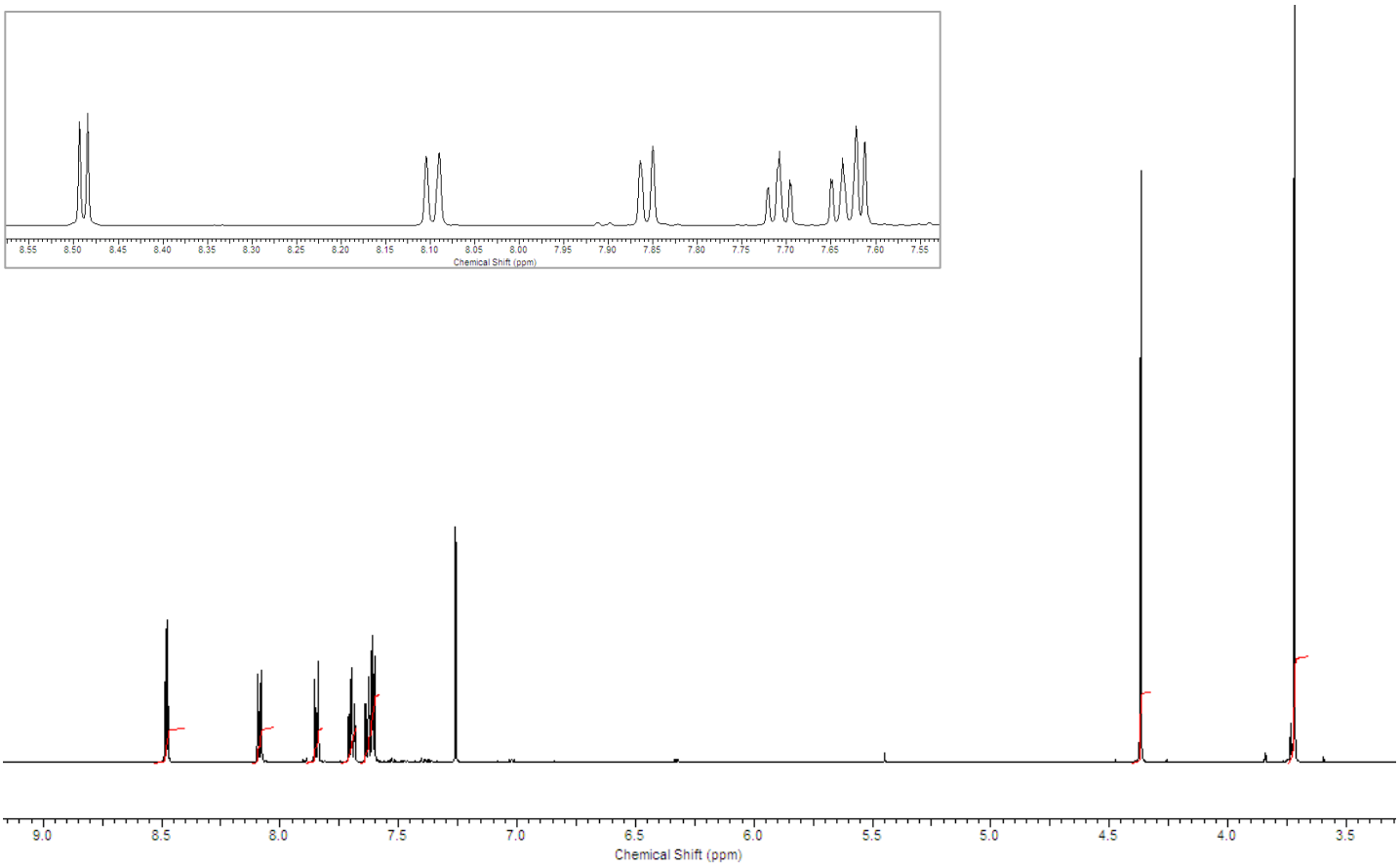


^{13}C NMR Spectrum of methyl 2-(3-methoxypyridin-2-yl)acetate (**6h**)

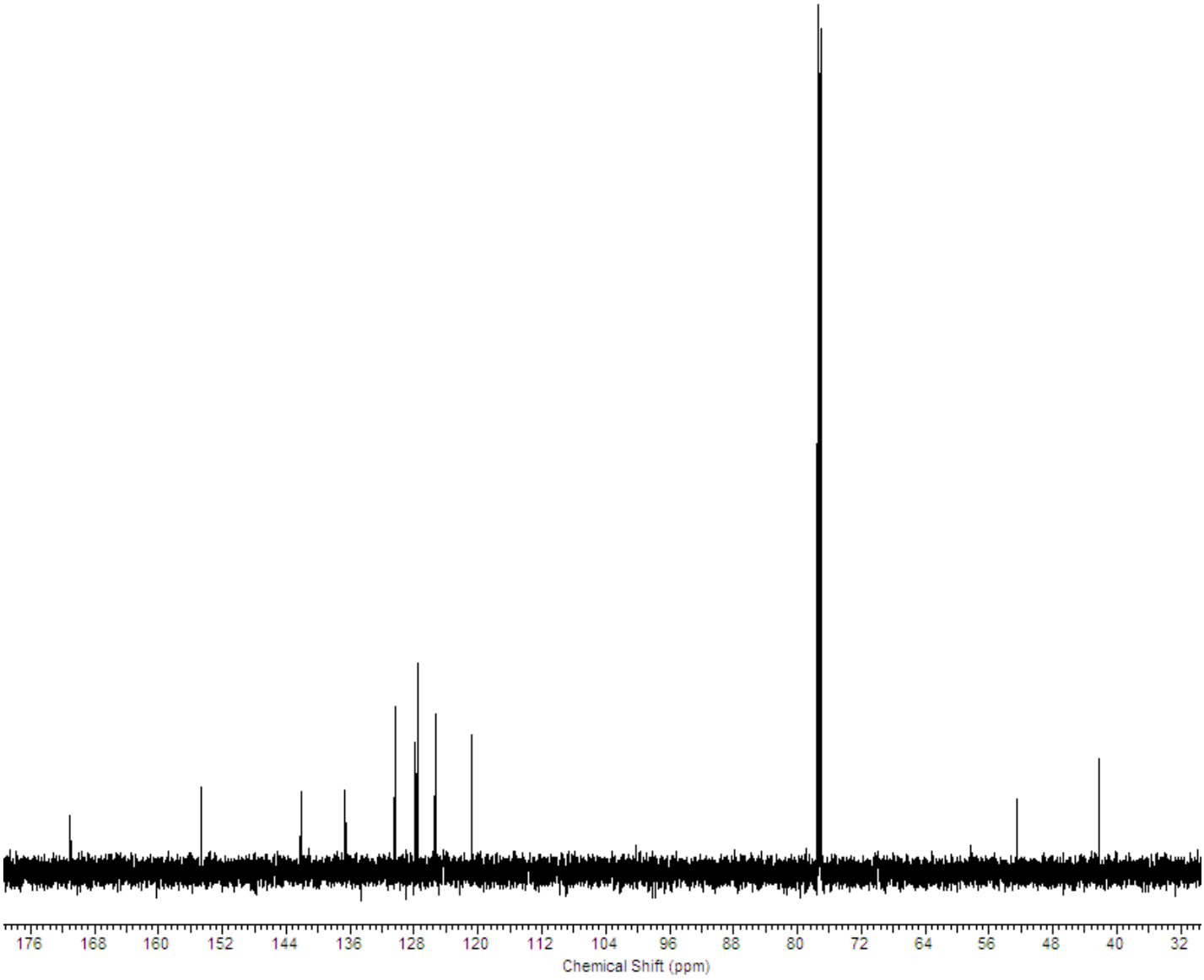


methyl 2-(isoquinolin-1-yl)acetate

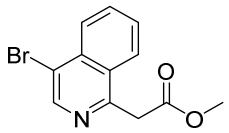
6i: Prepared in analogous fashion to **3** with isoquinoline-*N*-oxide. Tan solid (131 mg, 62%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, J=5.9 Hz, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.86 (d, J=8.2 Hz, 1H), 7.68-7.73 (m, 1H), 7.60-7.66 (m, 2H), 4.38 (s, 2H), 3.66-3.79 (m, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.6, 154.2, 141.8, 136.2, 130.0, 127.4, 127.2, 124.9, 120.3, 52.1, 41.8. HRMS Calculated for $C_{12}H_{12}NO_2$ $(M+H)^+$ 202.0863; Found 202.0868. FTIR (cm^{-1}) = 1738, 1242. MP = 115-120°C.



^{1}H NMR Spectrum of methyl 2-(isoquinolin-1-yl)acetate (**6i**)

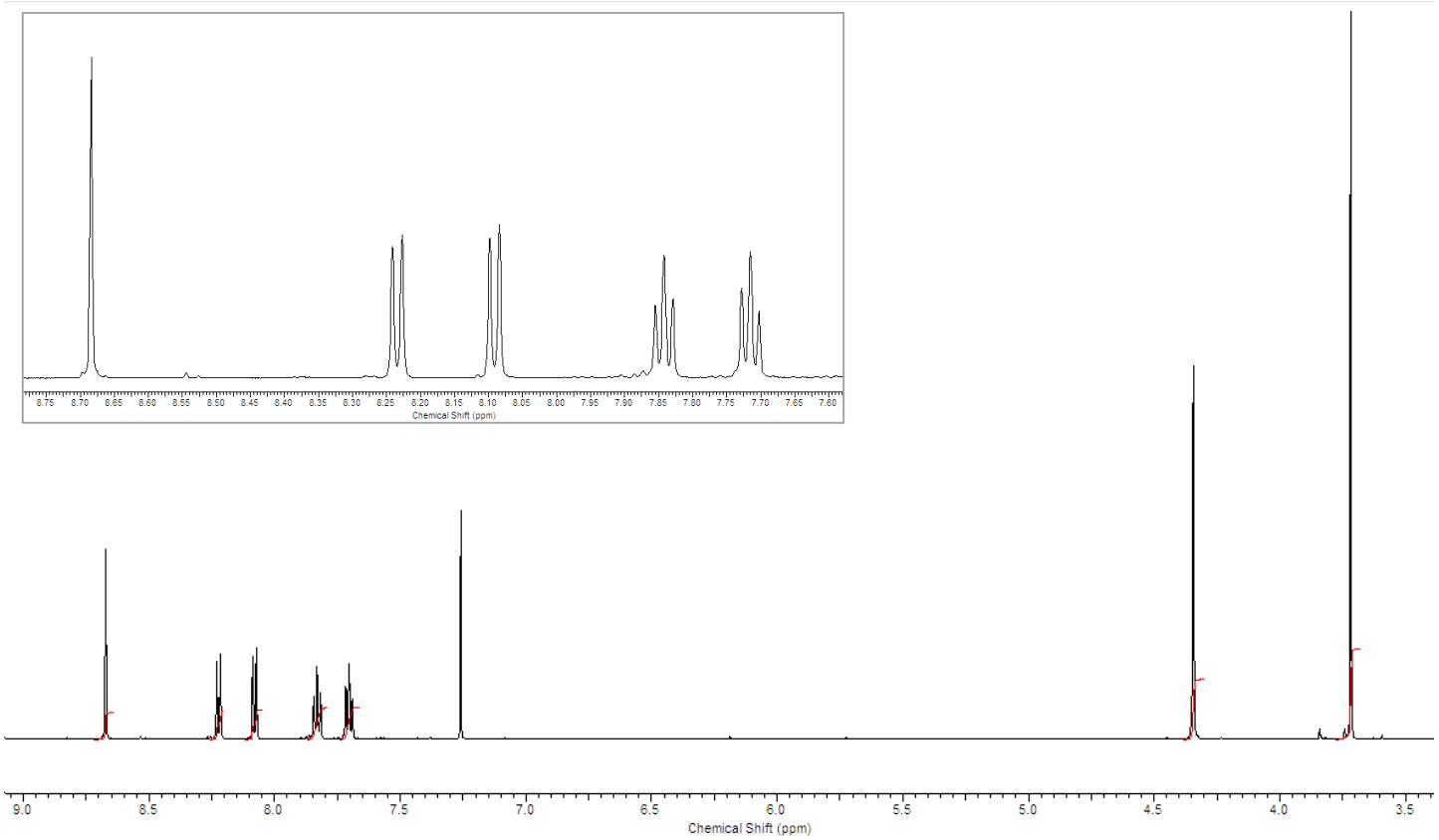


^{13}C NMR Spectrum of methyl 2-(isoquinolin-1-yl)acetate (**6i**)

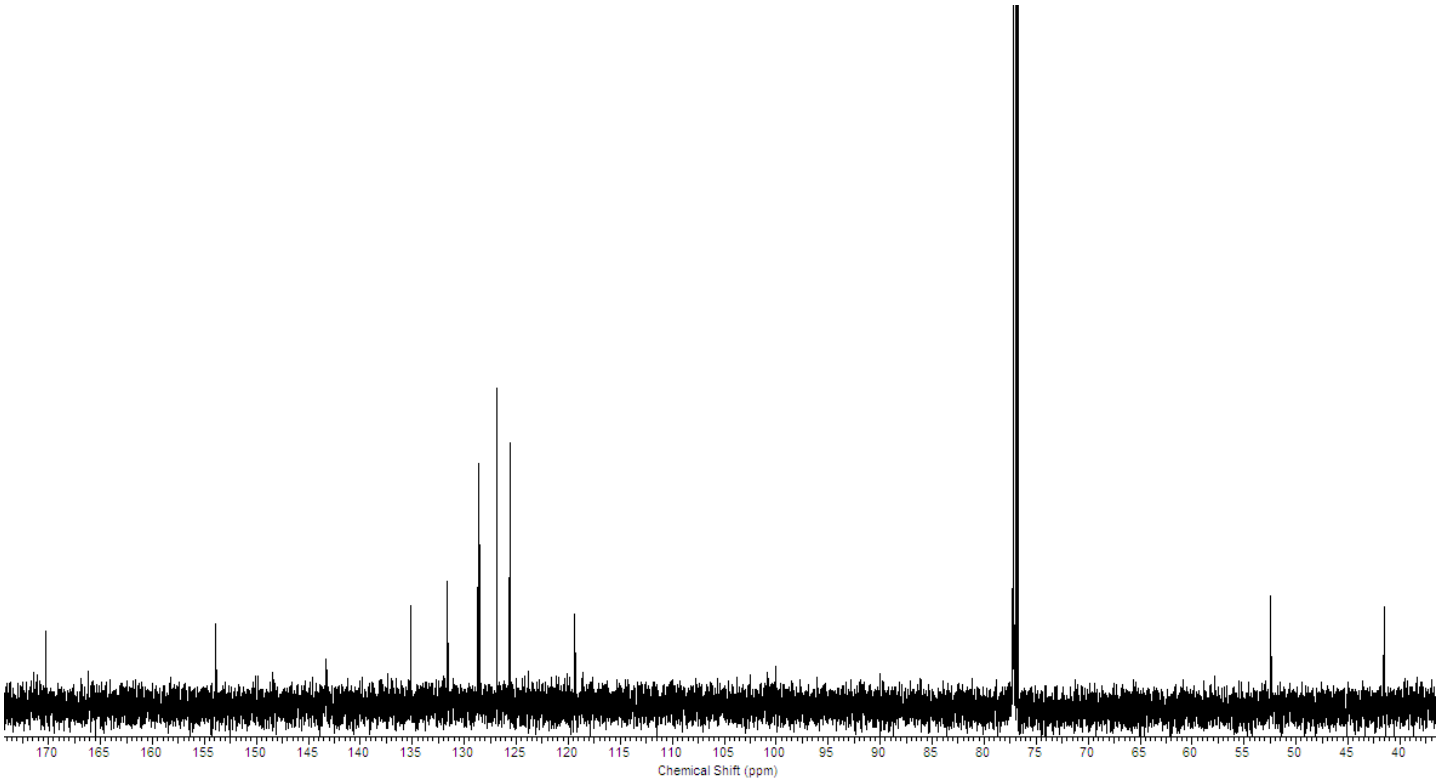


methyl 2-(4-bromoisoquinolin-1-yl)acetate

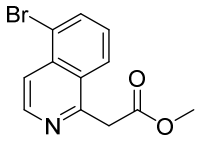
6j: Prepared in analogous fashion to **3** with 4-bromoisoquinoline-*N*-oxide. Yellow solid (205 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 8.23 (d, J=8.8 Hz, 1H), 8.09 (d, J=8.2 Hz, 1H), 7.84 (t, J=7.9 Hz, 1H), 7.73 - 7.69 (m, J=7.6 Hz, 1H), 4.36 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 153.9, 135.2, 131.6, 128.7, 128.5, 126.9, 125.7, 119.4, 52.4, 41.6. HRMS Calculated for $C_{12}H_{11}BrNO_2$ $(M+H)^+$ 279.9968; Found 279.9964. FTIR (cm^{-1}) = 1738. MP = 62-65^{o}C.



^{1}H NMR methyl 2-(4-bromoisoquinolin-1-yl)acetate (**6j**)



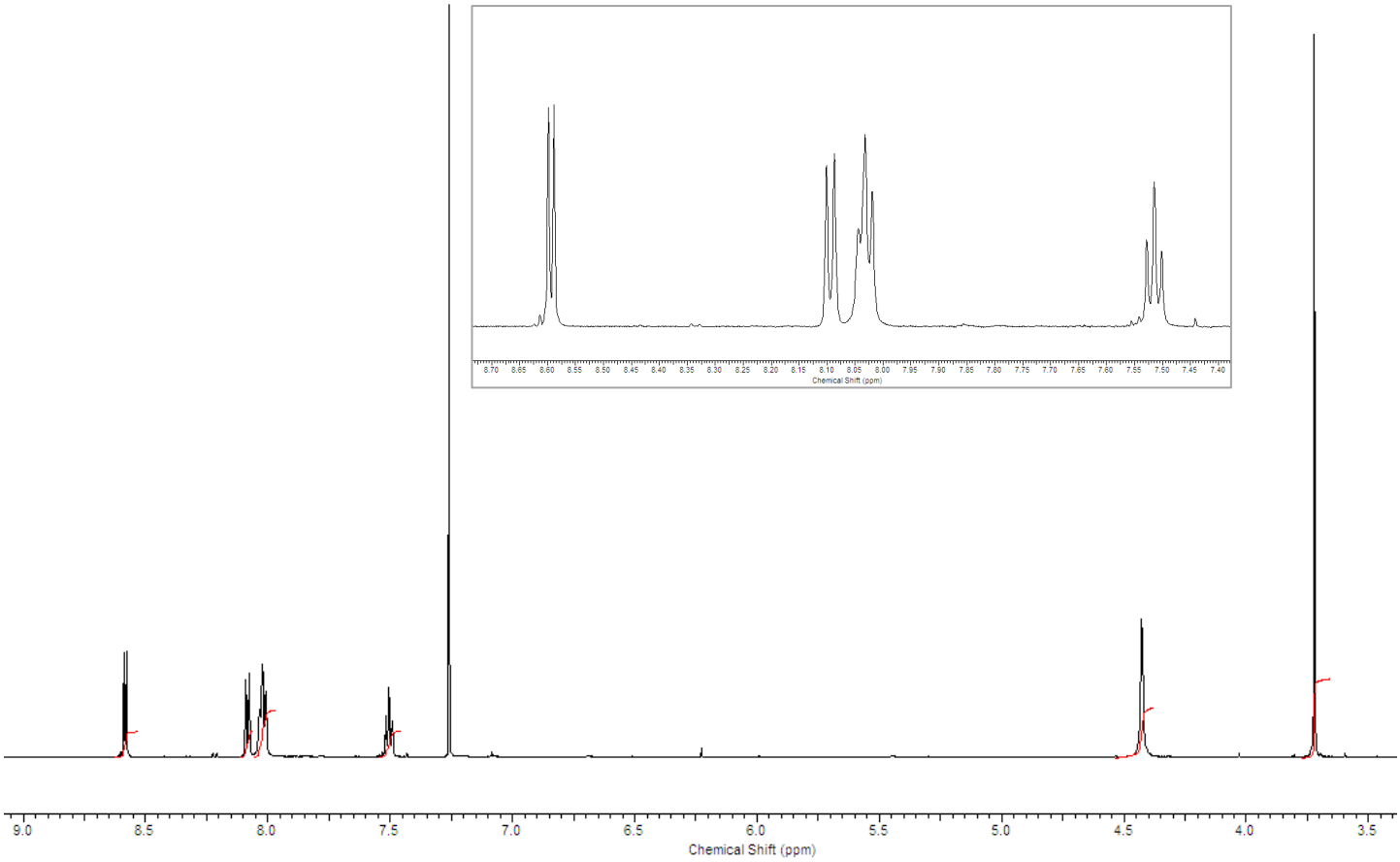
^{13}C NMR Spectrum of methyl 2-(4-bromoisoquinolin-1-yl)acetate (**6j**)



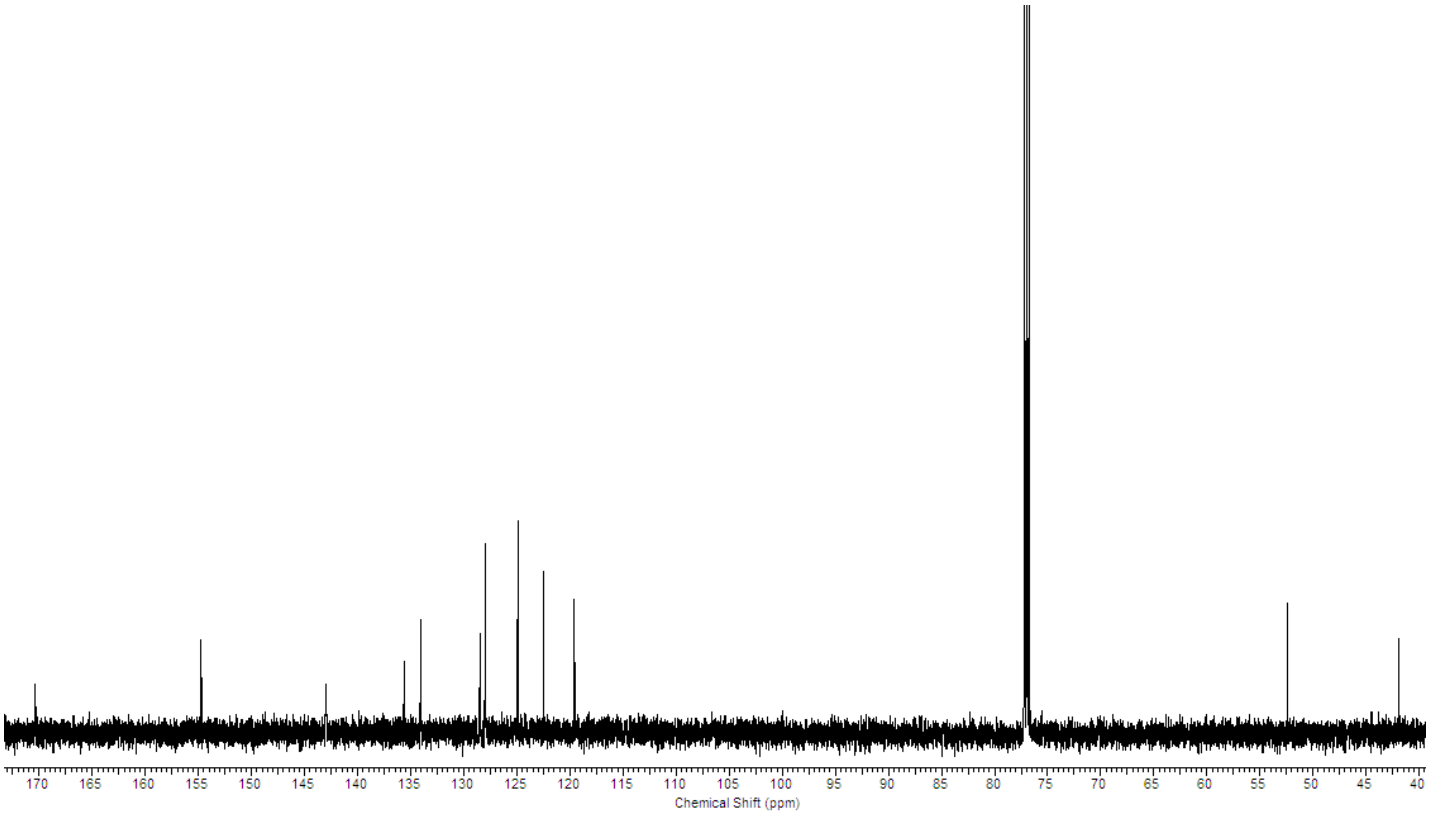
methyl 2-(5-bromoisoquinolin-1-yl)acetate

6k: In a 2-dram vial equipped with a magnetic stir bar, 5-bromoisoquinoline-*N*-oxide (112 mg, 0.50 mmol), *i*Pr_2EtN (269 µL, 1.50 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (219 µL, 1.00 mmol) and PyBroP (262 mg 0.55 mmol) were sequentially combined in THF (3 mL). The vial was capped and stirred vigorously at room temperature. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as yellow solid (84 mg, 60%).

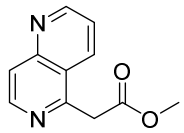
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J=5.9 Hz, 1H), 8.09 (d, J=8.2 Hz, 1H), 7.99-8.06 (m, 2H), 7.51 (t, J=7.9 Hz, 1H), 4.44 (br. s., 2H), 3.73 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.4, 154.8, 143.0, 135.6, 134.1, 128.5, 128.2, 125.0, 122.5, 119.6, 52.4, 41.9. HRMS Calculated for $C_{12}H_{11}BrNO_2$ $(M+H)^+$ 279.9968; Found 279.9969. FTIR (cm^{-1}) = 1742, 1177. MP =80-82°C.



^{1}H NMR Spectrum of methyl 2-(5-bromoisoquinolin-1-yl)acetate (**6k**)



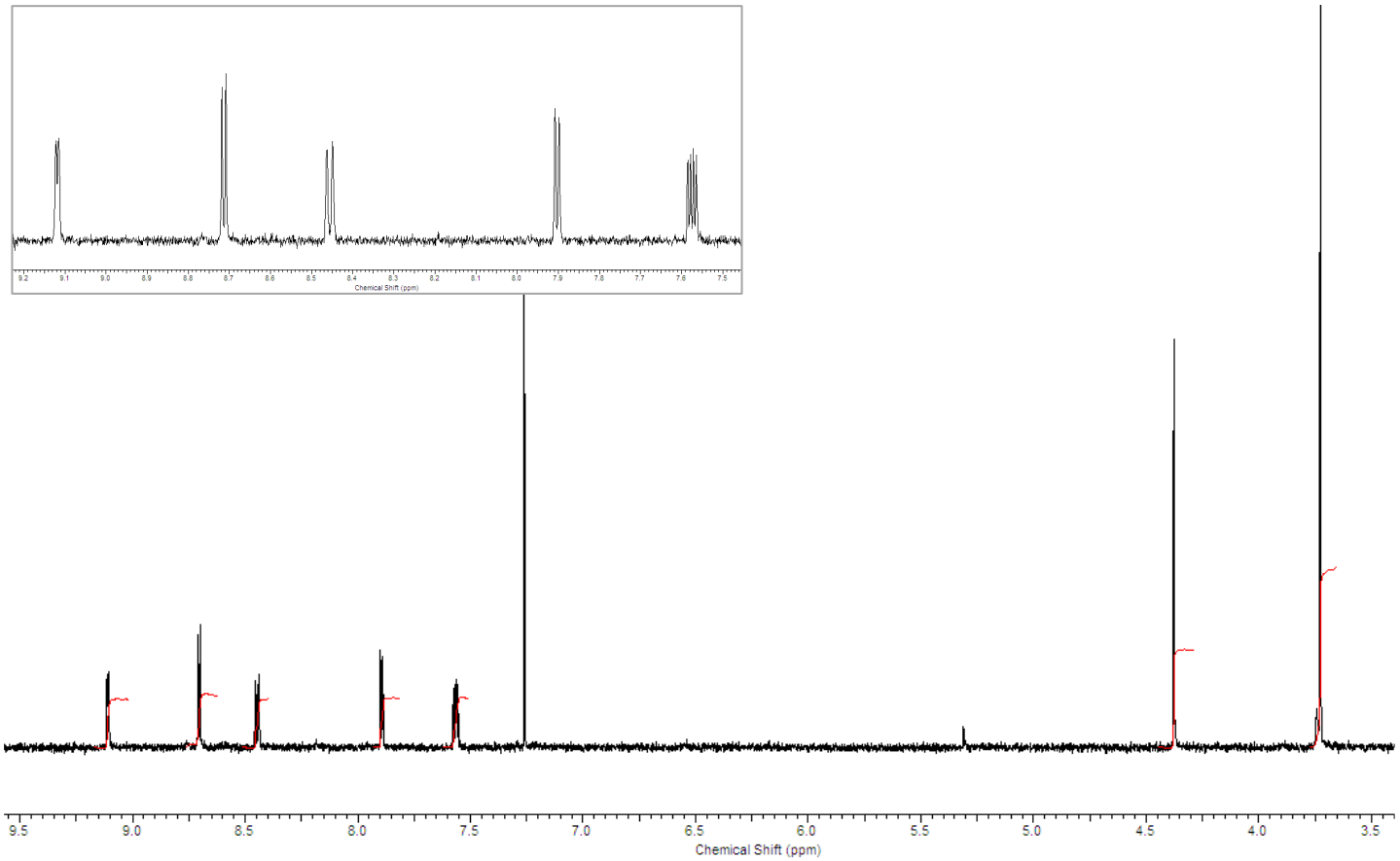
^{13}C NMR Spectrum of methyl 2-(5-bromoisoquinolin-1-yl)acetate (**6k**)



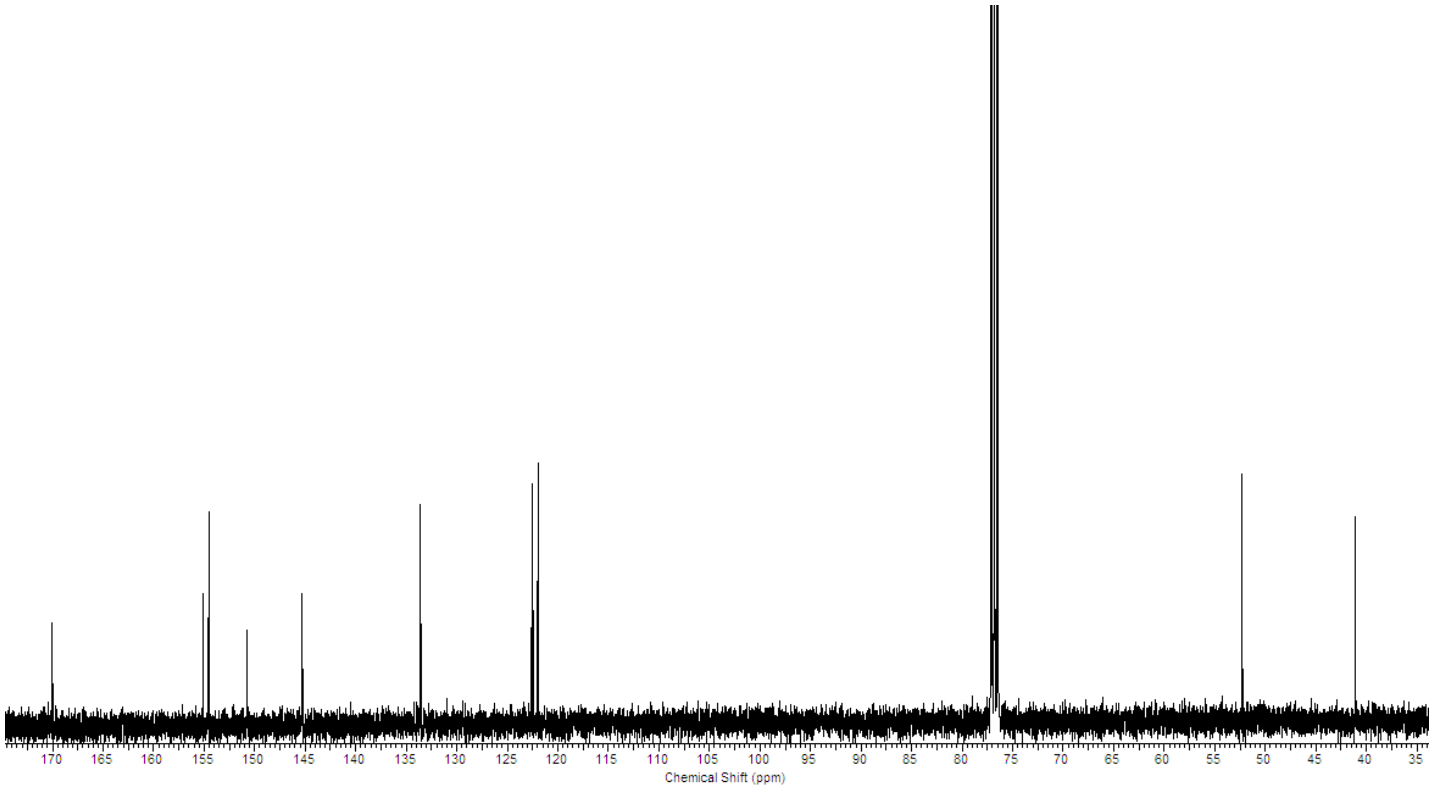
methyl 2-(1,6-naphthyridin-5-yl)acetate

6l: In a 2-dram vial equipped with a magnetic stir bar, 1,6-naphthyridine-6-oxide (18 mg, 0.12 mmol), *i*Pr_2EtN (66 μL, 0.37 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (54 μL, 0.25 mmol) and PyBroP (64 mg 0.14 mmol) were sequentially combined in THF (1 mL). The vial was capped and stirred vigorously at room temperature. Upon completion (TLC analysis), the reaction was poured into water (10 mL) and extracted with EtOAc (3x10 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-100% EtOAc: Heptanes) to afford the desired product as yellow oil (19 mg, 76%).

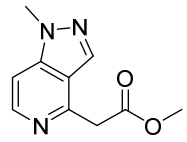
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.12 (d, J=4.1 Hz, 1H), 8.71 (d, J=5.9 Hz, 1H), 8.46 (d, J=8.2 Hz, 1H), 7.90 (d, J=5.9 Hz, 1H), 7.57 (dd, J=4.1, 8.2 Hz, 1H), 4.39 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.2, 155.3, 154.7, 151.0, 145.5, 133.8, 122.8, 122.7, 122.2, 52.5, 41.3. HRMS Calculated for $C_{11}H_{11}N_2O_2$ $(M+H)^+$ 203.0815; Found 203.0813. FTIR (cm^{-1}) = 1735.



^{1}H NMR Spectrum of methyl 2-(1,6-naphthyridin-5-yl)acetate (**6l**)



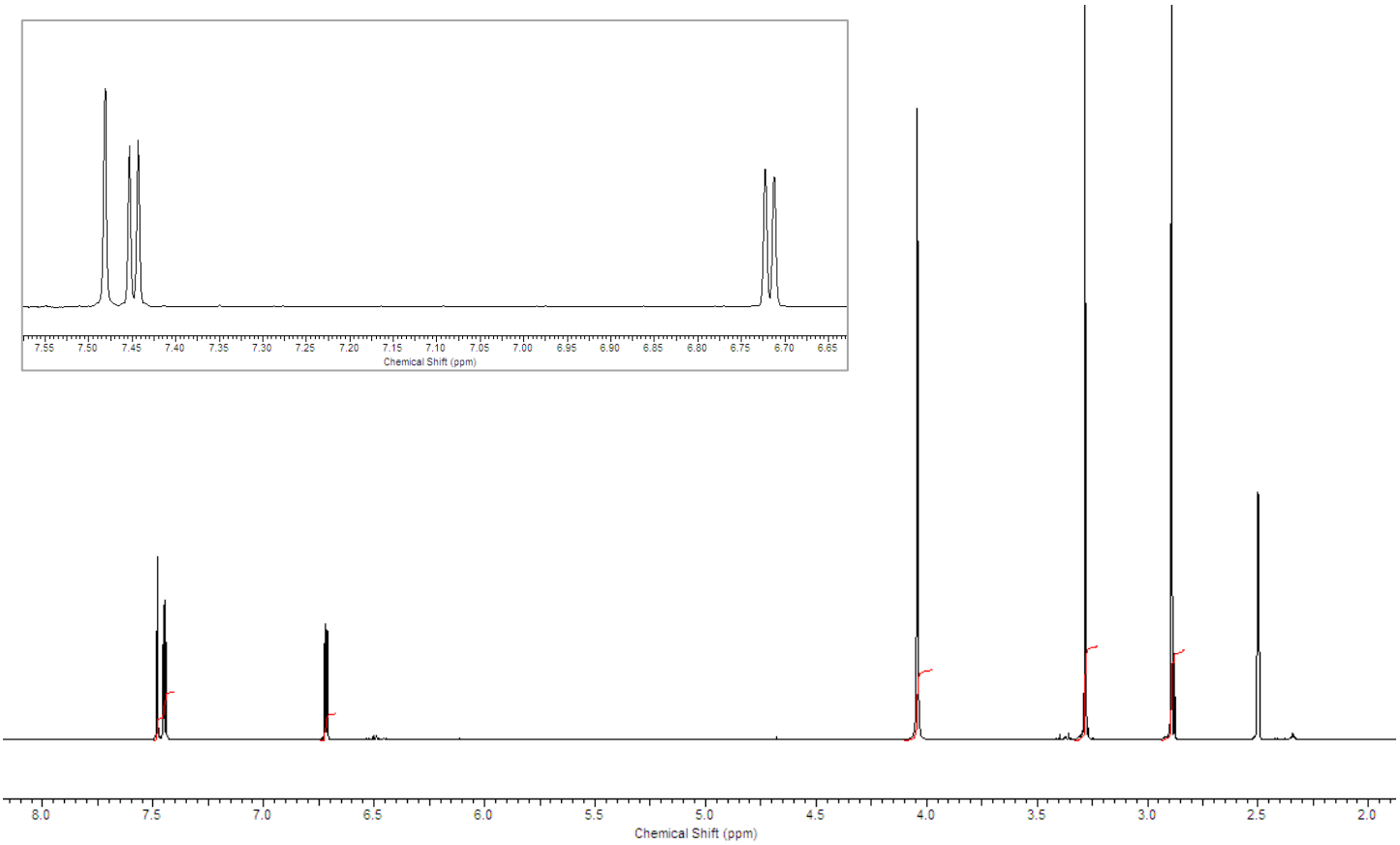
^{13}C NMR Spectrum of methyl 2-(1,6-naphthyridin-5-yl)acetate (**6l**)



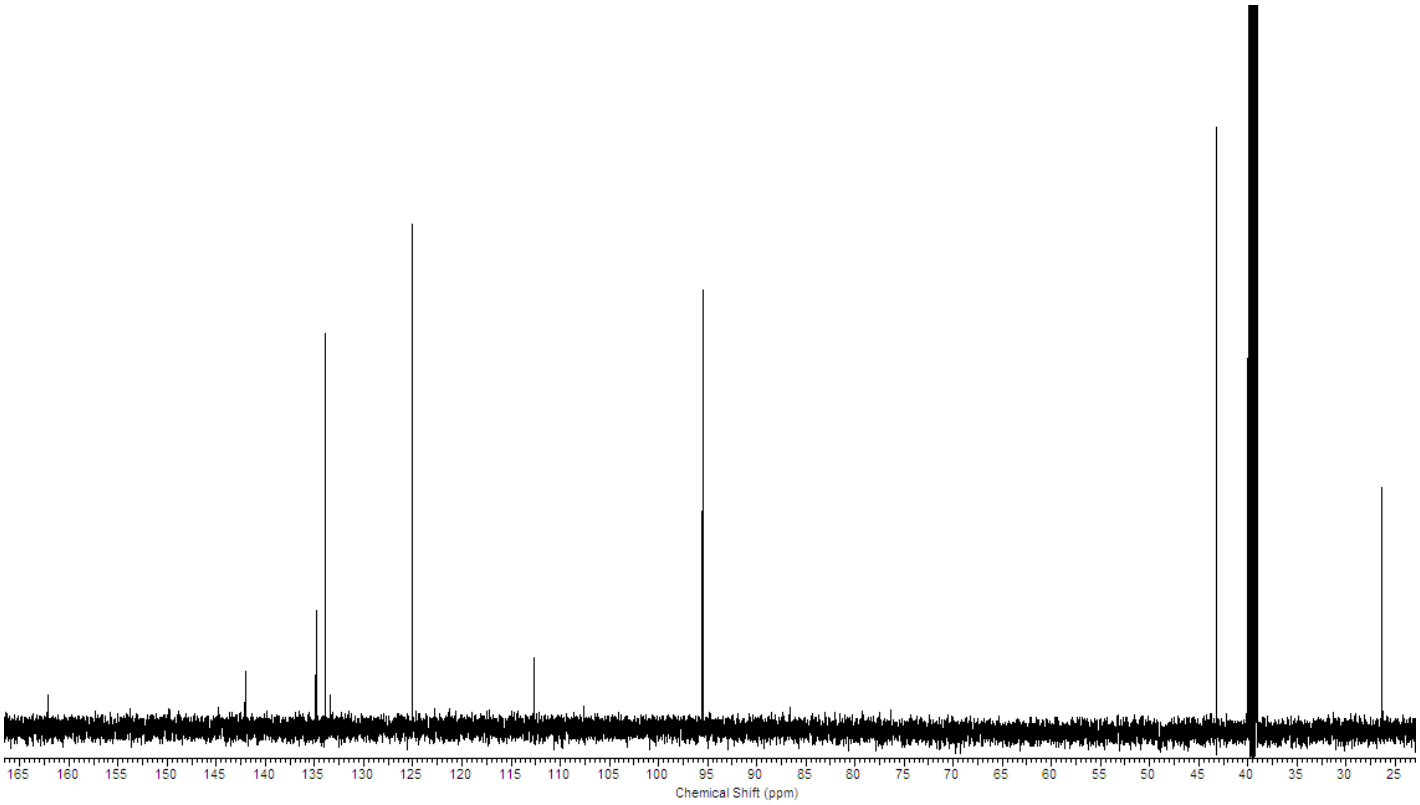
methyl 2-(1-methyl-1*H*-pyrazolo[4,3-*c*]pyridin-4-yl)acetate

6m: In a 2-dram vial equipped with a magnetic stir bar, 1-methyl-1H-pyrazolo[4,3-c]pyridine-5-oxide (75 mg, 0.50 mmol), *i*Pr_2EtN (269 μL, 1.50 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (219 μL, 1.00 mmol) and PyBroP (262 mg 0.55 mmol) were sequentially combined in THF (3 mL). The vial was capped and stirred vigorously at room temperature. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as a light-yellow gum (61 mg, 61%).

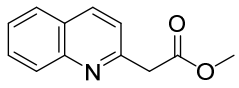
^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.48 (s, 1H), 7.45 (d, J=5.9 Hz, 1H), 6.72 (d, J=5.9 Hz, 1H), 4.04 (s, 2H), 3.28 (s, 3H), 2.89 (s, 3H). ^{13}C NMR (150 MHz, DMSO-*d6*) δ 162.1, 141.9, 134.8, 133.8, 124.9, 112.6, 95.4, 43.1, 26.2. HRMS Calculated for $C_{10}H_{12}N_3O_2$ $(M+H)^+$ 206.0924; Found 206.0920. FTIR (cm^{-1}) = 1739, 1160.



^{1}H NMR Spectrum of methyl 2-(1-methyl-1H-pyrazolo[4,3-c]pyridin-4-yl)acetate (**6m**)



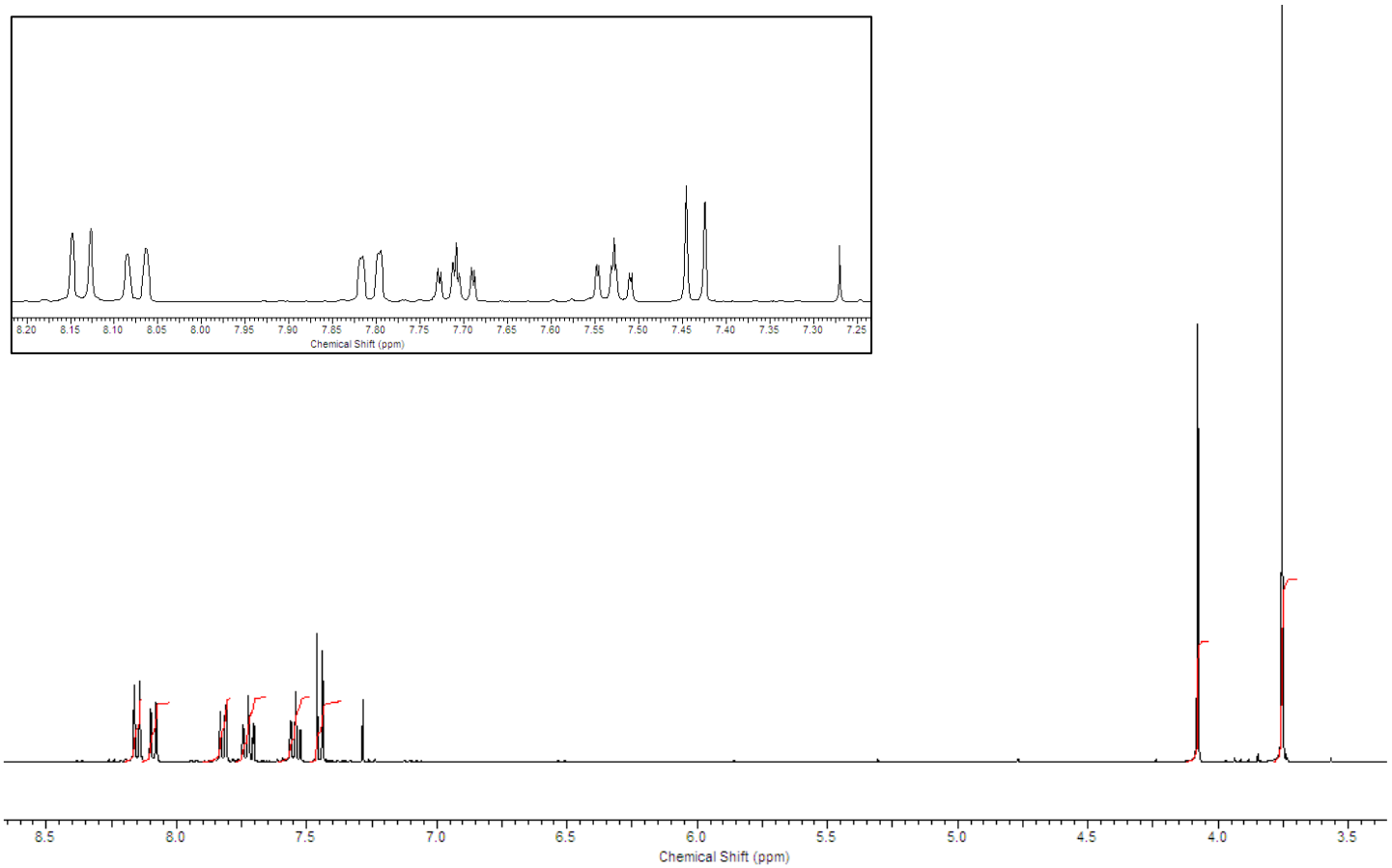
^{13}C NMR Spectrum of methyl 2-(1-methyl-1H-pyrazolo[4,3-c]pyridin-4-yl)acetate (**6m**)



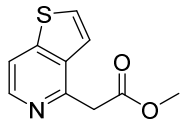
methyl 2-(quinolin-2-yl)acetate

6n: In a 2-dram vial equipped with a magnetic stir bar, quinoline-*N*-oxide* (50.0 mg, 0.34 mmol), *i*Pr_2EtN (185 μL, 1.03 mmol), 1-(tert-butyldimethylsilyloxy)-1-methoxyethene (151 μL, 0.69 mmol) and PyBroP (180 mg 0.38 mmol) were sequentially combined in THF (3 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, the reaction was heated to 45°C. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as a yellow oil (35 mg, 51%).
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J=8.8 Hz, 1H), 8.07 (d, J=8.2 Hz, 1H), 7.81 (d, J=8.2 Hz, 1H), 7.71 (t, J=7.3 Hz, 1H), 7.53 (t, J=7.6 Hz, 1H), 7.44 (d, J=8.2 Hz, 1H), 4.06 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 154.7, 147.9, 136.7, 129.7, 129.1, 127.5, 127.1, 126.5, 121.8, 52.2, 44.7. m/z = 202.2 $(M+H)^+$. LCMS = 98% purity.

*Not the hydrate.
The data for this compound is consistent with a previous literature preparation: Baruah, P. K. et al. *Bioorganic & Medicinal Chemistry*, **2012**, *20*, 3551-3564.

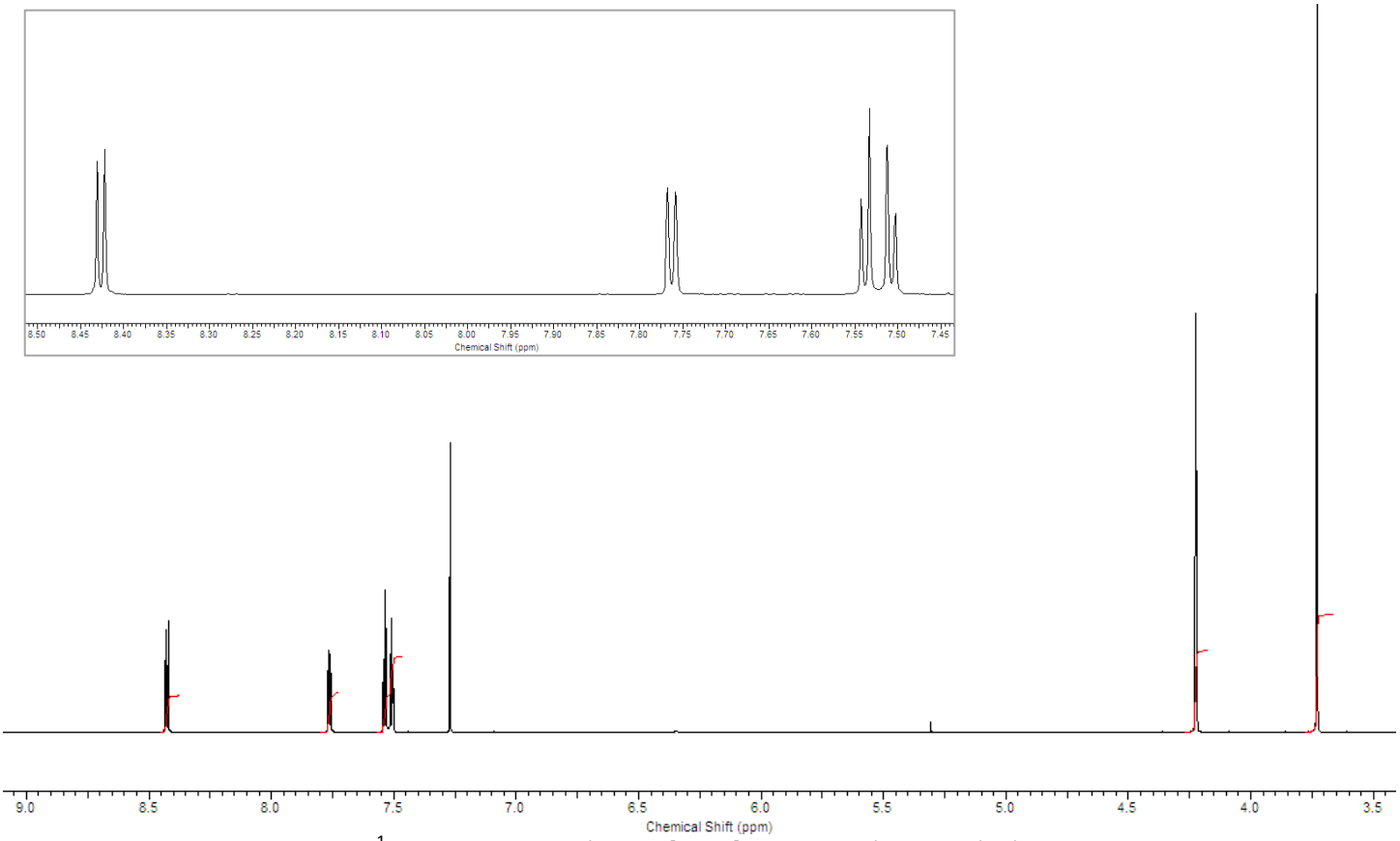


^{1}H NMR Spectrum of methyl 2-(quinolin-2-yl)acetate (**6n**)

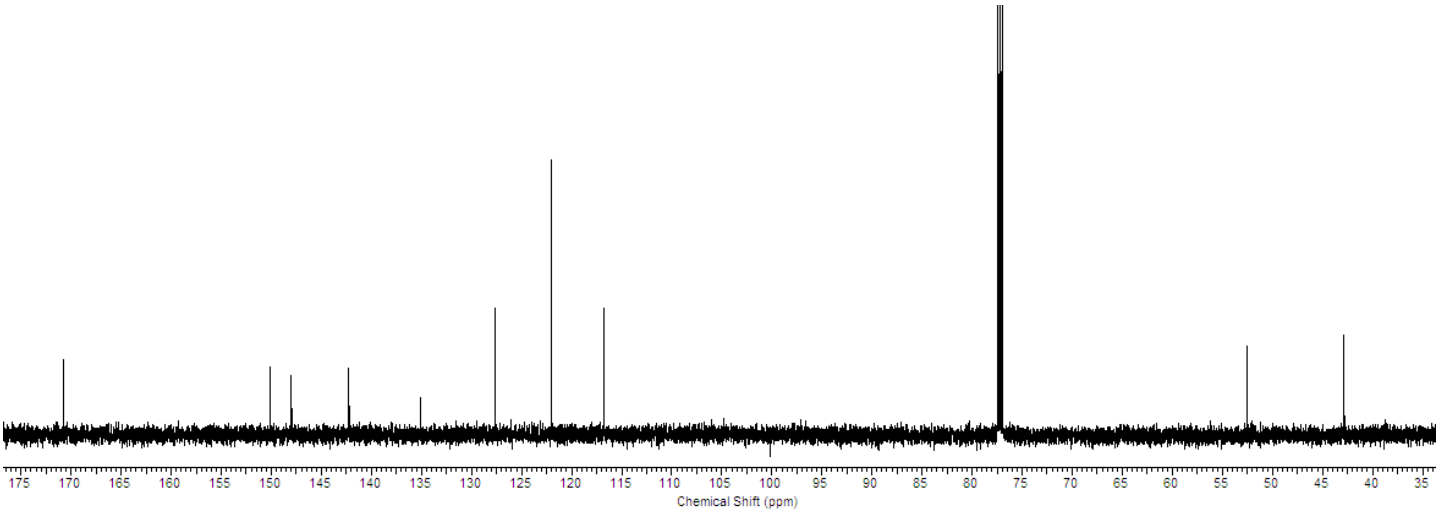


methyl 2-(thieno[3,2-*c*]pyridin-4-yl)acetate

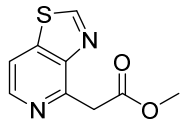
6o: Prepared in analogous fashion to **3** with thieno[3,2-c]pyridine-*N*-oxide. Light-yellow solid (186 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J=5.9 Hz, 1H), 7.76 (d, J=5.3 Hz, 1H), 7.54 (d, J=5.9 Hz, 1H), 7.51 (d, J=5.9 Hz, 1H), 4.22 (s, 2H), 3.73 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 150.1, 148.0, 142.3, 135.1, 127.7, 122.0, 116.8, 52.5, 42.9. HRMS Calculated for $C_{10}H_{10}BrNO_2S$ $(M+H)^+$ 208.0442; Found 208.0442. FTIR (cm^{-1}) = 1725, 1462, 1111. MP = 35-37°C.



^{1}H NMR methyl 2-(thieno[3,2-c]pyridin-4-yl)acetate (**6o**)



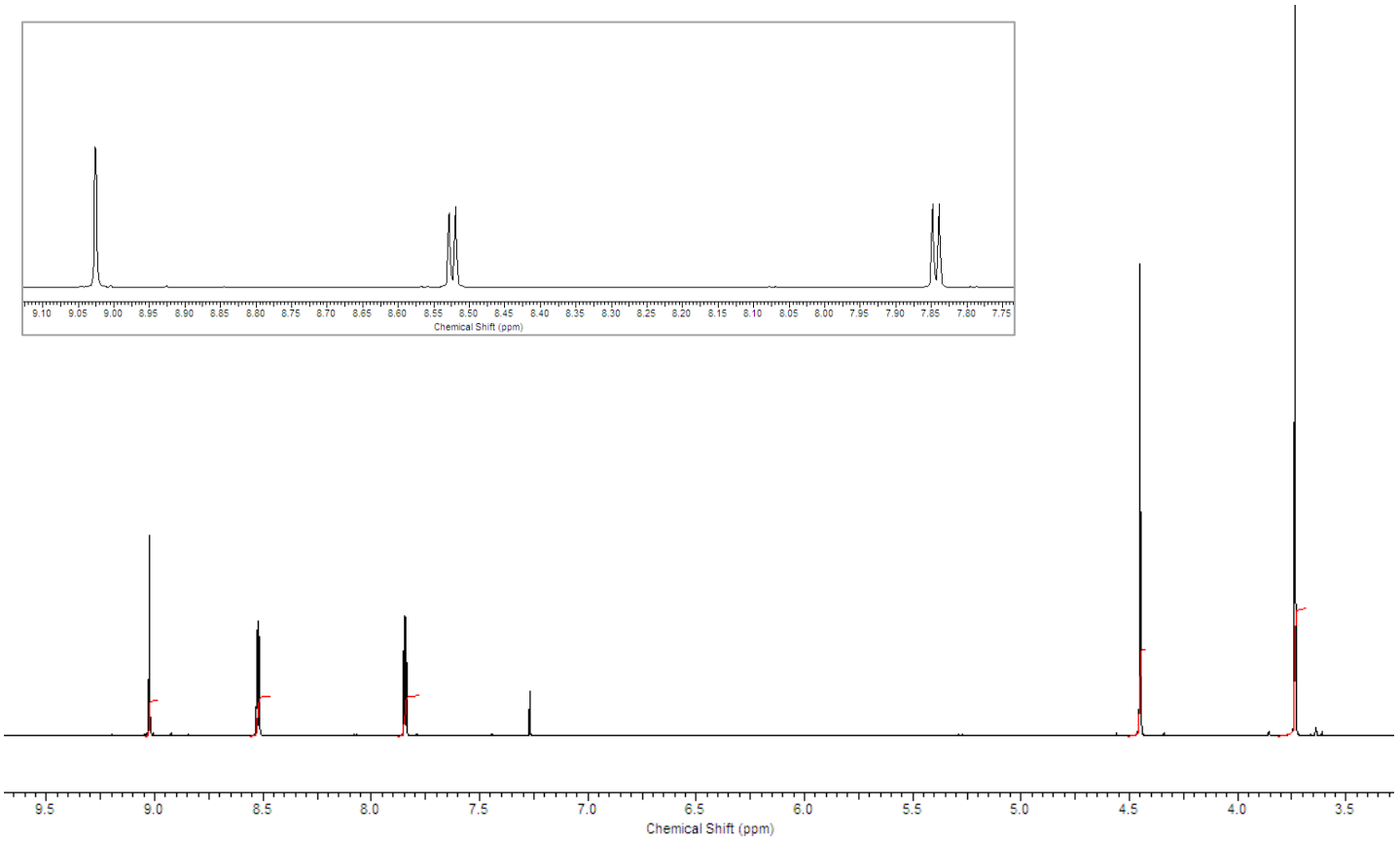
^{13}C NMR Spectrum of methyl 2-(thieno[3,2-c]pyridin-4-yl)acetate (**6o**)



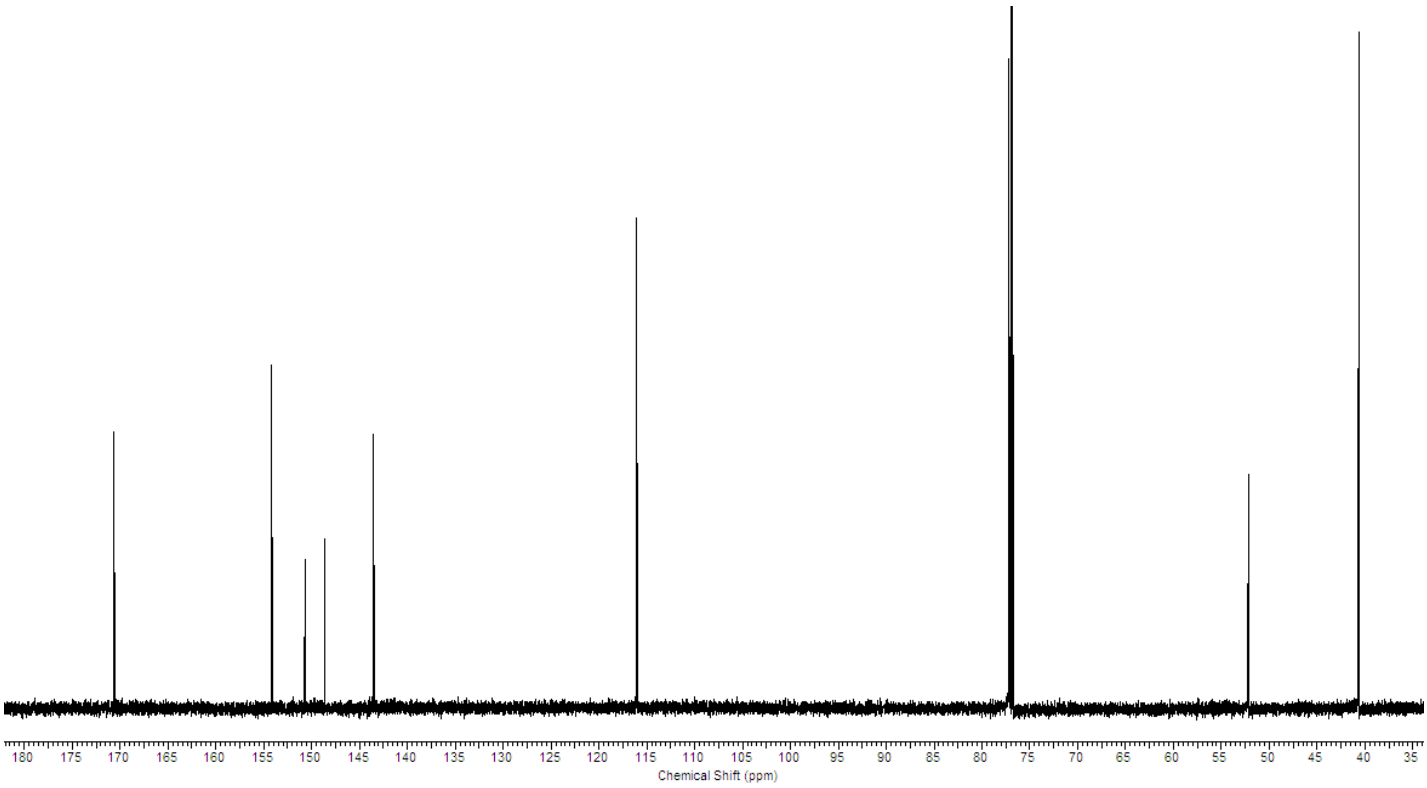
methyl 2-(thiazolo[4,5-*c*]pyridin-4-yl)acetate

6p: In a 2-dram vial equipped with a magnetic stir bar, thiazolo[4,5-c]pyridine-*N*-oxide (62 mg, 0.41 mmol), *i*Pr_2EtN (219 μL, 1.22 mmol), 1-(*tert*-butyldimethylsilyloxy)-1-methoxyethene (178 μL, 0.81 mmol) and PyBroP (213 mg 0.45 mmol) were sequentially combined in THF (2.5 mL). The vial was capped and stirred vigorously at room temperature. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as a light-yellow oil (55 mg, 65%).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 9.03 (s, 1H), 8.52 (d, J=5.3 Hz, 1H), 7.84 (d, J=5.3 Hz, 1H), 4.45 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (150 MHz, DMSO-*d6*) δ 170.7, 154.2 (2), 150.7, 148.7, 143.5, 116.0, 52.2, 40.7. HRMS Calculated for $C_9H_9N_2O_2S$ $(M+H)^+$ 209.0379; Found 209.0375. FTIR (cm^{-1}) = 1734, 1445.

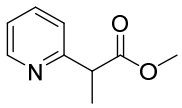


^{1}H NMR Spectrum of methyl 2-(thiazolo[4,5-c]pyridin-4-yl)acetate (**6p**)

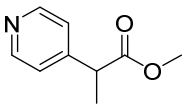


^{13}C NMR Spectrum of methyl 2-(thiazolo[4,5-c]pyridin-4-yl)acetate (**6p**)

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION FOR COMPOUNDS FOUND IN TABLE 2:



methyl 2-(pyridin-2-yl)propanoate

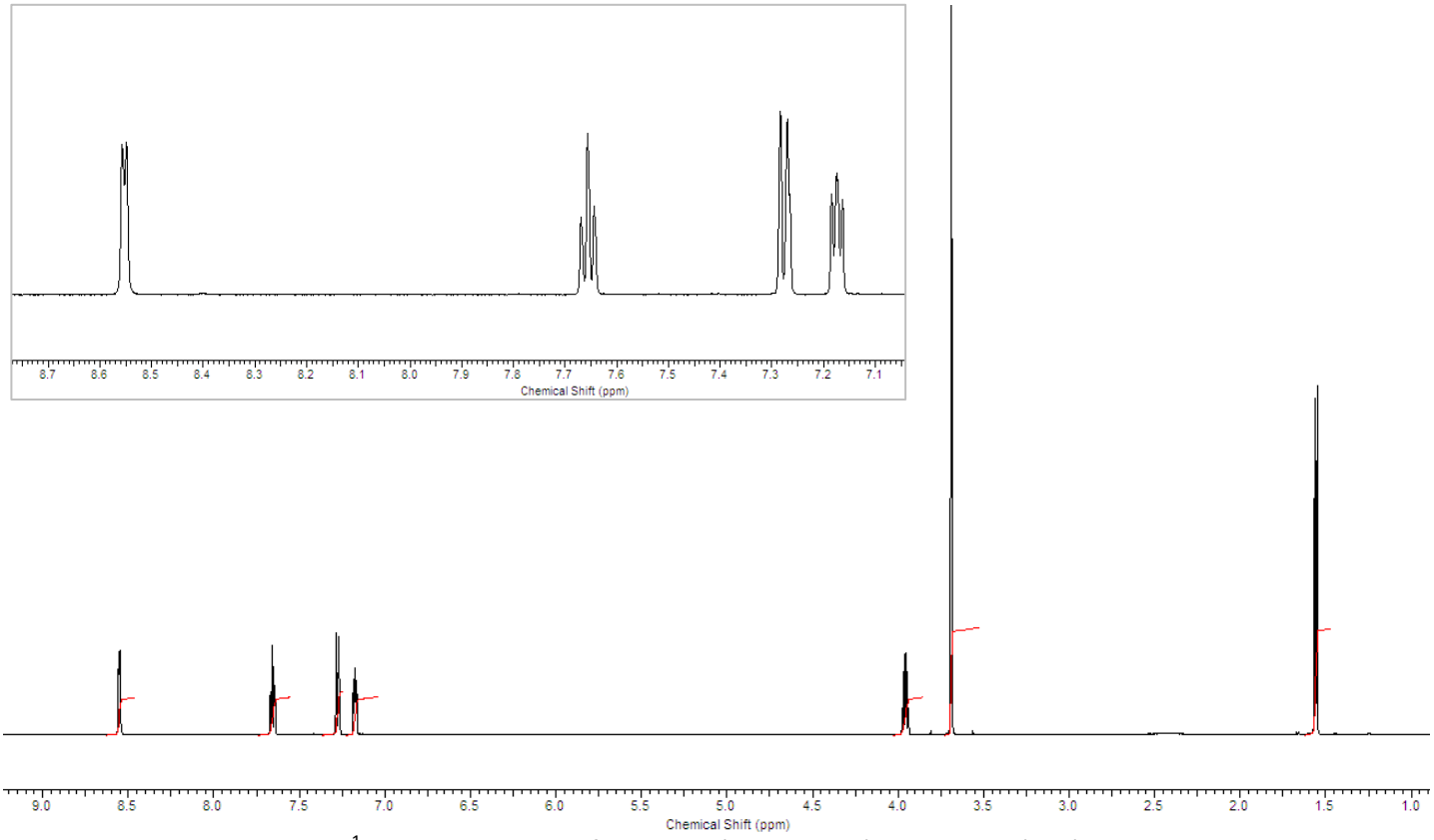


methyl 2-(pyridin-4-yl)propanoate

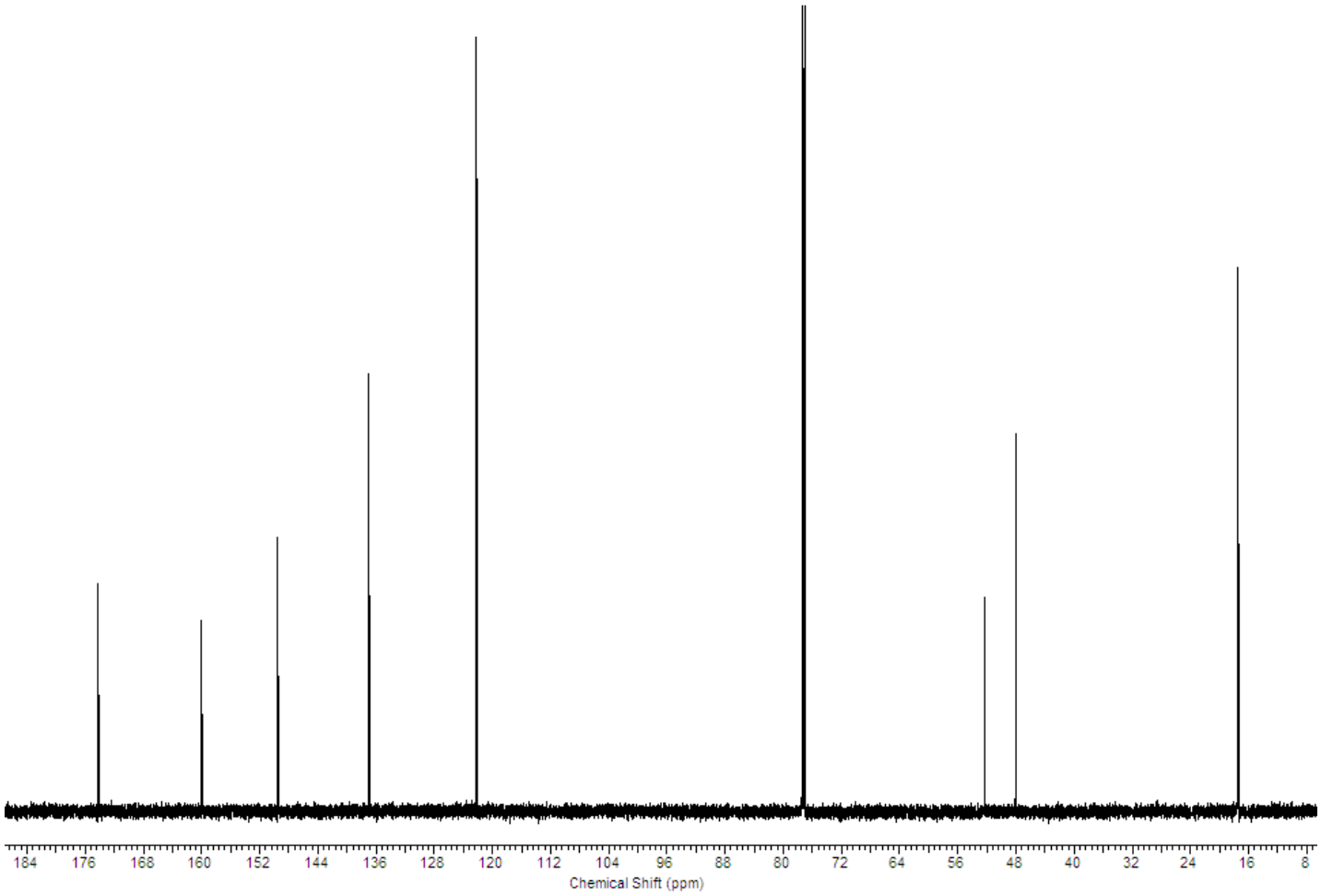
11a and **11b.** In a 2-dram vial equipped with a magnetic stir bar, pyridine-*N*-oxide (100 mg, 1.05 mmol), *i*Pr_2EtN (567 µL, 3.16 mmol), 1-(trimethylsilyloxy)-1-methoxypropene (388 µL, 2.10 mmol) and PyBroP (550 mg 1.16 mmol) were sequentially combined in THF (5 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, an exotherm was evident with considerable darkening of the solution. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired products as colorless oils.

Methyl 2-(pyridin-2-yl)propanoate (115 mg, 66%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54-8.60 (m, 1H), 7.67 (dt, J=1.8, 7.7 Hz, 1H), 7.29 (d, J=8.2 Hz, 1H), 7.19 (ddd, J=1.2, 5.0, 7.5 Hz, 1H), 3.98 (q, J=7.0 Hz, 1H), 3.71 (s, 3H), 1.57 (d, J=7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 159.6, 149.1, 136.6, 121.9, 121.8, 51.9, 47.6, 17.0. HRMS Calculated for $C_9H_{12}NO_2$ $(M+H)^+$ 166.0863; Found 166.0858. FTIR (cm^{-1}) = 1740, 1217, 1164.



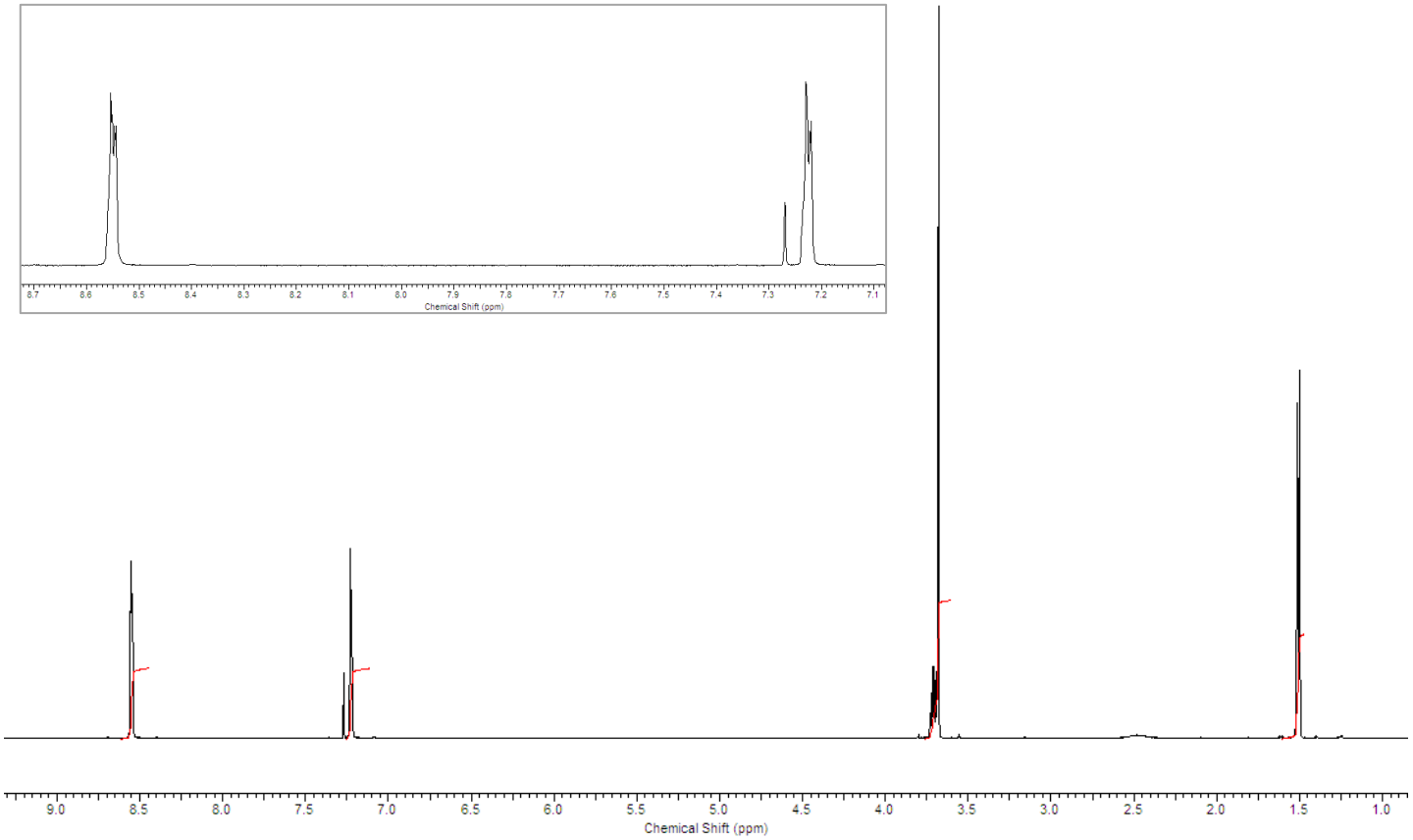
^{1}H NMR Spectrum of methyl 2-(pyridin-2-yl)propanoate (**11a**)



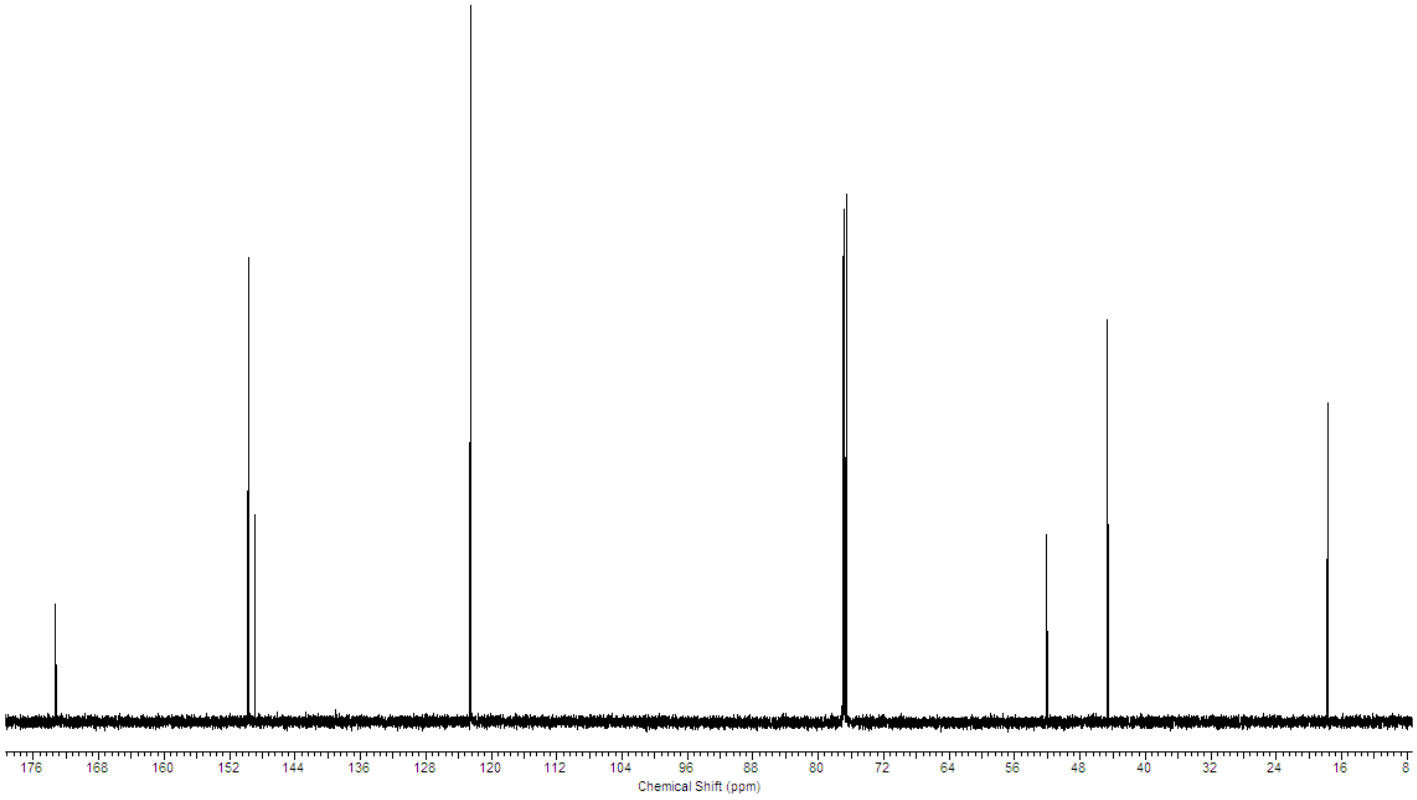
^{13}C NMR Spectrum of methyl 2-(pyridin-2-yl)propanoate (**11a**)

Methyl 2-(pyridin-4-yl)propanoate (30 mg, 17%).

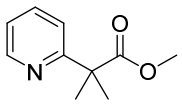
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (dd, J=1.5, 4.4 Hz, 2H), 7.22 (dd, J=1.8, 4.7 Hz, 2H), 3.73 - 3.69 (m, 1H), 3.68 (s, 3H), 1.51 (d, J=7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7, 150.2, 149.4, 123.0, 52.5, 45.1, 18.1. HRMS Calculated for $C_9H_{12}NO_2$ $(M+H)^+$ 166.0863; Found 166.0859. FTIR (cm^{-1}) = 1738, 1210



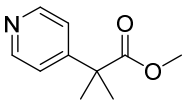
^{1}H NMR Spectrum of methyl 2-(pyridin-4-yl)propanoate (**11b**)



^{13}C NMR Spectrum of methyl 2-(pyridin-4-yl)propanoate (**11b**)



methyl 2-methyl-2-(pyridin-2-yl)propanoate

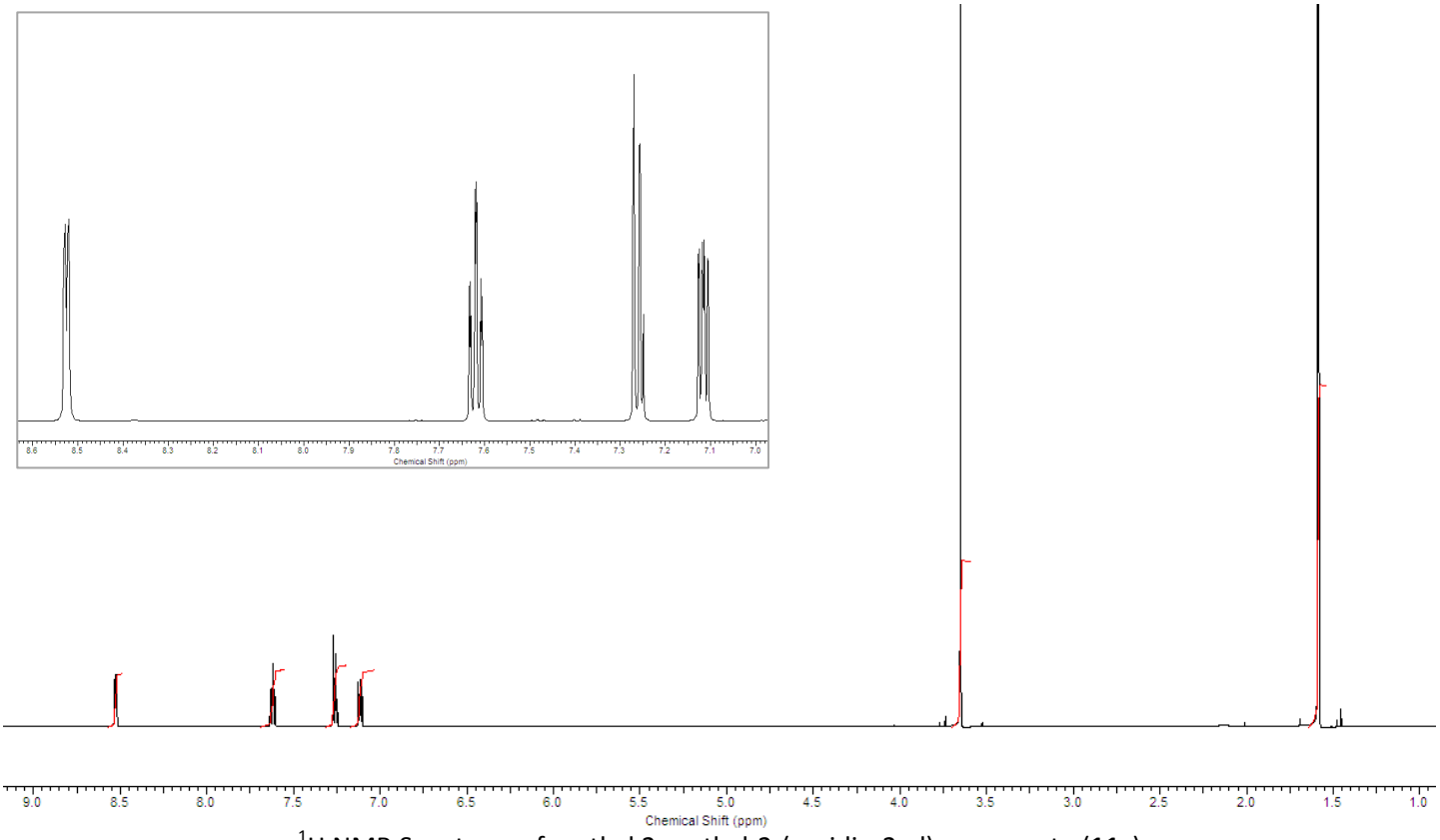


methyl 2-methyl-2-(pyridin-4-yl)propanoate

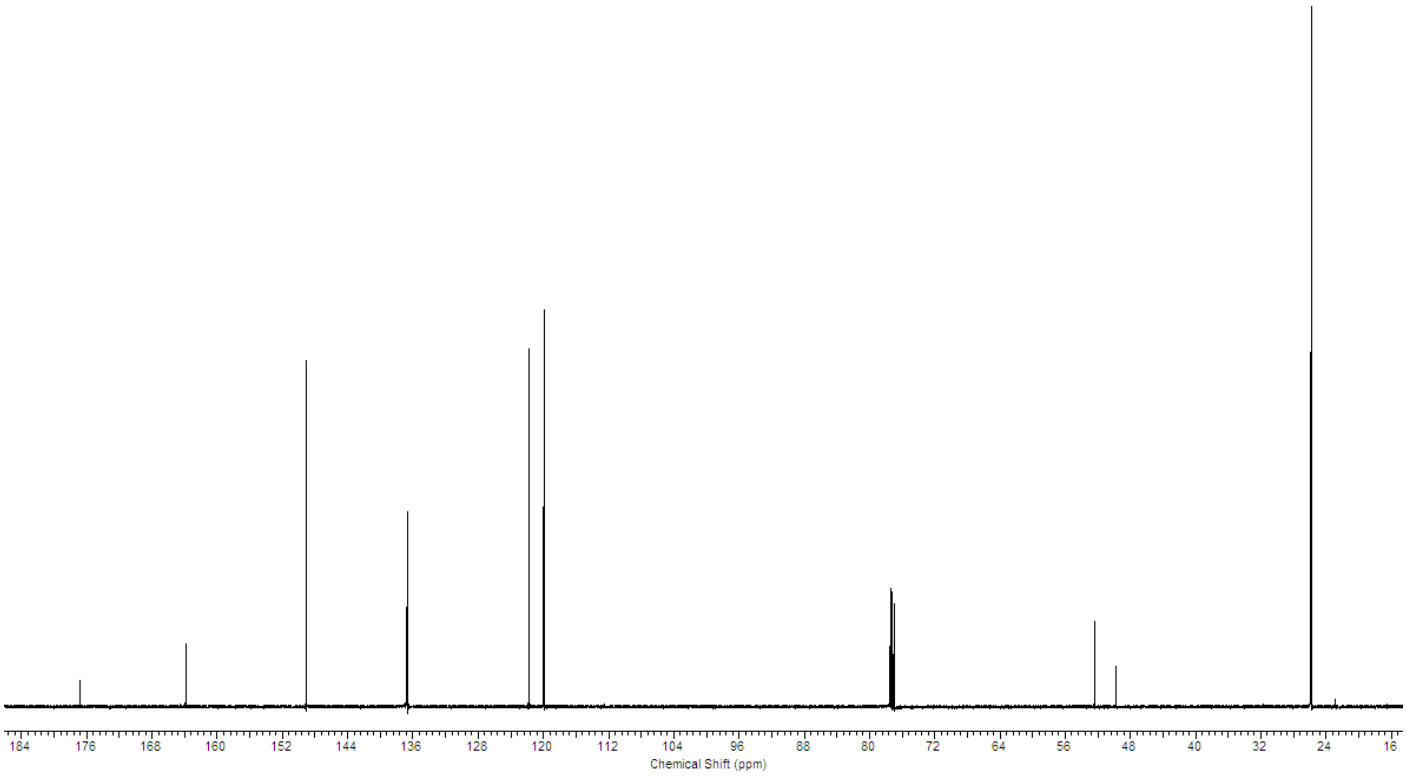
11c and **11d.** In a 2-dram vial equipped with a magnetic stir bar, pyridine-*N*-oxide (100 mg, 1.05 mmol), *i*Pr_2EtN (567 μL, 3.16 mmol), methyl-(trimethylsilyl)-dimethylketene acetal (428 μL, 2.10 mmol) and PyBroP (550 mg 1.16 mmol) were sequentially combined in THF (5 mL). The vial was capped and stirred at room temperature. After stirring for 2 minutes, an exotherm was evident with considerable darkening of the solution. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired products as colorless oils.

Methyl 2-methyl-2-(pyridin-2-yl)propanoate (40 mg, 21%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J=4.7 Hz, 1H), 7.65 (dt, J=1.8, 7.6 Hz, 1H), 7.29 (d, J=8.2 Hz, 1H), 7.15 (dd, J=5.3, 7.0 Hz, 1H), 3.69 (s, 3H), 1.62 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.4, 163.4, 148.7, 136.3, 121.4, 119.5, 51.9, 49.4, 25.4. HRMS Calculated for $C_{10}H_{14}NO_2$ $(M+H)^+$ 180.1019; Found 180.1024. FTIR (cm^{-1}) = 1734, 1154.



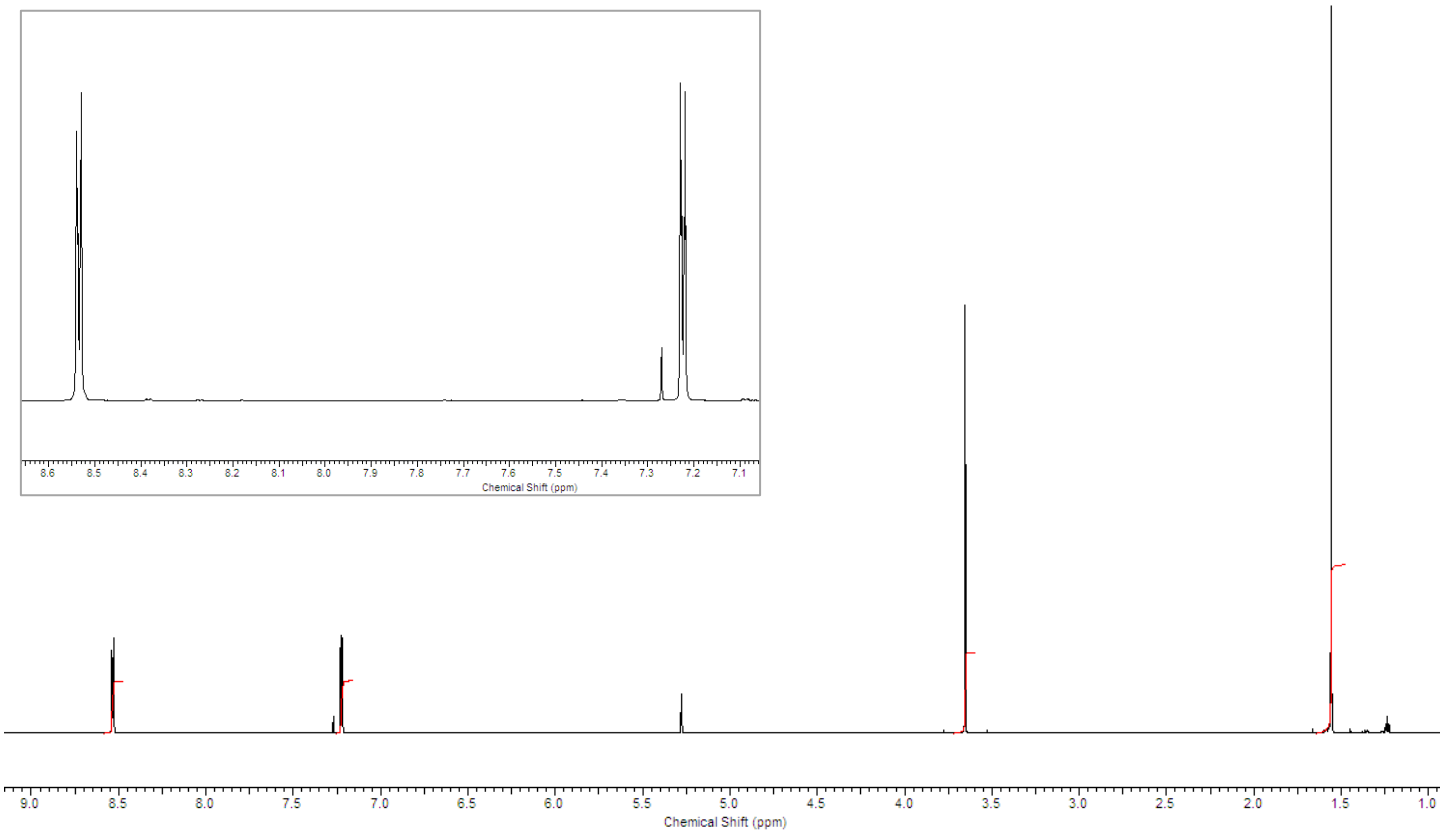
^{1}H NMR Spectrum of methyl 2-methyl-2-(pyridin-2-yl)propanoate (**11c**)



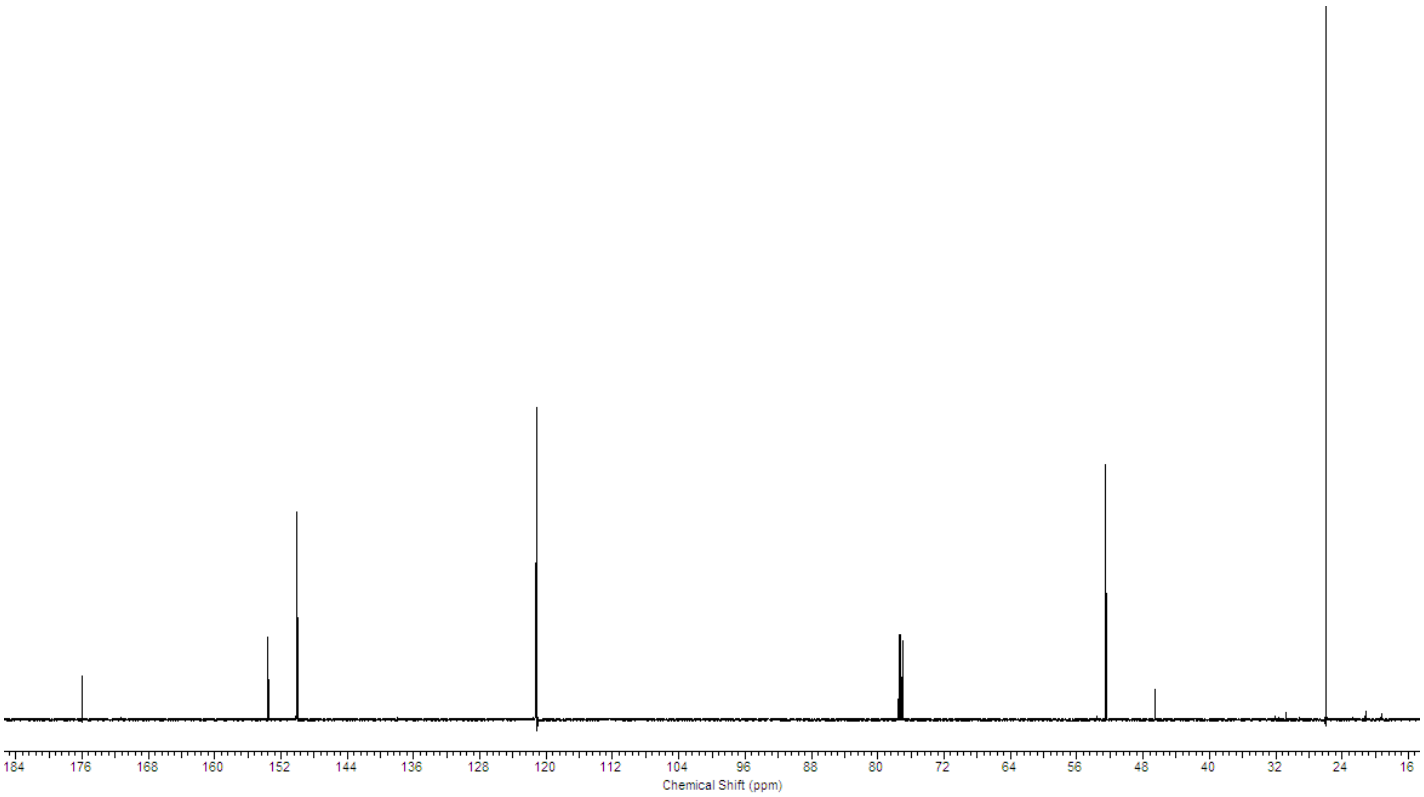
^{13}C NMR Spectrum of methyl 2-methyl-2-(pyridin-2-yl)propanoate (**11c**)

Methyl 2-methyl-2-(pyridin-4-yl)propanoate (80 mg, 42%).

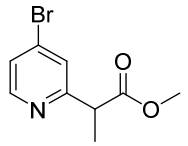
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J=1.2, 4.1 Hz, 1H), 7.22 (dd, J=1.8, 4.1 Hz, 1H), 3.65 (s, 3H), 1.56 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.8, 153.4, 149.8, 120.9, 52.4, 46.3, 25.8. HRMS Calculated for $C_{10}H_{14}NO_2$ $(M+H)^+$ 180.1019; Found 180.1018. FTIR (cm^{-1}) = 1734, 1154.



^{1}H NMR Spectrum of methyl 2-methyl-2-(pyridin-4-yl)propanoate (**11d**)



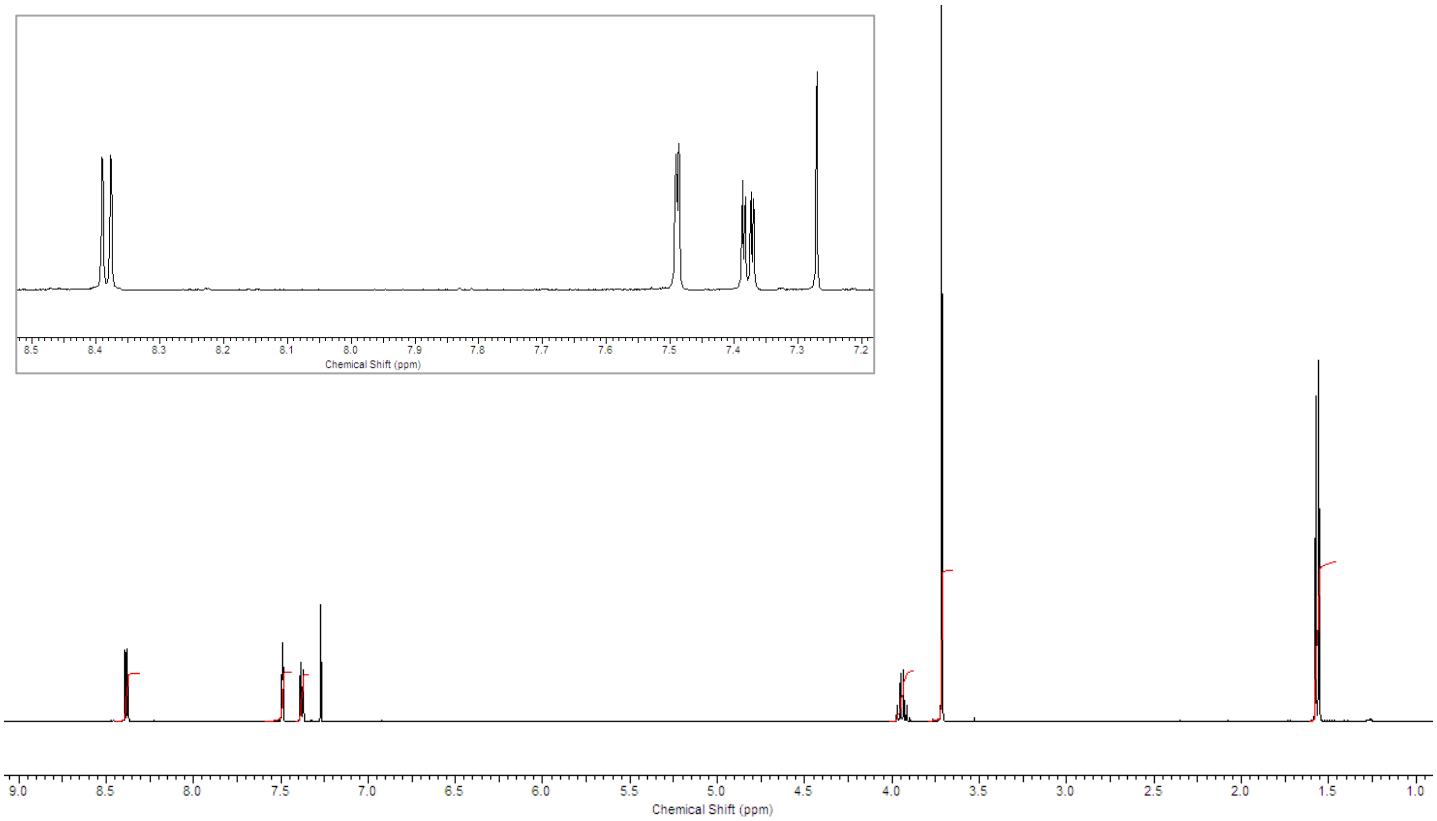
^{13}C NMR Spectrum of methyl 2-methyl-2-(pyridin-4-yl)propanoate (**11d**)



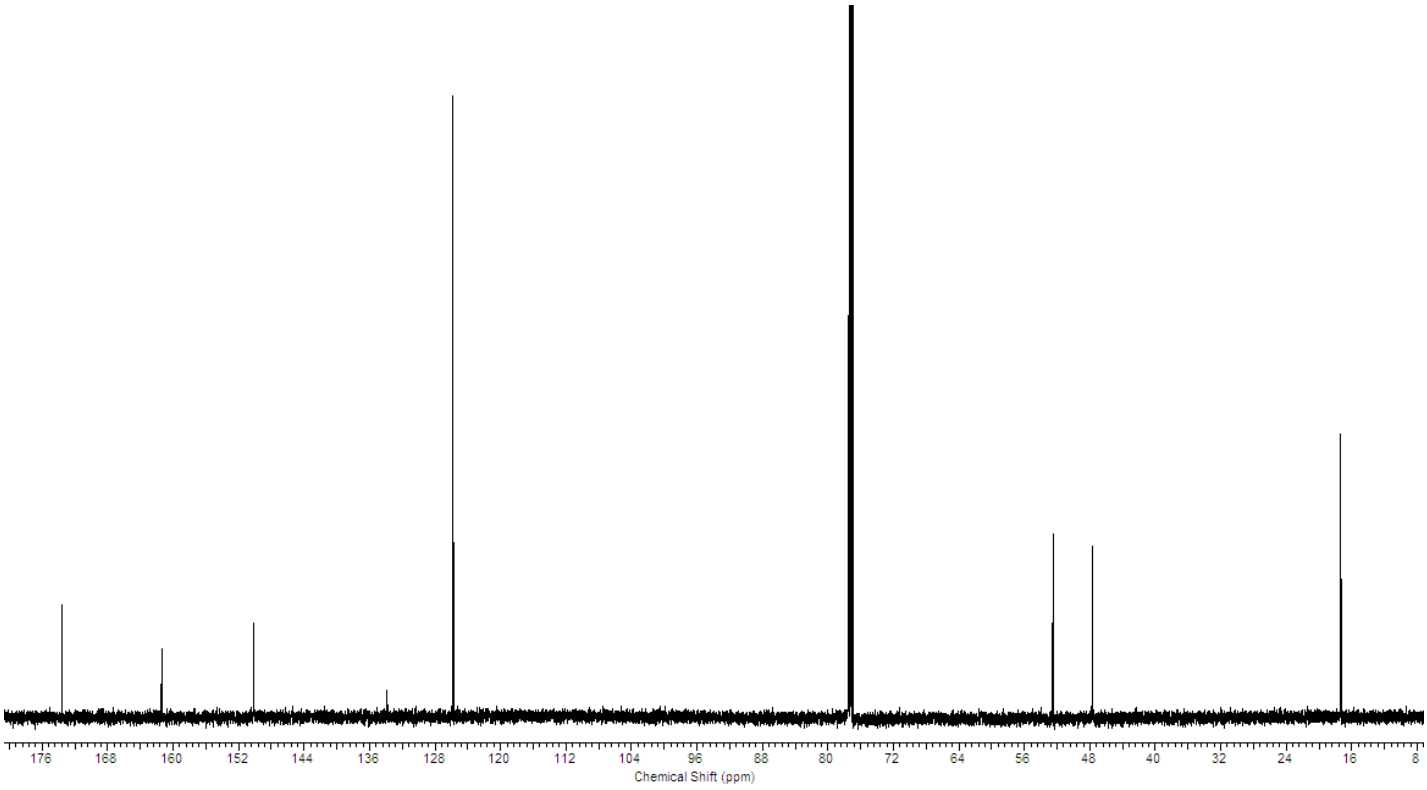
methyl 2-(4-bromopyridin-2-yl)propanoate

11e: In a 2-dram vial equipped with a magnetic stir bar, 4-bromopyridine-*N*-oxide (100 mg, 0.60 mmol), *i*Pr_2EtN (310 µL, 1.72 mmol), 1-(trimethylsilyloxy)-1-methoxypropene (212 µL, 1.15 mmol) and PyBroP (301 mg 0.63 mmol) were sequentially combined in THF (3 mL). The vial was capped and stirred at room temperature. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as a yellow oil (110 mg, 78%).

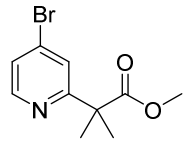
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (d, J=5.5 Hz, 1H), 7.49 (d, J=1.6 Hz, 1H), 7.38 (dd, J=1.8, 5.3 Hz, 1H), 3.94 (q, J=7.4 Hz, 1H), 3.73 (s, 3H), 1.57 (d, J=7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 161.4, 150.1, 134.2, 125.8, 52.5, 47.7, 17.3. HRMS Calculated for $C_9H_{10}BrNNaO_2$ $(M+Na)^+$ 265.9787; Found 265.9785. FTIR (cm^{-1}) = 1730, 1171.



^{1}H NMR methyl 2-(4-bromopyridin-2-yl)propanoate (**11e**)



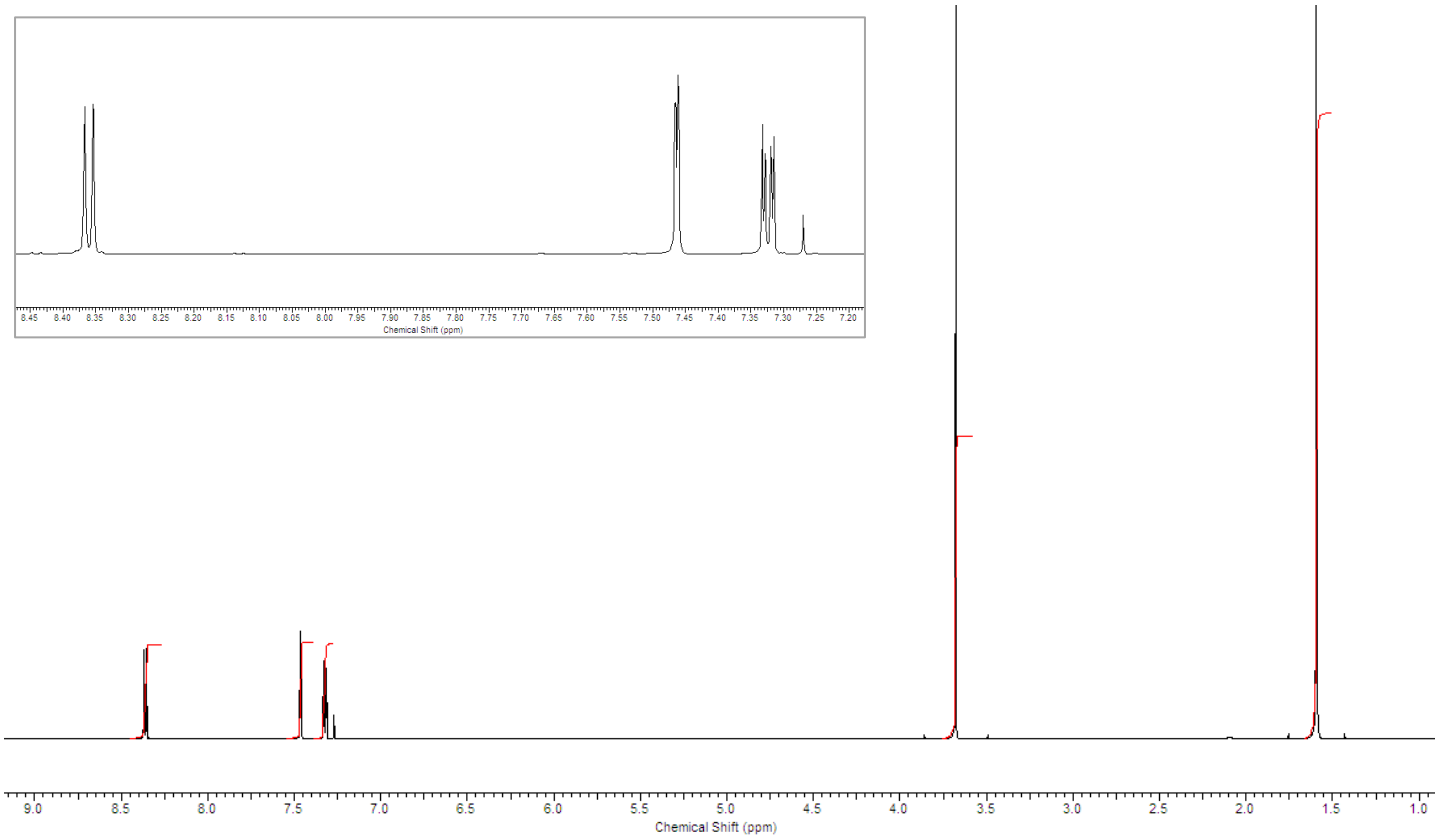
^{13}C NMR Spectrum of methyl 2-(4-bromopyridin-2-yl)propanoate (**11e**)



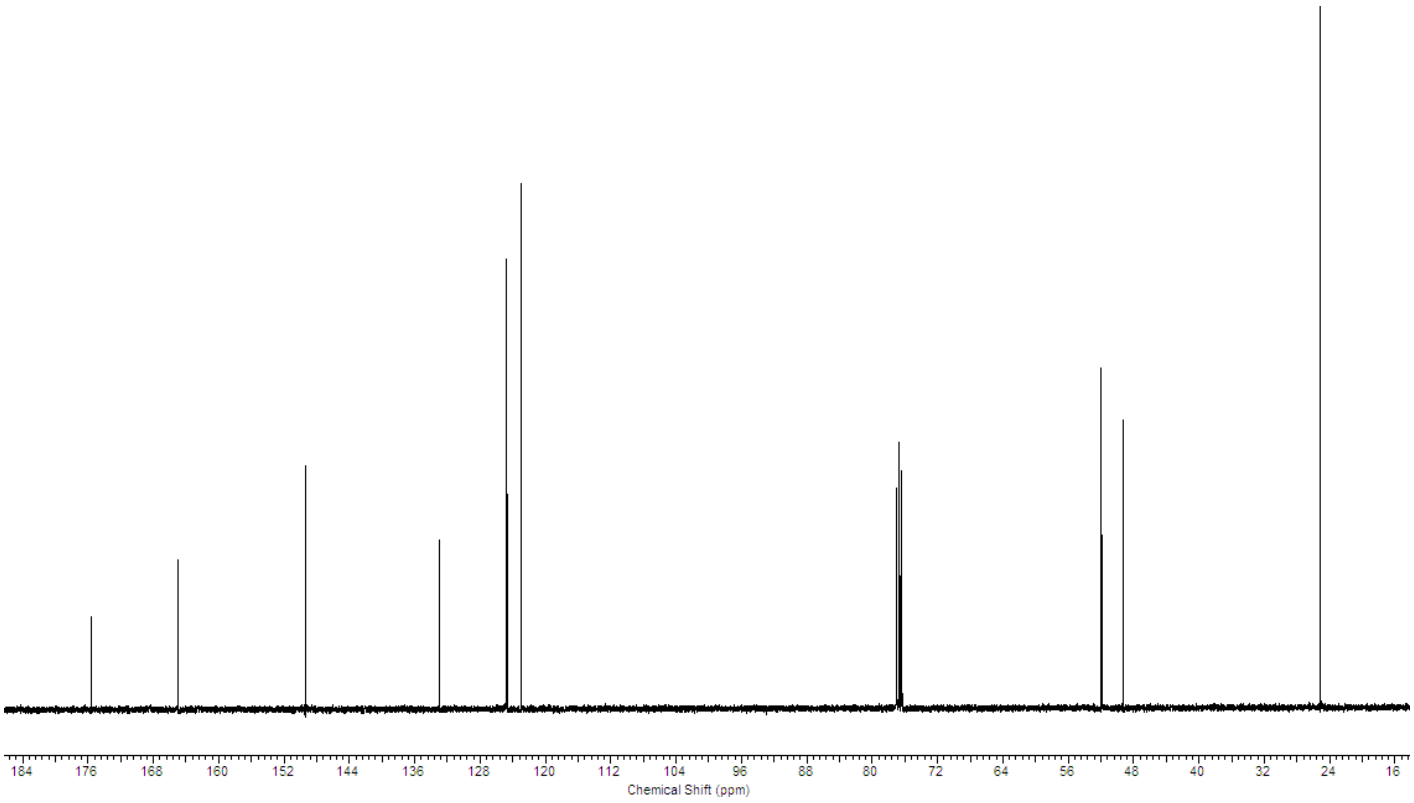
methyl 2-(4-bromopyridin-2-yl)-2-methylpropanoate

11f: In a 2-dram vial equipped with a magnetic stir bar, 4-bromopyridine-*N*-oxide (100 mg, 0.60 mmol), *i*Pr_2EtN (310 μL, 1.72 mmol), methyl-(trimethylsilyl)-dimethylketene acetal (234 μL, 1.15 mmol) and PyBroP (301 mg 0.63 mmol) were sequentially combined in THF (3 mL). The vial was capped and stirred at room temperature. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired product as a yellow oil (84 mg, 57%).

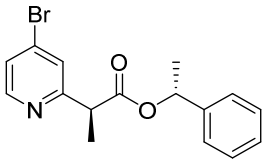
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J=5.1 Hz, 1H), 7.46 (d, J=1.6 Hz, 1H), 7.32 (dd, J=1.6, 5.1 Hz, 1H), 3.68 (s, 3H), 1.59 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.7, 164.9, 149.3, 133.0, 124.7, 123.9, 52.0, 49.2, 25.2. HRMS Calculated for $C_{10}H_{13}BrNO_2$ $(M+H)^+$ 258.0124; Found 258.0124. FTIR (cm^{-1}) = 1733, 1566.



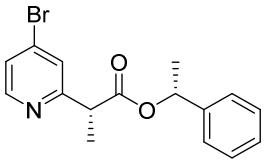
^{1}H NMR of methyl 2-(4-bromopyridin-2-yl)-2-methylpropanoate (**11f**)



^{13}C NMR Spectrum of methyl 2-(4-bromopyridin-2-yl)-2-methylpropanoate (**11f**)

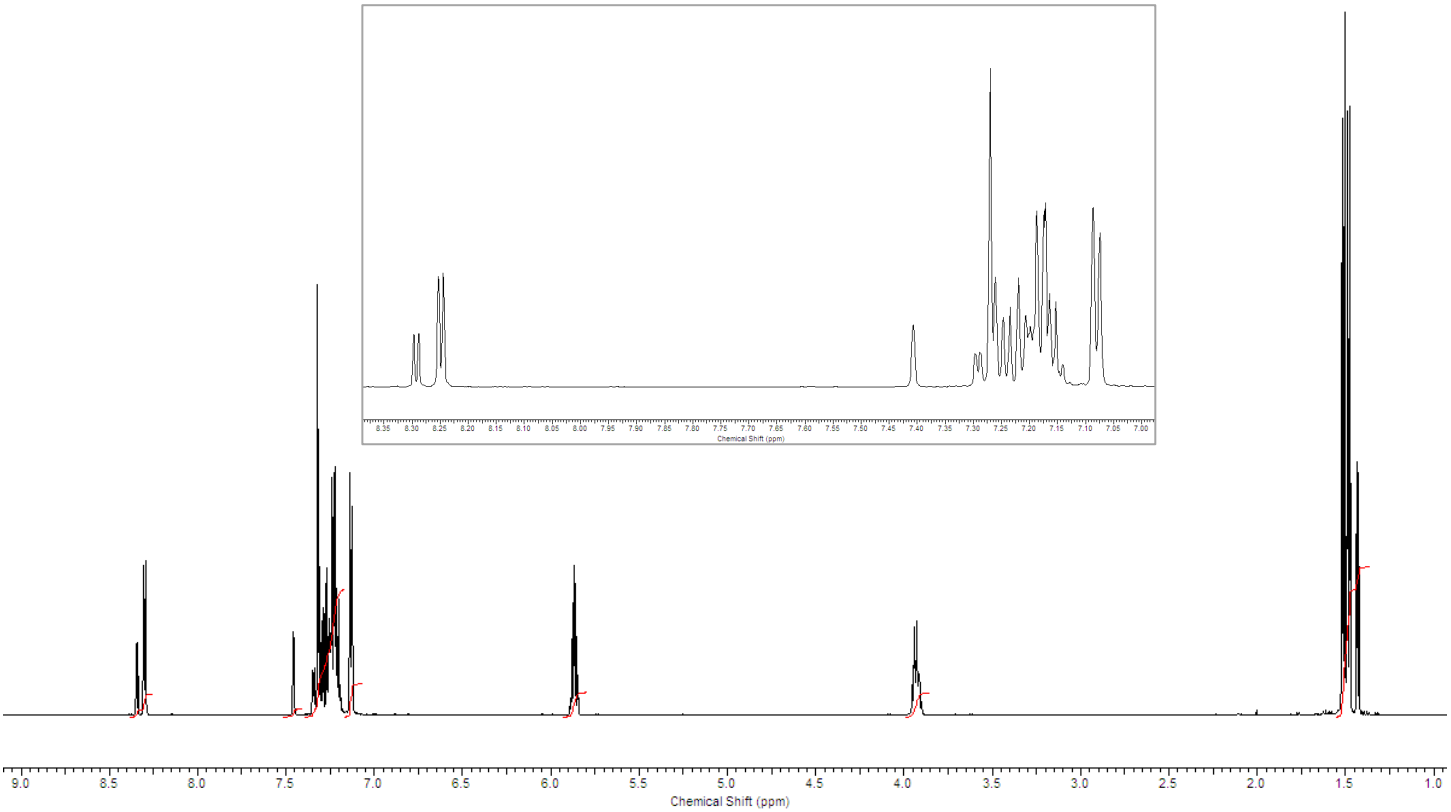


(*R*)-1-phenylethyl (*S*)-2-(4-bromopyridin-2-yl)propanoate

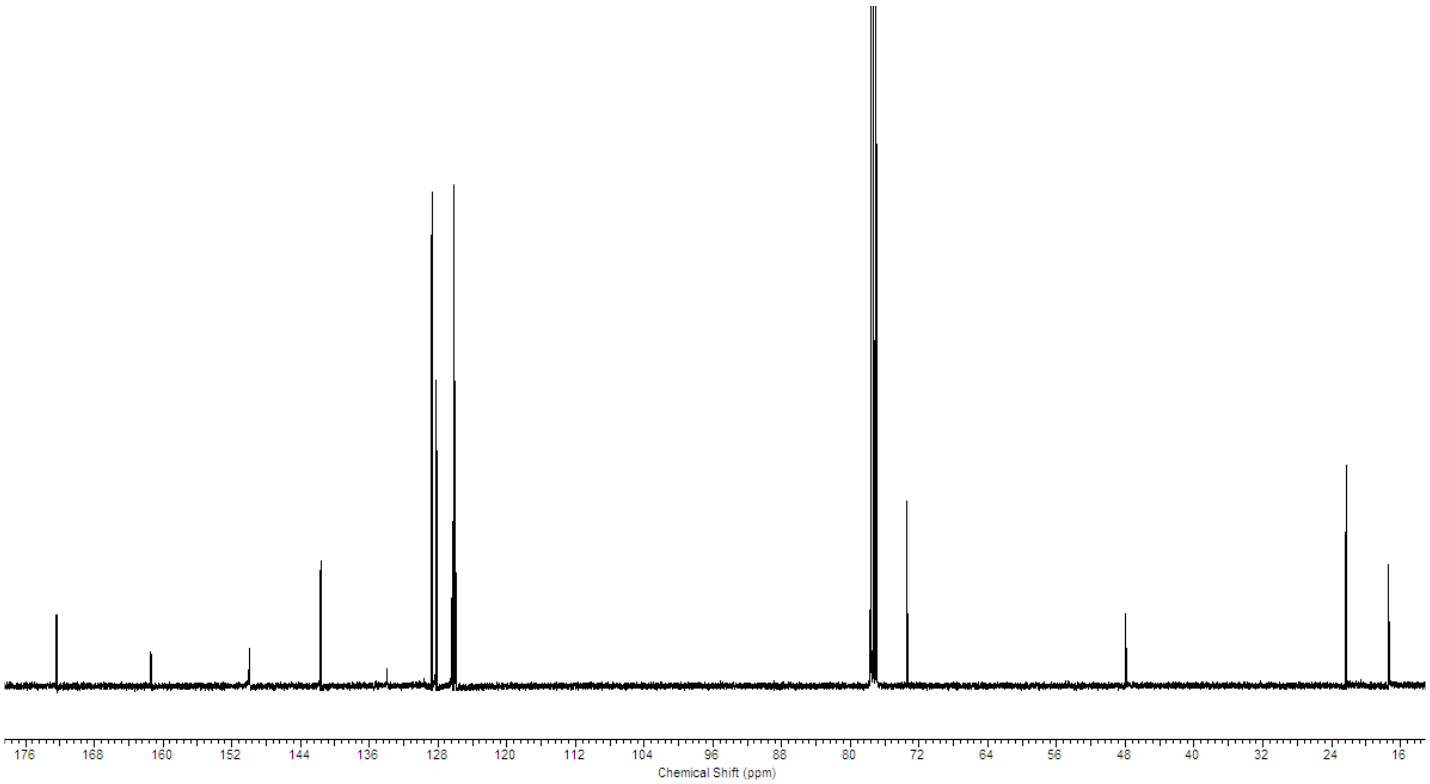


(*R*)-1-phenylethyl (*R*)-2-(4-bromopyridin-2-yl)propanoate

11g: In a 2-dram vial equipped with a magnetic stir bar, 4-bromopyridine-*N*-oxide (50 mg, 0.30 mmol), *i*Pr_2EtN (155 μL, 0.86 mmol), (R,E)-trimethyl((1-(1-phenylethoxy)prop-1-en-1-yl)oxy)silane (144 mg, 0.58 mmol) and PyBroP (150 mg 0.32 mmol) were sequentially combined in THF (2 mL). The vial was capped and stirred at room temperature. Upon completion (TLC analysis), the reaction was poured into water (20 mL) and extracted with EtOAc (3x15 mL). The pooled organics were dried (Na_2SO_4) and evacuated. The crude material was purified by column chromatography (0-50% EtOAc: Heptanes) to afford the desired products as an inseparable 2:1 mixture of diastereomers (61 mg, 64%, clear oil). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J=5.9 Hz, 1H), 8.25 (d, J=5.3 Hz, 1H), 7.41 (s, 1H), 7.32 - 7.13 (m, 11H), 7.08 (d, J=7.0 Hz, 2H), 5.85 - 5.78 (m, 2H), 3.93 - 3.84 (m, 2H), 1.46-1.42 (m, 9H), 1.38 (d, J=6.5 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.4, 172.3, 161.5, 161.4, 150.0, 149.9, 141.7, 141.6, 128.8, 128.7, 128.2, 128.1, 126.3, 126.1, 126.1, 126.0, 125.9, 125.9, 73.4, 73.4, 48.0, 47.9, 22.5, 22.3, 17.4, 17.4. HRMS Calculated for $C_{16}H_{17}BrNO_2$ $(M+H)^+$ 334.0437; Found 334.0438. FTIR (cm^{-1}) = 1738, 1573, 1173.



^{1}H NMR of (R)-1-phenylethyl (R)-2-(4-bromopyridin-2-yl)propanoate and (R)-1-phenylethyl (S)-2-(4-bromopyridin-2-yl)propanoate (**11g**)

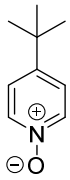


^{13}C NMR Spectrum of (R)-1-phenylethyl (R)-2-(4-bromopyridin-2-yl)propanoate and (R)-1-phenylethyl (S)-2-(4-bromopyridin-2-yl)propanoate (**11g**)

EXPERIMENTAL PROCEDURES AND CHARACTERIZATION FOR DE NOVO PREPARED REACATANTS AND REAGEANTS:

Azine-N-oxides

This section describes the synthesis of azine-*N*-oxides that were prepared *de novo* for this manuscript. All other substrates were obtained from commercial sources. Unless otherwise noted, the general procedure for 4-*tert*-butylpyridine-*N*-oxide was utilized.

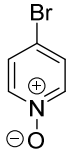


4-(*tert*-butyl)pyridine-*N*-oxide

A solution of 4-*tert*-butylpyridine (180 mg, 1.33 mmol) in DCM (10 mL) was treated with mCPBA (398 mg, 1.73 mmol) in portions. The reaction was stirred overnight at room temperature and then evacuated to ¼ volume. The crude reaction was loaded directly onto silica gel and eluted with 0-5% MeOH: DCM to afford the desired product as a white solid (180 mg, 90%). 1H NMR (400 MHz, $CDCl_3$) δ 8.16 (dd, J=2.0, 5.5 Hz, 2H), 7.27 (d, J=7.4 Hz, 1H), 1.32 (s, 9H).

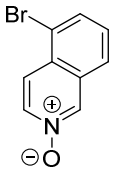
2-bromopyridine-*N*-oxide

Prepared in analogous fashion to 4-*tert*-butylpyridine-*N*-oxide with 2-bromopyridine. White solid (423 mg, 78%). ^{1}H NMR (400 MHz, MeOH-*d4*) δ 8.50 (dd, J=1.2, 6.6 Hz, 1H), 7.93 (dd, J=1.8, 8.0 Hz, 1H), 7.55 - 7.48 (m, 1H), 7.46 - 7.36 (m, 1H).



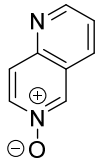
4-bromopyridine-*N*-oxide

Prepared in analogous fashion to 4-*tert*-butylpyridine-*N*-oxide with 4-bromopyridine. White solid (220 mg, 49%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J=7.0 Hz, 2H), 7.42 (d, J=7.0 Hz, 2H).



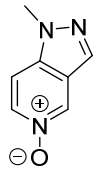
5-bromoisoquinoline-*N*-oxide

Prepared in analogous fashion to 4-*tert*-butylpyridine-*N*-oxide with 5-bromoisoquinoline. White solid (260 mg, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.25 (dd, J=1.5, 7.3 Hz, 1H), 8.10 (d, J=7.0 Hz, 1H), 7.89 (d, J=7.6 Hz, 1H), 7.74 (d, J=8.8 Hz, 1H), 7.51 (t, J=7.9 Hz, 1H).



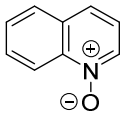
1,6-naphthyridine 6-oxide

Prepared according to Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis*, **1999**, *2*, 306-311.



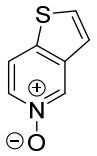
1-methyl-1*H*-pyrazolo[4,3-*c*]pyridine 5-oxide

Prepared in analogous fashion to 4-*tert*-butylpyridine-*N*-oxide with 1-methyl-1H-pyrazolo[4,3-c]pyridine. Light-yellow solid (170 mg, 95%). ^{1}H NMR (400 MHz, DMSO-*d6*) δ 8.76 (d, J=1.2 Hz, 1H), 8.12 - 8.07 (m, 2H), 7.79 (d, J=7.6 Hz, 1H), 4.06 (s, 3H).



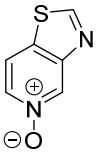
quinoline-*N*--oxide

Prepared in analogous fashion to 4-*tert*-butylpyridine-*N*-oxide with quinoline. White solid (253 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J=8.8 Hz, 1H), 8.59 (d, J=5.9 Hz, 1H), 7.90 (d, J=8.2 Hz, 1H), 7.84 - 7.73 (m, 2H), 7.67 (t, J=7.0 Hz, 1H), 7.33 (dd, J=6.5, 8.2 Hz, 1H)



thieno[3,2-*c*]pyridine-*N*-oxide

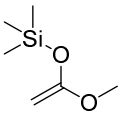
Prepared in analogous fashion to 4-*tert*-butylpyridine-*N*-oxide with thieno[3,2-c]pyridine. White solid (220 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.81 (d, J=1.5 Hz, 1H), 8.20 (dd, J=1.6, 7.0 Hz, 1H), 7.76 (d, J=7.1 Hz, 1H), 7.69 (d, J=5.6 Hz, 1H), 7.33 (dd, J=0.6, 5.5 Hz, 1H).



thiazolo[4,5-*c*]pyridine-*N*-oxide

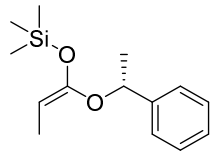
Prepared in analogous fashion to 4-*tert*-butylpyridine-*N*-oxide with thiazolo[4,5-c]pyridine. Light-yellow solid (64 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 9.12 (s, 1H), 8.34 (dd, J=1.2, 7.0 Hz, 1H), 7.86 (d, J=7.0 Hz, 1H).

Silyl Ketene Acetals



((1-methoxyvinyl)oxy)trimethylsilane

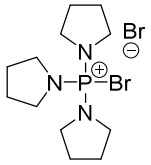
To a 0^{o}C solution of diisopropylamine (3.15 mL, 22.3 mmol) in THF (20 mL) was added nBuLi (9.66 mL, 21.3 mmol, 2.4 M in hexanes) dropwise. The reaction was stirred for 15 minutes, cooled to -78^{o}C, and treated with a THF (5 mL) solution of methyl acetate (1.61 g, 20.3 mmol) in a dropwise fashion over 5 minutes. The reaction was stirred for 30 minutes and then treated with TMSCl (3.17 mL, 24.3 mmol). The reaction was slowly warmed to room temperature over 3 hours. The reaction was evacuated to half volume (no heat was used in rotary evaporator bath) and the residue filtered through a pad of Celite, washing with petroleum ether (20 mL). The combined filtrate was evacuated (no heat was used in rotary evaporator bath) to afford 3.2 g of a yellow oil. The crude oil was purified by short-path vacuum distillation at (25^{o}C/5 mmHg) with a -78^{o}C cooling bath on the receiver to afford a clear oil (1.74 g, 82%).
^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.48 (s, 3H), 3.17 - 3.09 (m, 2H), 0.18 (s, 9H).



(*R*,*E*)-trimethyl((1-(1-phenylethoxy)prop-1-en-1-yl)oxy)silane

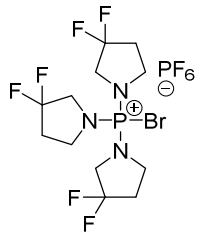
To a 0°C solution of diisopropylamine (1.32 mL, 9.35 mmol) in THF (10 mL) was added nBuLi (4.06 mL, 8.92 mmol, 2.4 M in hexanes) dropwise. The reaction was stirred for 15 minutes, cooled to -78°C, and treated with a THF (2 mL) solution of (R)-1-phenylethyl propionate (1.52 g, 8.50 mmol) in a dropwise fashion over 5 minutes. The reaction was stirred for 30 minutes and then treated with TMSCl (1.33 mL, 10.2 mmol). The reaction was a stirred for 2 hours at -78°C. The reaction was then warmed to room temperature and poured into a mixture of ice water and heptanes (60 mL). The organics were washed with brine, dried (Na_2SO_4) and evacuated to afford a yellow oil. The crude oil was purified by short-path vacuum distillation to afford a clear oil (1.74 g, 82%).
About an 8:2 E/Z mixture as determined by nOE.
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.30 (m, 5H), 5.19 (d, J=7.0 Hz, 1H), 3.67 (d, J=6.5 Hz, 1H), 1.53 (d, J=6.5 Hz, 3H), 1.51 (d, J=6.5 Hz, 3H), 0.12 - 0.10 (m, 9H).

PyBroP Derivatives



bromotri(pyrrolidin-1-yl)phosphonium bromide

8: Literature preparation (Castro, B.; Coste, J. PCT Int. Appl. WO9010009, 1990).
To a 0°C solution of tris-(1-pyrrolidino)-phosphine (500 mg, 2.07 mmol) in anhydrous diethyl ether (6 mL) under nitrogen was added bromine (106 μL, 2.07 mmol) dropwise. Tan solids immediately precipitated from solution. The reaction was warmed to room temperature and stirred for 20 minutes. The solids were vacuum-filtered under nitrogen, washed with ether and then dried under vacuum to afford a highly-hygroscopic yellow solid (260 mg, 31%) which was used immediately without further purification.



bromotris(3,3-difluoropyrrolidin-1-yl)phosphonium hexafluorophosphate(V)

9: To a -78°C mixture of 3,3-difluoro-pyrrolidine-HCl (1.00 g, 6.97 mmol) in CH_2Cl_2 (8 mL) was added triethylamine (4.91 mL, 34.8 mmol), followed by a solution of $POCl_3$ (164 μL, 1.74 mmol) in CH_2Cl_2 (1 mL). The reaction was allowed to warm to room temperature and stir overnight. The reaction was diluted with water (15 mL) and extracted with CH_2Cl_2 (2x25 mL). The pooled organics were washed with brine, dried (Na_2SO_4), and evacuated. The crude material was purified by silica gel chromatography (0-5% MeOH: DCM) to afford tris(3,3-difluoropyrrolidin-1-yl)phosphine oxide (390 mg, 61%) as a waxy yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34-3.52 (m, 12H), 2.34 (tt, J=7.1, 14.0 Hz, 6H). GCMS: m/z = 365.0.

To a solution of the tris(3,3-difluoropyrrolidin-1-yl)phosphine oxide (390 mg, 1.07 mmol) in CH_2Cl_2 (1 mL) under nitrogen was added a solution of $POBr_3$ (308 mg, 1.07 mmol) in CH_2Cl_2 (500 μL) in a dropwise fashion over 20 minutes. A slight exotherm was noted. The reaction was heated to 40°C for 2 hours and then cooled to 0°C. A solution of potassium hexafluorophosphate (198 mg, 1.07 mmol) in water (1 mL) was then added in a single portion with vigorous stirring. The reaction was stirred for 10 minutes and then extracted with DCM. The organics were dried (Na_2SO_4) and evacuated to afford **9** (175 mg, 29%) as an off-white solid. ^{1}H NMR (400 MHz, DMSO-*d6*) δ 3.44 (dt, J=3.9, 13.3 Hz, 6H), 3.30 (dt, J=3.7, 7.3 Hz, 6H), 2.34 (tt, J=7.2, 14.4 Hz, 6H). ^{31}P NMR (162 MHz, DMSO-*d6*) δ 10.1 (s, 1P), -136.4 – -153.0 (q, 1P). MP = 165-168°C.