PYRIDAZINES, 88.[1] ON THE ATTACK OF *S*-NUCLEOPHILES AT 3,6-DISUBSTITUTED *N*-METHYL-*N*-PHENYLPYRIDAZINE-4-CARBOXAMIDE[¤]

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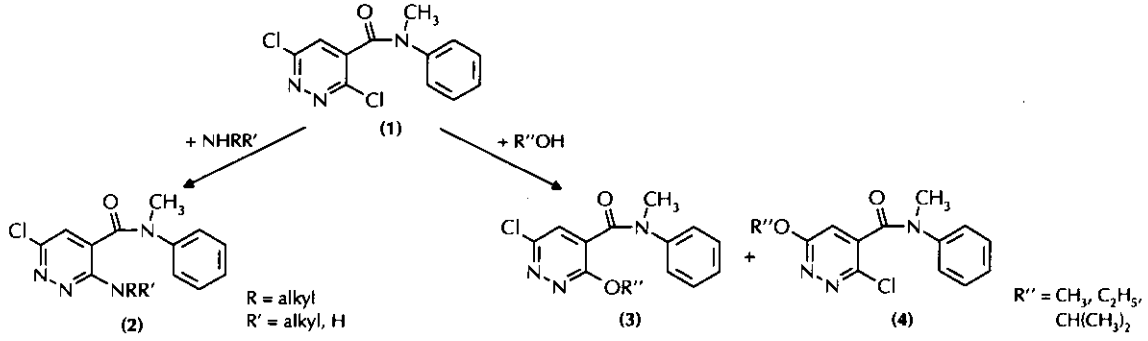
Abstract – Reactions of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide with *S*-nucleophiles (2-aminothiophenol, benzyl mercaptan) were studied, structural elucidation of the reaction products was achieved by means of X-Ray analysis and NMR experiments (NOE difference spectroscopy), respectively.

In search for novel potentially bioactive molecules we have recently investigated the reaction behavior of 3,6-dichloropyridazine-4-carboxylic acid derivatives towards a variety of *N*- and *O*-nucleophiles.[2-4] Whereas treatment of the amide (**1**) with *N*-nucleophiles expectedly led smoothly to 3-amino substituted compounds of type (**2**),[2,3,5] reactions of **1** with *O*-nucleophiles (methanol, ethanol, 2-propanol) surprisingly resulted in the formation of mixtures of 3- and 6-alkoxy congeners (**3**, **4**).[3,4] By choosing appropriate conditions we were able to shift the ratio of these isomers. Thus, it became possible to prepare both types of monoalkoxymonochloropyridazine-4-carboxamides in reasonable yields.[3,4]



¤ *Dedicated with best personal wishes to Professor Dr. Dieter MATTHIES on the occasion of his 65th anniversary.*

We now report on the reaction behavior of **1** towards *S*-nucleophiles employing 2-aminothiophenol and benzyl mercaptan as reactants.

Initial attempts to react **1** with 2-aminothiophenol in dry ethanol in the presence of sodium hydrogencarbonate resulted in the formation of a monosubstituted derivative, *albeit* in only low yield (28 %). Modification of the reaction conditions (reaction in ether/1,4-dioxane or in 1,4-dioxane in the presence of powdered sodium hydroxide) led to the same product in 46 and 86 % yields, respectively. ^{1}H-NMR spectroscopy did not permit unequivocal assignment of the position of the *S*-substituent. Moreover, attempts to prepare the corresponding dehalogenated product (ammonium formate/10 % palladium on charcoal) and to determine the substitution position *via* coupling constants (*ortho* coupling: $J \approx 5$ Hz, *meta* coupling: $J \approx 2$ Hz) in the latter failed, obviously due to the fact that thioether derivatives represent anticatalysts.[6] Structure elucidation, however, could be achieved by X-Ray analysis using material obtained by crystallisation from diisopropyl ether (Figure 1). Thus, the structure of a 6-(2-aminophenylthio)-3-chloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**5**) has to be assigned to the new compound.

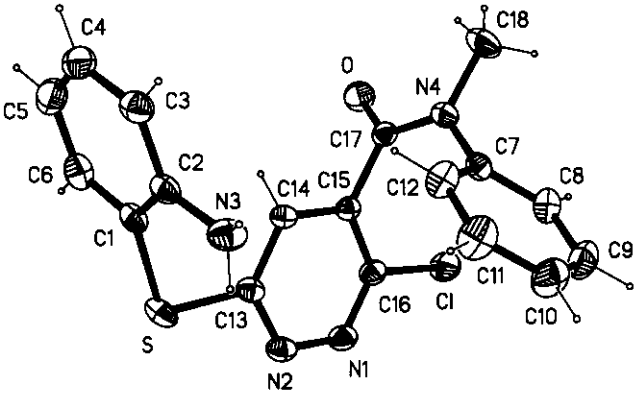


Figure 1. Molecular structure of **5** (20 % ellipsoids) in crystalline state. Selected bond lengths and angles (Å, deg): S-C(1) = 1.770(2), S-C(13) = 1.768(2), C(1)-S-C(13) = 102.0(1), Cl-C(16) = 1.729(2), N(1)-N(2) = 1.349(2), N(1)-C(16) = 1.313(2), N(2)-C(13) = 1.329(2), O-C(17) = 1.222(2), N(3)-C(2) = 1.369(2), N(4)-C(17) = 1.337(2), N(4)-C(18) = 1.465(2), N(4)-C(7) = 1.440(2).

Similarly treatment of **1** with benzyl mercaptan in dry dichloromethane in the presence of triethylamine resulted in the formation of the benzylthio-substituted pyridazine-4-carboxamide derivative (**6a**) (yield 14 %), the structure of which could be assigned by NOE difference spectroscopy: a positive NOE was observed for the pyridazine proton (H-5) upon irradiation of *S*-CH_2 (δ 4.45) (see Figure 2). Performing the

reaction in 1,4-dioxane in the presence of powdered sodium hydroxide enabled us to enhance the yield of **6a** to 54 %. Under these conditions also the disubstituted derivative (**6b**) is formed in 12 % yield.

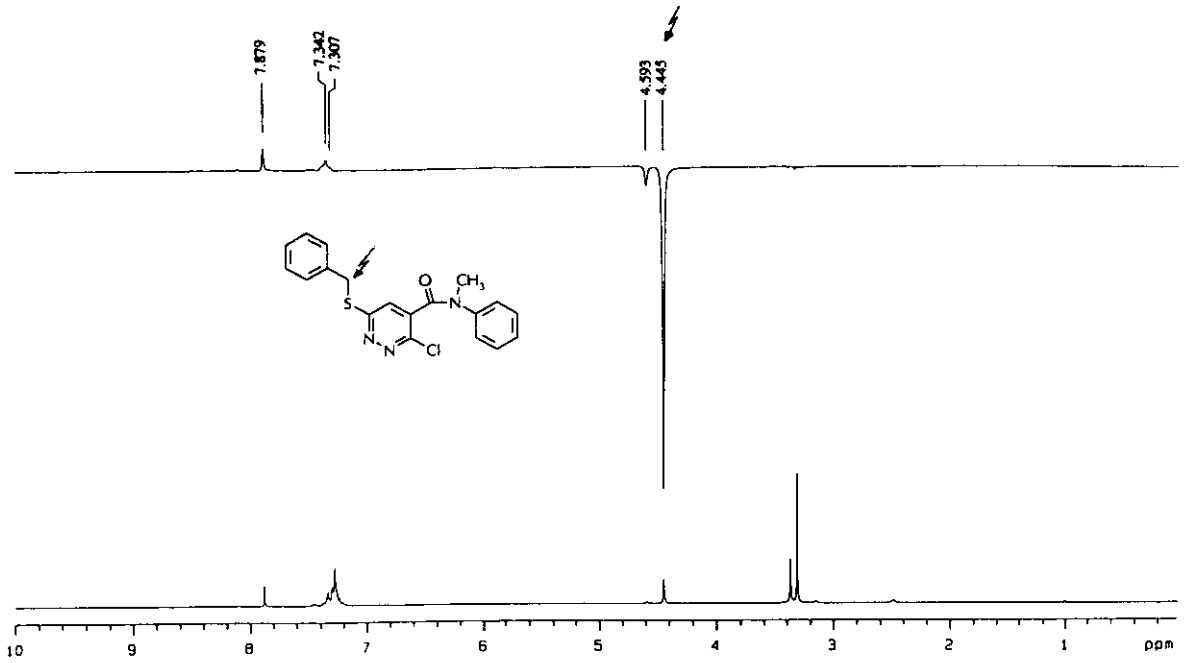
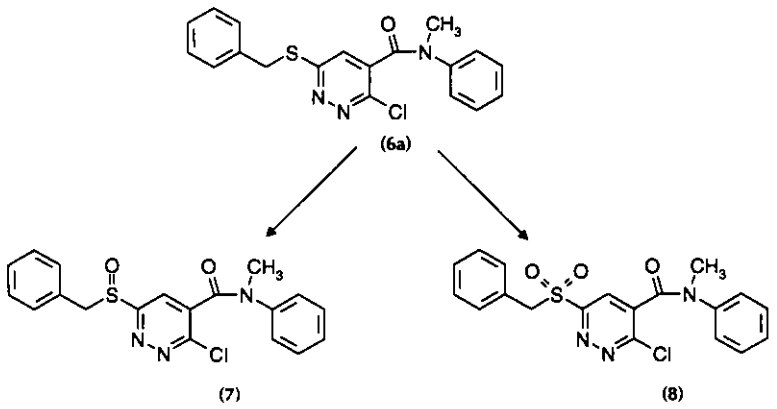


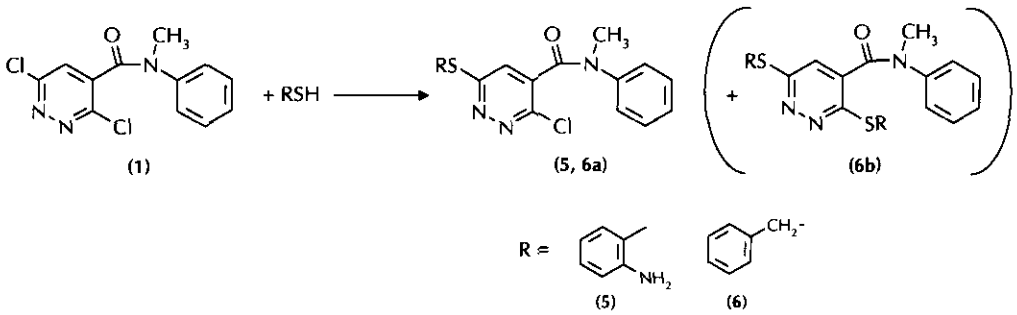
Figure 2. ^{1}H-NMR spectrum of compound (**6a**) and NOE difference spectrum of **6a** resulting from irradiation of *S*-CH_2.

By treating **6a** with sodium periodate or with *m*-chloroperoxybenzoic acid the so far not described sulfoxide (**7**) and the sulfone (**8**) became accessible in satisfactory yields.



The formation of 6-aryl(methyl)thiopyridazine derivatives upon reaction of **1** with *S*-nucleophiles is in

accordance with our previous findings[4] that the stronger the nucleophile the more favored is its attack at position 6 of the pyridazine system.



EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope (Reichert) and are uncorrected. IR spectra were taken on a Mattson Galaxy Series FT-IR 3000 spectrophotometer (KBr pellets). ^{1}H-NMR spectra were recorded on a Varian Gemini 200 spectrometer (^{1}H: 199.98 MHz). The centre of the solvent multiplet (DMSO-d_6 or $CDCl_3$) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 2.49 ppm (DMSO-d_6) or with δ 7.26 ppm ($CDCl_3$). The standard Varian programme NOEDIF was used to generate the NOE. MS spectra were obtained on a Finnigan MAT SSQ 7000. Reactions were monitored by TLC using Polygram® SIL G/UV_{254} (Macherey-Nagel) plastic-backed plates (0.25 mm layer thickness). Column chromatography was performed using Kieselgel 60 (0.040-0.063 mm, Merck). Microanalyses were performed at the Institute of Physical Chemistry (Mag. J. Theiner), University of Vienna, Austria.
Light petroleum refers to the fraction of bp 40-60 °C. The yields are not optimised.

Starting materials: 3,6-Dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**) was prepared by reaction of 3,6-dichloropyridazine-4-carboxylic acid chloride with *N*-methylaniline.[4] 3,6-Dichloropyridazine-4-carboxylic acid chloride was available from 3,6-dichloro-4-methylpyridazine[7] by oxidation with $K_2Cr_2O_7$ in H_2SO_4[8] and subsequent treatment with $SOCl_2$.[9]

Procedures for the Reaction of 1 with 2-Aminothiophenol:

Method A:

To a suspension of 2.5 mmol (0.705 g) of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**) in 15 mL of dry ethanol were added under a nitrogen atmosphere 5.0 mmol (0.626 g) of 2-aminothiophenol and

5.0 mmol (0.420 g) of sodium hydrogencarbonate. The reaction mixture was stirred at 40 °C until the starting material was completely consumed (TLC monitoring, dichloromethane/ethyl acetate 6:1, *ca.* 26 h). Then the solvent was removed *in vacuo* and the residue thus obtained was taken up in 100 mL of dichloromethane and the solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography (dichloromethane/ethyl acetate 6:1) and recrystallisation (diisopropyl ether).

Method B:

A suspension of 10.0 mmol (1.252 g) of 2-aminothiophenol and 5.0 mmol (0.200 g) of powdered sodium hydroxide in a mixture of 1 mL of dry 1,4-dioxane and 20 mL of dry ether was stirred at rt for 1 h. Then 5.0 mmol (1.410 g) of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**) was added and stirring was continued until the starting material was completely consumed (TLC monitoring, ca. 3 d). The reaction mixture was treated as described in method A.

Method C:

To a suspension of 2.5 mmol (0.705 g) of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**) in 10 mL of dry 1,4-dioxane were added under a nitrogen atmosphere 3.75 mmol (0.469 g) of 2-aminothiophenol and 2.5 mmol (0.100 g) of powdered sodium hydroxide. The reaction mixture was stirred at rt until the starting material was completely consumed (TLC monitoring, ca. 12 h). The reaction mixture was treated as described in method A.

6-(2-Aminophenylthio)-3-chloro-N-methyl-N-phenylpyridazine-4-carboxamide (**5**)

Yield 28 % (method A), 46 % (method B), 86 % (method C) of light yellow crystals, mp 156-162 °C, IR 1658, 3327, 3409 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.39-7.30 (m, 2H, phenyl-H), 7.26-7.19 (m, 3H, phenyl-H), 7.00-6.93 (m, 2H, phenyl-H), 6.84-6.76 (m, 2H, phenyl-H), 6.48 (s, 1H, pyridazine-H-5), 4.19 (s, 2H, NH_2), 3.40 (s, 3H, NCH_3). EI MS (70 eV): m/z = 370 [M^+]. *Anal.* Calcd for $C_{18}H_{15}N_4OClS$: C, 58.30; H, 4.08; N, 15.11. Found: C, 58.34; H, 3.85; N, 15.02.

X-Ray Structure Determination of 5

Crystal data: $C_{18}H_{15}N_4OClS$, M_r = 370.85, monoclinic, space group C2/c (No. 15), a = 25.836 (6) Å, b = 8.833 (2) Å, c = 16.147 (2) Å, α = 90°, β = 101.48 (1)°, γ = 90°, V = 3611 (2) Å^3, Z = 8, D_x = 1.364 Mg m^{-3}, λ = 0.71073 Å, μ = 0.341 mm^{-1}, T = 300 K.

A yellow prism was used for X-Ray diffraction investigations with a SIEMENS SMART CCD area detector three-circle diffractometer and graphite monochromatized Mo Kα radiation. The intensities of 11517 reflections with θ < 27° were measured by ω-scan frames (hemisphere, Δω = 0.3°, 20 sec. per frame). The data were corrected for absorption (multi-scan method, program SADABS, correction factors 0.70 - 0.93). Merging yielded 3926 unique reflections, R_{int} = 0.0218, R_{sigma} = 0.0249.

The structure was solved by direct methods. Structure refinement on F^2 was carried out with program *SHELXL*93.[10] All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were located from a

difference map. The C-bonded H-atoms were then idealised and were refined riding with the atoms to which they were bonded. The *N*-bonded methyl group showed an orientation disorder which was taken into account. The hydrogen atoms of amino group $N(3)H_2$ were refined in *x,y,z* without restraints. The final full-matrix least-squares refinement varied 235 parameters and used 3926 unique reflections weighted by $w = 1/[\sigma^2(F_o^2) + (0.054P)^2+0.56P]$, where $P = (F_o^2+2F_c^2)/3$. Final $R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o| = 0.050$, $wR2 = [\Sigma(w(F_o^2-F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.100$ and $S = 1.03$ for all data; $R1 = 0.036$ for the 3018 reflections with $F_o \geq 4\sigma(F_o)$. The final difference Fourier map showed minimum and maximum values of -0.29 and 0.17 e $Å^{-3}$.

The molecular structure of (**5**) in crystalline state is shown in Figure 1. The molecule adopts a non-planar and screw-like conformation with interplanar angles of 83.2, 84.1, and 72.6° between the four planar segments o-aminophenyl, pyridazine, *N*-methylcarboxamide, and N(4)-bonded phenyl. Bond lengths are consistent with the chemical structure diagram. Hydrogen bonds donated by the amino group $N(3)H_2$ to the pyridazine nitrogen atoms N(1) and N(2) (N···N = 3.21 and 3.32 Å) of two neighboring molecules contribute to the coherence of the structure.

Table 1. Atomic coordinates and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for $C_{18}H_{15}N_4OClS$ (**5**).[11] U_{eq} is defined as one third of the trace of the orthogonalised U_{ij} tensor.

	x	y	z	U_{eq}
S	0.49702(1)	0.24280(5)	0.04174(3)	63(1)
Cl	0.33168(2)	0.40164(6)	-0.27390(3)	80(1)
O	0.27669(5)	0.15760(13)	-0.13457(9)	76(1)
N(1)	0.42519(5)	0.3747(2)	-0.18114(9)	61(1)
N(2)	0.46129(5)	0.3413(2)	-0.11095(8)	59(1)
N(3)	0.44603(6)	0.4345(2)	0.15931(11)	70(1)
N(4)	0.26938(5)	0.40286(14)	-0.09763(8)	55(1)
C(1)	0.46229(5)	0.1774(2)	0.11881(9)	55(1)
C(2)	0.44291(5)	0.2815(2)	0.17093(9)	53(1)
C(3)	0.41772(6)	0.2226(2)	0.23336(10)	63(1)
C(4)	0.41313(7)	0.0691(2)	0.24371(11)	75(1)
C(5)	0.43222(8)	-0.0325(2)	0.19255(13)	79(1)
C(6)	0.45678(7)	0.0217(2)	0.13039(12)	71(1)
C(7)	0.29395(6)	0.5487(2)	-0.07950(9)	52(1)
C(8)	0.28443(8)	0.6614(2)	-0.14024(12)	71(1)
C(9)	0.30860(10)	0.8002(2)	-0.12343(15)	87(1)
C(10)	0.34195(10)	0.8261(2)	-0.0479(2)	91(1)
C(11)	0.35183(10)	0.7152(2)	0.01196(14)	93(1)
C(12)	0.32708(8)	0.5758(2)	-0.00292(11)	71(1)
C(13)	0.44502(5)	0.2860(2)	-0.04397(9)	48(1)
C(14)	0.39146(5)	0.2654(2)	-0.04196(9)	47(1)
C(15)	0.35454(5)	0.30382(14)	-0.11195(8)	44(1)
C(16)	0.37479(6)	0.3562(2)	-0.18097(9)	53(1)
C(17)	0.29621(6)	0.2820(2)	-0.11587(9)	49(1)
C(18)	0.21232(6)	0.3905(3)	-0.1024(2)	90(1)

Procedures for the Reaction of 1 with Benzyl mercaptan:

Method A:

A suspension of 2.5 mmol (0.705 g) of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**), 2.75 mmol (0.342 g) of benzyl mercaptan, and 3.75 mmol (0.379 g) of triethylamine in 15 mL of dry dichloromethane was stirred at 40 °C under a nitrogen atmosphere until the starting material was completely consumed (TLC monitoring, dichloromethane/ethyl acetate 19:1, *ca.* 3 d). Then 100 mL of dichloromethane was added and the solution was washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography (dichloromethane/ethyl acetate 19:1) and recrystallisation (ether, diisopropyl ether and light petroleum).

Method B:

To a suspension of 5.0 mmol (1.141 g) of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**) in 25 mL of dry 1,4-dioxane were added under a nitrogen atmosphere 7.5 mmol (0.932 g) of benzyl mercaptan and 5.0 mmol (0.200 g) of powdered sodium hydroxide. The reaction mixture was stirred at rt until the starting material was completely consumed (TLC monitoring, *ca.* 1 h). The solvent was removed, the residue thus obtained was treated as described in method A. The products (**6a**) and (**6b**) were separated by column chromatography (dichloromethane/ethyl acetate 6:1), pure compounds were obtained by recrystallisation from diisopropyl ether.

6-Benzylthio-3-chloro-N-methyl-N-phenylpyridazine-4-carboxamide (**6a**)

Yield 14 % (method A), 54 % (method B) of colourless crystals, mp 68-70 °C, IR 1656 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.38-7.22 (m, 8H, phenyl-H), 7.15-7.09 (m, 2H, phenyl-H), 6.97 (s, 1H, pyridazine-H-5), 4.47 (s, 2H, CH_2), 3.47 (s ,3H, CH_3). ^{1}H-NMR (DMSO-d_6) δ 7.88 (s, 1H, pyridazine-H-5), 7.34-7.24 (m, 10H, phenyl-H), 4.45 (s, 2H, CH_2), 3.37 (s ,3H, CH_3). EI MS (70 eV): m/z = 369 [M^+]. *Anal.* Calcd for $C_{19}H_{16}N_3OClS$: C, 61.70; H, 4.36; N, 11.36. Found: C, 61.65; H, 4.20; N, 11.37.

3,6-Dibenzylthio-N-methyl-N-phenylpyridazine-4-carboxamide (**6b**)

Yield 12 % (method B) of colourless crystals, mp 136-139 °C, IR 1648 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ 7.36-7.15 (m, 16H, phenyl-H, pyridazine-H-5), 4.51 (s, 2H, CH_2), 4.40 (s, 2H, CH_2), 3.30 (s, 3H, CH_3). EI MS (70 eV): m/z = 457 [M^+]. *Anal.* Calcd for $C_{26}H_{23}N_3OS_2$: C, 68.24; H, 5.07; N, 9.18. Found: C, 68.34; H, 5.09; N, 9.17.

6-Benzylsulfinyl-3-chloro-N-methyl-N-phenylpyridazine-4-carboxamide (**7**)

To a solution of 0.25 mmol (0.093 g) of 6-benzylthio-3-chloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**6a**) in 5 mL of methanol was added a solution of 0.32 mmol (0.068 g) of sodium periodate in 1 mL of water

and the mixture was stirred at rt for 2 d. Then, further 0.32 mmol (0.068 g) of sodium periodate in 1 mL of water was added and stirring was continued until the starting material was completely consumed (TLC monitoring, dichloromethane/ethyl acetate 9:1). The mixture was diluted with 15 mL of dichloromethane, washed with water and brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography (dichloromethane/ethyl acetate 9:1) and recrystallisation (diisopropyl ether) to yield 0.065 g (67 %) of colourless crystals, mp 127-131 °C, IR 1657, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.47 (s, 1H, pyridazine-H-5), 7.37-6.98 (m, 10H, phenyl-H), 4.35 (d, J = 13.2 Hz, 1H), 4.03 (d, J = 13.2 Hz, 1H) (CH_2), 3.47 (s, 3H, CH_3). EI MS (70 eV): m/z = 385 [M^+]. *Anal.* Calcd for $C_{19}H_{16}N_3O_2ClS$: C, 59.14; H, 4.18; N, 10.89. Found: C, 59.39; H, 4.22; N, 10.90.

***6-Benzylsulfonyl-3-chloro-N-methyl-N-phenylpyridazine-4-carboxamide* (8)**

To a solution of 0.2 mmol (0.074 g) of 6-benzylthio-3-chloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**6a**) in 5 mL of dichloromethane was added 0.6 mmol (0.148 g) of *m*-chloroperoxybenzoic acid (70-75 %) and the mixture was stirred at rt for 2.5 h. Then, further 0.6 mmol (0.148 g) of *m*-chloroperoxybenzoic acid (70-75 %) was added and stirring was continued until the starting material and the sulfoxide were completely consumed (TLC monitoring, dichloromethane/ethyl acetate 5:1, *ca.* 1 h). Then 15 mL of dichloromethane was added and the solution was washed with 2N NaOH, water and brine, dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography (dichloromethane/ethyl acetate 5:1) and recrystallisation (ether/light petroleum) to yield 0.060 g (75 %) of colourless crystals, mp 153-157 °C, IR 1661, 1328/1314, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.61 (s, 1H, pyridazine-H-5), 7.35-7.04 (m, 10H, phenyl-H), 4.73 (s, 2H, CH_2), 3.47 (s, 3H, CH_3). EI MS (70 eV): m/z = 401 [M^+]. *Anal.* Calcd for $C_{19}H_{16}N_3O_3ClS$: C, 56.79; H, 4.01; N, 10.46. Found: C, 57.05; H, 3.97; N, 10.38.

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