Efficient Mono- and Bis-Functionalization of 3,6-Dichloropyridazine using (tmp)₂Zn·2MgCl₂·2LiCl **

Stefan H. Wunderlich and Paul Knochel*

Ludwig Maximilians-Universität München, Department Chemie & Biochemie
Butenandtstrasse 5-13, Haus F, 81377 München (Germany)
Fax: (+49) 089 21 80 776 80
e-mail: paul.knochel@cup.uni-muenchen.de

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 ¹H-NMR (25 °C) and capillary GC. NMR spectra were recorded on solutions in deuterated chloroform (CDCl₃) with residual chloroform (δ 7.24 ppm for ¹H NMR and δ 77.0 ppm for ¹³C NMR). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, brought. Column chromatography was performed using silica gel (0.040–0.063 mm, 230–400 mesh ASTM) from Merck if not indicated. TMPH and liquid acid chlorides were distilled prior to use.

Typical Procedure 1: Preparation of the reagent (tmp)₂Zn·2MgCl₂·2LiCl (1):
In an argon-flushed Schlenk-flask, ZnCl₂ (53.0 mmol, 7.22 g) was dried in vacuo at 140 °C for 4 h. After cooling to 25 °C, dry THF (25 mL) and freshly titrated tmpMgCl·LiCl [⁰] (100 mmol, 1.00 M, 100 mL) was added slowly. The resulting mixture was stirred for 15 h at 25 °C. The freshly prepared (tmp)₂Zn·2MgCl₂·2LiCl (1) solution was titrated prior to use at 0°C with benzoic acid using 4-(phenylazo)diphenylamine as indicator. A concentration of 0.40 M in THF was obtained.

Typical procedure for the preparation of the zincated 3-6-dichloropyridazine (3) using (tmp)₂Zn·2MgCl₂·2LiCl:
A dry and argon flushed 25-mL Schlenck-tube, equipped with a magnetic stirring bar was charged with a solution of 3-6-Dichloropyridazine (2, 298 mg, 2.0 mmol) in dry THF (5 mL).
The solution was cooled to -78 °C and (tmp)$_2$Zn·2MgCl$_2$·2LiCl (1; 0.4 M in THF, 3.0 mL, 1.2 mmol) was added dropwise. The resulting mixture was stirred for 2 h at -78 °C. The completion of the metalation was checked by GC-analysis of reaction aliquots quenched with a I$_2$ solution in dry THF. Compound 3 was obtained in >90% yield as determined by titration with I$_2$.

**Synthesis of 3,6-dichloro-4-iodo-pyridazine (4a)**

![Chemical structure of 3,6-dichloro-4-iodo-pyridazine](structure1)

To a solution of the zincated dichloropyridazine 3, iodine (761 mg, 3.00 mmol) dissolved in THF (6 mL) was added dropwise and stirred for 1 h at -78 °C. The reaction mixture was quenched with a mixture of a sat. aq. NH$_4$Cl solution (10 mL) and a sat. aq. Na$_2$S$_2$O$_3$ solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 5:1) furnished the compound 4a (451 mg, 82%) as a colourless solid. m.p.: 145.1–146.6 °C. $^1$H-NMR (CDCl$_3$, 300 MHz) δ: 8.06 (s, 1H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) δ: 159.7, 153.9, 139.7, 105.4. MS (70 eV, EI) m/z (%): 274 (95) [M$^+$], 127 (23), 123 (10), 121 (70), 119 (100), 86 (15), 84 (43), 49 (8). IR (ATR) ν (cm$^{-1}$): 3092, 3020, 1796, 1516, 1488, 1464, 1332, 1296, 1276, 1236, 1152, 1136, 1060, 1044, 992, 956, 900, 812, 764, 728, 672, 660, 628, 608, 588, 564. HRMS (EI) for C$_4$HCl$_2$IN$_2$ (273.8561): 273.8538.

**Synthesis of 2-(3,6-dichloro-pyridazin-4-ylmethyl)-acrylic acid ethyl ester (4b)**

![Chemical structure of 2-(3,6-dichloro-pyridazin-4-ylmethyl)-acrylic acid ethyl ester](structure2)

To a solution of the zincated dichloropyridazine 3, CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the reaction mixture was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) was added and stirred for 1 h at -78 °C. The reaction mixture was quenched with a sat. aq. NH$_4$Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was
evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 4:1) furnished the compound 4b (451 mg, 82%) as a pale yellow oil. $^1$H-NMR (CDCl$_3$, 600 MHz) δ: 7.39 (s, 1H), 6.45 (s, 1 H), 5.75 (s, 1 H), 4.18 (q, $J$=7.2 Hz, 2 H), 3.72 (s, 2 H), 1.25 (q, $J$=7.2 Hz, 3 H). $^{13}$C-NMR (CDCl$_3$, 150 MHz) δ: 165.5, 156.8, 155.9, 141.4, 134.7, 129.9, 129.8, 61.5, 34.8, 14.1. MS (70 eV, EI) m/z (%): 260 (7) [M$^+$], 227 (22), 225 (77), 217 (10), 215 (16), 199 (34), 198 (9), 197 (100), 198 (8) 187 (11), 123 (9), 63 (9). IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2982, 1709, 1632, 1566, 1464, 1464, 1406, 1359, 1319, 1294, 1276, 1255, 1206, 1172, 1132, 1100, 1048, 1023, 957, 938, 918, 872, 858, 817, 772, 747, 729, 684, 640, 633, 617, 610, 607, 597, 583, 580, 570, 566. HRMS (EI) for C$_{10}$H$_{10}$Cl$_2$N$_2$O$_2$ (260.0119): 260.0113.

Synthesis of (3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (4c)

To a solution of the zincated dichloropyridazine 3, CuCN-2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at -78 °C. The reaction mixture was slowly warmed to -20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH$_4$Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 3:1) furnished the compound 4c (368 mg, 73%) as a colourless solid. m.p.: 100.2-101.5 °C. $^1$H-NMR (CDCl$_3$, 600 MHz) δ: 7.78 (d, $J$=7.2 Hz, 2 H), 7.72 (t, $J$=7.6 Hz, 1 H), 7.56 (t, $J$=7.9 Hz, 2 H), 7.51 (s, 1 H). $^{13}$C-NMR (CDCl$_3$, 150 MHz) δ: 189.1, 156.2, 151.7, 140.0, 135.5, 134.0, 130.0, 129.3, 127.7. MS (70 eV, EI) m/z (%): 254 (23), 252 (38) [M$^+$], 106 (21), 105 (97), 77 (100), 51 (28). IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3069, 1665, 1632, 1614, 1590, 1574, 1501, 1487, 1444, 1338, 1324, 1306, 1289, 1257, 1247, 1239, 1222, 1173, 1167, 1155, 1134, 1103, 1070, 1052, 1024, 999, 988, 981, 968, 932, 902, 852, 821, 799, 756, 714, 699, 681, 653, 624, 612, 599, 587, 584, 579, 575, 559. HRMS (EI) for C$_{11}$H$_6$Cl$_1$N$_2$O$_2$ (251.9857): 251.9844.

Synthesis of (3,6-dichloro-pyridazin-4-yl)-furan-2-yl-methanone (4d)
To a solution of the zincated dichloropyridazine 3, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, 2-furoyl chloride (326 mg, 2.5 mmol) was added at -78 °C. The reaction mixture was slowly warmed to -20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 3:1) furnished the compound 4d (330 mg, 68%) as a colourless solid. m.p.: 135.6-136.8 °C. ¹H-NMR (CDCl₃, 300 MHz) δ: 7.74 (d, J=0.7 Hz, 1 H), 7.56 (s, 1 H), 7.33 (d, J=3.2 Hz, 1 H), 6.72 (dd, J=3.6, 1.5 Hz, 1 H). ¹³C-NMR (CDCl₃, 75 MHz) δ: 175.8, 156.1, 151.8, 150.5, 149.4, 138.5, 127.9, 122.4, 113.7. MS (70 eV, EI) m/z (%): 244 (62), 242 (94) [M⁺], 96 (18), 95 (100), 84 (13). IR (ATR) ν (cm⁻¹): 3113, 3041, 1657, 1623, 1558, 1505, 1462, 1391, 1353, 1319, 1282, 1243, 1203, 1190, 1183, 1165, 1149, 1119, 1081, 1040, 1034, 981, 931, 927, 911, 883, 872, 864, 802, 789, 778, 768, 740, 692, 683, 644, 641, 630, 620, 591, 570, 552. HRMS (EI) for C₉H₄Cl₂N₂O₂ (241.9650): 241.9658.

Synthesis of (3,6-dichloro-pyridazin-4-yl)-thiophen-2-yl-methanone (4e)

To a solution of the zincated dichloropyridazine 3, CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, 2-thiophene acid chloride (346 mg, 2.5 mmol) was added at -78 °C. The reaction mixture was slowly warmed to -20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 3:1) furnished the compound 4e (339 mg, 66%) as a colourless solid. m.p.: 158.1-159.8 °C. ¹H-NMR (CDCl₃, 600 MHz) δ: 7.94 (d, J=6.2 Hz 1 H), 7.55 (s, 1 H), 7.46 (d, J=3.8 Hz, 1 H), 7.21-7.24 (m, 1 H). ¹³C-NMR
(CDCl₃, 150 MHz) δ: 180.6, 156.1; 151.7, 141.1, 139.3, 138.1, 136.8, 129.1, 127.4. MS (70 eV, EI) m/z (%): 260 (66), 258 (99) [M⁺], 113 (23), 112 (28), 111 (100), 84 (12), 83 (25), 57 (9). IR (ATR) ν (cm⁻¹): 3116, 3069, 1630, 1597, 1561, 1507, 1501, 1419, 1402, 1364, 1355, 1343, 1325, 1312, 1270, 1256, 1230, 1206, 1197, 1180, 1142, 1105, 1072, 1054, 1040, 958, 934, 911, 863, 860, 853, 826, 807, 793, 757, 735, 693, 678, 655, 610, 593, 579, 574, 570, 563, 553. HRMS (EI) for C₉H₄Cl₂N₂O₅ (257.9421): 257.9414.

Synthesis of (3,6,3',6')-tetrachloro-[4,4']bipyridazinyl (4f)

To a solution of the zin cated dichloropyridazine 3, chloranil (290 mg, 1.2 mmol) dissolved in THF (9 mL) was added dropwise and the reaction mixture was stirred for 4 h at -78 °C. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 1:1) furnished the compound 4f (262 mg, 88%) as a colourless solid. m.p.: 164.5–166.5 °C. ¹H-NMR (CDCl₃, 300 MHz) δ: 7.56 (s, 2H). ¹³C-NMR (CDCl₃, 75 MHz) δ: 156.1, 153.3, 134.8, 129.6. MS (70 eV, EI) m/z (%): 296 (100) [M⁺], 295 (9), 294 (72), 233 (19), 231 (21), 208 (11), 206 (15), 205 (10), 203 (9), 198 (19), 197 (12), 196 (29), 195 (15), 145 (10), 143 (12), 118 (11), 108 (8), 84 (17). IR (ATR) ν (cm⁻¹): 3031, 1684, 1546, 1434, 1392, 1349, 1327, 1281, 1139, 903, 781, 753, 712, 632, 568. HRMS (EI) for C₈H₂Cl₂N₄ (293.9034): 293.9037.

Synthesis of 4-(3,6-dichloro-pyridazin-4-yl)-benzoic acid ethyl ester (4g)

To a solution of the zincated dichloropyridazine 3, Pd(dba)₂ (56 mg, 5 mol%) and P(o-furyl)₃ (46 mg, 10 mol%) dissolved in THF (4 mL) were then transferred via cannula to the reaction
mixture, followed by the addition of ethyl 4-iodobenzoate (607 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was allowed to warm up within 4 h to -20 °C. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated \textit{in vacuo}. Purification by flash-chromatography (n-pentane/diethyl ether, 4:1) furnished the compound 4g (481 mg, 81%) as a colourless solid. m.p.: 81.4-82.0 °C. 

\[ \text{1H-NMR (CDCl₃, 300 MHz)} \delta: 8.18 (ddd, J=8.6, 1.9, 1.7 Hz, 2 H), 7.56 (ddd, J=8.6, 1.9, 1.7 Hz, 2 H), 7.51 (s, 1 H), 4.42 (q, J=7.1 Hz, 2 H), 1.42 (t, J=7.0 Hz, 3 H). \]

\[ \text{13C-NMR (CDCl₃, 75 MHz)} \delta: 165.6, 156.1, 154.5, 141.8, 137.2, 132.2, 130.0, 129.5, 128.9, 61.5, 14.3. \]

\[ \text{MS (70 eV, EI) m/z (%): 298 (23), 296 (39) [M⁺], 270 (34), 268 (53), 255 (11), 254 (12), 253 (62), 252 (17), 251 (100), 188 (10), 153 (17), 126 (11).} \]

\[ \text{IR (ATR) ν (cm⁻¹): 3062, 3038, 2984, 2910, 1716, 1612, 1556, 1540, 1482, 1408, 1390, 1350, 1328, 1314, 1274, 1186, 1136, 1126, 1102, 1060, 1040, 1016, 980, 964, 924, 880, 858, 842, 772, 750, 720, 700, 668, 654, 638, 612, 590, 554. HRMS (EI) for C₁₃H₁₀Cl₂N₂O₂ (296.0119): 296.0118.} \]

\[ \text{Synthesis of 3,6-dichloro-4-(4-methoxy-phenyl)-pyridazine (4h)} \]

To a solution of the zincated dichloropyridazine 3, Pd(dba)₂ (56 mg, 5 mol%) and P(ο-furyl)₃ (46 mg, 10 mol%) dissolved in THF (4 mL) were then transferred \textit{via} cannula to the reaction mixture, followed by the addition of 1-iodo-4-methoxybenzene (500 mg, 2.2 mmol) dissolved in THF (2 mL). The reaction mixture was allowed to warm up within 4 h to -20 °C. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated \textit{in vacuo}. Purification by flash-chromatography (n-pentane/diethyl ether, 6:1) furnished the compound 4h (366 mg, 76%) as a colourless solid. m.p.: 106.5-107.9 °C. 

\[ \text{1H-NMR (DMSO, 400 MHz)} \delta: 8.06 (s, 1 H), 7.61 (ddd, J=9.4, 2.9, 2.5 Hz, 2 H), 7.10 (ddd, J=9.4, 2.9, 2.5 Hz, 2 H), 3.83 (s, 3 H). \]

\[ \text{13C-NMR (DMSO, 100 MHz)} \delta: 160.7, 155.6, 154.5, 142.19, 131.0, 130.2, 124.9, 141.4, 55.34. \]

\[ \text{MS (70 eV, EI) m/z (%): 256 (58), 255 (12), 254 (100) [M⁺], 213 (11), 210 (17), 166 (11), 156 (11) 114 (8). IR (ATR) ν (cm⁻¹): 3016, 2934, 2842, 1604, 1578, 1552, 1510, 1464, 1448, 1440, 1372, 1360, 1332, 1314, 1288, 1258, 1244,} \]
Synthesis of 3,6-dichloro-4-(3-nitro-phenyl)-pyridazine (4i)

To a solution of the zincated dichloropyridazine 3, Pd(dba)$_2$ (56 mg, 5 mol%) and P(o-furyl)$_3$ (46 mg, 10 mol%) dissolved in THF (4 mL) were then transferred via cannula to the reaction mixture, followed by the addition of 1-iodo-3-nitrobenzene (510 mg, 2.1 mmol) dissolved in THF (2 mL). The reaction mixture was allowed to warm up within 4 h to -20 °C. The reaction mixture was quenched with a sat. aq. NH$_4$Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 3:1) furnished the compound 4i (415 mg, 77%) as a pale yellow solid. m.p.: 174.0-175.2 °C. $^1$H-NMR (DMSO, 400 MHz) $\delta$: 8.52 (t, $J$=8.2 Hz, 1 H), 8.40 (ddd, $J$=8.4, 2.3, 1.1 Hz, 1 H), 8.27 (s, 1 H), 8.09 (dt, $J$=7.8, 1.4 Hz, 1 H), 7.85 (t, $J$=8.2 Hz, 1 H). $^{13}$C-NMR (DMSO, 100 MHz) $\delta$: 155.7, 154.2, 147.6, 140.5, 135.9, 134.5, 131.2, 124.7, 124.3. MS (70 eV, EI) m/z (%): 273 (10) 271 (60), 270 (11), 269 (100) [M$^+$], 241 (11), 195 (14), 160 (35), 153 (16), 126 (11). IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 3094, 3056, 1614, 1580, 1558, 1522, 1494, 1478, 1348, 1328, 1304, 1280, 1244, 1226, 1190, 1176, 1136, 1112, 1100, 1090, 1066, 1046, 1002, 942, 920, 904, 838, 814, 790, 758, 730, 686, 668, 626, 598, 562. HRMS (EI) for C$_{11}$H$_2$Cl$_2$N$_2$O (254.0014): 254.0007.

Synthesis of 3,6-dichloro-4,5-iodopyridazin (5a)

A dry and argon flushed 25-mL Schlenck-tube, equipped with a magnetic stirring bar was charged with a solution of 6-dichloro-4-iodo-pyridazine (4a, 550 mg, 2.0 mmol) in dry THF (5 mL). The solution was cooled to -78 °C and (tmp)$_2$Zn·2MgCl$_2$·2LiCl (1; 0.4 M in THF,
3.00 mL, 1.2 mmol) was added dropwise and the resulting mixture was stirred for 3 h at -78 °C. Iodine (761 mg, 3.00 mmol) dissolved in THF (6 mL) was added dropwise and stirred for 1 h at -78 °C. The reaction mixture was quenched with mixture of a sat. aq. NH₄Cl solution (10 mL) and a sat. aq. Na₂S₂O₃ solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. Recrystallisation (CH₂Cl₂) furnished the compound 5a (448 mg, 56%) as a colourless solid. m.p.: 193.8 °C (decomposition). \( ^{1} \text{H-NMR (CDCl₃, 400 MHz) \delta: } \). \( ^{13} \text{C-NMR (CDCl₃, 100 MHz,)} \delta: \) 157.8, 124.8. MS (70 eV, EI) m/z (%): 400 (100) [M⁺], 254 (11), 247 (16), 245 (25), 237 (14), 236 (10), 126 (21), 120 (50), 118 (67), 83 (13). IR (ATR) \( \nu \) (cm⁻¹): 3092, 1516, 1488, 1464, 1332, 1296, 1276, 1236, 1152, 1136, 1060, 1044, 992, 956, 900, 812, 764, 728, 672, 660, 628, 608, 564. HRMS (EI) for C₄Cl₂I₂N₂ (399.7528): 399.7518.

**Synthesis of (5-benzoyl-3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (5b)**

A dry and argon flushed 25-mL Schlenck-tube, equipped with a magnetic stirring bar was charged with a solution of (3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (4c; 504 mg, 2.0 mmol) in dry THF (5 mL). The solution was cooled to -78 °C and (tmp)₂Zn·2MgCl₂·2LiCl (I; 0.4 M in THF, 3.00 mL, 1.2 mmol) was added dropwise and the resulting mixture was stirred for 3 h at -78 °C. CuCN·2LiCl (1.0 M solution in THF, 2.2 mL, 2.2 mmol) was added and the reaction mixture was stirred for 30 min. Then, benzoyl chloride (353 mg, 2.5 mmol) was added at -78 °C. The reaction mixture was slowly warmed to -20 °C and stirred at this temperature for 16 h. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 1:1) furnished the compound 5b (548 mg, 77%) as a pale yellow solid. m.p.: 166.8-168.3 °C. \( ^{1} \text{H-NMR (CDCl₃, 300 MHz) \delta: } \) 7.63-7.73 (m, 6 H), 7.46-7.51 (m, 4 H). \( ^{13} \text{C-NMR (CDCl₃, 75 MHz,)} \delta: \) 188.9, 152.0, 138.1, 135.5, 134.3, 129.9, 129.1. MS (70 eV, EI) m/z (%): 356 (7) [M⁺], 105 (100), 77 (26). IR (ATR) \( \nu \) (cm⁻¹): 1668, 1594, 1580, 1450, 1336, 1318, 1258, 1180, 1166, 1150, 1002, 990, 962, 852, 812, 798, 754, 714, 700, 680, 668, 628, 614, 566. HRMS (EI) for C₁₅H₁₂Cl₂N₂O₂ (356.0119): 356.0114.
Synthesis of 2-[3,6-dichloro-5-(furan-2-carbonyl)-pyridazin-4-ylmethyl]-acrylic acid ethyl ester (5c)

A dry and argon flushed 25-mL Schlenck-tube, equipped with a magnetic stirring bar was charged with a solution of (3,6-dichloro-pyridazin-4-yl)-furan-2-yl-methanone (4d; 486 mg, 2.0 mmol) in dry THF (5 mL). The solution was cooled to -78 °C and (tmp)₂Zn·2MgCl₂·2LiCl (I; 0.4 M in THF, 3.00 mL, 1.2 mmol) was added dropwise and the resulting mixture was stirred for 3 h at -78 °C. CuCN·2LiCl (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the reaction mixture was stirred for 5 min. Then, ethyl 2-(bromomethyl)acrylate (483 mg, 2.5 mmol) was added and stirred for 1 h at -78 °C. The reaction mixture was quenched with a sat. aq. NH₄Cl solution (10 mL), extracted with diethyl ether (5 × 20 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (n-pentane/diethyl ether, 2:1) furnished the compound 5c (534 mg, 75%) as a pale yellow solid. m.p.: 129.8-131.0 °C. ¹H-NMR (CDCl₃, 300 MHz) δ: 7.67 (d, \(J=2.4\) Hz, 1 H), 7.28 (d, \(J=3.4\) Hz, 1 H), 6.65-6.67 (m, 1 H), 6.22 (t, \(J=1.3\) Hz, 1 H), 5.24 (t, \(J=1.7\) Hz, 1 H), 4.16 (q, \(J=7.3\) Hz, 2 H), 3.58-3.85 (m, 2 H), 1.25 (t, \(J=7.0\) Hz, 4 H). ¹³C-NMR (CDCl₃, 75 MHz) δ: 165.3, 158.0, 151.6, 150.9, 149.1, 138.8, 138.2, 134.2, 127.9, 127.8, 113.7, 61.4, 32.0, 14.1. MS (70 eV, EI) m/z (%): 354 (1) [M⁺], 285 (11), 284 (10), 283 (62), 282 (22), 281 (100), 256 (13), 255 (12), 254 (17), 95 (71), 81 (25). IR (ATR) \(\nu\) (cm⁻¹): 1668, 1594, 1580, 1450, 1336, 1318, 1258, 1180, 1166, 1150, 1002, 990, 962, 852, 812, 798, 754, 714, 700, 680, 668, 628, 614, 566. HRMS (EI) for C₁₈H₁₀Cl₂N₂O₂ (354.0174): 354.0170.

Synthesis of 5-chloro-3-phenyl-1H-pyrazolo[3,4-c]pyridazin (6a)

A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (4c; 504 mg, 2.0 mmol) in EtOH (25 mL). N₂H₄·H₂O (0.6 mL, 6 mmol) was added in one portion and the resulting
mixture was refluxed for 30 min. After cooling to 25 °C CH₂Cl₂ (100 mL) was added and the organic layer was washed with water (3 x 30 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. The residue was recrystallised from MeOH giving 6a as a yellow solid (305 mg, 66%). m.p.: 255.6-256.6 °C. \( ^1H \text{-NMR} (\text{DMSO, 400 MHz}) \delta: 8.71 (s, 1 H), 8.04-8.09 (m, 2 H), 7.48, 7.54 (m, 2 H), 7.41-7.47 (m, 1 H). \( ^{13}\text{C-NMR} (\text{DMSO, 100 MHz}) \delta: 155.4, 147.4, 142.5, 131.2, 129.2, 129.1, 126.6, 120.5, 116.0. MS (70 eV, EI) m/z (%): 232 (26), 231 (11), 230 (100) [M⁺], 140 (18), 113 (15), 77 (8). IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)): 3093, 2993, 2974, 2918, 2893, 2841, 1587, 1510, 1457, 1433, 1394, 1382, 1362, 1287, 1258, 1194, 1177, 1145, 1083, 1068, 1037, 1030, 1004, 992, 932, 910, 879, 865, 832, 801, 786, 776, 756, 688, 676, 620, 604, 593, 584, 579, 575, 571, 559. HRMS (EI) for C\(_{11}\)H\(_7\)ClN\(_4\) (230.0359): 230.0339.

Synthesis of 5-chloro-3-furan-2-yl-1H-pyrazolo[3,4-c]pyridazine (6b)

A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension (3,6-dichloro-pyridazin-4-yl)-furan-2-yl-methanone (4d; 486 mg, 2.0 mmol) in EtOH (25 mL). N\(_2\)H\(_4\)·H\(_2\)O (0.6 mL, 6 mmol) was added in one portion and the resulting mixture was refluxed for 30 min. After cooling to 25 °C CH₂Cl₂ (100 mL) was added and the organic layer was washed with water (3 x 30 mL) and dried over anhydrous MgSO₄. After filtration, the solvent was evaporated in vacuo. The residue was recrystallised from MeOH giving 6b as a yellow solid (328 mg, 75%). m.p.: 256.8-257.5 °C. \( ^1H \text{-NMR} (\text{DMSO, 400 MHz}) \delta: 8.63 (s, 1 H), 7.86-7.92 (m, 1 H), 7.31 (d, \( J=3.5 \) Hz, 1 H), 6.72 (dd, \( J=3.2, 1.6 \) Hz, 1 H). \( ^{13}\text{C-NMR} (\text{DMSO, 100 MHz}) \delta: 154.9, 147.4, 145.9, 143.9, 135.2, 120.0, 115.3, 112.0, 109.2. MS (70 eV, EI) m/z (%): . IR (ATR) \( \tilde{\nu} \) (cm\(^{-1}\)): 3132, 3108, 3092, 3000, 2958, 2906, 2852, 1584, 1524, 1512, 1496, 1460, 1416, 1378, 1370, 1330, 1284, 1264, 1224, 1200, 1180, 1164, 1144, 1126, 1102, 1074, 1034, 1010, 968, 936, 900, 882, 844, 820, 798, 774, 738, 688, 668, 648, 624, 592, 570, 558. HRMS (EI) for C\(_9\)H\(_5\)ClN\(_4\)O (220.0152): 220.0139.

Synthesis of 3-chloro-5-phenyl-thieno[2,3-c]pyridazine-6-carboxylic acid methyl ester (7a)
A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension of (3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (4c; 504 mg, 2.0 mmol) in MeOH (25 mL). HSCH$_2$CO$_2$Me (265 mg, 2.5 mmol) and NEt$_3$ (500 mg, 5 mmol) were added in one portion and the resulting mixture was refluxed for 6 h. After cooling to 25 °C, CH$_2$Cl$_2$ (100 mL) was added and the organic layer was washed with water (3 x 30 mL) and NaOH (2 M, 30 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was evaporated in vacuo. The residue was recrystallised from MeOH giving 7a as a pale yellow solid (482 mg, 79%). m.p: 160.0-161.1 °C. $^1$H-NMR (CDCl$_3$, 600 MHz) $\delta$: 7.62 (s, 1 H), 7.50-7.55 (m, 3 H), 7.36 (dd, $J$=7.4, 2.1 Hz, 2 H), 3.85 (s, 3 H). $^{13}$C-NMR (CDCl$_3$, 150 MHz) $\delta$: 163.3, 161.5, 152.6, 139.5, 137.4, 135.9, 131.2, 129.4, 129.4, 128.7, 122.1, 53.1. MS (70 eV, EI) m/z (%): 306 (42), 305 (1), 304 (100) [M$^+$], 272 (22), 244 (27), 217 (21), 215 (46), 182 (25), 138 (12), 43 (16). IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): 2950, 1698, 1658, 1554, 1498, 1486, 1448, 1432, 1378, 1330, 1304, 1284, 1244, 1198, 1178, 1140, 1114, 1078, 1054, 1030, 998, 978, 918, 902, 864, 814, 778, 766, 742, 704, 676, 658, 622, 614, 592, 566, 560. HRMS (EI) for C$_{14}$H$_9$ClN$_2$O$_2$S (304.0073): 304.0060.

**Synthesis of 3-chloro-5-furan-2-yl-thieno[2,3-c]pyridazine-6-carboxylic acid methyl ester (7b)**

A 50-mL round bottom flask, equipped with a magnetic stirring bar was charged with a suspension (3,6-dichloro-pyridazin-4-yl)-furan-2-yl-methanone (4d; 486 mg, 2.0 mmol) in MeOH (25 mL). HSCH$_2$CO$_2$Me (265 mg, 2.5 mmol) and NEt$_3$ (500 mg, 5 mmol) were added in one portion and the resulting mixture was refluxed for 6 h. After cooling to 25 °C, CH$_2$Cl$_2$ (100 mL) was added and the organic layer was washed with water (3 x 30 mL) and NaOH (2 M, 30 mL) and dried over anhydrous MgSO$_4$. After filtration, the solvent was evaporated in vacuo. The residue was recrystallised from MeOH giving 7b as a pale yellow solid (500 mg, 85%). m.p.: 159.2-160.3 °C. $^1$H-NMR (CDCl$_3$, 300 MHz) $\delta$: 8.40 (s, 1 H), 7.67 (d, $J$=1.5 Hz,
1 H), 7.38 (d, J=3.4 Hz, 1 H), 6.64 (dd, J=3.5, 1.8 Hz, 1 H), 3.98 (s, 3 H). $^{13}$C-NMR (CDCl$_3$, 75 MHz) $\delta$: 162.8, 161.4, 152.7, 146.0, 143.7, 135.7, 133.2, 127.5, 123.9, 115.4, 112.1, 53.3. MS (70 eV, EI) m/z (%): . IR (ATR) $\tilde{\nu}$ (cm$^{-1}$): . HRMS (EI) for C$_{12}$H$_7$ClN$_2$O$_3$S (293.9866): 293.9873.

Reference:

3,6-Dichloro-4-iodo-pyridazine (4a)
2-(3,6-Dichloro-pyridazin-4-ylmethyl)-acrylic acid ethyl ester (4b)
(3,6-Dichloro-pyridazin-4-yl)-phenyl-methanone (4c)
(3,6-Dichloro-pyridazin-4-yl)-furan-2-yl-methanone (4d)
(3,6-Dichloro-pyridazin-4-yl)-thiophen-2-yl-methanone (4e)
(3,6,3',6')-Tetrachloro-[4,4']bipyridazinyl (4f)
4-(3,6-Dichloro-pyridazin-4-yl)-benzoic acid ethyl ester (4g)
3,6-Dichloro-4-(4-methoxy-phenyl)-pyridazine (4h)
3,6-Dichloro-4-(3-nitro-phenyl)-pyridazine (4i)
3,6-Dichlor-4,5-iodpyridazin (5a)
(5-Benzoyl-3,6-dichloro-pyridazin-4-yl)-phenyl-methanone (5b)
2-[3,6-Dichloro-5-(furan-2-carbonyl)-pyridazin-4-ylmethyl]-acrylic acid ethyl ester (5c)

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**Supplementary Material (ESI) for Chemical Communications**

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5-Chloro-3-phenyl-1H-pyrazolo[3,4-c]pyridazine (6a)
5-Chloro-3-furan-2-yl-1H-pyrazolo[3,4-c]pyridazine (6b)
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