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Supporting Information

Palladium-catalyzed C–H Functionalization of Heteroarenes with Aryl Bromides and Chlorides

Shunsuke Tamba, Youhei Okubo, Shota Tanaka, Daiki Monguchi, and Atsunori Mori *

Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan

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Experimental Section

General procedure for the reaction of thiophene derivatives with aryl halides: To a 20 mL Schlenk tube equipped with a magnetic stirring bar was added a 2.2 M THF solution of LiO*t*-Bu (1.5 mmol, 0.68 mL) under nitrogen atmosphere. The solvent was removed under reduced pressure. To the residue were successively added $Pd(P\textit{t}\text{-}Bu_3)_2$ (5.1 mg, 0.01 mmol), benzo[*b*]thiophene **1** (68 mg, 0.5 mmol), 4-bromotoluene (**2a**) (103 mg, 0.6 mmol), and DMF (2.0 mL). The mixture was stirred at 100 °C for 15 h. After cooling to room temperature, the reaction mixture was poured into water and the organic materials were extracted with diethyl ether. The organic layer was washed with water twice and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel using hexane as an eluent to afford 109 mg of 2-(4-methylphenyl)-benzo[*b*]thiophene (**3a**) as a colorless solid (97% yield).

2-(4-methylphenyl)benzo[*b*]thiophene (3a)[1]: Mp. 156.9-158.2 °C. (lit. 162-163 °C) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39 (3H, s), 7.24 (2H, d, *J* = 7.9 Hz), 7.28-7.38 (2H, m), 7.50 (1H, s), 7.51 (1H, s), 7.62 (2H, d, *J* = 8.0 Hz), 7.76 (1H, br d, *J* = 7.2 Hz), 7.82 (1H, br d, *J* = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 118.8, 122.2, 123.4, 124.1, 124.4, 126.4, 129.6, 131.5, 138.2, 139.3, 140.8, 144.4.

2-Phenyl-benzo[*b*]thiophene (3b)[2]: ^{1}H NMR (500 MHz, $CDCl_3$) δ7.29-7.37 (3H, m), 7.43 (2H, t, *J* = 7.6 Hz), 7.55 (1H, s), 7.73 (2H, dd, *J* = 8.4, 1.4 Hz), 7.78 (1H, d, *J* = 7.6 Hz), 7.83 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ119.4, 122.2, 123.5, 124.3, 124.5, 126.5, 128.2, 128.9, 134.3, 139.5, 140.7, 144.2.

2-(4-Methoxyphenyl)-benzo[*b*]thiophene (3c)[3]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86 (3H, s), 6.96 (2H, d, *J* = 8.8 Hz), 7.27-7.35 (2H, m), 7.43 (1H, s), 7.51 (1H, s), 7.65 (2H, d, *J* = 8.2 Hz), 7.74 (1H, br d, *J* = 7.8 Hz), 7.81 (1H, br d, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ55.4, 114.3, 118.2, 122.2, 123.2, 123.9, 124.4, 127.0, 127.7, 139.2, 140.9, 144.1, 159.8.

2-(4-Trifluoromethyl)benzo[*b*]thiophene (3d): Mp. 195.2-196.6 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26-7.34 (2H, m), 7.56 (1H, s), 7.60 (2H, d, *J* = 8.2 Hz), 7.72-7.76 (3H, m), 7.78 (1H, dd, *J* = 7.9, 0.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ121.03, 122.35, 123.95, 124.13 (q, $J_{C\text{-}F}$ = 279 Hz), 124.80, 124.98, 125.93 (q, $J_{C\text{-}F}$ = 4 Hz), 126.59, 130.00 (q, $J_{C\text{-}F}$ = 35 Hz), 137.72, 139.79, 140.40, 142.28; IR (neat) 824, 1070, 1111, 1168, 1330; HRMS (EI+) Calcd for $C_{15}H_9F_3S$: 278.0377; found: m/z 278.0377.

2-(4-fluorophenyl)benzo[*b*]thiophene (3e)[4]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (2H, t, *J* = 8.6 Hz), 7.29-7.38 (2H, m), 7.47 (1H, s), 7.68 (2H, dd, *J* = 8.6, 5.3 Hz), 7.77 (1H, d, *J* = 7.6 Hz), 7.83 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ115.57 (d, $J_{C\text{-}F}$ = 22 Hz), 119.42 (d, $J_{C\text{-}F}$ = 1.3 Hz), 122.23, 123.52, 124.36, 124.59, 128.16 (d, $J_{C\text{-}F}$ = 8 Hz), 130.56 (d, $J_{C\text{-}F}$ = 3 Hz), 139.42, 140.64, 143.04, 162.75 (d, $J_{C\text{-}F}$ = 248 Hz).

2-(4-*N*, *N*-dimethylaminophenyl)benzo[*b*]thiophene (3f)[5]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.01 (6H, s), 6.76 (2H, br d, *J* = 8.0 Hz), 7.22-7.33 (2H, m), 7.37 (1H, s), 7.60 (2H, d, *J* = 8.8 Hz), 7.71 (1H, d, *J* = 8.0 Hz), 7.78 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ40.3, 112.4, 116.6, 122.0, 122.4, 122.8, 123.4, 124.3, 127.4, 138.8, 141.1, 145.1, 150.4.

2-(2-Naphthyl)benzo[*b*]thiophene (3g)[6]: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, ddd, *J* = 7.5, 7.5, and 1.5 Hz), 7.38 (1H, ddd, *J* = 7.5, 7.5, and 1.1 Hz), 7.46-7.54 (2H, m), 7.68 (1H, br s), 7.81 (1H, br d, *J* = 7.4 Hz), 7.83-7.92 (5H, m), 8.15 (1H, br s); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 119.9, 122.3, 123.6, 124.3, 124.4, 124.6, 125.3, 126.4, 126.7, 127.7, 128.2, 128.6, 131.7, 133.1, 133.5, 139.6, 140.8, 144.2.

2-Methyl-5-(4-methylphenyl)thiophene (6a)[7]: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (3H, s), 2.50 (3H, s), 6.68-6.75 (1H, m), 7.06 (1H, d, *J* = 3.6 Hz), 7.16 (2H, br d, *J* = 8.1 Hz), 7.45 (2H, br d, *J* = 8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 21.1, 122.3, 125.4, 126.0, 129.4, 131.9, 136.7, 138.9, 142.1.

Synthesis of 2-bromo-3-hexyl-5-(4-methoxyphenyl)thiophene (2h): To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added $PdCl_2(PPh_3)_2$ (140 mg, 0.2 mmol), 2-bromo-3-hexylthiophene (1.0 mL, 4.8 mmol), 4-iodeanisole (972 mg, 4.0 mmol), potassium fluoride (581 mg, 10 mmol), and DMSO (13 mL) under a nitrogen atmosphere. The reaction was stirred at 100 °C for 5 h. Silver nitrate (1.02 g, 10 mmol) was then added in five portions with an hour interval. After cooling to room temperature, the mixture was passed through a Celite pad, which was washed repeatedly with chloroform. The filtrate was washed with water twice and brine. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel using hexane:ethyl acetate (20:1) as an eluent to afford 1.15 g of 2-bromo-3-hexyl-5-(4-methoxyphenyl)thiophene **2h** as an orange oil (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (3H, t, *J* = 6.9 Hz), 1.25-1.42 (6H, m), 1.54-1.66 (2H, m), 2.55 (2H, t, *J* = 7.7 Hz), 3.83 (3H, s), 6.88 (1H, s), 6.90 (2H, dd, *J* = 6.8, 2.2 Hz), 7.43 (2H, dd, *J* = 6.8, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.1, 22.6, 28.9, 28.9, 29.7, 31.6, 55.2, 106.8, 114.3, 122.9, 126.6, 126.7, 142.9, 143.5, 159.3; IR (neat) 822, 1036, 1178, 1251, 1291, 1511, 2928; HRMS (EI+) Calcd for $C_{17}H_{21}BrOS$: 352.0496; found: m/z 352.0498.

3'-Hexyl-5'-(4''-methoxyphenyl)-5-methyl-[2,2']bithiophene (6h): (60% isolated yield); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (3H, t), 1.28-1.46 (6H, m), 1.61-1.70 (2H, m), 2.51 (3H, s), 2.72 (2H, t, *J* = 7.8 Hz), 3.83 (3H, s), 6.70-6.73 (1H, m), 6.91 (2H, dd, *J* = 6.6, 2.1 Hz), 6.91 (1H, s), 7.02 (1H, s), 7.52 (2H, dd, *J* = 6.6, 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.1, 15.3, 22.6, 29.3, 29.4, 30.6, 31.7, 55.3, 114.2, 124.9, 125.5, 125.5, 126.7, 127.1, 129.6, 134.0, 139.7, 139.9, 141.3, 159.1; IR (neat) 825, 1036, 1177, 1251, 1511, 2926; HRMS (EI+) Calcd for $C_{22}H_{26}OS_2$: 370.1425; found: m/z 370.1424.

2-(4-methylphenyl)benzo[*b*]furan (8a)[8]: (47% isolated yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.40 (3H, s), 6.97 (1H, d, *J* = 0.9 Hz), 7.19-7.30 (4H, m), 7.48-7.54 (1H, m), 7.54-7.59 (1H, m), 7.77 (2H, dd, *J* = 6.5, 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ21.4, 100.5, 111.1, 120.7, 122.8, 124.0, 124.9, 127.7, 129.3, 129.5, 138.6, 154.8, 156.2.

2-(4'-Methoxyphenyl)benzo[*b*]furan (8c)[9]: Colorless solid (34% isolated yield) ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.87 (3H, s), 6.89 (1H, d, *J* = 0.9 Hz), 6.98 (2H, dd, *J* = 6.8, 2.2 Hz), 7.18-7.28 (2H, m), 7.47-7.58 (2H, m), 7.80 (2H, dd, *J* = 6.8, 2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.4, 99.7, 111.0, 114.2, 120.6, 122.8, 123.7, 126.4, 128.6, 129.5, 154.7, 155.6, 160.0.

2-(4-Methoxyphenyl)-5-(4-methylphenyl)thiazole (10a)[9]: Yellow solid (73% isolated yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.39 (3H, t), 3.87 (3H, t), 6.97 (2H, d, *J* = 8.9 Hz), 7.22 (2H, d, *J* = 7.9 Hz), 7.49 (2H, d, *J* = 7.9 Hz), 7.90 (2H, d, *J* = 8.9 Hz), 7.92 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 55.3, 114.5, 124.1, 126.1, 127.9, 129.6, 131.1, 138.0, 138.7, 140.0, 159.7, 166.5.

2-(4-methylphenyl)thiazole (11)[10]: Brown oil (74% isolated yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.40 (3H, s), 7.25 (2H, br d, *J* = 8.0 Hz), 7.30 (2H, d, *J* = 3.2 Hz), 7.84 (2H, d,

J = 3.2 Hz), 7.86 (2H, br d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 118.2, 126.4, 129.6, 130.9, 140.1, 143.4, 168.5.

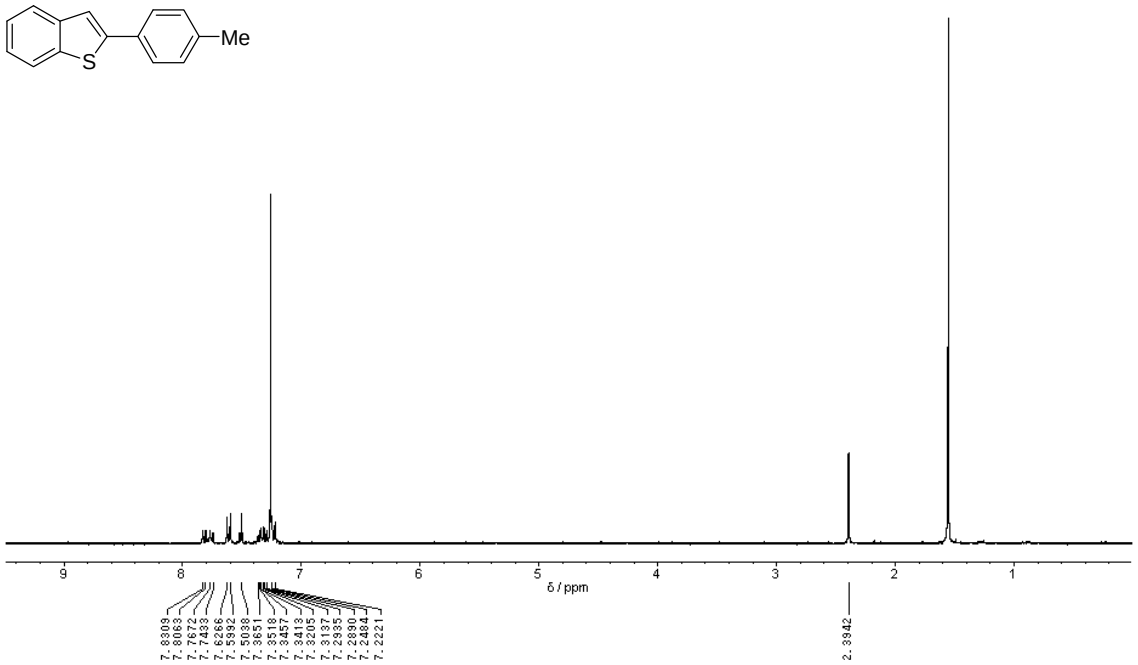
One-pot synthesis for differently substituted 2,5-diarylthiazole *via* Palladium-catalyzed C–H Arylation: To a 20 mL Schlenk tube equipped with a magnetic stirring bar was added a 2.2 M THF solution of Li*O*t-Bu (0.6 mmol, 0.27 mL) under nitrogen atmosphere. The solvent was removed under reduced pressure. To the residue were successively added $Pd(P$*t*$-Bu_3)_2$ (5.1 mg, 0.01 mmol), thiazole **17** (35 μL, 0.5 mmol), 4-bromotoluene (**2a**) (86 mg, 0.5 mmol), and anhydrous 1,4-dioxane (1.0 mL). The mixture was stirred at 100 °C for 5 h. After cooling to room temperature, 2.2 M THF solution of Li*O*t-Bu (1.5 mmol, 0.68 mL) was added to the mixture. The solution was removed under reduced pressure. 4-bromoanisole (**2c**) (63 μL, 0.5 mmol) and anhydrous DMF were added to the residue. The solution was stirred at 100 °C for 15 h. After cooling to room temperature, the reaction mixture was poured into water and the organic materials were extracted with diethyl ether. The organic layer was washed with water twice and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to leave a crude oil, which was purified by chromatography on silica gel using hexane/ethyl acetate (20:1) as an eluent to afford 78 mg of 5-(4-methoxyphenyl)-2-(4-methylphenyl)thiazole (**12c**) as a yellow solid (56% yield). Mp. 124.6-126.4 °C.[11]

Synthesis of 3-hexyl-2-(4'-methoxyphenyl)thiophene (13): To a 25 mL two-necked flask equipped with a magnetic stirring bar were added 2-bromo-3-hexylthiophene (1.0 mL, 5.0 mmol), 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)toluene (1.3 mL, 6.0mmol), and 30 mL of THF under a nitrogen atmosphere. Aqueous solution of 1M K_2CO_3 (15 mL, 15 mmol), $Pd(OAc)_2$ (56 mg, 0.25 mmol), triphenylphosphine (262 mg, 1 mmol) were then added. The resulting solution was refluxed for 14 h. After cooling the mixture to room temperature the mixture was poured into water and ethyl acetate and the organic phase were separated. The aqueous layer was extracted with ethyl acetate and the combined organic layer was dried over anhydrous sodium sulfate. Removal of the solvent left a crude oil, which was subjected to column chromatography on silica gel using hexane:ethyl acetate (20:1) as an eluent to afford 1.28 g of 3-hexyl-2-(4'-methoxyphenyl)thiophene **13** as a colorless oil (93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.86 (3H, t, *J* = 6.9 Hz), 1.19-1.34 (6H, m), 1.55-1.62 (2H, m), 2.62 (2H, t, *J* = 7.7 Hz), 3.85 (1H, s), 6.95 (2H, dd, *J* = 6.8, 2.1 Hz), 6.97 (2H, d, *J* = 5.2 Hz), 7.19 (2H, d, *J* = 5.2 Hz), 7.36 (2H, dd, *J* = 6.8, 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.0, 22.5, 28.5, 29.1, 30.9, 31.6, 55.1, 113.8, 122.9, 127.1, 129.2, 130.5, 137.5, 138.0, 158.9; IR (neat) 830, 1037, 1176, 1247, 1289, 1462, 1507, 1609, 2926; HRMS (EI+) Calcd for $C_{17}H_{22}OS$: 274.1391; found: m/z 274.1390.

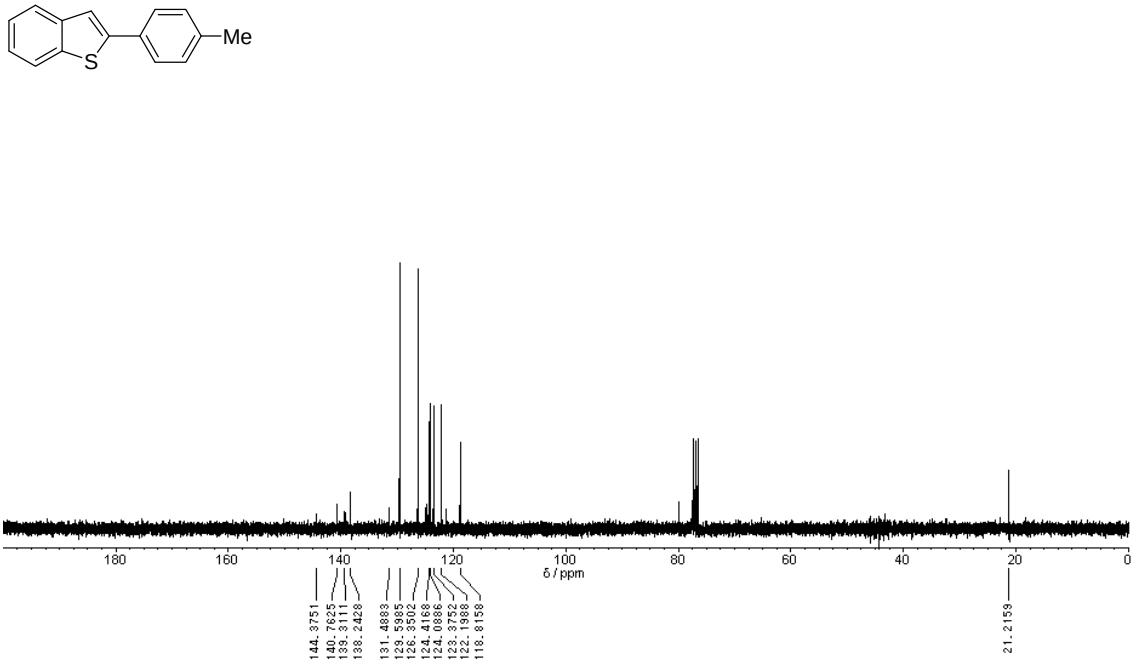
3-Hexyl-2-(4-methoxyphenyl)-5-(4-methylphenyl)thiophene (14a): (58% isolated yield); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (3H, t, *J* = 6.8 Hz), 1.19-1.41 (6H, m), 1.54-1.69 (2H, m), 2.36 (3H, s), 2.62 (2H, t, *J* = 7.8 Hz), 3.85 (3H, s), 6.95 (2H, dd, *J* = 6.7, 2.0 Hz), 7.14 (1H, s), 7.18 (2H, d, *J* = 8.0 Hz), 7.39 (2H, dd, *J* = 6.7, 2.0 Hz), 7.5 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ14.1, 21.2, 22.6, 28.8, 29.2, 31.0, 31.6, 55.3, 113.9, 125.0, 125.4, 127.2, 129.5, 130.4, 131.7, 136.7, 137.0, 139.1, 141.6, 158.9; IR (neat) 812, 829, 1037, 1177, 1248, 1290, 1461, 1504, 1608, 2926; HRMS (EI+) Calcd for $C_{24}H_{28}OS$: 364.1861; found: m/z 364.1868.

2-(4-Methoxyphenyl)benzothiazole (16a)[12]: (96% isolated yield) ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.43 (3H, s), 7.31 (2H, br d, *J* = 7.9 Hz), 7.38 (1H, ddd, *J* = 7.6, 7.6, and 1.0 Hz), 7.49 (1H, ddd, *J* = 7.6, 7.6, and 1.2 Hz), 7.90 (1H, d, *J* = 8.4 Hz), 7.99 (2H, br d, *J* = 8.1 Hz) , 8.06 (1H, d, *J* = 8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 121.4, 122.9, 124.9, 126.1, 127.3, 129.6, 130.8, 134.8, 141.2, 154.0, 168.1.

^{1}H NMR spectrum of **3a**



^{13}C NMR spectrum of **3a**



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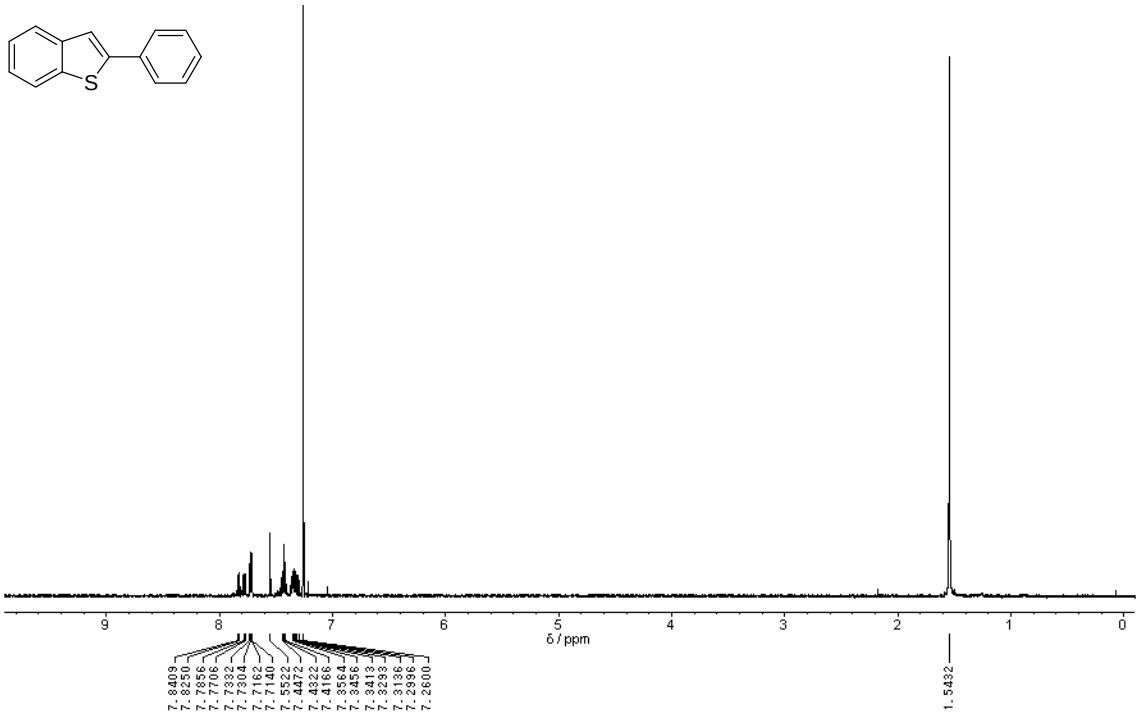
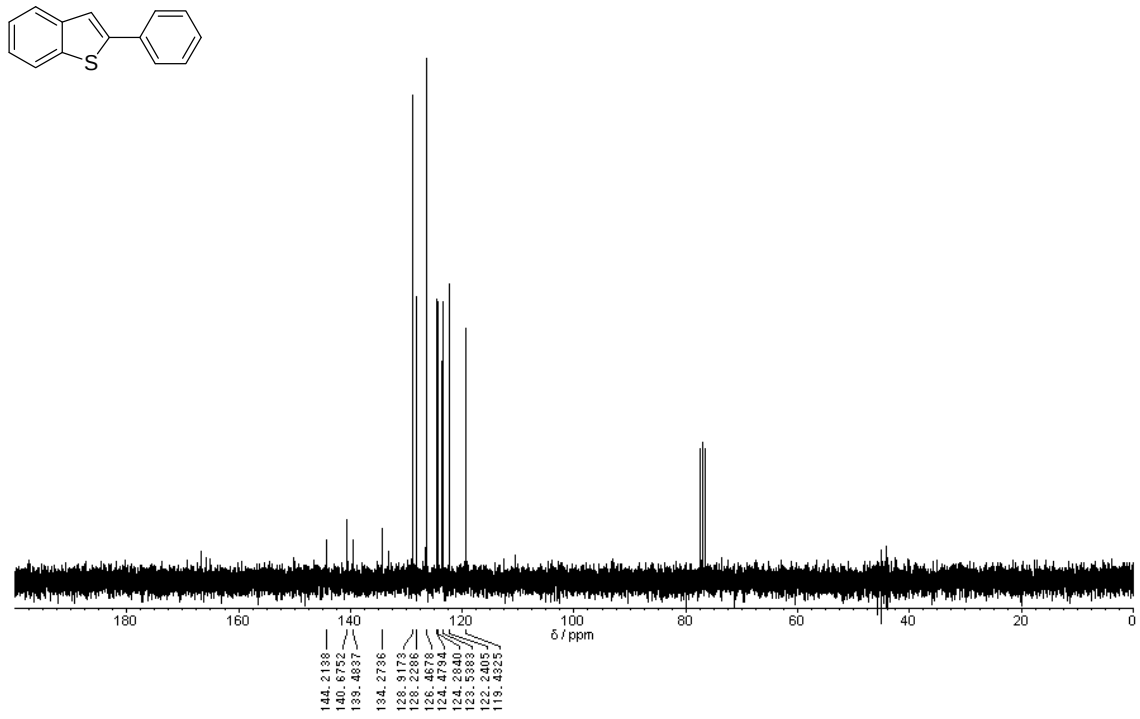
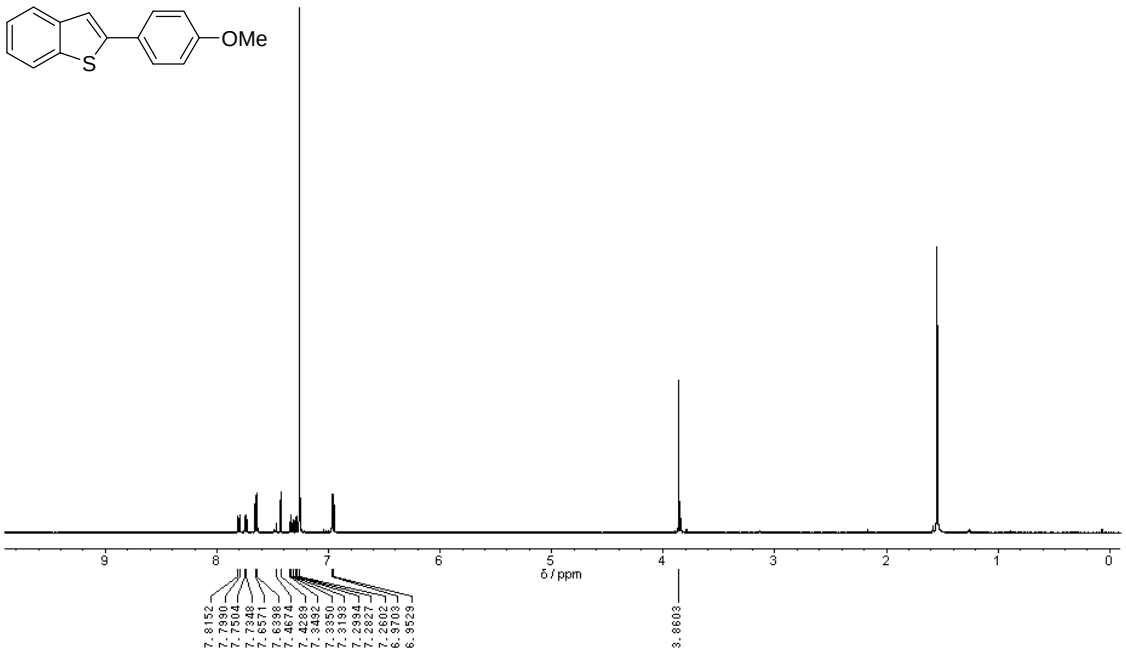


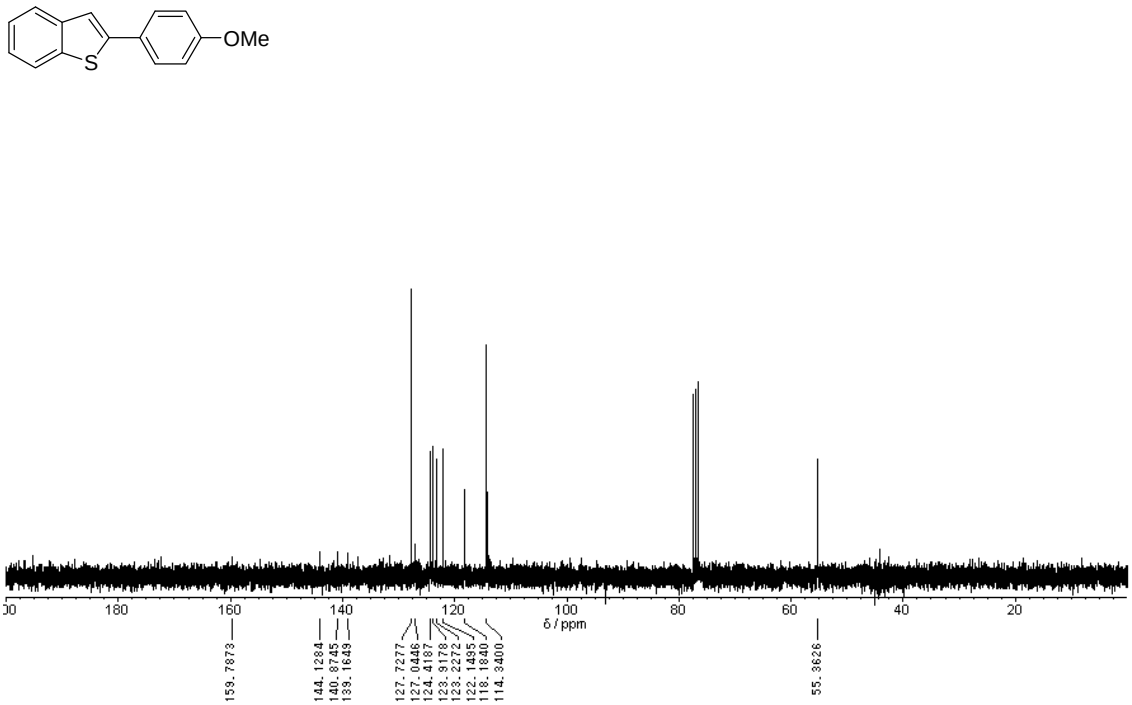
^{13}C NMR spectrum of **3b**



^{1}H NMR spectrum of **3c**



^{13}C NMR spectrum of **3c**



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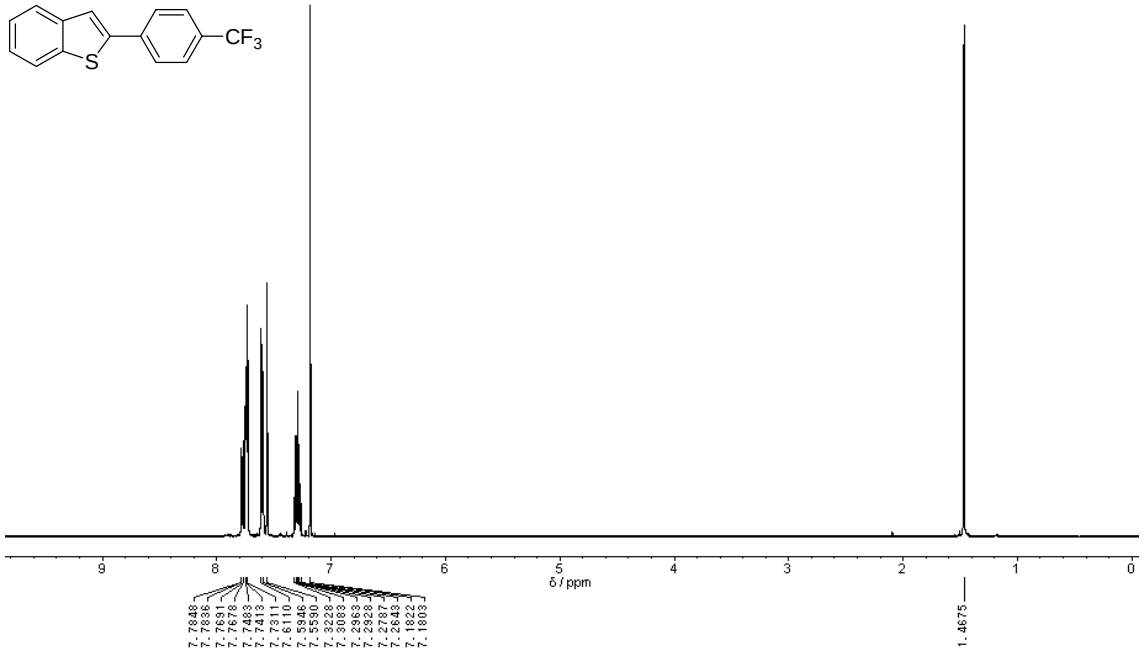

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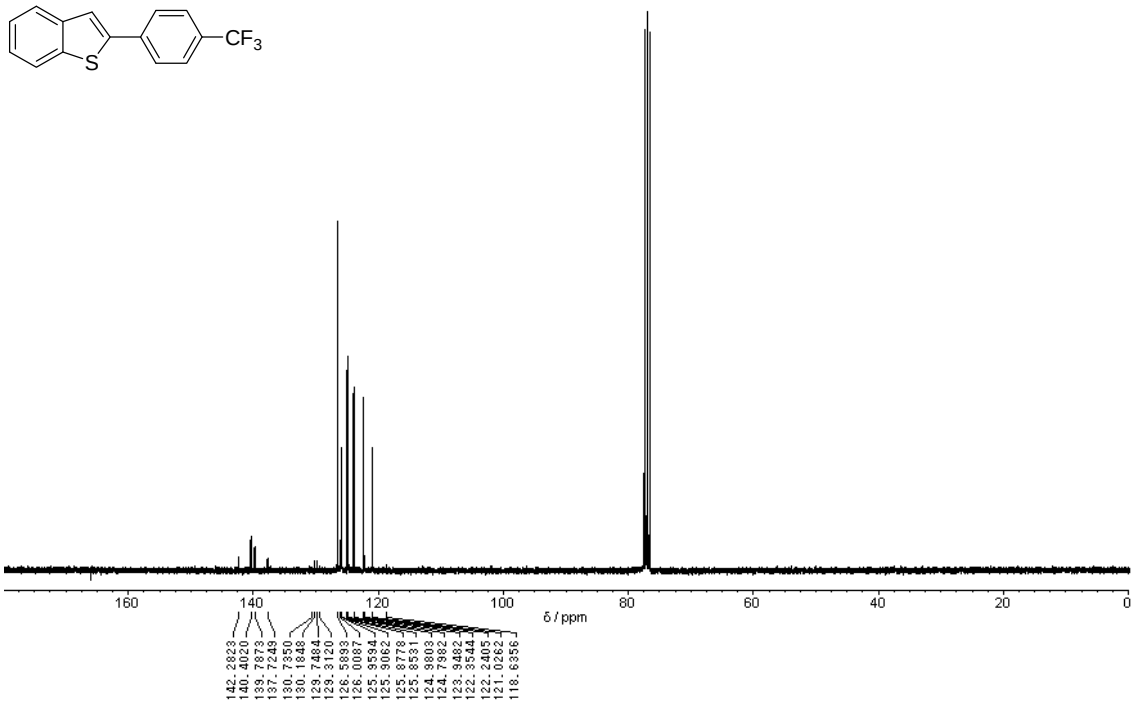

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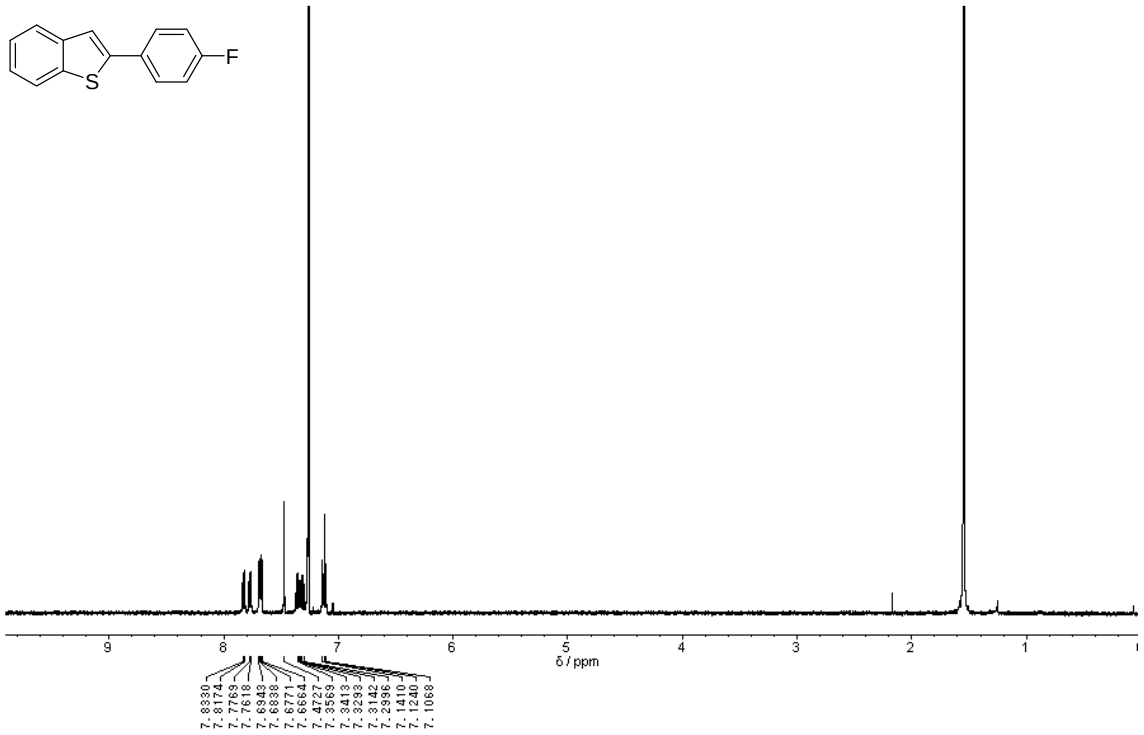

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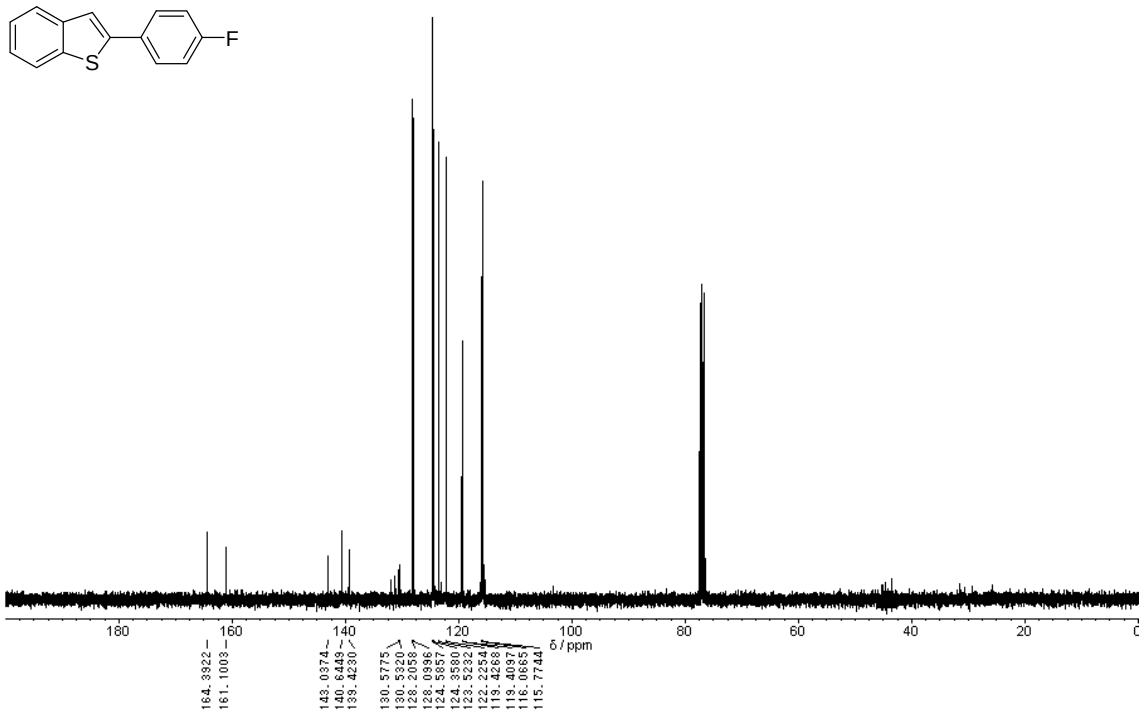
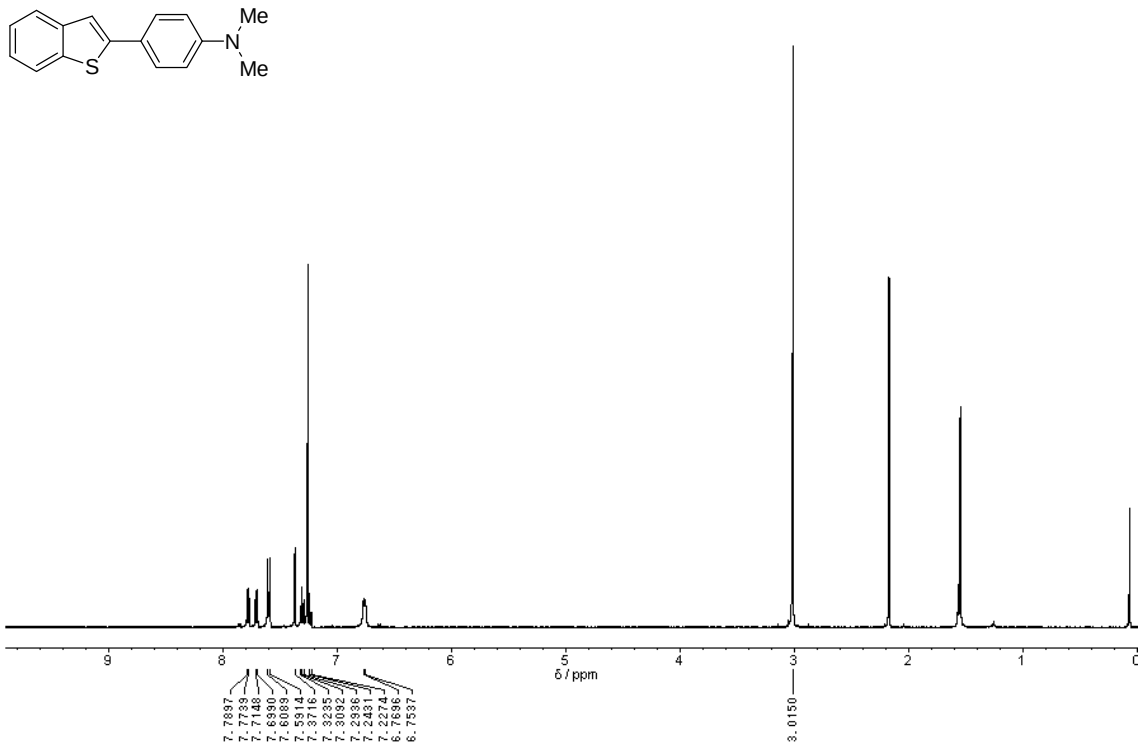
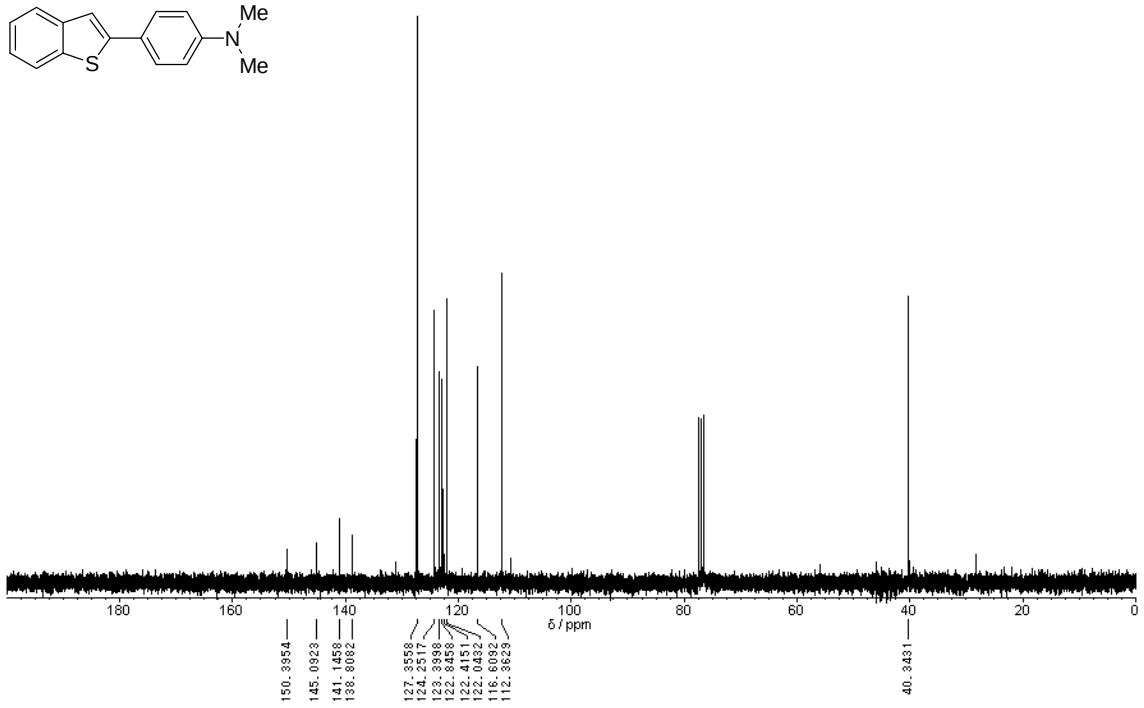


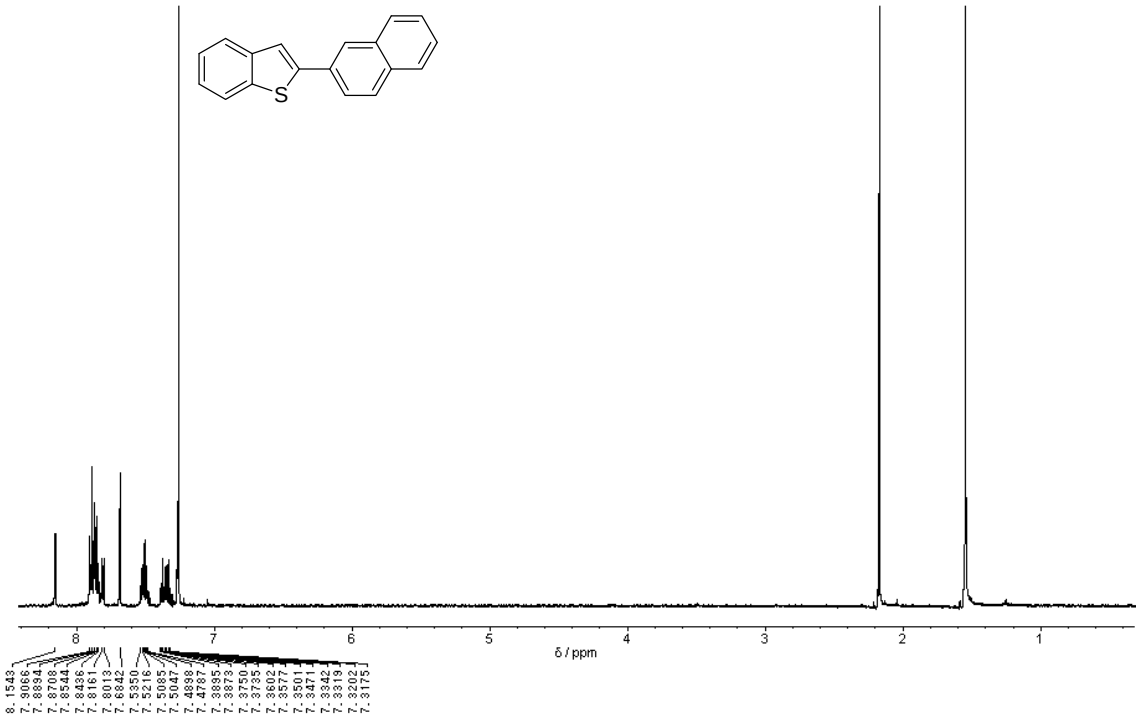
^{1}H NMR spectrum of **3f**



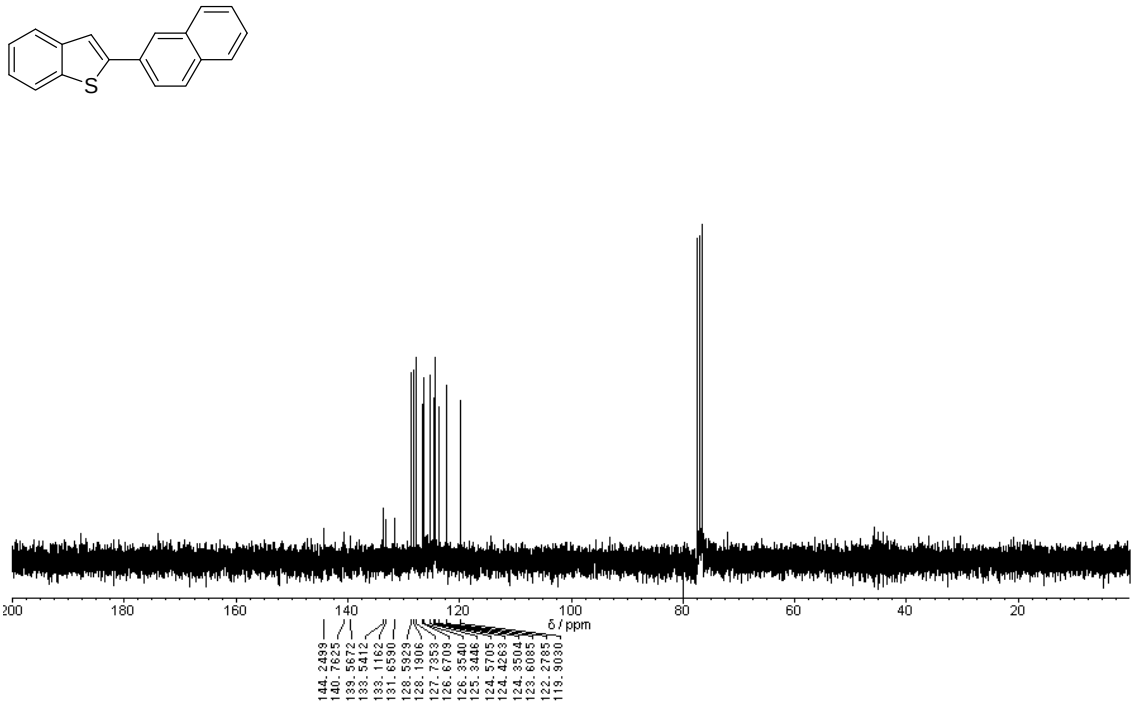
^{13}C NMR spectrum of **3f**



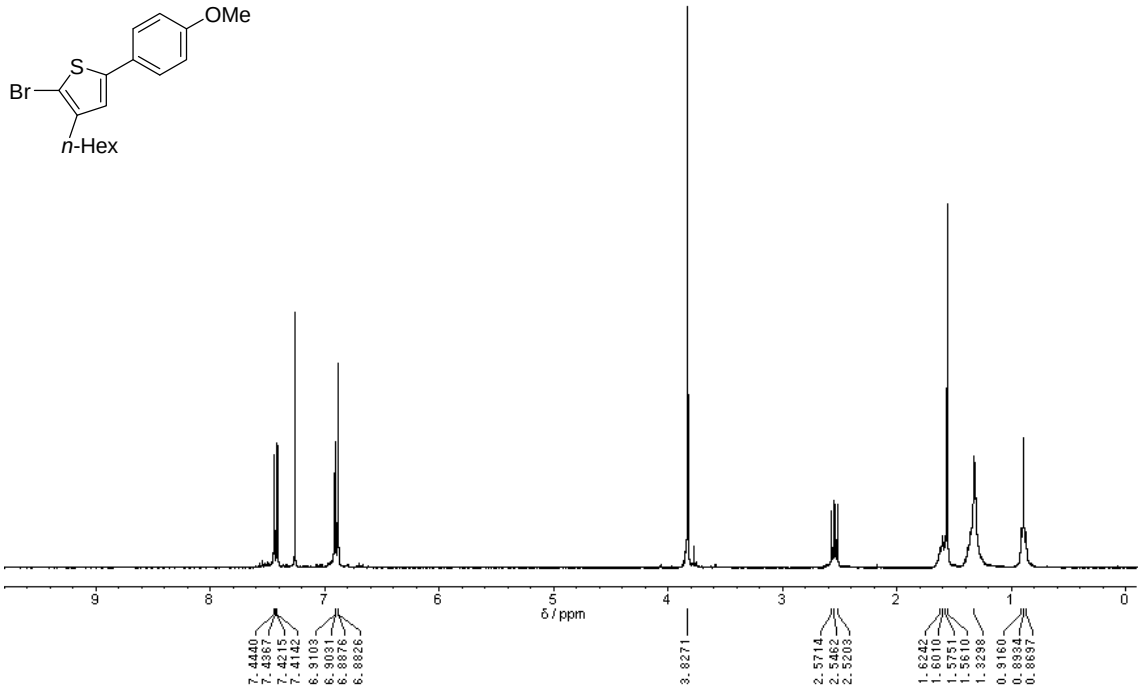
^{1}H NMR spectrum of **3g**



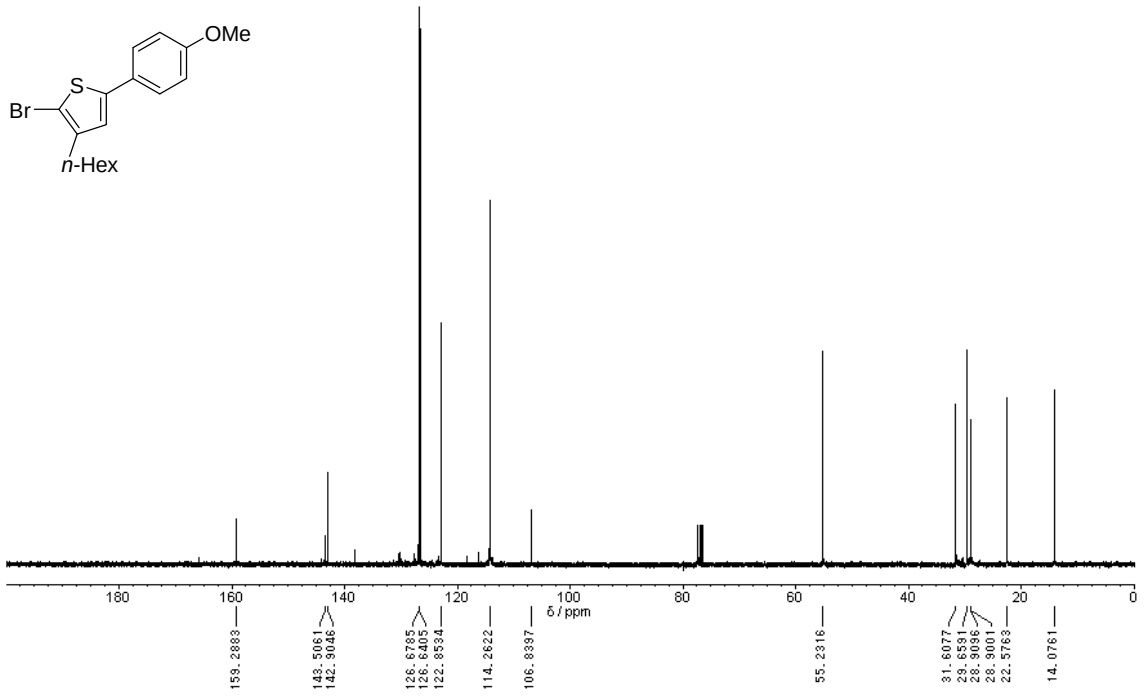
^{13}C NMR spectrum of **3g**



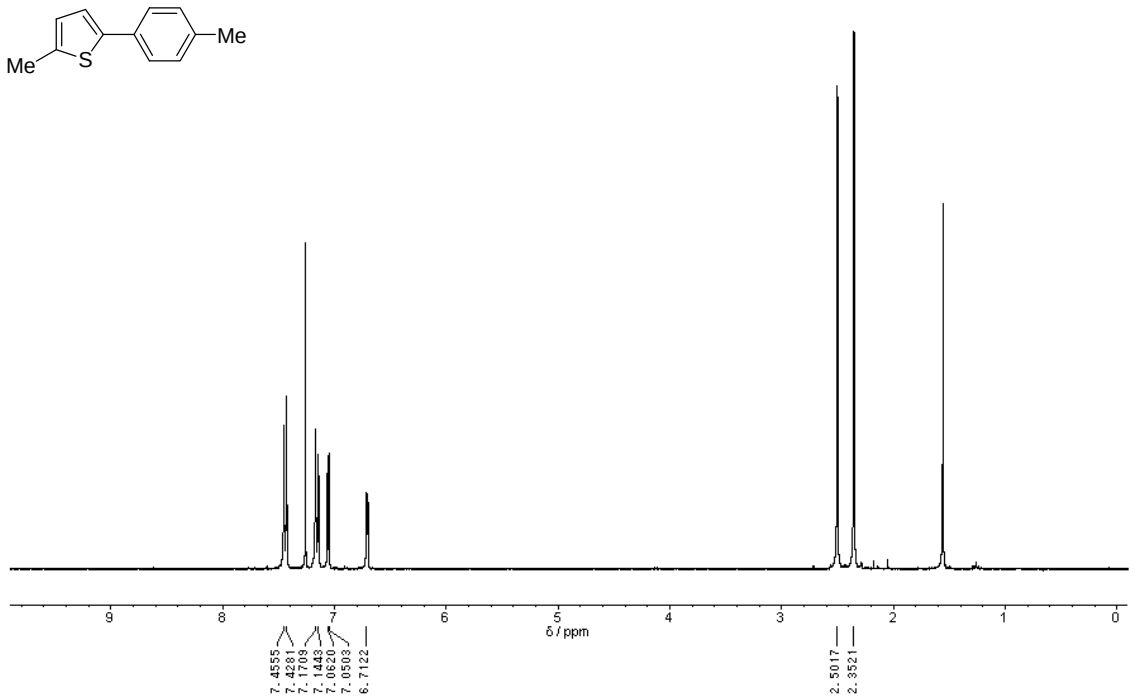
^{1}H NMR spectrum of **2h**



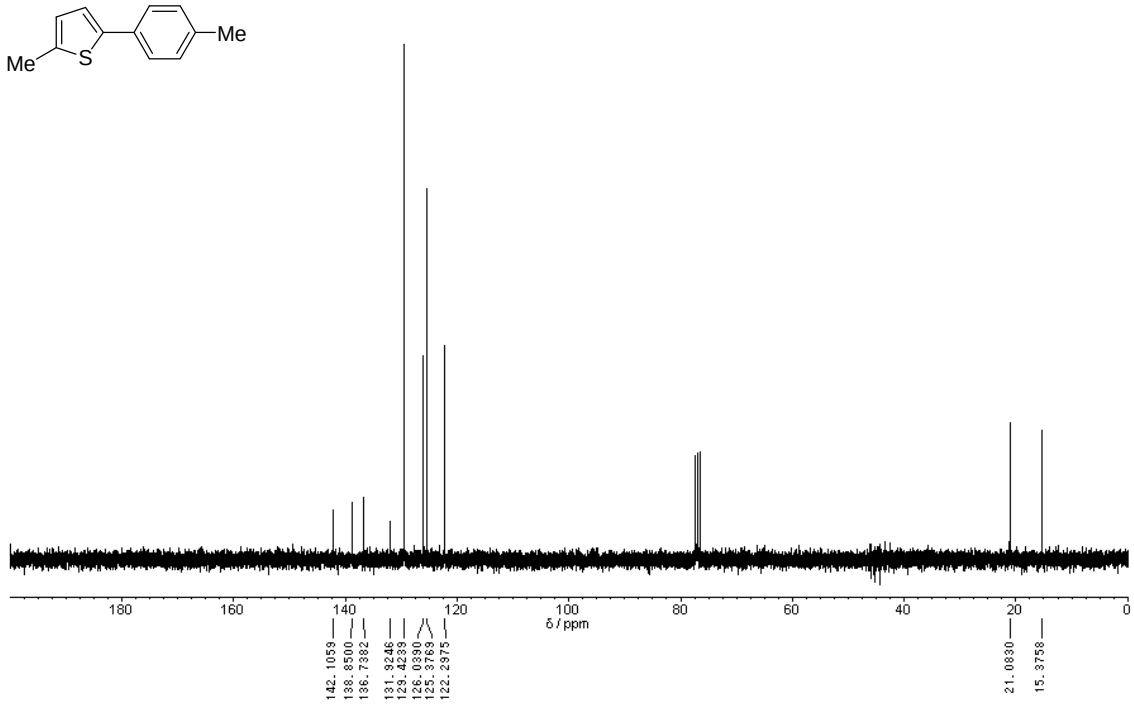
^{13}C NMR spectrum of **2h**



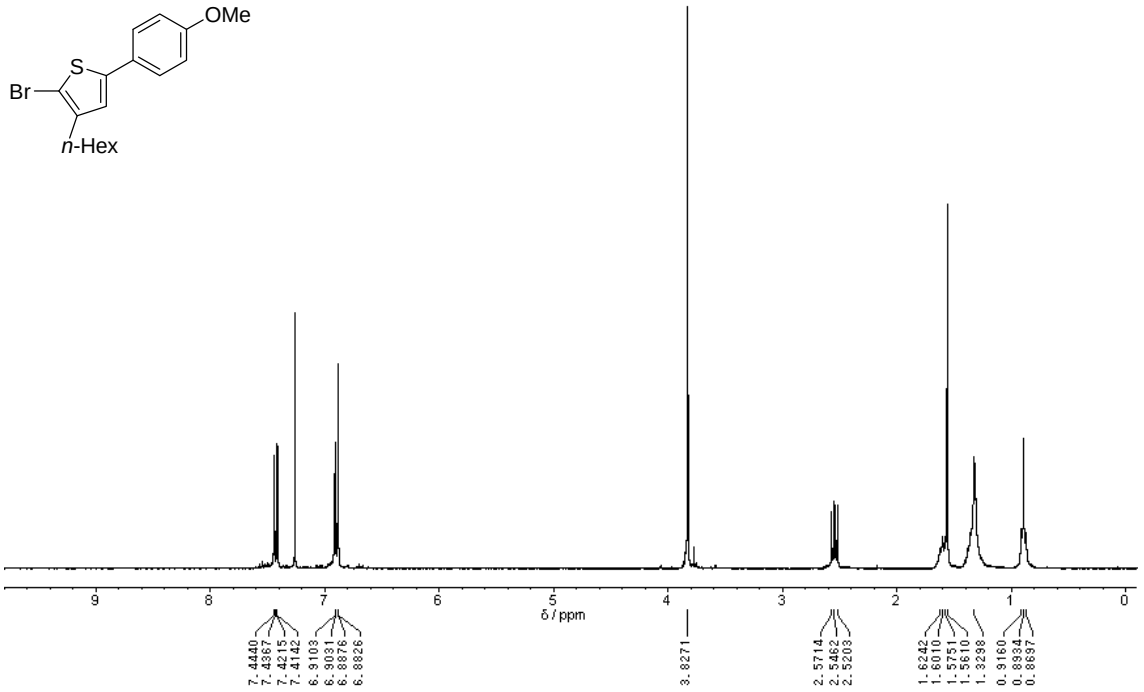
^{1}H NMR spectrum of **6a**



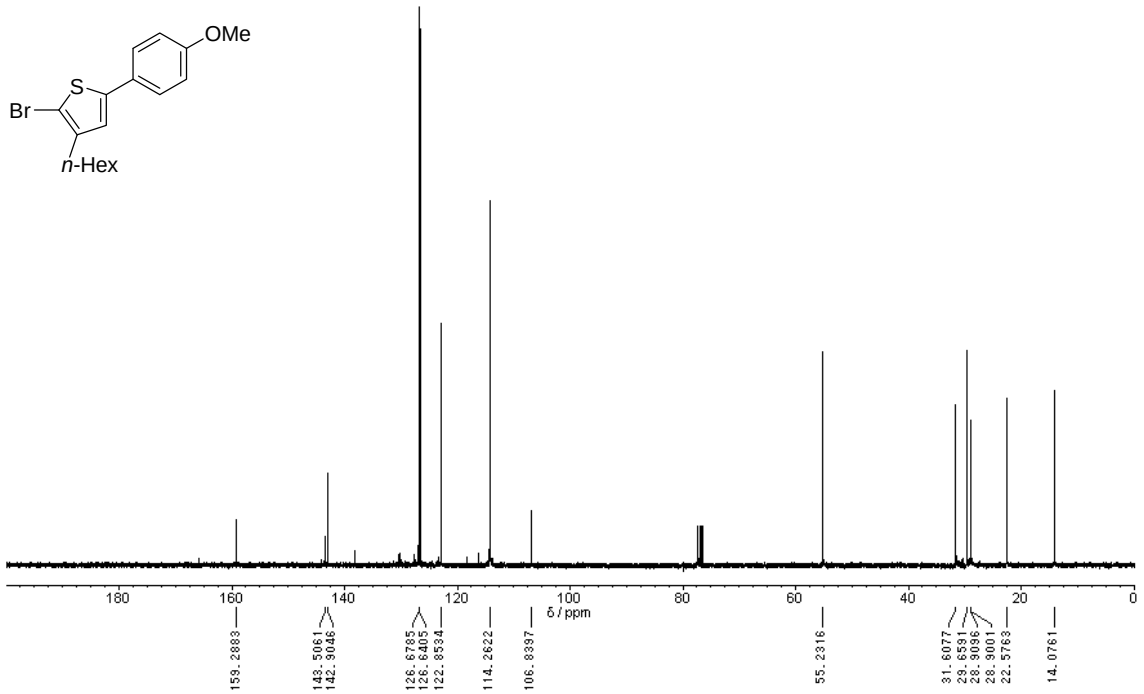
^{13}C NMR spectrum of **6a**



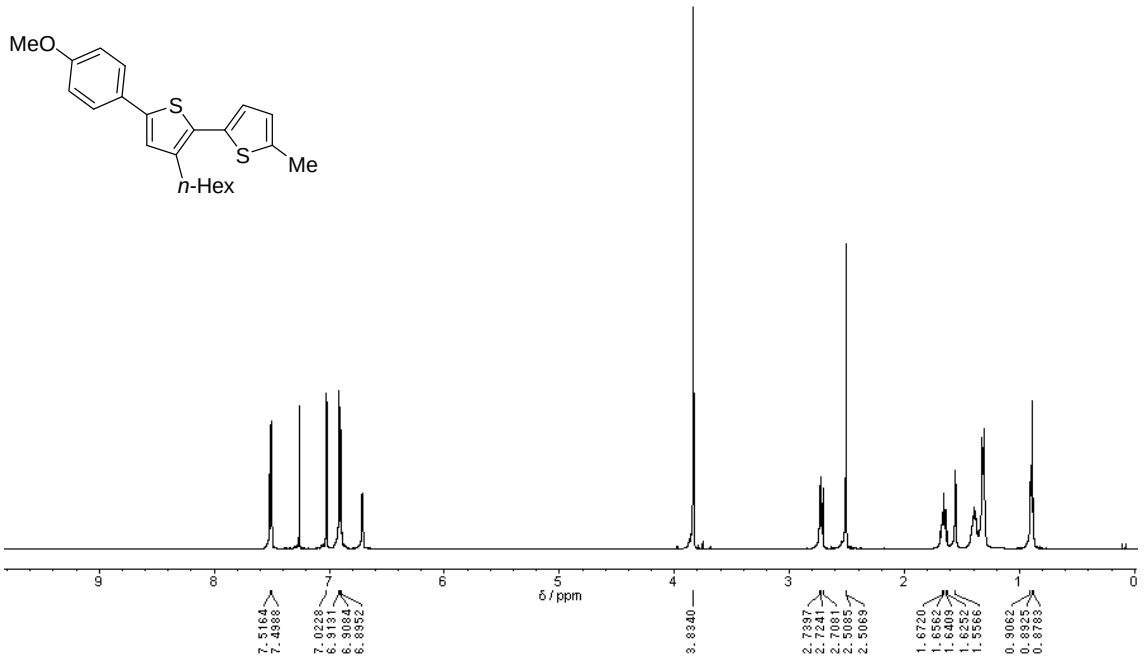
^{1}H NMR spectrum of **2h**



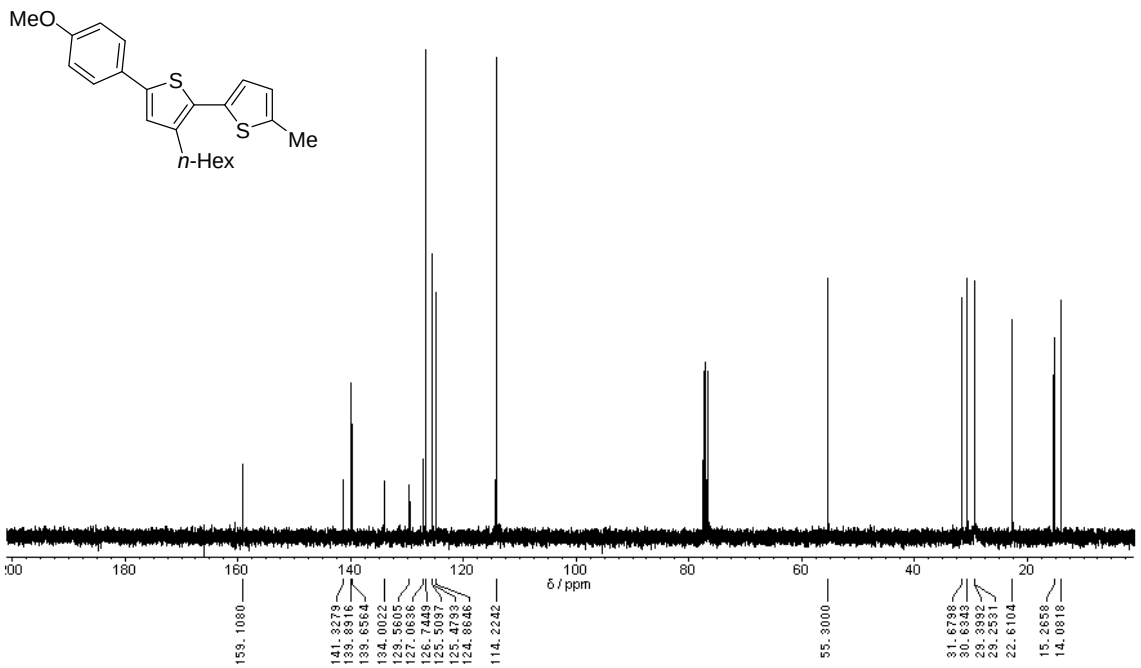
^{13}C NMR spectrum of **2h**



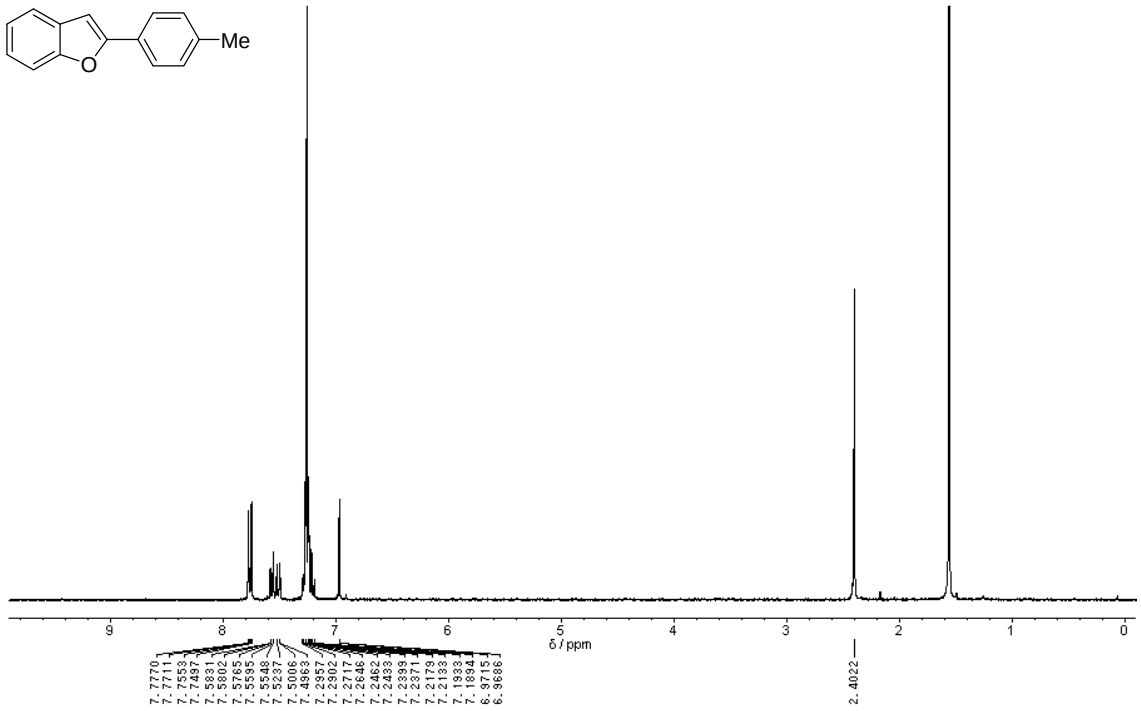
^{1}H NMR spectrum of **6h**



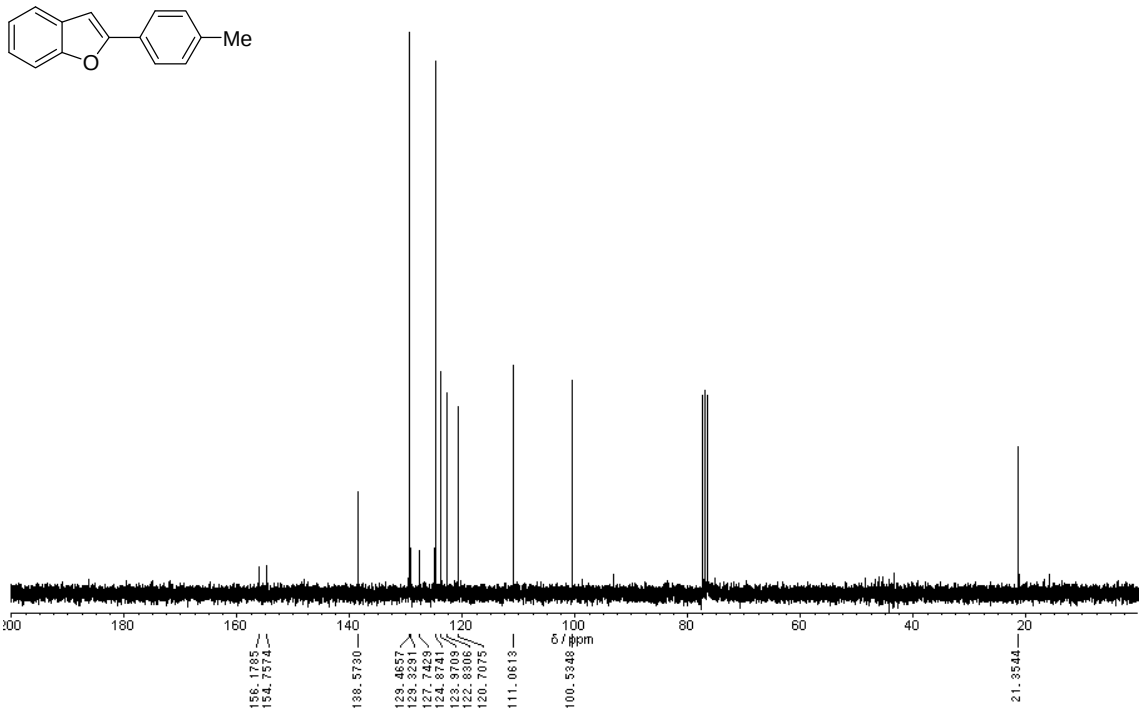
^{13}C NMR spectrum of **6h**



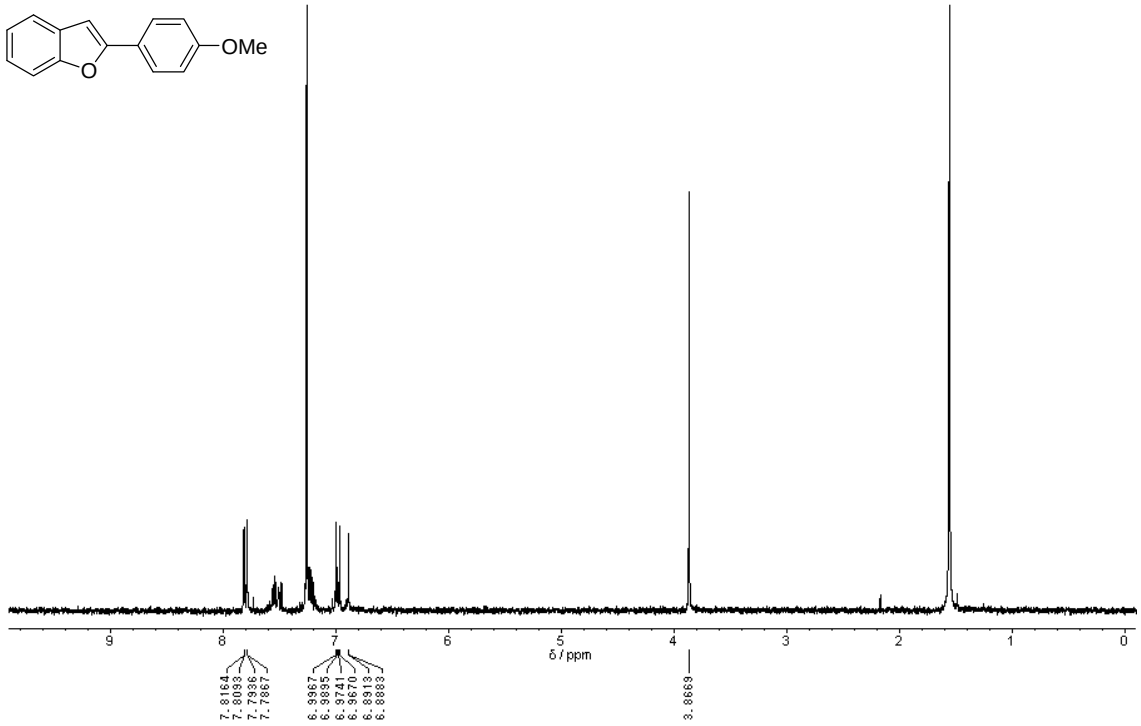
^{1}H NMR spectrum of **8a**



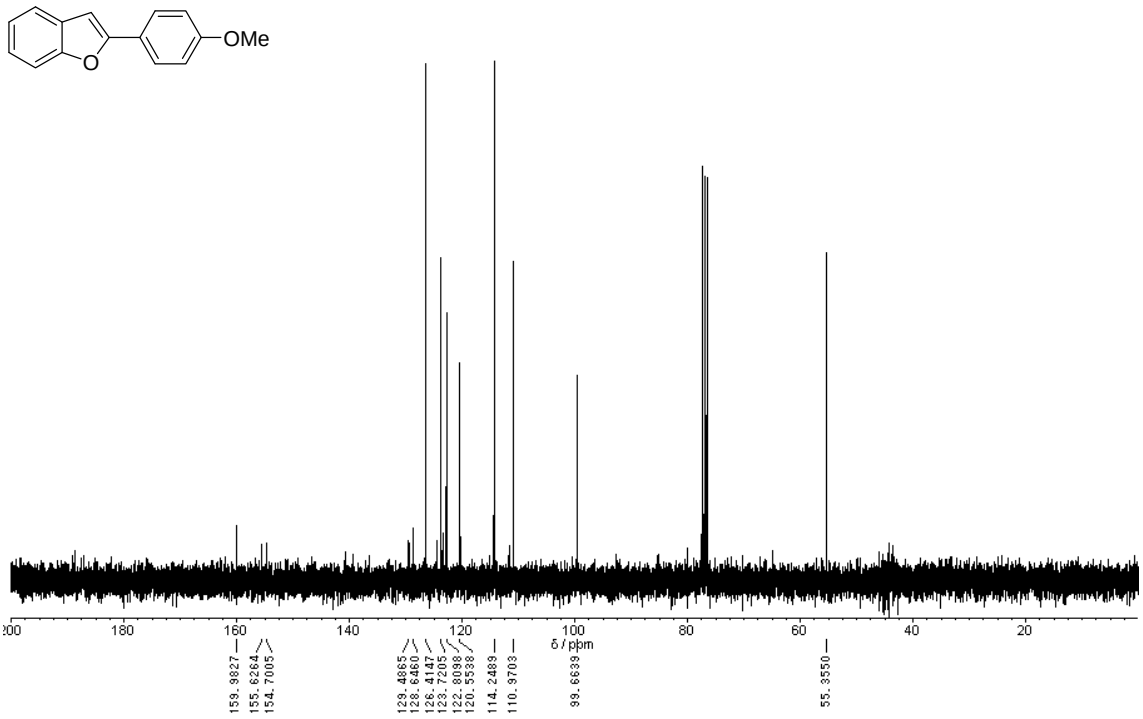
^{13}C NMR spectrum of **8a**



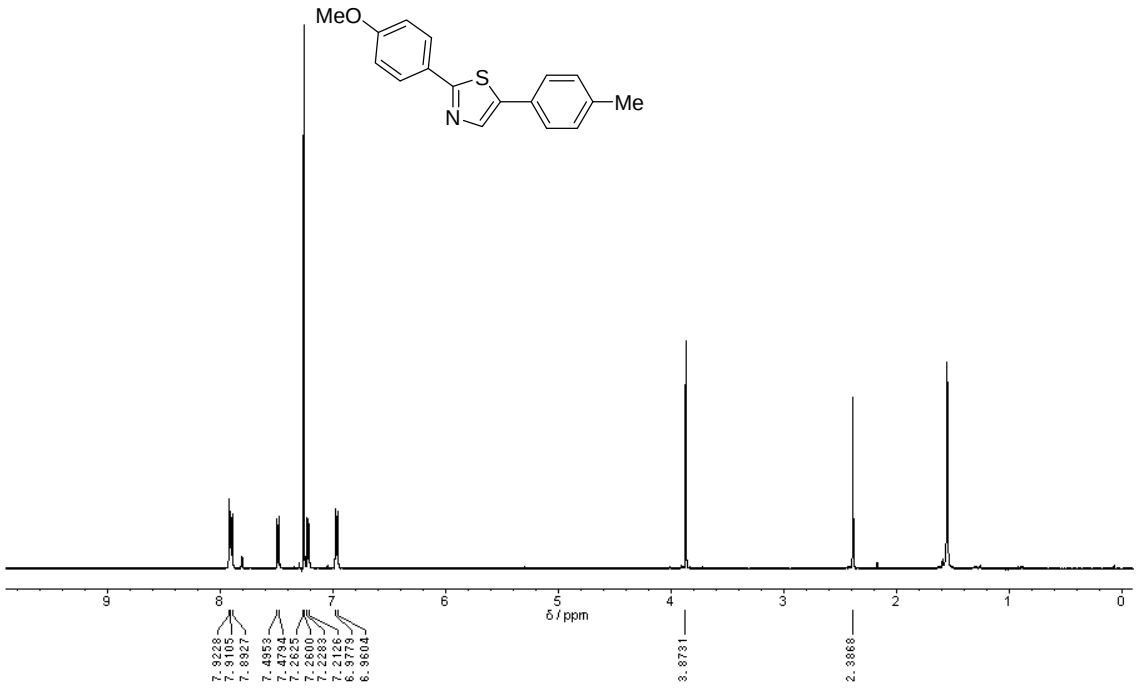
^{1}H NMR spectrum of **8c**



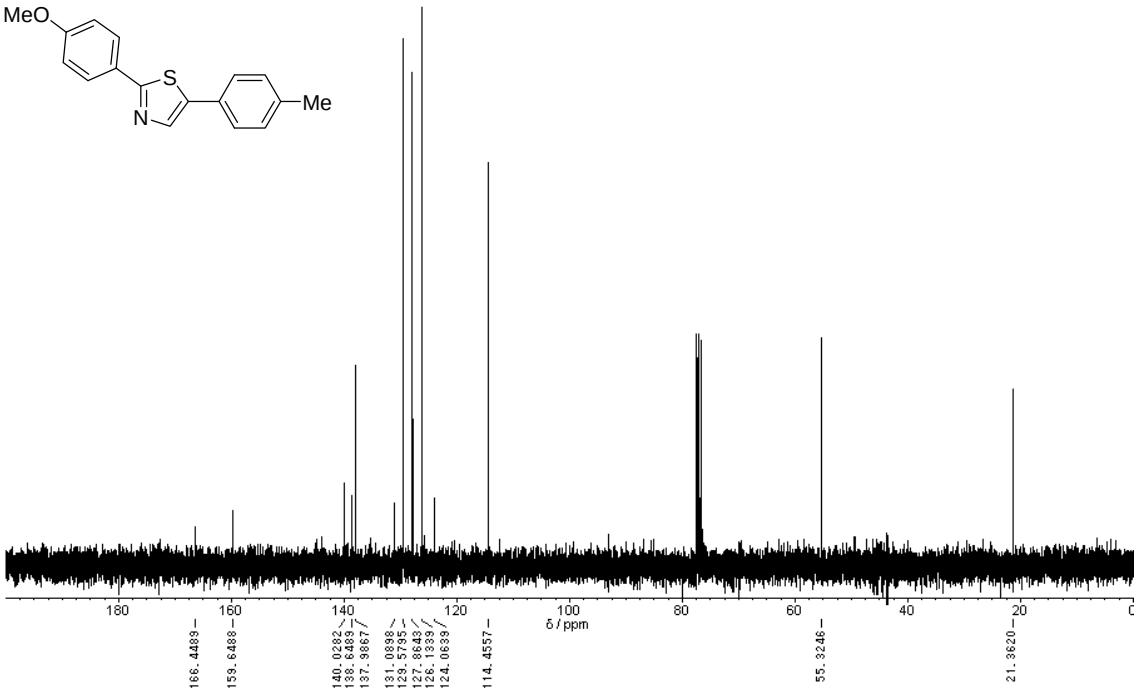
^{13}C NMR spectrum of **8c**



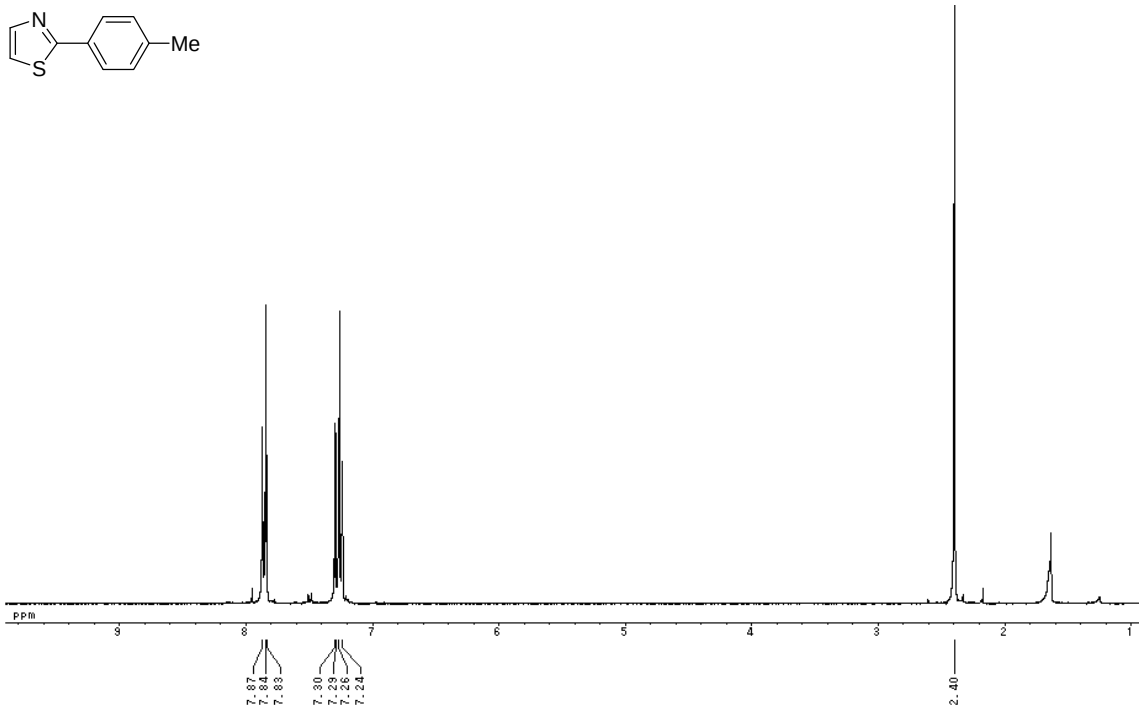
^{1}H NMR spectrum of **10a**



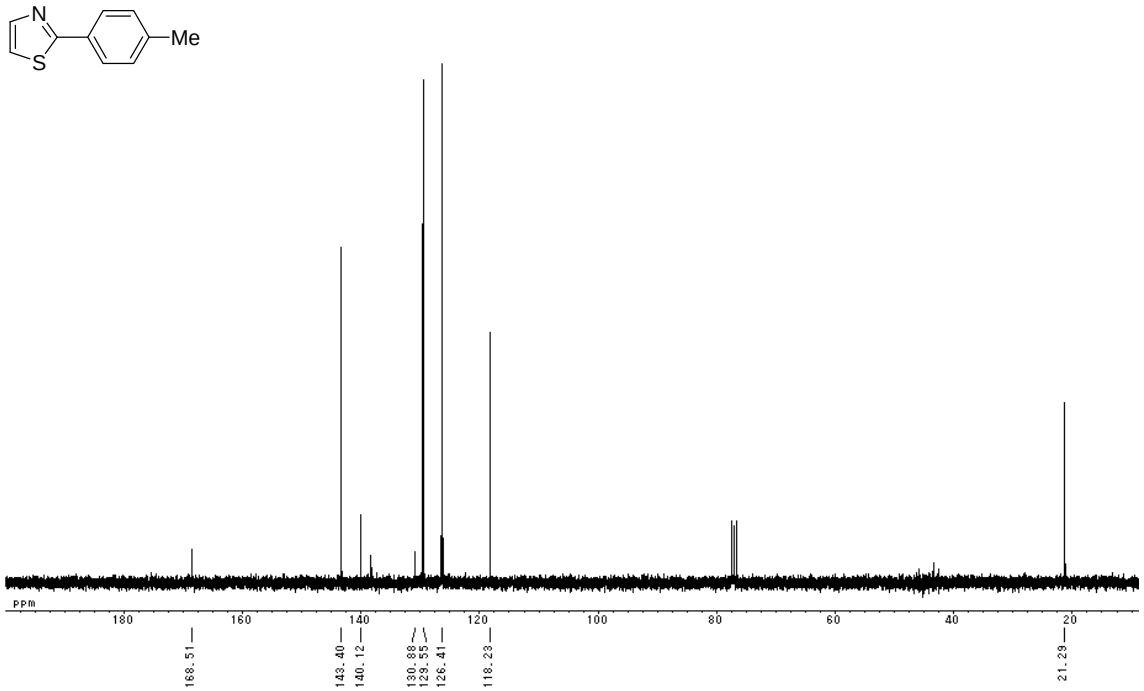
^{13}C NMR spectrum of **10a**



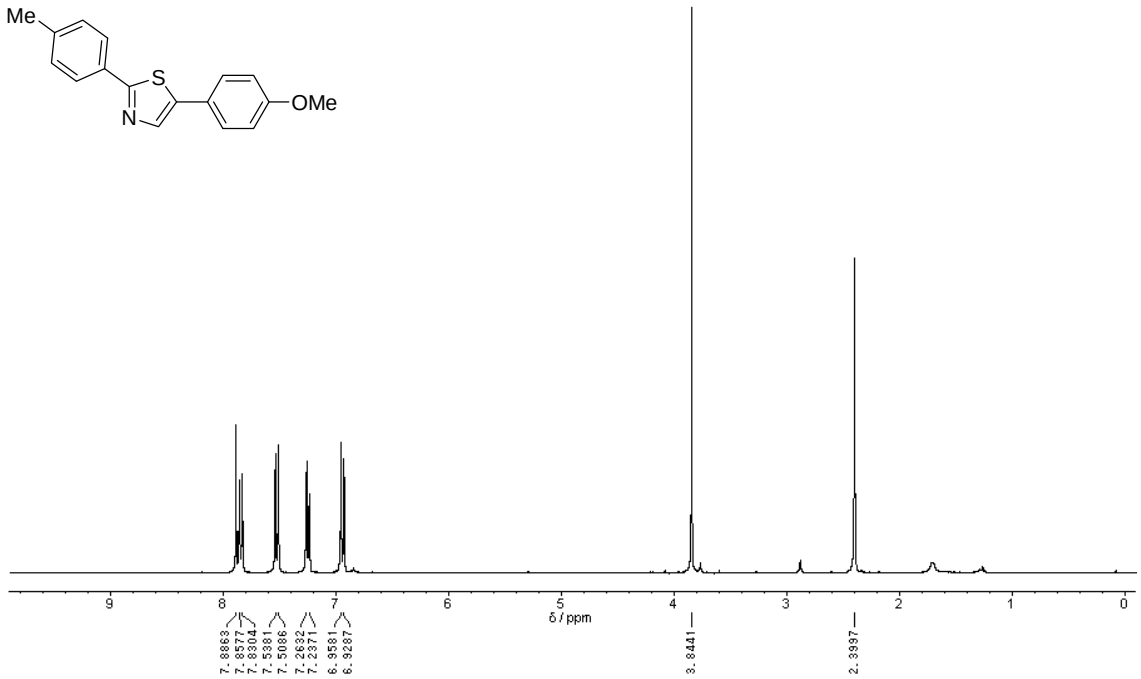
^{1}H NMR spectrum of **11**



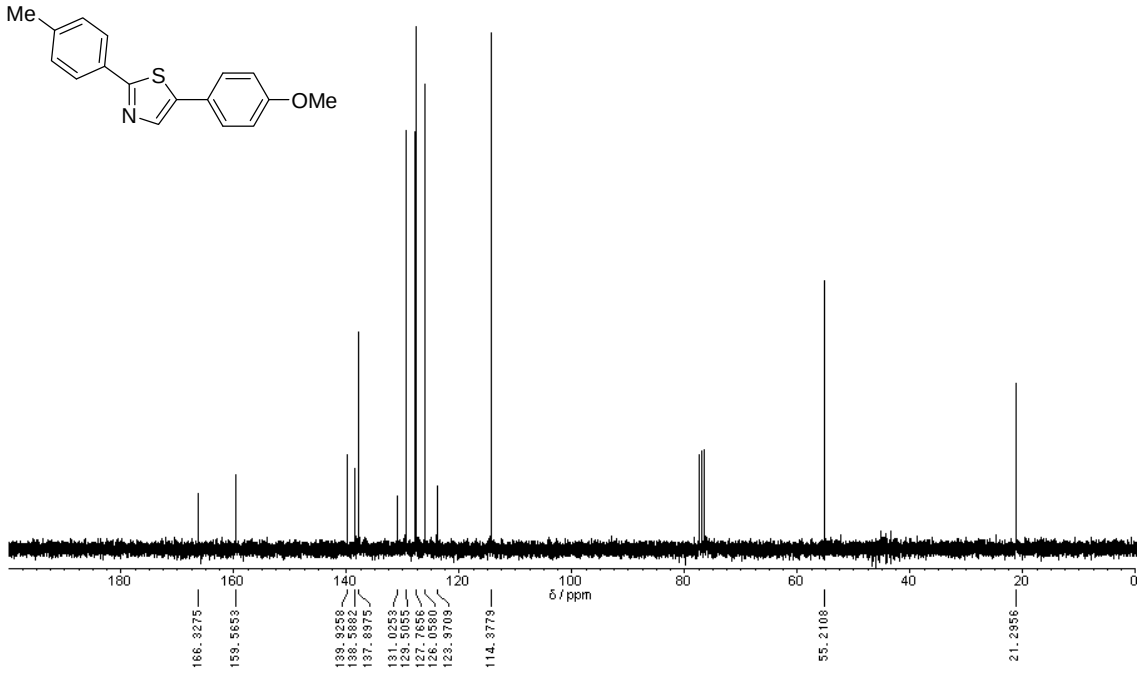
^{13}C NMR spectrum of **11**



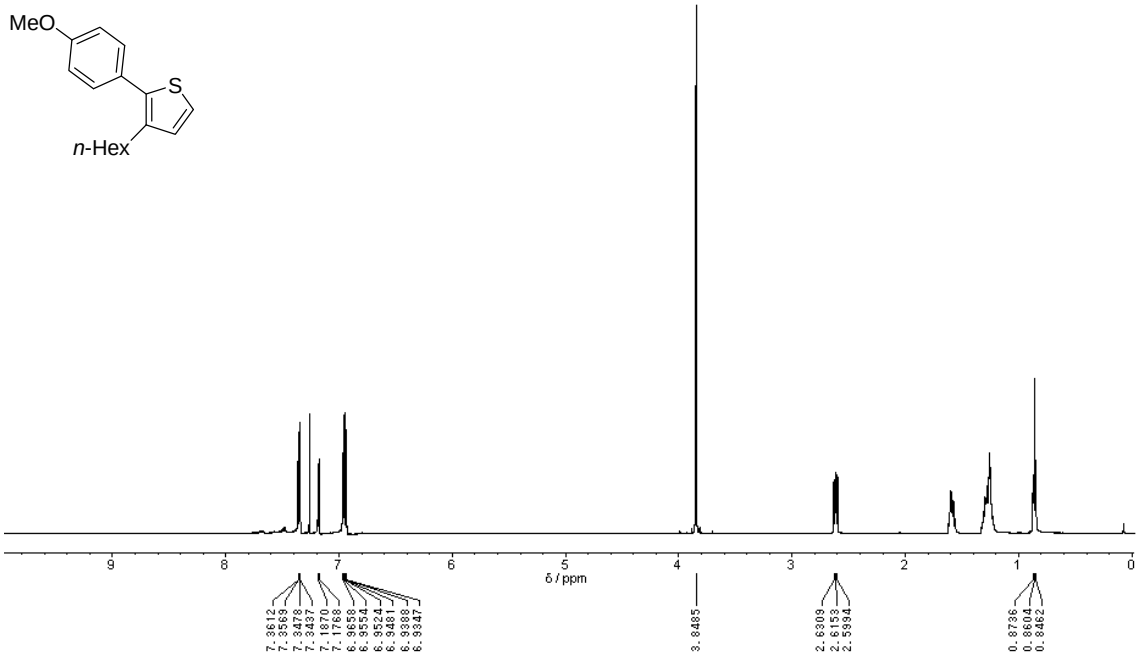
^{1}H NMR spectrum of **12c**



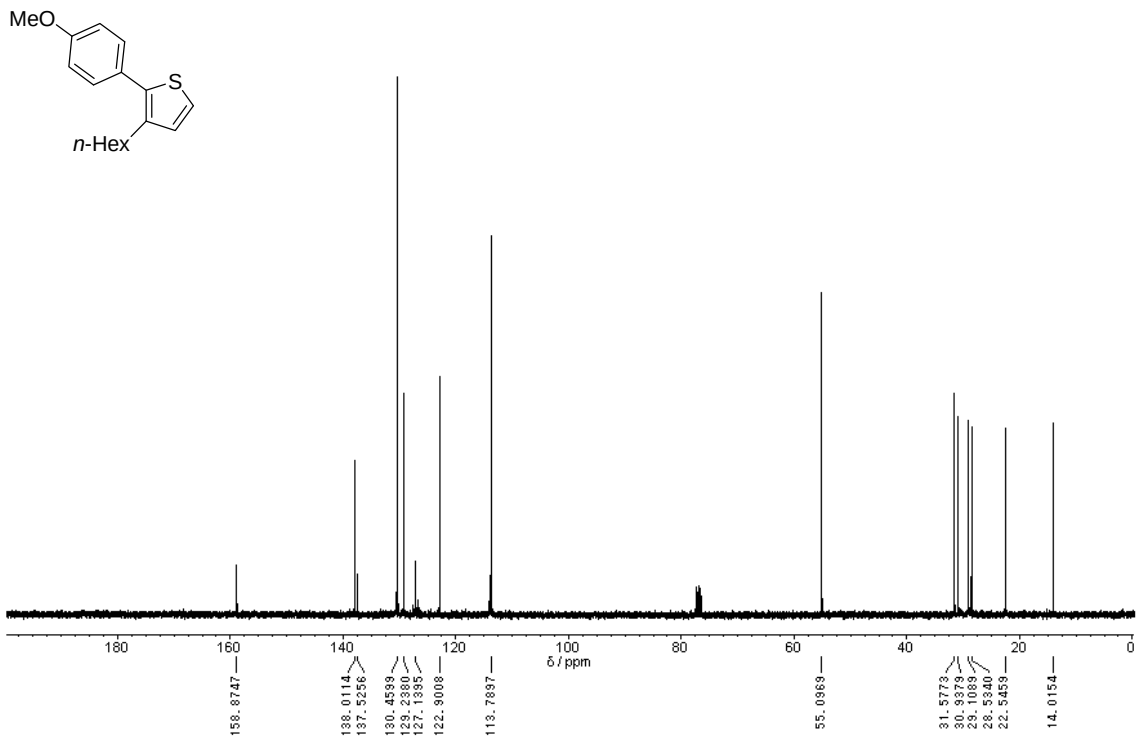
^{13}C NMR spectrum of **12c**



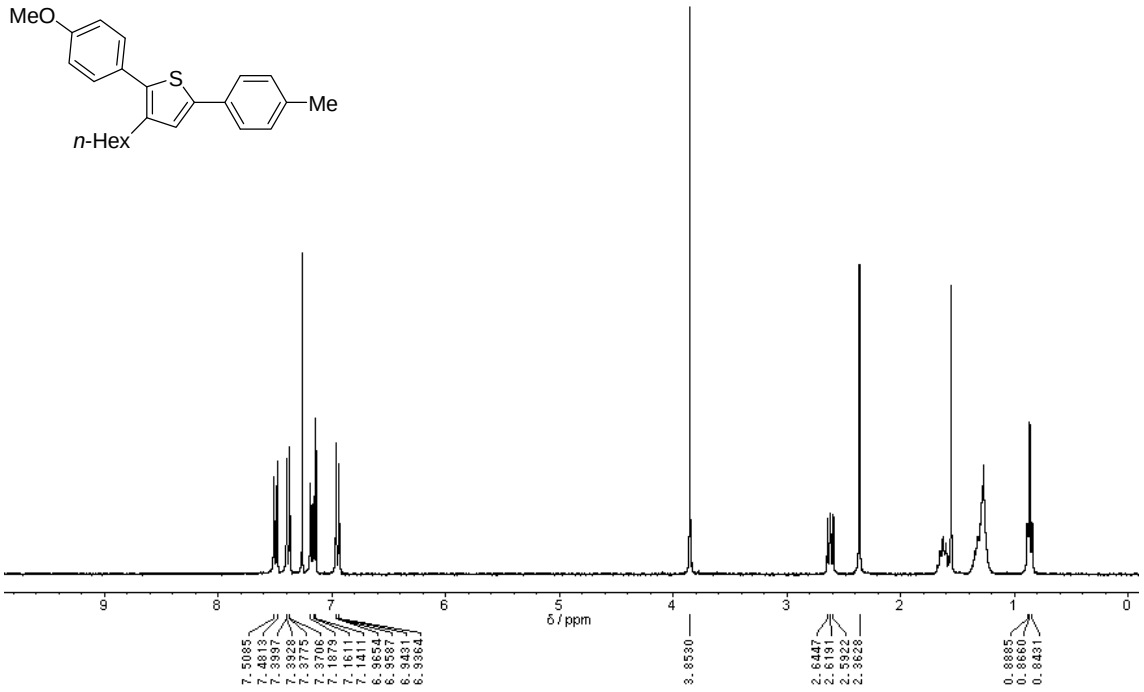
^{1}H NMR spectrum of **13**



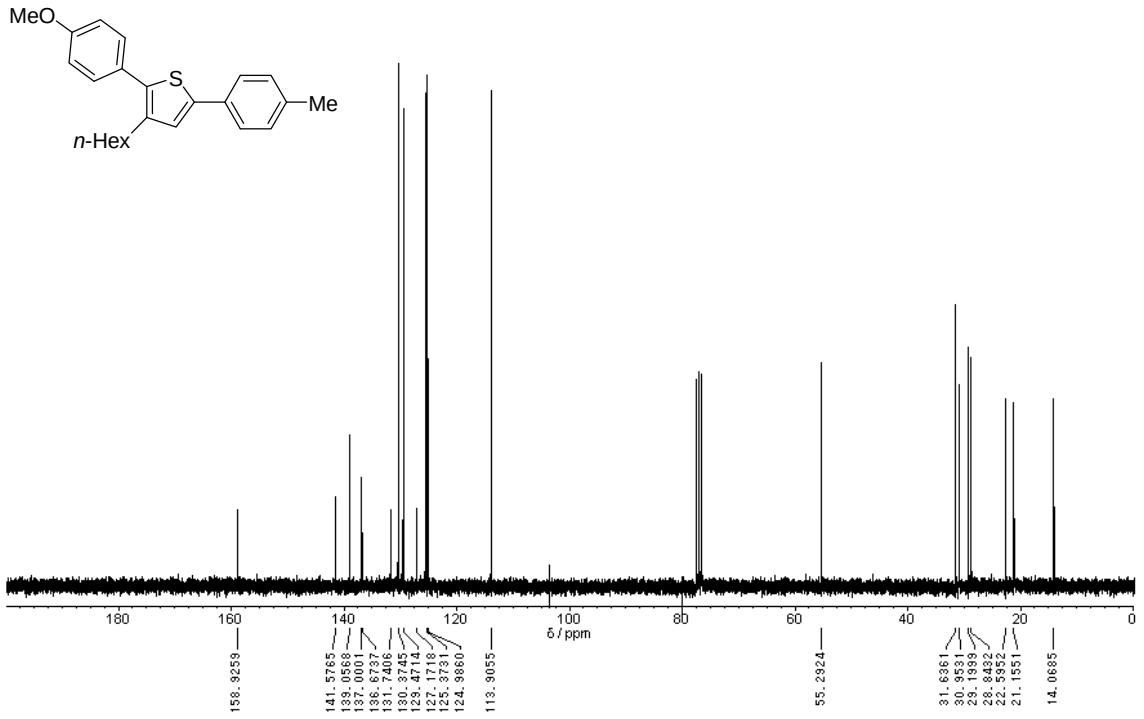
^{13}C NMR spectrum of **13**



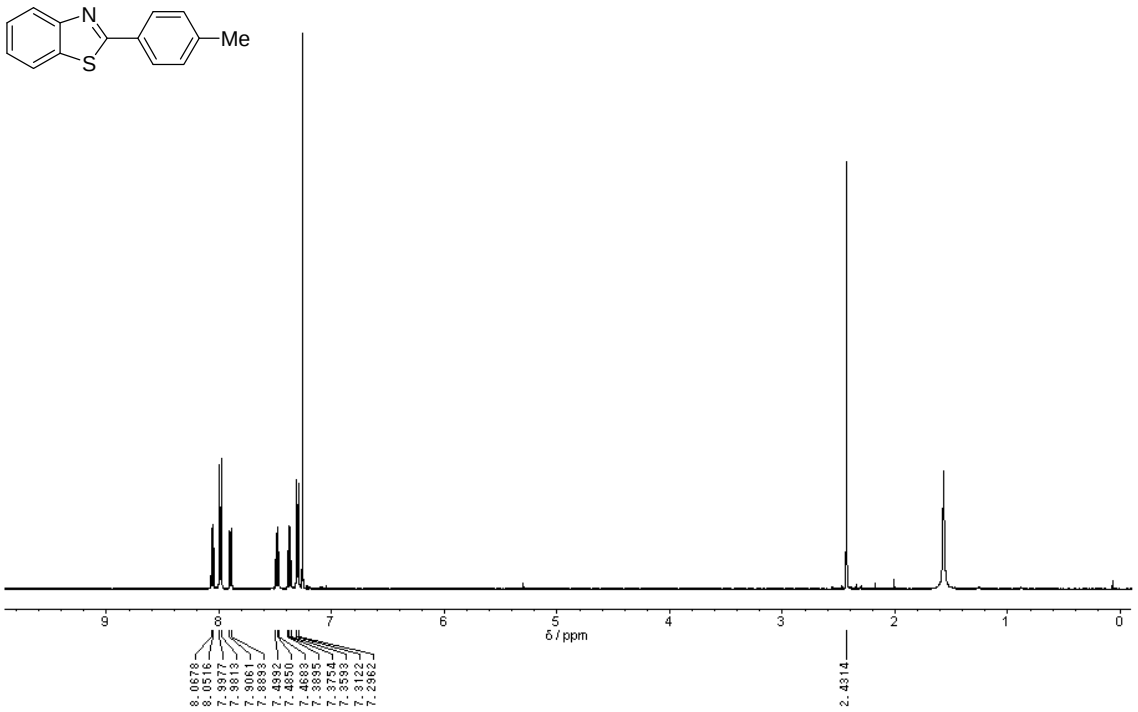
^{1}H NMR spectrum of **14a**



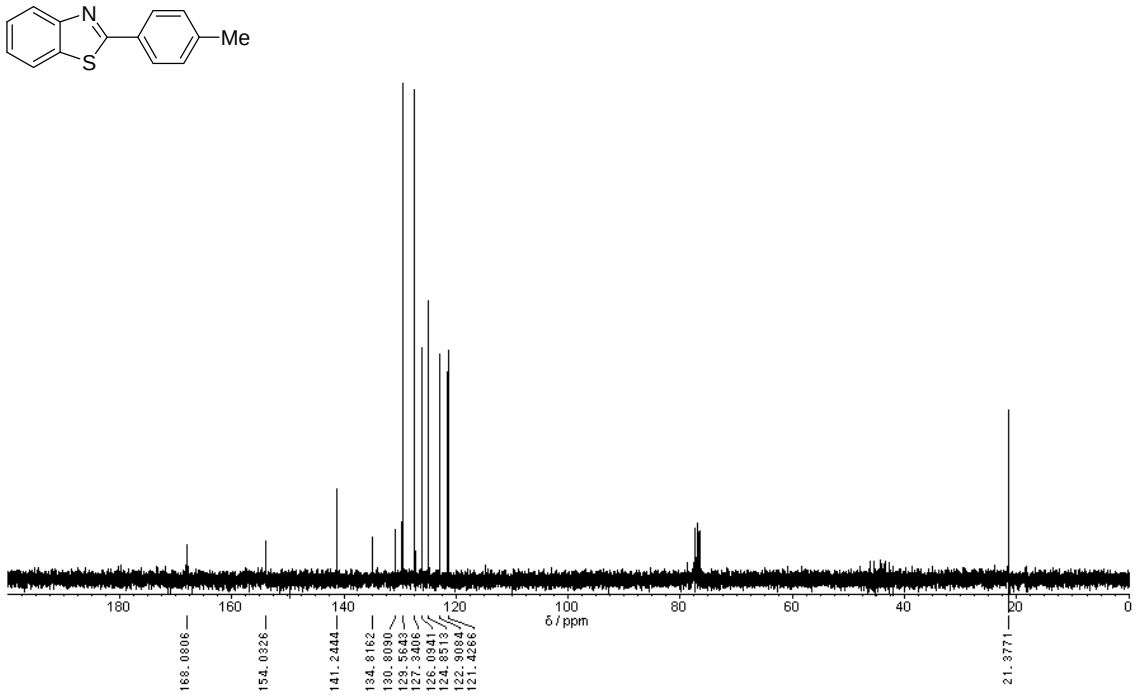
^{13}C NMR spectrum of **14a**



^{1}H NMR spectrum of **16a**



^{13}C NMR spectrum of **16a**



(1) Ohta, A.; Akita, Y.; Ohkuwa, T.; Chiba, M.; Fukunaga, R. *Heterocycles* **1990**, *31*, 1951.
(2) Klayman, D. L.; Shine, R. J.; Bower, J. D. *J. Org. Chem*. **1972**, *37*, 1537.
(3) Banfield, J. E.; Davies, W.; Gamble, N. W.; Middleton, S. *J. Chem. Soc.* **1956**, 4791.
(4) Bíró, A. B.; Kotschy, A. *Eur. J. Org. Chem.* **2007**, 1364.
(5) Chang, Y. S.; Jeong, J. M.; Lee, Y.-S.; Kim, H. W.; B, G. R.; Kim, Y. J.; Lee, D. S.; Chung, J.-K.; Lee, M. C. *Nucl. Med. Biol.* **2006**, *33*, 811.
(6) Robert, D.; Schuetz, L. C. *J. Org. Chem.* **1958**, *23*, 206.
(7) Shridhar, D. R.; Jogibhukta, M.; Shanthan, P. R.; Handa, V. J. *Synthesis* **1982**, 1061.
(8) G. W. Kabalka, L. Wang, R. W. Pagni, *Tetrahedron* **2001**, *57*, 8017.
(9) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc.* **2003**, *125*, 1700.
(10) Jensen, J.; Skjærbæk, N.; Vedsøc, P. *Synthesis* **2001**, 128.
(11) Dölling, K.; Zaschke, H.; Schubert, H. *J. Prakt. Chem*. **1979**, *321*, 643-654.
(12) Laskar, I. R.; Chen, T.-M. *Chem. Mater.* **2004**, *16*, 111.