SUPPORTING INFORMATION

A Simple Base-Mediated Halogenation of Acidic sp^2 C-H Bonds under Non-Cryogenic Conditions

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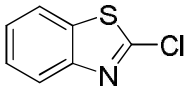
Experimental Section

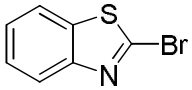
General considerations. Reactions were performed in 1-dram vials with PTFE/Liner caps. Flash chromatography was performed on 60Å silica gel (Sorbent Technologies). Purification by preparative HPLC was performed on a Shimadzu Prominence LC (LC-20AB) equipped with a SPD-20A UV-Vis detector and a Varian Dynamax (250 mm x 21.4 mm) column. GC-MS analyses were performed on a Shimadzu GCMS-QP5000 chromatograph equipped with a Restek column (Rtx-XLB, 30 m x 0.25 mm I.D.). The ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a GE QE-300 spectrometer using residual solvent peak as a reference. Hexafluorobenzene (1% in C_6D_6, δ = -164.9) was employed as an external standard in ^{19}F NMR spectra. Elemental analyses were performed by Atlantic Microlab Inc. of Norcross, GA. IR spectra were obtained using ThermoNicolet Avatar 370 FT-IR instrument. Analytical thin layer chromatography was performed on silica gel IB-F (Baker-flex) by J. T. Baker.

Materials. The following starting materials were obtained from commercial sources and were used without further purification: pentafluorobenzene, 1,3,5-trifluorobenzene, methyl 3,5-difluorobenzoate and 1,2,4,5-tetrafluorobenzene were bought from Oakwood. Carbon tetrabromide and iodine monochloride were obtained from Acros. Potassium phosphate, *m*-xylene, pyridine-*N*-oxide, 1-butylimidazole, and pentachlorobenzene were purchased from Aldrich. Benzothiazole, carbon tetrachloride, 1,2-diiodotetrafluoroethane and 2,3,5,6-tetrafluoroanisole were from Alfa Aesar. 2-Phenylpyridine, 3,5-difluorobenzonitrile and 3-fluoronitrobenzene were obtained from Matrix Scientific. Lithium *t*-butoxide was bought from Strem. 2-Phenylpyridine oxide was prepared from 2-phenylpyridine.[1]

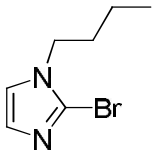
General procedure for halogenation. Outside the glovebox a 1-dram vial equipped with a magnetic stir bar was charged with substrate (1.0 mmol), halogenating reagent (1.5-4.0 equiv) and commercial, non-anhydrous DMF or a mixture (1/1) of DMF and xylene (1.0 mL). The vial was flushed with argon, capped and placed inside a glovebox. To this mixture was added base (K_3PO_4 or t-BuOLi, 2.0-4.0 equiv). The sealed vial was taken out of the glovebox and placed in a preheated oil bath (60-120 ^{o}C) for the indicated time. The reaction mixture was allowed to cool to room temperature and subjected to flash chromatography on silica gel (hexanes or pentane followed by appropriate solvent to elute the products). After concentrating the fractions containing the product, the residue was dried under reduced pressure to yield pure halogenation product.



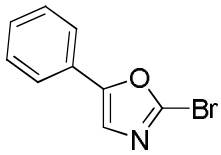
2-Chlorobenzo[d]thiazole (Entry 1, Table 1): Benzothiazole (135 mg, 1.0 mmol), carbon tetrachloride (308 mg, 2.0 mmol), t-BuOLi (200 mg, 2.5 mmol), and DMF/*m*-xylene (1.0 mL), 100 ^{o}C, 1 hours. After column chromatography (10% AcOEt in hexanes) 135 mg (80%) of a light tan oil was obtained. R_f = 0.53 (SiO_2, AcOEt/hexanes 1/4). This compound is known.[2] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.52 (m, 2H), 7.74-7.81 (m, 1H), 7.91-7.98 (m, 1H).



2-Bromobenzo[d]thiazole (Entry 2, Table 1): Benzothiazole (135 mg, 1.0 mmol), carbon tetrabromide (498 mg, 1.5 mmol), K_3PO_4 (636 mg, 3.0 mmol), and DMF (1.0 mL), 120 ^{o}C, 5 hours. After column chromatography (10% AcOEt in hexanes) 175 mg (82%) of a light tan oil was obtained. R_f = 0.53 (SiO_2, AcOEt/hexanes 1/4). This compound is known.[3] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.50 (m, 2H), 7.78-7.82 (m, 1H), 7.96-8.01 (m, 1H).

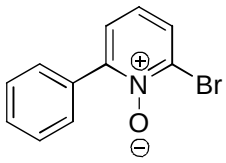


2-Bromo-1-butyl-1*H*-imidazole (Entry 3, Table 1): 1-Butylimidazole (124 mg, 1.0 mmol), carbon tetrabromide (498 mg, 1.5 mmol), t-BuOLi (160 mg, 2.0 mmol), and DMF (1.0 mL), 60 ^{o}C, 1 hour. After column chromatography (2/3 AcOEt/hexanes) 185 mg (91%) of a light tan oil was obtained. R_f = 0.38 (SiO_2, AcOEt/hexanes 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.30 (sextet, *J* = 7.4 Hz, 2H), 1.69 (quintet, *J* = 7.4 Hz, 2H), 3.86 (t, *J* = 7.4 Hz, 2H), 6.92 (d, *J* = 1.5 Hz, 1H), 6.95 (d, *J* = 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 20.1, 32.9, 48.0, 119.8, 122.3, 130.3. FT-IR (neat, cm^{-1}) υ 2960, 2933, 2873, 1469, 1435, 1382, 1348, 1269, 1207, 1128, 1095, 909, 737.

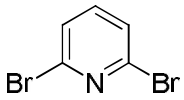


2-Bromo-5-phenyloxazole (Entry 4, Table 1): 5-Phenyloxazole (145 mg, 1.0 mmol), 1,2-dibromotetrafluoroethane (520 mg, 2.0 mmol), t-BuOLi (160 mg, 2.0 mmol), and DMF/*m*-

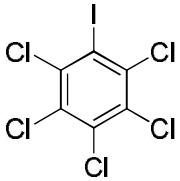
xylene (1.0 mL), 60 °C, 1 hour. After column chromatography (20% AcOEt in hexanes) 180 mg (80%) of a light tan oil was obtained. R_f = 0.51 (SiO_2, AcOEt/hexanes 1/4). This compound is known.[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.31-7.46 (m, 3H), 7.56-7.62 (m, 2H).



2-Bromo-6-phenylpyridine 1-oxide (Entry 5, Table 1): 2-Phenylpyridine oxide (171 mg, 1.0 mmol), carbon tetrabromide (830 mg, 2.5 mmol), t-BuOLi (320 mg, 4.0 mmol), and DMF/*m*-xylene (1.0 mL), 60 °C, 1 hour. After column chromatography (3/2 AcOEt/hexanes) 140 mg (56%) of a light tan solid was obtained. R_f = 0.22 (SiO_2, AcOEt/hexanes 1/1), mp 117-119 °C (from AcOEt/hexanes 1/1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.43-7.49 (m, 3H), 7.65 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.76-7.81 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 125.4, 126.5, 128.7, 129.9, 130.0, 130.4, 133.2, 135.1, 151.5. FT-IR (neat, cm^{-1}) υ 2929, 1534, 1458, 1367, 1247, 1052, 842, 792, 784, 768, 702. Anal calcd for $C_{11}H_8BrNO$ (250.09 g/mol): C, 52.83; H, 3.22; N, 5.60; Found. C, 52.94; H, 3.32; N, 5.43.



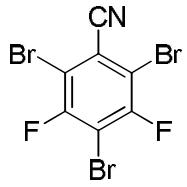
2,6-Dibromopyridine (Entry 6, Table 1): Pyridine oxide (95 mg, 1.0 mmol), carbon tetrabromide (830 mg, 2.5 mmol), t-BuOLi (240 mg, 3.0 mmol), and *m*-xylene (1.5 mL), 100 °C, 1 hour. After column chromatography (20% AcOEt in hexanes) 70 mg (30%) of a light tan solid was obtained. R_f = 0.49 (SiO_2, AcOEt/hexanes 1/4). This compound is known.[5] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.48 (m, 3H).



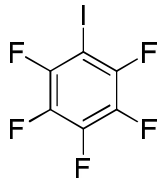
Pentachloroiodobenzene (Entry 7, Table 1): Pentachlorobenzene (250.5 mg, 1.0 mmol), ICl (243.8 mg, 1.5 mmol), t-BuOLi (240 mg, 3.0 mmol), and DMF (1.5 mL), 120 °C, 3 hours. After column chromatography (hexanes) 340 mg (90%) of a colorless solid was

obtained. R_f = 0.57 (SiO_2, hexanes). This compound is known.[6] ^{13}C NMR (75 MHz, $CDCl_3$) δ 103.6, 131.1, 134.6, 138.6.

2-Bromo-1-fluoro-3-nitrobenzene (Entry 8, Table 1): 3-Fluoronitrobenzene (141 mg, 1.0 mmol), carbon tetrabromide (498 mg, 1.5 mmol), t-BuOLi (200 mg, 2.5 mmol), and DMF (1.0 mL), 60 ^oC, 2 hours. After column chromatography (10% AcOEt in hexanes) 120 mg (55%) of a yellow solid was obtained. R_f = 0.19 (SiO_2, hexanes), mp 42.0-44.0 ^oC (from AcOEt/hexanes 1/9). ^1H NMR (300 MHz, $CDCl_3$) δ 7.36 (dt, J = 8.3 Hz, 1.0 Hz, 1H), 7.41-7.51 (m, 1H), 7.60-7.68 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -179.0- -178.9 (m, 1F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 104.2 (d, J_{C-F} = 24.0 Hz), 120.5 (d, J_{C-F} = 22.8 Hz), 121.4 (d, J_{C-F} = 3.6 Hz), 129.6 (d, J_{C-F} = 8.4 Hz), 151.6 (br s), 160.3 (d, J_{C-F} = 251.3 Hz). FT-IR (neat, cm^{-1}) υ 1533, 1456, 1356, 1292, 1264, 944, 814, 799, 736, 704. Anal calcd for $C_6H_3BrFNO_2$ (220.00 g/mol): C, 32.76; H, 1.37; N, 6.37; Found. C, 32.86; H, 1.26; N, 6.28.

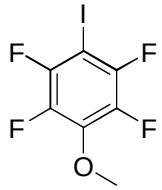


2,4,6-Tribromo-3,5-difluorobenzonitrile (Entry 9, Table 1): 3,5-Difluorobenzonitrile (139 mg, 1.0 mmol), carbon tetrabromide (1162 mg, 3.5 mmol), t-BuOLi (320 mg, 4.0 mmol), and DMF/*m*-xylene (1.5 mL), 60 ^oC, 2 hours. After column chromatography (15% AcOEt in hexanes) and preparative HPLC (5% AcOEt in hexanes) 150 mg (40%) of a colorless solid was obtained. R_f = 0.58 (SiO_2, AcOEt/hexanes 1/4). This compound is known.[7] ^{19}F NMR (282 MHz, $CDCl_3$) δ -169.0 (s, 2F).

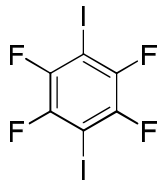


Pentafluoroiodobenzene (Entry 10, Table 1): Pentafluorobenzene (252 mg, 1.5 mmol), iodine (254 mg, 1.0 mmol), K_3PO_4 (424 mg, 2.0 mmol), and DMF (1.0 mL), 130 ^oC, 2 hours. After column chromatography (pentane) 250 mg (85%) of a colorless oil was obtained. R_f =

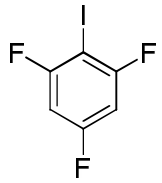
0.51 (SiO_2, hexanes). This compound is known.[8] ^{19}F NMR (282 MHz, $CDCl_3$) δ -157.6- -157.4 (m, 2F), -150.3 (t, J_F = 21.0 Hz, 1F), -117.4- -117.2 (m, 2F).



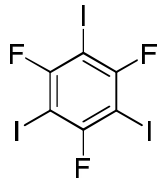
1,2,4,5-Tetrafluoro-3-iodo-6-methoxybenzene (Entry 11, Table 1): 2,3,5,6-Tetrafluoroanisole (180 mg, 1.0 mmol), iodine (381 mg, 1.5 mmol), t-BuOLi (160 mg, 2.0 mmol), and DMF (1.0 mL), 60 ^oC, 1 hour. After column chromatography (10% dichloromethane in hexanes) 300 mg (98%) of a colorless oil was obtained. R_f = 0.37 (SiO_2, hexanes). This compound is known.[9] ^1H NMR (300 MHz, $CDCl_3$) δ 4.08 (t, J = 1.5 Hz, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -153.6- -153.4 (m, 2F), -119.9- -119.7 (m, 2F).



1,2,4,5-Tetrafluoro-3,6-diiodobenzene (Entry 12, Table 1): 1,2,4,5-Tetrafluorobenzene (150 mg, 1.0 mmol), iodine (762 mg, 3.0 mmol), t-BuOLi (240 mg, 3.0 mmol), and DMF (1.5 mL), 60 ^oC, 2 hours. After column chromatography (hexanes) 380 mg (95%) of a colorless solid was obtained. R_f = 0.44 (SiO_2, hexanes). This compound is known.[10] ^{19}F NMR (282 MHz, $CDCl_3$) δ -116.3 (s, 4F).



1,3,5-Trifluoro-2-iodobenzene (Entry 13, Table 1): 1,3,5-Trifluorobenzene (396 mg, 3.0 mmol), ICl (162.5 mg, 1.0 mmol), t-BuOLi (160 mg, 2.0 mmol), and DMF (1.0 mL), 60 ^oC, 1 hour. After column chromatography (pentane) 150 mg (58%) of a colorless oil was obtained. R_f = 0.57 (SiO_2, hexanes). This compound is known.[11] ^1H NMR (300 MHz, $CDCl_3$) δ 6.66-6.77 (m, 2H). ^{19}F NMR (282 MHz, $CDCl_3$) δ -168.1- -168.0 (m, 2F), -106.1- -105.9 (m, 1F).



1,3,5-Trifluoro-2,4,6-triiodobenzene (Entry 14, Table 1): A 1 dram vial was charged with DMF (2.0 mL), 1,3,5-trifluorobenzene (132 mg, 1.0 mmol), ICl (492 mg, 3.0 mmol), and t-BuOLi (320 mg, 4.0 mmol) in the order listed. The reaction mixture was heated at 60 ^{o}C for 4 hours. After column chromatography (10% AcOEt in hexanes) 165 mg (32%) of a colorless solid was obtained. R_f = 0.36 (SiO_2, hexanes). This compound is known.[8] ^{19}F NMR (282 MHz, $CDCl_3$) δ -147.6 (s, 3F).

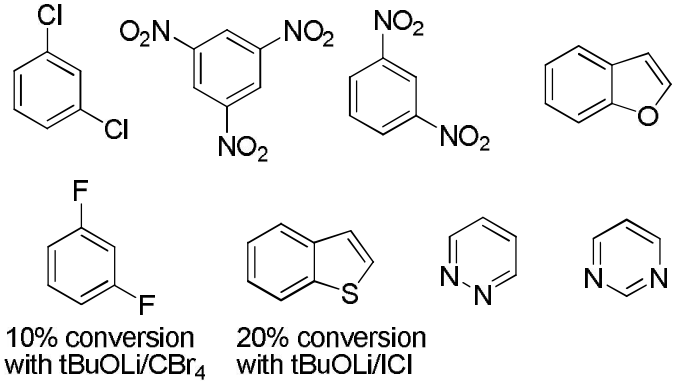


Figure S-1. List of substrates that do not undergo efficient halogenation.

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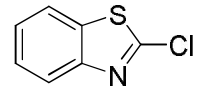
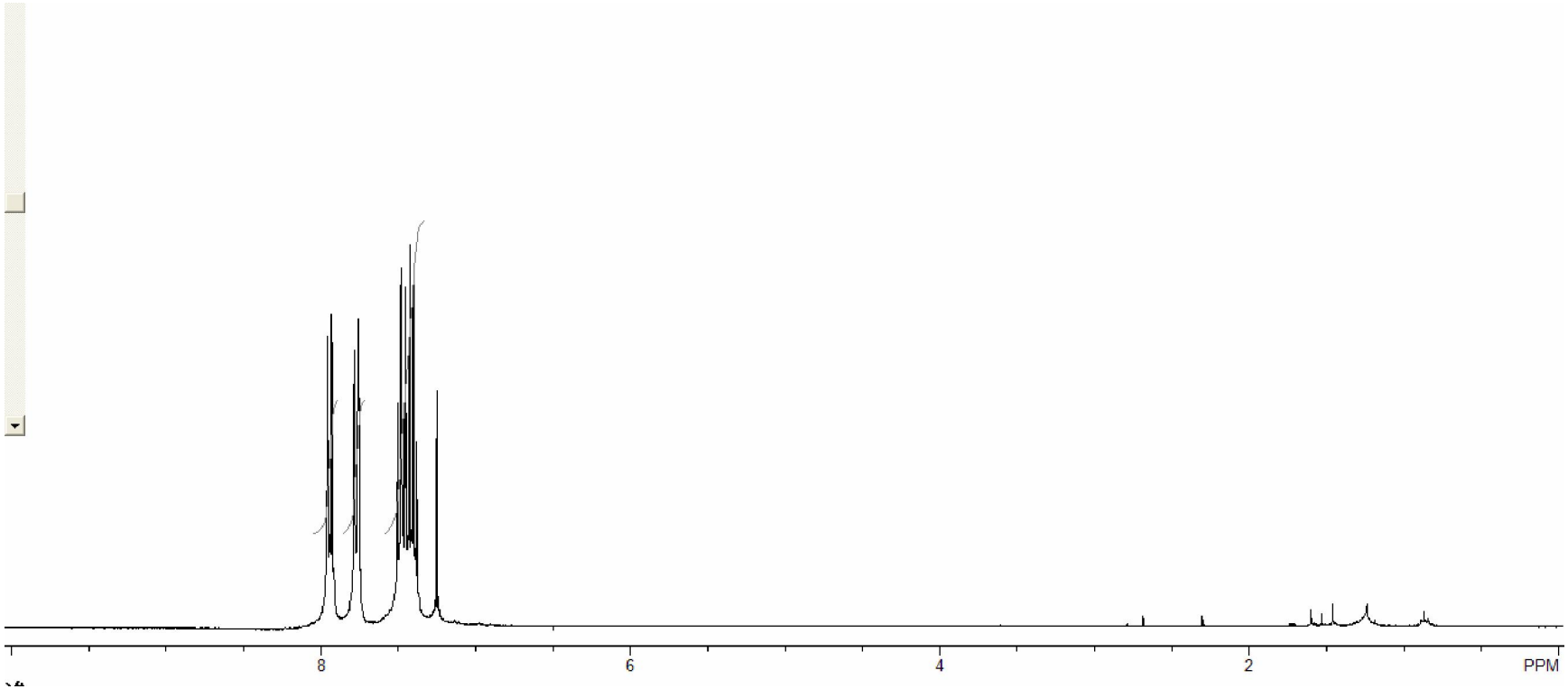
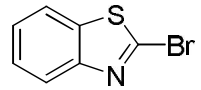


(Entry 1, Table 1)





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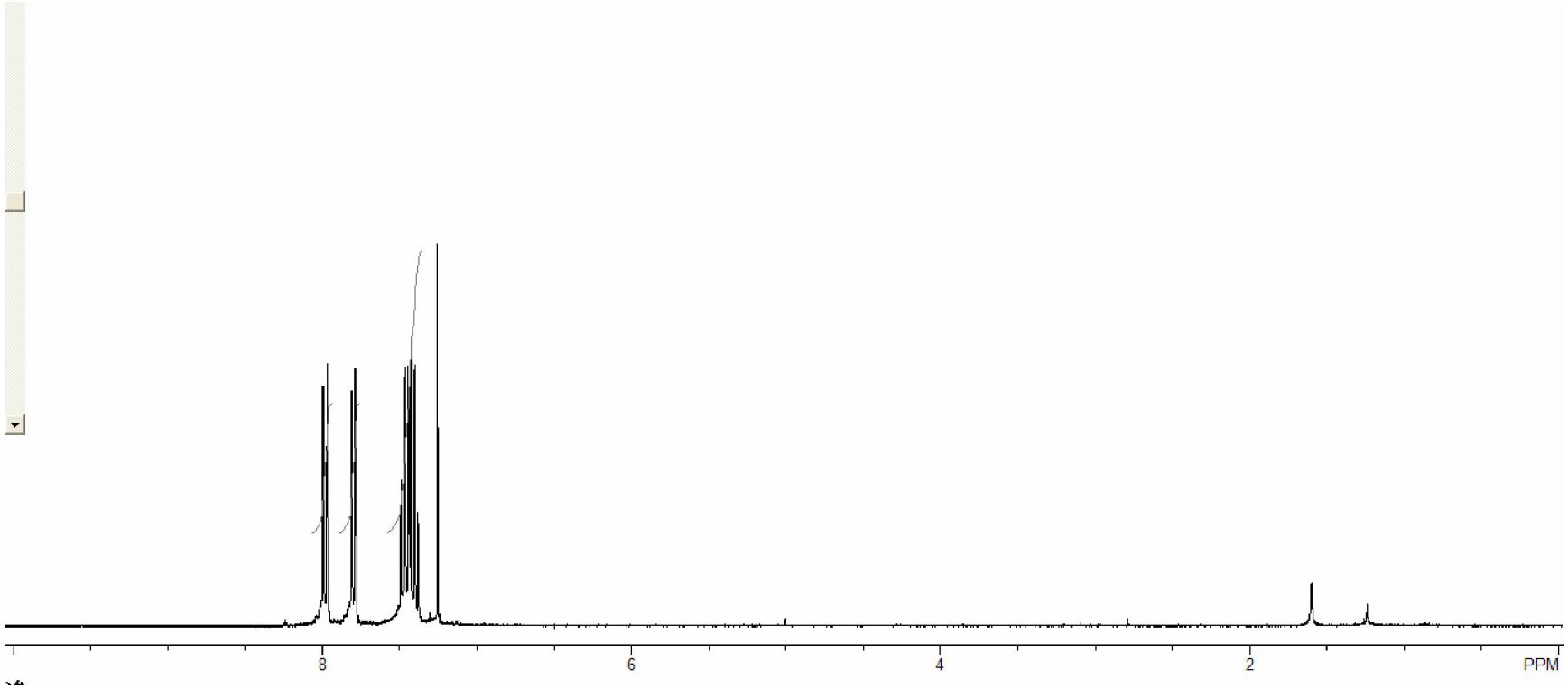

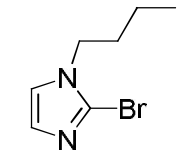

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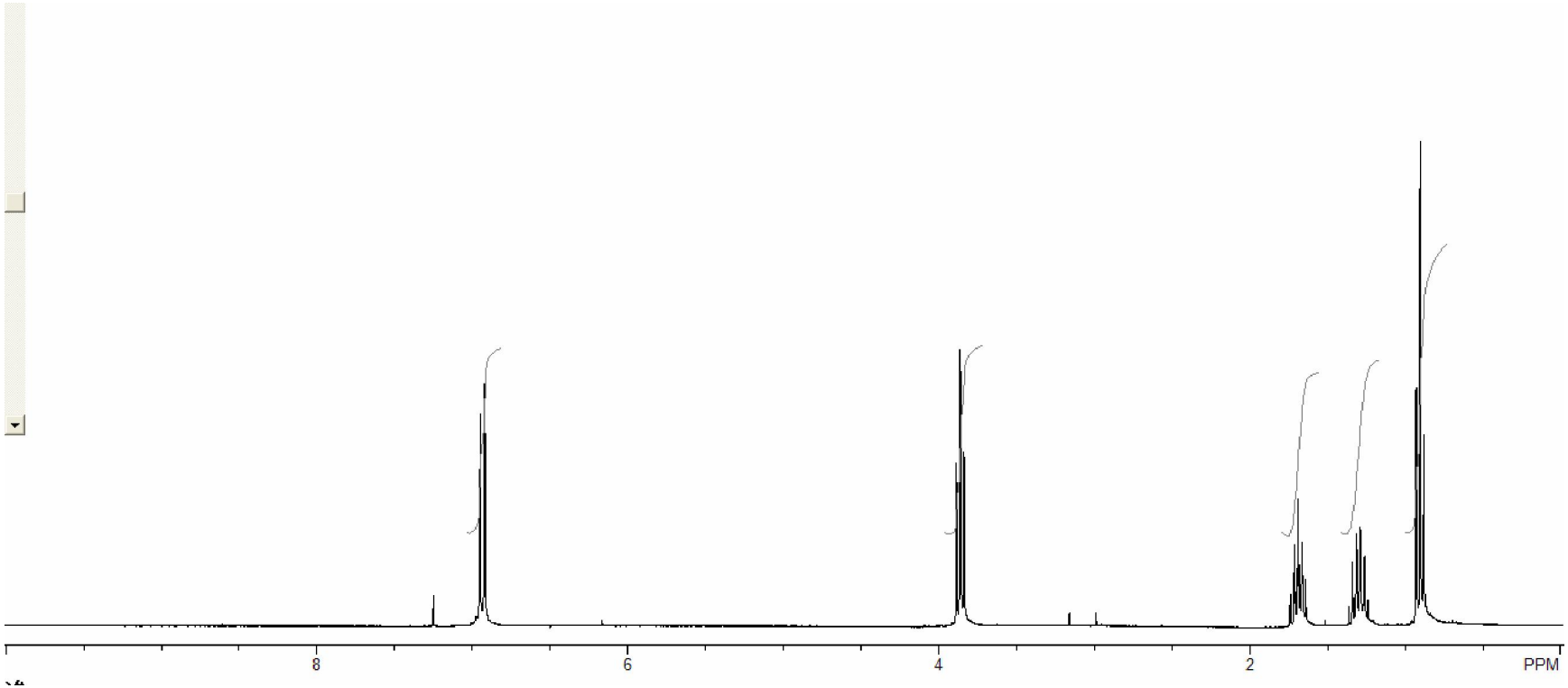

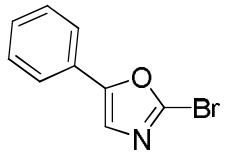

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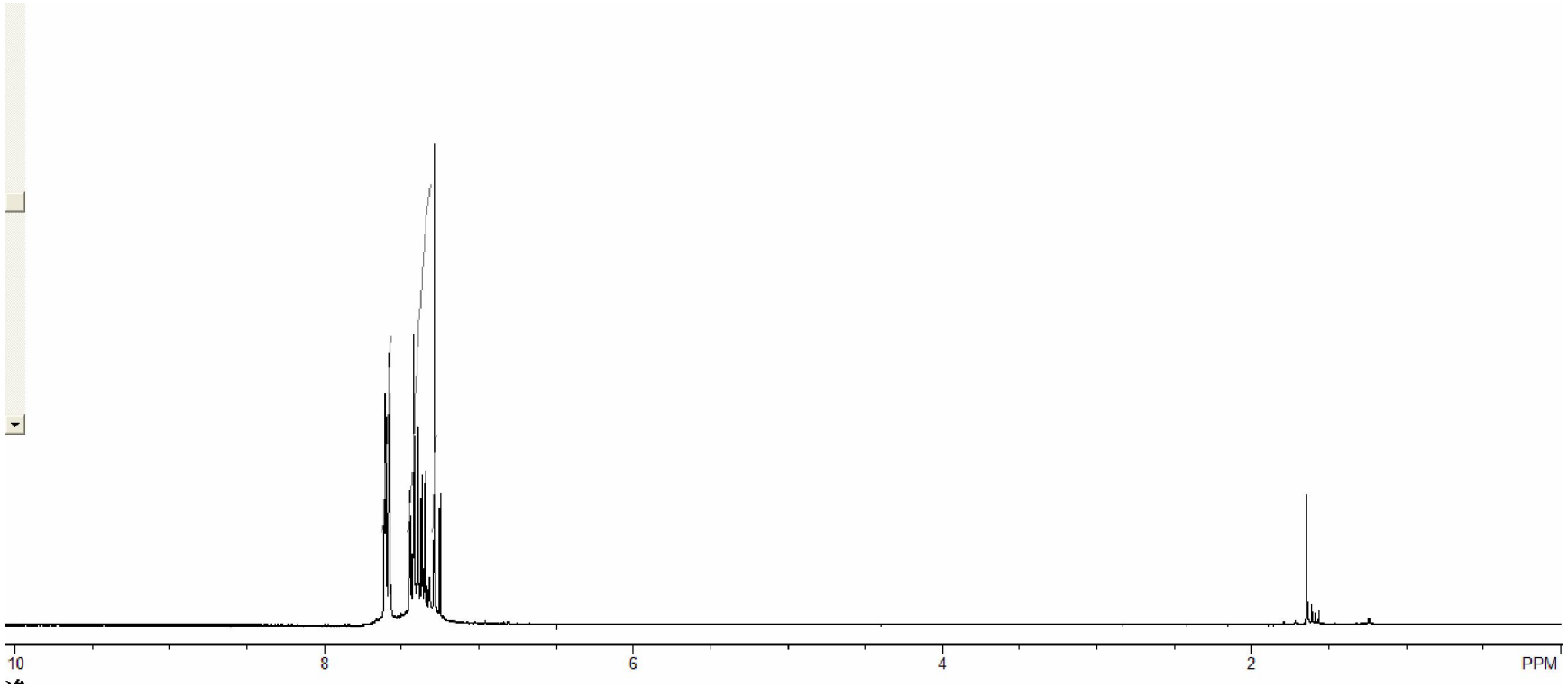

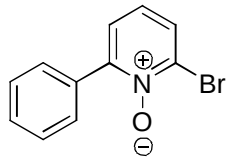

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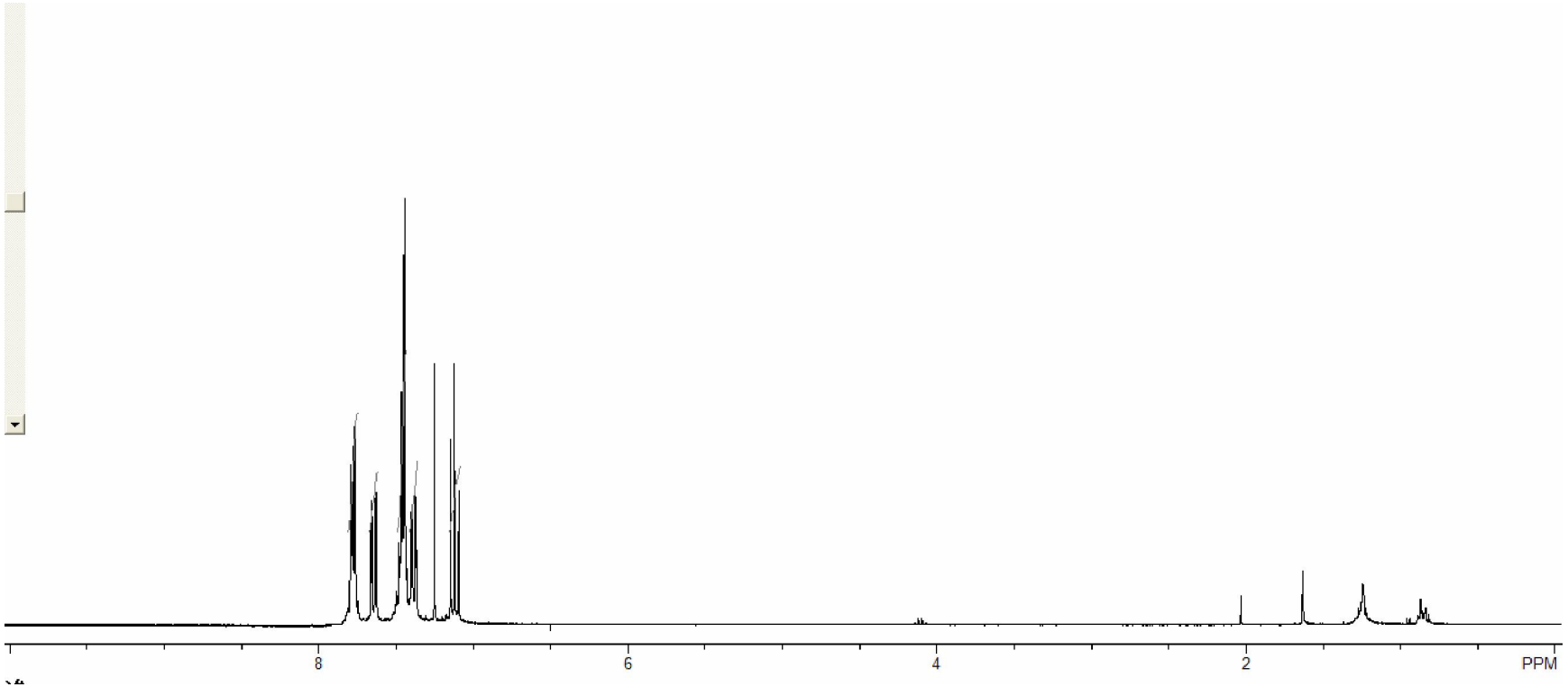
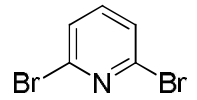
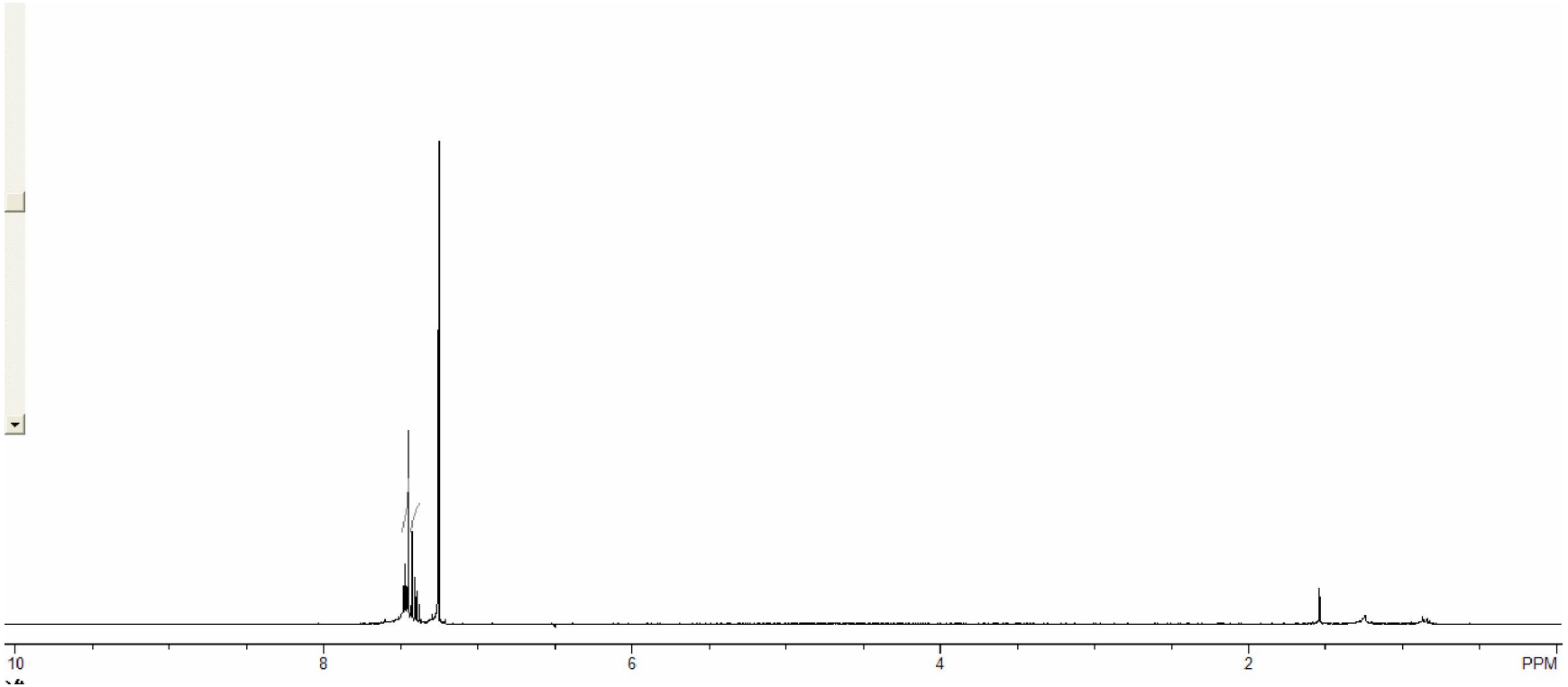
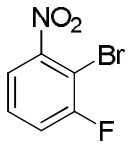


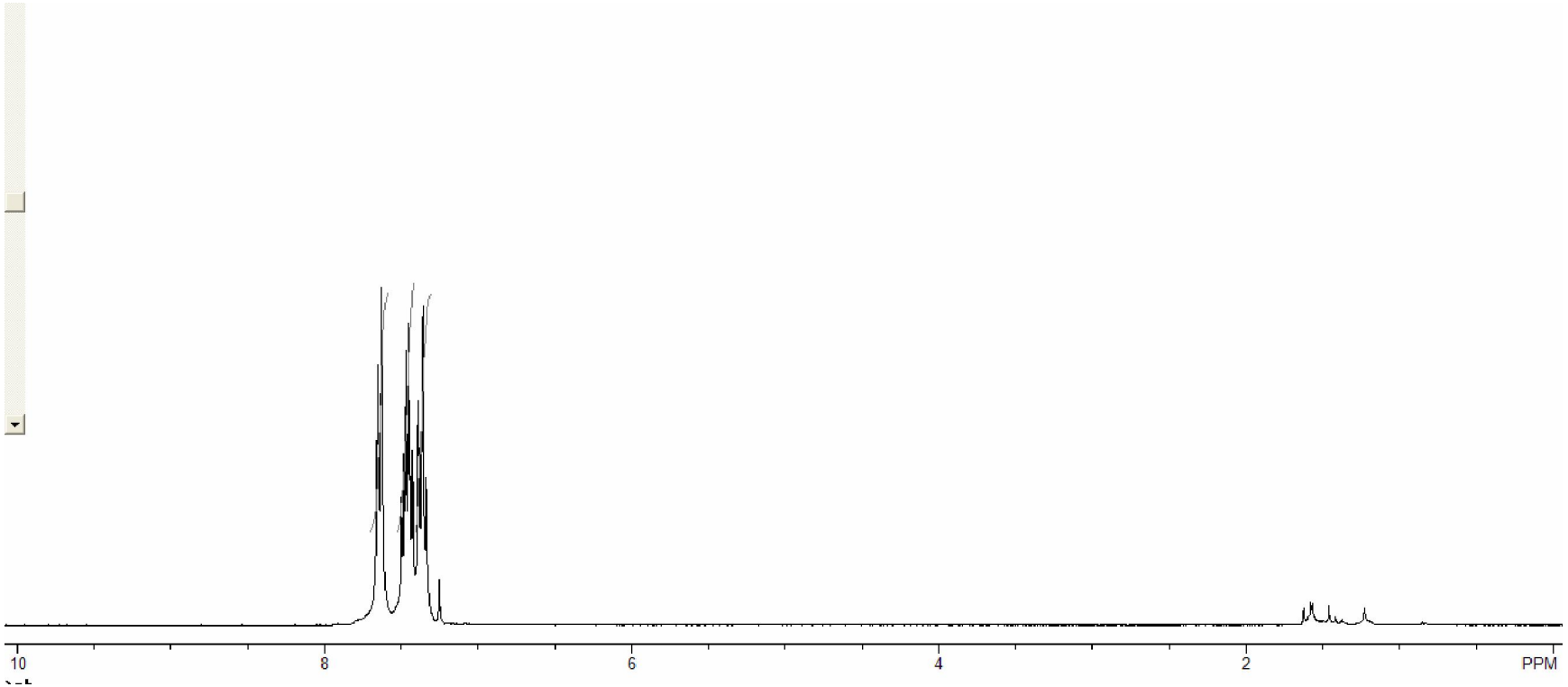


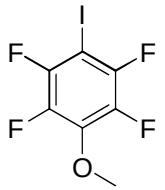
(Entry 6, Table 1)



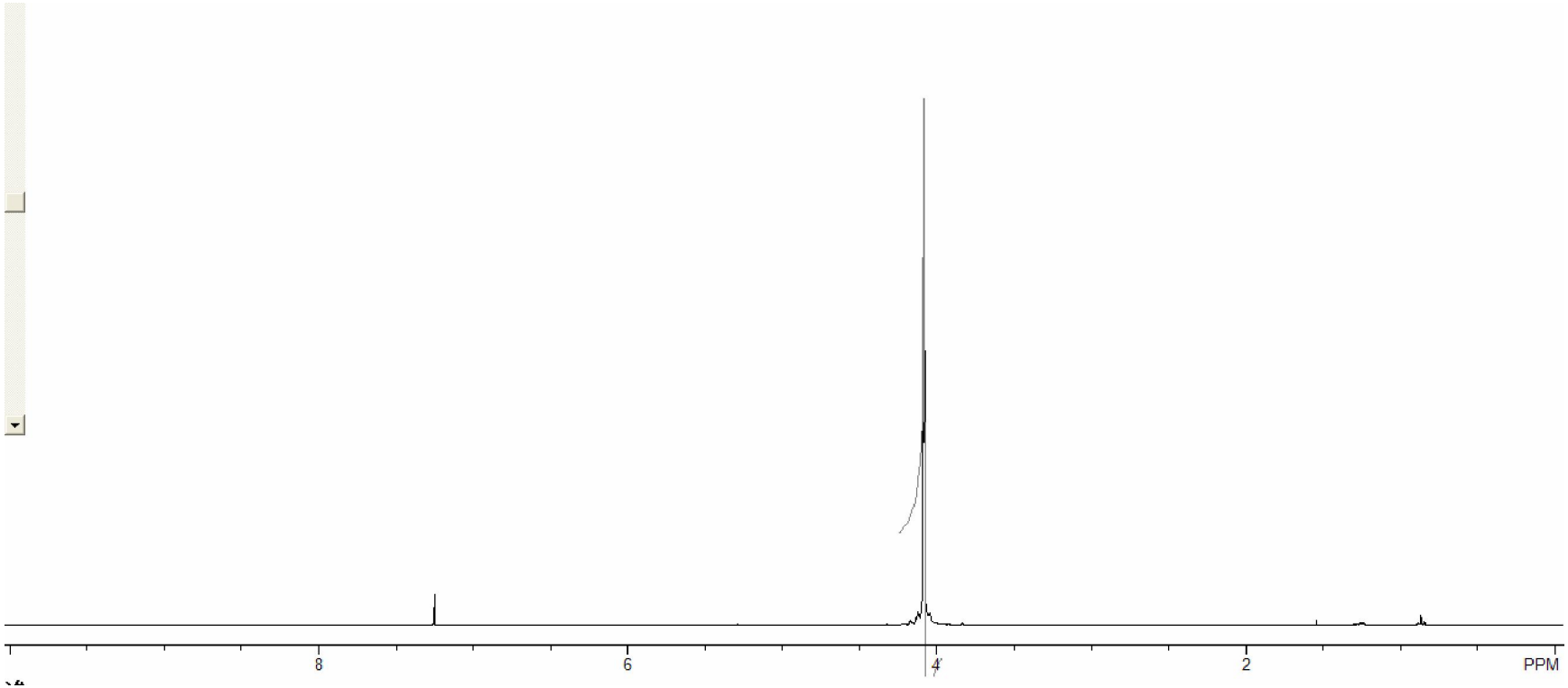


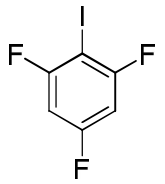
(Entry 8, Table 1)





(Entry 11, Table 1)





(Entry 13, Table 1)