HETEROCYCLES, Vol. 71, No. 1, 2007, pp. 141 - 151. © The Japan Institute of Heterocyclic Chemistry
Received, 20th October, 2006, Accepted, 1st December, 2006, Published online, 5th December, 2006. COM-06-10923

THE SELECTIVE FUNCTIONALIZATION OF PYRIDAZINO[4,5-*d*]-PYRIDAZINES USING POLAR ORGANOMETALLIC REAGENTS

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Dedicated to Prof. Pál Sohár on the occasion of his 70th birthday.

Abstract – Selected pyridazino[4,5-*d*]pyridazine derivatives were reacted with polar organometallic reagents to result in the addition of the organic moiety onto the 5-position of the ring system with high selectivity.

INTRODUCTION

Pyridazine is one of the fundamental structural elements in heterocyclic chemistry and its derivatives have attracted considerable attention both in organic and medicinal chemistry. The wide range of pharmacological effects associated with the pyridazine ring and its condensed analogues is well-documented in the literature.[1-7] In spite of this extensive knowledge surprisingly little attention has been paid to chemistry and pharmacology[8,9] of the related pyridazino[4,5-*d*]pyridazine system. This can be due to the fact that so far only a variety of 1,4-disubstituted pyridazino[4,5-*d*]pyridazine derivatives had been prepared from 4,5-disubstituted pyridazines by using commercial synthetic methods including ring closure with hydrazine.[8-14]

To open up new synthetic routes to selectively functionalized pyridazino[4,5-*d*]pyridazines we studied the reactivity of this condensed system towards polar organometallic reagents. The planned study was driven not only by the need for new synthetic routes, since the reactivity of the pyridazino[4,5-*d*]pyridazine system towards polar organometallic reagents is of theoretical interest too. Besides incorporating pyridazine moieties the selected bicyclic starting materials (**1a** and **1b**) can also be considered as extended analogues of tetrazine (**1c**) (Figure 1) and therefore offer the possibility of alternate reaction routes. If they behave pyridazine-like, then the attack of the incoming organometallic reagent is expected to take place following route *A*, or route *C*. The analogous reaction of pyridazines[15-17] and their benzanellated derivatives[18-25] is well documented in the literature. If the pyridazino[4,5-*d*]pyridazines behave

tetrazine-like, then the incoming nucleophile is expected to attack at a ring nitrogen atom (routes *B*), a transformation coined 'azaphilic addition'[26] that was so far mostly limited to tetrazines. This reaction was found to proceed readily on **1c** with lithium-, magnesium- and zincorganic reagents,[27] while other nuleophiles followed route *C* on **1c**.[28] The aim of the present study was to establish the reactivity of the pyridazino[4,5-*d*]pyridazine system towards polar organometallic reagents, develop a useful synthetic procedure for substituted pyridazino[4,5-*d*]pyridazines, and interpret the observed chemical behaviour.

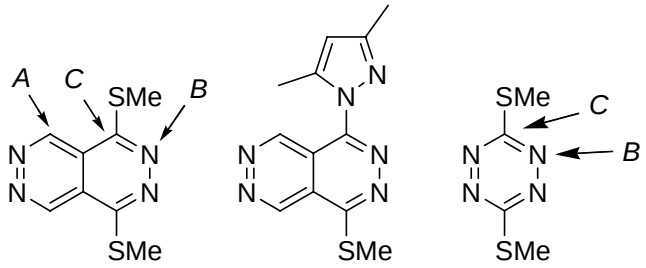

Figure 1. The compounds (**1a,b**) that are subject of this study, the analogous tetrazine derivatives (**1c**), and the possible sites for the attack of the polar organometallic reagents.

RESULTS AND DISCUSSION

Preliminary screening of the reaction of **1a** with different organometallic reagents revealed that the more polar organolithium and Grignard reagents (**2a-c**) initiate a clean transformation of the pyridazinopyridazine moiety already at -78 ^{o}C. Leaving the reaction mixtures to warm up to room temperature, followed by aqueous workup led to the isolation of a single product in all cases (Figure 2), usually in good yield (Table 1, entries 1-3). The structures were unambiguously identified by spectroscopic methods as the adduct **3a** and **3b** (route *A*). The use of the heterocuprate **2d** gave satisfactory results too (entry 4), although the exchange of copper(I) iodide to copper(I) cyanide stopped the process and only unreacted starting material was recovered even after prolonged standing at room temperature. Phenylzinc chloride was found to be similarly unreactive.

Extension of the reaction to other organolithium reagents (**2e-j**, entries 5,7,8,10-12) gave similar results. The only products whose formation is observed in these processes by TLC, ^{1}H- and ^{13}C NMR are the 5-substituted pyridazinopyridazine derivatives (**3c-g**), which were isolated in moderate to good yield. Deterioration of the isolated yield in certain cases might be due to the partial decomposition of the dihydro-compounds during chromatographic purification on silica gel. Presence of the aromatised derivatives of **3** that could be formed by oxidation during workup was never observed. It is interesting to note that the corresponding pyridyl derivative is present in the tautomeric **5h** form under these conditions, which is stabilized by nitrogen-sulphur close contact[29] generating a quasi six-membered ring, as

evidenced by mutual NOE's (12-16 %) between 4-SMe- and H6' protons and the lack of NOE between 4-SMe- and H3' protons.

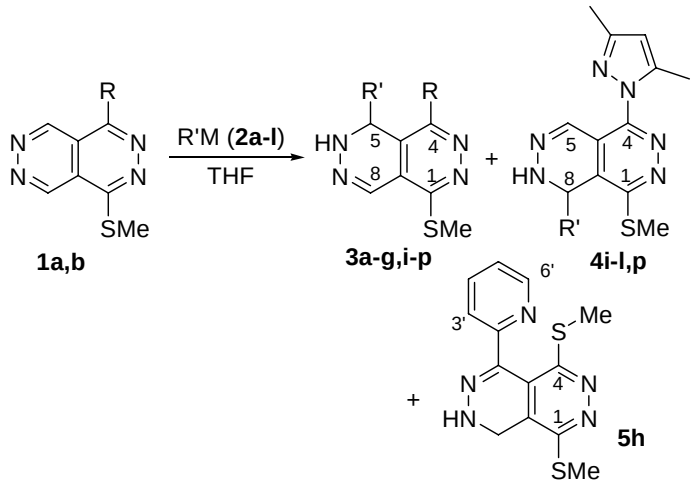

Figure 2. The reaction of pyridazino[4,5-*d*]pyridazines (**1a** and **1b**) with organometallic reagents.

By changing one of the methylthio groups in the starting material to pyrazole (**1b**) we were asking two new questions: is the chemoselectivity of the process (exclusive pyridazine-like addition) retained in the case of **1b**, and what is the regioselectivity of the process? Already the first examples (entries 13-15) revealed that the same chemoselectivity is prevailing for **1b** too. At the same time we also observed a reagent dependent regioselectivity in the process. The use of phenyllithium (**2a**, entry 13) led to the formation of two products, the major one bearing the phenyl group in the proximity of the pyrazole moiety (**3i**), and the other bearing the phenyl group in the proximity of the methylthio functionality (**4i**). On the other hand, the use of phenylmagnesium chloride (**2c**, entry 14) led to the exclusive formation of the formerly major isomer (**3i**), in excellent yield. The observed regioselectivity of the process and the difference in the product distribution using lithiumorganic and Grignard reagents might be attributed to the different coordination in the intermediate reactant-reagent complexes (*vide infra*). Interestingly the reaction of butyllithium with **1b** was practically blocked in the presence of copper(I) iodide (**2d**, entry 16) giving only poor conversion, a phenomenon also observed in the analogous transformation of tetrazine derivative (**1c**).[27]

The reaction of **1b** with other organolithium reagents (**2e-j**, entries 17,19,20,22-24) led to similar results, although with varying efficiency. The favoured products (**3k-p**) arose in all cases from the attack of the nucleophile at the 5-position, next to the pyrazole moiety. In certain cases (entries 18,19,24) we identified the presence of the other regioisomer (**4k**, **4l** and **4p**) in the crude product by ^{1}H- and ^{13}C NMR but, except for **4p**, attempts to isolate them in pure form remained in vain.

Table 1. Yields and product distribution in the reaction of **1a** and **1b** with organometallic reagents

Entry	Substrate	Reagent	Yield (%)
1	**1a**	PhLi (**2a**)	91 (**3a**)
2	**1a**	PhMgCl (**2c**)	40 (**3a**)
3	**1a**	BuLi (**2b**)	65 (**3b**)
4	**1a**	BuCuLiI (**2d**)	61 (**3b**)
5	**1a**	4-lithioanisole (**2e**)[a]	43 (**3c**)
6	**1a**	4-anisylmagnesium bromide (**2k**)	88 (**3c**)
7	**1a**	2-lithioanisole (**2f**)[b]	51 (**3d**)
8	**1a**	1-lithionaphthaline (**2g**)[a]	52 (**3e**)
9	**1a**	1-naphthylmagnesium bromide (**2l**)	90 (**3e**)
10	**1a**	2-lithionaphthaline (**2h**)[a]	33 (**3f**)
11	**1a**	2-lithiothiophene (**2i**)	90 (**3g**)
12	**1a**	2-lithiopyridine (**2j**)[a]	18 (**5h**)
13	**1b**	**2a**	35 (**3i**),11 (**4i**)[c]
14	**1b**	**2c**	93 (**3i**)
15	**1b**	**2b**	18 (**3j**), 9 (**4j**)[c]
16	**1b**	**2d**	substrate recovered
17	**1b**	**2e**[b]	18 (**3k**)
18	**1b**	**2k**	46 (**3k**), 19 (**4k**)[c]
19	**1b**	**2f**[c]	54 (**3l**), 9 (**4l**)[c]
20	**1b**	**2g**[b]	45 (**3m**)
21	**1b**	**2l**	69 (**3m**)
22	**1b**	**2h**[b]	74 (**3n**)
23	**1b**	**2i**	45 (**3o**)
24	**1b**	**2j**[b]	11 (**3p**), 35 (**4p**)
25	**1b**	**2a** + TMEDA	36 (**3i**)

[a] Reagent was prepared by lithium-halogen exchange.
[b] Reagent was prepared by *o*-lithiation using butyllithium
[c] This product was not separated. Yield is calculated on the basis of the crude product's NMR spectra and the yield of the major isomer.

The corresponding regioisomer pairs (**3** and **4**) were unambiguously identified by NOE interactions detected between SMe- and H8 protons (4-8 %) which are easily assignable on the basis of chemical

shifts, 2D-COSY, 2D-HMQC- and 2D HMBC measurements. It is also of diagnostic importance that the pyrazolyl N2 atom exerts a significant deshielding effect on the adjacent pyridazine-H5 atom pointing to the dominance of a conformation with a quasi six-membered ring. This was also supported by ^{1}H-^{15}N-HMBC measurements for **3k** and **4k** exhibiting an intensive cross peak between H5 and N2' atoms, which suggests that a weak hydrogen bond might be formed at least transitionally between them.

In certain cases, where the organolithium reagent was prepared by lithium-halogen exchange from the appropriate aryl halide and butyllithium (entries 10,17 and 20), besides obtaining only mediocre yields we also observed the formation of some side products by TLC, whose presence was attributed to the incomplete formation of the organometallic reagent. In the hope of improving the efficiency of the transformations we replaced some of the organolithium reagents with the appropriate Grignard reagent (**2c,k,l**, entries 6,9,18,21). To our pleasant surprise most of these reactions took place with almost complete regioselectivity, the detectable formation of a minor product (**4k**, entry 18) was only observed in the reaction of **1b** with 4-anisylmagnesium bromide (**2k**).

The different regioselectivity in reactions with organolithium and Grignard reagents (*cf.,* entries 13-14 and 20-21) arises probably from the different aggregation and coordination behaviour of these reagents. This hypothesis is also supported by the fact that the reaction of **1b** with phenyllithium (**2a**) in the presence of 1 eq. TMEDA (entry 25) gave **3i** (we were unable to detect the presence of **4i** in the reaction mixture). The preferred formation of the 5-alkyl/aryl adducts from **1b** might be attributed to the coordination of the organometallic reagent to the pyrazole moiety prior to the addition and the stabilization of the formed intermediate through the involvement of the sulphur atom. In case of the alternate attack at C8 the formed negative charge can not appear on C1 as for the C5 attack.

CONCLUSION

By studying the reactivity of the pyridazine[4,5-*d*]pyridazine system towards organometallic reagents we established that, independent of the coordinating ability of the substituents present on the system, the incoming nucleophiles attack the unsubstituted 5-position of the pyridazinopyridazine moiety. On systems, where two different substituents were present in position 1 and 4, the attack of the organometallic reagents proceeded with good to excellent regioselectivity. Studies on the utilization of the observed addition in the preparation of new ring systems are in progress in our laboratories.

EXPERIMENTAL

General Remarks: Melting points were determined with a Boetius microstage. IR spectra were recorded in KBr pellets with a BRUKER IFS 55 FT-spectrometer. ^{1}H-and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at rt, on a Bruker DRX 500 spectrometer at 500 (^{1}H)-, 125 (^{13}C) MHz,

using TMS as internal reference with the deuterium signal of the solvent as the lock. The ^{15}N-NMR data obtained from 2D-HMBC spectra (at 50 MHz) are given on the scale adjusted to the reference signal of liquid ammonia (δ = 0 ppm). The standard Bruker microprogram NOEMULT.AU to generate NOE was used with a selective preirradiation time. DEPT spectra were run in a standard manner, using only the Θ = 135^o pulse to separate CH/CH_3 and CH_2 lines phased „up" and „down", respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs INV4GS and INV4GSLPLRND, respectively. THF was distilled from potassium/benzophenone before use. 1,4-Bis(methyltio)pyridazino[4,5-*d*]pyridazine (**1a**) and 1-methylthio-4-(3',5'-dimethylpyrazol-1'-yl)-pyridazino[4,5-*d*]pyridazine (**1b**) were prepared following literature procedures.[12] 4-Lithioanisole (**2e**), 1-lithionaphthalene (**2g**) and 2-lithiopyridine (**2i**) were prepared from the appropriate aryl bromide and butyllithium in abs. THF at -78 ^{o}C. 2-Lithioanisole (**2f**) and 2-lithiothiophene (**2h**) were prepared by the deprotonation of the appropriate starting material using butyllithium.

General procedure for the reaction of pyridazino[4,5-d]pyridazine derivatives (1a,b) with organometallic reagents (2a-i): In a flame dried Schlenk flask **1a** or **1b** (1 mmol) was dissolved in abs. THF (2 mL) under argon and the solution was cooled to -78 ^{o}C. After the dropwise addition of a solution of 1.1 mmol of the appropriate organometallic reagent (**2a-i**) the mixture was left to stir at -78 ^{o}C for 1 h and then it was allowed to warm to rt. The reaction mixture was quenched by adding saturated aqueous ammonium chloride, and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and the volatiles were removed in vacuum. The residue was purified by column chromatography on silica gel using hexane–EtOAc mixtures as eluent.

1,4-Bis(methylthio)-5-phenyl-5,6-dihydropyridazino[4,5-d]pyridazine (3a): yellow solid, mp 146-148 °C; 1H NMR: δ 2.67 (s, 3H), 2.76 (s, 3H), 7.00 (br s, 1H), 7.27 (m, 2H), 7.33 (m, 3H), 7.43 (s, 1H); 13C NMR: δ 13.4, 13.7, 52.8, 119.2, 124.6, 127.3, 128.6 (two coalesced lines), 129.4, 140.0, 153.4, 157.6 ; IR ν_{max} 3233, 1457, 1293, 1280, 1245 cm-1; Anal. Calcd for $C_{14}H_{14}N_4S_2$: C 55.6 , H 4.67, N 18.53. Found: C 55.31, H 4.79, N 18.8%.

1,4-Bis(methylthio)-5-butyl-5,6-dihydropyridazino[4,5-*d*]pyridazine (3b): brown oil; ^{1}H NMR: δ 0.92 (t, J = 7.1 Hz, 3H), 1.34 (m, 2H), 1.32-1.44 (overlapping m's, 2H), 1.31-1.89 (overlapping m's, 2H), 2.72 (s, 3H), 2.73 (s, 3H), 4.43 (dd, J_1 = 10.3 Hz, J_2 = 2.3 Hz, 1H), 6.70 (br s, 1H), 7.44 (s, 1H); ^{13}C NMR: δ 13.3, 13.4, 14.3, 22.6, 27.3, 30.9, 49.9, 118.8, 126.3, 129.8, 153.2, 156.7 ; IR ν_{max} 3270, 1513, 1463, 1427, 1099 cm^{-1}.

5-(4'-Anisyl)-1,4-bis(methylthio)-5,6-dihydropyridazino[4,5-*d*]pyridazine (3c): orange solid, mp 149-150 ^{o}C; ^{1}H NMR: δ 2.64 (s, 3H), 2.75 (s, 3H), 3.77 (s, 3H), 5.39 (s, 1H), 6.83 (d, J = 8.5 Hz, 2H), 6.92 (s, 1H), 7.17 (d, J = 8.5 Hz, 2H), 7.41 (s, 1H); ^{13}C NMR: δ 13.4, 13.7, 52.3, 55.7, 114.7, 119.1, 124.8, 128.3, 128.7, 132.7, 153.3, 157.6, 160.5; IR ν_{max} 3242, 1652, 1510, 1456, 1292, 1279, 1249 cm^{-1};

Anal. Calcd for $C_{15}H_{16}N_4OS_2$: C 54.19, H 4.85, N 16.85. Found: C 54.25, H 4.67, N 16.90%.

5-(2'-Anisyl)-1,4-bis(methylthio)-5,6-dihydropyridazino[4,5-*d*]pyridazine (3d): tawny solid, mp 166-168 °C; ^{1}H NMR: δ 2.62 (s, 3H), 2.77 (s, 3H), 3.95 (s, 3H), 5.87 (s, 1H), 6.45 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.80 (t, J = 8.0 Hz, 1H),6.94 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.27 (td, J_1 = 8.0, J_2 = 1.2, 1H), 7.32 (br s, 1H), 7.4 (s, 1H); ^{13}C NMR: δ13.5, 13.7, 47.0, 55.9, 111.1, 120.5, 120.8, 123.4, 125.9, 128.8, 128.9, 130.3, 153.1, 156.9, 158.0 ; IR ν_{max} 3299, 1737, 1486, 1439, 1277, 1240 cm^{-1}; Anal. Calcd for $C_{15}H_{16}N_4OS_2$: C 54.19, H 4.85, N 16.85. Found: C 54.46, H 4.62, N 16.74%.

1,4-Bis(methylthio)-5-(1'-naphthyl)-5,6-dihydropyridazino[4,5-*d*]pyridazine (3e): yellow solid, mp 176-177 °C; ^{1}H NMR: δ 2.56 (s, 3H), 2.81 (s, 3H), 6.36 (s, 1H), 6.91 (dd, J_1 = 8.1 Hz, J_2 = 1.1 Hz, 1H), 6.97 (br s, 1H), 7.34 (t, J = 8.4 Hz, 1H), 7.44 (s, 1H), 7.56 (t, J = 8.0 Hz, 1H), 7.65 (t, J = 8.1 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 8.23 (d, J = 8.3 Hz, 1H); ^{13}C NMR: δ13.48, 13.5, 48.1, 120.3, 122.0, 124.5, 125.8, 126.6, 127.1, 127.9, 128.4, 129.9, 130.0, 130.1, 133.9, 134.9, 153.2, 158.0; IR ν_{max} 2867, 1738, 1501, 1269 cm^{-1}; Anal. Calcd for $C_{18}H_{16}N_4S_2$: C 61.34, H 4.58, N 15.90. Found: C 61.05, H 4.31, N 15.96%.

1,4-Bis(methylhtio)-5-(2'-naphthyl)-5,6-dihydropyridazino[4,5-*d*]pyridazine (3f): yellow solid, mp 190-191 °C; ^{1}H NMR: δ 2.65 (s, 3H), 2.78 (s, 3H), 5.63 (s, 1H), 6.98 (s, 1H), 7.40 (br s, 1H), 7.45 (dd, J_1 = 8.6, J_2 = 1.7 Hz, 1H), 7.47 (s, 1H), 7.48-7.49 (overlapping m's, 2H), 7.80-7.81 (overlapping m's, 2H), 7.82 (d, J = 8.6 Hz, 1H); ^{13}C NMR: δ13.4, 13.7, 53.0, 119.3, 124.5, 124.8, 126.6, 127.05, 127.11, 128.1, 128.7, 128.8, 129.7, 133.4, 133.8, 137.1, 153.4, 157.7; IR ν_{max} 3248, 1559, 1507, 1283, 1260 cm^{-1}; Anal. Calcd for $C_{18}H_{16}N_4S_2$: C 61.34, H 4.58, N 15.90. Found: C 61.05, H 4.24, N 15.59%.

1,4-Bis(methylthio)-5-(2'-thienyl)-5,6-dihydropyridazino[4,5-*d*]pyridazine (3g): yellow solid, mp 146-148 °C; ^{1}H NMR: δ2.69 (s, 3H), 2.75 (s, 3H), 5.73 (s, 1H), 6.91-6.94 (overlapping m's, 2H), 6.97 (s, 1H), 7.23 (dd, J_1 = 4.3 Hz, J_2 = 2.0 Hz, 1H), 7.26 (s, 1H); ^{13}C NMR: δ 13.4, 13.6, 48.3, 118.3, 124.8, 126.7, 126.8, 127.3 129.6, 142.3, 153.5, 157.1; IR ν_{max} 3236, 3090, 2923, 1427, 1331, 1290 cm^{-1}; Anal. Calcd for $C_{12}H_{12}N_4S_3$: C 46.73, H 3.92, N 18.16. Found: C 46.34, H 4.03, N 18.33%.

1,2-Dihydro-5,8-bis(methylthio)-4-(pyridin-2-yl)pyridazino[4,5-d]pyridazine (5h): yellow solid, mp 79-80 °C; ^{1}H NMR: δ 2.49 (s, 3H), 2.76 (s, 3H), 4.14 (s, 2H), 6.49 (br s, 1H), 7.33 (ddd, J_1 = 7.7 Hz, J_2 = 4.9 Hz, J_3 = 1.1 Hz, 1H),7.69 (br d, J = 7.7 Hz, 1H), 7.80 (td, J_1 = 7.7 Hz, J_2 = 1.7 Hz, 1H), 8.61 (br d, J = 4.7 Hz, 1H); ^{13}C NMR: δ13.8, 15.4, 41.4, 121.2, 123.1, 124.4, 128.1, 137.9, 146.6, 149.6, 154.2, 155.0, 155.9; IR ν_{max} 3435, 1635, 1559, 1472, 1287 cm^{-1}; Anal. Calcd for $C_{13}H_{13}N_5S_2$: C 51.46, H 4.32, N 23.08. Found: C 51.29, H 4.51, N 22.87%.

4-(3',5'-Dimethylpyrazol-1'-yl)-1-methylthio-5-phenyl-5,6-dihydropyridazino[4,5-*d*]pyridazine (3i): green solid, mp 85-87 °C; ^{1}H NMR: δ2.06 (s, 3H), 2.31 (s, 3H), 2.78 (s, 3H), 5.96 (s, 1H), 6.28 (s, 1H),

6.82 (d, 2H), 6.93 (br s, 1H), 7.10-7.20 (overlapping m's, 3H), 7.39 (s, 1H); ^{13}C NMR: δ 12.1, 13.5, 14.0, 51.9, 107.9, 122.1, 123.0, 126.1, 126.3, 129.0, 129.2, 142.1, 142.4, 151.1, 151.3, 156.0; IR ν_{max} 3257, 1563, 1528, 1457, 1423, 1122 cm^{-1}; Anal. Calcd for $C_{18}H_{18}N_6S$: C 61.69, H 5.18, N 23.98. Found: C 61.62, H 5.33, N 23.80%.

4-(3',5'-Dimethylpyrazol-1'-yl)-1-methylthio-8-phenyl-7,8-dihydropyridazino[4,5-d]pyridazine (4i): ^{1}H NMR: δ 2.32 (s, 3H), 2.46 (s, 3H), 2.74 (s, 3H), 5.55 (s, 1H), 6.07 (s, 1H), 6.97 (s, 1H), 7.10-7.20 (overlapping m's, 5H), 7.72 (s, 1H); ^{13}C NMR: δ 13.5, 13.8, 13.9, 52.9, 108.5, 111.4, 117.2, 127.3, 128.5 ,129.4, 129.7, 140.2, 160.2.

5-Butyl-4-(3',5'-dimethylpyrazol-1'-yl)-1-methylthio-5,6-dihydropyridazino[4,5-*d*]pyridazine (3j): brown oil containing also **4b**; ^{1}H NMR: δ 0.84 (t, J = 7.2, 3H), 1.1-1.3 (overlapping m's, 4H), 1.44-1.78 (m, 2H), 2.29 (s, 3H), 2.44 (s, 3H), 2.81 (s, 3H), 4.88 (dd, J_1 = 9.2 Hz, J_2 = 4.5 Hz, 1H), 6.05 (s, 1H), 6.80 (s, 1H), 7.55 (s, 1H); ^{13}C NMR: δ 12.8, 13.5, 14.1, 14.2, 22.3, 26.9, 31.1, 49.0, 108.1, 122.5, 123.7, 129.2, 142.7, 150.9, 151.0, 155.4; Anal. Calcd for $C_{16}H_{22}N_6S$: C 58.15, H 6.71, N 25.43. Found: C 57.98, H 6.82, N 24.93%.

8-Butyl-4-(3',5'-dimethylpyrazol-1'-yl)-1-methylthio-7,8-dihydropyridazino[4,5-*d*]pyridazine (4j): ^{1}H NMR: δ 0.94 (t, J = 6.9 Hz, 3H), 1.1-1.3 (overlapping m's, 4H), 1.37-2.08 (m, 2H), 2.33 (s, 3H), 2.44 (s, 3H), 2.80 (s, 3H), 4.23 (dd, J_1 = 10.0 Hz, J_2 = 3.0 Hz, 1H), 6.07 (s, 1H), 6.79 (s, 1H), 7.76 (s, 1H); ^{13}C NMR: δ 12.9, 13.6, 14.2, 14.3, 22.6, 27.4, 30.6, 50.1, 108.4, 116.7, 129.8, 130.8, 142.7, 151.3, 147.2, 159.2.

5-(4'-Anisyl)-4-(3',5'-dimethylpyrazol-1'-yl)-1-methylthio-5,6-dihydropyridazino[4,5-*d*]pyridazine (3k): orange solid, mp 73-75 ^{o}C; ^{1}H NMR: δ 2.02 (s, 3H), 2.28 (s, 3H), 2.76 (s, 3H), 3.71 (s, 3H), 5.93 (s, 1H), 6.15 (s, 1H), 6.65 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 7.20 (s, 1H), 7.33 (s, 1H); ^{13}C NMR: δ 12.1, 13.5, 14.0, 51.4, 55.6, 108.0, 114.5, 122.1, 123.4, 126.0, 127.5, 134.9, 142.5, 151.1, 151.2, 156.0, 160.5; ^{15}N NMR: δ 133 (NH pyridazine), 347 (N pyridazine), 205 (N1' pyrazole), 296 (N2' pyrazole); IR ν_{max} 3362, 1652, 1563, 1267 cm^{-1}; Anal. Calcd for $C_{19}H_{20}N_6OS$: C 59.98, H 5.30, N 22.09. Found: C 59.90, H 5.41, N 22.28%.

8-(4'-Anisyl)-4-(3',5'-dimethylpyrazol-1'-yl)-1-methylthio-7,8-dihydropyridazino[4,5-*d*]pyridazine (4k): ^{1}H NMR: δ 2.30 (s, 3H), 2.43 (s, 3H), 2.70 (s, 3H), 3.76 (s, 3H), 5.46 (s, 1H), 6.05 (s, 1H), 6.81 (d, J = 8.8 Hz, 2H), 7.15 (s, 1H), 7.22 (d, J = 8.8 Hz, 2H), 7.67 (s, 1H); ^{13}C NMR: δ 12.9, 13.8, 14.2, 52.6, 55.7, 108.7, 114.8, 117.2, 128.3, 128.9, 129.2, 132.6, 142.9, 147.1, 151.3, 160.2, 160.4; ^{15}N NMR: δ 132 (NH pyridazine), 345 (N pyridazine), 205 (N1' pyrazole), 300 (N2' pyrazole).

5-(2'-Anisyl)-4-(3',5'-dimethylpyrazol-1'-yl)-1-methylthio-5,6-dihydropyridazino[4,5-*d*]pyridazine (3l): greenish yellow solid containing also **4c**; ^{1}H NMR: δ 2.02 (s, 3H), 2.31 (s, 3H), 2.78 (s, 3H), 3.78 (s,

3H), 5.82 (s, 1H), 6.43 (s, 1H), 6.46 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.74 (t, J = 8.0 Hz, 1H), 6.82 (d, J= 7.9 Hz, 1H), 7.18 (td, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 7.29 (br s, 1H), 7.43 (s, 1H); ^{13}C NMR: δ 12.1, 14.0, 13.6, 46.7, 55.8, 107.6, 111.1, 120.5, 122.5, 122.7, 126.3, 127.4, 129.0, 129.9, 142.2, 150.9, 151.8, 155.5, 156.6; Anal. Calcd for $C_{19}H_{20}N_6OS$: C 59.98, H 5.30, N 22.09. Found: C 60.19, H 5.19, N 22.27%.

5-(3,5-Dimethylpyrazol-1-yl)-1-(2-Anisyl)-8-methylthio-1,2-dihydropyridazino[4,5-*d*]pyridazine (4l); ^{1}H NMR: δ 2.32 (s, 3H), 2.46 (s, 3H), 2.61 (s, 3H), 3.90 (s, 3H), 6.05 (s, 1H), 5.95 (s, 1H), 6.57 (dd, J_1 = 8.0 Hz, J_2 = 1.2 Hz, 1H), 6.80 (td J_1 = 8.0, J_2 = 1.2 Hz, 1H), 6.94 (d, J= 8.0 Hz, 1H), 7.23 (td J_1 = 8.0, J_2 = 1.2 Hz, 1H), 7.35 (br s, 1H), 7.69 (s, 1H); ^{13}C NMR: δ 12.9, 13.5, 14.1, 47.2, 55.9, 108.4, 112.2, 120.6, 122.2, 123.1, 127.1, 129.1, 129,7, 130.1, 142.7, 147.1, 151.4, 157.1, 160.7.

4-(3',5'-Dimethylpyrazol-1'-yl)-1-methylthio-5-(1'-naphthyl)-5,6-dihydropyridazino[4,5-*d*]-pyridazine (3m): greenish yellow solid, mp 178-180 ^{o}C; ^{1}H NMR: δ 1.90 (s, 3H), 1.92 (s, 3H), 2.84 (s, 3H), 5.51 (s, 1H), 6.90 (br s, 1H), 6.98 (d, J = 7.3 Hz, 1H), 7.02 (s, 1H), 7.27 (t, J = 7.8 Hz, 1H), 7.43 (s, 1H), 7.46 (t, J = 8.1 Hz, 1H), 7.50 (t, J = 8.1 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.82 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H) ; ^{13}C NMR: δ 12.4, 13.9 (two coalesced lines), 48.2, 107.6, 122.7, 123.3, 123.4, 125.4, 126.2, 126.7, 127.2, 127.4, 129.5 (two coalesced lines), 129.9, 134.5, 136.3, 142.0, 150.9, 151.3, 155.7; IR ν_{max} 3315, 1737, 1529, 1421, 1383,1302 cm^{-1}; Anal. Calcd for $C_{22}H_{20}N_6S$: C 65.98, H 5.03, N 20.98. Found: C 65.76, H 5.16, N 21.06%.

4-(3',5'-Dimethylpyrazol-1'-yl)-1-methylthio-5-(2'-naphthyl)-5,6-dihydropyridazino[4,5-*d*]-pyridazine (3n): greenish yellow solid, mp 79-80 ^{o}C; ^{1}H NMR: δ 1.99 (s, 3H), 2.33 (s, 3H), 2.77 (s, 3H), 5.96 (s, 1H), 6.46 (s, 1H), 6.99 (dd, J_1 = 8.3, J_2 = 1.9, 1H), 7.13 (br s, 1H), 7.17 (br s, 1H), 7.41 (s, 1H), 7.42-7.43 (m, 2H), 7.64 (m, 1H), 7.66 (d, J = 8.3, 1H), 7.73 (m, 1H); ^{13}C NMR: δ 12.0, 13.5, 14.1, 52.2, 108.0, 122.2, 122.9, 123.8, 125.1, 126.5, 126.9, 127.0, 128.0, 128.5, 129.4, 133.4, 133.5, 139.2, 142.6, 151.1, 151.4, 156.1; IR ν_{max} 3428, 1630, 1529, 1463, 1424, 1314 cm^{-1}; Anal. Calcd for $C_{22}H_{20}N_6S$: C 65.98, H 5.03, N 20.98. Found: C 66.20, H 5.00, N 20.80%.

4-(3',5'-Dimethylpyrazol-1'-yl)-1-methylthio-5-(2'-thienyl)-5,6-dihydropyridazino[4,5-*d*]pyridazine (3o): yellow solid, mp 117-118 ^{o}C; ^{1}H NMR: δ 2.20 (s, 3H), 2.30 (s, 3H), 2.78 (s, 3H), 5.99 (s, 1H), 6.53 (br d, J = 4.1 Hz, 1H), 6.62 (s, 1H), 6.79 (t, J = 4.1 Hz, 1H), 7.10 (br d, J = 4.1 Hz, 1H), 7.16 (br s, 1H), 7.53 (s, 1H); ^{13}C NMR: δ 12.5, 13.5, 14.1, 47.5, 108.2, 121.6, 122.8, 125.4, 126.4, 127.1, 128.0, 142.8, 143.8, 150.7, 151.5, 156.5; IR ν_{max} 3238, 1529, 1421, 1312, 1273, 1229 cm^{-1}; Anal. Calcd for $C_{16}H_{16}N_6S_2$: C 53.91, H 4.52, N 23.58. Found: C 53.80, H 4.68, N 23.79%.

4-(3',5'-Dimethylpyrazol-1'-yl)-1-methylthio-8-(2'-pyridyl)-7,8-dihydropyridazino[4,5-d]pyridazine (4p): yellow solid, mp 74-76 ^{o}C; ^{1}H NMR: δ 2.30 (s, 3H), 2.47 (s, 3H), 2.76 (s, 3H), 6.06 (s, 1H), 5.59 (s, 1H), 6.97 (d, J = 7.7 Hz, 1H), 7.23 (ddd, J_1 = 7.7 Hz, J_2 = 4.7 Hz, J_3 = 1.8 Hz, 1H), 7.78 (s, 1H), 7.62 (td,

J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.60 (br s, 1H), 8.63 (br dd, J_1 = 4.7 Hz, J_2 = 1.9 Hz, 1H); ^{13}C NMR: δ 12.8, 13.8, 13.3, 53.2, 109.1, 117.3, 122.1, 124.2, 127.5, 131.2, 138.0, 142.5, 147.4, 150.9, 151.2, 156.8, 160.5; IR ν_{max} 3446, 2926, 2856, 1772, 1653, 1541, 1457 cm^{-1}; Anal. Calcd for $C_{17}H_{17}N_7S$: C 58.10, H 4.88, N 27.90. Found: C 58.31, H 4.67, N 27.65%.

4-(3',5'-Dimethylpyrazol-1'-yl)-1-methylthio-5-(2'-pyridyl)-5,6-dihydropyridazino[4,5-*d*]pyridazine (3p): yellow solid, mp 65-67 ^{o}C; ^{1}H NMR: δ 2.14 (s, 3H), 2.36 (s, 3H), 2.80 (s, 3H), 5.92 (s, 1H), 6.14 (s, 1H), 6.79 (d, J = 7.7 Hz, 1H), 7.13 (ddd, J_1 = 7.7 Hz, J_2 = 4.7 Hz, J_3 = 1.8 Hz, 1H), 7.49 (s, 1H), 7.53 (td, J_1 = 7.7 Hz, J_2 = 1.8 Hz, 1H), 7.54 (br s, 1H), 8.48 (br dd, J_1 = 4.7 Hz, J_2 = 1.8 Hz, 1H); ^{13}C NMR: δ 12.4, 13.5, 13.6, 52.9, 108.1, 121.4, 121.5, 122.8, 123.2, 129.2, 136.7, 142.2, 150.1, 150.7, 152.0, 155.5, 158.5; IR ν_{max} 3430, 2924, 2853, 1559, 1540, 1457, 1420, 1261 cm^{-1}; Anal. Calcd for $C_{17}H_{17}N_7S$: C 58.10, H 4.88, N 27.90. Found: C 57.91, H 5.01, N 27.68%.

ACKNOWLEDGEMENTS

Financial support from the Hungarian Research Fund (OTKA F047125) and KPI (GVOP-3.2.1.-0358/3.0) are gratefully acknowledged.

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