Metalation of *t*-Butyl Sulfoxides, Sulfones and Sulfonamides of Pyridazine and Pyrazine. Metalation of Diazines. XX.

Alain Turck, Nelly Plé, Paméla Pollet and Guy Quéguiner*

INSA-IRCOF, Laboratoire de Chimie Organique Fine et Hétérocyclique,
UPRESA 6014, B.P. 08, 76131 Mont St Aignan, France

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In the pyridazine series, the use of *tert*-butylsulfinyl and *tert*-butylsulfonyl as *ortho* directing groups for metalation has been tested. Various functionalized products were obtained in good yields. In the case of 3-*tert*-butylsulfinyl-6-methoxypyridazine, the metalation was regioselective in *ortho* to the sulfinyl group. The metalation of 2-*tert*-butylsulfinyl and 2-*tert*-butylsulfonylpyrazine gave low to moderate yields. Synthesis of diazinesulfonamides were improved and the metalation of *N*-*tert*-butylsulfonamidopyrazine was achieved.

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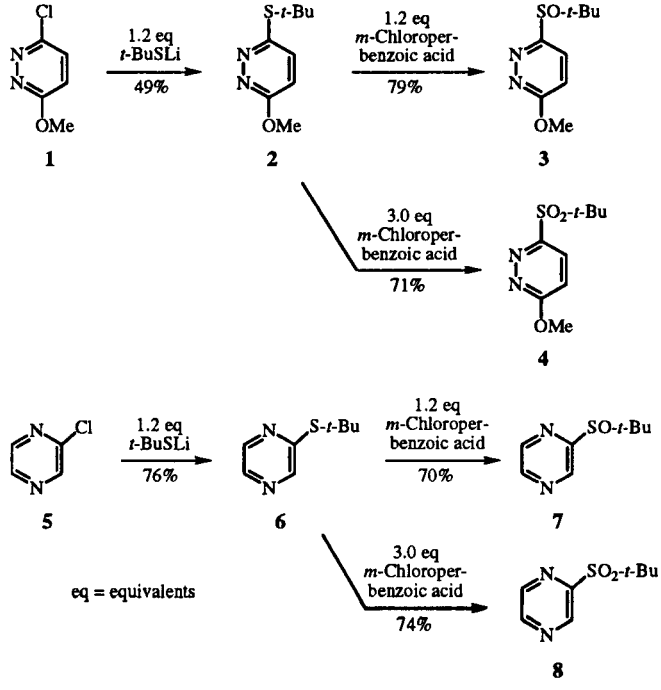
Introduction.

As a continuation of our study on sulfur derivatives as *ortho* directing groups for the metalation of diazines [1], we describe here the metalation and the reaction with some electrophiles of *tert*-butylsulfinyl and sulfonylpyridazines **3, 4** and pyrazines **7, 8**. The synthesis of diazine sulfonamides **14, 16** have been improved [9] and the results of their metalation are described. In the benzene series, Snieckus *et al* have studied the *ortho* directing properties of *tert*-butylsulfinyl and sulfonyl groups [2-4]. The metalation of *tert*-butylsulfonylnaphthalene has also been published [5-7]. In the pi-deficient series, the metalation of some pyridine sulfoxides, sulfones and sulfonamides has been described [2,8].

The synthesis of sulfinyl and sulfonyl derivatives in the diazine series is described below (Scheme 1):

Scheme 1



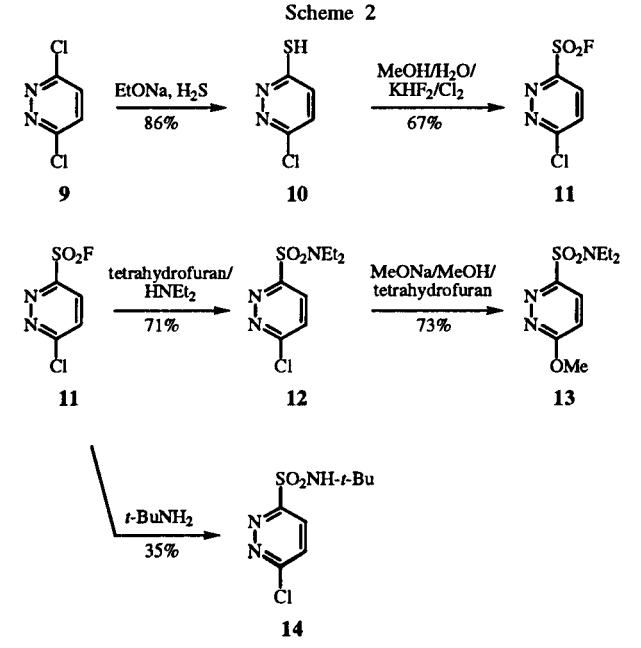
The lithium *tert*-butylthiolate solution was prepared by reaction of *n*-butyllithium with *tert*-butylmercaptan. The yield of compound **2** was moderate (49%) despite the numerous experimental conditions tested. The presence of an electron donating group (OMe) *para* to the chlorine atom did not favour substitution by the *tert*-butyl sulfide. When the substitution was carried out under more drastic conditions, the methoxy group was also substituted. Controlled oxidation with *m*-chloroperbenzoic acid afforded sulfoxides and sulfones in satisfactory yields.

The synthesis of sulfonamides in the diazine series has been described [8-10]. It was based on the reaction of sulfonyl chlorides with amines and the yields were moderate (40%).

It has been highlighted [11] that sulfonyl fluorides were more stable than the corresponding chlorides.

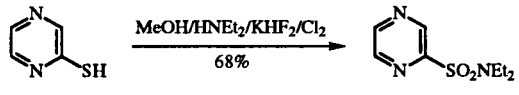
We could then synthezise some pyridazine and pyrazine sulfonamides from their fluoride derivatives in better yields (Scheme 2):

Scheme 2



It was possible to isolate in good yield (67%) and to store under dry atmosphere 3-chloro-6-fluorosulfonylpyridazine **11**. Unfortunately we could not isolate the fluorosulfonylpyrazine; so, in order to prepare 2-*N,N*-diethylsulfonamidopyrazine **16** we decided to use an "one pot" reaction in which the diethylamine was present at the beginning of the reaction, (Scheme 3):

Scheme 3



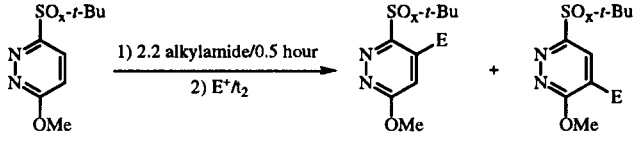
15 **16**

Metalation of the Sulfur Derivatives.

All the metalations have been performed at -78° in tetrahydrofuran with lithium alkylamides:lithium diisopropylamide or lithium 2,2,6,6-tetramethylpiperidide.

Metalation and reaction with electrophiles of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** and 3-*tert*-butylsulfonyl-6-methoxypyridazine **4** (Scheme 4, Tables 1, 2):

Scheme 4



x = 1 **3**
x = 2 **4**

17a-20a
21a-23a

19a-20b
21b-23b

With methyl iodide as the electrophile (entries 5, 6), 4% of the starting material was recovered and when iodine was used as the electrophile (entries 7, 8) some 4,5 diiodo derivatives were obtained (9% and 6%).

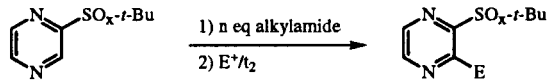
The functionalization was regioselective when aldehydes were reacted with the lithio derivatives; the regioselectivity was lower with methyl iodide and iodine. The presence of two chiral centers in compounds **17** and **18** led to diastereoisomers. It was easy to determine their percentages with their ^1H nmr spectra but we were not able to determine the structure of the major isomer (RR, SS) or (RS, SR). In view of our results (Table 1), we could assume that the ratio of diastereoisomers was mainly dependent on the reacted electrophiles.

Metalation and Reaction with Electrophiles of 3-*tert*-Butylsulfonylmethoxypyridazine **4** (Table 2).

Metalation of sulfone **4** required a stronger base than the metalation of the corresponding sulfoxide **3** and the regioselectivity was low.

Metalation and Reaction with Electrophiles of 2-*tert*-Butylsulfinyl and 2-*tert*-Butylsulfonylpyrazines **7** and **8** (Scheme 5, Tables 3, 4):

Scheme 5



x = 1 **7**
x = 2 **8**

24
25-27

Table 1 (x= 1)

Entry	E+	Product	Alkylamide	t_2 (hours)	Yield	Ratio of a/b	Ratio of diasteroisomers
1	CH_3CHO	**17a**	Lithium diisopropylamide	0.5	89%	100/0	74/26
2	CH_3CHO	**17a**	Lithium 2,2,6,6-tetramethylpiperidide	0.5	93%	100/0	75/25
3	PhCHO	**18a**	Lithium diisopropylamide	1	90%	100/0	54/46
4	PhCHO	**18a**	Lithium 2,2,6,6-tetramethylpiperidide	1	99%	100/0	56/44
5	CH_3I	**19a,b**	Lithium diisopropylamide	1	57%	93/7	
6	CH_3I	**19a,b**	Lithium 2,2,6,6-tetramethylpiperidide	1	81%	94/6	
7	I_2	**20a,b**	Lithium diisopropylamide	2	70%	83/17	
8	I_2	**20a,b**	Lithium 2,2,6,6-tetramethylpiperidide	2	63%	79/21	

Table 2 (x = 2)

E+	Product	Alkylamide	t_2 (hours)	Yield	Ratio of a/b
CH_3CHO	**21a,b**	Lithium diisopropylamide	0.5	28%	66/34
CH_3CHO	**21a,b**	Lithium 2,2,6,6-tetramethylpiperidide	0.5	94%	63/37
PhCHO	**22a,b**	Lithium diisopropylamide	1	55%	66/34
PhCHO	**22a,b**	Lithium 2,2,6,6-tetramethylpiperidide	1	75%	58/32
CH_3I [a]	**23a,b**	Lithium diisopropylamide	1	89%	60/40
CH_3I	**23a,b**	Lithium 2,2,6,6-tetramethylpiperidide	1	81%	60/40

[a] 7% of the 4,5 dimethyl derivative was obtained.

Table 3 (x = 1)

E+	Product	Alkylamide	n eq	Yield	Starting material	Ratio of diastereoisomers
CH_3CHO	**24**	Lithium 2,2,6,6-tetramethylpiperidide	1.2	0%	76%	
CH_3CHO	**24**	Lithium 2,2,6,6-tetramethylpiperidide	2.2	26%	8%	50/50
CH_3CHO	**24**	Lithium diisopropylamide	2.2	23%	65%	50/50
CH_3CHO	**24**	Lithium diisopropylamide	3.2	22%	5%	50/50

Whatever the nature or amount of the metalating agent may be, yields remained low. In view of these unsatisfactory results, we did not test other electrophiles.

Table 4 (x = 2)

E+	Product	Metalating agent	n eq	t_2 (hours)	Yield	Starting material
CH_3CHO	**25**	Lithium 2,2,6,6-tetramethylpiperidide	1.2	0.5	0%	62%
CH_3CHO	**25**	Lithium 2,2,6,6-tetramethylpiperidide	2.2	0.5	0%	23%
CH_3CHO	**25**	Lithium 2,2,6,6-tetramethylpiperidide	3.4	0.5	54%	9%
CH_3CHO	**25**	Lithium 2,2,6,6-tetramethylpiperidide	4	0.5	53%	24%
CH_3CHO	**25**	Lithium diisopropylamide	3.4	0.5	19%	45%
PhCHO	**26**	Lithium 2,2,6,6-tetramethylpiperidide	4	1	41%	0%
I_2	**27**	Lithium 2,2,6,6-tetramethylpiperidide	4	2	16%	0%

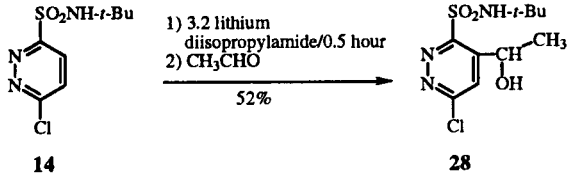
Metalation and reaction with sulfone **8** gave low to moderate yields. We can notice that a large excess of alkylamide was necessary.

Metalation and Reaction with Acetaldehyde of Sulfonamides **13**, **14**, and **16**.

Metalations of *N,N*-diethylsulfonamides **13** and **16** were unsuccessful. Lithium diisopropylamide and lithium 2,2,6,6-tetramethylpiperidide were examined in different amounts and with various experimental conditions; in all cases we recovered the starting material and/or a slurry without any identified products.

On account of the good results obtained with *N-tert*-butylcarboxamide [12], the *N-tert*-butylsulfonamide was tested as an *ortho* directing group in pyridazine **14** (Scheme 6):

Scheme 6



14 **28**

In that case, yield was moderate but regioselectivity was total in *ortho* to the sulfonamide group.

Discussion.

The metalation results of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** indicate that the *tert*-butylsulfinyl group is a very good *ortho* directing group for the metalation in the diazine series. This group is better than the phenylsulfinyl or the methylsulfinyl groups previously studied [1]. The low yields obtained in the pyrazine series should be explained by the good leaving and electron withdrawing properties of the *tert*-butylsulfinyl group which could favour a nucleophilic attack with abstraction of the *tert*-butylsulfinyl group.

In the 3-*tert*-butylsulfinyl-6-methoxypyridazine case, the good leaving group properties of *tert*-butyl sulfinyl were compensated by the presence of an electron donating group (OMe). This could explain the good yields obtained. The *tert*-butylsulfonyl group gave moderate to good yields. The *ortho* directing effect was lower than that of the corresponding sulfinyl group because the regioselectivity was low when it was opposed to a methoxy group in **4**. These results are close to those obtained with the phenylsulfonyl group. The methylsulfonyl group gave a competitive metalation on the methyl moiety [1].

The metalation of *N,N*-diethylsulfonamides **13** and **16** were unsuccessful but the *N-tert*-butylsulfonamide **14** gave an interesting result and this *ortho* directing group will be investigated more thoroughly.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. The ^1H nmr spectra were recorded in deuteriochloroform and deuterated dimethyl sulfoxide with hexamethyldisiloxane as internal reference on a Bruker AC 200 (200 MHz) spectrometer. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. The ir spectra were recorded on a Perkin Elmer 1650 spectrometer and were performed in potassium bromide pellets. The hplc separation was obtained on Waters 991, Photodiode array detector with a nucleosil C18 10µ (250 x 4.6 mm) column.

Tetrahydrofuran was distilled from benzophenone sodium and used immediately. Water content of the solvent was estimated by the modified Karl-Fischer method (tetrahydrofuran less than 50 ppm of water).

Metalations were performed under an argon atmosphere. Reagents were handled with syringes through septa.

General Procedure for Metalation.

A solution of *n*-butyllithium (1.6 *M* or 2.5 *M* in hexane) was added to cold (-40°), stirred, anhydrous tetrahydrofuran (30 ml) under an atmosphere of dry argon.

Diisopropylamine or 2,2,6,6-tetramethylpiperidine was added. The solution was warmed to 0° and kept at this temperature for 20 minutes. It was then cooled to -75°. A solution of the substrate to metalate dissolved in 5 ml of tetrahydrofuran was added, and the mixture was stirred for t_1 at -75°. The electrophile was added and stirring was continued for t_2 at -75°. Hydrolysis was then carried out at -75° using a mixture of 35% aqueous hydrochloric acid (1 ml), ethanol (4 ml) and tetrahydrofuran (5 ml). The solution was then warmed to 0°, made slightly basic with a saturated sodium hydrogen carbonate solution and evaporated *in vacuo* nearly to dryness. The residue was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness to afford a crude product which was purified by column chromatography on silica gel or by sublimation.

3-*tert*-Butylthio-6-methoxypyridazine (**2**).

A solution of *n*-butyllithium 1.6 *M* (3.30 ml, 8.3 mmoles) and tetrahydrofuran (30 ml) was cooled to 0° for 10 minutes. 2-methyl-2-propanethiol (0.90 ml, 8.3 mmoles) was added dropwise and the resulting mixture was stirred at 0° for 5 minutes. A solution of 3-chloro-6-methoxypyridazine **1** (1.00 g, 6.9 mmoles) in tetrahydrofuran (10 ml) was added slowly and the final mixture was stirred and heated under reflux for 6 hours. After cooling, water (10 ml) was added and the resulting solution was concentrated then extracted with dichloromethane (4 x 20 ml). The combined organic layers were dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (8:2) gave **2** as a yellow oil (0.67 g, 49%); ir (potassium bromide): ν 2961 (CH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.49 (s, 9H, *t*-Bu), 6.77 (d, 1H, J_{5-6} = 9.1 Hz, H5), 7.22 (d, 1H, J_{5-6} = 9.1 Hz, H4).

Anal. Calcd. for $C_9H_{14}N_2OS$: C, 54.59; H, 7.13; N, 14.18. Found: C, 54.4; H, 7.1; N, 14.4.

3-*tert*-Butylsulfinyl-6-methoxypyridazine (**3**).

A solution of *m*-chloroperbenzoic acid (0.71 g, 4.1 mmoles) in tetrahydrofuran (5 ml) was added dropwise into a cooled solution (-20°) of 3-*tert*-butylthio-6-methoxypyridazine **2** (0.67 g, 3.4 mmoles) in tetrahydrofuran (20 ml). After 35 minutes, a second solution of *m*-chloroperbenzoic acid (0.20 g, 1.02 mmoles) was added. The resulting mixture was vigorously stirred for 15 minutes then neutralized with a saturated sodium hydrogen carbonate solution (6 ml), concentrated and extracted with dichloromethane (4 x 20 ml). The combined organic layers were dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (1:1) afforded **3** as a white solid (0.58 g, 79%), mp 112°; ir (potassium bromide): ν 1034 (SO), 844 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, *t*-Bu), 4.20 (s, 3H, OCH_3), 7.17 (d, 1H, J_{4-5} = 9.2 Hz, H5), 7.98 (d, 1H, J_{4-5} = 9.2 Hz, H4).

Anal. Calcd. for $C_9H_{14}N_2O_2S$: C, 50.51; H, 6.59; N, 13.09. Found: C, 50.5; H, 6.6; N, 13.0.

3-*tert*-Butylsulfonyl-6-methoxypyridazine (**4**).

A solution of *m*-chloroperbenzoic acid (3.90 g, 23.0 mmoles) in tetrahydrofuran (20 ml) was added to a solution of 3-*tert*-butylthio-6-methoxypyridazine **3** (1.50 g, 7.5 mmoles) in tetrahydrofuran (20 ml). After 80 minutes at room temperature, the mixture was neutralized with a saturated sodium hydrogen carbonate solution (2.5 ml), concentrated and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (6:4) gave **4** as a white solid (1.24 g, 71%), mp 118°; ir (potassium bromide): ν 2943 (CH), 1306, 1115 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (s, 9H, *t*-Bu), 4.22 (s, 3H, OCH_3), 7.15 (d, 1H, J_{4-5} = 9.2 Hz, H5), 8 01 (d, 1H, J_{4-5} = 9.2 Hz, H4).

Anal. Calcd. for $C_9H_{14}N_2O_3S$: C, 47.00; H, 6.13; N, 12.18. Found: C, 47.1; H, 6.2; N, 12.0.

2-*tert*-Butylthiopyrazine (**6**).

To a solution of *n*-butyllithium 2.5 *M* (10.50 ml, 26.0 mmoles) was added at 0°, 2-methyl-2-propanethiol (3.00 ml, 26.0 mmoles) in tetrahydrofuran (50 ml). After 10 minutes, 2-chloropyrazine **5** (1.60 ml, 17.5 mmoles) was added slowly. The resulting mixture was stirred at 0° for 10 minutes then heated under reflux for 2.5 hours. After cooling, water (10 ml) was added and the resulting solution was concentrated and extracted with dichloromethane (4 x 20 ml). The combined organic layers were dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (7:3) gave **6** as a colourless oil (2.20 g, 76%); ^1H nmr (deuteriochloroform): δ 1.97 (s, 9H, *t*-Bu), 8.71 (d, 1H, J_{5-6} = 2.5 Hz, H5), 8.87 (q, 1H, J_{3-6} = 1.5 Hz, J_{5-6} = 2.5 Hz, H6), 8.92 (d, 1H, J_{3-6} = 1.5 Hz, H3).

Anal. Calcd. for $C_8H_{12}N_2S$: C, 57.19; H, 7.20; N, 16.67. Found: C, 57.3; H, 7.4; N, 16.5.

2-*tert*-Butylsulfinylpyrazine (**7**).

A solution of *m*-chloroprebenzoic acid (1.23 g, 7.1 mmoles) in tetrahydrofuran (10 ml) was added dropwise to a cooled (-20°) solution of 2-*tert*-butylthiopyrazine **6** (1.00 g, 5.9 mmoles) in tetrahydrofuran (15 ml) for 20 minutes. A second solution of *m*-chloroperbenzoic acid (0.20 g, 1.2 mmoles) was added. The resulting mixture was stirred vigorously 25 minutes at -20° then neutralized with a saturated sodium hydrogen carbonate solution (4 ml), concentrated and extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (1:1) afforded **7** as a yellow oil (0.69 g, 70%); ir (potassium bromide): ν 2963, 2926, 2867 (CH); 1048 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.19 (m, 9H, *t*-Bu), 8.54 (d, 1H, J_{5-6} = 2.0 Hz, H5 or H6), 8.63 (d, 1H, J_{5-6} =2.0 Hz, H5 or H6), 9.07 (s, 1H, H3).

Anal. Calcd. for $C_8H_{12}N_2OS$: C, 52.22; H, 6.57; N, 15.22. Found: C, 52.0; H, 6.7; N, 15.4.

2-*tert*-Butylsulfonylpyrazine (**8**).

A solution of *m*-chloroperbenzoic acid (3.10 g, 18.0 mmoles) in tetrahydrofuran (10 ml) was added to a solution of 2-*tert*-butylthiopyrazine **6** (1.00 g, 5.9 mmoles) in tetrahydrofuran (10 ml). The resulting mixture was stirred at room temperature for 90 minutes.

After neutralization with a saturated sodium hydrogen carbonate solution (14 ml), the final solution was concentrated then extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate. Column chromatography eluting with ethyl acetate gave **8** as a white solid (0.87 g, 74%), mp 85°; ir (potassium bromide): ν 2982 (CH), 1301, 1102 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.45 (s, 9H, *t*-Bu), 8 80 (d, 1H, J_{5-6} = 1.7 Hz, H5 or H6), 8.87 (d, 1H, J_{5-6} = 1.7 Hz, H5 or H6), 9.29 (s, 1H, H3).

Anal. Calcd. for $C_8H_{12}N_2O_2S$: C, 48.04; H, 6.05; N, 14.01. Found: C, 48.1, H, 6.2; N, 14.0.

3-Chloro-6-mercaptopyridazine (**10**).

A sodium ethoxide solution prepared from sodium (0.62 g, 26.8 mmoles) and ethanol (35 ml) was saturated with hydrogen sulfide. A solution of 3,6-dichloropyridazine **9** (2.00 g, 13.4 mmoles) in tetrahydrofuran (10 ml) was added quickly. The resulting mixture was stirred and heated under reflux for 1 hour. The solvent was removed and water (5 ml) was added. The *p*H was adjusted to 9 with an aqueous sodium hydroxide solution (2*N*). After filtration of the precipitate, the resulting solution was acidified up to *p*H = 2 with aqueous hydrochloric acid solution (30%). The resulting precipitate was collected and dried at 50 ° *in vacuo* affording **10** as a yellow solid (1.65 g, 86%), mp 160-162° dec; ir (potassium bromide): ν 2876 (NH), 1059 (C =S), 830 (SH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.39 (d, 1H, J_{4-5} = 9.4 Hz, H4), 7.61 (d, 1H, J_{4-5} = 9.4 Hz, H5 or H5'), 7 62 (d, 1H, J_{4-5} = 9.4 Hz, H5 or H5'), 8.07 (s, 1H, NH).

Anal. Calcd. for $C_4H_3N_2ClS$: C, 32.79; H, 2.06; N, 19.12. Found: C, 32.7; H, 2.1; N, 19.1.

3-Chloro-6-fluorosulfonylpyridazine (**11**).

A mixture of methanol (4 ml), water (4 ml), potassium hydrogen fluoride (6.50 g, 83.0 mmoles) and 3-chloro-6-mercaptopyridazine **10** (1.00 g, 6.8 mmoles) was cooled to -20° and stirred vigorously during 25 minutes. A stream of chlorine was adjusted to maintain the temperature between -20° and -10°. After 20-30 minutes, the resulting mixture was poured rapidly on an ice-water mixture (5 ml) then quickly filtered. The resulting precipitate was dried at 50° *in vacuo* for 4 hours. Sublimation (P = 1.5 mmHg, T = 100°) gave **11** as a white solid (0.45 g, 34%), mp 55-56°; ^1H nmr (deuteriochloroform): δ 7.91 (d, 1H, J_{4-5} = 7.4 Hz, H4), 8.20 (d, 1H, J_{4-5} = 7.4 Hz, H5).

Anal. Calcd. for $C_4H_2N_2ClFO_2S$: C, 24.45; H, 1.02; N, 14.26. Found: C, 24.6; H, 0.9; N, 14.3.

3-Chloropyridazine-6-(*N,N*-diethylsulfonamide) (**12**).

Diethylamine (0.20 ml, 2.4 mmoles) was added to a solution of 3-chloro-6-fluorosulfonylpyridazine **11** (0.40 g, 2.0 mmoles) in tetrahydrofuran (10 ml). The resulting mixture was stirred 30 minutes at room temperature then water (5 ml) was added. The final solution was extracted with dichloromethane (4 x 10 ml). The combined organic layers were dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (4:6) afforded **12** as a yellow solid (0.36 g, 71%); mp 100-104°; ir (potassium bromide): ν 1359, 1162 (SO_2N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.29 (t, 6H, $J_{CH_2CH_3}$ = 7.0 Hz, CH_3), 3.71 (q, 4H, $J_{CH_2CH_3}$ = 7.0 Hz, CH_2), 6.78 (d, 1H, J_{4-5} = 9.8 Hz, H4), 7.76 (d, 1H, J_{4-5} = 9.8 Hz, H5)

Anal. Calcd. for $C_8H_{12}N_3SO_2Cl$: C, 38.51; H, 4.85; N, 16.84. Found: C, 38.6; H, 4.6; N, 16.8.

3-Methoxypyridazine-6-(*N,N*-diethylsulfonamide) (**13**).

To a solution of sodium methoxide prepared from sodium (0.07 g, 3.0 mmoles) and methanol (20 ml) was added a solution of 3-chloropyridazine-6-(*N,N*-diethylsulfonamide) **12** (0.50 g, 2.0 mmoles) in tetrahydrofuran (5 ml). The resulting mixture was stirred at room temperature for 3 hours. The solvent was evaporated, the residue suspended in water (10 ml) and the mixture extracted with dichloromethane (3 x 20 ml). The combined organic layers were dried over magnesium sulfate. The solvent was removed and the yellow solid identified as the 3-methoxypyridazine-6-(*N,N*-diethylsulfonamide) **13**, was used without further purification (0.36 g, 73%), mp 197°; ir (potassium bromide): ν 2978, 2933 (CH), 1313, 1244 (SO_2N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (t, 6H, $J_{CH_2CH_3}$ = 7.1 Hz, CH_3), 3.61 (q, 4H, $J_{CH_2CH_3}$ = 7.1 Hz, CH_2), 4.72 (s, 3H, OCH_3), 7.43 (d 1H, J_{4-5} = 9.6 Hz, H5), 8.43 (d, 1H, J_{4-5} = 9.6 Hz, H4)

Anal. Calcd. for $C_9H_{15}N_3O_3S$: C, 44.15; H, 6.17; N, 17.15. Found: C, 44.5; H, 6.0; N, 16.9.

3-Chloropyridazine-6-(*N-tert*-butylsulfonamide) (**14**).

tert-Butylamine (0.90 ml, 8.9 mmoles) was added dropwise to a cooled (0°) solution of 3-chloro-6-fluorosulfonylpyridazine **11** (0.70 g, 3.6 mmoles) in tetrahydrofuran (10 ml). The mixture was stirred at room temperature for 6 hours. After removal of the solvent, the resulting oil was extracted with dichloromethane (30 ml), the precipitate was removed by filtration. The resulting solution was dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (1:1) gave **14** as a white solid (0.31 g, 35%), mp 185°; ir (potassium bromide): ν 3310, 2974 (CH), 1413, 1186 (SO_2N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55 (s, 9H, *t*-Bu), 5.40 (m, 1H, NH), 6.72 (d, 1H, J_{4-5} = 9.6 Hz, H4), 7.74 (d, 1H, J_{4-5} = 9.6 Hz, H5).

Anal. Calcd. for $C_8H_{12}N_3ClO_2S$: C, 38.51; H, 4.85; N, 16.84. Found C, 38.6; H, 5.1; N, 16.5.

2-Mercaptopyrazine (**15**).

A solution of sodium methoxide prepared from sodium (2.00 g, 0.09 mole) and methanol (60 ml) was saturated with hydrogen sulfide. The 2-chloropyrazine **5** (5.00 g, 0.04 mole) was added rapidly and the resulting mixture was heated under reflux for 1 hour. After cooling and addition of water (10 ml), the *p*H solution was adjusted to *p*H = 9 with a sodium hydroxide solution (2*N*) and the resulting precipitate was eliminated by filtration. The final mixture was acidified to *p*H = 2 with aqueous hydrochloric acid (30%). The precipitate was collected and dried at 50° *in vacuo* and gave **15** as a yellow solid (4.45 g, 91%); mp 170° dec; ir (potassium bromide): ν 2647 (SH), 1031 (C=S), 790 (SH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.58 (d, 1H, J_{5-6} = 4.0 Hz, H5 or H6), 7.77 (d, 1H, J_{5-6} = 4.0 Hz, H5 or H6), 8.50 (s, 1H, H3).

Anal. Calcd. for $C_4H_4N_2S$: C, 42.90; H, 3.60; N, 25.01. Found: C, 43.1; H, 3.4; N, 25.0.

Pyrazine-2-(*N,N*-diethylsulfonamide) (**16**).

A solution of 2-mercaptopyrazine **15** (0.50 g, 4.5 mmoles), potassium hydrogen fluoride (4.25 g, 54.9 mmoles), diethylamine (6 ml) and methanol (3 ml) (solvents were freshly distilled and stored over molecular sieves 3A) was stirred at -20° for 25 minutes. The stream of chlorine was adjusted to keep the temperature at -10°. When the temperature decreased at the end of the reaction the solution was stirred 15 minutes more. Water (10 ml) was added, the resulting mixture was extracted with dichloromethane (4 x 20 ml). The

combined organic layers were dried over magnesium sulfate. Column chromatography eluting with light petroleum ether/ethyl acetate (1:1) gave **16** as an orange oil (0.68 g, 68%), ir (potassium bromide): ν 2970, 2931, 2851 (CH), 1381, 1134 (SO_2N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.08 (t, 6H, $J_{CH_2CH_3}$ = 7.1 Hz, CH_3), 3.02 (q, 4H, $J_{CH_2CH_3}$ = 7.1, CH_2), 8.08 (d, 1H, $J_{5\text{-}6}$ = 2.6 Hz, H5), 8.20 (dd, 1H, $J_{5\text{-}6}$ = 2.6 Hz, $J_{3\text{-}6}$ = 1.5 Hz, H6), 8.57 (d, 1H, $J_{3\text{-}6}$ = 1.5 Hz, H3)

Anal. Calcd. for $C_8H_{13}N_3O_2S$: C, 44.69; H, 6.09; N, 19.54. Found: C, 44.5; H, 6.1; N, 19.8.

3-*tert*-Butylsulfinyl-4-(2-hydroxyethyl)-6-methoxypyridazine (**17a**).

Metalation of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.64 ml, 1.0 mmole) and 2,2,6,6-tetramethylpiperidine (0.17 ml, 3.1 mmoles), t_1 = 30 minutes, then reaction with acetaldehyde (1.00 ml, 18.0 mmoles), t_2 = 30 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (2:8) **17a** as an orange oil (0.11 g, 93%); ir (potassium bromide): ν 3400 (OH), 1037 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.31 (m, 9H, *t*-Bu), 1.47 (m, 3H, CH_3), 4.12 (m, 3H, OCH_3), 5.26 (q, 1H, $J_{CH\text{-}CH_3}$ = 6.3 Hz, CH [a]), 5.53 (q, 1H, $J_{CH\text{-}CH_3}$ = 6.3 Hz, CH [b]), 7.03 (s, 1H, H5 [a]), 7.23 (s, 1H, H5 [b]).

Anal. Calcd. for $C_{11}H_{18}N_2O_3S$: C, 51.21; H, 7.03; N, 10.86. Found: C, 51.0; H, 7.4; N, 10.7.

3-*tert*-Butylsulfinyl-4-hydroxybenzyl-6-methoxypyridazine (**18a**).

Metalation of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.64 ml, 1.0 mmole) and diisopropylamine (0.15 ml, 1.0 mmole), t_1 = 30 minutes, then reaction with benzaldehyde (0.10 ml, 1.0 mmoles), t_2 = 60 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (2:8) **18** as a yellow oil (0.13 g, 90%); ir (potassium bromide): ν 3316 (OH), 1017 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.21 (m, 6H, *t*-Bu), 1.38 (m, 3H, *t*-Bu), 4.07 (m, (3+1)H, OCH_3 + OH), 6.40 (s, 1H, CH [b]), 6.42 (s, 1H, CH [a]), 6.51 (s, 1H, H5 [b]), 6.93 (s, 1H, H5 [a]), 7.30 (m, 5H, Ph).

Anal. Calcd. for $C_{16}H_{20}N_2O_3S$: C, 60.05; H, 6.30; N, 8.75. Found: C, 60.3; H, 6.0; N, 8.8.

3-*tert*-Butylsulfinyl-4-methyl-6-methoxypyridazine (**19a**).

Metalation of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.64 ml, 1.0 mmole) and 2,2,6,6-tetramethylpiperidine (0.64 ml, 1.0 mmole), t_1 = 30 minutes, then reaction with methyl iodide (0.06 ml, 1.0 mmole), t_2 = 60 minutes gave after purification by column chromatography eluting with ethyl acetate **19a** as a colorless oil (0.08 g, 76%); ir (potassium bromide): ν 1025 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.32 (s, 9H, *t*-Bu), 2.57 (s, 3H, CH_3), 4.13 (s, 3H, OCH_3), 6.78 (s, 1H, H5).

Anal. Calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.68; H, 7.07; N, 12.29. Found: C, 52.4; H, 7.3; N, 12.4.

3-*tert*-Butylsulfinyl-5-methyl-6-methoxypyridazine (**19b**).

Metalation of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.64 ml, 1.0 mmole) and 2,2,6,6-tetramethylpiperidine (0.64 ml, 1.0 mmole), t_1 = 30 minutes, then reaction with methyl iodide (0.06 ml, 1.0 mmole), t_2 = 60 minutes gave after purification by column chromatography eluting with ethyl acetate **19b** as a colorless oil (0.01 g, 5%); ir (potassium bromide): ν 1025 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.26 (s, 9H, *t*-Bu), 2.31 (s, 3H, CH_3), 4.20 (s, 3H, OCH_3), 7.77 (s, 1H, H4).

Anal. Calcd. for $C_{10}H_{16}N_2O_2S$: C, 52.68; H, 7.07; N, 12.29. Found: C, 52.4; H, 7.3; N, 12.4.

3-*tert*-Butylsulfinyl-4-iodo-6-methoxypyridazine (**20a**).

Metalation of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.64 ml, 1.0 mmole) and diisopropylamine (0.15 ml, 1.0 mmoles), t_1 = 30 minutes, then reaction with iodine (0.14 g, 1.0 mmole), t_2 = 120 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (8:2) **20a** as a brown solid (0.09 g, 58%), mp 112-120°; ir (potassium bromide): ν 2946 (CH), 1049 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.36 (s, 9H, *t*-Bu), 4.17 (s, 3H, OCH_3), 7.54 (s, 1H, H5).

Anal. Calcd. for $C_9H_{13}N_2O_2IS$: C, 31.79; H, 3.85; N, 8.24. Found: C, 31.9; H, 3.6; N, 8.4.

3-*tert*-Butylsulfinyl-5-iodo-6-methoxypyridazine (**20b**).

Metalation of 3-*tert*-butylsulfinyl-6-methoxypyridazine **3** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.64 ml, 1.0 mmole) and diisopropylamine (0.15 ml, 1.0 mmole), t_1 = 30 minutes, then reaction with iodine (0.14 g, 1.0 mmole), t_2 = 120 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (8:2) **20b** as a brown oil (0.02 g, 12%); ir (potassium bromide): ν 2946 (CH), 1049 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.27 (s, 9H, *t*-Bu), 4.24 (s, 3H, OCH_3), 8.45 (s, 1H, H5).

Anal. Calcd. for $C_9H_{13}N_2O_2IS$: C, 31.79; H, 3.85; N, 8.24. Found: C, 31.9; H, 3.6; N, 8.4.

3-*tert*-Butylsulfonyl-4-(2-hydroxyethyl)-6-methoxypyridazine (**21a**).

Metalation of 3-*tert*-butylsulfonyl-6-methoxypyridazine **4** (0.10 g, 0.4 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.60 ml, 1.0 mmole) and 2,2,6,6-tetramethylpiperidine (0.16 ml, 1.0 mmole), t_1 = 30 minutes, then reaction with acetaldehyde (1.00 ml, 18.0 mmoles), t_2 = 30 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (4:6) **21a** as a beige solid (0.07 g, 59%), mp 100°; ir (potassium bromide): ν 3474 (OH), 2985, 2933, 2873 (CH), 1072 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.53 (m, 12 H, *t*-Bu + CH_3), 3.20 (s, 1H, OH), 4.20 (s, 3H, OCH_3), 5.60 (q, 1H, J_{CH_3CH} = 6.8 Hz, CH), 7.38 (s, 1H, H5).

Anal. Calcd. for $C_{11}H_{18}N_2O_4S$: C, 48.22; H, 6.62; N, 10.22. Found: C, 48.0; H, 6.9; N, 10.2.

3-*tert*-Butylsulfonyl-5-(2-hydroxyethyl)-6-methoxypyridazine (**21b**).

Metalation of 3-*tert*-butylsulfonyl-6-methoxypyridazine **4** (0.10 g, 0.4 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.60 ml, 1.0 mmole) and 2,2,6,6-tetramethylpiperidine (0.16 ml, 1.0 mmole), t_1 = 30 minutes, then reaction with aeetaldehyde (1.00 ml, 18.0 mmoles), t_2 = 30 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (4:6) a beige solid of **21b** (0.04 g, 35%), mp 100°; ir (potassium bromide): ν 3474 (OH),

2985, 2933, 2873 (CH), 1072 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.43 (m, 12 H, *t*-Bu), 1.49 (d, 3H, J_{CH3CH} = 6.5 Hz, CH_3), 3.03 (s, 1H, OH), 4.26 (s, 3H, OCH_3), 5.07 (q, 1H, J_{CH3CH} = 6.5 Hz, CH), 8.17 (s, 1H, H4).

Anal. Calcd. for $C_{11}H_{18}N_2O_4S$: C, 48.22; H, 6.62; N, 10.22. Found: C, 48.0; H, 6.9; N, 10.2.

3-*tert*-Butylsulfonyl-(4,5)-hydroxybenzyl-6-methoxypyridazines **22a,b**.

Metalation of 3-*tert*-butylsulfonyl-6-methoxypyridazine **4** (0.10 g, 0.4 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.60 ml, 1.0 mmole) and 2,2,6,6-tetramethylpiperidine (0.16 ml, 1.0 mmole), t_1 = 30 minutes then reaction with benzaldehyde (0.10 ml, 1.0 mmole), t_2 = 60 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (4:6) a yellow oil of two metalation isomers **22a** and **22b** (0.11 g, 75%); ir (potassium bromide): ν 3472 (OH), 1307, 1380, 1122 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (m, 9H, *t*-Bu [b]), 1.52 (m, 9H, *t*-Bu [a]), 4.00 (s, 2H, 2 x OH), 4.14 (s, 3H, OCH_3), 4.16 (s, 3H, OCH_3), 5.93 (s, 1H, CH [b]), 6.63 (s, 1H, CH [a]), 7.00 (s, 1H, H5 [a]), 7.30-7.38 (m, 10 H, Ph [a,b]), 8.37 (s, 1H, H4 [b]).

Anal. Calcd. for $C_{16}H_{20}N_2O_4S$: C, 57.19; H, 6.00; N, 8.34. Found: C, 56.9; H, 6.0; N, 8.6.

3-*tert*-Butylsulfonyl-(4,5)-methyl-6-methoxypyridazine (**23a,b**).

Metalation of 3-*tert*-butylsulfonyl-6-methoxypyridazine **4** (0.10 g, 0.4 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.60 ml, 1.0 mmole) and diisopropylamine (0.13 ml, 1.0 mmole), t_1 = 30 minutes, then reaction with methyl iodide (0.06 ml, 1.0 mmole), t_2 = 60 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (1:1) a yellow oil of two metalation isomers **23a** and **23b** (0.09 g, 89%); ir (potassium bromide): ν 2984, 2957 (CH), 1122, 1302 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (s, 9H, *t*-Bu [b]), 1.51 (s, 9H, *t*-Bu [a]), 2.28 (s, 3H, CH_3 [b]), 2.62 (s, 3H, CH_3 [a]), 4.15 (s, 3H, OCH_3 [a]), 4.21 (s, 3H, OCH_3 [b]), 6.87 (s, 1H, H5), 7.62 (s, 1H, H4)

Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.22; H, 6.61; N, 11.48. Found: C, 49.5; H, 6.9; N, 11.3.

2-*tert*-Butylsulfinyl-3-(2-hydroxyethyl)pyrazine (**24**).

Metalation of 2-*tert*-butylsulfinylpyrazine **7** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.75 ml, 1.2 mmoles) and 2,2,6,6-tetramethylpiperidine (0.20 ml, 1.2 mmoles), t_1 = 20 minutes then reaction with acetaldehyde (1.00 ml, 18.0 mmoles), t_2 = 30 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (1:9) **24** as a yellow oil (0.03 g, 26%); ir (potassium bromide): ν 3378 (OH), 2976, 2930 (CH), 1059 (SO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.32 (s, 9H, *t*-Bu), 1.55 (m, 3H, CH_3), 3.94 (m, 1H, OH), 4.42 (m, 1H, OH), 5.34 (m, 1H, CH), 5.64 (m, 1H, CH), 8.54 (d, 1H, J_{5-6} = 1.7 Hz, H5 or H6), 8.62 (m, 1H, H5 or H6).

We could not obtain satisfactory analysis of this product despite many attemps.

2-*tert*-Butylsulfonyl-3-(2-hydroxyethyl)pyrazine (**25**).

Metalation of 2-*tert*-butylsulfonylpyrazine **8** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (1.10 ml, 1.7 mmoles) and 2,2,6,6-tetramethylpiperidine (0.29 ml, 1.7 mmoles), t_1 = 20 minutes, then reaction with acetaldehyde (1.00 ml, 18.0 mmoles), t_2 = 30 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (2:8) **25** as an orange oil (0.07 g, 54%); ir (potassium bromide): ν 3482 (OH), 2979, 2933 (CH), 1305, 1124 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.48 (m, 9H, *t*-Bu), 1.58 (d, 3H, J_{CH3CH} = 6.3 Hz, CH_3), 3.65 (d, 1H, J_{CH-OH} = 9.6 Hz, OH), 5.73 (m, 1H, CH), 8.71 (d, 1H, J_{5-6} = 2.2 Hz, H5 or H6), 8.83 (d, 1H, J_{5-6} = 2.2 Hz, H5 or H6).

Anal. Calcd. for $C_{10}H_{16}N_2O_3S$: C, 49.22; H, 6.61; N, 11.48. Found: C, 49.1; H, 6.3; N, 11.8.

2-*tert*-Butylsulfonyl-3-hydroxybenzylpyrazine (**26**).

Metalation of 2-*tert*-butylsulfonylpyrazine **8** (0.10 g, 0.5 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (1.25 ml, 2.0 mmoles) and 2,2,6,6-tetramethylpiperidine (0.34 ml, 2.0 mmoles), t_1 = 20 minutes, then reaction with benzaldehyde (0.11 ml, 2.0 mmoles), t_2 = 60 minutes gave after purification by column chromatography eluting with ethyl acetate **26** as a brown oil (0.06 g, 41%); ir (potassium bromide): ν 3507 (OH), 3046, 2989 (CH), 1308, 1121 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.42 (m, 9H, *t*-Bu), 4.30 (m, 1H, OH), 6.85 (s, 1H, CH), 7.28 (m, 3H, Ph), 7.45 (m, 2H, Ph), 8.69 (d, 1H, J_{5-6} = 2.1 Hz, H5 or H6), 8.77 (d, 1H, J_{5-6} = 2.1 Hz, H5 or H6)

Anal. Calcd. for $C_{15}H_{18}N_2O_3S$: C, 58.88; H, 5.93; N, 9.15. Found: C, 58.6; H, 6.1; N, 9.3.

2-*tert*-Butylsulfonyl-3-iodopyrazine (**27**).

Metalation of 2-*tert*-butylsulfonylpyrazine **8** (0.06 g, 0.3 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.20 ml, 1.2 mmoles) and 2,2,6,6-tetramethylpiperidine (0.75 ml, 1.2 mmoles), t_1 = 20 minutes then reaction with iodine (0.09 g, 0.4 mmole), t_2 = 120 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (2:8) **27** as a brown oil (0.02 g, 16%); ir (potassium bromide): ν 2975, 2931 (CH), 1311, 1117 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55 (s, 9H, *t*-Bu), 8.53 (d, 1H, J_{5-6} = 2.2 Hz, H5 or H6), 8.65 (d, 1H, J_{5-6} = 2.2 Hz, H5 or H6).

Anal. Calcd. for $C_8H_{11}N_2O_2IS$: C, 29.48; H, 3.40; N, 8.59. Found: C, 29.7; H, 3.6; N, 8.2.

3-Chloro-5-(1-hydroxyethyl)pyridazine-6-*N*-*tert*-butylsulfonamide (**28**).

Metalation of 3-chloropyridazine-6-*N*-*tert*-butylsulfonamide **14** (0.10 g, 0.4 mmole) according to the general procedure with *n*-butyllithium 1.6 *M* (0.80 ml, 1.3 mmoles) and diisopropylamine (0.18 ml, 1.3 mmoles), t_1 = 30 minutes, then reaction with acetaldehyde (1.00 ml, 18.0 mmoles), t_2 = 30 minutes gave after purification by column chromatography eluting with light petroleum ether/ethyl acetate (1:1) **28** as a beige solid (0.06 g, 52%), mp 190-194°; ir (potassium bromide): ν 3300 (OH, NH), 2964 (CH), 1343, 1205 (SO_2N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.53 (s, 9H, *t*-Bu), 1.76 (d, 3H, J_{CH3CH} = 6.7 Hz, CH_3), 5.41 (m, 1H, OH), 5.63 (q, 1H, J_{CH3CH} = 6.7 Hz, CH), 6.52 (s, 1H, H4).

Anal. Calcd. for $C_{10}H_{16}N_3ClO_3S$: C, 40.92; H, 5.49; N, 14.32. Found: C, 41.0; H, 5.9; N, 14.6.

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