Palladium-catalyzed Arylation of Electron-rich Heterocycles with Aryl Chlorides

SUPPORTING INFORMATION

Hendrich A. Chiong and Olafs Daugulis*

Department of Chemistry, University of Houston, Houston, TX 77204-5003

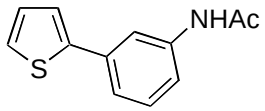
Experimental Section

General considerations: Reactions were performed in 2-dram vials with PTFE caps. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) HPLC equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC analyses were performed on a Shimadzu CG-2010 chromatograph equipped with a Restek column (Rtx®-5, 15m, 0.25 mm ID). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a GE QE-300 spectrophotometer using residual solvent peak as a reference. Melting points were measured on a Mel-Temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using ThermoNicolet Avatar 370 FT-IR instrument.

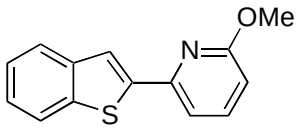
Materials. Palladium acetate used in this study was obtained from J&J Materials and was used as received. Powdered K_3PO_4 (Aldrich), anhydrous NMP (Acros) and butyldi-1-adamantylphosphine (Strem) were stored under argon. The following starting materials were obtained from commercial sources and were used without further purification: 2-*iso*-butylthiazole, 4-chlorobenzotrifluoride, 1-chloro-3-fluorobenzene, 3-chlorobenzotrifluoride, 5-chloro-*m*-xylene were purchased from Oakwood Products. 2,3-Benzofuran, benzoxazole, benzothiazole, 3-chloroacetanilide, chlorobenzene, 3-chloroanisole, 5-chloro-1,3-dimethoxybenzene, 2-chloroanisole were obtained from Acros. 1-*n*-Butylimidazole, thiophene and benzothiophene were purchased from Aldrich. 3,5-Dimethylisoxazole, caffeine, 1-chloronaphthalene and 2-chloropyridine were purchased from Eastman, *p*-chlorotoluene from Matheson, and 2-chloro-6-methoxypyridine from Alfa Aesar. The ethyl 3-chlorobenzoate was prepared from 3-chlorobenzoic acid (Aldrich).[1] 2-Pivaloylaminothiazole was prepared from 2-aminothiazole (Aldrich).[2] Benzothiazole and 2-deuterobenzothiazole[3] (>99% D by NMR integration) used in the kinetic experiments were purified by distillation under reduced pressure before use.

A. General procedure for coupling of chloroarenes with heterocyclic compounds. Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol %), heterocycle (1.0 mmol) and chloroarene (1.5 equiv). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added butyldi-1-adamantylphosphine (10 mol %), K_3PO_4 (2.0 equiv) and anhydrous NMP (4 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min and placed in a preheated oil bath (125 ^{o}C) for 24 h. The reaction mixture was allowed to cool to room temperature and quenched with 1% aqueous KOH (10 mL). Resulting suspension was extracted with dichloromethane (3 x 5 mL) and the organic layer filtered through a pad of Celite®. The filtrate was concentrated under vacuum to a volume of about 2 mL. The mixture was

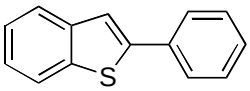
absorbed on silica gel and subjected to flash chromatography. After concentration of the fractions containing the product, the residue was dried under reduced pressure (40 ^{o}C) to yield pure arylated heterocycle.



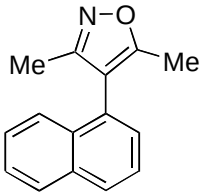
***N*-(3-Thiophen-2-yl-phenyl)-acetamide**:[4] Palladium acetate (11.4 mg, 0.05 mmol), thiophene (252 mg, 3.0 mmol), 3-chloroacetanilide (170 mg, 1.0 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4.0 mL). After column chromatography (1/1 ethyl acetate/hexanes) 117 mg (54 %) of light tan needles were obtained, mp 134-135 ^{o}C (2,2,4-trimethylpentane). R_f=0.42 (1/1 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H), 7.02-7.05 (m, 1H), 7.24-7.35 (m, 5H), 7.60 (dm, *J*=7.2Hz, 1H), 7.76 (s, 1H), 7.8 (br 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 25.1, 117.9, 119.6, 122.4, 124.0, 125.6, 128.6, 130.0, 135.7, 139.0, 144.4, 169.3. FT-IR (neat, cm^{-1}) υ 1664, 1482.



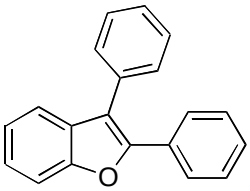
2-(6-Methoxy-1-pyridyl)benzothiophene: Palladium acetate (11.4 mg, 0.05 mmol), benzothiophene (134 mg, 1.0 mmol), 2-chloro-6-methoxypyridine (216 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425.0 mg, 2.0 mmol) and anhydrous NMP (4.0 mL). After column chromatography (1/9 ethyl acetate/hexanes) and preparative HPLC (2% ethyl acetate in hexanes) 174 mg (72 %) of a white solid was obtained, mp 94-95^{o}C (2,2,4-trimethylpentane). R_f=0.54 (1/9 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.06 (s, 3H), 6.68 (d, *J*=8.4 Hz, 1H), 7.33-7.37 (m, 3H), 7.58 (dd, *J*=7.2 Hz, 7.5 Hz, 1H), 7.78-7.88 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.0, 110.4, 112.8, 121.4, 122.5, 124.6, 125.0, 125.4, 139.6, 141.0, 141.1, 145.6, 150.5, 164.1. FT-IR (neat, cm^{-1}) υ 1573, 1461. Anal calcd for $C_{14}H_{11}NOS$ (241.31 g/mol): C, 69.68; H, 4.59; N, 5.80; Found. C, 69.74; H, 4.67; N, 5.82.



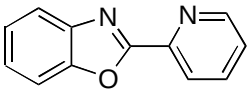
2-Phenylbenzo[b]thiophene: Palladium acetate (11.4 mg, 0.05 mmol), benzothiophene (134 mg, 1.0 mmol), chlorobenzene (169 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (1/9 ethyl acetate/hexanes) 132 mg (63 %) of a light yellow solid was obtained. This compound is known.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.47 (m, 5H), 7.56 (s, 1H), 7.71-7.85 (m, 4H).



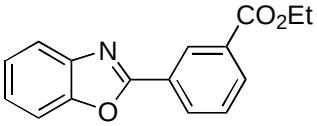
3,5-Dimethyl-4-(1-naphthyl)isoxazole: Palladium acetate (11.4 mg, 0.05 mmol), 3,5-dimethylisoxazole (97 mg, 1.0 mmol), 1-chloronaphthalene (244 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (1/9 ethyl acetate/hexanes) 170 mg (76 %) of a white solid was obtained. This compound is known.[6] ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.10 (s, 3H), 2.26 (s, 3H), 7.33 (dd, *J*=7.2 Hz, 0.9 Hz, 1H), 7.45-7.60 (m 4H), 7.89-7.94 (m, 2H).



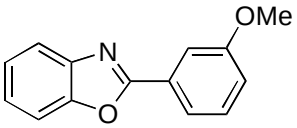
2,3-Diphenylbenzo[b]furan: Palladium acetate (11.4 mg, 0.05 mmol), benzofuran (118 mg, 1.0 mmol), chlorobenzene (338 mg, 3.0 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (1/99 ethyl acetate/hexanes) 184 mg (68 %) of a white solid was obtained. This compound is known.[7] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.39 (m, 5H), 7.44-7.61 (m, 7H), 7.69-7.73 (m, 2H).



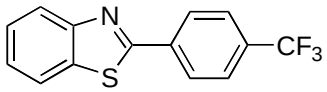
2-(2-Pyridyl)benzoxazole: Palladium acetate (11.4 mg, 0.05 mmol), benzoxazole (119 mg, 1.0 mmol), 2-chloropyridine (171 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (3/7 ethyl acetate/hexanes) 132 mg (67 %) of a white solid was obtained. This compound is known[8]. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.43 (m, 3H), 7.62-7.64 (m, 1H), 7.78-7.88 (m, 2H), 8.31-8.34 (m, 1H), 8.77-8.80 (m, 1H).



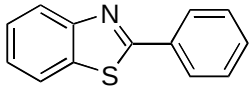
Ethyl 3-(2-benzoxazolyl)benzoate: Palladium acetate (11.4 mg, 0.05 mmol), benzoxazole (119 mg, 1.0 mmol) ethyl 3-chlorobenzoate (277 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (1/9 ethyl acetate/hexanes) 225 mg (84 %) of a light brown solid was obtained, mp 103-104^{o}C (2,2,4-trimethylpentane). R_f= 0.58 (1/9 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (t, *J*=7.2 Hz, 3H), 4.43 (q, *J*=7.2 Hz. 2 H), 7.35-7.38 (m, 2H), 7.57-7.62 (m, 2H), 7.77-7.80 (m, 1H), 8.19-8.21 (m, 1H), 8.41-8.44 (m, 1H), 8.88-8.89 (m 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 61.9, 120.7, 122.5, 125.2, 125.9, 128.1, 129.1, 129.6, 132.0, 132.1, 133.0, 142.5, 151.3, 162.6, 166.3. FT-IR (neat, cm^{-1}) υ 1715, 1240. Anal calcd for $C_{16}H_{13}NO_3$ (267.28 g/mol): C, 71.90; H, 4.90; N, 5.24; Found. C, 71.91; H, 5.14; N, 5.15.



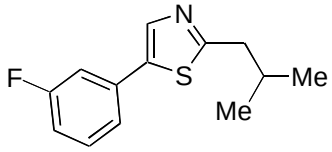
2-(3-Methoxyphenyl)benzoxazole: Palladium acetate (11.4 mg, 0.05 mmol), benzoxazole (119 mg, 1.0 mmol), 3-chloroanisole (214 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (2/8 ethyl acetate/hexanes) 131 mg (58 %) of a white solid was obtained. This compound is known.[9] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 7.02-7.06 (m, 1H), 7.30-7.41 (m, 3H), 7.52-7.55 (m, 1H), 7.74-7.83 (3H).



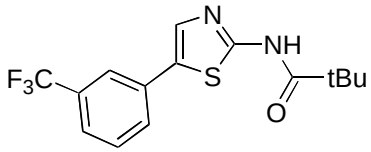
2-(4-Trifluoromethylphenyl)benzothiazole: Palladium acetate (11.4 mg, 0.05 mmol), benzothiazole (135 mg, 1.0 mmol), 4-chlorobenzotrifluoride (270 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (1/9 ethyl acetate/hexanes) 229 mg (82 %) of a white solid was obtained. This compound is known.[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.45 (m, 1H), 7.50-7.56 (m, 1H), 7.73 (d, *J*=8.7Hz, 2H), 7.91 (d, *J*=6.6 Hz, 1H), 8.09 (d, *J*=6.9 Hz, 1H), 8.18 (d, *J*=8.4 Hz, 2H).



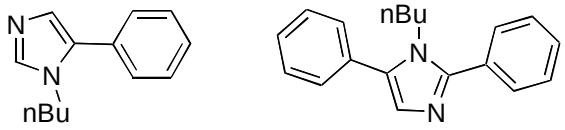
2-Phenylbenzothiazole: Palladium acetate (11.4 mg, 0.05 mmol), benzothiazole (135 mg, 1.0 mmol) 3-chlorobenzene (169 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (1/9 ethyl acetate/hexanes) 177 mg (84 %) of a light tan solid was obtained. This compound is known.[10] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.41 (m, 1H), 7.47-7.52 (m, 4H), 7.90 (d, *J*=6.9 Hz, 1H), 8.07-8.11 (m, 3H).



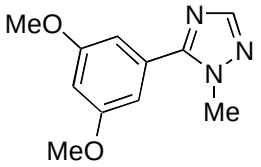
5-(3-Fluorophenyl)-2-isobutylthiazole: Palladium acetate (11.4 mg, 0.05 mmol), 2-isobutylthiazole (141 mg, 1.0 mmol), 3-fluorochlorobenzene (196 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (3/7 ethyl acetate/hexanes) 198 mg (83 %) of a tan oil was obtained, R_f= 0.27 (1/9 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, *J*=6.6 Hz, 6H), 2.12 (septet, *J*=6.6 Hz, 1H), 2.87 (d, *J*=6.6 Hz, 2H), 6.95-7.01 (m, 1H), 7.19-7.37 (m, 3H), 7.82 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8, 30.4, 43.1, 113.9 (d, *J*=22.4 Hz), 115.3 (d, *J*=21.5 Hz), 122.7, 131.1 (d, *J*=8.4Hz), 134.3 (d, *J*=7.4 Hz), 137.7, 138.8, 163.6 (d, *J*=246.6 Hz), 170.9. FT-IR (neat, cm^{-1}) υ 1612, 1585. Anal calcd for $C_{13}H_{14}FNS$ (235.32 g/mol): C, 66.35; H, 6.00; N, 5.95; Found. C, 66.79; H, 5.95; N, 5.77.



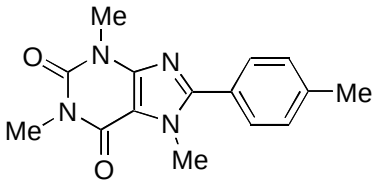
2-Pivaloylamino-5-(3-trifluoromethylphenyl)thiazole: Palladium acetate (11.4 mg, 0.05 mmol), 2-pivaloylaminothiazole (184 mg, 1.0 mmol), 3-chlorobenzotrifluoride (271 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (2/8 ethyl acetate/hexanes) 259 mg (79 %) of white needles were obtained, mp 170-172^{o}C (2,2,4-trimethylpentane). R_f=0.91 (2/8 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 7.47-7.77 (m, 5H), 9.69 (br, 1H).^{13}C NMR (75 MHz, $CDCl_3$) δ 27.7, 34.0, 123.2 (q, *J*=3.7 Hz), 124.3 (q, *J*=277.6 Hz), 124.8 (q, *J*=3.9 Hz), 126.6, 129.7, 130.2, 132.1 (q, *J*=32.5 Hz), 133.2, 134.3, 159.0, 176.9. FT-IR (neat, cm^{-1}) υ 1679, 1337. Anal calcd for $C_{15}H_{15}F_3N_2OS$ (328.35 g/mol): C, 54.87; H, 4.60; N, 8.53; Found. C, 55.29; H, 4.91; N, 8.47.



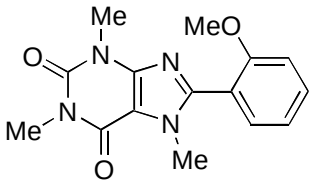
1-*n*-Butyl-2,5-diphenylimidazole and 1-*n*-butyl-5-phenylimidazole: Palladium acetate (11.4 mg, 0.05 mmol), 1-*n*-butylimidazole (124 mg, 1 mmol), chlorobenzene (169 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2 mmol) and anhydrous NMP (4 mL). The purification was performed by preparative TLC (9/1 ethyl acetate/hexanes). Diphenylderivative was isolated as light tan crystals (36 mg, 13%), mp 124-126 ^{o}C (2,2,4-trimethylpentane). R_f=0.69 (9/1 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.60 (t, *J*=6.9 Hz, 3H), 0.86-1.00 (m, 2H), 1.22-1.34 (m, 2H), 4.05-4.14 (m, 2H), 7.15 (s, 1H), 7.40-7.50 (m, 8H), 7.63-7.66 (m, 2H) .^{13}C NMR (75 MHz, $CDCl_3$) δ 13.8, 19.8, 32.9, 45.3, 128.5, 128.6, 129.1, 129.2, 129.3, 129.5, 129.6, 131.4, 132.2, 135.0 149.7. FT-IR (neat, cm^{-1}) υ 1464. Monophenylated derivative was isolated by extraction of the appropriate band with chloroform followed by washing with 10% $NaHCO_3$ (3x1 mL) and filtration. After drying, colorless oil was obtained, 104 mg (52 %). R_f=0.38 (9/1 ethyl acetate/hexanes). This compound is known.[11] ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.5 Hz, 3H), 1.14-1.32 (m, 2H), 1.53-1.68 (m, 2H), 3.90-4.04 (m, 2H), 7.06 (br s, 1H), 7.35-7.45 (m, 5H), 7.55 (br s, 1H).



5-(3,5-dimethoxyphenyl)-1-methyl-1*H*-1,2,4-triazole: Palladium acetate (11.4 mg, 0.05 mmol), 1-methyl-1,2,4-triazole (83 mg, 1.0 mmol), 5-chloro-1,3-dimethoxybenzene (259 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (1/1 ethyl acetate/hexanes) 167 mg (76 %) of light tan crystals were obtained. This compound is known.[12] ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 6H), 3.97 (s, 3H), 6.55 (t, *J*=2.1 Hz, 1H), 6.76 (d, *J*=2.1 Hz, 2H), 7.90 (s, 1H).

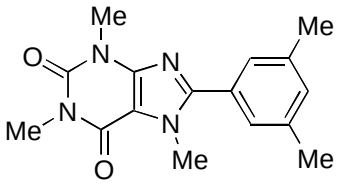


8-[4-Methylphenyl]-3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione: Palladium acetate (11.4 mg, 0.05 mmol), caffeine (194 mg, 1.0 mmol), 4-chlorotoluene (190 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (7/3 ethyl acetate/hexanes) 244 mg (86 %) of a white solid was obtained, mp 193-194 ^{o}C (acetone). R_f=0.57 (8/2 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.40 (s, 3H), 3.60 (s, 3H), 4.02 (s, 3H), 7.30 (d, *J*=8.0 Hz, 2H), 7.56 (d, *J*=8.0 Hz, 2H).[13]C NMR (75 MHz, $CDCl_3$) δ 22.0, 28.5 30.3, 34.4, 108.9, 122.5, 129.6, 130.1, 141.2, 148.8, 152.3, 152.8, 156.1. FT-IR (neat, cm^{-1}) υ 1692, 1651. Anal calcd for $C_{15}H_{16}N_4O_2$ (284.31 g/mol): C, 63.37; H, 5.67; N, 19.71; Found. C, 63.58; H, 5.67; N, 19.72.



8-[2-Methoxyphenyl]-3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione: Palladium acetate (11.4 mg, 0.05 mmol), caffeine (194 mg, 1.0 mmol), 2-chloroanisole (450 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425 mg, 2.0 mmol) and anhydrous NMP (4 mL). After column chromatography (7/3 ethyl acetate/hexanes) 213 mg (71 %) of a white solid was obtained, mp 236-237 ^{o}C (acetone). R_f=0.62 (65/35 ethyl acetate/hexanes). ^{1}H NMR (300 MHz,

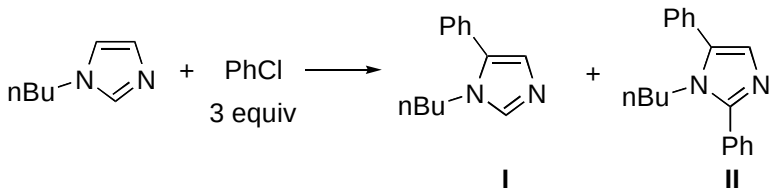
$CDCl_3$) δ 3.46 (s, 3H), 3.64 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 7.04 (d, *J*=8.4 Hz, 1H), 7.1 (t, *J*=7.0 Hz, 1H), 7.47-7.55 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 28.5, 30.3, 33.6, 56.1, 108.8, 111.7, 118.1, 121.7, 132.5, 132.8, 148.7, 150.9, 152.3, 156.1, 157.9. FT-IR (neat, cm^{-1}) υ 1704, 1668. Anal calcd for $C_{15}H_{16}N_4O_3$ (300.31 g/mol): C, 59.99; H, 5.37; N, 18.66; Found. C, 60.02; H, 5.42; N, 18.61.



8-[3,5-Dimethylphenyl]-3,7-dihydro-1,3,7-trimethyl-1*H*-purine-2,6-dione: Palladium acetate (11.4 mg, 0.05 mmol), caffeine (194 mg, 1.0 mmol), 5-chloro-*m*-xylene (211 mg, 1.5 mmol), butyldi-1-adamantylphosphine (38.5 mg, 0.1 mmol), K_3PO_4 (425.0 mg, 2.0 mmol), and anhydrous NMP (4.0 mL). After column chromatography (7/3 ethyl acetate/hexanes) 230 mg (77 %) of a white solid was obtained, mp 210-211 ^{o}C (acetone). R_f=0.65 (7/3 ethyl acetate/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.38 (s, 6H), 3.42 (s, 3H), 3.61 (s, 3H), 4.02 (s, 3H), 7.13 (s, 1H), 7.25 (s, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 21.9, 28.5, 30.3, 34.4, 108.9, 127.4, 128.7, 132.6, 139.2, 148.8, 152.3, 153.1, 156.1. FT-IR (neat, cm^{-1}) υ 1693, 1657. Anal calcd for $C_{16}H_{18}N_4O_2$ (298.34 g/mol): C, 64.41; H, 6.08; N, 18.78; Found. C, 64.41; H, 6.13; N, 18.91.

B. Optimization of conditions.

General procedure: Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol %), 1-*n*-butylimidazole (0.5 mmol) and chlorobenzene (3 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added ligand (10 mol % with respect to imidazole), base (2 mmol), MS 3Å (155 mg) and solvent. The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min and placed in a preheated oil bath (125 ^{o}C) for 16-17 h. After cooling the reaction mixture to room temperature, hexadecane internal standard was added (~50 μL). An aliquot of the mixture was diluted with ethyl acetate (1 mL) and used in determination of conversion by GC. The response factor was determined by a separate injection of a known mixture of starting material and internal standard.



I **II**

Table S1: Evaluation of phosphine ligands.[a]

Entry	Ligand, 10 mol%	% I	% II
A1	*n*BuAd$_2$P	40	12
A2	*t*Bu$_2$bP-P[b]	20	6
A3	*t*BuCy$_2$P	45	16
A4	IPr-HC[c] (5 mol %) + K*t*BuO (10 mol %)	12	4
A5	Ad$_2$POH	10	3

[a] Conditions: 5 mol % Pd(OAc)$_2$, 2 equiv Cs_2CO_3, 155 mg MS 3Å, 2.5 ml dry DMF, stir for 15 min at RT then for 16 h at 125 °C. Conversions were determined by GC using hexadecane as an internal standard. [b] 2-(di-*t*-Butylphosphino)biphenyl. [c] 1,3-Bis-(2,6-*i*-propylphenyl)-4,5-dihydroimidazolium chloride.

Table S2: Evaluation of base.[a]

Entry	Base, 2 equiv	% I	% II
B1	CsOAc	40	5
B2	CsF	48	5
B3	K_3PO_4	51	7
B4	K_2CO_3	41	7
B5	Cs_2CO_3	45	16

[a] Conditions: 5 mol % Pd(OAc)$_2$, 10 mol % *t*-BuCy$_2$P, 155 mg MS 3Å, 2.5 ml dry DMF, stir for 15 min at RT, then for 16 h at 125 °C. Conversions were determined by GC using hexadecane as an internal standard.

Table S3: Evaluation of Pd source.[a]

	Pd source, 5 mol%	% I	% II
C1	Pd_2dba_2-$CHCl_3$	8	1
C2	Pd/C 10%	2	0
C3	$Pd(OCOCF_3)_2$	1	0
C4	$PdCl_2$	11	1
C5	$Pd(OAc)_2$	51	7

[a] Conditions: 10 mol % *t*-BuCy$_2$P, 2 equiv K_3PO_4, 155 mg MS 3Å, 2.5 ml dry DMF, stir for 15 min at RT then for 16 h at 125 °C. Conversions were determined by GC using hexadecane as internal standard.

Table S4: Evaluation of solvent.[a]

	Solvent, 2.5 mL	% I	% II
D1	Toluene	13	3
D2	DMSO	8	1
D3	NMP	65	9
D4	*t*BuOH	26	6
D5	DMF	51	7

[a] Conditions: 5 mol % Pd(OAc)$_2$, 10 mol % *t*-BuCy$_2$P, 2 equiv K_3PO_4, 155 mg MS 3Å, stir for 15 min at RT, then for 16 h at 125 °C. Conversions were determined by GC using hexadecane as internal standard.

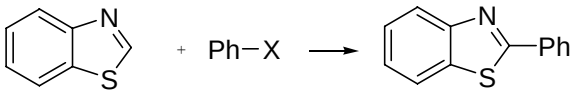
Table S5: Selection of final conditions.[a]

	Comparison at 3.5 mol% $Pd(OAc)_2$	% I	% II
E1	*t*-$BuCy_2P$, MS 3Å, NMP	32	3
E2	*t*-$BuCy_2P$, NMP	34	4
E3	*t*-$BuCy_2P$, DMA	47	9
E4	*n*-$BuAd_2P$, DMA	54	16
E5	*n*-$BuAd_2P$, NMP	52	11
E6	*t*-Bu_2MeP, DMA	19	5

[a] Conditions: 3.5 mol % $Pd(OAc)_2$, 2 equiv K_3PO_4, stir for 15 min at RT the for 17 h at 125 °C. Conversions were determined by GC using hexadecane as internal standard.

C. Comparison of the reactivity of Ph-X with benzothiazole.

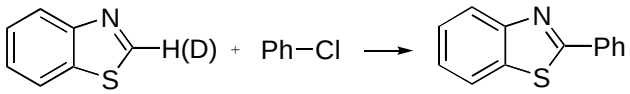
Table S6. Comparison of the yields with different Ph-X.[a]



	% product
PhCl	27
PhBr	21
PhI	13
PhOTf	39

[a] Conditions: 1 equiv benzothiazole, 10 equiv ArX 5 mol % $Pd(OAc)_2$, 2 equiv K_3PO_4, stir for 15 min RT, then 1 h 125 °C. Product is 2-phenylbenzothiazole. Yields were determined by GC using hexadecane as an internal standard. Average of two runs.

D. Determination of Kinetic Isotope Effects (KIE).



Outside the glovebox a 2-dram vial equipped with a magnetic stir bar was charged with $Pd(OAc)_2$ (5 mol %), benzothiazole (2-H or 2-D) (0.5 mmol) and chlorobenzene (5 mmol). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added butyldi-1-adamantylphosphine (10 mol %), K_3PO_4 (2 mmol) and anhydrous NMP (2 mL). The sealed vial was taken out of the glovebox, stirred at room temperature for 15 min and placed in a preheated oil bath (125 °C) for the designated time (1, 2, 3, or 4 hours). After cooling the reaction mixture (room temperature), a weighed amount of hexadecane internal standard was added (~50 μL). An aliquot of the reaction mixture was diluted with ethyl acetate (1 mL) and used in the determination of conversion by GC. The log (SM*i*/SM*f*) versus time was plotted (SM_i=mmol starting material introduced into reaction; SM_f=mmol starting material left unreacted after time t).

Table S7. Reaction of 2-H-benzothiazole with PhCl versus time (hours).

Benzothiazole (2-H)			
t, hour	**SM_i**	**SM_f**	**log (SM_i/SM_f)**
0	0.5	0.5	0.000
1	0.506	0.30	0.232
2	0.503	0.23	0.349
3	0.517	0.12	0.634
4	0.503	0.08	0.817

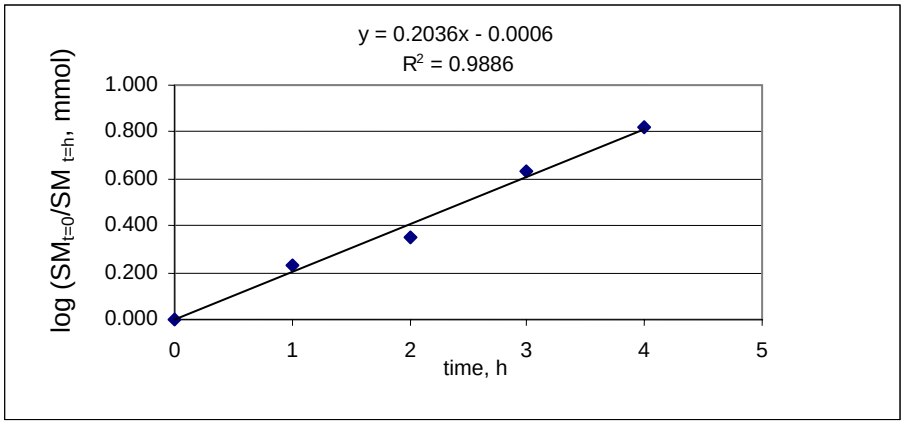


Figure S1. Graph of the reaction of 2-H-benzothiazole with PhCl versus time (h).

Table S8. Reaction of 2-D-benzothiazole with PhCl versus time (h).

Benzothiazole (2-D)			
t, hour	**SM_i**	**SM_f**	**log (SM_i/SM_f)**
0	0.5	0.5	0.000
1	0.506	0.33	0.188
2	0.502	0.27	0.274
3	0.504	0.15	0.537
4	0.504	0.13	0.593

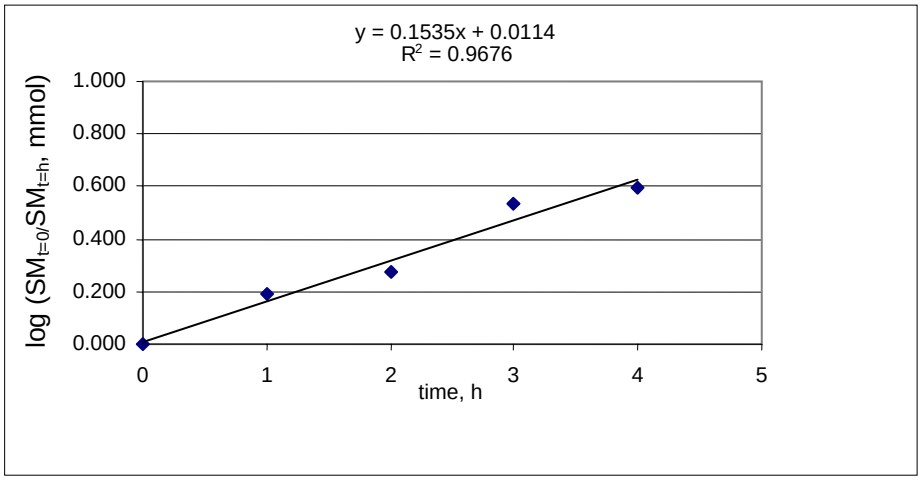


Figure S2. Graph of the reaction of 2-D-benzothiazole with PhCl versus time (h).

Calculation:

$$k_H/k_D = 0.2036/0.1535 = 1.33$$

[1] Smith, G.G.; Jones, D.A.; Brown, D.F. *J. Org. Chem* **1963**, *28*, 403.
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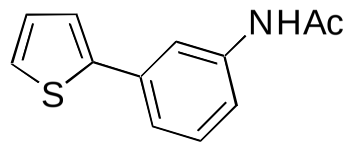

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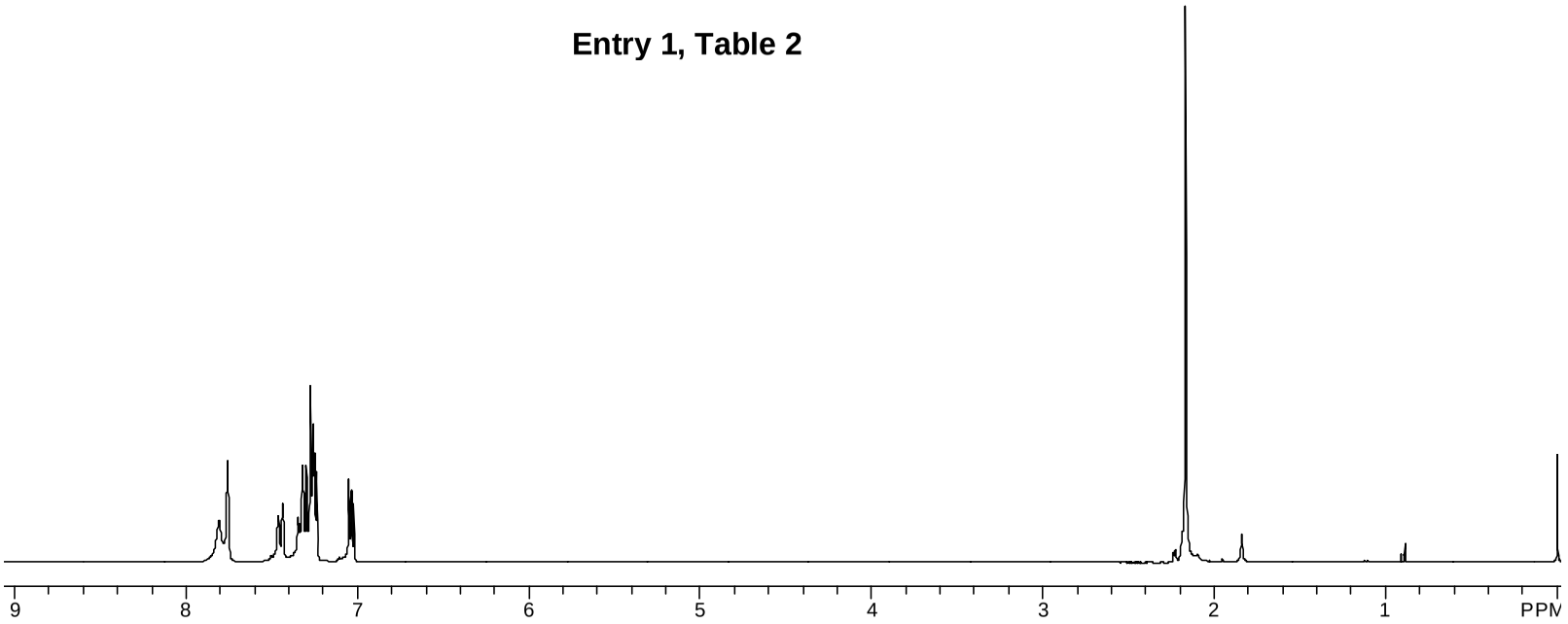

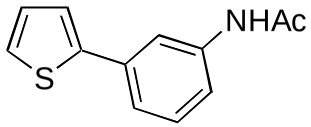

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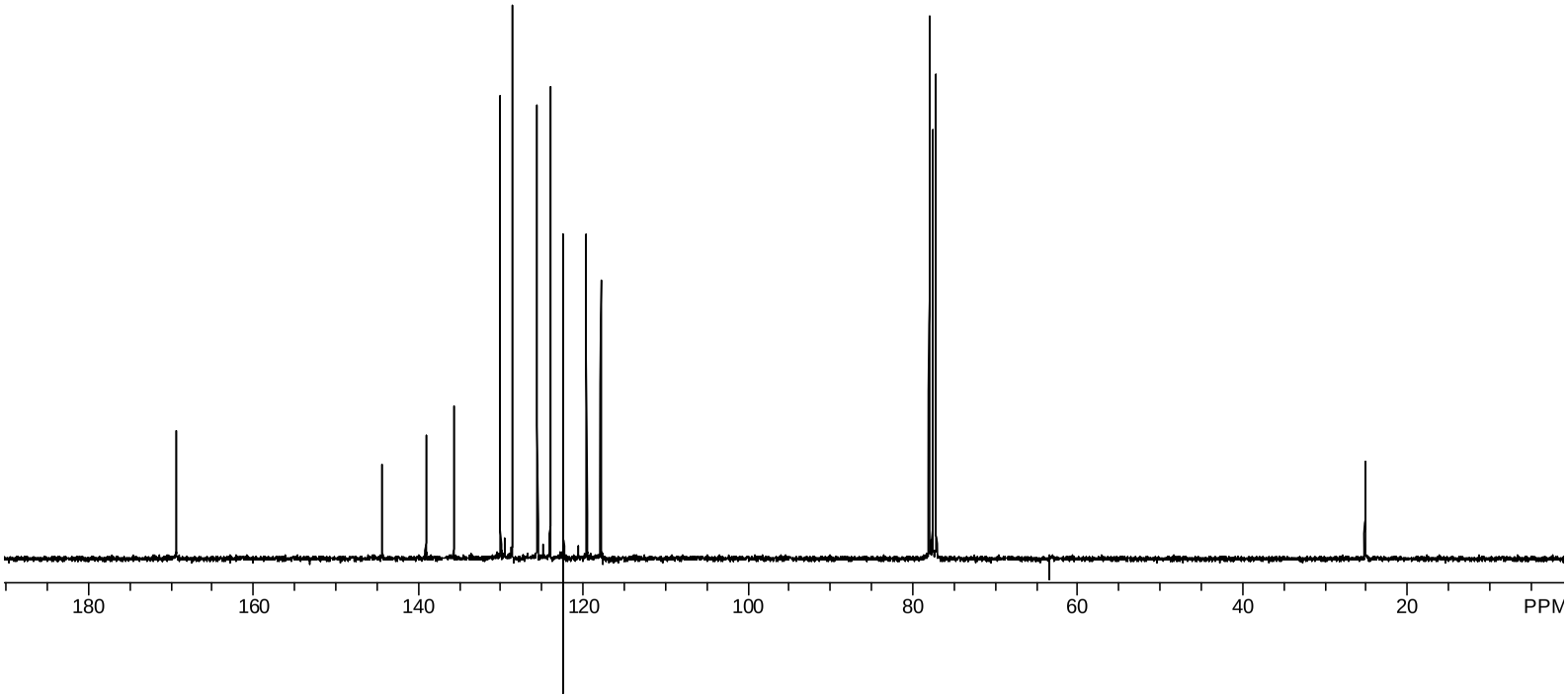

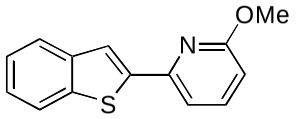

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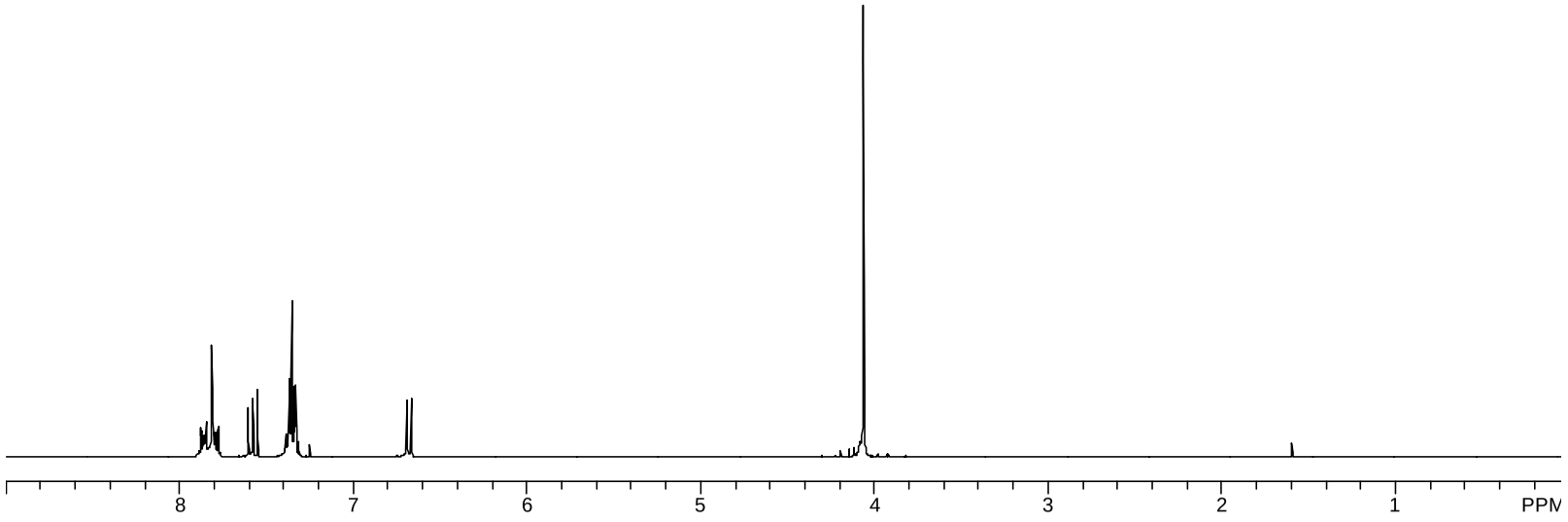

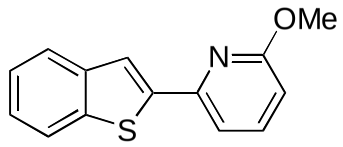

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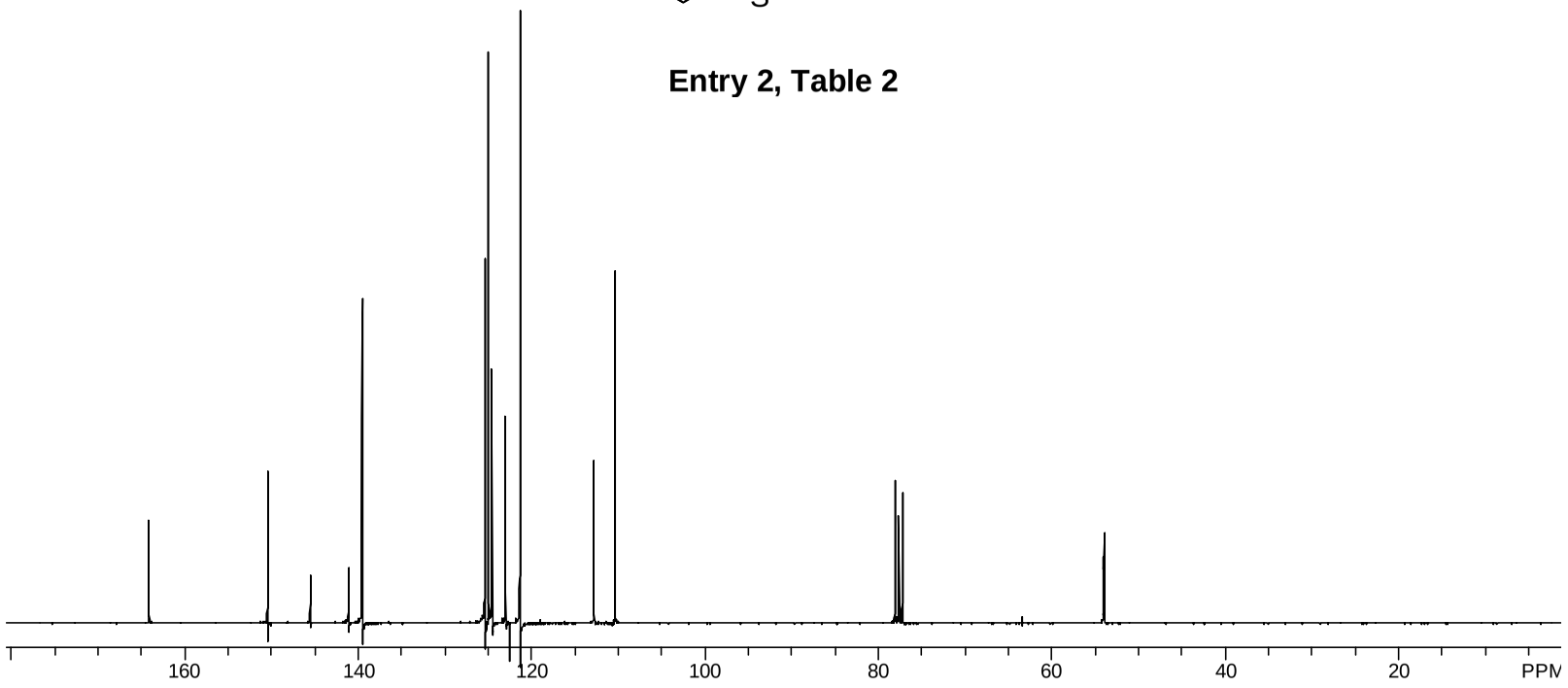

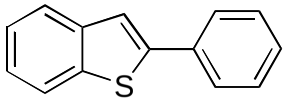

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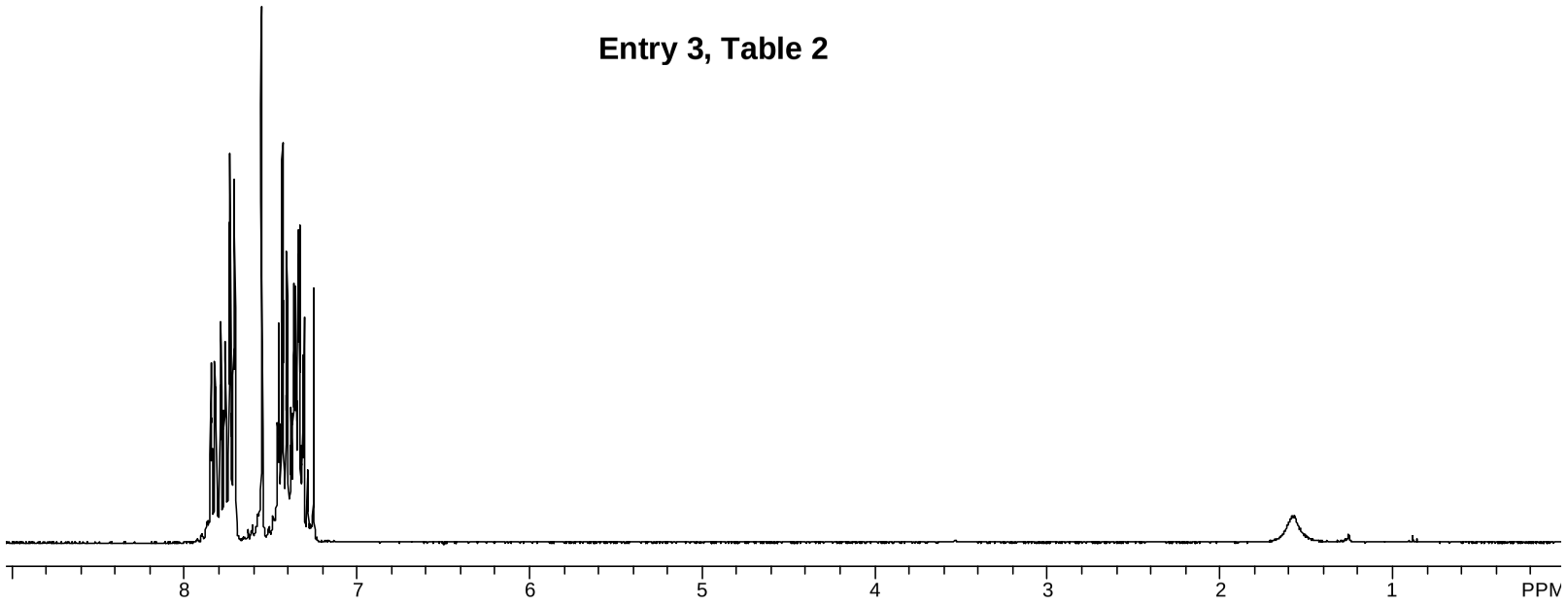

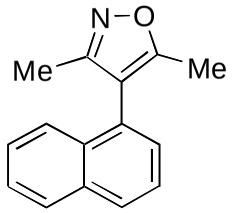

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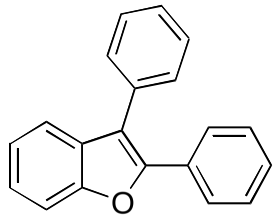

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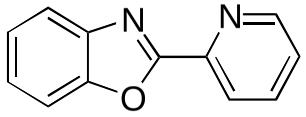

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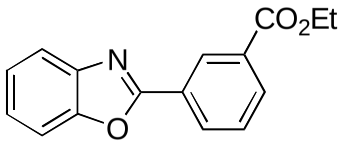

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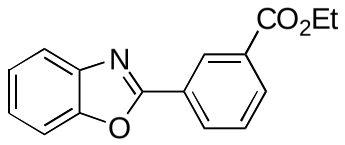

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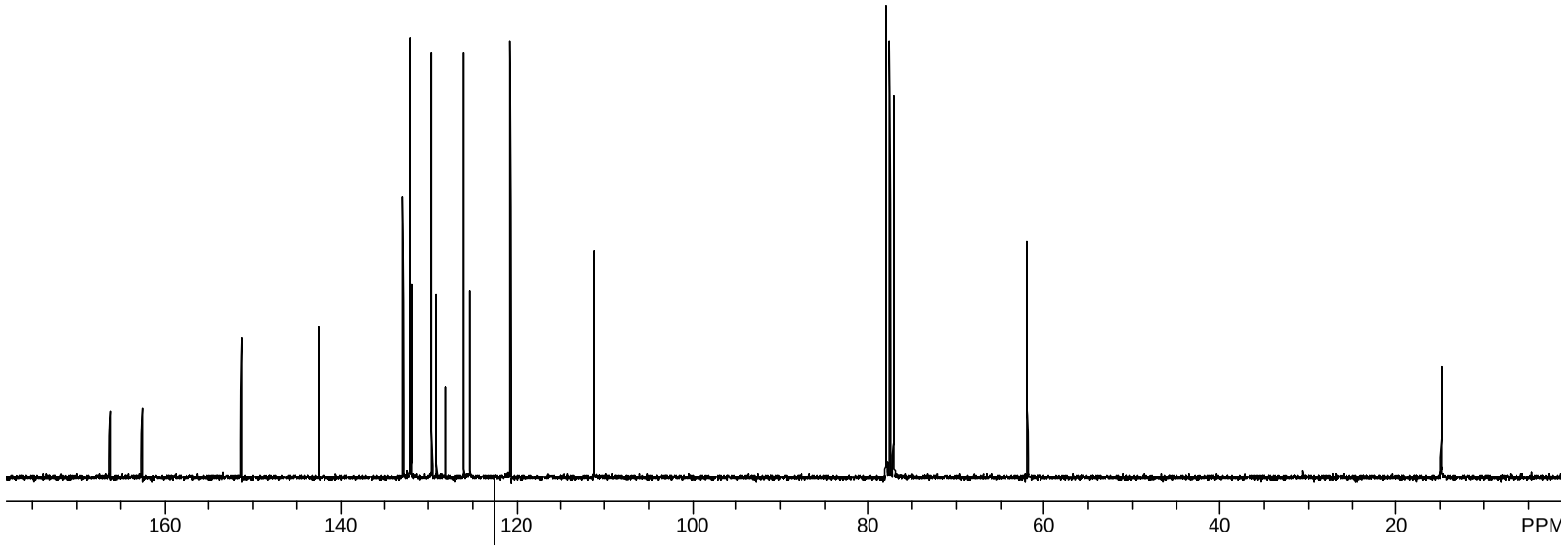

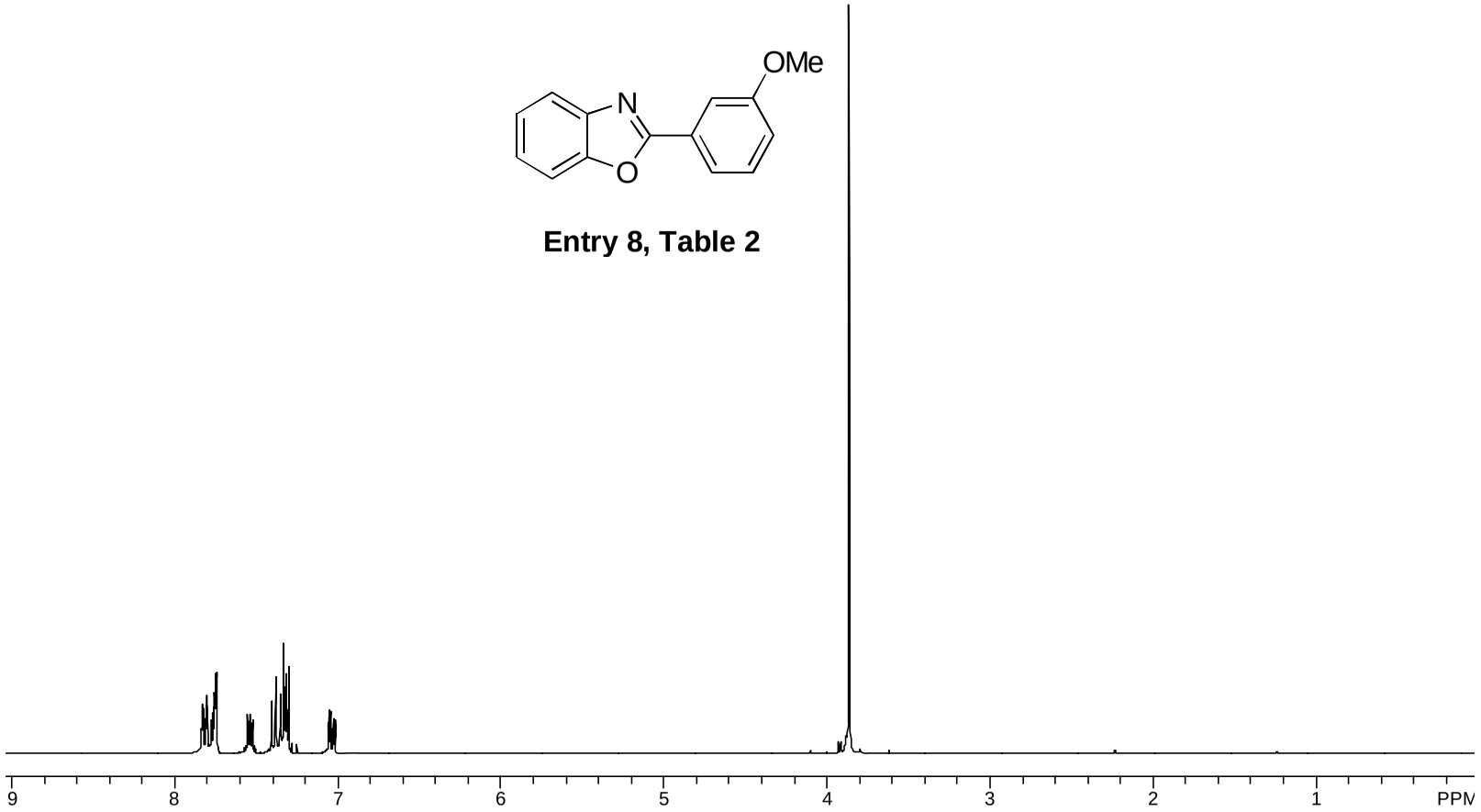

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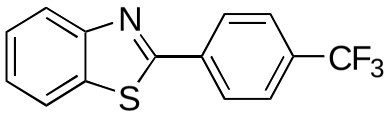

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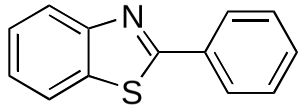

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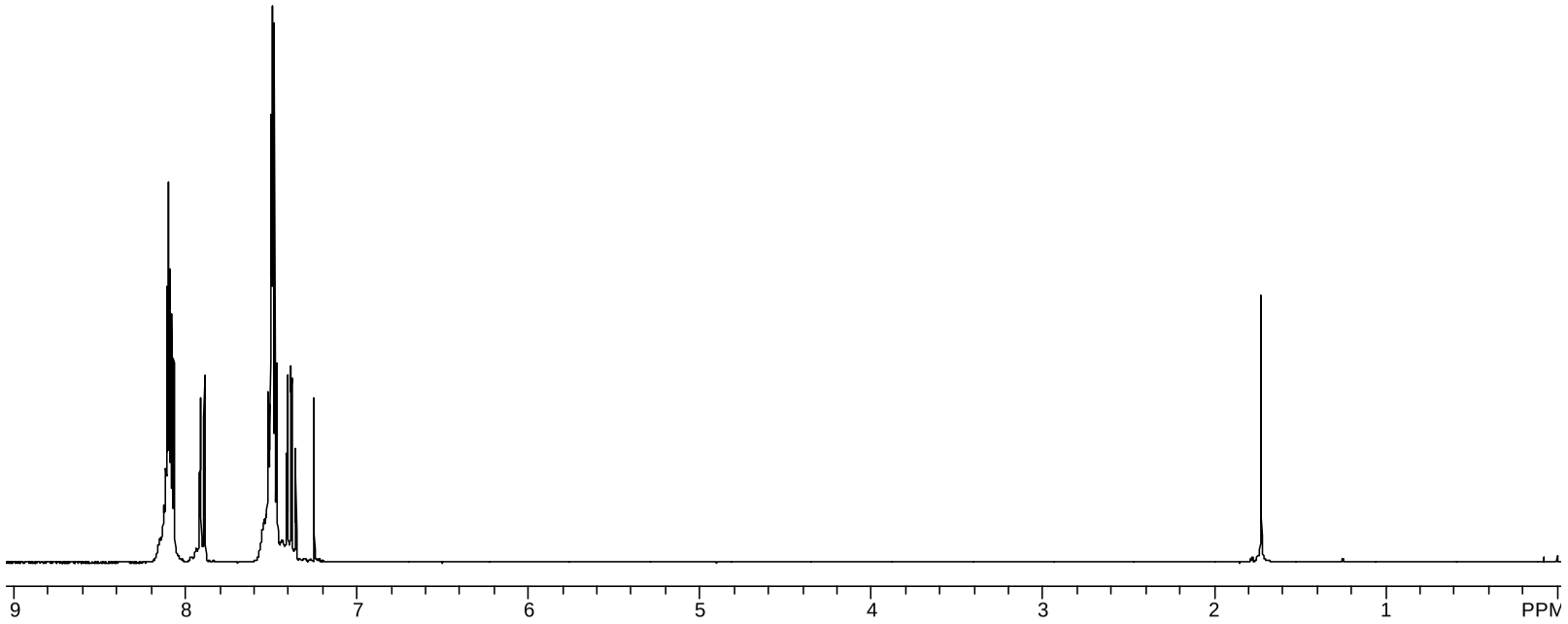

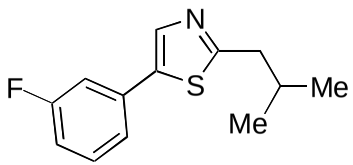

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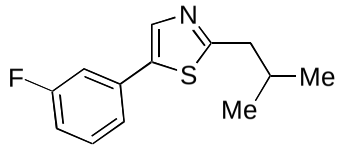

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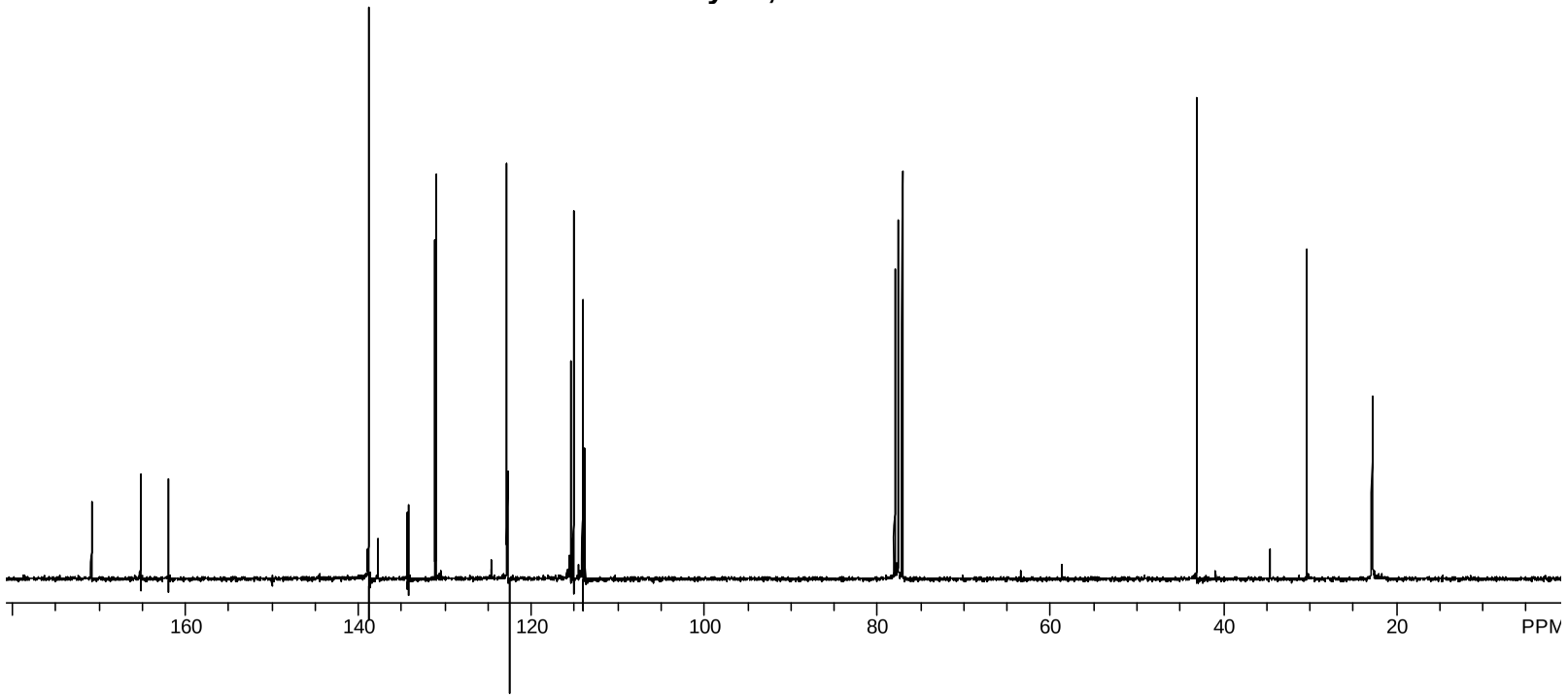

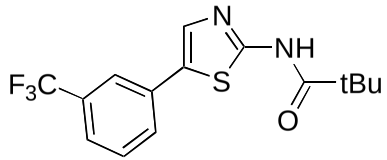

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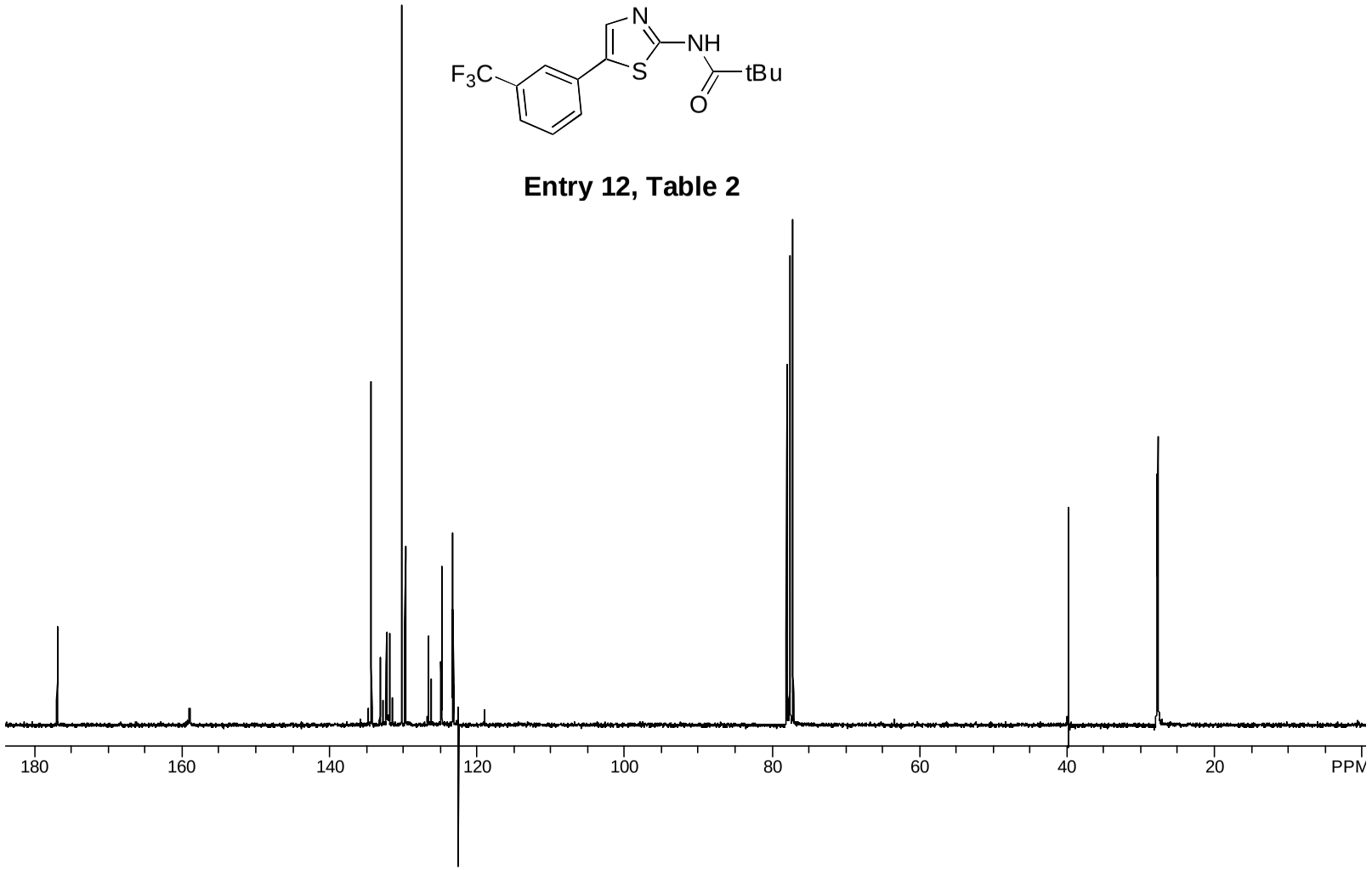

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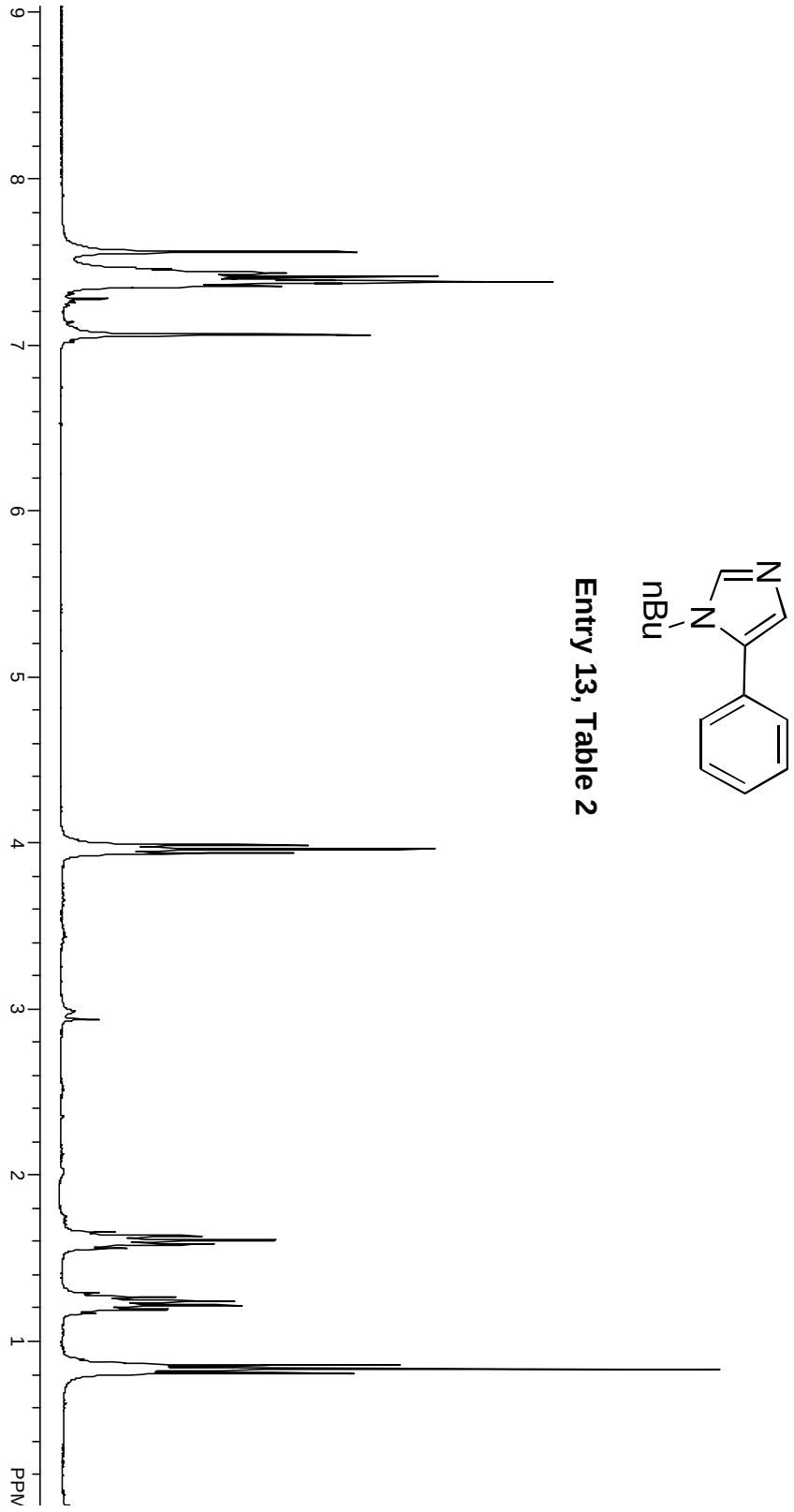

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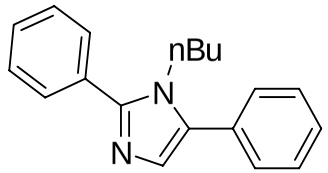

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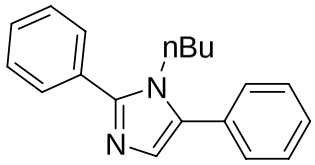
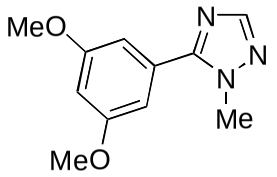
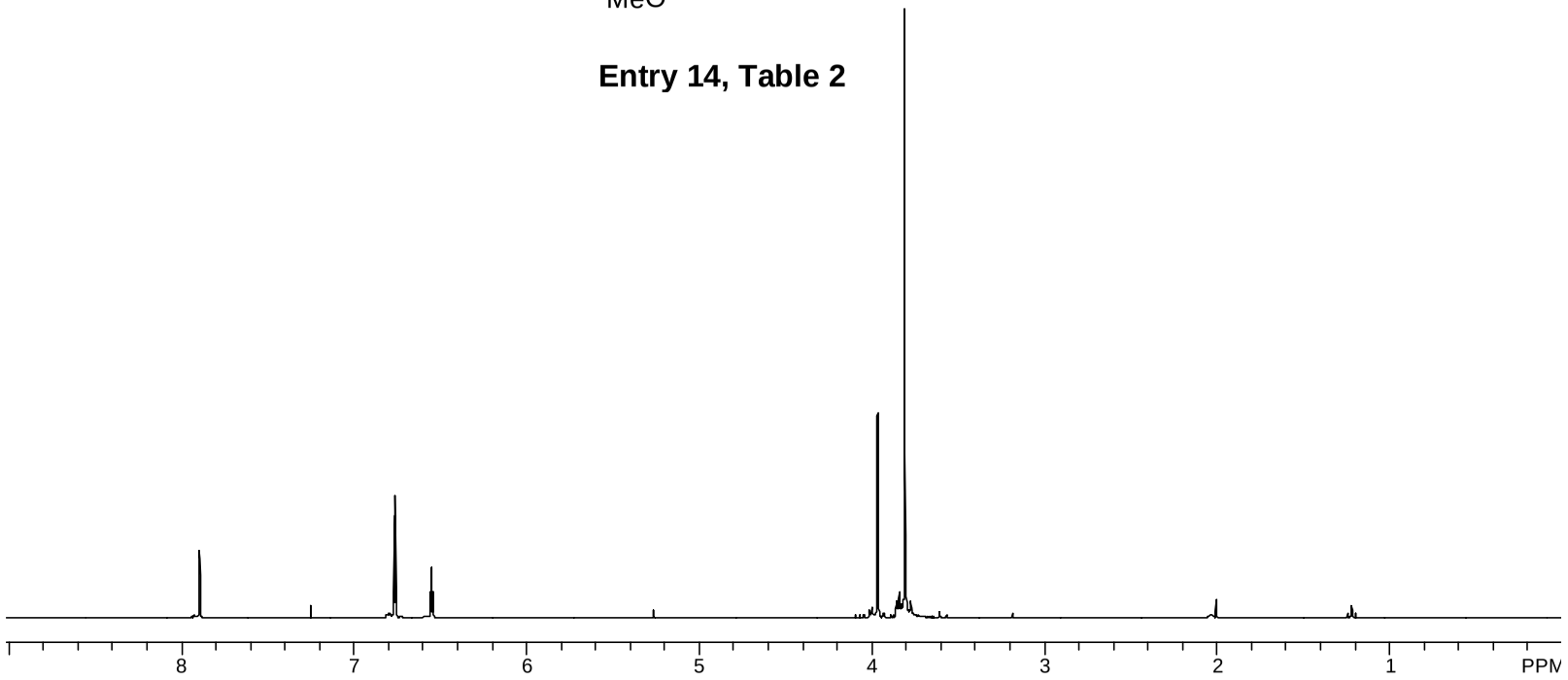
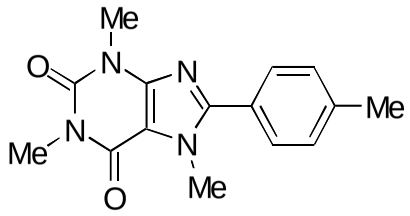


Entry 13 (biarylation), Table 2

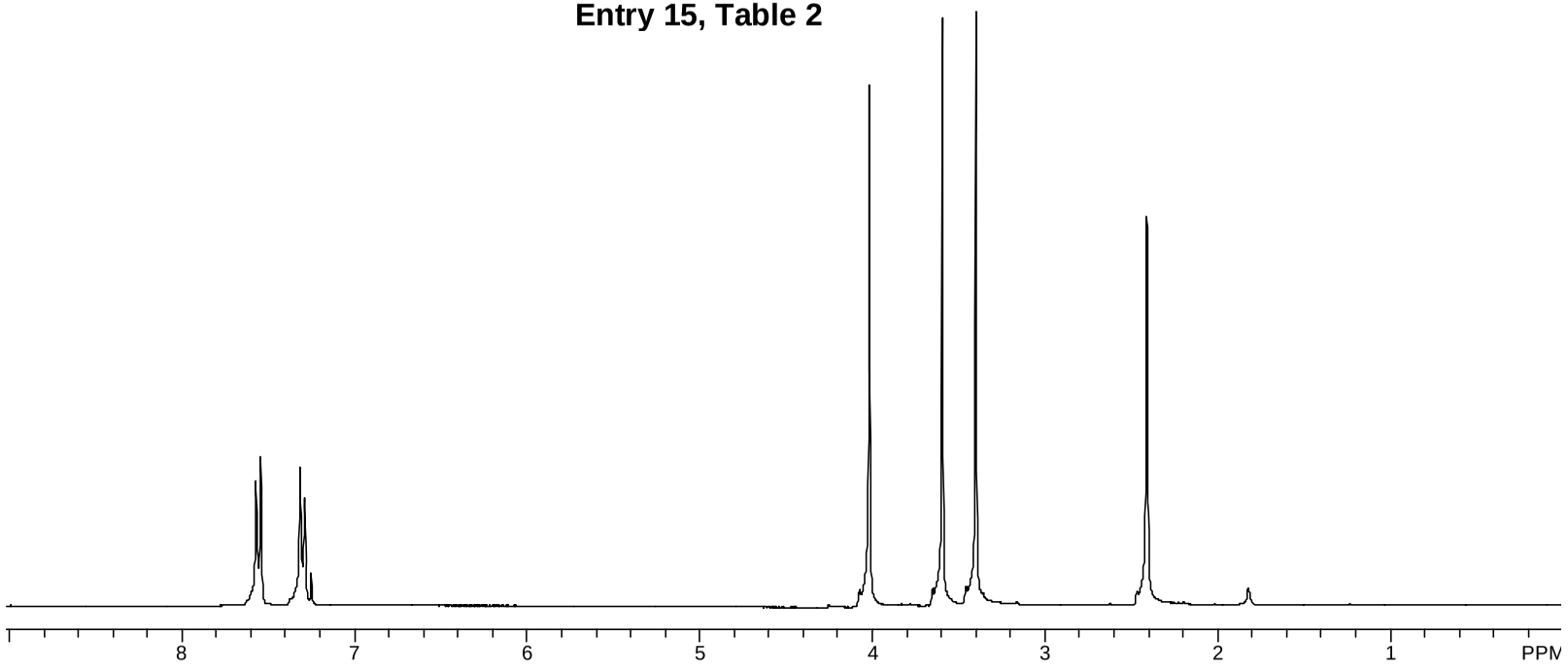


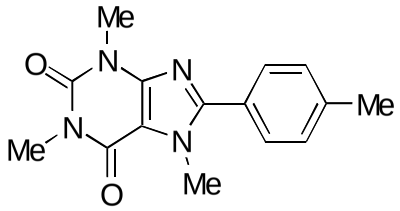
Entry 14, Table 2



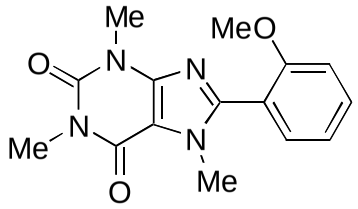


Entry 15, Table 2

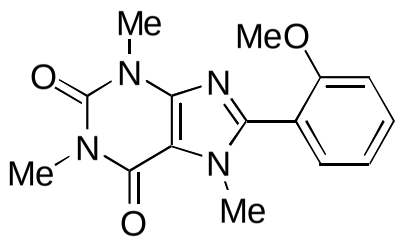




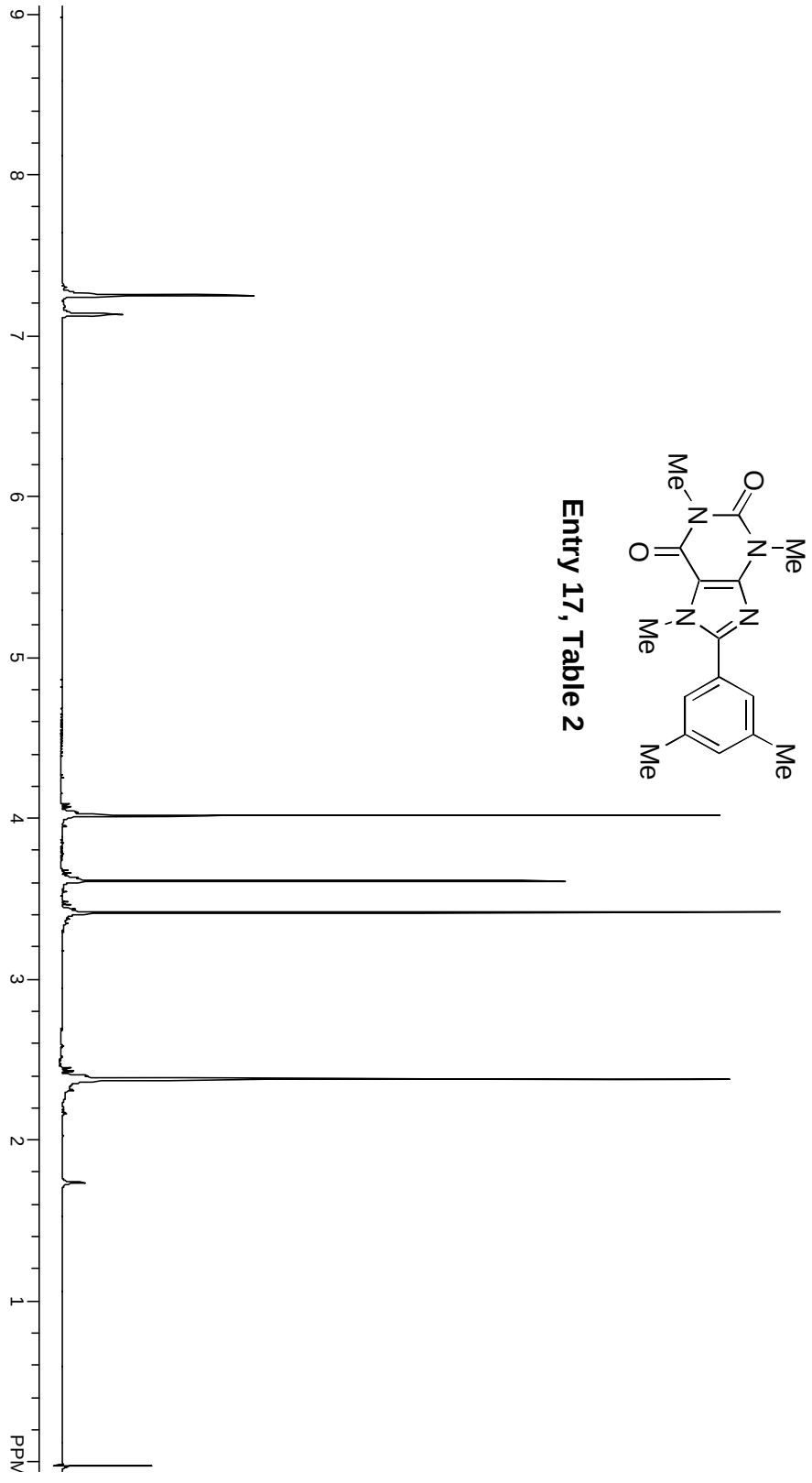
Entry 15, Table 2



Entry 16, Table 2



Entry 16, Table 2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Entry 17, Table 2
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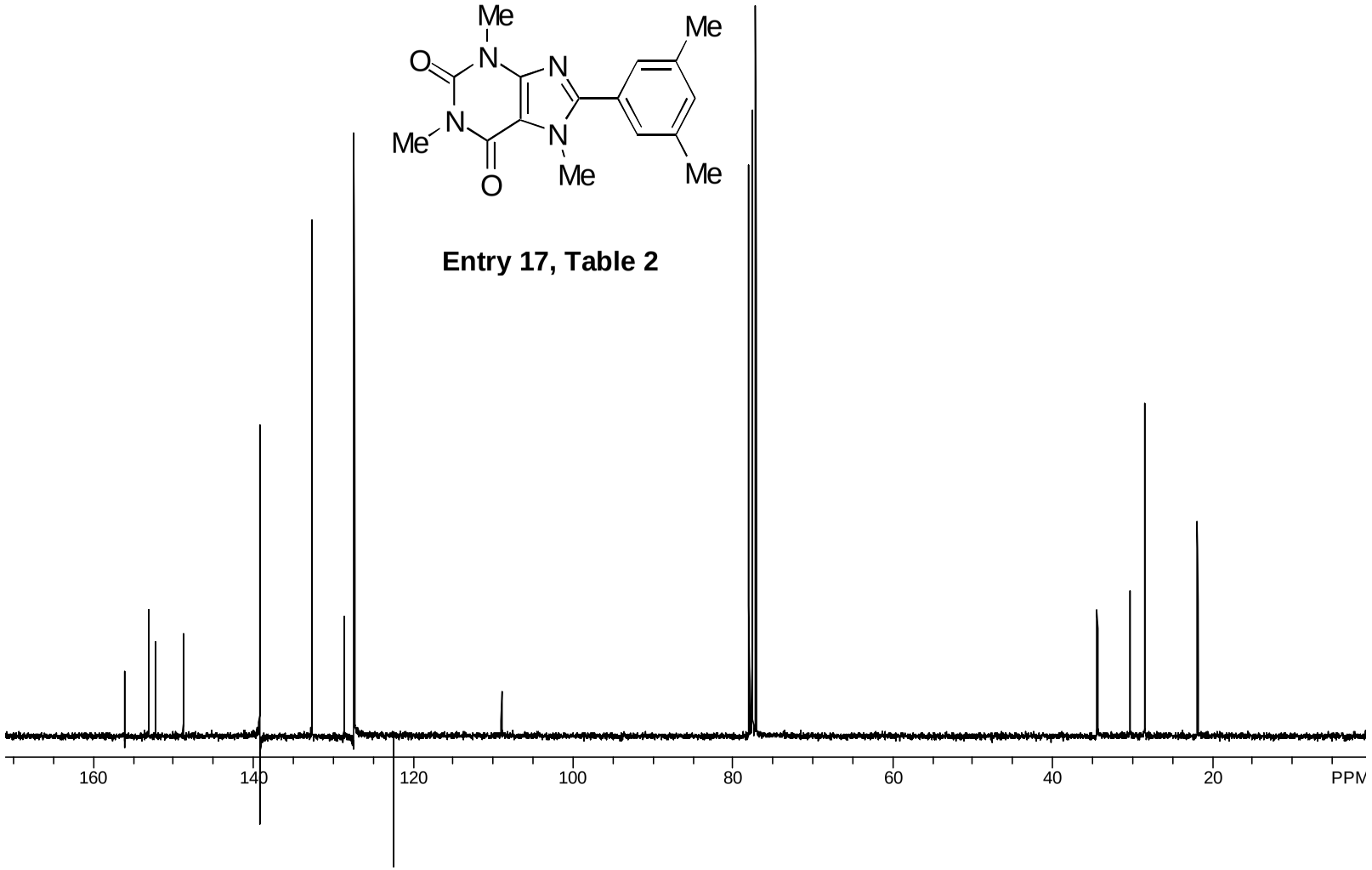

Entry 17, Table 2