Pd-Catalyzed Cross-Coupling of Functionalized Organozinc Reagents with Thiomethyl-Substituted Heterocycles

*Albrecht Metzger, Laurin Melzig, Christina Despotopoulou, and Paul Knochel**

Department of Chemistry and Biochemistry, Ludwig-Maximilians-University Munich,

Butenandtstrasse 5-13, Haus F, 81377 Munich (Germany)

Supporting Information

Table of contents

General All reactions were carried out under an argon atmosphere in dried glassware. All starting materials which were purchased from commercial sources were used without further purification. Solvents were dried according to the standard methods by distillation over drying agents under nitrogen atmosphere as follows: CH_2Cl_2 (CaH_2), toluene (Na), diethyl ether (Na/benzophenone). THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen before use. Yields refer to isolated yields of compounds estimated to be > 95% pure as determined by ^{1}H-NMR and capillary GC.

Typical Procedure for the Pd-catalyzed cross coupling reaction (TP1):

In a dry argon-flushed Schlenk flask equipped with a septum and a magnetic stirring bar, the aromatic thioether (1.00 mmol), $Pd(OAc)_2$ (2.5 mol %) and S-Phos (5.0 mol %) were dissolved in THF (1 mL). After 10 min of stirring, the zinc reagent (1.5 mmol) was added dropwise and the reaction mixture was stirred for the given time at the required temperature until GC-analysis of a hydrolyzed aliquot showed full consumption of the electrophile. The reaction mixture was quenched with saturated aqueous NH_4Cl-solution or Na_2CO_3-solution and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The product was purified by flash column chromatography.

Preparation of zinc reagents of type 1, 4 and 6:

All zinc reagents were prepared according to: (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 6040; (b) Metzger, A.; Schade, M. A.; Knochel, P. *Org. Lett.* **2008**, *10*, 1107; (c) Sase, S.; Jaric, M.; Metzger, A.; Malakhov, V.; Knochel, P. *J. Org. Chem.* **2008**, *73*, 7380.

Starting materials of type 2

Compound **2f** and **2j** are commercially available**.**

For the preparation of **2e** see: Despotopoulou, C.; Klier, L.; Knochel, P. *Org. Lett.* **2009**, DOI: 10.1021/ol901208d

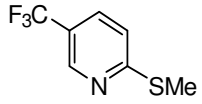
For the preparation of **2i** see: (a) Gosmini, C.; Nédélec J. Y.; Périchon, J. *Tetrahedron Letters* **2000**, 41, (2), 201; (b) see also: Rohbogner, C. J.; Wunderlich, S. H.; Clososki, G. C.; Knochel, P, *Eur. J. Org. Chem.* **2009**, 1781.

For the preparation of **2k** see: Despotopoulou, C.; Gignoux, C.; McConnel, D.; Knochel P. *Synthesis* **2009**, *in press*.

For the preparation of **2l** see: Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.

For the preparation of **2m** see: Majeed, A. J.; Antonsen, O.; Benneche, T. Undheim, K. *Tetrahedron* **1989**, *45*, 993.

2-(Methylthio)-5-(trifluoromethyl)pyridine (2a)



5-(Trifluoromethyl)pyridine-2-thiol (2.69 g, 15.0 mmol) was dissolved in THF (13.5 mL) and CH_3CN (1.5 mL) at 0 °C. DBU (2.51 g, 16.5 mmol) was added dropwise and the resulting reaction mixture was stirred for 20 min. Then, MeI (2.34 g, 16.5 mmol) was added, the ice-bath was removed and the reaction mixture was stirred for 12.5 h. Addition of H_2O (50 mL) was followed by extraction using EtOAc (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the pyridine **2a** (1.59 g, 55%) as a pale yellow liquid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.71-8.63 (m, 1H), 7.70-7.60 (m, 1H), 7.30-7.21 (m, 1H), 2.58 (s, 3H).

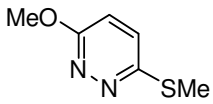
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.9 (q, $^4J_{C\text{-}F}$ = 1.5 Hz), 146.2 (q, $^3J_{C\text{-}F}$ = 4.4 Hz), 132.3 (q, $^3J_{C\text{-}F}$ = 3.4 Hz), 123.8 (q, $^1J_{C\text{-}F}$ = 271.6 Hz), 122.0 (q, $^2J_{C\text{-}F}$ = 33.0 Hz), 121.0, 13.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2932 (vw), 1596 (m), 1556 (w), 1475 (w), 1377 (w), 1321 (vs), 1251 (w), 1166 (m), 1113 (vs), 1073 (s), 1008 (m), 967 (w), 938 (w), 827 (m), 791 (w), 746 (w).

MS (EI, 70 eV): m/z (%) = 193 (M^+, 100), 147 (44), 127 (19), 78 (8).

HRMS ($C_7H_6F_3NS$): calc.: 193.0173; found: 193.0176 (M^+).

3-Methoxy-6-(methylthio)pyridazine (2b)



3-Chloro-6-methoxypyridazine (1.45 g, 10.0 mmol) and sodium thiomethanolate (780 mg, 11.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (20 mL) followed by extraction using EtOAc (3 x 20 mL). Recrystallisation from Et_2O afforded the pyridazine **2b** (1.49 g, 95%) as a white solid.

M.p. (°C) = 93-94.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.20 (d, *J* = 9.3 Hz, 1H), 6.80 (d, *J* = 9.3 Hz, 1H), 4.06 (s, 3H), 2.66 (s, 3H).

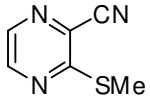
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.4, 163.2, 156.5, 129.0, 117.5, 54.6, 13.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2958 (vw), 1564 (s), 1542 (vs), 1454 (m), 1409 (m), 1363 (vs), 1299 (m), 1258 (s), 1143 (m), 1104 (s), 1021 (s), 1013 (m), 941 (m), 815 (s), 808 (s), 605 (w).

MS (EI, 70 eV): m/z (%) = 157 (7), 156 (M^+, 100), 155 (26), 123 (6), 111 (5), 99 (5), 98 (10), 85 (13), 80 (6), 79 (6).

HRMS ($C_6H_8N_2OS$): calc.: 156.0357; found: 156.0363 (M^+).

3-(Methylthio)pyrazine-2-carbonitrile (2c)



3-Chloropyrazine-2-carbonitrile (2.61 g, 18.7 mmol) and sodium thiomethanolate (2.10 g, 30.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (20 mL) followed by extraction using EtOAc (3 x 20 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 7:2) afforded the pyrazine **2c** (793 mg, 28%) as a yellow solid.

M.p. (°C) = 83-84.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.53 (d, *J* = 2.4 Hz, 1H), 8.30 (d, *J* = 2.4 Hz, 1H), 2.62 (s, 3H).

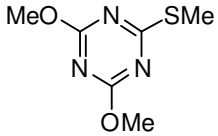
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.8, 145.9, 139.1, 128.1, 114.3, 12.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2230 (w), 1512 (m), 1424 (w), 1354 (s), 1339 (m), 1317 (m), 1196 (m), 1161 (s), 1153 (s), 1142 (m), 1085 (vs), 1074 (s), 1060 (s), 964 (m), 854 (s), 835 (m), 719 (m), 663 (m).

MS (EI, 70 eV): m/z (%) = 151 (M^+, 100), 137 (10), 122 (40), 112 (13), 93 (15), 84 (11), 77 (24), 52 (35).

HRMS ($C_6H_5N_3S$): calc.: 151 .0204; found: 151.0190 (M^+).

2,4-Dimethoxy-6-(methylthio)-1,3,5-triazine (2d)



2-Chloro-4,6-dimethoxy-1,3,5-triazine (1.76 mg, 10.0 mmol) and sodium thiomethanolate (780 mg, 11.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (30 mL) followed by

extraction using EtOAc (3 x 30 mL). Recrystallisation from Et_2O afforded the triazine **2d** (1.63 g, 87%) as a white solid.

M.p. (°C) = 117-120.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 3.99 (s, 6H), 2.52 (s, 3H).

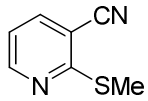
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 185.4, 170.9, 55.2, 13.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3000 (vw), 1549 (vs), 1531 (s), 1499 (s), 1453 (m), 1395 (m), 1345 (vs), 1327 (s), 1296 (s), 1286 (s), 1194 (m), 1105 (s), 1045 (s), 980 (m), 940 (m), 901 (m), 806 (s).

MS (EI, 70 eV): m/z (%) = 189 (4), 188 (7), 187 (M^+, 100), 186 (5), 172 (16), 142 (7), 141 (11), 126 (17), 101 (5), 70 (4).

HRMS ($C_6H_9N_3O_2S$): calc.: 187.0415; found: 187.0407 (M^+).

2-(Methylthio)nicotinonitrile (2g)



2-Chloronicotinonitrile (2.77 g, 20.0 mmol) and sodium thiomethanolate (2.31 g, 33.0 mmol) were dissolved in DMF (10 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (50 mL) followed by extraction using EtOAc (3 x 100 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:1) afforded the pyridine **2g** (665 mg, 22%) as a yellow solid.

M.p. (°C) = 90-91.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.57 (dd, *J* = 5.0 Hz, *J* = 1.8 Hz, 1H), 7.77 (dd, *J* = 7.7 Hz, *J* = 1.8 Hz, 1H), 7.05 (dd, *J* = 7.7 Hz, *J* = 5.0 Hz, 1H), 2.60 (s, 3H).

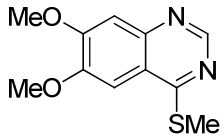
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.4, 152.0, 140.3, 118.2, 115.5, 107.2, 13.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3046 (w), 2929 (w), 2224 (m), 1574 (m), 1546 (m), 1391 (vs), 1316 (m), 1232 (m), 1184 (m), 1143 (m), 1078 (m), 959 (w), 801 (vs), 736 (m), 721 (m), 667 (m).

MS (EI, 70 eV): m/z (%) = 150 (M^+, 100), 123 (27), 104 (40), 79 (30), 75 (11), 45 (10), 43 (16).

HRMS ($C_7H_6N_3S$): calc.: 150.0252; found: 150.0245 (M^+).

6,7-Dimethoxy-4-(methylthio)quinazoline (2h)



4-Chloro-6,7-dimethoxyquinazoline (997 mg, 4.44 mmol in 5 mL DMF) and sodium thiomethanolate (346 mg, 4.88 mmol) were dissolved in DMF (5 mL). After stirring for 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (10 mL) followed by extraction using EtOAc (3 x 10 mL). Recrystallisation from Et_2O afforded the quinazoline **2h** (1.00 g, 95%) as a white solid.

M.p. (°C) = 165-166.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.85 (s, 1H), 7.24 (s, 1H), 7.18 (s, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 2.70 (s, 3H).

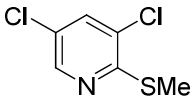
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.0, 155.5, 152.4, 149.9, 145.1, 119.1, 107.0, 101.4, 56.4, 56.2, 12.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2918 (w), 1614 (w), 1571 (w), 1542 (m), 1506 (s), 1450 (m), 1411 (s), 1358 (s), 1342 (s), 1230 (vs), 1204 (s), 1158 (vs), 1124 (s), 1019 (m), 970 (m), 871 (m), 845 (s), 827 (m), 799 (s), 700 (m), 658 (m).

MS (EI, 70 eV): m/z (%) = 237 (14), 236 (M^+, 100), 235 (21), 222 (7), 221 (48), 204 (7), 190 (10), 189 (11), 175 (9), 163 (14).

HRMS ($C_{11}H_{12}N_2O_2S$): calc.: 236.0619; found: 236.0616 (M^+).

3,5-Dichloro-2-(methylthio)pyridine (2n)



2,3,5-Trichloropyridine (3.65 g, 20.0 mmol) and sodium thiomethanolate (1.56 g, 22.0 mmol) were dissolved in DMF (20 mL). After stirring for 72 h at 25 °C, the reaction mixture was quenched with sat. aqueous K_2CO_3 solution (50 mL) followed by extraction using EtOAc (3 x 50 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 40:1) afforded the pyridine **2n** (763 mg, 20%) as a white solid.

M.p. (°C) = 66-68.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.32 (d, *J* = 2.2 Hz, 1H). 7.55 (d, *J* = 2.2 Hz, 1H), 2.54 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 156.4, 145.7, 135.1, 129.0, 126.9, 13.6.

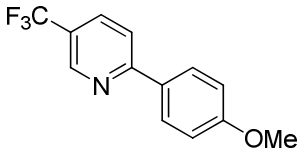
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3043 (w), 2922 (w), 1557 (w), 1415 (s), 1353 (vs), 1216 (m), 1153 (s), 1128 (m), 1111 (m), 1083 (m), 1038 (vs), 960 (w), 901 (m), 894 (m), 830 (m), 718 (m), 665 (m).

MS (EI, 70 eV): m/z (%) = 195 (77), 193 (M^+, 100), 162 (46), 160 (98), 158 (67), 112 (41), 59 (51), 57 (67), 55 (49), 43 (49).

HRMS ($C_6H_5Cl_2NS$): calc.: 192.9520; found: 192.9522 (M^+).

Products of type 3, 5 and 7

2-(4-Methoxyphenyl)-5-(trifluoromethyl)pyridine (3a)



According to **TP1** 2-(methylthio)-5-(trifluoromethyl)pyridine (**2a**) (193 mg, 1.00 mmol in 1 mL THF) was reacted with (4-methoxyphenyl)zinc iodide (**1a**) (1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 1 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 12:1) afforded the pyridine **3a** (241 mg, 95%) as a white solid.

M.p. (°C) = 121-123.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.91-8.86 (m, 1H), 8.05-7.96 (m, 2H), 7.96-7.88 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.05-6.96 (m, 2H).

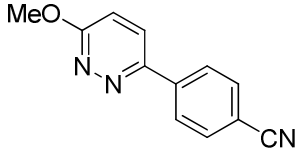
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 161.4, 160.2, 146.4 (q, $^3J_{C-F}$ = 4.1 Hz), 133.8 (q, $^3J_{C-F}$ = 3.4 Hz), 130.4, 128.7, 124.0 (q, $^2J_{C-F}$ = 32.9 Hz), 123.8 (q, $^1J_{C-F}$ = 271.9 Hz), 119.1, 114.3, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3031 (vw), 2970 (vw), 1599 (m), 1580 (m), 1563 (w), 1520 (w), 1483 (w), 1318 (m), 1301 (m), 1282 (m), 1253 (m), 1176 (m), 1166 (m), 1133 (s), 1114 (vs), 1084 (s), 1043 (s), 1024 (s), 1012 (s), 940 (m), 838 (s), 824 (vs), 774 (s), 712 (m).

MS (EI, 70 eV): m/z (%) = 253 (M^+, 100), 238 (25), 211 (73), 177 (61), 169 (28), 141 (24), 135 (21), 95 (23), 69 (31), 55 (35), 41 (26).

HRMS ($C_{13}H_{10}F_3NO$): calc.: 253.0714; found: 253.0706 (M^+).

4-(6-Methoxypyridazin-3-yl)benzonitrile (3b):



According to **TP1** 3-methoxy-6-(methylthio)pyridazine (**2b**) (156 mg, 1.00 mmol in 1 mL THF) was reacted with (4-cyanophenyl)zinc iodide (**1b**) (2.11 mL, 1.50 mmol, 0.71 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 4 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:6) afforded the pyridazine **3b** (161 mg, 76%) as a white solid.

M.p. (°C) = 161-162.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.11-8.15 (m, 2H), 7.76-7.82 (m, 3H), 7.10 (d, *J* = 9.2 Hz, 1H), 4.20 (s, 3H).

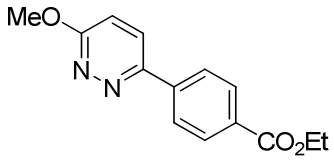
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.7, 140.2, 153.3, 132.7, 127.1, 127.0, 118.5, 118.0, 113.1, 55.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3059 (w), 2952 (w), 2224 (m), 1593 (m), 1548 (w), 1460 (s), 1408 (s), 1341 (m), 1299 (s), 1177 (m), 1116 (m), 1020 (m), 1001 (s), 860 (w), 834 (vs), 768 (w), 670 (w), 627 (w).

MS (EI, 70 eV): m/z (%) = 212 (15), 211 (100), 210 (72), 204 (12), 182 (39), 140 (60), 129 (31), 127 (17), 113 (13), 53 (14).

HRMS ($C_{12}H_9N_3O$): calc.: 211.0746; found: 211.0738 (M^+).

Ethyl 4-(6-methoxypyridazin-3-yl)benzoate (3c)



According to **TP1** 3-methoxy-6-(methylthio)pyridazine (**2b**) (156 mg, 1.00 mmol in 1 mL THF) was reacted with [4-(ethoxycarbonyl)phenyl]zinc iodide (**1c**) (2.03 mL, 1.50 mmol, 0.74 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 4 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the pyridazine **3c** (199 mg, 77%) as a white solid.

M.p. (°C) = 140-142.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.13–8.16 (m, 2H), 8.05–8.09 (m, 2H), 7.81 (d, *J* = 9.3 Hz, 1H), 7.06 (d, *J* = 9.3 Hz, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 4.18 (s, 3H), 1.40 (t, *J* = 7.2 Hz, 3H).

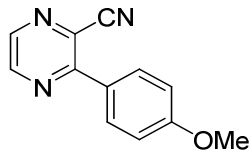
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.2, 164.5, 154.2, 140.1, 131.1, 130.1, 127.2, 126.3, 117.8, 61.1, 55.0, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2951 (w), 1712 (vs), 1596 (m), 1463 (s), 1411 (s), 1304 (s), 1262 (vs), 1180 (m), 1100 (s), 1020 (s), 1014 (s), 1002 (s), 874 (m), 829 (s), 782 (m), 756 (s), 702 (m).

MS (EI, 70 eV): m/z (%) = 259 (14), 258 (M^+, 100), 257 (72), 229 (15), 213 (31), 199 (7), 187 (7), 176 (8), 159 (10), 129 (7).

HRMS ($C_{14}H_{14}N_2O_3$): calc.: 258.1004; found: 258.1000 (M^+).

3-(4-Methoxyphenyl)pyrazine-2-carbonitrile (3d)



According to **TP1** 3-(methylthio)pyrazine-2-carbonitrile (**2c**) (151 mg, 1.00 mmol in 1 mL THF) was reacted with (4-methoxyphenyl)zinc iodide (**1a**) (1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 5 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:2 + 5-Vol% NEt_3) afforded the pyrazine **3d** (121 mg, 57%) as a yellow solid.

M.p. (°C) = 126-127.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.78 (d, *J* = 2.4 Hz, 1H), 8.57 (d, *J* = 2.4 Hz, 1H), 8.04-7.94 (m, 2H), 7.10-7.02 (m, 2H), 3.89 (s, 3H).

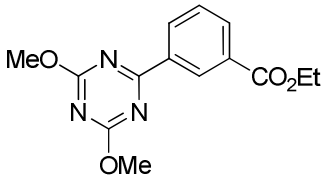
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.1, 156.5, 146.3, 142.2, 130.6, 127.1, 126.6, 116.7, 114.5, 55.5.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2925 (w), 2846 (w), 2232 (w), 1606 (s), 1576 (m), 1525 (w), 1515 (m), 1444 (w), 1435 (m), 1418 (m), 1398 (m), 1386 (m), 1313 (m), 1289 (w), 1254 (vs), 1183 (s), 1170 (s), 1118 (w), 1065 (w), 1033 (m), 1016 (s), 1005 (m), 966 (w), 874 (m), 842 (vs), 822 (m), 798 (m), 792 (m), 667 (w).

MS (EI, 70 eV): m/z (%) = 211 (M^+, 100), 196 (16), 168 (10), 158 (11), 133 (14), 114 (6), 90 (6).

HRMS ($C_{12}H_9N_3O$): calc.: 211.0746; found: 211.0736 (M^+).

Ethyl 3-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (3e)



According to **TP1** 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**2d**) (187 mg, 1.00 mmol in 1 mL THF) was reacted with [3-(ethoxycarbonyl)phenyl]zinc iodide (**1d**) (2.21 mL, 1.50 mmol, 0.68 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 21 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O / EtOAc = 8:1:1) afforded the triazine **3e** (242 mg, 84%) as a yellow solid.

M.p. (°C) = 103-105.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.12-9.07 (m, 1H), 8.69-8.60 (m, 1H), 8.25-8-18 (m, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 4.40 (q, *J* = 7.0 Hz, 2H), 4.12 (s, 6H), 1.40 (t, *J* = 7.1 Hz, 3H).

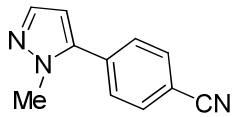
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 174.1, 172.9, 166.0, 135.5, 133.6, 133.1, 131.1, 130.0, 128.6, 61.2, 55.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3310 (vw), 3232 (vw), 1720 (s), 1592 (m), 1566 (s), 1549 (s), 1536 (s), 1504 (s), 1488 (m), 1458 (m), 1368 (s), 1356 (vs), 1298 (s), 1267 (vs), 1191 (m), 1177 (m), 1164 (m), 1118 (m), 1108 (m), 1074 (m), 1039 (s), 1022 (m), 922 (w), 873 (w), 830 (w), 818 (m), 768 (m), 714 (s), 672 (w).

MS (EI, 70 eV): m/z (%) = 289 (M^+, 100), 259 (27), 244 (91), 217 (90), 186 (11), 176 (11), 159 (18), 72 (10).

HRMS ($C_{14}H_{15}N_3O_4$): calc.: 289.1063; found: 289.1064 (M^+).

4-(1-Methyl-1H-pyrazol-5-yl)benzonitrile (3f)



According to **TP1** 1-methyl-5-(methylthio)-1H-pyrazole pyrazole (**2e**) (128 mg, 1.0 mmol in 1 mL THF) was reacted with (4-cyanophenyl)zinc iodide (**1b**) (2.31 mL, 1.50 mmol, 0.65 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 1.5 h at 50 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:4) afforded the pyrazole **3f** (96 mg, 52%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.79-7.69 (m, 2H), 7.58-7.49 (m, 3H), 6.37 (d, *J* = 2.1 Hz, 1H), 3.91 (s, 3H).

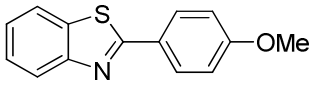
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 141.7, 138.7, 135.0, 132.5, 129.1, 118.3, 112.2, 107.0, 37.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2921 (w), 2224 (m), 1608 (m), 1489 (m), 1468 (w), 1425 (w), 1381 (m), 1279 (m), 1224 (w), 1182 (w), 1113 (w), 1067 (w), 1035 (w), 980 (m), 928 (m), 853 (s), 838 (s), 793 (m), 777 (vs), 708 (m), 664 (w), 649 (m).

MS (EI, 70 eV): m/z (%) = 183 (M^+, 100), 155 (14), 140 (7), 128 (10), 102 (5).

HRMS ($C_{11}H_9N_3$): calc.: 183.0796; found: 183.0792 (M^+).

2-(4-Methoxyphenyl)-1,3-benzothiazole (3g)



According to **TP1** 2-(methylthio)-1,3-benzothiazole (**2f**) (181 mg, 1.00 mmol in 1 mL THF) was reacted with (4-methoxyphenyl)zinc iodide (**1a**) (1.61 mL, 1.50 mmol, 0.93 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 2 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 9:1) afforded the benzothiazole **3g** (177 mg, 73%) as a white solid.

M.p. (°C) = 127-128.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.03-8.04 (m, 3H), 7.86 (d, *J* = 7.63 Hz, 1H), 7.45-7.48 (m, 1H), 7.33-7.36 (m, 1H), 6.99 (d, *J* = 8.58 Hz, 2H), 3.87 (s, 3H).

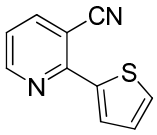
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 167.9, 161.9, 154.0, 134.7, 129.1, 126.3, 126.2, 124.8, 122.8, 121.5, 114.4, 55.4.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2994 (w), 2835 (w), 1604 (m), 1483 (m), 1433 (m), 1310 (m), 1255 (s), 1225 (s), 1171 (m), 1027 (m), 968 (s), 832 (vs), 791 (m), 758 (vs), 731 (s), 691 (m), 623 (m).

MS (EI, 70 eV): m/z (%) = 243 (5), 242 (14), 241 (100), 227 (6), 226 (33), 198 (27), 197 (8), 154 (5), 121 (5), 69 (4).

HRMS ($C_{14}H_{11}NOS$): calc.: 241.0561; found: 241.0557 (M^+).

2-(2-Thienyl)nicotinonitrile (3h)



According to **TP1** 2-(methylthio)nicotinonitrile (**2g**) (150 mg, 1.00 mmol in 1 mL THF) was reacted with (2-thienyl)zinc iodide (**1e**) (1.95 mL, 1.50 mmol, 0.77 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 18 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 4:1) afforded the pyridine **3h** (173 mg, 93%) as a yellow solid.

M.p. (°C) = 74-75.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.72 (dd, *J* = 4.8 Hz, *J* = 1.8 Hz, 1H), 8.26 (dd, *J* = 4.0 Hz, *J* = 1.1 Hz, 1H), 8.00 (dd, *J* = 7.9 Hz, *J* = 1.8 Hz, 1H), 7.54 (dd, *J* = 5.1 Hz, *J* = 0.9 Hz, 1H), 7.23 (dd, *J* = 7.9 Hz, *J* = 4.8 Hz, 1H), 7.17 (dd, *J* = 5.2 Hz, *J* = 3.9 Hz, 1H).

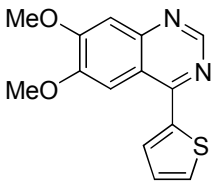
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 153.5, 152.5, 142.1, 141.6, 130.7, 128.9, 128.7, 120.8, 117.8, 103.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3066 (vw), 2921 (w), 2850 (vw), 2225 (w), 1574 (w), 1552 (w), 1528 (w), 1472 (vw), 1439 (s), 1414 (m), 1394 (w), 1358 (w), 1229 (w), 1109 (w), 1067 (w), 976 (w), 860 (w), 844 (w), 806 (w), 798 (w), 762 (s), 716 (vs), 676 (m), 619 (w).

MS (EI, 70 eV): m/z (%) = 186 (M^+, 100), 175 (7), 159 (12), 142 815), 69 (9), 57 (18), 55 (12), 44 (13).

HRMS ($C_{10}H_6N_2S$): calc.: 186.0252; found: 186.0239 (M^+).

6,7-Dimethoxy-4-(2-thienyl)quinazoline (3i)



According to **TP1** 6,7-dimethoxy-4-(methylthio)quinazoline (**2h**) (236 mg, 1.00 mmol in 1 mL THF) was reacted with (2-thienyl)zinc iodide (**1e**) (1.95 mL, 1.50 mmol, 0.77 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 10 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:4 + 2-Vol% NEt_3) afforded the quinazoline **3i** (259 mg, 95%) as a yellow solid.

M.p. (°C) = 149-150.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.10 (s, 1H), 7.83 (dd, *J* = 3.7 Hz, *J* = 1.2 Hz, 1H), 7.74 (s, 1H), 7.64 (dd, *J* = 5.1 Hz, *J* = 1.1 Hz, 1H), 7.38 (s, 1H), 4.08 (s, 3H), 4.03 (s, 3H).

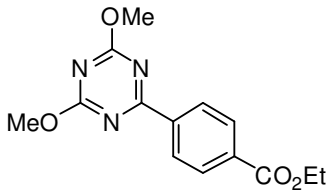
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 157.4, 155.8, 153.1, 150.9, 149.2, 141.3, 130.0, 130.0, 128.1, 117.5, 107.0, 103.4, 56.4, 56.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3102 (w), 2961 (w), 2920 (w), 2829 (vw), 1615 (w), 1572 (w), 1535 (w), 1499 (s), 1466 (s), 1450 (m), 1427 (s), 1367 (m), 1352 (m), 1296 (m), 1271 (w), 1236 (s), 1217 (s), 1194 (m), 1131 (m), 1101 (m), 1084 (w), 1021 (m), 996 (s), 960 (m), 942 (m), 867 (m), 838 (s), 778 (m), 739 (vs), 702 (m), 662 (m), 642 (m), 618 (m).

MS (EI, 70 eV): m/z (%) = 272 (M^+, 100), 257 (24), 242 (18), 202 (6), 159 (6), 86 (25).

HRMS ($C_{14}H_{12}N_2O_2S$): calc.: 272.0619; found: 272.0615 (M^+).

Ethyl 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (3j):



According to **TP1** 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**2d**) (187 mg, 1.00 mmol in 1 mL THF) was reacted with [4-(ethoxycarbonyl)phenyl]zinc iodide (**1c**) (2.03 mL, 1.50 mmol, 0.74 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 5 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 7:3) afforded the triazine **3j** (243 mg, 84%) as a yellow solid.

M.p. (°C) = 97-98.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.53 (d, *J* = 8.6 Hz, 2H), 8.13 (d, *J* = 8.6 Hz, 2H), 4.40 (q, *J* = 7.2 Hz, 2H), 4.12 (s, 3H), 1.41 (t, *J* = 7.2 Hz, 3H).

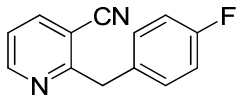
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 174.0, 173.0, 166.0, 138.9, 134.0, 129.6, 128.8, 61.3, 55.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2990 (w), 1714 (m), 1590 (m), 1541 (vs), 1496 (s), 1457 (s), 1354 (vs), 1274 (s), 1198 (m), 1128 (m), 1102 (s), 1034 (m), 1018 (s), 940 (m), 852 (w), 820 (m), 782 (m), 718 (m), 676 (w).

MS (EI, 70 eV): m/z (%) = 290 (17), 289 (M^+, 97), 288 (21), 261 (13), 259 (27), 245 (13), 244 (100), 216 (14), 186 (18), 159 (12).

HRMS ($C_{14}H_{15}N_3O_4$): calc.: 289.1063; found: 289.1057 (M^+).

2-(4-Fluorobenzyl)nicotinonitrile (5a)



According to **TP1** 2-(methylthio)nicotinonitrile (**2g**) (150 mg, 1.00 mmol in 1 mL THF) was reacted with (4-fluorobenzyl)zinc chloride (**4a**) (2.21 mL, 1.50 mmol, 0.68 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 2 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the pyridine **5a** (175 mg, 83%) as a yellow solid.

M.p. (°C) = 57–58.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.73 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.9 Hz, 1H), 7.24-7.36 (m, 3H), 6.94-7.02 (m, 2H), 4.34 (s, 2H).

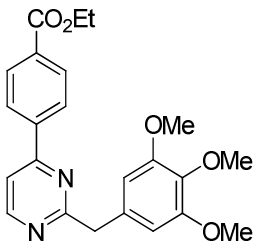
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.5, 161.8 (d, $^1J_{C-F}$ = 241.2), 152.7, 140.6, 133.1 (d, $^4J_{C-F}$ = 3.6 Hz), 130.6 (d, $^3J_{C-F}$ = 8.0 Hz), 121.4, 116.8, 115.5 (d, $^2J_{C-F}$ = 21.4 Hz), 42.3, 108.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3043 (vw), 2925 (w), 2854 (vw), 2223 (m), 1886 (vw), 1604 (w), 1578 (m), 1561 (m), 1506 (vs), 1428 (s), 1417 (m), 1215 (vs), 1159 (m), 1099 (m), 815 (s), 794 (vs), 717 (w), 606 (m).

MS (EI, 70 eV): m/z (%) = 295 (7), 294 (9), 212 (M^+, 45), 211 (100), 210 (14), 186 (15), 185 (10), 109 (22), 83 (8), 44 (7).

HRMS ($C_{13}H_9FN_2$): calc.: 212.0750; found: 212.0745 (M^+).

Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (5b)



According to **TP1** ethyl 4-[2-(methylthio)pyrimidin-4-yl]benzoate (**2i**) (261 mg, 0.95 mmol in 1 mL THF) was reacted with 3,4,5-trimethoxybenzylzinc chloride (**4b**) (1.67 mL, 1.50 mmol, 0.90 M in THF), $Pd(OAc)_2$ (5.3 mg, 2.5 mol %) and S-Phos (19.5 mg, 5.0 mol %). After 1.5 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL)

followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc pure) afforded the pyrimidine **5b** (343 mg, 88%) as a yellow solid.

M.p. (°C) = 121-122.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.75 (d, *J* = 5.5 Hz, 1H), 8.16 (s, 4H), 7.59 (d, *J* = 5.2 Hz, 1H), 6.69 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 4.29 (s, 2H), 3.84 (s, 6H), 3.80 (s, 3H), 1.41 (t, *J* = 7.1 Hz, 3H).

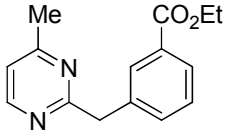
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 169.8, 166.0, 163.3, 157.8, 153.1, 140.6, 136.7, 133.7, 132.6, 130.1, 127.1, 114.7, 106.3, 61.3, 60.8, 56.1, 46.2, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2939 (w), 2838 (vw), 2826 (vw), 1712 (m), 1591 (m), 1570 (m), 1542 (w), 1506 (m), 1462 (m), 1444 (m), 1422 (m), 1408 (m), 1381 (w), 1369 (w), 1336 (m), 1280 (s), 1246 (m), 1124 (vs), 1009 (m), 845 (m), 829 (m), 784 (w), 754 (m), 700 (m), 658 (w), 650 (w), 636 (w), 619 (m).

MS (EI, 70 eV): m/z (%) = 408 (M^+, 100), 393 (58), 363 (5), 307 (4), 279 (3), 175 (4), 181 (3).

HRMS ($C_{23}H_{24}N_2O_5$): calc.: 408.1685; found: 408.1677 (M^+).

Ethyl 3-[(4-methylpyrimidin-2-yl)methyl]benzoate (5c)



According to **TP1** 4-methyl-2-(methylthio)pyrimidine (**2j**) (140 mg, 1.00 mmol in 1 mL THF) was reacted with (3-ethoxycarbonyl)benzylzinc chloride (**4c**) (1.19 mL, 1.50 mmol, 1.26 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 24 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica, pentane / Et_2O = 1:3) afforded the pyrimidine **5c** (188 mg, 73%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.49 (d, *J* = 5.2 Hz, 1H), 8.03 (s, 1H), 7.94-7.81 (m 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.34 (t, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 5.2 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 4.28 (s, 2H), 2.48 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H),.

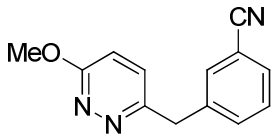
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 168.8, 167.4, 166.5, 156.8, 138.5, 133.6, 130.6, 130.2, 128.4, 127.7, 118.3, 60.8, 45.5, 24.1, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2981 (w), 1714 (vs), 1578 (s), 1555 (m), 1439 (s), 1387 (m), 1368 (m), 1279 (vs), 1190 (vs), 1105 (s), 1081 (m), 1023 (m), 929 (w), 839 (w), 754 (s), 740 (s), 697 (s), 672 (m), 651 (m).

MS (EI, 70 eV): m/z (%) = 256 (M^+, 97), 255 (100), 227 (54), 182 (62), 168 (21), 116 (13), 89 (19), 43 (39).

HRMS ($C_{15}H_{16}N_2O_2$): calc.: 256.1212; found: 256.1189 (M^+).

3-[(6-Methoxypyridazin-3-yl)methyl]benzonitrile (5d)



According to **TP1** 3-methoxy-6-(methylthio)pyridazine (**2b**) (156 mg, 1.00 mmol in 1 mL THF) was reacted with 3-cyanobenzylzinc chloride (**4d**) (1.05 mL, 1.50 mmol, 1.43 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 14 h at 50 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, EtOAc pure) afforded the pyridazine **5d** (160 mg, 71%) as a yellow solid.

M.p. (°C) = 76-78.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 7.57-7.49 (m, 3H), 7.43-7.39 (m, 1H), 7.18 (d, *J* = 9.2 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 4.26 (s, 2H), 4.10 (s, 3H).

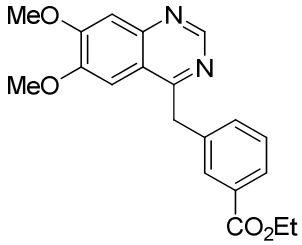
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 164.2, 156.5, 139.9, 133.5, 132.4, 130.5, 129.5, 129.5, 118.6, 118.2, 112.7, 54.8, 41.1.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3065 (vw), 2961 (w), 2923 (w), 2854 (w), 2227 (w), 1595 (w), 1458 (s), 1438 (m), 1412 (m), 1306 (s), 1260 (m), 1234 (w), 1091 (m), 1010 (vs), 900 (m), 858 (m), 784 (s), 718 (m), 688 (s).

MS (EI, 70 eV): m/z (%) = 225 (M^+, 30), 224 (100), 153 (4), 127 (5), 89 (3).

HRMS ($C_{13}H_{11}N_3O$): calc.: 225.0902; found: 225.0900 (M^+).

Ethyl 3-[(6,7-dimethoxyquinazolin-4-yl)methyl]benzoate (5e)



According to **TP1** 6,7-dimethoxy-4-(methylthio)quinazoline (**2h**) (236 mg, 1.00 mmol in 1 mL THF) was reacted with (3-ethoxycarbonyl)benzylzinc chloride (**4c**) (1.74 mL, 1.50 mmol, 0.86 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 12 h at 50 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash

chromatography (silica gel, pentane / EtOAc = 1:6) afforded the quinazoline **5e** (275 mg, 78%) as a pale yellow solid.

M.p. (°C) = 119-121.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 9.06 (s, 1H), 8.03-7.98 (m, 1H), 7.89-7.83 (m, 1H), 7.46-7.40 (m, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.27 (s, 1H), 7.21 (s, 1H), 4.54 (s, 2H), 4.31 (q, *J* = 7.2 Hz, 2H), 3.99 (s, 3H), 3.91 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

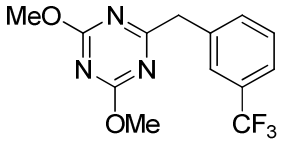
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 166.3, 165.3, 155.9, 153.1, 150.4, 148.3, 138.0, 133.2, 130.9, 129.9, 128.8, 128.0, 119.4, 107.1, 102.1, 99.4, 61.0, 56.4, 56.1, 41.3, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2982 (vw), 1709 (m), 1615 (w), 1552 (w), 1505 (s), 1425 (s), 1365 (s), 1288 (vs), 1270 (s), 1234 (vs), 1193 (s), 1123 (m), 1027 (m), 985 (m), 850 (s), 753 (s), 728 (m), 700 (m).

MS (EI, 70 eV): m/z (%) = 352 (M^+, 32), 323 (18), 321 (100), 307 (14), 291 (19), 277 (5), 263 (6).

HRMS ($C_{20}H_{20}N_2O_4$): calc.: 352.1423; found: 352.1414 (M^+).

2,4-Dimethoxy-6-[3-(trifluoromethyl)benzyl]-1,3,5-triazine (5f)



According to **TP1** 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**2d**) (187 mg, 1.00 mmol in 1 mL THF) was reacted with (3-trifluoromethyl)benzylzinc chloride (**4e**) (1.03 mL, 1.50 mmol, 1.45 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 5 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the pyridine **5f** (208 mg, 70%) as a yellow solid.

M.p. (°C) = 55-57.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.66 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H), 7.40-7.42 (m, 1H), 4.07 (s, 2H), 4.01 (s, 6H).

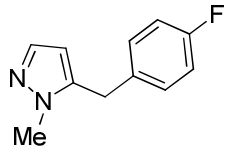
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 180.6, 176.2, 137.3, 132.8, 130.7 (q, $^2J_{C-F}$ = 32.2 Hz), 128.9, 126.3, (q, $^3J_{C-F}$ = 3.9 Hz), 124.1 (q, $^1J_{C-F}$ = 272.3 Hz), 123.8 (q, $^3J_{C-F}$ = 3.9 Hz), 55.2, 44.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2944 (vw), 1548 (s), 1502 (m), 1472 (m), 1386 (m), 1358 (s), 1326 (s), 1235 (m), 1162 (m), 1107 (vs), 1090 (s), 1066 (s), 943 (m), 923 (w), 902 (m), 836 (m), 810 (m), 772 (m), 737 (m), 699 (m), 687 (m), 604 (w).

MS (EI, 70 eV): m/z (%) = 300 (7), 299 (M^+, 43), 298 (100), 284 (26), 227 (8), 226 (7), 200 (18), 184 (9), 159 (16), 58 (9).

HRMS ($C_{13}H_{12}F_3N_3O_2$): calc.: 299.0882; found: 299.0872 (M^+).

5-(4-Fluoro-benzyl)-1-methyl-1*H*-pyrazole (5g)



According to **TP1** 1-methyl-5-(methylthio)-1H-pyrazole pyrazole (**2e**) (128 mg, 1.0 mmol in 1 mL THF) was reacted with 4-fluorobenzylzinc chloride (**4a**) (2.08 mL, 1.50 mmol, 0.72 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 12 h at 45 °C, the reaction mixture was quenched with sat. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc = 95:5) afforded the pyrazole **5g** (152 mg, 80%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.50 (d, *J* = 2.0 Hz, 1H), 6.75-6.70 (m, 2H), 6.66-6.63 (m, 2H), 5.80 (d, *J* = 1.8 Hz, 1H), 3.31 (s, 2H), 3.17 (s, 3H).

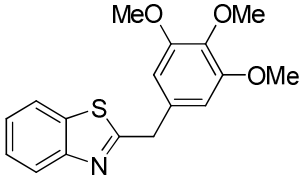
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 162.0 (d, $^1J_{C\text{-}F}$ = 244.1 Hz), 138.2, 133.7 (d, $^3J_{C\text{-}F}$ = 3.5 Hz), 130.1, 130.0, 115.5, (d, $^2J_{C\text{-}F}$ = 21.1 Hz), 105.9, 35.9, 30.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 1602 (w), 1508 (s), 1483 (m), 1440 (m), 1357 (m), 1284 (m), 1220 (s), 1157 (m), 1081 (s), 1016 (m), 891 (w), 835 (s), 767 (s), 733 (m).

MS (EI, 70 eV): m/z (%) = 191 (13), 190 (M^+, 100), 189 (40), 175 (30), 162 (12), 148 (19), 146 (17), 135 (5), 133 (9), 127 (7), 120 (6), 109 (17), 97 (6), 95 (35), 85 (8), 83 (7), 71 (10), 69 (7), 57 (17), 56 (6), 55 (10), 44 (7), 43 (12), 41 (9).

HRMS ($C_{11}H_{11}FN_2$): calc.: 190.0906, found: 190.0894 (M^+).

2-(3,4,5-Trimethoxybenzyl)-1,3-benzothiazole (5h)



According to **TP1** 2-(methylthio)-1,3-benzothiazole (**2f**) (181 mg, 1.00 mmol in 1 mL THF) was reacted with 3,4,5-trimethoxybenzylzinc chloride (**4b**) (1.56 mL, 1.50 mmol, 0.95 M in

THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %), S-Phos (20.5 mg, 5.0 mol %) and $Zn(OAc)_2$ (183 mg, 1.00 mmol). After 16 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 1:1) afforded the benzothiazole **5h** (222 mg, 70%) as a white solid.

M.p. (°C) = 105-107.

^{1}H-NMR (400 MHz, $CDCl_3$): δ / ppm = 8.01-7.96 (m, 1H), 7.82-7.76 (m, 1H), 7.47-7.41 (m, 1H), 7.36-7.29 (m, 1H), 6.57 (s, 2H), 4.35 (s, 2H), 3.83 (s, 6H), 3.82 (s, 3H).

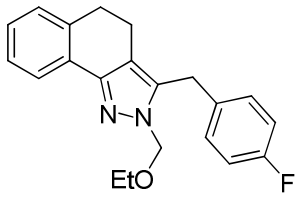
^{13}C-NMR (100 MHz, $CDCl_3$): δ / ppm = 171.0, 153.4, 137.1, 135.5, 132.6, 125.9, 124.8, 122.7, 121.5, 106.0, 60.8, 56.1, 40.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3051 (vw), 2936 (w), 2839 (w), 2361 (vw), 1590 (m), 1501 (m), 1422 (m), 1334 (m), 1238 (s), 1203 (w), 1154 (w), 1119 (vs), 1063 (m), 996 (s), 977 (m), 856 (m), 834 (m), 764 (vs), 732 (m), 722 (s), 663 (m), 642 (m).

MS (EI, 70 eV): m/z (%) = 315 (M^+, 100), 300 (53), 268 (5), 257 (5), 186 (10).

HRMS ($C_{17}H_{17}NO_3S$): calc.: 315.0929; found: 315.0925 (M^+).

2-Ethoxymethyl-3-(4-fluorobenzyl)-4,5-dihydro-2*H*-benzo[g]indazole (5i)



According to **TP1** 2-(ethoxymethyl)-3-(methylthio)-4,5-dihydro-2H-benzo[g]indazole (**2k**) (275 mg, 1.0 mmol in 1 mL THF) was reacted with 4-fluorobenzylzinc chloride (**4a**) (2.10 mL, 1.50 mmol, 0.72 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 12 h at 45 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc = 95:5) afforded the indazole **5i** (208 mg, 62%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.33 (d, J = 7.7 Hz, 1H), 7.22-7.18 (m, 2H), 7.10-7.07 (m, 2H), 6.78 (s, 2H), 6.76-6.75 (m, 1H), 5.18 (s, 2H), 3.71 (s, 2H), 3.42 (q, J = 7.0 Hz, 2H), 2.68 (t, J = 7.3 Hz, 2H), 2.30 (t, J = 7.3 Hz, 2H), 0.93 (t, J = 7.0 Hz, 3H).

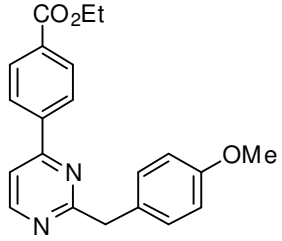
^{13}C-NMR ($CDCl_3$, 75 MHz): δ / ppm = 162.0 (d, $^1J_{C\text{-}F}$ = 244.4 Hz), 147.9, 136.8, 134.0 (d, $^3J_{C\text{-}F}$ = 3.4 Hz), 130.9, 130.1, 130.0, 128.6, 127.7, 127.3, 123.0, 116.7, 115.5 (d, $^2J_{C\text{-}F}$ = 21.4 Hz), 78.8, 64.3, 29.9, 29.2, 19.3, 14.9.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2929 (w), 1602 (m), 1508 (s), 1483 (m), 1440 (m), 1357 (m), 1309 (m), 1284 (m), 1220 (s), 1157 (m), 1081 (s), 1016 (m), 891 (w), 834 (m), 767 (s), 733 (m).

MS (EI, 70 eV): m/z (%) = 336 (M^+, 13), 293 (7), 292 (39), 291 (100), 290 (3), 289 (6), 277 (6), 233 (4), 197 (4), 183 (6), 181 (5), 169 (4), 115 (7), 109 (17), 97 (5), 83 (6), 71 (6), 70 (4), 69 (8), 57 (10), 56 (4), 55 (9), 40 (19), 38 (9), 37 (8).

HRMS ($C_{21}H_{21}FN_2O$): calc.: 336.1638, found: 336.1623 (M^+).

Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (5j)



To a solution of 2-bromo-4-(methylthio)pyrimidine (**2l**) (205 mg, 1.00 mmol), $Pd(dba)_2$ (14.4 mg, 2.5 mol%) and tfp (11.6 mg, 5.0 mol%) in THF (1 mL) was added dropwise 4-methoxybenzylzinc chloride (**4f**) (0.82 mL, 1.02 mmol, c = 1.24 M in THF). After stirring for 3 h at 25 °C, $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %) was added followed by [4-(ethoxycarbonyl)phenyl]zinc iodide (**1c**) (2.14 mL, 1.50 mmol, 0.70 M in THF) and the reaction mixture was stirred for additional 24 h. Then, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, CH_2Cl_2 / Et_2O = 1:1) afforded the pyrimidine **5j** (236 mg, 68%) as a yellow solid.

M.p. (°C) = 70-71.

^{1}H-NMR (600 MHz, C_6D_6): δ / ppm = 8.28 (d, *J* = 5.3 Hz, 1H), 8.23-8.20 (m, 2H), 8.00-7.92 (m, 2H), 7.48-7.41 (m, 2H), 6.83-6.77 (m, 2H), 6.68 (d, *J* = 5.3 Hz, 1H), 4. 38 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.27 (s, 3H), 1.03 (t, *J* = 7.2 Hz, 1H).

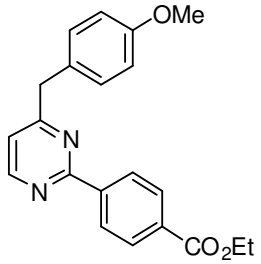
^{13}C-NMR (150 MHz, C_6D_6): δ / ppm = 171.0, 165.8, 162.6, 159.0, 158.1, 141.2, 132.9, 131.1, 130.7, 130.2, 128.3, 127.4, 114.3, 114.2, 61.1, 54.7, 45.7, 14.2.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2980 (w), 2934 (w), 2835 (vw), 1712 (s), 1611 (w), 1569 (s), 1547 (m), 1510 (s), 1438 (m), 1409 (m), 1383 (m), 1270 (vs), 1242 (vs), 1176 (s), 1105 (s), 1018 (s), 818 (m), 776 (s), 740 (s), 700 (s).

MS (EI, 70 eV): m/z (%) = 348 (M^+, 100), 333 (26), 305 (15), 160 (4), 121 (10).

HRMS ($C_{23}H_{24}N_2O_5$): calc.: 348.1474; found: 348.1467 (M^+).

Ethyl 4-[4-(4-methoxybenzyl)pyrimidin-2-yl]benzoate (5k)



To a solution of 4-iodo-2-(methylthio)pyrimidine (**2m**) (252 mg, 1.00 mmol), $Pd(dba)_2$ (14.4 mg, 2.5 mol%) and tfp (11.6 mg, 5.0 mol%) in THF (1 mL) was added dropwise 4-methoxybenzylzinc chloride (**4f**) (1.31 mL, 1.02 mmol, c = 0.78 M in THF). After stirring for 10 min at 25 °C, $Pd(OAc)_2$ (5.6 mg, 2.5 mol %), S-Phos (20.5 mg, 5.0 mol %) and THF (0.5 mL) was added followed by [4-(ethoxycarbonyl)phenyl]zinc iodide (**1c**) (2.14 mL, 1.50 mmol, 0.70 M in THF) and the reaction mixture was stirred for additional 20 h. Then, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / CH_2Cl_2 / Et_2O = 12:4:1) afforded the pyrimidine **5k** (280 mg, 80%) as a yellow solid.

M.p. (°C) = 71-73.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.67 (d, *J* = 5.2 Hz, 1H), 8.59-8.50 (m, 2H), 8.20-8.11 (m, 2H), 7.28-7.18 (m, 2H), 6.99 (d, *J* = 5.1 Hz, 1H), 6.93-6.81 (m, 2H), 4.40 (q, *J* = 7.1 Hz, 2H), 4.12 (s, 2H), 3.79 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H).

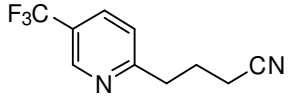
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 170.4, 166.4, 163.2, 158.6, 157.1, 141.5, 132.2, 130.3, 129.7, 129.5, 128.1, 118.5, 114.2, 61.1, 55.2, 43.5, 14.3.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2992 (w), 2980 (w), 2898 (w), 2836 (w), 1709 (vs), 1611 (w), 1583 (m), 1552 (s), 1512 (s), 1456 (w), 1438 (m), 1401 (s), 1386 (m), 1274 (vs), 1245 (vs), 1178 (s), 1110 (s), 1099 (s), 1018 (s), 921 (w), 884 (w), 875 (w), 845 (m), 820 (m), 763 (m), 755 (s), 699 (m), 614 (w).

MS (EI, 70 eV): m/z (%) = 348 (M^+, 100), 333 (24), 303 (8), 151 (5), 121 (15).

HRMS ($C_{23}H_{24}N_2O_5$): calc.: 348.1474; found: 348.1462 (M^+).

4-[5-(Trifluoromethyl)pyridin-2-yl]butanenitrile (7a)



According to **TP1** 2-(methylthio)-5-(trifluoromethyl)pyridine (**2a**) (193 mg, 1.0 mmol in 1 mL THF) was reacted with (3-cyanopropyl)zinc bromide (**6a**) (3.66 mL, 1.5 mmol, 0.41 M

in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 16 h at 25 °C, the reaction mixture was quenched with sat. Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (pentane / Et_2O = 1:1 + 2-Vol% NEt_3) furnished the pyridine **7a** (180 mg, 0.84 mmol, 84%) as a yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.83-8.76 (m, 1H), 7.85 (dd, *J* = 8.1 Hz, 2.4 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 3.02 (t, *J* = 7.3 Hz, 2H), 2.43 (t, *J* = 7.0 Hz, 2H), 2.23-2.09 (m, 2H).

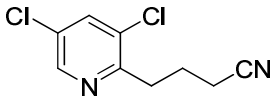
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 163.5 (q, $^4J_{C-F}$ = 1.4 Hz), 146.4 (q, $^3J_{C-F}$ = 4.0 Hz), 133.7 (q, $^3J_{C-F}$ = 3.5 Hz), 124.8 (q, $^2J_{C-F}$ = 33.1 Hz), 123.5 (q, $^1J_{C-F}$ = 272.3 Hz), 122.9, 119.2, 36.2, 24.4, 16.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2941 (vw), 2248 (vw), 1609 (m), 1574 (w), 1496 (vw), 1430 (w), 1396 (w), 1325 (vs), 1166 (m), 1121 (vs), 1079 (s), 1017 (s), 940 (w), 854 (w), 738 (w), 654 (w).

MS (EI, 70 eV): m/z (%) = 214 (M^+, <1), 195 (5), 174 (47), 161 (100), 147 (6), 86 (11), .

HRMS ($C_{10}H_9F_3N_2$): calc.: 214.0718; found: 214. 0697 (M^+).

4-(3,5-Dichloropyridin-2-yl)butanenitrile (7b)



According to **TP1** 3,5-dichloro-2-(methylthio)pyridine (**2n**) (194 mg, 1.00 mmol in 1 mL THF) was reacted with (3-cyanopropyl)zinc bromide (**6a**) (1.49 mL, 1.50 mmol, 1.01 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 5 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 8:2) afforded the pyridine **7b** (116 mg, 54%) as a yellow solid.

M.p. (°C) = 41-42.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 8.39 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 2.1 Hz, 1H), 3.04 (t, *J* = 7.3 Hz, 2H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.09-2.19 (m, 2H).

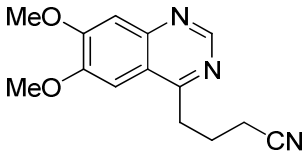
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 154.9, 146.1, 136.4, 131.4, 130.1, 119.3, 32.9, 23.2, 16.7.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 3056 (m), 2929 (w), 2246 (w), 1723 (w), 1566 (w), 1543 (w), 1444 (vs), 1384 (s), 1324 (m), 1116 (s), 1059 (s), 1038 (s), 916 (s), 858 (vs), 745 (vs), 700 (m), 657 (m).

MS (EI, 70 eV): m/z (%) = 176 (25), 174 (39), 165 (10), 164 (5), 163 (63), 162 (11), 161 (100), 160 (6), 147 (5), 126 (7).

HRMS ($C_9H_8Cl_2N_2$): calc.: 214.0065; found: 214.0071 (M^+).

4-(6,7-Dimethoxyquinazolin-4-yl)butanenitrile (7c)



According to **TP1** 6,7-dimethoxy-4-(methylthio)quinazoline (**2h**) (236 mg, 1.00 mmol in 1 mL THF) was reacted with (3-cyanopropyl)zinc bromide (**6a**) (1.49 mL, 1.50 mmol, 1.01 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 5 h at 25 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, Et_2O / EtOH = 10:1) afforded the quinazoline **7c** (190 mg, 74%) as a white solid.

M.p. (°C) = 156-157.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 9.01 (s, 1H). 7.30 (s, 1H), 7.22 (s, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.34 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 2.25-2.34 (m, 2H).

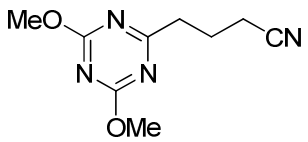
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 164.8, 155.8, 153.1, 150.5, 147.8, 119.6, 119.5, 107.2, 101.1, 56.4, 56.3, 31.7, 23.1, 16.8.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2972 (vw), 1615 (m), 1578 (w), 1553 (w), 1502 (vs), 1432 (s), 1361 (m), 1233 (vs), 1210 (s), 1175 (s), 1128 (m), 1026 (m), 1007 (m), 983 (m), 854 (vs), 830 (s), 732 (m), 606 (m).

MS (EI, 70 eV): m/z (%) = 257 (M^+, 11), 242 (4), 218 (3), 217 (19), 205 (12), 204 (100), 203 (3), 190 (5), 189 (15), 161 (7).

HRMS ($C_{14}H_{15}N_3O_2$): calc.: 257.1164; found: 257.1156 (M^+).

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)butanenitrile (7d)



According to **TP1** 2,4-dimethoxy-6-(methylthio)-1,3,5-triazine (**2d**) (187 mg, 1.00 mmol in 1 mL THF) was reacted with (3-cyanopropyl)zinc bromide (**6a**) (1.49 mL, 1.50 mmol, 1.01 M in THF), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 5 h at 25 °C the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / Et_2O = 3:7) afforded the triazine **7d** (137 mg, 66%) as a yellow solid.

M.p. (°C) = 48-50.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 4.01 (s, 6H). 2.88 (t, *J* = 7.3 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.11-2.21(m, 2H).

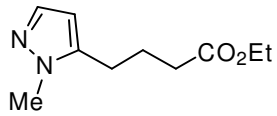
^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 180.9, 172.4, 119.1, 55.2, 36.6, 22.4, 16.6.

IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2931 (w), 2244 (vw), 1554 (vs), 1498 (m), 1456 (m), 1384 (m), 1364 (s), 1323 (m), 1306 (m), 1202 (m), 1112 (s), 1084 (m), 1068 (m), 999 (m), 951 (m), 931 (m), 898 (m), 818 (s), 786 (m).

MS (EI, 70 eV): m/z (%) = 207 (2), 169 (3), 168 (39), 156 (6), 155 (100), 126 (2), 125 (6), 72 (2), 69 (3), 58 (3).

HRMS ($C_9H_{12}N_4O_2$): calc.: 208.0960; found: 208.0951 (M^+).

Ethyl 4-(2-methyl-2*H*-pyrazol-3-yl)butanoate (7e)



According to **TP1** 1-methyl-5-(methylthio)-1H-pyrazole pyrazole (**2e**) (128 mg, 1.0 mmol in 1 mL THF) was reacted with (4-ethoxy-4-oxobutyl)zinc bromide (**6b**) (4.17 mL, 0.36 м in THF, 1.5 mmol), $Pd(OAc)_2$ (5.6 mg, 2.5 mol %) and S-Phos (20.5 mg, 5.0 mol %). After 12 h at 45 °C, the reaction mixture was quenched with sat. aqueous Na_2CO_3 solution (25 mL) followed by extraction using EtOAc (3 x 25 mL). Purification by flash chromatography (silica gel, pentane / EtOAc = 95:5) afforded the pyrazole **7e** (135 mg, 69%) as a pale yellow oil.

^{1}H-NMR (300 MHz, $CDCl_3$): δ / ppm = 7.36 (d, *J* = 1.5 Hz, 1H), 6.02 (d, *J* = 1.5 Hz, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.64 (t, *J* = 7.7 Hz, 2H), 2.36 (t, *J* = 7.1 Hz, 2H), 1.94 (quint, *J* = 7.3 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ / ppm = 173.0, 141.8, 137.9, 104.4, 60.4, 36.0, 33.3, 24.8, 23.6, 14.2.

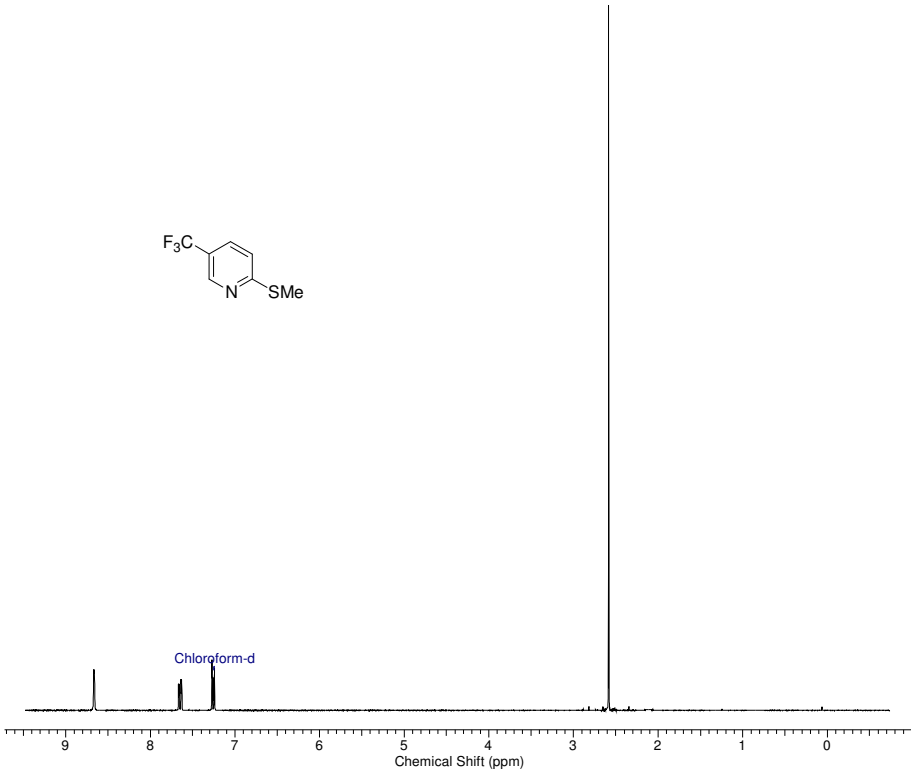
IR (Diamond-ATR, neat): $\tilde{\nu}$ / cm^{-1} = 2940 (w), 1728 (s), 1397 (w), 1375 (w), 1178 (m), 1025 (m), 930 (m), 859 (w), 771 (m), 651 (w).

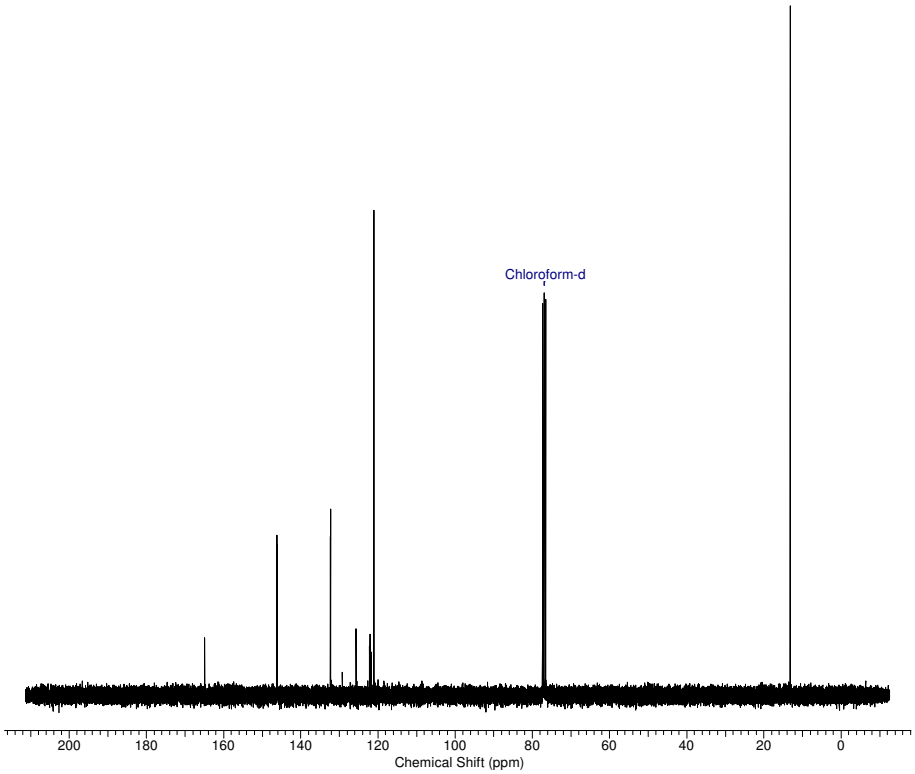
MS (EI, 70 eV): m/z (%) = 197 (3), 196 (M^+, 26), 152 (5), 151 (58), 124 (6), 123 (11), 121 (6), 110 (7), 109 (100), 108 (31), 107 (8), 96 (37), 95 (50), 80 (4), 68 (5), 61 (4), 60 (6), 55 (5), 52 (8), 42 (8), 41 (9).

HRMS ($C_{10}H_{16}N_2O_2$): calc.: 196.1212, found: 196.1205 (M^+).

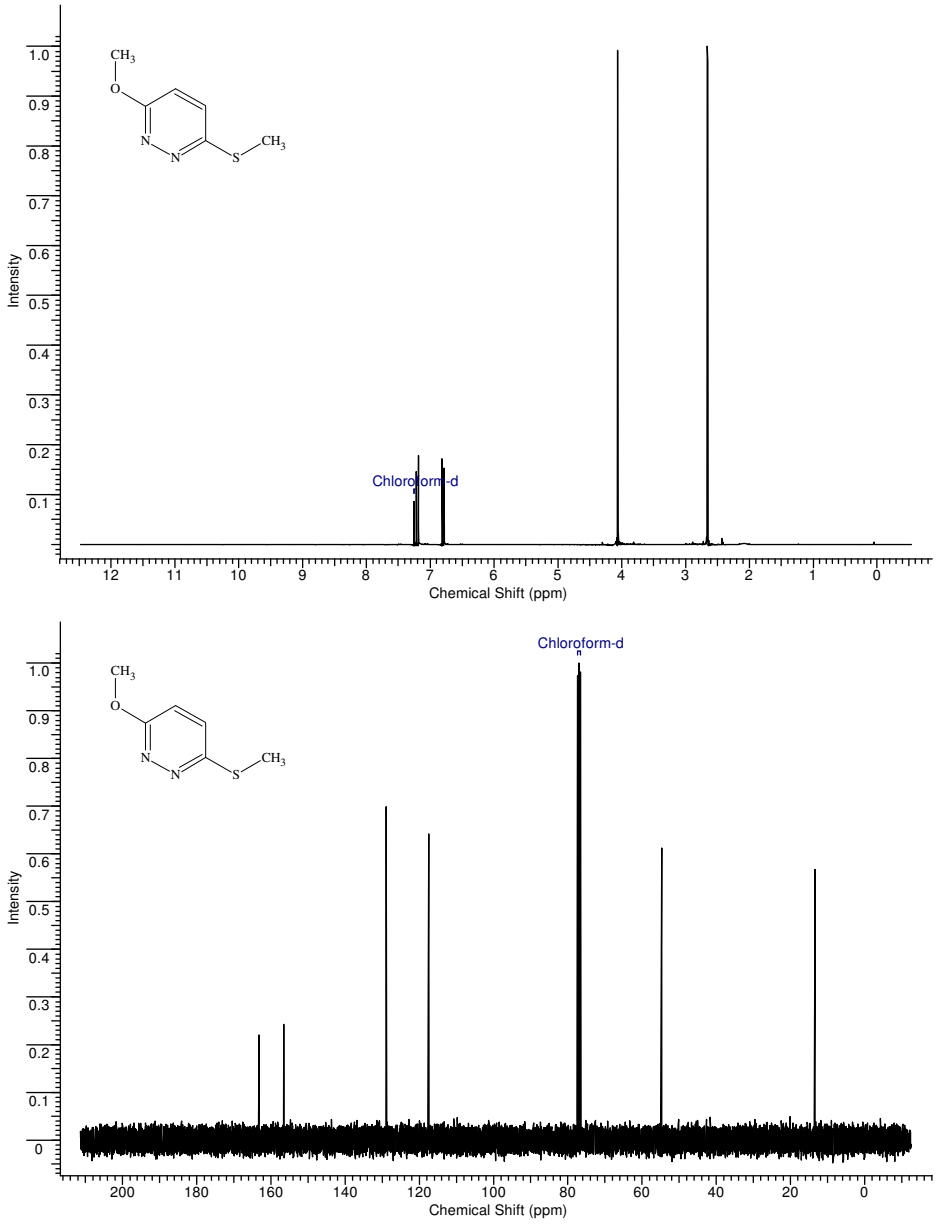
Starting materials of type 2.

2-(Methylthio)-5-(trifluoromethyl)pyridine (2a)

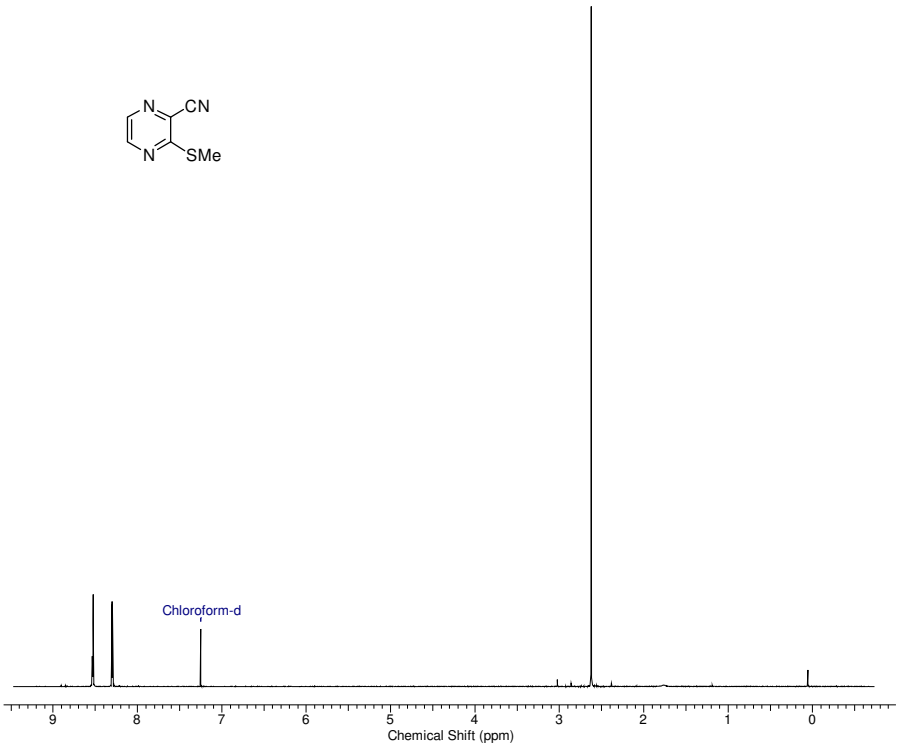


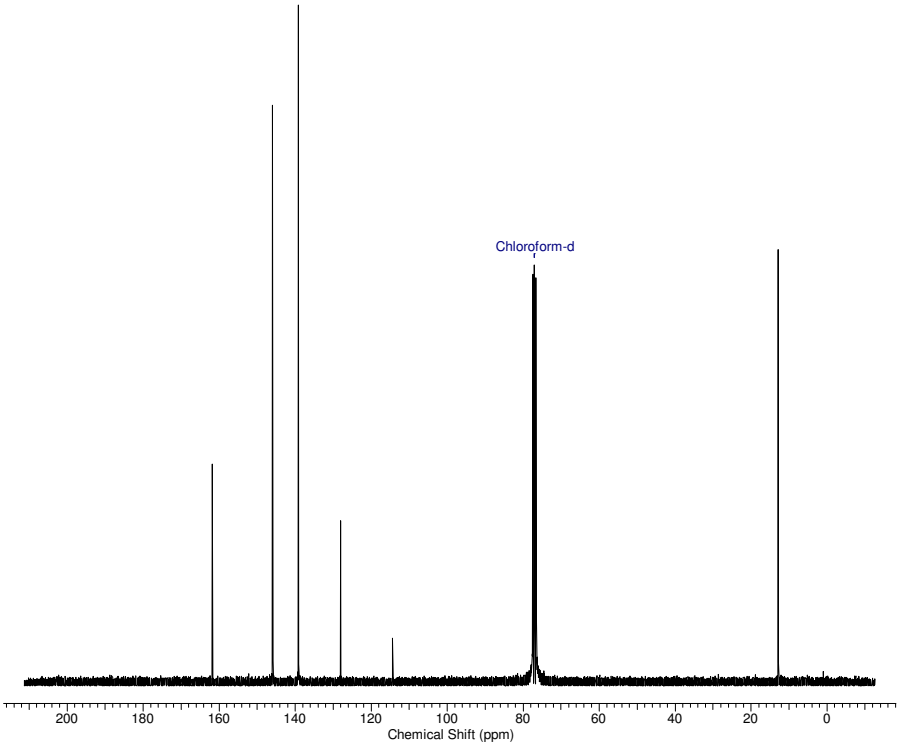


3-Methoxy-6-(methylthio)pyridazine (2b)

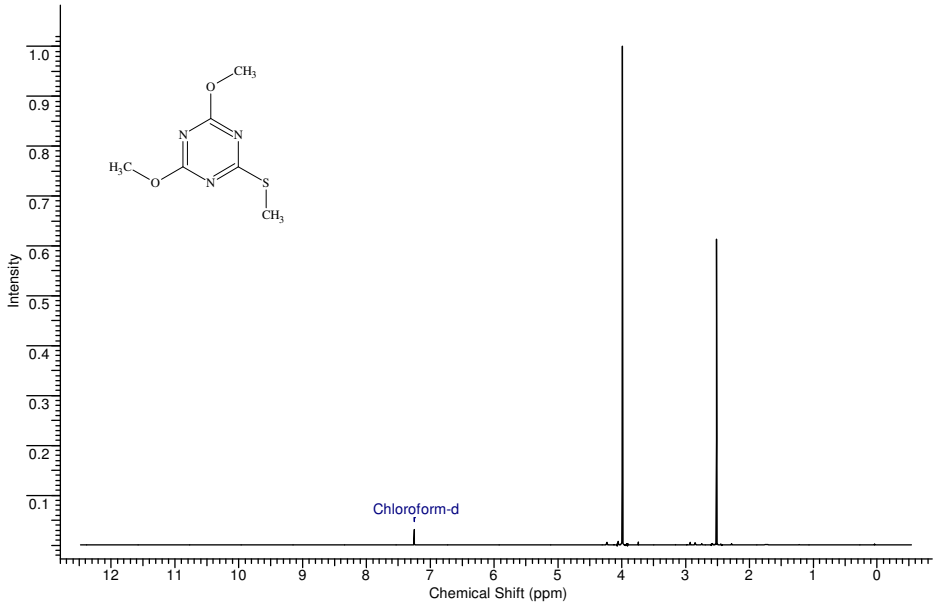


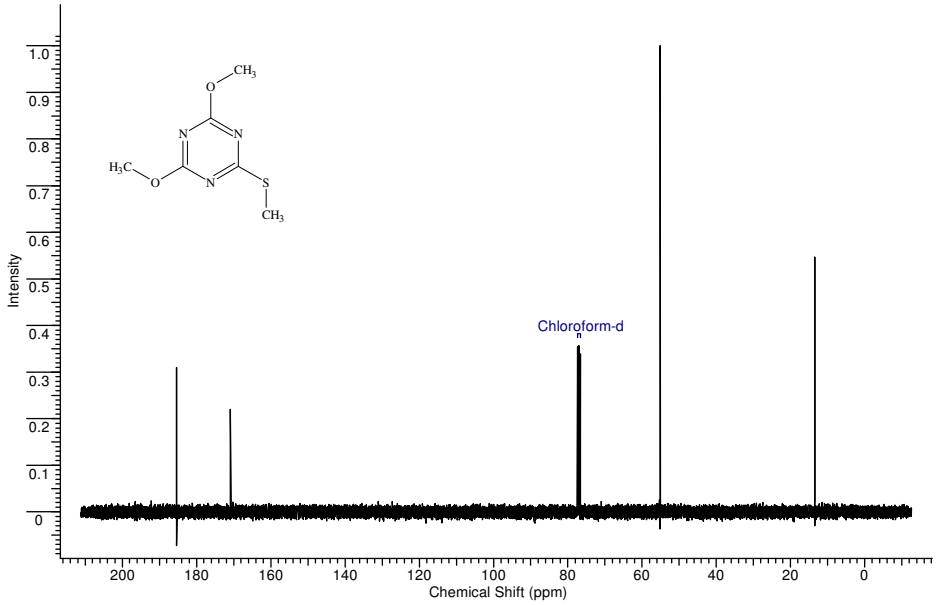
3-(Methylthio)pyrazine-2-carbonitrile (2c)



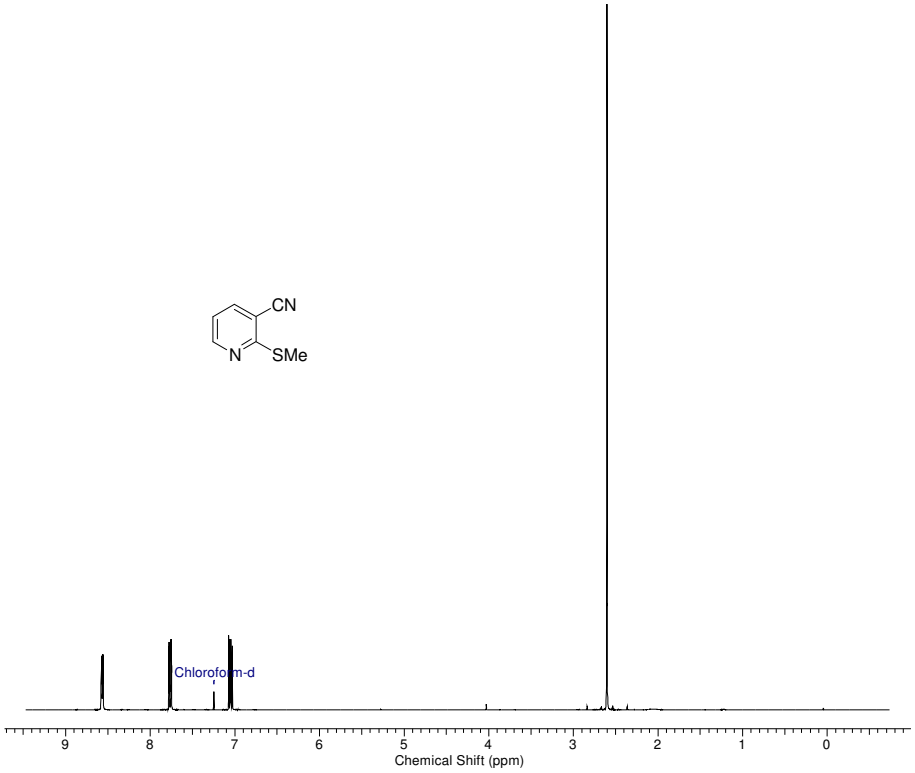


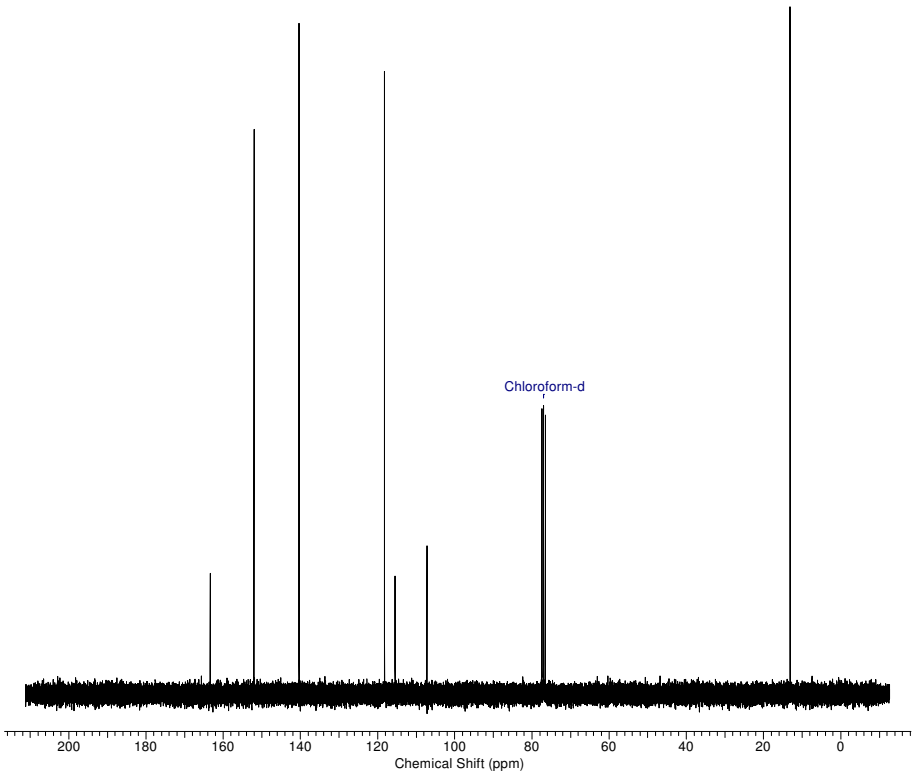
2,4-Dimethoxy-6-(methylthio)-1,3,5-triazine (2d)



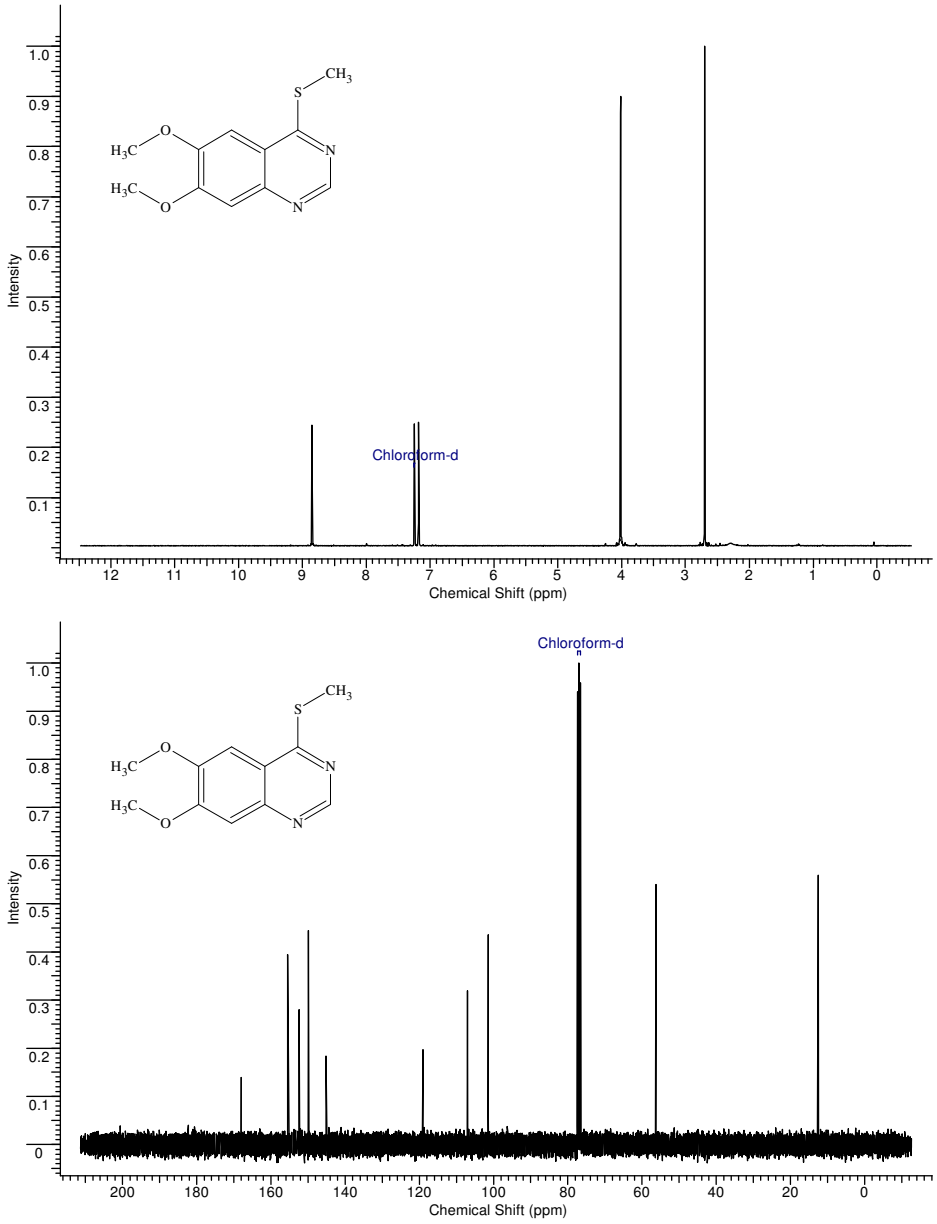


2-(Methylthio)nicotinonitrile (2g)

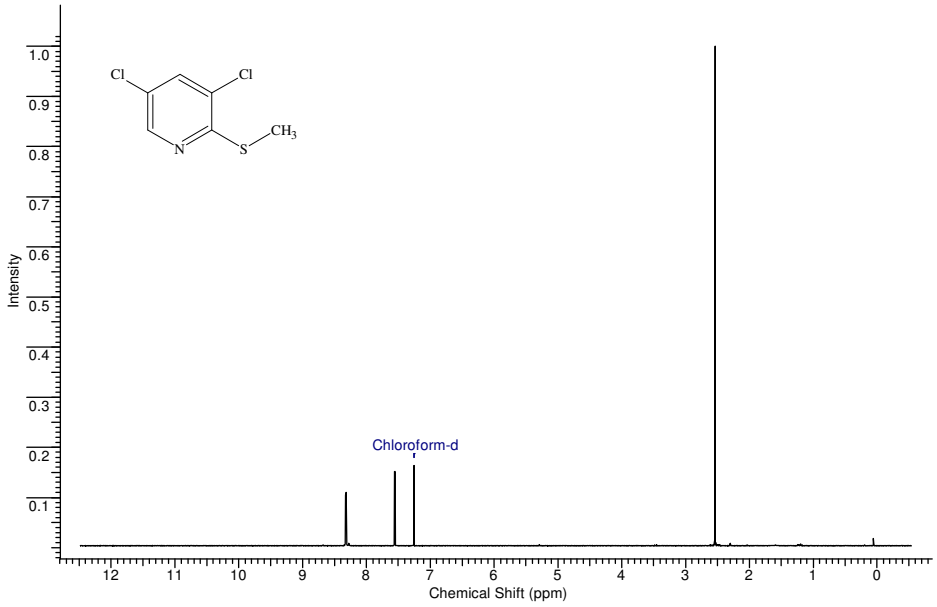


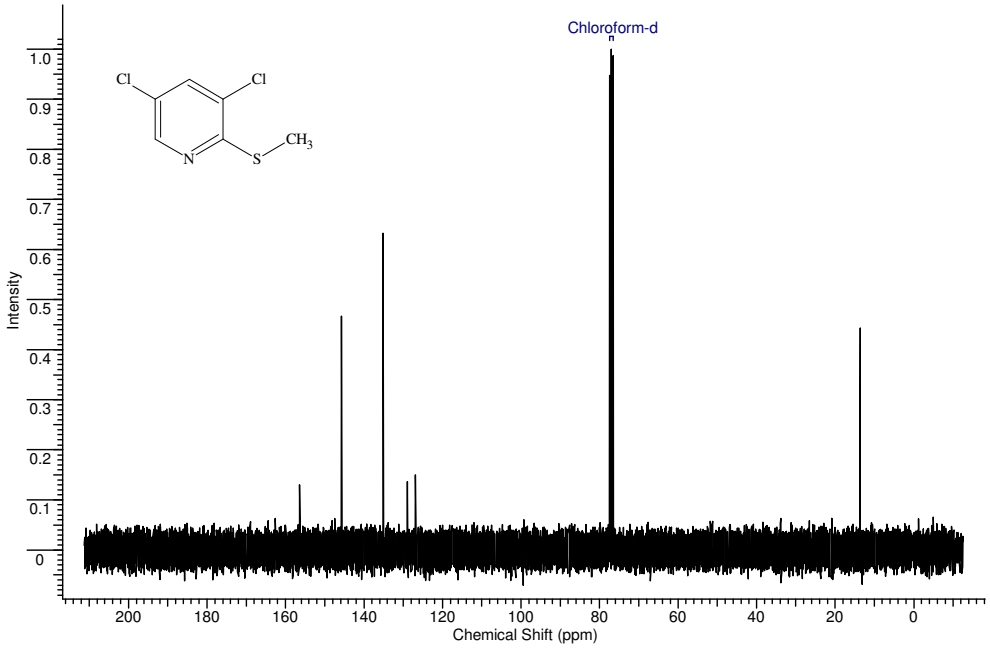


6,7-Dimethoxy-4-(methylthio)quinazoline (2h)



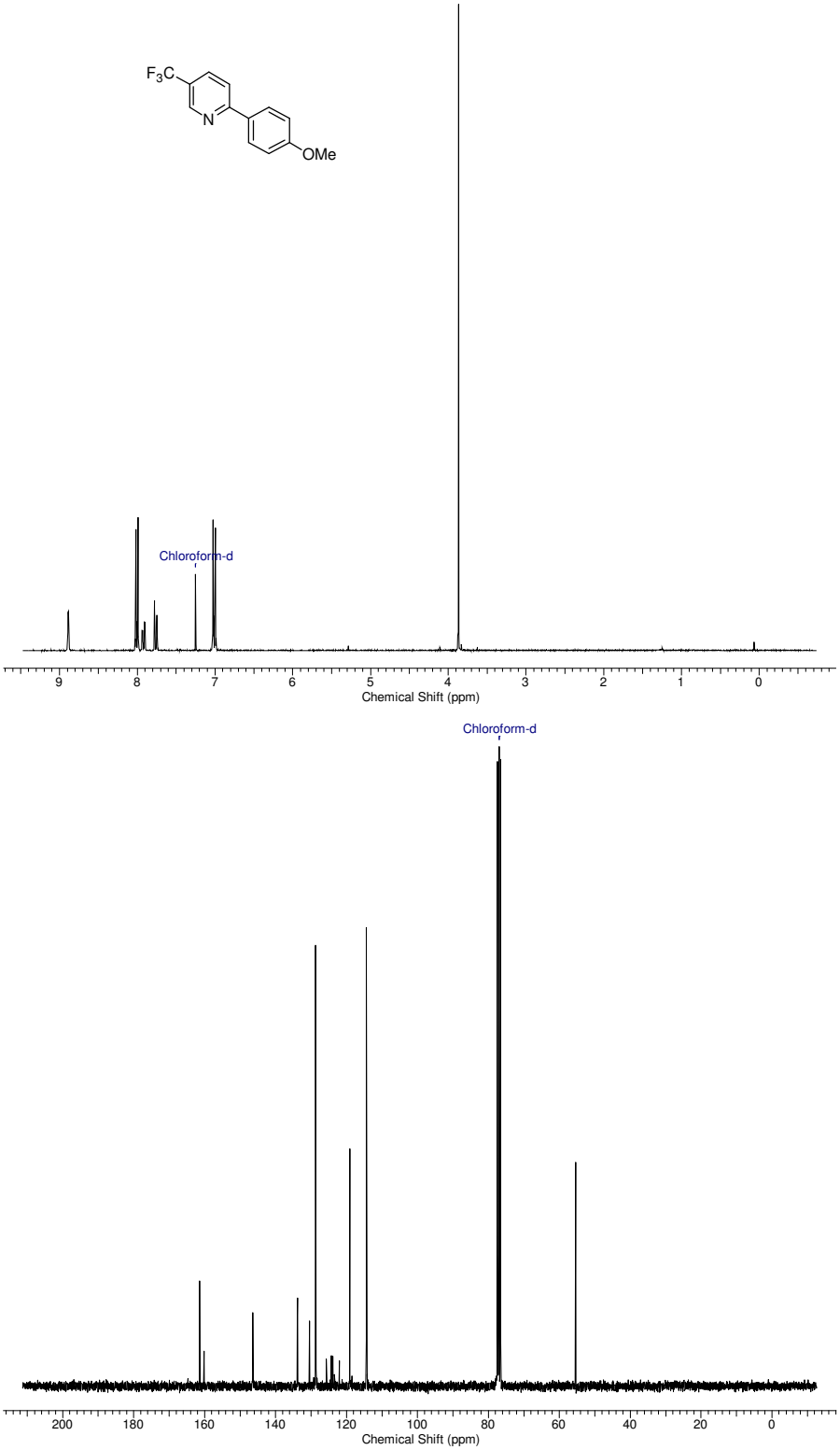
3,5-Dichloro-2-(methylthio)pyridine (2n)



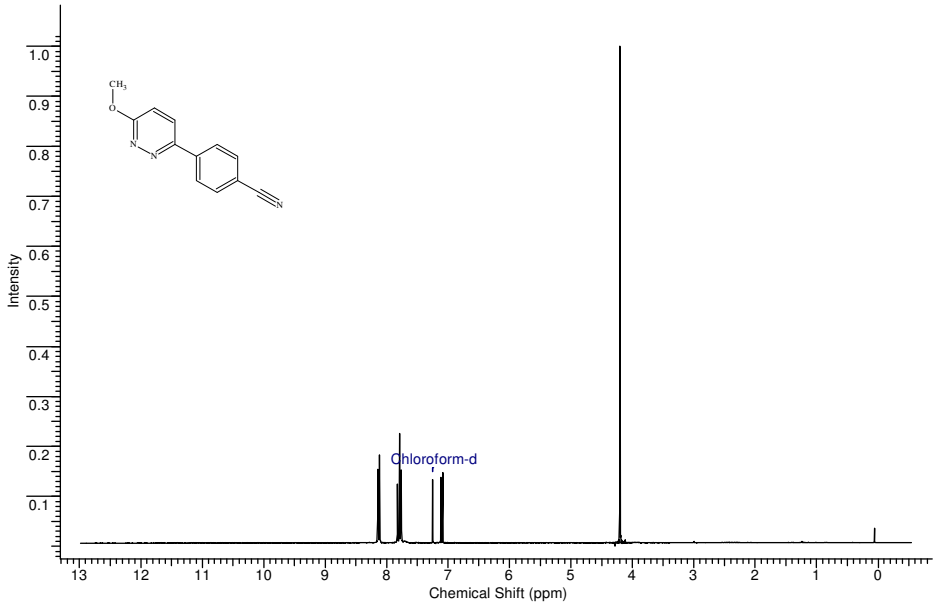


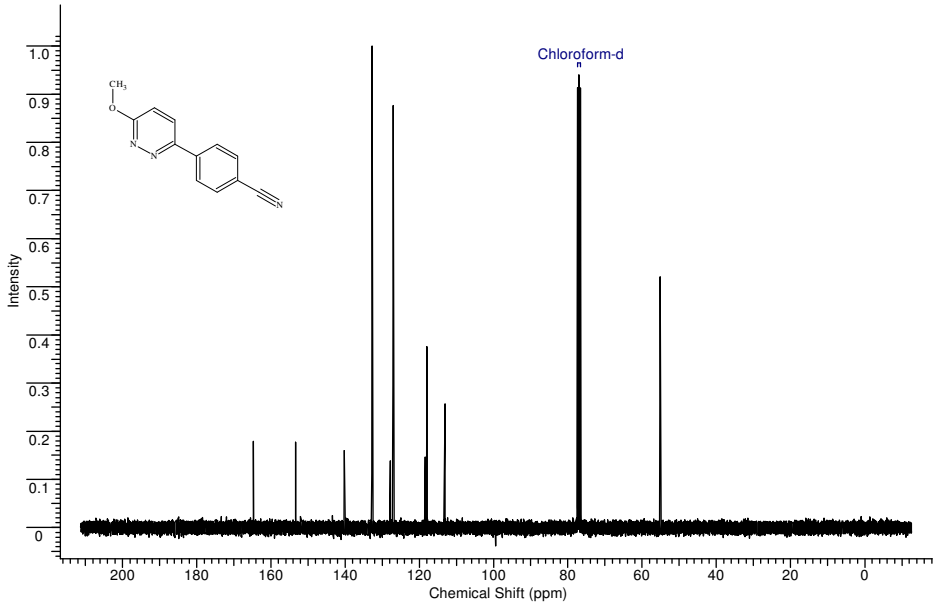
Products of type 3,5 and 7.

2-(4-Methoxyphenyl)-5-(trifluoromethyl)pyridine (3a)

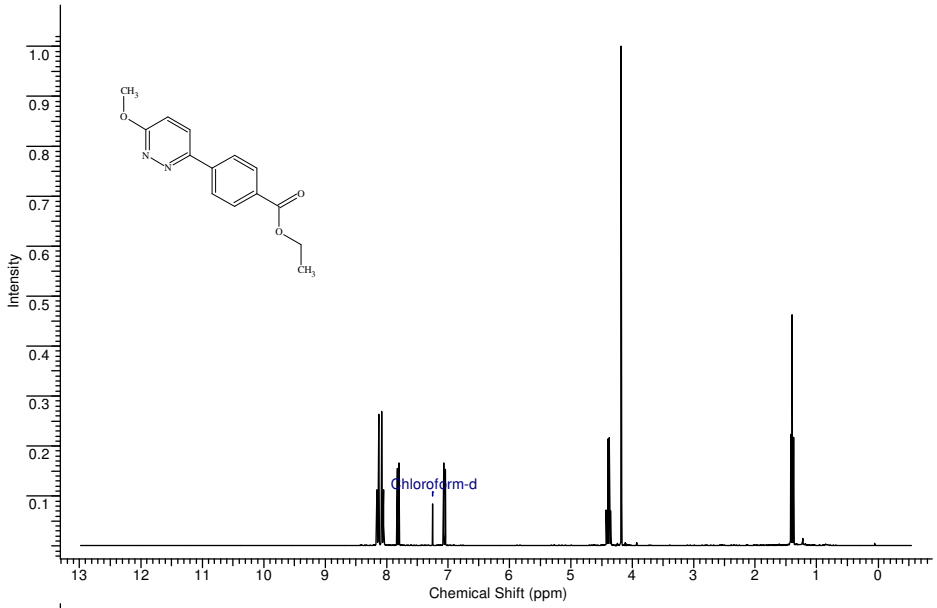


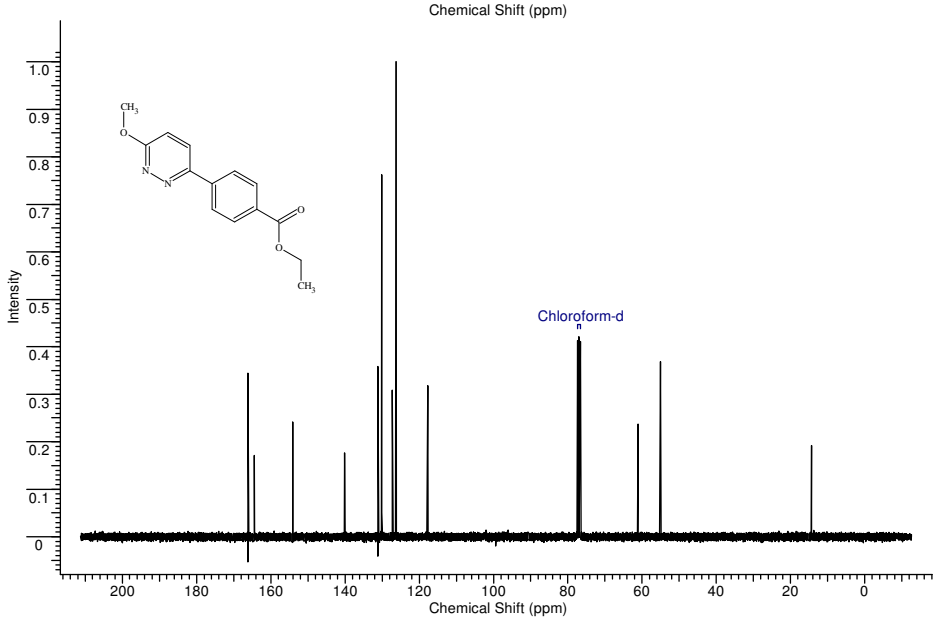
4-(6-Methoxypyridazin-3-yl)benzonitrile (3b)



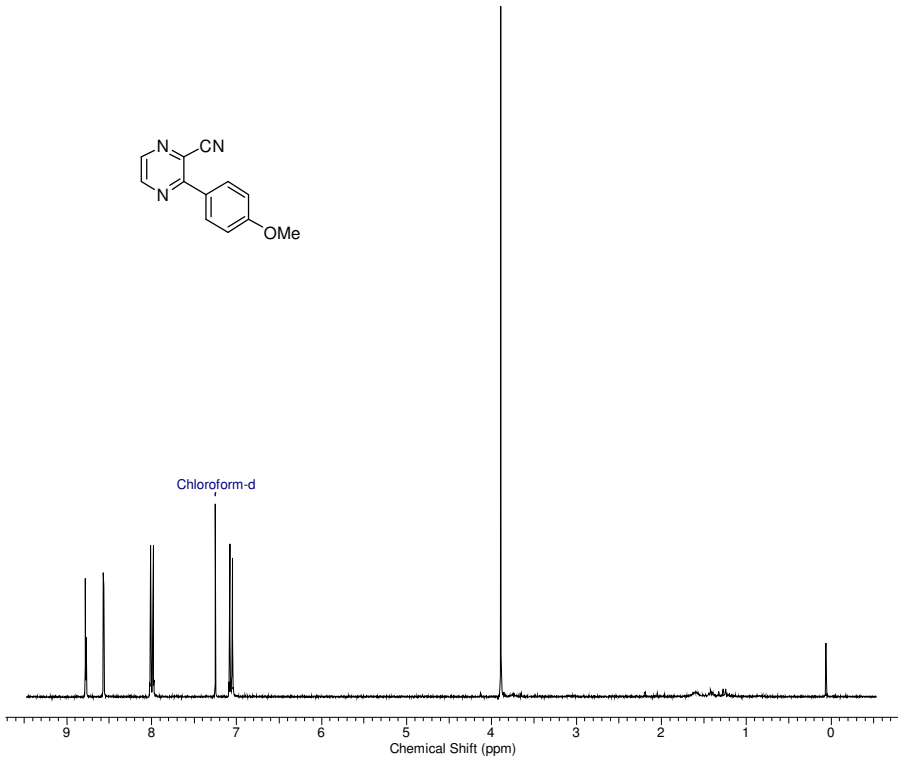


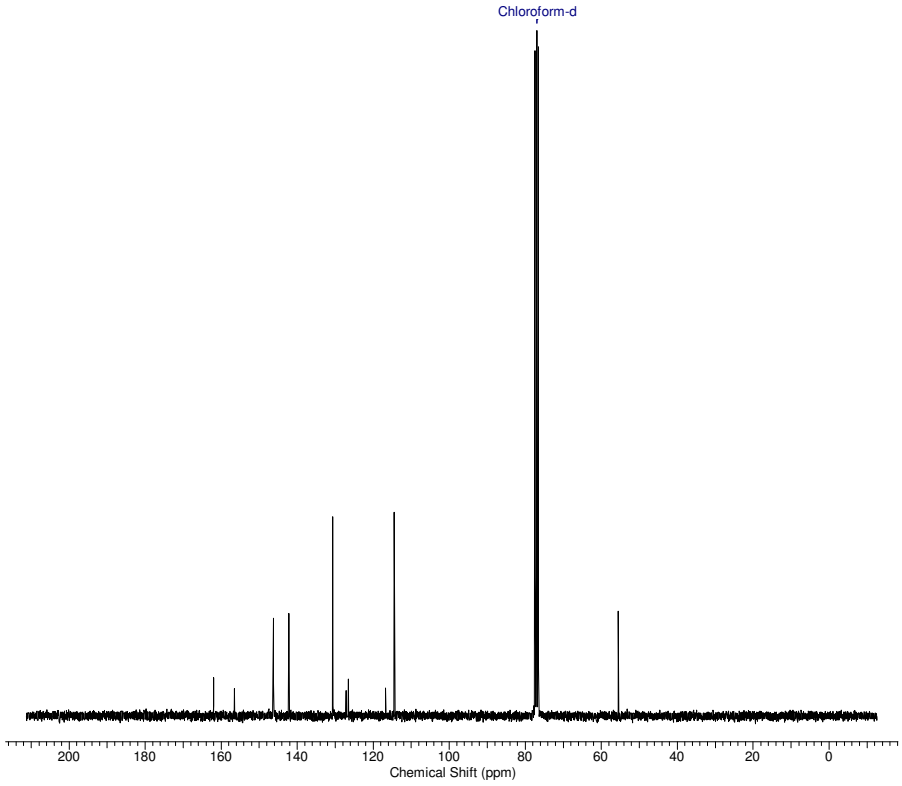
Ethyl 4-(6-methoxypyridazin-3-yl)benzoate (3c)



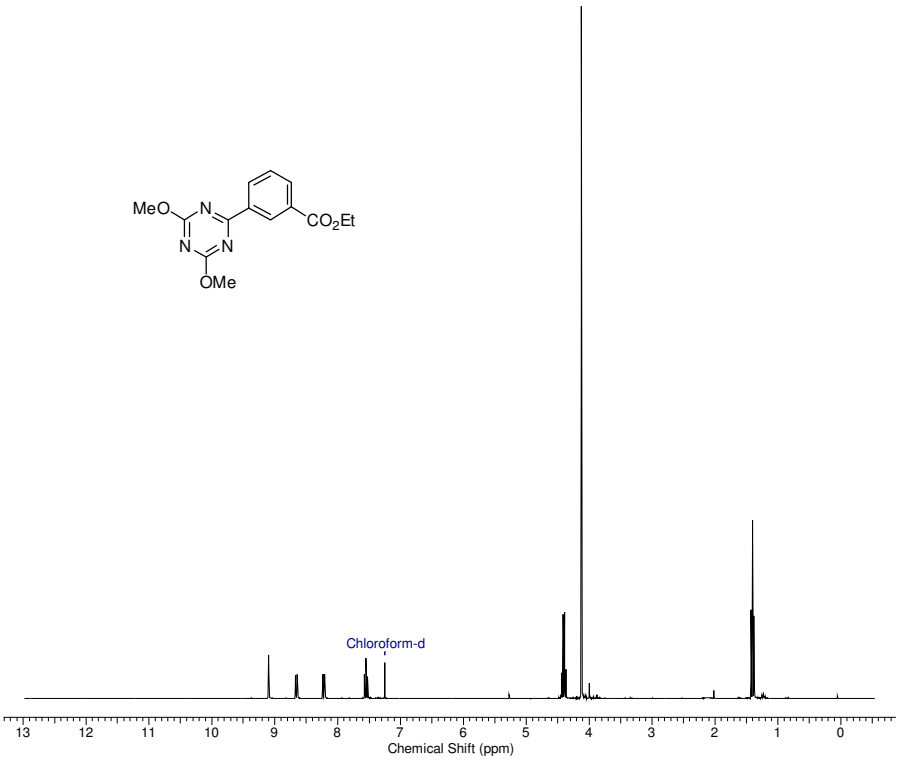


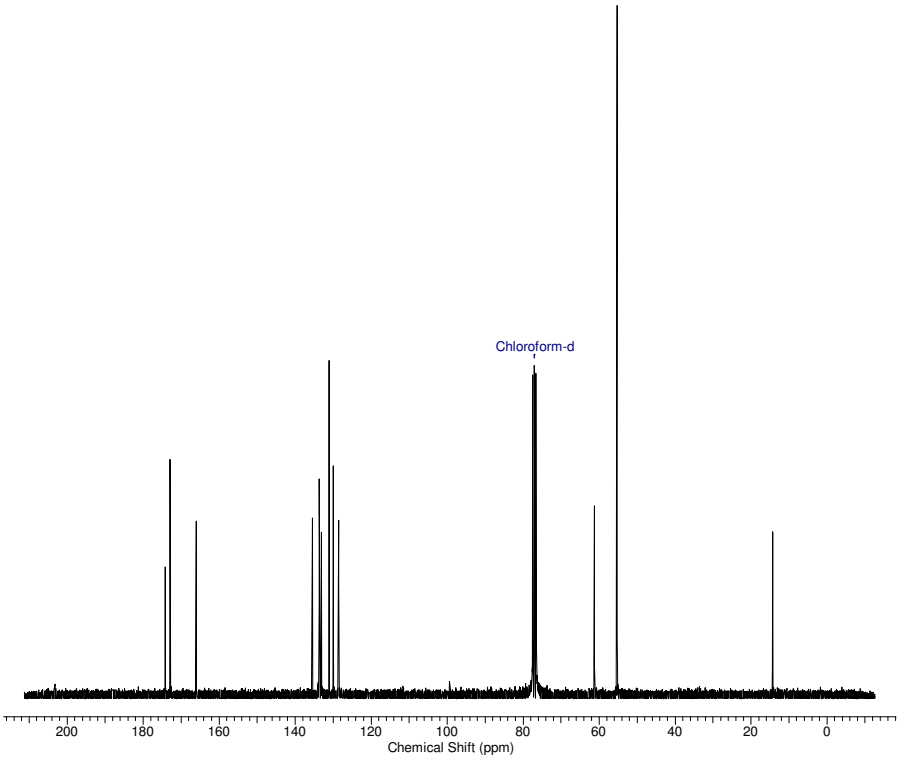
3-(4-Methoxyphenyl)pyrazine-2-carbonitrile (3d)



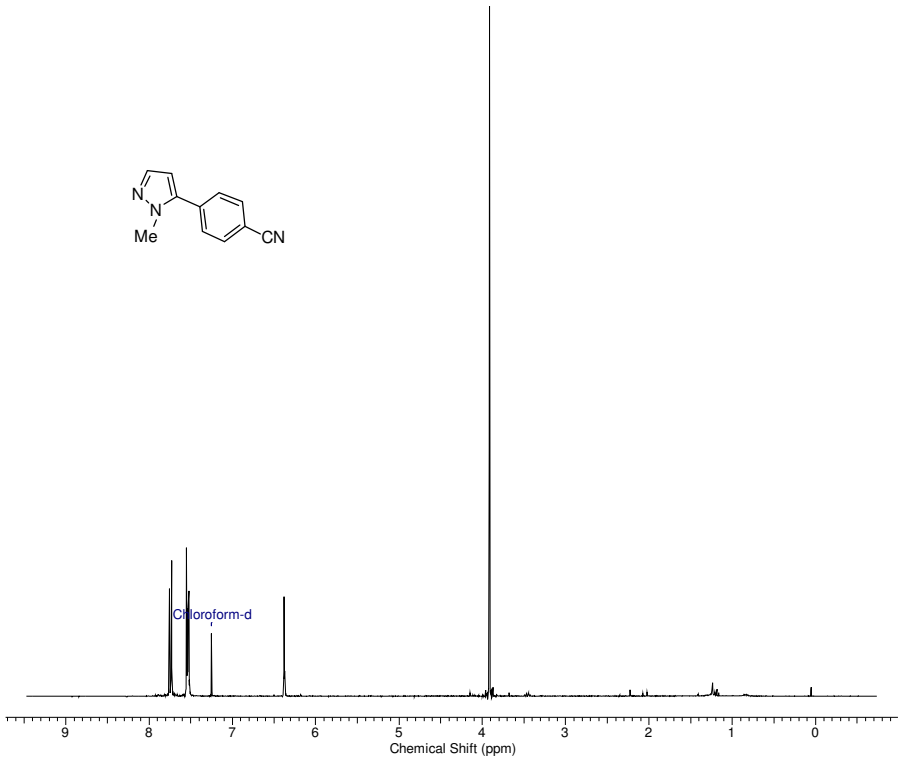


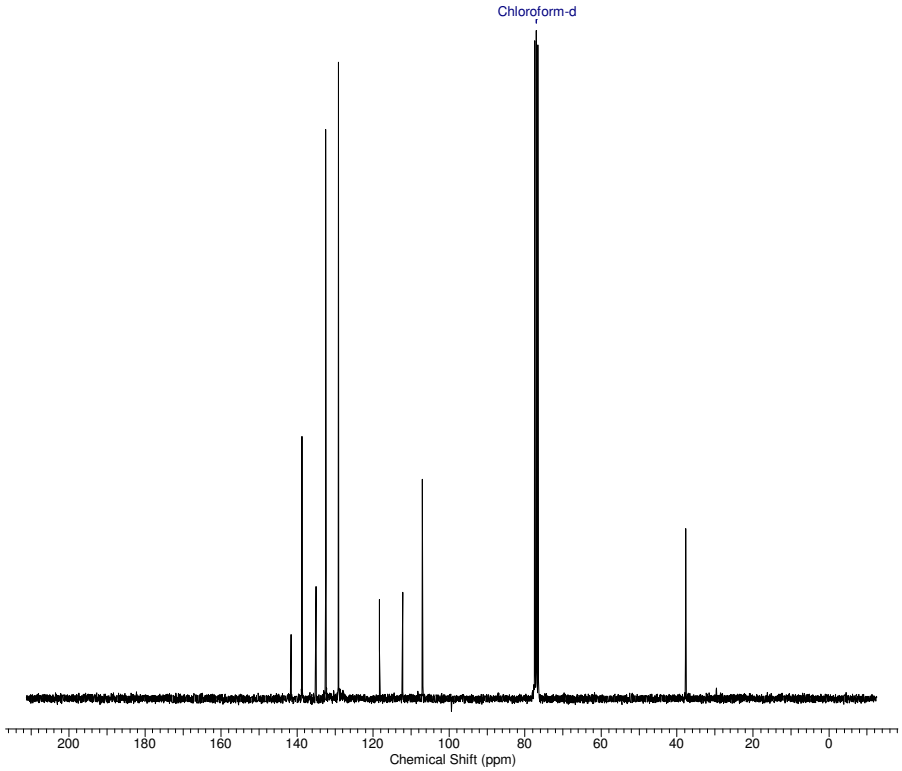
Ethyl 3-(4,6-dimethoxy-1,3,5-triazin-2-yl)benzoate (3e)



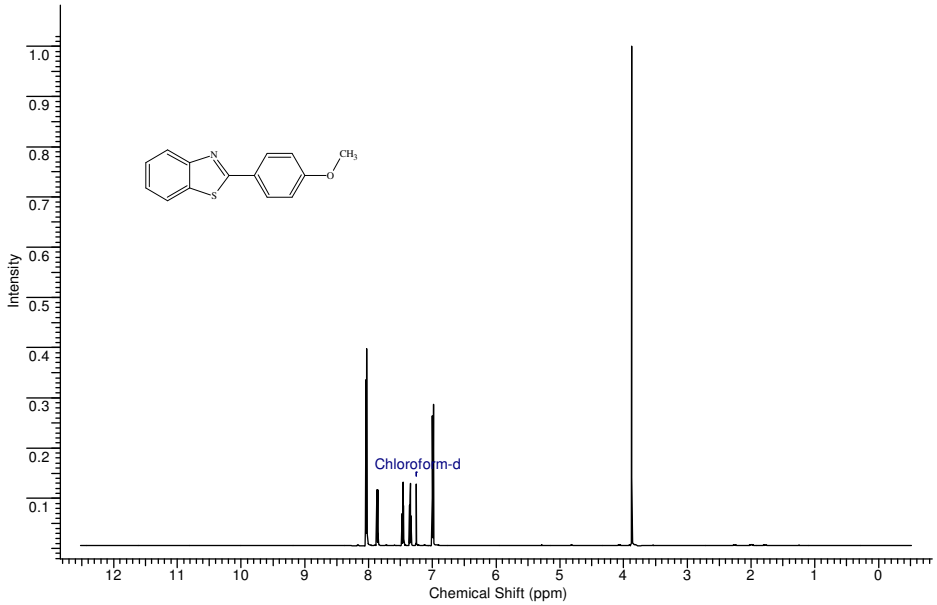


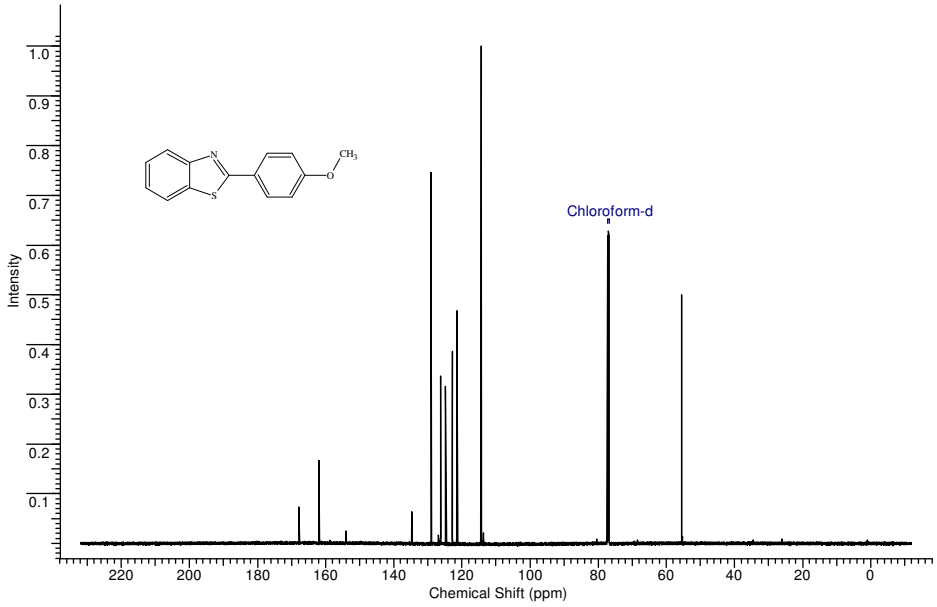
4-(1-Methyl-1H-pyrazol-5-yl)benzonitrile (3f)



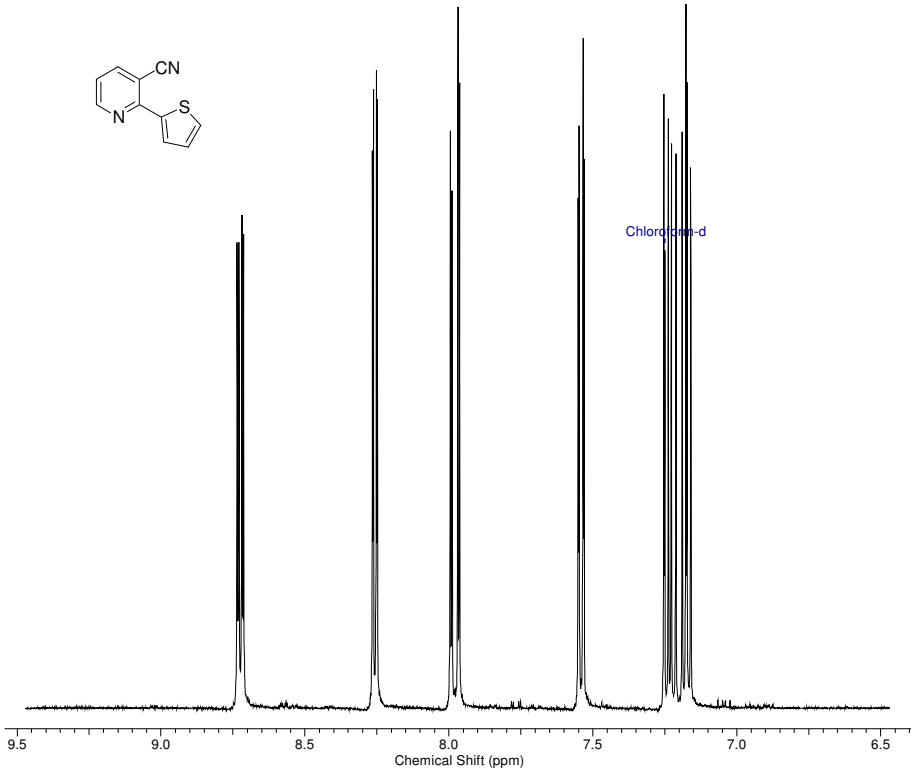


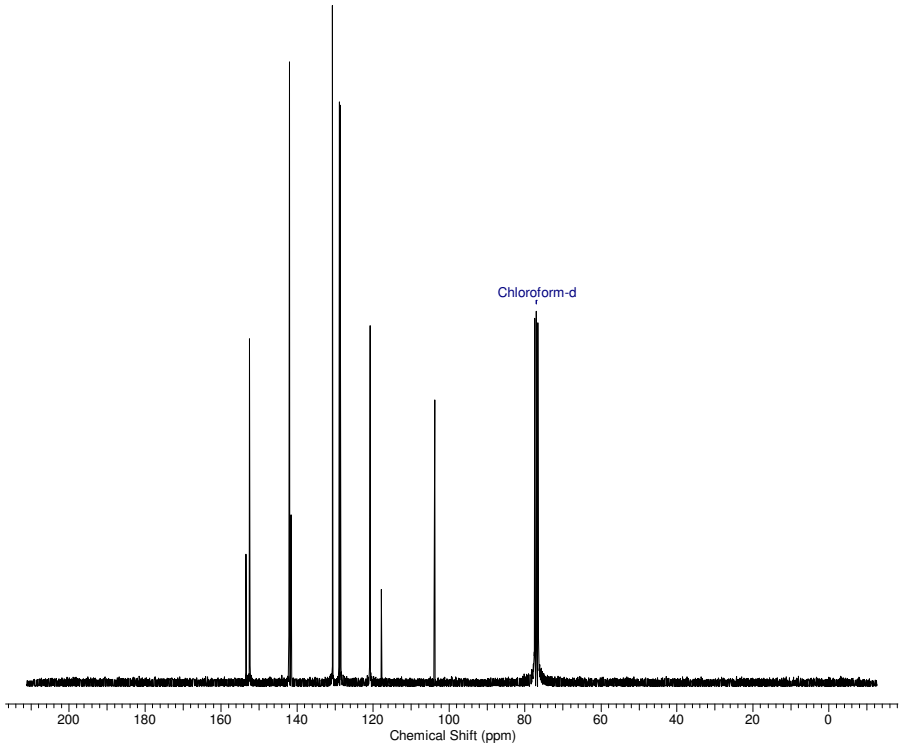
2-(4-Methoxyphenyl)-1,3-benzothiazole (3g)



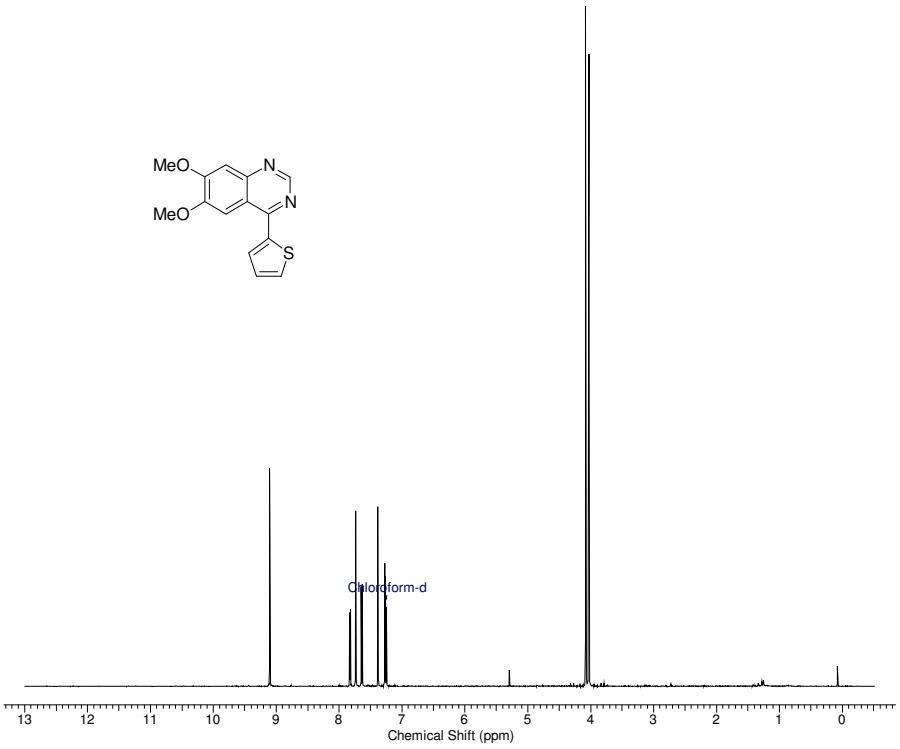


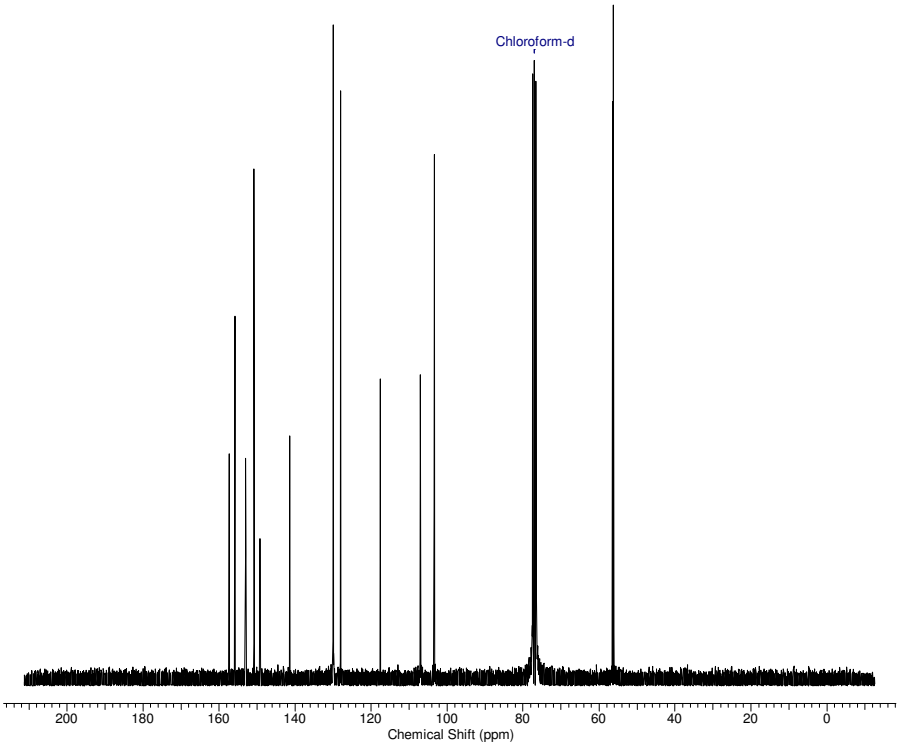
2-(2-Thienyl)nicotinonitrile (3h)



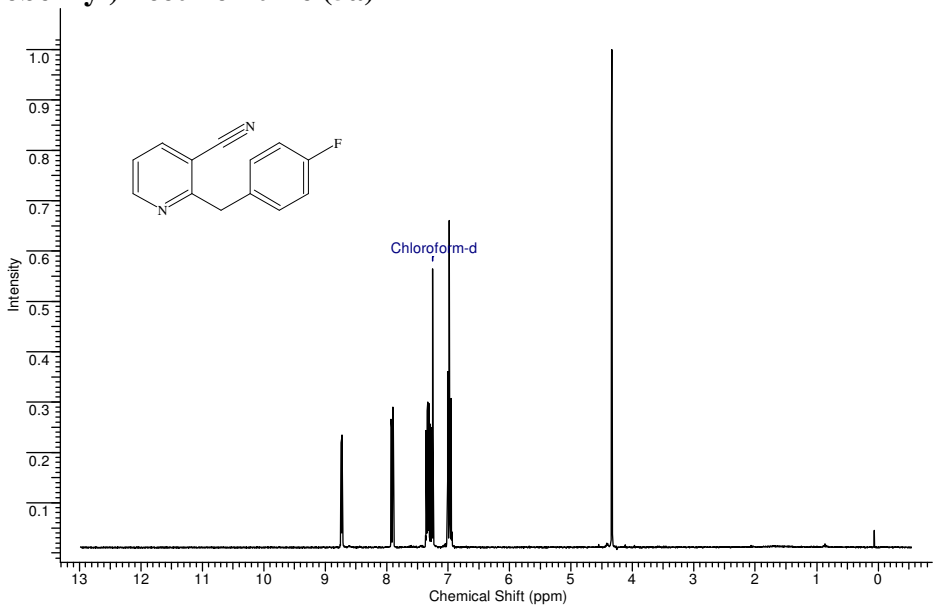


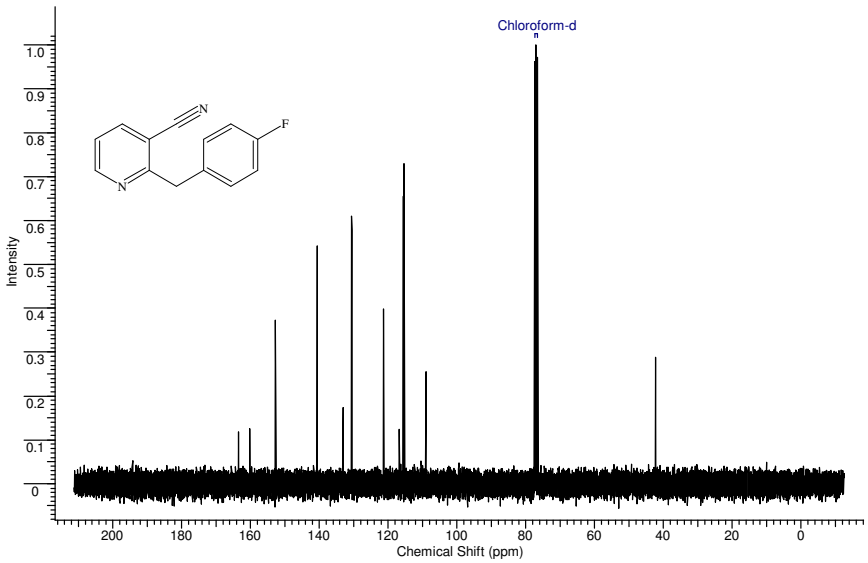
6,7-Dimethoxy-4-(2-thienyl)quinazoline (3i)



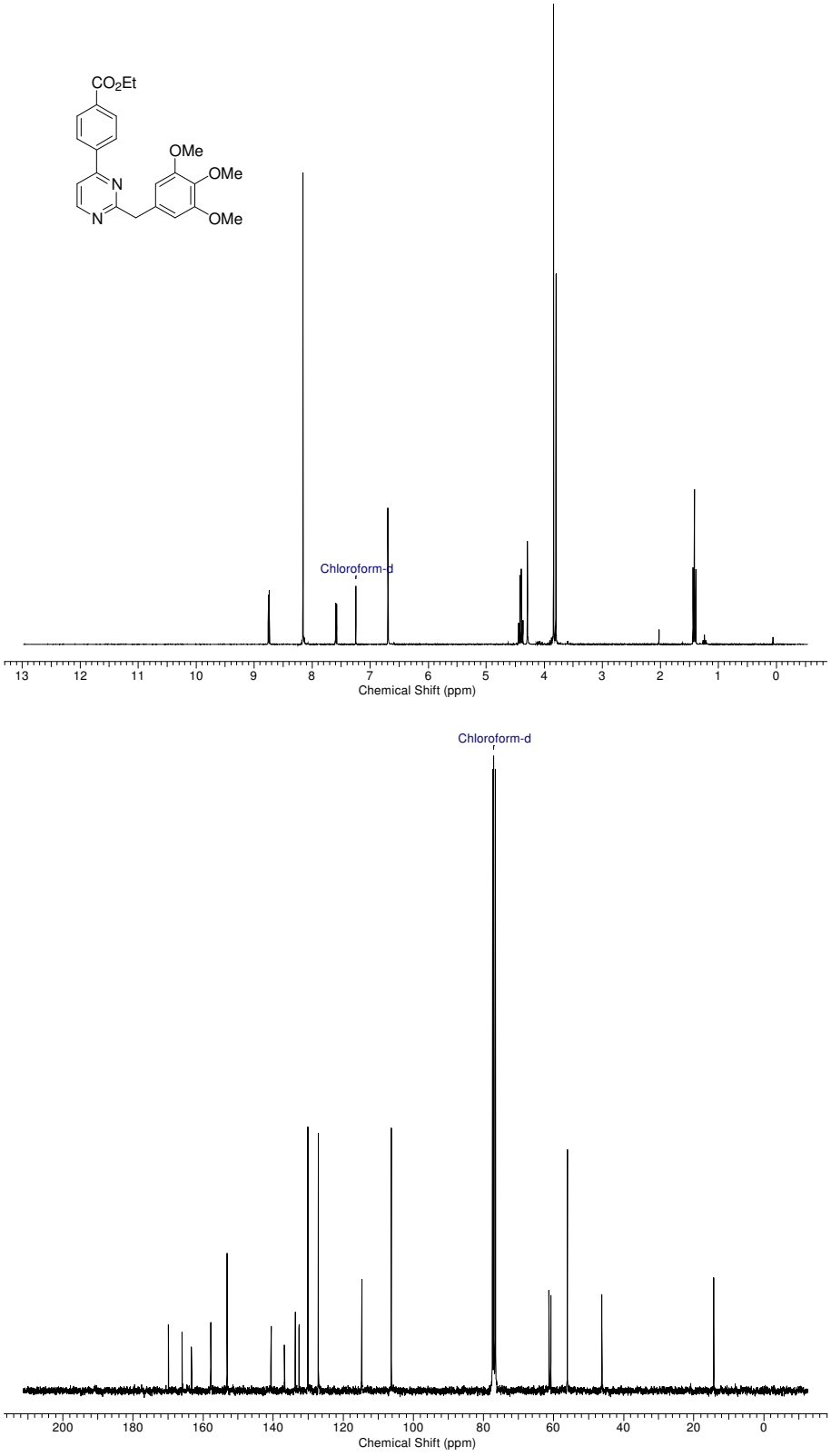


2-(4-Fluorobenzyl)nicotinonitrile (5a)

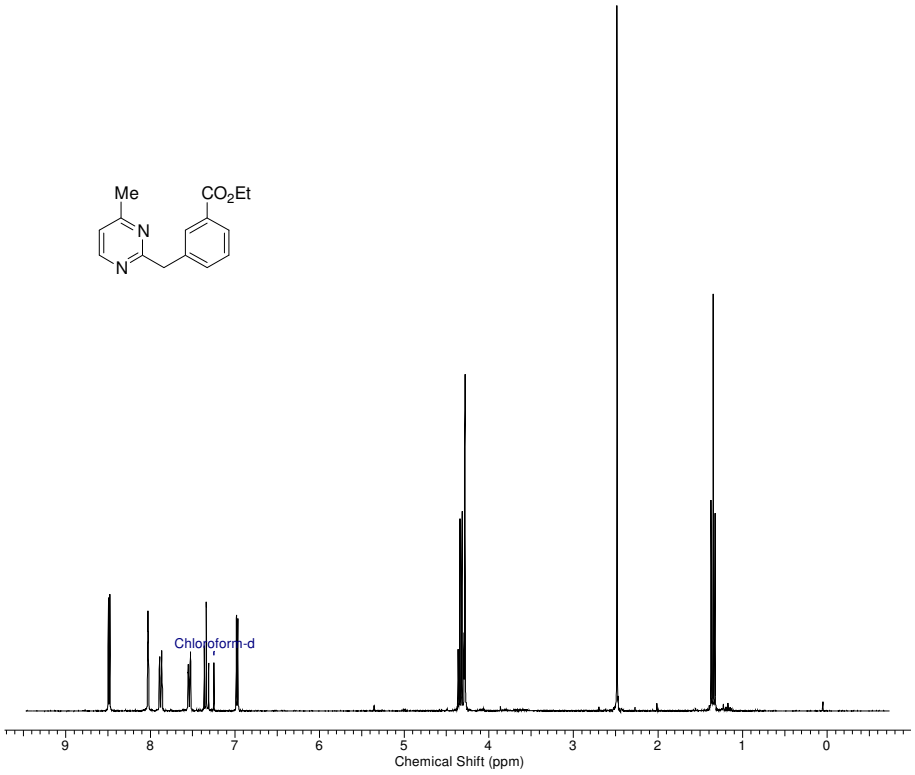


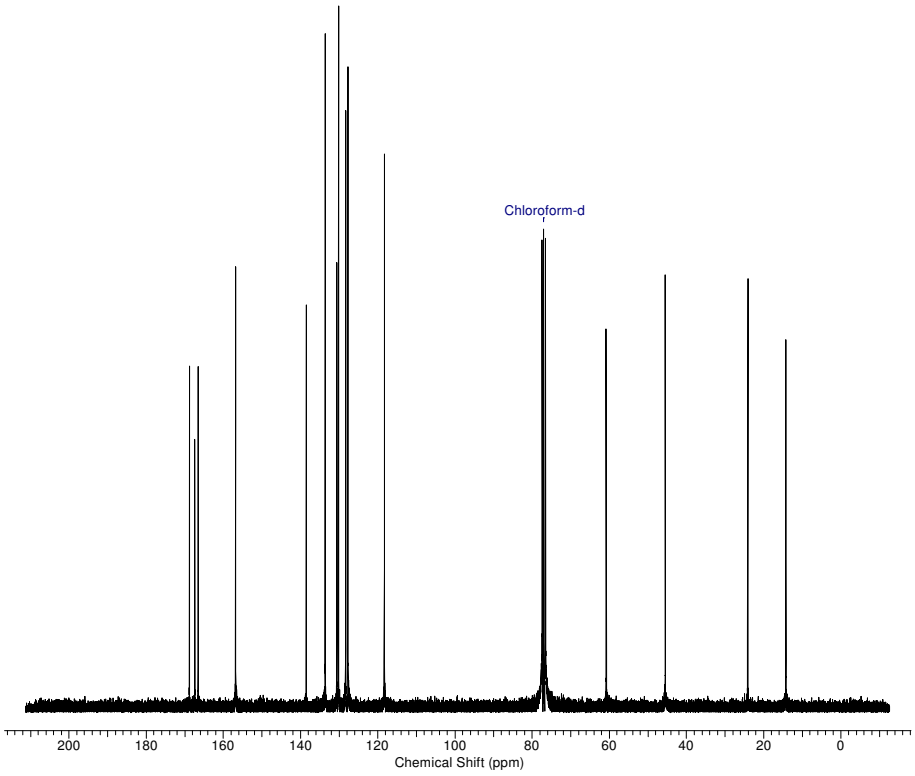


Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (5b)

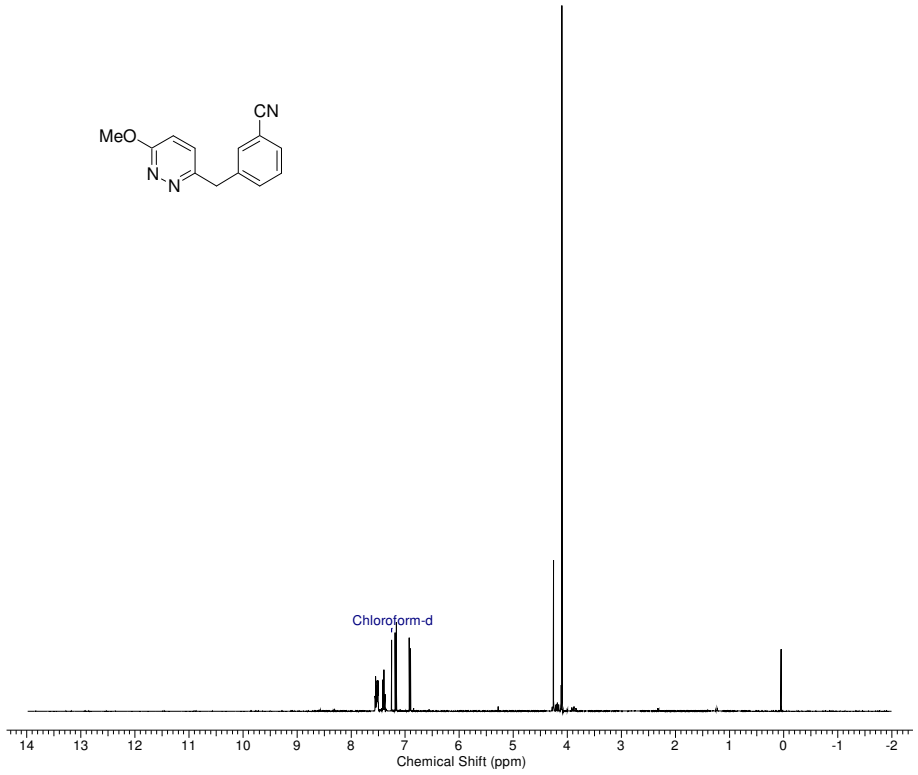


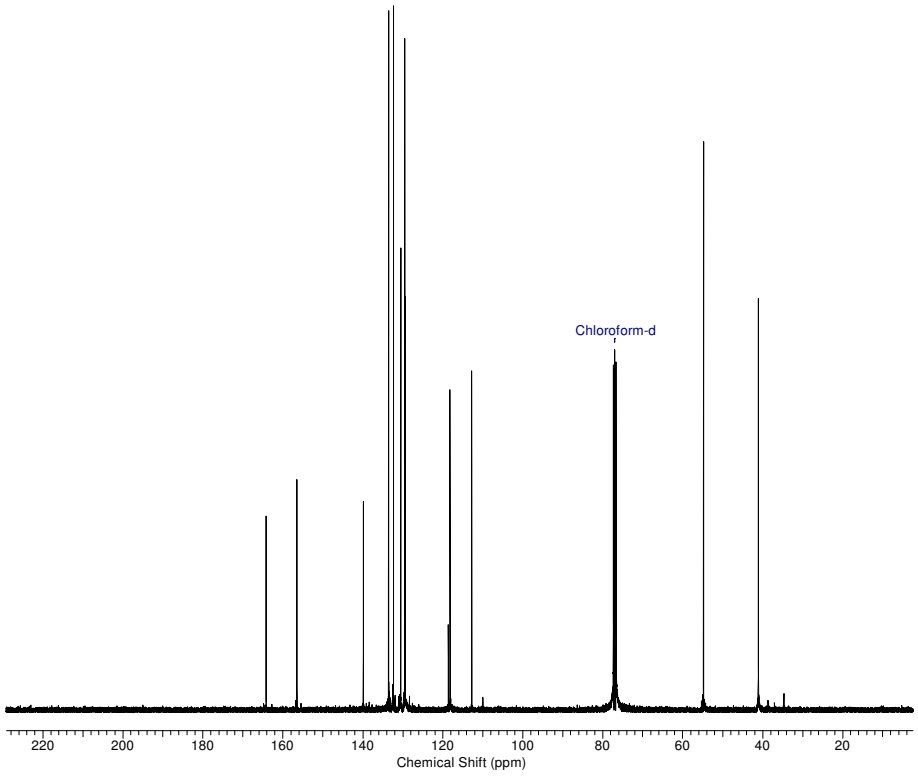
Ethyl 3-[(4-methylpyrimidin-2-yl)methyl]benzoate (5c)



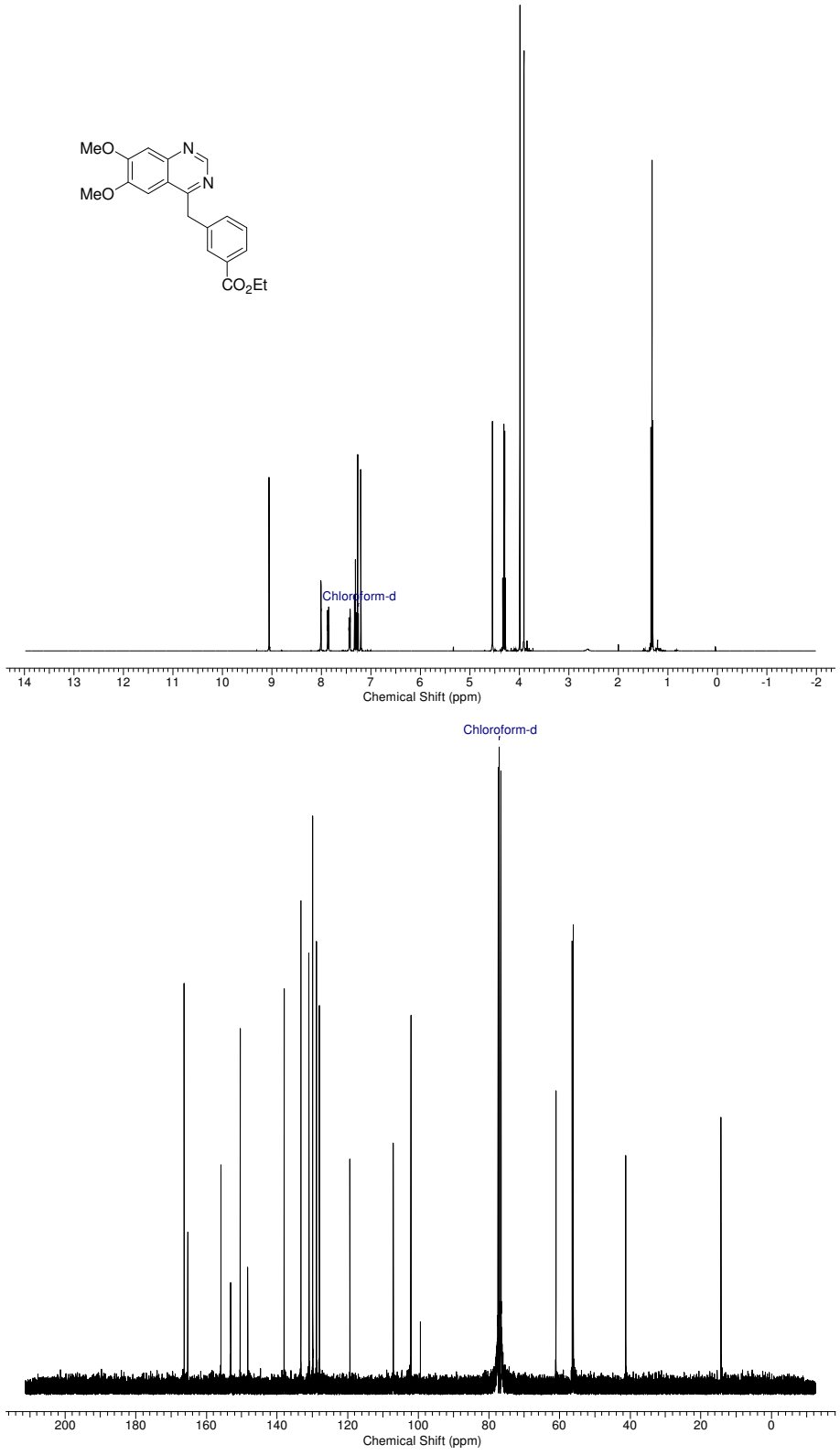


3-[(6-Methoxypyridazin-3-yl)methyl]benzonitrile (5d)

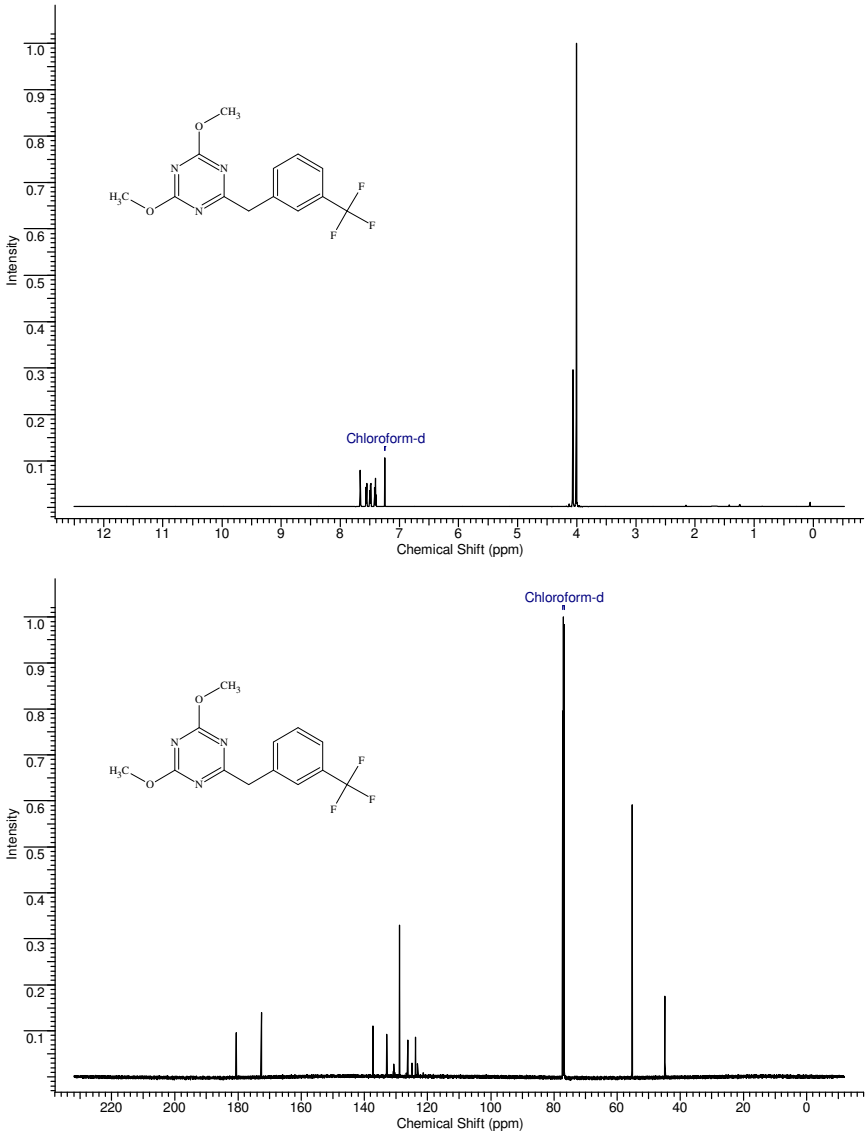




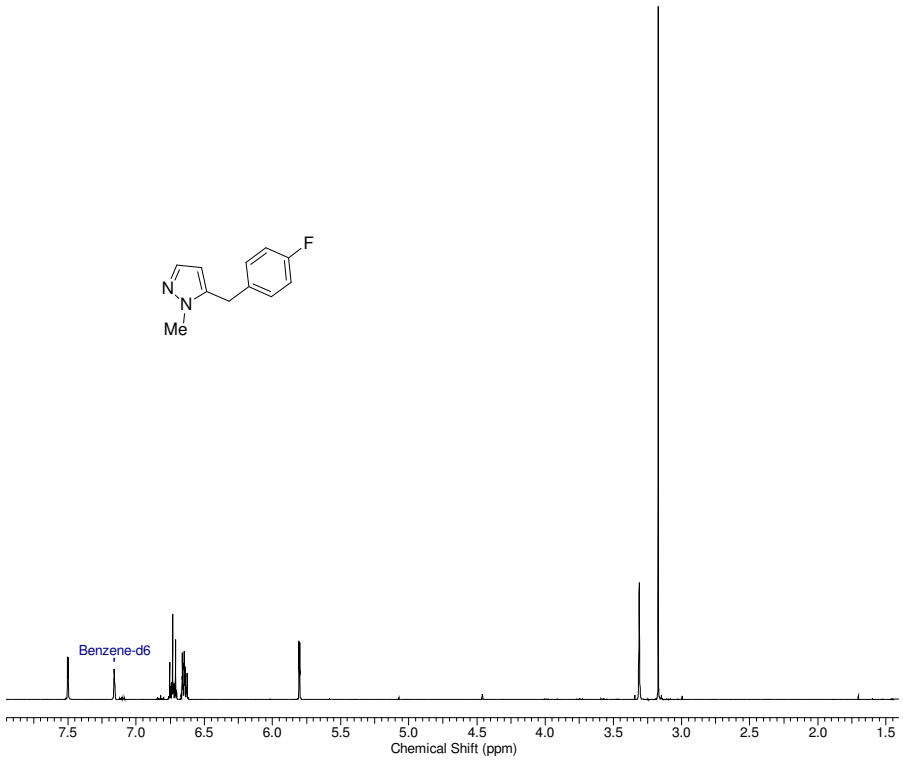
Ethyl 3-[(6,7-dimethoxyquinazolin-4-yl)methyl]benzoate (5e)

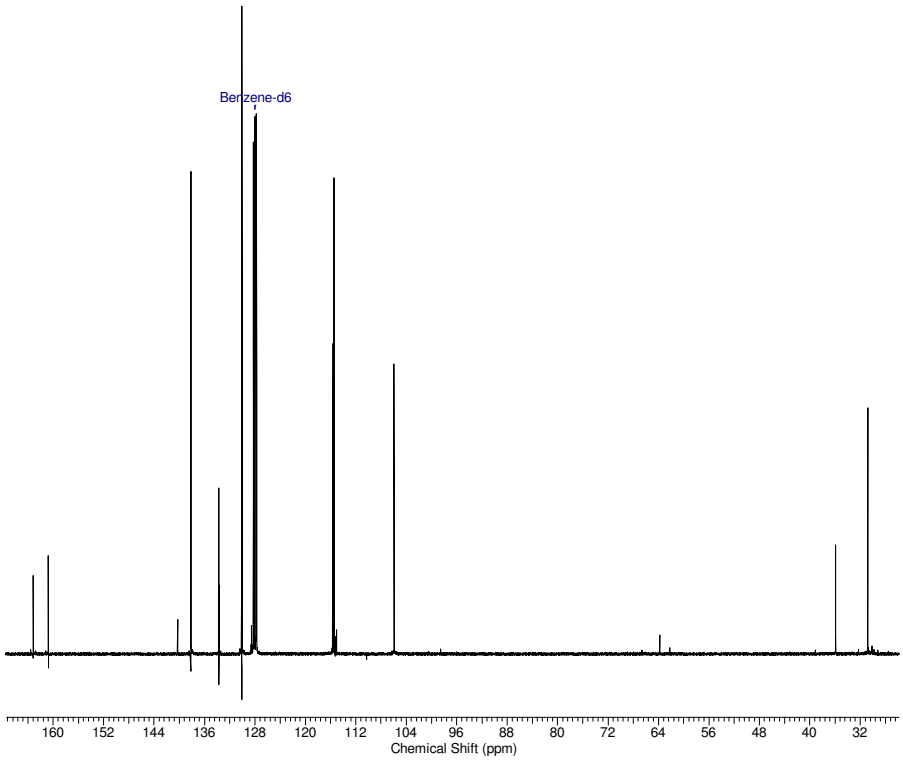


2,4-Dimethoxy-6-[3-(trifluoromethyl)benzyl]-1,3,5-triazine (5f)

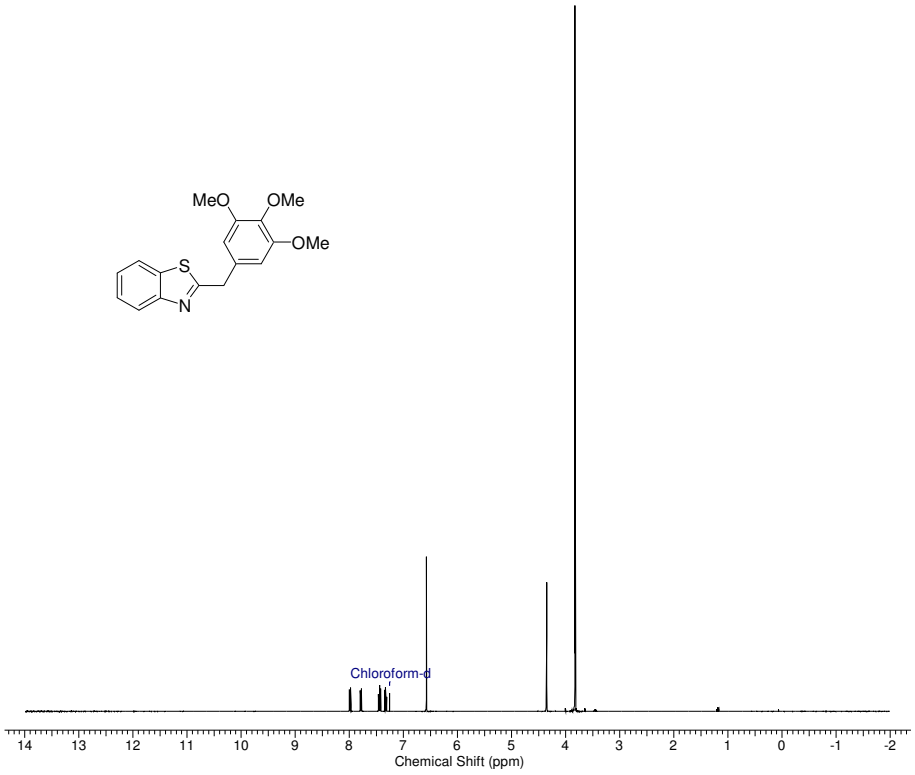


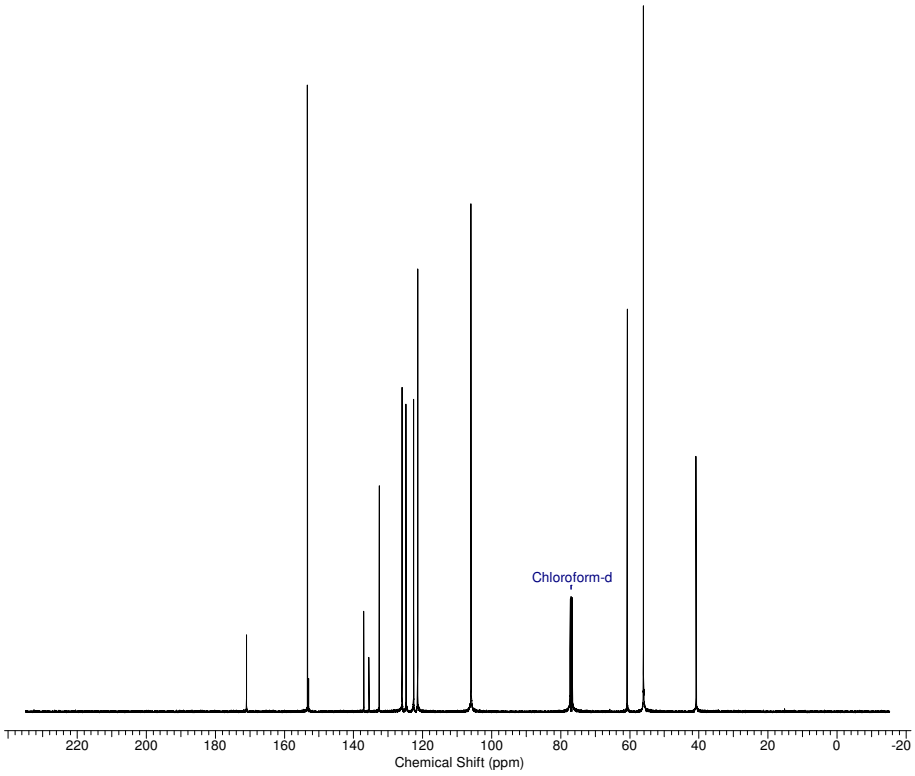
5-(4-Fluoro-benzyl)-1-methyl-1H-pyrazole (5g)



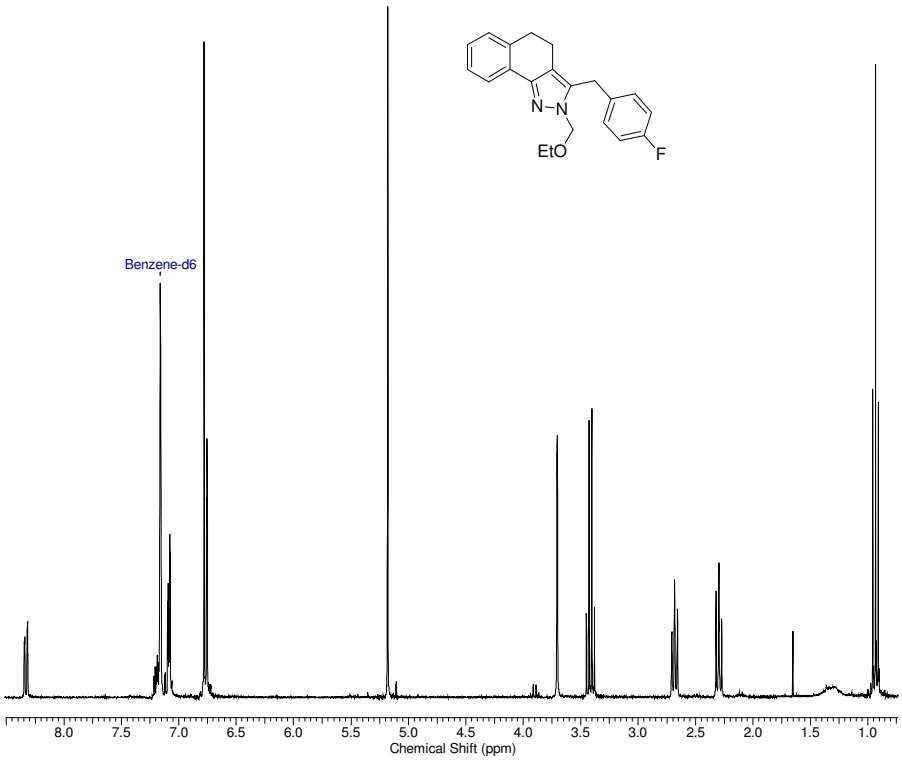


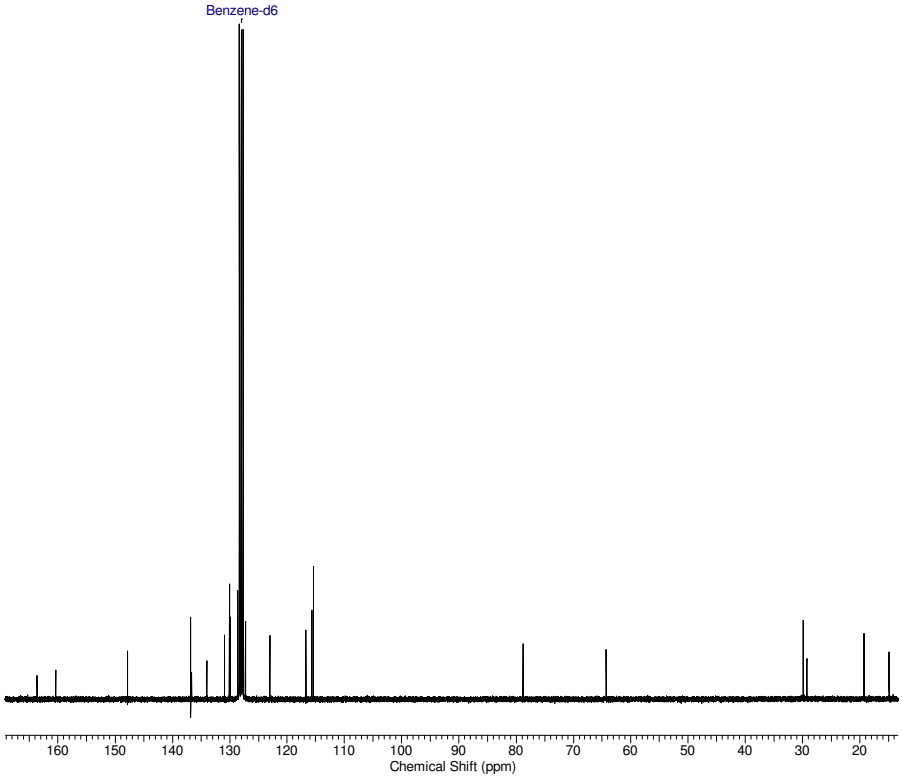
2-(3,4,5-Trimethoxybenzyl)-1,3-benzothiazole (5h)



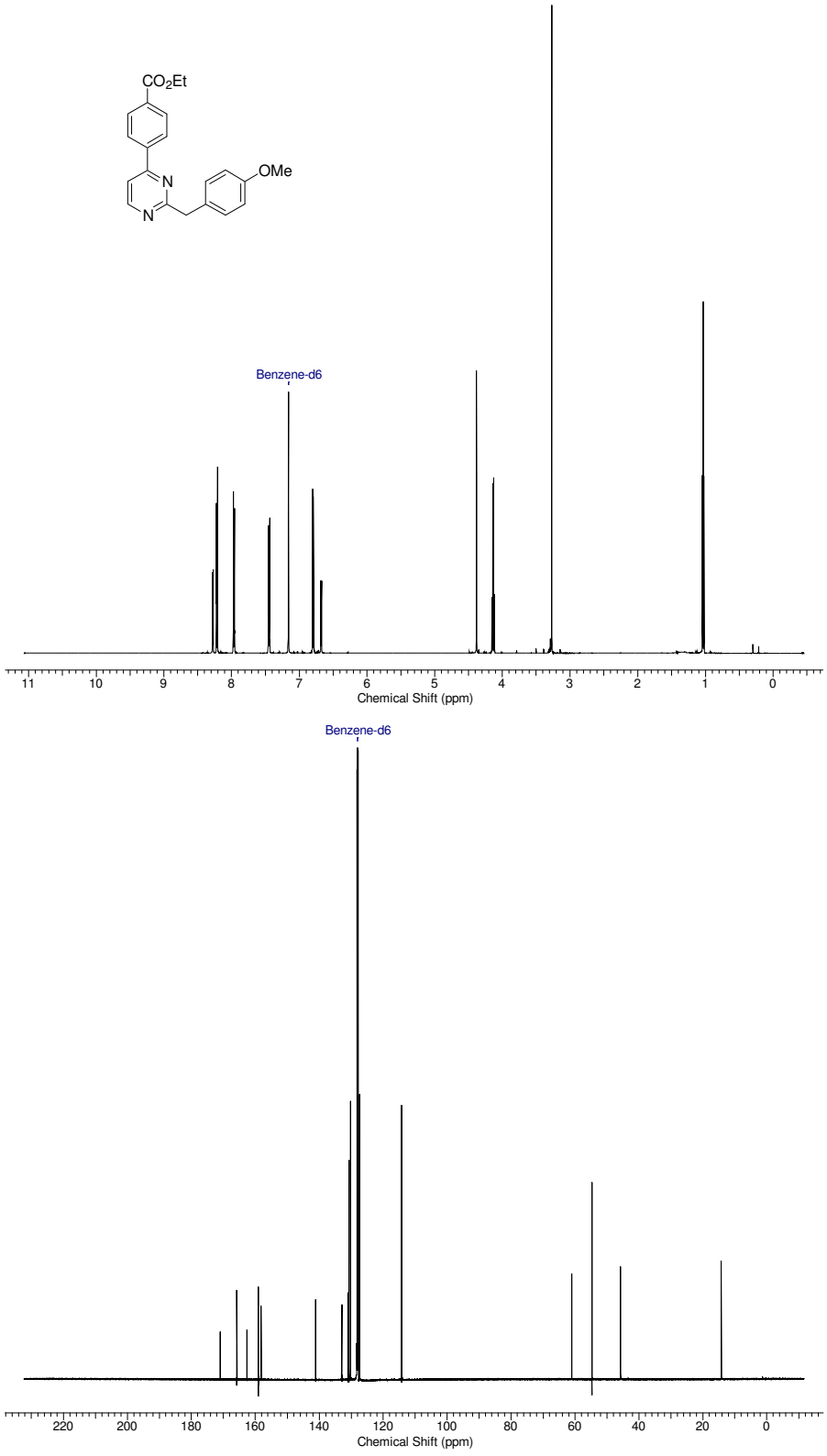


2-Ethoxymethyl-3-(4-fluorobenzyl)-4,5-dihydro-2H-benzo[g]indazole (5i)

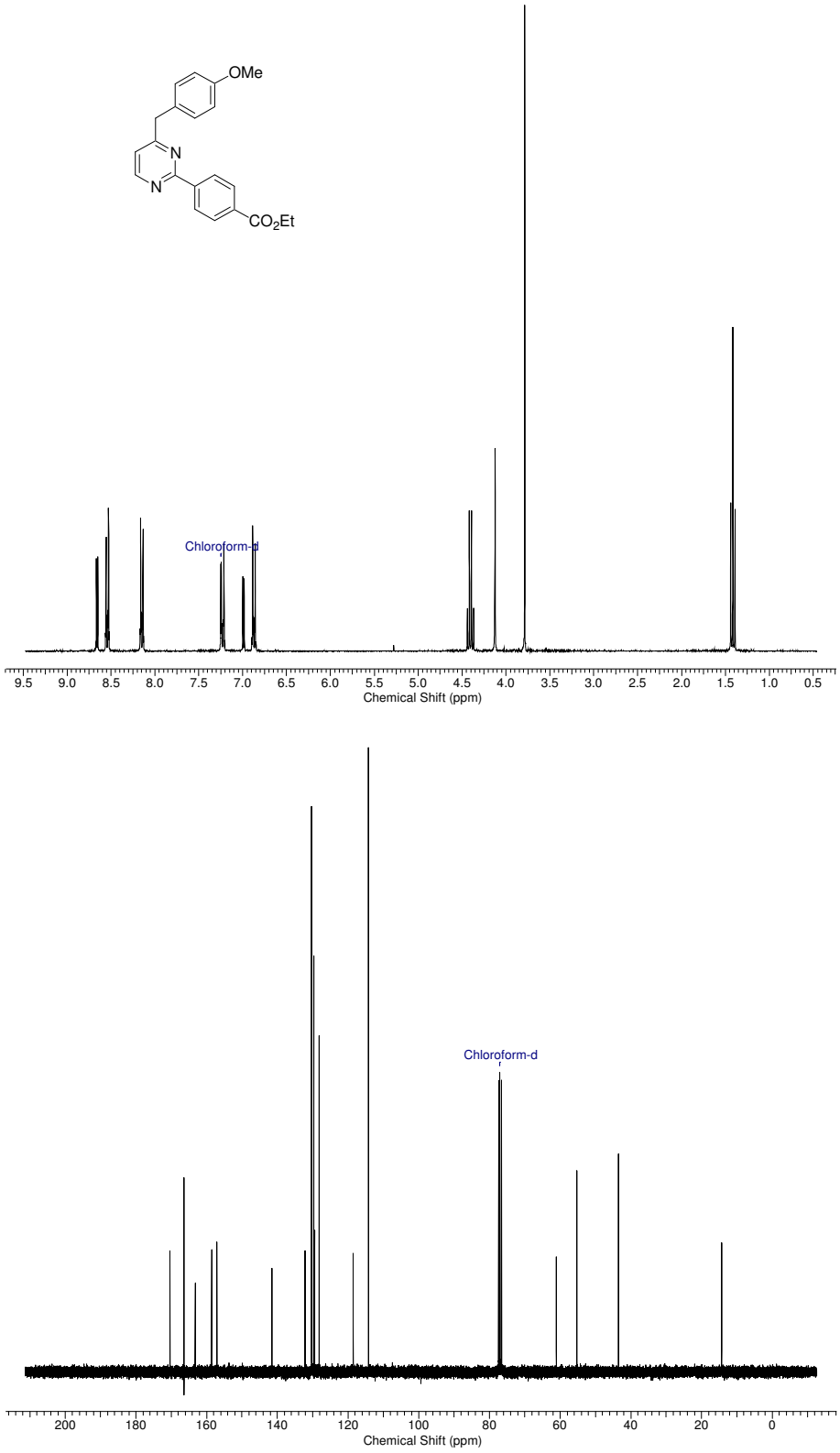




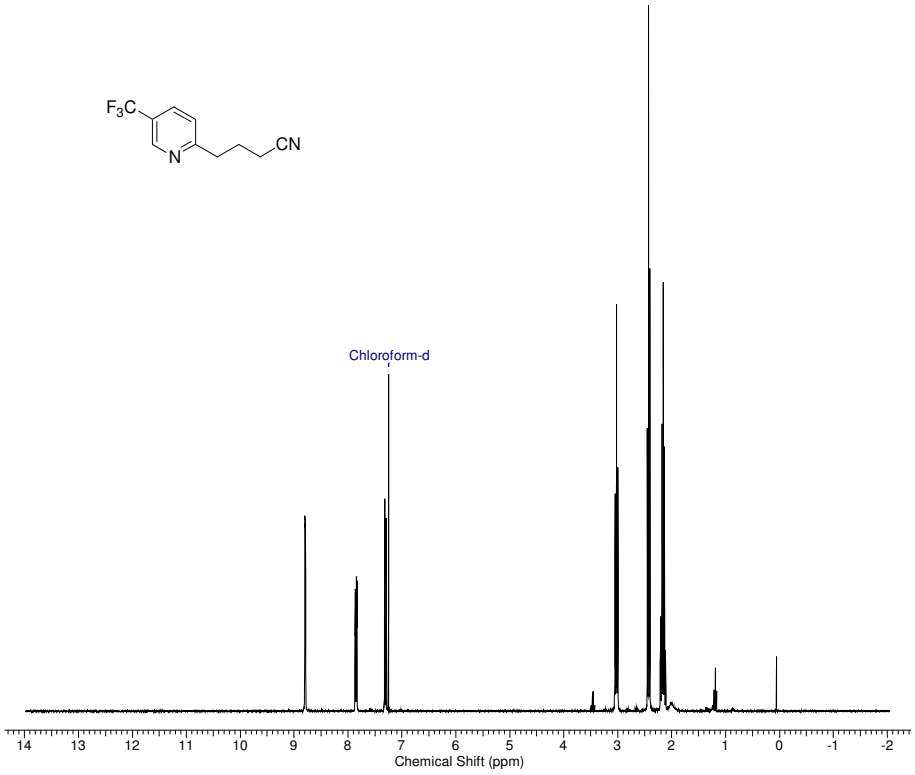
Ethyl 4-[2-(4-methoxybenzyl)pyrimidin-4-yl]benzoate (5j)

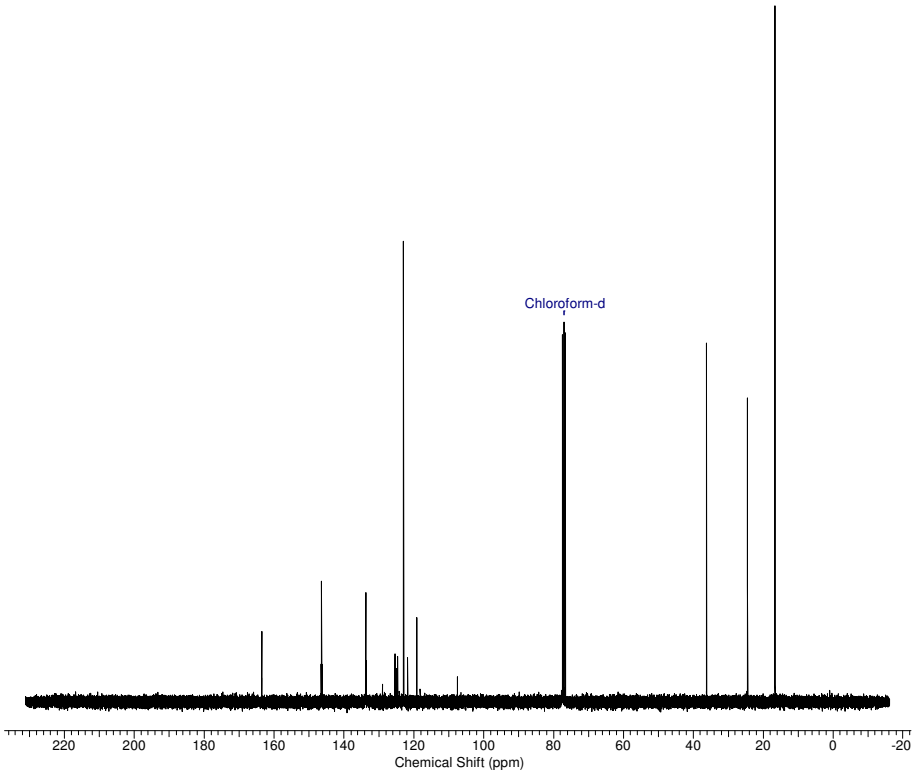


Ethyl 4-[4-(4-methoxybenzyl)pyrimidin-2-yl]benzoate (5k)

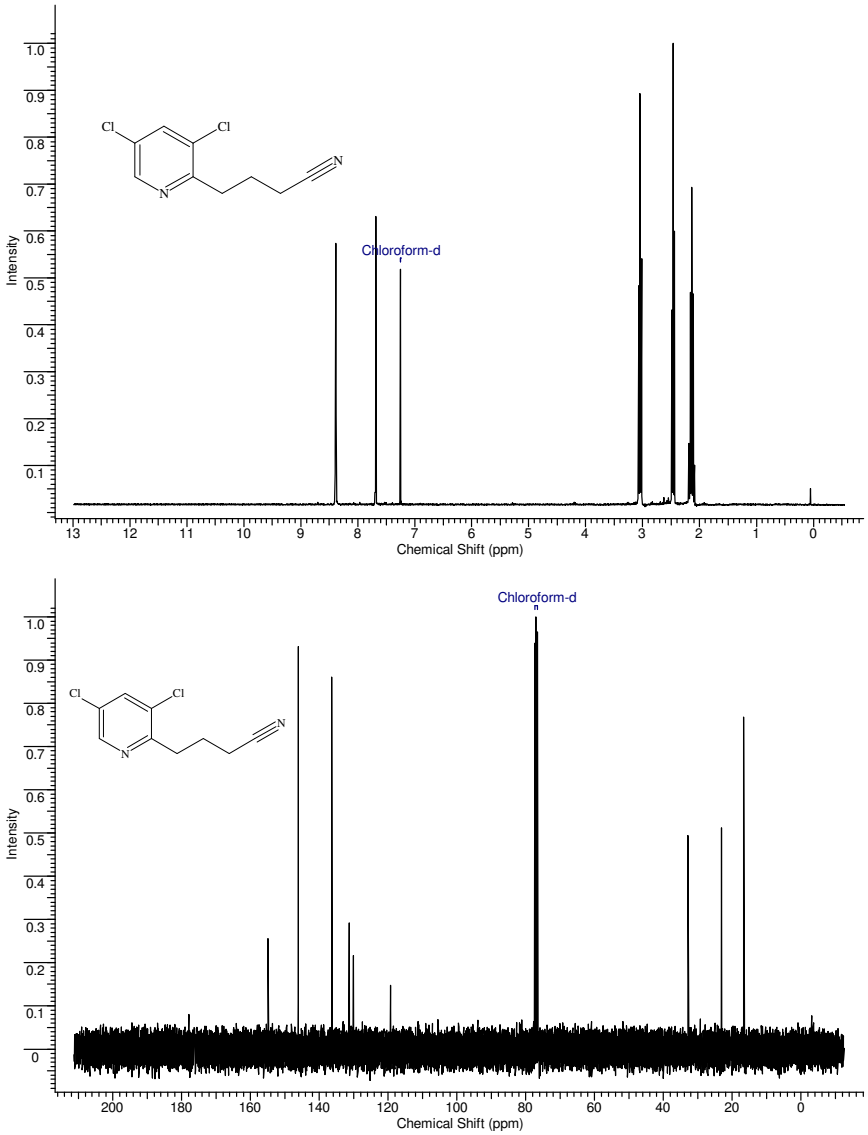


4-[5-(Trifluoromethyl)pyridin-2-yl]butanenitrile (7a)

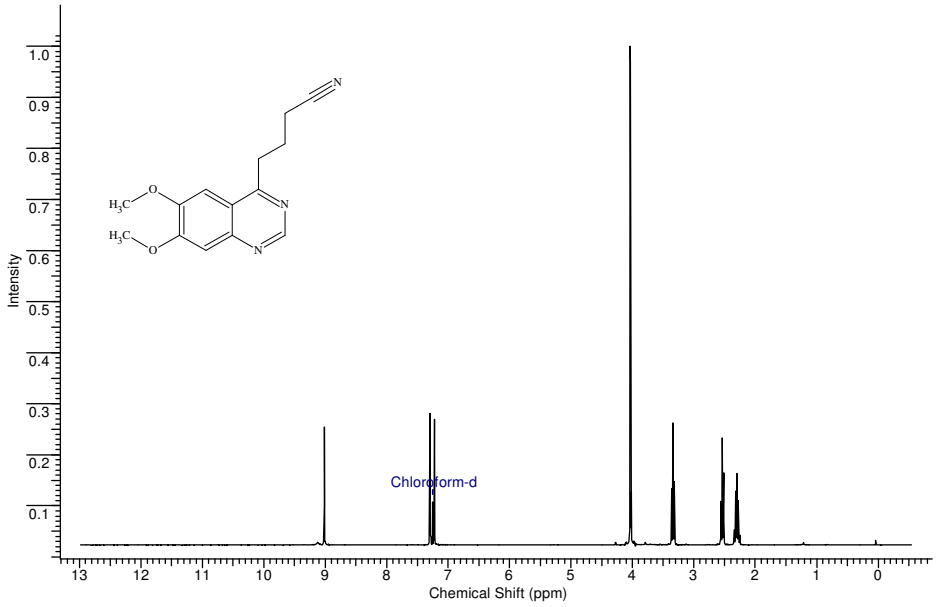


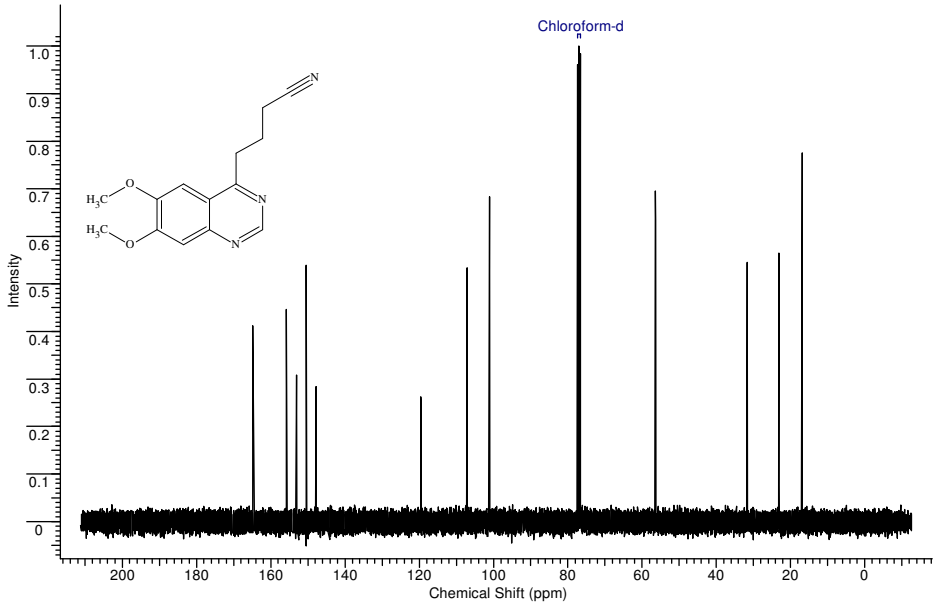


4-(3,5-Dichloropyridin-2-yl)butanenitrile (7b)

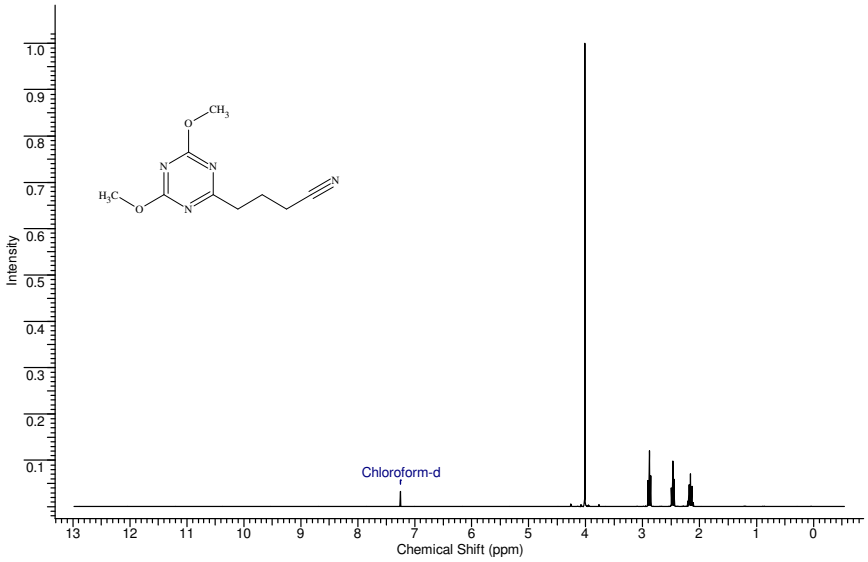


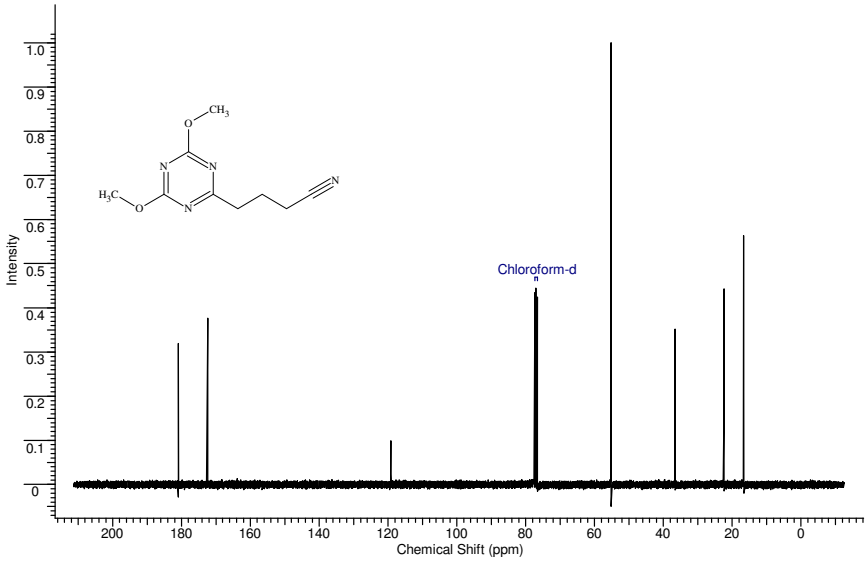
4-(6,7-Dimethoxyquinazolin-4-yl)butanenitrile (7c)





4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)butanenitrile (7d)





Ethyl 4-(2-methyl-2*H*-pyrazol-3-yl)butanoate (7e)