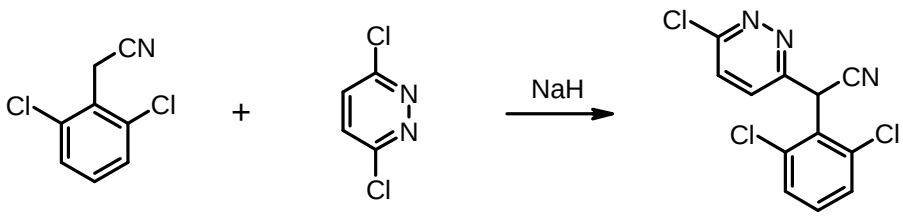
6-Chloro-α-(2,6-dichlorophenyl)pyridazine-3-acetonitrile (MT-521)



$C_8H_5Cl_2N$
186.04 g/mol

$C_4H_2Cl_2N_2$
148.98 g/mol

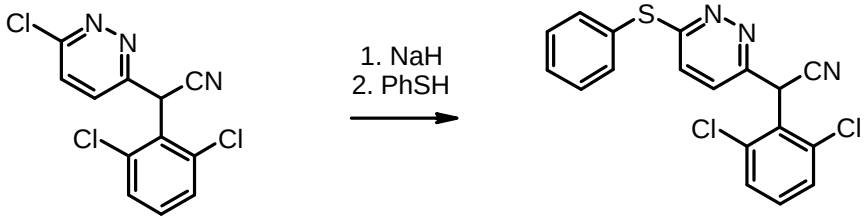
$C_{12}H_6Cl_3N_3$
298.56 g/mol

Sodium hydride (4.06 g, 84.5 mmol, 55% dispersion in mineral oil) was washed with anhydrous light petroleum (3 x 35 mL) and suspended in anhydrous THF (30 mL). 2,6-Dichlorobenzeneacetonitrile (13.1 g, 70.4 mmol) in anhydrous THF (50 mL) was added at RT and stirred for 30 min. at this temperature. 3,6-Dichloropyridazine in anhydrous THF (50 mL) was added at RT and stirred for 30 min. Saturated ammonium chloride solution (350 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 x 75 mL), the combined organic layers were washed with water (2 x 400 mL) and brine (1 x 400 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was dissolved in anhydrous EtOH (150 mL) and crystallized at – 20 °C for 48 h.

Yield: red crystals (8.70 g, 43%, Lit.: 28%).

The absence of signals of the benzylic proton and the complex peak pattern prove the formation of at least two tautomeric species of **MT-521**.

α-(2,6-Dichlorophenyl)-6-phenylthiopyridazine-3-acetonitrile (MT-522)



$C_{12}H_6Cl_3N_3$
298.56 g/mol

$C_{18}H_{11}Cl_2N_3S$
372.28 g/mol

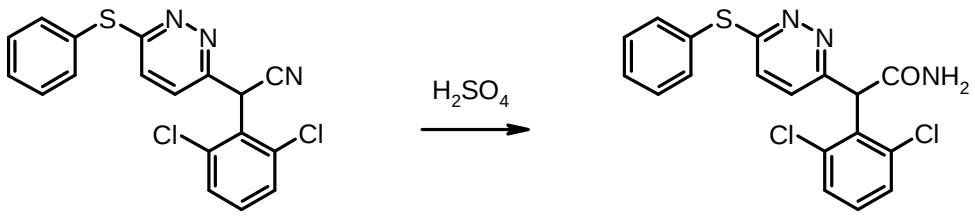
Sodium hydride (1.23 g, 28.1 mmol, 55% dispersion in mineral oil) was washed with anhydrous light petroleum (3 x 25 mL) and suspended in anhydrous DMF (10 mL). Thiophenol (3.10 g, 28.1 mmol) in anhydrous DMF (10 mL) was added at RT and stirred for

10 min. 6-Chloro-α-(2,6-dichlorophenyl)pyridazine-3-acetonitrile (8.00 g, 26.8 mmol) in anhydrous DMF (20 mL) was added at RT and stirred for 45 min. at 100 °C. The solution was cooled and partitioned between water (1000 mL) and EtOAc (200 mL). The aqueous layer was extracted with EtOAc (5 x 75 mL), the combined organic layers were washed with water (5 x 400 mL), 1 N NaOH (2 x 250 mL) and brine (1 x 500 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was crystallized from anhydrous EtOH (50 mL).

Yield: orange crystals (7.15 g, 72%, Lit.: 91%)

The absence of signals of the benzylic proton and the complex peak pattern prove the formation of at least two tautomeric species of **MT-522**.

a-**(2,6-Dichlorophenyl)-6-phenylthiopyridazine-3-acetamide (MT-523)**



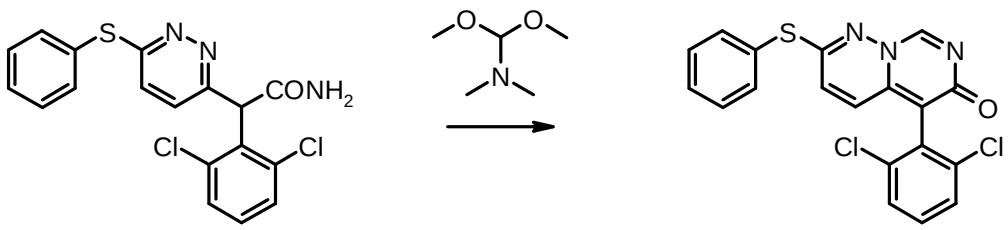
$C_{18}H_{11}Cl_2N_3S$
372.28 g/mol

$C_{18}H_{13}Cl_2N_3OS$
390.29 g/mol

α-(2,6-Dichlorophenyl)-6-phenylthiopyridazine-3-acetonitrile (6.50 g, 14.8 mmol) was stirred in concentrated H_2SO_4 (200 mL) at 100 °C for 75 min. The solution was cooled to RT, poured into cold water (4000 mL) and stirred for 10 min. The precipitate was filtered, washed with water (6 x 100 mL), dissolved in MeOH (25 mL)/EtOAc (100 mL), dried (Na_2SO_4), filtered, concentrated *in vacuo* and triturated with iPr_2O.

Yield: orange crystals (3.70 g, 64%, Lit.: 85%).

5-(2,6-Dichlorophenyl)-2-(phenylthio)-6H-pyrimido[1,6-b]pyridazin-6-one (MT-524)



$C_{18}H_{13}Cl_2N_3OS$
390.29 g/mol

$C_{19}H_{11}Cl_2N_3OS$
400.29 g/mol

α-(2,6-Dichlorophenyl)-6-phenylthiopyridazine-3-acetamide (3.40 g, 8.71 mmol) and N,N-dimethylformamide dimethyl acetal (2.51 g, 18.9 mmol) in anhydrous toluene (60 mL) were stirred at 100 °C for 2 h. The solution was stirred at RT for additional 2 h, and the precipitate was collected by suction filtration and washed with toluene (2 x 50 mL) and light petroleum (4 x 50 mL). The crude product was dissolved in hot AcOH (10 mL), then water (30 mL) was added dropwise, and the suspension was stirred at RT for 1 h. The precipitate was filtered off and washed with water (5 x 20 mL), iPrOH (3 x 20 mL) and iPr_2O (3 x 20 mL) and dried (50 °C/50 mbar).

Yield: yellow crystals (1.45 g, 41%, Lit.: ~ 10%); m. p.: 262 – 265 °C; microelemental analysis (JOS 1819): calcd. C, 57.01; H, 2.77; N, 10.50; found: C, 56.73; H, 2.97; N, 10.22; purity: > 99.5% (HPLC); ^{1}H NMR (CF_3COOD) δ 10.00 (s, 1H), 8.33 – 8.09 (m, 8H), 8.04 (s, 2H).