Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Supporting Information

Rhodium-Catalyzed Biheteroaryl-2-Carbonitriles Synthesis via Double C−H Activation

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1. General methods

NMR data were obtained for ^{1}H at 400 MHz or 600 MHz, and for ^{13}C at 100 MHz or 151 MHz.Chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard in $CDCl_3$ solution. ESI HRMS was recorded on a Waters SYNAPT G2 and Water XEVO G2 Q-ToF.UV detection was monitored at 220 nm. TLC was performed on glass-backed silica plates. Column chromatography was performed on silica gel (200-300 mesh), eluting with ethyl acetate and petroleum ether.

2. Screening reaction conditions

Many other conditions cannot increase the yield of **3a** (Table A).

Table A. Additional reaction conditions[a]

1a **2a** **3a**

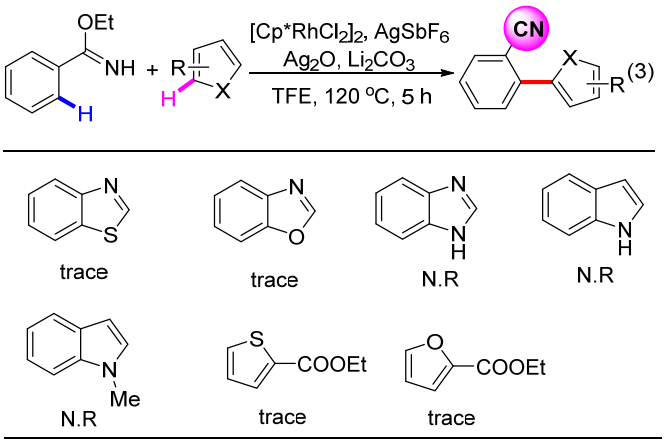
Entry	Cat.	Additive/[equiv.]	oxidant	Yield[b]/%
1	$[Cp^*IrCl_2]_2$	$AgSbF_6$	Ag_2O	8%
2	$Cp^*Co(CO)_2$	$AgSbF_6$	Ag_2O	N.R.
3	$Ru(p\text{-cymene})_2$	$AgSbF_6$	Ag_2O	N.R.
4	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2$	14%
5	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(acac)_2$	N.R.
6	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Ag_2CO_3	9%
7	$[Cp^*RhCl_2]_2$	$AgSbF_6$	$Cu(OAc)_2\ H_2O$	N.R.
8	$[Cp^*RhCl_2]_2$	$AgSbF_6$/NaOPiv	AgF	23%
9	$[Cp^*RhCl_2]_2$	$AgSbF_6$/NaOPiv	Ag_2CO_3	25%
10	$[Cp^*RhCl_2]_2$	$AgSbF_6$/HOAc	Ag_2O	N.R.
11	$[Cp^*RhCl_2]_2$	$AgSbF_6$/TsOH	Ag_2O	22%
12	$[Cp^*RhCl_2]_2$	AgOAc	Ag_2O	N.R.
13[c]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Ag_2O	N.R.
14[d]	$[Cp^*RhCl_2]_2$	$AgSbF_6$	Ag_2O	N.R.
15	$[Cp^*RhCl_2]_2$	--	Ag_2O	43%

[a] Reaction conditions unless otherwise specified:**1a** (0.1mmol), **2a** (0.12mmol), 5 mol% of catalyst, silver salts (30% mol), and oxidant (0.21 mmol) in DCE (0.5 mL) at 120 °C under Air for 5 h. 1-AdCOOH is the abbreviation of 1-adamantanecarboxylic acid. [b] Isolated yield. [c] 0.25 ml of DMF. [d] 0.25 ml of toluene.

3. Invalid examples

However, other heterocycles such as benzimidazole, benzoxazole, benzothiazole and N-methyl indole could not be tolerated under the optimized reaction conditions. In addition, ethyl thiophene-2-carboxylate or ethyl furan-2-carboxylate were not suitable substrates, probably due to the electronic effects (Scheme A).

Scheme A. Invalid substrates in the cascade reaction.



Scheme A

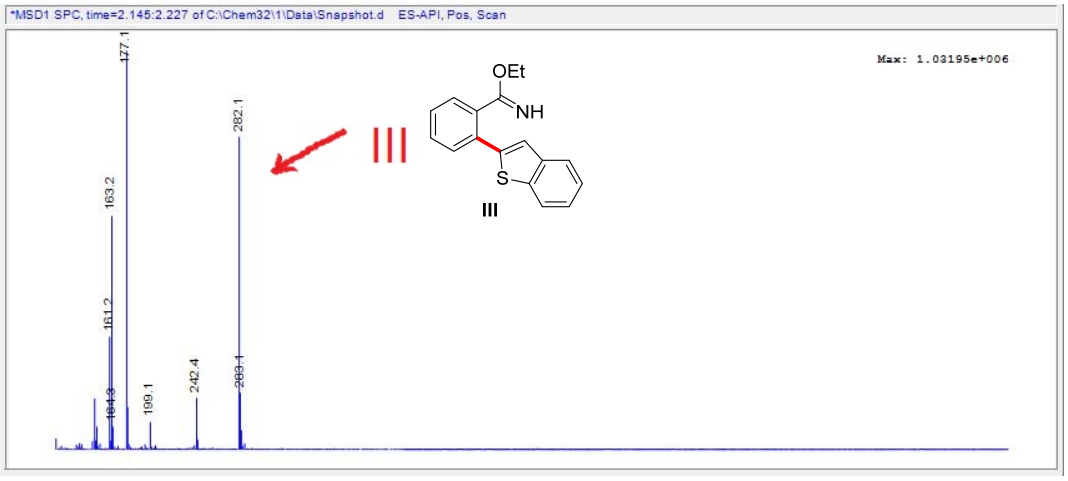
4. General procedure for synthesis of biheteroaryl-2-carbonitrile compounds

benzothiophene **1** (0.1 mmol), benzimidate **2** (0.12 mmol), $[Cp^*RhCl_2]_2$ (3 mg, 5 mol%), $AgSbF_6$ (5.2 mg, 30 mol%), Ag_2O (48.7 mg, 0.21 equiv.) and Li_2CO_3 (7.4 mg, 1 equiv.) were stirred in TFE (0.5 mL) under an air atmosphere at 120 °C for 1.5 h, then additional 0.1 mmol of **2** was added for 5 h. After completion, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:30) to give the product **3** and **4** as an off-white solid.

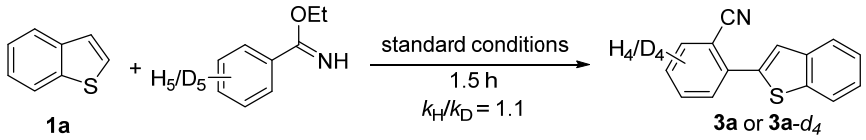
5. Mechanistic study

(1) Detection of the intermediate III

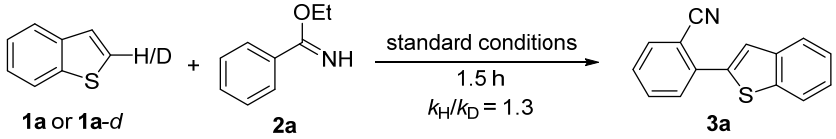
Benzothiophene **1a** (0.1 mmol), benzimidate **2a** (0.12 mmol), $[Cp^*RhCl_2]_2$ (3 mg, 5 mol%), $AgSbF_6$ (5.2 mg, 30 mol%), Ag_2O (48.7 mg, 0.21 equiv.) and Li_2CO_3 (7.4 mg, 1 equiv.) were stirred in TFE (0.5 mL) under an air atmosphere at 120 °C for 0.5 h. Then the reaction mixture was cooled to room temperature and analyzed by LC-MS without purification. The mass spectrum was obtained as below. LC-MS (ESI+): calculated for **III** m/z $[III + H]^+$ ($C_{17}H_{16}NOS$):282.1, found: 282.1



(2) Kinetic isotope experiments

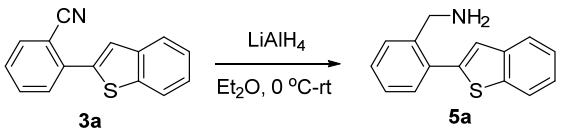


To a flask charged with benzothiophene **1a** (0.1 mmol), benzimidate **2a** or **2a**-d_5 (0.12 mmol), $[Cp^*RhCl_2]_2$ (3 mg, 5 mol%), $AgSbF_6$ (5.2 mg, 30 mol%), Ag_2O (48.7 mg, 0.21 equiv.) and Li_2CO_3 (7.4 mg, 1 equiv.) were stirred in TFE (0.5 mL). The reaction mixture was stirred at 120 °C for 1.5 h under air atmosphere. After cooled to room temperature, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:20) to give the desired product 7.6 mg of **3a** and 6.9 mg of **3a**-d_4. The KIE value of k_H/k_D= 1.1 was determined based on the product yield of **3a** and **3a**-d_4.

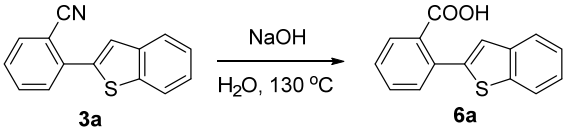


To a flask charged with benzothiophene **1a** or **1a**-*d* (0.1 mmol), benzimidate **2a** (0.12 mmol), $[Cp^*RhCl_2]_2$ (3 mg, 5 mol%), $AgSbF_6$ (5.2 mg, 30 mol%), Ag_2O (48.7 mg, 0.21 equiv.) and Li_2CO_3 (7.4 mg, 1 equiv.) were stirred in TFE (0.5 mL). The reaction mixture was stirred at 120 °C for 1.5 h under air atmosphere. After cooled to room temperature, the reaction mixture was purified by flash chromatography eluting with ethyl acetate and petroleum ether (1:20) to give the desired product 7.6 mg of **3a** and 6 mg of **3a** (from**1a**-*d*). The KIE value of k_H/k_D= 1.3 was determined based on the product yield of **3a**.

6. Synthetic application of 3

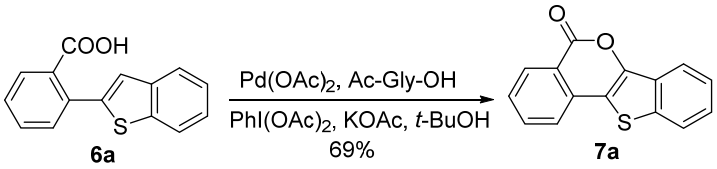


To a solution of 2-(benzo[b]thiophen-2-yl)benzonitrile **3a** (0.1 mmol, 23.5 mg) in Et_2O (0.5 mL) was added dropwise $LiAlH_4$ (0.4 mmol, 15.2 mg in 0.3 mL Et_2O) at 0°C and stirred for 0.5 h. 4 M NaOH was added slowly to until a clear solution was obtained. The Et_2O layer was separated and the aqueous phase was extracted with Et_2O (5 mL, 3 times). Combined the organic layers and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel with EtOAc. The product **5a** was obtained in 60% isolated yield as an off-white solid.

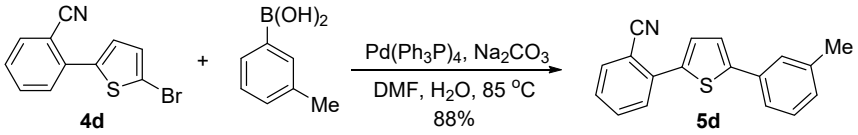


To a solution of 2-(benzo[b]thiophen-2-yl)benzonitrile **3a** (0.1 mmol, 23.5 mg) in ethylene glycol (2.5 mL) was added sodium hydroxide solution (120 mg NaOH in 2 mL water) and stirred at 130 °C to reflux overnight. After completion of the reaction, the mixture was cooled down to room temperature and extracted with DCM (5 mL, 3 times). Combined the organic layers and

dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel with EtOAc. The product **6a** was obtained in 82% isolated yield as white solid.



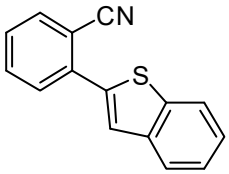
A flame-dried Schlenk tube with a magnetic stir bar was charged with *ortho*-carboxyl bi(hetero)arene **6a** (0.1 mmol), $Pd(OAc)_2$ (10.0 mol%), Ac-Gly-OH (20 mol %), $PhI(OAc)_2$ (2.0 equiv), KOAc (2.0 equiv) and *t*-BuOH (1 mL). The resulting mixture was heated at 120 ºC for 24 h. After completion, the reaction mixture was purified by column chromatography on silica gel to provide the desired product **7a**.



A flame-dried Schlenk tube with a magnetic stir bar was charged with 2-(5-bromothiophen-2-yl)benzonitrile **4d** (0.1 mmol), DMF (1 mL), 1M aqueous solution of sodium carbonate (0.25 mL) and boronic acid (1.1 mmol). The mixture was degassed with a steady stream of argon for 10min at room temperature. To this mixture, $Pd(Ph_3P)_4$ (0.1mmol) was added and the mixture was degassed with argon for 2 min after which it was heated under argon to 85 ºC for 3 h. After completion of the reaction, the mixture was extracted with EA (5 mL, 3 times). Combined the organic layers and dried over Na_2SO_4. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel. The product **5d** was obtained in 88% isolated yield as yellow oil.

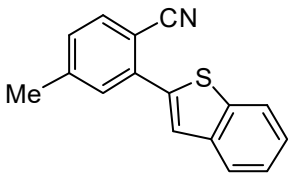
7. Characterization data for compounds

2-(benzo[b]thiophen-2-yl)benzonitrile (3a)



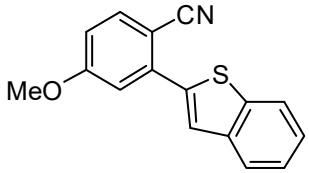
19.7 mg (84%); off-white solid; mp =109.3-113.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.88 – 7.84 (m, 2H), 7.78 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.71 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.64 (td, *J* = 7.7, 1.4 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.42 – 7.37 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.1, 139.1, 137.5, 134.4, 133.0, 130.2, 128.1, 125.2, 124.8, 124.5, 124.4, 122.1, 118.7, 110.4; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_9NNaS$: 258.0353, found 258.0358.

2-(benzo[b]thiophen-2-yl)-4-methylbenzonitrile (3b)



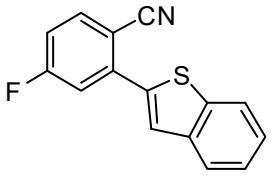
15.7 mg (63%); off-white solid; mp = 132.9-136.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 3H), 7.62 – 7.57 (m, 2H), 7.47 – 7.33 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 140.0, 139.3, 138.6, 134.7, 134.7, 133.9, 130.1, 125.1, 124.7, 124.4, 123.9, 122.1, 118.8, 110.2, 20.8; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{16}H_{11}NNaS$: 272.0510, found 272.0504.

2-(benzo[b]thiophen-2-yl)-4-methoxybenzonitrile (3c)



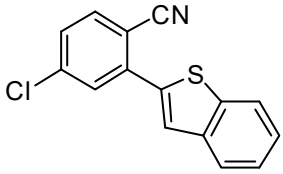
24.4 mg (92%); off-white solid; mp = 127.3-131.8 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.83 (m, 3H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.43 – 7.35 (m, 2H), 7.18 (d, *J* = 2.5 Hz, 1H), 6.94 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)δ 162.8, 140.2, 140.1, 139.4, 139.1, 136.2, 125.3, 124.8, 124.5, 124.5, 122.1, 119.1, 115.7, 114.0, 102.4, 55.7; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{16}H_{11}NNaOS$: 288.0459, found 288.0459.

2-(benzo[b]thiophen-2-yl)-4-fluorobenzonitrile (3d)



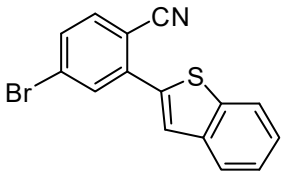
14.4 mg (57%); off-white solid; mp = 120.5-123.1 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.80 (m, 3H), 7.62 – 7.57 (m, 2H), 7.47 – 7.33 (m, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7 (d, *J* = 256Hz), 140.5(d, *J* = 10Hz), 140.1, 140.0, 137.7 (d, *J* =2Hz), 136.8 (d, *J* = 9Hz), 125.7, 125.1, 125.0, 124.7, 122.2, 118.1, 115.2 (d, *J* = 20Hz), 106.6, 99.9 (d, *J* = 17Hz); HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_8FNNaS$: 276.0259, found 276.0258.

2-(benzo[b]thiophen-2-yl)-4-chlorobenzonitrile (3e)



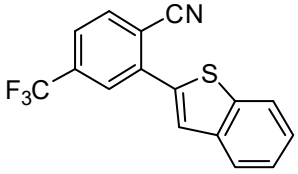
21.5 mg (80%); off-white solid; mp = 122.0-127.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.89 – 7.85 (m, 2H), 7.73 – 7.69 (m, 2H), 7.44 – 7.39 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.0, 139.6, 139.2, 137.6, 135.5, 130.3, 128.4, 125.7, 125.2, 125.0, 124.7, 122.2, 118.0, 108.8; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_8ClNNaS$: 291.9964, found 291.9965.

2-(benzo[b]thiophen-2-yl)-4-bromobenzonitrile (3f)



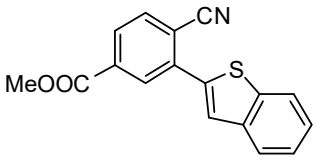
25.3 mg (81%); off-white solid; mp = 146.1-154.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.84 (m, 4H), 7.63 (d, *J* = 8.3 Hz, 1H), 7.58 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.45 – 7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.0, 139.2, 137.5, 135.4, 133.2, 131.3, 128.1, 125.7, 125.2, 125.0, 124.7, 122.2, 118.1, 109.3; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_8BrNNaS$: 335.9459, found 335.9457.

2-(benzo[b]thiophen-2-yl)-4-(trifluoromethyl)benzonitrile (3g)



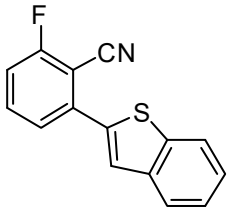
19.1 mg (63%); off-white solid; mp = 84.9-93.3 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.94 (d, *J* = 2.4 Hz, 1H), 7.93 – 7.87 (m, 3H), 7.70 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.45 – 7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 140.0, 138.6, 137.4, 135.1, 134.9 (d, *J* = 33Hz), 127.0 (q, *J* = 3Hz), 125.8, 125.5, 125.1, 124.8, 124.7 (q, *J* = 3Hz), 122.9 (q, *J* = 270Hz), 122.3, 117.5, 113.8; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{16}H_8F_3NNaS$: 326.0227, found 326.0228.

methyl 3-(benzo[b]thiophen-2-yl)-4-cyanobenzoate (3h)



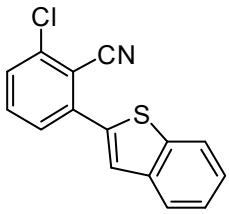
14.1 mg (48%); off-white solid; mp = 151.5-155.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 1.7 Hz, 1H), 8.07 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.93 (s, 1H), 7.91 – 7.85 (m, 3H), 7.44 – 7.39 (m, 2H), 3.99 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.2, 140.3, 140.1, 137.9, 134.6, 134.2, 131.0, 128.7, 125.6, 125.0, 125.0, 124.7, 122.2, 118.0, 114.1, 52.9; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{17}H_{11}NNaO_2S$: 316.0408, found 316.0410.

2-(benzo[b]thiophen-2-yl)-6-fluorobenzonitrile (3i)



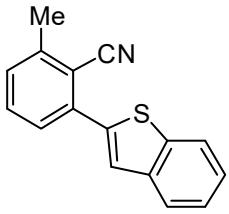
11.9 mg (47%);off-white solid; mp = 118.0-124.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.88 (dt, *J* = 9.6, 3.4 Hz, 2H), 7.63 (td, *J* = 8.1, 5.7 Hz, 1H), 7.52 (d, *J* = 7.9 Hz, 1H), 7.42 (q, *J* = 5.0, 4.4 Hz, 2H), 7.21 (t, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6 (d, *J* = 258Hz), 140.2, 140.1, 139.3, 137.9 (d, *J* = 2Hz), 134.5 (d, *J* = 9Hz), 125.7, 125.7, 125.1, 125.0, 124.7, 122.1, 115.2 (d, *J* = 20Hz), 113.5, 99.9 (d, *J* = 17Hz); HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_8FNNaS$: 276.0259, found 276.0258.

2-(benzo[b]thiophen-2-yl)-6-chlorobenzonitrile (3j)



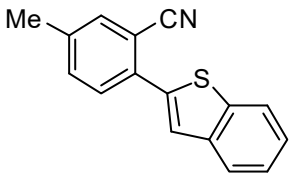
19.1 mg (71%); off-white solid; mp = 149.5-158.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.89 – 7.85 (m, 2H), 7.61 (dd, *J* = 7.7, 1.5 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.51 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.44 – 7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.0, 139.9, 138.9, 138.1, 133.4, 129.0, 128.4, 125.6, 125.2, 125.0, 124.7, 122.1, 115.6, 111.4; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_8ClNNaS$: 291.9964, found 291.9966

2-(benzo[b]thiophen-2-yl)-6-methylbenzonitrile (3k)



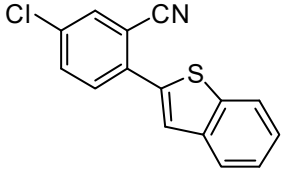
13.7 mg (55%); off-white solid; mp = 123.4-127.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 3H), 7.56 – 7.49 (m, 2H), 7.43 – 7.35 (m, 2H), 7.32 (t, *J* = 4.4 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.2, 140.2, 139.6, 137.9, 132.4, 129.6, 127.7, 125.1, 124.7, 124.4, 124.4, 122.1, 117.5, 111.2, 21.2; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{16}H_{11}NNaS$: 272.0510, found 272.0507.

2-(benzo[b]thiophen-2-yl)-5-methylbenzonitrile (3l)



11.7 mg (47%);off-white solid; mp = 48.2-56.2 °C; **1**H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 9.3 Hz, 4H), 7.52 (d, *J* = 4.8 Hz, 2H), 7.43 – 7.35 (m, 4H), 7.34 – 7.29 (m, 1H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.04, 140.23, 140.06, 139.32, 137.32, 134.38, 130.89, 129.03, 125.19, 124.78, 124.46, 124.30, 122.10, 118.97, 107.53, 21.83; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{16}H_{11}NNaS$: 272.0510, found 272.0504.

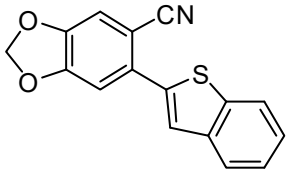
2-(benzo[b]thiophen-2-yl)-5-chlorobenzonitrile (3m)



13.7 mg (51%); off-white solid; mp = 151.4-155.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.85 (m, 3H), 7.76 (d, *J* = 2.1 Hz, 1H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.61 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.42 – 7.38 (m, 2H);

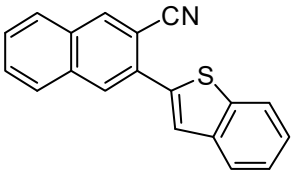
^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 140.1, 137.9, 136.1, 134.2, 133.9, 133.4, 131.4, 125.5, 125.0, 124.8, 124.6, 122.1, 117.4, 111.8; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_8ClNNaS$: 291.9964, found 291.9965.

6-(benzo[b]thiophen-2-yl)benzo[d][1,3]dioxole-5-carbonitrile (3n)



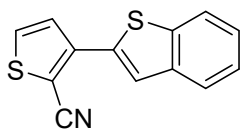
17.9 mg (64%); off-white solid; mp = 103.8-106.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.90 – 7.84 (m, 2H), 7.43 – 7.34 (m, 3H), 6.87 (d, *J* = 8.1 Hz, 1H), 6.18 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.4, 145.7, 140.4, 139.2, 132.8, 130.6, 126.0, 125.3, 124.6, 124.4, 122.1, 119.1, 118.8, 108.3, 104.1, 102.4; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{16}H_9NNaO_2S$: 302.0252, found 302.0254.

3-(benzo[b]thiophen-2-yl)-2-naphthonitrile (3o)



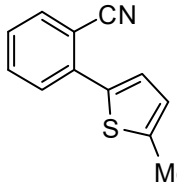
21.4 mg (75%); off-white solid; mp = 172.0-175.7 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 8.14 (s, 1H), 7.95 – 7.86 (m, 5H), 7.65 (ddd, *J* = 15.2, 14.1, 7.2 Hz, 2H), 7.44 – 7.37 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.4, 140.0, 139.4, 136.8, 134.6, 131.7, 131.4, 129.8, 129.7, 128.3, 128.1, 128.0, 125.1, 124.8, 124.4, 124.3, 122.1, 118.9, 108.6; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{19}H_{11}NNaS$: 308.0510, found 308.0519.

3-(benzo[b]thiophen-2-yl)thiophene-2-carbonitrile (3p)



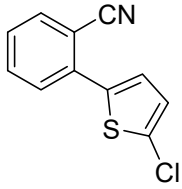
8.4 mg (35%); off-white solid; mp = 90.3-96.0 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.84 (dt, *J* = 7.0, 2.3 Hz, 2H), 7.59 (d, *J* = 5.2 Hz, 1H), 7.39 (td, *J* = 5.2, 2.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 139.9, 139.7, 134.8, 132.2, 127.9, 125.6, 125.0, 124.5, 123.7, 122.2, 114.7, 103.7; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{13}H_7NNaS_2$: 263.9918, found 263.9916.

2-(5-methylthiophen-2-yl)benzonitrile (4a)



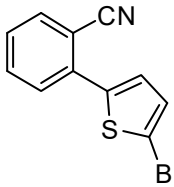
10.9 mg (55%); off-white solid; mp = 115.7-124.4 ºC;^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.59 – 7.54 (m, 2H), 7.45 (d, *J* = 3.6 Hz, 1H), 7.33 (ddd, *J* = 7.7, 5.4, 3.4 Hz, 1H), 6.81 (dq, *J* = 3.5, 1.1 Hz, 1H), 2.54 (d, *J* = 1.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 137.9, 137.0, 134.3, 132.9, 129.3, 127.7, 127.0, 126.6, 119.0, 109.5, 15.4; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{12}H_9NNaS$: 222.0353, found 222.0355.

2-(5-chlorothiophen-2-yl)benzonitrile (4b)



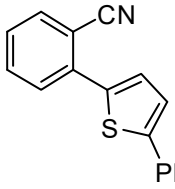
10.5 mg (48%); off-white solid; mp = 102.1-109.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.60 (td, *J* = 7.7, 1.4 Hz, 1H), 7.53 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.44 – 7.37 (m, 2H), 6.98 (d, *J* = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 136.7, 134.4, 133.1, 132.1, 129.4, 127.9, 127.4, 127.1, 118.5, 110.0; HRMS (EI) m/z $[M + Na]^+$ $C_{11}H_6ClNNaS$: 241.9807, found 241.9827.

2-(5-bromothiophen-2-yl)benzonitrile (4c)



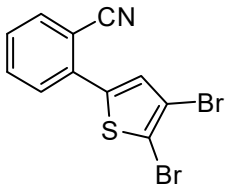
10.5 mg (40%); off-white solid; mp = 172.0-175.7 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.60 (td, *J* = 7.9, 1.3 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.40 (ddd, *J* = 7.1, 6.7, 2.6 Hz, 2H), 7.12 (d, *J* = 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.6, 134.5, 133.3, 123.0, 129.3, 128.7, 118.1, 115.0, 113.2, 110.; HRMS (EI) m/z $[M + Na]^+$calculated for $C_{11}H_6BrNNaS$:285.9302, found 285.9302.

2-(5-phenylthiophen-2-yl)benzonitrile (4d)



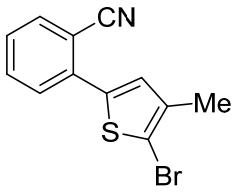
18.0 mg (69%); off-white solid; mp = 111.0-120.8 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.69 – 7.63 (m, 4H), 7.61 (td, *J* = 7.7, 1.4 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.37 – 7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 138.5, 137.4, 134.4, 133.7, 133.0, 129.3, 129.0, 128.6, 128.1, 127.5, 126.0, 124.2, 118.9, 109.7; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{17}H_{11}NNaS$:284.0510, found 284.0510.

2-(4,5-dibromothiophen-2-yl)benzonitrile (4e)



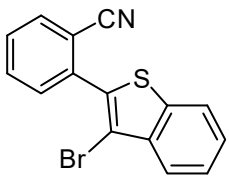
13.6 mg (40%); off-white solid; mp = 155.3-159.9 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.7 Hz, 1H), 7.63 (t, *J* = 7.7 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.6, 134.5, 133.3, 130.0, 129.0, 128.7, 118.1, 115.0, 113.2, 110.1; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{11}H_5Br_2NNaS$: 363.8407, found 363.8403.

2-(5-bromo-4-methylthiophen-2-yl)benzonitrile (4f)



14.1 mg (51%); off-white solid; mp = 114.2-121.5 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.55 (m, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.39 (td, *J* = 7.7, 1.1 Hz, 1H), 7.32 (s, 1H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.6, 136.8, 134.4, 133.1, 129.4, 129.2, 127.8, 118.6, 111.7, 109.6, 15.4; HRMS (EI) m/z $[M + Na]^+C_{12}H_8BrNNaS$: 299.9459, found 299.9456

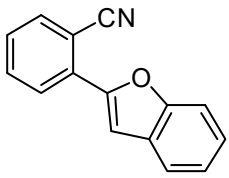
2-(3-bromobenzo[b]thiophen-2-yl)benzonitrile (4g)



18.2 mg (58%); off-white solid; mp = 155.9-162.3 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.88 (m, 1H), 7.87 – 7.81 (m, 2H), 7.71 (td, *J* = 7.7, 1.3 Hz, 1H), 7.63 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.60 – 7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.1, 136.7, 133.7, 133.5, 132.6, 132.0, 129.4, 126.2, 125.6, 124.1, 122.3, 117.5, 114.0, 109.1; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_8BrNNaS$:335.9459, found 335.9460.

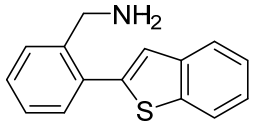
2-(benzofuran-2-yl)benzonitrile (4h)

7.0 mg (32%); off-white solid; mp = 75.0-83.4 ºC; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.72 (s, 1H), 7.70 – 7.64 (m, 2H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)



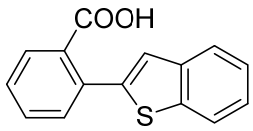
δ 154.7, 151.2, 134.4, 133.0, 133.0, 128.8, 128.2, 127.1, 125.7, 123.4, 122.0, 118.8, 111.3, 108.1, 106.8; HRMS (EI) m/z $[M + Na]^+$ calculated for $C_{15}H_9NNaO$:242.0582, found 242.0581.

(2-(benzo[b]thiophen-2-yl)phenyl)methanamine (5a)



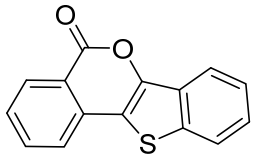
14.3 mg (60%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.82 (m, 1H), 7.79 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.51 (dd, *J* = 7.5, 1.4 Hz, 1H), 7.47 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.37 (ddtt, *J* = 14.7, 7.3, 3.8, 2.0 Hz, 4H), 7.29 (s, 1H), 4.89 (s, 2H), 4.07 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.6, 140.1, 140.0, 133.7, 131.3, 129.0, 128.8, 127.6, 124.6, 124.4, 123.7, 123.6, 122.0, 42.9; HRMS (EI) m/z $[M + H]^+$ calculated for $C_{15}H_{14}NS$: 240.0847, found 240.0845.

2-(benzo[b]thiophen-2-yl)benzoic acid (6a)



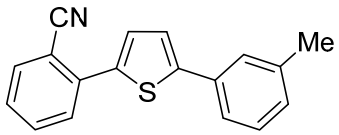
20.8 mg (82%); white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.83 (m, 1H), 7.79 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.72 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.56 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.52 (dd, *J* = 7.4, 1.6 Hz, 1H), 7.50 – 7.45 (m, 1H), 7.43 (s, 1H), 7.37 (td, *J* = 6.9, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 141.0, 140.3, 140.1, 135.3, 131.9, 130.9, 130.3, 128.8, 128.6, 124.7, 124.7, 123.9, 123.9, 122.1;

5H-benzo[4,5]thieno[3,2-c]isochromen-5-one (7a)



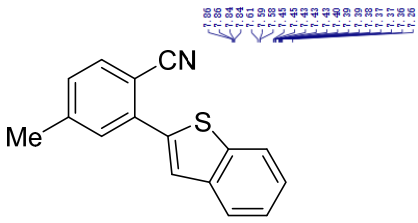
17.4 mg (69%); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dt, *J* = 8.0, 1.5 Hz, 1H), 8.01 (dt, *J* = 6.5, 2.0 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.60 (dd, *J* = 7.8, 2.3 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.50 – 7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.80, 144.94, 136.47, 135.32, 133.90, 131.19, 129.65, 128.40, 127.00, 125.33, 123.19, 122.84, 121.12, 119.82, 115.26.

2-(5-(m-tolyl)thiophen-2-yl)benzonitrile (5d)

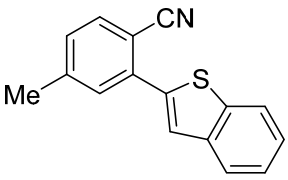


24 mg (88%); light yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dt, *J* = 8.0, 1.5 Hz, 1H), 8.01 (dt, *J* = 6.5, 2.0 Hz, 1H), 7.85 – 7.75 (m, 2H), 7.60 (dd, *J* = 7.8, 2.3 Hz, 1H), 7.54 (t, *J* = 7.7 Hz, 1H), 7.50 – 7.42 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.80, 144.94, 136.47, 135.32, 133.90, 131.19, 129.65, 128.40, 127.00, 125.33, 123.19, 122.84, 121.12, 119.82, 115.26.

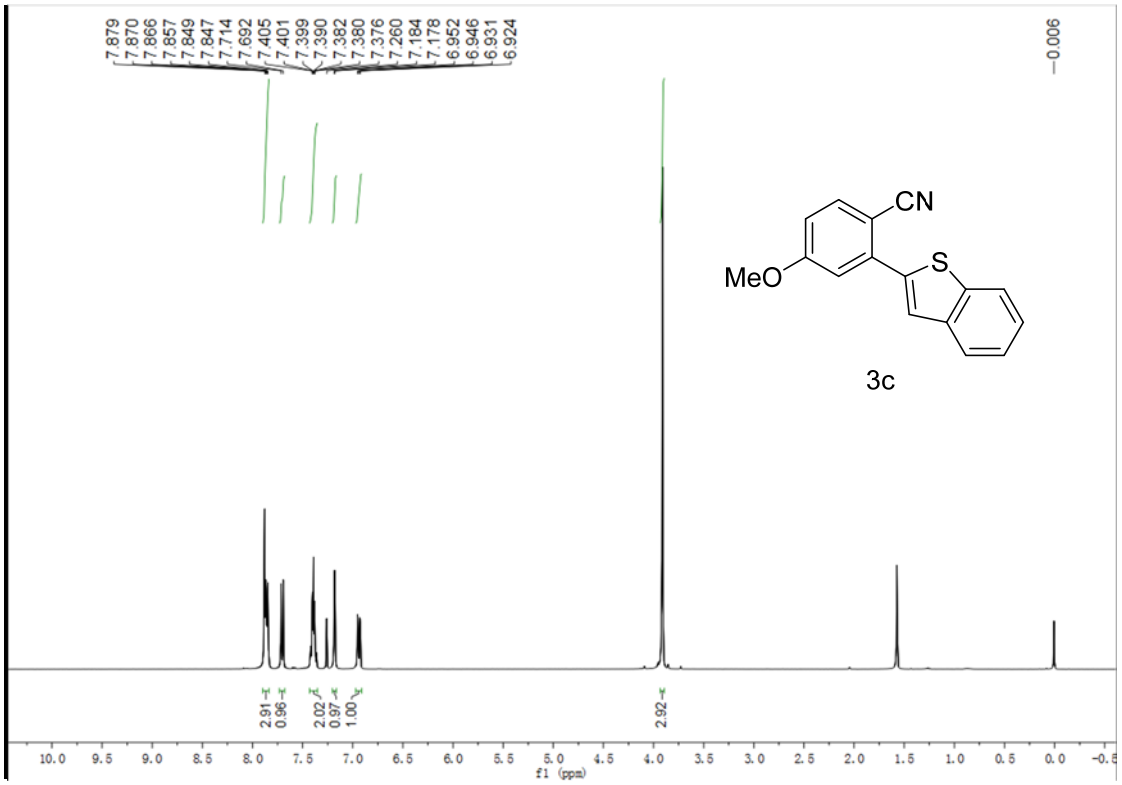
8. ^{1}H and ^{13}C NMR spectra.



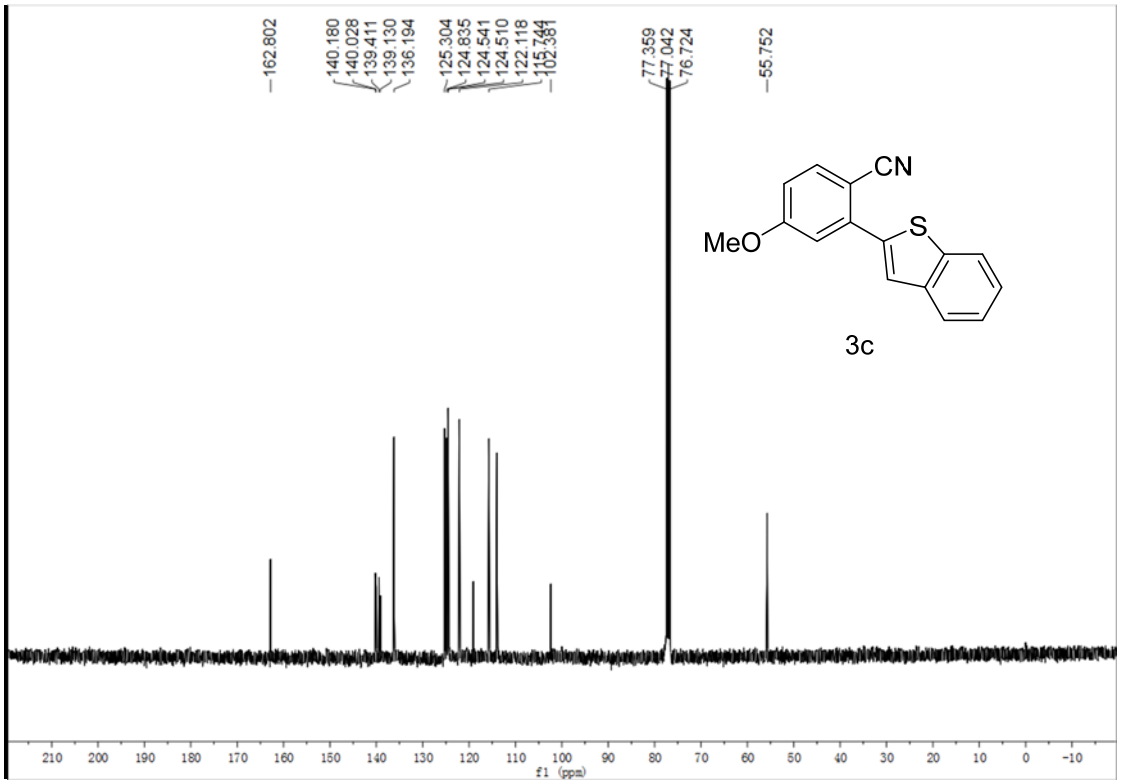
3b



3b


7.879
7.870
7.866
7.857
7.849
7.847
7.714
7.692
7.405
7.401
7.399
7.390
7.382
7.380
7.376
7.260
7.184
7.178
6.952
6.946
6.931
6.924
0.006
CN
MeO
S
2.91
0.96
2.02
0.97
1.00
2.92
f1 (ppm)

3c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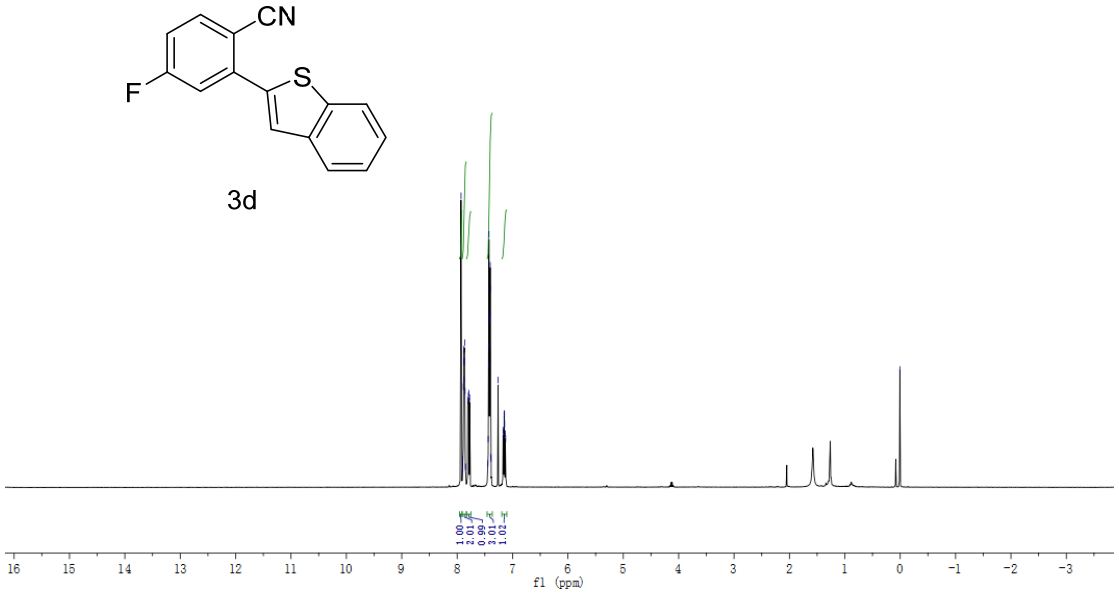
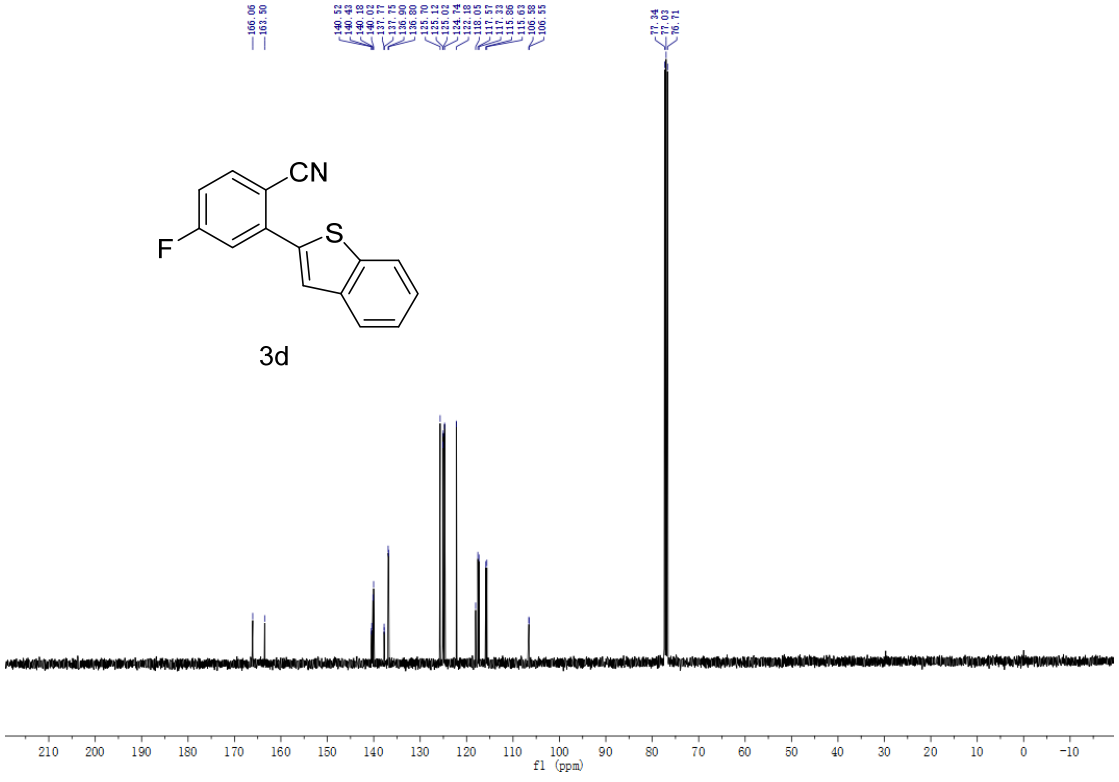
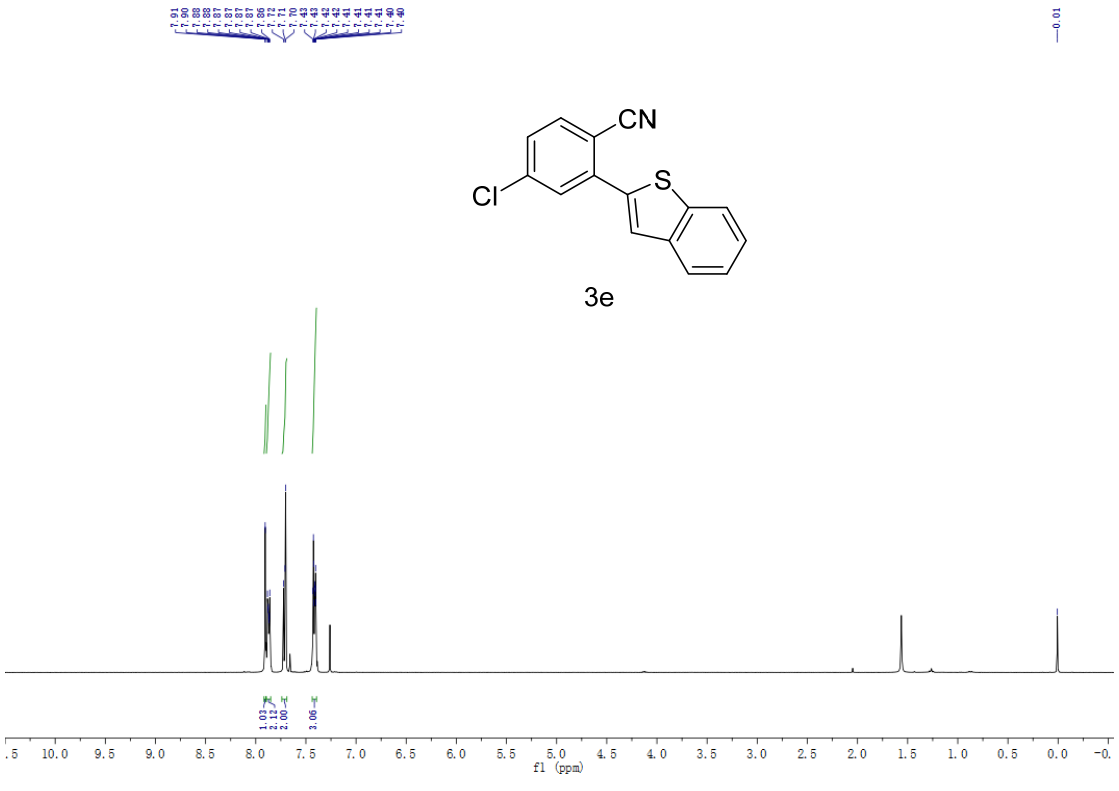
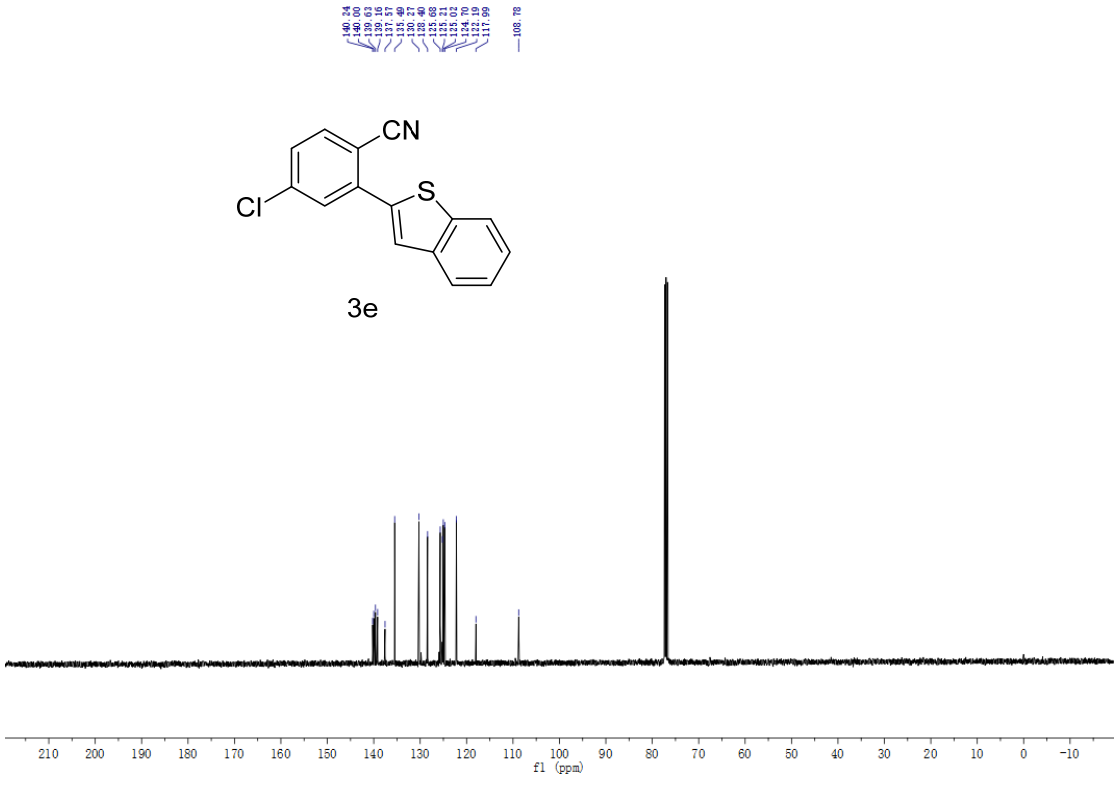
140.180
140.028
139.411
139.130
136.194
125.304
124.835
124.541
124.510
122.118
115.744
102.381
77.359
77.042
76.724
55.752
CN
MeO
S
f1 (ppm)

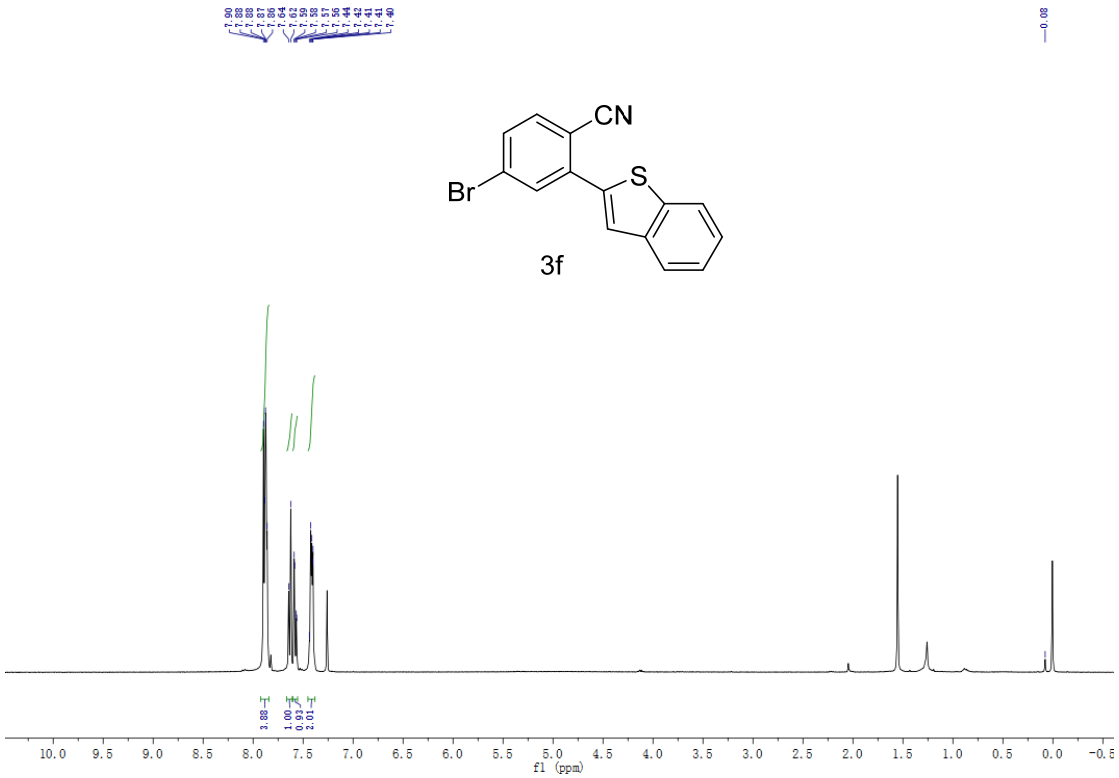
3c

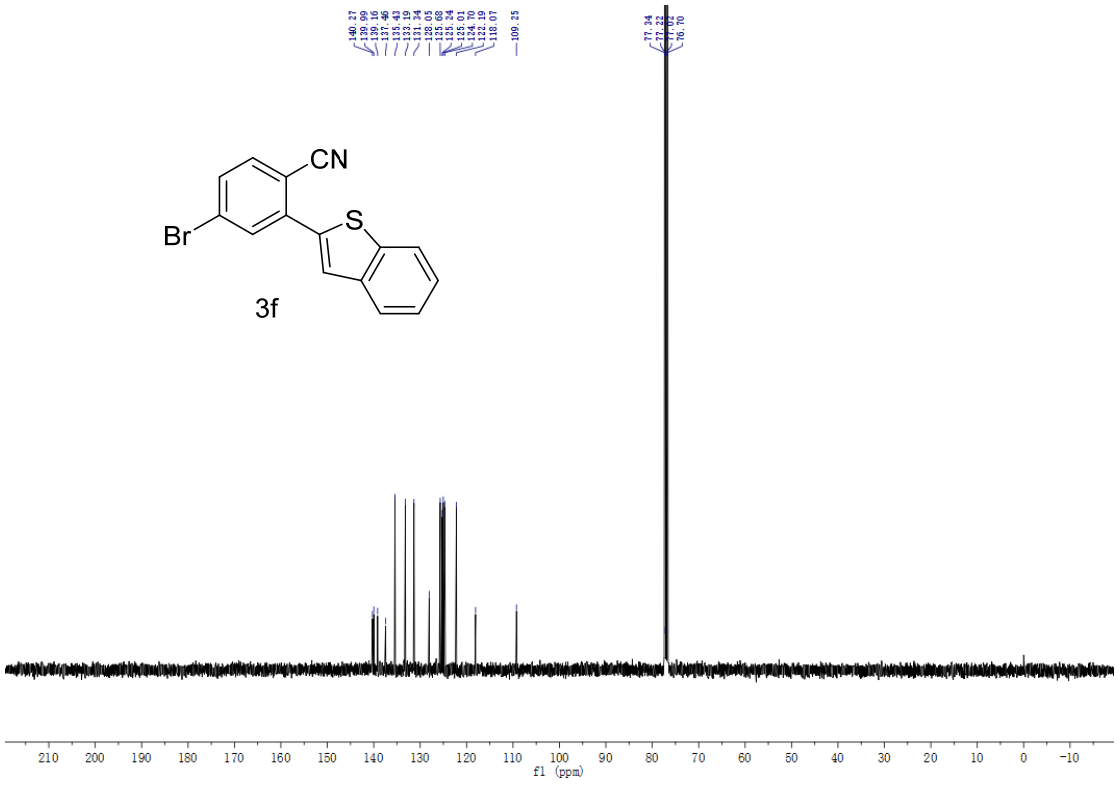

CN
F
S
3d
1.00
2.01
0.99
3.01
1.01
f1 (ppm)

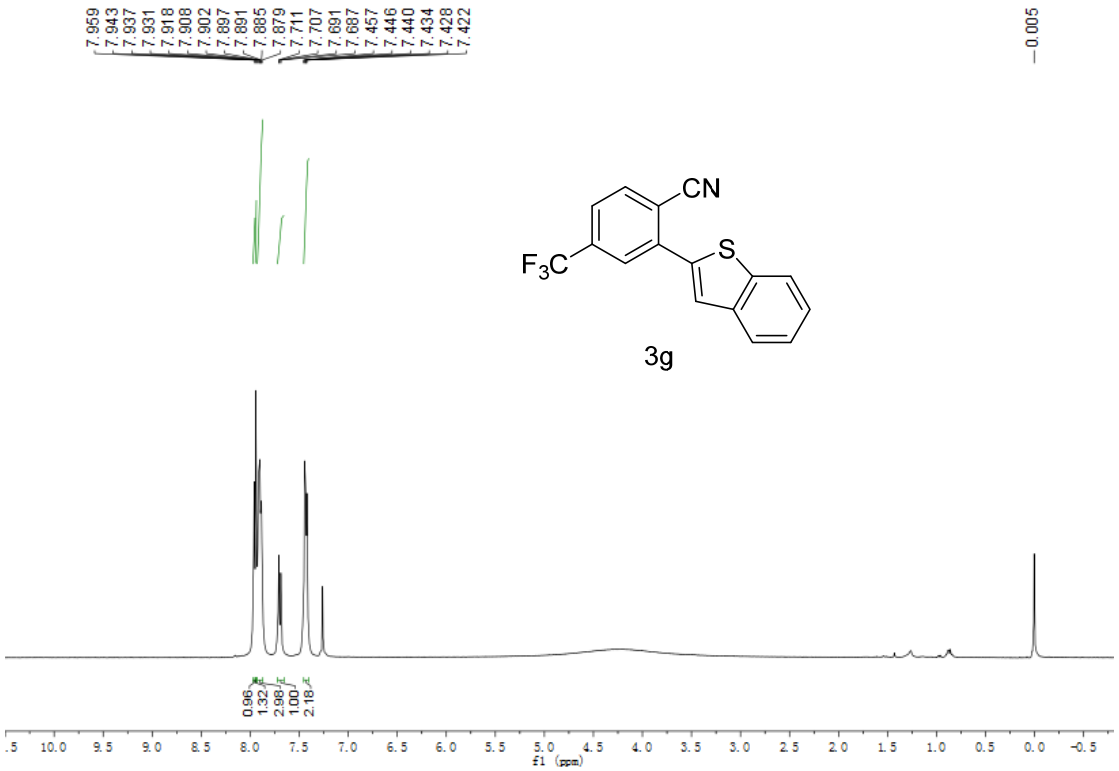

CN
F
S
3d
f1 (ppm)


CN
Cl
S
3e
1.03
2.12
2.00
3.06
f1 (ppm)


CN
Cl
S
3e
f1 (ppm)


CN
Br
S
3f
3.88
1.00
0.93
2.01
f1 (ppm)


CN
Br
S
3f
f1 (ppm)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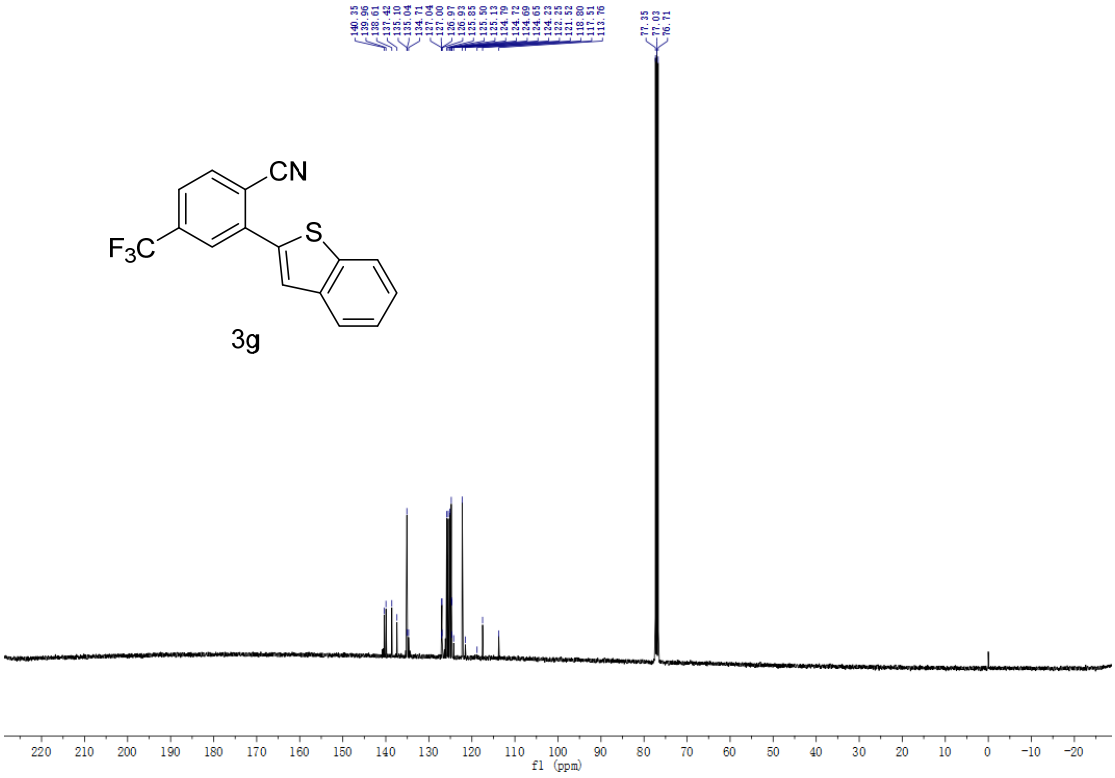
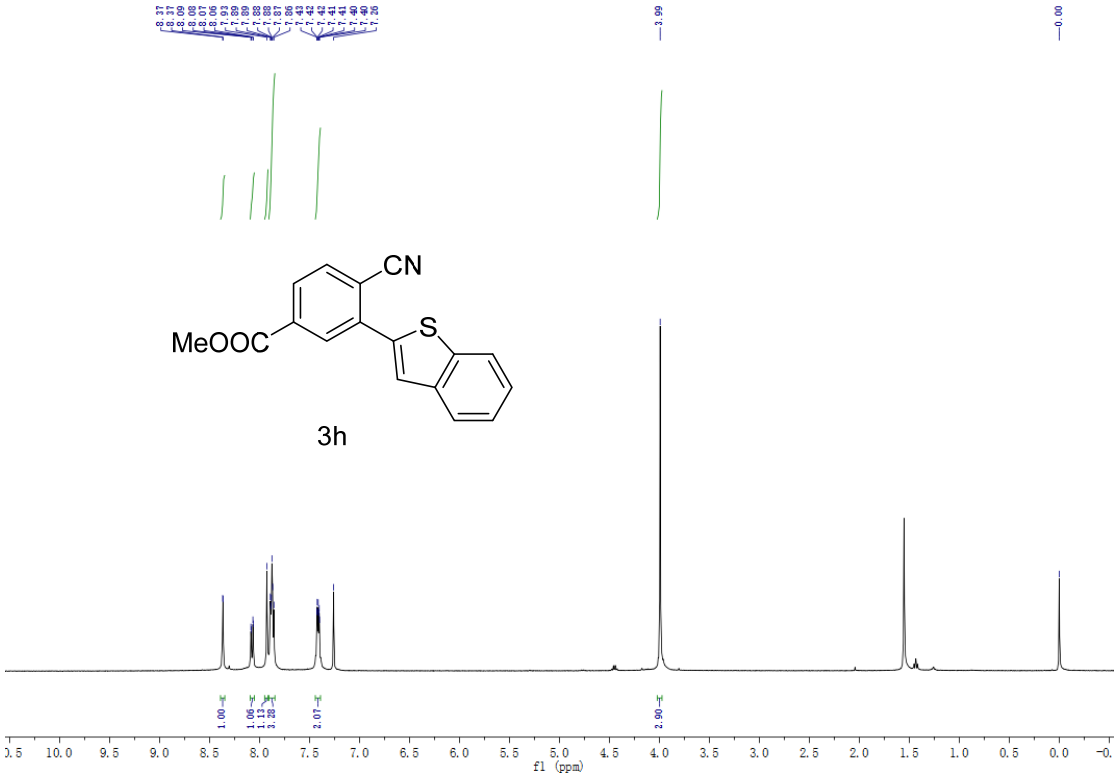
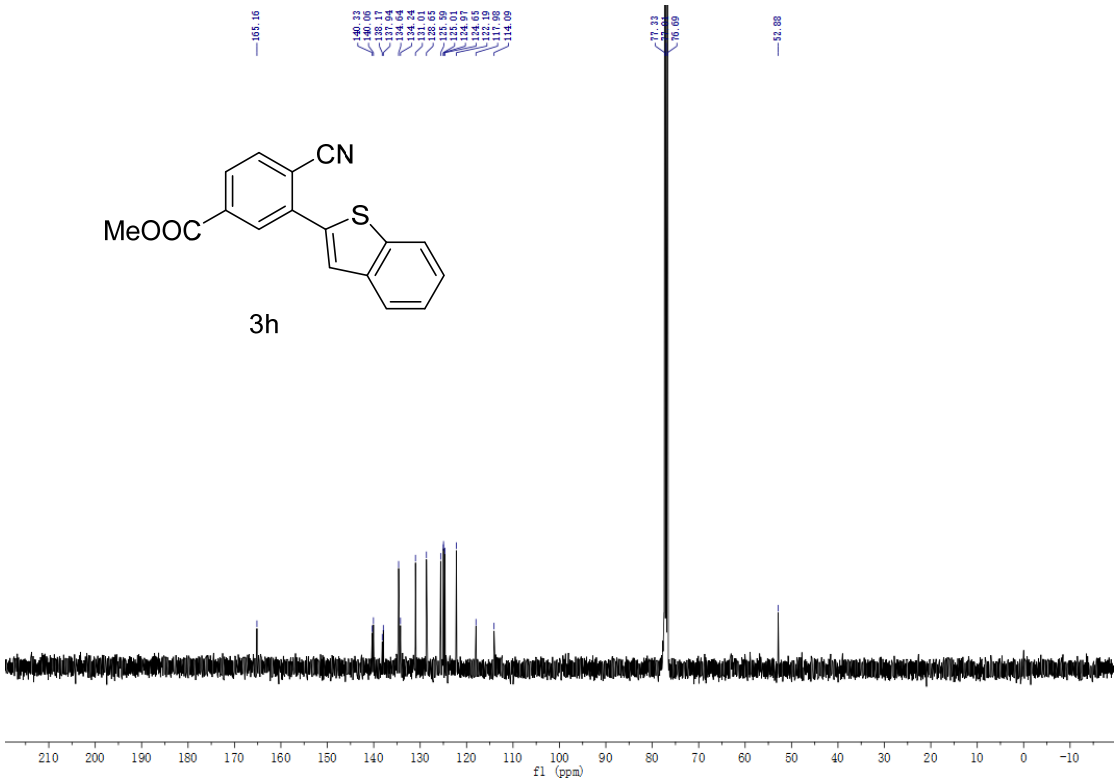
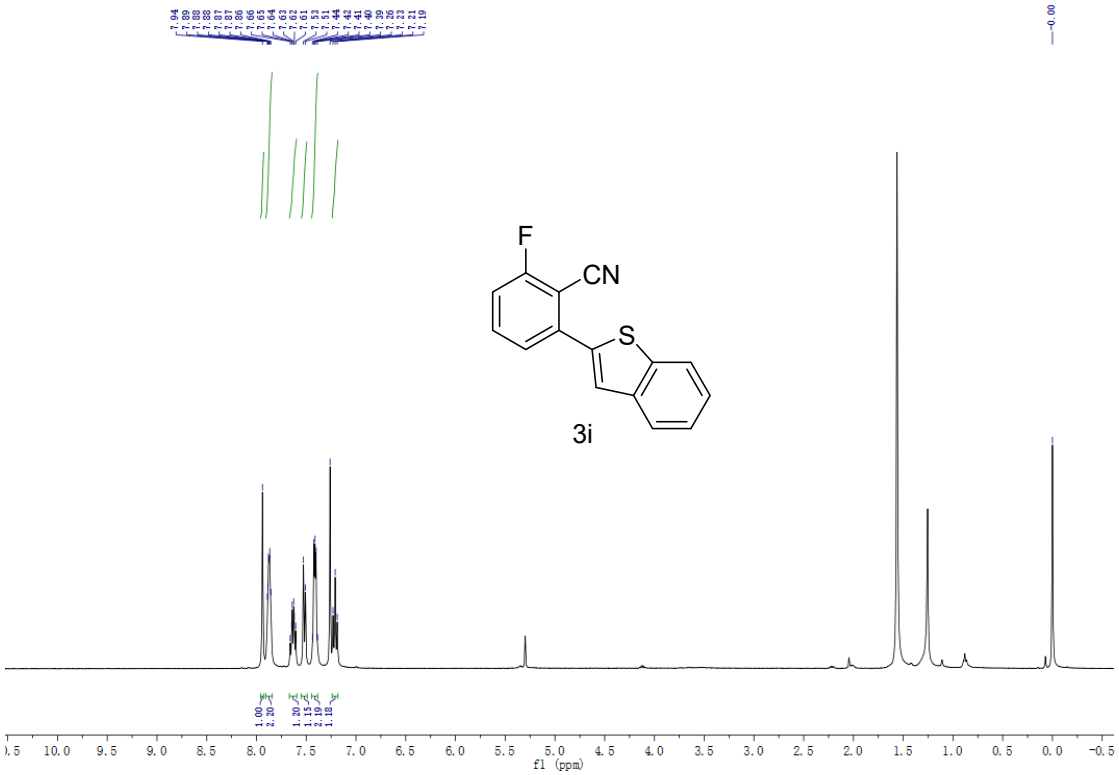
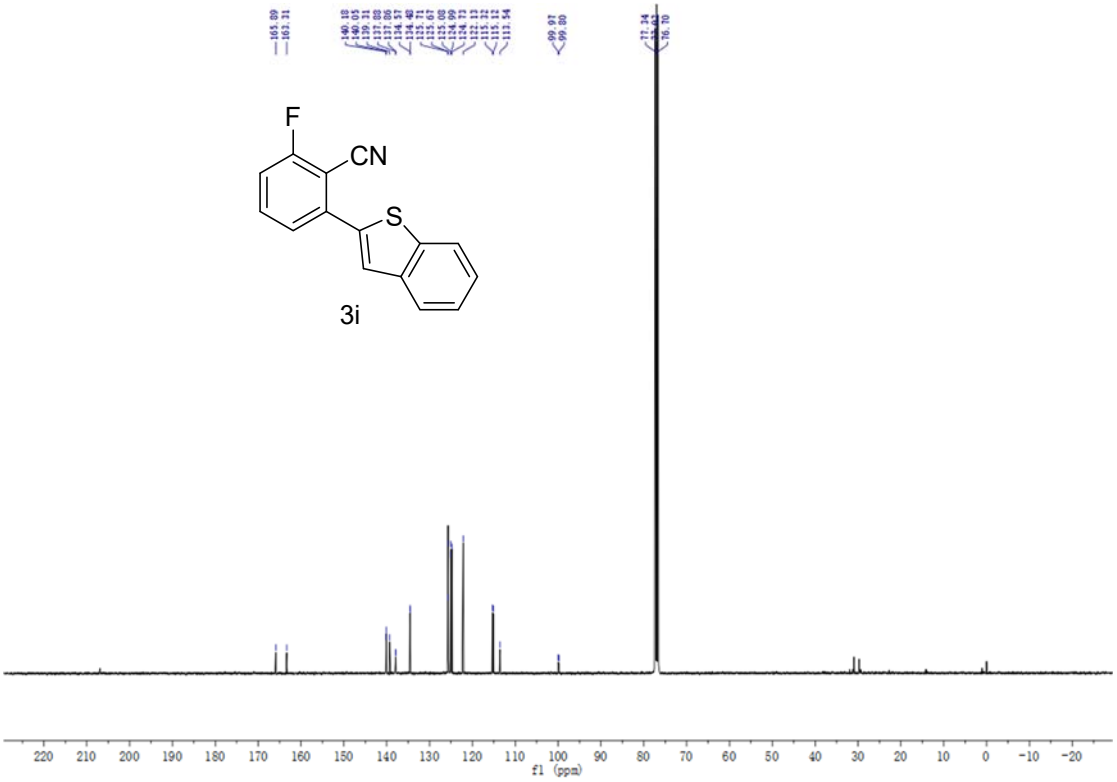
7.943
7.937
7.931
7.918
7.908
7.902
7.897
7.891
7.885
7.879
7.711
7.707
7.691
7.687
7.457
7.446
7.440
7.434
7.428
7.422
0.005
CN
F3C
S
3g
0.96
1.32
2.98
1.00
2.18
f1 (ppm)

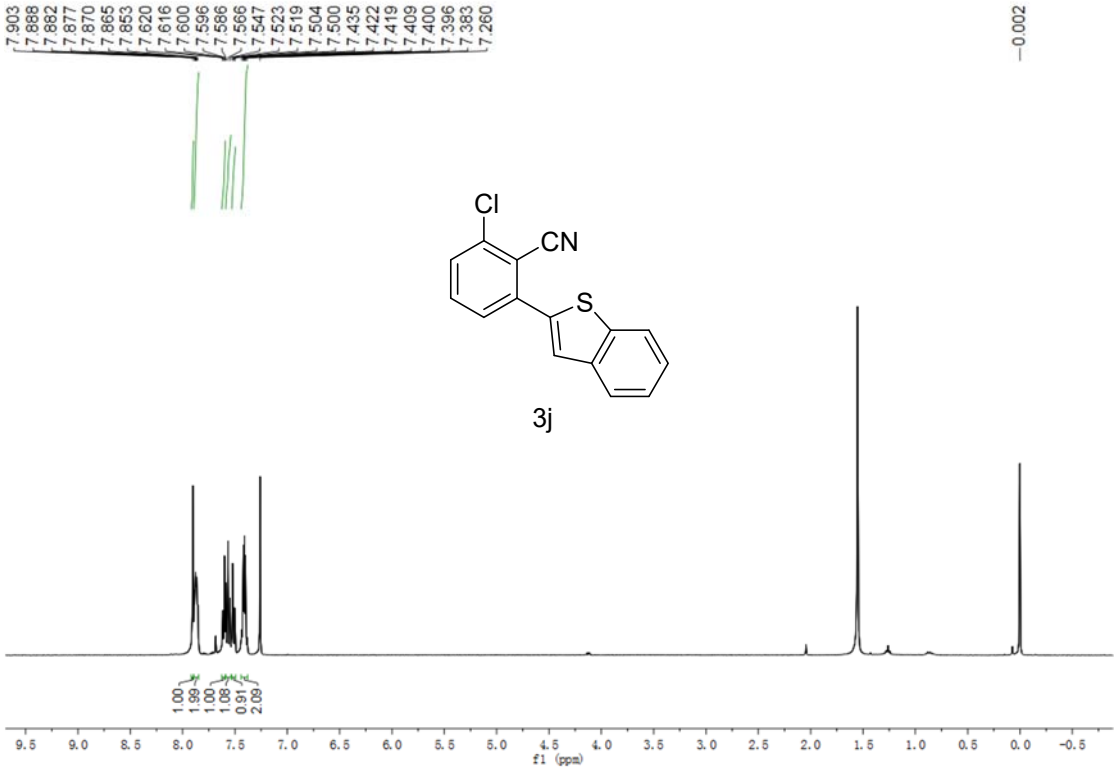

CN
F3C
S
3g
77.35
77.03
76.71
f1 (ppm)

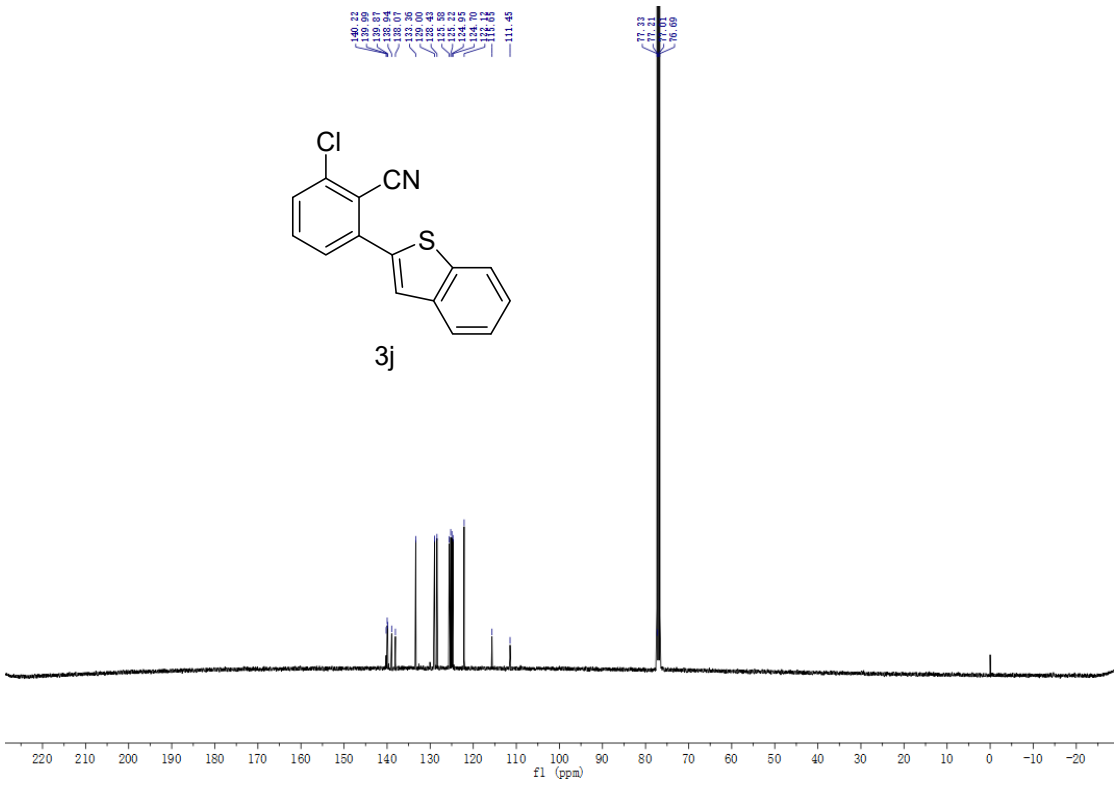

CN
MeOOC
S
3h
f1 (ppm)

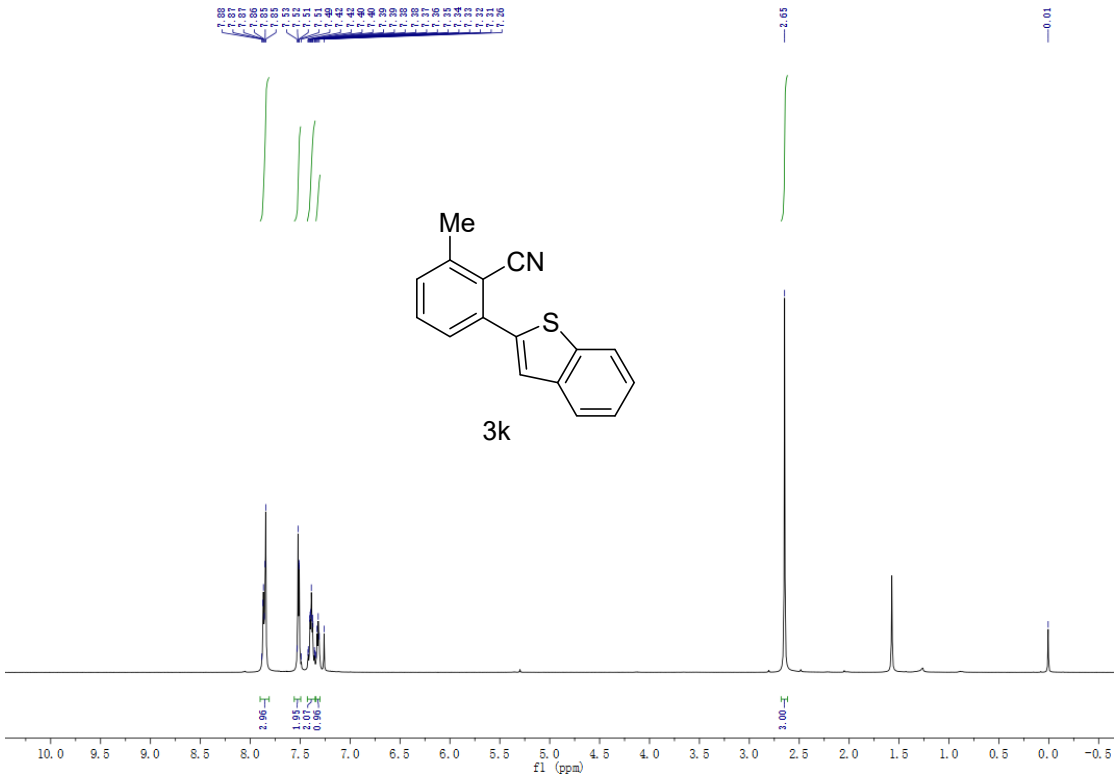

CN
MeOOC
S
3h
f1 (ppm)

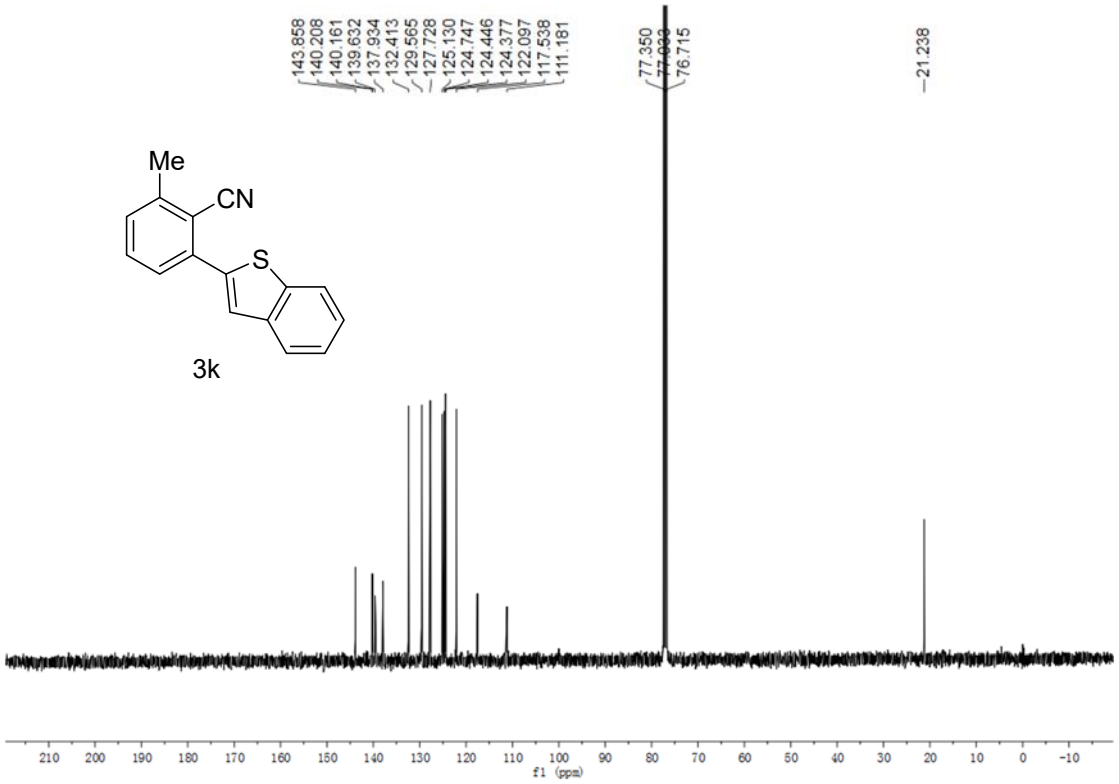

F
CN
S
3i
f1 (ppm)

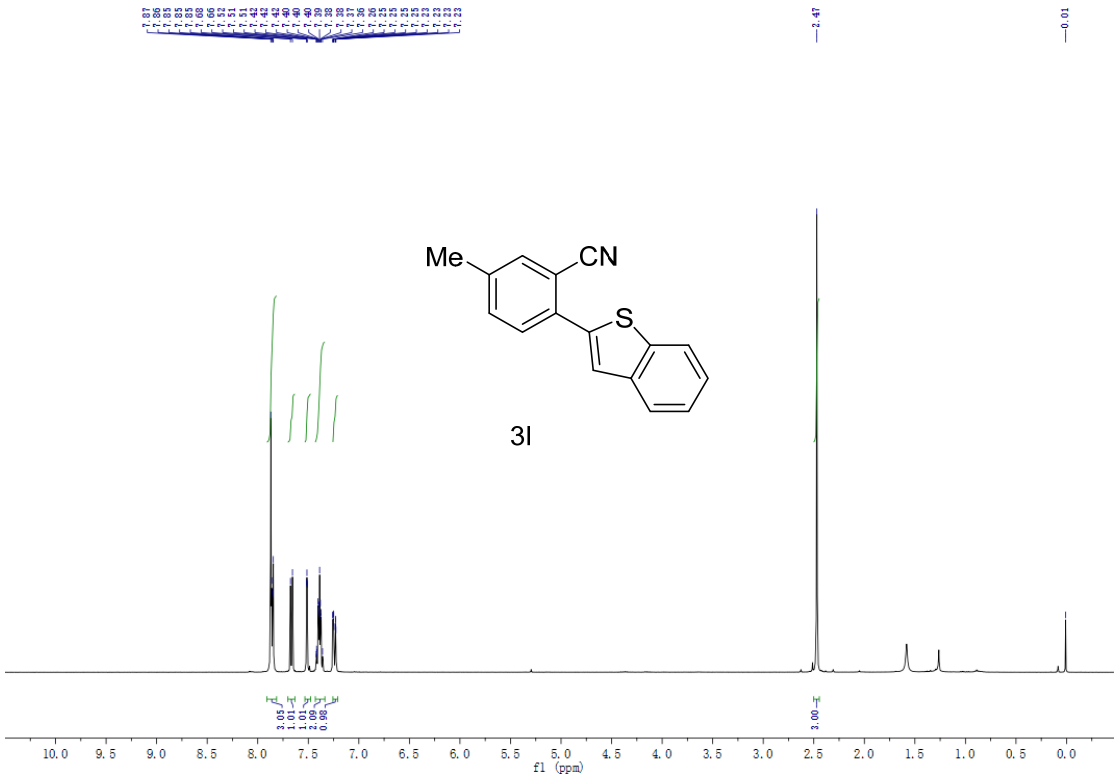

F
CN
S
3i
f1 (ppm)

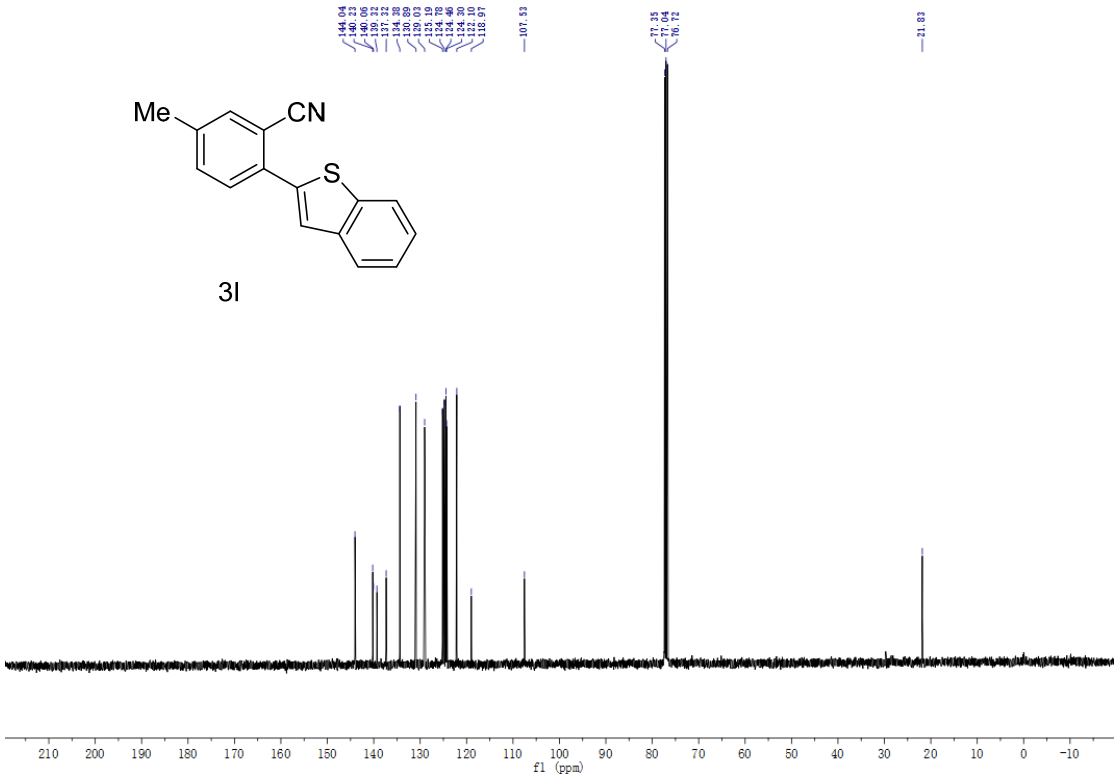

7.903
7.888
7.882
7.877
7.870
7.865
7.853
7.620
7.616
7.600
7.596
7.586
7.566
7.547
7.523
7.519
7.504
7.500
7.435
7.422
7.419
7.409
7.400
7.396
7.383
7.260
-0.002
Cl
CN
S
3j
1.00
1.99
1.00
1.08
0.91
2.09
f1 (ppm)

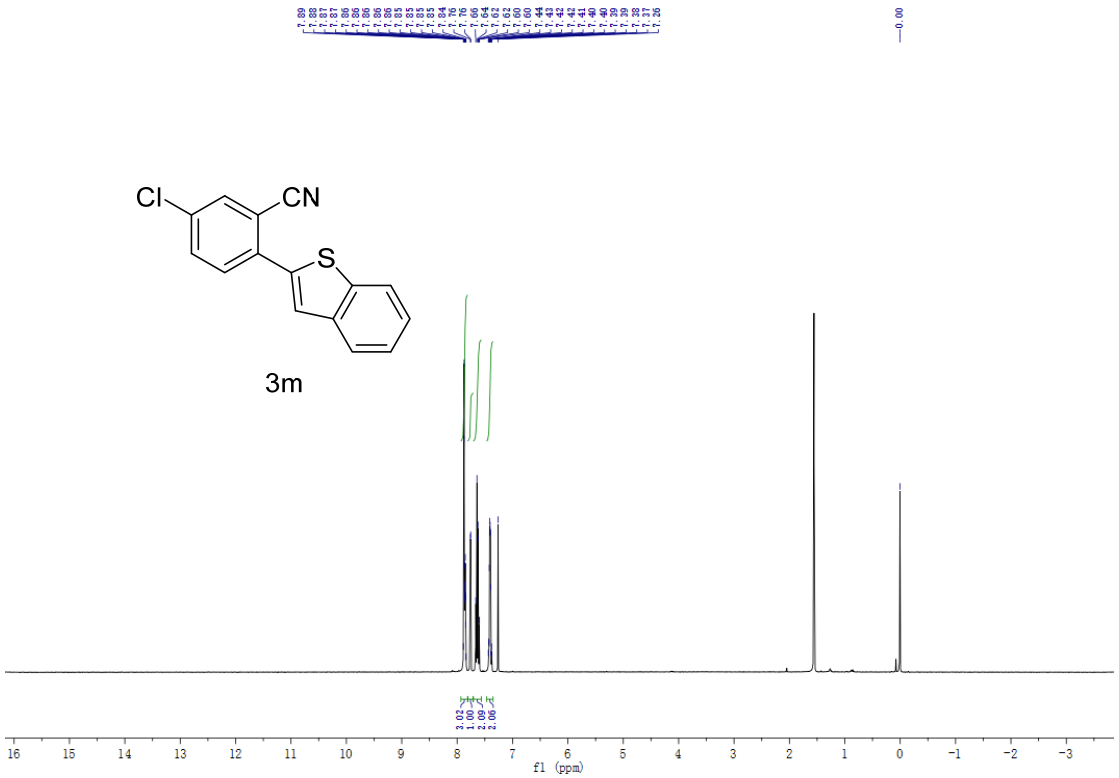

140.22
139.99
139.83
138.94
138.07
133.36
130.00
128.43
125.58
125.22
124.95
124.70
122.13
115.85
111.45
77.33
77.21
77.01
76.69
Cl
CN
S
3j
f1 (ppm)

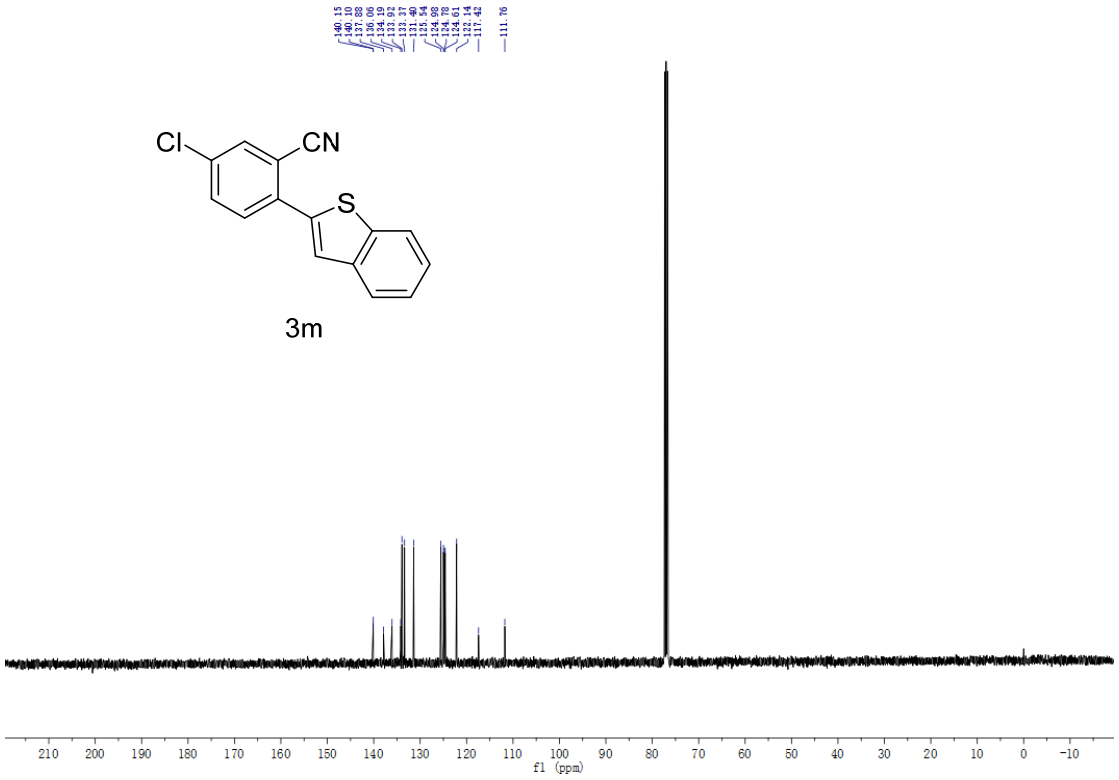

Me
CN
S
3k
2.65
0.01
2.96
1.95
2.07
0.96
3.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

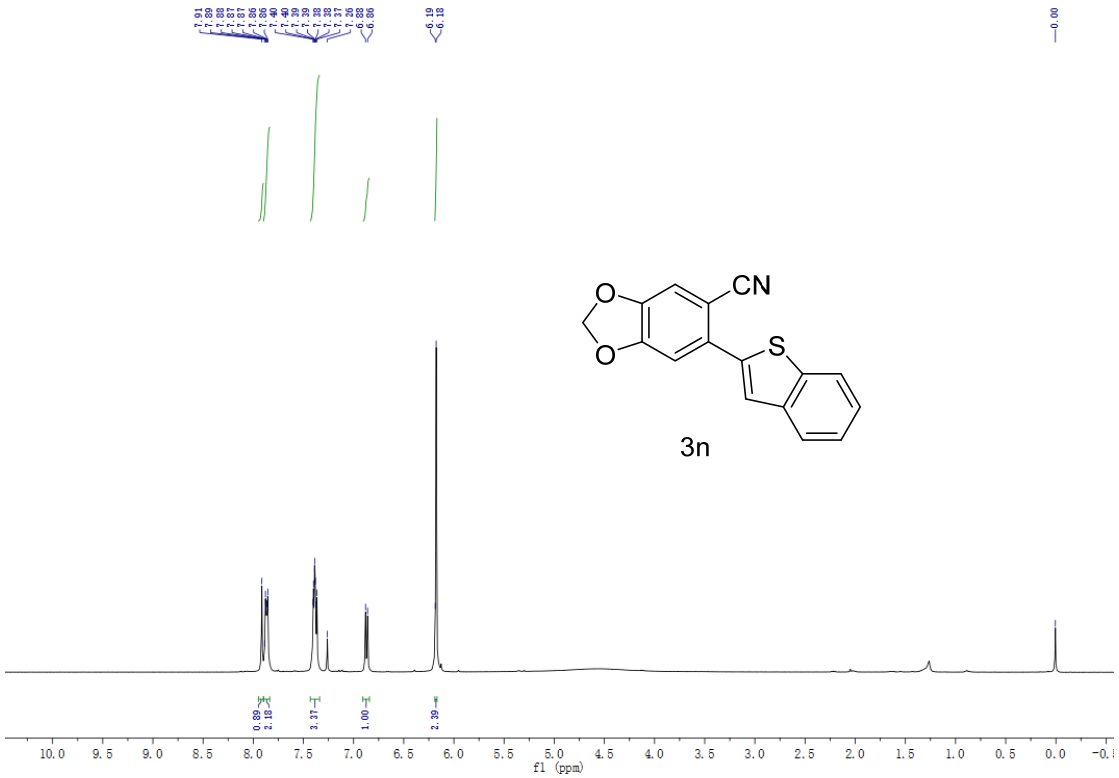

143.858
140.208
140.161
139.632
137.934
132.413
129.565
127.728
125.130
124.747
124.446
124.377
122.097
117.538
111.181
77.350
77.033
76.715
21.238
Me
CN
S
3k
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
CN
S
3l
3.05
1.01
1.01
2.09
0.98
3.00
f1 (ppm)


Me
CN
S
3l
f1 (ppm)


Cl
CN
S
3m
f1 (ppm)


Cl
CN
S
3m
f1 (ppm)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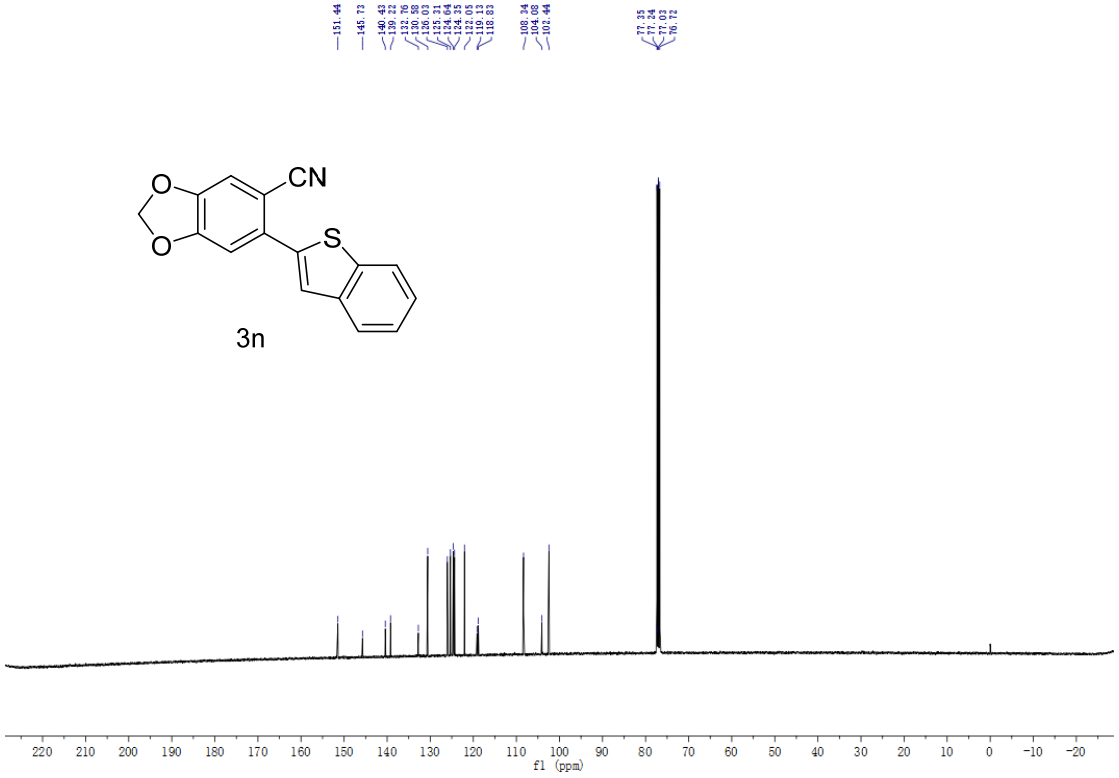
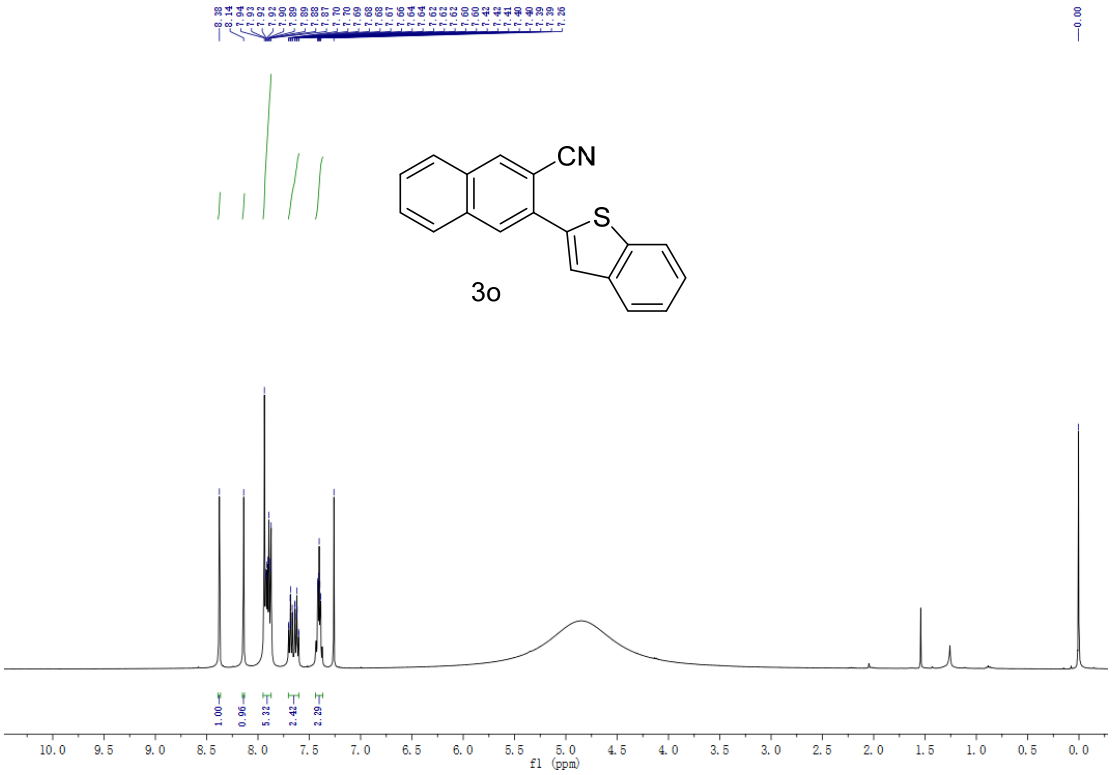
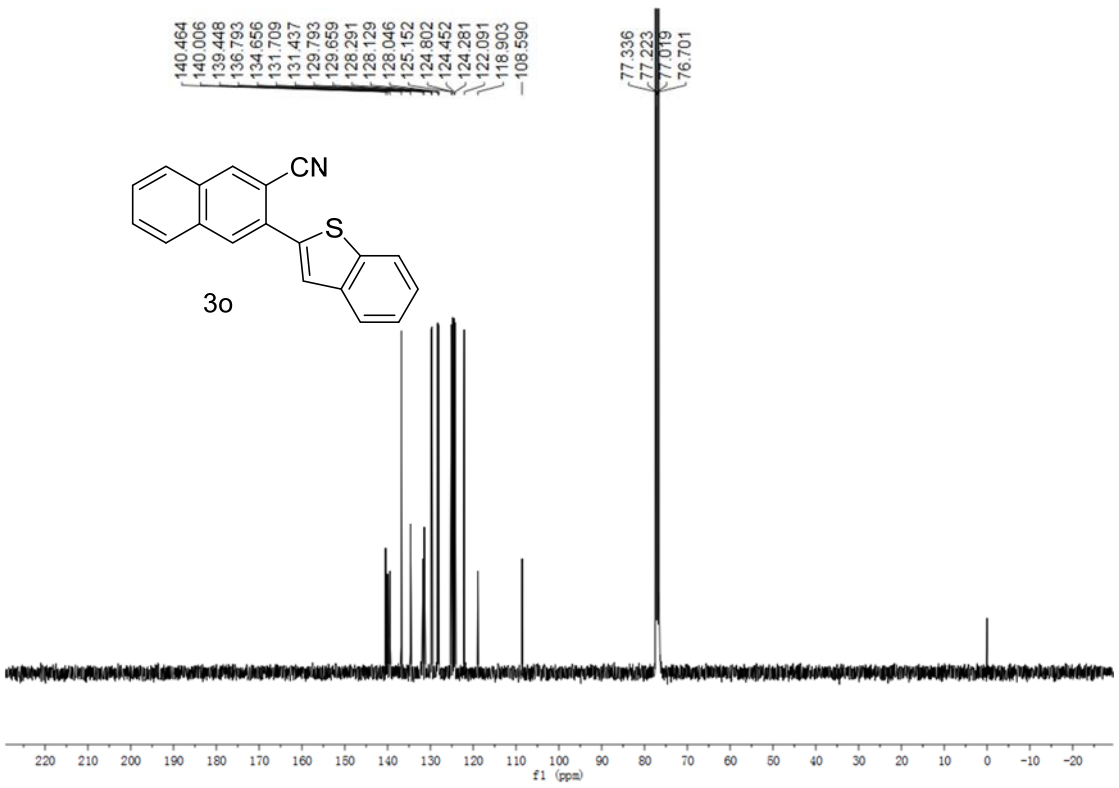
7.89
7.89
7.87
7.87
7.86
7.86
7.40
7.40
7.39
7.39
7.38
7.38
7.37
7.35
6.89
6.86
6.19
6.18
0.00
O
O
CN
S
3n
0.89
2.18
3.37
1.00
2.39
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


151.44
145.73
140.43
139.22
132.76
130.58
126.03
125.31
124.64
124.35
122.05
119.13
118.83
108.34
104.08
102.44
77.35
77.24
77.03
76.72
O
O
CN
S
3n
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)


CN
S
3o
1.00
0.96
5.33
2.42
2.29
f1 (ppm)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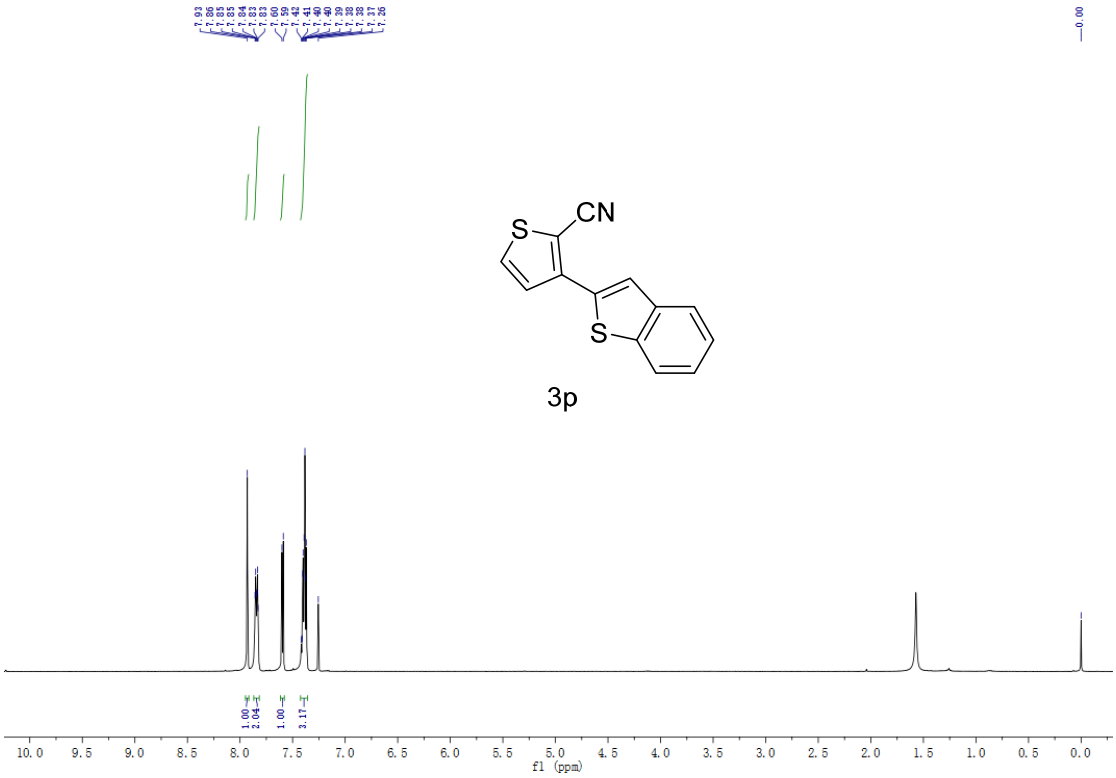
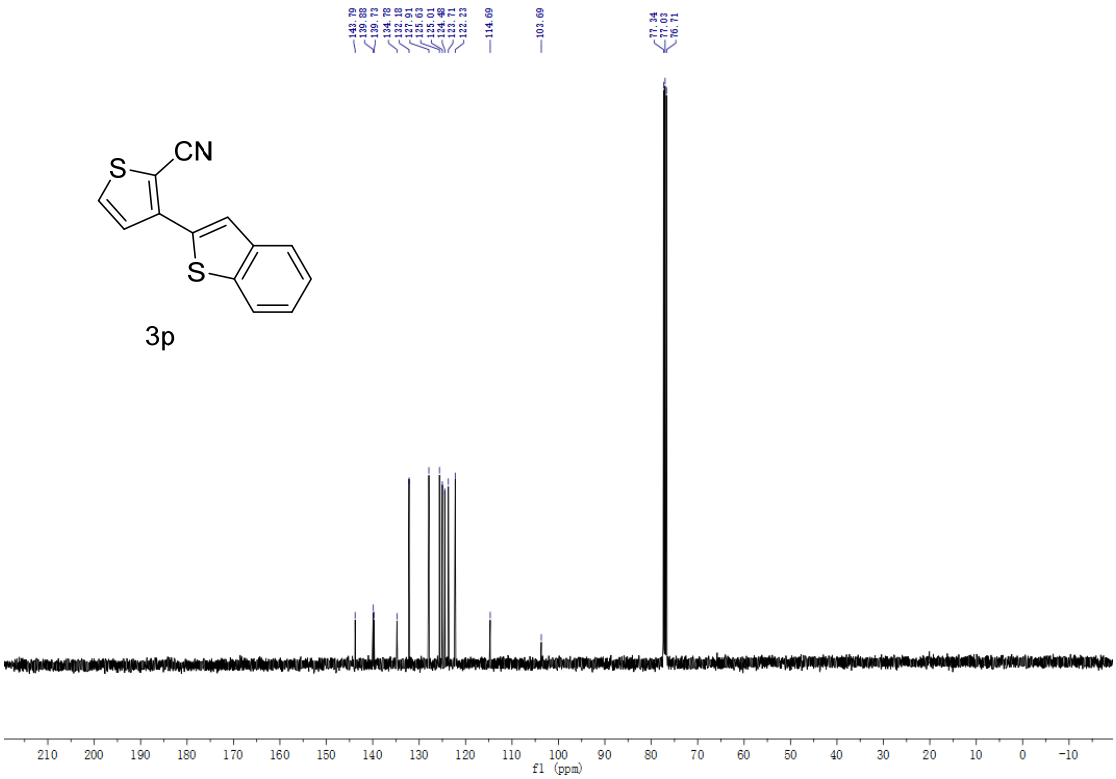
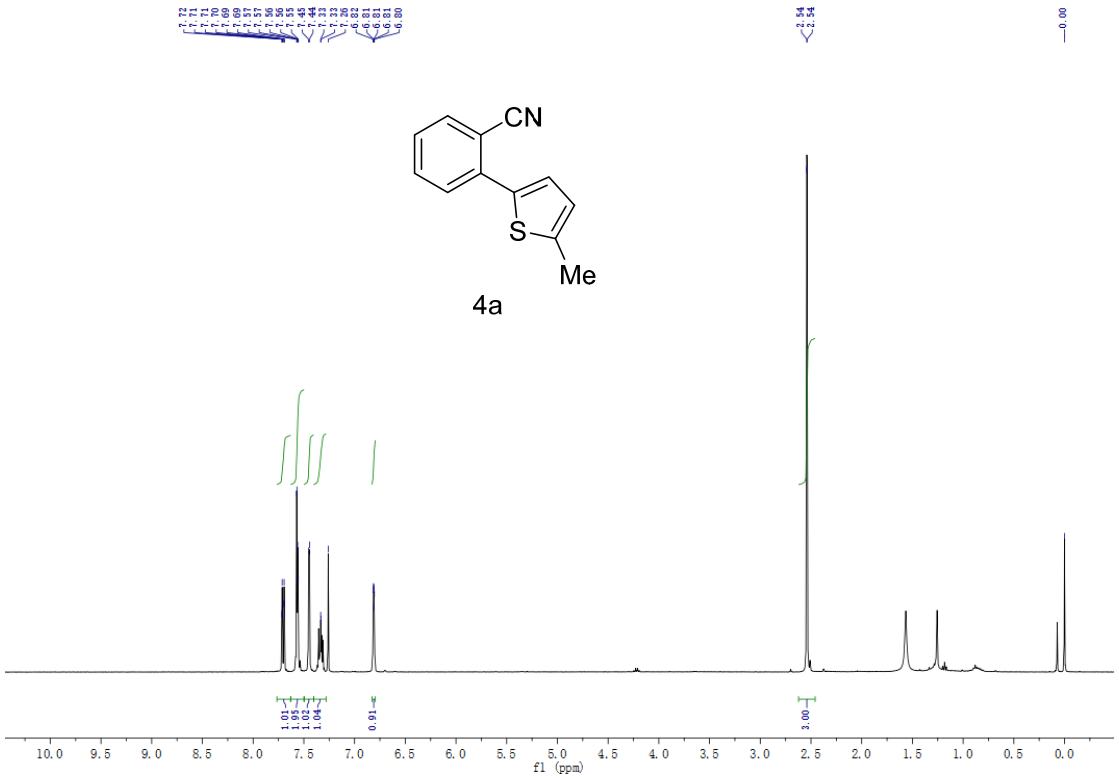
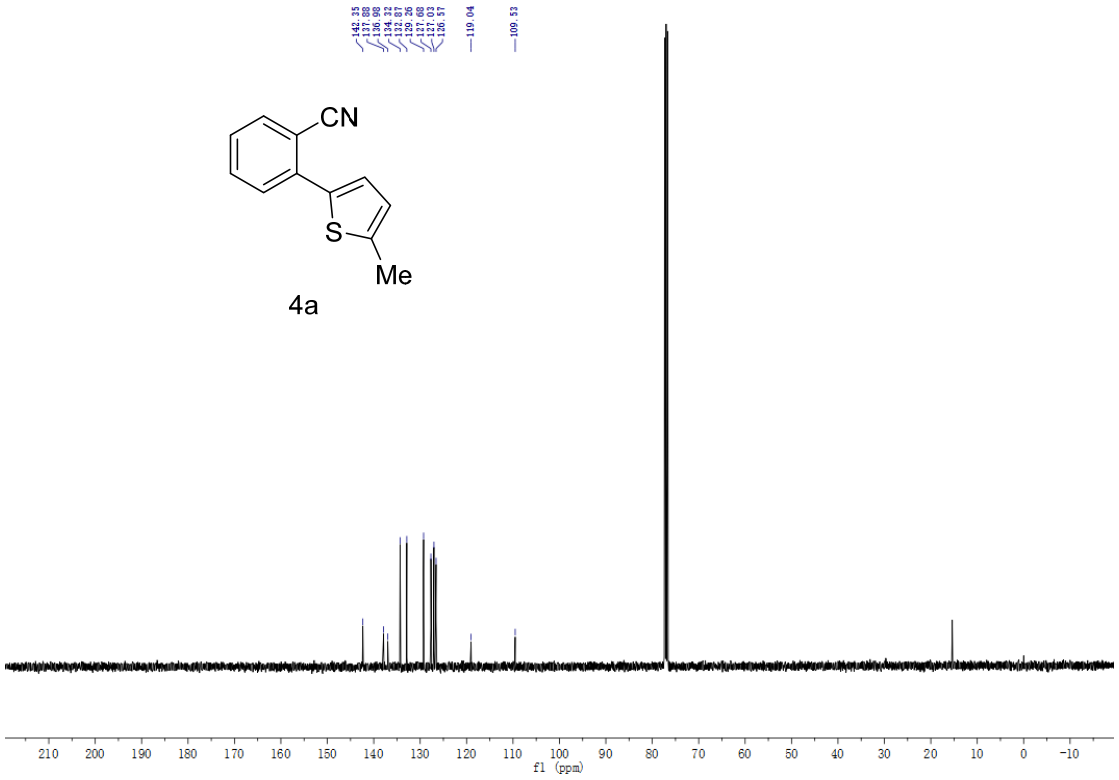
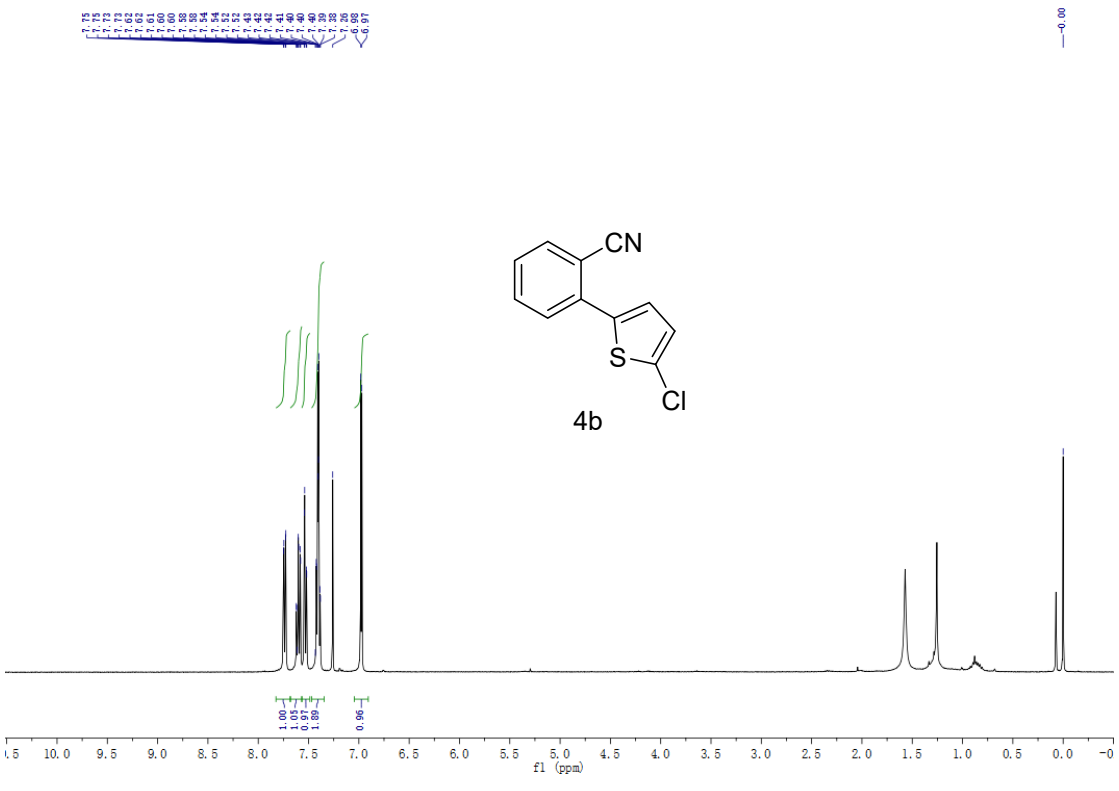
134.656
131.709
131.437
129.793
129.659
128.291
128.129
128.046
125.152
124.802
124.452
124.281
122.091
118.903
108.590
77.336
77.223
77.019
76.701
CN
S
3o
f1 (ppm)


CN
S
S
3p
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


CN
S
S
3p
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


CN
S
Me
4a
f1 (ppm)


CN
S
Me
4a
f1 (ppm)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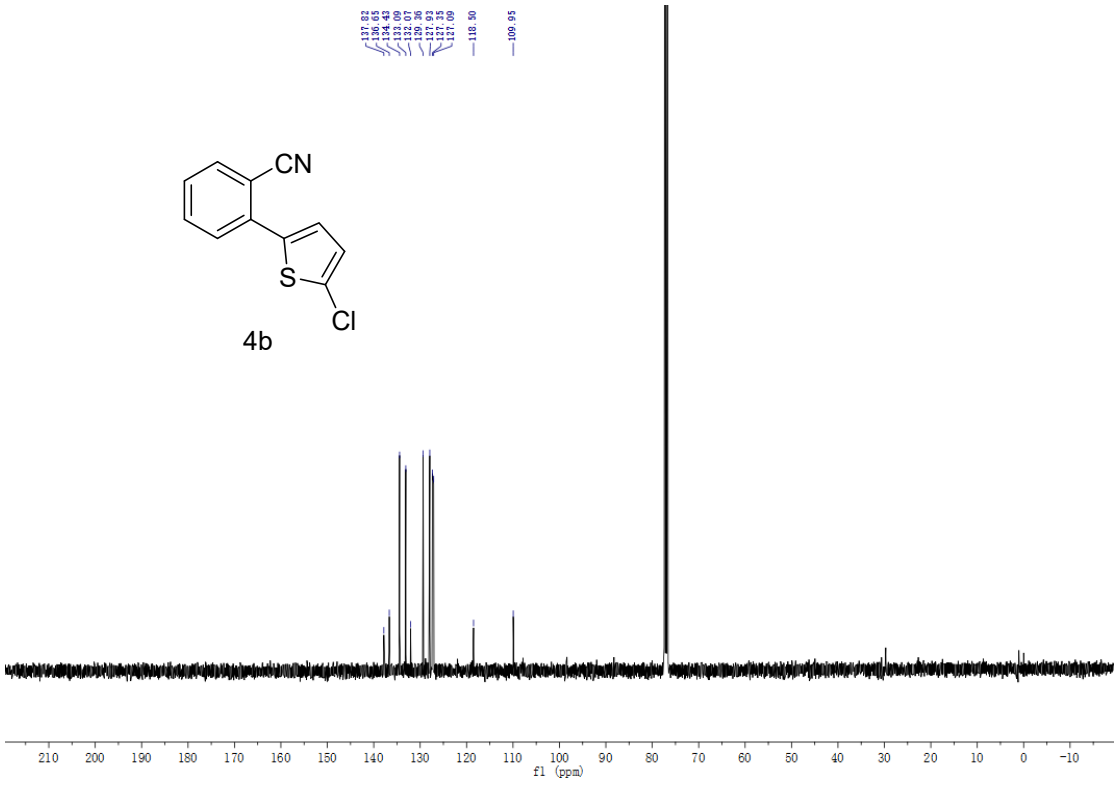
7.73
7.62
7.62
7.61
7.61
7.60
7.60
7.58
7.58
7.54
7.54
7.52
7.52
7.43
7.42
7.42
7.41
7.41
7.40
7.40
7.39
7.39
7.26
6.98
6.97
0.00
CN
S
Cl
4b
1.00
1.05
0.97
1.89
0.96
f1 (ppm)


137.82
136.65
134.43
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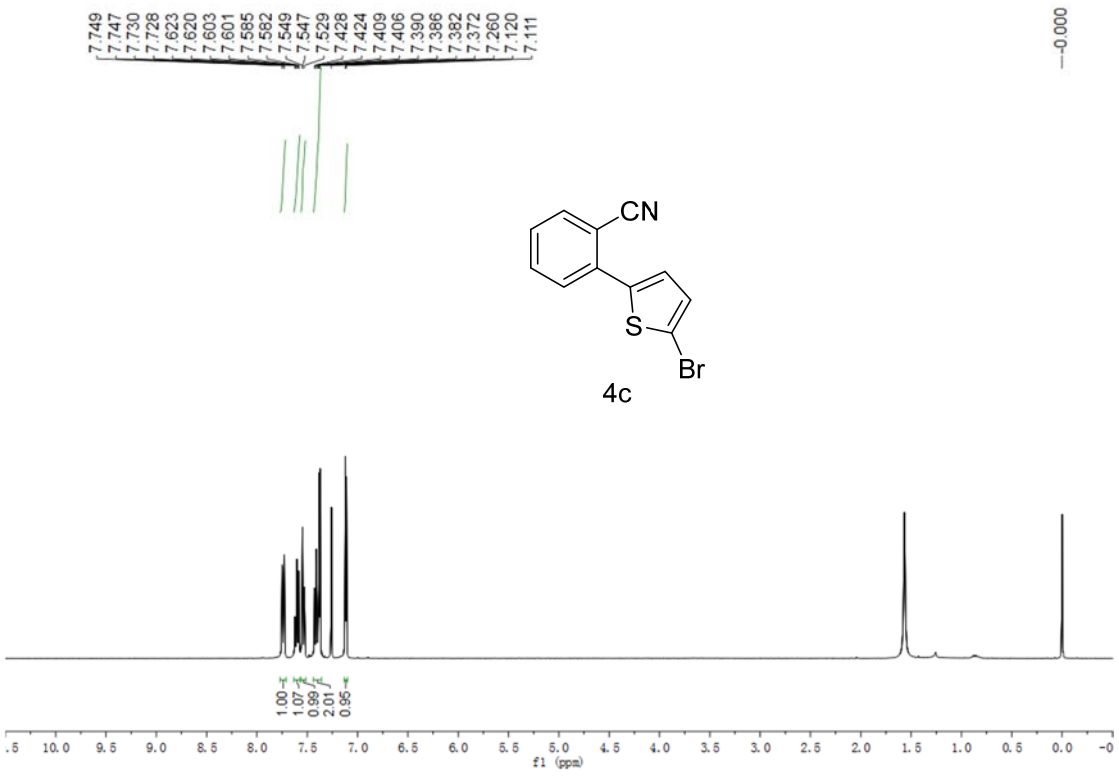
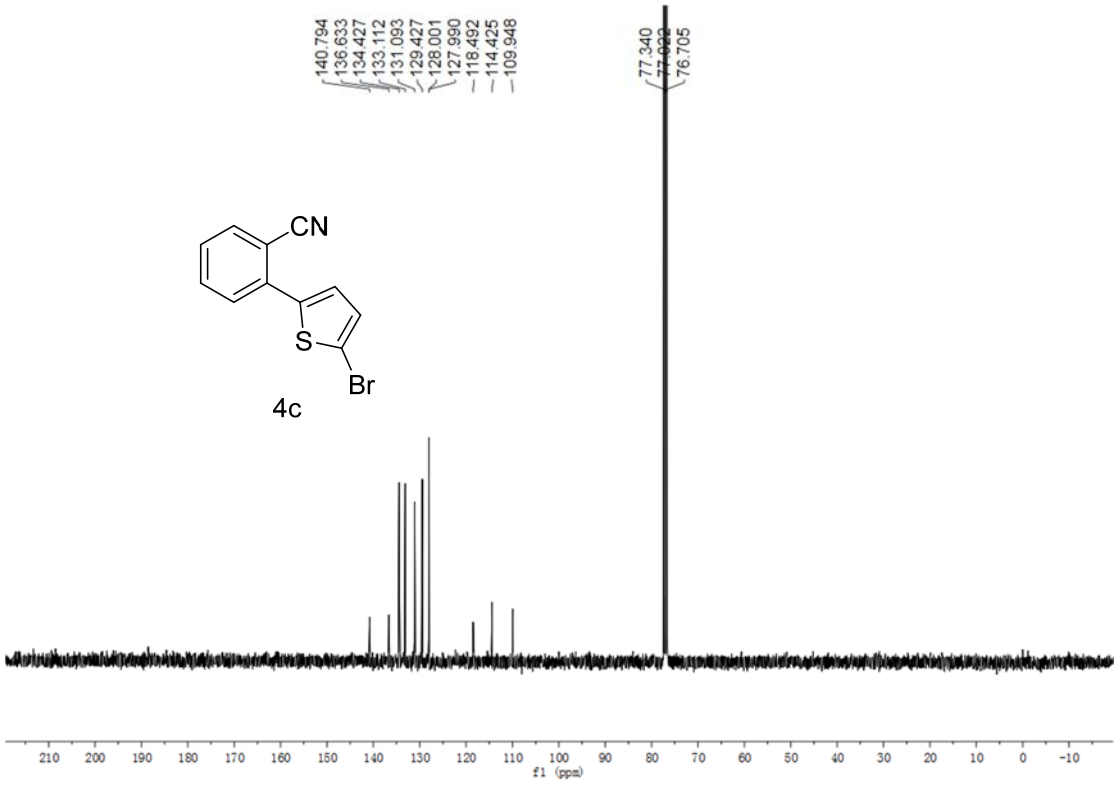
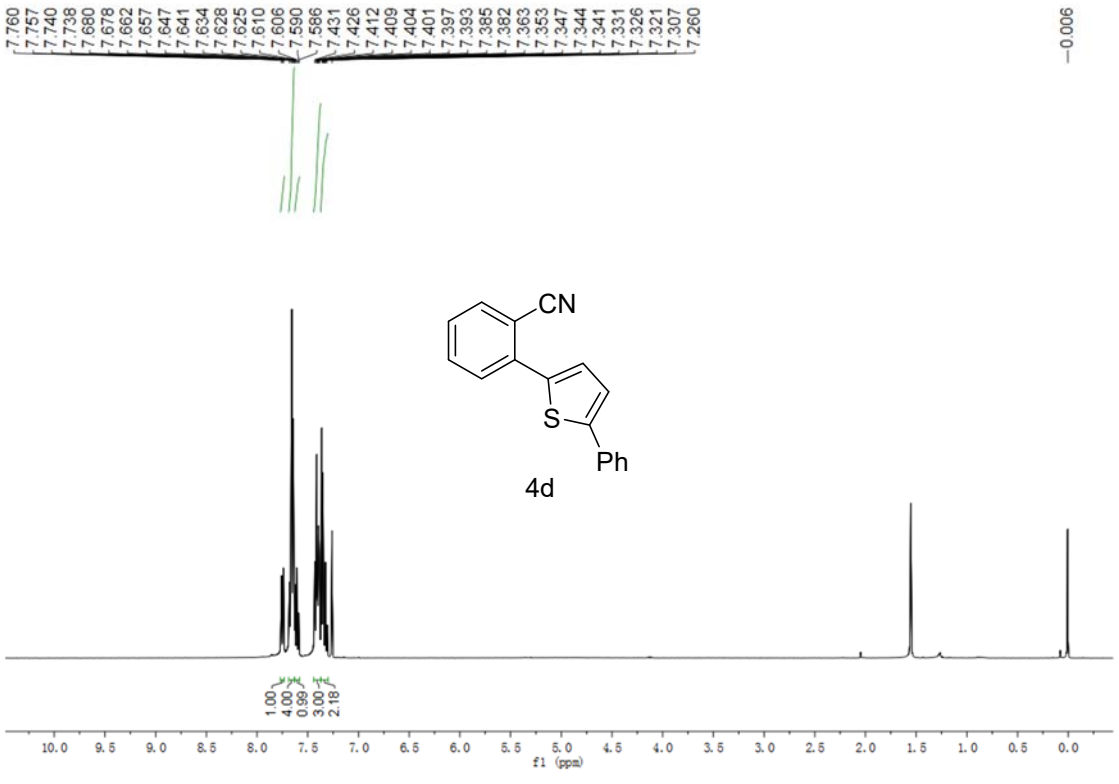
132.07
130.36
127.93
127.35
127.09
118.50
109.95
CN
S
Cl
4b
f1 (ppm)


7.749
7.747
7.730
7.728
7.623
7.620
7.603
7.601
7.585
7.582
7.549
7.547
7.529
7.428
7.424
7.409
7.406
7.390
7.386
7.382
7.372
7.260
7.120
7.111
-0.000
CN
S
Br
4c
1.00
1.07
0.99
2.01
0.95
f1 (ppm)


140.794
136.633
134.427
133.112
131.093
129.427
128.001
127.990
118.492
114.425
109.948
77.340
77.022
76.705
CN
S
Br
4c
f1 (ppm)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7.757
7.740
7.738
7.680
7.678
7.662
7.657
7.647
7.641
7.634
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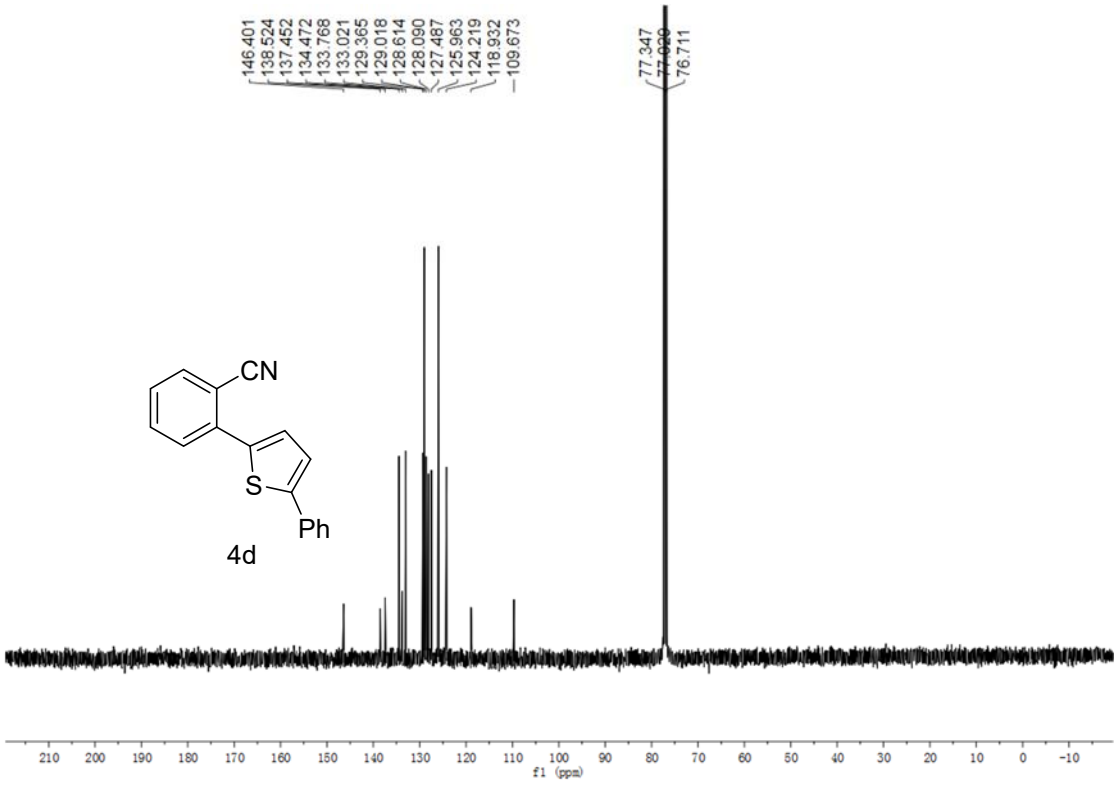
7.625
7.610
7.606
7.590
7.586
7.431
7.426
7.412
7.409
7.404
7.401
7.397
7.393
7.385
7.382
7.363
7.353
7.347
7.344
7.341
7.331
7.326
7.321
7.307
7.260
0.006
CN
S
Ph
4d
1.00
4.00
0.99
3.00
2.18
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)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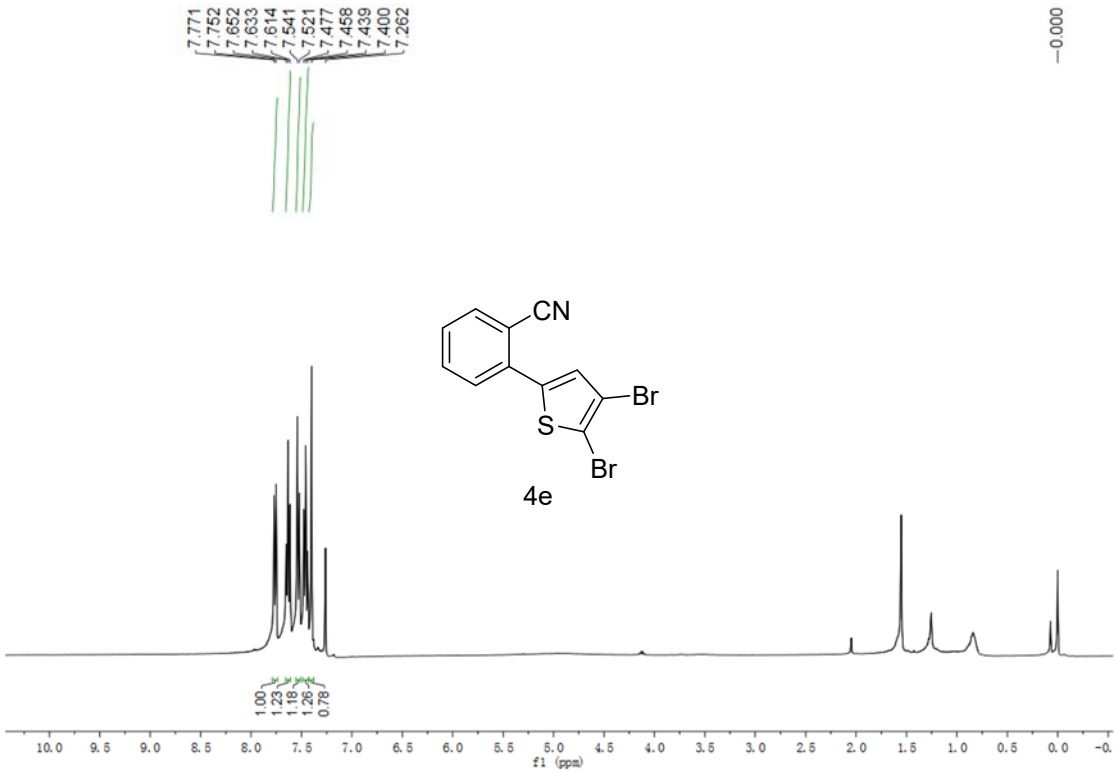
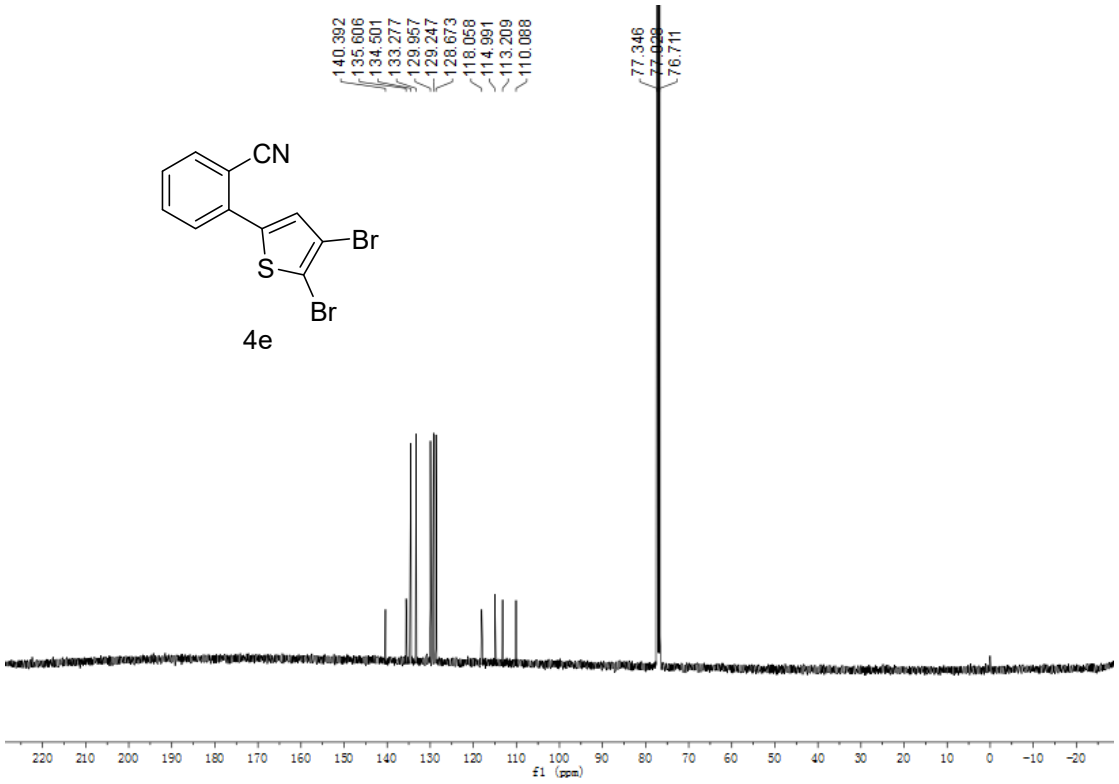
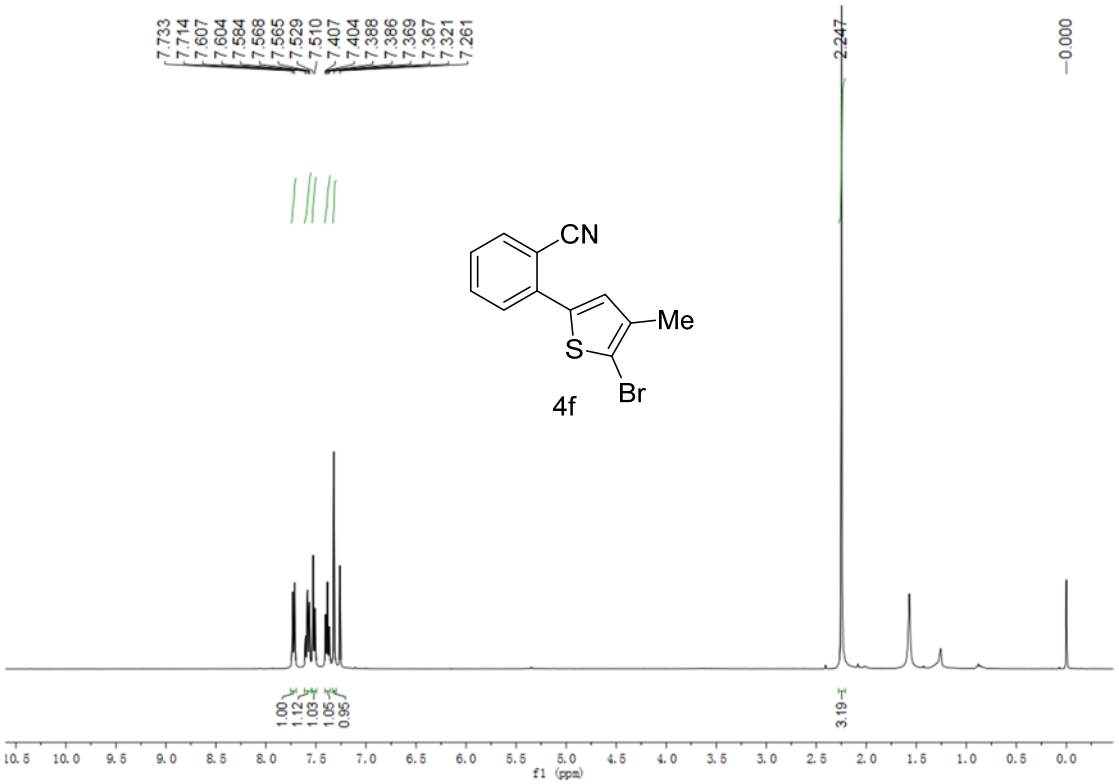
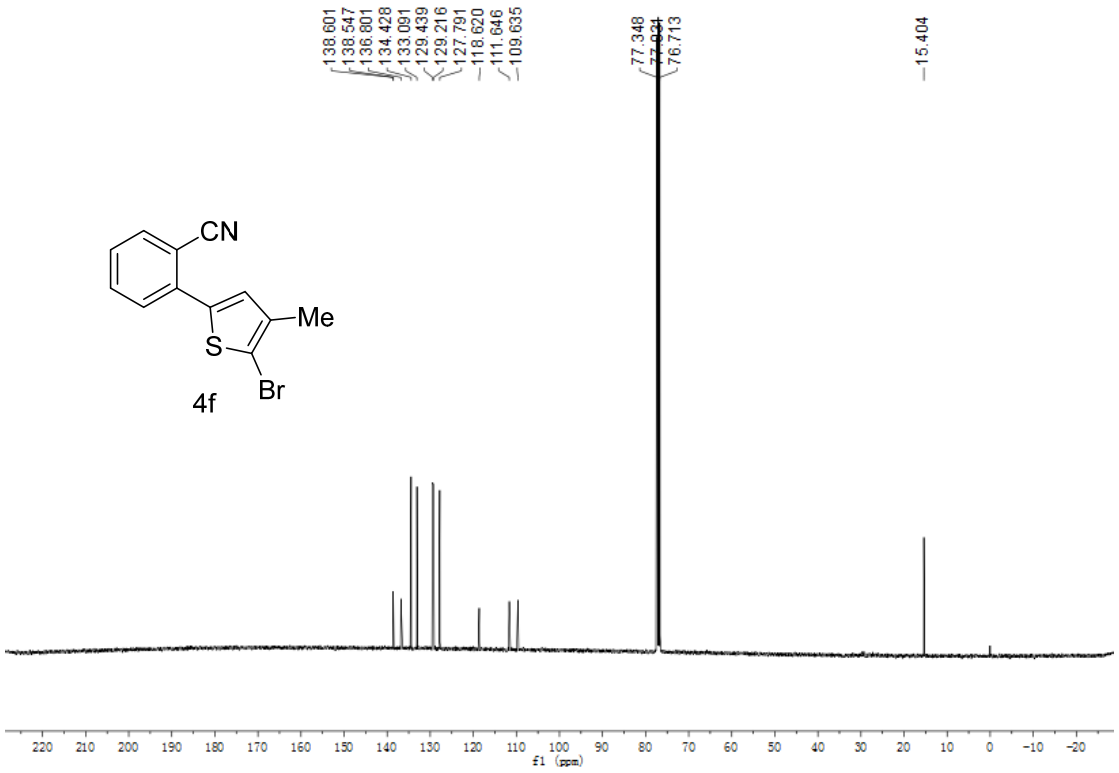
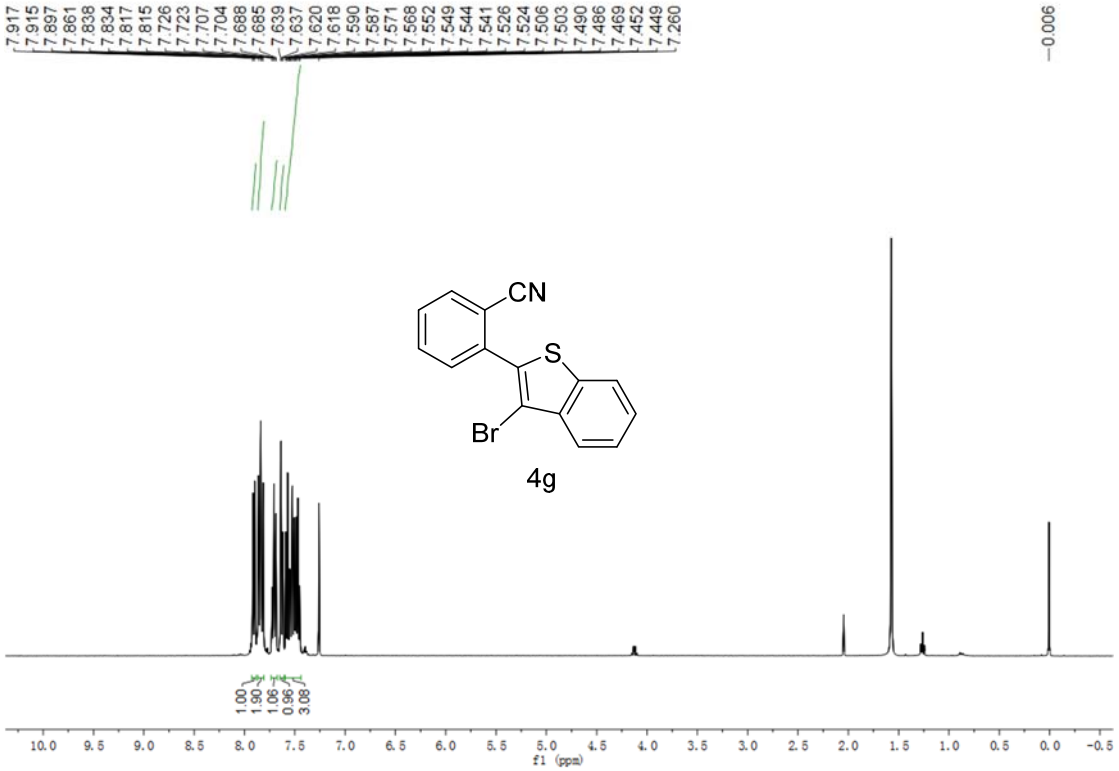
137.452
134.472
133.768
133.021
129.365
129.018
128.614
128.090
127.487
125.963
124.219
118.932
109.673
77.347
77.029
76.711
CN
S
Ph
4d
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)

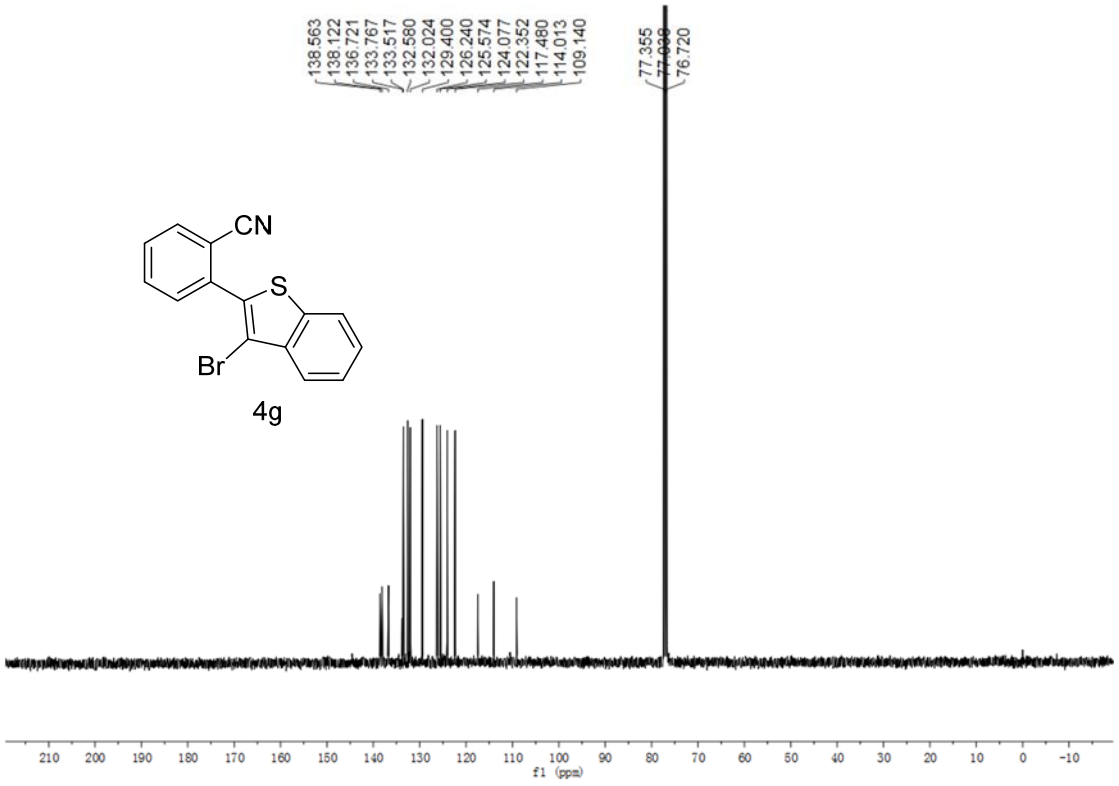

7.771
7.752
7.652
7.633
7.614
7.541
7.521
7.477
7.458
7.439
7.400
7.262
0.000
CN
Br
S
Br
4e
1.00
1.23
1.18
1.26
0.78
f1 (ppm)

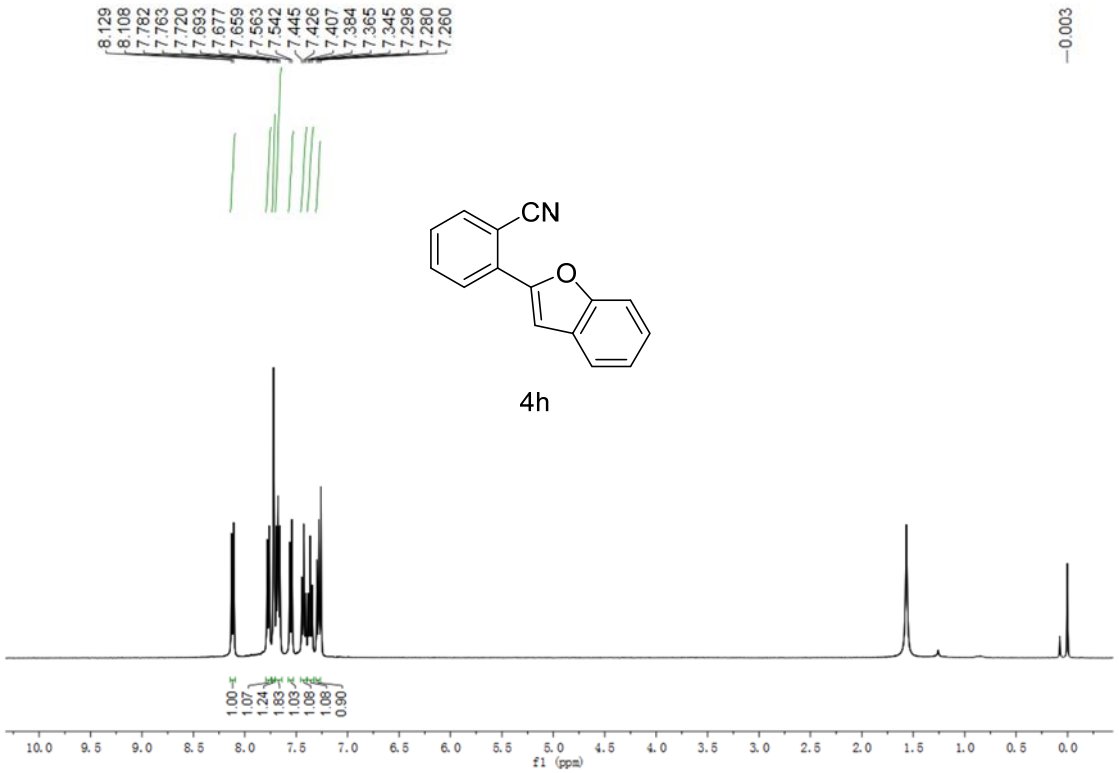

140.392
135.606
134.501
133.277
129.957
129.247
128.673
118.058
114.991
113.209
110.088
77.346
76.711
CN
Br
S
Br
4e
f1 (ppm)

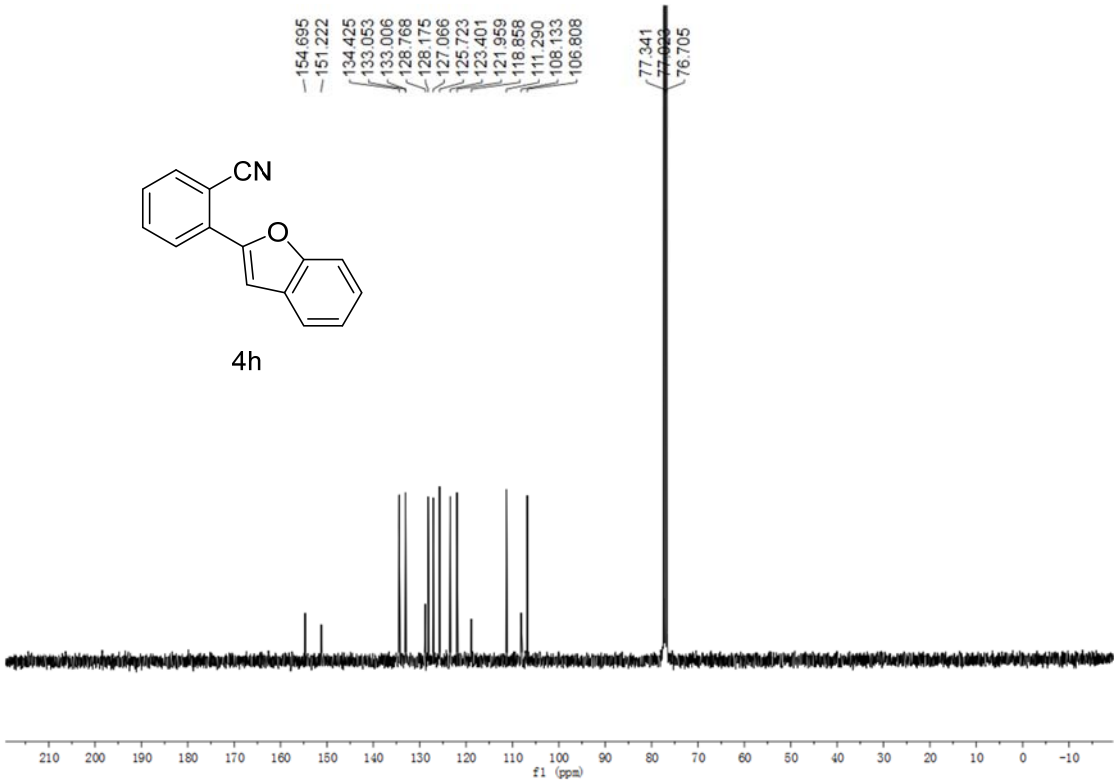

7.733
7.714
7.607
7.604
7.584
7.568
7.565
7.529
7.510
7.407
7.404
7.388
7.386
7.369
7.367
7.321
7.261
2.247
0.000
CN
Me
S
Br
4f
1.00
1.12
1.03
1.05
0.95
3.19
f1 (ppm)

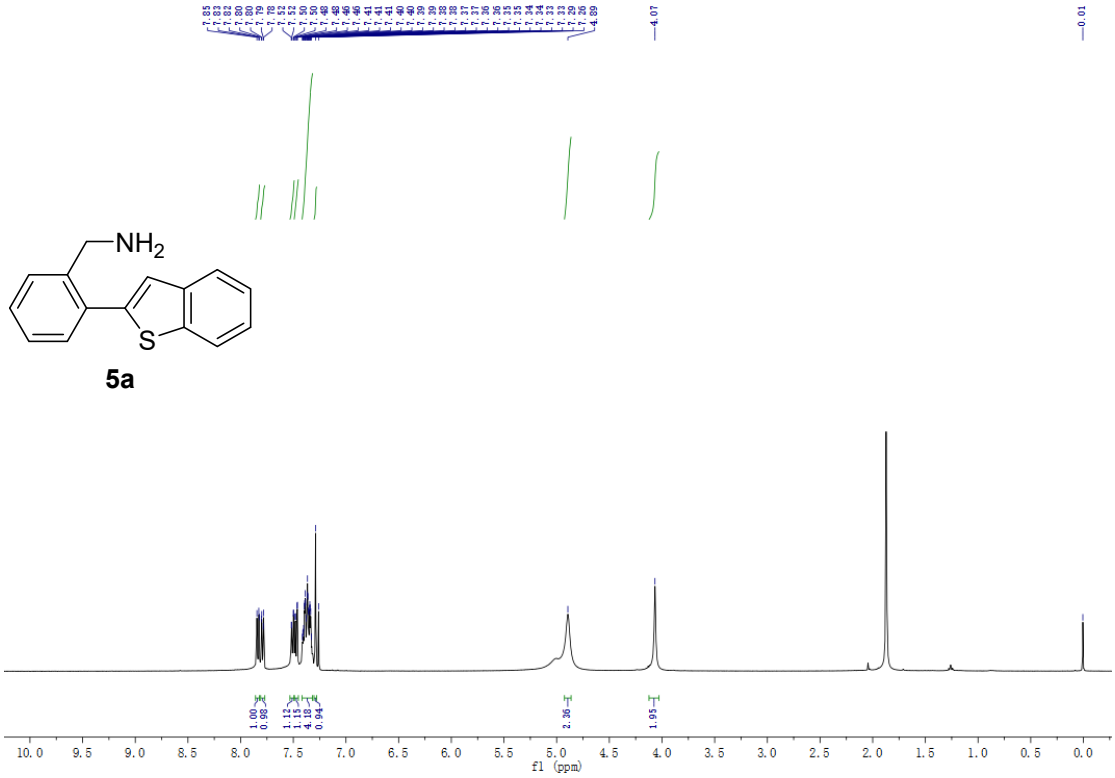

138.601
138.547
136.801
134.428
133.091
129.439
129.216
127.791
118.620
111.646
109.635
77.348
77.031
76.713
15.404
CN
Me
S
Br
4f
f1 (ppm)


7.917
7.915
7.897
7.861
7.838
7.834
7.817
7.815
7.726
7.723
7.707
7.704
7.688
7.685
7.639
7.637
7.620
7.618
7.590
7.587
7.571
7.568
7.552
7.549
7.544
7.541
7.526
7.524
7.506
7.503
7.490
7.486
7.469
7.452
7.449
7.260
0.006
CN
S
Br
4g
1.00
1.90
1.06
0.96
3.08
f1 (ppm)

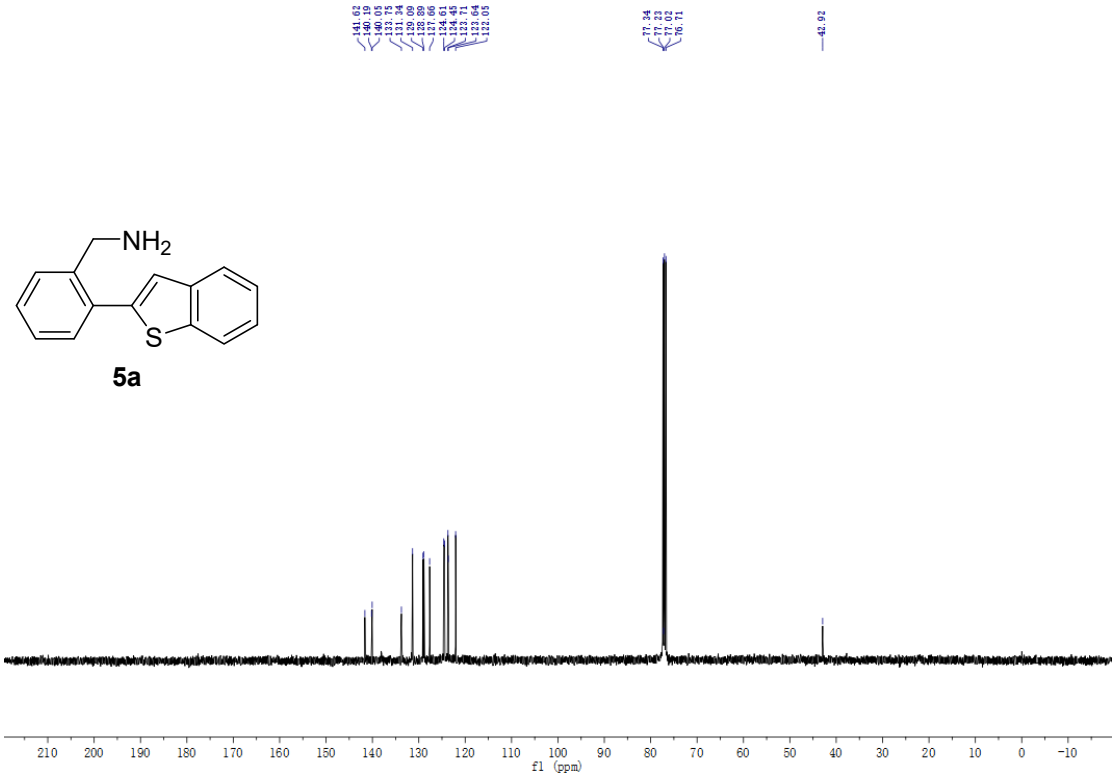

138.563
138.122
136.721
133.767
133.517
132.580
132.024
129.400
126.240
125.574
124.077
122.352
117.480
114.013
109.140
77.355
77.038
76.720
CN
S
Br
4g
f1 (ppm)


8.129
8.108
7.782
7.763
7.720
7.693
7.677
7.659
7.563
7.542
7.445
7.426
7.407
7.384
7.365
7.345
7.298
7.280
7.260
0.003
CN
O
4h
1.00
1.07
1.24
1.83
1.03
1.08
1.08
0.90
f1 (ppm)

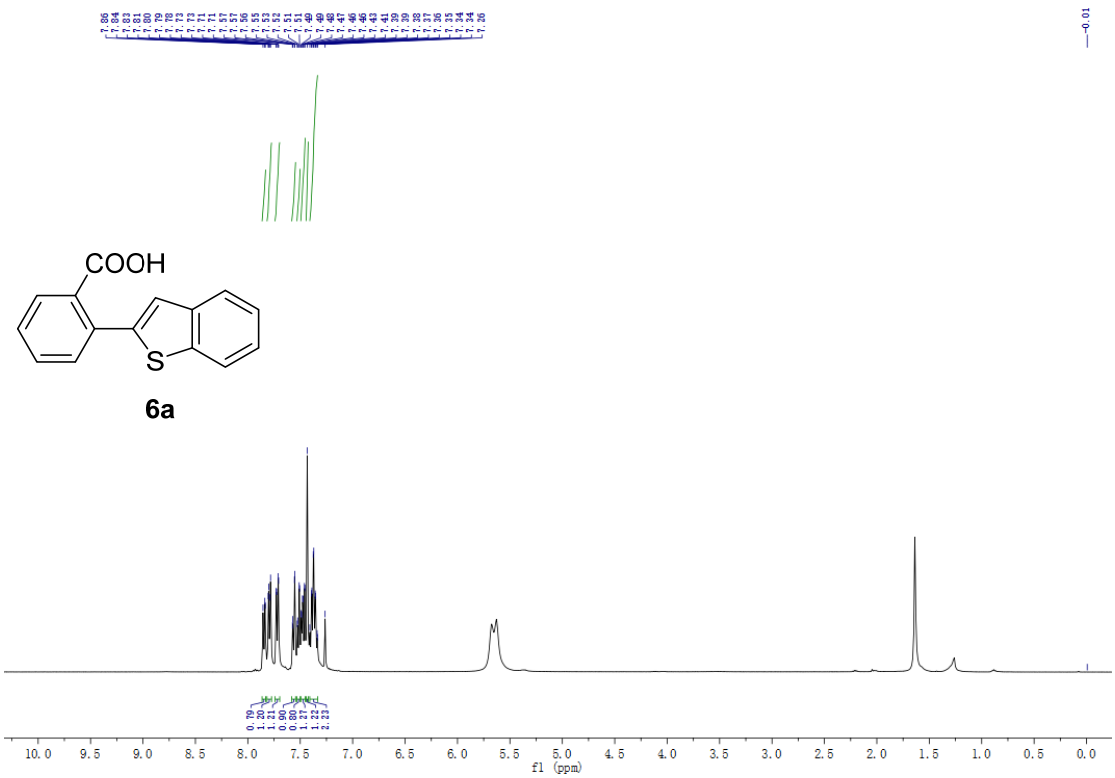

154.695
151.222
134.425
133.053
133.006
128.768
128.175
127.066
125.723
123.401
121.959
118.858
111.290
108.133
106.808
77.341
77.023
76.705
CN
O
4h
f1 (ppm)

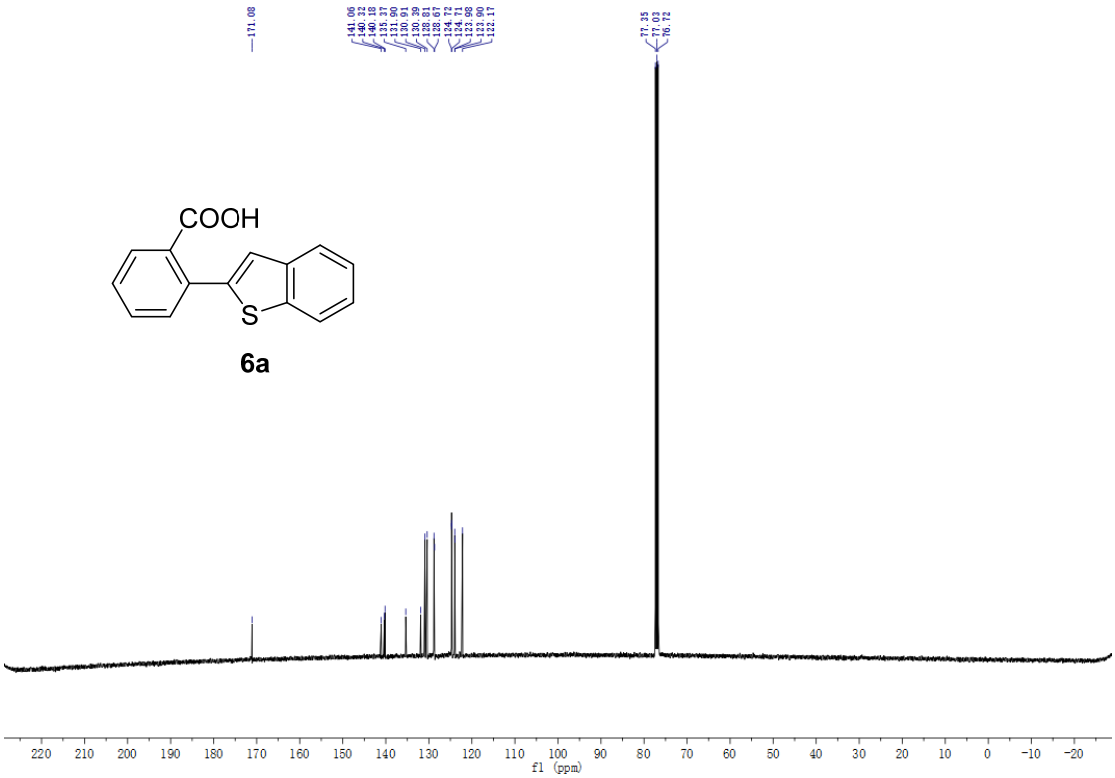


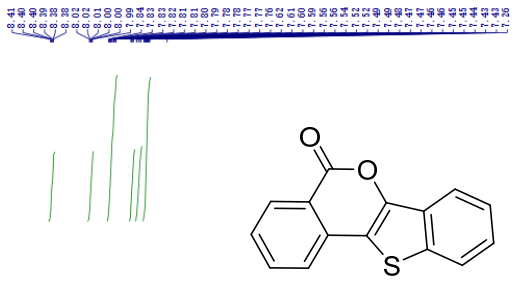
5a

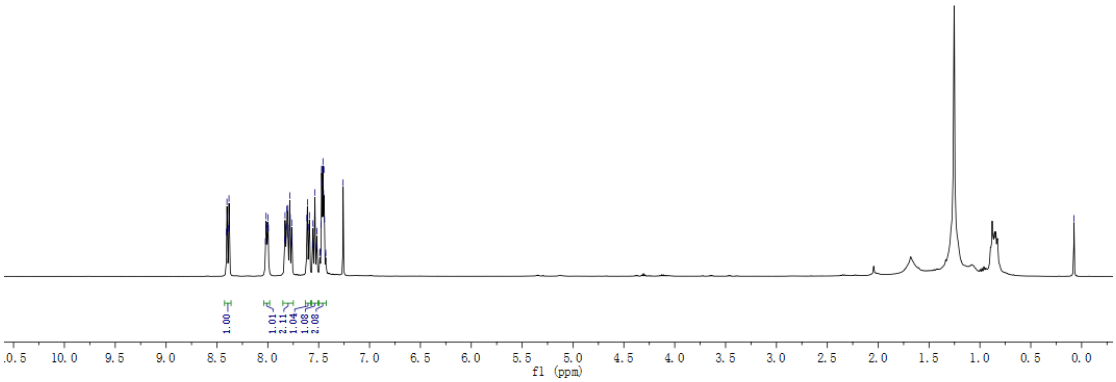


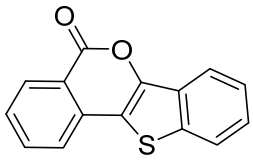
5a

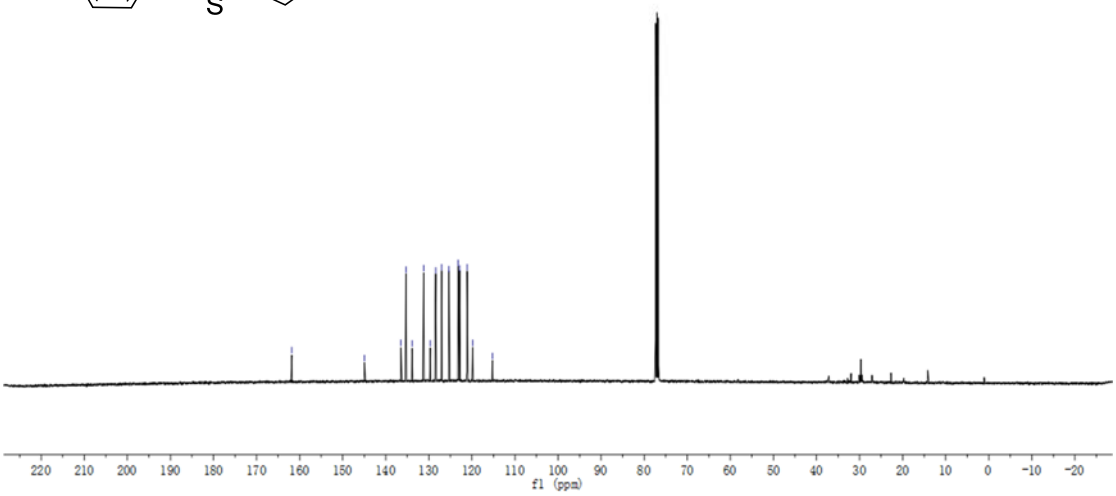

COOH
S
6a
f1 (ppm)

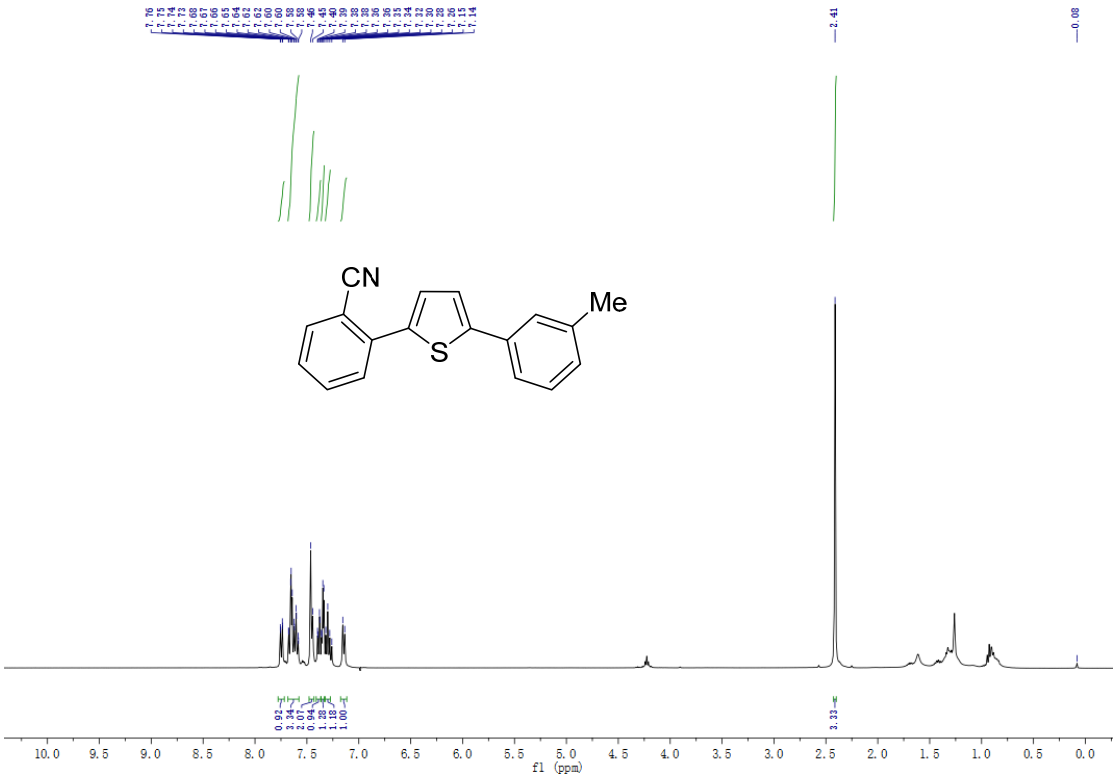

COOH
S
6a
f1 (ppm)

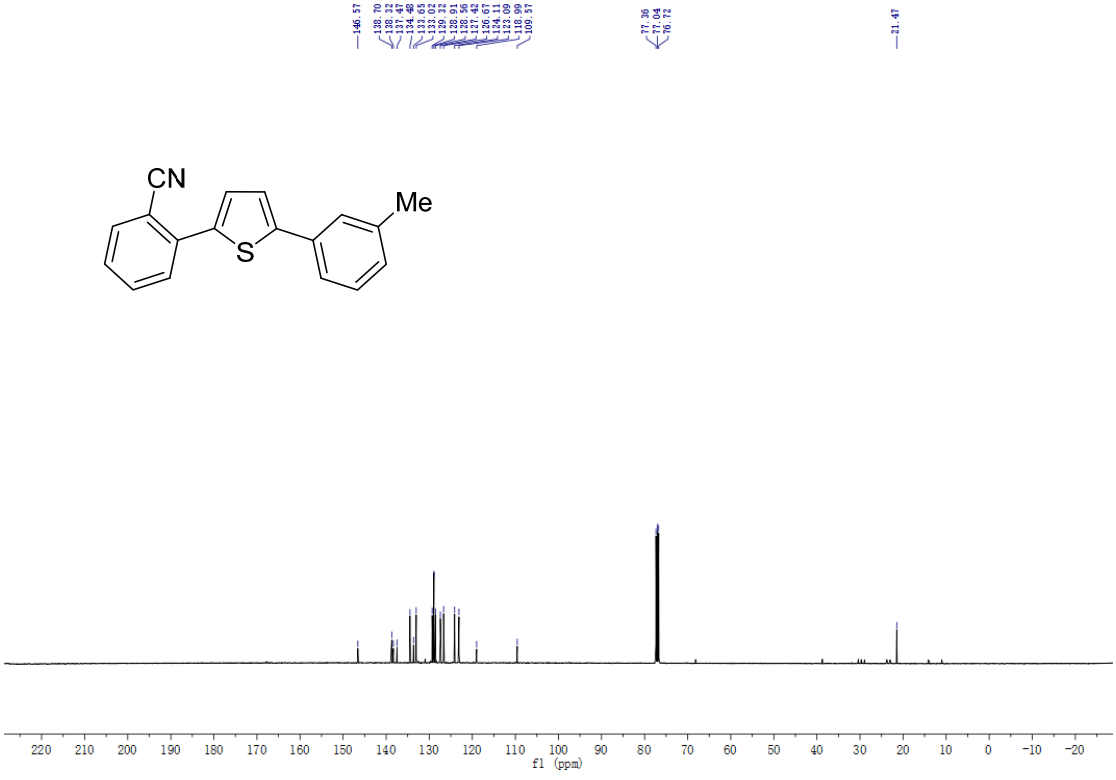



1.00
1.01
2.14
1.08
2.08
f1 (ppm)




f1 (ppm)


CN
Me
S
f1 (ppm)


CN
Me
S
f1 (ppm)