Regio- and Chemoselective Magnesiation of Protected Uracils and Thiouracils using TMPMgCl·LiCl and TMP_2Mg·2LiCl

Supporting Information

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General All reactions were carried out under an argon atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with argon prior to use. THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under nitrogen. Yields refer to isolated yields of compounds estimated to be > 95 % pure as determined by ^{1}H-NMR (25 °C) and capillary GC. Column chromatography was performed using SiO_2 (0.040 – 0.063 mm, 230 – 400 mesh ASTM) from Merck if not specially indicated.

Preparation of the reagent TMPMgCl·LiCl[1] (1):

A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with freshly titrated *i*-PrMgCl·LiCl (100 mL, 1.2 M in THF, 120 mmol). 2,2,6,6-Tetramethylpiperidine (TMPH) (17.8 g, 126 mmol, 1.05 equiv) was added dropwise at 25 °C. The reaction mixture was stirred at rt until gas evolution was completed (ca. – 48 h). The fresh TMPMgCl·LiCl (**1**) solution was titrated[2] at 25 °C with benzoic acid using 4-(phenylazo)-diphenylamine as indicator.

Preparation of the reagent TMP_2Mg·2LiCl[3] (3):

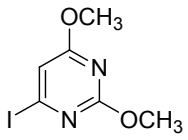
A dry and argon flushed 250 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with freshly 2,2,6,6-tetramethylpiperidine (5.07 mL, 30 mmol) dissolved in THF (30 mL).

This solution was cooled to -40 °C and BuLi (2.4 M in hexane, 12.5 mL, 30 mmol) was dropwise added. After the addition was complete, the reaction mixture was warmed to 0 °C and stirred at this temperature for 30 min. Freshly titrated TMPMgCl·LiCl (**1**) (1.0 M in THF, 30 mL, 30 mmol) was then dropwise added to the reaction mixture. It was stirred at 0 °C for 30 min, warmed to 25 °C, and stirred for 1 h. The solvents were then removed under vacuum affording a yellowish solid. Freshly distilled THF was then slowly added under vigorous stirring until the salts were completely dissolved. The resulting solution of TMP_2Mg·2LiCl (**3**) solution was titrated[2] prior to use at 0 °C with benzoic acid using 4-(phenylazo)diphenylamine as the indicator. A concentration of 0.7 M in THF was obtained.

General Procedure for the metalation:

A dry and argon flushed 10 mL Schlenk-flask, equipped with a magnetic stirrer and a septum, was charged with TMPMgCl·LiCl (**1**) (0.92 mL, 1.2 M in THF, 1.1 mmol, 1.1 equiv) or TMP_2Mg·2LiCl (**3**) (1.57 mL, 0.7 M in THF, 1.1 mmol, 1.1 equiv). The pyrimidine substrate (1.0 mmol) in THF (2 mL) was dropwise added at the temperature T_1. The completion of the metalation was checked by GC analysis of reaction aliquots quenched with a solution of I_2 in THF. The electrophile or its solution in THF was added at the temperature T_2. After the completion of the reaction (checked by GC analysis of reaction aliquots quenched with sat. aqueous NH_4Cl solution), the reaction mixture was quenched with sat. aqueous NH_4Cl solution (10 mL). The aqueous layer was extracted with ether (5 x 20 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by filter column chromatography (CH_2Cl_2/pentane).

Synthesis of 4-iodo-2,6-dimethoxypyrimidine (7a):



2,4-Dimethoxypyrimidine (**2**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**1**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to the general procedure. Iodine (381 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at -15 °C for 1 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution at –15 °C, followed by the addition of sat. aq. NH_4Cl and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:2) afforded **7a** (196 mg, 74%) as a white solid.

mp.: 100.5-101.9 °C.

IR (film): ν (cm^{-1}) = 3108 (m), 3020 (m), 2956 (m), 1542 (vs), 1458 (vs), 1392 (m), 1360 (vs), 1336 (s), 1232 (s), 1198 (s), 1116 (m), 1088 (s), 1006 (m), 972 (s), 926 (m), 830 (m), 808 (m), 776 (m).

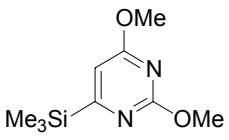
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): δ = 6.85 (s, 1 H), 3.96 (s, 3 H), 3.92 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): δ = 170.6, 163.6, 127.8, 112.5, 55.3, 54.1.

MS (EI, 70 eV): *m/z* (%) = 265 (100) [M^+], 264 (26), 235 (23), 139 (19), 124 (10), 82 (9).

HRMS $C_6H_7IN_2O_2$: calculated [M^+]: 265.9552 found: 265.9560

Synthesis of 2,4-dimethoxy-6-(trimethylsilyl)pyrimidine (7b):



2,4-Dimethoxypyrimidine (**2**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**1**) (1.1 M in THF,

1.0 mL, 1.1 mmol) at 25 °C for 15 min according to the general procedure. TMSCN (1.5 mmol, 149 mg, 1.5 equiv) was then added to the resulting mixture at 25 °C for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:1) afforded **7b** (149 mg, 70%) as a colourless oil.

IR (film): ν (cm^{-1}) = 2954 (m), 2899 (w), 1742 (s), 1570 (s), 1543 (s), 1470 (m), 1361 (m), 1327 (vs), 1247 (m), 1218 (w), 1200 (m), 1095 (m), 1030 (w), 881 (m), 835 (m), 820 (m), 755 (m).

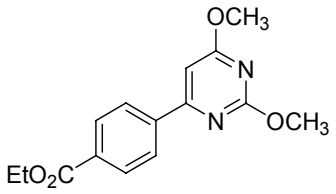
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): δ = 6.53 (s, 1 H), 3.95 (s, 3 H), 3.90 (s, 3 H), 0.23 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): δ = 179.2, 170.5, 164.7, 107.2, 54.4, 53.3, -2.6.

MS (EI, 70 eV): *m/z* (%) = 212 (10) [M^+], 197 (30), 92 (11), 80 (11), 44 (100).

HRMS $C_9H_{16}N_2O_2Si$: calculated [M^+]: 212.0981 found: 212.0969

Synthesis of ethyl 4-(2,6-dimethoxypyrimidin-4-yl)benzoate (7c):



2,4-Dimethoxypyrimidine (**2**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**1**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to the general procedure. Transmetalation with $ZnCl_2$ (1.2 mL, 1.2 equiv, 1.00 M in THF) was then performed at 25 °C for 20 min. In another flame-dried round bottom flask, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were dissolved in dry THF (2 mL) and stirred for 5 min followed by the addition of ethyl iodobenzoate (331 mg, 1.2 mmol, 1.2 equiv). The resulting solution was then transferred to the zinc reagent flask and refluxed for 2 h. The reaction mixture was

quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 3:2) afforded **7c** (216 mg, 75%) as a white solid.

mp.: 116.0-118.2 °C

IR (neat): ν (cm^{-1}) = 1714 (m), 1597 (m), 1578 (m), 1559 (s), 1467 (m), 1350 (s), 1274 (s), 1217 (m), 1104 (s), 1013 (m), 825 (s), 771 (s), 703 (s) .

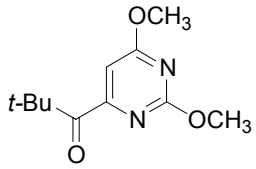
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.11 (m, 4H), 6.82 (s, 1H), 4.41 (q, *J* = 7.50 Hz, 2H), 4.09 (s, 3H), 4.02 (s, 3H), 1.41 (t, *J* = 7.05, 3H) .

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.7, 166.1, 165.6, 164.8, 140.7, 132.2, 129.9 (2 carbons), 126.9 (2 carbons), 98.0, 61.2, 54.9, 54.1, 14.3 ppm.

MS (EI, 70 eV): *m/z* (%) = 288 (M^+, 100), 258 (49), 243 (30), 143 (10), 99 (10).

HRMS (EI) $C_{15}H_{16}N_2O_4$ calculated [M^+]: 288.1110 found: 288.1097

Synthesis of 1-(2,6-dimethoxypyrimidin-4-yl)-2,2-dimethylpropan-1-one (7d):



2,4-Dimethoxypyrimidine (**2**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**1**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to the general procedure. Transmetalation with CuCN·2LiCl (1.0 mL, 1.0 equiv, 1.00 M in THF) was then performed at –30 °C and stirred at the same temperature for 15 min. Pivaloyl chloride (181 mg, 1.5 mmol, 1.5 equiv) was added to the resulting mixture at –30 °C and stirred at the same temperature for 5 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in*

vacuo. Purification by flash chromatography (SiO_2, *n*-pentane/ethyl acetate = 9:1) afforded **7d** (161 mg, 72%) as a white solid.

mp.: 67.8-69.0 °C.

IR (film): ν (cm^{-1}) = 2962 (w), 1689 (m), 1578 (s), 1560 (s), 1476 (s), 1459 (s), 1372 (s), 1344 (s), 1253 (w), 1196 (m), 1096 (m), 1030 (m), 978 (s), 939 (s), 857 (m), 772 (m), 679 (w).

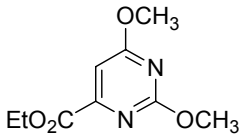
^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 6.76 (s, 1H), 4.01 (s, 3H), 3.97 (s, 3H), 1.39 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 205.1, 172.7, 164.7, 163.4, 101.1, 55.1, 54.2, 44.0, 26.9 (3 carbons).

MS (EI, 70 eV): *m/z* (%) = 224.1 [M^+] (7), 209.0 (7), 140.0 (100), 82.0 (9), 57.0 (23), 41.1 (18).

HRMS $C_{11}H_{16}N_2O_3$: calculated [M^+]: 224.1161 found: 224.1142

Synthesis of ethyl 2,6-dimethoxypyrimidine-4-carboxylate (7e):



2,4-Dimethoxypyrimidine (**2**) (140 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of TMPMgCl·LiCl (**1**) (1.1 M in THF, 1.0 mL, 1.1 mmol) at 25 °C for 15 min according to the general procedure. Ethyl cyanoformiate (198 mg, 2 mmol, 2.0 equiv) was then added to the resulting mixture at -60 °C and stirred at the same temperature for 10 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, *n*-pentane/ethyl acetate = 4:1) afforded **7e** (150 mg, 71%) as a white solid.

mp.: 67.2-68.9 °C

IR (ATR): 3104 (w), 2988 (w), 2956 (w), 2940 (w), 2868 (w), 1720 (m), 1600 (s), 1564 (s), 1484 (s), 1404 (s), 1352 (vs), 1264 (s), 1200 (s), 1100 (s), 1028 (vs), 880 (s), 776 (vs).

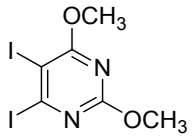
^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm): 7.03 (s, 1H), 4.44-4.37 (q, 2H, *J* = 7.0 Hz), 4.04 (s, 3H), 4.00 (s, 3 H), 1.41-1.37 (t, 3H, *J* = 7.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm): 172.8, 165.9, 163.9, 157.2, 103.1, 62.2, 55.1, 54.1, 14.1.

MS (EI, 70 eV): *m/z* (%) = 212 (21) [M^+], 211 (10), 182 (15), 167 (11), 140 (100), 139 (13), 125 (31), 82 (9).

HRMS (EI) $C_9H_{12}N_2O_4$: calculated [M^+]: 212.0797 found: 212.0794

Synthesis of 4,5-diiodo-2,6-dimethoxypyrimidine (8a):



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**1**, 11.0 mmol, 1.12 M, 9.8 mL, 1.1 equiv) and 2,4-dimethoxypyrimidine (**2**) (10.0 mmol, 1.40 g, 1.0 equiv) dissolved in dry THF (10 mL) was added dropwise at –40 °C. The reaction mixture was stirred for 12 h at this temperature and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. Iodine (11.0 mmol, 2.80 g, 1.2 equiv) was added and the reaction mixture was stirred for 2 h at –30 °C. The mixture was warmed to –30 °C and TMPMgCl·LiCl (**1**, 15.0 mmol, 1.12 M, 13.4 mL, 1.5 equiv) was added dropwise. The mixture was warmed to 0 °C and stirred for 2 h. Iodine (20 mmol, 5.14 g, 2 equiv) was added at 25 °C and the mixture was stirred for 3 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ (60 mL) solution at 0 °C, extracted with EtOAc (3 x 50 ml), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2) afforded **8a** (3.74 g, 87%) as a white solid.

mp.: 144.1-145.4 °C.

IR (ATR): ν (cm^{-1}) = 2996 (m), 2948 (m), 2864 (m), 1516 (vs), 1476 (s), 1450 (s), 1376 (s), 1336 (s), 1292 (s), 1222 (m), 1196 (s), 1102 (m), 1020 (m), 996 (s), 930 (m), 806 (m), 772 (m).

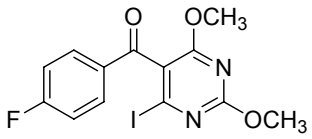
^{1}H-NMR ($CDCl_3$, 300 MHz): δ (ppm) = 3.98 (s, 3 H), 3.96 (s, 3 H).

^{13}C-NMR ($CDCl_3$, 75 MHz): δ (ppm) = 168.9, 163.6, 141.8, 84.1, 55.8, 55.6

MS (EI, 70 eV): *m/z* (%) = 391 (100) [M^+], 390 (23), 361 (16), 249 (20), 192 (10).

HRMS (EI) ($C_6H_6I_2N_2O_2$): calculated [M^+]: 391.8519 found: 391.8498

Synthesis of (4-fluorophenyl)(4-iodo-2,6-dimethoxypyrimidin-5-yl)methanone (8b):



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**1**, 1.1 mmol, 1.16 M, 0.96 mL, 1.1 equiv) and 4-iodo-2,6-dimethoxypyrimidine (**7a**) (1.0 mmol, 266 mg, 1.0 equiv) dissolved in dry THF (1.0 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at this temperature and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. CuCN·2LiCl (1 mL, 1 eq., 1.00 M in THF) was added at –20 °C and stirred for 15 min. Thereafter, 4-fluorobenzoyl chloride (190 mg, 1.2 mmol, 1.2 equiv) was added at –20 °C, and the reaction mixture was warmed to 25 °C for 5 h. The resulting mixture was quenched with sat. aq. NH_4Cl solution, extracted with EtOAc (3 x 10 ml), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, *n*-pentan/diethyl ether, 1:1) afforded **8b** (325 mg, 84%) as a white solid.

mp.: 151.9-157.1 °C

IR (neat): ν (cm^{-1}) = 1669 (m), 1595 (m), 1566 (s), 1525 (s), 1506 (m), 1475 (m), 1455 (m), 1381 (s), 1364 (s), 1312 (s), 1255 (s), 1245 (s), 1225 (s), 1158 (s), 1076 (s), 1015 (s), 920 (s).

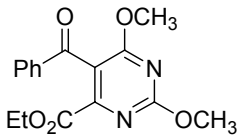
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.83-7.77 (m, 2H), 7.12-7.05 (m, 2H), 3.98 (s, 3H), 3.83 (s, 3H) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 191.4, 168.1, 167.2, 164.7, 163.5, 132.5, 132.1, 126.6, 120.1, 116.3, 116.1, 55.7, 54.8 ppm.

MS (EI, 70 eV), *m/z* (%): 388 (M^+, 66), 358 (5), 293 (31), 261 (10), 136 (25), 123 (100), 95 (80), 75 (24).

HRMS (EI): calcd. for $C_{13}H_{10}FIN_2O_3$ [M^+]:387.9720 found: 387.9722

Synthesis of ethyl 5-benzoyl-2,6-dimethoxypyrimidine-4-carboxylate (8c)



A dry and argon flushed flask, equipped with a magnetic stirring bar and a septum, was charged with TMPMgCl·LiCl (**1**, 1.1 mmol, 1.16 M, 0.96 mL, 1.1 equiv) and ethyl 2,6-dimethoxypyrimidine-4-carboxylate (**7e**) (1.0 mmol, 212 mg, 1.0 equiv) dissolved in dry THF (1.0 mL) was added dropwise at -40 °C. The reaction mixture was stirred for 2 h at this temperature and the completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with iodine using decane as internal standard. CuCN·2LiCl (1 mL, 1 equiv, 1.00 M in THF) was added at –40 °C and stirred for 1 h. Thereafter, benzoyl chloride (210 mg, 1.5 mmol, 1.5 equiv) was added at –40 °C, and the reaction mixture was warmed to 25 °C for 12 h. The resulting mixture was quenched with sat. aq. NH_4Cl solution, extracted with EtOAc (3 x 10 mL), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, *n*-pentan/diethyl ether, 1:1) afforded **8c** (246 mg, 78%) as a white solid.

mp.: 98.4-100.4 °C

IR (neat): ν (cm^{-1}) = 3067 (w), 2962 (w), 2925 (w), 1727 (s), 1668 (s), 1571 (s), 1556 (s), 1463 (m), 1447 (m), 1380 (s),1254 (s), 1229 (s), 1176 (m), 1082 (s), 1035 (s), 929 (m), 903 (s), 776 (s), 691 (s).

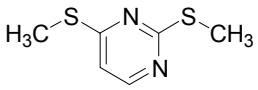
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.80-7.77 (m, 2H), 7.60-7.54 (m, 1H), 7.47-7.41 (m, 2H), 4.21-4.13 (q, 2H, *J* = 7.3 Hz), 4.11 (s, 3H),3.95 (s, 3H), 1.11-1.06 (t, 3H, *J* = 7.1 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 192.0, 169.9, 165.2, 163.3, 155.3, 137.0, 133.6, 128.9, 128.9, 128.7, 128.7, 116.1, 62.6, 55.5, 55.0, 13.5.

MS (EI, 70 eV): *m/z* (%): 316 (M^+, 45), 272 (67), 243 (55), 239 (54), 215 (19), 211 (27), 186 (12), 167 (62), 139 (24), 118 (12), 109 (12), 105 (100), 82 (17), 77 (83), 51 (14).

HRMS (EI): $C_{16}H_{16}N_2O_5$ calculated [M^+]: 316.1059 found: 316.1036

Synthesis of 2,4-bis(methylthio)pyrimdine (4):



A solution of sodium methanethiolate (5.05 g, 72 mmol, 3 equiv) and 2,4-dichloropyrimidine (3.58 g, 24 mmol) in 50 mL THF was heated at 80 °C for 4 h. A sat. aq. NH_4Cl solution (100 mL) was added and the crude was then extracted with ether (3 x 150 ml), dried over Na_2SO_4 and concentrated *in vacuo* to furnish the pure colourless oil **4** in a quantitative yield.

IR (neat): ν (cm^{-1}) = 3087 (w), 3003 (w), 2929 (w), 1523 (s), 1478 (s), 1431 (m), 1407 (m), 1354 (m), 1312 (w), 1288 (w), 1251 (s), 1170 (m), 1098 (m), 977 (w), 964 (w), 832 (w), 816 (w), 769 (s), 750 (w), 603 (w).

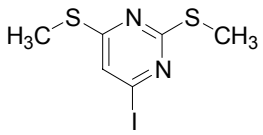
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.07 (d, 1H, *J* = 5.6 Hz), 6.78 (d, 1H, *J* = 5.6 Hz), 2.51 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 171.9, 170.4, 153.9, 113.7, 13.9, 12.2.

MS (EI, 70 eV): *m/z* (%) = 172 (M^+, 100), 157 (43), 139 (44), 125 (31), 111 (50), 47 (13).

HRMS (EI) $C_6H_8N_2S_2$ calculated [M^+]: 172.0129 found: 172.0122

Synthesis of 4-iodo-2,6-bis(methylthio)pyrimidine (10a):



2,4-Bis(methylthio)pyrimidine (**4**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg \cdot 2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -20 °C for 1 h according to the general procedure. Iodine (381 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at –20 °C for 1 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution at –20 °C, followed by the addition of sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:4) afforded **10a** (226 mg, 76%) as a white solid.

mp.: 122.8-123.5 °C

IR (neat): ν (cm^{-1}) = 2998 (w), 2921 (w), 1516 (s), 1505 (s), 1474 (m), 1434 (m), 1406 (s), 1348 (m), 1323 (w), 1283 (w), 1247 (s), 1205 (m), 1164 (m), 1096 (m), 975 (s), 961 (s), 821 (m), 754 (s), 748 (s).

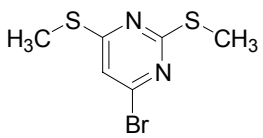
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.25 (s, 1H), 2.51 (s, 3H), 2.50 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 171.9, 170.5, 126.2, 123.5, 14.3, 12.5.

MS (EI, 70 eV): *m/z* (%) = 298 (M^+, 100), 283 (14), 265 (26), 98 (50), 83 (15).

HRMS (EI) $C_6H_7IN_2S_2$ calculated [M^+]: 297.9095 found: 297.9072

Synthesis of 4-bromo-2,6-bis(methylthio)pyrimidine (10b):



2,4-Bis(methylthio)pyrimidine (**4**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg·2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -20 °C for 1 h according to the general procedure. $(BrCCl_2)_2$ (488 mg, 1.5 mmol, 1.5 equiv) dissolved in THF (2 mL) was then added to the resulting mixture at –20 °C for 1 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution at –20 °C and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:3) afforded **10b** (203 mg, 81%) as a white solid.

mp.: 93.0-94.8 °C

IR (neat): ν (cm^{-1}) = 3087 (w), 2997 (w), 2923 (w), 1520 (s), 1481 (s), 1430 (m), 1404 (w), 1357 (m), 1325 (w), 1291 (w), 1254 (s), 1170 (m), 1098 (s), 974 (w), 959 (s), 832 (m), 816 (w), 774 (s), 748 (m).

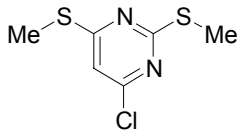
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.00 (s, 1H), 2.53 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.5, 171.6, 149.9, 116.4, 14.3, 12.6.

MS (EI, 70 eV): *m/z* (%) = 250 (100) [^{79}Br-M^+], 235 (36), 217 (83), 149 (35), 98 (69).

HRMS (EI) $C_6H_7BrN_2S_2$ calculated [M^+]: 249.9234 found: 249.9230

Synthesis of 4-chloro-2,6-bis(methylthio)pyrimidine (10c):



2,4-Bis(methylthio)pyrimidine (**4**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg·2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -20 °C for 1 h according to the general procedure. ClF_2CCFCl_2 (281 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at –35 to -20 °C for 3 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution at –20 °C and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash

chromatography (SiO_2, CH_2Cl_2/pentane = 1:4) afforded **10c** (161 mg, 78%) as a white solid.

mp.: 85.0-86.7 °C

IR (neat): ν (cm^{-1}) = 3093 (w), 2998 (w), 2925 (w), 1530 (s), 1491 (s), 1433 (m), 1410 (w), 1360 (m), 1324 (w), 1312 (w), 1259 (s), 1175 (m), 1097 (s), 966 (w), 809 (s), 748 (m).

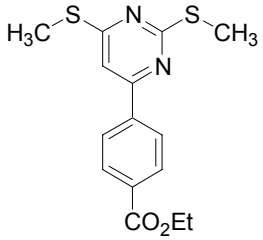
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 6.83 (s, 1H), 2.54 (s, 6H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.7, 172.1, 158.7, 112.5, 14.2, 12.7.

MS (EI, 70 eV): *m/z* (%) = 206 (M^+, 100), 191 (21), 173 (40), 145 (21).

HRMS (EI) $C_6H_7ClN_2S_2$ calculated [M^+]: 205.9739 found: 205.9721

Synthesis of 4-(2,6-bis(methylthio)pyrimidin-4-yl)-benzoic acid ethyl ester (10d):



2,4-Bis(methylthio)pyrimidine (**4**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg·2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -20 °C for 1 h according to the general procedure. Transmetalation with $ZnCl_2$ (1.2 mL, 1.2 equiv, 1.00 M in THF) was then performed at -60 to 25 °C for 3 h. In another flame-dried round bottom flask, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were dissolved in dry THF (2 mL) and stirred for 5 min followed by the addition of ethyl iodobenzoate (331 mg, 1.2 mmol, 1.2 equiv). The resulting solution was then transferred to the zinc reagent flask and refluxed for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:4) afforded **10d** (227 mg, 71%) as a white solid.

mp.: 108.7-110.2 °C

IR (neat): ν (cm^{-1}) = 2981 (m), 2920 (w), 1709 (s), 1575 (w), 1544 (s), 1505 (s), 1491 (s), 1471 (m), 1427 (w), 1407 (w), 1363 (w), 1307 (m), 1268 (s), 1248 (s), 1148 (w), 1120 (w), 1100 (s), 1078 (w), 1013 (w), 969 (w), 868 (w), 837 (s), 815 (m), 779 (s), 756 (s), 700 (s).

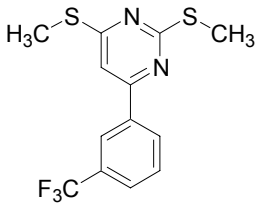
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.09 (d, 2H, *J* = 8.7 Hz), 8.05 (d, 2H, *J* = 8.7 Hz), 7.22 (s, 1H), 4.38 (q, 2H, *J* = 7.2 Hz), 2.61 (s, 3H), 2.58 (s, 3H), 1.39 (t, 3H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.1, 171.1, 166.0, 160.1, 140.3, 132.2, 129.8, 127.0, 109.7, 61.1, 14.3, 14.1, 12.4.

MS (EI, 70 eV): *m/z* (%) = 320 (M^+, 100), 305 (21), 287 (28), 275 (13), 213 (11).

HRMS (EI) $C_{15}H_{16}N_2O_2S_2$ calculated [M^+]: 320.0653 found: 320.0642

Synthesis of 2,4-bis(methylthio-6-(3-trifluoromethyl-phenyl))pyrimidine (10e):



2,4-Bis(methylthio)pyrimidine (**4**) (172 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg·2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -20 °C for 1 h according to the general procedure. Transmetalation with $ZnCl_2$ (1.2 mL, 1.2 equiv, 1.00 M in THF) was then performed at -60 to 25 °C for 3 h. In another flame-dried round bottom flask, $Pd(dba)_2$ (17 mg, 3 mol%) and P(*o*-furyl)$_3$ (14 mg, 6 mol%) were dissolved in dry THF (2 mL) and stirred for 5 min followed by the addition of 3-iodobenzotrifluoride (327 mg, 1.2 mmol, 1.2 equiv). The resulting solution was then transferred to the zinc reagent flask and refluxed for 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and

concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:5) afforded **10e** (251 mg, 80%) as a white solid.

mp.: 85.9-87.1 °C

IR (neat): ν (cm^{-1}) = 2929 (w), 1559 (s), 1516 (s), 1492 (m), 1437 (m), 1336 (s), 1313 (m), 1291 (s), 1252 (s), 1197 (s), 1180 (s), 1142 (s), 1113 (s), 1090 (s), 1074 (s), 964 (m), 926 (m), 919 (w), 876 (w), 836 (m), 802 (s), 761 (w), 690 (s), 670 (s).

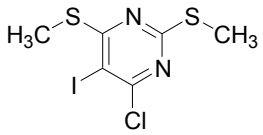
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 8.27 (s, 1H), 8.17 (d, 1H, *J* = 7.7 Hz), 7.70 (d, 1H, *J* = 7.7 Hz), 7.56 (t, 1H, *J* = 7.7 Hz), 7.20 (s, 1H), 2.62 (s, 3H), 2.58 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 172.2, 171.3, 159.6, 137.1, 131.2 q, *J* = 32.5 Hz), 130.2, 129.2, 127.2 (q, *J* = 3.6 Hz), 123.9 (q, *J* = 272.4 Hz), 123.8 (q, *J* = 3.9 Hz), 109.3, 14.1, 12.4.

MS (EI, 70 eV): *m/z* (%) = 316 (M^+, 100), 301 (18), 283 (27), 269 (13).

HRMS (EI) $C_{13}H_{11}F_3N_2S_2$ calculated [M^+]: 316.0316 found: 316.0305

Synthesis of 4-chloro-5-iodo-2,6-bis(methylthio)pyrimidine (11a):



4-Chloro-2,6-bis(methylthio)pyrimidine (**10c**) (207 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg·2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -5 °C for 45 min according to the general procedure. Iodine (381 mg, 1.5 mmol, 1.5 equiv) was then added to the resulting mixture at –5 °C for 1 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution at –5 °C, followed by the addition of sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:8) afforded **11a** (202 mg, 61%) as a white solid.

mp.: 100.9-102.5 °C

IR (neat): ν (cm^{-1}) = 2919 (m), 1486 (s), 1461 (s), 1405 (m), 1321 (m), 1273 (s), 1257 (s), 1187 (s), 994 (m), 966 (m), 843 (m), 801 (s), 742 (m).

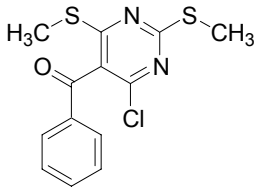
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 2.54 (s, 3H), 2.53 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 175.7, 171.0, 162.0, 86.8, 16.4, 14.5.

MS (EI, 70 eV): *m/z* (%) = 332 (M^+, 100), 205 (38), 159 (10).

HRMS (EI) $C_6H_6ClIN_2S_2$ calculated [M^+]: 331.8706 found: 331.8709

Synthesis of (4-chloro-2,6-bis(methylthio)pyrimidin-5-yl)-phenyl-methanone (11b):



4-Chloro-2,6-bis(methylthio)pyrimidine (**10c**) (207 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg·2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -5 °C for 45 min according to the general procedure. Transmetalation with CuCN·2LiCl (1.0 mL, 1.0 equiv, 1.00 M in THF) was then performed at –20 °C for 30 min. Benzoyl chloride (282 mg, 2.0 mmol, 2.0 equiv) was added to the resulting mixture at –30 °C to 25 °C for 12 h. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2/pentane = 1:3) afforded **11b** (201 mg, 65%) as a white solid.

mp.: 108.0-109.6 °C

IR (neat): ν (cm^{-1}) = 3061 (w), 3003 (w), 2929 (w), 1665 (s), 1594 (m), 1576 (w), 1533 (s), 1470 (s), 1446 (m), 1417 (m), 1346 (m), 1307 (m), 1278 (s), 1225 (s), 1188 (m), 1172 (m), 1101 (m), 1072 (w), 961 (w), 916 (s), 845 (w), 821 (s), 769 (w), 706 (m), 684 (m).

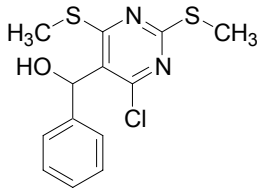
^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.45 – 7.84 (m, 5H), 2.60 (s, 3H), 2.53 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 191.7, 172.5, 169.6, 154.9, 135.3, 134.6, 129.5, 129.0, 123.9, 14.3, 13.2.

MS (EI, 70 eV): *m/z* (%) = 310 (M^+, 100), 295 (24), 277 (63), 241 (14), 233 (38), 219 (57), 105 (77), 77 (87).

HRMS (EI) $C_{13}H_{11}ClN_2OS_2$ calculated [M^+]: 310.0001 found: 310.0002

Synthesis of (4-chloro-2,6-bis-methylsulfanyl-pyrimidin-5-yl)-phenyl-methanol (11c):



4-Chloro-2,6-bis(methylthio)pyrimidine (**10c**) (207 mg, 1.0 mmol) dissolved in THF (2 mL) was added to a solution of $TMP_2Mg·2LiCl$ (**2**) (0.6 M in THF, 1.83 mL, 1.1 mmol) at -5 °C for 45 min according to the general procedure. PhCHO (212 mg, 2.0 mmol, 2.0 equiv) was then added to the resulting mixture at –5 °C for 30 min. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with ether (3 x 50 mL). The combined organic extracts were dried with Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, CH_2Cl_2) afforded **11c** (206 mg, 66%) as a white solid.

mp.: 117.0-119.3 °C

IR (neat): ν (cm^{-1}) = 3303 (bs), 3061 (w), 2997 (w), 2923 (w), 1602 (w), 1525 (s), 1470 (s), 1449 (m), 1415 (m), 1328 (w), 1304 (s), 1259 (s), 1220 (w), 1185 (w), 1117 (m), 1043 (m), 1027 (m), 964 (w), 919 (w), 882 (m), 837 (w), 814 (m), 776 (w), 719 (m), 695 (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ (ppm) = 7.29 – 7.41 (m, 5H), 6.40 (s, 1H), 3.02 (1H, bs), 2.57 (s, 3H), 2.52 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ (ppm) = 171.0, 170.3, 157.7, 139.8, 128.3, 127.6, 125.5, 125.1, 70.4, 14.2, 13.9.

MS (EI, 70 eV): *m/z* (%) = 312 (M^+, 82), 297 (100), 247 (49), 219 (35), 105 (65), 77 (47).

HRMS (EI) $C_{15}H_{16}N_2O_4$ calculated [M^+]: 312.0158 found: 312.0156

References

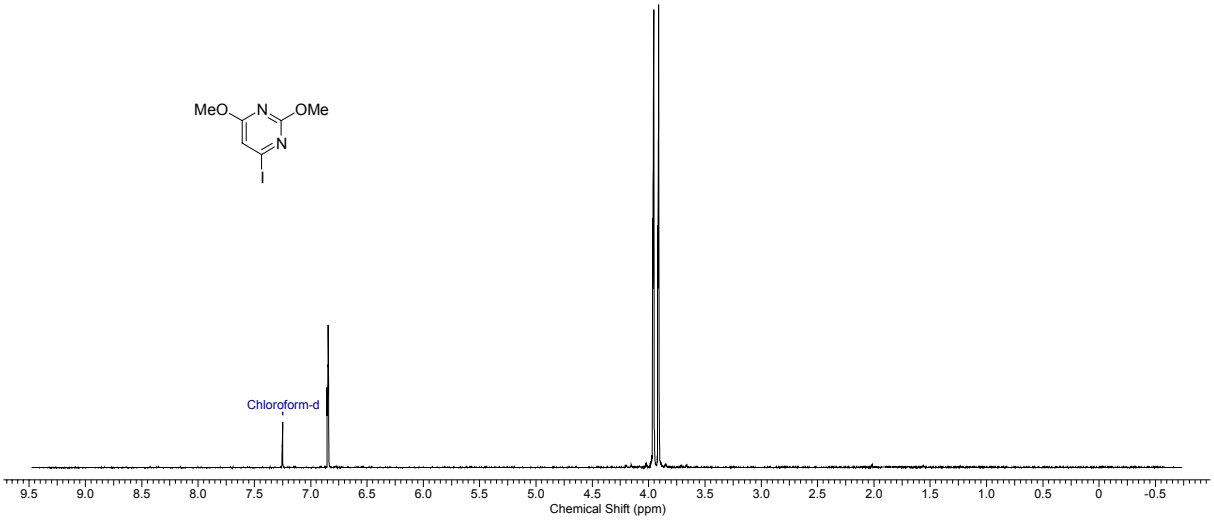
[1] A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.*, 2006, **45**, 2958.

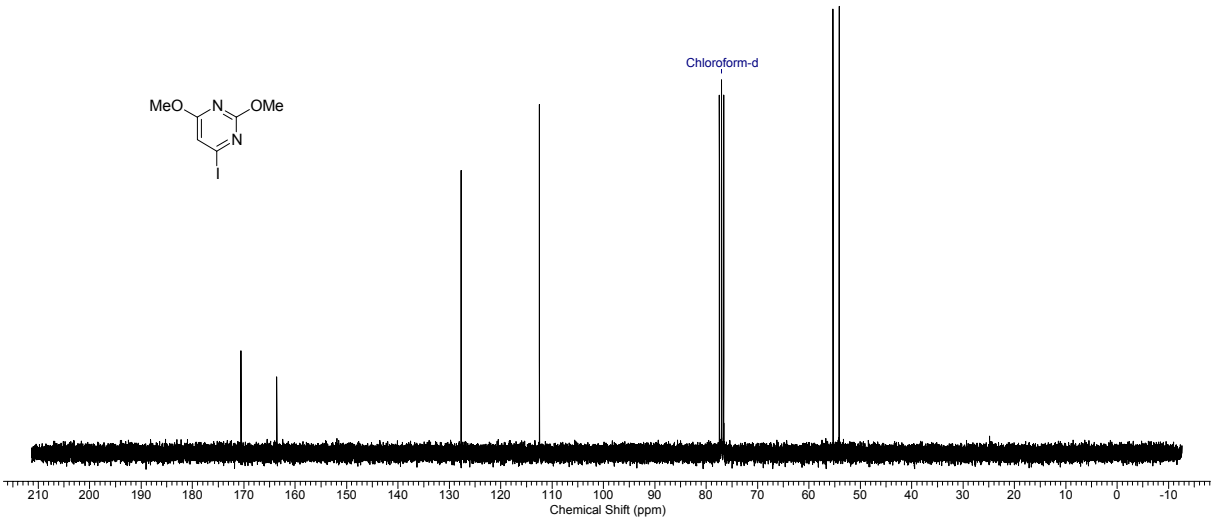
[2] L. P. Hammett, G. H. Walden, S. M. Edmonds, *J. Am. Chem. Soc.* 1934, **56**, 1092.

[3] G.C Clososki, C.J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.*, 2007, **46**, 7681.

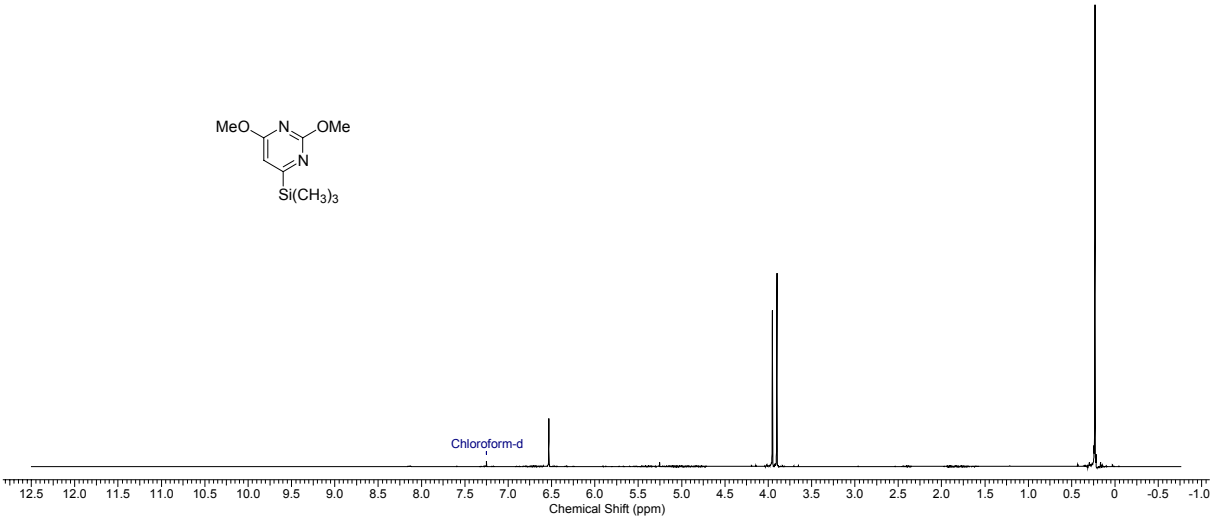
Copies of NMR-spectra:

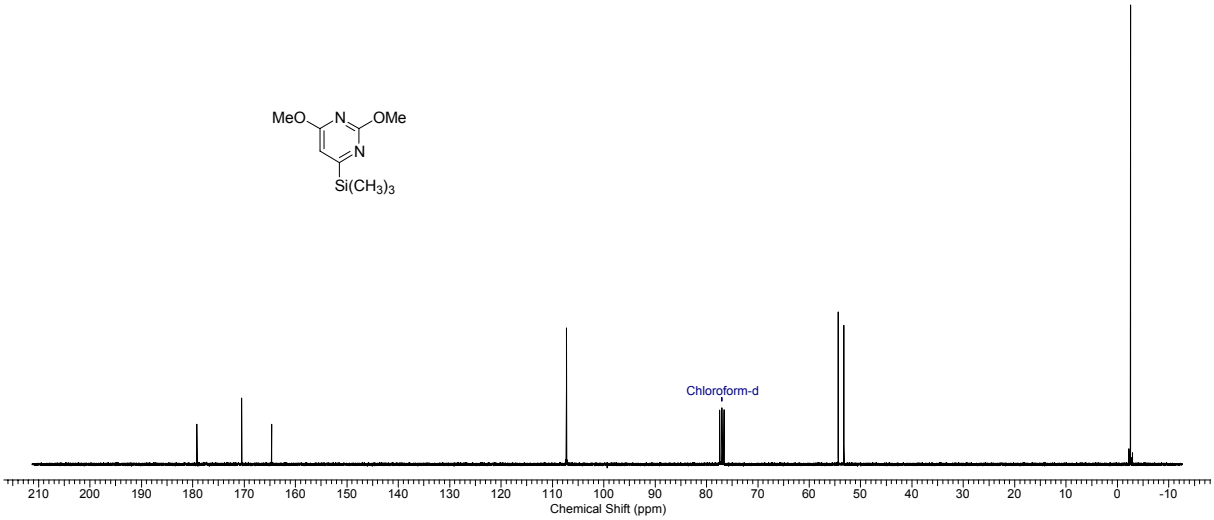
4-Iodo-2,6-dimethoxy-pyrimidine (7a):



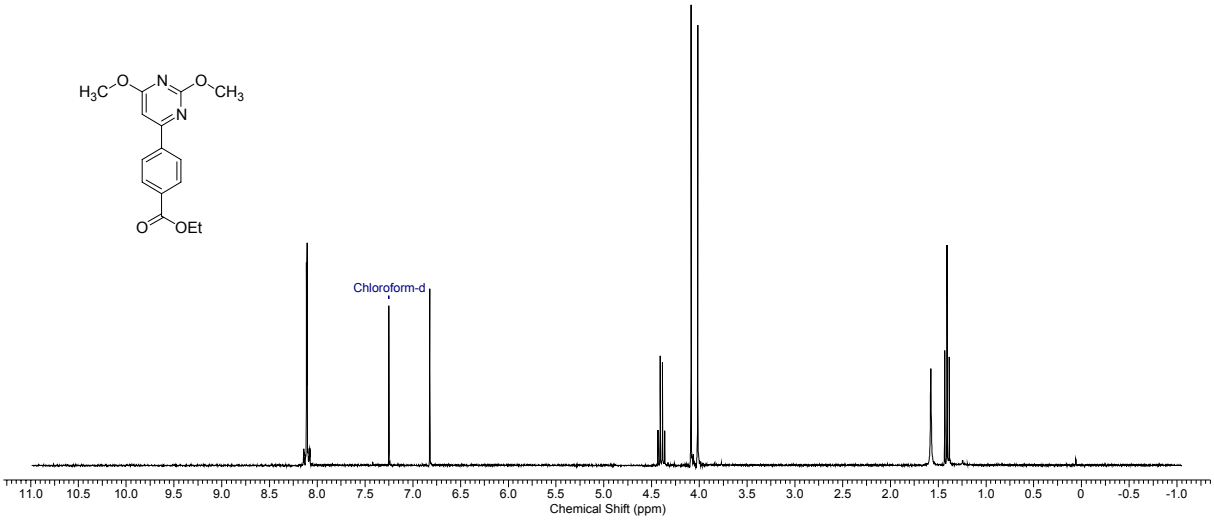


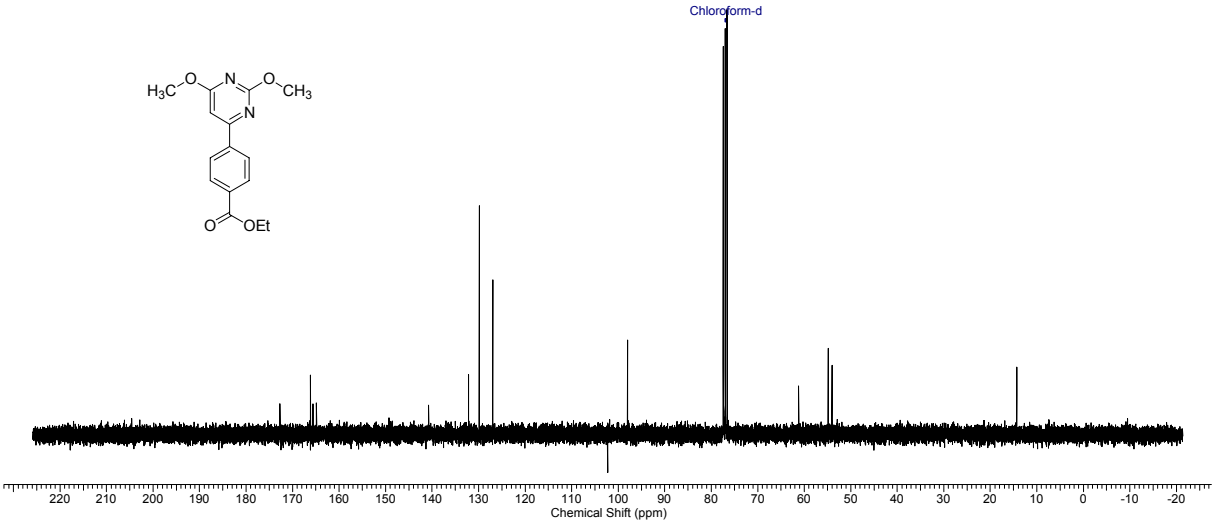
Synthesis of 2,4-dimethoxy-6-(trimethylsilyl)pyrimidine (7b):



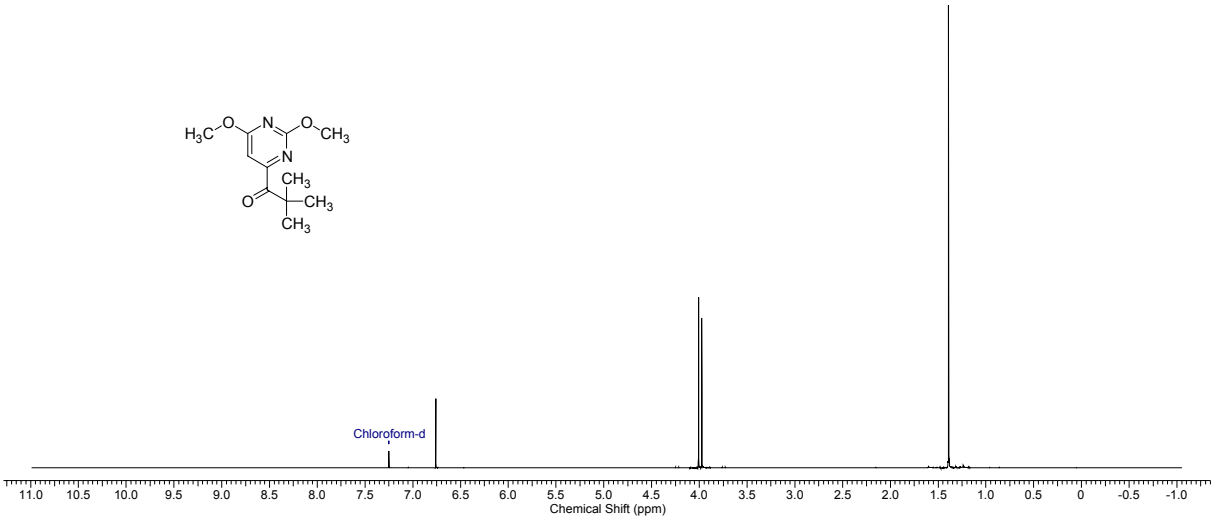


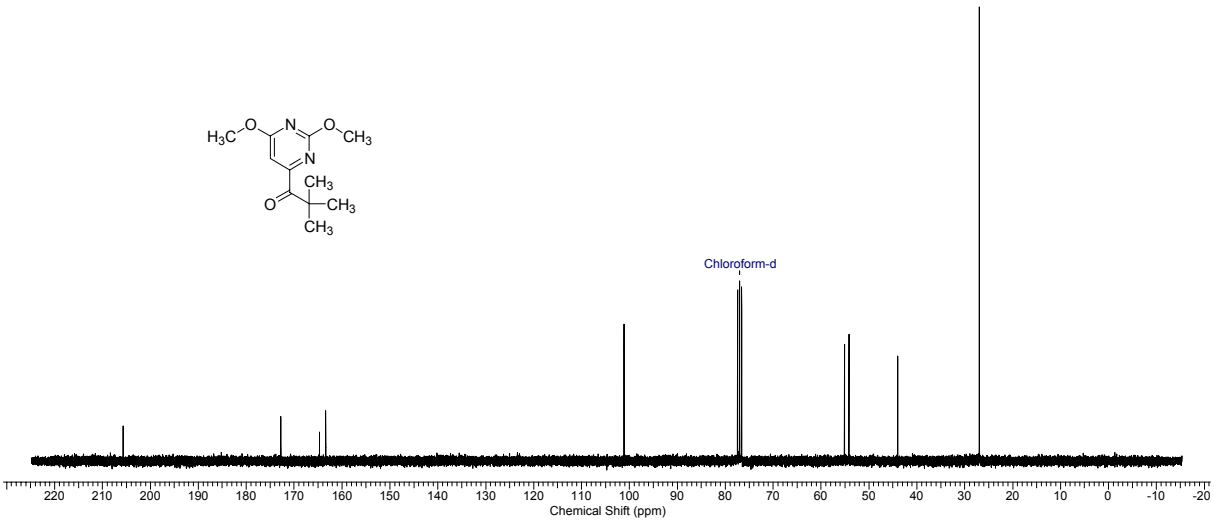
4-(2,6-Dimethoxy-pyrimidin-4-yl)-benzoic acid ethyl ester (7c):



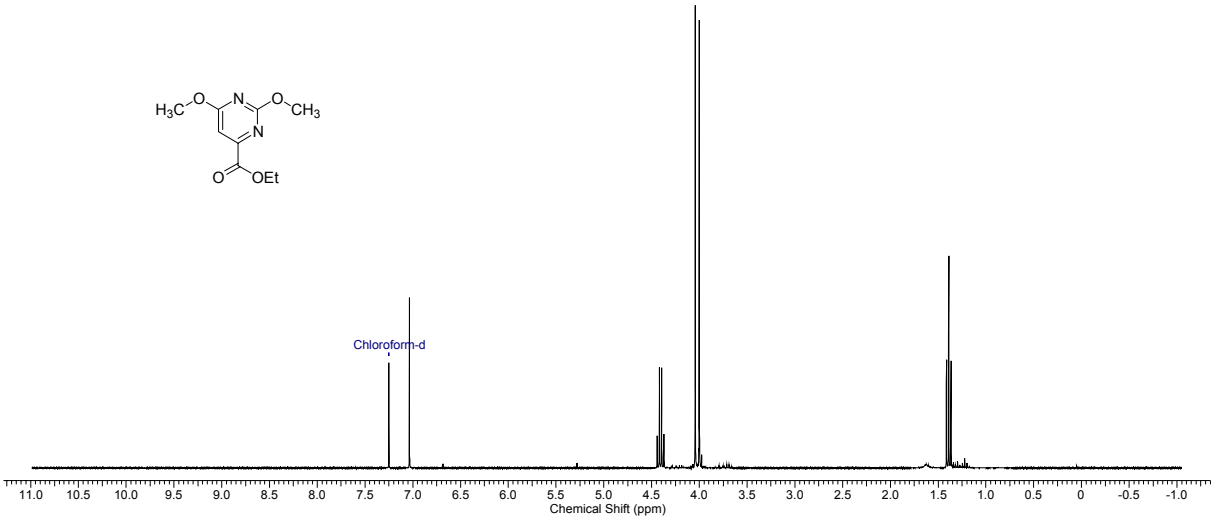


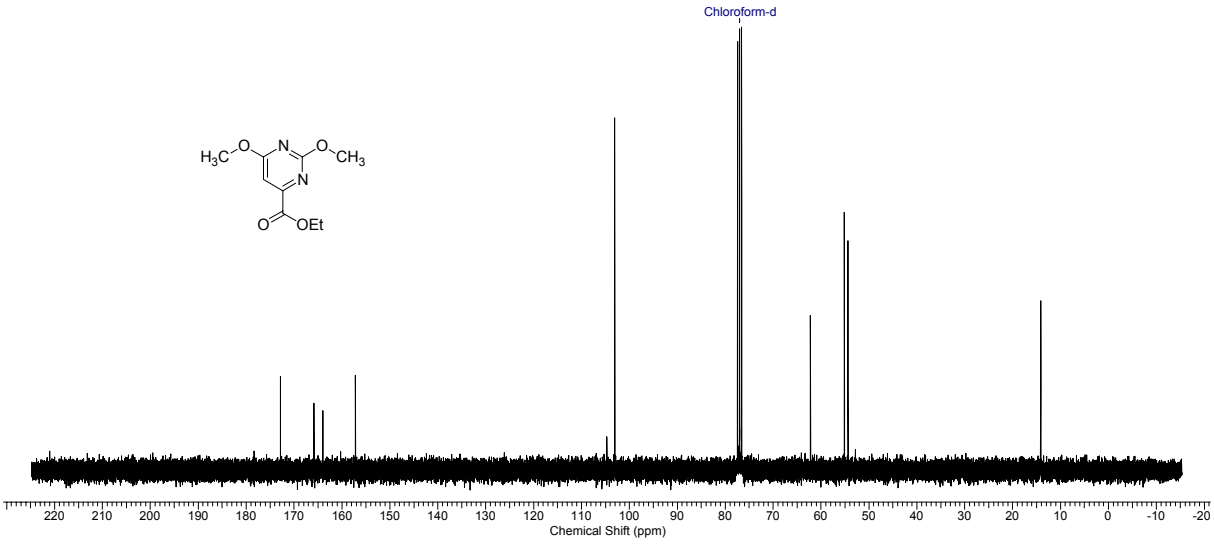
(2,6-Dimethoxy-pyrimidin-4-yl)-2,2-dimethyl-propan-1-one (7d):



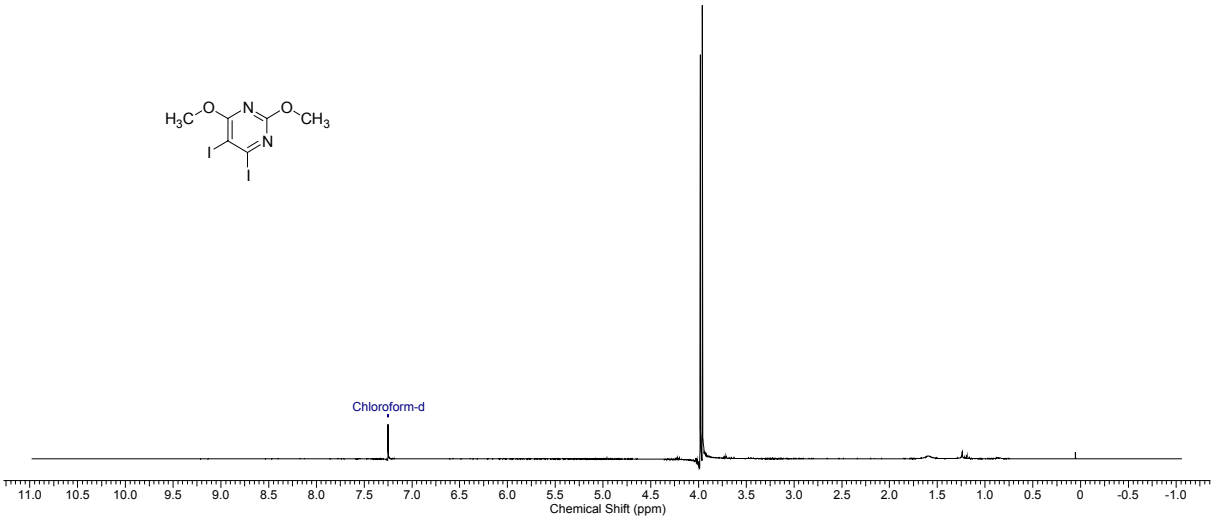


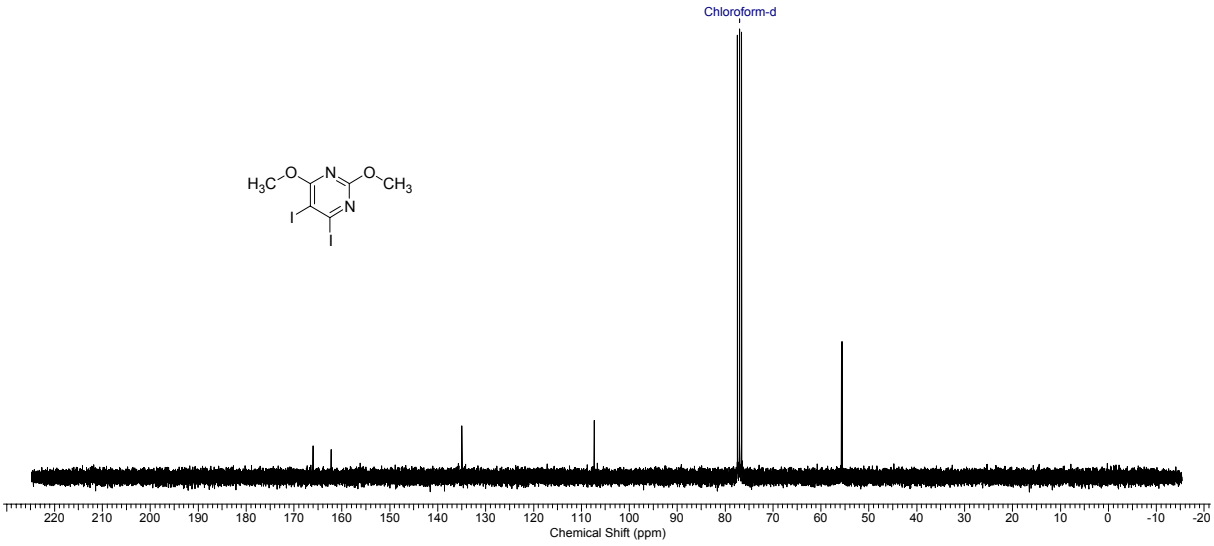
2,6-Dimethoxy-pyrimidine-4-carboxylic acid ethyl ester (7e):



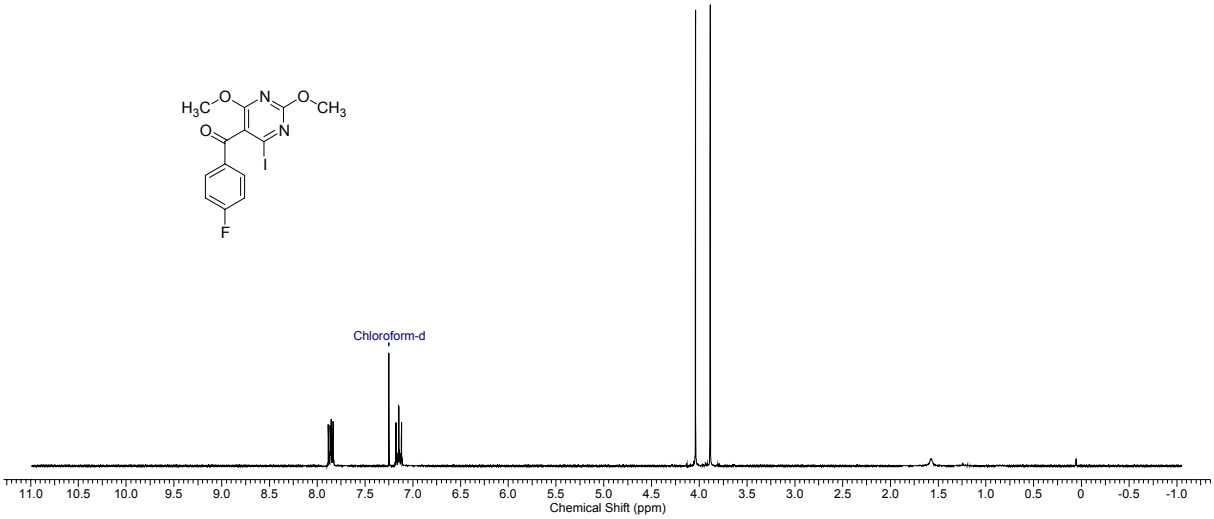


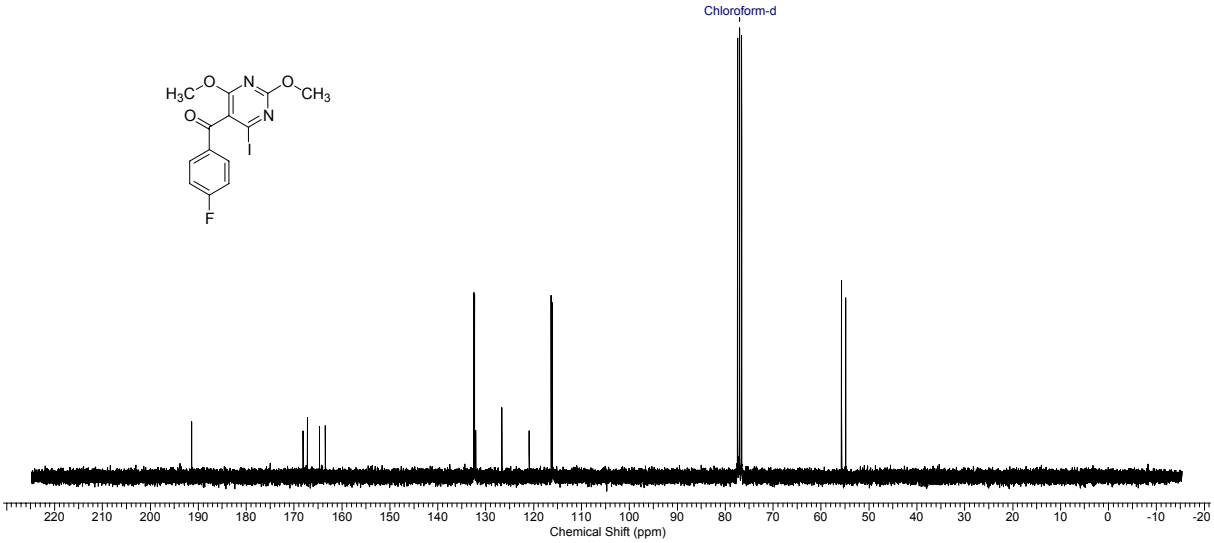
4,5-Diiodo-2,6-dimethoxy-pyrimidine (8a):



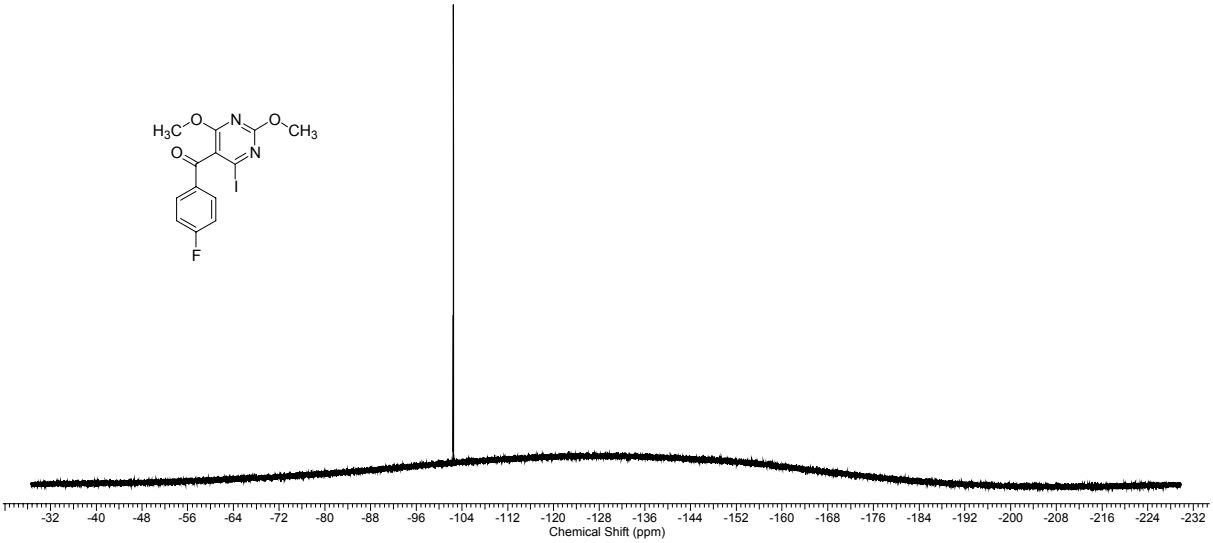


(4-Fluoro-phenyl)-(4-iodo-2,6-dimethoxy-pyrimidin-5-yl)-methanone (8b):

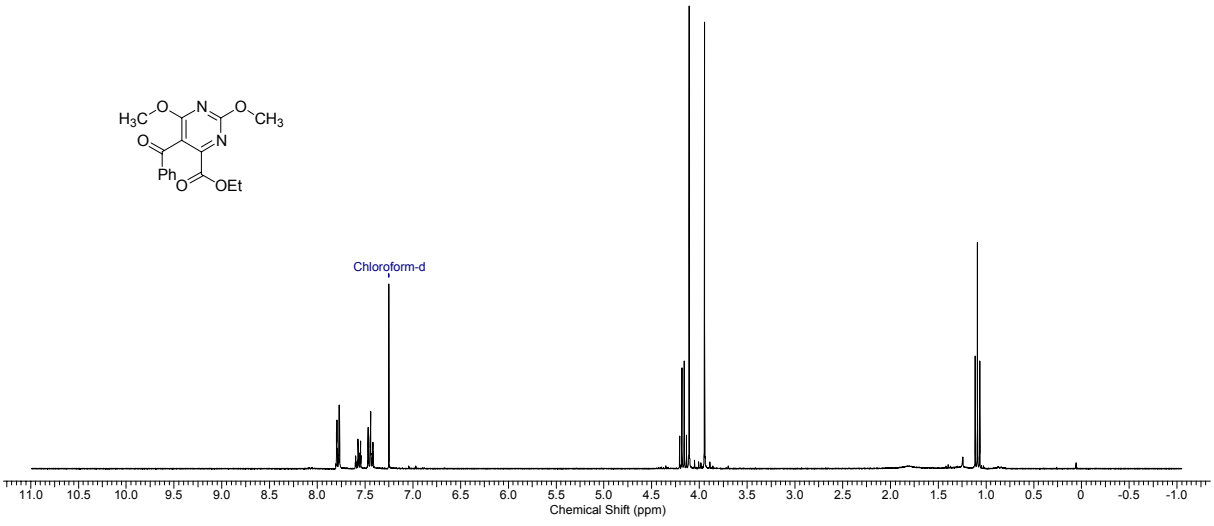


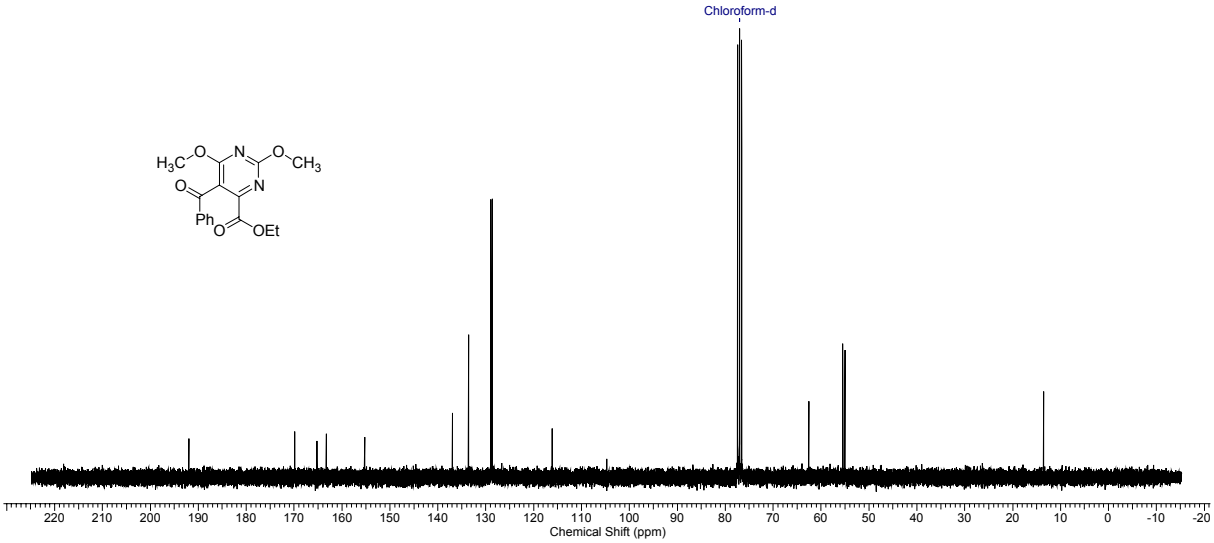


^{19} Fluor-NMR

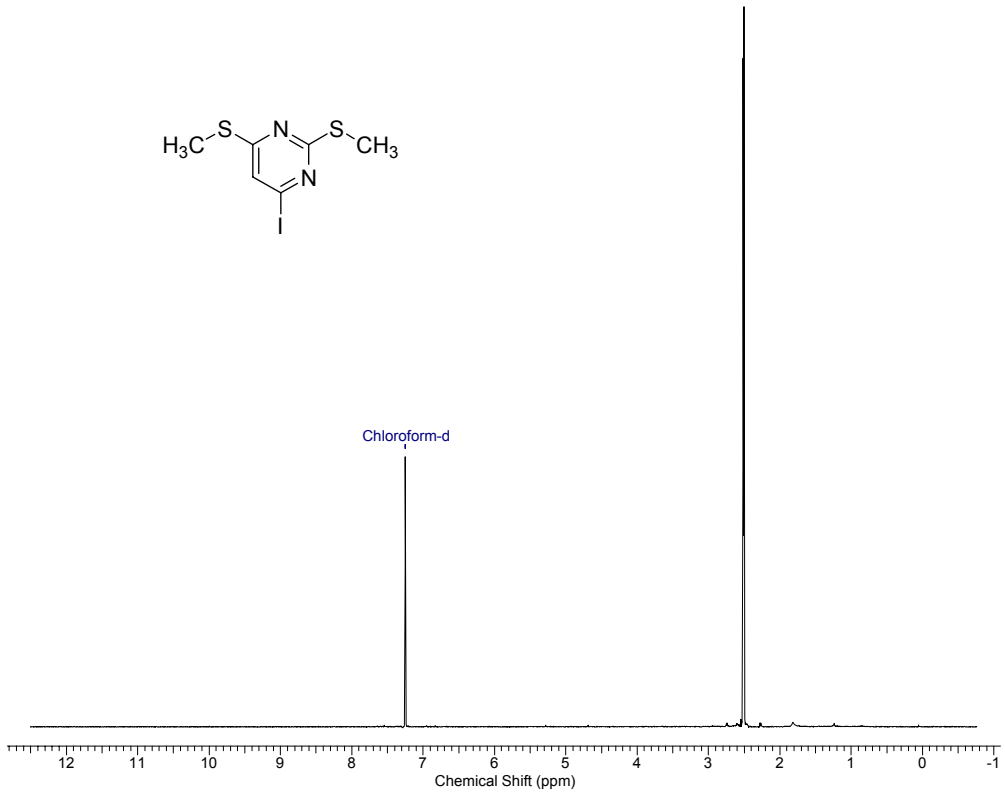


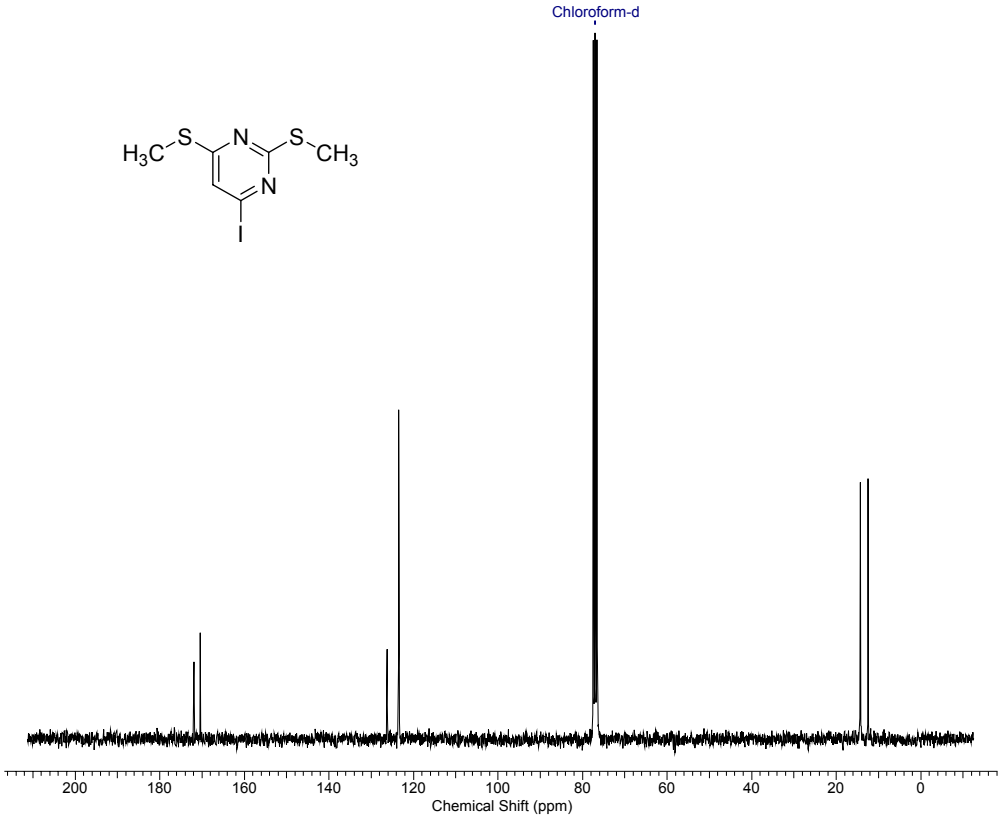
5-Benzoyl-2,6-dimethoxy-pyrimidine-4-carboxylic acid ethyl ester (8c):



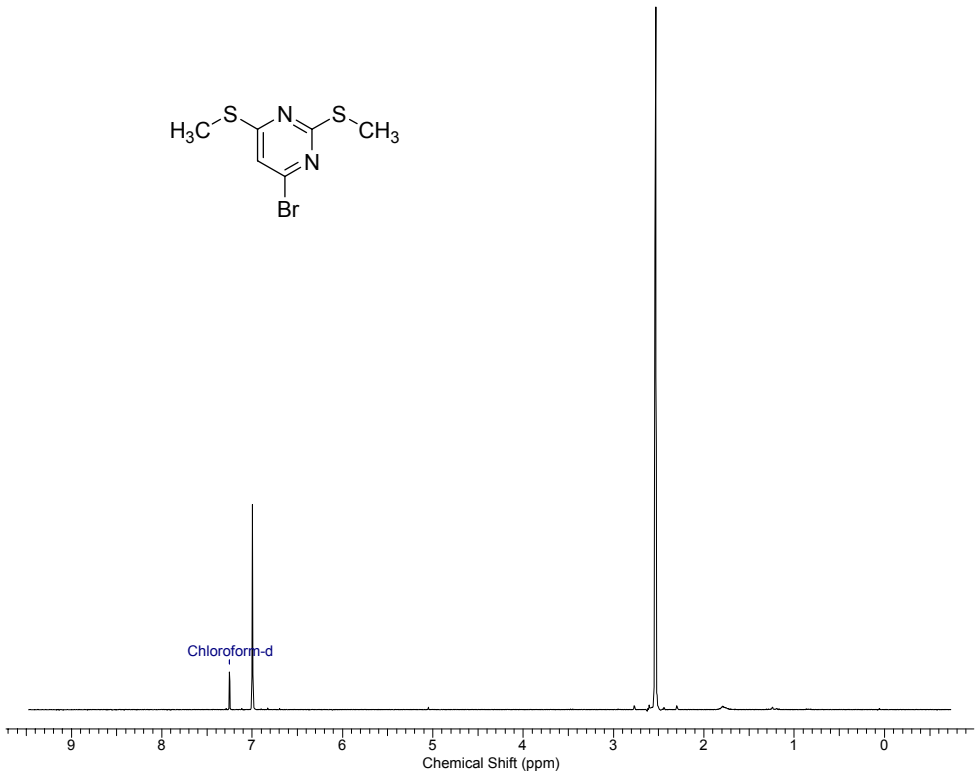


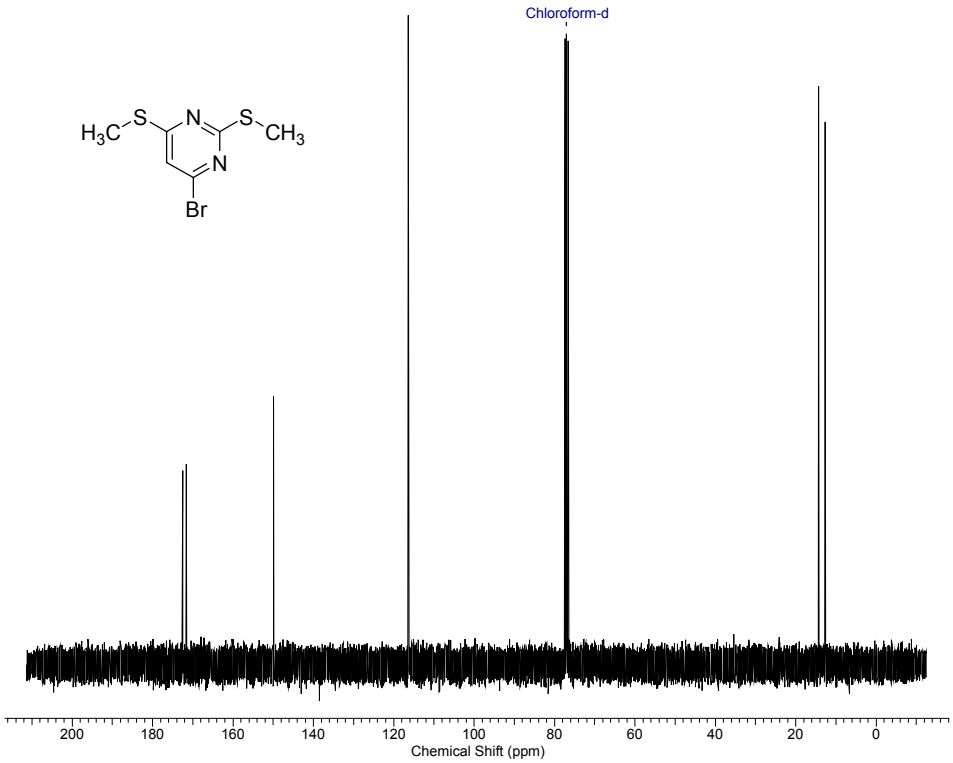
4-Iodo-2,6-bis(methylthio)pyrimidine (10a):



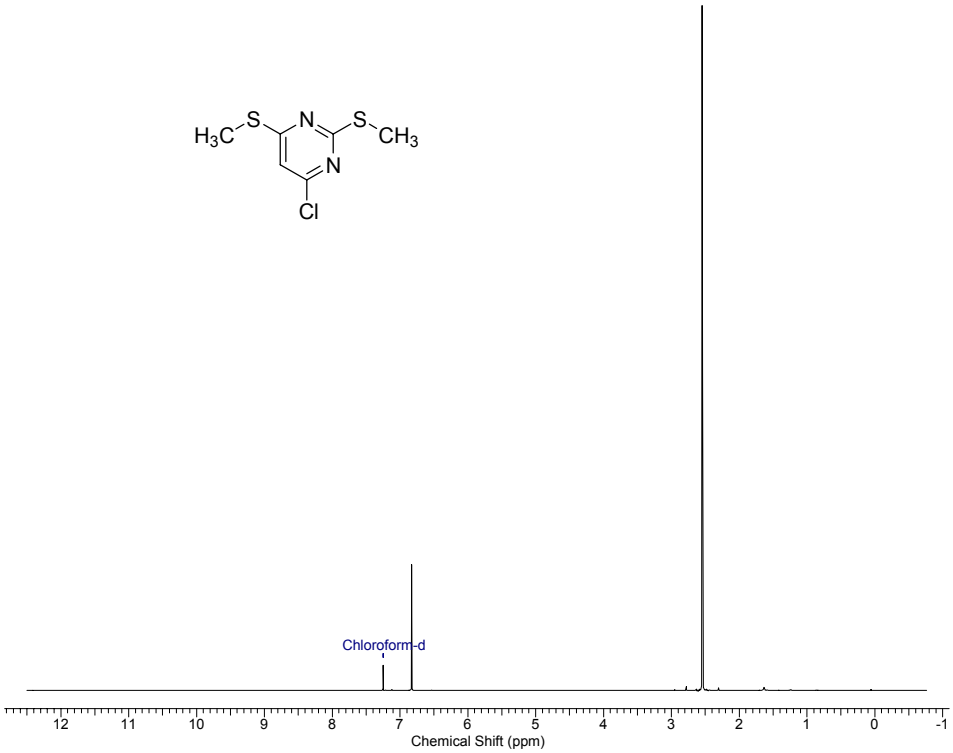


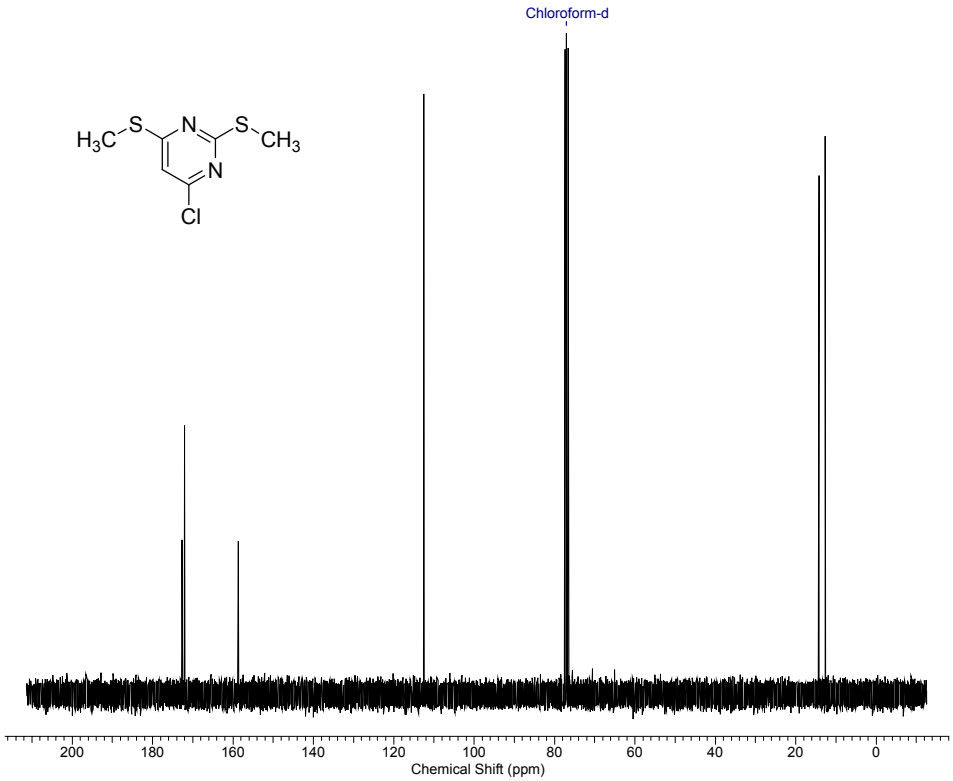
4-Bromo-2,6-bis(methylthio)pyrimidine (10b):



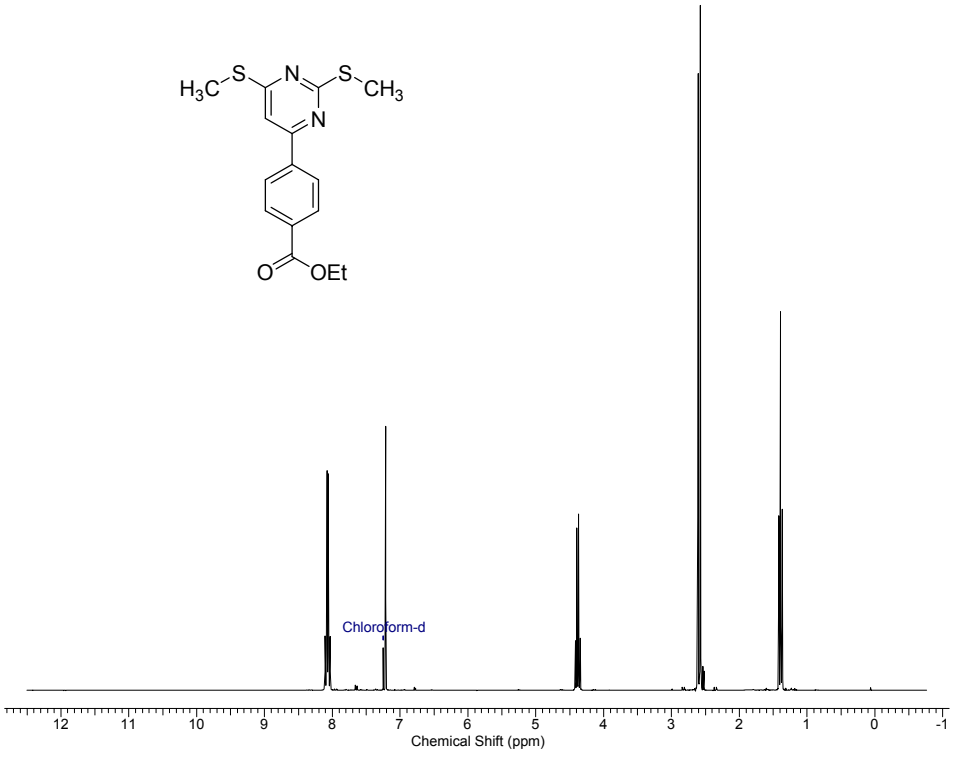


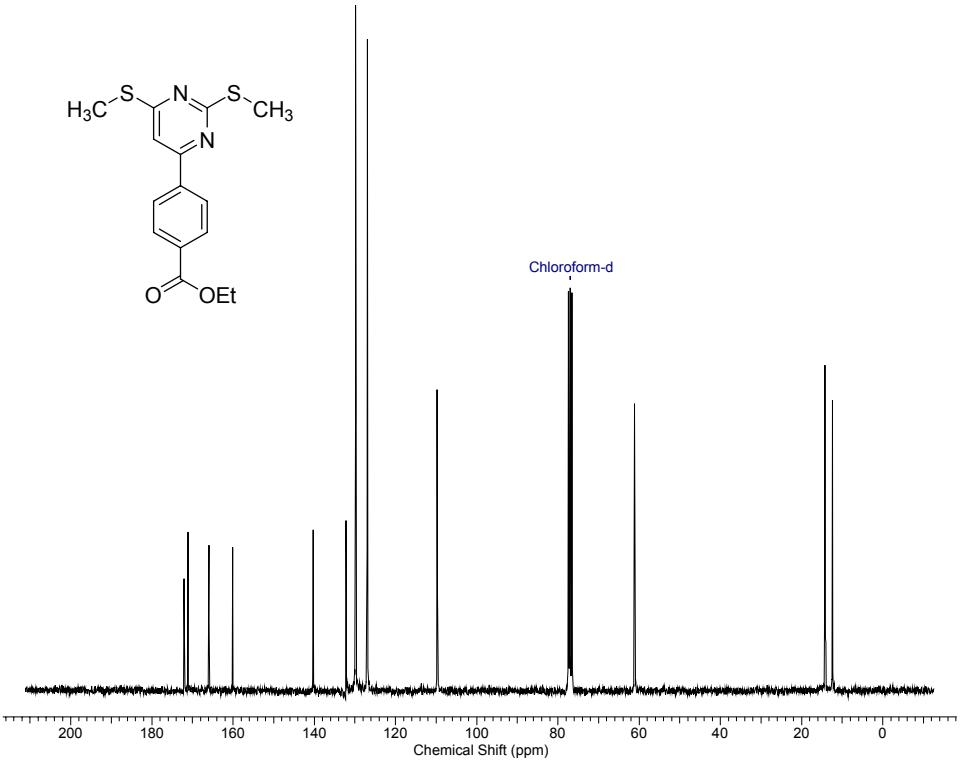
4-Chloro-2,6-bis(methylthio)pyrimidine (10c):



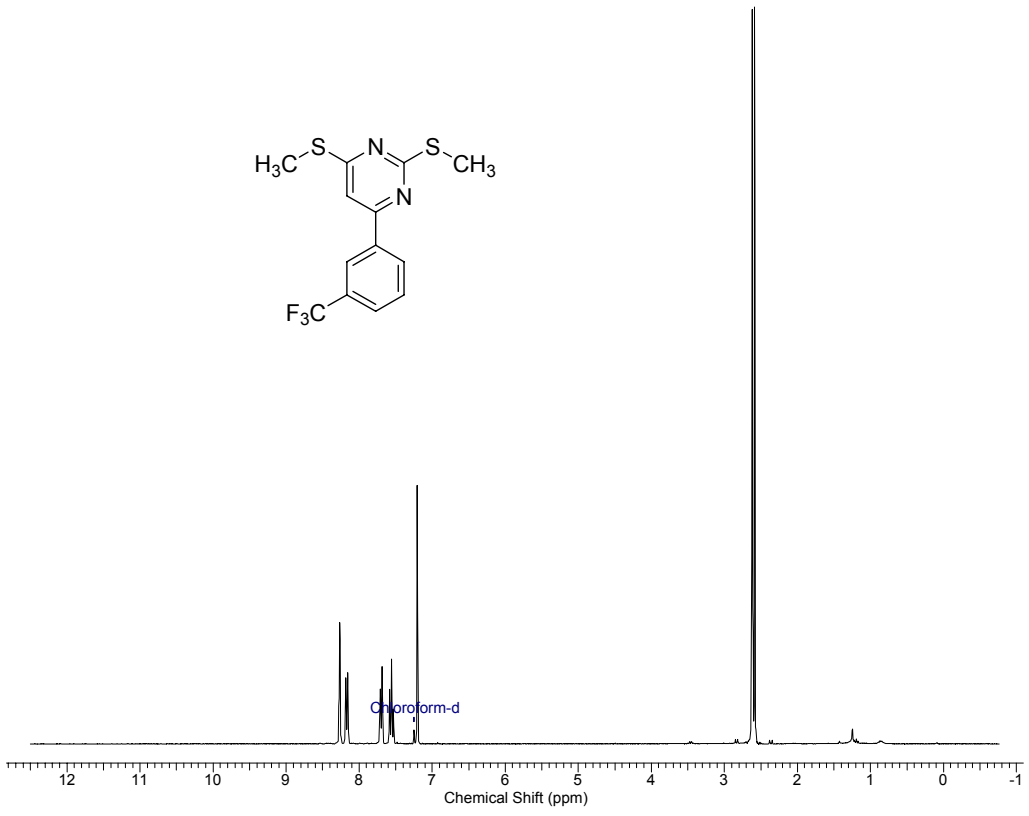


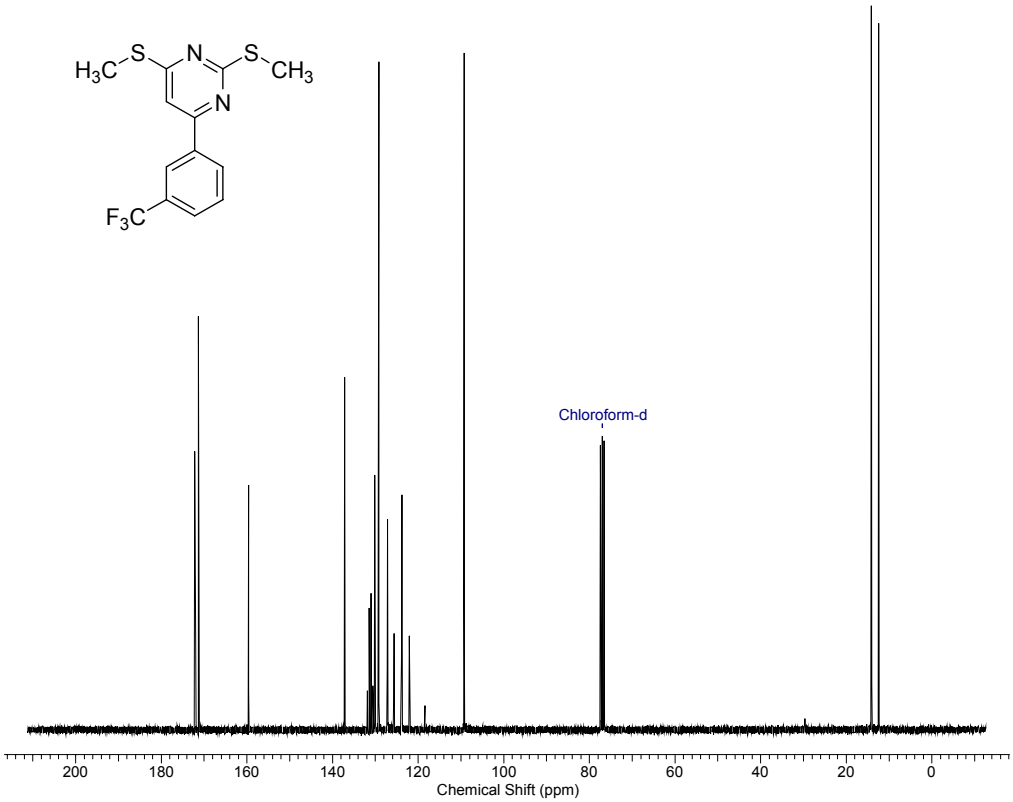
4-(2,6-Bis(methylthio)pyrimidin-4-yl)-benzoic acid ethyl ester (10d):



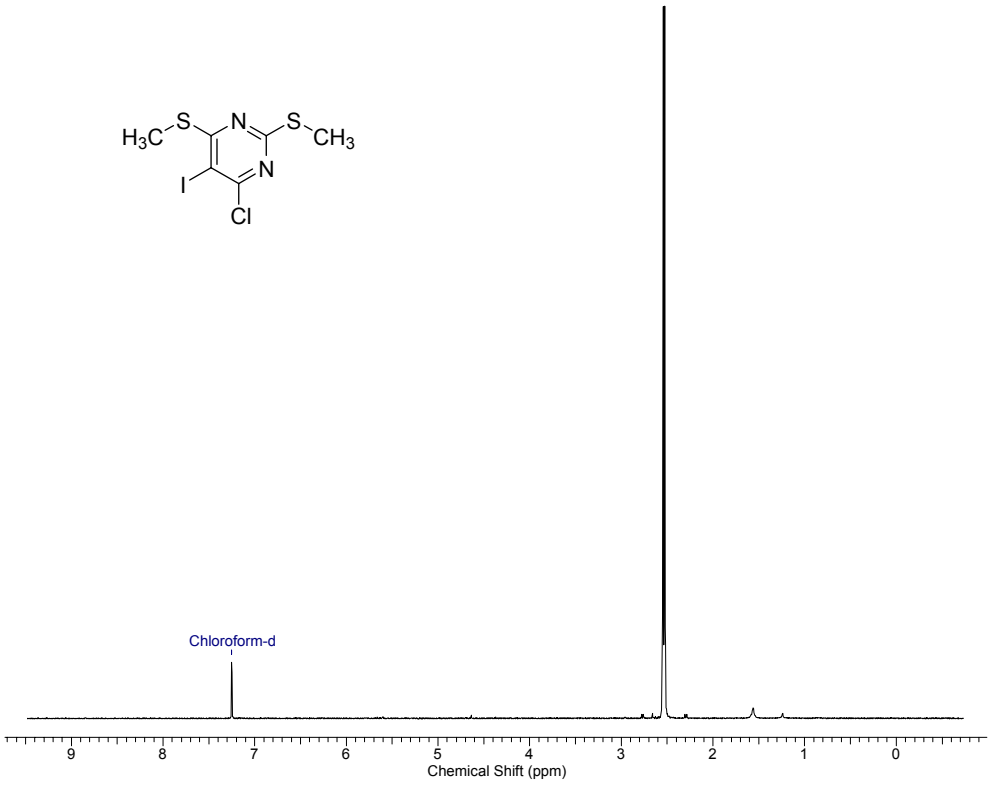


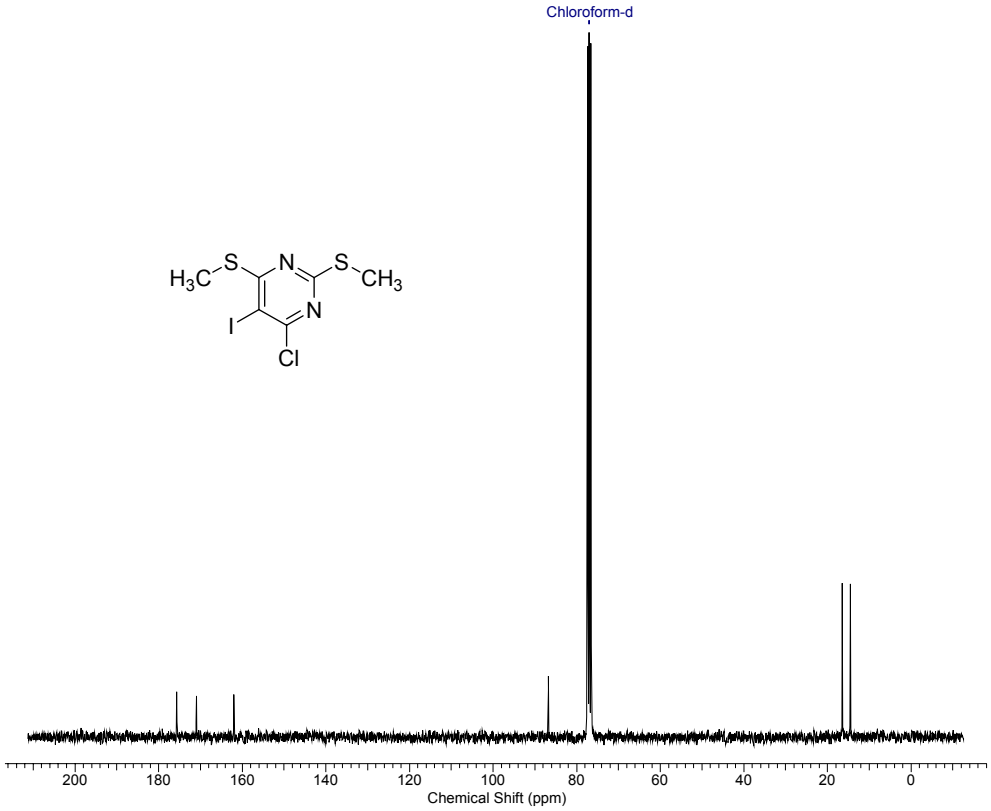
2,4-Bis(methylthio-6-(3-trifluoromethyl-phenyl))pyrimidine (10e):



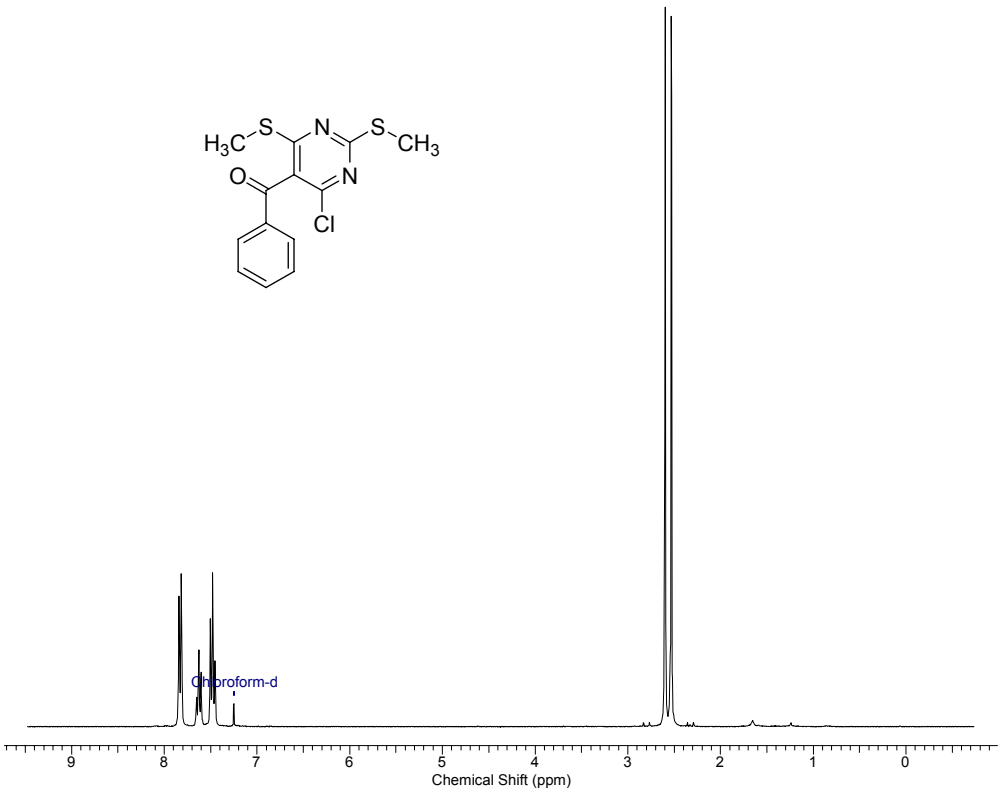


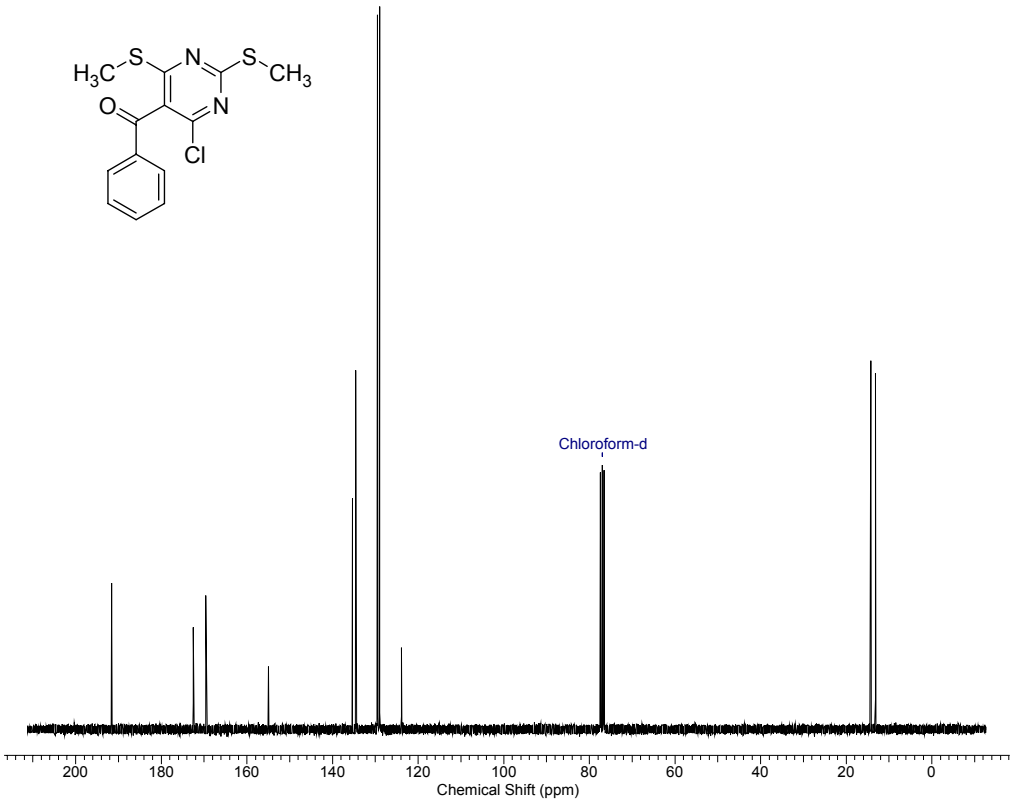
4-Chloro-5-iodo-2,6-bis(methylthio)pyrimidine (11a):



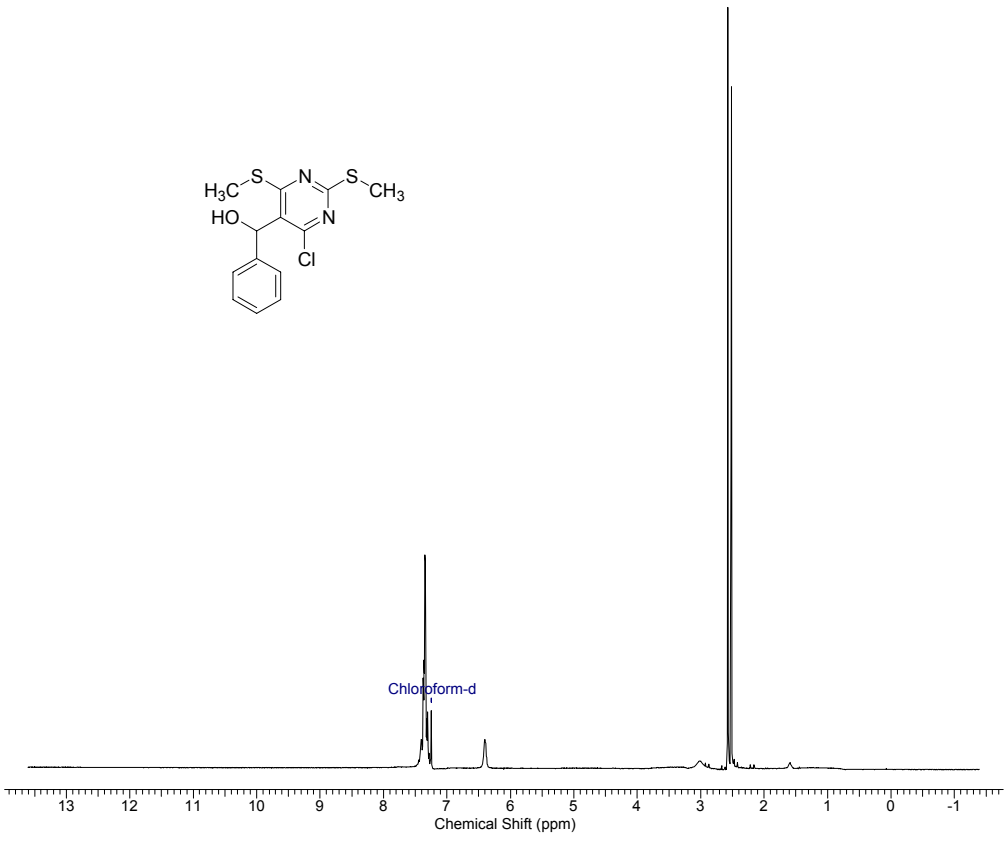


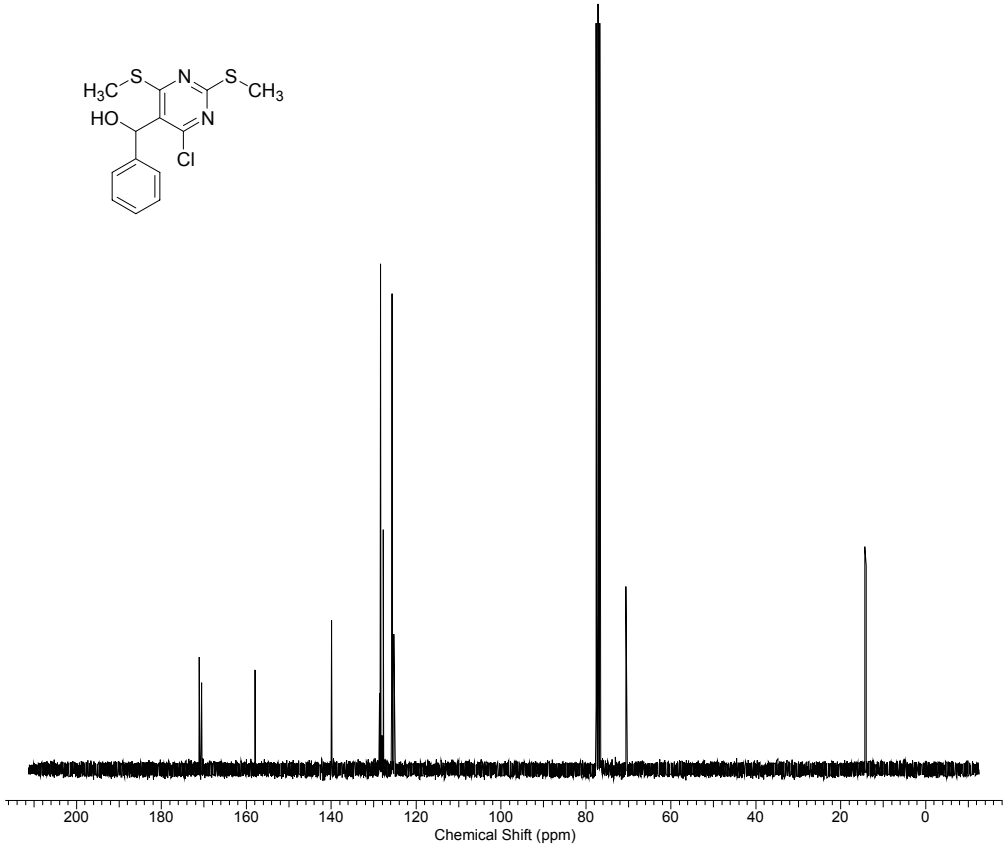
(4-Chloro-2,6-bis(methylthio)pyrimidin-5-yl)-phenyl-methanone (11b):





(4-Chloro-2,6-bis-methylsulfanyl-pyrimidin-5-yl)-phenyl-methanol (11c):




H3C
S
N
S
CH3
HO
N
Cl
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)