

A Novel Approach to Indoles by a Heck / Cyclization / Isomerization Process

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Supplementary Information

Base screen for the Heck reaction of aryl triflates with N-Boc allylamine

It was found that the choice of base was critical in minimizing the formation of the phenol and hence provide a more efficient Heck reaction. A screen of bases in the Heck reaction using aryl triflate **6b** was performed, with each reaction stopped after 14 hours and analyzed by HPLC (Table 1). Both inorganic and organic bases were studied, leading to various amounts of starting material **6b**, desired product **7b**, phenol **8b** and des-chloro **9b**. From this screen NaOAc was identified as a more efficient base for the transformation (entry 4).

Table 1. Base Screen in the Heck Reaction of Aryl Ester **6b**.^a

Entry	Base	6b (%) ^b	7b (%) ^b	8b (%) ^b	9b (%) ^b
1	K ₂ CO ₃	3.2	34.6	57.1	5.0
2	Cs ₂ CO ₃	<2	4	96	<1
3	KOAc	1.4	28.3	31.5	38.8
4	NaOAc	12.8	79.2	<1	7.9
5	Et ₃ N	2.0	57.1	3.5	37.5
6	DIPEA	5.1	66.8	4.0	24.1
7	DBU	65.6	1.1	24.1	9.3
8	DABCO	36.3	51.7	12.1	<1
9	Pyridine	77.6	9.4	2.5	10.4
10	Cy ₂ NMe	3.1	33.3	5.1	58.5

(a) Reagents and Conditions: (i) N-Boc allylamine (1.2 equiv), Pd(OAc)₂ (3 mol%), dppf (10 mol%), Base (1.5 equiv), MeCN, 80 °C, 14 h. (b) Determined by HPLC analysis of the crude reaction mixtures.

General Information: All materials were purchased from commercial suppliers and used without further purification. All reactions were conducted under an atmosphere of nitrogen unless noted otherwise. Reactions were monitored for completion by removing a small sample from the reaction mixture and analyzing the sample by HPLC. HPLC analyses were performed using the following system: Agilent Eclipse Plus C18, 1.8 μm, 50 × 4.60 mm column, and a mobile phase consisting of acetonitrile and 0.1% phosphoric acid. Melting points were obtained by DSC studies conducted using a TA Instruments MDSC 2920 with refrigerated cooling system (RCS) (TA Instruments, Leatherhead, UK). NMR spectra were recorded on a Bruker AVANCE DPX or DRX 400 (¹H NMR at 400 MHz, ¹³C NMR at 100 MHz) spectrometer. ¹H NMR data are reported as follows: chemical shifts are reported in ppm with the solvent resonance resulting from incomplete deuteration as the internal standard (CDCl₃: 7.26), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet or combinations thereof), and coupling constants. ¹³C NMR data are reported as follows: chemical shifts are reported in ppm with the solvent resonance as the internal standard (¹³CDCl₃: 77.16). High resolution mass spectrometry was performed on a Micromass LCT. GC mass spectrometry was performed on an Agilent 6890 Gas Chromatograph, with 5975C mass spectrometer using EI ionization.

General Procedure 1: For the preparation of the 2-chlorotriflates

The phenol (1 equiv.) was weighed into a round bottomed flask (rbf) containing a magnetic stirring bar and placed under nitrogen. CH₂Cl₂ (10 mL/g) was added and the solution was cooled to 0 °C. Triethylamine (1.2 equiv.) was added dropwise over 5 min, followed by the dropwise addition of

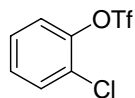
trifluoromethanesulfonic anhydride (1.1 equiv.) over 30 min. The mixture was allowed to warm to room temperature and stirred until HPLC indicated the reaction to be complete. The reaction mixture was cooled to 0 °C, and quenched by the dropwise addition of 2M HCl (2 equiv.) over 5 min. The mixture was allowed to stir at room temperature for 10 min. The aqueous layer was removed, and back-extracted with CH₂Cl₂ (4 mL/g). The combined organics were washed with NaHCO₃ (4 mL/g), water (4 mL/g), brine (4 mL/g), dried (Na₂SO₄) filtered, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution, 100% hexane to 50% MtBE in hexane) to provide the triflate product.

General procedure 2: For the Pd-Catalyzed Heck / cyclization / isomerization sequence.

To a round-bottomed flask (rbf) containing a magnetic stirring bar was added the chlorotriflate (1 equiv.), N-Boc allylamine (1.2 equiv.), Pd(OAc)₂ (3 mol%), dppf (10 mol%) and NaOAc (1.2 equiv.). The flask was fitted with a reflux condenser and the rbf was evacuated under vacuum and backfilled with nitrogen three times. MeCN (10 mL/g) was added and the flask evacuated under vacuum and backfilled with nitrogen three times. The reaction was heated to 80 °C until HPLC showed the Heck reaction to be complete. The reaction mixture was cooled to room temperature, then concentrated *in vacuo*. K₂CO₃ (1.5 equiv.) and DMF (10 mL/g) were added to the crude mixture and the flask evacuated under vacuum and backfilled with nitrogen three times. Pd(OAc)₂ (3 mol%) and XPhos (10 mol%) were added and the mixture evacuated under vacuum and backfilled with nitrogen three times. The mixture was heated to 80 °C until HPLC showed the cyclization reaction to be complete. The reaction mixture was cooled to room temperature and the crude mixture filtered through celite, washing with EtOAc (20 mL/g). The filtrate was washed with 5% LiCl (2 x 10 mL/g), then the LiCl wash back-extracted with EtOAc (10 mL/g). The combined organics were washed with water (10 mL/g), brine (10 mL/g), dried (Na₂SO₄), filtered and concentrated *in vacuo*. To this crude mixture, dichloromethane (6 mL/g) and CSA (20 mol%) were added and the mixture stirred at room temperature until HPLC showed the isomerization reaction to be complete. The reaction mixture was quenched with saturated NaHCO₃ (5 mL/g) and the organic phase removed. The aqueous was back-extracted with dichloromethane, the organics combined, dried with Na₂SO₄, filtered and concentrated *in vacuo*. The crude mixture was then purified by silica gel chromatography (gradient elution, 100% hexane to 50% *tert*-butylmethyl ether [MtBE] in hexane) to provide the indole products.

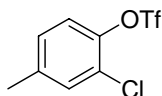
Preparation of the aryl triflates

2-chlorophenyl trifluoromethanesulfonate



Following general procedure 1: The chlorophenol (5.00 g, 38.9 mmol), trifluoromethanesulfonic anhydride (16.5 g, 58.4 mmol), triethylamine (4.62 g, 46.7 mmol) and CH₂Cl₂ (50 mL) were stirred for 60 min, and then the reaction quenched with 2M HCl (39 mL, 77.8 mmol). After silica gel chromatography the title compound was isolated as a clear oil (9.60 g, 95%). ¹H NMR: (400 MHz, CDCl₃): δ 7.41-7.46 (2H, m), 7.21-7.28 (2H, m). ¹³C NMR (100 MHz, CDCl₃): 146.1, 131.6, 129.6, 128.7, 127.6, 119.0 (q, *J* = 318 Hz). GCMS (nominal): 260 (M⁺).¹

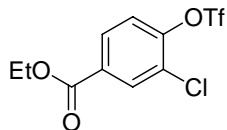
2-chloro-4-methylphenyl trifluoromethanesulfonate



Following general procedure 1: The chlorophenol (5.00 g, 35.1 mmol), trifluoromethanesulfonic anhydride (6.49 g, 38.6 mmol), triethylamine (4.26 g, 42.1 mmol) and CH₂Cl₂ (50 mL) were stirred for 60 min, and then the reaction quenched with

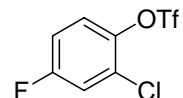
2M HCl (35.1 mL, 70.1 mmol). After silica gel chromatography the title compound was isolated as a clear oil (8.67 g, 90%). ¹H NMR: (400 MHz, CDCl₃): δ 7.31 (1H, s), 7.22 (1H, d, *J* = 8.4 Hz), 7.12 (1H, dd, *J* = 8.4, 1.6 Hz), 2.35 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ 143.9, 140.4, 131.8, 129.3, 126.9, 122.8, 119.1 (q, *J* = 319 Hz), 20.8. GCMS (nominal): 274 (M⁺).¹

3-chloro-4-[(trifluoromethyl)sulfonyloxy]ethylbenzoate



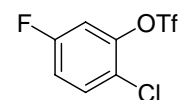
Following general procedure 1: The chlorophenol (5.15 g, 25.7 mmol), trifluoromethanesulfonic anhydride (7.97 g, 28.2 mmol), triethylamine (3.12 g, 30.8 mmol) and CH₂Cl₂ (50 mL) were stirred for 45 min, and then the reaction quenched with 2M HCl (25.7 mL, 51.3 mmol). After silica gel chromatography the title compound was isolated as a white solid (7.77 g, 91%). m.p. 53-56 °C. ¹H NMR: (400 MHz, CDCl₃): δ 8.20 (1H, s), 8.02 (1H, d, *J* = 8.8 Hz), 7.43 (1H, d, *J* = 8.4 Hz), 4.40 (2H, q, *J* = 7.2 Hz), 1.40 (3H, t, *J* = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 164.1, 148.6, 132.7, 131.7, 129.7, 127.7, 123.1, 118.7 (q, *J* = 320 Hz), 62.1, 14.3. GCMS (nominal): 332 (M⁺).¹

2-chloro-4-fluorophenyl trifluoromethanesulfonate



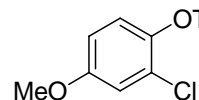
Following general procedure 1: The chlorophenol (10.0 g, 68.2 mmol), trifluoromethanesulfonic anhydride (21.2 g, 75.0 mmol), triethylamine (8.29 g, 82.0 mmol) and CH₂Cl₂ (100 mL) were stirred for 45 min, and then the reaction quenched with 2M HCl (51.2 mL, 102 mmol). After silica gel chromatography the title compound was isolated as a clear oil (17.8 g, 94%).² ¹H NMR: (400 MHz, CDCl₃): δ 7.34 (1H, dd, *J* = 9.2, 4.8 Hz), 7.28 (1H, dd, *J* = 7.6, 2.8 Hz), 7.07 (1H, ddd, *J* = 9.2, 7.2, 2.8 Hz).

2-chloro-5-fluorophenyl trifluoromethanesulfonate



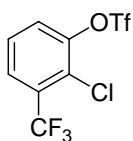
Following general procedure 1: The chlorophenol (5.09 g, 34.7 mmol), trifluoromethanesulfonic anhydride (10.8 g, 38.2 mmol), triethylamine (4.22 g, 41.7 mmol) and CH₂Cl₂ (50 mL) were stirred for 45 min, and then the reaction quenched with 2M HCl (26.0 mL, 52.1 mmol). After silica gel chromatography the title compound was isolated as a clear oil (8.38 g, 87%). ¹H NMR: (400 MHz, CDCl₃): δ 7.51 (1H, dd, *J* = 8.8, 5.6 Hz), 7.15 (1H, dd, *J* = 10.8, 2.8 Hz), 7.10 (1H, ddd, *J* = 8.8, 7.6, 2.8 Hz). ¹³C NMR: (100 MHz, CDCl₃): δ 161.4 (d, *J* = 250 Hz), 145.9 (d, *J* = 11 Hz), 132.1 (d, *J* = 9 Hz), 123.2 (d, *J* = 4.2 Hz), 119.0 (q, *J* = 318 Hz), 116.9 (d, *J* = 22 Hz), 111.7 (d, *J* = 27 Hz). GCMS (nominal): 278 (M⁺).¹

2-chloro-4-methoxyphenyl trifluoromethanesulfonate



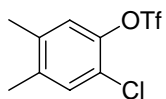
Following general procedure 1: The chlorophenol (5.00 g, 31.5 mmol), trifluoromethanesulfonic anhydride (9.79 g, 37.8 mmol), triethylamine (3.83 g, 37.8 mmol) and CH₂Cl₂ (50 mL) were stirred for 45 min, and then the reaction quenched with 2M HCl (31.5 mL, 63.1 mmol). After silica gel chromatography the title compound was isolated as a white solid (8.51 g, 93%).² ¹H NMR: (400 MHz, CDCl₃): δ 7.60 (1H, d, *J* = 9.2 Hz), 7.37 (1H, d, *J* = 2.8 Hz), 7.19 (1H, dd, *J* = 9.2, 2.8 Hz), 4.17 (3H, s).

2-chloro-3-(trifluoromethyl)phenyl trifluoromethanesulfonate



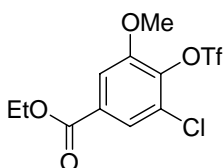
Following general procedure 1: The chlorophenol (5.00 g, 25.4 mmol), trifluoromethanesulfonic anhydride (10.8 g, 38.1 mmol), triethylamine (3.09 g, 30.5 mmol) and CH₂Cl₂ (50 mL) were stirred for 45 min, and then the reaction quenched with 2M HCl (25.4 mL, 50.8 mmol). After silica gel chromatography the title compound was isolated as a clear oil (7.04 g, 85%). ¹H NMR: (400 MHz, CDCl₃): δ 7.76 (1H, d, *J* = 7.6 Hz), 7.58 (1H, d, *J* = 8.0 Hz), 7.50 (1H, dd, *J* = 8.0, 7.6 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 147.2, 131.4 (q, *J* = 32 Hz), 128.5, 127.4 (q, *J* = 5 Hz), 126.7 (d, *J* = 1 Hz), 126.7, 122.4 (q, *J* = 272 Hz), 119.0 (q, *J* = 319 Hz). GCMS (nominal): 328 (M⁺).¹

2-chloro-4,5-dimethylphenyl trifluoromethanesulfonate



Following general procedure 1: The chlorophenol (5.00 g, 31.9 mmol), trifluoromethanesulfonic anhydride (13.5 g, 47.9 mmol), triethylamine (3.88 g, 38.3 mmol) and CH₂Cl₂ (50 mL) were stirred for 60 min, and then the reaction quenched with 2M HCl (32 mL, 63.9 mmol). After silica gel chromatography the title compound was isolated as a clear oil (8.39 g, 91%). ¹H NMR: (400 MHz, CDCl₃): δ 7.26 (1H, s), 7.11 (1H, s), 2.27 (3H, s), 2.26 (3H, s). ¹³C NMR (100 MHz, CDCl₃): δ 143.6, 138.9, 137.9, 131.8, 131.8, 123.8, 119.0 (q, *J* = 320 Hz), 19.6, 19.3. GCMS (nominal): 288 (M⁺).¹

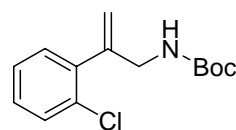
3-chloro-5-methoxy-4-[(trifluoromethyl)sulfonyloxy]ethylbenzoate



Following general procedure 1: The chlorophenol (2.00 g, 8.67 mmol), trifluoromethanesulfonic anhydride (2.69 g, 9.54 mmol), triethylamine (1.05 g, 10.4 mmol) and CH₂Cl₂ (20 mL) were stirred for 45 min, and then the reaction quenched with 2M HCl (6.50 mL, 13.0 mmol). After silica gel chromatography the title compound was isolated as a white solid (2.90 g, 90%). m.p. 77-80 °C. ¹H NMR: (400 MHz, CDCl₃): δ 7.77 (1H, d, *J* = 1.6 Hz), 7.61 (1H, d, *J* = 1.6 Hz), 4.40 (2H, q, *J* = 6.8 Hz), 3.99 (3H, s), 1.41 (3H, t, *J* = 6.8 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 164.6, 152.9, 138.8, 131.4, 128.7, 123.8, 118.9 (q, *J* = 318 Hz), 112.6, 62.4, 57.1, 14.6. GCMS (nominal): 362 (M⁺).¹

Indole Syntheses

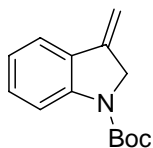
tert-butyl [2-(2-chlorophenyl)prop-2-en-1-yl]carbamate



To a rbf containing a magnetic stirring bar was added the chlorotriflate (1.00 g, 3.84 mmol), N-Boc allylamine (724 mg, 4.60 mmol), Pd(OAc)₂ (26 mg, 0.12 mmol, 3 mol%), dppf (213 mg, 0.384 mmol, 10 mol%) and NaOAc (378 mg, 4.60 mmol). The flask was fitted with a reflux condenser and the flask was evacuated under vacuum and backfilled with nitrogen three times. MeCN (10 mL) was added and the flask evacuated and backfilled with nitrogen three times. The reaction was heated to 80 °C for 16 hours, after which time HPLC showed the reaction to be complete. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and purified by silica gel chromatography (gradient elution, 100% hexane to 50% MtBE in hexane) to provide the title compound as a colorless solid (915 mg, 89%). m.p. 40-43 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.34 (1H, m), 7.23 -7.20 (3H, m), 5.39 (1H, s), 5.10 (1H, s), 4.79 (1H, br s), 4.04 (2H, d, *J* = 5.6 Hz), 1.39 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 156.09, 145.67,

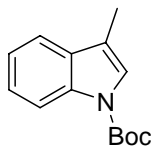
139.7, 132.7, 131.1, 129.8, 129.1, 127.0, 116.1, 79.7, 45.5, 28.7. HRMS (ESI+H⁺[-Boc]) calcd for C₉H₁₁NCl 168.0580, found 168.0579.

***tert*-butyl 3-methyleneindoline-1-carboxylate**



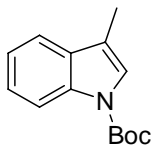
To a rbf containing a magnetic stirring bar was added the *tert*-butyl [2-(2-chlorophenyl)prop-2-en-1-yl]carbamate (685 mg, 2.56 mmol), K₂CO₃ (424 mg, 3.07 mmol), Pd(OAc)₂ (17 mg, 0.077 mmol, 3 mol%) and XPhos (122 mg, 0.256 mmol, 10 mol%). The flask was degassed by evacuating and backfilling with nitrogen three times. DMF (10 mL) was added and the mixture degassed by evacuating under vacuum and backfilling with nitrogen three times. The reaction mixture was heated to 80 °C and left to stir for 16 hours, after which time HPLC showed the reaction to be complete. The reaction mixture was cooled to room temperature and filtered through celite, washing with EtOAc (20 mL). The filtrate was washed with 5% LiCl (2 x 20 mL), then the LiCl wash back-extracted with EtOAc (20 mL). The combined organics were washed with water (20 mL), brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The crude was purified by silica gel chromatography (gradient elution, 100% hexane to 50% MtBE in hexane) to yield the title compound as a clear oil (323 mg, 55%). ¹H NMR (400 MHz, CDCl₃): δ 7.97 (1H, br s), 7.44 (1H, d, *J* = 7.6 Hz), 7.23 (1H, t, *J* = 8.4 Hz), 6.99 (1H, t, *J* = 7.6 Hz), 5.47 (1H, br s), 5.05 (1H, br s), 4.59 (2H, br s), 1.59 (9H, br s). ¹³C NMR (100 MHz, CDCl₃): δ 151.7, 145.4, 141.2, 130.0, 122.4, 120.4, 119.0, 115.5, 101.2, 80.9, 53.5, 28.5. HRMS (ESI+H⁺[-Boc]) calcd for C₉H₁₀N 132.0813, found 132.0808.

***tert*-butyl 3-methyl-1*H*-indole-1-carboxylate**

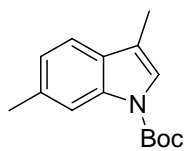


To a rbf containing a magnetic stirring bar was added the *tert*-butyl 3-methyleneindoline-1-carboxylate (198 mg, 0.890 mmol) and dichloromethane (4 ml). The flask was placed under nitrogen and CSA (40 mg, 0.17 mmol, 20 mol%) was added. The mixture was stirred at room temperature for 16 hours, after which time HPLC showed the reaction to be complete. The crude was purified by silica gel chromatography (gradient elution, 100% hexane to 50% MtBE in hexane) to yield the product as a yellow oil (178 mg, 90%). ¹H NMR, ¹³C NMR, MS: see below.

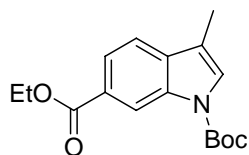
***tert*-butyl 3-methyl-1*H*-indole-1-carboxylate**



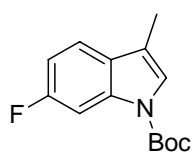
Following general procedure 2: Heck reaction; The chlorotriflate (1.0 g, 3.80 mmol), *N*-Boc allylamine (717 mg, 4.56 mmol), sodium acetate (374 mg, 4.56 mmol), Pd(OAc)₂ (25 mg, 0.11 mmol, 3 mol%), dppf (211 mg, 0.38 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 17 hours; cyclization: Pd(OAc)₂ (25 mg, 0.11 mmol, 3 mol%), XPhos (181 mg, 0.38 mmol, 10 mol%), K₂CO₃ (788 mg, 5.70 mmol) and DMF (10 mL) were stirred at 80 °C for 18 hours; isomerization: CSA (177 mg, 0.76 mmol) and dichloromethane (6 mL) were stirred at room temperature for 16 hours. After silica gel chromatography the title compound was isolated as a yellow oil (525 mg, 60%). ¹H NMR (400 MHz, CDCl₃): δ 8.13 (1H, br s), 7.51 (1H, d, *J* = 7.6 Hz) 7.37 (1H, br s), 7.24-7.35 (2H, m), 2.29 (3H, s), 1.68 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 150.1, 135.8, 131.7, 124.5, 123.1, 122.6, 119.2, 116.6, 115.4, 83.4, 28.5, 9.9. HRMS (ESI+H⁺[-^tBu]) calcd for C₁₀H₁₀NO₂ 176.0712, found 176.0699.

tert*-butyl 3,6-dimethyl-1*H*-indole-1-carboxylate*Table 1, Entry 1**

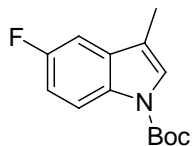
Following general procedure 2: Heck reaction; The chlorotriflate (1.0 g, 3.6 mmol), N-Boc allylamine (0.687 g, 4.37 mmol), sodium acetate (0.358 g, 4.37 mmol), Pd(OAc)₂ (25 mg, 0.11 mmol, 3 mol%), dppf (202 mg, 0.364 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 15 hours; cyclization: Pd(OAc)₂ (25 mg, 0.11 mmol, 3 mol%), XPhos (174 mg, 0.364 mmol, 10 mol%), K₂CO₃ (0.755 g, 5.46 mmol) and DMF (10 mL) were stirred at 80 °C for 15 h; isomerization: CSA (169 mg, 0.728 mmol, 20 mol %) and dichloromethane (6 mL) were stirred at room temperature for 2 days. After silica gel chromatography the title compound was isolated as a clear oil (689 mg, 77%). ¹H NMR (400 MHz, CDCl₃): δ 8.01 (1H, br s), 7.38 (1H, d, *J* = 8.0 Hz), 7.28 (1H, br s), 7.09 (1H, d, *J* = 8.0 Hz), 2.52 (3H, s), 2.24 (3H, s), 1.65 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 150.0, 136.0, 134.3, 129.3, 123.8, 122.2, 118.6, 116.4, 115.5, 83.1, 28.3, 22.1, 9.8. HRMS (ESI+H⁺[-Boc]) calcd for C₁₀H₁₂N 146.0970, found 146.0973.

1-*tert*-butyl 6-ethyl 3-methyl-1*H*-indole-1,6-dicarboxylate**Table 1, Entry 2**

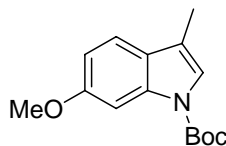
Following general procedure 2: Heck reaction; The chlorotriflate (1.0 g, 3.0 mmol), N-Boc allylamine (0.567 g, 3.61 mmol), sodium acetate (0.296 g, 3.61 mmol), Pd(OAc)₂ (20 mg, 0.090 mmol, 3 mol%), dppf (167 mg, 0.301 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 15 hours; cyclization: Pd(OAc)₂ (20 mg, 0.090 mmol, 3 mol%), XPhos (143 mg, 0.301 mmol, 10 mol%), K₂CO₃ (0.623 g, 4.51 mmol) and DMF (10 mL) were stirred at 80 °C for 15 hours; isomerization: CSA (140 mg, 0.601 mmol, 20 mol%) and dichloromethane (6 mL) were stirred at room temperature for 2 days. After silica gel chromatography the title compound was isolated as a white solid (651 mg, 71%). m.p. 87-91 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.81 (1H, br s), 7.95 (1H, d, *J* = 8.2 Hz), 7.51 (2H, d, *J* = 8.2 Hz), 4.40 (2H, q, *J* = 7.2 Hz), 2.27 (3H, s), 1.69 (9H, s), 1.42 (3H, t, *J* = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 167.4, 149.6, 135.1, 134.9, 126.3, 125.9, 123.6, 118.7, 117.1, 116.4, 84.0, 60.9, 28.3, 14.5, 9.7. HRMS (ESI+H⁺) calcd for C₁₇H₂₂NO₄ 304.1549 found 304.1549.

tert*-butyl 6-fluoro-3-methyl-1*H*-indole-1-carboxylate*Table 1, Entry 3**

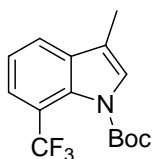
Following general procedure 2: Heck reaction; The chlorotriflate (1.0 g, 3.59 mmol), N-Boc allylamine (677 mg, 4.30 mmol), sodium acetate (352 mg, 4.30 mmol), Pd(OAc)₂ (24 mg, 0.11 mmol, 3 mol%), dppf (195 mg, 0.36 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 16 hours; cyclization: Pd(OAc)₂ (24 mg, 0.11 mmol, 3 mol%), XPhos (165 mg, 0.35 mmol, 10 mol%), K₂CO₃ (746 mg, 5.40 mmol) and DMF (10 mL) were stirred at 80 °C for 18 hours; isomerization: CSA (166 mg, 0.720 mmol) and dichloromethane (6 mL) were stirred at room temperature for 17 hours. After silica gel chromatography the title compound was isolated as a light brown solid (602 mg, 67%). m.p. 65-70 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.82 (1H, br s), 7.39 (1H, dd, *J* = 8.4, 5.2 Hz), 7.32 (1H, s), 6.99 (1H, td, *J* = 8.8, 2.0 Hz), 2.24 (3H, s), 1.66 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 161.0 (d, *J* = 238 Hz), 149.6, 135.6, 127.9, 123.0, 119.5 (d, *J* = 10 Hz), 116.2, 110.4 (d, *J* = 24 Hz), 102.6 (d, *J* = 29 Hz), 83.6, 28.2, 9.6. HRMS (ESI+H⁺[-^tBu]) calcd for C₁₀H₉NO₂F 194.0617, found 194.0628.

tert*-butyl 5-fluoro-3-methyl-1*H*-indole-1-carboxylate*Table 1, Entry 4**

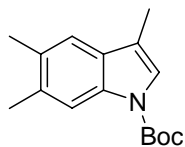
Following general procedure 2: Heck reaction; The chlorotriflate (1.0 g, 3.59 mmol), N-Boc allylamine (677 mg, 4.30 mmol), sodium acetate (352 mg, 4.30 mmol), Pd(OAc)₂ (24 mg, 0.11 mmol, 3 mol%), dppf (195 mg, 0.36 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 18 hours; cyclization: Pd(OAc)₂ (24 mg, 0.11 mmol, 3 mol%), XPhos (165 mg, 0.35 mmol, 10 mol%), K₂CO₃ (746 mg, 5.40 mmol) and DMF (10 mL) were stirred at 80 °C for 18 hours; isomerization: CSA (166 mg, 0.720 mmol) and dichloromethane (6 mL) were stirred at room temperature for 17 hours. After silica gel chromatography the title compound was isolated as a yellow solid (579 mg, 65%). m.p. 59-63 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.04 (1H, br s), 7.38 (1H, br s), 7.13 (1H, dd, *J* = 8.8, 2.4 Hz), 7.02 (1H, td, *J* = 9.2, 2.4 Hz), 2.23 (3H, s), 1.65 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 160.7, 158.3 (d, *J* = 237 Hz), 149.9, 132.7 (d, *J* = 9 Hz), 132.1, 124.6, 116.4 (d, *J* = 3 Hz), 112.1 (d, *J* = 25 Hz), 104.9, (d, *J* = 23 Hz), 83.8, 28.5, 9.9. HRMS (ESI+H⁺[-Boc]) calcd for C₉H₉NF 150.0719, found 150.0712.

tert*-butyl 6-methoxy-3-methyl-1*H*-indole-1-carboxylate*Table 1, Entry 5**

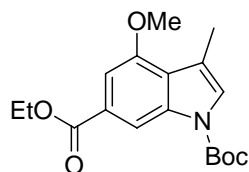
Following general procedure 2: Heck reaction; The chlorotriflate (1.0 g, 3.44 mmol), N-Boc allylamine (650 mg, 4.13 mmol), K₂CO₃ (570 mg, 4.13 mmol), Pd(OAc)₂ (23 mg, 0.10 mmol, 3 mol%), dppf (187 mg, 0.34 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 16 hours; cyclization: Pd(OAc)₂ (23 mg, 0.10 mmol, 3 mol%), XPhos (162 mg, 0.34 mmol, 10 mol%) K₂CO₃ (713 mg, 5.16 mmol) and DMF (10 mL) were stirred at 80 °C for 16 hours; isomerization: CSA (159 mg, 0.690 mmol) and dichloromethane (6 mL) were stirred at room temperature for 1 hour. After silica gel chromatography the title compound was isolated as a clear oil (552 mg, 65%). ¹H NMR (400 MHz, CDCl₃): δ 7.72 (1H, br s), 7.35 (1H, d, *J* = 8.6 Hz), 7.23 (1H, s), 6.88 (1H, d, *J* = 8.6 Hz), 3.66 (3H, s), 1.66 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 158.2, 150.2, 136.8, 125.6, 121.8, 119.7, 116.6, 111.9, 99.7, 83.4, 56.0, 28.6, 10.0. HRMS (ESI+H⁺[-^tBu]) calcd for C₁₁H₁₂NO₃ 206.0817, found 206.0818.

tert*-butyl 3-methyl-7-(trifluoromethyl)-1*H*-indole-1-carboxylate*Table 1, Entry 6**

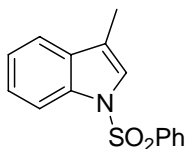
Following general procedure 2: Heck reaction; The chlorotriflate (1.0 g, 3.04 mmol), N-Boc allylamine (0.573 g, 3.65 mmol), sodium acetate (0.299 g, 3.65 mmol), Pd(OAc)₂ (20 mg, 0.090 mmol, 3 mol%), dppf (166 mg, 0.30 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 24 hours; cyclization: Pd(OAc)₂ (20 mg, 0.090 mmol, 3 mol%), XPhos (143 mg, 0.30 mmol, 10 mol%), K₂CO₃ (0.630 g, 4.56 mmol) and DMF (10 mL) were stirred at 80 °C for 48 hours; isomerization: CSA (141 mg, 0.61 mmol, 20 mol%) and dichloromethane (6 mL) were stirred at room temperature for 11 days. After silica gel chromatography the title compound was isolated as a yellow solid (490 mg, 54%). m.p. 83-86 °C. ¹H NMR: (400 MHz, CDCl₃): δ 7.66 (1H, d, *J* = 7.6 Hz), 7.61 (1H, d, *J* = 7.6 Hz), 7.33 (1H, dd, *J* = 7.6, 7.6 Hz), 7.32 (1H, d *J* = 0.8 Hz), 2.27 (3H, s), 1.62 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 150.3, 134.4, 131.4, 126.9, 124.5 (q, *J* = 270 Hz), 123.8 (q, *J* = 5 Hz), 123.0, 122.4, 118.6 (q, *J* = 33 Hz), 116.0, 84.5, 28.2, 9.7. HRMS (ESI+H⁺[-Boc]) calcd for C₁₀H₉NF₃ 200.0687, found 200.0678.

tert*-butyl 3,5,6-trimethyl-1*H*-indole-1-carboxylate*Table 1, Entry 7**

Following general procedure 2: Heck reaction; The chlorotriflate (1.00 g, 3.46 mmol), *N*-Boc allylamine (0.654 g, 4.16 mmol), sodium acetate (0.341 g, 4.16 mmol), Pd(OAc)₂ (23 mg, 0.10 mmol, 3 mol%), dppf (192 mg, 0.346 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 15 hours; cyclization: Pd(OAc)₂ (23 mg, 0.10 mmol, 3 mol%), XPhos (165 mg, 0.346 mmol, 10 mol%), K₂CO₃ (0.718 g, 5.20 mmol) and DMF (10 mL) were stirred at 80 °C for 23 hours; isomerization: CSA (161 mg, 0.693 mmol, 20 mol%) and dichloromethane (6 mL) were stirred at room temperature for 2 days. After silica gel chromatography the title compound was isolated as a white solid (605 mg, 67%). m.p 78-82 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.95 (1H, br s), 7.27-7.24 (2H, m), 2.39 (3H, s), 2.37 (3H, s), 2.24 (3H, s), 1.67 (9H, s). ¹³C NMR (100 MHz, CDCl₃): δ 150.0, 133.3, 131.0, 129.8, 126.0, 122.0, 119.4, 116.2, 115.9, 82.9, 28.4, 20.7, 20.2, 9.8. HRMS (ESI+H⁺[-Boc]) calcd for C₁₁H₁₄N 160.1126, found 160.1127.

1-*tert*-butyl 6-ethyl 4-methoxy-3-methyl-1*H*-indole-1,6-dicarboxylate**Table 1, Entry 8**

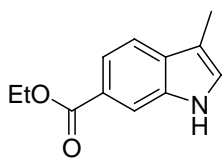
Following general procedure 2: Heck reaction; The chlorotriflate (120 g, 331 mmol), *N*-Boc allylamine (67.6 g, 430 mmol), K₂CO₃ (68.6 g, 496 mmol), Pd(OAc)₂ (2.23 g, 9.93 mmol, 3 mol%), dppf (18.3 g, 33.1 mmol, 10 mol%) and MeCN (1.2 L) were stirred at 80 °C for 15 hours; cyclization: Pd(OAc)₂ (1.82 g, 8.11 mmol, 3 mol%), XPhos (12.9 g, 27.0 mmol, 10 mol%), K₂CO₃ (56.1 g, 406 mmol) and DMF (700 mL) were stirred at 80 °C for 3 hours; isomerization: CSA (10.9 g, 23.4 mmol) and dichloromethane (390 mL) were stirred at room temperature for 2 days. Assay yield of the stream showed (88.2 g, 80%). Clear oil. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (1H, br s), 7.31 (1H, br s), 7.28 (1H, d, *J* = 1.2 Hz), 4.38 (2H, q, *J* = 7.2 Hz), 3.92 (3H, s), 2.38 (3H, s), 1.67 (9H, s), 1.40 (3H, *J* = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 167.5, 154.4, 149.7, 136.4, 127.3, 124.6, 124.5, 117.0, 110.9, 103.9, 84.0, 61.1, 55.7, 28.2, 14.7, 12.4. HRMS (ESI+H⁺) calcd for C₁₈H₂₄NO₅ 334.1654, found 334.1671.

3-methyl-1-(phenylsulfonyl)-1*H*-indole

Following general procedure 2: Heck reaction; The chlorotriflate (1.00 g, 3.84 mmol), *N*-Benzenesulfonyl allylamine (0.908 g, 4.60 mmol), sodium acetate (0.378 g, 4.60 mmol), Pd(OAc)₂ (26 mg, 0.11 mmol, 3 mol%), dppf (213 mg, 0.384 mmol, 10 mol%) and MeCN (10 mL) were stirred at 80 °C for 3 days; cyclization: Pd(OAc)₂ (26 mg, 0.116 mmol, 3 mol%), XPhos (183 mg, 0.384 mmol, 10 mol%), K₂CO₃ (0.637 g, 4.61 mmol) and DMF (10 mL) were stirred at 80 °C for 41 hours; isomerization: CSA (178 mg, 0.768 mmol, 20 mol%) and dichloromethane (6 mL) were stirred at room temperature for 7 days. After silica gel chromatography the title compound was isolated as a white solid (614 mg, 59%). m.p. 114-121 °C. ¹H NMR (400 MHz, CDCl₃): δ 7.99 (1H, d, *J* = 8.4 Hz), 7.87-7.85 (2H, m), 7.51 (1H, tt, *J* = 1.2, 8.0 Hz), 7.46-7.40 (3H, m), 7.34-7.30 (2H, m), 7.23 (1H, dd, *J* = 2.0, 6.8 Hz), 2.25 (3H, d, *J* = 1.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 138.7, 135.6, 133.9, 132.1, 129.5, 127.0, 125.0, 123.4, 123.3, 119.8, 119.1, 114.0, 10.0. HRMS (ESI+H⁺) calcd for C₁₅H₁₄NO₂S 272.0745, found 272.0739.

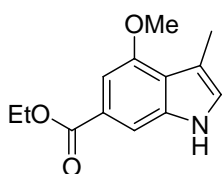
Example of Boc-removal

6-ethyl 3-methyl-1H-indole-6-carboxylate



The Boc-indole (220 mg, 0.725 mmol) was weighed into a rbf, placed under nitrogen and EtOH (2.2 mL) was added. Sodium ethoxide (99 mg, 1.5 mmol) was added in one portion and the reaction stirred at room temperature for 48 hours. HPLC analysis showed the reaction to be >98% conversion. Water (2 mL) was added to the reaction mixture, followed by EtOAc (20 mL). The aqueous was removed and back extracted with EtOAc (10 mL). The combined organics were washed with brine (5 mL), dried (Na₂SO₄), filtered, then concentrated *in vacuo*. The crude product was purified by silica gel chromatography (gradient elution, 100% hexane to 100% MtBE) to give the free indole product as a white solid, 132 mg, 90%. m.p. 105-110 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.37 (1H, br s), 8.14 (1H, s), 7.84 (1H, dd, *J* = 8.4, 1.2 Hz), 7.40 (1H, d, *J* = 8.4 Hz), 7.13 (1H, d, *J* = 1.2 Hz), 4.41 (2H, q, *J* = 7.2 Hz), 2.35 (3H, s), 1.42 (3H, t, *J* = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 168.1, 135.7, 131.9, 125.3, 123.9, 120.2, 118.5, 113.5, 112.1, 60.8, 14.5, 9.7. HRMS (ESI+H⁺) calcd for C₁₂H₁₄NO₂ 204.1025, found 204.1021.

6-ethyl 4-methoxy-3-methyl-1H-indole-6-carboxylate

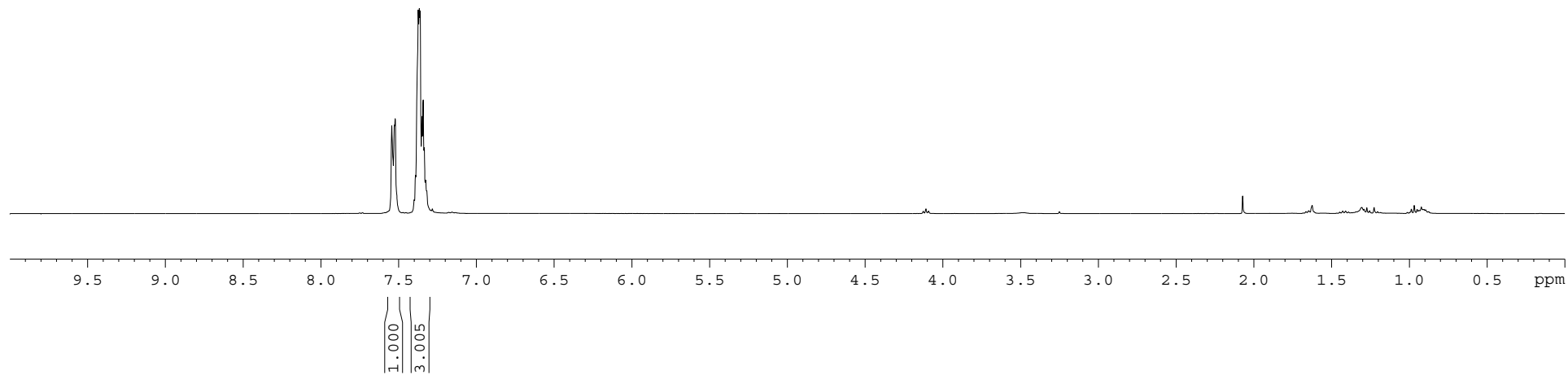
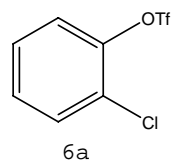


To the Boc-indole (73.3 g, 220 mmol) in DMF (390 mL) was added EtOH (230 mL), followed by sodium ethoxide (54.3 g, 234 mmol) over 3 minutes. The mixture was stirred at room temperature for 24 hours, after which HPLC analysis showed the reaction to be complete. Water (200 mL) was added to the reaction mixture, followed by MtBE (500 mL). 5% LiCl (500 mL) was added, the mixture transferred to a separating funnel and a further 300 mL MtBE was added. The aqueous was removed and back extracted with MtBE (400 mL). The organics were combined and washed with 5% LiCl (200 mL), saturated NH₄Cl (200 mL), water (200 mL), then concentrated *in vacuo* to approx. 600 mL. Assay yield of the stream showed 47.7 g, 93%. A crystallization from MtBE, heptane gave a light brown solid. m.p. 131-134 °C. ¹H NMR (400 MHz, CDCl₃): δ 8.16 (1H, br s), 7.74 (1H, d, *J* = 1.2 Hz), 7.14 (1H, s), 6.96 (1H, br s), 4.39 (2H, q, *J* = 7.2 Hz), 3.96 (3H, s), 2.47 (3H, s), 1.41 (3H, t, *J* = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃): δ 167.9, 154.8, 137.1, 124.9, 123.7, 121.7, 112.9, 107.5, 99.9, 60.9, 55.5, 14.6, 12.1. HRMS (ESI+H⁺) calcd for C₁₃H₁₆NO₃ 234.1130, found 234.1124.

References

- (1) Extensive efforts were made to obtain the HRMS data for the chlorotriflates. The nominal mass data using GCMS are presented.
- (2) The triflate have been prepared previously, see: Barluenga, J.; Jiménez-Aquino, A.; Aznar, F.; Valdés, C. *J. Am. Chem. Soc.* **2009**, *131*, 4031-4041.

h-1 drx400

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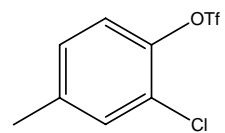
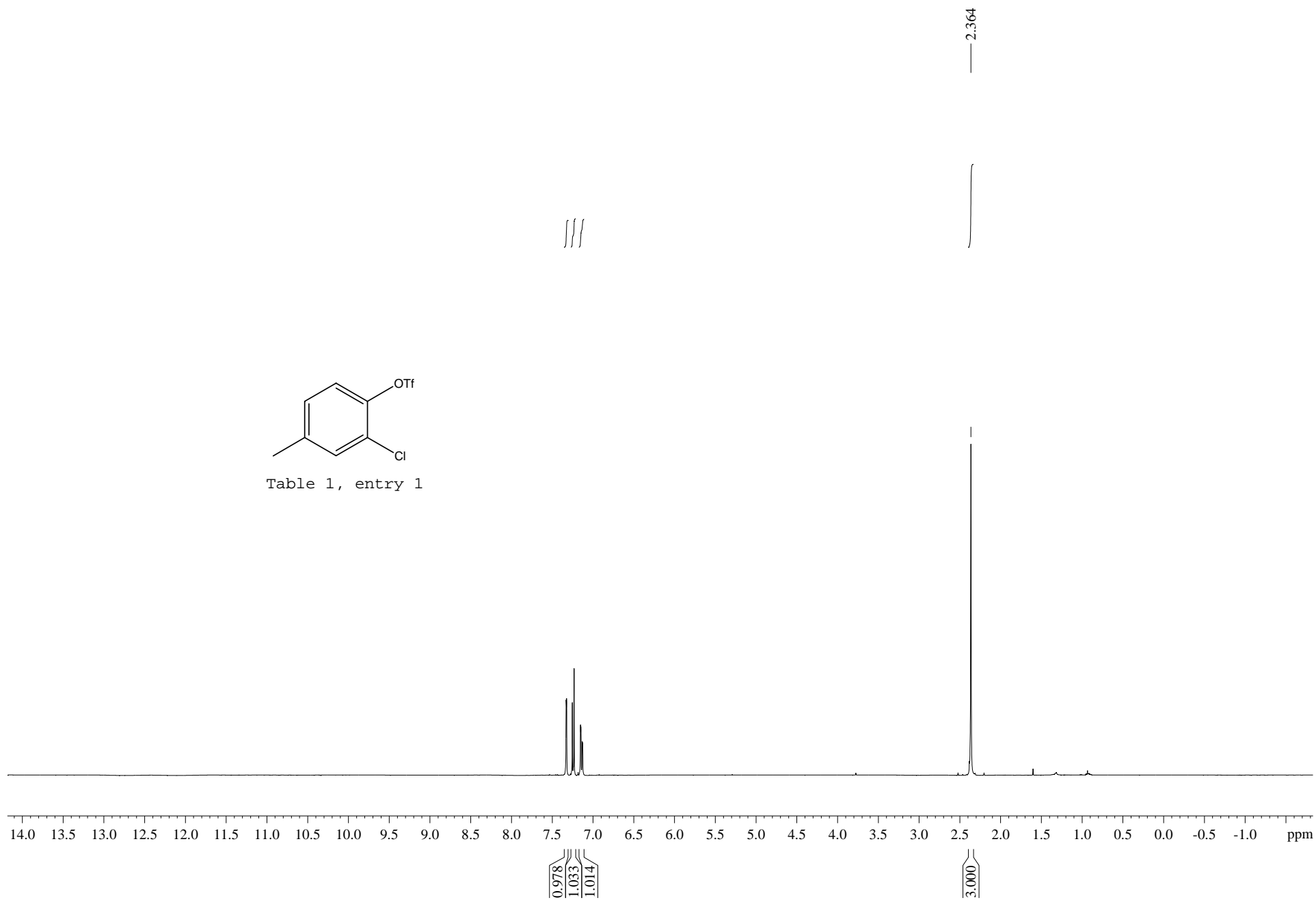
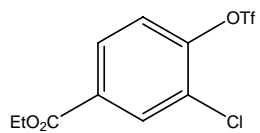


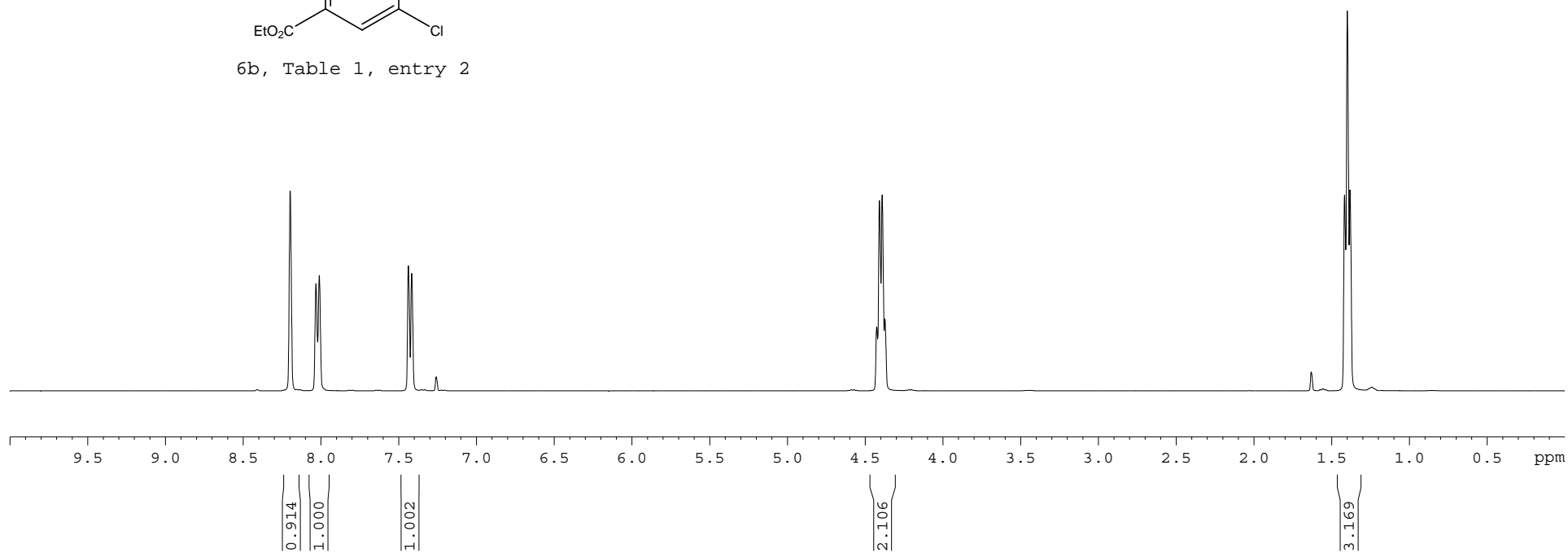
Table 1, entry 1



h-1 drx400



6b, Table 1, entry 2



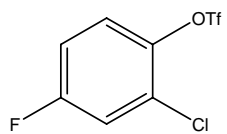
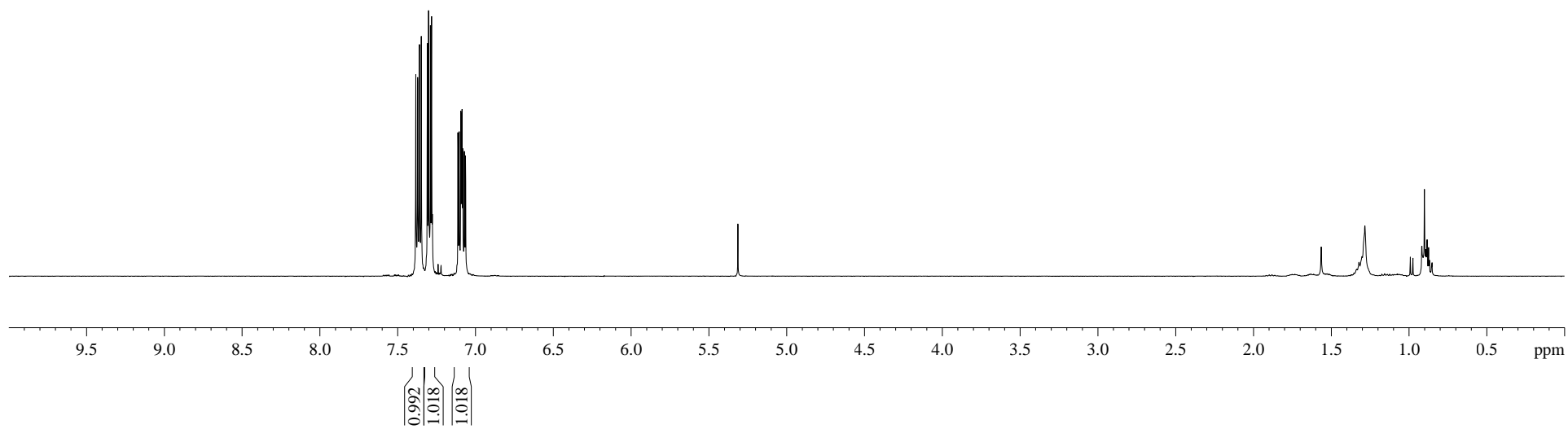


Table 1, entry 3





h-1 drx400

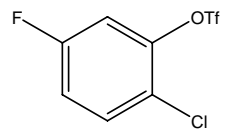
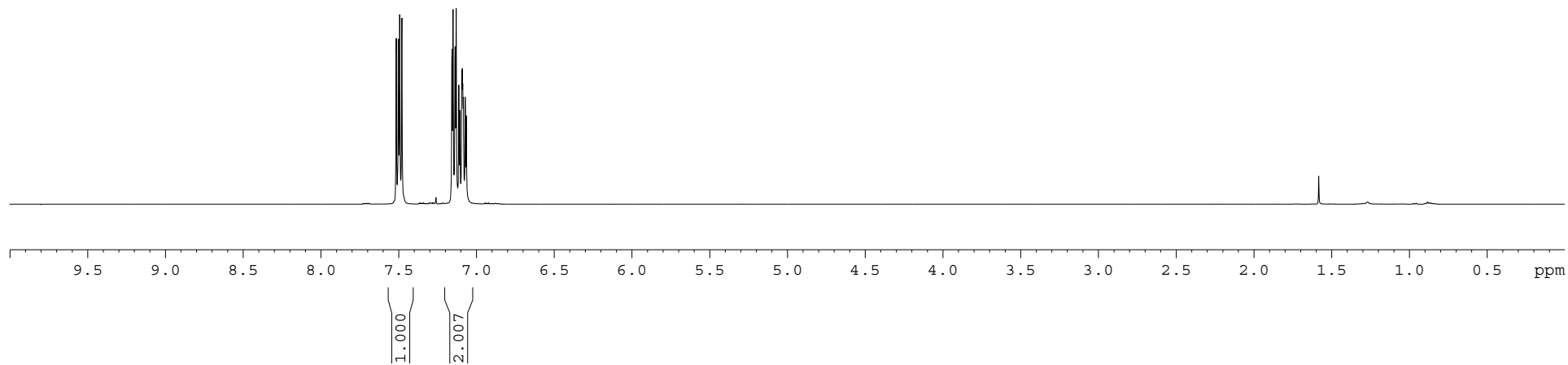


Table 1, entry 4



∫ ∫ ∫ ∫

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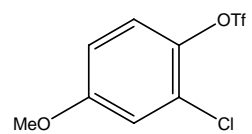
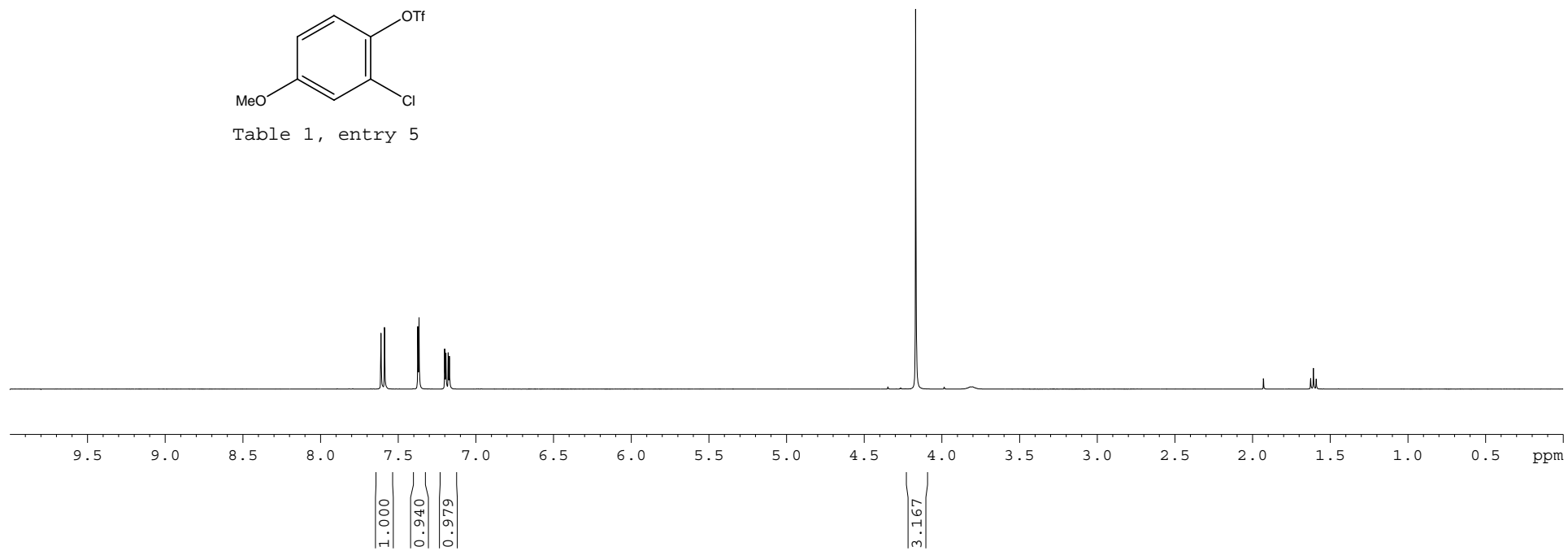


Table 1, entry 5



h-1 drx400

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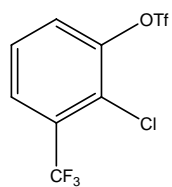
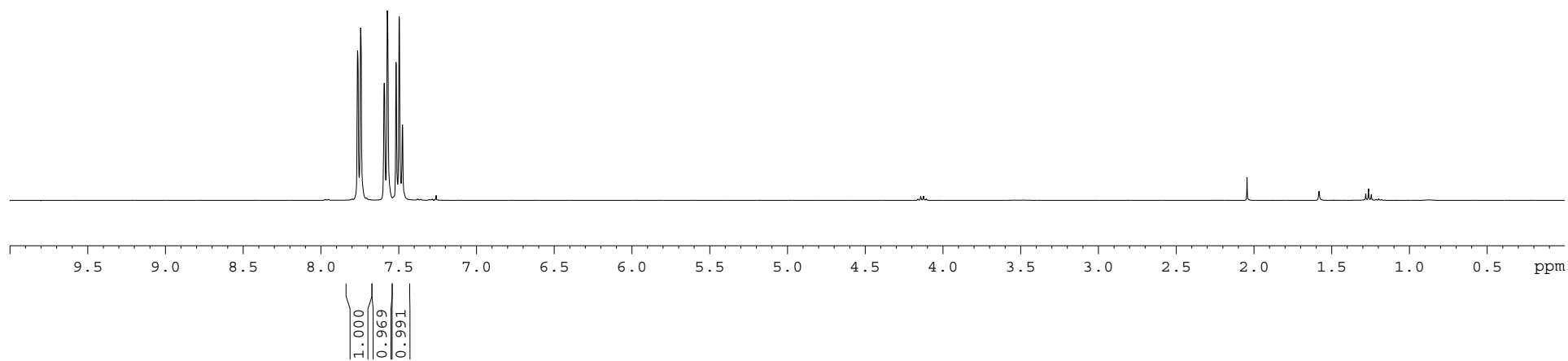


Table 1, entry 6



f f

f

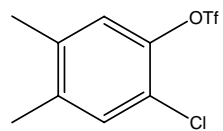
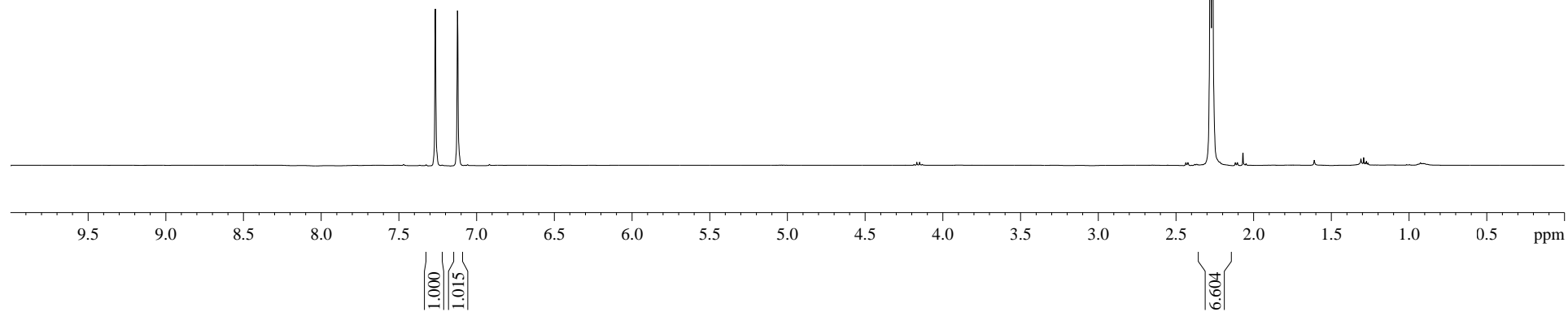
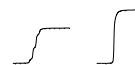


Table 1, entry 7





No title

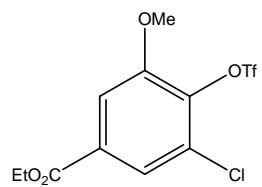
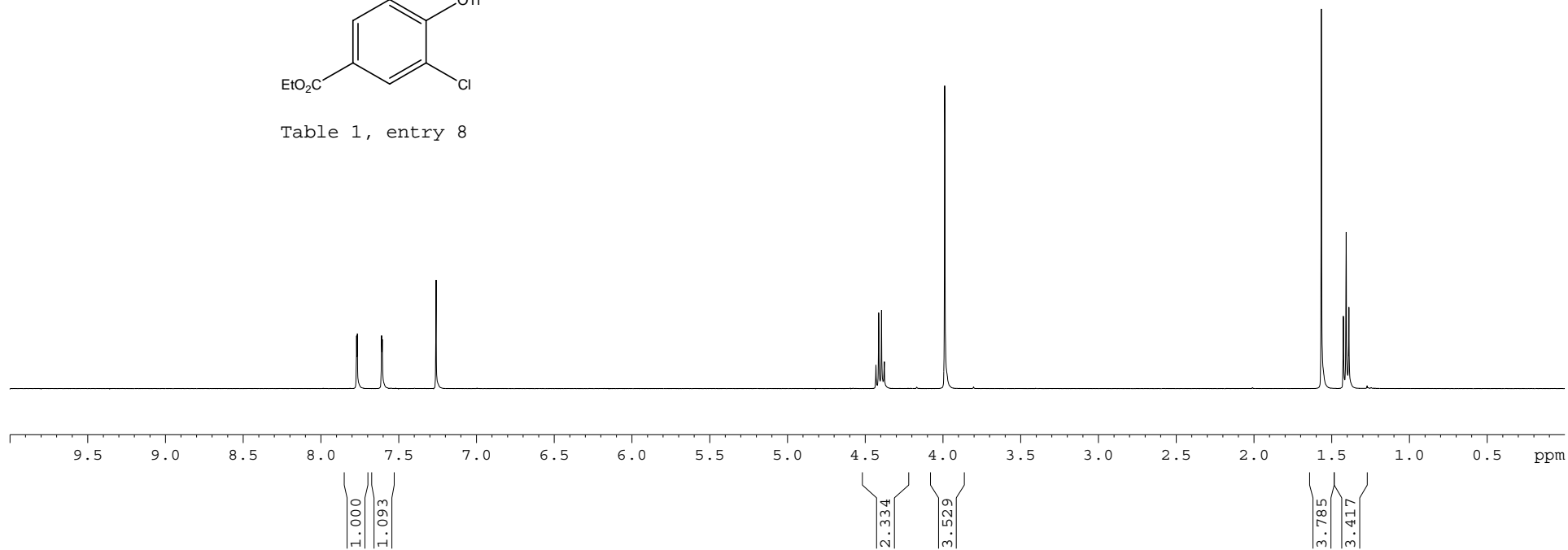
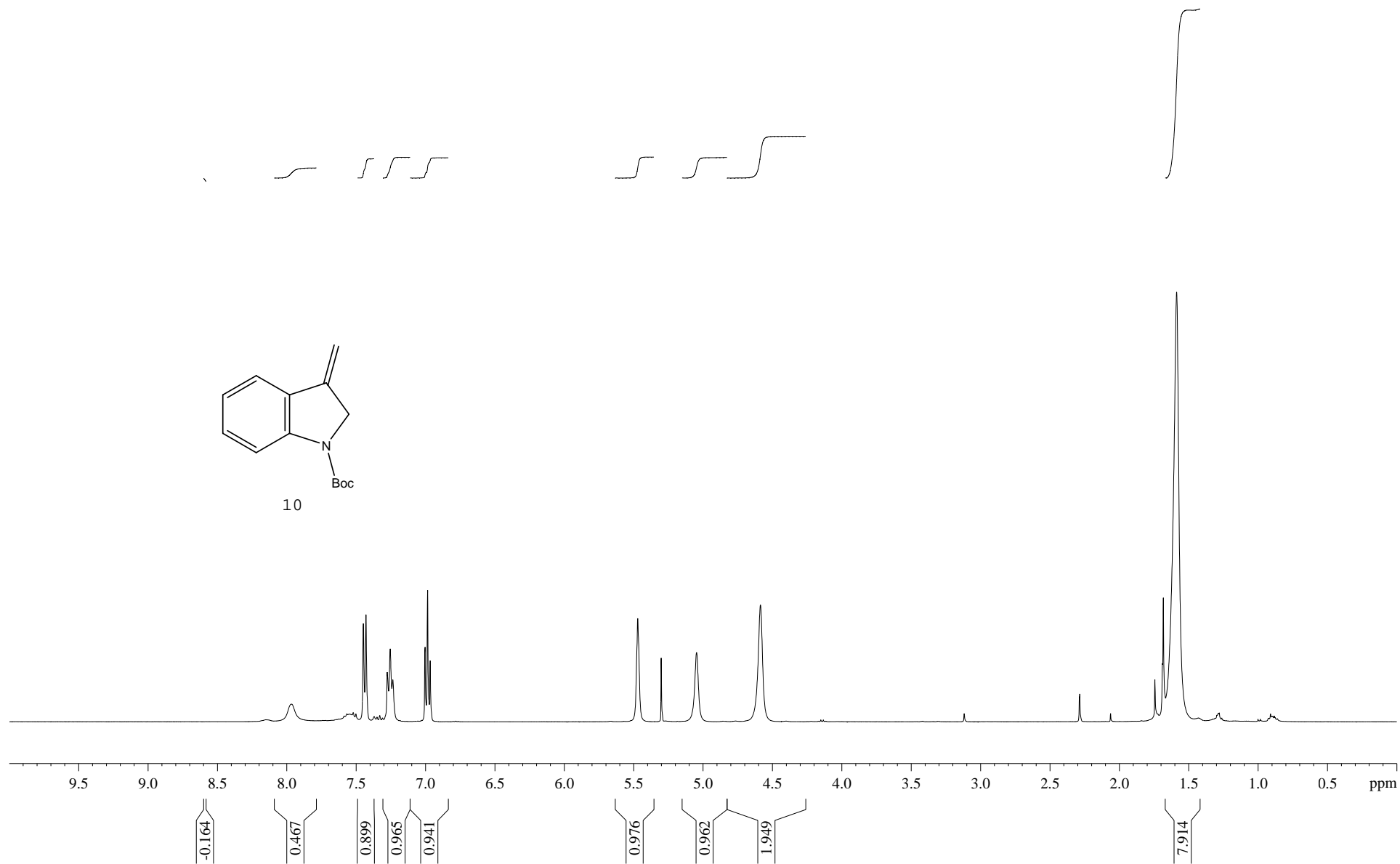
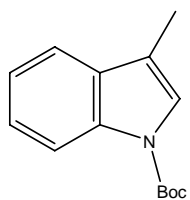


Table 1, entry 8

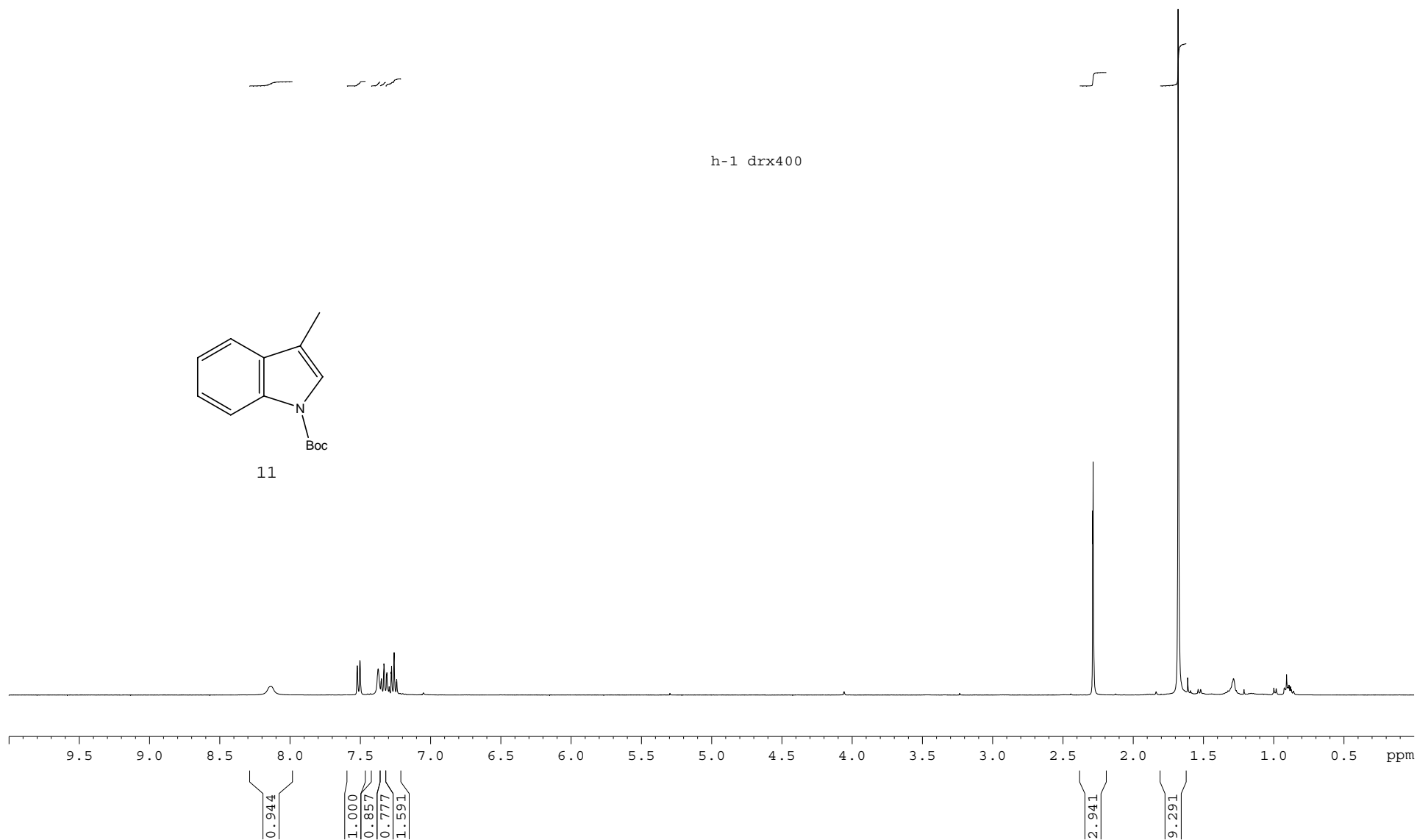




h-1 drx400



11



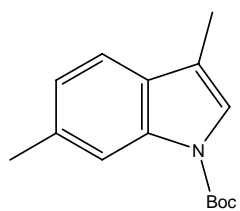
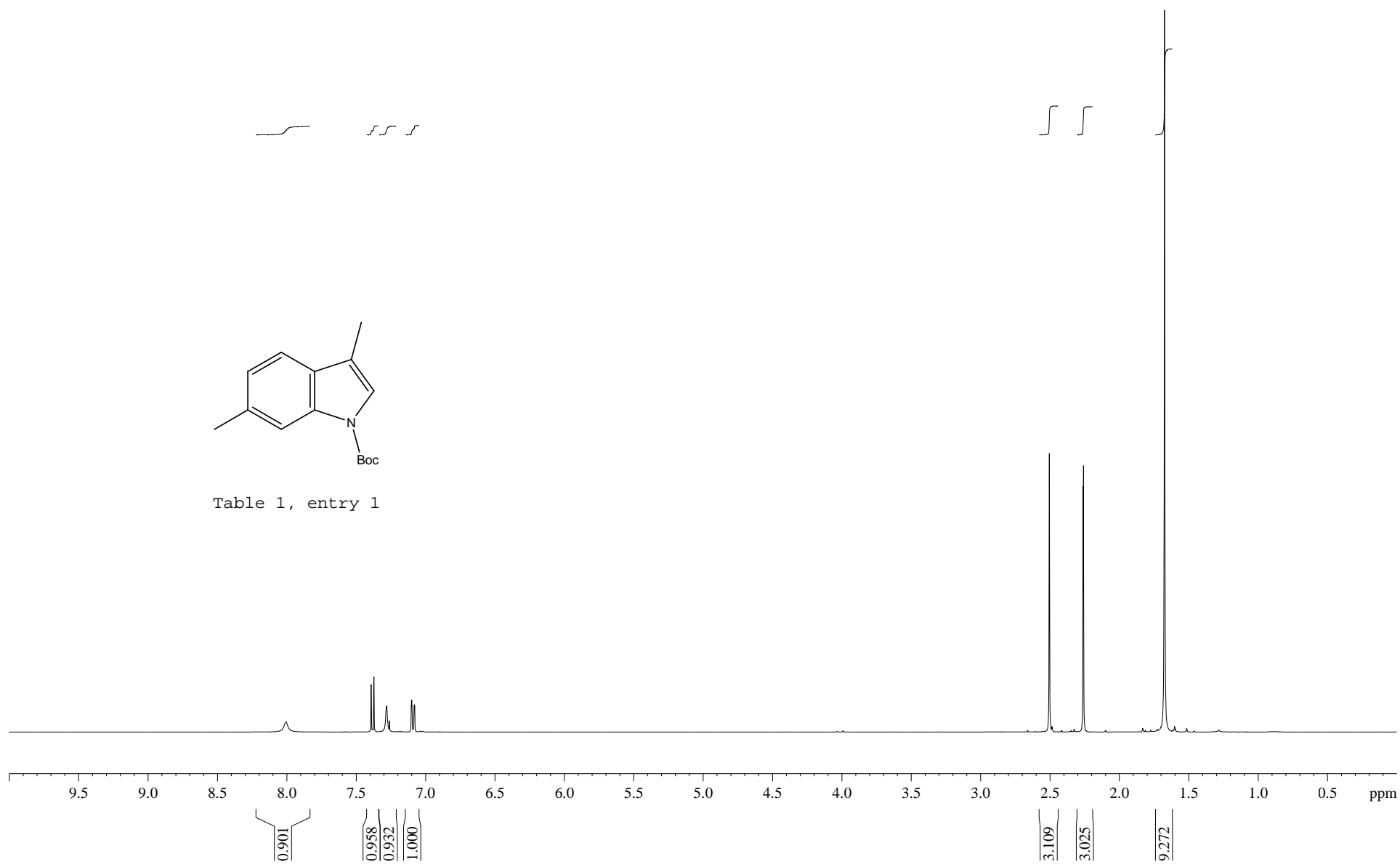


Table 1, entry 1



h-1 drx400

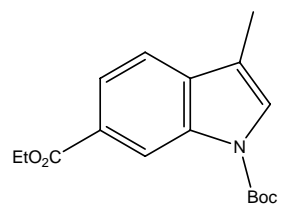
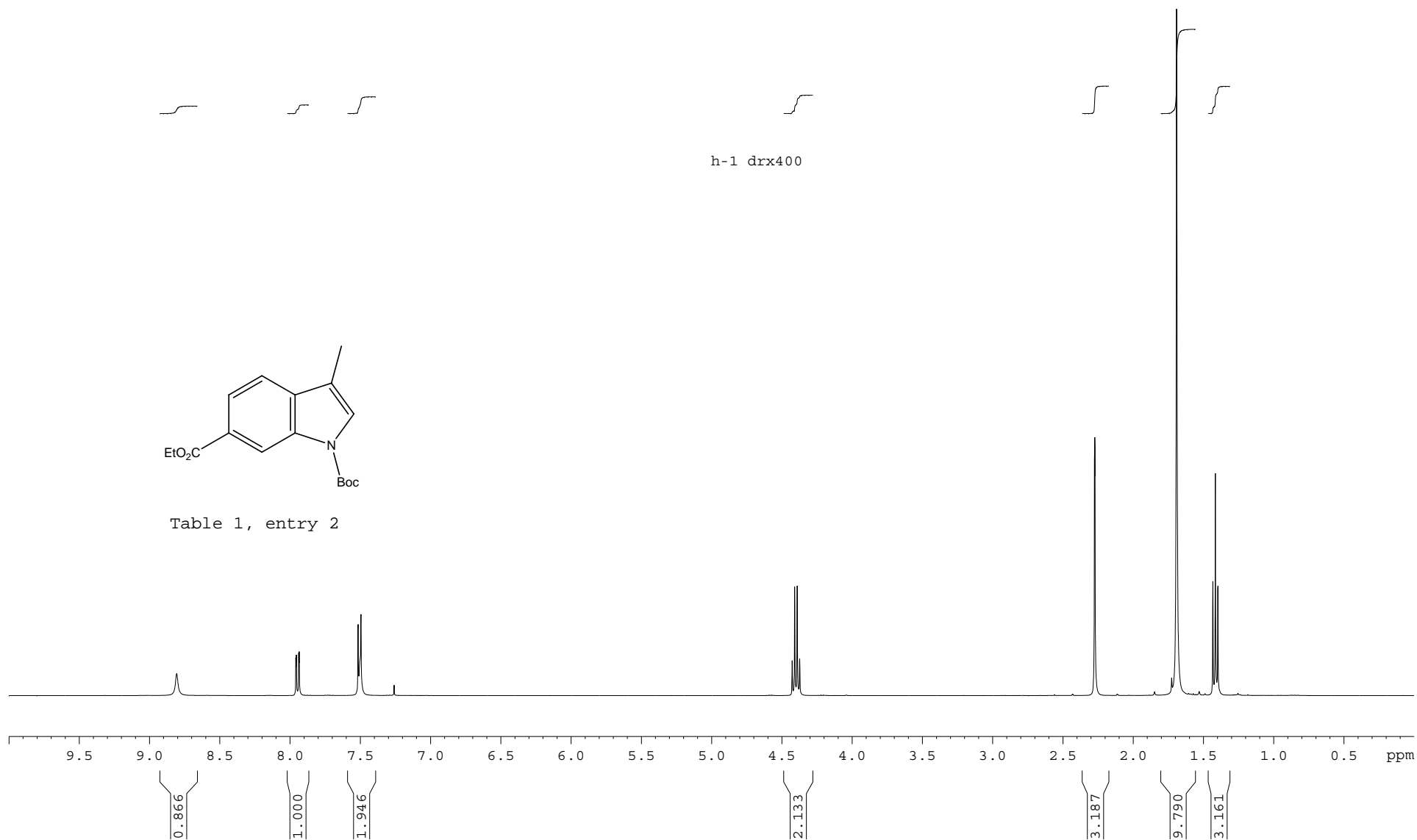


Table 1, entry 2



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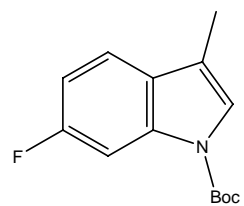
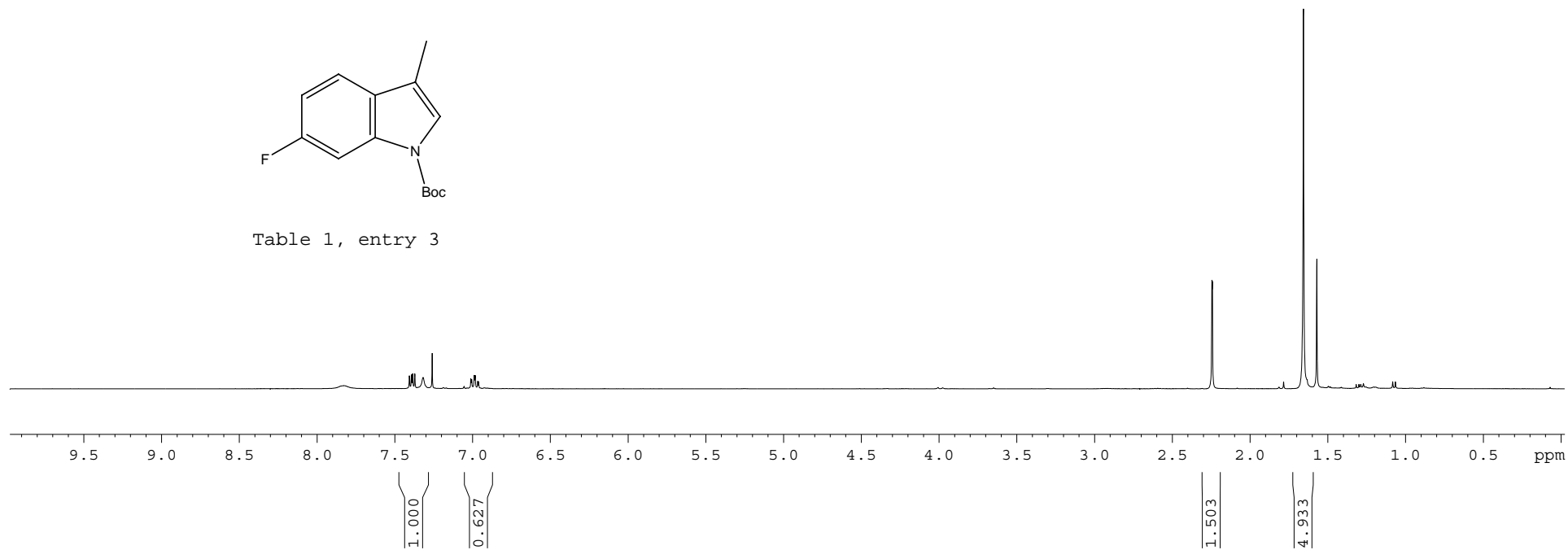


Table 1, entry 3



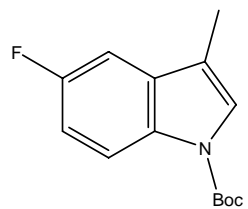
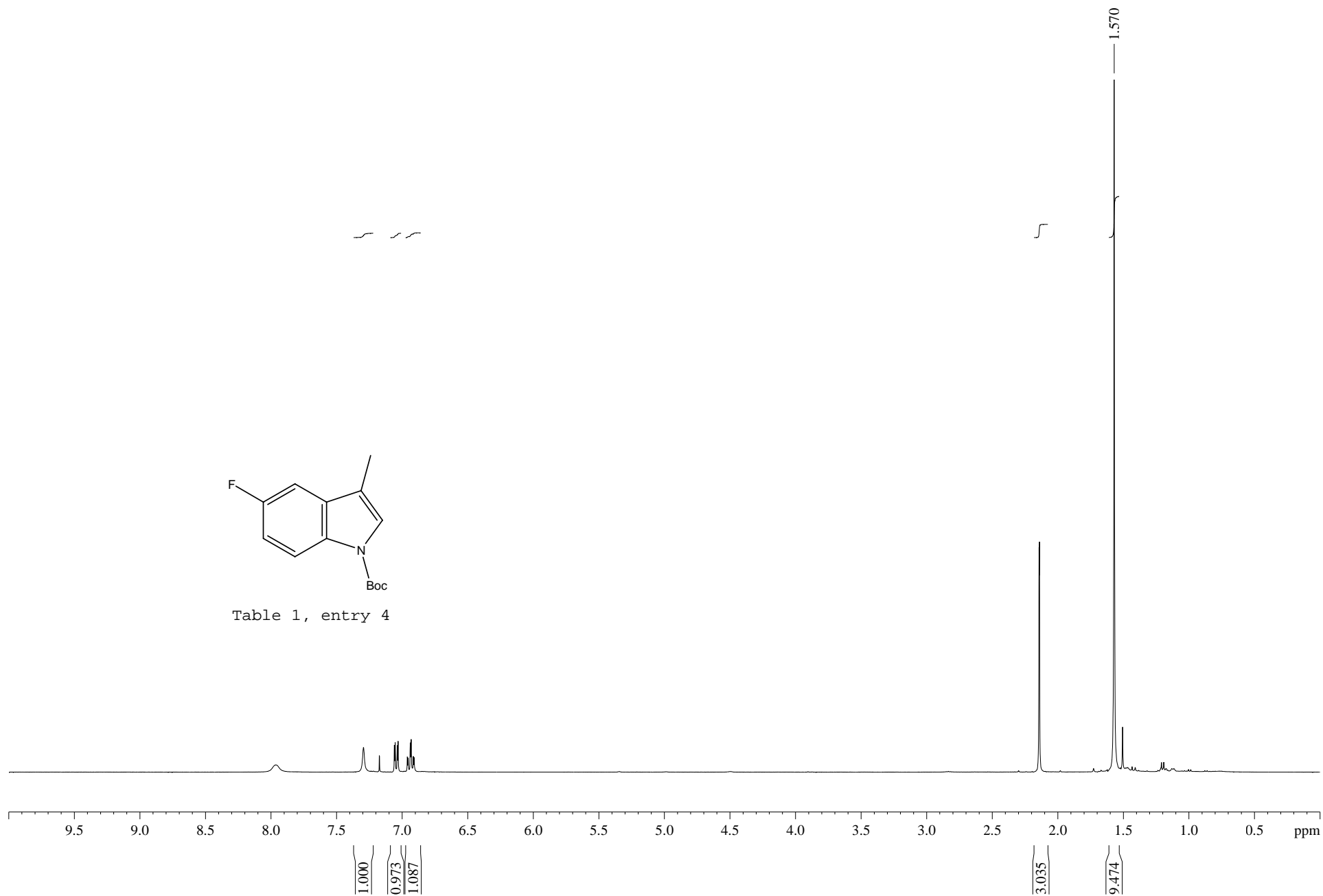


Table 1, entry 4



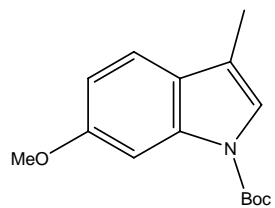
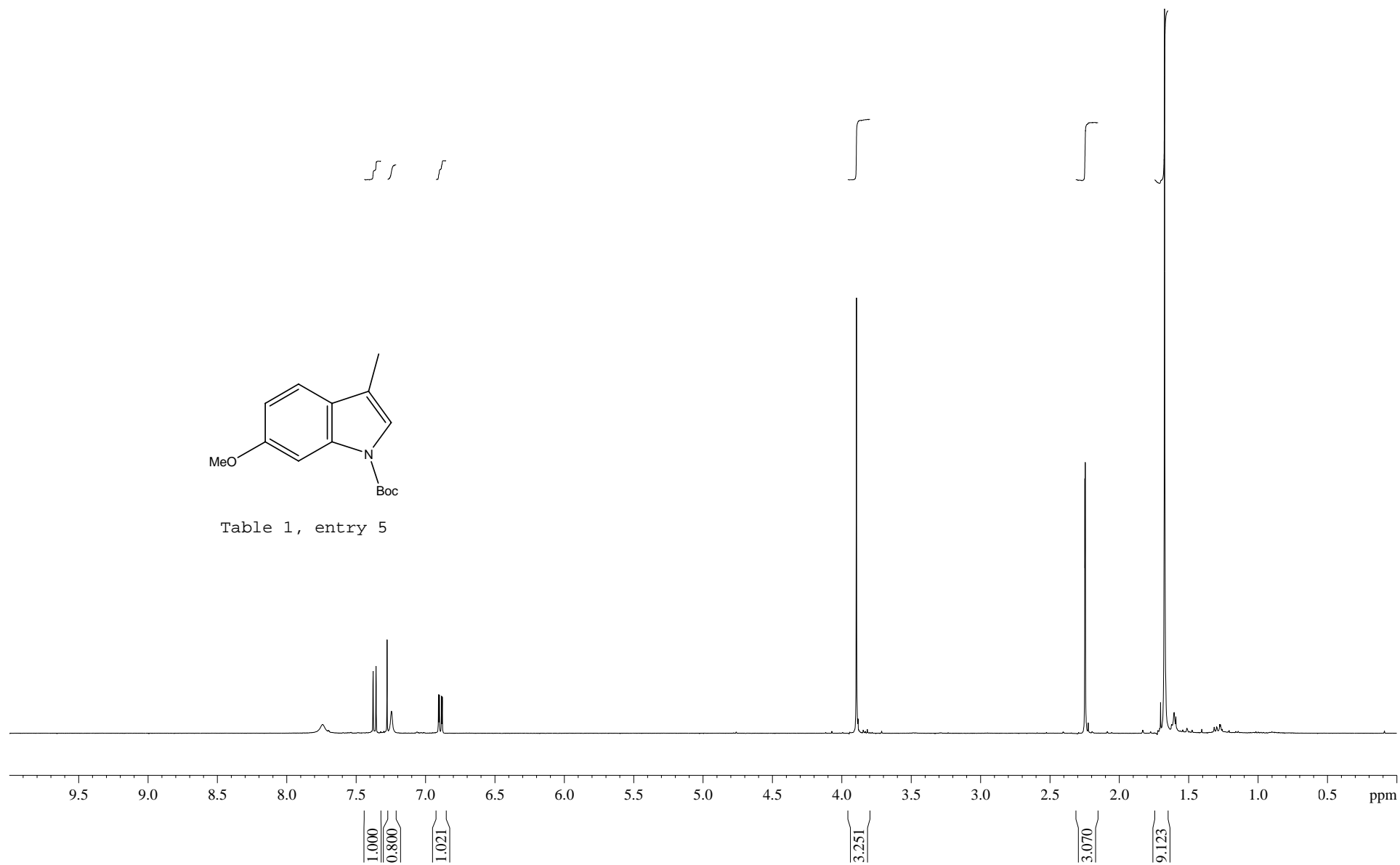


Table 1, entry 5



h-1 drx400

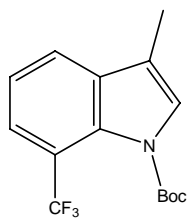
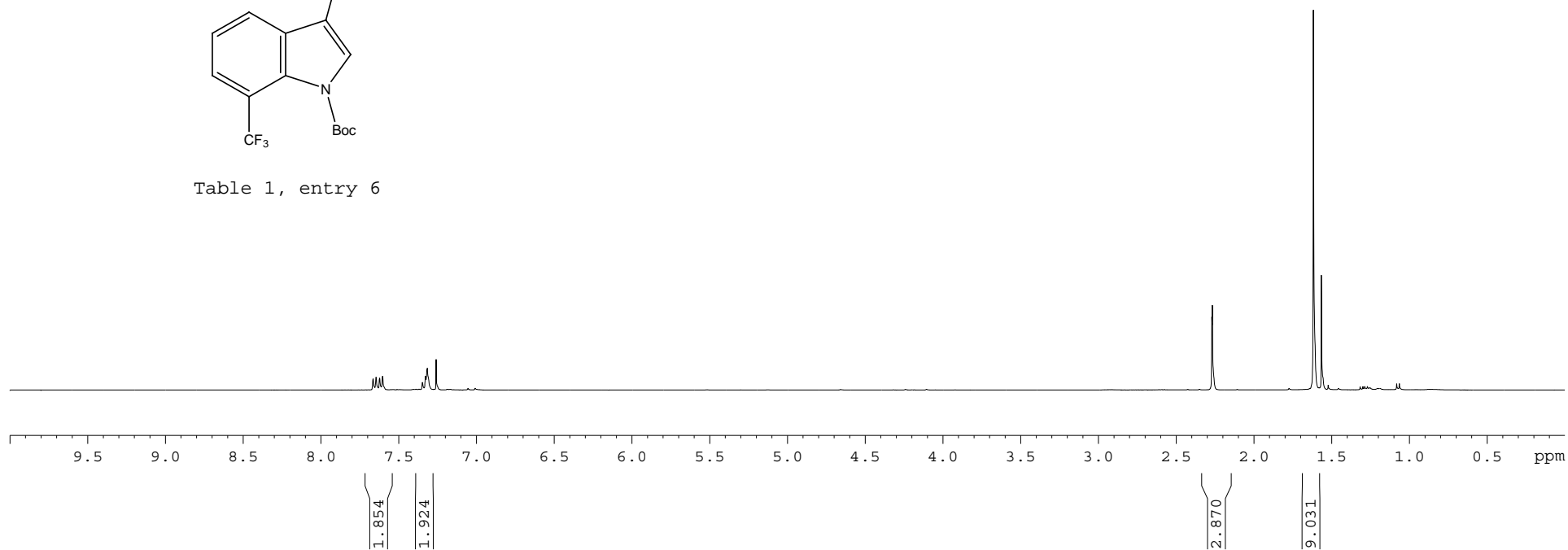


Table 1, entry 6



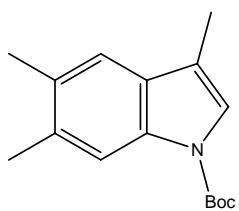
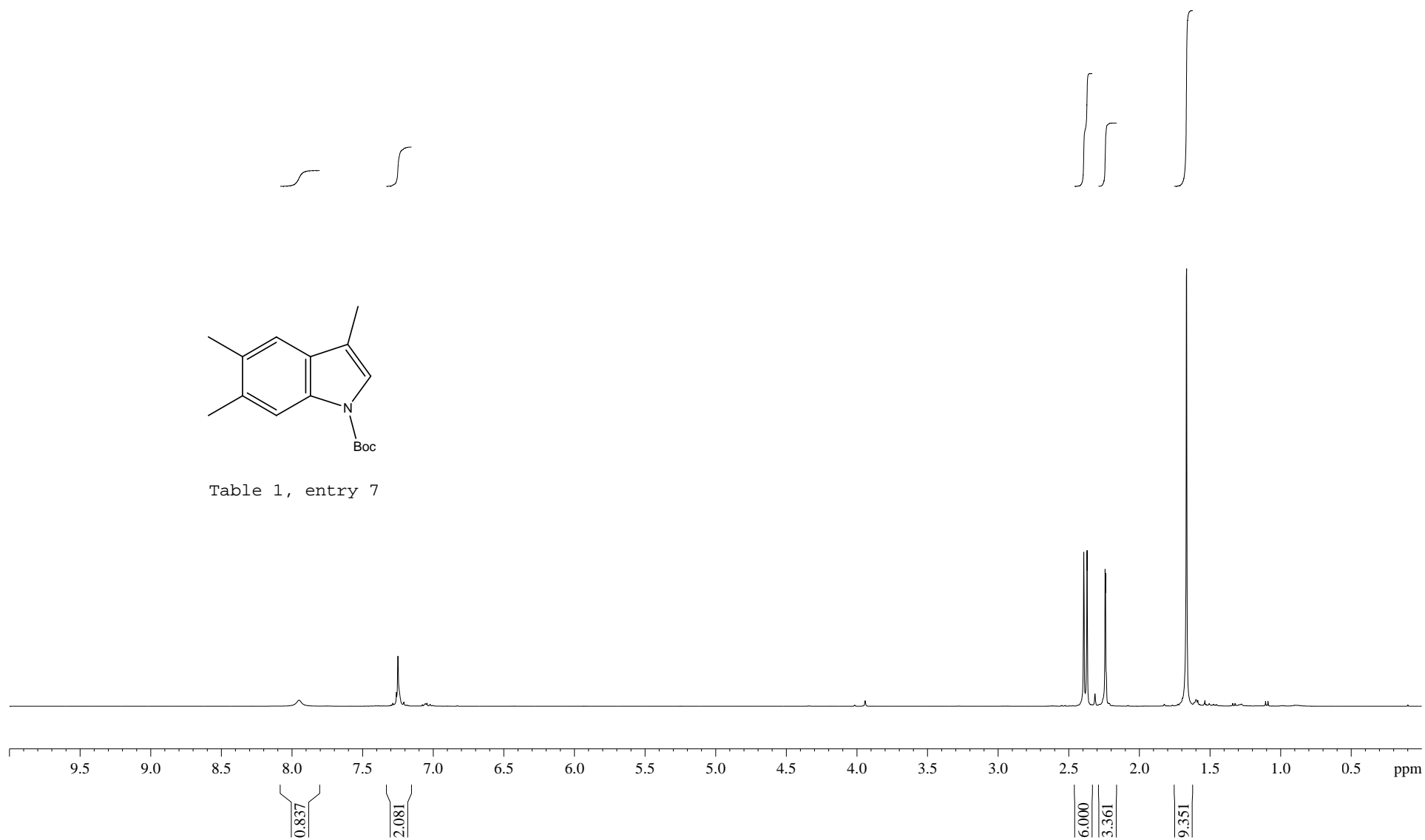


Table 1, entry 7



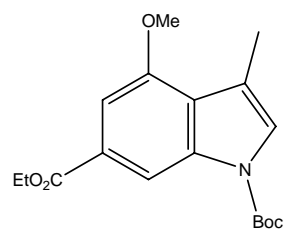
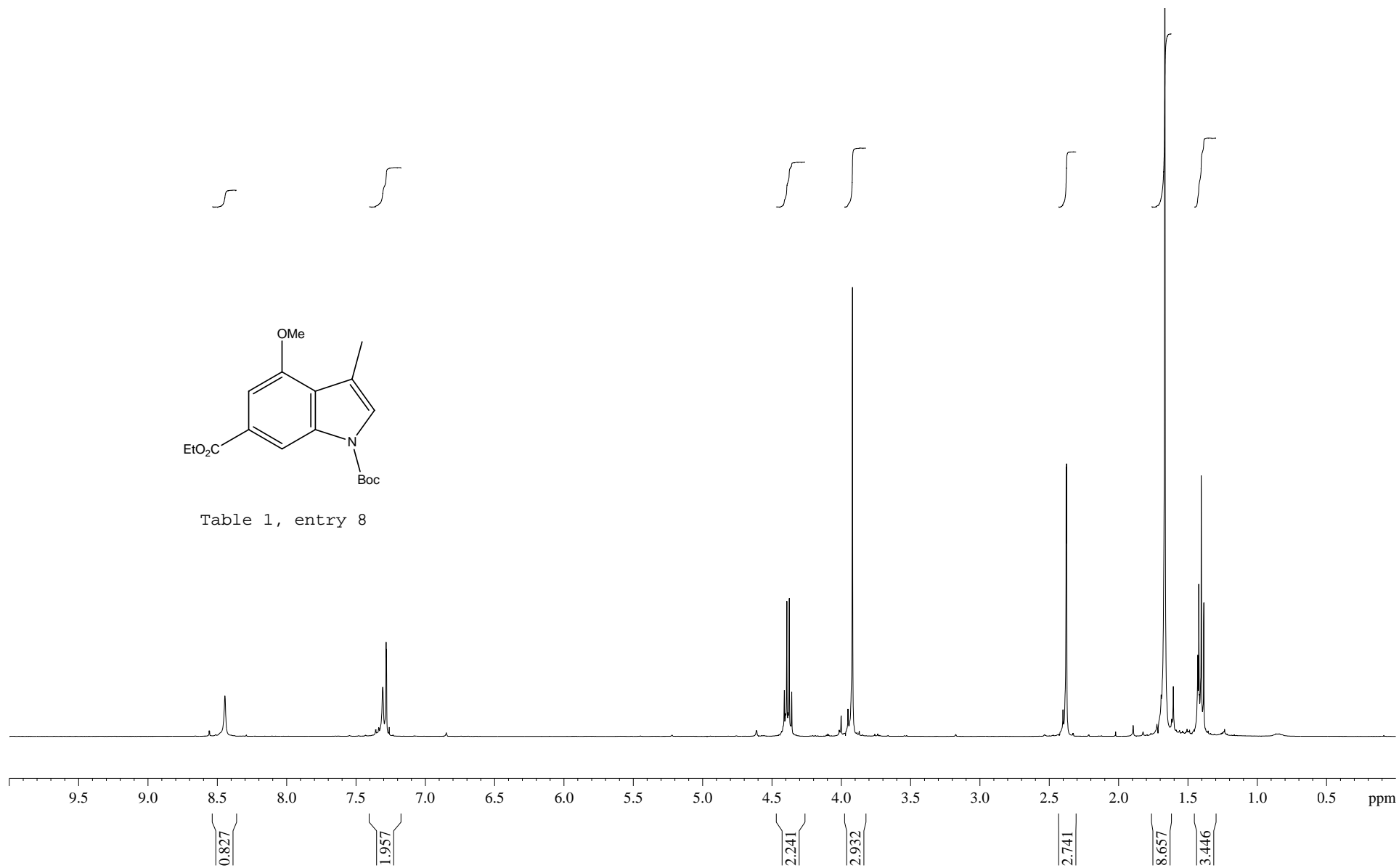
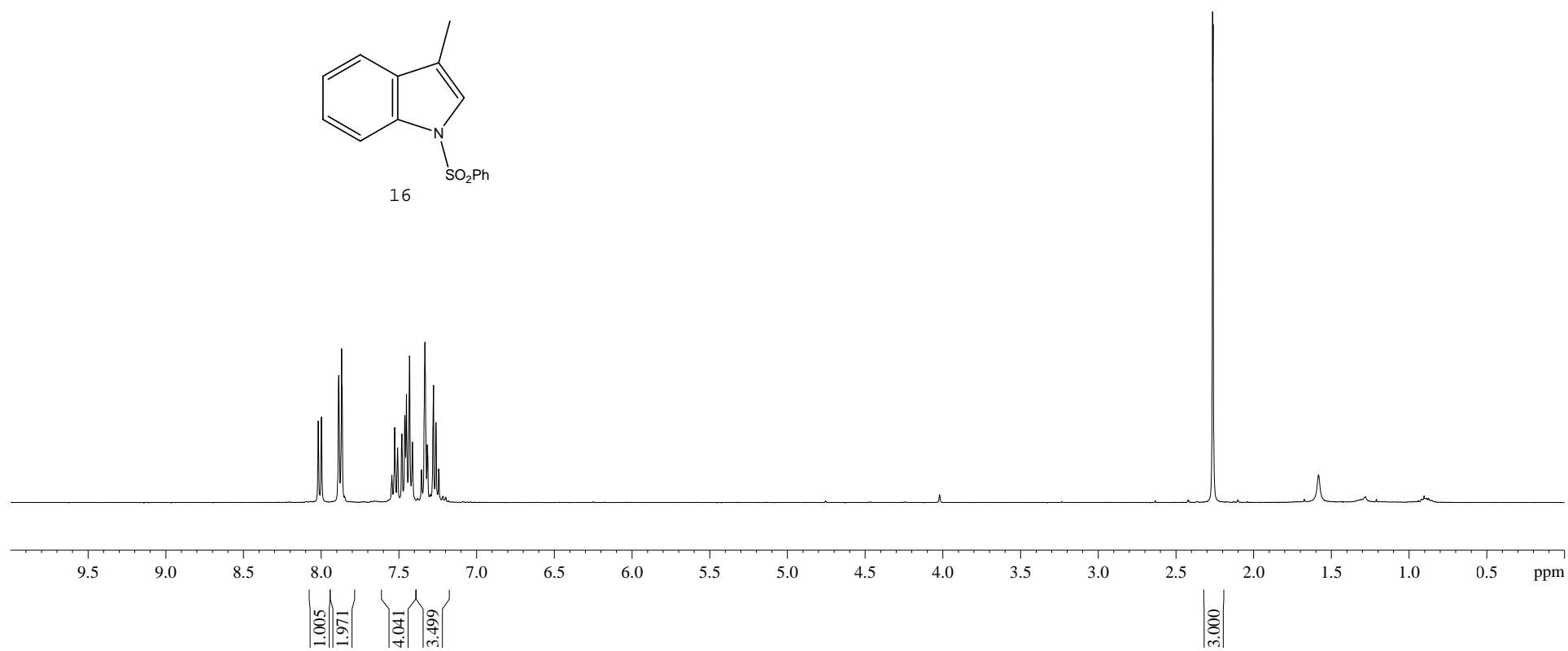
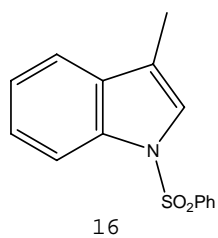
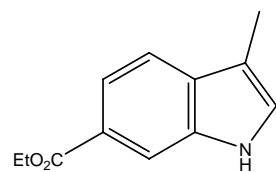


Table 1, entry 8







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