Syntheses of *N*-Diazinyl Thiocarboxamides and of Thiazolodiazines. Metalation Studies. Diazines XXXIII

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Two thiazolodiazines were prepared from the corresponding *N*-diazinylcarboxamides by use of Lawesson's reagent. Two *N*-diazinylthiocarboxamides were obtained from amino derivatives by reaction with methyl phenyldithiocarboxylate. The metalation of these four compounds was studied and the thiazolodiazines could be functionalized.

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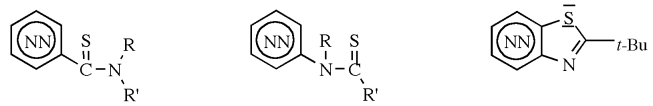
In the course of our studies on the metalation of diazines [1], we have recently published some syntheses and metalations of diazines thiocarboxamides [2]. In this paper we describe syntheses and metalations of new *N*-diazinylthiocarboxamides and thiazolodiazines (Scheme 1).

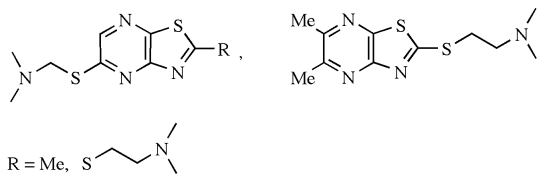
Scheme 1



It is also interesting to note that the thioamide bond is isosteric of the natural peptidic bond and that numerous peptides having thioamide bonds have been synthesized [3]. Some of these modified peptides have interesting biological properties [4].

In the heterocyclic series it has been highlighted that thiazolopyridines have various pharmaceutical activities as analgesic, antipyretic, antiinflamatory, antituberculosis and antiparasitic [5]. So, the 2-*tert*-butylthiazolo[4,5-*b*]-pyridine was the key intermediate in the synthesis of 1-aza-phenoxathiines which interacts with the central nervous system [6]. In the diazine series some thiazolopyrazines were known and are used as phleomycine amplifiers [7] (Scheme 2). They allowed the use of smaller amounts of phleomycine with better results against bacteria or tumors.

Scheme 2



In the pyridazine series many thiazolo[4,5-*d*]pyridazines are known but few thiazolo[4,5-*c*] were described [8]. This last ring system was studied for analgesic properties.

In order to prepare *N*-diazinylthiocarboxamides two synthetic pathways have been studied: the thionation of the corresponding amides with Lawesson's reagent (L.R.) or phosphorous pentasulfide, and reaction of dithioesters with aminodiazines.

Thionation of *N*-Diazinylcarboxamides.

Compound **1** was prepared from commercial aminopyrazine and pivaloyl chloride [9] and was submitted to thionation reagents (Scheme 3, Table 1).

Scheme 3

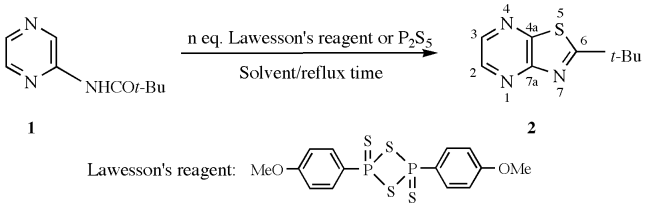


Table 1

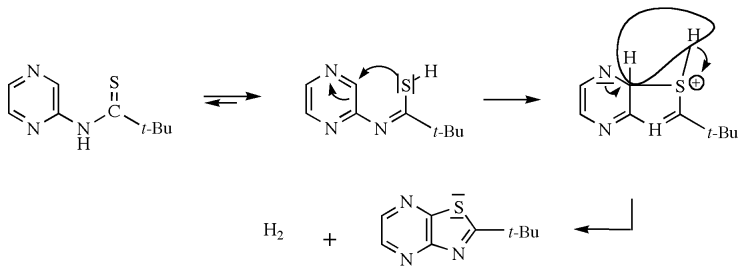
Thionation of Pivaloylaminopyrazine **1**

Entry	No. eq. thionation reagent	Solvent	Time (h)	Yield of **2**	Starting Material Recovered
1	0.6 L. R.	toluene	40	48%	22%
2	0.6 L.R.	//	115	42%	10%
3	1.1 L.R.	//	8	28%	56%
4	1.1 L.R.	//	115	70%	23%
5	1.5 P_2S_5	acetonitrile	24	51%	-
6**	1.5 P_2S_5	acetonitrile	48	51%	-

*L.R.: Lawesson's reagent; ** triethylamine added.

In all cases, only 6-*tert*-butylthiazolo[4,5-*b*]pyrazine **2** could be obtained. The best result was obtained in entry 4 with Lawesson's reagent and 5 days at the reflux temperature of toluene. The synthesis of the thiazolopyrazine **2** may be explained by a nucleophilic attack of the sulfur atom on the pyrazine ring (Scheme 4).

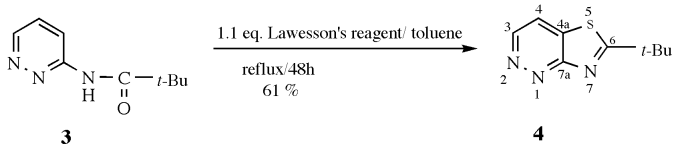
Scheme 4



This unexpected addition-elimination reaction was favored by the strong electronwithdrawing effect of the nitrogen atoms of the pyrazine ring. This electronwithdrawing effect was still more important in acidic medium or when these nitrogens were chelated with phosphorous. The addition of triethylamine (entry 6) did not change the yield, so the main effect might be the chelation with phosphorous.

The same reaction was tested in the pyridazine series with carboxamide **3** as the starting material [10]. (Scheme 5).

Scheme 5

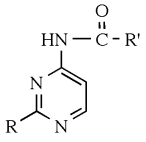


3 **4**

As in the pyrazine series, a thiazolodiazine: the 6-*tert*-butylthiazolo[4,5-*c*] pyridazine (**4**) was obtained, no starting material was recovered and an increase of the reaction time to 72 hours did not increase the yield (56%).

In the pyrimidine series, compounds (**5**-**10**) (Scheme 6) were reacted with Lawesson's reagent or phosphorous pentasulfide with various solvents (toluene, acetonitrile, tetrahydrofuran) at different temperatures (room temperature or reflux) during various times (0.5 hour to 7 days) and even under sonication. But no thiocarboxamides were obtained, the starting material was recovered or intractable tars were obtained when the experimental conditions were more drastic (longer time, higher temperature).

Scheme 6



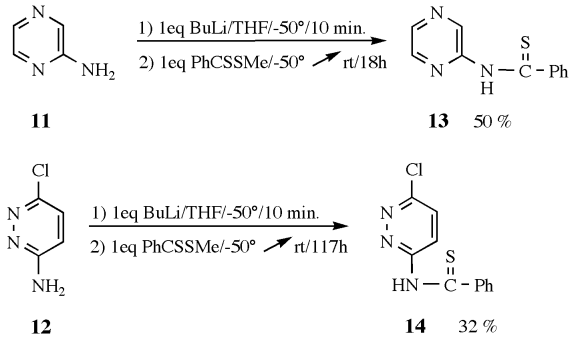
R = H	R' = Ph	**5**
R = H	R' = *t*-Bu	**6**
R = SMe	R' = Ph	**7**
R = SMe	R' = *t*-Bu	**8**
R = Cl	R' = Ph	**9**
R = Cl	R' = *t*-Bu	**10**

In summary, it was impossible to isolate *N*-diazinylthiocarboxamides when reacting Lawesson's reagent or P_2S_5 with the corresponding carboxamides. Only thiazolodiazines were obtained or the reaction failed (pyrimidines).

The second pathway used to synthesize the thiocarboxamides was the reaction of dithioesters with aminodiazines [11].

Deprotonation of aminodiazines **11** and **12** with *n*-butyl lithium and subsequent addition of methyl phenyldithiocarboxylate afforded the thiocarboxamides **13** and **14** (Scheme 7).

Scheme 7



11 **13** 50 %

12 **14** 32 %

Contrary to the previous syntheses with Lawesson's reagent or P_2S_5 the thiocarboxamides did not cyclize to thiazolodiazines like **2** or **4**. In the first syntheses, the reaction medium (Lawesson's reagent or phosphorous pentasulfide) was chelating, enforcing the electronwithdrawing effect of the diazine's nitrogens and by consequence the nucleophilic attack, whereas in the second syntheses the reaction medium was strongly basic.

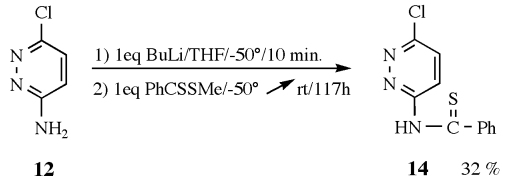
Metalation of Thiocarboxamides **13** and **14**.

To our knowledge no metalations of *N*-aromatic or *N*-heterocyclic thiocarboxamides have been reported. All the metalations were performed with tetrahydrofuran as the solvent.

The metalation of thiocarboxamide **13** was tested at -75 °C with lithium 2,2,6,6-tetramethylpiperidide, lithium diisopropylamide and BuLi as metalating agents in various amounts (2.1 – 4.0 equivalents) and various electrophiles

were tested (MeCHO, PhCHO, I_2). The reaction did not afford any isolable product and starting material was not recovered. When DCl was used as electrophile, only the starting material **13** (65%) was obtained. The use of methyl iodide as electrophile afforded compound **15** with good yield (Scheme 8).

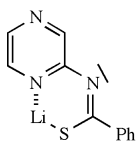
Scheme 8



12 **14** 32 %

Semi empiric Li/PM_3 [12] calculations indicated that the most stable lithio derivative is the chelate **16** in which the lithium atom is linked to the sulfur atom and to the N^1 nitrogen of pyrazine (Scheme 9).

Scheme 9



16

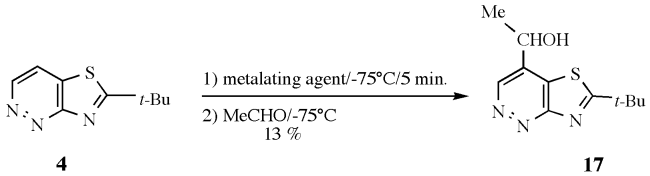
Compound **15** could be obtained by the reaction of methyl iodide with such a chelate. The reaction with DCl could afford a deuterated derivative on the sulfur atom which by a fast D → H exchange during work-up gave finally the starting material **13**.

The metalation was also tested with the pyridazine **14** and even with methyl iodide as the electrophile, an isolable product was not found and starting material was not recovered.

Metalation of Thiazolodiazines **2** and **4**.

The metalation reaction would allow for the functionalization of these compounds. The metalation of 6-*tert*-butylthiazolo[4,5-*c*]pyridazine **4** was performed (Scheme 10).

Scheme 10

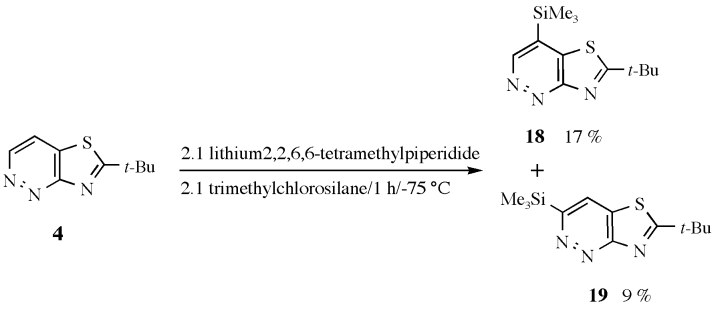


4 **17**

Lithium diisopropylamide was first used without results. The use of lithium 2,2,6,6-tetramethylpiperidide afforded with low yield (13%) the compound **17** when acetaldehyde was used as electrophile. When benzaldehyde was used as electrophile and lithium 2,2,6,6-tetramethylpiperidide as metalating agent, product was not isolated and some starting material **4** (8%) was recovered.

Another test was made with the "*in situ*" trapping method using trimethylchlorosilane as the electrophile (Scheme 11).

Scheme 11



4 **18** 17 % **19** 9 %

The two regioisomers **18** and **19** were obtained; the main isomer in 4 position **18** being the same as for the reaction with acetaldehyde. The predominance of the **4** isomer may be explained by an *ortho*-directing effect of the sulfur atom of the thiazole ring. However, this effect was weak because the yields were low and the regioselectivity moderate.

The metalation of 6-*tert*-butylthiazolo[4,5-*b*]pyrazine (**2**) was then tested with acetaldehyde as the electrophile (Scheme 12, Table 2).

Table 2

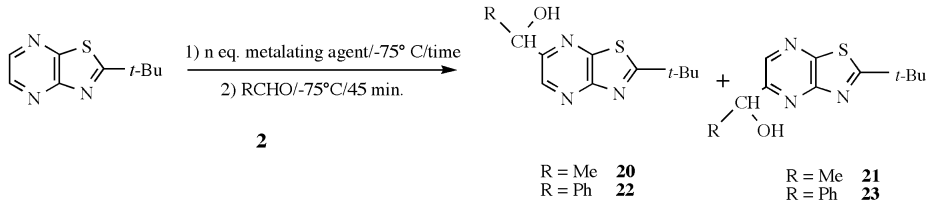
Metalation of 6-*tert*-Butylthiazolo[4,5-*b*]pyrazine **2**

Entry	No. eq. metalating agent	Time	Yield **20** + **21** (%)	Proportions*** **20**/**21** (%)	**2** (%)
1	1.1 LTMP*	1h	–	–	–
2	2.1 LTMP	2h	–	–	–
3	1.1 LTMP	15 min.	–	–	28
4	1.1 LDA**	15 min.	–	–	85
5	1.1 LTMP	5 min.	48	100/0	26
6	2.1 LTMP	5 min.	89	67/33	–
7	4.1 LTMP	5 min.	71	86/14	

*LTMP: lithium 2,2,6,6-tetramethylpiperidide; **LDA: lithium diisopropylamide; ***The proportions were calculated from the NMR spectra of the mixtures.

The metalation time was critical: when it was too long (1 hour) no isolable product could be obtained (entries 1,2) or only starting material was recovered (entries 3,4). A twofold excess of lithium 2,2,6,6-tetramethylpiperidide was necessary to obtain in five minutes a good yield of the two isomers **20** and **21** (89%) without starting material, (entry 6). It was also possible to perform a regioselective

Scheme 12



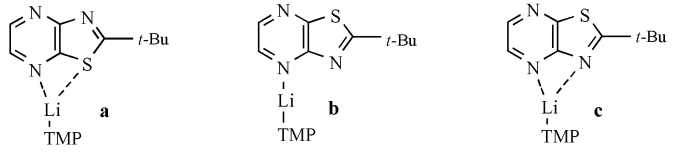
metalation at C_3 but with a lower yield (48%) (entry 5). Benzaldehyde was also used as electrophile and the yield of **22** + **23** was low (35%) the main isomer **22** still being in the 3 position (80/20) (Scheme 12). The identification of the two isomers was based on HMBC $^1H,^{13}C$ experiments by comparison of the spectra of **2** and **20** or **22**.

How can the higher percentage of the 3 isomer be explained ?

First, it must be noticed that the metalation was optimum with 2.1 equivalents of metalating agent. When 1.1 equivalent was used, only one half of the product (48 %, entry 5) was obtained, what corresponded also to 2 equivalents of base for 1 equivalent of **2**.

The first equivalent may form a chelate between the lithium atom, the cyclic nitrogen and/or the sulfur atom. A Li/PM3 [12] semi-empiric calculation indicated that (**c**) was the most stable chelate (Scheme 13).

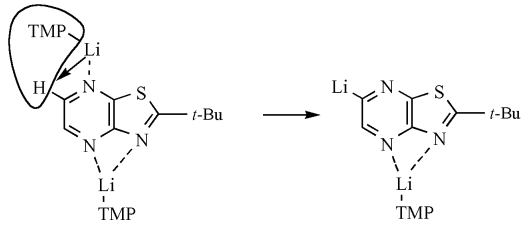
Scheme 13



ΔHf : 19.74 kcal/mol ΔHf : 18.40 kcal/mol ΔHf : 16.36 kcal/mol

This chelate (**c**) reacted with another equivalent of lithium 2,2,6,6-tetramethylpiperidide by chelation of the free nitrogen with the base and subsequent deprotonation of the vicinal 3 hydrogen (Scheme 14).

Scheme 14



A competitive pathway with direct deprotonation by free lithium 2,2,6,6-tetramethylpiperidide may explain the presence of the other regioisomers in 2 position.

Conclusion.

The access to thiocarboxamides of diazine was difficult and could only be performed *via* reaction of dithioester with aminodiazines, the thionation of amides with Lawesson's reagent or P_2S_5 afforded cyclized products: thiazolodiazines.

The *ortho*-directed metalation of *N*-diazinylthiocarboxamides was unsuccessful. The metalation of the thiazolopyridazines gave poor results, however in the pyrazine series it was possible to functionalize 6-*tert*-butylthiazolo[4,5-*b*]pyrazine with good yields and even regioselectively with moderate yield.

EXPERIMENTAL

General Data.

Melting points were determined on Kofler apparatus and are uncorrected. The ^1H NMR spectra were recorded at 300 MHz on a Brucker Avance-300 NMR spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield from an internal standard, tetramethylsilane in deuteriochloroform, or hexamethyldisiloxane in d_6-dimethylsulfoxide. Coupling constants (*J*) are given in hertz (Hz). Elemental analyses were performed on a Carlo-Erba CHN apparatus. Mass spectra were recorded on a JEOL JMS-AX500 mass spectrometer; samples were vaporized in a direct inlet system. Column chromatography was carried out on SiO_2, Merck-Geduran SI 60 (70-230 mesh).

6-*tert*-Butylthiazolo[4,5-*b*]pyrazine (**2**).

In a 50 ml round bottomed flask equipped with condenser and under magnetic stirring was placed pivaloylaminopyrazine **1** (0.896 g, 5 mmol.) and Lawesson's reagent (2.22 g, 5.5 mmol.) in 30 ml of toluene. The mixture was refluxed 5 days. After evaporation of the solvent, purification was accomplished by chromatography with neutral alumina (eluent: petroleum ether, ethyl acetate 14/1). Besides 0.203 g, (23%) of the starting material **1**, 2-*tert*-butylthiazolo[4,5-*b*]pyrazine **2** (0.678 g, 70%) was obtained as a cream oil which crystallized slowly. mp < 50°, ^1H nmr (deuteriochloroform): δ 1.40 (s, 9H, *t*-Bu), 8.34 (d, J = 2.5 Hz, 1H, H3), 8.51 (d, J = 2.5 Hz, 1H, H2); ^{13}C nmr (deuteriochloroform): δ 29.5 ($C(CH_3)$), 38.9 ($C(CH_3)$), 140 (C3), 141.5 (C2), 152.1 (C4a), 157.0 (C7a), 186.3 (C6); ms: m/z:194 (H^+).

Anal. Calcd. for $C_9H_{11}N_3S$ (193.3): C, 55.93; H, 5.74; N, 21.74; S, 16.59. Found: C, 55,64; H, 5.80; N, 21.44; S, 16.63.

6-*tert*-Butylthiazolo[4,5-*c*]pyridazine (**4**).

To a solution of pivaloylaminopyridazine **3** (1.255 g, 7 mmol.) in toluene (50 ml) was added Lawesson's reagent (3.11 g, 7.7

mmol.). The mixture was refluxed for 48 hours. After evaporation of toluene, the product was purified on a neutral alumina column with dichloromethane as eluent. Compound **4** (0.824 g, 61%) was obtained as a beige solid, mp 112°, ^{1}H nmr (deuteriochloroform): δ 1.46 (s, 9H, *t*-Bu), 8.09 (d, J = 5.5 Hz, 1H, H4), 9.05 (d, J = 5.5 Hz, 1H, H3); ^{13}C nmr (deuteriochloroform): δ 31.2 (C(*C*H$_3$)$_3$), 41.0 (*C*(CH$_3$)$_3$), 122.5 (C4), 135.8 (C4a), 146.9 (C3), 169.9 (C7a), 189.8 (C6); ms: m/z: 193.

Anal. Calcd. for $C_9H_{11}N_3S$ (193.3): C, 55.93; H, 5.74; N, 21.74; S, 16.59. Found: C, 56.04; H, 5.96; N, 21.38; S, 16.41.

N-Pyrazinylthiobenzamide (**13**).

To anhydrous tetrahydrofuran (100 ml) was added aminopyridazine (**11**) (4.76 g, 50 mmol.). The solution was cooled to-40° and *n*-butyllithium (2,5 *M*) (20 ml, 50 mmol.) was added. The solution was stirred for 10 minutes at -40°. Then a solution of methyl phenyldithiocarboxylate (8.4 g, 50 mmol.) in tetrahydrofuran (20 ml) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 48 hours. The solution was hydrolyzed with a saturated solution of hydrogenocarbonate and extracted with dichloromethane (4 x 50 ml). The dichloromethane solution was dried with magnesium sulfate. After concentration under vacuum the *N*-pyrazinylthiobenzamide (**13**) precipitated as an orange solid. After collecting the precipitate by filtration and washing with dichloromethane, **13** (5.416 g, 50%) was obtained as a yellow solid. mp: 144°, ^{1}H nmr (deuteriochloroform): δ 7.42 (m, 3H, HPh), 7.81 (m, 2H, HPh), 8.31 (dd, J = 1.5 Hz and 2.2 Hz, 1H, H6), 8.41 (d, J= 2.2 Hz, 1H, H5), 9.51 (br, 1H, NH), 10.31 (d, J = 1.5 Hz, 1H, H6); ^{13}C nmr (deuteriochloroform): δ 127.3 (CPh), 129.1 (CPh), 132.2 (CPh), 138.5 (C3), 141.9, 142.8 (C5 + C6), 143.2 (CPh), 149.5 (C2), 199.0 (CS); ms: m/z:215.

Anal. Calcd. for $C_{11}H_9N_3S$ (215.3): C, 61.37; H, 4.21; N, 19.52; S, 14.89. Found: C, 61.44; H, 4.17; N, 19.38; S, 14.42.

N-(6-Chloropyridazin-3-yl)thiobenzamide (**14**).

To anhydrous tetrahydrofuran (10 ml) was added 3-amino-6-chloropyridazine (**12**). The solution was cooled to -40° and *n*-butyllithium (2.5 *M*) in hexane (0.8 ml, 2 mmol.) was added. The solution was stirred for 10 minutes at -40°. Then a solution of methyl phenyldithiocarboxylate (0.346 g, 2 mmol.) in tetrahydrofuran (5 ml) was added dropwise. The mixture was then allowed to warm to room temperature and stirred for five days. The solution was hydrolyzed with a saturated solution of sodium hydrogenocarbonate then extracted with dichloromethane (4 x 25 ml). The dichloromethane solution was dried (magnesium sulfate) and the residue purified on a neutral alumina column with petroleum ether, ethyl acetate (9/1 then 7/3 then 0/1). Compound **14** (0.158 g, 32%) was obtained as a yellow powder. mp: 128°, ^{1}H nmr (deuteriochloroform): δ 7.33 (m, 2H, HPh), 7.45 (m, 2H, HPh), 7.88 (d, J = 8.3 Hz, 2H, HPh + H4), 9.07 (d, J = 8.3 Hz, 1H, H5), 11.01 (br, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 123.8 (CPh), 127.7 (CPh), 129.1 (CPh), 129.6 (C4), 132.7 (C5), 142.3 (CPh), 153.4 (C3), 156.3 (C6), 200.5 (CS); ms: m/z: 250.

Anal. Calcd. for $C_{11}H_8ClN_3S$ (249.7): C, 52.91; H, 3.23; N, 16.83; S, 12.84. Found: C, 52.85; H, 3.12; N, 16.62; S, 12.52.

S-Methyl-*N*-pyrazinylthiobenzamidate (**15**).

To a solution of 2,2,6,6-tetramethylpiperidine (0.25 ml, 1.5 mmol.) in tetrahydrofuran (15 ml) was added at -50° a solution of *n*-butyllithium (1.6 *M*) in hexane (0.92 ml, 1.5 mmol.). The solution was warmed to 0° and kept at this temperature for 20 minutes. This mixture was then cooled to -75° and a solution of *N*-pyrazinylthiobenzamide **13** (0.151 g, 0.7 mmol.) in tetrahydrofuran (5 ml) was added. After 10 minutes iodomethane (0.05 ml, 0.8 mmol.) was added and the mixture was stirred at -75° for 90 minutes. The solution was hydrolyzed at -75° with a mixture of tetrahydrofuran and ethanol (5 ml, 1/1) and warmed to room temperature. Water (10 ml) was added and the solvents were evaporated under vacuum. The resulting aqueous mixture was extracted with dichloromethane (4 x 15 ml). The dichloromethane solution was dried with magnesium sulfate and evaporated. Purification was accomplished by flash chromatography with neutral alumina, the eluent was a mixture of petroleum ether and ethyl acetate (7/3). Compound **15** was obtained as a pale yellow oil. ^{1}H nmr (deuteriochloroform): δ 2.44 (s, 3H, SCH$_3$), 7.21 (m, 5H, HPh), 7.87 (d, J = 1.1 Hz, 1H, H3), 8.04 (d, J = 2.6 Hz, 1H, H5), 8.17 (dd, J = 1.1 Hz, J = 2.6 Hz, 1H, H6); ^{13}C nmr (deuteriochloroform): δ 15.5 (SCH$_3$), 128.4 (CPh), 128.9 (CPh), 130.8 (CPh), 136.4 (CPh$_1$), 139.6 (C6), 139.4 (C5), 143 (C3), 158.7 (C2), 175.0 (CS).

Anal. Calcd. for $C_{12}H_{11}N_3S$ (229.3): C, 62.86; H, 4.84; N, 18.32; S, 13.97. Found: C, 62.81; H, 4.96; N, 18.21; S, 14.08.

6-*tert*-Butyl-4-(1-hydroxymethyl)thiazolo[4,5-*c*]pyridazine (**17**).

The solution of lithium tetramethylpiperidide was prepared as for **15**. After 10 minutes at -75° acetaldehyde (0.39 ml, 7 mmol.) was added and the solution was stirred for 45 minutes at -75°. The same procedure as for **15** was used to isolate the product except the eluent was a mixture of dichloromethane and ethylacetate (1/1). Compound **17** (0.022 g, 13%) was obtained as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.49 (s, 9H, *t*-Bu), 1.57 (d, J = 6.6 Hz, 3H, CH$_3$), 4.22 (br, 1H, OH), 5.25 (q, J = 6.6. Hz, 1H, CH), 8.84 (s, 1H, H3); ^{13}C nmr (deuteriochloroform): δ 24.0 (CH$_3$), 30.7 (C(*C*H$_3$)$_3$), 39.6 (*C*(CH$_3$)$_3$), 67.2 (CH), 131.0 (C4a), 140.8 (C4), 142.7 (C3), 169.7 (C7a), 190.4 (C6).

Anal. Calcd. for $C_{11}H_{15}N_3OS$ (237.3): C, 55.67; H, 6.37; N, 17.71; S, 13.51. Found: C, 55.49; H, 6.46; H, 17.98; S, 13.41.

6-*tert*-Butyl-4-trimethylsilylthiazolo[4,5-*c*]pyridazine (**18**) and 6-*tert*-Butyl-3-trimethylsilylthiazolo[4,5-*c*] pyridazine (**19**).

At the solution of lithium tetramethylpiperidide prepared as for **15**, was added simultaneously at -75° chlorotrimethylsilane (0.45 ml, 8.0 mmol.) and **4** (0.135 g, 0.7 mmol.) dissolved in tetrahydrofuran (5 ml). The mixture was stirred at -75° for two hours. Then the remainder of the experimental procedure was identical to **15**. The eluent for purification was a mixture of petroleum ether and ethyl acetate (12/1). Compounds **18** (0.031 g, 17%) and **19** (0.017 g, 9%) were obtained as pale yellow oils.

Compound **18**: ^{1}H nmr (deuteriochloroform): δ 0.36 (s, 9H, Si(CH$_3$)$_3$, 1.47 (s, 9H, *t*-Bu), 8.96 (s, 1H, H3); ^{13}C nmr (deuteriochloroform): δ -2.0 (Si(CH$_3$)$_3$), 30.3 (C(CH$_3$), 39.3 ((C(CH$_3$)$_3$), 133.0 (C4a), 139.6 (C4), 148.3 (C3), 167.0 (C7a), 187.3 (C6).

Anal. Calcd. for $C_{11}H_{19}N_3SSi$ (226.5): C, 54.3; H, 7.21; N, 15.83; S, 12.08. Found: C, 54.12; H, 7.45; N, 15.98; S, 12.35.

Compound **19**: ^{1}H nmr (deuteriochloroform): δ 0.35 (s, 9H, Si(CH$_3$)$_3$), 1.46 (s, 9H, *t*-Bu), 8.02 (s, 1H, H4).

Anal. Calcd. for $C_{11}H_{19}N_3SSi$ (226.5): C, 54.3; H, 7.21; N, 15.83; S, 12.08. Found: C, 54.64; H, 7.52; N, 15.62; S, 11.86.

6-*tert*-Butyl-3-(1-hydroxymethyl)thiazolo[4,5-*b*]pyrazine (**20**).

The metalating agent was prepared as for **15** with *n*-BuLi 1.6 *M* (0.55 ml, 0.9 mmol.) and 2,2,6,6-tetramethylpiperidine (0.15

ml, 0.9 mmol.). After 5 minutes stirring at -75°, acetaldehyde (0.45 ml, 8.0 mmol.) was added and the solution was maintained at this temperature for 45 minutes. Hydrolysis and purification was accomplished as for **15** with a mixture of petroleum ether and ethyl acetate (9/1) as eluent. Compound **20** (0.085g, 48%) was obtained as a yellow oil; ^{1}H nmr (deuteriochloroform): δ 1.46 (s, 9H, *t*-Bu), 1.54 (d, J = 6.6 Hz, 3H, CH_3), 3.72 (br, 1H, OH), 5.08 (q, J = 6.6 Hz, 1H, CH), 8.66 (s, 1H, H2); ^{13}C nmr (deuteriochloroform): δ 24.6 (CH_3), 30.6 ($C(CH_3)$), 39.9 ($C(CH_3)_3$), 68.9 (CH), 140.1 (C2), 151.3 (C4a), 155.8 (C3), 157.1 (C7a), 187.1 (C6).

Anal. Calcd. for $C_{11}H_{15}N_3OS$ (233.3): C, 56.58; H, 6.43; N, 18.0; S, 13.72. Found: C, 56.66; H, 6.67; N, 17.88; S, 13.59.

6-*tert*-Butyl-2-(1-hydroxymethyl)thiazolo[4,5-*b*]pyrazine (**21**).

The metalating agent was prepared as for **15** with *n*-BuLi 1.6 *M* (1 ml, 1.7 mmol.) and 2,2,6,6-tetramethylpiperidine (0.3 ml, 1.8 mmol.). After 5 minutes stirring, acetaldehyde (0.45 ml, 8.0 mmol.) was added and the solution was maintained at this temperature for 45 minutes. Hydrolysis and purification were accomplished as for **20**. A yellow oil (0.159 g, 89%) was obtained which was an inseparable mixture of **20** and **21** (2/3 – 1/3). **21**; ^{1}H nmr (deuteriochloroform): δ 1.46 (s, 9H, CH_3), 1.54 (d, J = 6.6 Hz, 3H, CH_3), 3.72 (br, 1H, OH), 5.08 (1H, CH), 8.66 (s, 1H, H2, **20**), 8.77 (s, 1H, H3, **21**).

Anal. Calcd. for $C_{11}H_{15}N_3OS$ (233.3) mixture of **20** + **21**: C, 56.58; H, 6.43; N, 18.00; S. 13.72. Found: C, 56.74; H, 6.78; N, 17.84; S, 13.52.

6-*tert*-Butyl-3- and -2-(1-hydroxyphenylmethyl)thiazolo[4,5-*b*]-pyrazines (**22**) and (**23**).

The metalating agent was prepared as for **15** with *n*-butyl-lithium 1.6 *M* (1.0 ml, 1.7 mmol.) and 2,2,6,6-tetramethylpiperidine (0.3 ml, 1.8 mmol.). The electrophile was benzaldehyde (0.09 ml, 0.88 mmol.). Hydrolysis and purification were accomplished as for **15** with, as eluent, a mixture of petroleum ether and ethyl acetate (12/1) was used. A yellow oil was obtained with both compounds **22** and **23** (0.085g, 35%) (**22**/**23** = 80/20); ^{1}H nmr (deuteriochloroform): δ 1.49 (s, 9H, *t*-Bu), 4.62 (br, 1H, OH), 5.95 (s, 1H, CH), 7.25 (m, 3H, HPh), 7.38 (m, J = 6.6 Hz, 2H, HPh), 8.43 (s, 1H, H3 **23**), 8.58 (s, 1H, H2 **22**).

Anal. Calcd. for $C_{16}H_{17}N_3OS$ (285.3): C, 67.28; H, 5.96; N, 14.72; S, 11.21. Found: C, 67.54; H, 6.28; N, 15.06; S, 11.55.

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