Synthesis of Fully Substituted Pyrazoles via Regio- and Chemoselective Metallations

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Supporting Information

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1) General considerations

Unless otherwise indicated, all reactions were carried out with magnetic stirring and in flame-dried glassware under argon. Syringes used to transfer reagents and solvents were purged with argon prior to use. Reactions were monitored by gas chromatography (GC and GC-MS) or thin layer chromatography (TLC). TLC was performed with aluminium plates covered with SiO_2 (Merck 60, F-254) and visualized either by UV detection or submerging in $KMnO_4$ solution (1.5 g $KMnO_4$, 10 g K_2CO_3, and 1.25 mL 10% NaOH solution in 200 mL H_2O). Purification via column chromatography was performed using Merck silica gel 60 (40 – 63 μm 230-400 mesh ASTM from Merck). Melting points were measured using a Büchi B-540 apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ or C_6D_6 and chemical shifts (δ) are reported in parts per million (ppm). Mass spectra and high resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) except where otherwise noted. GCs were recorded on machines of the types *Hewlett-Packard* 6890 or 5890 Series II (*Hewlett Packard*, 5% phenylmethylpolysiloxane; length: 10 m, diameter: 0.25 mm; film thickness: 0.25 μm).

*i*PrMgCl·LiCl solution was obtained from Chemetall (Frankfurt, Germany) as 14% solution (in THF), and titrated with iodine prior to use. A CuCN·2LiCl (1 M) solution was prepared by heating 1 equiv CuCN and 2 equiv LiCl under vacuum at 130 °C for 6 h. THF was added slowly and the solution was stirred overnight. Acid chlorides, liquid aldehydes were distilled and stored under argon prior to use. The bases TMPMgCl·LiCl (**1**)[1], $TMP_2Mg·2LiCl$ (**2**)[2], $TMP_2Zn·2MgCl_2·2LiCl$ (**3**)[3] were prepared according to literature procedures.

2) Experimental Procedures and Analytical Data

Typical procedure for the deprotonation reaction at the C5 position of the pyrazole ring (TP1):

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum, was charged with the pyrazole (1.00 mmol) and THF (1.0 mL). TMPMgCl·LiCl (1.00 mL, 1.10 M, 1.10 mmol) was added dropwise at 25 °C and the reaction mixture was stirred for 1 h. The completion of the deprotonation was checked by GC analysis of reaction aliquots quenched with I_2. After complete conversion, the electrophile (1.20 mmol) was added at 0 °C and the mixture was allowed to slowly warm up to 25 °C. The consumption of the organomagnesium reagent was checked by GC-analysis of hydrolyzed reaction aliquots and the reaction mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography furnished the desired products.

Typical procedure for the deprotonation reaction at the C3 position of the pyrazole ring (TP2):

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum, was charged with the pyrazole (1.00 mmol) and THF (1.0 mL). The reaction mixture was cooled to -15 °C and TMPMgCl·LiCl (1.00 mL, 1.10 M, 1.10 mmol) was added dropwise. The reaction mixture was stirred for 10 h. The completion of the deprotonation was checked by GC analysis of reaction aliquots

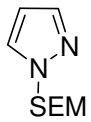
[1] Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958.
[2] Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.
[3] Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.

quenched with I_2. After complete conversion, the electrophile (1.20 mmol) was added at -20 °C and the mixture was allowed to slowly warm up to 25 °C. The consumption of the organomagnesium reagent was checked by GC-analysis of hydrolyzed reaction aliquots and the reaction mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography furnished the desired products.

Typical procedure for the deprotonation reaction at the C4 position of the pyrazole ring (TP3):

A dry and argon flushed flask equipped with a magnetic stirring bar and a septum, was charged with the pyrazole (1.00 mmol) and THF (1.0 mL). The reaction mixture was cooled to -20 °C and $TMP_2Mg{\cdot}2LiCl$ (2.00 mL, 0.56 M, 1.10 mmol) was added dropwise. The reaction mixture was stirred for 4 h at -20 °C. The completion of the deprotonation was checked by GC-analysis of reaction aliquots quenched with I_2. After complete conversion, the electrophile (1.20 mmol) was added at -20 °C and the mixture was allowed to slowly warm up to 25 °C. The consumption of the organomagnesium reagent was checked by GC-analysis of hydrolyzed reaction aliquots and the reaction mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography furnished the desired products.

Synthesis of 1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole[4] (4a):



A dry and argon flushed Schlenk-flask equipped with a magnetic stirring bar and a septum was charged with 1*H*-pyrazole (1.9 g, 28 mmol) dissolved in THF (30 mL). At 25 °C NaH (60% in oil; 720 mg, 31 mmol) was added and the mixture was stirred for 1 h. The reaction mixture was then cooled to 0 °C

[4] Fugina, N.; Holzer, W.; Wasicky, M. *Heterocycles* **1992**, *34*, 303.

followed by addition of (trimethylsilyl)-ethoxymethyl chloride (5.50 mL, 31 mmol). The completion of the reaction was checked by GC-analysis of hydrolyzed reaction aliquots. After 2 h stirring the mixture was quenched with brine and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and the solvent was removed *in vacuo*. The crude residue was purified by distillation (174-180 °C, 100 mbar), furnishing **4a** as a colourless oil (4.6 g, 83 %)

^{1}H-NMR (C_6D_6, 300 MHz): δ = 7.53 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 7.10 (d, $^3J_{H-H}$ = 2.3 Hz, 1 H), 6.07 (t, $^3J_{H-H}$ = 2.0 Hz, 1 H), 5.10 (s, 2 H), 3.52 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), 0.80 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), -0.10 (s, 9 H).

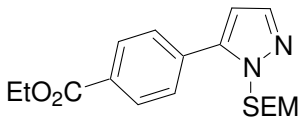
^{13}C-NMR (C_6D_6, 75 MHz): δ = 139.8, 129.1, 106.7, 80.1, 66.6, 17.8, -1.4.

IR (Diamond ATR): 1517 (m), 1391 (m), 1377 (m), 1288 (m), 1248 (s), 1085 (s), 1024 (w), 964 (w), 916 (m), 858 (m), 832 (s), 745 (s), 693 (m), 617 (m).

MS (EI, 70 eV) *m/z*, (%): 198 (M^+, 1), 155 (14), 125 (100), 115 (8), 98 (12), 97 (9), 82 (49), 81 (56), 73 (46), 70 (5), 69 (4), 59 (4), 43 (5).

HRMS (EI): calcd. for $C_9H_{18}N_2OSi$: 198.1188, found: 198.1202.

Synthesis of 4-[2-(2-trimethylsilanyl-ethoxymethyl)-2*H*-pyrazol-3-yl]-benzoic acid ethyl ester (6a):



According to **TP1**, 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**4a**; 198.0 mg, 1.00 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.00 mL, 1.10 м, 1.10 mmol) leading to the organomagnesium reagent **5a** which was transmetallated with $ZnCl_2$ (1.00 mL, 1.00 м, 1.00 mmol). Ethyl 4-iodobenzoate (331.0 mg, 1.20 mmol) dissolved in THF (1.0 mL) and mixed with 2 mol% $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and 4 mol% S-PHOS (16.5 mg, 0.04 mmol) was added at 25 °C to the zinc reagent. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **6a** as colourless oil (315 mg, 91%).

^{1}H-NMR (C_6D_6, 300 MHz): δ = 8.20 (d, $^3J_{H-H}$ = 8.6 Hz, 2 H), 7.65 (d, $^3J_{H-H}$ = 8.6 Hz, 2 H), 7.54 (d, $^3J_{H-H}$ = 1.8 Hz , 1 H), 6.22 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 5.21 (s, 2 H), 4.14 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 3.79 (t, $^3J_{H-H}$ = 8.0 Hz, 2 H), 1.03 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H), 0.87 (t, $^3J_{H-H}$ = 8.0 Hz, 2 H), -0.08 (s, 9 H).

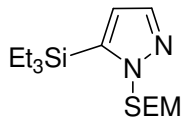
^{13}C-NMR (C_6D_6, 75 MHz): δ = 165.8, 143.3, 139.4, 134.9, 130.9, 130.3, 128.9, 107.6, 78.2, 67.0, 60.9, 18.0, 14.2, -1.4.

IR (Diamond ATR): 2953 (w), 1714 (s), 1614 (m), 1378 (m), 1271 (s), 1185 (m), 1084 (s), 1023 (m), 982 (w), 925 (w), 860 (m), 833 (s), 762 (s), 704 (m), 648 (w).

MS (EI, 70 eV) *m/z*, (%): 346 (M^+, 1), 303 (11), 301 (9), 287 (10), 273 (8), 259 (2), 245 (6), 230 (62), 229 (100), 216 (8), 201 (11), 185 (4), 171 (8), 157 (5), 114 (8), 73 (24).

HRMS (EI): calcd. for $C_{18}H_{26}N_2O_3Si$: 346.1713, found: 346.1702.

Synthesis of 5-Triethylsilanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole (6b):



According to **TP1,** the pyrazole **4a** (1.9 g, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (10 mL, 1.1 м, 11 mmol). After 1 h stirring, triethylsilyl chloride (1.8 mL, 11 mmol) was added to the mixture. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) afforded the desired compound **6b** as a yellow oil (2.64 g, 84%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.51 (d, $^3J_{H\text{-}H}$ = 1.7 Hz, 1 H), 6.45 (d, $^3J_{H\text{-}H}$ = 1.7 Hz, 1 H), 5.46 (s, 2 H), 3.48 (t, $^3J_{H\text{-}H}$ = 8.1 Hz, 2 H), 0.97-0.79 (m, 17 H), -0.05 (s, 9 H).

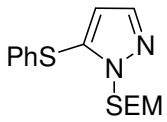
^{13}C NMR ($CDCl_3$, 75 MHz): δ = 140.0, 138.7, 117.2, 80.4, 66.1, 17.8, 7.2, 3.4, -1.5.

IR (Diamond ATR): 2954 (m), 2876 (m), 1458 (w), 1417 (w), 1249 (m), 1111 (s), 1079 (s), 1002 (m), 927 (m), 858 (s), 833 (s), 790 (m), 761 (s), 734 (s), 701 (s).

MS (70 eV, EI): ***m/z* (%)**: 312 (M^+, 1), 269 (13), 255 (14), 198 (13), 196 (23), 168 (41), 167 (12), 140 (15), 139 (16), 73 (100).

HRMS (EI): calcd. for $C_{15}H_{32}N_2OSi_2$: 312.2053, found: 312.2044.

Synthesis of 5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (6c):



According to **TP1,** 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**4a**; 1.98 g, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (10 mL, 1.1 M, 11 mmol). The resulting organomagnesium reagent **5a** was added dropwise at 0 °C to a solution of S-phenyl benzenesulfonothioate (3.0 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) afforded the desired compound **6c** as a yellow oil (2.5 g, 82%).

^{1}H-NMR (C_6D_6, 600 MHz): δ = 7.50 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 7.05 (d, $^3J_{H-H}$ = 8.3 Hz, 2 H), 6.90 (t, $^3J_{H-H}$ = 7.6 Hz, 2 H), 6.83 (t, $^3J_{H-H}$ = 7.3 Hz, 1 H), 6.35 (d, $^3J_{H-H}$ = 1.6 Hz, 1 H), 5.40 (s, 2 H), 3.57 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), 0.75 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), -0.10 (s, 9 H).

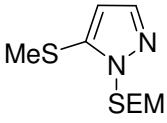
^{13}C-NMR (C_6D_6, 150 MHz): δ = 140.1, 136.4, 131.3, 129.3, 127.7, 126.4, 115.2, 77.9, 66.7, 17.8, -1.4.

IR (Diamond ATR): 1584 (m), 1479 (m), 1441 (w), 1372 (w), 1303 (w), 1285 (w), 1247 (m), 1114 (m), 1078 (s), 1024 (w), 998 (w), 920 (w), 857 (m), 833 (s), 791 (m), 738 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 306 (M^+, 7), 263 (22), 261 (15), 233 (24), 206 (21), 191 (12), 190 (83), 189 (52), 179 (11), 176 (19), 171 (14), 167 (9), 157 (23), 153 (11), 116 (13), 115 (7), 113 (12), 110 (8), 109 (14), 91 (22), 87 (20), 73 (100).

HRMS (EI): calcd. for $C_{15}H_{22}N_2OS$: 306.1222, found: 306.1223.

Synthesis of 5-methylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole (6d):



According to **TP1,** 1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (**4a**; 1.98 g, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (10 mL, 1.1 M, 11 mmol). The resulting organomagnesium reagent **5a** was added dropwise at 0 °C to a solution of methanethiosulfonic acid S-

methyl ester (1.5 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) afforded the desired compound **6d** as a yellow oil (1.76 g, 72%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.48 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 6.12 (d, $^3J_{H-H}$ = 2.0 Hz, 1 H), 5.41 (s, 2 H), 3.64 (t, $^3J_{H-H}$ = 8.0 Hz, 2 H), 1.96 (s, 3 H), 0.83 (t, $^3J_{H-H}$ = 8.0 Hz, 2 H), -0.09 (s, 9 H).

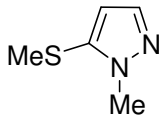
^{13}C-NMR (C_6D_6, 100 MHz): δ = 139.7, 136.9, 110.4, 77.7, 66.6, 18.9, 17.9, -1.4.

IR (Diamond ATR): 1420 (w), 1372 (w), 1287 (w), 1247 (m), 1113 (m), 1078 (s), 997 (w), 973 (w), 920 (w), 857 (s), 832 (s), 751 (s), 693 (m), 664 (w).

MS (EI, 70 eV) *m/z*, (%): 244 (M^+, 3), 201 (50), 199 (27), 186 (16), 172 (13), 171 (100), 153 (48), 144 (29), 128 (86), 127 (47), 116 (10), 114 (9), 73 (21).

HRMS (EI): calcd. for $C_{10}H_{20}N_2OSSi$: 244.1066, found: 244.1073.

Synthesis of 1-methyl-5-(methylthio)-1*H*-pyrazole (7a):



According to **TP1**, *N*-methylpyrazole (**4b**; 820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (10 mL, 1.1 M, 11 mmol). The resulting organomagnesium reagent **5b** was added dropwise at 0 °C to a solution of methanethiosulfonic acid S-methyl ester (1.5 g, 12 mmol) in THF (10 mL). After purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5), the desired compound **7a** was isolated as a yellow oil (1.01 g, 79%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.49 (d, $^3J_{H-H}$ = 1.8 Hz, 1 H), 6.11 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 3.46 (s, 3 H), 1.75 (s, 3 H).

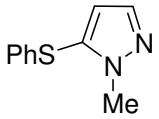
^{13}C-NMR (C_6D_6, 100 MHz): δ = 138.9, 135.3, 109.4, 36.1, 18.4.

IR (Diamond ATR): 1729 (w), 1682 (w), 1625 (w), 1412 (s), 1381 (s), 1319 (w), 1272 (m), 1192 (m), 1110 (w), 1038 (w), 992 (m), 973 (m), 924 (s), 870 (w), 778 (s), 707 (s), 650 (m).

MS (EI, 70 eV) *m/z*, (%): 130 (5), 129 (6), 128 (M^+, 100), 113 (33), 98 (4), 95 (14), 86 (9), 81 (5), 71 (7), 70 (14), 69 (11), 67 (20), 59 (3), 57 (4), 54 (5), 52 (5), 45 (10), 43 (4).

HRMS (EI): calcd. for $C_5H_8N_2S$: 128.0408, found: 128.0397.

Synthesis of 1-methyl-5-(phenylthio)-1*H*-pyrazole (7b):



According to **TP1,** *N*-methylpyrazole (**4b**; 820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (10 mL, 1.1 M, 11 mmol). The resulting organomagnesium reagent **5b** was added dropwise at 0 °C to a solution of S-phenyl benzenesulfonothioate (3.0 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **7b** as a yellow oil (1.58 g, 83%).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.57 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 7.26-7.24 (m, 2 H), 7.18-7.15 (m, 1 H), 7.06-7.04 (m, 2 H), 6.54 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 3.83 (s, 3 H).

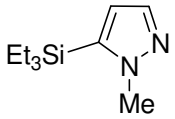
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 138.6, 135.2, 129.3, 127.1, 126.3, 114.0, 36.7.

IR (Diamond ATR): 2970 (m), 1739 (s), 1582 (w), 1478 (m), 1440 (m), 1408 (m), 1380 (m), 1217 (m), 1081 (m), 922 (m), 782 (m), 737 (s), 688 (s), 651 (m).

MS (EI, 70 eV) *m/z*, (%): 190 (M^+, 100), 175 (11), 162 (12), 157 (4), 147 (6), 134 (3), 130 (3), 121 (8), 118 (12), 109 (3), 103 (5), 91 (4), 77 (7), 69 (3), 57 (5), 44 (23).

HRMS (EI): calcd. for $C_{10}H_{10}N_2S$: 190.0565, found: 190.0563.

Synthesis of 1-methyl-5-(triethylsilyl)-1*H*-pyrazole (7c):



According to **TP1,** *N*-methylpyrazole (**4b**; 820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (10 mL, 1.1 M, 11 mmol). The resulting organomagnesium reagent **5b,** was added dropwise at 0 °C to a solution of triethylsilyl chloride (1.8 g, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **7c** as a yellow oil (1.56 g, 80%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.48 (d, $^3J_{H-H}$ = 1.9 Hz, 1 H), 6.37 (d, $^3J_{H-H}$ = 1.7 Hz 1 H), 3.94 (s, 3 H), 0.98-0.92 (m, 9 H), 0.86-0.77 (m, 6 H).

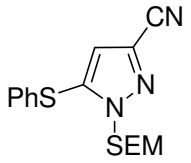
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 139.5, 138.2, 115.7, 39.7, 7.3, 3.5.

IR (Diamond ATR): 2954 (s), 1738 (s), 1370 (s), 1229 (m), 1045 (m), 929 (w), 716 (s).

MS (EI, 70 eV) *m/z*, (%): 219 (5), 196 (M^+, 7), 167 (57), 149 (2), 139 (100), 111 (59), 109 (2), 97 (2), 82 (7), 71 (3), 57 (5), 55 (3), 44 (7).

HRMS (EI): calcd. for $C_{10}H_{20}N_2Si$: 196.1396, found: 196.1383.

Synthesis of 5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carbonitrile (8a):



According to **TP2,** the pyrazole **6c** (306 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 м, 1.1 mmol). TsCN (217 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **8a** as a yellow oil (225 mg, 68%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.30-7.18 (m, 5 H), 6.73 (s, 1 H), 5.49 (s, 2 H), 3.50 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), 0.77 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), -0.08 (s, 9 H).

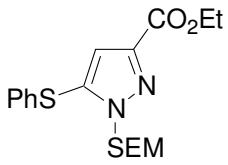
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 136.1, 132.8, 129.61, 129.56, 128.0, 125.5, 117.8, 113.3, 78.7, 67.4, 17.6, -1.5.

IR (Diamond ATR): 2970 (s), 2243 (w), 1739 (s), 1365 (m), 1217 (m), 1073 (m), 1000 (w), 834 (s), 740 (m), 688 (m), 615 (w).

MS (EI, 70 eV) *m/z*, (%): 331 (M^+, 3), 288 (23), 286 (11), 274 (14), 273 (48), 272 (42), 258 (27), 215 (33), 206 (12), 201 (6), 196 (5), 182 (5), 179 (6), 150 (6), 146 (3), 135 (3), 129 (5), 121 (3), 116 (3), 109 (8), 103 (3), 91 (25), 84 (5), 77 (5), 73 (100), 65 (3), 59 (3), 45 (6).

HRMS (EI): calcd. for $C_{16}H_{21}ClN_3OSSi$: 331.1175, found: 331.1160.

Synthesis of ethyl 5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (8b):



According to **TP2,** the pyrazole **6c** (306 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M, 1.1 mmol). $NCCO_2Et$ (120 mg, 1.2 mmol) was added dropwise at -15 °C and the mixture was allowed to slowly warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **8b** as a yellow oil (268 mg, 71%).

^{1}H-NMR ($CDCl_3$, 600 MHz): δ = 7.30-7.17 (m, 5 H), 6.99 (s, 1 H), 5.56 (s, 2 H), 4.40 (q, $^3J_{H-H}$ = 7.2 Hz, 2H), 3.55-3.50 (m, 2 H), 1.38 (t, $^3J_{H-H}$ = 7.2 Hz, 3H), 0.80-0.74 (m, 2 H), -0.07 (s, 9 H).

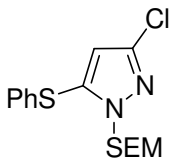
^{13}C-NMR ($CDCl_3$, 150 MHz): δ = 161.8, 143.9, 134.6, 134.1, 129.4, 128.7, 127.2, 116.5, 78.6, 67.0, 61.2, 17.7, 14.3, -1.5.

IR (Diamond ATR): 2970 (s), 1739 (s), 1365 (m), 1204 (s), 1091 (m), 834 (m), 740 (w), 688 (w).

MS (EI, 70 eV) *m/z*, (%): 378 (M^+, 1), 333 (21), 305 (29), 291 (6), 277 (100), 262 (54), 261 (33), 248 (16), 233 (29), 229 (24), 215 (9), 202 (8), 197 (4), 185 (15), 153 (4), 146 (6), 139 (4), 123 (3), 109 (9), 91 (12), 73 (36).

HRMS (EI): calcd. for $C_{18}H_{26}N_2O_3SSi$: 378.1433, found: 378.1426.

Synthesis of 3-chloro-5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (8c):



According to **TP2,** the pyrazole **6c** (306 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M, 1.1 mmol). The resulting organomagnesium reagent was added dropwise at -15 °C to Cl_2FCCF_2Cl (372 mg, 2.0 mmol) dissolved in THF (1.0 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **8c** as a yellow oil (221 mg, 65%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.31-7.19 (m, 5 H), 6.38 (s, 1 H), 5.43 (s, 2 H), 3.53 (t, $^3J_{H-H}$ = 8.2 Hz, 2H), 0.81 (t, J_{H-H} = 8.3 Hz, 2H), -0.05 (s, 9 H).

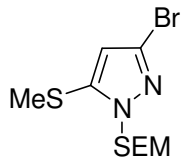
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 140.1, 135.1, 133.9, 129.4, 128.8, 127.3, 112.6, 77.8, 66.9, 17.7, -1.5.

IR (Diamond ATR): 1582 (m), 1468 (m), 1441 (m), 1362 (m), 1275 (w), 1231 (m), 1083 (s), 1022 (m), 957 (s), 740 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 340 (M^+, 2), 297 (33) 295 (16), 282 (20), 267 (19), 224 (67), 223 (43), 205 (23), 189 (15), 147 (38), 141 (11), 134 (10), 121 (12), 111 (14), 109 (15), 99 (14), 97 (19), 93 (14), 91 (26), 85 (47), 83 (26), 77 (12), 73 (100), 71 (57), 69 (23), 57 (70), 55 (24), 44 (52), 43 (40), 41 (17).

HRMS (EI): calcd. for $C_{15}H_{21}ClN_2OSSi$: 340.0832, found: 340.0827.

Synthesis of 3-bromo-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (8d):



According to **TP2**, the pyrazole **6d** (245 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 м, 1.1 mmol). Dibromtetrachlorethane (390 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **8d** as a yellow oil (242 mg, 75%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.29 (s, 1 H), 5.42 (s, 2 H), 3.50 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), 2.43 (s, 3 H), 0.88 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), -0.03 (s, 9 H).

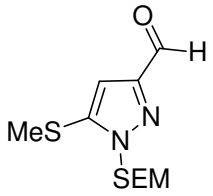
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 140.1, 126.4, 111.5, 77.7, 66.8, 18.7, 17.8, -1.5.

IR (Diamond ATR): 2952 (w), 1472 (m), 1355 (w), 1292 (m), 1248 (m), 1083 (s), 956 (m), 913 (w), 857 (s), 833 (s), 755 (s), 693 (m).

MS (EI, 70 eV) *m/z*, (%): 322 (M^+, 1), 280 (11), 279 (22), 277 (12), 266 (15), 264 (15), 251 (29), 249 (25), 233 (12), 231 (12), 213 (4), 208 (42), 207 (25), 206 (40), 205 (21), 194 (4), 192 (4), 170 (4), 139 (11), 137 (11), 127 (18), 115 (4), 105 (16), 103 (4), 86 (16), 79 (4), 74 (8), 73 (100), 61 (5), 59 (5), 45 (7).

HRMS (EI): calcd. for $C_{10}H_{19}BrN_2OSSi$: 322.0171, found: 322.0169.

Synthesis of 5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carbaldehyde (8e):



According to **TP2**, the pyrazole **6d** (245 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M, 1.1 mmol). DMF (0.12 mL, 1.5 mmol), was added at -15 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **8e** as a yellow oil (207 mg, 76%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 10.08 (s, 1 H), 6.66 (s, 1 H), 5.20 (s, 2 H), 3.53 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), 1.78 (s, 3 H), 0.70 (t, $^3J_{H-H}$ = 7.9 Hz, 2 H), -0.10 (s, 9 H).

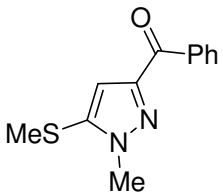
^{13}C-NMR (C_6D_6, 100 MHz): δ = 185.5, 151.9, 140.9, 107.7, 78.6, 67.0, 17.8, 17.7, -1.47.

IR (Diamond ATR): 2953 (w), 1699 (s), 1413 (w), 1306 (w), 1247 (m), 1183 (w), 1097 (m),1069 (m), 913 (w), 858 (m), 834 (s), 775 (m), 752 (s), 694 (w).

MS (EI, 70 eV) *m/z*, (%): 272 (M^+, 1), 229 (4) 227 (12), 214 (11), 201 (10), 200 (17), 199 (100), 156 (86), 155 (14), 143 (7), 127 (4), 116 (3), 109 (3), 100 (4), 85 (3), 83 (6), 78 (5), 73 (85), 69 (3), 61 (6), 59 (5), 57 (6), 43 (6), 39 (17).

HRMS (EI): calcd. for $C_{11}H_{20}N_2O_2SSi$: 272.1015, found: 272.1003.

Synthesis of (1-methyl-5-methylsulfanyl-1*H*-pyrazol-3-yl)-phenyl-methanone (9a):



According to **TP2,** 1-methyl-5-(methylthio)-1*H*-pyrazole (**7a**; 128 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M, 1.1 mmol). The resulting organomagnesium reagent was transmetallated with CuCN·2LiCl (1.0 mL, 1.0 M, 1.0 mmol) at -15 °C. Benzoyl chloride

(168 mg, 1.2 mmol) was added and the reaction mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **9a** as a pale yellow solid (181 mg, 78%).

m.p.: 52.8-54.2 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 8.65-8.62 (m, 2 H), 7.21-7.19 (m, 3 H), 7.02 (s, 1 H), 3.26 (s, 3 H), 1.70 (s, 3 H).

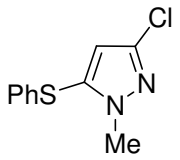
^{13}C-NMR (C_6D_6, 100 MHz): δ = 186.3, 151.0, 138.5, 138.0, 132.5, 131.1, 128.2, 111.2, 36.6, 17.5.

IR (Diamond ATR): 1716 (w), 1645 (s), 1597 (w), 1576 (w), 1449 (m), 1395 (m), 1364 (m), 1282 (m), 1233 (s), 1175 (w), 1133 (w), 1014 (w), 966 (w), 896 (s), 781 (m), 730 (s), 698 (s), 672 (m), 640 (m).

MS (EI, 70 eV) *m/z*, (%): 234 (4), 233 (12), 232 (M^+, 100), 231 (4), 217 (3), 204 (8), 191 (2), 189 (6), 185 (16), 158 (13), 157 (6), 155 (44), 144 (3), 105 (26), 80 (4), 77 (28).

HRMS (EI): calcd. for $C_{12}H_{12}N_2OS$: 232.0670, found: 232.0665.

Synthesis of 3-chloro-1-methyl-5-(phenylthio)-1*H*-pyrazole (9b):



According to **TP2**, 1-methyl-5-(phenylthio)-1*H*-pyrazole (**7b**; 190 mg, 1.0 mmol) dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M, 1.1 mmol). The resulting organomagnesium reagent was added dropwise at -15 °C to a solution of Cl_2FCCF_2Cl (372 mg, 2.0 mmol) in THF (1.0 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **9b** as a yellow oil (168 mg, 75%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 6.88-6.80 (m, 5 H), 6.27 (s, 1 H), 3.21 (s, 3 H).

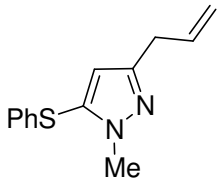
^{13}C-NMR (C_6D_6, 100 MHz): δ = 134.9, 132.7, 129.6, 127.5, 126.7, 125.3, 115.9, 36.4.

IR (Diamond ATR): 1582 (m), 1465 (s), 1441 (m), 1363 (s), 1278 (w), 1084 (w), 1070 (w), 1024 (m), 958 (s), 754 (m),738 (m), 722 (s), 688 (s), 637 (m), 617 (m).

MS (EI, 70 eV) *m/z*, (%): 226 (41), 225 (11), 224 (M^+, 100), 209 (12), 196 (6), 189 (10), 174 (5), 156 (6), 148 (5), 135 (7), 130 (5), 121 (8), 109 (7), 91 (7), 77 (9), 71 (6), 57 (9), 44 (22).

HRMS (EI): calcd. for $C_{10}H_9ClN_2S$: 224.0175, found: 224.0171.

Synthesis of 3-allyl-1-methyl-5-(phenylthio)-1*H*-pyrazole (9c):



According to **TP2**, the pyrazole **7b** (190 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M, 1.1 mmol). The resulting organomagnesium reagent was transmetallated with CuCN·2LiCl (0.1 mL, 1.0 M, 0.1 mmol) at -15 °C. Allyl bromide (146 mg, 1.2 mmol) was added and the reaction mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **9c** as a yellow oil (179 mg, 78%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 6.95-6.78 (m, 5 H), 6.32 (s, 1 H), 6.09-5.99 (1 H), 5.12-5.00 (m, 2 H), 3.43 (s, 2 H), 3.41 (s, 3 H).

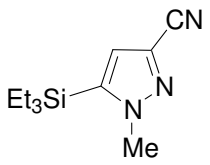
^{13}C-NMR (C_6D_6, 100 MHz): δ = 150.7, 136.4, 136.3, 129.5, 128.3, 126.8, 126.1, 115.9, 113.2, 36.1, 33.4.

IR (Diamond ATR): 2970 (m), 1739 (s), 1641 (w), 1582 (w), 1507 (m), 1478 (m), 1440 (m), 1365 (m), 1217 (m), 1075 (w), 1024 (w), 914 (m), 804 (w), 737 (s), 688 (s), 652 (w).

MS (EI, 70 eV) *m/z*, (%): 231 (13), 230 (M^+, 100), 229 (21), 215 (2), 204 (18), 197 (1), 189 (3), 121 (22), 109 (6), 105 (2), 94 (2), 80 (5), 77 (3).

HRMS (EI): calcd. for $C_{13}H_{14}N_2S$: 230.0878, found:230.0871.

Synthesis of 1-methyl-5-(triethylsilyl)-1*H*-pyrazole-3-carbonitrile (9d):



According to **TP2,** the pyrazole **7c** (196 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with TMPMgCl·LiCl (1.0 mL, 1.1 M, 1.1 mmol) at 25 °C. After 5 h stirring, full conversion to the

organomagnesium reagent was achieved. TsCN (217 mg, 1.2 mmol), dissolved in THF (1.0 mL) was added dropwise at -15 °C and the mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **9d** as a yellow oil (135 mg, 61%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 6.69 (s, 1 H), 3.95 (s, 3 H), 0.95-0.89 (m, 9 H), 0.85-0.76 (m. 6 H).

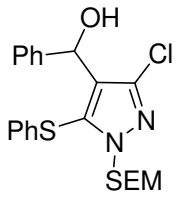
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 142.4, 123.7, 120.9, 114.2, 40.6, 7.0, 3.1.

IR (Diamond ATR): 2956 (m), 2877 (m), 2239 (m), 1457 (w), 1416 (w), 1392 (m), 1288 (w), 1239 (w), 1145 (w), 1088 (m), 1012 (s), 810 (m), 723 (s), 695 (s).

MS (EI, 70 eV) *m/z*, (%): 221 (M^+, 2), 192 (67), 164 (100), 136 (40), 124 (3), 107 (2), 91 (3),

HRMS (EI): calcd. for $C_{11}H_{19}N_3Si$: 221.1348, found: 221.1341.

Synthesis of (3-chloro-5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(phenyl)methanol (10a):



According to **TP3,** the pyrazole **8c** (370 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with $TMP_2Mg{\cdot}2LiCl$ (1.8 mL, 0.6 м, 1.1 mmol). After completion of the deprotonation, benzaldehyde (127 mg, 1.2 mmol) was added and the solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **10a** as a pale yellow oil (317 mg, 71%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.43-7.40 (m, 2 H), 7.11-6.77 (m, 8 H), 6.02 (s, 1 H) 5.22-5.15 (m, 1H), 5.18 (s, 1 H), 3.50 (t, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H), 2.01 (s, 1 H), 0.68 (t, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H), -0.13 (s, 9 H).

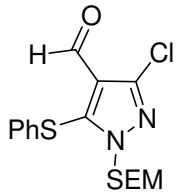
^{13}C-NMR (C_6D_6, 100 MHz): δ = 142.6, 139.3, 135.0, 131.4, 129.4, 128.4, 127.4, 126.7, 126.3, 78.0, 68.4, 67.1, 17.7, -1.4.

IR (Diamond ATR): 1728 (m), 1430 (w), 1378 (m), 1301 (m), 1249 (m), 1098 (s), 1019 (m), 937 (w), 923 (w), 860 (s), 835 (s), 759 (s), 737 (s), 694 (s), 687 (s).

MS (EI, 70 eV) *m/z*, (%): 446 (M^+, 7), 403 (21), 369 (16), 330 (19), 328 (11), 311 (16), 309 (10), 295 (24), 293 (29), 243 (18), 241 (12), 239 (33), 109 (12), 105 (22), 91 (35), 77 (14), 73 (100).

HRMS (EI): calcd. for $C_{22}H_{27}ClN_2O_2SSi$: 446.1251, found: 446.1245.

Synthesis of 3-chloro-5-phenylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole-4-carbaldehyde (10b):



According to **TP3**, the pyrazole **8c** (370 mg, 1.0 mmol) was treated with $TMP_2Mg{\cdot}2LiCl$ (1.8 mL, 0.6 M, 1.1 mmol). DMF (0.12 mL, 1.5 mmol) was then added and the reaction mixture was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **10b** as a pale yellow oil (239 mg, 65%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 9.89 (s, 1 H), 7.01-6.99, (m, 2 H), 6.82-6.80 (m, 3 H), 5.10 (s, 2 H), 3.48-3.43 (m, 2 H), 0.72-0.68 (m, 2 H), -0.12 (s, 9 H).

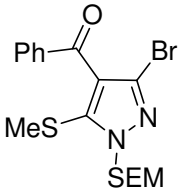
^{13}C-NMR (C_6D_6, 100 MHz): δ = 182.1, 142.0, 139.5, 133.4, 129.7, 129.4, 121.6, 77.9, 67.6, 17.7, -1.5.

IR (Diamond ATR): 2970 (w), 2952 (w), 2900 (w), 1739 (s), 1690 (s), 1494 (m), 1412 (m), 1354 (m), 1297 (w), 1248 (m), 1217 (m), 1096 (s), 858 (s), 833 (s), 776 (s), 740 (m), 687 (m).

MS (EI, 70 eV) *m/z*, (%): 368 (M^+, 10), 327 (16), 326 (9), 325 (47), 323 (30), 312 (15), 311 (47), 310 (37), 309 (99), 303 (9), 297 (10), 295 (21), 254 (19), 253 (16), 252 (48), 251 (29), 232 (18), 229 (13), 219 (10), 217 (33), 110 (14), 109 (25), 93 (14), 91 (21), 73 (100).

HRMS (EI): calcd. for $C_{16}H_{21}ClN_2O_2SSi$: 368.0782, found: 368.0768.

Synthesis of [3-bromo-5-methylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-phenyl-methanone (10c):



According to **TP3**, the pyrazole **8d** (323 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with $TMP_2Mg{\cdot}2LiCl$ (1.8 mL, 0.6 M, 1.1 mmol). After completion of the deprotonation, CuCN·2LiCl (1.0

mL, 1.0 M, 1.0 mmol) was added and the mixture was stirred for 5 min before adding benzoyl chloride (169 mg, 1.2 mmol). The solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **10c** as a pale yellow oil (320 mg, 75%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.82-7.79 (m, 2 H), 7.62-7.56 (m, 1 H), 7.48-7.43 (m, 2 H), 5.60 (s, 2 H), 3.70 (t, $^3J_{H-H}$ = 8.3 Hz, 2 H), 2.37 (s, 3 H), 0.92 (t, $^3J_{H-H}$ = 8.2 Hz, 2H), 0.00 (s, 9 H).

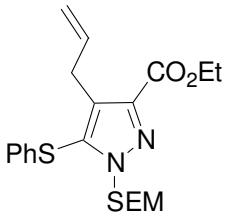
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 189.7, 140.2, 137.2, 133.5, 129.9, 128.4, 126.6, 125.6, 78.0, 67.4, 20.2, 17.9, -1.44.

IR (Diamond ATR): 1657 (s), 1598 (w), 1482 (m), 1365 (m), 1247 (s), 1230 (s), 1175 (w), 1088 (s), 1015 (W), 903 (m), 833 (s), 765 (m), 731 (m), 692 (s).

MS (EI, 70 eV) *m/z*, (%): 426 (M^+, 1), 385 (15), 383 (23), 381 (10), 369 (6), 355 (12), 353 (13), 337 (19), 335 (20), 317 (12), 312 (34), 311 (16), 310 (33), 309 (11), 293 (7), 279 (7), 256 (6), 231 (36), 139 (8), 137 (8), 105 (70), 91 (9), 77 (35), 73 (100), 43 (11).

HRMS (EI): calcd. for $C_{17}H_{23}O_2N_2SSi$: 426.0433, found: 426.0428.

Synthesis of ethyl 4-allyl-5-(phenylthio)-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole-3-carboxylate (10d)



Ethyl 5-(phenylthio)-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole-3-carboxylate (**8b**; 380 mg, 1.0 mmol) was dissolved in THF (1.0 mL) and added to a flame-dried flask equipped with a magnetic stirring bar, an argon inlet and a septum. The mixture was cooled to -30 °C and TMPMgCl·LiCl (**1**; 1.0 mL, 1.1 M in THF, 1.1 mmol) was added while stirring. Upon completion of the exchange (determined by GC analysis of reaction aliquots quenched with I_2, 2 h), CuCN·2LiCl (0.1 mL, 1.0 M in THF, 0.1 mmol) was added and the reaction mixture was stirred for 5 min before adding allyl bromide (146 mg, 1.2 mmol). The solution was then allowed to slowly warm up to 25 °C. After stirring at room temperature for 2 h, the reaction mixture was quenched according to **TP3**. Removal of the solvent *in*

vacuo and purification by flash chromatography (SiO_2, initially neutralized with 3% Et_3N, pentane:EtOAc, 9:1) afforded the desired product as a yellow oil (314 mg, 75 %).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.24-7.13 (m, 3 H), 7.02-6.99 (m, 2 H), 5.91-5.78 (m, 1 H), 5.56 (s, 2 H), 4.93-4.87 (m, 2 H), 4.43 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 3.57-3.49 (m, 4 H), 1.40 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H), 0.77-0.71 (m, 2 H), -0.08 (s, 9 H).

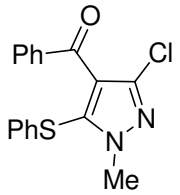
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 162.2, 141.6, 135.7, 134.9, 131.6, 130.0, 129.2, 126.9, 126.4, 115.4, 78.7, 67.0, 61.0, 28.8, 17.7, 14.4, -1.5.

IR (Diamond ATR): 2970 (s), 1718 (s), 1480 (w), 1365 (m), 1306 (w), 1247 (s), 1091 (s), 912 (w), 834 (s), 738 (m), 688 (m).

MS (EI, 70 eV) m/z, (%): 418 (M^+, 10), 373 (30), 346 (13), 345 (51), 331 (16), 318 (13), 317 (57), 315 (13), 302 (50), 301 (25), 299 (14), 288 (28), 287 (34), 256 (16), 255 (17), 242 (14), 230 (23), 229 (100), 228 (24), 213 (12), 190 (12), 111 (13), 109 (17), 97 (28), 91 (45), 85 (12), 83 (16), 81 (12), 75 (16), 73 (80), 71 (17), 69 (19), 59 (13), 57 (24), 55 (17), 44 (24).

HRMS (EI): calcd. for $C_{21}H_{30}N_2O_3SSi$:418.1746, found:418.1749.

Synthesis of (3-chloro-1-methyl-5-phenylsulfanyl-1*H*-pyrazol-4-yl)-phenyl-methanone (11a):



According to **TP3**, the pyrazole **9b** (225 mg, 1.0 mmol), dissolved in THF (1.0 mL) was treated with $TMP_2Mg·2LiCl$ (1.8 mL, 0.6 M, 1.1 mmol). After completion of the deprotonation CuCN·2LiCl (1.0 mL, 1.0 M, 1.0 mmol) was added and the mixture was stirred for 5 min before adding benzoyl chloride (169 mg, 1.2 mmol). The solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **11a** as a pale yellow oil (240 mg, 73%).

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.80-7.78 (m, 2 H), 7.11-6.76 (m, 8 H), 3.16 (s, 3 H).

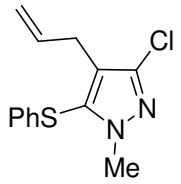
^{13}C-NMR (C_6D_6, 100 MHz): δ = 188.1, 138.7, 138.1, 135.1, 133.8, 133.1, 130.0, 129.6, 128.6, 128.5, 127.1, 124.3, 36.8.

IR (Diamond ATR): 2970 (m), 1737 (s), 1653 (s), 1580 (w), 1478 (m), 1378 (m), 1244 (s), 1078 (m), 906 (m), 812 (w), 732 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 330 (24), 329 (16), 328 (M^+, 66), 295 (3), 255 (34), 254 (14), 253 (100), 224 (6), 196 (4), 188 (3), 175 (3), 136 (2), 109 (5), 107 (3), 105 (32), 77 (20).

HRMS (EI): calcd. for $C_{17}H_{13}ClN_2OS$: 328.0437, found: 328.0430.

Synthesis of 4-allyl-3-chloro-1-methyl-5-(phenylthio)-1*H*-pyrazole (11b):



According to **TP3**, the pyrazole **9b** (225 mg, 1.0 mmol) dissolved in THF (1.0 mL) was treated with $TMP_2Mg{\cdot}2LiCl$ (1.8 mL, 0.6 M, 1.1 mmol). After completion of the deprotonation, CuCN·2LiCl (0.1 mL, 1.0 M, 0.1 mmol) was added and the mixture was stirred for 5 min before adding allyl bromide (146 mg, 1.2 mmol). The solution was allowed to warm up to 25 °C. Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/95:5) furnished the desired compound **11b** as a colourless oil (185 mg, 70%).

^{1}H-NMR ($CDCl_3$, 400 MHz): δ = 7.29-7.12 (m, 3 H), 7.03-7.00 (m, 2 H), 5.86-5.76 (m, 1 H), 5.02-4.97 (m, 2 H), 3.80 (s, 3 H), 3.28-3.26 (m, 2 H).

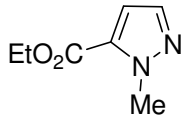
^{13}C-NMR ($CDCl_3$, 100 MHz): δ = 138.4, 134.7, 134.5, 130.4, 129.4, 126.7, 126.4, 122.1, 115.8, 37.1, 28.1.

IR (Diamond ATR): 2970 (m), 1739 (s), 1582 (w), 1365 (s), 1217 (s), 1078 (m), 910 (m), 805 (w), 737 (s), 688 (s).

MS (EI, 70 eV) *m/z*, (%): 266 (30), 265 (19), 264 (M^+, 100), 263 (23), 249 (19), 237 (14), 235 (11), 230 (20), 202 (9), 201 (9), 196 (26), 189 (15), 187 (39), 185 (11), 173 (9), 161 (11), 160 (11), 155 (10), 151 (11), 120 (17), 119 (30), 115 (7), 114 (10), 113 (25), 44 (49).

HRMS (EI): calcd. for $C_{13}H_{13}ClN_2S$: 264.0488, found: 264.0480.

Synthesis of ethyl 1-methyl-1*H*-pyrazole-5-carboxylate (14):



According to **TP1,** the pyrazole **4b** (820 mg, 10 mmol), dissolved in THF (10 mL) was treated with TMPMgCl·LiCl (10 mL, 1.1 M, 11 mmol). The resulting organomagnesium reagent was added dropwise at 0 °C to a solution of ethyl cyanoformate (990 mg, 12 mmol) in THF (10 mL). Purification by flash chromatography (SiO_2 initially neutralized with 3% Et_3N, pentane:EtOAc/9:1) furnished the desired compound **14** as a yellow oil (1.19 g, 77%).

^{1}H-NMR ($CDCl_3$, 300 MHz): δ = 7.42 (d, $^3J_{H\text{-}H}$ = 2.2 Hz, 1 H), 6.80 (d, $^3J_{H\text{-}H}$ = 2.2 Hz 1 H), 4.34-4.27 (q, $^3J_{H\text{-}H}$ = 7.2 Hz, 2H), 4.15 (s, 3H), 1.34 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3H).

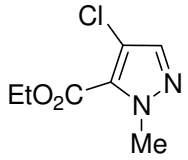
^{13}C-NMR ($CDCl_3$, 75 MHz): δ = 159.8, 137.6, 132.4, 111.1, 60.9, 39.5, 14.2.

IR (Diamond ATR): 2982 (w), 1719 (s), 1516 (m), 1472 (m), 1392 (m), 1317 (s), 1249 (s), 1113 (s), 1022 (s), 930 (m), 761 (s), 653 (m).

MS (EI, 70 eV) *m/z*, (%): 169 (6), 154 (M^+, 57), 131 (6), 126 (35), 118 (11), 109 (100), 95 (10), 81 (8), 72 (3), 69 (17), 54 (6), 44 (9).

HRMS (EI): calcd. for $C_7H_{10}N_2O_2$: 154.0742, found: 154.0745.

Synthesis of 4-chloro-2-methyl-2*H*-pyrazole-3-carboxylic acid ethyl ester (15):



A flask equipped with a magnetic stirring bar was charged with the pyrazole **14** (462 mg, 3.0 mmol) dissolved in acetic acid (10 mL). At 25 °C NaOCl (13% aq. solution; 7.0 mL, 12 mmol) was added and the reaction mixture was stirred for 6 h. Complete reaction conversion was checked by GC-analysis of hydrolyzed reaction aliquots. The mixture was quenched with water and extracted with EtOAc (3 x 50 mL). The organic extracts were dried over anhydrous Na_2SO_4 and filtered. Removal of the solvents furnished the product **15** as a white solid in (525 mg, 93%) yield.

m.p.: 33.7-34.2 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.27 (s, 1 H), 3.97 (q, $^3J_{H-H}$ = 7.1 Hz, 2 H), 3.68 (s, 3 H), 0.96 (t, $^3J_{H-H}$ = 7.1 Hz, 3 H).

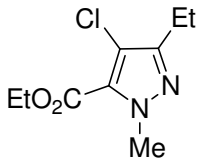
^{13}C-NMR (C_6D_6, 100 MHz): δ = 158.9, 137.5, 127.9, 115.2, 61.0, 40.6, 14.0.

IR (Diamond ATR): 2929 (w), 1718 (s), 1453 (m), 1422 (m), 1388 (m), 1266 (s), 1110 (s), 1031 (m), 991 (m), 863 (m), 840 (m), 776 (m), 748 (w), 649 (w).

MS (EI, 70 eV) *m/z*, (%): 190 (28), 188 (M^+, 100), 162 (11), 161 (13), 160 (43), 159 (36), 146 (4), 145 (22), 144 (12), 143 (86), 142 (6), 141 (12), 131 (6), 129 (19), 116 (9), 115 (11), 114 (8), 88 (10), 80 (5), 61 (5), 52 (4).

HRMS (EI): calcd. for $C_7H_9ClIN_2O_2$: 188.0353, found: 188.0350.

Synthesis of 4-chloro-5-ethyl-2-methyl-2*H*-pyrazole-3-carboxylic acid ethyl ester (17):



In a dry and argon-flushed Schlenk-flask equipped with a magnetic stirring bar and a septum, pyrazole **15** (188 mg, 1.00 mmol) was dissolved in THF (1.0 mL). At 25 °C $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (2.80 mL, 0.4 м, 1.10 mmol) was added dropwise and the mixture was stirred for 30 min. Completion of the metallation was checked by GC-analysis of reaction aliquots previously quenched with I_2. After full conversion was achieved, I_2 (305.0 mg, 1.20 mmol) was added to the mixture and the consumption of the metallated reagent was checked by GC-analysis of hydrolyzed reaction aliquots. After 30 min stirring, iodide **16** was mixed with 2 mol% $Pd(OAc)_2$ (4.5 mg, 0.02 mmol) and 4 mol% S-PHOS (16.5 mg, 0.04 mmol). To this mixture, a pre-mixed solution of EtMgCl (0.53 mL, 2.80 м, 1.50 mmol) and $InCl_3$ in THF (0.50 mL, 1.00 м in THF, 0.50 mmol) was added dropwise. The reaction mixture was stirred for 8 h and completion of the cross-coupling was determined by GC-analysis. The mixture was quenched with water and extracted with EtOAc (3 x 20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, pentane:EtOAc/9:1) furnished the desired compound **17** as a white solid (149 mg, 69%).

m.p.: 33.4-34.8 °C.

^{1}H-NMR (C_6D_6, 300 MHz): δ = 4.01 (q, $^3J_{H-H}$ = 7.2 Hz, 2 H), 3.73 (s, 3 H), 2.63 (q, $^3J_{H-H}$ = 7.5 Hz, 2 H), 1.25 (t, $^3J_{H-H}$ = 7.5 Hz, 3 H), 0.00 (t, $^3J_{H-H}$ = 7.2 Hz, 3 H).

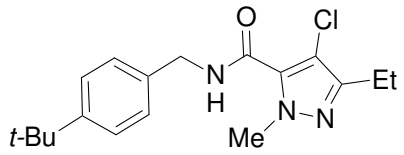
^{13}C-NMR (C_6D_6, 75 MHz): δ = 159.1, 150.2, 129.2, 113.1, 60.9, 40.3, 19.6, 14.0, 12.9.

IR (Diamond ATR): 2977 (w), 1714 (s), 1476 (m), 1449 (m), 1414 (w), 1272 (s), 1242 (m), 1117 (s), 1069 (m), 1032 (s), 872 (w), 774 (m), 626 (w).

MS (EI, 70 eV) *m/z*, (%): 219 (3), 218 (26), 217 (10), 216 (M^+, 100), 215 (9), 203 (13), 201 (40), 190 (5), 189 (11), 188 (16), 187 (35), 175 (15), 173 (60), 171 (26), 157 (9), 143 (4), 135 (3), 88 (3).

HRMS (EI): calcd. for $C_9H_{13}ClN_2O_2$: 216.0666, found: 216.0669.

Synthesis of 4-chloro-5-ethyl-2-methyl-2*H*-pyrazole-3-carboxylic acid 4-tert-butyl-benzylamide (13):



In a dry and argon-flushed Schlenk-tube equipped with a magnetic stirring bar and a septum, *4-tert*-butylbenzylamine (196 mg, 1.2 mmol), dissolved in THF (1.0 mL) was deprotonated with NaH (60% in oil; 60 mg, 1.5 mmol). After gas emission had ceased, pyrazole **17** (216 mg, 1.0 mmol) dissolved in THF (1.0 mL) was added to the mixture at 25 °C. The reaction mixture was stirred for 3 h, quenched with water and extracted with EtOAc (3 x 20 mL). The organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography (SiO_2, pentane: EtOAc/9:1) furnished Tebufenpyrad (**13**) as colourless crystals (250 mg, 75%).

m.p.: 55.7-57.4 °C.

^{1}H-NMR (C_6D_6, 400 MHz): δ = 7.26-7.24 (m, 2 H), 7.19-7.16 (m, 2 H), 6.69 (s, br, 1 H), 4.44 (d, $^3J_{H-H}$ = 5.7 Hz, 2 H), 3.96 (s, 3 H), 2.55 (q, $^3J_{H-H}$ = 7.6 Hz, 2 H), 1.23 (t, $^3J_{H-H}$ = 7.6 Hz, 3 H), 1.20 (s, 9 H).

^{13}C-NMR (C_6D_6, 100 MHz): δ = 158.3, 150.5, 149.2, 135.5, 131.5, 127.8, 125.9, 107.4, 43.2, 40.5, 34.4, 31.4, 19.5, 12.9.

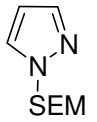
IR (Diamond ATR): 3309 (w), 2966 (m), 1646 (s), 1546 (s), 1512 (m), 1449 (w), 1290 (s), 1270 (m), 1094 (w), 986 (w), 828 (w), 789 (w), 622 (m).

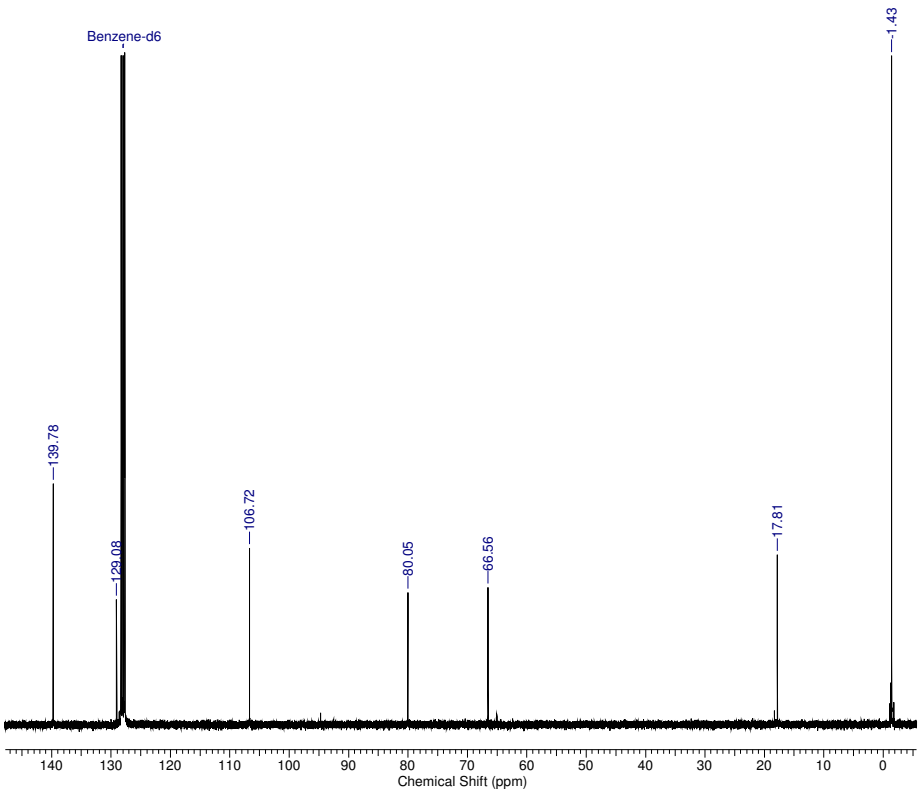
MS (EI, 70 eV) *m/z*, (%): 336 (4), 335 (22), 334 (14), 333 (M^+, 75), 321 (5), 320 (29), 319 (17), 318 (100), 298 (6), 278 (12), 277 (7), 276 (39), 173 (22), 172 (6), 171 (78), 162 (6), 159 (7), 152 (5), 147 (7), 146 (7), 145 (18), 138 (9), 137 (12), 131 (14), 117 (8).

HRMS (EI): calcd. for $C_{18}H_{24}ClN_3O$: 333.1608, found: 333.1601.

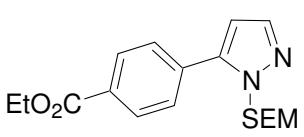
3) NMR Spectra

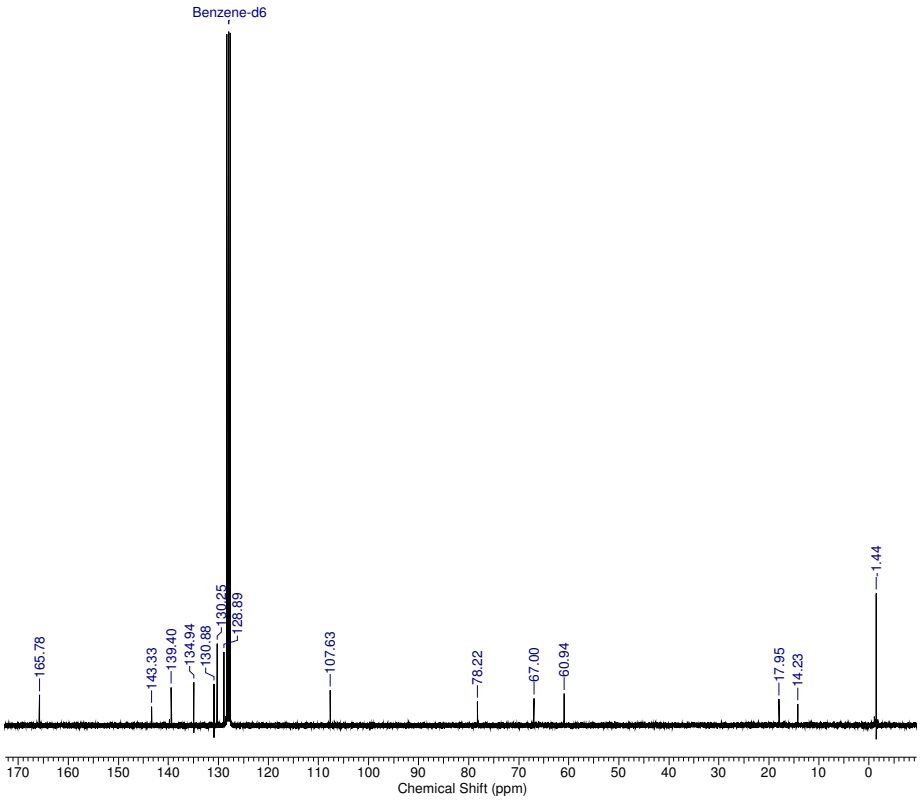
1-(2-Trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole (4a):



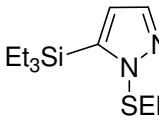


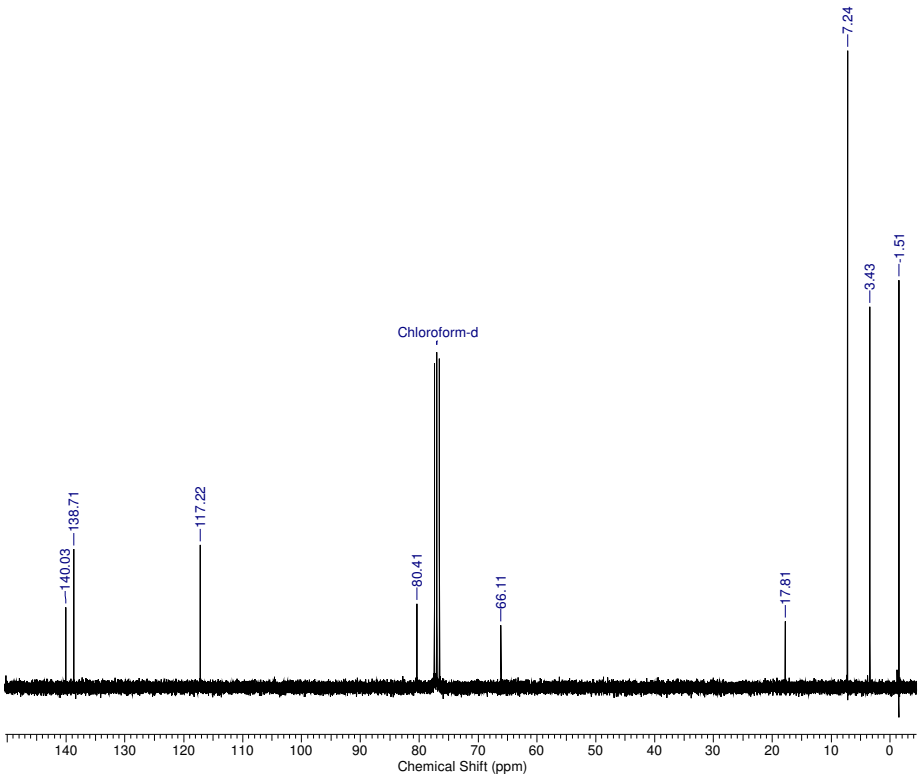
4-[2-(2-Trimethylsilanyl-ethoxymethyl)-2*H*-pyrazol-3-yl]-benzoic acid ethyl ester (6a):



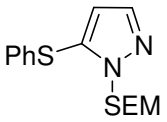


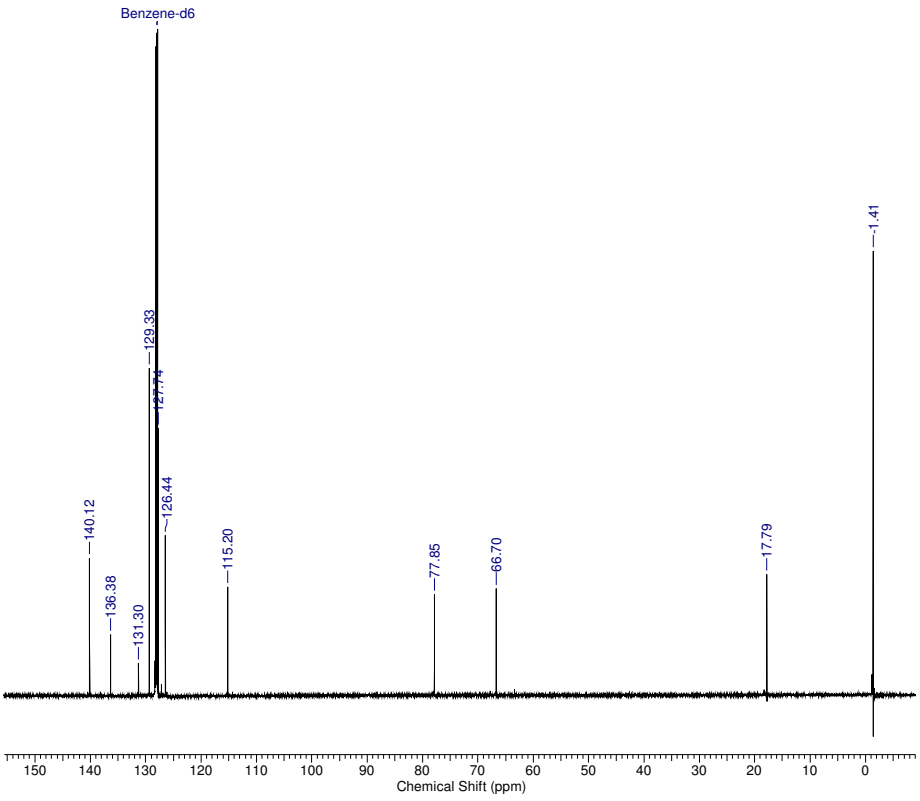
5-Triethylsilanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole (6b):



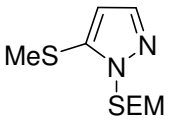


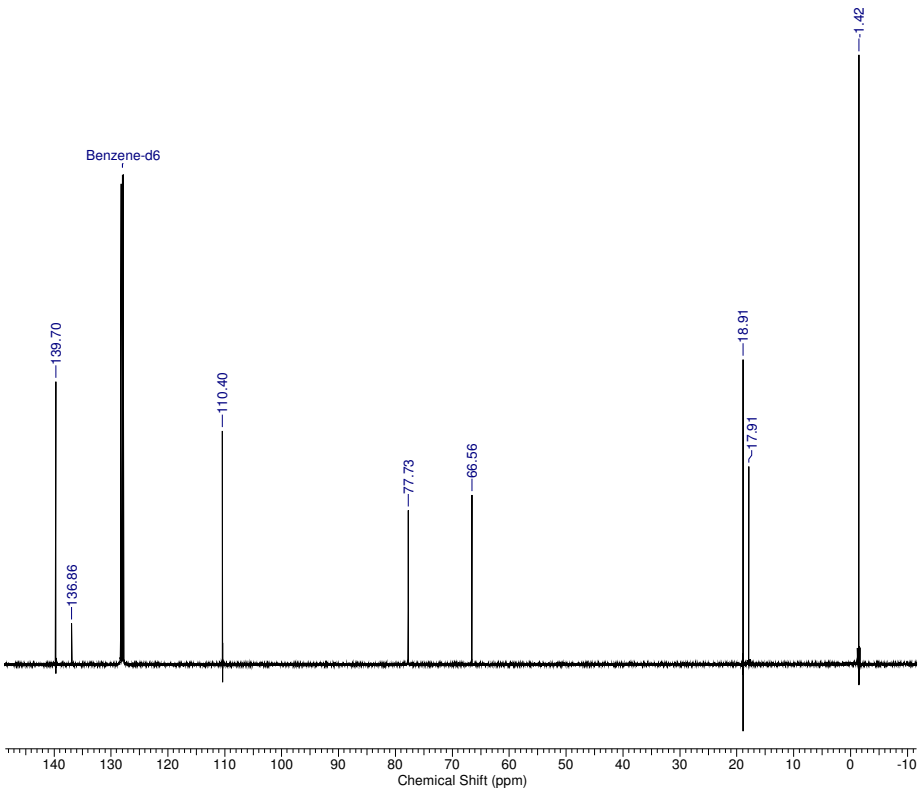
5-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (6c):



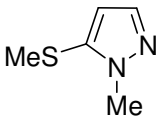


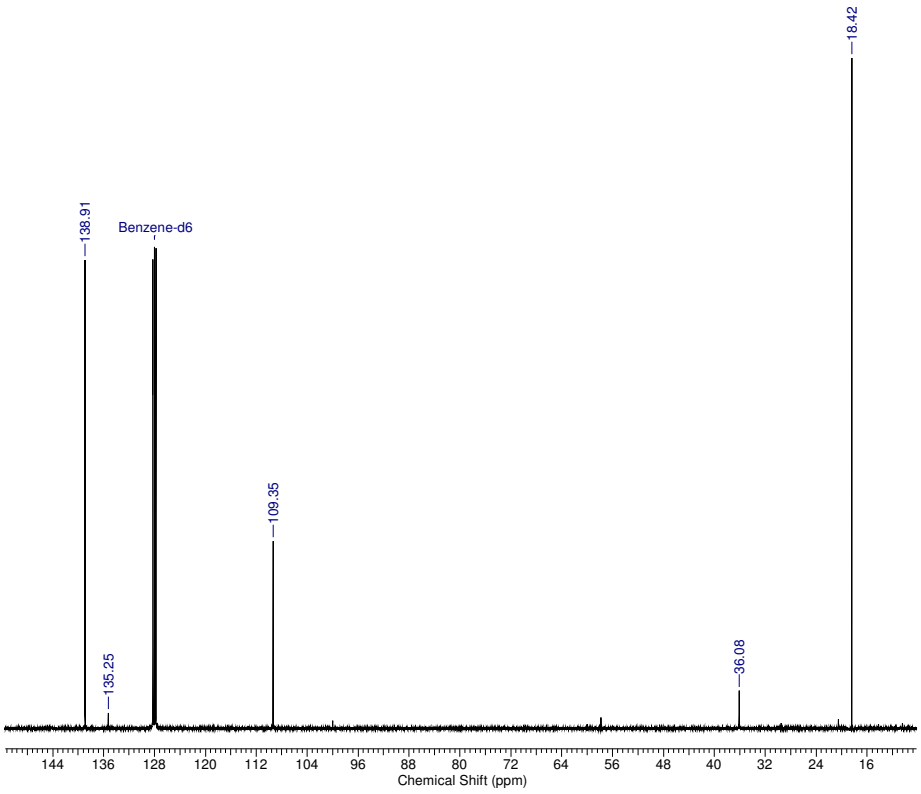
5-Methylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole (6d):



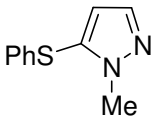


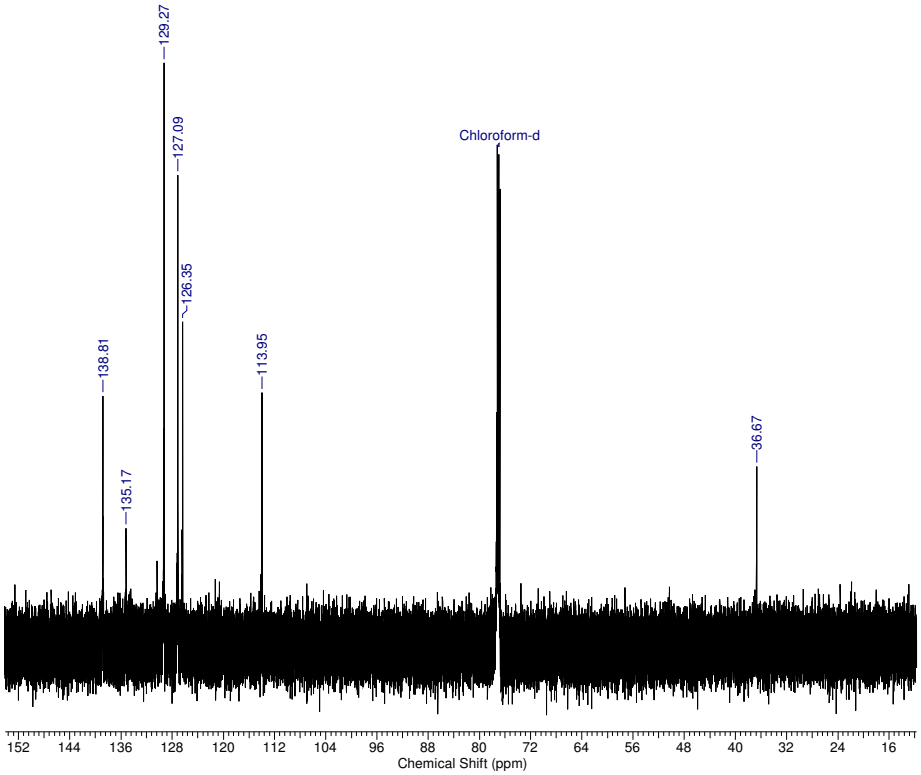
1-Methyl-5-(methylthio)-1*H*-pyrazole (7a):



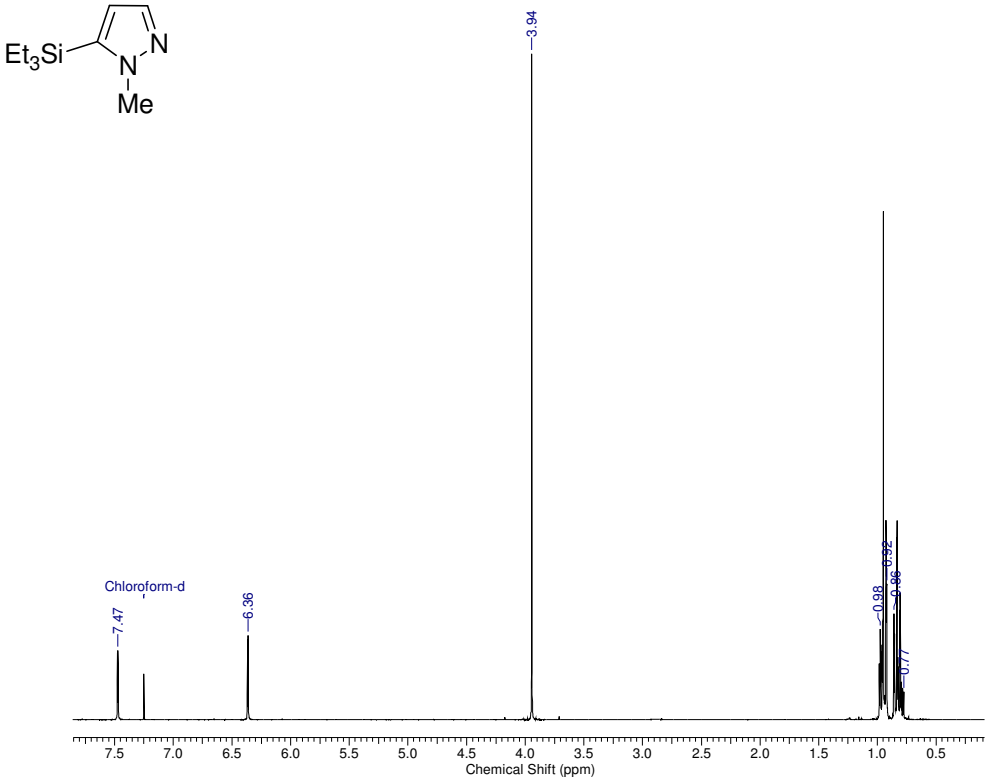


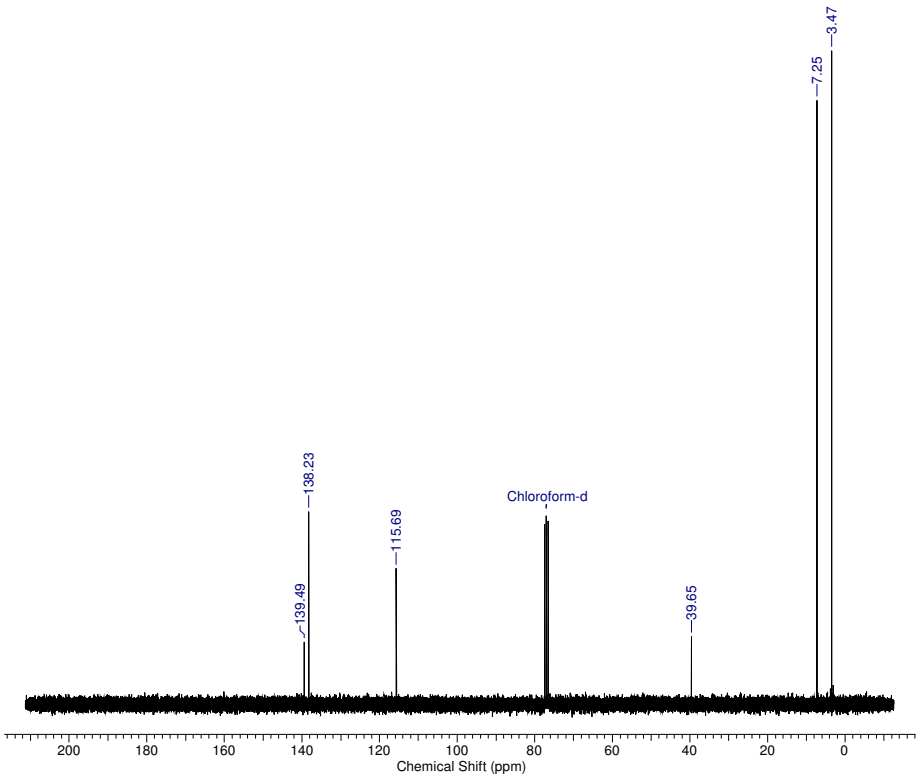
1-Methyl-5-(phenylthio)-1*H*-pyrazole (7b):



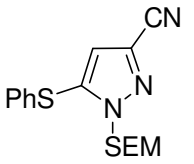


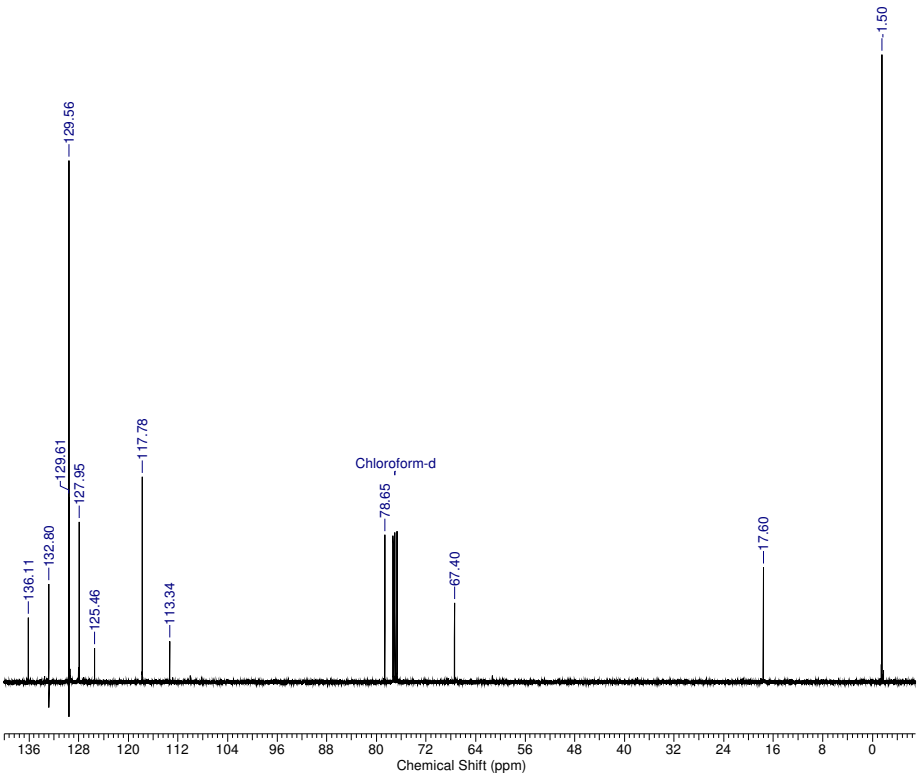
1-Methyl-5-(triethylsilyl)-1*H*-pyrazole (7c):



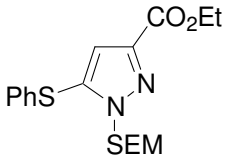


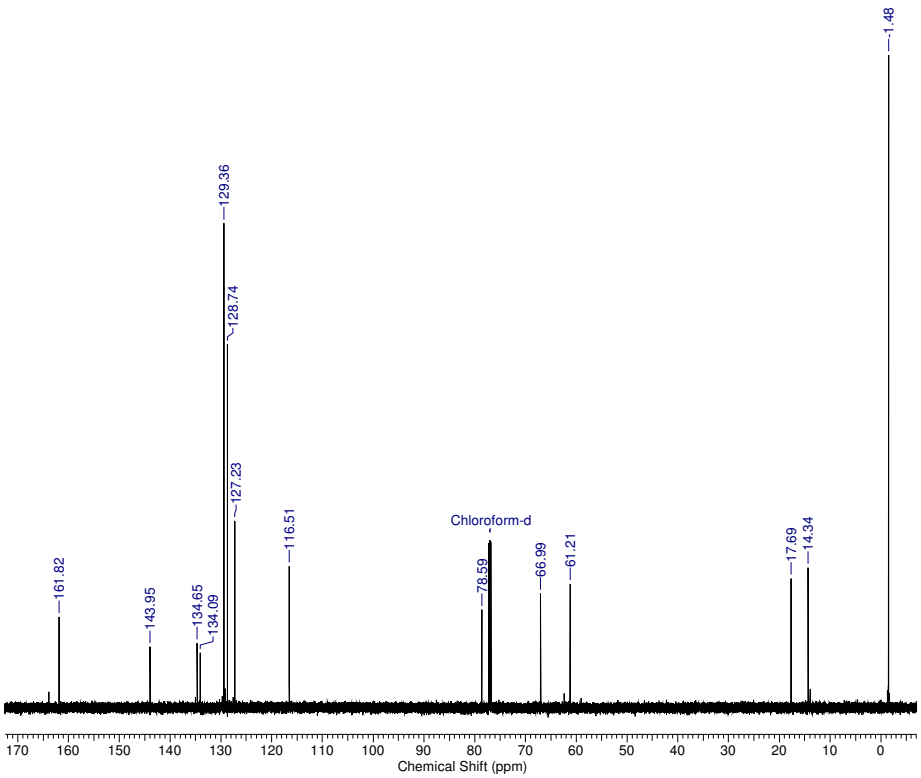
5-(Phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carbonitrile (8a):



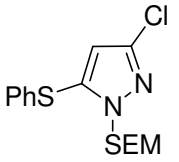


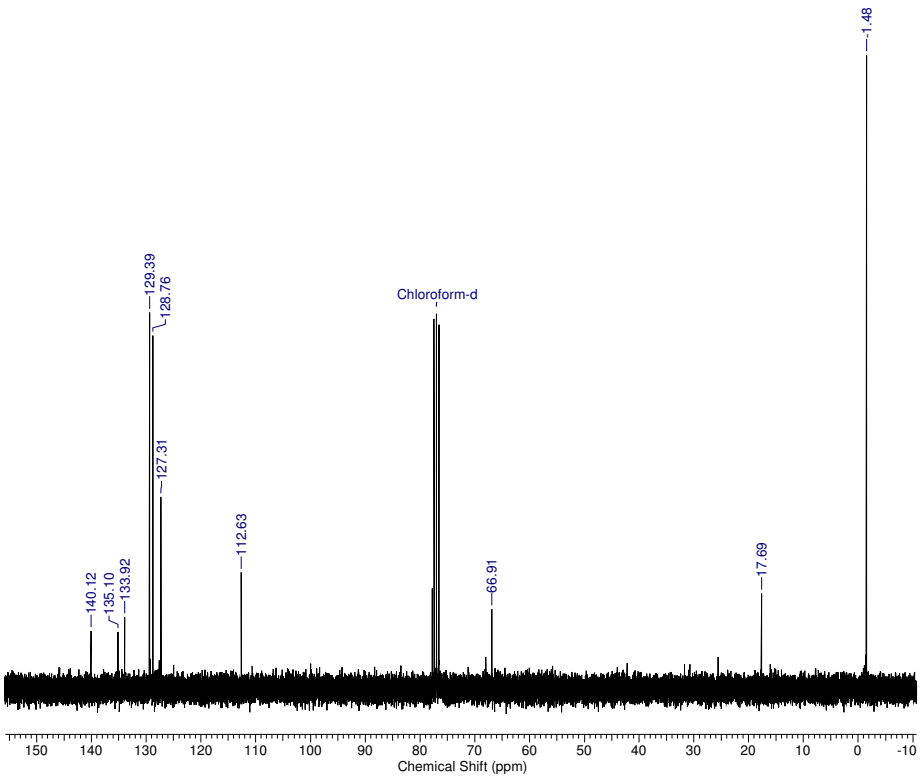
Ethyl 5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carboxylate (8b):



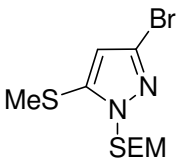


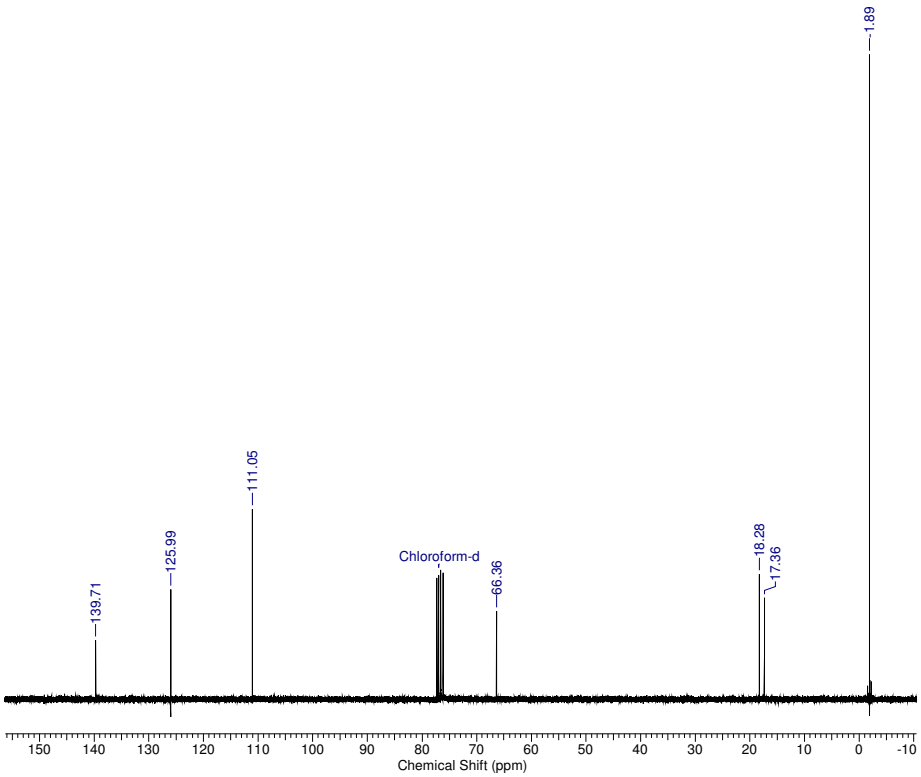
3-Chloro-5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (8c):



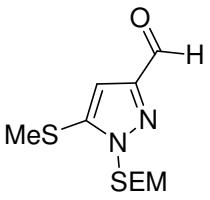


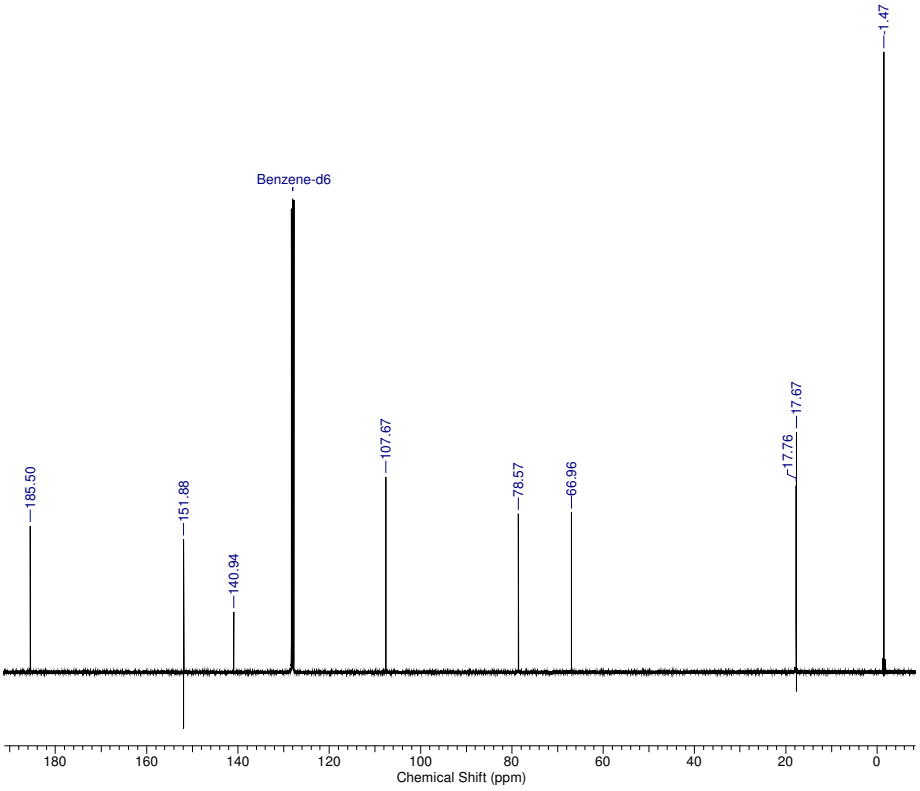
3-Bromo-5-(methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole (8d):



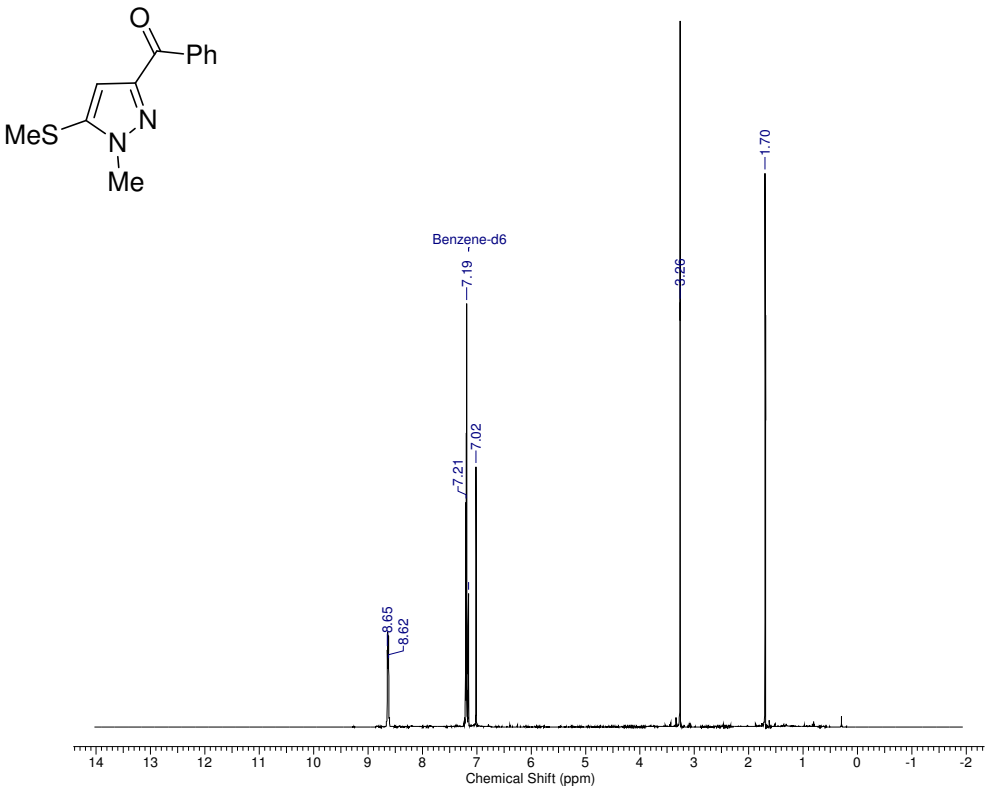


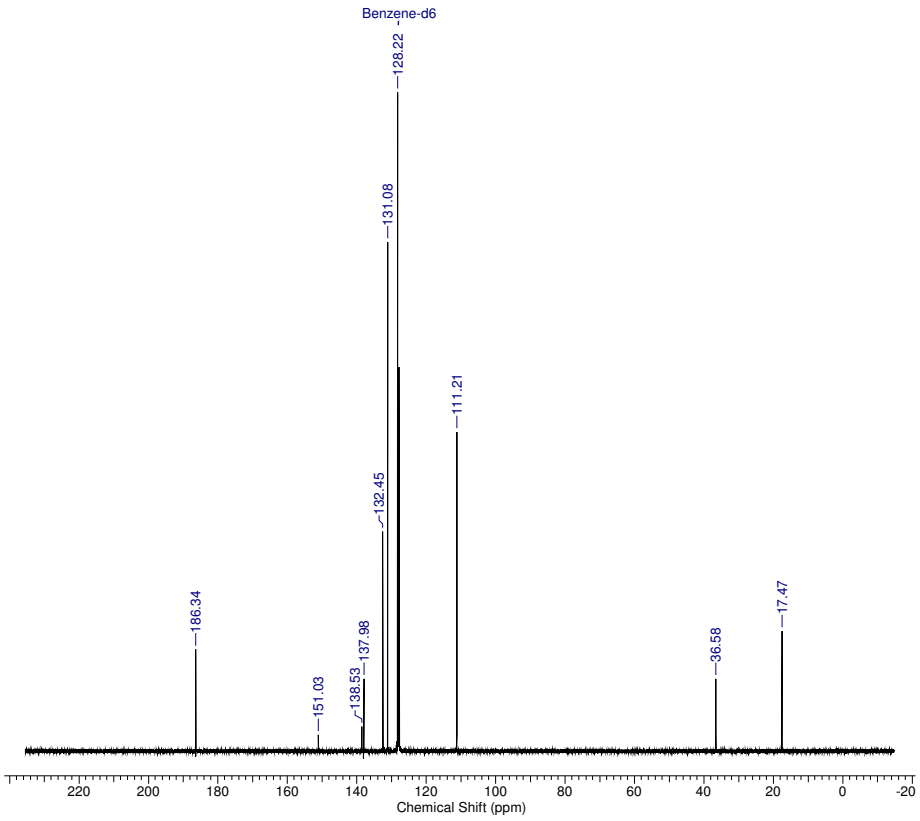
5-(Methylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazole-3-carbaldehyde (8e):



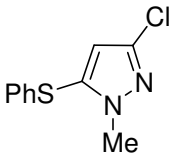


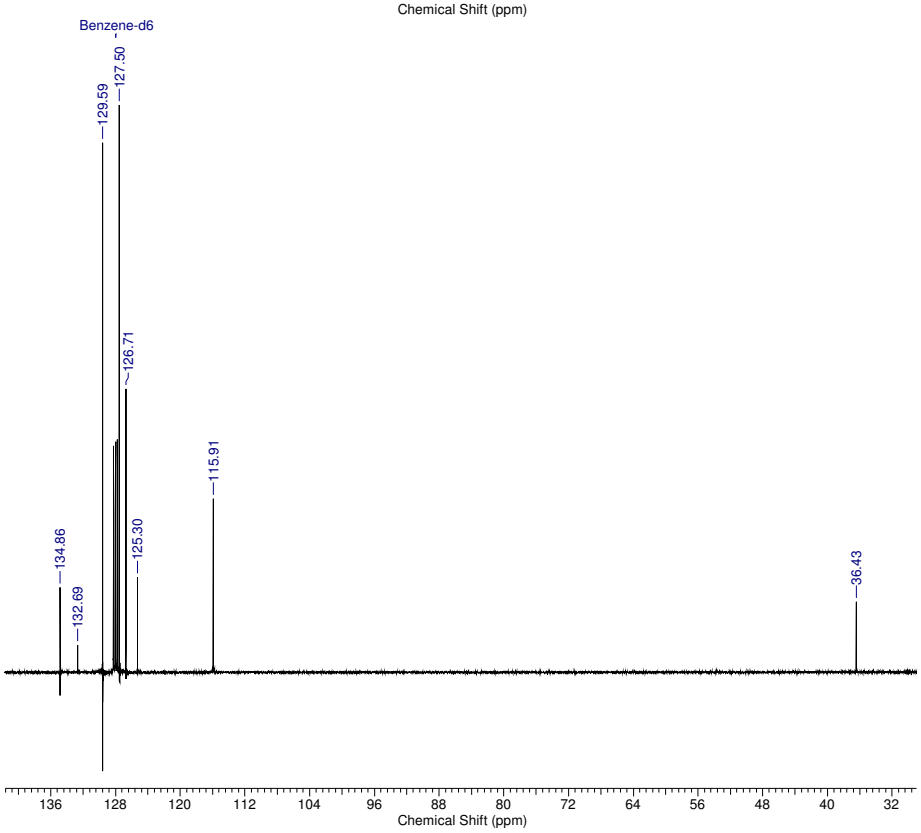
(1-Methyl-5-methylsulfanyl-1*H*-pyrazol-3-yl)-phenyl-methanone (9a):



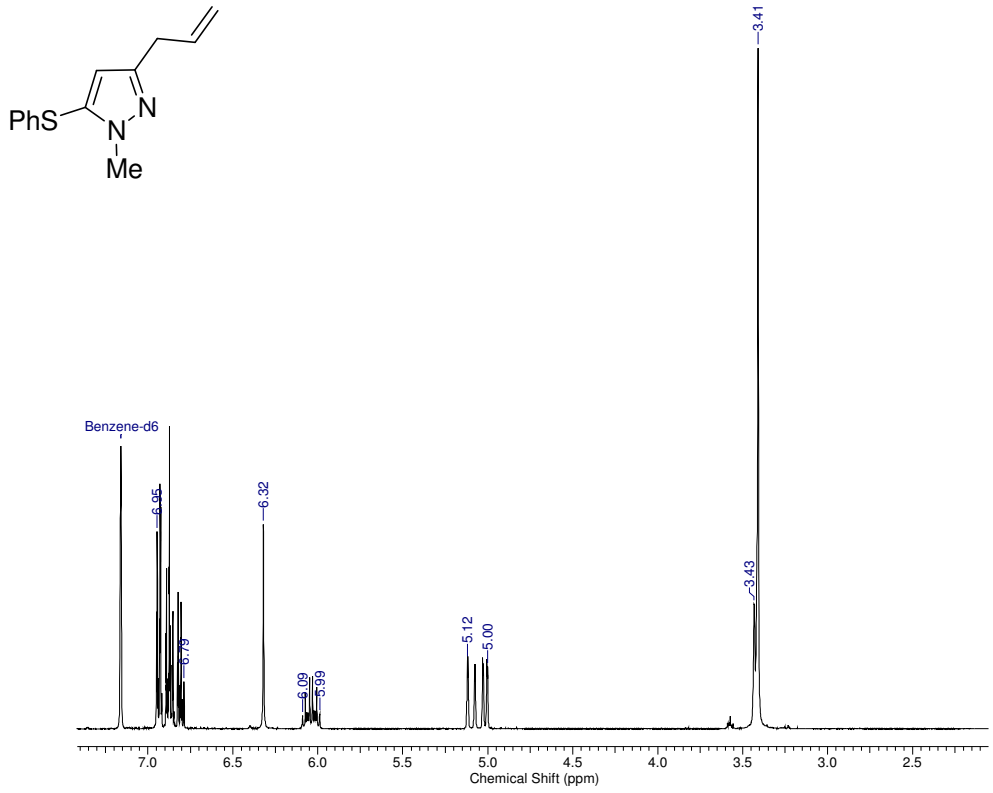


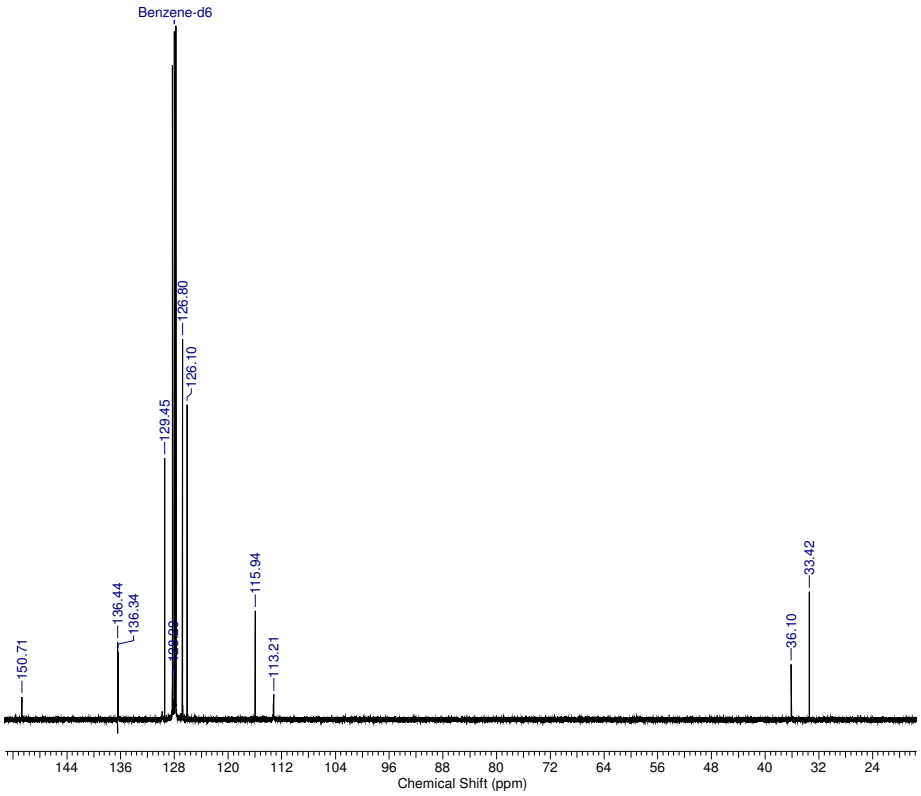
3-Chloro-1-methyl-5-(phenylthio)-1*H*-pyrazole (9b):



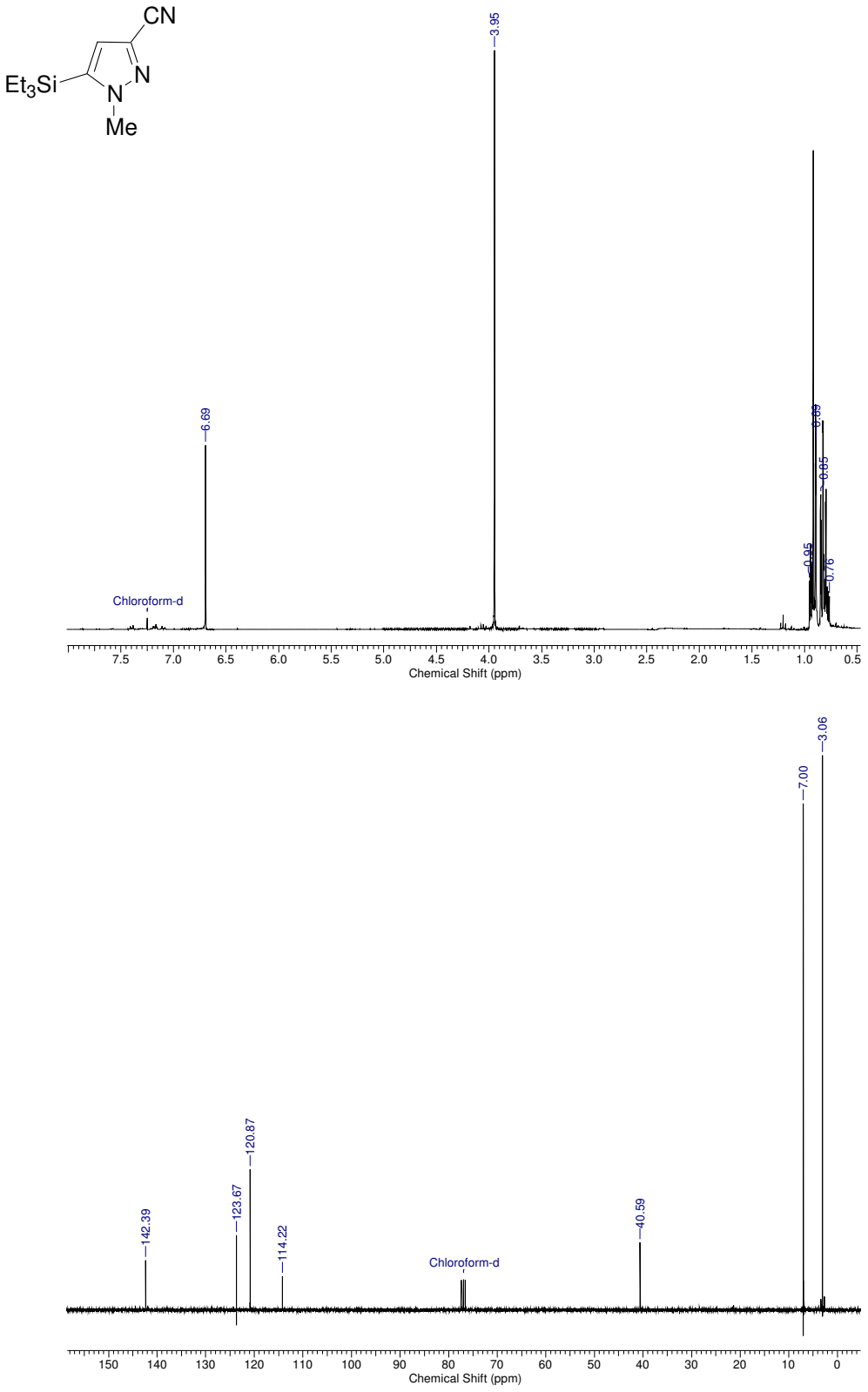


3-Allyl-1-methyl-5-(phenylthio)-1*H*-pyrazole (9c):

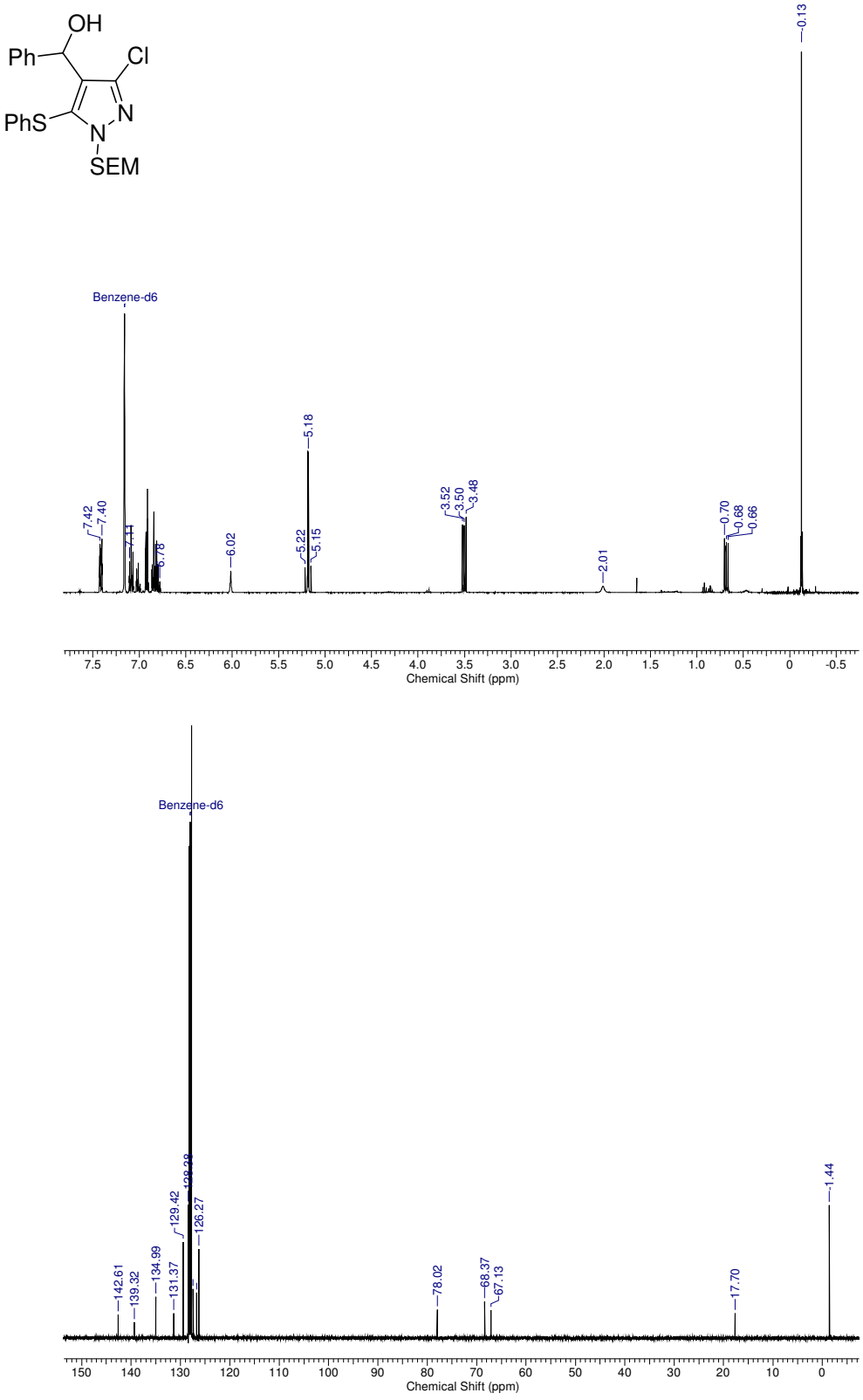




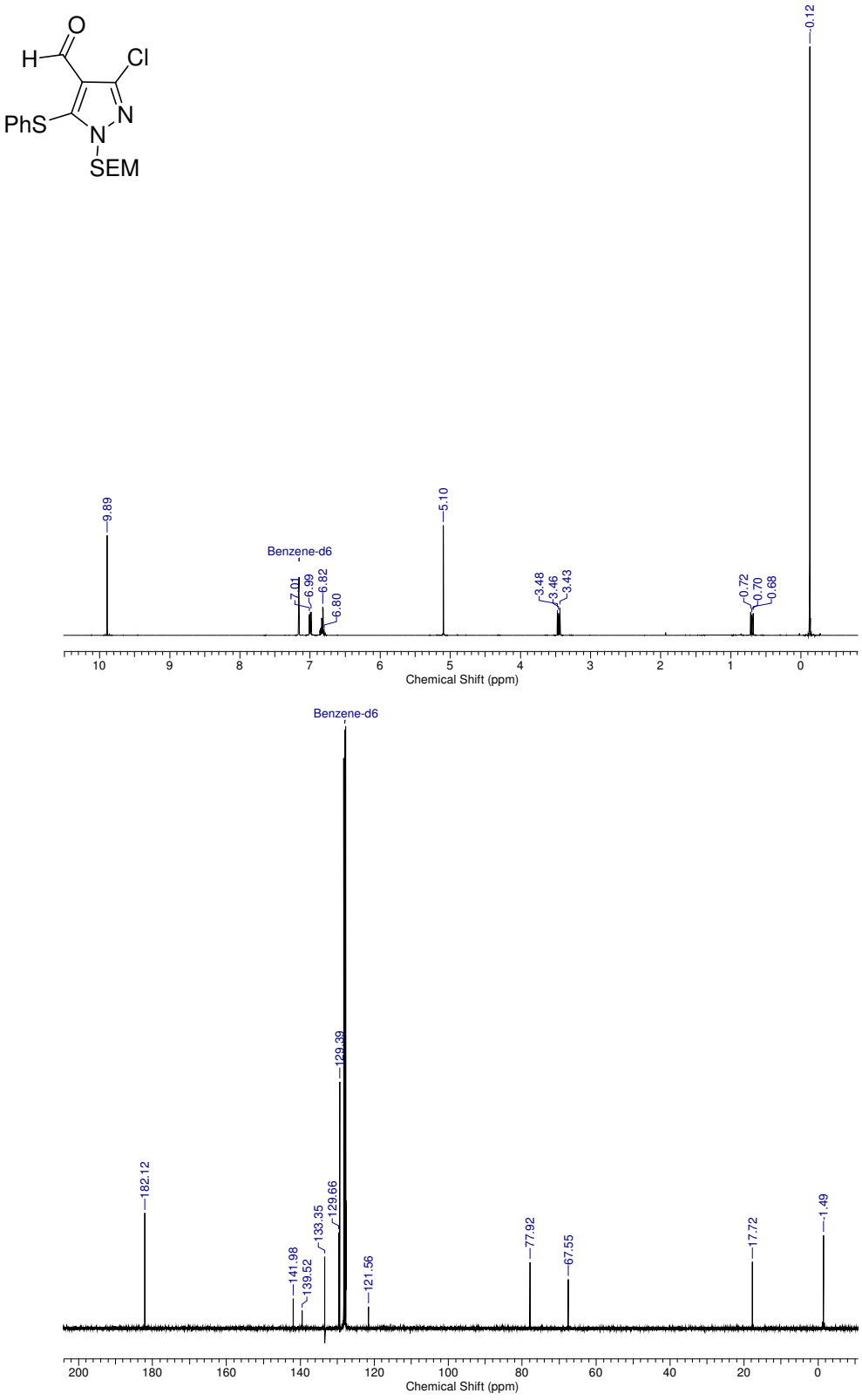
1-methyl-5-(triethylsilyl)-1*H*-pyrazole-3-carbonitrile (9d):



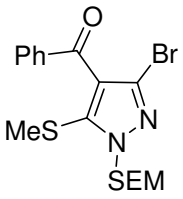
(3-chloro-5-(phenylthio)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-pyrazol-4-yl)(phenyl)methanol (10a):

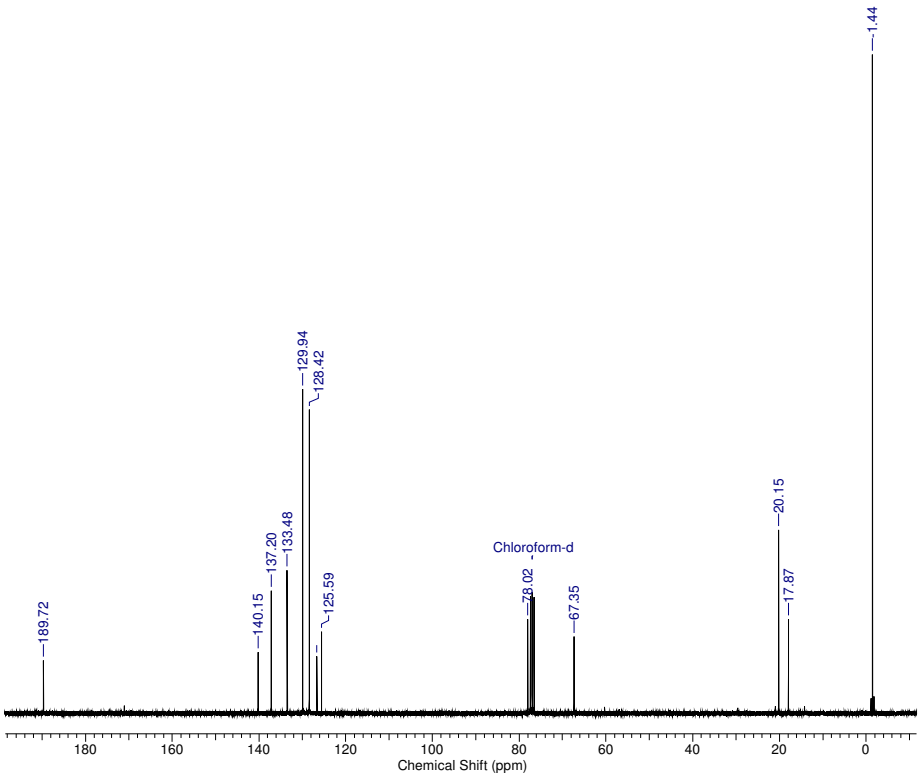


3-chloro-5-phenylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazole-4-carbaldehyde (10b):

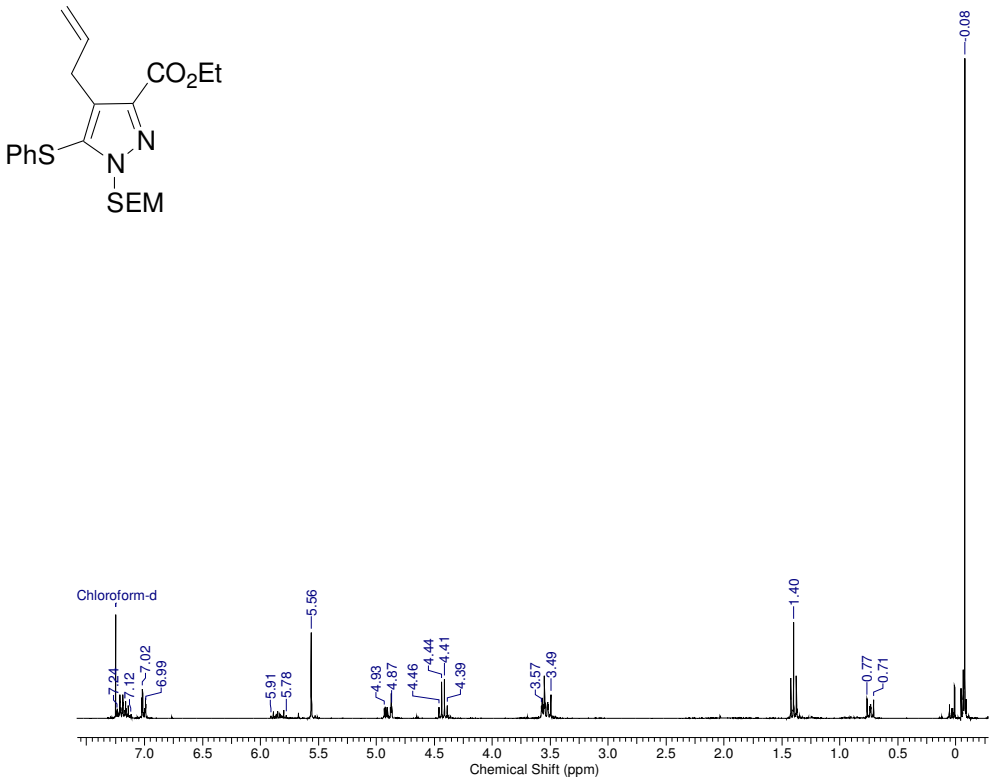


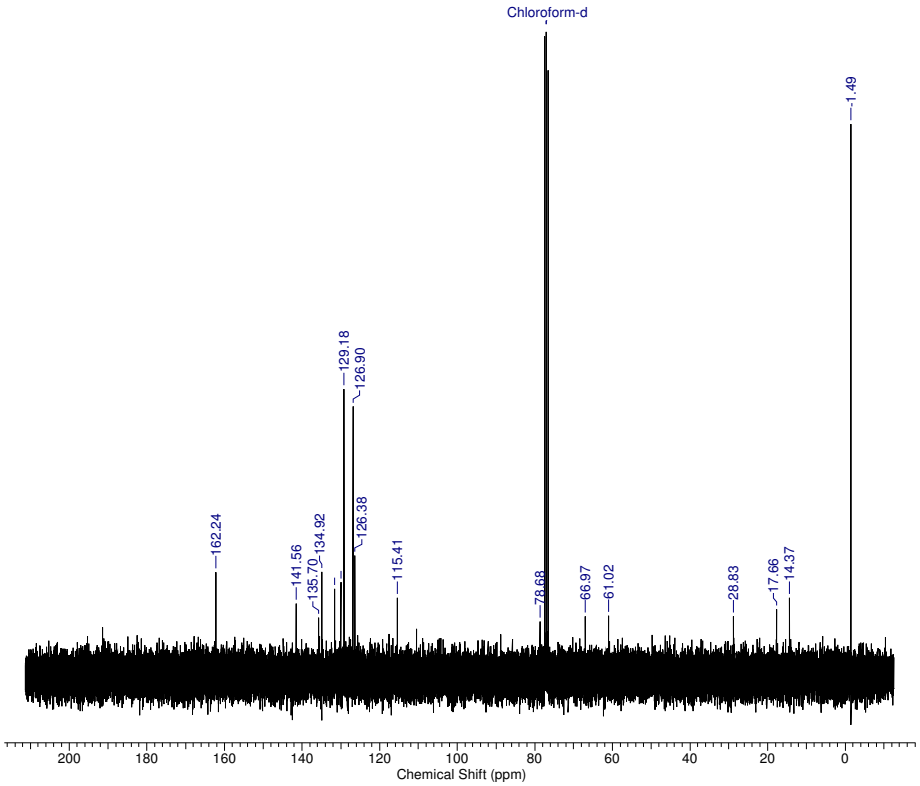
[3-bromo-5-methylsulfanyl-1-(2-trimethylsilanyl-ethoxymethyl)-1*H*-pyrazol-4-yl]-phenyl-methanone (10c):



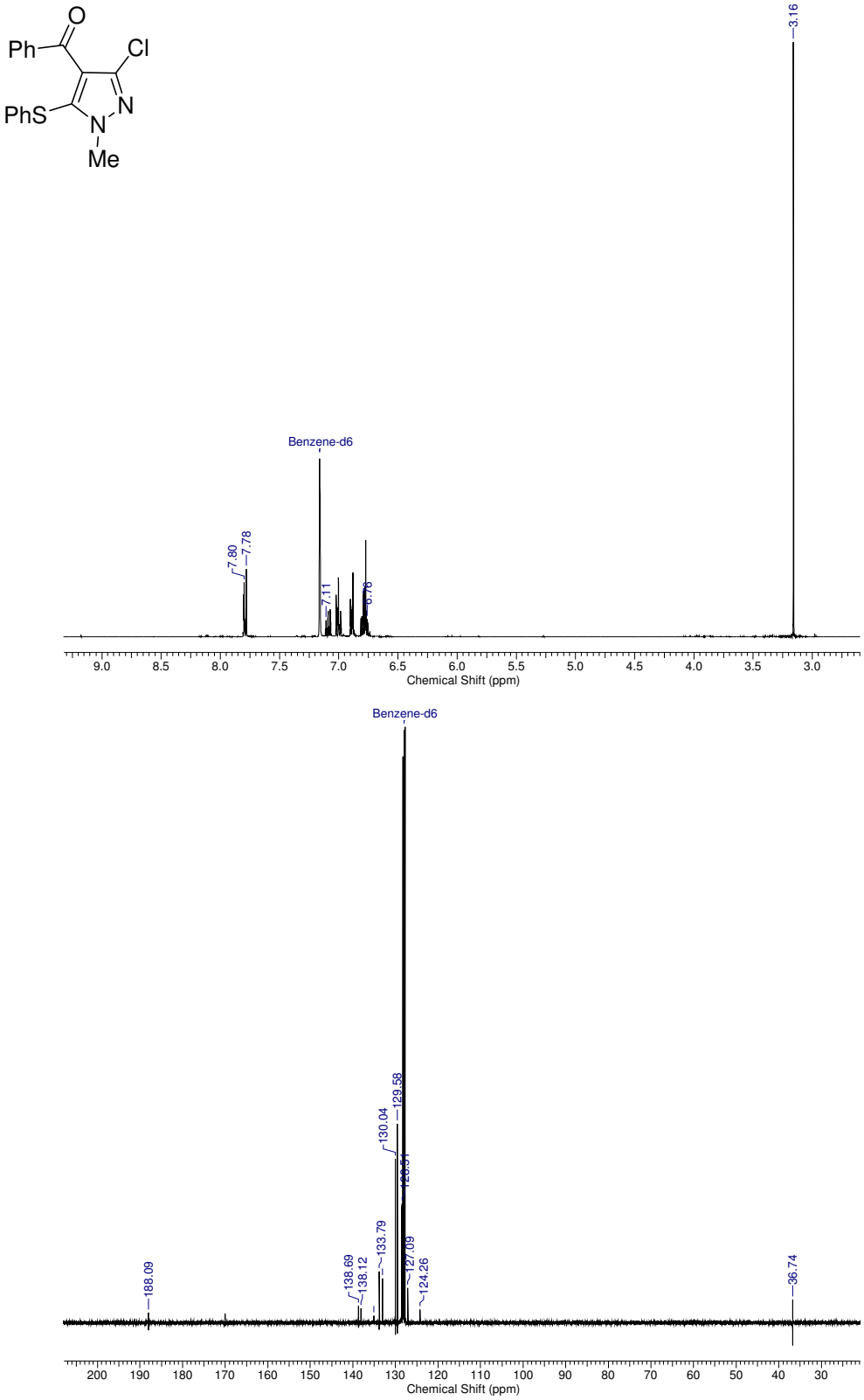


Ethyl 4-allyl-5-(phenylthio)-1-(2-trimethylsilylethoxymethyl)-1*H*-pyrazole-3-carboxylate (10d)

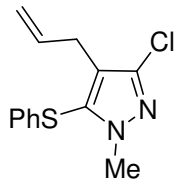


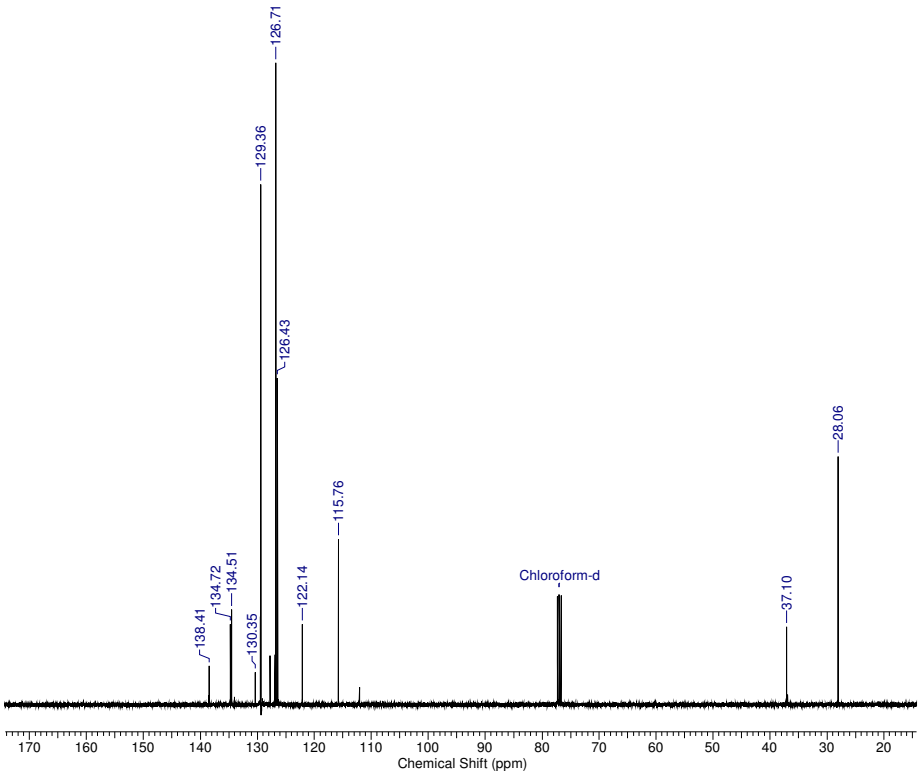


(3-chloro-1-methyl-5-phenylsulfanyl-1*H*-pyrazol-4-yl)-phenyl-methanone (11a):

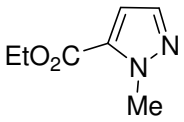


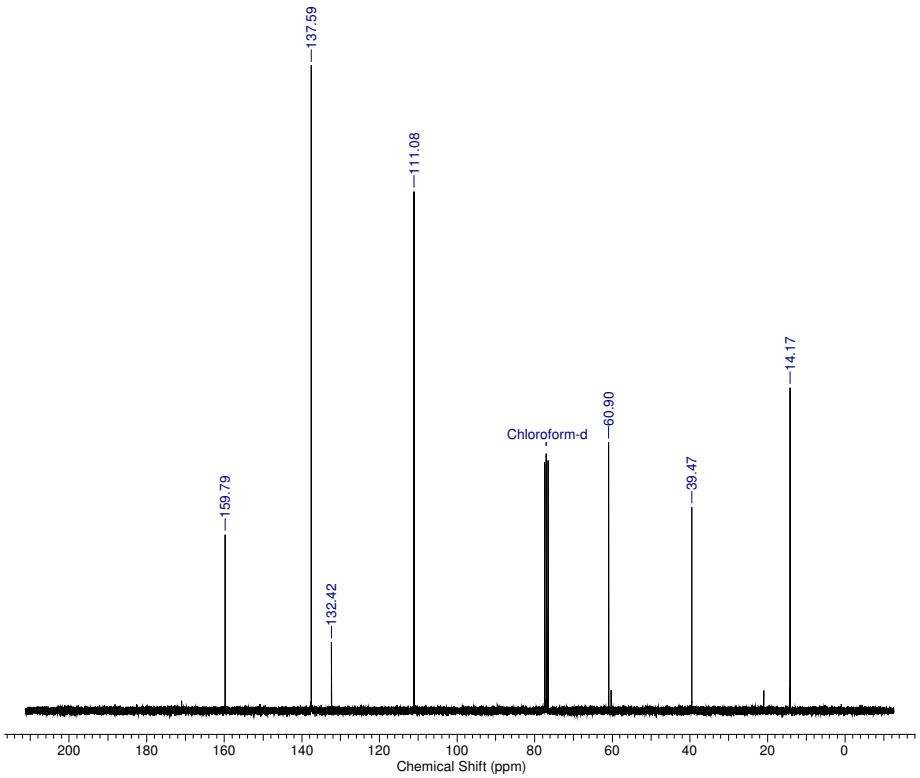
4-allyl-3-chloro-1-methyl-5-(phenylthio)-1*H*-pyrazole (11b):



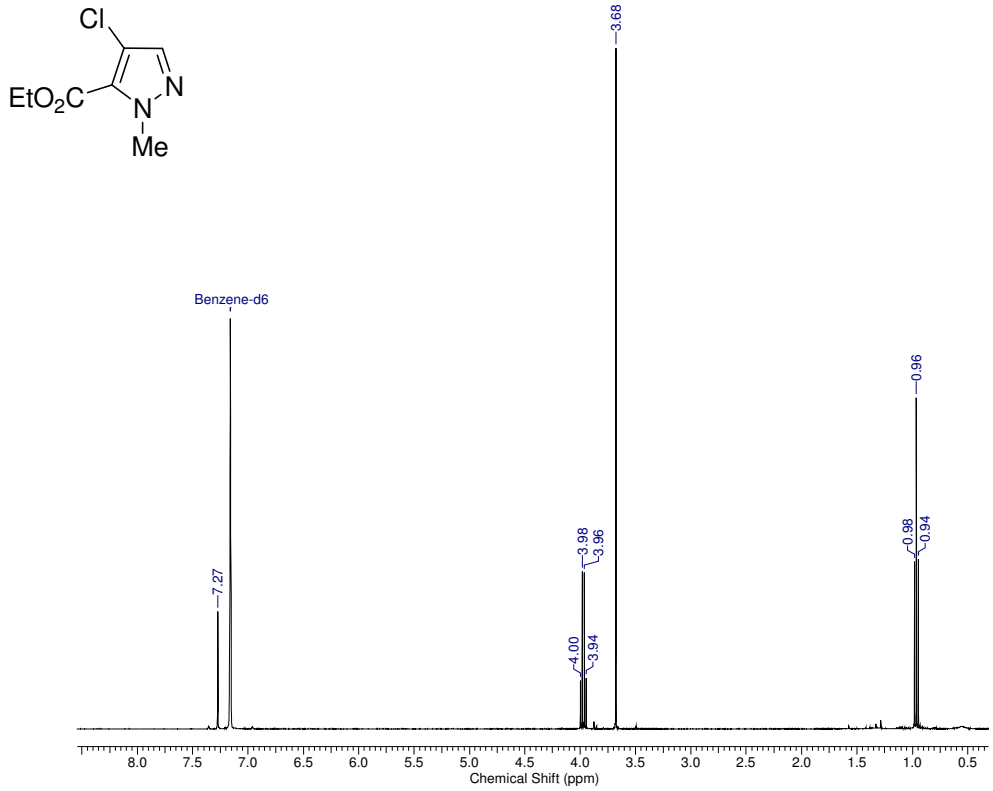


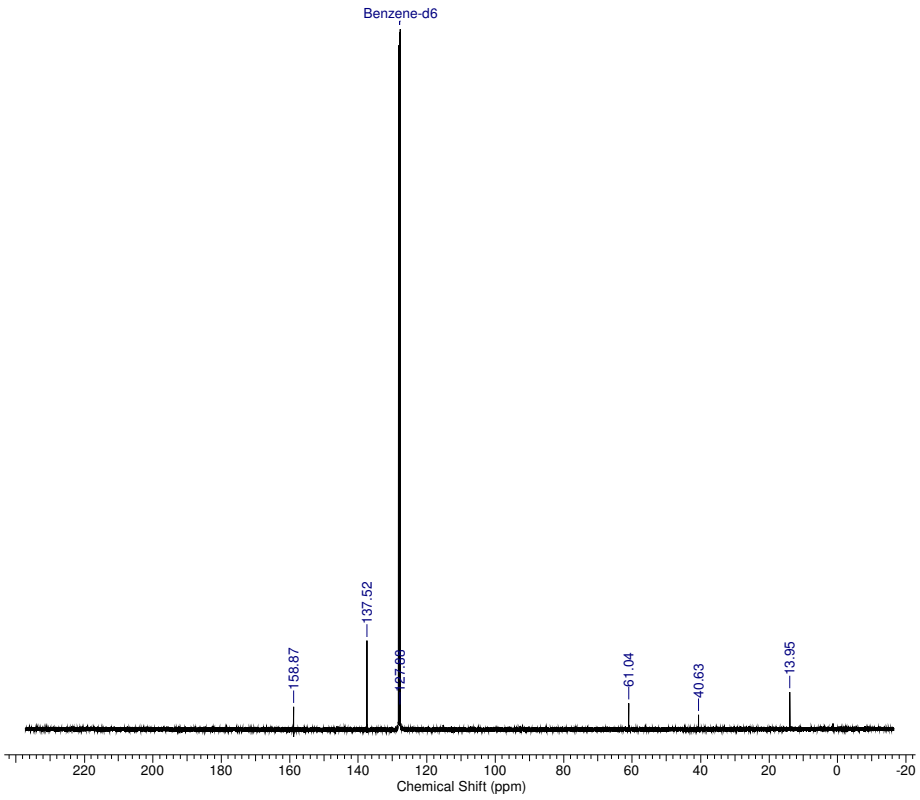
ethyl 1-methyl-1*H*-pyrazole-5-carboxylate (14):



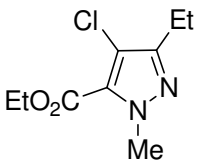


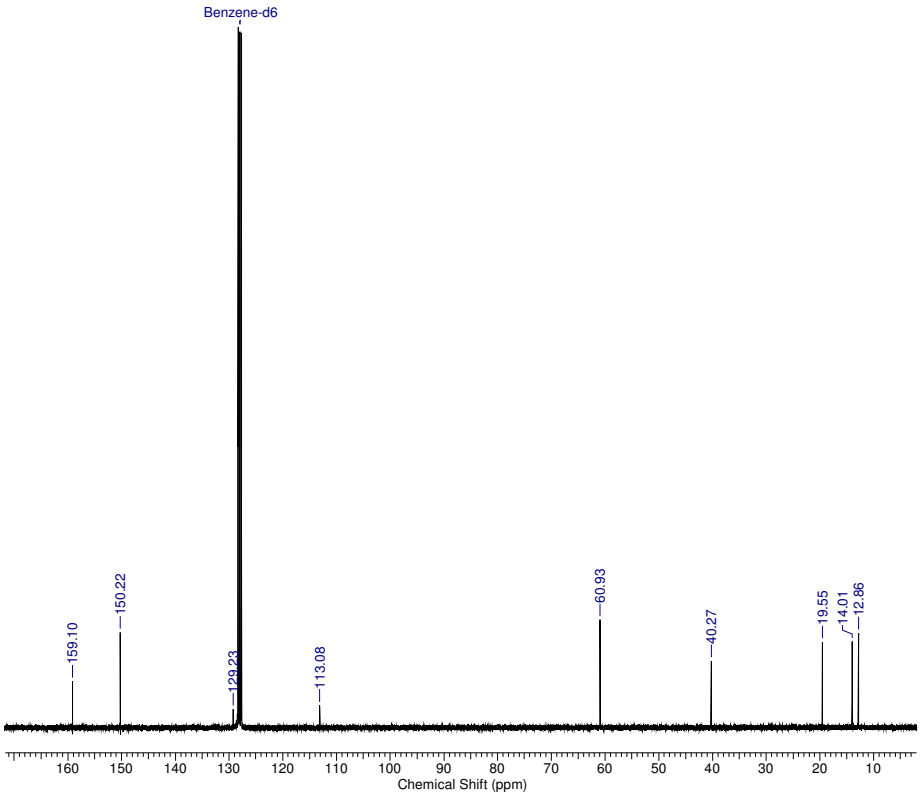
4-chloro-2-methyl-2*H*-pyrazole-3-carboxylic acid ethyl ester (15):





4-chloro-5-ethyl-2-methyl-2*H*-pyrazole-3-carboxylic acid ethyl ester (17):





4-chloro-5-ethyl-2-methyl-2*H*-pyrazole-3-carboxylic acid 4-tert-butyl-benzylamide (13):