PYRIDAZINES, 85.[1] ON THE REGIOSELECTIVITY OF ATTACK OF *O*-NUCLEOPHILES AT 4-SUBSTITUTED 3,6-DICHLOROPYRIDAZINES[2]

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Abstract - The influence of reaction parameters on the regioselectivity of substitution of a chloro function in 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide by an alkoxy group was studied. It is shown that by choosing appropriate conditions, the attack of the nucleophile can be directed either to C-3 or C-6, thus providing convenient access to both series of alkoxychloropyridazines and their dehalogenated congeners.

3,6-Dichloropyridazines – conveniently available from 3,6-dihydroxypyridazines [3-5] – are important intermediates in the synthesis of amino or alkoxy substituted pyridazine derivatives. It is well documented in the literature that in the case of 4-substituted 3,6-dichloropyridazines monosubstitution of a chloro atom by a nucleophile in general yields two isomeric compounds.[4, 6-9] For the reaction of 3,6-dichloro-4-methylpyridazine with nucleophiles it is described that treatment with ammonia affords a mixture with the 6-amino isomer far predominating.[4, 8, 10] On the other hand, reaction of 3,6-dichloro-4-methylpyridazine with sodium methoxide yields the 3-methoxy isomer as the main product, but with increasing size of the alkoxide group 6-alkoxylation is preferred.[4, 6, 8, 10] Moreover, treatment of 3,6-dichloro-4-cyanopyridazine with secondary amines has been reported to yield mixtures of the corresponding 3-amino and 6-amino compounds.[11] By contrast, selective exchange of the halogen in position 3 by hydrazino or alkoxy group is reported for 4-amino- or 4-sulfonamido-3,6-dichloropyridazines.[4] Likewise, it is described that in reactions of 3,6-dichloropyridazine-4-carboxamide derivatives with *N*- and *O*-nucleophiles the chloro atom in position 3 is substituted preferentially.[12-13] The latter regioselectivity can be explained by the fact that the substructure Cl-C(3)=C(4)-CONRR' has to be considered as a vinylogous carbamoyl chloride.

Based on recent observations of interesting biological activities of 3-amino-substituted pyridazine-4-carboxamides, alkoxypyridazine-4-carboxamide derivatives became an object of interest, too. In the course

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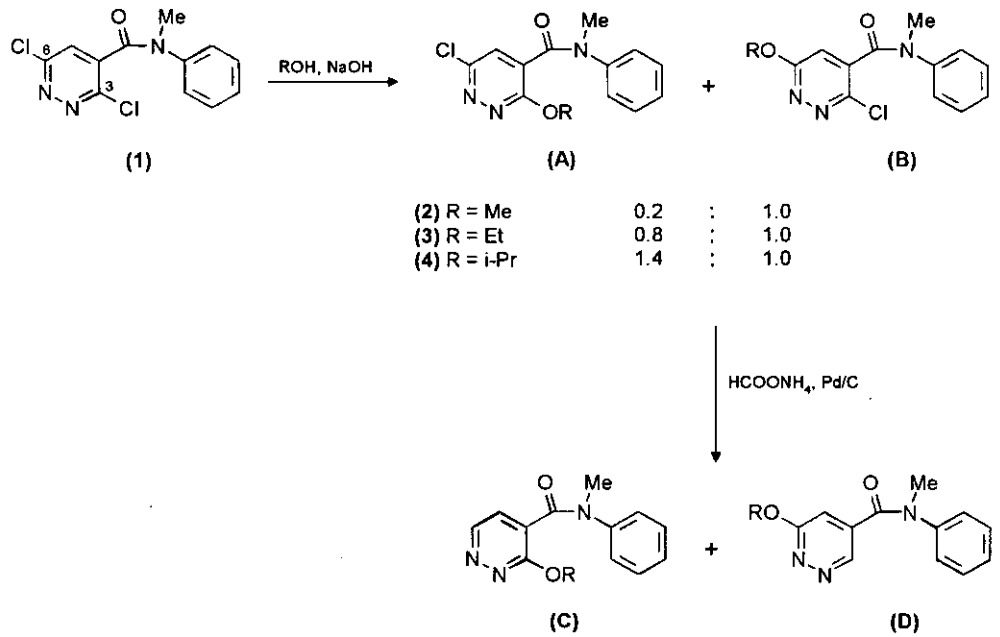
of these investigations we now observed that surprisingly 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide **(1)**[14] reacts in methanol, ethanol, or isopropanol, respectively, in the presence of one equivalent of sodium hydroxide at room temperature to yield not solely the expected 3-alkoxy-6-chloro compounds of type **(A)** but a mixture of **A** and the isomeric 6-alkoxy-3-chloro derivatives **(B)** in varying ratios (see Scheme 1 and Table 1)[15]. The analytically pure isomers **2a/b**, **3a/b**, and **4a/b** could be isolated after recrystallisation (**2**, **4**) or column chromatography (**3**), respectively.



Scheme 1. Reaction of **1** with *O*-nucleophiles.

The assignment of the ratios of the isomers was performed by ^{1}H-NMR spectroscopy after work up of the reaction mixtures obtained by subsequent reductive dehalogenation (using ammonium formate as hydrogen source and palladium on charcoal as catalyst). In the NMR spectra ($CDCl_3$) of compounds of type **C**, the coupling constants of two doublet peaks (pyridazine-H-5 and H-6) showed *ortho* coupling ($J \approx 5$ Hz) whereas the pyridazine protons in compounds of type **D** showed *meta* coupling with $J \approx 2$ Hz.

The unexpected regioselectivity prompted us to investigate the influence of the reaction conditions on the ratio of isomers in order to elaborate efficient pathways to either 3-alkoxy-6-chloro- or 6-alkoxy-3-chloro-pyridazine-4-carboxamides and thus also to their dechloro congeners.

Based on the finding that stronger nucleophiles (methanol, ethanol) tend to attack preferentially position 6 of the pyridazine system (see Scheme 1 and Table 1) we anticipated that employment of a stronger base (which should increase the nucleophilicity of the attacking agent) would lead mainly to 6-alkoxy derivatives. Indeed, we observed that replacement of sodium hydroxide by potassium hydroxide results in increased formation of 6-ethoxy and 6-isopropoxy derivatives. In the reaction of **1** with methanol, however, no influence of the nature of the base on product distribution was observed indicating that additional parameters contribute to the outcome of the reaction.

Thus, the influence of the solvent was investigated too. For this purpose, the reactions were performed in tetrahydrofuran or 1,4-dioxane, respectively. The results shown in Table 1 indicate that there is indeed a clear influence of the polarity of the solvent (tetrahydrofuran: $\varepsilon = 7.58$ [16], 1,4-dioxane: $\varepsilon = 2.21$ [16], methanol: $\varepsilon = 32.70$ [16], ethanol: $\varepsilon = 24.55$ [16], isopropanol: $\varepsilon = 19.92$ [16]) on the ratio of isomers formed: the lower the polarity of the solvent the higher is the yield of 3-alkoxy-6-chloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamides (**A**). This may be interpreted as follows: formation of a hydrogen bond from the alcohol to a ring nitrogen atom activates the chloro atom in ortho position as well as the nucleophile (preformed RO^-). An analogous solvent effect has been described for pyridine and pyrimidine derivatives.[7, 17] On this basis one may explain the attack of *O*-nucleophiles at position 6 of the pyridazine core in the reactions of **1** in polar solvents by hydrogen bonding preferentially to the N-1. N-2 has to be considered "less basic" since it is part of a formal vinylogous urea derivative (N(2)-C=C-CONRR').

Table 1.

conditions		methanol	ethanol	isopropanol
base	**solvent**			
NaOH	ROH	6-OMe : 3-OMe = 1 : 0.2	6-OEt : 3-OEt = 1 : 0.8	6-OiPr : 3-OiPr = 1 : 1.4
KOH	ROH	6-OMe : 3-OMe = 1 : 0.2	6-OEt : 3-OEt = 1 : 0.3	6-OiPr : 3-OiPr = 1 : 0.6
NaOH	THF	6-OMe : 3-OMe = 1 : 1.3	6-OEt : 3-OEt = 1 : 1.2	6-OiPr : 3-OiPr = 1 : 3.0
NaOH	1,4-dioxane	6-OMe : 3-OMe = 1 : 6.0	6-OEt : 3-OEt = 1 : 5.9	6-OiPr : 3-OiPr = 1 : 15.8

In summary, we have shown that the ratio of mixtures of 3- and 6-alkoxy-*N*-methyl-*N*-phenylpyridazine-4-carboxamides resulting in reactions of the corresponding 3,6-dichloro compound (**1**) can be varied by appropriate variation of the base and the solvent employed. Thus, starting from **1**, either 3-alkoxy-6-chloro- or 6-alkoxy-3-chloropyridazines (**2a/b**, **3a/b**, **4a/b**) can be prepared efficiently which in turn provide convenient access to either 3-alkoxy- or 6-alkoxypyridazine-4-carboxamides.

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 and ^{13}C NMR spectra were recorded on a Varian Gemini 200 spectrometer (^{1}H: 199.98 MHz). The centre of the solvent multiplet ($CDCl_3$) was used as internal standard (chemical shifts in δ ppm), which was related to TMS with δ 7.26 ppm for ^{1}H. 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) or aluminium oxide (neutral). 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-Dichloropyridazine-4-carboxylic acid chloride was available from 3,6-dichloro-4-methylpyridazine[5] by oxidation with $K_2Cr_2O_7$ in H_2SO_4 [18] and subsequent treatment with $SOCl_2$.[12a]

3,6-Dichloro-N-methyl-N-phenylpyridazine-4-carboxamide (1)

To an ice-cooled solution of *N*-methylaniline (8.04 g, 75.00 mmol) and triethylamine (7.56 g, 75.00 mmol) in dry dichloromethane (50 mL) was added dropwise a solution of 3,6-dichloropyridazine-4-carboxylic acid chloride (10.57 g, 50.00 mmol) in dry dichloromethane (20 mL) under a nitrogen atmosphere. The mixture was stirred at rt for 3 h, then the solution was diluted with dichloromethane. The dichloromethane phase was washed with 1*N* HCl, water, and brine, dried over sodium sulphate, and evaporated. The residue thus obtained was purified by recrystallisation from ethyl acetate to yield 12.70 g (90 %) of light beige crystals, mp 122-128 °C, IR 1657 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.36-7.25 (m, 3 H, phenyl-H), 7.21 (s, 1 H, pyridazine-H-5), 7.18-7.13 (m, 2 H, phenyl H), 3.51 (s, 3H, CH_3). EI MS (70 eV): m/z = 281 [M^+]. Anal. Calcd for $C_{12}H_9N_3OCl_2$: C, 51.09; H, 3.22; N, 14.89. Found: C, 51.19; H, 2.92; N, 14.86.

General Procedure for the Reaction of 1 with O-Nucleophiles:

Method A:

To a suspension of 2.5 mmol (0.71 g) of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**) in 15 mL of methanol, ethanol, or isopropanol, respectively, were added under a nitrogen atmosphere 2.5 mmol of powdered NaOH or KOH, respectively. The reaction mixture was stirred at rt until the starting material was completely consumed (TLC monitoring, diisopropyl ether, or GC/MS monitoring). Then the solvent was removed *in vacuo* and the residue thus obtained was taken up in dichloromethane. This solution was washed with water and brine, dried over anhydrous sodium sulphate and evaporated. The crude products were purified by column chromatography (dichloromethane/ethyl acetate 9:1).

Method B:

To a solution of 1.0 mmol (0.28 g) of 3,6-dichloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide (**1**) in 10 mL of dry tetrahydrofuran, or 10 mL of dry 1,4-dioxane were added 10 mmol of methanol, ethanol, or isopropanol, respectively, and 1.0 mmol of powdered NaOH of KOH, respectively. The reaction mixture was stirred at rt until the starting material was completely consumed (TLC monitoring, diisopropyl ether, or GC/MS monitoring). Then the solvent was removed *in vacuo* and the residue thus obtained was taken up in dichloromethane. This solution was washed with water and brine, dried over anhydrous sodium sulphate and evaporated. The crude products were purified by column chromatography (dichloromethane/ethyl acetate 9:1).

6-Chloro-3-methoxy-N-methyl-N-phenylpyridazine-4-carboxamide **(2a)** and ***3-Chloro-6-methoxy-N-methyl-N-phenylpyridazine-4-carboxamide*** **(2b)**

Method A: Yield: 79 % of the isomeric mixture. Separation of the isomers **2a/b** was performed by fractional crystallisation from diisopropyl ether (first fraction: 3-methoxy isomer, second fraction: 6-methoxy isomer).

6-Chloro-3-methoxy-N-methyl-N-phenylpyridazine-4-carboxamide **(2a)**

Colourless crystals, mp 97 °C, IR 1653 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.26-7.01 (m, 6H, phenyl-H, pyridazine-H-5), 3.98 (s, 3H, OCH_3), 3.47 (s, 3H, NCH_3). EI MS (70 eV): m/z = 277 [M^+]. Anal. Calcd for $C_{13}H_{12}N_3O_2Cl$: C, 56.23; H, 4.39; N, 15.13. Found: C, 56.45; H, 4.52; N, 15.04.

3-Chloro-6-methoxy-N-methyl-N-phenylpyridazine-4-carboxamide **(2b)**

Colourless crystals, mp 114-116 °C, IR 1658 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.32-7.07 (m, 5H, phenyl-H), 6.67 (s, 1H, pyridazine H-5), 4.02 (s, 3H, OCH_3), 3.49 (s, 3H, NCH_3). EI MS (70 eV): m/z = 277 [M^+]. Anal. Calcd for $C_{13}H_{12}N_3O_2Cl$: C, 56.23; H, 4.39; N, 15.13. Found: C, 56.58; H, 4.49; N, 15.02.

6-Chloro-3-ethoxy-N-methyl-N-phenylpyridazine-4-carboxamide **(3a)** and ***3-Chloro-6-ethoxy-N-methyl-N-phenylpyridazine-4-carboxamide*** **(3b)**

Method A: Yield: 84 % of the isomeric mixture. The isomers **3a/b** were separated by column chromatography (neutral aluminium oxide; dichloromethane/ethyl acetate 19:1).

6-Chloro-3-ethoxy-N-methyl-N-phenylpyridazine-4-carboxamide **(3a)**

Colourless crystals (diisopropyl ether), mp 78-82 °C, IR 1654 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.29-7.06 (m, 6H, phenyl-H, pyridazine H-5), 4.42 (q, J = 7.0 Hz, 2H, OCH_2), 3.48 (s, 3H, NCH_3), 1.39 (t, J = 7.0 Hz, 3H, CH_3). EI MS (70 eV): m/z = 291 [M^+]. Anal. Calcd for $C_{14}H_{14}N_3O_2Cl$: C, 57.64; H, 4.84; N, 14.40. Found: C, 57.84; H, 4.57; N, 14.45.

3-Chloro-6-ethoxy-N-methyl-N-phenylpyridazine-4-carboxamide **(3b)**

Colourless needles, mp 95-96 °C, IR 1656 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.34-7.14 (m, 5H, phenyl-H), 6.64 (s, 1H, pyridazine H-5), 4.43 (q, J = 7.1 Hz, 2H, OCH_2), 3.49 (s, 3H, NCH_3), 1.35 (t, J = 7.1 Hz, 3H, CH_3). EI MS (70

eV): m/z = 291 [M^+]. Anal. Calcd for $C_{14}H_{14}N_3O_2Cl$: C, 57.64; H, 4.84; N, 14.40. Found: C, 57.89; H, 4.85; N, 14.48.

6-Chloro-3-isopropoxy-N-methyl-N-phenylpyridazine-4-carboxamide (4a) and *3-Chloro-6-isopropoxy-N-methyl-N-phenylpyridazine-4-carboxamide* (4b)

Method A: Yield: 80 % of the isomeric mixture. Separation of the isomers **4a/b** was performed by fractional crystallisation from diisopropyl ether (first fraction: 3-methoxy isomer, second fraction: 6-methoxy isomer).

6-Chloro-3-isopropoxy-N-methyl-N-phenylpyridazine-4-carboxamide (4a)

Colourless crystals, mp 91-111 °C, IR 1663 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.30-7.07 (m, 6H, phenyl-H, pyridazine H-5), 5.50-5.31 (m, 1H, OCH), 3.47 (s, 3H, NCH_3), 1.32 (d, J = 6.0 Hz, 6H, 2× CH_3). EI MS (70 eV): m/z = 305 [M^+]. Anal. Calcd for $C_{15}H_{16}N_3O_2Cl$: C, 58.92; H, 5.27; N, 13.74. Found: C, 58.95; H, 5.31; N, 13.45.

3-Chloro-6-isopropoxy-N-methyl-N-phenylpyridazine-4-carboxamide (4b)

Colourless needles, mp 75-97 °C, IR 1663 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 7.33-7.14 (m, 5H, phenyl-H), 6.60 (s, 1H, pyridazine H-5), 5.49-5.31 (m, 1H, OCH), 3.49 (s, 3H, NCH_3), 1.31 (d, J = 6.2 Hz, 6H, 2× CH_3). EI MS (70 eV): m/z = 305 [M^+]. Anal. Calcd for $C_{15}H_{16}N_3O_2Cl$: C, 58.92; H, 5.27; N, 13.74. Found: C, 59.12; H, 5.22; N, 13.67.

General Procedure for Dehalogenation:

A mixture of 1 mmol of the corresponding alkoxychloro-*N*-methyl-*N*-phenylpyridazine-4-carboxamide, 5 mmol of ammonium formate (315 mg) and 114 mg of Pd/C (10%) in 20 mL of methanol was stirred under a nitrogen atmosphere at 48°C for 30 min. The catalyst was filtered off, the solvent was removed *in vacuo*, and the residue was taken up in dichloromethane. This solution was washed with water and brine, dried over anhydrous sodium sulphate and evaporated. The products thus obtained were purified by column chromatography (ethyl acetate), followed by recrystallisation (*diisopropyl ether*).

3-Methoxy-N-methyl-N-phenylpyridazine-4-carboxamide (2c) and *3-Methoxy-N-methyl-N-phenylpyridazine-5-carboxamide* (2d)

Yield: 81 %; separation of the isomers **2c/d** was performed by column chromatography (ethyl acetate)

3-Methoxy-N-methyl-N-phenylpyridazine-4-carboxamide (2c)

Colourless crystals (diisopropyl ether), mp 101 °C, IR 1649 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.71 (d, J = 4.6 Hz, 1H, pyridazine H-6), 7.25-7.05 (m, 6H, phenyl-H, pyridazine H-5), 4.01 (s, 3H, OCH_3), 3.48 (s, 3H, NCH_3). EI MS (70 eV): m/z = 243 [M^+]. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.26; H, 5.45; N, 17.16.

3-Methoxy-N-methyl-N-phenylpyridazine-5-carboxamide (**2d**)

Colourless crystals (diisopropyl ether), mp 133 °C, IR 1647 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.56 (d, J = 1.7 Hz, 1H, pyridazine-H6), 7.30-7.24 (m, 3H, phenyl-H), 7.09-7.04 (m, 2H, phenyl-H), 6.82 (d, J = 1.7 Hz, 1H, pyridazine H-4), 4.05 (s, 3H, OCH_3), 3.49 (s, 3H, NCH_3). EI MS (70 eV): m/z = 243 [M^+]. Anal. Calcd for $C_{13}H_{13}N_3O_2$: C, 64.19; H, 5.39; N, 17.27. Found: C, 64.17; H, 5.44; N, 17.04.

3-Ethoxy-N-methyl-N-phenylpyridazine-4-carboxamide (**3c**) and *3-Ethoxy-N-methyl-N-phenylpyridazine-5-carboxamide* (**3d**)

Yield: 85 %; separation of the isomers **3c/d** was performed by column chromatography (ethyl acetate).

3-Ethoxy-N-methyl-N-phenylpyridazine-4-carboxamide (**3c**)

Colourless crystals (diisopropyl ether), mp 77 °C, IR 1646 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.70 (d, J = 4.6 Hz, 1H, pyridazine-H-6), 7.24-7.04 (m, 6H, phenyl-H, pyridazine-H-5), 4.46 (q, J = 7.0 Hz, 2H, OCH_2), 3.49 (s, 3H, NCH_3), 1.40 (t, J = 7.0 Hz, 3H, CH_3). EI MS (70 eV): m/z = 257 [M^+]. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.16; H, 5.89; N, 16.16.

3-Ethoxy-N-methyl-N-phenylpyridazine-5-carboxamide (**3d**)

Yield: 85 % (starting from pure **3b**), colourless crystals (diisopropyl ether), mp 81-83 °C, IR 1648 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.53 (s, 1H, pyridazine-H-6), 7.32-7.25 (m, 3H, phenyl-H), 7.08-7.05 (m, 2H, phenyl-H), 6.82 (d, J = 1.8 Hz, 1H, pyridazine H-4), 4.50 (q, J = 7.1 Hz, 2H, OCH_2), 3.50 (s, 3H, NCH_3), 1.39 (t, J = 7.1 Hz, 3H, CH_3). EI MS (70 eV): m/z = 257 [M^+]. Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.24; H, 5.85; N, 16.29.

3-Isopropoxy-N-methyl-N-phenylpyridazine-4-carboxamide (**4c**) and *3-Isopropoxy-N-methyl-N-phenylpyridazine-5-carboxamide* (**4d**)

Yield: 55 %; separation of the isomers **4c/d** was performed by column chromatography (ethyl acetate).

3-Isopropoxy-N-methyl-N-phenylpyridazine-4-carboxamide (**4c**)

Light yellow oil, IR 1653 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.67 (d, J = 4.6 Hz, 1H, pyridazine-H6), 7.31-7.06 (m, 6H, phenyl-H, pyridazine-H-5), 5.59-5.40 (m, 1H, OCH), 3.48 (s, 3H, NCH_3), 1.33 (d, J = 6.0 Hz, 6H, 2× CH_3). EI MS (70 eV): m/z = 271 [M^+]. Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.23; H, 6.37; N, 15.26.

3-Isopropoxy-N-methyl-N-phenylpyridazine-5-carboxamide (**4d**)

Colourless crystals (diisopropyl ether), mp 66 °C, IR 1659 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 8.50 (d, J = 1.6 Hz, 1H, pyridazine-H-6), 7.34-7.06 (m, 5H, phenyl-H), 6.79 (d, J = 1.6 Hz, 1H, pyridazine H-4), 5.59-5.40 (m, 1H, OCH), 3.49 (s, 3H, NCH_3), 1.34 (d, J = 6.2 Hz, 6H, 2× CH_3). EI MS (70 eV): m/z = 271 [M^+]. Anal. Calcd for $C_{15}H_{17}N_3O_2$: C, 66.40; H, 6.32; N, 15.49. Found: C, 66.11; H, 6.24; N, 15.22.

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