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Syntheses and metalation of pyridazinecarboxamides and thiocarboxamides. Diazines. Part 32

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Abstract—The syntheses of new pyridazinethiocarboxamides are described using the reaction of Lawesson's reagent with pyridazine carboxamides or by reacting lithiopyridazines with phenylisothiocyanate. Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamides and carboxamides with LTMP followed by reaction of the lithio derivatives with various electrophiles gave access to a wide range of poly-substituted pyridazines. An unexpected regioselectivity at the *meta* position of the thiocarboxamide group was observed and explained.

1. Introduction

The main purpose of this work is the synthesis and functionalization, via the metalation reaction, of pyridazine thiocarboxamides. This work follows a previous study in the pyrazine series that we have recently published.[1]

Heterocyclic thiocarboxamides (pyridine, diazines) have shown an inhibitory effect on the acidity of gastric secretions.[2] The second important pharmaceutical property is an action against mycobacteria, in particular against *mycobacterium tuberculosis*.[3]

2. Results

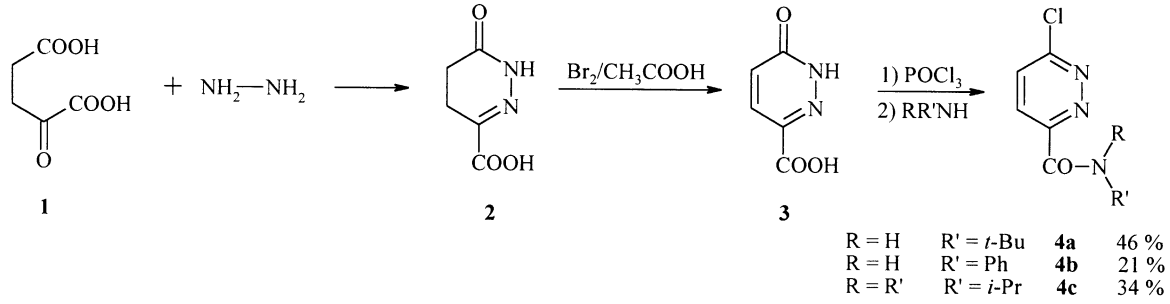
2.1. Synthesis of carboxamides

One of the most developed routes to thiocarboxamides is the thionation of carboxamides with phosphorus pentasulfide or with Lawesson's reagent.[4–7] It was thus necessary to synthesize diazine carboxamides. The complete pathway to 6-chloropyridazinecarboxamides (**4a**,**b**,**c**) starting from 2-oxopentanedioic acid is described below (Scheme 1).

The synthesis of **3** has been previously described[8,9] with yields in the 30–40% range. We have been able to increase the yield of **3** to 68% by a careful purification of intermediate **2**. Starting from **3**, carboxamides **4a–c** were obtained with moderate or low yields. In order to obtain various pyridazinethiocarboxamides, the 6-chloro atom of **4a** was substituted by a hydrogen atom, a methoxy and a methylsulfanyl group (Scheme 2).

The thionation of carboxamides **4a–7** was tested with Lawesson's reagent (L.R.) under various experimental conditions (Scheme 3, Table 1).

In all cases except entry 7 a twofold amount of L.R. was necessary to obtain good yields without recovery of the



Scheme 1.

Keywords: pyridazine; metalation; thiocarboxamide; thionation.
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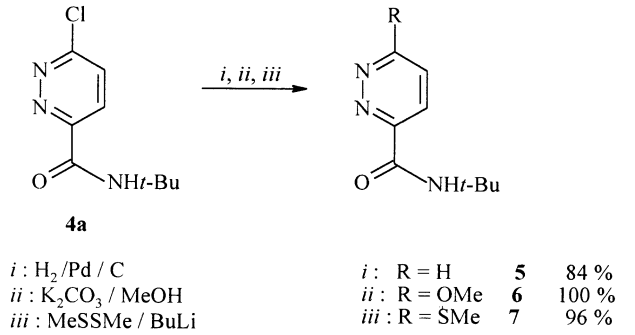
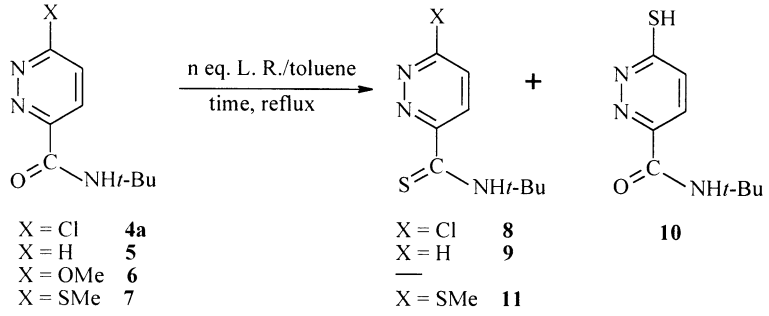


Scheme 2.



Scheme 3.

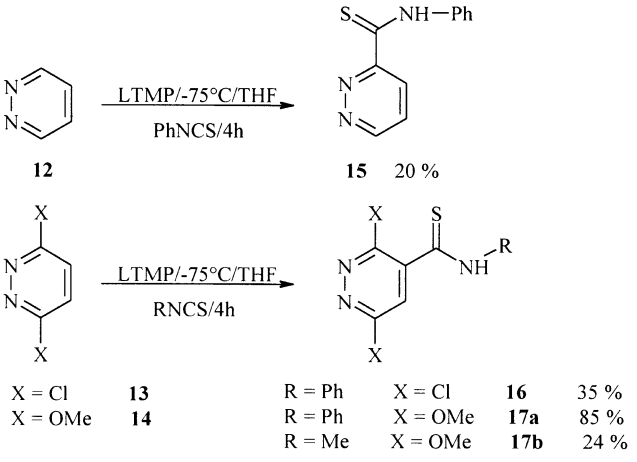
starting material (S.M.). With compounds **4a** and **6**, the chlorine atom or the methoxy group in position 6 were substituted by a sulfanyl group leading to compound **10** (entries 2,5,6) and it was not possible to effect chemioselectively the thionation of the carboxamides. With compound **7** in which the 6 substituent is a methylsulfanyl group (entry 7) no replacement of this group was observed.

Another way to prepare thiocarboxamides is the reaction of an organometallic derivative with isothiocyanates.[10] The metalation of pyridazine **12**, 3,6-dichloropyridazine **13** and 3,6-dimethoxypyridazine **14** with LTMP was effected using the 'in situ' trapping method with phenyl isothiocyanate as the electrophile (Scheme 4).

The reactions of **12** and **14** with methyl and *tert*-butylisothiocyanate were also tested. All the reactions failed with **12** while reaction of methylisothiocyanate with **14** led to *N*-methyl-3,6-dimethoxy-4-pyridazinethiocarboxamide **17b** with a 24% yield.

Table 1. Thionation of carboxamides

Entry	S.M.	L.R. *n* (equiv.)	Time (h)	Compound (yield)	S.M. (%)
	4a	0.6	8	**8** (16%)	55
2	**4a**	1.1	5	**10** (76%)	–
3	**5**	0.6	24	**9** (66%)	17
4	**5**	1.1	24	**9** (92%)	–
5	**6**	0.6	24	**10** (23%)	–
6	**6**	1.1	24	**10** (71%)	–
7	**7**	0.6	46	**11** (97%)	



Scheme 4.

2.2. Metalation of pyridazinecarboxamides and thiocarboxamides

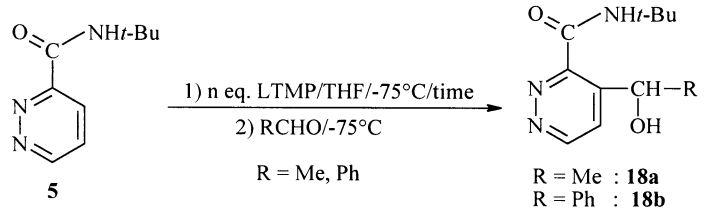
In the carboxamide series, the carboxamide **4a** has been previously metalated by Ndzi[11] in our laboratory and the *ortho*-directing efficiencies of the chlorine atom and of the carboxamide group were compared. The main products obtained were substituted *ortho* to the carboxamide group when LTMP was used as the metalating agent.

In these series, the metalation of carboxamide **5** was not described and in order to compare it with the thiocarboxamide **9**, the metalation of **5** was studied (Scheme 5, Table 2).

A large excess of LTMP was necessary to obtain a good yield (entry 2), the stoichiometric amount giving only about 50% of the metalation product (entry 1). The need for an excess of metalating agent has also been highlighted when methoxy or alkoxy groups were used as *ortho*-directing group.[12]

The use of iodine as electrophile (entry 5) afforded a 5-iodo compound **19**. This product could be the result of a 'halogen-dance' reaction resulting from a lithium/iodine exchange as was previously demonstrated in this series[13] (Scheme 6).

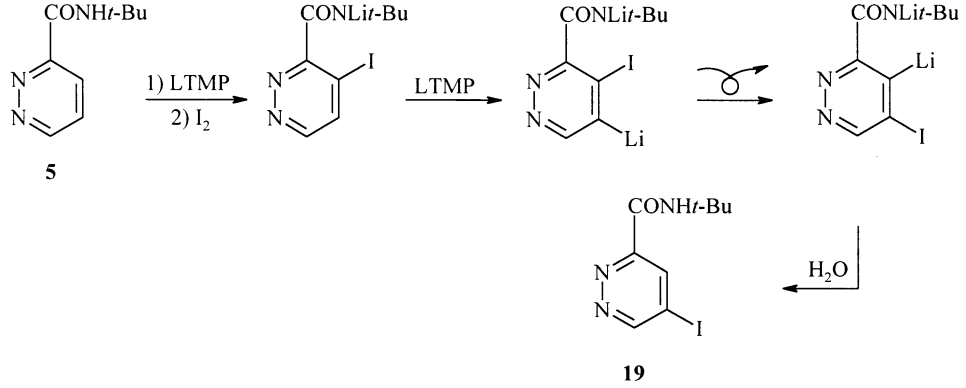
In summary, in the 3-substituted pyridazinecarboxamide series, all the metalations tested took place *ortho* to the carboxamide group even when iodine was used as the electrophile, in this case a 5-substituted product **19** was obtained after an isomerisation reaction.



Scheme 5.

Table 2. Metalation of carboxamide **5**

Entry	LTMP *n* (equiv.)	Time (h)	Electrophile	Compound (yield)	S.M. (%)
1	2.2	1	MeCHO	**18a** (49%)	47
2	4	1	MeCHO	**18a** (96%)	–
3	4	0.5	PhCHO	**18b** (57%)	32
4	4	1	PhCHO	**18b** (89%)	–
5	4	1	I_2	**19** (65%)	20



Scheme 6.

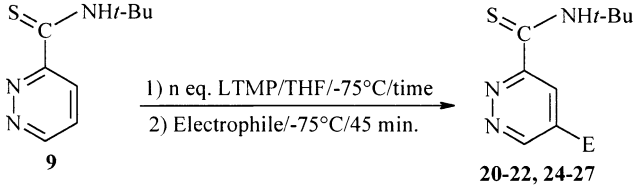
In the 4-substituted pyridazinecarboxamide series, the metalation of 4-*N*-*tert*-butylpyridazinecarboxamide has been previously described[14] and an *ortho* metalation at C_5 was also observed.

After having demonstrated the good *ortho*-directing power of some carboxamides, the thiocarboxamide group was then tested.

The best experimental conditions for the metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** were determined with acetaldehyde as the electrophile (entries 1–3) (Scheme 7, Table 3).

The unexpected result of these experiments was that the metalation took place mainly at the 5 position, i.e. at the *meta* position of the supposed *ortho* directing group (^{1}H NMR, two doublets, J=2 Hz), contrary to what occurred with the carboxamide and thiocarboxamide groups previously studied.

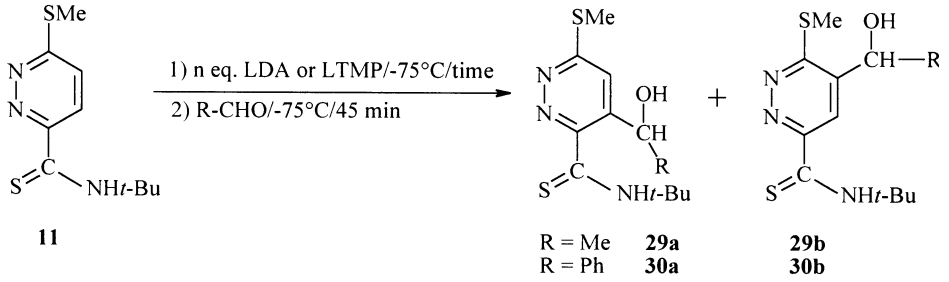
When 2.2 equiv. of LTMP were used the metalation was not



Scheme 7.

Table 3. Metalation of thiocarboxamide **9**

Entry	LTMP *n* (equiv.)	Time (h)	Electrophile	Compound (yield)	Other compound (yield)
1	2.2	1	MeCHO	**20** (27%)	S.M. (32%)
2	3.1	1	MeCHO	**20** (51%)	S.M. (4%)
3	3.1	2	MeCHO	**20** (19%)	S.M. (6%)
4	3.1	1	PhCHO	**21** (34%)	–
5	3.1	1	Ph_2CO	**22** (39%)	**23** (23%)
6	3.1	1	Bu_3SnCl	**24** (63%)	–
7	3.1	1	MeI	**25** (41%)	–
8	3.1	1	I_2	**26** (14%)	S.M. (23%)
9	3.1	1	C_2Cl_6	**27** (17%)	**28** (20%)



Scheme 8.

Table 4. : Metalation of **11**

Entry	Metalating agent	LTMP *n* (equiv.)	Electrophile RCHO	Time	Compound (yield)	Compound (yield)	S.M. (%)	Total yield (%)
1	LTMP	2.2	Me	0.5 h	**29a** (28%)	**29b** (22%)	28	78
2	LTMP	3.1	Me	0.5 h	**29a** (35%)	**29b** (25%)	–	60
3	LDA	3.1	Me	0.5 h	**29a** (28%)	**29b** (54%)	13	95
4	LDA	4.1	Me	0.5 h	**29a** (7%)	**29b** (59%)	17	83
5	LDA	3.1	Me	5 min	–	**29b** (38%)	38	76
6	LDA	3.1	Me	1.5 h	–	**29b** (43%)	22	65
7	LDA	3.1	Ph	0.5 h	–	**30b** (63%)	10	73

complete (entry 1). The use of 3.1 equiv. of LTMP with a metalation time of 1 h allowed obtainment of compound **20** with a 51% yield and with little starting material remaining (entry 2). An increase of the metalation time (entry 3) lowered the yield of compound **20** to 19%. In all cases a fair amount of tar was obtained in addition to compound **20** and the starting material **9**. These results are similar to those observed when the metalation of pyridazine was performed in the absence of an *ortho*-directing group:[10] in which deprotonation with LTMP was achieved with low yields and was accompanied by formation of a large amount of tar.

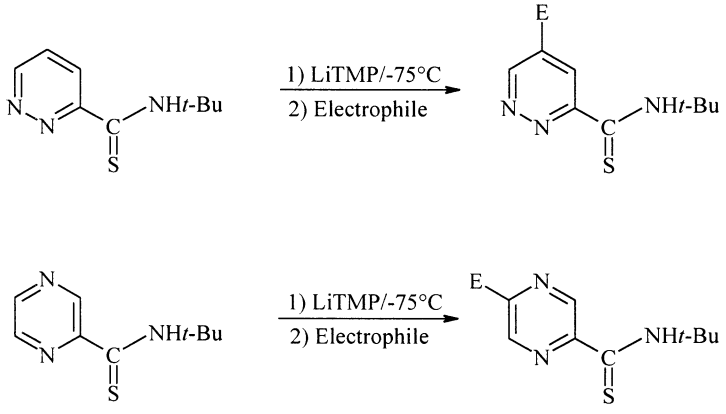
Various electrophiles were then used under the experimental conditions of entry 2. The use of benzophenone as the electrophile (entry 5) afforded in addition to the 5-substituted product **22**, the 4-substituted derivative **23**. Oddly, the most bulky electrophile (benzophenone) was the only one which led to substitution *ortho* to the bulky *N-tert*-butylthiocarboxamide group.

When C_2Cl_6 was used as the electrophile, 3-*N-tert*-butyl-5,6-dichloropyridazinethiocarboxamide (**28**) was also obtained, probably resulting from a further metalation of the initially formed 5-chloro derivative **27**.

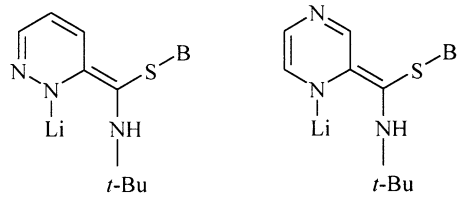
The same experimental conditions were used with a phenyl substituted nitrogen atom: with the 3-*N*-phenylpyridazinethiocarboxamide (**15**) and acetaldehyde as the electrophile, only a small amount of starting material was recovered and no isolable product was found.

The yields of metalation of **9** were moderate (14–63%). This may be explained by the absence of stabilization of the lithio derivative by chelation with a vicinal group. We then tested the metalation of compound **11** which has a methylsulfanyl group in position 6 with LTMP and LDA as metalating agents. (Scheme 8, Table 4).

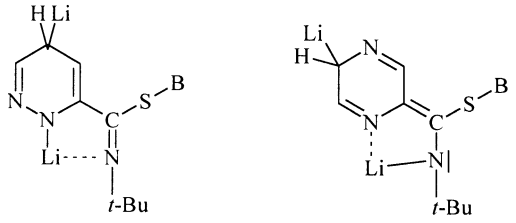
The overall yields were much better than for the metalation of **9** (60–95%) as expected, but when LTMP was used as the metalating agent (entries 1,2) mixtures of the two isomers **29a** and **29b** were obtained. The use of LDA allowed obtainment of only the 5-substituted isomers **29b** and **30b** with moderate yields (entries 5–7). The better selectivity of



Scheme 9.



Scheme 10.



Scheme 11.

LDA may be due to its lower reactivity (p*K*a LDA: 35.7; LTMP: 37.3).[17]

2.3. Discussion

In the literature, two publications describe the metalation of thiocarboxamides in the benzene series but none in the pyridine series. Gschwend[15] studied the metalation of *N*-methylthiobenzamides substituted in the *para*-position by chlorine or a methoxy group. Substitution *ortho* to the thiocarboxamide was observed in all cases. Later, Beak[16] compared the competitive deprotonation of carboxamides and thiocarboxamides in the benzene series. Only carboxamides were metalated. The metalation of *N*,*N*-diisopropylthiocarboxamide was also tested without success.

From our experiments it may be concluded that contrary to the carboxamide group, the thiocarboxamide group is not suitable for the *ortho*-directed metalation in the pyridazine series. The same conclusion has previously been drawn in the pyrazine series.[1] However, in the pyridazine series, *meta*-substituted compounds were obtained whereas *para*-substituted compounds were obtained in the pyrazine series (Scheme 9).

In order to understand these unexpected regioselectivities, it must first be noticed that the corresponding carboxamides are good *ortho*-directing groups[18] so that the difference must come from the sulfur atom of the thiocarboxamide group. The main difference between a carbonyl and a thiocarbonyl group is that a nucleophilic attack on the sulfur atom of the latter group may occur. The metalating agent (M.A.) which plays the role of a strong base, is also a nucleophile and the first reaction with a thiocarboxamide could be a nucleophilic attack of the M.A. on the sulfur atom rather than the deprotonation of the thiocarboxamide's nitrogen which is hindered by the *tert*-butyl group (Scheme 10).

This reaction would be followed by deprotonation of the thiocarboxamide's nitrogen and isomerisation to the most stable *para*-dihydrodiazine: 2,5 for pyrazine[19] and 1,4 for pyridazine[20] (Scheme 11).

The reaction with an electrophile followed by hydrolysis of the S–B bond would afford the substituted compounds with the observed regioselectivity (Scheme 12).

In summary we have prepared regioselectively some new pyridazinethiocarboxamide derivatives and we propose a mechanism to explain the 'unexpected' regioselectivity of the diazinethiocarboxamide metalations tested.

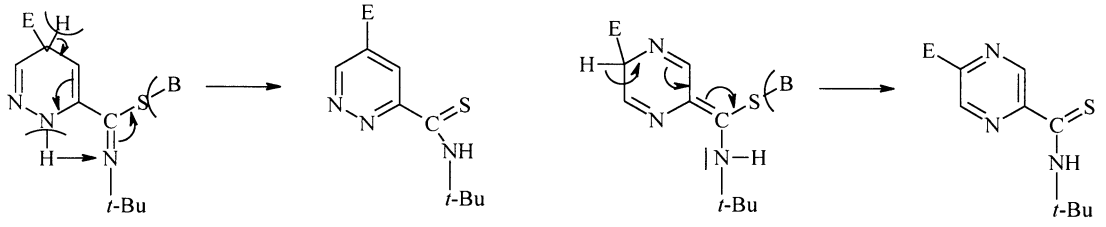
3. Experimental

The IR spectra were obtained as potassium bromide pellets with a Perkin–Elmer FMR 1650 spectrophotometer. The NMR spectra were recorded on a Bruker Avance (300 MHz) spectrometer. All NMR spectra were carried out with deuteriochloroform solutions and δ are given in ppm. Microanalysis were performed with a Carlo Erba 1106 apparatus. Melting points were determined with a Kofler hot-stage.

Metalations were performed under an argon atmosphere. Reagents were handled with syringes through septa. Tetrahydrofuran (THF) was distilled from benzophenone sodium and used immediately (water content <60 ppm). Column chromatography were performed with silica gel Merck (70–230 mesh ASTM) or neutral alumina gel Acros (0.0050–0.200 mm).

3.1. General procedure for synthesis of pyridazinecarboxamides (4)

In 100 mL three necked round bottomed flask equipped with condenser was placed **3** in phosphorus oxychloride and the suspension was heated at reflux during 45 min. Excess of phosphorus oxychloride was evaporated under vacuum and 25 mL of dry THF was added to the resulting black residue under an atmosphere of dry argon. The mixture was cooled to 0°C and triethylamine and the suitable amine was added dropwise The resulting mixture was allowed to warm to room temperature and was stirred overnight (18 h). The solvent was evaporated under vacuum and 20 mL of water



Scheme 12.

was poured on to the mixture. A solution 3 N of sodium hydroxide was added until reaching pH=8. The aqueous layer was extracted continuously with dichloromethane during one night. The organic layer was dried over magnesium sulphate and evaporated.

3.1.1. 3-*N*-*tert*-Butyl-6-chloropyridazinecarboxamide (4a). Synthesis of **4a** was performed according to the general procedure with **3** (5.14 g, 36.6 mmol) in 25 mL of phosphorus oxychloride, triethylamine (5.1 mL, 36.6 mmol) and *tert*-butylamine (11.6 mL, 110 mmol). A flash chromatography on silica gel (dichloromethane) followed by sublimation gave **4a** (3.57 g, 46%) as a white solid. Mp 92°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.50 (s, 9H, CH_3); 7.87 (d, J=8.8 Hz, 1H, H_5); 7.96 (br, 1H, NH); 8.25 (d, J=8.8 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=28.5 ($C(CH_3)_3$); 51.5 ($C(CH_3)_3$); 127.6 (C_4); 129.2 (C_5); 152.2 (C_3); 158.6 (C_6); 160.3 (C=O). IR (KBr) (cm^{-1}): 3380; 3065; 2970; 1675; 1565. Anal. Calcd for $C_9H_{12}N_3OCl$: C, 50.58; H, 5.62; N, 19.67. Found: C, 50.31; H, 5.53; N, 19.46.

3.1.2. 3-*N*-Phenyl-6-chloro-pyridazinecarboxamide (4b). Synthesis of **4b** was performed according to the general procedure with **3** (1.401 g, 10 mmol) in 15 mL of phosphorus oxychloride, triethylamine (1.4 mL, 10 mmol) and aniline (2.7 mL, 30 mmol). A flash chromatography on silica gel (dichloromethane) followed by sublimation gave **4b** (0.511 g, 21%) as a white solid. Mp 217°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=6.91 (t, J=6.0, 1.1 Hz, 1H, H_{benz}); 7.16 (t, J=6.0, 7.3 Hz, 2H, H_{benz}); 7.66 (dd, J=7.3, 1.1 Hz, 2H, H_{benz}); 7.91 (d, J=8.8 Hz, 1H, H_5); 8.10 (d, J=8.8 Hz, 1H, H_4); 10.82 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=121.1 (C_{benz}); 124.8 (C_{benz}); 129.0 (C_{benz}); 129.7 (C_4); 130.8 (C_5); 153.3 (C_3); 158.7 (C_6); 161.0 (C=O). IR (KBr) (cm^{-1}): 3336; 3060; 1675; 1604; 1528; 1445; 1397; 1142; 1126. Anal. Calcd for $C_{11}H_8N_3OCl$: C, 56.65; H, 3.43; N, 18.02. Found: C, 56.33; H, 3.72; N, 18.22.

3.1.3. 3-*N*,*N*-Diisopropyl-6-chloro-pyridazinecarboxamide (4c). Synthesis of **4c** was performed according to the general procedure with **3** (1.401 g, 10 mmol) in 15 mL of phosphorus oxychloride, triethylamine (1.4 mL, 10 mmol) and diisopropylamine (4.2 mL, 30 mmol). A flash chromatography on silica gel (dichloromethane) gave **4c** (0.816 g, 34%) as a white solid. Mp 135°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.06 (d, $J_{CH,CH3}$=6.8 Hz, 6H, CH_3); 1.38 (d, $J_{CH,CH3}$=6.8 Hz, 6H, CH_3); 3.45 (sept, $J_{CH,CH3}$=6.8 Hz, 1H, CH); 3.79 (sept, $J_{CH,CH3}$=6.8 Hz, 1H, CH); 7.54 (m, J=8.9 Hz, 2H, H_4+H_5). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=20.6 (CH_3); 21.0 (CH_3); 46.8 (CH); 51.7 (CH); 129.2 (C_4); 129.5 (C_5); 157.0 (C_3); 157.9 (C_6); 165.3 (C=O). IR (KBr) (cm^{-1}): 2970; 1640; 1561; 1474; 1407; 1371; 1350; 1203; 1145. Anal. Calcd for $C_{11}H_{16}N_3OCl$: C, 54.61; H, 6.62; N, 17.38. Found: C, 54.55; H, 6.78; N, 17.62.

3.1.4. 3-*N*-*tert*-Butylpyridazinecarboxamide (5). To a solution of 3-*N*-*tert*-butyl-6-chloropyridazinecarboxamide **4a** (2.135 g, 10 mmol) in water (20 mL) containing 3 mL of concentrated ammonia was added 0.150 g of 5% Pd/C. The resulting mixture was stirred under H_2 atmosphere at room temperature overnight. The reaction mixture was filtered, the filter was washed with ethanol, the ethanol was then evaporated and the aqueous layer was extracted with dichloromethane (4×30 mL). The combined organic layer was dried over anhydrous magnesium sulfate and evaporated. A flash chromatography on silica gel with petroleum ether–ethyl acetate (7:3) as eluent gave **5** (1.5 g, 84%) as a white solid. Mp 71°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.44 (s, 9H, CH_3); 7.60 (dd, $J_{H4,H5}$=8.8 Hz, $J_{H5,H6}$=4.9 Hz, 1H, H_5); 8.08 (br, 1H, NH); 8.22 (dd, $J_{H4,H5}$=8.8 Hz, $J_{H4,H6}$= 1.8 Hz, 1H, H_4); 9.19 (dd, $J_{H5,H6}$=4.9 Hz, $J_{H4,H6}$=1.8 Hz, 1H, H_6). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=28.3 ($C(CH_3)_3$); 51.6 ($C(CH_3)_3$); 125.4 (C_5); 128.0 (C_4); 152.9 (C_6); 162.0 (C=O); 165.5 (C_3). IR (KBr) (cm^{-1}): 3367; 3084; 2969; 1678; 1525; 1367; 1238; 770; 623. Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.62; H, 7.10; N, 23.29.

3.1.5. 3-*N*-*tert*-Butyl-6-methoxypyridazinecarboxamide (6). To a solution of 3-*N*-*tert*-butyl-6-chloropyridazinecarboxamide **4a** (1.067 g, 5 mmol) in 30 mL of methanol was added potassium carbonate (1.4 g, 10 mmol) by portion. The resulting mixture was heated and stirred during 24 h. Then the reaction mixture was cooled down to room temperature. After filtration of excess potassium carbonate, solvent was evaporated under reduced pressure to give **6** (1.045 g, 100%) as a pale yellow solid. Mp=80°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.29 (s, 9H, CH_3); 3.97 (s, 3H, OCH_3); 6.91 (d, $J_{H4,H5}$=9.1 Hz, 1H, H_5); 7.97 (d, $J_{H4,H5}$=9.1 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$, 300 MHz): δ= 28.9 ($C(CH_3)_3$); 50.9 ($C(CH_3)_3$); 55.1 (OCH_3); 117.7 (C_5); 127.9 (C_4); 149.3 (C_3); 161.1 (C_6); 165.9 (C=O). IR (KBr) (cm^{-1}): 3390; 3083; 2974; 2515; 1668. Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.74; H, 7.17; N, 20.09. Found: C, 57.78; H, 7.08; N, 20.18.

3.1.6. 3-*N*-*tert*-Butyl-6-methylsulfanylpyridazinecarboxamide (7). In a 100 mL three necked round bottomed flask equipped with condenser was placed 30 mL of dry THF under an atmosphere of dry nitrogen. The temperature was lowered to −20°C, methyldisulfide (0.56 mL, 6.2 mmol) and *n*-buthyllithium (2.5 M) (2.5 mL, 6.2 mmol) were added dropwise. The mixture was stirred for 10 minutes at −20°C and **4a** (1.067 g, 5 mmol) in 5 mL of tetrahydrofuran was added. The resulting mixture was warmed to 60°C and was stirred for 2 h. Then the reaction mixture was cooled to room temperature and hydrolysis was then carried out using water. The solvent was evaporated and the aqueous layer was extracted with dichloromethane (4×30 mL). The combined organic layer was dried over anhydrous magnesium sulfate and evaporated to give **7** (1.080 g, 96%) as a pale yellow solid. Mp=102°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.38 (s, 9H, CH_3); 2.63 (s, 3H, SCH_3); 7.37 (d, $J_{H4,H5}$=8.9 Hz, 1H, H_5); 7.87 (br, 1H, NH); 7.91 (d, $J_{H4,H5}$=8.9 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=14.6 (SCH_3); 28.9 ($C(CH_3)_3$); 50.9 ($C(CH_3)_3$); 123.8 (C_5); 126.4 (C_4); 149.8 (C_3); 161.3 (C_6); 164.9 (C=O). IR (KBr) (cm^{-1}): 3381; 3053; 2970; 2935; 1670. Anal. Calcd for $C_{10}H_{15}N_3OS$: C, 53.30; H, 6.66; N, 18.65; S, 14.21. Found: C, 53.34; H, 6.67; N, 18.26; S, 13.78.

3.2. General procedure for synthesis of pyridazinethiocarboxamides (8, 9, 11)

A solution of the appropriate 3-pyridazinecarboxamide (x mmol) and the Lawesson's reagent (0.6x or 1.1x mmol)

in toluene (20 mL) was heated for 5–46 h at reflux temperature, the reaction progress being controlled by thin-layer chromatography (neutral alumina gel, dichloromethane as eluent). When the reaction was complete, the solvent was evaporated under reduced pressure. The residue was purified on a column packed with neutral alumina gel with petroleum ether–ethyl acetate (10:1) or dichloromethane as eluent.

3.2.1. 3-*N*-*tert*-Butyl-6-chloropyridazinethiocarboxamide (8). Synthesis of **8** was performed according to the general procedure with 3-*N*-*tert*-butyl-6-chloropyridazinecarboxamide **4a** (0.401 g, 1.9 mmol) and 0.6 equiv. of Lawesson's reagent (0.460 g, 1.1 mmol) during 8 h. After a flash chromatography on neutral alumina gel with dichloromethane as eluent, the thiocarboxamide **8** was isolated as a yellow oil in 16% yield (0.072 g) and **4a** was recovered in 55% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.68 (s, 9H, CH_3); 7.84 (d, J=9.1 Hz, 1H, H_5); 8.86 (d, J=9.1 Hz, 1H, H_4); 10.06 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=29.1 ($C(CH_3)_3$); 51.9 ($C(CH_3)_3$); 125.1 (C_4); 127.7 (C_5); 151.1 (C_6); 161.7 (C_3); 183.3 (C=S). IR (KBr) (cm^{-1}): 3210; 2966; 2928; 1517; 1418; 1387; 1217; 1091. Anal. Calcd for $C_9H_{12}N_3SCl$: C, 47.05; H, 5.27; N, 18.29; S, 13.96. Found: C, 47.24; H, 5.44; N, 17.99; S, 14.08.

3.2.2. 3-*N*-*tert*-Butylpyridazinethiocarboxamide (9). Synthesis of **9** was performed according to the general procedure with 3-*N*-*tert*-butylpyridazinecarboxamide **5** (0.356 g, 2.0 mmol) and 1.1 equiv. of Lawesson's reagent (0.890 g, 2.2 mmol) during 24 h. After a flash chromatography on neutral alumina gel with dichloromethane as eluent, the thiocarboxamide **9** was isolated as a yellow oil in 92% yield (0.354 g). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.63 (s, 9H, CH_3); 7.57 (dd, $J_{H4,H5}$=8.7 Hz, $J_{H5,H6}$=4.9 Hz, 1H, H_5); 8.80 (dd, $J_{H4,H5}$=8.7 Hz, $J_{H4,H6}$=1.7 Hz, 1H, H_4); 9.15 (dd, $J_{H5,H6}$=4.9 Hz, $J_{H4,H6}$=1.7 Hz, 1H, H_6); 10.20 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=27.8 ($C(CH_3)_3$); 55.9 ($C(CH_3)_3$); 127.6 (C_5); 127.9 (C_4); 152.6 (C_6); 154.1 (C_3); 186.8 (C=S). IR (KBr) (cm^{-1}): 3280; 2967; 2930; 1555; 1519; 1436; 1230; 1054; 1001; 751. Anal. Calcd for $C_9H_{13}N_3S$: C, 55.67; H, 6.70; N, 21.65; S, 16.50. Found: C, 55.46; H, 6.92; N, 21.23; S, 16.24.

3.2.3. 3-*N*-*tert*-Butyl-6-sulfanylpyridazinecarboxamide (10). Synthesis of **10** was performed according to the general procedure with 3-*N*-*tert*-butyl-6-methoxypyridazinecarboxamide **6** (0.210 g, 1.0 mmol) and 1.1 equiv. of Lawesson's reagent (0.445 g, 1.1 mmol) during 24 h. After a flash chromatography on neutral alumina gel with petroleum ether–ethyl acetate (10:1) as eluent, the carboxamide **10** was isolated as a yellow solid in 71% yield (0.150 g). Mp=213°C (dec.). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.46 (s, 9H, CH_3); 7.39 (d, $J_{H4,H5}$=8.9 Hz, 1H, H_5); 7.77 (br, 1H, NH); 7.91 (d, $J_{H4,H5}$=8.9 Hz, 1H, H_4). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=28.9 ($C(CH_3)_3$); 50.9 ($C(CH_3)_3$); 123.6 (C_5); 126.4 (C_4); 149.8 (C_3); 160.3 (C_6); 164.6 (C=O). IR (KBr) (cm^{-1}): 3399; 3163; 3084; 3018; 2973; 2927; 1665; 1595; 1559; 1234. Anal. Calcd for $C_9H_{13}N_3OS$: C, 51.18; H, 6.16; N, 19.90; S, 15.16. Found: C, 51.38; H, 6.14; N, 19.68; S, 15.01.

3.2.4. 3-*N*-*tert*-Butyl-6-methylsulfanylpyridazinethiocarboxamide (11). Synthesis of **11** was performed according to the general procedure with 3-*N*-*tert*-butyl-6-methylsulfanylpyridazinecarboxamide **7** (0.525 g, 2.3 mmol) and 0.6 equiv. of Lawesson's reagent (0.566 g, 1.4 mmol) during 46 h. After a flash chromatography on neutral alumina gel with dichloromethane as eluent, the thiocarboxamide **11** was isolated as a yellow solid in 97% yield (0.538 g). Mp=66°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.69 (s, 9H, CH_3); 2.77 (s, 3H, SCH_3); 7.44 (d, J=9.1 Hz, 1H, H_5); 8.65 (d, J=9.1 Hz, 1H, H_4); 10.07 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=13.3 (SCH_3); 27.4 ($C(CH_3)_3$); 55.2 ($C(CH_3)_3$); 125.8 (C_4); 126.2 (C_5); 150.9 (C_3); 164.7 (C_6); 186.3 (C=S). IR (KBr) (cm^{-1}): 3292; 3268; 2962; 2929; 1569; 1515; 1416; 1387; 1218; 1161; 1091; 842. Anal. Calcd for $C_{10}H_{15}N_3S_2$: C, 49.76; H, 6.22; N, 17.41; S, 26.54. Found: C, 49.33; H, 6.31; N, 17.77; S, 26.53.

3.3. General procedures for metalation

Method A. A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−75°C), stirred, anhydrous tetrahydrofuran (15 mL) under an atmosphere of dry argon, then 2,2,6,6-tetramethylpiperidine or diisopropylamine was added and the mixture was warmed to 0°C and kept at this temperature for 15 min in order to achieve a complete formation of the metalating agent. The solution was cooled to −75°C and a solution of thiocarboxamide (x mmol) in 5 mL of tetrahydrofuran was added and the mixture was stirred for t min at −75°C. Then the electrophile (1.2 equiv. mmol) was added dropwise and stirring was continued for t min at −75°C. Hydrolysis was then carried out at −75°C using a mixture of ethanol (1 mL) and tetrahydrofuran (1 mL) or a saturated aqueous solution of NH_4Cl (5 mL) in the case of isothiocyanate as electrophile. The solution was gently warmed to 0°C and the solvent was evaporated under reduced pressure. The residue was extracted with dichloromethane (4×25 mL) or ethyl acetate (4×25 mL) in the case of using an isothiocyanate. The organic extract was dried with magnesium sulfate and evaporated. The crude product was purified by column chromatography on neutral alumina.

Method B (in situ trapping method). A solution of *n*-butyllithium (1.6 or 2.5 M in hexane) was added to cold (−75°C), stirred, anhydrous tetrahydrofuran (15 mL) under an atmosphere of dry argon, then 2,2,6,6-tetramethylpiperidine or diisopropylamine was added and the mixture was warmed to 0°C and kept at this temperature for 15 min. The solution was cooled to −75°C and a mixture of the thiocarboxamide (x mmol) and the electrophile (1.2 equiv. mmol) in 5 mL of tetrahydrofuran was added slowly, then the mixture was stirred for 2 h at −75°C. Hydrolysis was carried out at −75°C using a mixture of ethanol (1 mL) and tetrahydrofuran (1 mL) or a saturated aqueous solution of NH_4Cl (5 mL) in the case of isothiocyanate as electrophile. The solution was gently warmed to 0°C and the solvent was evaporated under reduced pressure. The residue was extracted with dichloromethane (4×25 mL) or ethyl acetate (4×25 mL) in the case of using an isothiocyanate. The organic extract was dried with magnesium sulfate and evaporated. The crude product was purified by column chromatography on neutral alumina.

3.3.1. 3-*N*-Phenylpyridazinethiocarboxamide (15). Metalation of pyridazine (0.22 mL, 3.0 mmol) was performed

according to the general procedure (method B) with *n*-butyllithium 1.6 M (2.4 mL, 4.0 mmol) and 2,2,6,6-tetramethylpiperidine (0.68 mL, 4.0 mmol), phenyl isothiocyanate (0.43 mL, 3.6 mmol), t=4 h giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (7:3) as the eluent, **15** (0.131 g, 20%) as a yellow solid. Mp=116°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.42 (m, 3H, H_{benz}); 7.67 (dd, $J_{H4,H5}$=8.8 Hz, $J_{H5,H6}$=4.9 Hz, 1H, H_5); 8.06 (dd, J=8.4 Hz, 2H, H_{benz}); 8.82 (dd, $J_{H4,H5}$=8.8 Hz, $J_{H4,H6}$=1.6 Hz, 1H, H_4); 9.20 (dd, $J_{H5,H6}$=4.9 Hz, $J_{H4,H6}$=1.6 Hz, 1H, H_6); 11.15 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=122.7 (C_{benz}); 126.9 (C_{benz}); 127.4 (C_5); 128.3 (C_4); 128.9 (C_{benz}); 138.2 (C_{benz}); 152.3 (C_6); 153.3 (C_3); 185.3 (C=S). IR (KBr) (cm^{-1}): 3173; 3051; 1592; 1516; 1446; 1345; 980; 777; 729. Anal. Calcd for $C_{11}H_9N_3S$: 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.

3.3.2. 4-*N*-Phenyl-3,6-dichloropyridazinethiocarboxamide (16). Metalation of 3,6-dichloropyridazine **13** (0.150 g, 1.0 mmol) was performed according to the general procedure (method B) with *n*-butyllithium 1.6 M (0.88 mL, 1.4 mmol) and 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.4 mmol), phenyl isothiocyanate (0.14 mL, 1.2 mmol), t=4 h giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (4:1) as the eluent, **16** (0.101 g, 35%) as a yellow oil. ^{1}H NMR (DMSO, 300 MHz): δ=7.54 (d, J=7.9 Hz, 1H, H_{benz}); 7.68 (m, 2H, H_{benz}); 8.10 (d, J=8.4 Hz, 2H, H_{benz}); 8.45 (s, 1H, H_5); 12.76 (br, 1H, NH). ^{13}C NMR (DMSO, 300 MHz): δ=122.8 (C_{benz}); 127.6 (C_5); 129.4 (C_{benz}); 138.8 (C_{benz}); 143.6 (C_4); 151.0 (C_6); 156.3 (C_3); 186.7 (C=S). IR (KBr) (cm^{-1}): 3280; 2967; 2930; 1555; 1519; 1436; 1362; 1210; 1001; 751; 689. Anal. Calcd for $C_{11}H_7N_3Cl_2S$: C, 46.49; H, 2.48; N, 14.79; S, 11.28. Found: C, 46.62; H, 2.35; N, 14.71; S, 11.18.

3.3.3. 4-*N*-Phenyl-3,6-dimethoxypyridazinethiocarboxamide (17a). Metalation of 3,6-dimethoxypyridazine **14** (0.140 g, 1.0 mmol) was performed according to the general procedure (method B) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.2 mmol), phenyl isothiocyanate (0.14 mL, 1.2 mmol), t=4 h giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (4:1) as the eluent, **17a** (0.234 g, 85%) as a yellow solid. Mp=171°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.09 (s, 3H, OCH_3); 4.26 (s, 3H, OCH_3); 7.35 (m, 1H, H_{benz}); 7.45 (m, 2H, H_{benz}); 7.81 (d, J=8.4 Hz, 2H, H_{benz}); 7.88 (s, 1H, H_5); 10.86 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=55.4 (OCH_3); 56.1 (OCH_3); 124.1 (C_{benz}); 127.8 (C_5); 129.5 (C_{benz}); 131.2 (C_4); 139.0 (C_{benz}); 156.1 (C_6); 163.6 (C_3); 189.0 (C=S). IR (KBr) (cm^{-1}): 3256; 3200; 3136; 3053; 2981; 2948; 1555; 1496; 1466; 1382; 1247; 1003; 757; 687. Anal. Calcd for $C_{13}H_{13}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26; S, 11.65. Found: C, 56.67; H, 4.53; N, 15.04; S, 11.40.

3.3.4. 4-*N*-Methyl-3,6-dimethoxypyridazinethiocarboxamide (17b). Metalation of 3,6-dimethoxypyridazine **14** (0.14 g, 1.0 mmol) was performed according to the general procedure (method B) with *n*-butyllithium 2.5 M (0.92 mL, 2.3 mmol) and 2,2,6,6-tetramethylpiperidine (0.41 mL, 2.4 mmol), methyl isocyanate (0.088 g, 1.2 mmol), t=4 h giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (7:5) as the eluent, **17b** (0.067 g, 24%) as a yellow solid (unstable, keep in freezer and in the dark). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.36 (d, J=4.8 Hz, 3H, CH_3); 4.07 (s, 3H, OCH_3); 4.19 (s, 3H, OCH_3); 8.02 (s, 1H, H_5); 9.51 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=34.1 (CH_3); 54.9 (OCH_3); 55.6 (OCH_3); 124.2 (C_5); 128.6 (C4); 156.1 (C6); 166.5 (C3); 190.9 (C=S). IR (KBr) (cm^{-1}): 3215; 3063; 3016; 2998; 2950; 1517; 1468; 1390; 1370; 1261; 1217; 1028; 1003; 981; 921; 845; 769. Anal. Calcd for $C_8H_{11}N_3O_2S$: C, 56.71; H, 4.76; N, 15.26; S, 11.65. Found: C, 56.73; H, 4.94; N, 15.39; S, 11.65.

3.3.5. 3-*N*-*tert*-Butyl-4-(1-hydroxyethyl)pyridazinecarboxamide (18a). Metalation of 3-*N*-*tert*-butylpyridazinecarboxamide **5** (0.143 g, 0.8 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (2.0 mL, 3.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.56 mL, 3.3 mmol), t_1=60 min, then reaction with acetaldehyde (0.30 mL, 5.0 mmol), t_2=30 min giving, after purification by column chromatography on silica gel with a mixture of ether petroleum–ethyl acetate (4:1) as the eluent, **18a** (0.171 g, 96%) as a cream oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.01 (d, J=6.5 Hz, 3H, (CH)CH_3); 1.41 (s, 9H, CH_3); 4.95 (br, 1H, OH); 5.40 (q, J=6.5 Hz, 1H, CH); 7.70 (d, J=5.3 Hz, 1H, H_5); 8.17 (br, 1H, NH); 9.10 (d, J=5.3 Hz, 1H, H_6). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=21.8 (CH_3); 27.6 (C(CH_3)$_3$); 50.7 (C(CH_3)$_3$); 64.7 (CH); 124.5 (C_5); 145.6 (C_4); 150.0 (C_3); 151.7 (C_6); 162.8 (C=O). IR (KBr) (cm^{-1}): 3373; 3072; 2972; 2932; 1667; 1651; 1520; 1366; 1224; 1125; 1085. Anal. Calcd for $C_{11}H_{17}N_3O_2$: C, 59.17; H, 7.67; N, 18.82. Found: C, 58.88; H, 7.85; N, 18.94.

3.3.6. 3-*N*-*tert*-Butyl-4-phenylhydroxymethylpyridazinecarboxamide (18b). Metalation of 3-*N*-*tert*-butylpyridazinecarboxamide **5** (0.143 g, 0.8 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (2.0 mL, 3.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.56 mL, 3.3 mmol), t_1=60 min, then reaction with benzaldehyde (0.10 mL, 1.0 mmol), t_2=90 min giving, after purification by column chromatography on silica gel with a mixture of ether petroleum–ethyl acetate (4:1) as the eluent, **18b** (0.202 g, 89%) as a beige oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.40 (s, 9H, CH_3); 6.02 (br, 1H, OH); 6.34 (s, 1H, CH); 7.24 (m, 5H, H_{benz}); 7.36 (d, J=5.3 Hz, 1H, H_5); 8.01 (br, 1H, NH); 9.07 (d, J=5.3 Hz, 1H, H_6). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=30.3 (C(CH_3)$_3$); 53.6 (C(CH_3)$_3$); 73.3 (CH); 128.6 (C_5); 128.7 (C_{benz}); 129.5 (C_{benz}); 130.1 (C_{benz}); 142.1 (C_{benz}); 146.4 (C_4); 153.8 (C_3); 154.3 (C_6); 165.8 (C=O). IR (KBr) (cm^{-1}): 3369; 3071; 2973; 2935; 1668; 1650; 1520; 1368; 1224; 1085. Anal. Calcd for $C_{16}H_{19}N_3O_2$: C, 67.33; H, 6.71; N, 14.73. Found: C, 67.12; H, 6.67; N, 14.66.

3.3.7. 3-*N*-*tert*-Butyl-5-iodopyridazinecarboxamide (19). Metalation of 3-*N*-*tert*-butylpyridazinecarboxamide **5** (0.143 g, 0.8 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (2.0 mL, 3.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.56 mL, 3.3

mmol), t_1=3 h, then reaction with iodine (0.228 g, 0.9 mmol), t_2=90 min giving, after purification by column chromatography on silica gel with a mixture of dichloromethane–ethyl acetate (1:1) as the eluent, **19** (0.159 g, 65%) as an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.42 (s, 9H, CH_3); 7.94 (br, 1H, NH); 8.63 (d, J=1.8 Hz, 1H, H_4); 9.41 (d, J=1.8 Hz, 1H, H_6). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=29.1 (C(CH_3)$_3$); 52.1 (C(CH_3)$_3$); 103.1 (C_5); 134.9 (C_4); 153.0 (C_3); 159.7 (C_6); 160.6 (C=O). IR (KBr) (cm^{-1}): 3292; 3048; 2967; 2924; 1529; 1436; 1391; 1362; 1331; 1250; 1205; 1001; 891; 680. Anal. Calcd for $C_9H_{12}N_3OI$: C, 35.43; H, 3.96; N, 13.77. Found: C, 35.32; H, 4.10; N, 13.75.

3.3.8. 3-*N*-*tert*-Butyl-5-(1-hydroxyethyl)pyridazinethiocarboxamide (20). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol), t_1=60 min, then reaction with acetaldehyde (0.40 mL, 7.0 mmol), t_2=45 min giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (1:1) as the eluent, **20** (0.084 g, 51%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.49 (d, J=6.8 Hz, 3H, (CH)CH_3); 1.65 (s, 9H, CH_3); 3.84 (br, 1H, OH); 5.00 (q, J=6.8 Hz, 1H, CH); 8.73 (d, J=2.0 Hz, 1H, H_4); 9.20 (d, J=2.0 Hz, 1H, H_6); 10.16 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=23.3 (CH_3); 26.1 (C(CH_3)$_3$); 54.3 (C(CH_3)$_3$); 65.5 (CH); 122.7 (C_4); 145.2 (C_5); 149.0 (C_6); 152.2 (C_3); 185.2 (C=S). IR (KBr) (cm^{-1}): 3284; 2973; 2930; 1521; 1439; 1397; 1212; 759. Anal. Calcd for $C_{11}H_{17}N_3OS$: C, 55.20; H, 7.16; N, 17.56; S, 13.40. Found: C, 55.52; H, 6.74; N, 17.88; S, 13.22.

3.3.9. 3-*N*-*tert*-Butyl-5-phenylhydroxymethylpyridazinethiocarboxamide (21). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol), t_1=60 min, then reaction with benzaldehyde (0.08 mL, 0.8 mmol), t_2=90 min giving, after purification by column chromatography on silica gel with a mixture of ether petroleum–ethyl acetate (7:3) as the eluent, **21** (0.072 g, 34%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.68 (s, 9H, CH_3); 3.55 (br, 1H, OH); 5.88 (s, 1H, CH); 7.34 (m, 5H, H_{benz}); 8.86 (d, J=2.0 Hz, 1H, H_4); 9.16 (d, J=2.0 Hz, 1H, H_6); 10.20 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=25.7 (C(CH_3)$_3$); 53.8 (C(CH_3)$_3$); 71.6 (CH); 122.9 (C_4); 125.0 (C_{benz}); 127.0 (C_{benz}); 127.4 (C_{benz}); 139.5 (C_{benz}); 142.5 (C_5); 148.9 (C_6); 151.8 (C_3); 184.8 (C=S). IR (KBr) (cm^{-1}): 3285; 2924; 2854; 1725; 1674; 1519; 1454; 1364; 1214; 760. Anal. Calcd for $C_{16}H_{19}N_3OS$: C, 63.76; H, 6.35; N, 13.94; S, 10.64. Found: C, 63.64; H, 6.54; N, 13.82; S, 10.45.

3.3.10. 3-*N*-*tert*-Butyl-5-diphenylhydroxymethylpyridazinethiocarboxamide (22). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol), $t1_1$=60 min, then reaction with benzophenone (0.136 g, 0.8 mmol), t_2=90 min giving, after purification by column chromatography on silica gel with a mixture of ether petroleum–ethyl acetate (4:1) as the eluent, **22** (0.103 g, 39%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.62 (s, 9H, CH_3); 4.33 (br, 1H, OH); 7.19 (m, 4H, H_{benz}); 7.25 (m, 6H, H_{benz}); 8.86 (d, J=2.0 Hz, 1H, H_4); 9.02 (d, J=2.0 Hz, 1H, H_6); 10.15 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=27.9 (C(CH_3)$_3$); 56.0 (C(CH_3)$_3$); 80.4 (C(OH)); 126.1 (C_4); 128.1 (C_{benz}); 128.6 (C_{benz}); 128.9 (C_{benz}); 144.8 (C_{benz}); 148.0 (C_5); 152.2 (C_6); 153.8 (C_3); 187.0 (C=S). IR (KBr) (cm^{-1}): 3272; 3050; 2967; 1518; 1492; 1395; 1362; 1209; 1046; 1012; 757; 700. Anal. Calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13; S, 8.94. Found: C, 69.85; H, 6.03; N, 11.36; S, 8.73.

3.3.11. 3-*N*-*tert*-Butyl-4-diphenylhydroxymethylpyridazinethiocarboxamide (23). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol), t_1=60 min, then reaction with benzophenone (0.136 g, 0.8 mmol), t_2=90 min giving, after purification by column chromatography on silica gel with a mixture of ether petroleum–ethyl acetate (7:3) as the eluent, **23** (0.062 g, 23%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.51 (s, 9H, CH_3); 4.10 (br, 1H, OH); 7.30 (m, 10H, H_{benz}); 7.59 (d, J=5.3 Hz, 1H, H_5); 9.28 (d, J=5.3 Hz, 1H, H_6); 10.05 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=30.4 (C(CH_3)$_3$); 55.3 (C(CH_3)$_3$); 79.6 (C(OH)); 122.1 (C_5); 127.0 (C_{benz}); 127.8 (C_{benz}); 128.5 (C_{benz}); 129.2 (C_{benz}); 140.8 (C_{benz}); 144.2 (C_{benz}); 149.9 (C_4); 151.1 (C_6); 153.1 (C_3); 187.2 (C=S). IR (KBr) (cm^{-1}): 3387; 3061; 2970; 1705; 1447; 1391; 1216; 1075; 969; 955; 760; 700. Anal. Calcd for $C_{22}H_{23}N_3OS$: C, 70.00; H, 6.14; N, 11.13; S, 8. 94. Found: C, 70.12; H, 6.42; N, 10.98; S, 8.56.

3.3.12. 3-*N*-*tert*-Butyl-5-tributylstannylpyridazinethiocarboxamide (24). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.105 g, 0.5 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.1 mL, 1.8 mmol) and 2,2,6,6-tetramethylpiperidine (0.30 mL, 1.8 mmol), t_1=60 min, then reaction with tributyltin chloride (0.15 mL, 0.55 mmol), $t1_2$=120 min giving, after purification by column chromatography on silica gel with a mixture of ether petroleum–ethyl acetate (20:1) as the eluent, **24** (0.173 g, 63%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=0.83 (m, 9H, CH_2CH_3); 1.13 (m, 6H, CH_2); 1.26 (m, 6H, CH_2); 1.62 (s, 9H, CH_3); 8.89 (d, J=1.1 Hz, 1H, H_4); 9.10 (d, J=1.1 Hz, 1H, H_6); 10.20 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=10.1 (CH_2); 14.0 (CH_3); 27.6 (CH_2); 28.0 (C(CH_3)$_3$); 29.3 (CH_2); 55.9 (C(CH_3)$_3$); 136.4 (C_4); 145.0 (C_5); 152.3 (C_6); 158.7 (C_3); 188.0 (C=S). Anal. Calcd for $C_{21}H_{39}N_3SSn$: C, 47.53; H, 7.35; N, 7.92; S, 6.03. Found: C, 47.89; H, 7.69; N, 8.23; S, 6.39.

3.3.13. 3-*N*-*tert*-Butyl-5-methylpyridazinethiocarboxamide (25). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine

(0.39 mL, 2.3 mmol), t_1=60 min, then reaction with methyl iodide (0.05 mL, 0.8 mmol), t_2=90 min giving, after purification by column chromatography on neutral alumina gel with a mixture of dichloromethane–ethyl acetate (1:1) as the eluent, **25** (0.060 g, 41%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.47 (s, 3H, CH_3); 1.67 (s, 9H, CH_3); 8.69 (d, J=2.1 Hz, 1H, H_4); 9.05 (d, J=2.1 Hz, 1H, H_6); 10.26 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ= 27.9 (C(CH_3)$_3$); 29.1 (CH_3); 56.0 (C(CH$_3$)$_3$); 128.1 (C_4); 139.1 (C_5); 153.7 (C_6); 154.2 (C_3); 187.3 (C=S). IR (KBr) (cm^{-1}): 3337; 3275; 2967; 2927; 1682; 1591; 1522; 1440; 1395; 1213; 1016. Anal. Calcd for $C_{10}H_{15}N_3S$: C, 57.38; H, 7.22; N, 20.08; S, 15.32. Found: C, 57.49; H, 7.55; N, 19.94; S, 15.38.

3.3.14. 3-*N*-*tert*-Butyl-5-iodopyridazinethiocarboxamide (26). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol), t_1=60 min, then reaction with iodine (0.190 g, 0.75 mmol), t_2=120 min giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (4:1) as the eluent, **26** (0.031 g, 14%) as a beige oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.61 (s, 9H, CH_3); 9.22 (d, J= 2.2 Hz, 1H, H_4); 9.38 (d, J=2.2 Hz, 1H, H_6); 10.04 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=27.9 (C(CH_3)$_3$); 56.2 (C(CH$_3$)$_3$); 102.0 (C_5); 137.1 (C_4); 153.6 (C_6); 159.1 (C_3); 185.5 (C=S). IR (KBr) (cm^{-1}): 3292; 3048; 2967; 2924; 1529; 1436; 1391; 1362; 1331; 1250; 1205; 1001; 891; 680. Anal. Calcd for $C_9H_{12}N_3IS$: C, 33.66; H, 3.77; N, 13.09; S, 9.98. Found: C, 34.07; H, 3.65; N, 12.87; S, 10.14.

3.3.15. 3-*N*-*tert*-Butyl-5-chloropyridazinethiocarboxamide (27). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol), t_1=60 min, then reaction with hexachloroethane (0.189 g, 0.8 mmol), t_2=120 min giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (12:1) as the eluent, **27** (0.028 g, 17%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.68 (s, 9H, CH_3); 8.91 (d, J=2.2 Hz, 1H, H_4); 9.19 (d, J=2.2 Hz, 1H, H_6); 10.15 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=27.9 (C(CH_3)$_3$); 56.2 (C(CH$_3$)$_3$); 127.7 (C_4); 139.6 (C_5); 152.4 (C_6); 154.6 (C_3); 185.5 (C=S). IR (KBr) (cm^{-1}): 3293; 2969; 2928; 1557; 1517; 1431; 1362; 1208; 1006; 901; 637. Anal. Calcd for $C_9H_{12}N_3ClS$: C, 47.06; H, 5.27; N, 18.29; S, 13.96. Found: C, 46.89; H, 5.44; N, 18.59; S, 14.23.

3.3.16. 3-*N*-*tert*-Butyl-5,6-dichloropyridazinethiocarboxamide (28). Metalation of 3-*N*-*tert*-butylpyridazinethiocarboxamide **9** (0.136 g, 0.7 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.4 mL, 2.2 mmol) and 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol), t_1=60 min, then reaction with hexachloroethane (0.189 g, 0.8 mmol), t_2=120 min giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (12:1) as the eluent, **28** (0.037 g, 20%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.60 (s, 9H, CH_3); 8.90 (s, 1H, H_4); 9.90 (br, 1H, NH). IR (KBr) (cm^{-1}): 3298; 2926; 2855; 1526; 1506; 1418; 1343; 1252; 1212; 1018; 753. Anal. Calcd for $C_9H_{11}N_3Cl_2S$: C, 40.92; H, 4.20; N, 15.91; S, 12.14. Found: C, 41.24; H, 4.28; N, 15.77; S, 12.47.

3.3.17. 3-*N*-*tert*-Butyl-4-(1-hydroxyethyl)-6-methylsulfanylpyridazinethiocarboxamide (29a) and 3-*N*-*tert*-butyl-5-(1-hydroxyethyl)-6-methylsulfanylpyridazinethiocarboxamide (29b). Metalation of 3-*N*-*tert*-butyl-6-methylsulfanylpyridazinethiocarboxamide **11** (0.123 g, 0.5 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 2.5 M (0.63 mL, 1.6 mmol) and di*iso*propylamine (0.24 mL, 1.7 mmol), t_1= 30 min, then reaction with acetaldehyde (0.30 mL, 5.1 mmol), t_2=45 min giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (7:3) as the eluent, **29a** (0.041 g, 28%) and its isomer **29b** (0.079 g, 54%) as a yellow oil, respectively.

29a: ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.50 (d, J=6.0 Hz, 3H, (CH)CH_3); 1.67 (s, 9H, CH_3); 2.69 (s, 3H, SCH_3); 3.97 (br, 1H, OH); 5.50 (q, J=6.0 Hz, 1H, CH); 7.52 (s, 1H, H_5); 8.73 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=13.7 (SCH_3); 21.7 (CH_3); 27.8 (C(CH_3)$_3$); 57.1 (C(CH$_3$)$_3$); 63.9 (CH); 124.8 (C_5); 142.8 (C_4); 156.7 (C_6); 164.6 (C_3); 191.7 (C=S). IR (KBr) (cm^{-1}): 3518; 3300; 2968; 1780; 1681; 1531; 1416; 1366; 1212; 1089. Anal. Calcd for $C_{12}H_{19}N_3OS_2$: C, 50.52; H, 6.31; N, 14.73; S, 22.45. Found: C, 50.64; H, 6.58; N, 15.08; S, 22.65.

29b: ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.46 (d, J=6.0 Hz, 3H, (CH)CH_3); 1.63 (s, 9H, CH_3); 2.72 (s, 3H, SCH_3); 3.26 (br, 1H, OH); 4.95 (q, J=6.0 Hz, 1H, CH); 8.72 (s, 1H, H_4); 9.98 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=13.5 (SCH_3); 22.2 (CH_3); 27.4 (C(CH_3)$_3$); 55.4 (C(CH$_3$)$_3$); 65.0 (CH); 122.0 (C_4); 144.1 (C_5); 151.7 (C_6); 161.9 (C_3); 186.9 (C=S). IR (KBr) (cm^{-1}): 3522; 3290; 2965; 1529; 1515; 1359; 1317; 1204; 1016. Anal. Calcd for $C_{12}H_{19}N_3OS_2$: C, 50.52; H, 6.31; N, 14.73; S, 22.45. Found: C, 50.81; H, 6.10; N, 14.43; S, 22.35.

3.3.18. 3-*N*-*tert*-Butyl-5-phenylhydroxymethyl-6-methylsulfanylpyridazinethiocarboxamide (30b). Metalation of 3-*N*-*tert*-butyl-6-methylsulfanylpyridazinethiocarboxamide **11** (0.130 g, 0.54 mmol) was performed according to the general procedure (method A) with *n*-butyllithium 1.6 M (1.10 mL, 1.8 mmol) and diisopropylamine (0.25 mL, 1.8 mmol), t_1=30 min, then reaction with benzaldehyde (0.07 mL, 0.65 mmol), t_2=90 min giving, after purification by column chromatography on neutral alumina gel with a mixture of ether petroleum–ethyl acetate (13:3) as the eluent, **30b** (0.118 g, 63%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=1.69 (s, 9H, CH_3); 2.68 (s, 3H, SCH_3); 3.02 (br, 1H, OH); 5.81 (s, 1H, CH); 7.32 (m, 5H, H_{benz}); 9.03 (s, 1H, H_4); 10.07 (br, 1H, NH). ^{13}C NMR ($CDCl_3$, 300 MHz): δ=15.9 (SCH_3); 29.6 (C(CH_3)$_3$); 57.5 (C(CH$_3$)$_3$); 73.5 (CH); 124.9 (C_4); 129.9 (C_{benz}); 130.8 (C_{benz}); 130.9 (C_{benz}); 141.1 (C_{benz}); 143.6 (C_5); 153.7

(C_6); 164.5 (C_3); 189.1 (C═S). IR (KBr) (cm^{-1}): 3478; 3281; 2962; 2926; 1529; 1513; 1359; 1095. Anal. Calcd for $C_{17}H_{21}N_3OS_2$: C, 58.80; H, 6.05; N, 12.10; S, 18.44. Found: C, 59.15; H, 6.48; N, 11.89; S, 18.74.

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