KINETIC AND THEORETIC ASPECTS OF REGIOCHEMISTRY IN THE REACTION OF 4,5-DIHALO-3(2*H*)-PYRIDAZINONES WITH BENZYLAMINES

Péter Mátyus,[a]* Klára Czakó,[a] Ágnes Behr,[a] Ildikó Varga,[a] Benjamin Podányi,[b] Malte von Arnim,[c] and Péter Várkonyi[b]

[a]Institute for Drug Research, Berlini út 47-49, Budapest, H-1045, Hungary. [b]Chinoin Research Centre, Tó utca 1-5, Budapest, H-1045, Hungary. [c]Lehrstuhl für Theoretische Chemie der Universität Bonn, Wegelerstr. 12, Bonn, D-5300, Germany

Abstract — Regioselectivity of nucleophilic substitution reactions of 4,5-dihalo-3(2*H*)-pyridazinones (**1a-d**) with benzylamines was studied under different conditions. Second-order kinetics were obtained for reactions of **1a** with benzylamine in ethanol-d_6 and toluene-d_8 as well. Experimental results obtained were interpreted on the bases of Klopman-Salem equation and analyses of the reaction paths.

INTRODUCTION

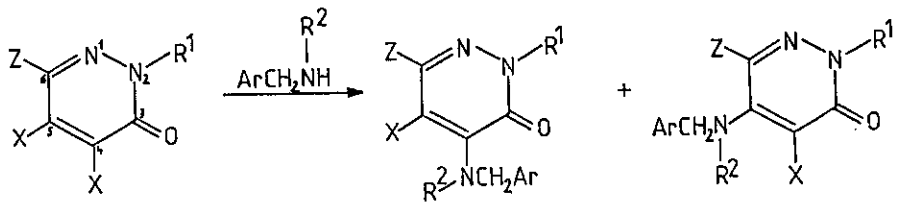
The chemistry of 4(5)-benzylamino-5(4)-chloro-3(2*H*)-pyridazinones and structurally related compounds has recently received considerable attention due to their biological activities[1,2] and synthetic values in constructing of fused pyridazines.[3,4] A simple and efficient approach to these compounds involves as key step the reaction of an amine with a 4,5-dihalo-3(2*H*)-pyridazinone derivative. It has been well recognized that the synthetic potency of this route would be particularly enhanced, if the nucleophilic substitutions of halogens proceeded with high degrees of regioselectivity or were at least predictable. Factors governing the selectivity have already been documented.[5-7] Even though CNDO/2[5a] and MNDO[7] calculations on 4,5-dichloro-2-methyl-3(2*H*)-pyridazinones have been done orientation rules appeared so far are on empirical rather than theoretical bases, and a general, reasonable explanation for regioselectivity of these reactions has not yet been available.

We wish to report here our results on reactions of pyridazinones (**1a-d**) with benzylamines and our attempts to get a better understanding of the factors controlling the selectivity.

RESULTS AND DISCUSSIONS

Reactions of 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone (**1a**) with benzylamine, 4-chloro-, 4-methoxy-, and *N*-methylbenzylamines, respectively, were carried out to investigate the effect of the amine, whereas pyridazinones (**1b-d**) were reacted with benzylamine to explore the influence of the pyridazine part on the product ratio *(Scheme 1)*. The solvent effect was studied in ethanol and toluene *(Table 1)*.

Scheme 1



1 **2-5** **6-9**

a: $R^1 = CH_3$, X = Cl, Z = H
b: $R^1 = CH_3$, X = Cl, $Z = NO_2$
c: $R^1 = CH_3$, X = Br, Z = H
d: $R^1 = C_6H_5$, X = Cl, Z = H

2, **6** : Ar = C_6H_5, R^2 = H
3, **7** : Ar = 4-ClC_6H_4, R^2 = H
4, **8** : Ar = 4-$CH_3OC_6H_4$, R^2 = H
5, **9** : Ar = C_6H_5, $R^2 = CH_3$

In each case, kinetically controlled monosubstitution occurred only at 4- and 5-positions of the pyridazinone ring affording 4- and 5-benzylamino derivatives ('4- and 5-isomers'), respectively, and formations of 6-benzylamino-4-chloropyridazinone derivatives by elimination-addition mechanism[5b] or 4,5-dibenzylamino derivatives by disubstitution could not be detected. The 5/4 isomer ratios were given by intensity ratios of the benzylic-C*H*$_2$ protons appeared as separate doublets (singlets in **5** and **9**) in ^{1}H nmr spectrum ($CDCl_3$) of each isomer pair. The assignment was based on the difference in chemical shifts of these protons of isomer pairs. In 4-isomers (except **5a**), the benzylic signals resonate significantly downfield as compared to those of the 5-isomers, presumably as a consequence of anisotropic effect of the neighboring carbonyl group.

Additional support for this assignment was provided with nOe obtained between benzylic and 6-C*H* protons only in 5-isomers. The structures of **2b**, **5a** and **6b**, **9a** were also confirmed by ^{13}C nmr data, assignments were based on data published for relating compounds.[5c] In all cases and in a lot of solvent systems the 4-isomers show considerably higher retention value in thin layer chromatography than the corresponding 5-isomers. The data collected in *Table 1* indicate several important characteristics for these reactions.

Table 1

Reaction of compounds (1) with benzylamines in different sovents at 77°C

Entry	reaction	mol ratio amine/pyridazinone	solvent	reaction time (h)	conversion	product ratio (5/4)
1	**1a**+$C_6H_5CH_2NH_2$	3.5	ethanol	3	0.4	3.1
2		3	toluene[a]	9	0.3	0.1
3		5	toluene[a]	9	0.5	0.1
4		7	toluene[a]	9	0.6	0.1
5	**1a**+4-$ClC_6H_4CH_2NH_2$	3.5	ethanol	3	0.3	4.2
6	**1a**+4-$MeOC_6H_4CH_2NH_2$	3.5	ethanol	3	0.6	3.5
7		3.5	ethanol	12	0.9	3.5
8	**1a**+$C_6H_5CH_2NHCH_3$	3.5	ethanol	3	0.4	7.0
9	**1b**+ $C_6H_5CH_2NH_2$	3	ethanol	3	1.0	2.9
10		3	toluene	3	1.0	1.7
11	**1c**+$C_6H_5CH_2NH_2$	3.5	ethanol	3	0.6	3.7
12		7	toluene	6.5	0.5	0.15
13	**1d**+$C_6H_5CH_2NH_2$	3.5	ethanol	3	0.8	>10
14		3.5	toluene	12	0.2	0.25

[a]This reaction was carried out at 98 °C.

i) In toluene as compared to ethanol, rates of substitutions of 5- and 4-chloro atoms were considerably reduced, though at a lesser extent for 4-isomers, suggesting that both transition states of the rate-determining steps are much more polar than the corresponding ground states. As exception, 6-nitro derivative (**1b**) proved to be almost equally reactive toward benzylamine in both solvents and afforded a 5/4 isomer ratio >1 in toluene too.

ii) The pyridazinone substituent at 2-position could also significantly contribute to yield relatively high 5/4 isomer ratios as examplified by Entries 13, 14 *vs.* 1, 2, respectively.

iii) Of benzylamines, the secondary amine gave the highest 5/4 ratio (Entry 8). However, the isomer ratio was scarcely influenced by the 4-substituent of primary amines (Entries 5-7). Thus, steric rather than electronic effects may be important in this respect.

iv) The isomer ratio was not dependent on excesses of benzylamine (Entries 2-4), at least in the range indicated.

v) When instead of **1a** its bromo analogue, compound (1c), was used, only slight rate increases were obtained for both isomers (*i.e.* k_{Br}/k_{Cl} are small) also serving as an evidence for addition-elimination mechanism.

From the above experiments, it could be reasonably concluded that these reactions, similarly to analogue nucleophilic vinylic or aromatic substitutions,[8] followed two-stage mechanism involving the initially attack of the amine, and expulsion of halogenide subsequently, as shown for **1a** with benzylamine in *Scheme 2*.

Rate constants were also calculated for reaction of **1a** with benzylamine in ethanol-d_6 and toluene-d_8. Concentrations of the starting pyridazinone and the products (**2a**, **6a**) were measured by ^{1}H nmr spectroscopy. Not surprisingly, the intermediates (I) and (II) were not detectable because of their short life-times and consequently low concentrations.

Applying the steady state approximation to *Scheme 2*, expression *(1)* gives the value of k_{obs}, which can be occasionally further simplefied to expressions *(2)* and *(3)* depending on the relations of k_{-1} to $k_2 + k_3$ (*cf.* lit.,[10]).

$$k_{obs} = \frac{k_1\{k_2 + k_3[B]\}}{k_{-1} + k_2 + k_3[B]} \qquad (Ex\ 1)$$

$$\text{if } k_{-1} << k_2 + k_3[B], \quad k_{obs} = k_1 \qquad (Ex\ 2)$$

$$\text{if } k_{-1} >> k_2 + k_3[B], \quad k_{obs} = \frac{k_1 k_2}{k_{-1}} + \frac{k_1 k_3[B]}{k_{-1}} \qquad (Ex\ 3)$$

where [B] is the concentration of benzylamine.

We obtained *second-order kinetics* for both reactions in both solvents reflecting that the rate-determining step is the attack of benzylamine at C-4 and C-5, respectively. On the other hand, 'mixed' (second- and third-order) kinetics, which could be expected if both stages of substitution were contributed to the rate at similar extents, was ruled out on the basis of statistical analysis obtained by SimuSolv program[11] *(Table 2)*. Accordingly the isomer ratios correspond to k^5/k^4.

Scheme 2

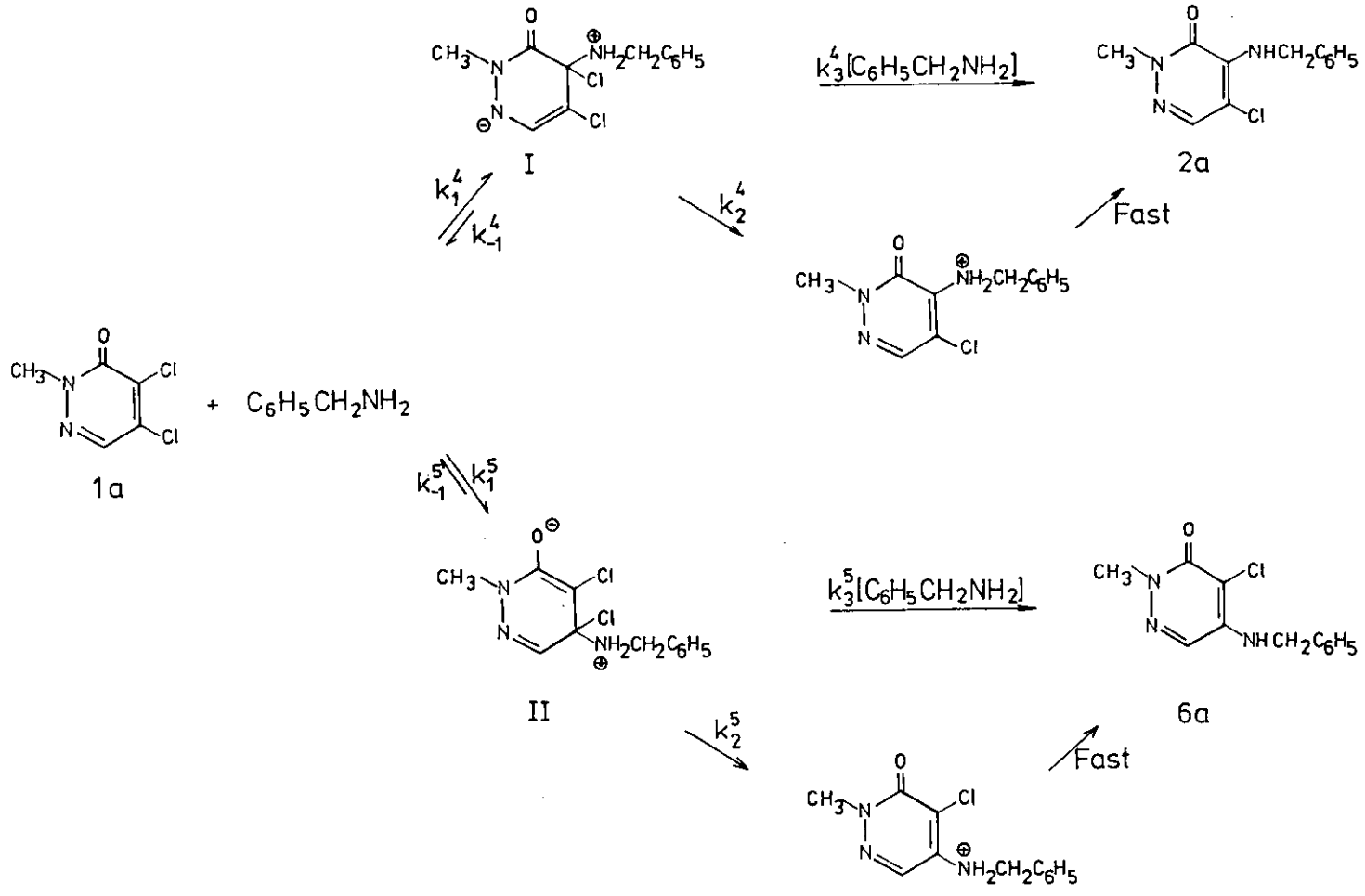

1a
+ C6H5CH2NH2
I
II
2a
6a
k4[C6H5CH2NH2]
k5[C6H5CH2NH2]
Fast
Fast

Table 2.

Rate constants for reaction of **1a** with benzylamine[a]

Solvent	Temp. °C	Second-order kinetics $10^6k_1^4$ L mol^{-1} sec^{-1}	$10^5k_1^5$ L mol^{-1} sec^{-1}	LL	'Mixed' kinetics[b] $10^6k_{II}^4$ L mol^{-1} sec^{-1}	$10^5k_{III}^4$ L^2 mol^{-2} sec^{-1}	$10^5k_{II}^5$ L mol^{-1} sec^{-1}	$10^5k_{III}^5$ L^2 mol^{-2} sec^{-1}	LL
E	44	3.06±0.04	1.47±0.07	147.2	<0.005	1.29±0.03	1.30±0.09	0.8±0.4	138.2
E	57	9.02±0.20	3.55±0.04	164.5	<0.04	4.01±0.16	3.42±0.36	0.9±1.4	152.8
E	70	24.4 ±0.50	8.01±0.08	158.9	8.72±4.02	6.96±1.75	7.92±0.68	1.2±2.8	160.9
T	80	6.30±0.03	0.06±0.002	134.5	3.2 ±0.7	1.3 ±0.3	<0.001	2.4±0.06	134.3

[a]abbreviations: E: ethanol-d_6; T: toluene-d_8, LL: log likelyhood.
In this symbolism $k_{II} = k_1k_2/k_{-1}$ and $k_{III} = k_1k_3/k_{-1}$ (see *Ex 3*).

In ethanol-d_6, the differences between the activation enthalpies ($\Delta\Delta H^{\neq} = \Delta H_5^{\neq} - \Delta H_4^{\neq}$) and entropies ($\Delta\Delta S^{\neq} = \Delta S_5^{\neq} - \Delta S_4^{\neq}$) *(Table 3)* govern the regioselectivity just oppositely. Since $\Delta\Delta H^{\neq}$ contributes to $\Delta\Delta G^{\neq}$ more significantly, the substitution of 5-chloro atom is more preferable. Both transition states should be highly solvated but the transition state leading to the 5-isomer (**6a**) is less solvated.

Table 3

Activation parameter for reaction of **1a** with benzylamine in ethanol-d_6

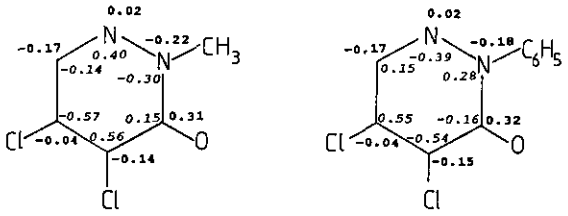
compound	$\Delta H^{\neq}$ (kcal/mol)	$\Delta S^{\neq}$ (cal/mol deg)	$\Delta G^{\neq}$ (kcal/mol)
2a	16.56+0.54	-31.7±1.6	27.4
6a	13.44±0.25	-38.4±0.7	26.6

Theoretic considerations.

Two approaches have been used for interpretation of the experimental results. The simplefied Klopman-Salem equation *(Eq. 1)*[13] was expected to be applicable to these reactions, since perturbations of pyridazinones with amines proceed in the rate-determining step. Using this equation, in which solvent dielectric constant is also implicitely involved, one might hope to get information on the origin of solvent effects.

$$\Delta E_p \simeq -\frac{Q_{Nu}Q_{El}}{\varepsilon R} + \frac{2(c_{Nu}^{HOMO}\ c_{El}^{LUMO}\beta)^2}{E_{Nu}^{HOMO} - E_{El}^{LUMO}} \qquad (Eq.\ 1)$$

The HOMO and LUMO coefficients, energies and net atomic charges for **1a,d** *(Figure 1)* and benzylamines *(Table 4)* were calculated by AM1 method.[14] For benzylamines data for nitrogen as reacting center were only given. Considering the LUMO coefficients and atomic charges of pyridazinones (**1a,d**), one would rush to the conclusion that only a charge controlled reaction could result in such degrees of regioselectivity. In fact, the large gaps existing between the LUMO of pyridazinones and HOMO of benzylamines suggest also charge control for these reactions. Nevertheless, the orbital term should still play a role in the regiochemistry too by reversing the reactivity order of C-3 *vs.* C-5 and C-4, predicted exclusively on the basis of their net charges. The differences between the values of coefficients of C-4, C-5 and C-3 (see *Figure 1*), respectively, are apparently large enough to satisfy this requirement.



ΔH^f	(kcal/mol)	13.2	49.8
E^{LUMO}	(EV)	-1.04	-1.13
E^{HOMO}	(EV)	-9.56	-9.28
μ	(D)	2.37	2.20

Figure 1

AM1 data of 2-methyl- and 2-phenyl-4,5-dichloro-3(2*H*)-pyridazinones
The net atomic charges are in bolds, while the p_z coefficients in LUMO are printed in italics.

Thus the preference of the substitution of the 5-chloro *vs.* 4-chloro atom in ethanol can be satisfactorily explained by the *charge difference* between C-5 and C-4 (moreover, an enhanced polarization could be expected in polar medium, *cf* lit.,[16]). Paradoxically, in strict sense, these reactions may not yet be considered to be charge controlled because of the above argumentation. The similar selectivities obtained with 4-substituted benzylamines can also be understood, the nitrogen has the same charge and similar coefficient in the effective HOMO in each compound *(see Table 4)*.

Table 4

Net atomic charge (Q) p orbital coefficent (c) of nitrogen in 'effective' HOMO, energy values (E) and heat of formation (ΔH^f) calculated by AM1 method for benzylamines

Compound	Q (au)	c	E_1 (ev) HOMO[a]	LUMO	ΔH^f (kcal/mol)
$C_6H_5CH_2NH_2$	-0.35	0.26	-9.81	0.46	19.8
$4\text{-}ClC_6H_5CH_2NH_2$	-0.35	-0.23	-9.96	0.09	12.1
$4\text{-}CH_3OC_6H_4CH_2NH_2$	-0.35	-0.22	-9.78	0.46	-18.6
$C_6H_5CH_2NHCH_3$	-0.30	-0.10	-9.46	0.52	22.3

[a] 'effective' HOMO[15]

However, the opposite regioselectivity obtained in toluene cannot be explained on this basis, and even a much higher 5/4-ratio would be predicted in this solvent than in ethanol by comparing their ε values (2.4, 26). *In order to try to explore the origin of this contradiction*, we next investigated the change of the energies along the reaction path to intermediates (I) and (II), *i.e.* for the rate determining step, using the C-N distances as reaction coordinates (*Figure 2*).

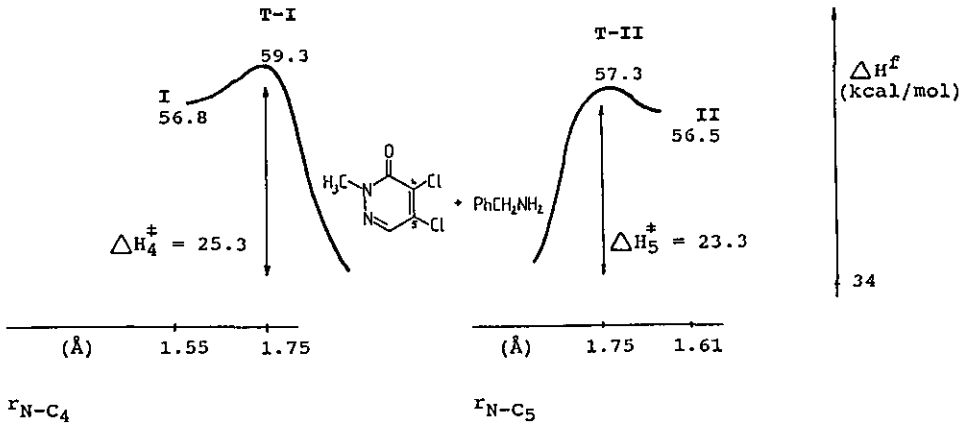


Figure 2

The reaction profile for the reaction of 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone with benzylamine calculated by AM1 method

In both reactions, as the nucleophile approaches the pyridazinone ring, the energy rises monotonically to the transition states (T-I), (T-II), and then lowers to the intermediates (I) and (II). The activation barriers

($\Delta H^{\neq}$) are given by differences between the heats of formation of T-I, T-II and the separated reactants, respectively *(Table 5)*.

Table 5

Heats of formation and dipole moments of T-I and T-II

		T-I	T-II
ΔH^{f}	(kcal/mol)	59.3	57.3
$\Delta H^{\neq}_{calcd.}$	(kcal/mol)	25.3	23.3
μ	(D)	5.13	7.59

The calculated activation energies $[\Delta H^{f}_{T}-(\Delta H^{f}_{1a}-\Delta H^{f}_{amine})]$, which correlate well with $\Delta G^{\neq}$ values obtained in ethanol-d_6 experimentally,[17] favour again the formation of the 5-isomer. However, comparing the transition states (T-I) and (T-II) in details, there still exists a striking difference between them, namely in dipole moments. We believe it may actually be one important reason for the reversed selectivity obtained in toluene. As a consequence of the higher dipole moment of T-II, it should be more solvated in both solvents. This would result in more negative $\Delta S^{\neq}_{S}$ and consequently more positive $\Delta G^{\neq}_{S}$. In other words, the decreased need for participation of solvent molecules in the transiton state (T-I) may account for the preference of substitution reaction at 4-position of **1a** with benzylamine. Of course, this enhancement caused by $\Delta S^{\neq}$ in $\Delta G^{\neq}$ may be counter- or even overbalanced by lowering $\Delta H^{\neq}$ through solvation. The more polar the transition state is, the more lower $\Delta H^{\neq}$ will be obtained - as it has been found for the formation of the 5-isomer in ethanol. The 'anomalous' behaviour of the 6-nitro derivative (**1b**) with benzylamine affording high 5/4-isomer ratio in toluene could be explained by 'built-in solvation' operating in the transition state of the 5-isomer as described for *ortho*-nitrohalobenzenes.[18]

CONCLUSIONS

Our results presented here indicate that in reactions of 4,5-dihalo-3(2*H*)-pyridazinones with benzylamines the attack of the nucleophile at C-4 or C-5 is the rate-determining step. The regioselectivities can reach modest- to high level influenced mainly by the solvent and the substituent(s) of the pyridazinone ring. Generally, the results are predictable by considering the transition states (T-I), and (T-II). The differences between their energies (characterized by ΔE_{p} or

$\Delta H^{\neq}_{calc.}$), or their dipole moments seem to be manifested depending on the polarity of the medium. Formations of 5- or 4-isomers are favored in ethanol or toluene, respectively.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. Spectral data were recorded on the following instruments: ^1H and ^{13}C nmr: Bruker AC 250 and AC 400 in $CDCl_3$ (unless otherwise stated). All chromatographic separations were done using Merck silica gel (Kieselgel 60) and chloroform-ethyl acetate mixtures as eluent. Syntheses of compounds (**1a**),[18] (**1b**),[20] (**1c**),[21] (**1d**)[22] were performed to the quoted literatures. All reagents and solvents were purified just before use by standard methods.

Kinetic measurements.

- Reaction of **1a** *with benzylamine in ethanol-d_6 and toluene-d_8.*
Stock solutions of each reagent (0.2 and 0.6 mol/l, respectively) were prepared and the reaction was started by mixing 0.25 ml of both solutions in a nmr tube thermostated for the reaction temperature. At known intervals, at least up to conversion of 0.7 ^1H nmr spectra were recorded at the same temperature. Concentrations of the starting pyridazinone (**1a**), and products (**2a**, **6a**) were calculated as avarage values based on the integrations of 6-C*H*, N-CH_3 and N-CH_2 signals. These data were used as inputs for SimuSolv program.

Computational procedure.

The calculations reported in this work were carried out at the AM1 semi-empirical level by using the 'Program Version 2.3' for Convex C120 (Walter Thiel, Wuppertal, 1989). Molecular geometries were fully optimized (except for the C-N distances in reaction profile calculations). The transition states obtained by these calculations are to be considered as only approximations to the true transition states.

Investigation of isomer ratios and conversions of reactions of pyridazinones **1a-d** *with benzylamines; preparation of the 4- and 5-isomers,* **2-5** *and* **6-9**.
Reactions were carried out in 0.1 mol/l concentration for **1a-d** under conditions given in *Table 1* (in each run 2 mmol of the starting pyridazinone were used). The reaction mixtures were cooled to 20°C and the solvent was evaporated *in vacuo* at this temperature. The residue taken up in 10 ml of

water was made acidic to pH = 5 with 2N HCl and extracted with ethyl acetate. The organic layers were dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The obtained residues were analyzed by ^1H nmr in $CDCl_3$ (the data are collected in *Table 1*), and they were chromatographed in experiments according to Entries 1,4,5, 7-11, 13 and 14 (see *Table 1*). The products were characterized by spectroscopic data, melting points and elemental analyses.

4-Benzylamino-5-chloro-2-methyl-3(2H)-pyridazinone (**2a**)
- ^1H nmr: δ 3.68 (s, 3H, N-CH_3), 4.93 (d, J = 6.5 Hz, 2H, N-CH_2), 6.25 (br, 1H, NH), 7.20-7.40 (m, 5H, Ph-H), 7.50 (s, 1H, 6-CH) ppm; mp 97-98 °C (lit.,[3] 98° C); Anal. Calcd for $C_{12}H_{12}N_3OCl$: C, 57.73; H, 4.84; N, 16.83. Found C, 57.91; H, 4.81; N, 16.70.

5-Benzylamino-4-chloro-2-methyl-3(2H)-pyridazinone (**6a**)
- ^1H nmr: δ 3.71 (s, 3H, N-CH_3), 4.58 (d, J = 6.0 Hz, 2H, N-CH_2), 6.21 (t, J = 6.0 Hz, 1H, NH), 7.25-7.45 (m, 5H, Ph-H), 7.51 (s, 1H, 6-CH) ppm; mp 184-185 °C (lit., [3] 183-185 °C); Anal. Calcd for $C_{12}H_{12}N_3OCl$: C, 57.73; H, 4.84; N, 16.83. Found C, 57.64; H, 4.90; N, 16.71.

5-Chloro-4-(4-chlorobenzylamino)-2-methyl-3(2H)-pyridazinone (**3a**)
- ^1H nmr: δ 3.72 (s, 3H, N-CH_3), 4.88 (d, J = 6.7 Hz, 2H, N-CH_2), 6.23 (br, 1H, NH), 7.22 (d, J = 8.4 Hz, 2H, 3,5-Ph), 7.31 (d, J = 8.4 Hz, 2H, 2,6-Ph), 7.47 (s, 1H, 6-CH) ppm; mp 110-112 °C; Anal. Calcd for $C_{12}H_{11}N_3OCl_2$: C, 50.72; H, 3.90; N, 14.79. Found C, 50.55; H, 3.78; N, 14.74.

4-Chloro-5-(4-chlorobenzylamino)-2-methyl-3(2H)-pyridazinone (**7a**)
- ^1H nmr: δ 3.70 (s, 3H, N-CH_3), 4.50 (d, J = 6.0 Hz, 2H, N-CH_2), 5.63 (br, 1H, NH), 7.28 (br, 4H, Ph), 7.40 (s, 1H, 6-CH) ppm; mp 181-182 °C; Anal. Calcd for $C_{12}H_{11}N_3OCl_2$: C, 50.72; H, 3.90; N, 14.79. Found C, 50.70; H, 3.86; N, 14.74.

5-Chloro-4-(4-methoxybenzylamino)-2-methyl-3(2H)-pyridazinone (**4a**)
- ^1H nmr: δ 3.71 (s, 3H, N-CH_3), 3.79 (s, 3H, OCH_3), 4.85 (d, J = 5.8 Hz, 2H, N-CH_2), 6.17 (t, J =5.8 Hz, 1H, NH), 6.86 (d, J = 8.7 Hz, 2H, 3,5-Ph), 7.22 (d, J = 8.7 Hz, 2H, 2,6-Ph), 7.47 (s, 1H, 6-CH) ppm; oil; Anal. Calcd for $C_{13}H_{14}N_3O_2Cl$: C, 55.81; H, 5.04; N, 15,02. Found C, 56.10; H, 5.34; N 14.82.

4-Chloro-5-(4-methoxybenzylamino)-2-methyl-3(2H)-pyridazinone (**8a**)
- ^{1}H nmr: δ 3.72 (s, 3H, N-CH_3), 3.80 (s, 3H, OCH_3), 4.47 (d, J = 6.4 Hz, 2H, N-CH_2), 5.22 (br, 1H, NH), 6.89 (d, J = 8.6 Hz, 2H, 3,5-Ph), 7.22 (d, J = 8.6 Hz, 2H, 2,6-Ph), 7.51 (s, 1H, 6-CH) ppm; oil; Anal. Calcd for $C_{13}H_{14}N_3O_2Cl$: C, 55.81; H, 5.04; N, 15,02. Found C, 55.87; H 5.18; N, 14.78.

5-Chloro-4-(N-methylbenzylamino)-2-methyl-3(2H)-pyridazinone (**5a**)
- ^{1}H nmr: δ 2.96 (s, 3H, C_4-N-CH_3), 3.73 (s, 3H, 2-N-CH_3), 4.65 (s, 2H, N-CH_2), 7.2-7.4 (m, 5H, Ph), 7.47 (s, 1H, 6-CH) ppm; ^{13}C nmr: δ 40.2, 40.3 (2 x N-CH_3), 57.3 (N-CH_2), 121.9 (C-5), 127.2, 127.8, 128.4, 138.3 (Ph + C-6), 144.6 (C-4), 159.2 (C-3) ppm; oil; Anal. Calcd for $C_{13}H_{14}N_3OCl$: C, 59.20; H, 5.35; N, 15.93. Found C, 59.21; H, 5.43; N, 15.94.

4-Chloro-5-(N-methylbenzylamino)-2-methyl-3(2H)-pyridazinone (**9a**)
- ^{1}H nmr: δ 3.04 (s, 3H, C_5-N-CH_3), 3.75 (s, 3H, 2-N-CH_3), 4.62 (s, 2H, N-CH_2), 7.2-7.4 (m, 5H, Ph), 7.57 (s, 1H, 6-CH) ppm; ^{13}C nmr: δ 39.4, 40.3 (2 x N-CH_3), 56.9 (N-CH_2), 113.8 (C-4), 127.1 127.6, 128.7 136.5 (Ph), 130.2 (C-6), 147.2 (C-5), 158.7 (C-3) ppm; oil; Anal. Calcd for $C_{13}H_{14}N_3OCl$: C, 59.20; H, 5.35; N, 15.93. Found C, 58.81; H, 5.45; N, 15.73.

4-Benzylamino-5-chloro-2-methyl-6-nitro-3(2H)-pyridazinon (**2b**)
-^{1}H nmr: δ 3.70 (s, 3H, N-CH_3), 4.98 (d, J = 6.5 Hz, 2H, N-CH_2), 6.50 (br, 1H, NH), 7.35 (s, 5H, Ph) ppm; ^{13}C nmr: δ 40.1 (N-CH_3), 48.11 (N-CH_2), 96.9 (C-5), 127.2, 128.0, 128.9, 137.4 (Ph), 141.2 (C-4), 149.5 (C-6), 155.1 (C-3) ppm; mp 123-125 °C; Anal. Calcd for $C_{12}H_{11}N_4O_3Cl$: C, 48.90; H, 3.76; N, 19.01. Found C, 49.22; H, 3.84; N, 18.71.

5-Benzylamino-4-chloro-2-methyl-6-nitro-3(2H)-pyridazinon (**6b**)
-^{1}H nmr :δ 3.70 (s, 3H, N-CH_3), 4.85 (d, J = 6.0, 2H, N-CH_2), 6.70 (br, 1H, NH), 7.35 (s, 5H, Ph) ppm; ^{13}C nmr: δ 41.0 (N-CH_3), 49.2 (N-CH_2), 110.6 (C-4), 127.3, 128.1, 129.0, 137.0 (Ph), 139.0, 139.6 (C-5, C-6), 157.7 (C-3) ppm; mp 123-125 °C; Anal. Calcd for $C_{12}H_{11}N_4O_3Cl$: C, 48.90; H, 3.76; N, 19.01. Found C, 48.62; H, 3.84; N, 18.81.

4-Benzylamino-5-bromo-2-methyl-3(2H)-pyridazinone (**2c**)
- ^{1}H nmr: δ 3.73 (s, 3H, N-CH_3), 4.97 (d, J = 6.5 Hz, 2H, N-CH_2), 6.20 (br, 1H, NH), 7.3-7.4 (m, 5H, Ph), 7.60 (s, 1H, 6-CH) ppm; mp 83-84 °C; Anal. Calcd for $C_{12}H_{12}N_3OBr$: C, 48.99; H, 4.11; N, 14.27; Br, 27.19. Found C, 48.95; H, 3.95; N, 14.05; Br, 27.32.

5-Benzylamino-4-bromo-2-methyl-3(2H)-pyridazinone (**6c**)
- ^{1}H nmr: δ 3.75 (s, 3H, N-CH_3), 4.55 (d, J = 6.0 Hz, 2H, N-CH_2), 5.20 (br, 1H, NH), 7.30-7.40 (m, 6H, Ph + 6-CH) ppm; mp 133-134 °C, Anal. Calcd for $C_{12}H_{12}N_3OBr$: C, 48.99; H, 4.11; N, 14.27; Br,27.19. Found C, 49.10; H, 4.04; N, 14.03; Br; 27.20.

4-Benzylamino-5-chloro-2-phenyl-3(2H)-pyridazinone (**2d**)
- ^{1}H nmr: δ 4.98 (d, J = 6.5 Hz, 2H, N-CH_2), 6.30 (br, 1H, NH), 7.2-7.8 (m, 11H, 2xPh, 6-CH), ppm; mp 110-112 °C (lit.,[3] 109-110 °C); Anal. Calcd for $C_{17}H_{14}N_3OCl$: C, 65.48; H, 4.53; N, 13.48. Found C, 65.46; H 4.50; N, 13.58.

5-Benzylamino-4-chloro-2-phenyl-3(2H)-pyridazinone (**6d**)
- ^{1}H nmr: δ 4.62 (d, J = 6.0 Hz, 2H, N-CH_2), 5.8 (br, 1H, NH), 7.3-7.6 (m, 10H, 2xPh), 7.70 (s, 1H, 6-CH) ppm; mp 210-212 °C (lit.,[3] 213-215 °C); Anal. Calcd for $C_{17}H_{14}N_3OCl$: C, 65.48; H, 4.53; N, 13.48. Found C, 65,55; H, 4.71; N, 13.38.

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